

# Quantifying the health benefits of genetic tests: The importance of a population perspective

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The completion of the human genome project is expected to usher in a new era of personalized health care and prevention based on individual genetic susceptibility to disease.<sup>1,2</sup> While traditional genetic testing has been used for the diagnosis and management of individuals and families with single-gene disorders, we are seeing the emergence of a new type of genetic tests for ascertaining genetic susceptibility to developing disease in the future.<sup>3</sup> These tests examine the presence or absence of several genetic polymorphisms (or gene expressions or products) at one or more loci that are involved in the biologic pathways of disease or metabolism of certain drugs and chemicals (the so called “genomic profile” such as cardiogenomic and carcinogenomic profiles). This information is used to assess disease risks<sup>4</sup> or response to pharmacologic treatment of individuals with certain diseases.<sup>5</sup> Some tests are now marketed directly to the public in the US and Europe.<sup>6</sup>

In this paper, we highlight the importance of a population perspective on genetic tests and propose an analytic framework to quantify health benefits resulting from application of these types of tests, as compared to not applying them. We illustrate how population health benefits from gene-based intervention can be quantified in two ways: absolute and proportional risk reduction in the burden of a specific disease or adverse health outcome. In addition, we emphasize that in measuring health benefits of genetic tests, it is necessary to quantify the additional health benefit of a genetic test compared with the relevant baseline. The baseline may consist of doing nothing for pre-symptomatic individuals, in the case of an intervention that is only appropriate for individuals with known genotype or clinical disease (e.g., dietary treatment for phenylketonuria) or current practice in promoting a generic intervention that is recommended for all individuals in a population (e.g., smoking cessation).

None of the ideas presented here is new. However, we hope to focus this discussion on the importance of quantifying health benefits of genetic tests from a population perspective. Quantification of health benefits is a first step toward decision

analyses that involve balancing of benefits and harms as well as economic considerations.

## QUANTIFYING HEALTH BENEFITS: A POPULATION PERSPECTIVE

While general criteria for population screening with or without the use of genetic tests are well known,<sup>7-9</sup> there has been little discussion on how to quantify the health benefits from genetic testing for an emerging group of genetic tests that could be used for primary, secondary and tertiary prevention and delivery of health services (e.g., medications). Primary prevention may include the use of genomic profiles of risk to increase uptake of physical activity or smoking cessation. Secondary prevention will include using genetic tests for early diagnosis of various diseases such as colorectal cancer. Tertiary prevention is best illustrated by the use of pharmacogenomic tests to target drug treatments or adjust dosages in the treatment of various diseases. The change in health outcomes depends in part on what is assumed to be the baseline. Often, the baseline is defined as the “natural history” of the disorder, but this may be a misleading concept, since it is rare for there to be no treatment or prevention for a disorder. More realistically, there may be a range of curative services and preventive interventions that are available. The potential benefit of a genetic test depends on the relative probabilities of uptake and effectiveness of interventions based on knowledge of genotype. For example, periodic screening is effective in reducing mortality from colorectal cancer. The potential contribution of genetic testing depends on the probability of receiving screening with and without knowledge of genotype.

Our perspective here is to define the usefulness of a genetic test in terms of the opportunity to reduce the population burden of morbidity, disability, and mortality (i.e., public health utility<sup>10</sup>). Quantification of health benefits requires the specification of metrics of disease burden, including numbers of cases of specific diseases and types of disability, costs associated with caring for people with disease or disability, and numbers of lives or life-years lost. In order to compare the burden of different diseases, or to combine the impact of disease, disability, and deaths, it is necessary to use a summary measure of population health, one of the most commonly employed being the quality-adjusted life year (QALY).<sup>11</sup>

The population-level impact of an intervention depends not only on the preventable burden of disease but the level of resources consumed by the intervention. This is because of the opportunity cost of scarce resources that could otherwise be

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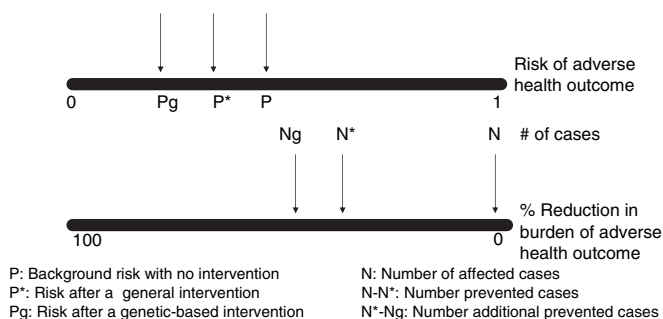
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used to fund effective interventions. If we compare two interventions that cost the same to implement, holding everything else constant, the one that yields more health benefits provides greater public health utility. On the other hand, a set of interventions that are targeted to narrow population subsets may in the aggregate provide greater population health impact than a single population-based intervention. For this reason, the Partnership for Prevention several years ago chose to rank preventive services on two indicators, preventable burden (measured in QALYs) and cost-effectiveness (measured in cost per QALY).<sup>11</sup>

