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Predictive value of testing for multiple genetic variants in multifactorial diseases: implications for the discourse on ethical, legal and social issues.

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Abstract

Multifactorial diseases such as type 2 diabetes, osteoporosis, and cardiovascular disease are caused by a complex interplay of many genetic and nongenetic factors, each of which conveys a minor increase in the risk of disease. Unraveling the genetic origins of these diseases is expected to lead to individualized medicine, in which the prevention and treatment strategies are personalized on the basis of the results of predictive genetic tests. This great optimism is counterbalanced by concerns about the ethical, legal, and social implications of genomic medicine, such as the protection of privacy and autonomy, stigmatization, discrimination, and the psychological burden of genetic testing. These concerns are translated from genetic testing in monogenic disorders, but this translation may not be appropriate. Multiple genetic testing (*genomic profiling*) has essential differences from genetic testing in monogenic disorders. The differences lie in the lower predictive value of the test results, the pleiotropic effects of susceptibility genes, and the low inheritance of genomic profiles. For these reasons, genomic profiling may be more similar to nongenetic tests than to predictive tests for monogenic diseases. Therefore, ethical, legal, and social issues that apply to predictive genetic testing for monogenic diseases may not be relevant for the prediction of multifactorial disorders in genomic medicine.

Key words: genomics, ethics, medicine, screening,

Introduction

Multifactorial diseases such as type 2 diabetes, osteoporosis, and cardiovascular disease are caused by a complex interplay of many genetic and nongenetic factors, each of which conveys a minor increase in the risk of disease. Although the genetic origin of these diseases is still poorly understood, enormous progress in the identification of susceptibility genes is expected from the large-scale genome-wide associations [1,2] and biobank initiatives that have been launched worldwide to investigate the role of genetic factors in common multifactorial diseases.[3] The vast amount of information that will come from these studies will fuel the search for useful applications of genetic testing for the prevention and early detection of common diseases with great public health impact. One of the greatest promises is that the unraveling of the genetic origins of common diseases will lead to individualized medicine, in which prevention and treatment strategies are personalized on the basis of the results of predictive genetic tests. Examples of multifactorial diseases showing promise for predictive genetic testing include type 2 diabetes and age-related macular degeneration.[4,5]

This great optimism, however, is counterbalanced by concerns about the ethical, legal, and social implications of genomic medicine, such as the protection of privacy and autonomy, stigmatization, discrimination, and the psychological burden of genetic testing.[6,7] These concerns about potential adverse consequences are translated from genetic testing in monogenic disorders, which is available for more than 1,000 disorders. [8] Most of these applications are to confirm diagnoses in rare syndromes, but others are used for prenatal testing, newborn screening, and presymptomatic carrier testing. For example, pregnant women can be tested for selected congenital anomalies in their offspring, and relatives of patients with Huntington disease and hereditary forms of cancer can be tested for their predisposition to disease long before the onset of symptoms.

Multifactorial diseases, however, are essentially different from monogenic diseases, which raises the question of to what extent the same ethical, legal, and social issues are relevant. The participants of the Bellagio initiative clearly emphasized that the discussion of ethical, legal, and social issues should acknowledge the fundamental differences between predictive

genetic testing for monogenic diseases and that for multifactorial diseases: "the widespread use of Huntington's disease as a paradigm for genetics in medicine should be actively discouraged as it gives a very misleading idea of the predictive power of genetic information for most people."[9] Essential differences between genetic testing for monogenic diseases and that for multifactorial diseases include the predictive value of the test results, the pleiotropic effects of susceptibility genes, and the inheritance of genomic profiles. In this article, we elucidate and illustrate these three differences and discuss how they may influence the discussion about ethical, legal, and social issues in genomic medicine.

