

### ***4.1.1 Genetic Testing & Counseling***

Genetic testing can provide valuable information to support informed decision making about personal health risks and care options as well as reproductive choices. The fact that genetic information carries implications for others to whom the individual is biologically related raises ethical challenges of balancing confidentiality against the well-being of others.

Because genetic contribution to disease can be complex and highly variable, interpreting findings and helping patients understand the implications for their health and health care requires special skill and attention.

Genetic testing is most appropriate when the results of testing will have meaningful impact on the patient's care. Physicians should not encourage testing unless there is effective therapy available to prevent or ameliorate the condition tested for. Whether a genetic test is performed to help diagnose an existing health condition, or to predict future health risks, or to provide information for managing a disease, it is important that the patient receives appropriate counseling.

Physicians who order genetic tests (individually or as part of a multi-test panel or large-scale sequencing) or who offer clinical genetic services should:

- (a) Have appropriate knowledge and expertise to counsel patients about heritable conditions, risks for disease, and implications for health management, and to interpret findings of individual genetic tests or collaborate with other health care professionals who can provide these services, such as licensed genetic counselors.
- (b) Adhere to standards of nondirective counseling and avoid imposing their personal moral values or judgment on the patient.
- (c) Discuss with the patient:
  - (i) what can and cannot be learned from the proposed genetic test(s) and reasons for and against testing, including the possibility of incidental findings. Physicians should ascertain whether the patient wishes to be informed about findings unrelated to the goal of testing;
  - (ii) medical and psychological implications for the individual's biological relatives;
  - (iii) circumstances under which the physician will expect the patient to notify biological relatives of test findings; and
  - (iv) that the physician will be available to assist in communicating with relatives.

- (d) Obtain the individual's informed consent for the specific test or tests to be performed.
- (e) Ensure that appropriate measures are taken to protect the confidentiality of the patient's and their biological relatives' genetic information.

***AMA Principles of Medical Ethics: II,IV,V,VI***

*Background report(s):*

CEJA Report 3-A-16 Modernized *Code of Medical Ethics*

CEJA Report 1-I-96 Multiplex genetic testing

Report of the Judicial Council A-A-83 Genetic counseling

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## CEJA Report 1 – I-96 Multiplex Genetic Testing

### INTRODUCTION

Among the most significant advances in the development of genetic medicine is the ability to test for genetic origins of specific conditions. In previous reports, has addressed many ethical issues associated with the application of the growing body of genetic information and accompanying technologies.<sup>1-5</sup> Here, analysis is offered regarding testing for multiple genetic conditions simultaneously, “multiplex genetic testing.”<sup>6</sup>

The term “multiplex genetic testing” can mean different things. It commonly refers to testing for multiple mutations that give rise to a single disorder, such as cystic fibrosis or phenylketonuria. This report deals instead with multiplex genetic testing where tests for completely different conditions are offered in a single session. As the mapping of the human genome progresses and tests for newly-discovered genes are developed, the possibility has arisen that many different testing “packages” could be administered simultaneously. This latter kind of multiplex testing creates a new level of complexity because the modes of heredity, social implications, and availability of treatment can differ greatly among the conditions tested.

There are three broad categories into which existing tests can be divided. First, tests can be performed to find genetic conditions that will lead to future inevitable disease onset as in the case of Huntington’s disease. Second, tests can be designed to find specific genetic information that indicates a heightened risk to possible disease onset. Often referred to as “susceptibility testing,” this type of test can be used to provide information about the possibility of contracting specific cancers, such as colon or breast cancer. Finally, genetic tests can be used to determine a patient's carrier status, providing information about the existence of a gene or gene mutation that is not necessarily manifested in an individual's phenotype, but which may be passed to children. The implications of information conveyed by each test are different, and are best addressed in separate ethical analyses.

