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Title:

Direct-to-consumer misleading information on cancer risks calls for an urgent clarification of health genetic testing performed by commercial companies.

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Abstract

DTC commercial companies offer genetic tests that are presented as allowing individuals the opportunity to increase their capacities to be in charge of their own healthcare managements. DTC companies deny performing medical tests, yet they provide data based on sequencing multigene panel or whole exome. This contradiction allows these companies to escape the requirements of a regulated medical practice that guarantees the quality of the tests, as well as the information and support for tested individuals. Herein, we illustrate the lack of such requirements by analyzing the bad experience of a young man who dealt with DTC health genetic testing companies. There is an emergency for DTC testing to be either deprived of any medically relevant information, or carried out in a legally regulated medical framework.

A striking example of bad practices

Mr. C., a 33-year-old French man with no relevant personal or family history of cancer or genetic disease, had an experience with a DTC commercial company which illustrates how “health” genetic tests are *de facto* medical information. This young man decided in December 2018 “by curiosity” to benefit from a Christmas discount on the Whole Genome Sequencing (WGS) offered by a DTC company. Mr. C. chose the *Premium Whole Genome for Health* test that proposed the analysis of genes involved in 70 genetic diseases or syndromes, and thus to “get actionable insights to drive his personalized prevention”. By ordering the test on the company’s website, Mr. C. was supposed to accept a 10,000-word “Terms of service” agreement, consisting of no less than 29 clauses, with only one of them referring to WGS, or rather, its limitations. In fact, Mr. C. did not give any specific consent. He sent a salivary sample in January 2019. Three months later, he received an e-mail to download an eighteen-page PDF file of genetic results. This “Wellness and Lifestyle Report” listed the results of the 70 explored diseases, each of them annotated by a green or red light. Among them, eight

cancer predisposition syndromes were listed, with notable exception of both Hereditary Breast and Ovarian Cancer syndrome (HBOC caused by *BRCA1* and *BRCA2* genes) and Hereditary Non-Polyposis Colorectal Cancer syndrome (HNPCC caused by mismatch repair genes). Mr. C.'s report exhibited two “red lights” in the “cancer” section, and therefore two supposed monoallelic pathogenic variants: one in the *APC* gene associated with familial adenomatous polyposis (FAP), and one in the *TP53* gene associated with Li-Fraumeni Syndrome (LFS). FAP confers a very high risk of colorectal cancer before the age of 40, and requires preventive removal of the colon and rectum when polyposis occurs. LFS is associated with a major risk of multiple cancers including sarcoma and brain tumors, often diagnosed within the pediatric age range with a recommended annual whole-body MRI monitoring. In addition, the risk of transmission to the child for both these high-risk cancer predispositions, following an autosomal dominant inheritance, is 50%. The PDF file sent to Mr C. included a simple cut and paste from text published by National Institutes of Health (NIH) on exposed cancer risks and prevention modalities regarding these two predispositions. However, the file did not state that Mr. C. should consult a healthcare specialist provider, nor that these results need to be confirmed by an independent test. Terrified to learn that he was at very high risk for multiple and early-onset cancers, Mr. C. contacted the Institut Curie Genetics Department by email and sent the report. Even though the nomenclature used to name the pathogenic variants did not follow the Human Genome Variation Society (HGVS) guidelines,[1] we confirmed that both variants have indeed been reported as pathogenic for a period of time: NM_000038.5: c.423-1G>A, p.?, and NM_000546.5: c.734G>A, p.(Gly245Asp) (HGVS nomenclature), at the *APC* and *TP53* loci respectively.[2,3]

We then quickly arranged a meeting with Mr. C. at our genetic clinics. We inquired on his current state of health, as well as his personal and family medical histories. We proposed to carry out genetic testing targeted on the *APC* and *TP53* reported variants on two independent

tissue samples (whole blood and buccal swab), as is routine. Mr. C. agreed to the analysis and signed a consent form. During the five-week wait for the results, and seeing as Mr. C. mentioned some occasional rectal bleeding, a gastro-intestinal endoscopy was performed. This examination turned out to be normal and no histopathological abnormalities were detected in systematic gastric and colonic biopsies.

Sanger DNA sequencing failed to detect any of the variants reported by the DTC laboratory. We then asked Mr. C. to get back in contact with the company in order to obtain the raw data of his WGS analysis. He sent us the FASTQ (raw sequencing data) and VCF (*variant call format*, listing all detected genetic variants) files. The low sequencing depth at these positions, the poor quality of the variant calling, as well as the low allelic ratios of altered-to-wildtype alleles (data available on request), indicated that both variants were indeed obvious false positives.

