KU Leuven
Biomedical Sciences Group
Faculty of Medicine
Department of Public Health and Primary Care

KU LEUVEN

DOCTORAL SCHOOL
BIOMEDICAL SCIENCES

REPRODUCTIVE GENETIC CARRIER SCREENING FOR MONOGENIC CONDITIONS

FACILITATING INFORMED CHOICE AND DECISION-MAKING

Eva VAN STEIJVOORT

Jury:

Supervisor:	Prof. Pascal Borry (KU Leuven, Belgium)
Co-supervisor:	Prof. Hilde Peeters (UZ Leuven, KU Leuven, Belgium)
	Prof. Karen Peeraer (UZ Leuven, KU Leuven, Belgium)
Chair examining committee:	Prof. Johan Van Lint (KU Leuven, Belgium)
Chair public defence:	Prof. Patrick Callaerts (KU Leuven, Belgium)
Jury members:	Prof. Martin Hiele (UZ Leuven, KU Leuven, Belgium)
	Prof. Peter Witters (UZ Leuven, KU Leuven, Belgium)
	Prof. Heidi Mertes (UGent, Belgium)
	Prof. Lidewij Henneman (Amsterdam UMC, The Netherlands)
	Dr. Celine Lewis (UCL Great Ormond Street Institute of Child Health, United Kingdom)

Dissertation presented in partial fulfilment of the requirements for the degree of Doctor in Biomedical Sciences

Oktober 2022

‘*After climbing a great hill, one only finds that there are many more hills to climb.*’ – Nelson Mandela

TABLE OF CONTENT

ABSTRACT

Reproductive genetic carrier screening (RGCS) allows to identify couples with an increased likelihood of conceiving a child with an autosomal recessive (AR) or X-linked condition. Information gained through RGCS can be used to make reproductive choices. The general objective of this research project was to study informed choice and reproductive decision-making with regard to RGCS for expanded test panels of monogenic conditions. Specific objectives were (1) to synthesize evidence from empirical studies that assess the interest in RGCS among individuals and couples in the general population, (2) to gain insights into the potential impact of RGCS on the subsequent reproductive decision-making of at-risk couples, (3) to assess the perceived susceptibility of being a carrier/conceiving a child with a hereditary condition, the acceptability of offering RGCS, the intention to participate in RGCS, knowledge of RGCS, attitudes towards RGCS and preferences for the practical organization of a RGCS offer amongst men and women (of reproductive age) in Flanders (Belgium), (4) to implement and evaluate a RGCS offer in a reproductive context among non-pregnant couples. To meet objective (1) and (2) we performed two systematic reviews of empirical literature following the PRISMA guidelines. In line with objective (3), this dissertation reports the findings of two cross-sectional survey studies on the perspectives of reproductive-aged women and men with regard to RGCS. Finally, we performed a longitudinal survey through a gynecologist practice in Flanders (Belgium) (a) to study the interest of non-pregnant couples in a preconception RGCS offer, (b) to assess the extent to which couples make informed decisions regarding participation in preconception RGCS and (c) to assess the level of satisfaction, anxiety, long-term knowledge retention, psychosocial & counseling related aspects among couples who choose to have reproductive genetic carrier screening. Our results show that there may be discrepancies between prospective parents' reported intentions to undergo RGCS and their actual uptake, particularly during the preconception period. Most couples with an increased likelihood of conceiving a child with an AR or X-linked condition chose reproductive options to reduce the risk of a child affected . Most of our study participants showed positive attitudes towards RGCS and found it acceptable to offer RGCS to couples planning a family. Self-reported intention to have RGCS didn't always translate into actual test-uptake. Within our study where the Belgian RGCS test was offered free of charge to non-pregnant couples from the general population, 53% of women (meeting our study inclusion criteria) who initially showed the intention to have RGCS decided to accept the offer. We observed high rates of informed choice among non-pregnant couples who accepted a free RGCS offer after they were offered up to 30 minutes of pre-test counselling. We recommend that RGCS should ideally be implemented through a tailored implementation strategy whereby individual needs and preferences can be taken into account. Future research should try to assess if high levels of informed choice can also be achieved outside a controlled research context with more limited resources.

LIST OF ABBREVATIONS

In alphabetical order

ACMG: American College of Medical Genetics and Genomics
ACOG: American College of Obstetricians and Gynaecologists
ARC: at-risk couples
ART: Assisted reproductive technology
CF: Cystic fibrosis
CINAHL: Cumulative Index to Nursing and Allied Health Literature
DNA: Deoxyribonucleic Acid
ECS: Expanded Carrier Screening
ESHG: European Society of Human Genetics
ICF: Informed Consent Form
ICSI: Intracytoplasmic sperm injection
IVF: In vitro fertilisation
MGS: Massive parallel sequencing
NIPT: Non-invasive prenatal testing
NSGC: National Society of Genetic Counselors
PGT-M: Preimplantation genetic testing for monogenic/single gene defects
PNDx: Prenatal diagnosis
PQF: Perinatal Quality Foundation
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RGCS: Reproductive genetic carrier screening
SHC: Superior Health Council
SMFM: Society for Maternal-Fetal Medicine
SWEPP: Swedish Pregnancy Planning study
TSD: Tay-Sachs disease

CHAPTER 1

GENERAL INTRODUCTION

BACKGROUND

The human genome contains a total of 46 chromosomes in each somatic cell including one pair of sex chromosomes (X or Y) and 22 pairs of autosomes. Each human individual inherits a complete set of chromosomes from their mother and the other set from their father. These chromosomes contain genes which are made up of DNA. Most genes include instructions for the production of proteins. The total number of protein-coding genes has been estimated to be between 20.000 and 25.000 according to the findings of the Human Genome Project, which aimed to obtain the first accurate sequence of the human genome (1). A change in the DNA-sequence is called a variant. While some variants are benign with no impact on a person's health, others are pathogenic and may cause or increase the likelihood to develop a certain condition. It is estimated that worldwide 7.9 million children are born each year with a birth defect of genetic or partially genetic origin (2, 3). The prevalence of these birth defects varies greatly between countries which could be explained by various factors like disparities in maternal and child health services, poverty, differences in the frequency of consanguineous marriages, differences in child bearing age, wide variations in the availability/prevalence of prenatal screening/diagnosis, different views with regard to termination of a pregnancy, etc. (2, 4). For example, the birth defects prevalence per 1000 live births in France is estimated to be 40 compared to 82 in Sudan (2). Congenital anomalies can be either caused by genetic or environmental factors or an interaction between both. While for about half of known birth defects a cause has been identified, for others (~50%) the underlying cause still remains unclear.

Monogenic conditions are caused by a pathogenic variant in one single gene and can be passed on to future generations through different modes of inheritance. The mode of inheritance can be either recessive or dominant. Two faulty copies of a gene must be present for an autosomal recessive (AR) condition (e.g. cystic fibrosis) to develop. While only one faulty copy of a gene is sufficient to cause an autosomal dominant condition or an X-linked condition (e.g. hemophilia A) in males, as they only have one X-chromosome. Most female carriers of an X-linked condition are typically healthy and therefore not aware of the fact that they have an increased risk of having an affected son. But some may also experience mild symptoms (e.g. Fragile X syndrome). In contrast, dominant conditions (e.g. Huntington's disease) can manifest in individuals with only one copy of the disease-associated gene (5). Recessive conditions are individually rare but when considered collectively, they account for approximately 20% of infant mortality and 10% of all paediatric hospitalizations (6, 7). The March of Dimes Global Report on Birth Defects (2006) indicated that worldwide the birth prevalence for recessive single gene disorders is 7.4 per 1000 live births and 1.3 per 1000 live births for X-linked single gene disorders; with a considerable observed variation in birth prevalence for the recessive single gene disorders between low-income (9.9 per 1000 live births), middle- income (4.6 per 1000 live births) and high-income countries (2.5 per 1000 live births) (3). Heterozygous individuals with only one altered copy of a certain recessive gene are called 'carriers'. The carrier burden for severe paediatric recessive conditions is estimated at 2.8 pathogenic variants per person (6). Carriers are

most often not aware of their own carrier status because they usually don't experience any condition-associated symptoms and because of a negative family history for genetic conditions. They can however pass on their disease-causing variant to their offspring. When both reproductive partners are carriers of an abnormal variant associated with an AR condition, there's a 25% chance within each pregnancy that both partners pass on the abnormal variant to their offspring. In this case, their child will have two altered copies of the gene and therefore be at risk to develop the genetic condition. In addition, there is a 50% chance within each pregnancy that their child will also be a carrier and a 25% chance that the abnormal variant is not passed on (Figure 1). When the mother is a carrier of an X-linked condition, there is a 50% chance that the couple's male offspring will be affected (Figure 2) Daughters of a female carrier of an X-linked condition have a 50% chance of also being a carrier and can in turn pass on the condition-associated gene to the next generation. It is estimated that approximately 1-2 in 100 couples are at risk of having a child affected with an autosomal recessive or X-linked condition (8, 9). On average, the likelihood of conceiving a child with a recessive condition is estimated to be equal to the chance of a child with Trisomy 21 (Down Syndrome) for a 37 year old women (8).

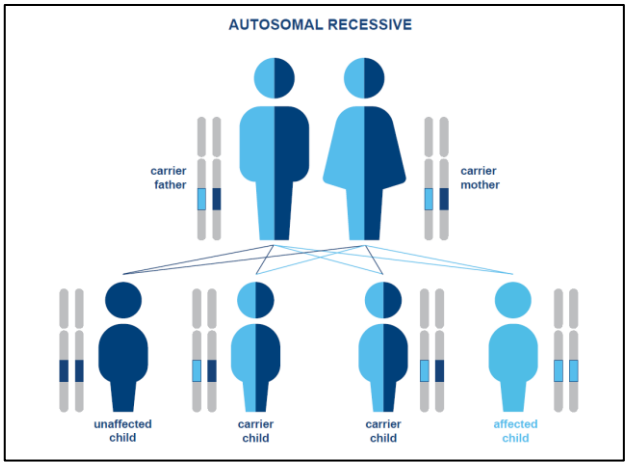


Figure 1: Autosomal recessive inheritance

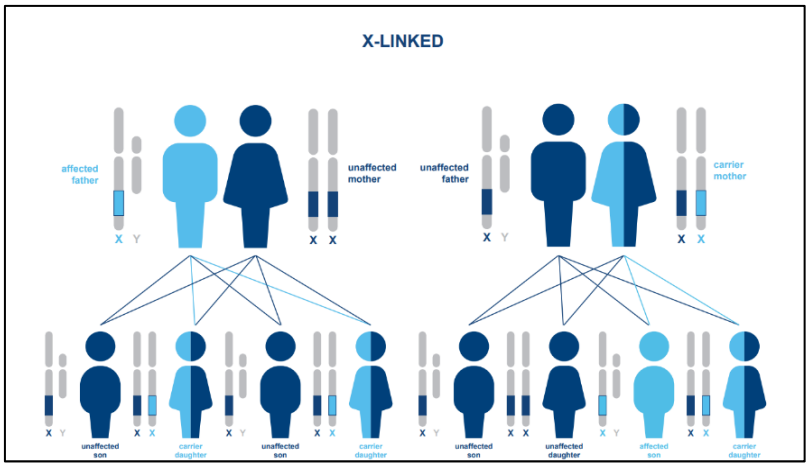


Figure 2: X-linked inheritance

Reproductive genetic carrier screening for recessive monogenic conditions

Reproductive genetic carrier screening (RGCS) allows for '*the detection of carriers of autosomal recessive and X-linked conditions in individuals or couples who do not have an a priori increased likelihood of being a carrier based on their or their partners' personal or family history*' (10). RGCS can be offered to individuals or couples before pregnancy (preconception) or to couples during pregnancy (prenatal) as part of screening programme (population-based) or on an occasional basis. Blood samples from both reproductive partners can be obtained simultaneously or sequentially (second partner is only screened if the first partner is identified as a carrier) (10, 11). Disclosure of test results can be either couple-based (carrier status is only being disclosed when both partners are carriers for the same condition) or on an individual level (disclosure of all individual test-results) (10). Information gained through RGCS can be used to make informed reproductive decisions before or after conception. Prior to conception, couples at risk can consider different reproductive options like IVF/ICSI combined with pre-implantation genetic testing for monogenic conditions (PGT-M), gamete donation, adoption or refrain from having children together. At risk couples can also opt to have additional testing during pregnancy (prenatal diagnosis) to confirm the presence or absence of the condition in the fetus.

This can either be done by chorionic villus sampling (CVS) or amniocentesis. Both diagnostic tests come with an additional risk of miscarriage of approximately 0.5 to 1%. CVS can be done between 10 and 14 weeks gestation by means of a puncture through the abdominal wall (transabdomincal) or by means of a thin tube through the cervix (transcervical). This procedure involves taking a sample of tissue from the placenta. Because CVS can be performed earlier, it can decrease time of uncertainty and allow for earlier pregnancy termination if desired. Amniocentesis examines the cells in the amniotic fluid that come from the skin and mucous membranes of the fetus. A limited amount of amniotic fluid is withdrawn via a thin needle through the abdominal wall. An amniocentesis is usually performed from the 15-16th week of pregnancy, but can be performed at any gestational age after 15 weeks. The laboratory examination can take between 3 days and 3 weeks for both diagnostic procedures (12, 13). When the condition is present, couples can either decide to terminate the pregnancy or to prepare for a child with a recessive condition (10). In Belgium, an abortion for psychosocial (non-medical) reasons is allowed up to 12 weeks of pregnancy. After 12 weeks, abortion is only possible if the pregnancy poses a serious threat to the health of the woman or if it is established that the child will suffer from an extremely serious and incurable condition. Information gained through RGCS can also help to reduce the time necessary to diagnose an affected child. In addition, the acquired knowledge can help to develop a specific postnatal management plan which could include potential treatment options or palliative care if applicable (14).

Traditionally, RGCS has focused on highly prevalent conditions with significant morbidity and/or a reduced life expectancy as a result of cognitive or physical disabilities or a requirement for lifelong

medical therapies. Furthermore, these conditions had a well-defined phenotype and an early childhood onset (11). The first carrier screening initiatives were targeted to specific groups based on an increased individual risk based on family history (e.g. cystic fibrosis (CF)), an increased population risk on the basis of race or ethnicity (e.g. Tay-Sachs screening in individuals of Ashkenazi Jewish descent) or an increased risk based on geographic location (e.g. beta-thalassaemia in several at-risk populations in the Mediterranean area) (14). Simultaneous screening for a large number of conditions at a faster turnaround time became feasible following the introduction of new technological advances like massive parallel sequencing (MGS) and a decrease in analysis and sequencing related costs in recent years (14, 15). The development of the first commercial expanded RGCS product which screened for 108 Mendelian conditions was reported in 2010 (16). Three years later the first results revealed that 24% (n=23.453 individuals) of those screened were a carrier for at least one of these 108 conditions (17). Compared to traditional carrier screening initiatives these expanded test panels are screening all individuals for the same amount of conditions regardless of family history, race/ethnicity or geographic location and therefore do not rely on patients having accurate knowledge of their family history or race/ethnicity (11). Several recent studies have demonstrated that carrier screening approaches based on ethnicity, geographic origin or family history are not optimally aligned with the actual distribution of carrier frequencies for severe genetic disease. Offering ECS to all reproductive-aged individuals could therefore lead to a substantial increase of identified at-risk couples (17-19). During the last decade several providers have made expanded test panels available to the general population which resulted in a highly variable testing landscape. An analysis of available expanded screening tests in 2017 by Chokoshvili et al. showed how the number of conditions ranged from 41 to 1792, with only three conditions screened for by all identified providers (n=16) (15). In addition, this study reported remarkable differences in pathogenic variantsscreened for, variant interpretation and reporting strategies.

Professional organisations like the American College of Medical Genetics and Genomics (ACMG), the American College of Obstetricians and Gynecologists (ACOG) and the European Society of Human Genetics (ESHG) have published multiple recommendations about RGCS since 2013 (10, 14, 20, 21). These organisations emphasize that RGCS should always be voluntary and based on an informed choice. Overall, there is consensus that RGCS should ideally be offered before pregnancy in the preconception period (10, 11, 22) and that the selection of condition-associated variants to be included in tests panels should be guided by specific criteria (14, 20-22). For example, a well-defined phenotype for which the severity may impact reproductive decision making, childhood onset manifestation, etc. Conditions and/or variants screened for by (commercial) providers don't always answer to the criteria recommended by these professional organisations (e.g. inclusion of variants of unknown significance or variants that are not clearly pathogenic) (10, 23). While some have criticized commercial providers to use a 'more is better' marketing approach to be able to differentiate their product to patients and health care providers, others have claimed that the false

reassurance of a false negative result is still better than the current practice of not informing individuals and/or couples about the possibility to have RGCS (23, 24). Most recent guidelines by the ACMG propose a new tier-based system (Figure 3) to ensure a consistent and equitable approach for offering RGCS to all individuals during pregnancy or preconception (20). These recent guidelines underline once again that RGCS can't replace previous risk-based screening recommendations for individuals with a family history of a certain genetic condition or couples with consanguinity (14, 20). Nor can it replace non-invasive prenatal testing (NIPT) or newborn screening. The role of RGCS has to be seen as complementary (10, 20).

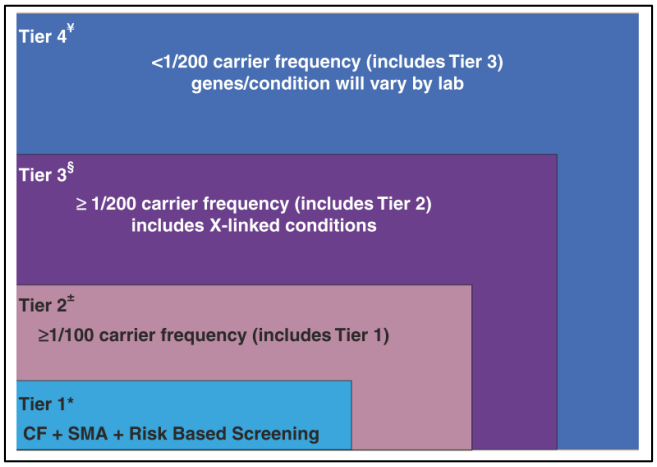


Figure 3: A tiered system based on carrier frequency[25]

The ACMG recommends to offer Tier 3 to all pregnant patients and those planning a pregnancy and Tier 4 to all consanguineous relationships (second cousins or closer) or when a family or personal medical history calls for it. To ensure equity in care the ACMG recommend to no longer offer Tier 1 and Tier 2.

In 2017, the Belgian Superior Health Council (SHC) published an advisory report regarding the implementation of RGCS for severe AR and X-linked conditions in a reproductive context (22). This report recommended a stepwise introduction of RGCS within the Belgian health care system, where RGCS would be available through a sequential screening approach (with the possibility of collecting both samples at the same time) to couples planning a pregnancy and results would be reported by focusing on information that is of relevance for the reproductive decision-making process of the couple (couple-based test results). According to the SHC, a stepwise introduction would facilitate a responsible implementation of RGCS as it allows to consider societal and ethical issues of interest. The Belgian medical centres for human genetics have jointly responded to the recommendations of the SHC by establishing an outline for the development and introduction of a RGCS test for the Belgian population. In 2019, a Belgian RGCS offer became available to couples planning a pregnancy which includes more than 1000 genes associated with autosomal recessive (AR) and X-linked conditions. Informed consent has to be documented through a written form. Blood samples are taken from both reproductive partners simultaneously and the analysis is performed through the accredited laboratories of the Belgian genetic centres. Results are communicated as either a 'normal couple result' which means that there is no demonstrable increased risk or as an 'abnormal couple

result' which entails that there is an increased risk of having a child with one of the genetic conditions screened for. In addition, individuals obtain their individual carrier status for seven of the most frequent AR conditions (ACADM, CFTR, DHRC7, GJB2, HBB, PAH and SMN1) and the X-linked conditions (female) to allow for cascade testing.

In comparison to the Belgian example, multiple non-commercial RGCS panels have been developed and implemented in the The Netherlands. In 2016, the Amsterdam University Medical Centers (Amsterdam UMC) implemented a pilot study in which the RGCS offer screened for 50 autosomal recessive conditions. The offer is currently available to all couples planning a pregnancy. At the Amsterdam UMC, couples can choose between simultaneaous or sequential testing of both reproductive partners. Furthermore, all individual test results are disclosed(26). In contrast, the University Medical Centre in Groningen (UMCG) offers a RGCS test couple-test that includes 70 autosomal recessive conditions through three General Practitioners practices(27, 28). An important difference with the RGCS offer from the Amsterdam UMC is that no individual results are being reported. Finally, the Maastricht University Medical Center offers a panel of more than 2,000 genes associated with known autosomal recessive disorders to consanguineous couples(29). In the Netherlands, insurance provides a (partial) reimbursement for high-risk groups (e.g. founder population in Volendam, consanguinity, etc.). In our other neighboring country France, preconception RGCS can only be proposed for a limited number of genetic conditions to relatives of a child diagnosed with an autosomal recessive condition or X-linked condition or to consanguineous couples. But also in France, there is currently an ongoing debate on expanding RGCS to a wider population (30, 31).

Ethical and (psycho)-social issues related to RGCS

The idea of population-based RGCS programs have raised many ethical and (psycho)-social issues that should be taken into account to be able to ensure a responsible implementation. Different views on the aim of RGCS exist with outcomes focusing on individuals and their families ('reproductive autonomy') or outcomes for populations ('prevention') (32).

Early carrier screening initiatives aimed to reduce the prevalence of certain genetic conditions in communities with a high burden ('ancestry-based screening') (10, 33, 34). A well-known example is the reduction in incidence of Tay-Sachs disease (TSD) by more than 90% in the Jewish population in the United States and Canada following the introduction of a screening program for TSD (35). The focus on prevention within these initiatives stems from the public health paradigm which typically focuses on improving the health of a population (33). Another context in which detection of carrier status has occurred for several years is clinical carrier testing (≠ screening) where individuals with a relevant family history were the ones of interest (e.g. carrier testing for cystic fibrosis). Within this

last context, carrier testing has been influenced by the clinical testing paradigm as it has been perceived as a more clinical intervention (33).

Within the last decade expanded test panels became available to a much larger population while screening for a wider range of genetic conditions regardless of family history or ancestry. The shift to offer RGCS at a population scale ('population-based screening') has led to an ongoing debate of the underlying goals of RGCS. The current view on the aim of population-based RGCS is predominantly informed by the clinical paradigm (emphasis on outcomes for individuals, freedom of choice and autonomy) and assumes that RGCS should initially aim to increase reproductive autonomy and enable informed reproductive decision-making by identifying those couples with an increased likelihood of conceiving a child with an AR or X-linked condition (10, 11, 20, 22, 33, 34). Hereby, reproductive autonomy specifically refers to the capacity to reflect on one's values and preferences (e.g. long-term goals) relevant to inform choices with regard to reproduction decision making (e.g. when to become pregnant, whether to continue a pregnancy, etc.) (33). The focus on reproductive autonomy may lead to the idea that RGCS is a clinical intervention. However, RGCS could also be seen as a public health intervention because of common features with other screening offers available to the public (e.g. testing of individuals without an a priori risk). While acknowledging that prevention of certain genetic conditions as a main goal for RGCS is problematic because of the possibility of implicit judgements, it's important to acknowledge social and relational factors (e.g. socio-economic conditions) beyond an individual's sphere of control that can undermine or limit reproductive choices (33). It has been argued that an approach with multiple compatible goals would be ethically acceptable. For example, increasing reproductive autonomy through enabling informed reproductive decision making and reducing inequity in access to health interventions (33, 36).

Some have criticized RGCS for being eugenic in its aim or possible outcomes. Eugenics refers to a range of practices that seek to improve the genetic composition of a population group/future generations by selecting desired heritable characteristics. The term immediately brings to mind a range of unethical programmes (e.g. involuntery sterilization of individuals with genetic conditions) that were performed during the 20th century (37). The most known example, are the highly unethical activities undertaken under the Nazi regime in Germany. After the end of the Second World War, eugenics was widely condemned. Until now the concept of eugenics is still strongly stigmatized to the point of being taboo. In consequence, there is a fierce reluctance to acknowledge the potentially eugenic aspects of reproductive genetics, including RGCS (37). While RGCS doesn't aim to change or improve the genetic composition of the whole population compared to some past eugenics programs it's important to acknowledge potentially eugenic effects at a societal level. Improving informed reproductive decision-making could result in a reduction of the prevalence of conditions screened for when at-risk couples opt to have prenatal diagnoses followed by pregnancy termination of an affected fetus, to undergo PGT-M, to use donor gametes, to adopt or to refrain from having

biological children together (10). In addition to emphasizing the voluntary nature of participation in RGCS and the freedom of choice we must recognize the potential shift in societal norms that shape individual reproductive choices (37). The success of RGCS should therefore not only be measured by the uptake of screening. A measure of informed choice should also be included to assess if the choice to accept or decline RGCS was based on adequate knowledge and consistent with one's values (38). While not considered a primary aim, RGCS could also contribute to a reduction in morbidity and mortality as it could allow for an earlier diagnosis (through a close monitoring of children born to carrier couples) and early therapeutic procedures (10). Finally, RGCS can be motivated by the desire to avoid painful experiences such as having to witness one's child suffering or to grief the loss of a child (32).

An often mentioned ethical issue that requires cautious reflection is how to organize an equitable distribution of scarce health care resources. Compared to traditional carrier screening initiatives - which were reserved for specific groups with an a priori increased risk of being a carrier – more recent RGCS test panels could be of possible interest to every individual in the general population as they screen for a large amount of genetic conditions (20). However, testing all individuals will also identify more couples at risk of conceiving a child with a particular genetic condition. This could possibly result in more invasive confirmatory diagnostic tests which in turn also leads to a more intensive use of health care resources and health care providers. Yet, one could also argue that there would be a significant decrease in costs associated with the care and treatment of individual affected with these genetic conditions. A systematic review, conducted by Wang et al. (2021) critically assessed the economic evaluations of reproductive carrier screening since 1990 and found that cost-effectiveness conclusions varied largely within the identified studies. This because studies used various clinical pathways/strategies and screened conditions when implementing a carrier screening program. The authors conclude that further research is still required to establish the cost-effectiveness of carrier screening programs for multiple conditions (39).

In the future, health care providers could also be faced with even more difficult decisions in the field of reproduction when more at-risk couples are identified prior to conception. While it is common practice to offer PGT-M for e.g. cystic fibrosis, this option might not be found acceptable for some less severe conditions included in test panels. In most countries, RGCS is currently not available as an organized screening program but under the form of opportunistic screening for example within the context of assisted reproductive healthcare. Fodder for debate is the question whether it is fair to offer RGCS selectively to some couples while other couples are at the same risk? And extra dimension to the whole debate is the concern that high-risk populations (e.g. consanguineous couples, founder populations) might run the risk of being overlooked when RGCS is offered as a population-based screening program, as specific genes or variants might not be covered (10, 40). A

more in depth risk analysis and study of familial variants is still highly recommended in this specific context to address the specific familial risk (11).

It is well documented that large-scale human genomic studies have been predominantly performed on populations of European ancestry (41). This bias has important implications because the under-representation of more ethnically diverse populations directly impacts our ability to translate genetic research into clinical practice. In the context of RGCS, this may result in inaccurate risk assessments of under-studied populations (42). There is an urgent need to recognize the importance of studying under-represented populations to avoid health inequalities because the benefits of genomic research is not distributed fairly and to maximize the potential for new discoveries (41). By including populations that reflect the full diversity of human populations in genomic studies, genomic variants associated with various health outcomes at the individual and population levels could be identified. This will allow to better define a person's risk of developing a specific disease and to pursue genomic medicine strategies that benefit specific populations (43).

Another issue of justice is that of discrimination and stigmatization. This applies to individuals who are identified as carriers and those individuals living with genetic conditions screened for. Earlier screening programs targeted at specific subpopulations have revealed feelings of discrimination or social stigma among carriers. An example of this are the early mandatory screening programs for sickle cell anemia during the 1970s where African-American carriers were refused health and life insurance or employment opportunities because carrier status for sickle cell anemia was equated with the condition itself (26). Even though RGCS might not be intended for individuals with disabilities with a genetic basis and/or their relatives, there is the potential for significant impacts for them. The disability rights movement has criticized RGCS because of its tendency to negatively shape public opinion about disabilities, the possible reduction in social and peer support of affected families and a possible decline in public funding into treatments and cures (44). While some have argued that the potential use of RGCS to avoid the birth of children with certain genetic conditions expresses a negative view to and about those living with these conditions others have emphasized that offering RGCS to all individuals could also reduce the risk of stigmatization and create more understanding and support (10, 45). When the practice of carrier screening becomes better known among the general population, there might come a greater general awareness that we are all carrier of certain monogenic conditions (5). Making RGCS for monogenic conditions available to all couples with a desire to have children could therefore also possibly help prevent stigmatization or discrimination of particular subgroups (8).

Information gained through RGCS can have certain social consequences (e.g. informing family members) but could also possibly have an impact on psychological well-being and health perception (e.g. feeling less healthy after being identified as a carrier). Anxiety levels might for example increase

while waiting for screenings results or after being identified as a carrier or an at-risk couple (10). Adequate pre- and post-test counseling initiatives are considered to be crucial to minimize this risk as they help to better understand screening results (10). Overall, there is consensus that screening panels should only include severe childhood-onset conditions. It is advised to not include adult-onset conditions due to the possible violation of the minor's autonomy and the right to self-determination (10, 11, 21, 22, 46). However, in the absence of a clear legal definition for what constitutes a 'severe' condition its interpretation tends to be rather subjective (32, 47). There are also some ethical issues related to the classification of certain identified variants. Because not everyone with the same genetic variant will develop the same symptoms related to a particular genetic condition (reduced or incomplete penetrance) and the same genetic condition can manifest differently among affected individuals (variable expressivity), it has been recommended to make the inclusion of certain conditions optional based on the principle of nonmaleficence (21). Hereby it's important to emphasize that a false positive result may mean additional uncertainty for the couple or could lead to unnecessary tests or interventions. While the choice to not report a potential condition-associated variant means that a couple might make reproductive decisions based on limited information (32, 47).

Informed choice & informed decision making

As mentioned before, the success of RGCS should not only be measured by the uptake of screening but should also include a measure of informed choice to assess if the choice to accept or decline RGCS was based on adequate knowledge and consistent with one's values (38). A systematic review by Ames et al. (38) identified different definitions and approaches to measure informed choice in reproductive genetic screening. While a choice refers to the end product of a decision, a decision refers to the process of choosing between alternatives, preceding that choice. Compared to the definition of an informed choice, the definition of informed decision making includes an extra element (e.g. inclusion of deliberation).

Definitions of informed choice/decision making

'Informed choice or decision making generally involves three components: information, comprehension, and voluntary choice.' (Summers, 1994)(48)

'An effective decision is defined as informed, consistent with personal values, and acted upon'. (O'Connor, 1995) (49)

'An informed decision is made when an individual evaluates the relevant information about the advantages and disadvantages of all the possible courses of action, in accord with their beliefs, to reach a decision, …' (Bekker, 2004) (50)

'An informed decision making process includes: understanding the screening test, its risks, benefits, and alternatives, understanding personal values and preferences, weighing the pros and cons of the test …' (Rimet et al., 2004) (51)

The most common approach to measure informed choice in reproductive genetic screening is the Multidimensional Measure of Informed Choice (MMIC) developed by Marteau et al. (38, 52). This measure defines an informed choice as '*one that is based on relevant knowledge, consistent with the decision-maker's values and behaviourally implemented'* (52). Some have questioned to what extent autonomous and/or informed choice is possible in a context where normative perceptions of people can be influenced when a certain practice becomes routine. As a result people may regard RGCS as standard practice instead of an additional reproductive choice that is optional (45, 53). In addition it has been suggested that offering RGCS for certain conditions is not a neutral activity as it could be interpreted as a sign that some action should be taken when an increased reproductive risk is identified on the basis of the test results (32, 54, 55). In this way it could create pressure to prevent the birth of (possibly) affected children (22). This may become even more outspoken when RGCS is being reimbursed by a health insurance.

Since decisions can be influenced by many different internal and external factors it's important to start from a place of a free, informed and autonomous choice. This implies that every individual also has the right not to know and to decline a RGCS offer. The final decision to accept or decline RGCS and subsequent reproductive choices should reside with an individual or a couple. Therefore it's of utmost importance that one is aware of the purpose of RGCS and the possible implications. While genetic screening usually doesn't entail any physical risks, it's important that those considering RGCS understand that they might be faced with difficult choices such as considering invasive diagnostic testing (e.g. amniocentesis) or a pregnancy termination.

Where in the past it was possible to provide extensive information about a specific genetic condition, larger test panels make it practically impossible to discuss information about every genetic condition screened for. While less detailed information could possibly lead to a less informed choice, there's also the possible risk of 'information overload' which could undermine the aim of a meaningful choice in a reproductive context (10). A generic consent process has been proposed in the context of RGCS for large test panels to avoid 'misinformed consent' as a results of 'information overload' (21, 54). This generic consent process entails an approach where the focus lies on broader concepts (e.g. AR inheritance pattern), issues in genetic screening (e.g. residual risk, variable expressivity and reduced penetrance), reproductive options which could be considered, costs of screening, potential disclosure to other family members, etc. (54). The choice to provide generic information to obtain consent should however not be understood as a waiver of the patient's right to information (54). It's possible that some people might require more specific and in-depth information to be able to make a choice. Therefore, the possibility to obtain additional information or to ask questions should still be available. In addition, more detailed information and follow-up counseling should also be provided to those identified as individual carriers or as couples with an increased likelihood of conceiving a child with a particular monogenic condition.

Earlier studies focusing on carrier screening for cystic fibrosis (CF) showed overall positive attitudes among individuals in the general population to routinely offer CF screening (56). Even though participants believed that the best time to have CF carrier screening would be before pregnancy, preconception screening was associated with a lower uptake than prenatal screening. These findings suggest that there may be discrepancies between prospective parents' reported intentions to undergo carrier screening and their actual uptake. As the availability and accessibility of RCS grow, more couples will be presented with the choice to accept or decline such an offer. Their attitudes and beliefs, as well as the perceived usefulness of this screening modality will likely determine whether ECS is to become a widespread reproductive genetic test. More insights are needed to understand how individuals and couples process information when RGCS is offered to them and which factors affect couples decisions to undergo or forgo RGCS. In Belgium, the SHC recommended that RGCS should be made available to all couples considering pregnancy. However, the SHC also recognized that to ensure a successful implementation a number of challenges would need to be addressed, including the interest and participation rate of the target population and how to ensure adequate pre-test information/counseling and post-test counseling to facilitate informed reproductive decision-making. The present project addresses these recommendations of the SHC.

OBJECTIVES AND OUTLINE OF THE THESIS

OBJECTIVES

The general objective was to study informed choice and reproductive decision-making with regard to RGCS for expanded test panels of monogenic conditions.

Specific Objectives were:

1. To synthesize evidence from empirical studies that assess the interest in RGCS among individuals and couples in the general population
2. To gain insights into the potential impact of RGCS on the subsequent reproductive decision-making of at-risk couples.
3. To assess the perceived susceptibility of being a carrier/conceiving a child with a hereditary condition, the acceptability of offering RGCS, the intention to participate in RGCS, knowledge of RGCS, attitudes towards RGCS and preferences for the practical organization of a RGCS offer amongst men and women (of reproductive age) in Flanders (Belgium).
4. To implement and evaluate a RGCS offer in a reproductive context, namely in non-pregnant couples.

   In order to assess the success of the small-scale pilot project, the following specific evaluative objectives will be included:

   a. To assess the intention to participate in preconception RGCS and the uptake of a free RGCS offer among participants who showed the intention to have RGCS.
   b. To assess the extent to which couples make informed decisions regarding participating in preconception RGCS.
   c. To assess the level of satisfaction, anxiety, long-term knowledge retention, psychosocial & counseling related aspects among couples who choose to have reproductive genetic carrier screening

OUTLINE

This dissertation is composed of nine chapters. Six of these chapters (chapters two to seven) have already been published in international peer-reviewed journals, whereas chapter eight has been submitted and is currently under review. References have been standardised with the Vancouver reference style for the purpose of this dissertation. Supplementary materials for all chapters can be found at the end of this manuscript. Over the years, many terms have been used to correctly label carrier screening for multiple monogenic conditions. At the start of this doctoral research project we used the term expanded carrier screening (ECS) as mentioned in chapters two, three and four. Following, most recent guidelines we have updated this name to reproductive genetic carrier screening (RGCS) as mentioned in all other chapters. We would like to underline once again that the general aim of this research project was to study informed choice and reproductive decision-

making with regard to RGCS for expanded test panels of multiple monogenic conditions. Therefore the empirical study results presented in this manuscript should be interpreted within this specific context. The term ‘couple(s)’ is used to describe a broad range of family structures with a desire to have children. The phrasing ‘couple’ refers to the genetic parents of the pregnancy or intended pregnancy.

METHODOLOGY

A more detailed description of the methods used in each study is provided below.

Chapter 2: Systematic Review

A systematic review of empirical literature was carried out following the PRISMA guidelines (57) to identify empirical studies that focused on the assessment of the intention to undergo a (hypothetical) carrier screening test, uptake of an actual carrier screening offer, or both. Four databases (PubMed, Web of Science, CINAHL, and Cochrane Library) were systematically searched to identify English language studies performed between January 2009 and January 2019 using the following search string: ‘carrier’ AND (‘testing’[tw] OR ‘screening’ [tw]) AND (attitude [tw] OR intention [tw] OR interest [tw] OR views [tw] OR opinions [tw] OR perspectives [tw] OR uptake [tw]). Studies were eligible for inclusion if they reported on intentions to undergo a (hypothetical) RGCS test, uptake of an actual RGCS offer or both. A multistep selection process was performed by two researchers independently for validation purposes.

Chapter 3: Systematic Review

A systematic review of empirical literature was carried out following the PRISMA guidelines (57) to identify original research articles reporting reproductive decisions of couples and females identified as being at risk of having a child affected with an autosomal recessive and/or an X-linked recessive condition. Four online databases (PubMed, Web of Science, CINAHL and Cochrane Library) were searched by using the following search string: ‘carrier’ AND (‘testing’[tw] OR ‘screening’ [tw]) AND (reproductive behaviour [tw] OR reproductive choices [tw] OR reproductive decision-making [tw] OR outcomes [tw] OR clinical decision making [tw]). Studies were eligible for inclusion when they reported reproductive decisions of carrier couples (in autosomal recessive disorders) and/or female individuals (in X-linked recessive disorders) who, through carrier screening, were found to be at risk of having an affected child. As our objective was to investigate how prospective parents in the general population may act on their carrier status information, we decided to exclude studies primarily focused on couples/ individuals with previously known risk of having an affected child. A multistep selection process was performed by two researchers independently for validation purposes.

Chapter 4: Cross-sectional survey study

Pharmacists of public pharmacies (n=315) throughout Flanders (Belgium) were asked to distribute flyers with an invitation to participate in an online survey about RGCS to non-pregnant women of reproductive age (18-49 years) who came in for a prescribed contraception. The online survey could be administered through the link or QR-code mentioned on the distributed flyers. Prior to completing the questionnaire participants were briefly informed about RGCS. The questionnaire was only available in Dutch and took approximately 15 min to complete. The online questionnaire was available between May 2019 and January 2020.

Chapter 5: Cross-sectional survey study

Participants were recruited through five public pharmacies in Flanders (Belgium). Potential participants were approached by researchers present within the pharmacies and were asked to fill in the anonymous self-administered questionnaire on the spot after reading an information sheet explaining some key concepts. The questionnaire that had to be completed within the pharmacy took ~15 min to fill in. Data collection was carried out between September 2019 and December 2019.

Chapter 6-8: Longitudinal survey study

Non-pregnant women of reproductive age visiting their gynecologist were invited to answer a self-administered questionnaire assessing interest and attitudes regarding RGCS (objective 4a). Prior to filling in the questionnaire, participants were briefly informed about RGCS. Participants who showed the intention to have RGCS were asked to consider participation in a follow-up clinical study where RGCS would be offered free of charge. At least one week after the initial contact moment, the researcher re-contacted participants to inquire about their decision to accept or decline the RGCS offer. If participants (=two reproductive partners) were interested to participate they were sent an extensive information leaflet prior to a pre-test counselling session. If couples agreed to have RGCS they were asked to complete a second questionnaire (objective 4b) after their blood samples were taken and a third questionnaire (objective 4c) when receiving back their test results. Participants were initially informed about their test results over the phone by a researcher (E.V.S.) between September 2019 and January 2021. Subsequently, a written report of test results was sent by registered mail to all participants.

REFERENCES

1. International Human Genome Sequencing C. Finishing the euchromatic sequence of the human genome. Nature. 2004;431(7011):931-45.
2. Zarocostas J. Serious birth defects kill at least three million children a year. BMJ (Clinical research ed). 2006;332(7536):256.
3. Christianson A, Howsen PH, Modell B. Global Report on Birth Defects: The hidden toll of dying and disabled children. New York: March of Dimes; 2006.
4. Khoshnood B, Greenlees R, Loane M, Dolk H, Committee obotEPM, Group aEW. Paper 2: EUROCAT public health indicators for congenital anomalies in Europe. Birth Defects Research Part A: Clinical and Molecular Teratology. 2011;91(S1):S16-S22.
5. Chial H. Mendelian Genetics: Patterns of Inheritance and Single-Gene Disorders. Nature Education 2008;1(1):63.
6. Bell CJ, Dinwiddie DL, Miller NA, Hateley SL, Ganusova EE, Mudge J, et al. Carrier testing for severe childhood recessive diseases by next-generation sequencing. Science translational medicine. 2011;3(65):65ra4-ra4.
7. Blencowe H, Moorthie S, Petrou M, Hamamy H, Povey S, Bittles A, et al. Rare single gene disorders: estimating baseline prevalence and outcomes worldwide. J Community Genet. 2018;9(4):397-406.
8. Ropers HH. On the future of genetic risk assessment. J Community Genet. 2012;3(3):229-36.
9. Fridman H, Yntema HG, Mägi R, Andreson R, Metspalu A, Mezzavila M, et al. The landscape of autosomal-recessive pathogenic variants in European populations reveals phenotype-specific effects. Am J Hum Genet. 2021;108(4):608-19.
10. Henneman L, Borry P, Chokoshvili D, Cornel MC, van El CG, Forzano F, et al. Responsible implementation of expanded carrier screening. European journal of human genetics : EJHG. 2016;24(6):e1-e12.
11. Edwards JG, Feldman G, Goldberg J, Gregg AR, Norton ME, Rose NC, et al. Expanded carrier screening in reproductive medicine-points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine. Obstet Gynecol. 2015;125(3):653-62.
12. Carlson LM, Vora NL. Prenatal Diagnosis: Screening and Diagnostic Tools. Obstetrics and gynecology clinics of North America. 2017;44(2):245-56.
13. Alfirevic Z, Navaratnam K, Mujezinovic F. Amniocentesis and chorionic villus sampling for prenatal diagnosis. The Cochrane database of systematic reviews. 2017;9(9):Cd003252.
14. Obstetricians ACo, Gynecologists. Carrier screening in the age of genomic medicine. Committee Opinion No. 690. Obstet Gynecol. 2017;129:e35-e40.

15. Chokoshvili D, Vears D, Borry P. Expanded carrier screening for monogenic disorders: where are we now? Prenat Diagn. 2018;38(1):59-66.
16. Srinivasan BS, Evans EA, Flannick J, Patterson AS, Chang CC, Pham T, et al. A universal carrier test for the long tail of Mendelian disease. Reproductive BioMedicine Online. 2010;21(4):537-51.
17. Lazarin GA, Haque IS, Nazareth S, Iori K, Patterson AS, Jacobson JL, et al. An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals. Genet Med. 2013;15(3):178-86.
18. Westemeyer M, Saucier J, Wallace J, Prins SA, Shetty A, Malhotra M, et al. Clinical experience with carrier screening in a general population: support for a comprehensive pan-ethnic approach. Genet Med. 2020;22(8):1320-8.
19. Peyser A, Singer T, Mullin C, Bristow SL, Gamma A, Onel K, et al. Comparing ethnicity-based and expanded carrier screening methods at a single fertility center reveals significant differences in carrier rates and carrier couple rates. Genet Med. 2019;21(6):1400-6.
20. Gregg AR, Aarabi M, Klugman S, Leach NT, Bashford MT, Goldwaser T, et al. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(10):1793-806.
21. Grody WW, Thompson BH, Gregg AR, Bean LH, Monaghan KG, Schneider A, et al. ACMG position statement on prenatal/preconception expanded carrier screening. Genet Med. 2013;15(6):482-3.
22. Belgium S. Advisory report of the superior health council no. 9240. Expanded carrier screening in a reproductive context Towards a responsible implementation in the healthcare system. 2017.
23. Stevens B, Krstic N, Jones M, Murphy L, Hoskovec J. Finding Middle Ground in Constructing a Clinically Useful Expanded Carrier Screening Panel. Obstet Gynecol. 2017;130(2):279-84.
24. Nazareth SB, Lazarin GA, Goldberg JD. Changing trends in carrier screening for genetic disease in the United States. Prenatal diagnosis. 2015;35(10):931-5.
25. Gregg AR, Aarabi M, Klugman S, Leach NT, Bashford MT, Goldwaser T, et al. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). Elsevier; 2021. p. The Euler diagram shows an overlapping tiered approach to carrier screening.
26. van Dijke I, Lakeman P, Sabiri N, Rusticus H, Ottenheim CPE, Mathijssen IB, et al. Couples' experiences with expanded carrier screening: evaluation of a university hospital screening offer. European journal of human genetics : EJHG. 2021;29(8):1252-8.
27. Plantinga M, Birnie E, Abbott KM, Sinke RJ, Lucassen AM, Schuurmans J, et al. Population-based preconception carrier screening: how potential users from the general population view a test for 50 serious diseases. European journal of human genetics : EJHG. 2016;24(10):1417-23.

28. Schuurmans J, Plantinga M, Lucassen A, Fenwick A, Abbott K, Birnie E, et al. Short and long-term psychological impact of an active GP-provided couple-based ECS test-offer in the Dutch general population 2018.
29. Sallevelt S, Stegmann APA, de Koning B, Velter C, Steyls A, van Esch M, et al. Diagnostic exome-based preconception carrier testing in consanguineous couples: results from the first 100 couples in clinical practice. Genet Med. 2021;23(6):1125-36.
30. Bonneau V, Nizon M, Latypova X, Gaultier A, Hoarau E, Bézieau S, et al. First French study relative to preconception genetic testing: 1500 general population participants' opinion. Orphanet journal of rare diseases. 2021;16(1):130.
31. Pujol P, Fodil-Chérif S, Mandel JL, Baertschi B, Sanlaville D, Zarca D, et al. Ethical issues in expanding preconception genetic carrier screening: French debate and the opinion of the French Society of Predictive and Personalized Medicine
Réflexions éthiques sur le dépistage génétique préconceptionnel en population générale : le débat français et l'avis de la Société Française de Médecine Prédictive et Personnalisée. Ethics, Medicine and Public Health. 2020;12:100439.
32. Dive L, Newson AJ. Ethical issues in reproductive genetic carrier screening. Medical Journal of Australia. 2021;214(4):165-7.e1.
33. Dive L, Newson AJ. Ethics of Reproductive Genetic Carrier Screening: From the Clinic to the Population. Public Health Ethics. 2021;14(2):202-17.
34. van der Hout S, Dondorp W, de Wert G. The aims of expanded universal carrier screening: Autonomy, prevention, and responsible parenthood. Bioethics. 2019;33(5):568-76.
35. Kaback MM. Population-based genetic screening for reproductive counseling: the Tay-Sachs disease model. European journal of pediatrics. 2000;159 Suppl 3:S192-5.
36. Dive L, Newson AJ. Ethically robust reproductive genetic carrier screening needs to measure outcomes that matter to patients. European Journal of Human Genetics. 2022.
37. Dive L, Newson AJ. Reproductive carrier screening: responding to the eugenics critique. Journal of medical ethics. 2021:medethics-2021-107343.
38. Ames AG, Metcalfe SA, Dalton Archibald A, Duncan RE, Emery J. Measuring informed choice in population-based reproductive genetic screening: a systematic review. European journal of human genetics : EJHG. 2015;23(1):8-21.
39. Wang T, Bahrampour M, Byrnes J, Scuffham P, Kirk E, Downes M. Economic evaluation of reproductive carrier screening for recessive genetic conditions: a systematic review. Expert Review of Pharmacoeconomics & Outcomes Research. 2022;22(2):197-206.
40. Mathijssen IB, van Maarle MC, Kleiss IIM, Redeker EJW, Ten Kate LP, Henneman L, et al. With expanded carrier screening, founder populations run the risk of being overlooked. J Community Genet. 2017;8(4):327-33.
41. Popejoy AB, Fullerton SM. Genomics is failing on diversity. Nature. 2016;538(7624):161-4.

42. Sirugo G, Williams SM, Tishkoff SA. The Missing Diversity in Human Genetic Studies. Cell. 2019;177(4):1080.
43. NIH. Diversity in Genomic Research: National Human Genome Research Institute; 2021 [updated 7/12/2021. Available from: https://www.genome.gov/about-genomics/fact-sheets/Diversity-in-Genomic-Research.
44. Boardman FK, Hale R. How do genetically disabled adults view selective reproduction? Impairment, identity, and genetic screening. Mol Genet Genomic Med. 2018;6(6):941-56.
45. Kihlbom U. Ethical issues in preconception genetic carrier screening. Ups J Med Sci. 2016;121(4):295-8.
46. Borry P, Stultiens L, Nys H, Cassiman JJ, Dierickx K. Presymptomatic and predictive genetic testing in minors: a systematic review of guidelines and position papers. Clinical genetics. 2006;70(5):374-81.
47. Savell K, Karpin I. The meaning of "serious disability" in the legal regulation of prenatal and neonatal decision-making. Journal of law and medicine. 2008;16(2):233-45.
48. Summers A. Informed choice in prenatal screening. Canadian Family Physician. 1994;40:1688.
49. O'Connor AM. Validation of a decisional conflict scale. Medical decision making. 1995;15(1):25-30.
50. Bekker H. Genetic screening: facilitating informed choices. 2003.
51. Rimer BK, Briss PA, Zeller PK, Chan EC, Woolf SH. Informed decision making: what is its role in cancer screening? Cancer: Interdisciplinary International Journal of the American Cancer Society. 2004;101(S5):1214-28.
52. Marteau TM, Dormandy E, Michie S. A measure of informed choice. Health Expect. 2001;4(2):99-108.
53. Kater-Kuipers A, de Beaufort ID, Galjaard RH, Bunnik EM. Ethics of routine: a critical analysis of the concept of 'routinisation' in prenatal screening. Journal of medical ethics. 2018;44(9):626-31.
54. Elias S, Annas GJ. Generic consent for genetic screening. N Engl J Med. 1994;330(22):1611-3.
55. Asch A. Prenatal diagnosis and selective abortion: a challenge to practice and policy. American journal of public health. 1999;89(11):1649-57.
56. Ioannou L, McClaren BJ, Massie J, Lewis S, Metcalfe SA, Forrest L, et al. Population-based carrier screening for cystic fibrosis: a systematic review of 23 years of research. Genet Med. 2014;16(3):207-16.
57. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Journal of Clinical Epidemiology. 2009;62(10):e1-e34.

CHAPTER 2

INTEREST IN EXPANDED CARRIER SCREENING AMONG INDIVIDUALS AND COUPLES IN THE GENERAL POPULATION: SYSTEMATIC REVIEW OF THE LITERATURE

Van Steijvoort, E., Chokoshvili, D., Cannon, J.W., Peeters, H., Peeraer, K., Matthijs, G. & Borry, P. (2020) Interest in expanded carrier screening among individuals and couples in the general population: systematic review of the literature. *Human Reproduction Update, 26*(3), 335-355. doi: 10.1093/humupd/dmaa001

ABSTRACT

BACKGROUND: Through carrier screening, prospective parents can acquire information about whether they have an increased risk of conceiving a child affected with an autosomal recessive or X-linked condition. Within the last decade, advances in genomic technologies have facilitated a shift from condition-directed carrier screening to expanded carrier screening (ECS). Following the introduction of ECS, several studies have been performed to gauge the interest in this new technology among individuals and couples in the general population.

OBJECTIVE AND RATIONALE: The aim of this systematic review was to synthesize evidence from empirical studies that assess the interest in ECS among individuals and couples in the general population. As the availability and accessibility of ECS grow, more couples who are a priori not at risk based on their personal or family history will be presented with the choice to accept or decline such an offer. Their attitudes and beliefs, as well as the perceived usefulness of this screening modality, will likely determine whether ECS is to become a widespread reproductive genetic test.

SEARCH METHODS: Four databases (PubMed, Web of Science, CINAHL, and Cochrane Library) were systematically searched to identify English language studies performed between January 2009 and January 2019 using the following search terms: carrier screening, carrier testing, attitudes, intention, interest, views, opinions, perspectives and uptake. Studies were eligible for inclusion if they reported on intentions to undergo a (hypothetical) ECS test, uptake of an actual ECS offer or both. Two researchers performed a multistep selection process independently for validation purposes.

OUTCOMES: Twelve empirical studies performed between 2015 and 2019 were included for analysis. The studies originated from the USA (n = 6), the Netherlands (n =3), Belgium (n = 1), Sweden (n = 1) and Australia (n = 1). The sample size of the studies varied from 80 to 1669. In the included studies, 32%–76% of respondents were interested in a (hypothetical) ECS test, while uptake rates for actual ECS offers ranged from 8% to 50%. The highest overall uptake was observed when ECS was offered to pregnant women (50%). By contrast, studies focusing on the preconception population reported lower overall uptake rates (8–34%) with the exception of one study where women were counselled preconception in preparation for IVF (68.7%).

WIDER IMPLICATIONS: Our findings suggest that there may be discrepancies between prospective parents' reported intentions to undergo ECS and their actual uptake, particularly during the preconception period. As ECS is a new and relatively unknown test for most future parents, the awareness and comprehension within the general population could be rather limited. Adequate pre- and post-test counselling services should be made available to couples offered ECS to ensure informed reproductive decision-making, together with guidelines for primary health care professionals. Due to the restricted nature of the samples and methods of the underlying primary studies, some of the reported results might not be transferable to a broader population. More research is needed to see if the observed trends also apply to a broader and more diverse population.

Key words: expanded carrier screening / reproductive genetics / attitudes / intention / interest / uptake

INTRODUCTION

Through carrier screening, prospective parents can acquire information about whether they have an increased risk of conceiving a child affected with a recessive genetic condition. When both partners are identified as carriers of the same autosomal recessive disorder, they have a 25% chance of having an affected child in each pregnancy. When the mother is a carrier of an X-linked recessive disorder, there is a 50% chance that the couple's male offspring will be affected. Approximately, 1–2% of couples in the general population have an increased risk of conceiving a child affected with an autosomal recessive or X-linked condition ('carrier couples') (1). Because carriers are typically healthy and lack family history for genetic conditions, they are usually unaware of their reproductive risk until their child is diagnosed with a genetic disorder (2).

Carrier screening for recessive conditions was first made available in the early 1970s. Traditionally, genetic carrier screening has focused on recessive disorders with significant morbidity and reduced life expectancy in specific ethnic communities. Examples are carrier screening for Tay–Sachs disease affecting the Ashkenazi Jewish population and beta-thalassaemia in several at-risk populations in the Mediterranean area (3). Recent advances in genomic technologies are facilitating a shift from condition-directed carrier screening to expanded carrier screening (ECS). ECS offers carrier screening for a large number of recessive conditions in the same panel, regardless of ancestry and geographic origin of users (4). The development of the first commercial ECS test, which screened for 108 recessive conditions, was reported in 2010 (5). This introduction was followed by various (commercial) providers that made ECS tests available to prospective parents (6).

In most Western countries, there is a consensus that carrier screening should strengthen reproductive autonomy and enable informed reproductive choices based on the personal values and preferences of a couple (2). When 'carrier couples' want to act upon positive screening results they can opt for prenatal diagnosis, IVF/ICSI combined with preimplantation genetic testing (PGT), gamete donation, adoption or refraining from having children together (2). In contrast, carrier couples who are identified during pregnancy only have the option to undergo prenatal diagnosis or not. If the fetus is found to be affected, the couple has the option to prepare for a child with a particular recessive condition or to terminate the pregnancy.

Several medical professional organizations have published recommendations regarding ECS within the last few years. In 2015, the American College of Medical Genetics and Genomics (ACMG), the American College of Obstetricians and Gynaecologists (ACOG), the National Society of Genetic Counsellors, the Perinatal Quality Foundation and the Society for Maternal-Fetal Medicine issued a joint statement on ECS, which stated that 'women of reproductive age should ideally be offered carrier screening before conception' (4). Following this statement, ACOG released a Committee Opinion in 2017 stating that 'health care providers should establish approaches where carrier

screening is consistently offered to and discussed with each patient, if possible before pregnancy' (7). In 2016, the European Society of Human Genetics also issued recommendations regarding the responsible implementation of ECS. These recommendations emphasized 'that ECS should preferably be offered before pregnancy' (2).

Even though existing professional guidelines emphasize that ECS should ideally be offered before conception, practical limitations could be encountered when trying to reach for this specific group. Experience shows that pregnant women, in comparison to couples planning a pregnancy, are more easily reachable through health care providers who guide them through their pregnancy (2). Earlier studies focusing on condition-specific carrier screening (e.g. cystic fibrosis (CF) screening) showed overall positive attitudes toward carrier screening among individuals in the general population. In these studies, highly educated Caucasian women who had no children and were planning future pregnancies were more likely to accept an offer of screening (8). Even though participants believed that the best time to have CF carrier screening would be before pregnancy, preconception screening was associated with a lower uptake than prenatal screening (2, 9, 10). According to Poppelaars et al. (2003) (11), this might be due to a lack of interest in carrier screening during the preconception period, an absence of established preconception healthcare services through which to offer screening and a high number of unplanned pregnancies (11). Conversely, pregnancy has been identified as a strong motivating factor for undergoing CF carrier screening, suggesting that CF carrier screening may be perceived as more relevant during pregnancy by expectant parents (8, 11).

As the availability and accessibility of ECS grow, more couples will be presented with the choice to accept or decline such an offer. Their attitudes and beliefs, as well as the perceived usefulness of this screening modality will likely determine whether ECS is to become a widespread reproductive genetic test. It is possible that similar factors are influencing the decision-making process of prospective parents regarding ECS in comparison to single gene carrier screening. It may be assumed that carrier couples who do not feel comfortable with the available reproductive options (e.g. IVF/ICSI combined with PGT) will also not be interested in ECS. However, it is also possible that the expansion of panels may increase the perceived benefits of screening (2). More insights are needed to understand how individuals and couples process information when ECS is offered to them and which factors affect individuals' decisions to undergo or forgo ECS. Following the introduction of ECS, several studies have been performed to gauge the interest in ECS among the general population. The aim of this systematic review is to synthesize evidence from empirical studies that assess the interest in/uptake rates for ECS among individuals and couples in the general population and to identify factors associated with the decision to accept or decline ECS.

METHODS

Design and search strategy

We used a comprehensive search approach to identify empirical studies that focused on the assessment of the intention to undergo a (hypothetical) carrier screening test, uptake of an actual carrier screening offer, or both. The review process consisted of three main steps. First, we systematically searched for relevant publications in four online databases (PubMed, Web of Science, CINAHL and Cochrane Library) that were published from January 2009 to January 2019. Because pan-ethnic screening or ECS was introduced to the market in 2009, studies published prior to 2009 were not included in this review (5, 12). In order to identify relevant studies, the following search string was used: 'carrier' AND ('testing'[tw] OR 'screening' [tw]) AND (attitude [tw] OR intention [tw] OR interest [tw] OR views [tw] OR opinions [tw] OR perspectives [tw] OR uptake [tw]). Second, we consulted references of the relevant papers identified through the systematic search in order to find any additional publications warranting inclusion in the review (i.e. snowball method). Finally, we carried out a 'related search' strategy (Google Scholar) to track for any other potentially relevant studies based on the studies identified through the systematic search of the four online databases. Our review followed PRISMA guidelines for systematic reviews of the medical literature (13).

Inclusion and exclusion criteria

Studies were included in the review if they met all of the following criteria: quantitative studies assessing the intention to take a (hypothetical) carrier screening test and/or an actual uptake of a carrier screening offer; the study population was a priori not at risk based on their personal or family history; and studies published between January 2009 and January 2019. Studies/articles were excluded if they met any of the following criteria: studies assessing the interest in or uptake of genetic tests aimed at obtaining non-reproductive medical information (e.g. predictive genetic testing/predisposition as in breast cancer or diagnostic testing in patients with disease symptoms); studies focused on genetic tests targeting dominant genetic disorders; studies assessing the interest in or uptake of a carrier screening test within specific communities (e.g. Ashkenazi Jewish Community); publications other than original research articles (e.g. reviews or opinion articles); publications in a language other than English. When the results of a single research project were reported in multiple publications, we only included one research article for this review.

Search outcomes

Records identified through searching the four databases were subsequently aggregated into a single library, containing 1554 unique records (excluding duplicates). Initially, all 1554 items were screened based on their title, and the records deemed potentially relevant by at least one of the two researchers were retained. Subsequently, 209 abstracts were read by both researchers. As a final step, 23 full-text articles were read by both researchers after the exclusion of non-relevant abstracts. The review of the collected literature was performed by two researchers (E.V.S. and D.C.) who

worked independently and continually discussed their findings to identify and resolve any differences. The decision on whether to retain an abstract or article was made based on mutual agreement. Our search led to the identification of nine studies that were included in the review. We also included two additional studies (14, 15) identified through snowball sampling, as well as one study that was published days after performing the search to identify relevant empirical studies (16). These 12 studies have either surveyed respondents on their willingness to undergo ECS, offered an actual ECS test to prospective parents or retrospectively reviewed medical records of women who had preconception/prenatal ECS. For each identified study our 'relevant search' strategy displayed 100 related articles. No new studies were identified throughout this final step. Figure 1 graphically summarizes the literature search process. The flowchart is organized according to the PRISMA guideline outlined in Liberati et al., (2009) (13).

Quality appraisal

We performed an indicative quality appraisal of each of the included articles using the tool developed by Hawker et al. (2002)(17). By using this system, we were able to indicate the methodological rigor of the included study based on the information provided by the authors of the included studies. Articles were not excluded from our systematic review based on their methodological quality. The quality appraisal was performed independently by two researchers. In case of disagreement, the specific item was discussed until mutual agreement.

RESULTS

Quality appraisal

The results of the quality appraisal are summarized in Table I. Almost all studies included in this review had well-structured abstracts with a clear description of the study and a clear title. In addition, the full text articles included in this review provided a concise literature review and a clear statement aim of the study. The methodology of the included studies was clearly explained and appropriate to the study aim, including an overview off the data collection tools and methods. Most of the studies provided a fairly detailed description of the data analysis performed, but only one study clearly outlined the hypothesis behind the statistical test selection. The results section of the included articles reported results directly related to the aims and were logical and easy to understand. Findings presented were supported with sufficient data. All studies gained necessary ethical approval but only a few studies addressed ethical issues in more detail. Most authors gave a clear description of the sampling strategy used to address the aims. However, the sample size was not always justified and specific groups were often targeted using convenience sampling. As a result, the transferability and generalizability of some of the reported results are questionable. Most of the studies provided implications for policy and practice and some suggested ideas for further research. However, the implications and usefulness of the reported results of some studies might not be transferable to a broader population. The authors of these specific papers acknowledge this limitation

and underline the importance to expand upon the reported findings by increasing sample size and population diversity.

Study characteristics

A detailed overview of the underlying study methods of the primary empirical studies included in this systematic review is presented in Table II. Variables for which data were sought include the country where the study took place, the type of record, the study aim, the study duration, the study population (including sample size), inclusion/exclusion criteria, recruitment strategy, data collection, data analysis, ethical considerations and costs for participants. The publication range of the 12 studies included in this systematic review dates from 2015 to 2019. The articles originate from five different countries: the USA (n = 6), the Netherlands (n =3), Belgium (n = 1), Sweden (n = 1) and Australia (n =1). The sample size of the studies varied greatly from 80 to 1669. The majority of the studies (n = 10) used a survey methodology with a custom developed questionnaire. The other two remaining studies used a retrospective medical record review.

Main findings

The main study findings of this systematic review are summarized in Table III, including the composition of the test panel, the outcome measures used and some key figures on participants' characteristics.

Intention to take a (hypothetical) ECS test

Attitudinal studies gauging respondents' interest in a hypothetical ECS test have yielded diverging results. For example, while surveys conducted in Sweden (18) and the Netherlands (19, 20) found that approximately one-third of the respondents would consider ECS, in an Australian study (21) about two-thirds of the surveyed individuals indicated interest in a hypothetical ECS test for a large number of recessive disorders. The authors of the Australian study attribute this finding to the media attention to preconception carrier screening in Australia. However, they also note that in their study population, the willingness to undergo ECS was associated with the nature of disorders to be included in the test. For example, 92% of the respondents interested in ECS indicated they would take ECS if the test included diseases affecting the lifespan of children or infants. By contrast, 61% would take the test if ECS were performed for adult-onset disorders. In the Dutch study of Plantinga et al. (2016) (20), the age of onset of the screened disorders was not found to influence respondents' intentions to consider ECS. However, respondents were less likely to express interest in ECS for non-health-related predispositions (e.g. athletic ability). Other studies in Belgium (22) and the USA (23) reported that 54% and 49% of the respondents, respectively, expressed interest in preconception carrier screening. The highest intention to participate in preconception ECS was observed in the study of Spencer et al. (2018) (24) where adopted individuals were surveyed. Although only 56% of the respondents were considered to be of reproductive age (i.e. <43 years

Female; <50 years Male), 76% of all respondents indicated interest in ECS. Curiosity and the desire to inform other biological relatives (such as a child or sibling) were the most frequently cited reasons for showing interest in ECS (24). Within this study, no statistically significant difference was found for indicated interest between adopted individuals having some knowledge of their family medical history and adopted individuals without any knowledge of their family medical history (24). Four out of twelve studies reported on the proportion of respondents that were undecided or uncertain about having ECS (18-21). In the Dutch study by Plantinga et al. (2016) (20) just over half of respondents (51%) were undecided regarding whether they would be willing to participate if ECS were offered to them. Likewise, 42% of Swedish parents surveyed as part of the Swedish Pregnancy Planning (SWEPP) study were uncertain about having ECS prior to a pregnancy (18). In the Australian study of Ong et al. (2018) (21), 22% of participants were unsure about whether they would take a preconception ECS test. Finally, 33% of all respondents were uncertain if they would take a preconception ECS test in the Dutch study by Nijmeijer et al. (2019) (19).

