Medical and Ethical Issues in Genetic Screening—An Academic View

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This article is intended to acquaint those whose principal concerns are the health and safety of workers with genetic screening and some of the medical and ethical issues it raises. Population-based genetic screening increasingly is being considered for predicting future disease in the person being screened. A major problem in screening for alleles that contribute to the development of common, multifactorial disorders is low sensitivity and positive predictive value. In many instances, no demonstrably effective prophylaxis or treatment is available to help those with positive test results. This creates ethical problems of assuring that testing is in the person's best interest and raises in turn issues of autonomy, discrimination, and privacy. Instead of screening for genetic predispositions to harm from workplace exposures, other means of improving the health of workers may bring greater benefits to a higher proportion of workers. The current state of genetic tests for chronic beryllium disease are considered. None are suitable for screening. — Environ Health Perspect 104(Suppl 5):987–990 (1996)

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Introduction

The appendage, "An Academic View," to the title of this article is not my creation. Perhaps the meeting organizers thought that the incorporation of genetic screening into health care, including occupational health, would occur faster than was warranted by the concerns I raised, hence making them "academic." Alternatively, the appurtenance might have been intended to distinguish my views from either a labor or a management position. Or, it could be the organizers' recognition that I have had little direct experience in occupational health. This, I must confess, is the case (the closest being a course I took on occupational epidemiology and service on an Office of Technology Assessment (OTA) Advisory Council on Genetic Testing and Occupational Disease (1)). In view of this shortcoming, the papers and discussion in the symposium have greatly enlightened me. If anything, I am more cautious than before, as I will explain, first by defining genetic testing and considering both medical and ethical aspects, and second by examining genetic screening for predispositions to chronic beryllium disease.

Medical Issues in Genetic Screening

Genetic screening is population-based testing for the presence of inherited disease-causing or susceptibility-conferring alleles to predict the risk of future disease in the person being tested or in his or her future children. (A positive result might also provide information about genetic risks of already-born children, siblings, cousins, and other relatives.) The disease can be single gene (Mendelian) in origin, or complex, involving more than one gene or a combination of genetic and environmental factors. Genetic screening does not include testing for the presence of acquired mutations or chromosomal aberrations that might result from occupational exposures. Such testing is referred to as "monitoring" (1). It provides a sensitive indicator of potentially toxic exposure levels but not of inherited genetic susceptibilities.

Before beginning routine genetic screening, a pilot phase is often needed to validate the test. People with positive test results, and a sample of those with negative results, are systematically followed to determine the sensitivity, specificity, and positive predictive value (PPV) of the test. The benefits and risks of follow-up interventions also need to be established in those with positive test results. If—and only if—screening improves the outcome in ways that would not be possible by waiting for the disease to appear, is there value in it (2). PPV—the chance that a person with a positive result will get the disease—depends on the prevalence of the disease in the population being tested; for a test of certain specificity and sensitivity, the greater the prevalence, the greater the PPV. When the cutpoint for distinguishing positive from negative results can be varied (e.g., as in measuring enzyme activity or metabolite concentration), a cutpoint that gives the best ratio of false negatives to false positives can be chosen. Selecting this cutpoint will depend on the relative costs, in both economic and medical terms, of false negatives and false positives. When a definitive treatment that greatly improves outcome is available and is effective only as a consequence of presymptomatic detection, and when an independent, simple, inexpensive method is available to determine whether a result is a true or false positive, the cutpoint can be set to maximize sensitivity. Screening of newborn infants for phenylketonuria is an example. Unfortunately, particularly in genetic testing, independent, confirmatory tests are not often available. Then, a false positive could be much more costly, subjecting people to unnecessary treatment that might last a lifetime. A false positive in prenatal diagnosis could result in the abortion of an unaffected fetus.

For direct DNA tests, including tests for histocompatibility alleles, as well as tests for HLA antigens, the cutpoint, in the traditional sense, cannot be varied. These are qualitative, binary tests that look for the presence or absence of specific mutations or their consequences on protein structure. For many genetic diseases, hundreds of mutations can each interfere with the function of a single gene; with current technology, it is not possible to detect all of them or their functional consequences. Consequently, false negatives are inevitable. Thus if the adult population were to be
offered screening for genetic susceptibilities to breast or colon cancer, not all people possessing inherited susceptibility mutations (ISMs) would be detected. Nor would those without ISMs who will still get the cancer. Yet they comprise the vast majority of those who will develop the malignancy.

