

# Considerations for Designing a Prototype Genetic Test for Use in Translational Research

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## Key Words

Clinical utility · Common disease · Genetic epidemiology · Genetic testing

## Abstract

**Background:** Translational research is needed to explore how people will respond to personal genetic susceptibility information related to common health conditions. Maximizing the rigor of this research will require that genetic test results be returned to study participants. Currently, there is no established method that guides the selection of genetic variants to be used in research with these objectives. **Methods and Results:** To address this question, we designed a process to identify gene variants and health conditions to be included in a prototype genetic test for use in a larger research effort, the Multiplex Initiative. The intention of this exploration was to facilitate research that generates individual genetic test results that are returned to study participants. Inclusion criteria were developed as part of a transdisciplinary and iterative process that considered the weight of evidential support for genetic association with common health conditions, the appropriateness of use in human subjects research, and the recommendations of expert peer reviewers. **Conclusions:** The selection process was designed to identify gene variants for the limited purpose of translational research and, therefore, should not be seen as produc-

ing a valid clinical test. However, this example of an applied selection process may provide guidance for researchers who are designing studies to evaluate the implications of genetic susceptibility testing through the return of personalized genetic information. As the rate of genomic discoveries increases, such research will be essential in steering the translation of this information towards the greatest public health benefit.

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A primary objective of the Human Genome Project was to improve public health by creating an infrastructure that could speed the identification of genes associated with health and disease [1, 2]. One possible medical benefit of finding such genes is that they could enable personalized risk prediction that, when provided to individuals, may motivate risk-reducing lifestyle changes. However, much research is needed to evaluate whether and how these risk communications might influence recipients. To this end, it is necessary to develop tools that could facilitate translational research related to genetic

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testing, that is, to explore the clinical utility, public uptake, and social and behavioral impact of such testing [3]. This research is needed prior to applying these genetic testing approaches if they are to inform and guide responsible integration of these applications into medical practice. Alternatively, findings of these studies could reveal that these tests have little clinical potential and thereby help deter their inappropriate use. The need for careful research on the implications of genetic susceptibility testing is underscored by a growing number of private companies that are bypassing the medical community to offer genetic testing services results directly to consumers [4–6].

To facilitate the rigorous research needed to evaluate the public health potential of genetic susceptibility testing, scientists must provide target groups with individual genetic test results. Experience tells us that using hypothetical genetic testing scenarios often produces results that are inconsistent with what is observed in practice [7]. Studies involving the return of actual genetic test results are common for high-penetrance genes that convey considerable risk for rare familial diseases [8]. However, there is limited research exploring the implications of conveying test results for low-penetrance genetic variants associated with common health conditions [see for example 9–13]. Furthermore, these studies have generally focused on feedback related to a single genotype, which is an unlikely model for how these types of results would be conveyed in practice [14]. The following discussion will focus on the implications of genetic susceptibility testing for common health conditions, because these diseases have the largest impact on overall public health in the U.S. and, increasingly, worldwide.

A topic of considerable debate among health researchers is whether the small increases in genetic risk typically found for common health conditions (generally an odds ratio [OR] of  $<2$ ) will inspire risk reductions that can improve on traditional behavioral interventions [15–20]. Although many questions that are central to this debate can best be answered through empirical studies, few have pursued this line of investigation. This is partially due to a perception that the evidential support for most gene-disease associations is insufficient to justify returning individual genetic test results from research and that such information might have insufficient benefits to outweigh potential psychological harm [21, 22]. However, these specific concerns are coming into question as scientifically reproducible genetic risk factors are rapidly emerging [23–25] and numerous social and behavioral research studies have found no evidence of inappropriate

psychological distress following positive genetic test results [26–31].

