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.

Jason N. Batten, MA is a fifth-year medical student at Stanford University School of Medicine and a graduate fellow at the Stanford Center for Biomedical Ethics in Stanford, California. He previously taught high school chemistry and physics for 6 years in low-income schools in South Central Los Angeles as a Teach For America corps member and an employee of Green Dot Public Schools. After earning a master's degree in bioethics, he worked in the clinical ethics department of a community hospital in Los Angeles. He aspires to be a physician-ethicist. His research applies theoretical and empirical approaches to communication, decision making, and institutional policy in critical and palliative care.

Conflict of Interest Disclosure
The author(s) had no conflicts of interest to disclose.

The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.