



Genetics Society of America
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Medical Genetics Ethics Cases Facilitator Notes

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Learning Objectives

At the end of this section, the student should be able to:

1. Consider the potential advantages and disadvantages of widespread use of whole genome sequencing approaches and direct-to-consumer initiatives.
2. Identify the critical need to protect individual privacy of genetic test results and genetic databases to safeguard their impact on a patient's family relationships, their employment status, and their ability to secure health insurance.
3. Appraise the nuances and consequences of the current recommendations around reporting of genetic test results with respect to whole genome sequencing.
4. Recognize the economic ramifications of genetic technology for precision medicines and patented inventions.

Cases and Notes

Implications of genetic testing

Case study 1: Cystic fibrosis testing

Mary and Bill Jones have a child, Kevin, with cystic fibrosis. Mary is 6 weeks pregnant with her second child, and they are pursuing prenatal diagnosis of this child for cystic fibrosis. Since the diagnosis is more accurate when the parental mutations are known, Mary and Bill are both genotyped for the CFTR gene. Mary carries the common $\Delta F508$ mutation, but Bill was not found to have the same, or any recognizable, mutation. It is still possible that Bill has an undetected mutation, but it may not be possible to ascertain this by future testing.

Question prompts

- 1. Is there potential for misattributed paternity in this case?*
- 2. What should be done?*
- 3. To whom should the genetic counselor disclose this information and to whom does the physician owe confidentiality?*
- 4. Should the testing have been carried out differently?*

Genetic testing has limitations in accuracy resulting from the test design. For instance, genetic tests often only identify the most frequent mutations found in a population. In order to give more confidence to a negative test result in a patient, it is important to compare their genotype with that of additional family members known to carry the mutant gene. If the mutation cannot be identified in the family members or the patient, the negative result cannot necessarily provide peace of mind to the patient. Moreover, the necessity of familial sample analysis also complicates many of the issues involved in genetic testing (Case study 1). In the case above, the most appropriate strategy would have been to test the affected family member first to identify the disease-causing mutations before then testing the individual of unknown status. This

strategy would have avoided the confusion demonstrated in the case above because then the known disease-causing mutations would have been identifiable in the biological parents.

Implications of genetic testing further reading

M Lappé, JM Gustafson, and R Roblin, for the Research Group on Ethical, Social and Legal Issues in Genetic Counseling and Genetic Engineering of the Institute of Society, Ethics and the Life Sciences (1972) Ethical and Social Issues in Screening for Genetic Disease. N Engl J Med. 286:1129-1132. doi: 10.1056/NEJM197205252862104.

Direct-to-consumer genetic testing

Case study 2: Direct-to-consumer tests in college

“Bring your genes to Cal” was launched as a common educational experience for incoming freshmen in the class of 2014 at UC Berkeley. Freshmen received testing kits in the mail and were invited to swab their own DNA and voluntarily submit DNA samples for testing of genes involved in folate metabolism, lactose intolerance, and alcohol metabolism. The original plan was to report the results back to the individual students in the absence of genetic counseling and to offer a prize of further genetic testing from 23andMe to students who won a creative contest on the theme of personalized medicine. After a ruling from the California State Department of Public Health, UC Berkeley modified their testing plans to proceed with the testing but not report individual results. Instead, they would consider only community results.

Question prompts

- 1. Has the modified testing plan addressed the issues around direct-to-consumer testing appropriately?*
- 2. Were any of the students involved minors?*
- 3. Is it dangerous to promise genetic testing results related to alcohol metabolism to college students away from home for the first time?*
- 4. Does the free nature of the test introduce an element of coercion?*
- 5. Describe some potential harms of direct-to-consumer genetic testing.*

Case study 3: Advertising BRCA1 and BRCA2 testing

In late 2002, Myriad Genetics started television and print advertisements for “BRCAAnalysis,” their BRCA1 and BRCA2 testing kits. The kits cost approximately \$440 if the familial mutation is known and over \$4000 if complete analysis of both genes is required. In test markets, the advertisements increased calls to the company hotline by 40%. Myriad Genetics was targeting primary care doctors and gynecologists to conduct these tests.

