

From Genetics to Genomics: Facing the Liability Implications in Clinical Care

by Gary Marchant, Mark Barnes, James P. Evans, Bonnie LeRoy, Susan M. Wolf

forthcoming in JOURNAL OF LAW, MEDICINE, AND ETHICS, SPECIAL ISSUE ON LAWSEQSM:
BUILDING A SOUND LEGAL FOUNDATION FOR TRANSLATING GENOMICS INTO CLINICAL
APPLICATION (2020 *in press*)

Corresponding Author: Gary Marchant

Gary Marchant, Center for Law, Science & Technology, Sandra Day O'Connor College of Law, Arizona State University, 111 E. Taylor St, Mail Code 9520, Phoenix, AZ 85004-4467. Phone: 480-965-3246 (office); 480-388-7004 (cell). Email (preferred): gary.marchant@asu.edu. Degrees: B.SC. (Biology), University of British Columbia, Vancouver, Canada, 1980; Ph.D. (genetics), University of British Columbia, Vancouver, Canada, 1986; J.D., Harvard Law School, Cambridge, MA, 1990; M.P.P., John F. Kennedy School of Government, Harvard University, Cambridge, MA, 1990. Bio: Gary Marchant is Regents' Professor, Lincoln Professor of Emerging Technologies, Law & Ethics, and Faculty Director of the Center for Law, Science & Innovation at ASU. He researches, teaches and speaks about governance of a variety of emerging technologies including genomics, biotechnology, neuroscience, nanotechnology and artificial intelligence. Prior to starting at ASU in 1999, he was a partner in the Washington, D.C. office of Kirkland & Ellis.

Mark Barnes, Ropes & Gray LLP, 800 Boylston St., Prudential Tower, Boston, Massachusetts, 02199. Phone: 917-597-5257 (cell); 617-951-7827 (office); email (preferred): mark.barnes@ropesgray.com. Degrees: JD, Yale Law School, New Haven, Connecticut; LLM, Columbia Law School, New York, New York. Bio: Mark Barnes is a partner in the life sciences practice at Ropes & Gray LLP; teaches health care law and the law of biomedical research at Yale Law School; and is founder and co-director of the Multi-Regional Clinical Trials Center (MRCT Center) of Harvard University and Brigham and Women's Hospital. He has served in senior appointed roles in the New York City and State departments of health; founded and directed Harvard's PEPFAR-funded HIV treatment programs in Nigeria, Botswana, and Tanzania; and was the chief administrative officer of St. Jude Children's Research Hospital.

James P. Evans,. Phone: 919-843-1517 (office); 919-619-6248 (cell). Email (preferred): jamesphilpevans@gmail.com. Degrees: M.D. and Ph.D. from University of Kansas Medical School, Kansas City, Kansas. Bio: James P. Evans, MD, PhD, is a Medical Geneticist and Internist who is currently retired, but pursued a long-standing interest in genomics and its broad social implications. He is Professor Emeritus, University of North Carolina at Chapel Hill, Department of Genetics.

Bonnie LeRoy, M.S., L.G.C., is Professor and Director of the Graduate Program in Genetic Counseling in the Department of Genetics, Cell Biology and Development at the University of Minnesota, 321 Church Street, 6-160 Jackson Hall, Minneapolis, MN 55455. Phone: 612-624-7193 (office). Email (preferred): leroy001@umn.edu. Degrees: MS in Human Genetics (Genetic Counseling Program at Sarah Lawrence College, NY). Bio: Bonnie LeRoy is a licensed genetic counselor with over 20 years of clinical experience. She developed and now directs the Graduate

Program in Genetic Counseling at the University of Minnesota. She is a past president of the National Society of Genetic Counselors, the American Board of Genetic Counseling and the Association of Genetic Counseling Program Directors.

Susan M. Wolf, J.D., Law School, Medical School, and Consortium on Law and Values in Health, Environment & the Life Sciences, University of Minnesota, 101 Pleasant Street SE, Minneapolis, MN 55455. Phone: 612-301-3905 (office). Email (preferred): swolf@umn.edu. Degrees: J.D. (Yale Law School). Bio: Susan M. Wolf, JD, is McKnight Presidential Professor of Law, Medicine & Public Policy; Faegre Baker Daniels Professor of Law; Professor of Medicine; and Chair of the Consortium on Law and Value in Health, Environment & the Life Sciences at the University of Minnesota. She is a Principal Investigator on the LawSeqSM project funded by NIH.

Acknowledgment: Preparation of this article was funded by National Institutes of Health (NIH) National Human Genome Research Institute (NHGRI) and National Cancer Institute (NCI) grant #1R01HG008605 on “LawSeqSM: Building a Sound Legal Foundation for Translating Genomics into Clinical Application.” (Susan M. Wolf, Ellen Wright Clayton, Frances Lawrenz, Principal Investigators). Thanks to Susan Berry, Wylie Burke, Barbara Evans, Hank Greely, Gail Javitt, Michelle Penny, Pilar Osorio, Mark Rothstein, and Leslie Wolf for helpful comments and to Lauren Clatch, Kate Hanson, Daniel Moss, and Jon Watkins for excellent research assistance.

Abstract: Health care is transitioning from genetics to genomics, in which single-gene testing for diagnosis is being replaced by multi-gene panels, genome-wide sequencing, and other multi-genic tests for disease diagnosis, prediction, prognosis, and treatment. This health care transition is spurring a new set of increased or novel liability risks for health care providers and test laboratories. This article describes this transition in both medical care and liability, and addresses 11 areas of potential increased or novel liability risk, offering recommendations to both health care and legal actors to address and manage those liability risks.

From Genetics to Genomics: Facing the Liability Implications in Clinical Care

Introduction

The first decade of the 21st century witnessed a transition from genetic testing to genomic testing and sequencing in medical practice. Genetic testing (usually of a single gene in a patient) became well established in the second half of the 20th century, leading to enactment of state and federal laws in the United States regulating such testing and the adjudication of litigated cases on issues such as malpractice and negligence in the performance, interpretation, and communication of genetic tests. The late 20th century also saw the emergence of population-wide newborn screening for particular genetic diseases such as phenylketonuria (PKU), with accompanying developments in public health law. However, the completion of a draft sequence of the human genome in 2001 and the emergence and implementation of technologies to perform genomic assessment of patients by testing larger panels of genes, performing microarrays, conducting exome sequencing, and even conducting whole genome sequencing, marked the transition from genetics to genomics in medical care, a transition that is still under way.

The emergence of genomics poses challenges to the established law regarding the practice of clinical genetics. The goal of this paper is to map those challenges in the domain of legal liability and to suggest how state and federal statutes, regulations, and common law should develop to meet the challenges of genomics and to support successful implementation of genomics in clinical care. This paper is part of a larger project funded by the National Institutes of Health (NIH) on “LawSeqSM: Building a Sound Legal Foundation for Translating Genomics into Clinical Application.”¹ While this paper focuses on the question of how the law of liability should adjust to meet the challenge of genomics, other papers from this project focus on how other aspects of the law should change, specifically the law governing the quality of genomic

analysis and interpretation, the law addressing the privacy of genomic data and who has access to results, and the law addressing the boundaries between research, clinical care, public health screening, and direct-to-consumer (DTC) genomics.

This paper concentrates on the potential liability of clinicians, laboratories, and health care institutions regarding genomic testing. Other entities in the genomics landscape, such as companies developing and marketing genomic panels and sequencing platforms as well as sequencing instruments and interpretive algorithms also raise important legal questions, including the reliability of those panels and interpretations, FDA status of interpretive algorithms, and contract and commercial liability, but are generally beyond the scope of this paper. This paper focuses primarily on liability in the context of clinical genomics but also includes translational genomics research that has a clear clinical dimension. Examples of such research are studies involving affected patients, which produce results that are incorporated into those patients' medical records, or used for diagnosis or treatment of those patients.²

It is important to note that the law of genetics and genomics builds on and incorporates more general legal principles and precedents. This includes, but is not limited to, state law on liability for medical malpractice and negligence; the law governing informed consent; and principles of vicarious, institutional, and organizational liability that can render health care organizations liable. This paper is not arguing for a separate body of law to govern genomics. However, it addresses both state and federal law that include genetics-specific statutes and case law involving genetics and genomics,³ as well as more generally applicable law. Thus, the paper analyzes new challenges posed by genomics, the adequacy of current law and precedent bearing on liability associated with genomics, and the developments and (in some instances) changes in law required to support successful integration of genomics into clinical care.

The article begins in Part I by elaborating on the current transition from genetics to the genomics. Part II then explores what this transition means for the responsibilities of the various actors in the clinical ecosystem, including clinicians (both generalists and genetic specialists), testing labs, and health care systems and institutions. Part III discusses the role and challenges the liability system will experience in dealing with a rapidly evolving medical field such as clinical genomics. Finally, Part IV describes eleven types of medical liability that are likely to be expanded, modified, or created by clinical genomics. For each of these eleven types of liability claims, we provide specific recommendations for health care actors and institutions and for legal actors and the legal system to manage these liability risks.

I. The Transition from Genetics to Genomics

The transition under way from genetics to genomics forms the background for analysis of the legal challenges posed by genomics. Genetics focuses on single gene mutations, whereas genomics involves multi-gene tests, usually on a large scale. The frequency of genomic testing has increased in contexts such as cancer risk prediction and treatment, diagnosis of children with puzzling neurodevelopmental conditions, and assessment of what pharmaceuticals should be prescribed for some patients and in what doses. Some clinics and DTC companies are also offering genomic assessment to healthy individuals to assess health risks, including genome-scale sequencing (GSS).⁴ A number of commentators have anticipated the possibility of wider future use of genomics as part of prenatal testing, newborn screening, and general clinical practice.⁵

The emergence of genomic testing has partly been driven by the limitations of genetic testing. Genetic testing primarily consists of testing for variants in specific genes that indicate significant risk for medical conditions such as breast and colon cancer, as well as single-gene

Mendelian diseases such as cystic fibrosis, Huntington’s Disease, sickle cell disease, and Tay-Sachs syndrome. However, there are relatively few gene variants common in the population that single-handedly confer a major risk of disease. Other than the Mendelian genetic disease genes and a handful of highly-expressed cancer risk genes such as *BRCA1*, *BRCA2*, and *APC* (adenomatous polyposis coli), few single-gene tests have demonstrated clinical utility.⁶ This limitation largely explains the evolution of gene science and medicine from single-gene tests to more inclusive genome-wide assays such as gene panels and exome and genome sequencing that assess many or all of a patient’s genetic variants. These “genomic” (as distinguished from single-gene “genetic” tests) will sometimes identify a single gene variant that may be clinically significant but may also reveal multiple variants with combined clinical implications, and may aggregate the effect of multiple mutations using an algorithm to provide an overall risk or prognosis score.

The shift from genetic to genomic testing presents new opportunities and complexities. For example, in addition to testing genotypes, genomic testing also enables a broader range of tests, such as mutation assays of tumors or pathogens that are unique to the patient, and gene expression analysis that can help to understand the disease process of a specific patient. Thus, while single-gene genetic testing has primarily been used for risk prediction, disease diagnosis, and assessing carrier status, genomic analysis is enabling additional functions, such as disease prognosis and treatment selection.

The greater applications and complexities of genomic testing relative to genetic testing will undoubtedly impose greater responsibilities on health care providers and institutions. This is likely to lead to new medical malpractice and other liability claims and exposure. The next section explores the expanded responsibilities of health care providers and institutions in the new

era of genomic medicine. Then, we briefly summarize the challenges of keeping both medical and legal practice current with the rapidly developing science of genomics. This leads to our analysis of 11 potential legal claims that may eventuate. We provide recommendations on how clinical providers and institutions should respond to these new issues and what legal developments and changes are needed to support successful integration of genomics into clinical care.

II. New Responsibilities for Health Care Professionals & Institutions

The advent of tools to interrogate the human genome has significant implications for medical practice and will affect a variety of health care professionals, entailing new duties and challenges. Most immediately, those affected will be genetics specialists, such as medical geneticists and genetic counselors, the clinicians already grappling with how best to employ complex new genomic tools including gene panel assays, GSS, and a variety of modalities that are not sequencing-based, such as microarray analysis of gene expression. However, as other medical specialties such as oncology increasingly use genetic and genomic testing in their practices, emerging challenges and responsibilities will fall on a broader array of practitioners, including clinicians who have not been schooled in navigating the complexities of genomic analysis. The demands created by this new class of medical tests will also extend beyond practitioners to those who direct and operate clinical laboratories. Finally, the rise of precision medicine, involving genomic analyses of the general population for purposes of screening or to direct “personalized” treatments for a variety of ailments, will involve still more clinicians, requiring that they be knowledgeable about personalized medicine techniques and their ethical and legal responsibilities in this domain.⁷

A major challenge already confronting those who employ sequencing as a diagnostic test is determining the appropriate breadth of testing to implement. For example, in the realm of hereditary cancer predisposition testing, there are many offerings from commercial laboratories that allow sequencing of a panel of genes, yet the size of those panels varies from 4 or 5 genes to over 80. There is no consensus and no formal policy in either genetics or oncology to guide the choice of panel size so that the scope of testing is appropriate in a given clinical situation. Rather, the onus of that decision falls on the practitioner, who at present is typically the medical oncologist, genetic counselor, or the medical geneticist, perhaps in consultation with the patient's health insurer.⁸ These specialists will be increasingly at risk for accusations of inappropriate or inadequate testing.

Claims of inappropriate scope of testing might not be confined to the scenario in which a practitioner is accused of not testing broadly enough (though this is perhaps the most likely claim). They could also include claims that testing that is too broad and encompasses too many genes, leading to spurious, irrelevant findings that then lead to what might be considered unnecessary "downstream" medical care of a patient and/or family members, such as risk-reducing surgery or surveillance.⁹ This challenge falls most immediately on genetics professionals and medical oncologists, but as testing broadens could conceivably be a threat to generalists as well. Finally, it is possible that the laboratories might be at risk for including genes on offered panels despite insufficient information about those genes and their associated health risks.

The field of genetics previously faced a somewhat similar (albeit more limited) challenge when genetic testing for cystic fibrosis became possible in the 1990s. At that time there was concern that laboratories were offering testing that was too broad and that this would produce an

“arms race,” with labs competing based solely on an inappropriate metric of “number of variants” tested.¹⁰ This could have had adverse consequences for the liability of practitioners, but the threat was largely averted by the formulation of guidelines by the American College of Medical Genetics and Genomics (ACMG), which recommended a “standard panel” of variants to test that was subsequently widely adopted, thus providing needed guidance for the field.¹¹

The interpretation of genomic sequencing (and microarray) results represents one of the most significant challenges to the appropriate implementation of genomics in medicine today.¹² The ability to accurately interpret whether any given genomic variant is actually related to human disease is often difficult (depending on the nature of the disease and the patient’s family history) and usually relies on a suite of imperfect measures. These include *in silico* prediction models and functional assays that typically depend upon biochemical knowledge that is still lacking for most genes.

One of the most powerful means by which genetics professionals seek to ascertain the meaning and clinical significance (or lack thereof) of a given variant found in testing a patient is by comparing the variant to data from a variety of existing databases.¹³ If, for example, a variant found in an individual is relatively common in the general population, then it is unlikely that the variant is disease-causing (otherwise a corresponding percentage of the general population would manifest the disease in question). The specific cut-off for what constitutes “too common to be pathogenic” varies for different genes and is the subject of debate.¹⁴ Further complicating the statistical inference of pathogenicity from population data is the fact that some human genes tolerate variation without adverse impact on function, while other genes are easily disrupted by what would be considered minor variation in another gene.

Finally, the ancestral background of an individual can matter greatly when interpreting a variant using a database. Different populations demonstrate widely variable genomic architecture depending on their ancestry. For example, populations that have been reproductively isolated for many generations (due to either geographical barriers or cultural barriers to reproducing with those outside the group) will have different levels of variation in particular genes. Thus, when interpreting a person's variant using a database, it is crucial that the database includes many individuals from the same ancestral background as that person. All of these considerations make it imperative that large, diverse, and well-annotated databases be created and maintained. Such efforts are under way in the genomics community but remain inadequate at present, complicating the interpretation of genomic variants, especially for those individuals who are of non-Western European ancestry.¹⁵ Failure to consult relevant databases when adjudicating variants could clearly be a cause for misinterpretation of variants and thus, legal claims.

The stakes are high when assigning pathogenicity to a variant. When the interpretation is wrong, producing a false positive where the patient is erroneously informed their variant is pathogenic, the patient and family members may be subjected to modalities ranging from surgery to life-long surveillance. Alternatively, where there is a false negative, those who would actually benefit from such interventions fail to receive them. Given the combination of high stakes and limited interpretive capacity at present, there could be liability for both clinicians and laboratorians as a consequence of misinterpretation of variants. The professional genetics community has begun to take action to support quality and mitigate liability by formulating guidelines for variant adjudication.¹⁶ However, such adjudication remains an error-prone endeavor and one that varies considerably by lab, virtually guaranteeing that legal cases based on interpretative issues will arise.¹⁷ This particular liability threat will likely fall on both clinical

laboratories and clinicians, and will spread to specialties such as cardiology, ophthalmology, and oncology as those fields embrace such testing.

Given the rapid pace of discovery in genomics, as well as the still highly-imperfect methods available for interpreting genomic variants, there will naturally be some legitimate differences among quality laboratories with regard to variant interpretation. For the time being, the most important indicator of whether appropriate care has occurred will likely be whether the laboratory followed professional guidelines for variant interpretation as promulgated by professional societies such as the ACMG.¹⁸ Also of relevance will be whether the professionals interpreting variants used appropriate databases¹⁹ for examining the population prevalence of variants. Even with proper use of such tools, some discrepancy in variant interpretation is to be expected. However, at a minimum, those professionals interpreting variants will be expected to use such resources, or malpractice claims could be legitimately made.

