TITLE: Taking the risk. A systematic review of ethical reasons and moral arguments in the clinical use of Polygenic Risk Scores

ABSTRACT

Debates about the prospective clinical use of polygenic risk scores (PRS) have grown considerably in the last years. The potential benefits of PRS to improve patient care at individual and population levels have been extensively underlined. Nonetheless, the use of PRS in clinical contexts presents a number of unresolved ethical challenges and consequent normative gaps that hinder their optimal implementation. Here, we conducted a systematic review of reasons of the normative literature discussing ethical issues and moral arguments related to the use of PRS for the prevention and treatment of common complex diseases. In total, we have included and analyzed 34 records, spanning from 2013 to 2023. The findings have been organized in 3 major themes: in the first theme, we consider the potential harms of PRS to individuals and their kin. In the theme 'Threats to health equity', we consider ethical concerns of social relevance, with a focus on justice issues. Finally, the theme 'Towards best practices' collects a series of research priorities and provisional recommendations to be considered for an optimal clinical translation of PRS. We conclude that the use of PRS in clinical care reinvigorates old debates in matters of health justice; however, open questions regarding best practices in clinical counseling, suggest that the ethical considerations applicable in monogenic settings will not be sufficient to face PRS emerging challenges.

Keywords: polygenic risk scores; PRS; ethics; ELSI; clinical genetics

Authors and affiliations:

Lara Andreoli [1]
Hilde Peeters [2]
Kristel Van Steen [2]
Kris Dierickx [1]

[1] Department of Public Health and Primary care, Centre for Biomedical ethics and law, KU Leuven, Belgium
[2] Department of Human Genetics, KU Leuven, Belgium

Author Contributions: Lara Andreoli: Conceptualization, methodology, data analysis, data curation, writing – original draft, review and editing. Hilde Peeters: conceptualization, data analysis, writing - review and editing. Kristel Van Steen: conceptualization, data analysis, writing - review and editing. Kris Dierickx: conceptualization, data analysis, writing - review and editing.

Corresponding author: Correspondence to Lara Andreoli (lara.andreoli@kuleuven.be)

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request

Conflict of interest: The authors have no conflict of interest to declare

Funding: This work has received funding from the European Union Horizon 2020 research and innovation program: "Precision Medicine at the interface of Translational Research and Systems Medicine (TranSYS)" - H2020-MSCA-ITN-2019

Acknowledgments: KVS would like to thank also the CAN.HEAL consortium (EU4H-2021-PJ2) for the insightful discussions, which inspired the development of the present work.

ORCID:

Lara Andreoli: https://orcid.org/0009-0008-9790-7122
Hilde Peeters: http://orcid.org/0000-0002-7295-3375
Kristel Van Steen: http://orcid.org/0000-0001-9868-5033
Kris Dierickx: http://orcid.org/0000-0002-1016-1145

INTRODUCTION

Complex diseases such as Cardiovascular Diseases (CD), Type 2 Diabetes (T2D) and Breast Cancer (BC) affect a considerable part of the general population and represent a conspicuous amount of the public health expenditure (1–3). The etiology of such conditions is typically determined by a multiplicity of factors, including genetics, lifestyle and the environment. In some cases, a monogenic cause can be identified: it is the case of Maturity-onset diabetes of the young (MODY), long-QT syndrome and BRCA-related breast cancer. Single-gene mutations, however, are rare in a population, and thus explain only part of the heritability of a complex condition (4).

Understanding and estimating the contribution of genetic factors to complex diseases can be key to the implementation of early prevention strategies and more personalized approaches to disease risk management (5). Therefore, great efforts have been made in the last decades of human genetics research to unlock the genetic basis of diseases. After the completion of the Human Genome Project (HGP), Genome Wide Association Studies (GWAS) have cast light on the polygenic architecture of many common conditions, allowing for the calculation of Polygenic Risk Scores (PRS) (6). As statistical protocols that capture the cumulative effect of hundreds or thousands of genetic variants to a specific phenotype, PRS can estimate an individual DNA based disease susceptibility (5). So far, PRS have been routinely used in biomedical research (7). Proposals to implement them in clinical contexts are more recent and motivated by the prospective benefits that PRS would bring both at individual and population level. In individual care, PRS could serve to refine risk prediction, improve counselling and shorten diagnostic pathways; at a population level, on the other hand, proponents highlight their role in risk stratification and their use as means of primary and secondary prevention (8). Despite the enthusiasm surrounding PRS applications, it is widely acknowledged that the clinical translation of PRS is still bound to the solution of a number of scientific limitations as well as ethical questions (9) regarding expected harms to individuals, the fair distribution of the technology's benefits and the existence of a set of guidelines defining best practices.

As pointed in recent reviews (10,11), currently there is no unequivocable proof of PRS clinical utility to improve patients' outcomes compared to the current standard of care. However, studies have shown that the clinical validity of some PRS is robust, and the demonstration of their clinical utility is expected to follow in the upcoming years via randomized clinical trials (11) potential implications for patient care, a thorough examination of the ethical landscape surrounding the clinical use of PRS seems timely and essential. With this systematic review of reasons, therefore, we aim to investigate the moral arguments and ethical issues raised in the existing peer-reviewed literature about the prospective clinical use of PRS in the prevention and treatment of common complex diseases. To our knowledge, no systematic review on the topic has been published yet. Besides filling the gap, with this paper we aim to provide evidence to inform policymaking, future guidelines and clinical decision-making.

METHODOLOGY

Search strategy and outcomes

We conducted a systematic review of the normative literature according to the method outlined by Sofaer and Stretch (12,13). The reporting protocol is based on the PRISMA checklist for systematic reviews (14). A systematic search of PubMed, Scopus and Web of Science electronic databases was first conducted on 14th March 2023. The search strings consisted of a combination of two categories of words, corresponding to the core concepts of polygenic risk and ethics (available in supplementary material). The concept-associated terms are part of databases specific controlled vocabulary, such as PubMed MeSH terms and Emtree terms. Other non-controlled terms were added based on keywords found in relevant papers. In total, 2903 articles were found in the different databases. Results were merged and duplicates (n=694) were deleted via the software Rayyan (15) before conducting title, abstract and full-text screening. The snowball method was also used to identify additional relevant publications. Updates for new potential publications continued from the databases until 25th May 2023. A PRISMA flow diagram for the publication screening and selection process is provided in Figure 1.

Eligibility criteria

Articles were selected and included in the review if and only if they met the predefined inclusion/exclusion criteria (Table 1).

178 **Table 1: Inclusion and Exclusion criteria**[1]

179

INCLUDED	EXCLUDED	
Publications that mention relevant ethical issues and/or moral arguments in the clinical use of PRS	(R1) Publications that do not discuss normative issues (R2) Empirical studies	Type of publication
Ethical issues are clearly presented and cover a substantial part of the text	(R3) Ethical issues are not sufficiently developed or are just briefly mentioned throughout the text	
The publications are peer-reviewed and published in an academic journal, book or Ph.D. Thesis	(R4) Grey literature	
Publications that address ethical issues in the clinical use of PRS for prediction and prevention of common multifactorial diseases	(R5) Publications that only consider ethical issues in research and development of PRS (R6) Publications that focus only on general ethical issues in genomics and precision medicine or pharmacogenomics (R7) Publications that only address ethical issues in the use of PRS for embryo screening in in vitro fertilization (IVF) and pre-implantation genetic testing (PGT)	Topic
English publications	(R8) Non-English publications	Language

180

181

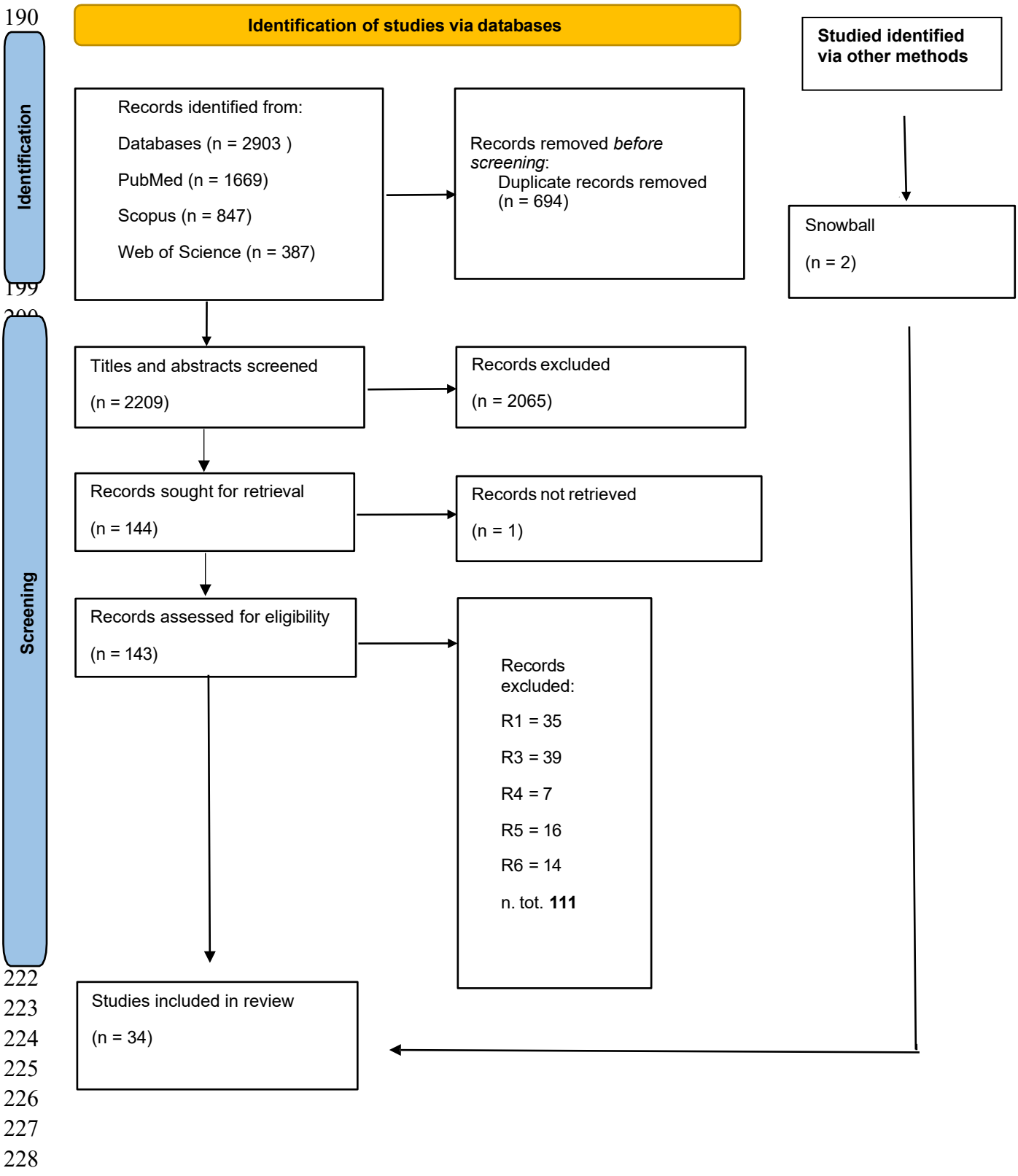
182

183

[1] Legend: R = reason for exclusion

Figure 1: PRISMA Flow Chart

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



Data collection and extraction process

Each publication was read multiple times to identify reason mentions (RMs), namely parts of the text that express ethical issues or ethical arguments concerning the clinical use of PRSs. All RMs, regardless of their length or content, were first highlighted and then extracted. RMs give an idea of the recurrence of certain concerns and arguments across the literature. However, the frequency of a RM is not to be intended as an immediate indicator of its moral significance (13). Following Braun and Clarke (2006), an inductive thematic analysis of the extracted data was conducted. Each RM was first assigned a code, or a brief descriptor which summarizes the RM. Similar codes were then categorized inductively into progressive levels of abstraction. The themes represent the most general level into which the RMs can fit, while the topics represent specific sub-categories within a certain theme (16). The analysis of the data was performed jointly by all the members of the research team. When the same RM was categorized under different topics and themes by the reviewers, conflicts were verbally discussed during in person meetings until resolution. Finally, further data regarding the articles' overarching thesis, country of publication and authors' background were collected.