Question prompts

- 1. Will the meaning of a positive or negative test result be properly conveyed by the medical professional and understood by the patients?*
- 2. Will the patients be able to distinguish between a true negative and a false negative?*
- 3. Will the 2013 Supreme Court ruling against Myriad’s patenting of genes help to bring these costs down?*
- 4. Can ClinGen and ClinVar eventually make other company’s cancer genetic tests as informative as Myriad Genetics?*

Case study 4: Consumer genetic tests for athletic ability

In December 2008, Atlas Sports Genetics began selling a genetic test for ACTN3, the α -actinin-3 gene. One of the variants in this gene is a nonsense mutation (R577X) that prevents production of the protein. It has been found that individuals with reduced amounts of α -actinin-3 tend to have a higher proportion of slow twitch muscle fibers than fast twitch muscle fibers. Conversely, because α -actinin-3 is expressed only in fast twitch muscle fibers, the presence of 1 or 2 copies of the wild type allele of the gene can tilt the physiological balance in favor of fast twitch fibers. This physiological association has been extended to elite athletes to show a modest enrichment of XX genotypes among endurance athletes and RR genotypes among sprint and power athletes. The company advocated testing children, even before their first birthday, as a performance indicator for their future athletic ability. Moreover, they contended that this genetic test is a more accurate prognostic indicator than physical tests before age 9 because these young children have not developed mature motor skills yet. The test results were reported to the families as the client's "genetic advantage."

Question prompts

- 1. Are parents acting in the best interest of their child when performing non-essential genetic tests on them at these young ages?*
- 2. Is it appropriate to base lifestyle decisions about childhood enrichment activities on genetics alone?*
- 3. To what extent can a single gene influence athletic ability?*

Because genetic tests and numerous other medical treatments require highly specialized knowledge for proper analysis, direct-to-consumer marketing is a highly worrisome business practice. As evidenced by the demands of parents for antibiotic prescriptions for their children's viral infections, a little bit of misinformation can complicate proper medical intervention. Likewise, incomplete education on genetic tests can inadvertently take advantage of vulnerable populations, including students, (Case study 2) and can lead to ill-informed decisions (Case study 3). It is critical that results of genetic

tests are accurately and sensitively conveyed as these results often have an immeasurable psychological impact and are the basis for important lifestyle (Case study 4) and reproductive decisions.

Nevertheless, private interests saw the profit potential in this treasure trove of data and moved quickly to commercialize this information into various types of genome-wide direct-to-consumer tests. Although these types of tests do have their fair share of concerns, they also have positive benefits, including extending preventative testing to individuals who might not otherwise be identified until they see a specialist. Also, this would allow individuals who have been adopted to get some information about their own genetic family history. However, in this era where consumers are increasingly more informed about their health care options, there is a significant worry that patients will seek out these genome-wide scans (microarrays) and even full genome sequencing with little possible idea of what to do with the information once they have it. Depending on the particular company offering the test, medical professionals are involved at varying levels. Some companies have their own hotlines with genetic counselors available to help clients process their test results. Other companies compile information written by physicians and scientists, leaving interpretation to the clients. Even with the involvement of physicians, the data retrieved can be difficult to apply. For well-characterized conditions, such as learning of carrier status (for instance, for cystic fibrosis) or a genetic predisposition for drug response, there is a relatively straightforward medical interpretation if guided by a medical expert. However, for these weak susceptibility alleles identified in GWA studies, even the most enlightened physician may find him or herself at a loss to give informed advice to his patient. Because these tests are surprisingly affordable, patients will be walking into their physician's office armed with these new and complex lab results on an increasingly frequent basis, and physicians will have to step in as intermediaries and assist with interpretation.

Because of the complexities inherent in interpreting this type of data, the American College of Medical Genetics has released a policy statement strongly recommending that a knowledgeable genetics professional is involved in this type of testing, from the time when an individual is deciding whether or not to get tested to the interpretation of the results themselves. Furthermore, the FDA has grown increasingly concerned about direct-to-consumer genetic tests for similar

