Review

Medical Ethics for the Genome World

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Kelly E. Ormond

*From the Department of Genetics, Stanford University,
Stanford, California*

Medical genetics, and in particular the areas of genetic testing and genetic counseling, are replete with ethical and social issues. This review provides readers with a summary of the genetic testing and counseling process, as well as the clinical challenges that can lead to ethical dilemmas during these processes. Using a clinical medical ethics approach, several hypothetical case scenarios are presented and discussed to provide examples of the ethical issues that can arise. (J Mol Diagn 2008, 10:377–382; DOI: 10.2353/jmoldx.2008.070162)

Patients and families consider and undergo genetic testing for a range of reasons, including testing for conditions that are heritable (typically in a Mendelian manner) or those that occur because of molecular or cytogenetic variation in an individual, either in a heritable or *de novo* manner. Additionally, such testing may occur at various points throughout the life cycle. Prospective parents may contemplate prenatal diagnosis through amniocentesis or chorionic villus sampling, or even serum screening or ultrasound, to gain information on the health of their future child; some testing can even be performed through preimplantation genetic diagnosis.¹ Prenatal genetic testing may occur either because of a family history, in response to a screening test (eg, serum screening or an ultrasound) that suggests an increased risk for a genetic and/or congenital disorder, or because of age or ethnicity (as is the case with genetic carrier testing done on parents). Parents with a child who has medical or cognitive problems may request a genetic evaluation and/or genetic testing to help determine whether there is an underlying genetic disorder that is causing their child's medical issues, and to gain information about future prognosis and reproductive recurrence risks. Teens or adults with a medical problem may undergo genetic testing to deter-

mine a cause for their medical issues. Finally, individuals with a family history of a known or potential genetic condition may undergo predictive testing to determine whether they carry a gene mutation that increases their susceptibility to the condition.²

For all genetic testing, regardless of the clinical situation, there are several challenges that can lead to ethical dilemmas. First, it is important to remember that genetic diagnoses can be made not only by tests that examine DNA through mutation analysis, sequencing, or karyotyping but also through biochemical analysis (eg, through an amino acid screen that diagnoses phenylketonuria) or even through tumor immunohistochemistry (when pathognomonic findings are identified). Even when a DNA test is performed, some mutations might have decreased penetrance, and the detection of a mutation or variant of uncertain significance might have unclear clinical implications for the individual. Genetic testing, which may have decreased sensitivity depending on the type of testing performed, is always made more interpretable by testing an affected family member to establish informativeness. If an unaffected individual tests negative, it is unclear whether he/she did not inherit the familial mutation or whether a mutation exists in another gene, and therefore testing of an affected family member to identify whether a mutation can be detected is most clinically useful.³ The need for family samples in some clinical genetic testing and/or genetic research studies may, however, increase the chance that nonbiological family relationships may be revealed (eg, nonpaternity), and clinicians may need to determine whether this information should be, or needs to be, revealed and if so in what manner and to whom.⁴ Once a mutation is detected (or not), responses to this genetic information can be complex, and

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Address reprint requests to Kelly Ormond, 300 Pasteur Dr. H315, Stanford CA 94305-5208. E-mail: kormond@stanford.edu.

in contrast to traditional medicine in which the individual patient is the focus, genetic test results impact this individual and his/her family, and this should be considered in testing situations.⁵

Genetic testing results can lead to a range of responses by individuals and families, and it is important for those conducting genetic testing to consider these issues. True negative results (meaning that an individual does not carry a known mutation in the family) can lead to relief and a reduction in unnecessary invasive screening,^{6,7} but they can also lead to survivor guilt, concerns over care-giving responsibilities if the individual is the only unaffected family member, and the need to entirely reframe one's self-image.⁸ Positive results may lead to informed decisions regarding medical screening and interventions (eg, increased or earlier surveillance, prophylactic surgeries to reduce risks),^{6,7} but they can also lead to anxiety about if and when medical problems may occur^{9,10} and, in some extreme cases, the avoidance of screening because of a sense of genetic determinism. Positive results can also lead to anxiety about reproductive decision-making and can influence social life planning in various ways (eg, education, employment decisions). Finally, positive results can raise challenges in terms of informing other at-risk family members, particularly when family members are not socially close,^{5,11} and various demographic factors such as the gender of the proband and relative seem to impact who receives information regarding family genetic information.^{5,12}

