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Growing complexity of (expanded) carrier screening: Direct-to-consumer, physician-mediated, and clinic-based offers

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Since the introduction of out-of-hospital health-related genetic tests more than a decade ago, the landscape of genetic testing services has grown in complexity. Although initially most genetic tests for health purposes were offered as direct-to-consumer services, that is, without the mediation of a medical professional, currently many commercial providers require that their tests be ordered by a licensed physician. At the same time, some commercially developed health-related genetic tests are gaining support from the professional medical community and are finding their way into clinical practice. Therefore, we differentiated between three types of genetic testing offers: direct-to-consumer, physician-mediated, and clinic-based genetic testing. Expanded carrier screening tests for recessive disorders are currently available through all the three models of genetic testing. Herein, we review the present landscape of expanded carrier screening offers by highlighting the distinct issues associated with each of the three types of genetic testing.

Introduction

Following the emergence of next-generation sequencing technologies in the mid-2000s, it has become possible to perform an increasing number of medical genetic tests in a faster, cheaper, and more accurate manner [1]. Although technological progress has significantly accelerated the use of genetic tests in the clinical setting, it has also facilitated the growing availability of genetic tests even

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Table 1
Three models of genetic testing offers.

Model of genetic testing	Key characteristics
Direct-to-consumer genetic testing (DTCGT)	* The provider of the test is a commercial company operating outside the healthcare setting * The test can be ordered online directly by the consumer (i.e., without mediation of a physician)
Physician-mediated genetic testing (PMGT)	* The provider of the test is a commercial company operating outside the healthcare setting * The test must be ordered by a licensed healthcare professional on behalf of a consumer
Clinic-based genetic testing (CBGT)	* The provider of the genetic testing service is a medical institution such as a general hospital or a specialized clinic * The test is integrated into the clinical care

outside the clinic. More than a decade ago, some commercial companies started offering health-related genetic tests through the Internet, typically without any medical supervision or the involvement of a certified healthcare professional. This practice has been traditionally referred to as direct-to-consumer genetic testing (DTCGT) [2,3], emphasizing the absence of medical professionals in the testing process. However, in the subsequent years, many commercial providers of genetic testing services have revised their business model and now require that their health-related genetic tests are ordered by a medical professional, although still advertising products directly to consumers [3,4]. At the same time, some established healthcare providers, such as specialized medical clinics and hospitals, have also started offering some of the genetic tests that were previously only available outside the healthcare setting. In recognition of this growing heterogeneity of the genetic testing market, we have delineated three models of the provision of genetic tests (Table 1).

Direct-to-consumer genetic testing

We use the term DTCGT to describe commercial genetic testing offers that are entirely organized outside the healthcare setting. In this approach, commercial providers of genetic tests advertise their products through the Internet directly to consumers, who can order the test online and have a sample collection kit delivered at home [5]. Traditionally, proponents of this model have pointed out that DTCGT empowers individuals by increasing their access to personal genomic information [6]. However, DTCGT has been received with vigorous criticism from both academics and professional medical organizations. It has been emphasized that although most DTCGT services lacked demonstrable analytic and/or clinical validity,[1] marketing campaigns of genetic testing companies would present these tests in an overwhelmingly positive light. Consequently, concerns have been raised that not only were consumers misinformed about the limited predictive power of commercial genetic tests but they could also be at risk of harm if inaccurate test results were to be used to inform health decisions [2,3,8,9]. These concerns have resulted in considerable regulatory scrutiny of DTCGT practices. For example, in the US, the Food and Drug Administration (FDA) has taken an active role in regulating the genetic testing industry and, beginning in 2010, issued warning letters to various DTCGT companies, instructing them to stop marketing health-related genetic testing services directly to consumers [4]. Moreover, in November 2013, in a widely publicized case, the FDA sent a warning letter to *23andMe*, one of the most well-known companies in the genetic testing industry, instructing it to discontinue the marketing of its health-related genetic test [6,10]. (The FDA subsequently softened its decision, permitting *23andMe* to market a direct-to-consumer genetic test for carrier status in February 2015 [11]). In Europe, genetic testing without medical supervision is prohibited by national legislation in several countries, such as France, Portugal, and Switzerland [12]. Although the European parliament proposed to limit genetic testing to a prescription-only intervention, the new in vitro diagnostic medical device directive in the European Union did not adopt this proposal.

[1] Analytic validity refers to the accuracy with which the test can identify a particular genetic variant. Clinical validity is defined as the accuracy with which the test can predict clinical outcomes [7].