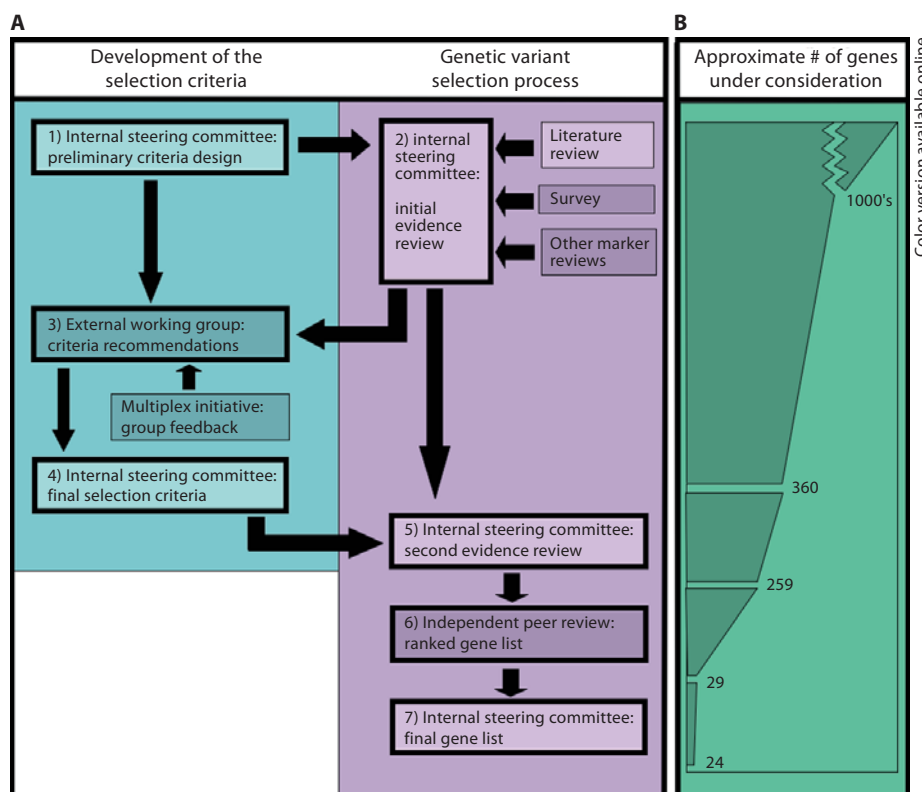
The return of individual genetic test results to research participants has many practical and ethical implications. Briefly, the debate over when it is appropriate to return results generally focuses on the likely impact on study participants, the quality of the evidence for a genetic risk, the health implications of the genetic risk, the capacity of participants to take action to avoid illness, and the context of the research [see for example 32–40]. While some reports have provided informative criteria and guidance concerning returning individual genetic test results, these recommendations are often broad, are not focused on translational research, and have not been developed in the context of actual research applications [38–40]. Given this starting point, the question for clinical, social, and behavioral researchers seeking to conduct empirical research becomes how to determine and apply specific standards to produce a prototype genetic susceptibility test.

In this report, we describe the process, considerations, and challenges we addressed in developing a prototype genetic susceptibility test to be used as a translational research tool for the Multiplex Initiative [41]. As such a test would impact different areas of science and medicine, we used a transdisciplinary process to incorporate a variety of perspectives [42]. This approach included multiple rounds of review by an internal steering committee, an external working group, and peer reviewers. The objective of the process was to develop and implement a set of criteria for selecting health conditions and candidate genetic variants that could be included in a research prototype genetic susceptibility test. While the approach used in this study will not be directly applicable to all research objectives, it is intended to be an informative example of one attempt to move from theoretical considerations to actual research practice.

## Methods

### *Process Overview*

This project was part of the foundational work conducted to develop the Multiplex Initiative. The Multiplex Initiative has been described elsewhere [41], but in brief it is a transdisciplinary research effort that aims to begin exploring the public health implications of genetic susceptibility testing for common health conditions. Selecting gene variants and health conditions for the Multiplex Initiative involved a number of interactive steps, as outlined in figure 1A. Initially, working groups that included a broad representation of scientists from different disciplines engaged in deliberations to develop selection criteria and apply these criteria to



**Fig. 1.** Outline of the study process. **A** Flow diagram of the study. Boxes with heavy outlines represent major steps in the process. Lightened boxes indicate steps performed at NHGRI, while darkened boxes represent steps performed by external groups. **B** Representative chart showing the number of genetic variants under consideration at different points in the genetic variant selection process. Not to scale.

the evidence base for genetic variants associated with common health conditions. Gene variants that met criteria identified by the working groups were subjected to an independent peer review by an expert panel whose recommendations were used to develop a final list of gene variants. In the following sections, we describe the specific steps that this process comprised.

