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Clinical Integration of Next Generation Sequencing: A Policy Analysis

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Précis

Clinical next generation sequencing (NGS) technologies are challenging existing regulatory paradigms. We advocate a coordinate policy approach, which first requires a comprehensive understanding of the existing regulatory and legal structures. This paper introduces four key policy domains, including quality assurance, insurance coverage, intellectual property management, and data sharing, that must be addressed to ensure high quality clinical NGS. In bringing these policy issues into conversation through this special issue for the *Journal of Law, Medicine, and Ethics* we hope to lay the foundation for further discussion by a range of stakeholder groups with diverse and strong interests in the governance of NGS.

In 1996, President Clinton offered a promissory vision for human genetics when he said: “I think it won’t be too many years before parents will be able to go home from the hospital with their newborn babies with a genetic map in their hands that will tell them, here’s what your child’s future will likely be like.”[1]

The rapid evolution of genetic sequencing technologies has advanced that vision. In October 2006, the cost of sequencing an entire human genome was $10.4 million; in 2014 the cost has decreased a thousand fold.[2] The term next generation sequencing (NGS) describes a variety of laboratory methods that allow efficient determination of the precise order of nucleotides in a DNA sequence. The papers in this issue of the Journal of Law, Medicine & Ethics focus on “clinical NGS,” which refers to rapid DNA sequencing using second, third and fourth-generation sequencing technologies to perform genome-wide sequencing of multiple genes or alleles for clinical prognostic, diagnostic, and therapeutic purposes.

The most touted advantage of NGS technology is the collection of accurate genetic sequence data at far greater speeds and higher volumes than possible a decade ago, producing much greater amounts of information than traditional Sanger sequencing.[3] The College of American Pathologists described NGS as “shifting DNA sequencing into hyperdrive.”[4] NGS

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is potentially transformative for genetic testing applications because it allows clinicians to look broadly across the genome to identify a wide range of genetic changes that are, or may in the future be, clinically significant, as well as to more precisely diagnose and treat disease.[5] The potential expansion of clinical utility and the decreasing costs have brought NGS methods to the cusp of mainstream clinical diagnostic testing.[6] As clinical potential is demonstrated for a growing list of applications, and some insurance companies begin to cover the cost of NGS, a growing number of diagnostic laboratories are adding NGS to their menu of services.

Some experts think genomic sequencing is ready for routine clinical use. However, the volume and breadth of data generated by NGS testing, the bioinformatics requirements for clinical interpretation,[7] and the need to accurately parse and communicate meaningful information to patients[8] potentially counter-balance the sequencing efficiency gains and present a host of policy challenges for its clinical integration and reimbursement. Many companies and laboratories involved in clinical NGS are working to address these issues, but there continues to be much variability in analysis.[9] The current regulatory frameworks that guide single-gene diagnostic testing and newborn screening were not designed with the complexity and challenges of NGS in mind. NGS requires new types of training and expertise, more accurate, comprehensive, and freely available variant databases, and algorithms to facilitate more efficient and consistent filtering of the sequence data that are generated. Clear standards for interpretation and reporting of NGS-based results—including so-called “incidental findings,” and privacy protection for patients and their sequence data also require attention. These are not areas that fit easily within existing regulatory paradigms.[10] New policy approaches will be needed to establish a system that promotes appropriate, broad access to high-quality sequence data and valid reports while encouraging innovation.[11] Yet, it remains unclear whether and to what extent regulators will, or even should, oversee this technology.

Each agency typically focuses on the issues related to their system of oversight, but we believe that a more coordinated approach to policy development is needed, since NGS technology presents several challenges that lie outside existing regulatory frameworks. Such an approach first and foremost requires a comprehensive understanding of the existing regulatory structures and legal jurisidictions and the unique challenges raised by NGS. In this special issue, we discuss four major policy domains and the issues raised by NGS technology in each. First, Gail Javitt and Katherine Carner discuss regulation of clinical NGS tests by the Center for Medicare and Medicaid Services (CMS) through its Clinical Laboratory Improvement Amendments (CLIA), state law, and the U.S. Federal Food and Drug Administration (FDA).[12] As she points out, most clinical tests using NGS are developed in-house (laboratory-developed tests), and the FDA has traditionally exercised its enforcement discretion and refrained from regulation of these laboratory-developed tests. In 2011, however, in response to several companies that were selling NGS tests directly to consumers, the FDA announced its decision to begin regulating clinical NGS. After almost 3 years of internal discussion and broad public engagement, the FDA approved the first NGS platforms in November of 2013.[13] Javitt and Carner describe the FDA’s current oversight approach and explore potential theories under which it might seek to regulate different aspects of NGS test quality.

Patricia Deverka provides a comprehensive review of the coverage and reimbursement environment confronting clinical NGS tests.[14] Effective integration of NGS technology will require utility data sufficient to satisfy the evidentiary standards of third party payers. Clinical laboratories are currently offering NGS tests in a variety of contexts,[15] but uncertainty around reimbursement policies could significantly limit its use. At least one major company has decided not to reimburse for whole exome sequencing under any circumstances, because to date it lacks proven utility and is therefore considered investigational.[16] Deverka explores the similarities and differences between NGS testing and medical diagnostic testing more broadly and discusses reimbursement issues unique to NGS.

