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SYSTEMATIC REVIEW

REVISED Sharing behavior and health care utilization following direct-to-consumer genetic testing: a systematic review

[version 2; peer review: 1 approved, 2 approved with reservations]

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Abstract

Background

Direct-to-consumer genetic testing (DTC-GT) which provides genetic information directly to the public, has become widely available at a moderate cost. Since DTC-GT companies frequently recommend that consumers consult healthcare professionals for assistance in interpreting and using genetic health risk information, this could potentially have an impact on healthcare systems.

Methods

We performed a systematic review to assess: (1) the sharing behavior of actual DTC-GT consumers, (2) experiences of healthcare professionals regarding DTC-GT consumers sharing their test results and (3) healthcare utilization following DTC-GT, with a particular focus on validation of DTC-GT results and subsequent clinical actions. Our systematic review was registered in PROSPERO under the registration number CRD42024517079.

Results

Our search identified 40 unique articles eligible for inclusion that were published between 2009 en 2022. The proportion of participants who shared their DTC-GT test results with a health care professional ranged from 1% to 57%. DTC-GT consumers most commonly reported sharing their results with a primary healthcare professional. The

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proportion of health care professionals that had experiences with DTC-consumers sharing their test results ranged from 19% to 76%. The percentage of participants sharing their DTC-GT test with family members ranged from 18% to 98%. More detailed analysis indicated that this was frequently the case with partners, parents, and siblings. Sharing of test results with extended family members occurred less frequently. Several studies reported on instances of DTC-GT result validation and clinical actions performed based on the DTC-GT findings

Conclusion

Conclusion While initial concerns about the impact of DTC-GT on health care systems have not fully materialized, the increasing number of consumers consulting with healthcare professionals underscores the need for preparedness and appropriate policy responses. Future research should prioritize standardizing study methodologies and expanding investigations beyond the U.S. context to better capture the global impact of DTC-GT.

Keywords
Genetic testing, Direct to consumer, Public Health, Prevention, Genomics, Screening, Predictive Testing



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REVISED **Amendments from Version 1**

In response to the reviewers' comments, we have revised the manuscript to improve clarity and more explicitly acknowledge certain limitations, with targeted updates to the Introduction, Results, and Discussion sections of the manuscript. The Introduction has been refined to more accurately capture the full spectrum of health-related direct-to-consumer genetic testing (DTC-GT) evaluated in our review, ensuring that the scope of the study is clearly communicated. In the Results section, we have provided a more detailed account of the quality appraisal. We have also added further explanations for the included figures through footnotes, facilitating a clearer understanding of the presented data. We have also expanded the description of data distribution in the main text, detailing median values, interquartile ranges, and overall ranges to present a more comprehensive and transparent view of the findings. To address concerns raised by reviewers, we have included a dedicated Limitations section. This section acknowledges the absence of MeSH term searches, the limitations inherent to the available data of the primary studies, and the potential for duplication of outcomes across some included studies. By explicitly discussing these aspects, we aim to enhance transparency and provide a more balanced interpretation of the study's findings. Importantly, these revisions do not alter the core results or conclusions of the manuscript. Rather, they serve to improve the precision, clarity, and overall presentation of the work, ensuring that readers can fully appreciate the study's scope, methodology, and implications.

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Introduction

The field of genetic and genomic medicine, considered to hold substantial potential for personalized medicine, is increasingly rapidly evolving. While it initially focused on diagnosing rare monogenic conditions, it has expanded to include risk prediction for more prevalent, complex diseases from primarily focusing on rare monogenic conditions to the prediction of risk for prevalent complex conditions[1,2]. This evolution has also contributed to a wider interest in the use of genetic testing across a variety of contexts, including both clinical and consumer-driven settings. Providing information on predispositions for specific diseases or conditions is seen as a way forward to empower citizens and patients, enabling them to proactively manage their health and potentially prevent the (early) onset of certain conditions[3]. This growing interest in personal genetic risk information has also been capitalized on by private companies, resulting in the rise of direct-to-consumer genetic testing (DTC-GT). The utilization of genetic information to inform lifestyle changes aimed at improving health outcomes, has also captured the attention of private companies. Over the past two decades we have witnessed the emergence of several models to provide genetic testing information directly to the public. Commercial laboratories have been increasingly marketing and selling a wide range of genetic tests online, allowing consumers to purchase them directly without requiring a healthcare professional's involvement or prescription[4]. The online format of DTC-GT quickly gained popularity due to its accessibility and affordability[3,5].

The model of direct-to-consumer genetic testing (DTC-GT) deviates from the traditional provision of genetic testing information, in which a healthcare professional is responsible for ordering, testing, interpreting, and communicating genetic testing results[4,6]. In the DTC-GT model, consumers usually order a test kit online after approving terms of services. Upon receiving a test kit at home, consumers are instructed to produce a saliva sample and to send it to the DTC-GT company for genetic analysis. Once the analysis is complete, test results are directly delivered to the consumer through a personalized online platform or mobile application[7,8].

DTC-GT offerings cover a broad spectrum of services and are generally divided into health-related and non-health-related categories. Non-health-related DTC-GT tests include services such as ancestry testing, paternity testing, and assessments of specific traits (e.g. earwax type). Health-related DTC-GT, on the other hand, encompass various types of testing, including susceptibility testing for polygenic and multifactorial conditions (e.g. cardiovascular disease, type 2 diabetes), carrier screening for autosomal recessive conditions (e.g. cystic fibrosis) and/or X-linked conditions (e.g. Fragile X syndrome) to inform reproductive decision making, and pharmacogenomic tests to provide insights into personal drug responses[9]. Differentiating between health and non-health-related DTC-GT offers can however be complex, particularly with the availability of third-party interpretation services. These services allow consumers to analyze their uninterpreted raw genetic data. As a result, they may also report certain variants and risk scores that fall outside the scope of the DTC-GT test that was originally purchased[3,10,11]. Therefore, these services blur the line between genetic health risk information and non-health-related DTC-GT products, which adds complexity to regulatory efforts[12,13].

DTC-GT offers that provide health information are currently widely available in many countries at a moderate cost[2,5]. As of 2023, 23andMe – a prominent player in the field – has a customer base exceeding 14 million genotyped customers[14]. Surveys in the USA and Australia found that the majority (77% and 65% respectively) of those with experience with genetic testing were consumers of DTC-GT[15,16]. While the exact number of consumers in Europe remains unknown to date, the uptake of DTC-GT is also believed to be substantial[4]. The global DTC-GT market is expected to further grow and to be worth over $4 billion by 2025 because of advances in technology, increased consumer demand and the desire for personalized health management[3,17,18]. The rapid growth of the DTC-GT market has however raised several concerns with regard to the privacy and security of genetic data, as well as the accuracy/validity of the test results[3,19]. The reliability of a positive test or increased risk result after DTC-GT remains limited, as the development of many genetic conditions is also influenced by other factors such as the environment and lifestyle choices. The majority of DTC-GT also do not sequence the entire genome. Instead, they often use SNP-chip genotyping, a method examining the presence or absence of specific variants in the genetic code, including single nucleotide polymorphisms (SNPs) or small insertions or deletions. While

SNP-chip genotyping is effective in detecting common genetic variants, it tends to have a higher error rate when analyzing very rare variants, which can lead to an increased likelihood of false positives[11].

More recently, some commercial companies have also started to offer whole genome or exome sequencing and the return of raw genomic data without interpretation[4,11]. These tests sequence nearly the entire genetic code and identify the genetic variants within it. The capability to predict disease risk through whole genome or exome sequencing data might motivate an increasing number of individuals to explore genomic technologies for personal health risk prediction[20]. Yet even though data obtained from whole genome or exome sequencing can be valuable for understanding rare conditions in specific individuals, there is currently inadequate evidence to prove that expanding this technology to the general population would result in considerable benefits[21,22]. Interpretation of genetic variants is still challenging and largely depends on context[11]. The predictive significance of a "disease-causing variant" is often substantially diminished when identified without the presence of a family history linked to the relevant condition[23]. To date, the scientific understanding of genomic sequencing data remains incomplete, creating uncertainties about the real added value of this extensive information.

Since the emergence of DTC-GT, stakeholders have voiced and debated several potential risks and benefits[1]. A particular concern has been the potential impact of DTC-GT on healthcare systems, particularly in terms of downstream effects, such as an increased demand for specialist consultations and follow-up testing. Since DTC-GT companies frequently recommend that consumers consult healthcare professionals for assistance in interpreting and using genetic health risk information, this could potentially have an impact on healthcare systems. Healthcare professionals have also voiced that they feel obligated to refer patients to specialists or suggest additional screening procedures based on DTC-GT results[24]. A previous systematic literature review by Stewart *et al.* (2018), which covered studies up to January 2017, found that one-third of participants shared their results with at least one healthcare professional, often leading to additional follow-up tests[25]. This review, however, specifically focused on sharing behavior and health care utilization following multiplex genetic testing, excluding tests related to nutrigenetics, pharmacogenetics, sports genetics, as well as those for highly penetrant genes and prenatal or neonatal testing[25]. Furthermore, Stewart *et al.* (2018) focused solely on the sharing behavior of DTC-GT consumers and did not include any findings on the experiences of healthcare professionals regarding DTC-GT consumers sharing their test results[25].