Figure 1 lays out a simple framework for quantifying absolute and proportional population health benefits of a genetic test-based intervention. In the absence of an intervention, let us assume that  $P$  is the risk of disease or adverse health outcome (e.g., per 100 individuals over a specific period of time). In the presence of an intervention that does not take into account people's genotypes (e.g., physical activity, diet, smoking cessation), we assume the disease risk will decline to  $P^*$ , depending on the effectiveness and the compliance with the intervention. When the population is stratified by susceptibility genotype(s), we assume that a genotype-based intervention will be available for genotype-positive people and that the general intervention will still be available to everyone, leading to a decline in the risk of disease to  $P_g$ .  $P^*$  and  $P_g$  are functions of background disease risk, genotype prevalence, various risk ratios, and compliance uptakes of population and genotype-based interventions.

Although Figure 1 shows that  $P$  is larger than  $P^*$  which is larger than  $P_g$ , the actual relationships between  $P$ ,  $P^*$  and  $P_g$  can be more complicated and can only be derived from empirical data. Using the well-known epidemiologic formula of population attributable risk,<sup>12</sup> we can estimate the impact of the genetic intervention on risk as  $P - P_g$ , the impact of the general intervention as  $P - P^*$ , and the added benefit of the genetic based intervention compared to the general intervention as  $P^* - P_g$ . The frequency of cases of disease is not necessarily a useful measure of health benefit; what we ultimately care about is the impact in terms of prevented symptoms, disability, and premature death. For example, use of mammography leads to an increase in the number of diagnosed cases of breast cancer, because of earlier detection of sub-clinical tumors, but results in reduced mortality.



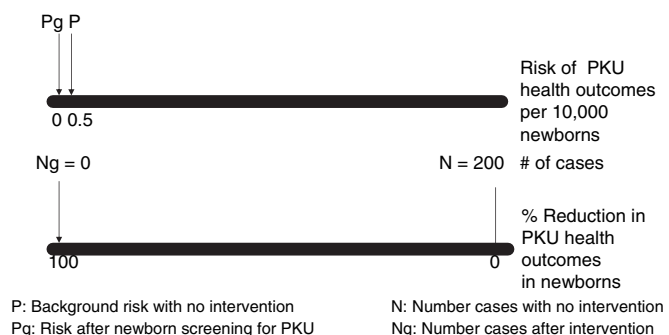
**Fig. 1.** Quantifying population health benefits of genetic-based intervention in terms of absolute and proportional risk reduction of an adverse health outcome.

In addition, we can calculate the reduction in numbers of cases or deaths for the population intervention ( $N - N^*$ ) and the genetic-based intervention ( $N - N_g$ ) and the added number of cases prevented from the genetic based intervention compared to the population intervention ( $N^* - N_g$ ).<sup>12</sup> As already noted, it is essential to translate numbers of cases into health outcomes that matter, such as premature deaths averted. The absolute numbers of health outcomes are important for comparing diseases of different incidences in the population, interventions in different subsets of the population, and when conducting economic analyses (e.g., cost per death or QALY prevented).

Moreover, we can derive the impact of general and genetic-based interventions on the proportional reduction in the burden of disease in the population, measured in terms of population attributable fraction (PAF), which is the proportion of cases prevented using an intervention in a well defined population.<sup>12</sup> The proportion of cases prevented by the general intervention is  $(P - P^*)/P$ , and that by the genetic-based intervention is  $(P - P_g)/P$ . To measure the additional health benefit of the genetic based intervention compared to the general intervention, the PAF is  $(P^* - P_g)/P$ . These measures could be also written in terms of number of cases, using  $N$ ,  $N^*$ , and  $N_g$ .

When we have interventions that apply to different subsets of the population (as shown in the example of familial hypercholesterolemia below), we can derive the impact on the PAF in the whole population by relating the numbers of cases after intervention not only to the number of cases in the population subset but to the number of cases in the total population. For example, if an intervention reduces the number of cases from 100 to 20 in a subset of the population, the PAF for this subset is 80%. If the number of cases in the whole population is 1,000, this intervention would have a PAF of  $1,000 - 920 / 1,000$ , or 8%, although this would not mean that the intervention would be less valuable or deserving of resources.

