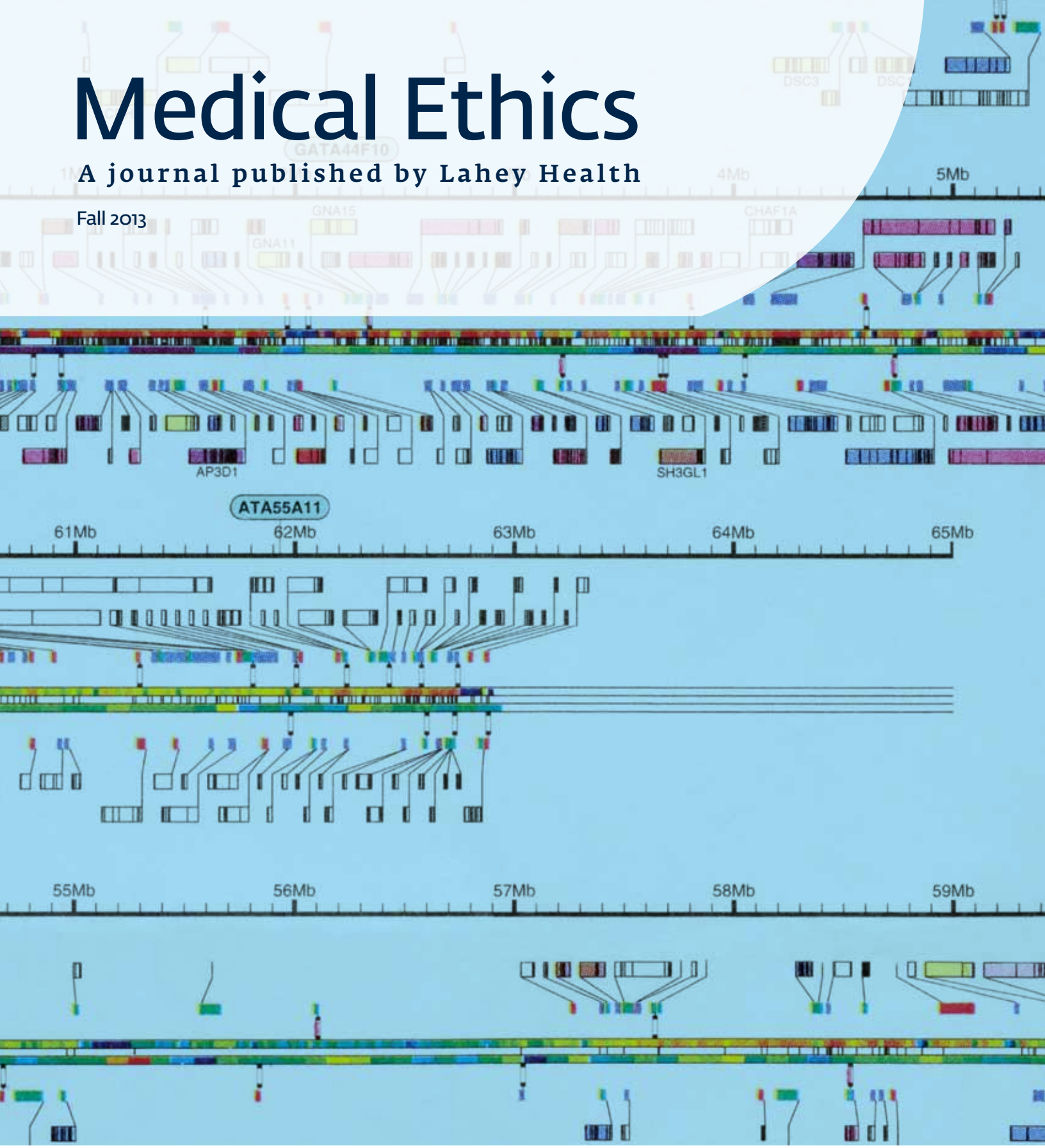
Medical Ethics

A journal published by Lahey Health

Fall 2013



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Quote to note

"For an idea that does not at first seem insane, there is no hope."

—Albert Einstein

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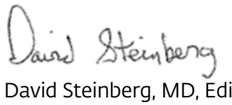
A note from the editor

Dear Readers,

Welcome to the inaugural edition of the *Lahey Health Journal of Medical Ethics*. Although our name has changed, after 18 years of publication as the *Lahey Clinic Journal of Medical Ethics*, our mission to address challenging questions in bioethics has not. The name change reflects the growth of our parent organization; we continue our valuable collaboration with the Dartmouth-Hitchcock Medical Center.