Genetic counseling is a process that often accompanies genetic testing, and is primarily performed by individuals with special training in genetics, such as masters trained genetic counselors (National Society of Genetic Counselors, www.nsgc.org), clinical geneticists, or nurse geneticists. Other health care providers also perform genetic counseling on various levels as part of their scope of practice. The genetic counseling process initially involves a diagnostic component whereby information is collected to establish a differential diagnosis in the family or individual (often collecting family medical history and reviewing medical records). This is a critical component of the genetic counseling process because the accuracy of a differential diagnosis substantially influences the specific testing that is performed, and an incorrect test with negative results can be misleading to patients. Risk assessment involves reviewing the family and personal medical histories to estimate the likelihood of the individual(s) having the genetic condition in question. Patients are then educated about the range of options for genetic testing and the risks and benefits of undergoing genetic testing. Information should be tailored to the individual circumstances and values, and the genetic counselor should help the patient determine what impact testing decisions may have.^{2,3}

In genetics, there are a range of areas that lead to potential ethical dilemmas: i) confidentiality and privacy issues, which relates to disclosure of genetic information and results to third parties, and the concept of duty to warn as it may relate to at-risk relatives; ii) the potential for genetic discrimination; iii) autonomy and informed consent in decision-making; iv) just resource allocation and access, including the question of who should be tested,

when and who makes these decisions; and v) issues related to variation, including aspects of disease versus trait. As in all medical ethics, issues of decisional capacity, surrogate decision-making, and end of life issues can also arise, although they are more generalizable to other areas of medicine. When conducting an ethical case analysis, Jonsen and colleagues¹³ suggest that one must consider the medical facts (and the level of certainty or uncertainty associated with the facts), patient preferences, quality of life aspects including prognosis and biases, and the social and familial context. Other approaches to ethical analysis include a principles-based approach (eg, Beauchamp and Childress),¹⁴ or a casuistry model, using case-based reason from related case types as the basis to ethically analyze a case (eg, Jonsen and Toulmin).¹⁵ Finally, although legal aspects relevant to one's clinical actions remain separate from ethical considerations, both the law and professional standards and recommendations should be reviewed and considered when formulating a plan for action in a case that presents ethical difficulties.

Case Studies

Below are several hypothetical cases to illustrate these issues:

Case 1: Informed Consent

A 33-year-old patient presents to a genetic counselor for Tay-Sachs carrier screening because she and her partner are of Ashkenazi Jewish descent; she is at 15 weeks gestation. Your laboratory currently screens for 11 conditions (including Tay-Sachs) that are more common in the Ashkenazi Jewish population; the carrier frequencies range from ~1 in 10 (Gaucher disease) to >1 in 100 (Bloom syndrome and Fanconi anemia) and have a range of clinical severity ranging from fatal in early childhood (Tay-Sachs, Canavan disease) to having significant variability up to diagnosis in adulthood with reduced penetrance and expression (Gaucher disease). Only Gaucher disease is currently treatable. The patient's genetic counselor explains that there are multiple conditions for which testing is available and that the patient and her partner are at increased risk of carrying. (S)he also explains to the patient that test results will take ~2 weeks, and if she is found to be a carrier the next step will be to test the patient's partner. If both are found to carry the same condition, the fetus will be at 25% risk of having that condition, and prenatal testing would be available and highly accurate, but if testing is performed in this step-wise manner, prenatal diagnosis would be offered at ~19 to 20 weeks of gestation with results not available until 21 to 22 weeks of gestation. Because this may then limit and/or complicate the patient's decision-making and reproductive options if the fetus is found to be affected, the patient may want to undergo concurrent screening of the partner at the same time, to save up to 2 to 3 weeks on this timeline in the event that prenatal diagnosis is performed. The patient states that she only wants herself screened and only for Tay-Sachs disease because this is the only condition that her doctor has mentioned to her.