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Physician-mediated genetic testing

Owing partly to legal challenges associated with the marketing of DTCGT services, many commercial providers have transitioned to a new model of commercial genetic testing. In this model, although genetic tests are still advertised through the Internet, they cannot be ordered directly by the consumer and must instead be requisitioned by a licensed healthcare professional [4]. We refer to this model as physician-mediated genetic testing (PMGT). In principle, PMGT has the potential to resolve some of the ethical issues inherent to DTCGT by involving a medical professional who can guide the consumers through the testing process and assist them in interpreting test results. However, in practice, many medical professionals may lack adequate training in genetics and may be ill prepared to support patients undergoing genetic testing [13,14]. Moreover, the PMGT model could give rise to conflicts of interest as commercial companies may approach medical professionals and offer them gratuities, for example, in the form of specialized training in genetics or commissions for patient referrals [4,15]. Medical professionals who receive such benefits are more likely to prescribe commercial genetic tests when confronted with a request without critically assessing its adequacy or may actively recommend a genetic test to their patients, even where limited benefits are anticipated. In the most ethically problematic scenario, a healthcare professional may be hired by a commercial company to simply "sign off" on orders without ever seeing the patient [4]. Finally, intermediation by a medical professional, even when they are comfortable with interpreting genetic information and have no conflict of interest, does not address the issue of analytical validity and clinical validity of the test [14,15]. However, commercial companies typically do not disclose this information on their websites, making analytic and clinical validity difficult to assess prior to testing [16].

Clinic-based genetic testing

Some of the practical issues inherent to the PMGT model can be partly mitigated by integrating genetic testing services into clinical practice. In this clinic-based genetic testing (CBGT) approach, providers of genetic testing services may collaborate with medical institutions that will routinely offer testing in the clinical context. The principal advantage of CBGT, compared to the other models of genetic testing, is that in CBGT, testing is embedded in the context of clinical care and can be routinely supported by ancillary services, such as genetic counseling and, where necessary, specialized follow-up care. However, adoption of genetic testing services by a large number of medical clinics may only be possible where a genetic test has already gained substantial support among the professional medical community. An example of such a process is noninvasive prenatal testing (NIPT) for chromosomal abnormalities. The first commercial NIPT was made available in 2011 and, within the next 3 years, was adopted by a growing number of medical clinics in most developed countries [17]. NIPT is in many ways superior to invasive chromosomal aneuploidy screening, and it is exclusively provided in the CBGT model where pregnant women have access to individualized medical supervision. However, in the absence of a standardized approach, the quality and clinical characteristics of NIPT vary across laboratories. Because most laboratories performing NIPT are operated by commercial companies, there are reports of healthcare professionals being rewarded by test providers for patient referrals [18]. This suggests that CBGT may not be completely immune to some of the flaws of the PMGT model.

One type of health-related genetic testing that is currently available in all three models is carrier screening for recessive disorders. Therefore, in the remainder of the paper, we focus on reviewing the present landscape of carrier screening offers to better illustrate the distinct ethical and legal challenges of providing particular tests through the three models.

Carrier screening for recessive genetic disorders

Carrier screening is performed for reproductive purposes to identify healthy individuals who are at risk of having a child affected with a recessive genetic disorder. Such individuals, commonly referred to as carriers, have one mutated copy of the gene associated with the disorder and one normal copy. This is sufficient for the gene to remain functional, and carriers of recessive disorders are typically asymptomatic. However, there is a 25% risk of conceiving an affected child if both members of a

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reproductive couple are carriers of the same autosomal recessive disorder or if the female member is the carrier of an X-linked disorder [19]. Because of the recessive pattern of inheritance, most at-risk couples have no family history for the disorder and are thus unaware of their carrier status [20,21]. Therefore, it has been common for carrier couples to learn about their reproductive risks retrospectively after giving birth to a child with the disorder [22]. Carrier screening can benefit such couples by prospectively identifying their reproductive risks and providing them with actionable information. In addition, carrier screening offers the greatest benefits if performed preconceptionally as nonpregnant carrier couples can choose among multiple reproductive options including foregoing spontaneous pregnancy and instead opting for artificial reproduction with preimplantation genetic diagnosis or by using donor gametes or adopting a child. When performed during pregnancy, the options are limited to undergoing prenatal diagnosis, possibly followed by pregnancy termination if the fetus is found to be affected. Alternatively, some carrier couples may choose to accept their reproductive risks and pursue natural pregnancy or decide to carry an affected pregnancy to term [15,23].

Because of technical constraints and cost considerations, carrier screening tests have historically been limited to a small number of recessive disorders mostly occurring within specific ethnic groups. Continuous advances in molecular genetics resulted in the emergence of expanded carrier screening (ECS) toward the end of the 2000s [23,24]. ECS refers to the process where a large number of recessive disorders are screened for simultaneously in a single diagnostic assay [25]. ECS tests typically use next-generation sequencing technologies and may screen for anywhere between a few dozen to more than a thousand recessive disorders.