The reinterpretation of the medical significance of genomic variants over time as knowledge advances is an emerging liability threat whose scope has little precedent in other fields of medicine. This threat is especially acute in genomics due to (1) the rapid pace of genomic innovation and implementation, (2) the potential significance to health of genomic findings, and (3) the fact that the genomic sequence itself may remain stable without need to re-sequence, while its interpretation changes significantly.²⁰ The field is moving at such a rapid pace that “calling” a given variant as pathogenic or not shifts over time,²¹ and what may have been seen as an innocuous variant two years ago is now considered pathogenic (or vice versa). There exist no clear standards that tell a laboratory or clinician what their duty is, if any, with regard to re-examination of test results generated one, two, or five years ago. Even if genomic results are systematically reexamined at given time intervals, other questions remain with

liability implications, such as who will pay for such re-evaluation and who (*e.g.*, the clinician or the laboratory), if anyone, ought to be responsible for re-contacting the patient.

Other changes will be triggered by the widespread clinical uptake of genomics. For example, some envision that pharmacogenomic (PGx) testing will be routinely used in the future to guide the prescription of many drugs with the intent of tailoring individual drug choice and dosage to the individual patient, using their genomic information.²² If this vision becomes reality, liability could emerge based upon perceived harm from lack of application, misapplication, or misinterpretation of PGx information that resulted in the prescription of the wrong agent, administration of the wrong dose, or the failure to prescribe an appropriate and life-saving drug in a given clinical situation.

Another possible legal threat to those implementing genomic medicine derives from choices about what portions of a patient's genetic sequence to analyze. At present some commentators urge sequencing the genome of individuals as a "lifelong resource."²³ Given how much of the genome is still not understood, this is often coupled with a proposed strategy to limit analysis and report only on those genes that are well understood. However, once a genome sequence resides in a computer, whether it has been analyzed or not, one can envision a claim that the laboratory and clinician are liable for what they chose **not** to analyze and report. This argument is akin to some objections that have been raised in the debates over reporting of secondary findings.²⁴ Such potential legal liability may be an argument for clinicians and laboratories to routinely focus on the analysis of genes that are well understood and to limit GSS to those situations in which casting a broad net is necessary to make a diagnosis. Such a parsimonious approach to testing accords with what has become an axiom of clinical medicine:

to seek only information that clinicians truly understand and that will guide their medical actions in the current episode of care.

In addition to the liability of laboratorians and clinicians, health care systems and institutions could be found liable under theories of organizational and institutional liability²⁵ if they have failed to provide adequate resources for providers to function in the rapidly changing context of genomic medicine. For example, current electronic health record (EHR) systems are generally poorly equipped to contain, categorize, and display the results of genetic testing, much less genomic testing. As the field moves increasingly to the sequencing of large gene panels and even entire genomes, institutions will need to grapple with how to store such information and how to present it to clinicians and laboratorians who query the medical record of patients in search of genomic information relevant to their patients' care. Moreover, simply storing and presenting such information (as difficult as that may be) is not sufficient. The amount of data in a given genomic analysis is immense and sorting through those data to identify those small pieces that may be of importance to a patient's care is daunting. This reality, coupled with the fact that providers who are not well trained in genomics may increasingly be accessing and using such information, leads to the need for clinical decision support (CDS) systems that proactively alert providers to important information.²⁶ For example, when pharmacogenomics information is relevant to prescribing medications for a patient, CDS systems may need to be in place so that an alert is generated in "real time" notifying the provider that potentially critical PGx information needs to be considered. If such systems come into use at major health systems, then other institutions' failure to build and maintain such systems as part of patient safety efforts could ground liability claims.

Finally, many envision the screening of entire populations for genomic risk of preventable disease as part of the future of precision medicine.²⁷ For example, there already exist commercial offerings to screen individuals in the general population for *BRCA1/2* mutations²⁸ and other high-risk genetic syndromes so as to allow implementation of preventive modalities such as risk-reducing bilateral mastectomy, bilateral salpingo-oophorectomy, or ongoing surveillance. Likewise, efforts are under way to develop expanded panels that would scrutinize genes involved in familial hypercholesterolemia and other conditions in which early treatment could be of benefit. Indeed, there are prominent appeals for GSS of the general population.²⁹ Such expansion of genomic analysis into the general population will increase the threat of liability, as applying tests in a low-risk (*i.e.*, general) population will uncover many more false positives than testing affected individuals in the clinical setting.³⁰ The legal threats thus increase as genomic testing is applied to the general population.

Ultimately, managing the emerging liability threats will require both advances in knowledge (such as the ability to interpret genomic variants properly) and the formulation of evidence-based policies for scope of testing, interpretation of results, and reinterpretation of genomic variants. Yet such advances will take many years. In the meantime, the courts are likely to see a growing number of lawsuits alleging harm from the application, failure to apply, and misapplication of genomic medicine.

III. The Role of Liability Litigation in an Era of Dynamic Technology Change

Recommending how to navigate the liability issues raised by genomics requires considering the intended purposes of medical liability, especially in the context of rapidly evolving medical technology such as genomics. Medical malpractice liability has two intended purposes. First, it is intended to deter health care providers from engaging in substandard and

unreasonable health care practices, while incentivizing appropriate uptake of improved medical technologies and practices. Second, medical malpractice liability is intended to compensate those patients who are injured by negligent medical care.

Notwithstanding general acceptance of these intended purposes of medical malpractice liability, empirical analyses have fueled serious criticism of the medical malpractice system in practice. The medical malpractice system fails to compensate the majority of patients injured by negligent health care.³¹ Moreover, the compensation paid in damages is poorly correlated with the harm caused by malpractice.³² The threat of liability, especially when the expectations of medical malpractice doctrine are unclear, may lead providers to protect themselves from liability by engaging in defensive medicine, which can subject patients to unnecessary procedures and treatments.³³

Medical malpractice liability is particularly challenged by fast-moving technologies, such as genomics. Empirical studies have demonstrated that new technologies are one of the most powerful drivers of malpractice liability.³⁴ This is because physicians and other providers are often unfamiliar with the new technologies and thus make more frequent mistakes, plus there is differential uptake of the technologies, which can lead to disputes over whether the standard of care at a given time requires use of the new technology.³⁵

When a technology is evolving as fast as genomics, providers' skill set and knowledge base can be quickly outdated, resulting in clinicians practicing with inadequate capabilities. This is already happening with genetics and now genomics – most physicians practicing today received little genetics training in medical school, and so are being left behind as genetics and genomics assume increasing importance in health care delivery.³⁶ Physicians may be shielded from liability by the traditional custom-based standard of care, in which physicians are held to be

complying with the standard of care if they are acting consistently with what other similar providers (such as other physicians in the same specialty) would do. This protection will be most effective in jurisdictions applying a local, rather than a national, standard of care.³⁷ However, this liability life jacket is gradually deflating, as an increasing number of states are moving to a more objective, reasonableness-based standard of care rather than one based on custom, and a growing number are embracing a national standard of care.³⁸

The clinical and knowledge support systems that clinicians use to stay current may lag in a time of rapid technology change. For example, professional societies and others promulgating clinical guidelines, which provide guidance on best medical practice in many different fields of medicine, may struggle to stay current with new genomic science. These guidelines can take months if not years to be developed and approved, but may be obsolete by the time they are published because of the dynamic changes in genomic science. The inability of clinical guidelines to keep pace with rapidly evolving genomic science puts clinicians in jeopardy. The problem is exacerbated when other practice aids such as CDS systems also fail to keep pace. Yet, when dealing with such a rapidly evolving area of clinical medicine that is new to many practitioners, up-to-date guidelines will be critical to support sound practice and to help the legal system evaluate clinical decisions and actions.³⁹

One step toward greater clarity on expectations would be to see jurisdictions that still use a local standard of care move toward a national standard.⁴⁰ Good clinical practice related to genomics should be consistent across the country, and so the standard of care should not vary from state to state. In addition, patients may get their care in multiple states, even in a single episode of care.

Genomics is provoking not only changes in clinician practice, but also changes in what is expected of health care institutions. Modern health care, driven by big data and genomics, is becoming much more of a systems-based practice. A patient's care may involve several providers, including the primary care physician, one or more specialists, and perhaps a genetic counselor. Laboratories that analyze and communicate genetic and genomic results from a patient's samples play an increasingly central role in modern health care. Finally, health care institution must provide the necessary equipment, data sources, and practice aids to support modern molecular health care. Along with these greater responsibilities for labs and institutions come new liability risks. It is not only the knowledge and practice of the individual physician that is changing, but also the evolution and coordination of an entire health care ecosystem around each patient, creating new liability risks.

In the next section, we identify 11 key claims that lawyers may consider bringing as patients experience the transition to genomic medicine. These claims raise overlapping issues, but parsing those claims helps identify the liability challenges raised by new and expanded responsibilities for health care providers, laboratories, and health care institutions. After analyzing changing circumstances and responsibilities, we recommend how health care actors and institutions should cope with these responsibilities to control their liability exposure. We then address what legal development and changes are needed to support successful implementation of genomic medicine in clinical care. As noted in the Introduction, in some cases the legal issues are comparable with those presented in other types of diagnostic malpractice cases, with perhaps just minor perturbations needed to address the unique aspects of genomics, whereas in other cases the legal issues are more novel. In addressing all these genomic liability issues, we strive to balance the important role of liability in encouraging uptake of new and

better technologies to incentivize good care for patients, against the potential downside of liability in discouraging innovation and pushing providers to undertake defensive medicine and order unnecessary tests that risk imposing unnecessary costs and detracting from patient well-being.

IV. Potential Liability Claims

This Part analyzes 11 potential claims of liability that may be advanced as genomics is integrated into clinical care. **Table 1** shows the roster of claims analyzed below. Though these claims may raise overlapping issues, we analyze them individually, as attorneys bringing suit may distinguish among them in deciding what specific legal claims to bring. Yet, it is worth noting that a pervasive source of uncertainty and potential liability for health care providers and institutions is the need for better evidence and guidelines to support sound practice in this time of evolving genomic science.⁴¹ As elaborated in other scholarship from the LawSeqSM project, there is a need for provisional advice to clinicians that recognizes the uncertainties in determining risks and benefits of genomic testing. This provisional advice would be subject to regular updating in response to evolving evidence and would have several components. First, it would address credentialing, by addressing who within health care systems should be able to order different types of genomic tests. Second, there should be guidelines, perhaps more transient and less developed than traditional clinical guidelines, which are developed cooperatively by all relevant stakeholders, providing provisional recommendations on genomic testing at a time of incomplete and uncertain evidence. Finally, there should be opportunities and encouragement for health care systems and laboratories to contribute to evidence generation. These goals and principles help guide the recommendations provided for the 11 specific legal issues discussed below.

Table 1. Potential liability claims with the integration of genomics into clinical care.

1	Failure to Test
2	Over-testing and Incomplete Information
3	Choice of Specific Panels or Tests
4	Inappropriate Use of or Reliance on a Test
5	Incorrect Variant Calls
6	Failure to Accurately Communicate Results to Patients
7	Failure to Communicate Results & Share Data with Clinicians within a Health Care System
8	Failure to Analyze and Offer Incidental Findings or Secondary Results
9	Failure to Update and Recontact
10	Failure to Warn Family Members
11	Error and Failures in Direct-to-Consumer (DTC) Testing

1. Failure to Test

A. Analysis

Failure to test in the genomics era will likely mirror what we already see with genetic testing in medicine. Mostly, failure to test will be the result of the provider's failure to recognize a risk in an individual. In many cases, family history is the known indicator that there may be an inherited risk for specific individuals, even if this family history does not follow a Mendelian pattern. However, in the case of many conditions (most of them rare) finding the gene or genes involved is difficult and in the absence of a clear family history through multiple generations, risk to individuals is often missed. Of course, such a failure will result in liability only if it fails to meet the standard of care – not all adverse outcomes or wrong choices are the result of negligence.

A classic example of failure to test involves the belief on the part of the patient, and often the clinician, that pathogenic variants in breast cancer genes cannot be passed down through a male in the family. A clinician may also fail to consider genomic testing for an individual who is the only person affected in a family where everyone else is healthy. It is not uncommon for clinicians to fail to consider that a single affected person might have a genetic condition and

therefore fail to test that patient. This could result in failure to make a diagnosis for the affected individual and failure to identify others in the family (including potentially future children) who are also at risk.

There is a lack of guidelines for when to use genomic testing and how best to interpret and manage results. Genomic testing is not always the best choice, interpreting the results is often confusing, and the diagnostic yield is variable depending upon the indications for testing and laboratory that completed the testing. How to follow up on a test that failed to yield a diagnosis may not be clear and the fact that the results may look different when coming from different laboratories complicates the decision to test. Lastly, the literature continues to show that health care providers not trained in genetics lack the knowledge and skills needed to assess risk.⁴²

B. Recommendations

Recommendations for Health Care Actors or Institutions:

- In order to ensure quality care and to prevent liability, health care organizations should determine who within their organization is qualified to order genomic testing. Appropriate training is necessary to understand the type of genomic test to order (e.g., gene panel vs GSS), communicate the results to patients, and incorporate the results into patient care. If a clinician does not have relevant training, the clinician should refer the patient or obtain a clinical consult with a provider (physician or genetic counselor) who does have the requisite training.
- Professional societies should give higher priority to issuing clinical practice guidelines, guidance, and/or recommendations to assist clinicians in making genomic testing decisions. In the absence of updated clinical guidelines, health care organizations and professional societies should provide guidance on appropriate use of genomic testing that incorporate the perspective of all relevant stakeholders.
- Health care institutions have responsibilities to offer or facilitate access to (1) continuing education on these topics, (2) genetic and genomic laboratory capacity and professionals, and (3) clinical processes (including clinical decision support (CDS) and adequate electronic health record (EHR) representation of genetic and genomic tests results) to support good clinical practice.

- Genetic counselors have a crucial role to play in clinician, patient, and family education and counseling.
- When genomic testing is indicated, the clinician should discuss this with the patient and offer a referral if the patient's health care institution does not offer genomic tests.

Recommendations for Legal Development & Change:

- When clinicians are accused of negligence or malpractice for failure to order genomic testing, attorneys and courts should access and consider clinical practice guidelines (CPGs), other recommendations and resources from professional societies, and the relevant medical literature, which may be germane to but not determinative of the standard of care.
- Because genomics is a developing field, doctrines recognizing multiple schools of professional thought may be relevant to adjudication. Highly competent genomics professionals may disagree on the question of when testing is indicated, the appropriate type of testing, and the interpretation of results.
- In some domains of genomics, standards are already clear on when testing is indicated. When that is not the case, it would be helpful to have guidance stating current uncertainties and options in order to make clear that providers must make professional judgments in light of uncertain evidence. In such situations of uncertainty, health care institutions and providers can protect themselves from liability by documenting that they had in place a reasonable process for deciding whether and what kind of genomic testing is warranted in light of the uncertain evidence, and that they explained the available choices to the patient.

2. Over-Testing and Incomplete Information

A. Analysis

When considering testing, it often seems that more is better. The more data that can be gleaned from genomic testing, the greater the likelihood of an answer for the patient and the family, or so one would think. However, in the current state of genomic testing, this is often not the case. Whole genome and exome testing can lead to information that is not wanted, does not aid the diagnosis or management of the case, and cannot be interpreted. In some cases, the results of GSS can give results that can be misinterpreted or over-interpreted, which can potentially harm the patient by encouraging additional testing and even medical procedures that may not be warranted and might even be dangerous.⁴³

An exome as opposed to a targeted test does not have the same coverage of potentially critical genomic regions. Exome testing could miss the critical area that might lead to a diagnosis. Exome testing sequences the coding regions of the genome, covering about one to two percent of the genome.⁴⁴ It is designed to provide a certain depth of coverage to ensure accuracy.⁴⁵ However, this is less than the coverage that would occur when testing for a specific gene. The increased potential for error in exome sequencing could result in failure to identify an area critical to diagnosis. In contrast, a targeted panel is more comparable to a single gene test. It is more specific, and the coverage is higher. A significant risk to clinicians is believing that whole genome or exome sequencing “looked at everything” and thus assuming that if nothing was found, then there is no genetic basis for the phenotype. This assumption may be incorrect.

B. Recommendations

Recommendations for Health Care Actors or Institutions:

- Clinicians should determine the scope of testing to order in a particular case by considering clinical practice guidelines (if any), other recommendations from professional societies and the scientific literature, and consultation with their testing laboratory.
- Clinicians ordering genomic analyses should be familiar with the testing options, their characteristics, and the trade-offs among them, in order to make a well-grounded determination of which tests to order.
- The scope of testing or sequencing ordered should optimize clinical utility (*e.g.*, diagnostic yield), while minimizing results that are not relevant to the indication for testing. Parsimony in testing can be beneficial to prevent false positives and results that may be misinterpreted or over-interpreted.
- If clinicians, their laboratory, and/or their health care institution consider enlarging the scope of testing to include a set of secondary or incidental findings (*e.g.*, those recommended by ACMG⁴⁶), this should be discussed with the patient as part of the informed consent process before testing. The patient should have the option of refusing some or all of these added analyses.

Recommendations for Legal Development & Change:

- Courts should recognize the over-testing (*i.e.*, ordering tests not called for by the patient’s symptoms, conditions, or history) can produce false positive results that can harm patients by requiring additional follow-up procedures that may prove iatrogenic.
- Most genetic malpractice cases to date involve a provider’s failure to test for a particular genetic condition or variant. However, due to the uncertain nature and large volume of data generated by genomic tests such as GSS, it may be negligent to recommend over-testing in some situations.