The implications of genetic tests also differ depending on the population targeted for testing. For instance, genetic information provided to couples in the process of making reproductive decisions will likely have a different impact than information provided to an individual with no intentions of having children. Similarly, providing genetic tests to children at the request of their parents may have different ramifications than providing the same tests to consenting adults.<sup>5</sup> These differences are crucial to any analysis of genetic testing and must be given careful consideration as the availability of genetic medicine continues to grow.

Multiplex testing may compound the ethical complexities associated with single genetic tests rather than simply combining them. It should not be concluded that safeguards designed to limit the ethical risks associated with single genetic tests will be sufficient to meet the challenges that arise when tests are offered in combination. While this may be true in limited circumstances, in general the clinical application of multiplex testing should not proceed without a careful examination of the associated regulatory and ethical issues. Marketing of multiplex testing, both directly to consumers and through physicians’ offices, could provide appealing financial returns to the biotechnology industry as well as to genetic testing centers.<sup>7</sup> In the face of these incentives encouraging rapid development and distribution of multiplex tests, it is critical to confront the relevant ethical issues before these tests are widely conducted without necessary safeguards. As a response to this need and as a part of its continued efforts to address the ethical implications of

genetic medicine, the Council on Ethical and Judicial Affairs present the following analysis of multiplex genetic testing.

#### MULTIPLEX GENETIC TESTS – SENSITIVITY, SPECIFICITY AND PREDICTIVE VALUE

Among the variety of genetic tests, some yield high rates of false-positive and false-negative results while others are characterized by findings which are precise but of uncertain clinical or predictive value.<sup>7</sup> These problems with current genetic testing technology are complicated rather than reduced when single tests are combined to form a multiplex test.

Any single test's clinical validity is determined by three factors—the test's sensitivity, its specificity, and its positive predictive value. Sensitivity measures the test's ability to register true-positive results while specificity measures its ability to provide true-negative results. The positive predictive value of a test is the probability that a person with a true positive will get the disease. A key determinant of the total number of false results is the frequency of the trait in the tested population. As an example, for a test which yields false positives ten percent of the time, if that test is used to screen a population of 100 people in which 90 people actually have the disease, then of the ten people who are actually negative we can expect that one of them will test positive. In this case, the number of false positives would be one in one hundred. Thus, when high-risk groups are tested, positive results can be interpreted with greater confidence than when general populations of unknown risk are tested. Conversely, if low-risk groups are tested, the likelihood of false-positive results is correspondingly higher.

Consider the BRCA1 mutation and its relative predominance among Ashkenazi Jews. It is estimated that approximately 1.0% of all women of Ashkenazi Jewish descent carry the mutation while approximately 0.1% women in the population at large carry a mutated gene.<sup>9</sup> If only Ashkenazi Jewish women were tested for the trait, the rate and number of false-positives would be much lower than if all women were tested for the BRCA1 mutation. If, on the other hand, BRCA1 were tested as part of a multiplex test which targeted populations without an elevated risk for the BRCA1 mutation, the rate of false-positives would be high.

Multiplex testing contributes to the problem of false results by combining several tests, each of which carries its own risk of producing a false result. The chance that the multiplex test will yield a false positive result increases as the number of tests increases. For example, consider a single test that produces accurate results in 90% of cases. If five tests with similar rates of accuracy are conducted at once, the laws of probability suggest that the chance that they will all yield accurate results falls just below 60%.

The positive predictive value—another key component of a test's clinical validity—is also questionable in multiplex genetic testing. Even when tests are accurate, providing a meaningful interpretation of the results is often complicated.<sup>8</sup> Genetic tests can only provide information about the state of genetic material (genotype) without saying much about physical manifestations (phenotype). In some cases where the gene mutation is manifested phenotypically in all patients who inherit the gene, a genetic test can provide results that are entirely predictive, as in the case of Huntington's Disease. In many cases, however, genetic tests attempt to assess presymptomatic risk for developing a disease. With these susceptibility tests, a positive result does not ensure development of the disease, and a negative result does not preclude one from risk. Tests for the BRCA1 mutation are helpful in illustrating this point. By age 70, the risk of breast cancer among carriers of the BRCA1 mutation has been shown to be 56 percent and the risk of ovarian cancer, 16 percent.<sup>10</sup> It is important to recognize, however, that those identified as having the BRCA1 mutation may not actually develop either form of cancer. Furthermore, it has been shown that

only 7% of women with a family history of breast cancer had this specific genetic mutation, and that therefore over 90% of individuals with supposed risk would gain no predictive advantage from a genetic test.<sup>11</sup> In fact, obtaining the negative results of a BRCA1 test might provide false reassurance and discourage the use of important screening techniques such as breast self-examination and mammography.