ECS represents a considerable improvement in carrier screening technology, facilitating the identification of a greater number of carriers in the general population, regardless of ethnicity [26]. This has been recognized by professional membership organizations both in the US and Europe, which have welcomed the emergence of ECS and issued detailed recommendations for its implementation in reproductive healthcare [27,28]. Despite these efforts, ECS is not yet systematically implemented in the healthcare setting, and currently, most ECS tests are offered in the form of commercial genetic testing.

An overview of the genetic testing market for expanded carrier screening

In 2010, the health technology company *Counsyl* reported the development of a “universal carrier test” that screened for more than 100 recessive disorders [29], effectively launching the market for ECS. *Counsyl*'s test was first made available to consumers through the company's website in February 2010, primarily as a DTCGT service. At the time, *Counsyl*'s website read, “You can order the test directly from our website to receive your kit immediately. Everyone has a prescription: the American College of Medical Genetics recommends that adults of reproductive age be offered carrier testing for cystic fibrosis and spinal muscular atrophy, two of the many conditions assayed by the [Test]. Alternatively, you may get the test through your doctor.” [3] However, in May 2010, *Counsyl* discontinued its DTCGT offer, retaining PMGT as the primary model of provision [15]. At the same time, *Counsyl* also adopted the CBGT model by beginning to collaborate with specialized medical clinics, such as fertility centers, that would routinely offer the company's ECS test to their patients [30]. Subsequently, several other companies started advertising their own ECS tests, almost all of which have been sold through PMGT and CBGT models. As of late 2016, PMGT and CBGT remain the dominant models of ECS test offers. In reviewing the global landscape of Internet-based ECS offers, we have identified more than 20 providers, including both commercial companies and academic laboratories, the vast majority of which provided their tests through healthcare professionals and/or medical clinics (unpublished data). In contrast, only two companies (*23andMe* and *Macrogen*) used the DTCGT model. Of note, *Macrogen* is a South Korean company whose ECS test cannot be purchased by consumers located in most Western countries. This paucity of DTCGT offers can be explained by adverse regulatory frameworks in Europe and the US. As discussed earlier, several European countries explicitly prohibit genetic testing without medical supervision, which also applies to carrier screening. In the US, carrier screening tests for autosomal recessive disorders (i.e., excluding X-linked disorders) can be marketed directly to consumers. However, any company willing to do so must comply with special additional requirements of the FDA, such as conducting “pre- and post-test user comprehension studies to assess user ability to understand the possible results of a carrier test and their clinical meaning” [31]. These additional

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requirements, along with the FDA's traditionally active supervision of the DTCGT market, may discourage commercial providers to opt for the direct-to-consumer model. From a provider's point of view, another disadvantage of the DTCGT model is the fact that the cost of testing in this approach is typically borne by the consumer alone, whereas genetic tests prescribed by a healthcare professional can be covered by insurance. For example, *23andMe*'s "health + ancestry service," which includes ECS, costs $199.00, the lowest price among all US-based ECS providers [32]. As a comparison, *Counsyl*'s ECS test, called the "Family Prep Screen," costs $349.00. However, because all of *Counsyl*'s tests are ordered by a physician, many consumers are eligible for partial coverage by their health insurance. Because of this, *Counsyl* states on its website that "The majority of our … patients pay less than $199.00 for the Family Prep Screen" [33]. Given the regulatory challenges to obtaining the FDA's approval and the absence of insurance coverage, it is not surprising that DTCGT offers of ECS are rare. To date, *23andMe* is the only provider that has been authorized by the FDA to market its ECS test directly to consumers.

In addition to ECS services offered by commercial genetic testing companies, a growing number of medical institutions are also offering ECS tests using the CBGT model. These are primarily clinics specializing in reproductive healthcare services, such as in vitro fertilization and preimplantation genetic diagnosis. In addition, CBGT providers also include general hospitals and nonprofit community public health initiatives, particularly those organized within the Ashkenazi Jewish community. In general, CBGT providers of ECS do not have proprietary ECS tests and rely on a third party for laboratory services. However, two CBGT providers, *Mount Sinai Health System* (New York, US [34]) and *Academic Medical Center*, in collaboration with *VU University Medical Center Amsterdam* (Amsterdam, the Netherlands [35]), use internally developed bespoke ECS tests in clinical practice.