Genetic screening could be justified from a medical (but not necessarily an economic) perspective if the people detected would derive benefit, if offered those or harm they means would make little sense in the mistaken belief that they are not at risk. They could disregard means of detecting the disease early (e.g., mammography or colonoscopy) or of reducing the chance of its occurrence (e.g., diet modification). For complex diseases, such as cancer, it is also possible that a person found to have an ISM will never develop the disease; other genetic and environmental factors, usually not elucidated, will be needed. Thus, despite the elegance of this new technology we have problems of false positives as well as false negatives. From an economic perspective, screening would make little sense when the cost of screening is high in relation to the averted costs. These will be low if only a small proportion of those at risk for the disease either opt for screening or have a disease detected. The averted costs are more likely to be low (if we exclude years of life lost from the analysis) if the disease is rapidly fatal rather than chronic.

When we consider screening for genetic predispositions to disease from occupational exposures, we also have to consider additional problems. First, the exposure may have more than one harmful effect, e.g., cancer as well as chronic lung disease. A person who has a negative test result for a predisposition to one harmful effect might still be vulnerable to another. Second, false positive results could result in unnecessary loss of livelihood and health benefits if the employees are fired, or quit voluntarily in the mistaken belief that the exposure will harm them. They could also be transferred to less rewarding jobs.

**Ethical Issues in Genetic Screening**

With genetic tests increasingly used to predict disease in apparently healthy people, but with inherent uncertainty about safety and effectiveness, ethical concerns arise more often than with most other tests usually used in people with overt disease. I will deal with four: autonomy, discrimination, privacy, and justice.

**Autonomy**

Unaware that they may be at increased risk of future disease, or of the ability of genetic tests to predict risks, people may not initiate requests to be tested. Healthcare providers could obtain specimens without even asking permission. For DNA tests, obtaining the specimen is often less risky than drawing blood; plucking a few hairs or swabbing the buccal mucosa usually suffices. So with minimal risks of testing per se and the recognition that most people will have negative results, why bother informing them beforehand? The answer lies in the implications of the test as well as the uncertainties attached to both positive and negative results. In the case of carrier and prenatal genetic testing, a positive test result raises reproductive options, including abortion, that are so abhorrent to some people that they would prefer to remain ignorant of the risks. Similarly, the uncertainty of results could make some people so uncomfortable that they would rather forego knowledge of their risk. For instance, as long as there was even a small amount of uncertainty involved in testing for Huntington disease, some people who knew they were at risk preferred not to be tested (3). In addition, health or life insurance companies could require results of genetic tests performed by the patient's own physician and use them to deny or limit coverage or to charge higher premiums. So, here too, some people might decide they would be better off not knowing their risks. To make such a decision, people have to be informed about testing, and its implications and uncertainties, and given the opportunity to decide whether or not they want the test. Only then is autonomy respected.

Personal autonomy can be curtailed in testing by employers. Although employers can no longer test at will under the Americans with Disabilities Act (ADA), they can require tests after a conditional offer of employment has been made. If a test result indicates a reasonable probability of imminent threat to the worker or to others in the performance of a specific job, the conditional offer can be withdrawn (4). Genetic tests could reveal susceptibility to harm from a workplace exposure, or a condition that could harm the worker or others regardless of exposure. (In Marfan disease, for instance, rupture of an aortic aneurism on the job could acutely incapacitate the worker and thereby hurt also others on the job.) Under the ADA, workers with positive test results who can perform the essential functions of the job without threat to themselves or others decide whether to accept a job that may adversely affect their health (5).

Until recently, the Equal Employment Opportunities Commission (EEOC), the agency that enforces the ADA, maintained that an individual is not covered under the law until he or she is symptomatic (6). Recently, however, the EEOC reversed itself and ruled that a healthy individual with a genetic trait that increased the risk of future illness was protected (7). Consequently, genetic testing cannot be used before a conditional offer of employment is made.

