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FROM THE EDITOR IN CHIEF

Illustratio

Audiey C. Kao, MD, PhD

Edmund Pellegrino, MD was one of my shining mentors as a young physician. He was widely recognized as an exemplar of what it means to be a healer. What was less well known, or at least acknowledged, was that he was not particularly "tech savvy." Pellegrino never used email to communicate and rarely, if ever, bothered with personal computing devices that most of us cannot seem to live without. Tweeting and other social media exchanges would almost certainly have been anathema to him. During his many years at Georgetown University, he relied on his longtime assistant to translate his academic work in bioethics for dissemination in the digital world. Therefore, it seems ironic that he would not have been a reader of the online ethics journal that I cofounded nearly 20 years ago.

This month's issue marks the official launch of a completely redesigned *AMA Journal of Ethics*. From an aesthetic standpoint, regular readers will notice a dramatic increase in the use of visual assets. In line with the journal's editorial mission of "illuminating the art of medicine," the clean, uncluttered layout provides a canvas where visuals complement insights and guidance proffered in the text of numerous and cross-disciplinary articles. A concerted effort is underway to publish a wider spectrum of "art of medicine" content in response to the Call for Artwork and Conley Art of Medicine contest. Future articles will be authored by curators from and highlight collections of one of the world's leading art institutions—the Art Institute of Chicago. This exciting partnership with the Art Institute reflects our mutual appreciation of the provocative power of the arts to inform and inspire ethical inquiry and the practice of healing.

The journal design is now more user friendly and functional; navigation is more straightforward and intuitive. Content, whether included as a continuing medical education offering, podcast, or part of the ethics case library, for example, is readily searchable and easily accessible. Educators of medical students or resident physicians are able to filter and download content based on the core competencies established by the Accreditation Council for Graduate Medical Education[1-3] or by specialty area. Articles are also identified according to a set of core topics (eg, disparities in health and health care/social determinants, end-of-life care/spirituality, patient safety/error disclosure, conflicts of interest/dual role as clinicians and researchers) that are relevant to the substance of a specific article.

Issues of the *AMA Journal of Ethics* are a blend of manuscripts solicited from experts and those submitted (unsolicited) for peer-review consideration. Each monthly issue focuses on a specific theme selected by the editorial staff among those submitted by medical students, resident physicians, or fellows who are chosen in response to a call for theme issue editors. Additionally, we are also planning to publish 1 or 2 issues per year in collaboration with leading centers of bioethics. The October 2018 issue, for example, on health and food ethics, expresses our work with faculty at the Johns Hopkins Berman Institute of Bioethics.

Regardless of theme issue, the *AMA Journal of Ethics*, as an editorially independent journal, has always been freely available to all learners and educators interested in ethically important and complex matters in patient care and health policy. Fostering careful deliberation, thoughtful decision making, and ethical behavior among those caring for sick and injured patients by publishing high-quality ethics and humanities content is considered a public good by the journal's editors and publisher.

Lastly, it has been more than 5 years since Pellegrino passed away at the age of 92. I can only hope that he, as a learned man of strong Catholic faith, is smiling down on us and sending some illumination (or *illustratio* in Latin) our way as the *AMA Journal of Ethics* embarks on the next chapter of its editorial life.

References

1. Epstein RM. Assessment in medical education. *N Engl J Med*. 2007;356(4):387-396.
2. Potts JR III. Assessment of competence: the Accreditation Council for Graduate Medical Education/Residency Review Committee perspective. *Surg Clin North Am*. 2016;96(1):15-24.
3. Vanderbilt AA, Perkins SQ, Muscaro MK, Papadimos TJ, Baugh RF. Creating physicians of the 21st century: assessment of the clinical years. *Adv Med Educ Pract*. 2017;8:395-398.

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FROM THE EDITOR

How Stratification Unites Ethical Issues in Precision Health

Jason N. Batten, MA

Precision approaches to medicine and health are hailed as a paradigm shift in our approach to disease prevention, diagnosis, and treatment. This issue of the *AMA Journal of Ethics* maps out many of the ethical issues that arise in the context of precision medicine and health. One of the reasons these ethical issues are so challenging to address—and worthy of an entire journal issue—is that they seem disparate and unrelated at first glance, covering a large swath of territory: privacy, informed consent, shared decision making, disclosure, social justice, valuation practices, regulation of human subjects research, and so on. We can more effectively address ethical issues in such diverse areas if we have a conceptual basis for understanding how they are united in a coherent whole.

Arriving at this understanding requires that we accurately identify the basis of precision health, which is often falsely characterized as the incorporation of genetic information into health care. In actuality, the unifying feature of all precision approaches is *stratification*. Precision approaches, whether or not they use genetic information, divide patients into smaller subgroups for the purpose of targeted, ie, precise, interventions. Stratification in health care is not new: existing clinical practices include using antigen testing to match patients with blood products of the right type or using receptor testing to target hormonal therapies to patients whose cancers will respond.[1] These are cited as early examples of precision medicine because clinicians use biomarkers to stratify patients into new groups to better target clinical interventions. What is novel about the current precision health approaches is their scale and speed: they use larger data sets with faster turnaround than traditional biomedical research.

Although these emerging approaches have received the label "precision" from the federal government[2] and some health care systems (eg, my own institution[3]), this label is something of a misnomer. It fails to convey that greater precision is achieved through stratification.[4] The centrality of stratification is evident in the decision of the United Kingdom's Medical Research Council to brand a national research strategy as the Stratified Medicine Initiative, the goal of which is described as follows: "Stratified medicine is based on identifying subgroups of patients with distinct mechanisms of disease, or particular responses to treatments. This allows us to identify and develop treatments that are effective for particular groups of patients."[4]

The contributors to this issue address many of the ethical issues that arise in the context of precision health. Although none addresses the idea of stratification directly, the concept of stratification links their contributions together, since stratification is the basis of all precision health efforts. Stratification has only rarely been explored as a concept with ethical fallout[5-7] and is often downplayed in favor of the label "precision." Therefore, this editorial lays out how the ethical issues explored by our contributors and in precision health more broadly are united and organized by the concept of stratification.

Goal and Degree of Stratification

First is the question of group size: how small should we aim to stratify? The transition from *personalized* medicine (implying treatment tailored to the individual) and *precision* medicine or health (implying stratification into subgroups or subpopulations) reflects the importance of this question.[8,9] These shifts in rhetoric raise questions about the goal of stratification: are we seeking to individualize treatment, provide more targeted interventions to existing patient groups, or improve public health? Eric T. Juengst and Michelle L. McGowan trace the historical development of these various goals by examining the rhetorical shifts from personalized medicine, to precision medicine, to precision health, and the emerging wellness genomics.

Similarly, considerations about the appropriate degree of stratification raise practical issues of cost and feasibility: how valuable is it to stratify patients into ever-smaller groups, and what are the costs of doing so? In exploring these questions, Holly K. Tabor and Aaron Goldenberg make an analogy to patients with rare diseases—the smallest of subgroups—in order to explore the practical lessons we can learn about precision health from our experience with rare diseases.

Quality and Collection of Data Used for Stratification

Next is the question of basis: which data should we use to stratify individuals into subgroups? While some approaches stratify on the basis of single biomarkers, others use complex analytic processes (eg, machine learning) to stratify on the basis of large data sets. These data sets include a broad array of data on individuals, sometimes including the whole genome sequence or the entire electronic health record (EHR). Armed with the modern tools of bioinformatics, which have the capability to process this information, we must question the impact of using socially sensitive or poor quality data. Brittany Hollister and Vince L. Bonham examine possible limitations and biases in the collection and interpretation of social and behavioral data in the EHR (eg, race, socioeconomic status) and the influences of using such data in the large cohort research programs that have come to define precision health. And Clara C. Hildebrandt and Jonathan M. Marron argue that, in order to provide equitable access to therapies resulting from CRISPR/Cas9 gene editing technology, we must partner with underrepresented groups in order to enhance diversity in our genomic databases.

While precision approaches require data, in practice this data can be ethically challenging to obtain. At times, this data is collected at great cost—even harm—to patients, which raises questions about how to balance benefits and burdens of implementing a stratified approach to patient care. Anava A. Wren and K. T. Park explore ethical challenges encountered in the fraught context of pediatric inflammatory bowel disease. One of these challenges is the choice between guiding precision therapy using data from repeated endoscopies (which provide higher-quality data but pose risks to patients) as opposed to patient-reported outcomes (which are subjective and less reliable, eg, pain). Rebekah Davis Reed and Erik L. Antonsen argue that though there are challenges in preserving the privacy and confidentiality of astronauts' genetic data, federal law allows the National Aeronautics and Space Administration (NASA) to collect employees' genetic data for purposes of occupational surveillance, research, and development of personalized pharmaceuticals. And this month's podcast explores the potential benefits—and ethical challenges—associated with the National Institutes of Health's All of US program, which aims to collect health data from 1 million Americans. Ysabel Duron and Katie Johansen Taber explain why it's crucial for precision health initiatives to ensure inclusion of participants and perspectives from underserved communities.

Once data is collected, it must be stored safely and used only in ways for which individuals have given consent. The context of precision health poses challenges to traditional notions of privacy and informed consent due to the volume and nature of data being collected, the tools used to collect the data, and the many unanticipated uses of such large data sets. Cynthia E. Schairer, Caryn Kseniya Rubanovich, and Cinnamon S. Bloss explore how the terms of use of mobile health devices—especially apps, which have the potential to capture large amounts of data for precision health efforts—undermine the tenets of informed consent for research and how researchers might negotiate terms of use with commercial partners.

Meaning and Uses of Stratification

In many cases, stratification itself—that is, how subgroups are labeled and defined—becomes ethically charged. For example, if patients are grouped into a socially undesirable category, the stratification itself becomes sensitive information. Nicole Martinez-Martin, Laura B. Dunn, and Laura Weiss Roberts explore how basic demographic data can be used to stratify patients with psychosis into those predicted to have a good or poor prognosis. Since a prediction of poor prognosis in psychosis carries significant social ramifications, clinicians face ethical challenges in deciding whether to generate and disclose these prognostic estimates. Conversely, Sathyaraj Venkatesan and Sweetha Saji examine in graphic pathographies how stratification by prognosis (ie, survival or nonsurvival) creates uncertainty and anxiety for patients and their families and impedes clinician understanding of the illness experience. Two artistic contributions also illustrate the meaning of stratification. Samuel Rodriguez and Nick Love's *Precision Portrait*—a child against a backdrop of DNA sequences and electronic health record

data—serves to remind clinicians that patients are people, not merely collections of data. And Audrey Gray's *Kaleidescope*—repeated collections of pills in a quilt-like pattern—highlights that patients can be stratified by their use or abuse of prescription pain medications, raising issues of how clinicians can meet patients' needs for pain relief without contributing to the crisis created by diversion.

Lastly, what will new methods of stratification be used for and what ethical issues does their use raise? As these methods are still emerging, the practical details and ethical issues remain uncertain. Michelle Huckaby Lewis discusses an unexpected use of genotype-based stratification for guiding health care organizations' response to influenza pandemics: giving disease-prone individuals patient care assignments with lower risk of exposure to the virus, which, while beneficial for patients, raises issues of fairness, autonomy, and data privacy for employees. Emily L. Evans and Danielle Whicher examine the use of clinical decision support systems, arguing that they should be subject to regulations requiring, among other things, protections for patient data and transparency about the use of the systems. Focusing on patients' rather than clinicians' use of precision health tools, Kyle B. Brothers and Esther E. Knapp explore the challenges that primary care physicians will face when patients arrive at clinic with stratification results in hand from direct-to-consumer genetic testing. Finally, Camillo Lamanna and Lauren Byrne argue that machine learning algorithms trained on social media as well as EHR data can be used to assist clinicians in ascertaining the treatment preferences of patients who lack decision-making capacity.

Conclusion

Because increased funding and excitement have coalesced around precision medicine and health, we cannot avoid the complex ethical questions raised in this issue of the *AMA Journal of Ethics*. We can gain increased traction on these issues by remembering how they are united: through the concept of stratification, the basis of all precision health efforts.

References

1. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med*. 2015;372(9):793-795.
2. White House. The Precision Medicine Initiative. https://obamawhitehouse.archives.gov/node/333101. Accessed March 23, 2018.
3. Stanford Medicine. Precision health. http://med.stanford.edu/precisionhealth.html. Accessed March 23, 2018.
4. Medical Research Council. Stratified medicine. https://www.mrc.ac.uk/research/initiatives/stratified-medicine. Accessed March 23, 2018.

5. Smart A, Martin P, Parker M. Tailored medicine: whom will it fit? The ethics of patient and disease stratification. *Bioethics*. 2004;18(4):322-342.
6. Feudtner C, Schall T, Nathanson P, Berry J. Ethical framework for risk stratification and mitigation programs for children with medical complexity. *Pediatrics*. 2018;141(suppl 3):S250-S258.
7. Braithwaite RS, Stevens ER, Caplan A. Is risk stratification ever the same as "profiling"? *J Med Ethics*. 2016;42(5):325-329.
8. Committee on a Framework for Developing a New Taxonomy of Disease, National Research Council. *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease*. Washington, DC: National Academies Press; 2011.
9. Juengst ET, Settersten RA Jr, Fishman JR, McGowan ML. After the revolution? Ethical and social challenges in "personalized genomic medicine." *Per Med*. 2012;9(4):429-439.

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CASE AND COMMENTARY

Is It Ethical to Use Prognostic Estimates from Machine Learning to Treat Psychosis?

Nicole Martinez-Martin, JD, PhD, Laura B. Dunn, MD, and Laura Weiss Roberts, MD, MA

Abstract

Machine learning is a method for predicting clinically relevant variables, such as opportunities for early intervention, potential treatment response, prognosis, and health outcomes. This commentary examines the following ethical questions about machine learning in a case of a patient with new onset psychosis: (1) When is clinical innovation ethically acceptable? (2) How should clinicians communicate with patients about the ethical issues raised by a machine learning predictive model?

Case

Dr K is a psychiatrist who regularly attends in an inpatient psychiatric ward at an academic medical center. In this role, Dr K regularly sees patients admitted from the emergency department who present with new onset psychosis. A major challenge with these patients is that clinicians are unable to predict an individual patient's clinical outcomes: some return to baseline, others experience only mild symptoms, while others deteriorate and might even become severely disabled.

Dr K is interested in piloting a study based on a recently published predictive model for patients who present with their first episode of psychosis.[1] The model was developed by applying machine learning methods to a large, multisite European database of patients with psychosis and offers 2 potentially helpful pieces of information to clinicians. First, the model yields a prognostic estimate. Using the patient's baseline information such as sex, occupational status, and history of major depressive episodes, the model predicts whether the patient will have a good or a poor outcome 1 year later. A good or poor outcome is defined by the Global Assessment of Function (GAF), a validated method for quantifying a patient's overall functional status. A good outcome—defined as a GAF score of greater than or equal to 65—typically indicates that a patient is able to function with minimal impairments. A poor outcome—a GAF score of less than 65—can indicate a broad range of impairment severity.[2] At GAF scores at the higher end of poor outcome (50-65), patients can experience moderate impairment in their social or occupational functioning. At GAF scores at the lower end of poor outcome (0-10), patients might be

unable to handle their own personal hygiene or be persistently suicidal. Of note, the model predicts a good or poor outcome with approximately 75% accuracy. Second, the model guides treatment choice for some patients. Although psychiatrists have access to a variety of antipsychotic agents to treat psychosis, patients predicted to have a poor outcome benefit more from amisulpride or olanzapine than other agents.

Dr K and colleagues think this model can enhance their treatment of psychotic patients and would like to incorporate it into their practice. However, they wonder whether the prognostic estimate, in particular, should be disclosed. While this information might help patients and their families plan and make decisions, they also wonder whether, when, and how this information could cause more harm than good.

Commentary

Dr K is considering piloting a predictive model for patients with first-episode psychosis that relies on machine learning applied to large data sets drawn from European sites and patients. Machine learning is a technique used to build algorithms for computational analysis that improves as a function of experience.[3] Algorithms can be used to analyze massive data sets to determine patterns and predict future outcomes. Machine learning is expected to bring major advances to psychiatry by improving prediction, diagnosis, and treatment of mental illness.[4,5] The above scenario illustrates some of the ethical considerations that will arise as machine learning techniques move from the lab to the clinic. Although the model in this case has been statistically validated, it is not yet validated as a clinical intervention that will lead to improved outcomes. This essay first examines whether Dr K is ethically justified in implementing this clinical innovation. We then discuss whether the target population for the predictive algorithm—ie, patients with psychotic disorders—raises special ethical issues regarding informed consent that should be considered.

When Should Clinicians Implement a Clinical Innovation?

Dr K's piloting of the predictive model would be considered a clinical innovation—that is, a novel use of an intervention or model that has not been shown to be definitively clinically superior to standard practice. Clinical innovation falls into a category somewhere between clinical practice and research, as these activities were distinguished in terms of their ethical mandates in the Belmont Report.[6] What would constitute sufficient ethical justification to implement the clinical innovation described in this case?

First, there must be a demonstrated need for the innovative practice.[7] Psychotic disorders exert a considerable personal, social, and financial burden on those affected. The recovery rate (10%-15%) after a first episode of psychosis, with routine clinical care, has remained the same for decades.[8] Timely intervention after a first episode of psychosis and treatment with antipsychotic medications can improve outcomes,[9] but treatment tolerance, adherence, and response can be highly variable.[10,11] Given the

potential severity of new onset psychosis, as well as the lack of adequate treatments, there is a demonstrable need for the proposed innovation.

Next, we must consider whether the risk posed by the innovation is ethically acceptable relative to risks of the underlying condition.[7] First, Dr K will need sufficient evidence that the proposed innovation can deliver the promised benefit. While accuracy of the proposed psychosis predictive model is supported by the study conducted in Europe, it is not known whether variables present in the local context—such as differences in psychiatric practice and social support—would affect the model's validity and ability to improve outcomes for Dr K's patient population. The model will need to be calibrated to account for relevant local variables.[12] Because of the "black box" nature of machine learning algorithms, software developers do not always know or might not understand how the system has used input data to arrive at decisions.[13] Thus, designers of the system will not likely know exactly which variables need to be addressed to validate the model for a new context; additional patients' data from the local clinical setting will be needed to perform a calibration.

Calibration will need to take into account not only local variables but also error and bias. Machine learning is often presented as more objective than human judgment, but it is susceptible to operator error. When faulty data are used as input, flawed analyses can result.[14] Machine learning algorithms can also reinforce existing biases in data.[15] For example, depending upon the way an algorithm accounts for socioeconomic status or race, decisions made on the basis of that algorithm could unintentionally reinforce existing structural deficits for vulnerable patients. On the other hand, with proper calibration, the algorithm could be used to reduce bias in health care. Finally, use of the predictive model will itself influence the care patients receive, impacting how psychiatrists make treatment decisions and allocate resources. Initially, the effect of the predictive model on cases might not be adequately accounted for in its analyses. In order to ensure an ethically acceptable balance of risks and benefits in implementing a predictive model, clinicians will need to be actively involved in validating the predictive algorithm in the local context by ensuring that the calculations are attuned to the particular patient population and by outlining the associated protocols for moving from prediction to treatment.

At the same time, physicians using the algorithm may not know the variables and rationale behind predictions it generates, making it difficult for them to assess and justify resulting treatment decisions. Justifying use of a predictive model will require addressing issues of transparency and bias that arise in the use of machine learning systems by implementing strategies such as training physicians on how machine learning systems work, including physicians in their creation, and even supporting efforts to implement machine learning systems that can give insight into the reasons for their predictions. Clinicians who use the machine learning systems will need to learn more about how they

are constructed, the underlying data sets that inform their recommendations, and their limitations.[16]

Informed Consent for the Target Population

In order to ensure trust and transparency in using predictive models, there must be careful attention to ethical issues related to informed consent. Currently, informed consent is not explicitly required to use patients' data in applying and improving predictive algorithms.[12] Furthermore, patients are generally not aware when physicians use computer-based decision aids in the course of their care and are rarely informed of sources that inform their physician's judgment.[12] These facts raise the question: Do machine learning predictive algorithms such as this psychosis prediction model involve novel ethical issues that necessitate a different ethical approach?

How machine algorithms differ from existing risk assessment tools, such as those used to assess risk of heart attack or stroke, has to do with their potential impact on therapeutic relationships. As physicians increasingly turn to machine learning algorithms to inform diagnostic and treatment decisions, these algorithms might become more than just support tools.[16] Furthermore, as machine learning systems are integrated into health care settings, decisions regarding treatment or resource allocation that stem from a predictive tool could come from rules or protocols set by hospital administration rather than a treating physician. Thus, machine learning tools can reconfigure physicians' roles in their relationships with patients.[16] As machine learning systems become more integrated into care, careful examination of the fiduciary dimension of relationships between patient and machine learning decision systems in health care institutions will be needed.[16]

Because technology can intrude upon patient-clinician relationships by influencing how a physician makes decisions and directs resources to care for a patient and will impact confidentiality as machine learning systems are integrated with electronic health records,[16] patients should be notified about uses of predictive algorithms at their health care institutions. Patients will need sufficient information to consider how machine learning systems can influence their care, the confidentiality of their information, and the privacy of their data. We suggest that patients should be alerted that their data could be used to formulate or improve predictive algorithms and that predictive tools might play a role in their care. In the case of early psychosis, decisions would need to be made about when to notify patients, given that patients and families are invariably coping with severe disease-related and psychosocial stress at the time of patients' hospitalization for psychosis that could make it even more difficult to digest and retain complex information, such as the use of predictive algorithms. Community stakeholders could provide input on how to formulate the content of such notices and the procedures for engaging with patients and families meaningfully.[12]

Should a prognosis delivered by a predictive algorithm be disclosed to a patient as a part of informed consent for treatment? Informed consent does not require explanation of *all* details that inform a treatment recommendation, but it does require that explanation of *pertinent* information about the nature, risks, and benefits of treatment options be conveyed to a patient.[17,18] Therefore, clinicians would need sufficient education regarding a machine learning system in order to communicate information about an algorithm's treatment recommendation. Before disclosing a prognosis generated by a predictive model, it would be helpful to have at least some data generated by a machine learning algorithm on the effects of sharing a prognosis on patient distress and outcomes.

Given that Dr K's patients have new onset psychosis, there might be concerns that providing information regarding the algorithm's prediction could lead to psychological distress in some patients or their families. In general, assumptions that persons with severe mental illness have impaired ability to make autonomous and well-informed research and treatment decisions have frequently not borne up under rigorous scrutiny.[19,20] Such concerns need to be empirically examined rather than accepted at face value.[21] Patients might want more or less detail regarding treatment depending upon factors such as their education levels, how they assess their own decisional capacity, or their satisfaction with treatment.[22] The capacity for voluntarism—ie, the ability to make choices that are free from coercion and are consonant with an individual's values and history—is another critical component of informed consent,[18] one that necessitates engaging with patients to discern their preferences in the context of specific decisions. Attending to the individual needs and capacity of a patient for informed consent remains key, including supporting a patient's capacity to engage meaningfully in health care decisions and identifying tools that help assess decisional capacity,[23] especially relative to understanding predictive algorithms.

Conclusion

In order to implement the predictive tool in an ethical manner, Dr K will need to carefully consider how to give appropriate information—in an understandable manner—to patients and families regarding use of the predictive model. In order to maximize benefits from the predictive model and minimize risks, Dr K and the institution as a whole will need to formulate ethically appropriate procedures and protocols surrounding the instrument. For example, implementation of the predictive tool should consider the ability of a physician to override the predictive model in support of ethically or clinically important variables or values, such as beneficence. Such measures could help realize the clinical application potential of machine learning tools, such as this psychosis prediction model, to improve the lives of patients.

References

1. Koutsouleris N, Kahn RS, Chekroud AM, et al. Multisite prediction of 4-week and 52-week treatment outcomes in patients with first-episode psychosis: a machine learning approach. *Lancet Psychiatry*. 2016;3(10):935-946.
2. Hall RC. Global assessment of functioning. A modified scale. *Psychosomatics.* 1995;36(3):267-275.
3. Dwyer DB, Falkai P, Koutsouleris N. Machine learning approaches for clinical psychology and psychiatry. *Annu Rev Clin Psychol*. 2018;14:91-118.
4. Iniesta R, Stahl D, McGuffin P. Machine learning, statistical learning and the future of biological research in psychiatry. *Psychol Med*. 2016;46(12):2455-2465.
5. Darcy AM, Louie AK, Roberts LW. Machine learning and the profession of medicine. *JAMA*. 2016;315(6):551-552.
6. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont report: ethical principles and guidelines for the protection of human subjects of research. https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html. Published April 18, 1979. Accessed July 23, 2018.
7. Ghaemi SN, Goodwin FK. The ethics of clinical innovation in psychopharmacology: challenging traditional bioethics. *Philos Ethics Humanit Med*. 2007;2(1):26. doi:10.1186/1747-5341-2-26.
8. Fusar-Poli P, McGorry PD, Kane JM. Improving outcomes of first-episode psychosis: an overview. *World Psychiatry*. 2017;16(3):251-265.
9. Singh SP. Early intervention in psychosis. *Br J Psychiatry*. 2010;196(5):343-345.
10. Stevenson JM, Reilly JL, Harris MS, et al. Antipsychotic pharmacogenomics in first episode psychosis: a role for glutamate genes. *Transl Psychiatry*. 2016;6:e739. doi:10.1038/tp.2016.10.
11. Millan MJ, Andrieux A, Bartzokis G, et al. Altering the course of schizophrenia: progress and perspectives. *Nat Rev Drug Discov*. 2016;15(7):485-515.
12. Cohen IG, Amarasingham R, Shah A, Xie B, Lo B. The legal and ethical concerns that arise from using complex predictive analytics in health care. *Health Aff (Millwood)*. 2014;33(7):1139-1147.
13. Maini V. Machine learning for humans. *Medium*. August 19, 2017. https://medium.com/machine-learning-for-humans/why-machine-learning-matters-6164faf1df12. Accessed March 12, 2018.
14. Bzdok D, Meyer-Lindenberg A. Machine learning for precision psychiatry: opportunities and challenges. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2017;3(3):223-230.
15. Tunkelang D. Ten things everyone should know about machine learning. *Forbes*. September 6, 2017. https://www.forbes.com/sites/quora/2017/09/06/ten-things-everyone-should-know-about-machine-learning/. Accessed January 13, 2018.

