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The prediction of disease risk in genomic medicine

Scientific prospects and implications for public policy and ethics

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In recent years, the phrase 'genomic medicine' has increasingly been used to describe a new development in medicine that holds great promise for human health. This new approach to health care uses the knowledge of an individual's genetic make-up to identify those that are at a higher risk of developing certain diseases and to intervene at an earlier stage to prevent these diseases. Identifying genes that are involved in disease aetiology will provide researchers with tools to develop better treatments and cures. A major role within this field is attributed to 'predictive genomic medicine', which proposes screening healthy individuals to identify those who carry alleles that increase their susceptibility to common diseases, such as cancers and heart disease. Physicians could then intervene even before the disease manifests and advise individuals with a higher genetic risk to change their behaviour—for instance, to exercise or to eat a healthier diet—or offer drugs or other medical treatment to reduce their chances of developing these diseases. These promises have fallen on fertile ground among politicians, healthcare providers and the general public, particularly in light of the increasing costs of health care in developed societies. Various countries have established databases on the DNA and health information of whole populations as a first step towards genomic medicine. Biomedical research has also identified a large number of genes that could be used to predict someone's risk of developing a certain disorder. But it would be premature to assume that genomic medicine will soon become reality, as many problems remain to be solved. Our knowledge about most

disease genes and their roles is far from sufficient to make reliable predictions about a patient's risk of actually developing a disease. In addition, genomic medicine will create new political, social, ethical and economic challenges that will have to be addressed in the near future.

During the past several decades, biomedical research has identified almost 1,500 so-called mendelian disorders, in which a mutation in a single gene predicts a high risk of developing a disease (Yoon *et al*, 2000). But genetic testing for these disorders—of which Huntington's disease is the most prominent example—has had only a limited impact on health care for two reasons. First, few effective interventions are available to treat or prevent many of these conditions, other than contraception or abortion of an affected fetus, and second, these conditions collectively account for only 5% of the total disease burden in developed countries (Khoury *et al*, 2004). The vast majority of illnesses are common multifactorial disorders, namely heart disease, cancers, major depression, arthritis, asthma and diabetes (Murray & Lopez, 1997). Nevertheless, family and twin studies indicate that, in addition to environmental risk factors, there is indeed a substantial genetic contribution to the aetiology of many of these disorders. Heritability estimates for these conditions and some of their biological risk factors range from 39% to 80% (Evans *et al*, 2003), which suggests that it may be possible to identify those genes and use them for predictive tests. Although research has identified a few single dominant genes that are strongly associated with disease risk, such as *BRCA1* and *BRCA2* in breast cancer and *FAP* in colorectal cancer, these represent a minority of disease cases, and finding new alleles that predict susceptibility to most common diseases remains a

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major challenge (Schork, 1997). The main strategy used so far has been to look for associations between a disorder and either genetic markers or specific candidate alleles. Both types of study typically involve a case–control design to compare the prevalence of specific alleles, genotypes or genetic markers (for example, single-nucleotide polymorphisms, SNPs) in individuals who have the disease with matched controls (Hirschhorn *et al*, 2002; Zondervan & Cardon, 2004). The results have been disappointing. Meta-analyses of association studies to identify susceptibility alleles for heart disease, cancers, depression, asthma and diabetes have shown that many initially positive findings have not been replicated in later studies (Hirschhorn *et al*, 2002). Furthermore, the associations that have been replicated are rather modest: typically, people with these susceptibility alleles are 1.2–1.5 times more likely to develop these disorders (Ioannidis, 2003). The failure to successfully identify susceptibility genes has been attributed to several factors: using study samples that are too small to detect modest associations; poor sampling and study design; using genetic markers that are only modestly correlated with 'disease genes'; and bias on the part of journals that favour the publication of early positive associations over failed replications (Hirschhorn *et al*, 2002; Colhoun *et al*, 2003; Zondervan & Cardon, 2004).

