CSESM
Journal of Intercultural Management and Ethics (JIME)

Journal of Intercultural Management and Ethics

JIME

ISSN 2601 - 5749, ISSN-L 2601 - 5749

published by

Center for Socio-Economic Studies and Multiculturalism
Iasi, Romania
www.csesm.org

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KNOWING MORE IS NOT ALWAYS KNOWING BETTER AN ETHICAL APPROACH TO THE DIRECT-TO-CONSUMER GENETIC TESTS

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Abstract.
Introduction. The completion of human genome sequencing in 2003 opened the door to new research on understanding diseases that affect the human being and the risk of their occurrence, as well as detailed knowledge of population and parenthood. Moreover, in recent years, more and more kits with simple use at home have been marketed, through which the population can find out details about their own genetic load. But these tests are not without risks. **Material and method**. The authors conducted a literature research to identify the ethical issues raised by the use of rapid genetic testing kits at home. **Results**. Direct-to-consumer genetic tests involve collecting a smear of epithelial cells from the jugal mucosa or a saliva sample. The benefits of these tests are at the individual level, allowing people to find detailed information about ancestors and their heritage, establishing parenting, certain genetic traits that characterize them or if they are carriers of a genetic mutation responsible for the occurrence of various diseases. On the other side these analyzes are accompanied by risks that should not be neglected: the strong emotional load- especially in the case of health risks or parenting, relatively low accuracy with the possibility of false positive or false negative results, the security of data stored in databases, data confidentiality, use of information for commercial purposes. Also, the direct-to-consumer genetic tests call into question the observance of individual autonomy by the fact that the individuals who use them often have incomplete or incorrect information regarding the relevance of the obtained results. **Conclusions**. Although advances in science bring the possibility of genetic analysis into the homes of ordinary people, it must not be forgotten that the benefits must always be weighed against the associated risks, as genetic analysis can provide sensitive information that must be properly protected and understood.

Key words: rapid genetic testing, risks, benefits, ancestral origin, genetic predisposition

Introduction.

The completion of the sequencing of the human genome in 2003 opened the door to new research on the understanding of diseases that affect the human being and the risk of their occurrence (Floris et al. 2020; Shuren, 2010). This is possible because the links between genetic variants (which differentiate individuals from each other) and certain diseases have been identified (Shuren, 2010).

At the same time, the sequencing of the human genome allowed researchers to know in detail the other human characteristics with genetic determinism such as sports abilities, personality (Horton et al., 2019), the body's response to certain substances (Barbarino et al., 2018), ancestral origin (Dick, 2012; Horton et al. 2019), eye color (Cernat, Bashir, & Ungar, 2022) to name a few.

The usefulness of sequencing the human genome, with the identification of variants that differentiate individuals, was seen as a marketing opportunity by numerous commercial companies long before scientists introduced them into current medical practice. In this regard, various companies have begun to market through the Internet kits for genetic testing at home - also known as direct-to-consumer (DTC) genetic testing, for which buyers did not need a prescription, companies thus bypassing the medical system (Dick, 2012). Moreover, the number of companies and easy-to-use genetic tests at home that they offer to consumers who are eager to find out information about their health has had a rapid upward trend- comparable to the growth rate of other types of medical tests at home, becoming practically an industry in the true sense of the word (Dick, 2012; Goddard et al., 2009). From the approximately 14 genetic DTC tests in 2004 intended for searching various aspects of health (e.g. lifestyle, nutrigenomics, hemochromatosis, thrombosis, chronic diseases, etc.) available in 2003, they increased to 53 tests in just 6 years (Goddard et al., 2009). An analysis conducted in 2020 shows that 49 traits can be assessed through home tests only regarding nutrition (e.g. food intolerances, macronutrients, micronutrients, hormones, oxidative stress, etc.). In terms of the number of people performing such tests, some estimates indicate over 26 million DNA profiles entered in the databases of four major companies by 2019 (Friend et al., 2018).

These huge numbers can be explained in several ways. On the one hand, by the low costs of a home genetic testing kit- because advances recorded in science in recent years have made genotyping and genome sequencing possible at lower costs (Floris et al., 2020). In addition, the growing number of companies selling such kits has imposed a reduction in costs due to market competition. On the other hand, the large number of people who buy such tests can be explained by the simple procedure of collecting and sending the sample. Most kits involve simply collecting a smear of epithelial cells from the jugal mucosa with a mouth swab or collecting a saliva sample. The samples are then mailled to the company, where specialists perform the DNA extraction and subsequently identify the genetic variants involved in the onset of certain diseases or in determining certain traits of the DNA donor (Floris et al., 2020).

