Ethical Issues in Precision Medicine
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Objectives:
1. Describe how ethical issues are created by scientific approaches of precision medicine (PM)
2. Respond to the ethical challenges PM presents for patients, families, clinicians, and institutions
3. Identify institutional policies needed to help address these challenges

What is Precision Medicine?
Personalized or precision medicine (PM) “does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment” and to concentrate “preventive and therapeutic interventions ... on those who will benefit, sparing expense and side effects for those who will not.” PM is evidence-based, epidemiologically-based medicine: genetic studies (or clinical trials in which participants’ genotypes figure in recruitment or data analysis) still yield only average results for a given population. Prevention/treatment recommendations based on such studies still hold only a population-based probability of benefitting an individual patient who is relevantly similar to the studied population.

PM is also stratification-based medicine: dividing those who are likely to benefit from those not likely to, by first dividing people based on their genotype. Dividing people based on identified inherent traits has a long history of resulting in disparities and discrimination, disenfranchisement and even death (genocide). Thus, societies, institutions, and professionals should take special care when embracing the promise of PM. They should carefully scrutinize the value-laden decisions that take place behind-the-scenes (or before the clinical scene), for example, in enrolling representative study populations, interpreting genetic variants (as benign, pathological, or of unknown significance), and implicitly adopting evidence as good enough to be “actionable” or clinically relevant.

PM research should investigate environmental and behavioral, not just genetic components of disease; however, interest in the genetic/genomic contributions to disease risk seem to eclipse concern for the other part of the gene-environment interactions responsible for diseases and traits. For clinicians and institutions, many of PM’s ethical challenges do involve managing and employing genetic/genomic information (GI), resulting from clinical testing or being brought by patients, perhaps from direct-to-consumer (DTC) testing.

Institutions should develop policies for incorporating GI into electronic health records (EHR) and clinical practice guidelines, implement clinical decision support (CDS) systems to prompt and guide clinicians’ uses of GI, and establish policies to reinterpret GI, protect patient privacy, and manage disclosure of GI to patients and perhaps others. Clinicians need to help patients understand probabilistic risk information to guide preventive and therapeutic interventions, and reproductive and other personal decisions. The familial nature of GI complicates these responsibilities.
Case 1
Mr. Gordon, a 55-year-old African-American man, informs his doctor that he has been feeling increasingly depressed since his sister died of cancer three years ago. He wants to stop feeling sad and hopeless; his wife persuaded him to seek a prescription for antidepressants. Missing his sister prompted him to do DTC genetic testing to search for more family connections. He received ancestry and health-related results, and was surprised to learn he is “33% Caucasian/European,” has increased risk for type-2 diabetes (T2D), and has a CYP2D6 variant related to drug metabolism. The results surprise him because he has always considered himself a “proud Black man” and is physically fit. The pharmacogenomic finding also troubles him. His sister had pharmacogenomic testing to inform her cancer treatment, and it feels strange to have a pharmacogenomic finding when he doesn’t have cancer.

Direct-to-consumer genetic testing, pharmacogenomics, and clinical considerations
Pharmacogenomics (PGx)—the study of the relationship between genetic variation among individuals and their drug responses in order to develop new drugs and inform prescribing practices—is often considered less ethically challenging than other domains of PM. Who could object to prescribing “the right drug for the right patient at the right time?” Who would discriminate against someone based on his drug metabolism rate? Nevertheless, PGx presents ethical challenges, which differ depending on whether the genetic variation relevant to drug response is found in an individual’s genotype (an inherited variant), as with Mr. Gordon, or is tissue-specific (an acquired variant), as with his sister’s tumor.

Issues associated with tissue-specific acquired variants may relate to the cost of drugs developed, for example, to target a particular tumor type with specific chemotherapy or to guide immunotherapy. Issues include whether particular agents should be covered by insurance companies and included on institutional formularies, how society will finance extremely expensive treatments, and what degree of benefit (measured, for example, in Quality Adjusted Life Years) will be demanded to counterbalance such high costs.

