

*Virtual Mentor*  
American Medical Association Journal of Ethics

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Ethical Questions in Genetic Testing

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# Virtual Mentor

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## If You Build It

Ten years and counting. This month marks a decade of continuous publication for *Virtual Mentor* (*VM*). Numerous feature and layout improvements have been made since we built and debuted our first issue of *VM*. Through all the changes, our editorial mission has remained true and unchanging—to strengthen the ethics and professionalism of the next generation of physicians.

We have strived to fulfill this mission by delivering practical guidance to help medical students and resident physicians better address ethical scenarios in their everyday professional lives. Hundreds of case-based scenarios, each accompanied by expert commentaries, have been published and are archived in *VM* for easy access and use. These cases and the “mentoring” guidance that accompany them form the editorial foundation for every issue of *VM*.

To further ensure that we are covering topics of relevance to our core audience, most *VM* issues for the past 6 years have been edited by either a medical student or resident physician. Student and resident “theme issue” editors are selected each year through a competitive process. Each editor is responsible for selecting a topic to explore and works closely with the *VM* editorial staff from idea to ultimate publication of the issue. This journal has benefited tremendously from the energy, creativity, and dedication of our large and growing alumni group of issue editors.

These and other improvements that we have instituted no doubt contributed to the decision by the National Library of Medicine to accept *Virtual Mentor* as a MEDLINE-indexed journal. The development is an important milestone for any journal, and I want to extend my sincerest appreciation to all, especially editors and authors, who have contributed their time and expertise to the continuing growth and evolution of *VM*.

If you build (and renovate) it, they will come. I am happy to say that our readership has grown steadily over the past 10 years. I am confident that this growth reflects not only our value to our readers and stakeholders, but also our shared commitment to upholding and strengthening the core values of medicine.

My best,

A handwritten signature in black ink, appearing to be 'Ad' followed by a long horizontal flourish.

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# Virtual Mentor

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## FROM THE EDITOR

### Examining the Benefits and Harms of Genetic Information

This issue of *Virtual Mentor* is filled with questions about what kind of genetic information should be available to patients and their families. What conditions should we screen for in newborns? Is it too easy for patients to gain access to misleading information through Internet-based testing? Do doctors share too little with patients about the prospects of people with inherited disease and disability? Definitive answers to such questions, if there are any, may prescribe a course of action for physicians, but those actions will focus on the management of and access to genetic information more than the selection of medical therapy.

One fascinating aspect of the discussions in this month's *Virtual Mentor* is the role that patient autonomy plays in commentators' analyses of the desirability of genetic testing. This is most evident in the difference between commentators' opinions on genetic testing of minors and adults. In the case of minors, there is a suggestion that genetic information—the actual knowledge generated by genetic tests—has the potential to limit the child's future autonomy. In commenting on a clinical case of a toddler, Josh, whose parents want him tested for Huntington's disease, Robert Klitzman, Roberto Andorno, and Leon Dure come to the same conclusion—testing Josh now deprives him of his future right not to know about his risk (a choice made by 80 percent of adults at risk for Huntington's disease). Josh's father has inherited the gene for this degenerative neurologic disease, so Josh has a 50 percent chance of having it also. Klitzman, Andorno, and Dure also argue against the test because nothing can be done to stave off or cure the disease, so the information will not benefit Josh who, after all, is the patient. Moreover, positive test results could lead to parental decisions, about investing in education, for example, that would discriminate against Josh.

These reservations about the impact of genetic information reflect the policy of the American Medical Association, which states in its *Code of Medical Ethics*,

When a child is at risk for a genetic condition with adult onset for which preventive or other therapeutic measures are not available, genetic testing of children should not be undertaken" [1].

Anne-Marie Laberge and Wylie Burke, in their commentary on a case about a woman with the BRCA1 gene, believe that physicians' legal and professional duty to warn does not cover genetic risk. In the health law article Kristin E. Schleiter continues to touch on physicians' legal duty to warn both a patient and the patient's blood relatives who may be at risk from a genetically transmissible condition. Court cases have agreed that physicians have a duty to warn patients' at-risk relatives but

have disagreed on whether or not telling the patient of the familial risk satisfies that duty.

The thinking about genetic-testing practices changes when the discussion shifts from children to adults. The right of adults to seek genetic testing places an increased demand for information sharing on the counselor or physician supervising the test. In this context, respect for patient autonomy demands that physicians provide patients with a relatively sophisticated understanding of the implications of possible results of the test obtained. Kelly E. Ormond, a genetic counselor, points out ways in which physicians can become better prepared to help their patients achieve that understanding. In their commentary on a case about prenatal genetic testing, Anam Pal and Lubna Pal place similar emphasis on ensuring that physicians understand the risks and benefits of in vitro fertilization and preimplantation genetic diagnosis when discussing the topics with patients. Tali Geva and Ora Gordon describe how a thorough family history can invert this dynamic, making the patient the source of crucial information. Their thoughts on effective ways to take a family history are an important reminder that good medicine requires effective listening just as much as talking on the part of physicians.

In her policy forum article, Emily E. Anderson addresses the significant gaps in the regulation of direct-to-consumer (DTC) genetic tests, testing laboratories, and advertising that pose threats to consumers who are inadequately prepared to understand the meaning of and limitations to the information they receive. Oversight and restrictions can be imposed on each of these areas—and probably should be—because the DTC market for genetic testing is growing rapidly. Shane K. Green and Mike Spear also examine DTC genomic testing, suggesting the ways in which even genomic testing obtained without the assistance of a physician has the ability to empower patients, making them, perhaps, more responsible in their approach to health care decisions. Of course, they warn, the knowledge that one has increased risk of developing a gene-mediated illness may lead some people to give up and accept what they mistakenly think is their genetic fate.

Bernard M. Dickens and Ariel Williams examine conscientious objection and describe a form of professional obligation that prohibits physicians from placing their own values above their respect for patient autonomy when the standard of care in a given field conflicts with the physician's personal moral code.

The link between patient education and patient autonomy is central to Adrienne Asch and David Wasserman's position on the ethics of prenatal testing. In general, they support recent federal legislation that requires sharing different sorts of information with parents about the social and psychological prospects for children with diagnoses of genetic impairment. The heart of their argument is that patients should understand the broad implications of the diagnosis in order to make a rational, autonomous decisions. Don B. Bailey and his policy forum coauthors discuss emerging dilemmas in newborn screening, urging policy makers to think in terms of benefits rather than unsubstantiated possible harms when considering whether or not to test for a specific

condition.

Because genetic testing and the specific information it yields are relative newcomers to clinical practice, this issue of *Virtual Mentor* contains many well-examined—but ultimately unanswered—questions. There is some consensus about not testing children for adult-onset diseases for which there are no preventions or cures. But there are many more areas that have yet to be settled—by law, regulatory policy, and professional consensus. I hope we have succeeded in laying a solid and accurate foundation for your future consideration of these topics that are gaining in clinical importance each day.

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## Virtual Mentor

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### CLINICAL CASE

#### Duty to Warn At-Risk Family Members of Genetic Disease

Commentary by Anne-Marie Laberge, MD, PhD, and Wylie Burke, MD, PhD

Ms. Holmes was a healthy, 31-year-old administrative assistant with three sisters and a mother who had died in her 40s from complications of breast cancer. After reading online that breast cancer can run in the family, Ms. Holmes decided to ask her primary care physician, Dr. Wagner, about options for genetic testing. Together, they concluded that Ms. Holmes should be tested for mutations in BRCA1 and BRCA2, two genes associated with increased risk for breast and ovarian cancer.

When the results came back 1 month later, they showed that Ms. Holmes had the BRCA1 mutation. Dr. Wagner made room in her schedule for Ms. Holmes to return to clinic that day and the two went over the risks associated with BRCA mutations and scheduled an appointment for the next week to discuss options for monitoring and cancer prophylaxis.

When Ms. Holmes arrived the next week, she had already made a decision.

“I did some research on my own, Dr. Wagner,” she said. “I couldn’t just sit at home and not deal with this. I decided that I want to have a mastectomy on both sides. I still want a family, so I’m not going to have the ovary surgery. But I think they can do a pretty good job at reconstructing my breasts. If I don’t do this, I’ll just feel like there is a time bomb waiting to go off.”

“It sounds like you have done some careful thinking,” said Dr. Wagner. “Tell me what you found out about the different options over the past week.” Ms. Holmes gave a detailed description of the research she had done, citing numerous studies and web sites that Dr. Wagner considered accurate and reliable.

“Well, you have obviously put a lot of thought into this, and your information is very accurate,” said Dr. Wagner. “The next step is to put you in touch with a good breast surgeon. Before we do that, though, let’s talk about how you want to share this information with your siblings.”

The blood drained from Ms. Holmes’ face. She pushed her chair away from Dr. Wagner.

“There’s no way I’d tell my sisters about this, even if we were close,” she said. “Which we’re not. To be honest, it’s none of your business who I tell and who I



don't. If I had known you were going to pull this on me, I would have gone to another doctor.”

### **Commentary**

The conflict between Dr. Wagner's duty to warn third parties of their familial risk of genetic disease and her duty to respect Ms. Holmes' confidentiality is rooted in a conflict between ethical principles [1-3]. The duty to preserve patient confidentiality is based on the principle of respect for autonomy. Physicians should protect the patient's medical information and disclose it to third parties only with his or her consent. The principles of beneficence and nonmaleficence, on the other hand, support the disclosure of genetic information to at-risk relatives because to do so gives them access to surveillance and preventive measures that could reduce their risk of disease or complications and benefit them. Not disclosing this information could cause harm because at-risk relatives might develop the familial condition without their knowledge, and delayed diagnosis could affect treatment options or even curability. At the same time, disclosure to family members may not respect their autonomy and right *not* to know. The principle of justice suggests that Ms. Holmes' family members should have the same access to testing and related risk-reducing options that she has.

Current legal and professional policies privilege respect for patient autonomy and allow disclosure to third parties without the patient's consent only as a last resort in exceptional situations. One reason is that physicians' duty to protect patient confidentiality is stronger than their duty to family members with whom they have no patient-physician relationship.

### **When Does a Physician Have a Legal Duty to Warn?**

Case law addresses the physician's duty to warn. In *Tarasoff v. Regents of the University of California*, a woman was killed by her stalker after he had confided his intention of killing her to his therapist [4]. The court concluded that a physician or therapist has a duty to warn if: (1) he or she has a special relationship with either the person who may cause the harm or the potential victim, (2) the person at risk is *identifiable*, and (3) the harm is *foreseeable* and *serious*. This definition is now commonly used in legal settings and was called upon in two suits regarding physicians' duty to inform families of inherited cancer risks [2].

In *Pate v. Threlkel*, a woman received treatment for medullary thyroid carcinoma, which can be associated with an autosomal-dominant condition called multiple endocrine neoplasia (MEN) [5]. Three years later, her adult daughter was diagnosed with the same type of cancer. The daughter filed a complaint against the doctor who had treated her mother, arguing that if she had known earlier about the genetic risk of thyroid cancer, she could have taken preventive action and her condition would have been avoided or detected at an earlier and curable stage. The court agreed with her argument that the physician had a duty to warn of the risk to his patient's children, but concluded that this duty was satisfied by warning the patient about the risk to her relatives.

In *Safer v. Estate of Pack*, a woman was diagnosed with colorectal cancer due to familial adenomatous polyposis, an autosomal-dominant condition predisposing to colorectal cancer [6]. She filed a complaint against the estate of Dr. Pack, the deceased physician who treated her father for the same condition 30 years earlier, alleging a violation of duty on the part of this physician because he failed to warn her of her own health risks. She argued that if she had known about her risk of having this condition, her cancer could have been detected at an early and curable stage through regular surveillance. In a decision that differed from that of the *Pate v. Threlkel* court, the *Safer v. Estate of Pack* court found that the physician's duty to warn may not be satisfied in all cases by informing the patient of the risk to his relatives. The court asserted that the physician must take reasonable steps to guarantee that immediate family members are warned. This ruling defines a duty to warn that extends to family members in the case of hereditary conditions.

The disclosure of medical information without the patient's consent is regulated by the Health Insurance Portability and Accountability Act of 1996 (HIPAA) [7]. In language reminiscent of the Tarasoff ruling, HIPAA allows exceptions to its strict nondisclosure policy in the case of a serious and imminent threat to the public or to an identifiable third party when the physician has the capacity to avert that harm. It is unclear for now whether the threat of cancer associated with hereditary cancer predispositions would fall under this exception. Future case law will help define the limits of HIPAA when it comes to a physician's duty to warn patients and their family members of the risks associated with the presence of an inherited condition.

#### Does the Physician Have a Professional Duty to Warn?

The American Medical Association's Council on Ethical and Judicial Affairs examined the consequences of genetic information for relatives in a report on informed consent for genetic testing, which led to a section on disclosure of familial risk in genetic testing in the association's *Code of Medical Ethics* [8]. The council agreed that physicians have a duty to protect their patient's genetic information, but that they should discuss the implications of genetic information for family members prior to testing and should define circumstances under which patients would be expected to notify their relatives of the risks associated with that information.

The American Society of Human Genetics' policy statement on professional disclosure of familial genetic information emphasizes the conflict between the physician's duty of confidentiality to his or her patient and the duty to warn family members [9]. The report concludes that physicians have at the very least the duty to inform patients of potential genetic risks to their relatives. The existence of legal and statutory exceptions to patient confidentiality in other circumstances (e.g., infectious diseases, violent crimes), suggests that physicians may have the right to warn family members when attempts to encourage the patient to do so have failed; the harm is serious, imminent, and likely; the at-risk relative(s) are identifiable; prevention or treatment is available; and a physician in similar circumstances would disclose the information (i.e., disclosing would be considered standard practice).

The American Society of Clinical Oncology Policy Statement on Genetic Testing for Cancer Susceptibility recommends that physicians and counselors address the importance of communicating genetic test results to family members in the pre-test counseling and informed-consent processes prior to testing [10]. Their position is that the health professionals' obligations to at-risk relatives are fulfilled by communicating the risks for family members to the patient and emphasizing the importance of sharing this information so that family members may also benefit from it. After careful consideration of the HIPAA privacy rules, this society explicitly concludes that genetic-risk information does not meet the necessary criteria for disclosing without the patient's consent.

### **The Importance of Pre-Test Counseling**

Professional recommendations highlight the importance of discussing disclosure of potentially relevant genetic information to at-risk family members prior to testing, a discussion that should address potential barriers to disclosure. Ms. Holmes would probably be less shocked by Dr. Wagner's intervention if disclosure to her sisters had been included in the informed-consent process.

### **Conclusion**

Ideally, Dr. Wagner should have discussed the implications of the test results for Ms. Holmes' sisters and the importance of informing them of a positive result as part of the pre-test counseling and informed-consent process, in keeping with the AMA, ASHG, and ASCO recommendations. Because disclosure to family members was not discussed ahead of time, the shock of the positive test result is exacerbated by the unexpected discussion of disclosure to her sisters. Dr. Wagner has a duty to warn Ms. Holmes of the implications of the test results for her sisters, each of whom has a 50 percent risk of having inherited the same mutation and could potentially benefit from the same surveillance and prophylactic measures she is planning to take advantage of. Dr. Wagner should bring up disclosure to her sisters again on a subsequent visit once the initial shock of the test results has worn off, and should only disclose Ms. Holmes' test results to her sisters without her consent as a last resort.

