

# Uncertainties in Genetic Testing for Chronic Disease

Sequencing an individual's DNA seems destined to become an increasingly prominent part of medical care. Once a genetic alteration has been identified and characterized by researchers, testing for it is relatively simple, requiring only white blood cells obtained via a routine blood draw. Because so many diseases are influenced by heredity, investigators are likely to identify numerous alterations associated with illness in the human genome. In the past, genetic testing concerned the next generation: decisions about whether to have a child (eg, Tay-Sachs disease, cystic fibrosis, and Down syndrome) and screening of newborns (eg, phenylketonuria and sickle cell anemia).

Increasingly, genetic testing now concerns the current generation: testing ourselves for susceptibility to chronic disease. This domain includes more common conditions (eg, heart disease, diabetes, and cancer) and a future has been promised in which medicine's emphasis will be shifted from treatment of the sick to prevention in those at risk.<sup>1</sup> But the immediate future is more likely to be characterized by confusion. The confusion created by false-positive and false-negative tests will be familiar to clinicians. A less familiar source of confusion will also be present: because the absence of a genetic risk factor will rarely (if ever) reduce risk much below average, those with truly negative test results must be reminded that they remain at risk.

However, the greatest challenge is what to tell those with truly positive test results. These persons may be best characterized as "pre-patients." In this article, we examine 4 uncertainties that clinicians will have to communicate to pre-patients: the nature of risk, the generalizability of risk estimates, the time at which risk information is useful, and the utility of intervention.

## Uncertainty About Who Will Develop Disease

*"You have a 75% risk of developing colon cancer."*

For most physicians, genetics training involved the concept of a simple, single gene model. The pattern of inheritance was Mendelian and was either autosomal recessive, autosomal dominant, or X-linked recessive. In each case, it was clear who would develop disease (homozygotes, heterozygotes, and males inheriting the disease-causing mutation). This model is useful in understanding a few conditions such as hemoglobinopathies, cystic fibrosis, and phenylketonuria.

But this simple model breaks down for most common diseases because a "positive" genetic test result does not precisely forecast the associated clinical condition. Geneticists describe this relationship as *incomplete penetrance* and emphasize that genotype does not necessarily predict phenotype. Since genetic alterations that uniformly predict significant disease (ie, complete penetrance) are so obvious, it is likely that most of those responsible for substantial disease burden have already been identified. Consequently, incomplete pen-

etrance is destined to be the norm for genes associated with common chronic diseases.

Uncertainty about who will develop disease is an inherent part of genetic testing. Although this uncertainty is part of any diagnostic effort intended to stratify risk (eg, cholesterol testing), it may be particularly important to communicate in this setting. Genetic information is laden with symbolic meaning<sup>2</sup> and extra attention may be required to avoid having persons equate a "defective gene" (or a "genetic mutation") with a death sentence for them and their family. Most mutations associated with common diseases do not warrant this interpretation. For example, the Factor V Leiden mutation should be considered a risk factor for thromboembolism vs a certain predictor of disease.<sup>3</sup> Better ways to help clinicians communicate probabilities to patients are needed.

## Uncertainty About How Much the Risk Has Been Overstated

*"You have at most a 75% risk of developing colon cancer."*

Quantifying the probability of developing disease is made more difficult by multiple genetic alterations and multiple modifiers. For example, at least 4 genes are associated with nonpolyposis colon cancer and 1 of the genes associated with breast cancer (*BRCA1*) has more than 500 mutations.<sup>4</sup> Different genes and different mutations add to the complexity of the testing process and test interpretation. Different mutations may have different levels of penetrance, which can be further modified by other genes or environmental factors, as shown by the finding that *APOE ε4* predicted Alzheimer disease in whites but not in blacks and Hispanics.<sup>5</sup> This complexity implies a range of risks for the clinical condition. But there are reasons to suspect that first-reported risk estimates are likely to be at the top of that range.

Early investigations tend to report on exceptionally high-risk individuals, a selection bias resulting in overestimates of both risk and consequences of disease. Mutations are first sought in families in which the target disease affects many members, has an early age of onset, and is severe (and, with cancer, often occurs at multiple sites). For example, the original study of breast cancer risk in women with a *BRCA1* mutation produced the oft-quoted cumulative risk of 87% by age 70 years.<sup>6</sup> For inclusion in the study, families had to have at least 4 members with any ovarian cancer or breast cancer diagnosed before age 60 years. Also, the risk was calculated by measuring incidence of contralateral breast cancer in those women who had already had breast cancer, suggesting 2 sources of excess risk, selection of families with dramatic profiles of early cancer (possibly reflecting genetic and nongenetic factors) and selection of women in whom gene penetrance is complete. Thus, the reported risk estimates did not reflect simply a *BRCA1* effect, but also other factors that influence breast cancer risk.<sup>7-9</sup>

Another more subtle problem may bias risk estimates upward in the future. Persons in whom risk is identified are likely to be counseled to receive additional surveillance to detect the phenotypic changes (eg, the disease) early. Subtle anatomic

From the Department of Veterans Affairs Medical Center, White River Junction, VT (Dr Welch), and the University of Washington, Seattle (Dr Burke).