Predictive value of genetic testing

Monogenic diseases

Monogenic diseases such as Huntington disease, familial hypercholesterolaemia, cystic fibrosis, and several hereditary forms of cancer are completely or predominantly caused by mutations in a single gene. Predictive testing for these causal genes is very informative because disease risks differ substantially between carriers and noncarriers of the mutations. Shown in Figure 1 are the differences in disease risk between carriers and noncarriers of the risk variants for Huntington disease, hereditary breast cancer, and nonpolyposis colorectal cancer.[10-12] These mutations are typically rare, and therefore carriers have a substantial increased risk of disease, and noncarriers have a disease risk that approximates the population average.

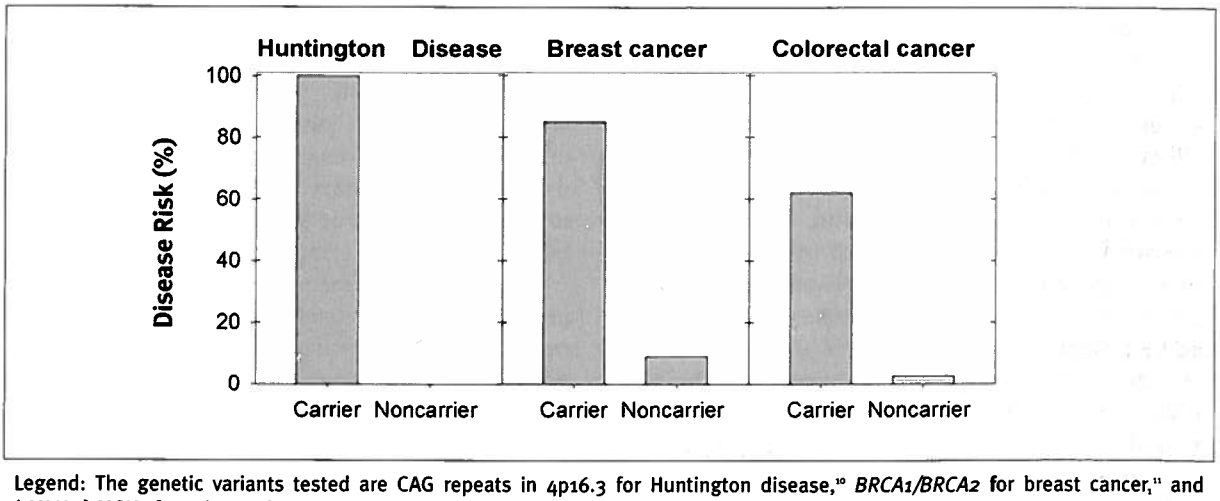
Because of the large differences in disease risk between carriers and noncarriers, genetic testing can be useful for targeting preventive or therapeutic interventions to the relatively small group of individuals at increased risk of disease. Examples include intensive surveillance and prophylactic surgery for breast and ovarian cancer and prescription of statins for familial hypercholesterolemia. Genetic testing is also considered valuable in the absence of effective interventions to relieve uncertainty—also in the case of positive test results—and to prepare for the future. But the high predictive value of genetic testing can also be used for undesired purposes—from the perspective of the individual who tests positive—for example, by insurers to determine the conditions and premiums of insurance. It is for this reason that ethical, legal, and social issues are an integral part of the evaluation of genetic testing.

Multifactorial diseases

Because multifactorial diseases are caused by a complex interplay of many genetic and non-genetic factors, the predictive value of testing for a single genetic variant is limited. The disease risk in carriers of the risk variant is only slightly higher than that in non-carriers. For example, several examples of genetic test results for predicting type 2 diabetes are shown in Figure 2. Because risk variants are generally common (>1%), carriers and noncarriers have disease risks that are only slightly higher or lower, respectively, than the population average. The differences in disease risk are less profound, and noncarriers retain a substantial risk of disease.