16. Char DS, Shah NH, Magnus D. Implementing machine learning in health care—addressing ethical challenges. *N Engl J Med*. 2018;378(11):981-983.
17. Hall DE, Prochazka AV, Fink AS. Informed consent for clinical treatment. *CMAJ*. 2012;184(5):533-540.
18. Roberts LW. Informed consent and the capacity for voluntarism. *Am J Psychiatry*. 2002;159(5):705-712.
19. Dunn LB, Candilis PJ, Roberts LW. Emerging empirical evidence on the ethics of schizophrenia research. *Schizophr Bull*. 2006;32(1):47-68.
20. Humphreys K, Blodgett JC, Roberts LW. The exclusion of people with psychiatric disorders from medical research. *J Psychiatr Res*. 2015;70:28-32.
21. Roberts LW, Roberts B. Psychiatric research ethics: an overview of evolving guidelines and current ethical dilemmas in the study of mental illness. *Biol Psychiatry*. 1999;46(8):1025-1038.
22. Hamann J, Mendel R, Reiter S, et al. Why do some patients with schizophrenia want to be engaged in medical decision making and others do not? *J Clin Psychiatry*. 2011;72(12):1636-1643.
23. Palmer BW, Harmell AL. Assessment of healthcare decision-making capacity. *Arch Clin Neuropsychol*. 2016;31(6):530-540.

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CASE AND COMMENTARY

How Should Primary Care Physicians Respond to Direct-to-Consumer Genetic Test Results?

Kyle B. Brothers, MD, PhD and Esther E. Knapp, MD, MBE

Abstract

In this case, a primary care physician is presented with direct-to-consumer genetic test results and asked to provide counseling and order follow-up diagnostics. In order to deal effectively with this situation, we suggest physicians need look no further than the practice principles that guide more routine clinical encounters. We examine the rationale behind 2 major clinical ethical considerations: (1) physicians have obligations to help their patients achieve reasonable health goals but are not obligated to perform procedures that are not medically indicated; and (2) primary care physicians do not need to know everything; they just need to know how to get their patients appropriate care.

Case

A 34-year-old woman, Sarah, schedules a routine visit with her family physician, Dr S, to discuss results of a direct-to-consumer genetic test she ordered from an online vendor. After sending a saliva sample, Sarah received several reports that she accessed online and printed for her visit with Dr S.

The first report shows information about Sarah's likely ancestry. The second report contains genetic information and states that Sarah's genetic make-up includes heterozygosity for the e4 variant of the *APOE* gene, which confers an increased risk for late-onset Alzheimer disease. The second report also states that Sarah is a carrier of a pathogenic variant in the *PKHD1* gene, which is associated with autosomal recessive polycystic kidney disease (ARPKD).

Sarah has many questions for Dr S about this information. First, she wants to know what she can do about her increased risk for Alzheimer disease. Should she change her approach to retirement planning, for example? Second, Sarah is concerned about being a carrier for a *PKHD1* pathogenic variant. Although her first child was born without evidence of ARPKD and is now 2 years old, Sarah wonders about the risk of passing on this disease if she tries to have another child.

Dr S listens carefully to Sarah's questions. Although the 2 reports are written in a straightforward, consumer friendly manner, the information in the second report, in particular, contains technical and specific genetic information that is outside of her expertise.

Commentary

Nearly every primary care clinician has experienced a complicated patient request that demands significant time. Until recently, however, requests to interpret and follow up on direct-to-consumer (DTC) genetic testing were not particularly common. A turning point might have been 2017, when the number of people who sought genetic results through DTC testing companies increased dramatically.[1] Given that interest in pursuing DTC testing remains robust,[2,3] it is likely that the use of this type of consumer service will continue to grow and that primary care physicians will increasingly be asked to help their patients interpret these results. In recent years, primary care physicians have faced increasing demands from patients for this kind of assistance, so there is precedent for thinking about how they can respond and assume new, time-intensive responsibilities. In this discussion of the case of Sarah and Dr S, we will first examine challenges that could be raised by the widespread use of DTC testing and then explore how traditional practice guidelines can be drawn upon by primary care clinicians seeking to help patients interpret and respond to DTC genetic testing results.

Potential Problems with DTC Genetic Testing

A number of technical and practical concerns have been raised about DTC genetic testing. First, DTC genetic testing companies vary widely in their laboratory practices, including which genotyping technologies they use and the techniques used to validate results. A recent study showed that 40% of genetic variants identified in DTC laboratories (using various genotyping technologies) were not confirmed when Sanger sequencing (a rigorous testing method) was employed for confirmation.[4] In the same study, several variants that were successfully confirmed by Sanger sequencing had been misclassified as conferring risk for a condition. These types of errors can be reduced by using laboratory practices that adhere to requirements of the Clinical Laboratory Improvement Amendments of 1988, which emphasizes the importance of ensuring that only valid and technically rigorous results are returned to patients.[5] DTC genetic testing companies can also address these concerns by using high-quality criteria for pathogenicity. Criteria proposed by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, for example, specify types of direct and indirect evidence needed to classify a genetic variant as pathogenic. A finding that a variant occurs at a higher frequency in persons affected by a certain condition compared with unaffected persons is, for example, one piece of evidence that could legitimately be used to conclude that a variant is pathogenic.[5]

Another major challenge for the widespread use of DTC genetic tests is the lack of skilled physicians and other professionals who can properly interpret these results. DTC genetic testing companies sometimes offer access to genetic counselors by phone, but these conversations are inherently limited. In order to contextualize a genetic finding within the overall health of an individual, it is typically necessary for a patient's own clinician to assess her medical and family history and perform a physical examination. With the proper clinical skill and knowledge related to genetics, such information can be synthesized to guide a shared decision-making process. While primary care clinicians typically possess the necessary history and physical exam skills, physicians typically do not have sufficient expertise to interpret and assess risk conferred by individual genetic variants and to develop either a diagnostic or a surveillance program tailored to a patient's particular needs. In one systematic review, two-thirds of studies highlighted insufficient knowledge as a significant barrier to provision of genetic services.[6] Even subspecialty-trained physicians can feel reluctant to interpret such test results. For example, a recent study conducted at a large comprehensive pediatric cancer center demonstrated low confidence among pediatric oncologists in interpreting results of germline genetic sequencing.[7] A majority of physicians (93%) in the study wished to speak to a genetic counselor before disclosing germline test results.[7]

Given both primary care and subspecialist physicians' limited comfort with interpreting and responding to genetic test results, it seems that a dramatic increase in DTC genetic testing is likely to create significant challenges for clinicians. The current workforce of geneticists and genetic counselors is already insufficient to meet estimated needs,[8] so primary care clinicians will be obligated to fill the gap. This scenario is problematic not only because primary care clinicians rarely possess skill for interpreting and assessing genetic information, but also because most primary care practices are generally not designed to accommodate the time-intensive visits that counseling on DTC genetic testing results typically require.

~~Counseling on DTC Genetic Testing:~~ There Are No Stupid Questions

If there is a first rule of medicine, it is that physicians should never order a test unless there is a foreseeable benefit from ordering that test. No test is completely risk free. Invasive tests, like phlebotomy, confer obvious risks such as infection. But even noninvasive tests, like cheek swabs and ultrasounds, have risks of a false positive result that could lead to something more invasive or a false negative result that could provide false reassurance or forestall future testing. While most of these risks are unavoidable, diagnostic tests can be justified if there is an anticipated benefit that obtaining the test results will likely provide. When diagnostic tests offer no significant benefit, even small risks can provide compelling reasons not to order a test.

Because so many physicians strive to prevent harms to their patients by following this rule, DTC genetic testing results can seem out-of-place in clinical contexts. If physicians

feel that it was a bad idea to purchase DTC testing in the first place, they might want to either disavow an obligation to discuss these results with patients or at least try to convince patients to ignore the results. This latter response is particularly tempting, given the risk concerns discussed above. These types of negative clinician responses are similar to how some clinicians respond when they are asked to provide guidance on other diagnostic tests or treatments that they would not typically recommend. Examples include radiography performed in chiropractic clinics, DTC Lyme disease testing, topical cosmetic treatments, over-the-counter medications, and complementary and alternative treatments.

Primary care clinicians have learned through experience—sometimes tragic experience—that ignoring patients' use of alternative diagnostic and treatment options—or worse, deriding patients for them—can be harmful. These responses make patients feel even more distanced from their biomedical practitioners and less willing to disclose alternative treatments they are using. It is far better for clinicians to educate themselves about the types of products that patients are using. Physicians also have duties to respond to questions about these products in respectful ways that encourage patients to ask questions and enable meaningful opportunities for clinicians and patients to engage in conversation, build trust, and consider professional advice.

~~Referring for Management of DTC Genetic Testing Results:~~ Know What You Know, and Know What You Don't Know

If primary care clinicians are going to field questions about DTC genetic testing, they need to be ready to help patients think about responding to those results. In the short term, however, it will likely be extremely difficult for most primary care physicians to develop an adequate understanding of genetics and genomics to counsel their patients appropriately. This is not only because requests of this sort are still relatively uncommon, but also because the science behind genetic testing results develops and changes rapidly. Numerous nuances deserve consideration prior to responding to a genetic test result that might indicate a patient's risk for developing a condition. Which evidence supports the claim that a particular genetic variant confers risk for this condition? Which preventative or surveillance measures are available to potentially mitigate risk, and what are their potential risks and benefits? These questions are not just difficult to answer; the potential answers change rapidly as new scientific knowledge is gained. Of particular importance is recent evidence that many of the genetic variants formerly thought to be pathogenic (even by more traditional laboratories) might confer less risk than thought or might confer no risk at all.[9] This evidence, combined with variations in testing quality,[4] significantly increases the likelihood that a DTC genetic test result will be a false positive.

For the present, then, primary care clinicians will need to be aware of what they do not (indeed, cannot) know about genetic testing. They can initially respond to patients' requests for counseling by explaining possible quality problems with DTC genetic testing

and welcoming their questions. For now, most primary care clinicians should refer their patients to appropriate experts to interpret and further evaluate DTC test results to ensure their patients receive the best care possible.

In general, primary care clinicians have significant leeway in deciding which types of care fall within their scope of practice and which they will refer to specialists. There are relatively narrow ethical obligations to provide care for certain problems in primary care settings. For example, clinicians might be obligated to assume dimensions of specialty care when specialists are not readily available or when referring a patient would create a harmful delay. Since it is not reasonable at this point to expect primary care physicians to have extensive knowledge of DTC genetic testing performed by private companies, primary care clinicians should have the option to refer patients to specialists for both interpretation and treatment of a DTC genetic testing result as long as genetic specialists are willing to accept them. Given current shortages of these specialists, however, it might not take long for medical geneticists and genetic counselors to become overwhelmed with these types of referrals.[10] The day will soon come, then, when practical constraints will force many primary care clinicians to learn more and begin counseling patients about DTC genetic results without involving genetics specialists.

~~Follow-Up Testing from DTC Genetic Results:~~ Look before You Leap

One implication of DTC genetic testing is that persons who use this service will likely seek follow-up testing to clarify their risk for developing conditions identified through these tests. In this case, Sarah might request that Dr S order a renal ultrasound, a test that is often perceived to be harmless. However, diagnostic tests of this sort carry significant risks precisely because they are intended to guide future medical care. A renal ultrasound in a child might incidentally reveal a renal mass, which might then prompt a needle biopsy or even a surgery. While this kind of follow-up might be appropriate, the Japanese experience with population screening for neuroblastoma suggests that renal masses discovered in infants and toddlers often do not require surgery, a finding made after many infants were exposed to unnecessary surgeries.[11] While unnecessary surgeries as a result of DTC genetic test results will be exceedingly rare, what happened in Japan highlights that clinicians have an important obligation to help patients carefully weigh the potential benefit of peace of mind with the potential risks of unneeded follow-up tests.

When responding to DTC genetic testing results, physicians should advise against unnecessary follow-up tests or interventions and instead propose a surveillance plan informed by clinical parsimony. Deciding upon a course of action will fall to individual patients and physicians, like Sarah and Dr S, working together. Shared decision making does not, however, mean that primary care physicians should order any test a patient wants. Shared decision making is about seriously engaging in conversation together so that physicians understand their patients' unique circumstances and concerns and so

patients have opportunities to benefit from their clinicians' expertise, including learning about the first rule of medicine: a test should never be ordered in the absence of a foreseeable benefit.

References

1. Regalado A. 2017 was the year consumer DNA testing blew up. *MIT Technology Review*. February 12, 2018. https://www.technologyreview.com/s/610233/2017-was-the-year-consumer-dna-testing-blew-up/. Accessed July 20, 2018.
2. Landry L, Nielsen DE, Carere DA, Roberts JS, Green RC; PGen Study Group. Racial minority group interest in direct-to-consumer genetic testing: findings from the PGen study. *J Community Genet*. 2017;8(4):293-301.
3. Roberts JS, Gornick MC, Carere DA, Uhlmann WR, Ruffin MT, Green RC. Direct-to-consumer genetic testing: user motivations, decision making, and perceived utility of results. *Public Health Genomics*. 2017;20(1):36-45.
4. Tandy-Connor S, Guiltinan J, Krempely K, et al. False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care [published online ahead of print March 22, 2018]. *Genet Med*. doi:10.1038/gim.2018.38.
5. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405-424.
6. Suther S, Goodson P. Barriers to the provision of genetic services by primary care physicians: a systematic review of the literature. *Genet Med*. 2003;5(2):70-76.
7. Johnson LM, Valdez JM, Quinn EA, et al. Integrating next-generation sequencing into pediatric oncology practice: an assessment of physician confidence and understanding of clinical genomics. *Cancer*. 2017;123(12):2352-2359.
8. Bennett RL, Waggoner D, Blitzer MG. Medical genetics and genomics education: how do we define success? Where do we focus our resources? *Genet Med*. 2017;19(7):751-753.
9. Weck KE. Interpretation of genomic sequencing: variants should be considered uncertain until proven guilty. *Genet Med*. 2018;20(3):291-293.
10. Stoll K, Kubendran S, Cohen SA. The past, present and future of service delivery in genetic counseling: keeping up in the era of precision medicine. *Am J Med Genet C Semin Med Genet*. 2018;178(1):24-37.
11. Tsubono Y, Hisamichi S. A halt to neuroblastoma screening in Japan. *N Engl J Med*. 2004;350(19):2010-2011.

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CASE AND COMMENTARY

Should Genetic Testing for Variants Associated with Influenza Infection Be Mandatory for Health Care Employees?

Michelle Huckaby Lewis, MD, JD

Abstract

Scientists are beginning to understand more about the role of host genetics in individuals' responses to influenza virus exposure. This fictional case addresses a situation in which a health care organization proposes requiring all health care practitioners with direct patient care responsibilities to undergo mandatory genetic testing for genetic variants used to (1) predict individuals' responses to the influenza vaccine, (2) determine individual susceptibility to influenza infection, and (3) identify individuals at increased risk for severe disease. This commentary will discuss ethical and legal issues associated with use of genetic test results to determine employee work assignments during an influenza pandemic.

Case

Influenza is an acute infectious illness spread by casual contact via respiratory droplets. Depending on the strain of virus and the characteristics of the infected individual (host), the severity of illness ranges from a mild, self-resolving upper respiratory tract infection to severe respiratory compromise and death. Due to the virus's high transmissibility and constantly changing genome, influenza can cause pandemic infections. However, the efficacy of current vaccines and treatments are variable, suggesting that limiting exposure and transmission is the most promising strategy for improving health outcomes during pandemics.

Scientists have begun to identify host genetic variants that confer resistance to influenza or limit its transmission. If a genetic test is developed to identify whether individuals possess these variants, the information could be used to determine the genotype of the clinical and public health workforce and to predict whether these workers are resistant to influenza or whether they easily transmit infection to others.

Health care organization (HCO) A is considering mandating that all health care professionals who have direct patient care responsibilities be tested for genetic variants associated with influenza infection. Such host genetic variant information might allow a structured response to influenza that limits the spread of the infection. However,

collecting and using this information might place unacceptable limits on individual autonomy. Some of the professionals working for HCO A do not want to consent to be tested; others are willing to be tested but do not want their genetic information to be stored. How should the HCO A leadership respond?

Commentary

The World Health Organization defines a pandemic as "the worldwide spread of a new disease."[1] The 1918 influenza pandemic caused the deaths of an estimated 50 million to 100 million people, 3% to 5% of the world's population.[2] In contrast, the 2014-2016 West Africa Ebola outbreak resulted in 11 310 deaths in Guinea, Liberia, and Sierra Leone as of April 13, 2016.[3] The Ebola outbreak was not as widespread or as destructive as the 1918 influenza pandemic, but it demonstrated how ill prepared the world is to address infectious disease outbreaks. For decades, experts have warned that another severe infectious disease pandemic could occur at any time.[2] It is not a question of "if" but "when" the next serious pandemic will occur. Like earthquakes, what worries infectious disease experts is the occurrence of "the big one."

Seasonal influenza must be distinguished from pandemic influenza. Human influenza A and B viruses cause seasonal epidemics of disease. These viruses circulate in all parts of the world and cause seasonal epidemics when there is widespread occurrence of influenza infection in a particular geographic community at a particular time. Seasonal influenza epidemics typically occur during the winter months in temperate climates but can occur throughout the year in tropical climates. An influenza pandemic is a global outbreak of a *novel* influenza A virus. Because the virus is new to humans, very few people will have immunity against the virus, and many people might become ill. For both seasonal and pandemic influenza, the strain of the influenza virus and the characteristics of the host affect the severity of disease.[4] A number of host genetic variants associated with response to the influenza vaccine, susceptibility to influenza infection, and severity of disease if infected recently have been identified.[5-7]

Because health care delivery systems might become overwhelmed during an influenza pandemic, all health care organizations in the United States should be prepared to respond when an influenza pandemic arises. Vaccination, monitoring, and management of health care personnel will be key to limiting exposure to the influenza virus in the health care setting. Information about whether individual health care practitioners possess genetic variants associated with influenza could be helpful in the management of health care personnel during an influenza pandemic and potentially could reduce the spread of disease, both to patients and to other health care practitioners.

HCO A has proposed a requirement that all health care personnel with direct patient contact undergo genetic testing for these variants in order to structure its response to an influenza pandemic to limit the spread of disease. This requirement would serve three main purposes: (1) allow HCO A to fulfill its obligation to provide a safe work environment

for its employees; (2) minimize the risk of additional harm from exposure to influenza to persons who seek health care from HCO A; and (3) preserve the employee workforce, a resource that is vital to the ability of HCO A to continue to provide health care services during an influenza pandemic. However, HCO A employees might have significant concerns about the fairness of such a policy and about their autonomy, genetic privacy, and potential loss of employment opportunities if this requirement is implemented. This commentary considers this tension between the needs of employers and the concerns of workers.

Rationale for Mandatory Genetic Testing of Employees for Variants Associated with Influenza Infection

HCO A's rationale for mandatory genetic testing is based on the duties owed by a health care delivery system to its employees, its patients, and society.

Duty to provide safe work environments for employees. Health care organizations are obligated by law to provide a safe work environment for their employees. The US Occupational Safety and Health Administration promulgates standards to protect health care workers from exposure to bloodborne, droplet, and airborne transmissible infectious agents. In addition, the General Duty Clause of the Occupational Safety and Health Act of 1970 requires that employers provide a workplace that is free from recognized hazards that are likely to cause death or serious physical harm to employees.[8] A health care institution by its very nature cannot eliminate all risk of contagion from infectious disease for its employees, but it is required to take steps to minimize this risk.

During an influenza pandemic, occupational exposure to the influenza virus during direct patient care is likely to occur. A genetic test for variants associated with increased susceptibility to influenza infection and for vaccine nonresponders could allow HCO A to identify those employees at increased risk of contracting influenza if exposed to the virus. During an influenza pandemic, these employees could be given patient care assignments with lower risk of exposure to the virus, ie, they could be assigned to care for patients who need medical care but are not known to be infected with influenza. Assignment of patient care duties based upon genotype may be one way to decrease risk of exposure and infection in both patients and employees.

Duty to minimize risk of nosocomial infections. Health care institutions also owe legal and ethical duties of care to patients. These duties entail an obligation to safeguard patients from harm and minimize the likelihood of nosocomial infection while they are in the care of the health care institution. HCO A has a responsibility to its patients to limit their risk of exposure to influenza when they seek medical care from HCO A. Current standards of care require that health care institutions have protocols in place to limit the spread of infectious disease. These protocols can include a range of precautions, from requiring that health care practitioners wash their hands before and after patient contact to isolation of patients with specific suspected or confirmed infectious diseases when

possible. The assignment of employees who are more susceptible to influenza infection or who are vaccine nonresponders to low-risk patient care activities during an influenza pandemic is another way HCO A could minimize patients' risk of exposure to influenza while they are receiving medical care.

Duty to preserve the health care workforce during an influenza pandemic. Health care practitioners are a vital resource that may become scarce during an influenza pandemic as health care personnel become ill with influenza themselves. Although elective medical care might be deferred during an influenza pandemic, health care institutions must continue to provide urgent care to patients who do not have influenza as well as treat patients infected with the virus. Consideration of how this health care workforce resource should be allocated must be part of the pandemic preparedness planning of any health care organization.

Employee Concerns about Mandatory Genetic Testing for Variants Associated with Influenza Infection

This type of mandatory genetic testing may raise concerns for some employees about fairness, autonomy, or how the information may be used.

Fairness. The requirement that HCO A employees with direct patient care responsibilities undergo mandatory genetic testing for variants associated with influenza potentially could reduce the risk of influenza infection in certain employees; however, this risk cannot be eliminated entirely. Employees who do not possess the variant that confers increased susceptibility to infection are still at risk of contracting the disease if exposed to the virus. A practice of assigning employees who are more susceptible to the virus to low-risk patient care activities confers benefit to these at-risk employees but also means that employees who are less susceptible to the virus must be assigned to care for the patients with influenza. From the standpoint of these less-susceptible employees, it can be argued that random assignment of patient care responsibilities, not assignment based upon employee genotype, would more fairly balance the risk of exposure among individual health care practitioners.

Similarly, if employees who do not possess the variant associated with severe disease are assigned to care for infected patients, they could still become ill even though their illness may not be severe. Illness nevertheless has consequences for these employees. They may suffer loss of wages from not being able to work; they and their families could be quarantined; they could spread the disease to others, including those who are at risk of severe disease; and they could face family and child care difficulties.

Finally, for those employees who receive the influenza vaccine because they do not possess the genetic variant associated with vaccine nonresponse, the vaccine might not be completely effective. If these employees are assigned to care for patients with influenza because they have received the influenza vaccine and the vaccine is not

completely effective, it can be argued that these employees were unfairly exposed to the virus while other employees were not exposed.

These fairness issues are unavoidable under HCO A's policy, but requiring groups of employees to assume differential risks may be justified during a pandemic that causes severe disease with a high mortality rate.

Employee autonomy. Absent extraordinary circumstances, mandatory genetic testing for variants associated with influenza might be unacceptable to some employees. In general, competent adult patients have the right to make their own decisions about their health care, including decisions about whether to undergo genetic testing. Some patients decide not to undergo genetic testing because they do not want to know whether they possess genetic variants that indicate increased risk of disease. The requirement by HCO A that employees undergo mandatory testing for genetic variants associated with influenza would limit the autonomy of their employees in this regard and deny them the right not to know whether they possess genetic variants associated with influenza infection.

Concerns about HCO A possession of genetic information. Employees might prefer that HCO A not obtain knowledge about their personal genetic information for a number of reasons. Some employees may have concerns about the security of their genetic information, including concerns about where genetic testing results will be stored and who will have access to the information. Employees also might be concerned that the genetic information could be used by HCO A to discriminate against employees with a particular genotype by limiting the amount or type of work they do or limiting their opportunities for professional advancement.

Current Policies

Genetic testing for variants associated with influenza infection has not yet been developed, so implementation of mandatory genetic testing for these variants by HCO A would not be possible at the current time. Furthermore, the federal Genetic Information Nondiscrimination Act of 2008 (GINA)[9] and genetic privacy laws in some states[10] currently prohibit the use of genetic information in the employment setting. However, the Public Health Service Act allows the US Secretary of Health and Human Services (HHS) to determine that a public health emergency exists in cases of severe infectious disease outbreaks.[11] A public health emergency determination gives the HHS secretary broad powers to assist states in the prevention and treatment of disease.

A severe influenza pandemic could jeopardize the lives of millions of people. If an influenza pandemic of this level of severity and magnitude develops and genetic testing for variants associated with influenza infection is available, overriding the prohibitions against the use of genetic information in the workplace may be justified and necessary. The extent to which a determination of an influenza pandemic as a public health emergency could be used to override GINA's and state genetic privacy laws' prohibitions

on uses of genetic information in employment settings is unclear. It is possible, perhaps likely, that these provisions would be overridden in the face of a severe influenza pandemic in which millions of live are at stake.