3. Choice of Specific Panels or Tests

A. Analysis

Genomics creates an additional level of complexity compared to genetics in requiring that a physician or other health care provider choose which specific test(s) to order for a particular patient. In the past, the provider would assess whether the patient had a predisposition or illness that might be informed by genetic testing, and then would recommend a genetic test for that condition. Typically, this would involve testing a single gene. For example, a physician or genetic counselor may recommend carrier testing of a prospective parent for a mutation in the *CFTR* gene associated with cystic fibrosis or testing for mutations in the *APC* gene for a member of a family with a history of familial adenomatous polyposis (FAP). While different test manufacturers or labs may offer their own test for that particular gene, perhaps with different variants assayed by the test, there is usually no issue as to what gene to test for, only which test might include the most robust and relevant set of variants for that single gene.

An important difference in the genomic era is the shift from testing of a single gene to testing panels of genes or even exome or genome sequencing.⁴⁷ With the realization that the risk of almost all diseases (at least all non-Mendelian diseases) is affected by many genes, a patient believed to be at risk for a specific disease can best be assessed with a gene panel that packages into one test platform assays for a number of different genes that may affect the risk of that particular disease. Disease risk may be determined by “hits” within specific genes included in the

panel, or by an algorithmic score that takes into account the testing results for all the genes in the panel. Test manufacturers and testing laboratories are increasingly using gene panels to test patients for a specific disease risk such as GeneDx's panel for epilepsy, which currently includes over 200 genes associated with multiple disorders where epilepsy is one symptom. As more genes are found to be associated with epilepsy, companies can add those genes to the panels. Another example is the CustomNext-Cardio[®] panel by Ambry Genetics.⁴⁸ In this case, the panel allows the clinician to choose a group of disorders from a list of potential diagnoses such as lipid disorders, aortic aneurysms, cardiomyopathies, etc., to test for pathogenic variants associated with these diagnoses

The novel liability risk associated with gene panels is that the health care provider may face liability if he or she recommends an inferior panel for an individual patient, and it turns out that the testing misses an important variant that would have been detected if a better panel had been recommended. Bringing a lawsuit for such a faulty recommendation would present some practical proof problems. The plaintiff (or their attorney) would need to discover that another gene panel was available and would be covered by the patient's insurer, and that the alternative panel had genes in it that would have been more informative and affected the outcome if the physician had recommended that panel instead. Often potential plaintiffs and their attorneys will not be aware of the potential consequences of testing with a different gene panel, but if this is discovered by a plaintiff's expert, for example, who finds that the plaintiff was adversely affected by the failure to detect a mutation that was included in an alternative panel, this could be the basis of a potential medical malpractice claim. Specifically, the plaintiff would need to show that (1) an alternative gene panel was available and would have been utilized by the patient, (2) that this alternative panel would have disclosed information that would have resulted in a better

outcome for the plaintiff, and (3) the physician should have had some reason to suspect that the alternative gene panel would have produced a superior result. This opens an additional potential claim for a plaintiff alleging genomic malpractice.

The choice of an appropriate panel may also implicate the lab or institution.

Traditionally, the clinician orders a test (often designated by the patient's health insurer), and the lab performs that test and reports results back to physician. As we move into the genomic era, however, the relationship between the clinician and test lab is becoming more complex and variable. In some cases, the lab may provide feedback or recommendations on the test panel the physician ordered, sometimes suggesting a different panel or perhaps adding in a few additional genes based on the individual patient. As labs perform this advisory role, physicians may actively consult the lab for recommendations on what gene panel to order. The choice of gene panel will be influenced by a number of factors in addition to the genes present on each panel, including each panel's coverage of relevant gene variants, the rate at which they detect specific variants, their cost and available insurance coverage, and how good they are at interpreting variants of unknown significance (VUSs). In other institutions, the labs play an even more active role, and are in active partnership with clinicians in the patients' care. In still other contexts, the lab has developed its own test panel, and gives the physician the binary choice of whether to order that test panel or not. Depending on how active a role the lab had in selecting the specific test panel, the lab may assume some or all liability for an erroneous choice of a test panel. The health care institution may also bear responsibility if it creates a process or committee that reviews or recommends test orders.

B. Recommendations

Recommendations for Health Care Actors or Institutions:

- Given the uncertainty and rapid evolution of genomic tests, greater transparency on the evidentiary basis and performance of available genomic tests would be highly beneficial, including those commercially available.
- The government or professional societies should publish and regularly update a listing and comparison of test panels and sequencing approaches that can be used to evaluate a particular genetic risk.
- Professional societies should whenever feasible identify specific tests or test parameters that are recommended for patients with specific risk profiles, and physician compliance with those recommendations should be evidence of reasonable care. These recommendations need to be updated on a regular basis as new tests and evidence become available.
- When the gene variants or algorithms incorporated in a test are changed, there should be a process and standardized format to notify providers of this change and the basis for the change.

Recommendations for Legal Development & Change:

- Given the tradeoffs that may be inherent in constructing genetic test panels and algorithms, there should not be liability for test selection simply because it produces an inferior result in a specific patient.
- The choice of a test is particularly prone to the well-known phenomenon of “hindsight bias” in litigation,⁴⁹ in that various testing options may have strengths and weaknesses that may look very different before and after the testing is done and outcomes occur. Courts should restrict, under the rule against prejudicial evidence, attorneys from insisting that all negative outcomes show malpractice and should instruct juries carefully to avoid hindsight bias.
- The learned intermediary doctrine⁵⁰ should be interpreted as requiring test developers to be transparent with ordering clinicians and labs about the strengths and weaknesses of their tests in order to get protection from liability under the doctrine.

3. Inappropriate Use of or Reliance on a Test

A. Analysis

The shift to genomic medicine will provide a much larger set of data on which health care providers can rely for disease prediction, diagnosis, prognosis, and treatment. The availability of data from genomic tests will inevitably lead to second-guessing of how a provider used that data in a patient’s care, especially when the patient had a bad outcome.

An example is reliance on a genomic test that predicts recurrence of breast cancer, and thus whether a patient should undergo chemotherapy after surgical removal of a tumor. In the past, many breast cancer patients unnecessarily incurred the costs and side effects of chemotherapy, because no information was available on their individual recurrence risk. Now genomic tests such as Oncotype Dx[®] and MammaPrint[®] predict the recurrence risk for an individual breast cancer patient. These tests are probabilistic not deterministic, and thus cannot predict with certainty whether a breast cancer will recur, but rather provide a probability known as a recurrence score. If a treating physician recommends that a patient undertake such testing, and if (for example) the test provides a low recurrence score so that the patient on the advice of the physician forgoes chemotherapy, can the patient sue the physician if the cancer nonetheless recurs? Or alternatively, if a physician fails to recommend such a test, and the test would have indicated a high recurrence score that would have indicated chemotherapy, would a patient have a claim against the physician for failing to recommend such a test?

An important principle of medical malpractice is that a physician is not, and should not be treated as, a guarantor of the patient's good outcome.⁵¹ Most medical procedures and decisions involve inherent uncertainties and risks, and sometimes the treatment will result in a bad outcome even if the physician's judgment to recommend that course of treatment was reasonable at the time the decision was made. Nevertheless, when a patient does have a bad outcome, there will often be a temptation to second-guess the physician's decision on whether or not to have recommended a genomic test that may have resulted in a different outcome.⁵² A practical difficulty in bringing this type of lawsuit is that a patient may never know if their result would have been different if the test had or had not been recommended, because the test results are probabilistic rather than deterministic.

At least one such case has already been reported. In that case, a breast cancer patient was diagnosed as having a non-invasive cancer, which was treated but later returned and metastasized. The patient alleged that if she had been given the Oncotype Dx assay her tumor would have produced a recurrence score of 41, which would have indicated the need for chemotherapy, which may have prevented the tumor recurrence.⁵³ She brought a medical malpractice lawsuit against her physician for failing to recommend an Oncotype Dx assay, and the case eventually settled.⁵⁴

B. Recommendations

Recommendations for Health Care Actors or Institutions:

- The lack of clinical data to evaluate predictive value and clinical utility for many genomic tests presents a challenge to providers in determining whether a particular test is valid and reliable. Researchers, test developers, regulators, payers, and professional societies should work to ensure that sufficient clinical evidence supports available genomic tests, including those commercially available.
- Professional societies and others generating clinical practice guidance need to provide physicians with clear recommendations regarding what genomic tests are ready for application in the clinic, and for what indications or risk profiles.
- The reliability of genomic tests will depend on the robustness of the data on which they are based, including data that are representative of the patients for whom the test is recommended. Test developers and research funders should ensure that genomic tests are based on data from a diverse and representative cross-section of the population.
- Physicians need to explain carefully the limitations and uncertainties associated with the specific genomic tests they recommend to their patients, so the patient can make an informed decision on whether to assume the risk and make medical decisions on tests that are inherently imperfect (at least for the time being).

Recommendations for Legal Development & Change:

- Many genomic tests will give probabilistic rather than deterministic outcomes – in other words, the test will indicate that patients may have a certain risk. The fact that an individual patient has a bad outcome is not in and of itself evidence of negligence, and in this area of clinical practice as in others, the clinician cannot be a guarantor of the patient's positive outcome. Rather, the negligence inquiry should focus on whether the clinician's recommendation of and reliance on a test was reasonable in the circumstances of the individual patient and consistent with the prevailing standard of care.

- A key factor in whether a provider is negligent in recommending or not recommending a genomic test for a particular patient is whether the provider adequately explained the options, uncertainties, and risks of different courses of action. Documenting such discussions will often be critical to defending against liability.

5. Incorrect Variant Calls

A. Analysis

Determining whether a particular gene variant is of clinical significance, and what should be communicated to the patient, is a major challenge in genomic medicine, particularly when exome or genome sequencing is conducted. Such sequencing will invariably (at least for the foreseeable future) generate a large number of VUSs.⁵⁵ Both the testing laboratory (which usually makes the initial “call” on the clinical significance of variants) and the patient’s physician or genetic counselor who communicates the test results to the patient will have responsibilities that may be second-guessed in litigation.

There is often inconsistency between reference databases on whether a particular variant is pathogenic, likely pathogenic, or of uncertain significance. If a test laboratory or provider reports to the patient that a variant was of uncertain significance (a VUS), when in fact the variant turns out to be clinically significant and the delay in understanding the risk results in injury, the patient could bring a lawsuit claiming the lab or provider erred in classifying the variant as a VUS. The playing field in such cases may be tilted against the defendant if subsequent information makes clear that the variant is significant – things always look clearer in hindsight, even though the legal fact-finder is supposed to evaluate the decision based on the information available to the defendant at the time the challenged action occurred. If the lab or provider did not report the variant to the patient at all because it was deemed to be of uncertain significance, this action could again be second-guessed in a legal claim for failure to disclose.

The first case presenting such issues is currently pending in South Carolina -- the *Athena v. Williams* case.⁵⁶ In that case, a child suffering from seizures was genetically tested, and a variant determined to be of unknown significance was detected in a potentially relevant gene known to be associated with epilepsy (*SCN1A*). The child died from his condition in 2008, after being treated with a drug that is now known to be contra-indicated by the gene variant carried by the child. The testing lab issued a revised report in 2015 re-categorizing the VUS as a pathogenic mutation. The mother subsequently brought a lawsuit contending that the testing lab should have known the variant was pathogenic at the time it issued its original report, or that it should have updated its report promptly when it did discover that the variant was pathogenic and communicated that revised result to the patient.

B. Recommendations

Recommendations for Health Care Actors or Institutions:

- Inconsistent classifications of the same variant by different sources and databases present a major problem for communicating test results to patients. Ongoing efforts to reconcile or integrate different variant databases will be very helpful in providing clearer guidance to labs and physicians in interpreting the clinical significance of genetic variants.
- A physician should be responsible for communicating and explaining to a patient any variants reasonably classified as pathogenic or likely pathogenic that are reported to the physician by the lab in response to the physician's order for genomic testing.
- The physician should also be able to explain "negative" results (benign or likely benign) if relevant to the patient's condition, risks, or concerns.
- There is controversy over whether and when providers should communicate VUSs. When the patient has a family history or other evidence of a specific genetic problem, and testing of the relevant gene(s) indicates only VUSs, the physician should communicate information about the specific VUS if clinically appropriate and urge the patient to continue to follow-up on the relevant variant(s) going forward in future interactions with health care providers.
- Policy makers, health care institutions and professional societies should seek to integrate different interpretive databases to provide the most robust and consistent evidence on the pathogenicity of genetic variants.

Recommendations for Legal Development & Change:

- Courts and attorneys should pay careful attention to clinical practice guidelines and other recommendations and guidance from professional associations on making variant calls. These resources provide helpful evidence on reasonable practices even if they do not conclusively establish the standard of care.
- A physician may be held liable for failing to disclose and explain a variant that has been identified as “pathogenic” by the test laboratory. However, if the lab uses more than one database for making variant calls, and reports that the databases give inconsistent results on whether a particular variant is pathogenic, the physician generally should disclose to the patient both the pathogenic and non-pathogenic determinations and explain why different databases may give inconsistent results and what this means for the patient. A physician may offer their own professional opinion as to why a particular database result may or may not be compelling.
- A physician should not have a legal duty to go beyond the lab report and look at other sources that may classify a variant differently, unless that physician has good reason to know or suspect there are different interpretations available. Failure to disclose alternative variant interpretations should be the responsibility of the lab, not the physician. As with its other testing operations, a laboratory should have a legal duty to consult known and respected data sources in providing variant interpretation to the physician (and ultimately to the patient).
- A physician should not have a general duty to communicate and explain specific VUSs to a patient. However, the physician should explain VUSs in genes of relevance, caution that some of these variants may become of known significance in the future, and inform a patient that he or she should consider seeking re-interpretation of these test results at a later time.

6. Failure To Communicate Results To Patient Accurately

A. Analysis

Genomics will dramatically increase the challenges in communicating information to patients. Even in past genetic testing examining a single gene, many patients had difficulty understanding the results, as those often involved probabilistic and sometimes uncertain risk estimates.. Communicating genomic information that may involve dozens or hundreds of gene variants will be even more confusing for patients.

In addition, physicians who are not specialists in genomics will experience increased difficulties in comprehending genomic information. Again, studies have shown that physicians

often do not understand genetic information involving just one or two genes.⁵⁷ Now with the even more complex data from genomics, non-specialist physicians and other providers will be hard-pressed to understand the data and its significance, much less to communicate that information to patients in an accurate and understandable manner. This creates a risk that the clinician will misinterpret and incorrectly communicate the test results and their significance to the patient. Even genetic counselors and physicians with expertise in genetics may have trouble understanding and communicating more complex genomic tests if they do not obtain additional training.

For example, consider a physician seeking to report the results of an exome sequence back to a patient. There may be thousands of variants in any patient's exome that differ from the reference sequence, though a relatively small percentage will be associated with known genetic traits. Of those, an even smaller percentage will be of medical significance to that patient and recognized as "pathogenic." But a "pathogenic" classification may be tenuous and involve uncertainties that the provider will need to communicate to the patient.⁵⁸ In addition, different databases may classify the same variant differently as to its pathogenicity, and those classifications may change with time as new data are collected.

Given this complexity, along with the limitations of the providers' and patients' understanding, conveying this information from provider to patient in an accurate and understandable manner will be a major challenge for the foreseeable future. If the patient fails to grasp the full significance of what is conveyed, and based on that misunderstanding makes treatment, reproductive, or behavioral choices that result in adverse outcomes, the patient may seek to sue the provider for inadequate communication of risks or information. In the genetic era, such lawsuits for failure to adequately communicate or disclose genetic information were

common.⁵⁹ This type of misunderstanding and subsequent lawsuit is likely to be even more frequent in the genomic era. In genetic malpractice cases, the physician's medical chart notes of what was communicated to the patient verbally could be critical for resolving such disputes – that is likely to be even more the case in the genomic era.

B. Recommendations

Recommendations for Health Care Actors or Institutions:

- Clinicians are responsible for communicating to patients the results of genomic tests that the clinicians have ordered, and doing so accurately. Accurate communication requires an adequate understanding of genetics and genomics and the specific tests results.
- Clinicians may need assistance from genetic counselors and medical geneticists to do this.
- Information about the nature and meaning of genomic results, and about how to communicate them accurately and meaningfully to patients, should be integrated into medical school curricula and post-graduate training programs. Providers should consider delivering genomic results to patients both orally and in writing to aid comprehension and allow patients to seek further assistance in understanding their results.
- Laboratory reports should be in a form that is accurate and can be understood by the average clinician without specialty training in genetics and genomics.

Recommendations for Legal Development & Change:

- Many medical malpractice cases against physicians for alleged negligence relating to genetic testing involve factual disputes about what the provider told or did not tell the patient. Courts should expect providers to document in patient records the information that was communicated to the patient about the results of genomic testing.
- Providers have a legal duty to communicate clinically relevant genomic information to their patients in a manner that is both understandable and informative.

7. Failure To Communicate Results & Share Data with Clinicians within a Health Care System

A. Analysis

The increased complexity of genomics relative to genetics will increase the responsibilities of health care providers to communicate and share relevant genomic data and related practice resources within their systems. For example, over time the case for pharmacogenomic (PGx) testing to guide drug prescribing will likely become stronger,⁶⁰

particularly for patients who have already had genetic sequencing, allowing their providers to use that data to identify relevant variants affecting drug metabolism.⁶¹ However, for this to work, the health care system must ensure that two types of information are easily accessible to providers in their system. First, the relevant variants affecting drug metabolism in a patient's sequencing data must be flagged so that the prescriber will be notified of the relevant variants in the patient's genome. Second, the PGx variants that are known to have clinical utility must be listed and linked to the individual patient's profile when a prescription is written.