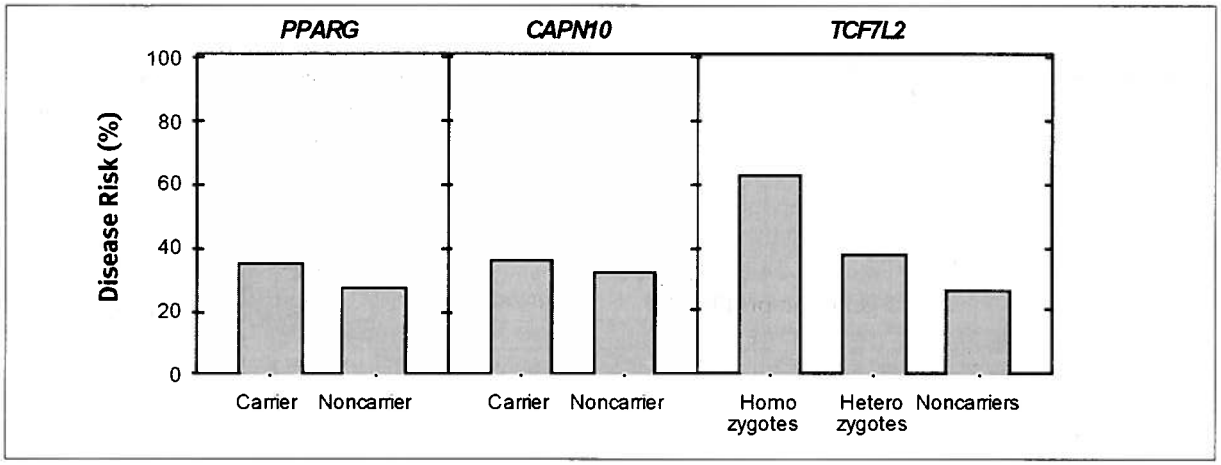
An exception is the *TCF7L2* gene for which homozygous carriers of the risk variant have a risk of type 2 diabetes of 63% compared with 26% in noncarriers. This does not necessarily imply that that *TCF7L2* carrier testing is useful in a prevention program for type 2 diabetes, however. Although homozygous carriers (7% of the

Figure 1. Disease risks of carriers and noncarriers in genetic testing for monogenic disorders



Legend: The genetic variants tested are CAG repeats in 4p16.3 for Huntington disease,[10] *BRCA1/BRCA2* for breast cancer,[11] and *hMLH1/hMSH2* for colorectal cancer.[12]

Figure 2. Disease risks of carriers and noncarriers in single genetic testing for multifactorial disorders



Legend: Data on the odds ratios of the genetic variants are obtained from the literature (*PPARG*[30], *CAPN10*[31], *TCF7L2*[32]). For the calculation of the disease risks from the published odds ratios, we assumed a lifetime risk of type 2 diabetes of 33%.[33]

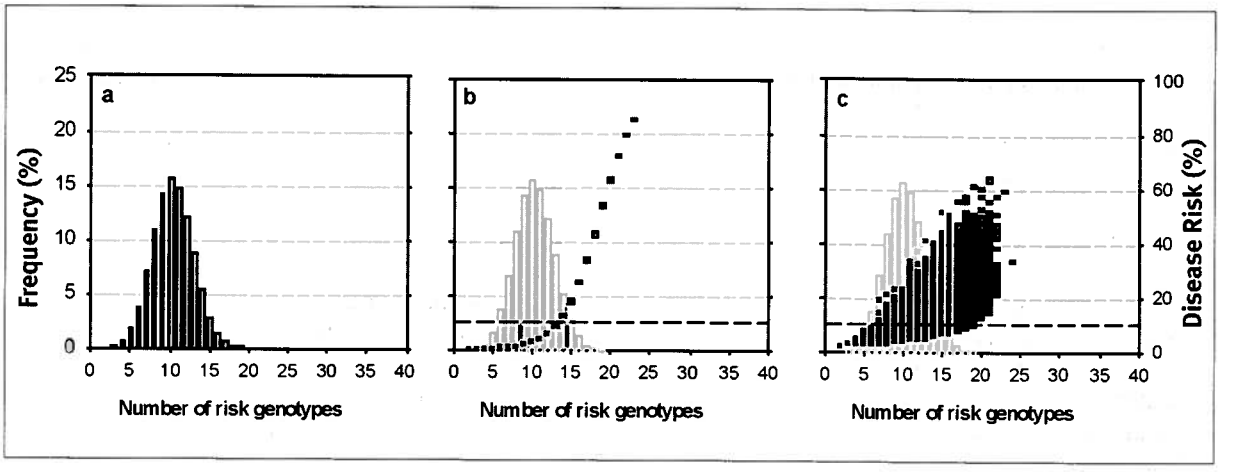
population) may be more motivated to adopt a healthier lifestyle to lower their diabetes risk, in practice behavioral changes are difficult to achieve.[13] Moreover, even if a 100% effective treatment were available to eliminate the negative effects of the risk alleles, 63% of the homozygous and 88% of the heterozygous carriers would not benefit from the intervention because they either would not develop diabetes despite their *TCF7L2* carrier status or would develop diabetes for other reasons.[14]