Several issues arise in this case regarding autonomy, specifically whether or not the patient is providing informed consent for the genetic carrier screening. Informed consent is not just a signature on a consent form, but rather it is a process that ensures that patients have the ability to comprehend the relevant issues and the freedom from coercion (autonomy) to make a decision.^{16,17} In this case, the question arises as to whether the patient is making an autonomous and informed decision based on an understanding of the testing process, or if she is simply responding to the direction provided by her physician. Patients make decisions in different ways; it may be perfectly appropriate for this patient to defer to her physician's recommendations, but it is also possible that she is doing so as a reaction to the overwhelming amount and type of information she is receiving. What information should be provided, at a bare minimum, to patients contemplating genetic testing? And how does the quantity and quality of information provided relate to the woman's reproductive decisions, including the potential future choice to terminate a pregnancy affected with a condition ranging in symptoms from Tay-Sachs to Gaucher disease? As genetic testing, particularly carrier testing, increases in the number and range of conditions for which testing is offered as part of a single panel, it becomes complicated to determine what information should be provided to prospective parents so that they can make an adequately informed decision about whether to undergo screening or not.¹⁸ Data suggest that patients can become overwhelmed and anxious in response to significant amounts of information, but there is little data available to provide health care providers with information about the best ways to inform patients about testing options or what patients want to know. Assuring that patients have the information and opportunity to make informed decisions as testing options continue to increase will remain a clinical challenge.

Case 2: Family Disclosure, Confidentiality, and Duty to Warn

A neurologist at your center calls to state that he has recently seen a female patient with a family history of Huntington's disease (HD). The patient expressed a desire for predictive testing for HD, and blood was drawn. After 6 weeks, the patient called for results and was informed that the laboratory would not process the sample unless she went through a formal testing protocol (Huntington's Disease Society of America; www.hdsa.org and Benjamin et al¹⁹). The patient met with a genetic counselor, who learned through taking the family history that the patient's grandmother had HD, but that her father, who was at 50% a priori risk, had no symptoms to date (although he had not been formally evaluated by a neurologist) and did not want to know his predictive status. At his age and assuming he was truly asymptomatic, his residual risk to carry a CAG expansion in the HD gene was 31.5%.²⁰ The genetic counselor explained to the patient that if she was tested and had a positive result, it would in effect also predictively diagnose her father with HD. A negative result would not provide infor-

mation on her father's HD status. The genetic counselor also learned that the broader family was not aware of the HD (the patient had inadvertently learned of it and discussed it only with her father); the patient had a brother who had recently had a baby, and she did not intend to tell him about the familial risks for HD or her own testing process because she did not want to dampen the excitement about the new baby.

With genetic information we challenge the traditional medical paradigm that medical information is individual and protected as such; genetic information is, by default, about the family and can potentially impact other individuals. This case raises the questions "whose information is it?" and "who should decide when testing is performed?" Does the health care provider and laboratory have any duty to protect the father's right not to know his HD status? Is there an obligation (either by the health care or laboratory providers, or the patient's father) to provide this information to the daughter, who may make social decisions, such as regarding her job, marriage, or reproductive decisions, based on her at-risk status? What about obligations to warn the brother about his at-risk status, potentially before he and his partner have additional children? Would our obligations to the various family members change if this condition were one in which surveillance and/or treatment were available?

When considering this case using a principles-based approach, the health care provider can first consider the potential for beneficence (doing good) and for maleficence (doing harm) to both the patient and the other family members; often what is a beneficent for one person has the potential of causing harm in another. For example, although it may promote beneficence for the patient to maintain the patients' confidentiality, doing so may ultimately create risk and maleficence for her relatives and may restrain their autonomy as they cannot make informed decisions regarding their health risks. Similarly, conflicts may occur in trying to promote the autonomy of both the father (and his desire for privacy and decision not to know) and daughter (who desires to know her at-risk status). Principles-based approaches do not always resolve these conflicts, although one may take into account that only the daughter is officially your patient.