#### Step One

A subset of us (CHW, CMM, and LCB) served as an internal steering committee that outlined and oversaw the steps involved in developing criteria and candidates for a research prototype test. This committee has expertise in public health research, social and behavioral research, bioethics, and genetic epidemiologic research. The internal steering committee created a broad set of criteria to screen through the evidence for gene-disease associations. In brief, these criteria focused on health conditions that might plausibly have an impact on public health and for which there had been some evidence of association with common genetic variants.

#### Step Two

To identify candidate genetic variants from among the vast number of reported gene-disease associations, the internal steering committee used a multi-step process that drew on a range of informational resources. The goal of this process was not to identify every single genetic variant with the possibility of inclusion through a systematic review, but rather to explore the existing literature to identify a set of variants that would be appropriate for the research goals of the Multiplex Initiative. Additionally, while the process was aimed at identifying multiple variants that could

be used in a multi-gene (multiplex) genetic test, we do not intend the risk information from these variants to be combined to create an overall disease risk, as there currently is little evidence clarifying how genetic risks interact. First, an informal online survey of genetic epidemiologists was conducted to solicit suggestions of gene variants that, in these experts' opinions, had the 'best' evidence to support a robust association with common health conditions. This survey elicited responses from 25 researchers, with a resultant list of about 50 proposed genes. Additionally, the internal steering committee identified and integrated other gene variant lists that were publicly available [for example 43, 44] or that had been published in overviews of the genetic epidemiology of common health conditions. Finally, the internal steering committee surveyed the literature using references and PubMed searches between 7/05 and 4/06 (while information on the risk associations that were identified was updated, genetic risks reported subsequent to these dates did not go through the complete selection process). Examples of search terms included combinations of health condition names (e.g., osteoporosis), 'genetic,' 'meta-analysis,' 'review,' gene name (e.g., Calpain 10), gene symbol (e.g., *CETP*), and polymorphism (e.g., 677C>T, rs1801133). Because of the open-ended nature of the process and the broad informational needs of the study, this was not conducted as a formal literature review aimed at hypothesis testing. The search applied the broad initial selection criteria designated by the internal steering committee to find studies and meta-analyses, which were then used to identify other gene associations and evaluate the evidential support for the genes recommended in the survey and other review projects.

**Table 1.** Examples of applied selection criteria

Category	Criteria	Example of excluded disease/gene	Example of included disease/gene
Health condition	Large public health impact Adult onset Accepted clinical recommendations for prevention Applicable to everyone tested	Chronic beryllium disease Asthma Drug metabolism Prostate and breast cancer	Lung cancer Osteoporosis Type 2 diabetes Colorectal cancer
Genetic variant	Consistent replication of the disease association Studies include at least 500 cases Minimum of 10% change in risk Over 5% frequency in major US population No pleiotropy with another disease without primary prevention measures	<i>CASR</i> (osteoporosis) <i>KIP2</i> (osteoporosis) <i>NAT2</i> (lung cancer) <i>AAT</i> (pulmonary disease) <i>APOE4</i> (cardiovascular and Alzheimer's disease)	<i>MC1R</i> (melanoma) <i>MTHFR</i> (colorectal cancer) <i>TCF7L2</i> (type 2 diabetes) <i>GSTM1</i> (lung cancer) <i>CETP</i> (cardiovascular disease)

### Step Three

An external working group was responsible for weighing the different issues relevant to determining which health conditions and gene-disease associations had a sufficient evidence base to be appropriate for returning individual genetic test results. The external working group was composed of 6 researchers in the fields of molecular biology, genetic counseling, nutrition, epidemiology, medical research, and genetic epidemiology. Group members were drawn from academic and government institutions. The external working group reviewed the steering committee's selection criteria and examples of genetic variants meeting the criteria. The group met regularly over a period of 4 months, developed the selection criteria, and integrated suggestions from a diverse group of 25 outside clinicians and researchers who were involved with the Multiplex Initiative. The external working group then assembled a report detailing the criteria and considerations for designing a prototype test.