Mr. Gordon’s inherited variant related to drug metabolism raises different issues. First, because DTC companies can vary in their quality, accuracy, and interpretations of variants, his physician needs to decide whether to rely on the DTC test results, whether to include these results in his EHR, or whether to re-test to verify the results. Second, people of European ancestry are vastly overrepresented in PGx and most genomics studies; therefore, it is complicated for laboratories to generalize study results to people of African ancestry. Interpretation of GI depends on comparing a person’s genome to a reference genome and interpreting the significance of variants discovered; however, variants are not as well-characterized (i.e., their meaning is not as frequently and reliably established) for members of under-represented populations. To help ensure that he receives a therapeutic dose, and avoids adverse drug responses (ADR) or side-effects, before prescribing a selective serotonin reuptake inhibitor (SSRI) antidepressant, Mr. Gordon’s physician should investigate the meaning of his CYP2D6 variant, but also consider the reliability of its interpretation in light of his continental ancestry.

If she orders PGx testing, prior to prescribing an SSRI (as the Food and Drug Administration often recommends, but seldom requires for a range of drugs), Mr. Gordon’s physician should engage in an informed consent process. This might seem surprising, because diagnostic tests usually don’t require specific informed consent unless they present some risk of physical harm. However, because of pleiotropy—the phenomenon of one gene influencing multiple traits—identification of a PGx variant might simultaneously reveal genetic information about disease risk, information that Mr. Gordon might not want to receive. Moreover, information regarding an inherited genetic variant may have relevance for Mr. Gordon’s family members, and he should be prompted to consider in advance whether and how he would share GI with them. These issues are discussed below in relation to Case 2.
Polygenic risk scores, health disparities, and the usefulness of Precision Medicine

Considerations of continental ancestry also complicate the clinical application of the GI Mr. Gordon received regarding risk for T2D. Such a polygenic risk score (PRS)—the quantification of the cumulative effect of many genes on a phenotype (his risk for developing T2D)—may be 4.5 times more accurate for people of European ancestry than those of African ancestry. Disparities in enrolling people in genome-wide association studies exacerbate health disparities, because those already disadvantaged in health and healthcare do not benefit from PM as much as their European ancestry counterparts. Moreover, for a wide range of conditions, GI and PM may not be very useful. In the case of T2D, lifestyle factors or a family history of T2D (which may reflect both genomic and shared lifestyle factors) are more predictive of T2D than a PRS. Moreover, learning GI frequently does not lead to health behavior change, and even prompts some people to adopt a fatalistic, “why bother” attitude. Mr. Gordon’s physician might instead suggest that starting an exercise regimen and taking regular walks with his wife may improve his mood—his current concern—while also promoting overall physical and emotional health. GI is not necessary to make these recommendations. Moreover, PM’s stratification of populations and individualization of responsibility for disease risk (locating it in the individual’s genome) do little to address the range of social, environmental, and nonindividual lifestyle factors associated with the increasing prevalence of T2D among myriad other common, chronic conditions.

Race, ancestry, and social meaning of genes

Finally, there is Mr. Gordon’s “33% European ancestry.” Also a PRS, this finding could be reported with greater confidence if it were based on analysis of a sample population that is more representative than the roughly 80% European ancestry populations that are currently available in databases.

That Mr. Gordon found it surprising, even disconcerting, to learn that he likely has more European ancestors than he realized demonstrates that seemingly innocuous GI can have psychosocial sequellae, including disruption of self-concept. His reaction also reflects the complicated relationship between race as a social construction and continental ancestry (for which race is sometimes used as a surrogate), as well as the legacies of colonization and rape associated with the mixing of some continental ancestries.

Case 2

Ms. Anderson brings her 4-year-old daughter, Mary, to neurology specialists at Children’s Hospital because Mary has seizures—sometimes 20 a week—for which no one has been able to find a cause or effective treatment. During her neuro-evaluation, Whole Exome Sequencing (WES) is offered to learn whether there is a genetic contribution to the seizure disorder, information that might help guide treatment. Most likely the trio of Mary-mother-and-father would be sequenced. Ms. Anderson has heard about “Precision Medicine” and that “epilepsy might run in families.”

In obtaining informed consent for the WES, the neurologist discusses the possibility of learning other genetic information—not relevant to her daughter’s seizures, but perhaps relevant to other aspects of her daughter’s health or to other family members. Would Ms. Anderson want to be informed of these “incidental findings”—results that are not related to the reason for testing/sequencing, but have potential health or reproductive significance?

