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Genetic Identification of Susceptibility to Common Diseases: A New Era of Preventive Medicine?

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ABSTRACT

The benefits, harms and limitations of screening for genetic susceptibility in order to prevent common diseases are discussed. Reasons that premature or unwise application of genetic identification may occur are enumerated. It is concluded that the identification of susceptible "risk" genotypes by screening is unlikely to be an effective or equitable strategy for the prevention of common complex diseases of environmental-gene interaction. The need for public policy, and the criteria to be met before screening should be permitted, are outlined.

Introduction

At first blush, offering susceptibility screening to the population for common conditions such as heart disease or cancer, seems a very good idea, as it might allow the avoidance of those diseases. Screening programs are defined as such by their approach - by the fact that it is health professionals who initiate the screening, not patients with symptoms or questions. Genetic screening may be offered to the general population or to particular sub-populations, defined on some basis other than health.

This article focuses on genetic screening for susceptibility to common disorders, not on pre-symptomatic genetic testing, which is testing which is carried out on healthy people with regard to a specific disease inherited in a Mendelian fashion, for example breast or colon cancer associated with a known mutation, where healthy blood relatives of identified patients may be tested. In that situation, if individuals have inherited the genotype they have a highly significant likelihood of developing the disease - the gene is highly penetrant. Population genetic screening,
on the other hand, is done to provide information about the genetic component in a multifactorial common disorder. The genotypes involved are of low penetrance, that is, they simply increase statistical risk of later disease. The genetic identification predates the onset of disease, if disease does eventually occur, by significant periods of time - there may be no symptoms for decades.

As genetic screening for susceptibility is examined more closely, it becomes evident that it is very questionable as to whether it is a good policy. Because screening engages apparently healthy people, the medical and ethical standards for benefits of screening should be high, as any adverse outcome such as cost, stigmatization or injury is iatrogenic. Clearly, labelling people as more susceptible to heart disease, or cancer, or other significant illness has harms as well as potential benefits. It may lead to anxiety; it creates in currently healthy people a new category, the "not yet ill"; and it may lead to an altered self concept. In addition, it may leave individuals open to unfair discrimination in the workplace or in life insurance. Also, if there is no effective intervention, screening may be pointless and not worth the cost. In that case, being identified as susceptible simply raises anxiety, and robs people of their perceived health.¹

It is easier for people who have been trained and socialized into one of the medically related professions, to focus on the benefits rather than the harms of genetic screening, as they are aware in detail of the detrimental effects of disease. They feel a duty to detect and help people avoid it; so claims of benefit should be assessed carefully. Another impetus in that policy direction comes from sectors of society (medical laboratories, biotechnology companies, genetic scientists, genetic service providers, etc.) that would benefit from a move to a greater emphasis on genetic screening. However, if genetic screening for susceptibility is permitted to be marketed, the effects of so called "private" decisions about using it are not confined to those individuals tested - for example, marketing and promotion of susceptibility testing may cause
collective harm by increasing health care costs without corresponding benefit, as well as causing the individual harms mentioned.

**Background on genetics**

Disorders with a genetic component can be viewed as being on a continuum. For individuals at one end of this continuum, having a particular gene makes it impossible for them function normally in the usual range of environments - these are usually referred to as Mendelian or single gene disorders. In these disorders the gene is highly penetrant - having the gene usually means having the disease. Such diseases are rare and make up a very small proportion of the disease burden in populations. At the other end of the continuum, environmental circumstances are so detrimental (such as starvation, or major physical trauma) that individuals' genotypes make little difference. These diseases too are not common in developed countries. By far the great majority of the most common diseases in our society today, are complexly determined by many factors interacting. The commonest diseases - common cancers, cardiovascular disease, and mental illness, for example, result from interactions over the life course between genetic make-up and environmental factors. They should not be categorized as "genetic" disorders. Not only are the genes that are involved in this interaction of low penetrance, but in some cases such genes may not even be necessary, let alone sufficient.