**Discrimination**

Denying employment to asymptomatic job applicants with positive genetic test results constitutes discrimination. Society might view it as “fair” discrimination when, as discussed above, hiring a worker with a genetic susceptibility to a particular disease poses an imminent threat to the worker or others in the performance of the job and the employer cannot make a reasonable accommodation to protect the worker. Instead of refusing to hire, the employer could place the worker in a job in which he or she would not be at risk. If this job had comparable worth, this would not be unfair discrimination. If no such job is available, and the threat is exclusively to the predisposed worker, the courts have ruled that workers have the right to decide whether to take the risky job (8).

To individuals with genetic susceptibilities, and to the society that ultimately foots the bill, denying health insurance to people with positive genetic test results (or excluding from coverage the condition to which tests predict they are predisposed) is unfair discrimination (9). Insurance companies who pay health benefits maintain, on the other hand, that such discrimination is fair; people with higher risks should pay more (10). If they did not and were granted insurance at the standard premium, the costs incurred as they became ill (or, in the case of life insurance, as they purchased more in anticipation of dying early) would increase the company's costs, which are passed on to those without the predisposition in the form of higher premiums. The standard premium takes into consideration the prevalence of diseases that cannot be predicted. The development
of predictive tests allows insurance companies to exclude people with predispositions and lower the premium for others, thereby compensating for the exclusion by increasing demand for its product. Employers could exclude the conditions to which testing reveals some workers to be predisposed from their health benefits if there were an actuarial basis for doing so. Some states have prohibited genetic testing by employers if the test is not job related (11,12). State laws do not cover employers who insure themselves. The federal law that covers them (Employee Retirement Income Security Act [ERISA]) does not prohibit such discrimination.

Privacy
The list of parties interested in the results of genetic tests does not stop with insurers and employers. Adoption agencies, schools, banks, mortgage companies, and family members might all claim an interest in the test result. Access to the results by all of these groups, except possibly family members, might lead to action detrimental to persons being tested or to their offspring. In view of the limitations of genetic tests, which might not be appreciated by all those seeking access, the actions might be groundless. Fear that third parties will have access to results could well deter people from being tested even though they believe that they would benefit. Similarly, were health care providers to reveal people’s genetic status to family members from whom the people feared retribution, confidence in the provider could be undermined. In a recent study of cystic fibrosis carrier screening, we found that fear of being stigmatized was one of the few variables that predicted which people would agree to be tested (13).

In certain circumstances (previous section) employers have legitimate interests in the implications of genetic test results for workers’ abilities to perform jobs safely and effectively. Regardless of whether tests are performed by, or reported to, employers’ agents (as is likely when the test is for predisposition to conditions for which workplace exposures might cause harm) or performed outside the workplace by workers’ private physicians, employers do not need to know the result of any specific test but only whether work restrictions or accommodations are needed (14). Even then, as Sheldon Samuels points out (personal communication), if a new genetic screening program in the workplace is followed by the simultaneous transfer of 30% of workers, it is obvious who is predisposed.

Workers have the right to consent to who should receive test results. They also have the right to know their own test results. Moreover, in testing for susceptibilities to harm from workplace exposures or for predisposition to future serious disease, they should be apprised of the risks and what could be done to lower them.

Justice
In many instances, genetic testing will reveal only a small proportion of people at risk of developing disease. The population from which these people are drawn may have many more prevalent health problems or problems that are more amenable to prevention or cure than is the case for genetic predispositions. This raises the problem of allocation of scarce resources. Some people will be harmed if one action is taken, whereas others will be harmed if another course is chosen. When screening cannot be economically justified, investment should be placed elsewhere or other means of preventing the particular disease or reducing its burden sought.

Genetic Screening for Susceptibility to Harm from Beryllium
Saltini’s work makes it clear that we do not yet have a test that meets the criteria for genetic screening. Testing for HLA-DPB1 Glu69 has a sensitivity for predicting chronic beryllium disease (CBD) of 80% and a specificity of 69.7%. With a prevalence of CBD of 3.9%, the test for Glu69 has a PPV of only 9.8% (C Saltini, unpublished data).