Clinical characteristics of ECS tests marketed to consumers

Characteristics of consumer ECS tests vary immensely across providers. For example, *23andMe* currently screens for 41 autosomal recessive disorders by using targeted genotyping of known pathogenic variants. In contrast, *Macrogen* screens for more than 1700 recessive conditions, both autosomal and X-linked, using a whole-exome sequencing approach. Other providers fall between these two extreme examples, with most screening for between 100 and 400 autosomal and X-linked recessive disorders. These differences in the characteristics of ECS tests can be explained by the combination of the providers' operating models and the applicable regulatory framework. For example, being an FDA-compliant DTCGT company, *23andMe* must follow the requirements outlined in the Code of Federal Regulations 21CFR866.5940. The scope of this legal document is limited to autosomal recessive disorders, which prevents the inclusion of X-linked conditions in FDA-authorized ECS tests. Furthermore, the document lays out rigid criteria for the clinical validity of carrier screening tests. In particular, it states that "[C]linical validity of each variant detected and reported by the test … must be well-established in peer-reviewed journal articles, authoritative summaries of the literature … or similar summaries of valid scientific evidence, and/or professional society recommendations" [31]. There are two implications of this requirement. First, it effectively forestalls the use of nontargeted sequencing, which may identify mutations previously unreported in the literature. Second, it discourages the inclusion of extremely rare disorders where genetic research is scarce and genotype–phenotype correlations may not be well elucidated. While these restrictions may translate into relatively low carrier detection rates, they also ensure that FDA-approved ECS tests have a very high positive predictive value. In other words, approximately 100% of couples identified as being at risk by these tests will have a one-in-four chance of conceiving an affected child in each pregnancy. In contrast, the use of nontargeted sequencing, particularly of lesser-studied recessive disorder genes, translates into low positive predictive value, meaning that the test will incorrectly identify many couples to be at risk [36]. This is highly problematic as some of these couples will experience undue anxiety or may undergo prenatal diagnosis and selective termination of pregnancy on the basis of false information about the fetus' affected status [37].

Although the majority of commercial providers are based in the US, they do not have FDA authorization, and their ECS tests do not conform to the Code of Federal Regulations 21CFR866.5940. These ECS tests typically use nontargeted sequencing, but they interrogate a relatively limited number of genes (between 100 and 400) associated with recessive disorders. In this way, commercial providers

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strive to achieve greater carrier detection rates without substantially lowering the positive predictive value of the ECS test. However, in the absence of clinical evidence, providers using nontargeted sequencing tend to rely on different criteria when deciding which genes to screen for and how to interpret the test results. Such differences give rise to cases where a particular mutation is reported as pathogenic by one provider, whereas others may regard it as a variant of unknown significance or a benign polymorphism [38]. This highlights the need for better monitoring of the clinical validity of ECS consumer genetic tests in general, rather than focusing solely on the DTCGT model.

Provision of pretest information and genetic counseling

To ensure informed and voluntary participation in screening, it is essential that all consumers undergoing ECS tests receive adequate information about the purpose, potential benefits, and main limitations of the test [27,28,39]. However, in practice, the amount and the quality of pretest information communicated to potential consumers vary greatly among ECS providers. Depending on the operating model adopted by the provider, they can choose different strategies to impart this information. For example, companies in the DTCGT may rely exclusively on using web-based communication, whereas PMGT and CBGT models may additionally incorporate pretest consultation with a medical professional or a geneticist.

In general, it is problematic where the decision to purchase a genetic test is based solely on the information presented on the website of a genetic testing company because such websites tend to emphasize the benefits of testing and downplay its disadvantages [40]. However, in the case of *23andMe*'s ECS service, it is encouraging that the company provides high-quality information to its consumers, such as an extensive description of its test and sample reports for the disorders being screened [41]. Using sample reports may be particularly helpful, as shown by *23andMe*'s study that found more than 90% user comprehension rates of these reports [42]. Furthermore, the company recommends its potential consumers to discuss carrier screening with their healthcare provider and/or a genetic counselor and provides a link to the National Society of Genetic Counselors [41]. However, it is unclear whether consumers purchasing *23andMe*'s carrier screening service actually take time to familiarize themselves with this information or seek a medical consultation if in doubt. What is particularly problematic in the context of providing adequate pretest information is the fact that *23andMe* offers its ECS service in combination with ancestry and health testing, rather than as a standalone test [43]. Research with users of DTCGT services has revealed that some consumers find it difficult to grasp the difference between carrier status and being affected by a disorder [44]. Therefore, it is likely that combining carrier screening with other types of genetic tests in a single service will increase the potential confusion of the customer over the purpose and expected outcomes of carrier screening.