Given the rapid expansion of the DTC-GT market and the increasing diversity of test offers and DTC-GT users, we aim to provide an updated overview based on the current available evidence. Therefore, the goal of this systematic review was to assess: (1) the sharing behavior of actual DTC-GT consumers, (2) experiences of healthcare professionals regarding DTC-GT consumers sharing their test results and (3) healthcare utilization following DTC-GT, with a particular focus on validation of DTC-GT results and subsequent clinical actions.

Methods

This systematic review was registered in PROSPERO under the registration number CRD42024517079.

Design and search strategy

Our review process consisted of three steps. First, we performed a systematic literature search to identify relevant publications in three different databases: Web of Science, PubMed, and EMBASE. No restrictions on the publication date were applied during the initial search. On January 2nd 2024, we made use of the following search string: ("Direct-to-consumer genomics" OR "Direct-to-consumer genetic testing" OR "direct-to-consumer personal genomic testing" OR "personal genetic testing" OR "personal genomics" OR "consumer genomics" OR "personal genomic testing" OR "Direct Access Genetic Testing" OR "personal genetics" OR "Direct-to-consumer genome scanning" OR "Direct-to-Consumer genome wide Profiling"). In a second phase, we consulted references from relevant papers to find any additional publications warranting inclusion (i.e. snowball method). Our review followed PRISMA guidelines for systematic reviews[26]. (see Figure 1) Initially, all records identified were screened based on their title and abstract by two individual researchers (EVS and KD). After the exclusion of non-relevant records, the same two researchers (EVS and KD) independently assessed the full texts of the remaining records. Any disagreements during the selection procedure were discussed until consensus was achieved.

Inclusion and exclusion criteria

Studies were eligible for inclusion if they were published in English and provided empirical research findings. Studies reporting on non-empirical work (e.g. case studies, commentaries, review, books, guidelines, etc.) were excluded. Only studies that evaluated the sharing behavior of DTC-GT consumers after they had received their test results were eligible for inclusion. Actual DTC-GT consumers were defined as individuals who either paid for DTC-GT out of pocket or were offered DTC-GT at a subsidized rate or for free in a research context. Studies that assessed the willingness to share DTC-GT results prior to obtaining the test results or in a hypothetical context (non-actual DTC-GT consumers) were excluded from this review. Likewise, we also excluded studies that reported on health care professionals being asked questions by patients about DTC-GT before undergoing the test. When a single research project was reported in multiple publications (evaluation of sharing behavior at multiple time points), we included the publication that evaluated sharing behavior at the most recent time point. When the data on the desired outcomes were not clearly reported in the article or accessible as supplementary materials, we reached out to the corresponding authors of the articles to inquire about the possibility of obtaining the data of interest.

Data extraction

Data extraction was carried out by KD, KG, AS and checked for consistency by EVS. Any discrepancies were resolved through discussion until a consensus was reached. All data were

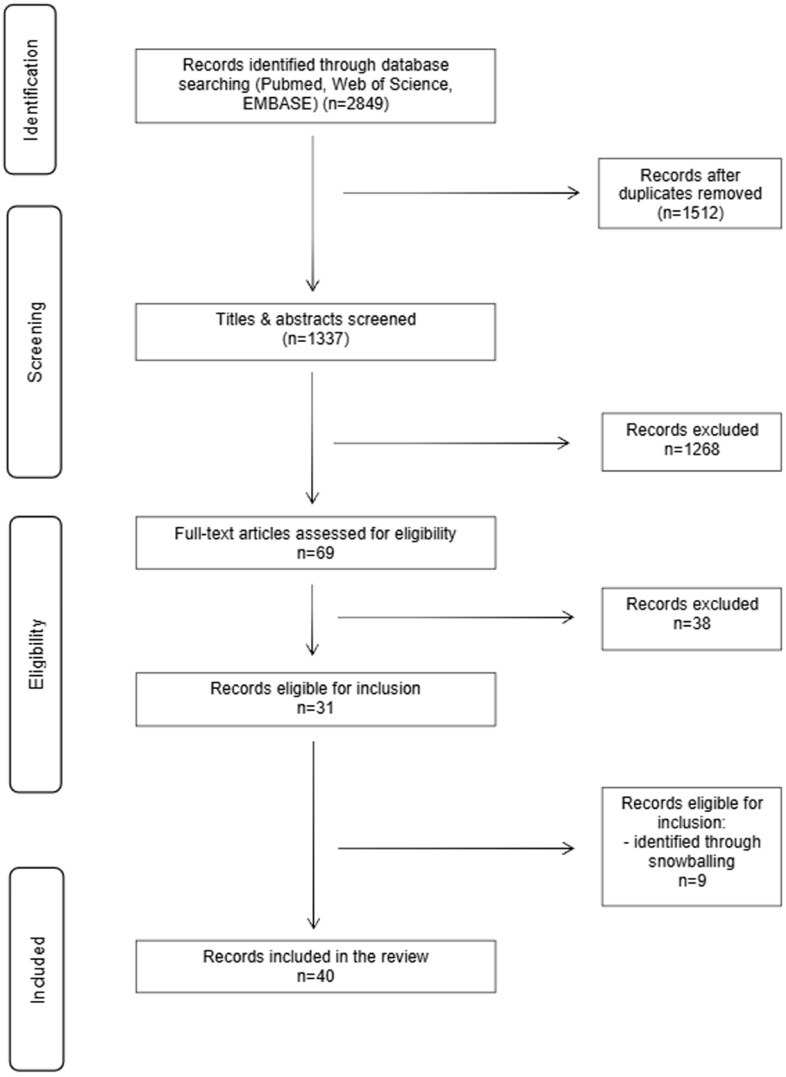

Figure 1. Graphically summarizes the literature search process in accordance with the PRISMA guidelines[26].

extracted by using an extraction form that was created with Excel. In the first round of data extraction, we assessed study characteristics by focusing on the following variables for studies examining the sharing behavior of DTC-GT consumers: first author, year of publication, country of the research team, study name (if applicable), research methods, key demographic characteristics of study participants, information on which DTC-GT product/service participants had used, actual or hypothetical DTC-GT consumers, whether sharing behavior of DTC-GT consumers was assessed before or after receiving test results and whether DTC-GT consumers paid out-of-pocket or were offered DTC-GT at a subsidized rate or for free in a research context. In addition, the following information was sought for those studies that explored the experiences of different health care professionals with DTC-GT consumers sharing their test results: first author, year of publication, country of the research team, research methods, type of health care professionals. In the second phase, we extracted data about the sharing behavior of DTC-GT consumers. For this, we focused on whether DTC-GT consumers shared their test results with health care professionals (including primary care professional; genetic counselor; clinical geneticist, and other healthcare professionals) or family members (such as spouse, parents, siblings, children, and other extended family members). Other healthcare professionals (e.g. oncologist, clinical nurse) were grouped into a single overarching category. Extended family members were defined to include aunts, uncles, cousins or grandparents. Within the studies that explored the experiences of health care professionals with DTC-GT consumers sharing their test results we focused on whether participants had patients sharing DTC-GT with them and the number of patients who brought in results from DTC-GT. In a final stage, we examined

healthcare utilization following DTC-GT. We specifically investigated whether results from DTC-GT were validated through further testing and whether any subsequent clinical actions were performed based on the DTC-GT findings.

Quality appraisal

We performed an indicative quality appraisal of the included primary studies using the tool developed by Hawker *et al.* (2002)[27]. Articles were not excluded from our systematic review based on their methodological quality. The quality appraisal was performed independently by two researchers (KG & AS) and checked for consistency by MS. In case of disagreement, the specific item was discussed until mutual agreement was reached.

Results

I. Search outcomes

Our database search led to the identification of 2849 articles. After the removal of duplicates (n=1512), we proceeded to the screening of 1337 records. Based on the evaluation of titles and abstracts, 1268 records were excluded. Subsequently, 69 full-text articles were assessed for eligibility. Of these, 38 articles were excluded for the following reasons: not reporting empirical findings or outcomes of interest, only reporting hypothetical sharing behavior, publications from a research project that resulted in multiple publications or data on outcomes of interest were not clearly reported and/or available (n=2[15,28]); despite efforts to reach corresponding authors). After consulting the references of the remaining 31 records that were eligible for inclusion, we identified 9 more relevant papers warranting inclusion. In total, 40 unique articles were included for the final analysis.

II. Quality appraisal

The quality appraisal of the included studies conducted using Hawker *et al.*'s (2002) framework, revealed that most articles were of good quality across key domains such as titles and abstracts, introductions, methodology, data analysis, results, and implications. However, recurring limitations emerged in areas related to sampling, ethics, and bias, as well as transferability or generalizability, where many studies were rated only "fair" or occasionally "poor." Despite these weaknesses, all studies were judged to present findings that were useful and relevant to the research questions. The detailed findings of the quality assessment can be found in the supplementary information (see extended data).