Wacholder<sup>12</sup> introduced the concept of attributable community risk (ACR), which is identical to population attributable risks shown in Figures 2–4. In this paper, we extend this concept of ACR by comparing the ACR for a population level intervention to one based on genetic testing followed by an intervention. The difference between these two parameters



**Fig. 2.** Quantifying population health benefits of genetic-based intervention in terms of absolute and proportional risk reduction of an adverse health outcome: Newborn screening for PKU.

the population health implications of genetic testing for these association is far from clear.

### NEWBORN SCREENING FOR PHENYLKETONURIA

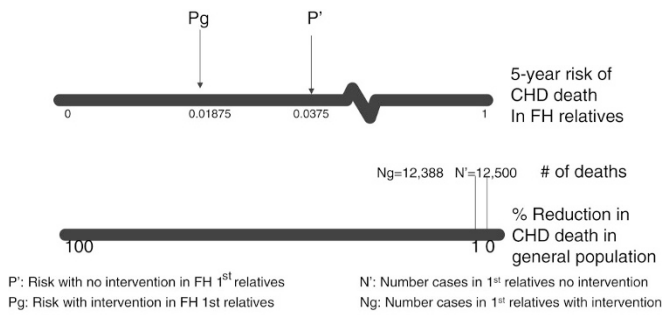
PKU illustrates the most simplistic example of a genotype-based intervention. (Fig. 2) In the United States, about 1 in 20,000 neonates have classic PKU, defined by clinical deficiency of phenylalanine hydroxylase, an enzyme that is crucial in the metabolism of phenylalanine in the diet.<sup>13</sup> PKU is an autosomal recessive disorder that occurs among individuals who carry two mutations at the *PAH* locus. In the absence of early detection and treatment, most individuals with classic PKU develop neurological impairment during the first year of life, resulting in severe intellectual disability (IQ < 50) and autistic symptoms.<sup>14</sup> The intervention is to identify infants soon after birth through laboratory testing of dried blood spot samples for hyperphenylalanemia (a phenotypic screening test) and put them on a low phenylalanine diet.

In this instance, there is no population-based intervention (low phenylalanine diet is harmful for persons without PKU). Newborn screening, if accompanied by strict adherence to the special diet, can reduce the risk of adverse health effects (notably mental retardation) associated with classic PKU from 1 per 20,000 to almost 0. This translates to 200 prevented cases in a cohort of 4 million births per year (Fig. 2). The population-attributable fraction for PKU-related adverse health effects is virtually 100%. It is noteworthy that if we define the disease or phenotype as isolated severe mental retardation, which has a risk of 1 per 1,000 births,<sup>15</sup> a much smaller fraction (~5%) of mental retardation cases are preventable by early detection and treatment of PKU.

### PREVENTION OF CORONARY HEART DISEASE IN FIRST-DEGREE RELATIVES OF PATIENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA COMPARED TO POPULATION WIDE CHOLESTEROL SCREENING.

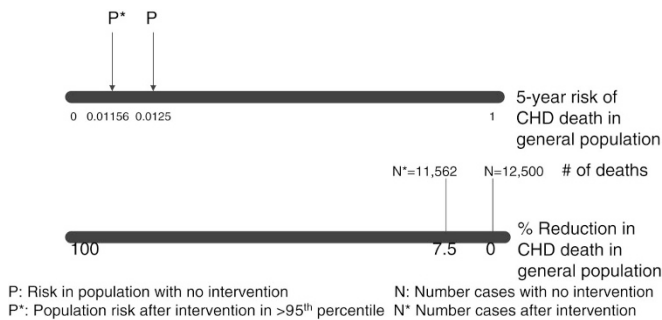
Familial hypercholesterolemia (FH) is an autosomal dominant disorder of cholesterol metabolism that affects about 1 in 500 individuals in the U.S. population and is associated with very high risk of premature heart disease. Austin et al.<sup>16</sup> conducted an analysis of coronary heart disease (CHD) mortality among first-degree relatives of patients with FH. They calculated that family-based testing of relatives of patients with FH, followed by effective lipid lowering drug treatment, could potentially prevent 44% and 57% of five-year CHD mortality among male and female first-degree FH relatives, respectively.

