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6 Categorizing Genetic Tests

Based on Burke, W., Pinsky, L., and Press, N. (2001). "Categorizing genetic tests to identify their ethical, legal, and social implications." *American Journal of Medical Genetics*, 106:233-240. Adapted with permission.

1 What if you could go to the doctor and present a card that contained all your genetic information? Your doctor could scan the card and see whether you were more likely to have an allergic reaction to a particular drug, or whether you were at increased risk for a disease or disorder. Every year, scientists come closer to making this scenario a reality. More than 1,500 genetic tests are currently available[1], and the number of tests available has more than doubled in the past eight years. Genetic testing companies are making it increasingly possible for consumers to have portions of their DNA sequenced, and to receive some information about what the results might mean. The growth of these "direct-to-consumer" testing companies has resulted in the ability of individuals to learn unprecedented amounts of information about their own genes.

2 There are a variety of genetic tests available. For example, some tests are performed on early embryos formed by ***in vitro fertilization*** (in which egg cells are fertilized by sperm outside the body) to determine whether they are disease-free and should be implanted in a woman (**Pre-implantation Genetic Diagnosis, or PGD**). **Prenatal** genetic tests test cells from a developing fetus before birth. Newborn screening tests are provided to children immediately upon birth. **Diagnostic tests** are used to identify (or rule out) a particular genetic condition and **carrier tests** are used to identify whether an individual who may not show any condition him/herself carries a particular gene.

3 Genetic tests have tremendous value in helping doctors diagnose and treat diseases. They can also predict who may develop a disease in the future, helping patients take a proactive role in their health care. Knowing an individual's genetic makeup may also help doctors identify the best treatments, as some drugs might be more effective for patients with particular genetic variations. They can also provide information to individuals that may affect their choices about having children in the future.

4 However, genetic tests also raise some challenging issues. For example, patients might encounter discrimination in various forms, or might experience stress as a result of knowing the outcome of a test. While the federal Genetic Information Non-Discrimination Act (GINA) of 2008 sets a baseline for patient protection with regard to insurance and employment, there are areas it does not cover (for example, companies with fewer than fifteen employees are exempt). GINA also does not prohibit health insurers from obtaining and using genetic test results to determine who should receive health insurance payments. Another concern is that the results of genetic tests impact not only the individual taking the test but entire families, who often share much of the same genetic information. Even a test that shows that a person does not have a genetic disorder might cause stress in the form of "survivor guilt" if other family members are affected by the disorder.

5 Genetic tests can be characterized according to their **clinical validity** and the availability of effective treatments. The term "clinical validity" means how accurately a test predicts a certain clinical outcome (such as getting a particular disease or symptom). Different types of tests raise different ethical issues and require different types of genetic counseling.

High Clinical Validity – Lack of Effective Treatment

6 Traditionally, genetic counselors have been guided by the view that recommendations should be "non-directive;" in other words, people should be provided with information and then allowed to make their own choices. This view acknowledges that many decisions regarding health care are currently driven

by personal preference. For example, the decision of whether to terminate a pregnancy because of a genetic disorder is viewed as a private matter. Non-directive approaches also apply to some genetic testing situations that do not involve reproductive choices. For example, an individual whose parent had **Huntington's disease (HD)** might want to find out if he or she carries the mutation that results in the disease. Because HD has a high penetrance (in other words, an individual with the mutation has a large chance of developing the disease), an individual who tests positive receives information that might be helpful in planning for his or her life. However, there are currently no effective treatments to delay or prevent the disease, so an individual who tests positive for the HD mutation cannot use this information to make decisions about medical treatments that might help them.

7 In addition, there is the possibility that a person with a positive test may face discrimination or harmful psychological effects (including the stress of knowing that they have the mutation). A counselor might explain the different concerns and issues related to taking the genetic test, but the decision to test is ultimately left to the patient. Ethical issues often focus on making sure that people consider the kind of information the test will provide and the lack of treatment options.

High Clinical Validity – Effective Treatment

8 Newborn screening tests, by contrast, are required by all states. Newborns are screened for a variety of disorders. In some states, parents may choose not to have their children screened (for example, for religious reasons). A classic example of a newborn screening test is the test for a disease called **Phenylketonuria (PKU)**. If a child who has the PKU mutation is diagnosed early in life, a modified diet can be given and mental retardation prevented. There is broad agreement that testing for PKU is extremely beneficial because a highly successful treatment—a modified diet—exists. Ethical concerns related to such genetic tests often focus on making sure that eligible people have access to the tests and treatment.