Some health care systems have begun developing CDS systems to help identify and flag relevant PGx variants for providers.⁶² However, most others have not, especially at smaller and medium-sized systems. If a patient has a bad reaction to a drug (or a failure of drug effectiveness) that could have been prevented by PGx-based prescribing, by either prescribing a different dose or a different drug to a genetically at-risk patient, there may be a malpractice lawsuit.⁶³ This lawsuit could target the provider for failing to utilize the relevant genomic information in prescribing the drug, but could also target the health care system for failure to put in place a reasonable CDS system that would ensure the most relevant information is flagged for the prescribing physician.

However, both medical and legal decision-making in this field of PGx is complicated by the slow uptake of such genomic testing in clinical practice.⁶⁴ This slow adoption of PGx testing can be attributed to a number of factors, including lack of proven clinical utility, physician unfamiliarity and resistance to such testing, the lack of payer coverage, and other factors.⁶⁵ The FDA has now put genomic information on the "labels" (patient package inserts) of well over 100 different drugs.⁶⁶ However, an FDA label does not determine the standard of care, although it

may provide relevant evidence, and many if not most physicians are not (yet) following the genetic testing guidance on many drug labels.⁶⁷

There are a handful of cases where it would likely be malpractice today if a physician prescribed a drug without a genetic test and the patient had a bad outcome. Examples include HLA-B testing for the anti-HIV drug abacavir,⁶⁸ and testing for *TPMT* genetic polymorphisms before treating childhood leukemia patients.⁶⁹ However, other notable examples such as clopidogrel and warfarin, once thought to be the poster children for PGx testing, and which have FDA recommendations for genetic testing on their labels, are not routinely being used with PGx testing in clinical practice today.⁷⁰ Part of the problem is that the delay and cost (unreimbursed) of PGx testing may hamper its use, but this situation may change if patients have already been tested for the relevant PGx variants in DTC testing or with genome sequencing, potentially allowing the clinician to check the patient's genetic susceptibility before prescribing the drugs with no additional costs or delays. In addition, the rise of GSS is likely to accelerate the potential for PGx testing by enabling the detection of a more comprehensive set of relevant PGx markers.⁷¹

B. Recommendations

Recommendations for Health Care Actors or Institutions:

- Optimally, health care providers should have access to clinical decision support (CDS) systems that indicate genetic variants (and genetic or genomic tests where appropriate) that should be considered when providers within their system prescribe treatments.
- A health care system that uses sequencing data in clinical care should seek to develop CDS and electronic health records (EHR) systems for ensuring that a sequenced patient's clinically significant genetic variants are made available to physicians in an easily accessible format.
- As the field of health informatics and genomic testing changes rapidly, institutions should track emerging trends in information systems and legal expectations.

Recommendations for Legal Development & Change:

- FDA warning labels, clinical guidelines, and other professional society guidance should provide probative but not conclusive evidence of standard of care for pharmacogenomic (PGx) testing. Professional societies should seek to produce regularly updated guidance that incorporates the most recent information to help guide decisions by clinicians and laboratories.
- In determining the evidentiary case for requiring PGx testing, courts should give the highest weight to peer-reviewed, published, randomized control trials that demonstrate clinical utility. Peer-reviewed observational studies and meta-analyses can also be considered but should be given less weight. Commentaries, anecdotal reports, and non-peer reviewed studies should not factor into the evidentiary weighing.
- A stronger case for institutional or professional liability is present when a patient has previously been genetically tested or sequenced for the relevant polymorphisms affecting drug susceptibility, and the results are readily available to the health care provider, but the provider does not take this available information into account in a prescribing decision that results in harm to the patient.

8. Failure to Analyze & Offer Incidental Findings or Secondary Results

A. Analysis

Incidental or secondary findings (hereinafter called “incidental findings”) in clinical genomics are “genomic variants of potential medical relevance unrelated to the medical reason for ordering the test.”⁷² It is widely recognized that genomic sequencing will routinely generate incidental findings, depending on the scope of that sequencing and subsequent analysis.⁷³ A robust literature now addresses return of genomic results and incidental or secondary findings in a range of contexts – research,⁷⁴ clinical care,⁷⁵ and public health screening.⁷⁶ We focus here on management of incidental findings in clinical care, addressing findings initially identified in clinical sequencing or public health screening (both of which use CLIA-compliant laboratories⁷⁷). We then address incidental findings initially found in research sequencing (which may or may not use CLIA-compliant laboratories) and communicated to the research participant or the participant’s clinician for clinical evaluation. Finally, we address patients’ right to access

completed laboratory reports and the contents of the “designated record set” (DRS) in HIPAA-covered entities, as those reports and the DRS may contain incidental findings.

In clinical care, liability can result from a failure to analyze and communicate genomic incidental findings, from incorrect analysis of incidental findings (including a false positive), or from miscommunication of incidental findings. Liability could also result from failure to properly manage incidental findings ascertained in the research context and then communicated to clinicians because of their potential health implications.⁷⁸

Clayton and colleagues published a 2013 analysis of legal cases to date in which clinicians faced assertions of liability for mishandling of incidental findings, focusing on cases involving imaging/radiology since no cases involving genetics had been reported at the time.⁷⁹ They found that clinicians could face liability for a range of behaviors, if those behaviors breached the applicable standard of care. The behaviors included failure to recognize an incidental finding or appreciate its clinical significance, failure to notify the patient and/or the patient’s clinician, and failure to refer the patient to a clinician with the needed expertise. In each of these cases, the patient would need to show that the failure caused harm – for example, by depriving the patient of a chance to seek care that could have averted harm or improved the patient’s status. These authors, however, were careful to identify a number of reasons why liability should be less common in genetics.

In radiology, professional societies have formulated guidelines to assist radiologists and other clinicians in reading scans of various types and determining what incidental findings they should recognize, analyze, and report.⁸⁰ There is less guidance and more controversy in clinical genomics. In 2013, an ACMG committee published the recommendation that whenever clinical sequencing was undertaken for any indication, the laboratory should routinely analyze 56

additional pathogenic genes to report these to the patient's clinician to avert harm.⁸¹ This recommendation was widely debated; objections included that this represented opportunistic screening without adequate evidence of likely net benefit, the initial recommendation failed to allow patients to consent to sequencing but to refuse ascertainment of these extra findings, and the recommendation applied to children even when the genes in question were irrelevant to the child's health before the age of majority because they involved adult-onset conditions.⁸² ACMG modified the recommendations to allow patients to opt-out of ascertainment of the extra findings and to enlarge the list from 56 to 59.⁸³

The radiology analogy suggests that clinicians are obligated to recognize and report incidental findings when this is likely to avert or minimize harm to the patient or improve future health. However, the scope of genomic analysis that laboratories and clinicians are obligated to undertake remains unclear. If the lab discovers a pathogenic incidental finding within the scope of genomic analysis that was ordered, and reporting that finding is likely to avert or reduce harm, the lab is probably obligated to report that. However, the question remains how much further the lab should look in search of incidental findings. As an ethics matter, many scholars have argued against a "duty to hunt" for incidental findings, though much of that literature addresses the research context instead of the clinical one.⁸⁴ The ACMG recommendations attempt to set up a process of offering limited extra analysis of a pre-defined set of incidental findings that a patient may accept or decline.

Once the laboratory has reported an incidental finding with health implications for the patient, the clinician is obligated to offer disclosure of that finding to the patient and obligated to manage the finding in keeping with the standard of care (either directly or through appropriate referral). Patients may decline to receive the finding, exercising what the ethics literature calls

the “right not to know.”⁸⁵ However, there is controversy about the scope of that right,⁸⁶ and a clinician whose patient declines to know about a pathogenic finding that warrants clinical intervention or heightened surveillance faces a difficult situation that may warrant seeking ethics advice and legal counsel.

In the context of public health screening -- including newborn screening and other forms of genetic screening on a population, subpopulation, or opportunistic screening basis – consideration of using larger panels, as well as exome and genome sequencing⁸⁷ raises the potential to identify incidental findings. Because public health screening is conducted using CLIA-compliant laboratories, communication of incidental findings to the clinician will trigger the same obligations that are triggered when clinically ascertained incidental findings are identified.

In the research context, an incidental finding may be defined as “a finding concerning an individual research participant that has potential health...importance and is discovered in the course of conducting research, but is beyond the aims of the study.”⁸⁸ Once an incidental finding from research is communicated to a clinician because of its potential health implications, the clinician will need to seek CLIA confirmation of the finding (if it was originally ascertained in a non-CLIA laboratory) before clinical use of that finding. The clinician will then need to assess the health implications of the finding in the context of clinical evaluation.⁸⁹

The question of whether researchers have duties to analyze and offer to the patient (or patient’s clinician) incidental findings discovered in research is an evolving one. An extensive literature argues that researchers should offer back to research participants those findings that are pathogenic and clinically actionable, and that researchers may in their discretion offer back a larger set of findings.⁹⁰ Milstein has argued that failure to offer back incidental findings that are

pathogenic and clinically actionable may be malpractice.⁹¹ Wolf and colleagues have suggested that federal research regulations (the Common Rule and FDA equivalent) offer support for researcher duties to alert prospective participants to the possibility of discovering incidental findings and the researchers' plan for managing and disclosing them.⁹² In addition, the authors argue that the regulations support a duty to disclose, if such disclosure "may relate to the subject's willingness to continue participation" in the trial.⁹³ A court may find negligence if the court finds that the researcher-participant relationship creates duties that run from the researcher to participant and that those duties may have been breached causing harm.⁹⁴ When the researcher is also the participant's clinician, the court may find medical malpractice.⁹⁵

Some authors have cautioned that expecting researchers to analyze and offer disclosure of incidental findings invites participants to confuse research for clinical care (in what is sometimes called the "therapeutic misconception") and risks depletion of research budgets for a clinical activity.⁹⁶ However, there appears to be wide agreement at this point that researchers should offer back to research participants at least those findings that are pathogenic and clinically actionable.⁹⁷

When researchers ascertain incidental or secondary findings with potential health implications, they may seek to communicate those findings to the research participant for evaluation with the participant's clinician and may communicate them directly to the clinician. If those findings were ascertained or confirmed in a CLIA-compliant laboratory, the findings may be communicated and directly used in clinical care. If the findings were discovered in a non-CLIA certified laboratory, there is some disagreement over whether the findings can be communicated to the participant and/or clinician for the purpose of seeking clinical confirmation and evaluation.⁹⁸

Ordering appropriate CLIA confirmation (if needed), interpreting the test results in the context of patient evaluation, and recommending next steps may generate liability if the clinician fails to meet the applicable standard of care. In addition, the clinician should appreciate the limits of their expertise and seek consultation with a medical geneticist, genetic counselor, or other clinician when needed.

Note that some genomic research is intrinsically translational, mixing research and clinical care.⁹⁹ Such research often involves patients affected with illness, genomic sequencing to produce findings that may be relevant to care, inclusion of those findings in the medical record, and treatment decisions based on those findings.¹⁰⁰ In such translational research, courts may find that there is a clinical duty to analyze and offer incidental findings to the patient-participants.

Finally, patients, individuals subject to public health screening, and research participants may access incidental findings by asserting their rights under federal law to access completed laboratory reports¹⁰¹ and their right of access to the contents of the DRS in HIPAA-covered entities.¹⁰² State law may also create rights of access. Once patients bring these incidental findings to the attention of their clinical caregiver, the clinician will need to deal with those findings responsibly, as outlined above.

B. Recommendations

Recommendations for Health Care Actors or Institutions:

- Clinicians ordering genomic analyses including sequencing should be aware of key recommendations in the literature and from professional societies on analysis and return of incidental or secondary findings. Legal counsel should additionally be aware of the relevant law and legal analyses, in order to provide advice when needed.
- Clinicians should work with their genomics laboratory to clarify the scope of prospective analyses and how analysis and reporting of incidental or secondary findings will proceed. They should clarify how results will be reported, using what format, and with what entry

in the EHR. They should also clarify how patients' requests for completed laboratory reports will be handled, and how patients will be able to access their data upon request.

- Genomics laboratories and institutions should formulate written policy on the scope of their analysis, including how they will manage incidental findings ascertained in clinical, public health, and research genomic analyses. Laboratories and institutions should have in place a system and operating procedures for ascertaining, recording, and communicating incidental findings. Laboratories and institutions should also clarify how patients' requests for completed laboratory reports will be handled, and whether patients will be given raw data or data files and in what format. Laboratory and institutional policy and practices on return of incidental findings and data should be publicly posted and communicated to patients.
- Clinicians ordering genomic analyses should be clear on what incidental or secondary findings the laboratory may discover and the patient's option to decline ascertainment and notification of such findings.
- When patients are offered clinical genomic analyses, they should be informed of what incidental or secondary findings may be discovered and allowed to opt-out.
- When a clinician is notified by patients or researchers of incidental findings discovered in research, the clinician should clarify whether the findings were ascertained in a CLIA-compliant laboratory. If they were not so ascertained, then the clinician should order confirmation in a CLIA-compliant laboratory before use in diagnosis, treatment, prevention, or health assessment, in keeping with the CLIA statute and regulations. The clinician will need to assess the clinical importance of confirmed findings in the context of performing a clinical evaluation of the patient.
- Researchers using genomic analyses should specify how they will manage incidental or secondary findings. Their protocol should specify what results (if any) will be offered, to whom, and how. Researchers should clarify whether results offered will originate from a CLIA-compliant laboratory, or will be confirmed in such a laboratory before being offered to the research participant, or will be offered for clinical confirmation and then evaluation.
- Clinicians, public health authorities, and researchers should specify their approach to return of results and incidental or secondary findings when the research participant is a minor, an adult without decisional capacity, or is deceased.
- Researchers should address how they plan to handle requests for the participant's raw data or data files from any of those listed above.

Recommendations for Legal Development & Change:

- The DHHS Office of Civil Rights (OCR) should enforce patients' and research participants' existing rights of access to information in the DRS.
- Federal authorities (OCR and the Centers for Medicare & Medicaid Services (CMS)) should enforce patients' existing right of direct access to completed laboratory reports.
- Given that research may generate incidental findings for clinical evaluation and that some research analyses are conducted in non-CLIA laboratories, CMS should withdraw its

2014 pdf purporting to bar return of individual-specific results from such laboratories.¹⁰³ When the results do not originate in a CLIA-certified (or CLIA-exempt) laboratory, CMS should acknowledge that the research team may confirm the result in such a laboratory or may communicate the result to the participant and/or clinician with clear warnings that the result is not being returned for diagnosis, treatment, or health assessment, and should be confirmed in a CLIA-certified (or CLIA-exempt) laboratory before clinical use.

9. Failure to Update and Recontact

A. Analysis

Genomic medicine will impose new opportunities and pressures for health care providers to recontact patients to provide updated interpretations of genomic information. Health care providers have always had a legal and ethical duty to try to recontact previous patients when they discover, or should have discovered, that their initial diagnosis or treatment recommendations were erroneous when originally provided.¹⁰⁴ In the context of genomics, the question of whether the initial diagnosis, interpretation, or recommendation was erroneous will not be as clear-cut as some other areas of medical malpractice. Given that a particular variant could be categorized as ranging from benign to pathogenic, and different databases may reflect divergent expert interpretations and classifications of the same result,¹⁰⁵ it will not always be clear, even in retrospect, whether the initial decision of the physician to classify a variant or recommend a treatment regime based on that classification was erroneous at the time.

However, when the provider's actions were not erroneous at the time the advice was delivered, courts have recognized a duty to recontact patients in only two limited circumstances.¹⁰⁶ The first is when a physician administers a procedure or treatment that requires an established follow-up procedure or test, and if such follow-up is not provided, the physician could be liable for "abandonment."¹⁰⁷ The second situation arises when a patient is being treated with a drug or device prescribed by the physician, and the physician learns of new risks associated with that treatment, such as a new warning issued by the FDA.¹⁰⁸ The theory behind

these two limited duties is that the patient is still undergoing treatment that the physician initiated.

Other than those limited situations, courts have not recognized a general duty for a health care provider to affirmatively recontact their patients with new information.¹⁰⁹ Genomic sequencing presents new questions about whether a physician and testing lab can and should update results and recontact patients. Genome sequencing will initially identify many VUSs, but their clinical significance will change over time.¹¹⁰ This then raises the questions of whether there is a duty for testing labs or physicians to determine whether a variant's reinterpretation applies to previous patients, and if so, if the new information is clinically relevant, whether the testing lab and/or physician has any ethical or legal duty to try to recontact the patient with that updated information.

A recent survey of the literature on a physician's legal duties to recontact a former patient to provide later findings identified a number of articles discussing a potential duty to recontact, such that the failure to do so could result in liability to former patients under a theory of negligence.¹¹¹ Approximately one half of the articles reached no clear conclusion regarding whether there is a duty to recontact former patients to provide updated genomics findings; of 28 that drew a conclusion, "6 concluded that a duty to recontact does apply and 22 concluded that it does not."¹¹² Accordingly, scholars have concluded that "there is no generally held legal basis for recontacting in clinical genetics, although it is often considered desirable by both [health care providers] and patients."¹¹³ However, no court has yet considered this potential legal duty in the context of updated genomic interpretations.¹¹⁴ A number of factors are relevant to any potential future ethical or legal duty to update genetic interpretations and recontact patients.

Imposing a responsibility on physicians to identify when new information changes the genetic risk for former patients is problematic, as most physicians will lack sufficient knowledge and confidence to identify and address the need for an update.¹¹⁵ Any potential future duty of physicians to update persons who receive genomic tests would likely vary depending on the nature, and inherent expectations, of the physician-patient relationship. The potential that the physician-patient relationship could give rise to a recognized duty to recontact or update patients could vary in at least three sets of circumstances, depending upon the relationship of the genomic results to the area of treatment.