Cascade testing of FH first-degree relatives is one targeted strategy for the prevention of CHD that can be compared with another strategy targeting a high-risk subgroup of the population, people at the upper fifth percentile of cholesterol values. Austin et al.<sup>16</sup> calculated that only 5–10% of all fatal CHD cases in the general population could be prevented through population wide cholesterol screening with interventions to lower cholesterol levels for people at the upper fifth percentile of



#### Number of prevented coronary heart disease (CHD) deaths in 5 years per million US residents (N-Ng = 112)

**Fig. 3.** Quantifying population health benefits of genetic-based intervention in terms of absolute and proportional risk reduction of an adverse health outcome: Testing first-degree relatives in familial hypercholesterolemia.



#### Number of prevented coronary heart disease (CHD) deaths in 5 years per million US residents (N-N\* = 938)

**Fig. 4.** Quantifying population health benefits of genetic-based intervention in terms of absolute and proportional risk reduction of an adverse health outcome: Population screening for high serum cholesterol.

represents the value added of genetic testing in terms of health benefits to the population.

### ILLUSTRATIONS

We consider two relatively simple examples of the population health benefits of genetic-based interventions. These examples are not genetic tests per se, but use biochemical or phenotypic measurements for targeting interventions to subsets of the population with specific genetic disorders. Figure 2 summarizes analyses of population newborn screening and intervention for phenylketonuria (PKU). This strategy has a large population impact on the proportion of disease burden but not a large impact on absolute risks since the disease is rare to begin with. Figure 3 shows the example of cascade testing and intervention among first-degree relatives of patients with familial hypercholesterolemia (FH). This strategy leads to a large decline in disease risk for the population of relatives tested, but very little impact on the proportion of disease burden in the general population. For comparison, we show the impact of population screening for cholesterol levels and intervention at the upper fifth percentile (Fig. 4). It is to be noted that for the vast majority of reported gene-disease associations,

cholesterol values. On the other hand, the pool of relatives of FH patients is much smaller than the number of people with high cholesterol levels. Figure 3 shows the impact of the cascade intervention strategy (following up first degree relatives of persons with FH) and Figure 4 shows the impact of population cholesterol screening followed by intervention among persons in the upper fifth percentile. It should be noted that the numbers presented here are based on several simplifying assumptions, such as universal uptake of interventions and 100% effectiveness of interventions.

Let us suppose that the annual mortality rate from CHD is 2.5 per 1,000 for adults 40 years and older (data derived from the Physicians' Health Study).<sup>17–18</sup> This makes a cumulative CHD mortality of approximately 12.5 per 1,000 people over a five-year period. Second, from Austin's analysis, we assume 50% risk reduction (midpoint of 44%–57%) in first-degree relatives, and 7.5% risk reduction in the overall population (midpoint of 5–10%) when treating the top fifth percentile of cholesterol levels. The five-year CHD mortality risk ratio among first-degree relatives of FH patients is about 3 (2.6 in males and 3.7 in females) compared to the general population.<sup>16</sup> This translates to an expected total of 37.5 CHD deaths per 1,000 FH first-degree relatives over five years, or an excess of 25.0 deaths per 1,000 people in this subgroup. As shown in Figure 3, testing and intervention among relatives of FH patients will reduce the risk of CHD mortality among this subpopulation from 37.5 to 18.7 per 1,000 people in five years (representing a 75% reduction in the excess risk). Assuming an FH prevalence of 1 in 500, and 3 in 500 people are first-degree relatives of FH patients (three first-degree relatives per case), the overall reduction of CHD mortality in the population at large is 112 CHD deaths in five years in a cohort of 1 million adults over age 40. This is <1% of the total burden of CHD deaths. Similar to the PKU example, if we define the health outcome as death from premature heart attacks (say under age 50 years), the proportional contribution of FH will be larger.

Figure 4 shows the impact on mortality risks of population wide cholesterol screening. Using the strategy of targeted intervention among the upper fifth percentile, the CHD mortality reduction looks more modest from the perspective of tested populations (most CHD deaths occur among people with normal cholesterol). Nevertheless, this approach could reduce the burden of CHD mortality in the population by about 8%, leading to 938 prevented CHD deaths in a cohort of 1 million adults in five years. Some of the assumptions include universal screening uptake and post screening drug interventions as well as effective interventions both in the population and among relatives of FH patients. Complete analyses of health benefits must take into account many other factors, including uptake of screening and interventions as well as differential costs for testing families and populations.

## DISCUSSION

The two examples illustrate the quantification of population health benefits for the simplest models of genetic-based inter-

ventions. Our primary objective was not to give definitive pronouncements on the utility of specific testing scenarios but to show the importance of a population perspective in quantifying the health benefits of a genetic test-based intervention. These examples also illustrate the well-known “prevention paradox” discussed by Geoffrey Rose.<sup>19</sup> This paradox is that population-level interventions, which have the potential to achieve a large impact on population health, may provide little gain to most individuals, whereas individual-level therapies are more readily accepted: “a preventive measure which brings much benefit to the population offers little to each participating individual. This has been the history of public health—of immunization and the wearing of seat belts and now the attempt to change the various lifestyle characteristics.”