reasons. In November of 2013, it demanded that the leading provider of these tests, 23andMe, must stop marketing its health-related genetic tests until it can be determined definitively if they are safe, if they do what they claim to do, and if the results are communicated in a way the consumer can understand. The company has (temporarily) discontinued a portion of their health related genetic tests, but consumers may still pursue ancestry and, more recently, carrier testing through the company. In February 2015, 23andMe was granted permission by the FDA to offer carrier testing for Bloom Syndrome, and as of October 2015, the company was permitted to offer expanded carrier results for 36 conditions such as cystic fibrosis. Furthermore, in April 2017, the FDA allowed marketing of a version of this test that would convey genetic health risk (not just carrier status) for 10 conditions including Parkinson's and Alzheimer's diseases. The most notable aspect of the 2017 announcement is the exemption of future 23andMe genetic health risk tests from premarket FDA review, so we expect the number of these types of tests offered to consumers to grow rapidly. Generally speaking, the carrier tests available are not especially comprehensive, particularly for individuals of ancestral backgrounds not typically associated with the condition in question. Also of note, individuals are actually still able to access their raw genetic data, just not the complete health interpretation, and there are already a number of publicly available work-arounds to allow individuals to self-interpret their genotypic results. Interestingly, neither Canada nor the UK has deemed pre-market approval necessary for this product, so individuals who reside in these areas are able to purchase personal genetic testing kits with health analysis, and the company seeks further expansion abroad. It seems likely that direct-to-consumer genetic testing will continue to expand in the US market in the near future, particularly as additional companies move into this space including some using whole exome sequencing approaches, and it will be important to monitor the FDA's position on this evolving issue.

Direct-to-consumer further reading

1. A DNA Education (2010) *Nature*. 465(7300):845-6. doi: 10.1038/465845b.
2. SL Callier (2012) Swabbing Students: Should Universities Be Allowed to Facilitate Educational DNA Testing? *Am J Bioeth.* 12(4): 32-40. doi:10.1080/15265161.2012.656803.

3. J Macurnov (2008) Born to Run? Little Ones Get Test for Sports Gene NY Times. NOV. 29, 2008. Retrieved from <http://www.nytimes.com/2008/11/30/sports/30genetics.html> on November 1, 2016.
4. R Cook-Deegan and A Niehaus (2014) After Myriad: Genetic Testing in the Wake of Recent Supreme Court Decisions about Gene Patents. *Curr Genet Med Rep.* 2014; 2(4): 223–241. doi: 10.1007/s40142-014-0055-5.
5. ACMG Board of Directors (2016) Direct-to-consumer genetic testing: a revised position statement of the American College of Medical Genetics and Genomics. *Genetics in Medicine.* 18, 207–208. doi:10.1038/gim.2015.190.
6. A Gutierrez (2013) Inspections, Compliance, Enforcement, and Criminal Investigations: Warning Letter to A Wojcicki for 23andMe, Inc. Retrieved from <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm376296.htm> on November 1, 2016.
7. EC Hayden (2015) Out of regulatory limbo, 23andMe resumes some health tests and hopes to offer more. *Nature.* doi:10.1038/nature.2015.18641.
8. FDA allows marketing of first direct-to-consumer tests that provide genetic risk information for certain conditions. (2017) Retrieved from <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm551185.htm> on October 20, 2017.

Regenerative medicine

Case study 5: The Nash family

Molly Nash was a six-year-old with Fanconi anemia, an inherited anemia that leads to bone marrow failure. Bone marrow transplant from a matched sibling can cure 85% of these cases. Molly, however, did not have a sibling, so her parents decided to have a second child who was chosen through PGD for his healthy stem cells. After four in vitro fertilization attempts, Baby Adam was born and donated umbilical and placental stem cells to his sister. The transplant cured Molly's bone marrow failure, but she is still at risk for life-threatening complications from infections and for solid tumor cancers.

Question prompts

- 1. Is it appropriate to have a second child for the purpose of having a source of therapeutic tissue?*
- 2. Do the characteristics chosen for in a prenatal setting matter?*
- 3. Who should pay for the PGD and IVF of this child?*
- 4. What are the ethical issues having to do with sources of totipotent vs. pluripotent stem cells?*