The *Lahey Health Journal of Medical Ethics*, which publishes twice yearly, goes to people who have requested complimentary subscriptions. Our 30,000 readers come from every state as well as 39 foreign countries. We invite our readers to submit comments about our articles and suggestions for future topics.

Sincerely,



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Health analytics and big data

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It is estimated that between 21 and 47 percent of what we spend on healthcare in the United States is of no value.[1] Adverse events may occur in one-third of hospital admissions.[2] Overcoming safety, waste and inefficiency challenges[3] requires a fundamental transformation that includes evidence-supported decisions. That goal is greatly hampered by our limited access to data.

A distinct challenge is to make better use of available information both in the United States and around the world. However, we live in an era of big data, characterized by four Vs: volume, velocity, variety and veracity.[4] Volume is the amount of data; velocity is the speed with which the data is transmitted; variety refers to the many types of information; and veracity is the concern about the quality and reliability of the data. The fourth V is sometimes offered as value or variability. Managing and using big data requires powerful analytic tools. Without them, we will be overwhelmed by big data, and our decision-making ability would be as limited by too much data as by no data at all. The challenge of big data has been an impetus for an evolution in information management called "cognitive computing."

Cognitive systems differ from traditional programmable systems in several ways. Programmable computing is limited to fixed calculation. Performance is improved by increasing processor speed and linking more systems together. Cognitive computing focuses on the data, uses statistical analysis, and handles the uncertainty associated with big data. The computer systems "understand" data rather than just perform calculations.

Decision support can roughly be divided into two classes: knowledge-driven and data-driven. Knowledge-driven data support assumes that the data exists in documents such as journal articles, guidelines, textbooks or even the free-text portion of an electronic health record. The challenge is to extract relevant information from the text and present it to the decision maker in a usable way. Data-driven decision support involves using resources, such as electronic health records for large populations to perform comparative effectiveness evaluations with existing data to create evidence and insights that can be used for individual patients.

The use of IBM's computer Watson for healthcare decisions is an example of knowledge-driven decision support. Watson is a natural language-processing system that actually understands written English. Natural language is the usual language of communication, which we use for writing or speaking. Watson demonstrated that skill by winning the *Jeopardy!* quiz game against the show's two most successful champions. Playing the game required that Watson understand the clues (in the form of answers requiring a question in response) well enough to read large volumes of text information and extract the information necessary to create an appropriate response. The version of Watson that played *Jeopardy!* was able to read and understand 200 million pages of text in three seconds. Watson learned how to play in large part through a process called machine learning. In machine learning, the computer teaches itself how to improve performance. Watson was fed thousands of answer-question pairs from previous *Jeopardy!* episodes so that it could teach itself about proper responses. Watson was then fed thousands of other previous *Jeopardy!* answers and asked to respond with a question. Watson was then told whether it was right or wrong and used that information to modify its processing and use of information sources.

Watson is learning about healthcare decision support in the same way. Watson learns the critical attributes from the history of a cancer patient and then reviews literature and guidelines to collect the information needed to offer suggestions on therapeutic options. Watson is then told whether or not its suggestions were valuable and learns from the feedback to improve its performance.

Data-driven decision support uses existing data from populations served by or available to healthcare systems. The goal is to extract inferences from data about large numbers of people that can be used to help make decisions about individuals or groups of people. In one approach, a patient is described by potentially thousands of characteristics, not just diagnoses or medications. Then a cohort of patients very similar to the index patient is created from the entire population of patients for whom information is available. The data from the similarity cohort is then mined for patterns that help identify treatments or processes that work better for such patients. The data might also allow the prediction of future adverse events, affording healthcare providers the opportunity to intervene in time to mitigate the impact.

Managing and using big data is challenging. However, for many analytic tools, more data is better. Data on more patients allows the identification of more subtle patterns. It could also allow providers to be more detailed about a specific cohort of similar patients so that they can deal with less common conditions more effectively. IBM is currently working with Memorial Sloan-Kettering Cancer Center and Wellpoint, a large private health insurer, to develop Watson to help choose therapies for patients with cancer. Watson has learned to identify critical attributes from the electronic health record of a cancer patient; review thousands of documents, such as guidelines and journal articles; and make suggestions about therapeutic options. For example, take the case of a woman with metastatic lung cancer. She is ambulatory, but limited by shortness of breath, and has a history of diabetic neuropathy. Watson would review the literature to extract suggestions that would benefit the patient but that did not exacerbate her existing co-morbidities. The data-driven decision support tools might identify a cohort of 250 people very similar to the index patient and find that patients receiving an additional drug, not reported in the literature, had better outcomes.