RESULTS

Study characteristics

We identified 34 relevant publications, whose characteristics are summarized in Table 2.[2] The publication dates ranged from 2013 to 2023. To determine the country of publication, we considered the affiliations of the first authors. As shown in Fig.2a, most authors were affiliated to institutions situated in the United States and the United Kingdom. In most records, ethical issues in the clinical use of PRSs are considered generally, without a focus on a particular field of medicine or condition. 8 of the included records, however, belong to the psychiatric field (Fig.2b). The majority of first authors are physicians or have a background in medicine, followed by bioethicists and/or philosophers (Fig.2c). Authors' position towards the desirability of the clinical implementation of PRSs was also considered. More than half of the included records (n=18) endorse a moderate stance, whereby the ethical challenges of PRSs clinical use are emphasized with the need of establishing best practices and guidelines. A group of remaining records is more optimistic in their conclusions (n=8), highlighting PRSs' prospective benefits. In 6 of the included records skepticism prevails and the focus shifts to PRSs' challenges, potential harms and/or contribution to health disparities in a public health perspective. In 2 publications a clear stance *contra* is elaborated (Fig.3). While the ethical downsides of PRS clinical use are the result of ethical arguments, optimistic stances are not always inferred from ethical propositions. This trend explains the prevalence of topics discussing the harms and challenges of PRS in our results.

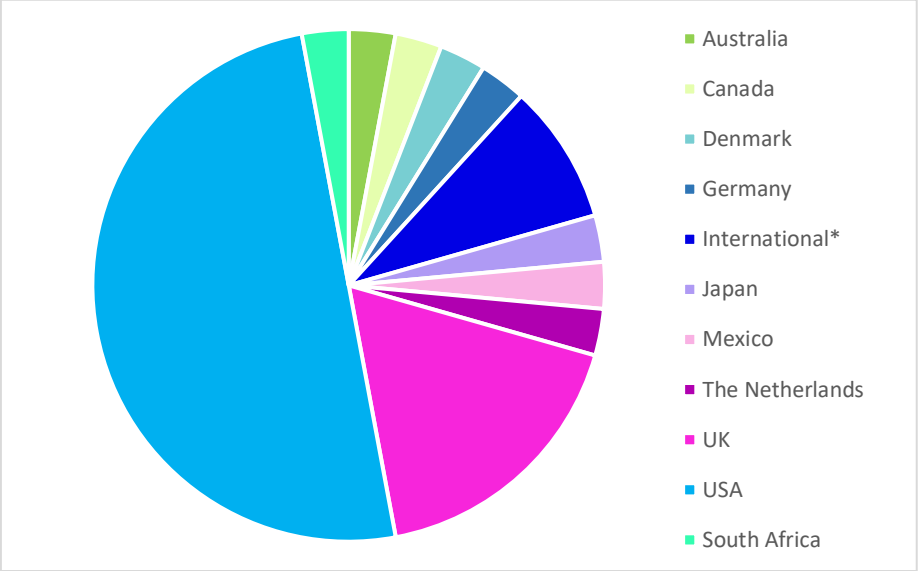
Themes and topics overview

The results will be presented in 3 overarching themes: (1) Potential harms, (2) Threats to health equity and (3) (Towards) Best practices. These major themes are respectively characterized into several topics, as shown below in Figure 4. Figure 5, instead, represents the distribution of RMs across topic in each theme. Under the theme 'Potential harms' we considered the risks posed by epistemic failures

[2] One of the included records focusses on ethical concerns in the commercial use of PRS for suicide. The decision to include the study in the present review is that authors consider suicide as a psychiatric trait. Furthermore, we have found consistent overlap between the ethical concerns presented there and in other included publications that discuss the ethics of PRS for psychiatric diseases.

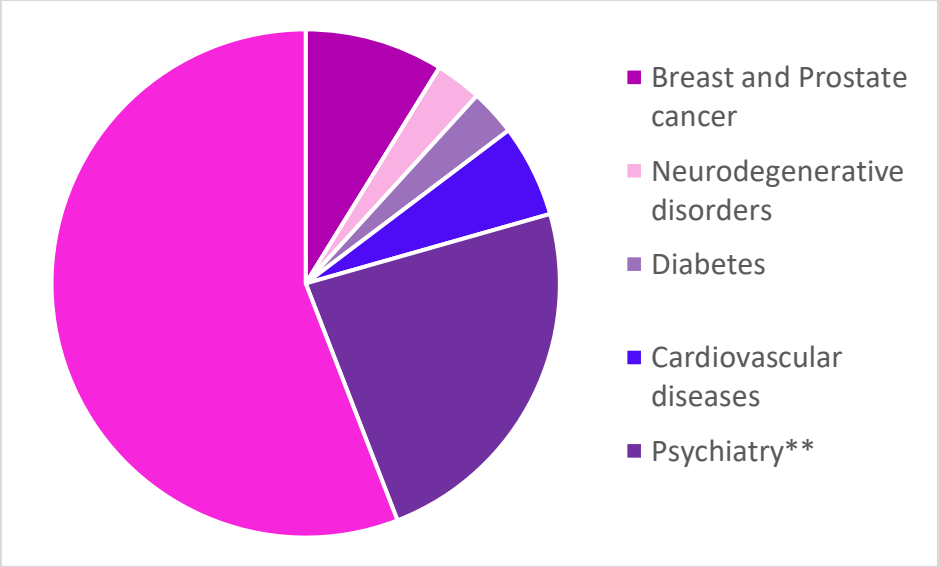
and the misuse of PRS primarily to individuals and their kin. The theme 'Threats to health equity' considers ethical issues in a societal perspective, with a focus on justice concerns; here potential risks of PRS clinical use regard individuals as members of social groups and the public health system. Finally, the topics following under the theme '(Towards) Best practices', consider a series of provisional recommendations, research priorities and suggested actions to be undertaken for an optimal implementation of PRS in the clinic.

Figure 2a: Countries of authorship



*Consortium of experts or equal contribution from authors with different affiliation

Figure 2b: Publications' field



**one publication refers to the use of PRS in the pediatric population

Figure 2c: First authors' background

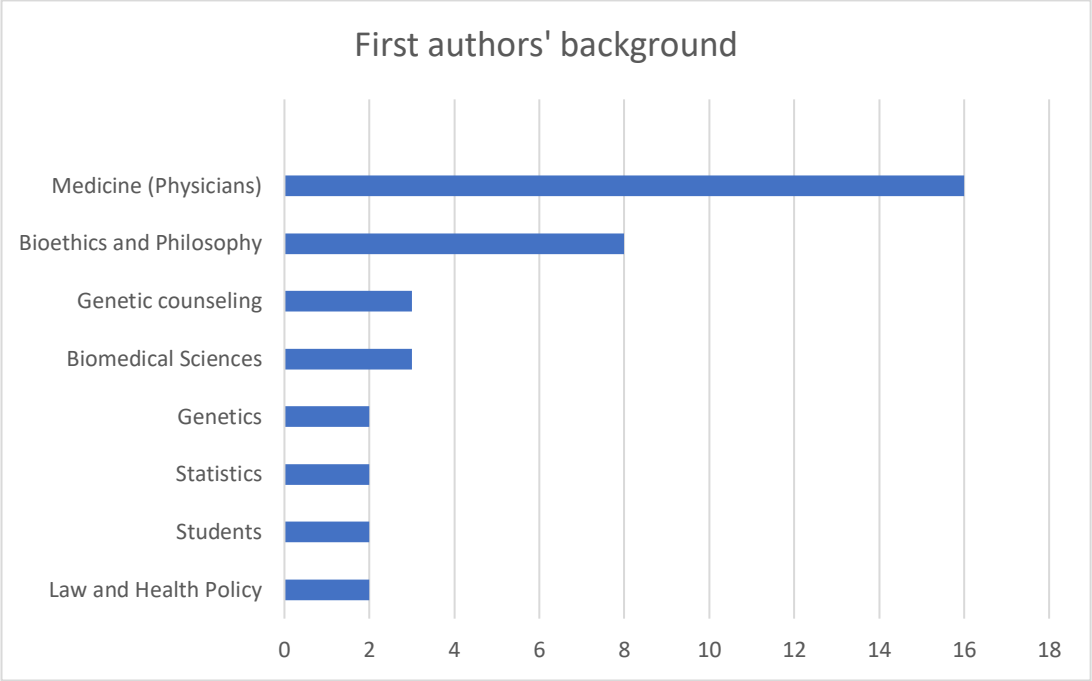
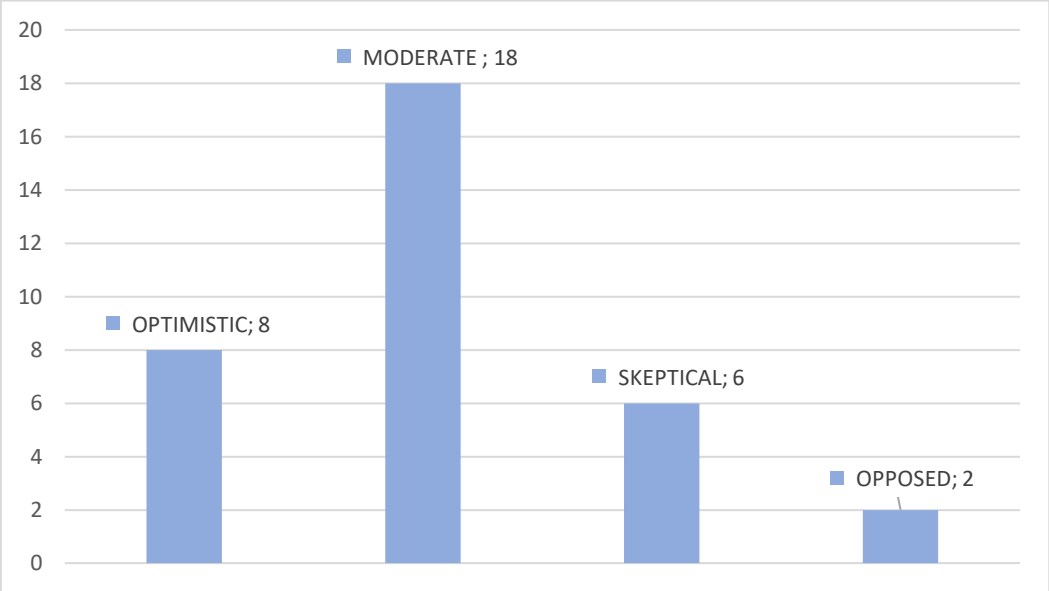