9 These examples show that the availability of an effective treatment makes a big difference in thinking about the implications of a genetic test, whether the use of that test is justified, and how health care providers should counsel families. In fact, health care providers have a duty (supported by court cases) to clearly tell patients if there are tests available in cases where successful treatments exist and non-treatment can lead to serious harm. If there are no effective treatments, non-directive counseling provides an appropriate framework for talking to patients about the possibility of testing.

Low Clinical Validity – Lack of Effective Treatment

10 Clinical validity is affected not only by the penetrance of the mutation, but also by how good a test is at predicting whether someone will eventually get the disease. In other words, if a patient receives a positive test, how high is the likelihood that they will eventually become ill with that disease? In some cases, such as testing for the ApoE4 genotype (which may result in an increased risk for **Alzheimer's disease**), a positive result may show an increased risk, but the actual lifetime risk for the disease is uncertain. People with two ApoE4 alleles are ten times more likely to have Alzheimer's disease than those with other versions of the gene, but because Alzheimer's can occur late in life, someone might have two ApoE4 alleles and die of something else before Alzheimer's sets in. No treatment is available to reduce the risk.

11 As with testing for HD, the main risks are related to psychological effects on those who are tested, as well as discrimination. However, the HD test provides a highly accurate prediction about future risk. The risk associated with the ApoE4 test is less certain. Many experts recommend not testing for ApoE4, based on the ethical obligations for health care providers to avoid harm. Many genes that contribute to human disease have been identified. However, since the corresponding genetic tests may not be clinically valid, the real impacts of a positive test may be difficult to interpret, and few treatments may be available. Many direct-to-consumer tests fall into this category; they provide information related to disease risk that is difficult to evaluate due to uncertainty about the validity of the test as well as a lack of effective treatment.

Low Clinical Validity – Effective Treatment

12 So far, the examples presented have been ones that either predict diseases well (HD and PKU), but differ as to the treatments available, or that do not predict the disease well and also do not have an effective treatment (Alzheimer's – ApoE4). A fourth case is when there is an effective treatment, but the test is not clinically valid. For example, mutations in the HFE gene can lead to susceptibility to a disease called **hemochromatosis**. This disease causes iron overload and has potentially life-threatening consequences. However, only a small proportion of individuals with mutations in both copies of their HFE gene actually show symptoms of disease (low penetrance); therefore, the clinical validity of the test is low. Periodic blood draws, however, can help prevent dangerous complications such as liver cancer. So, in the case of HFE, the clinical validity of the test is low, but the treatment is minimal and beneficial. The benefit to the patient in terms of health outcomes may outweigh the potential psychological effects of testing or the potential social stigma of being labeled a carrier of a genetic disease. Ethical discussions about these types of tests, therefore, tend to be framed in terms of balancing potential harms and benefits. Tests that do not predict outcomes very well might be acceptable when the "label" associated with the disease has little social stigma (for example, hypertension).

13 *BRCA1* and *BRCA2* are interesting to analyze using this framework. There is uncertainty about how penetrant the *BRCA1* and *BRCA2* mutations are. The lifetime risk of breast cancer associated with *BRCA1* or *BRCA2* mutations ranges from 36%-85%, with a wide variation in how the cancer manifests itself (as breast cancer, ovarian cancer, or both). The penetrance is probably determined by the exact type of mutation (many *BRCA1* and *BRCA2* mutations are known) as well as environmental and other genetic factors. In a "high risk" family (four or more relatives affected by breast/ovarian cancer before age 60), females with mutations in *BRCA1* or *BRCA2* are estimated to have a lifetime risk of 85% for breast cancer. The effectiveness of the different treatments offered to carriers of *BRCA1* or *BRCA2* mutations is also subject to debate. The options include early mammograms, ovarian cancer screening, and surgery before any cancer appears. Most women with *BRCA1* or *BRCA2* mutations do not opt for such preventative surgery, especially if they do not have other risk factors in their history. However, those in a "high risk" family might consider the test to be highly predictive and the treatment effective.

14 A genetic test, therefore, should be evaluated based on both the test's clinical validity and the treatments available for those individuals with positive results. It may take many years for researchers to gauge how accurate a test is at predicting a disease outcome. The development of treatments and tests of their effectiveness in patients also requires time. This framework can help guide researchers in making decisions about which kinds of information to seek about tests, and can help patients think about the characteristics of the tests they are considering. It also explains why some tests have become widely accepted while others have not. As more genetic tests with limited clinical validity and predictive value become available, and more direct-to-consumer tests are marketed to the general public, it will be increasingly important to consider carefully how those tests are used.