Watson is still early in development for use in the healthcare system. Watson's use for oncology is going to be rolled out to two community-based oncology groups for their evaluation at the end of 2013. Watson's use for utilization management, that is, helping to make decisions on pre-authorization for payment for medical interventions, is close to completion.

There is always the concern that computerized data can be used for negative purposes, such as to discriminate against individuals, to deny employment, insurance, healthcare services, and so on. Access to more information often means sharing information from multiple sources or institutions, which increases the chances for loss or corruption of data. Even the strongest safeguards cannot guarantee that privileged information won't be lost and misused. Hackers might try to access healthcare information and patients should be made aware of the effect of loss or corruption of data. None of the analytics resources change the existing risks for misuse or loss of healthcare information. Those risks are more reflective of human behavior than they are of the tools. Watson, for example, makes it easier to make an evidence-supported decision by giving physicians and other healthcare providers access to the ideas from more literature than they could otherwise use.

How that power is used is in the hands of the decision maker. On the one hand, if the provider's goal is to deny care, for example, one could accomplish that with a far more cursory review. On the other hand, law and concerns about privacy may inhibit healthcare research.[5] The use of de-identified data may help limit the impact on individuals, but it is not clear that data can be made completely anonymous. For example, it may be possible to identify study participants using de-identified genetic data.[6] In January 2013, a bill was submitted to the Virginia Senate effectively prohibiting the use of healthcare data for analytics. Fortunately, the bill was voted down in committee.[7] The challenge will be to balance the potentially competing interests of all the stakeholders.

Memorial Sloan-Kettering Cancer Center and Wellpoint are developing Watson, a workload-optimized system powered by IBM POWER7, to help choose therapies for patients with cancer.

It has long been necessary to get consent from a patient to use health information or participate in a study. With the explosion of new information, such as genomics, and with new ways to re-use existing information for analyses, the process of consent is now more complicated.[8] Informed consent could now require a discussion of risks in sharing or losing information as well as the extent of the consent. Is the person consenting for the use of personal data for just this one study or for some or all possible future studies? It is hard to imagine that informed consent could be given for an unknown future event. If Watson performs a research study on computerized data obtained years earlier for a different study, should subsequent consent be obtained or should we develop a new concept of consent? If a population study performed by Watson or another powerful computer, where a specific patient is not a target subject, shows possibly medically important information, should that patient be notified? If so, who is responsible for making the notification?

We are developing powerful tools to use health and other personal information to help make more personalized and beneficial decisions. There is clear value in sharing and using as much information as possible in that pursuit. However, the tools and the variety and extent of the information becoming available create threats to privacy and security, as well as the risk for misuse. It will be difficult for rules and regulations to keep up with the challenges as information moves faster than the legal process. Obtaining the benefit of the increasingly broad uses of information for research while protecting the interests of all stakeholders will be a continuous task. ■

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Ask the ethicist

Can a surgeon refuse to perform a second cardiac valve replacement on a patient with IV drug abuse?

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Question: A 26-year-old man underwent successful bioprosthetic tricuspid valve replacement two years ago for a valve infection complicating right-sided endocarditis resulting from intravenous (IV) heroin abuse. He was referred to a drug rehabilitation program on discharge but did not follow through and continued using IV heroin. He has now developed recurrent right-sided endocarditis and a prosthetic tricuspid valve infection from *S. aureus* that clearly resulted from IV drug abuse. The cardiothoracic surgeon who performed the first valve replacement was consulted and refused to perform a second valve replacement, arguing that the patient is responsible for his illness, that he may need more valve replacements after this one, and that it is squandering society's scarce resources to replace his valve prosthesis. The Bioethics Committee was consulted. How would you advise?