An example of regenerative medicine could involve a scenario where stem cells are isolated from an individual and used to treat a condition in the same individual (after manipulation to correct a genetic defect). Similarly, stem cells can be isolated from a healthy individual who is a donor match for the affected individual, as in Case 5 above. These strategies hold a great deal of promise in curing degenerative and hematological diseases in particular, but since the source of stem cells is ethically-charged, there have been a number of political issues associated with development of these technologies. You will remember that totipotent embryonic stem cells are particularly valuable because of their ability to differentiate into any of the body's cell types. In contrast, pluripotent adult stem cells can be isolated to match a patient's MHC genotype, and recent work in this area has shown promising results, however, they simply have a less diverse array of tissues in which they can be differentiated. The federal government has reversed course a few times regarding its support

for stem cell research. The consequences of the temporary legislative limitation on this research included an international brain drain where US stem cell researchers were looking overseas for new opportunities in stem cell research. Since then, an Executive Order on Removing Barriers to Responsible Scientific Research Involving Human Stem Cells was issued, which restored federal funding to this field, but because of the sensitive nature of these debates, this issue is far from settled.

The ability to distinguish the scientific issues from the political backdrop is becoming more difficult, and the possibility of forming non-partisan committees of scientists and ethicists will be necessary for careful evaluation of constantly developing genetic and stem cell therapeutics (Case study 5). Along these lines, a committee assembled by the National Academies recently proposed a set of guidelines to direct appropriate stem cell research, and leaders in the field of genome editing also conducted a conference to consider the ethical implications of their work. The National Academies committee's recommendations included informed consent from embryo donors without financial coercion, the protection of the identity of the donor, the formation of a stem cell research oversight committee at all institutions hosting this type of work, the establishment of a national organization to periodically review these research guidelines, and a prohibition on transplanting of animal embryonic stem cells into human embryos (although the reverse would be supported with careful review).

Regenerative medicine further reading

1. L Rivard (2013) Case Study in Savior Siblings. Scitable by Nature Education. Retrieved from <http://www.nature.com/scitable/forums/genetics-generation/case-study-in-savior-siblings-104229158> on November 1, 2016.
2. G Pennings, R Schots, and I Liebaers (2002) Ethical considerations on preimplantation genetic diagnosis for HLA typing to match a future child as a donor of haematopoietic stem cells to a sibling. *Hum Reprod.* 17(3):534-8. doi: 10.1093/humrep/17.3.534.

Privacy of genetic information

Case study 6: Burlington Northern Santa Fe Railroad

Burlington Northern Santa Fe Railroad (BNSF, Fort Worth, TX) medically tested employees seeking disability payments for carpal tunnel syndrome. Included in these tests were genetic tests for a mutation in HNPP, a gene connected to hereditary neuropathy and pressure palsies. The symptoms caused by mutations in HNPP either closely mimic the symptoms of or predispose patients to carpal tunnel syndrome itself. These genetic tests were conducted without the employees' knowledge or consent. The Equal Employment Opportunity Commission stopped the testing in 2002 and BNSF settled claims with its employees.

Question prompts:

- 1. How should BNSF have proceeded?*
- 2. What protections do patients have that safeguard the privacy of their genetic information?*

Case study 7: Sickle cell anemia population screening

In the 1970s, a population screening initiative was in place for sickle cell anemia in the African American population. Many employers used the information to terminate employment of heterozygous employees who were not in danger of even developing the condition.

Question prompts

- 1. Is it appropriate to use genetic diagnoses to make decisions about employment status?*
- 2. What about the example of an individual with sickle cell trait who wants to join the Air Force or serve as a flight attendant (i.e. work in low O₂ pressure environments)?*
- 3. Or how would one evaluate the job fitness of someone predicted to develop Huntington's disease?*

With the advent of these many genetic tests, individual's genomic fingerprints will be stored with multiple organizations. This sensitive information needs to be safeguarded to prevent inappropriate requisitions of the data, for instance from employers who claim a right to the information because tests were paid for through workplace health insurance (Case studies 6 and 7).

The US government has liberally interpreted old statutes regarding equity in the workplace to include genetic inequities. For instance, the Americans with Disabilities Act has been adopted by the Equal Employment Opportunities Commission to include persons with genetic conditions. However, Supreme Court justices have publicly expressed hesitation for supporting this inclusion. Similarly, the Civil Rights Act could be liberally read to include protection against workplace discrimination towards persons of a particular ancestral group (that might, for instance, have a higher incidence of a particular genetic condition). Unfortunately, neither one of these statutes explicitly protects an employee from the use of genetic information against them in the workplace. However, at least there has been legislation in place (2000) to protect federal employees from this type of discrimination.