Robert Cook-Deegan and Subhashini Chandrasekharan examine current case law related to the patenting of human genes.[17] There has been considerable legal controversy about the patentability of human genes, which creates policy uncertainty for NGS test developers and users who may be unsure whether NGS generally, or a specific test or business model, would infringe on gene patents. Cook-Deegan and Chandrasekharan provide an overview of the current legal landscape around gene patents and discuss the implications of current court cases and the outstanding intellectual property questions that remain for NGS broadly, and whole genome sequencing specifically.

Finally, Barbara Evans discusses the ways in which the NGS industry is evolving and the types of new business models that are emerging.[18] This, in turn, creates novel regulatory concerns, including economic regulatory considerations that have not been previously considered. As Evans points out, “The need for regulation tends to be framed along two dimensions: (1) privacy and ethical protections and (2) consumer health-and-safety regulation.”[19] Evans makes the case that laboratories must be guaranteed access to proprietary databases of pathogenic variants in order to interpret a genome and that not doing so will have both ethical and health consequences. She goes on to suggest judicial and legislative policy approaches based on antitrust law to address issues of access to clinical variant databases.

However, many of the critical issues in the two broad categories that Evans raises are not addressed in detail in this issue. Defining the indications for which WGS should be used; storing and integrating genomic data into medical records; clarifying issues of data ownership; maintaining patient privacy while facilitating clinical and research interpretations of genomic sequence; identifying and developing new personnel and training needs; and deciding whether the technology is best used for diagnostic purposes or health screening all demand attention. Some in the clinical sequencing and molecular laboratory industries have taken up these issues and begun to develop their own policies and practices. As policymakers and others move to assure the quality of clinical NGS it will be important to understand how the industry self-regulates itself in each of these areas.

As an example of how companies are self-regulating in this space, we examined the websites of 64 companies engaging in activities and services along the clinical NGS pipeline and analyzed their publicly available privacy policies and terms of service.[20] Of the 64 clinical NGS companies, 16 had policies available on their websites that addressed in some part the use of genetic, medical, and/or protected health-care information (PHI), while 48 did not

have a publicly available privacy policy pertaining to these types of information. Identified policy documents were analyzed for content related to measures to ensure privacy and details about use and access to this information (e.g., future uses of samples and information; risks and/or benefits to patients; ownership of information; the ability to opt out or withdraw samples and data from research studies; plans in place for bankruptcy or acquisition).

Most of the policies focused on use and access to information. Six policies addressed the future use of collected information, usually in reference to research permitted on de-identified and aggregated data. Almost two thirds (n=10) discussed third party access, including insurers collecting payment and law enforcement authorities collecting information for legal proceedings or public health concerns. Five of the companies directly discussed ownership of information, and this was often covered in conjunction with disclosure that if another company acquired the company, its aggregated genetic information would most likely be counted as an asset. Very few (n=3) discuss the risks associated with inadvertent release of personal genetic or medical information, although several did provide information about The Genetic Information Nondiscrimination Act of 2008 (GINA) (n=7) and The Health Insurance Portability and Accountability Act of 1996 (HIPAA) (n=12). Seven companies also specified that clients could withdraw their information from stored databases at anytime.

This survey of publicly available documents from 64 companies demonstrates considerable heterogeneity in the industry's approach to and transparency about privacy polices. This points to a significant policy gap in what arguably should be publicly communicated to clients of NGS services. At a minimum, all companies should have publicly available policies that clearly communicate the types of information covered in the policy, methods to ensure privacy, and details about use of and access to this information. Only 16 of the 64 identified clinical NGS companies had publicly available privacy policies, and very few provided comprehensive information, suggesting a need for greater transparency and consistency with this information.

As this special issue makes apparent, there are numerous policy needs that require the attention of stakeholder groups with diverse, strong interests in the governance of NGS. One outstanding question is how FDA's risk-based approach applies to a clinical NGS test, which could simultaneously produce a result with clear utility, a result with unintended consequences, and a result whose interpretation will change with future research. From the reimbursement perspective it is unclear how insurers will address the complexity of the information created by NGS technology and whether the lack of clinical utility data will limit or prevent coverage. And from the intellectual property perspective, while it is unlikely that patents will restrict complete genome offerings, licensing restrictions may reduce the utility of the available sequence.

With little empiric data available to answer such questions, there is a large degree of uncertainty about the nature and relative importance of these policy domains. We do not argue for regulation simply for regulation's sake alone. In fact, it can be argued that for a multi-faceted tool like NGS, with numerous clinical applications still in their infancy, data

using a variety of methods should be systematically collected and compared before setting standards and best practices. There is an immediate need, however, for critical thought about what the highest policy priorities surrounding clinical NGS are and how we may begin to address them. To develop policy priorities for clinical NGS in the absence of robust clinical data we suggest input and deliberation from a broad array of stakeholders, including NGS technology and informatics companies, clinical laboratories, health care professionals, insurers, regulatory and public health agencies, health economists, and patient groups. Expert stakeholder discussions can sharpen the focus on policy needs, identify those that appear most tractable, and flag points of agreement and disagreement between stakeholders. It is our hope that the scholarship in this issue of the Journal of Law, Medicine & Ethics will begin to generate such conversations, and provide policymakers with access to sound policy options based on wide-ranging expert opinions and rigorous research.

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18. Please add a cross-citation to Barbara Evans' article in this same issue.
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