III. Study characteristics

A detailed overview of the primary empirical studies included in this systematic review is presented in Tables 1 and 2 (underlying data). The publication range of the 40 unique studies eligible for inclusion dates from 2007 to 2022. The majority (n=28/40)[29–56] of studies assessed the sharing behavior of DTC-GT consumers (see Table 1) (underlying data), while 13 studies[29,57–68] reported on the experiences of health care professionals with DTC-GT consumers sharing their test results (see Table 2 underlying data). Almost 90% of the identified records originated from research projects that were carried out by research teams based in the USA (n=35/40)[15,28–47,49,50,52–55,57–59,61,63,64,66–71]. Most studies used quantitative research methods (n=33/40)[29,30,32–35,37,38,40–47,49,50,52–68], whereas a smaller number used qualitative (n=3/40)[31,36,39] or mixed methods approaches (n=4/40)[48,49,51,68]. Most articles (n=21/28) included study participants who had paid out-of-pocket for their DTC-GT[29,30,33,36,37,40–55]. In contrast, three studies had provided a DTC-GT for free to study participants[31,32,39] and ten had offered a DTC-GT at a subsidized rate as part of a research project[34,35,38,40–42,44–46,56]. Within the studies assessing sharing behavior of DTC-GT consumers, six articles were the result of the 'Impact of Personal Genomics (PGen)' where consumers of two DTC-GT companies (23andMe and Pathway Genomics) based in the USA were surveyed[40–42,44–46] and three articles resulted from the American 'Scripps Genomic Health Initiative (SGHI)', which was a research project where study participants received the Navigenics Health Compass at a subsidized rate[34,35,38]. An overview of key characteristics of study participants from the primary studies included in this review is available as in Table 1 and 2 (Extended data).

IV. Main findings

A. Sharing behavior

Sharing behavior of DTC-GT consumers with health care professionals

A total of 28 studies reported study findings of research projects that had assessed the extent to which DTC-GT consumers shared their genetic test results with healthcare professionals, with the number of participants included in the studies ranging from 20 to 30385 (see Table 3A) (underlying data)[29–56]. The proportion of participants who shared their DTC-GT test results with a health care professional ranged from 1%[32] to 57% (median=30%, IQR=11-41%)[37]. Overall, the rate of sharing appears to have remained relatively stable over the years. Between 2007 and 2011, the sharing rate ranged from 10% to 53%[29,30]. From 2012 to 2016, it fluctuated from 1% to 57%[31–33,37,40–44], and between 2017 and 2022, it ranged from 6% to 45%[45,47–50,53–55]. Among participants who paid out of pocket, the sharing rate ranged from 6% to 57%[29,30,33,37,43,47–50,53–55]. For those who received a subsidized test, the sharing rate was between 19% and 39%[34,35,38,40–42,44–46,56], while participants who received a free test shared their results at a rate ranging from 1% to 42%[31,32,39].

A more detailed analysis of the data on sharing behavior with specific healthcare professionals revealed that DTC-GT consumers most commonly reported sharing their results with a primary healthcare professional, with the proportion ranging from 8% to 78% (median=27%, IQR=20-39%)[33,34,36,38,39,41,44–47,49–51,54,56]. Interestingly, those that received a subsidized or free DTC-GT more often shared their DTC-GT with a primary health care professionals (range 27%–78%)[34,38,39,41,44–46,56] compared to those that paid out of pocket (8–25%)[33,36,47,49–51,54]. To a lesser extent, data were shared with a trained genetic professional (median=2%, IQR=1-3%, range=1-3%))[41,44,45,49] like a genetic counselor (median=4%, IQR=1-14%, range=0.4-19%)[33–36,38,46,47,50,54] or a clinical geneticist (median=5%)[36,50,54]. Participants in the Scripps Genomic Health Initiative, where

genetic counseling was provided at no cost by a Navigenics counselor and proactive outreach was conducted based on their test results, reported a slightly higher frequency of sharing their results with a Navigenics genetic counselor compared to participants in other studies that specifically examined sharing behavior towards trained genetic professionals[34,35,71] (see Table 3A) (underlying data). Finally, some DTC-GT consumers also reported to have shared their DTC-GT results with other health care professionals (e.g. oncologist, nurse practitioner, etc.) (median=16%, IQR=7-17%, range=1-19%)[33,36,41,44–47,49,50,52,54] (see Figure 2).

Motivations behind sharing behavior of DTC-GT consumers

Only a small proportion of the primary studies we identified examined the actual motivations behind DTC-GT consumers' sharing behavior (n=4/28)[31,35,44,47]. In the Scripps Genomic Health Initiative study, participants who were given the opportunity to consult a Navigenics counselor free of charge provided several reasons for utilizing the offered service[35]. These included the desire to take advantage of a free service, seeking additional information on risk calculations, the fact that they were actively contacted by a genetic counselor, seeking guidance on managing their health, the chance to discuss family history, and addressing a perceived lack of understanding regarding their genetic results. On the other hand, those who chose not to utilize the free genetic counseling service often felt they already had a clear understanding of their results and did not perceive a need for further explanation, or they planned to consult with the genetic counselor in the future[35]. Similar patterns were observed in a study by Gordon *et al.* (2012), where some DTC-GT consumers shared their results with their general practitioner in order to gain assistance with the interpretation of their DTC-GT results or to receive advice on how to reduce their risk, while others informed their general practitioner without expecting any follow-up or further testing. Other participants chose not to share their results, as they considered the information to be of limited relevance to their healthcare provider[31]. Another study by van der Wouden *et al.* (2016), reported that while many participants who discussed their DTC-GT results with primary care professionals or other health care professionals cited health improvement as a key motivation, a substantial proportion expressed concerns about the potential inclusion of genetic results in their medical records[44]. Furthermore, 42% of participants did not consider their results important enough to share, while 38% intended to discuss their results with a health care professional but had not yet done so due to time constraints[44]. Finally, in a study by Wang *et al.* (2017), the likelihood of sharing DTC-GT results with medical professionals was influenced by the consumers' reasons for using third-party interpretation services. Health-related motivations to use third-party interpretation services, including concerns about individual and family health, were found to be significantly associated with an increased likelihood of sharing results with healthcare professionals compared to ancestry-related motivations[47].

Experiences of health care professionals with DTC-GT consumers sharing their test results

Our review identified thirteen studies that explored the experiences of healthcare professionals regarding patients who disclosed their DTC-GT results[29,57–68] (see Table 3B) (underlying data). The proportion of health care professionals that had been asked questions about DTC-GT results varied, ranging from 19% to 76%. In a study by Goddard *et al.* (2007) 7% of primary care physicians and pediatricians aware of DTC-GT reported having at least one patient who discussed their DTC-GT results with them[29]. Similar low percentages (3–17%) were observed in other studies conducted between 2010 and 2012[57–61]. In contrast, another study performed by Howard and Borry in 2013 found that 44% of European clinical geneticists (n=54/121) had seen at least one DTC-GT consumer for the sole purpose of reviewing DTC-GT results[62]. Most of these participants had been contacted by one to five patients with DTC-GT results[62]. A more recent American study revealed that 40% of genetic counselors had seen at least one DTC-GT consumer specifically for reviewing results[67]. Likewise, a study assessing physicians' (primary and specialty care) experiences reported that 35% of participants had patients sharing their DTC-GT results within the past year[63]. Another American study, focusing on the experiences of genetic counselors with clinical cancer genetics as primary specialty, reported that 94% of study participants had encountered health-related DTC-GT results, and 69% had reviewed health-related third-party interpretation data[66]. More specifically, these study participants provided counseling for a median of 3 DTC-GT results in the last year[66]. In addition, McGrath *et al.* (2019) reported that 58% of specialists (genetic counselors and clinical geneticists) had experience with patients bringing their DTC-GT results compared to 17% within the group of primary care healthcare professionals surveyed within their study[64] (see Table 3B) (underlying data). Finally, Millward *et al.* (2020) reported that 114 DTC-GT related referrals were received by 11 different Australian genetic services since 2010[65].

Sharing behavior of DTC-GT consumers with family members

Our search also identified twelve studies that assessed to what extent DTC-GT consumers had shared their genetic test results with their family members, with the number of participants ranging from 20 to 29478[32,34,36,37,39,43,47,49,50,54,56,72] (see Table 4) (Underlying data). The percentage of participants sharing their DTC-GT test with family members ranged from 18%[32] to 98% (median=83%, IQR=41–92%)[53]. More detailed analysis indicated that this was frequently the case with partners (median=30%, IQR=16–47%, range=6%-48%)[32,36,43,48,50,54], parents (median=30%, IQR=20–31%, range=20%-31%)[36,50,54], and siblings (18%–35%(mean=20%, IQR=18–35%, range=18%–35%)[36,50,54]. Sharing of test results with extended family members occurred less frequently (mean=3%, IQR=3-29%, range=3%–29%))[36,50,54] (see Figure 3).