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Wylie Burke, MD, PhD, is professor and chair of the Department of Bioethics and Humanities at the University of Washington in Seattle. She is also principal investigator of the University of Washington Center for Genomics and Healthcare Equality, an NIH-funded Center of Excellence in Ethical, Legal, and Social Implications (ELSI) Research.

#### **Related in VM**

[Presymptomatic Testing of Children for Huntington's Disease](#), September 2009

[A Physician's Duty to Warn Third Parties of Hereditary Risk](#), September 2009

[Testing Minors for Breast Cancer](#), January 2007

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## **Virtual Mentor**

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### **CLINICAL CASE**

#### **Presymptomatic Testing of Children for Huntington's Disease**

Commentary by Robert Klitzman, MD, Roberto Andorno, JD, JSD, and  
Leon Dure, MD

Dr. Carpenter had taken care of 3-year-old Josh since he was born. One afternoon, Dr. Carpenter received a call from Josh's parents, both of whom were successful professionals. Josh's dad had just been diagnosed with Huntington's disease, a degenerative, neurological disorder, and the parents wanted Josh to be tested for the disease. The genetic polymorphism for Huntington's is autosomal dominant, so Josh had a 50-50 chance of inheriting the gene from his father, and, if he did, he would develop the disease if he lived to middle age.

After offering her condolences to Josh's parents, Dr. Carpenter expressed what she considered to be a consensus opinion on the matter: "At present, there is no prevention, treatment, or lifestyle change that has an effect on expression of the gene. For these reasons, pediatric and genetic medicine specialty societies advise against testing children. Josh will have plenty of time to decide whether he wants to be tested once he is an adult."

"I disagree completely," said Josh's mom. "If Josh grows up knowing he has this condition, he will be much better prepared to deal with it as an adult. He'll be forming his identity over the next 18 years. Assuming he has the disease, he won't face the trauma of having his identity and life plan change all at once."

"But you'll be denying him the chance to make the decision as an adult," replied Dr. Carpenter. "Maybe he will decide not to know."

"Isn't that what parents do?" said Josh's dad. "They make decisions for their children. If we take your approach, Josh may be 25 when he discovers that he wishes he knew all along whether or not he has Huntington's. But he won't have that option because of our decision not to test him. The choice to do nothing is still a choice, Dr. Carpenter."

#### **Commentary 1**

by Robert Klitzman, MD

Josh's case raises several complex and important issues at the intersection of medicine, psychology, and ethics. His parents argue that it is their right to decide whether Josh should be tested, saying "Isn't that what parents do? They make decisions for their children." Yet, in fact, parents do not always do so. Parents do not

decide, for example, how their children will vote in elections once they turn 18. So, too, in this case, this decision is one best made by offspring after they are adults.

Several medical facts about the disease are highly relevant to the case. Huntington's disease (HD) is a fatal autosomal-dominant disease with adult onset (usually when the individual is in his or her 40s or 50s) that causes several neurological and psychiatric symptoms. To date, no effective treatment exists.

Most patients have seen the devastating effects and lethality of the diagnosis in a parent. To learn that one carries the mutation can cause psychological distress and trauma, in part because there is nothing that can be done to stop or prevent the disease.

An adult may nonetheless decide to undergo testing. Such information could potentially inform decisions of whether to have children or pursue lengthy years of graduate school. Some at-risk individuals, particularly those who are health care professionals, may want to know, since they feel relatively more comfortable with such diagnoses and prognoses, having treated patients who confront these dilemmas.

Yet, not surprisingly, most at-risk individuals decide against testing. The prospect of finding out that one has an untreatable lethal mutation and having to decide whom then to tell are simply too frightening [1, 2]. Given the intensely personal nature of these preferences and decisions, standard medical practice is to recommend that individuals contemplating this decision meet with trained genetic counselors to discuss the difficult pros and cons at length.

Ethically, the principle of respect for autonomy dictates that individuals make these decisions for themselves. Thus, an adult may decide to get tested. But a parent's right to exercise autonomy does not necessarily extend to decisions about his or her children. Arguably, a mutation-positive HD test result can harm more than help a young child. Hence, for a parent to test a child may violate principles of beneficence and nonmaleficence—i.e., benefits to an individual should be maximized, and harms minimized.

Of note here, Dr. Carpenter says that the parents would be denying Josh the opportunity to make the decision as an adult. Dr. Carpenter could perhaps have argued that the parents' decision may in fact cause stress, anxiety, and depression for Josh. Children do not fully understand death and disease. With emotional and cognitive development, individuals gradually become better able to cope with such stresses. A child's difficulty understanding and responding to the stresses of serious disease and death can lead to behavioral problems, and "acting out" (e.g., becoming involved in drugs).

In essence then, the critical conflict is not between the rights of the parents and the paternalism of the physician, but between the rights of the parents and the rights of the child. The parents' decision affects a third party—Josh. Dr. Carpenter must

follow the principles of beneficence and nonmaleficence and decide what is best for Josh—what will potentially produce the most benefit and the least harm for him. These principles lead to a recommendation not to test Josh, which conflicts with the parents' views of their rights to decide for him. In weighing these competing sets of principles, however, beneficence and nonmaleficence for the child outweigh the parents' underlying claim of autonomy. From a utilitarian perspective, the overall harm of testing outweighs the potential benefit to the parties involved.

These issues might be viewed differently if key aspects of the disease were different. For example, if disease symptoms appeared in childhood and an effective treatment existed that could then be started, testing would offer clear benefits to the child, and failure to test and treat the child could in fact be harmful. Presumably in such a case, the physician would recommend testing and agree with the parents, and problems would occur if for some reason the parents opposed testing, saying that they did not want their offspring to know. Indeed, such a conflict pitching the rights of the parents against those of the child occasionally arises in the case of HIV, where late adolescents who were infected at birth need treatment, but the parents do not want to tell the adolescent that he or she has HIV in part because they feel embarrassed and ashamed at having infected the child. Many physicians believe that if the adolescent is 16 or 17 and becomes sexually active, the benefits of disclosing the diagnosis outweigh the benefits of respecting the parents' autonomy, in part because the adolescent is more likely to transmit the virus to a sexual partner if he or she does not know about the diagnosis [3].

Similarly, if a genetic disease has adult onset, but effective treatment is available that could be advantageously started in childhood, testing would benefit the child. If effective treatment were available, physicians would recommend testing, hoping the parents would agree.

Josh's case asks whether a doctor has a right to oppose a family's values, but that conflict does not appear to be the critical one. Physicians have a professional responsibility to "first do no harm," and I know of no established religious or cultural tradition that would support the parents in the present case, given the ratio of potential harm to potential benefit involved in testing the child.

Physicians can attempt to address and resolve their disagreement with the parents by discussing the issues with them and presenting the ethical arguments against testing.

At some point in the future, parents and clinicians will face dilemmas of whether to avoid these decisions altogether by using nondisclosing preimplantation genetic diagnosis. In this procedure, a physician screens embryos for HD and other mutations, and implants only mutation-negative embryos without informing the parent at risk whether any mutation-positive embryos were in fact found. In this way, a parent who is at risk (i.e., has had a parent with HD) can have a child without the mutation while avoiding having to confront the stress of knowing his or her own HD status or having to decide whether to test a child [4].

Genetic markers are being discovered for a growing number of disorders, and direct-to-consumer marketing of these tests has begun. Hence, rising numbers of patients may either ask physicians about the value of such testing or undergo testing and then ask physicians to interpret the results. Thus, physicians will need to know how to approach such complex decisions. Doctors will need to be able to offer assistance in judging the pros and cons of genetic testing to both adult patients and their offspring.

Many of these decisions raise complex challenges due to scientific uncertainties and patients' varying psychological needs and desires. In many regards, HD is unique. Most diseases are not autosomal dominant, lethal, and without treatment. Rather, most common diseases appear to involve multiple genetic and environmental factors, and the relative contributions and roles of these genes in causing such diseases vary widely. For example, the so-called BRCA 1/2 mutations for breast cancer account for approximately 10 percent of all breast cancer, and the presence of a mutation results in disease about 40 to 60 percent of the time. Whether a patient should take this test is a highly individual and subjective decision.

Parents may want to test their children for other conditions for which tests exist, but effective treatment does not. Or a treatment may offer a small amount of possible benefit, while testing may again potentially cause some harm. Physicians then have to weigh a possible small benefit against a possible harm. These decisions entail uncertainties, subtly, and nuance, and physicians will need to feel comfortable confronting such choices.

Ideally, in all of the above genetic scenarios, doctors should refer patients to genetic counselors for assistance as needed. Unfortunately, the United States and other Western countries have severe shortages of genetic counselors. Many physicians do not know of a genetic counselor to whom they can refer patients. Thus, doctors will need to find some way to address these issues and feel comfortable doing so.

In coming years, scientific understanding of genetics will surely continue to mushroom, posing critical medical, ethical, and psychological challenges for which clinicians will need to be prepared. This preparation will help Josh, his parents, and countless others who face these conundrums.

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## **Commentary 2**

by Roberto Andorno, JD, JSD

Huntington's disease (HD) is a hereditary neurological disorder that leads to serious physical and mental disabilities. Initial symptoms usually appear between the ages of 35 and 50 and may include difficulty in concentration, memory loss, depression, and uncontrolled muscle movements. As the disease advances, uncoordinated movements become more apparent, and the decline in mental abilities generally results in dementia.

Presymptomatic genetic testing is available to determine whether a person has the faulty gene that causes HD. Every child born to a person who has the disease has a 50 percent chance of inheriting the faulty gene. If the mutation is present, the person's risk of developing the disease is virtually 100 percent. At present, there is no cure for HD, and there is no known way to stop it from progressing.

The foregoing case presents a conflict between a child's parents and the child's doctor regarding the advisability of performing genetic testing on the minor for Huntington's disease. The parents want the test to be performed on the grounds that their son, Josh, will be better prepared to cope with the disease if he—and they—know from an early age that he will develop it sometime during his lifetime. In contrast, Dr. Carpenter does not want to order the test, arguing that Josh should not be deprived of the opportunity to decide for himself at a later age whether or not to be tested and potentially receive such harmful information. So, who is right? Is Dr. Carpenter interfering with the parental control of Josh or simply committed to his best interests?

### **What Is Best for the Child?**

For adult patients, the choice to have genetic testing is a very personal decision that, in general, should be respected by health care professionals. This is clear when the result of such testing can be clinically useful medical information. But even if there are no preventive or therapeutic measures available (as it is the case for most genetically related diseases), a case can be made for taking the test and being told the results. Certain studies indicate that some people prefer to be tested for HD and to know the results of such testing because they feel that the relief of testing negative would outweigh the possibility of testing positive. Some feel that in such a situation nothing is worse than uncertainty [1].

But when children are considered for genetic testing for Huntington's disease, there are additional concerns that weigh against the reasonableness of testing. In the United States several medical bodies have issued statements advising their members that presymptomatic genetic testing of children for diseases usually manifested later in life, and for which there is no prevention or cure, should be strongly discouraged [2-4]. The main arguments supporting this position are, (1) the absence of a clear medical benefit to the child; (2) the psychological harm that the child may experience as a consequence of his or her parents' knowledge of the test results; and (3) the preservation of the minor's right to make an autonomous decision in the future. Moreover, testing of children for HD may expose them to discrimination or stigmatization and even result in deteriorating sibling relationships [5, 6].

At the international level, the widely accepted view is similar to that in the United States: all major guidelines on the matter strongly discourage genetic testing on children for late onset disorders [7]. The vast majority of clinical geneticists in a number of countries, including the United States, agree with the existing guidelines [8].

### **The Child's Right Not to Know**

An additional argument against the testing of children for late onset disorders is the preservation of the child's right not to know. The right not to know one's genetic information is increasingly recognized by international and domestic regulations as a response to the growing availability of genetic tests, which may burden people with more information than they can bear. This new right can be regarded as a legitimate expression of personal autonomy, although its ultimate foundation is people's interest in not being psychologically harmed by such potentially devastating information about their health status [9]. It is indeed unjustifiable, or even inhumane, to take away hope from people by exposing them to knowledge they do not want, especially when there is no treatment [1, 10].

If one accepts that adults have a legitimate interest in not knowing their genetic information and continuing their lives in peace, then it seems fair to preserve children's right to choose until they can decide for themselves whether their life is better lived with that knowledge or without [11]. In other words, allowing children to be tested for late onset disorders compromises their future autonomy [12]. Support

for this conclusion comes from empirical studies in which only about 20 percent of people at risk for Huntington's disease decide to undergo the testing [13]. If the vast majority of adults prefer not to know whether they will suffer from HD or not, how can we assume that a 3-year-old boy would benefit from such devastating information? Should we not rather try to preserve in such a case what Feinberg calls "the child's right to an open future" [14]?

### Conclusion

Parents generally have the legal authority to consent to genetic testing of their children, and in doing so they are expected to make the best decision for the child. Health care professionals, however, have an ethical and legal duty to intervene in a minor's interests if the parental request for a test may harm the child. In this case, Dr. Carpenter is not improperly interfering with the legitimate rights of the parents to make decisions on Josh's behalf. He is simply keeping to the widely accepted recommendations of professional bodies that state children should only be tested when it is in their interests and some treatment can be offered, and that they should not be tested for late onset disorders.

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### **Commentary 3**

by Leon Dure, MD

This clinical case is particularly relevant for at least two reasons. First, the development of greater awareness of genetic testing for specific diseases by the public requires that clinical care professionals be knowledgeable not only about the types and meanings of tests, but also of the consequences of obtaining such tests. Secondly, there are significant ethical issues that are brought to light by this case, especially as they relate to genetic testing of minor children.

### **Physician's Perspective**

Dr. Carpenter is essentially correct with respect to her interpretation of professional guidelines for testing of minor children at risk for Huntington's disease (HD). Both lay and professional organizations in the United States, Canada, and Europe recommend that testing of asymptomatic children await an age at which the child's consent can be reliably given [1-3]. Justification for this policy comes from the fact that there is no cure, nor are there any proven lifestyle modifications or treatments that can delay or alter the onset and course of the condition. Thus, from a health care professional's perspective, it can be argued there is no medical reason for obtaining the test. This does not imply that testing may only be offered when a child meets an "official" age of consent, depending on a state or country's definition, but at the very least it indicates a preference that children exhibit some understanding of the test and its consequences. An emancipated minor, for example, could undergo testing. An important distinction is made in the case of symptomatic testing—a child with clinical symptoms of early-onset or juvenile HD. Here, testing is often entertained as a means of identifying a particular diagnosis and avoiding further invasive or intrusive tests. In this case of a healthy 3-year-old, however, such reasoning does not apply.

Another point from Dr. Carpenter's perspective is the identification of Josh as the patient. Practicing physicians who care for children rely on parents to collaborate on decisions relating to health care. Tensions can arise, however, when parents'

motivations or decisions are at odds with those of a child's caregivers. Such conflicts commonly occur in the context of scheduled vaccinations in childhood, and parent-driven requests for genetic testing may develop into a similar problem. Despite these potential areas of disagreement, physicians must acknowledge their duty to a patient and act accordingly.

