CLINICAL PRACTICE

Direct-to-consumer genetic testing: To test or not to test, that is the question

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In direct-to-consumer (DTC) genetic testing, laboratory-based genetic services are offered directly to the public without an independent healthcare professional being involved. The committee of the Southern African Society for Human Genetics (SASHG) appeals to the public and clinicians to be cautious when considering and interpreting such testing. It is important to stress that currently, the clinical validity and utility of genetic tests for complex multifactorial disorders such as type 2 diabetes mellitus and cardiovascular diseases is questionable. The majority of such tests are not scientifically validated and are based on a few preliminary studies. Potential consumers should be aware of the implications of genetic testing that could lead to stigmatisation and discrimination by insurance companies or potential employers of themselves and their family members. Guidelines and recommendations for DTC genetic testing in South Africa (SA) are currently lacking. We provide recommendations that seek to protect consumers and healthcare providers in SA from possible exploitation.

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In recent years the number of molecular genetic tests on offer and the demand for these tests has burgeoned. These tests are a major area of development in an effort to reap tangible medical benefits from the significant resources that have been invested in basic biomedical research as part of the Human Genome Project. Tests are now not only offered for diagnosis, carrier, presymptomatic, prenatal and pre-implantation testing, but also for pharmacogenetics, disease susceptibility, nutrigenetics and genetic relatedness. These tests have traditionally only been available through healthcare providers (such as clinicians and genetic counsellors) who would order the applicable test from a laboratory, collect and send the samples, interpret the test results and provide appropriate pre- and post-test counselling.

What is direct-to-consumer genetic testing?

Direct-to-consumer (DTC) genetic testing differs from traditional genetic testing in that the consumer or client can order tests and receive results **without** a healthcare provider being involved. DTC tests are usually marketed via the internet, television or print media. Typically, the sample collection kit is mailed directly to the consumer and the test usually involves collection of a sample for DNA analysis from swabbing the inside of the cheek or, in some cases, a blood sample following a visit to a health clinic. The sample is mailed back to the laboratory and consumers are notified of their results by mail, telephone, or via the internet. Service providers offering these tests are based locally and overseas.

The vast majority of DTC genetic testing companies either do not provide genetic counselling services, or provide inadequate counselling. As a result, the significance of findings is open to misinterpretation by consumers. In the South African (SA) context, no information is available regarding the extent of uptake of DTC genetic testing. However, anecdotally there are numerous instances where members of the public (some distraught) have approached independent clinical geneticists and genetic counsellors to explain the meaning and implications of their results. It is anticipated that the number of consumers in SA accessing DTC genetic tests will rise as a result of increased awareness and an assumed benefit of these tests on the part of the lay public. There are many types of genetic tests, including those that aim to show how an individual might respond to a particular diet or athletic performance. This article, however, focuses on those tests for health-related traits.

Genetic testing for complex multifactorial disorders is premature

Genetic tests offered for health-related traits can be broadly divided into two main classes: tests for monogenic and for complex multifactorial disorders. Monogenic disorders are more straightforward in terms of testing because the genetic defect (pathogenic mutation) in a single gene is the direct cause of the disorder. These disorders, referred to as Mendelian, comprise different modes of inheritance including autosomal dominant (e.g. Huntington's disease and some forms of hereditary nonpolyposis colorectal cancer), autosomal recessive (e.g. cystic fibrosis and galactosaemia) and X-linked disorders (e.g. Duchenne muscular dystrophy and haemophilia). For these conditions, there is a clear relationship between cause and effect, i.e. if a mutation is shown to be present, it is likely that the individual will develop the disorder. There is a strong case for genetic testing when these types of disorder are present in a family, provided that appropriate genetic counselling is available. In fact, the European Academies Science Advisory Council (EASAC) recommends that monogenic disorders should be excluded from the services offered by DTC genetic testing companies unless accompanied by appropriate medical supervision and genetic counselling.[1]

In contrast, the majority of human disorders with a heritable component are of a complex and multifactorial nature. In these disorders, genetic variation in many genes as well as environmental risk factors,

including nutrition and lifestyle choices, increase the susceptibility for developing the condition. This means that no single genetic variant, or even a small number of variants, can be used to accurately predict risk. Despite this level of complexity, many DTC companies advocate the use of genetic tests for predicting susceptibility to develop complex disorders such as hypertension, Alzheimer's disease, prostate cancer and cardiovascular diseases. We caution that at the present time, genetic tests for these conditions are premature and are **not supported** by rigorous scientific evidence. In addition, and very importantly, many of them have not been studied in different (e.g. African) populations where they potentially might have a different genetic aetiology.

Sequencing of the human genome has yielded important information including the number of human genes, the complexity of the genome and the sequence similarity to other species. However, it is still not understood how the thousands of proteins encoded by these genes interact in every cell and work together to ensure proper functioning of that cell. Even less is understood regarding the mechanisms that go awry and which might lead to disease.[2] If potential environmental contributions are added into the equation, the picture becomes even more complex and the exact genetic role players in unravelling the disease process become difficult to pin-point.