Conclusion

A requirement that all health care employees with direct patient care responsibilities undergo genetic testing for variants associated with influenza infection might provide HCO A with information that could be used to determine patient care responsibilities during an influenza pandemic. Assigning health care practitioners at increased risk from influenza exposure to low-risk patient care activities during an influenza pandemic could protect these individuals from exposure and limit the spread of disease. However, this practice could expose individuals at lower risk from influenza exposure to a greater extent than they would have been if genotype was not used to determine work assignments and therefore may be unacceptable to some employees. Moreover, this practice would limit employee autonomy, and some employees might have concerns about genetic privacy or the potential use of genetic test results to limit employment opportunities. Current state and federal genetic privacy laws prohibit HCO A from mandating this type of genetic testing. In the future, these considerations may be overridden in the face of a public health emergency caused by a severe influenza pandemic.

References

1. World Health Organization. What is a pandemic? http://www.who.int/csr/disease/swineflu/frequently_asked_questions/pandemic/en/. Published February 24, 2010. Accessed June 19, 2018.
2. Barry JM. *The Great Influenza: The Story of the Deadliest Pandemic in History*. New York, NY: Penguin Books; 2009.
3. Centers for Disease Control and Prevention. Case counts: number of cases and deaths in Guinea, Liberia, and Sierra Leone during the 2014-2016 West Africa Ebola outbreak. https://www.cdc.gov/vhf/ebola/history/2014-2016-outbreak/case-counts.html. Updated December 27, 2017. Accessed June 19, 2017.
4. Centers for Disease Control and Prevention. Pandemic basics. https://www.cdc.gov/flu/pandemic-resources/basics/index.html. Updated November 3, 2016. Accessed June 19, 2018.
5. Keynan Y, Malik S, Fowke KR. The role of polymorphisms in host immune genes in determining the severity of respiratory illness caused by pandemic H1N1 influenza. *Public Health Genomics*. 2013;16(1-2):9-16.
6. Poland GA. Influenza vaccine failure: failure to protect or failure to understand? *Expert Rev Vaccines*. 2018;17(6):495-502.
7. Aracano AC, Mazzocco G, de Oliveira SF, Plewcyznski D, Radomski JP. Role of the host genetic variability in the influenza A virus susceptibility. *Acta Biochim Pol*. 2014;61(3):403-419.

8. Occupational Safety and Health Act of 1970, Pub L No. 91-596, §5(a), 84 Stat 1590.
9. Genetic Information Nondiscrimination Act of 2008, Pub L No. 110-233, 122 Stat 881.
10. Or Rev Stat §659A.300 (2017).
11. Emergency Management Assistance Compact, Pub L No. 104-321, 110 Stat 3877.

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STATE OF THE ART AND SCIENCE: PEER-REVIEWED ARTICLE

Justice in CRISPR/Cas9 Research and Clinical Applications

Clara C. Hildebrandt, MD and Jonathan M. Marron, MD, MPH

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Abstract

CRISPR/Cas9 is a rapidly developing gene editing technology that will soon have many clinical applications. As with many other new technologies, somatic gene editing with CRISPR/Cas9 raises concerns about equitable access to therapies by historically disenfranchised racial and ethnic minorities. We describe justice concerns related to CRISPR/Cas9, including its potential impact on historically mistreated populations through underrepresentation of minorities in genomic databases and the potential for disparate access to somatic gene therapies when they become clinically available. We then describe ongoing work that aims to address these justice concerns. We conclude by highlighting important considerations to ensure equitable access to therapies going forward, including enhancing diversity in genomic sequencing efforts, improving education and transparency, and building partnerships with underserved and socially disenfranchised communities.

Introduction

Gene editing has been possible for years with tools such as Zinc-finger nucleases and TALENs (transcription activator-like effector nucleases).[1] CRISPR/Cas9 is one such adaptable and specific tool in which an RNA "guide" binds to a specific stretch of DNA and directs the Cas9 nuclease to introduce a cut in the genetic sequence. Other functional groups can be added to further alter the stretch of DNA.[2,3] CRISPR/Cas9 has many potential clinical applications. The initial focus has been on cancer immunotherapy and correction of single gene disorders.[4-6] For example, several teams have used the CRISPR/Cas9 system to correct pathogenic variants underlying beta thalassemia, a hemoglobinopathy.[7] CRISPR/Cas9 offers multiple options to correct such defects, including changing the genetic code at the locus containing the pathogenic variant or creating an alternate hemoglobin product that can reduce severity of disease. With the

advent of CRISPR/Cas9 come new considerations of when and how this technology should be applied in the clinical setting.

A key ethical distinction in discussions of human genome editing is that between germline applications (alterations that will be passed down to future generations) and somatic applications (those that will not be passed down),[8] which is addressed in detail in the consensus report of the International Summit on Human Gene Editing.[9] Germline editing is controversial because of ethical and clinical risks inherent in making a genetic change that would be inherited. Although the National Academies of Sciences, Engineering, and Medicine (NASEM) have recently begun to discuss criteria for ethical germline editing,[10] most professional societies—including the NASEM, the American Society of Human Genetics, the European Society of Human Genetics, and the American College of Medical Genetics and Genomics—currently forbid germline gene editing.[9,11-13] For this reason, this discussion will be limited to somatic gene editing only.

For CRISPR/Cas9 to be maximally beneficial to all communities—and to potentially mitigate, rather than exacerbate, health care disparities—equitable opportunities to participate in and benefit from research are paramount. This article will detail several barriers to equitable participation in and benefit from this kind of research and opportunities to overcome these barriers.

Barriers to Equitable Participation in and Benefit from Research

Mistrust of research. Minority groups in the United States have repeatedly experienced unequal and unethical treatment in research, ranging from participation without adequate informed consent to forced or coerced participation in treatments and studies. This mistreatment is perhaps most notable among African Americans in light of transgressions such as those in the US Public Health Service Tuskegee Syphilis Study, but numerous other groups have experienced similar mistreatment.[14-16] Scars from this mistreatment still create mistrust of the medical and scientific community, as evidenced by low enrollment rates of African Americans and other minority groups in many research studies.[14,17,18] Furthermore, minority communities are aware of health disparities and that they often receive inferior care compared to wealthier, nonminority groups.[19,20] Concerns of minority groups in the US include unjust distribution of new resources and the potential for genetic enhancements to actually exacerbate disparities.[21] These concerns must be addressed in the enrollment phase of new trials of CRISPR/Cas9 to ensure adequate representation of minority patients and adequate protection of these historically mistreated groups.

Underrepresentation in research. A second barrier to equitable participation in research is underrepresentation of minority patients in genetic databases that inform future research. While the National Institutes of Health (NIH) Human Genome Project and the United Kingdom's 100,000 Genomes Project have expanded general knowledge of the

human genome, overall there has been a lack of diversity in large-scale genome projects.[22,23] Recent work estimates that only 3% of participants in genome-wide association studies (GWAS) published in the GWAS catalogue are of African descent.[24,25] These studies are crucial for understanding associations between genetic variants and disease within specific populations. Without adequate understanding of the range of clinical variants, it will be harder to tailor therapies specifically to minority populations if less is known about their genomic makeup. Consequently, underrepresented minorities will likely miss out on potential gene therapy benefits.[26]

Disparate access to research benefits. Racial and ethnic minorities in the US have very disparate health outcomes and access to health care. In this country, socioeconomic status is strongly associated with race and ethnicity,[27,28] raising concerns that the benefits of gene therapy will prove unavailable to some of the neediest groups for financial reasons.[29,30] Gene therapy treatments might initially be funded through research, but these are likely to be prohibitively expensive for many once commercially available. When such new therapies are introduced to the market, minority populations are less likely to have access to them.[31] Some of this inequity in access is hypothesized to be a result of overt or subconscious racism and differential treatment in medicine.[17,32] There is likely also a disincentive to participate in research if potential participants perceive that benefits of research might not be available to them, although research is needed to support this hypothesis.

Taking Steps Forward

To overcome the aforementioned barriers to minorities' participating in and benefiting from research, the scientific community must ensure diversity in genomic sequencing, build trust and partnerships, and advocate for equitable access to emerging therapies. An early attempt to address the lack of diversity in genomic databases was the Human Genome Diversity Project, through which human genomes from around the globe were sequenced in order to better understand genomic diversity.[33] A further step is the NIH's All of Us research project, a national effort to enhance diversity in genome sequencing in part through partnerships with numerous hospital systems and community health advocacy groups such as the Black Women's Health Imperative.[34] This work and that of other organizations has promise as a step toward making clinical applications of gene editing more equitable across all populations, but further work is necessary.

Increasing diversity of genomic databases is necessary not only to produce more relevant research and clinical applications, but also to create a sense of inclusion and trust among historically disenfranchised minority communities. Establishing such partnerships in somatic gene therapy research and its clinical applications must happen on a health systems level, not just on a patient-clinician level. The duty of balancing risks and ensuring informed consent cannot solely be fulfilled by adhering to the normal human subjects protections procedures provided by institutional review boards.[16]

Medical and research communities need to prove to the public that inclusion of minority groups in genetic research and equal access to the benefits of this research are high priorities and that opinions and concerns of minority communities are considered when designing protocols and developing new therapies.[14] Input from stakeholder groups—both experts and laypeople—tasked specifically with considering long-term implications of somatic gene therapy for minority groups is crucial. These stakeholder groups should be assembled from communities that will face the direct risks and potential benefits of research. If a gene editing study for sickle cell disease (SCD) is conducted, for example, input should be sought from patients with SCD and from advocacy groups like the Sickle Cell Disease Association of America to promote equitable access to somatic gene therapy upon its arrival in the clinic.

Partnerships with minority communities must involve transparency, education of the public about gene editing and research studies design, and meticulous informed consent.[6,35] The National Human Genome Research Institute has several groups dedicated to exploring health disparities in genomics along with avenues of engaging minority groups and the public.[36-38] These initiatives should be expanded and serve as models for larger-scale efforts to engage minority groups and build trust. Transparency will require translating published materials of relevant studies into language interpretable by the public and making discussions of the ethics and science related to applications of gene editing available outside academic medical centers and scientific journals. The scientific community should devote resources not only to engage and educate the public but also to study the effectiveness of these interventions. The same methodological rigor that is applied to the science of gene editing must be applied to public education and dissemination of research results.

Conversations about the ethics of clinical applications of gene editing and its potential impacts on minorities have been happening for years.[9,11,39] These conversations should continue to move into the public sphere. NIH funding is now available to study the ethics of genomics and its applications; the issues of access and justice need urgent exploration.[40] It will be important to reach out to minority communities directly to ascertain their specific concerns. One such study, examining perspectives of SCD patients on gene editing in SCD, is already underway.[41]

Conclusions

To ensure just distribution of risks and benefits of research, the medical-scientific community must foster trust and open communication with historically disenfranchised groups. Basic scientists, physicians, and health policymakers must work to ensure justice in gene therapy locally and worldwide. While gene editing poses a risk of maintaining or even widening health inequities, it could also be a tool to reduce them. One main goal of CRISPR/Cas9 somatic gene therapy can and should be its use as a form of preventive medicine to address specific racial and ethnic disparities in health outcomes. Toward this

end, researchers and clinicians must continue to act as educators, builders of community partnerships, and advocates for just and equitable access to these new technologies.

References

1. Jasin M. *Scientific Background on Gene Editing Technologies*. New York, NY: Vimeo; 2015. https://vimeo.com/149184042. Accessed April 27, 2016.
2. Doudna J, Charpentier E. Genome editing. The new frontier of genome engineering with CRISPR-Cas9. *Science*. 2014;346(6213):1258096. doi:10.1126/science.1258096.
3. Mali P, Esvelt KM, Church GM. Cas9 as a versatile tool for engineering biology. *Nat Methods*. 2013;10(10):957-963.
4. CAR T cells more powerful when built with CRISPR, MSK researchers find [press release]. New York, NY: Memorial Sloan Kettering Cancer Center; February 22, 2017. https://www.mskcc.org/press-releases/car-cells-more-powerful-when-built-crispr-msk-researchers-find. Accessed August 22, 2017.
5. Clinicaltrials.gov. Search term: CRISPR. https://clinicaltrials.gov/ct2/results?cond=&term=crispr&cntry1=&state1=&SearchAll=Search+all+studies&recrs. Accessed August 18, 2017.
6. Wirth T, Parker N, Ylä-Herttuala S. History of gene therapy. *Gene*. 2013;525(2):162-169.
7. Cai L, Bai H, Mahairaki V, et al. A universal approach to correct various HBB gene mutations in human stem cells for gene therapy of beta-thalassemia and sickle cell disease. *Stem Cells Transl Med*. 2018;7(1):87-97.
8. Buchanan A, Brock D, Daniels N, Wikler D. Positive and negative genetic interventions. In: *From Chance to Choice: Genetics and Justice*. Cambridge, UK: Cambridge University Press; 2007:107-154.
9. National Academies of Sciences, Engineering, and Medicine. *Human Genome Editing: Science, Ethics, and Governance*. Washington, DC: National Academies Press; 2017.
10. De Wert G, Pennings G, Clarke A, et al; European Society of Human Genetics; European Society of Human Reproduction and Embryology. Human germline gene editing: recommendations of ESHG and ESHRE [published online ahead of print January 12, 2018]. *Eur J Hum Genet*. doi:10.1038/s41431-017-0076-0.
11. On human gene editing: international summit statement [press release]. Washington, DC: National Academies of Sciences, Engineering, Medicine; December 3, 2015. http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12032015a. Accessed March 29, 2018.
12. Ormond KE, Mortlock DP, Scholes DT, et al. Human germline genome editing. *Am J Hum Genet*. 2017;101(2):167-176.

13. ACMG Board of Directors. Genome editing in clinical genetics: points to consider—a statement of the American College of Medical Genetics and Genomics. *Genet Med*. 2017;19(7):723-724.
14. Corbie-Smith G, Thomas SB, Williams MV, Moody-Ayers S. Attitudes and beliefs of African Americans toward participation in medical research. *J Gen Intern Med*. 1999;14(9):537-546.
15. Grady D. White doctors, black subjects: abuse disguised as research. *New York Times*. January 23, 2017. http://www.nytimes.com/2007/01/23/health/23book.html?mcubz=0. Accessed March 29, 2018.
16. Shivayogi P. Vulnerable population and methods for their safeguard. *Perspect Clin Res*. 2013;4(1):53-57.
17. Gee GC, Ford CL. Structural racism and health inequities: old issues, new directions. *Du Bois Rev*. 2011;8(1):115-132.
18. Bulger RE, Bobby EM, Fineberg HV, eds; Institute of Medicine Committee on the Social and Ethical Impacts of Developments in Biomedicine. The social context of bioethical problem solving. In: *Society's Choices: Social and Ethical Decision Making in Biomedicine*. Washington, DC: National Academy Press; 1995:43-53.
19. Hunt KA, Gaba A, Lavizzo-Mourey R. Racial and ethnic disparities and perceptions of health care: does health plan type matter? *Health Serv Res*. 2005;40(2):551-576.
20. Benz J, Espinosa O, Welsh V, Fontes A. Awareness of racial and ethnic health disparities has improved only modestly over a decade. *Health Aff (Milwood)*. 2011;30(10):1860-1867.
21. Rainie L, Hefferon M, Sciupac EP, Anderson M. American voices on ways human enhancement could change our future. Pew Research Center. http://www.pewinternet.org/2016/07/26/american-voices-on-ways-human-enhancement-could-shape-our-future/. Published July 26, 2016. Accessed August 17, 2017.
22. Venter JC, Adams MD, Myers EW, et al. The sequence of the human genome. *Science*. 2001;291(5507):1304-1351.
23. Genomics England website. https://www.genomicsengland.co.uk/about-genomics-england/how-we-work/. Accessed April 27, 2018.
24. Popejoy AB, Fullerton SM. Genomics is failing on diversity. *Nature*. 2016;538(7624):161-164.
25. National Human Genome Research Institute; European Bioinformatics Institute. GWAS catalog. https://www.ebi.ac.uk/gwas/. Accessed January 17, 2018.
26. Lessard S, Francioli L, Alfoldi J, et al. Human genetic variation alters CRISPR-Cas9 on- and off-targeting specificity at therapeutically implicated loci. *Proc Natl Acad Sci USA*. 2017;114(52):e11257-e11266.
27. United States Census Bureau. Wealth, asset ownership, and debt of households detailed tables: 2013.

https://www.census.gov/data/tables/2013/demo/wealth/wealth-asset-ownership.html. Updated May 4, 2017. Accessed January 17, 2018.
28. Williams DR, Priest N, Anderson NB. Understanding associations between race, socioeconomic status and health: patterns and prospects. *Health Psychol*. 2016;35(4):407-411.
29. National Center for Health Statistics. *Health, United States, 2015: With Special Feature on Racial and Ethnic Health Disparities*. Hyattsville, MD: National Center for Health Statistics; 2016. https://www.cdc.gov/nchs/data/hus/hus15.pdf. Accessed August 17, 2017.
30. Williams DR. Miles to go before we sleep: racial inequities in health. *J Health Soc Behav*. 2012;53(3):279-295.
31. Wang J, Zuckerman IH, Miller NA, Shaya FT, Noel JM, Mullins CD. Utilizing new prescription drugs: disparities among non-Hispanic whites, non-Hispanic blacks, and Hispanic whites. *Health Serv Res*. 2007;42(4):1499-1519.
32. Hardeman RR, Medina EM, Kozhimannil KB. Structural racism and supporting black lives—the role of health professionals. *N Engl J Med*. 2016;375(22):2113-2115.
33. Stanford University. Human Genome Diversity Project. http://www.hagsc.org/hgdp/. Accessed November 5, 2017.
34. National Institutes of Health. All of Us Research Program website. https://allofus.nih.gov. Accessed November 5, 2017.
35. Marron JM, Joffe S. Ethical considerations in genomic testing for hematologic disorders. *Blood*. 2017;130(4):460-465.
36. National Human Genome Research Institute. Community outreach and public education. https://www.genome.gov/10001279/community-outreach-education/. Published December 12, 2016. Accessed August 18, 2017.
37. National Human Genome Research Institute. Education and community involvement branch. https://www.genome.gov/11008538/education-and-community-involvement-branch/. Published December 1, 2016. Accessed August 17, 2017.
38. National Human Genome Research Institute. Initiatives and resources for minority and special populations. https://www.genome.gov/10001192/initiatives-and-resources-for-minority-and-special-populations/. Published February 3, 2017. Accessed August 17, 2017.
39. Personal Genetics Education Project. Industry forum for forging community partnerships. https://pged.org/industry-forum. Accessed July 30 2017.
40. National Institutes of Health. Ethical, legal, and social implications (ELSI) of genomics exploratory/developmental research grant program (R21). https://grants.nih.gov/grants/guide/pa-files/PA-17-323.html. Published August 3, 2017. Accessed August 18, 2017.

41. National Institutes of Health Clinical Center. Examining the knowledge, attitudes, and beliefs of sickle cell disease patients, parents of patients with sickle cell disease, and providers towards the integration of CRISPR in clinical care. https://clinicaltrials.gov/ct2/show/NCT03167450?term=crispr&rank=3. Published June 15, 2017. Accessed August 15, 2017.

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STATE OF THE ART AND SCIENCE

What Precision Medicine Can Learn from Rare Genetic Disease Research and Translation

Holly K. Tabor, PhD and Aaron Goldenberg, PhD, MPH

Abstract

The goal of this article is to examine the intersections of precision health and rare diseases. Specifically, we propose 3 lessons from the last decade of applying genomics to rare diseases: (1) precision can end one odyssey and start another; (2) precise interventions can exacerbate health disparities and create other ethical dilemmas; and (3) democratization of data will transform research and translation. By studying experiences of patients with rare diseases, researchers, clinicians, and policymakers can anticipate similar challenges in precision medicine and hopefully mitigate potential harms or injustices.

Rare Diseases and Precision Medicine

More than 25 million Americans suffer from one of over 7000 rare conditions,[1] each one of which has an incidence of 1 in 200 000 or less. The rarity of these conditions creates challenges, such as convincing agencies and companies to fund development of effective and affordable treatments, provide programmatic support, and facilitate patient interaction and support opportunities.

In contrast, *precision health* or *precision medicine* has focused on big data approaches to studying more common complex conditions such as heart disease, diabetes, and high blood pressure. The National Institutes of Health defines precision medicine as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."[2] While this definition does not mention disease frequency, one core aspirational goal of many precision health initiatives will be to identify smaller subgroups based either on genomic and/or socioenvironmental variation or on response to specific drug interventions. Identification of subgroups could in turn create new subcategories of common diseases that might ultimately suffer from similar research, health care, and policy challenges as "rare diseases."

The goal of this paper is to examine the intersection of precision health and rare disease. Specifically, we propose 3 lessons from the applications of genomics to rare disease in the last decade that may be important for researchers, clinicians, and policymakers to

consider as precision health ripens and evolves to have impacts on larger numbers of individuals and populations.

Precision Can End One Odyssey and Start Another

Many rare disease patients and families undergoing genomic sequencing have been on extensive and lengthy diagnostic odysseys involving serial tests and clinic visits, sometimes over many years, all with the hope of identifying an etiology.[3] In recent years, sequencing efforts have been successful at identifying known but missed diagnoses as well as novel and newly characterized rare syndromes.[4] For rare disease patients, a genetic result can signify not only the end of a diagnostic odyssey but also the beginning of a therapeutic odyssey. Knowing the causal genetic variant(s) may provide some reproductive risk information for the patient or family members and may eliminate some prognostic uncertainty, but far too frequently it does not provide a clear therapeutic or preventative alternative. This scenario is especially challenging, since over 90% of rare diseases do not currently have an approved treatment.[5]

This failure to identify potential therapies for rare genetic diseases is not surprising. After all, the long-term goal of rare disease genomic research is first to identify genes to target for prevention and treatment and then to develop and test effective interventions, perhaps over many decades. Unfortunately, such long-term objectives are often lost amid the pressure to provide diagnostic answers to "help" patients who may otherwise have few alternatives and to offer hope for the future. If precision health only succeeds in identifying etiological subsets of patients over the next decade and fails to develop approaches to treat them, then it risks falling far short of the many public promises being made by the government, health care institutions, and research studies.[6] These kinds of inflated promises have long been targets of criticism in genomics[7] and may risk undermining the public's trust in science and in federally funded research.[8,9]

Precision health can learn from the frustrations of patients with rare diseases and their families, who have transitioned from diagnostic to therapeutic odysseys. For example, the kind of research that translates into better therapies for rare diseases, such as better understanding of the natural history of a rare disease or even testing therapeutic targets in clinical trials, can be significantly hindered by lack of sufficient statistical power (due to smaller numbers and the broader geographic distribution of potential patients) and paucity of funding. Precision health research that identifies rare genotypes or genetic variants can run into similar problems when researchers try to translate large population data into clinical research on "rare" groups. Researchers and clinicians can and should be more transparent and forthcoming about the timelines for the realization of the full promise of precision health approaches. They can develop empirically based advice for "the newly rare" who may benefit in the future from targeted therapies but who will likely have to wait a long time to do so. Laws like the Orphan Drug Act, which supports rare disease research,[10] might need to be expanded to include increased resources for

newly discovered rare genotypes. There is also increased interest in new approaches to clinical trials that include smaller samples, or even so-called *N*-of-1 trials, which can help to promote research on therapeutic targets for rarer conditions and genetic variants.[11]

Precise Interventions Might Exacerbate Health Disparities and Create Ethical Dilemmas

Even if expectations that precision health would discover effective treatments for specific subsets of people are fulfilled, challenges might not end for patients and families. One example is the recent approval of nusinersen for the treatment of spinal muscular atrophy (SMA), a rare recessive neuromuscular condition that is the most common cause of infant death in the United States. Nusinersen is a "miracle" to many because it seemingly stops progression of SMA in patients across subtypes and severities of disease and prevents death when administered early enough in infancy.[12,13] Despite these spectacular results, the advent of treatment for a previously untreatable condition has resulted in substantial challenges. In particular, there have been significant barriers in ensuring access. Because it is administered intrathecally, limited numbers of facilities and clinicians can safely administer the drug and provide follow up care.[14,15] The astronomical cost of $370 000 per year for life (after $750 000 in the first year) is insurmountable for many, especially since insurance coverage seems to vary by region, insurance company, and individual symptom profiles.[14,15] There are several other innovative SMA therapies in the drug development pipeline,[16] and consequently patients and clinicians are unclear about what advice to take or to give about the relative benefits and risks of as yet unproven alternatives that might be even more "precise."

Treatment with nusinersen for SMA is just one of several recent examples of innovative targeted and precise therapies based on genetic diagnosis that have had implications for patients beyond effectiveness. High-cost and high-risk interventions that are available primarily to those with power, money, and access will likely exacerbate existing health disparities and potentially exacerbate the burdens of specific diseases or disease risks. As precision health evolves, researchers, clinicians, and policymakers will need to develop strategies for proactively identifying some of these ethical challenges in therapeutic translation as well as policies and guidance to mitigate adverse impacts of successful precision-based therapies.