All these factors do have a role, but a more troubling possibility is that the failure to replicate many association studies may instead reflect the complexity of the genetics of common diseases. Although some authors take an optimistic stance and suggest that these diseases may be influenced by only a small number of rare alleles (Risch, 2001), the more popular view now is that these disorders are polygenic (Balmain *et al*, 2003; Pharoah *et al*, 2002). Thus, modest associations between susceptibility alleles and disease would be the 'norm', and genes such as *FAP*, *BRCA1* and *BRCA2* would be the exception. Plausible estimates of the number of susceptibility alleles for major cancers range between tens and hundreds (Peto, 2001, 2002), all of which increase disease risk only modestly because their effects depend on interactions with other genes and with the environment. Consequently, the success of genetic mapping efforts to improve the prediction of disease risk will depend on various factors: the number of genes influencing each condition; the frequency of susceptibility alleles in the population; the penetrance of these alleles (how strongly they predict disease risk); how these alleles interact with each other, and under different genetic backgrounds; and interactions between these alleles and other risk factors.

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Optimists point to the 'common disease, common variant' (CDCV) hypothesis, which states that susceptibility alleles for common diseases reflect mutations that occurred in the human population 100,000 years ago (Balmain *et al* 2003), which can therefore be identified in large association studies with 1000 to 5000 cases and controls (Zondervan & Cardon 2004). But if the CDCV hypothesis turns out to be false, the prospects for predictive genomics are rather bleak. If there are large numbers of novel mutations for each common disease and if these mutations occur with low frequency and vary between populations, it will be very difficult to identify susceptibility alleles for these diseases, even in extremely large case control studies using full genome scans (Wright & Hastie 2001; Balmain *et al* 2003). Further research will show which side is correct. But even if the optimists prevail, other major challenges for genomic medicine remain, mainly in developing tests and effective treatments, and in public health policy and ethics.

First, there is simply not yet enough knowledge about susceptibility genes and their role in the development of most diseases, which limits our ability to design efficient tests to predict disease risk with some reliability. Of the genetic tests available, fewer than 5% test for susceptibility to common diseases (Yoon *et al*, 2000) and most of these use rare alleles with a high predictive power. Sceptics therefore maintain that predictive genetic screening for polygenic disorders will not prove feasible. They argue that single alleles will be poor

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indicators of disease risk unless the lifetime risk of the disease is 5% or more and the genotype is either rare or increases disease risk 20 times or more (Holtzman & Marteau, 2000; Khoury *et al*, 2004; Wald *et al*, 1999). Others contend that it will simply be economically unviable for a country's healthcare system to screen the whole population for susceptibility alleles to prevent only a small number of these disorders (Vineis *et al*, 2001).

Advocates of predictive genomics counter that testing of multiple genetic variants, which are individually only weak factors, might nevertheless give a better prediction of future disease risk (Khoury, 2003). Indeed, simulations of plausible scenarios indicate that such tests could substantially improve if multiple susceptibility alleles were tested and the results combined statistically to produce a risk score (Khoury *et al*, 2004; Pharoah *et al*, 2002). The efficiency of genomic screening could be further enhanced if the decision to test for multiple susceptibility alleles was based on a person's family history of the disease (Khoury, 2003; Khoury *et al*, 2003). Indeed, such knowledge is a good risk factor for all major common diseases and it could be used to stratify the population into three broad risk groups. The average-risk group would have no affected first-degree relatives; the moderate-risk group would have a family history of late-onset disorders; and the high-risk group would have two or more affected first-degree relatives or a first-degree relative with an early onset of the disorder (Khoury, 2003). Scheuner *et al* (1997) estimated that 30%–50% of the population would fall into the moderate-risk group, 10% into the high-risk group and 40%–60% in the average-risk group. Triaging genetic screening on the basis of family history could approximately halve the number of people to be tested and improve the performance of genetic tests in people whose environment and behaviour place them at increased risk of developing the disorder. Epidemiological modelling of breast cancer genetics suggests that additional genetic information based solely on family history indeed improves predictions (Pharoah *et al*, 2002), but more direct evaluations are needed.