### **Parental Perspective**

The parental viewpoint touches on ethical issues that are unique to medical care of children. Parents are considered surrogate decision makers for their children, as minors are for the most part considered unable to make independent health care decisions [4]. It must be noted that children are distinct from other populations with impaired decision-making capacity, notably individuals who, by virtue of an injury or condition occurring early in life, will never develop competence and individuals who may have lost the ability to make decisions through injury, aging, or disease. Children, on the other hand, are considered "precompetent," in that they are expected to develop the resources and capabilities to make independent health care decisions. As a general concept, the goal of health care decision making is to ensure an open future for children by preserving as many options as possible for the time when they develop into competent individuals and members of society.

In this case, the parents state their conviction that, should Josh test positive for Huntington's disease now, he would be better prepared and have more time to accept the diagnosis. Moreover, the parents assert that they know best and have the right to make decisions for Josh. The conflict pits parental autonomy against the potential threat that testing for HD could have on a child's open future.

### **Prevailing Views**

Most professional organizations argue that testing for Huntington's disease and the determination of a positive test (meaning possession of the mutation for HD) would imperil the open future that is the ideal for a child. Consequences of a child's testing positive for HD could include stigmatization, discrimination, damage to self-esteem, and perhaps limitations on educational and other pursuits that might be enjoyed by any other individual.

Because specific data on children is sparse, it is informative to consider how adults have responded to genetic testing for HD. Overall, it is estimated that only 10 to 20 percent of at-risk individuals undertake presymptomatic testing for HD, despite availability of the test since the mid-1990s. Adults have reported a number of concerns about the consequences of testing, ranging from obvious fears of discrimination by insurers to less-tangible concerns regarding how testing could be communicated to other family members [5, 6]. Interestingly, the issues of communication arise regardless of the test results. The fact that a minority of eligible adults undergoes genetic testing despite ready access suggests that any particular child would have a fairly high likelihood of refusing testing after attaining adulthood. Testing a child would thus restrict choices that would be available in adulthood.

Critics of this view point out that there is little evidence to substantiate these concerns [7]. Moreover, they argue that testing of a minor child has a 50 percent chance of indicating no risk of HD and that withholding such information could have deleterious effects. As is true of the converse, this contention suffers from minimal supportive evidence, leaving health care professionals to navigate the course themselves. One approach has been to consider the best-interest standard, a construct that is very much in line with the societal goal of providing an open future to children [8]. When this standard is applied to the issue of childhood testing for HD, it is clear that, by refusing to test, the clinical community is exercising a duty to foster a best interest. Parents acting as surrogate decision makers for children also may have the same motives. Given the general acceptance of professional guidelines, though, it is apparent that physicians who care for children consider the risks of HD testing to outweigh potential benefit.

### **Clinician's Response**

So, what should Dr. Carpenter do? A compromise approach would be to investigate how the family is coping with the father's new diagnosis of HD. Dr. Carpenter should attempt to understand each parent's perspective of genetic testing and determine whether there is any particular conflict between their views. It would be important to establish whether the family plans to tell Josh, and when. Even critics of professional guidelines have indicated that the reason for testing is to have an open exchange of information and to share this information with the child and other family members. Given that Josh is a toddler, every effort should be made to convince the family that testing should be done when he is more mature.

Finally, it must be noted that many of the concepts and ideas regarding childhood testing for HD derive from the fact that there is little data relating to the attitudes of testing in childhood, nor is much known about how families typically tell their children about the disease. There is some evidence that people who have been tested while still minors have experienced both negative and positive consequences, but available data is not without controversy [9-11]. Research has only recently examined patterns of information transmission in families [12]. With respect to risk of HD, these data indicate that children are not informed early on about their own risk of disease and are typically not given such information until the second decade. Therefore, Dr. Carpenter should work to educate Josh's parents about developing a long-term plan regarding how they could approach genetic testing, emphasizing the reasons for a judicious approach. Much of the basis for a disinclination to test is that HD has no cure and no effective treatment. If, on the other hand, a rational treatment strategy is developed for HD, the balance of arguments for and against testing will change dramatically.

This case illustrates a number of significant tensions not only within the medical community but also between physicians and parents of minor children. A final word to the reader: physicians must be clear that, in this case, the child is the patient, and a best-interest standard may be in conflict with parental wishes.

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# Virtual Mentor

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## CLINICAL CASE

### Evaluating Requests for Preimplantation Genetic Diagnosis

Commentary by Anam Pal and Lubna Pal, MBBS, MSc

Mr. and Mrs. Anderson were both in their mid-30s. Mr. Anderson was a carpenter and built wood furniture by hand for internationally renowned designers. Mrs. Anderson was a college field hockey player and now the head field hockey coach at a local college. They both wanted a child and, having tried without success to conceive for over a year, they made the decision to consult Dr. Wells, a reproductive endocrinologist.

After 6 months of standard testing and therapy, the Andersons still had not conceived; Dr. Wells suggested that the couple consider in vitro fertilization (IVF).

The Andersons were eager to start IVF and had also begun to investigate the possibility of preimplantation genetic testing of candidate embryos. The couple knew a family who had a child with congenital defects of both hands and an atrial septal defect (ASD). Mrs. Anderson was concerned that a child with a heart defect, even a relatively easily treated defect such as an ASD, would be at a disadvantage as an athlete. Mr. Anderson told Dr. Wells that he did not want to have a child who was unable to work with his or her hands because he would be unable to share his love for woodworking with such a child.

Dr. Wells was open to facilitating preimplantation genetic testing for the Andersons but had reservations about discarding embryos with mutations that would lead to disabilities he considered relatively minor.

Is Dr. Wells justified in offering testing only for conditions that significantly impact quality of life as he defines it? Should he communicate his own sense of what makes life valuable with the Andersons?

## Commentary

This case describes a young and otherwise healthy infertile couple's consideration of proceeding with IVF, with an expressed interest in utilizing preimplantation genetic diagnosis (PGD) to minimize the risk of conceiving a child affected with Holt-Oram syndrome (HOS) [1-5]. The couple wishes to ensure against having a child who is affected by either cardiac defects or upper-limb anomalies, both integral to HOS—a rare genetic disorder that inflicts a risk of both aforementioned structural malformations [1].

HOS is a familial, heart-hand syndrome inherited in an autosomal dominant fashion with a high level of penetrance [2-5]. It is characterized by a combination of congenital cardiac anomalies and upper-limb malformations, with the type and severity of the specific deformities in a future generation being unpredictable [2-5]. ASD is the most common cardiac malformation seen in HOS; upper-limb abnormalities are fairly universal and of varying severity and nature.

Aspects of this dilemma worth perusing are: (1) the use of a sophisticated and expensive methodology (PGD) by a healthy couple with no discernable genetic risk beyond the age-comparable risk in the general population, leading to a tussle between the concept of patient autonomy and principles of nonmaleficence and justice reflected in Dr. Wells' reluctance to offer PGD to this couple; (2) the limitations of PGD that preclude ensuring against structural nongenetic anomalies; and, (3) while not explicitly stated, the suggestion that certain specific fetal anomalies (i.e., relatively minor variants of ASD or structural upper-limb deformities) might induce this couple to opt for an elective termination of a pregnancy because the fetus is afflicted by abnormalities that some people may consider minor [6]. (Given that a clear relationship between phenotypic expression of the genotype is lacking for HOS, however, Dr. Wells' conjecture that phenotypic expressions of the disorder may be minor is additionally simplistic.)

Although HOS is a rare genetic disease, it is the most common of heart-hand syndromes, with a frequency of approximately 1 in 100,000 live births [5]. Corrective surgical approaches are the mainstay in management of the respective structural anomalies. Genetic mutations in the TBX5 transcription factor are identified as the molecular mechanism underlying HOS, though a clear relationship between genotype and phenotype is far from apparent [7]. Prenatal diagnosis of HOS is feasible through chorionic villus sampling and amniocentesis; more recently, PGD has also been successfully employed in a patient with known HOS whose progeny have a 50 percent chance of being afflicted by this disorder [7].

Whilst the safety and efficacy of PGD in ensuring healthy progeny for genetically affected parents are well described, it remains an invasive and costly intervention that may have thus far unappreciated ramifications [1]. The potential for imprudent use of PGD cannot be ignored in the context of this scenario. The absence of HOS in the family and the cost of PGD for a rare monogenic syndrome such as HOS render the technique of no benefit to the couple. Therefore, though its use may satisfy patient autonomy, it falls short in fulfilling the physician's duty of beneficence. And, in the absence of a reasonable indication, the procedure may even carry potential for harm; hence PGD in this case may hold implications for slighting the principle of nonmaleficence, as reflected by anecdotal reports on PGD-related misdiagnoses and recent concerns regarding reduced success of IVF cycles following PGD in certain patient populations [8, 9].

Genetic screening for TBX5 in both partners may be reassuring, albeit unnecessary, given the high level of gene penetrance. More importantly, while heart-hand

anomalies are classically seen in HOS, individual structural defects may occur sporadically in the absence of any known genetic mutation; hence PGD for TBX5 cannot ensure against nongenetic structural anomaly, and this aspect must be discussed at length with the couple. Prenatal testing methods, including a first-trimester screen (ultrasound and biomarkers) and a second-trimester ultrasound, may be the optimal methodology for screening for heart and limb malformations in this couple [10].

Identifying the best screening methodology for the deformities of concern is the simpler of the issues at hand; the implications of detecting nonlethal and minor structural anomalies in an otherwise healthy fetus are more complex [10, 11]. While the logical sequence of events is to proceed with prenatal genetic testing to rule out fetal karyotype anomalies by amniocentesis, the couple, in light of their concerns, may decide to undergo elective termination of a fetus identified with structural anomalies with regardless of karyotype status. The onus remains upon the physician to communicate that, although any grade of abnormality may be devastating for the parents-to-be, they should bear in mind that many minor anomalies are not universally detrimental to the child's overall functionality and quality of life. Indeed, spontaneous closure of minor ASDs is well described without any long-term adverse sequelae for physical or athletic capabilities of an individual [12].

Elective termination of a structurally abnormal fetus, disregarding the severity of the anomaly, falls within the purview of respect for patient autonomy; the concept, however, remains highly debatable and well beyond the scope of this discussion. Suffice it to state that the likelihood of structural anomalies in a conceptus of an otherwise healthy infertile couple is quite small; recent data suggest that this risk may be higher, albeit slightly, in couples undergoing IVF with intracytoplasmic sperm injection [13, 14].

The concept that both genetic and nongenetic contributions to structural anomalies exist must be communicated to the couple and discussed at length. Prenatal testing utilizing first- and second-trimester ultrasound scans is the optimal screening methodology to identify a fetus afflicted by structural anomalies of the heart and upper limbs. The couple's decision to undergo an elective termination of a structurally malformed fetus, while medically reasonable, holds potential for ethical concerns that may not be dismissible easily.

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# Virtual Mentor

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## MEDICAL EDUCATION

### What Is the Role of Nongeneticist Physicians, and Are They Prepared for It?

Kelly E. Ormond, MS, CGC

You are a specialist physician, and someone comes into your office for a new patient evaluation—your differential diagnostic possibilities include several conditions for which a genetic test is available. Or you are a primary care physician, and, in taking your new patient's family history, you realize that this 30-year-old woman has a family history of breast and ovarian cancer that suggests she may be at increased risk herself. Or finally, an established patient comes into your office with results from direct-to-consumer genetic testing and would like for you to explain the meaning of the SNP test results. Now what?

Do you feel prepared to handle your patient's genetic histories, order appropriate testing, interpret the results, and discuss their implications for the patient and family? If not, you are not alone. Genetic-testing technologies are moving at a fast pace, and even physicians in a single specialty area can have difficulty keeping up-to-date on what tests are available, which laboratories are offering the most sensitive test, and the most effective way to proceed with testing. Moreover, most of these technologies had not been discovered when the majority of practicing physicians received their medical genetics training (often through a single course in the first year of medical school), and, for them, genetics and genomics are even more challenging.

A number of studies have assessed what nongeneticist physicians know about genetic testing, their ability to interpret test results, and their comfort with handling genetics cases. In one study, only 10 percent of respondents felt they knew "all [I] need to know about genetics for my job" [1]. Baars et al. suggested low levels of genetics knowledge in various physician groups, and another study suggested that the knowledge of carriers for hereditary nonpolyposis colon-cancer mutation equaled that of their physicians [2, 3]. Other studies document that a high percentage of physicians misinterpreted genetic test results and that they did not use published screening criteria appropriately [4, 5]. Studies like these consistently suggest that both primary care and specialist physicians feel uncomfortable with their ability to manage genetics-related scenarios that arise in their clinical practice. So what do doctors need to know to practice medicine in the age of genetics?

There is no uniformly accepted answer to this question. Medical genetics is considered a primary specialty by the AMA, but the American College of Medical Genetics estimates that there are only about 1,100 board-certified medical geneticists working across the United States, primarily at tertiary medical centers [6]. For the past 40 years, genetic counselors (now certified by the American Board of Genetic

Counseling and, in a handful of states, licensed) have assisted in providing genetic care. There are approximately 3,000 genetic counselors working in the United States with both medical geneticists and other physician specialists—primarily in oncology, cardiology, and neurology, but the number of areas in which genetic counselors work is continuously expanding. There is a smaller number of nurse geneticists who assist in caring for patients with genetic conditions. Given the relatively small numbers of genetic specialists and the fact that they are located primarily at academic medical centers, it is unlikely that physicians will be able to refer all their genetics-related patient issues to specialists. As summarized by Korf et al.,

...genetics is expected to be incorporated into routine care across all of medicine, and whereas a board-certified physician geneticist will not be involved in every medical decision based on family history information or interpretation of a genetic test, a physician geneticist will be understood to be the expert in these areas [7].

So what should the primary care and nongenetics specialist physician know about genetics? Several publications have presented competencies for offering appropriate genetic and genomic health care [8, 9].

### **What Physicians Should Know about Genetics**

From a practical standpoint, all physicians should have a solid understanding of modes of Mendelian inheritance, which is critical to accurate risk assessment. Specifically, physicians should be fluent in the concept of penetrance (whether or not a genetic mutation results in symptoms in a patient—nonpenetrance is the genetic explanation for conditions “skipping a generation”) and variable expression (that a single genetic mutation can result in different features and age of onset even within the same family). Physicians should also understand the concepts of polygenic inheritance (meaning that multiple genes, often with low penetrance as demonstrated by small odds ratios in genetic association studies, contribute to the occurrence of a complex disorder) and multifactorial inheritance (meaning that some combination of genes and environment leads to the phenotype).

With regard to genetic testing, it is key for physicians to understand that the sensitivity of genetic tests varies dramatically based on the type of testing performed and that, at present, no single genetic test detects 100 percent of mutations in a given condition. Variants of uncertain significance may be detected that require additional family studies or laboratory reclassification as deleterious or benign. Initially, testing an affected family member remains the most efficient way to determine the usefulness of a genetic test within a family. For terminally ill affected family members who are not found to carry a genetic mutation through currently available testing, DNA banking for future testing can be suggested, given how rapidly our knowledge in this area is evolving.

All physicians should be able to take a comprehensive three-generation family history to assess the risk to various family members, provide counseling to their patients about which family members may be at risk for the condition, and encourage

patients to inform relevant family members about the risks. Physicians should also be able to recognize the red flags of common adult-onset conditions that have a strong underlying genetic basis (e.g., earlier onset than is typical, multiple affected family members, occurrence in the less-frequent sex, or bilateral occurrence). Finally, physicians should be aware of how and when to make referrals to genetic specialists or other specialist physicians who manage genetic conditions and should have local or regional contacts available for such referrals.