### Step Four

The internal steering committee used the recommendations of the external working group to decide on the final selection criteria (table 1). The criteria underwent further refinement at this point. For example, where the external working group suggested a range, the final criteria specified an exact cut-off value. The final criteria for selecting health conditions and genetic variants are as follows:

**Health Condition Selection Criteria.** The common health conditions that were identified by the internal steering committee and external working group as being candidates for inclusion in a genetic susceptibility test were chosen based on several considerations (table 1). The first was that the health condition should have public health importance in the U.S. (i.e., based on prevalence, severity, and associated healthcare costs). Second, the health condition had to be adult-onset, since return of individual genetic susceptibility test results to children would be too controversial and, all agreed, premature. Another consideration was that the health condition be preventable, that is, there be accepted clinical recommendations for reducing risk for the health condition. A final consideration was that the health condition be relevant to a broad population, and not specific to a gender or ethnic group.

**Genetic Variant Selection Criteria.** We specified minimum criteria for genetic variants to be considered appropriate for inclusion in any prototype test (step 3 and 4, table 1). First, the genetic association must have robust evidence in the literature, including replication of the risk association. Second, we required that the evidence base include studies of sufficient size to support the association, optimally derived from a meta-analysis, but with the criterion of including a minimum of 500 cases. Whenever possible, the epidemiologic quality of the research and existence of plausible biological explanations for the association were also evaluated. Third, the minimum strength of association was selected based on the range of associations likely to be observed for genetic risks for common health conditions, and therefore associated risks were required to have at least a 10% increase or decrease in susceptibility to be considered (excepted from this criterion were statistical measures of biological states, such as cholesterol levels). As the intention was to select gene variants for a test to be used in population-based research, the risk gene variant needed to be carried by a reasonably large proportion of the population (>5% in a major U.S. population). We used the risk unit reported in the original association papers (usually a single genotype, but sometimes reports combined genotypes) in determining whether the genetic variant met the magnitude of the association and the population prevalence requirements. Finally, we excluded genetic variants that were associated with multiple health conditions (i.e., pleiotropic) if any of the conditions lacked evidence-based prevention strategies.

### Step Five

In step 5, the internal steering committee applied the final selection criteria to identify candidate conditions and genes for test inclusion. Each gene was ranked based on their appropriateness for returning individual test results to study participants. This process resulted in a gene variant list that was stratified into four tiers, with the top two tiers containing the strongest candidates for inclusion.

### Step Six

The internal steering committee solicited peer reviews of the candidate gene variants from six leaders in the field of genetic epidemiology. Using the established marker selection criteria, the

peer reviewers were instructed to evaluate the weight of the evidence for the association of each gene variant on the list and submit their own rankings on a range from 'unacceptable' to 'strong.' Any gene variant that on average received an 'acceptable,' 'good,' or 'strong' ranking was kept on the list, while those receiving lower ranking on average were removed.

#### *Step Seven*

The recommendations of the independent peer reviewers were then used by the internal steering committee to develop a final list of gene variants meeting all selection criteria.

## **Results**

### *Identification of Genetic Variants*

To start the processes, an initial information-gathering step was conducted that examined the breadth of data available on genetic associations with disease. It was deliberately designed to cast a wide net that allowed the inclusion of health conditions and gene variants covering a range of public health significance. While the processes for identifying genetic variants was not intended to be exhaustive of all possible candidates, it did use a range of different types of informational sources aimed at exploring the many associations in the literature (see Methods). In total, 360 gene variants with potential for inclusion based on reported associations with increased risk for a health condition (figure 1B) were identified.

### *Health Condition Criteria*

Application of the final selection criteria for health conditions developed by the internal steering committee (step 5) reduced the pool of variants to those associated with the largest public health threats. Following the application of these selection criteria, 259 genetic variants associated with several health conditions (e.g., cardiovascular disease, obesity, type 2 diabetes, osteoporosis, and several cancers) remained under consideration. To illustrate the deliberative nature of this selection process, we present a series of examples where the criteria were used in assessing various health conditions (see below and table 1).

*Health Condition Criterion 1.* Health conditions were expected to have a substantial public health impact, as measured by prevalence, severity, and healthcare costs. For example, health conditions such as chronic beryllium disease may be addressed by genetic susceptibility testing for those who have an environmental exposure to beryllium [45]. However, chronic beryllium disease is uncommon, affecting ~1% of a distinct group, generally industrial metal workers exposed to beryllium dust [45]. Thus,

while genetic testing might be appropriate for this targeted group, chronic beryllium disease was excluded from consideration for a research genetic susceptibility test that is focused on the general population. By comparison, lung cancer is a relatively rare disease in the absence of smoking, but given the high prevalence of tobacco use, there is an approximately 7% lifetime risk of developing the disease in the U.S. population [46]. Additionally, the 5-year survival rate is only about 15%. Therefore, lung cancer was found to meet this criterion.