Democratization of Data Will Transform Research and Translation

Historically, genetic data have been available to a minority of patients: only those referred to a clinical geneticist for testing, who receive only confirmed and clinically actionable or reproductively meaningful results. In the last 5 years, however, there has been a revolution in the democratization of genetic data that has been initiated at the intersection of rare disease research and clinical care. The most publically reported example is the story of Cristina and Matt Might and their successful efforts to identify the cause of their son's rare condition through a combination of enrolling in traditional research and networking with similar families through social media.[17,18] Similarly, Karen

Park and Peter Lorentzen used social media to identify other families with the same genetic variants of uncertain significance and with similar phenotypes as their son, ultimately culminating in the identification of the gene causing their son's condition.[19,20] In these ways, the patients themselves used their genetic data to transform the model of genetic research and gene discovery and shift the balance of power away from researchers and towards patients and families.[18]

This shift has not been limited to rare or previously undiagnosed conditions. Other small patient subgroups have successfully used social media to leverage their communities, transforming the role of participants in research and accelerating the timeline of therapeutic translation. For example, the ALK Positive organization started as a Facebook support group for people affected by nonsmall cell lung cancer who have rare somatic mutations of or rearrangements in the anaplastic lymphoma kinase gene (ALK).[21] After connecting more than 700 patients from around the world, the organization has expanded its mission to promote fundraising and grant making for research on the development of specific precision interventions for this population and is currently undergoing its first grant review cycle.[22]

These rare disease examples of patient empowerment and democratization of data provide important signposts for the future of precision health. When larger numbers of patients open the Pandora's box of their genomic data, they can use this information to demand influence on the research agenda in order to maximize its potential impact for the conditions they share and for the genetic and etiologic subgroups to which they belong.[18] The democratization of data could prove beneficial by increasing participant enrollment in and the statistical power of studies for the development and testing of new therapies.

On the other hand, democratization of data and empowerment of patients may have both negative and positive consequences for individual patients. For example, someone with lung cancer may be seen as ineligible for some kinds of treatment or research because she is part of the roughly 5% of nonsmall cell lung cancers with an ALK gene rearrangement.[23] Instead of being one of many with a common condition, lung cancer, she is one of a small number with a rare genetic etiology. Membership in such a small group could make the patient one of the "forgotten few," because hers is not a large enough population to merit pharmaceutical or federal research investment in drug development. Yet as one of the potentially "chosen few" who could benefit from targeted treatments, she could be eligible for enrollment in specific clinical trials or for reimbursement of specific kinds of effective, if expensive, drugs. While rare disease patients and families are well acquainted with such challenges, those with common diseases targeted by precision health may not be aware of or expecting them. There is a critical need to study the clinical experiences of rare disease patients as new therapies

are developed and implemented in order to maximize the benefits of data democratization while minimizing the harms of potential marginalization.

Maximizing the Potential of Precision Medicine

In conclusion, understanding the experiences of patients, families, researchers, clinicians, and policymakers in rare disease is critical to the success of the enterprise of precision health. For precision health to realize its full potential, better approaches must be developed to leverage small groups of individuals and their data at every stage of the translational pipeline, including screening, prevention, and intervention. Rather than thinking "big" and common in their scope, practitioners of precision health research and treatment will have to think small and rare and be proactive in anticipating challenges and mitigating what would otherwise be unanticipated consequences.

References

1. Genetic and Rare Disease Information Center, National Institutes of Health. FAQs about rare diseases. https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases. Accessed March 26, 2018.
2. Garrido P, Aldaz A, Vera R, et al. Proposal for the creation of a national strategy for precision medicine in cancer: a position statement of SEOM, SEAP, and SEFH. *Clin Transl Oncol*. 2018;20(4):443-447. Quoted by: National Institute of Health. What is precision medicine? https://ghr.nlm.nih.gov/primer/precisionmedicine/definition. Accessed August 5, 2017.
3. Reuter CM, Brimble E, DeFilippo C, et al. A new approach to rare diseases of children: the Undiagnosed Diseases Network. *J Pediatr*. 2018;196:291-297.e2. doi:10.1016/j.jpeds.2017.12.029.
4. Boycott KM, Rath A, Chong JX, et al. International cooperation to enable the diagnosis of all rare genetic diseases. *Am J Hum Genet*. 2017;100(5):695-705.
5. Austin CP, Cutillo CM, Lau LPL, et al; International Rare Diseases Research Consortium (IRDiRC). Future of rare diseases research 2017-2027: an IRDiRC perspective. *Clin Transl Sci*. 2018;11(1):21-27.
6. Comfort N; AEON. The overhyping of precision medicine. *Atlantic*. December 12, 2016. https://www.theatlantic.com/health/archive/2016/12/the-peril-of-overhyping-precision-medicine/510326/. Accessed July 25, 2018.
7. Eisen JA. Some history of hype regarding the human genome project and genomics. *Tree of Life*. December 6, 2014. https://phylogenomics.blogspot.co.uk/2014/12/some-history-of-hype-regarding-human.html.
8. Caulfield T, Condit C. Science and the sources of hype. *Public Health Genomics*. 2012;15(3-4):209-217.

9. Bubela T. Science communication in transition: genomics hype, public engagement, education and commercialization pressures. *Clin Genet*. 2006;70(5):445-450.
10. The balancing act of orphan drug pricing. *Lancet*. 2017;390(10113):2606.
11. Schork NJ. Personalized medicine: time for one-person trials. *Nature*. 2015;520(7549):609-611.
12. Finkel RS, Mercuri E, Darras BT, et al; ENDEAR Study Group. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N Engl J Med*. 2018;377(18):1723-1732.
13. Mercuri E, Darras BT, Chiriboga CA, et al; CHERISH Study Group. Nusinersen versus sham control in later-onset spinal muscular atrophy. *N Engl J Med*. 2018;378(7):625-635.
14. Burgart AM, Magnus D, Tabor HK, et al. Ethical challenges confronted when providing nusinersen treatment for spinal muscular atrophy. *JAMA Pediatr*. 2018;172(2):188-192.
15. Johnson CY. Here's why pharma is happy to help foot the bill for this $750,000 drug. *Washington Post*. June 17, 2017. https://www.washingtonpost.com/business/heres-why-pharma-is-happy-to-help-foot-the-bill-for-this-750000-drug/2017/06/09/f29da05a-4a14-11e7-9669-250d0b15f83b_story.html?utm_term=.f6b03bc9e9a1. Accessed March 26, 2018.
16. Shorrock HK, Gillingwater TH, Groen EJN. Overview of current drugs and molecules in development for spinal muscular atrophy therapy. *Drugs*. 2018;78(3):293-305.
17. Mnookin S. One of a kind: what do you do if your child has a condition that is new to science? *New Yorker*. July 21, 2014. https://www.newyorker.com/magazine/2014/07/21/one-of-a-kind-2. Accessed March 26, 2018.
18. Might M, Wilsey M. The shifting model in clinical diagnostics: how next-generation sequencing and families are altering the way rare diseases are discovered, studied, and treated. *Genet Med*. 2014;16(10):736-737.
19. Chong JX, Yu JH, Lorentzen P, et al. Gene discovery for Mendelian conditions via social networking: de novo variants in KDM1A cause developmental delay and distinctive facial features. *Genet Med*. 2016;18(8):788-795.
20. Snow K. Families isolated by rare genetic conditions find new ways to reach out. *NPR*. June 5, 2016. https://www.npr.org/sections/health-shots/2016/06/05/480373533/families-isolated-by-rare-genetic-conditions-find-new-ways-to-rh-out. Accessed March 26, 2018.
21. ALK Positive. About us. https://www.alkpositive.org/about. Accessed March 26, 2018.
22. ALK Positive. Letter from ALK Positive Outreach Management team to ALK Positive Community, family, and friends. https://www.alkpositive.org/wp-

content/uploads/2018/03/ALK-Positive_Outreach-Update_20180315.pdf. Published March 15, 2018. Accessed March 26, 2018.
23. Arbour KC, Riely GJ. Diagnosis and treatment of anaplastic lymphoma kinase-positive non-small cell lung cancer. *Hematol Oncol Clin North Am*. 2017;31(1):101-111.

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STATE OF THE ART AND SCIENCE

Targeted Dosing as a Precision Health Approach to Pharmacotherapy in Children with Inflammatory Bowel Disease

Anava A. Wren, PhD and K. T. Park, MD, MS

Abstract

As clinicians have begun to provide targeted pharmacotherapy for children with inflammatory bowel disease (IBD), several ethical challenges have arisen. In this paper, we review 3 challenges related to applying a precision health approach to pediatric IBD populations: selection of a disease monitoring method, pharmacotherapy optimization, and economic considerations in clinical decision making.

Precision Health Approaches for Pediatric Patients with Inflammatory Bowel Disease

Over the past several years, there has been increased attention directed towards precision health in pediatric medical care.[1] Precision health is particularly relevant when considering how to manage pediatric chronic disease and, specifically, how to personalize medical care that considers children's unique needs. Inflammatory bowel disease (IBD) is an example of a pediatric chronic illness for which precision health is particularly valuable.

IBD, consisting of Crohn's disease and ulcerative colitis, is an autoimmune condition affecting the gastrointestinal tract.[2] This disease process is marked by periods of disease flares (eg, intractable bloody diarrhea, marked weight loss and growth failure, debilitating abdominal pain, fatigue) and remission. The primary treatment for IBD in both children and adults consists of immune suppressive medications, nutritional support, and abdominal or colorectal surgery when necessary.

Patients who are diagnosed with IBD during childhood often have a more severe disease course than patients who are diagnosed during adulthood. Enduring periods of relapsing and remitting disease from a young age can lead to significant functional limitations (eg, not able to go to school or work) and poor quality of life throughout patients' lives.[3,4] When considering precision health in this vulnerable pediatric population with IBD—for example, for differential diagnosis or prognostication[5,6]—the central focus should be a more targeted approach to immune suppressive pharmacotherapy that limits the opportunity loss described above and supports health gains throughout a child's life.

The current Food and Drug Administration (FDA) approach to pharmacotherapy for pediatric IBD is a one-size-fits-all dosing strategy in which drug dosing and guidance are extrapolated from adult trials.[5] This approach is problematic and raises ethical concerns because pharmacokinetic data in children suggest that they have significantly different dosing needs than adults.[7] Yet drug approvals for children remain stagnant, and off-label use is the norm for most medications prescribed to children.[8] Specifically, there is a lack of pediatric clinical trial data from phase 2 and 3 drug trials, resulting in data from adult studies informing best-guess drug dosing of adult-only approved medications in clinical care for children.

Targeted pharmacotherapy is increasingly recognized as a preferable treatment approach as it accounts for differences in children's genes, environment, psychosocial functioning, and lifestyle. However, ethical challenges arise when clinicians apply a precision health approach to pediatric IBD by adopting targeted dosing strategies. This article outlines 3 key ethical challenges: choice of disease monitoring method during targeted pharmacotherapy, optimization of targeted pharmacotherapy, and economic considerations in targeted pharmacotherapy.

First Challenge: Choice of Disease Monitoring Method during Targeted Pharmacotherapy

When applying a precision health approach to pediatric IBD patients undergoing pharmacotherapy that suppresses the immune system, choosing age-appropriate disease monitoring methods is of utmost importance since off-label drug use is often standard of care.[9] In adult IBD care, monitoring disease by endoscopy with mucosal biopsies is the best method to optimize health outcomes. In pediatric IBD care, repeated endoscopy is not feasible given the repeated general anesthesia requirement.[10] Since the gold standard in IBD treatment is to visualize healed mucosa by endoscopy, pediatric IBD specialists need to judiciously recommend endoscopy at strategic points in care (eg, at diagnosis or when changing therapies) and rely on the best approximation of endoscopy (ie, blood tests, stool markers, disease activity scores) to make decisions about targeted pharmacotherapy.

The primary ethical challenge facing pediatric IBD specialists is the equipoise of risk versus benefit of repeated endoscopies in children (and associated complications including adverse neurological effects of repeated general anesthesia during early childhood).[11] The risk versus benefit tradeoff is often patient-specific and cannot be generalized to the entire pediatric IBD population. The clear benefit of endoscopies is precision and accuracy in assessing true disease burden and the associated confidence in treatment decisions. While noninvasive blood and stool monitoring tests are available, they are less precise and pose challenges. For example, consistent adherence to stool collection for fecal calprotectin levels (a potentially accurate surrogate for endoscopy[12]) can be impractical for children.[13]

Another important ethical question relates to reliance on patient-reported outcomes in children for purposes of monitoring treatment effects for targeted pharmacotherapy. While patient-reported outcomes provide valuable information about the patient experience and IBD symptoms,[14] reliance on patient-reported outcomes is inherently subjective and has been shown to be an imprecise measure of mucosal-level inflammation.[15] The challenges associated with patient-reported outcomes can be seen clearly when considering abdominal pain. Complaints of abdominal pain in youth are often indicative of active disease and chronic inflammation. However, more than a quarter of youth experience recurrent abdominal pain during disease remission that is not related to inflammation.[14,16] Thus, patients' reporting of abdominal pain on patient-reported outcomes could reflect an active IBD flare or pain related to non-IBD causes (eg, irritable bowel syndrome, hypersensitivity, functional abdominal pain). Solely relying on patients' reporting of abdominal pain for disease monitoring raises ethical concerns as it can result in increased and unnecessary interventions (eg, endoscopies, ionizing radiographic tests) and pharmacotherapy (eg, opioids or escalating use of steroids and biologics).[17,18] Exposing children to such treatments can result in negative health outcomes such as adverse neurological effects of anesthesia, including developmental and behavioral problems,[19] and increased risk for future opioid misuse.[20,21] Given these challenges and risks, it is important for clinicians to actively listen to and validate patients' experiences and reporting of physical symptoms while not solely relying on patient-reported outcomes to guide IBD treatment decisions when applying a precision health approach.

Second Challenge: Optimization of Targeted Pharmacotherapy

Once a child has been diagnosed with IBD or disease activity progresses, initiating or escalating treatment is warranted. Infliximab (IFX) is the mainstay therapy to achieve remission in pediatric and adult populations with IBD.[22,23] As highlighted above, pediatric dosing is based on adult clinical trials. However, pediatric IFX dosing needs often exceed recommended dosing guidance. For example, reliance on adult dosing in children with Crohn's disease can lead to less than 41% probability of adequate drug exposure.[24] Such significant discrepancies in drug clearance profiles between children and adults can result in early drug failure and worse outcomes for children with IBD.[24]

Choosing the correct pharmacotherapy and targeting pharmacotherapy in an evidence-based way is critical to ensuring appropriate patient care aimed at optimizing future health gains. Early modification of IBD through targeted pharmacotherapy can potentially lead to a milder disease course later in life.[25] Conversely, inadequately treated disease during childhood can potentially lead to more refractory disease during adulthood.[26] The ethical challenge arises when dosing guidance by governing bodies, including the FDA, is based on populations (ie, adults) that are inherently different than the treated population (ie, children), as is the case with IFX. Using guidelines that do not promote best quality care for pediatric IBD populations and that potentially lead to

negative long-term health outcomes poses a significant conundrum for clinicians. There is a significant need for more IBD pharmacotherapy trials (eg, of IFX) with pediatric IBD populations to address ethical concerns—namely, beneficence—that arise when large-scale trials on the safety and efficacy of IBD pharmacotherapies do not include children.

Third Challenge: Economic Considerations in Targeted Pharmacotherapy

In today's era of biologics, IBD therapies have become increasingly effective but costly.[27] Prior to the advent of biologics like IFX, cost-effective IBD care was traditionally focused on containing acute care costs, such as frequent hospitalizations and emergency department visits. Currently, however, the cost of these deliverables is outpaced by the cost of pharamcotherapies.[28] Approximately half of all costs for Crohn's disease are attributed to medications.[28] Since children endure worse disease severity and need early immune-modifying therapies, pediatric patients with IBD are more expensive to treat than adults.[29] The incidence of pediatric-onset IBD has also increased and is higher than previously anticipated.[30] For these reasons, applying targeted pharmacotherapy to pediatric IBD patients can lead to high costs for patients, families, and hospital systems.

Given the increasing demand for biologics and rising health care costs, appropriate IBD treatment has come under scrutiny. Finding the right drug and dose for an individual patient must balance the clinical appropriateness of the medication against the likely cost to the patient and society. While precision in monitoring and dosing is more difficult without consensus-driven outcome measures (ie, repeated endoscopy) and pediatric clinical trial data, overtreating or undertreating pediatric IBD has long-term consequences, often for both the individual and society.

Clinicians sometimes face the ethical challenge of altering pharmacotherapy strategies based on whether a patient has commercial insurance or Medicaid. Health systems are well aware of what commercial payers will reimburse and what Medicaid will not. When expensive therapies that are not covered or not covered fully under Medicaid are started for patients with Medicaid, health systems invariably lose money. Reimbursements from private insurers subsidize the therapy plans of those patients who have inadequate insurance coverage. Some clinicians are aware of the intricate bidirectionality of revenue streams, which may factor into pediatric IBD clinical decision making. Prioritizing hospital revenue and society over the individual (eg, not using biologics on children with Medicaid due to lack of reimbursement) runs the risk of undertreating vulnerable populations of children, leading to inadequate disease management and worse longer-term health outcomes. An important future direction would be to assess the extent to which economic considerations factor into pharmacotherapy decisions among pediatric IBD specialists. This data would support further discussion between clinicians and hospital systems about the ethical challenges related to targeted pharmacotherapy and how to provide the best quality care to pediatric IBD patients while protecting all parties from financial harm.

Resolving Ethical Challenges for Pediatric IBD Patients

In summary, children with chronic diseases such as IBD are vulnerable, and in an effort to provide precision health to them, numerous ethical considerations arise that highlight the opportunity for individual-level and system-level improvement.[31] Children with IBD are not small-sized adults, and clinical endpoints of therapy using age-appropriate, noninvasive methods of disease monitoring are urgently needed.[32,33] Extrapolation of drug dosing guidance from adult IBD data can lead to a suboptimal, one-size-fits all approach for children that can impair pharmacotherapy effectiveness, affect long-term outcomes, and raise safety concerns. Finally, economic considerations are increasingly a part of clinical decision making that will require patient-centered discussions and systematic thought from all stakeholders.

References

1. Hawcutt D, Conney L, Oni L, Pirmohamed M. Precision dosing in children. *Expert Rev Precis Med Drug Dev*. 2016;1(1):69-78.
2. Crohn's and Colitis Foundation of America. The facts about inflammatory bowel diseases. http://www.crohnscolitisfoundation.org/assets/pdfs/updatedibdfactbook.pdf. Published November 2014. Accessed April 12, 2018.
3. Knowles SR, Graff LA, Wilding H, et al. Quality of life in inflammatory bowel disease: a systematic review and meta-analyses—part I. *Inflamm Bowel Dis*. 2018;24(4):742-751.
4. Knowles SR, Keefer L, Wilding H, et al. Quality of life in inflammatory bowel disease: a systematic review and meta-analyses—part II. *Inflamm Bowel Dis*. 2018;24(5):966-976.
5. Bousvaros A, Antonioli DA, Colletti RB, et al; Colitis Foundation of America. Differentiating ulcerative colitis from Crohn disease in children and young adults: report of a working group of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the Crohn's and Colitis Foundation of America. *J Pediatr Gastroenterol Nutr*. 2007;44(5):653-674.
6. Cuffari C. Diagnostic considerations in pediatric inflammatory bowel disease management. *Gastroenterol Hepatol (N Y)*. 2009;5(11):775-783.
7. Frymoyer A, Hoekman DR, Piester TL, et al. Application of population pharmacokinetic modeling for individualized infliximab dosing strategies in Crohn Disease. *J Pediatr Gastroenterol Nutr*. 2017;65(6):639-645.
8. Frattarelli SA, Galinkin JL, Green TP. Off-label use of drugs in children. *Pediatrics*. 2014;133(3):563-567.
9. Baldassano RN, Piccoli DA. Inflammatory bowel disease in pediatric and adolescent patients. *Gastroenterol Clin North Am*. 1999;28(2):445-458.
10. Griffiths AM, Otley AR, Hyams J, et al. A review of activity indices and end points for clinical trials in children with Crohn's disease. *Inflamm Bowel Dis*. 2005;11(2):185-196.

11. Van de Vijver E, Schreuder AB, Cnossen WR, Muller Kobold AC, van Rheenen PF; North Netherlands Pediatric IBD Consortium. Safely ruling out inflammatory bowel disease in children and teenagers without referral for endoscopy. *Arch Dis Child*. 2012;97(12):1014-1018.
12. Rutgeerts P, Vermeire S, Van Assche G. Mucosal healing in inflammatory bowel disease: impossible ideal or therapeutic target? *Gut*. 2007;56(4):453-455.
13. Saverymuttu SH, Camilleri M, Rees H, Lavender JP, Hodgson HJF, Chadwick VS. Indium 111-granulocyte scanning in the assessment of disease extent and disease activity in inflammatory bowel disease. A comparison with colonoscopy, histology, and fecal indium 111-granulocyte excretion. *Gastroenterology*. 1986;90(5, pt 1):1121-1128.
14. Heida A, Park KT, van Rheenen PF. Clinical utility of fecal calprotectin monitoring in asymptomatic patients with inflammatory bowel disease: a systematic review and practical guide. *Inflamm Bowel Dis*. 2017;23(6):894-902.
15. Halpin SJ, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol*. 2012;107(10):1474-1482.
16. Zubin G, Peter L. Predicting endoscopic Crohn's Disease activity before and after induction therapy in children: a comprehensive assessment of PCDAI, CRP, and fecal calprotectin. *Inflamm Bowel Dis*. 2015;21(6):1386-1391.
17. Watson KL, Kim SC, Boyle BM, Saps M. The prevalence and impact of functional abdominal pain disorders in children with inflammatory bowel disease (IBD-FAPD). *J Pediatr Gastroenterol Nutr*. 2017;65(2):212-217.
18. Regueiro M, Greer JB, Szigethy E. Etiology and treatment of pain and psychosocial issues in patients with inflammatory bowel diseases. *Gastroenterology*. 2017;152(2):430-439.e4. doi:10.1053/j.gastro.2016.10.036.
19. Flick RP, Katusic SK, Colligan RC, et al. Cognitive and behavioral outcomes after early exposure to anesthesia and surgery. *Pediatrics*. 2011;128(5):e1053-e1061. doi:10.1542/peds.2011-0351.
20. Miech R, Johnston L, O'Malley PM, et al. Prescription opioids in adolescents and future opioid misuse. *Pediatrics.* 2015;136(5):1169-1177.
21. Wren AA, Bensen R, Sceats L, et al. Starting young: trends in opioid therapy among US adolescents and young adults with inflammatory bowel disease in the Truven MarketScan database between 2007 and 2015 [published online ahead of print July 7, 2018]. *Inflamm Bowel Dis*. doi:10.1093/ibd/izy222.
22. Hyams J, Crandall W, Kugathasan S, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology*. 2007;132(3):863-873.
23. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2005;353(23):2462–2476.

24. Frymoyer A, Piester TL, Park KT. Infliximab dosing strategies and predicted trough exposure in children with Crohn disease. *J Pediatr Gastroenterol Nutr*. 2016;62(5):723-727.
25. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. *Gut*. 2012;61(11):1619-1635.
26. Colombel JF, Rutgeerts P, Reinisch W, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology*. 2011;141(4):1194-1201.
27. Park KT, Bass D. Inflammatory bowel disease-attributable costs and cost-effective strategies in the United States: a review. *Inflamm Bowel Dis*. 2011;17(7):1603-1609.
28. Park KT, Colletti RB, Rubin DT, Sharma BK, Thompson A, Krueger A. Health insurance paid costs and drivers of costs for patients with Crohn's disease in the United States. *Am J Gastroenterol*. 2016;111(1):15-23.
29. Kappelman MD, Rifas-Shiman SL, Porter CQ, et al. Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. *Gastroenterology*. 2008;135(6):1907-1913.
30. Benchimol EI, Bernstein CN, Bitton A, et al. Trends in epidemiology of pediatric inflammatory bowel disease in Canada: distributed network analysis of multiple population-based provincial health administrative databases. *Am J Gastroenterol*. 2017;112(7):1120-1134.
31. Bousvaros A, Sylvester F, Kugathasan S, et al; Challenges in Pediatric IBD Study Groups. Challenges in pediatric inflammatory bowel disease. *Inflamm Bowel Dis*. 2006;12(9):885-913.
32. Sun H, Vesely R, Taminiau J, et al; International Inflammatory Bowel Disease Working Group. Steps toward harmonization for clinical development of medicines in pediatric ulcerative colitis—a global scientific discussion, part 1: efficacy endpoints and disease outcome assessments. *J Pediatr Gastroenterol Nutr*. 2014;58(6):679-683.
33. Sun H, Vesely R, Nelson RM, et al; International Inflammatory Bowel Disease Working Group. Steps toward harmonization for clinical development of medicines in pediatric ulcerative colitis—a global scientific discussion, part 2: data extrapolation, trial design, and pharmacokinetics. *J Pediatr Gastroenterol Nutr*. 2014;58(6):684-688.

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POLICY FORUM: PEER-REVIEWED ARTICLE

Should NASA Collect Astronauts' Genetic Information for Occupational Surveillance and Research?

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Abstract

Humans exploring beyond low-Earth orbit face environmental challenges coupled with isolation, remote operations, and extreme resource limitations in which personalized medicine, enabled by genetic research, might be necessary for mission success. With little opportunity to test personalized countermeasures broadly, the National Aeronautics and Space Administration (NASA) will likely need to rely instead on collection of significant amounts of genomic and environmental exposure data from individuals. This need appears at first to be in conflict with the statutes and regulations governing the collection and use of genetic data. In fact, under certain conditions, the Genetic Information Nondiscrimination Act (GINA) of 2008 allows for the use of genetic information in both occupational surveillance and research and in the development of countermeasures such as personalized pharmaceuticals.

What Is the Genetic Information Nondiscrimination Act?