Physicians should be cognizant that genetic conditions, by definition, involve not only their individual patient but the family and may raise issues concerning confidentiality and disclosure. Most professional societies do not recommend genetic testing of children unless test results will change medical management for the child in the near future; in particular, predictive testing for adult-onset conditions is discouraged in order to preserve the child's future right to decide whether he or she wants to be tested. Physicians should also be aware of state laws on protection of genetic information and the federal Genetic Information Nondiscrimination Act which protects against discrimination by health insurance companies and employers on the basis of genetic information, including family history.

Beyond the above general issues, specialty physicians should be aware of the current status of genetic testing for conditions within their specialty, including medical management of individuals with specific mutations. For symptomatic patients, genetic testing may refine the diagnosis (particularly when testing has ruled out other probable diagnoses), and mutation status may become increasingly relevant in clinical trials or treatment protocols. The identification of a mutation in an affected person may suggest the need for predictive testing of relatives. Identified mutation carriers can undergo earlier surveillance or treatment to minimize or delay the onset of symptoms, and those who test negative can avoid unnecessary future screening. Predictive testing also gives individuals information on which to base long-term life decisions, including reproductive planning.

Nevertheless, many do not want such knowledge, particularly if no medical surveillance or treatment is available for the condition. As a result, physicians should work closely with genetics experts to ensure they (the physicians) are securing informed consent (particularly for predictive testing) and that they are ordering and interpreting genetic test results accurately. In some settings, this may mean the incorporation of a genetic counselor or geneticist into a multidisciplinary clinic setting. In others, it may mean that the specialist develops expertise in this area, making referrals to genetics specialists for more complicated cases.

### **Teaming Up to Provide Genetic Information**

How can physicians gain the genetic knowledge they need to provide their patients with the best care? Teamwork among genetic specialists and other health care professionals is a start. Primary care and nongenetics specialists share the advantage of having longer-term relationships with their patients than do genetic specialists, who function primarily in a consultant role. When combined with their ability to



facilitate medical decisions and discuss probabilistic outcomes, primary care and specialist physicians are well positioned to play a role in the provision of genomic-based health care. Genetics professional organizations such as the American Society of Human Genetics, American College of Medical Genetics, and National Society of Genetic Counselors can be resources for genomic information, educational programs, and referrals. Physicians can also make use of web resources such as [genereviews.org](http://genereviews.org), [genetests.org](http://genetests.org), and OMIM to obtain information about the genetic basis of various conditions and current status of genetic testing.

Few articles document what is currently being taught in medical schools, in either the preclinical and clinical curriculum years, or in a GME setting [10-13]. Most medical schools teach genetics primarily through a first-year course that includes a combination of basic science and clinical information. It appears that a minority of clerkships include required medical genetics training, but this has been poorly documented. Basic genetics knowledge such as Mendelian and non-Mendelian inheritance, principles of risk assessment, and the skill of accurately taking and interpreting a family history should be taught in the preclinical years and reinforced during clinical training and residency. General clinical principles, including medical-test interpretation (e.g., clinical and analytic validity and utility) and the ability to critically read and evaluate current literature remain central, given the fast pace of genetic technology and testing, and these skills should also be reinforced in the clinical setting as they apply to genetic cases. Finally, since data supports the need to reinforce genetics knowledge and skills during the clinical training years of medical school and residency, the use of genetics objective structured clinical exams (OSCE) cases and practical reinforcement of cases in rounds and on the wards will be critical, but will also require clinical educators to be informed and comfortable with the material to teach and reinforce it in their own clinical settings [11, 13].

The promise of genetics and genomics goes beyond the potential for testing our patients: increased knowledge about genomics allows us to better understand the underlying pathophysiology of disease, modifiers that influence disease onset and progress (both genetic and environmental), and treatments including pharmacogenomic therapies. If physicians don't feel comfortable with the technology, the promise will not be fully realized. Physicians should find ways to educate themselves about the implications of genomic health care and identify genetic specialists who can serve as their partners in providing high-quality care to patients.

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# Virtual Mentor

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## THE CODE SAYS

### *AMA Code of Medical Ethics' Opinions on Genetic Testing*

#### **Opinion 2.131 - Disclosure of Familial Risk in Genetic Testing**

(1) Physicians have a professional duty to protect the confidentiality of their patients' information, including genetic information.

(2) Pre- and post-test counseling must include implications of genetic information for patients' biological relatives. At the time patients are considering undergoing genetic testing, physicians should discuss with them whether to invite family members to participate in the testing process. Physicians also should identify circumstances under which they would expect patients to notify biological relatives of the availability of information related to risk of disease. In this regard, physicians should make themselves available to assist patients in communicating with relatives to discuss opportunities for counseling and testing, as appropriate.

(3) Physicians who order genetic tests should have adequate knowledge to interpret information for patients. In the absence of adequate expertise in pre-test and post-test counseling, a physician should refer the patient to an appropriate specialist.

(4) Physicians should encourage genetic education throughout a medical career. Based on the report "Disclosure of Familial Risk in Genetic Testing," adopted June 2003.

#### **Opinion 2.137 - Ethical Issues in Carrier Screening of Genetic Disorders**

All carrier testing must be voluntary, and informed consent from screened individuals is required. Confidentiality of results is to be maintained. Results of testing should not be disclosed to third parties without the explicit informed consent of the screened individual. Patients should be informed as to potential uses for the genetic information by third parties, and whether other ways of obtaining the information are available when appropriate.

Carrier testing should be available uniformly among the at-risk population being screened. One legitimate exception to this principle is the limitation of carrier testing to individuals of childbearing age. In pursuit of uniform access, physicians should not limit testing only to patients specifically requesting testing. If testing is offered to some patients, it should be offered to all patients within the same risk category. The direction of future genetic screening tests should be determined by well-thought-out and well-coordinated social policy. Third parties, including insurance companies or employers, should not be permitted to discriminate against carriers of genetic

disorders through policies which have the ultimate effect of influencing decisions about testing and reproduction.

Based on the report "Ethical Issues in Carrier Screening for Cystic Fibrosis and Other Genetic Disorders," adopted June 1991.

### **Opinion 2.138 - Genetic Testing of Children**

Genetic testing of children implicates important concerns about individual autonomy and the interest of the patients. Before testing of children can be performed, there must be some potential benefit from the testing that can reasonably be viewed as outweighing the disadvantages of testing, particularly the harm from abrogating the children's future choice in knowing their genetic status. When there is such a potential benefit, parents should decide whether their children will undergo testing. If parents unreasonably request or refuse testing of their child, the physician should take steps to change or, if necessary, use legal means to override the parents' choice. Applying these principles to specific circumstances yields the following conclusions:

- (1) When a child is at risk for a genetic condition for which preventive or other therapeutic measures are available, genetic testing should be offered or, in some cases, required.
- (2) When a child is at risk for a genetic condition with pediatric onset for which preventive or other therapeutic measures are not available, parents generally should have discretion to decide about genetic testing.
- (3) When a child is at risk for a genetic condition with adult onset for which preventive or other therapeutic measures are not available, genetic testing of children generally should not be undertaken. Families should still be informed of the existence of tests and given the opportunity to discuss the reasons why the tests are generally not offered for children.
- (4) Genetic testing for carrier status should be deferred until either the child reaches maturity, the child needs to make reproductive decisions, or, in the case of children too immature to make their own reproductive decisions, reproductive decisions need to be made for the child.
- (5) Genetic testing of children for the benefit of a family member should not be performed unless the testing is necessary to prevent substantial harm to the family member.

When a child's genetic status is determined incidentally, the information should be retained by the physician and entered into the patient record. Discussion of the existence of this finding should then be taken up when the child reaches maturity or needs to make reproductive decisions, so that the individual can decide whether to request disclosure of the information. It is important that physicians be consistent in disclosing both positive and negative results in the same way since if physicians raise the existence of the testing results only when the results are positive, individuals will

know what the results must be. This information should not be disclosed to third parties. Genetic information should be maintained in a separate portion of the medical record to prevent mistaken disclosure.

When a child is being considered for adoption, the guidelines for genetic testing should be the same as for other children.

Based on the report "Testing Children for Genetic Status," adopted June 1995.

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# Virtual Mentor

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## JOURNAL DISCUSSION

### Conscientious Objection: A Medical Student Perspective

Ariel Williams

**Frader J, Bosk CL. The personal is political, the professional is not: conscientious objection to obtaining/providing/acting on genetic information. *Am J Med Genet C Semin Med Genet.* 2009;151C(1):62-67.**

During the third year of medical school, the question, “Do you know what specialty you’re going into?” comes up daily. While some students know what they want to do from the beginning of medical school, others find this question more vexing. Students in the latter group spend tremendous mental and emotional energy comparing and contrasting various aspects of different specialties in an attempt to decide which one is right for them. These students often take months before arriving at a final decision and seek advice from many advisors and faculty mentors along the way.

Medical students and their mentors, however, rarely discuss the potential that the standard of care in certain fields might conflict with the student’s personal moral code. Perhaps students with ethical concerns are reluctant to address them with housestaff and attending physicians they hope to impress. Regardless, students who have ethical objections to certain routine medical services should keep their objections in mind when choosing a specialty. For example, it is perfectly legitimate for a person morally opposed to emergency contraception to question whether he or she should pursue a career in pediatrics.

This issue reflects the well-publicized debate currently taking place among health care professionals on the acceptable limits of conscientious objection. The fields of obstetrics and gynecology, pediatrics, medical genetics, and genetic counseling are most often implicated. A number of physicians already established in their chosen specialties object on moral grounds to the medical services delivered by most of their fellow practitioners and claim the prerogative to refuse to provide these services to their own patients. Some take this a step further, refusing to refer patients to others who offer the services or even refusing to inform their patients of the availability of the services. These “conscientious objectors” cite physician autonomy, the immorality of complicity, and the responsibility to act in patients’ best interest by preventing them from engaging in morally objectionable behavior as justification for their refusals [1-3].

In “The Personal is Political, the Professional is Not: Conscientious Objection to Obtaining/Providing/Acting on Genetic Information,” Frader and Bosk examine

these arguments in the context of genetic screening [4]. In their view, the health care professional is morally obligated to inform patients in advance of any standard services he or she does not offer. When a patient has not been so advised and requests such a service, the health care professional is bound to expeditiously arrange care for him or her elsewhere.

The authors frame their argument in terms of the many privileges enjoyed by physicians. Society offers medical doctors a specialized fund of knowledge to use on their patient's behalf. We grant them high economic and social status to secure their role as their patients' fiduciaries. In return, we expect them to put patients' interests first, even when matters of conscience are involved.

Physicians who object on the basis of conscience often risk undermining their patients' autonomy in asserting their own right. Most patients lack the medical knowledge and resources to learn about and access treatment options on their own. They are unable to exercise autonomy in making health care decisions unassisted and are thus left completely in their physician's power. Physicians who withhold information or treatment from patients fail to meet their obligation to put the patient's best interest before their own.

Frader and Bosk note that conscientious objectors have historically been disenfranchised individuals. In contrast, conscientious objectors in modern medicine are among the most privileged and secure members of society. Their authority, social and economic status, and knowledge far exceed that of most of their patients. This disparity makes their claim to the right to exercise their moral prerogative at their patient's expense seem particularly exploitative and selfish.

Frader and Bosk ask why individuals would choose a specialty in which they find providing routine services to be objectionable. They also urge associations of professional specialists to more forcefully protect patients' right to access these services. This stance implies that, by choosing a given specialty, a medical student is obligated to ensure that his or her future patients have access to services that are considered standard of care by that specialty's professional association. Frader and Bosk do not claim, however, that this obligation binds the physician to providing that care himself or herself. So long as a physician promptly discloses what services are not offered, fully informs patients about the nature of these services, and, when necessary, makes provisions for patients to receive these services elsewhere, it is acceptable for him or her to decline to provide them. In summary, Frader and Bosk's position is that a medical student must be prepared to facilitate access to care that he or she finds morally objectionable, though he or she is not be obligated to provide the care.

Julie Cantor, in critiquing a December 2008 Department of Health and Human Services Regulation that extends protections for conscientious objectors, takes an even stronger stance [5]. In her view, a physician should act in a morally neutral fashion, offering to each patient all legal treatment options. In most cases, it is not

possible for a physician to disclose moral opposition to a particular plan of care and maintain a morally neutral stance. Thus, Cantor provides a warning to medical students that is stronger than the one issued by Frader and Bosk: Do not choose a specialty in which you will object to routine treatments that are considered standard of care; more often than not, professional duty requires you to carry out such treatments, regardless of your moral stance.

Frader, Bosk, and Cantor are united in a conception of medical professionalism that is overlooked in undergraduate medical education. In their eyes, professionalism demands that one concede moral authority for deciding which services should or should not be offered to the legal system, a professional organization, or the informal consensus of one's peers. I believe that this arrangement discourages physicians from restricting patient care based on personal values, maximizes patient autonomy and trust in the medical profession, and keeps misguided paternalism to a minimum. It does not undermine the autonomy of the individual practitioner inasmuch as he or she is free to leave the profession at any time or, more appropriately, to choose a different career path as a medical student. I do not believe that a medical student's ability to practice the specialty that he or she finds most interesting or enjoyable outweighs the right of patients to receive a full range of medical services in a morally open environment that respects the pluralism of our society. A physician who asserts his or her right to conscientiously object on the basis of moral pluralism must extend the same consideration to patients and, in so doing, loses all ground for refusing to facilitate their access to clinically appropriate services they desire.

Medical students considering a specialty where certain standards of care are at odds with their own personal belief systems must seriously question whether that specialty is the right choice. In the United States, obstetrics and gynecology residents with an ethical or religious objection to abortions are not required to perform them [6]. Some residency programs and many medical centers do not provide controversial services for religious reasons. Thus, medical students presented with the possibility of conscientious objection can select practice scenarios in which they are not obligated to perform the services in question. If they do not plan to ensure that their patients have access to these services elsewhere, however, they are committing themselves to a form of medical practice that results in substandard patient care and that has the potential to erode the trust between society and physicians.

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## Virtual Mentor

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### CLINICAL PEARL

#### Capturing the Power of the Family History

Tali Geva, MS, CGC, and Ora Gordon, MD, MS

Family history plays an invaluable role in patient health, providing important clues and insight that allow physicians to predict and detect disease before obvious symptoms appear. The key to using family history effectively is having the knowledge to filter the relevant from the irrelevant and pick up on the subtle clues that provide clarity (in a perhaps muddled pool of family lore and misinformation).

Families share not only genetic makeup but environment and lifestyle habits, all of which contribute to health. For example, a family that spends a lot of time outdoors exposed to the sun will have members who are at an increased risk for skin cancer, regardless of their “genes.” These shared factors are what give family history an impact on an individual patient’s health. While many health conditions and diseases are not strictly hereditary and cannot easily be observed to be passed on in families, the history of such conditions in families can help to determine whether, in your patient’s case, the information has significance for future screening and management.