Although the scientific problems mentioned above may be solved through biomedical research in the near future, the possibility of predicting someone's risk of developing a common polygenic disorder also raises ethical, social and policy challenges that science alone cannot address. Screening whole or subpopulations for a large number of susceptibility alleles is only socially and economically justifiable if physicians can follow up on a diagnosis of increased risk with an effective intervention to prevent this disorder (Evans *et al*, 2001; Rose, 1992; Khoury *et al*, 2003). For some common cancers, such as colorectal and breast cancer, regular monitoring and early treatment have been shown to reduce fatality. Preventive medications to treat hypercholesterolaemia and high blood pressure also exist, but are prescribed on the basis of traditional diagnoses of symptoms. It will take some time and large controlled trials to indicate whether intervening with healthy individuals who are at increased genetic risk of developing a given disease reduces premature mortality.

Although some medications and other treatments exist, most interventions aimed at reducing disease risk still depend on the patient changing his or her behaviour. Much needs to be learned about how to present and explain information about genetic risks for common disorders to achieve this goal (Bottorff *et al*, 1998; Edwards *et al*, 2003). Whether simply giving individuals this information motivates them to change their lifestyle, such as quitting smoking (Khoury, 2003), remains to be seen. Some researchers have already become concerned that inappropriate communication of risks may instead result in demoralization and reduce a person's self-confidence in their ability to change their health behaviour (Wright *et al*, 2003). A recent review (Braithwaite *et al*, 2004) indicated that genetic counselling does not lead to adverse outcomes, but further research on this topic is needed.

Probability and relative risk data are difficult for most people to understand, and we need to consider using natural frequencies, a common denominator, framing both positive and negative perspectives and using visual aids (Gigerenzer, 2002; Gigerenzer & Edwards, 2003; Paling, 2003; Robins & Metcalfe, 2004). Research on risk communication also highlights the importance of social and linguistic contexts in explaining to patients their personal risk score for common diseases (Alaszewski & Horlick-Jones, 2003; Moxey & Sanford, 2000).

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A related concern is that screening will unnecessarily raise anxiety about disease risk in individuals who are found to have susceptibility alleles, but who are at low risk of developing the disorder (Marteau & Croyle, 1998). Furthermore, there is no evidence that genetically based risk information gives a stronger motivation to change health behaviour than classic family history information (Hicken & Tucker, 2002). Clearly, the success of genomic medicine will depend largely on finding effective ways of communicating genetic risk to induce desirable changes in behaviour.

In addition, there are concerns that genomic medicine and widespread screening will affect classic public health policies that address and reduce overall health risks in the population. These strategies aim, for instance, to reduce the prevalence of cigarette smoking or per capita alcohol consumption or to advise people to eat healthily and exercise regularly to reduce high blood pressure, diabetes, and heart and lung diseases (Rose, 1992). By contrast, the 'high-risk' strategy (Rose, 1992) of predictive genomic medicine shifts the focus to targeting individuals who have been identified as having a high genetic risk of developing a disease (Khoury *et al*, 2004). Thus, important policy questions for genomic medicine will be 'When should public health officials use population-based strategies?' and 'When should they identify and intervene with those at highest genetic risk?'

There are clearly some cases in which population strategies are more efficient. It is a more sensible policy to reduce cigarette smoking by high taxation on tobacco products and restrictions on cigarette advertising than by spending resources on identifying those at increased genetic risk of becoming nicotine dependent or developing tobacco-related diseases if they smoke (Hall *et al*, 2002; Khoury *et al*, 2004). Similar arguments have recently been made in favour of prescribing a 'polypill' to all adults over 50 years of age as an efficient way of reducing cardiovascular disease mortality by 80% in developed societies (Wald & Law, 2003). But genomic medicine may shift the focus, and funds, away from public health policies. A major challenge for policy makers will therefore be to reap the health benefits of genomic medicine without undermining effective public health policies (Khoury *et al*, 2004).

The concerns about the ethical and policy implications of genetic testing have been much influenced by the mendelian disorders, such as Huntington's disease. Because the mutations that cause this serious disorder are strongly predictive, genetic testing creates serious ethical and other dilemmas for affected individuals and their families (Marteau & Richards, 1996). It also raises real concerns that health and life insurers and employers might make discriminatory use of this information (Billings *et al*, 1992; Taylor, 1998). But, as pointed out above, the mendelian disorders represent only a small number of cases compared with the overall incidence of common polygenic diseases. And the discussion of the ethical implications of predictive genomics has not even begun to consider efficient strategies for its use in preventing these diseases. If the pessimists are right, these ethical and policy issues will not arise at all, because we will not be able to identify any useful predictive alleles for common diseases.