Ms. Anderson knows her sister is planning to start a family, and wonders whether she might learn something from WES relevant for her sister’s reproductive decision making. She also wonders how her husband might respond to an incidental finding (IF). Because he has been estranged from his brother for ten years, discovering a genetic risk of disease on her husband’s side could be difficult to handle. Also, because she and her husband are planning to start their own small business, she worries about how they would handle the stress of other disease risks, along with stresses of a new business.
venture and their daughter’s health issues. She asks whether they could receive the possible diagnostic benefits of WES without the risks of learning anything not directly relevant to Mary’s current condition.

**Informed Consent, Incidental Findings, Discrimination, and Distress**

Unlike many other diagnostic tests, genetic testing or genome/exome sequencing warrants an informed consent process for at least two reasons: the familial nature of GI and the possibility of discovering an IF. Clinicians should discuss the possibility that any type of genetic testing may yield IFs, and should discuss in advance of testing whether the patient wants (or here, whether the parents want) to be offered such findings.

In 2013, the American College of Medical Genetics and Genomics (ACMG) recommended that laboratories conducting clinical sequencing should engage in opportunistic screening for increased risk of several serious conditions. It recommended that laboratories “seek and report” pathogenic variants in a set of 57 clinically actionable genes associated with these conditions, even though it admitted that “there are insufficient data on clinical utility to fully support these recommendations.” The ACMG therefore also recommended that the initial list of 57 such genes be updated annually, resulting in the current “ACMG 59.” Searching for and reporting on these IFs or “secondary findings,” is not a legal requirement, but could become a standard of care so that laboratories, clinicians, and institutions may face legal liability if they do not. While the ACMG initially suggested that patients not be given a choice about whether to receive these IFs, this “take-it or leave-it, all-or-nothing” approach was quickly abandoned, reaffirming the importance of respecting patients’ autonomy and privacy.

Imagine that Mary were discovered to have a BRCA1 mutation increasing her risk for breast and ovarian cancer. Either her father or mother is likely to have the mutation as well. Testing of children for adult onset conditions is generally discouraged, so that children can themselves decide about testing when they reach the age of majority. But, discovering the BRCA1 mutation as an IF and reporting it to Mary’s parents would enable them to be tested for their health benefit (and perhaps to inform future reproductive decisions, if they would want to avoid the risk of passing on a cancer-related gene to other offspring).

Discovering this IF would raise the question of what GI the Andersons should share with their siblings and other relatives. Ms. Anderson anticipated the stress this potential “duty to warn” might cause her husband, and the benefit/stress the information might present to her sister contemplating reproductive decisions. However, Ms. Anderson may not have considered the economic implications of learning of a genetic risk for cancer.

The Genetic Information Nondiscrimination Act of 2008 (GINA) prohibits employers from using GI to make hiring, firing, and promotion decisions, and prohibits health insurers from using GI to deny or charge differential rates for health insurance. Life, disability, long-term care, and automobile insurers, however, are not prohibited from using GI in underwriting. If the Andersons need life insurance to obtain a small business loan, their learning about increased cancer risk could be problematic. Although learning of the BRCA1 mutation may initiate or increase surveillance and result in early detection and treatment, some patients/families may have reasons not to learn such risk information, at least not at particular times.

Further, sequencing the family trio could reveal misattributed parentage, that Ms. Anderson’s husband is not Mary’s genetic father. All of these informational risks and potential benefits should be disclosed during the informed consent process. Moreover, it may be prudent to establish an institutional policy that each member of a family must have a private informed consent conversation with the clinician prior to sequencing, so that parties involved can make plans to deal with GI that may be revealed.

**Institutional Policies and Professional Responsibilities**
There are multiple policies that institutions should develop regarding the management of IFs of genetic testing/sequencing. If a laboratory returns GI to the clinician, allowing patients to opt out of receiving it may expose the clinician or healthcare institution to future legal liability (even if, ethically, the patient’s informed refusal of GI should be respected and should indemnify the clinician and institution against a future lawsuit). A better option would be to ask laboratories to mask results—i.e., not interpret variants at particular loci in the genome that are likely to produce IFs. But, if a variant is interpreted and reported by mistake, or if due to pleiotropy an IF is discovered at a locus examined to address the clinical question, institutions and clinicians need to have a plan to manage those findings and need to disclose that plan during the informed consent process prior to testing/sequencing.