Some health conditions are strictly hereditary, passed down in a dominant, recessive, or X-linked manner. Others involve more complex interaction of genes, while still others are caused by a combination of genetic inheritance and environment. Recessive conditions may be masked, with some members being unknown carriers for a condition that is only revealed when two carriers produce an affected offspring. Hence parental consanguinity can unmask a recessive condition in a family. Clues to detection of carrier status lie in the family’s ancestry. For example, certain populations, including individuals of Mediterranean, Middle Eastern, and Far Eastern ancestry have a higher carrier frequency for Beta-thalassemia, and, when a member of the family is born with this condition, all other members may be tested for carrier status to determine their likelihood of having a child with Beta-thalassemia. Table 1 highlights some conditions that are more common among specific ethnic groups.

Table 1: Incidences of conditions more common in specific ethnic groups

Ethnicity	Disorder	Carrier frequency
European American	Cystic fibrosis	1/29
Ashkenazi Jewish	Tay-Sachs	1/30
	Canavan	1/40
	Familial dysautonomia	1/30
	Cystic fibrosis	1/29

	Gaucher disease	1/15
Asian	Alpha-thalassemia	1/20
	Beta-thalassemia	1/50
	Cystic fibrosis	1/90
African American	Sickle cell anemia	1/10
	Beta-thalassemia	1/75
	Cystic fibrosis	1/65
Hispanic	Cystic fibrosis	1/46
	Beta-thalassemia	1/30-1/50
Mediterranean	Beta-thalassemia	1/25
	Sickle cell anemia	1/40
French Canadian	Tay-Sachs	1/15
	Cystic fibrosis	1/29

Identifying dominant conditions is generally straightforward; an individual with the dominant genetic alteration or mutation expresses the trait, and one can see the condition being passed on from generation to generation. Such is the case with Huntington’s disease. The presence of some of these conditions, such as hereditary breast and ovarian cancer, can be masked by variable expressivity or incomplete penetrance, appearing to skip generations. Men are as likely to carry a BRCA mutation as women, but have much less risk of cancer, thus are often “silent” carriers.

The same genetic alteration can cause different presentations of the same condition within individually affected family members. Due to this variable expressivity, individuals within the same family who have neurofibromatosis type 1 may manifest symptoms ranging from cafe au lait spots and Lisch nodules only to plexiform neurofibromas and optic gliomas. Similarly, individuals with the same hereditary condition can have premutations of the disease symptoms that forewarn of a possible full mutation and its associated disease in generations to come. For example, the X-linked condition, fragile X syndrome involves repeats of the nucleotides that make up our DNA. A certain number of repeats within a specific range on the chromosome causes mental retardation, specific behaviors, and various dysmorphic features. If a male child has a premutation (not enough genetic repeats to cause fragile X syndrome, but more than the average number), he may develop fragile X-associated tremor/ataxia syndrome as an adult; a female child with the premutation may develop fragile X-associated premature ovarian failure, with menopause occurring under the age of 40. If these characteristics are seen within a family, they can increase suspicion for fragile X, and the testing of individuals in the family may identify carriers that could lead to full-spectrum fragile X mental retardation in subsequent generations.

Another genetic phenomenon that can mask the presence of a hereditary condition is incomplete penetrance. Here, the underlying genetic mutation is present but the condition does not necessarily manifest itself physically in that individual. Hemochromatosis is an example of a condition that is incompletely penetrant. It has

been determined by large population testing that many Caucasian individuals harbor the genetic mutations that cause hemochromatosis, but never develop symptoms of the disease. This is a caution against broad-based population genetic screening, as many variations in our DNA are not good predictors of ultimate disease.

A chronic common disease such as type 2 diabetes clearly involves hereditary or familial predisposition, but may only manifest in the presence of certain lifestyle or environmental factors, such as obesity and being sedentary. Similarly, these common diseases have more than one possible etiology. For example, approximately 10 percent of cancers are strictly hereditary, caused by a single genetic mutation that confers high risk of cancer. Another 20 percent of breast cancers are caused by familial predisposition, with multiple weak genetic factors as well as environmental influences playing a role in risk. The remaining 70 percent of cancers are currently considered sporadic, meaning that unaffected members of the family have minimal or no increased risk of developing the cancer.

The goal of taking a family history is to be able to capture the histories that indicate a possible risk to patients or their offspring and to then be able to make appropriate recommendations and referrals based on this information. While the role of a geneticist or genetic counselor is to make sense of a family history, it is important for physicians to recognize which patients should receive this type of referral. Though most physicians agree on the importance of family history to clinical care, they admit that the lack of detail in the family histories does not allow them to properly identify those patients who would benefit from referral to a geneticist or genetic counselor [1].

### **Barriers to Family History Taking**

Several barriers to sufficient family history taking have been identified. Most often cited is time constraint. Many physicians report a lack of time to take a detailed family history for each patient [1, 2]. One solution might be inclusion of family history questions in a patient's previsit paperwork, which could then be followed by specific questions during the patient's visit. The SCREEN tool (table 2), created as a starting point for family history questioning, may be useful in previsit paperwork [3]. This can then be expanded upon when the patient is seen. Once a family history has been obtained, the information should be updated during each successive visit because family history is dynamic. While a grandmother with post-menopausal breast cancer wouldn't be of great concern, if the patient's mother then developed ovarian cancer, suspicion of a possible predisposition to hereditary disease would increase

Table 2: SCREEN for family history

SC	Some concerns	Do you have some concerns about conditions that run in your family?
R	Reproduction	Have there been problems with infertility, birth defects, miscarriages, or other pregnancy problems in your family?
E	Early disease, death, or disability	Has anyone in the family become ill or died at an early age?
E	Ethnicity	What is the ethnic background of your family?
N	Nongenetic	Are there other risk factors that run in your family?

Another reported barrier to good family history taking is the patient's lack of information [1, 4]. Some families are genealogists, while others tend to be rather secretive about health information, and still others have beliefs and barriers that limit their exposure to health care and proper diagnosis. A good tool for such patients is the death certificate. Death certificates are often used in the genetics realm to identify the actual cause of death or the primary cancer diagnosis or to rule out questionable conditions that are part of the family lore. These documents can be easily obtained online. Patients can be encouraged to obtain medical records and pathology reports for family members affected with health conditions because it provides a wealth of information for that individual's own health.

Lastly, physicians cite as barriers their own lack of comfort with being able to identify patients who are at risk based on the family history. For these reasons, use of published family history tools and recommendations can supply valuable insight.

### **Making Sense of the Family History**

Inquiries into family history should go back three degrees from the patient—in other words, it is not only the immediate family that is important but information on aunts, uncles, grandparents, and cousins also. Healthy family members are as noteworthy as those with medical problems. Relatives' causes of and ages at death and ages at diagnoses are important. A family history of one paternal aunt who had myocardial infarction at age 45 and 10 healthy siblings who lived to old age is of less concern than a paternal aunt with a myocardial infarction at age 45 who had one brother—the patient's father, who died at a young age in an accident. Equal weight should be given to both sides of the family, even if the condition in question is one that is only observed in one sex, such as ovarian or prostate cancer. While these cancers only occur in individuals of a specific sex, predisposition can be passed on from either side of the family.

Some hereditary or familial conditions raise red flags. These include conditions that present at an unusually young age, conditions that appear in multiple family members on the same side of the family, multiple rare conditions that present on one side of the family, more than one unusual condition or primary cancer diagnosis in a single individual, or a clear pattern of inheritance. For example, a family history of a mother with breast cancer at 65 is of less concern than a family history of a sister with bilateral breast cancer at 40, due to the unusually early age of diagnosis and the bilateral presentation.

Rare physical characteristics also have clinical value. Unusually short or tall stature can suggest a skeletal dysplasia that can have other health consequences. Dysmorphic features or mental retardation may be part of specific genetic syndromes. A good question to ask is whether there is anyone in the family who is blood related and looks very different from the rest of the family. Hypotonia, multiple birth anomalies, and ambiguous genitalia are examples of other physical characteristics that may be present in family members and impact health care for patients or their offspring. A family history that reveals these conditions may warrant referral for genetic counseling.

For patients considering reproduction, a history of birth defects, infertility, and miscarriage are critical. Family or personal history of such birth defects as cleft lip, ventricular septal defect, and spina bifida will have a bearing on risk for a patient's offspring. History of infertility or multiple miscarriages can be clues to an underlying genetic cause, such as being a carrier of a balanced chromosomal translocation. Though that individual has a normal genetic complement, the unusual arrangement of the chromosomes can lead to genetic aberration in offspring.

Some patterns and occurrences warrant suspicion of a hereditary condition. If the family history raises concern, the next step is evaluation or appropriate referral. Geneticists and genetic counselors are trained to take thorough family histories and determine whether there is any risk to the patient or his or her offspring based on the information collected. A strong family history of specific illness, such as early heart disease, may warrant enhanced screening in itself, and, if properly identified, can lead to early detection and treatment [5].

Online tools have been created to help the clinician and patient in gathering more thorough family histories, some of which can be updated by the patient and his or her family on a regular basis [2, 6]. The Office of the Surgeon General has named Thanksgiving "Family History Day," encouraging people to collect, share, and update their medical family history when they gather for the holiday every year. After all, family is the core of family history, and, in the world of genetics, what provides information for your patient does so for the entire family.

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# Virtual Mentor

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## HEALTH LAW

### A Physician's Duty to Warn Third Parties of Hereditary Risk

Kristin E. Schleiter, JD, LLM

People are increasingly obtaining genetic information about themselves that, unlike other medical information, may directly concern not only them, but also their biological relatives [1]. This aspect of genetic information poses ethical issues for physicians by challenging the limits of medical confidentiality when it comes to genetic test results [1]. While recognizing the need for confidentiality [2], the *Code of Medical Ethics* of the American Medical Association stresses that pre- and post-genetic counseling must include implications of genetic information for patients' biological relatives [3]. According to the code, physicians should tell patients who are considering undergoing genetic testing the circumstances under which they would expect those patients to notify biological relatives of the availability of information related to risk of disease [4].

#### Legal Decisions on the Duty to Warn

It was not until 1995 that the courts recognized a legal duty to warn both a patient and the patient's immediate blood relative that they may be at risk from a genetically transmissible condition [5]. This duty stands, irrespective of the duty of confidentiality between patient and physician, and regardless of whether a treatment relationship exists between the physician and the patient's relatives. The two primary cases that established this duty both recognized a duty to warn, though they arrived at different conclusions about what that warning might entail.

*Pate v. Threlkel*. In *Pate v. Threlkel*, the Supreme Court of Florida found that a physician has a duty to warn patients of the genetically transferable nature of the condition for which they are being treated [6]. Though this duty extends to informing the patient's children, the court held that the duty is satisfied by warning the patient of the familial implications of genetic testing [6].

Three years after her mother, Marianne New, was treated for medullary thyroid carcinoma, a genetically transferable disease, Heidi Pate learned that she had an advanced form of the disease [6]. Pate and her husband filed suit against the physicians who had treated her mother, alleging that: (1) the physicians knew or should have known of the likelihood that New's children would inherit the condition; (2) the physicians were under a duty to warn New that her children should be tested for the disease; (3) had New been warned 3 years prior to her discovery of her condition, she would have had her children tested at that time; and (4) if Pate had been tested at that time, she would have taken preventive action, and her condition

would have most likely been curable [6]. Pate was an adult at the time New was undergoing treatment for medullary thyroid carcinoma [6].

The court first determined whether New’s physicians had a duty to warn New of the genetically transferable nature of her disease. The court answered this question in the affirmative, since a reasonably prudent physician would give such a warning to his or her patient in light of all relevant circumstances [6]. The court then moved on to the question of whether, given the duty to warn a patient of the genetically transferable nature of her disease, a physician also has a duty to warn the patient’s children or other third parties [6]. This question was a matter of first impression in Florida, meaning that it was the first time the court was presented with the issue.

The court recognized that the prevailing standard of care—a duty to warn the patient—was “obviously developed for the benefit of the patient’s children as well as the patient” [6]. The court further found that, when the physician knows of the existence of these third parties, the physician’s duty to warn extends to them [6]. This holding, however, did not require that the physician himself warn the patient’s children of the disease; sharing this information with third parties without the patient’s permission would conflict with Florida’s confidentiality statute [6]. In circumstances where the physician has a duty to warn of a genetically transferable disease, the *Pate* court said that duty could be satisfied by simply notifying the patient [6].

*Safer v. Estate of Pack*. Shortly after *Pate*, the court in *Safer v. Pack* held that a physician’s duty to warn those known to be at risk of avoidable harm from a genetically transferable condition might not be satisfied by telling only the patient [7].

The plaintiff in *Safer* suffered from cancerous blockage and multiple polyposis of the colon, a condition her father had been treated for when she was a minor [7]. Pack brought suit against the estate of her father’s physician (who died in 1969), alleging that the disease was hereditary and that the physician had breached duty to inform those who were potentially at risk of developing the condition [7].

While the court warned that an overly broad and general application of the physician’s duty to warn might lead to confusion, conflict, or unfairness, the court was confident that the duty to warn of avertable risk from genetic causes was sufficiently narrow to serve the interests of justice [7]. The court employed the concept of a “genetic family”—the idea that genetic information is not just personal medical information but is simultaneously personal and familial [8]—in extending the duty to warn beyond the patient to members of the patient’s immediate family [7]. The court took a step beyond *Pate* by noting that the duty to warn could not always be satisfied by informing the patient of the transferable nature of his or her disease [7].

### **Ethics Policy on the Duty to Warn**

In the wake of *Pate* and *Safer*, the American Society of Human Genetics (ASHG) published a policy paper that reaffirmed the general rule of confidentiality and set forth factors defining the circumstance under which a physician should directly warn the patient's immediate family. The ASHG policy favors discretion on the part of physicians in disclosing information about genetically transferable conditions to those at risk for developing them [8]. ASHG recommended a two-part approach to disclosure that respects the confidentiality of genetic information while acknowledging that the information is both individual and familial in nature [8].

ASHG's policy first provides that physicians, under a standard duty of care, must inform patients prior to and following testing about the familial implications of genetic testing [8]. This step, similar to that found in AMA Opinion 2.131, preserves the duty of confidentiality while providing the patient with information necessary to inform or not to inform his or her family of test results [4]. But the ASHG goes further. After satisfying the duty to warn the patient, ASHG says, the physician can use the discretion to notify at-risk members of the patient's family when four factors are present:

- Attempts to encourage disclosure on the part of the patient have failed.
- The harm is highly likely to occur and is serious and foreseeable.
- The at-risk relative is identifiable.
- The disease is preventable, treatable, or medically accepted standards indicate that early monitoring will reduce the genetic risk [8].

Similarly, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research suggested that disclosure without the patient's consent is only justified if: (1) reasonable efforts to elicit voluntary consent to disclosure have failed; (2) there is a high probability both that harm will occur if the information is withheld and that the disclosed information will actually be used to avert harm; (3) the harm the identifiable individuals would suffer would be serious; and (4) appropriate precautions are taken to ensure that only the genetic information needed for diagnosis or treatment of the disease in question is disclosed [1]. Unlike the courts in *Pate* and *Safer*, the AMA and other organizations clearly recognize and respect a physician's duty of confidentiality, particularly with regard to highly sensitive genetic information. Only when the third-party interests are so great as to override this duty of confidentiality should a physician balance a competing duty to warn.