Figure 3: Publications' overarching thesis on the desirability of PRS clinical use



- Optimistic = emphasizing prospective benefits
- Moderate = focus on challenges and need of best practices before clinical implementation
- Skeptical = emphasizing challenges and prospective harms and/or contribution to health disparities in public health perspective
- Opposed*

*One publication on suicide risk scores and one on neurodegenerative disorders

Figure 4: Concept map: themes and topics

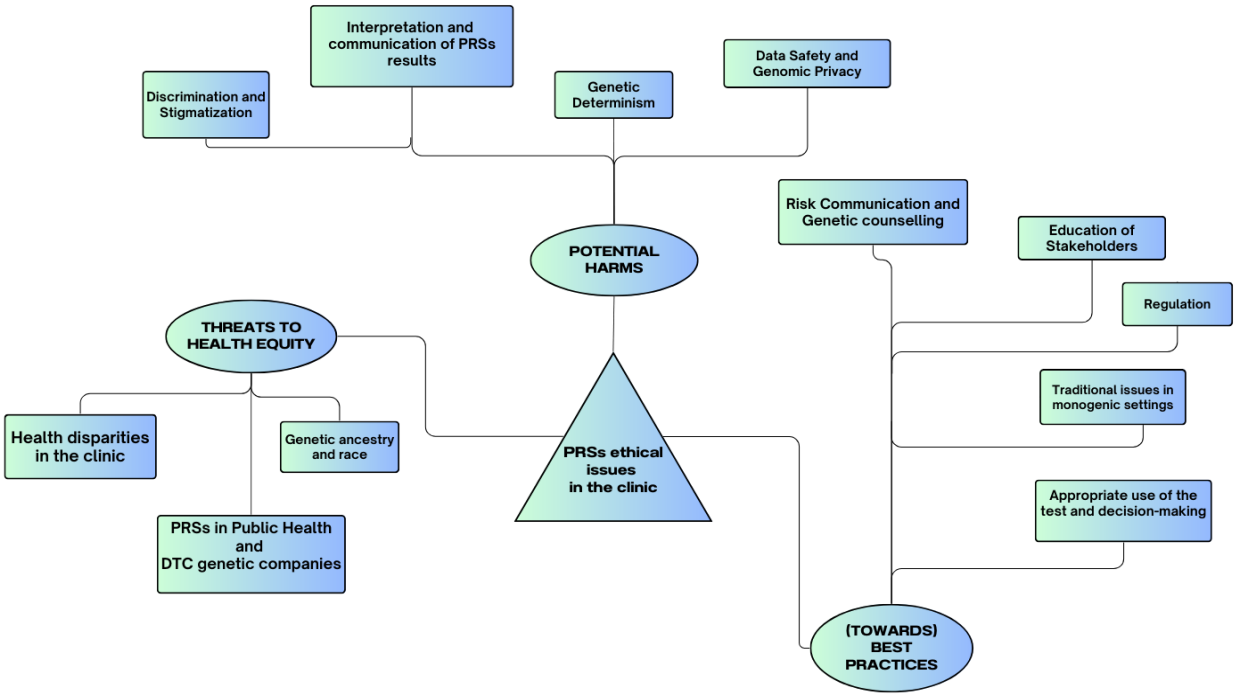
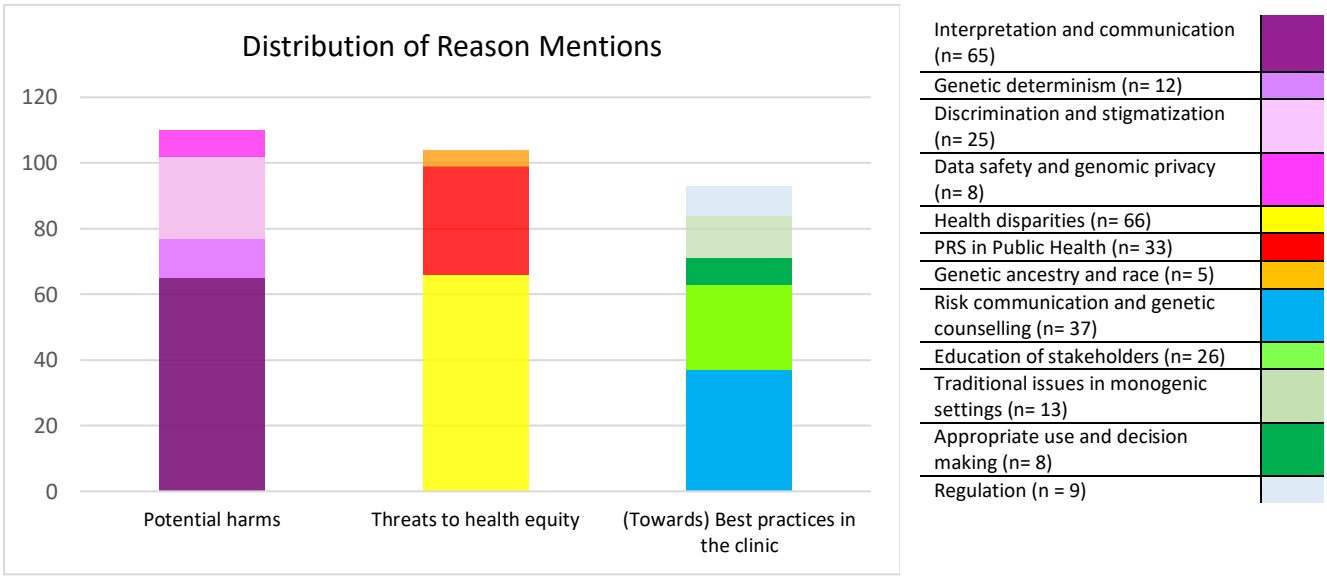


Figure 5: Distribution of Reason Mentions across topics in each theme



311 **Table 2: Included publications**

AUTHOR	YEAR	FIELD	PUBLICATION TYPE	JOURNAL	TITLE	COUNTRY
Chowdhury et al.	2013	Breast and prostate cancer	Review	Genetics in Medicine	Incorporating genomics into breast and prostate cancer screening: assessing the implications	UK
Khouri et al.	2013	General	Special article	Genetics in Medicine	How can polygenic inheritance be used in population screening for common diseases?	USA
Pashayan et al.	2013	General	Review	Journal of Internal Medicine	Public health genomics and personalized prevention: lessons from the COGS project	UK
Torkamani et al.	2018	General	Review	Nature: Reviews Genetics	The personal and clinical utility of polygenic risk scores	USA
Martin et al.	2019	General	Perspective	Nature: Genetics	Clinical use of current polygenic risk scores may exacerbate health disparities	USA
Palk et al.	2019	Psychiatric disorders	Review	Philosophy, Ethics, and Humanities in Medicine (BMC)	Potential use of clinical polygenic risk scores in psychiatry – ethical implications and communicating high polygenic risk	South Africa

Rashkin et al.	2019	General	Special issue	Journal of Genetic Counseling	Genetic counseling, 2030: An on-demand service tailored to the needs of a price conscious, genetically literate, and busy world	USA
Manrique de Lara et al.	2019	Neurodegenerative disorders	Review	American Journal of Medical Genetics (AJMG): Neuropsychiatric genetics	Ethical issues in susceptibility genetic testing for late-onset neurodegenerative diseases.	Mexico
Roberts et al.	2019	General	Perspective	Ethnicity and Disease	The Clinical Use of Polygenic Risk Scores: Race, Ethnicity, and Health Disparities	USA
Lewis & Vassos	2020	General	Review	Genome Medicine (BMC)	Polygenic risk scores: from research tools to clinical instruments	UK
Yanes et al.	2020	General	Review	Human Molecular Genetics	The emerging field of polygenic risk scores and perspective for use in clinical care	Australia
Folkersen et al.	2020	General	Research article	Frontiers (in: Genetics)	Impute.me: An Open-Source, Non-profit Tool for Using Data From Direct-to-Consumer Genetic Testing to Calculate and Interpret Polygenic Risk Scores	Denmark
Ikeda et al.	2020	Psychiatric disorders	Review	Journal of Human Genetics	Polygenic risk score as clinical utility in psychiatry: a clinical viewpoint	Japan
Peay	2020	Psychiatric disorders	Review	Perspectives in Medicine	Genetic Risk Assessment in Psychiatry	USA

Ronald	2020	Psychiatric disorders	Editorial	Journal of Child Psychology and Psychiatry	Polygenic scores in child and adolescent psychiatry – strengths, weaknesses, opportunities and threats	UK
Lewis & Green	2021	General	Opinion article	Genome Medicine (BMC)	Polygenic risk scores in the clinic: new perspectives needed on familiar ethical issues	USA
Slunecka et al.	2021	General	Review	Human Genomics (BMC)	Implementation and implications for polygenic risk scores in healthcare	USA
Adeyemo et al.	2021	General	Perspective article	Nature: Medicine	Responsible use of polygenic risk scores in the clinic: potential benefits, risks and gaps	International
Eeltink et al.	2021	Psychiatric disorders	Review	Neuroscience and Biobehavioral Reviews	Polygenic risk scores for genetic counseling in psychiatry: Lessons learned from other fields of medicine.	Netherlands
Knoppers et al.	2021	Breast cancer	Review	Journal of Personalized Medicine (MDPI)	Of Screening, Stratification, and Scores	Canada
Docherty et al.	2021	Psychiatric disorders	Research article	American Journal of Medical Genetics (AJMG)	Ethical concerns relating to genetic risk scores for suicide	USA

Kaplan & Fullerton	2022	General	Opinion	Philosophical Transactions	Polygenic risk, population structure and ongoing difficulties with race in human genetics	USA
Clarke & van El	2022	General	Perspective	Human Genetics	Genomics and justice: mitigating the potential harms and inequities that arise from the implementation of genomics in medicine	UK, Netherlands
Wand et al.	2022	General	Practical resource	Journal of Genetic Counseling	Clinical genetic counseling and translation considerations for polygenic scores in personalized risk assessments: A Practice Resource from the National Society of Genetic Counselors	USA
Araujo & Wheeler	2022	General	Spotlight	Cell Reports Medicine	Genetic and environmental variation impact transferability of polygenic risk scores	USA
Klarin & Natarajan	2022	Coronary Artery Disease	Review	Nature: Reviews Cardiology	Clinical utility of polygenic risk scores for coronary artery disease	USA
O' Sullivan et al.	2022	Cardiovascular Diseases	Review	Circulation (AHA Journals)	Polygenic Risk Scores for Cardiovascular Disease: A Scientific Statement From the American Heart Association	USA