Because multiple genetic and nongenetic factors each have only a minor role in the etiology of multifactorial diseases, genetic prediction of disease will be based on testing for multiple genetic variants simultaneously. This is called *genomic profiling*. A genomic profile describes the genotype status for all tested variants. Suppose we test five genetic variants to predict disease, which each come in two genotypes: a risk genotype (R) that increases the risk and a normal genotype (N) that decreases the risk of disease. The possible results of this combined test include N-N-R-R-N and R-N-N-N-R, which represent two among the 32 that are possible based on five variants with two genotypes. These profiles may reflect different underlying pathways for developing the disease that may not necessarily be prevented or treated with the same interventions. Yet, when the aim is prediction of disease rather than positive response to specific interventions, then these underlying pathways can be considered secondary. That is, what counts is the genotype status of the genes tested and the degree to which they increase or decrease the risk of disease.

The risk of disease associated with a genomic profile is a function of the person's genotype status for all genetic variants that increase or decrease the disease risk. When single genetic variants are equally associated with increased risk of disease, e.g., when all risk variants increase the risk of disease by 50%, it does not matter for the prediction of disease on which gene a risk variant is carried. In the aforementioned example, both profiles have two risk and three normal genotypes out of five variants tested. Prediction of disease can then simply be based on the number of risk genotypes in the genomic profiles: the more risk genotypes, the higher the risk of disease. This is also illustrated in Figure 3, which simulates a population of 1 million persons for whom genotype and disease status are known and in which the average disease risk is 10%. The data were simulated using a procedure that has been described previously in more detail.[15] The hypothetical frequencies of risk genotypes for 40 genes vary from 1% to 60%. Figure 3a gives the expected distribution of the number or risk genotypes when the 40 genes are tested simultaneously. The figure shows that all individuals have at least some risk genotypes and none have risk genotypes for all genes tested. Figure 3b shows the associated risk when each single risk genotype increases the risk of disease by 50% (odds ratio = 1.5). The figure shows that the more risk genotypes that are present, the higher the risk of disease. Multiple genetic testing could identify genomic profiles associated with very high disease risks, but these are rare. Most of the individuals have disease risks that are only slightly higher or lower than the average disease risk in the population.

Finally, in Figure 3c we consider a more realistic scenario in which some genetic factors are stronger predictors of disease than others. The

Figure 3. Disease risks associated with profiles in genetic testing for multifactorial disorders



Legend: Bars indicate the frequency distribution of the genomic profiles quantified by the number of risk genotypes in the profile. The frequencies are presented on the left axis. The scatter plots represent the disease risks associated with the genomic profiles when all individual variants have the same odds ratio (OR=1.5; Figure 3b) and when the odds ratios vary (Figure 3c). The disease risks are presented on the right axis. Genomic profiles were constructed using a previously described method.[15] We assumed that the disease risk in the population was 10% and that the frequencies of the risk genotypes varied between 1 and 60% (incremental from 1 to 19% by 1% and from 20 to 60% by 2%). In Figure 3c we assumed that the odds ratios varied from 1.05 to 2.0 (incremental from 1.05 to 1.19 by 0.01 and from 1.20 to 2.0 by 0.05).