## INFORMED CONSENT AND COUNSELING

It is critical to assess the degree to which the nature of current genetic tests could impact the ability of patients to give informed consent. Patient autonomy is given its clearest voice in the process of consent, and the medical community has established conditions that must be met to ensure that the freedom of patients to make decisions is protected.<sup>12,13</sup> One of the most crucial of these conditions is disclosure by the physician of all relevant information. Without such disclosure, the patient cannot reasonably be expected to make a decision that represents a clear analysis of available options and possible outcomes. The nature of genetic information, however, provides several challenges to this requirement.

As with many laboratory tests, results from genetic testing are typically assumed by patients to be correct. Many genetic tests do not validate these assumptions of near-perfect performance.<sup>8</sup> Communicating the problems of specificity and predictive value—and the need for caution when interpreting test results—to patients (who may believe that tests are by their very nature conclusive) is a difficult task. This difficulty is amplified when factors such as specificity vary for each of the different tests the multiplex.

Tests conducted for diagnostic purposes, susceptibility, and carrier status have different implications and counseling needs. While tests for diagnosis are associated with near-certain predictions of disease development, susceptibility tests provide information only about illness risk. Counseling in the latter cases must, for instance, include interpretation of the risks associated with particular mutations. Carrier screening is designed to provide information to potential parents about the possibility of passing a gene mutation to children. Although a carrier test itself may be fairly straightforward, assessing the implications of the test requires, for instance, an understanding of reproductive genetics. In cases involving a single genetic mutation that is either dominant or recessive, a basic discussion of Mendelian inheritance may be sufficient. However, in more complicated cases of polygenic traits or linked genes, a substantially more sophisticated understanding of biology may be required. If tests for all three purposes detailed above were combined to form a single multiplex test, substantially more counseling would be required in order to convey all the information relevant to a patient's final decision.

Not only does each type of test require different, unique information backgrounds, the tests trigger different social or personal contextual concerns. For instance, different susceptibility tests have different implications for patients, and the information required for meaningful interpretation of the results may vary substantially.<sup>14</sup> As a result, grouping tests by general category will not necessarily alleviate the problems associated with counseling for multiplex tests.

The third principal challenge to obtaining informed consent lies in the nature of the information resulting from many genetic tests, particularly those designed to determine susceptibility. In many cases, receiving a positive test result for a genetic mutation does not provide any conclusive predictive evidence of eventual disease development. There may also be instances in which test results can provide insight into actual future disease onset, but in which no preventive measures

or treatments exist with which to stave off or mitigate the inevitable condition. In still other cases such as tests for cystic fibrosis, patients may be asked to consider that certain tests may predict disease onset but cannot distinguish between the often vastly disparate levels of severity. When these uncertainties are coupled with the possibilities of false results, providing patients with the information necessary to consider a multiplex test appears difficult at best.

Some will argue that clinicians can overcome these difficulties by carefully counseling patients and working through the complexities with those considering testing. Behind this position is the view that physicians should not assume that there is anything their patients cannot understand and consider in the process of giving informed consent. Furthermore, it would be paternalistic to deny them access to tests simply because the profession recognizes the possibility that appropriate information might be lost in the process of disclosure. These are certainly compelling points; however it is also important to examine how closely our current medical system can approximate the conditions under which adequate counseling could occur. A Human Genome Project survey found that only 54% of the physicians surveyed had even one course in basic genetics.<sup>15</sup> Experts in medical genetics concur with this finding, arguing that there currently exists a shortage of clinicians trained in genetic counseling and interpreting genetic tests.<sup>15</sup> In sum, many physicians who will be asked to provide patients with tests and information about genetics will not have the background necessary to answer those demands.