In brief, the lack of both pre and post-genetic testing information, the lack of consent, the lack of post-result accompaniment, the generated anxiety and the prescription of an at-risk medical examination, induced by two false positive results, summarize the bad experience of Mr. C. in the brand new world of DTC health genetic testing by commercial companies.

A critical need for clarification

While this report might seem anecdotal, it is unfortunately not an isolated case and it illustrates how DTC genetic testing often blurs the lines between a medical device and a consumer product.[4,5] Most DTC companies have aggressive commercial marketing plans based on the enhanced autonomy of consumers and their allegedly increased capacity to be in charge of their own healthcare, without the intermediary of physicians and long waiting lists

for specialist appointments.[6] However, there is often a strong contradiction between, on the one hand DTC company results they report that *de facto* have medical value, and on the other hand pre-test information – when the consumer reads it carefully – which declines all responsibility for the results. This deliberate ambiguity allows DTC commercial companies to escape both the legal requirements of medical practice, and the regimented recommendations made to health providers in the field of genetics.[7,8] In addition, because people who have received such positive DTC test results are often afraid and seek advice from public genetic clinics, undue costs to public services are induced.[9]

The two false positive results of this report also illustrate how loose sequence interpretation, left to algorithms and automatic report writing devices, with no one officially responsible for the result, can lead to a disaster. Indeed, any professional with skills in medical genetics would have been cautious facing such a result. A young adult without any symptoms or family history, carrying two unlinked pathogenic variants, each associated with a high-risk cancer predisposing syndrome, whose prevalence in the general population is individually less than 1/10,000, the likelihood of observing both in a single individual being less than $1/10^8$. This result seems virtually impossible in an asymptomatic adult. A recent study has indicated that 40% of variants in a variety of genes reported in DTC raw data were false positives, underlying the importance of confirming any positive DTC results in a clinical grade laboratory with a legally recognized competence in medical genetics.[10] In addition, genetic tests with medical purposes performed by DTC companies could be falsely reassuring for customers. Indeed, “whole genome sequencing” appellation can be misleading if some genes (causing HBOC or HNPCC for instance) are not analyzed, as in the case of Mr C.. Another source of falsely reassuring information is the use of technologies that do not cover the whole coding sequence of analyzed genes. For example, the Food and Drug Administration allowed

in 2017 the company 23andMe to test three frequent *BRCA1* and *BRCA2* pathogenic variants. It is clear that testing only three variants does not provide much medical information. On the contrary, a negative result can provide false reassurance. Actually, alleged “health” information sold to customers might be a pretext to get their genetic data on which they lose any control. [11]

Besides wrongly interpreting sequencing results, another cause of false positives is the over-interpretation of variants of unknown significance (VUS, class 3) - or even benign variants-, some of them being often reported as disease causing. In a survey of 3,672 women who had *BRCA1/BRCA2* testing, Kurian *et al.* reported that in the USA 51% of women carrying a *BRCA1/BRCA2* VUS underwent bilateral prophylactic mastectomy even in the absence of a significant family history.[12] Although not specific to them, these misinterpretations of VUS are at higher risks in DTC companies than in accredited laboratories. Here again, the contradiction between a market-driven genetic testing proposal, and the will to escape any possible medical responsibility, explains many reported cases of variant over-interpretation. Another essential criterion of the quality of a genetic test is the demonstration of its predictive value, that is indeed its clinical utility, a criterion little known by DTC companies, especially when they recommend specific diets or physical exercises according to non-validated genetic data.[7,8,13] At last difficult question raised here is that, by definition, DTC tests are aimed at the general population, ignoring the possible modifying factors of the penetrance of a genetic trait. This is of particular concern for cancer predisposing genes, such as the *BRCA1* and *BRCA2* genes. Yet still a subject of debate, the United States Preventive Services Task Force (USPSTF) and the American College of Medical Genetics (ACMG) do not encourage general population *BRCA1/2* testing and recently made cautious recommendations toward broadening criteria.[14–16] At present, the knowledge of medical genetics, and in particular cancer genetics, is still in progress. It is the time of worldwide epidemiological genetic studies

conducted by international consortia such as ENIGMA, IBCCS and InSiGHT in the field of cancer.[17–19]

Predictive genetic tests leading to irreversible cancer-preventive surgical decisions, to specific cancer treatments or to the identification of recessive disease carrier for reproductive purposes, are indeed already present in the field of medical practice. DTC practices challenge the current legislation. There is an emergency for DTC testing to be either really deprived of any medically relevant information or carried out in a legally regulated medical framework guaranteeing the quality of tests, as well as the information and support of individuals. The fact that individuals have the free will to access information on and from their own genome, does not imply that laboratories can freely deliver false and dangerous information, on the contrary. With the risk of losing credibility due to such improper practices, driven by the market rather than the clinical utility, the future of medical genetics is at stake.

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