Achieving informed participation in carrier screening also remains a challenge where the test is ordered through a healthcare professional, as in the PMGT model. In particular, where the physician's primary function is to approve consumer orders, involvement of a physician may be little more than a formality. An example of this is *Good Start Genetics'* carrier screening test VeriYou, launched in October 2016 [45]. Although by screening for only two disorders (cystic fibrosis and spinal muscular atrophy) VeriYou should not be considered an ECS test as such, we choose to discuss the product here as VeriYou is one of the few genetic tests to be offered through amazon.com and is accessible to potential consumers through the company's website [46]. This, for all practical purposes, makes VeriYou a DTCGT service. However, consumers do not directly order the test. Instead, they request it online by providing information on the company's website. Consumer requests are then reviewed and approved by *Good Start Genetics'* licensed physician, who orders the test on behalf of the consumer. Although the role of the licensed physician is largely ceremonial, technically this makes VeriYou a PMGT test. Although the case of VeriYou is exceptional in that it has clear characteristics of a DTCGT offer, employing licensed healthcare professionals to validate test orders is not unique to this product, and several other commercial providers of carrier screening services facilitate consumers' access to the test through a healthcare professional employed by the company. One such provider, *Baby Genes*, which offers ECS for 71 autosomal recessive disorders, displays the following information on their website: “All Baby Genes tests are ordered by a physician—either your own or one of ours who will review your information and

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can order testing on your behalf." [47] The possibility of accessing the test through a company-affiliated physician raises the concern that, in practice, the primary function of such a physician may be approving test orders, rather than addressing the pretest information needs of potential consumers. Involvement of a healthcare professional could be viewed as the company's strategy to avoid being subjected to rigorous regulatory supervision while, for all practical purposes, selling testing services through the DTCGT model [4]. In addition, in PMGT, some potential consumers may choose to address their own healthcare provider for ordering a commercial ECS test. Although these healthcare providers are less likely to have a conflict of interest, many of them may not be prepared to offer qualified advice regarding ECS to their patients. For example, one study in the US found that more than one-third of reproductive healthcare professionals did not know the probability of passing down a recessive disease allele to one's offspring and more than 40% could not accurately estimate the likelihood of having an affected child when both parents are carriers [48]. Advising patients on the appropriateness of ECS will require an in-depth understanding of medical genetics on the part of healthcare providers. Where this knowledge is lacking, ordering an ECS test through a healthcare professional is unlikely to improve informed decision-making among consumers.

Embedding ECS in the clinical setting, in accordance with the CBGT model, may be the most effective strategy to enhance potential consumers' understanding of the testing process. This is primarily because CBGT typically entails a pretest consultation with a geneticist or a medical professional with expertise in clinical genetics. However, the extent to which such a consultation is unbiased will depend on whether the medical professional has an incentive to encourage their patients to take the test. As suggested by the experience with NIPT, conflicts of interest among practicing clinicians are not uncommon [18], which has to be considered when implementing ECS through the CBGT model.

Reporting of results and post-test counseling

Similar to other aspects of ECS, practices regarding the reporting of results and/or post-test genetic counseling vary considerably across ECS providers. For example, *23andMe* sends individual written reports to its consumers without post-test genetic counseling. These reports are limited to describing heterozygosity for autosomal recessive disorders screened for by the *23andMe*'s panel. Given the >90% comprehension rate of *23andMe*'s test reports among consumers [42], their strategy of issuing written reports, without face-to-face genetic counseling, may be sufficient for communicating results in most cases. However, this may prove inadequate for informing at-risk couples, where post-test genetic counseling is strongly recommended to assist them in reproductive decision-making [27,28]. As *23andMe* offers its ECS test to individuals, it may be challenging to ensure that all carrier couples are appropriately followed up and receive post-test genetic counseling. This concern is also present in the PMGT model, where all companies make their tests available to individual consumers. However, some commercial providers, such as *Counsyl* and *Natera*, offer complimentary post-test genetic counseling services to all individual consumers (unpublished data). Although these services are discretionary and, typically, should be explicitly requested by the consumer, their availability nevertheless makes it more likely that at-risk couples receive adequate counseling and follow-up. In the context of CBGT, because post-test genetic counseling is fully integrated into the clinical practice of medical clinics offering ECS, at-risk couples routinely receive in-person counseling and follow-up (unpublished data).

In addition to different approaches to post-test counseling, ECS providers also differ in terms of reporting information to their consumers. For example, *23andMe*'s carrier screening reports exclude information relevant to the screened individual's own health that may be incidentally identified in the process of screening. The test does not report if the individual has two pathogenic variants associated with the same disorder and are, therefore, likely to be affected themselves [49]. This is typically not the case with other ECS providers that are not subject to the same regulation as *23andMe,* and they typically communicate incidentally identified health-related information to consumers. However, such providers usually allow consumers to opt out of receiving health-related data (unpublished data). Those ECS providers that use nontargeted sequencing and in-house variant interpretation approaches typically limit the reporting of results to the variants categorized as clearly or likely pathogenic. However, some providers may also report variants of unknown significance (VUS) under certain circumstances. For example, *Baby Genes* communicates the findings of "VUS that result in

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nonsynonymous protein changes with no known clinical association" [50]. These discrepancies across providers indicate the need for using harmonized criteria for interpreting and reporting variants.

