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Perspective

Direct-to-consumer genetic testing with third party interpretation: beware of spurious results

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Direct-to-consumer (DTC) genetic tests aim to provide insights into issues as varied as ancestry, nutrition, athletic ability and child talent, and some also report on disease risks. DTC companies tend to present their tests as uniformly beneficial, but the quality of the information they provide can be doubtful. Tests often invite people to step between territories, from the consumer in search of 'fun' information to potential patient, and the boundaries between these roles become even murkier when individuals explore the raw data from their DTC tests using third-party interpretation websites. We discuss two composite cases from U.K. genetics centres where patients used third party interpretation services to analyse raw data from DTC genetic tests. They then presented to NHS clinical services requesting interventions based on the disease-associated variants found, only to find that these variants were not actually present: their 'pathogenic results' were spurious. We highlight the risk of false positives (as well as false negatives) from DTC genetic tests, and discuss whether these cases represent the start of a worrying trend, where publicly funded clinicians and clinical scientists increasingly need to spend time and money investigating genetic results of dubious validity.

Introduction

Direct-to-consumer (DTC) genetic tests can be purchased online and in shops. Many of these tests work via SNP (single nucleotide polymorphism) genotyping, quickly and cheaply establishing a person's genotype at thousands of points across the genome [1]. SNP genotyping, however, is a highly inaccurate method for detecting very rare variants: recent research comparing SNP genotyping data with exome sequencing data for participants in U.K. Biobank found that over 85% of the very rare variants (with a frequency <0.001%) detected by SNP genotyping were false-positives [2]. DTC companies directly reporting on the presence of very rare variants would need to undertake additional validation in order to ensure that their assays could accurately determine the presence or absence of these variants.

Third-party interpretation services take raw genetic data which was collected aiming to answer particular questions (for example about a person's ancestry), and process this with different questions in mind (for example about health). This increases the potential for error, as third party interpretation services will not have access to platform validation information from each DTC company, and so will not be calibrated to disregard the artefacts that each different DTC genetic testing platform will inevitably produce [3]. Many third-party interpretation services simply search freely available databases like dbSNP for any variants said to be present in a person's raw genetic data, and aggregate the variant classifications found into an automated report, without expert oversight [4]. Many of the classifications in these databases will be outdated and incorrect, relics from a time before the vast range of normal genetic variation began to be widely appreciated [5]. We discuss two composite cases where patients found spurious results when using third party interpretation services to interpret raw data from DTC genetic tests.

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Briony

Briony was given a DTC ancestry genetic test for mother's day. After her ancestry results came back, she ran the raw data from her test through several third-party interpretation websites, which all indicated that she had a disease-causing *BRCA1* variant. Briony was generally healthy but had a family history of breast cancer (although not in close relatives, and its onset was at an older age, so NHS *BRCA1* or *BRCA2* gene testing would not have been recommended) [6]. Briony saw her GP and requested a referral to a breast surgeon, as she had read that bilateral mastectomies could reduce her breast cancer risk. The breast care team discussed surgical options with her and agreed a date for her surgery. They also referred her to an NHS clinical genetics service. Briony saw a clinician there shortly before her planned operation date, who advised that Briony's *BRCA1* result needed to be confirmed in an accredited laboratory before she had surgery. Using next-generation sequencing (NGS) to screen *BRCA1* and *BRCA2*, and targeted Sanger sequencing, the NHS laboratory found that Briony did not have the disease-causing *BRCA1* variant that she was purported to have. The raw data files from the ancestry test and the NHS NGS testing were compared: this indicated that the ancestry test had indeed been undertaken on Briony's sample, but the ancestry test raw data contained an artefact in *BRCA1* that the third party interpretation programmes had taken to be a true variant. Briony was advised that risk-reducing surgery was not indicated and that its risks far outweighed any likely benefits.

Paul

Paul had a DTC ancestry test while researching his family history, then used a third-party interpretation service to look at the raw data, finding an *MLH1* variant predicted to cause Lynch syndrome. Paul was generally healthy and was not aware of any family history consistent with the condition, so NHS genetic testing for Lynch syndrome would not have been recommended. Paul saw his GP who referred him to an NHS clinical genetics service to discuss screening options and family testing. NHS genetic testing showed that Paul did not have the *MLH1* variant. Paul was reassured and no additional screening was advised.