Uptake of ECS

Studies reporting the actual uptake of ECS offers among prospective parents (n = 5) have found variable uptake rates (8%–50%) in ECS across different study populations. Gilmore et al. (2017) (25) found that 34% of women who were offered a preconception ECS test free of charge in a research setting accepted the offer. The main reasons for declining participation included lack of time, lack of interest and not wanting the information. Another study of Propst et al. (2018) (26), found that 50% of a cohort of 80 pregnant women accepted an offer of an out-of-pocket ECS test (expenses that are not reimbursed by health insurance). The most cited reasons for declining ECS in this study were lack of family history for genetic conditions, low perceived risk of being a carrier couple and the fact that results would not influence their reproductive choices in (future) pregnancies. The main reasons for accepting the commercial offer were the desire to learn about the risk of having a child affected with a recessive condition, interest in genetic information and seeking the ability to make informed decisions regarding pregnancy (26). The uptake for an out-of-pocket ECS (8%) offer was considerably lower among couples with primary or secondary infertility in an earlier study by Higgins et al. (2015) (14). However, the authors noted that the uptake had increased from 3.3% to 17.5% during the observation period (2010–2013) following the reduction of out-of-pocket cost associated with the ECS test. Larsen et al. (2019) (16) retrospectively reviewed medical records of women who had a prenatal or preconception genetic counselling session at a large academic genetic counselling service in an urban private hospital-based outpatient clinic and observed an overall ECS uptake rate of 39.8%. Significantly more women counselled preconception (68.7%; n =67) accepted ECS compared to women who were counselled during pregnancy (35.1%; P <0.001; n =416). The highest acceptance rate within this study was measured among women who were counselled preconception in preparation for IVF (74.5%; n = 38/51). Within the prenatal group, women counselled at an earlier gestational stage were also more likely to accept testing (16). In a more recent study conducted in

the Netherlands, 4295 women were invited to participate in a preconception ECS offer for couples, which resulted in 117 couples undergoing screening. While this number suggests low uptake, the exact uptake rate could not be documented as some invitees may not have been eligible to participate (for example because they were single) (15).

Factors influencing interest and uptake of ECS

Multiple studies included in this review have looked into various factors that could possibly influence the decision to accept or decline ECS. An overview of the factors studied and the results can be found in Table IV.

Socio-demographic factors

Gender, relationship status, employment status and having Medicaid insurance were not identified to be associated with the intention to undergo a (hypothetical) ECS test or uptake of an actual carrier screening offer. In contrast, associations between the decision to accept or decline ECS and other socio-demographic factors, such as age, religion, income, education level or ethnicity, were identified by at least one study included in this review. In the study of Gilmore et al. (2017) (25), younger women were more likely to decline an ECS offer. Younger respondents were also more often undecided about preconception ECS in the study of Plantinga et al. (2016) (20). Furthermore, increased age was positively associated with the interest in preconception ECS in the studies by Ragnar et al. (2016) (18) and Chokoshvili et al. (2017) (22). However, not all of the primary studies identified age as an influencing factor. Age was not found to be associated with acceptance rates for ECS in six other studies (16, 19, 21, 24, 26). Three studies reported on an inverse relation between religion and the intention to participate in preconception ECS. Respondents with religious beliefs were less likely to be interested compared to nonreligious respondents (19-21). In the Belgian study by Chokoshvili et al. (2017) (22), religion was not found to be an influencing factor when respondents were asked if they would consider having a carrier screening test together with their partner. The interest in and uptake for ECS was positively associated with income in the studies by Gilmore et al. (2017) (25) and Ong et al. (2018) (21). Participants with a higher income were more likely to show interest in or accept an ECS offer. Conversely, household income was not found to influence parents' interest in preconception ECS in the Swedish study by Ragnar et al. (2016) (18). Decliners of an ECS offer were found to be less educated compared to acceptors in the study of Gilmore et al. (2017) (25). In contrast, a negative association between education level and interest in ECS was found in the studies of Chokoshvili et al. (2017) (22) and Ong et al. (2018) (21); within these studies, less educated respondents were more likely to show interest in ECS. However, in five other studies included in this review, the education level of respondents was reported not to influence the interest in ECS (18-20, 24, 26). In the study of Propst et al. (2018) (26) white non-Hispanic individuals (60.7%) were more likely to accept ECS compared to non-white individuals (21.7%; P =0.003). Other studies by Gilmore et al. (2017) (25) and Larsen et al. (2019) (16) reported no difference between

women who accepted and who declined ECS across races/ethnicities. However, in the study of Larsen et al. (2019) (16), where the retrospective medical record review identified a diverse population of women, some differences were noted, although these were statistically non-significant. Women of Ashkenazi Jewish decent were more likely to accept ECS (n = 7/12; 58.3%; P = 0.195) than women of Asian descent (n = 12/41; 29.3%; P = 0.186) or mixed ethnicities (n = 7/25; 28.0%; P = 0.241) (16).

Factors related to reproduction

Women who already had children were more likely to decline ECS in the study of Gilmore et al. (2017) (25). However, Propst et al. (2018) (26), Spencer et al. (2018) (24) and Larsen et al. (2019) (16) observed no significant associations between the interest or uptake of ECS and the number of children or pregnancies. Respondents with a (future) child wish were more likely to show interest in ECS in the study of Nijmeijer et al. (2019) (19). Three other studies (20, 21, 24) did not identify a significant association between child wish and the intention to have ECS. Finally, women pursuing assisted reproductive technology (ART) to get pregnant were more likely to accept ECS in comparison to women who got pregnant with the help of ART but who were not offered ECS (16). Within the study cohort of the SWEPP study, women's interest in preconception ECS was positively associated with having undergone prenatal diagnostics, wanting to know the sex of the baby prior to the delivery and having positive attitudes toward fetal sex selection. Furthermore, the male partners' interest was associated with having had a planned pregnancy and having undergone prenatal diagnostics (18). Other examined factors that were not found to be associated with interest/uptake in ECS were previous miscarriage (16, 18, 26), twin pregnancy (16) and a pregnancy established through egg and/or sperm donation (16).

Factors related to genetic screening

Knowing someone with a genetic condition or having a family member with a genetic condition was positively associated with the uptake of ECS in the study of Gilmore et al. (2017) (25). In contrast, Nijmeijer et al. (2019) (19) reported that knowing someone with a genetic condition was not associated with the intention to participate in ECS. Likewise, a positive maternal and/or paternal family history of genetic disease was not associated with ECS acceptance rates in the retrospective medical record review by Larsen et al. (2019) (16). In the same study, the indication for genetic counselling during pregnancy (e.g. advanced maternal age or abnormal ultrasound result) was also not significantly associated with the uptake of ECS. Having undergone previous carrier screening (26) or receiving positive CF test results (25) also did not influence the uptake of ECS. Ong et al. (2018) (21) identified several (genetic) knowledge factors that were associated with the intention to have preconception ECS. Respondents who had prior knowledge or awareness of ECS were more likely to be sure of their intention to either accept or decline ECS. Their study results also show that people who knew about ECS from family members or through internet searches were more likely to

show interest in ECS. In addition, the likelihood of accepting ECS was higher for respondents with 'high', 'good' or 'some' genetic knowledge compared to those with 'low' genetic knowledge.

Other related factors

A potentially interesting factor that was investigated in some of the studies included in this review is the impact of the cost of testing and/or insurance coverage. Plantinga et al. (2016) (20) reported that 58% of respondents would be willing to pay for ECS, with a median cost of €75. Nearly half of the adoptees surveyed by Spencer et al. (2018) (24) were willing to pay $1 to $100 for ECS themselves. In the study of Briggs et al. (2017) (23), 28% of participants were unwilling to pay out-of- pocket and 37% of participants were willing to pay at least $50 to $100. In the Australian study by Ong et al. (2018) (21), 19% of respondents would do ECS for free, 22% would be willing to pay <$AUD 50 and another 34% would do ECS if it would cost between $AUD 50 and $AUD 200. Finally, only 9% of individuals surveyed by Nijmeijer et al. (2019) (19) were willing to pay for ECS themselves. In the same study, 55% of respondents agreed that ECS should be completely reimbursed by health insurance. The out-of-pocket cost (max. US $350—if insurance did not cover the test) did not seem to have an impact on the decision of test acceptors in the study of Propst et al. (2018) (26). However, 15% of test decliners in the same study indicated 'Insurance might not cover the full cost of testing' as a reason for declining ECS. Gilmore et al. (2017) (25) found no significant difference between women who declined or accepted ECS based on insurance type (Medicaid or not). The impact of the cost of testing/insurance type on the decision-making process could not be addressed in the study of Larsen et al. (2019) (16).

DISCUSSION

Results of the attitudinal studies around ECS suggest that there is considerable interest in ECS among (reproductive age) individuals in the general population (15, 18, 20-24). However, our findings show that actual test uptake among prospective parents is substantially lower (14-16, 25, 26). These results support the idea that self-reported intention to have ECS does not always translate into actual uptake when ECS is offered. The psychosocial aspects of genetic testing have been studied previously in the area of familial cancer syndromes and Huntington's disease (HD). In the case of HD, the intention of at- risk individuals to take a predictive genetic test for HD tends to be high (70–80%), while uptake rates tend to be much lower (10–20%). A real opportunity to learn genetic information seems to be more difficult to process and less appealing compared to a hypothetical test offer (27, 28). This phenomenon is well documented in the literature as the 'Intention–Behaviour Gap'. This theory states that three pivotal tasks must be accomplished to secure intention realization: people need to initiate, maintain and close goal pursuit (28). Having the intention to undergo a (hypothetical) ECS test can be seen as part of the initiation phase, but not everyone who initiates a goal pursuit will eventually close it.

Many internal and external factors can possibly influence actual behaviour, whereby the behaviour might no longer correlate with the values and attitudes of the individual. For instance, the out-of-pocket cost of testing might persuade someone to decline despite his interest in ECS. The results of the studies focusing on the intention to take a (hypothetical) ECS test show that a considerable proportion of respondents are willing to pay for ECS themselves. However, the amount they are willing to pay is considerably lower than actual prices for ECS panels currently being offered. In the study of Gilmore et al. (2017) (25), test decliners more commonly cited lack of interest and lack of time as reasons to decline an ECS offer. A similar result was observed in a theory-guided review by Chen and Goodson (2007) (29) where lack of time was the factor most frequently associated with the decision to decline CF carrier screening. However, caution is needed when interpreting these statements as practical or logistical reasons given for declining ECS might also mask reasons not mentioned by respondents. Participants might be hesitant to discuss more personal reasons with researchers they are not familiar with (25).

It is possible that participants would have made other decisions regarding ECS in a more clinical context in interaction with health care providers with whom they have a relationship of trust. The influence of health care providers and/or a perceived difficulty or inability to refuse ECS as an influencing factor in the decision-making of patients were identified in multiple studies included in the systematic reviews of Chen and Goodson (2007) (29) and Ioannou et al. (2014) (8). Health care providers should be aware of this possible influence when informing prospective parents to make sure that couples are feeling able to refuse ECS when they are not interested.

Information gained through ECS might be perceived as irrelevant by test decliners because of the low perceived risk of being a carrier based on their personal or family history (26, 29, 30). Lack of family history was also found to be one of the strongest predictors of declining carrier screening in earlier studies focusing on single gene carrier screening (8, 29). In the study of Gilmore et al. (2017) (25) test-intending non-participants were more likely to decline the offer because of privacy- or discrimination related concerns and emotional reasons. It is possible that the extensive amount of information regarding ECS in the informed consent form that was sent to them might have influenced their decision to opt-out, given the fact that these women previously had accepted CF carrier screening (25). Providing multiple opportunities for prospective participants to learn information and ask questions might facilitate informed decision-making because it allows prospective parents to think and reflect about their future reproductive plans before accepting or declining ECS (25, 31).Following the recommendation of the ACMG (32), more efforts should be made to establish services where ECS can be offered and discussed with couples planning a pregnancy.

The highest overall uptake was observed in a study where ECS was offered to pregnant women (26). In contrast, most studies focusing on preconception ECS reported lower overall uptake rates.

Similar results have been reported within the context of population-based CF carrier screening, where preconception screening was generally associated with lower uptake rates compared to prenatal screening (2, 8). Based on these findings it appears that potential users may perceive carrier screening to be more immediately relevant and useful during pregnancy. However, an exception to this general pattern was reported in the study of Larsen et al. (2019) (16), in which significantly more women who were counselled preconception (68.7%) accepted ECS, compared to women who were counselled during pregnancy (35.1%) (16). Within the group counselled prior to conception, the highest acceptance rate (74.5%) was observed among women who were counselled preconception in preparation for IVF (n = 51/67) (16). Furthermore, non-pregnant women planning to pursue IVF were significantly more likely to accept ECS compared to women who became pregnant following IVF. One potential explanation for this finding, also suggested by the authors themselves, is that physicians might be more inclined to actively direct patients preparing for IVF to have ECS because of the immediate availability of PGT following positive screening results (3). However, this group might also be more interested in ECS prior to conception as they are already undergoing fertility treatment and thus ECS in combination with PGT might be perceived as part of the ongoing treatment.

Studies included in this review explored the interest in ECS among individuals and couples in the general population. Differences in the outcome measures might also be explained by heterogeneity across the surveyed populations or the recruitment methods of these studies. While some studies focused on exploring the views of respondents in a reproductive context (couples planning a pregnancy, couples undergoing fertility evaluation or treatment, pregnant women, women attending a preconception consultation), other studies surveyed a much more demographically diverse population where respondents were not always of reproductive age (21, 22, 24). Even though professional guidelines are clearly stating that ECS should be available to couples considering pregnancy or already pregnant, studies focusing on the views of demographically diverse populations can also give valuable insights. These results can contribute to the ongoing debate about the desirability and acceptability of offering ECS by offering a societal point of view.

The proportion of women who were undecided or uncertain about having ECS should not be ignored when assessing the interest in ECS. As ECS is a new and relatively unknown test for most future parents, the awareness and comprehension within the general population could be rather limited. Efforts should be made to ensure that prospective parents make decisions regarding ECS based on accurate and sufficient knowledge. Genetics professionals have expressed the need for adequate pre- and post-test counselling services that should be made available to couples considering ECS to ensure informed reproductive decision-making together with additional guidelines for primary health care professionals (33-35).

Study limitations

First, it is possible that some biases exist in the primary empirical studies of this review. Most of the studies included in this review used convenience sampling or targeted very specific groups within the population who were conveniently available to participate. It is possible that certain groups of people were more inclined to participate, for example individuals with more outspoken opinions on the topic (36). Consequently, the study findings should not be generalized. Second, by focusing on publications written in English, we might have missed relevant publications to include within this systematic review. Third, our search only identified studies from five Western countries. It is possible that populations in different countries may hold different views on ECS towing to differences in healthcare systems and differences in exposure to (critical) information (cultural bias) (22). Sufficient attention should be made to this when drawing conclusions based on these findings.

Implications for future research

More research is needed to see if the observed trends also apply to a broader and more diverse population (20, 25, 26). As only five studies have looked into the uptake of ECS there is a high need for more implementation studies. This would allow for an assessment of the extent to which individuals or couples make informed decisions regarding ECS and which factors are associated with informed decision-making. More prospective studies where ECS is offered to couples showing an interest in ECS could yield additional insights into the complexity of the intention–behaviour gap and the decision-making process of couples regarding ECS. It will also allow us to gain a better understanding of the motives for or against ECS (among prospective parents), the concerns people might have toward ECS and the doubts people might experience when considering ECS. To understand why certain individuals/couples are undecided or uncertain on whether or not they would like to participate in ECS, future research should try to synergize both quantitative and qualitative research methods: qualitative research may provide valuable insights into the decision-making process and experiences of patients in ways that quantitative analysis cannot. These results can be used to further facilitate responsible implementation of ECS and inform and guide healthcare providers interacting with prospective parents who are considering ECS. Future research should also focus more on the impact of the costs of testing and/or insurance coverage on the decision-making process of couples considering ECS as this is likely to be an important factor.

Implications for practice

With the continued decline in the cost of ECS, combined with the growing number of recommendations of professional membership organizations, it is likely that the perceived value of ECS in the context of reproductive healthcare will continue to grow (2, 4, 7, 14). Therefore, it is to be expected that an increasing number of couples in the general population will actively seek information about ECS and pursue testing in the future. Building a strong network of preconception healthcare services through which screening could be offered could be a way to integrate ECS in a

responsible way and to make sure that couples can learn about the possibility of having ECS prior to pregnancy. This will however demand a critical reflection on how to prioritize resources within preconception care (18). As ECS is a new and relatively unknown test for most future parents, the awareness and comprehension within the general population could be rather limited. In the coming years it will be very important to focus more on providing continuous high-quality information to the general public in order to improve genetic literacy, to reduce misconceptions and to manage expectations (21, 22). Adequate pre- and post-test counselling services should be made available to couples being offered ECS to ensure informed reproductive decision-making. Complete and transparent information will help prospective parents in weighing the advantages and disadvantages associated with ECS so that they can make fully informed reproductive decisions (18, 22). Primary health care providers will have an important role to play when guiding couples who are planning a pregnancy through the available reproductive screening services (18). Hence, there will be a growing need for widely accessible information and guidelines for primary health care providers alongside patient friendly genetic counselling tools (16).

CONCLUSION

The aim of this systematic review was to synthesize evidence from empirical studies that assess the interest in/uptake of ECS among individuals and couples in the general population. Results of the primary studies included in this review demonstrate that there is considerable interest in ECS among (reproductive age) individuals in the general population. However, actual uptake of ECS seems to be substantially lower than prospective parents' reported intentions to undergo ECS. In the included studies, 32–76% of respondents were interested in a (hypothetical) ECS test, while uptake rates for actual ECS offers ranged from 8% to 50%. The highest overall uptake was observed when ECS was offered to pregnant women (50%). By contrast, studies focusing on the preconception population reported lower overall uptake rates (8–34%) with the exception of one study where women were counselled preconception in preparation for IVF (68.7%). Due to restricted nature of the samples and methods of the underlying primary studies, some of the reported results might not be transferable to a broader population. More research is needed to see if the observed trends also apply to a broader and more diverse population.

AUTHOR'S CONTRIBUTIONS

J.C., D.C, E.V.S. and P.B designed the study. The comprehensive search approach, selection and screening of articles were carried out by D.C. and E.V.S. The quality appraisal was performed by E.V.S. and K.H. A first draft of the article was written by E.V.S. and critically discussed and revised by J.C., D.C., P.B., H.P., K.P. and G.M. P.B coordinated the study. All the authors have approved the final version.

ACKNOWLEDGEMENTS

We would like to thank Amicia Phillips for checking our manuscript for linguistic accuracy. Furthermore, we are grateful to Kathleen Holemans for her contribution to the quality appraisal.

Figure 1: Identification and selection of articles in a systematic review of the interest in ECS among individuals and couples in the general population

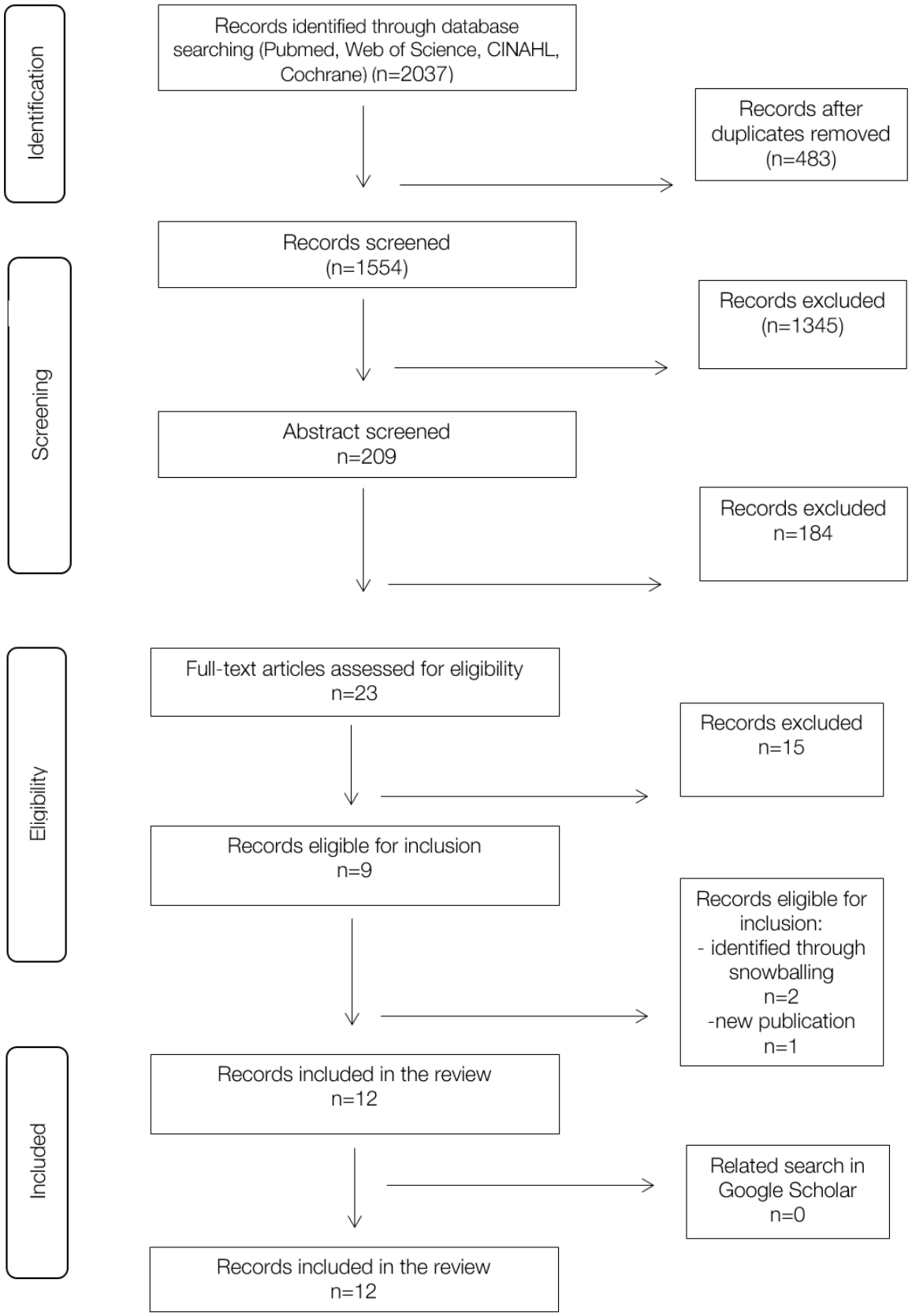


Table 1: Quality appraisal of studies included in this systematic review-

Study	Abstract and Title	Introduction and Aims	Method and Data	Sampling	Data analysis	Ethics and bias	Results	Transferability and Generalizability	Implication and usefulness	Overall Assessment
Higgins et al. 2015	Good	Good	Good	Fair	Fair	Poor	Fair	Fair	Fair	High
Plantinga et al. 2016	Good	Good	Good	Good	Fair	Fair	Good	Fair	Good	High
Ragnar et al. 2016	Good	Good	Good	Good	Good	Good	Good	Fair	Good	High
Chokoshvili et al. 2017	Good	Good	Good	Fair	Fair	Poor	Good	Fair	Fair	High
Briggs et al. 2017 *	Good	NA	NA	NA	NA	NA	NA	NA	NA	NA
Gilmore et al. 2017	Good	Good	Good	Poor	Fair	Fair	Good	Poor	Good	High
Ong et al. 2018	Good	Good	Good	Fair	Good	Fair	Good	Fair	Fair	High
Propst et al. 2018	Good	Good	Good	Poor	Fair	Fair	Good	Poor	Good	High
Spencer et al. 2018	Fair	Good	Good	Fair	Fair	Good	Good	Poor	Good	High
Schuurmans et al. 2018 *	Good	NA	NA	NA	NA	NA	NA	NA	NA	NA
Nijmeijer et al. 2019	Good	Good	Good	Good	Fair	Fair	Good	Fair	Fair	High
Larsen et al. 2019	Good	Good	Good	Fair	Fair	Poor	Fair	Poor	Good	High

The quality appraisal was performed using the tool developed by Hawker et al. 2002. For each included study the following questions were scored: Did they provide a clear description of the study?; Was there a good background and clear statement of the aims of the research?; Is the method appropriate and clearly explained?; Was the sampling strategy appropriate to address the aims?; Was the description of the data analysis sufficiently rigorous?; Have ethical issues been addressed, and was necessary ethical approval gained?; Is there a clear statement of the findings?; Are the findings of this study transferable to a wider population?; How important are these findings to policy and practice?

*Conference abstracts: quality appraisal was only performed for the provided abstract.

Table 2: Overview of the underlying study methods of the primary empirical studies on ECS included in this systematic review

Study (Country)	**Type**	**Study aim**	**Study duration**	**Study Population**	**Inclusion criteria**	**Exclusion criteria**	**Recruitment**	**Data-collection**	**Data-analysis**	**Ethical considerations**	**Costs for participants**
Higgins et al. 2015 (USA)	Full-text article	To determine whether availability of a more comprehensive, affordable genetic screening tool increased the number of patients choosing to have preconception screening.	36 months (retro-spective)	Patients evaluated for primary or secondary infertility. (n=1669)	Evaluation for either primary or secondary infertility including both male and female factors (low or abnormal sperm counts, recurrent miscarriages, PCOS, ovarian dysfunction, uterine abnormalities, or female infertility of unknown origin).	Couples seeking genetic counselling or referred for genetic counselling who did not have complaints of infertility, family members seeking genetic screening when abnormalities where found on screening results.	Search of the electronic medical records at Sanford Health Fertility and Reproductive Medicine AND Counsyl Database	Retrospective medical record review	Descriptive analysis	Institutional review board approved study.	The maximum out-of-pocket cost for patients was $349 and decreased to $99 in May 2012.
Plantinga et al. 2016 (The Netherlands)	Full-text article	To investigate potential users' intentions to undertake preconception carrier screening and through which provider they would like to see it offered.	1 month	Men and women with a partner in the reproductive age. Sample was stratified according to gender, educational level and geographical region. (n=504)	Individuals aged 18-40 years, having a partner, living in the Netherlands.	/	Online recruit-ment by a survey research sampling company.	Online Survey; Custom Developed Questionnaire	Descriptive analysis, Fisher's Exact tests	Ethical approval from the Medical Ethical Review Committee of the University Medical Centre Groningen.	NA

Ragnar et al. 2016 (Sweden)	Full-text article	To investigate parents' interest and motives towards preconception genetic carrier screening (PCS) as well as factors associated with interest in PCS.	10 months	Pregnant women recruited at registration in the antenatal clinic. Study sample consists of parents couples who had responded to all questionnaires. (n=777)	Pregnancy, registration in antenatal clinic.	/	Swedish Pregnancy Planning Study – longitudinal cohort study	Survey; One questionnaire in early pregnancy, one questionnaire around gestational week 34, one questionnaire 12 months post-partum, partner-questionnaire 12 months post-partum	Descriptive analysis, McNemer-Bowker's test, Binary Logistic Regression	Approval by the regional ethical review board in Uppsala (Sweden), voluntary participation, participants were informed that care given at the antenatal clinic was not related to study participation, informed consent was obtained from all participants.	NA
Chokoshvili et al. 2017 (Belgium)	Full-text article	To explore the views of the Belgian public on various topics surrounding genetics and genetic testing.	2 months	Visitors of the annual cartoon festival (convenience sampling). (n=1182)	Aged 18 or older (minors aged 16 or older were also included, provided they were accompanied by an adult family member and actively expressed interest in participation), fluency in Dutch.	/	Cartoon festival	Survey; Custom developed questionnaire administered in person	Descriptive analysis, Mann-Whitney U Test, Kruskal-Wallis test	Ethical approval from the Social and Societal Ethics Committee of the University of Leuven.	NA
Briggs et al. 2017 (USA)	Abstract	To evaluate the awareness and attitudes among women regarding preconception carrier screening and factors that may influence decision-making in a family planning context.	/	Women who were pregnant, undergoing gynaecologic care who were considering future fertility and infertility patients. (n=521)	/	/	Academic University Practice	Survey; Questionnaire	Descriptive analysis	/	NA

Gilmore et al. 2017 (USA)	Full-text article	To evaluate reasons for declining preconception carrier screening.	/	Members of Kaiser Permanente Northwest (KPNW) (healthcare delivery system). (n=240)	Current member of KPNW, not pregnant, stating to plan future pregnancies, previously completed preconception carrier screening for CF through clinical care at KPNW.	Pregnant at the time of recruitment or consent visit, not access to email, a known cognitive impairment, not able to speak English, not aged 21-50 years.	Database KPNW health-care delivery system	Telephone Survey; Custom developed questionnaire.	Descriptive analysis, Fisher's Exact tests, Multivariable logistic regression	Approval by the Kaiser Permanente Northwest Institutional Review Board. Verbal consent was obtained from all participants.	NA
Ong et al. 2018 (Australia)	Full-text article	To explore baseline levels of genetic knowledge and awareness regarding preconception carrier screening (PCS) in Western Australia prior to the implementation of any public health campaign without specifying what PCS means AND to investigate factors that might influence knowledge and attitudes to participation in any future PCS program implemented in Western Australia.	2 weeks	Individuals on four online panels of Western Australian residents. (n=832)	Aged 18 years or older, residing in Western Australia.	/	Online recruitment by a market research agency	Online Survey; Custom developed questionnaire	Descriptive analysis, Chi-Square test of independence, multinomial logistic regression, ordinal logistic regression	Ethical approval from the Human Research Ethics Committee of the University of Western Australia	NA

Propst et al. 2018 (USA)	Full-text article	To explore pregnant woman's perspectives to expanded carrier screening, including reasons for electing or declining and anxiety associated with tis decision-making.	4 months	Pregnant Women. (n=80)	Female, pregnancy, able to read and speak English, aged 18 year or older, individuals who previously had ethnicity-based carrier screening.	Minors, not pregnant, not able to read or speak English, individuals who already had ECS.	Pregnant women under-going prenatal genetic coun-selling prior to pursuing aneu-ploidy screening at North-western Medicine	Survey; Custom developed questionnaire	Descriptive analysis, Mann-Whitney U Test, Chi-Square test of indepen-dence	Approval by the North-western University Institutional Review Board.	Up to $350 out-of-pocket if participant' insurance did not cover the test.
Spencer et al. 2018 (USA)	Full-text article	To better understand the opinions and attitudes of adopted individuals on the use of ECS in determining a patient's reproductive genetic risks.	8 weeks	Adult adoptees. (n=124)	Aged 18 years or older, to have been adopted.	/	Distri-bution of study invitation through multiple non-profit organizati ons in the adoption communit y.	Online Survey; Custom developed questionnaire	Descriptive analysis, Chi-Square test of indepen-dence, Fisher' Exact test, Gamma Correlation Test, Binary Logistic Regression	Approval by the North-western University Institutional Review Board. Consent was implied once participants initiated the online survey.	NA
Schuurmans et al. 2018 (The Netherlands)	Abstract	To investigate short and long term psychological impact as well as uptake and feasibility of a GP-provided couple-based ECS-test.	Longitudi nal	Patients from GP-practices. (n=190)	Female, having a male partner, planning children and not being pregnant.	/	GP's from nine practices invited female patients from their practice register	Longitudinal survey study; Custom developed questionnaire	T-tests/non-parametric tests	/	Free of charge

Nijmeijer et al. 2019 (The Netherlands)	Full-text article	To assess public attitudes towards preconception ECS for autosomal recessive disorders in order to learn more about public acceptance and to address possible misconceptions.	12 months (retrospective)	A stratified sample of Dutch individuals (n=781)	Aged 18-45 years	/	Online recruitment by a market research agency	Online Survey; Custom developed questionnaire	Descriptive analysis, Chi-Square test of independence, independent sample t-test, multivariate logistic regression analysis	Informed consent was obtained from participants prior to completing the online questionnaire. The study was approved by the Medical Ethics Committee of Amsterdam UMC.	NA
Larsen et al. 2019 (USA)	Full-text article	To identify factors associated with individual decisions to proceed with ECS after genetic counselling.	1 month	Women who had a prenatal or preconception genetic counselling encounter with genetic counsellors for various indications. (n=483)	Individualized genetic counselling by board-certified genetic counsellors. Being offered expanded carrier screening.	/	Database with 500 medical records from woman who had a prenatal or preconception genetic counselling encounter at a genetic clinic counselling service in an urban private hospital-based outpatient clinic.	Retrospective medical record review.	Descriptive analysis, Chi-Square test of independence, Two-tailed t-tests.	Approval by institutional review board for human subject's research.	NA

Table 3: Main findings of studies exploring interest/uptake in/of ECS

Study	Composition of test panel	Study population	Reported measures relevant to ECS	Main findings	Participants characteristics
Higgins et al. 2015	106 genetic conditions	Couples undergoing fertility evaluation at Sanford Health Fertility and Reproductive Medicine were offered a commercial ECS test between 2010-2013. (n=1669)	Uptake of ECS	134 couples (8%) underwent screening for either one or both partners (48.5% of the couples screened both partners and 44% screened only the female partner). The uptake increased from 3.3% to 17.5% following the decrease in out-of-pocket cost of screening from $350 to $99.	97% non-Hispanic Caucasian (94% of the total cohort offered ECS were non-Hispanic Caucasian); 31% of individuals were identified as carriers of at least one serious genetic disease.
Plantinga et al. 2016	Hypothetical test panel for 50 diseases	Dutch residents aged 18-40 years with a partner. (n=504)	Intention to participate in preconception ECS	Over one-third (34%) of the respondents indicated they would take the test if it were offered, 15% reported they were unlikely to take the test, and 51% were undecided.	72% of respondents were female; mean age was 29 (SD 6.19); 65% of respondents were not religious; 34% had a high education level; 70% of respondents expressed the desire to have children with their current partner.
Ragnar et al. 2016	Hypothetical generic test panel	Couples enrolled in the Swedish Pregnancy Planning study (SWEPP). (n=777)	Intention to participate in preconception ECS	Approximately one-third (30% of women; 33.6% of men) of the respondents indicated interest in screening; 25.5% of women and 28.2% of men were not interested, while 44.5% of women and 38.2% of men were uncertain.	Mean age was 29.8 (SD 4.6) for woman and 35.3 (SD 5.6) for men; 59.8% of women had a university/college degree compared to 44% of men; 78.2% of women already had children; 23% of women had a previous miscarriage; approximately 80% of pregnancies were planned; 59.6% of respondents had experiences of prenatal diagnostics; 54.6% of women had a future child wish compared to 43.6% of men.
Chokoshvili et al. 2017	Hypothetical generic test panel	Visitors of the annual Cartoon festival. (n=1182)	Intention to participate in preconception ECS	54% of the respondents showed intention to participate in preconception carrier screening for recessive disorders.	52.5% of respondents were female; mean age was 48.5 years (SD 16.8); 31.6% described themselves as (somewhat) actively religious; 34.8% had an academic degree.
Briggs et al. 2017	Hypothetical generic test panel	Pregnant women, women undergoing gynaecologic care who were considering future fertility and infertility patients. (n=521)	Intention to participate in genetic carrier screening	51% of the respondents reported no desire for testing.	/
Gilmore et al. 2017	750 autosomal recessive, X-linked and mitochondrial conditions + 100 medically actionable secondary findings	Non-pregnant women (aged 21-50) who had declined to undergo a preconception ECS offered free of charge in the research setting. (n=240)	Uptake of ECS; Reasons for declining testing	In total, 816 women were offered preconception ECS, 540 (66%) of whom declined the offer. Among the decliners, 240 (44%) agreed to participate in the telephone interview study.	76% of respondents were non-Hispanic white; 77% had a Bachelor's degree or higher; 82% of respondents were 30 years or older; 38% of women had children.

Ong et al. 2018	Hypothetical generic test panel	Residents of Western Australia aged 18 years or older. (n=832)	Intention to participate in preconception ECS	In overall, 68% (n=562) of the respondents indicated interest in ECS, although the intention to undergo ECS varied (61%-92%) depending on the nature of disorders to be included in the test. Only 10.1% of participants reported that they would decline the PCS test if it were offered to them. Another 22.4% of participants indicated that they were unsure about taking the test if PCS was offered to them.	84.5% of respondents were of reproductive age (18-44); 54% were females; 71.3% were in a relationship; 49.9% were parents; 70.6% of respondents had a future child wish; 59% were not religious; 37% completed university.
Propst et al. 2018	79 conditions with the option of adding fragile X	Pregnant women who had been offered an ECS test (N=80). The out-of-pocket cost of the test was up to $350, unless covered by medical insurance.	Uptake of ECS; Reasons for accepting or declining testing	Forty individuals (50%) accepted, and 40 (50%) declined the offer.	92.5% of women were under 40; 70.9% of respondents were non-Hispanic white; 53.8% of women didn't yet have children; 87.5% had a Bachelor's degree or higher; 75% of respondents didn't have any previous carrier screening.
Spencer et al. 2018	Hypothetical generic test panel	Adoptees aged 18 years or older. (n=124)	Intention to participate in preconception ECS	76% of participants said they would want to have the test.	Mean age was 44 (SD 14.7); 88% of the study population was female; 74% of respondents were Caucasian and 11% Asian/Pacific; 59% of participants had at least a Bachelor's degree; 60% of respondents were married or in a committed relationship; 65% had children and 63% reported not to have a future child wish.
Schuurmans et al. 2018	50 serious recessive conditions	Non-pregnant women aged 18-40 who were offered a couple-based ECS free of charge in the research context. (N=190)	Uptake of ECS	117 couples accepted the offer. True uptake rate cannot be measured, as it is not possible to determine how many invitees were eligible to participate.	/
Nijmeijer et al. 2019	Hypothetical test panel for 50 diseases	Dutch individuals of reproductive age (18-45 years). (n=781)	Intention to participate in preconception ECS	Of all participants, 31% reported that they probably or certainly would take a preconception ECS test. Another 36% did not want to be tested and 33% were uncertain.	Mean age was 31.2 (SD 7.33); 49% of respondents were female; 33% had a high educational level; 54% had religious beliefs; 75% of respondents were married or in a relationship; 41% were considering a (future) pregnancy; 3% was currently pregnant.
Larsen et al. 2019	> 100 conditions	Women who had a prenatal or preconception genetic counselling encounter. (n=483)	Uptake of ECS	An overall acceptance rate of 39,8% was found. A significantly higher proportion of women counselled preconceptionally (68,7%) accepted the ECS comparing with those women seen during pregnancy (35,1%).	43.9% were Caucasian, 17.6% Hispanic and 13.7% African American; 76.2% of women were younger than 35.

Table 4: Factors influencing Interest and Uptake of ECS

	Higgins et al. (2015)	Plantinga et al. (2016)	Ragnar et al. (2016)	Chokoshvili et al. (2017)	Briggs et al. (2017)	Gilmore et al. (2017)	Ong et al. (2018)	Propst et al. (2018)	Spencer et al. (2018)	Schuurmans et al. (2018)	Nijmeijer et al. (2019)	Larsen et al. (2019)
SOCIO-DEMOGRAPHIC FACTORS												
Gender		NS	NS	NS			NS				NS	
Relationship status		NS				NS	NS				NS	
Employment status						NS						
(Household) Income			NS			SA (p=0.001)	SA (p=0.030)					
Education level		NS	NS	SD (p<0.01)		SA (p<0.001)	SA (p=0.033)	NS	NS		NS	
Religion		SA (p<0.001)		NS			SA (p=0.03)				SD (p=0.034)	
(Self-reported) Ethnic Background						NS		SA (p=0.003)				NS
Medicaid						NS						
FACTORS RELATED TO REPRODUCTION												
Having Children						SA (p=0.029)		NS	NS			NS
Previous miscarriage			NS					NS				NS
(Future) Child Wish		NS					NS		NS		SD (p=0.011)	
Pregnancy Planning			SA (male p=0.01)									
Prenatal Diagnostics			SA (male & female p<0.001)									
Gestational Age												SA (p<0.001)
Twin Pregnancy												NS
Wanting to know the sex of the baby			SA (female p<0.001)									
Gender selection			SA (female p<0.001)									
Pursuing assisted reproductive technology												SA (p<0.001)

Pregnancy through egg and/or sperm donation												NS
FACTORS RELATED TO GENETIC SCREENING												
Previous carrier screening						NS		NS				
Indication for genetic counselling												NS
Genetic condition in the family						SA (p<0.001)						NS
Knowing someone with a genetic condition						SA (p<0.001)					NS	
Prior knowledge/awareness of ECS							SA (p<0.001)					
Know about it from family members							SA (p<0.01)					
Know about it through searches on the internet							SA (p<0.048)					
Genetic knowledge							SA (p<0.005)					
OTHER FACTORS												
Cost of testing	SD											

SD: significant difference
SA: significant association
NS: not significant

REFERENCES

1. Ropers HH. On the future of genetic risk assessment. J Community Genet. 2012;3(3):229-36.
2. Henneman L, Borry P, Chokoshvili D, Cornel MC, van El CG, Forzano F, et al. Responsible implementation of expanded carrier screening. European journal of human genetics : EJHG. 2016;24(6):e1-e12.
3. Kaback MM. Population-based genetic screening for reproductive counseling: the Tay-Sachs disease model. European journal of pediatrics. 2000;159 Suppl 3:S192-5.
4. Edwards JG, Feldman G, Goldberg J, Gregg AR, Norton ME, Rose NC, et al. Expanded carrier screening in reproductive medicine-points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine. Obstet Gynecol. 2015;125(3):653-62.
5. Lazarin GA, Haque IS, Nazareth S, Iori K, Patterson AS, Jacobson JL, et al. An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals. Genet Med. 2013;15(3):178-86.
6. Chokoshvili D, Vears D, Borry P. Expanded carrier screening for monogenic disorders: where are we now? Prenat Diagn. 2018;38(1):59-66.
7. Committee on G. Committee Opinion No. 691: Carrier Screening for Genetic Conditions. Obstet Gynecol. 2017;129(3):e41-e55.
8. Ioannou L, McClaren BJ, Massie J, Lewis S, Metcalfe SA, Forrest L, et al. Population-based carrier screening for cystic fibrosis: a systematic review of 23 years of research. Genet Med. 2014;16(3):207-16.
9. Clayton EW, Hannig VL, Pfotenhauer JP, Parker RA, Campbell PW, 3rd, Phillips JA, 3rd. Lack of interest by nonpregnant couples in population-based cystic fibrosis carrier screening. Am J Hum Genet. 1996;58(3):617-27.
10. Henneman L, Bramsen I, van Kempen L, van Acker MB, Pals G, van der Horst HE, et al. Offering preconceptional cystic fibrosis carrier couple screening in the absence of established preconceptional care services. Community Genet. 2003;6(1):5-13.
11. Poppelaars FA, van der Wal G, Braspenning JC, Cornel MC, Henneman L, Langendam MW, et al. Possibilities and barriers in the implementation of a preconceptional screening programme for cystic fibrosis carriers: a focus group study. Public Health. 2003;117(6):396-403.
12. Srinivasan BS, Evans EA, Flannick J, Patterson AS, Chang CC, Pham T, et al. A universal carrier test for the long tail of Mendelian disease. Reproductive biomedicine online. 2010;21(4):537-51.
13. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100.

14. Higgins A, Flanagan J, Von Wald T, Hansen KA. An Expanded Carrier Screening Tool Enhances Preconception Cystic Fibrosis Screening in Infertile Couples. Open Journal of Obstetrics and Gynecology. 2015:412-6.
15. Schuurmans J, Plantinga M, Lucassen A, Fenwick A, Abbott K, Birnie E, et al. Short and long-term psychological impact of an active GP-provided couple-based ECS test-offer in the Dutch general population 2018.
16. Larsen D, Ma J, Strassberg M, Ramakrishnan R, Van den Veyver IB. The uptake of pan-ethnic expanded carrier screening is higher when offered during preconception or early prenatal genetic counseling. Prenat Diagn. 2019.
17. Hawker S, Payne S, Kerr C, Hardey M, Powell J. Appraising the evidence: reviewing disparate data systematically. Qualitative health research. 2002;12(9):1284-99.
18. Ragnar ME, Tyden T, Kihlbom U, Larsson M. Swedish parents' interest in preconception genetic carrier screening. Ups J Med Sci. 2016;121(4):289-94.
19. Nijmeijer SCM, Conijn T, Lakeman P, Henneman L, Wijburg FA, Haverman L. Attitudes of the general population towards preconception expanded carrier screening for autosomal recessive disorders including inborn errors of metabolism. Molecular genetics and metabolism. 2019;126(1):14-22.
20. Plantinga M, Birnie E, Abbott KM, Sinke RJ, Lucassen AM, Schuurmans J, et al. Population-based preconception carrier screening: how potential users from the general population view a test for 50 serious diseases. European journal of human genetics : EJHG. 2016;24(10):1417-23.
21. Ong R, Howting D, Rea A, Christian H, Charman P, Molster C, et al. Measuring the impact of genetic knowledge on intentions and attitudes of the community towards expanded preconception carrier screening. Journal of medical genetics. 2018;55(11):744-52.
22. Chokoshvili D, Belmans C, Poncelet R, Sanders S, Vaes D, Vears D, et al. Public Views on Genetics and Genetic Testing: A Survey of the General Public in Belgium. Genetic testing and molecular biomarkers. 2017;21(3):195-201.
23. Briggs A, Nouri P, Galloway M, Yaklic JL, Maxwell R, Lindheim S. Patients' Awareness and Attitudes Towards Genetic Carrier Screening. Obstet Gynecol. 2017;129:88S-S.
24. Spencer S, Ewing S, Calcagno K, O'Neill S. Adopted Individuals' Views on the Utility and Value of Expanded Carrier Screening. Journal of Genetic Counseling. 2018;27(6):1341-8.
25. Gilmore MJ, Schneider J, Davis JV, Kauffman TL, Leo MC, Bergen K, et al. Reasons for Declining Preconception Expanded Carrier Screening Using Genome Sequencing. Journal of Genetic Counseling. 2017;26(5):971-9.
26. Propst L, Connor G, Hinton M, Poorvu T, Dungan J. Pregnant Women's Perspectives on Expanded Carrier Screening. Journal of genetic counseling. 2018;27(5):1148-56.
27. Lerman C, Croyle RT, Tercyak KP, Hamann H. Genetic testing: psychological aspects and implications. J Consult Clin Psychol. 2002;70(3):784-97.

28. Sheeran P, Webb TL. The Intention-Behavior Gap. Soc Personal Psychol. 2016;10(9):503-18.
29. Chen LS, Goodson P. Factors affecting decisions to accept or decline cystic fibrosis carrier testing/screening: A theory-guided systematic review. Genet Med. 2007;9(7):442-50.
30. Ioannou L, Massie J, Lewis S, McClaren B, Collins V, Delatycki MB. 'No thanks'-reasons why pregnant women declined an offer of cystic fibrosis carrier screening. J Commun Genet. 2014;5(2):109-17.
31. Robinson JO, Carroll TM, Feuerman LZ, Perry DL, Hoffman-Andrews L, Walsh RC, et al. Participants and Study Decliners' Perspectives About the Risks of Participating in a Clinical Trial of Whole Genome Sequencing. Journal of Empirical Research on Human Research Ethics. 2016;11(1):21-30.
32. Obstetricians ACo, Gynecologists. Carrier screening in the age of genomic medicine. Committee Opinion No. 690. Obstet Gynecol. 2017;129:e35-e40.
33. Cho D, McGowan ML, Metcalfe J, Sharp RR. Expanded carrier screening in reproductive healthcare: perspectives from genetics professionals. Human reproduction (Oxford, England). 2013;28(6):1725-30.
34. Janssens S, Chokoshvili D, Vears DF, De Paepe A, Borry P. Pre- and post-testing counseling considerations for the provision of expanded carrier screening: exploration of European geneticists' views. BMC Med Ethics. 2017;18(1):46.
35. Lazarin G, Detweiler S, Nazareth S, Ashkinadze E. Genetic Counselors' Perspectives and Practices Regarding Expanded Carrier Screening after Initial Clinical Availability. Journal of Genetic Counseling. 2016;25(2):395-404.
36. Delgado-Rodríguez M, Llorca J. Bias. Journal of epidemiology and community health. 2004;58(8):635-41.

CHAPTER 3

HOW DOES CARRIER STATUS FOR RECESSIVE DISORDERS INFLUENCE REPRODUCTIVE DECISIONS? A SYSTEMATIC REVIEW OF THE LITERATURE

Cannon, J.W., Van Steijvoort, E., Borry, P. & Chokoshvili D. (2019) How does carrier status for recessive disorders influence reproductive decisions? A systematic review of the literature. *Expert review of molecular diagnostics*, *19*(12), 1117-1129. doi:10.1080/14737159.2020.1690456

ABSTRACT

INTRODUCTION: Carrier screening for recessive disorders is undertaken by prospective parents to inform their reproductive decisions. With the growing availability of affordable and comprehensive expanded carrier screening (ECS), it is expected that carrier screening will become a standard practice in the future. However, the impact of positive carrier screening results on the reproductive decisions of at-risk couples (ARCs) remains underexplored.

AREAS COVERED: We performed a systematic literature review to identify peer-reviewed publications describing the reproductive decisions of ARCs. Our search identified 19 relevant publications spanning the period 1994–2018. By synthesizing available evidence, we found that most ARCs chose to prevent the birth of an affected child and the decision to utilize preventive reproductive options was strongly influenced by the clinical nature of a disorder. However, there was also some heterogeneity in reproductive decisions within the same recessive disorders, suggesting that choices of ARCs can be influenced by factors other than the clinical nature of a disorder.

EXPERT OPINION: ECS is becoming increasingly common, which will result in the routine identification of many ARCs. Reproductive decision-making by ARCs is a complex and emotionally challenging process, highlighting the critical role of genetic counselling in the care for these potentially vulnerable patients.

ARTICLE HIGHLIGHTS

● A growing number of prospective parents pursue expanded carrier screening (ECS) to inform their reproductive decisions, leading to the identification of carrier couples who are at risk of having a child with a recessive (autosomal or X-linked) genetic disorder.

● Our systematic literature review revealed that most carrier couples chose to prevent the birth of an affected child. If already pregnant, the majority of carrier couples opted to undergo prenatal diagnosis followed by an elective termination of an affected pregnancy. If identified preconceptionally, most carrier couples pursued in-vitro fertilization (IVF) with pre-implantation genetic testing (PGT).

● The decision to utilize preventive reproductive options appears to be strongly influenced by the clinical nature of a disorder. Disorders associated with less severe clinical phenotypes were generally less likely to result in altered reproductive choices among at-risk couples.

● However, there was some heterogeneity in reproductive decision making within the same recessive disorders, suggesting that choices of at-risk couples can be influenced by factors other than the clinical nature of a disorder.

● Infertile and sub-fertile at-risk couples who had carrier screening performed as part of their infertility work-up more readily accepted PGT, which was also true for relatively mild, low-penetrant, and treatable disorders.

● Reproductive decision-making of carrier couples is a complex and emotionally challenging process, which highlights the critical role of genetic counselling to ensure that at-risk couples are supported in dealing with their newfound carrier status.

This box summarizes key points contained in the article.

INTRODUCTION

Carrier screening is a form of genetic testing that aims to identify couples at risk of having a child with a recessive (autosomal or X-linked) genetic disorder (1). In autosomal recessive disorders, both reproductive partners of an at-risk couple carry a pathogenic variant in the same gene, while in X-linked recessive disorders, only the female member of the couple is a carrier. These at-risk couples (ARCs; also referred to as 'carrier couples') have a one-in-four chance of conceiving an affected child with the disorder in each pregnancy (2). However, because they are typically healthy and lack family history for the disorder, ARCs are usually unaware of their reproductive risk until their child is diagnosed with the disorder (3).

The goal of carrier screening is to identify unsuspecting ARCs prospectively, ideally prior to conception, to allow them to make informed reproductive choices. Carrier couples who learn about their risk before pregnancy can choose from several reproductive options, including: deciding against having biological children with their current partner, undergoing in-vitro fertilization (IVF) with pre-implantation genetic testing (PGT) or using donor gametes, or accepting their risk and proceeding with a natural pregnancy. For ARCs who are already pregnant, options are limited to deciding whether to undergo prenatal diagnosis (PNDx), potentially followed by pregnancy termination if the fetus is affected (4).

The first carrier screening initiatives commenced more than 40 years ago with carrier screening offers for heritable recessive disorders such as Tay-Sachs disease (TSD) among the Ashkenazi Jewish community and sickle cell anaemia in several Mediterranean countries (5, 6). The reason behind these early initiatives was a relatively high prevalence of certain life-threatening genetic disorders among select ethnic groups, which created a need for identifying couples at risk of having affected children (7). Ethnicity-based carrier screening programs were well received by prospective parents and they became an integral part of family planning in many ethnic communities (8). In the subsequent decades, as genetics of more recessive disorders were elucidated and the costs of molecular testing diminished, it became feasible to incorporate additional disorders into carrier screening tests. Following the adoption of next-generation sequencing (NGS) in the mid-2000s, screening for large number of recessive disorders in a single test became feasible, leading to the development of expanded carrier screening (ECS) (9). ECS tests, which typically screen for more than 100 disorders, are currently available to prospective parents through various commercial providers (9). Unlike traditional carrier screening tests, ECS is not limited to disorders or pathogenic variants predominantly observed within specific ethnic groups, allowing ECS to identify carriers of recessive disorders in the general population, regardless of ethnicity (10). At the same time, the cost of ECS has been steadily declining, making testing increasingly affordable for prospective parents (11).

Since 2015, several authoritative medical professional organizations have recognized the benefits of ECS, recommending that ECS be made available to couples planning a pregnancy or already pregnant (1, 12, 13). It has been estimated that in the United States alone, approximately 200,000 ECS tests are performed annually (14). As the availability and accessibility of ECS grows, an increasing number of couples are exposed to the choice of using this test. Consequently, the uptake of ECS is likely to further increase, with ECS potentially becoming a routine test performed in the reproductive context. Given that a comprehensive ECS test could identify 1–5% of couples as being at risk of having an affected child (15, 16), a large number of couples in the general population may receive positive results following an ECS. When a couple discovers they are an ARC, they could be prompted to make decisions about their newfound reproductive risk. It is important for healthcare providers to understand how carrier couples might process this information, what decisions they could face, and what kind of support they will require. Therefore, the aim of this systematic review is to gain insights into the potential impact of ECS on the subsequent reproductive decision-making of ARCs, by reviewing the outcomes of different carrier screening offers described in the literature. This will contribute to a better understanding of the potential impact of positive carrier screening results on at-risk couples, including the extent to which such results may influence reproductive decision-making.

METHODS

We conducted a systematic literature review to identify original research articles on carrier screening reporting reproductive decisions of couples and females identified as being at risk of having a child affected with an autosomal recessive and an X-linked recessive disorder, respectively. The search for relevant research articles was carried out in four online databases (PubMed, Web of Science, CINAHL, Cochrane Library) using the following search string: ‘carrier’ AND (‘testing’[tw] OR ‘screening’ [tw]) AND (reproductive behaviour [tw] OR reproductive choices [tw] OR reproductive decision-making [tw] OR outcomes [tw] OR clinical decision making [tw]). Following the systematic search of the four databases, we additionally consulted references of the identified papers in order to find any remaining publications of relevance to our systematic review. To further ensure the comprehensiveness of our search strategy, we also carried out a related search using Google Scholar based on the studies identified through the systematic search. This review followed PRISMA guidelines for systematic reviews of medical literature (17). In order to be included in this systematic review, studies should have reported reproductive decisions of carrier couples (in autosomal recessive disorders) and/or female individuals (in X-linked recessive disorders) who, through carrier screening, were found to be at risk of having an affected child. As our objective was to investigate how prospective parents in the general population may act on their carrier status information, we decided to exclude studies primarily focused on couples/ individuals with previously known risk of having an affected child. For example, studies where prospective parents were referred for genetic testing due mostly to the family history of a specific recessive disease were excluded. Only full-length

English-language articles published in peer-reviewed journals were included in this systematic review. The search was undertaken in January 2019 and was carried out by two researchers (E.V.S. and D.C.) who worked independently and continually compared their findings to discuss the differences, if any.

RESULTS

The systematic literature search process is summarized in Figure 1. In total, the systematic search identified 17 distinct studies reported in 19 peer-reviewed publications describing reproductive choices of couples and females (in X-linked recessive disorders) at risk of having affected children (18-36). The main characteristics of these studies are summarized in Table 1.

Owing to the relative novelty of ECS, studies investigating the impact of positive carrier screening results on couples pursuing ECS specifically comprise a minority (3/17) of the studies included in this review. Consequently, most studies can be described as either ethnicity-specific or population-based, focused on single disorders such as cystic fibrosis (CF) or a handful of disorders relatively common in a certain population (e.g. (35)). In most studies (15/17), the target population to whom carrier screening was offered comprised couples and individuals who were considering pregnancy or were already pregnant. In autosomal recessive disorders, the most commonly employed screening strategy was the sequential or stepwise screening method, where screening is initiated in one member of a couple (typically the female), followed by the screening of the reproductive partner only if the initial proband is found to be a carrier. This approach was particularly common in earlier, pre-ECS studies, in which participants were typically recruited through antenatal clinics and women's healthcare providers. Two notable exceptions were an ethnicity-based screening program targeting Ashkenazi Jewish population in Montreal, Canada (22), and a population-based carrier screening offer for haemoglobin disorders in France (25), both of which were aimed at high school students.

Reproductive decisions of carrier couples (in autosomal recessive disorders) and females (in X-linked recessive disorders) are summarized in Table 2. Throughout the studies, the most commonly screened disorder was CF (10/17), having been offered both as a stand-alone test and as part of a wider panel. The vast majority of couples identified as carriers of CF took steps to prevent the birth of an affected child through PNDx followed by an elective termination of an affected pregnancy or, if identified preconceptionally, pursued IVF-PGT. However, studies also report cases where at-risk couples decided to accept their reproductive risk or chose not to terminate an affected pregnancy. While it was not always possible to determine how couples had arrived at specific reproductive decisions, in several cases, authors provided insightful comments that shed light on the reproductive decision-making process among such couples. For example, Levenkron et al. describe an ARC that declined PNDx, where the female stated she 'had not thought through the "consequences" of being

at risk for a CF child prior to [screening]' and, following a more extensive deliberation, decided against PNDx as she 'would not terminate an affected pregnancy' (21). In another notable case discussed by Witt et al., a twin pregnancy was diagnosed with CF, with both concordant twins identified as homozygous for the Phi508del. mutation. The authors report that '[the] couple of the affected twin pregnancy chose to continue their pregnancy after lengthy deliberations and counselling' (23). Similarly, in haemoglobin disorders, screening for which was described in 6 studies (including two studies utilizing ECS), at-risk couples typically underwent PNDx, and the majority of affected pregnancies were terminated. Most notably, in a large cohort of couples in the study of Tongsong et al., the proportion of at-risk couples who pursued PNDx and the proportion of affected pregnancies that were terminated were 97% and 98%, respectively (31). An exception to this general trend was observed by Colah et al., who noted that in their study, while all four pregnancies identified as affected were terminated, as many as 16/37 (43%) carrier couples did not return to the clinic for PNDx. Although the authors mention distinct characteristics of their study population, such as low socioeconomic status, they do not offer a clear explanation for the low uptake of PNDx (28). In addition, as with CF, several studies on haemoglobin disorders included cases where at-risk couples knowingly declined to alter their reproductive plans. For example, Tongsong et al., and Mitchell et al. both report a single case where a couple was found to have an affected pregnancy and decided against pregnancy termination, delivering a child with Beta-thalassemia/HbE disease and Beta-thalassemia, respectively (22, 31).

Several studies provide insights into how medical characteristics of a disorder, such as severity, may affect the reproductive decision-making of ARCs. For example, Zuckerman et al. reviewed reproductive outcomes of 83 couples identified as carriers of Gaucher disease (GD) in an Ashkenazi Jewish screening program in Israel, comparing outcomes of prospective parents across subtypes of GD (27). The authors report that among couples at risk of having a child with the mild type 1 GD, PNDx was performed in 53/73 (73%) pregnancies and 2/13 (15%) of the affected pregnancies were electively terminated. In contrast, among the couples at risk of having a child with the moderate type 1 GD, PNDx was undertaken in 15/17 (88%) pregnancies and 2/3 (67%) affected pregnancies were electively terminated. Similarly, in two recent studies that surveyed carrier couples who had utilized a commercial ECS test, the nature of a disorder was found to be an important factor in determining the extent to which carrier couples acted on their test results. Ghiossi et al., whose sample comprised 64 carrier couples, compared reproductive decisions among three groups of carrier couples stratified by disease severity ('profound', 'severe', and 'mild'). They observed that 32/45 (71%) couples at risk of having a child with a disorder categorized as 'profound' or 'severe', reported having taken or planning to take an action, such as undergoing IVF-PGT or, if already pregnant, using PNDx. By contrast, in disorders categorized as 'moderate' (e.g. Alpha-1 Antitrypsin Deficiency and GJB2-related non-syndromic hearing loss), 4/19 couples (21%) reported having acted or planning to act on the results. Additional comments provided by some respondents further illustrated that the

perceived severity of the identified disorder played an important role in couples' decisions (34). These findings were subsequently corroborated by Taber et al., whose study used a larger sample of carrier couples (N = 391) identified through the same ECS test (36). In particular, Taber et al. found that the proportion of the couples who had used or intended to use their test results to avert the birth of an affected child increased with severity, among both non-pregnant and pregnant couples, with differences between the 'profound' and 'moderate' groups being the most prominent. Taber et al. also observed that carrier couples who had been identified during pregnancy (n = 154) were significantly less likely to alter their reproductive plans than those who had received their test results preconceptionally (n = 235). More specifically, approximately one-third of couples in the former group indicated having undergone prenatal diagnosis, as opposed to three-quarters of carrier couples identified preconceptionally electing to avoid the birth of an affected child, primarily through IVF-PGT. The authors partly attribute these findings to the fact that many couples in their study population were IVF patients at the time of screening, receiving treatment for infertility. They suggest the possibility that patients undergoing IVF may be willing to readily accept PGT as part of the artificial reproduction treatment, while at the same time displaying reluctance toward PNDx once a pregnancy has been achieved (36). The willingness of IVF patients to undergo PGT was also discussed by Franasiak et al., who noted that pursuing PGT may be an appealing reproductive option for at-risk couples receiving IVF treatment, even for treatable and low penetrant disorders (32).

Four studies (including two ECS-based studies) also discussed reproductive decisions around X-linked recessive disorders among at-risk females who typically lacked family or personal history suggestive of the disorder. Fragile X syndrome (FXS) was the X-linked recessive disorder for which reproductive decisions were most extensively documented, primarily through the studies of Cronister et al. and Archibald et al. In the former study, 22 female carriers of an expanded FMR1 allele were identified. This included 14 carriers of an intermediate FMR1 allele (45–55 CGG repeats) who were offered PNDx for a reason unrelated to FXS. Notably, among these females, 7 (50%) requested testing of their fetus specifically for FXS, despite having been counselled on the low probability of having an affected child. According to the authors, the decision of these females was motivated by the desire to gain reassurance (26). In the study of Archibald et al., which describes reproductive choices among carriers of premutation (55–200 CGG repeats) and full mutation (200< CGG repeats) FMR1 alleles, the majority of pregnant carriers (16/22; 73%) pursued PNDx. Subsequently, two fetuses were found to harbour a full mutation and both pregnancies were terminated. Two pregnant female carriers (2/22; 9%) declined PNDx and did not pursue any further testing of the fetus on the grounds that they perceived the risk of having an affected pregnancy as low or would not terminate an affected pregnancy (carriers of 55 CGG repeats and 72 CGG repeats, respectively) (33).

DISCUSSION

In this systematic review, we analysed the reproductive decisions of couples and females identified to be at risk of conceiving a child with a recessive disorder (collectively referred to as carrier couples or at-risk couples (ARCs)). Based on the reproductive outcomes among ARCs reported in different studies, it can be concluded that most ARCs used their carrier status information to inform their family planning decisions. There is considerable evidence indicating that the clinical nature of a disorder the future child is at risk for may influence the extent to which couples act on their carrier status information. For example, carrier screening offers for life-limiting conditions such as CF and haemoglobin disorders have revealed that the vast majority of couples at risk of having an affected child with these disorders utilized preventive reproductive options, such as IVF-PGT, or PNDx followed by pregnancy termination. However, the literature also describes a small number of cases in which ARCs chose to accept their reproductive risk and declined further testing, or underwent PNDx but decided against terminating an affected pregnancy. By the same token, in disorders associated with less severe clinical phenotypes, ARCs were generally less likely to alter their reproductive plans. Most notably, in the study of Zuckerman et al., while the majority of couples at risk of having a child with the mild type 1 GD pursued PNDx, only two of the eleven (15%) couples with an affected fetus elected to terminate the affected pregnancies (27). This is a markedly low pregnancy termination rate of affected pregnancies compared to most studies included in the present review. Similarly, two studies with a large number of carrier couples who had undergone ECS found that ARCs at risk of having a child with milder recessive disorders were less likely to alter their reproductive plans, compared to carriers of more severe, life-limiting, or debilitating conditions (34, 36).

These results suggest that the clinical nature of a disorder may strongly influence the reproductive decision-making of ARCs. It is probable that most carrier couples at risk of having a child with a mild or more clinically manageable disorder use their carrier status information to prepare for the care of an affected child, as opposed to altering their reproductive plans. However, given that studies also observed some heterogeneity in reproductive decisions within the same recessive disorders, it is also clear that the clinical nature of a disorder is not the only factor informing couples' choices. Because decisions around reproduction are intensely personal, ARCs may factor in other considerations such as their risk perception, their ability to care for a child with special needs, and their personal views regarding available reproductive options (37). The reproductive decision-making process that carrier couples go through can be highly complex and emotionally challenging, as indicated by a small number of empirical studies around this matter. Three qualitative interview studies with couples at risk of having an affected child revealed that ARCs typically experienced shock upon learning their reproductive risks and endured significant emotional distress in the period following the receipt of test results. In particular, ARCs often reported experiencing grief, tainted mental image of their (future) family and, in some cases, strained personal relationships with family

members. However, in the longer term, most couples found their carrier status information actionable and made adjustments to their reproductive plans, with many couples in retrospect expressing high degree of satisfaction over undergoing screening (35, 38, 39). It should be noted, however, that these three qualitative studies focused on life limiting disorders typically resulting in significant childhood onset morbidity. By contrast, in milder disorders, such as type 1 GD, some ARCs interviewed by Zuckerman et al. several years following screening, expressed dissatisfaction for participating in carrier screening, with several couples who had terminated their affected pregnancies regretting their decision (40).

These findings highlight the importance of genetic counselling to ensure that ARCs are supported in dealing with their newfound carrier status. In this regard, the dual role of genetic counselling should be recognized, where genetic counsellors both provide psychological support to ARCs and educate them regarding available reproductive options (41). As ECS tests include a wide range of disorders with variable clinical characteristics, genetic counsellors should be aware that the informational and psychosocial needs of ARCs will likely vary across disorders, requiring ever more personalized approaches to ensure that couples' needs are addressed. Ensuring that ARCs have access to the support of genetic counsellors is an important part of the care of these potentially vulnerable patients.

Several studies included in this review found that many infertile and sub-fertile ARCs who had carrier screening performed as part of their infertility work-up readily accepted PGT. Notably, PGT was commonly pursued also for relatively mild, low-penetrant, and treatable disorders (32, 34). This finding can be explained by several considerations. First, as the process of assisted reproduction already entails an array of medical interventions, integration of PGT into the IVF trajectory may be relatively uncomplicated, associated with little additional burden for the patient. Second, providers of assisted reproduction services may adopt a view whereby the conception of a child with any preventable genetic disorder, however mild, is considered an iatrogenic failure and should therefore be avoided through PGT (42, 43). Third, given that PGT takes place prior to conception, it can be argued that selection of embryos based on their predisposition to genetic diseases is less morally problematic than, for example, terminating an ongoing pregnancy for the same condition (42). While these factors potentially explain the appeal of PGT for all recessive disorders in the context of IVF, authors have also raised concerns over potential inequalities due to the fact that couples undergoing assisted reproduction may have access to more comprehensive testing options than couples in the general population (42).