Discussion

ECS is becoming widely available in reproductive medicine, with authors estimating that more than 200 000 ECS tests were performed in 2015 in the US alone [51]. At the same time, the current landscape of ECS is highly fragmented, with ECS tests being available through all three models of genetic testing: DTCGT, PMGT, and CBGT.

Since February 2015, DTCGT offers of carrier screening for autosomal recessive disorders in the US are regulated by the Code of Federal Regulations 21CFR866.5940. This new regulation of direct-to-consumer carrier tests aims at maximizing the positive predictive value of the test, improving the quality of information on the website of the provider, and ensuring comprehensibility of test reports sent to consumers. Although the regulation can be seen as restrictive in that it limits the screening of autosomal recessive disorders and only allows targeted genotyping, it effectively addressed some of the main challenges traditionally associated with DTCGT. As such, the Code of Federal Regulations 21CFR866.5940 offers an illustrative example of how specific regulation can be designed to govern the provision of a particular DTCGT service.

On the basis of our review of Internet-based ECS offers, we conclude that the PMGT model appears to be the most problematic approach for several reasons. First, in the context of PMGT, the involvement of a licensed healthcare professional can be a mere formality, where the role of the physician is limited to approving consumers' requests. Second, because some physician-ordered genetic tests are often subject to partial health insurance coverage and may involve low out-of-pocket costs, a concern would be that some PMGT providers might charge higher fees for their services, even though the reliability of their ECS tests may not necessarily be higher. Third, PMGT may lead to situations where a consumer chooses to order a commercial ECS through their healthcare professional, who is poorly prepared to handle such requests and guide the patient through the testing process. Under these circumstances, involvement of a healthcare professional is unlikely to result in improved patient outcomes. Fourth, PMGT offers of ECS, in practice, are not subject to specific regulation, such as the FDA's 21CFR866.5940. This results in widely varying ECS panels and/or variant interpretation methodologies across PMGT providers. As a consequence, it is not uncommon for a particular mutation in a recessive disease gene to be reported as a pathogenic variant by some providers while being considered as a variant of unknown significance by others [38]. Given these challenges, more regulation may be required in physician-ordered genetic tests.

In addition, the CBGT model is considered superior to other models of genetic testing in terms of providing high-quality care and individualized medical supervision. Presently, a substantial share of CBGT offers of ECS take place in the context of fertility treatment [52]. In addition, some providers are general hospitals [34,35] and nonprofit community health initiatives [53]. However, similar to PMGT offers, ECS tests used in the context CBGT differ in terms of their clinical characteristics. A more standardized approach may be necessary to ensure that all patients undergoing clinic-based ECS receive equally high-quality services. Moreover, some conflicts of interest may be present in the CBGT model if a medical clinic stands to gain from selling an additional test item. Finally, the CBGT model raises concerns over equal access to ECS: a recent US-based survey of at-risk couples who had accessed ECS primarily in the clinical context showed that more than 70% of these couples were college-educated and 60% had annual household incomes in excess of $100 000 [52]. To achieve more equal access to testing, implementation of ECS in the context of public health may be necessary.

Summary

Since the emergence of commercial genetic tests for health purposes, the genetic testing industry has undergone significant changes, resulting in an increasingly heterogeneous landscape of genetic tests. In recognition of this heterogeneity, we have delineated three models of genetic testing: direct-to-consumer genetic testing (DTCGT), physician-mediated genetic testing (PMGT), and clinic-based genetic testing (CBGT). Expanded carrier screening (ECS), which is gaining the acceptance of the professional medical

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community, is currently available through all the three models of genetic testing. In our review, we found that ECS services differ widely among providers in terms of their clinical characteristics, pretest information, and post-test counseling practices. Some of these differences can be attributed to the model through which the ECS test is provided. Although all the three models are characterized by distinct challenges, we found that in practice, ECS offers through the PMGT model appear to be the most problematic, thus warranting greater regulatory scrutiny into this kind of testing offers.

Practice points

- As evidenced by ECS, innovation by out-of-hospital commercial companies may lead to the emergence of a medically recommended genetic test.
- The FDA's new regulation (21CFR866.5940) illustrates how devising test-specific regulation has the potential to improve the quality of DTCGT services.
- ECS tests offered through the PMGT model are the most problematic, and their provision requires a greater regulatory scrutiny
- Efforts are required to reduce differences in the quality of ECS tests among PMGT and CBGT providers.
- Public health authorities should consider implementing ECS in the healthcare setting

Research agenda

- Clinical validity of ECS tests (panel composition, variant interpretation)
- Utility of ECS in the out-of-hospital setting as opposed to clinic-based ECS
- Effectiveness of institutional regulation of genetic testing providers
- Strengths and weaknesses of DTCGT, PMGT, and CBGT models based on a genetic test other than carrier screening

Conflict of interest

The authors have no conflict of interest to declare.