Anticipating the rapid development of genomics and its implications for both use and misuse, in February of 2000, President William J. Clinton signed Executive Order (EO) 13145, which prohibited genetic discrimination in the federal workplace. The EO barred discrimination based on genetic information, while allowing federal employers to conduct genetic testing for use in occupational surveillance and in other human research conducted under the Common Rule.[1] Eight years later, in 2008, the passage of the Genetic Information Nondiscrimination Act (GINA) extended the EO's protections beyond the federal government to the general public and beyond employment to health insurance.[2] Ten years after the passage of GINA, the National Aeronautics and Space Administration (NASA) has just begun to seriously engage with genomics as a means to understand and mitigate the health consequences of space flight.

GINA's protections are broad: it prevents employers from using genetic information for hiring, firing, or promotion decisions and for any decisions regarding terms of employment. In the context of the human spaceflight program, GINA prevents NASA from collecting and using genetic information to determine whether an applicant will be selected to become an astronaut and whether an astronaut is qualified for assignment to a particular mission.

Although genetic information cannot legally be used to determine eligibility for employment, it is likely to become critical for some types of occupational surveillance and for mitigating some occupational risks. Genetic research is becoming critical to understanding differences in patients' responses to treatments and to predicting individuals' responses to targeted therapy,[3] tasks made more complex when the goal is to understand and protect workers from negative health impacts of occupational environments. Despite more than 7 decades of human spaceflight, NASA astronauts work in a unique and poorly characterized environment. With limited opportunities to test personalized countermeasures before sending humans on a 2-year trip to Mars, NASA will need to rely instead on collection of significant amounts of genomic and environmental exposure data from individual astronauts.[4]

Collecting genetic information for the purpose of occupational surveillance appears at first to be in conflict with statutes and regulations governing the collection and use of genetic data just discussed. In fact, under certain conditions, GINA allows for use of genetic information in both research and occupational surveillance and in developing countermeasures such as personalized pharmaceuticals.

Application of GINA to NASA

NASA currently collects little genetic information about astronauts, but it is actively exploring how genetic information might improve understanding of health risks of spaceflight and mitigate those risks. As applied to NASA, GINA governance of collecting genetic information is complicated by that fact that NASA does not fit neatly into any of the categories defined in GINA; rather, NASA plays several roles. NASA is an employer that makes employment and flight selection decisions; it is a clinical care provider insofar as it provides primary care and health maintenance to the active astronaut corps, ongoing surveillance of former astronauts, and flight medicine support during training and flight; it performs occupational health surveillance and wellness promotion by monitoring and characterizing the influences of space environment hazards on crew and seeking to train and prepare crew members appropriately; and it is a research organization that performs fundamental and applied research to understand—and develop countermeasures to minimize—unique harms of the spaceflight environment, such as toxic radiation and microgravity exposure. NASA is permitted to collect genetic information in the course of providing clinical care, providing occupational surveillance and protection, and doing research to ensure the health and safety of future explorers.

This collection process must be consistent with the statutory requirements of GINA as well as those of the Privacy Act of 1974,[5] which defines government obligations to protect personal information in federal records; the Common Rule,[6] which establishes ethical requirements for human subject research; and Occupational Safety and Health Administration (OSHA) guidelines,[7] which mandate how employers must protect workers' health.

NASA's Collection of Genetic Information for Research

GINA's rules do not limit the authority of a federal department or agency to conduct or sponsor occupational research or other health research under the Common Rule.[8] Equal Employment Opportunity Commission (EEOC) federal regulations, which interpret GINA, state that GINA should be construed so that it does not "limit the authority of a Federal department or agency to conduct or sponsor occupational or other health research."[9]

The astronaut corps is a unique employee population. Small in number and highly visible in the public eye, astronauts face special challenges maintaining the privacy and confidentiality of their data. NASA's policy on genetic research recognizes these challenges and places significant restrictions on how genetic information gathered as part of research is used and shared.[1] Participation in genetic research is voluntary, and NASA is keenly aware of the potential for actual or perceived coercion in an environment of limited flight opportunities. As a result, NASA maintains rigorous informed consent processes overseen by the NASA Flight Institutional Review Board (IRB). Control over access to retrospective data is maintained by the Lifetime Surveillance of Astronaut Health (LSAH) advisory board, which is delegated authority from the system of records administrator.

One recent and well-publicized example of genetic research on astronauts is the Twins Study,[10] an ambitious research program using personalized medicine techniques to discern individual responses to long-term exposure to a spaceflight environment. The Twins Study is the first of its kind and compares the molecular profile of a pair of identical twins, Scott and Mark Kelly, one current and one former astronaut, while one spent a year in space and the other remained on Earth. The study is a series of 10 separate studies that attempt to link genetic, epigenomic, proteomic, and metabolomics data at a molecular level to whole-body and brain function at a macroscopic level. Insights gained from this research are expected to inform how NASA defines its occupational surveillance needs and its approach to countermeasures for mitigating risks of spaceflight. Because of the very small sample size of the study and the highly identifiable nature of both subjects, there was no option that would protect their privacy and preserve the confidentiality of their health information. The twin who flew in space during this study—the first US 1-year crew member—retired from NASA shortly after his flight. As a result of all these factors, NASA's ability to demonstrate its capacity to protect research data from improper use was not tested.

NASA's Collection of Genetic Information for Occupational Surveillance

Unlike the voluntary nature of their participation in research, crew cannot opt out of occupational surveillance, which is part of the provision of health care. Occupational surveillance differs from research governed by the Common Rule. The Common Rule defines research as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."[11] Occupational surveillance, intended only for use within NASA to inform its understanding of the hazards associated with human spaceflight and to develop countermeasures against those hazards, does not meet this criterion.[11] Genetic data collected as a part of NASA's occupational surveillance must be properly safeguarded to ensure its storage and use in accordance with GINA and the Privacy Act.

As a part of occupational surveillance, GINA allows employers to collect genetic information to monitor biological effects of toxic substances in the workplace.[12] The space environment, an astronaut's workplace, contains inherently dangerous conditions such as exposure to radiation and microgravity. For instance, the US Department of Health and Human Services' Agency for Toxic Substances and Disease Registry classifies ionizing radiation as a toxic substance.[13] Collecting genetic information to monitor the impact of the hazardous space environment on astronauts and in ground analogs is consistent both with GINA's allowance for collecting genetic information for occupational surveillance and with the toxic substances exemption from OSHA's general prohibition on collecting genetic data.[12]

The EEOC and GINA specify that employers may only acquire genetic information for use in monitoring biological effects of toxic substances in a workplace under specific conditions.[12] Under GINA, an employer must provide written notice of monitoring to the employee, and the employee must be informed of the monitoring results. An employer may not retaliate or otherwise discriminate against employees due to their refusal to participate in genetic monitoring, and employees must give prior knowing, voluntary, and written authorization. Finally, an employer may only obtain results in the aggregate.[14] Currently, NASA has not begun collecting genetic information for genetic monitoring. It is likely, however, to do so in the near future. Compliance with GINA will be feasible in all respects except one: aggregation of data.

NASA collects health data on individual employees, and it is responsible for the Privacy Act systems of records in which employees' clinical and research data are stored. By definition, NASA would have access to genetic information collected from individually identifiable astronauts. The small number of astronauts and the importance of understanding individual genetic differences make it difficult to aggregate and anonymize genetic information. In our view, applying the GINA requirement for aggregated data would limit NASA's authority to conduct occupational and health

research and thus would be invalid as applied to NASA's occupational and health research activities. Because of the small number of astronauts and the necessity of matching an individual's genetic information to that individual's specific exposures, such as time in space and radiation events, once NASA begins collecting individuals' genetic information, the data cannot be both aggregated and useful for identifying health impacts from the hazards of spaceflight and for developing countermeasures.

NASA can maintain safeguards currently in place that segregate clinical data from research data and regulate processes of selecting and qualifying crew for flight assignments. Access to clinical and research health records are moderated through several NASA boards that make need-to-know determinations for identifiable records, ensure that proper consent is obtained if data is used for research purposes, and verify that NASA's epidemiologists have anonymized data sufficiently to allow its release to requestors. These same processes could be used to ensure that genetic information is logically segregated from other health data in electronic health records and not released for purposes of making medical qualifications for flight decisions. NASA has already removed questions relating to family medical history (which is considered genetic information) from its astronaut selection processes. NASA can also implement privacy measures that would protect astronauts from discrimination.

Genetic Information as a Part of Occupational Health

GINA and EEOC regulations also support collection and use of genetic information for health care delivery and apply to NASA as the primary health care provider for the astronaut corps. GINA's prohibitions against requesting or collecting genetic information do not apply to employers that offer health or genetic services, provided such services "are reasonably designed to promote health or prevent disease."[15] NASA's Flight Medicine Program is an occupational health program designed to identify and treat injury and illness resulting from occupational exposures during training and spaceflight, maintain optimal health and performance of NASA's astronauts, and support development of measures to counter long-term health effects of space flight. Thus the program meets the OSHA regulatory exemption from the general prohibition on collecting genetic data for employers that offer health services designed to promote health and prevent disease.[12] Currently, NASA's flight medicine program does not collect genetic information other than family history, which supports clinical care. Once it begins to collect genetic data, those data will become part of an astronaut's health record and part of the system of records discussed above. Those data, like all clinical data, are available for use in treating individual astronauts and for occupational surveillance of the astronaut corps as a whole. Like genetic data collected for research, these data are also walled from consideration for flight selection purposes.

Genetic information will be critical to protecting crew members' health as NASA moves from low-Earth orbit to planetary exploration missions. Personalized countermeasures

developed through efforts like pharmacogenomics will be necessary as NASA sends humans on multiyear missions with fully autonomous medical systems and no resupply or medical evacuation capability. For example, general medication safety and efficacy is highly variable among patients in space. The European Space Agency recently found that individual response to roughly one-third of drugs currently available on the International Space Station is affected by polymorphic metabolizing enzymes.[16] This finding suggests that tracking and using individual astronauts' genetic information could lead to a significantly more effective and personalized pharmacy for future exploration missions. Personalized pharmacies will minimize the chance of providing ineffective medications to crews unable to access alternative medications due to the remote nature of their missions. Since exploration missions will be extremely resource constrained, allowing NASA to fly only the most effective medications for the assigned crew will make room for a broader onboard formulary.

As mentioned, GINA generally prohibits employers from receiving genetic information collected for the purpose of providing care, except in the aggregate. However, there is a specific exception for circumstances that make data aggregation impossible, such as when the number of subjects is so small that information is readily identifiable with no effort on the employer's part.[17] Criteria for this exception are met in the case of astronauts. For reasons discussed above, it would be impossible to aggregate data and accord the regulatory exception. As a result, we believe that NASA may properly collect individualized genetic data for clinical purposes. Even so, NASA may only use collected data for activities not prohibited by GINA, such as the provision of health care, occupational surveillance and research, and development of countermeasures—not for astronaut selection or flight assignments.

Protecting and Treating Astronauts While Avoiding Discrimination

As NASA looks to expand the reach of human exploration to Mars and beyond, human health will be one of the most significant risks to mission success. As a result, expanding the frontiers of human exploration is closely tied to expanding the frontiers of medicine. Exploring Mars and someday beyond our solar system will require advanced autonomous medical capabilities and personalizing medicine to respond to needs of individual crew members in their unique work environments. Genetic information and research is critical to enabling these advances and to protecting the health of future explorers. NASA's particular challenge arises in striving to meet its ethical and legal obligations to each astronaut whose genetic information will be collected. As a primary care provider, employer, and research investigator, NASA will need to create appropriate information and policy structures to ensure that genetic information is used to protect and treat members of the astronaut corps, not to discriminate against them unjustly.

References

1. Executive Order 13145—to prohibit discrimination in federal employment based on genetic information. *Fed Regist*. 2000;65(28):6877-6880. https://www.gpo.gov/fdsys/pkg/FR-2000-02-10/pdf/00-3331.pdf. Accessed April 12, 2018.
2. Genetic Information Nondiscrimination Act of 2008, Pub L No. 110-233, 122 Stat 881.
3. Hamburg MA, Collins FS. The path to personalized medicine. *N Engl J Med*. 2010;363(4):301-304.
4. Schork NJ. Personalized medicine: time for one-person trials. *Nature*. 2015;520(7549):609-611.
5. Privacy Act, 5 USC §552a (1974).
6. 45 CFR part 46, subpart A (2017).
7. 29 CFR part 1910 (2017).
8. 29 CFR §1635.11(a)(5) (2010).
9. Regulations under the Genetic Information Nondiscrimination Act of 2008. *Fed Regist*. 2010;75(216):68912-68939. https://www.gpo.gov/fdsys/pkg/FR-2010-11-09/pdf/2010-28011.pdf. Accessed April 12, 2018.
10. NASA. Twin study. https://www.nasa.gov/twins-study. Updated March 26, 2018. Accessed April 12, 2018.
11. 45 CFR §46.102(d) (2009).
12. 29 CFR §1635.8 (b)(5) (2010).
13. Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention. Toxic substances portal. https://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=86. Accessed January 27, 2017.
14. 29 CFR §1635.8 (b)(5)(i) (2010).
15. 29 CFR §1635.8 (b)(2)(i)(A) (2010).
16. Stingl JC, Welker S, Hartmann G, Damann V, Gerzer R. Where failure is not an option—personalized medicine in astronauts. *PLoS One*. 2015;10(10):e0140764. doi:10.1371/journal.pone.0140764.
17. 29 CFR §1635.8 (b)(2)(i)(E) (2010).

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POLICY FORUM

What Should Oversight of Clinical Decision Support Systems Look Like?

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Abstract

A learning health system provides opportunities to leverage data generated in the course of standard clinical care to improve clinical practice. One such opportunity includes a clinical decision support structure that would allow clinicians to query electronic health records (EHRs) such that responses from the EHRs could inform treatment recommendations. We argue that though using a clinical decision support system does not necessarily constitute a research activity subject to the Common Rule, it requires more ethical and regulatory oversight than activities of clinical practice are generally subjected to. In particular, we argue that the development and use of clinical decision support systems should be governed by a framework that (1) articulates appropriate conditions for their use, (2) includes processes for monitoring data quality and developing and validating algorithms, and (3) sufficiently protects patients' data.

Learning Health Systems and Patient-Centered Care

The increasing adoption of electronic health records (EHRs) and other technological advances allowing for routine collection of patient-generated data contributes to the infrastructure needed to transform health systems within the United States and abroad into learning health systems. A learning health system has been defined by the National Academy of Medicine (NAM) as one "in which science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience."[1]

The ability to leverage routinely collected data, both within and across health systems, holds promise for improving the organization and quality of care delivered to patients and for informing diagnostic, treatment, and other decisions based on patients' needs and individual characteristics. For example, some have argued that clinical decision support systems leveraging data aggregated from patients with similar clinical presentations could be designed to provide real-time, point-of-care feedback to help inform personalized treatment choices.[2] However, a number of scientific, ethical, and regulatory

questions remain regarding development and use of such clinical decision support systems for the purpose of making treatment recommendations.

In this paper, we focus on the question, What constitutes appropriate regulatory oversight of clinical decision support systems? We argue that while use of these systems does not necessarily constitute a research activity subject to the Common Rule,[3] development and implementation of these systems requires a greater level of ethical and regulatory oversight than is generally applied to activities of clinical practice or other health systems-level decisions about care delivery. In particular, ethical and regulatory oversight should ensure that (1) conditions for use of these systems (including adherence to evidence-based approaches) and the basis for the recommendations they generate are appropriately articulated, (2) systems rely on validated algorithms and address issues of data quality, and (3) sufficient privacy protections exist for patients whose data are used.

Applicability of Regulatory Oversight Requirements for Human Subjects Research to Clinical Decision Support Systems

Within the United States, the Common Rule provides the primary framework for ethical and regulatory oversight of federally funded biomedical and behavioral research involving human subjects.[3] The Common Rule defines types of research activities subject to regulations; these definitions draw heavily on the distinction between research and treatment articulated in the Belmont Report.[4] Under the Common Rule, research is defined as "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge."[3] The tenability and utility of this distinction—and the resulting research and clinical oversight practices—are increasingly challenged by activities within learning health care systems, which cannot be classified exclusively as either research or practice.[5] However, much discussion around the need for a new ethical and regulatory framework has focused on reducing barriers to research activities rather than on strengthening oversight of clinical practice activities.[4] Amid debates about how to address "overprotection" of research participants, concerns persist about comparable lack of oversight for clinical practice and risks to which patients are exposed.[5,6]

A clinical decision support system that allows clinicians to query EHRs to inform individual point of care treatment recommendations (hereafter referred to as CDS-EHR) would generally not be considered research under the Common Rule's definition and would, therefore, not be subject to federal regulation. The objective of a CDS-EHR is not to produce generalizable knowledge but rather to provide a specific recommendation to a clinician and patient regarding appropriate treatment options. The use of this system has more in common with traditional "static" clinical prediction models (CPMs) and other decision tools currently used in clinical practice to inform treatment recommendations (eg, the Framingham Risk Score). A CDS-EHR simply applies previously developed

algorithms to existing data for the purpose of generating one-off estimates of potential risks and benefits of interventions under consideration by a clinician and a patient at the point of care. Development and validation of such a CPM might constitute research under the Common Rule, as might the evaluation of outcomes for patients whose treatment choices were informed by the use of these systems.

A CDS-EHR is better understood as what Faden et al. describe as a "learning activity," namely, an activity that involves integration of clinical care delivery with the objective of learning how to improve clinical practice or health care delivery.[7] Oversight of learning activities requires a framework that establishes conditions and governance for ensuring their sound scientific and ethical conduct.

Oversight Approaches for Clinical Decision Support Systems

To date, there have been several efforts to clarify appropriate oversight mechanisms for clinical decision support tools. For example, the 21st Century Cures Act identifies 4 conditions that must be met for clinical decision support software to *not* be defined as a device regulated by the Federal Food and Drug Administration (FDA)[8]; the FDA has also issued draft guidance to clarify the agency's interpretation of those 4 conditions.[9] Broadly, a CDS-EHR would be excluded from FDA regulation as a device if (1) it is intended for displaying, analyzing, or printing medical information, including information about a patient (eg, test results); (2) it is intended to support or provide recommendations to health care professionals about prevention, diagnoses, or treatment of medical conditions; (3) health care professionals are able to independently review the basis for such recommendations and do not rely primarily on the CDS-EHR in making treatment recommendations for an individual patient; and (4) it does not acquire, process, or analyze information from diagnostic devices.

Regardless of the status of CDS-EHRs with respect to current (or pending) regulatory requirements or proposed voluntary guidance,[10] we argue that transparent and responsible use of CDS-EHRs requires adherence to a set of baseline requirements.

First, CDS-EHRs are largely meant to aid in the decision-making process and should not be the sole source of information used to inform a clinical decision. Therefore, it is imperative that clinicians understand the basis of recommendations generated and the appropriate conditions for using the software, including that recommendations generated are not meant to replace existing guidelines. In particular, CDS-EHR software should be transparent about sources of patient-specific information and sources of clinical information or decision rules (eg, guidelines) used to generate recommendations.[9] When possible, the CDS-EHR software should also describe levels of certainty or reliability of recommendations and their clinical rationale.[10] Finally, clinicians using CDS-EHRs should have sufficient expertise to make the clinical decisions in question without the software and adequate time to consider generated recommendations in the context

of other clinically relevant information, including guidelines. Clinicians should also inform patients of how they arrived at their recommendations and how patients' data might be used in generating recommendations for other patients.[10]

Second, oversight is also needed to ensure that development, validation, and upkeep of a CDS-EHR adhere to best methodological practices. The need to adhere to best methodological practices, and not simply standard software validation practices, reflects pervasive concerns about how clinical prediction models are developed and validated.[11,12] There are several issues that should be addressed as part of this oversight. First, the quality of data used to develop a model must be carefully examined. For example, despite opportunities presented by access to increasing amounts of EHR data, such data can be incomplete, inaccurate, or otherwise unfit for use in research, including in developing CDS-EHRs.[12] Second, all methods used to develop models, no matter how sophisticated, have limitations; their potential impact on the validity and reliability of the models and of resulting treatment recommendations should be assessed. Third, models developed using data from one particular population might not produce valid and reliable recommendations when used in different patient populations without appropriate recalibration procedures.[12] Fourth, a CDS-EHR is not self-sufficient; once implemented, oversight is required to ensure its upkeep and evaluation.

Finally, insofar as a CDS-EHR actively queries an EHR system at the point of care, the recommendations generated can reveal protected health information (PHI) to clinicians, particularly in cases of rare diseases or small patient populations. (Even when recommendations are based on aggregate data, the relevant comparison group might be so small as to result in inadvertent disclosure of PHI.) Depending on the level of detail a clinician shares with a patient regarding a treatment recommendation's underlying rationale, such information could also be inadvertently revealed to a patient being treated. As with other activities in a learning health system, oversight of CDS-EHRs is needed to ensure sufficient privacy protections for patients whose data are used as part of the system.

Oversight of CDS-EHRs with respect to these baseline requirements requires identifying (or creating) the institution(s) with the appropriate independence, expertise, and enforcement capabilities, especially for systems not defined as devices subject to FDA regulations. A national independent body is needed to ensure appropriate use of these systems by clinicians and to establish and monitor adherence to standards for data quality and model validation. Whether an existing federal agency is adequately positioned to assume this role or whether a nongovernmental agency should be charged with this responsibility requires further deliberation. Local hospitals or health care systems, however, might be sufficient for ensuring patient privacy.

Improving Oversight to Ensure Patient-Centered Care

While a CDS-EHR is not research as defined by the Common Rule, we argue that such systems constitute learning activities that should be subject to appropriate oversight. Although CDS-EHRs hold great promise for informing patients' and clinicians' point-of-care decision making by leveraging large amounts of routinely generated data, they could result in increased risk of harm to patients (eg, inappropriate treatment recommendations, privacy breaches). Therefore, it is imperative that CDS-EHRs be developed using high-quality data and valid and reliable models. It is also imperative that clinicians are informed about appropriate use of CDS-EHRs, that they sufficiently understand the recommendations generated, and that the privacy of patients' data used by such systems is adequately protected.

Efforts to improve oversight of CDS-EHRs should also consider where oversight authority should be situated. Regardless of which agencies are charged with oversight, we believe that compliance with oversight policies or regulations should be required rather than voluntary, especially since individuals and organizations developing these systems can be influenced by incentives not always consistent with improving outcomes for patients. Systems developers, methodologists, clinicians, patients, and other health care stakeholders should be involved in efforts to inform development of appropriate policies and methodological standards for developing, validating, and maintaining CDS-EHRs to ensure high-quality, patient-centered care.

References

1. National Academy of Medicine. The learning health system series. https://nam.edu/programs/value-science-driven-health-care/learning-health-system-series/. Accessed March 21, 2018.
2. Longhurst CA, Harrington RA, Shah NHA. A "green button" for using aggregate patient data at the point of care. *Health Aff (Millwood)*. 2014;33(7):1229-1235.
3. Federal policy for the protection of human subjects; final rule. *Fed Regist*. 2017;82(12):7149-7274. https://www.gpo.gov/fdsys/pkg/FR-2017-01-19/pdf/2017-01058.pdf. Accessed April 6, 2018.
4. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: ethical principles and guidelines for the protection of human subjects of research. https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html. Published April 18, 1979. Accessed April 6, 2018.
5. Kass NE, Faden RR, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. The research-treatment distinction: a problematic approach for determining which activities should have ethical oversight. *Hastings Cent Rep*. 2013;43(suppl 1):S4-S15.
6. Beauchamp TL, Saghai Y. The historical foundations of the research-practice distinction in bioethics. *Theor Med Bioeth*. 2012;33(1):45-56.

7. Faden RR, Kass NE, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. An ethics framework for a learning health care system: a departure from traditional research ethics and clinical ethics. *Hastings Cent Rep*. 2013;43(suppl 1):S16-S27.
8. 21st Century Cures Act, HR 34, 114th Cong, 2nd Sess (2016).
9. US Food and Drug Administration. Clinical and patient decision support software: draft guidance for industry and Food and Drug Administration staff. https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm587819.pdf. Accessed March 18, 2018.
10. Clinical Decision Support Coalition. Introductory memorandum. http://cdscoalition.org/wp-content/uploads/2017/08/CDS-3060-Guidelines-Final-2.pdf. Published August 30, 2017. Accessed March 18, 2018.
11. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *Ann Intern Med*. 2015;162(1):55-63.
12. Hersh WR, Weiner MG, Embi PJ, et al. Caveats for the use of operational electronic health record data in comparative effectiveness research. *Med Care*. 2013;51(8)(suppl 3):S30-S37.

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POLICY FORUM

How Could Commercial Terms of Use and Privacy Policies Undermine Informed Consent in the Age of Mobile Health?

Cynthia E. Schairer, PhD, Caryn Kseniya Rubanovich, MS, and Cinnamon S. Bloss, PhD

Abstract

Granular personal data generated by mobile health (mHealth) technologies coupled with the complexity of mHealth systems creates risks to privacy that are difficult to foresee, understand, and communicate, especially for purposes of informed consent. Moreover, commercial terms of use, to which users are almost always required to agree, depart significantly from standards of informed consent. As data use scandals increasingly surface in the news, the field of mHealth must advocate for user-centered privacy and informed consent practices that motivate patients' and research participants' trust. We review the challenges and relevance of informed consent and discuss opportunities for creating new standards for user-centered informed consent processes in the age of mHealth.

Privacy and Informed Consent in the Age of Mobile Health

Mobile health (mHealth) refers to the use of technologies such as smartphone apps or wearable sensors to monitor health. In the past decade, there has been increasing enthusiasm for the role of mHealth in promoting precision medicine and learning health systems.[1] However, there are significant risks to collecting, transmitting, and storing personal health data that experts and the public alike have been slow to recognize. Current news about the sheer amount of data shared or sold by health technology companies and by platforms like Facebook, the lack of transparency about these activities, and the many possible malicious uses of these data have sparked a "techlash" reflecting public unease about many technologies central to mHealth research and clinical care.[2-4] In the current climate, demonstrating a clear and consistent commitment to the tenets of informed consent will be more important than ever for conscientious scientists and health care practitioners who wish to maintain the trust of participants and patients involved in mHealth studies or clinical interventions.