Another possible solution to the difficulties is to refer patients to genetic counselors. Again, however, the feasibility of this solution must be evaluated in terms of currently available resources. The process of counseling a patient about a genetic condition is a time-consuming process consisting of pre-test information sessions, informed consent sessions, and post-test counseling sessions. Many of these sessions last over three hours, and as a result some counselors see as few as 300 new patients a year.<sup>16</sup> Even without the availability of the multiplex test, trained genetic counselors are under strain to meet the increasing demand for genetic services. The time demanded of these professionals will only increase with the combination of several tests conveying different information and implications with varying levels of accuracy. This poses a problem. Despite the fact that multiplex testing will require genetic clinicians to spend significantly more time with each patient, no systemic change has been proposed to handle this potentially overwhelming shift in practice. This raises profound questions about clinicians' ability realistically to meet the information needs of patients attempting to make decisions about multiplex tests.

It should be noted that the increase in time demanded of counseling physicians by multiplex testing would come at a time when physicians are often under considerable pressure to economize their interactions with patients. Incentives currently in place often have the intended or secondary effect of requiring physicians to see more patients in the course of their practice rather than fewer. In this environment, it is unlikely that physicians will be able to meet the counseling requirements presented by multiplex testing. Even if the burden of conveying strictly genetic information is shifted to non-physicians, the process of counseling must include the consideration of clinical implications which can only be conveyed by physicians.

#### PHYSICIAN RESPONSIBILITY TO INDIVIDUAL PATIENTS

Past Council opinions on genetic testing have assumed a link between testing and risk, addressing those circumstances in which individuals considered "at risk" for a specific condition are offered testing for genetic status.<sup>1-5</sup> Yet, as more conditions are included in a multiplex test, a wider group of the general population becomes at-risk for at least one of the included genetic traits. It is likely that these patients will be offered the entire panel of tests rather than the single, clinically

relevant test. As genome research continues, the genetic root of an increasing number of conditions will be established, thereby expanding the pool of patients considered eligible for genetic tests. It seems safe to predict that eventually virtually all patients will be shown to have a genetic disposition for some trait, and that might encourage a trend for a large proportion of the population to seek evaluative genetic testing. If these tests are grouped in multiplex packages without concern for the relevant risks of the individual, a substantial number of patients would receive results from evaluations that are not clinically indicated.

Experience with laboratory test panels (often referred to as “chem 7,” “chem 12,” etc.) supports the assertion that multiplex testing would lead to a breakdown in the link between clinical indication and genetic evaluation. In daily practice, it is often less expensive and equally convenient to order a fixed battery of laboratory tests rather than each individual test suggested by the patient's condition. It may not be readily apparent, especially to a busy practitioner, why genetic tests should be treated differently, particularly if multiplex tests could provide a less expensive alternative to single trait testing.

The eventuality described above is cause for some concern. Abnormal results from specific tests in laboratory panels are routinely provided to patients even if the test in question was not clinically indicated. In some instances, the information may be benign, or there may be treatments available that can be of material benefit to the patient. In other cases, however, information provided by non-indicated testing may result in unnecessary psychological distress, lifestyle modifications that negatively impact quality of life with no resulting benefit, or requests for treatment that are founded on misconceptions rather than medical science. While these problems may be resolved in cases where communication of information is unimpeded and straightforward, they are significantly more serious when associated with those tests, including genetic tests, that convey information that is difficult to explain and to understand.