Limitations

The purpose of this review was to gain insights into the reproductive choices of ARCs who learn about their reproductive risks through carrier screening. To this end, we only included studies reporting outcomes of carrier screening offers in the general population, that is, not limited to couples

and individuals with a previously known risk for having a child with a specific recessive disorder. Nevertheless, in several population-wide carrier screening offers included in this review, some ARCs had a known increased risk prior to participating in screening. At the same time, these studies did not always indicate whether a particular ARC had a pre-existing known risk or had first learned about their reproductive risk through carrier screening. Previous research has found that reproductive decisions may differ significantly between ARCs with a known personal or familial history for a recessive disorder and those who first learn about their reproductive risk through carrier screening (44). In the absence of this important information, we are limited in our ability to contextualize the reproductive decisions of ARCs reported in the studies. It should be noted that how prospective parents perceive the severity of a specific disease may change over time, particularly as new effective therapeutic interventions targeting the disease are developed. In several recessive diseases for which carrier screening has long been available, therapeutic options have improved over the past decades, resulting in increased life expectancy and better quality of life for patients. Potentially, this progress has implications for the reproductive decision-making of carrier couples. As a particular recessive disease is perceived increasingly treatable through improving medical interventions, fewer carrier couples may be inclined to prevent the birth of a child with this disease. Instead, they may use their carrier status information to prepare for the birth of an affected child, in order to initiate treatment early in the newborn's life. This consideration potentially limits direct comparability of studies around the reproductive decision-making of carrier couples, if such studies have been carried out decades apart. Finally, our systematic review only included studies published in English. As a consequence, it is possible that our search strategy failed to identify relevant publications in languages other than English. We sought to address this possibility by carefully reviewing references cited in the included articles, which did not lead to the identification of additional studies in other languages.

CONCLUSION

In this systematic review, we analysed available evidence around the reproductive decision-making of couples and female individuals at 1-in-4 risk of having a child with a recessive disorder (collectively referred to as at-risk couples – ARCs). By synthesizing reproductive outcomes reported in 19 publications, we found that most ARCs tended to act on their carrier status information, either through IVF-PGT or, if pregnant, using PNDx and subsequently deciding on whether to terminate an affected pregnancy. In general, studies showed that the clinical characteristics of a disorder, primarily its severity, significantly influenced the extent to which ARCs utilized preventive reproductive options. However, the studies also observed some heterogeneity in reproductive decisions within the same recessive disorders, suggesting that choices of ARCs can be determined by factors other than the clinical nature of the disorder. These findings highlight the importance of post-test genetic counselling and psychological support to ensure the provision of adequate care to ARCs. Given the growing availability and accessibility of expanded carrier screening (ECS), healthcare professionals

will increasingly be confronted by ARCs who receive a positive ECS test result. The insights gained through this systematic review shed more light on the reproductive decision-making process these couples undergo, which could better inform medical care provided to these potentially vulnerable patients.

AUTHOR'S CONTRIBUTIONS

J.C., D.C, E.V.S. and P.B designed the study. The comprehensive search approach, selection and screening of articles were carried out by D.C. and E.V.S. A first draft of the article was written by D.C. and critically discussed and revised by J.C., D.C., P.B., H.P., K.P. and G.M. P.B coordinated the study. All the authors have approved the final version.

EXPERT OPINION

Expanded carrier screening (ECS) is rapidly emerging as a new standard of care in reproductive medicine. The rise in ECS utilization is driven by a combination of different factors, including the growing interest in ECS among prospective parents, increasing coverage of testing by insurance companies, and, more recently, endorsement from reputable professional medical societies. Over the past few years, the size of ECS tests has grown to include several hundreds of recessive disorder genes which are typically analysed using next-generation sequencing methods. The outcome of this expansion is a highly comprehensive ECS test capable of identifying reproductive risks in prospective parents for a wide range of recessive disorders. However, the psychosocial implications of such a comprehensive ECS for future parents are far from uncomplicated. On the one hand, couples who, following an ECS test, learn that they are not carriers of a recessive disorder, can be reasonably certain that they will not have an affected child, since their residual risk is extremely low. On the other hand, couples who receive a positive test result will be faced with difficult decisions.

First, some of these couples will not be true biologic carriers; the purportedly pathogenic variants they carry may currently be misclassified and in reality not be causative of the disorder. This is particularly true in cases where low-penetrance pathogenic variants are involved. Since in the absence of family history for the disorder, no additional predictive information is available, such couples will need to make reproductive decisions under considerable uncertainty. Second, some carrier couples will learn that the disorder their future child is at risk of inheriting is associated with mild and treatable clinical symptoms. As illustrated by carrier screening program for Gaucher disease in Israel, such couples may find it challenging to decide whether it is warranted to act on their carrier status information and may even regret that they underwent screening in the first place. Third, a portion of carrier couples will be at risk of having a child with a severely debilitating or lethal recessive disease. Arguably, these couples stand to benefit the most from ECS, and the vast majority of them will decide not to have an affected child. However, the emotional challenges associated with altering

reproductive plans due to genetic risks should not be underestimated. Therefore, in all three scenarios, it is critical that couples are provided with adequate genetic counselling and continued psychological support throughout their reproductive trajectory.

It is safe to say that the ‘traditional’ carrier screening is disappearing, giving way to ECS. Going forward, we only expect the size of ECS panels to keep growing. Although there is an upper limit to the number of recessive disorders that can be added to ECS, it is highly likely that ECS tests of the future will also incorporate a sub-set of dominant and polygenic diseases. This is understandable: after all, the majority of prospective parents want to know as much as possible about their reproductive risks, whereas laboratories offering ECS tests strive to develop more comprehensive testing solutions than their competitors. What is critical to ensure is that these developments are coupled with efforts aimed at improving medical and psychosocial care for those couples who receive positive ECS test results.

Figure 1: Identification and selection of articles.

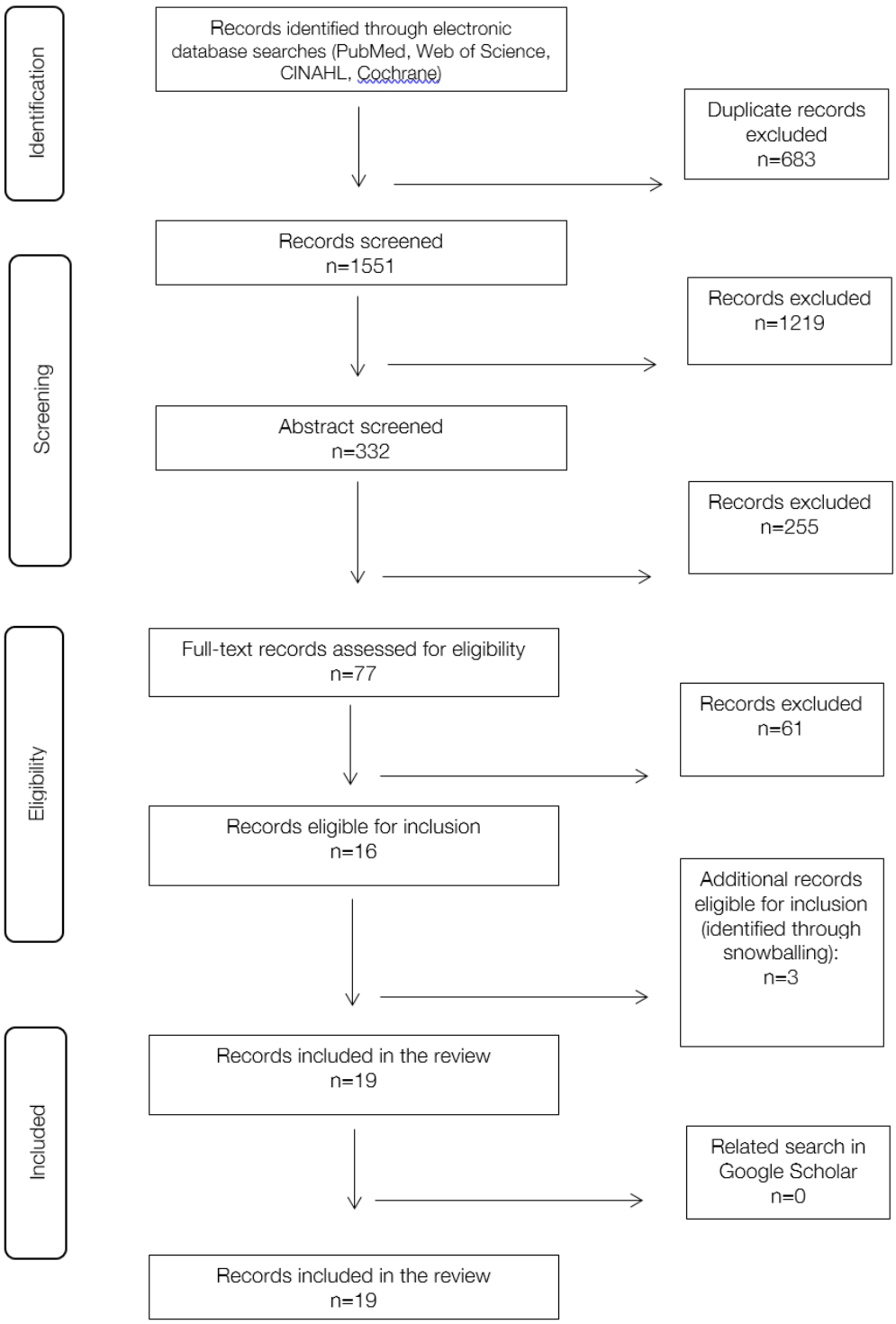


Table 1: Studies included in the systematic review

Author & publication year	Location	Type of carrier screening offered	Target population	Period of screening	Number of tests performed	Method for assessing reproductive outcomes
Livingstone et al. (1994) Brock et al. (1996)	United Kingdom (Edinburgh)	Population screening for CF	Women/couples attending a consultation at antenatal clinics	October 1990 - May 1995	17 544 couple units*	Retrospective outcomes review
Loader et al. (1996) Levenkron et al. (1997)	United States (Rochester, New York)	Population screening for CF	Female patients aged 18 or above considering pregnancy or already pregnant	1994 - 1995	4 879 females followed by 106 male partners of carriers	Prospective study
Mitchell et al. (1996)	Canada (Montreal)	Ethnicity-based (Ashkenazi Jewish) screening for TSD and Beta-thalassemia.	High school students aged 14-16	1973 - 1992	Tay-Sachs Disease: 14 844 students; Beta-thalassemia: 25 274 students	Retrospective outcomes review
Witt et al. (1996)	United States (California)	Population screening for CF	Pregnant women/couples attending a Kaiser Permanente facility for a medical visit	December 1991 - September 1992	5 161 females followed by 116 male partners of carriers	Prospective study
Kronn et al. (1998)	United States (New York)	Ethnicity-based (Ashkenazi Jewish) Carrier Screening for TSD, CF, and GD	Ashkenazi Jewish couples and individuals	January 1994 – 1997	1 000 individuals. (600 females; 400 males. Number of couples unknown)	Retrospective outcomes review
Lena-Russo et al. (2002)	France (Marseille)	Population screening for haemoglobinopathies	High school students aged 14-16	1978 - 1985	35 289 high school students	Retrospective outcomes review
Cronister et al. (2005)	United States (multi-centric)	Population-based screening for FXS	Women attending a genetic counselling session	2001 - 2002	2 292 females	Retrospective outcomes review
Zuckerman et al. (2007)	Israel	Ethnicity-based (Ashkenazi Jewish) screening for GD	Jewish couples considering pregnancy or in early pregnancy	January 1995 - March 2003	Unclear	Retrospective outcomes review; telephone interviews
Colah et al. (2008)	India (Mumbai)	Population screening for Beta-thalassemia	Pregnant women registered for their first antenatal check-up	1997 - 2003	61 935 females, followed by 713 male partners of carriers	Retrospective outcomes review
Christie et al. (2009)	Australia (New South Wales)	Population screening for CF	Females and couples considering pregnancy or early in pregnancy	January 2003 - December 2007	1 000 individuals	Prospective study
Massie et al. (2009)	Australia (Victoria)	Population screening for CF	Women or couples prior to pregnancy or in the early stages of pregnancy.	January 2006 - December 2008	3 000 females, 200 males (106 males were screened following a positive test result in their partner)	Prospective study
Tongsong et al. (2013)	Thailand	Population screening for thalassemia (alpha, beta, Haemoglobin E)	Pregnant women attending antenatal care clinics. (Anaemic patients and known carriers were excluded)	August 2009 - December 2011	12 874 females, followed by 3 229 male partners of carriers	Prospective study

Ghiossi et al. (2016)	United States	ECS (Counsyl's Family Prep ™ test for 108 disorders)	Individuals and couples	April 2014 - August 2015	207 095 individuals	Online survey
Franasiak et al. (2016)	United States (New Jersey)	ECS for more than 100 disorders (three different ECS panels were used)	Infertile and sub-fertile couples receiving fertility treatment	January 2011 - April 2014	6 643 individual tests in 3 738 couples	Retrospective outcomes review
Archibald et al. (2017)	Australia (Victoria)	Population screening for CF, SMA, and FXS	Females and couples considering pregnancy or in early pregnancy.	2012 - 2016	12 000 individuals (11 448 females, 552 males)	Prospective study
Mathijssen et al. (2018)	The Netherlands	Ethnicity-based (Dutch founder population) preconception/prenatal carrier screening for 4 recessive disorders**	Individuals originating from the genetically isolated village of Volendam.	September 2012 - June 2014	349 individuals from 195 couples	Semi-structured interviews
Taber et al. (2018)	United States	ECS (Counsyl's Foresight ™ test for 176 disorders)	Individuals and couples	September 2015 - December 2017	270 000+ individuals	Online survey

CF – Cystic Fibrosis; TSD – Tay-Sachs disease; SMA – Spinal Muscular Atrophy; FXS – Fragile X syndrome; GD – Gaucher disease; ECS – Expanded carrier screening;
* Couples where either only the female was screened or both partners were screened
** pontocerebellar hypoplasia type 2 (PCH2), fetal akinesia deformation sequence (FADS), rhizomelic chondrodysplasia punctata type 1, and osteogenesis imperfecta (OI) type IIB/ III.

Table 2: Reproductive decisions of carrier couples and female carriers of X-linked disorders

Study	Number of at-risk couples/females	Additional information	Reproductive outcomes in at-risk couples
Livingstone et al. (1994) Brock (1996)	CF: 22 couples		Twenty couples (91%) opted for prenatal diagnoses in a total of 27 pregnancies. Eight affected fetuses were identified and all eight affected pregnancies (100%) were terminated (including two affected pregnancies in the same couple). Two couples (9%), including one couple with a twin pregnancy, declined prenatal diagnosis.
Loader et al. (1996) Levenkron et al. (1997)	CF: 5 couples		Four couples (80%) elected to undergo PNDx. Of these, three couples were found to carry an unaffected fetus. The fourth coupled had a miscarriage as a result of amniocentesis. However, the couple requested PNDx in their subsequent pregnancy with the fetus found to be disease-free. One couple (20%) declined prenatal diagnosis, citing as the reason that they would not terminate an affected pregnancy.
Mitchell et al. (1996)	TSD: 16 couples (Including 6 couples with known risk)	*Estimates are based on the number of couples who sought genetic counselling*	The 16 carrier couples had a total of 32 pregnancies monitored through PNDx. Eight affected pregnancies were identified (including 4 in couples with known risk) and all eight (100%) pregnancies were terminated. Twenty-four unaffected children were born to the carrier couples
	Beta-Thalassemia: 32 couples (Including 8 couples with known risk)	*Estimates are based on the number of couples sought genetic counselling and the number of reported affected births*	Thirty-one (97%) couples had a total of 56 pregnancies monitored through PNDx. One couple (3%) had counselling only and elected to have no children. Twelve affected pregnancies were identified (including 4 in couples with known risk), 11 of which (92%) were electively terminated. One couple already had a child with beta-thalassemia and decided against terminating an affected pregnancy, delivering an affected child. In addition, one more affected child was born to a different couple due to the false-positive result of a CVS-based PNDx.
Witt et al. (1996)	CF: 7 couples		All seven couples (100%) elected PNDx. However, three couples miscarried prior to undergoing it. The remaining four couples all underwent PNDx, including one couple that had two pregnancies tested (i.e. five instances of PNDx in total). Of the five pregnancies tested, one was found to be affected. The couple was pregnant with twins, both of whom were homozygous for Phi508del. Following "lengthy deliberations and counselling", the couple decided to continue the pregnancy
Kronn et al. (1998)	CF: 2 couples		Both couples underwent PNDx. One pregnancy was found to be affected with CF and was electively terminated
	GD: 1 couple		The couple underwent PNDx. The fetus was found to be unaffected
	TSD: 1 couple		The couple underwent PNDx. The fetus was found to be unaffected
Lena-Russo et al. (2002)	Beta-thalassaemia: 4 couples	*Based on the number of couples who sought genetic counselling*	All four couples asked for genetic counselling and subsequently requested PNDx. This resulted in 8 instances of PNDx and the identification of three affected pregnancies, all of which were terminated. No affected children were born to these four parents
	Sickle cell disease: 2 couples	*Based on the number of reported cases of affected offspring [Retrospective estimates] The actual N of carrier couples may well have been higher*	Two affected children were born to participants of the screening program. One of the two carrier couples declined genetic counselling and did not undergo PNDx. In case of the other couple, the carrier status information was misunderstood by prospective parents who did not understand their reproductive risks.
Cronister et al. (2005)	FXS: 22 women	16 carriers of an intermediate allele (45-54 CGG repeats)	The 16 women were counselled on the low probability of an intermediate allele expanding into a full mutation. Fourteen women were offered PNDx for a reason unrelated to Fragile X syndrome. Twelve patients (86%) accepted the offer and 7 (50%) requested testing the fetus for Fragile X syndrome to gain reassurance. No expansion into full mutation was detected. Pregnancy outcomes are not known

		6 premutation carriers (55-200 CGG repeats);	Three patients (50%) declined PNDx. This included two carriers in the 60-65 CGG range, who were informed that they carried a cytogenically abnormal fetus and terminated based on these results alone. The third patient was a 55 CGG repeat carrier, who declined PNDx because of the low risk of an expansion and the female gender of the fetus. Three patients accepted PNDx. Two of these patients were found to have transmitted a normal allele to their fetus. One patient had transmitted a 74-CGG-repeat allele, but the fetus was female. Pregnancy outcomes are not known
Zuckerman et al. (2007)	GD: 83 couples	Mild Type 1 (non-neuropathic) GD: 70 couples *(64/70 couples were at risk of having an offspring homozygous for the N370S mutation)*	(Reproductive outcomes are known for 53 couples). All 53 couples had at least one pregnancy during the study period, with the number of total pregnancies being 73. Prenatal diagnoses were performed in 53/73 (73%) pregnancies. Thirteen affected pregnancies were identified (all homozygous for the N370S mutation); 2 of the affected pregnancies (15%) were terminated and 11 (85%) were carried to term.
		Moderate Type 1 (non-neuropathic) GD: 12 couples	All 12 couples had at least one pregnancy during the study period, with the number of total pregnancies being 17. Prenatal diagnoses were performed in 15/17 (88%) pregnancies. Three affected fetuses were identified, two of which (67%) were terminated: N370S/84insG genotype (terminated); L444P/R496H genotype (terminated); N370S/IVS2DS+1G-A genotype (carried to term).
		Severe type 2/3 GD: 1 couple	The couple was identified preconceptionally and did not pursue pregnancy
Colah et al. (2008)	Hemoglobinopathies: 37 couples		All couples were counselled. Sixteen couples (43%) did not come back for PNDx and were lost to follow-up. Four couples were ineligible for PNDx due to advanced pregnancy (3rd trimester) and 2 pregnancies were miscarried prior to PNDx. In total, 15 (41%) couples underwent prenatal diagnoses, resulting in the identification of 4 affected pregnancies. All four (100%) affected pregnancies were electively terminated
Christie et al. (2009)	CF: 4 couples	Two couples without known family history for CF	One couple was not pregnant and elected IVF with PGT, resulting in the conception of a CF-free pregnancy. The other couple was pregnant and pursued PNDx through CVS. The fetus was unaffected.
		Two couples with known family history for CF	Both couples were not pregnant. One of the couples became pregnant, and pursued PNDx through CVS. The couple was found to carry an affected fetus and chose to terminate the pregnancy. The other couple was not considering pregnancy yet but stated their interest in IVF/PGD at a later time.
Massie et al. (2009)	CF: 9 couples		Seven couples were pregnant or got pregnant shortly after carrier screening was performed. All seven (100%) couples underwent PNDx using CVS. Two affected pregnancies were identified and both (100%) were terminated. The remaining two couples who were not pregnant at the time of the study indicated they were likely to pursue IVF through PGT in subsequent pregnancies
Tongsong et al. (2013)	Thalassemias: 281 couples	*b-thalassemia/HbE disease: 156 couples; HbBart's disease: 87 couples; b-thalassemia major: 46 couples; (8 couples were at risk for more than one of these disorders)*	273/281 (97%) couples underwent prenatal diagnoses and 56 affected fetuses were identified. Of the affected pregnancies, 55 (98%) were terminated, with one couple (2%) choosing to carry an affected pregnancy to term and delivering a diseased child (b-thalassemia/HbE disease). Among the 8 couples who decided not to undergo prenatal diagnosis, 2 couples had an affected child, one with b-thalassemia/HbE disease and the other with b-thalassemia major.
Ghiossi et al. (2016)	Various recessive disorders: 64 couples	"Profound" disorders (e.g. Smith-Lemli-Opitz Syndrome; Carnitine Palmitoyltransferase II Deficiency): 11 couples	Seven carrier couples were identified preconceptionally, six of whom (86%) had undergone or intended to undergo IVF through PGT. Reproductive outcomes or intentions of one couple (14%) were unclear. Four carrier couples were identified during pregnancy, two of whom (50%) had pursued PNDx. Two pregnant couples (50%) had decided against PNDx. In total, 8/11 (73%) of the couples reported an action to prevent the birth of an affected child.
		"Severe" disorders (e.g CF; Biotinidase deficiency): 34 couples	Twenty-three carrier couples were identified preconceptionally, 18 of whom (78%) had taken or intended to take a preventive measure (IVF/PGT and PNDx were indicated by 13 (57%) and 5 (22%) couples, respectively). Reproductive outcomes or intentions of two couples were unclear. Eleven couples were identified during pregnancy, six of whom (55%) had pursued PNDx. In total, 24/34 (71%) of couples reported an action to prevent the birth of an affected child

		"Moderate" disorders (e.g. Alpha-1 Antitrypsin Deficiency; GJB2-related DFNB1 Nonsyndromic Hearing Loss): 19 couples	Fifteen carrier couples were identified preconceptionally, 4 of whom (27%) had taken or intended to take a preventive measure (IVF/PGD and PNDx were indicated by 3 couples (20%) and 1 couple (7%), respectively). Reproductive outcomes or intentions of one couple (7%) were unclear. Four carrier couples were identified during pregnancy, none of whom (0%) had pursued prenatal diagnosis. In total, 4/19 (21%) of the couples reported an action to prevent the birth of an affected child
Franasiak et al. (2016)	CF: 3 couples	All three couples had a known risk of conceiving a CF-affected child and were screened using ECS for other disorders	In all three cases, the couples planned IVF-PGT, but none of them underwent the procedure. In one case, the couple became pregnant and had a PNDx through CVS. The remaining two couples elected not to pursue fertility treatment and were not followed up on.
	Carnitine palmitoyltransferase II deficiency: 1 couple	Both partners were carriers of CPT2:c.1238_1239delAG (Q413fs)	The couple underwent IVF-PGT and delivered an unaffected child
	GJB2-related DFNB-1 Nonsyndromic Hearing Loss: 1 couple	Both partners were carriers of GJB2: 35delG	The couple underwent IVF-PGT and delivered an unaffected child
	GD: 1 couple	Both partners were carriers of GBA: c.1226A>G	The couple underwent IVF-PGT and delivered an unaffected child
	Dihydrolipoamide dehydrogenase deficiency: 1 couple	Both partners were carriers of DLD: c.685G>T	The couple underwent IVF-PGT and delivered an unaffected child
Archibald et al. (2017)	CF: 14 couples		Nine couples were pregnant and all of them (100%) had PNDx. Four affected pregnancies were identified, of which three (75%) were terminated.
	SMA: 1 couple		The carrier couple was pregnant and pursued PNDx. The fetus was found to be affected and the couple elected pregnancy termination
	FXS: 35 females (premutation carriers)	34 premutation (PM) carriers (55 – 200 CGG repeats); 1 full mutation (FM) carrier of 200+ CGG repeats 55 - 64 (PM): 24 carriers 65 – 74 (PM): 8 carriers 75 – 84 (PM): 2 carriers 85 – 94 (PM): 1 carrier 100 – 199 (PM): 1 carrier 200+ (FM): 1 carrier	Twenty-two of the 35 carriers were pregnant at the time of the study. Most pregnant carriers (16/22; 73%) underwent PNDx, 10 of whom were found to have passed on an expanded FMR1 allele to the fetus. In eight fetuses, the FMR1 allele was in the PM range. However, in two pregnancies, PM alleles had expanded to FMs (71 → 113/1,607 mosaic male; 123 → 508–1,118 female) and both pregnancies were electively terminated. Of the six carriers who did not have PNDx, two miscarried; two carriers did not pursue further testing due to low risk or because she would not terminate an affected pregnancy (carriers of 55 CGG repeats and 72 CGG repeats, respectively); two carriers (55 and 57 CGG repeats) utilized non-invasive prenatal screening to determine the sex of the fetus and decided against PNDx after learning the fetus was female.
Mathijssen et al. (2018)	Disorders predominant in the Dutch founder population: 8 couples	pontocerebellar hypoplasia type 2 (PCH2): 5 couples; fetal akinesia deformation sequence (FADS): 2 couples; osteogenesis imperfecta (OI): 1 couple	Reproductive decisions of 7 couples are known. One couple (14%) refrained from having more children. Six couples had at least one more pregnancy and utilized PNDx (4 couples), IVF-PGT (1 couple), or both IVF-PGT and PNDx (1 couple). In total, 8 at-risk pregnancies were monitored through PNDx. Five pregnancies were unaffected, while 3 were found to be affected and all three (100%) were electively terminated.
Taber et al. (2018)	Various recessive disorders: 389 couples [Data are presented for 368 couples who specified the disorder for which their (future) pregnancies were at risk].	"Profound" disorders (e.g. Smith-Lemli-Opitz Syndrome; Tay-Sachs Disease): 49	Thirty-four carrier couples were identified preconceptionally, 31 of whom (91%) had pursued or were planning to undertake one or more of the following preventive actions: IVF-PGT - 23 couples (68%); PNDx - 8 couples (24%); Donor gametes - 4 couples (12%); Adoption - 3 (8.8%); No longer planning to get pregnant - 1 couple (2.9%).
			Fifteen carrier couples were identified during pregnancy, 7 of whom (47%) underwent PNDx. Four pregnancies were found to be affected. Two of the affected pregnancies (50%) were electively terminated, while in two cases (50%), couples chose to carry an affected pregnancy to term

		"Severe" disorders (e.g. CF; Biotinidase deficiency): 257 couples	153 carrier couples were identified preconceptionally, 118 of whom (77%) had pursued or were planning to undertake one or more of the following preventive actions: IVF/PGT - 92 couples (60%); PNDx - 31 couples (20%); Donor gametes - 11 couples (7.2%); Adoption - 9 couples (5.9%); No longer planning to get pregnant - 6 couples (3.9%).
			104 carrier couples were identified during pregnancy, 40 of whom (38%) underwent PNDx. Elven pregnancies were found to be affected and five affected pregnancies (45%) were terminated, with six affected pregnancies (56%) having been carried to term.
		"Moderate" disorders (e.g. GJB2-related DFNB1 Nonsyndromic Hearing Loss; Congenital adrenal hyperplasia): 62 couples	Thirty-four carrier couples were identified preconceptionally, 22 of whom (65%) had pursued or were planning to undertake one or more of the following preventive actions: IVF/PGT - 20 couples (59%); PNDx - 6 couples (18%); Donor gametes - 1 couple (2.9%); No longer planning to get pregnant - 1 couple (2.9%).
			Twenty-eight carrier couples were identified during pregnancy, 8 of whom (29%) underwent PNDx. Four pregnancies were found to be affected and one affected pregnancy (25%) was terminated, with three (75%) couples choosing to carry an affected pregnancy to term.

CF – Cystic Fibrosis; TSD – Tay-Sachs disease; SMA – Spinal Muscular Atrophy; FXS – Fragile X syndrome; GD – Gaucher disease; ECS – Expanded carrier screening
PNDx – prenatal diagnosis; CVS – chorionic villus sampling; IVF-PGT – in vitro fertilization with pre-implantation genetic testing;

REFERENCES

1. Henneman L, Borry P, Chokoshvili D, Cornel MC, van El CG, Forzano F, et al. Responsible implementation of expanded carrier screening. European journal of human genetics : EJHG. 2016;24(6):e1-e12.
2. Metcalfe SA. Carrier screening in preconception consultation in primary care. J Community Genet. 2012;3(3):193-203.
3. Cornel MC. A higher impact of less specific preconception carrier screening: a plea for a “one size fits all” approach. Journal of Xiangya Medicine. 2017;2:14-.
4. Borry P, Henneman L, Lakeman P, ten Kate LP, Cornel MC, Howard HC. Preconceptional genetic carrier testing and the commercial offer directly-to-consumers. Human reproduction (Oxford, England). 2011;26(5):972-7.
5. Kaback MM. Population-based genetic screening for reproductive counseling: the Tay-Sachs disease model. European journal of pediatrics. 2000;159 Suppl 3:S192-5.
6. Zlotogora J, Carmi R, Lev B, Shalev SA. A targeted population carrier screening program for severe and frequent genetic diseases in Israel. European journal of human genetics : EJHG. 2009;17(5):591-7.
7. De Wert GM, Dondorp WJ, Knoppers BM. Preconception care and genetic risk: ethical issues. J Community Genet. 2012;3(3):221-8.
8. Scott SA, Edelmann L, Liu L, Luo M, Desnick RJ, Kornreich R. Experience with carrier screening and prenatal diagnosis for 16 Ashkenazi Jewish genetic diseases. Human mutation. 2010;31(11):1240-50.
9. Chokoshvili D, Vears D, Borry P. Expanded carrier screening for monogenic disorders: where are we now? Prenat Diagn. 2018;38(1):59-66.
10. Lazarin GA, Haque IS, Nazareth S, Iori K, Patterson AS, Jacobson JL, et al. An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals. Genet Med. 2013;15(3):178-86.
11. Chokoshvili D, Vears DF, Borry P. Growing complexity of (expanded) carrier screening: Direct-to-consumer, physician-mediated, and clinic-based offers. Best practice & research Clinical obstetrics & gynaecology. 2017;44:57-67.
12. Edwards JG, Feldman G, Goldberg J, Gregg AR, Norton ME, Rose NC, et al. Expanded carrier screening in reproductive medicine-points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine. Obstet Gynecol. 2015;125(3):653-62.
13. Committee Opinion No. 691: Carrier Screening for Genetic Conditions. Obstet Gynecol. 2017;129(3):e41-e55.

14. Lazarin GA, Haque IS. Expanded carrier screening: A review of early implementation and literature. Seminars in perinatology. 2016;40(1):29-34.
15. Beauchamp KA, Johansen Taber KA, Muzzey D. Clinical impact and cost-effectiveness of a 176-condition expanded carrier screen. Genet Med. 2019;21(9):1948-57.
16. Martin J, Asan, Yi Y, Alberola T, Rodríguez-Iglesias B, Jiménez-Almazán J, et al. Comprehensive carrier genetic test using next-generation deoxyribonucleic acid sequencing in infertile couples wishing to conceive through assisted reproductive technology. Fertility and sterility. 2015;104(5):1286-93.
17. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100.
18. Livingstone J, Axton RA, Gilfillan A, Mennie M, Compton M, Liston WA, et al. Antenatal screening for cystic fibrosis: a trial of the couple model. BMJ (Clinical research ed). 1994;308(6942):1459-62.
19. Brock DJ. Prenatal screening for cystic fibrosis: 5 years' experience reviewed. Lancet (London, England). 1996;347(8995):148-50.
20. Loader S, Caldwell P, Kozyra A, Levenkron JC, Boehm CD, Kazazian HH, Jr., et al. Cystic fibrosis carrier population screening in the primary care setting. Am J Hum Genet. 1996;59(1):234-47.
21. Levenkron JC, Loader S, Rowley PT. Carrier screening for cystic fibrosis: test acceptance and one year follow-up. American journal of medical genetics. 1997;73(4):378-86.
22. Mitchell JJ, Capua A, Clow C, Scriver CR. Twenty-year outcome analysis of genetic screening programs for Tay-Sachs and beta-thalassemia disease carriers in high schools. Am J Hum Genet. 1996;59(4):793-8.
23. Witt DR, Schaefer C, Hallam P, Wi S, Blumberg B, Fishbach A, et al. Cystic fibrosis heterozygote screening in 5,161 pregnant women. Am J Hum Genet. 1996;58(4):823-35.
24. Kronn D, Jansen V, Ostrer H. Carrier screening for cystic fibrosis, Gaucher disease, and Tay-Sachs disease in the Ashkenazi Jewish population: the first 1000 cases at New York University Medical Center, New York, NY. Archives of internal medicine. 1998;158(7):777-81.
25. Lena-Russo D, Badens C, Aubinaud M, Merono F, Paolasso C, Martini N, et al. Outcome of a school screening programme for carriers of haemoglobin disease. Journal of medical screening. 2002;9(2):67-9.
26. Cronister A, DiMaio M, Mahoney MJ, Donnenfeld AE, Hallam S. Fragile X syndrome carrier screening in the prenatal genetic counseling setting. Genet Med. 2005;7(4):246-50.
27. Zuckerman S, Lahad A, Shmueli A, Zimran A, Peleg L, Orr-Urtreger A, et al. Carrier screening for Gaucher disease: lessons for low-penetrance, treatable diseases. Jama. 2007;298(11):1281-90.
28. Colah R, Surve R, Wadia M, Solanki P, Mayekar P, Thomas M, et al. Carrier screening for beta-thalassemia during pregnancy in India: a 7-year evaluation. Genetic testing. 2008;12(2):181-5.

29. Christie LM, Ingrey AJ, Turner GM, Proos AL, Watts GE. Outcomes of a cystic fibrosis carrier testing clinic for couples. The Medical journal of Australia. 2009;191(9):499-501.
30. Massie J, Petrou V, Forbes R, Curnow L, Ioannou L, Dusart D, et al. Population-based carrier screening for cystic fibrosis in Victoria: the first three years experience. The Australian & New Zealand journal of obstetrics & gynaecology. 2009;49(5):484-9.
31. Tongsong T, Charoenkwan P, Sirivatanapa P, Wanapirak C, Piyamongkol W, Sirichotiyakul S, et al. Effectiveness of the model for prenatal control of severe thalassemia. Prenat Diagn. 2013;33(5):477-83.
32. Franasiak JM, Olcha M, Bergh PA, Hong KH, Werner MD, Forman EJ, et al. Expanded carrier screening in an infertile population: how often is clinical decision making affected? Genet Med. 2016;18(11):1097-101.
33. Archibald AD, Smith MJ, Burgess T, Scarff KL, Elliott J, Hunt CE, et al. Reproductive genetic carrier screening for cystic fibrosis, fragile X syndrome, and spinal muscular atrophy in Australia: outcomes of 12,000 tests. Genet Med. 2018;20(5):513-23.
34. Ghiossi CE, Goldberg JD, Haque IS, Lazarin GA, Wong KK. Clinical Utility of Expanded Carrier Screening: Reproductive Behaviors of At-Risk Couples. Journal of genetic counseling. 2018;27(3):616-25.
35. Mathijssen IB, Holtkamp KCA, Ottenheim CPE, van Eeten-Nijman JMC, Lakeman P, Meijers-Heijboer H, et al. Preconception carrier screening for multiple disorders: evaluation of a screening offer in a Dutch founder population. European journal of human genetics : EJHG. 2018;26(2):166-75.
36. Johansen Taber KA, Beauchamp KA, Lazarin GA, Muzzey D, Arjunan A, Goldberg JD. Clinical utility of expanded carrier screening: results-guided actionability and outcomes. Genet Med. 2019;21(5):1041-8.
37. Chokoshvili D, Vears DF, Borry P. Reproductive autonomy in expanded carrier screening: more than meets the eye? Expert review of molecular diagnostics. 2018;18(12):993-4.
38. Myring J, Beckett W, Jassi R, Roberts T, Sayers R, Scotcher D, et al. Shock, adjust, decide: reproductive decision making in cystic fibrosis (CF) carrier couples--a qualitative study. Journal of genetic counseling. 2011;20(4):404-17.
39. Ioannou L, Delatycki MB, Massie J, Hodgson J, Lewis S. "Suddenly Having two Positive People who are Carriers is a Whole New Thing" - Experiences of Couples Both Identified as Carriers of Cystic Fibrosis Through a Population-Based Carrier Screening Program in Australia. Journal of genetic counseling. 2015;24(6):987-1000.
40. Zuckerman S, Lahad A, Zimran A, Levy-Lahad E, Sagi M. Attitudes of couples identified through screening as carriers of Gaucher disease type 1. Clinical genetics. 2008;74(6):566-70.
41. Chokoshvili D, Borry P, Vears DF. A systematic analysis of online marketing materials used by providers of expanded carrier screening. Genet Med. 2018;20(9):976-84.

42. Chokoshvili D, Van Steijvoort E, Borry P. Ethical challenges in offering expanded carrier screening in the context of third-party reproduction. Médecine De La Reproduction, Gynécologie Et Endocrinologie. 2018;20(4):334-9.
43. Mertes H, Lindheim SR, Pennings G. Ethical quandaries around expanded carrier screening in third-party reproduction. Fertility and sterility. 2018;109(2):190-4.
44. Scotet V, Duguépéroux I, Audrézet MP, Blayau M, Boisseau P, Journel H, et al. Prenatal diagnosis of cystic fibrosis: the 18-year experience of Brittany (western France). Prenat Diagn. 2008;28(3):197-202.

CHAPTER 4

EXPANDED CARRIER SCREENING IN FLANDERS (BELGIUM): AN ONLINE SURVEY ON THE PERSPECTIVES OF NONPREGNANT REPRODUCTIVE-AGED WOMEN

Van Steijvoort, E., Devolder, H., Geysen, I., Van Epperzeel, S., Peeters, H., Peeraer, K., Matthijs, G. & Borry, P. (2021). Expanded carrier screening in Flanders (Belgium): an online survey on the perspectives of nonpregnant reproductive-aged women. *Personalized medicine, 18*(4), 361-373. doi: 10.2217/pme-2020-0155

ABSTRACT

AIM: Despite a considerable interest in expanded carrier screening (ECS) in the general population, actual uptake of ECS remains low. More insights are needed to better understand the perspectives of reproductive-aged individuals.

MATERIALS & METHODS: Nonpregnant women of reproductive age recruited through public pharmacies throughout Flanders (Belgium) were invited to participate in an online survey.

RESULTS: Most participants (63.6%) indicated they would consider ECS for themselves in the future. About one in two participants showed a positive attitude toward ECS.

CONCLUSION: This study reports valuable insights in the perspectives of nonpregnant reproductive-aged women in Flanders (Belgium) regarding ECS that can be used in the ongoing debate on the responsible implementation of ECS.

Keywords: attitudes / expanded carrier screening / genetic counselling / health policy / intention / knowledge/ patient perspectives / preconception care / reproductive genetics / survey

LAY ABSTRACT

Previous studies have reported a considerable interest in carrier screening for hereditary conditions among individuals in the general population, but actual uptake remains low. This study examines the perspectives of nonpregnant reproductive-aged women in Flanders (Belgium) regarding expanded carrier screening (ECS) for hereditary conditions to gain more insights in factors that possibly influence the opinions of reproductive-aged women. These insights are crucial to ensure a responsible implementation of ECS within healthcare services and to make sure that future parents are making informed choices when they are presented with the choice to accept or decline ECS. The results of this study can be used by healthcare providers interacting with couples planning a pregnancy to improve pre-/post-test counselling services. Which in turn can help to manage expectations and reduce misconceptions among potential users of ECS.

SUMMARY POINTS

• Expanded carrier screening (ECS) allows the identification of couples who have an increased risk of conceiving a child affected with an autosomal recessive or X-linked condition.

• Information gained through ECS can help future parents to make informed reproductive decisions regarding their offspring.

• Prior to conception, carrier couples can opt for IVF/ICSI combined with pre-implantation genetic testing, prenatal diagnosis, gamete donation, adoption or refraining from having children together.

• The aim of this study was to explore perspectives of nonpregnant reproductive-aged women in Flanders (Belgium) regarding ECS and to identify individual's characteristics that possibly influence these perspectives.

• The majority of the women in our study sample assessed offering ECS to couples with a (future) child wish to be acceptable.

• Most participants showed the intention to participate in ECS in the future, but a considerable number of participants were still undecided about their intention to participate in ECS.

• Participants preferred ECS to be available through the gynecologist, to receive individual test results and to have a free choice in the list of conditions for which they would be screened. Most participants were willing to pay for ECS themselves, yet the amount they would be willing to pay is considerably lower than the costs of the current test offer.

• Efforts should be made to educate/engage primary healthcare providers in preconception care to make sure that couples planning a pregnancy are informed in a timely manner about the possibility to have ECS. As not everyone may be willing to delay reproductive plans while waiting for their results, these services should be available to individuals in their early reproductive years to allow enough time for reproductive planning following result disclosure.

INTRODUCTION

The average genomic carrier burden for severe paediatric recessive pathogenic variants in humans is estimated at 2.8 pathogenic variants per person, ranging from 0 to 7 (1). According to estimates, 1–2% of couples in the general population are 'carrier couples' (where both partners are carriers of the same pathogenic variant) and therefore have an increased risk of conceiving a child with a genetic condition (2). Carriers of recessive pathogenic variants are typically healthy and therefore often unaware of their carrier status. As a result, 'carrier couples' are in most cases only identified after the birth of a child with a genetic condition. When both partners are carriers of the same autosomal recessive condition, they have a 25% chance of conceiving a child that will be affected by that condition in each pregnancy (3). When the future mother is a carrier of an X-linked condition, there is a 50% chance that the couple's male offspring will be affected. In the last decade, expanded carrier screening (ECS) has been made available to (prospective) parents by multiple (commercial) providers (4).

Through ECS, individuals or couples can be screened for a large number of recessive conditions at once. The information gained through ECS can help future parents to make informed reproductive decisions regarding their offspring. Prior to conception, carrier couples can opt for in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) combined with pre-implantation genetic testing, prenatal diagnosis, gamete donation, adoption or refraining from having children together. While couples undergoing ECS during an already established pregnancy only have the option to additionally undergo prenatal diagnosis to confirm the screening results when they are identified as a carrier couple. When the fetus is found to be affected, couples can either decide to terminate the pregnancy or to prepare for a child with a recessive condition.

In 2017, the Superior Health Council (SHC) of Belgium published an advisory report regarding ECS in a reproductive context (5). The report contained a specific set of recommendations to ensure responsible implementation of ECS in the Belgian healthcare system. In consequence, the Belgian medical centres for human genetics (CME) have jointly responded to the recommendations by establishing an outline for the development and introduction of an ECS test for the Belgian population including more than 1000 genes associated with autosomal recessive and X-linked hereditary conditions. The carrier screening offer, which became available in October 2019, is intended specifically for couples considering having children in the future and is therefore only offered preconceptionally to reproductive partners. The test is performed by taking a blood sample from both partners simultaneously. Disclosure of test results is mainly couple-based, where carrier status is only communicated when both partners carry a pathogenic or likely pathogenic disease-causing variants in the same gene. In addition, it was decided to report individual carrier status for seven of the most frequent autosomal recessive conditions (such as cystic fibrosis and spinal muscular atrophy) and the X-linked conditions (such as Fragile X syndrome) included in the test panel to allow

the identification of carriers in the population through cascade testing. In its advisory report, the SHC underlined among others the importance to assess the intention of the target population to participate in ECS and the need for a public debate on the implementation of ECS in the Belgian healthcare setting.

Within our previous published systematic review (6), we identified a limited number of empirical studies that assessed the interest in ECS among individuals and couples in the general population. Results demonstrated a considerable interest (32–76%) in ECS among individuals in the general population. However, actual uptake (8–50%) of ECS seemed to be lower than reported intentions to undergo ECS. In addition, various studies reported conflicting results on the possible influence of certain factors (such as age, religiosity, education level, having children, having a [future] child wish, the familiarity with genetic conditions and prior knowledge of ECS) on the intention to participate in ECS/uptake. As these studies used convenience sampling or targeted very specific groups within the population who were conveniently available to participate, the findings of these studies have to be interpreted with caution and should not be generalized. To our knowledge, very little research has been done on this topic within Belgium. More scientifically reliable data are needed to gain more insights in the opinion of reproductive-aged individuals considering having children in the future. The aim of this study was to explore perspectives of nonpregnant reproductive-aged women in Flanders (Belgium) regarding ECS and to identify individual's characteristics that possibly influence these perspectives.

MATERIALS & METHODS

Study Design

Within this study, we tried to explore the perceived susceptibility of being a carrier/conceiving a child with a hereditary condition, the acceptability of offering ECS, the intention to participate in ECS, knowledge of ECS, attitudes toward ECS and preferences for the practical organization of a population-based ECS offer among nonpregnant reproductive-aged women in Flanders (Belgium). In addition, we also sought which socio-demographic characteristics may influence these factors. To do so, we carried out a novel approach to recruit nonpregnant women of reproductive age who purchased a prescribed contraceptive at a public pharmacy within Flanders. The choice to recruit through these public pharmacies was made based on the results of a nationwide health survey that was conducted in 2018. The results of this survey showed that 83.8% of sexually active women aged 15–49 in Belgium had used a (prescribed) contraceptive in the past 12 months (7). As (prescribed) contraceptives are usually purchased through public pharmacies in Belgium we assumed to reach a broad and diverse population by applying this recruitment approach.

Participants & procedures

Pharmacists of public pharmacies (n = 315) throughout Flanders (Belgium) were asked to distribute flyers with an invitation to participate in an online survey about ECS to nonpregnant women of reproductive age (18–49 years) who came in for a prescribed contraception. A good geographical spread throughout Flanders and a correct balance of rural and urban areas were taken into account when selecting the public pharmacies. Researchers went to each selected public pharmacy to explain the study aim and approach. As a reminder, the research team recontacted pharmacists willing to distribute flyers by telephone approximately 1 month after the initial contact moment. The online survey could be administered through the link or QR-code mentioned on the distributed flyers. Prior to completing the questionnaire participants were briefly informed about ECS (Supplementary Text A). The questionnaire was only available in Dutch and took approximately 15 min to complete. The online questionnaire was available between May 2019 and January 2020.

Survey instrument

The questionnaire (Supplementary Text B) used in the study was a compilation of questionnaires used in earlier studies (8-14) and newly developed questions. Socio-demographic characteristics that were requested from participants included age, highest level of completed education, religiosity, extent of religious involvement, having children, having a (future) child wish and relationship status. In order to assess the familiarity with hereditary conditions, participants were asked if they had ever had a consultation at the CME. Perceived susceptibility of being a carrier/conceiving a child with a hereditary condition, the acceptability of offering ECS and the intention to participate in ECS were measured using a 5-point Likert scale. Three items, also using a 5-point Likert scale, measured reflections of participants regarding the possible pressure on future parents to undergo ECS, the possible increase in anxiety for couples considering pregnancy and the possibility of devaluation of the lives of people living with hereditary conditions. A total of 14 knowledge questions were compiled into a knowledge scale. These items were a compilation of earlier studies (10, 13) and items that were newly developed by the research team for the purpose of this study. The knowledge scale was developed to assess knowledge of the following key concepts: carrier status of recessive conditions, autosomal recessive inheritance, X-linked recessive inheritance, preconceptional ECS, target group ECS, residual risk and available reproductive options for carrier couples. Each knowledge question could be answered by the participant as ‘true’, ‘false’ or ‘I don’t know’. The attitude scale used in this study included five bipolar words pairs (harmful/beneficial; unimportant/important; bad thing/good thing; not reassuring/reassuring; undesirable/desirable). This scale has been developed and validated in a previous study investigating women’s attitudes toward non-invasive prenatal test (NIPT) in the prenatal setting (15, 16). Finally, participants were asked to indicate their preferred manner through which ECS should be available, if they preferred individual or couple-based reporting of test results, their preferred level of involvement in the choice of the test-offer (all or

nothing, categories with similar conditions, free choice), their willingness to pay for ECS and the amount they would be willing to pay out-of-pocket.

Data analyses

Statistical analyses were performed using IBM SPSS® Statistics 26 for Windows. Descriptive analyses were used to describe the characteristics of the participants within our sample. To ensure meaningful comparison across groups we dichotomized all socio-demographic variables with more than two groups as followed: age (18–34 years; 35–49 years), highest level of completed education (low/intermediate and high), extent of religious involvement (not active; [somewhat] active), (future) child wish (yes and no/I'm not sure) and relationship status (not living together and living together/married). The number of participants that were willing to pay for an ECS test themselves was recoded from five to three groups for further analysis (<150 euro/150–300 euro/>300 euro). Nonparametric statistical tests were used to compare differences between independent groups. When both the independent and dependent variables were at the nominal level of measurement, we performed the Chi-Square test of independence. When the critical assumptions for the Chi-Square test of independence were not met, we carried out a Fisher's Exact test (2 × 2 tables) or a Fisher-Freeman-Holton (r × c tables). The Mann–Whitney U test was used to compare differences between two groups (dichotomous demographic variables) on a dependent variable that was at least at the ordinal level of measurement. For nonidentical distributions, statistically significant differences in the mean ranks of the dependent variable in terms of the two groups were determined. A two-sided p-value < 0.05 was considered statistically significant. We hypothesized that no significant differences (H0) would be found among different groups.

Knowledge & attitude scale

Frequencies were calculated for each knowledge question to give an overview of participant's answers. Subsequently, a knowledge score (min 0 to max 14) was calculated for each participant by combining the responses of the 14 knowledge items. If a question was answered correctly this resulted in one point. No points were given for questions that were answered incorrectly or when participants indicated not knowing the answer. Missing data on the knowledge questions were also treated as incorrect answers. Finally, a new categorical variable was created by dividing the knowledge score into three categories: 'low knowledge' (0–4 correct answers), 'moderate knowledge' (5–9 correct answers) and 'high knowledge' (10–14 correct answers). Based on the answers of the five bipolar word pairs we computed an overall attitude score (min 5 to max 25). This new variable was also reclassified into three categories: negative attitude (5–11), neutral attitude (12–18) and positive attitude (19–25). Reliability of the knowledge and attitude scales were assessed using Cronbach's alpha (Table 1). The alpha coefficient for the attitude scale indicated good internal reliability (five items, $\alpha = 0.908$). Retention of any of the five items would have resulted in a lower Cronbach's alpha. The reliability analyses for the knowledge scale showed a lower internal reliability

(14 items, α = 0.626). Similar to the attitude scale, removing one of the knowledge items did not result in a higher Cronbach's alpha (17).

Ethics

The study protocol received ethical approval from the Research Ethics Committee UZ/KU Leuven (MP010414). Participants were informed that participation was voluntary, that they had the right not to participate or to withdraw at any time. As participants had to actively use the link/QR-code to complete the online survey we opted for the 'opt-in' approach. If participants had questions, they could contact the research team through the provided contact information.

RESULTS

Socio-demographic

A total of 191 women used the link or QR-code to access the online survey. Data from 40 participants were excluded from further analysis due to incomplete completion of the questionnaire. Our sample comprised of 151 nonpregnant reproductive-aged women (18–49), of which 80.1% were between 18 and 34 years of age. More than half of participants (54.3%) held an academic degree from a University or a PhD, 21.9% had completed nonuniversity higher education and 23.8% did not complete any higher education studies. Only 27.8% of participants indicated to be religious, of which 26.2% stated to be (somewhat) actively involved in their religion. A majority of participants were in a relationship (71.5%), did not have children (75.5%) and expressed having a (future) child wish (69.5%). Only ten participants (6.6%) had had a consultation at a CME (Table 2).

Perceived susceptibility (risk perception)

Most participants (57.6%) estimated their chance of being a carrier of a hereditary condition (very) low. Participants who already had children (mean rank = 60.18) estimated their chance of being a carrier of a hereditary condition to be lower compared with participants not having children (mean rank = 81.14) (p = 0.008). Those expressing a (future) child wish (mean rank = 81.87) estimated their chance of being a carrier of a hereditary condition to be higher than participants indicating not having a (future) child wish or being unsure about it (mean rank = 62.61) (p = 0.009). Finally, women who already had had a consultation at a CME estimated their chance of being a carrier for a hereditary condition higher (mean rank = 106.35) compared with those who have not had a consult (mean rank = 73.85) (p = 0.018) (Table 3). Similar results were found regarding the perceived susceptibility of conceiving a child with a hereditary condition, where most women (65.6%) also estimated their risk to be (very) low. Women who clearly expressed having a future child wish (mean rank = 81.66) perceived their risk to conceive a child with a hereditary condition to be higher compared with those women who were unsure or did not have a future child wish (mean rank = 63.08) (p = 0.012). Participants who already had a consultation at a CME also estimated their chance

of conceiving a child with a hereditary condition to be higher (mean rank = 122.15) in comparison to those who haven't had a consult prior to the study (mean rank = 72.73) ($p < 0.001$) (Table 3).

Acceptability & Intention to participate in ECS

Offering ECS to couples with a child wish was assessed as (totally) acceptable by most participants (83.5%). A small proportion of our sample (6.3%) valued offering ECS to couples with a child wish as (totally) unacceptable. No statistically significant differences were found when comparing the acceptability of offering ECS to couples with a child wish among different independent groups (Table 4). A majority of the women within our sample (63.6%) would definitely or probably consider participating in ECS in the future, whereas 16.5% of participants reported to definitely or probably not to be willing to participate in ECS. Almost one in five participants (19.9%) were still undecided about their intention to participate in ECS (Table 4). Our comparative analysis showed that younger participants (age 18–34) expressed a higher intention to participate in ECS (mean rank = 79.61) compared with older participants (age 35–49; mean rank = 61.43)
($p = 0.034$).

Knowledge

The mean knowledge score for our study sample was 10.6 (standard deviation 2.61, interquartile range [IQR] 9–12). A Mann–Whitney U test revealed that knowledge scores were statistically higher in women with a high level of completed education (mean rank = 83.37) compared with those with a low/moderate level of completed education (mean rank = 51.61) ($p < 0.001$) (Table 5). The majority of the women within our sample (71.5%) had a high knowledge level based on our newly developed scale, answering at least ten out of 14 knowledge questions correctly. Only 2.2% answered less than five knowledge questions correctly resulting in a low knowledge level. All other remaining participants (36.5%) had a moderate knowledge level. Some knowledge questions were answered correctly less often (Table 5). For instance, only 57.7% of our participants knew that a carrier screening test does not examine if you yourself are at risk for developing one or more hereditary conditions. Furthermore knowledge items 10 and 11, about the probability of conceiving a child with a hereditary condition when both partners are identified as carriers of a pathogenic variant for the same recessive hereditary condition or if both partners are identified as carriers of a pathogenic variant for a different recessive hereditary condition, were only answered correctly by 42.3 and 36.5% of participants, respectively.

Attitudes

About one in two participants (49%) showed a positive attitude toward ECS, 40.4% had a neutral attitude toward ECS and 10.6% had a negative attitude. Most participants judged ECS to be beneficial (62.9%), important (51.7%), a good thing (64.3%), reassuring (57%) and desirable (51%). Other participants marked ECS as harmful (7.9%), unimportant (19.8%), a bad thing (7.9%), not

reassuring (17.9%) and undesirable (21.8%). The mean attitude score toward ECS was 18.1 (standard deviation 4.82, IQR 15–22). Women who had had a consultation at a CME (mean rank = 112.3) had a statistically significant higher attitude score (or more positive attitude) compared with those who had not (mean rank = 73.43) (p = 0.006) (Table 6). More than half of women who participated in our survey (54.3%) agreed with the statement that the pressure on future parents to have ECS will become great in the future, whereas 20.5% did not agree with this statement and 25.2% expressed a more neutral opinion. A similar proportion of participants (53.6%) expressed concerns that ECS may lead to greater anxiety/worry among couples who want to become pregnant. Hereby, we observed a statistically significant difference in the responses of the different age groups. Younger women (aged 18–34) were more likely to agree with this statement (mean rank = 80.6) compared with older age group (aged 35–49; mean rank = 57.45) (p = 0.007). In addition, women who had had a consultation at a CME prior to participating in our survey tended to agree less (mean rank = 50.5) compared with those who had not (mean rank = 77.81) (p = 0.046). Almost one in four participants (24.5%) agreed with the statement that offering ECS for certain hereditary conditions would make the lives of people living with these conditions seem inferior. Just over half of participants (51%) did not agree with the statement and another 24.5% had a more neutral opinion. Our analysis showed that those who did not have a genetic consult in the past (mean rank = 78.06) were more likely to agree with this statement compared with those who had (mean rank = 47) (p = 0.025).

Preferences

Eight out of ten women (82.8%) within our sample indicated that ECS should be available through the gynaecologist, followed by the CME (61.6%) and the general practitioner (50.3%). Smaller proportions of our sample chose for the option to provide ECS through the pharmacist (17.9%), the midwife (14.6%) and the school system (2%). When asked how ECS should best be offered, 43.7% of the women in our sample indicated they would prefer to have a free choice in the list of conditions for which they would be screened, 24.4% would prefer to have a choice between categories consisting of similar conditions and 31.9% of those surveyed expressed a preference for the ‘all or nothing’ approach where everyone would be offered the same fixed list of conditions. Our analysis showed a significant association between the preference for the test offer and having had a consultation at the CME (p = 0.007). Of the participants who had a genetic consult 90% preferred to have a free choice in the selection of the conditions screened for. For those who had not, only 40% opted for the same approach. More than half of participants (57%) within our sample had a preference for individual test results where both partners receive information about the conditions for which they are carriers. Just under a third (30.4%) of participants preferred to only receive information about those conditions for which both partners are carriers (couple-based results). Finally, one out of ten women (12.6%) expressed to have no preference regarding the approach used for reporting test results (Table 7). A small proportion of those surveyed (8.1%) were not at all willing to pay for ECS, while 54.8% of participants were willing to pay for ECS themselves and 37%

were not sure if they would pay out-of-pocket. There was a significant association between the willingness to pay and the completed level of education ($\chi 2[2] = 6.722$, $p = 0.035$). Our results showed that most highly educated women (64.9%) would be willing to pay for ECS themselves, compared with 42.6% of low/moderate educated women. Of those willing to pay out-of-pocket, 37.8% would be willing to pay less than 150 euro, 39.2% would be willing to pay between 150 and 300 euros and 23% would be willing to pay more than 300 (Table 7).

DISCUSSION

The aim of this study was to explore perspectives of nonpregnant reproductive-aged women in Flanders (Belgium) regarding ECS and to identify patient's characteristics that possibly influence these perspectives. Our findings show that offering ECS to couples with a (future) child wish was found to be acceptable by a large proportion (83.5%) of our study sample. This percentage is considerably higher compared with the results of an earlier Belgian survey where 63.9% of participants agreed that all couples planning a pregnancy should be offered the possibility to have ECS (8). In a Dutch study by Nijmeijer et al., only 55% of participants agreed that ECS should be offered to all couples that want to have children (14). The differences between our results and those of the previous mentioned studies could possibly be explained by the differences in the surveyed populations. For example, 59% of the participants in the study by Nijmeijer et al. indicated not to have a (future) child wish compared with only 30.5% within our own study. In addition, the median age of respondents in the study by Chokoshvili et al. was 48.5 whereas 80.1% of our participants where between the ages of 18 and 34.

A large proportion (63.6%) of the women in our sample expressed the intention to participate in ECS, while 19.9% were still undecided. These results are in line with the results of the primary studies reported in our systematic review, where between 32 and 76% of participants were interested in a (hypothetical) ECS test and considerable proportions (22–51%) were still undecided (6). Kauffman et al. reported that only 16% of participants in The NextGen study (who received genome sequencing for ECS) hoped to learn about their carrier status for autosomal recessive or X-linked conditions. In contrast, participants were overwhelmingly interested in secondary findings like Hereditary Breast and Ovarian Cancer pathogenic variants. The authors indicate that this might be partly due to the fact that not everyone knows an autosomal recessive or X-linked condition and that women were informed that (Hereditary Breast and Ovarian Cancer) pathogenic variants could be found as a secondary finding during the recruitment and consent process (18).

Most participants in our study sample estimated their risk of being a carrier of a recessive pathogenic variant and/or their risk of conceiving a child with a hereditary condition rather low. These findings are similar to the results reported in the study by Lakeman et al. were the perceived susceptibility among participants to be a carrier of cystic fibrosis (CF), sickle cell disease and/or thalassemia was

also rather low (12). As familiarity with recessive conditions in the general population is presumably limited, it is not surprising that participants in our study perceived their risk to be a carrier/conceive a child with a hereditary condition to be rather low and that a considerable proportion was still undecided about their intention to participate in ECS. It is however surprising that such a large proportion of our study sample showed the intention to participate in ECS as no public education or information campaign has been carried out to this date. Therefore, pre-test information should include information about the risk estimates of being a carrier/being a carrier couple, the available reproductive options for identified carrier couples, potential consequences of ECS for relatives and the limitations of ECS (e.g., residual risk after negative screen results) to facilitate informed reproductive decision-making (19).

Within our study, participants were briefly informed about the concept of ECS prior to filling in the survey. Most participants answered at least ten out of 14 knowledge questions correctly. It is remarkable that knowledge items with regard to inheritance patterns were answered less often correctly even though the correct answer was provided within the background information section. It is possible that not all participants took the time to carefully read the background information that was provided to them. Nevertheless, we can also assume that the information on the inheritance patterns was misunderstood by some participants. In an Australian study by Ong et al. where no background information on ECS was provided to participants, knowledge questions regarding probability and inheritance of pathogenic variants were only answered correctly by a minority of participants (10). Our findings confirm once again the importance of providing understandable pre-test information and pre-test counselling services when offering ECS. Long-term public education campaigns as proposed by European clinical recommendations could contribute to a better general knowledge understanding of genetics and carrier screening (14, 19).

In our study, most participants indicated that ECS should be available through the gynaecologist, followed by the CME (61.6%) and the general practitioner (50.3%). This result is in contrast with findings of earlier studies in the Netherlands (11, 14) and Australia (10) where the majority of participants preferred to have access to ECS through their general practitioner. This could possibly be explained by means of the specific Belgian healthcare context where the gynaecologist often acts as the primary care physician for specific female-related health problems or routine reproductive health consultations (e.g., contraception prescriptive, PAP-smear test). Therefore, interactions with gynaecologists are rather common for women in Flanders (Belgium). The advisory report of the SHC indicated that healthcare professionals such as gynaecologists and general practitioners are well placed to inform couples about ECS as they are actively involved in guiding pregnant women or in guiding families planning a pregnancy (5). It would be very interesting to investigate this finding in more detail to understand why women of reproductive age in Flanders (Belgium) prefer their gynaecologist as the healthcare provider through which ECS should be offered. In addition, research

should focus on the ability and willingness of healthcare professionals like general practitioners and gynaecologists to provide pre-test counselling services with regard to ECS as proposed by the SHC. These professions might have specific educational needs to be able to take on this task given the fact that they are not specialized in genetics. Efforts should be made to educate/engage primary healthcare providers in preconception care to make sure couples planning a pregnancy are informed in a timely manner about the possibility to have ECS. As not everyone may be willing to delay reproductive plans while waiting for their results, these services should be available to individuals in their early reproductive years to allow enough time for reproductive planning following result disclosure (18).

The majority of the women in our study sample indicated they would prefer to have a free choice in the list of conditions for which they would be screened. This finding might have been different when participants would have been informed about the size of the current test panel (>1000 conditions). Even though our results show that most participants would like to have a free choice in the list of conditions, from a practical point of view it might be rather impossible to accomplish this in practice. Within the NextGen study – where participants were presented different categories of conditions – 93% of individuals decided to receive findings for all categories. Participants indicated that this option made them feel respected, empowered and more prepared for result disclosure (20, 21). These findings suggest that providing and supporting choice may help to give future parents a sense of control over the information they choose to receive (21). More than half of participants (57%) within our sample had a preference for individual test results. This finding is in line with the results reported by Nijmeijer et al. where 60% of participants preferred to receive individual test results (14). Earlier research on CF carrier screening by Henneman et al. (22) found that most participants preferred individual test results because they did not want any information to be withheld from them (58.6%), to be able to inform other family members (25%) or to just to be informed about their carrier status (13%). As the current offer by the Belgian medical CME mainly provides couple-based test results (with the exception of individual test results for some more frequent genes included in the test panel) more qualitative research on why participants mainly prefer individual test results could be helpful to feed the ongoing discussion between professionals on the most ideal way to disclose carrier screening test results.

Just over half of the participants were willing to pay out-of-pocket for ECS. This finding is similar to the results reported by Plantinga et al. where 58% of those who said they would likely take the test if it was offered were willing to pay for ECS themselves (11). In contrast, Nijmeijer et al. reported that only 9% of participants were willing to pay for the test themselves (14). This could possibly be explained by the fact that participants were informed that the test costs a couple of hundred euros in contrast with our own study and the study of Plantinga et al. where participants did not receive information about the cost of the test (11). The amount people were willing to pay out-of-pocket was

considerably lower than the current cost (€1400), with only five of our participants willing to pay more than €600. When only those who can afford it will be able to have ECS, this may lead to an unequal access of ECS. Within our study we tried to assess the possible influence of familiarity with hereditary conditions on the different dependent variables by asking participants if they had ever had a consultation at the CME. This decision was made based on the finding of previous studies that the concept of hereditary conditions is often misinterpreted by participants (14, 23). Our results showed that women who had had a consultation at a CME prior to participating in our survey estimated their chance of being a carrier for a hereditary condition/conceiving a child with a hereditary condition to be higher, had a more positive attitude toward ECS, expressed less concerns that ECS may lead to greater anxiety/worry among couples who want to become pregnant, were less concerned that offering ECS for certain hereditary conditions would make the lives of people living with these conditions seem inferior and preferred to have a free choice in the selection of the conditions screened for. Having had a genetic consult in the past was however not associated with the intention to participate in ECS within our sample. Holtkamp et al. made mention of the fact that prior experiences with genetic conditions could possible influence the assessment of the utility of ECS and the decision-making process of couples considering ECS (24). As we only had ten participants that had a consultation at a CME in the past, we have to be extremely careful with interpreting these results as they might not be representable for this specific group. More research is absolutely necessary to see if these observed trends are confirmed within a larger study sample. To reach this specific population, a more targeted sampling approach would probably be more appropriate.

Study limitations

Our study has some limitations, one of which is our small sample size (n = 151) of highly educated women that might not be fully representative for all nonpregnant reproductive-aged women in Flanders (Belgium). Our attempt to reach a broad and diverse population resulted in a dependence on the willingness to cooperate of the public pharmacies. We noticed that many pharmacists who wanted to cooperate at first, forgot to give our flyers to potential participants and/or indicated to feel uncomfortable bringing up the topic of ECS to their customers. Therefore, it has not been possible to calculate a true response rate of potential participants receiving a flyer with the invitation to participate. Second, our Dutch questionnaire was quite long causing some participants to drop out early before finishing the entire questionnaire. Finally, we tried to assess the understanding of ECS by using our newly developed knowledge scale (14 items, $\alpha = 0.626$). Our results show that ± 70% of participants answered at least ten out 14 knowledge questions correctly which we classified as a high knowledge level. We do however acknowledge that this classification might not be perfect. It is also possible that some participants did not take the time to read the provided background information. Further in-depth research on the understanding of ECS would be very valuable.