It is likely that HLA-DPB1 Glu69 is not the only risk factor for CBD in exposed workers. Both Saltini and Kreiss (K Kreiss, unpublished data) reported that the odds that machinists would get CBD are considerably higher than for other exposed workers. Machinists apparently have the highest exposure to beryllium and, in one ceramics plant, their exposure exceeded the permissible limit (M Mroz, unpublished data). According to Saltini’s data, being a machinist and having HLA-DPB1 Glu69 are independent risk factors for CBD. Rossman’s work (15) suggests that HLA-DR might also play a role in CBD. Kreiss (K Kreiss, unpublished data) suggests that smokers may have delayed onset of CBD, perhaps because smoking inhibits the immune response even when DPB1 Glu69 is present. It is possible that testing for the simultaneous presence of the susceptibility-conferring HLA-DR and DP alleles might improve both sensitivity and specificity, leading to greater predictive value.

Even if the DPB1 Glu69 test accurately predicted those who will get CBD, there may be other consequences of beryllium exposure that the test fails to detect. At very high doses, beryllium might be sensitizing regardless of the immunoreceptors present; at such doses it apparently leads to an acute disease and may also be carcinogenic (16). Cancer might also be more likely to occur in those with CBD; the data are not good enough to allow us to confirm that.

We should note, too, that the beryllium-specific lymphocyte proliferation test (BelPPT) is not perfectly sensitive (17,18). Thus workers with negative test results might not be protected from harm from beryllium exposure. Finally, if either the BeLPT or DPB1 Glu69 test were to be used routinely, more laboratories would get into the act and laboratory error, which has been demonstrated for both tests, could become a significant problem [(15); T Markham, unpublished data].

I doubt that even tests for all known genetic susceptibilities to CBD will have high enough sensitivities or PPVs to warrant screening. Moreover, with almost one-third of the labor force having one genetic risk factor (HLA-DPB1 Glu69), a large number of workers who would never get CBD could be denied jobs (although the EEOC ruling that the ADA covered genetic screening for susceptibility might prevent that). Employers might tolerate this high exclusion rate if the supply of qualified labor is plentiful. But if that is the case, it means other jobs are not available and the spin of the genetic roulette wheel will determine who will remain unemployed. Some people looking for jobs would, out of desperation, take their chances on getting a disease in the future in return for feeding their families in the present.

Genetic studies will often prove more important for research into mechanisms than for routine testing. In conducting research, the worker has the right to know what hypotheses are being tested. If the purpose of the research is to determine the frequency of an allele known to predispose a worker to harm from workplace exposure, the worker has a right to know the results as well, even if no action is planned when those with genetic predispositions are found. Until genetic screening can be shown to have high sensitivity and PPV, justice would dictate that other means be sought for reducing the occurrence of CBD. One means of doing so, particularly
important in light of the reports showing that workers (machinists) with higher exposure are more likely to get CBD, is to lower ambient levels of beryllium. The failure to do so brings me to my second concern: whether most of the research on CBD is really intended to benefit workers. If it were, this symposium might have included more talks about interventions in workers sensitized to beryllium. In this entire conference there was not one presentation on the effectiveness of treatment. Rossman indicated that there "have been no controlled studies to determine the optimal treatment" for CBD (16). At the very least, this gives the appearance that concern for the welfare of the worker is not really uppermost. The rejoinder, of course, is that by identifying predisposed workers or sensitized workers they can be removed from exposure. This serves the employer at least as well as it serves the worker, first, by reducing worker's compensation payments and second, by obviating the need to reduce workplace exposures, or even more drastically, finding less toxic substitutes for beryllium. With almost 1 in 25 workers getting CBD (C Saltini, unpublished data), one cannot consider CBD a trivial problem.

Conclusions

1. Genetic screening poses issues that do not arise for many other medical tests.
2. Few genetic tests have sufficient sensitivity and PPV to be used in the workplace. The U.S. Congress Office of Technology Assessment reached this conclusion in two separate studies (1,19).
3. In the workplace and elsewhere, looking for genetic determinants of disease becomes a form of victim blaming and excuses industry from its responsibility in the prevention and treatment of disease.

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