Informed Consent in mHealth

Whether used for precision medicine research, health-related citizen science, *N*-of-1 studies, or clinical care, mHealth tools pose challenges for the process of obtaining meaningful informed consent from users.[5-8] The sensitivity and value of health information, along with the complexity of mHealth ecosystems, create unique privacy risks that are difficult to foresee and understand.[7,9,10] The risks are wide ranging and can include insurance discrimination based on data from mHealth technologies integrated into workplace wellness programs,[11] inadvertent invasion of privacy of family members or other "bystanders" with collection of data in home environments,[12] compromising community safety (as in military presence recently revealed by the Strava app[13,14]), and political manipulation through profiling based on health data, which has the potential to be far more personal than Facebook posts.[2,15] In many mHealth contexts, use of remote consent can exacerbate communication difficulties, especially if traditional informed consent forms are simply migrated to remote platforms. Improvements to the informed consent process, such as Sage Bionetworks eConsent for the Apple ResearchKit Parkinson mPower study,[16,17] rely on researcher initiative and commitment to implement such innovations.[18,19]

Among the many challenges to informed consent in mHealth, the problem of reconciling commercial terms of use with informed consent is perhaps most pressing for the field. Compared to most commercial contexts, the Common Rule[20] and the Health Insurance Portability and Accountability Act (HIPAA) set high standards for the protection of patient and research participant data in medical settings. However, cost effective applications of mHealth technologies in medical care and research depend on bringing apps and devices developed in commercial contexts into medical settings. Maintaining a high standard of privacy protection in research and health care utilizing mHealth technologies will require attention to important differences between informed consent and commercial terms of use documents—specifically, differences in readability, content, and the protections afforded. We argue that the principles that underlie informed consent should guide professionals who adopt mHealth technology as they seek to maintain transparency and protect the interests of mHealth participants and patients. If legitimate health research and care are to incorporate these tools, health professionals and their institutions must work to promote transparency and public trust by addressing the challenges to informed consent. We point to opportunities for institution-based researchers to lead the way in this effort.

Ubiquity of Commercial Terms of Use and Privacy Policies

The unique obstacle for mHealth with respect to informed consent is that users—whether research participants, patients, or "lifeloggers" (people who digitally record all aspects of their lives)—are nearly always required to agree to terms of use of the underregulated commercial entities supplying mHealth devices and services. Typical terms of use for commercially developed apps and devices, including those used in

research, include lengthy legalese and may stipulate the release or selling of personal identifiable data,[9,10,21-24] thus representing a significant departure from the principles of informed consent. Moreover, in medical settings, institutional review boards (IRBs) often require clear and explicit language stating risks—including risks to privacy—as well as statements of how confidentiality will be protected, but there is a challenge in reconciling IRB-approved informed consent documents with the terms of use set forth by commercial entities.[25]

While some researchers might have the resources and expertise to develop their own devices or apps, in most cases mHealth researchers will make use of commercially available tools for their studies. In these cases, researchers broker a relationship between study participants and the company supplying the technologies or acting as the first point of collection for the data. Thus, they are put in the position of requiring that participants accept commercial terms of use as a condition of study participation, thereby subjecting participants to any risks related to those terms. Furthermore, the number of required documents proliferates for each sensor, smartphone, app, or data service used. For example, a study led by the senior author (CSB) required participants to agree to up to 5 different terms of use documents in addition to an IRB-approved informed consent.[26] Requiring participants to review such a large number of agreements makes it less likely that they will be able to devote the necessary energy to understand the content before consenting, rendering such consent "uninformed" rather than informed. In theory, this situation could be an opportunity for researchers to protect participants from questionable consumer contracts or commercial use of their data, either by subjecting commercial terms of use to IRB review or by negotiating with companies to create more user-centered terms of use. In practice, however, IRBs may or may not have adequate resources or expertise to thoroughly evaluate these terms. In addition, companies may resist changes to these terms as they are designed to limit their legal exposure and protect their commercial interests. The burden of convincing companies to incur the potential liability and expense of altering terms of use cannot be borne by individual researchers or clinicians,[27] and hence this task requires collective action.

Continued Importance of Informed Consent in the Age of mHealth

The tradition of informed consent will serve as an invaluable resource for the field of mHealth as it faces the challenge of protecting user interests in privacy and transparency. Maintaining public trust and willingness to engage with new technologies is, after all, essential to realizing the power of mHealth to improve both individual and population health.

Studies of attitudes toward data sharing indicate that people prefer to be asked for permission to use their data in research, especially when health information is involved.[6,28-31] A recent survey showed that 68% of users of digital self-tracking

technologies said they would share personal health information "if privacy were assured" and 67% felt anonymity was "very" or "extremely" important.[6] Another survey found that respondents across generations were concerned about health privacy,[32] contrary to popular assumptions about millennial disinterest in privacy. While it might be assumed that early adoption of health technologies is coupled with a disinterest in privacy, a qualitative study of privacy attitudes among early adopters of personal wearable sensors and health apps demonstrated that members of this group placed a value on personal data privacy and expressed the desire to control their personal data.[31] Such findings underscore the importance of notification about data uses and consent in maintaining relations of trust when asking for personal health information.

The European Union's (EU's) new General Data Protection Regulation (GDPR) is another indication of current interest in protecting privacy and in transparent consent. The GDPR requires that, in most commercial situations, contracts present explicit opportunities for signers to consent to the collection and use of any personal information.[33] Furthermore, the GDPR demands that requests for consent be legible and accessible, that the purpose of collecting data be stated, and that consent be obtained at the point of data collection and be easy to withdraw.[34,35] While not law outside of the EU, the GDPR reflects some common expectations about privacy and has the potential to become an international gold standard for individuals concerned about their personal privacy.

Opportunities to Promote Informed Consent and the Protection of Privacy

In our view, the challenges we have raised are best approached as opportunities for health care and research institutions seeking to leverage mHealth technologies to lead the important work of creating user-centered informed consent procedures.

The first step for those who wish to incorporate mHealth into medical research or clinical practice is to be aware that commercial data collection, transmission, storage, access, and use are underregulated and not standardized. For this reason, researchers and physicians should take the opportunity to be savvy consumer advocates when selecting the products they recommend and keep in mind that commercial partners typically use collected data for their own purposes. As an example, Fitabase, a company that serves as a bridge between academic researchers and Fitbit, a company that makes devices and apps to monitor fitness-related metrics, suggests that researcher-initiated strategies for protecting privacy such as creating anonymous Fitbit accounts with limited demographic data, not collecting GPS data, and maintaining a schedule for deleting data could be worthwhile.[36]

Ultimately, though, what is needed are strategies to ensure that data-sharing practices are safe and transparent without limiting the potential of mHealth tools to improve health. The GDPR is one attempt to reign in current unregulated activities through a comprehensive law, but the strategies the GDPR uses are similar to, and perhaps more

stringent than, HIPAA and the Common Rule, which some argue strangle 21st century US medical research.[37] In an attempt to facilitate research, recent changes to the Common Rule have expanded exemptions for informed consent,[6,7] but expanding exemptions may become an increasingly unpopular option for mHealth research as the public becomes more concerned about privacy in relation to consumer devices and apps. Other ideas include individualized or granular consent[38] or adopting "opt out" policies in certain contexts such as learning health care systems where the potential benefits of mHealth research for collective health may outweigh the importance of individual autonomy. Finally, Evans[39] has suggested a model of health data commons—new systems of governance that would allow individuals to lend their health data to research as part of a collective that would democratically set the terms for data use. All these approaches are ways to reinvent informed consent. Even the innovation of a data commons would not be the lack of consent—individuals would make the choice to join or leave the collective—but rather the opportunity to collectively negotiate the terms of that consent.

The national Precision Medicine Initiative project, All of Us, may be well situated to lead in creating user-centered terms of use for mHealth users. All of Us aims to enroll "one million or more people living in the United States" in the largest precision medicine cohort study to date.[40] Participants will be asked to contribute information via mHealth platforms in addition to genetic material and survey responses. The wide reach, resources, and scale of All of Us affords a unique opportunity for the cooperating institutions to negotiate with commercial partners for terms of use that meet stricter standards for both the presentation of informed consent documents and the data handling practices they use. This goal might be accomplished, for example, by creating a consortium of mHealth researchers working under the umbrella of All of Us to purchase products and services together under conscientious privacy policies designed to minimize data sharing among commercial partners. At present, we are not aware of any such coordinated efforts. Whatever policies and practices are developed by All of Us could serve as a model for smaller precision medicine projects as well as set a standard for handling mHealth data in any context.

Conclusion

Leaders in health care and research who seek to leverage mHealth technologies should draw upon the strength of informed consent as they face the challenge of managing unique privacy risks to users. For research participants and patients, informed consent expresses an exercise of autonomy and choice and is a symbol of professionals' good faith to handle personal data with integrity and transparency. Informed consent can strengthen trust in relationships across research and clinical practice, and therefore research and health care institutions should seek opportunities to promote and develop better systems of consent and oversight in the age of mHealth.

References

1. Steinhubl SR, Muse ED, Topol EJ. Can mobile health technologies transform health care? *JAMA*. 2013;310(22):2395-2396.
2. Lee MYH, Timberg C. How Cambridge Analytica broke into the US political market through Mercer-allied conservative groups. *Washington Post*. March 23, 2018. https://www.washingtonpost.com/politics/how-cambridge-analytica-broke-into-the-us-political-market-through-mercer-allied-conservative-groups/2018/03/23/141adba8-2ead-11e8-b0b0-f706877db618_story.html?utm_term=.8c858252e3fc. Accessed April 6, 2018.
3. King J. Facebook fallout: American's privacy at risk across entire tech, information industry. University of California. https://www.universityofcalifornia.edu/news/facebook-fallout-americans-privacy-risk-across-entire-tech-information-industry?utm_source=fiat-lux&utm_medium=internal-email&utm_campaign=article-general&utm_content=text. Published March 22, 2018. Accessed March 25, 2018.
4. Shah H. Use our personal data for the common good. *Nature*. 2018;556(7699):7.
5. Samuel JP, Burgart A, Wootton SH, Magnus D, Lantos JD, Tyson JE. Randomized *n*-of-1 trials: quality improvement, research, or both? *Pediatrics*. 2016;138(2):e20161103. doi:10.1542/peds.2016-1103.
6. Bietz MJ, Bloss CS, Calvert S, et al. Opportunities and challenges in the use of personal health data for health research. *J Am Med Inform Assoc*. 2016;23(e1):e42-e48. doi:10.1093/jamia/ocv118.
7. Rothstein MA, Wilbanks JT, Brothers KB. Citizen science on your smartphone: an ELSI research agenda. *J Law Med Ethics*. 2015;43(4):897-903.
8. Grady C, Cummings SR, Rowbotham MC, McConnell MV, Ashley EA, Kang G. Informed Consent. *N Engl J Med*. 2017;376(9):856-867.
9. Roosa S. A deep dive into the privacy and security risks for health, wellness and medical apps. IAPP. https://iapp.org/news/a/a-deep-dive-into-the-privacy-and-security-risks-for-health-wellness-and-medical-apps/. Published April 6, 2015. Accessed March 20, 2018.
10. Privacy Rights Clearinghouse. Mobile health and fitness apps: what are the privacy risks? https://www.privacyrights.org/consumer-guides/mobile-health-and-fitness-apps-what-are-privacy-risks. Published July 1, 2013. Updated December 16, 2016. Accessed March 26, 2018.
11. Wicklund E. mHealth-based workplace wellness programs face congressional scrutiny. mHealth Intelligence. https://mhealthintelligence.com/news/mhealth-based-workplace-wellness-programs-face-congressional-scrutiny. Published March 13, 2017. Accessed March 28, 2018.
12. Nebeker C, Lagare T, Takemoto M, et al. Engaging research participants to inform the ethical conduct of mobile imaging, pervasive sensing, and location tracking research. *Transl Behav Med*. 2016;6(4):577-586.

13. Nurse JRC. Strava storm: why everyone should check their smart gear security settings before going for a jog. Conversation. http://theconversation.com/strava-storm-why-everyone-should-check-their-smart-gear-security-settings-before-going-for-a-jog-90880. Published January 31, 2018. Accessed March 28, 2018.
14. Hsu J. The Strava heat map and the end of secrets. *Wired*. January 29, 2018. https://www.wired.com/story/strava-heat-map-military-bases-fitness-trackers-privacy/. Accessed Feb 9, 2018.
15. Frenkel S, Benner K. To stir discord in 2016, Russians turned most often to Facebook. *New York Times*. February 17, 2018. https://www.nytimes.com/2018/02/17/technology/indictment-russian-tech-facebook.html. Accessed April 6, 2018.
16. Doerr M, Suver C, Wilbanks J. Developing a transparent, participant-navigated electronic informed consent for mobile-mediated research. Social Science Research Network. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2769129. Published April 22, 2016. Accessed March 20, 2018.
17. Doerr M, Maguire Truong A, Bot BM, Wilbanks J, Suver C, Mangravite LM. Formative evaluation of participant experience with mobile eConsent in the app-mediated Parkinson mPower study: a mixed methods study. *JMIR Mhealth Uhealth*. 2017;5(2):e14. doi:10.2196/mhealth.6521.
18. ResearchKit. Obtaining consent. http://researchkit.org/docs/docs/InformedConsent/InformedConsent.html. Updated September 26, 2017. Accessed March 22, 2018.
19. Ouellette J. Apple's health experiment is riddled with privacy problems. *Gizmodo*. July 21, 2016. https://gizmodo.com/apple-s-health-experiment-is-riddled-with-privacy-probl-1783878924. Accessed March 24, 2018.
20. Federal policy for the protection of human subjects; final rule. *Fed Regist*. 2017;82(12):7149-7274. https://www.gpo.gov/fdsys/pkg/FR-2017-01-19/pdf/2017-01058.pdf. Accessed July 26, 2018.
21. Das G, Cheung C, Nebeker C, Bietz M, Bloss C. Privacy policies for apps targeted toward youth: descriptive analysis of readability. *JMIR Mhealth Uhealth*. 2018;6(1):e3. doi:10.2196/mhealth.7626.
22. Sunyaev A, Dehling T, Taylor PL, Mandl KD. Availability and quality of mobile health app privacy policies. *J Am Med Inform Assoc*. 2015;22(e1):e28-e33. doi:10.1136/amiajnl-2013-002605.
23. Steinhubl SR, Muse ED, Topol EJ. The emerging field of mobile health. *Sci Transl Med*. 2015;7(283):283rv3. doi:10.1126/scitranslmed.aaa3487.
24. Peppet SR. Regulating the internet of things: first steps toward managing discrimination, privacy, security and consent. *Tex Law Rev*. 2014;93:85-178.

25. Nebeker C, Harlow J, Espinoza Giacinto R, Orozco-Linares R, Bloss CS, Weibel N. Ethical and regulatory challenges of research using pervasive sensing and other emerging technologies: IRB perspectives. *AJOB*. 2017;8(4):266-276.
26. Bloss CS, Wineinger NE, Peters M, et al. A prospective randomized trial examining health care utilization in individuals using multiple smartphone-enabled biosensors. *PeerJ*. 2016;4:e1554. doi:10.7717/peerj.1554.
27. Bloss C, Nebeker C, Bietz M, et al. Reimagining human research protections for 21st century science. *J Med Internet Res*. 2016;18(12):e329. doi:10.2196/jmir.6634.
28. Tomlinson T, De Vries R, Ryan K, Kim H, Lehpamer N, Kim S. Moral concerns and the willingness to donate to a research biobank. *JAMA*. 2015;313(4):417-419.
29. Botkin JR, Rothwell E, Anderson R, Stark LA, Mitchell J. Public attitudes regarding the use of electronic health information and residual clinical tissues for research. *J Community Genet*. 2014;5(3):205-213.
30. Riordan F, Papoutsi C, Reed JE, Marston C, Bell D, Majeed A. Patient and public attitudes towards informed consent models and levels of awareness of electronic health records in the UK. *Int J Med Inform*. 2015;84(4):237-247.
31. Cheung C, Bietz MJ, Patrick K, Bloss CS. Privacy attitudes among early adopters of emerging health technologies. *PLoS One*. 2016;11(11):e0166389. doi:10.1371/journal.pone.0166389.
32. Pereira S, Robinson JO, Peoples HA, et al. Do privacy and security regulations need a status update? Perspectives from an intergenerational survey. *PLoS One*. 2017;12(9):e0184525. doi:10.1371/journal.pone.0184525.
33. Council of the European Union, European Parliament. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).
34. Luger E, Moran S, Rodden T. Consent for all: revealing the hidden complexity of terms and conditions. In: Proceedings of the SIGCHI conference on Human factors in Computing Systems; April 27-May 2, 2013; Paris, France:2687-2696.
35. EU General Data Protection Regulation. GDPR key changes: an overview of the main changes under GDPR and how they differ from the previous directive. https://www.eugdpr.org/key-changes.html. Accessed February 23, 2018.
36. Fitabase. Fitabase security and privacy information. https://www.fitabase.com/media/1718/fitabase-security-and-privacy.pdf. Accessed March 19, 2018.
37. Evans BJ. Barbarians at the gate: consumer-driven health data commons and the transformation of citizen science. *Am J Law Med*. 2016;42(4):651-685.
38. Kim H, Bell E, Kim J, et al. iCONCUR: informed consent for clinical data and bio-sample use for research. *J Am Med Inform Assoc*. 2017;24(2):380-387.

39. National Institutes of Health. All of Us research program website. https://allofus.nih.gov/. Accessed February 23, 2018.

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HISTORY OF MEDICINE

Why Does the Shift from "Personalized Medicine" to "Precision Health" and "Wellness Genomics" Matter?

Eric T. Juengst, PhD and Michelle L. McGowan, PhD

Abstract

Efforts to conceptualize the application of human genomics to health care have displayed an evolving set of translational research goals. Under *personalized genomic medicine*, the aim was to individualize treatment and empower patients to take more responsibility for their own health. With the rise of interest in expert interpretation of multifactorial risk stratification, emphasis shifted to giving clinicians better tools and more authority to use them under the rubric of *precision medicine*. The statistical nature of risk stratification, in turn, led to the movement's importing public health goals and expanding its scope to *precision prevention* at the population level. Today, the confluence of precision medicine and precision prevention in *precision health* is leading to *wellness genomics* aimed at achieving goals beyond health care entirely. Each of these reorientations suggests important ethical questions for the medical community.

Introduction

A century ago, American medical intellectuals and public health pioneers were galvanized by the prospect that newly deciphered laws of heredity would revolutionize their efforts to improve the population's health. They called their approach eugenics. Fifty years later, eugenics had come to signify scientific racism, coercive reproductive policies, and the politicization of medicine. Both its goals of "preserving the germ-plasm" from the degradations of miscegenation, immigration, and feeble-mindedness and its methods for "breeding better humans" were repudiated as bad science and worse medicine.[1] Instead, the scientific literature of the 1960s was full of enthusiasm for the new biology inspired by the recently deciphered molecular genetic code, and technophilic physicians looked forward to the dawn of a genetic medicine that could use "genetic engineering" to do for stubborn constitutional conditions what germ theory and antibiotics had done for infectious disease.[2] For these physicians and scientists, the hope was that techniques for cutting and splicing DNA molecules would allow genetic diseases like sickle cell anemia to be reinterpreted as "molecular diseases" and that new "gene therapies" could be devised to tackle them at the molecular level.[3]

But even as the first human gene transfer trials got underway to mark that dawn in 1990, it was clear that a genetic medicine aimed at compensating for rare Mendelian disorders like sickle cell anemia would only address a tiny fraction of the population's health problems. Instead, the attention of the molecular biology community turned to the promise of mapping and sequencing the whole human genome to provide a new paradigm for health care in general, based on a finer-grained understanding of individual genetic variation.[4] Its promoters and architects dubbed this vision *personalized medicine* and predicted that it would set the course for medical progress into the future by allowing physicians to tailor pharmaceutical interventions and lifestyle prescriptions to each patient's unique genomic profile and thereby empower patients to take more responsibility for their own health.

But as the rush to market personalized medicine directly to consumers underscored, the promises of "personalization" also came with caveats for clinicians suddenly faced with patients wielding uncertain and limited information about their genomic profiles. As a result, by 2013, the luster of personalized medicine was waning for the genomics research community that had promoted it.[5] The label that leaders of the genomics community rapidly switched to in the titles of articles, conferences, and institutional programs was *precision medicine*, both because it reemphasized the need for professional judgment and because it opened up the prospect of taking genetic risk stratification beyond the individual patient to the population level. Subsequently, with the emergence of *precision public health* and *precision prevention* aimed at using genomic and environmental data to address population-level health disparities, many began extending the reach of human genomics beyond patient-based clinical medicine into public health and health promotion contexts under the label of *precision health*. Furthermore, today in the commercial sector we see services promoted under the banner of *wellness genomics* to indicate an interest in using genomic data to improve our understanding of perfectly normal human traits with the goal of enhancing our lives beyond managing health risks.

As labels for particular visions of what the science of human genetics and genomics might contribute to human welfare, the use of the terms "eugenics," "genetic medicine," "personalized medicine," "precision medicine," "precision health," and "wellness genomics" reflects the progression of a long conversation between basic scientists, physicians, and the larger society. Each successive term represents an effort at ethical and scientific course correction in response to the pitfalls of the preceding model. Although applied human genomics entails a very different set of social practices than applied human genetics under eugenics, each vision has been celebrated in its day by both science and medicine as the wave of the future, and all share a common commitment to scientific meliorism—ie, the conviction that the primary goal of human genetic research is to promote human welfare.[6]

A century from now, will precision health and wellness genomics be used as eugenics is today, to label ideas and programs that critics find morally wrongheaded and socially dangerous? It depends entirely on how these labels are interpreted and applied by the rising generation of physicians and public health planners. We do not yet know how things will go, but we can pick up some clues to possible directions through the connotations of the very names themselves. Like most labels, all the names that have been coined for the practice of applying genetic knowledge to human problems connote tacit values, goals, and assumptions that shape how their proponents think and act.

In this essay, we illustrate this thesis by reviewing three critical rebranding episodes in contemporary genomics: the recent transition from personalized to precision medicine, the ongoing transition from precision medicine to precision health, and the incipient transition from precision health to wellness genomics. Just as genetic medicine reclaimed applied human genetics from the ideological biases of eugenics by giving it traditional medical goals and personalized medicine marked a moral emphasis on individual patients' responsibilities, so each of these shifts within genomics highlights a different set of ethical commitments that will be important to monitor as the field matures.

From Personalized to Precision Medicine

To distinguish the anticipated health benefits of genomic research by a term that was remote from both the historical shadow of eugenics and the relatively mechanical metaphors of genetic engineering, a wide range of translational genomic researchers, medical institutions, and commercial entities turned to *personalized genomic medicine* to describe their translational goal in the first decade of the 21st century. As the name suggests, the idea was that genomic profiling would empower individuals to take more control over—and responsibility for—their health by clinicians' provision of individually tailored genetic health risk assessments that they could use to guide treatment, prevention, and lifestyle choices.[7]

Unfortunately, neither the methods of genetic research nor the realities of clinical genomics fit very well with this laudably patient-centered vision. First, genomic science could not individualize prescriptions because the health risks associated with individuals' genetic variants are always population-level risks based on stratifying patients into different statistical subgroups. Furthermore, the amount and complexity of statistical information that genome-wide screening and sequencing generate makes it difficult for individual patients to assimilate and interpret, which risked simply encouraging patient confusion rather than empowering more responsible health-related decisions. As a result, critics argued that the rhetoric of personalized medicine overpromised the potential of genomic information to provide individualized health recommendations that clinicians and patients could meaningfully use to manage health outcomes.[8,9] In the face of widespread exploitation of the language of individual empowerment by commercial

genetic testing companies,[10] scholars defended the role of professional judgment as an argument for keeping genomics within the purview of the clinic as opposed to abdicating it to direct-to-consumer applications.[5]

As a result of these challenges, almost immediately after personalized medicine was declared a "revolution" in medical thinking,[7] the application of genomics to medicine was reconceived by the leaders of the genome research community as a feature of a new movement called precision medicine.[11] Discussing the National Research Council report that introduced the new label, genome scientist Maynard Olson wrote, "I think 'personalized medicine' was perhaps a useful rubric with which to launch this activity, but it sends a misleading message—actually both to ourselves and the broader community."[12] Precision medicine was intended to contextualize genetic health risks by integrating large amounts of data from multiple sources to identify causal factors that might influence health. Interpreting this information sensibly requires even more professional involvement than an individual genomic scan, making claims to patient empowerment even more hollow in this context. Indeed, "precision" carries very different connotations than "personalization" as to whom this approach is intended to empower, since in common parlance precision equipment is designed to be used by experts, not amateurs. If precision medicine primarily provides tools for physicians, it is clear that clinicians should bear more responsibility for making decisions about their use. This shift in ethical priorities was reflected in the first round of professional policymaking debates about the clinical use of genomic sequencing related to opportunistic clinical identification and disclosure of genetic risk markers without specific patient consent.[13] In giving health care professionals authority to disregard or avoid soliciting patients' preferences about identifying and disclosing their genetic risks, precision medicine seemed to be creating new social responsibilities for patients to be accountable to their health care professionals' recommendations.[9,14,15]

From Precision Medicine to Precision Health

Dogging the heels of precision medicine are efforts by public health officials and health care institutions to rebrand the biomedical uses of translational genomics as a feature of precision health.[16] This move is driven by precision medicine's commitment to correlating genomic data with information about people's lifestyles, environments, and communities and its subsequent need to shift applications from individual patients to the populations to which they belong.[17] Of course, health sciences—such as epidemiology, environmental health science, and health behavior—elucidate extra-genetic health risks and have traditionally been concerned with protecting and promoting the public's collective health rather than with individuals' medical treatment. The movement's incorporation of population sciences has led to the emergence of new banners—precision prevention, precision public health, and precision health—that allow this aspirational goal to translate easily between individual and population levels. By applying the tools of precision medicine to disease prevention and early identification of risk,

proponents argue that "'precision prevention' then may be useful in using both science and limited resources for targeting prevention strategies to subsets of the population."[18]

The reorientation of translational genomic research towards public health goals raises two particularly important professional ethical and social policy questions. The first is the danger of interpreting information about genetic variation across populations in ways that reinforce culturally situated or politically constructed social categories like race, ethnicity, and nationality. For example, a recent National Institutes of Health initiative seeking to use genetic variation data to address health care outcome disparities defined the "disparity populations" of interest entirely in terms of racial and ethnic categories, implying that these categories rest on underlying genetic differences between the groups.[19] Not only does this definition risk reifying group identities in ways that might exacerbate social tensions, but it also risks misdirecting attention from important social determinants of health such as poverty, education, and nutrition.[20] These dangers are reflected in the widespread promotion of translational genomic research as an approach to reduce health disparities between different subgroups in the population, when in fact these disparities are driven by social determinants of health.[21]

The second danger posed by the adoption of public health goals for translational genomics flows from the logic of prevention itself. Traditionally, early preventive interventions have been seen as the most efficient and effective forms, and the goal of public health research has been to identify interventions that allow people to avoid exposure to the causes of morbidity entirely.[22] When these causes are interpreted as genetic variants, this logic has historically been understood to prescribe interventions that prevent the intergenerational transmission of "pathogenes," just as infection control measures prevent horizontal transmission of pathogens. Although we now criticize the authoritarian practices and punitive attitudes this logic supported during the eugenics movement, the temptation to think about genetic health problems as "vertically transmitted infectious disease"[23] and to attribute preventive responsibilities accordingly continues to appear irresistible to some influential health policy and bioethics scholars today.[24] But how to prevent genetic health problems without recreating the authoritarian practices and punitive attitudes we still criticize in the historical eugenics movement is unclear.[25]

From Precision Health to Wellness Genomics?