**Susceptibility screening**

Through examining an individual's DNA it has now become possible to identify genetic markers or genotypes associated with some common diseases. All of these "susceptibility" genes are of low penetrance. It has been promoted by some, often by those who stand to gain, that identification of risk in this way is beneficial and should be widely available. Although there is scant evidence to support the claims of benefit, under the current regulatory framework there is a
danger that some of these tests for susceptibility will not be rigorously evaluated and provided in properly resourced, equitable programs, but will be prematurely brought to market in an ad hoc way. This is dangerous, because the public is not clear that having a susceptibility gene does not mean that the person will develop the disease. If people with the identified genotype do not experience relevant environmental factors, or if they do not possess the other genetic factors that may also be necessary, they will remain well. Conversely, some people without the gene will develop the disease if they have enough exposure to the environmental factors that play a role. This is complicated to communicate, but marketing tends to be simple - "know your risk" - and the public in general is not very knowledgeable about genetics.

Considerable interest has been shown in exploring identification of genetic susceptibility both within the health care system and by commercial interests, and it is clear that population wide testing would represent a very large and profitable potential market to biotechnology/pharmaceutical companies. The main health-related justification for offering such population screening would be if it enabled individuals at higher risk for a particular common disorder to take preventive measures or to receive treatment earlier in their lives. In principle, it is possible to modify a person's micro-environment with the aim of avoiding exposure to the factors that trigger the disorder. For example, people could change their diet or take medication. This reasoning has led to suggestions by some that population screening programs will be established in future to test everyone for susceptibility genes for common diseases.

The story that "the gene causes the disease", sounds plausible, and is easily understood. Unfortunately it is an approach that has not usually been successful, even for single gene disorders where the mutation has been known and identified for many years. The same approach
when applied to common diseases such as heart disease, or lung or colon cancer, where multiple genes as well as environmental influences are interacting, is even more unlikely to be effective. So it is important that the implications be thought through before embarking on population screening programs for genetic susceptibility to common diseases.

**Limitations**

At present, the likely health benefits of susceptibility screening in terms of better prevention or earlier treatment, are very uncertain; its usefulness in providing individuals with reliable information about the likelihood they will develop a common disease later in life is deficient in many important respects. Although someone with a particular genotype may have an increased likelihood of becoming ill, the data are not usually sufficient to say how many people who have the particular form of the gene actually get the disorder, and how this risk compares to that of others in the general population who lack that genotype.\(^5\) To answer these questions it would require correlational studies, comparing the clinical history of those with a particular genotype to those in the general population who do not have it.\(^6\) Collecting reliable information on this is likely to be difficult, because the genetic variation that contributes to susceptibility may be due to several genes, each of small effect, interacting with differing exposures over time.

It is sobering to realize that we are far from understanding gene/environment interactions even for single gene diseases where the gene is highly penetrant. We are learning that even clear, single gene determined diseases such as thalassemia do not have simple relationships with the environment.\(^7\)–\(^8\) Another example is familial hypercholesterolemia. Medical geneticists and internists have assumed that having this genotype means you are likely to die prematurely of a heart attack. However a study of a Dutch family where this dominant gene is segregating\(^9\) has shown that mortality among those who had this mutation was not increased in the 19\(^{th}\) century.
Mortality for individuals with the gene for familial hypercholesterolemia only became greater than for others in the population after 1915, demonstrating that possession of the gene is compatible with a normal life span in some environmental conditions but not others.

Haemochromatosis is another example of a Mendelian disorder that cautions us not to think too simplistically. Haemochromatosis is a disease that has been regarded as a candidate for population genetic screening because it is readily treated by blood letting, and it is common, with 5 per 1000 Northern Europeans being homozygous for the C282Y mutation. An expert panel in 2000 held that 95% of people over 45 years who were homozygous would have significant illness. We need to test this kind of assumption empirically, and a recent study did just that. It screened over 41000 people and identified 152 individuals as homozygous for haemochromatosis.\(^\text{10}\) The startling finding was that these 152 individuals were no more likely to have illness than the rest of the population. The main point is that gene penetrance, even in Mendelian genetic diseases, may be much lower than was estimated by doing studies of families of those who came to medical attention. Even in monogenic diseases, the environment and other genes have important effects.