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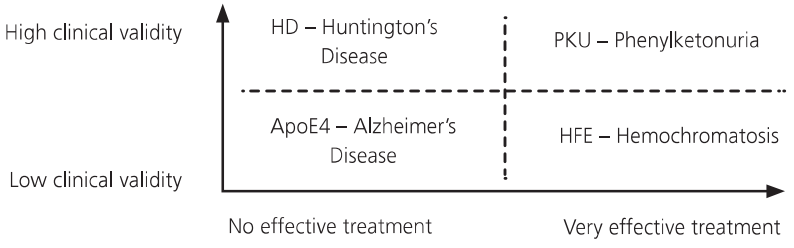
Genetic Test Categories



Genetic Conditions Glossary

Alzheimer's disease: A brain disease that causes problems with memory (such as difficulty remembering people and events), thinking, and behavior. It is most common in people over 65, but up to five percent of people with the disease have early-onset Alzheimer's (also known as younger-onset), which can appear in the patient's 40s or 50s. Alzheimer's worsens over time, and there is no cure, though some treatment options are available that appear to reduce the speed with which the condition worsens.

Carrier test: A genetic test to determine whether an individual carries a particular gene but may not show any conditions themselves. For example, a carrier test may be used to determine whether two parents both carry a copy of a recessive trait, which may be passed on to their child(ren).

Clinical validity: How accurately a test predicts whether a person will get a particular disease or symptom (known as the "clinical outcome"). This is often related to the penetrance of the gene involved, and whether or not the condition is polygenic.

Diagnostic test: A genetic test used to identify (or rule out) a particular genetic condition. For example, diagnostic genetic testing is used to determine whether a baby has Phenylketonuria (PKU).

Effective treatment availability: Whether or not there are treatment options available for a particular disease or condition. This is sometimes thought of as a "cure" although most genetic conditions are "treated" rather than "cured."

Hemochromatosis: An autosomal recessive genetic disease that results in the body absorbing too much iron from food. This extra iron is stored in the body, including in organs like the liver and pancreas. The extra iron results in pain, organ damage, cancer, heart problems, and in some cases, death. Symptoms usually begin around age 30 to 40, but may begin in childhood. There is no cure, but the condition can be controlled with a specific diet, removal of blood (to remove the extra iron), and medication.

Huntington's disease (HD): An autosomal dominant genetic disease causing nerve cells to waste away gradually, resulting in uncontrolled movements, severe problems with balance, clumsiness, emotional distress, problems swallowing, and loss of mental function. The condition usually begins when a person is in their 40s, and gets worse with age. The condition is ultimately fatal, and there is no cure.

***In vitro* fertilization:** A process in which egg cells are fertilized by sperm outside the body. This is often used to help couples who have difficulty getting pregnant.

Penetrance: The frequency that individuals with a specific genotype will express a specific phenotype. For example, as seen in *Lesson Three*, approximately 85% of women with particular *BRCA1* mutations will develop breast or ovarian cancer. *BRCA1* is said to have "high penetrance" because an individual with a cancer-causing mutation in *BRCA1* has a large chance of developing breast cancer.

Phenylketonuria (PKU): A rare autosomal recessive genetic disease in which the body does not make an enzyme necessary to convert the amino acid phenylalanine to the amino acid tyrosine, causing phenylalanine to build up in the body to unsafe levels. This can cause mental retardation, brain damage, and seizures during infancy and early childhood. While a modified diet, including special protein supplements, can reduce the severity of PKU's symptoms, new research suggests that diet alone is not enough to prevent symptoms.

Pre-implantation Genetic Diagnosis (PGD): Performing a genetic test on an embryo created by *in vitro* fertilization before placing it in the mother.

Prenatal: Before birth. For example, some genetic tests are performed on a developing fetus while s/he is still in the mother's womb.

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6 Weighing the Risks and Benefits of Direct-to-Consumer Genetic Testing: Who Should Decide?

Concerns about Direct-to-Consumer Genetic Testing

1 Direct-to-consumer (DTC) genetic testing has offered personal genetic data to consumers since 2006, without the need for—or potential benefit of—medical doctors or genetic counselors. However, medical providers and those in government have been concerned that the risks of DTC genetic testing may outweigh the benefits.