U.S. legislators have long been aware of the importance of protecting the privacy of genetic information, and legislation has been introduced multiple times to try to formalize this requirement over the last decade or so. After 13 years of legislative limbo, the Genetic Information Nondiscrimination Act of 2008 (GINA) finally passed. The act is designed to protect individuals from health insurance and employment discrimination as a result of their genetic information, and as such, Senator Ted Kennedy called this the “first new major civil rights bill of the new century.” GINA prohibits health plans from denying coverage to or raising insurance premiums of clients solely on the basis of predisposition to developing a genetic condition in the future. GINA also prevents employers from using genetic information in hiring, firing, job placement, or promotion decisions; however, these protections do not extend to services members in the military or to employees working at an entity with fewer than 15 employees. Passage of these types of protections for patients will likely make subject recruitment for genetic studies easier as well, and ultimately, will lead to more effective treatments for genetic disorders.

Privacy of genetic information further reading

1. KL Hudson (2007) Prohibiting Genetic Discrimination. *N Engl J Med.* 356:2021-2023. doi: 10.1056/NEJMp078033.
2. KL Hudson, MK Holohan, and FS Collins (2008) Keeping Pace with the Times – The Genetic Information Nondiscrimination Act of 2008. *N Engl J Med.* 358:2661-2663. doi: 10.1056/NEJMp0803964.

Economics of precision medicine

Case study 8: Nitromed and BiDil

BiDil is a combination pill containing two drugs used to treat heart failure: isosorbide dinitrate (an NO donor) and hydralazine (a vasodilator and antioxidant). Roughly five million Americans suffer from heart failure, and many are successfully treated with ACE (angiotensin converting enzyme) inhibitors. In the original clinical trials conducted by Medco Research, BiDil did not seem to offer any statistically significant improvement to heart failure treatments and was not approved for use by the FDA. Later on, when Nitromed acquired the rights to the BiDil compound, they reanalyzed the same data and noticed a 47% reduction in one-year mortality among African Americans.

Consequently, they rushed to file a patent for race-specific use of BiDil which protects this market for them until 2020. Clinical trials have verified the initial observation; in these studies, BiDil offers a 43% reduction in mortality after one year. Because of these dramatic effects, the trial was halted, and BiDil was offered to all participants, including those who had been taking placebos. The FDA Cardiovascular and Renal Drugs Division approved the use of BiDil as the first race-specific drug in June 2005. Under this definition, Nitromed risks overlooking numerous non-African American patients who could benefit from this drug. In fact, because most (70%) European American heart failure is due to heart attack or chronic heart disease while much (50%) African American heart failure is a result of hypertension, scientists have speculated that BiDil is actually more effective for hypertensive patients than the more general racial categories. In addition, racial groupings do not take into account environmental or social factors such as access to healthcare.

Question prompts

- 1. Is race an appropriate placeholder for genetic information?*
- 2. Is Nitromed trying to inappropriately capitalize on the projected one billion dollar revenue protected by their race-specific patent?*

Case study 9: Cassidy v. SmithKline Beecham

SmithKline Beecham (SKB) developed a Lyme disease vaccine that, after FDA approval, it became apparent that about one-third of the population would react poorly to the vaccine. Individuals with the HLA-DR4+ genotype were susceptible to developing autoimmune arthritis in response to the vaccine. SKB did not warn patients of this complication on the label, and was sued in a class action lawsuit by individuals who developed autoimmune arthritis in response to vaccination. Due to negative publicity, sales of the vaccine plummeted, and SKB had to pull the product from the market.

Question prompts

- 1. What conditions would have to be met before such a vaccine could be responsibly released to the American public?*
- 2. What are some unintended economic consequences of development of genetic and pharmacogenetic treatments?*

Pharmacogenetic technology's expense poses a problem to the end consumer, but these expenses could potentially prevent the product from even making it to the market. The higher cost of pharmaceutical development for a smaller target population violates elementary market analysis and business strategy. However, the potential to improve performance in clinical trials, thereby sparing the expense of a late stage clinical trial failure and enhancing market views of the product, may make the development of these drugs worthwhile. One potential complication that may arise from distribution of these types of drugs is that they may become associated with a particular race or ethnicity rather than individuals of a particular genotype. In fact, the FDA recently approved the first race-based medication (Case study 8).