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Even in the most optimistic scenario, predictive genomics will not test whole populations for mendelian mutations. Instead, predictive genetic testing may be offered to 20%–50% of the population on the basis of a family history of disease. A minority of those tested would have rare quasi-mendelian forms of some common diseases, such as *FAP* for colorectal cancer, or *BRCA1* or *BRCA2* for breast cancer. In these cases, the ethical issues identified with mendelian disorders—namely, discrimination and concerns about third-party use of genetic information—would have to be addressed. The majority of individuals with a family history,

however, would just have an elevated risk score as defined by a number of common susceptibility alleles.

Fear of discrimination may nonetheless deter people from taking genetic tests that could benefit them. Similar fears may also discourage individuals from participating in research on common diseases, thereby impairing the acquisition of knowledge for efficient prevention and treatment of serious diseases, which would benefit the community in the long term. It remains to be seen how concerns about third-party use of genetic information, possible discrimination and stigmatization will impede the success of predictive genomics. Governments and industry will have to address these issues in ways that are understood and accepted by the public.

Another major challenge for implementing predictive genomic medicine in health care will be to educate the public about its benefits and shortcomings. Current understanding of genetics among the general public (Morris *et al*, 2003; Richards & Ponder, 1996) and health providers (Robins & Metcalfe, 2004) is not high, but it would be wrong to assume that the public will be only passive consumers of information about genetics (Dietrich & Schibeci, 2003). Popular understanding of genetics is often deterministic, with many people believing that if you have 'the gene for X' you are very likely to develop that disorder and, conversely, that you will be at low risk of doing so if you do not have this gene (Khoury *et al*, 2000). These views reflect the media's focus on mendelian disorders, such as Huntington's disease and cystic fibrosis (Khoury *et al*, 2000).

Some authors have therefore called for educational campaigns to improve public understanding of genetics (Godard *et al*, 2003), but others have cautioned that such education must build on pre-existing knowledge about disease and genetics (Richards & Ponder, 1996). Thus, various organizations and experts argue for a much broader and more wide-ranging general public discussion of current and future developments in genetics and their implications for public and individual health (Dietrich & Schibeci, 2003; McQueen, 2002; Nuffield Trust, 2000). The challenge for public education will be to explain the personal and public health implications of common polygenic disorders in which individual alleles weakly predict risk and interact with each other and with the person's environment. If it is done well, such education may allay some anxieties that are based on reports of genetic discrimination experienced by some patients with mendelian disorders.

However, public education will have to avoid giving the unintended message that public health strategies can be simply replaced by genomic medicine (Merikangas & Risch, 2003; Willett, 2002). The best way for many individuals in developed societies to reduce their disease risks remains simple: stop smoking, reduce calorie intake and increase exercise (Merikangas & Risch, 2003; Rose, 1992; Vineis *et al*, 2001). To avoid wholly blaming individuals for their risk status, we need to modify our physical and social environments and our social policies, to facilitate and sustain desirable changes in risky behaviour.

There are substantial technical and scientific challenges in realizing the promise of predictive genomics in reducing the burden of the common diseases that affect developed societies. One major scientific challenge is to identify the more commonly occurring, strongly predictive susceptibility alleles for these disorders. Most susceptibility genes that have been identified only weakly predict disease risk, so academic and industry researchers need to design tests based on multiple alleles to have any prospect of predicting individual risk. Even if such tests can be developed, the costs of screening and counselling large populations to identify the small number at high risk may be difficult to justify, especially in the absence of effective preventive strategies for many conditions. Policy makers also have to consider that population health strategies are more efficient in some cases, particularly when it comes to cigarette smoking and preventing heart disease.

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In addition, predictive genomic medicine still needs to tackle many ethical and policy issues. Its proponents have to address valid concerns about privacy and the possibility of discrimination and abuse of genetic information. Any implementation of genetic testing, whether for individuals or larger populations, also has to be accompanied by education campaigns about the genetics of common diseases and research on how to present such genetic information in ways that motivate behavioural change and do not undermine successful public health strategies.

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