References

[1] Schuster SC. Next-generation sequencing transforms today's biology. Nat Methods 2008;5:16–8.
[2] Caulfield T, Ries NM, Ray PN, et al. Direct-to-consumer genetic testing: good, bad or benign? Clin Genet 2010;77:101–5.
[3] Borry P, Cornel MC, Howard HC. Where are you going, where have you been: a recent history of the direct-to-consumer genetic testing market. J Community Genet 2010;1:101–6.
[4] Howard HC, Borry P. Is there a doctor in the house?: the presence of physicians in the direct-to-consumer genetic testing context. J Community Genet 2012;3:105–12.
[5] van der Wouden CH, Carere DA, Maitland-van der Zee AH, et al. Consumer perceptions of interactions with primary care providers after direct-to-consumer personal genomic testing. Ann Intern Med 2016;164:513–22.
*[6] Annas GJ, Elias S. 23andMe and the FDA. N Engl J Med 2014;370:985–8.
[7] Burke W, Atkins D, Gwinn M, et al. Genetic test evaluation: information needs of clinicians, policy makers, and the public. Am J Epidemiol 2002;156:311–8.
[8] Janssens AC, Gwinn M, Bradley LA, et al. A critical appraisal of the scientific basis of commercial genomic profiles used to assess health risks and personalize health interventions. Am J Hum Genet 2008;82:593–9.
[9] Borry P, Genetics ESH. Statement of the ESHG on direct-to-consumer genetic testing for health-related purposes European Society of Human Genetics. Eur J Hum Genet 2010;18:1271–3.
[10] The United States Food and Drug Administration. FDA to 23andMe, Inc.. 2013. Available at: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm376296.htm [Last accessed 30 November 2016].
[11] Stoekle HC, Mamzer-Bruneel MF, Vogt G, et al. 23andMe: a new two-sided data-banking market model. BMC Med Ethics 2016;17:19.
*[12] Borry P, van Hellemondt RE, Sprumont D, et al. Legislation on direct-to-consumer genetic testing in seven European countries. Eur J Hum Genet 2012;20:715–21.
[13] Selkirk CG, Weissman SM, Anderson A, et al. Physicians' preparedness for integration of genomic and pharmacogenetic testing into practice within a major healthcare system. Genet Test Mol Biomarkers 2013;17:219–25.