B. Health care utilization

Overall, we identified 13 studies assessing healthcare utilization following DTC-GT, with a particular focus on the validation of DTC-GT results and subsequent clinical actions. An early study by Powel *et al.* (2012) found that four out of five primary care physicians who encountered patients bringing in DTC-GT results did not alter their patient's medical management[61]. However, other studies did report on several instances of DTC-GT result validation and clinical actions performed based on the DTC-GT findings. Krieger *et al.* (2016) reported

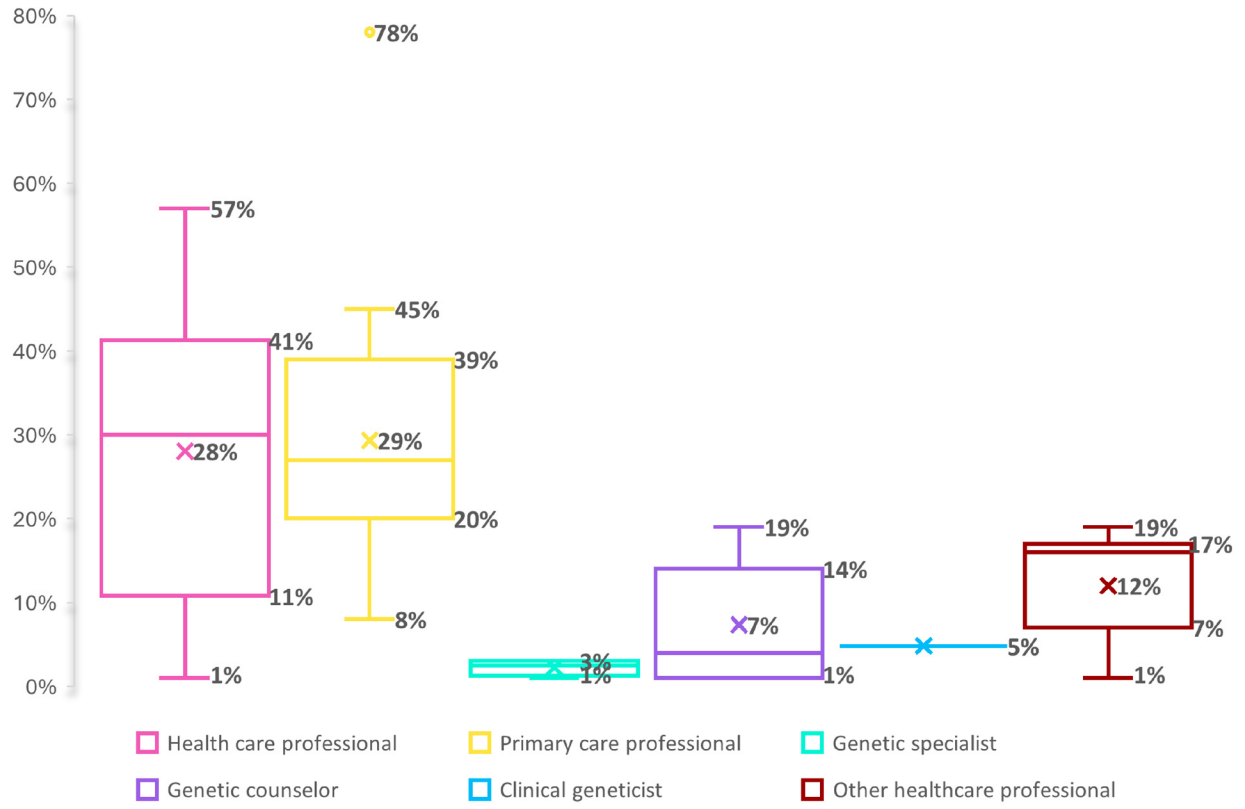

Figure 2. Sharing behavior of DTC-GT consumers with health care professionals. * For the boxplots shown, the line inside the box indicates the median value, whereas the 'x' marks the mean. * Categories are not mutually exclusive but were retained as defined in the original studies for consistency.

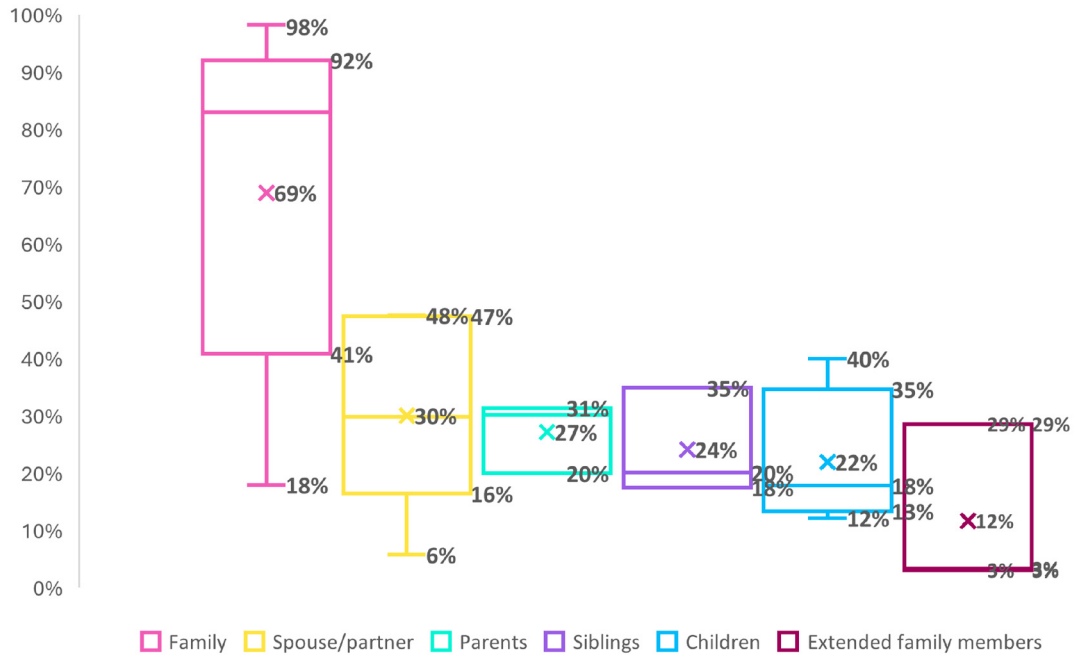

Figure 3. Sharing behavior of DTC-GT consumers with family members. * For the boxplots shown, the line inside the box indicates the median value, whereas the 'x' marks the mean. * Categories are not mutually exclusive but were retained as defined in the original studies for consistency.

that 9% (n=55/617) of participants stated to have received additional genetic tests, medical exams, screenings, procedures, and/or scans as a result of the genetic information they had received through DTC-GT[42]. A similar result was reported by Lee *et al.* (2020) in a web-based survey among adult adoptees following DTC-GT. In this study 18% (n=5) of respondents received additional testing or procedures based on DTC-GT results[53]. A qualitative interview study by Francke *et al.* (2013) examined the experiences of 11 women who tested positive for BRCA through DTC-GT. Among them, one had undergone a prophylactic mastectomy, while three others had planned the procedure. Additionally, three had undergone oophorectomies, and four had planned to do so after completing childbearing. Five participants sought breast exams and imaging following their results, while seven participants who neither had nor planned to undergo mastectomies reported continuing regular breast cancer monitoring. Furthermore, 30 secondary BRCA tests were conducted on family members as a result of the initial DTC-GT result, either through a health care professional or 23andMe, yielding 13 positive and 17 negative results. In one mutation-positive secondary case, early-stage breast cancer was detected. Several family members with BRCA-positive results had already undergone prophylactic mastectomy and oophorectomy, while others indicated plans to pursue these risk-reducing procedures in the future[36].

Jonas *et al.* (2019) reported that 40% of healthcare professionals (primary and specialty care physicians) who received DTC-GT results from patients made referrals to other healthcare professionals in the preceding year. Among these referrals, 78% were made to clinical geneticists and genetic counselors, while 22% were made to other health care professionals (e.g. clinical pharmacists)[63]. Trained genetic professionals also reported to have referred patients to other health care professionals in the study by Giovanni *et al.* (2010). In this study, 15 specialists in clinical genetics (n=15/22, 68%) had referred patients to at least one other health care professional[57]. In the Australian study conducted by Millward *et al.* (2020), which examined clinical genetics service referrals related to DTC-GT over ten years (2010–2019), there was considerable variation in the number of DTC-GT related referrals across the different publicly funded services surveyed[65]. While most services lacked specific procedures/guidelines for managing DTC-GT related referrals, six services reported that validating DTC-GT results was the most frequently performed clinical action following an appointment[65]. Overall, these services estimated that they had attempted to validate DTC-GT results for 34 patients, of which only 3 (9%) were confirmed as correct[65]. In the PGen study, 11% (n=105/961) of DTC-GT consumers stated to have undergone follow-up tests, examinations, and procedures based on their DTC-GT results six months after obtaining their test results[45]. A similar finding was also reported by Kaufman *et al.* (2012) where on average 10% of DTC-GT consumers reported following up their results with additional laboratory tests. This percentage was higher among those participants who had shared their DTC-GT test results with a health care professional (26%) compared to those who did not (2%)[33]. Interestingly, 27% of participants in the SGHI research study reported that their physicians had ordered additional tests based on the DTC-GT results they received[34]. Another American study by Elson *et al.* (2020) explored the outcomes of receiving DTC-GT results for the two most common genetic risk factors for venous thromboembolism (Factor V Leiden and prothrombin 20210G>A). In this study, 21% of variant-positive individuals were advised by health care professionals to undergo repeat genetic testing in a clinical lab, 13% were advised to have additional testing for other clotting disorders, and 15% were recommended to have relatives tested. About 28% (n=82/294) of cases reported that their relatives also underwent genetic testing based on their DTC-GT results. Within this group, 34% (n=28/82) reported that their family members received genetic testing through a healthcare professional and 17% (n=14/82) through a combination of DTC-GT and a health care professional[50]. In another study by Koop *et al.* (2021), six participants indicated to have pursued evaluation with a specialist in hereditary hemochromatosis (HH) due to their positive DTC-GT result. Additionally, three participants saw a HH specialist because a family member tested positive on commercial DNA testing for HH. Three participants also stated that a primary care physician ordered additional genetic testing due to a positive DTC-GT result, with one participant receiving conflicting results from formal gene testing[52]. Finally, in the study by Ashenhurst *et al.* (2022), 26.4% of participants with a physician-diagnosed Alpha-1 antitrypsin deficiency (AATD) received their diagnosis only after receiving their 23andMe test results and 50% of individuals with a PI*ZZ genotype (identified through DTC-GT) had received a diagnosis of AATD by a physician[54].