odds ratios of the individual genetic variants vary from 1.05 for the frequent risk genotypes to 2.0 for the rare risk genotypes. In this case, the disease risks not only increase with the number of risk genotypes in the profiles, but also within each category defined by the number of risk genotypes. The result is a scatter of disease risks rather than clearly distinguishable risk categories. This scenario, in which both the frequency and the effect size of the risk genotype vary, is the most likely scenario to be expected for the distribution of disease risks associated with genomic profiles. Note, however, that these examples do not consider the role of environmental factors. These factors would contribute to further variation in disease risks for individuals with the same genomic profile.

Pleiotropic effects of susceptibility genes

In the next decades, genome-wide association studies and biobank initiatives will help to identify the numerous weak susceptibility genes involved in multifactorial diseases. These discoveries will lead to the construction of genomic profiles for the prediction of common disorders, such as type 2 diabetes, osteoporosis, asthma, Alzheimer disease, and cancer. Separate profiles will be constructed for different diseases and will therefore differ in the genetic variants included. Many susceptibility genes, however, are associated with increased risk of more than one disease, and hence can be included in more than one genomic profile. An example is the tumor necrosis factor α (TNF-α) -308G/A polymorphism, for which carriers of the risk allele have an increased risk of non-hodgkin lymphoma, obesity, and asthma.[16-18] Such pleiotropic effects typically occur when diseases share causal pathogenetic pathways. In the extreme case, when there is considerable overlap in the causal pathways between two diseases, for example, as for hypertension and coronary heart disease, a genomic profile designed for one disease can also be predictive of the other, albeit with a lower predictive value.

Not only can susceptibility genes be involved in multiple disorders, but they can also increase the risk of some diseases and decrease the risk of others. For example, deletions in the angiotensin-converting enzyme (ACE) gene insertion/deletion (I/D) polymorphism are associated with a decreased risk of Alzheimer disease and an increased risk of stroke,[19,20] and homozygous carriers of the interleukin-6 (IL-6) -174G/C polymorphism also have a decreased risk of Alzheimer disease and an increased risk of intima media thickness, a risk factor for stroke and myocardial infarction.[21,22] This could have important implications for the prevention of disease, particularly when genomic profiling is applied for targeting pharmacogenomic interventions. Preventive and therapeutic interventions aimed at eliminating the negative effects of a single genetic variant for one disease may increase the risk of another disease.

Inheritance of genomic profiles

A third essential difference between genetic testing for autosomal dominant monogenic

disorders and genomic profiling for complex diseases is the disease implications for relatives. Results of genetic tests for autosomal dominant conditions are also informative for close relatives, particularly parents and children. When one parent is identified as a heterozygous carrier of an autosomal dominant gene, children have a 50% risk of inheriting the risk variant from that parent and, depending on the penetrance, have a substantial risk of developing the disease.

When testing multiple genetic variants simultaneously, however, it is less likely that close relatives share identical profiles. The probability of inheriting the same genomic profile depends on the number of genetic variants that are tested simultaneously and is low when the number is large. In fact, when 20 autosomal dominant susceptibility variants are tested and one parent is a heterozygous carrier for all variants, then the probability that a child inherits all risk alleles from that parent is 0.50^{20}, or approximately 1 in one million. This probability is higher when the other parent also contributes risk alleles, which is likely when risk alleles are common. Generally, however, inheriting exactly the same profile is unlikely.

Implications for ethical, legal, and social issues of genetic testing

Ensuring the appropriate evaluation of genetic testing and genome-based prevention programs is fundamentally an ethical concern for those responsible for efforts to promote population health.[9] This includes the prevention and monitoring of potential adverse ethical, legal, and social consequences of genetic testing. Yet, *which* issues are relevant in the evaluation of predictive genetic testing also depends on the nature of the test. We have described three differences between genetic testing for monogenic disorders and that for multifactorial disorders, which not only influence the clinical and public health utility of genetic testing, [14,15,23] but also may affect the discussion of ethical, legal, and social issues, especially discrimination and stigmatization, privacy, and the psychological impact of genetic testing.

