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Introducing the medical journalism column

The purpose of this new column that I will be writing is to provide TWS readers with a new facet of medical writing: medical journalism. Medical journalists have to keep up-to-date with recent developments in biomedical science, to observe how society as a whole reacts to them, to make use of good judgment based on scientific knowledge, and to merge it with a healthy portion of criticism.

In my choice of launching the column with an article on predictive genetic testing, I was inspired by my work in the field of Huntington's disease. It often led me to think of how I would behave and what decisions I would choose if I were at risk of this fatal disease. The topic also seemed appropriate because of the debate on preimplantation genetic diagnosis at the German Parliament (Bundestag) earlier this year and the 10th anniversary of the first human genome project publication.

Predictive genetic testing: To know or not to know?

by Diana Raffelsbauer

If you knew you were at a high risk of developing a fatal, late-onset genetic disease, would you undergo predictive genetic testing while you are healthy to find out whether or not you have inherited the gene that will later cause the disease? If your answer is no, would you change your mind if you knew that a cure for that disease had been found, or if you could prevent the disease or delay its onset by changing your lifestyle or diet? Would you be willing to accept the impact this test may have on your family members? This article aims to discuss some of the issues in predictive genetic testing in view of the recent advancements in human genetics.

The Human Genome Project

Launched in 1990, the Human Genome Project was a huge scientific endeavour aiming to determine the sequence of the 3 billion base pairs that make up the human genome and to identify all the approximately 25,000 human genes [1]. Although the project was finished in 2003, annotation of all genes and understanding their function and regulation are far from being complete. Analyses of the data will continue for many years, requiring the development and improvement of a whole range of bioinformatics methods and tools. The Human Genome Project was also committed to the transfer of technology to the private sector, opening new opportunities to pharmaceutical and biotechnology companies for the development of new medicinal products.

I am particularly interested in ethics in clinical research, in how people's interests may be different from those of for-profit companies and, most importantly, in whether people are aware of this. In the context of predictive genetic testing, it is legitimate to ask whether we should make use of all resources that current technology enables, although their potential to improve health-related quality of life is unquestionably welcome. At some point, we have to critically consider the advantages and disadvantages of the options and make the decision whether or not to use them. However, people (especially those without a medical background) are often left alone with answers that they might not be able to understand properly, or they are faced with an action for which they might not be psychologically prepared. So far, the impact of predictive genetic testing on mental health has been poorly investigated.

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Linking genomes to diseases

Now that we have the code, what’s next? In fact, only 1.1% to 1.4% of the genome’s sequence codes for proteins; the rest is non-coding DNA, which was formerly called ‘junk DNA’. Erroneously, because many types of non-coding DNA sequences do have known biological functions, including transcriptional and translational regulation of protein-coding sequences. Linkage mapping often identifies chromosomal regions associated with a disease that have no evidence of functional coding genes within the region, suggesting that disease-causing genetic variants also lie in the non-coding DNA [6].

Searching for genetic roots of diseases inevitably leads to the search for differences between individuals. While human DNA sequences are 99.9% identical to each other, the 0.1% of variation is expected to provide many of the clues to the genetic risk for common illnesses [7]. Genetic variation gives rise to polymorphisms, such as single nucleotide polymorphisms (SNPs). A SNP is a DNA sequence variation occurring when a single nucleotide in the genome differs between individuals. In a companion volume to the ‘Book of Life’ (the human genome sequence), scientists have created a catalogue of 1.4 million SNPs and specified their exact locations in the human genome [8].

Following the Human Genome Project, research has focused on studying genetic variants that may be associated with increased risks for common diseases like cancer, diabetes or neurodegenerative disorders. The International HapMap Project initiated in 2002 aimed to determine common patterns of genetic variation in the human genome [9]. Such variations may not only affect general health and disease predisposition, but also mechanisms of responses to drugs and environmental factors. Haplotype maps were released in 2005 [10] and 2007 [11], revealing more than 3.1 million common SNPs in the human genome.

Together, the Human Genome Project and other open-access projects like the HapMap Project have opened new avenues for understanding the complex relationships between genomes and diseases. Medicine has benefited from data sharing among large consortia, which has enabled the rapid and precise localisation of many disease-associated regions. To date, over 800 common SNPs have been strongly linked to 150 traits and diseases via genome-wide association studies [12]. For instance, three new genes (CLU, PICALM and CR1) were reported in 2009 to be significantly associated with an increased risk of developing late-onset Alzheimer’s disease [13,14]. A quick PubMed search indicates that roughly one in every six papers published on schizophrenia, bipolar disorder or autism refers to genetics [15]. As of the end of 2010, there were more than 40 confirmed genetic loci associated with type 2 diabetes [16]. The Cancer Genome Atlas in the USA [17] and the Cancer Genome Project in the UK [18] are underway aiming to improve our ability to diagnose, treat and prevent cancer through a better understanding of the molecular basis of the disease using high-throughput genome analysis techniques. Genome-wide association studies in cancer have already identified over 150 regions associated with two dozen specific cancers [19]. As of June 2011, a search at PubMed using the terms ‘genome-wide association studies’ and ‘cancer’ yielded 100 articles published in 2011 alone. Since the 1990s, more than 15 breast cancer susceptibility genes have been identified, the most important being BRCA1 [20] and BRCA2 [21], and genetic testing for mutations in these genes in high-risk families is now well established [22]. However, less than 30% of familial risk of breast cancer is due to known genes [23].