First, a physician could order a genomics test that reveals a variant that is later determined to be associated with a disease risk unrelated to the physician's area of practice, and therefore outside the area of care that the patient received from the physician. In such a case, there would be a relatively lower risk that a court would impose liability on the physician for not recontacting and updating the former patient.

Second, the physician could order genomic sequencing in the course of providing continuing care to the patient. If the test identifies a genomic variant associated with a disease risk related to ongoing care, a court would be much more likely to determine that the physician has a duty to recontact and update the patient. However, a court might be less willing to impose liability on a physician in the context of offering ongoing treatment if the new genomic variant were in a field unrelated to the physician's area of practice and if the physician were unaware of the relevance of the new variant to the patient.

Third, there is the possibility of an intermediate scenario, in which the patient sees a physician for a discrete episode of care (*e.g.*, cardiac surgery and follow-up) after which the physician's relationship with the patient ends. If a genomic test were ordered in the course of the

treatment relationship and then a variant identified by the genomic test were later determined to be associated with a disease risk related to the problem for which the patient sought care, it is unlikely that the physician would have a duty to recontact the patient and update regarding the risk; the physician has no ongoing relationship with the patient, and one episode of care cannot impose a lifetime, continuing duty on a provider. Indeed, some scholars have suggested that any duty to contact would be “unlikely to extend in perpetuity or to require more than reasonable effort.”¹¹⁶

In contrast to physicians, testing labs generally do have the requisite expertise to recognize and conduct reinterpretations of previous VUSs. Indeed, some labs are now periodically rechecking their previous interpretations and sending updated interpretations that are clinically relevant to the physician who ordered the genetic testing.¹¹⁷ However, there are no laboratory guidelines, court decisions, or other statements of standard of care that impose a duty on testing labs to periodically reinterpret genetic test results. Moreover, test labs generally do not have the immediate relationship or the proper training to report new genetic interpretations directly to patients.

If a responsibility to update genomic test results does emerge, it would likely put the onus on labs to identify the reinterpretation and then to send it to the ordering physician for communication to the patient. Yet, creating such a duty would involve significant practical and implementation issues.¹¹⁸ How long would the hypothetical duty to recontact extend into the future for – a limited time period, or in perpetuity? Perhaps it would extend as long as there is a physician-patient relationship between the provider and patient at issue, but it is not always clear when such a relationship ceases. Is it when the doctor last sees the patient, or has not seen the patient for some length of time, or when the patient has changed their care to another physician?

The end date of a physician-patient relationship is often not clear, and may depend on whether it was a one-time appointment with a specialist, a repeated series of appointment with a primary care physician, or perhaps a comprehensive care arrangement such as with an accountable care organization or institutional provider like Kaiser. In the past, a clear termination date for the physician-patient relationship may not have been legally significant in most cases, but given the looming possibility of an ongoing duty to update interpretations of genetic test results, it may behoove providers to contractually specify a more precise termination date for their care.¹¹⁹

Many other practical difficulties confound a possible ongoing duty to update. Who would pay for the additional efforts by the lab and physician? What if the patient has moved and was not easily located? What if the patient did not want to know the updated results? What if the patient has died in the interim? These and other practical difficulties in implementing a possible duty to update should be resolved before any such duty is imposed.

In the future, information technology and patient apps may help make the reinterpretation tasks more routine and patient-focused. It is likely that computer programs and apps will be developed that automatically notify patients when clinically significant new information becomes available that affects the interpretation of their genetic results. Indeed, a program called “GenomeConnect: The ClinGen Patient Registry” has already been launched that among other things alerts patients to significant updates in the interpretation of their genetic test results.¹²⁰

B. Recommendations

Recommendations for Health Care Actors or Institutions:

- If a provider discovers that the previous information communicated to the patient was erroneous at the time of the communication, the provider should notify the patient of the corrected information as soon as possible.
- Health care providers who are responsible for ordering or interpreting genetic tests for a patient should expressly inform the patient that some of the results may have a different or changing interpretation in the future.

- Some testing labs are periodically updating their interpretations of previous patient test results in light of constantly evolving information. If during such a review, the lab determines that the interpretation of a patient's genetic information has changed to now provide an actionable response to a significant risk, the lab should make reasonable efforts to communicate that revised finding to the ordering physician.
- If a physician is notified by a testing laboratory that a previous interpretation of a patient's genetic variant has changed in such a manner that may materially affect the patient's health, the physician should make reasonable efforts to pass on the updated interpretation to the patient. In many or even most cases, this would not be feasible, due to patient loss to follow up and limited provider resources.
- A physician who is treating a patient for a condition and who refers the patient for a genetic consultation that provides no clinically relevant information should consider re-referring the patient for an updated genetic consultation every few years if clinically indicated (*e.g.*, condition has not been resolved and is not being successfully treated and physician has reason to suspect there may be a previously undetected genetic underpinning).
- Any duty of a physician to recontact and update a patient regarding newly identified genomic testing results should depend on various factors including: (1) the correspondence, if any, between the physician's area of expertise and the genomic result, (2) whether the patient is under the physicians' current and continuing care, and (3) the period of time that has elapsed between the physician's care.
- In the future, software programs and apps may become available to automatically notify patients and their treating physician that a clinically relevant updated interpretation of their genomic data is available.

Recommendations for Legal Development & Change:

- Courts and legislatures have to date established no general legal duty for a test lab or health care provider to continuously update previous interpretations of a patient genetic variant(s).
- A provider who is actively treating a patient for a specific condition, and that patient has been genetically tested in the past, should be held legally responsible for taking reasonable steps to communicate updated clinically-relevant genetic information to the patient if the updated information has been communicated to the physician, and that information is within the physician's scope of expertise or would otherwise be within the standard of care for the physician to be aware of the updated information.
- A health care provider who is provided with a materially updated interpretation of a patient's genetic information from a test lab should try to make reasonable efforts to pass that information on to the patient. Although no legal duty currently exists for a provider to communicate those updated test results to their patient, providers should be aware that courts may impose such a duty in the future, perhaps retroactively. However, legal systems should understand that this is in many, even most, cases not feasible, given patient loss to follow up and limited provider resources, and thus should condition any such duty on a reasonableness determination.

- Courts and legislatures to date have imposed no general duty on testing labs to regularly update the results from previous patients or to alert ordering physicians of clinically relevant updates. However, given that some labs have started to do such updates as a regular part of their business, they may be establishing a new standard of care especially in jurisdictions where test labs are considered to be health care providers that are subject to a standard of care based on local or national custom.
- Professional societies should provide recommendations on what is a reasonable effort that providers and test labs should undertake to update patient information with relevant new findings. Relevant factors should include the nature of the patient-provider interaction, the duration since the last patient appointment, whether the patient has provided the provider with their most recent address and contact information, the clinical significance of the new findings, and how often any duty to update test results should occur.

10. Failure to Warn Family Members

A. Analysis

Health care providers have been concerned for many years about potential liability relating to failing to warn family members of patients about their genetic risks.¹²¹ Genetic information differs from most other medical data in that it is directly relevant to family members who may share the patient's genetic variants that confer a disease risk. Courts have held that a health care provider has a legal duty to warn relatives of a patient of genetic risks that become apparent through treatment of the patient by instructing the patient to warn their immediate family members of their potential genetic risk.¹²² However, with some limited exceptions discussed below, courts have generally not held that providers have a duty to communicate genetic information to a patient's relatives directly, and such disclosure without the patient's consent is generally prohibited by the Health Information Health Insurance Portability and Accountability Act (HIPAA). Some medical association guidelines such as those from the American Medical Association (AMA), American Society of Human Genetics (ASHG), and National Society of Genetic Counselors (NSGC) suggest that a health care provider may (but it is not required to) directly disclose genetic risk information to a patient's relatives in the absence of

the patient's consent in rare, exceptional circumstances.¹²³ Some experts contend, however, that any such narrow discretionary right to disclose genetic information to a patient's relatives was foreclosed by the 2003 privacy rule implementing HIPAA (discussed further below).¹²⁴

This duty to warn the patient to disclose family risks may be more difficult and complex to discharge in the era of genomics than genetics. With genetics, usually a mutation in a single gene is at issue, and therefore it is relatively straightforward for a provider to discern and communicate to the patient the inheritance pattern of that mutation (*e.g.*, dominant vs. recessive, autosomal vs. sex-linked). The potential risks to immediate family members can then be conveyed to the patient with a recommendation that such information be passed on to blood relatives. With genomic test results, including test results of a large number of gene variants with varying degrees of significance, the task of determining what information (if any) should be communicated to the patient's relatives is much more difficult. For example, some of the mutations in a patient's genome may have been inherited, while others may be *de novo*, especially with mutations such as copy number variants (CNVs). Even for variants that appear to have been inherited, there is a lack of clarity on how much clinical significance and certainty about a variant is necessary to trigger a duty by the provider to counsel the patient to communicate the risk information to relatives. Even if a physician's duty is discharged by recommending information for the patient to tell his or her direct relatives, the shift from genetics to genomics will make this legal duty more complex and potentially subject to retrospective criticism in any litigation.

At the same time, the shift from single-gene genetics to genomics in health care may create more cases where there may be a duty to disclose to relatives for a couple of reasons. First, as a purely quantitative matter, as more people get their genes tested, there will be more cases

where communication of those results to relatives will be clinically important. Second, to the extent that genomics progresses to various types of population-level screening, this too will create more opportunities and legal risks relating to disclosing information to relatives. For example, if sequencing of newborns becomes more prevalent, this will create enormous additional family disclosure issues. An example of a genomic test creating a duty to relatives is *Polaski v. Whitson*, where the court ruled that a physician treating a patient for heart disease may have legally harmed the patient's son by failing to order a gene panel test for the father for hypertrophic cardiomyopathy, which might have then informed the son's disease risk.¹²⁵

The increased number of potential cases where genetic information may be relevant to a patient's relatives is offset at least partially by the fact that as more people undergo genome testing, they will no longer need to receive their relatives' results to learn of risk, since they will have the results from their own genome. However, the long-standing fear of many physicians is that the duty to disclose to relatives could be imposed directly on the physician, such that the physician will be tasked with informing the relatives directly if the patient is unwilling or incapable of doing this. This fear was catalyzed by the 1996 decision in *Safer v. Pack*,¹²⁶ where a New Jersey court suggested that a doctor may have such a duty in at least some circumstances. The New Jersey legislature subsequently overturned the decision by enacting a genetic privacy statute that required patient consent for disclosure,¹²⁷ and no subsequent court case in the United States has held that a physician has a legal duty to inform relatives of their genetic risk over the patient's objections (or even without the patient's permission).¹²⁸

To obligate physicians to warn relatives directly would be problematic on both practical and legal grounds. First of all, disclosing over a patient's objections violates the clinician's millennia-old obligation to protect confidentiality. From a practical perspective, if a patient is

uncooperative and unwilling to notify their own relatives, it will often be difficult for a physician to identify and locate at-risk relatives, who may be scattered in faraway places. The costs and burdens of contacting and communicating genetic risks to such relatives would likely not be reimbursed and could be quite substantial. Moreover, the relatives who receive the genetic warnings may not want to be informed of their genetic risks, having not consented to any communication, or may even be minors.

Legally, disclosing a patient's health information to relatives without the patient's approval would violate the HIPAA privacy rule.¹²⁹ There are HIPAA exceptions to the consent usually required for the disclosure of medical information by a health care provider or institution that could theoretically apply to the unconsented disclosure of genetic risk information to the patient's relatives, including disclosures "to avert a serious threat to health or safety" or where "required by law." These exceptions have primarily been applied to imminent and serious risks from contagious diseases or mental health problems. While there has been some debate in the academic literature about whether either of these provisions could apply to familial disclosure of genetic information, the nature of harm from non-disclosure of genetic information is unlikely to rise to the level of "serious threat" of harm and is not included with the regulatory explanation of the "required by law" exception.¹³⁰ Furthermore, the 2013 amendments to the HIPAA rules do not expressly extend these HIPAA exceptions to cover sharing genetic results with a patient's relatives without the patient's consent, with the narrow exceptions described below.

HIPAA does allow a physician to send results about a patient's genetic risks to another provider treating a relative of the first patient, provided the patient has not forbidden such sharing.¹³¹ This allows sharing genetic results within families as more and more providers consider genetic data in their clinical care of patients. However, if the patient requests that

information not be shared through this mechanism, *and* the physician agrees with that restriction, then the physician may not share genetic data with a physician treating a relative.¹³² Some other exceptions may apply in certain situations. Researchers and other actors outside the clinical context that work in institutions that are not “covered entities” under HIPAA are not precluded by HIPAA from sharing genetic test results with relatives in appropriate circumstances.¹³³ Moreover, some states assign the rights to medical information (including genetic data) to relatives of a deceased patient.¹³⁴ Finally, because HIPAA allows a personal representative of the patient to gain access to a patient’s medical information, some relatives will gain access to patient genetic data through that mechanism.¹³⁵

However, as a general matter, a physician not only has no duty to disclose patient genetic risk information to the patient’s relatives, but may be violating HIPAA if the physician attempts to disclose such information without the patient’s consent (and the patient is still alive¹³⁶).

B. Recommendations

Recommendations for Health Care Actors or Institutions:

- Clinicians ordering genomic analyses including sequencing should be aware of key recommendations in the literature and from professional societies on sharing results and data or data files with family member(s) or their physician(s), including after the patient’s loss of decisional capacity or death. Legal counsel should additionally be aware of the relevant law and legal analyses, in order to provide advice when needed.
- Genomic data and interpreted results qualify as an individual’s protected health information (PHI) and should generally be protected as private and confidential information. Researchers and clinicians should encourage individuals to share their results with family member(s) when those results have implications for those family member(s), and should offer support for that process as needed. It may be particularly helpful to provide the patient with an informational document to share with family members.
- Clinicians should specify their approach to disclosure of results to family members when the patient is a minor, an adult without decisional capacity, or is deceased. Clinicians should consider eliciting the patient’s preferences on sharing results with family members, including after participant loss of decisional capacity or death.

- Clinicians should address how they plan to handle requests for patient results from the patient’s family member(s), parent(s) or guardian, the patient’s Legally Authorized Representative (LAR), or the patient’s Personal Representative (under state and federal law); the LAR and/or the Personal Representative may be a family member.
- Clinicians and test labs should address how they plan to handle requests for the patient’s raw data or data files from any of those listed above.
- There may be cases in which the patient refuses to share results that have a high likelihood of averting imminent harm if shared. In these instances, the clinician may have a privilege to warn the family member(s) at risk, although some legal experts argue that any such disclosure would violate HIPAA. Ethics and legal consultation is recommended before sharing.

Recommendations for Legal Development & Change:

- Provisions in HIPAA and state law allowing broader sharing of genomic PHI with family members should be scrutinized and amended if necessary to ensure that sharing of genomic PHI without authorization from the source individual is limited to reliable results of high value to the family member(s) in question and that the benefit to the family member(s) warrants the privacy risks to the source individual, including after death.
- Courts and other actors should clarify where necessary that under current law health care providers do not have a duty to disclose genetic test results to relatives of a patient if the patient does not consent to such disclosure.
- Some courts have held that a person has a cause of action and standing to bring a lawsuit against a clinician for negligent genetic testing of a family member, on the theory that the erroneous testing or reporting of the test results injured the relative bringing the lawsuit (*e.g.*, by depriving the plaintiff of accurate genetic information about their relative that may have also pertained to them).¹³⁷ Such lawsuits have the potential to significantly expand the duty and liability exposure of clinicians. If similar claims are recognized in the future, courts should clearly establish limits on any such duties to protect clinicians from overly-expansive liability exposure.

11. Direct-To-Consumer (DTC) Testing

A. Analysis

Direct-to-consumer (DTC) genetic testing is a relatively new arrangement for genetic testing that is likely to become even more common in the future as regulatory restrictions are relaxed and more consumers become interested in obtaining their own genomic information. In DTC genetic testing, a company sends a test kit directly to a consumer who purchases testing;

the consumer provides a buccal swab, spit, or blood sample in a vial that is mailed back to the DTC company; and then the DTC company after analyzing the sample provides the genetic test results directly to the consumer, usually through a password-protected website. The patient's personal physician is usually not involved in the ordering or initial receipt of the genetic test results, although the DTC company may have a physician on staff who technically "orders" the genetic testing to comply with regulatory requirements.¹³⁸ However, many patients may bring their DTC genetic results to their personal physician for consultation and advice.

Providing genetic results through DTC companies raises many controversial policy and ethical concerns,¹³⁹ and the FDA has been increasingly involved in regulation of DTC testing. Our focus here is on potential liability issues faced by a health care provider who is provided with or reviews a patient's DTC test results.¹⁴⁰

DTC genetic testing can present liability risks for providers. For example, if a patient seeks to share with their physician DTC results that show disease susceptibility or PGx information about a certain pharmaceutical (*e.g.*, warfarin), and the physician knows of these results but fails to take them into account in providing medical advice, the physician may be faced with a medical malpractice claim, if that failure directly resulted in adverse effects on the patient. However, given that many DTC results, especially if self-reported, may not be accurate or reliable, any such physician duty to take such results into account must be tempered, and indeed, no cases have been reported in which physicians or other providers have been held liable for failing to consider DTC results in their care and treatment. If the DTC test results are potentially clinically significant, the best practice is for the patient's physician to order the test be validated in a CLIA-approved or CLIA-exempt laboratory, so that the results will be reliable. Nonetheless, a physician who ignores a patient's DTC results without getting the results

validated, especially when brought to the provider's attention by the patient, may be at risk of liability.