Pinzón-Espinosa et al.	2022	Psychiatric disorders	Review	Translational Psychiatry	Barriers to genetic testing in clinical psychiatry and ways to overcome them: from clinicians' attitudes to sociocultural differences between patients across the globe	International
Brown et al.	2022	Psychiatric disorders	Perspective	Frontiers (in: Psychiatry)	Psychiatric genomics, mental health equity, and intersectionality: A framework for research and practice	USA
Chapman	2022	General	Narrative Review	Journal of Community Genetics	Ethical, legal, and social implications of genetic risk prediction for multifactorial disease: a narrative review identifying concerns about interpretation and use of polygenic scores	USA
Griffin	2022	Diabetes	Review	Diabetologia	Diabetes precision medicine: plenty of potential, pitfalls and perils but not yet ready for prime time	UK
Driver et al.	2023	General	Commentary	Translational Behavioral Medicine	Returning complex genetic risk information to promote better health-related behaviors: a commentary of the literature and suggested next steps	USA
Fritsche et al.	2023	General	Perspective	Frontiers (in: Genetics)	Ethical layering in AI-driven polygenic risk scores - New complexities, new challenges	Germany
Sud et al.	2023	Breast and prostate cancer	Analysis	BMJ	Realistic expectations are key to realising the benefits of polygenic scores	UK

POTENTIAL HARMS

Interpretation and communication of PRS results

A constant in the literature is the mention that current interpretation challenges would lead to major ethical issues in the clinical use of PRS. Most concerns originate from the limited explanatory power of the tests. While PRS recapitulate only the genetic architecture of a condition, the etiology of multifactorial diseases is complex and determined by genetic as well as environmental and lifestyle factors, which are mutable throughout a life course (17). Some authors point that PRSs are also blind to rare monogenic mutations (8,18) and other indirect genetic effects such as gene-gene interactions, structural variants, or the phenomenon of genetic nurture (Khoury et al., 2013; Lewis & Green, 2021; Slunecka et al., 2021). How to incorporate this piece of partially known and unknown information into a dynamic risk assessment tool, and what conclusions to infer from a score for a particular individual is currently considered problematic (20,21). In the included records, uncertainties of interpretation are linked to the risk of placing individuals into wrong risk categories, resulting in false positives, overdiagnosis and overtreatment or false reassurance (8,9,22–24). Should such risks materialize, authors point at the cost of unnecessary clinical interventions, physical and psychological harms for those undergoing the screening (17,22). Khouri et al. (2013) conclude that, currently, PRS do not predict better than other clinical risk factors. Given that family members often share the same environment and gene-environment interactions, the same authors maintain that currently family history remains the most relevant predictor for multifactorial conditions (19).

The communication of PRS results is also amply discussed in the included records. Many authors maintain that communicating the uncertainties inherent to the probabilistic nature of the test represents a significant challenge and might lead to potential harms (9,22,25,26). In particular, authors focus on the difficulties of vehiculating notions of dynamic and relative risk to broader patients' audiences (8,23,27). Since human's understanding of genetic risk is usually fixed and binary (27), authors argue that it is possible that patients will overemphasize the significance of a high or low score while downsizing the role played by the environment and other social determinants (28). Furthermore, additional challenges will arise from the communication of the long-term implications of PRS. As more genetic data becomes available and research advances, individuals might have their risk category shifted over time; therefore the question of how and under what circumstances patients should be informed (8,20,29). In general, authors place failures in delivering effective risk communication and appropriate counseling about risk-reducing strategies at the source of unwarranted health-related decisions, psychosocial harms such as anxiety and distress or, conversely, false reassurance (5,22,24,30). Finally, some of the authors who discuss the clinical use of PRS in the field of psychiatry and neurogenerative disorders reflect on the potential impact of receiving genetic risk information on the concept of self-identity (27,30,31).

While PRS are not routinely offered as a standard of care in public health systems, individuals can decide to obtain their PRS for a variety of conditions via direct-to-consumer (DTC) genetic companies. A recurrent topic in the studied records regards the role of expert intermediation and the harms deriving from a lack of appropriate counselling in the provision of PRS results (9,25,27,30,32). Clarke and van El, for instance, consider the possible scenario where an individual with a strong family history of common cancer does not seek clinical advice in virtue of a low or average PRS provided by a DTC genetic company (18). O' Sullivan proposes that genetic companies start contemplating medical follow-up workflows at least for individuals who fall in the high-risk percentile, highlighting the benefits of a closer collaboration between private companies and the healthcare system. Authors also

rise questions of responsibility regarding the scientific and medical suitability of commercial tests (30) and warn about the prioritization of commercial interests – leading to a hyping of results – (27) over high quality genetic knowledge (25).

Genetic determinism

Several articles note that inappropriate communication of the limitations of PRS and an excessive focus on the biogenetic level in the reporting of results might reinforce deterministic attitudes towards disease risk (31,27,8,33). Some authors give separate attention to the topic of genetic determinism, or the idea that 'genes alone define biology' (17) to argue that fatalistic beliefs might affect and individual's perception of self-agency (31) and thus have detrimental effects on health behaviors and prognostic outcomes (27). In some records, in fact, the conflation of risk susceptibility with risk inevitability is considered to play a role in the phenomenon of self-fulfilling prophecies, whereby the adverse psychological effects, and the lack of motivation to engage in risk mitigating actions (24) contribute to the disease onset (8,18,27,33). Next to the risk of psychosocial harm, Lewis and Vassos (2020) also urge to consider the potential negative impact of fatalistic beliefs on life planning and personal choices (17). Authors acknowledge the intrinsic difficulties of measuring deterministic attitudes, which are highly contextual and might depend on cultural and religious factors (31). As reported by Docherty et al. (2021), current empirical data on the topic are contrasting. However, while most research has been conducted on deterministic beliefs around monogenic conditions, Lewis and Green (2021) urge that more efforts should be made in polygenic settings (9).

Discrimination and Stigmatization

The risk of genetic discrimination, which has been amply discussed in monogenic settings, is mentioned in several of the reviewed records. In general, authors express the old concern that genetic information becomes available to third parties such as insurance companies or employers and used for discriminatory purposes (9,21,30,33,34). Chowdhury et al. (2103), for instance, notice that the mere participation in a screening program could be mis-used by insurers to establish premiums. Along these lines, some authors argue that if PRS were to be used clinically and on a large scale, many individuals would probably refrain from screening – and thus miss out potential benefits (9). Legislation is considered pivotal in ensuring adequate protection to individual rights and reassuring people, although it has limitations. American authors discuss the Genetic Information Nondiscrimination Act (GINA) as an example of protection against employer and insurance discrimination, which, nonetheless, does not extend to life and disability insurance (32,35). Reinforcing and updating current legislation with legal precedents of discriminatory use of genetic information (22,35) is recommended. Along with discrimination, stigmatization is regarded by authors as one of the possible aftermaths of receiving a high disease susceptibility score. Although it is recognized that social stigma may surround a variety of diseases, almost all the RMs about stigmatization found in our review are formulated in the context of psychiatric conditions (23,27,31,36,37). According to some authors, the well-documented existence of stigmatizing assumptions around mental illnesses could negatively impact the perception that individuals at high risk have of their own self and lead to negative self-labelling. To this regard, in one of the included publications special concerns are expressed towards the testing of children and teenagers (31). Furthermore, given the high heritability of certain psychiatric conditions, some authors give attention to the phenomenon of associative stigma**,** namely the possibility that the marginalization which affects individuals seeking testing extends to their family members (31,38). Docherty et al. (2021) argue that

PRS information, however, can also contribute to the de-stigmatization of some conditions if used benevolently by institutions to develop treatments and expand access to social preventive measures (27). Finally, several concerns are raised towards research studies that investigate the correlation between genetic susceptibility to psychiatric disorders and behavioral traits such as drug and alcohol consumption. Contextually, authors consider the way in which research findings are disseminated to the wide public of crucial importance to limit the spreading of discriminatory stances (9,31).

Data safety and genomic privacy

This topic focuses on data ethics issues that typically arise from the implementation of genomics into healthcare, and thus apply also to the clinical use of PRS. Ethical questions regard the right to access genomic data, the purpose for which such data is shared and how it is stored and safeguarded (21,23,39) in the light of the aforementioned potential risks of discrimination and stigmatization. Fritzsche et al. (2023) argue that - leaving the traditional discourse on genetic exceptionalism on a side - genomic data is peculiar for the challenges it poses in a data-driven medicine environment, and privacy concerns will need to be reconsidered as we move towards increasingly more complex AI-driven PRS models, generated with large amount of genomic and health data from electronic health records (EHR). Key questions in such contexts will regard the tradeoff between transparency of the models and protection of personal data, as well as the possibility of actually ensuring anonymization (40). On the other hand, while anonymizing genetic data would guarantee privacy, Rashkin et al. (2019) point at the risk that anonymization would hinder their clinical and research use. In this regard, they argue for the need of an intermediate category of de-identified data and related techniques aiming at balancing data safety and privacy concerns with scientific needs. Finally, the same authors argue that should PRS become available in the clinic, genetic counselors will need to be educated to answer the aforementioned questions in consultation settings and address the psychosocial counterpart of patients' related concerns (41).

THREATS TO HEALTH EQUITY

Health disparities in the clinic

A recurrent argument in the studied literature is that the implementation of PRS in the clinic would improve health outcomes only for individuals of European ancestry, while contributing to the exacerbation of already existing health disparities among ethnic groups. The same RM appears 66 times in the studied records and represents the normative counterpart of the so-called 'transferability problem', by which authors refer to the inferior predictive performance of PRS in individuals of non-European ancestry (5,8,9,17,18,20,22,23,26,27,29,30,32,34,35,40–47). The cause of such imbalance is almost unanimously identified in the lack of diversity in GWAS studies, which have been predominantly conducted in Western countries on subjects of recent European descent (5,8,17,20,22,29–31,38,44–46,48). However, as pointed by Slunecka et al. (2021), the burden of common diseases is mostly carried by individuals belonging to non-European ancestry groups. Mistrust towards medical research is identified as a further factor that determines the low participation - and the consequent underrepresentation - of ethnic minorities in genomic cohorts (8). Although technical efforts to correct the imbalance are on the way, cross-ancestry portability remains

a great epistemic and ethical hurdle in the clinical translation of PRS, and, for some authors, it is currently 'the most critical limitation to genetics in precision medicine' (44). While in most of the included studies the remedies to lever the disparity are generally identified in the inclusion of more diverse ancestral groups in genomic research (9,20,33,35,44,45) , only a minority of authors underlines the limitations of such approach. To this regard, Kaplan & Fullerton (2022) maintain that data sourced from a broader range of population genetic backgrounds, when accessible, still needs to be organized before creating and validating new PRS. However, pre-determined genetic clusters do not account for the complexity of human population patterns, meaning that it is not possible to establish, before screening, which clusters will be biomedically significant. Therefore, the authors conclude that any chosen stratification approach will still fall short for many patients whose genetic makeup doesn't align with the chosen categories (43).