The BiDil case highlights the potential abuse of using race as a proxy for information about pharmacogenetics – that is the genes that contribute to a patient's drug response. On the other hand, when the pharmacogenetic information is known, if patients of a particular genotype are not adequately informed of the relationship between their genotype and the clinical

outcome of taking the medication, the pharmaceutical company may be left responsible for any negative outcome (Case study 9).

Case study 10: The Pseudo Xanthoma Elasticum patent

After having two children with Pseudo Xanthoma Elasticum (PXE), Sharon and Patrick Terry became founders and administrators of PXE International, a patient support group. PXE is a genetic disorder that causes connective tissue in the skin, eyes, and arteries to calcify, eventually leading to blindness, premature aging, and gastrointestinal bleeding. To understand the genetic basis of PXE, the two created a Biobank of samples that they provided to University of Hawaii researchers. Both PXE International and the University of Hawaii are listed as inventors on the patent application that resulted from the discovery of the PXE gene. This is the first example of intellectual property and benefit sharing by the patients and the inventors, and the Terry's are working towards establishing additional Biobanks for more genetic diseases with the same intellectual property conditions of use.

Question prompts

- 1. Will patients' setting intellectual property conditions hinder the progress or pace of research?*
- 2. What should happen to the money rewarded back to the patient support groups?*
- 3. Should companies profit from patient sample banks?*
- 4. How do legal context and business practices impact availability and efficacy of genetic and genomic tests?*
- 5. What is being done in the scientific community in order to place the well-being of the patients first?*

Another economic aspect of genetics involves patenting rights to inventions. Of course, before a genetic technology can be developed therapeutically, scientists must understand more about the genetic basis of their disease of interest. This typically requires access to sample banks of patient DNAs and tissues. Many of the resulting inventions, of course, will be based directly on the sequence of the gene they involve, and when genes were first being sequenced, there was a bonanza on gene patents issued by the US Patent and Trademark Office (USPTO); in fact, currently 20% of our genes are patented. Since that time, the USPTO has developed a more scientific understanding of how to apply their thresholds of novelty, innovation, and utility to genetic patents. Furthermore, issues related to gene patents were put on trial in a case filed by the ACLU (Association for Molecular Pathology v. Myriad Genetics). Myriad's monopoly on the BRCA1 and BRCA2

genes was put to an end when the Supreme Court ruled on June 13, 2013 that because “genes are products of nature,” they cannot be patented. However, even with the appropriate granting of patents for innovative genetic tests, there have been unintended consequences, such as the exclusive holding of research information concerning genetic mutations that are pathogenic, including Myriad’s proprietary database of breast and ovarian cancer-causing mutations. The American College of Medical Genetics has issued a statement that this information should be deposited in publically accessible databases, and the NIH has stepped up by sponsoring creation of the ClinGen and ClinVar databases for this purpose. Research scientists funded by the NIH are required to deposit relevant correlations between disease and genetic variants in these databases, and some companies have even started depositing de-identified test results as well. With patent criteria becoming more established, a remaining question becomes how does a corporation appropriately recognize the contribution of the patients to its invention (Case study 10)?

Economics of precision medicine further reading

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2. MG Bloche (2004) Race-Based Therapeutics. *N Engl J Med* 2004; 351:2035-2037. doi: 10.1056/NEJMp048271.
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5. KL Hudson (2011) Genomics, Health Care, and Society. *N Engl J Med* 2011; 365:1033-1041. doi: 10.1056/NEJMra1010517.

