



# A Primer on Precision Medicine: The Legal and Ethical Considerations Faced by Modern Medicine's New Frontier

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The National Institutes of Health (NIH) defines “precision medicine” as

*[A]n emerging health care model for disease treatment and prevention strategies that takes into account each person's genetic variations, environment and lifestyle.<sup>1</sup>*

Precision medicine was thrust into the national conversation in 2015 when President Obama announced a \$215 million U.S. funding commitment known as the Precision Medicine Initiative (PMI).<sup>2</sup> In President Obama's words, the goal of precision medicine is to provide clinicians with new tools, knowledge, and therapies that will enable them to select “the right treatments, at the right time, every time to the right person.”<sup>3</sup>

Though scientists disagree about the extent to which precision medicine will translate into genuine improvements in health care delivery, even the most skeptical of experts cannot deny recent advancements in genetic testing and targeted therapeutics.

PMI drastically expanded precision medicine's presence in scientific research. As evidence, later this year, the PMI cohort program, "All of Us," will begin enrolling participants in a million person data set of genetic, lifestyle, and health information for further study of the interaction of genetics, environment, and lifestyle.<sup>4</sup>

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## Genetic Testing

Laboratories across the world assess risk and diagnose disease by analyzing genomes.<sup>6</sup> The advent of 23andMe and other direct-to-consumer genetic testing products permit patients from their homes and personal computers to identify and assess their unique risk of developing disease.<sup>7</sup>

Although early genetic tests were developed to detect rare, relatively straightforward single-gene variations that were highly correlated with specific diseases, today's genetic tests (e.g., next generation sequencing (NGS)) are able to detect a wide range of genetic variants from a single sample.<sup>8</sup> NGS allows scientists to identify more common, complex diseases and provides patients information to assess their individual risk of developing a myriad of diseases.<sup>9</sup> In 2018, a single laboratory

can sequence an entire human genome in less than 24 hours for just under \$1,000.<sup>10</sup> For less than \$200, 23andMe offers consumers "genetic health risk reports" that detect variants related to late-onset Alzheimer's disease, Parkinson's disease, alpha-1 antitrypsin deficiency, celiac disease, hereditary hemochromatosis, hereditary thrombophilia, and age-related macular degeneration.<sup>11</sup>

## Targeted Therapeutics

Even more astounding is that scientists can now offer certain patients targeted treatments for a variety of illnesses and conditions.<sup>12</sup> These targeted therapeutics provide medicines specified to treat individual genetic mutations with exactitude.<sup>13</sup> The Food and Drug Administration (FDA) has approved a number of these medications.<sup>14</sup> To name a few, targeted therapeutics are now made available for certain breast cancers, melanomas, colorectal cancers, leukemias, lymphomas, ovarian cancers, pancreatic cancers, rheumatoid arthritis, and lupus conditions.<sup>15</sup>

In addition, recent advances in Clustered Regularly Interspersed Short Tandem Repeat (CRISPR) technology now allow scientists to artificially alter genes; the promise of CRISPR technology knows no bounds.<sup>16</sup>

Precision medicine's emergence in modern day medicine is here; and, the potential that the field offers is vast. However, its promise must manifest itself within our current legal and regulatory system; and, as every health care attorney knows, innovation is often fraught with complex and sometimes novel legal and regulatory barriers.

## Pre-Market Approval and Clinical Oversight: FDA and CMS

*[T]he FDA is currently finding its regulatory foothold during [this] transition in the practice of medicine.<sup>17</sup>*

Two federal regulatory agencies currently oversee the development of genetic diagnostic tests and targeted therapeutics: the FDA and the Centers for Medicare & Medicaid Services (CMS).

The FDA is responsible for protecting and promoting public health by assuring "the safety, effectiveness, [and] quality" of medical drugs and devices by the authority granted to it under the Federal Food, Drug and Cosmetic Act (FDCA) and the Medical Device Amendments of 1976.<sup>18</sup> Consequently, the FDA is a gatekeeper to advances in precision medicine.

For example, the FDA regulates in vitro diagnostic tests (IVDs) as a subset of medical devices.<sup>19</sup> FDA approval of medical devices typically requires analytical and clinical validation.<sup>20</sup> In the case of IVDs, manufacturers must prove that an IVD can (1) accurately identify a sample (i.e., accurately read a specific set of DNA bases in the human genome) and (2) link particular genetic variants to specific diseases (i.e., provide meaningful clinical information).<sup>21</sup> Though this regulatory threshold seems simple enough, a narrow interpretation of the pre-market approval regulatory framework could lead to an unintended absurdity: namely that because the FDA typically bases its pre-market approval decision on evidence dependent

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upon large, randomized clinical trials, the FDA could arguably require separate analytical studies to prove the analytical and clinical validation of each of the many billion nucleotides in the human genome.<sup>22</sup>