DTC-derived 'results' in the clinic

DTC genetic testing companies are commercially driven to support the idea that their tests will reliably predict the future in a useful way. It is in their financial interest to present their tests as a fun and glamorous route to learning 'your DNA story', and a way to take responsibility for one's health. For example, the DTC company 23andMe organised a 'spit party' at New York Fashion Week in order to promote its tests [7]. Many DTC companies offer the raw genetic data for customers who want to take 'an advanced view' [1], implying that there is more to uncover. Although there are disclaimers regarding interpretation of data for health predictions, due to the popular rhetoric around genetics that tends to present all genetic tests as meaningful and accurate, people may understandably see this raw data as a natural extension of 'their DNA story' rather than as an un-sifted mass of genetic variants that might be spiked with artefacts, or of dubious clinical relevance [8, 9].

Results derived from DTC genetic test raw data are therefore increasingly being brought by consumers to the clinic, but many patients and clinicians do not realise that these results are not of equivalent quality to results produced via more conventional pathways using technologies targeted to the clinical question at hand [10]. Most DTC genetic tests are purchased without discussion with a clinician, and without asking a specific clinically driven question. DTC companies state the limitations and risks of their tests as part of their disclaimers but clearly, the potential consequences of taking results found from their raw data at face value are not always emphasised enough.

Patients often receive DTC test results online or via email, and are left to make sense of these themselves in the absence of professional support. Even when patients with worrying DTC results are seen quickly by clinical services, there is a time interval between them obtaining the DTC result and receiving NHS testing to confirm or refute this. During this time, people may experience considerable anxiety, which can also cascade through their families as they worry that they too are at risk of a serious genetic condition. This anxiety is much easier to create than it is to take away — discussions at GenethicsUK (a forum to discuss ethical issues arising in genetic medicine -www.genethicsUK.org) demonstrate that some patients continue to worry about health risks identified via DTC tests, even when subsequent NHS tests show that the variants said to confer the health risk were never actually there.

A further concern is that people will be falsely reassured by negative results from DTC genetic tests. NHS genetic tests aim to answer specific clinical questions but many DTC tests take a scattergun approach and do not tailor their testing strategy depending on the clinical context. For example, the 23andMe *BRCA* 'genetic health risk' report only includes three disease-causing variants common in people with Ashkenazi Jewish ancestry, and would miss ~80% of people with disease-causing *BRCA* variants in the general population [11, 12]. On the flipside of cases of the false alarm, there is also the worry that there are patients that clinical services never get to see — people with a strong personal and family history suggesting a likely genetic condition, who assume that reassuring results from a DTC genetic test exclude a genetic basis for that condition.

An escalating drain on public resources

DTC genetic testing presents a policy challenge to the NHS — how should publicly-funded services respond to the results of tests accessed privately, often without a clear clinical indication? The importance of facilitating and respecting patient choice within the NHS is often emphasised [13], and the NHS often has to deal with the consequences of choices made without discussion with a health professional (for example choices to smoke). Advertising for DTC companies sometimes presents the choice to test as an active way to take responsibility for your own health [14], so many patients might understandably expect that the NHS would welcome the chance to discuss their DTC test results and personalise their future healthcare.

However, routinely engaging with DTC test results would drain NHS resources. For example, based on personal and family history, neither Briony nor Paul would have been offered genetic testing on the NHS to investigate a possible cancer predisposition syndrome, and neither were found to have such a tendency on fuller investigation. Their accessing such testing via DTC services, then needing an NHS response to the outcome, meant that other people with a much greater a priori risk of having a strong genetic predisposition to cancer were pushed further back in the queue. NHS laboratory resources were also drained: the consumables used and scientist time required for analysis and bespoke reporting of these spurious results was far greater than for typical NHS tests.

The increasing number of patients referred to NHS clinical genetic services to discuss DTC genetic test results is regularly flagged at regional genetics meetings and GenethicsUK. Referrals to clinical genetics are often declined because many DTC genetic test results do not represent a substantial change to a person's absolute risk of developing a condition, and even where they do, evidence-based screening or treatment is often unavailable. However, cases such as the ones described here are difficult to turn away. The patients left in this situation are often understandably worried and vulnerable, and the consequences of clinicians accepting their DTC-derived results at face value may be very serious, and very costly.