CONCLUSION

The majority of the women in our study sample assessed offering ECS to couples with a (future) child wish to be acceptable and showed the intention to participate in ECS. Risk perception to be a carrier of a hereditary condition or to conceive a child with a hereditary condition was perceived to be rather low. Most participants showed a positive attitude toward ECS. Nevertheless, a considerable number of participants were still undecided about their intention to participate in ECS and showed a more neutral attitude. With regard to the practical organization of a population-based ECS offer, participants preferred ECS to be available through the gynaecologist, to receive individual test results and to have a free choice in the list of conditions for which they would be screened. Most participants were willing to pay for ECS themselves, yet the amount they would be willing to pay is considerably lower than the costs of the current test offer. While acknowledging the study limitations, this study reports interesting results that give valuable insights in the perspectives of nonpregnant reproductive-aged women in Flanders (Belgium) regarding ECS. These findings can be used in the on-going debate on the implementation of ECS in the Belgian healthcare setting (or countries with a similar healthcare context).

AUTHOR'S CONTRIBUTIONS

E.V.S., H.D., I.G., S.V.E. and P.B. designed the study. The data-collection was carried out by H.D., I.G., S.V.E. and E.V.S. The data-analysis was performed by E.V.S. A first draft of the article was written by E.V.S. and critically discussed and revised by H.D., I.G., S.V.E., P.B., H.P., K.P. and G.M. P.B. coordinated the study. All the authors have approved the final version.

ACKNOWLEDGMENTS

The authors would like to express their gratitude to all public pharmacies throughout Flanders that distributed our flyers to potential participants. Furthermore, they would like to thank all participants that took a moment of their time to complete our online questionnaire.

Table 1: Internal reliability analysis of knowledge and attitude scale.

Measure	Description	Items	Reliability	Range	Cut-off	Mean (SD)	Outcome
Knowledge scale	Knowledge of ECS	14 ques-tions (True/ False/I don't know)	0.626	0-14	0-4 = Low knowledge; 5-9 = Moderate knowledge; 10-14 = High knowledge	10.61 (2.61)	Low knowledge = 2.2%; Moderate knowledge = 26.3%; High knowledge = 71.5%
Attitude scale	Attitudes towards having ECS	Five bipolar words pairs (5-point Likert scale)	0.908	5-25	5-11= Negative attitude; 12-18= Neutral attitude; 19-25= Positive attitude	18.15 (4.82)	Negative attitude = 10.6%; Neutral attitude = 40.4%; Positive attitude = 49%

Table 2: Sociodemographic Characteristics of participants

	N (%)
Age (n=151)	
18-34	121 (80.1)
35-49	30 (19.9)
Highest level of completed education (n=151)	
Low/intermediate	69 (45.7)
High	82 (54.3)
Religiosity (n=151)	
Yes	42 (27.8)
No	109 (72.2)
Extent of religious involvement (n=42)	
Not active	31 (73.8)
(Somewhat) active	11 (26.2)
Children (n=151)	
Yes	37 (24.5)
No	114 (75.5)
(Future) Child wish (n=151)	
Yes	105 (69.5)
No/I don't know	46 (30.5)
Relationship (n=151)	
Yes	108 (71.5)
No	43 (28.5)
Relationship status (n=108)	
Not living together	34 (31.5)
Living together/ Married	74 (68.5)
Consultation at Centre for Human Genetics (CME) (n=151)	
Yes	10 (6.6)
No	141 (93.4)

Table 3: Perceived susceptibility

N (%)				
Perceived susceptibility of being a carrier of a hereditary condition (n=151)				
Very low	Low	Average	High	Very high
30 (19.9)	57 (37.7)	38 (25.2)	11 (7.3)	15 (9.9)
Perceived susceptibility of conceiving a child with a hereditary condition (n=151)				
Very low	Low	Average	High	Very high
40 (26.5)	59 (39.1)	37 (25.4)	10 (6.6)	5 (3.3)

Table 4: Acceptability & intention to participate in ECS

N (%)				
Acceptability of offering ECS to couples with a child wish				
Totally unacceptable	Unacceptable	Neutral	Acceptable	Totally acceptable
1 (0.7)	8 (5.3)	16 (10.6)	51 (33.8)	75 (49.7)
Intention to participate in ECS				
Definitely will not consider	Probably will not consider	Undecided	Probably will consider	Definitely will consider
13 (8.6)	12 (7.9)	30 (19.9)	45 (29.8)	51(33.8)

Table 5: Knowledge about ECS related concepts

Knowledge Score (n=137)				
	Mean (SD)	10.6 (2.61)		
	IQR	9-12		
	Range	2-14		
Level of genetic knowledge (n=137)		N (%)		
	Low	3 (2.2)		
	Moderate	36 (26.3)		
	High	98 (71.5)		
Knowledge scale (Correct answers)				
		True N (%)	False N (%)	I don't know N (%)
1	A carrier of a hereditary condition carries a mutation for that condition but does not have the condition himself/herself.	114 (83.2)	12 (8.8)	11 (8)
2	All serious conditions are determined by a genetic predisposition.	7 (5.1)	130 (94.9)	0 (0)
3	All hereditary conditions are expressed during childhood (<18 years).	3 (2.2)	117 (85.4)	17 (12.4)
4	A carrier screening test examines if you are at risk for developing one or more hereditary conditions.	36 (26.3)	79 (57.7)	22 (16.1)
5	Genetic carrier screening is only intended for individuals with an increased family risk (families where genetic conditions have already occurred).	32 (23.4)	83 (60.6)	22 (16.1)
6	You can be a carrier of a hereditary condition without this condition occurring in your own family	108 (78.8)	10 (7.3)	19 (13.9)
7	A carrier of a hereditary condition will always develop that specific condition and get related health problems.	1 (0.7)	128 (93.4)	8 (5.8)
8	If you are a carrier of a hereditary condition, all your offspring will also be a carrier of that specific hereditary condition.	8 (5.8)	121 (88.3)	8 (5.8)
9	If the (future) mother is a carrier of a recessive hereditary condition, all her children will develop this condition.	4 (2.9)	122 (89.1)	11 (8)
10	If both partners are carriers of a mutation for the same recessive hereditary condition, they a 50% chance each pregnancy to conceive a child with the condition for which they are carriers	58 (42.3)	58 (42.3)	21 (15.3)
11	If both partners are carriers of a mutation for a different recessive hereditary condition, they have a 25% chance each pregnancy to conceive a child with one of both condition.	50 (36.5)	50 (36.5)	37 (37)
12	Two healthy individuals without health problems can have a child with an inherited condition.	118 (86.1)	9 (6.6)	10 (7.3)
13	When a preconceptional genetic carrier screening test does not identify an increased risk, this means with certainty that this couple will have a healthy child.	8 (5.8)	119 (86.9)	10 (7.3)
14	If both partners are carriers of the same genetic condition, they cannot conceive children naturally without this specific genetic condition.	5 (3.6)	107 (78.1)	25 (18.2)

Table 6: Attitudes towards ECS

Attitude score						
Mean (SD)	18.1 (4.82)					
IQR	15-22					
Range	5-25					
Attitude groups	N (%)					
Negative attitude	16 (10.6)					
Neutral attitude	61 (40.4)					
Positive attitude	74 (49)					
Attitude scale						
	N (%)					
Harmful	4 (2.6)	8 (5.3)	44 (29.1)	50 (33.1)	45 (29.8)	Beneficial
Unimportant	12 (7.9)	18 (11.9)	43 (28.5)	43 (28.5)	35 (23.2)	Important
Bad thing	5 (3.3)	7 (4.6)	42 (27.8)	54 (35.8)	43 (28.5)	Good thing
Not reassuring	9 (6)	18 (11.9)	38 (25.2)	48 (31.8)	38 (25.2)	Reassuring
Undesirable	13 (8.6)	20 (13.2)	41 (27.2)	39 (25.8)	38 (25.2)	Desirable

Attitude statements				
N (%)				
Pressure				
Definitely not	Probably not	Neutral	Probably yes	Definitely yes
4 (2.6)	27 (17.9)	38 (25.2)	57 (37.7)	25 (16.6)
Anxiety/worry				
Definitely not	Probably not	Neutral	Probably yes	Definitely yes
8 (5.3)	23 (15.2)	39 (25.8)	61 (40.4)	20 (13.2)
Inferiority				
Definitely not	Probably not	Neutral	Probably yes	Definitely yes
29 (19.2)	48 (31.8)	37 (24.5)	31 (20.5)	6 (4)

Table 7: Preferences for the practical organization of a population-based ECS offer

N (%)					
Availability (n=151, multiple answers possible)					
Gynaecologist	GP	CME	Pharmacist	Midwife	School
125 (82.8)	76 (50.3)	93 (61.6)	27 (17.9)	22 (14.6)	3 (2)

Test offer (n=135)		
All or nothing	Categories	Free choice
43 (31.9)	33 (24.4)	59 (43.7)
Results reporting (n=135)		
Individual	Couple-based	No preference
77 (57)	41 (30.4)	17 (12.6)
WTP (n=135)		
Yes	No	I'm not sure
74 (54.8)	11 (8.1)	50 (37)
WTP (n=135)		
<150 euro	151-300 euro	>300 euro
28 (37.8)	29 (39.2)	17 (23)

REFERENCES

1. Bell CJ, Dinwiddie DL, Miller NA, Hateley SL, Ganusova EE, Mudge J, et al. Carrier testing for severe childhood recessive diseases by next-generation sequencing. Science translational medicine. 2011;3(65):65ra4-ra4.
2. Ropers H-H. On the future of genetic risk assessment. J Commun Genet. 2012;3(3):229-36.
3. Edwards JG, Feldman G, Goldberg J, Gregg AR, Norton ME, Rose NC, et al. Expanded carrier screening in reproductive medicine—points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine. Obstetrics & Gynecology. 2015;125(3):653-62.
4. Chokoshvili D, Vears D, Borry P. Expanded carrier screening for monogenic disorders: where are we now? Prenatal diagnosis. 2018;38(1):59-66.
5. Belgium S. Advisory report of the superior health council no. 9240. Expanded carrier screening in a reproductive context Towards a responsible implementation in the healthcare system. 2017.
6. Van Steijvoort E, Chokoshvili D, W Cannon J, Peeters H, Peeraer K, Matthijs G, et al. Interest in expanded carrier screening among individuals and couples in the general population: systematic review of the literature. Human reproduction update. 2020;26(3):335-55.
7. Charafeddine R, Braekman E, Gisle L, Drieskens S. Gezondheidsenquête 2018: Seksuele gezondheid. Brussel, België: Sciensano; 2018. Contract No.: Sciensano Rapportnummer: D/2019/14.440/60. .
8. Chokoshvili D, Belmans C, Poncelet R, Sanders S, Vaes D, Vears D, et al. Public views on genetics and genetic testing: a survey of the general public in Belgium. Genetic testing and molecular biomarkers. 2017;21(3):195-201.
9. Ekstrand Ragnar M, Tydén T, Kihlbom U, Larsson M. Swedish parents' interest in preconception genetic carrier screening. Ups J Med Sci. 2016;121(4):289-94.
10. Ong R, Howting D, Rea A, Christian H, Charman P, Molster C, et al. Measuring the impact of genetic knowledge on intentions and attitudes of the community towards expanded preconception carrier screening. Journal of medical genetics. 2018;55(11):744-52.
11. Plantinga M, Birnie E, Abbott KM, Sinke RJ, Lucassen AM, Schuurmans J, et al. Population-based preconception carrier screening: how potential users from the general population view a test for 50 serious diseases. European journal of human genetics : EJHG. 2016;24(10):1417-23.
12. Lakeman P, Plass AMC, Henneman L, Bezemer PD, Cornel MC, Ten Kate LP. Preconceptional ancestry-based carrier couple screening for cystic fibrosis and haemoglobinopathies: what determines the intention to participate or not and actual participation? European Journal of Human Genetics. 2009;17(8):999-1009.
13. Mathijssen IB, Holtkamp KCA, Ottenheim CPE, van Eeten-Nijman JMC, Lakeman P, Meijers-Heijboer H, et al. Preconception carrier screening for multiple disorders: evaluation of a screening

offer in a Dutch founder population. European journal of human genetics : EJHG. 2018;26(2):166-75.
14. Nijmeijer SCM, Conijn T, Lakeman P, Henneman L, Wijburg FA, Haverman L. Attitudes of the general population towards preconception expanded carrier screening for autosomal recessive disorders including inborn errors of metabolism. Molecular genetics and metabolism. 2019;126(1):14-22.
15. Van Den Berg M, Timmermans DR, Ten Kate LP, Van Vugt JM, Van Der Wal G. Are pregnant women making informed choices about prenatal screening? Genet Med. 2005;7(5):332-8.
16. Lewis C, Hill M, Skirton H, Chitty LS. Development and validation of a measure of informed choice for women undergoing non-invasive prenatal testing for aneuploidy. European Journal of Human Genetics. 2016;24(6):809-16.
17. Tavakol M, Dennick R. Making sense of Cronbach's alpha. International journal of medical education. 2011;2:53.
18. Kauffman TL, Irving SA, Leo MC, Gilmore MJ, Himes P, McMullen CK, et al. The NextGen Study: patient motivation for participation in genome sequencing for carrier status. Molecular Genetics & Genomic Medicine. 2017;5(5):508-15.
19. Henneman L, Borry P, Chokoshvili D, Cornel MC, van El CG, Forzano F, et al. Responsible implementation of expanded carrier screening. European journal of human genetics : EJHG. 2016;24(6):e1-e12.
20. Wilfond BS, Kauffman TL, Jarvik GP, Reiss JA, Richards CS, McMullen C, et al. Lessons learned from a study of genomics-based carrier screening for reproductive decision making. Health Affairs. 2018;37(5):809-16.
21. Kraft SA, McMullen CK, Porter KM, Kauffman TL, Davis JV, Schneider JL, et al. Patient perspectives on the use of categories of conditions for decision making about genomic carrier screening results. American journal of medical genetics Part A. 2018;176(2):376-85.
22. Henneman L, Ten Kate L. Preconceptional couple screening for cystic fibrosis carrier status: couples prefer full disclosure of test results. Journal of medical genetics. 2002;39(5):e26-e.
23. Henneman L, Timmermans DR, Van der Wal G. Public experiences, knowledge and expectations about medical genetics and the use of genetic information. Public Health Genomics. 2004;7(1):33-43.
24. Holtkamp KC, Mathijssen IB, Lakeman P, van Maarle MC, Dondorp WJ, Henneman L, et al. Factors for successful implementation of population-based expanded carrier screening: learning from existing initiatives. The European Journal of Public Health. 2017;27(2):372-7.

CHAPTER 5

KNOWLEDGE, ATTITUDES AND PREFERENCES REGARDING REPRODUCTIVE GENETIC CARRIER SCREENING AMONG REPRODUCTIVE-AGED MEN AND WOMEN IN FLANDERS (BELGIUM)

Van Steijvoort, E., Devolder, H., Geysen, I., Van Epperzeel, S., Peeters, H., Peeraer, K., Matthijs, G. & Borry, P. (2022). Knowledge, attitudes and preferences regarding reproductive genetic carrier screening among reproductive-aged men and women in Flanders (Belgium). *European Journal of Human Genetics*. doi:10.1038/s41431-022-01082-1

ABSTRACT

Through carrier screening couples at-risk of conceiving a child with an autosomal recessive or X-linked condition can be identified prior to conception. The aim of this study was to assess knowledge, attitudes and preferences regarding reproductive genetic carrier screening (RGCS) among reproductive-aged men and women in Flanders (Belgium). Women and men of reproductive age visiting their pharmacist were invited to answer a self-administered questionnaire. Prior to filling in the questionnaire, participants were asked to read an information leaflet explaining some key concepts about RGCS. Our sample included 387 individuals of reproductive age, of which 68.5% were female and 31.5% were male. Most of the participants were below 34 years old (72.9%), didn't have children (68.6%) and were currently in a relationship (69.1%). Offering RGCS to couples that want to have children was found acceptable by 86% of participants. However, fewer participants would consider RGCS for themselves in the future (61%). We observed a positive correlation between attitude score/knowledge score and the intention to have RGCS. Half of the participants (50.9%) preferred the disclosure of individual test results. Most of participants indicated that RGCS should be offered through the gynaecologist (81.1%), followed by the GP (71.5%) and the Centre for Human Genetics (64.8%). About 68.9% of participants were willing to pay out-of-pocket for a RGCS test. We recommend that RGCS should ideally be implemented through a tailored implementation strategy whereby individual needs and preferences can be taken into account.

INTRODUCTION

Through reproductive genetic carrier screening (RGCS) it can be determined if a couple has an increased reproductive risk to conceive a child that might develop a recessive condition screened for. At-risk couples can consider multiple reproductive options, including accepting their reproductive risk and proceeding with a natural pregnancy, deciding against having biological children together with their partner, prenatal diagnosis (possibly followed by pregnancy termination if the unborn child is affected), undergoing IVF/ICSI with pre-implantation genetic testing for monogenic conditions (PGT-M), using donor gametes or adoption/being a foster parent (1). Most children with recessive conditions are born to parents who are unaware of their own carrier status (1, 2). In an Australian study by Archibald et al., 88% of identified carriers had no family history of the condition (3). These findings emphasize the importance to not solely rely on family history to guide screening decisions.

The current variability in screening programs around the world can be explained by multiple factors like variation in carrier frequency of genetic conditions, differences in health care systems, financial, cultural or religious factors (4). Most often RGCS has been made available for those able to pay out-of-pocket, but some countries also have government-funded screening programs. For example in Israel, the whole population is eligible for a carrier screening program, which includes screening for CF, SMA and FXS. Based on the ethnicity of the couple additional carrier-screening tests are also being offered. While in the Netherlands, RGCS is available to interested couples on a fee for service basis with a partial reimbursement by health insurance for high-risk couples like consanguineous couples. A government funded trial of reproductive carrier screening is currently running in Australia where the objective is to assess the feasibility of a national government-funded screening program (4).

While new genomic technologies allow screening for an ever increasing number of disease-causing variants, many ethical, legal and social questions still remain unanswered. Implementation of new research findings/technologies into healthcare can be complex and challenging. Evidence-based strategies are required to ensure the implementation of evidence into practice. Opinions on the harms and benefits with regard to RGCS might differ between different stakeholders. It is important to explore the perspectives of all stakeholders involved and especially with the general public in order to achieve a responsible implementation of RGCS. More reliable evidence on the views and/or perceptions of the public would help to establish interventions that strengthen reproductive choices (5, 6).

We already carried out an online survey study to assess the perspectives of non-pregnant reproductive-aged women in Flanders (Belgium) with regard to RGCS. The results of this previous study have been published elsewhere (7). Almost half (49%) of the study participants within this study showed a positive attitude towards RGCS and most of them (83%) found it acceptable to offer

RGCS to couples that want to have children. A large proportion (64%) of these participants also indicated that they would consider RGCS in the future (7). Our attempt to reach a broad and diverse population however didn't turn out as we had hoped. Unfortunately this resulted in a small study sample of highly educated women. To ascertain if the observed trends also apply to a broader and more diverse population we decided to repeat the study with a modified recruitment approach.

MATERIALS AND METHODS

Men and women of reproductive age (18–49 years old) visiting their pharmacist were invited to answer a self-administered questionnaire. Based on our sample size calculation we aimed to collect 385 completed questionnaires. Data collection was carried out between September 2019 and December 2019 by multiple researchers (EVS, HD, IG and SVE) who personally approached participants with the question whether they had time to complete a questionnaire in five different pharmacies throughout Flanders (Belgium). Participants were approached after they had met with their pharmacist. Prior to filling in the questionnaire, participants were asked to read an information leaflet explaining some key concepts. The questionnaire that had to be completed within the pharmacy took ~15 min to fill in.

Survey Instrument

The questionnaire included items or scales measuring perceived susceptibility of being a carrier/conceiving a child with a hereditary condition, acceptability of offering RGCS, intention to participate in RGCS, ethical reflections, knowledge of RGCS, attitudes towards RGCS and preferences for the practical organization of a population-based RGCS offer. The questionnaire used in this study has been described in detail elsewhere (7).

Data analyses

Statistical analyses were performed using IBM SPSS® Statistics 27 for Windows. Descriptive analyses were used to describe characteristics. To ensure meaningful comparison across groups we dichotomized all sociodemographic variables (7). Non-parametric statistical tests (Chi-Square test of independence; Fisher's Exact test (2 × 2 tables) or a Fisher-Freeman-Holton (r x c tables); Mann–Whitney U test) were used to compare differences between independent groups. For non-identical distributions, statistically significant differences in the mean ranks of the dependent variable in terms of the two groups were determined. A two-sided p-value <0.05 was considered statistically significant. Finally, we used the Spearman's rank-order correlation to determine whether there was an association between our continuous/ordinal variables.

Knowledge and attitude scale

Reliability of the knowledge and attitude scales were assessed using Cronbach's alpha (Table 1). The alpha coefficient for the attitude scale indicated good internal reliability (5 items, α = 0.889). The reliability analyses for the knowledge scale showed a lower internal reliability (14 items, α = 0.729) (8).

Ethical approval

The study protocol received ethical approval from the Research Ethics Committee UZ/KU Leuven (MP010414). The questionnaire was anonymous and participation was voluntary.

RESULTS

Socio-demographic

In total, 409 individuals completed the self-administered questionnaire. Data from 22 participants were excluded from further analysis because they didn't meet the age inclusion criteria. Our sample included 387 individuals of reproductive age (18–49), of which 68.5% were female and 31.5% were male. Most participants were between 18 and 34 years old (72.9%). A minority of participants held a university degree (29.1%) and stated to be religious (32.9%; n = 127) of which 66.7% (n = 84/127) stated to not be actively involved in their religion. A majority of participants didn't have children (68.6%) and were in a relationship (69.1%; n = 266) of which 52.1% intended to have a child in the future (n = 138/266). Three women within our sample were pregnant (0.8%). Merely 7% of our participants had had a genetic consult in the past (see Supplementary Material). Study participants were significantly older ($p = 0.009$), had a lower level of completed education ($p < 0.001$) and were less likely to want children ($p = 0.019$) compared to the study sample of our previous published survey (7).

Perceived susceptibility (risk perception)

Half (53.6%) of our study sample perceived their risk of being a carrier of a hereditary condition to be low-very low, while 22.5% perceived a high-very high risk. In addition, only one out of ten participants estimated their risk of conceiving a child with a hereditary condition to be high-very high (Table 2). Participants who already had children (mean rank = 176.25) estimated their chance of being a carrier of a hereditary condition to be lower compared to participants who didn't have children (mean rank = 199.98) ($p = 0.044$). While those expressing a desire to have children in the future (mean rank = 141.53) estimated their risk to conceive a child with a hereditary condition to be higher compared to those who were unsure or did not intend to have children (mean rank = 123.73) ($p = 0.047$). Those who already had had a genetic consult in the past estimated their chance of being a carrier for a hereditary condition higher (mean rank = 241.46) compared to those who didn't have a genetic consult (mean rank = 189.34) ($p = 0.015$). In addition, this specific group also estimated their chance of conceiving a child with a hereditary condition to be higher (mean rank = 226.28) ($p < 0.001$) (see Supplementary Material).

Acceptability and Intention to participate in RGCS

Most participants considered RGCS for couples with a desire to have children to be acceptable-totally acceptable (86%). A small proportion of our study sample judged it to be unacceptable-totally unacceptable (2.6%) while other participants had a neutral opinion (11.4 %) (Table 2). Participants who stated not to be religious (mean rank = 201.25; p = 0.032), who were married or living together with their partner (mean rank = 139.16; p = 0.034) and who had had a genetic consult in the past (mean rank = 245.98; p = 0.005) rated offering RGCS to couples with a desire to have children to be more acceptable (see Supplementary material). Six out of ten participants (61%) within our study sample would definitely or probably consider participating in RGCS in the future while 17.3% would definitely or probably not consider it. About a fifth (21.7%) of our participants were still undecided about their intention to participate in RGCS (Table 2). Participants who were between the ages of 18 and 34 (mean rank = 207.61, p < 0.001), who didn't have children (mean rank = 201.73; p = 0.018), who clearly expressed a desire to have children in the future (mean rank = 142.09; p = 0.037) and those who had had a genetic consult in the past (mean rank = 265.19; p < 0.001) were more likely to consider participation in RGCS in the future (see Supplementary material).

Knowledge

The mean knowledge score of our participants was 9.6 (SD 2.61, IQR 8–12). We observed a statistically significant higher knowledge score within the young age category (mean rank = 201.4; p = 0.009), females (mean rank = 202.59, p = 0.008), highly educated participants (mean rank = 238.27; p < 0.001), participants who expressed to be not actively involved in their religion (mean rank = 67.51; p = 0.045), those who didn't have children (mean rank = 200.54; p = 0.017), those who clearly expressed having a desire to have children (mean rank = 142.96, p = 0.014) and participants in a relationship but not living together (mean rank = 151.84; p 0.001) (see Supplementary material). About 1 in 2 (55.2%) of those surveyed answered at least 10 out of 14 knowledge questions correctly which resulted in a high level of knowledge. A minority of participants (4.7%) gave a correct answer to less than five knowledge items and were given a low knowledge level. All other participants (40.1%) had a moderate knowledge level based on our knowledge scale. Individual knowledge questions were answered correctly by 33.9% till 88.3% of participants (Table 3).

Attitudes

The mean attitude score among our study participants was 18 (SD 4.49, IQR 15–21). Participants who stated to be religious (mean rank = 176.78; p = 0.039) and those who didn't have a genetic consult in the past (mean rank = 186.75; p < 0,001) had a significantly lower attitude score. Almost half of our study sample (47.5%) had a positive attitude towards RGCS, 43.9% had a neutral attitude and 8.5% had a negative attitude. Most individuals surveyed within this study found RGCS for themselves to be beneficial (64.3%), important (51%), a good thing (61.9%), reassuring (54.5%) and

desirable (46.6%) while others stated it would be harmful (7%), unimportant (18.7%), a bad thing (8.2%), not reassuring (23.3%) and undesirable (18.7%). The pressure on future parents to have preconception RGCS will become great according to 51.4% of our participants. Others (28.2%) had a neutral opinion regarding this statement and 20.4% stated that this would probably or definitely not be the case. We observed that religious participants (mean rank = 209.94; p = 0.035) tended to agree more with this pressure statement in comparison to those who weren't religious (mean rank = 185.44). In addition, 48% of participants stated that carrier screening will probably or definitely lead to greater anxiety among couples who want to become pregnant while 27.7% believed that this would probably or definitely not be the case. Another 24.3% indicated to have a more neutral opinion. Finally, 24% of those surveyed believed that carrier screening would probably or definitely make the lives of people living with these conditions seem inferior while 53.7% stated this would probably or definitely not be the case. One in five participants had a neutral opinion regarding this latest statement (Table 4).

Preferences

Most participants believed that RGCS should be made available through the gynaecologist (80.9%) followed by the general practitioner (71.3%) and the centre for human genetics (Reference Centre for Genetic Counselling in Belgium) (64.6%). A small share of those surveyed stated that RGCS should be available through the pharmacist (17.1%), the midwife (17.6%), the internet (3.9%) or the school system (3.1%). The gynaecologist was more often chosen by female participants (84.9%) compared to males (72.17%) (p = 0.003) while the GP was more often chosen by males (79.5%) compared to females (67.5%) (p = 0.016). In addition, the GP was also more often chosen by low/intermediate educated individuals (74.4%) compared to highly educated participants (63.4%) (p = 0.031) (see Supplementary material). About 41.1% of participants indicated to prefer to have a free choice in the number of conditions screened for while another 36.8% of participants gave preference to the same fixed list of conditions for everyone who opts to have RGCS. The remaining 22.1% would prefer to be able to choose between categories of conditions. Within our study sample most individuals preferred to receive individual test results (50.9%). Another 35.2% of participants indicated to prefer to receive couple-based test results. A small proportion of participants (13.9%) stated to have no preference on how test results would be reported back to them. Our analysis showed a significant association between the preferences of results reporting and the relationship status of our participants. Those who weren't in a relationship had a higher preference for individual test results (59.8%) compared to those participants who were in a relationship (46.9%) ($\chi 2[2] = 10.769$, p = 0.005) (see Supplementary material). Most participants (68.9%) were willing to pay for RGCS out-of-pocket, 21% were not sure if they would be and 10.1% indicated they wouldn't be willing to pay for RGCS themselves. Of those willing to pay, 45.3% would be willing to pay up to 150 euro, 40% would be willing to pay between 151 and 300 euro and 14.7% would be willing to more than 300 euro (Table 4). We observed that highly educated study participants (80.4%) were more

often willing to pay compared to individuals with a low/intermediate education level (64.3) ($\chi 2[2]= 10.11$, p=0.006). Our data also indicate that individuals with a low/intermediate education level (24.6%) were more uncertain if they would be willing to pay themselves for RGCS compared to highly educated individuals (11.6%). In addition, we found that study participants in a relationship (73.6%) more often showed the willingness to pay for RGCS compared to those who weren't in a relationship (58.8%) ($\chi 2[2]=14.132$, p=0.001). Lastly, religious individuals who stated to be actively involved in their religion were willing to pay less. Within this group 68% would be willing to pay a maximum of 150 euro compared to 32.8% of religious individuals who stated to not be actively involved in their religion ($\chi 2[2]=8.905$, p=0.012) (see Supplementary material).

Associations between continuous/ordinal variables

A Spearman's rank-order correlation was run and showed there was a positive relationship between the intention to have RGCS and the acceptability to offer RGCS to couples with a desire to have children ($r_s = 0.445$, $p < 0.001$). In addition, the intention to have RGCS was also positively related to the perceived susceptibility of being a carrier ($r_s= 0.226$, $p < 001$), the perceived susceptibility of conceiving a child with a hereditary condition ($r_s = 0.158$, $p = 0.002$) and the conviction that the pressure on future parents to have preconception RGCS will become great ($r_s = 0.103$, $p = 0.042$). In contrast, the intention to have RGCS was negatively correlated with the belief that RGCS would lead to greater anxiety among couples who want to become pregnant ($r_s = −0.102$, $p = 0.044$) and the belief that RGCS would make the lives of people living with these conditions seem inferior ($rs = −0.110$, $p = 0.031$). We observed a statistically significant, positive correlation between attitude score and the risk perception of being a carrier ($r_s = 0.123$, $p = 0.015$), the perceived risk of conceiving a child with a hereditary condition ($r_s = 0.119$, $p = 0.019$), the acceptability of offering RGCS ($rs = 0.471$, $p < 0.001$) and the intention to have RGCS ($r_s = 0.712$, $p < 0.001$). The higher the attitude score, the more participants agreed with the statement that the pressure on future parents to have preconception RGCS will become great ($r_s = 0.106$, $p = 0.038$). In contrast, the higher the attitude score the more they disagreed with the statements that RGCS would lead to greater anxiety among couples who want to become pregnant ($r_s = −0.186$, $p < 0.001$) and that carrier screening would make the lives of people living with these conditions seem inferior ($r_s = −0.136$, $p = 0.007$). There was a statistically significant, positive correlation between the calculated knowledge score and the risk perception of being a carrier ($r_s = 0.198$, $p < 0.001$), the perceived susceptibility of conceiving a child with a hereditary condition ($r_s = 0.101$, $p = 0.048$), the acceptability of offering RGCS to couples with a desire to have children ($r_s = 0.135$, $p = 0.008$) and the intention to have RGCS ($r_s = 0.119$, $p = 0.019$). Within our study sample the acceptability of RGCS was negatively correlated with the opinion that RGCS would lead to greater anxiety among couples who want to become pregnant ($r_s = −0.195$, $p < 0.001$) and the belief that RGCS would make the lives of people living with these conditions seem inferior ($r_s = −0.172$, $p = 0.001$). Furthermore, the higher participants estimated their risk of being a carrier the higher they estimated their risk of conceiving a child with a hereditary

condition (r_s = 0.672, p < 0.001) and the more they agreed to the statement that RGCS would lead to greater anxiety among couples who want to become pregnant (r_s = 0.138, p = 0.007). The more participants were worried that offering RGCS would make the lives of people living with these conditions seem inferior, the more they agreed with statements on pressure (r_s = 0.253, p < 0.001) and anxiety (r_s = 0.368, p < 0.001). Likewise, we found a positive association between the answers on the pressure and anxiety statements (r_s = 0.188, p < 0.001).

DISCUSSION

This study aimed to assess if earlier observations and trends on the perspectives of highly educated nonpregnant reproductive-aged women in Flanders (Belgium) would also apply to a broad and more diverse population (7). Compared to our earlier published study participants were significantly older, had a lower level of completed education and were less likely to want children (7). Yet, highly educated individuals had once more significantly higher knowledge scores and were more willing to pay out-of-pocket. Within the study of van Dijke et al. (9)—where couples' experiences with RGCS were evaluated—uninformed choice to have RGCS was mainly explained because of poor knowledge levels. These results indicate the possible impact of knowledge on reproductive decision-making.

Within our study, we also found a positive correlation between the calculated knowledge score and the intention to have RGCS. As there is no golden standard to measure knowledge on RGCS or an objective way of defining sufficient knowledge on RGCS, it could also be beneficial to focus on self-reported knowledge of individuals within the target population by assessing the perception of their own knowledge level. This could give possible insights whether people feel like they have enough knowledge to make an informed decision to accept or decline a RGCS offer. Furthermore, we saw a confirmation of the earlier finding that participants with children estimated their risk of being a carrier to be lower compared to those without children and were also less likely to consider participation in RGCS in the future. To avoid the misconception that RGCS is only of relevance for first-time parents, pre-test counselling initiatives should underline the fact that we are all carriers of recessive genetic conditions (10) and that the reproductive risk of carrier couples to conceive a child with a hereditary condition is present within each pregnancy. The main objective of doing so is of course not to put pressure on parents or to make them worry but rather to empower them to make informed reproductive decisions based on accurate information.

Within this study we also surveyed men of reproductive age which allowed us to explore possible differences between both sexes. Our comparative analysis showed for example that the majority of the women in our study sample indicated that RGCS should be available through the gynaecologist while the majority of the male participants preferred the general practitioner. In addition, we observed also better knowledge scores amongst female participants. We would like to advocate that future

research projects and interventions with regard to RGCS should not merely focus on females or pregnant women. As men play an essential role in reproduction, they should be acknowledged as equal partners in reproductive decision-making. Research shows that preconception health interventions and messages mainly focus on women. This contributes to the normative belief that women have a greater responsibility when it comes to pregnancy/childbearing (11). The current lack of information about men's views supports the idea that men are secondary to reproduction (12). If we want couples to make informed reproductive decisions together we have to take into account the way in which decisions are made and the context that influences them (13). It is therefore important to note that men also matter in the pre- and peri-conception window (12).

While it is often mentioned that offering an expanded (gene) panel instead of a ancestry-based (limited gene) panel for high-risk groups could achieve more equity of access to screening, attention should be given to equal access when individuals have to pay out of pocket. An Australian study by Robsen et al. (14) found a strong socioeconomic gradient in the uptake of RGCS, with those living in the most advantages areas across Australia being more likely to have RGCS compared to those living in the most disadvantaged areas. The authors highlight the important problem that could arise when those with the fewest resources to care for an affected child are least likely to access RGCS (14). Reimbursement of test costs should therefore be considered to minimalize social and financial barriers that could limit equal access.

Consistent with our previously published results, participants who had had a genetic consult in the past had a higher risk perception of being a carrier/conceiving a child with a hereditary condition and expressed more positive attitudes towards RGCS. In addition, this time around our results also showed that these individuals assessed offering RGCS to couples with a desire to have children to be more acceptable and were more likely to have the intention to participate in RGCS. These findings are in line with the results of a Dutch study by Nijmeijer et al. (15) in which relatives of patients with the severe autosomal recessive (AR) condition mucopolysaccharidosis type III (MPS III) were questioned regarding their attitudes toward preconception RGCS. Within this study being a parent or relative of an MPS III patient was the strongest variable associated with the intention to have RGCS. These results may indicate a possible influence from the knowledge gained through the experience of a genetic consult. The authors emphasize however that health care providers should not assume that people with experiential knowledge of a particular AR genetic condition will automatically have a better understanding of the risk of being a carrier for other genetic conditions given the fact that the most cited reason to decline RGCS was no family history for other AR conditions (15). Our study findings highlight the possible influence of certain factors such as gender, having children, etc. Therefore we believe that RGCS should ideally be implemented through a tailored implementation strategy where individual needs and preferences can be taken into account. For example, attention can be given to making the offer available in such a way that everyone can

be informed about the existence of the screening offer. For the healthcare setting in Flanders (Belgium) this could mean to offer RGCS through multiple health care providers. This could be done by gynaecologists and general practitioners who are actively involved in guiding families planning a pregnancy and pregnant women. But information about RGCS could also be given through for example paediatricians who are in close contact with young parents to avoid the misconception that RGCS is only of relevance for first-time parents. In addition, reimbursement of test costs could be considered to improve equal access.

Study limitations

Our study employed convenience sampling to recruit participants, therefore our reported results should be interpreted with caution. Another limitation of our study is that we didn't offer an actual RGCS test to participants so some results are only hypothetical. Actual participation might differ from the intention to do a behaviour.

CONCLUSION

We observed a positive correlation between attitude score/knowledge score and the intention to have RGCS. Furthermore our results indicate a possible influence of certain socio-demographic factors such as gender, education level, having children, etc. on the knowledge, attitudes and preferences regarding reproductive genetic carrier screening among reproductive-aged men and women. Based on our study findings we recommend to implement RGCS through a tailored implementation strategy where individual needs and preferences can be taken into account.

AUTHOR'S CONTRIBUTIONS

E.V.S, H.D., I.G., S.V.E. and P.B. designed the study. The data-collection was carried out by H.D., I.G., S.V.E. and E.V.S. The data-analysis was performed by E.V.S. A first draft of the manuscript was written by E.V.S. and critically discussed and revised by H.D., I.G., S.V.E., P.B., H.P., K.P. and G.M. P.B. coordinated the study. All the authors have approved the final version.

ACKNOWLEDGEMENTS

The authors would like to express their gratitude to all pharmacies throughout Flanders that allowed our research team to recruit potential participants in their pharmacies. Furthermore they would like to thank all participants that took a moment of their time to complete our questionnaire.

Table 1: Internal Reliability Analyses of Knowledge and Attitude scale

Measure	Description	Items	Reliability	Range	Cut-off	Mean	Outcome
Knowledge scale	Knowledge of ECS	14 questions (True/False/I don't know)	0.729[a]	0-14	0-4 = Low knowledge; 5-9 = Moderate knowledge; 10-14 = High knowledge	10.61 (2.61)	Low knowledge = 2.2%; Moderate knowledge = 26.3%; High knowledge = 71.5%
Attitude scale	Attitudes towards having ECS	Five bipolar words pairs (5-point Likert scale)	0.889[b]	5-25	5-11= Negative attitude; 12-18= Neutral attitude; 19-25= Positive attitude	18.15 (4.82)	Negative attitude = 10.6%; Neutral attitude = 40.4%; Positive attitude = 49%

[a] Removing knowledge item 5 would result in a slightly higher Cronbach's Alpha (13 items, α=0.739).
[b] Removing attitude item 4 would have resulted in a slightly higher Cronbach's Alpha (4 items, α=0.892). We decided against removal of these items because of the minimal differences in scores.

Table 2: Perceived susceptibility, acceptability & intention to participate in RGCS

N (%)				
Perceived susceptibility of being a carrier of a hereditary condition (n=386)				
Very low	Low	Average	High	Very high
75 (19.4)	132 (34.2)	92 (23.8)	54 (14)	33 (8.5)
Perceived susceptibility of conceiving a child with a hereditary condition (n=386)				
Very low	Low	Average	High	Very high
100 (25.9)	150 (38.9)	90 (23.3)	34 (8.8)	12 (3.1)
Acceptability of offering ECS to couples with a child wish (n=387)				
Totally unacceptable	Unacceptable	Neutral	Acceptable	Totally acceptable
2 (0.5)	8 (2.1)	44 (11.4)	144 (37.2)	189 (48.8)
Intention to participate in ECS (n=387)				
Definitely will not	Probably will not	Undecided	Probably will consider	Definitely will consider
27 (7)	40 (10.3)	84 (21.7)	105 (27.1)	131 (33.9)

Table 3: Knowledge about ECS related concepts

Knowledge Score				
Mean (SD)	9.6 (2.74)			
IQR	8-12			
Range	0-14			
Level of genetic knowledge	N (%)			
Low	18 (4.7)			
Moderate	154 (40.1)			
High	212 (55.2)			
Knowledge scale (Correct answers)				
	(Correct answers)	True N (%)	False N (%)	I don't know N (%)
1	A carrier of a hereditary condition carries a mutation for that condition but does not have the condition himself/herself.	299 (78.1)	37 (9.7)	47 (12.3)
2	All serious conditions are determined by a genetic predisposition.	22 (5.7)	321 (83.3)	40 (10.4)
3	All hereditary conditions are expressed during childhood (<18 years).	12 (3.1)	313 (81.7)	58 (15.1)
4	A carrier screening test examines if you are at risk for developing one or more hereditary conditions.	135 (35.3)	174 (45.5)	73 (19.1)
5	Genetic carrier screening is only intended for individuals with an increased family risk (families where genetic conditions have already occurred).	90 (23.6)	221 (58)	70 (18.4)
6	You can be a carrier of a hereditary condition without this condition occurring in your own family	270 (70.3)	56 (14.6)	58 (15.1)
7	A carrier of a hereditary condition will always develop that specific condition and get related health problems.	9 (2.3)	339 (88.3)	36 (9.4)
8	If you are a carrier of a hereditary condition, all your offspring will also be a carrier of that specific hereditary condition.	19 (5)	337 (88)	27 (7)
9	If the (future) mother is a carrier of a recessive hereditary condition, all her children will develop this condition.	7 (1.8)	288 (75.2)	88 (23)
10	If both partners are carriers of a mutation for the same recessive hereditary condition, they a 50% chance each pregnancy to conceive a child with the condition for which	147 (38.3)	141 (36.7)	96 (25)
11	If both partners are carriers of a mutation for a different recessive hereditary condition, they have a 25% chance each pregnancy to conceive a child with one of both condition.	94 (24.5)	130 (33.9)	159 (41.5)
12	Two healthy individuals without health problems can have a child with an inherited condition.	315 (82)	23 (6)	46 (12)
13	When a preconceptional genetic carrier screening test does not identify an increased risk, this means with certainty that this couple will have a healthy child.	17 (4.4)	308 (80.4)	58 (15.1)
14	If both partners are carriers of the same genetic condition, they cannot conceive children naturally without this specific	24 (6.3)	251 (65.5)	108 (28.2)

Table 4: Attitudes towards RGCS & Preferences for the practical organization of a population-based RGCS offer

Attitude Score (n=387)						
Mean (SD)	18 (4.49)					
IQR	15-21					
Range	5-25					
Attitude groups(n=387)	N (%)					
Negative attitude	33 (8.5)					
Neutral attitude	170 (43.9)					
Positive attitude	184 (47.5)					
Attitude scale (n=387)						
	N (%)					
Harmful	7 (1.8)	20 (5.2)	111 (28.7)	141 (36.4)	108 (27.9)	Beneficial
Unimportant	27 (7)	45 (11.7)	117 (30.3)	115 (29.8)	82 (21.2)	Important
Bad thing	11 (2.8)	21 (5.4)	115 (29.8)	143 (37)	96 (24.9)	Good thing
Not reassuring	20 (5.2)	50 (12.9)	106 (27.4)	101 (26.1)	110 (28.4)	Reassuring
Undesirable	23 (6)	49 (12.7)	134 (34.7)	100 (25.9)	80 (20.7)	Desirable
Attitude statements						
N (%)						
Pressure (n=387)						
Definitely not	Probably not	Neutral	Probably yes	Definitely yes		
15 (3.9)	64 (16.5)	109 (28.2)	140 (36.2)	59 (15.2)		
Anxiety/worry (n=387)						
Definitely not	Probably not	Neutral	Probably yes	Definitely yes		
29 (7.5)	78 (20.2)	94 (24.3)	134 (34.6)	52 (13.4)		
Inferiority (n=387)						
Definitely not	Probably not	Neutral	Probably yes	Definitely yes		
83 (21.4)	125 (32.3)	86 (22.2)	76 (19.6)	17 (4.4)		
Availability (n=387, multiple answers possible)						
Gynaecologist	GP	CME	Pharmacist	Midwife	Internet	School
313 (80.9)	276 (71.3)	250 (64.6)	66 (17.1)	68 (17.6)	15 (3.9)	12 (3.1)
Test offer (n=380)						
All or nothing	Categories	Free choice				
140 (36.8)	84 (22.1)	156 (41.1)				
Results reporting (n=381)						
Individual	Couple-based	No preference				
194 (50.9)	134 (35.2)	53 (13.9)				
WTP (n=386)						
Yes	No	I'm not sure				
266 (68.9)	39 (10.1)	81 (21)				
WTP (n=265)						
<150 euro	151-300 euro	>300 euro				
120 (45.3)	106 (40)	39 (14.7)				

REFERENCES

1. Henneman L, Borry P, Chokoshvili D, Cornel MC, van El CG, Forzano F, et al. Responsible implementation of expanded carrier screening. European journal of human genetics : EJHG. 2016;24(6):e1-e12.
2. Morris J, Law M, Wald N. Is cascade testing a sensible method of screening a population for autosomal recessive disorders? American Journal of Medical Genetics Part A. 2004;128(3):271-5.
3. Archibald AD, Smith MJ, Burgess T, Scarff KL, Elliott J, Hunt CE, et al. Reproductive genetic carrier screening for cystic fibrosis, fragile X syndrome, and spinal muscular atrophy in Australia: outcomes of 12,000 tests. Genet Med. 2018;20(5):513-23.
4. Delatycki MB, Alkuraya F, Archibald A, Castellani C, Cornel M, Grody WW, et al. International perspectives on the implementation of reproductive carrier screening. Prenatal diagnosis. 2020;40(3):301-10.
5. Best S, Long J, Theodorou T, Hatem S, Lake R, Archibald A, et al. Health practitioners' perceptions of the barriers and enablers to the implementation of reproductive genetic carrier screening: A systematic review. Prenatal Diagnosis. 2021;41(6):708-19.
6. Braithwaite J, Marks D, Taylor N. Harnessing implementation science to improve care quality and patient safety: a systematic review of targeted literature. International Journal for Quality in Health Care. 2014;26(3):321-9.
7. Van Steijvoort E, Devolder H, Geysen I, Van Epperzeel S, Peeters H, Peeraer K, et al. Expanded carrier screening in Flanders (Belgium): an online survey on the perspectives of nonpregnant reproductive-aged women. Personalized medicine. 2021;18(4):361-73.
8. Tavakol M, Dennick R. Making sense of Cronbach's alpha. International journal of medical education. 2011;2:53.
9. van Dijke I, Lakeman P, Sabiri N, Rusticus H, Ottenheim CPE, Mathijssen IB, et al. Couples' experiences with expanded carrier screening: evaluation of a university hospital screening offer. Eur J Hum Genet. 2021;29(8):1252-8.
10. Bell CJ, Dinwiddie DL, Miller NA, Hateley SL, Ganusova EE, Mudge J, et al. Carrier testing for severe childhood recessive diseases by next-generation sequencing. Science translational medicine. 2011;3(65):65ra4-ra4.
11. Mello S, Stifano S, Tan AS, Sanders-Jackson A, Bigman CA. Gendered Conceptions of Preconception Health: A Thematic Analysis of Men’s and Women’s Beliefs about Responsibility for Preconception Health Behavior. Journal of Health Communication. 2020;25(5):374-84.
12. Almeling R, Waggoner MR. More and less than equal: How men factor in the reproductive equation. Gender & Society. 2013;27(6):821-42.
13. Johnston J, Zacharias RL. The future of reproductive autonomy. Hastings Center Report. 2017;47:S6-S11.

14. Robson SJ, Caramins M, Saad M, Suthers G. Socioeconomic status and uptake of reproductive carrier screening in Australia. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2020;60(6):976-9.
15. Nijmeijer S, Conijn T, Lakeman P, Henneman L, Wijburg FA, Haverman L. Attitudes of relatives of mucopolysaccharidosis type III patients toward preconception expanded carrier screening. European Journal of Human Genetics. 2020;28(10):1331-40.

CHAPTER 6

REASONS AFFECTING THE UPTAKE OF REPRODUCTIVE GENETIC CARRIER SCREENING AMONG NON-PREGNANT REPRODUCTIVE AGED WOMEN IN FLANDERS (BELGIUM)

Van Steijvoort, E., Demuynck, R., Peeters, H., Vandecruys, H., Verguts, J., Peeraer, K., Matthijs, G. & Borry, P. (2022) Reasons affecting the uptake of reproductive genetic carrier screening among non-pregnant reproductive aged women in Flanders (Belgium). *Journal of Genetic Counseling.* doi:10.1002/jgc4.1575

ABSTRACT

Reproductive genetic carrier screening (RGCS) allows to identify couples who have an increased likelihood of conceiving a child affected with an autosomal recessive or X-linked monogenic condition. Multiple studies have reported on a wide and fragmented set of reasons to accept or decline RGCS. Only few studies have been performed to assess the uptake of RGCS. Non-pregnant women visiting their gynaecologist were invited to complete a questionnaire assessing perceived susceptibility, the acceptability of offering RGCS, attitudes, the intention to participate in RGCS, reasons to accept or decline RGCS, as well as socio-demographic characteristics. Women who showed the intention to have RGCS were asked to consider a free RGCS offer. Most women (n=127) were between 25-34 years old (60%), in a relationship (91%) and wanted to have children (65%). Study participants had positive attitudes towards RGCS and the intention to consider RGCS in the future. Reasons to accept RGCS were being able to share genetic information with children or relatives (n=104/127, 82%), to prevent the birth of a child affected with a hereditary condition (n=103/127, 81%) and/or to know the chance of conceiving a child with a hereditary condition (n=102/127, 80%). Reasons for declining RGCS were the possible concerns that could arise when receiving test results (n=27/127, 21%), having no family history of hereditary disorders (n=19/127, 15%) and not wanting to take action based on test-results (n=13/127, 10%). Among test-intenders that met the inclusion criteria, 53% decided to participate in RGCS together with their male reproductive partner. More in depth research on the decision making process behind the choice to accept or decline a RGCS offer would be highly valuable to make sure couples are making informed reproductive choices.

Keywords: carrier screening / decision making / attitudes / perceived susceptibility / uptake / intention / carrier testing / preconception / risk perception

INTRODUCTION

Recessive conditions are individually rare but when considered collectively, they account for an important public health burden accounting for approximately 20% of infant mortality and 10% of all paediatric hospitalizations (1, 2). In the light of the Sustainable Development Goals of the United Nations, morbidity and disability outcomes are becoming increasingly important, especially in those settings where child mortality rates from preventable diseases have dropped significantly and non-communicable conditions represent a larger relative proportion of all under-five deaths (2). Reproductive genetic carrier screening (RGCS) for autosomal recessive and X-linked conditions allows for the identification of couples who have an increased likelihood of conceiving a child with a genetic condition. Information gained through carrier screening can be used to make informed reproductive decisions with regard to family planning (3). During the last decade, carrier screening has become available for an increasing number of pathogenic variants and is being made available to individuals regardless of family history, ethnic and/or geographic origin. Previous studies have shown an overall positive attitude towards RGCS and a considerable interest in RGCS within the general population (4-10). Actual uptake of RGCS is observed to be much lower than reported intentions to undergo RGCS (11-15).

Multiple studies have reported on a wide and fragmented set of factors to accept or decline RGCS. Some studies asked participants to elect the factor they considered the most important to either accept or decline RGCS (8, 16). In other studies participants were allowed to elect multiple response options (6, 11, 14, 17, 18). The desire to know the chance of having a child with a genetic condition and the ability to make informed reproductive decisions were mentioned as main reasons to elect RGCS by participants in different studies (14, 17, 19). In the American study by Rabkina et al. (2021) (19) more than half of participants who stated to be favourable or undecided about RGCS rated the feeling of reassurance after a negative test result as a very important factor that would influence their motivation to pursue RGCS. Similarly, the relief that would be felt following negative test results was an important factor for participants in two Dutch studies (8, 16). Different studies also assessed whether individuals would opt for RGCS: to spare the future child a life with a severe genetic condition (30%-53%) (6, 8, 9, 16, 18), to prevent the birth of an affected child (6% - 50%) (6, 8, 9, 16-18) or to prepare for a child with a genetic condition (2%-33%) (6, 8, 9, 14, 16, 18, 19). Some individuals (10%-27%) indicated that they viewed RGCS as an act of responsibility as a future parent (8, 9, 16). Other factors in favour of RGCS that were less often chosen by those surveyed are: a family history of a genetic condition (5%-17%) (6, 14, 19), a high perceived chance (10%-17%) (6, 18), the ability to share genetic information with family members (3%-15%) (6, 14, 18), the fear of regret (13%) (6, 18), the possibility to avoid an abortion (9%-11%) (8, 16), or advise and/or (social) expectations by others/partner (1%-6%) (6, 8, 9, 14, 18, 19).

The most common reasons to decline RGCS that have been reported so far are a negative family history for genetic conditions (48%-78%) (6, 14), a low perceived susceptibility (20% - 60%) (6, 14) and costs related to the screening test (11%-60%) (6, 14, 17, 19). Some individuals questioned the utility of RGCS as they would not act upon results (11%-38%) (6-8, 14, 16, 19). A general lack of interest to find out genetic information (27%-32%) (7, 11) or not wanting to know such information (3%- 23%) (8, 9, 11, 16, 17) have also been raised as factors to decline RGCS. While some individuals indicated they were opposed to such a way of child selection (4% - 32%) (8, 9, 16), others would decline RGCS because of practical (e.g. time) (11) or test limitations (e.g. too new, too many conditions included, etc.) (6, 14, 17, 19). Within the Dutch study of Nijmeijer et al. (2019) (6), some participants selected 'being afraid of test results' as a reason against RGCS. Likewise, some pregnant women in the studies by Propst et al. (2018) (14) (28%) and Cheng et al. (2020) (17) (21%) would decline RGCS because of the possible anxiety that could be felt after being identified as a carrier. In the Australian study by Ong et al. (2018) (7), some participants would choose against RGCS because of concerns regarding the negative impact test results could have on: their personal life (21%), on family members (18%) or on their ability to obtain heath, life and/or disability insurance (19%). Similarly, some participants in the Dutch studies of Schuurmans et al. (2020) (16) (9%) and Plantinga et al. (2016) (8) (13%) would turn down RGCS because they were afraid of the consequences for their relationship if both partners would be identified as carriers. Other reasons against RGCS that were reported are: privacy/discrimination issues (2%-13%) (7, 8, 11, 16, 19), trust issues (e.g. test results/companies that offer RGCS) (3%-10%) (7, 8, 16), partner's resistance (4%-6%) (6, 11), medicalization of pregnancy/medical treadmill (5%-13%) (7, 8, 16). Finally in the American study of Rabkina et al. (2021) (19), some participants within the group who were not interested in RGCS rated 'not wanting to be offered additional invasive testing during pregnancy' as a very important factor that would influence their decision.

So far, differences in study design, target population, study outcomes, etc. have limited meaningful comparison of the existing literature and/or conclusions that can be drawn from the body of evidence. We identified four studies (12, 13, 20, 21) that performed a retrospective review of databases containing medical records to assess uptake of RGCS. To the best of our knowledge, only four prospective research studies (11, 14, 16, 22) have assessed the uptake of RGCS for multiple conditions. Two of these studies (11, 16) offered RGCS free of charge in a research setting while participants in the two others studies (14, 22) had to pay out-of-pocket or relied on their insurance for (a partial) reimbursement. The aim of our study was twofold. First, we wanted to assess the perceived susceptibility of being a carrier/conceiving a child with a hereditary condition, the acceptability of offering RGCS to specific groups, attitudes towards RGCS, the intention to participate in RGCS and reasons to accept or decline RGCS among non-pregnant women of reproductive age visiting their gynaecologist. Second, we wanted to assess the uptake of a free RGCS offer among participants who showed the intention to have RGCS.

METHODS

For this study a cross-sectional survey was conducted using purposive sampling. Non-pregnant women of reproductive age (18-49 years) visiting a group practice of fourteen gynaecologists located in a city in Flanders (Belgium) were invited to answer a self-administered questionnaire (see supplementary material) between May 2019 and March 2020. Women were briefly informed about the study by their gynaecologist and were then referred to a researcher present within the private practice who was available for further assistance. Prior to completing the anonymous questionnaire, participants were asked to read a brief information leaflet (see supplementary material). Exclusion criteria were: women <18 or >49 years old, limited proficiency in Dutch and a current pregnancy.

The questionnaire was based on earlier studies assessing attitudes towards RGCS and the intention to have RGCS (5-8, 23). Participants were asked about their: age, highest level of completed education, religiosity, extent of religious involvement, relationship status, parity, future child wish and experience with genetic counselling. Five-point Likert scales were used to assess the perceived susceptibility of being a carrier/conceiving a child with a hereditary condition, the acceptability of offering RGCS, attitudes towards RGCS (24), the intention to participate in RGCS and reasons to accept or decline RGCS. All participants were asked to rate nine already listed reasons in favour of RGCS and seven against RGCS. In addition, participants had the option to name other reasons to accept or decline RGCS that were not mentioned yet. While designing our study questionnaire we followed the example of Cheng et al. (2020) (17), Ragnar et al. (2016) (9) and Ong et al. (2018) (7) to assess different reasons to accept or decline RGCS. Within these studies participants were asked to indicate whether a particular factor in favour or against RGCS would influence their choice to accept or decline. We hypothesized that this strategy would produce more insightful results with regard to the reasoning behind the choice to either accept or decline RGCS. In addition, we also believe that this way of questioning would allow a more meaningful comparison in between different studies.

Women who completed the questionnaire and who showed the intention to have RGCS (=answered yes to question 24 of the questionnaire – see supplementary material) were asked to consider participation together with their male partner in a clinical study where RGCS was offered free of charge. A separate contact form could be filled in by participants if they wished to be re-contacted by the researcher. At least one week after the initial contact moment, the researcher re-contacted participants to inquire about their decision to accept or decline the RGCS offer. The free RGCS offer was not presented to pregnant women and those not in a relationship. In addition, women over the age of 40 were also excluded. This decision was made in function of the specific Belgian context where insurance only provides a refund of IVF/ICSI related costs for women under the age of 43. As a result, identified carrier couples would still have the option to consider available reproductive options without a potential financial barrier. Participants were offered the test panel that was

developed by the Belgian medical centres for Human Genetics, including more than 1000 genes associated with autosomal recessive and X-linked conditions (25).

Data-analysis

Statistical analyses were performed using IBM SPSS® Statistics 28 for Windows. Descriptive analysis was used to describe socio-demographic characteristics and frequencies of all items included in the questionnaire. An overall attitude score was calculated for each participant, based on their answers to the five items of the attitude scale (min 5 - max 25) (24). This new variable was also reclassified into three categories: negative attitude (5–11), neutral attitude (12–18) and positive attitude (19–25). Some variables were recoded in meaningful groups for our comparative analysis. Participants were classified as highly educated when they held an academic degree from a University or a PhD, intermediate when they had completed non-university higher education and low when they did not complete any higher education studies. Rank-based non-parametric tests were performed to assess if there were any statistically significant differences between 2 (Mann-Whitney U) or more groups (Kruskall Wallis) of the independent socio-demographic variables. Post hoc pairwise comparisons were performed using Dunn's (1964) (26) procedure with a Bonferroni correction. A two-sided p-value <0.05 was considered statistically significant.

Ethics

Approval to conduct this human subject's research was obtained by the Research Ethics Committee UZ/KU Leuven (S62558, S63243). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Implied informed consent was obtained for individuals who voluntarily completed the survey questionnaire. The completed questionnaires were kept separate from contact forms to be offered a test. Participants gave written consent to be re-contacted by the researcher when filling in the contact form. Written informed consent for genetic testing was obtained from all individuals undergoing testing.

RESULTS

Socio-demographics

In total, 127 women completed the questionnaire, all of whom were not pregnant at the time. Most women were between 25-34 years old (61%, n=77/127), were in a relationship (91%, n=115/127), had completed some form of higher education (68%, n=87/127) and stated not to be religious (63%, n=80/127). A considerable of women indicated to have a future child wish (66%, n=83/127), while 43% (n=55/127) already had children at the time of completing the questionnaire. A small share of our study sample had received genetic counselling at a centre for human genetics in the past (9%, n=11/127) (Table 1).

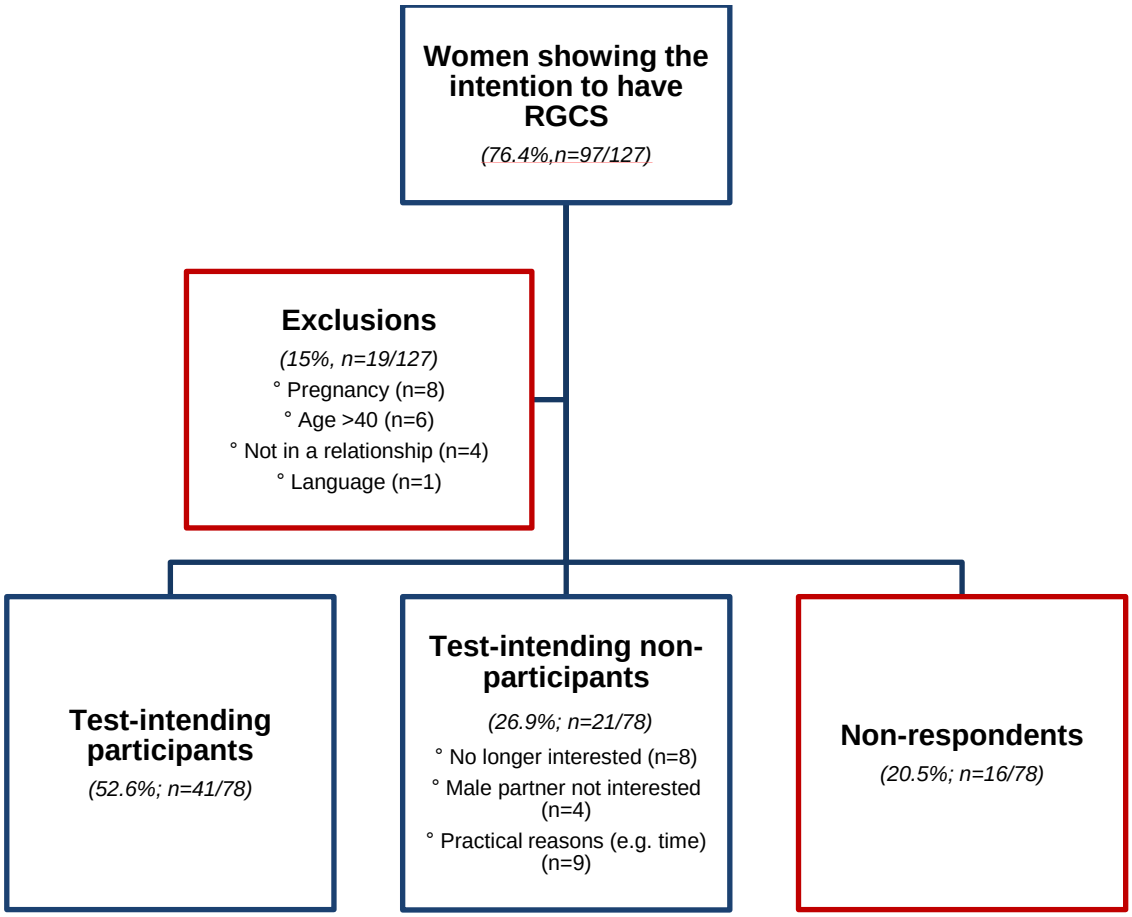
Perceived susceptibility & acceptability

A minority of the women in our study sample perceived the chance of being a carrier of a hereditary condition (17%, n=21/126) or the probability to conceive a child with a hereditary condition to be (very) high (13%, n=16/126). Our analysis showed a high degree of acceptability amongst study participants to offer RGCS to individuals (87%, n=111/127), to couples with a child wish (92%, n=117/127) or to pregnant women (90%, n=114/127). Non-religious participants (U=2262, z=2.140 p= 0.032) and participants without children (U=2358, z=2.063, p=0.039) showed a greater acceptance to offering RGCS to pregnant women.

Intention to have RGCS

Approximately 81% (n=102/126) of those surveyed would definitely/probably consider participating in RGCS. The majority of participants (86%, n=109/127) indicated that they would accept a RGCS offer if it was offered to them free of charge. Among women who expressed to have a future child wish, up to 90% (n=75/83) would accept the free offer compared to 77% (n=33/43) of participants who indicated to not have a (future) child wish or to be unsure about it ($\chi 2[1] = 4.283$, $p = 0.038$). Of those who were in a relationship at the time, 66% (n=76/115) believed that their reproductive partner would want to participate in RGCS (Table 2). A large proportion of women (76%, n=97/127) who were referred by their gynaecologist left their contact information with the researcher to be re-contacted in the context of the clinical study where RGCS was offered free of charge. Nineteen women who completed the questionnaire were not offered the free RGCS offer because they didn't meet the inclusion criteria. Within the group of test-intenders that met the inclusion criteria, 53% (n=41/78) decided to participate in the clinical study together with their male reproductive partner. Another 27% (n=21/78) of women were no longer interested to participate despite their initial intention to have RGCS. The remaining 20% (n=16/78) of test-intending participants became non-respondents who no longer answered our attempts to re-contact them (see Figure 1).

Figure 1: Overview of recruitment and inclusion of study participants



Attitudes

We observed a mean attitude score of 20.7 (SD 4.1, IQR 9-25). The largest group of participants had positive attitudes towards RGCS (72%, n=91/127). Only 2 women (2%) expressed a more negative attitude towards RGCS. The remaining participants had attitudes that were neutral (27%, n=34/127) based on our attitude scale. RGCS was found to be beneficial (80%, n=102/127), important (75%, 95/127), a good thing (78%, n=99/127), reassuring (69%, 88/127) and desirable (76%, n=96/127) by a large proportion of our participants. Only a minority of women believed RGCS to be harmful (5%, n=7/127), unimportant (6%, n=8/127), a bad thing (2%, n=3/127), not reassuring (7%, n=9/127) and undesirable (5%, n=6/127). Some participants were of the opinion that the pressure on future parents to have preconception RGCS will become substantial (38%, n=48/127) and that RGCS would lead to greater anxiety among couples who want to conceive (28%, 35/217). Religious participants expressed a higher concern regarding the pressure on future parents to have RGCS (U=1414, z=-2.416, p=0.016) while those in a relationship were more worried about the fact that RGCS may lead to more anxiety among couples who want to conceive (U= 438, z=-2.152, p=0.031). In addition, a small share of participants also expressed their concern that RGCS for hereditary conditions would make the lives of people living with these conditions seem inferior (8%, n=10/127) (Table 3).

Reasons to accept or decline RGCS

The vast majority of our study participants would accept RGCS because they want to be able to share genetic information with their own children/family members (82%, n=104/127), to prevent having a child with a hereditary condition (81%, n=103/127) or to know their chance of conceiving a child with a hereditary condition (80%, n=102/127). In addition, three quarters of participants agreed that wanting to spare a child a life with a hereditary condition (76%, n=96/127) and being able to prepare in advance for the possibility of having a child with a hereditary condition (76%, n=96/127) would be reasons to accept RGCS for them personally. About 68% (n=86/127) of our study sample indicated that they would accept RGCS out of curiosity to know their carrier status. Fewer participants would accept RGCS to not have regrets afterwards (48%, n=61/127) or out of fear of not being able to deal with a child with a hereditary condition (36%, n=46/127). A minority (8%, n=10/127) of the women in our study sample would accept RGCS because others expect them to do so. One in five (21%, n=27/127) participants agreed that they would decline RGCS because of the anxiety they might feel as a result of test results.