In type 2 diabetes mellitus (T2DM), which is projected to double in prevalence by 2030 in low- and medium-income countries, several genes are involved in the way insulin is produced and used by the body. Interaction of the genes involved in the T2DM pathway, with various dietary and lifestyle factors, work together to influence the development of the condition, as illustrated in Fig. 1. Also, different sequence variants could result in the lowering, increasing or complete lack of certain gene products, which could influence the severity of the condition as well as the age at which the disease manifests. Thus, if a variant in a gene – such as the sulfonylurea receptor gene (*SUR1*) – is offered as a genetic test, several factors need to be understood, including: (*i*) how it was determined that this particular variant is predictive of T2DM; (*ii*) its overall contribution relative to other potential variants in the hundreds of genes involved in insulin metabolism; and (*iii*) how these variants interact with the environment to increase or decrease. Similarly, an individual's response to anti-diabetic drugs cannot be accurately predicted based on variants in a single gene, but requires knowledge of the role of variants in several genes and a thorough understanding of gene-gene and gene-environment interactions.

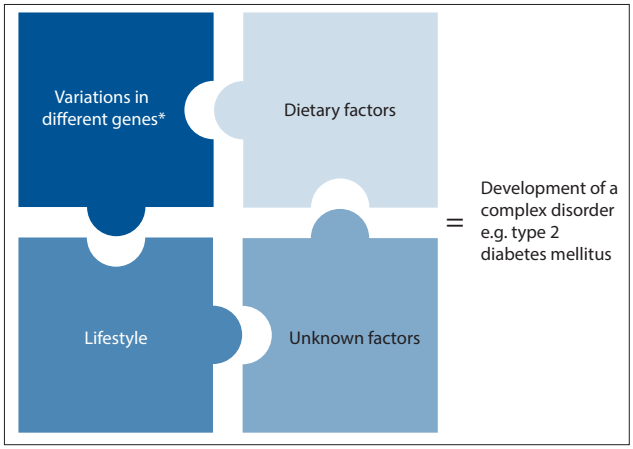

*Fig. 1. A complex disorder such as T2DM develops as a result of genetic variation in a number of different genes in combination with various dietary, lifestyle and other currently unknown factors. *More information on the genes involved in T2DM can be found at the Kegg pathway database (http://www.genome.jp/kegg-bin/show_pathway?hsa04930).*

Both clinicians, and the general public who lack the relevant genetic knowledge, could be misled into thinking that genetic testing can be done for any inherited disorder or any disease with a heritable component. One company in SA offers genetic tests for predisposition to various conditions including obesity, heart attack, and even offers a 'well-being' genetic test! Many of the tests are based on preliminary research studies with small sample sizes, borderline significance of association and small effects on increased risk for developing disease. This does not constitute sufficient scientific evidence for use in a clinical setting. Therefore, many of the claims that are made by service providers are not justified, as there are currently **no scientifically validated** diagnostic or predictive genetic tests for complex conditions. Furthermore, it is unlikely that there will be in the immediate future.[3,4]

Medical and ethical concerns

We are aware that DTC genetic testing is here to stay and that it does have some advantages. Some of these benefits include the accessibility of tests to the public, increased awareness of genetic disorders and enabling consumers to play a proactive role in their healthcare. DTC genetic testing companies can empower individuals by making available/accessible tests that are difficult to access through the healthcare system. In addition, they offer interesting opportunities for 'genetic hobbyists' to learn about their ancestral origins and recreational genetics outcomes, such as whether one has the genetic variations that make Brussels sprouts taste bitter or that determine whether one has wet or dry ear-wax.

However, there are major concerns about tests that claim to accurately predict susceptibility to complex diseases owing to misinterpretation of results, unrealistic expectations, anxiety and inappropriate medical decisions.[1] Parkinson's disease (PD), a debilitating, progressive neurodegenerative disorder, currently without a cure, illustrates some of these concerns. The pathogenic mutation, G2019S, found in the leucine-rich repeat kinase 2 (*LRRK2*) gene, is present in about 1 - 2% of sporadic PD cases (these are families in which there is only a single affected individual). As a result of founder effects (where a mutation occurs at a relatively high frequency in a specific population due to its small number of ancestors) the frequency of G2019S in the PD population of Ashkenazi Jewish and North African Arabic origin is approximately 1 in every 5 patients[5] and 1 in every 3 patients,[6] respectively. Due to the high frequency of G2019S in these two patient populations, and its virtual absence in healthy individuals and those with other neurodegenerative disorders, it is now offered to the public as a genetic test for PD.