To answer the questions raised about duty to warn, we can also consider classic legal cases such as *Tarasoff v the Regents of the University of California*,²¹ currently existing policies regarding medical confidentiality, and federal laws such as the *Health Information Portability and Accountability Act (HIPAA)*. Traditional medical confidentiality protections suggest that we hold information about patients to be private and that disclosure without the patients' permission can only occur if the person at-risk is identifiable, the situation at risk is severe and potentially preventable (ie, *Tarasoff*). As has already been stated, the doctor-patient relationship (and therefore its privacy obligations and other duties) extends only to the person with whom the medical relationship exists, rather than to their family members; this means that a patient's autonomous decision not to tell potentially at-risk family members is typically honored. Few conditions (eg, infectious and sexually transmitted diseases) meet the standards to

breach confidentiality, which include substantial risk to an identifiable person and the chance that harm can be averted or minimized because of breach of confidentiality, and that these risks are less than the risks from not disclosing the information.¹⁷

The question arises as to whether inherited conditions that meet the criteria used in other disclosure situations, and which by definition can impact family members beyond the single patient in the doctor-patient relationship, should broaden the clinical view of the patient to include the family, thereby suggesting a duty to warn other at-risk individuals. Beyond the clear responsibility for health care professionals to inform patients of genetic risk (as was found in *Pate v Threlkel*²²), it seems reasonable that they should also strongly encourage individuals to relate genetic risk information to their at-risk relatives (as was found in *Safer v Estate of Pack*²³). However, it remains unclear how such cases should be handled if the patient is aware of a potential or known heritability and if they actively decline to tell at-risk relatives. Of note, the only two legal cases that have tried the concept of duty to warn in the genetics specialty (*Pate v Threlkel*²²; *Safer v Estate of Pack*²³) were both inherited cancer cases, in which the potential for surveillance and/or early intervention may have impacted the at-risk offspring. *Pate*²² found that informing the patient of the inherited nature of the condition was adequate, and *Safer*²³ found that the physician had a higher duty to strongly encourage the provision of this information to at-risk relatives. However, it remains unclear what the legal and moral duties are for professionals to warn at-risk relatives when they are not otherwise being informed by their relatives, and the decisions may vary depending on the severity, treatability, and surveillance available for the condition in question.²⁴

Case 3: An Inadvertent Genetic Test

A 60-year-old man presents with late-stage colon cancer. There is no family history of colon cancer, but the man's mother died of endometrial cancer in her 60s. Immunohistochemistry testing performed on his colon tumor suggests that the man probably has hereditary nonpolyposis colorectal cancer, an autosomally dominant form of cancer with moderate penetrance. Although a genetic test will now be performed to confirm this result, his health care provider tells him these results and informs him that his adult children may be at increased risk and should be informed so that they can begin regular screening immediately. The man is primarily concerned about his own cancer treatment, and does not know how or when to tell his family about the information. He did not realize that he was even having this testing performed when he had surgery, and he did not know that it might reveal predisposition to cancer for his family members or impact their medical management. He does not want to give the family anything else to worry about and feels guilty that they will now need to worry about this.

Genetic testing can be performed on symptomatic individuals to determine the cause of their symptoms (eg, doing

an ataxia panel on a patient with ataxia), and genetic information can also be inadvertently obtained through pathognomonic findings on other tests. In these situations, patients may not provide informed consent for this information and may not even be aware that such results can and will be obtained. Although unexpected medical results can arise from a variety of medical tests (and are not limited to genetic test results), this can lead to significant psychological impact and anxiety when patients are given the genetic information and informed that it may change the management of their condition (eg, change their surgical options) and that their family members are at-risk and should be informed. For laboratory directors, this case also raises the question about what role, if any, they have in ensuring that patients are providing appropriate informed consent for tests that provide genetic information.

After genetic tests confirm a mutation that is associated with hereditary nonpolyposis colorectal cancer, the man decides ultimately to tell his family, and his son contemplates undergoing genetic testing, which would be highly accurate for the known family mutation. However, because the son works for a small company, he is concerned that if he undergoes testing and is found to carry the same hereditary nonpolyposis colorectal cancer mutation that his father has he might not be able to obtain health insurance coverage or even to get the colonoscopies that his doctor has recommended. He is also worried that if he changes jobs, a predisposition mutation would be considered a pre-existing condition if he applied for new insurance. He is frustrated in deciding whether to have the genetic test or not given his potential fears about genetic discrimination.