Most participants stated they wouldn't decline RGCS because of a negative family history (78%, n=99/127) or because it concerns rare conditions (78%, n=99/127). Likewise, most participants wouldn't decline RGCS because they are afraid of needles and blood (87%, n=111/127) or because it would take too much time and/or effort (87%, n=111/127). Finally, a minority would decline RGCS because they don't want to take action based on test results (10%, n=13/127) or because they are against the selection of children based on carrier screening test results (9%, n=11/127) (Table 4). Some participants provided other reasons to decline RGCS like: the cost of RGCS (n=1/127), pregnancy (n=1/127), low perceived susceptibility (n=1/127), trust issues about test results (n=1/127), composition of test panel (n=1/127) and the possible influence on the desire to have children (n=1/127). Younger participants (18-34 years, U= 2162, z=2.847, p=0.004), highly educated individuals (H(2) = 11, p=0.004) and women clearly expressing a future child wish (U=2171, z=2.146, p=0.032) were less likely to agree they would accept RGCS to be able to share genetic information with their own children or family members. A post hoc analysis using Dunn's procedure (26) with a Bonferroni correction for multiple comparisons revealed significant differences between those with a low and high (U=24, z=3.051, p=0.007), and intermediate and high (U=20, z=2.735, p=0.019) completed level of education. In addition, older participants (35-49 years) were more likely to agree they would accept RGCS to be able to spare child a life with a hereditary condition (U=2050, z=2.2, p=0.028). Finally, women expressing a future child wish were also more likely to agree they would accept RGCS out of curiosity to know their carrier status (U=1388, z=-2.13, p=0.033).

DISCUSSION

Our study results reveal a low perceived susceptibility of being a carrier/conceiving a child with a hereditary condition and a high degree of acceptability to offer RGCS among non-pregnant women of reproductive age visiting their gynaecologist. Participants showed positive attitudes towards RGCS and the intention to have RGCS in the future. Up to 80% of our participants would consider participating in RGCS in the future. Interestingly, even more participants (86%) stated that they would accept a RGCS offer if it was offered to them free of charge. Nevertheless only 76% of participants considered to participate in a clinical study where RGCS was indeed offered free of charge. The final uptake dropped even further to eventually 53% of participants.

In an American study by Nesbit et al. (2021) (22) reproductive-aged women presenting for a gynaecologic consult were recruited to determine the level of interest in preconception RGCS. Of all participants who were offered participation, only 41% (n=79/193) desired a referral to genetic counselling but less than half (44%, n=35/79) of these couples indeed scheduled and attended a counselling session. In the end, 37% (n=13/35) of non-pregnant women who attended a pre-test counselling session underwent preconception carrier screening for recessive conditions. Most participants within this group underwent expanded carrier screening (n=9/13) while some participants choose to have targeted screening (n=4/13). The differences between this and our study could possibly be explained by differences in study design like the fact that our participants received RGCS free of charge while participants in the American study by Nesbit et al. (2021) (22) had to pay out-of-pocket or relied on their insurance for (a partial) reimbursement. Schuurmans et al. (2020) (16) reported a test-offer acceptance of 4% (n=130/4295) among the total invited population of women aged 18-40 who were recruited through nine general practitioner (GP) practices in the Netherlands. The uptake of offer-acceptors who attended a pre-test consultation with their GP was 90% (n=117/130). Within our own study sample, all test-intending participants who attended the pre-test counselling session decided to accept the RGCS offer. While acknowledging that some participants who filled out our questionnaire were excluded because they didn't meet the inclusion criteria of the clinical study (e.g. pregnancy, age >40, etc.), our findings are in line with the earlier discussed discrepancy of reported intention to undergo RGCS hypothetically and actual uptake in particular during the preconception period (27).

Despite initially showing the intention to have RGCS, some women declined RGCS when they were re-contacted by telephone. For some individuals it might be easier to decline over the phone or to voice their choice to someone with whom they have no trusting relationship (e.g. researcher). Further reflection on the desirability to have RGCS might have caused one to switch choices. But some participants also indicated that they were still interested in the offer but declined because of practical reasons or the reluctant attitude of their male partner. This finding is in line with the results of Gilmore et al. (2017) (11) were most women who declined RGCS did this because of practical/logistical

issues (e.g. lack of time). We agree with the statement of the authors that the effort required to participate in RGCS could be estimated to be too high by participants according to the personal perceived potential value of RGCS at that specific moment in time.

Our study design deliberately provided a reflection period to participants to be able to discuss their choice to accept or decline the RGCS offer with their male partner. Therefore on-the-spot screening was not being offered. As raised by Nestbit et al. (2021) (22), we believe that we should be attentive to the way RGCS is being offered to avoid that participants accept RGCS out of convenience. Ideally, RGCS should therefore not be offered at the same time when patients are being informed about the option to undergo RGCS. In addition, efforts should be made to provide understandable, evidence-based and non-directive pre-test counselling.

Multiple studies (6-9, 11, 14, 16-19) have reported on a wide and fragmented set of factors to accept or decline RGCS. All these studies presented a specific list of factors in favour or against RGCS. Similarly to study participants (90%) in the American study by Propst et al. (2018) (14), most participants agreed with the statement that they would accept RGCS to know their chance of conceiving a child with a hereditary condition (80%). In contrast, our study results show quite different findings with previously reported results. More than three quarters of our study participants indicated that they would accept RGCS because they want to be able to share genetic information with their own children of family members. While in the studies of Propst et al. (2018) (14), van Dijke et al. (2021) (18) and Nijmeijer et al. (2019) (6) only very few participants (3%-15%) selected this reason in favour of RGCS. The differences in results could be possibly explained by the differences in answer possibilities. This example shows that some reasons might not be judged as the most important factor in favour of RGCS but could however still influence decision-making of participants. Another example to support our argument would be the ability to prepare in advance for the possibility of having a child with a hereditary condition. Within our study sample, up to 75% of participants agreed they would accept RGCS because of this reason while other studies (6, 8, 14, 16, 18) - with a different way of questioning - reported that this reason was not often chosen by study participants (2%-33%). Compared to earlier studies, our findings also show a larger share of participants who would elect RGCS to prevent the birth of an affected child or because of the fear of regret afterwards. Only a minority of our participants stated that they would elect RGCS because of the expectation of others. This last result is in line with earlier results reported by others studies (6, 8, 9, 18). Some participants (21%) in our study sample indicated that they would decline RGCS because of possible concerns that could arise when receiving test results. This finding is in line with the studies by Cheng et al. (2020) (17), Propst et al. (2018) (14) and Gilmore et al. (2017) (11) where a small share of participants indicated that they would be too anxious to be identified as a carrier of a recessive condition. In contrast, only 15% of participants would decline RGCS because of a negative family history compared to 78% of participants in the American study by Propst et al. (2018)

(14) and 48% in the Dutch study by Nijmeijer et al. (2019) (6). Interestingly, most participants (79%) in the study by Propst et al. (2018) (14) knew that they could be a carrier even without family history. Irrespective of background information provided, patients might have personal biases regarding perceived susceptibility. To avoid misconceptions, pre-test counselling initiatives could be improved by drawing more attention to this matter in particular.

Our study findings highlight many different reasons which could affect the uptake of RGCS. Pre-test genetic counselling services will be essential to ensure that those who are being offered RGCS will be able to make informed choices. More research is needed to identify ideal approaches to deliver these services, especially when offered in settings with a limited number of trained counsellors (22).

Study strengths & limitations

Our study has some limitations, including the fact that some participants might have been informed about the free RGCS offer prior to completing the questionnaire. As women were referred by their gynaecologist to the researcher, we are also not able to report on the proportion of women who declined participation in the survey questionnaire or their reasons for doing so. A large group of participants in our study sample had positive attitudes towards RGCS and showed the intention to have RGCS. As a result, our study results might not be a good representation of those who are more reluctant towards RGCS. In addition, participants were not excluded of study participation if they didn't have a (future) child wish. Therefore, some participants might have judged the potential value of RGCS to be rather low for them personally at the time of recruitment. Nevertheless, we don't believe RGCS should only be offered/available to couples with a very active child wish – because couples actively planning a family might not be willing to wait on test results to become pregnant. This would mean a missed opportunity to make informed reproductive decisions. As RGCS was offered free of charge within our research setting, we weren't able to assess the influence of the cost of RGCS. The strengths of this study lie in the prospective study design, the standardized way of providing background information, one researcher (E.V.S.) who acted as the central contact person throughout the study, the way of questioning reasons to accept or decline RGCS and the reflection period provided to study participants to be able to discuss their choice to accept or decline the RGCS offer with their male partner.

CONCLUSION

Our study results demonstrate that most non-pregnant women visiting their gynaecologist show the intention to have RGCS. However, not all test intending participants decided to take part in the clinical study where RGCS was offered free of charge. We observed an uptake of 53% of women who met our study inclusion criteria and showed the intention to have RGCS during the initial contact moment. Being able to share genetic information with children or relatives, to prevent the birth of a child affected with a hereditary condition and to know the chance of conceiving a child with a hereditary condition were reasons to accept RGCS for most of our participants. A small share of participants

stated they would decline RGCS because of possible concerns that could arise when receiving test results, having no family history of hereditary disorders and not wanting to take action based on test-results. More in depth research on the decision making process behind the choice to accept or decline a RGCS offer would be highly valuable to make sure couples are making informed reproductive choices. To be able to make evidence-based practice recommendations for the implementation of RGCS, future research projects should focus on meaningful outcomes for evaluation.

AUTHOR'S CONTRIBUTIONS

E.V.S., H.P., H.V., J.V., K.P., G.M. and P.B. designed the study. The data-collection was carried out by E.V.S. The data-analysis was performed by E.V.S. A first draft of the manuscript was written by E.V.S. and critically discussed and revised by R.D., P.B., H.P., H.V., J.V., K.P. and G.M. P.B. coordinated the study. All the authors have approved the final version.

ACKNOWLEDGEMENTS

The authors would like to thank all participants that took a moment of their time to complete our questionnaire. In addition they would like to express their gratitude to the team of gynaecologists who referred patients to the researcher.

Table 1: Socio-demographic characteristics of study participants

	N (%)
Gender (n=127)	
Female	127 (100%)
Age (n=127)	
18-34	90 (70.9)
35-49	37 (29.1)
Religion (n=127)	
Religious	47 (37)
Not religious	80 (63)
Religiosity (n=47)	
Not active	21 (44.7)
(Somewhat) active	26 (55.3)
Highest level of completed education (n=127)	
Primary/Secondary Education	40 (31.5)
Non-university higher education	49 (38.6)
University higher education	38 (29.9)
Relationship (n=127)	
Yes	115 (90.6)
No	12 (9.6)
Relationship status (n=113)	
Not living together	14 (12.4)
Living together/Married	99 (87.6)
Pregnancy (n=127)	
No	127 (100%)
Children (n=127)	
Yes	55 (43.3)
No	72 (56.7)
(Future) Child wish (n=126)	
Yes	83 (65.9)
No/ I don't know	43 (34.1)
Consultation at Centre for Human Genetics (n=127)	
Yes	11 (8.7)
No	116 (91.3)

Table 2: Risk perception, acceptability & intention to participate in RGCS[1]

N (%)				
Perceived susceptibility of being a carrier of a hereditary condition (n=126)				
Very low	Low	Average	High	Very high
26 (20.6)	42 (33.3)	37 (29.4)	16 (12.7)	5 (4)
Perceived susceptibility of conceiving a child with a hereditary condition (n=126)				
Very low	Low	Average	High	Very high
27 (21.4)	52 (41.3)	31 (24.6)	15 (11.9)	1 (0.8)
Acceptability of offering ECS to individuals (n=127)				
Totally unacceptable	Unacceptable	Neutral	Acceptable	Totally acceptable
0 (0)	4 (3.1)	12 (9.4)	31 (24.4)	80 (63)
Acceptability of offering ECS to couples with a child wish (n=127)				
Totally unacceptable	Unacceptable	Neutral	Acceptable	Totally acceptable
0 (0)	3 (2.4)	7 (5.5)	35 (27.6)	82 (64.4)
Acceptability of offering ECS to pregnant women (n=127)				
Totally unacceptable	Unacceptable	Neutral	Acceptable	Totally acceptable
1 (0.8)	3 (2.4)	9 (7.1)	45 (35.4)	69 (54.3)
Intention to participate in ECS (n=126)				
Definitely will not consider	Probably will not consider	Undecided	Probably will consider	Definitely will consider
2 (1.6)	6 (4.8)	16 (12.7)	28 (22.2)	74 (58.7)
Acceptance Free offer (n=127)				
Yes	I'm not sure	No		
109 (85.8)	15 (11.8)	3 (2.4)		
Acceptance Partner (n=115) (those in a relationship)				
Yes	I'm not sure	No		
76 (66.1)	32 (27.8)	7 (6.1)		

[1] Reproductive Genetic Carrier Screening

Table 3: Attitudes towards RGCS[1]

Attitude Score						
Mean (SD)			20.7 (4.1)			
IQR			18-25			
Range			9-25			
Attitude groups			N (%)			
Negative attitude			2 (1.6)			
Neutral attitude			34 (26.8)			
Positive attitude			91 (71.7)			
Attitude scale						
	N (%)					
Harmful	3 (2.4)	4 (3.1)	18 (14.2)	40 (31.5)	62 (48.8)	Beneficial
Unimportant	2 (1.6)	6 (4.7)	24 (18.9)	36 (28.3)	59 (46.5)	Important
Bad thing	1 (0.8)	2 (1.6)	25 (19.7)	40 (31.5)	59 (46.5)	Good thing
Not reassuring	3 (2.4)	6 (4.7)	30 (23.6)	33 (26)	55 (43.3)	Reassuring
Undesirable	2 (1.6)	4 (3.1)	25 (19.7)	41 (32.3)	55 (43.3)	Desirable
Attitude statements						
N (%)						
Pressure (n=127)						
Definitely not	Probably not		Neutral	Probably yes	Definitely yes	
12 (9.4)	22 (17.3)		45 (35.4)	36 (28.3)	12 (9.4)	
Anxiety/worry (n=127)						
Definitely not	Probably not		Neutral	Probably yes	Definitely yes	
14 (11)	35 (27.6)		43 (33.9)	28 (22)	7 (5.5)	
Inferiority (n=127)						
Definitely not	Probably not		Neutral	Probably yes	Definitely yes	
57 (44.9)	43 (33.9)		17 (13.4)	7 (5.5)	3 (2.4)	

[1] Reproductive Genetic Carrier Screening

Table 4: Reasons to accept or decline RGCS[1]

I would accept ECS because …				
		(Strongly) disagree	Neutral	(Strongly) Agree
1	… I am curious to know my carrier status.	21 (16.5)	20 (15.7)	86 (67.7)
2	… I want to prevent having a child with a hereditary condition.	10 (7.9)	14 (11)	103 (81.1)
3	… I want to spare a child a life with a hereditary condition.	8 (6.3)	23 (18.1)	96 (75.6)
4	… I am afraid of not being able to deal with a child with a hereditary condition	51 (40.2)	30 (23.6)	46 (36.2)
5	… I want to be able to prepare in advance for the possibility of having a child with a hereditary condition.	13 (10.2)	18 (14.2)	96 (75.6)
6	… I don't want to have regrets afterwards.	36 (28.3)	30 (23.6)	61 (48)
7	… I want to be able to pass on genetic information to my own children or family members.	6 (4.7)	17 (13.4)	104 (81.9)
8	… others expect this from me.	112 (88.2)	5 (3.9)	10 (7.9)
9	… I want to know my risk of conceiving a child with a hereditary condition.	7 (5.5)	18 (14.2)	102 (80.3)
I would decline ECS because …				
1	… there are no genetic conditions that run in the family.	99 (78)	9 (7.1)	19 (15)
2	… it concerns rare conditions.	99 (78)	16 (12.6)	12 (9.4)
3	… I don't want to take action based on test-results (before or during pregnancy).	97 (76.4)	17 (13.4)	13 (10.2)
4	… of the anxiety I might feel as a result of the test results.	73 (57.5)	27 (21.3)	27 (21.3)
5	… I am against the selection of children based on carrier screening test results	95 (74.8)	21 (16.5)	11 (8.7)
6	… I'm afraid of needles and blood.	111 (87.4)	7 (5.5)	9 (7.1)
7	… it would take too much time and/or effort.	111 (87.4)	7 (5.5)	9 (7.1)

[1] Reproductive Genetic Carrier Screening

REFERENCES

1. Bell CJ, Dinwiddie DL, Miller NA, Hateley SL, Ganusova EE, Mudge J, et al. Carrier testing for severe childhood recessive diseases by next-generation sequencing. Science translational medicine. 2011;3(65):65ra4-ra4.
2. Blencowe H, Moorthie S, Petrou M, Hamamy H, Povey S, Bittles A, et al. Rare single gene disorders: estimating baseline prevalence and outcomes worldwide. J Community Genet. 2018;9(4):397-406.
3. Henneman L, Borry P, Chokoshvili D, Cornel MC, van El CG, Forzano F, et al. Responsible implementation of expanded carrier screening. European journal of human genetics : EJHG. 2016;24(6):e1-e12.
4. Briggs A, Nouri P, Galloway M, Yaklic JL, Maxwell R, Lindheim S. Patients' Awareness and Attitudes Towards Genetic Carrier Screening. Obstet Gynecol. 2017;129:88S-S.
5. Chokoshvili D, Belmans C, Poncelet R, Sanders S, Vaes D, Vears D, et al. Public Views on Genetics and Genetic Testing: A Survey of the General Public in Belgium. Genetic testing and molecular biomarkers. 2017;21(3):195-201.
6. Nijmeijer SCM, Conijn T, Lakeman P, Henneman L, Wijburg FA, Haverman L. Attitudes of the general population towards preconception expanded carrier screening for autosomal recessive disorders including inborn errors of metabolism. Molecular genetics and metabolism. 2019;126(1):14-22.
7. Ong R, Howting D, Rea A, Christian H, Charman P, Molster C, et al. Measuring the impact of genetic knowledge on intentions and attitudes of the community towards expanded preconception carrier screening. Journal of medical genetics. 2018;55(11):744-52.
8. Plantinga M, Birnie E, Abbott KM, Sinke RJ, Lucassen AM, Schuurmans J, et al. Population-based preconception carrier screening: how potential users from the general population view a test for 50 serious diseases. European journal of human genetics : EJHG. 2016;24(10):1417-23.
9. Ragnar ME, Tyden T, Kihlbom U, Larsson M. Swedish parents' interest in preconception genetic carrier screening. Ups J Med Sci. 2016;121(4):289-94.
10. Spencer S, Ewing S, Calcagno K, O'Neill S. Adopted Individuals' Views on the Utility and Value of Expanded Carrier Screening. Journal of Genetic Counseling. 2018;27(6):1341-8.
11. Gilmore MJ, Schneider J, Davis JV, Kauffman TL, Leo MC, Bergen K, et al. Reasons for Declining Preconception Expanded Carrier Screening Using Genome Sequencing. Journal of Genetic Counseling. 2017;26(5):971-9.
12. Higgins AS, Flanagan JD, Von Wald T, Hansen KA. Preconception Cystic Fibrosis Screening in Infertile Couples Using an Expanded Carrier Screening Test. Obstetrics & Gynecology. 2014;123:97S.

13. Larsen D, Ma J, Strassberg M, Ramakrishnan R, Van den Veyver IB. The uptake of pan-ethnic expanded carrier screening is higher when offered during preconception or early prenatal genetic counseling. Prenat Diagn. 2019.
14. Propst L, Connor G, Hinton M, Poorvu T, Dungan J. Pregnant Women's Perspectives on Expanded Carrier Screening. Journal of genetic counseling. 2018;27(5):1148-56.
15. Schuurmans J, Birnie E, van den Heuvel LM, Plantinga M, Lucassen A, van der Kolk DM, et al. Feasibility of couple-based expanded carrier screening offered by general practitioners. Eur J Hum Genet. 2019;27(5):691-700.
16. Schuurmans J, Birnie E, Ranchor AV, Abbott KM, Fenwick A, Lucassen A, et al. GP-provided couple-based expanded preconception carrier screening in the Dutch general population: who accepts the test-offer and why? European journal of human genetics : EJHG. 2020;28(2):182-92.
17. Cheng HYH, Wong GCY, Chan YK, Lee CP, Tang MHY, Ng EH, et al. Expanded Carrier Screening in Chinese Population - A Survey on Views and Acceptance of Pregnant and Non-Pregnant Women. Frontiers in genetics. 2020;11:594091.
18. van Dijke I, Lakeman P, Sabiri N, Rusticus H, Ottenheim CPE, Mathijssen IB, et al. Couples' experiences with expanded carrier screening: evaluation of a university hospital screening offer. Eur J Hum Genet. 2021;29(8):1252-8.
19. Rabkina L, Swanson A, Aufox S, Propst L, Fiddler M, Wagner A, et al. What women want: General population perspectives and access to preconception expanded carrier screening. Prenat Diagn. 2021;41(9):1057-65.
20. Giles Choates M, Stevens BK, Wagner C, Murphy L, Singletary CN, Wittman AT. It takes two: uptake of carrier screening among male reproductive partners. Prenat Diagn. 2020;40(3):311-6.
21. Simone L, Khan S, Ciarlariello M, Lin J, Trackman S, Heiman GA, et al. Reproductive male partner testing when the female is identified to be a genetic disease carrier. Prenat Diagn. 2021;41(1):21-7.
22. Nesbit CB, Pollack CC, Mascia NS, LaCroix VH, Applebee DM, Bosco AW, et al. Interest in and uptake of genetic counseling for preconception carrier screening when offered to predominantly white reproductive-age persons seeking gynecologic care at a single U.S. academic medical center. Journal of genetic counseling. 2021.
23. Lakeman P, Plass AMC, Henneman L, Bezemer PD, Cornel MC, Ten Kate LP. Preconceptional ancestry-based carrier couple screening for cystic fibrosis and haemoglobinopathies: what determines the intention to participate or not and actual participation? European Journal of Human Genetics. 2009;17(8):999-1009.
24. Lewis C, Hill M, Skirton H, Chitty LS. Development and validation of a measure of informed choice for women undergoing non-invasive prenatal testing for aneuploidy. European Journal of Human Genetics. 2016;24(6):809-16.

25. Van Steijvoort E, Devolder H, Geysen I, Van Epperzeel S, Peeters H, Peeraer K, et al. Expanded carrier screening in Flanders (Belgium): an online survey on the perspectives of nonpregnant reproductive-aged women. Personalized medicine. 2021;18(4):361-73.
26. Dunn OJ. Multiple Comparisons Using Rank Sums. Technometrics. 1964;6(3):241-52.
27. Van Steijvoort E, Chokoshvili D, W Cannon J, Peeters H, Peeraer K, Matthijs G, et al. Interest in expanded carrier screening among individuals and couples in the general population: systematic review of the literature. Human reproduction update. 2020;26(3):335-55.

CHAPTER 7

EXPLORING INFORMED CHOICE IN PRECONCEPTION REPRODUCTIVE GENETIC CARRIER SCREENING BY USING A MODIFIED MULTIDIMENSIONAL MEASURE OF INFORMED CHOICE

Van Steijvoort, E., Peeters, H., Vandecruys, H., Verguts, J., Peeraer, K., Matthijs, G. & Borry, P. (2022) Exploring informed choice in preconception reproductive genetic carrier screening by using a modified Multidimensional Measure of Informed Choice. *Patient Education and Counseling.* doi:10.1016/j.pec.2022.07.014

ABSTRACT

OBJECTIVES: To explore informed choice in reproductive genetic carrier screening (RGCS).

METHODS: Women visiting a gynaecologist practice in Flanders (Belgium) were asked to consider participation in a study where RGCS was offered for free to them and their male partner. A modified Multidimensional Measure of Informed Choice was used to determine whether couples who opted for RGCS made an informed choice. In addition, we assessed risk perception, feelings towards RGCS, anxiety and decisional conflict.

RESULTS: Most participants (82%, n=63/77) made an informed choice with regard to RGCS according to our modified MMIC. Thirteen participants made an uninformed choice due to insufficient knowledge and one participant because of insufficient knowledge and value-inconsistency. Anxiety scores were elevated for three participants. Two participants presented with decisional conflict.

CONCLUSION: Our results show high rates of informed choice among non-pregnant couples who were offered RGCS in a research study and received up to 30 minutes of pre-test counselling. Limited resources outside a research context may impact informed choice. Pre-test counselling initiatives for RGCS should ideally be organized in such a way that information can be provided at multiple time points to avoid information overload and to allow for a reflection period.

INTRODUCTION

Reproductive genetic carrier screening (RGCS) allows couples to identify whether they have an increased risk of conceiving a child with a particular genetic condition. If both parents are carriers of a pathogenic variant in the same autosomal recessive gene, they have a 25% chance of having an affected child in each pregnancy. When the mother is a carrier of an X-linked recessive condition, there is a 50% chance that the couple's male offspring will be affected. Several reproductive options are available to carrier couples like prenatal diagnosis, IVF/ICSI combined with preimplantation genetic testing for monogenic conditions (PGT-M), gamete donation, adoption or choosing not to have biological children (1).

Since 2019, RGCS has been available in Belgium for reproductive partners with a desire to have children in the future. The current Belgian screening offer includes more than 1000 genes associated with autosomal recessive and about a hundred X-linked conditions with parallel testing of both reproductive partners. For the majority of the conditions, carrier status is only being disclosed when both partners carry a pathogenic or likely pathogenic disease-causing variant in the same gene. In addition, individual carrier status for seven autosomal recessive conditions ((Medium-chain acyl-CoA dehydrogenase deficiency (ACADM), Cystic fibrosis (CFTR), Smith–Lemli–Opitz syndrome (DHRC7), Congenital deafness (GJB2), Beta-thalassemia (HBB), Phenylketonuria (PAH) and Spinal Muscalar Atrophy (SMN1)) and X-linked conditions (e.g. Duchenne Muscular Dystrophy (DMD)) is being communicated to allow cascade testing of biological relatives. Professional organizations, like the American College of Medical Genetics and Genomics and the European Society of Human Genetics, have emphasized that the success of RGCS should not solely be measured screening uptake. An assessment of whether or not individuals/couples are making informed choices with regard to RGCS is considered to be at least as important (1, 2).

A systematic review by Ames et al. (3) identified different approaches to measure informed choice in reproductive genetic screening. The most widely used and validated measure is the Multidimensional Measure of Informed Choice (MMIC) developed by Marteau et al. (3, 4). This measure defines an informed choice as 'one that is based on relevant knowledge, consistent with the decision-maker's values and behaviourally implemented' (4). While the MMIC originally was developed for Down syndrome screening (DSS), it has already been modified and applied in the context of carrier screening for single gene conditions like Fragile X Syndrome (5, 6) or carrier screening for multiple conditions (7, 8). To the best of our knowledge only two recent Dutch studies (7, 8) have assessed informed choice with regard to RGCS for multiple recessive conditions by using a modified version of the MMIC. One study by van Dijke et al. (8) assessed experiences of both high-risk individuals (n=89) and individuals with a general population risk (n=43) who paid for RGCS themselves. Within this study, 86% of individuals who opted to have RGCS in a non-commercial clinical setting made an informed choice (8). No significant differences were found between both

groups of participants. Another study by Schuurmans el al. (7) reported how the proportion of participants (n=237) who made an informed choice raised from 83% to 97% after a pre-test counselling session provided by general practitioners (GP) who received a specific training in the context of the implementation study. Within this study, RGCS was offered free of charge to couples planning to have children. Results from our previous survey studies indicate that reproductive aged men and women in Flanders (Belgium) find it acceptable to offer RGCS to couples with a desire to have children (84%-92%). Most participants also stated that they would consider to participate in RGCS in the future (61%-81%). The majority of those surveyed selected the gynaecologist as the preferred provider of RGCS (81%-90%). (9, 10).

It is known that the intention to have a hypothetical screening offer doesn't always translate into actual test uptake. Many internal and external factors can have an influence on actual behaviour. As a result, behaviour might no longer correlate with the values of an individual (11, 12). To gain more insights into the complexity of the intention–behaviour gap (11) and the decision-making process of couples regarding RGCS we performed a prospective study where RGCS was offered free of charge to couples who showed the intention to have RGCS. The aim of this study was to assess risk perception, feelings towards RGCS, informed choice, anxiety and decisional conflict among couples who were offered RGCS for free. The findings presented in this article are part of a larger research project on the implementation of RGCS in Belgium.

METHODS

Women visiting a gynaecologist practice in Flanders (Belgium) were asked to consider participation in a research study where RGCS was offered for free to them and their male partner. Participation was conditional on completing an anonymous questionnaire that assessed reasons to accept or decline RGCS, etc. (13). A separate contact form could be filled in by female participants if they wished to be re-contacted by the researcher. At least one week after the initial contact moment, the researcher re-contacted the female participants to inquire about their decision to accept or decline the RGCS offer. If participants were interested, an appointment was scheduled for a counselling session with the researcher. Both reproductive partners had to be present during this counseling session. All counselling sessions were performed by the same researcher who has a background in Midwifery and Health Promotion (E.V.S.). Prior to the counselling session, participants were sent an information brochure about the study and the informed consent (ICF) form by email. This information brochure was specifically developed in the context of this research project by the research team.

During each counselling session participants were provided with information on RGCS as well as on the research project, and specific questions of participants were answered (+/- 30 minutes). More details on the information provided within the study brochure and the counseling session can be found in 'Supplementary Materials'. Couples who wished to proceed with RGCS were asked to read

and both sign the ICF. Subsequently, participants were asked to complete an individual self-administered questionnaire assessing risk perception, feelings towards RGCS, the Multidimensional Measure of Informed Choice (MMIC) (4), the State-Trait Anxiety Inventory (STAI-6) and a low-literacy version of the decisional conflict scale (DCS) (14). Blood samples were collected after informed consent had been obtained and questionnaires were completed. Women who were pregnant, >40 year old women, individuals with a history of bone marrow transplantation, minors and those not able to read and write in Dutch or not able to give informed consent were excluded from participation in this study. Study materials were only available in Dutch. Recruitment took place between May 2019 and September 2020.

Questionnaire

Perceived susceptibility (risk perception)

The perceived susceptibility of being a carrier of a hereditary condition and the perceived susceptibility of conceiving a child with a hereditary condition was measured using a 5-point Likert scale.

Feelings towards RGCS

To assess feelings towards RGCS participants were asked to indicate to what extent they agreed with eleven statements on a 5-point Likert scale.

Multidimensional measure of informed choice

A modified MMIC was used to determine whether an informed choice had been made. This measure included a knowledge scale, an attitude scale (15, 16) and test-uptake. An informed choice was made when participants had good knowledge and attitudes were consistent with test–uptake. Uninformed choice could occur because of value-inconsistency or due to insufficient knowledge. Reliability of the knowledge (14 items, $\alpha = 0.729$) and attitude scales (five items, $\alpha=0.889$) have been assessed before using Cronbach's Alpha and indicated good internal consistency (9, 10).

Knowledge scale

A knowledge scale containing 14 items that was previously developed (9) was used as part of the MMIC. The knowledge scale was developed to assess knowledge of the following key concepts with regard to RGCS: carrier status of recessive conditions, autosomal recessive inheritance, X-linked recessive inheritance, preconceptional RGCS, target group RGCS, residual risk and available reproductive options for carrier couples. Each knowledge question could be answered by the participant as 'true', 'false' or 'I don't know'. A knowledge score (min 0 to max 14) was calculated for each participant by combining the responses of the 14 knowledge items. If a question was answered correctly this resulted in one point. No points were given for questions that were answered incorrectly

or when participants indicated not knowing the answer. Missing data on the knowledge questions were also treated as incorrect answers. The cut-off for good knowledge was set at 10 out of 14 questions answered correctly. This cut-off score for good knowledge was determined by consensus among the involved researchers after our literature search identified different scales to assess knowledge and cut-off scores to define good knowledge (7, 8).

Attitude scale

The attitude scale used in this study included five antonyms (harmful/beneficial; unimportant/important; bad thing/good thing; not reassuring/reassuring; undesirable/desirable). This scale has been used and validated in previous research focusing on informed decision making in the context of (non-invasive) prenatal screening (15, 16). Based on the answers of the five antonyms we computed an overall attitude score (min. 5 to max. 25). This new variable was also reclassified into three categories: negative attitude (5–11), neutral attitude (12–18) and positive attitude (19-25) (15, 16). Participants with a neutral attitude with respect to RGCS were excluded from the analysis. A decision was value-consistent when there was consistency between the participant's attitude (values) and test-uptake (behaviour).

Decision-making outcomes

Within this study we included additional items related to the decision making process that are not included in the MMIC. Anxiety was measured using the STAI-6 (17) and transferred to prorated 20-item STAI scores (score range 20–80). A score ≥40 was considered clinically relevant (8, 18, 19). To assess how participants felt regarding their choice we included the low literacy version of the DCS (20). This validated scale assesses the perceived uncertainty about which course of action should be taken. Rather than evaluating whether the decision was informed, the DCS measures how an individual feels about the decision. Scores range from 0 (no decisional conflict) to 100 (extremely high decisional conflict). Decisional conflict is present when participants have a score ≥ 37.5. In addition, participants were asked to rate the level of difficulty to make a choice with regard to the RGCS offer for them personally and as a couple on a 5-point Likert Scale and to identify who had the biggest influence on the choice made (multiple choice question). The alpha coefficient for the STAI-6 (six items, $\alpha = 0.825$) and the DCS (ten items, $\alpha = 921$) indicated good internal reliability (21).

Data analysis

Statistical analyses were performed using IBM SPSS® Statistics 27 for Windows. Each participant was considered as an individual study subject. Descriptive analysis was used on single items. Non-parametric statistical tests were used to compare differences between independent groups. Post hoc pairwise comparisons were performed using Dunn's (1964) (22) procedure with a Bonferroni correction. To ensure meaningful comparison across groups some variables were regrouped as followed: age (18-24;25-34;35-44;45-49;>49), highest level of completed education

(low;intermediate;high) and child wish (yes; no/I'm don't know). A two-sided p-value < 0.05 was considered statistically significant.

Ethics

The study protocol received ethical approval by the Research Ethics Committee UZ/KU Leuven (S63243). Participation was voluntary and participants had the right to stop at any time. All participants gave written informed consent. The research was conducted in accordance with the Declaration of Helsinki and local statutory requirements.

RESULTS

Socio-demographic characteristics

In total, 41 couples (82 individuals) accepted the free RGCS offer. The mean age was 30 years (standard deviation 5, interquartile range [IQR] 27-33). Most participants didn't yet have children (83%) and showed to the desire to have children in the future (78%). Ten participants (12%) indicated that they already received genetic counselling in the past. Other socio-demographic characteristics of participants are presented in Table 1.

Perceived susceptibility (risk perception)

Almost half (48%) of participants perceived their chance of being a carrier of a hereditary condition to be moderate. Only a minority of participants perceived their risk of being a carrier (12%) or to conceive a child with a hereditary condition (1%) to be (very) high (Table 2). Over half of those surveyed perceived the risk of conceiving a child with a hereditary condition to be (very) low (57%).

Feelings towards RGCS

Being asked to think about RGCS before conception wasn't considered to be difficult by the vast majority of participants (91%). Most participants also stated that they wouldn't find it difficult to accept that they are a carrier of a hereditary condition while their partner is not (67%). Likewise, 78% of participants said they wouldn't find it difficult to accept that their partner is a carrier of a hereditary condition while they are not. One fifth of participants (21%) agreed that they would find it difficult to inform family members of their increased risk of being a carrier of a hereditary condition. Only some individuals agreed with the statements that the pressure on future parents to have RGCS before pregnancy will become great (15%), that the possibility to have RGCS will lead to increased anxiety among couples with a desire to have children (13%) and that they would feel less healthy if they would be identified as a carrier for a hereditary condition (12%). Most participants didn't believe that people would treat them differently if they knew their carrier status (79%), that RGCS would make the lives of people living with these conditions seem inferior (90%) or that RGCS would lead to a society in which there is no place for people living with certain hereditary conditions (88%).

Furthermore, 67% of participants disagreed with the statement that RGCS would lead to unrealistic expectations of conceiving a 'healthy child'. Male participants (mean rank=47.4 p=0.019) and participants who had had a genetic consult in the past (p=0.035) more often agreed that RGCS would lead to unrealistic expectations compared to female participants (mean rank=47.4) and participants who had never received genetic counselling (mean rank=39.04). Finally, participants who clearly expressed to have a desire to have children in the future were significantly less worried about the pressure on future parents to have RGCS before pregnancy (mean rank=38.03, p=0.010) or that RGCS would lead to a less inclusive society (mean rank=38.8, p=0.027). More detailed responses to the above discussed items can be found in 'Supplementary Materials'.

Multidimensional measure of informed choice

The mean observed knowledge score among participants was 10.4 (standard deviation 1.8, interquartile range [IQR] 5–12) and the mean observed attitude score was 22.4 (standard deviation 2.9, IQR 21-25). We observed significantly lower knowledge scores for religious participants (mean rank=30.6, p = 0.003) compared to those who stated not to be religious (mean rank=46.6). A Kruskal-Wallis test also revealed significant differences in knowledge score between groups that differed in completed education level (H(2)=10.8, p=0.004). A post hoc analysis using Dunn's procedure with a Bonferroni correction for multiple comparisons revealed that those with a low (mean rank= 29.36) completed level of education had a lower knowledge score compaered to those with ahigh (mean rank=49.36), p=0.003) completed level of education. Responses to individual knowledge and attitude items can be found in 'Supplementary Materials'. Five questionnaires were removed for the informed choice calculation because participants were classified as having a neutral attitude towards RGCS. Value-consistency was measured for 99% (n=76/77) of participants and 82% (n=63/77) of participants made a choice with sufficient knowledge. In total, 82% of participants made an informed choice with regard to RGCS according to our modified MMIC version. Thirteen participants (17%) made an uninformed choice due to insufficient knowledge and one participant (1%) because of insufficient knowledge and value-inconsistency (Table 3). Most individual participants that made an uninformed choice had a low education level (70%, n=9/13) and were between 35 and 44 years old (54%, n=7/13). For 25 couples (69%, n=25/36), both partners made an informed choice. In addition, there were 2 (6%, n=2/36) couples where neither of the partners made an informed choice which was due to poor knowledge. Lastly, there were also nine couples (25%, n=9/36) where one partner made an informed choice and the other partner made an uninformed choice. This group included three female and six male participants. One out of nine had a negative attitude and all nine had poor knowledge.

Decision-making outcomes

The vast majority of participants experienced the decision to have RGCS to be (very) easy on an individual basis (91%) and as a couple (91%). While some participants indicated that they had the biggest influence on the decision to accept the RGCS offer (37%), others indicated that their partner had dominated the decision (20%). For approximately four out of ten participants (38%), the decision to have RGCS was a shared choice between them and their partner. Four participants (5%) indicated that their decisions was influenced by family members (Table 4). There was a statistically significant association between sex and the influence on the decision to accept the RGCS offer ($p<0.001$). Within the group of women, 63% indicated they had the biggest influence compared to 10% of the men in our study sample. Just over half of male participants (52%) stated that the decision to have RGCS was a shared choice between them and their partner compared to 24% of female participants. The mean observed STAI score was 26.13 (standard deviation 7.9, IQR 20-33.3). Anxiety scores were elevated (score ≥40) and clinically relevant for three participants (4%, n=4/80). Two participants (2%, n=2/81) in our study sample presented with decisional conflict (score ≥37.5). Responses to items can be found in 'Supplementary Materials'.

DISCUSSION

The aim of this study was to assess risk perception, feelings towards RGCS, informed choice, anxiety and decisional conflict among couples who were offered RGCS for free. Almost half (48%) of our participants perceived their susceptibility of being a carrier to be moderate compared to 24% of respondents who participated in an earlier survey study we performed among reproductive aged men and women (10). While it is possible that those who perceive their risk of being a carrier to be higher are more inclined to participate in RGCS, this finding could also be explained by the fact that participants received an extensive information leaflet and face-to-face pre-test counselling where it was emphasized that according to estimates we are all carriers of recessive pathogenic variants (23). Noteworthy is the fact that only 12% of participants perceived their risk to be carrier of a recessive condition to be (very) high despite the information that was provided on multiple occasions.

According to our modified version of the MMIC, 82% of participants made an informed choice. This result is in line with the results of van Dijke et al. (86%) (8) and Schuurmans et al. (90%) (7) who both reported high levels of informed choice. However, caution is required when comparing these results as all three studies used their own knowledge scale to assess knowledge levels of participants and different cut-off's to define sufficient knowledge. This raises the question which specific knowledge someone needs to be able to make an informed choice with regard to RGCS (24). We agree with Richardson et al. (25) that a core outcome set is needed to avoid heterogeneity in outcomes and methods of measurement. This will indeed lead to more good quality research evidence that can be used to support the responsible implementation of RGCS and to inform policy makers.

Within our study, all but one of our participants made choices that were value-consistent (consistency between the participant's values and behaviour). Uninformed choice was mostly due to insufficient knowledge. These findings align with the results of the two previously discussed Dutch studies (7, 8). The proportion of participants in this study who had a good level of knowledge (82%) was considerably higher compared to respondents of our earlier survey (55%) study among reproductive-aged men and women (10). Knowledge items (K10-K11) with regard to inheritance patterns remained the least well-answered questions on our entire knowledge scale (9, 10). We believe that some understanding about the inheritance patterns of autosomal and X-linked recessive conditions is essential to be able to make an informed choice with regard to RGCS. As knowledge items are perceived to be important to varying degrees (24), we argue that more reflection is necessary to assess if all knowledge items should have an equal weight in the calculations of good knowledge. Knowledge scores were significantly higher for highly education individuals and non-religious participants which corresponds to the results of our previously published survey studies (9, 10). This finding might indicate that some individuals have specific information needs to gain knowledge to be able to make an informed choice. A more tailored approach to inform individuals about the possibility to have RGCS would be ideal, as this allows to taken into account individual needs.

Our study design required participants to undergo face-to-face pre-test counselling and to have a follow-up consultation, which may have influenced our study results. In practice, limited resources may restrict the availability of face-to-face pre-test counselling or a follow-up visit which could impact knowledge and therefore informed choice (8, 15, 26). Lewis et al. (26) reported how the rates of informed choice dropped from 89% in a highly controlled research environment to 75% when non-invasive prenatal testing was offered as part of routine clinical service. We believe pre-test counselling initiatives for RGCS should ideally be organized in such a way that information can be provided at multiple time points to avoid information overload and to allow for a reflection period. Providing information in advance could facilitate efficient and effective pre-test counseling (8). Interactive education tools like a decision aid could help clarify theoretical concepts in a non-directive way and stimulate a process of deliberation in settings with limited resources. In the Australian Reproductive Genetic Carrier Screening Program (ARGCSP), also known as "Mackenzie's Mission" (MM) a decision aid prompted discussion within couples and facilitated in depth consideration of screening (27). A decision aid could therefore be a very useful tool in supporting couples' decision-making and contribute to RGCS being feasible for scaled- up implementation. Future research exploring this outside a controlled research environment would be highly valuable. Overall, levels of anxiety and decisional conflict were within acceptable limits at the group level. But some individual participants did present with increased anxiety scores or decisional conflict. Similar results were reported by Birnie et al. (18) (same study as Schuurmans et al. (7) where most test acceptors had low levels of anxiety and high decisional conflict occurred only within 8% of participants after having

received genetic counselling. This could possibly be explained by to the fact that some individuals are more anxious than others or due to the fact that individuals received unsolicited information about the risk of conceiving a child with a genetic condition (18). Likewise, the mean anxiety score was not clinically elevated in the study of van Dijke et al. (8). Participants within the high risk group and pregnant women had higher anxiety levels compared to individuals from the general-risk group and non-pregnant women.

It's interesting - but maybe not surprising - that more female participants (63%) indicated that they had the biggest influence on the decision to have RGCS compared to male participants (10%). This could be explained by the fact that we initially recruited women visiting their gynaecologist and men were informed about the study by their partner at first. In the study of Schuurmans et al. (7) recruitment of couples also took place by inviting eligible women registered in the practices of the participating GP's. While we understand the rationale behind the choice of targeting females within the reproductive age category we would like to underline the importance of considering the role of male partners in RGCS. Two retrospective reviews of medical databases with clinical records have already reported that not all male partners of identified female carriers have concurrent screening for reproductive risk clarification (28, 29). This could potentially lead to a limited clinical utility of RGCS, especially in the context where RGCS is offered to individuals separately.

Study limitations

Our study has some limitations, one of which is our small sample size of test acceptors due to time and logistical constraints (e.g. budget). Additionally, the recruitment of participants was delayed because of the impact of the COVID-19 pandemic. Our study methodology didn't include test decliners because we wanted to focus on couples who opted for RGCS. But we acknowledge it is equally important to assess informed choice among test decliners. It is possible that some individuals declined participation because of the research context (inconvenience, timing) and not because they weren't interested in RGCS. We chose to use a modified MMIC to assess informed choice as this is the most widely used and validated measure currently available. Yet, this measure might not be able to pick up subtle nuances or take into account practical reasons (e.g. return visit) (15). Therefore we also performed qualitative interviews with some of our participants. Results of these interviews will also be reported in future publications. In addition, results of all individual items are provided and evaluated individually instead of only aggregate measures (24) to offer greater transparency. The quoted statistical significance levels should be interpreted with caution because of the use of multiple statistical testing.

CONCLUSION

This is the first prospective study exploring informed choice with regard to RGCS for a large test panel including more than 1000 genes associated with autosomal recessive and X-linked conditions.

Our results show high rates of informed choice among couples who were offered RGCS in a research study where participants received up to 30 minutes of pre-test counselling. Future research should assess if high levels of informed choice could also be achieved outside a controlled research context.

AUTHOR'S CONTRIBUTIONS

E.V.S., H.P., H.V., J.V., K.P., G.M. and P.B. designed the study. The data-collection was carried out by E.V.S. The data-analysis was performed by E.V.S. A first draft of the manuscript was written by E.V.S. and critically discussed and revised by P.B., H.P., H.V., J.V., K.P. and G.M. P.B. coordinated the study. All the authors have approved the final version.

ACKNOWLEDGEMENTS

The authors would like to thank all participants that participated in our study. In addition they would like to express their gratitude to the team of gynaecologists who referred patients to the researcher. Finally, we would like to thank Amicia Phillips for checking our manuscript for linguistic accuracy.

Table 1: Sociodemographic Characteristics of participants

	N (%)
Age (n=80)	
Mean (SD)	30 (5)
IQR	27-33
Range	19-51
Sex (n=82)	
Female	41 (50)
Male	41 (50)
Highest level of completed education (n=81)	
Low	22 (27.2)
Intermediate	23 (28.4)
High	36 (44.4)
Religiosity (n=82)	
Yes	26 (31.7)
No	56 (68.3)
Extent of religious involvement (n=26)	
Not active	17 (65.4)
Somewhat	9 (34.6)
Active	0 (0)
Children (n=82)	
Yes	14 (17.1)
No	68 (82.9)
(Future) Child wish (n=82)	
Yes	64 (78)
No/I don't know	18 (22)
(Future) Child wish – timing (n=64)	
< 1 year	25 (39.1)
1 – 2 years	23 (35.9)
> 2 years	16 (25)
Consanguinity (n=82)	
Yes	1 (1.2)
No	79 (96.3)
I'm not sure	2 (2.4)
Pregnancy (n=82)	
No	79 (96.3)
I'm not sure	3 (3.7)
Prior genetic consultation (n=81)	
Yes	10 (12.3)
No	71 (87.7)

Table 2: Perceived susceptibility (risk perception)

N (%)				
Perceived susceptibility of being a carrier of a hereditary condition (n=82)				
Very low	Low	Average	High	Very high
9 (11)	24 (29.3)	39 (47.6)	8 (9.8)	2 (2.4)
Perceived susceptibility of conceiving a child with a hereditary condition (n=82)				
Very low	Low	Average	High	Very high
14 (17.1)	33 (40.2)	31 (37.8)	3 (3.7)	1 (1.2)

Table 3: Multidimensional Measure of Informed Choice

Value-Consistency (n=77)			
	Attitudes	**Uptake**	**N (%)**
Value-consistent	Positive	Yes	76 (98.7)
Value-inconsistent	Negative	Yes	1 (1.3)
Knowledge-based (n=77)			
	Knowledge	**Uptake**	**N (%)**
Sufficient knowledge	High	Yes	63 (81.8)
Insufficient knowledge	Poor	Yes	14 (18.2)
MMIC (n=77)			
	Knowledge	**Attitudes**	**Uptake**	**N (%)**
Informed choice	High	Positive	Yes	63 (81.8)
Uninformed choice	High	Negative	Yes	0 (0)
	Poor	Positive	Yes	13 (16.9)
	Poor	Negative	Yes	1 (1.3)

Table 4: Decision-making outcomes

N (%)				
Individual level				
Very difficult	Difficult	Neutral	Easy	Very Easy
1 (1.2)	1 (1.2)	5 (6.1)	17 (20.7)	58 (70.7)
Couple level				
Very difficult	Difficult	Neutral	Easy	Very Easy
0 (0)	2 (2.4)	5 (6.1)	24 (29.3)	51 (62.2)
Influence on decision				
Me	My partner	My partner and me	Family	Friends
30 (37)	16 (19.8)	31 (38.3)	4 (4.9)	0 (0)

REFERENCES

1. Henneman L, Borry P, Chokoshvili D, Cornel MC, van El CG, Forzano F, et al. Responsible implementation of expanded carrier screening. European journal of human genetics : EJHG. 2016;24(6):e1-e12.
2. Gregg AR, Aarabi M, Klugman S, Leach NT, Bashford MT, Goldwaser T, et al. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(10):1793-806.
3. Ames AG, Metcalfe SA, Dalton Archibald A, Duncan RE, Emery J. Measuring informed choice in population-based reproductive genetic screening: a systematic review. European journal of human genetics : EJHG. 2015;23(1):8-21.
4. Marteau TM, Dormandy E, Michie S. A measure of informed choice. Health Expect. 2001;4(2):99-108.
5. Ames AG, Jaques A, Ukoumunne OC, Archibald AD, Duncan RE, Emery J, et al. Development of a fragile X syndrome (FXS) knowledge scale: towards a modified multidimensional measure of informed choice for FXS population carrier screening. Health Expect. 2015;18(1):69-80.
6. Metcalfe S, Jacques A, Archibald A, Burgess T, Collins V, Henry A, et al. A model for offering carrier screening for fragile X syndrome to nonpregnant women: results from a pilot study. Genet Med. 2008;10(7):525-35.
7. Schuurmans J, Birnie E, van den Heuvel LM, Plantinga M, Lucassen A, van der Kolk DM, et al. Feasibility of couple-based expanded carrier screening offered by general practitioners. Eur J Hum Genet. 2019;27(5):691-700.
8. van Dijke I, Lakeman P, Sabiri N, Rusticus H, Ottenheim CPE, Mathijssen IB, et al. Couples' experiences with expanded carrier screening: evaluation of a university hospital screening offer. Eur J Hum Genet. 2021;29(8):1252-8.
9. Van Steijvoort E, Devolder H, Geysen I, Van Epperzeel S, Peeters H, Peeraer K, et al. Expanded carrier screening in Flanders (Belgium): an online survey on the perspectives of nonpregnant reproductive-aged women. Personalized medicine. 2021;18(4):361-73.
10. Van Steijvoort E, Devolder H, Geysen I, Van Epperzeel S, Peeters H, Peeraer K, et al. Knowledge, attitudes and preferences regarding reproductive genetic carrier screening among reproductive-aged men and women in Flanders (Belgium). Eur J Hum Genet. 2022.
11. Sheeran P, Webb TL. The Intention-Behavior Gap. Soc Personal Psychol. 2016;10(9):503-18.
12. Van Steijvoort E, Chokoshvili D, W Cannon J, Peeters H, Peeraer K, Matthijs G, et al. Interest in expanded carrier screening among individuals and couples in the general population: systematic review of the literature. Human reproduction update. 2020;26(3):335-55.

13. Van Steijvoort E, Demuynck R, Peeters H, Vandecruys H, Verguts J, Peeraer K, et al. Reasons affecting the uptake of reproductive genetic carrier screening among nonpregnant reproductive-aged women in Flanders (Belgium). Journal of Genetic Counseling.n/a(n/a).
14. Linder SK, Swank PR, Vernon SW, Mullen PD, Morgan RO, Volk RJ. Validity of a low literacy version of the Decisional Conflict Scale. Patient Educ Couns. 2011;85(3):521-4.
15. Lewis C, Hill M, Skirton H, Chitty LS. Development and validation of a measure of informed choice for women undergoing non-invasive prenatal testing for aneuploidy. European Journal of Human Genetics. 2016;24(6):809-16.
16. van den Berg M, Timmermans DR, ten Kate LP, van Vugt JM, van der Wal G. Informed decision making in the context of prenatal screening. Patient Educ Couns. 2006;63(1-2):110-7.
17. Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). Br J Clin Psychol. 1992;31(3):301-6.
18. Birnie E, Schuurmans J, Plantinga M, Abbott KM, Fenwick A, Lucassen A, et al. Couple-based expanded carrier screening provided by general practitioners to couples in the Dutch general population: psychological outcomes and reproductive intentions. Genetics in medicine : official journal of the American College of Medical Genetics. 2021;23(9):1761-8.
19. Julian LJ. Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S467-72.
20. O'Connor AM. Validation of a decisional conflict scale. Med Decis Making. 1995;15(1):25-30.
21. Tavakol M, Dennick R. Making sense of Cronbach's alpha. International journal of medical education. 2011;2:53.
22. Dunn OJ. Multiple Comparisons Using Rank Sums. Technometrics. 1964;6(3):241-52.
23. Bell CJ, Dinwiddie DL, Miller NA, Hateley SL, Ganusova EE, Mudge J, et al. Carrier testing for severe childhood recessive diseases by next-generation sequencing. Science translational medicine. 2011;3(65):65ra4-ra4.
24. Ghanouni A, Renzi C, Meisel SF, Waller J. Common methods of measuring 'informed choice' in screening participation: Challenges and future directions. Prev Med Rep. 2016;4:601-7.
25. Richardson E, McEwen A, Newton-John T, Manera K, Jacobs C. The Core Outcome DEvelopment for Carrier Screening (CODECS) study: protocol for development of a core outcome set. Trials. 2021;22(1):480.
26. Lewis C, Hill M, Chitty LS. Offering non-invasive prenatal testing as part of routine clinical service. Can high levels of informed choice be maintained? Prenat Diagn. 2017;37(11):1130-7.
27. King E, Halliday J, Archibald AD, Delatycki M, Barlow-Stewart K, Newson AJ, et al. Development and use of the Australian reproductive genetic carrier screening decision aid. European Journal of Human Genetics. 2022;30(2):194-202.

28. Giles Choates M, Stevens BK, Wagner C, Murphy L, Singletary CN, Wittman AT. It takes two: uptake of carrier screening among male reproductive partners. Prenat Diagn. 2020;40(3):311-6.
29. Simone L, Khan S, Ciarlariello M, Lin J, Trackman S, Heiman GA, et al. Reproductive male partner testing when the female is identified to be a genetic disease carrier. Prenat Diagn. 2021;41(1):21-7.

CHAPTER 8

EXPERIENCES OF NON-PREGNANT COUPLES AFTER RECEIVING REPRODUCTIVE GENETIC CARRIER SCREENING RESULTS IN FLANDERS (BELGIUM)

ABSTRACT

OBJECTIVE: To assess the level of satisfaction, anxiety, long-term knowledge retention, psychosocial and counseling related aspects among couples who choose to have reproductive genetic carrier screening.

METHODS: Participants were initially informed about their screening results by telephone. After obtaining a written report of test results participants were asked to complete an individual self-administered questionnaire.

RESULTS: All participants (n=82) felt they had enough information to make an informed choice. None of the participants regretted their choice to have RGCS. The meaning of the obtained test results was sufficiently clear for most participants. Test results were most often shared with parents (61.2%) or siblings (37.3%). While some participants felt worried while waiting for the test results (16.4%) we observed no significant changes in anxiety levels over time ($p<0.262$). The mean knowledge score significantly increased from pre-intervention to post-intervention ($p<0.001$).

CONCLUSION: Our findings demonstrate that the information/counseling and reporting strategy that was used in the context of this study led to high participant satisfaction, an increase in knowledge over time and favorable psychosocial and counseling related outcomes.

INTRODUCTION

Reproductive genetic carrier screening (RGCS) allows the identification of couples who have an increased likelihood of conceiving a child with a particular monogenic recessive condition. The information gained through RGCS can be used to make informed reproductive decisions when planning for a future pregnancy (1).

In 2019, a Belgian RGCS offer became available to couples considering having children in the future including more than 1000 genes associated with multiple autosomal recessive (AR) and X-linked conditions. The screening offer is specifically intended for individuals who have no personal or family history for genetic conditions. All individuals who wish to undergo RGCS are asked to sign an informed consent form. Blood samples are taken from both reproductive partners simultaneously and the analysis is performed exclusively through the accredited laboratories of the Belgian genetic centres. Results are communicated as either a 'normal couple result' which means that there is no demonstrable increased risk or as an 'abnormal couple result' which entails that there is an increased risk of having a child with one of the genetic conditions screened for. In addition, patients obtain individual carrier status for seven of the most frequent AR conditions (ACADM, CFTR, DHRC7, GJB2, HBB, PAH and SMN1) and the X-linked conditions (female) to allow for cascade testing. Following the introduction of the Belgian RGCS offer we wanted to implement and evaluate a small-scale longitudinal study with three specific evaluative objectives. First, we wanted to assess the intention to have RGCS among non-pregnant couples in the general population recruited via a group practice of fourteen gynecologists located in a city in Flanders (Belgium). Secondly, we wanted to assess the extent to which couples make informed choices regarding participation in RGCS. Thirdly, we wanted to assess the level of satisfaction, anxiety, long-term knowledge retention, psychosocial and counseling related aspects among couples who choose to have RGCS and obtained their screening test results. Findings related to the first two objectives have been described elsewhere (2, 3). Within our study, most nonpregnant women visiting their gynecologist (81%) showed the intention to have RGCS (2). However, only a minority of those decided to accept the free RGCS offer. We have reported high rates of informed choice (82%) among couples who did choose to have RGCS (3). Here, we present the results related to the third objective of the research project.

METHODS

A detailed overview of the recruitment strategy and study set-up of this longitudinal study has been described earlier (2, 3). Participants were initially informed about their test RGCS results over the phone by a researcher (E.V.S.) between September 2019 and January 2021. Subsequently, a written report of test results was sent by registered mail to all participants. Each participant received an individual report including their couple-result, their individual test results for seven autosomal recessive conditions (ACADM, CFTR, DHRC7, GJB2, HBB, PAH and SMN1) and X-linked conditions (female participants). If there were any ambiguities or questions, participants were free to

contact the researcher for further explanation. Together with the written report of test results, participants also received the final questionnaire of the research project that was partially based on the research study performed by Lakeman et al. (2009)(4). Participants were asked to return the completed questionnaires by using the prepaid envelope that was provided to them. A one-time reminder email was sent to all the participants to help improve the response rate. The questionnaire assessed participant's satisfaction, long-term knowledge retention, anxiety and psychosocial/counseling related aspects. To assess knowledge and anxiety we used the same measures that were used within the questionnaires that participants were asked to fill out at the end of the pre-test counseling session (3). The knowledge scale including 14 knowledge items (score range 0-14) that were specifically developed for this research project has been described elsewhere (5, 6). Anxiety was measured using the State-Trait Anxiety Inventory (STAI-6) (7) and transferred to prorated 20-item STAI scores (score range 20–80). A score ≥40 was considered clinically relevant (8-10).

Data-analysis

Statistical analyses were performed using IBM SPSS® Statistics 28 for Windows. Descriptive analysis was used to describe socio-demographic characteristics and frequencies of all items included in the questionnaire. To determine changes over time in knowledge and STAI scores we used a Wilcoxon signed-rank test. Rank-based non-parametric tests (Mann-Whitney U) were performed to assess differences on knowledge scores and anxiety levels between independent groups (gender and carrier status). A two-sided p-value <0.05 was considered statistically significant.

Ethics

The research was conducted in accordance with the Declaration of Helsinki and local statutory requirements. Approval to conduct this human subject's research was obtained by the Research Ethics Committee UZ/KU Leuven (S63243). Written informed consent was obtained from all participants. Participation was voluntary and participants had the right to stop at any time.

RESULTS

The mean turnaround time for reporting test results was 39 weeks (SD 9, IQR 38-42). Twelve study participants (n=12/82; 14.6%) were identified as a carrier of one autosomal recessive (AR) condition and one female participant was identified to be carrier of an X-linked condition. We did not identify any 'carrier couples' where both partners were carriers of the same AR condition (see table 1). In total, 67 out of 82 participants who obtained their screening test results returned a completed questionnaire by mail resulting in a response rate of 81.7% (n=67/82). This group of 67 participants included nine participants who were identified as a carrier and eight participants whose partner was identified as a carrier of a genetic condition. Seven female participants were pregnant when receiving

their test results (n=7/41; 17.1%) One couple broke up while waiting for results, all other participants were still in a relationship with the same partner.

Satisfaction

None of the participants regretted their choice to have RGCS. The majority of participants also indicated that they would make the same choice to have RGCS if they had to decide again (n=62/67; 92.5%) and that they would recommend RGCS to couples with a desire to have children (n=63/67; 94%). All test results were initially communicated over the phone by the researcher (E.V.S.) who performed the pre-test counseling sessions and who acted as the central contact person throughout the study. Thirty couples chose the female partner as the first point of contact (n=30/41; 73.2%) to receive the test results and four couples (n=4/41; 9.8%) the male partner. In addition, seven couples (n=7/41; 17.1%) preferred to be informed individually. The vast majority of participants indicated to be (somewhat or completely) satisfied with the way results were communicated (n=61/67; 91%). The turnaround time was considered to be (way) too long by 58.2% (n=39/67) of participants (see supplementary material).

Psychosocial outcomes

If test results were shared with others (n=51/67; 76.1%), this was mostly done with parents (n=41/67; 61.2%), siblings (n=25/67; 37.3%) or friends (n=20/67; 29.8%). Some participants had communicated their test results to their gynaecologist (n=11/67; 16.4%), their general practitioner (n=4/67; 6%), other family members (n=6/67; 8.9%) or colleagues (n=3/67; 4.5%) at the time of completing the questionnaire. All identified carriers shared their test results with someone else (n=9; 100%) such as their parents (n=8/9; 89%), their siblings (n=6/9; 66.7%), friends (n=5/9; 56%), their general practitioner (n=3/9: 33%), their gynaecologist (n=3/9, 33%) or other family members (n=1/9; 11%). Only a minority of participants (n=5/67; 7.5%) indicated that they were concerned about the possibility that their family members could be carriers of the conditions that are included in the test. The decision to have RGCS did not impact the relationship of study participants (n=67/67; 100%). Similarly, most participants stated that the decision to have RGCS (n=63/67; 94%) and the test results they received (n=61/67, 91%) didn't impact the (possible) desire to have children with their current partner. A small proportion of participants felt worried while waiting for the test results (n=11/67; 16.4%). All participants felt confident that the screening results that they received were correct and 92.5% (n=62/67) of participants indicated not to feel worried about their own screening results. None of the participants agreed with the statement to feel less healthy after receiving their screening results (see supplementary material).

Counseling related aspects

The information brochure that study participants received through email before coming to the pre-test counseling session was completely read by 65.7% (n=44/67) of participants and partly by 31.1%

(n=21/67). All study participants stated that they had the feeling to have enough information to make an informed choice. Three participants (4.5%) looked up additional information before coming to the pre-test counseling session through the internet. Specifically, they searched for more information about the principles of inheritance (n=2) and more information about reproductive options of couples with an increased likelihood of conceiving a child with a hereditary condition (n=1). Most participants indicated that based on the information they obtained, it was sufficiently clear what their own individual result (n=64/67; 95.5%) and their couple result (n=66/67; 98.5%) entailed. One fifth of study participants (n=14; 20.9%) looked up additional information after receiving their screening results. This group of fourteen individuals, included nine individuals that were identified as a carrier of a monogenic condition and four partners of individuals that were identified as a carrier of a monogenic condition. Twelve participants looked up additional information through the internet,while two participants consulted their gynaecologist and two other participants consulted their general practitioner. Participants specifically sought more information about the principles of inheritance (n=1), more information on the condition of which they are a carrier (n=6) and more information about the conditions included in the test panel (n=8).

Knowledge

The mean knowledge score for our study sample was 11.8 (SD 2.5, IQR 10-14). Most participants (n=55/65; 84.6%) answered at least 10 out of 14 knowledge questions correctly. Most knowledge items on the knowledge scale were answered correctly by the vast majority of participants (83.6%-98.5%), with the exception of the questions assessing participants understanding of autosomal recessive inheritance which were answered correctly by far fewer participants (K10=40.3%; K11=56.7%) (see Table 2). No significant differences in knowledge scores were observed between female (n=41) and male (n=41) participants (U=400, z=-0.75, p=0.451) and those that were identified as a carrier (n=13) and those who were not (n=69) (U=247, z=-0.10, p=0.922). Knowledge scores improved over time for 45 participants and declined for six participants. In addition, no changes in knowledge score were observed for nine participants. A Wilcoxon signed-rank test determined a statistically significant median increase in knowledge scores from pre-intervention (median knowledge score during the pre-test counseling session=11) to post-intervention (median knowledge score after receiving screening results=13) (p<0,001, z=5.46). Nine out of ten participants (n=61/67; 91%) correctly answered that couples who receive a normal couple result still have a chance of conceiving a child with a hereditary condition and 97% (n=65/67) of participants understood that the risk for a couple with an increased likelihood of conceiving a child with a hereditary condition is not absolute.

State-Trait Anxiety Inventory

The mean STAI score for our study sample was 26.9 (SD 7.8, IQR 20-33.3). Five participants (7.5%) had anxiety scores that are considered clinically relevant (score ≥40) (see Table 3). Out of the five

participants with a clinically relevant STAI scores there was one individual that was identified as an individual carrier of an autosomal recessive conditions. Anxiety did not differ based on gender (U=449.5, z=-0.23, p=0.818) or carrier status (U=224, z=-0.7, p=0.484). The STAI score increased over time for 28 participants and declined for 16 participants. In addition, no changes in the STAI score were observed for another 16 participants. No statistically significant changes in STAI were observed from pre-intervention (median STAI score during the pre-test counseling session=23) to post-intervention (median STAI score after receiving screening results=23.3) ($p<0.262$, $z=1.12$).

DISCUSSION

Our study results demonstrate that most participants were satisfied with their choice to have RGCS (100%) and the way results were communicated (91%) which is in line with a previous Dutch study by van Dijke et al. (2021) where couples' experiences with a RGCS offer for 50 severe AR conditions were evaluated (10). All study participants stated that they had the feeling to have enough information to make an informed choice and that based on the information they obtained, it was sufficiently clear what their own individual result and their couple result entailed. We have previously shown that 82% of our study participants also made an informed choice with regard to RGCS according to our modified version of the Multidimensional measure of informed choice (3, 11). The information brochure that was developed in the context of the research study was not completely read by all participants. We would therefore like to underline the added value of giving information at multiple time-points and through different ways (e.g. information brochure, pre-test counseling session, telephone reporting of results, written test report) like it was organized in our study setting. We believe that an information brochure could complement but not replace more in-depth counseling. Providing information in advance could facilitate efficient and effective pre-test counseling (9). Interactive education tools like a patient decision aid could help clarify theoretical concepts in a non-directive way and stimulate a process of deliberation in settings with limited resources. If participants looked up additional information this was mostly done through the internet. Which also demonstrates the need to offer good quality information via this route.