PRS in Public Health and direct to consumer (DTC) genetic companies

This topic focuses on the ethical challenges arising from the implementation of PRS within the public health system. Some of the RMs presented under this category focus on axiological considerations arising from the use of PRS' in separate clinical contexts: in individual care to refine risk prediction and inform clinical decision-making and in public health as tools of primary and secondary prevention (8). Some authors argue that these two fields typically prioritize different sets of values. While in individual care patients' autonomy is key, public health ethics focuses on the optimization and the equitable distribution of health benefits within a certain population (9,30,43). It is therefore within the latter ethical framework that, according to some authors, the use of PRS in public health should be evaluated. A key topic of discussion in the included publications is whether the use of PRS in public health settings would further prevention strategies that target only individuals at high risk rather than the population at large, and the potential downsides of this approach. A group of authors clearly states that an excessive focus on the individual and biological level in determining disease risk detracts attention from other social and economic determinants, which considerably contribute to the etiology of common diseases (18,34,42,43,49). As put by Sud et al. (2023): 'Childhood postcode, for example, is probably as good a predictor of risk for most common diseases as most polygenic scores'. While discussing the limitations of precision medicine approaches in Type 2 Diabetes, Griffin (2022) completes the argument with the remark that even if PRS can help identifying a fraction of individuals at high risk, they are not as effective as well-established public health approaches. Traditional preventive strategies such as campaigns promoting a more active lifestyle, on the other hand, target a wider range of people and of conditions e.g.: diabetes and cardiovascular diseases (49). The ethical ambiguity of maximizing population benefits via PRS is also framed by these authors in terms of contrast between individual and collective responsibility. Lewis and Green (2021), for instance, notice that while patients' autonomy plays a pivotal role in the decision to participate in a screening program, determining to what extent individuals can and should be held accountable for their health is normatively problematic. The normative implications of the so-called 'individualization of health' are outlined in the argument that the *de facto* disparity in access to health-related resources based on wealth and status creates a situation where individuals who are more privileged have easier access to genomic technologies and are more likely to adopt healthy but sometimes expensive lifestyles (18,49). Clarke & van El (2022) consider ethical questions related to the phenomenon of DTC genetic companies under the same lenses. The authors claim that eventual additional costs to the healthcare system generated by individuals who have privately purchased a PRS would create further disparities by reducing the share of health resources destined to the disadvantaged. Consequently,

supporters of this argument consider it morally important to draw a line between actions that can be delegated to the individual's agency and those which should fall under the domain of political responsibility (18,49). As pointed in some of the included publications, (18,23,25,41), the principle of autonomy is usually advocated in discourses supporting the right of individuals to obtain their PRS and access their genomic information in general. Rashkin et al. (2019) amply discuss the rise of on-demand genomic services. They explore the idea that people are motivated to seek information about their genetic risks for both medical and non-medical conditions because it gives them a sense of agency and empowerment. Contrary to what claimed by the opposers of the 'individualization of health' argument, Rashkin et al. (2019) support an approach in genetic counseling that emphasizes autonomy. They suggest counselors should have discussions that go beyond clinical utility, including, for instance, patients' motivations for getting tested.

Genetic ancestry and race

A topic of concern in the included publications regards the potential overlap between the biological concept of genetic ancestry and the socio- political construct of race (9,46). Some authors notice that there is still a lack of consensus on how the scientific community understands and uses genetic ancestry's categories to stratify populations according to disease risk. Wand et al. (2023) underline that in several areas of medicine genetic ancestry is either not tested or substituted with continental categories, which are closely related to old racial ones. Along these lines, the operation of linking races instead of ancestries to disease susceptibility via PRS is epistemically incorrect and ethically problematic for two reasons: first, it could reinforce pre-existing racial stereotypes; second, it could detract attention from the way in which race-belonging influences health outcomes (9,50). Indeed, a widespread argument in the studied literature is that while categories of race do not explain the underlying biology of common diseases, race (and racism) can be important social determinants of health and thus be relevant to risk prediction (9,46,50).

(TOWARDS) BEST PRACTICES IN THE CLINIC

Risk communication and Genetic Counseling

Many publications discuss how the challenging of communication and reporting of PRS should be faced through a series of best practices in the clinic intended to minimize potential harms. In particular, authors (8,9,21–23,31,33,46) address the need for standardized clinical guidelines, which is considered a priority for the test clinical use. It is argued that such guidelines should provide uniform instructions on how to communicate PRS accurately while avoiding overwhelming patients with unnecessary information or, conversely, oversimplifications (8,21,31,46). Pashayan et al. (2013) also report the need to establish policies that instruct on how to diversify communication according to different risk levels. The provision of professional counseling services is typically seen as a virtuous practice intended to minimize the series of potential harms of receiving PRS results (30,33,38). In particular, genetic counseling pre-testing should focus on helping patients making sense of the etiology of the disease, by explaining the interplay between genetic versus lifestyle and environmental factors (28,42). Some authors underline how counseling about complex disease in polygenic settings would require genetic counselors to engage also with broader issues of social justice and public health (46). That means, genetic counselors should be ready to discuss the impact of social factors on access to genomic services and appropriate risk-reducing interventions (31), which, according to some

authors, should always follow the communication of PRS results (24,31). Post-testing, it is considered good practice to frame the reporting of PRS in terms of modifiable disease risk through lifestyle choices and, if needed, the uptake of therapeutic recommendations. As suggested in some of the included records, the moment of risk communication can be empowering for individuals (47,33,46), who are called to play an active role in the reduction of their disease risk. However, Driver et al. (2023) point at the lack of empirical evidence that proves a significant correlation between receiving PRS results and positive behavioral change. According to the authors, the delivery of PRS results is currently not informed by theoretical perspectives on behavioral change that, for instance, would explain aspects of patients' motivations for health behavior. Therefore, research should move in this direction to ensure that the clinical reporting of PRS is useful and effective (23,24). A further recurrent topic is the importance of tailoring PRS' communication and reporting according to patients' genomic literacy, education, and social background (25,30,46). More personalized and participatory communication strategies that take into account patients' personal utility for undertaking the test are generally recommended (25,39,46). Finally, in one of the included records it is mentioned how the goal of engaging with different populations in counseling would be better achieved by promoting more diversity in the counseling profession (46). A few authors, however, express concerns regarding the feasibility of providing such personalized counseling services on a wide scale, such as in population-screening or DTC scenarios (22,41)

Education of stakeholders

A widespread argument in the included literature is that the successful clinical implementation of PRS will depend on the education of several stakeholders, in particular healthcare providers (HP) (21,22) and the public. A group of authors argue that since PRS are calculated for common conditions, it is likely that the request and delivery of PRS in clinical settings will be delegated to primary healthcare providers (9) with no specific expertise in genetics and little understanding of risk estimates and probability (8,31,33). Such a phenomenon is also expected to increase as PRS are routinely embedded in healthcare and, consequently, genetic counselors highly demanded (5,29,41). Most authors believe that specific training programs should be provided as part of medical education; the goal is to offer support HPs in their interpretation and communication tasks and make sure that the counseling offered to patients is meaningful (5,8,23,31,33,39). It is also suggested that educating HPs should address questions of appropriate use and justifiability of the test (31,33) as well as interpretation challenges in absence of family history (30). Furthermore, it is argued that HPs' genetic knowledge needs to be constantly updated as the field progresses fast (33). To tackle the issue, Rashkin et al. (2019) propose that genetic counselors play an active role in setting up educational material and trainings directed to non-genetics HPs. Authors also consider the improvement of patients and the public's genetic literacy a priority on the agenda (8,23,35,40). As pointed by Klarin & Natarajan (2022), mainstream knowledge of genetics is still highly influenced by mendelian concepts, which might convey the message that polygenic risk is deterministic. Policies should be designed to educate the public, although, as pointed by Manrique de Lara et al. (2019), public's attitudes towards genetic testing do not depend only on knowledge. Socio-cultural factors, such as stigma towards some diseases also play a pivotal role and, according to the authors, it is responsibility of institutions to fight potential preconceptions through education.

Appropriate use of the test and decision-making

Determining the scope and the most appropriate use of PRS is a central ethical topic in included publications. Authors maintain that the existence of a test is not sufficient for its widespread adoption: arguments on PRS introduction in clinical care should be based on their clinical utility (8,17) and healthcare providers should thoroughly evaluate whether receiving PRS' results could positively impact a patient' s quality of life (8). Along these lines, included publications suggest that the use of PRS in the clinic should be limited to clinically actionable diseases and avoided in cases like Alzheimer Disease and other neurodegenerative disorders (8,30). Generally, it is recommended that PRS are used as a complementary risk assessment tool to other traditional, non-genetic clinical risk factors (22,42,48). At the moment, however, authors report a lack of clinical guidelines that would support healthcare providers in their clinical recommendations and shared decision-making based on PRS information, with the exception of the cardiovascular field (22).

Traditional issues in monogenic settings

Relevance of findings to family members and testing of minors

Some of the included records consider the relevance of a high polygenic risk score for family members. While Brown et al. (2022) reflect on the sense of familial obligation that might lead to PRS cascade testing for highly heritable conditions, Clarke & van El (2022), for instance, express their concern about such hypothesis. According to the authors, cascade testing would convey the wrong idea that complex diseases are mostly genetically determined, whereas they follow multifactorial inheritance patterns. Other address the question of whether physicians would have a duty to inform relatives of subjects at high polygenic risk (9,29,30). A group of authors argues that while it is responsibility of physicians to discuss the potential relevance of genetic information to family members, the correlation of PRS among first-degree family members is not as straightforward as in monogenic cases (23,41,51). That means, it is still uncertain what risk threshold would imply a duty to warn family members. Similarly, Eeltnik et al. (2021) refer to existing Dutch guidelines (NL), which state that family members should be actively informed only when there is a 50% chance of inheriting a disease. Manrique de Lara et al. (2019), finally, argue that for neurodegenerative disorders, there are currently no benefits in disclosing PRS information to relatives because of the highly probabilistic nature of the scores. Few reason mentions are raised with regard to the ethical justifiability of testing and returning PRS results to minors. The authors mostly focus on typical consent issues and potential harms in the pediatric population (22,27). Furthermore, Lewis and Green (2021) argue that although a PRS can be potentially calculated from birth, the decision to return PRS results to minors should be tailored on the age of onset of a condition and its actionability (9).

Regulation

Regulatory issues are addressed in the included records as part of the safe and equitable implementation of PRS in the clinic. Authors maintain that the most important question at the moment concerns the classification of PRS as medical or non-medical devices (22,20,40). As reported by the authors, such classification is complicated by two factors: first, the current scientific and technical limitations of PRS (20); second, the internationally fragmented regulatory landscape, for which PRS would qualify as medical devices only in some jurisdictions (20,22,40). In the included records, there is consensus on the need for legislative clarification to ascertain that PRSs abide to adequate standards of safety and effectiveness. However, authors argue that excessively stringent regulatory requirements would impose high costs on the equitable accessibility and the further development of the PRS technology (23,52). As pointed by Knoppers et al. (2021), 'the legal

classifications used by the regulators […] are not value neutral', meaning that legislators need to consider the impact of regulatory labels on the achievement of public health goals for which PRS are designed. Adeyemo (2021) argues that the costs of complying with current regulations of medical devices 'will be higher than those associated with following best practices' of validation and quality assurance. Finally, all authors conclude that it is imperative to establish harmonized regulatory frameworks, which are sufficiently dynamic to incorporate updates as the science of PRS evolves and, at the same time, ensure that patients can equally enjoy its benefits.