When we move from highly penetrant single gene disorders to consider the genesis of common disease, we have not yet come close to understanding the complicated gene/gene and gene/environment interactions that occur. For example, the disease endpoints of heart disease, of breast cancer, or of diabetes may be arrived at by different pathways. How important the genetic component in these different pathways is, differs from case to case - but only a small minority (<5%) of pathways to these commonly occurring disease endpoints are monogenic, with a highly penetrant gene involved.\(^\text{11}\) Most cases are due to numerous genes interacting with different environmental exposures, so several different genes may indicate susceptibility to a given
particular disorder. Some individuals may have more than one of these, each of which changes their risk to a different extent.

Finally, to complicate the picture still further, some people have what might be called "protective genes", which actually reduce their susceptibility to particular disorders. And even the same, given gene may be related to disease risk in different ways. Having the NA2 slow genotype, although it increases the risk for bladder cancer, decreases the risk for colon cancer. An understanding of these complicated aspects of susceptibility testing is not only difficult to communicate, but it limits the usefulness of the DNA identification.

Two more aspects are relevant to evaluating the appropriate role of genetic risk identification for improving the health of the population. The first is Geoffrey Rose's insight that an approach that identifies "outliers" on some biological (or genetic) measurement of risk, is inherently limited in what it can achieve. Because the great majority of cases of common disease are made up of people at low or moderate genetic risk, this approach can only truncate the distribution curve of disease incidence at the high end. And it can do that only if it is effective in allowing the small number who are outliers to avoid disease. If disease incidence is to be significantly lowered in the population, what needs to be done is to shift the whole curve of incidence to the left. This can only be done by addressing the causes of disease incidence in a population, which for common diseases are not genetic but environmental (diet, smoking, poverty etc.). An example illustrating this importance of environment is provided by colon cancer. In the 1950's, age adjusted colon cancer mortality rates in Japan were less than one fifth of those in the U.S., and for people of Japanese ancestry living in the U.S. they were similar to U.S. Caucasian rates. Today, diets and lifestyle have changed in Japan, and colon cancer
mortality rates there are as high as in the U.S.\textsuperscript{15} This is too short a time frame for genetics to be an explanation.

**Will identification lead to prevention?**

People can derive benefit from the screening only if knowledge of their susceptibility allows them to avoid the development of disease. Other than a healthy life style, with a balanced diet, lots of fruit and vegetables, moderate exercise and no smoking (advice that applies to us all), for most disorders, there is no effective preventive intervention available at present. So there is no health benefit to individuals from knowing their genetic susceptibility - other than frequent check-ups in the hope of early detection. We know very little as yet about the identity or interaction of the specific environmental factors that trigger the development of many common diseases. Moreover, some of the factors known to affect complexly determined multifactorial disorders - such as the quality of social relationships and support networks- are very difficult to measure.\textsuperscript{16}

Even if a prevention strategy is identified, how likely is it that individuals at risk would change their behaviour and follow it? Rates of compliance with medical treatment regimes are often around 50%, even when people are already acutely ill.\textsuperscript{17-21} In the case of susceptibility genes, where there is no illness present to serve as a motivating factor, it is likely that compliance rates would be lower still.\textsuperscript{22} Smokers whose genetic test results showed a 2 to 4 times increased risk of lung cancer were no more likely to quit smoking than those who got standard counselling, so the knowledge of susceptibility may not lead to the hoped for behaviour change. The ability of individuals and the health care system to react to and make beneficial use of information provided by genetic susceptibility screening of the general population is likely to remain quite limited for a long time to come.
In contrast, the potential for harm is considerable. As noted earlier, susceptibility screening creates a new category of people who are not ill but who know that they have an increased statistical risk of disease. How will this affect their self-image and sense of identity? Will it have a negative effect on their family and other relationships? In addition, disclosure of their risk status could lead to stigmatization, or unfair discrimination for insurance, or employment. The likelihood of stigmatization is likely to decline as tests are developed for more and more genotypes, because there would be increasing recognition that the majority of us carry genes that makes us "susceptible" to one common multifactorial disorder or another. But initially, those who carried the genes that could be tested for might well encounter discrimination or bias in their personal, school, or work lives, and we do not yet have proper protections against this in place.