2 What if the estimates for how likely someone is to develop a disease prove to be incorrect, either overestimating or underestimating a person's risk? If someone found out that their risk for a disease like Alzheimer's was well above average, would they become depressed? Would they alter their behavior for better, for worse, or perhaps not at all?

3 These concerns have led some states – including New York and California – to either ban DTC genetic testing, or strictly limit it. According to a report by the Genetics and Public Policy Center in June 2007, only about half the states in America permitted DTC genetic testing with no restrictions.[1]

4 The US Food and Drug Administration (FDA) does not currently provide oversight of the DTC genetic testing industry. In March 2011, the Molecular and Clinical Genetics Panel, an advisory committee to the FDA, suggested more oversight. They expressed concern that consumers may misunderstand genetic results without medical counseling, or that the disease risk estimates provided in those results may be incorrect, as there is currently no standard about the level of evidence needed by DTC genetic test manufacturers to make claims about their genetic tests. The FDA panel noted that, while DTC genetic tests seem similar to other at-home medical tests like those for blood sugar or pregnancy, "many DTC clinical genetic tests often carry a disclaimer stating that they are intended for 'educational and informational' purposes, and that the individual receiving the test results may wish to take them to their clinician for follow-up."[2]

5 A member of the FDA panel noted that companies have a right to sell their products to the public, but the FDA has an obligation to compare the risks and benefits of these products, set product standards, and make sure information is understandable by the public.

Response from a DTC Company: 23andMe

6 23andMe is a DTC company. According to the creators of the company, "23andMe was founded on the belief that individuals have a right to access their own genetic information, and this conviction is still as firmly held as ever," but 23andMe is assured that the FDA will take a "reasoned approach to integrating the feedback it received from the panel."[3] However, they hope that feedback will come from all involved parties, as 23andMe notes that the FDA panel had a panel member who represented the consumer and the patient, but they did not "hear directly from consumers and others who have first-hand experience with the information provided by direct-access genetic testing services."[3] 23andMe encourages consumers to make their voices heard about their experiences with DTC genetic testing.

7 In addition, DTC genetic testing companies like 23andMe use the genetic information of their customers to further our understanding of human genetics, if customers consent. In a study published in the scientific journal PLoS Genetics, 23andMe used customer data and web-based surveys to evaluate genetic variation in a number of common human genetic traits, such as hair color, eye color, and freckling.[4] This may not seem like a giant scientific breakthrough, but it makes an important contribution to our understanding of ***how*** we can conduct genetic research. Genetic studies often require a great deal of time and money to recruit study participants, perform genotyping, document phenotypes, and perform genetic analyses. The 23andMe approach offers a potentially powerful new way to conduct these types of studies with willing DTC genetic testing customers, using less time and at lower cost.

Challenges to Understanding Genetic Test Results

8 According to the American Medical Association (AMA), "[t]he results of genetic tests (whether DTC or ordered by a physician) can be challenging to interpret. A positive result does not necessarily indicate a clinical diagnosis. Often, a positive result indicates an increased risk for developing a disease or condition."[5] The AMA goes on to say that the same mutation in different people can mean different things, based on penetrance, environment, and other factors. "Also, since only a fraction of testable mutations are identified for genetically based diseases, a genetic test with a negative result is not indicative of the absence of disease risk." The AMA recommends that any patient undergoing genetic testing (DTC or otherwise), do so "under the guidance of a qualified health care provider."[5]

9 The American Society for Human Genetics (ASHG) noted in a report released in September 2007 that the federal government currently has limited oversight of the "analytic validity" of genetic tests (the ability of the test to correctly detect a particular genetic variant), and no oversight of the "clinical validity" of genetic tests (the ability of the test to correctly predict whether someone will develop a particular disease).[6] The ASHG recommends that all DTC genetic testing companies provide consumers with information about genetic testing accuracy, including the strength of the scientific evidence about genetic test results, and that the federal government improve regulation of DTC genetic testing companies, to ensure the accuracy of the information provided to consumers.