Finally, another trend under the precision health banner has been to bring what translational genomic research learns about population-level variation back to individuals through prescriptions for health promotion and wellness beyond the management of disease risk. As goals for health applications of genomic research have turned to "wellness," living "longer lives," and "thriving," the domain of applied genomics expands again, this time beyond the range of traditional health care.[26-28] This expansion is fueled by rising scientific interest in identifying genetic variants associated with

phenotypes at the superlative end of our species' functional range to better understand and support human biology when everything is working particularly well. These beneficial genetic variants include those linked to unusual resistance to disease,[29] alleles associated with above-average longevity and good health,[30] and genetic predictors of high levels of physical and cognitive performance.[31]

In animal research settings, gene editing technologies are being used to actively enhance desirable traits,[32] which means that medicine and society might soon face an interesting conundrum: once we discover which variants are not just "benign" but associated with especially high levels of functioning, why not extend the use of human gene editing beyond the preventive goal of reducing the incidence of problematic variants to offer individuals opportunities for genomic optimization, even if they go beyond what is typical for our species?[33] From one perspective, taking people beyond the normal range of functionality seems like the very definition of genetic enhancement, which science policy bodies like the National Academies of Sciences, Engineering, and Medicine (NASEM) continue to eschew as a morally problematic use of human gene editing techniques.[34] On the other hand, enabling individuals to acquire resistance, for instance, against HIV infection through CCR5 gene editing seems very much like the moral equivalent of developing an HIV vaccine. If, like the NASEM, we include strengthening the body to resist disease as a medically appropriate form of prevention,[34] then any gene editing research aimed at inserting variants associated with phenotypes at the desirable extreme of health-related functioning—such as superlative immune response, outlier tissue regeneration capacities, or world-class tolerance for environmental toxins—might be legitimized if those variants were understood to be more protective against disease than their normal versions. In fact, might not human gene editing aimed at inducing unusually acute sensory abilities, cognitive capacities, prolongevity, and exceptional strength and endurance also be counted as "strengthening human capacities to resist disease,"[34] as long as these phenotypes can be shown to have preventive potential?[35]

The marketplace is already populated by the scores of wellness genomics labs that currently offer commercial testing for putative beneficial genetic variants—from exceptional HIV resistance[36] to athletic talent[37,38]—and their financial future is said to be bright.[39] As bona fide precision health research provides more reliable genomic predictors of exceptional capacities, the philosophical gray zone between prevention and enhancement that they will accentuate in current policy thinking about the limits of gene editing will be increasingly important to understand and address. If the paternalistic emphasis of precision medicine, the essentialism of precision prevention, and the perfectionism of wellness genomics go unnoticed and unchecked, precision health risks becoming merely another step on the road towards a new *eugenomics* that society could come to regret.

References

1. Bashford A, Levine P, eds. *The Oxford Handbook of the History of Eugenics*. New York, NY: Oxford University Press; 2018.
2. Hotchkiss RD. Portents for a genetic engineering. *J Hered*. 1965;56(5):197-202.
3. Juengst E. Concepts of disease after the human genome project. In: Caplan A, McCartney J, Sisti D, eds. *Health, Disease and Illness: Concepts in Medicine*. Washington, DC: Georgetown University Press; 2004:243-263.
4. Baird PA. Genetics and health care: a paradigm shift. *Perspect Biol Med*. 1990;33(2):203-213.
5. McGuire AL, McCullough LB, Evans JP. The indispensable role of professional judgment in genomic medicine. *JAMA*. 2013;309(14):1465-1466.
6. Comfort N. *The Science of Human Perfection: How Genes Became the Heart of American Medicine*. New Haven, CT: Yale University Press; 2012.
7. Collins FS. *The Language of Life: DNA and the Revolution in Personalized Medicine.* New York, NY: Harper Collins; 2010.
8. Juengst ET, Flatt MA, Settersten RA Jr. Personalized genomic medicine and the rhetoric of empowerment. *Hastings Cent Rep*. 2012;42(5):34-40.
9. Juengst E, McGowan ML, Fishman JR, Settersten RA Jr. From "personalized" to "precision" medicine: the ethical and social implications of rhetorical reform in genomic medicine. *Hastings Cent Rep*. 2016;46(5):21-33.
10. McGowan ML, Fishman JR, Lambrix MA. Personal genomics and individual identities: motivations and moral imperatives of early users. *New Genet Soc*. 2010;29(3):261-290.
11. Committee on a Framework for Development of a New Taxonomy for Disease, National Research Council. *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease.* Washington, DC: National Academies Press; 2011.
12. Katsnelson A. Momentum grows to make "personalized" medicine more "precise." *Nat Med.* 2013;19(3):249.
13. Evans JP, Berg JS. Next-generation DNA sequencing, regulation, and the limits of paternalism: the next challenge. *JAMA*. 2011;306(21):2376-2377.
14. Lázaro-Muñoz G, Conley JM, Davis AM, Van Riper M, Walker RL, Juengst ET. Looking for trouble: preventive genomic sequencing in the general population and the role of patient choice. *Am J Bioeth*. 2015;15(7):3-14.
15. McGowan ML, Fishman JR, Settersten RA Jr, Lambrix MA, Juengst ET. Gatekeepers or intermediaries? The role of clinicians in commercial genomic testing. *PLoS One*. 2014;9(9):e108484. doi:10.1371/journal.pone.0108484.
16. Khoury MJ, Iademarco MF, Riley WT. Precision public health for the era of precision medicine. *Am J Prev Med*. 2016;50(3):398-401.
17. Chatterjee N, Shi J, García-Closas M. Developing and evaluating polygenic risk prediction models for stratified disease prevention. *Nat Rev Genet*. 2016;17(7):392-406.

18. Khoury MJ. The success of precision medicine requires a public health perspective. *Genomics and Health Impact Blog*. January 29, 2015. https://blogs.cdc.gov/genomics/2015/01/29/precision-medicine/. Accessed July 11, 2018
19. National Institute on Minority Health and Health Disparities, US Department of Health and Human Services. NIMHD transdisciplinary collaborative centers for health disparities research focused on precision medicine (U54). http://grants.nih.gov/grants/guide/rfa-files/RFA-MD-15-013.html. Published May 20, 2015. Accessed July 26, 2018.
20. Sankar P, Cho MK, Condit CM, et al. Genetic research and health disparities. *JAMA*. 2004;291(24):2985-2989.
21. Meagher KM, McGowan ML, Settersten RA Jr, Fishman JR, Juengst ET. Precisely where are we going? Charting the new terrain of precision prevention. *Annu Rev Genomics Hum Genet*. 2017;18(1):369-387.
22. Faust H, Menzel P. *Prevention vs. Treatment: What is the Right Balance?* New York, NY: Oxford University Press; 2011.
23. Battin MP, Francis LP, Jacobsen JA, Smith CB. *The Patient as Victim and Vector: Ethics and Infectious Disease*. New York, NY: Oxford University Press; 2009.
24. Buchanan A, Brock D, Daniels N, Wikler D. *From Chance to Choice: Genetics and Justice*. New York, NY: Cambridge University Press; 2000.
25. Hens K, Dondorp W, Handyside AH, et al. Dynamics and ethics of comprehensive preimplantation genetic testing: a review of the challenges. *Hum Reprod Update*. 2013;19(4):366-375.
26. University of Michigan. Precision health. http://precisionhealth.umich.edu. Accessed March 19, 2018.
27. Cedars-Sinai. About precision health. https://www.cedars-sinai.edu/Precision-Health/About-Precision-Health.aspx. Accessed March 19, 2018.
28. Minor L. We don't just need precision medicine, we need precision health. Stanford Medicine. http://med.stanford.edu/school/leadership/dean/dean-minor-on-precision-health.html. Accessed March 19, 2018.
29. Resilience Project website. http://resilienceproject.com/. Accessed March 21, 2018.
30. Deelen J, Beekman M, Uh HW, et al. Genome-wide association meta-analysis of human longevity identifies a novel locus conferring survival beyond 90 years of age. *Hum Mol Genet*. 2014;23(16):4420-4432.
31. Guth LM, Roth SM. Genetic influence on athletic performance. *Curr Opin Pediatr*. 2013;25(6):653-658.
32. Burkard C, Lillico SG, Reid E, et al. Precision engineering for PRRSV resistance in pigs: macrophages from genome edited pigs lacking CD163 SRCR5 domain are fully resistant to both PRRSV genotypes while maintaining biological function. *PLoS Pathog*. 2017;13(2):e1006206. doi:10.1371/journal.ppat.1006206.

33. Comfort N. *The Science of Human Perfection: How Genes Became the Heart of American Medicine.* New Haven, CT: Yale University Press; 2012.
34. National Academies of Sciences, Engineering, and Medicine. *Human Genome Editing: Science, Ethics, and Governance.* Washington, DC: National Academies Press; 2017.
35. Juengst ET. Crowd-sourcing the moral limits of human gene editing. *Hastings Cent Rep*. 2017;47(3):15-23.
36. Delta-32 website. http://www.delta-32.com/. Accessed March 22, 2018.
37. Atlasgene website. http://www.atlasgene.com/. Accessed March 23, 2018.
38. Webborn N, Williams A, McNamee M, et al. Direct-to-consumer genetic testing for predicting sports performance and talent identification: consensus statement. *Br J Sports Med*. 2015;49(23):1486-1491.
39. Grand View Research. *Predictive Genetic Testing and Consumer/Wellness Genomics Market by Application (Cancer, Diabetic Screening, Parkinsonism, Cardiovascular, Orthopedic and Musculoskeletal, Nutria Genetics, Skin and Metabolism Genetics), and Trend Analysis from 2018 to 2025*: report summary. https://www.grandviewresearch.com/industry-analysis/predictive-genetic-testing-consumer-wellness-genomics-market. Published January 2017. Accessed March 22, 2018.

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ART OF MEDICINE

The Precision Portrait

Samuel Rodriguez, MD and Nick Love, PhD

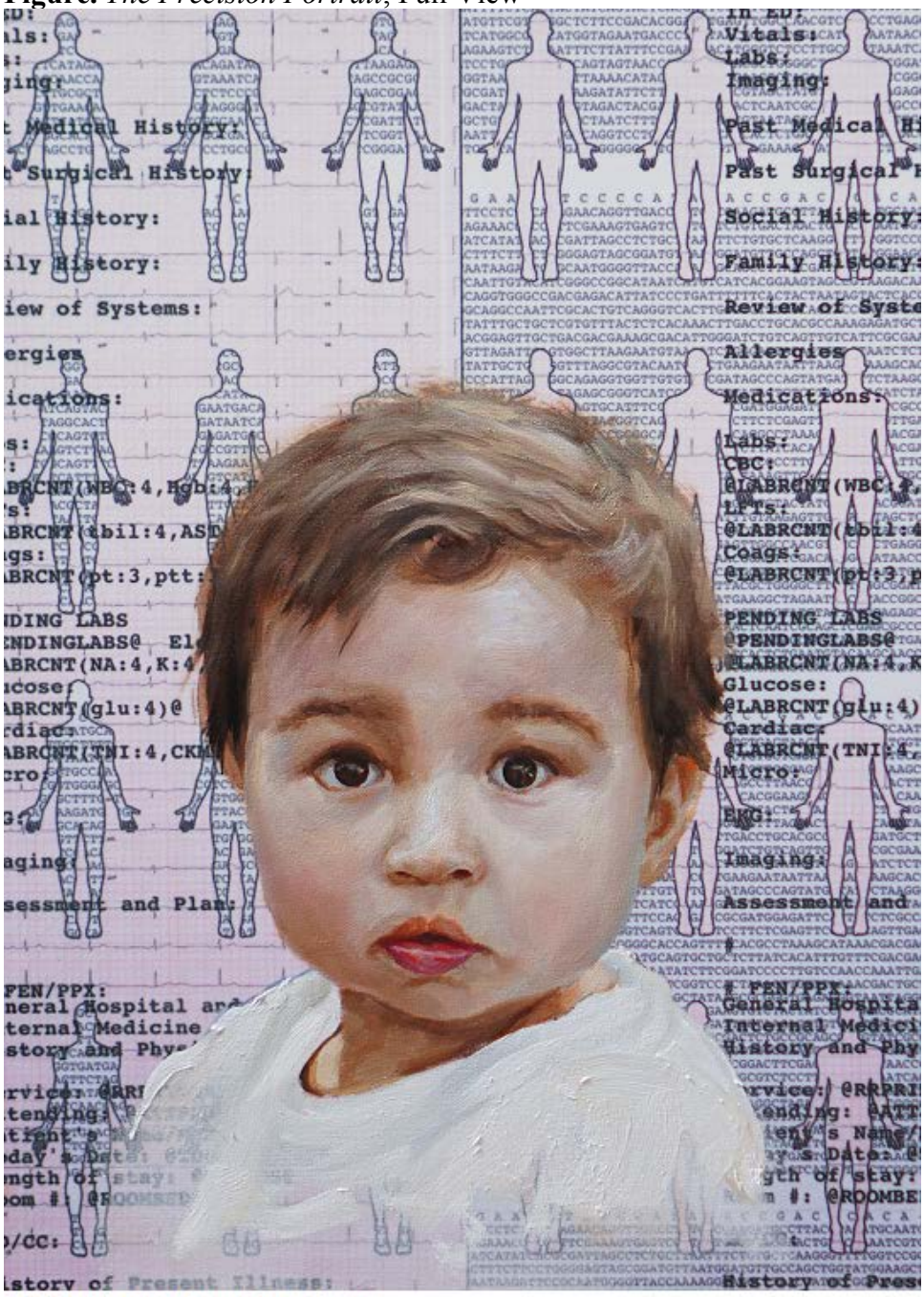
Abstract

The Precision Portrait is a mixed-media portrait illustrating the future of precision medicine and its ethical challenges.

Figure. *The Precision Portrait*, Close-Up View

Samuel Rodriguez, MD and Nick Love, PhD

Figure. *The Precision Portrait*, Full View



Samuel Rodriguez, MD and Nick Love, PhD

Media

Oil painting on aluminum digital illustration.

Caption

The portrait foreground features a child, represented in buttery oil paint with enumerable brushstrokes and subtleties in color. This hand-painted portrait sits atop an aluminum

digital illustration depicting lab values, DNA sequences, EKG strips, and excerpts from a health record. With ever more clinical data at our disposal, new tools can help improve decision making and craft targeted approaches for the care of each patient. *The Precision Portrait* seeks to remind current and future physicians that our patients are more than collections of data to be input into the next machine-learning algorithm. Each data point represents a grandmother, a teacher, an artist, or someone's child.

Samuel Rodriguez, MD is a pediatric anesthesiologist and educator in medical humanities at Stanford University School of Medicine in Stanford, California.

Nick Love, PhD is a medical student at Stanford University School of Medicine in Stanford, California. He has a background in mixed-media fine arts, and his work has appeared in numerous exhibitions and publications.

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ART OF MEDICINE

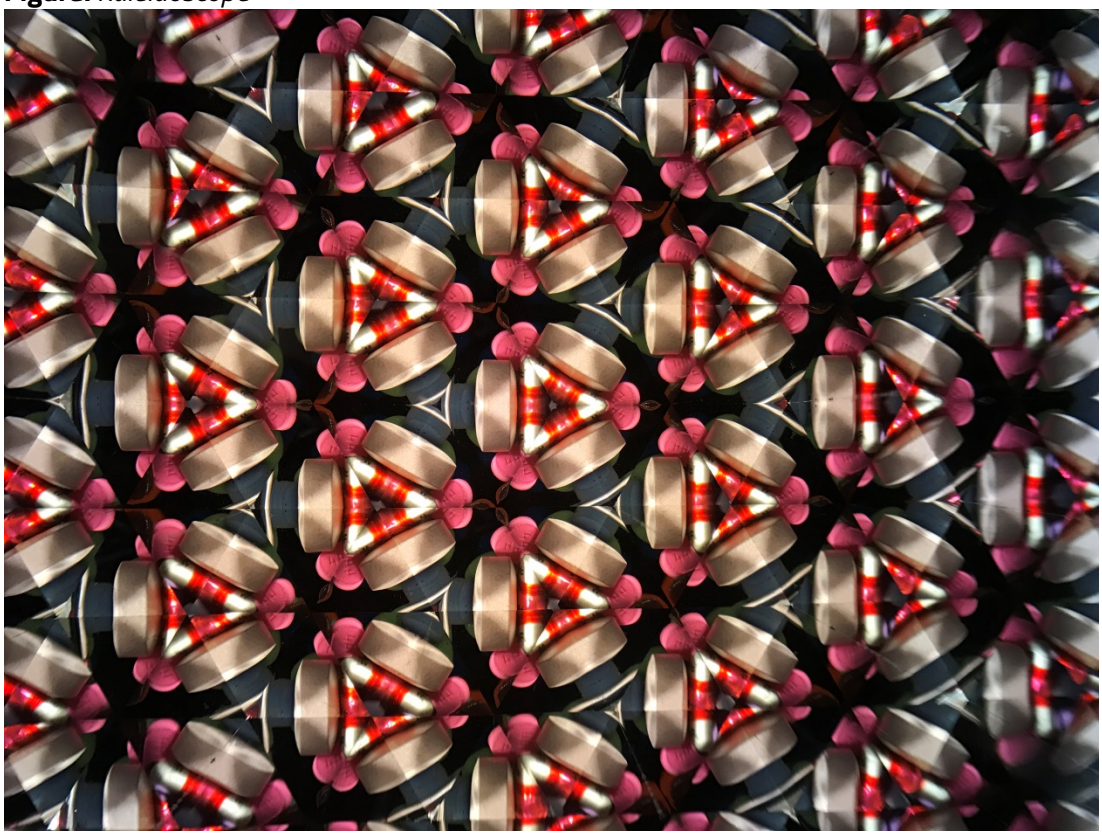
Kaleidoscope

Audrey Gray, MD, MPH

Abstract

This image seeks to iteratively represent themes related to the availability of life-saving and life-threatening medications. The photograph also suggests the importance of several ethical questions.

Figure. *Kaleidoscope*



Media

Digital photograph.

Caption

This image seeks to iteratively represent themes related to the availability of life-saving and life-threatening medications. Today there are many medications available for

previously deadly diseases, such as immunotherapy for cancer, dozens of HIV drugs, and ever more blood thinners for a host of cardiac issues. However, many of these drugs are out of reach for the average person. For example, medication for hepatitis C costs tens of thousands of dollars per patient.[1] Treating hepatitis C can prevent deadly sequelae in the infected person and prevent spread of the infection to others, and there are public health benefits to society at large. But who shoulders the price of the drug? Most cannot afford such an expensive medication. All budgets are finite, though, so who decides which individuals get treatment? Which ethical guidelines should guide such decisions? Should drug companies be allowed to charge so much for this treatment?

Another ethical issue suggested by the photograph has to do with the abundance of potentially life-threatening medications, such as opiates. The US is in the midst of an opioid epidemic. More than 100 people died *daily* from opioid-related drug overdoses in 2016, and more than 11 million people misused prescribed opioids that year.[2] How do we balance the needs of some patients in pain against the needs of those misusing opioids? We, as members of the medical profession, contributed to this crisis. How can we best serve addicted patients? In medicine, we do much more than just prescribe pills. Yet the ethical issues surrounding access to medications, or lack thereof, influence our prescribing practices.

References

1. Gonzalez Gompf S. Hepatitis C cure: symptoms, transmission, treatments, and costs. MedicineNet. https://www.medicinenet.com/hepatitis_c_cure_symptoms_and_treatment_costs/article.htm#what_is_hepatitis_c_hcv_hep_c. Accessed July 14, 2018.
2. US Department of Health and Human Services. What is the US opioid epidemic? https://www.hhs.gov/opioids/about-the-epidemic/. Reviewed March 6, 2018. Accessed July 14, 2018.

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PERSONAL NARRATIVE

Graphic Medicine and the Limits of Biostatistics

Sathyaraj Venkatesan, PhD and Sweetha Saji, MA

Abstract

Increasing reliance on statistics for treatment and clinical risk assessment not only leads to the reductive interpretation of disease but also obscures ambiguities, distrust, and profound emotions that are important parts of a patient's lived experience of illness and that should be regarded as clinically and ethically relevant. Enabling critique of the limitations of statistics and illustrating their hegemonic impact on the patient's experience of illness, graphic medicine emerges as a democratic platform where marginalized perspectives on illness experiences are vindicated. Through a close reading of two carer narratives, *Mom's Cancer* (2006) and *Janet & Me: An Illustrated Story of Love and Loss* (2004), we illustrate how graphic pathographies represent experiential features of illness that are obscured by overreliance on statistical data.

Statistics in Clinics and Comics

"Your survival rate is 10%!" the oncologist pronounced after a quick glance at the pathology report of our friend. Although the physician was objectively stating our friend's chances of survival, it had a paralyzing impact on us. Five years has passed since his diagnosis of lung cancer; today, our friend is a successful entrepreneur and a motivational speaker inspiring thousands of cancer patients with his survival saga. In retrospect, the physician's statistical assertion inspired dread in him and all those who were close to him each day. Today, we are relieved that reality was far different from those figures. It was during this span of 5 years of uncertainty that we came across a website called graphicmedicine.org as well as numerous other online sources about illness and survival. The website featured several comics that boldly explored those aspects of illness and health care that physicians and the medical system at large don't convey to patients.

The increasing reliance on and ritualistic use of medical statistics for treatment, risk assessment, and other related purposes not only leads to the reductive interpretation of disease but also obscures the ambiguities, distrust, fear, and profound emotions that are important aspects of a patient's lived experience of illness. In *Illness as Narrative*, Ann Jurecic characterizes such a chasm as "a fundamental incompatibility"[1] between personal experience of illness and statistically mediated measurement. Through critiquing and

exposing the limitations of statistics and illustrating their hegemonic role and impact on patients' experience of illness, graphic medicine—the intersection of comics and health care—emerges as a democratic platform where marginalized perspectives on illness experiences are vindicated. Although several text-based illness narratives document the private psychosomatic sufferings of patients and caregivers, as we have written elsewhere, "the structural singularity and formal affordances of the comics medium" that extend into "the subjective realities of sufferers" make graphic medicine unique.[2]

In reading graphic pathographies, we have been intrigued by several passing references to the impact of biostatistical data on patients. For instance, in Emily Steinberg's 2014 webcomic on her medical experience of infertility, *Broken Eggs*,[3] the physicians guarantee the success rate of an infertility clinical trial and coerce her to undergo treatment, promising her that "it worked 70% of the time."[3] Despite repeated failures, the author is made to suffer various treatments until she is squarely categorized as "damaged goods."[3] Her resentment is encapsulated in her repetition of the physicians' remark, "you are damaged goods," and in her crouched posture. Here, not only does the physicians' obsessive reliance on success rates generate false hope in Steinberg, but also their unsympathetic response to her clinical status demeans her personhood to "goods."

In this article, we do a close reading of two cancer narratives written by caregivers, Brian Fies's *Mom's Cancer* (2006)[4] and Stan Mack's *Janet & Me: An Illustrated Story of Love and Loss* (2004),[5] in order to expose the medical establishment's obsessive reliance on statistics and to further illustrate how graphic pathographies intimately convey the patient's and family's experience of illness, which is not captured by statistics. Notably, we show that these 2 graphic pathographies function as a critique of biostatistics in that they not only demonstrate the negative impact of statistics on patients but also expose incongruities in statistics-based risk assessment. In so doing, these graphic pathographies reveal what it means to be human in the age of biomedicine.