The turn-around time was found to be too long by our study participants. The initially set turn-around time of +/- six months was not achieved in the majority of cases because of multiple reasons (COVID-19 pandemic, difficulties encountered during the analysis). Even though the turn-around time has currently been reduced to +/- 3 months, this finding shows how important it is to inform couples with a desire to have children about the possibility to have RGCS in due time to allow for informed reproductive decision-making. Some of the couples (10%) who participated in the study did not wait for their screening test results to get pregnant. This result might even be an underestimation given the fact that couples were also eligible to participate in this study when they were not actively planning for a family and the drop-out we encountered due to noncooperation of certain participants. At the moment of the pre-test counseling session 64 study participants (n=64/82, 78%) indicated to

have a desire to have children, of which 39.1% (n=25/64; 13 women and 12 men) within the timeframe of the next coming year. The seven women that became pregnant while waiting for the test results were indeed part of this group (n=7/13; 54%), whereas the six other female participants stated not to be pregnant at the time of filling out the questionnaire.

The mean knowledge score among study participants significantly increased from pre-intervention to post-intervention. While it is possible that participants looked up information while completing the questionnaire or discussed the knowledge questions with their partner in their home environment this finding could also be due to the fact that participants received information at multiple times. To the best of our knowledge there are no other studies that have assessed long-term knowledge retention of individuals from the general population without an a priori increased risk who had RGCS for multiple monogenic conditions. Previous studies focusing on screening for single gene conditions (e.g. Cystic Fibrosis, Tay-Sachs disease) have also reported a reasonable retention of knowledge among those who had screening (12-14). Noteworthy, is the study of Ioannou et al. (2010) where knowledge decreased among Ashkenazi Jewish high school student following the expansion of a screening programme for Tay Sachs disease with six additional conditions. The authors indicate that the increase in provided information on multiple conditions might have resulted in a lower level of genetic knowledge.

Only a small proportion of our study participants (7.5%) had STAI scores that were clinically relevant (≥40) after receiving their screening test results. In addition, no significant changes in anxiety levels were measured over time from pre-intervention to post-intervention. These results are in line with the findings of a Dutch study by Birnie et al. (2021) and an American study by Kraft et al. (2018) where no significant differences in mean STAI scores were found over time among couples from the Dutch general population who accepted a couple-based RGCS offer for 50 AR conditions provided by GP's (15) and couples who took part in a clinical study of preconception carrier screening using genome sequencing (16). Within the Dutch study of Birnie et al. (2021), 12.7% of test-acceptors had clinically relevant anxiety at six months after the counseling session with their GP (15). As Birnie et al. (2021) have pointed out, the absence of adverse psychological outcomes on a group level does not mean that the RGCS offer was anxiety-free for everyone. Our results have also shown that a RGCS offer can still potentially lead to increased anxiety for some individuals.

About three quarters of the participants (76.1%) shared their screening test results with others, and this was mainly with parents (61.2%) and/or siblings (37.3%). Test results were only shared to a very limited extent with health care providers like the gynaecologist (16.4%) and/or the general practitioner (6%). Participants that were identified as a carrier most often shared results with parents (89%) and siblings (66.7%) but only one identified carrier shared this information with other family members. These results may be explained by the fact that the questionnaires were sent out together

with the written report of test results and that therefore participants might not yet have had the opportunity to share their screening results with their health care providers or other family members. Carriers identified through CF population screening in an Australian study by Gorrie et al. (2018) most often reported speaking with a sibling and/or parent about their increased risk of being a carrier of CF (17) and much less with those outside the immediate family which is in line with our study results. It has been suggested that family members don't always receive sufficient information to be able to make an informed choice with regard to carrier screening (18). We believe that family communication after carrier identification through reproductive genetic carrier screening needs further investigation to assess to what extent cascade screening is being used in this context and which factors influence the decisions of family members. This would allow to have a more critical reflection on the desirability and utility of reporting individual test results for the opportunity to offer cascade screening in a context with limited resources for follow-up. In addition, it is noteworthy that some participants within the American study by Kraft et al. (2018) did not share their negative test results with their health care provider because they did not see the need to do so or because they assumed results were already included in their medical record (16). Health care providers should be aware of their responsibility for proper follow-up of patients to avoid that the implications of negative results are misunderstood by their patients.

Study strengths & limitations

One of the strengths of this study is that we recruited couples from the general population in a setting where RGCS will most likely be offered in the near future. In addition, the counseling sessions weren't performed by a trained genetics professional but by a researcher with a background in midwifery and health promotion. Within this study we focused on test-acceptors. As a result, we are not able to report on the views/experiences of test-decliners or those who initially showed the intention to have RGCS but finally decided not to participate in our study. Future research should pay specific attention to these specific groups. An additional study limitation is the fact that we only identified few carriers and no carrier couples. Our findings show that not all participants read the information brochure before coming to the pre-test counseling session. As this was one of the core aspects of information provision, this could have impacted test results. Future research projects might benefit from a more substantial evaluation of the methods of information used and/or a more diverse use of methods (e.g. animation video, comic, etc.) The last survey of our implementation study was also sent out together with the written report of test results immediately after participants received their screening results over the phone. Therefore we are not able to report long-term impact of receiving screening results (e.g. family communication,reproductive decision-making of at-risk couples, etc.). In addition, there should also be a close monitoring and evaluation of the clinical utility of the RGCS offer within the context of the ethical principles of autonomy, beneficence, and nonmaleficence. Especially considering that to date the clinical significance of pathogenic variants is incomplete (19).

Finally, results should be interpreted with caution due to the limited sample size and the drop-out we encountered due to noncooperation of certain participants.

CONCLUSION

Our results show that most participants were satisfied with their choice to have RGCS. Overall, anxiety levels were low and no significant changes were measured over time from pre-intervention to post-intervention while knowledge levels were generally high and significantly increased over time. The decision to have RGCS did not impact the relationship of participants or their desire to have children in the future. Only a small proportion of participants felt worried while waiting for the test results. Most participants positively evaluated the information/counseling and reporting strategy that was used in the context of this study.

AUHTOR'S CONTRIBUTIONS

E.V.S., H.P., H.V., J.V., K.P., G.M. and P.B. designed the study. The data-collection was carried out by E.V.S. The data-analysis was performed by E.V.S. A first draft of the manuscript was written by E.V.S. and critically discussed and revised by P.B., H.P., H.V., J.V., K.P. and G.M. P.B. coordinated the study. All the authors have approved the final version.

ACKNOWLEDGEMENTS

The authors would like to thank all individuals that participated in this study. In addition, they would like to express their gratitude to the team of gynecologists who have contributed to this study.

Table 1: Overview of identified carriers

N°	Sex	Inheritance	Condition
4M	Men	AR	Medium Chain AcylCoA dehydrogenase (MCAD) Heterozygote p.Lys329Glu mutation (HGVS nomenclatuur: NM_000016.5:c.985A>G) ACADM gene
7V	Women	AR	Cystic Fibrosis Heterozygote F508del (HGVS nomenclatuur: c.1521_1523del) CFTR gene
9M	Men	AR	Phenylketonuria Heterozygote p.Ser349 Pro (HGVS nomenclatuur: NM_000277.2:c.1045T>C) PAH gene
9V	Women	X-linked	Hemophilia A Heterozygote p.Glu132Asp (HGVS nomenclatuur: NM_000132.3:c.396A>C) FVIII gene
12V	Women	AR	Smith-Lemli-Opitz Syndrome Heterozygote p.Trp151* (HGVS nomenclatuur: NM_001360.2:c.452G>A) DHCR7 gene
12M	Men	AR	Congenital deafness Heterozygote p.Gly12Valfs*2 (HGVS nomenclatuur: NM_004004.5:c.35delG) GJB2 gene
21V	Women	AR	Medium Chain AcylCoA dehydrogenase (MCAD) Heterozygote p.Lys329Glu (HGVS nomenclatuur: NM_000016.5:c.985A>G). ACADM gene
24V	Women	AR	Medium Chain AcylCoA dehydrogenase (MCAD) Heterozygote p.Lys329Glu (HGVS nomenclatuur: NM_000016.5:c.985A>G). ACADM gene
25V	Women	AR	Spinal Muscular Atrophy 1 SMN1 gene
31V	Women	AR	Congenital deafness Heterozygote p.Met34Thr (HGVS nomenclatuur: NM_004004.5:C.101T>C). GJB2 gene
32V	Women	AR	Smith-Lemli-Opitz Syndrome Heterozygote p.Trp151* (HGVS nomenclatuur: NM_001360.2:c.452G>A) DHCR7 gene
34V	Women	AR	Medium Chain AcylCoA dehydrogenase (MCAD) Heterozygote p.Leu84Phe (HGVS nomenclatuur: NM_000016.5:c.250C>T) ACADM gene
38V	Women	AR	Cystic Fibrosis Heterozygote F508del (HGVS nomenclatuur: c.1521_1523del) CFTR gene

Table 2: Knowledge about RGCS related concepts

Knowledge Score				
	Mean (SD)	11.8 (2.5)		
	IQR	10-14		
	Range	5-14		
Level of genetic knowledge		**N (%)**		
	Low (0-4)	0 (0)		
	Moderate (5-9)	10 (15.4)		
	High (10-14)	55 (84.6)		
Meaning of a normal couple result (n=67)				
	Yes	61 (91)		
	No	6 (9)		
Meaning of an abnormal couple result (n=67)				
	Yes	65 (97)		
	No	2 (3)		
Knowledge scale				
		True N (%)	**False N (%)**	**I don't know N (%)**
1	A carrier of an hereditary condition carries a mutation for that condition but does not have the condition himself/herself.	61 (91)	4 (6)	2 (3)
2	All serious conditions are determined by a genetic predisposition.	1 (1.5)	59 (89.4)	6 (9.1)
3	All hereditary conditions are expressed during childhood (<18 years).	3 (4.5)	57 (85.1)	7 (10.4)
4	A carrier screening test examines if you are at risk for developing one or more hereditary conditions.	3 (4.5)	64 (95.5)	0 (0)
5	Genetic carrier screening is only intended for individuals with an increased family risk (families where genetic conditions have already occured).	1 (1.5)	65 (98.5)	0 (0)
6	You can be a carrier of a hereditary condition without this condition occuring in your own family	56 (83.6)	2 (3)	9 (13.4)
7	A carrier of a hereditary condition will always develop that specific condition and get related health problems.	1 (1.5)	62 (92.5)	4 (6)
8	If you are a carrier of a hereditary condition, all your offspring will also be a carrier of that specific hereditary condition.	5 (7.5)	57 (85.1)	5 (7.5)
9	If the (future) mother is a carrier of a recessive hereditary condition, all her children will develop this condition.	0 (0)	62 (92.5)	5 (7.5)
10	If both partners are carriers of a mutation for the same recessive hereditary condition, they have a 50% chance each pregnancy to conceive a child with the condition for which they are carriers	33 (49.3)	27 (40.3)	7 (10.4)
11	If both partners are carriers of a mutation for a different recessive hereditary condition, they have a 25% chance each pregnancy to conceive a child with one of both condition.	17 (25.4)	38 (56.7)	12 (17.9)
12	Two healthy individuals without health problems can have a child with an inherited condition.	61 (91)	5 (7.5)	1 (1.5)
13	When a preconceptional genetic carrier screening test does not identify an increased risk, this means with certainty that this couple will have a healthy child.	5 (7.5)	61 (91)	1 (1.5)
14	If both partners are carriers of the same genetic condition, they cannot conceive children naturally without this specific genetic condition.	4 (6)	59 (88.1)	4 (6)

Table 3: State-Trait Anxiety Inventory (STAI)

Knowledge Score (n=62)				
	Mean (SD)	26.9 (7.8)		
	IQR	20-33.3		
	Range	20-53		
N (%)				
I feel calm				
Not at all		Somewhat	Moderately	Very much
0 (0)		5 (7.5)	12 (17.9)	50 (74.6)
I am tense				
Not at all		Somewhat	Moderately	Very much
51 (76.1)		12 (17.9)	4 (6)	0 (0)
I feel upset				
Not at all		Somewhat	Moderately	Very much
63 (94)		4 (6)	0 (0)	0 (0)
I am relaxed				
Not at all		Somewhat	Moderately	Very much
1 (1.5)		2 (3)	23 (34.3)	41 (61.2)
I feel content				
Not at all		Somewhat	Moderately	Very much
1 (1.5)		5 (7.5)	25 (37.3)	36 (53.7)
I am worried				
Not at all		Somewhat	Moderately	Very much
45 (67.2)		19 (28.4)	3 (0)	0 (0)

REFERENCES

1. Henneman L, Borry P, Chokoshvili D, Cornel MC, van El CG, Forzano F, et al. Responsible implementation of expanded carrier screening. Eur J Hum Genet. 2016;24(6):e1-e12.
2. Van Steijvoort E, Demuynck R, Peeters H, Vandecruys H, Verguts J, Peeraer K, et al. Reasons affecting the uptake of reproductive genetic carrier screening among nonpregnant reproductive-aged women in Flanders (Belgium). Journal of Genetic Counseling.n/a(n/a).
3. Van Steijvoort E, Peeters H, Vandecruys H, Verguts J, Peeraer K, Matthijs G, et al. Exploring informed choice in preconception reproductive genetic carrier screening by using a modified Multidimensional Measure of Informed Choice. Patient Educ Couns. 2022.
4. Lakeman P, Plass AM, Henneman L, Bezemer PD, Cornel MC, ten Kate LP. Three-month follow-up of Western and non-Western participants in a study on preconceptional ancestry-based carrier couple screening for cystic fibrosis and hemoglobinopathies in the Netherlands. Genet Med. 2008;10(11):820-30.
5. Van Steijvoort E, Devolder H, Geysen I, Van Epperzeel S, Peeters H, Peeraer K, et al. Expanded carrier screening in Flanders (Belgium): an online survey on the perspectives of nonpregnant reproductive-aged women. Personalized medicine. 2021;18(4):361-73.
6. Van Steijvoort E, Devolder H, Geysen I, Van Epperzeel S, Peeters H, Peeraer K, et al. Knowledge, attitudes and preferences regarding reproductive genetic carrier screening among reproductive-aged men and women in Flanders (Belgium). Eur J Hum Genet. 2022.
7. Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). Br J Clin Psychol. 1992;31(3):301-6.
8. Julian LJ. Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S467-72.
9. Schuurmans J, Birnie E, van den Heuvel LM, Plantinga M, Lucassen A, van der Kolk DM, et al. Feasibility of couple-based expanded carrier screening offered by general practitioners. Eur J Hum Genet. 2019;27(5):691-700.
10. van Dijke I, Lakeman P, Sabiri N, Rusticus H, Ottenheim CPE, Mathijssen IB, et al. Couples' experiences with expanded carrier screening: evaluation of a university hospital screening offer. Eur J Hum Genet. 2021;29(8):1252-8.
11. Marteau TM, Dormandy E, Michie S. A measure of informed choice. Health Expect. 2001;4(2):99-108.
12. Barlow-Stewart K, Burnett L, Proos A, Howell V, Huq F, Lazarus R, et al. A genetic screening programme for Tay-Sachs disease and cystic fibrosis for Australian Jewish high school students. Journal of medical genetics. 2003;40(4):e45.
13. Gordon C, Walpole I, Zubrick SR, Bower C. Population screening for cystic fibrosis: Knowledge and emotional consequences 18 months later. American Journal of Medical Genetics Part A. 2003;120A(2):199-208.

14. Henneman L, Bramsen I, van der Ploeg HM, ten Kate LP. Preconception cystic fibrosis carrier couple screening: impact, understanding, and satisfaction. Genetic testing. 2002;6(3):195-202.
15. Birnie E, Schuurmans J, Plantinga M, Abbott KM, Fenwick A, Lucassen A, et al. Couple-based expanded carrier screening provided by general practitioners to couples in the Dutch general population: psychological outcomes and reproductive intentions. Genetics in medicine : official journal of the American College of Medical Genetics. 2021;23(9):1761-8.
16. Kraft SA, Schneider JL, Leo MC, Kauffman TL, Davis JV, Porter KM, et al. Patient actions and reactions after receiving negative results from expanded carrier screening. Clinical genetics. 2018;93(5):962-71.
17. Gorrie A, Archibald AD, Ioannou L, Curnow L, McClaren B. Exploring approaches to facilitate family communication of genetic risk information after cystic fibrosis population carrier screening. J Commun Genet. 2018;9(1):71-80.
18. McClaren BJ, Aitken M, Massie J, Amor D, Ukoumunne OC, Metcalfe SA. Cascade carrier testing after a child is diagnosed with cystic fibrosis through newborn screening: investigating why most relatives do not have testing. Genet Med. 2013;15(7):533-40.
19. Silver J, Norton ME. Expanded Carrier Screening and the Complexity of Implementation. Obstet Gynecol. 2021;137(2):345-50.

CHAPTER 9

GENERAL DISCUSSION

Throughout this doctoral dissertation I have explored a number of key challenges addressed in the advisory report of the Superior Health Council (SHC) with regard to the responsible implementation of RGCS within the Belgian health care sector (1). We have reported evidence from empirical studies assessing the interest in RGCS among individuals and couples from the general population (Chapter 2) (2) and the potential impact of RGCS on the subsequent reproductive decision-making of couples with an increased likelihood to conceive a child with an AR or X-linked monogenic condition (Chapter 3) (3). In addition, we performed two cross-sectional survey studies to assess the perceived susceptibility of being a carrier/conceiving a child with a hereditary condition, the acceptability of offering RGCS, the intention to participate in RGCS, the knowledge of RGCS, the attitudes towards RGCS and the preferences for the practical organization of a RGCS offer amongst reproductive-aged men and women in Flanders (Belgium) (Chapter 4-5) (4, 5). At last, we performed a longitudinal survey study to assess the intention of non-pregnant couples to participate in a preconception RGCS offer, the uptake of a free RGCS offer among participants who showed the intention to have RGCS, the extent to which couples make informed decisions regarding participating in preconception RGCS and the level of satisfaction, anxiety, long-term knowledge retention, psychosocial and counseling related aspects among couples who choose to have reproductive genetic carrier screening (Chapter 6-8) (6) (under review). The above mentioned studies have provided valuable insights that can be used to facilitate a responsible implementation of RGCS in the Belgian health care sector. Within the final chapter of this dissertation we focused on the main findings for each research objective and the main strengths and limitations of the research project in order to arrive at some concrete recommendations for further research and practice.

Research Objective 1: To synthesize evidence from empirical studies that assess the interest in/uptake of RGCS among individuals and couples in the general population.

Previous empirical studies have reported a considerable interest (32%-76%) in RGCS among individuals in the general population. However, actual uptake (8-50%) of RGCS seemed to be lower than reported intentions to undergo RGCS (2). Offering preconception RGCS was associated with a lower uptake compared to prenatal RGCS which could mean that RGCS is perceived to be more relevant during pregnancy. An exception to this finding was the observation of a high uptake for RGCS among women who were counselled in preparation for IVF (7) . Couples seeking assisted reproduction might be particularly interested in RGCS (2, 8) and health care professionals might be more inclined to direct patients preparing for IVF/ICSI to have RGCS because they are easier to reach during the preconception window and because of the immediate availability of PGT-M following positive screening results (7) . More research is however needed to assess the intention to participate in RGCS among couples seeking assisted reproduction, their reproductive choices after ‘positive’ results, the psychosocial impact of screening within this specific context, the impact of

possible tensions between a doctor's professional responsibility and the reproductive autonomy of patients, etc. (8).

Research Objective 2: To gain insights into the potential impact of RGCS on the subsequent reproductive decision-making of at-risk couples.

Our systematic review of the literature revealed that most couples with an increased likelihood of conceiving a child with a monogenic condition used their carrier status information to inform their family planning decisions. The vast majority of identified carrier couples used preventive reproductive options. Most non-pregnant couples pursued IVF/ICISI with PGT-M, while pregnant couples most often underwent prenatal diagnosis followed by an elective termination of an affected pregnancy (3). However, some identified carrier couples also decided to accept their reproductive risk and declined any further testing. The severity of the clinical phenotype seems to influence reproduction decision making, as alternation of reproductive plans was less likely for less severe clinical phenotypes. Nevertheless, primary studies included in our systematic review also reported heterogeneity in reproductive decisions of carrier couples for the same monogenic condition. This suggest that other factors could also influence reproductive decision-making (e.g. negative view towards pregnancy termination) (3). Only a minority of the primary studies identified through our systematic review reported on the impact of positive carrier screening results of couples who underwent RGCS for larger test panels. Future RGCS screening programs should ideally include a long-term systematic monitoring and evaluation process that helps to gain more insights into the potential impact of RGCS on the subsequent reproductive decision-making of at-risk couples.

Research Objective 3: To assess the perceived susceptibility of being a carrier/conceiving a child with a hereditary condition, the acceptability of offering RGCS, the intention to participate in RGCS, knowledge of RGCS, attitudes towards RGCS and preferences for the practical organization of a RGCS offer amongst men and women (of reproductive age) in Flanders (Belgium).

Perceived susceptibility, acceptability and intention

Our findings indicate that reproductive aged men and women from the general population in Flanders (Belgium) find it acceptable (84%-92%) to offer RGCS to couples with a desire to have children (5, 6, 9). Even though most participants perceived the susceptibility of being a carrier of a hereditary condition (53-58%) or to conceive a child with a hereditary condition (53-66%) to be rather low, the majority indicated that they would consider to have RGCS in the future (61%-81%) (Figure 1-2) (4-6). Interestingly, only a minority of participants within our implementation study perceived their risk of being a carrier of a monogenic condition to be (very) high (10). While this finding is in line with the results of our other cross-sectional survey studies (Chapter 4 and 5), it's also noteworthy because these participants were repeatedly informed (information brochure, counseling session) about the

fact that on average every human being is a carrier of 2.8 severe recessive pathogenic variants (11). We believe this finding is important as people may not be responsive to RGCS when they are unaware of their personal risk of being a carrier. In this case, information gained through RGCS could be perceived as irrelevant. When screening is already being perceived as not relevant before weighing up the pros and cons, this may lead to a missed opportunity to make an informed decision (12). Earlier studies focusing on population-based carrier screening for CF and FXS observed that the initial judgement of relevance centered around the participant's reproductive stage of life (e.g. considering a pregnancy) and the presence or absence of health-related life experiences (e.g. empathic or embodied experiential knowledge about a specific genetic condition) (12). Individuals should ideally be encouraged to explore and critically reflect on how their prior experiences/perceptions of health/disability/genetic conditions and their current reproductive stage of life might be influencing their perceptions of RGCS. By doing so, healthcare professionals could identify and correct misconceptions and if necessary provide and discuss additional information (12).

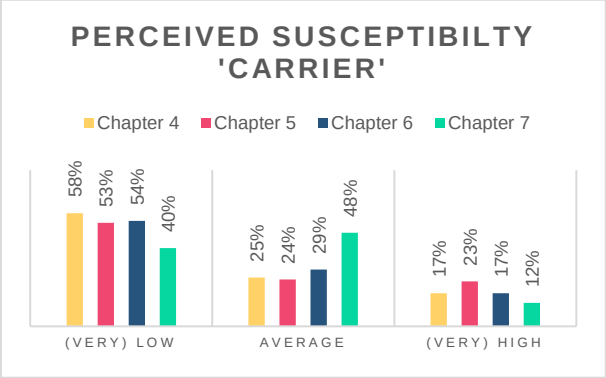


Figure 1: Perceived susceptibility of being a carrier for a monogenic condition

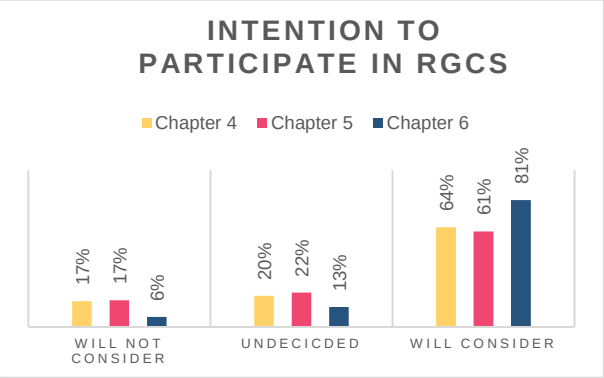


Figure 2: Intention to participate in RGCS

In line with the results of our systematic review (Chapter 2) we also found that a considerable amount of participants were still undecided about their intention to participate in RGCS (20-22%) (4, 5). This undecidedness could be explained by the fact that RGCS is still a relatively unknown test for most people and that the awareness for the included conditions might be rather limited. The Australian study by Ong et al. (2018) reported that those with prior knowledge or awareness of RGCS were less likely to be undecided whether to accept or decline RGCS (13). Efforts must be made to provide continuous, understandable, evidence-based and non-directive information to the public to improve genetic literacy, to reduce misconceptions and to manage expectations (13, 14). This will also allow to inform couples planning a pregnancy about the possibility to have RGCS in a timely manner.

Knowledge and attitudes

Within the context of this research project we developed a new knowledge scale (14 knowledge items) to assess knowledge about key concepts related to RGCS. This newly developed scale was part of the questionnaires used in the survey studies in chapter four, five, seven and eight. A majority of study participants throughout these different studies could answer at least 10 out of 14 knowledge items correctly (55%-85%) which we classified as a high level of knowledge. We have acknowledged the limitations of this classification to evaluate knowledge related to RGCS. As there is no golden standard to measure knowledge on RGCS or an objective way of defining sufficient knowledge on RGCS, we also assessed if individuals who participated in our implementation study felt like they had enough knowledge to make an informed choice to accept or decline a RGCS offer. This was the case for all study participants. In addition, next to aggregated measures we have always reported data on all individual knowledge items included in the knowledge scale to provide transparency in the way we assessed knowledge.

Within our implementation study we have observed a statistically significant median increase in knowledge scores from pre- to post-intervention on a group level which indicates that participants retained their accumulated knowledge over time. Compared to participants of our two cross-sectional survey studies (Chapter 4-5) these individuals also more often knew that RGCS doesn't examine if someone is at risk for developing one or more hereditary conditions and that RGCS is not only intended for individuals with an increased family risk (families where genetic conditions have already occurred) (Figure 3). Nevertheless, knowledge items (K10-K11) with regard to inheritance patterns remained the least well-answered questions on our entire knowledge scale (4, 5, 10) (under review). We believe that some understanding about the inheritance patterns of autosomal and X-linked recessive conditions is essential to be able to make an informed choice with regard to RGCS. Therefore, more reflection is needed on how to communicate specific theoretical concepts. A possible way forward could be the development of supporting tools that can help health care professionals in communicating genetic information to their patients. An example of this are the creative short film fragments that were created by the Society and Ethics Research Group from the Wellcome Genome Campus (Cambridge, UK) to explain genetic concepts in a non-scientific way by using appealing metaphors based around the theme of music (15). These videos were specifically developed to create a bridge between the science of genetics and the public and could be used to support health care professionals during the counseling process or to improve genetic of the general population.

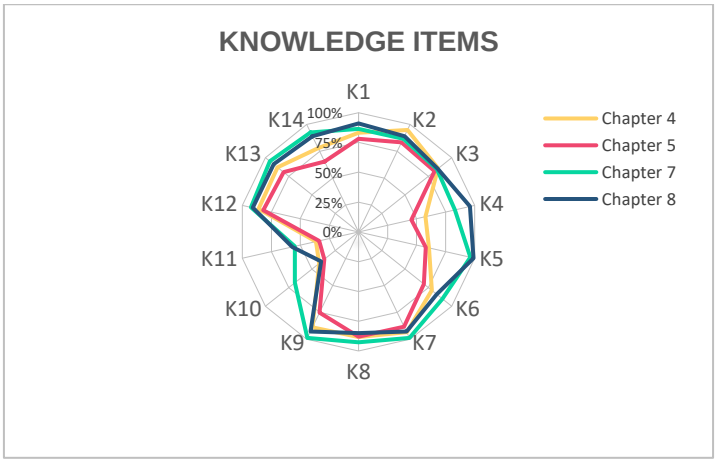


Figure 3: Knowledge items

In accordance with earlier studies focusing on CF carrier screening we found overall positive attitudes among individuals from the general population (4-6, 16, 17). As expected, we also found very positive attitudes towards RGCS among participants who decided to take part in our implementation study where RGCS was offered free of charge. It is noteworthy, that participants who were recruited through the gynaecologist practice (Chapter 6) already showed more positive attitudes and a higher intention to participate in RGCS compared to those who were recruited through the public pharmacies (Chapter 4-5). Health care providers should be aware that the way in which they describe/offer RGCS could have a possible influence on their patient's attitudes and beliefs, as well as the perceived utility of RGCS. Increased attention to the attitudes and genetics literacy of primary health care providers might be needed to ensure they can meet the needs of their patients. To ensure a responsible implementation of RGCS in Belgium, more insights are needed into the views, ability, willingness and educational needs of these specific health care professionals.

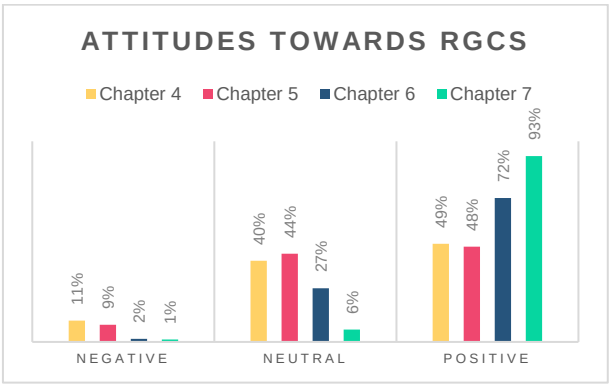


Figure 4: Attitudes towards RGCS

Preferences

Our findings have revealed that reproductive-aged individuals in Flanders (Belgium) prefer RGCS to be offered through the gynaecologist (4, 5). This result is in contrast with findings of earlier studies in the Netherlands (18, 19) and Australia (13) where the majority of participants preferred to have access to ECS through their general practitioner. A possible explanation of this result could be that

within the Belgian healthcare context the gynaecologist often acts as the primary care physician for reproductive health consultations (e.g. PAP-smear test). However, our results also showed that men and individuals with a lower completed level of education more often preferred the general practitioner (5). Therefore we have recommended that RGCS should ideally be implemented through a tailored implementation strategy whereby individual needs/preferences of patients and specific characteristics of a health care system can be taken into account.

A considerable proportion of participants (41-44%) within in our cross-sectional survey studies indicated that they would prefer to have a free choice in the list of conditions screened for (4, 5), while only 17% of participants preferred this option within our implementation study (10). This difference could possibly be explained by the fact that participants in the implementation study received more information about the number of conditions included in the test panel. Interestingly, within an American study where genome sequencing was used for RGCS and where participants where given the option to choose between different categories of conditions 93% of participants wished to received findings for all categories. By being involved in the selection of categories participants felt more respected, empowered and prepared for results disclosure (20). Offering a free choice out of a list of conditions might be impractical when it comes to test panels including a large number of conditions. This is because most patients might not be acquainted with the included conditions and it would not be feasible to explain every single condition in detail (21). But these findings also highlight the possible added value of providing and supporting choice and autonomy when it comes to RGCS. Some have proposed to generate a taxonomy based on expert judgment to simplify patient decisions about the conditions for which patients want to be screened. Hereby, patients would be able to choose from a small and manageable set of categories which are described in terms that are familiar and understandable by patients (22-24). Further evaluation of the feasibility and appropriateness of this approach in practice is however still needed (25).

Participants in our cross-sectional survey studies also more often preferred to receive individual test results (51-57%) compared to participants who decided to take part in our implementation study (38%) (4, 5). This could possibly be due to the fact these participants received more in depth counseling about RGCS (e.g. utility of screening results, current approach of results reporting). It is important to mention that none of the participants who received their screening results insisted on receiving all their individual screening results. This finding might suggest that even though someone prefers to receive individual test results, a couple-based approach to report test results might also be found acceptable by those who opt to have RGCS. A different way of questioning might be more opportune to assess to what extent individuals consider it to be acceptable to only receive couple-based results within the context of RGCS. In the Dutch survey study by Plantinga et al. (2019), 76% of all participating couples reported that they would have no objection to only receive couple-based results (26).

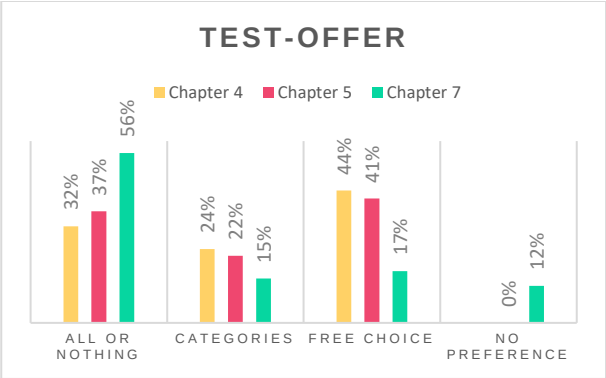


Figure 6: Test-offer

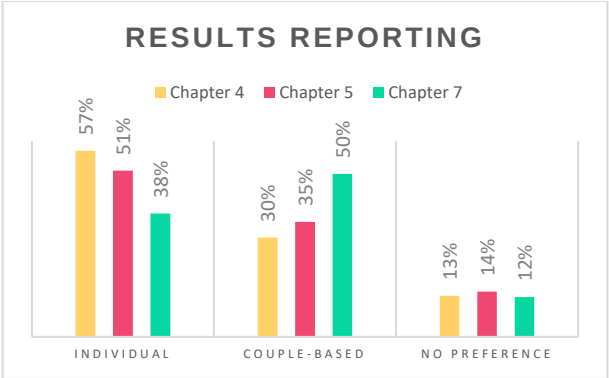


Figure 7: Results reporting

Most participants were willing to pay for RGCS (55-69%), yet the amount they would be willing to pay was considerably lower than the costs of the current test offer (€1400)(4, 5). The majority of participants (89%) who took part in our implementation study were also of the opinion that RGCS should be reimbursed (unpublished data). To avoid additional health care disparities, (partial) reimbursement of test costs should be considered (25, 27).

Research objective 4: To implement and evaluate a RGCS offer in a reproductive context, namely in non-pregnant couples.

According the most recent data of Statbel, a mother is on average 31 years old at birth of a child and the co-parent 34 years (28). In 2020, 72% of the children born in Flanders had a mother between the ages of 25 and 35 (29). If we compare these numbers with the study sample of our implementation study we can see that the studied population matches quiet well to target audience of RGCS (=prospective parents). Within our study sample, 74% of participants were between the age of 25 and 34.

a) To study the intention to participate in/uptake of a preconception RGCS offer.

From the very beginning there has been a debate on whether RGCS is being introduced due to a supply push rather than an actual demand of the population (30). By definition, all screening programs are in a way characterized by a top-down approach because they entail an unsolicited offer to a healthy population (31). A British study that assessed the acceptability and feasibility of offering carrier screening for cystic fibrosis in a primary care setting found that the strongest factor in determining uptake was the active approach of offering immediate testing by a health care professional (30). Earlier studies focusing on CF carrier screening have also reported that some individuals perceived a certain difficulty or inability to refuse a screening offer (17, 30). Within our implementation study we deliberately provided a reflection period to participants who showed the intention to participate in RGCS. This was to allow them to discuss the offer with their male partner but also because of our active recruitment strategy for an unsolicited offer. Because of this setup we were able to measure that self-reported intention to have RGCS (80%) doesn't always translate into

actual uptake. Within our study where the Belgian RGCS test was offered free of charge to non-pregnant couples from the general population, 53% of women (meeting our study inclusion criteria) who initially showed the intention to have RGCS decided to accept the offer. While our implementation study mainly focused on the decision-making process and lived experiences of test-acceptors, our experience has taught us that some of our test-intending participants finally decided to decline the RGCS offer because of practical/logistical issues (e.g. lack of time) which is in line with earlier studies focusing on carrier screening for one single condition (e.g. cystic fibrosis) (32). This could mean that the effort required to participate in RGCS could be estimated to be too high by participants according to the personal perceived utility of RGCS at that specific moment in time.

b) To assess the extent to which couples make informed choices regarding participating in preconception RGCS.

We observed high rates of informed choice (82%) among couples who were offered the Belgian RGCS offer free of charge in a research study where participants received up to 30 minutes of pre-test counseling. Uninformed choice among study participants occurred mostly due to insufficient knowledge (18.2%) (10). We argue that pre-test counselling initiatives for RGCS should ideally be organized in such a way that information can be provided at multiple time points to avoid information overload and to allow for a reflection period. Providing information in advance could facilitate efficient and effective pre-test counseling (33). Interactive education tools like a patient decision aid could help clarify theoretical concepts in a non-directive way and stimulate a process of deliberation in settings with limited resources. In the Australian Reproductive Genetic Carrier Screening Program (ARGCSP)[1], also known as “Mackenzie’s Mission” (MM) a decision aid prompted discussion within couples and facilitated in depth consideration of screening (34). A decision aid could therefore be a very useful tool in supporting couples’ decision-making and contribute to RGCS being feasible for scaled- up implementation.

c) To assess the level of satisfaction, anxiety, long-term knowledge retention, psychosocial & counseling related aspects among couples who choose to have reproductive genetic carrier screening.

After obtaining their test results, most participants (92.5%) indicated that they would make the same choice to accept the RGCS offer that was proposed to them in the context of this study. Most participants positively evaluated the information/counseling and reporting strategy that was used in the context of this study. Overall, anxiety levels were low and no significant changes were measured over time from pre-intervention to post-intervention while knowledge levels were generally high and significantly increased over time. Only a small proportion of participants felt worried while waiting for

[1] A research study providing reproductive genetic carrier screening to up to 10,000 couples across Australia.

the test results. All of these previous findings are in line with earlier studies which reported little direct psychosocial harm to patients receiving negative RGCS or single-condition carrier screening results (35, 36). The choice to have RGCS didn't impact the relationship of participants or their desire to have children in the future. One in five participants (21%) agreed that they would find it difficult to inform family members of their increased risk of being a carrier of a hereditary condition. Participants that were identified as a carrier most often shared results with parents (89%) and siblings (66.7%) but only one identified carrier shared this information with other family members (under review). Therefore, we have emphasized that family communication after carrier identification through RGCS needs further investigation to assess to what extent cascade testing is being used in this context and which factors influence the decisions of family members. This would allow couples to have a more critical reflection on the desirability and utility of reporting individual test results for the opportunity to offer cascade testing in a context with limited resources for follow-up. Finally, we would like to emphasize that health care professionals should be aware of their responsibility for proper follow-up of patients to avoid that the implications of negative results are misunderstood by their patients (e.g. residual risk, iterative process of variant interpretation and how it relates to carrier screening results). Especially because misunderstanding of results could lead to an increased use of unnecessary downstream medical services (37, 38). Especially in a context where screening results are reported through an online portal or through mail. Hereby it's important to note that only a minority of our study participants actively shared their test results with their doctor, which is line with an American study by Kraft et al. (2018) (36). Within this study some participants never discussed their RGCS results with their doctor because they felt it was not important given their negative RGCS results or because they assumed their provider had already seen their RGCS results.

Limitations

Our research project had some limitations with regard to our research design, methodology, study materials, etc., which may have impacted the findings of our study. It's possible that our study participants are not a good representation of the population we intended to study, as we used convenience sampling and our sample sizes were rather limited. In Chapter 3 and 4 we wanted to study perspectives with regard to RGCS amongst women and men of reproductive age in Flanders (Belgium). In the online survey presented in Chapter 3 we had a limited study sample with an over-representation of highly educated individuals. While we did extra efforts to avoid this in the survey study of Chapter 4, we can't exclude the idea of over- and of under-representation of specific groups (e.g. individuals who are more interested in genetics). Within our implementation study, participants were also recruited through one single group practice of gynaecologists which limits the geographic scope of our study sample. Furthermore, we only recruited participants by targeting females within the reproductive age category which could have led to a selection bias. Therefore some caution is needed when interpreting our study results and findings should not be generalized without further reflection. Future research projects could benefit by using probability sampling, where individuals are selected at random within the population of interest.

We tried to assess the knowledge of participants with regard of RGCS by using our newly developed knowledge scale. This scale was based on previous survey studies and input from the research team. However, we did not make a substantial evaluation of this scale before using it in our survey questionnaires. Future research projects that would like to asses knowledge through a knowledge scale could benefit to first perform a Delphi procedure with diverse stakeholders (e.g. trained genetic professionals, education specialists, etc.) to identify the most important knowledge items, to identify important knowledge items that might be missing, to assess difficulty of questions, etc. In addition, the newly developed scale could also be evaluated through a pilot with members of the population of interest to receive feedback on comprehension, question order, etc.

In addition, study materials were only available in Dutch which excluded non-Dutch speakers from participating in our studies. During the roll-out of this project we were faced with some practical limitations which forced us to be flexible with the time we had available. While this PhD project started in May 2018, the Belgian RGCS offer only became available in October 2019 resulting in a delay in the recruitment of participants. Like other studies, this research project was also impacted by the global COVID-19 pandemic causing the recruitment phase to be halted. Furthermore we encountered some difficulties during the analysis of the test samples. Within our implementation study we wanted to focus on couples who opted for RGCS to see if they made informed choices. Unfortunately, we weren't able to gain more in depth insights into the decision-making process of test decliners or test intending non-participants who originally showed the intention to participate in

RGCS. We acknowledged this limitation and have repeatedly mentioned the importance of investigating this further. An additional study limitation is the fact that we only identified few carriers and no carrier couples. Because the Belgian RGCS offer was offered free of charge to study participants, we weren't able to assess the impact of the costs of testing and/or insurance coverage on the decision-making process.

Implications for further research

Based on our findings and experiences we would like to recommend the following topics for future research projects and make some suggestions for study design:

1. To assess the decision-making process of individuals/couples who are uncertain/undecided about RGCS or who decline RGCS.

   We believe this could be best assessed by performing a qualitative interview study with individuals that are uncertain/undecided about RGCS or who decline RGCS. This would allow to gain more in-depth insights in to the reasoning of these particular groups, to understand their concerns, their doubts/remaining questions, etc. Participants could be recruited through (practices of) health care professionals that offer RGCS to the public. For example, a couple that declines RGCS that has been offered in the context of a preconception consult could be invited by the health care professional to consider participation in the study.

2. To assess the impact of the costs of testing and/or insurance coverage on the decision-making process.

   Most participants were willing to pay for RGCS, yet the amount they would be willing to pay was considerably lower than the costs of the current Belgian RGCS offer (€1400). Within the context of our implementation study, the Belgian RGCS offer was offered free of charge to study participants therefore we couldn't assess the impact of costs of testing and/or insurance coverage on the decision-making process. We believe this requires further attention in future studies. This could also be addressed in a qualitative interview study where both test-acceptors and test-decliners are included. Hereby it would be important to include a diverse study population (e.g. socio-economic characteristics).

3. To assess the intention to participate in RGCS among non-pregnant couples undergoing fertility treatment, their reproductive choices after 'positive' screening results, the psychosocial impact of screening within this specific context, the impact of possible tensions between a doctor's professional responsibility and the reproductive autonomy of patients, etc.

   For this study a Sequential Explanatory Mixed Method design could be used. Initially, data could be collected and analysed by means of quantitative research methods (questionnaire research). To gain more insights from the quantitative data, semi-structured interviews could also be conducted. We believe this study can be designed in a similar way (e.g. time points of collecting data) like the implementation study presented in this manuscript. But in this case

extra attention should be given to the previous mentioned limitations with regard to research design, methodology, study materials, etc. Participants could be recruited through fertility centres. In addition, we believe it would be worthwhile to also conduct a qualitative interview study with health care professionals working in this specific context to gain more insights in their views on (the implementation of) RGCS and their professional responsibility.

4. To assess interest, attitudes and preferences regarding RGCS among a broad range of family structures (e.g. third party reproduction).

   We believe more research is needed with regard to RGCS in a broad range of family structures (e.g. third party reproduction). For example with regard the disclosure of screening results to gamete donors. This could be done by setting up a research study that explores perspectives of all involved stakeholders (e.g. medical staff at fertility clinics, gamete donors, the intended parents, etc.)

5. To assess interest, attitudes and preferences regarding RGCS among parents with a child with a rare genetic disease, to whom exome sequencing was offered in a clinical context.

   We believe this could be assessed by performing a qualitative interview study. In the context of this study, parents with a child with a rare genetic condition could be recruited through the centre for human genetics or through patient organisations.

6. To explore views, ability, willingness, educational needs and current practices with regard to RGCS among gynaecologists and general practitioners in Flanders (Belgium).

   While this thesis manuscript focused on views of the target population of RGCS, our results did show that most of these individuals saw a key role in RGCS for gynaecologists and general practitioners. This finding is in line with the recommendations of the Superior Health Council of Belgium. Nevertheless, to the best of our knowledge, there hasn't been any study looking into the views of these health care professionals. We believe this could possibly be assessed by performing a qualitative interview study, where semi-structured interviews are performed with Flemish gynaecologists and general practitioners. This will allow to gain more in-depth insights about their ability, willingness, education needs and current practices.

7. To assess to what extent cascade testing is being used in the context of RGCS and which factors influence the decisions of family members.

Our research found that screenings results were only shared to a limited extent with other family members. We believe that family communication after carrier identification through reproductive genetic carrier screening needs further investigation to assess to what extent cascade screening is being used in this context and which factors influence the decisions of family members. This would allow to have a more critical reflection on the desirability and utility of reporting individual test results for the opportunity to offer cascade screening in a context with limited resources for follow-up. This could be possibly be studied by setting up a multi-centre study between the different centres for human genetics.

8. To explore the roles and responsibilities of health care professionals to inform patients about variant reinterpretation (e.g. rescreening in subsequent pregnancies).

   Considering that to date the clinical significance of pathogenic variants is incomplete, we believe there needs to be a more substantial reflection on the roles and responsibilities of health care professionals. This could be done by qualitative or quantitative research methods to explore the views of these health care professionals on key issues like initiation of reinterpretation, which variants should/should not be reported, concerns about consent, concerns about liability, concerns about costs, etc.

Implications for clinical practice

1. Implementation plan for RGCS

   Evidence-based strategies are required to ensure the implementation of evidence into practice and to ensure high-quality and effective health services. By this we mean strategies that have shown to be based on scientific evidence. An example of this could be to only offer couple-based test results if evidence shows that this strategy has less adverse effects and is acceptable by the population of interest. The field of implementation science could provide valuable input in planning and evaluating RGCS. This emerging field has a broader scope compared to traditional clinical research as it focuses on different levels of healthcare (patient, provider, organisation, policy) (39).To successfully implement RGCS, attention should be given to barriers and possible enablers on all these levels. The creation of preconception services through which RGCS could be offered could be a possible enabler in countries with a lack of focus on preconception health services (barrier). Likewise, identifying and training health care professionals who could take on a central role in RGCS (e.g. GP, Gynaecologist, Midwife, etc.) could be a possible enabler to tackle the lack of workforce capacity (barrier) (40).

2. Continuous monitoring and evaluation

   Future RGCS screening programs should ideally include a long-term systematic monitoring and evaluation (M&E) process that helps to gain more insights into the decision-making process of couples and the potential impact of RGCS on the subsequent reproductive decision-making of at-risk couples. In addition, there should also be a close M&E of the clinical utility of the RGCS offer within the context of the ethical principles of autonomy, beneficence, and nonmaleficence. Especially considering that to date the clinical significance of pathogenic variants is incomplete (37).

3. Preconception health services

   More attention should be given to the creation of holistic and multidisciplinary preconception health care services through which RGCS could be offered. This would allow prospective parents to be informed about the existence of RGCS before pregnancy. Furthermore this would also allow to counsel prospective parents about other important aspects during the preconception, periconception and prenatal period (e.g. adequate consumption of folic acid, dietary and lifestyle habits, mental health, etc.). Preconception care services could be integrated through the education system (e.g. reproductive and sexual health school program), the health system (e.g. preconception consult in primary care) or other platforms (e.g. media campaign through TV, radio/podcast, print and social media).

4. Reproductive partners

We would like to advocate that interventions with regard to RGCS should not merely focus on women or pregnant women. As men play an essential role in reproduction, they should be acknowledged as equal partners in reproductive decision-making with regard to RGCS. The decision to accept or decline RGCS has to be made by both members of the couple and should be mutually agreed upon. Therefore we believe that both partners should attend the pre-test counselling session together, and we recommend to a parallel screening approach where samples from both partners are collected simultaneously. As suggested by Schuurmans et al. (2019), practical barriers to attend counselling together could be reduced by offering web-consultations of face-to-face consultations at times that are feasible for the target population (e.g. evenings/weekends) (33).

5. Timing

We believe RGCS should ideally be offered to couples before conception so those with an increased likelihood of conceiving a child with a genetic condition are able to consider all available reproductive options with less time constraint or emotional distress. However, following the advisory report of the Superior Health Council of Belgium, we believe that RGCS should not be excluded during pregnancy (1). This would entail an adjustment to the current rule to only offer the Belgian RGCS offer to non-pregnant couples. Our experiences showed that some couples were not willing to delay reproductive plans while waiting for their results and became pregnant before receiving their screening results. In addition, while it might seem logical in theory to only offer RGCS preconceptionally in practice this might be a rather difficult rule to implement. Finally, information gained through prenatal RGCS might still be relevant to make informed reproductive decisions or to prepare for the possibility of a child with a particular genetic condition. It is, however, crucial that couples opting for prenatal RGCS receive adequate pre-test counseling, especially with regard to the more limited reproductive options.

6. Sampling & results reporting

Considering the reproductive context and the limited available resources, we recommend taking blood samples from both reproductive partners at the same time and to only report couple-based tests results. We believe this approach would be most appropriate to avoid an increase in anxiety and the potential need of post-test counselling when only one partner is identified as a carrier of a specific AR monogenic condition. Furthermore, this would allow to maximize the clinical utility of RGCS by focusing on meaningful information that can be used to guide family planning based on personal values and limit time spent by health care professionals to facilitate and perform follow-up. Whilst some have argued that individual

results are important given the fact that some relationships end or to share that information with relatives, it's also important to acknowledge the evolving nature of variant classification based on genetic knowledge advances. Given the possibility for reclassification of certain variants over a relatively short period, and the potential clinical relevant implications, it has been suggested that some might still benefit from a repeat screening in subsequent pregnancies (37). Therefore we believe that the focus should be put on providing meaningful and relevant information which could impact reproductive decision-making, based on the scientific knowledge at that specific point in time. However, this limitation should be addressed in an understandable and transparent way during pre-test counseling.

7. Health Care Professionals

In order to adequately prepare non-genetic health care professionals, more attention should be given to guidelines and education tools for health care professionals without a specialized training in genetics so that they can fulfil their role within RGCS correctly. A possible way forward could be to train specialist health care providers in preconception care (e.g. midwife, general practitioner, etc.) which could counsel prospective parents about other relevant topics during the preconception, periconception and prenatal period (33).

8. Information provision

As most autosomal recessive and X-linked conditions are rare, most individuals within the general population will not be aware of them. Therefore, more efforts are needed to increase awareness, to improve genetic literacy, to address personal benefits of screening in a non-directive way and to facilitate a public debate (41). In addition, qualitative and transparent information should be made available to couples considering to have RGCS reduce misconceptions and manage expectations. Some background information on how conditions and genes are selected together with the regularly updated list of included genes and conditions should be made publicly available. In the absence of relevant life experiences, attention should also be given to provide information about the lived personal and family experience of a genetic condition (12). Hereby, the focus could be on what it means to have the condition, to be a carrier for that condition or to have a relative impacted by that condition (12). Pre- and post- test genetic counseling will be essential in order for patients to understand RGCS, including its benefits and limitations. Providing information in advance could facilitate efficient and effective pre-test counseling (14). Based on our experiences and findings we highly recommend an implementation strategy where information is provided at multiple time points to avoid information overload. To avoid that patients [2] decide to have RGCS just because it's offered we are of the opinion that the integration of a reflection period would be mostly appropriate. Post-test counselling of

couples with an increased likelihood of conceiving a child with a monogenic condition should ideally be performed by a trained genetic health-care professional.

<u>Pre-test counselling services should cover the following topics:</u>

a. *Description of what it means to be a carrier of a monogenic condition*
    i. *Every human being is a carrier*
    ii. *Autosomal recessive inheritance + example*
    iii. *X-linked inheritance + example*
    iv. *Monogenic conditions vs. other genetic conditions or multifactorial conditions*
b. *Description of RGCS*
    i. *Objective*
    ii. *Target population*
    iii. *Relevance of family history*
c. *Description of carrier couple*
    i. *Population risk of being a carrier couple*
    ii. *Reproductive options available for carrier couples (e.g. prenatal diagnosis, IVF/ICSI + PGT, gamete donation, adoption, termination of pregnancy)*
d. *Description of the Belgian RGCS offer*
    i. *Generic description of the total number and type of conditions included*
    ii. *Screening for most common pathogenic variants*
    iii. *Based on current scientific knowledge/ Possibility of new insights over time / iterative process of variant interpretation (additional variants may be included in newer screening panels)*
    iv. *Reduced penetrance & variable expressivity of phenotypes for certain conditions*
    v. *Test-procedures: sampling & analysis*
    vi. *Cost of Belgian RGCS offer*
    vii. *List of included conditions/genes*
e. *Information on results reporting*
    i. *Turn-around time to obtain screening results*
    ii. *Focus on couple-based results with individuals results for 7 conditions → possibility to offer cascade screening for relatives*
    (this can be omitted with exclusive couple-based results)
    iii. *Meaning of an abnormal couple result (= increased reproductive risk)*
    iv. *Meaning of a normal couple result*
    v. *Meaning on results when one of both partners is identified as a carrier of a monogenic condition*
    vi. *Incidental findings (medically relevant information will be reported)*

f. *Limitations of RGCS*
    i. *Residual risk*
    ii. *Risk for false positive and false negative results*
    iii. *Couple-based screenings results only applicable to the unique combination of two reproductive partners*
    iv. *RGCS doesn't replace NIPT or newborn screening*
    v. *RGCS not sufficient for consanguineous couples or those with a family history of a genetic condition*
g. *Possible consequences of RGCS*
    i. *Stress, worry and anxiety*
    ii. *Significance of information gained through RGCS for other family members*
h. *The right not to know*

Post-test counselling services should cover the following topics:

a. *Explanation of the screening results*
    i. *Increased reproductive risk*
        1. *Meaning of a screen-positive result*
        2. *Information about the clinical nature of the specific genetic condition(s) in question*
        3. *Discussion of reproductive options available, including their risks and benefits*
        4. *Discussion of the latest and emerging therapeutic interventions*
        5. *Discussion of the residual risk for other monogenic conditions*
        6. *Discussion of disclosure of diagnostic test results*
        7. *Encouragement to inform family members about the possibility to have carrier testing*
        8. *Results based on current scientific knowledge/ possibility of new insights over time / iterative process of variant interpretation (reinterpretation of variants)*
    ii. *No increased reproductive risk*
        1. *Meaning of a screen-negative result*
        2. *Discussion of the residual risk*

Before consenting to RGCS, it might be difficult for patients to imagine how they would react to a positive screening result and which reproductive options they would consider (42). Yet, RGCS might do more harm than good if certain issues do not receive proper attention (31). Therefore pre-test counselling initiatives should not be limited to information provision of theoretical concepts related to RGCS but should also stimulate a critical reflection and

deliberation process. This could be initiated by asking questions as adequate pre- and post-test counselling services can be time and labour intensive. We believe new models for information provision should be developed. Interactive education tools like a patient decision aid could help clarify theoretical concepts in a non-directive way and stimulate a process of deliberation in settings with limited resources. This approach would also allow to provide the same high-quality information to all prospective parents. A decision aid could therefore be a very useful tool in supporting couples' decision-making and contribute to RGCS being feasible for scaled- up implementation (34).

Conclusion

New technical advances in the field of reproductive medicine are emerging rapidly. After the introduction of prenatal ultrasound screening, newborn screening and non-invasive prenatal screening there is now the possibility to offer reproductive genetic carrier screening for multiple autosomal recessive and X-linked conditions to couples who do not have an a priori increased likelihood of being a carrier based on their or their partners' personal or family history. Underlying beliefs and values shape opinions about the appropriate use of new reproductive genetic technologies, including reproductive genetic carrier screening.

Within this research project we have synthesized evidence from empirical studies that assessed the interest in RGCS among individuals and couples from the general population and evidence from empirical studies that assessed the impact of RGCS on the subsequent reproductive decision-making of at-risk couples. We have found that there is a considerable interest in RGCS but that actual uptake is much lower. Couples that were identified to have an increased risk of conceiving a child with an autosomal or X-linked condition most often used preventive reproductive options.

Findings from our own empirical research studies within Flanders (Belgium) show that there is also a considerable interest in RGCS among nonpregnant reproductive aged men and women in Flanders. The perceived susceptibility of being a carrier or to conceive a child with an autosomal recessive or X-linked condition was found to be rather low. Overall, we found rather positive attitudes towards RGCS. Nevertheless, a considerable amount of individuals surveyed showed a more neutral attitude towards RGCS and were still undecided about their intention to participate in RGCS. Within our implementation study, most non-pregnant women visiting their gynaecologist showed the intention to have RGCS. However, not all test intending participants decided to take part in the clinical study where RGCS was offered free of charge. We observed an uptake of 53% of women (meeting our study inclusion criteria) who initially showed the intention to have RGCS decided to accept the offer.

While acknowledging that caution is needed when interpreting these study results because of study limitations, we believe this research project has provided interesting study results that give valuable insights in the perspectives of nonpregnant reproductive aged men and women in Flanders (Belgium). These findings could be of used in the ongoing debate on the implementation of RGCS in the Belgian health context (or related contexts), but could also be of value to health care professionals who are involved in guiding those trying to conceive to enable informed reproductive decision-making.

REFERENCES

1. Belgium S. Advisory report of the superior health council no. 9240. Expanded carrier screening in a reproductive context Towards a responsible implementation in the healthcare system. 2017.
2. Van Steijvoort E, Chokoshvili D, W Cannon J, Peeters H, Peeraer K, Matthijs G, et al. Interest in expanded carrier screening among individuals and couples in the general population: systematic review of the literature. Human reproduction update. 2020;26(3):335-55.
3. Cannon J, Van Steijvoort E, Borry P, Chokoshvili D. How does carrier status for recessive disorders influence reproductive decisions? A systematic review of the literature. Expert Review of Molecular Diagnostics. 2019;19(12):1117-29.
4. Van Steijvoort E, Devolder H, Geysen I, Van Epperzeel S, Peeters H, Peeraer K, et al. Expanded carrier screening in Flanders (Belgium): an online survey on the perspectives of nonpregnant reproductive-aged women. Personalized medicine. 2021;18(4):361-73.
5. Van Steijvoort E, Devolder H, Geysen I, Van Epperzeel S, Peeters H, Peeraer K, et al. Knowledge, attitudes and preferences regarding reproductive genetic carrier screening among reproductive-aged men and women in Flanders (Belgium). European journal of human genetics : EJHG. 2022.
6. Van Steijvoort E, Demuynck R, Peeters H, Vandecruys H, Verguts J, Peeraer K, et al. Reasons affecting the uptake of reproductive genetic carrier screening among nonpregnant reproductive-aged women in Flanders (Belgium). Journal of Genetic Counseling.n/a(n/a).
7. Larsen D, Ma J, Strassberg M, Ramakrishnan R, Van den Veyver IB. The uptake of pan-ethnic expanded carrier screening is higher when offered during preconception or early prenatal genetic counseling. Prenat Diagn. 2019;39(4):319-23.
8. de Wert G, van der Hout S, Goddijn M, Vassena R, Frith L, Vermeulen N, et al. The ethics of preconception expanded carrier screening in patients seeking assisted reproduction. Hum Reprod Open. 2021;2021(1):hoaa063.
9. Van Steijvoort E, Devolder H, Geysen I, Van Epperzeel S, Peeters H, Peeraer K, et al. Expanded carrier screening in Flanders (Belgium): an online survey on the perspectives of nonpregnant reproductive-aged women. Personalized medicine. 2021;18(4):361-73.
10. Van Steijvoort E, Peeters H, Vandecruys H, Verguts J, Peeraer K, Matthijs G, et al. Exploring informed choice in preconception reproductive genetic carrier screening by using a modified Multidimensional Measure of Informed Choice. Patient Educ Couns. 2022.
11. Bell CJ, Dinwiddie DL, Miller NA, Hateley SL, Ganusova EE, Mudge J, et al. Carrier testing for severe childhood recessive diseases by next-generation sequencing. Science translational medicine. 2011;3(65):65ra4-ra4.
12. Archibald AD, McClaren BJ. Perceived relevance of genetic carrier screening: observations of the role of health-related life experiences and stage of life in decision making. J Community Genet. 2012;3(1):47-54.

13. Ong R, Howting D, Rea A, Christian H, Charman P, Molster C, et al. Measuring the impact of genetic knowledge on intentions and attitudes of the community towards expanded preconception carrier screening. Journal of medical genetics. 2018;55(11):744-52.
14. Chokoshvili D, Belmans C, Poncelet R, Sanders S, Vaes D, Vears D, et al. Public Views on Genetics and Genetic Testing: A Survey of the General Public in Belgium. Genetic testing and molecular biomarkers. 2017;21(3):195-201.
15. Middleton A, editor 'Music of Life' a new metaphor for genomics, delivered as film within genetic counselling. EMPAG conference within European Society of Human Genetics Conference; 2018 16th June 2018. Milan.
16. Ioannou L, McClaren BJ, Massie J, Lewis S, Metcalfe SA, Forrest L, et al. Population-based carrier screening for cystic fibrosis: a systematic review of 23 years of research. Genet Med. 2014;16(3):207-16.
17. Chen LS, Goodson P. Factors affecting decisions to accept or decline cystic fibrosis carrier testing/screening: A theory-guided systematic review. Genet Med. 2007;9(7):442-50.
18. Plantinga M, Birnie E, Abbott KM, Sinke RJ, Lucassen AM, Schuurmans J, et al. Population-based preconception carrier screening: how potential users from the general population view a test for 50 serious diseases. European journal of human genetics : EJHG. 2016;24(10):1417-23.
19. Nijmeijer SCM, Conijn T, Lakeman P, Henneman L, Wijburg FA, Haverman L. Attitudes of the general population towards preconception expanded carrier screening for autosomal recessive disorders including inborn errors of metabolism. Molecular genetics and metabolism. 2019;126(1):14-22.
20. Kauffman TL, Irving SA, Leo MC, Gilmore MJ, Himes P, McMullen CK, et al. The NextGen Study: patient motivation for participation in genome sequencing for carrier status. Molecular Genetics & Genomic Medicine. 2017;5(5):508-15.
21. Schneider JL, Goddard KA, Davis J, Wilfond B, Kauffman TL, Reiss JA, et al. "Is It Worth Knowing?" Focus Group Participants' Perceived Utility of Genomic Preconception Carrier Screening. Journal of genetic counseling. 2016;25(1):135-45.
22. Leo MC, McMullen C, Wilfond BS, Lynch FL, Reiss JA, Gilmore MJ, et al. Patients' ratings of genetic conditions validate a taxonomy to simplify decisions about preconception carrier screening via genome sequencing. American journal of medical genetics Part A. 2016;170(3):574-82.
23. Korngiebel DM, McMullen CK, Amendola LM, Berg JS, Davis JV, Gilmore MJ, et al. Generating a taxonomy for genetic conditions relevant to reproductive planning. American journal of medical genetics Part A. 2016;170(3):565-73.
24. Kraft SA, McMullen CK, Porter KM, Kauffman TL, Davis JV, Schneider JL, et al. Patient perspectives on the use of categories of conditions for decision making about genomic carrier screening results. American journal of medical genetics Part A. 2018;176(2):376-85.

25. Wilfond BS, Kauffman TL, Jarvik GP, Reiss JA, Richards CS, McMullen C, et al. Lessons Learned From A Study Of Genomics-Based Carrier Screening For Reproductive Decision Making. Health Aff (Millwood). 2018;37(5):809-16.
26. Plantinga M, Birnie E, Schuurmans J, Buitenhuis AH, Boersma E, Lucassen AM, et al. Expanded carrier screening for autosomal recessive conditions in health care: Arguments for a couple-based approach and examination of couples' views. Prenat Diagn. 2019;39(5):369-78.
27. Robson SJ, Caramins M, Saad M, Suthers G. Socioeconomic status and uptake of reproductive carrier screening in Australia. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2020;60(6):976-9.
28. Statbel. Mother is on average 31 years old at birth of child 2021 [updated 8/7/2021. Available from: https://statbel.fgov.be/en/news/mother-average-31-years-old-birth-child.
29. Het Kind in Vlaanderen 2020. Agentschap Opgroeien; 2020.
30. Bekker H, Modell M, Denniss G, Silver A, Mathew C, Bobrow M, et al. Uptake of cystic fibrosis testing in primary care: supply push or demand pull? BMJ (Clinical research ed). 1993;306(6892):1584-6.
31. van der Hout S, Holtkamp KC, Henneman L, de Wert G, Dondorp WJ. Advantages of expanded universal carrier screening: what is at stake? European journal of human genetics : EJHG. 2016;25(1):17-21.
32. Gilmore MJ, Schneider J, Davis JV, Kauffman TL, Leo MC, Bergen K, et al. Reasons for Declining Preconception Expanded Carrier Screening Using Genome Sequencing. Journal of Genetic Counseling. 2017;26(5):971-9.
33. Schuurmans J, Birnie E, van den Heuvel LM, Plantinga M, Lucassen A, van der Kolk DM, et al. Feasibility of couple-based expanded carrier screening offered by general practitioners. European journal of human genetics : EJHG. 2019;27(5):691-700.
34. King E, Halliday J, Archibald AD, Delatycki M, Barlow-Stewart K, Newson AJ, et al. Development and use of the Australian reproductive genetic carrier screening decision aid. European Journal of Human Genetics. 2022;30(2):194-202.
35. Lakeman P, Plass AM, Henneman L, Bezemer PD, Cornel MC, ten Kate LP. Three-month follow-up of Western and non-Western participants in a study on preconceptional ancestry-based carrier couple screening for cystic fibrosis and hemoglobinopathies in the Netherlands. Genet Med. 2008;10(11):820-30.
36. Kraft SA, Schneider JL, Leo MC, Kauffman TL, Davis JV, Porter KM, et al. Patient actions and reactions after receiving negative results from expanded carrier screening. Clinical genetics. 2018;93(5):962-71.
37. Silver J, Norton ME. Expanded Carrier Screening and the Complexity of Implementation. Obstet Gynecol. 2021;137(2):345-50.

38. Henneman L, Borry P, Chokoshvili D, Cornel MC, van El CG, Forzano F, et al. Responsible implementation of expanded carrier screening. European journal of human genetics : EJHG. 2016;24(6):e1-e12.
39. Bauer MS, Damschroder L, Hagedorn H, Smith J, Kilbourne AM. An introduction to implementation science for the non-specialist. BMC psychology. 2015;3(1):32.
40. Best S, Long J, Theodorou T, Hatem S, Lake R, Archibald A, et al. Health practitioners' perceptions of the barriers and enablers to the implementation of reproductive genetic carrier screening: A systematic review. Prenatal Diagnosis. 2021;41(6):708-19.
41. Holtkamp KCA, Mathijssen IB, Lakeman P, van Maarle MC, Dondorp WJ, Henneman L, et al. Factors for successful implementation of population-based expanded carrier screening: learning from existing initiatives. European journal of public health. 2017;27(2):372-7.
42. Fakih A, Spector-Bagdady K. Should Clinicians Leave "Expanded" Carrier Screening Decisions to Patients? AMA journal of ethics. 2019;21(10):E858-64.

GENERAL BIBLIOGRAPHY

Alfirevic Z, Navaratnam K, Mujezinovic F. Amniocentesis and chorionic villus sampling for prenatal diagnosis. The Cochrane database of systematic reviews. 2017;9(9):Cd003252.

Almeling R, Waggoner MR. More and less than equal: How men factor in the reproductive equation. Gender & Society. 2013;27(6):821-42.

Ames AG, Jaques A, Ukoumunne OC, Archibald AD, Duncan RE, Emery J, et al. Development of a fragile X syndrome (FXS) knowledge scale: towards a modified multidimensional measure of informed choice for FXS population carrier screening. Health Expect. 2015;18(1):69-80.