*Health Condition Criterion 2.* Requiring that the diseases be adult-onset resulted in the elimination of several health conditions. Asthma, although levying a major public health burden, was excluded because it generally presents in childhood [47]. In contrast, osteoporosis was included because it generally develops in people over the age of 50 [48]. Although it could be argued that preventive strategies for osteoporosis are most effective when initiated in childhood, almost all adult-onset health conditions would have been omitted if held strictly to this standard.

*Health Condition Criterion 3.* Availability of accepted clinical recommendations for prevention excluded gene variants associated with drug metabolism, often considered under the rubric of pharmacogenomics. Although the evidence base in this domain is perhaps the best-explored topic for genetic variation research, there are few well-developed drug dose recommendations based on genetic test results [49]. By comparison, genetic variants associated with type 2 diabetes were included as it is accepted that weight loss, exercise, and diet restrictions significantly reduce the risk of developing the disease [50].

*Health Condition Criterion 4.* Requiring the health conditions to be relevant to a broad range of the population (defined as everyone having a significant likelihood of developing a disease) excluded a number of diseases. For example, prostate and breast cancer were not included because they are gender-specific. However, gene variants associated with colorectal cancer, which has similar incidence rates between men and women, were included for consideration [46].

### *Genetic Variant Criteria*

The exercise of applying selection criteria for gene variants met several challenges. First and foremost was the need to evaluate a vast and diverse body of evidence in the scientific literature. Initial selection of genetic variants was carried out by the internal steering committee over a period of 6 months (step 5). The results of these ef-

forts were subsequently reviewed by the independent peer reviewers (step 6). The recommendations of this external review were then applied in the final selection (step 7) with the result that only 24 of the 259 gene variants considered met the selection criteria described in this report (for further information see supplementary table 1, [www.karger.com/doi/10.1159/000236061](http://www.karger.com/doi/10.1159/000236061)). To illustrate this process, examples of the deliberations over which genetic variants to include based upon the selection criteria are provided below.

**Genetic Variant Criterion 1.** Requiring that genetic associations should be replicated in most follow-up studies to indicate sufficiently stable evidence to justify the return of results excluded the *CASR* A986S polymorphism. Despite promising initial findings of an association of this polymorphism with bone density [51, 52], subsequent reports did not confirm this association [53–55]. In contrast, there is a highly consistent association with the RHC (red hair color) variants that disrupt the function of the *MC1R* gene and an increased risk of melanoma [56–58].

**Genetic Variant Criterion 2.** Requiring that the evidence to support associations be based on studies with at least 500 cases excluded the *CDKN1C* (*KIP2*) homozygous deletion genotype that has been associated with osteoporosis [59]. Although one study showed a significant association of this genotype with osteoporosis, the sample size was only 154 participants [59]. Without further published work to support this finding, *CDKN1C* did not meet our criterion for robust evidence and so was excluded from consideration. By comparison, the significant association of the *MTHFR* 677C>T polymorphism with increased risk for colorectal cancer has been examined in studies totaling over 8,000 cases and was included in the final list [60].

**Genetic Variant Criterion 3.** Requiring gene variants to be associated with at least a 10% increase or decrease in risk for the health condition eliminated the *NAT2* slow acetylation polymorphism from consideration as a risk marker for lung cancer. Although some studies have found an association of this polymorphism with lung cancer, the *NAT2* slow acetylation polymorphism does not appear to have a strong overall impact on disease risk, with an OR of 1.04 (0.96–1.14) [61]. However, an example of a robust association included in the final list is the *TCF7L2* rs12255372 variant which has a per allele OR of 1.48 (1.37–1.60) for type 2 diabetes [62].

**Genetic Variant Criterion 4.** Requiring that the genetic risk variants have a population prevalence of at least 5% eliminated the Z variant of alpha-1 antitrypsin gene (*AAT*). Although this variant is a well-established risk

factor for chronic obstructive pulmonary disease, the Z allele is found in only 2–4% of the U.S. population [63]. In contrast, the homozygous *GSTM1* null-null genotype, which is associated with lung cancer risk, has a prevalence of approximately 50% in the U.S. [64] and was included in the final list.