Although the impressive advancements in genomics have improved some of our basic understanding of the molecular biology and pathogenesis of different diseases, it would be naive to believe that genes are the sole determinants of our health, and bad SNPs are dictators of diseases. The scenario might be simpler in monogenic diseases, but becomes far more complex when many genes are involved, each harbouring a variant that confers a modest degree of increased risk. These variants interact with each other and the environment in complex ways, rendering their identification exponentially more difficult than for single-gene defects [2]. The modest effect of many of the common genetic variants identified so far, as well as the fact that they account for a small portion of the total heritability of inherited disease variation, have led to the re-examination of the contribution of environment, gene-gene and gene-environment interactions, and rare genetic variants in complex diseases [24]. Copy number variations are very frequent in the human genome [25], and they may have impact on disease predisposition as well, especially in psychiatric disorders [15].

Predictive genetic testing

When the genetic factors associated with a particular disease are known, predictive genetic testing offers at-risk individuals the opportunity to learn their predisposition. Knowledge of the gene status may enable people with positive test results to take preventive measures to reduce the risk, impact and severity of the disease in the future. Such measures include medical surveillance (e.g. breast cancer screening), lifestyle modifications (e.g. physical activity), diet, and drug or gene therapy. As of mid-2008, there were more than 1,200 clinically applicable genetic tests available, with an additional 300 available on a research basis only [26]. And this number was predicted to increase by 25% annually.

There are two distinct categories of predictive genetic testing: 1) Presymptomatic genetic testing, which is genetic testing in apparently healthy adults who are at risk for a single-gene disorder. This type implies testing for genetic disorders which are rare, but have a high risk of transmission to offspring; they are caused by mutations which have a very high correlation with an abnormal phenotype
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> (a high predictive value) and usually have poor treatment options. Apart from a few exceptions, these disorders are fully penetrant, i.e. they occur with virtually 100% certainty in people who have inherited a specific gene mutation in one allele (in the case of dominant inherited diseases, e.g. Huntington’s disease), or in both alleles (in the case of recessive genetic diseases, e.g. cystic fibrosis); and 2) Susceptibility (predispositional) genetic testing, which is genetic testing in apparently healthy adults to determine whether they are at increased risk, relative to the general population, for a specific future disease (e.g. breast cancer). This type tests for common disorders which have a low risk of being transmitted to offspring, are caused by a mixture of environmental and genetic factors (the latter having, at least so far, a very poor predictive value), and can be usually prevented through treatments or lifestyle changes. In this case, a positive test result (finding a mutation) does not necessarily mean that a person will develop a future disease. Disease onset may depend on other factors, e.g. other susceptibility genes or environmental factors.

Predictive genetic testing can detect single-gene mutations as disease cause, as well as genetic variants associated with increased risks and predisposition to a variety of diseases. Depending on our current knowledge of the pathogenesis of the disease in question, the test can tell us the disease risk with 100% certainty (in the case of presymptomatic genetic testing) or only a risk estimate (in the case of susceptibility genetic testing). However, as research continues to improve our understanding of disease mechanisms and their interactions with genomic and environmental factors, we may in future reach a point where we can provide accurate risk estimations for any disease. Hence, at least for some genetic diseases, it may be a question of time before susceptibility genetic testing becomes presymptomatic genetic testing.

Because of the dramatic impacts that presymptomatic genetic testing may have on one’s life, it also raises many psychological, social, ethical, legal and financial issues. People considering whether to undergo the test must weigh the ‘pros’ and ‘cons’ in view of the decision of continuing to live with all the uncertainty caused by the unknown gene status or disclosing it. Therefore, genetic counselling by a multidisciplinary team is recommended in many European countries, both pre- and post-testing. Guidelines for genetic testing for some diseases have been published to advise clinicians and geneticists on counselling individuals and administering the test.

Ideally, genetic testing should meet specific ethical and professional criteria. However, an increasing number of companies are offering direct-to-consumer (DTC) genetic tests, in which individuals can collect their samples at home and send them directly to laboratories without genetic counselling. According to a report in The Lancet, an undercover study of 15 DTC genetic tests by the US Government Accountability Office found “egregious examples of deceptive marketing, in addition to poor or non-existent advice from supposed consultation experts” [27]. Another ethical concern is that some risk predictions offered by DTC genetics firms are associated with conditions for which consumers might not be able to take any action, says Erynn Gordon, the director of genetic counseling at the Coriell Personalized Medicine Collaborative. This raises the question of whether taking some tests “can cause more harm than good.” Another risk that DTC genetic testing cannot exclude is surreptitious testing, since some companies are willing to analyze DNA left on discarded items such as chewing gums, used Q-tips, cigarette butts or strands of hair. Currently, the USA has no strong federal regulation moderating the DTC market.