Ames AG, Metcalfe SA, Dalton Archibald A, Duncan RE, Emery J. Measuring informed choice in population-based reproductive genetic screening: a systematic review. European journal of human genetics : EJHG. 2015;23(1):8-21.

Archibald AD, McClaren BJ. Perceived relevance of genetic carrier screening: observations of the role of health-related life experiences and stage of life in decision making. J Community Genet. 2012;3(1):47-54.

Archibald AD, Smith MJ, Burgess T, Scarff KL, Elliott J, Hunt CE, et al. Reproductive genetic carrier screening for cystic fibrosis, fragile X syndrome, and spinal muscular atrophy in Australia: outcomes of 12,000 tests. Genet Med. 2018;20(5):513-23.

Asch A. Prenatal diagnosis and selective abortion: a challenge to practice and policy. American journal of public health. 1999;89(11):1649-57.

Barlow-Stewart K, Burnett L, Proos A, Howell V, Huq F, Lazarus R, et al. A genetic screening programme for Tay-Sachs disease and cystic fibrosis for Australian Jewish high school students. Journal of medical genetics. 2003;40(4):e45.

Beauchamp KA, Johansen Taber KA, Muzzey D. Clinical impact and cost-effectiveness of a 176-condition expanded carrier screen. Genet Med. 2019;21(9):1948-57.

Bekker H, Modell M, Denniss G, Silver A, Mathew C, Bobrow M, et al. Uptake of cystic fibrosis testing in primary care: supply push or demand pull? BMJ (Clinical research ed). 1993;306(6892):1584-6.

Belgium S. Advisory report of the superior health council no. 9240. Expanded carrier screening in a reproductive context Towards a responsible implementation in the healthcare system. 2017.

Belgium S. Advisory report of the superior health council no. 9216. Recommendations on the use of artificial UV devices in Belgium. 2017.

Bell CJ, Dinwiddie DL, Miller NA, Hateley SL, Ganusova EE, Mudge J, et al. Carrier testing for severe childhood recessive diseases by next-generation sequencing. Science translational medicine. 2011;3(65):65ra4-ra4.

Best S, Long J, Theodorou T, Hatem S, Lake R, Archibald A, et al. Health practitioners' perceptions of the barriers and enablers to the implementation of reproductive genetic carrier screening: A systematic review. Prenatal Diagnosis. 2021;41(6):708-19.

Birnie E, Schuurmans J, Plantinga M, Abbott KM, Fenwick A, Lucassen A, et al. Couple-based expanded carrier screening provided by general practitioners to couples in the Dutch general

population: psychological outcomes and reproductive intentions. Genet Med. 2021;23(9):1761-8.

Blencowe H, Moorthie S, Petrou M, Hamamy H, Povey S, Bittles A, et al. Rare single gene disorders: estimating baseline prevalence and outcomes worldwide. J Community Genet. 2018;9(4):397-406.

Boardman FK, Hale R. How do genetically disabled adults view selective reproduction? Impairment, identity, and genetic screening. Mol Genet Genomic Med. 2018;6(6):941-56.

Bonneau V, Nizon M, Latypova X, Gaultier A, Hoarau E, Bézieau S, et al. First French study relative to preconception genetic testing: 1500 general population participants' opinion. Orphanet journal of rare diseases. 2021;16(1):130.

Borry P, Henneman L, Lakeman P, ten Kate LP, Cornel MC, Howard HC. Preconceptional genetic carrier testing and the commercial offer directly-to-consumers. Human reproduction (Oxford, England). 2011;26(5):972-7.

Borry P, Stultiens L, Nys H, Cassiman JJ, Dierickx K. Presymptomatic and predictive genetic testing in minors: a systematic review of guidelines and position papers. Clinical genetics. 2006;70(5):374-81.

Braithwaite J, Marks D, Taylor N. Harnessing implementation science to improve care quality and patient safety: a systematic review of targeted literature. International Journal for Quality in Health Care. 2014;26(3):321-9.

Briggs A, Nouri P, Galloway M, Yaklic JL, Maxwell R, Lindheim S. Patients' Awareness and Attitudes Towards Genetic Carrier Screening. Obstet Gynecol. 2017;129:88S-S.

Brock DJ. Prenatal screening for cystic fibrosis: 5 years' experience reviewed. Lancet (London, England). 1996;347(8995):148-50.

Cannon J, Van Steijvoort E, Borry P, Chokoshvili D. How does carrier status for recessive disorders influence reproductive decisions? A systematic review of the literature. Expert Review of Molecular Diagnostics. 2019;19(12):1117-29.

Carlson LM, Vora NL. Prenatal Diagnosis: Screening and Diagnostic Tools. Obstetrics and gynecology clinics of North America. 2017;44(2):245-56.

Chen LS, Goodson P. Factors affecting decisions to accept or decline cystic fibrosis carrier testing/screening: A theory-guided systematic review. Genet Med. 2007;9(7):442-50.

Cheng HYH, Wong GCY, Chan YK, Lee CP, Tang MHY, Ng EH, et al. Expanded Carrier Screening in Chinese Population - A Survey on Views and Acceptance of Pregnant and Non-Pregnant Women. Frontiers in genetics. 2020;11:594091.

Chial H. Mendelian Genetics: Patterns of Inheritance and Single-Gene Disorders. Nature Education 2008;1(1):63.

Cho D, McGowan ML, Metcalfe J, Sharp RR. Expanded carrier screening in reproductive healthcare: perspectives from genetics professionals. Human reproduction (Oxford, England). 2013;28(6):1725-30.

Chokoshvili D, Belmans C, Poncelet R, Sanders S, Vaes D, Vears D, et al. Public Views on Genetics and Genetic Testing: A Survey of the General Public in Belgium. Genetic testing and molecular biomarkers. 2017;21(3):195-201.

Chokoshvili D, Borry P, Vears DF. A systematic analysis of online marketing materials used by providers of expanded carrier screening. Genet Med. 2018;20(9):976-84.

Chokoshvili D, Van Steijvoort E, Borry P. Ethical challenges in offering expanded carrier screening in the context of third-party reproduction. Médecine De La Reproduction, Gynécologie Et Endocrinologie. 2018;20(4):334-9.

Chokoshvili D, Vears D, Borry P. Expanded carrier screening for monogenic disorders: where are we now? Prenat Diagn. 2018;38(1):59-66.

Chokoshvili D, Vears DF, Borry P. Growing complexity of (expanded) carrier screening: Direct-to-consumer, physician-mediated, and clinic-based offers. Best practice & research Clinical obstetrics & gynaecology. 2017;44:57-67.

Chokoshvili D, Vears DF, Borry P. Reproductive autonomy in expanded carrier screening: more than meets the eye? Expert review of molecular diagnostics. 2018;18(12):993-4.

Christianson A, Howsen PH, Modell B. Global Report on Birth Defects: The hidden toll of dying and disabled children. New York: March of Dimes; 2006.

Christie LM, Ingrey AJ, Turner GM, Proos AL, Watts GE. Outcomes of a cystic fibrosis carrier testing clinic for couples. The Medical journal of Australia. 2009;191(9):499-501.

Clayton EW, Hannig VL, Pfotenhauer JP, Parker RA, Campbell PW, 3rd, Phillips JA, 3rd. Lack of interest by nonpregnant couples in population-based cystic fibrosis carrier screening. Am J Hum Genet. 1996;58(3):617-27.

Colah R, Surve R, Wadia M, Solanki P, Mayekar P, Thomas M, et al. Carrier screening for beta-thalassemia during pregnancy in India: a 7-year evaluation. Genetic testing. 2008;12(2):181-5.

Committee on G. Committee Opinion No. 691: Carrier Screening for Genetic Conditions. Obstet Gynecol. 2017;129(3):e41-e55.

Cornel MC. A higher impact of less specific preconception carrier screening: a plea for a “one size fits all” approach. Journal of Xiangya Medicine. 2017;2:14-.

Cronister A, DiMaio M, Mahoney MJ, Donnenfeld AE, Hallam S. Fragile X syndrome carrier screening in the prenatal genetic counseling setting. Genet Med. 2005;7(4):246-50.

De Wert G, van der Hout S, Goddijn M, Vassena R, Frith L, Vermeulen N, et al. The ethics of preconception expanded carrier screening in patients seeking assisted reproduction. Hum Reprod Open. 2021;2021(1):hoaa063.

De Wert GM, Dondorp WJ, Knoppers BM. Preconception care and genetic risk: ethical issues. J Community Genet. 2012;3(3):221-8.

Delatycki MB, Alkuraya F, Archibald A, Castellani C, Cornel M, Grody WW, et al. International perspectives on the implementation of reproductive carrier screening. Prenatal diagnosis. 2020;40(3):301-10.

Delgado-Rodríguez M, Llorca J. Bias. Journal of epidemiology and community health. 2004;58(8):635-41.

Dive L, Newson AJ. Ethical issues in reproductive genetic carrier screening. Medical Journal of Australia. 2021;214(4):165-7.e1.

Dive L, Newson AJ. Ethically robust reproductive genetic carrier screening needs to measure outcomes that matter to patients. European Journal of Human Genetics. 2022.

Dive L, Newson AJ. Ethics of Reproductive Genetic Carrier Screening: From the Clinic to the Population. Public Health Ethics. 2021;14(2):202-17.

Dive L, Newson AJ. Reproductive carrier screening: responding to the eugenics critique. Journal of medical ethics. 2021:medethics-2021-107343.

Dunn OJ. Multiple Comparisons Using Rank Sums. Technometrics. 1964;6(3):241-52.

Edwards JG, Feldman G, Goldberg J, Gregg AR, Norton ME, Rose NC, et al. Expanded carrier screening in reproductive medicine-points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine. Obstet Gynecol. 2015;125(3):653-62.

Ekstrand Ragnar M, Tydén T, Kihlbom U, Larsson M. Swedish parents' interest in preconception genetic carrier screening. Ups J Med Sci. 2016;121(4):289-94.

Elias S, Annas GJ. Generic consent for genetic screening. N Engl J Med. 1994;330(22):1611-3.

Franasiak JM, Olcha M, Bergh PA, Hong KH, Werner MD, Forman EJ, et al. Expanded carrier screening in an infertile population: how often is clinical decision making affected? Genet Med. 2016;18(11):1097-101.

Fridman H, Yntema HG, Mägi R, Andreson R, Metspalu A, Mezzavila M, et al. The landscape of autosomal-recessive pathogenic variants in European populations reveals phenotype-specific effects. Am J Hum Genet. 2021;108(4):608-19.

Ghanouni A, Renzi C, Meisel SF, Waller J. Common methods of measuring 'informed choice' in screening participation: Challenges and future directions. Prev Med Rep. 2016;4:601-7.

Ghiossi CE, Goldberg JD, Haque IS, Lazarin GA, Wong KK. Clinical Utility of Expanded Carrier Screening: Reproductive Behaviors of At-Risk Couples. Journal of genetic counseling. 2018;27(3):616-25.

Giles Choates M, Stevens BK, Wagner C, Murphy L, Singletary CN, Wittman AT. It takes two: uptake of carrier screening among male reproductive partners. Prenat Diagn. 2020;40(3):311-6.

Gilmore MJ, Schneider J, Davis JV, Kauffman TL, Leo MC, Bergen K, et al. Reasons for Declining Preconception Expanded Carrier Screening Using Genome Sequencing. Journal of Genetic Counseling. 2017;26(5):971-9.

Gordon C, Walpole I, Zubrick SR, Bower C. Population screening for cystic fibrosis: Knowledge and emotional consequences 18 months later. American Journal of Medical Genetics Part A. 2003;120A(2):199-208.

Gorrie A, Archibald AD, Ioannou L, Curnow L, McClaren B. Exploring approaches to facilitate family communication of genetic risk information after cystic fibrosis population carrier screening. Journal of community genetics. 2018;9(1):71-80.

Gregg AR, Aarabi M, Klugman S, Leach NT, Bashford MT, Goldwaser T, et al. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(10):1793-806.

Grody WW, Thompson BH, Gregg AR, Bean LH, Monaghan KG, Schneider A, et al. ACMG position statement on prenatal/preconception expanded carrier screening. Genet Med. 2013;15(6):482-3.

Hawker S, Payne S, Kerr C, Hardey M, Powell J. Appraising the evidence: reviewing disparate data systematically. Qualitative health research. 2002;12(9):1284-99.

Henneman L, Borry P, Chokoshvili D, Cornel MC, van El CG, Forzano F, et al. Responsible implementation of expanded carrier screening. European journal of human genetics : EJHG. 2016;24(6):e1-e12.

Henneman L, Bramsen I, van der Ploeg HM, ten Kate LP. Preconception cystic fibrosis carrier couple screening: impact, understanding, and satisfaction. Genetic testing. 2002;6(3):195-202.

Henneman L, Bramsen I, van Kempen L, van Acker MB, Pals G, van der Horst HE, et al. Offering preconceptional cystic fibrosis carrier couple screening in the absence of established preconceptional care services. Community Genet. 2003;6(1):5-13.

Henneman L, Ten Kate L. Preconceptional couple screening for cystic fibrosis carrier status: couples prefer full disclosure of test results. Journal of medical genetics. 2002;39(5):e26-e.

Henneman L, Timmermans DR, Van der Wal G. Public experiences, knowledge and expectations about medical genetics and the use of genetic information. Public Health Genomics. 2004;7(1):33-43.

Het Kind in Vlaanderen 2020. Agentschap Opgroeien; 2020. Available from: https://www.opgroeien.be/sites/default/files/documents/kind_in_vlaanderen_2020_0.pdf

Higgins A, Flanagan J, Von Wald T, Hansen KA. An Expanded Carrier Screening Tool Enhances Preconception Cystic Fibrosis Screening in Infertile Couples. Open Journal of Obstetrics and Gynecology. 2015:412-6.

Higgins AS, Flanagan JD, Von Wald T, Hansen KA. Preconception Cystic Fibrosis Screening in Infertile Couples Using an Expanded Carrier Screening Test. Obstetrics & Gynecology. 2014;123:97S.

Holtkamp KC, Mathijssen IB, Lakeman P, van Maarle MC, Dondorp WJ, Henneman L, et al. Factors for successful implementation of population-based expanded carrier screening: learning from existing initiatives. The European Journal of Public Health. 2017;27(2):372-7.

Fakih A, Spector-Bagdady K. Should Clinicians Leave "Expanded" Carrier Screening Decisions to Patients? AMA journal of ethics. 2019;21(10):E858-64.

International Human Genome Sequencing C. Finishing the euchromatic sequence of the human genome. Nature. 2004;431(7011):931-45.

Ioannou L, Delatycki MB, Massie J, Hodgson J, Lewis S. "Suddenly Having two Positive People who are Carriers is a Whole New Thing" - Experiences of Couples Both Identified as Carriers of Cystic Fibrosis Through a Population-Based Carrier Screening Program in Australia. Journal of genetic counseling. 2015;24(6):987-1000.

Ioannou L, Massie J, Lewis S, McClaren B, Collins V, Delatycki MB. 'No thanks'-reasons why pregnant women declined an offer of cystic fibrosis carrier screening. J Commun Genet. 2014;5(2):109-17.

Ioannou L, McClaren BJ, Massie J, Lewis S, Metcalfe SA, Forrest L, et al. Population-based carrier screening for cystic fibrosis: a systematic review of 23 years of research. Genet Med. 2014;16(3):207-16.

Janssens S, Chokoshvili D, Vears DF, De Paepe A, Borry P. Pre- and post-testing counselling considerations for the provision of expanded carrier screening: exploration of European geneticists' views. BMC Med Ethics. 2017;18(1):46.

Johansen Taber KA, Beauchamp KA, Lazarin GA, Muzzey D, Arjunan A, Goldberg JD. Clinical utility of expanded carrier screening: results-guided actionability and outcomes. Genet Med. 2019;21(5):1041-8.

Johnston J, Zacharias RL. The future of reproductive autonomy. Hastings Center Report. 2017;47:S6-S11.

Julian LJ. Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S467-72.

Kaback MM. Population-based genetic screening for reproductive counseling: the Tay-Sachs disease model. European journal of pediatrics. 2000;159 Suppl 3:S192-5.

Kater-Kuipers A, de Beaufort ID, Galjaard RH, Bunnik EM. Ethics of routine: a critical analysis of the concept of 'routinisation' in prenatal screening. Journal of medical ethics. 2018;44(9):626-31.

Kauffman TL, Irving SA, Leo MC, Gilmore MJ, Himes P, McMullen CK, et al. The NextGen Study: patient motivation for participation in genome sequencing for carrier status. Molecular Genetics & Genomic Medicine. 2017;5(5):508-15.

Khoshnood B, Greenlees R, Loane M, Dolk H, Committee obotEPM, Group aEW. Paper 2: EUROCAT public health indicators for congenital anomalies in Europe. Birth Defects Research Part A: Clinical and Molecular Teratology. 2011;91(S1):S16-S22.

Kihlbom U. Ethical issues in preconception genetic carrier screening. Ups J Med Sci. 2016;121(4):295-8.

King E, Halliday J, Archibald AD, Delatycki M, Barlow-Stewart K, Newson AJ, et al. Development and use of the Australian reproductive genetic carrier screening decision aid. European Journal of Human Genetics. 2022;30(2):194-202.

Korngiebel DM, McMullen CK, Amendola LM, Berg JS, Davis JV, Gilmore MJ, et al. Generating a taxonomy for genetic conditions relevant to reproductive planning. American journal of medical genetics Part A. 2016;170(3):565-73.

Kraft SA, McMullen CK, Porter KM, Kauffman TL, Davis JV, Schneider JL, et al. Patient perspectives on the use of categories of conditions for decision making about genomic carrier screening results. American journal of medical genetics Part A. 2018;176(2):376-85.

Kraft SA, Schneider JL, Leo MC, Kauffman TL, Davis JV, Porter KM, et al. Patient actions and reactions after receiving negative results from expanded carrier screening. Clinical genetics. 2018;93(5):962-71.

Kronn D, Jansen V, Ostrer H. Carrier screening for cystic fibrosis, Gaucher disease, and Tay-Sachs disease in the Ashkenazi Jewish population: the first 1000 cases at New York University Medical Center, New York, NY. Archives of internal medicine. 1998;158(7):777-81.

Lakeman P, Plass AM, Henneman L, Bezemer PD, Cornel MC, ten Kate LP. Three-month follow-up of Western and non-Western participants in a study on preconceptional ancestry-based carrier couple screening for cystic fibrosis and hemoglobinopathies in the Netherlands. Genet Med. 2008;10(11):820-30.

Lakeman P, Plass AMC, Henneman L, Bezemer PD, Cornel MC, Ten Kate LP. Preconceptional ancestry-based carrier couple screening for cystic fibrosis and haemoglobinopathies: what determines the intention to participate or not and actual participation? European Journal of Human Genetics. 2009;17(8):999-1009.

Larsen D, Ma J, Strassberg M, Ramakrishnan R, Van den Veyver IB. The uptake of pan-ethnic expanded carrier screening is higher when offered during preconception or early prenatal genetic counselling. Prenat Diagn. 2019.

Lazarin G, Detweiler S, Nazareth S, Ashkinadze E. Genetic Counselors' Perspectives and Practices Regarding Expanded Carrier Screening after Initial Clinical Availability. Journal of Genetic Counseling. 2016;25(2):395-404.

Lazarin GA, Haque IS, Nazareth S, Iori K, Patterson AS, Jacobson JL, et al. An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals. Genet Med. 2013;15(3):178-86.

Lazarin GA, Haque IS. Expanded carrier screening: A review of early implementation and literature. Seminars in perinatology. 2016;40(1):29-34.

Lena-Russo D, Badens C, Aubinaud M, Merono F, Paolasso C, Martini N, et al. Outcome of a school screening programme for carriers of haemoglobin disease. Journal of medical screening. 2002;9(2):67-9.

Leo MC, McMullen C, Wilfond BS, Lynch FL, Reiss JA, Gilmore MJ, et al. Patients' ratings of genetic conditions validate a taxonomy to simplify decisions about preconception carrier screening via genome sequencing. American journal of medical genetics Part A. 2016;170(3):574-82.

Lerman C, Croyle RT, Tercyak KP, Hamann H. Genetic testing: psychological aspects and implications. J Consult Clin Psychol. 2002;70(3):784-97.

Levenkron JC, Loader S, Rowley PT. Carrier screening for cystic fibrosis: test acceptance and one year follow-up. American journal of medical genetics. 1997;73(4):378-86.

Lewis C, Hill M, Chitty LS. Offering non-invasive prenatal testing as part of routine clinical service. Can high levels of informed choice be maintained? Prenat Diagn. 2017;37(11):1130-7.

Lewis C, Hill M, Skirton H, Chitty LS. Development and validation of a measure of informed choice for women undergoing non-invasive prenatal testing for aneuploidy. European Journal of Human Genetics. 2016;24(6):809-16.

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100.

Linder SK, Swank PR, Vernon SW, Mullen PD, Morgan RO, Volk RJ. Validity of a low literacy version of the Decisional Conflict Scale. Patient Educ Couns. 2011;85(3):521-4.

Livingstone J, Axton RA, Gilfillan A, Mennie M, Compton M, Liston WA, et al. Antenatal screening for cystic fibrosis: a trial of the couple model. BMJ (Clinical research ed). 1994;308(6942):1459-62.

Loader S, Caldwell P, Kozyra A, Levenkron JC, Boehm CD, Kazazian HH, Jr., et al. Cystic fibrosis carrier population screening in the primary care setting. Am J Hum Genet. 1996;59(1):234-47.

Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). Br J Clin Psychol. 1992;31(3):301-6.

Marteau TM, Dormandy E, Michie S. A measure of informed choice. Health Expect. 2001;4(2):99-108.

Martin J, Asan, Yi Y, Alberola T, Rodríguez-Iglesias B, Jiménez-Almazán J, et al. Comprehensive carrier genetic test using next-generation deoxyribonucleic acid sequencing in infertile

couples wishing to conceive through assisted reproductive technology. Fertility and sterility. 2015;104(5):1286-93.

Massie J, Petrou V, Forbes R, Curnow L, Ioannou L, Dusart D, et al. Population-based carrier screening for cystic fibrosis in Victoria: the first three years experience. The Australian & New Zealand journal of obstetrics & gynaecology. 2009;49(5):484-9.

Mathijssen IB, Holtkamp KCA, Ottenheim CPE, van Eeten-Nijman JMC, Lakeman P, Meijers-Heijboer H, et al. Preconception carrier screening for multiple disorders: evaluation of a screening offer in a Dutch founder population. European journal of human genetics : EJHG. 2018;26(2):166-75.

Mathijssen IB, van Maarle MC, Kleiss IIM, Redeker EJW, Ten Kate LP, Henneman L, et al. With expanded carrier screening, founder populations run the risk of being overlooked. J Community Genet. 2017;8(4):327-33.

McClaren BJ, Aitken M, Massie J, Amor D, Ukoumunne OC, Metcalfe SA. Cascade carrier testing after a child is diagnosed with cystic fibrosis through newborn screening: investigating why most relatives do not have testing. Genetics in medicine : official journal of the American College of Medical Genetics. 2013;15(7):533-40.

Mello S, Stifano S, Tan AS, Sanders-Jackson A, Bigman CA. Gendered Conceptions of Preconception Health: A Thematic Analysis of Men's and Women's Beliefs about Responsibility for Preconception Health Behavior. Journal of Health Communication. 2020;25(5):374-84.

Mertes H, Lindheim SR, Pennings G. Ethical quandaries around expanded carrier screening in third-party reproduction. Fertility and sterility. 2018;109(2):190-4.

Metcalfe S, Jacques A, Archibald A, Burgess T, Collins V, Henry A, et al. A model for offering carrier screening for fragile X syndrome to nonpregnant women: results from a pilot study. Genet Med. 2008;10(7):525-35.

Metcalfe SA. Carrier screening in preconception consultation in primary care. J Community Genet. 2012;3(3):193-203.

Middleton A, editor 'Music of Life' a new metaphor for genomics, delivered as film within genetic counselling. EMPAG conference within European Society of Human Genetics Conference; 2018 16th June 2018. Milan.

Mitchell JJ, Capua A, Clow C, Scriver CR. Twenty-year outcome analysis of genetic screening programs for Tay-Sachs and beta-thalassemia disease carriers in high schools. Am J Hum Genet. 1996;59(4):793-8.

Morris J, Law M, Wald N. Is cascade testing a sensible method of screening a population for autosomal recessive disorders? American Journal of Medical Genetics Part A. 2004;128(3):271-5.

Myring J, Beckett W, Jassi R, Roberts T, Sayers R, Scotcher D, et al. Shock, adjust, decide: reproductive decision making in cystic fibrosis (CF) carrier couples--a qualitative study. Journal of genetic counseling. 2011;20(4):404-17.

Nazareth SB, Lazarin GA, Goldberg JD. Changing trends in carrier screening for genetic disease in the United States. Prenatal diagnosis. 2015;35(10):931-5.

Nesbit CB, Pollack CC, Mascia NS, LaCroix VH, Applebee DM, Bosco AW, et al. Interest in and uptake of genetic counselling for preconception carrier screening when offered to predominantly white reproductive-age persons seeking gynaecologic care at a single U.S. academic medical centre. Journal of genetic counselling. 2021.

NIH. Diversity in Genomic Research: National Human Genome Research Institute; 2021 [updated 7/12/2021. Available from: https://www.genome.gov/about-genomics/fact-sheets/Diversity-in-Genomic-Research.

Nijmeijer S, Conijn T, Lakeman P, Henneman L, Wijburg FA, Haverman L. Attitudes of relatives of mucopolysaccharidosis type III patients toward preconception expanded carrier screening. European Journal of Human Genetics. 2020;28(10):1331-40.

Nijmeijer SCM, Conijn T, Lakeman P, Henneman L, Wijburg FA, Haverman L. Attitudes of the general population towards preconception expanded carrier screening for autosomal recessive disorders including inborn errors of metabolism. Molecular genetics and metabolism. 2019;126(1):14-22.

Obstetricians ACo, Gynecologists. Carrier screening in the age of genomic medicine. Committee Opinion No. 690. Obstet Gynecol. 2017;129:e35-e40.

O'Connor AM. Validation of a decisional conflict scale. Med Decis Making. 1995;15(1):25-30.

Ong R, Howting D, Rea A, Christian H, Charman P, Molster C, et al. Measuring the impact of genetic knowledge on intentions and attitudes of the community towards expanded preconception carrier screening. Journal of medical genetics. 2018;55(11):744-52.

Peyser A, Singer T, Mullin C, Bristow SL, Gamma A, Onel K, et al. Comparing ethnicity-based and expanded carrier screening methods at a single fertility center reveals significant differences in carrier rates and carrier couple rates. Genet Med. 2019;21(6):1400-6.

Plantinga M, Birnie E, Abbott KM, Sinke RJ, Lucassen AM, Schuurmans J, et al. Population-based preconception carrier screening: how potential users from the general population view a test for 50 serious diseases. European journal of human genetics : EJHG. 2016;24(10):1417-23.

Plantinga M, Birnie E, Schuurmans J, Buitenhuis AH, Boersma E, Lucassen AM, et al. Expanded carrier screening for autosomal recessive conditions in health care: Arguments for a couple-based approach and examination of couples' views. Prenat Diagn. 2019;39(5):369-78.

Popejoy AB, Fullerton SM. Genomics is failing on diversity. Nature. 2016;538(7624):161-4.

Poppelaars FA, van der Wal G, Braspenning JC, Cornel MC, Henneman L, Langendam MW, et al. Possibilities and barriers in the implementation of a preconceptional screening programme for cystic fibrosis carriers: a focus group study. Public Health. 2003;117(6):396-403.

Propst L, Connor G, Hinton M, Poorvu T, Dungan J. Pregnant Women's Perspectives on Expanded Carrier Screening. Journal of genetic counselling. 2018;27(5):1148-56.

Charafeddine R, Braekman E, Gisle L, Drieskens S. Gezondheidsenquête 2018: Seksuele gezondheid. Brussel, België: Sciensano; 2018. Contract No.: Sciensano Rapportnummer: D/2019/14.440/60.

Rabkina L, Swanson A, Aufox S, Propst L, Fiddler M, Wagner A, et al. What women want: General population perspectives and access to preconception expanded carrier screening. Prenat Diagn. 2021;41(9):1057-65.

Ragnar ME, Tyden T, Kihlbom U, Larsson M. Swedish parents' interest in preconception genetic carrier screening. Ups J Med Sci. 2016;121(4):289-94.

Richardson E, McEwen A, Newton-John T, Manera K, Jacobs C. The Core Outcome DEvelopment for Carrier Screening (CODECS) study: protocol for development of a core outcome set. Trials. 2021;22(1):480.

Robinson JO, Carroll TM, Feuerman LZ, Perry DL, Hoffman-Andrews L, Walsh RC, et al. Participants and Study Decliners' Perspectives About the Risks of Participating in a Clinical Trial of Whole Genome Sequencing. Journal of Empirical Research on Human Research Ethics. 2016;11(1):21-30.

Robson SJ, Caramins M, Saad M, Suthers G. Socioeconomic status and uptake of reproductive carrier screening in Australia. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2020;60(6):976-9.

Ropers HH. On the future of genetic risk assessment. J Community Genet. 2012;3(3):229-36.

Saffi M, Howard N. Exploring the Effectiveness of Mandatory Premarital Screening and Genetic Counselling Programmes for beta-Thalassaemia in the Middle East: A Scoping Review. Public Health Genomics. 2015;18(4):193-203.

Sallevelt S, Stegmann APA, de Koning B, Velter C, Steyls A, van Esch M, et al. Diagnostic exome-based preconception carrier testing in consanguineous couples: results from the first 100 couples in clinical practice. Genet Med. 2021;23(6):1125-36.

Savell K, Karpin I. The meaning of "serious disability" in the legal regulation of prenatal and neonatal decision-making. Journal of law and medicine. 2008;16(2):233-45.

Schneider JL, Goddard KA, Davis J, Wilfond B, Kauffman TL, Reiss JA, et al. "Is It Worth Knowing?" Focus Group Participants' Perceived Utility of Genomic Preconception Carrier Screening. Journal of genetic counseling. 2016;25(1):135-45.

Schuurmans J, Birnie E, Ranchor AV, Abbott KM, Fenwick A, Lucassen A, et al. GP-provided couple-based expanded preconception carrier screening in the Dutch general population: who accepts the test-offer and why? European journal of human genetics : EJHG. 2020;28(2):182-92.

Schuurmans J, Birnie E, van den Heuvel LM, Plantinga M, Lucassen A, van der Kolk DM, et al. Feasibility of couple-based expanded carrier screening offered by general practitioners. European journal of human genetics : EJHG. 2019;27(5):691-700.

Schuurmans J, Plantinga M, Lucassen A, Fenwick A, Abbott K, Birnie E, et al. Short and long-term psychological impact of an active GP-provided couple-based ECS test-offer in the Dutch general population 2018.

Scotet V, Duguépéroux I, Audrézet MP, Blayau M, Boisseau P, Journel H, et al. Prenatal diagnosis of cystic fibrosis: the 18-year experience of Brittany (western France). Prenat Diagn. 2008;28(3):197-202.

Scott SA, Edelmann L, Liu L, Luo M, Desnick RJ, Kornreich R. Experience with carrier screening and prenatal diagnosis for 16 Ashkenazi Jewish genetic diseases. Human mutation. 2010;31(11):1240-50.

Sheeran P, Webb TL. The Intention-Behavior Gap. Soc Personal Psychol. 2016;10(9):503-18.

Silver J, Norton ME. Expanded Carrier Screening and the Complexity of Implementation. Obstet Gynecol. 2021;137(2):345-50.

Simone L, Khan S, Ciarlariello M, Lin J, Trackman S, Heiman GA, et al. Reproductive male partner testing when the female is identified to be a genetic disease carrier. Prenat Diagn. 2021;41(1):21-7.

Sirugo G, Williams SM, Tishkoff SA. The Missing Diversity in Human Genetic Studies. Cell. 2019;177(4):1080.

Spencer S, Ewing S, Calcagno K, O'Neill S. Adopted Individuals' Views on the Utility and Value of Expanded Carrier Screening. Journal of Genetic Counseling. 2018;27(6):1341-8.

Srinivasan BS, Evans EA, Flannick J, Patterson AS, Chang CC, Pham T, et al. A universal carrier test for the long tail of Mendelian disease. Reproductive biomedicine online. 2010;21(4):537-51.

Statbel. Mother is on average 31 years old at birth of child 2021 [updated 8/7/2021. Available from: https://statbel.fgov.be/en/news/mother-average-31-years-old-birth-child.

Stevens B, Krstic N, Jones M, Murphy L, Hoskovec J. Finding Middle Ground in Constructing a Clinically Useful Expanded Carrier Screening Panel. Obstet Gynecol. 2017;130(2):279-84.

Tavakol M, Dennick R. Making sense of Cronbach's alpha. International journal of medical education. 2011;2:53.

Tongsong T, Charoenkwan P, Sirivatanapa P, Wanapirak C, Piyamongkol W, Sirichotiyakul S, et al. Effectiveness of the model for prenatal control of severe thalassemia. Prenat Diagn. 2013;33(5):477-83.

van Den Berg M, Timmermans DR, Ten Kate LP, Van Vugt JM, Van Der Wal G. Are pregnant women making informed choices about prenatal screening? Genet Med. 2005;7(5):332-8.

van den Berg M, Timmermans DR, ten Kate LP, van Vugt JM, van der Wal G. Informed decision making in the context of prenatal screening. Patient Educ Couns. 2006;63(1-2):110-7.

van der Hout S, Holtkamp KC, Henneman L, de Wert G, Dondorp WJ. Advantages of expanded universal carrier screening: what is at stake? European journal of human genetics : EJHG. 2016;25(1):17-21.

van der Hout S, Dondorp W, de Wert G. The aims of expanded universal carrier screening: Autonomy, prevention, and responsible parenthood. Bioethics. 2019;33(5):568-76.

van Dijke I, Lakeman P, Sabiri N, Rusticus H, Ottenheim CPE, Mathijssen IB, et al. Couples' experiences with expanded carrier screening: evaluation of a university hospital screening offer. European journal of human genetics : EJHG. 2021;29(8):1252-8.

Van Steijvoort E, Chokoshvili D, W Cannon J, Peeters H, Peeraer K, Matthijs G, et al. Interest in expanded carrier screening among individuals and couples in the general population: systematic review of the literature. Human reproduction update. 2020;26(3):335-55.

Van Steijvoort E, Demuynck R, Peeters H, Vandecruys H, Verguts J, Peeraer K, et al. Reasons affecting the uptake of reproductive genetic carrier screening among nonpregnant reproductive-aged women in Flanders (Belgium). Journal of Genetic Counseling.n/a(n/a).

Van Steijvoort E, Devolder H, Geysen I, Van Epperzeel S, Peeters H, Peeraer K, et al. Expanded carrier screening in Flanders (Belgium): an online survey on the perspectives of nonpregnant reproductive-aged women. Personalized medicine. 2021;18(4):361-73.

Van Steijvoort E, Devolder H, Geysen I, Van Epperzeel S, Peeters H, Peeraer K, et al. Knowledge, attitudes and preferences regarding reproductive genetic carrier screening among reproductive-aged men and women in Flanders (Belgium). European journal of human genetics : EJHG. 2022.

Wang T, Bahrampour M, Byrnes J, Scuffham P, Kirk E, Downes M. Economic evaluation of reproductive carrier screening for recessive genetic conditions: a systematic review. Expert Review of Pharmacoeconomics & Outcomes Research. 2022;22(2):197-206.

Westemeyer M, Saucier J, Wallace J, Prins SA, Shetty A, Malhotra M, et al. Clinical experience with carrier screening in a general population: support for a comprehensive pan-ethnic approach. Genet Med. 2020;22(8):1320-8.

Wilfond BS, Kauffman TL, Jarvik GP, Reiss JA, Richards CS, McMullen C, et al. Lessons learned from a study of genomics-based carrier screening for reproductive decision making. Health Affairs. 2018;37(5):809-16.

Witt DR, Schaefer C, Hallam P, Wi S, Blumberg B, Fishbach A, et al. Cystic fibrosis heterozygote screening in 5,161 pregnant women. Am J Hum Genet. 1996;58(4):823-35.

Zarocostas J. Serious birth defects kill at least three million children a year. BMJ (Clinical research ed). 2006;332(7536):256.

Zlotogora J, Carmi R, Lev B, Shalev SA. A targeted population carrier screening program for severe and frequent genetic diseases in Israel. European journal of human genetics : EJHG. 2009;17(5):591-7.

Zuckerman S, Lahad A, Shmueli A, Zimran A, Peleg L, Orr-Urtreger A, et al. Carrier screening for Gaucher disease: lessons for low-penetrance, treatable diseases. Jama. 2007;298(11):1281-90.

Zuckerman S, Lahad A, Zimran A, Levy-Lahad E, Sagi M. Attitudes of couples identified through screening as carriers of Gaucher disease type 1. Clinical genetics. 2008;74(6):566-70.

ADDENDUM

'What we know matters, but who we are matters more. Being rather than knowing requires showing up and letting ourselves be seen. It requires us to dare greatly, to be vulnerable.' – Brené Brown

ABOUT THE AUTHOR

Eva Van Steijvoort was born on 3 October 1991 in Brasschaat, Belgium. She received her secondary education in 2009 at the Sint-Ludgardisschool Merksem where she studied sciences and modern languages. She obtained a bachelor's degree in midwifery (Artesis Hogeschool Antwerpen, 2012) and a master's degree in health education and promotion (UGent, 2015). As a midwifery student, she completed a three-month internship on the labour ward of the Mwananyamala Regional Hospital in Dar Es Salaam, Tanzania. In her master's thesis, she investigated knowledge, attitudes and behaviors regarding cervical cancer screening & HPV vaccination among ethnic minorities in Flanders and Brussels. After graduation, Eva started working for the Belgian development agency in Brussels. From May 2016 to March 2018 she was based in Niger as a junior expert monitoring and evaluation on a "Girls Education" project that aimed to increase the retention rate of girls in rural secondary schools. After returning to Belgium, she started a PhD project on reproductive genetic carrier screening in Flanders (Belgium) under the supervision of Professor Pascal Borry, Professor Hilde Peeters and Professor Karen Peeraer.

AUTHOR'S CONTRIBUTIONS

LIST OF CONTRIBUTERS

Eva Van Steijvoort
PhD candidate, Centre for Biomedical Ethics and Law
Department of Public Health and Primary Care, Faculty of Medicine, KU Leuven
Kapucijnenvoer 35 – Block 3 Box 7001, 3000 Leuven, Belgium

Pascal Borry, PhD
Supervisor, Centre for Biomedical Ethics and Law
Department of Public Health and Primary Care, Faculty of Medicine, KU Leuven
Kapucijnenvoer 35 – Block 3 Box 7000, 3000 Leuven, Belgium

Hilde Peeters, MD, PhD
Co-supervisor, Laboratory for Genetic Epidemiology,
Department of Human Genetics, Faculty of Medicine, KU Leuven
ON1 Herestraat 49 - box 606, 3000 Leuven, Belgium

Karen Peeraer, MD, PhD
Co-supervisor, Woman and Child
Department of Development and Regeneration, Faculty of Medicine, KU Leuven
ON4 Herestraat 49 - box 7003, 3000 Leuven, Belgium

Gert Matthijs, PhD
Laboratory for Molecular Diagnosis
Department of Human Genetics, Faculty of Medicine, KU Leuven
ON1 Herestraat 49 - box 606, 3000 Leuven, Belgium

Davit Chokoshvili, PhD
Bioinformatics Core, Université du Luxembourg
Avenue du Swing 6, L-4367 Belvaux

Hilde Vandecruys, MD and Jasper Verguts, MD, PhD
Department of Gynecology and Obstetrics, Jessa Hospital
3500 Hasselt, Belgium

Heleen Devolder, Inne Geysen and Silke Van Epperzeel
Master of Science in Pharmaceutical Care

DESCRIPTION OF CONTRIBUTIONS

Eva Van Steijvoort was the main researcher of this project and had a leading role in the study design, the recruitment of participants, the data-collection, the daily supervision, the data-analysis and the reporting of study findings. She has succeeded to publish study findings as scientific output in international peer-reviewed journals. Prof. dr. Pascal Borry, Prof. dr. Hilde Peeters, Prof. dr. Karen Peeraer and Prof. dr. Gert Matthijs supervised this doctoral research project. They contributed to the design and implementation of all included studies and were involved in the writing and revision of the all included chapters. Dr. Davit Chokoshvili actively contributed to the two systematic review studies in chapter one and two. Prof. dr. Jasper Verguts and dr. Hilde Vandecruys contributed to the study design and recruitment of participants for the studies described in chapters six, seven and eight. In addition they provided feedback during the writing process. Heleen Devolder, Inne Geysen and Silke Van Epperzeel actively contributed to the study design and the data-collection of the studies described in chapter four and five while carrying out their master's thesis in pharmaceutical science. They also reviewed the manuscript of these two chapters.

CONFLICT OF INTEREST

All authors who have contributed to this manuscript have no conflict of interest to report.

CURRICULUM VITAE OF THE MAIN RESEARCHER

Education

- Master of Science in Health Education and Health Promotion (2012-2015, Ghent University)
  - Master thesis: 'Cervical cancer prevention: knowledge, attitudes and behaviours regarding screening & HPV vaccination among ethnic minorities in Flanders and Brussels'.
- Bachelor of Midwifery (2009-2012, Artesis Hogeschool Antwerpen)
  - Internships in Belgium: Maternity ward, Labour ward, Fertility, Gynaecology, Neonatology, Maternal Intensive Care
  - Internships abroad: Labour ward, Mwananyamala Regional Hospital (Dar Es Salaam, Tanzania)
- ASO Modern Languages/Sciences (2003-2009, Sint-Ludgardis Merksem)

Professional Experience

- PhD student, Centre for Biomedical Ethics and Law KU Leuven (May 2018 – October 2022)
  - Implementation of a reproductive genetic carrier screening offer for couples (FWO-funder project)
- Junior Assistant Monitoring & Evaluation/ Action Research,
  Enabel (The Belgian Development Agency) – Location: Niger (May 2016 – March 2018)
- Administrative Assistant Infocycle,
  Enabel (The Belgian Development Agency) – Location: Brussels (July 2015 – April 2016)

Publications

- **Van Steijvoort, E.**, Peeters, H., Vandecruys, H., Verguts, J., Peeraer, K., Matthijs, G., Borry, P. (2022) Exploring informed choice in preconception reproductive genetic carrier screening by using a modified Multidimensional Measure of Informed choice (Accepted for publication in Patiend Education and Counseling, *In production*)
- **Van Steijvoort, E.**, Demuynck, R., Peeters, H., Vandecruys, H., Verguts, J., Peeraer, K., Matthijs, G., Borry, P. (2022) Reasons affecting the uptake of reproductive genetic carrier screening among nonpregnant reproductive-aged women in Flanders (Belgium). Journal of Genetic Counseling, 00, 1– 11. doi: 10.1002/jgc4.1575
- **Van Steijvoort, E.**, Devolder, H., Geysen, I., Van Epperzeel, S., Peeters, H., Peeraer, K., Matthijs, G., Borry, P. (2022) Knowledge, attitudes and preferences regarding reproductive genetic carrier screening among reproductive-aged men and women in Flanders (Belgium). European Journal of Human Genetics doi: 10.1038/s41431-022-01082-1

- **Van Steijvoort, E.**, Devolder, H., Geysen, I., Van Epperzeel, S., Peeters, H., Peeraer, K., Matthijs, G., Borry, P. (2021). Expanded carrier screening in Flanders (Belgium): an online survey on the perspectives of nonpregnant reproductive-aged women. Personalized Medicine, 18 (4), 361-373. doi: 10.2217/pme-2020-0155
- **Van Steijvoort, E.**, Chokoshvili, D., Cannon, J., Peeters, H., Peeraer, K., Matthijs, G., Borry, P. (2020). Interest in expanded carrier screening among individuals and couples in the general population: systematic review of the literature. Human Reproduction Update. doi: 10.1093/humupd/dmaa001
- Cannon, J., **Van Steijvoort, E.**, Borry, P., Chokoshvili, D. (2019). How does carrier status for recessive disorders influence reproductive decisions? A systematic review of the literature. Expert Review of Molecular Diagnostics, 19 (12), 1117-1129. doi: 10.1080/14737159.2020.1690456
- Chokoshvili, D., **Van Steijvoort, E.**, Borry, P. (2018). Ethical challenges in offering expanded carrier screening in the context of third-party reproduction. Médecine de la Reproduction, Gynécologie et Endocrinologie. doi: 10.1684/mte.2019.0722

Conference participation

- Oral Presentations

- **Van Steijvoort, E.**, Geysen, I., Van Epperzeel, S., Devolder, H., Peeters, H., Peeraer, K., Matthijs, G., Borry, P. (2020). Knowledge, attitudes and preferences regarding expanded carrier screening among reproductive-aged men and women in Belgium. In: HUMAN REPRODUCTION: vol. 35, (123-123). Presented at the 36th Virtual Annual Meeting of the European Society of Human Reproduction and Embryology (ESHRE), 5 July 2020 – 8 July 2020.
- **Van Steijvoort, E.** (2020). Dépistage préconceptionnel. Presented at the 6ième Edition SFMPP: Médicine Génomique & Oncogénomique, 25 June 2020
- **Van Steijvoort, E.** (2019) Dépistage des hétérozygotes de maladies génétiques graves en préconceptionnel. Presented at the 29ième Salon de Gynaecologie-Pratique, Paris, France, 21 March 2019 – 22 March 2019.

- Poster Presentations

- **Van Steijvoort, E.,** Peeters, H., Vandecruys, H., Verguts, J., Peeraer, K., Matthijs, G., Borry, P. (2022) Are couples making informed choices when opting for reproductive genetic carrier screening? Presented at the 52nd Conference of the European Society of Human Genetics (ESHG), Vienna, Austria, 11 June 2022 – 14 June 2022.
- **Van Steijvoort, E.**, Peeters, H., Vandecruys, H., Verguts, J., Peeraer, K., Matthijs, G., Borry, P. (2021) Uptake of preconception carrier screening when offered to non-pregnant women of reproductive age visiting their gynaecologist. Presented at the 21th annual Belgian Society

of Human Genetics (BeSHG) meeting: Reproductive Genetics, Brussels, 27 September 2021.

- **Van Steijvoort, E.**, Demuynck, R., Peeters, H., Peeraer, K., Matthijs, G., Borry, P. (2021). Why do Belgian reproductive-aged women choose to accept or decline expanded carrier screening? (P23.009.A) Presented at the 54th Conference of the European Society of Human Genetics (ESHG), Virtual Conference, 28 August 2021 – 31 August 2021.
- **Van Steijvoort, E.**, Devolder, H., Geysen, I., Van Epperzeel, S., Peeters, H., Peeraer, K., Matthijs, G., Borry, P. (2020). Expanded carrier in screening in Flanders (Belgium): an online survey of knowledge, attitudes and preferences among non-pregnant reproductive-aged women. In: Abstract book, (Abstract No. P27), (83-83). Presented at the 20th annual Belgian Society of Human Genetics (BeSHG) meeting: Genome for all? , Brussels, 6 March 2020 – 6 March 2020.
- Chokoshvili, D., **Van Steijvoort, E.**, Borry, P. (2019). Interest in expanded carrier screening among prospective parents: systematic review of the literature. In: EUROPEAN JOURNAL OF HUMAN GENETICS: vol. 27, (1179-1179). Presented at the 52nd Conference of the European Society of Human Genetics (ESHG), Gothenburg, SWEDEN, 15 June 2019 – 18 June 2019.
- **Van Steijvoort, E.**, Peeters, H., Vandecruys, H., Peeraer, K., Matthijs, G., Chokoshvili, D., Borry, P. (2019). Expanded carrier screening in Belgium: intentions and attitudes of potential users visiting their gynaecologist. In: Online abstracts, (Abstract No. P01.06). Presented at the European Human Genetics Conference (ESHG), Gothenburg, Sweden, 15 June 2019 – 18 June 2019.

DATA AVAILABILITY

Eva Van Steijvoort and Prof. dr. Pascal Borry confirm that they have full access to all the data and take responsibility for the integrity of the data and the accuracy of the data analysis. All of the authors gave final approval of this version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

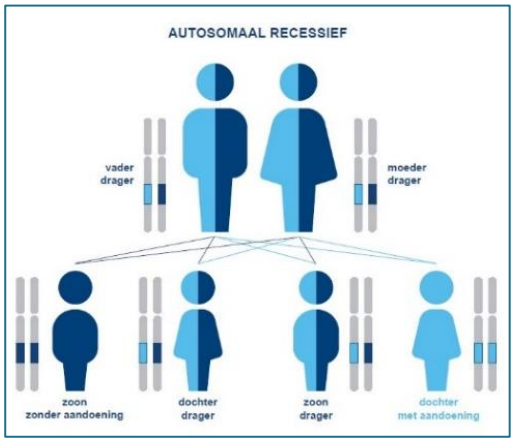
FUNDING SOURCE

This study was supported by the Research Foundation - Flanders (FWO; Dutch: Fonds voor Wetenschappelijk Onderzoek - Vlaanderen). Grant number G094518N.

SUPPLEMENTARY MATERIALS

CHAPTER 4 (https://doi.org/10.2217/pme-2020-0155)

Text A: Background information



The genetic information that we inherit from our parents determines part of our personal characteristics, for example our hair color. But heredity can also play a role when it comes to certain conditions. Carrier status for certain conditions can be determined by a screening test. Being a carrier usually has no consequences for your own health. As a result, people are often not aware of their carrier status. Couples considering having children in the future can be screened for multiple recessive (non-dominant) hereditary conditions. This screening test is performed using a blood test from both reproductive partners. If both partners are carriers of a mutation in the same gene, they have a 25% chance of conceiving a child with a recessive inherited condition in each pregnancy. When the mother is a carrier of an X-linked recessive condition, there is a 50% chance that the male offspring of the couple will develop the condition in each pregnancy. It is estimated that approximately 1-2% of couples in are at risk of conceiving a child with a recessive hereditary condition.

A preconceptional (takes place before conception) carrier screening test can be used to determine whether a couple has an increased reproductive risk. This information can help couples to make reproductive choices related to future pregnancies. When both partners are carriers of the same hereditary condition they have the choice between accepting the increased risk of conceiving a child with this specific hereditary condition, prenatal diagnosis (additional tests during pregnancy), IVF/ICSI in combination with pre-implantation genetic testing (embryo-selection), gametes donation (sperm or egg donation) adoption or to renounce their desire to have children together (depending on the particular condition).

Within this project we focus on preconception carrier screening. Meaning a carrier screening offer for couples considering having children but who are not yet pregnant. We would like to find out more about the knowledge, attitudes and preferences of potential users towards preconception carrier screening. Even if you are not familiar with this topic, your opinion is still very valuable.

Text B: Questionnaire

1. What is your gender?
☐ Male
☐ Female

2. What is your age?
☐ < 18
☐ 18-24
☐ 25-34
☐ 35-44
☐ 45-49
☐ >49

3. What is your highest completed level of education?
☐ Primary education
☐ Secondary education
☐ Non-university higher education
☐ University higher education
☐ PhD

4. Are you religious?
☐ Yes
☐ No (go to question 6)

5. To what extent are you active in your religion?
☐ Not active
☐ Somewhat active
☐ Active

6. Do you have children?
☐ Yes
☐ No

7. Are you currently in a relationship?
☐ Yes
☐ No (go to question 9)

8. Please, specify:
☐ Not living together
☐ Living together
☐ Married

9. Do you have a (future) child wish?
☐ Yes
☐ No
☐ I'm not sure

10. Have you ever had a consultation at a Centre for Human Genetics? (= centre specialized in hereditary conditions)
☐ Yes
☐ No

11. How do you estimate your chance to be a carrier of a hereditary condition?

Very low	1	2	3	4	5	Very high

12. How do you estimate your chance of conceiving a child with a hereditary condition?

Very low	1	2	3	4	5	Very high

13. To what extent do you find it acceptable to offer carrier screening for hereditary conditions to couples with a child wish?

Totally un-acceptable	1	2	3	4	5	Totally acceptable

14. Would you consider a carrier screening test for yourself in the future?

Definitely will not consider	1	2	3	4	5	Definitely will consider

15. I find a preconception carrier screening test for myself to be:

Harmful	1	2	3	4	5	Beneficial
Not important	1	2	3	4	5	Important
Negative	1	2	3	4	5	Positive
Not Reassuring	1	2	3	4	5	Reassuring
Not desirable	1	2	3	4	5	Desirable

16. The pressure on future parents to have preconception carrier screening for hereditary conditions will become great.

Definitely not	1	2	3	4	5	Definitely yes

17. Carrier research for hereditary conditions will lead to greater anxiety among couples who want to become pregnant.

Definitely not	1	2	3	4	5	Definitely yes

18. Carrier research for hereditary conditions will make the lives of people living with these condition seem inferior

Definitely not	1	2	3	4	5	Definitely yes

19. We would like to ask you some knowledge questions about preconception carrier screening for hereditary conditions. For each statement, please put a cross in one of the columns on the right. If you don't know the answer, please choose the "I don't know" box.

		True	False	I don't know
1	A carrier of an hereditary condition carries a mutation for that condition but does not have the condition himself/herself.			
2	All serious conditions are determined by a genetic predisposition.			
3	All hereditary conditions are expressed during childhood (<18 years).			
4	A carrier screening test examines if you are at risk for developing one or more hereditary conditions.			
5	Genetic carrier screening is only intended for individuals with an increased family risk (families where genetic conditions have already occured).			
6	You can be a carrier of a hereditary condition without this condition occuring in your own family			
7	A carrier of a hereditary condition will always develop that specific condition and get related health problems.			
8	If you are a carrier of a hereditary condition, all your offspring will also be a carrier of that specific hereditary condition.			
9	If the (future) mother is a carrier of a recessive hereditary condition, all her children will develop this condition.			
10	If both partners are carriers of a mutation for the same recessive hereditary condition, they a 50% chance each pregnancy to conceive a child with the condition for which they are carriers			
11	If both partners are carriers of a mutation for a different recessive hereditary condition, they have a 25% chance each pregnancy to conceive a child with one of			
12	Two healthy individuals without health problems can have a child with an inherited condition.			
13	When a preconception genetic carrier screening test does not identify an increased risk, this means with certainty that this couple will have a healthy child.			
14	If both partners are carriers of the same genetic condition, they cannot conceive children naturally without this specific genetic condition.			

20. Preconception carrier screening for hereditary conditions should be available through …? (multiple options possible)

☐ The Centre for Human Genetics
☐ The General Practitioner
☐ The Gynaecologist
☐ The Pharmacy
☐ The Midwife
☐ The School
☐ The Internet
☐ This test should not be made available
☐ Others, namely:……

21. Suppose a couple that wants to have children has taken the carrier screening test. How should test results be communicated?

☐ Individual test results: both partners receive information about the conditions of which they are carriers.
☐ Couple-based test result: the couple receives information about whether they are both carriers of the same condition or not (individual test results are not given)
☐ I have no preference

22. How do you think an offer of preconception carrier screening is offered best?
- ☐ All or nothing: the list of conditions is fixed. Everyone is screened for the same conditions.
- ☐ Categories: the list of conditions is divided into certain categories. A category includes similar conditions. People interested in the screening offer can choose for which different categories they would like to be screened.
- ☐ Free choice: those interested are free to choose for which conditions they would like to be screened.

23. Are you willing to pay for a preconception carrier screening test yourself?
- ☐ Yes
- ☐ No
- ☐ I'm not sure

24. How much are you willing to pay for a preconception carrier screening test yourself?
- ☐ < 150 euro
- ☐ 151 – 300 euro
- ☐ 301 – 450 euro
- ☐ 451 – 600 euro
- ☐ 600 euro

This is the end of the questionnaire. We would like to thank you for filling in this questionnaire and sharing your opinion. If you have any questions after completing this questionnaire or if you are interested in the study results, please contact: eva.vansteijvoort@kuleuven.be

Text C: Supplementary data

Sociodemographic Characteristics

Table 8: Sociodemographic Characteristics of participants	
	N (%)
Age (n=151)	
18-24	59 (39.1)
25-34	62 (41.1)
35-44	24 (15.9)
45-49	6 (4.0)
Highest level of completed education (n=151)	
Primary Education	1 (0.7)
Secondary Education	35 (23.2)
Non-university higher education	33 (21.9)
University higher education	81 (53.6)
PhD	1 (0.7)
Religiosity (n=151)	
Yes	42 (27.8)
No	109 (72.2)
Extent of religious involvement (n=42)	
Not active	31 (73.8)
Somewhat	9 (21.4)
Active	2 (4.8)
Children (n=151)	
Yes	37 (24.5)
No	114 (75.5)
(Future) Child wish (n=151)	
Yes	105 (69.5)
No	30 (19.9)
I don’t know	16 (10.6)
Relationship (n=151)	
Yes	108 (71.5)
No	43 (28.5)
Relationship status (n=108)	
Not living together	34 (31.5)
Living together	42 (38.9)
Married	32 (29.6)
Consultation at Centre for Human Genetics (CME) (n=151)	
Yes	10 (6.6)
No	141 (93.4)

Perceived susceptibility

Table 9: Perceived susceptibility
Comparison on outcomes amongst independent samples
Perceived susceptibility of being a carrier of a hereditary condition
Age (U=1488, z=-1.589, p=0.112)[a] Education (U=3245.5, z=1.621, p=0.105)[a] Religiosity (U=2121.5, z=-0.725, p=0.469)[a] Extent of religious involvement (U=140.5, z=-0.924, p=0.396)[a,b] Children (U=2694.5, z=2.639, **p=0.008**)[a] (Future) Child wish (U=1799, z=-2.595, **p=0.009**)[a] Relationship (U=2406.5, z=0.363, p=0.717)[a] Relationship status (U=1114.5, z=-0.990, p=0.322)[a] CME (U=401.5, z=2.366, **p=0.018**)[a]
Perceived susceptibility of conceiving a child with a hereditary condition
Age (U=1614, z=-0.984, p=0.325)[a] Education (U=2637, z=-0.753, p=0.451)[a] Religiosity (U=2278, z=-0.048, p=0.962)[a] Extent of religious involvement (U=157, z=-0.416, p=0.714)[a,b] Children (U=2494.5, z=1.751, p=0.080)[a] (Future) Child wish (U=1820.5, z=-2.524, **p=0.012**)[a] Relationship (U=2534.5, z=0.920, p=0.358)[a] Relationship status (U=1322, z=0.446, p=0.656)[a] CME (U=243.5, z=-3.626, **p<0.001**)[a]

[a] *Mann-Whitney U test.*
[b] *Exact significance is displayed.*

Acceptability & intention to participate in ECS

Table 10: Acceptability & intention to participate in ECS
Comparison on outcomes amongst independent samples
Acceptability of offering ECS to couples with a child wish
Age (U=1793, z=-0.112 p=0.911)[a] Education (U=2794, z=-0.143, p=0.886)[a] Religiosity (U=2416.5, z=0.579 p=0.563)[a] Extent of religious involvement (U=129, z=-1.281, p=0.245)[a,b] Children (U=2024.5, z=-0.399, p=0.690)[a] (Future) Child wish (U=2241, z=-0.769, p=0.442)[a] Relationship (U=1996.5, z=-1.466, p=0.143)[a] Relationship status (U=1270.5, z=0.092, p=0.927)[a] CME (U=677.5, z=-0.225, p=0.822)[a]
Intention to participate in ECS
Age (U=1378, z=-2.118, **p=0.034**)[a] Education (U=2897, z=0.264, p=0.792)[a] Religiosity (U=2505.5, z=0.934, p=0.350)[a] Extent of religious involvement (U=116.5, z=-1.593, p=0.124)[a,b] Children (U=2500.5, z=1.760, p=0.078)[a] (Future) Child wish (U=2083.5, z=-1.393, p=0.164)[a] Relationship (U=2500, z=0.763, p=0.446)[a] Relationship status (U=1253.5, z=-0.031, p=0.975)[a] CME (U=564, z=-1.096, p=0.273)[a]

[a] *Mann-Whitney U test.*
[b] *Exact significance is displayed.*

Knowledge about ECS related concepts

Table 11: Knowledge about ECS related concepts
Comparison of outcomes amongst independent samples
Knowledge Score
Age (U=1340.5, z=-1.392, p=0.164)[a]
Education (U=3403, z=4.714, **p<0.001**)[a]
Religiosity (U=1763.5, z=-0.424, p=0.672)[a]
Extent of religious involvement (U=96, z=-1.076, p=0.302)[a,b]
Children (U=2067, z=1.407, p=0.159)[a]
(Future) Child wish (U=1682, z=-1.478, p=0.139)[a]
Relationship (U=1643, z=-1.293, p=0.196)[a]
Relationship status (U=1040.5, z=0.015, p=0.988)[a]
CME (U=571.5, z=-0.531, p=0.595)[a]

[a] *Mann-Whitney U test.*
[b] *Exact significance is displayed.*

Attitudes towards ECS

Table 12: Attitudes towards ECS
Comparison of outcomes amongst independent samples
Attitude Score
Age (U=1710, z=-0.491, p=0.623)[a]
Education (U=3242, z=1.548, p=0.122)[a]
Religiosity (U=2432, z=0.596, p=0.551)[a]
Extent of religious involvement (U=137.5, z=-0.948, p=0.350) [a,b]
Children (U=2170, z=0.265, p=0.791)[a]
(Future) Child wish (U=2224, z=-0.775, p=0.438)[a]
Relationship (U=2102, z=-0.910, p=0.363)[a]
Relationship status (U=1387.5, z=0.86, p=0.390)[a]
CME (U=342, z=-2.726, **p=0.006**)[a]
Pressure
Age (U=1964.5, z=0.727, p=0.467)
Education (U=3229.5, z=1.56, p=0.119)
Religiosity (U=1889.5, z=-1.730, p=0.084)
Extent of religious involvement (U=170.5, z=<0.001, p=1)[a,b]
Children (U=1963, z=-0.659, p=0.510)
(Future) Child wish (U=2297, z=-0.497, p=0.619)
Relationship (U=2271, z=-0.219, p=0.826)
Relationship status (U=1296.5, z=0.264, p=0.792)
CME (U=753.5, z=0.378, p=0.705)
Anxiety/worry
Age (U=1258.5, z=-2.719, **p=0.007**)
Education (U=2514, z=-1.233, p=0.218)
Religiosity (U=2037, z=-1.096, p=0.273)
Extent of religious involvement (U=169, z=-0.047, p=0.978)[a,b]
Children (U=2282, z=0.784, p=0.433)
(Future) Child wish (U=2101.5, z=-1.328, p=0.184)
Relationship (U=2186, z=-0.588, p=0.557)
Relationship status (U=1143, z=-0.794, p=0.427)
CME (U=960, z=1.999, **p=0.046**)
Inferiority
Age (U=1650, z=-0.795, p=0.427)
Education (U=3071, z=0.934, p=0.350)
Religiosity (U=2352.5, z=0.272, p=0.785)
Extent of religious involvement (U=187, z=0.486, p=0.652)[a,b]
Children (U=2274.5, z=0.740, p=0.460)
(Future) Child wish (U=2323, z=-0.384, p=0.701)
Relationship (U=2410.5, z=0.377, p=0.706)
Relationship status (U=1141, z=-0.803, p=0.422)
CME (U=995, z=2.241, **p=0.025**)

[a] *Mann-Whitney U test.*
[b] *Exact significance is displayed.*

Preferences for the practical organization of a population-based ECS offer

Table 13: Preferences for the practical organization of a population-based ECS offer
Comparison on outcomes amongst independent samples
Availability (Gynaecologist)
Age (χ2(1)=2.924, p=0.087, V=0.139) Education (χ2(1)=0.003, p=0.959, V=0.004) Religiosity (χ2(1)=1.153, p=0.283, V=0.087) Extent of religious involvement (p=0.593*) Children (χ2(1)=1.412, p=0.235, V=0.097) (Future) Child wish (χ2(1)=2.08, p=0.149, V=0.117) Relationship (χ2(1)=0.581, p=0.446, V=0.062) Relationship status (χ2(1)=4.307, **p=0.038**, V=0.200) CME (p=0.683*)
Availability (GP)
Age (χ2(1)=0.135, p=0.713, V=0.030) Education (χ2(1)=0.173, p=0.678, V=0.034) Religiosity (χ2(1)=0.604, p=0.437, V=0.063 Extent of religious involvement (p=0.726*) Children (χ2(1)=0.020, p=0.886, V=0.012) (Future) Child wish (χ2(1)=0.166, p=0.684, V=0.033) Relationship (χ2(1)=1.466, p=0.226, V=0.099) Relationship status (χ2(1)=0.651, p=0.420, V=0.078) CME (p=0.533*)
Availability (CME)
Age (χ2(1)=2.183, p=0.140, V=0.120) Education (χ2(1)=0.255, p=0.614, V=0.041) Religiosity (χ2(1)=0.105, p=0.746, V=0.026) Extent of religious involvement (p=0.305*) Children (χ2(1)=1.561, p=0.211, V=0.102) (Future) Child wish (χ2(1)=0.368, p=0.544, V=0.049) Relationship (χ2(1)=1.668, p=0.197, V=0.105) Relationship status (χ2(1)=0202, p=0.653, V=0.043) CME (p=1*)
Test offer
Age (χ2(2)=2.597, p=0.273, V=0.139) Education (χ2(2)=0.756, p=0.685, V=0.075) Religiosity (χ2(2)=2.240, p=0.326, V=0.129) Extent of religious involvement (p=0.487**) Children (χ2(2)=0.846, p=0.655, V=0.079) (Future) Child wish (χ2(2)=0.261, p=0.878, V=0.044) Relationship (χ2(2)=0.108, p=0.947, V=0.028) Relationship status (χ2(2)=2.323, p=0.313, V=0.155) CME (**p=0.007****)
Results reporting
Age (χ2(2)=1.462, p=0.481, V=0.104) Education (χ2(2)=3.842, p=0.146, V=0.169) Religiosity (χ2(2)=3.776, p=0.151, V=0.167) Extent of religious involvement (p=0.208**) Children (χ2(2)=0.697, p=0.706, V=0.072) (Future) Child wish (χ2(2)=1.039, p=0.595, V=0.088) Relationship (χ2(2)=3.472, p=0.176, V=0.160) Relationship status (χ2(2)=2.168, p=0.338, V=0.150) CME (p=0.719**)
WTP
Age (χ2(2)=1.793, p=0.408, V=0.115) Education (χ2(2)=6.722, **p=0.035**, V=0.223) Religiosity (χ2(2)=2.571, p=0.277, V=0.138) Extent of religious involvement (p=0.655**) Children (χ2(2)=0.643, p=0.725, V=0.069) (Future) Child wish (χ2(2)=0.337, p=0.845, V=0.050) Relationship (χ2(2)=4.855, p=0.088, V=0.190) Relationship status (χ2(2)=1.393, p=0.498, V=0.120)CME (p=0.687**)

WTP (Amount)
Age (χ2(2)=1.017, p=0.601, V=0.117)
Education (χ2(2)=1.743, p=0.418, V=0.153)
Religiosity (χ2(2)=1.206, p=0.547, V=0.128)
Extent of religious involvement (p=0.072**)
Children (χ2(2)=1.259, p=0.533, V=0.130)
(Future) Child wish (χ2(2)=5.164, p=0.076, V=0.264)
Relationship (χ2(2)=0.854, p=0.652, V=0.107)
Relationship status (χ2(2)=1.913, p=0.384, V=0.183)
CME (p=0.887**)

Chi-Square test of independence notation: χ2(df), p-value, V (Cramer's V , measure for the strength/magnitude of the association)

** Fisher-Exact test*

***Fisher-Freeman-Holton test*

CHAPTER 5 (https://doi.org/10.1038/s41431-022-01082-1)

Supplementary Figures and Tables

Table 5: Sociodemographic Characteristics of participants			
	Paper Survey	Online Survey	p[a]
Age	(n=387)	(n=151)	
18-24[c]	171 (44.2)	59 (39.1)	**p = 0.009**
25-34[c]	111 (28.7)	62 (48.6)	
35-44[c]	63 (16.3)	24 (24.4)	
45-49[c]	42 (10.9)	6 (13.5)	
Gender	(n=387)	(n=151)	
Male[c]	122 (31.5)	0 (0)	**p < 0.001**
Female[c]	265 (68.5)	151 (100)	
Highest level of completed education	(n=385)	(n=150)	
Primary Education[c]	2 (0.5)	0 (0)	**p < 0.001**
Secondary Education[c]	155 (40.3)	35 (53.5)	
Non-university higher education[c]	116 (30.1)	33 (41.9)	
University higher education[c]	107 (27.8)	81 (52.9)	
PhD[c]	5 (1.3)	1 (1.7)	
Religiosity	(n=386)	(n=151)	
Yes[c]	127 (32.9)	42 (27.8)	p = 0.254
No[c]	259 (67.1)	109 (72.2)	
Extent of religious involvement	(n=126)		
Not active	84 (66.7)	31 (73.8)	p = 0.604
Somewhat	37 (29.4)	9 (21.4)	
Active	5 (4)	2 (4.8)	
Pregnancy	(n=383)		
Yes	3 (0.8)		
No	380 (99.2)		
Children	(n=385)	(n=151)	
Yes[c]	121 (31.4)	37 (24.5)	p = 0.114
No[c]	264 (68.6)	114 (75.5)	
Relationship	(n=385)	(n=151)	
Yes[c]	266 (69.1)	108 (71.5)	p = 0.581
No[c]	119 (30.9)	43 (28.5)	
Relationship status[b]	(n=264)		
Not living together	93 (35.2)	34 (31.5)	p = 0.657
Living together	90 (34.1)	42 (38.9)	
Married	81 (30.7)	32 (29.6)	
Desire to have children[b]	(n=265)	(n=108)	
Yes[c]	138 (52.1)	73 (67.6)	**p = 0.019**
No[c]	91 (34.3)	23 (21.3)	
I don't know[c]	36 (13.6)	12 (11.1)	
Consultation at Centre for Human Genetics (CME)	(n=386)	(n=151)	
Yes[c]	27 (7)	10 (6.6)	p = 0.878
No[c]	359 (93)	141 (93.4)	

[a]Demographic variables were compared by Chi-Square tests. A p-value <0.05 was considered statistically significant.
[b]Relationship status and the desire to have children was only assessed for those individuals in a relationship.
[c]Results are displayed according to the following notation: n (%).