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# Virtual Mentor

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## POLICY FORUM

### **Direct-to-Consumer Personal Genome Services: Need for More Oversight**

Emily E. Anderson, PhD, MPH

Genetic tests have been developed for approximately 1,500 diseases. Most of these tests have not yet been incorporated into standard primary care due to limited evidence regarding their clinical validity and utility; the complex and not well-understood role that genes play in the development of many common diseases; physicians' limited knowledge of genetics; and public fear of genetic discrimination [1]. Despite these concerns, genetic tests are increasingly being sold direct-to-consumer (DTC)—predominantly over the Internet and with minimal or, in many cases, no involvement of health care professionals. The American public generally assumes that the government has assessed the safety and efficacy of all consumer (including medical) products. But there are significant gaps in the regulation of genetic testing that pose threats to consumer health and safety. Despite rapid scientific developments made during the last decade, the regulatory environment has changed very little [2].

While individual genetic tests have been available DTC for some time, within the last few years several companies have started to offer personal genome services, which scan a person's genome at hundreds to thousands of sites and provide risk information for a variety of health and nonhealth-related traits. About nine companies including 23andMe, deCODEme, DNA Direct, and Navigenics currently offer personal genome services [3-6]. (The precise number is difficult to determine and is constantly changing. DTC genetic testing is likely to grow rapidly given the easy market entry, especially for Internet-based sales, high consumer interest, and the rapid pace of genetic research [7].) Tests are purchased and results delivered via the Internet. Prices vary, and companies test for somewhat different diseases, but for anywhere between \$200 and \$2,500, customers can mail in a saliva sample or cheek swab and receive a personalized report within a matter of months. Depending on the company, risk can be assessed for type 2 diabetes, venous thromboembolism, various cancers (including breast, lung, skin, and stomach), obesity, male infertility, hemochromatosis, Parkinson's disease, Alzheimer's disease, bipolar disorder, schizophrenia, and back pain, in addition to many other diseases and traits. Individual data are compared to the results of genome-wide association studies (GWAS), which look for statistically significant correlations between genomic variations at specific locations on a given chromosome (single-nucleotide polymorphisms, or SNPs) and increased susceptibility to disease. Most SNPs discovered in GWAS are associated with very small increases in risk (odds ratios of 1.5 or less), calling into question the usefulness of this information for clinical decision making [8].

Genetic testing provides information that can be the basis for many important health care decisions—attempting to quit smoking, losing weight, having children, terminating a pregnancy, or starting on a drug regimen. How much information consumers have prior to the decision to purchase DTC personal genome services and their experience receiving and interpreting test results significantly influences their health-related behavior, future health care decisions, and overall trust in the application of genetics and genomics in medicine. Because of these significant public health implications, it is critical that appropriate protections are in place so that consumers are only offered tests that are accurate, reliable, and meaningful. To this end, it is important to understand three criteria used to evaluate diagnostic tests:

1. Analytic validity—in the case of genetic tests this is the ability of a test to accurately and reliably identify and measure the genotype of interest. There is not much concern about the analytic validity for most genetic tests sold DTC, although small sampling errors or poor quality control could affect test performance [8].
2. Clinical validity—the ability of the test to detect or predict the associated disorder. The clinical validity of any diagnostic test includes considerations of sensitivity, specificity, and positive and negative predictive value. There is much skepticism regarding the clinical validity of genetic tests based on GWAS. First, much of the data used to determine associations between SNPs and disease susceptibility is preliminary. Studies could benefit from larger and more representative sample sizes. Second, most of the diseases screened for by companies offering personal genome services are complex diseases known to be caused by multiple gene variants, interactions between gene variants, or interactions between gene variants and environmental factors; therefore, identification of the genotype associated with increased risk is only part of the overall risk profile [8, 9].
3. Clinical utility—the likelihood that the test will lead to an improved health outcome [10]. Currently, almost no data are available regarding the effects of DTC testing on health behavior and outcomes. It is likely that systematic study will determine that some tests have good clinical utility while others do not [11].

There are several challenges to oversight of the marketing and sales of DTC genetic tests. Regulations for the testing of human biological materials in general are vague and were not developed with the DTC context in mind. There is also lack of agreement about the type of oversight that is appropriate for DTC tests and the level of consumer protection that is needed. Regulation is complicated by the range and heterogeneity of genetic tests, the laboratories that perform them, and the modes of testing, delivery of results, and advertising. Several regulatory entities are involved, all of which are understaffed [1, 2].

### **Regulation of Laboratories that Perform Genetic Tests**

Laboratories that perform tests on human biological materials are certified by the Center for Medicare and Medicaid Services (CMS) under the Clinical Laboratory

Improvement Amendments (CLIA) [12]. CMS has the authority to assess laboratory personnel, quality control, and proficiency. CLIA regulates laboratories' operations but does not assess the analytic validity, clinical validity, or clinical utility of specific genetic tests performed by labs (although CMS does assess such factors in other types of laboratories and tests) [13]. While there are specialty areas for cytology and other complex testing services, there are no laboratory quality or proficiency standards specific to genetic testing. Laboratories can choose to be accredited by a private accrediting body with higher standards, however, such as the College of American Pathologists [2]. Several groups have lobbied for a genetics laboratory specialty, but CMS has repeatedly denied requests, citing costs [13]. CMS has no adequate mechanism for publicly sharing information regarding the CLIA-certification status of individual labs.

Those states that have chosen to adopt standards that are stricter than CLIA's require authorization by a professional to obtain a laboratory test. Based on current information, 13 states (including New York and California) prohibit consumers from ordering tests (i.e., a physician or other authorized health care professional must order and receive test results). Another 12 states prohibit consumers from ordering certain kinds of tests but do not name genetic tests specifically in this category. Twenty-five states and the District of Columbia allow consumers to order genetic and other tests without restrictions [9]. But state regulations that essentially prohibit DTC testing are difficult to enforce when tests are bought and sold via the Internet, and companies have tried to skirt professional-authorization requirements by employing physicians who then order all tests. These physicians never come in direct contact with consumers who buy the tests, although some companies offer physician counseling to assist with interpretation of test results for an additional fee. To address this practice of skirting state regulations, the California and New York State Departments of Public Health sent "cease and desist" letters to several companies in 2008, ordering them to either submit a plan to become compliant or face sanctions [14].

### **Regulation of Genetic Tests**

Oversight of the tests themselves falls under broad Food and Drug Administration (FDA) statutes regulating "in vitro diagnostic devices" (IVDs) [15]. Premarket review requirements for IVDs are not nearly as burdensome as regulations for pharmaceutical products, and, to date, genetic tests have been subject to far less regulation than other medical devices. As explained below, many genetic tests are not regulated at all. There are three types of genetic tests:

1. **Test kits**, in which components are bundled together, labeled for a particular use, and sold to laboratories as a unit. Of the hundreds of genetic tests currently available DTC, only about a dozen are sold as test kits. Test kits must undergo premarket review by the FDA to establish safety, effectiveness, and clinical validity prior to commercial distribution, but the amount and type of evidence required depends on the specific claims of the manufacturer.
2. **Laboratory-developed tests (LDTs)**, sometimes referred to as "home brews," are developed in-house by laboratories and do not become part of a

test kit. Most genetic tests sold DTC are of this type. The FDA has the jurisdiction over all LDTs as medical devices but thus far has decided not to regulate them.

3. LDTs that include **analyte-specific reagents** (ASRs), the active ingredients in a test that can be manufactured for sale or made in-house by a laboratory. The FDA has some oversight of ASRs, specifically regarding to whom they can be sold and how they must be labeled. FDA regulations require LDTs developed using commercially distributed ASRs to be ordered by a physician or other person as authorized by state law, but the extent to which this is actually enforced is unclear [16].

Because the vast majority of genetic tests sold DTC are laboratory developed and therefore *not* reviewed by the FDA, consumers have no way of determining whether there is adequate scientific evidence to support the claims of the company selling the test—i.e., if a test will be accurate in diagnosing or predicting disease. The Centers for Disease Control and Prevention (CDC) sponsors the Evaluation of Genomic Applications in Practice and Prevention (EGAPP), which aims to establish a systematic, evidence-based process for assessing the validity and utility of genetic tests [17]. It is unlikely, however, that individual consumers will gain access to EGAPP information.

### **Regulation of Advertising Claims**

There is concern that advertising for DTC genetic tests provides insufficient information for consumer decision making, leaving great potential for consumer misunderstanding of results or overestimation of clinical value [1]. Studies assessing the marketing practices of companies that offer genetic testing services online consistently find a genetically reductionist view of health; inconsistent, unreliable, and incomplete information (as well as overwhelming amounts of information); and limited provisions for physician involvement and genetic counseling [18]. FDA premarket review of test kits includes assessment of advertising claims, but since laboratory-developed tests (the majority of tests sold DTC) are not reviewed by the FDA, consumers are vulnerable to false or misleading advertising claims [2].

The Federal Trade Commission (FTC) Act [19] prohibits false advertising (including omission of facts as well as false representation) to induce the purchase of medical devices. The FTC has the authority to take action against false advertising claims, but it does not have adequate staff to monitor the genetic-testing industry and therefore can only respond to complaints filed against specific companies. They have not done so thus far, despite having received complaints [2], but the FTC did issue a general consumer warning against at-home genetics tests in July 2006 [20].

Congress also has the authority to investigate companies it suspects to be making false advertising claims. In 2006, the General Accounting Office (GAO) issued testimony to the Senate Special Committee on Aging entitled, “Nutrigenetic Testing, Tests Purchased from Four Web Sites Mislead Consumers,” which found that tests purchased from four unnamed companies “mislead consumers by making predictions



that are medically unproven and so ambiguous that they do not provide meaningful information to consumers” [21].

### **Proposed Legislation and Other Recommendations**

In 2007, two bills were introduced in Congress to strengthen oversight of genetic tests in general and DTC genetics tests in particular. The Laboratory Test Improvement Act (introduced by Senators Kennedy and Smith) would have granted the FDA the explicit authority to regulate LDTs as medical devices, meaning that LDTs sold directly to consumers would have to undergo FDA review before entering the market. The Genomics and Personalized Medicine Act of 2007 (introduced by Senators Obama and Burr) would have mandated the Department of Health and Human Services (DHHS) to improve the safety and effectiveness of genetic tests; specifically, the DHHS would be required to commission an Institute of Medicine (IOM) study to make recommendations regarding which genetic tests should be regulated and how, and the CDC would be mandated to study consumer impact of DTC testing [2]. Neither bill passed.

The Secretary’s Advisory Committee on Genetics, Health, and Society (SACGHS) advises the Secretary of the DHHS on health and societal issues raised by the development, use, and potential misuse of genetic technologies. In April 2008, SACGHS issued the report, “U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services,” which recommended actions to close critical gaps in the regulation of genetic tests and the laboratories that conduct them. The report recommended specific mechanisms to address the clinical validity and utility of the tests as well as the educational needs of health professionals and consumers [22]. In an April 2009 letter to the DHHS Secretary Kathleen Sebelius, a coalition of diverse organizations—including genetic testing laboratories, patient advocacy groups, and health policy researchers—called for a more “reasonable and responsible regulatory framework” for genetic tests and recommended (1) FDA oversight of all LDTs (not just test kits); (2) development of a publicly accessible registry that includes information on laboratories that perform genetic tests and companies that develop tests as well as information to support claims about how useful tests are in improving clinical care; and (3) strengthening CMS oversight of laboratories [23].

In accord with many other professional organizations, the 2008 American Medical Association (AMA) Board of Trustees report, “Direct-to-Consumer Advertising and Provision of Genetic Testing,” discourages DTC genetic testing [10]. Based on this report, AMA Directive D-480.987 [24] was modified to recommend that genetic testing be made available only under the supervision of a qualified health care professional, that physicians be educated about DTC testing, and that the FTC enhance its regulation of the marketing of DTC genetic tests.

### **Conclusion**

There is a wide range of possible policy options to fill existing gaps in the oversight of DTC genetic testing. While a total ban on all DTC testing and advertising or a free

market with absolutely no restrictions are both unrealistic, the kinds of tests sold DTC can be restricted (e.g., to those that are identified as appropriate without medical referral), the kinds of entities that can sell genetic tests DTC can be limited (e.g., to those that meet specific licensure or quality control requirements), and the conditions under which genetic tests are sold DTC can be limited (e.g., to those tests that undergo premarket review and meet certain standards for clinical validity and utility). Advertising can also be limited to certain media or types of tests, and specific disclosures can be required [2]. Perhaps the most critical concern is that there currently is no single agency that assesses whether genetic tests provide information to physicians and consumers that is clinically useful [17]. DTC sale of worthless genetic tests has the potential to undermine public trust in personalized medicine—a development widely touted as the future of American health care and largely built on the science of the Human Genome Project. Genetic tests are not all the same, and therefore they should not all be regulated in the same way.

Physicians now face the possibility of being asked by patients to interpret the results of genetic tests the patients purchased over the Internet. In the case of personal genome services, even a physician with advanced understanding of genetics is challenged to provide a meaningful explanation of test results to a patient who may have just spent a significant amount of money on this test, perhaps with the expectation that his or her physician would know how to make sense of the results and act accordingly. Given the current regulatory context in which tests of questionable validity and clinical utility are commercially available, physicians would be well-advised to caution patients who are interested in personal genome services about the serious limitations of commercially available tests [8].

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# Virtual Mentor

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## POLICY FORUM

### Emerging Dilemmas in Newborn Screening

Don B. Bailey, Jr., PhD, Debra Skinner, PhD, Myra I. Roche, MS, CGC, and  
Cynthia Powell, MD, MS

Newborn screening is an initiative designed to identify infants with serious health conditions who could benefit from early detection and treatment. Begun in the 1970s and governed at the state level, newborn screening expanded gradually as cost-effective tests developed or new treatments were discovered, and has recently undergone an unprecedented phase of growth and change. While many embrace and encourage these changes, they create a number of dilemmas that must be addressed to ensure that the practice grows in a rational and ethical fashion.

A report issued by the American College of Medical Genetics (ACMG) in 2006 established a template for grading the suitability of screening for newly proposed conditions [1]. Based on expert ratings of 87 conditions, the report recommended that all states screen for 29 core conditions and disclose the results of an additional 25 secondary conditions that are obligatorily detected by tandem mass spectrometry when screening for the core conditions. The report, together with advocacy initiatives, prompted broad changes in state screening programs. In 2005, most states screened for fewer than 10 conditions; currently, most screen for at least 25 conditions, a total that continues to increase. To address cross-state discrepancies and provide states with ongoing guidance, a Secretary's Advisory Committee on Newborn Screening for Heritable Disorders was established by the U.S. Department of Health and Human Services. Recognizing the need for a coherent national program of coordinated research, the National Institute of Child Health and Human Development issued a contract to build the infrastructure for a National Newborn Screening Translational Research Network. This network will link state programs and clinical centers, develop a national research informatics system, establish a research repository of residual dried blood spots, and facilitate research on conditions proposed for testing or laboratory tests.

For the most part, newborn screening enjoys wide public support and strong endorsement by the public health community. But developments in screening technology have made it possible to identify conditions for which there is no immediate treatment—a long-standing criterion for selecting which conditions to screen. A number of bioethicists have questioned whether disclosing results for untreatable conditions is desirable.