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Reprints: H. Gilbert Welch, MD, MPH, VA Outcomes Group IIIB, White River Junction, VT 05009 (e-mail: gilbert.welch@dartmouth.edu).

changes will be sought using advanced imaging and faint biochemical abnormalities will be pursued in the clinical laboratory. As with population-based screening in general,<sup>10,11</sup> surveillance is likely to identify cases not found in its absence. Surveillance will certainly identify cases earlier in their course. Finding more cases at an earlier age among those with the genotype will tend to magnify the apparent risk of disease (or reinforce an overestimate).

### Uncertainty Regarding the Right Time to Learn the Information

*"You have at most a 75% risk of developing colon cancer if you live to age 65."*

A unique aspect of genetic testing for chronic disease is that the genetic abnormalities can be detected long before being expressed as phenotypic abnormalities. For example, newborns could be tested for gene mutations associated with hemochromatosis, even though the average age for developing disease symptoms is in the fifth decade.<sup>12</sup> Thus, the lead time of diagnosis can be extraordinarily long.

The longer the lead time, the greater the opportunity for early intervention. But long lead time also means that possible beneficial intervention effects occur in the distant future. Untoward effects, on the other hand, may be immediate and, consequently, increase in importance. Either the diagnosis itself or interventions that result from it may cause harm. The diagnosis may label persons unnecessarily early in life and cause them to experience anxiety for an extended time. It may also lead to personal financial problems, particularly in regard to obtaining and maintaining insurance.<sup>13</sup> Interventions contemplated for the genetic diagnosis, including surveillance, carry their own risks. Also, because lead times can be so long, some persons will die of other causes before disease develops, making all such interventions for naught.

The potential for lead times measured in decades raises the issue of test timing. What is the right time (or right age) to test? It doesn't make sense to test newborns for genetic mutations associated with diseases not manifested until 50 years later, but it does not make sense to wait until age 50 years, either. Determining the optimal time to test (to maximize presumptive long-term benefits yet minimize near-term anxiety and unnecessary treatment) will require careful investigation. In the meantime, clinicians need to communicate the nature of the gamble (that information from the test may or may not prove relevant to the individual) and the role of competing risks.<sup>14</sup>

### Uncertainty About the Benefits of Early Intervention

*"You have at most a 75% risk of developing colon cancer if you live to age 65 and we are not sure that actions based on this information will improve your life."*

Long lead times create a more troubling problem by providing confusing signals. Consider testing 30-year-olds for genetic mutations associated with breast, thyroid, prostate, and colon cancers. Those with mutations are invited to undergo regular surveillance (eg, intensive screening to identify phenotypic expression), which leads to more detected neoplasia,<sup>15,16</sup> which, in turn, provides further impetus for the strategy. Because these cases are detected at an early stage and include more slowly progressive forms, case-based outcome measures (stage at diagnosis, 5-year survival) are favorable. The positive feedback about outcome encourages widespread population-based genetic

screening. But because of lead time and length biases there is no certainty that these patients have been helped. Even without early therapy, these measures would be expected to improve simply as a result of testing and surveillance.

Long lead times make assessing the value of early intervention difficult. Although cursory evaluations of the efficacy of interventions following genetic testing will be subject to powerful biases, unbiased experiments could consume entire careers. The "gold-standard" approach for evaluating genetic testing would be a randomized trial involving testing, surveillance, and treatment that would require many years to carry out, be expensive, and likely have many subjects lost to follow-up. Even if these randomized trials could be done easily, they would still be limited to the evaluation of a small number of alternative strategies (generally 2, at most 6).

Multiple alternative strategies for genetic testing are likely to emerge. There are many answers to apparently simple questions: Who should be tested? At what age? What constitutes a positive result (which mutation)? Which test will be used for surveillance and how frequently? Because of the expense of randomized trials and the need to assess multiple strategies, it is likely that quantitative decision analysis will play a major role in assessing the benefit of genetic testing. Because of the powerful effect of modeling design and assumptions on their results, however, such analyses should be supported by sources and performed by researchers independent of industry. Such efforts should be viewed as a public good and should garnish public resources.