Policies are also needed to address recording of GI in the EHR, including whether children’s GI will be stored for them to access when they mature (and how ‘maturity’ is defined) and whether it will be shared with their parents in the meantime. Sharing a child’s GI may enable parents to seek testing for their own health benefit, and children have an interest in having health parents. But growing up with one’s parents knowing about one’s carrier status for an autosomal recessive condition (e.g., cystic fibrosis) or for an adult onset condition, could result in one’s parents exerting pressures on one’s health and reproductive decisions/behaviors and eliminates the possibility of keeping one’s GI private.

Plans to reinterpret genetic findings at regular intervals need to be established and explained to patients at the time of testing/sequencing. While a person’s genome is relatively stable over her lifetime, the interpretation of it may change as knowledge increases. Variants in disease-risk-related genes, initially classified as ‘benign’, ‘likely benign’, or ‘variant of uncertain significance’, may be reclassified as ‘pathogenic’ or ‘likely pathogenic’, or the reverse. Different laboratories doing genome/exome sequencing interpret variants differently based on their assessment of the literature and variants reported to databases. At the time of testing/sequencing, patients need to be informed both that understanding of GI is evolving and that a reassuring report containing no findings of increased risk does not signal an entirely “clean bill of genetic health,” but only a failure to find variants currently known to increase risk. Nor is it a “clean bill of health,” as nongenetic factors may be sufficient to result in disease. Only 5-10% of breast cancers, for example, are believed to be associated with inherited genetic variants. A false sense of security could result from misunderstanding the meaning of results that report no known genetic risks. In turn, a patient might neglect standard preventive measures thinking that they are unnecessary. In short, clinicians have a responsibility to explain the limitations of genetic testing/sequencing.

Institutions have a responsibility to develop policies and practices to mitigate the negative sequelae of these limitations. Reinterpretation of results at regular intervals, developing infrastructure to maintain contact with patients over time to provide updated information to them, implementing CDS systems to help clinicians use of GI—these are infrastructural elements of PM. An often-overlooked need for policy concerns the sharing of GI with family members following a patient’s death. Such information may be of value to them, and patients should be given an opportunity to designate whether and to whom genetic (and other health-related) information may be given post-mortem.

**Is there a “duty to warn”***?

The question of whether clinicians have a duty to inform or warn a patient’s family members of GI that has potential relevance for them has received substantial attention. The general consensus is that clinicians fulfill their responsibility to a patient’s family members by explaining to the patient the familial implications of her GI and suggesting (even urging) that she share the information with her family. The clinician should offer both to provide written information the patient may pass along and to facilitate referrals of family members for genetic counseling and/or testing. A key legal case in the genetics “duty to warn” context is *Pate v Threlkel*, which held that the clinician’s duty to inform did not extend to the patient’s family members. A second case, *Safer v Estate of Pack*, in contrast, suggested
that a trial court could consider whether, in a particular case, a clinician had a “duty to warn those known to be at risk of avoidable harm from a genetically transmissible condition,” but before a jury ruled on that question, the case was settled.\textsuperscript{11} Whether a clinician may have a legal responsibility to inform a patient’s relatives of health-relevant GI remains unclear. What is clear, however, is that attempting to do so would be expensive and often practically impossible. It is both feasible and ethically required, however, for a clinician to inform her patient of the familial implications of GI. Then, unless there are strong countervailing reasons not to, the patient should assume some degree of responsibility to inform family members of the relevant GI.\textsuperscript{12} Whether the reason for Mr. Anderson’s estrangement from his brother would constitute sufficient reason not to share GI with his brother would require ethical evaluation—evaluation on Mr. Anderson’s part, not the clinician’s.

Would Mr. Gordon have a similar responsibility to share his PGx information with his family members? Unlike testing for BRCA variants which might not be performed in the absence of a family cancer history, PGx testing is increasingly relevant to the prescribing of many drugs and may be ordered without any familial indication. This fact reduces the importance of intrafamilial sharing of PGxT results. Moreover, the opportunity for increased surveillance and early detection of cancer afforded by BRCA testing would likely be considered a greater potential benefit than being prompted to learn about one’s risk for ADR or ineffective treatment. Typically, both ADR and ineffective treatment may be discovered and addressed empirically. But, ADR can be life-threatening, and even ineffective treatment can be life-threatening, as when ineffectively treated depression leads to suicide. Further, ADR and ineffective treatment are costly to the healthcare system. Thus, it would be good (though perhaps not required) that he share information about his CYP2D6 variant with them.