Although there are few cases of documented genetic discrimination in asymptomatic individuals, the fear of genetic discrimination keeps some individuals from undergoing genetic testing, or sharing results with their health care providers, when it could be helpful to their medical management.^{25,26} Federal legislation is currently under consideration (see summary at Genetic Information Nondiscrimination Act: 2007–2008 at <http://www.genome.gov/24519851>, accessed February 6, 2008), and many states have protection for health insurance and employment discrimination, but coverage varies from state to state (National Conference of State Legislatures: Genetics Laws and Legislative Activity: <http://www.ncsl.org/programs/health/genetics/charts.htm>, accessed February 6, 2008²⁶) and may not encompass small employers who self-insure. Patients should be apprised of the small potential for genetic discrimination as part of the informed consent process and should weigh this risk against the potential benefits of genetic testing.

Case 4: Access and Justice Issues in Genetic Test Development

You are contacted by the head of a support group for Detroit disease (note: not a real condition). This is a relatively rare condition, and the gene has not yet been localized. The support group is willing to provide your laboratory with 200 samples to map and localize the gene

for Detroit disease because they want their families to have access to genetic testing as soon as possible. You find and patent the gene and begin to offer testing. Several years later, your laboratory has developed sequencing methodology that makes it substantially easier and less expensive to sequence the gene for Detroit disease. Through a licensing agreement, other commercial laboratories now offer tests for the 15 or 30 more common mutations at a cost of \$150 or \$250, respectively. Knowing that only ~50% of those who carry the mutation will be detected by these other tests, and therefore that you will have a solid market for the testing, you set the price for sequencing at \$3000.

The ethical principle of justice implies that individuals should have just access to medical services, such as genetic testing. To provide services in ethical accord with this principle, there are several issues that arise. First, there is the need to develop genetic tests for rare disorders, a process that typically begins with a research laboratory developing and offering a test for a condition and ultimately leads to clinical testing availability through CLIA-approved laboratories. Patents, which are typically thought of as incentives to produce new products, have been seen as inhibitory to the genetic testing process.²⁵ Clinical genetics services report that gene patents increase fees to laboratories and patients (typically through licensing of the right to test for variants in a gene) and that they are increasingly likely not to develop or perform certain tests because of such patents.²⁵ This leads to concerns that only those who can afford expensive genetic tests will be able to access this potentially important technology. There are several reports of gene patents being used to charge significantly increased test fees, and conflicts with patient groups who have contributed their biological samples and are subsequently unhappy with family members and other affected persons being required to pay substantial test fees. Some groups have even developed a process to maintain joint ownership of any intellectual property developments arising from genetic research (eg, PXE International).^{27,28} It is critical that we find ways to ensure that patients of all socioeconomic status and cultural backgrounds are able to learn about and afford genetic testing if they desire it.

Note Added in Proof

After this paper was accepted, the Genetic Information Nondiscrimination Act: 2007–2008 was signed into law (May 21, 2008).

Conclusions

Clinical genetics and genetic testing raise a range of ethical issues related to patient autonomy, patient confidentiality, informed consent, and justice. All health care professionals, from physicians and nurses to laboratory professionals, should be aware of these issues, and should take them into consideration when they are involved in the

genetic testing process and when setting policies regarding genetic testing.