Response: Bacterial endocarditis has long been recognized as a catastrophic illness. In the pre-antibiotic era, its signs and symptoms were well recognized but treatment was at best palliative. With the advent of antibiotics in the 1940s, and cardiac surgery in the 1950s and 1960s, aggressive therapy became possible.[1] During the next five decades, successful treatment of a majority of patients with native valve endocarditis became the norm. Infection of a prosthetic heart valve, however, remains more ominous and has less favorable outcomes, partly because of the presence of foreign material at the site of the infection.[2,3] While patients whose native valve is infected with low-virulence organisms may be cured with antibiotics alone, patients with high virulence organisms (*S. aureus, pseudomonas*, fungi) usually require valve replacement coupled with antibiotics. Patients with prosthetic endocarditis almost always require valve re-replacement, especially if the organism is known to be virulent.

A surgeon's decision to operate is generally tempered by the balance of likely outcomes with and without intervention. In a young patient without overt malignancy, surgery may be the only chance for survival, even if risks of death or poor outcome are high. Generally, a surgeon will recommend against surgery only if it represents an exercise in futility—as in extreme old age.

In this case, the initial surgeon has decided not to operate, primarily for reasons of broad social implications. The patient had behaved in a manner that jeopardized his new valve. There is no guarantee that he will not continue to abuse drugs. The long-term risk of death in intravenous drug abusers who require valve replacement for endocarditis is very high, perhaps 90 percent over 10 years.[4] The team may be exposed to infectious agents common in this group of patients, such as HIV and hepatitis C. Dollars, blood products and other scarce resources will be used that, arguably, might provide better benefit to a more compliant patient. Finally, the surgeon has a right to refuse his services.

Surgeons generally care for one patient at a time, with concern focused on all that afflicts that patient and for the good he or she can do versus the potential harm of surgical and nonsurgical care. While social issues cannot be denied, they are secondary to the focus on one individual patient in trouble. Many, if not most, of the illnesses physicians and surgeons treat are directly caused or made much worse by patient behaviors, such as alcohol consumption, tobacco use, morbid obesity, non-compliance with medication and illicit drug use. This patient's situation is not dissimilar to the trauma patient in a motor vehicle accident who has a high blood alcohol level, or to the active smoker who presents with coronary artery disease and requires coronary stenting or bypass surgery. He deserves a second valve replacement, and an equally aggressive effort to treat his drug addiction. Neither intervention alone will offer him a good chance at survival.[5]

A surgeon should never feel forced to operate on a patient. Arguments are never meant to coerce a surgeon to perform a procedure about which he or she has strong reservations. Ultimately it is a very personal agreement between the surgeon and the patient. To be sure, there are situations in which a surgeon may choose not to do surgery, such as in extremes of risk; HIV infection, with its risk to the team; a Jehovah's Witness patient who needs heart surgery but refuses blood transfusion; or a termination of pregnancy. In such cases, the patient is almost always referred to another surgeon or another institution where care will be provided. In this instance, with acute bacterial prosthetic valve infection with a virulent organism, valve re-replacement must be conducted quickly. Social concerns are relevant to the bigger picture but should play a smaller role when a person's life hangs in the balance.

Outcome: Following a discussion with surgical colleagues and bioethical consultants, the surgeon performed the valve replacement. ■

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The legal column

Patients' online reviews of physicians

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Online patient reviews are becoming a major force in the healthcare industry, but some healthcare providers lament this development. In fact, an opportunistic vendor, Medical Justice, preyed on healthcare provider fears and sold healthcare providers a form contract that asked patients to waive their rights to post reviews. Medical Justice eventually recognized the errors of that approach and did a complete reversal; it is now selling healthcare providers a service, eMerit, that monitors search engines and doctor rating sites.

Medical Justice's contracts prohibiting online reviews have not been definitively tested in court, but attempts to restrict patient reviews are problematic. Anti-review contracts prevent consumers from expressing their views, and they deprive other consumers of information that can help them make better marketplace choices. The provisions also create serious legal risks for the businesses imposing them, as illustrated by the following three incidents:

- In the late 1990s, software company Network Associates restricted buyers from publishing reviews of its software. In 2003, a New York court enjoined Network Associates from continuing to use that restriction.[1]
- The U.S. Department of Health and Human Service's Office of Civil Rights required a doctor to stop using Medical Justice's anti-review form.[2] The agreement prohibited the patient from "directly or indirectly publishing or airing commentary about the physician, his expertise, and/or treatment in exchange for the physician's compliance with the Privacy Rule."
- New York dentist Stacey Makhnevich and her practice Aster Dental required that patients sign a Medical Justice–based confidentiality agreement as a precondition to treatment. This version of the agreement tried to silence patients by assigning to the dentists a copyright over any comments related to their treatment. The patient, Robert Lee, had a dental emergency and signed the agreement to get treatment. He later sued to invalidate the agreement. The court's initial opinion signaled serious skepticism about the legitimacy of the dentist's conduct.[3]

Even more important than the legal risks, asking patients to restrict their rights to review a healthcare provider sends a terrible message to patients and sets the stage for distrust.