Similarly, the promises of companies about the results (Horton et al., 2019) and the desire of people to prevent disease or receive an incentive to change the lifestyle to a healthy one, are other reasons that explain the large number of requests for such tests.

Types of direct-to-consumers genetic tests

Direct-to-consumer genetic tests offer a wide range of genetic information about health: the risk for diseases such as different types of cancer (Floris et al., 2020; Goddard et al., 2009); the risk of complications of pregnancy (Goddard et al., 2009); fitness-related features such as performance and injury tests (Guasch-Ferré, Dashti, & Merino, 2018); immunological diseases (Floris et al., 2020; Goddard et al., 2009) such as ankylosing spondylitis and celiac disease (Goddard et al., 2009); neurological diseases (Floris et al., 2020); diabetes (Cernat et al., 2022; Floris et al., 2020; Goddard et al., 2009); glaucoma and macular degeneration (Goddard et al., 2009); Alzheimer’s disease and other types of dementia (Floris et al., 2020; Goddard et al., 2009); osteoporosis; pediatric conditions; hemochromatosis; thrombosis- by identifying prothrombotic genetic variants, which can induce, for example, increased resistance of the individual to activated protein C, which has anticoagulant effect (Goddard et al., 2009).

Genetic information can be used to identify predisposition to certain diseases by direct analysis of quantitative traits, such as values of physiological parameters- like body mass index (with implications for obesity), or blood levels of various metabolites (Horton et al., 2019).

Still in the health-related area, there are tests aimed at the field of pharmacogenetics, i.e., the relationship between the presence of certain genetic variants and the body's response to the administration of various drugs (Dick, 2012; Goddard et al., 2009). Some tests, according to the companies that sell them, can make predictions regarding lifestyle changes, such as smoking cessation (Goddard et al., 2009).

Direct-to-consumer genetic tests also provide information outside the state of health, such as: ancestral origin (Dick, 2012; Horton et al., 2019); eye color (Cernat et al., 2022); the sex of the child (Goddard et al., 2009) or even the talents the child might have (Horton et al. 2019), elements related to personality or sports skills (Horton et al., 2019). A combination of health-related and non-health-related elements is framed in dermagenetics, with companies using genetic information to formulate personalized recommendations regarding the use of skin care products (Goddard et al., 2009).

A particular category of tests, which are becoming increasingly popular, focuses on nutrigenetics and nutrigenomics. Nutrigenetics studies the role of genetic variants in regulating metabolism and the body's response to various nutrients. Nutrigenomics examines how different nutrients can control gene expression (Floris et al., 2020). The study by Floris et al. (2020), which looked at companies that offer nutrigenetics kits, shows that companies generally investigate traits such as food intolerance (e.g. lactose or fructose intolerance), food sensitivity (e.g. alcohol, sulphites, nickel, refined carbohydrates), macronutrients (e.g. lipid, carbohydrate and protein metabolism), micronutrients (e.g. vitamins, iron, calcium, sodium), eating behavior (e.g. weight management, hunger and appetite control, eating habits, food craving), psysiological parameters (e.g. levels of lipid profile, BMI, blood presure, bitter taste), oxidative stress (e.g. antioxidant and detoxifying capacity, antioxidant needs), food-related hormones (e.g. insulin sensitivity and resistance, risk of developing insulin resitance) (Floris et al., 2020). Thus, the role of these genetic tests consists mainly in controlling and maintaining a healthy body mass and adapting the diet according to the individual genetic background (Guasch-Ferré et al., 2018), offering personalized diet plans (Dick, 2012). This aspect is all the more important as many diseases have a nutritional etiopathogenic component, and establishing an individualized dietary plan, adapted to the genetic background can contribute to the prevention of those diseases (Floris et al., 2020). However, the recommendations offered by home genetic testing companies are based on a limited number of genetic markers, while the scientific reality is that metabolism and nutrient response are regulated by a multitude of genetic variants (Floris et al., 2020).

For health-related tests, the most commonly used method of analysis is SNP-chip genotyping (Horton et al., 2019). The principle of this method is the analysis of the genetic code (a large part of the genome, but not its totality) to identify the genetic variety-variants of the same gene, which allow the differentiation of individuals (Horton et al., 2019).

However, it should be noted that not all genetic variants are associated with clinically manifested health disorders, developmental disorders or particular reaction to substances (Floris et al., 2020), but some may be silent.