References

1. Simpson JL, Elias S: Genetics in Obstetrics and Gynecology, ed 3. Philadelphia, Saunders, 2003
2. Ciarleglio LJ, Bennett RL, Williamson J, Mandell JB, Marks JH: Genetic counseling through the lifecycle. *J Clin Invest* 2003, 112:1280–1286
3. Bennett RL, Hampel HL, Mandell JB, Marks JH: Genetic counselors: translating genomic science into clinical practice. *J Clin Invest* 2003, 112:1274–1279
4. Lucast EK: Informed consent and the misattributed paternity problem in genetic counseling. *Bioethics* 2007, 21:41–50
5. Ormond KE, Mills PL, Lester LA, Ross LF: Effect of family history on disclosure patterns of cystic fibrosis carrier status. *Am J Med Genet C Semin Med Genet* 2003, 119:70–77
6. Botkin JR, Smith KR, Croyle RT, Baty BJ, Wylie JE, Dutson D, Chan A, Hamann HA, Lerman C, McDonald J, Venne V, Ward JH, Lyon E: Genetic testing for a BRCA1 mutation: prophylactic surgery and screening behavior in women 2 years post testing. *Am J Med Genet A* 2003, 118:201–209
7. Lynch HT, Snyder C, Lynch JF, Karatoprakli P, Trowonou A, Metcalfe K, Narod SA, Gong G: Patient responses to the disclosure of BRCA mutation tests in hereditary breast-ovarian cancer families. *Cancer Genet Cytogenet* 2006, 165:91–97
8. Valverde KD: Why me? Why not me? *J Genet Couns* 2006, 15:461–463
9. Kerruish NJ, Campbell-Stokes PL, Gray A, Merriman TR, Robertson SP, Taylor BJ: Maternal psychological reaction to newborn genetic screening for type 1 diabetes. *Pediatrics* 2007, 120:e324–e335
10. Michie S, Bobrow M, Marteau TM: On behalf of the FAP Collaborative Research Group: predictive genetic testing in children and adults: a study of emotional impact. *J Med Genet* 2001, 38:519–526
11. Green J, Richards M, Murton F, Statham H, Hallowell N: Family communication and genetic counseling: the case of hereditary breast and ovarian cancer. *J Genet Couns* 1997, 6:45–60
12. Patenaude AF, Dorval M, DiGianni LS, Schneider KA, Chittenden A, Garber JE: Sharing BRCA1/2 test results with first degree relatives: factors predicting who women tell. *J Clin Oncol* 2006, 24:700–706
13. Jonsen AR, Siegler M, Winslade WJ: Clinical Ethics, ed 4. San Francisco, McGraw Hill, 1998
14. Beauchamp TL, Childress JF (2008). Principles of Biomedical Ethics. 6th ed. Oxford University Press. New York, NY
15. Jonsen AR, Toulmin S (1998). The abuse of casuistry: A history of moral reasoning. University of California Press. Berkeley, CA
16. Lidz CW, Applebaum PS, Meisel A: Two models of implementing informed consent. *Arch Intern Med* 1988, 148:1385–1389
17. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research: Making Health Care Decisions. Washington, DC, GPO, 1982
18. Ormond KE, Iris M, Banuvar S, Minogue J, Annas GJ, Elias S: What do patients prefer: informed consent models for genetic carrier testing. *J Genet Couns* 2007, 16:539–550
19. Benjamin CM, Adam S, Wiggins S, Theilmann JL, Copley TT, Bloch M, Squitieri F, McKellin W, Cox S, Brown SA, Kremer HPH, Burgess M, Meshino W, Summers A, Macgregor D, Buchanan J, Greenberg C, Carson N, Ives E, Frecker M, Welch JP, Fuller A, Rosenblatt D, Miller S, Dufrasne S, Roy M, Anderman E, Prevost C, Khalifa M, Girard K, Taylor S, Hunter A, Goldsmith C, Whelan D, Eisenberg D, Sultan H, Kane J, Shokeir MHK, Gibson A, Cardwell S, Bamforth S, Grover S, Suchowersky O, Klimek M, Garber T, Gardner HA, MacLeod P, Hayden MR: Proceed with care: direct predictive testing for Huntington disease. *Am J Hum Genet* 1994, 55:606–617
20. Harper PS, Newcombe RG: Age at onset and life table risks in genetic counseling for Huntington's disease. *J Med Genet* 1992, 29:239–242
21. Tarasoff v the Regents of the University of California, 551 P 2d 334 (Cal 1976)
22. Pate v Threlkel, 661 So 2d 278 (Fla 1995)
23. Safer v Estate of Pack, 677 A2d 1188 (NJ App), appeal denied, 683 A2d 1163 (NJ 1996)

24. Offit K, Groeger E, Turner S, Wadsworth EA, Weiser MA: The "duty to warn" a patient's family members about hereditary disease risks. *JAMA* 2004, 292:1469–1473
25. Apse KA, Biesecker BB, Giardiello FM, Fuller BP, Bernhardt BA: Perceptions of genetic discrimination among at risk relatives of colorectal cancer patients. *Genet Med* 2004, 6:510–516
26. Clayton EW: Ethical, legal and social issues of genomic medicine. *N Engl J Med* 2003, 349:562–569
27. Cho MK, Illangasekare S, Weaver MA, Leonard DG, Merz JF: Effects of patents and licenses on the provision of clinical genetic testing services. *J Mol Diagn* 2003, 5:3–8
28. Smaglick P: Tissue donors use their influence in deal over gene patent terms. *Nature* 2000, 407:821