In December of 2008, the President's Council on Bioethics issued a report that examined many issues associated with expanded screening [2]. A major theme

reflected in the report and expressed by some bioethicists was that mandatory screening was expanding too rapidly nationwide without adequate consideration of the potential harms that could occur when disclosing information about conditions for which: (1) the natural history has not been described, (2) the potential range of impact of the genetic change is unknown (including the possibility that some identified children will be unaffected), and (3) treatments are not available. Disclosure under these circumstances could cause parental anxiety, disrupt parent-child bonding, contribute to hypervigilant parenting, lead some parents to try unproven treatments in anticipation of possible symptoms, result in stigmatization or discrimination, or cause the child to worry.

Our own work with fragile X syndrome (FXS) exemplifies these issues [3]. FXS, a trinucleotide repeat expansion disorder, is the most common inherited form of intellectual disability. Located on the X chromosome, the *FMR1* gene affects the production of a protein (FMRP) known to be essential for normal brain development. Males with FXS have moderate to severe intellectual impairment and can have co-occurring conditions such as anxiety, hyperactivity, or autism. Females are typically more mildly affected. There is considerable variability in the effects of the gene mutation on both males and females. Diagnosis of FXS typically does not occur until around 3 years of age, which limits timely access to early intervention programs and can result in the birth of a second child with FXS prior to the diagnosis of the first [4, 5]. Newborn screening would identify children much earlier, but this action has several implications for which concerns have been raised [6]. For example:

- There is currently no effective medical treatment that would prevent or reduce the consequences of FXS.
- Screening will identify some children who are phenotypically normal.
- Screening will identify children who are carriers and are at increased risk for adult-onset conditions such as premature ovarian insufficiency or neurological symptoms that include tremor and ataxia.

How should we make decisions about screening for a heterogeneous group of conditions such as those caused by changes in the *FMR1* gene? State-mandated genetic testing of children rises to a level of scrutiny that should invoke a moral and ethical analysis. We suggest that traditional criteria for decision making (being able to treat the condition, doing no harm) should be revised to a more nuanced goal in which benefits are maximized while harms are minimized. Using this definition, we offer several factors to consider when making decisions about newborn-screening policy:

- For the most part, the potential harms of expanded screening are speculative. Although it is possible that each harm could occur in isolated situations, there is no empirical evidence that any would occur at such a frequency or be so long-lasting that it would warrant withholding information from parents and children. Screening decisions should not be made on the mere assumption of harm but, rather, should recognize that harm also occurs if information gained from screening is not shared with families.

- Most research shows that parents want information relating to their child's health and their family, even when biomedical treatments are not available. Information itself should be considered as a potential benefit from screening, even when no treatment is available.
- Benefit has historically been narrowly defined and limited to improved health. Policy decisions should weigh other potential benefits for the child (e.g., preventing secondary conditions, enhancing development, maximizing quality of life), family (e.g., avoiding financial and emotional costs of the "diagnostic odyssey," enabling advocacy, knowing reproductive risk), or society (e.g., assuring equitable access to timely information, accelerating understanding of genetic variations and consequences, enabling treatment discovery, maximizing efficient public health services).
- Relying on benefit as the primary guiding moral principle devalues other equally salient moral frameworks, rights, and duties (e.g., distributive justice, social justice, fairness, equity, duty to inform, right to know).
- We should consider the possibility that it would be morally untenable *not* to report potentially useful health-related information and examine social and legal ramifications of the failure to disclose such results.

Inevitable advances in technology will identify hundreds of genetic variants at relatively low cost, radically changing both the possibilities and the realities of newborn screening. What would we do if whole-genome sequencing suddenly became cheap enough to use for newborn screening? How would we decide whether and how to disclose genetic information such as an increased susceptibility to Alzheimer's disease or cardiovascular disease? What is the appropriate demarcation between private-market screening and public health screening? Would limiting public health screening to a few treatable conditions lead to a burgeoning private market for expanded screening that exacerbates discrepancies in equitable access to health-related information?

Ultimately, the line separating disclosed results from those not reported (i.e., deciding whether a result is clinically relevant) will become increasingly difficult to draw. Technological advances, gene discovery, genotype-phenotype association studies, and treatment research will make the customary state-by-state, condition-by-condition approach to research outdated, and it will be nearly impossible for health policy to keep up with this rapidly shifting landscape.

Research is needed on issues, using a few prototype conditions that exemplify the concerns that bioethicists consider problematic. This research should examine broad questions of family adaptation to complicated, nuanced, presymptomatic information and identify the supports families need to assure that the disclosure of such information results in benefit rather than harm. Assessing medical and genetic literacy, developing novel methods of obtaining consent, and promoting and evaluating informed decision making will necessarily be part of next-generation newborn screening. Research must also examine methods by which families can become knowledgeable about the benefits and limitations of screening to enable

them to make knowledgeable decisions about what information they want. Only a systematic and integrated research agenda such as this can provide the data needed to adequately inform newborn-screening policy decisions.

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### **MEDICINE AND SOCIETY**

#### **Getting Personal with DNA: From Genome to Me-Ome**

Shane K. Green, PhD, and Mike Spear

*When Jen S. McCabe got her direct-to-consumer (DTC) test results from 23andMe she posted a video of herself on Posterous.com as she went over the results. The video blog entry ended with this statement: “Personal health action item 1: Ask doctor at appointment Friday about celiac’s disease variant.” Like many other consumers of these new DTC genomic analysis services, Jen had taken our new knowledge of the human genome and made it her own; in Jen’s case, bringing others along for the ride by using Twitter to talk about her “me-ome.”*

Jen is not alone. The proverbial “gene-ie” of personal genomics is out of the bottle and no amount of regulation is going to stuff it back in; it may well be the job of researchers and the health care community to play catch-up.

#### **Getting into Your Genes**

After 13 years and billions of dollars poured into the fledgling field of genomics research, the first draft of the complete human genome—the DNA code that directs the development of the human species—was published in 2001. A little more than 8 years later, it is now possible to sequence an entire genome in a matter of weeks for tens of thousands of dollars or less.

Since 2007, for a few hundred to a few thousand dollars the genetically curious consumer can have his or her genome analyzed. The costs are significantly discounted or waived entirely if the consumer agrees to be part of a research program. Information varies in its usefulness but covers ancestry, drug response, ideal diet, and disease risk. It has been called recreational genetic testing by some, but many consumers are treating the results with much more than passing interest.

A recent survey by the Genetics and Public Policy Center identified more than 35 companies offering DTC genetic tests, nine of which are classified as personal genome services [1]. The personal genome analyses provide a profile of many of the known single nucleotide polymorphisms (SNPs, pronounced “snips”)—relatively common variations in known locations across the genome. Our individual combination of these SNPs helps give us our unique genetic identity. Arguably the best known and most examined to date are U.S. companies 23andMe and Navigenics, and Iceland’s deCODEme, though new competitors such as San Diego-based Pathway Genomics are continuing to enter the marketplace in apparent anticipation of increased demand for services.

Any doubt about personal genomics going mainstream was put to rest in May 2009, when a European male was the successful, though only, bidder in an online auction on eBay to have his complete genome sequenced for \$68,000 [2]. One recent study of Facebook users found that, while only 6 percent of respondents had thus far used the services of a personal genomics company, more than 60 percent said they would consider doing so in the future [3]. Interestingly, of those who said they would not use personal genomics services, over half felt the information would not be useful, while 40 percent were deterred by cost. New technology and more demand are driving down prices for these services and for whole genome sequencing. With price and access barriers coming down, the same \$1,000 you might spend today on a genetic profile could reveal your complete genome sequence within a few years.

As tests become easier and cheaper, there are still significant concerns about the utility of the information provided by genomic analysis. DTC genomic profiles in particular have been criticized as providing little information of genuine value from a health perspective. Academics, clinicians, medical professional organizations, and government agencies in the United States, Canada, the United Kingdom, and elsewhere have voiced concerns about the analytic validity, clinical validity, and clinical utility of the tests. The main concern lies with the uncertain or weak associations of individual genetic variants and the poor sensitivity and positive predictive value of the results.

This lack of predictive power stems at least in part from the fact that our understanding of the influence of specific variants on disease predisposition is based on a body of knowledge that is constantly evolving, so that a SNP profile currently offers only a snapshot of a rapidly changing landscape of understanding. Moreover, SNP tests do not take into account other genetic variations (e.g., copy number variations), epigenetic factors, or gene-environment interactions, any of which can profoundly influence gene expression.

DTC personal genome service providers seem to acknowledge these limitations by carrying disclaimers that the results they deliver to consumers are for informational or educational purposes only and not for health care decision making *per se*. Despite the caveats, studies are showing that users of DTC testing and personal genomics services in particular, see the tests as providing information relevant to their health.

The same technological advances that are enabling sequencing costs to plummet are also greatly improving the speed, accuracy, and comprehensiveness of studies aimed at finding and validating genetic links to diseases and disorders, and providing new insights into epigenomics and genome-environment interplay. It is likely that at some point in the not-too-distant future, our understanding of the genome and of the health implications of the information it contains will be advanced enough that individual genome sequences or even SNP profiles—if the latter are not obsolete by then—will offer meaningful information their owners can use in proactively managing their health. But will they?

Advocates of DTC genomic profiling have argued that knowledge of their genetic makeups empowers consumers to be proactive about their health. But knowledge is empowering only if it is useful. In this case, usefulness requires that the knowledge be accurate, understandable, and actionable in some way. We have a ways to go before these criteria will be met for DTC genomic profiles, but it is possible if not likely that the criteria *can* be met and, moreover, it may be only a matter of time before they *are* met. In this future, consumers empowered to be more proactive will still face the challenge of changing their behavior in whatever ways are warranted—e.g., changes to lifestyle, diet or exercise regimens, or increased monitoring or screening.

It has also been suggested that there is a risk that changes undertaken may not be for the better. For some, the perception that genetic information is hard-coded and thus immutable, combined with an exaggerated sense of the particular influence of genes on health, may lead toward fatalism, causing them to believe that they lack power to make any difference to a genetically predetermined fate. Feeling powerless to overcome their genetic destiny, individuals may actually react to their profiling by choosing not to make positive behavioral changes, including changes they should be making regardless of any genomic profiling they undertake, such as improving diet or exercising. Finally, there is also the question of what kind of behavioral change would—or should—one make in light of a finding of being at reduced risk for, say, a condition such as coronary artery disease?

The question of whether and how genomic profiling will motivate behavioral changes in consumers has only begun to receive the research attention it richly deserves. How do these tests influence consumers' perception of their health, their present, and their future? Perhaps not surprisingly, since it is still early days for the DTC genomic profiling industry, scant data are available regarding the impact of personal genomic information on individuals' perceptions and behaviors.

Leaving aside clinical testing for rare single-gene diseases and disorders (e.g., BRCA1 testing for breast and ovarian cancer risk), the data we have on the influence of genetic information on behavioral change are not promising. Even where the information is more reliably predictive than much of the information that one gleans from DTC genomic profiles, some studies support the notion that genetic information has the power to motivate behavioral change, while others have shown that it leads to little or no significant and sustained changes in behavior. These studies, however, predate DTC genomic profiling and thus do not consider its niche in the genetic testing landscape.

New studies are now under way in a fresh attempt to address these questions and concerns in the specific context of DTC genomic profiling. For example, Navigenics has partnered with the Scripps Translational Science Institute, Affymetrix, and Microsoft to conduct a large-scale study of the impact of genomic profiling on consumers' behaviors [4]. As of July 2009, more than 5,000 individuals had enrolled in the study.

But for now, the question remains: Will individuals change their behaviors—and in positive, health promotional ways—based on genetic information?

Jen McCabe has. So has Mike Spear.

### **Lessons from Early Adopters**

Jen and Mike are just two examples, but they are informative. Their actions represent at least a subset of a growing number of early adopters of DTC genomic profiling, some of whom have chosen to share their experiences through social media.

23andMe recently offered a \$99 Research Revolution version of its test that gives general information on disease risks, research reports, and traits but does not give access to some features such as the raw data. As soon as the service was offered, the social media site Twitter was buzzing with the information and thoughts from bloggers, researchers, and people generally interested in genetic testing. As soon as this service had been around long enough for results to come in, consumers in the social media space were raising questions about their results and, perhaps more interestingly, were reporting changes in behavior and diet, and plans to go to their doctor for follow-up discussions and tests.

Here are just a few of these consumers' quotes lifted off Twitter and Facebook (names removed):

- @ this point, I'm the only one interpreting my #23andMe data, although I have a docs appointment this week, will use there 2.
- Full version!!!! Haven't been this obsessed with a data stream since I first started getting credit card statements.
- Having a young family and needing to provide and wanting to be there for them for years to come, the information in the report really helps me focus on my health and understand what I need to do to achieve my goals in life.

Co-author Mike Spear submitted spit-kits to 23andMe and deCODEme in 2008, and complemented the analyses he received from the companies by using an online platform called Promethease to analyze his data via comparison to SNPedia (SNPedia.com), a third-party Wikipedia-style database that, when coupled with the Promethease software, takes the raw data from DTC profiles and analyzes it against collated SNP linkage data. There are currently 33 public information sets listed in SNPedia [5], some of which are full genome sequences while others are SNP analyses from 23andMe, deCODEme, and Navigenics.

With results in hand, Mike has been exploring and blogging about the experience and his perceptions of what the results have meant. The analyses from 23andMe and deCODEme showed him to be at increased risk for age-related macular degeneration (ARMD) and rheumatoid arthritis (RA). With no actual cure for ARMD, he has committed to regular eye testing to monitor for signs of ARMD, and, since previous

blood tests for RA were negative, he is prepared to wait from some symptoms to appear before taking further action.

The SNPedia analysis, however, raised a few more questions that led Mike to take a proactive approach to his health. Unlike the 23andMe and deCODEme analyses, the SNPedia analysis revealed a significantly increased (17 times) risk of negative effects when taking statin drugs (used to lower cholesterol levels), which is something he told his general practitioner about in case it becomes relevant some day. The SNPedia data also showed an increased risk of suicidal thoughts when taking certain antidepressants, which he also shared with his general practitioner to keep in mind down the road.

His general practitioner's reaction to the information is typical of what many doctors report. They do not have the background or training in genetics, genomics, or genetic counseling to know exactly what to do with much or most of the information provided through these services. With doctors either lacking the training or time to tackle such questions from consumers, and without enough qualified genetic counselors available—despite the counseling offered by some of the DTC genomic profiling companies—consumers may turn to other sources of information; in an age where Google is now both a noun and a verb, these sources are often online databases, software packages, or social networks.

Some consumers are turning to social media communities such as Twitter or Facebook to help them interpret their data, often resulting in person-on-the-street style discussions, which may or may not be rooted in reliable knowledge and understanding. On Facebook, for example, lay groups have been formed to share information, results, and actions—both potential and undertaken—in response to positive test results for the BRCA1 risk factor. Even DTC genomic profiling companies offer social-media-style exchanges of information through their own web sites. The companies do not generally insert themselves into the discussions, which feature broad interactions among people who have had the tests and are exchanging ideas, advice, and health-related lifestyle changes.

### **Looking Ahead**

Whether from companies, physicians, or social networks, more and more people are coming to expect unfettered access to all the information they can find about their health, including arguably premature glimpses into their genome. Some will act on that information, imbuing it with relevance it may or may not actually have, while others will ignore it much like they choose to ignore warnings about the dangers of smoking.

Going forward, it is important that:

- Existing regulations against false advertising are enforced and that the benefits of DTC genetic services are not overhyped.
- Proper certification for profiling labs is maintained and their quality controlled.