Discussion

The findings of this systematic review offer a detailed synthesis of the sharing behavior and healthcare utilization following DTC-GT, based on the most current available scientific evidence. Compared to the previous review by Stewart *et al.* (2018), which identified 14 articles on the sharing behavior of DTC-GT consumers, our review identified 40 articles which specifically examined the sharing behavior of actual DTC-GT consumers, experiences of health care professionals with DTC-GT consumers sharing their test results and/or healthcare utilization following DTC-GT[25]. Our analysis indicates that a considerable number of individuals who underwent DTC-GT have disclosed their test results to both healthcare professionals and family members. The proportion of DTC-GT consumers who report to have shared their DTC-GT results with healthcare professionals has remained relatively stable in recent years. However, the likelihood of sharing these results seems to be influenced, to some extent, by the cost of the test. Specifically, those who received subsidized or free tests were more likely to share their results, particularly to primary healthcare professionals, compared to those who paid out-of-pocket. This suggests that individuals who pay out-of-pocket for DTC-GT tests may be less motivated to engage with healthcare professionals. Surprisingly, only four of the primary studies we identified assessed the motivations behind consumers' decisions to share their DTC-GT results[31,35,44,47]. The choice to either share or withhold DTC-GT results from healthcare professionals appears

to be driven by a variety of motivational factors. Given that not all instances of sharing DTC-GT results will automatically lead to increased medical utilization, as was also demonstrated by the included studies, it is important to gain a better understanding of the underlying motivations of DTC-GT consumers for sharing their test results.

While not all DTC-GT consumers shared their test results with healthcare professionals, there is a notable trend of increasing interactions between DTC-GT consumers and health care professionals. This is particularly visible in studies assessing the experiences of genetic health professionals. For example, data from a 2017 survey of genetic counselors active in the US reveal that 40% had seen at least one consumer in the clinic solely for the purpose of reviewing DTC-GT test results, and 76% had been queried about DTC-GT by at least one patient[67]. This represents a significant rise from an earlier survey performed in 2008, where only 14% of genetic counselors reported receiving such requests[58]. This increase could be explained by the growing number of actual DTC-GT consumers. Considering the ongoing growth in the DTC-GT industry, it is likely that the impact of DTC-GT on healthcare systems will continue to increase in the future[67]. As more DTC-GT companies continue to develop partnerships with physician intermediaries in the ordering and test reporting process, patients may also potentially turn to these professionals for additional health information and advice[63]. Findings from the Scripps Genomic Health Initiative indicate that offering free genetic counseling and proactive outreach organized by DTC-GT companies could increase the likelihood of DTC-GT consumers discussing their DTC-GT results with a trained genetic professional[34,35,38]. This highlights the importance of facilitating proactive post-test communication through trained healthcare professionals employed by DTC-GT companies, which could help consumers better understand their results and potentially reduce the need for (unnecessary) follow-up consultations within the healthcare system[30,67]. By prioritizing ethical and consumer-focused practices, DTC-GT companies could enhance transparency, improve accessibility, and build trust in their services.

The impact of DTC-GT on healthcare systems has been a subject of considerable debate[57,62]. Initial concerns about DTC-GT suggested that it could lead to a significant burden on healthcare systems, including increased downstream tests, procedures, and referrals to specialists. Many of the anticipated issues have not manifested as expected based on current findings. It seems that previous studies that assessed sharing behavior more hypothetically have overestimated the proportion of consumers that would share DTC-GT results with a health care professional[33]. Most recent study findings indicate that patients sharing results from DTC-GT only constitute a small proportion of the total amount of patient visits in clinical (genetics) services[63,65]. Nevertheless, clinical actions (e.g. testing of family members) were taken for some DTC-GT related referrals clinical actions, which also demonstrates the impact that DTC-GT could have on the health care system[65]. The ongoing shift from testing for monogenic disorders to screening for polygenic conditions could also further impact the healthcare system, as polygenic risk scores add complexity, making interpretation more challenging for both consumers and healthcare professionals[73,74]. As genetic information becomes more complex, more individuals may seek professional guidance, potentially increasing demand for healthcare services and straining healthcare resources. Unlike monogenic conditions, where genetic variants typically have well-established clinical significance, polygenic risk scores remain less straightforward to interpret and validate. Without standardized guidelines and sufficient resources, inconsistent interpretation could again lead to unnecessary consultations and inefficient use of healthcare services.

A recent Australian study investigating the impact of DTC-GT on clinical genetics services revealed that while most referrals resulted in patient appointments, the willingness of services to offer appointments varied[65]. Healthcare professionals have also voiced to feel pressured to refer patients for clinical confirmatory testing of DTC-GT results and/or additional screening/testing, especially considering the evidence of the high error rate of DTC-GT. A recent American study by Tandy-Connor *et al.* (2018) found that 63% (31/49) of patients that were seeking confirmatory testing of their obtained raw data through third-party interpretation services did not receive important genetic health risk information within their original DTC-GT report[75]. In the same study, it was also discovered that 40% of the reported variants across a range of patient samples turned out to be false positives[75]. Results were even more concerning in the survey study among Australian clinical genetics services, where fewer than 10% of variants were confirmed among referrals of DTC-GT consumers who had used third-party interpretation services[65]. The need for confirmatory testing to prevent inappropriate patient care and medical management could present significant challenges in healthcare systems facing financial constraints and systemic barriers, such as limited access to specialized care or testing services. Furthermore, appointments involving DTC-GT consumers may also redirect healthcare resources away from patients with a clear clinical indication which might present challenges to ensure equitable healthcare delivery[12]. In response to these issues, the Royal College of General Practitioners and the British Society for Genetic Medicine issued a position statement in 2019 advising against referrals to clinical genetics services solely based on DTC-GT results. Instead, they recommend conducting a thorough risk assessment and evaluating family medical history prior to considering referrals in accordance with standard clinical pathways and protocols[76]. This differs from the position statement issued by the National Society of Genetic Counselors (NSGC) which recommend that "Results obtained through at-home genetic tests should be reviewed with a genetics specialist, as some findings may need to be confirmed in a clinical laboratory before being used in healthcare decision-making"[77].

Interestingly, our findings indicate that DTC-GT consumers more often shared their results with primary health care professionals (e.g. GP) rather than with trained genetic professionals[46]. Prior research has demonstrated that primary healthcare professionals lack time and feel unprepared or unqualified to take on the gatekeeping role expected of them when helping their

patients navigating DTC-GT results[59,69,78,79]. A particular proportion of referrals to the Australian clinical genetics services that were surveyed in the study of Millward *et al.* (2020) were made by GPs who were unsure about the significance of the results that their patients had received[65]. These findings underscore the urgent need for better education and training for GPs and primary care health care professionals in handling genetic information. As primary points of contact in the healthcare system, these health care professionals must be equipped with concrete practice guidelines to guide decisions about referral and follow-up care for those results requiring specialist attention[46,63]. In a study by McGrath *et al.* (2019), medical providers without specific training in genetics but with prior experience consulting DTC-GT consumers were more likely to accurately interpret genetic test results compared to those without any prior experience with genetic test consultations[64]. This improved ability may stem from these providers actively seeking additional information to assist with interpretation and counseling, which ultimately helps them develop and enhance their skills in this area[64]. This finding suggests that integrating genetics education into the curricula of various (primary) healthcare professionals could be highly beneficial[64,79].

Limitations

Our search strategy incorporated a wide range of commonly used keywords and phrases related to direct-to-consumer genetic testing, we did however not include MeSH terms such as "Direct-To-Consumer Screening and Testing," "Direct-To-Consumer Screening," or "Direct-To-Consumer Testing." Including these terms may have improved search sensitivity in certain databases. Future updates of this review might incorporate these MeSH terms to enhance the precision and comprehensiveness of the search strategy. Variability in follow-up duration across studies may have influenced the observed rates of information sharing and medical follow-up, as participants with longer follow-up periods may have had more opportunities to act upon the information received. However, detailed information on the exact timing of follow-up was not consistently available across all studies, limiting our ability to adjust for this factor. This should be taken into consideration when interpreting cross-study comparisons. Additionally, some included articles originated from the same research projects (e.g., PGen Study, Scripps Genomic Health Initiative), raising the possibility of overlapping participant data. While each publication addressed distinct research questions or subgroups, some duplication of outcomes—particularly related to data sharing and health care utilization—may have occurred. We mitigated this by analyzing each article independently and clearly reporting the origin of each study to support transparency and allow readers to interpret the findings in context.