The individual risk or predisposition to a particular disease is calculated using a polygenic score, resulting from the combination of several common variants in the genome. However, medical experts question the validity and usefulness of these scores as real predictors for a particular condition (Horton et al., 2019). In this sense, some tests verify the carrier status of certain specific gene variants for recessive diseases, providing results such as: "one variant detected in the CFTR gene. If you and your partner are both carriers, each child may have a 25% chance of having this condition." But some do not consider the ancestral component of these tests, in the sense that the results are specific to certain population groups. A user from a different population group could receive a negative result for that variant, but could be the bearer of another variant, which is not verified by the test being performed (Horton et al., 2019).

Direct-to-consumer genetic tests- an ethical analysis

It is universally accepted that prevention is the best weapon in the fight against diseases. Thus, it is important to take the necessary measures when we have the opportunity. An "opportunity" may be to perform a genetic test after collecting a saliva sample at home, and there are more and more companies dealing with such tests. However, the promises that these companies make must be interpreted in the context of the accuracy and validity of the tests offered, aspects that are often called into question by researchers and regulators (Dick, 2012).

From an ethical perspective, DTC genetic tests require a rigorous assessment of the benefits and risks involved, given the obligation to maximize benefits while minimizing risks in all medical interventions, starting from the classic ethical principle "First, do no harm".

The companies that produce these tests and their supporters say that the tests they perform support the health of the population by mobilizing them to make concrete, positive changes in their lifestyle in a personalized way- whether it is food or whether it is physical activity or giving up behaviors that are harmful to health (Cernat et al., 2022; Floris et al., 2020). The reality is that the results of these tests have the potential to encourage such decisions, but most of the time consumers limit themselves to the intention to make changes and do not really act in a practical way in these directions. Studies show that most of the users of these tests do not fully read the results of the tests and little to moderate take concrete measures after knowing their genetic features (Cernat et al., 2022). Also, the decision to implement lifestyle change measures in line with the test results may be associated rather with an intrinsic motivation of the people being tested, who generally want to be well and work for success in such a direction and not because the results of the tests themselves motivate them. In this regard, studies question the reality of lifestyle change motivation based on DTC genetic tests results (Cernat et al., 2022).

For example, in the case of Alzheimer's dementia, associated with the degradation of decision-making competence, the benefits of knowing the risk are multidirectional. On the one hand, it allows measures to be taken to delay the morbidity associated with the progression of the disease and to control subsequent psychiatric symptoms, all the more so as there are medication that can delay the cognitive decline, institutionalization of those affected and thus reduce costs associated with caring for these patients (Callahan, Hendrie, & Tierney, 1995). On the other hand, it facilitates the possibility of establishing in advance a therapeutic plan and measures that will be taken at different points in time, when the individual's decision-making capacity will be altered by the disease (Kier & Molinari, 2003). Added to this is the fact that the diagnosis of dementia is associated with a strong emotional load, and the thought that at some point they will be taken by surprise by this diagnosis makes people trust any oasis of hope offered by companies who perform genetic testing fast and cheap (Kier & Molinari, 2003). This is all the more true, and the psychological attraction is all the stronger for consumers who already experience symptoms that they correlate with the onset of dementia (Kapp, 2003).

Recommendations resulting from the analysis of nutrigenetics tests could help to improve the applicant's lifestyle, but in the absence of appropriate, scientifically based explanations, they may become useless (Floris et al., 2020).

When it comes to the risk of disease revealed by these tests, an element that should not be underestimated is the multifactorial nature of most genetic diseases, i.e., the occurrence of the disease is determined on the one hand by mutational changes in genes and on the other hand by environmental factors (Dick ,2012). Moreover, the presence of a certain gene variant does not automatically mean the development of the disease, just as its absence does not mean the absence of the risk of developing the disease. All the more so as the results of genetic tests performed at home are not accompanied by genetic advice or at least by an opinion of a specialist (Dick, 2012; Kier & Molinari, 2003). Thus, researchers point out that the predictive value of genetic testing is limited when family history does not suggest the need for such testing (Horton et al., 2019).

Under these circumstances, the American Medical Association is sounding the alarm about misinterpretation and miscalculation of risk, which will implicitly lead to wrong decisions, unnecessary lifestyle changes and wasted money (Dick, 2012). Also, the U.S. Government Accountability Office published in 2010 a report on the activity of companies that sell DTC genetic tests, showing a lack of accuracy in the results after the same sample was analyzed by four different companies and each established the donor’s risk for the same disease differently (US Government Accountability Office, 2010).