Alternatively, a physician could be liable for over-relying on DTC genetic test results, and recommending prophylactic surgery, pharmaceutical treatment, or some other unnecessary and possibly risky procedure without adequately validating and verifying the DTC genetic results.¹⁴¹ Recent studies have shown that DTC results are often erroneous,¹⁴² and even the DTC companies generally recommend that patients validate DTC results before relying on them for clinical decision-making. A physician who relies on DTC results without validating the results therefore also faces a liability risk. However, the physician may be put in a catch-22 situation if the patient's insurer will not pay for the clinical validation, and the patient cannot afford to pay for the validation test out-of-pocket. The physician then faces the dilemma of either relying on a potentially erroneous test result, or alternatively ignoring a test result that may be valid. Either way, the patient may be harmed and the physician may be sued.

B. Recommendations

Recommendations for Health Care Actors or Institutions:

- DTC genetic test results will usually include results from tests that are not clinically indicated. Such testing provides results that are more likely to be false positives and are not clinically useful compared to genetic testing in symptomatic or at-risk patients that is clinically indicated. Clinicians should be wary of relying on results from DTC tests which are not clinically indicated, and should require a confirmatory test before making clinical diagnoses or recommendations. Obtaining confirmatory testing could be problematic if, for example, the patient does not have insurance willing to pay for such confirmatory testing.
- DTC genomics companies should ensure that they clearly explain the limitations of their tests and coverage, and in particular the potential for erroneous results and the potential for other untested variants to present risk to the patient.
- Providers delivering general care as well as more specialized care should be informed of the limitations and risks of DTC genetic testing, as well as any benefits in terms of costs and privacy, and be prepared to counsel their patients about such issues if and when patients inquire about such testing.

- Providers should not refuse to consider genetic information that a patient offers to share with their physician when there are reasonable grounds to believe that information may relate to a specific complaint or condition the patient is presenting. However, clinicians generally do not have the knowledge or resources to be the primary explainer of the DTC test results that all their patients receive, and should not be expected to review and understand all the relevant information that may be contained in those test results.
- A provider should not base clinical decisions solely on DTC test results. Rather, if the DTC test results indicate a potential problem or meaningful health indication, the provider should seek to have the test result replicated by a CLIA-compliant test laboratory.

Recommendations for Legal Development & Change:

- When a provider fails to take into account specific actionable genetic test results (from any reliable source) that the patient brings to the provider's attention relating to a health condition or risk that the provider is treating, and the failure to consider that genetic information causes harm to the patient, the provider may be held liable for medical malpractice. However, providers should not be assigned the legal duty to be aware of and to take action on all the information in patient DTC genetic test results, in particular genetic test results from tests that are not clinically indicated, except for the narrow exception described above.
- A provider who recommends clinical action based on the results of a DTC genetic test, without first verifying the validity of those DTC test results, may be held liable for harm that results to the patient from the reliance on inaccurate and unverified DTC test results.

Conclusion

Just as the transition from genetics to genomics will both transform and complicate clinical care, so too will it transform and complicate liability for health care providers. In this article, we have projected some of the general themes and trends. We then address eleven specific liability topics that will be important in the era of genomics medicine. Some of these topics merely represent an expansion of the importance and frequency of legal issues that have been with us since the onset of genetic testing, whereas others presentative novel legal issues that are unique to genomics. In both cases, these liability issues will challenge and exert pressure on actors in both the medical and legal professions to respond in appropriate and innovative ways. We have provided our recommendations on how both the health care and legal systems should respond, hoping to stimulate debate on these tough questions, recognizing that our

recommendations may be just the first shot rather than the final word on how these difficult but important liability issues are resolved.

Predicting how the various liability risks relating to clinical genomics will manifest in actual cases is difficult given that the outcome of such claims will often depend on the specific facts, parties, attorneys, experts, judge, and jury. The early court decisions will have a big influence on the future feasibility and frequency of similar claims, as both medical and legal actors will rely on those initial decisions. The precise evolution of these liability claims is unpredictable, but litigation in this realm will likely follow the historical trend that new medical technologies breed new waves of malpractice liability lawsuits.¹⁴³

It is important to emphasize that liability is only one in a set of tools that should be used together in promoting genomic medicine that is high quality, effective, cost-effective, ethical, and accountable. Education and training, clinical guidelines, practice support tools, corporate management and accountability, open sharing of data and methods, and individual and institutional ethics are all vital tools as well. Liability can be an important component of that toolbox, but if applied too broadly can impede the uptake of genomic medicine, and if applied too sparsely and inconsistently, will not play the role it should in protecting patients and promoting good care and the successful implementation of genomic medicine.

References

¹ National Human Genome Research Institute (NHGRI) and National Cancer Institute (NCI) grant #1R01HG008605 (Wolf, Clayton, Lawrenz, PIs).

² Examples of translational research projects in genomics include a number of projects in the Clinical Sequencing Exploratory Research (CSER) Consortium, at <<https://cser1.cser-consortium.org>> (last visited May 25, 2019). See R. C. Green et al., “The Clinical Sequencing Exploratory Research Consortium: Accelerating the Evidence-Based Practice of Genomic Medicine,” *American Journal of Human Genetics* 98, no. 6 (2016): 1051-1066; G. E. Henderson et al., “The Challenge of Informed Consent and Return of Results in Translational Genomics: Empirical Analysis and Recommendations,” *Journal of Law, Medicine & Ethics* 42, no. 3 (2014): 344-355.

³ See, e.g., Genetic Information Nondiscrimination Act of 2008, H.R. 493, 110th Congress, Pub. L. 110-343, available at <<https://www.govtrack.us/congress/bills/110/hr493/text>> (last visited May 25, 2019); *Pate v. Threlkel*, 661 So. 2d 278 (Fla. 1995); *Williams v. Quest Diagn., Inc.*, 423 S.C. 547 (S.C. 2018).

⁴ In this paper, we use the term “genome-scale sequencing” or GSS to refer to large-scale genetic sequencing, including whole genome sequencing and exome sequencing. See, e.g., J. R. Botkin and E. Rothwell, “Whole Genome Sequencing and Newborn Screening,” *Current Genetic Medicine Report* 4, no. 1 (2016): 1-6 (using “GSS” for “genome-scale sequencing”).

⁵ See L. Franciscatto and N. Katsanis, “Newborn Screening and the Era of Medical Genomics,” *Seminars in Perinatology* 39, no. 8 (2015): 617-622; L. Farnaes et al., “Rapid Whole-Genome Sequencing Decreases Infant Morbidity and Cost of Hospitalization,” *Genomic Medicine* 3, no. 10 (2018): 1-8; see also J. M. Friedman et al., “Genomic Newborn Screening: Public Health Policy Considerations and Recommendations,” *BMC Medical Genomics* 10, no. 9 (2017); J. E. Petrickin et al., “Rapid Whole Genome Sequencing and Precision Neonatology,” *Seminars in Perinatology* 39, no. 8 (2015): 623-631.

⁶ See W. Burke, “Genetic Tests: Clinical Validity and Clinical Utility,” *Current Protocols in Human Genetics* 81, no. 9 (2014): 15.1-15.8; Y. Yang et al., “Clinical Whole-Exome Sequencing for the Diagnosis of Mendelian Disorders,” *New England Journal of Medicine* 369, no. 16 (2013): 1502-1511 (comparing diagnostic yield of exome sequencing to traditional molecular techniques); S. D. Grosse and M. J. Khoury, “What Is the Clinical Utility of Genetic Testing?,” *Genetics in Medicine* 8, no. 7 (2006): 448-450. But see S. H. Katsanis and N. Katsanis, “Molecular Genetic Testing and the Future of Clinical Genomics,” *Nature Reviews Genetics* 14, no. 6 (2013): 415-426 (describing the continuing relevance of non-sequencing, molecular diagnostic techniques).

⁷ See, e.g., National Research Council, *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease* (Washington, D.C.: National Academies Press, 2011): at 59-74.

⁸ L. G. Biesecker and R. C. Green, “Diagnostic Clinical Genome and Exome Sequencing,” *New England Journal of Medicine* 370, no. 25 (2014): 2418-2425; National Cancer Institute, *PDQ Cancer Genetics Risk Assessment and Counseling, The Option of Genetic Testing*, at <https://www.cancer.gov/about-cancer/causes-prevention/genetics/risk-assessment-pdq#section/77> (last updated March 1, 2019) (last visited May 25, 2019) (synthesizing the considerations of the clinical decision-making process); V. Okur and W. Chung, “The Impact of Hereditary Cancer Gene Panels on Clinical Care and Lessons Learned,” *Cold Spring Harbor Molecular Case Studies* 3, no. 6 (2017): 1-15.

⁹ See J. P. Evans, B. C. Powell, and J. S. Berg, “Finding the Rare Pathogenic Variants in a Human Genome,” *JAMA* 317, no. 18 (2017): 1904-1905.

¹⁰ W. W. Grody, G. R. Cutting, and M. S. Watson, “The Cystic Fibrosis Mutation ‘Arms Race’: When Less Is More,” *Genetics in Medicine* 9, no. 11 (2007): 739-744.

¹¹ J. Amos et al., American College of Medical Genetics, “Technical Standards and Guidelines for CFTR Mutation Testing,” *Genetics in Medicine* 4, no. 5 (2002): 379-391.

¹² D. Skinner et al., “‘Possibly Positive or Certainly Uncertain?’ Participants’ Responses to Uncertain Diagnostic Results from Exome Sequencing,” *Genetics in Medicine* 20, no. 3 (2018): 313-319; K. E. Weck, “Interpretation of Genomic Sequencing: Variants Should Be Considered Uncertain Until Proven Guilty,” *Genetics in Medicine* 20, no. 3 (2018): 291-293.

¹³ See, e.g., Evans et al., *supra* note 9, at 1904.

¹⁴ See, e.g., S. Richards et al., “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,” *Genetics in Medicine* 17, no. 5 (2015): 406-407.

¹⁵ See A. K. Manrai et al., “Genetic Misdiagnoses and the Potential for Health Disparities,” *New England Journal of Medicine* 375, no. 7 (2016): 655-665; see also J. Caswell-Jin et al., “Racial/Ethnic Differences in Multiple-Gene Sequencing Results for Hereditary Cancer Risk,” *Genetics in Medicine* 20, no. 2 (2018): 234-239; A. Yorzcyk et al., “Use of Panel Tests in Place of Single Gene Tests in the Cancer Genetics Clinic,” *Clinical Genetics* 88, no. 3 (2014): 278-282 (demonstrating that minorities have higher rates of VUSs).

-
- ¹⁶ D. G. MacArthur et al., “Guidelines for Investigating Causality of Sequence Variants in Human Disease,” *Nature* 508, no. 7497 (2014): 469-476.
- ¹⁷ T. Ray, Genomeweb, *Mother’s Negligence Suit against Quest’s Athena Could Broadly Impact Genetic Testing Labs*, at <<https://www.genomeweb.com/molecular-diagnostics/mothers-negligence-suit-against-quests-athena-could-broadly-impact-genetic#.Wqx5wIjwbSE>> (last visited May 25, 2019).
- ¹⁸ Richards et al., *supra* note 14, at 405-424.
- ¹⁹ One example is Genome Aggregation Database, at <<http://gnomad.broadinstitute.org/>> (last visited May 25, 2019).
- ²⁰ Y. A. Stevens, G. Senner, and G. E. Marchant, “Physicians’ Duty to Recontact and Update Genetic Advice,” *Personalized Medicine* 14, no. 4 (2017): 367-374. The quality and coverage of genome-wide sequencing has improved over time, so relying on old sequence data may not be reliable and it may be justified to redo the sequencing where there is a medical need to do so. However, as genome-wide sequencing continues to improve, it may not be necessary to redo the sequencing and instead continue to rely on the previous sequence data over time. This ongoing reliance on previous genomic sequence results without periodic retesting is unique in medical testing.
- ²¹ H. L. Rehm et al., “ClinGen—The Clinical Genome Resource,” *New England Journal of Medicine* 372, no. 23 (2015): 2235-2242.
- ²² J. M. Beck, “Product Liability Implications of Pharmacogenomics Advances,” For the Defense, September 2015, at 33, available at <<https://www.reedsmith.com/en/perspectives/2015/09/product-liability-implications-of-pharmacogenomic>> (last visited May 25, 2019); T. Kelton, “Pharmacogenomics: The Rediscovery of the Concept of Tailored Drug Therapy and Personalized Medicine,” *The Health Lawyer* 19, no. 3 (2007): 3-10.
- ²³ J. H. Yu et al., “Self-Guided Management of Exome and Whole Genome Sequencing Results: Changing the Results Return Model,” *Genetics in Medicine* 15, no. 9 (2013): 684-690; see also B. Rabbani, M. Tekin, and N. Mahdieh, “The Promise of Whole-Exome Sequencing in Medical Genetics,” *Journal of Human Genetics* 59, no. 1 (2014): 5-15.
- ²⁴ A. Richardson, “Incidental Findings and Future Testing Methodologies: Potential Application of the ACMG 2013 Recommendations,” *Journal of Law and the Biosciences* 1, no. 3 (2014): 378-397; G. Lázaro-Muñoz, “The Fiduciary Relationship Model for Managing Clinical Genomic ‘Incidental’ Findings,” *Journal of Law, Medicine & Ethics* 42, no. 4 (2014): 576-589.
- ²⁵ See generally A. Stein, “Toward a Theory of Medical Malpractice,” *Iowa Law Review* 97, no. 4 (2012): 1229-1232.
- ²⁶ While alerts would provide more support than is now available, it should be noted that high-volume usage may make alerts less effective. D. Murphy et al., “Notifications Received by Primary Care Practitioners in Electronic Health Records: A Taxonomy and Time Analysis,” *American Journal of Medicine* 125, no. 2 (2012): 209.e1-209.e7.
- ²⁷ See, e.g., J. P. Evans and M. J. Khoury, “The Arrival of Genomic Medicine to the Clinic Is Only the Beginning of the Journey,” *Genetics in Medicine* 15, no. 4 (2013): 268-269; M. J. Khoury et al., “How Can Polygenic Inheritance Be Used in Population Screening for Common Disease?,” *Genetics in Medicine* 15, no. 6 (2013): 437-443; M. J. Khoury et al., “Population Screening in the Age of Genomic Medicine,” *New England Journal of Medicine* 348, no. 1 (2003): 50-58; see also S. G. Nicholls et al., “Attitudes to Incorporating Genomic Risk Assessment into Population Screening Programs: The Importance of Purpose, Context and Deliberation,” *BMC Medical Genomics* 9, no. 25 (2016): 1-13.
- ²⁸ Color Genomics Inc., available at <https://www.color.com/> (last visited May 25, 2019); 23andMe, available at <https://www.23andme.com/> (last visited May 25, 2019).
- ²⁹ See The 1000 Genomes Project Consortium, “A Map of Human Genome Variation from Population-Scale Sequencing,” *Nature* 467, no. 7319 (2010): 1061-1073; N. Roberts et al., “The Predictive Capacity of Personal Genome Sequencing,” *Science Translational Medicine* 4, no. 33 (2012): 1-9 (exploring potential determinative value of genomic testing in monozygotic twins); M. C. Adams et al., “The Promise and Peril of Genomic Screening in the General Population,” *Genetics in Medicine* 18, no. 6 (2016): 593-599. But see J. L. Vassy et al., “The Impact of Whole-Genome Sequencing on the Primary

Care and Outcomes of Healthy Adult Patients: A Pilot Randomized Trial,” *Annals of Internal Medicine* 167, no. 3 (2017): 159-169 (“Although some PCPs may be able to manage the results appropriately, WGS may prompt additional clinical actions without evidence of short-term distress or clinical utility.”).

³⁰ See Evans et al., *supra* note 9, at 1905.

³¹ D. M. Studdert, M. Mello, and T. Brennan, “Medical Malpractice,” *New England Journal of Medicine* 350, no. 3 (2004): 283-292; D. M. Studdert et al., “Negligent Care and Malpractice Claiming Behavior in Utah and Colorado,” *Medical Care* 38, no. 3 (2000): 250-260; A. R. Localio et al., “Relation Between Malpractice Claims and Adverse Events Due to Negligence: Results of the Harvard Medical Practice Study III,” *New England Journal of Medicine* 325, no. 4 (1991): 245-251. For further context on the Harvard Medical Practice Study, see T. A. Brennan et al., “Incidence of Adverse Events and Negligence in Hospitalized Patients—Results of the Harvard Medical Practice Study I,” *New England Journal of Medicine* 324, no. 6 (1991): 370-376; L. L. Leape, “The Nature of Adverse Events in Hospitalized Patients — Results of the Harvard Medical Practice Study II,” *New England Journal of Medicine* 324, no. 6 (1991): 377-384.

³² Studdert, Mello, and Brennan, *supra* note 31, at 283-292.

³³ D. M. Studdert et al., “Defensive Medicine Among High-Risk Specialist Physicians in a Volatile Malpractice Environment,” *JAMA* 293, no. 21 (2005): 2609-2917; D. Kessler and M. McClellan, “Do Doctors Practice Defensive Medicine?,” *Quarterly Journal of Economics* 111, no. 2 (1996): 353-390. There is significant disagreement about the extent and overall costs of defensive medicine in clinical care, with some experts suggesting that the costs of defensive medicine are minimal. See, e.g., A. Brateanu et al., “Quantifying the Defensive Medicine Contribution to Primary Care Costs,” *Journal of Medical Economics* 17, no. 11 (2014): 810-816, at 810 (“Defensive medicine appears to have minimal impact on primary care costs.”).