In some cases, this may be the only mutation that a particular service provider will screen for in their PD screening test. A negative test for the G2019S mutation does not necessarily mean that the individual will never develop PD, as they may still harbour any one of the many other PD-causing mutations or they could develop the disease as a result of environmental risk factors, many of which are still unknown. Conversely, individuals who test positive for the G2019S mutation may never develop PD, as evidenced by some G2019S-positive individuals who live to their seventies and never develop neurological signs.[7]

There are many ethical issues to consider when providing genetic tests for disorders like PD for which there are currently no preventive measures or a cure.[8] In a symptomatic individual, this gene test would not help to improve the efficacy of treatment, patient care or prognosis (although this may change as the function(s) of the gene(s) involved is better understood, and targeted treatments are developed). Mutation carriers may consider prenatal or even pre-implantation genetic testing to avoid transmitting the mutation to their offspring. The selective termination of a fetus that may develop an adult-onset disorder is itself a subject of considerable ethical debate. Moreover, the implications of a positive test result for relatives, who themselves have not taken the test, requires consideration as an individual's parents, siblings and children

are in fact 'indirectly' tested when a mutation is found. In the case of a dominant condition, if the test is positive it will reveal that one of the parents is an obligate mutation carrier and also implies that the siblings have a 50% chance of carrying the mutation. This 'unsolicited' information may be resented by some family members as they might not have considered the disorder to be hereditary and had not given consent to receiving such information. Consumers may also experience an invasion of their privacy if the testing companies use their genetic data in an unauthorised manner e.g. selling the data to a third party such as insurance companies or potential employers who may, based on these findings, discriminate against them. According to the Association for Savings and Investments SA (ASISA) guideline, insurance companies have rights to access the results of genetic tests performed prior to application for cover. Consumers should be aware of this before they request DTC genetic tests as it may influence their risk profile. It is therefore essential that the consumer receive appropriate **pre-** and **post-**test genetic counselling and that they carefully consider the ethical issues. Counselling guidelines have been developed for presymptomatic genetic testing to ensure patient choice and safety and could be adapted for other scenarios.[9] Further research is needed on appropriate counselling guidelines and defining the boundaries of this profession as examination of the genetic counselling services offered by some DTC genetic testing service providers revealed several points of concern.[10]

Another contentious issue with DTC genetic testing is 'surreptitious genetic testing', which is the collection of a biological specimen for DNA extraction and the disclosure of the genetic information without obtaining consent from the person tested.[11] For some DTC testing companies, the request for specimens such as a blood sample or a cheek swab may prevent surreptitious sample collection; but other companies are willing to analyse DNA from items such as strands of hair, bubble gum or cigarette butts. Such testing could have medical and legal implications. This includes inappropriate treatment and initiation of parentage disputes and lawsuits, notwithstanding the potential quality control concerns such as chain of custody, and questionable laboratory practice.

Absence of regulation in SA

Despite the numerous concerns associated with DTC genetic testing, in SA, and in Africa as a whole, there is a lack of guidelines and regulations governing these tests. In Europe and North America, various organisations have developed guidelines and recommendations for their governments and policy makers. In Europe, the EASAC has produced a document in which they advise against DTC genetic testing as they state that it has little clinical value at present and has the potential to be harmful.[12] Notably in Germany, the Genetic Diagnostics Act requires involvement of a physician in all forms of genetic testing, thereby effectively prohibiting DTC genetic testing. The UK Human Genetics Commission has provided a list of principles to ensure the provision of a high-quality DTC genetic testing service that meets the expectations of the consumer while safeguarding their interests.[13] The American Society for Human Genetics has published a statement which calls for education of healthcare providers regarding the potential benefits and limitations of these tests as well as the certification of all DTC genetic testing laboratories.[14] Also, the American College of Medical Genetics has issued a list of minimum requirements for a DTC genetic testing protocol that includes the provision of the scientific evidence on which the test is based in a readily understandable format.[15] In 2008, the US government passed the Genetic Information Non-discrimination Act (GINA), protecting their citizens against discrimination based on their genetic information when it comes to health insurance and employment. It is apparent that, since service providers are often based in different geographic locations to the clients they serve, DTC genetic testing will require guidelines from various international professional bodies, universally applicable regulations and mutual agreement on a widely accepted 'code of practice'.[16]

Recommendations for SA

We recommend that the SA National Department of Health establish an expert monitoring body to comprehensively and systematically evaluate all genetic tests provided by DTC genetic testing companies in SA. The evaluation must include the following key issues:

1. All genetic testing must be based on rigorous peer-reviewed scientific evidence and quality assurance should comprise 3 main parameters:[17]
   - analytical validity (a test's accuracy in detecting a particular genetic variant when present and not detecting the variant when absent)
   - clinical validity (the test's ability to distinguish between those who have/will develop a disorder/condition and those who will not)
   - clinical utility (the likelihood of the test to significantly improve patient outcomes).
2. Service providers must be transparent in their dealings with their clients and must provide all relevant scientific information on the accuracy and usefulness of the tests they offer.
3. Advertising for genetic tests must not be exploitative and must not overstate the benefits of the test.
4. A genetic counsellor, clinical geneticist or a clinician **must be consulted** before the genetic test is performed, to determine if the test is appropriate and valid, and afterwards to assist with interpretation of the results. A list of some SA genetic counsellors is available online.[18]
5. SA legislation must be reviewed and amended to prevent stigmatisation and discrimination on the basis of genetic testing by insurance companies and/or potential employers.

These measures are necessary to ensure that consumers in SA and their healthcare providers are protected from the potential harms and possible exploitation associated with this industry, and that their decision whether or not to be tested is based on a well-informed choice.

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