**The influence of the biotechnology industry**

Some of the motivations for the interest in susceptibility testing are not related to better health care and personal benefit of the tested individuals. Increasing numbers of human genes and gene testing procedures have been patented in recent years, with more than 25,000 DNA-based patents having been issued by the end of 2000. Numerous biotechnology companies hope to reap economic returns when these are used in genetic testing. This use of patents has led to unanticipated consequences in the area of human health. For example, evidence is emerging that academic research is being hampered by patents on genes, and in some instances they are already limiting patients' access to genetic testing. Myriad Genetics has filed an exclusive patent related to testing for genes that predispose to breast cancer, and as a result, in some provinces, including British Columbia, access to this testing is no longer available, unless an individual can afford the cost out of pocket. This story with regard to breast cancer exemplifies what is going to
be a growing issue facing health care systems. There will be an increasing number of instances where gene testing for appropriately selected individuals with a strong family history would be of benefit, and in a few sub-populations, genetic screening for Mendelian diseases, but because of commercial presence and patents, access becomes limited. It may become necessary to re-think whether and how patents should apply to human genes.\textsuperscript{25}

It is unlikely there will be a spontaneous upsurge in requests to be screened for common diseases when the screening is of uncertain predictive value. However, strong marketing could change that. The number of trained geneticists is quite small, and aggressive marketing to other physicians who are not well equipped to assess the claims is likely. Commercial motivation in the area of genetic susceptibility testing has already led to increased marketing, especially in the U.S., which may have the effect of promoting premature and inappropriate overuse of genetic identification in an ad hoc way. There has been much genetic "hype" with full page advertisements aimed at the public.\textsuperscript{26} We are in a context of increased marketing by industry, with drug advertising to U.S. consumers costing $2.5B in 2000, and marketing to physicians costing $4.04B that same year - an increase of 64\% since 1996.\textsuperscript{27} In particular, direct to consumer advertising of genetic testing, is occurring.\textsuperscript{28, 29} Numerous biotechnology companies now have websites promoting testing (www.genetests.org) and most companies simply provide test results, they do not provide pre- and post test counselling and interaction. Marketing is a powerful tool and it is in industry's interest to see rapid uptake of genetic identification.

Continuing to track genotypes potentially related to certain common complexity determined multifactorial diseases, such as cancer in large families with a strong history, has value, as such research projects may well help elucidate some disease processes and contribute to our understanding of the mechanisms involved. But, at this time, these studies must be viewed as
research, with all those involved giving fully informed consent and receiving the protection accorded participants in medical research, such as approval by a research ethics board.

Criteria to be met before screening is beneficial

The public well-being will suffer if identification of genetic susceptibility is marketed to the public and occurs on an opportunistic, inequitable, ad hoc basis and is treated simply as a "consumer good". The public are vulnerable and most people do not know enough about genetics to assess the claims. Screening should only be done as part of a unified, well-planned public health program. Governments should be considering what measures to put in place to ensure that if any genetic susceptibility screening is offered to the general population, it is in an ethical and beneficial manner, with informed consent, and that it is not driven solely by commercial goals. To obtain approval to offer susceptibility screening to healthy people, it should be necessary to meet several conditions. The disease should be significant, and its prevalence known. Reliable information on the actual risk posed by having the "susceptible " genotype is an essential prerequisite. The screening program should have been shown to be cost effective based on lessons of carefully monitored pilot studies. To bring benefit from the population's point of view, the genotype would have to be quite common, and would have to increase susceptibility by a very significant amount with the odds of being affected given a positive result being high.\textsuperscript{11}

Counselling to ensure informed consent from an objective, arm's length source is important. Counselling is personnel-intensive and time-consuming, because conveying risk information is complex, and perceptions of risk differ widely.\textsuperscript{30, 31} Hiring and training personnel qualified to carry this out is expensive. Services for follow-up diagnosis should be available, as well as an effective intervention acceptable to those screened.
The test itself should have been shown to be safe, valid and reliable and there should be mechanisms in place to assure the quality and reliability of laboratory test results. There should be measures and protections in place to ensure unfair discrimination in the workplace, or with regard to life insurance, is not going to happen. Regulation requiring genetic testing for susceptibility to be available only though a physician (analogous to the requirement for prescription drugs), might be considered.

