

## Genetic counselling in post-genomic era-to be or not to be

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### Abstract

With the surge of genetic tests and technologies, genetic counsellors are faced with the challenge of translating emerging scientific knowledge into practical information for patients, clinicians and public health policy makers. The new tests and technologies also are associated with new psychosocial and ethical considerations. New guidelines are needed for each new discovery of the genomic impact on phenotype, pathology and disease while "old" syndromes and "old" pathology, continue to require attention. In the new post-Human Genome Project era, genetic counsellors will be an integral part of translating genomic discoveries into beneficial impact on human disease, health care, and medical benefits. The needs for genetic counselling should be designed into genomic research at the onset. Genetic counsellors need to handle old while rapidly assimilating new information and the principal challenge is to be up to date and updated.

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**Key words:** Genetic counseling; Clinical application; Translating emerging scientific knowledge; Direct-to-

consumer genetic testing; Clinicians and public health policy makers

**Core tip:** This paper aims at discussing the aspects and challenges which have to be faced during genetic counselling in the new post-Human Genome Project era with beneficial impact on human disease, health care, and medical benefits. With the surge of genetic tests and technologies, genetic counsellors are faced with the challenge of translating emerging scientific knowledge into practical information for patients, clinicians same as for public health policy makers and the needs for genetic counselling should be designed into genomic research at the onset. Genetic counsellors need to handle old while rapidly assimilating new information.

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### INFLUENCE ON GENETIC COUNSELLING/ COUNSELLORS AND OTHER HEALTH PROFESSIONALS

The spectacular progress in understanding the genetic nature of disease has deeply changed the daily practice of medicine. With the surge of genetic tests and technologies, genetic counsellors are faced with the challenge of translating emerging scientific knowledge into practical information for patients, clinicians and public health policy makers. The new tests and technologies also are associated with new psychosocial and ethical considerations. As reported by Bennett *et al*<sup>[1]</sup>, the field of genetic counselling arose from the need to educate, manage and counsel individuals and their families diagnosed with, or at risk for, genetic diseases with respect to how these conditions may affect the psychological, medical, finan-

cial and social aspects of one's life.

Genetic counselling is now a necessary component of the practice of virtually all medical specialties. Physicians must help their patients understand a genetic diagnosis and assist them in making and coping with decisions relating to the diagnosis. As each new genetic test is made available in the clinic, developing the appropriate counselling for each new diagnosis is necessarily a multidisciplinary endeavour that includes involvement of a Specialist of Medical Genetics<sup>[2,3]</sup>. This paper aims at discussing the aspects and challenges which have to be faced during genetic counselling.

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## WHAT'S NEW?

The Human Genome Project provide us not only with information regarding the basic architecture of human genome, it also gave rise to impressive advances in molecular technologies. It is now possible to routinely assess genetic variation at a population level. For example, it is routine to assess over a million single nucleotide polymorphisms (SNPs) on thousands of individuals within a single study and it is routine to combine studies into meta-analyses across hundreds of thousands of individuals<sup>[4]</sup>. An excellent review of Gao *et al*<sup>[4]</sup> discussed the use of genome-wide association studies (GWAS). This strategy is based upon the common disease common variant hypothesis<sup>[5]</sup>, in which it is proposed that high-prevalence traits are determined by high-frequency genetic variants. Some successful examples are given by meta-analyses in GWAS in Parkinson's disease<sup>[6]</sup>, type 2 diabetes<sup>[7,8]</sup>, type 1 diabetes<sup>[9]</sup>, chronic kidney disease<sup>[10]</sup>, retinal microcirculation<sup>[11]</sup>, Crohn's disease<sup>[12]</sup>, and others. Beyond simply examining nucleotide variations, new technology allows researchers to assess other aspects of genomic variations including whole transcriptome profiling and genome-wide epigenetic modifications. Now the major challenge in genomics is to apply this rapidly expanding plethora of genetic data in meaningful ways-to further improve our understanding of human biology<sup>[13]</sup> and to generate knowledge about the genetic contribution to human diseases<sup>[14]</sup>.

While research focuses on how to put the human genome in context, it should not be forgotten that it is quite "tricky" to translate these research data into appropriate genetic counselling of each client. Especially if we consider that the next step in personal genomics is to associate an individual's specific variation with clinical disease phenotypes, counselling must help individuals discriminate between medically important variation and benign polymorphic variation. Data of genomic variations must be carefully translated by a genetic counsellor with care to educate the clients of the presumed significance of genes and mutations, imprinting, and the likelihood of benign versus causative genomic changes<sup>[15,16]</sup>. This means that genetic counsellors are at the forefront of introducing and applying the advances from genome

science to the lives of individuals and their families, by translating the complex language of genomic medicine into terms that are easy to understand<sup>[1]</sup>.

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## WHAT HAS BEEN CHANGED AS CONSEQUENCE OF NEW DIAGNOSTIC APPROACHES?