An article on the risks of presymptomatic DTC genetic testing alerted to the fact that most genetic tests currently are not conform with the principles of population screening: “a suitable and acceptable test addressing an important health problem that has a recognizable latent or early symptomatic state, a well-understood natural history, and an accepted and available treatment or intervention” [28]. Moreover, DTC genetic screening may place a substantial burden on the healthcare system without providing demonstrable benefit.

Living with a positive predictive test result

Does early detection of disease risks improve health in presymptomatic individuals? The benefit of prediction or early detection is closely related to the ability to interfere with the natural course of the disease in a positive way. It also depends on the nature of the diagnostic and treatment procedures (if available), and the risks they may bear for affected or at-risk individuals. Last, it also depends on the degree to which each individual will be affected. Those expected to be most severely or least severely affected are likely to benefit less from early detection than those with intermediate severity [29].

Today’s technology is able to decode our genome, but are we ready to understand the answer it may give us and cope with its consequences? Is society as a whole equipped enough to make reasonable choices based on the information offered by this technology? Indeed, for most diseases, the impact of predictive genetic testing on psychological well-being has not yet been adequately studied, neither in the short nor long term. A study in a small cohort (N = 119) of individuals at risk for Huntington’s disease who had undergone predictive testing identified depression as a very frequent symptom post-testing [30]. Surprisingly, 27% of non-carriers of the mutant gene did not cope well with a favourable result, and 24% of them were depressed (versus 58% of the mutation carriers). The study also reported three suicide attempts in the non-carrier group (versus one attempt in the carrier group). These findings reiterate the
importance of post-test counselling independently from the test outcomes. Another study in Huntington’s disease patients published recently found that a small sub-set of patients (N = 45) without family history had a disease onset nearly 10 years later than would have been expected based on their mutation [31]. This means that not being aware of the disease and not knowing the gene status was an advantage that allowed people to have more disease-free years in their life. Despite intensive efforts in research on Huntington’s disease in the last decade, no genetic or environmental factor has been identified so far that could delay the onset of this incurable disease by 10 years. These findings demonstrate that the benefits of presymptomatic genetic testing are not only linked to the disease burden and to chances of treatment, but also to a psychological dimension.

A positive presymptomatic test result has far-reaching impact on different aspects of life and many decision-making processes, for example, when deciding how many years to invest in education, what profession to choose, and whether to have children or not. It may also lead to stigmatisation and discrimination both in social relationships and in the working environment, even in countries where laws exist protecting against genetic discrimination. And it may make arrangements of health, disability and life insurances or mortgages difficult.

Depending on the severity of the disease, those individuals with positive predictive test results who want to have children face the challenges of deciding for natural conception (and subsequent prenatal testing and whether to abort or not) or, alternatively, preimplantation genetic diagnosis (PGD) in countries where these procedures are permitted and available. They may find themselves in the very difficult situation of deciding what is worth living and what is not. This ‘playing God’ situation sounds familiar to pregnant women aged over 35 who are offered prenatal testing for the Down syndrome, a routine practice in many countries. In the case of late-onset diseases, prospective parents have to make this decision decades before their offspring develop the symptoms, not knowing what treatment options might be available in the future. Another polemic issue is that, in some countries, prenatal testing and abortion are allowed, whereas PGD, an in vitro fertilisation procedure that prevents passing on a genetic disease to the next generation, is prohibited. People who have been tested positive after the birth of their children have to choose whether and when to tell the offspring about their genetic risks. They have to balance the fear and panic this
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> information may cause against the advantages that any preventive measure or treatment may offer, whilst taking the age of the children into account. As a rule, predictive testing for late-onset diseases is not allowed in minors.

In a recent issue of Science commemorating the 10th anniversary of the first human genome sequence publication, Tom Hudson (president of the Ontario Institute for Cancer Research) said that what amazes him in retrospect is the fact that genomic information and technologies grew more than a million-fold in the following decade and, in a way, leapfrogged other critical initiatives in health research [32]. "Now," he said, "clinicians are more and more concerned by over-detection, over-diagnosis, and overtreatment of diseases, as a result of sensitive tests. Whether the disease involves cancer, metabolism, inflammation, or neurodegeneration, it becomes apparent that we have a limited knowledge of disease processes over time and, consequently, limited knowledge of when to intervene and to what degree. In some patients, this leads to unnecessary complications, whereas in others, the failure to act early is irreparable."

For predictable diseases, accurate information on disease risks might be available out there, but do we really want to know it? For the time being, predictive testing is only beneficial if medicine is able to provide effective preventive measures or treatments for the disease in question. The problem is that curative medicine does not hold the current pace of disease diagnostics, and preventive medicine strives to close the gaps between both, often with unspecific, common-sense health recommendations. Hence, the most important factor in deciding whether or not to undergo predictive genetic testing is probably choosing the right time to do it.

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