Thus, it was raised the issue of the psychological consequences that the results of these tests could have, in terms of stress, anxiety and dangerous behaviors, on individuals overreacting to the risk of disease (Cernat et al., 2022; Dick, 2012; Kier & Molinari, 2003). This is all the more important as the results of a third party, in specialized medical laboratories, often contradict the results of companies that sell DTC genetic tests online.

For example, a woman who receives a result showing the presence of a variant of the BRCA1 gene, which predisposes her to breast cancer, may require breast resection surgery to prevent the onset of cancer. If that result is false positive, the mastectomy would have been done unnecessarily. If the woman does an authorized re-test before the surgery and the result is negative, she can cancel the surgery, but at the same time she can still experience the anxiety related to her risk of cancer (Horton et al., 2019). Regarding the genes for breast cancer, experts draw attention to the genotyping method used by most of the companies, i.e., SNP-chip genotyping, which is still not reliable enough when testing very rare genetic variants. In this regard, the study conducted by Weedon et al. (2019), who analyzed the BRCA1 and BRCA2 genes available in the UK Biobank, show that 96% of the genetic variants identified by the mentioned method were false positive (Weedon et al. 2019).

Another negative consequence of the DTC genetic testing is directed towards the medical system. If these tests are done by people on their own initiative, out of curiosity or even like a play, without the recommendation of a medical specialist after identifying a suggestive personal and family medical history, scientifically unfounded results could lead users to seek additional medical consultations and tests, increasing the overload of the medical system and the medical costs with unnecessary analyzes. Moreover, the risk of iatrogenicity should not be ruled out if patients are subjected to the risks of medically unjustified tests, even if requested by them (Cernat et al., 2022; Dick 2012).

At the opposite pole, a false negative result or one that indicates a low risk of disease could provide individuals a false assurance that they will not develop the medical condition in question (Dick, 2012). However, the companies test a limited percentage of the genetic variants that may be involved in the determinism of a particular disease. Examples of this are variants of the BRCA1 and BRCA2 genes incriminated in the occurrence of breast cancer. Specifically, according to Horton et al. (2019), companies are generally looking for only three gene variants (out of thousands available), specific to individuals with Ashkenazi Jewish origins, which could lose from the sight 80% of people with other BRCA variants in the general population (Horton et al., 2019).

A major concern with DTC genetic tests is the proper information of the potential consumer before purchasing the test and its fully informed decision on taking it (Hogarth, Javitt, & Melzer, 2008). In this regard, the studies highlight alarming issues such as the lack of complete information provided by companies trading DTC genetic tests on their websites, to which is added the difficulty of obtaining relevant information or providing information in a confusing language (Cernat et al., 2022). Incomplete information questions the validity of the consumer’s decision to take the test and raises the issue of violation of the principle of autonomy by virtue of which the individual has the freedom to decide on his own life, in an informed manner.

Tests marketed via the Internet can create additional problems when they do not have/do not require a way to verify the sample donors, which could guarantee/certify their autonomy. Moreover, in their advertisements, companies even encourage “hidden” or involuntary testing - if, for example, a woman wants to know the paternity of the child or when spouses want to discover the infidelity of their partners (Phillips, 2016).

Last but not least, another risk of DTC genetic testing is the lack of a system to ensure the protection of the individuals in terms of privacy, confidentiality and security, given that the test results are stored in a database. Companies that have a privacy policy inform users that the results can be used by third parties- either for research, by pharmaceutical companies that buy the information and then make profits from the research, or for legal purposes (for example, the information being provided to law enforcement agencies for the identification of a criminal) (Cernat et al., 2022). There is a risk that users will not understand what this means, will not see this as a problem or will not read these privacy policies- often listed in the footnotes. So, although consumers are given the opportunity to delete their information from databases, they choose not to do so, because they do not understand the risks to which they are exposed. In addition to the companies that mention these policies, many others do not in fact offer any kind of privacy policy to buyers (Du & Wang, 2020). No less important is the risk that databases may be broken and information may reach unauthorized persons, who may use it for various illegal purposes.

Conclusions.

The progress of science is more and more present in our lives. Technology fascinates and promises, improves our lives but brings with it various risks and, above all, ethical challenges. Through DTC genetic testing, genetics becomes available to all, but in order to represent a benefit, the associated risks must be fully understood. The DTC genetic testing provides sensitive personal information, which on the one hand must be interpreted with caution and, on the other hand, must be adequately protected because knowing more is not always knowing better .

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