Implications for future research

Variations in research designs, outcome measures, and participant characteristics across the identified studies complicate direct comparisons and hinder the ability to draw definitive conclusions. This observed heterogeneity underscores the need for more standardized approaches. Conducting further international studies with consistent outcome measures would be highly beneficial in gaining deeper insights into the broader impact of DTC-GT on healthcare systems. Such research would not only enable more meaningful comparisons but also contribute to a clearer understanding of DTC-GT's implications across diverse healthcare contexts. The current body of literature remains heavily focused on the U.S. context, with limited exploration of sharing behavior and health care utilization following DTC-GT in other regions of the world. As healthcare systems, cultural norms, and healthcare access vary greatly across regions, conducting studies in diverse international contexts would provide a more comprehensive view of the global implications of DTC-GT.

Conclusion

The findings of this systematic review provide a comprehensive overview of the current scientific evidence on the sharing behaviors and healthcare utilization patterns following DTC-GT. While initial concerns about DTC-GT's impact on the health care system have not fully materialized, the increasing number of consumers engaging with healthcare professionals underscores the need for preparedness and appropriate policy responses. Policymakers and healthcare institutions must also take proactive measures to equip health care professionals—particularly those in primary care—with the knowledge and tools necessary to navigate the evolving challenges associated with DTC-GT. Given that general practitioners are often the first point of contact for DTC-GT consumers, enhancing their genetic literacy through targeted training programs and decision-support tools could help mitigate the risk of unnecessary referrals, misinterpretation of results, and inefficient healthcare utilization. As the majority of existing literature focuses on high-income countries, significant gaps remain in understanding how DTC-GT is utilized in regions with differing healthcare infrastructures, regulatory frameworks, and access to genetic services. Future research should therefore prioritize standardizing study methodologies and expanding investigations beyond the U.S. context to better capture the global impact of DTC-GT.

Ethics and consent

No ethics and consent were required.

Data availability statement

KU Leuven RDR (Dataverse): Data related to the manuscript: Sharing behavior and health care utilization following direct-to-consumer genetic testing: a systematic review. https://doi.org/10.48804/EWC2MA[80]

This project contains the following underlying data:

- Figure1 PRISMA.pdf

- PRISMA_2020_abstract_checklist.pdf

- README file _DTCGT Review.txt

- Supplementary materials.pdf

- Table 1_DTCGTConsumer.pdf

- Table2_HCP.pdf

- Table3_Sharingbehavior.pdf

- Table4_Family.pdf

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0) (https://creativecommons.org/licenses/by/4.0/).

Reporting guidelines

KU Leuven RDR (Dataverse): PRISMA checklist for 'Sharing behavior and health care utilization following direct-to-consumer genetic testing: a systematic review'. https://doi.org/10.48804/EWC2MA[80]

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http://www.doi.org/10.48804/EWC2MA

Open Peer Review

Current Peer Review Status: ? ? ✓

Version 2

Reviewer Report 05 January 2026

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✓ **Diane C. Seibert**
Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA

Interesting and useful article --- and I appreciate (changes made in response to comments made by the 1st reviewers (MeSH terms), etc.

My only comments were about formatting -- all are are on pages 7 & 8. Please review all the times you refer the reader to a Table and then mention 'underlying data'. I'm not sure what you mean by 'underlying data'....that's what I'm going to a table to review, no?? You could just delete those 2 words, and it would be fine. BUT if you leave them in, please be consistent in your use of parentheses and case (upper/lower). Also, in the paragraph beginning with "Sharing behavior ofDTC-GT consumers with family members, please review the use 2nd to last sentence and the contents in the final parentheses. I'm not sure what the 18%-35% revers to ...median perhaps?

Otherwise, I think it's ready to index.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: 20+ year history of educating health professionals (Nurse Practitioners

genomic literacy, fluency and competency) has been my focus.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 06 November 2025

https://doi.org/10.21956/openreseurope.23058.r60661

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Kurt Christensen
Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, Massachusetts, USA

Review of Revision to "Sharing Behavior and Health Care Utilization Following Direct-to-Consumer Genetic Testing: A Systematic Review"

The authors have done a commendable job addressing concerns raised during the initial review. I have only a few remaining issues:

Treatment of Duplicate Data Reporting:
The handling of repeated reporting of the same results remains problematic. While the authors have been transparent in their analytic approach, it is clear that citations 40, 41, and 44 from the PGen Study report data from the same participant cohort, not distinct subgroups. Variations in sharing percentages stem from differing analytic strategies (e.g., handling of missing data), not from subgroup differences. Treating these findings as independent data points artificially triples the weight of a single study in the boxplots. I recommend omitting data from citations 40 and 41 when constructing the boxplots. Additionally, using boxplots that assign equal weight to studies with 20 participants and those with over 30,000 is methodologically questionable.

Discussion of Study Design Differences:
The Discussion section should address differences in DTC recipients and study designs as potential sources of data discrepancies. For example, the study reporting only 1% of participants sharing results with clinicians was the Multiplex Initiative, which (a) excluded patients with any of the eight common conditions examined by the genetic test, and (b) conducted follow-up only three months post-disclosure. The combination of a very healthy cohort and short follow-up likely explains the low clinician-sharing rate.

Clarification of the Multiplex Initiative's Nature:
Technically, the Multiplex Initiative was a clinical service offered to insured patients of the Henry Ford Health System. However, its methodology was intentionally designed to mirror the processes of DTC companies wherever feasible

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Medical, behavioral, and economic impact of genomic testing of healthy individuals

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Version 1

Reviewer Report 02 June 2025

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Lola Cook
Indiana University Bloomington, Bloomington, Indiana, USA

This article is a systematic review of sharing behavior and health care usage after genetic testing through a direct-to-consumer company. It is a timely article with important points and well written. It builds upon prior evidence.
Major comments:
Authors should address overall quality of evidence in the body of the text so the reader can easily refer to and understand any gaps; also though they use the Hawker method to assess quality this does not include addressing any bias within the literature. Most of the numerical analysis in the text involves ranges across studies that are often large and thus, somewhat meaningless, (i.e.1% to 57% is given as the proportion who share their test results with a HCP) and do not necessarily support their conclusions in the Discussion such as "Our analysis indicates that a considerable number of individuals who underwent DTC-GT have disclosed their test results to both healthcare professionals and family members". When they discuss the detailed results, specifically these large ranges, they refer to the box plot figures without further characterization of the data displayed. More details regarding how the data are distributed would be helpful and perhaps support some of the conclusions. They correctly compare ranges across categories. Also lacking are summarizing key demographic features of respondents such as level of education which could impact results and conclusions. An overview of the types of results reported would also be informative. There are additional limitations of the data not reported such as few articles about family sharing broke down categories of family members, for example, so please note any gaps or deficiencies in the literature your reviewed. For example, it is noted that the data tend to be US-centric.
Minor comments:
Check for typos throughout article including in Abstract.

Define AATD.
This statement is confusing: "Participants in the Scripps Genomic Health Initiative, where genetic counseling was provided at no cost by a Navigenics counselor and proactive outreach was conducted based on their test results, reported a slightly higher frequency of sharing their results with a genetic counselor compared to participants in other studies" since it is not clear that the sharing reported is with the counselor at the DTC company or external.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: genetic counseling, genetic testing, Parkinson disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 29 Aug 2025

eva Van Steijvoort

We appreciate your careful review of our manuscript and the detailed, constructive feedback provided. Your comments have helped clarify our analyses, highlight limitations more explicitly, and improve the overall presentation of the work. Below, we respond to each of the points raised. Major comments:

- Authors should address overall quality of evidence in the body of the text so the reader can easily refer to and understand any gaps; also though they use the Hawker method to assess quality this does not include addressing any bias within the literature.

We would like to clarify that the Hawker method does incorporate evaluation of ethical considerations and potential sources of bias within its appraisal criteria, and these aspects were systematically assessed for all studies included in our review. To ensure transparency, we have integrated the following paragraph into the body of the text. *“The quality appraisal of the included studies, conducted using Hawker et al.’s (2002) framework, revealed that most articles were generally of good quality across key domains such as titles and abstracts, introductions, methodology, data analysis, results, and implications. However, recurring limitations emerged in areas related to sampling, ethics, and bias, as well as transferability or*

generalizability, where many studies were rated only "fair" or occasionally "poor." Despite these weaknesses, nearly all studies were judged to present findings that were useful and relevant to the research questions."

- Most of the numerical analysis in the text involves ranges across studies that are often large and thus, somewhat meaningless, (i.e.1% to 57% is given as the proportion who share their test results with a HCP) and do not necessarily support their conclusions in the Discussion such as "Our analysis indicates that a considerable number of individuals who underwent DTC-GT have disclosed their test results to both healthcare professionals and family members". When they discuss the detailed results, specifically these large ranges, they refer to the box plot figures without further characterization of the data displayed. More details regarding how the data are distributed would be helpful and perhaps support some of the conclusions. They correctly compare ranges across categories.