10 However, some are concerned that, without direct government oversight, the DTC genetic testing industry may not do a good job regulating themselves. The Government Accountability Office (GAO) testified in 2010 before the US House of Representatives about their 2006 investigation of DTC genetic testing companies. They obtained 10 genetic tests from four DTC genetic testing companies, using DNA from two donors, and compared the results.[7] According to the GAO report, "GAO's fictitious consumers received test results that are misleading and of little or no practical use." One fictitious donor received contradictory results from each of the companies: below average, average, and above-average risks of developing hypertension and prostate cancer. Many of the estimates of genetic disease risks are based on scientific studies, but often these studies contain too few African American or Asian participants to make meaningful conclusions about these groups. In addition, "follow-up consultations offered by three of the companies failed to provide the expert advice that the companies promised."7 There were also examples of deceptive marketing, in which two companies claimed that donor genetic information could be used to create personalized supplements to "repair damaged DNA" or cure disease, or predict which sports donors' children would do well in. Experts say these claims lack scientific evidence, and the GAO has referred all four of the companies "for appropriate action" to the FDA and the Federal Trade Commission (which regulates marketing of products).[7]

What Do Consumers Think about DTC Genetic Testing?

11 But is all of this concern really necessary? If these tests are truly for "educational and informational purposes only," do we really need government agencies to regulate them as they would regulate genetic tests in a doctor's office? What do patients think? Has anyone asked them? Two studies provide insights about what DTC genetic testing consumers think about these products.

12 A paper published in the *New England Journal of Medicine* in February 2011 describes preliminary results from the Scripps Genomic Health Initiative, which measures the psychological and behavioral effects of DTC genetic testing on subjects recruited from health and technology companies.[8] Study subjects purchased genetic tests using the Navigenics Health Compass (Navigenics is a DTC genetic testing provider) at a discounted price—$225 instead of $400 to $2,000. Researchers then followed the subjects for three months using web-based surveys to measure anxiety level, diet, exercise, whether the DTC genetic tests caused subjects any distress, and whether subjects used more medical screening tests after receiving their genetic test results.

13 What did these researchers find? About half of the study subjects said that they intended to use more medical screening tests after receiving their DTC genetic test results, and about half did not. There was no clear increase in anxiety level, dietary fat intake, and exercise behavior among these subjects—who were all in general good health at the beginning of the study. About 10% of the subjects said they discussed their test results with the Navigenics board-certified genetic counselor, and about 26% said they discussed their results with their doctor. In fact, most of the study subjects did not do anything different after obtaining their study results: they did not talk to their doctor, they did not change their diet or exercise, and they did not seem to be upset by any of their test results.

14 In another report published in *Health Economics* in 2010, researchers studied how much, if anything, people would be willing to pay for DTC genetic tests that predicted their risk of future diseases.9 The study included 1,463 people randomly chosen to participate through web-based surveys. They were asked about their willingness to pay for testing for Alzheimer's disease, arthritis, breast cancer, or prostate cancer, using tests that were "perfect" or "not perfectly accurate." Between 70-88% of study participants said they would pay for these genetic tests, with rates lower for Alzheimer's or "not perfectly accurate tests" and higher for prostate cancer or "perfect" tests, even if there were no direct impact on the person's medical treatment options.

15 The costs of DNA sequencing and analysis technologies continue to go down, making genetic testing available to more people at lower costs. Consumers, DTC genetic testing companies, and the US government will have to decide how best to move forward – balancing the rights of companies to sell their products, the rights of individuals to have access to their own genetic information through accurate and scientifically valid genetic testing, and the obligations of the federal government to protect its citizens.

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6 Critical Reasoning Analysis Form

Point of View What is the point of view of the authors, and how does that particular perspective show through	
Purpose Why was this material written?	
Questions What questions are addressed by the authors? What questions do you have about the material?	
Information What are some of the most important facts included?	

Concepts What are the main ideas and concepts addressed?	
Implications What is the larger meaning? What are the consequences of the decision to be made?	
Assumptions What assumptions are the authors making? Are any of these assumptions questionable?	
Inferences What can you infer and conclude based on the material?	

Credit: Foundation for Critical Thinking, http://www.criticalthinking.org, and Paula Fraser, Bellevue School District PRISM Program.

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6 Open-Ended Questions for a Socratic Seminar

When preparing for a Socratic Seminar, write questions using these sentence frames to stimulate your thinking about the article you read. Choose and complete five of the following:

- What puzzles me is…_____

_____

- I'd like to talk with people about…_____

_____

- I'm confused about…_____

_____

- Don't you think this is similar to…_____

_____

- Do you agree that the big ideas seem to be…_____

_____

- I have questions about…_____

_____

- Another point of view is…_____

_____

- I think it means…_____

_____

- Do you think…_____

_____

- What does it mean when the author says…_____

_____