

## Review

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# Predictive genetic testing for complex diseases: a public health perspective

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## Summary

From a public health perspective, systematic, evidence-based technology assessments and economic evaluations are needed to guide the incorporation of genomics into clinical and public health practice. However, scientific evidence on the effectiveness of predictive genetic tests is difficult to obtain. This review first highlights the similarities and differences between traditional screening tests and predictive genetic testing for complex diseases and goes on to describe frameworks for the evaluation of genetic testing that have been developed in recent years providing some evidence that currently genetic

tests are not used in an appropriate way. Nevertheless, evidence-based recommendations are already available for some genomic applications that can reduce morbidity and mortality and many more are expected to emerge over the next decade. The time is now ripe for the introduction of a range of genetic tests into healthcare practice, but this will require the development of specific health policies, proper public health evaluations, organizational changes within the healthcare systems, capacity building among the healthcare workforce and the education of the public.

## Introduction

The decade following the completion of the human genome project in 2003 has been marked by divergent claims about the utility of genomics for improving the health of populations. Some people contend that interventions based on environmental changes will be more effective than those focused on individual behavior change. In contrast, others argue that increasing knowledge of genomics and molecular pathology could unlock effective diagnostic techniques and treatments and better target public health interventions.<sup>1</sup>

Writing in 1999, Francis S. Collins<sup>2</sup> predicted that the availability of the human genome sequence 'will dramatically accelerate the development of new

strategies for the diagnosis, prevention, and treatment of disease, not just for single-gene disorders but also for more common complex diseases for which genetic differences may contribute to the risk of contracting the disease and the response to particular therapies'. Accordingly, former directors of the National Institute of Health (NIH) stated that the NIH was strategically investing in genetic and genomic research,<sup>3</sup> but at same time there were worries that the expanded use of genetic information might further escalate the cost of healthcare.<sup>4</sup> Genetic tests can not only be expensive, but may also lead to downstream costs that follow from testing. Such costs include the so-called 'cascade effect', defined as a chain of events initiated by an

unnecessary test, an unexpected result or patient or physician anxiety, which results in further expensive tests or treatments that may also cause avoidable adverse effects and/or morbidity.<sup>5</sup>

From a public health perspective, systematic, evidence-based technology assessments and economic evaluations are needed to establish the use of genomics in clinical and public health practice. Walter Holland<sup>6</sup> argued that ‘caution is essential... While genetic screening can certainly help to evaluate risk and may be appropriate in certain high-risk groups if nothing can be done to alter the finding, the need for, and use of, such information must be very carefully considered. Is it useful to diagnose without being able to treat?’ Even if the information given by genetic tests could sometimes be regarded as worthwhile in itself (i.e. to inform reproductive choices or to make life-planning decisions), there is also the risk that in many situations this information could be harmful. Therefore, predictive testing is clearly indicated only if early diagnosis will allow an intervention that reduces morbidity and mortality. In 1968, Wilson and Jungner<sup>7</sup> developed principles of population screening, identifying a set of criteria that should be met in order to initiate a screening program that could be applied in the case of disorders with a genetic component.

### **Traditional screening tests and predictive genetic testing for complex diseases**

When evaluating a traditional screening test it is very important to consider the predictive values of the test, particularly the positive predictive value, that is, the probability of having the disease given a positive test result. This conditional probability depends on the sensitivity and specificity of the test and is known to increase with the prevalence of the disease among the population. It is for this reason that screening programs are generally targeted to high-risk groups, among which the prevalence of disease is reasonably high, so that an acceptable positive predictive value of the screening test may be achieved.

Can we treat predictive genetic testing of complex diseases similarly? Probably not. Predictive genetic tests do not allow early diagnosis of a specific disease, but instead, they identify the presence of a genotype mutation that increases the risk of developing the disease in the future. Therefore, the positive predictive value is the probability, given a positive test result, of having this mutation and the risk of developing the disease in the future depends

not only on the sensitivity/specificity of the test and on the prevalence of the mutation among the population, but also on the lifetime risk of the disease and on the ‘relative risk’, i.e. the increased risk of disease given the presence of the genotype mutation.<sup>8</sup> Thus, the implementation strategies of screening programs at population levels are more complex. To increase the clinical positive predictive value, i.e. the probability of developing the disease given a positive test result, both the baseline risk of disease and the relative risk should be ‘raised’. Consequently, predictive genetic testing should be targeted to high-risk groups, i.e. individuals already exposed to known risk factors that may interact with the genotype mutation and should search simultaneously for the various mutations, which, if they are all present, multiply the relative risk.<sup>8–10</sup>

Although traditional screening tests and predictive genetic tests are different, the criteria that should be met for the implementation of a particular test are the same in principle, with some modifications.<sup>11</sup> For example, the domain knowledge of disease was extended to include knowledge of the population and knowledge of risk and susceptibility. The criterion that a treatment should be available was diverted into the notion that interventions that have physical, psychological and net social benefits should be available. Cost considerations should encompass the broader societal and health system issues. Overall, much more attention is paid to ethical, legal and social issues.