While contractually restricting patients' reviews is not the right answer, some healthcare providers are frustrated by their perceived inability to publicly defend themselves from negative patient reviews. Providers have ethical and legal obligations to maintain patient confidentiality, with severe penalties for noncompliance. These restrictions seemingly impose a gag order on doctors to rebut patient misstatements.

If a patient's review misstates facts, healthcare providers actually have several options:

- A patient may consent to discussing the matter publicly. Angie's List prospectively requires this consent from patients who review doctors.[4]
- Most patients' criticisms of their healthcare provider don't relate to individualized medical advice. As one recent study found, "Unhappy patients who post negative online reviews of their doctors complain about poor customer service and bedside manner four times more often than misdiagnoses and inadequate medical skills."[5] If a healthcare provider feels the need to publicly respond, he or she can rebut most of these issues without discussing confidential patient information.
- If patients discuss their specific medical situations, the healthcare provider may discuss its general philosophies and standard protocols without disclosing confidential patient information.

Doctors also can bring lawsuits to redress negative patient reviews, but litigation isn't a great option. There is no point in suing online review websites for patient reviews. Review websites are categorically protected from liability for third-party content except in cases involving intellectual property (see 47 U.S.C. §230). No doctor has ever successfully won in court against an online review website for publishing patient reviews.

Suing patients is only marginally more attractive than suing review websites, even if a patient has lied. Inevitably the patient will respond with a malpractice claim or a complaint against a provider's license; a lawsuit calls more attention to the patient's assertions; doctors suing patients often look like they have something to hide; and, perhaps most importantly, doctors are not likely to win in court. Over the past decade, I've identified about two dozen doctor vs. patient lawsuits over online reviews. Doctors have rarely won against their patients in court and, even worse, some doctors have been ordered to pay their patients' attorneys' fees.[6]

The legal analysis is more complicated if it can be proven that a competitor or vindictive party is posting fake reviews. Those lawsuits are more winnable than lawsuits against patients, but often the time and costs required to win simply aren't worth it.

Online patient reviews remain a work-in-progress; more work needs to be done, especially on the part of review websites, to improve the credibility of patient reviews. Still, online patient reviews are good news to the healthcare industry, not bad news. Patient reviews will improve the industry's service levels, providing valuable customer feedback to healthcare providers and help them improve their service. Good healthcare providers will be recognized for the quality services they provide. ■

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Ethics and the humanities

Eben Alexander's *Proof of Heaven: A Neurosurgeon's Journey into the Afterlife*

Book review by Albert Howard Carter, III, PhD
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Proof of Heaven: A Neurosurgeon's Journey into the Afterlife, a *New York Times* best-seller, is a dramatic and extraordinary account of Eben Alexander's sudden illness—a viral meningitis that put him into a coma for a week—and his extraordinary recovery to full health. Alexander interweaves several stories. The first three we would expect: 1) his personal story of his condition (sinking, desperate, near death); 2) the medical treatment given by his medical caregivers; and 3) the impact on his family and friends, who are all distraught by his sudden and precipitous path toward death. His case is dramatic because he does not die (as he statistically should) and because he makes a full recovery.

The extraordinary aspect of this case lies in two more stories: 4) not only medical interventions but also psychic interventions rescue him from his coma; and 5) while his brain is shut down by infection, he experiences an intense vision of what he calls heaven. His book claims that he has *proof of heaven* and that the universe is pervaded by loving consciousness—if only we could perceive it.

The fourth story is about a psychic intervention by Susan Reintjes, a psychic with experience in contacting coma patients. She reached Alexander telepathically and also told his wife, Holley, by phone, that "it wasn't his time to die" and "his body knew what to do." Reintjes asked Holley to repeat those two phrases aloud at her husband's bedside. Alexander reports that such messages and other prayers got through to him and gave him energy for his return.

Before his illness, Alexander had attended church now and then and felt that he had largely lost his religious faith. After his illness, he is convinced that there is a God, angels and heaven, and that the entire universe is permeated with divine love.