We recognize that the reported ranges across studies are wide, reflecting considerable variability in the primary data. To ensure comprehensive transparency, all underlying data and study-specific results, including sample sizes and contextual details, are provided in the accompanying tables. In response to this concern, we have enhanced the boxplot figures by including more detailed information to better depict the data distribution. Furthermore, the manuscript text has been expanded to describe these features more thoroughly and offer clearer context for interpreting the figures. We believe these improvements increase clarity about the distribution of the data and strengthen the support for our conclusions.

- Also lacking are summarizing key demographic features of respondents such as level of education which could impact results and conclusions.

We would like to underline that this information is available to the reader in Table 1.

- An overview of the types of results reported would also be informative.

We would like to emphasize that the data provided in the primary studies do not permit such detailed analysis and reporting. In many cases, it is unclear which specific types of results participants received. When available, we have included details of the company and test used in Table 1; however, we acknowledge that this information remains limited.

- There are additional limitations of the data not reported such as few articles about family sharing broke down categories of family members, for example, so please note any gaps or deficiencies in the literature your reviewed. For example, it is noted that the data tend to be US-centric.

We would like to direct your attention to the final paragraph of our discussion section, where we address these concerns. We highlight the considerable variation and heterogeneity in study designs and measures that complicate direct comparisons, emphasizing the need for more standardized approaches in future research. Additionally, we discuss the current U.S.-centric focus of the literature and underscore the importance of conducting more international studies to better capture diverse healthcare systems and cultural contexts. *"Variations in research designs, outcome measures, and participant characteristics across the identified studies complicate direct comparisons and hinder the ability to draw definitive conclusions. This observed heterogeneity underscores the need for more standardized approaches. Conducting further international studies with consistent outcome measures would be highly beneficial in gaining deeper insights into the broader impact of DTC-GT on healthcare systems. Such research would not only enable more meaningful comparisons but also contribute to a clearer understanding of DTC-GT's implications across diverse healthcare*

contexts. The current body of literature remains heavily focused on the U.S. context, with limited exploration of sharing behavior and health care utilization following DTC-GT in other regions of the world. As healthcare systems, cultural norms, and healthcare access vary greatly across regions, conducting studies in diverse international contexts would provide a more comprehensive view of the global implications of DTC-GT." Minor comments:

- Check for typos throughout article including in Abstract.

We have carefully checked the entire article, including the Abstract, for any typos and corrected them accordingly.

- Define AATD.

The definition of AATD has now been added to the manuscript for clarity.

- This statement is confusing: "Participants in the Scripps Genomic Health Initiative, where genetic counseling was provided at no cost by a Navigenics counselor and proactive outreach was conducted based on their test results, reported a slightly higher frequency of sharing their results with a genetic counselor compared to participants in other studies" since it is not clear that the sharing reported is with the counselor at the DTC company or external.

We understand the confusion. While this information was included in Table 3A, we have now also clarified in the manuscript that the sharing reported was specifically with a Navigenics counselor.

Competing Interests: No competing interests were disclosed.

Reviewer Report 07 May 2025

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Kurt Christensen
Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, Massachusetts, USA

This manuscript reported findings from a systematic review of studies of information sharing and health care utilization following direct-to-consumer genetic testing. The article is generally well-written, particularly in the Discussion section which presents thoughtful recommendations to address data gaps and methodological inconsistencies, as well as challenges for primary care professionals and other clinicians. I'm uncertain about how well some arguments are supported, however, due to uncertainties about how data in the examined studies were analyzed and due to instances where the authors did not note important differences testing approaches or study populations. The manuscript would benefit from addressing these following concerns:

- The authors note that six articles they analyzed were products of the PGen study and three articles were products of the Scripps Genomic Health Initiative. How did the authors

address the potential for double-counting sharing data and health care utilization data?
- Adoptees are a focus of a few articles, including the one where 98% of study participants reported sharing results with family members. The manuscript would benefit from greater sensitivity to studies that focused on particular populations and study designs that deliberately tried to offer to DTC-GT to populations who may not have been motivated to pursue testing (e.g., the Multiplex Initiative).
- The introduction is appropriately sensitive to differences between health-related and non-health-related DTC-GTs, as well as the differences in the types of health information provided by health-related DTC-GTs. Yet, the review's analyses don't seem sensitive to these important differences. Analyses of sharing with health care providers and health care utilization greater sensitivity to studies where health-relevant information was unlikely to be generated (e.g. ancestry-focused testing) and, conversely, studies where information sharing may be more likely (e.g., studies where testing provided carrier status).

Other Important Concerns

I did not see any key articles missing, but I encourage the authors to include "Direct-To-Consumer Screening and Testing," "Direct-To-Consumer Screening" and "Direct-To-Consumer Testing" in their search strings given that these are the preferred MeSH entries (perhaps intersecting with the MeSH term, "genetic testing").

The time frame of the analyses is a little hard to identify for each study and may have a strong association with the likelihood of information sharing and medical follow-up.

In analyses of data from the Scripps Genomic Health Initiative, health care utilization was assessed as follows: "13 health screening behaviours were assessed by asking
about actual completion of a given screening test…" Are the authors sure that they're summarizing data about health care utilization motivated by DTC-GT findings? Some of those services (e.g., glucose exam, blood test, mammogram) are common for patients as part of overall preventive care.

Minor Issues

The manuscript starts with a focus on monogenic disease risks and risk predictions and feels out-of-focus with the majority of their analyses which address broader range of DTC-GTs.

In the Introduction, the authors write, "The reliability of a positive test or increased risk result after DTC-GT remains limited, as the development of many genetic conditions is also influenced by other factors such as the environment and lifestyle choices." I encourage the authors to address some of the challenges they address later in the manuscript related to high rates of analytic false positives, as well as concerns about potential misinterpretations of uninformative findings as negatives for genetic risk factors.

In Table 3A, the cell "Shared with HCP (=yes)" looks like it should have slightly different content and formatting.

Figures 2 and 3 would benefit from captions. I was unsure if lines represented medians across studies and x's represent means. Also, some categories (genetic specialist, genetic counselor, medical geneticist) are not mutually exclusive.

In one place, those authors write that the Stewart paper was published in 2017.

The authors write, "Specifically, those who received subsidized or free tests were more likely to share their results, particularly to primary healthcare professionals, compared to those who paid out-of-pocket." It may be helpful to understand whether those receiving subsidized or free tests were studies where testing was encouraged by researchers, and to note that individuals often pursue DTC-GT to avoid having results put in their medical records, as noted by the authors.

I don't think the literature about the use of 3rd party interpretation services is very relevant in the Introduction or Discussion, although I agree that the use of these services following DTC-GT is of great concern.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Partly

Is the statistical analysis and its interpretation appropriate?
Partly

Are the conclusions drawn adequately supported by the results presented in the review?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Medical, behavioral, and economic impact of genomic testing of healthy individuals

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 29 Aug 2025

eva Van Steijvoort

We appreciate your careful review of our manuscript and the detailed, constructive feedback provided. Your comments have helped clarify our analyses, highlight limitations more explicitly, and improve the overall presentation of the work. Below, we respond to each of the points raised.

- The authors note that six articles they analyzed were products of the PGen study and three articles were products of the Scripps Genomic Health Initiative. How did the

authors address the potential for double-counting sharing data and health care utilization data?

We appreciate the question regarding the potential for double-counting data in our analysis, particularly given that six of the included articles originated from the PGen Study and three from the Scripps Genomic Health Initiative. We have been transparent about the inclusion of multiple publications stemming from these two projects. This was clearly disclosed in our results sections. While the studies may share an overarching participant base, the individual publications addressed distinct research questions and often reported on participant subgroups. We recognize that there may be some overlap in study populations, which could pose limitations. By being transparent about the origins of the studies included, we enable readers to interpret the findings with appropriate context. We believe this transparency, combined with our careful analysis of each article, supports a methodologically sound and comprehensive synthesis. We have included the following paragraph in the Limitations section of the Discussion to fully and transparently address this issue. "Additionally, some included articles originated from the same research projects (e.g., PGen Study, Scripps Genomic Health Initiative), raising the possibility of overlapping participant data. While each publication addressed distinct research questions or subgroups, some duplication of outcomes—particularly related to data sharing and health care utilization—may have occurred. We mitigated this by analyzing each article independently and clearly reporting the origin of each study to support transparency and allow readers to interpret the findings in context."

- Adoptees are a focus of a few articles, including the one where 98% of study participants reported sharing results with family members. The manuscript would benefit from greater sensitivity to studies that focused on particular populations and study designs that deliberately tried to offer to DTC-GT to populations who may not have been motivated to pursue testing (e.g., the Multiplex Initiative).