DTC genetic tests also present a regulatory challenge [15]. The US Food and Drug Administration regulates DTC genetic tests for 'moderate to high-risk medical purposes' as medical devices [16], and within the EU, genetic tests with a medical purpose fall under laws on *in vitro* diagnostic medical devices [15]. Whilst it is clearly appropriate that DTC tests claiming to provide health information conform to regulations around medical products, provision of DNA to commercial companies may also have ramifications well outside of healthcare. For example, an online genetic genealogy database based on DTC ancestry tests was used to identify a suspect in the Golden State Killer case in California [17, 18].

There have been pushes to improve standards relating to DTC genetic tests, for example a Human Genetics Commission 2010 report set out various principles for the provision of genetic testing services directly to the consumer [19]. The principles aimed to '*identify areas where individual providers, professional organisations, regulatory bodies, and/or national jurisdictions should have defined measures in place, and the nature of those measures*' and covered issues including advertising; information provision; consent; and interpretation and provision of test results. They also foresaw increasing use of third party interpretation services, recommending that '*test providers who interpret un-interpreted data obtained from genetic tests that have been provided by a third party laboratory should comply with all the aspects of these Principles that are relevant to the services they provide*' (which include '*ensur[ing] that the interpretation of genetic test results is accurate*'). However, application and enforcement of the principles depends on the engagement of the relevant stakeholders, and this is not a given. For example, a 2017 analysis of fifteen DTC genetic testing companies advertising to potential U.K. customers found that none complied with all of the principles for good practice regarding consumer information set out by the commission, suggesting that '*the industry has not so far embraced the self-regulatory approach that was envisaged at the time these [guidelines] were developed*' [20].

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The drive to offer genetic testing to less targeted populations is not restricted to DTC genetic testing firms: the recent U.K. Life Sciences Sector Deal [21] included an aspiration to analyse and communicate information from genomes from five million people. Such a service would presumably include quality control mechanisms to prevent artefacts being interpreted as true results, but what would be included in their reports? Each person has around 100 000 rare genomic variants [5], and working out what they might mean is far from easy. Over 2% of people have a (likely) disease-causing variant in one of the 59 'medically actionable' disease genes which the American College of Medical Genetics and Genomics (ACMG) recommends are opportunistically examined when people have clinical sequencing [22], but the ACMG recently stressed that this gene list was not developed with population screening in mind [23]. Whilst exome and genome sequencing may be highly useful in finding explanations for people affected by rare conditions [24], there is currently limited evidence that this technology would lead to clinical benefit if offered to the population at large [25]. Population-level genome analyses should shake our confidence in our ability to predict the consequences of even well-understood genetic variants when found outside the context of a personal or family history of the relevant disease: their penetrance will be lower than current estimates, which have generally been derived from studying the experiences of people who had targeted testing because they were considered to be at high risk of disease [26].

Conclusion

Although the impact is currently felt most acutely by clinical genetics services, the ready availability of DTC genetic testing has wider consequences. It is crucial that healthcare professionals are sceptical about genetic information obtained via DTC routes; failure to appreciate this can lead to patients being exposed to serious harms such as inappropriate surgery [27]. The cases we discuss illustrate situations where results obtained via DTC tests turned out to be fundamentally inaccurate, but clinicians acting in good faith, in what they believed were the best interests of their patients, had started to make plans based on them. We are concerned that the next few years will see numerous cases where patients are harmed by attempts to obviate health risks diagnosed purely on the basis of DTC genetic test results. We highlight the need to introduce greater scepticism about results accessed via DTC genetic testing into the popular discourse around genomics, in order to safeguard patients against serious harm. We also argue that DTC genetic testing companies and third-party interpretation services need to take greater responsibility to ensure that their customers are not misled by their tests. In the cases we discuss, online warnings that results are for personal purposes only and should not be regarded as medical information have evidently not been enough to inform patients that their results need further scrutiny before being used to direct clinical care.

Summary

- Results obtained via DTC genetic tests may be inaccurate, especially where third party interpretation services are used.
- Strongly positive popular discourse around genetic testing means that many patients might expect results derived from DTC genetic data to be highly accurate.
- Wider awareness of the potential limitations of results from DTC genetic testing is needed in order to avoid individuals being harmed by overzealous attempts to mitigate alleged high health risks that are not founded in evidence.

Abbreviations

DTC, Direct-to-consumer; NGS, next-generation sequencing; SNP, single nucleotide polymorphism.

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Competing Interests

Non-remunerated: Anneke Lucassen declares her relationships as Chair of the British Society for Genetic Medicine, Member of the Ethics Advisory Committee for Genomics England, and Chair of the Ethics Advisory Committee for U.K. Biobank.

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