A sixth story begins after the conclusion of the book: upon his complete recovery, Alexander has become a missionary in his own country, even within his own medical tribe. When he tells the story of his illness and spiritual adventures to doctors, however, they do not believe him. He understands the doctors' reluctance because he was previously a rationalist and a materialist; before his illness, he also did not believe patients who told him similar accounts.

Since that time, Alexander has co-founded an institute called Eternea, which will sponsor research into near-death experiences, the "physics of consciousness" and related matters.

When I first read *Proof of Heaven*, I was thrilled. Here was a dramatic, personal and exciting story by a neuroscientist who could give us details from the patient's point of view. However, others, including neurologist Oliver Sacks, have found flaws and inconsistencies that make it hard to believe that the book constitutes any sort of proof. Sacks, in *The Atlantic*, December 12, 2012, argues that there was no vision during coma, rather a near-death experience that consisted of a brief hallucination when Alexander emerged from coma. Michael Schermer, writing in *Scientific American* (April 2013), calls the book "proof of hallucination not heaven." What is clear, however, is that readers, who have purchased nearly two million copies of the book, deeply want to believe in such a tale. Alexander himself continues to stand by what he wrote, apparently believing that his mind did indeed go to heaven. The book has been aggressively marketed, and in Alexander's new life he is an apologist for his vision. He has a website with videos, CDs, meditations and bracelets.

Are Alexander's claims true, illusory or fabricated? Why are the millions of people who have purchased this book and his other materials apparently willing to believe his *proof of heaven*, a claim that lacks scientific proof? Is there a heaven? Are there angelic beings? Is the universe permeated by love? Even if Alexander's interpretation of his experience is wrong, his book is fascinating and provocative. ■

Legal, continued from page 6

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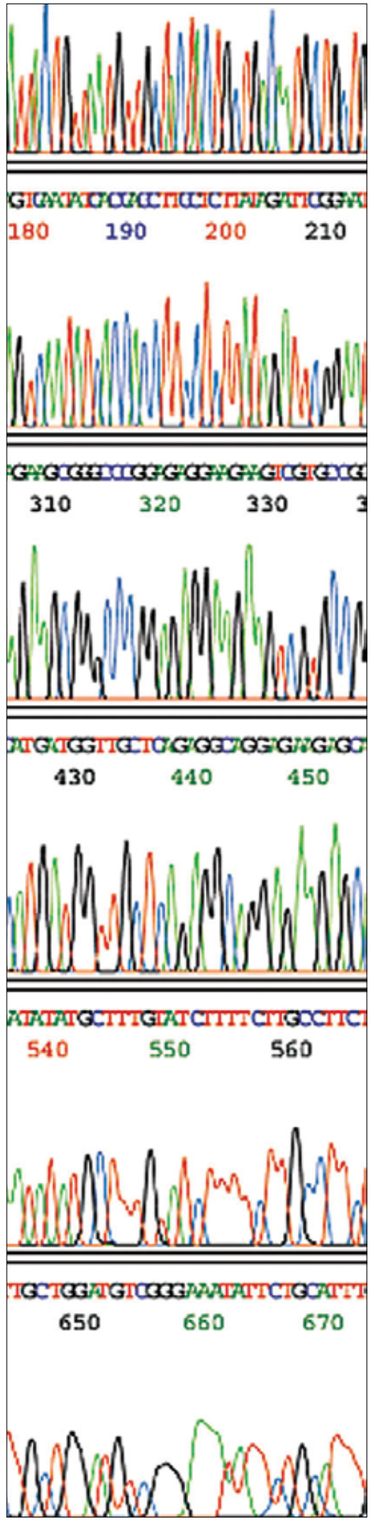
[3] Lee v. Makhnevich, 2013 WL 1234829 (S.D.N.Y. March 27, 2013).

[4] Angie's List Membership Agreement, April 25, 2012, ∫ 13, http://my.angieslist.com/angieslist/aluseragreement.aspx ("You also acknowledge that the healthcare or wellness provider about whom you submit Content may submit Service Provider Content that contain your private or confidential health information in response to Content you submit").

[5] Press Release: *Online Doctor Reviews: Four Times More Patients Peeved About Service & Bedside Manner Than Medical Skills*, April 30, 2013, http://www.reuters.com/article/2013/04/30/idUSnGNX736vBG+1c3+GNW20130430.

[6] See the complete chart at http://digitalcommons.law.scu.edu/cgi/viewcontent.cgi?article=1289&context=historical.