³⁴ W. M. Sage, “Medical Liability and Patient Safety,” *Health Affairs* 22, no. 4 (2003): 26-36; K. De Ville, “Medical Malpractice in Twentieth Century United States. The Interaction of Technology, Law and Culture,” *International Journal of Technology Assessment in Health Care* 14, no. 2 (1998): 197-211.

³⁵ M. D. Greenberg, “Medical Malpractice and New Devices: Defining an Elusive Standard of Care,” *Health Matrix* 19, no. 2 (2009): 423-445; A. J. Sokol and C. J. Molzen, “The Changing Standard of Care in Medicine: E-Health, Medical Errors, and Technology Add New Obstacles,” *Journal of Legal Medicine* 23, no. 4 (2002): 449-490.

³⁶ J. Plunkett-Rondeau et al., “Training Future Physicians in the Era of Genomic Medicine: Trends in Undergraduate Medical Genetics Education,” *Genetics in Medicine* 17, no. 11 (2015): 927-934; M. Baars et al., “Deficient Knowledge of Genetics Relevant for Daily Practice Among Medical Students Nearing Graduation,” *Genetics in Medicine* 7, no. 5 (2005): 295-301.

³⁷ M. H. Lewis, J. K. Gohagan, and D. J. Merenstein, “The Locality Rule and the Physician’s Dilemma: Local Medical Practice vs the National Standard of Care,” *JAMA* 297, no. 23 (2007): 2633-2637.

³⁸ *Id.*; P. G. Peters, Jr., “The Quiet Demise of Deference to Custom: Malpractice Law at the Millennium,” *Washington & Lee Law Review* 57, no. 1 (2000): 163-205.

³⁹ In our recommendations that follow, we frequently recommend the adoption or updating of clinical guidelines to help medical and legal actors navigate the complex issues that will be raised by clinical genomics. We condition this reliance on guidelines on the assumption that they can be adopted and updated on a timely basis.

⁴⁰ As of 2007, twenty-nine states and the District of Columbia use a national standard, but twenty-one states define the standard of care in part or whole through reference to a “particular locality.” Lewis, Gohagan, and Merenstein, *supra* note 37, at 2634. In some states with a national standard of care, the rule is mediated by resource-based considerations, such as “the availability of facilities and the proximity of specialists,” but in those states, locality is irrelevant to “skill, learning, and clinical competence” *Id.* Using a national standard of care satisfies the intuitive desire for patients to receive competent care no matter where they are, and removes a procedural barrier to malpractice suits, since patients can call expert witnesses who work outside the locality. *Id.*

-
- ⁴¹ W. Burke et al., “Improving Recommendations for Genomic Medicine: Building an Evolutionary Process from Clinical Practice Advisory Documents to Guidelines,” *Genetics in Medicine* 2019 Jun 4. doi: 10.1038/s41436-019-0549-3. [Epub ahead of print]
- ⁴² See, e.g., N. A. Mikat-Stevens, I. A. Larson, and B. A. Tarini, “Primary-care Providers’ Perceived Barriers to Integration of Genetics Services: A Systematic Review of the Literature,” *Genetics in Medicine* 17, no. 3 (2015): 169-176.
- ⁴³ See, e.g., S. K. Warring et al., “Inaccurate Diagnosis of Brugada Syndrome in a Healthy Woman Based on SCN5A Mutation Classification,” *Heart Rhythm Case Reports* 3, no. 10 (2017): 450-454; J. R. Giudicessi, A. A. M. Wilde, and M. J. Ackerman, “The Genetic Architecture of Long QT Syndrome: A Critical Reappraisal,” *Trends in Cardiovascular Medicine* 28, no. 7 (2018): 453-464 (referring to the “VUS crisis” of variants improperly or hastily classified as influencing susceptibility to specific diseases).
- ⁴⁴ T. A. Manolio, “Genomewide Association Studies and Assessment of the Risk of Disease,” *New England Journal of Medicine* 363, no. 2 (2010): 166-176 (stating that non-coding regions are also associated with the pathogenesis of disease).
- ⁴⁵ In this context, depth of coverage refers to repeated readings of the same nucleotide during sequencing. Higher coverage augments the ability to accurately distinguish errors from variants. D. Sims et al., “Sequencing Depth and Coverage: Key Considerations in Genomic Analyses,” *Nature Reviews Genetics* 15, no. 2 (2014): 121-132.
- ⁴⁶ R. C. Green et al., “ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing,” *Genetics in Medicine* 15, no. 7 (2013): 565-574; R. C. Green, H. Rehm, and I. Kohane, “Clinical Genome Sequencing,” in *Genomic and Personalized Medicine* (G. Ginsburg & H. Willard, eds., 2d ed. 2012): at 102-123; R. C. Green et al., “Exploring Concordance and Discordance for Return of Incidental Findings from Clinical Sequencing,” *Genetics in Medicine* 14, no. 4 (2012): 405-410; see also Henderson, *supra* note 2, at 344-355.
- ⁴⁷ See, e.g., S. M. Domcheck and K. L. Nathanson, “Panel Testing for Inherited Susceptibility to Breast, Ovarian, Colorectal Cancer,” *Genetics in Medicine* 16, no. 11 (2014): 827-829; L. E. Minion et al., “Predisposition to Ovarian Cancer, Looking Beyond BRCA1/BRCA2,” *Gynecologic Oncology* 137, no. 1 (2015): 86-92; see also R. Kamps et al., “Next-Generation Sequencing in Oncology: Genetic Diagnosis, Risk Prediction and Cancer Classification,” *International Journal of Molecular Science* 18, no. 2 (2017): 308 (57 pages); Yorczyk, *supra* note 15.
- ⁴⁸ <https://www.ambrygen.com/clinician/genetic-testing/32/cardiology/customnext-cardio-r> (last visited Oct. 18, 2019).
- ⁴⁹ See, e.g., J. J. Rachlinski, “A Positive Psychological Theory of Judging in Hindsight,” 65 *University of Chicago Law Review* 65, no. 2 (1998): 571-625; E. M. Harley, “Hindsight Bias in Legal Decision Making,” *Social Cognition* 25, no. 1 (2007): 48-63; N. J. Roese and K. D. Vohs, “Hindsight Bias,” *Perspectives on Psychological Science* 7, no. 5 (2012): 411-426.
- ⁵⁰ Manufacturers have a responsibility to provide information regarding their product to the health care provider but not the patient. The liability then falls on the health care provider, who is responsible for adequately informing the patient of the risks and benefits of a product’s use. The provider’s recommendations are tailored to an individual patient’s situation. D. B. Dobbs, P. T. Hayden, and E. M. Bublick, *Dobbs’ Law of Torts* (St. Paul, MN: West Academic Publishing, 2018): at § 466.
- ⁵¹ S. E. Pegalis, *American Law of Medical Malpractice* (St. Paul, MN: West Academic Publishing, 2017): at § 20:23; Stein, *supra* note 25, at 1201-1257; P. Moffett and G. Moore, “The Standard of Care: Legal History and Definitions: The Bad and Good News,” *Western Journal of Emergency Medicine* 12, no. 1 (2011): 109-112.
- ⁵² G. E. Marchant and R. A. Lindor, “Genomic Malpractice: An Emerging Tide or Gentle Ripple?,” *Food & Drug Law Journal* 73, no. 1 (2018): 1-37; G. E. Marchant and R. A. Lindor, “Personalized Medicine and Genetic Malpractice,” *Genetics in Medicine* 15, no. 12 (2013): 921-922; R. A. Lindor and G. E. Marchant, “A Review of Medical Malpractice Claims Related to Clinical Genetic Testing,” *Journal of Clinical Oncology* 29, no. 15 (2011): 6073.

-
- ⁵³ Virginia Lawyers Media, “Verdicts & Settlements: Metastatic Cancer Originally Diagnosed as Non-Invasive,” *Virginia Lawyers Weekly*, Dec. 29, 2014, available at <<http://www.tavss.com/library/VLW-Tavss-Fletcher-122914.pdf>> (last visited May 25, 2019); E. R. Carrier et al., “High Physician Concern About Malpractice Risk Predicts More Aggressive Diagnostic Testing in Office-Based Practice,” *Health Affairs* 32, no. 8 (2013): 1383-1391.
- ⁵⁴ Virginia Lawyers Media, *supra* note 53.
- ⁵⁵ N. M. Lindor, S. N. Thibodeau, and W. Burke, “Whole Genome Sequencing in Healthy People,” *Mayo Clinic Proceedings* 92, no. 1 (2017): 159-172.
- ⁵⁶ A. Thorogood, R. Cook-Deegan, and B. M. Knoppers, “Public Variant Databases: Liability?,” *Genetics in Medicine* 19, no. 7 (2017): 838-841; Ray, *supra* note 17.
- ⁵⁷ A. W. Kurian et al., “Gaps in Incorporating Germline Genetics Testing into Treatment Decision-Making for Early-Stage Breast Cancer,” *Journal of Clinical Oncology* 35, no. 20 (2017): 2232-2239; J. Armstrong et al., “Utilization and Outcomes of BRCA Genetics Testing and Counseling in a National Commercially Insured Population,” *JAMA Oncology* 1, no. 9 (2015): 1251-1260.
- ⁵⁸ A. K. Manrai, J. P. A. Ioannidis, and I. S. Kohane, “From Pathogenicity Claims to Quantitative Risk Estimates,” *JAMA* 315, no. 12 (2016): 1233-1234, at 1233 (“A report of pathogenicity has major limitations for decision making. First, it is imprecise—how likely is a patient with a pathogenic variant to express disease? Second, it is coarse—2 distinct pathogenic variants need not convey the same disease risk. Third, it reduces a variant to a single role—a pathogenic variant may not be pathogenic in patients with a different genomic background and different nongenomic risk factors; the risk for disease and the need for treatment or other action may vary substantially across these patients.”).
- ⁵⁹ Lindor & Marchant, *supra* note 52, at 6073.
- ⁶⁰ See *supra* note 22 and accompanying text.
- ⁶¹ G. E. Marchant, K. Scheckel, and D. Campos-Outcalt, “Contrasting Medical and Legal Standards of Evidence: A Precision Case Study,” *Journal of Law, Medicine & Ethics* 44, no. 1 (2016): 194-204, at 201.
- ⁶² See T. A. Manolio et al., “Implementing Genomic Medicine in the Clinic: The Future is Here,” *Genetics in Medicine* 15, no. 4 (2013): 258-267; O. Gottesman et al., “The Electronic Medical Records and Genomics (eMERGE) Network: Past, Present, and Future,” *Genetics in Medicine* 15, no. 10 (2013): 761-771; P. H. O’Donnell et al., “The 1200 Patients Project: Creating a New Medical Model System for Clinical Implementation of Pharmacogenomics,” *Clinical Pharmacology & Therapeutics* 92, no. 4 (2012): 446-449.
- ⁶³ See Marchant & Lindor, “Genomic Malpractice: An Emerging Tide or Gentle Ripple?,” *supra* note 52, at 9.
- ⁶⁴ E. J. Stanek et al., “Adoption of Pharmacogenomic Testing by US Physicians: Results of a Nationwide Survey,” *Clinical Pharmacology & Therapeutics* 91, no. 3 (2012): 450-458.
- ⁶⁵ K. A. Johansen Taber and B. D. Dickinson, “Pharmacogenomic Knowledge Gaps and Educational Resource Needs Among Physicians in Selected Specialties,” *Pharmacogenomics & Personalized Medicine* 7, no. 1 (2014): 145-162; P. J. Caraballo et al., “Multidisciplinary Model to Implement Pharmacogenomics at the Point of Care,” *Genetics in Medicine* 19, no. 4 (2017): 421-429; M. C. Roberts et al., “The Current State of Implementation Science in Genomic Medicine: Opportunities for Improvement,” *Genetics in Medicine* 19, no. 8 (2017): 858-863.
- ⁶⁶ Food and Drug Administration (FDA), *Table of Pharmacogenomic Biomarkers in Drug Labeling*, at <<https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm>> (last updated March 26, 2019) (last visited May 25, 2019).
- ⁶⁷ See, e.g., *Richardson v. Miller*, 44 S.W.3d 1, 16 (Tenn. Ct. App. 2000) (“majority of jurisdictions have determined that a prescription drug’s labeling... is admissible to prove the standard of care, but only if the plaintiff also introduces other expert testimony regarding the standard of care”). But see *Arnold v. Lee*, 720 N.W.2d 194, 194 (Iowa Ct. App. 2006) (package insert not admissible as evidence of standard of care).
- ⁶⁸ S. Mallal et al., “HLA-B*5701 Screening for Hypersensitivity to Abacavir,” *New England Journal of Medicine* 358, no. 6 (2008): 568-579.

-
- ⁶⁹ T. Moriyama et al., “NUDT15 Polymorphisms Alter Thiopurine Metabolism and Hematopoietic Toxicity,” *Nature Genetics* 48, no. 4 (2016): 367-373.
- ⁷⁰ Marchant, Scheckel, and Campos-Outcalt, *supra* note 58, at 194-204; L. H. Cavallari and E. A. Nutescu, “Warfarin Pharmacogenetics: To Genotype or Not to Genotype, That is the Question,” *Clinical Pharmacology & Therapeutics* 96, no. 1 (2014): 22-23.
- ⁷¹ J. Yi et al., “Clinical Pharmacogenomics Testing in the Era of Next Generation Sequencing: Challenges and Opportunities for Precision Medicine,” *Expert Review of Molecular Diagnostics* 18, no. 5 (2018): 411-421.
- ⁷² J. B. Krier and R. C. Green, “Management of Incidental Findings in Clinical Genomic Sequencing,” *Current Protocols in Human Genetics* 9, no. 23 (2013): 1-13 (citing R. C. Green, H. L. Rehm, and I. Kohane, “Challenges in the Clinical Use of Genome Sequencing,” in G. Ginsberg and H. Willard, eds., *Genomic and Personalized Medicine* (New York: Academic Press, 2d ed. 2013): 283-292). The Presidential Commission for the Study of Bioethical Issues similarly notes that incidental findings have been defined as “results that arise that are outside the original purpose for which the test or procedure was conducted.” Presidential Commission for the Study of Bioethics Issues, “Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in Clinical, Research, and Direct-to-Consumer Contexts” (Dec. 2013), at 2, available at <https://bioethicsarchive.georgetown.edu/pcsbi/sites/default/files/FINALAnticipateCommunicate_PCSBI_0.pdf> (citing S. M. Wolf et al., “Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations,” *Journal of Law, Medicine & Ethics* 36, no. 2 (2008): 219-248).
- ⁷³ See, e.g., I. S. Kohane, M. Hsing, and S. W. Kong, “Taxonomizing, Sizing, and Overcoming the Incidentalome,” *Genetics in Medicine* 14, no. 4 (2012): 399-404.
- ⁷⁴ For analysis in the context of research, see, e.g., R. R. Fabsitz et al., “Ethical and Practical Guidelines for Reporting Genetic Research Results to Study Participants: Updated Guidelines from a National Heart, Lung, and Blood Institute Working Group,” *Circulation: Cardiovascular Genetics* 3, no. 6 (2010): 574-580; Wolf et al., “Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations,” *supra* note 72; S. M. Wolf et al., “Managing Incidental Findings and Research Results in Genomic Research Involving Biobanks & Archived Datasets,” *Genetics in Medicine* 14, no. 4 (2012): 361-384; G. P. Jarvik et al., “Return of Results to Research Participants: The Floor, the Ceiling, and the Choices in Between,” *American Journal of Human Genetics* 94, no. 6 (2014): 818-826; S. M. Wolf, W. Burke, and B. A. Koenig, “Mapping the Ethics of Translational Genomics: Situating Return of Results and Navigating the Research-Clinical Divide,” *Journal of Law, Medicine & Ethics* 43, no. 3 (2015): 486-501; S. M. Wolf et al., “Returning a Research Participant’s Genomic Results to Relatives: Analysis & Recommendations,” *Journal of Law, Medicine & Ethics* 43, no. 3 (2015): 440-463. For recent debate, compare National Academies of Science, Engineering, and Medicine, “Returning Individual Research Results to Participants: Guidance for a New Research Paradigm” (2018), available at <<https://www.nap.edu/catalog/25094/returning-individual-research-results-to-participants-guidance-for-a-new>> (last visited January 31, 2018), with S. M. Wolf and B. J. Evans, “Return of Results and Data to Study Participants,” *Science* 362, no. 6411 (2018): 159-160, and B. J. Evans and S. M. Wolf, “A Faustian Bargain that Undermines Research Participants’ Privacy Rights and Return of Results,” *Florida Law Review* (forthcoming 2019)..
- ⁷⁵ For analysis in the context of clinical care, see, e.g., J. S. Berg, M. J. Khoury, and J. P. Evans, “Deploying Whole Genome Sequencing in Clinical Practice and Public Health: Meeting the Challenge One Bin at a Time,” *Genetics in Medicine* 13, no. 6 (2011): 499-504; S. M. Wolf, “The Continuing Evolution of Ethical Standards for Genomic Sequencing in Clinical Care: Restoring Patient Choice,” *Journal of Law, Medicine & Ethics* 45, no. 3 (2017): 333-340; Green et al., “ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing,” *supra* note 44; M. I. Roche and J. A. Berg, “Incidental Findings with Genomic Testing: Implications for Genetics Counseling Practice,” *Current Genetic Medicine Reports* 3, no. 4 (2015): 166-176.
- ⁷⁶ For analysis in the context of public health screening, see, e.g., B. M. Knoppers et al., “Whole-Genome Sequencing in Newborn Screening Programs,” *Science Translational Medicine* 6, no. 229 (2014):

229cm2; M. J. Khoury, M. F. Iademarco, and W. T. Riley, "Precision Public Health for the Era of Precision Medicine," *American Journal of Preventative Medicine* 50, no. 3 (2016): 398-401; R. F. Green et al., "Genomics in Public Health: Perspective from the Office of Public Health Genomics at the Centers for Disease Control and Prevention," *Healthcare* 3, no. 3 (2015): 830-837; W. Burke et al., "The Path from Genome-Based Research to Population Health: Development of an International Public Health Genomics Network," *Genetics in Medicine* 8, no. 7 (2006): 451-458.