### **The public health evaluation of predictive genetic testing for complex diseases**

Scientific evidence on the effectiveness of predictive genetic tests is without any doubt difficult to obtain. An ‘ideal’ randomized control trial, able to demonstrate the efficacy of a particular genetic test in prolonging survival or improving the quality of life, is simply impossible to perform, mainly because it would need to be carried out over a long period of time, during which the genetic test would very likely become obsolete. In the absence of such trials, an analytical framework is needed to collect the appropriate evidence in three main domains: analytic validity, clinical validity and clinical utility. The analytic validity of a genetic test focuses on the laboratory component and defines its ability to accurately measure the genotype of interest. The clinical validity refers to the ability of a genetic test to predict the associated disorder (phenotype). The clinical utility defines the

elements that need to be considered when evaluating the risks and benefits associated with the introduction of a genetic test into routine practice. For each of these three domains, scientific evidence should be obtained through the most appropriate epidemiological studies and then translated into grades of recommendations in clinical practice guidelines. Current systems for grading the strength of recommendations are based on consideration of study design, study quality, consistency of results of different individual studies and directness; the strength of recommendations depends on the quality of evidence, the net benefit of the intervention and cost considerations.<sup>12</sup> Using these approaches, genetic tests could be introduced into public health and clinical practice in a responsible manner, without being 'penalized' by the fact that the scientific evidence relating to their effectiveness is limited.

Elaborate frameworks for the evaluation of genetic testing have been developed in recent years; these take into consideration the setting in which a genetic test is used (for instance, in a screening program) and combine this with quantitative information about the disorder and the test to be applied. ACCE (Analytic validity, Clinical validity, Clinical utility and associated Ethical, legal and social implications) is an example of such a framework, quantifying as many criteria as possible (e.g. public health burden, quality of a test, etc.) and thereby facilitating more detailed and rational assessment of the potential benefits of testing or screening.<sup>13</sup> The Centers for Diseases Control and Prevention (CDC) initiated another project, the Evaluation of Genomic Application in Practice and Prevention (EGAPP), in order to support the development of a systematic process for evaluating genetic tests and other genomic applications that are in transition from research to clinical and public health practice.<sup>14</sup> So far, EGAPP has provided evidence reports on several genetic tests. Similar approaches have been taken in Canada, the UK and Germany.<sup>11</sup>

Given limited healthcare resources, the economic evaluation of genetic tests is strategic to the decision-making process and providing information about both costs and health consequences of alternative courses of action. In fact, genetic testing is currently a major topic of health economics, with a number of recently published systematic reviews covering full economic evaluations of genetic tests.<sup>11</sup> Nevertheless, evidence on the cost-effectiveness of most genetic tests is scarce, particularly because evidence for the efficacy of the tests themselves, which is a prerequisite for the assessment of cost-effectiveness, is still limited.

## Is predictive genetic testing for complex diseases being used appropriately?

In an ideal world, the availability of genetic tests should be based on professional recommendations founded on empirical evidence. After the development and validation of a new genetic test, its context should be explored, including an understanding of the prevalence of the disease and the respective mutation; the accuracy of the genetic test in identifying the presence of the mutation; the association between the genotype and the clinical phenotype; the availability and efficacy of interventions to prevent the disease and the costs associated with screening, follow-up and preventive treatments. Professional recommendations could then be based on these analyses, practice guidelines formulated and the test made available to clinicians and public health professionals. In actuality, the availability of genetic tests appears to be driven more by the tests' technical feasibility and commercial potential than by evidence-based medicine. Genetic tests have often proceeded directly from development and preliminary validation into practice, with little understanding of the public health, economic and psychosocial implications of their use.<sup>15</sup>