Note: This essay does not provide legal advice. Please consult your own attorney before making any decisions regarding the topics in this essay.



Dialogue

Whole genome sequencing: Clinical and ethical challenges

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Jennifer McCormick, PhD, MPP, does an excellent job outlining some of the key issues that arise with the advent of whole genome sequencing (WGS) (*Lahey Clinic Journal of Medical Ethics*, spring 2013). She describes the various reasons why genome and exome sequencing might be performed. She also discusses their potential benefits, including uncovering a new diagnosis in a complicated medical case and/or providing tailored treatment as a result of increased knowledge of the pathophysiology of disease. Despite these exciting benefits, we are in full agreement with her statement that WGS poses the potential of "being translated too quickly," since the current analytic validity, clinical validity and clinical utility of WGS remain below the thresholds one would expect in an evidence-based practice.

McCormick's commentary stresses two key clinical issues that arise frequently: the presence of "variants of uncertain significance" (VUS) and the determination of what incidental results should be provided to patients/consumers. We will elaborate on these issues based on our own experiences providing genetic counseling for patients and research subjects who are receiving clinical interpretation of their whole genome or exome (WES) sequences. We will briefly mention several additional areas that pose further ethical and clinical challenges.

First, one of the most complicated issues arising in the clinical interpretation of WGS results is how to evaluate novel or rare variants that are discovered. Even after using bioinformatics to narrow variation down to those variants that are mostly likely to pose a relevant difference (those that occur in conserved areas of a coding sequence in a gene implicated in human diseases and that change the protein in some manner), for instance, most reported genomes have several hundred variants that meet these criteria and require further individualized assessment by hand. Such "manual curation" can be time consuming and, since there is not currently a centralized resource for such data, may require evaluation using various databases and modeling algorithms. Few will be easily categorized into "known pathogenic variant" or "known benign polymorphism," and the vast majority will remain novel and unclassified as VUS.

For example, one study showed that several clinical laboratories provided different interpretations of the results of testing for inherited cardiomyopathies (between VUS and "pathogenic" categories), even when citing the same or very similar data.[1] These findings are consistent with our anecdotal experiences in classifying novel or rare variants, as well as experiences in clinical interpretation of genotype data,[2] and suggest low clinical validity to WGS findings. Over time, variants of uncertain significance may be reclassified as benign or pathogenic based on information, such as frequency in control datasets, family segregation analysis, concurrent presence of the variant with a known pathogenic mutation, and functional studies. There is a movement to collect such data in a publicly available registry.[3] This also raises the ethical question of whether clinicians, laboratories or researchers should be encouraged or even obligated to recontact patients when

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variants are reclassified, and whether this process could be managed on a practical level. A recent comparison of six laboratories providing clinical WES demonstrated significant differences in results management. Some laboratories stated that they would proactively contact the ordering provider if any variant were reclassified to pathogenic; others would recontact the ordering provider only if the primary result was reclassified; still others placed the onus on the ordering provider to periodically check for variant classification updates.[4]

When one is performing a genetic test, or even a panel of genetic tests, for a clinical indication (e.g., a patient undergoes a next-generation sequencing panel to try to determine the cause of breast cancer within her family) most, but not all, laboratories and clinicians would disclose the presence of a VUS and do their best to put the finding in context for the individual patient and family. However, when one obtains a VUS (or dozens of them) in an otherwise healthy person with no specific clinical indication, the disclosure of results becomes more complicated. In March 2013, an American College of Medical Genetics and Genomics (ACMG) workgroup suggested that the return of incidental findings should be limited to those variants that are considered known or highly probable pathogenic variants. While this suggestion is controversial, the workgroup also selected a small set of conditions (24 cancer genes, 31 cardiology genes and two genes related to malignant hyperthermia) that are highly penetrant monogenic disorders with significant medical implications, that can have onset as early as childhood, and that are considered medically actionable.[5] Results meeting these criteria would be considered of such medical importance that it would be unethical not to return them; therefore, it should be "obligatory" for return to both adults and children.[6-8] Yet, while many clinicians conceptually agree that disclosing results that have the potential for medical intervention is reasonable,[9-10] it is difficult to reach consensus around what constitutes "clinically actionable" and how to incorporate advances in medical interventions once genomic results have been delivered.