The challenges facing physicians who attempt to help patients deal with fears and to help clarify misconceptions by providing sufficient information about many genetic tests are not limited to the scientific and personal contextual uncertainties discussed earlier. Current popular conceptions regarding the information contained in a genetic test also complicate significantly the task of patient communication. There is a substantial body of misleading information relayed to the public almost daily about the implications of genetics. Stories in the media repeatedly claim that science has uncovered an inheritable gene responsible for a wide variety of conditions and behaviors, often implying that a cure is not far behind. The response among many members of the general public is to believe that genetic information is the key to understanding future disease onset and to establishing the immutability of certain traits and characteristics. In short, genes are often portrayed as the source of inevitable outcomes and pre-determined conditions. To many, genes are even thought to represent the essence of human beings. Providing accurate information in the face of these powerful assumptions is extremely difficult.

In general terms, many patients perceive genetic information to be an indicator of their fundamental health. Despite the fact that diseases and traits cannot be reduced to solely their genetic components and that environmental and behavioral influences are critical components to the development of most conditions, current social conceptions of self place tremendous significance on genetic composition. Physicians have a responsibility to appreciate the power of genetic information and to exercise appropriate caution when providing access to tests that may be interpreted by patients as evaluations of their basic “wellness.”

The far-reaching, conceptual impact genetic information may have on patients strengthens the claim that only those tests which are clinically indicated should be offered to patients. Providing



general access to testing in the clinical setting validates misconceptions that genetic information is inherently valuable and that surveying genes is a legitimate assessment of overall health. Furthermore, even seemingly benign tests that provide information about genetic status but which have no bearing on phenotypic expression or reproductive decisions may have a psychological impact on the patient who interprets the presence of a mutation as a deep-seated flaw.

Given the significance of genetic information, it is also critical to ensure that test results are accurate. It has already been established that providing access to tests that are not justified by the clinical evidence may substantially compromise the clinical validity of a multiplex test. The increased risk of false-positive results inherent in expanding the pool of tested patients beyond those with a personal or family history outweigh the benefits gained by those patients who seek genetic tests to provide a survey of their genes, even if there is a small chance the test could provide information valuable to the patient. It is critical to recognize the limitations of testing as well as the potential impacts of affording access to genetic information that may be incorrect.

### POPULATION TARGETING AND MULTIPLEX TESTS

Targeting of genetic testing to individuals who have an elevated risk for a specific condition has many merits. The challenge is to define and find those patients who are eligible according to this approach. One possibility that some will propose is to design multiplex packages based on patterns of risk found in different populations. These populations could be identified by rates of disease incidence, and multiplex tests could be constructed which target the conditions found in a particular population. This method has been explored by a group of practitioners within the Department of Human Genetics at the Mount Sinai School of Medicine who developed a multi-disease carrier screening program consisting of a multiplex test designed to target diseases found in an Ashkenazi Jewish population.<sup>17</sup> Their multiplex test encompassed individual tests for Tay-Sachs disease, cystic fibrosis, and Type I Gaucher disease.

There are a number of potential problems with designing multiplex tests on the basis of incidence patterns in defined populations. The assumption of such testing is that elevated rates of risk are distributed throughout the selected population, such that every individual within the population presents a history that supports the need for testing. However, this assumption relies upon a history of reproductive isolation that is not evident in many socially defined populations. Individuals tend to associate according to cultural features; these may not be representative of gene pools that track with targeted mutations. The reproductive overlap between populations may be extensive. Programs that rely upon the patient's self-identification with a population to determine eligibility for testing risk targeting cultural features rather than appropriate genetic inheritance. If tests are provided to those who are not in fact members of high-risk groups, the number of false-positive results will increase and possible harm could result. These problems, both with defining a broad population that actually represents a pool of patients each having elevated risk and with selecting patients whose membership in that group is established biologically, present compelling arguments against designing multiplex tests on the basis of populations.

Proceeding with programs to test socially defined populations for multiple genetic mutations using specifically designed multiplex tests could result in different forms of discrimination. Because of the problems defining "at-risk" populations that should in fact be eligible for multiplex testing, it is likely that any such testing programs will disproportionately subject one group of patients to the negative impacts either of false results or forms of genetic discrimination. Patients who are tested according to actual risk based on clinical evaluation will benefit from

more accurate test results than those given tests because of their membership in an inevitably ill-defined genetic population.