Discrimination and stigmatization concern the differential treatment of individuals based, in this case, on their genetic predisposition for a particular disease. The most illustrative example is the use of genetic test results by insurers to determine the conditions and premiums of insurance. Although fear of discrimination may lead individuals to decide against predictive genetic testing,[6] most insurance applicants are accepted at the standard conditions.[24] Discrimination and stigmatization based on genetic predisposition require clearly distinguishable subgroups between which the disease risks differ to such an extent that differentiation of the conditions and premiums outweighs the costs of obtaining additional information about genetic predisposition. Knowing that genomic profiling yields a continuum of disease risks rather than distinct risk categories, that most individuals will have risks that are only slightly higher or lower than the population average, and that individuals may be at increased risk of some diseases and at decreased risk of others makes it less likely that genomic profiling can be used for purposes other than disease prediction. Also, genetic discrimination of relatives of patients with multifactorial diseases may be unlikely because of the low probability of inheriting the completely same profile.

The protection of privacy is a key issue in predictive genetic testing because the results of genetic tests also inform close relatives about their carrier status, even when they have no intention toward genetic testing themselves, and because the test results can inform *asymptomatic* individuals about their disease risks in later life. These issues are particularly important in monogenic disorders, for which close relatives have a substantial risk of carrying the same risk genotype and for which carrier status has high predictive value. These issues may be less relevant in predictive testing for multifactorial diseases by genomic profiling, because the probability of inheriting the same genomic profile is very low and disease risks associated with most genomic profiles are only moderately higher or lower than the population average. Moreover, disease risks are codetermined by environmental factors, which leaves the door open for personal or medical interventions to reduce the effect of the risk information.

The adverse psychological consequences of genetic testing for monogenic diseases such as hereditary cancers and Huntington disease have been intensively studied.[25;26] These studies indicate that after a period of distress during and around the time of the testing procedures, individuals generally cope well with the adverse results of genetic testing.[25,26] Nevertheless, researchers warn that psychological distress is underestimated in longitudinal studies because of a selective loss to follow-up.[27,28] A question is whether adverse psychological consequences should also be expected in genomic profiling. Most at-risk profiles are associated with disease risks that are only moderately higher than the population average. Moreover, genetic predisposition for multifactorial disorders is less deterministic in the sense that these diseases are caused by an interplay of genetic

and nongenetic factors, and the latter often allow for risk reduction through changes in lifestyle factors such as diet, smoking and exercise. These factors combined suggest that the adverse consequences of predictive genetic testing for common diseases may not be that severe.

While ethical, legal and social issues that apply in monogenic testing may be less relevant for genomic profiling, new issues may arise. One concern is whether it is ethical to offer genetic tests with low predictive value or tests that have not been thoroughly and systematically examined for their predictive value. Genomic profiling is already available through the internet e.g., for personalized lifestyle and diet recommendations. Although these tests are presently not validated and not recommended clinically, people buy these online tests. Apart from being uninformative and misleading, such premature use of genetic information may hamper the trustworthiness and integrity of future applications.

Concluding remarks

Ethical, legal, and social issues are an integral part of the evaluation of health care and are not unique to genomic medicine.[29] Many issues that apply in predictive genetic testing, such as privacy and autonomy, have a broader scope because they apply to all or most medical procedures and programs. Some other issues are particularly relevant to predictive testing, irrespective of whether it is genetic or nongenetic; some are particularly relevant in genetic testing, irrespective of whether it is predictive or diagnostic; and others are specific for predictive genetic testing. In this article, we made a further distinction and elucidated that ethical, legal, and social issues that apply to predictive genetic testing for monogenic diseases may not be relevant for the prediction of multifactorial disorders. This distinction is important to ensure that the progress in genomics research and the development of genome-based prevention programs are accompanied by a meaningful debate of the ethical, legal, and social issues.

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