DISCUSSION

The scope of the present review was to identify ethical issues and arguments related to the clinical use of PRS through a systematic study of the normative literature. As shown in our results, harm-related arguments are widespread in the included studies and seem to outdo the prospective benefits of PRS clinical implementation. Two reasons could explain the imbalance of perspectives. The first reason is methodological, as normative arguments have been elaborated more frequently in discussions of the harms or challenges of PRS. The second reason could be contingent, as the acquisition of prospective benefits, although highly desirable, is still bound to the solution of a series of practical challenges, both ethical and scientific. Nonetheless, authors of the included studies and in relevant literature have also expressed great interest in expediting the clinical translation of PRS, which have been described as a 'scientific revolution' in complex disease understanding and prediction (53).

The results of our review have also revealed a variegated landscape, with indisputable peaks and unexpected troughs of moral concerns.

The interpretation of PRS is one of such peaks. A consideration of the type and amount of harm deriving from interpretation 'failures' in the included records seems to depend on the solution of a set of more fundamental questions, namely: what is a PRS? Or, in other words, what type of information do they provide and for what purpose?

Often, PRS are defined as statistical tools that mirror *only* the genetic liability of common diseases. As shown in our findings, such a definition of PRS is implicit in many moral arguments which identify the main challenge of clinical interpretation in weighing this genetic contribution against a fragmented risk picture, whereby environment and lifestyle may rather be determinant. Here, two aspects of the challenge can and should be distinguished: first, the interpretation of genetic liability; second, the integration of different types of information (genetic vs environmental and lifestyle). In the first case, because of the inherent scientific limitations of PRS and knowledge gaps, family history has been used as the 'standard indirect measure of inherited susceptibility in clinical care' (54). The position of Kouri et al. (2013) about the role of family history in risk prediction reflected indeed a consensus statement in the genetics community until the last decade. The recent study of Mars et al. (2022), however, demonstrates that family history and PRS represent independent, complementary information, which is not interchangeable and can be read jointly for a comprehensive assessment of susceptibility. Accordingly, research has shown that polygenic background can substantially modify the penetrance of the disease in patients who have inherited a monogenic variant (55). As a result, 'accounting for polygenic background is likely to increase the accuracy of risk estimation' in such cases and, therefore, improve genetic counselling and decision-making regarding follow-up clinical interventions (55). In other cases, PRS have been found to account for residual genetic risk in patients with family history of breast cancer but no pathogenic variant in monogenic risk genes (56).

A further, innovative insight into the informative value of PRS to individual risk assessment is offered by Lu et al. (2021). With their study, they have explored the idea that PRS might also play a role in the identification of individuals with rare pathogenic variants across 5 complex diseases. Their results have confirmed the hypothesis that a *low* polygenic risk correlates positively with the presence of a rare genetic variant, and thus could be used 'in prioritizing patients who should undergo sequencing based genetic tests for known disease-causing genes' (57). These findings altogether suggest that the value of PRS in individual disease risk prediction cannot be separated from a consideration of further genetic information and family history, alongside environmental and lifestyle data. In this framework, reflecting on the definition of PRS, and thereby limiting its corresponding concept, seems paramount for an accurate interpretation of results, the technology at large, its limitations and opportunities.

Such opportunities are becoming more concrete especially in the cancer clinic, where proposals to bundle PRS into comprehensive risk prediction models, including germline sequencing and traditional risk factors, are independent of commercial offerings. In the breast cancer setting, for instance, research has shown that the addition of PRS to family history in unaffected BRCA-negative patients, led to substantial changes in clinical recommendations; one of the current proposals, therefore, is to improve risk stratification in these individuals by integrating PRS with risk models such as Tyrer-Cuzick and CanRisk (53). Recent guidelines on germline testing, moreover, have pointed that even our knowledge of the risk associated with pathogenic or likely pathogenic variants is still incomplete: 'after adjustment for proposed polygenic risks scores [...] a substantial proportion of unaffected women with pathogenic variants in CHEK2 or ATM have a cumulative lifetime risk below the 20% threshold that is used to indicate breast MRI surveillance in the United States.' (58). Along these lines, authors have concluded that Mendelian mutations and polygenic risk information are rather complementary and integrated approaches to risk assessment can be key to the achievement of personalized care in oncology (53).

These proposals relate to a further aspect of the interpretation challenge, namely the integration of qualitatively different factors (genetic susceptibility, lifestyle and environment), which remains a key objective of personalized disease risk assessment. In our results, such tasks are typically delegated to HPs, who should be able to infer tailored conclusions for individuals. As amply acknowledged in the studied literature, educational gaps and the lack of standardized guidelines pose challenges to the main principles of medical ethics and expose patients to the risk of iatrogenic harm. The improvement of PRS models through their integration with existing disease risk prediction models is already part of a research agenda aiming at boosting their clinical introduction (59). However, as anticipated by Fritzsche et al. (2023), the application of AI via Deep Learning techniques to PRS protocols is bound to change the terms of the interpretation problem in those of *interpretability*. In this context, the challenge for HPs will be to make sense of the ratio behind output scores resulting from the integration of EHRs, genomic and environmental data in their complex interplay. As noticed by the authors, the power of AI to magnify existing challenges in the clinical use of PRS calls for urgent interdisciplinary ELSI work on the topic (40).

Communicating PRS results is also a dominant topic in the included studies. The literature on genetic risk communication and related best practices is robust, although mostly limited to monogenic settings. As argued by Lewis and Green (2021), many challenges in traditional clinical genetics will continue to be valid in polygenic contexts. In the field of risk communication, principles of best practices that suggest, for instance, tailoring communication to patients' genetic literacy, socio-economic background and preferences will continue to apply. At the same time, the communication

of PRS results will represent a new endeavor under certain aspects and will require, therefore, new perspectives and practical solutions (9). First of all, common diseases are typically managed by HPs whose field of expertise does not extend to genetics: communicating and answering patients' questions about the meaning of test will require additional training, as also confirmed by recent empirical studies (60). A second novelty of PRS communication is the chance that patients' risk categories shift across time as the predictive power of the models improves and more health-related data become available. In the studied literature, few authors acknowledge the challenge of conveying risk updates. Contextually, they raise questions regarding potential physicians' duties of informing patients about their risk-shifts, the inclusion of such possibility in the informed consent process as well as the modality of this communication (8,20). While several are the proposals on the way to address the need for HPs' education (41,61), to our knowledge the problem of risk-shifts is still underexplored and will certainly require further attention.

A rather singular aspect of polygenic risk information that is meant to have an impact on clinical practices is its relevance for family members. In our results, some authors have reflected on whether and under what circumstances blood relatives should be warned of a high polygenic risk. While it is unprecise to speak of a legal duty to warn (62), the same idea of a moral obligation to inform relatives has been questioned in the light of the non-Mendelian inheritance patterns followed by polygenic diseases (41). Such considerations might *prima facie* suggest that while in monogenic settings the family is an important domain of moral concerns, against which the autonomy of individuals needs to be pondered, the same concerns may not be as relevant in polygenic contexts. However, the study of Reid et al. (2021) has shown that PRS 'correlate strongly across siblings' and high PRS of 4 cardiometabolic diseases are concordant among these individuals. The same authors underline the implications of such findings for the clinical practice and genetic counselling, including the possibility of cascade testing to identify relatives at high risk. In the light of these results, the idea that family at large will cease to be object of ethical concerns requires careful consideration. While it is still unclear what obligations and best practices would apply in these contexts, the ethics of disclosing polygenic information might demand a shift of focus from the vertical parent-offspring relatedness, as in the identification of monogenic risk, to the re-definition of relevant family bonds.

Similarly, ethical issues related to the testing of minors are still underdeveloped in the included studies, with few exceptions (9,27). A way to start thinking of the ethics of pursuing polygenic risk information in children and adolescents is referring to existing guidelines for predictive or susceptibility test in minors. While testing of minors is always considered appropriate if diagnostic, predictive testing is generally recommended only for conditions that are actionable in childhood and on the basis of family history; for diseases with adult-age of onset and actionability, however, there is consensus on postponing the test until the minor has reached the informed consent age (63,64). As noticed by Lewis and Green (2021), PRS are developed for a broad spectrum of diseases with different age-onsets, meaning that future ethical guidelines should need to adjust accordingly. The study of Isgut et al. (2021), however, raises questions regarding the sufficiency of such guidelines. Here it is shown that PRS for CD such as myocardial infarction – a condition with age of onset that spans between 55 and 62 years old (65) - do not improve cardiovascular risk stratification in middle-aged population compared to other clinical risk factors (66). On the other hand, authors conclude that PRS of CD are better risk predictors at birth, 'when other risk factors are unknown, helping to identify individuals most susceptible to development of heart disease' (59,66). Although PRS of CD are approaching the clinic and a series of preliminary guidelines available for this field, work on key ELSI topics, such as the returning of findings in pediatric populations, is still in its infancy (67). Uncertainties

and open questions about best practices on traditional issues in clinical genetics, furthermore, suggest that the ethical considerations and guidelines developed for monogenic diseases will not be sufficient to face the emerging challenges of PRS in the clinic. Increasing the number of studies assessing stakeholders' perspectives on such topics is part of the necessary work to fill the normativity gap. When moving from the individual to the collective level, ethical considerations surrounding the potential contribution of PRS to health disparities are recurrent and stronger in those records that approach the ethics of PRS from a public health perspective. The tension between individual and collective values is inherent to PRS as they serve a double function: first, refining risk prediction in individual care, whereby respect for the autonomy of individuals is imperative; second, improving risk stratification at a population level, and thus serving public health goals of health equity. Questions regarding the prioritization of one or the other principle characterize the attempt to define an ethics framework for the clinical use of PRS especially in this latter sense, as tools of precision public health. The limitations of promoting individualistic values in a field which relies on precision medicine but still targets populations (or communities) are outlined by Newson (2022), who criticizes the rhetoric of autonomy and empowerment featuring in discourses about the value of genomic information on the same lines of Clarke and van El (2022). According to this view, any axiological framework for evaluating the appropriateness of precision public health initiatives (including risk stratification via PRS) and oriented at the leverage of health disparities will still need to be informed by key public health values of social justice and solidarity (68). Nonetheless, the 'individualization of health' argument continues to sustain many consumer genomics campaigns. Sabatello & Juengst (2019) have shed light on the link between the marketing of DTC genetic screening products 'in terms of knowing oneself and personal identity' and the perpetuation of essentialist and deterministic attitudes, with their related harms. Given that polygenic risk information in the context of complex diseases is inherently non-deterministic, more transparent public communication about the scopes and the limits of PRS could, on the other hand, benefit the cultural process of de-exceptionalizing genomic information. Our findings, however, show that issues of public communication and public trust are only briefly addressed in ethical discourses, as also pointed out in some of the included records (46,40,5).