The example of cholesterol screening reflects only part of the story. We compared cascade cholesterol screening among first-degree relatives of FH patients with cholesterol screening for the whole population followed by drug interventions among persons in the top 5% of the cholesterol distribution. Screening for the top 5% of cholesterol values in the population could theoretically ascertain most if not all first-degree relatives of FH patients who have FH. Consequently, there may not be an added value for the family based intervention compared to the general intervention. Additionally, both approaches still represent a form of targeted intervention strategy (one targeted for 5% of the population and the other targeted to even a smaller subset of the population, at most 0.6%). Because the vast majority of CHD cases occur among individuals with “normal” cholesterol levels, population screening for cholesterol may not be a good overall screening test.<sup>20</sup> Small downward shifts of the total cholesterol distribution in the population through other measures (diet, physical activity) may even lead to higher reduction of CHD mortality in the whole population than either of these scenarios presented here.

What is the overall population health benefit of the emerging types of genetic tests such as the ones that are purported to measure a person's susceptibility to future CHD risks (cardiogenomic profile based on a combination of genetic polymorphisms at different loci that are risk factors for CHD) so that individualized intervention and prevention strategies can be implemented?<sup>2,21</sup> We have shown in a previous theoretical analysis that the combination of several genetic polymorphic risk factors even with modest genetic effects (say relative risks under 2) can lead to high individual positive predictive value for a disease but a reduced impact on the population attributable fraction if interventions are targeted to persons with the greatest number of susceptibility genetic variants.<sup>10</sup> Data on health benefits need to be accrued using observational studies and randomized clinical trials to assess real world effectiveness and uptake of interventions based on knowledge of genotype as compared to population-level health promotion of interventions not based on genetic information. Because most interventions are generic in nature (diet, physical activity, etc), it is not clear a priori what would be the additional health benefits to an individual or a population that can be conferred by knowledge of susceptibility genotypes.



Perhaps the greatest driver of population health benefits of a genetic test is the combination of a high a priori probability of disease and the availability of an acceptable and effective strategy to reduce that risk. This scenario plays itself out in diagnostic testing when people have signs and symptoms consistent with the presence of a certain disease and therefore have a high a priori risk of the disease. It is also illustrated by the example of FH relatives that have a high a priori probability of having the mutation and a high disease risk given the mutation. For most gene-disease associations, however, there is a lower a priori probability of disease, the available interventions may not reduce disease risks to null, and more importantly, these interventions may not be specific to persons with genetic susceptibility factors.

Population parameters of risk reduction can be used in cost-effectiveness analysis of genetic tests (such as pharmacogenomic applications<sup>22</sup>). The net beneficial result of any intervention in a population would weigh the number of prevented cases (as discussed above) against the costs of the intervention and harms from the intervention. This is illustrated in a cost-effectiveness analysis of pharmacogenetic testing in treating acute lymphoblastic leukemia in children.<sup>23</sup> Economic assessments may be sensitive to even subtle changes in epidemiologic parameters (e.g., changes in population prevalence of the susceptibility genotype as well as risk of drug complications attributable to the genotype).

Finally, the population framework for genetic-based intervention applies to other risk stratification methods, including family history of disease or the combination of family history with genetic or other tests (as illustrated in the FH example presented above). Because a family history of common diseases such as CHD, cancer and diabetes is common in the population,<sup>24</sup> family history stratification for a given disease could serve as a tool for combining population-based interventions with family-based interventions. This strategy would not only identify families with single gene disorders but also the much more prevalent families with one or more affected relatives that are at increased risk of disease. The presence of disease in these families does not conform to simple Mendelian inheritance but more likely is due to the combination of shared genetic and environmental factors.<sup>25</sup> Family history stratification has been the basis for the ongoing Surgeon General family history campaign<sup>26</sup> and the CDC family history public health initiative.<sup>27</sup>

We are currently working on theoretical and empirical analyses to assess the combination of parameters for measuring the population health benefits of genetic tests and how the complex interaction among these parameters and economic factors can influence decisions about use of genetic tests. Ultimately, quantifying population health benefits of a genetic susceptibility test for a common complex disorder will depend on acquiring observational epidemiologic and controlled clinical trial data along two lines: the risk reduction of the adverse health outcome based on the intervention, and the incremental ben-

efit in risk reduction of the genetic-based intervention compared to a general intervention.

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