The era of genomic medicine challenges traditional definitions of "healthy" and "diseased". Traditionally, medical attention is only sought regarding a present illness. Now genetic testing permits the diagnosis of healthy individuals who are expected to develop or have an increased susceptibility to develop a disorder<sup>[17,18]</sup>. Testing for susceptibility genes will push into the world of medicine millions of individuals who have no personal experience of any disease, as emphasized by Professor Dallapiccola<sup>[19]</sup>. Some of them will benefit from the information, but many will become "unpatients", *i.e.*, individuals who are neither patients under treatment nor healthy individuals free of any medically relevant condition. This new class of individuals (it seems appropriate to call them "clients") who are watching and waiting for a sign of disease must be advised to undertake appropriate systematic clinical and instrumental monitoring while avoiding the development of psychosomatic symptoms. It is thus necessary to rethink the genetics revolution in medicine in terms of benefits and harm considering that the general rule for all physicians is: "*Primum non nocere*" ("First, do no harm"). After all, when we think about applications of genetics in daily practice, genetic counselling included, we should take in mind, J. Watson's observation: "I have benefited a lot from being the first human to have his or her personal genome made publicly available on the web. So far, knowledge of my personal genetic risks has not cost me an hour of sleep. I doubt, however, whether I would feel so positively if this knowledge had been given to me at a much earlier stage of my life"<sup>[16,20]</sup>.

It is necessary to introduce into genomic research consideration of computational strategies which permit translation of genetic information into clinically useful probability estimation. Personalized cancer risk assessment is an example of this integration. Algorithms in conjunction with testing have been successfully applied to predict the probability to carrier germinal at-risk mutations, as BRCAPRO for breast and ovarian cancer syndromes<sup>[21-24]</sup>, PancPRO for familial pancreatic cancer<sup>[25]</sup> and Melapro for melanoma families<sup>[26]</sup>, *etc.*

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## ITALIAN EXPERIENCE

The Italian genetic testing survey 2004<sup>[27]</sup>, could be seen as starting point (at least for us who are working in Italy) for understanding the necessity to link testing and genetic counselling in order to cut the costs, and to widen the number of available services. This survey also stressed the necessity for constant training of the general practi-

tioner and education of the consumer with regard to the appropriate use of genetic tests. A more sparing use of genetic tests, which should always follow specific clinical indications, ideally flank and sustain good clinical practice. Conversely, inappropriate genetics testing do harm by imparting a false sense of reassurance in individuals found not to have a gene mutation who are not informed of the limitation of tests and are major contributors to increasing health care costs<sup>[28,29]</sup>.

## “DO-IT-YOURSELF” GENOMIC TESTING

Direct-to-consumer genetic testing (DTC-GT) provides personalized genetic risk information directly to consumers. DTC-GT has generated a considerable controversy about its potential benefit, harms, and regulatory status since its entry into the mainstream marketplace in 2006<sup>[30,31]</sup> largely as a result of the unclear link between DTC-GT results, consumer risk and cost effective health care decisions.

With DTC-GT, clients without the guidance of genetic counselling will often purchase a genetic test that is not clinically indicated. Individuals ordering and interpreting genetic tests for tens or hundreds of conditions with varying clinical validity and utility, in the absence of a healthcare professional, could lead to unnecessary or incorrect healthcare decisions or emotional distress in the clients<sup>[32]</sup>. Furthermore afterwards clients may communicate the results to health-care professionals-it is left to these professionals to discuss the testing guidelines and clinical/diagnostic protocols and the usefulness and significance of the results, opening the door to distrust and misunderstandings if the test results are discounted<sup>[33]</sup>.

Obviously access to DTC-GT can be seen as a right for consumers to purchase the offered product and services. However, the open issues about whether and how to regulate the new heterogeneous DTC-GT industry should be systematically and carefully studied to ascertain the clinical utility, referral patterns and downstream costs<sup>[32,33]</sup>.

## SOME PERSPECTIVES WHICH ARE BECOMING REALITY, IS THIS SCIENCE OR SCIENCE FICTION?

Autism spectrum disorders (ASDs) are an example of an emerging area for genomic diagnosis that will require parallel development of genetic counselling. ADS are a heterogeneous group of neurodevelopmental disorders affecting social communication, language and behavior.

There have been reports of applying panels of common SNPs to assess ASD risk<sup>[34,35]</sup>, but these approaches require more testing/investigation before SNPs can be associated with risk. With rapid emergence of whole-genome sequencing studies, there will be an explosion of new data leading to more comprehensive genotype and phenotype studies<sup>[36-38]</sup>. In addition to seeking to identify

genes that influence diseases, scientists are looking for genes which influence biological markers of disease or endophenotype. One example of this approach is the emerging field of imaging genomics which discover important variants associated with brain structure and function. In these studies, a high degree of correlation has been observed between genome and image-derived maps giving some explanation on how these variations influence disease risk and fundamental cognitive processes<sup>[39]</sup>.

Parents of children with ASDs are generally aware that their subsequent children are at increased risk to be ‘on the spectrum’, but parents often over- or underestimate this risk. While the studies to date indicate that it may be possible, as yet no definitive genomic diagnostic or prognostic indicators of ASD have been found that can be used for risk estimation. The genetic testing and counselling approach to individuals with ASDs will continue to evolve as we learn more about the genetic factors involved and their relative contributions. The next step is to interpret this data and translate it in comprehensive and useful genetic counselling.

## LAST BUT NOT LEAST

The scope of genomic counselling are growing rapidly. New guidelines are needed for each new discovery of the genomic impact on phenotype, pathology and disease while “old” syndromes and “old” pathology, for example Downs Syndrome, continue to require attention. That is one of the reasons why the guidelines such as those published by National Society of Genetic Counsellors-Sheets *et al*<sup>[40]</sup>, will be always welcomed and “evergreen”.

In the new post-Human Genome Project era, genetic counsellors will be an integral part of translating genomic discoveries into beneficial impact on human disease, health care, and medical benefits. The needs for genetic counselling should be designed into genomic research at the onset. Genetic counsellors need to handle old while rapidly assimilating new information. The principal challenge is to be up to date and updated.

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