Congress recognized the barriers that the FDA's regulatory policies posed to the technological advances anticipated by precision medicine. Their response was the 21st Century Cures Act (Act), which encouraged the FDA to develop new regulatory approaches for the oversight of genetic technologies.<sup>23</sup>

Following the Act, the FDA issued two draft guidances intended to address “issues that may arise when co-developing a therapeutic product and a corresponding companion diagnostic.”<sup>24</sup> The draft guidances “recommend approaches to streamline the submission and review of data supporting the clinical and analytical validity” of genetic tests.<sup>25</sup>

The first draft guidance, the *Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing-Based in Vitro Diagnostics*, proposes to “allow developers to use data from FDA-recognized public databases of genetic variants to support a test’s validity.”<sup>26</sup> The second draft guidance, the *Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing-Based In Vitro Diagnostics Used for Diagnosing Germline Diseases*, proposes to “allow test developers to cite data and assertions from FDA-recognized public genome databases as valid scientific evidence to support clinical claims for their tests.”<sup>27</sup>

Though these draft guidances are a start to streamlining regulations associated with pre-market approval of precision medicine devices, they are not the federal agency’s final word on precision medicine oversight. The FDA proclaims that their recommendations may change, “as technology advances, standards can be updated to help ensure test accuracy.”<sup>28</sup>

In addition to FDA oversight of precision medicine drugs and devices, the Clinical Laboratory Improvement Amendments of 1988 (CLIA) grants CMS regulatory oversight of

clinical laboratories, including those operating with precision medicine devices and/or drugs.<sup>29</sup> Unlike FDA requirements, CMS requirements do not address clinical validity. Instead, CLIA standards ensure the reliability and accuracy of laboratory test results and address the overall operation of the laboratory by assessing the training of lab personnel, proficiency testing, and quality control.<sup>30</sup> CLIA regulations “establish quality standards for laboratory testing performed on specimens from humans . . . for the purpose of diagnosis, prevention, or treatment of disease, or assessment of health.”<sup>31</sup>

Researchers and manufacturers must ensure that they adhere to and comply with FDA and CLIA standards; but, the buck does not stop there. Within the space of precision medicine, legal considerations associated with intellectual property abound.

### Intellectual Property

In *Moore v. Regents of California*,<sup>32</sup> *Washington University v. Catalona*,<sup>33</sup> and *Greenberg v. Miami Children’s Hospital Research Institute, Inc.*,<sup>34</sup> federal courts declined to recognize individual property interests in information obtained through analysis of their biological material.<sup>35</sup> The courts reasoned that the recognition of personal property rights in genetic data would “cripple medical research.”<sup>36</sup>

Though these cases suggest that researchers and manufacturers are no longer at risk of losing potential property interests in precision medicine to genetic donors, they must consider whether they will be able to obtain property interests, at all—especially when attempting to patent genetic information.

In *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, the U.S. Supreme Court redefined legal requirements for patentable subject matter when it held that the sequence of naturally occurring DNA was not subject to patent protection.<sup>37</sup> Effectively, the Court eliminated what some biopharma companies had seen as a risk of patent infringement.

Alleviating this risk will likely open the diagnostic testing market to new entrants, which means that consumer protection regulations will be even more important to ensure product safety and prevent false or misleading marketing in the precision medicine space.

### Consumer Protection: Consent, Privacy, and Confidentiality

Though bulk collection of our personal data is increasingly common, the linkage of genetic information, past medical history, lifestyle, and other personal information raises concerns about consent, privacy, and confidentiality. Unlike credit card information, that can be modified if stolen, genetic information cannot. Genetic information is arguably the most personal of all data—we have one genome, for life. Scholars have identified concerns regarding the possibility that genetic information could be used for insurance rating, setting job qualifications, or marketing to specific individuals.

However, as the promise of precision medicine is vast, patients will likely be willing to participate in precision medicine initiatives to the extent that they can rely on strong privacy and security protections.

Patients may be surprised that current Health Insurance Portability and Accountability Act (HIPAA) regulations do not require individual consent for data that has been “de-identified” so that it cannot be traced back to the original research participant.<sup>38</sup>

Some scholars argue that such “de-identified” research should be presumptively permitted without individual consent to eliminate regulatory hurdles to precision medicine research.<sup>39</sup> They argue that researchers should be deterred from immoral or illegal use of genetic information by common law liability.<sup>40</sup> However, at least one scholar has noted a particular weakness with this approach; that individuals who are more likely to carry genetic anomalies meriting study may be particularly sensitive to risks associated with re-identification and less likely to participate in research, which would lead to systematic consent bias.<sup>41</sup>

Scholars subscribing to philosophies grounded in patient autonomy believe that all precision medicine initiatives should promote patient choice and trust through a dynamic and ongoing informed consent process. They argue that participants should be informed of how data will be collected and used, along with the potential risks and benefits of participation, including privacy and security risks.<sup>42</sup>

After all, one of the principal risks of precision medicine is the possibility that de-identified data would be re-identified and associated with the individuals that supplied such information. Today, there is no general legal prohibition on re-identification of individuals from their genetic data. The ramifications of re-identification of de-identified data are concerning whether re-identification is nefarious or accidental.