The obligatory disclosure aspect of these guidelines also stands in contrast to previous recommendations; several studies suggest patient autonomy is the most important factor in determining which incidental findings are ultimately disclosed.[10-12] Already, some clinical laboratories have responded by offering patients the option to decline findings in the ACMG-guideline supported genes,[13-14] while others have fully adopted such guidelines as their incidental finding policies in clinical WES/WGS.[15] As the ACMG guidelines themselves suggest, these recommendations are likely to evolve as short- and long-term data emerge about the disclosure of incidental findings.

Finally, a key area that was only briefly raised by Dr. McCormick is the concept of informed consent for WGS. What should patients and research participants be told, and is it even possible for them to conceptualize the potential impact of the predictive information that they may learn from WGS? There is significant concern that the current single-gene disorder paradigm for obtaining informed consent is not practical in the context of WGS and WES and could be overwhelming to the patient.[5, 11, 16-17]

A "generic consent approach"[12, 18] and use of techniques that facilitate communication and reporting of data, such as categorization of results, have been proposed.[19, 20] Research on biobank participants and WGS research participants suggest that people expect to receive broad information about potential genetic risks.[16, 21-23]

However, most studies assessing psychosocial impact of predictive genetic information involves testing performed on the basis of personal or family history and mostly assess short-term outcomes. Limited data on healthy individuals receiving direct-to-consumer genotyping data suggests that significant psychosocial impacts are unlikely (e.g., anxiety), but also that people are unlikely to share information with their physicians or to effect behavior change on the basis of such results.[24] Even more limited is long-term psychosocial follow-up of healthy individuals who unexpectedly learn they carry a highly penetrant variant.[25] More data is needed that will represent the general population and appropriately assess validated and long-term measures of psychosocial outcomes.

Many ethical and clinical challenges accompany the clinical use of WGS and WES, made even more difficult by the rate at which these tests are being offered. We strongly encourage research that will assess the clinical effectiveness, short- and long-term psychosocial implications, and patient satisfaction related to genomic counseling. ■

Response: I thank Ms. Ormond and Ms. Grove for their thoughtful response, and I wholeheartedly agree with the points they raised. I would like to comment further on the statement from the group of experts from the ACMG. The goal of the statement's authors was to provide some clarity to clinical laboratories performing WES or WGS on what to do with incidental findings. As noted, the group has taken the position that any variant of known or unknown significance (VUS) discovered in any of the 57 significant genes these experts identified should be reported by the laboratory to the ordering clinician. The group also said that clinical laboratories should actually look for variants in these 57 genes.

It is intriguing that a genetic incidental finding is considered by many to be something that is "accidentally" or "unexpectedly" found—not actively sought. Some commentators have noted that, in fact, the experts' position of obligatory seeking of VUS in the 57 genes is right in line with standard clinical practice. For example, in the review of film from a clinical CT scan of a particular body organ, a radiologist will systematically review and report any irregular findings. Some irregularities may actually be "incidental" to the original condition that prompted the CT scan in the first place.[1,2] Others, however, have noted that the goal of using WES and WGS for a particular clinical indication is not to scrutinize the entire genome for any and every variant (known or unknown)—or, in other words, test for all kinds of genetic conditions and risk factors. Rather, the aim is to use the power of the technology to identify genetic associations for a condition; or, in the case of a cancer, also identify a potential drug target in the tumor genome.[3] A mandate to actively look for variants is akin to mandating genetic testing, similar to mandated newborn screening, for the conditions associated with the 57 genes determined to be of significant clinical import by these experts. Is that the direction in which we should be moving?

The list of 57 genes is also interesting. BRCA1 and 2 are on the list; these are highly penetrant, and there are preventive measures that can be taken. However, experience has shown that some women with a family history of breast and ovarian cancer (two conditions associated with these two genes) opt not to be tested, because they wish not to know whether they carry the gene. Similarly, some individuals with family histories of Huntington Disease opt not to undergo genetic testing. One could ask why CDH1, which increases one's risk for gastric cancer and lobular breast cancer, is not on the list. A different group of equally qualified experts may have created a slightly different version of 57 genes, in which variants should be sought and should be reported.

I agree with Ormond and Grove that we need more empirical data assessing the clinical usefulness and impact, and the short- and long-term psychosocial implications of learning about genetic risk information, especially when it is not expected. As we continue to negotiate translation of WES/WGS into clinical practice, we must maintain an active dialogue among all stakeholders to ensure that ethical, policy and social implications are considered. ■

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