**Genetic Variant Criterion 5.** Requiring that the gene variant should not have pleiotropic associations with health conditions with no established prevention measures eliminated the *APOE* *e4* variant. *APOE* *e4* has been associated with increased risk of cardiovascular disease and with Alzheimer's disease. As there are no validated prevention strategies for Alzheimer's disease, *APOE* *e4* was excluded from consideration. In contrast, the cardiovascular disease risk variant, *CETP* *Taq1B*, has been studied in the context of several health conditions [65], but was included in the final list because it does not yet appear to have a sufficiently strong association with other non-preventable health condition to warrant exclusion.

An example of an optimal variant to be included in a prototype genetic susceptibility test would be *KCNJ11*. Research indicates that *KCNJ11* is associated with type 2 diabetes, a significant public health problem that is the 6th leading cause of mortality in the U.S. [66] and has a lifetime risk of approximately 35% [67]. The *KCNJ11* gene encodes a component of the ATP-sensitive K<sup>+</sup> channel, which is involved in glucose-induced insulin secretion [68]. The function of this channel has been shown to be disrupted by the E23K polymorphism, providing it with biological plausibility as a possible factor in disease development [69]. Case-control studies have broadly replicated the E23K polymorphisms association with type 2 diabetes, with more than 7,700 subjects examined in over 9 studies [68]. Additionally, the increase in risk is significant, with an OR of 1.12 and 1.44 for heterozygotes and homozygotes, respectively. This association with type 2 diabetes has recently been confirmed in several genome-wide association studies [70]. Given this evidence, *KCNJ11* is representative of a gene variant selected by our deliberative process that constitutes an ideal candidate for inclusion in a genetic susceptibility test where research subjects are to receive information about their personal genetic risks.

## Discussion

If the knowledge gained from the Human Genome Project is going to be used to improve public health, translational research exploring clinical applications will

be required. Unfortunately, in contrast to the rapid pace of discovery of gene-disease associations for common health conditions, research to understand the clinical potential of these findings has lagged. This gap in knowledge could slow appropriate uses of genetic susceptibility testing and fail to deter the premature application of tests that have little clinical utility.

The transdisciplinary and iterative process we used to arrive at a prototype genetic susceptibility test for translational research illustrates one approach for advancing a field of investigation. We do not suggest this approach as *the* definitive process for determining which gene variants are appropriate for conveying test results. Rather, this process has both strengths and limitations expected in an initial exploration of a complex research question. Among the strengths of this study is the fact that it used multiple information sources, including expert recommendations, the scientific literature, and other related research. Also, input on the criteria for the test was elicited from experts in a range of disciplines and institutions at multiple steps in the process. This approach was intended to increase the likelihood that considerations relevant to the project would be effectively addressed. Weaknesses include the fact that we used an evolving and exploratory approach to our investigation of the literature to account for new suggestions and input throughout the process, rather than a formal literature review. Additionally, we relied heavily on expert opinion and did not exclude meta-analysis with significant heterogeneity. Others considering similar efforts may also want to consider alternative approaches. These may range from the decision to select a single information source (e.g., scientific publications) or analysis group (e.g., an expert panel) to an expansive approach that attempts to integrate as much data and perspectives as possible. One could also choose between a more informal process and a comprehensive analysis combined with multiple rounds of review. Regardless of the approach chosen to meet the needs of a particular study, our experience provided us with a perspective and an operational framework that may be informative for future projects.

Our selection criteria have similarities to recommendations reported by others in that we engaged with a set of questions about appropriate genetic evidence and disease impact. The existing differences in perspective hinge primarily on the fact that other reports focused on genetic epidemiological studies (where returning individual genetic test results was a secondary concern), while we focused on developing a translational research test where the very purpose of the study was to provide study par-

ticipants with their individual genetic test results. In the context of clinical, social, and behavioral research objectives, different criteria were seen as important. For example, we were willing to consider returning individual test results for genetic variants that have a comparatively small impact on risk for a health condition (as opposed to criteria for genetic epidemiology studies where a previously suggested cutoff was an OR of 2.0 [38]). This decision recognizes that relative risks associated with genetic variants for common health conditions will remain low even as evidence continues to accrete and that translational research should reflect this reality [71]. Additionally, we added criteria eliminating health conditions without preventive measures, along with genetic variants that had pleiotropic risks for these types of health conditions. These criteria made sense for research studying the use of genetic risk factors in the prevention of common health conditions because there should be an appropriate behavior change recommendation.