There are also particular issues to be considered in countries such as ours with publicly supported medical care systems, where any susceptibility screening should be evaluated and scrutinized for its opportunity costs. If judged to be of clear benefit in improving health outcomes, screening should be considered for coverage within that system. If genetic susceptibility identification is instead permitted to be done in an ad hoc way outside the system, as a "consumer choice" it may then lead to invasive, inequitable and expensive diagnostic testing or on-going monitoring, and lead to a misuse of health care resources.

**Public awareness**

People need to learn to be sceptical of "genetic hype", and to know that with regard to future risk of common diseases like heart disease, adult onset diabetes, or common cancers, an individual's environmental profile (smoking, activity, income, education) is usually as or more informative than the genetic profile. Provision of objective, balanced information to the public and in the educational system is needed. Unfortunately, one of the impediments to public understanding is that it is easier to transmit the idea that "genes cause illness" than the idea that genetic makeup interacts over a life time with life circumstances - social, physical, and economic - to determine health. High penetrance single gene disorders like Huntington disease have shaped the public's image of genetics - but this image is misleading and inappropriate to apply to
common diseases with their complex pathogenesis. The public does not understand that although a genetic test may be exquisitely accurate in detecting if an individual has a given genotype, it is not yet understood what having that genotype signifies. The presence of a genetic marker should not be viewed as if it were a clinical disease.

Many genetics researchers in academia have been recruited into collaborations with industry, and certainly in the U.S., a minority of genetics researchers now have no ties at all to for-profit companies. The enormous investments needed to exploit genetics "may have driven a more exuberant set of claims than usual, designed to appeal not only to the public but also to investors". The training of genetics service providers does not emphasize the importance of non-genetic determinants of health, so they are understandably focused on genetics. While particular sectors would profit from an individual genetic approach, no particular sector profits from population based approaches that lower everyone's risk by changing things to support healthy eating, no smoking and an active life. So while there is lobbying for a genetic risk identification approach, no particular sector sees the need to lobby for implementing population based policies to support us all in leading healthier lives. One defence against all this is to improve public awareness, another is to require evidence and evaluation.

**Summary**

The goal of avoiding the onset of common diseases is a worthy one, but a genetic approach is limited in what it can achieve. In essence, there are three important aspects that limit improvements to health with the approach of genetic susceptibility screening. The first aspect is the great importance of life circumstances in determining health. The second is the great complexity of gene/gene, gene/environment interaction, with common gene variants related to
common diseases all being of low penetrance. The third limiting aspect is human behaviour with regard to compliance with medical recommendations.

While there is no doubt DNA based genetic testing has become an essential tool for the prevention and control of single gene disorders, it is doubtful whether population wide identification of susceptible "risk" genotypes will translate into safe, cost effective and equitable strategies for the prevention of complex diseases of environmental-gene interaction. We should not get carried away with the false promise of a technological fix for disease where the incidence is related to the action of factors such as unhealthy diets, tobacco, deficient physical activity, poverty, or industrial contaminants. It would be of concern if pressure from commercial interests in the biotech and pharmacology industries to introduce genomic products for determining individual genetic susceptibilities diverts attention and resources from modification of health determinants that affect all the population. For the foreseeable future, widespread genetic susceptibility screening would not be an ethical or appropriate use of resources - it would provide minimal benefit at too high an opportunity cost and has the potential to cause serious harm. If in future population based genetic screening for susceptibility is offered, it should only occur in a context of clear social policy, with regulation and accountability in place. How genetics is used will have major implications for the sustainability of the health care system as well as for the overall health of the population.
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