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[14] McGowan ML, Fishman JR, Settersten Jr RA, et al. Gatekeepers or intermediaries? The role of clinicians in commercial genomic testing. PLoS One 2014;9:e108484.
*[15] Borry P, Henneman L, Lakeman P, et al. Preconceptional genetic carrier testing and the commercial offer directly-to-consumers. Hum Reprod 2011;26:972–7.
[16] Covolo L, Rubinelli S, Ceretti E, et al. Internet-based direct-to-consumer genetic testing: a systematic review. J Med Internet Res 2015;17:e279.
[17] Allyse M, Minear MA, Berson E, et al. Non-invasive prenatal testing: a review of international implementation and challenges. Int J Womens Health 2015;7:113–26.
[18] Minear MA, Lewis C, Pradhan S, et al. Global perspectives on clinical adoption of NIPT. Prenat Diagn 2015;35:959–67.
[19] Metcalfe SA. Carrier screening in preconception consultation in primary care. J Community Genet 2012;3:193–203.
[20] Modell B. Cystic fibrosis screening and community genetics. J Med Genet 1990;27:475–9.
[21] Ropers HH. On the future of genetic risk assessment. J Community Genet 2012;3:229–36.
[22] Cao A. Carrier screening and genetic counselling in beta-thalassemia. Int J Hematol 2002;76(Suppl. 2):105–13.
*[23] Nazareth SB, Lazarin GA, Goldberg JD. Changing trends in carrier screening for genetic disease in the United States. Prenat Diagn 2015.
[24] Bell CJ, Dinwiddie DL, Miller NA, et al. Carrier testing for severe childhood recessive diseases by next-generation sequencing. Sci Transl Med 2011;3:65ra4.
[25] McGowan ML, Cho D, Sharp RR. The changing landscape of carrier screening: expanding technology and options? Health Matrix 2013;23:15–33.
[26] Lazarin GA, Haque IS, Nazareth S, 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;15:178–86.
*[27] Henneman L, Borry P, Chokoshvili D, et al. Responsible implementation of expanded carrier screening. Eur J Hum Genet 2016.
*[28] Edwards JG, Feldman G, Goldberg J, 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;125:653–62.
*[29] Srinivasan BS, Evans EA, Flannick J, et al. A universal carrier test for the long tail of Mendelian disease. Reprod Biomed Online 2010;21:537–51.
[30] Higgins A, Flanagan J, Von Wald T, et al. An expanded carrier screening tool enhances preconception cystic fibrosis screening in infertile couples. Open J Obstet Gynecol 2015;5:412.
*[31] The United States Food and Drug Administration. Autosomal recessive carrier screening gene mutation detection system. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=866.5940. [Last accessed 30 November 2016].
[32] 23andme. Available at: https://www.23andme.com/. [Last accessed 8 December 2016].
[33] Counsyl. Patient billing guide. Available at: https://www.counsyl.com/price/preorder/. [Last accessed 30 November 2016].
[34] Mount Sinai Health System. NextStep Carrier Screening test. Available at: http://nextsteptest.com/. [Last accessed 30 November 2016].
[35] Academisch Medisch Centrum, VU Medisch Centrum. Dragerschapstest. Available at: https://www.dragerschapstest.nl/ [in Dutch]. [Last accessed 30 November 2016].
[36] Gambin T, Jhangiani SN, Below JE, et al. Secondary findings and carrier test frequencies in a large multiethnic sample. Genome Med 2015;7:54.
[37] Chokoshvili D, Janssens S, Vears D, et al. Designing expanded carrier screening panels: results of a qualitative study with European geneticists. Per Med 2016;13:553–62.
[38] Heger M. Carrier screening firms question methods of study that finds their assays deficient. Genomeweb; 2016. Available at: https://www.genomeweb.com/sequencing-technology/carrier-screening-firms-question-methods-study-finds-their-assays-deficient [Last accessed 30 November 2016].
[39] Grody WW, Thompson BH, Gregg AR, et al. ACMG position statement on prenatal/preconception expanded carrier screening. Genet Med 2013;15:482–3.
*[40] Singleton A, Erby LH, Foisie KV, et al. Informed choice in direct-to-consumer genetic testing (DTCGT) websites: a content analysis of benefits, risks, and limitations. J Genet Couns 2012;21:433–9.
[41] 23andme. 23andMe Carrier Status Tests: What you should know. Available at: https://www.23andme.com/carrierstatus-fda/. [Last accessed 8 December 2016].
[42] The United States Food and Drug Administration. Evaluation of automatic class III designation for the 23andMe personal genome service carrier screening test for bloom syndrome. Available at: http://www.accessdata.fda.gov/cdrh_docs/reviews/DEN140044.pdf; 2015 [Last accessed 30 November 2016].
[43] 23andme. Discover what your 23 pairs of chromosomes say about you. Available at: https://www.23andme.com/dna-health-ancestry/. [Last accessed 8 December 2016].
[44] Ostergren JE, Gornick MC, Carere DA, et al. How well do customers of direct-to-consumer personal genomic testing services comprehend genetic test results? Findings from the impact of personal genomics study. Public Health Genom 2015;18:216–24.
[45] Good Start Genetics. Good Start Genetics Announces New Tier of Offerings Making Genetic Testing More Accessible for Couples Planning a Family. Available at: https://www.goodstartgenetics.com/wp-content/uploads/VeriYou-October-13. [Last accessed 21 December 2016].
[46] Amazon.com. VeriYou. Available at: https://www.amazon.com/VeriYou-Pre-Pregnancy-Testing-Fibrosis-Muscular/dp/B01JUOY5JI. [Last accessed 21 December 2016].
[47] Baby Genes. Process Flow – Carrier. Available at: https://www.babygenes.net/process-flow-carrier/. [Last accessed 30 November 2016].
[48] Ready K, Haque IS, Srinivasan BS, et al. Knowledge and attitudes regarding expanded genetic carrier screening among women's healthcare providers. Fertil Steril 2012;97:407–13.

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[49] 23andme. Sample report for Bloom Syndrome. Available at: https://permalinks.23andme.com/pdf/sample_report.pdf. [Last accessed 8 December 2016].
[50] Baby Genes. Client Informed Consent for Genetic Testing. Available at: https://www.babygenes.net/wp-content/uploads/BabyGenes_Informed_Consent_20160524.pdf. [Last accessed 30 November 2016].
*[51] Lazarin GA, Haque IS. Expanded carrier screening: a review of early implementation and literature. Semin Perinatol 2016; 40:29–34.
[52] Ghiossi C, Goldberg JD, Haque IS, et al. Clinical utility of expanded carrier screening: reproductive behaviors of at-risk couples. bioRxiv 2016:069393.
[53] JScreen. About JScreen. Available at: jscreen.org/about-jscreen/. [Last accessed 8 December 2016].

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