The criteria for this study were selected with the goals of the Multiplex Initiative in mind and the understanding that each study may find it necessary to develop customized approaches. Under certain circumstances, it may make sense to disregard some of our criteria or to make them more stringent. For instance, if the target population had been men, it might have made sense to include more gender-specific markers, such as those that increase risk for prostate cancer, and exclude markers indicating osteoporosis risk. Alternatively, if the objective is to provide direct medical recommendations of treatments or interventions that are made on the basis of a specific genotype, then it may be necessary to require more stringent criteria for evidence that more closely resemble what would be expected from a clinical test. It also may be helpful to create other criteria, be they population-specific (e.g., requiring that a variant has been studied in groups with similar ancestry to the study participants), disease-specific (e.g., the variant must be involved in the metabolic syndrome), platform-specific (e.g., the variant can be tested using Illumina bead arrays), age-specific (e.g., the average age of disease onset should be between 20 and 40), culture-specific (e.g., the variants should not have implications that could influence the stigmatization of a group), or any of a range of other considerations relevant to a study. Furthermore, it may be appropriate to select multiple or single gene variants for one or several health conditions. For example, of the genetic variants identified in this paper, the genetic test used in the Multiplex Initiative contains 15 genetic variants for several overarching health conditions [41].

One of the major challenges of this project was to identify gene variants in an environment where new disease-gene associations are reported almost weekly. In fact, such reviews are likely to become more difficult as further gene-gene and gene-environment interactions are uncovered. As a consequence of these changes, lists of genetic variants appropriate for test inclusion may have a fairly short shelf life. For example, subsequent to our initial selection process there has been a torrent of published genome-wide association (GWA) studies [25]. As of early 2008, GWA studies found associations with 8 of the genes identified in our initial review that reached genome-wide significance [23, 70, 72–83]. Interpreting the implications for the other genetic variants examined that did not show an association is complicated by the fact that most GWA studies have a low power to detect genetic variants with a modest impact on disease risk [84]. It remains to be seen how many of the other genetic variants will be verified as future GWA studies examine more disease states and further replicate associations. In addition to these findings, many previously unknown genetic associations have been reported in GWA studies, such that a review similar to the one we performed would produce more genetic variants if conducted today (we estimate that our criteria would include another 30 genes if applied to GWA studies published through early 2008). While the pace of discovery using this method may slow once the most easily identified variants are found, we expect that the majority of common disease phenotypes will have genes associated with them in the near future. These rapid changes are notable for those planning research because as a prospective study is in process, new markers may need to be added or removed from the test and scientific updates communicated to study participants in the form of newsletters or other correspondence.

It will also be important to consider the implications of research that clarifies gene-gene interactions and results in combined genetic risk estimates for different diseases. For example, one study that looked at type 2 diabetes risk with three genetic markers found a gradient of risk that increased with the number of genetic risk variants carried [85]. This risk ranged up to a nearly 6-fold increase in those carrying 6 risk alleles, which is much larger than the 20–30% increases expected for most individual variants. Such research may increase the relevance of testing for genetic susceptibility variants in the context of public health, because it can identify those individuals with high combined genetic risks [14].

This study may have implications in a broader scientific and policy context. The process described here uses

selection criteria that were intended only for this limited exercise of developing a prototype genetic test to be used for translational research. The genetic variants selected should not be taken as appropriate for clinical testing. However, it is worth noting that many of the genetic markers on our list are already available through commercial genetic tests. In fact, of the 24 genetic markers identified in the initial review, more than half are now available for purchase by individual consumers. Given this context, research using these markers may have implications for the wider debate over the appropriateness of direct-to-consumer genetic testing. Furthermore, while a genetic susceptibility test derived from our set of genetic markers will not fully represent the characteristics of the tests that could eventually be used in a clinical context, it may be able to model the type of information that could arise from personal genome sequencing. Such research holds the potential to uncover the crucial factors that allow genetic susceptibility testing to be directed towards the greatest public health benefit.

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