\textbf{A final question: what if there is no “right treatment,” at this time, for this patient?}

The promise of PM is identifying the right intervention at the right time—sometimes preventively or preemptively, sometimes in response to symptoms. But what if Mr. Gordon’s depression did not respond to the medications which PGx testing indicated would have the best chance for success? What if sequencing Mary’s exome does not indicate that she is a candidate for a newly developed medication found to be effective in people with a different genotype? PGx testing is supposed to be more precise than the trial-and-error prescribing that clinicians employed in the past. But should results of PGx testing or exome/genome sequencing prohibit clinicians from trying an intervention either when PM-guided interventions fail, or when patients want to try something different? What if Mr. Gordon’s testing indicates Antidepressant-A has a superior profile for him (lower risk of ADR, greater chance of being effective), but he prefers the convenience or finds more tolerable the side effects of Antidepressant-B? Should his insurance company only cover the drugs indicated by his PGx testing? Should clinicians allow patients to assume the risk of an ADR to receive the drug of their choice? If Mr. Gordon’s sister’s tumor typing did not indicate that Chemotherapy-C would be effective, should she nevertheless have had access to it as a “last ditch effort” to save her life?

While GINA prohibits health insurers from discriminating against people based on GI to deny them coverage or charge higher rates, insurers are permitted to use genetic information to determine medical need and, in turn, what is “medically necessary” treatment. A strong family history of breast cancer or positive BRCA1 mutation testing, for example, may be used to establish a young woman’s medical need and insurance coverage for mammography that would not otherwise be covered until age 40. By analogy, insurance plans might argue that Chemotherapy-C was not medically necessary or appropriate for Mr. Gordon’s sister, and that only Antidepressant-A is appropriate for treating his depression.

When institutions develop clinical practice guidelines, or insurers draft policies governing reimbursement/coverage, concern for patient well-being, just allocation of resources, and containing healthcare costs supports taking into account both patients’ medical need and the growing body of PGx
Nevertheless, concern for well-being and fairness also suggests that an individual whose genotype indicates a relatively lower probability of positive treatment response should not be categorically denied access to (or coverage for) that intervention, so long as three conditions obtain: (1) the intervention is otherwise available/covered; (2) no other intervention is available that is likely (more) effective for patients with that genetic variation; and (3) the risk or burden of the intervention to the individual—i.e., the probability and magnitude of ADR—is not unduly burdensome given the magnitude and probability of benefit. With regard to (3), it may be argued that an individual should be allowed to assume those risks and not be denied the opportunity to seek even remote benefit when no other good alternative exists, especially if others with a different genotype have access to the intervention.

Especially if the intervention or drug with a remote (or relatively lower) prospect of benefit could be administered at the patient’s own expense, it would seem quite reasonable to allow the patient to assume the risk of ADR, or to opt for a personally-preferred drug over the one most recommended. But, most patients cannot afford to self-pay for medication or chemotherapy. Moreover, if a serious ADR resulted, a patient should not be forced to self-pay to have that ADR treated. It is reasonable for institutions to consider these downstream costs when considering exceptions to clinical guidelines, and for insurers to consider them when adjudicating appeals for coverage. Nevertheless, decisions to deny an individual, on the basis of her/his genotype, an intervention that is available to others should not be made lightly or categorically. Appropriate appeal processes should be established.

In sum, the stratification intrinsic to PM should not be used to disadvantage people who would be afforded a chance to benefit from treatment in the absence of such stratification.

Discussion questions

Conceptual: How do your patient populations stand to benefit from PM, or to be less well-served by PM, and why?
Pragmatic: How will your institution meet challenges of PM infrastructure, including changes in work flow, referrals for genetic counseling, opportunistic screening, inclusion in electronic health record, and clinical decision support?
Strategic: How can institutional policies and practices mitigate potential harms of PM?

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10 Pate v Threlkel, 661 So2d 278 (Fla 1995).