Today, the HIPAA Privacy Rule permits all uses and disclosures of individually identifiable health information for treatment purposes without any consent or authorization by the patient.<sup>43</sup> This means that providers are permitted to access and disclose comprehensive and longitudinal genetic health information for treatment without any minimum limit.<sup>44</sup>

That being said, PMI’s “All of Us” research initiative recommends that participants must consent to collection of identifying information, with the understanding that it will be kept securely, and that they must provide permission to use identifiers, link data across disparate sources, and share data for future research uses.<sup>45</sup>

Patients may assume that they should have access to their full genetic reports. However, they may be surprised to know that in 2016, complaints were filed with the Department of Health and Human Services (HHS) when patients alleged a leading diagnostic company refused to provide their full genetic reports.<sup>46</sup> Though patients might assume that when new information is available regarding their genetic data, it will be made available to them; laws related to this idea have yet to be developed. These concerns are notable. As science advances, there are inherent risks that companies may discover months after revealing genetic diagnosis to patients that initial genetic interpretations were incorrect. Will they have a duty to disclose the new information?

In addition to concerns related to undeveloped privacy laws and regulations, the issue of whether targeted therapy and diagnostics is reimbursable by third-party payers is yet another unknown.

## Reimbursement

*As an approach that is playing an increasingly important role in obtaining genetic information from patients, [reimbursement for precision medicine diagnostics and therapeutics] may be viewed by the public and private payors either positively, as an enabler of the promised benefits of personalized medicine, or as “the perfect storm” resulting from the confluence of high market demand, an unproven technology, and an unprepared delivery system.<sup>47</sup>*

It is no secret that payers require persuasive scientific evidence to support claims of clinical utility before approving payment for diagnostic tests and targeted therapies. Seeking reimbursement for precision medicine diagnostics and therapeutics will require consideration of the value of such tests and treatments in meeting our broader health system needs.

Though historically Medicaid has covered molecular diagnostic tests for cancer, and Medicare now covers NGS reimbursement, many other commercial payers have yet to follow suit.<sup>48</sup> Reimbursement considerations are a substantial barrier to precision medicine’s growth. As recently as this January, one pharmaceutical company proposed a precision medicine drug should cost \$850,000 per treatment.<sup>49</sup> Separately, the Institute

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for Clinical and Economic Review (IECR), an independent nonprofit that evaluates drug effectiveness, approved new CAR-T cancer therapies that genetically modify a patient's own immune cells at \$475,000 per treatment.<sup>50</sup>

The economic costs of developing targeted treatments matched to individual genomes are likely enormous.<sup>51</sup> However, targeted treatments offered to individuals with certain genetic mutations may be cost-effective, depending upon their costs.<sup>52</sup>

Reimbursement in the area of precision medicine is simply anyone's guess—which brings to mind the multitude of ethical issues associated in the precision medicine industry.

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## Ethical Issues

*The regulatory challenges presented by precision medicine are reformulations of old tensions: community welfare versus individual liberty, risk versus benefit, autonomy versus paternalism.*<sup>53</sup>

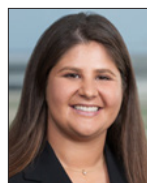
Many assume that precision medicine will be available to all of us, with unrestricted access; but, this is unlikely the case.<sup>54</sup> Though precision medicine offers great promise to those suffering from disease, it has the potential to worsen existing disparities in health care delivery.<sup>55</sup> This could increase the gap between the least and most educated of health care consumers, and cannot be ignored as we develop policies related to the industry going forward.

## Conclusion

Although significant scientific advancements have been made, much is still unknown about the implications that precision medicine will have on our wellbeing and health care delivery model. The voice of skeptics is heard. Many more clinical trials will need to be designed and targeted therapies approved to truly reap the promises of the industry. The design and approval process is not without its legal and regulatory considerations; many of which have yet to be developed.

Though it would be an offense to humankind for legal and regulatory requirements to obstruct the advancement and promise of precision medicine, the absence of such standards would inevitably pose grave risks to human life.

All health care attorneys should invest time to consider the legal issues that overwhelm the scientists, providers, and tech companies entrenched in the promise of diagnosing and curing disease. Each of us must promote the advent of medical innovation by providing the requisite professional and legal guidance to leaders in the precision medicine industry. It is our professional duty to assist these leaders in the navigation of complex and ever-evolving laws and regulations. Together, we promote safe, quality, efficient health care delivery to all. **C**



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