Mom's Cancer

In his graphic memoir, *Mom's Cancer*, Brian Fies delineates his mother's struggle with metastatic lung cancer and the practical and emotional impacts of the disease on his family using the affordances of comics. "The Five Percent Solution" particularly illustrates the emotional impact of statistical information on Fies's mom (whose name is Barbara). The physician's remark on her chance of recovery after radiation and chemotherapy ("Keep it up and you'll be one of the five percent who makes it!"[4]) induces emotional turmoil and perturbation in mom, signified by mom's depiction as silent during the drive home from the physician's office, followed by her expressing a sudden profusion of frantic doubts over the phone, such as "What did she mean by 'five percent'?," "Does that mean five percent from now?"[4] Fies's illustrations following the oncologist's statement about mom's 5% chance of recovery capture the anxiety and despair that we experienced more than 5 years ago in the oncologist's cabin when the 5-

year survival rate in the US for stage IV nonsmall cell lung cancer was less than 5%.[6] The horror and disbelief with which mom accepts the news that only 5% of the people with her diagnosis survive drowns her in conflicting emotions of contentment and trepidation, provoking Fies to comment thus: "her strength floats on a fragile bubble of hope and confidence" that could easily burst.[4]

Fies conveys the intensity of mom's bewilderment in a single-panelled page of her shaved head against a dark background with her mouth agape and tears rolling down her face (see figure 1). Her raised eyebrows and disbelief ("five percent?!"[4]) express her desperation to know whether she is among the 5% who will survive. Although she had been drawing strength from "a bit of deliberate ignorance," Fies recollects how the physician's invocation of statistics had been "very demoralizing" (written communication, March 24, 2018). Validating the individual patient's experience, graphic pathographies not only concretize intangible emotions but also constitute an affective language. Although statistics such as survival rates are based on observations, analysis, and calculations, they erase the individual's identity, undervalue the existential and visceral dimensions of illness experience, and leave patients and families constantly vexed about the patient's chances of survival.

Figure. Excerpt from *Mom's Cancer*

© 2006 Brian Fries. Reprinted by permission of Brian Fies.

Janet & Me

Janet & Me: An Illustrated Story of Love and Loss, published 2 years before *Mom's Cancer*, also delineates the determinative role of statistics and their impact on the patient's experience of illness. In so doing, the memoir expresses skepticism about physicians' overreliance on population-based statistics, which may, in many instances, prove wrong in individual cases. For instance, Laura, the physician, unrestrainedly follows the 70% success rate of the chemotherapy drug trastuzumab and prescribes it for treating Janet's breast cancer. Although Laura describes the drug as "the wave of the future,"[5] suggesting the medicine's potential to destroy cancer cells, it does not cure Janet. Elsewhere, Mack remarks that the new drug, despite its ineffectiveness, has exhausted Janet's energy and subsequently worsened her physical condition.[5] If the drug's 70%

success rate gave Janet false hopes, the news of our friend's 10% chance of survival had a devastating impact that plagued us throughout the course of 5 years. Physicians' and the medical establishment's overreliance on statistics for prescribing and prognosticating reduces patients to specimens in a clinical trial.

Lessons from Graphic Pathographies

In their defense of the subjective experience of illness via verbal-visual codes, graphic pathographies validate individual experience. Graphic pathographies characterize the experience of illness as a complex movement between doubt and hope, anxiety and comprehension, thereby challenging the completeness and absoluteness of statistics, such as recovery rates. The above-analyzed graphic pathographies taking the form of comic vignettes critique overreliance on biostatistics not only through illustrating their material and emotional implications but also through imagining a result at least as extreme as the one statistically prognosticated. While *Mom's Cancer* delineates the impact of survival rates on mom, which alters her perception of life and death forever, *Janet & Me* illustrates the physician's obsessive reliance on statistics at the cost of individual lives. Fies attests to the unavoidable impact of statistics on patients when physicians "confuse groups with individuals" (written communication, March 24, 2018). He observes that responsible physicians, on the other hand, would regard statistics to be meaningful for populations but not individuals. Rather than being oriented to fulfil their ethical duty to disclose every fact about a patient's illness, Fies argues that, in practice, "physicians and others have to gauge how much their patients will understand and whether that understanding will help or hurt their treatment" (written communication, March 24, 2018).

Graphic pathographies such as these inform physicians about the need to contextualize statistics better and to communicate more effectively and empathetically with patients. While both memoirs acknowledge the importance of biostatistics, they also attend to the undue reliance on statistics for treatment and risk assessment; after all, as Jurecic reminds us, "survival cannot be completely explained or accounted for by statistics."[1] In essence, graphic medicine exposes the negative effects of statistically arbitrated notions of health and illness by conveying a patient's affective experiences of the (un)certainty of life.

References

1. Jurecic A. *Illness as Narrative.* Pittsburgh, PA: University of Pittsburgh Press; 2012.
2. Venkatesan S, Saji S. Rhetorics of the visual: graphic medicine, comics and its affordances. *Rupkatha J Interdiscip Stud Humanit.* 2016;8(3):221-231.
3. Steinberg E. *Broken Eggs*. https://emilysteinberg.com/artwork/3522562-Broken-Eggs.html. Published 2014. Accessed March 25, 2018.
4. Fies B. *Mom's Cancer.* New York, NY: Abrams ComicArts; 2006.

5. Mack S. *Janet & Me: An Illustrated Story of Love and Loss.* New York, NY: Simon and Schuster; 2004.
6. Cetin K, Ettinger DS, Hei YJ, O'Malley CD. Survival by histologic subtype in stage IV nonsmall cell lung cancer based on data from the Surveillance, Epidemiology and End Results Program. *Clin Epidemiol*. 2011;3:139-148.

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VIEWPOINT: PEER-REVIEWED ARTICLE

Should Artificial Intelligence Augment Medical Decision Making? The Case for an Autonomy Algorithm

Camillo Lamanna, MMathPhil, MBBS and Lauren Byrne, MBBS

To claim one AMA PRA Category 1 Credit™ *for the CME activity associated with this article, you must do the following: (1) read this article in its entirety, (2) answer at least 80% of the quiz questions correctly, and (3) complete an evaluation. The quiz, evaluation, and form for claiming* AMA PRA Category 1 Credit™ *are available through the* AMA Education Center.

Abstract

A significant proportion of elderly and psychiatric patients do not have the capacity to make health care decisions. We suggest that machine learning technologies could be harnessed to integrate data mined from electronic health records (EHRs) and social media in order to estimate the confidence of the prediction that a patient would consent to a given treatment. We call this process, which takes data about patients as input and derives a confidence estimate for a particular patient's predicted health care-related decision as an output, the *autonomy algorithm*. We suggest that the proposed algorithm would result in more accurate predictions than existing methods, which are resource intensive and consider only small patient cohorts. This algorithm could become a valuable tool in medical decision-making processes, augmenting the capacity of all people to make health care decisions in difficult situations.

The Case for an AI-Assisted Autonomy Algorithm

In this article, we argue that artificial intelligence (AI) can be used to mine data from electronic health records (EHRs) and social media in order to predict an incapacitated person's preferences regarding health care decisions. The argument proceeds in three steps.

We first show that a significant proportion of patients do not have the capacity to make health care decisions and motivate the search for a reliable mechanism to predict patient preferences. We describe the triple burden that incapacity creates: the ethical burden upon health care systems to respect the wishes of these patients; the emotional burden upon surrogates to make difficult decisions; and the economic burden upon society to fund investigations and treatments that the incapacitated patient would have declined.

The second part of the argument concerns existing tools to identify patient preferences. We discuss the literature on identifying patient factors that predict patient treatment preferences and then suggest that AI will lead to a step change in our power to predict these preferences. We sketch how existing AI technologies could integrate data mined from EHRs and social media in order to estimate the confidence of the prediction that a patient would consent to a given treatment. We call this computational process—which takes data about patients as input and derives a confidence estimate for a particular patient's predicted health care-related decision as an output—the *autonomy algorithm*.

In the third section, we consider some ethical issues raised by this approach. First, an autonomy algorithm must be interpreted with caution: simply because we can be confident that a person would choose treatment X, it does not follow that this person *should* choose X. The second point is more hypothetical: if increasingly massive data sets enable the autonomy algorithm to offer very high levels of predictive accuracy, should AI replace human decision makers, regardless of a patient's decision-making capacity?

It is concluded that an AI-assisted autonomy algorithm, if thoughtfully implemented and judiciously used, could offer some relief from the aforementioned triple burden posed by incapacitated patients: it could lead to improved respect for autonomy, reduced burnout of surrogates, and economic gains for society. However, we must tread carefully in the implementation of the proposed technology and remember that algorithms function as decision aids, not dictates.

Decision-Making Capacity and Surrogate Decision Making

Decision-making capacity consists of the ability to understand the information related to a decision, to appreciate its significance, to reason about the costs and benefits of different courses of action, and to communicate the decision one has made. Although thinkers use terms such as "understand," "appreciate," and "reason" in a variety of ways, in broad terms this is the definition accepted by the medical community.[1]

Incapacity is no small problem: estimates suggest that more than one-third of elderly and psychiatric hospital inpatients lack decision-making capacity.[2,3] Moreover, in one study, health care professionals failed to identify incapacity in 42% of cases.[4] When clinicians do correctly identify a patient without decision-making capacity, the evidence suggests that they often fail to match their treatment plan to the patient's preferences.[5] Reasons for this disconnect are multifactorial and include clinicians' difficulty in synthesizing information about the patient and cognitive biases at work in the hospital environment.[6,7]

Making life-and-death decisions for incapacitated patients takes a considerable toll upon clinicians, as studies indicate an association between end-of-life decision-making and health care professional burnout.[8,9] Involving family members or patient surrogates in

the decision-making process, however, is no panacea. Surrogates predict patients' preferences incorrectly in roughly one-third of cases, typically projecting their own wishes onto the patient concerned.[10,11] Moreover, many surrogates experience subsequent stress and mental health problems, with the effects sometimes persisting for years.[12] One proposed solution to this problem is the advance directive or advance care plan. The ethical and practical issues with these tools have been discussed elsewhere; for the purposes of this paper, we consider only patients who have not indicated advance preferences for their care.

One corollary of the difficulty in predicting an incapacitated patient's preferences is overtreatment. Every day, patients without decision-making capacity are subjected to investigations and treatments to which they would not have consented. Indeed, unnecessary investigations and treatments are not only ethically troubling but also place undue economic strain upon already-stretched health care systems.[13]

We suggest that just as AI algorithms enable online vendors to predict which products a customer is most likely to buy or which films they are most likely to enjoy, so AI could be harnessed to predict which health care choices a patient would make.

Using Data to Make Predictions

According to some studies, using only the base rate (ie, the proportion of *all* patients favoring treatment X over treatment Y) to predict a given patient's preferences is as accurate as using a surrogate.[14-16] Provided there are data sets that contain the relevant information, it follows that creating a patient preference predictor that is more accurate than a surrogate would require minimal fine tuning.[17,18]

One area that has been well researched is the treatment choices made by patients with localized prostate cancer. In particular, it has been shown that younger patients tend to prefer more aggressive treatment,[19] a finding echoed by other studies on preferences for surgery.[20,21] Furthermore, men who are married are more likely to opt for aggressive treatment,[22] and those who are more prone to risk taking prefer a watch-and-wait approach.[23] Thus, for this example, one could create a regression model that takes age and marital status as input variables and yields a probability that a given patient would opt for surgery. As surrogates are no more accurate than the base rate (ie, population) preference in predicting a given patient's preference, a model that is trained on a data set that contains the two additional features of age and marital status will likely be more accurate than surrogates. However, deriving such a model for treatment preferences for localized prostate cancer requires significant time, manpower (eg, investigators, data collectors, and statisticians), and funding because potential determinants of preference (eg, age, marital status) need to be identified, health records need to be read and coded, and statistical analyses need to be performed. Perhaps more importantly, traditional regression analysis only allows for a handful of preselected determinants to be analyzed

in one study. As a result, important predictors may be overlooked if researchers do not expect them: regression can only predict treatment choices based on the input variables given.

We propose that AI would be able to revolutionize both the availability and accuracy of predictions regarding health care decisions. Two strong assumptions, however, are required: AI must have access to population-wide electronic health records (EHRs) and these EHRs must be interpretable by AI.

Suppose a clinician wants to know if a patient would wish to undergo risky surgery that might restore his or her power of speech, which was lost due to brain cancer. A machine learning algorithm would be trained on the EHRs of patients who faced a decision about a similarly risky surgery for brain cancer but, due to the location of their tumor, were able to communicate their decision. The input vector, therefore, would include demographic indicators (eg, age, marital status, ethnicity) as well as detailed information from the EHR regarding prior health care consultations, treatments, side effects, investigations, previously expressed preferences and desires, and antecedent choices in other health-related decisions. The output would be a probability estimate that the patient would choose to have surgery.

In this way, algorithmic analyses of EHRs would be able to perform a predictive function similar to human-run studies but complete them in a much shorter timeframe, handling much larger sets of observations and analyzing a wider range of predictors.[24] Whereas a human-run study would incur the aforementioned costs for each treatment choice that one wished to predict, an AI algorithm would only need to be developed once: each time it is given a new preference to predict (eg, type of treatment in localized prostate cancer), it uses the same logic to derive its prediction model. Already, by applying machine learning techniques to EHRs, it is possible to predict outcomes after cardiac surgery more accurately than using traditional regression analyses.[25] Accordingly, it seems reasonable to assume that one would see the same increase in accuracy when using machine learning tools to predict patient preferences, provided the relevant data sets exists and are machine-readable.

However, the machine learning approach need not be confined to EHRs. Examining a person's social media profile can already reliably predict his or her religious and political preferences, propensity for risk-taking behavior, and happiness.[26] There is evidence that an algorithm analyzing only Facebook "likes" outperforms spouses in predicting a person's personality traits.[27] Given that personality traits also appear to predict one's preferences regarding end-of-life treatment decisions,[28] it follows that using data from social media in addition to data from EHRs could lead to more precise predictions regarding health care decisions than using data from EHRs alone. Suppose, for example, that machine learning detected a robust connection between "liking" the organization

Death with Dignity National Center and an expressed preference for comfort-focused end-of-life care in the general population. Then, even if an index patient made no explicit statement regarding her end-of-life treatment preferences, if she "liked" Death with Dignity, the probability would increase that she would prefer comfort-based care. What we call the autonomy algorithm takes patients' EHR and social media footprint as input and generates a confidence estimate for a particular patient's predicted treatment preference as an output.

Ethical Issues

There would certainly be benefits to an effective autonomy algorithm. In addition to increased accuracy, a computerized approach could alleviate some of the weight of making life-and-death decisions. An algorithm will not lose sleep if it predicts with a high degree of confidence that a person would wish for a life-support machine to be turned off. The surrogate who ends life-support may rest a little easier knowing that the autonomy algorithm has also concluded that this is likely what the patient would have wanted. Moreover, the autonomy algorithm is truly patient centered. While it can be trained on population-wide data sets, ultimately, it does not receive explicit input from doctors or family members regarding their thoughts on the correct medical decision; rather, it examines data provided by the patient themselves, be it implicitly through the investigations, treatments, diagnoses, and choices recorded on their EHR or more explicitly through social media activity. However, the use of an autonomy algorithm to estimate confidence of predicted treatment decisions raises some practical and ethical questions.

The first question is practical: the use of the aforementioned machine learning tools can simply reflect existing biases. In the research regarding treatment for prostate cancer outlined above, one study found that the most significant predictor of treatment choice was the specialty of the consulting doctor; patients referred to urologists were most likely to choose surgery and those referred to radiation oncologists were most likely to choose radiotherapy.[19] An algorithm trained on this data set would therefore generate a high confidence estimate for the prediction that a patient seeing a urologist would choose surgery. While this might be true, the association (we assume) is not due to genuine patient preference but reflective of the fact that patients are prone to being talked into a certain therapy by their clinician; it would be a bug and not a feature of the proposed autonomy algorithm to reinforce this fact.

Indeed, algorithms can propagate even more insidious associations. Supposing those with lower health literacy are more disposed to choose the (less effective) treatment X, then an algorithm trained on this data set might generate a high confidence estimate for the prediction that a patient with low health literacy would choose X. Of course, this does not mean that patients *should* choose X. There are numerous examples of algorithms in other fields "learning" prejudice; there is no reason to assume health care would be any

different.[29] Therefore, the autonomy algorithm's confidence estimates must be examined critically by patients and health care professionals: incorrectly applied, the autonomy algorithm might just reinforce an undesirable status quo.[30]

This potential for bias leads us to ask to what extent we should be prepared to accept the outputs of the autonomy algorithm. We should recall that surrogates predict preferences of incapacitated patients roughly a third of the time. It would appear reasonable, therefore, to use the output of the autonomy algorithm to help refine one's decision in the context of surrogate decision making. But what if a patient with full capacity was faced with a decision regarding surgery for localized prostate cancer? Health care decisions are inherently stressful and increasingly involve a reasonably sophisticated understanding of probability and uncertainty.[31] It is well known that decision-making processes in these contexts are subject to bias and error.[32] Suppose our hypothetical cancer patient was told that the autonomy algorithm had analyzed the data of millions of patients in similar situations and found that the patients most similar to him opted for a watch-and-wait approach 90% of the time and that, moreover, the rate of decisional regret was higher in the 10% who opted for active treatment. This would be useful, patient-centered information. However, as outlined above, one must guard against unreflexively deferring to the output of the algorithm.

Conclusions

In this essay, we have made the case that it should be possible to construct an autonomy algorithm to estimate confidence for predicted preferences of incapacitated patients by using machine learning technologies to analyze population-wide data sets, including EHRs and social media profiles. The proposed algorithm would result in more accurate predictions than existing methods, which are resource intensive and examine only small patient cohorts.

It was noted that this tool would both help incapacitated patients realize their preferences in spite of being unable to express them and reduce the significant burdens of patients' incapacity by lowering the emotional strain on proxies and reducing the economic costs of unwanted tests and treatments. Moreover, it was suggested that the algorithm could function as a decision aid to patients with decision-making capacity who are facing complex decisions regarding their own health care.

We also highlighted that the proposed autonomy algorithm could potentially propagate established yet erroneous decision-making practices and hence insidiously reinforce health inequalities. In particular, we noted that if less health literate patients typically chose an inferior treatment X in the algorithm's data set, the algorithm would generate a high confidence estimate for the prediction that a less health literate patient would choose the inferior treatment X. If the algorithm was blindly applied with patients automatically opting to choose treatment X, it would strengthen the association

between low health literacy and treatment X in the data set and thereby propagate health inequality. The outputs of the autonomy algorithm need to be carefully interpreted by both clinicians and patients in order to avoid this trap.

In conclusion, we submit that it is the process of making a decision that is humanizing and autonomy affirming. Therefore, it would be dehumanizing to automate this process and defer to algorithmic outputs as a matter of course. Nonetheless, it appears the autonomy algorithm should form part of the decision-making process. If correctly implemented, it would not be liable to the varied biases, projections, and misapprehensions of human decision makers; rather, it would make reliable estimates based on a wealth of real-world data. In this way, the autonomy algorithm could become a valuable tool in the stressful medical decision-making process, augmenting the capacity of all people to make decisions in difficult situations.

References

1. Grisso T, Appelbaum PS, eds. *Assessing Competence to Consent to Treatment: A Guide for Physicians and Other Health Professionals*. New York, NY: Oxford University Press; 1998.
2. Fitten LJ, Waite MS. Impact of medical hospitalization on treatment decision-making capacity in the elderly. *Arch Intern Med*. 1990;150(8):1717-1721.
3. Lepping P, Stanly T, Turner J. Systematic review on the prevalence of lack of capacity in medical and psychiatric settings. *Clin Med (Lond)*. 2015;15(4):337-343.
4. Sessums LL, Zembrzuska H, Jackson JL. Does this patient have medical decision-making capacity? *JAMA*. 2011;306(4):420-427.
5. Teno JM, Fisher E, Hamel MB, et al. Decision-making and outcomes of prolonged ICU stays in seriously ill patients. *J Am Geriatr Soc*. 2000;48(5)(suppl):S70-S74.
6. Saposnik G, Redelmeier D, Ruff CC, Tobler PN. Cognitive biases associated with medical decisions: a systematic review. *BMC Med Inform Decis Mak*. 2016;16:138. doi:10.1186/s12911-016-0377-1.
7. Janz NK, Wren PA, Copeland LA, et al. Patient-physician concordance: preferences, perceptions, and factors influencing the breast cancer surgical decision. *J Clin Oncol*. 2004;22(15):3091-3098.
8. Embriaco N, Papazian L, Kentish-Barnes N, Pochard F, Azoulay E. Burnout syndrome among critical care healthcare workers. *Curr Opin Crit Care*.2007;13(5):482-488.
9. Chuang CH, Tseng PC, Lin CY, Lin KH, Chen YY. Burnout in the intensive care unit professionals: a systematic review. *Medicine (Baltimore)*. 2016;95(50):e5629. doi:10.1097/MD.0000000000005629.
10. Shalowitz DI, Garrett-Mayer E, Wendler D. The accuracy of surrogate decision makers: a systematic review. *Arch Intern Med*. 2006;166(5):493-497.

11. Marks MA, Arkes HR. Patient and surrogate disagreement in end-of-life decisions: can surrogates accurately predict patients' preferences? *Med Decis Making*. 2008;28(4):524-531.
12. Wendler D, Rid A. Systematic review: the effect on surrogates of making treatment decisions for others. *Ann Intern Med*. 2011;154(5):336-346.
13. Cardona-Morrell M, Kim JCH, Turner RM, Anstey M, Mitchel IA, Hillman K. Non-beneficial treatments in hospital at the end of life: a systematic review on extent of the problem. *Int J Qual Health Care*. 2016;28(4):456-469.
14. Smucker WD, Houts RM, Danks JH, et al. Modal preferences predict elderly patients' life-sustaining treatment choices as well as patients' chosen surrogates do. *Med Decis Making*. 2000;20(3):271-280.
15. Houts RM, Smucker WD, Jacobson JA, Ditto PH, Danks JH. Predicting elderly outpatients' life-sustaining treatment preferences over time: the majority rules. *Med Decis Making*. 2002;22(1):39-52.
16. Shalowitz DI, Garrett-Mayer E, Wendler D. How should treatment decisions be made for incapacitated patients, and why? *PLoS Med*. 2007;4(3):e35. doi:10.1371/journal.pmed.0040035.
17. Rid A, Wendler D. Treatment decision making for incapacitated patients: is development and use of a patient preference predictor feasible? *J Med Philos*. 2014;39(2):130-152.
18. Rid A, Wendler D. Can we improve treatment decision-making for incapacitated patients? *Hastings Cent Rep*. 2010;40(5):36-45.
19. Sommers BD, Beard CJ, D'Amico AV, Kaplan I, Richie JP, Zeckhauser RJ. Predictors of patient preferences and treatment choices for localized prostate cancer. *Cancer*. 2008;113(8):2058-2067.
20. Kurd MF, Lurie JD, Zhao W, et al. Predictors of treatment choice in lumbar spinal stenosis: a spine patient outcomes research trial study. *Spine (Phila Pa 1976)*. 2012;37(19):1702-1707.
21. Heit M, Rosenquist C, Culligan P, Graham C, Murphy M, Shott S. Predicting treatment choice for patients with pelvic organ prolapse. *Obstet Gynecol*. 2003;101(6):1279-1284.
22. Denberg TD, Beaty BL, Kim FJ, Steiner JF. Marriage and ethnicity predict treatment in localized prostate carcinoma. *Cancer*. 2005;103(9):1819-1825.
23. López-Pérez B, Barnes A, Frosch DL, Hanoch Y. Predicting prostate cancer treatment choices: the role of numeracy, time discounting, and risk attitudes. *J Health Psychol*. 2017;22(6):788-797.
24. Obermeyer Z, Emanuel EJ. Predicting the future—big data, machine learning, and clinical medicine. *N Eng J Med*. 2016;375(13):1216-1219.
25. Allyn J, Allou N, Augustin P, et al. A comparison of a machine learning model with EuroSCORE II in predicting mortality after elective cardiac surgery: a decision curve analysis. *PLoS One*. 2017;12(1):e0169772. doi:10.1371/journal.pone.0169772.

26. Kosinski M, Stillwell D, Graepel T. Private traits and attributes are predictable from digital records of human behavior. *PNAS*. 2013;110(15):5802-5805.
27. Youyou W, Kosinski M, Stillwell D. Computer-based personality judgments are more accurate than those made by humans. *PNAS*. 2015;112(4):1036-1040.
28. Lattie EG, Asvat Y, Shivpuri S, et al. Associations between personality and end-of-life care preferences among men with prostate cancer: a clustering approach. *J Pain Symptom Manage*. 2016;51(1):52-59.
29. O'Neil C. *Weapons of Math Destruction: How Big Data Increases Inequality and Threatens Democracy*. New York, NY: Penguin Random House; 2016.
30. Char DS, Shah NH, Magnus D. Implementing machine learning in health care—addressing ethical challenges. *N Engl J Med*. 2018;378(11):981-983.
31. Reyna VF, Nelson WL, Han PK, Dieckmann NF. How numeracy influences risk comprehension and medical decision making. *Psychol Bull*. 2009;135(6):943-973.
32. Kahneman D, Slavic P, Tversky A, eds. *Judgment under Uncertainty: Heuristics and Biases*. Cambridge, UK: Cambridge University Press; 1982.

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