### Conclusion

As genetic tests become increasingly accessible, clinicians must be careful not to be inappropriately swayed by their eagerness to help high-risk persons. The messages about presumptive benefit of testing may be compelling. An insidious cycle may develop, beginning with an overestimation of disease risk associated with the mutation, followed by perception of elevated risks, which in turn prompts unproven surveillance strategies, which are then reinforced by the positive feedback of apparent benefit. Three caveats may help guard against such misplaced enthusiasm.

**Population-Based Risk Estimates Should Be Obtained Before Acting on Genetic Data.**—The previously described biases demand that a major effort be undertaken to determine the true risks associated with various mutations. This requires population-based data that can address 2 questions: How common is the mutation and how often does it result in serious disease? The most pragmatic study design would be case-control: cases, those who die of the target disease; controls, an age- and sex-matched sample of those alive; and exposure, the mutation. A single national effort could provide the data resources for investigation of genetic mutations in general. Genetic necropsy data might most naturally come from the Surveillance, Epidemiology, and End Results areas, while a genetic registry on those alive could come from the National Center for Health Statistics (which has already collected but not analyzed some 10 000 DNA samples as part of the Health and Nutrition Examination Survey).<sup>17</sup> Although such an effort will require resolution of difficult ethical questions<sup>17-20</sup> (eg, what constitutes informed consent for obtaining DNA? Can previously collected blood samples be used to address new genetic questions? Should subjects expect notification when mutations are identified? How many associated

variables can be retained and it still be legitimately argued that the DNA data remain anonymous?), they are relatively small compared with ethical questions raised by acting on genetic data without accurate risk estimates.

**Knowledge About Surveillance (and Treatment) Strategies Must Be Rigorously Defined.**—An expectation that all genetic testing strategies be subjected to randomized trials is unrealistic. It is more realistic to expect rigorous evaluation of surveillance strategies recommended for high-risk persons. Thus, while we may never see a randomized trial of testing for mutations associated with colon cancer, it is reasonable to expect a rigorous evaluation of colonoscopy. This is also a plea for more forthrightness about quality and generalizability of existent knowledge. In particular, clinicians must take care to avoid extrapolating results from higher- to lower-risk populations (eg, annual colonoscopy may benefit those with a 70% lifetime risk of colon cancer, with no benefit for those with a 10% risk). Ignoring the relevance of baseline risk size can lead to harm.<sup>21</sup> Efforts to rigorously evaluate evidence quality and applicability regarding follow-up have already begun for those with selected mutations.<sup>22,23</sup> This process will need to be continued and broadened and the results communicated to patients.<sup>24</sup>

**Untoward Effects Must Be Considered, Even Though They Are Difficult to Measure.**—For decades, genetics has largely been the province of select pediatricians and obstetricians. Recently, however, a sea change has become evident. In the future, genetic information could become the predominate model clinicians use to explain ill health to patients. It will be difficult to document whether this new model causes real psychological harm, fosters discrimination, or inflames ethnic prejudice.<sup>25,26</sup> But it is easy to see that shifting emphasis from the role of nurture to the role of nature will likely produce untoward effects. If ill health is seen as being preprogrammed, patients may no longer view health care as a process in which they can participate (by modifying lifestyle or environment). If genetics becomes the way clinicians explain illness, it may also become the way they define illness. And because all of us are bound to harbor some mutation, this new model could make all of us “sick.”<sup>27</sup>

H. Gilbert Welch, MD, MPH  
Wylie Burke, MD, PhD

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## Editorials

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# Treatment of a Single Brain Metastasis

## The Role of Radiation Following Surgical Resection

Metastatic brain tumors are the most common intracranial neoplasms.<sup>1</sup> Fifteen percent to 30% of patients with cancer develop cerebral metastases during the course of their illness.<sup>2,3</sup> Carcinomas of the lung, breast, colon, and kidney and malignant

melanoma are the common primary sources. At the time of neurologic diagnosis, 50% of patients will have a single brain metastasis shown on computed tomographic scan,<sup>4,5</sup> whereas fewer than 30% will have only 1 lesion shown on magnetic resonance imaging, a more sensitive imaging method.<sup>6</sup> The median survival of untreated patients with brain metastases is approximately 1 month,<sup>7</sup> although survival time can be doubled by the use of corticosteroids.<sup>8</sup> When added to corticosteroid treatment, whole-brain radiation therapy may further improve

From the Department of Surgery, Division of Neurosurgery, Faculty of Health Sciences, McMaster University, Hamilton, Ontario (Dr Mintz), and the Departments of Clinical Neurological Sciences and Oncology, University of Western Ontario, London, Ontario (Dr Cairncross).

Reprints: J. Gregory Cairncross, MD, London Regional Cancer Center, 790 Commissioners Rd E, London, Ontario, Canada N6A 4L6.