A further question is whether the clinical use of PRS in psychiatry would represent an exceptional case requiring exceptional deliberation and protection. In our results, 8 publications out of 34 discuss the ethical issues of PRS in this field, while other records express singular concerns. All the RMs regarding the risk of stigmatization, associative stigma and negative self-labelling, furthermore, are elaborated with regard to psychiatric conditions. As shown in our findings, authors have also pointed at the ethical downsides of research agendas that correlate susceptibility to psychiatric conditions and negative socio-behavioral traits. In contrast to these results, Plomin and von Stumm (2022) highlight the benefits of furthering research to enhance the predictive power of PRS in the cognitive and behavioral domain. Although PRS do not reveal causal pathways, they would 'serve as an early warning system to prevent problems before they occur' and thus have a high practical value (69). The reason why other authors have pointed at the need for special ethical oversight seems to dwell in the merging of two fields, genetics and psychiatry, which have been protagonists of a history of discrimination and, at the same time, considered revealing of people's identities. In both cases, exceptional protection will need to be guaranteed as long as genomic and psychiatric information is considered exceptional in the eyes of society (70).

Finally, our results have shown that ethical considerations regarding the clinical use of PRS and the desirability of their actual implementation is not only informed by the prospective achievement of their clinical utility but can be driven by deeper convictions about the same concept of disease.

Authors' leaning towards a preference for biogenetics or socio-relational explanations is an important driver in arguments that weigh PRS against the role of social-determinants in the etiology of common diseases. The potential of PRS to weaken the political attention on such determinants has given rise to well-justified concerns about their desirability; at the same time, ethical reflections on the clinical use of PRS are currently reinvigorating old debates about institutional responsibilities, the pursuit of health as a key social goal and the role of collective values in the era of data-driven genomic medicine.

Limitations

A limitation of this review is that it includes only publications written in the English language. The prevalence of publications originating from Western countries, furthermore, indicates a dominance of Western perspectives and related values in our findings. The articles included in the review are those retrieved until the latest database search update. Therefore, further advancements in the field that were made since the data collection have not been included. Another limitation is that the database search and screening of the records has been conducted only by the first author. Finally, as highlighted in the discussion, the goal of our review was to report on the ethical issues and moral arguments related to the clinical use of PRS. The elaboration of full normative stances, however, was rarer in the context of the analysis of the benefits of PRS. This resulted into a prevalence of harm-related arguments in our findings.

BIBLIOGRAPHY

1. Europa Donna [Internet]. [cited 2023 Oct 24]. Breast Cancer. Available from: https://www.europadonna.org/breast-cancer/

2. Cardiovascular diseases (CVDs) [Internet]. [cited 2023 Oct 24]. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)

3. Mathieu C, Soderberg J, Del Prato S, Felton AM, Cos X, de Beaufort C, et al. The European Diabetes Forum (EUDF): a forum for turning the tide on diabetes in Europe. Diabetologia. 2023 Feb 1;66(2):247–52. doi:10.1007/s00125-022-05831-1

4. Johansson Å, Andreassen OA, Brunak S, Franks PW, Hedman H, Loos RJF, et al. Precision medicine in complex diseases—Molecular subgrouping for improved prediction and treatment stratification. J Intern Med. 2023;294(4):378–96. doi:10.1111/joim.13640

5. Torkamani A, Wineinger NE, Topol EJ. The personal and clinical utility of polygenic risk scores. Nat Rev Genet. 2018 Sep;19(9):581–90. doi:10.1038/s41576-018-0018-x

6. Manolio TA. Genomewide Association Studies and Assessment of the Risk of Disease. N Engl J Med. 2010 Jul 8;363(2):166–76. doi:10.1056/NEJMra0905980

7. Kullo IJ, Lewis CM, Inouye M, Martin AR, Ripatti S, Chatterjee N. Polygenic scores in biomedical research. Nat Rev Genet. 2022 Sep;23(9):524–32. doi:10.1038/s41576-022-00470-z PubMed PMID: 35354965; PubMed Central PMCID: PMC9391275.

8. Slunecka JL, van der Zee MD, Beck JJ, Johnson BN, Finnicum CT, Pool R, et al. Implementation and implications for polygenic risk scores in healthcare. Hum Genomics. 2021 Dec;15(1):46. doi:10.1186/s40246-021-00339-y

9. Lewis ACF, Green RC. Polygenic risk scores in the clinic: new perspectives needed on familiar ethical issues. Genome Med. 2021 Dec;13(1):14. doi:10.1186/s13073-021-00829-7

10. Koch S, Schmidtke J, Krawczak M, Caliebe A. Clinical utility of polygenic risk scores: a critical 2023 appraisal. J Community Genet. 2023 Oct;14(5):471–87. doi:10.1007/s12687-023-00645-z PubMed PMID: 37133683; PubMed Central PMCID: PMC10576695.

11. Kumuthini J, Zick B, Balasopoulou A, Chalikiopoulou C, Dandara C, El-Kamah G, et al. The clinical utility of polygenic risk scores in genomic medicine practices: a systematic review. Hum Genet. 2022 Nov;141(11):1697–704. doi:10.1007/s00439-022-02452-x PubMed PMID: 35488921; PubMed Central PMCID: PMC9055005.

12. Sofaer N, Strech D. The Need for Systematic Reviews of Reasons. Bioethics. 2012 Jul;26(6):315–28. doi:10.1111/j.1467-8519.2011.01858.x PubMed PMID: 21521251; PubMed Central PMCID: PMC3458717.

13. Strech D, Sofaer N. How to write a systematic review of reasons. J Med Ethics. 2012 Feb;38(2):121–6. doi:10.1136/medethics-2011-100096 PubMed PMID: 22080465; PubMed Central PMCID: PMC3262986.

14. 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. PLOS Med. 2009 Jul 21;6(7):e1000100. doi:10.1371/journal.pmed.1000100

15. Johnson N, Phillips M. Rayyan for systematic reviews. J Electron Resour Librariansh. 2018 Jan 2;30(1):46–8. doi:10.1080/1941126X.2018.1444339

16. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol. 2006 Jan 1;3(2):77–101. doi:10.1191/1478088706qp063oa

17. Lewis CM, Vassos E. Polygenic risk scores: from research tools to clinical instruments. Genome Med. 2020 Dec;12(1):44. doi:10.1186/s13073-020-00742-5

18. Clarke AJ, van El CG. Genomics and justice: mitigating the potential harms and inequities that arise from the implementation of genomics in medicine. Hum Genet. 2022 May;141(5):1099–107. doi:10.1007/s00439-022-02453-w PubMed PMID: 35412078; PubMed Central PMCID: PMC9160156.

19. Khoury MJ, Janssens ACJW, Ransohoff DF. How can polygenic inheritance be used in population screening for common diseases? Genet Med Off J Am Coll Med Genet. 2013 Jun;15(6):437–43. doi:10.1038/gim.2012.182 PubMed PMID: 23412608; PubMed Central PMCID: PMC4692802.

20. Knoppers BM, Bernier A, Granados Moreno P, Pashayan N. Of Screening, Stratification, and Scores. J Pers Med. 2021 Aug;11(8):8. doi:10.3390/jpm11080736

21. Pashayan N, Hall A, Chowdhury S, Dent T, Pharoah PDP, Burton H. Public health genomics and personalized prevention: lessons from the COGS project. J Intern Med. 2013 Nov;274(5):451–6. doi:10.1111/joim.12094 PubMed PMID: 24127941; PubMed Central PMCID: PMC4283043.

22. Adeyemo A, Balaconis MK, Darnes DR, Fatumo S, Granados Moreno P, Hodonsky CJ, et al. Responsible use of polygenic risk scores in the clinic: potential benefits, risks and gaps. Nat Med. 2021 Nov 1;27(11):1876–84. doi:10.1038/s41591-021-01549-6

23. Chapman CR. Ethical, legal, and social implications of genetic risk prediction for multifactorial disease: a narrative review identifying concerns about interpretation and use of polygenic scores. J Community Genet. 2022 Dec 19. doi:10.1007/s12687-022-00625-9 PubMed PMID: 36529843.

24. Driver MN, Kuo SIC, Dick DM. Returning complex genetic risk information to promote better health-related behaviors: a commentary of the literature and suggested next steps. Transl Behav Med. 2023 Feb 28;13(2):115–9. doi:10.1093/tbm/ibac071 PubMed PMID: 36125098; PubMed Central PMCID: PMC9972341.

25. Folkersen L, Pain O, Ingason A, Werge T, Lewis CM, Austin J. Impute.me: An Open-Source, Non-profit Tool for Using Data From Direct-to-Consumer Genetic Testing to Calculate and Interpret Polygenic Risk Scores. Front Genet. 2020 Jun 30;11:578. doi:10.3389/fgene.2020.00578 PubMed PMID: 32714365; PubMed Central PMCID: PMC7340159.

26. Ronald A. Editorial: Polygenic scores in child and adolescent psychiatry – strengths, weaknesses, opportunities and threats. J Child Psychol Psychiatry. 2020;61(5):519–21. doi:10.1111/jcpp.13246

27. Docherty A, Kious B, Brown T, Francis L, Stark L, Keeshin B, et al. Ethical concerns relating to genetic risk scores for suicide. Am J Med Genet B Neuropsychiatr Genet. 2021 Dec;186(8):433–44. doi:10.1002/ajmg.b.32871

28. Peay HL. Genetic Risk Assessment in Psychiatry. Cold Spring Harb Perspect Med. 2020 Dec 1;10(12):a036616. doi:10.1101/cshperspect.a036616 PubMed PMID: 31570376; PubMed Central PMCID: PMC7706580.

29. Eeltink E, van der Horst MZ, Zinkstok JR, Aalfs CM, Luykx JJ. Polygenic risk scores for genetic counseling in psychiatry: Lessons learned from other fields of medicine. Neurosci Biobehav Rev. 2021 Feb;121:119–27. doi:10.1016/j.neubiorev.2020.11.021 PubMed PMID: 33301779.

30. Manrique de Lara A, Soto-Gómez L, Núñez-Acosta E, Saruwatari-Zavala G, Rentería ME. Ethical issues in susceptibility genetic testing for late-onset neurodegenerative diseases. Am J Med Genet B Neuropsychiatr Genet. 2019;180(8):609–21. doi:10.1002/ajmg.b.32699

31. Palk AC, Dalvie S, de Vries J, Martin AR, Stein DJ. Potential use of clinical polygenic risk scores in psychiatry – ethical implications and communicating high polygenic risk. Philos Ethics Humanit Med PEHM. 2019 Feb 27;14:4. doi:10.1186/s13010-019-0073-8 PubMed PMID: 30813945; PubMed Central PMCID: PMC6391805.