- More genetic testing-related information and related training is made available to health care professionals.
- Ways to increase the numbers of qualified genetic counselors are sought.

Probably the most important step, though, is straight-forward public awareness of the benefits, limitations, and risks of genomic profiling. One potentially promising approach will be for knowledgeable researchers, scientists, and clinicians to begin inserting themselves into the places to which information-starved consumers are turning, such as online communities. In this way, they can help consumers understand the meaning and impact of the information in their profiles and help them understand the limitations of that same information.

It has been widely suggested that personal genomics is here to stay. We agree. Although we are already seeing some hints of apparently beneficial impact of these services, we eagerly look forward to the future advancements in science, health care education, and community engagement that will be necessary for DTC genomic profiling to truly empower and affect meaningful action toward personal health care and prevention.

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**Disclosure**

The opinions expressed are those of the authors and do not necessarily reflect the positions of the Ontario Genomics Institute or Genome Alberta.

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## OP-ED

### **Informed Consent and Prenatal Testing: The Kennedy-Brownback Act**

Adrienne Asch, PhD, and David Wasserman, JD

For more than 2 decades, some supporters of reproductive choice have contended that the manner in which prenatal testing is typically offered to pregnant women, and positive results typically explained, does not adequately ensure informed consent [1, 2]. These critics have objected to the descriptions of testing given to women by their physicians and have challenged the type and quality of information women receive about diagnosed fetal conditions. Recent legislation provides the impetus for long-sought reforms, but, while we applaud its potential, we think it valuable to acknowledge its limitations.

Reproductive health professionals face difficult questions in providing pregnant women with accurate, relevant, and balanced information about prenatal testing for disease and disability. Among these questions are: (1) when is the best time to introduce the subject of testing; (2) what type of information about the tests do prospective parents want or need; (3) what is the proper balance between medical information and information on nonmedical aspects of life with a particular disease or disability; (4) how can the perspectives of people living with the conditions and their families best be included; and (5) how can uncertainty about the applicability of general information to a specific child and family situation be conveyed? These questions have taken on greater urgency as the number of conditions for which tests are available proliferates and their use becomes increasingly routine. In October 2008, Congress made a promising start in addressing these questions by enacting the Prenatally and Postnatally Diagnosed Conditions Awareness Act (referred as the “Kennedy-Brownback Act” or “Brownback-Kennedy Act”) with broad bipartisan support [3].

The act requires the federal government to arrange for the collection and dissemination of up-to-date, evidence-based information about the conditions subject to prenatal and early postnatal diagnosis. This information encompasses “the range of outcomes for individuals living with the diagnosed condition, including physical, developmental, educational, and psychosocial outcomes.” Such information should provide a powerful corrective to the “bad news” typically delivered to pregnant women whose fetuses are diagnosed with the tested conditions. A body of research suggests that much of the information now supplied is heavily biased, outdated, highly inaccurate, and almost always narrowly clinical [4]. The act may have an even greater impact on prenatal decision making, however, if it helps to reframe how women and their physicians view decisions about continuing or terminating a pregnancy in the face of positive test results.

Information on the range of outcomes for individuals *living with* the diagnosed condition (emphasis added) may help pregnant women and their partners see their decision as one about parenting a child who will have a disabling trait, not about preventing disability. Ideally, the information will enable them to resist the tendency to see the fetus or child merely as the bearer of a disability or disease. Receiving that information may shift attention from the accuracy of a positive test result to its significance for the lives of prospective parents. As the Boston Women's Health Book Collective notes in its 2007 chapter on prenatal testing addressed to pregnant women:

The main reason that the test won't give you as much information as you might like is that knowing your child has Down syndrome, cystic fibrosis, or spina bifida tells you little or nothing about your child's future interests, talents, appearance, or personality. The test provides only one piece of information. You will need to consider how a child's spina bifida, for example, will be a part of the child's life and yours. Imagine that one of your family activities is camping. Can you learn what you would need to know to help a child with a mobility impairment to camp with you? If your family loves reading and intellectual conversation, can you imagine raising a child who has cognitive impairments from Down syndrome and won't be able to always understand what others are talking about [5]?

If the doctor herself lacks access to developmental, educational, and psychosocial information to supplement data on medical outcomes of people with Down syndrome, cystic fibrosis, sickle cell anemia, and other conditions that can now be diagnosed, she is unlikely to be of much help in addressing these questions. Too many professionals who offer prenatal testing do not know that most people with disabilities lead complex lives that are not constantly dominated by their impairments. Even generally well-informed and conscientious physicians may not have the necessary experience or knowledge, since their exposure to individuals with the diagnosed condition is often limited to acute health crises and requests for medical services. Admittedly, the act does not require doctors to obtain or communicate information about the lives of people with the diagnosed conditions. But it ensures that they and their patients can easily acquire such information, as well as information about laws, services, and family support geared to those raising children with the hundreds of disabilities for which diagnostic testing is available.

Two recent studies suggest that the broader focus encouraged by the act may have an impact on reproductive decision making. Gottfredsdottir et al. found that the minority of prospective parents who declined prenatal-disability screening tended to be familiar with individuals who had disabilities [6]. And Kelly discovered that parents who already had a child with a congenital disability generally declined to select against future children with that condition; the largest group had no additional children; the second largest declined testing in later pregnancies; and the third largest group tested only for information, with no intent to abort based on the test results [7]. These studies suggest that prospective parents who see disability in the context of full human lives—those of the children they are raising or of their friends and

acquaintances—are less likely than other prospective parents to use prenatal testing at all or to use it to screen out children with disabilities.

For all its potential value, the act has a built-in limitation: it mandates better information only for women who have already been tested and received positive results, not for women deciding whether to obtain testing. In 1997, Press and Browner reported that women were being presented with prenatal testing as part of routine prenatal care, often calling it “just another blood test” [8]. Many were not told that the test concerned fetal health, not their own health, or that the results would not help them or their doctor manage their pregnancy or improve the health of their fetus. The option of abortion in the face of positive results was rarely mentioned. A 2009 study suggests the continuing failure of health professionals to explain the implications of prenatal testing to pregnant women: “Approximately one half of the women surveyed who underwent both ultrasound and biochemical screening did not foresee that they might ultimately be confronted with the need to make the decision about whether or not to terminate the pregnancy” [9]. This failure should trouble conscientious health professionals because it means that pregnant women are being led to obtain information they may not want to have and to make decisions they may not want to make.

Because the Kennedy-Brownback Act is not directed to women facing the threshold decision about whether to test, the information it mandates may come too late in the process to be fully effective in reframing prenatal decision making. A woman who has already been led to regard such testing as a routine part of fetal medical care may have difficulty in seeing the testing as a prelude to a decision about what kind of child she is willing to parent. She might not want to make that decision, and, if she had understood the test’s purpose before consenting to it, she might have refused to put herself in a position where she had to make it.

Women who want to test their fetuses prenatally should be able to do so, but they should only be offered testing as part of a process of exploring their goals and values for parenting and family. Reproductive autonomy requires that pregnant women have access to comprehensive information about the potential rewards and challenges of living with, or raising a child with, a disability. The kind of information they need depends on their goals and values.

We conclude, then, that the Kennedy-Brownback Act is best seen as the first stage in restructuring the prenatal-testing process. Testing should never be routine; it should only be introduced in discussing the expectations, goals, and values of the prospective parents. What do they imagine for their child, children, and themselves? Would their aspirations and dreams be thwarted or compromised by having a child with Down syndrome, spina bifida, retinoblastoma, or hemophilia? Full reproductive autonomy will only be possible when professionals can convey to prospective parents that they are free to test their fetuses or to decline testing and that it is as legitimate to become the parent of a child who will have a disability as it is to decline to do so. The act is an important first step, but only a first step, in ensuring that

pregnant women can make genuinely informed and uncoerced choices about prenatal testing.

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## OP-ED

### **Unethical Protection of Conscience: Defending the Powerful against the Weak**

Bernard M. Dickens, PhD, LLD

In “The Personal is Political, the Professional is Not: Conscientious Objection to Obtaining/Providing/Acting on Genetic Information,” Joel Frader and Charles L. Bosk [1] make a compelling argument that the invocation of personal conscience violates medical professional ethics. They believe that provisions like those in new federal legislation and regulations that prohibit discrimination against health care professionals who refuse to provide services or referrals on religious or moral grounds violate medical ethics.

The rules on protection of conscience issued by the federal Department of Health and Human Services (DHHS) were given legal effect January 20, 2009, as a final gesture of the Bush administration, and are now under review by the Obama administration. They were proposed under three laws: the Weldon Amendment, named after former Representative Dave Weldon (R-FL), which amends the HHS Appropriations Act; section 245 of the Public Health Service Act, signed by President Clinton in 1996; and the Church Amendments, named after former Senator Frank Church (D-ID), and enacted following the Supreme Court’s 1973 decision in *Roe v. Wade* [2] to ensure that physicians and hospitals were not required to perform abortions or sterilizations as a condition of receipt of federal funds. At least seven states and two abortion-rights groups are in federal court claiming that the Bush administration provisions are unconstitutional on the grounds that they interfere with state laws guaranteeing access to abortion-related and comparable health care services.

The protection that the federal provisions offer is glaringly at odds with the self-sacrifice that has characterized the four historically reputable professions, namely medicine, religious ministry, the profession of arms, and the law. Physicians tend to the sick and risk succumbing to their infections. For instance, Dr. Carlo Urbani, who first diagnosed and named the severe acute respiratory syndrome (SARS) in 2003, died from the disease. Ministers of religion have similarly attended the sick and infected, counseled, and consoled the worst of sinners. Lawyers defend the legal rights and interests of heinous offenders, at times without fee, and serve clients whose lawful purposes they personally deplore. Those in military service, whether as volunteers or conscripts, risk and, too often in conflicts pay with, their lives. By contrast with this tradition of self-sacrifice, the federal provisions protect health care professionals who object to participation in legal health care services and allow them instead to abandon patients or sacrifice patients’ interests to their own.

The federal provisions' wide if not comprehensive scope governs performing, participating in, referring for, learning about, teaching, or administering procedures for abortion, sterilization, contraception, and some forms of end-of-life care. Although introduced under a claim to protect health care professionals against discrimination, the rules risk making such procedures unavailable to dependent patients who are lawfully entitled to have access to them. Patients whose care is not religiously or morally contentious and who require such procedures as safe removal of a dead fetus or of cancerous reproductive organs or sedation following trauma for routine therapeutic purposes face possible harm from the dearth of health care professionals who are trained to perform or participate in those procedures.

Health care professionals who place their own religious or moral interests above their patients' health care interests experience an especially unethical conflict of interest because physicians enjoy the power of a legal monopoly over the provision of medical services. If they choose not to avoid this conflict, e.g., by selecting a health care or research specialty that is unrelated to reproductive or end-of-life medicine, they should disclose their conflict of interest to patients, those considering becoming their patients, and hospital and other agencies that assign them to care for patients.

This ethical requirement is reinforced by laws on negligence and fiduciary duty. Fiduciary duties of disclosure are particularly relevant. They are based on rules of equity derived from the historical English Court of Chancery—the “court of conscience.” Those seeking protection of their rights of conscience are reciprocally required to observe their duties of conscience. Leading U.S. courts [3] have ruled that physicians' legal duty of care requires disclosure to patients of all treatments that are suitable according to the professional standard of care. This applies whether or not the physicians recommend such care or are able or willing to provide it, and includes disclosure of information about where such care is available, if it is not through the physicians themselves.

The federal provisions on protection of conscience prohibit discriminatory practices by federal, state, and local agencies that receive funds from the federal DHHS and perhaps other federal funds. It is not clear, however, and appears doubtful that the federal provisions bind courts that determine patients' rights to nonnegligent care and to physicians' discharge of their fiduciary responsibilities. Whether federal legislation supersedes states' law or is subject to it is a matter for judicial interpretation. Regulatory provisions developed within administrative units of government and not by legislatures are usually interpreted to be subject to legislation rather than displacing or changing it. Although courts will usually not compel health care professionals to participate directly in procedures that violate their personal faith or conscience, they construe objections of associated “complicity” narrowly (as “performing”) and thus may require health care professionals to provide their patients with reasonable information about access to appropriate treatments [4].

Physicians and other health care professionals are usually free to decline to accept applicants for their care on a wide variety of nondiscriminatory grounds without assuming any responsibility to refer them to other health care professionals. Once a patient-physician or comparable relationship exists, however, the AMA recognizes an ethical duty of referral [5]. Legal duties arise under negligence, fiduciary, and contract law that binds physicians to protect patients' interests in gaining access to requested services, notwithstanding physicians' own legal protections against unlawful discrimination. Since not every exercise of a legal power is ethical, health professional licensing authorities and medical associations are free to declare what legal protections they consider unethical, even if individual sanctions for professional misconduct cannot be applied. Such declarations serve the legislated or moral mandate to protect patients against unethical professional conduct.

Courts may find it negligent or a breach of fiduciary duty for health care professionals to care for patients to whom they have not previously disclosed the procedures within their expected scope of practice that they will refuse to provide. As Frader and Bosk observe, patients for genetic counseling and prenatal diagnosis may reasonably presume that they will be informed of tests that meet their requirements and choices that are available in response to the test results that follow. Health care professionals who refuse or fail to disclose accessible tests or consequent choices, on grounds of conscience or otherwise, face legal liability, for instance for wrongful pregnancy, wrongful birth, and breach of contract or of fiduciary duty, when refusing to participate in or inform patients about their lawful options of contraception, sterilization, or abortion. Federal provisions on conscience may protect health care professionals against discrimination, for instance, in appointment to and promotion within institutions that receive federal funds, but they do not empower those physicians to enforce their religious or moral convictions and deprive patients of their lawful rights to reproductive or comparable decision making.

The key ethical failing of the federal provisions is their blindness to the special category of professional obligations that physicians agree to assume when they join the profession. Protection of conscience in itself is worthy and necessary. The United States has ratified the United Nations' International Covenant on Civil and Political Rights, a central pillar of human rights that gives legal force to the 1948 UN Universal Declaration of Human Rights. Article 18(1) of the Covenant states:

Everyone shall have the right to freedom of thought, conscience and religion. This right shall include freedom to have or to adopt a religion or belief of his choice, and freedom, either individually or in community with others and in public or private, to manifest his religion or belief in worship, observance, practice and teaching.

Article 18(3), however, provides the balance that:

Freedom to manifest one's religion or beliefs may be subject only to such limitations as are prescribed by law and are necessary to protect public safety, order, health or morals or the fundamental rights and freedoms of others [6].

The federal provisions protect health care professionals' conscience to refuse participation in, for instance, certain reproductive and terminal-care procedures, but fail to recognize their professional commitment to undertake them [7]. The provisions allow health care professionals to exploit the power of their superior knowledge over that of patients, promote their own interests, and protect their careers, by subordinating of the interests of patients they have a legal monopoly to treat.

In protecting and privileging health care professionals who withhold information that their patients depend upon, the provisions reduce health care professionals to the status of self-serving traders in an unequal market who may take advantage of those obliged or unwise enough to trust them and rely on their integrity. The provisions underscore the challenge that conscientious objection poses to health care professionalism [8]. To allow physicians to deny or frustrate a patient's rights of conscience by enforcing their own through nonreferral, as the new regulations do, is unethical. It is ethically justifiable to be intolerant of religious or other fundamentalist intolerance.

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## **Virtual Mentor**

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