Table 6: Perceived susceptibility
Comparison on outcomes amongst independent samples
Perceived susceptibility of being a carrier of a hereditary condition
Age (U=13252, z=-1.590, p=0.112)[a] Gender (U=16809.5, z=0.790, p=0.430)[a] Education (U=15824.5, z=0.619, p=0.536)[a] Religiosity (U=14974.5, z=-1.419, p=0.156)[a] Extent of religious involvement (U=1622, z=-0.763, p=0.446)[a] Children (U=13945, z=-2.012, **p=0.044**)[a] Desire to have children (U=8014, z=-1.244, p=0.214)[a] Relationship (U=14230, z=-1.509, p=0.131)[a] Relationship status (U=7190, z=-1.330, p=0.184)[a] CME (U=6141.5, z=2.426, **p=0.015**)[a]
Perceived susceptibility of conceiving a child with a hereditary condition
Age (U=13118.5, z=-1.755, p=0.079)[a] Gender (U=17563, z=1.5, p=0.134)[a] Education (U=14628.5, z=-0.64, p=0.522)[a] Religiosity (U=16286, z=-0.099, p=0.921)[a] Extent of religious involvement (U=1596.5, z=-0.906, p=0.365)[a] Children (U=15817.5, z=-0.097, p=0.922)[a] Desire to have children (U=7585.5, z=-1.984, **p=0.047**)[a] Relationship (U=15264, z=-0.449 p=0.653)[a] Relationship status (U=8178.5, z=0.403, p=0.687)[a] CME (U=6811.5, z=9.72, **p<0.001**)[a]

[a] Mann-Whitney U test.

Table 7: Acceptability & intention to participate in ECS
Comparison on outcomes amongst independent samples
Acceptability of offering ECS to couples with a child wish
Age (U=15152.5, z=0.390, p=0.697)[a] Gender (U=16710.5, z=0.585, p=0.558) Education (U=16272.5, z=1.09, p=0.276)[a] Religiosity (U=14438.5, z=-2.139 **p=0.032**)[a] Extent of religious involvement (U=1512.5, z=-1.403, p=0.161)[a] Children (U=16319, z=0.376, p=0.707)[a] Desire to have children (U=9141.5, z=0.672, p=0.501)[a] Relationship (U=16823.5, z=1.085, p=0.278)[a] Relationship status (U=9090, z=2.125, **p=0.034**)[a] CME (U=6263.5, z=2.78, **p=0.005**)[a]
Intention to participate in ECS
Gender (U=16481, z=0.321, p=0.748) Age (U=10967, z=-4.068, **p<0.001**)[a] Education (U=16608.5, z=1.382, p=0.167)[a] Religiosity (U=14625, z=-1.834, p=0.067)[a] Extent of religious involvement (U=1614.5, z=-0.796, p=0.426)[a] Children (U=13666, z=-2.360, **p=0.018**)[a] Desire to have children (U=7508, z=-2.082, **p=0.037**)[a] Relationship (U=14246.5, z=-1.624, p=0.104)[a] Relationship status (U=7731, z=-0.385, p=0.701)[a] CME (U=6782, z=3.590, **p<0.001**)[a]

[a] Mann-Whitney U test.

Table 8: Knowledge about ECS related concepts
Comparison of outcomes amongst independent samples
Knowledge Score
Age (U=11969.5, z=-2.613, p=**0.009**)[a] Gender (U=18505, z=2.66, p=**0.008**) Education (U=20358, z=5.365, **p<0.001**)[a] Religiosity (U=14280.5, z=-1.889, p=0.059)[a] Extent of religious involvement (U=1343.5, z=-2.003, p=**0.045**)[a] Children (U=13352.5, z=-2.378, **p=0.017**)[a] Desire to have children (U=7129.5, z=-2.452, p=**0.014**)[a] Relationship (U=14543, z=-1.043, p=0.297)[a] Relationship status (U=5949, z=-3.216, **p=0.001**)[a] CME (U=4628, z=-0.347, p=0.729)[a]

[a] Mann-Whitney U test.

Table 9: Attitudes towards ECS
Comparison of outcomes amongst independent samples
Attitude Score
Age (U=12935, z=-1.917, p=0.055)[a] Gender (U=15183, z=0.963, p=0.335)[a] Education (U=15772.5, z=0.490, p=0.624)[a] Religiosity (U=14323.5, z=-2.068, **p=0.039**)[a] Extent of religious involvement (U=1566, z=-1.028, p=0.304) [a] Children (U=15620.5, z=-0.704, p=0.481)[a] Desire to have children (U=8640, z=-0.198, p=0.843)[a] Relationship (U=16449.5, z=-0.619, p=0.536)[a] Relationship status (U=8132, z=0.306, p=0.760)[a] CME (U=7268.5, z=4.345, **p<0.001**)[a]
Pressure
Age (U=14857, z=0.055, p=0.956) [a] Gender (U=15264.5; z=-0.917, p=0.359) [a] Education (U=14779.5, z=-0.534, p=0.593) [a] Religiosity (U=18534.5, z=2.112, **p=0.035**) [a] Extent of religious involvement (U=1667, z-0.526, p=0.599)[a] Children (U=16913, z=0.967, p=0.334) [a] Desire to have children (U=9207, z=0.743, p=0.457) [a] Relationship (U=16522, z=0.717, p=0.473)[a] Relationship status (U=8006.5, z=0.097, p=0.923) [a] CME (U=5263.5, z=0.777, p=0.437)[a]
Anxiety/worry
Age (U=15458.5, z=0.691, p=0.489)[a] Gender (U=15957, z=-0.211, p=0.833)[a] Education (U=15914, z=0.653, p=0.514)[a] Religiosity (U=17862, z=1.422, p=0.155)[a] Extent of religious involvement (U=1854, z=0.484, p=0.628)[a] Children (U=16840, z=0.886, p=0.375)[a] Desire to have children (U=7711, z=-1.745, p=0.081)[a] Relationship (U=16295.5, z=0.481, p=0.631)[a] Relationship status (U=7779.5, z=-0.3, p=0.764)[a] CME (U=3982.5, z=-1.6, p=0.110)[a]
Inferiority
Age (U=14709.5, z=-0.101, p=0.920)[a] Gender (U=17970.5, z=1.824, p=0.068)[a] Education (U=16587.5, z=1.353, p=0.176)[a] Religiosity (U=17602, z=1.159, p=0.247)[a] Extent of religious involvement (U=1786, z=0.117, p=0.907)[a] Children (U=16270, z=0.303, p=0.762)[a] Desire to have children (U=8710, z=-0.088, p=0.930)[a] Relationship (U=14534, z=-1.323, p=0.186)[a] Relationship status (U=7934, z=-0.031, p=0.976)[a] CME (U=4585, z=-0.483, p=0.629)[a]

[a] Mann-Whitney U test.

Table 10: Preferences for the practical organization of a population-based ECS offer
Comparison on outcomes amongst independent samples
Availability (Gynaecologist)
Gender ($\chi2(1)=8.815$, **p=0.003**, V=0.151) Age ($\chi2(1)=1.3$, p=0.254, V=0.058) Education ($\chi2(1)=0.410$, p=0.522, V=0.033) Religiosity ($\chi2(1)=0.848$, p=0.357, V=0.047) Extent of religious involvement ($\chi2(1)=2.314$, p=0.128, V=0.136) Children ($\chi2(1)=0.005$, p=0.943, V=0.004) Desire to have children ($\chi2(1)=0.773$, p=0.379, V=0.054) Relationship ($\chi2(1)=1.175$, p=0.278, V=0.055) Relationship status ($\chi2(1)=2.528$, p=0.112, V=0.098) CME ($\chi2(1)=0.003$, p=0.957, V=0.003)
Availability (GP)
Gender ($\chi2(1)=5.843$, **p=0.016**, V=0.123) Age ($\chi2(1)=0.050$, p=0.823, V=0.011) Education ($\chi2(1)=4.655$, **p=0.031**, V=0.110) Religiosity ($\chi2(1)=3.511$, p=0.061, V=0.095) Extent of religious involvement ($\chi2(1)=0.018$, p=0.894, V=0.012) Children ($\chi2(1)=0.694$, p=0.405, V=0.042) Desire to have children ($\chi2(1)=0.250$, p=0.617, V=0.031) Relationship ($\chi2(1)=0.316$, p=0.574, V=0.029) Relationship status ($\chi2(1)=0.796$, p=0.372, V=0.055) CME ($\chi2(2)=0.297$, p=0.586, V=0.028)
Availability (CME)
Gender ($\chi2(1)=0.251$, p=0.617, V=0.025) Age ($\chi2(1)=10.931$, **p<0.001**, V=0.168) Education ($\chi2(1)=3.153$, p=0.076, V=0.090) Religiosity ($\chi2(1)=0.544$, p=0.461, V=0.038) Extent of religious involvement ($\chi2(1)=1.697$, p=0.193, V=0.116) Children ($\chi2(1)=2.286$, p=0.131, V=0.077) Desire to have children ($\chi2(1)=1.303$, p=0.254, V=0.070) Relationship ($\chi2(1)=0$, p=0.993, V=0) Relationship status ($\chi2(1)=4.383$, **p=0.036**, V=0.129) CME ($\chi2(1)=0.46$, p=0.830, V=0.011)
Test offer
Gender ($\chi2(2)=0.424$, p=0.809, V=0.033) Age ($\chi2(2)=3.471$, p=0.176, V=0.096) Education ($\chi2(2)=1.589$, p=0.452, V=0.065) Religiosity ($\chi2(2)=2.508$, p=0.285, V=0.081) Extent of religious involvement ($\chi2(2)=1.198$, p=0.549, V=0.098) Children ($\chi2(2)=3.857$, p=0.145, V=0.101) Desire to have children ($\chi2(2)=0.258$, p=0.879, V=0.032) Relationship ($\chi2(2)=0.851$, p=0.653, V=0.047) Relationship status ($\chi2(2)=1.503$, p=0.472,V=0.076) CME ($\chi2(2)=1.803$, p=0.406, V=0.069)
Results reporting
Gender ($\chi2(2)=2.719$, p=0.257, V=0.084) Age ($\chi2(2)=0.038$, p=0.981, V=0.010) Education ($\chi2(2)=2.437$, p=0.296,V=0.08) Religiosity ($\chi2(2)=2.797$, p=0.247, V=0.086) Extent of religious involvement ($\chi2(2)=2.554$, p=0.279, V=0.144) Children ($\chi2(2)=2.677$, p=0.262, V=0.084) Desire to have children ($\chi2(2)=4.433$, p=0.109, V=0.130) Relationship ($\chi2(2)=10.769$, **p=0.005**, V=0.169) Relationship status ($\chi2(2)=4.194$, p=0.123, V=0.127) CME ($\chi2(2)=4.461$, p=0.107, V=0.108)

WTP
Gender (χ2(2)=0.321, p=0.852, V=0.029) Age (χ2(2)=2.752, p=0.253, V=0.084) Education (χ2(2)=10.11, **p=0.006**, V=0.162) Religiosity (χ2(2)=2.211, p=0.331, V=0.076) Extent of religious involvement (χ2(2)=1.164, p=0.559, V=0.096) Children (χ2(2)=0.014, p=0.993, V=0.006) Desire to have children (χ2(2)=0.868, p=0.648, V=0.057) Relationship (χ2(2)=14.132, **p=0.001**, V=0.192) Relationship status (χ2(2)=1.358, p=0.507, V=0.072) CME (χ2(2)=5.445, p=0.066, V=0.119)
WTP (Amount)
Gender (χ2(2)=0.977, p=0.614, V=0.061) Age (χ2(2)=0.405, p=0.817, V=0.039) Education (χ2(2)=0.253, p=0.881, V=0.031) Religiosity (χ2(2)=0.951, p=0.622, V=0.060) Extent of religious involvement (χ2(2)=8.905, **p=0.012**, V=0.328) Children (χ2(2)=0.122, p=0.941, V=0.021) Desire to have children (χ2(2)=1.26, p=0.533, V=0.081) Relationship (χ2(2)=1.559, p=0.459, V=0.077) Relationship status (χ2(2)=0.421, p=0.810, V=0.047) CME (χ2(2)=1.676, p=0.433, V=0.080)

Chi-Square test of independence notation: χ2(df), p-value, V (Cramer's V, measure for the strength/magnitude of the association)

Table 11 : Associations between continuous/ordinal variables

			Risk Perception (Carrier)	Risk Perception (child)	Acceptability	Intention	Pressure	Anxiety	Worry	Attitude score	Knowledge score
Spearman's rho	Risk Perception (Carrier)	r_s	1,000	,672**	,055	,226**	,043	,138**	,000	,123*	,198**
		p	.	**,000**	,283	**,000**	,403	,007	,998	**,015**	**,000**
	Risk Perception (Child)	r_s	,672**	1,000	,003	,158**	,058	,098	-,023	,097	,101*
		p	**,000**	.	,952	**,002**	,256	,054	,649	,057	**,048**
	Acceptability	r_s	,055	,003	1,000	,445**	-,019	-,195**	-,172**	,471**	,135**
		p	,283	,952	.	**,000**	,710	**,000**	**,001**	**,000**	**,008**
	Intention to have ECS	r_s	,226**	,158**	,445**	1,000	,103*	-,102*	-,110*	,712**	,119*
		p	**,000**	**,002**	**,000**	.	**,042**	**,044**	**,031**	**,000**	**,019**
	Pressure	r_s	,043	,058	-,019	,103*	1,000	,188**	,253**	,106*	,011
		p	,403	,256	,710	**,042**	.	**,000**	**,000**	**,038**	,829
	Anxiety	r_s	,138**	,098	-,195**	-,102*	,188**	1,000	,368**	-,186**	,057
		p	**,007**	,054	**,000**	**,044**	**,000**	.	**,000**	**,000**	,262
	Worry	r_s	,000	-,023	-,172**	-,110*	,253**	,368**	1,000	-,136**	,082
		p	,998	,649	**,001**	**,031**	**,000**	**,000**	.	**,007**	,108
	Attitude score	r_s	,123*	,097	,471**	,712**	,106*	-,186**	-,136**	1,000	,063
		p	**,015**	,057	**,000**	**,000**	**,038**	**,000**	**,007**	.	,215
	Knowledge score	r_s	,198**	,101*	,135**	,119*	,011	,057	,082	,063	1,000
		p	**,000**	**,048**	**,008**	**,019**	,829	,262	,108	,215	.

**. Correlation is significant at the 0.01 level (2-tailed). *. Correlation is significant at the 0.05 level (2-tailed).

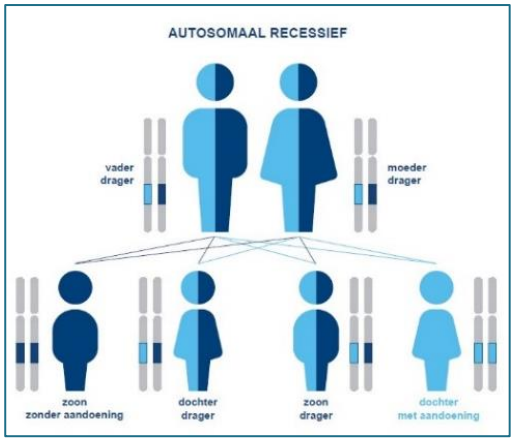
CHAPTER 6 (https://doi.org/10.1002/jgc4.1575)

Supplementary data

Table 5: Socio-demographic characteristics of study participants	
Characteristic	n(%)
Gender (n=127)	
- Female	127 (100%)
Age (n=127)	
- 18-24	13 (10.3)
- 25-34	77 (60.6)
- 35-45	28 (22.0)
- 45-49	9 (7.1)
Religion (n=127)	
- Religious	47 (37)
- Not religious	80 (63)
Religiosity (n=47)	
- Not active	21 (44.7)
- Somewhat	21 (44.7)
- Active	5 (10.6)
Highest level of completed education (n=127)	
- Primary Education	3 (2.4)
- Secondary Education	37 (29.1)
- Non-university higher education	49 (38.6)
- University higher education	35 (27.6)
- PhD	3 (2.4)
Relationship (n=127)	
- Yes	115 (90.6)
- No	12 (9.6)
Relationship status (n=113)	
- Not living together	14 (12.4)
- Living together	59 (52.2)
- Married	40 (35.4)
Pregnancy (n=127)	
- No	127 (100%)
Children (n=127)	
- Yes	55 (43.3)
- No	72 (56.7)
(Future) Child wish (n=126)	
- Yes	83 (65.9)
- No	30 (23.8)
- I don’t know	13 (10.3)
Consultation at Centre for Human Genetics (n=127)	
- Yes	11 (8.7)
- No	116 (91.3)

Table 6 : Reasons to accept or decline RGCS						
Reasons to accept						
		Strongly disagree	Disagree	Neutral	Agree	Strongly Agree
1	… I am curious to know my carrier status.	8 (6.3)	13 (10.2)	20 (15.7)	40 (31.5)	46 (36.2)
2	… I want to prevent having a child with a hereditary condition.	1 (0.8)	9 (7.1)	14 (11)	37 (29.1	66 (52)
3	… I want to spare a child a life with a hereditary condition.	2 (1.6)	6 (4.7)	23 (18.1)	35 (27.6)	61 (48)
4	… I am afraid of not being able to deal with a child with a hereditary condition	29 (22.8)	22 (17.3)	30 (23.6)	28 (22)	18 (14.2)
5	… I want to be able to prepare in advance for the possibility of having a child with a hereditary condition.	5 (3.9)	8 (6.3)	18 (14.2)	52 (40.9)	44 (34.6)
6	… I don't want to have regrets afterwards.	24 (18.9)	12 (9.4)	30 (23.6)	34 (26.8)	27 (21.3)
7	… I want to be able to pass on genetic information to my own children or family members.	2 (1.6)	4 (3.1)	17 (13.4)	48 (37.8)	56 (44.1)
8	… others expect this from me.	101 (79.5)	11 (8.7)	5 (3.9)	8 (6.3)	2 (1.6)
9	… I want to know my risk of conceiving a child with a hereditary condition.	3 (2.4)	4 (3.1)	18 (14.2)	43 (33.9)	59 (46.5)
Reasons to decline						
1	… there are no genetic conditions that run in the family.	73 (57.5)	26 (20.5)	9 (7.1)	14 (11)	5 (3.9)
2	… it concerns rare conditions.	65 (51.2)	34 (26.8)	16 (12.6)	7 (5.5)	5 (3.9)
3	… I don't want to take action based on test-results (before or during pregnancy).	65 (51.2)	32 (25.2)	17 (13.4)	9 (7.1)	4 (3.1)
4	… of the anxiety I might feel as a result of the test results.	45 (35.4)	28 (22)	27 (21.3)	17 (13.4)	10 (7.9)
5	… I am against the selection of children based on carrier screening test results	64 (50.4)	31 (24.4)	21 (16.5)	8 (6.3)	3 (2.4)
6	… I'm afraid of needles and blood.	102 (80.3)	9 (7.1)	7 (5.5)	5 (3.9)	4 (3.1)
7	… it would take too much time and/or effort.	109 (85.8)	9.4 (9.4)	3 (2.4)	3 (2.4)	0 (0)

TEXT A: Background information



The genetic information that we inherit from our parents determines part of our personal characteristics, for example our hair color. But heredity can also play a role when it comes to certain conditions. Carrier status for certain conditions can be determined by a screening test. Being a carrier usually has no consequences for your own health. As a result, people are often not aware of their carrier status. Couples considering having children in the future can be screened for multiple recessive (non-dominant) hereditary conditions. This screening test is performed using a blood test from both reproductive partners. If both partners are carriers of a mutation in the same gene, they have a 25% chance of conceiving a child with a recessive inherited condition in each pregnancy. When the mother is a carrier of an X-linked recessive condition, there is a 50% chance that the male offspring of the couple will develop the condition in each pregnancy. It is estimated that approximately 1-2% of couples in are at risk of conceiving a child with a recessive hereditary condition.

A preconceptional (takes place before conception) carrier screening test can be used to determine whether a couple has an increased reproductive risk. This information can help couples to make reproductive choices related to future pregnancies. When both partners are carriers of the same hereditary condition they have the choice between accepting the increased risk of conceiving a child with this specific hereditary condition, prenatal diagnosis (additional tests during pregnancy), IVF/ICSI in combination with pre-implantation genetic testing (embryo-selection), gametes donation (sperm or egg donation) adoption or to renounce their desire to have children together (depending on the particular condition).

Within this project we focus on preconception carrier screening. Meaning a carrier screening offer for couples considering having children but who are not yet pregnant. We would like to find out more about the knowledge, attitudes and preferences of potential users towards preconception carrier screening. Even if you are not familiar with this topic, your opinion is still very valuable.

Text B: Questionnaire

1. What is your gender?
☐ Male
☐ Female

2. What is your age?
☐ < 18
☐ 18-24
☐ 25-34
☐ 35-45
☐ 45-49

3. What is your highest completed level of education?
☐ Primary education
☐ Secondary education
☐ Non-university higher education
☐ University higher education
☐ PhD

4. Are you religious?
☐ Yes
☐ No (go to question 6)

5. To what extent are you active in your religion?
☐ Not active
☐ Somewhat active
☐ Active

6. Do you have children?
☐ Yes
☐ No

7. Are you currently in a relationship?
☐ Yes
☐ No (go to question 9)

8. Please, specify:
☐ Not living together
☐ Living together
☐ Married

9. Are you pregnant?
☐ Yes
☐ No
☐ I'm not sure

10. Do you have a (future) child wish?
☐ Yes
☐ No
☐ I'm not sure

11. Have you ever had a consultation at a Centre for Human Genetics? (= centre specialized in hereditary conditions)
☐ Yes
☐ No

12. How do you estimate your chance to be a carrier of a hereditary condition?

Very low	1	2	3	4	5	Very high

13. How do you estimate your chance of conceiving a child with a hereditary condition?

Very low	1	2	3	4	5	Very high

14. To what extent do you find it acceptable to offer carrier screening for hereditary conditions to individuals?

Totally un-acceptable	1	2	3	4	5	Totally acceptable

15. To what extent do you find it acceptable to offer carrier screening for hereditary conditions to couples with a child wish?

Totally un-acceptable	1	2	3	4	5	Totally acceptable

16. To what extent do you find it acceptable to offer carrier screening for hereditary conditions to pregnant women?

Totally un-acceptable	1	2	3	4	5	Totally acceptable

17. Would you consider a carrier screening test for yourself in the future?

Definitely will not consider	1	2	3	4	5	Definitely will consider

18. I find a preconception carrier screening test for myself to be:

Harmful	1	2	3	4	5	Beneficial
Not important	1	2	3	4	5	Important
Negative	1	2	3	4	5	Positive
Not Reassuring	1	2	3	4	5	Reassuring
Not desirable	1	2	3	4	5	Desirable

19. I would accept RGCS because

… I am curious to know my carrier status.						
Strongly disagree	1	2	3	4	5	Strongly agree
… I want to prevent having a child with a hereditary condition.						
Strongly disagree	1	2	3	4	5	Strongly agree
… I want to spare a child a life with a hereditary condition.						
Strongly disagree	1	2	3	4	5	Strongly agree
… I am afraid of not being able to deal with a child with a hereditary condition						
Strongly disagree	1	2	3	4	5	Strongly agree
… I want to be able to prepare in advance for the possibility of having a child with a hereditary condition.						
Strongly disagree	1	2	3	4	5	Strongly agree
… I don’t want to have regrets afterwards.						
Strongly disagree	1	2	3	4	5	Strongly agree

… I want to be able to share genetic information with my own children or family members.						
Strongly disagree	1	2	3	4	5	Strongly agree
… others expect this from me.						
Strongly disagree	1	2	3	4	5	Strongly agree
… I want to know my risk of conceiving a child with a hereditary condition.						
Strongly disagree	1	2	3	4	5	Strongly agree

20. I would decline RGCS because

… there are no genetic conditions that run in the family.						
Strongly disagree	1	2	3	4	5	Strongly agree
… it concerns rare conditions.						
Strongly disagree	1	2	3	4	5	Strongly agree
… I don't want to take action based on test-results (before or during pregnancy).						
Strongly disagree	1	2	3	4	5	Strongly agree
… of the anxiety I might feel as a result of the test results.						
Strongly disagree	1	2	3	4	5	Strongly agree
… I am against the selection of children based on carrier screening test results						
Strongly disagree	1	2	3	4	5	Strongly agree
… I'm afraid of needles and blood.						
Strongly disagree	1	2	3	4	5	Strongly agree
… it would take too much time and/or effort.						
Strongly disagree	1	2	3	4	5	Strongly agree

21. The pressure on future parents to have preconception carrier screening for hereditary conditions will become great.

Definitely not	1	2	3	4	5	Definitely yes

22. Carrier screening for hereditary conditions will lead to greater anxiety among couples who want to become pregnant.

Definitely not	1	2	3	4	5	Definitely yes

23. Carrier screening for hereditary conditions will make the lives of people living with these condition seem inferior

Definitely not	1	2	3	4	5	Definitely yes

24. Would you accept a preconception carrier screening offer if it was offered to you free of charge

☐ Yes
☐ No
☐ I'm not sure

25. I think my partner is of the opinion that we should have preconception RGCS (only applicable if you have a partner)

☐ Yes
☐ No
☐ I'm not sure

Informed Consent Form

Title: Preconception reproductive genetic carrier screening in Belgium: evaluation of a test offer in a reproductive context

I, the undersigned, do hereby confirm that I consent to participate in the above-mentioned study.

I declare that:

- I have received the information leaflet and the informed consent form from the researcher and have taken note of the contents.
- The nature, purpose, potential benefits and risks/discomforts of the study have been adequately explained to me by the researcher.
- I have had the opportunity to ask questions that came to my mind and I have received clear answers.
- I have had sufficient time to read the information, discuss it with others and decide whether or not to participate in the study.
- I understand that my participation in this study is voluntary and that I am free to discontinue my participation in this study at any time without having to give a reason.
- I understand that data about me will be collected during my participation in this study and that the researchers involved ensure the confidentiality of this data in accordance with the European General Data Protection Regulation.
- I understand that the results of this study will be used for scientific publications where the results will be displayed so that participants in this study cannot be identified.
- I understand that my test results will be communicated by telephone after +/- 6 months by a involved KU Leuven researcher.
- I understand that genetic counseling is offered by a Clinical Geneticist in the event of an abnormal couple result or in this case of individual carrier status.
- I understand that the blood samples taken as part of this study will be destroyed upon completion of this study (max. 6 years after the collection of the samples).
- I understand that secondary findings that may provide relevant health information will be communicated if this information may lead to preventive or therapeutic actions.
- I understand that this test does not rule out the risk of having a child with a hereditary condition. In case of a normal couple result, there is no demonstrably increased risk of having a child with one of the tested conditions.

We choose the following way to receive the test result:

☐ Researcher calls us separately Name Female partner: …….. Tel Female partner: …… Name Male Partner: …….. Tel Male Partner: ……	☐ Researcher calls one of us Name: …….. Tel: ……

PARTICIPANTS

Female partner
Name + Surname:
Date:
Address:
Tel:
Signature:

Male partner
Name + Surname:
Date:
Address:
Tel:
Signature:

RESEARCHER

I, the undersigned ……., authorized researcher, declare that I have provided the necessary information regarding this study orally as well as a copy of the information document to the participant. I confirm that no pressure has been exerted on the participant to agree to participate in the study and I am willing to answer any additional questions that may arise. I confirm that I work in accordance with the ethical principles as stated in the "Declaration of Helsinki", the "Good Clinical Practice" and the Belgian law of 7 May 2004 on experiments on the human person

Date and Signature Researcher

Information provision

The information that was provided to participants was based on the information leaflet of the Belgian RGCS offer that was developed by representatives of the 8 Centres for Human Genetics in Belgium and the scientific literature and included the following topics:

- Description of a carrier of a monogenic condition
  - Every human being is a carrier
  - Autosomal recessive inheritance + example
  - X-linked inheritance + example
  - Monogenic conditions vs. other genetic conditions or multifactorial conditions
- Description of RGCS
  - Objective
  - Target population
  - Relevance of family history
  - Description of carrier couple
  - Population risk of being a carrier couple
  - Reproductive options available for carrier couples
- Description of the Belgian RGCS offer
  - Generic description of the total number and type of conditions included
  - Screening for most common pathogenic variants
  - Based on current scientific knowledge/ Possibility of new insights over time (additional variants may be included in newer screening panels)
  - Reduced penetrance & variable expressivity of phenotypes for certain conditions
  - Test-procedures: sampling & analysis
  - Cost of Belgian RGCS offer
- Information on results reporting
  - Turn-around time to obtain screening results
  - Focus on couple-based results with individuals results for 7 conditions → possibility to offer cascade screening for relatives
  - Meaning of a screen-negative result
  - Meaning of a screen-positive result
  - Meaning on results when one of both partners is identified as a carrier of a monogenic condition
  - Incidental findings (medically relevant information will be reported)
- Limitations of RGCS
  - Residual risk
  - Couple-based screenings results only applicable to the unique combination of two reproductive partners
  - RGCS doesn't replace NIPT or newborn screening
  - RGCS not sufficient for consanguineous couples or those with a family history of a genetic condition
- Possible consequences of RGCS
  - Stress, worry and anxiety
  - Significance of information gained through RGCS for other family members
- The right not to know

List of included genes within the BeGECS

AAAS
AARS2
ABAT
ABCA1
ABCA12
ABCA3
ABCA4
ABCB11
ABCB4
ABCB7
ABCC2
ABCC6
ABCC8
ABCD1
ABCD3
ABCG5
ABCG8
ABHD12
ABHD5
ACAD9
ACADM
ACADS
ACADSB
ACADVL
ACAT1
ACE
ACO2
ACOX1
ACP5
ACSF3
ACSL4
ACTA1
ACY1
ADA
ADAMTS10
ADAMTS13
ADAMTS17
ADAMTS2
ADAMTSL2
ADAR
ADGRG1
ADGRV1
ADSL
AFG3L2
AGA
AGK
AGL
AGPAT2
AGPS
AGT
AGTR1
AGXT
AHCY
AHI1
AICDA
AIMP1
AIPL1
AIRE
AK1
AK2
AKR1C2
ALAD
ALAS2
ALDH18A1
ALDH1A3
ALDH3A2
ALDH4A1
ALDH5A1
ALDH7A1
ALDOB
ALG1
ALG11
ALG12
ALG2
ALG3
ALG6
ALG8
ALG9
ALMS1
ALOX12B
ALPL
ALS2
ALX3
ALX4
AMACR
AMH
AMHR2
AMN
AMPD1
AMT
ANO10
ANO5
ANOS1
ANTXR2
AP3B1
AP4B1
APOB
APOC2
APRT
APTX
AQP2
AR
ARFGEF2
ARG1
ARL13B
ARL6
ARSA
ARSB
ARSE
ARX
ASAH1
ASL
ASNS
ASPA
ASPM
ASS1
ATF6
ATIC
ATM
ATP13A2
ATP6V0A2
ATP6V0A4
ATP6V1B1
ATP7A
ATP7B
ATP8A2
ATP8B1
ATR
ATRX
AUH
B3GALNT2
B3GALT6
B3GALTL
B3GAT3
B3GNT1
B4GALT1
B9D1
B9D2
BBIP1
BBS1
BBS10
BBS12
BBS2
BBS4
BBS5
BBS7
BBS9
BCKDHA
BCKDHB
BCOR
BCS1L
BEST1
BIN1
BLM
BLOC1S6
BMP1
BMPER
BMPR1B
BRCA2
BRIP1
BSCL2
BSND
BTD
BTK
BUB1B

C10ORF2
C12ORF57
C12ORF65
C19ORF12
C2ORF71
C5ORF42
C8B
CA2
CACNA1F
CANT1
CAPN3
CASK
CASQ2
CASR
CAV3
CBS
CC2D2A
CCBE1
CCDC28B
CCDC39
CCDC40
CD19
CD3D
CD3E
CD3G
CD40LG
CD96
CDAN1
CDC6
CDH23
CDK5RAP2
CDKL5
CDT1
CENPJ
CEP152
CEP164
CEP290
CEP41
CEP57
CERKL
CFP
CFTR
CHAT
CHM
CHMP1A
CHRNA1
CHRNB1
CHRND
CHRNE
CHRNG
CHST14
CHST3
CHST6
CHSY1
CIITA
CKAP2L
CLCN1
CLCN2
CLCN5
CLCN7
CLDN1
CLDN14
CLDN16
CLDN19
CLN3
CLN5
CLN6
CLN8
CLRN1
CNGA1
CNGA3
CNGB1
CNGB3
CNNM4
CNTN1
CNTNAP2
COG1
COG4
COG7
COG8
COL11A1
COL11A2
COL17A1
COL18A1
COL1A2
COL27A1
COL2A1
COL4A3
COL4A4
COL4A5
COL6A1
COL6A2
COL6A3
COL7A1
COL9A2
COLEC11
COLQ
COQ2
COQ4
COQ8A
COQ9
COX10
COX15
COX6B1
COX7B
CP
CPS1
CPT1A
CPT2
CRB1
CRLF1
CRTAP
CRYAB
CSPP1
CSTB
CTC1
CTH
CTNS
CTSA
CTSC
CTSD
CTSK
CUBN
CUL4B
CUL7
CYB5R3
CYBA
CYBB
CYP11A1
CYP11B1
CYP11B2
CYP17A1
CYP19A1
CYP1B1
CYP21A2
CYP24A1
CYP27A1
CYP27B1
CYP2U1
CYP4V2
CYP7B1
D2HGDH
DARS
DARS2
DBH
DBT
DCHS1
DCLRE1C
DCX
DDB2
DDC
DDHD2
DDX59
DES
DFNB31
DGUOK
DHCR24
DHCR7
DHDDS
DHH
DHODH
DIS3L2
DKC1
DLD
DLL3
DLX5
DMD
DMP1
DNAAF1
DNAH11
DNAH5

DNAI1
DNAI2
DNAJC19
DNM2
DNMT3B
DOCK6
DOCK8
DOK7
DOLK
DPAGT1
DPM1
DPYD
DSC2
DSG1
DSP
DUOX2
DUOXA2
DYM
DYNC2H1
DYSF
EARS2
EBP
ECEL1
ECM1
EDA
EDAR
EDARADD
EDN3
EDNRB
EFEMP2
EFNB1
EGR2
EIF2AK3
EIF2B1
EIF2B2
EIF2B3
EIF2B4
EIF2B5
EIF4A3
ELAC2
EMD
EMG1
ENPP1
EOGT
EPB42
EPCAM
EPG5
EPM2A
ERBB3
ERCC1
ERCC2
ERCC3
ERCC4
ERCC5
ERCC6
ERCC8
ERLIN2
ESCO2
ESRRB
ETFA
ETFB
ETFDH
ETHE1
EVC
EVC2
EXOSC3
EYS
F11
F13A1
F2
F5
F7
F8
F9
FA2H
FAH
FAM126A
FAM161A
FAM20C
FANCA
FANCB
FANCC
FANCD2
FANCE
FANCF
FANCG
FANCI
FANCL
FARS2
FAS
FASTKD2
FAT4
FBLN5
FBXL4
FECH
FERMT3
FGA
FGB
FGD1
FGD4
FGF3
FGFR2
FGFR3
FGG
FH
FHL1
FIG4
FKBP14
FKRP
FKTN
FLNA
FLNB
FLVCR2
FMO3
FMR1
FOLR1
FOXE1
FOXN1
FOXP3
FOXRED1
FRAS1
FREM1
FREM2
FRMPD4
FSHR
FTCD
FTO
FUCA1
G6PC
G6PC3
G6PD
GAA
GALC
GALE
GALK1
GALNS
GALNT3
GALT
GAMT
GAN
GATA1
GATM
GBA
GBA2
GBE1
GCDH
GCH1
GCSH
GDAP1
GDF1
GDF5
GDF6
GFM1
GH1
GHR
GIPC3
GJA1
GJB1
GJB2
GJB6
GJC2
GK
GLA
GLB1
GLDC
GLE1
GLIS3
GLRA1
GLUL
GMPPB
GNAT2

GNE
GNMT
GNPAT
GNPTAB
GNPTG
GNRHR
GNS
GP1BA
GP1BB
GP9
GPC3
GPC6
GPI
GPIHBP1
GPSM2
GRHPR
GRIA3
GRIP1
GRM1
GRN
GSS
GTDC2
GTF2H5
GUCY2D
GUSB
GYG1
GYS2
H6PD
HADH
HADHA
HADHB
HAL
HAMP
HAX1
HBB
HCCS
HCFC1
HDAC8
HEPACAM
HES7
HESX1
HEXA
HEXB
HFE
HFE2
HGD
HGSNAT
HIBCH
HLCS
HMGCL
HMGCS2
HOGA1
HOXA2
HPD
HPGD
HPRT1
HPS1
HPS3
HPS4
HPS6
HSD11B2
HSD17B10
HSD17B3
HSD17B4
HSD3B2
HSD3B7
HSPG2
HTRA1
HYAL1
HYLS1
IBA57
ICK
IDS
IDUA
IER3IP1
IFNGR1
IFNGR2
IFT122
IFT140
IFT172
IFT27
IFT80
IGBP1
IGF1
IGHMBP2
IHH
IKBKAP
IKBKG
IL12B
IL12RB1
IL1RN
IL2RG
IL36RN
IL7R
IMPG2
INPP5E
INSR
INVS
IQCB1
IQSEC2
ISPD
ITGA2B
ITGA6
ITGA8
ITGB2
ITGB3
ITGB4
IVD
IYD
JAK3
JAM3
JUP
KARS
KCNJ1
KCNJ11
KCNJ13
KCNQ1
KCNV2
KCTD7
KDM5C
KHDC3L
KIAA0196
KIAA1279
KIAA2022
KIF14
KIF1A
KIF7
KISS1R
KRT14
KRT18
KRT5
KRT8
L1CAM
L2HGDH
LAMA1
LAMA2
LAMA3
LAMB1
LAMB2
LAMB3
LAMC2
LAMC3
LAMP2
LARGE
LARS2
LBR
LCA5
LCAT
LDLR
LEPRE1
LHB
LHCGR
LHX3
LIFR
LIG4
LIPA
LMBR1
LMNA
LOXHD1
LPIN2
LPL
LRAT
LRP2
LRP4
LRP5
LRPPRC
LRRC6
LRTOMT
LTBP2
LTBP4
LYST

LZTFL1
MAK
MAN1B1
MAN2B1
MASP1
MAT1A
MBTPS2
MC2R
MCCC1
MCCC2
MCEE
MCOLN1
MCPH1
MED12
MED17
MEFV
MEGF10
MEOX1
MERTK
MESP2
MFN2
MFSD8
MGAT2
MGP
MID1
MKKS
MKS1
MLC1
MLH1
MMAA
MMAB
MMACHC
MMADHC
MMP2
MOCS1
MOCS2
MOGS
MPDU1
MPI
MPL
MPV17
MPZ
MRE11A
MRPS16
MRPS22
MSH2
MSH6
MTFMT
MTHFR
MTM1
MTR
MTRR
MTTP
MUSK
MUT
MUTYH
MVK
MYD88
MYH2
MYH7
MYO15A
MYO5A
MYO5B
MYO6
MYO7A
NAA10
NAGA
NAGLU
NAGS
NBAS
NBEAL2
NBN
NCF2
NDE1
NDP
NDRG1
NDUFAF2
NDUFAF4
NDUFAF5
NDUFS1
NDUFS2
NDUFS3
NDUFS4
NDUFS6
NDUFS7
NDUFS8
NDUFV1
NEB
NEFL
NEK1
NEU1
NEUROG3
NHEJ1
NHLRC1
NHS
NIN
NKX2-5
NLRP7
NMNAT1
NPC1
NPC2
NPHP1
NPHP3
NPHP4
NPHS1
NPHS2
NPR2
NR0B1
NR2E3
NSDHL
NSUN2
NT5C2
NT5C3
NTHL1
NTRK1
NUBPL
NUP62
OAT
OCA2
OCLN
OCRL
OFD1
OPA3
OPHN1
OPTN
ORAI1
ORC1
ORC4
ORC6
OSTM1
OTC
OTOA
OTOF
OXCT1
PAH
PAK3
PANK2
PAPSS2
PARK2
PAX3
PC
PCBD1
PCCA
PCCB
PCDH15
PCDH19
PCNT
PDE6A
PDE6B
PDE6C
PDE6D
PDE6H
PDHA1
PDHB
PDHX
PDP1
PDSS1
PDSS2
PDX1
PEPD
PEX1
PEX10
PEX11B
PEX12
PEX13
PEX14
PEX16
PEX19
PEX2
PEX26
PEX3

PEX5
PEX6
PEX7
PFKM
PGK1
PGM1
PHF6
PHF8
PHGDH
PHKB
PHYH
PIEZO2
PIGA
PIGL
PIGV
PINK1
PIP5K1C
PKHD1
PKLR
PLA2G6
PLCB4
PLCE1
PLEC
PLEKHG5
PLG
PLK4
PLOD1
PLOD3
PLP1
PMM2
PMP22
PMS2
PNKP
PNP
PNPLA2
PNPLA6
PNPO
POLG
POLH
POLR1C
POLR3A
POLR3B
POMC
POMGNT1
POMK
POMT1
POMT2
POR
PORCN
POU1F1
POU3F4
PPIB
PPT1
PQBP1
PRDM5
PREPL
PRF1
PRG4
PRKN
PROC
PRODH
PROM1
PROP1
PROS1
PRPH2
PRPS1
PRRX1
PRSS56
PRX
PSAP
PSAT1
PTH1R
PTS
PUS1
PVRL1
PYCR1
PYGL
PYGM
RAB18
RAB23
RAB27A
RAB3GAP1
RAB3GAP2
RAD51C
RAG1
RAG2
RAPSN
RARS2
RAX
RBM10
RBM8A
RD3
RDH12
RECQL4
RELN
REN
RFT1
RFX6
RHO
RIPK4
RLBP1
RMND1
RMRP
RNASEH2A
RNASEH2B
RNASEH2C
RNU4ATAC
ROGDI
ROR2
RP1
RP2
RPE65
RPGR
RPGRIP1
RPGRIP1L
RPS6KA3
RRM2B
RS1
RSPH4A
RTEL1
RTTN
RYR1
SACS
SAMHD1
SBDS
SC5DL
SCARB2
SCARF2
SCN4A
SCN5A
SCN9A
SCNN1A
SCNN1B
SCNN1G
SCO1
SCO2
SDCCAG8
SDHA
SDHD
SEC23A
SEC23B
SEPN1
SEPSECS
SERPINA1
SERPINF1
SETX
SFTPB
SGCA
SGCB
SGCD
SGCG
SH2D1A
SH3PXD2B
SH3TC2
SHROOM4
SI
SIL1
SIX6
SLC12A1
SLC12A3
SLC12A6
SLC16A1
SLC16A2
SLC17A5
SLC19A3
SLC22A12
SLC22A5
SLC25A13
SLC25A15
SLC25A19
SLC25A20

SLC25A22
SLC25A4
SLC26A2
SLC26A3
SLC26A4
SLC27A4
SLC2A1
SLC2A10
SLC2A2
SLC2A9
SLC30A10
SLC34A2
SLC35A1
SLC35A2
SLC35A3
SLC35C1
SLC35D1
SLC37A4
SLC39A4
SLC3A1
SLC45A2
SLC46A1
SLC4A1
SLC4A11
SLC52A3
SLC5A5
SLC6A3
SLC6A5
SLC6A8
SLC7A7
SLC7A9
SLC9A6
SLX4
SMARCAL1
SMC1A
SMN1
SMN2
SMOC1
SMPD1
SMS
SNAP29
SNIP1
SOD1
SOX3
SP110
SPATA7
SPG11
SPG7
SPINT2
SPR
SPTBN2
SRD5A2
SRD5A3
ST3GAL3
ST3GAL5
STAC3
STAMBP
STAR
STAT1
STIL
STIM1
STRA6
STS
STX11
STXBP2
SUCLA2
SUCLG1
SUMF1
SUOX
SURF1
SYN1
SYNE1
SYP
TACR3
TACSTD2
TAF2
TAT
TAZ
TBC1D20
TBC1D24
TBCE
TBX15
TBX22
TBX6
TCAP
TCIRG1
TCTN1
TCTN2
TCTN3
TECPR2
TECTA
TERT
TFR2
TG
TGM1
TH
TIMM8A
TJP2
TK2
TMC1
TMCO1
TMEM138
TMEM216
TMEM231
TMEM237
TMEM5
TMEM67
TMEM70
TMIE
TMPRSS3
TNFRSF11A
TNFRSF11B
TNFRSF13B
TNNT1
TNXB
TPI1
TPK1
TPM3
TPO
TPP1
TRAPPC9
TREM2
TREX1
TRIM32
TRIM37
TRIOBP
TRIP11
TRMU
TRPM6
TSEN2
TSEN34
TSEN54
TSFM
TSHB
TSHR
TSPAN7
TSPYL1
TTC19
TTC21B
TTC8
TTN
TTPA
TUBA8
TUBGCP6
TUFM
TULP1
TUSC3
TYK2
TYMP
TYR
TYROBP
UBA1
UBE3B
UBR1
UGT1A1
UNC13D
UPF3B
UQCRB
UQCRQ
UROS
USH1C
USH1G
USH2A
USP9X
VAX1
VDR
VIPAS39
VLDLR
VPS13A
VPS13B
VPS33B

VPS45
VRK1
VSX2
VWF
WAS
WDPCP
WDR19
WDR34
WDR35
WDR60
WDR62
WDR81
WFS1
WISP3
WNK1
WNT10A
WNT10B
WNT3
WNT4
WNT7A
WRN
WWOX
XPA
XPC
XRCC4
XYLT1
YARS2
ZAP70
ZDHHC9
ZFYVE26
ZIC3
ZMPSTE24
ZNF423
ZNF469

Table 5: Sociodemographic Characteristics of participants	
	N (%)
Age (n=80)	
Mean (SD)	30 (5)
IQR	27-33
Range	19-51
Gender (n=82)	
Female	41 (50)
Male	41 (50)
Highest level of completed education (n=81)	
Primary Education	1 (1.2)
Secondary Education	21 (25.9)
Non-university higher education	23 (28.4)
University higher education	32 (39.5)
PhD	4 (4.9)
Religiosity (n=82)	
Yes	26 (31.7)
No	56 (68.3)
Extent of religious involvement (n=26)	
Not active	17 (65.4)
Somewhat	9 (34.6)
Active	0 (0)
Children (n=82)	
Yes	14 (17.1)
No	68 (82.9)
(Future) Child wish (n=82)	
Yes	64 (78)
No	7 (8.5)
I don’t know	11 (13.4)
(Future) Child wish – Timing (n=64)	
< 1 year	25 (39.1)
1 – 2 years	23 (35.9)
> 2 years	16 (25)
Consanguinity (n=82)	
Yes	1 (1.2)
No	79 (96.3)
I’m not sure	2 (2.4)
Pregnancy (n=82)	
Yes	0 (0)
No	79 (96.3)
I’m not sure	3 (3.7)
Consultation at Centre for Human Genetics (CME) (n=81)	
Yes	10 (12.3)
No	71 (87.7)

Table 6: Internal Reliability Analyses of Knowledge and Attitude scale							
Measure	Description	Items	Reliability	Range	Cutoff	Mean (SD)	Outcome
Knowledge scale	Knowledge of ECS	14 questions (True/False/I don't know)	0.545	0-14	0-4 = Low knowledge; 5-9 = Moderate knowledge; 10-14 = High knowledge	10.4 (1.8)	Low knowledge = 0%; Moderate knowledge = 18.3%; High knowledge = 81.7%
Attitude scale	Attitudes towards having ECS	Five bipolar words pairs (5-point Likert scale)	0.873	5-25	5-11= Negative attitude; 12-18= Neutral attitude; 19-25= Positive attitude	22.4 (2.9)	Negative attitude = 1.2%; Neutral attitude = 6.1%; Positive attitude = 92.7%
Anxiety scale (STAI-6)	Anxiety	6 items (4-point Likert scale). Reverse coding of items 1, 4 and 5.	0.825	20-80	Score >40 is considered to be clinically relevant	26.1 (7.9)	3.7% of participants had an elevated level of anxiety that was considered to be clinically relevant
Decisional conflict scale – Low Literacy	State of uncertainty about a course of action	10 items (3 response categories questions)	0.921	0-100	Score ≥37.5 is categorized as a decisional conflict	3.4 (11.8)	2.5% of participants felt uncertain about their decision

Table 7: Knowledge about RGCS related concepts (n=82) (Correct answers)				
Knowledge Score				
	Mean (SD)	10.4 (1.76)		
	IQR	10-12		
	Range	5-12		
Level of genetic knowledge		N (%)		
n=82	Low	0 (0)		
	Moderate	15 (18.3)		
	High	67 (81.7)		
n=77	Good	66 (85.7)		
	Poor	11 (14.3)		
Knowledge scale				
		True N (%)	False N (%)	I don't know N (%)
1	A carrier of an hereditary condition carries a mutation for that condition but does not have the condition himself/herself.	70 (86.4)	5 (6.2)	6 (7.4)
2	All serious conditions are determined by a genetic predisposition.	8 (9.8)	71 (86.6)	3 (3.7)
3	All hereditary conditions are expressed during childhood (<18 years).	6 (7.3)	69 (84.1)	7 (8.5)
4	A carrier screening test examines if you are at risk for developing one or more hereditary conditions.	14 (17.1)	68 (82.9)	0 (0)
5	Genetic carrier screening is only intended for individuals with an increased family risk (families where genetic conditions have already occured).	2 (2.4)	79 (96.3)	1 (1.2)
6	You can be a carrier of a hereditary condition without this condition occuring in your own family	74 (90.2)	5 (6.1)	3 (3.7)
7	A carrier of a hereditary condition will always develop that specific condition and get related health problems.	0 (0)	81 (98.8)	1 (1.2)
8	If you are a carrier of a hereditary condition, all your offspring will also be a carrier of that specific hereditary condition.	6 (7.3)	76 (92.7)	0 (0)
9	If the (future) mother is a carrier of a recessive hereditary condition, all her children will develop this condition.	1 (1.2)	81 (98.8)	0 (0)
10	If both partners are carriers of a mutation for the same recessive hereditary condition, they a 50% chance each pregnancy to conceive a child with the condition for which they are carriers	26 (31.7)	56 (68.3)	0 (0)
11	If both partners are carriers of a mutation for a different recessive hereditary condition, they have a 25% chance each pregnancy to conceive a child with one of both condition.	32 (39)	45 (54.9)	5 (6.1)
12	Two healthy individuals without health problems can have a child with an inherited condition.	75 (92.6)	3 (3.7)	3 (3.7)
13	When a preconceptional genetic carrier screening test does not identify an increased risk, this means with certainty that this couple will have a healthy child.	3 (3.7)	78 (95.1)	1 (1.2)
14	If both partners are carriers of the same genetic condition, they cannot conceive children naturally without this specific genetic condition.	6 (7.3)	76 (92.7)	0 (0)

Table 8: Attitudes towards ECS (n=82)						
Attitude Score						
Mean (SD)			22.4 (2.9)			
IQR			21-25			
Range			7-25			
Attitude groups			N (%)			
Negative attitude			1 (1.2)			
Neutral attitude			5 (6.1)			
Positive attitude			76 (92.7)			
Attitude scale						
	N (%)					
Harmful	1 (1.2)	0 (0)	2 (2.4)	17 (20.7)	62 (75.6)	Beneficial
Unimportant	1 (1.2)	1 (1.2)	8 (9.8)	21 (25.6)	51 (62.2)	Important
Bad thing	1 (1.2)	0 (0)	3 (3.7)	20 (24.4)	58 (70.7)	Good thing
Not reassuring	0 (0)	1 (1.2)	20 (24.4)	31 (37.8)	30 (36.6)	Reassuring
Undesirable	1 (1.2)	0 (0)	4 (4.9)	25 (30.5)	52 (63.4)	Desirable
Attitude statements						
N (%)						
I would feel less healthy if I were told I was a carrier of a hereditary condition.						
Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree		
32 (39)	20 (24.4)	20 (24.4)	9 (11)	1 (1.2)		
I think people would treat me differently if they knew I'm a carrier of a hereditary condition.						
Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree		
45 (54.9)	20 (24.4)	13 (15.9)	3 (3.7)	1 (1.2)		
I would find it difficult to accept that I am a carrier of a hereditary condition when my partner is not.						
Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree		
34 (42)	20 (24.7)	17 (21)	7 (8.6)	3 (3.7)		
I would find it difficult to accept that my partner is a carrier of a hereditary condition when I am not.						
Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree		
46 (56.1)	18 (22)	12 (14.6)	5 (6.1)	1 (1.2)		
I would find it difficult to inform my family members of their increased risk of being a carrier of a hereditary condition.						
Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree		
30 (36.6)	21 (25.6)	14 (17.1)	12 (14.6)	5 (6.1)		
I find it difficult to think about RGCS before I (or my partner) become(s) pregnant.						
Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree		
65 (79.3)	10 (12.2)	4 (4.9)	2 (2.4)	1 (1.2)		
The pressure on future parents to have preconception RGCS will become great.						
Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree		
22 (26.8)	18 (22)	30 (36.6)	8 (9.8)	4 (4.9)		
RGCS will lead to greater anxiety among couples who want to become pregnant.						
Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree		
30 (37)	26 (32.1)	14 (17.3)	9 (11.1)	2 (2.5)		
RGCS will make the lives of people living with these condition seem inferior.						
Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree		
49 (59.8)	25 (30.5)	6 (7.3)	2 (2.4)	0 (0)		
I am concerned that RGCS will lead to a society in which people with certain hereditary disorders have no place.						
Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree		
49 (59.8)	23 (28)	5 (6.1)	4 (4.9)	1 (1.2)		
RGCS will give future parents unrealistic expectations of having a 'healthy child'.						
Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree		
30 (36.6)	25 (30.5)	22 (26.8)	5 (6.1)	0 (0)		

Table 9 : STAI			
N (%)			
I feel calm (n=82)			
Not at all	Somewhat	Moderately	Very much
0 (0)	4 (4.9)	23 (28)	55 (67.1)
I am tense (n=81)			
Not at all	Somewhat	Moderately	Very much
65 (80.2)	15 (18.5)	1 (1.2)	0 (0)
I feel upset (n=81)			
Not at all	Somewhat	Moderately	Very much
79 (97.5)	1 (1.2)	0 (0)	1 (1.2)
I am relaxed (n=81)			
Not at all	Somewhat	Moderately	Very much
0 (0)	9 (11.1)	25 (30.9)	47 (58)
I feel content (n=80)			
Not at all	Somewhat	Moderately	Very much
0 (0)	5 (6.3)	18 (22.5)	57 (71.3)
I am worried (n=80)			
Not at all	Somewhat	Moderately	Very much
58 (72.5)	20 (25)	2 (2.5)	0 (0)

Table 10: Decisional Conflict Scale		
N (%)		
1. Do you know which options are available to you? (n=82)		
Yes	Unsure	No
79 (96.3)	1 (1.2)	2 (2.4)
2. Do you know the benefits of each option? (n=82)		
Yes	Unsure	No
77 (93.9)	4 (4.9)	1 (1.2)
3. Do you know the risks and side effects of each option? (n=82)		
Yes	Unsure	No
76 (92.7)	5 (6.1)	1 (1.2)
4. Are you clear about which benefits matter most to you? (n=82)		
Yes	Unsure	No
78 (95.1)	4 (4.9)	0 (0)
5. Are you clear about which risks and side effects matter most to you? (n=82)		
Yes	Unsure	No
73 (89)	7 (8.5)	2 (2.4)
6. Do you have enough support from others to make a choice? (n=81)		
Yes	Unsure	No
77 (95.1)	3 (3.7)	1 (1.2)
7. Are you choosing without pressure from others? (n=81)		
Yes	Unsure	No
78 (96.3)	1 (1.2)	2 (2.5)
8. Do you have enough advice to make a choice? (n=81)		
Yes	Unsure	No
79 (97.5)	1 (1.2)	1 (1.2)
9. Are you clear about the best choice for you? (n=81)		
Yes	Unsure	No
78 (96.3)	1 (1.2)	2 (2.5)
10. Do you feel sure about what to choose? (n=81)		
Yes	Unsure	No
78 (96.3)	2 (2.5)	1 (1.2)

A. CHAPTER 8

Supplementary Materials

Satisfaction & Counseling related aspects			
		N (%)	
If you had to decide again, would you make the same choice to have RGCS?			
	Yes	62 (92.5)	
	No	0 (0)	
	I'm not sure	5 (7.5)	
Would you recommend RGCS to couples with a desire to have children?			
	Yes	63 (94)	
	No	0 (0)	
	I'm not sure	4 (6)	
Did you share the test results with others?			
	Yes	51 (76.1)	
	Multiple options possible	- Parents	41 (61.2)
		- Siblings	25 (37.3)
		- Friends	20 (29.8)
		- Other family members	6 (8.9)
		- Gynaecologist	11 (16.4)
		- General Practitioner	4 (6)
		- Colleagues	3 (4.5)
	No	16 (23.9)	
Did the decision to have RGCS impact your relationship with your partner?			
	No	67 (100)	
Did the decision to have RGCS impact the (possible) desire to have children with your current partner?			
	Yes	4 (6)	
	No	63 (94)	
Did the test results have an impact on the (possible) desire to have children with your current partner?			
	Yes	6 (9)	
	No	61 (91)	

I felt worried while waiting for the test results.				
Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly agree
37 (55.2)	10 (14.9)	9 (13.4)	10 (14.9)	1 (1.5)
I feel worried about the screenings results I received.				
Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly agree
57 (85)	5 (7.5)	3 (4.5)	2 (3)	0 (0)
I feel less healthy after receiving my screening results.				
Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly agree
66 (98.5)	1 (1.5)	0 (0)	0 (0)	0 (0)
I am confident that the screening results that I got are correct.				
Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly agree
0 (0)	0 (0)	0 (0)	13 (19.4)	54 (80.6)
I regret my choice to have RGCS.				
Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly agree
66 (98.5)	1 (1.5)	0 (0)	0 (0)	0 (0)
I am concerned about the possibility that my family members are carriers of the conditions that are included in the test.				
Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly agree
51 (76.1)	5 (7.5)	6 (9)	2 (3)	3 (4.5)

Did you read the information brochure before coming to the pre-test counseling session?		
	Yes, completely	44 (65.7)
	Yes, partly	21 (31.3)
	No	2 (3)
Did you feel you had enough information to make an informed choice?		
	Yes	67 (100)
Did you look up additional information before coming to the pre-test counseling session?		
	Yes	3 (4.5)
	No	64 (95.5)
How satisfied were you with the way the screening results were communicated?		
	Neither satisfied or dissatisfied	6 (9)
	Somewhat satisfied	25 (37.3)
	Completely satisfied	36 (53.7)
Based on the information you obtained, was it sufficiently clear to you what your own individual result entailed?		
	Yes	64 (95.5)
	No	3 (4.5)
Based on the information you obtained, was it sufficiently clear to you what your couple result entailed?		
	Yes	66 (98.5)
	No	1 (1.5)
Did you look up additional information after receiving the screeningresults?		
	Yes	14 (20.9)
	No	53 (79.1)
How would you evaluate the waiting period to receive the screening results?		
	Neutral	28 (41.8)
	Too long	29 (43.3)
	Way too long	10 (14.9)

ACKNOWLEDGEMENTS

De afgelopen vier jaren waren intens en leerrijk. Gevuld met groeimogelijkheden, inspirerende ontmoetingen en een occasioneel piekermomentje. Zoveel nieuwe zaken geleerd door te lezen, door te luisteren en door te doen. Een terugblik naar Mei 2018, het moment waarop Professor dr. Pascal Borry en Professor dr. Hilde Peeters een eerste keer mijn pad kruisten tijdens mijn sollicitatiegesprek enkele dagen na mijn terugkeer uit Niger. Ik was na twee jaar te wonen en werken in het buitenland nog volop aan het acclimatiseren en heel erg zoekende naar wat de juiste volgende stap zou zijn in mijn professionele loopbaan. Ik voelde meteen een klik tijdens dat sollicitatiegesprek, alsof alle puzzelstukjes in elkaar vielen. Wat ben ik hen ongelooflijk dankbaar voor het potentieel dat ze toen in me zagen en de kans die ze mij gaven om dit project te realiseren. Elk met hun eigen stijl hielpen ze me de afgelopen jaren op weg en stonden ze klaar met raad en daad.

Beste Pascal, dankjewel voor de begeleiding en het vertrouwen van de afgelopen jaren. Van bij de start was je mijn grootste supporter wat me steeds heeft gestimuleerd in het bolwerken van dit project. Je gaf me de vrijheid voor het uitstippelen van mijn eigen weg maar stond ook steeds klaar met advies en een kritisch blik wanneer nodig.
Beste Hilde, dankjewel om me vanaf het begin van dit verhaal mee op sleeptouw te nemen naar Hasselt om voeling te krijgen met de praktijk. Bedankt voor de zeer warme contacten en leerrijke gedachten uitwisselingen wanneer we elkaar zagen. Ondanks je drukke agenda was er op die momenten naar mijn gevoel altijd een overvloed aan tijd beschikbaar.
Beste Karen, onze wegen kruisten net iets later. Dankjewel voor je betrokkenheid in dit verhaal. Ik zal jouw persoonlijk telefoontje en peptalk de dag na een presentatie die iets minder goed liep nooit vergeten. Ik wist toen nog maar net zelf dat ik zwanger was en de coronacrisis lag toen al op de loer. Nog maar eens een bevestiging dat kleine dingen soms een groot verschil kunnen maken.
Beste Gert, mijn niet-officiële maar daarom niet minder waardevolle co-promotor, dankjewel voor al je hulp achter de schermen bij het realiseren van dit project en voor de constructieve commentaren bij het schrijven van de verschillende hoofdstukken.

Dank aan mijn interne juryleden Prof. Hiele en Prof. Witters voor hun engagement en hun kritische blik doorheen de jaren. And also a special thanks to my external jury members Prof. dr. Lidewij Henneman, dr. Celine Lewis and Prof. dr. Heidi Mertes. Your work has inspired me a lot over the years and I'm truly grateful you've accepted to serve as a member of my examining committee.

Bedankt aan alle personen die de tijd namen om deel te nemen aan één van deze studies en aan mijn coauteurs Davit Chokoshvili, Jeffrey Cannon, Silke Van Epperzeel, Inne Geysen, Heleen Devolder, Jasper Verguts en Hilde Vandecruys voor hun hulp bij het tot stand brengen van dit werk.

Dear past and present colleagues of the Centre of Biomedical Ethics and Law, many thanks to each and every one of you for all the nice chats in between, for sharing your experiences and for your encouragement. Dear Alice, you have been the most wonderful office mate. I'm so grateful that you crossed my path. We are so different yet so much the same. Thank you for your (sometimes brutal) honesty and constructive comments, for always making the time to listen and for your endless support. Lieve Myriam, wat ben ik ontzettend blij dat ik jou heb leren kennen. Je stond op eender welk moment klaar en dit zowel op professioneel als persoonlijk vlak. Ik ben je ontzettend dankbaar voor alles wat je deed, altijd recht uit het hart. Jij bent goud waard!

Lieve vriendinnen en familie, dankjewel om mijn avonturen altijd met zoveel enthousiasme te volgen. We zien elkaar lang niet meer zoveel als vroeger maar wat is het fijn om steeds weer mijn verhaal te mogen doen. Dankzij de gezellige etentjes, wandelingetjes, etc. kon ik altijd weer even helemaal ontspannen en opladen om er vervolgens weer volop tegen aan te gaan.

Lieve Mama en Papa, jullie hadden ongetwijfeld niet gedacht dat dit moment ooit zou komen. Dank jullie wel voor alle kansen die jullie me hebben gegeven en om me te steunen in het verwezenlijken van mijn dromen.

Aan mijn allerliefste en uiterst getalenteerde zus Ellen, wat ben ik je dankbaar voor alles wat je doet en bent. Zonder jou ben ik veel minder mij. Je kent me als geen ander en voelt hoe het met me gaat. Vele telefoontjes, een paar schetsen en schema's hier en daar, een prachtige cover voor dit werk – niets wat teveel gevraagd. Dankjewel om er zo voor mij te zijn, tijdens de felste regenbuien en in de mooiste zonneschijn. Nakupenda!

Lieve Ilou, jij gaf me twee jaar geleden de mooiste titel van allemaal! Wat ben ik trots om jouw Mama te mogen zijn. Je bent zo mooi met de allerliefste en guitigste lach. Jouw deugniet snoetje doet me elke dag weer beseffen wat echt belangrijk is. Wat kijk ik uit naar alles wat nog komen zal! Blijf altijd dromen zonder grenzen. Ik hou van jou tot aan de maan en terug!

Mon chèr mari Bacho, notre histoire n'est pas exactement ce que nous pensions qu'elle serait. Aller à contre-courant pour arriver là où nous voulions être. Nous avons tellement grandi individuellement et en couple au cours des dernières années. Merci d'avoir cru en moi, de m'avoir soutenu dans l'atteinte de mes objectifs et d'avoir partagé cette aventure avec moi. Tu es aimé si profondément!