We agree that studies focusing on specific populations—such as adoptees or participants in initiatives like the Multiplex Initiative—offer unique perspectives on engagement with DTC-GT, particularly among individuals who may not have actively sought out testing on their own. Throughout the manuscript, we have been attentive to the focus and context of each included study. We describe the study populations, recruitment strategies, and design features to ensure that readers understand the diversity of approaches and participant experiences represented in the literature. These details are integrated into our results and discussion sections, where we consider how differences in study design and target populations may influence outcomes such as result-sharing behavior or health care utilization. *"For those who received a subsidized test, the sharing rate was between 19% and 39% 34,35,38,40–42,44–46,56, while participants who received a free test shared their results at a rate ranging from 1% to 42%31,32,39." "Interestingly, those that received a subsidized or free DTC-GT more often shared their DTC-GT with a primary health care professionals (range 27%–78%)34,38, 39,41,44–46,56 compared to those that paid out of pocket (8–25%)33,36,47,49–51,54." "... However, the likelihood of sharing these results seems to be influenced, to some extent, by the cost of the test. Specifically, those who received subsidized or free tests were more likely to share their results, particularly to primary healthcare professionals, compared to those who paid out-of-pocket. This suggests that individuals who pay out-of-pocket for DTC-GT tests may be less motivated to engage with healthcare professionals."*

- The introduction is appropriately sensitive to differences between health-related and non-health-related DTC-GTs, as well as the differences in the types of health

information provided by health-related DTC-GTs. Yet, the review's analyses don't seem sensitive to these important differences. Analyses of sharing with health care providers and health care utilization greater sensitivity to studies where health-relevant information was unlikely to be generated (e.g. ancestry-focused testing) and, conversely, studies where information sharing may be more likely (e.g., studies where testing provided carrier status).

We agree with the reviewer that such a stratified analysis would be informative and insightful and would add valuable nuance to analyses of information sharing with healthcare providers and subsequent healthcare utilization. However, we would like to emphasize that the data reported in the primary studies do not support such a detailed analysis. In many instances, it is not clear what specific types of results participants received, and few studies distinguish between those who received health-related findings (e.g., carrier status) and those whose results were limited to non-health-related information (e.g., ancestry). Moreover, as discussed in our manuscript, the distinction between health-related and non-health-related DTC-GT results has become increasingly difficult to draw. The widespread availability of third-party interpretation services enables consumers to upload their raw genetic data and receive additional analyses. These services often provide information on genetic variants or risk scores that were not part of the original DTC-GT offering, thereby extending the scope of interpretation beyond what was initially intended. As a result, the line between health-related and non-health-related genetic information is increasingly blurred, complicating research efforts. This complexity limits our ability to meaningfully categorize participants' experiences based on the original test type and highlights the need for more detailed reporting in future studies to be able to draw any meaningful conclusions. Other Important Concerns I did not see any key articles missing, but I encourage the authors to include "Direct-To-Consumer Screening and Testing," "Direct-To-Consumer Screening" and "Direct-To-Consumer Testing" in their search strings given that these are the preferred MeSH entries (perhaps intersecting with the MeSH term, "genetic testing"). We would like to thank the reviewer for this suggestion regarding the inclusion of additional MeSH terms such as "Direct-To-Consumer Screening and Testing," "Direct-To-Consumer Screening," and "Direct-To-Consumer Testing." We agree that these are relevant terms and acknowledge their potential value for enhancing comprehensiveness. Our original search strategy, however, employed a broad range of commonly used text-based terms and phrases that align closely with MeSH indexing. As was noted by the reviewer, our current search did not appear to miss any key studies. Given this, and in the interest of maintaining consistency and transparency in our review process, we have elected not to re-run the search at this stage. However, we will make note of this in the limitations and would recommend incorporating these MeSH terms in future replications or updates of the review. The following paragraph was added to the end of the discussion section: *"Our search strategy incorporated a wide range of commonly used keywords and phrases related to direct-to-consumer genetic testing, we did however not include MeSH terms such as "Direct-To-Consumer Screening". Including these terms may have improved search sensitivity in certain databases. Future updates of this review might incorporate these MeSH terms to enhance the precision and comprehensiveness of the search strategy."*

The time frame of the analyses is a little hard to identify for each study and may have a strong association with the likelihood of information sharing and medical follow-up. When available, information regarding the follow-up duration was included in Table 3. However, this information was not reported in all the studies included in our systematic review. We

have addressed this limitation by incorporating the following paragraph into the Discussion section: *"Variability in follow-up duration across studies may have influenced the observed rates of information sharing and medical follow-up, as participants with longer follow-up periods may have had more opportunities to act upon the information received. However, detailed information on the exact timing of follow-up was not consistently available across all studies, limiting our ability to adjust for this factor. This should be taken into consideration when interpreting cross-study comparisons."* In analyses of data from the Scripps Genomic Health Initiative, health care utilization was assessed as follows: "13 health screening behaviours were assessed by asking
about actual completion of a given screening test…" Are the authors sure that they're summarizing data about health care utilization motivated by DTC-GT findings? Some of those services (e.g., glucose exam, blood test, mammogram) are common for patients as part of overall preventive care. We understand the concern raised by the reviewer; however, we would like to emphasize that the results reported in our systematic review specifically focus on the validation of DTC-GT results and the subsequent clinical actions taken based on those results. We did not include any screening behaviors that may be part of general preventive care, as described by the reviewer, in our results section. Minor Issues The manuscript starts with a focus on monogenic disease risks and risk predictions and feels out-of-focus with the majority of their analyses which address broader range of DTC-GTs. We appreciate the reviewer's observation. Our intention in the introductory paragraph was to provide context for the emergence of direct-to-consumer genetic testing (DTC-GT) by outlining the broader evolution of genetic and genomic medicine—from its initial focus on rare monogenic disorders to its expansion into complex disease risk prediction. However, we recognize that this framing may have inadvertently implied a narrower scope than was intended. To address this, we have revised the introduction to more accurately reflect the full range of health-related DTC-GT examined in our review. In the Introduction, the authors write, "The reliability of a positive test or increased risk result after DTC-GT remains limited, as the development of many genetic conditions is also influenced by other factors such as the environment and lifestyle choices." I encourage the authors to address some of the challenges they address later in the manuscript related to high rates of analytic false positives, as well as concerns about potential misinterpretations of uninformative findings as negatives for genetic risk factors. We have indeed briefly addressed the challenges related to analytic false positives and the potential for misinterpretation of uninformative findings in the manuscript. However, as the primary aim of our review is to assess sharing behaviors, healthcare professional experiences, and healthcare utilization following DTC-GT, an in-depth exploration of these technical and interpretive limitations lies beyond its scope. We believe these issues have been comprehensively addressed in previous literature, and our focus remains on the downstream clinical and behavioral impacts of DTC-GT results. In Table 3A, the cell "Shared with HCP (=yes)" looks like it should have slightly different content and formatting. We are not entirely sure what is meant by the comment regarding the content and formatting of the "Shared with HCP (=yes)" cell in Table 3A. To clarify, this column was not intended to serve as an overarching header for the adjacent columns. In some studies, only a general percentage of participants who shared results with "a healthcare provider" was reported, without further specification of provider type. We hope this explanation clarifies the presentation of the data.

Figures 2 and 3 would benefit from captions. I was unsure if lines represented medians

across studies and x's represent means. Also, some categories (genetic specialist, genetic counselor, medical geneticist) are not mutually exclusive. We have added a footnote explaining that for the boxplots shown, the line inside the box indicates the median value, whereas the 'x' marks the mean. While we acknowledge that these categories are indeed not mutually exclusive, the primary studies included in our analysis varied considerably in how they defined and reported these roles. To maintain consistency and accuracy, we chose to adhere closely to the categorizations as originally presented in the source studies. The following footnote was added to the figures to clarify this: *"Categories are not mutually exclusive but were retained as defined in the original studies for consistency."* In one place, those authors write that the Stewart paper was published in 2017. Adjusted in the manuscript. The authors write, "Specifically, those who received subsidized or free tests were more likely to share their results, particularly to primary healthcare professionals, compared to those who paid out-of-pocket." It may be helpful to understand whether those receiving subsidized or free tests were studies where testing was encouraged by researchers, and to note that individuals often pursue DTC-GT to avoid having results put in their medical records, as noted by the authors. We agree that understanding whether individuals who received subsidized or free tests were part of studies where testing was actively encouraged would provide valuable context. Unfortunately, the available data in the included studies do not consistently provide detailed information on the extent of such encouragement or on participants' motivations for pursuing testing. This limits our ability to draw firm conclusions about the relationship between subsidized testing and sharing behaviors. We have interpreted these findings with caution and noted the need for future research to explore how motivations influence result sharing and health care engagement. I don't think the literature about the use of 3rd party interpretation services is very relevant in the Introduction or Discussion, although I agree that the use of these services following DTC-GT is of great concern. We appreciate the concern regarding relevance; however, we believe that discussing these services in the Introduction and Discussion is important for several reasons. Third-party interpretation services have become a significant and growing component of the DTC-GT landscape, influencing how consumers understand and act upon their genetic results. DTC-GT users may turn to these services to seek additional explanation or clinical interpretation that may not be provided directly by DTC companies. This behavior has important implications for how genetic information is shared with family members and health care providers, as well as for subsequent health care utilization. By including this literature, we provide a more comprehensive view of the consumer experience and the broader context in which DTC-GT results are interpreted and acted upon. Omitting this could overlook a key factor shaping downstream behaviors and potential challenges in clinical integration. Therefore, we believe that maintaining the discussion of third-party interpretation services enhances the depth and relevance of our manuscript.

Competing Interests: No competing interests were disclosed.