Whole exome / genome sequencing

Case study 11: The Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) Project

The National Human Genome Research Institute is sponsoring a series of studies to explore the implications, challenges, and opportunities associated with genomic sequencing of newborns. One of these studies, the BabySeq project, aims to assess the risks and benefits of sequencing newborns' DNA in comparison to conventional newborn screening using biochemical analysis of blood obtained from a neonatal heel prick. The project is designed to conduct full exome sequencing for both healthy and very sick infants to assess the full protein-coding portion of the babies' genomes. Initial results from the first 51 participants have uncovered a range of findings including frequent identification of carriers for recessive disorders, two babies with pharmacogenetic variants, three with mutations associated with heart conditions (although the babies and their parents appear healthy), and one with a mutation in the BRCA2 gene. The American Society of Human Genetics has taken the position that only newborns with undiagnosed conditions should undergo genome sequencing, preferably only analyzing genes that are likely to explain the disorder, ostensibly to minimize the possibility of incidental/secondary findings. Sequencing of healthy newborns does not fall within this guideline, and the sharing of the BRCA2 finding does not fall within this recommendation either, but it *is* considered an actionable medical finding by the American College of Medical Genetics and Genomics. As such, this result was returned to the family of the baby, after reconsideration of the scientists' initial agreement to only tell parents about variants that would impact babies during their childhood.

Question prompts

- 1. Do you believe that informed consent guidelines for proceeding with genetic testing should differ between targeted gene tests versus whole genome sequencing?*
- 2. Should a patient's right not to know apply to informing a patient of incidental/secondary findings in whole genome sequencing?*
- 3. How does a patient's right not to know apply to children versus adults?*

4. *Will testing of healthy individuals lead to unnecessary medical follow-up?*
5. *How should duty to re-contact be managed if variant interpretation changes in the future?*

Genetic testing can be a powerful tool in preventative medicine, but the value of testing when no treatment is indicated or available has been widely contested. The American College of Medical Genetics (ACMG) recommends in their Policy on Genetic Testing in Children and Adolescents that *"if the medical or psychosocial benefits of a genetic test will not accrue until adulthood, as in the case of carrier status or adult-onset diseases, genetic testing generally should be deferred."* Therefore, testing prenatally or neonatally for adult-onset diseases is generally not recommended. The results of this type of test, when administered prenatally, could potentially be used to selectively terminate pregnancies for conditions that may be treatable once the child grows old enough to exhibit the phenotype. Although this recommendation from the ACMG does guide geneticists in what prenatal tests can be offered, this is clearly not a one-size-fits-all recommendation. Furthermore, there are no legal guidelines stemming from these recommendations, so the same "slippery slope" of what types of traits can be tested for by preimplantation genetic diagnosis (PGD) applies to prenatal testing. Notably, there are already documented cases of PGD for BRCA1 mutations, for example.

The ethical complexities of genetic testing are especially evident in the case of whole genome or whole exome sequencing. A recent ACMG policy recommends sharing the results of a particular set of medically actionable, whole exome sequencing incidental/secondary findings. This list of genes to be reported back to the patient included adult-onset conditions, regardless of the age of the patient. Furthermore, the patient is not able to opt out of receiving these test results because of the complexities of gaining informed consent for each and every individual genetic test result included on the list of reportable incidental/secondary findings. This blanket strategy seeks to simplify the informed consent process, but it doesn't give due consideration to the approach of generic consent, where categories of genetic tests could be considered together. Importantly, the ability to accurately classify variants as pathogenic, benign, or of unknown significance will change over time, and as these classifications change, the question of whether there is a duty to recontact the patients

emerges as well. The experts who participated in drafting this policy readily admit it is imperfect and suggest frequent review of these standards as the technology is developing at breakneck pace.

Whole exome / genome sequencing further reading

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6. Y Yang et al. (2013) Clinical Whole-Exome Sequencing for the Diagnosis of Mendelian Disorders. *N Engl J Med.* 369:1502-1511. doi: 10.1056/NEJMoa1306555.
7. IAP Derks-Smeets et al. (2014) Hereditary breast and ovarian cancer and reproduction: an observational study on the suitability of preimplantation genetic diagnosis for both asymptomatic carriers and breast cancer survivors. *Breast Cancer Research and Treatment.* 145(3): 673–681. doi: 10.1007/s10549-014-2951-5.
8. LG Biesecker and RC Green (2014) Diagnostic Clinical Genome and Exome Sequencing. *N Engl J Med.* 370: 2418-2425. doi: 10.1056/NEJMra1312543.
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Along with the remarkable pace of scientific progress comes new responsibilities for the scientists, particularly in these cases, to make sure genetic information and concepts are used responsibly. It is the job of our health professionals to remain educated on these developments and to impart expertise to the many social debates of this post-genomic era. Good luck!