There is some evidence that genetic tests are not used in an appropriate way. In Italy, for example, there are many medical genetics organizations, each with geographical differences. Counseling is infrequently performed and there is a high number of private (for-profit) organizations.<sup>16</sup> Physicians, who in the field of genetic testing, as in other medical fields, are the final decision-makers, are not yet ready to play an appropriate role in the context of predictive genetic testing of cancer, for example.<sup>17</sup> Public health professionals may have the necessary attitudinal background to contribute to the proper use of predictive genetic testing for chronic diseases, but they need additional training to increase their methodological knowledge (C Marzuillo, C De Vito, M D'Addario, P Santini, A Boccia, P Villari, personal communication). There is a clear need for specific post-graduate courses in evidence-based medicine (EBM) for physicians, not least because by improving physicians' knowledge of the main instruments of EBM (such as clinical trials, meta-analyses, economic evaluations and practice guidelines), the professional behavior of physicians is likely to become more evidence based.<sup>18,19</sup>

The integration of genome-based knowledge in a responsible and effective way into public health practice requires the development of a specific

health policy, as is currently being drawn up in Italy by the Ministry of Health in the form of a dedicated National Plan for Public Health Genomics (PHG-NP).<sup>20</sup> Included among the actions to be taken are a systematic health technology assessment of predictive genetic tests for complex diseases, the promotion of genomics education among physicians and the general public and the development of capacity building among all potential stakeholders for the healthcare appropriate provision and management of predictive genetic testing.

## Public health genomics: looking forward

Even if the quality and quantity of the available scientific evidence on the effectiveness of genetic tests are limited, evidence-based recommendations are already available for some genomic applications that can reduce morbidity and mortality and many more are expected to emerge in the next decade.<sup>11,21,22</sup> To consider the readiness of genomic applications for practice, a useful framework has been developed that considers a genomic application's analytic validity, clinical validity, clinical utility, balance of benefits and harms and the existence of an evidence-based recommendation.<sup>23</sup> The tiers of the classification system are characterized as follows:

- (i) Tier 1 applications, including, for example, genetic tests for hereditary breast/ovarian cancer, Lynch syndrome and familial hypercholesterolemia have demonstrated analytic validity, clinical validity, clinical utility and there are evidence-based guidelines encouraging their use.
- (ii) Tier 2 applications have demonstrated analytic and clinical validity, but there is no evidence yet for clinical utility.
- (iii) Tier 3 applications have not yet demonstrated adequate analytic validity, clinical validity or clinical utility and have not demonstrated evidence of harm.

Organizational changes are needed within healthcare systems to provide genetic tests at the tier 1 classification level both effectively and efficiently. In theory, predictive genetic testing can be used: (i) in population screening programs led by public health professionals (genetic tests for patients with cancer and 'cascade' genetic tests for relatives; newborn screening programs with a battery of tests for high penetrance genes with low prevalence among the population; cancer screening programs with stratification on the grounds of genetic predisposition) and (ii) in primary care settings for early case detection and intervention to effect behavioral changes. Today, there is a limited evidence base

to support both genetic population screening programs and personalized individual predictive genetic tests, but the scenario is likely to change significantly in the future.<sup>1,22</sup> Whether in a state-funded system (such as in the UK) or in more pluralistic service environments (such as in the USA), an important priority is to think strategically about how health systems need to be changed to meet the needs of genomic science in the context of the growing burden of chronic diseases.

This challenge to model the public health genomic programs and the primary care services should be met while taking into account the additional priorities of: (i) ensuring an appropriate evidence-based translation of genomic applications into clinical practice and (ii) delivering adequate provider and consumer education.<sup>23</sup> The systematic health technology assessment of genetic and genomic applications can mitigate against 'premature translation' of new technologies into practice, while at the same time ensuring that such technologies are not 'lost in translation'. The training, education and development of capacity in the health service workforce is crucial, as is the education of the public, not least because of the increasing use of direct-to-consumer genetic testing.<sup>24</sup>

The past decade has seen the emergence of public health genomics, a multidisciplinary field that has established scientific and policy foundations for the appropriate translation of the new science of genomics into health benefits to individuals and populations.<sup>22</sup> The time is now ripe for the appropriate introduction of a range of genetic tests into healthcare practice, but this will require the development of specific health policies, proper public health evaluations, organizational changes within the healthcare systems, capacity building among the healthcare workforce and the education of the public. In the next decade, rapidly evolving genomic tools, including whole genome sequencing and a slew of gene-based products such as gene-expression profiles, proteomics, epigenomics and metabolomics will become available. Public health has already established methods for assessing the balance of benefit and harm of genomic applications in populations, for implementing validated applications throughout the population and for evaluating their impact on healthcare and disease prevention.

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