32. O'Sullivan JW, Raghavan S, Marquez-Luna C, Luzum JA, Damrauer SM, Ashley EA, et al. Polygenic Risk Scores for Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation. 2022 Aug 23;146(8):e93–118. doi:10.1161/CIR.0000000000001077

33. Pinzón-Espinosa J, van der Horst M, Zinkstok J, Austin J, Aalfs C, Batalla A, et al. Barriers to genetic testing in clinical psychiatry and ways to overcome them: from clinicians' attitudes to sociocultural differences between patients across the globe. Transl Psychiatry. 2022 Oct 11;12(1):442. doi:10.1038/s41398-022-02203-6 PubMed PMID: 36220808; PubMed Central PMCID: PMC9553897.

34. Sud A, Horton RH, Hingorani AD, Tzoulaki I, Turnbull C, Houlston RS, et al. Realistic expectations are key to realising the benefits of polygenic scores. BMJ. 2023 Mar 1;380:e073149. doi:10.1136/bmj-2022-073149 PubMed PMID: 36854461.

35. Klarin D, Natarajan P. Clinical utility of polygenic risk scores for coronary artery disease. Nat Rev Cardiol. 2022 May;19(5):291–301. doi:10.1038/s41569-021-00638-w PubMed PMID: 34811547; PubMed Central PMCID: PMC10150334.

36. Ikeda M, Saito T, Kanazawa T, Iwata N. Polygenic risk score as clinical utility in psychiatry: a clinical viewpoint. J Hum Genet. 2021;66(1):53–60. Located at: Scopus. doi:10.1038/s10038-020-0814-y

37. Pinzon-Espinosa J, van der Horst M, Zinkstok J, Austin J, Aalfs C, Batalla A, et al. Barriers to genetic testing in clinical psychiatry and ways to overcome them: from clinicians' attitudes to sociocultural differences between patients across the globe. Transl PSYCHIATRY. 2022 Oct 11;12(1). Located at: WOS:000866136400002. doi:10.1038/s41398-022-02203-6

38. Ikeda M, Saito T, Kanazawa T, Iwata N. Polygenic risk score as clinical utility in psychiatry: a clinical viewpoint. J Hum Genet. 2021 Jan;66(1):1. doi:10.1038/s10038-020-0814-y

39. Chowdhury S, Dent T, Pashayan N, Hall A, Lyratzopoulos G, Hallowell N, et al. Incorporating genomics into breast and prostate cancer screening: assessing the implications. Genet Med. 2013 Jun;15(6):423–32. doi:10.1038/gim.2012.167 PubMed PMID: 23412607; PubMed Central PMCID: PMC3941015.

40. Fritzsche MC, Akyüz K, Cano Abadía M, McLennan S, Marttinen P, Mayrhofer MTh, et al. Ethical layering in AI-driven polygenic risk scores—New complexities, new challenges. Front Genet [Internet]. 2023 [cited 2023 Aug 15];14. Available from: https://www.frontiersin.org/articles/10.3389/fgene.2023.1098439

41. Rashkin MD, Bowes J, Dunaway K, Dhaliwal J, Loomis E, Riffle S, et al. Genetic counseling, 2030: An on-demand service tailored to the needs of a price conscious,

genetically literate, and busy world. J Genet Couns. 2019;28(2):456–65. doi:10.1002/jgc4.1123

42. Brown JEH, Young JL, Martinez-Martin N. Psychiatric genomics, mental health equity, and intersectionality: A framework for research and practice. Front Psychiatry [Internet]. 2022 [cited 2023 Aug 15];13. Available from: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.1061705

43. Kaplan JM, Fullerton SM. Polygenic risk, population structure and ongoing difficulties with race in human genetics. Philos Trans R Soc B Biol Sci. 2022 Apr 18;377(1852):20200427. doi:10.1098/rstb.2020.0427

44. Martin AR, Kanai M, Kamatani Y, Okada Y, Neale BM, Daly MJ. Clinical use of current polygenic risk scores may exacerbate health disparities. Nat Genet. 2019 Apr;51(4):4. doi:10.1038/s41588-019-0379-x

45. Roberts MC, Khoury MJ, Mensah GA. Perspective: The Clinical Use of Polygenic Risk Scores: Race, Ethnicity, and Health Disparities. Ethn Dis. 2019 Jul 18;29(3):513–6. doi:10.18865/ed.29.3.513

46. Wand H, Kalia SS, Helm BM, Suckiel SA, Brockman D, Vriesen N, et al. Clinical genetic counseling and translation considerations for polygenic scores in personalized risk assessments: A Practice Resource from the National Society of Genetic Counselors. J Genet Couns. 2023;32(3):558–75. doi:10.1002/jgc4.1668

47. Yanes T, McInerney-Leo AM, Law MH, Cummings S. The emerging field of polygenic risk scores and perspective for use in clinical care. Hum Mol Genet. 2020 Oct 20;29(R2):R165–76. doi:10.1093/hmg/ddaa136

48. Araújo DS, Wheeler HE. Genetic and environmental variation impact transferability of polygenic risk scores. Cell Rep Med. 2022 Jul 19;3(7):100687. doi:10.1016/j.xcrm.2022.100687

49. Griffin S. Diabetes precision medicine: plenty of potential, pitfalls and perils but not yet ready for prime time. Diabetologia. 2022 Nov 1;65(11):1913–21. doi:10.1007/s00125-022-05782-7

50. Kaplan JM, Fullerton SM. Polygenic risk, population structure and ongoing difficulties with race in human genetics. Philos Trans R Soc B Biol Sci. 2022 Apr 18;377(1852):20200427. doi:10.1098/rstb.2020.0427

51. Lewis ACF, Green RC. Polygenic risk scores in the clinic: new perspectives needed on familiar ethical issues. Genome Med. 2021 Jan 28;13(1):14. doi:10.1186/s13073-021-00829-7 PubMed PMID: 33509269; PubMed Central PMCID: PMC7844961.

52. Knoppers BM, Bernier A, Granados Moreno P, Pashayan N. Of Screening, Stratification, and Scores. J Pers Med. 2021 Jul 28;11(8). doi:10.3390/jpm11080736 PubMed PMID: 34442379; PubMed Central PMCID: PMC8398020.

53. Lanchbury JS, Pederson HJ. An apparent quandary: adoption of polygenics and gene panels for personalised breast cancer risk stratification. BJC Rep. 2023 Sep 18;1(1):1. doi:10.1038/s44276-023-00014-w

54. Mars N, Lindbohm JV, Parolo P della B, Widen E, Kaprio J, Palotie A, et al. Systematic comparison of family history and polygenic risk across 24 common diseases. Am J Hum Genet. 2022 Dec 1;109(12):2152–62. doi:10.1016/j.ajhg.2022.10.009

55. Fahed AC, Wang M, Homburger JR, Patel AP, Bick AG, Neben CL, et al. Polygenic background modifies penetrance of monogenic variants for tier 1 genomic conditions. Nat Commun. 2020 Aug 20;11:3635. doi:10.1038/s41467-020-17374-3 PubMed PMID: 32820175; PubMed Central PMCID: PMC7441381.

56. Yanes T, Young MA, Meiser B, James PA. Clinical applications of polygenic breast cancer risk: a critical review and perspectives of an emerging field. BREAST CANCER Res. 2020 Feb 17;22(1). doi:10.1186/s13058-020-01260-3

57. Lu T, Zhou S, Wu H, Forgetta V, Greenwood CMT, Richards JB. Individuals with common diseases but with a low polygenic risk score could be prioritized for rare variant screening. Genet Med. 2021 Mar 1;23(3):508–15. doi:10.1038/s41436-020-01007-7

58. Bedrosian I, Somerfield MR, Achatz MI, Boughey JC, Curigliano G, Friedman S, et al. Germline Testing in Patients With Breast Cancer: ASCO–Society of Surgical Oncology Guideline. J Clin Oncol. 2024 Jan 4;JCO.23.02225. doi:10.1200/JCO.23.02225

59. Sowmiya Moorthie, Chantal Babb de Villiers, Tanya Brigden, Louise Gaynor L, Alison Hall, Emma Johnson, et al. Polygenic scores, risk and cardiovascular disease. PHG Foundation; 2019. Report No.

60. Lewis ACF, Perez EF, Prince AER, Flaxman HR, Gomez L, Brockman DG, et al. Patient and provider perspectives on polygenic risk scores: implications for clinical reporting and utilization. Genome Med. 2022 Oct 7;14(1):114. doi:10.1186/s13073-022-01117-8 PubMed PMID: 36207733; PubMed Central PMCID: PMC9540716.

61. Bafligil C, Thompson DJ, Lophatananon A, Ryan NAJ, Smith MJ, Dennis J, et al. Development and evaluation of polygenic risk scores for prediction of endometrial cancer risk in European women. Genet Med. 2022;24(9):1847–56. Located at: Scopus. doi:10.1016/j.gim.2022.05.014

62. Rothstein MA. Reconsidering the duty to warn genetically at-risk relatives. Genet Med Off J Am Coll Med Genet. 2018 Mar;20(3):285–90. doi:10.1038/gim.2017.257 PubMed PMID: 29388945.

63. 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. Clin Genet. 2006;70(5):374–81. doi:10.1111/j.1399-0004.2006.00692.x

64. Moore AM, Richer J. Genetic testing and screening in children. Paediatr Child Health. 2022 Jul 18;27(4):243–7. doi:10.1093/pch/pxac028 PubMed PMID: 35859684; PubMed Central PMCID: PMC9291346.

65. Sharif Nia H, Sivarajan-Froelicher E, Haghdoost AA, Moosazadeh M, Huak-Chan Y, Farsavian AA, et al. The estimate of average age at the onset of acute myocardial infarction in Iran: A systematic review and meta-analysis study. ARYA Atheroscler. 2018 Sep;14(5):225–32. doi:10.22122/arya.v14i5.1739 PubMed PMID: 30783413; PubMed Central PMCID: PMC6368197.

66. Isgut M, Sun J, Quyyumi AA, Gibson G. Highly elevated polygenic risk scores are better predictors of myocardial infarction risk early in life than later. Genome Med. 2021 Jan 28;13(1):13. doi:10.1186/s13073-021-00828-8 PubMed PMID: 33509272; PubMed Central PMCID: PMC7845089.

67. Terek S, Del Rosario MC, Hain HS, Connolly JJ, Behr MA, Harr M, et al. Attitudes among Parents towards Return of Disease-Related Polygenic Risk Scores (PRS) for Their Children. J Pers Med. 2022 Dec;12(12):12. doi:10.3390/jpm12121945

68. Newson AJ. The promise of public health ethics for precision medicine: the case of newborn preventive genomic sequencing. Hum Genet. 2022;141(5):1035–43. Located at: Scopus. doi:10.1007/s00439-021-02269-0

69. Plomin R, von Stumm S. Polygenic scores: prediction versus explanation. Mol Psychiatry. 2022 Jan;27(1):49–52. doi:10.1038/s41380-021-01348-y PubMed PMID: 34686768; PubMed Central PMCID: PMC8960389.

70. Sabatello M, Juengst E. Genomic Essentialism: Its Provenance and Trajectory as an Anticipatory Ethical Concern. Hastings Cent Rep. 2019;49(S1):S10–8. doi:10.1002/hast.1012