Multiplex tests that attempt to group individuals into broader populations could disrupt the patient-physician relationship by introducing an element of perceived discrimination into the clinical setting. One of the primary duties of physicians is to treat each patient according to his or her individual medical needs. To the extent that ethnic heritage may contribute to particular health concerns, it is clinically material and should be considered. Offering multiplex tests that are bundled according to race or ethnicity, however, serves to categorize patients rather than to address their distinct needs. Furthermore, the criteria upon which this categorization is based are the genetic mutations and diseases prevalent in a population. The profession can ill-afford the perception that science is being used to bring attention to the genetic flaws present in lines of inheritance.

Perhaps the most troubling potential application of multiplex tests would be the construction of panels explicitly designed to discriminate against specific ethnic groups. For instance, a multiplex test could be built around a single test for which elevated risk exists in a particular population. The other tests in the multiplex bundle could be any tests for which reasonable risk exists in the general population. By using the one race-related trait to target the population, the remainder of the tests could point to mutations that exist in other populations but which go unnoticed for lack of testing. The insidious implication of such testing would be that one ethnic group had an abundance of mutations and must therefore be considered inferior. While this possibility might seem improbable, history provides many examples of such discrimination in other contexts, and society must not discount the possibility of such unprincipled actions.

#### POTENTIAL FOR DISCRIMINATION

In any discussion of genetic tests, one of the most common fears expressed by patients and society is the possibility that this private information might be used in discriminatory practices. Safeguards and regulations must be put in place to prevent insurers and health care service organizations from denying coverage for or discriminating against people who have tested positive for a genetic trait. This basic premise should also be extended to employers, especially self-insured employers, who could use genetic information in their hiring and promotion decisions.

Potential discrimination by insurance companies and employers could be further complicated by multiplex tests designed to target specific groups. For example, a test that coupled BRCA1 and Tay Sachs could be used to disproportionately discriminate against Ashkenazi Jews. A similar test coupling sickle-cell anemia and prostate cancer could discriminate against African-Americans males. The formulation of the test itself and the determination by society, industry, and health care providers of conditions to be tested could become a powerful means of social control.

#### CONCLUSION

Increasingly, genetic science is helping to characterize the etiology of illnesses. Genes are inherited and passed on to future generations. Viewed by many as fundamental to conceptions of self, knowledge of their genes may influence many important decisions and options in peoples' lives. However, the impact of environmental factors and behaviors on health should not be ignored, and diseases should not be reduced to their genetic components only.

Multiplex testing presents a series of challenges to adequate communication between the patient and the physician. It increases the total number of marginally indicated or non-indicated tests, thereby bolstering the rate of false results. These results may lead to psychological stress and misinformed life-altering decisions, and may also impact the ability of a physician to obtain informed consent. The inherently uncertain nature of genetic information as well as the lack of clinical geneticists and counselors available to provide adequate information also suggest that standards of disclosure will be difficult if not impossible to maintain.

Finally, multiplex testing and its resultant information may have widespread societal implications. When coupled with society's emphasis on the primary role of genetics in pathology and suffering, expanded provision of genetic tests might lead to varied forms of discrimination against those with genetic conditions. Furthermore, multiplex tests could be constructed to specifically target defined populations which could lead to selective discrimination against particular populations.

Although multiplex tests have not reached the general health care market, the potential for their widespread application is readily apparent. Before such tests reach health care providers, clinics, and drugstores, the ethical and social implications of these tests must be well-understood, and careful restrictions and regulations must be established.

#### RECOMMENDATIONS

The Council has the following recommendations on the future possibilities of multiplex genetic testing.

- 1) Physicians should not routinely order tests for multiple genetic conditions.
- 2) Tests for more than one genetic condition should be ordered only when clinically relevant and after the patient has had full counseling and has given informed consent for each test.
- 3) Efforts should be made to educate clinicians and society about the uncertainty surrounding genetic testing.

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