⁷⁷ "CLIA-compliant" refers here to both laboratories that are CLIA-certified and those that are CLIA-exempt because they comply with state law requirements that have been found to equal or exceed those imposed by the federal CLIA scheme. Currently, the two states that qualify are New York and Washington.

⁷⁸ For literature addressing this translational character of incidental findings that are discovered in research with implications for clinical care, see, e.g., S. M. Wolf, "Return of Individual Research Results and Incidental Findings: Facing the Challenges of Translational Science," *Annual Review of Genomics and Human Genetics* 14 (2013): 557-577; Wolf et al., "Mapping the Ethics of Translational Genomics," *supra* note 73.

⁷⁹ E. W. Clayton et al., "Managing Incidental Genomic Findings: Legal Obligations of Clinicians," *Genetics in Medicine* 15, no. 8 (2013): 624-629.

⁸⁰ See, e.g., L. L. Berland et al., "Managing Incidental Findings on Abdominal CT: White Paper of the ACR Incidental Findings Committee," *Journal of the American College of Radiology* 7, no. 10 (2010): 754-773; H. MacMahon et al., "Guidelines for the Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017," *Radiology* 284, no. 1 (2017): 228-243.

⁸¹ Green et al., "ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing," *supra* note 47. These recommendations have since been updated. See note 83 *infra*.

⁸² See, e.g., S. M. Wolf, G. J. Annas, and S. Elias, "Patient Autonomy and Incidental Findings in Clinical Genomics," *Science* 340, no. 6136 (2013): 1049-1050; A. L. McGuire et al., "Ethics and Genomic Incidental Findings," *Science* 340, no. 6136 (2013): 1047-1048; W. Burke et al., "Recommendations for Returning Genomic Incidental Findings? We Need to Talk!," *Genetics in Medicine* 15, no. 11 (2013): 854-859; E. W. Clayton et al., "Addressing the Ethical Challenges in Genetic Testing and Sequencing of Children: Recent Statements by the American Academy of Pediatrics and the American College of Medical Genetics and Genomics," *American Journal of Bioethics* 14, no. 3 (2014): 3-9; Wolf, "The Continuing Evolution of Ethical Standards for Genomic Sequencing in Clinical Care: Restoring Patient Choice," *supra* note 74; R. Klitzman, P. S. Appelbaum, and W. Chung, "Return of Secondary Genomic Findings vs Patient Autonomy: Implications for Medical Care," *JAMA* 310, no. 4 (2013): 369-370.

⁸³ American College of Medical Genetics and Genomics (ACMG), "Incidental Findings in Clinical Genomics: A Clarification," *Genetics in Medicine* 15, no. 8 (2013): 664-666; ACMG Board of Directors, "ACMG Policy Statement: Updated Recommendations Regarding Analysis and Reporting of Secondary Findings in Clinical Genome-Scale Sequencing," *Genetics in Medicine* 17, no. 1 (2015): 68-69; S. S. Kalia et al., "Recommendations for Reporting of Secondary Findings in Clinical Exome and Genome Sequencing, 2016 Update (ACMG SF v2.0): A Policy Statement of the American College of Medical Genetics and Genomics," *Genetics in Medicine* 19, no. 2 (2017): 249-255.

⁸⁴ See, e.g., Jarvik, *supra* note 72, at 820; S. M. Wolf, J. Paradise, and C. Caga-anan, "The Law of Incidental Findings in Human Subjects Research: Establishing Researchers' Duties," *Journal of Law, Medicine & Ethics* 36, no. 2 (2008): 361-383.

⁸⁵ See, e.g., B. M. Knoppers, "From the Right to Know to the Right Not to Know," *Journal of Law, Medicine & Ethics* 42, no. 1 (2014): 6-10.

⁸⁶ See, e.g., Knoppers, *supra* note 84; C. Allen, K. Sénécal, and D. Avar, "Defining the Scope of Public Engagement: Examining the 'Right Not to Know' in Public Health Genomics," *Journal of Law, Medicine & Ethics* 42, no. 1 (2014): 11-18; P. Borry, M. Shabani, and H. C. Howard, "Is There a Right Time to Know? The Right Not to Know and Genetic Testing in Children," *Journal of Law, Medicine & Ethics* 42, no. 1 (2014): 19-27; G. Helgesson, "Autonomy, the Right Not to Know, and the Right to Know Personal Research Results: What Rights are There, and Who Should Decide About Exceptions?," *Journal of Law,*

Medicine & Ethics 42, no. 1 (2014): 28-37; N. Juth, “The Right Not to Know and the Duty to Tell: The Case of Relatives,” *Journal of Law, Medicine & Ethics* 42, no. 1 (2014): 38-52; G. Laurie, “Recognizing the Right Not to Know: Conceptual, Professional, and Legal Implications,” *Journal of Law, Medicine & Ethics* 42, no. 1 (2014): 53-63.

⁸⁷ See, e.g., Friedman et al., *supra* note 5, at 1-13.

⁸⁸ Wolf et al., *supra* note 74, at 219.

⁸⁹ The *Ande v. Rock* case addressed return of genetic/genomic results in the context of research. *Ande v. Rock*, 647 N.W.2d 265 (Wisc. Ct. App. 2002). Parents sued physicians at a university conducting research, claiming that the physicians failed to alert the parents to their child’s positive test for cystic fibrosis. The court rejected the claim on the grounds that there was no physician/patient relationship between the child and the defendant physicians, a necessary part of a malpractice claim. However, the court did not consider whether the researchers negligently breached their duties as researchers.

⁹⁰ See, e.g., S. Vos et al., “Moral Duties of Genomics Researchers: Why Personalized Medicine Requires a Collective Approach,” *Trends in Genetics* 33, no. 2 (2017): 118-128; Wolf et al., *supra* note 72.

⁹¹ A. C. Milstein, “Research Malpractice and the Issue of Incidental Findings,” *Journal of Law, Medicine & Ethics* 36, no. 2 (2008): 356-360. Cf. *Grimes v. Kennedy Krieger Institute*, 782 A.2d 807 (Md. 2001) (vacating summary judgment for defendant researchers who failed to communicate to parents the researchers’ findings concerning the lead exposure of individual children enrolled in the study).

⁹² Wolf, Paradise, and Caga-anan, *supra* note 84. The 2017 revision to the Common Rule includes provisions regarding return of research results, which would include incidental or secondary findings. These changes recognize that researchers may have duties to alert prospective participants to the possibility of discovering incidental findings and the researchers’ plan for managing and disclosing them. See, e.g., “Federal Policy for the Protection of Human Subjects,” *Federal Register* 82 (2017): 7149-7274, at 7266, available at <<https://www.govinfo.gov/app/details/FR-2017-01-19-2017-01158>> (last visited May 26, 2019).

⁹³ Wolf, Paradise, and Caga-anan, *supra* note 84, at 367 (quoting 45 C.F.R. §46.116(b) and citing 21 C.F.R. §50.25(b)).

⁹⁴ See *id.* at 369-73, analyzing *Grimes*, 782 A.2d 807 and *Blaz v. Michael Reese Hosp. Found.*, 74 F. Supp. 2d 803 (N.D. Ill. 1999).

⁹⁵ Cf. *Moore v. Regents of the Univ. of Cal.*, 793 P.2d 479 (Cal. 1990).

⁹⁶ See, e.g., A. L. Bredenoord et al., “Disclosure of Individual Genetic Data to Research Participants: The Debate Reconsidered,” *Trends in Genetics* 27, no. 2 (2011): 41-47; G. E. Henderson et al., “Clinical Trials and Medical Care: Defining the Therapeutic Misconception,” *PLOS Medicine* 4, no. 11 (2007): e324.

⁹⁷ See J. S. Berg et al., “Processes and Preliminary Outputs for Identification of Actionable Genes as Incidental Findings in Genomic Sequence Data in the Clinical Sequencing Exploratory Research Consortium,” *Genetics in Medicine* 15, no. 11 (2013): 860-867; W. Burke, B. J. Evans, and G. P. Jarvik, “Return of Results: Ethical and Legal Distinctions between Research and Clinical Care,” *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* 166, no. 1 (2014): 105-111.

⁹⁸ Jarvik, *supra* note 73, at 818–826. For further discussion that post-dates the article by Jarvik et al., see National Academies of Science, Engineering, and Medicine, *supra* note 73; Wolf & Evans, *supra* note 73; Evans & Wolf, *supra* note 73.

⁹⁹ See S. M. Wolf et al., “Navigating the Research-Clinical Interface in Genomic Medicine: Analysis from the CSER Consortium,” *Genetics in Medicine* 20, no. 5 (2018): 545-553; Wolf et al., “Mapping the Ethics of Translational Genomics,” *supra* note 74.

¹⁰⁰ See, e.g., Henderson, *supra* note 2.

¹⁰¹ See Dep’t of Health and Human Services, “HHS Strengthens Patients’ Right to Access Lab Test Reports,” available at <<https://www.hhs.gov/hipaa/for-professionals/special-topics/cli/index.html>> (last visited January 31, 2019).

¹⁰² See Department of Health and Human Services, “Individuals’ Right under HIPAA to Access their Health Information 45 CFR § 164.524,” available at <<https://www.hhs.gov/hipaa/for-professionals/privacy/guidance/access/index.html>> (last visited February 1, 2019).

¹⁰³ See National Academies of Science, Engineering, and Medicine, *supra* note 71, at Appendix C; Wolf & Evans, *supra* note 71; U.S. Department of Health & Human Services, Secretary’s Advisory Committee on Human Research Protections (SACHRP), “Attachment C: Return of Individual Results and Special Consideration of Issues Arising from Amendments of HIPAA and CLIA,” *available at* <<https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2015-september-28-attachment-c/index.html>> (last visited February 10, 2019).

¹⁰⁴ In one case, a patient’s misdiagnosis with *BRCA1* and *BRCA2* resulted in unnecessary mastectomy and hysterectomy. See T. Camp, “Woman Has Unnecessary Mastectomy, Hysterectomy After Misdiagnosis,” *available at* <<https://www.abc12.com/content/news/435684723.html>> (last updated July 20, 2017) (last visited May 29, 2019); see also *McCauley v. Lake County Dept. of Child Services, Indiana*, 2008 WL 5333324 (N.D. Ind. 2008) (hospital’s request for summary judgment denied; court found that the failure to correct a misdiagnosis constituted negligence); *M.M.H. v. U.S.*, 966 F.2d 285 (7th Cir. 1992) (court found that while the U.S. Army had immunity for an initial misdiagnosis of HIV, it could be held liable for its failure to inform the patient of the misdiagnosis upon its discovery). Cf. The Irish Times, “Hospital apologizes to woman given wrong test result for breast cancer gene,” (“[W]oman who was given the incorrect ‘normal’ diagnosis for a breast cancer gene test nine years ago... now seriously ill with ovarian cancer.”), *available at* <<https://www.irishtimes.com/news/crime-and-law/courts/high-court/hospital-apologises-to-woman-given-wrong-test-result-for-breast-cancer-gene-1.3908212>> (last updated May 29, 2019) (last visited June 3, 2019).

¹⁰⁵ S. L. Van Dries et al., “Association of Arrhythmia-Related Genetic Variants with Phenotypes Documented in Electronic Medical Records,” *JAMA* 315, no. 1 (2016): 47–57.

¹⁰⁶ Stevens et al., *supra* note 20, at 368.

¹⁰⁷ *Id.*; C. T. Drechsler, “Liability of Physician Who Abandons Case,” *American Law Reports 2nd* (Originally published in 1958): 432-509.

¹⁰⁸ Stevens et al., *supra* note 20, at 368; *Tresemmer v. Burke*, 86 Cal. App. 3d 656 (1978).

¹⁰⁹ Stevens et al., *supra* note 20, at 368.

¹¹⁰ See e.g., Y. Bombard et al., “The Responsibility to Recontact Research Participants after Reinterpretation of Genetic and Genomic Results,” *American Journal of Human Genetics* 104, no. 4 (2019): 578-595, at 580 (“More recent reclassification reports in both clinical and research settings demonstrate that the majority of reclassifications are downgrades, largely because of the emergence of resources to document allele frequencies in diverse populations as well as more rigorous criteria for classifying pathogenic sequence variants.”); K. Klast, P. Wimberger, and N. Arnold, “Changes in Classification of Genetic Variants in *BRCA1* and *BRCA2*,” *Archives of Gynecology and Obstetrics*, 297, no. 2 (2018): 279-280, at 279 (“All variants with a change in classification in our cohort were downstaged towards no clinical significance by a panel of experts of the German Consortium for Hereditary Breast and Ovarian Cancer.”); S. Macklin et al., “Observed Frequency and Challenges of Variant Reclassification in a Hereditary Cancer Clinic,” *Genetics in Medicine* 20, no. 3 (2017): 346-350, at 346 (“A total of 1,103 hereditary cancer tests were ordered. Fewer than 5% (40/1,103) of the initial reports were updated during that time period. Most reclassifications (29/40) were downgrades of VUS to likely benign. Only three reclassifications could potentially alter medical management.”).

¹¹¹ E. Otten et al., “Is There a Duty to Recontact in Light of New Genetic Technologies? A Systematic Review of the Literature,” *Genetics in Medicine* 17, no. 8 (2015): 668-678.

¹¹² *Id.* at 674.

¹¹³ *Id.* at 677.

¹¹⁴ The issue is raised in *Williams v. Quest Diagnostics, Inc.*, 353 F. Supp. 3d 432-52 (D.S.C. 2018) (court denied in part a motion to dismiss, finding that defendant genetic diagnostic company may be liable for providing incorrect genetic diagnosis upon which physicians relied to the detriment of the patient-decedent). For more, see T. Ray, “In Quest/Athena Wrongful Death Suit, District Court Judge Holds Hearing on Motion to Dismiss,” *GenomeWeb* (“[Plaintiff] alleges [defendant’s] misclassification of

[decendent's] SCN1A mutation as a VUS is the proximal cause of his death, because it led his doctors down the wrong diagnostic path... doctors continued to treat him as if he had a mitochondrial disorder, giving him increasing doses of sodium channel-blocking drugs...[which] worsen[s] seizures in Dravet patients[.]"), available at <<https://www.genomeweb.com/molecular-diagnostics/questathena-wrongful-death-suit-district-court-judge-holds-hearing-motion#.XPXQ29NKiqQ>> (last updated January 6, 2017) (last visited June 3, 2019).

¹¹⁵ C. G. Selkirk et al., "Physicians' Preparedness for Integration of Genomic and Pharmacogenetic Testing into Practice Within a Major Health care System," *Genetic Testing & Molecular Biomarkers* 17, no. 3 (2013): 218-225.

¹¹⁶ Otten et al., *supra* note 1118 (citing Clayton et al., *supra* note 77).

¹¹⁷ J. M. Daniel et al., "A Survey of Current Practices for Genomic Sequencing Test Interpretation and Reporting Processes in US Laboratories," *Genetic Medicine* 19, no. 5 (2017): 575-582.

¹¹⁸ Stevens et al., *supra* note 20, at 370-372.

¹¹⁹ Stevens et al., *supra* note 20, at 369.

¹²⁰ See <<https://www.genomeconnect.org/>> (last visited Oct. 18, 2019).

¹²¹ See, e.g., E. W. Clayton, "What Should the Law Say About Disclosure of Genetic Information to Relatives?," *Health Care Law & Policy* 1, no. 2, (1998): 373-390; S. Suter, "Whose Genes Are These Anyway? Familial Conflict over Access to Genetic Information," *Michigan Law Review* 91, no. 7 (1993): 1854-1908; K. Offit et al., "The 'Duty to Warn' a Patient's Family Members about Hereditary Disease Risks," *JAMA* 292, no. 12 (2004): 1469-1473. Cf. R. Branum & S. M. Wolf, "International Policies on Sharing Genomic Research Results with Relatives: Approaches to Balancing Privacy with Access," *Journal of Law, Medicine & Ethics* 43, no. 3 (2015): 576-593.

¹²² *Pate v. Threlkel*, 661 So.2d 278 (Fla. 1995); Offit, *supra* note 121, at 1470-1471.

¹²³ See American Medical Association, Council on Ethical and Judicial Affairs, *Disclosure of Familial Risk in Genetic Testing*, Report 9 (A-03) (2007); American Society of Clinical Oncology, "Policy Statement of the American Society of Clinical Oncology Update: Genetic Testing for Cancer Susceptibility," *Journal of Clinical Oncology* 21, no. 12 (2003): 2397-2406; American Society of Human Genetics Social Issues Subcommittee on Familial Disclosure, "Professional Disclosure of Familial Genetic Information," *American Journal of Human Genetics* 62, no. 2 (1998): 474-483.

¹²⁴ M. A. Rothstein, "Reconsidering the Duty to Warn Genetically At-Risk Relatives," *Genetics in Medicine* 20, no. 3 (2018): 285-290.

¹²⁵ No. 2011-C-2583, 2015 WL 5244960, at *1-7 (Pa. Ct. C.P., June 30, 2015).

¹²⁶ *Safer v. Estate of Pack*, 677 A.2d 1188 (N.J. App. 1996), *cert. denied*, 683 A.2d 1163 (N.J. 1996).

¹²⁷ N.J. Stat. Ann. § 10:5-47 (2001).

¹²⁸ The closest case is *Molloy v. Meier*, 679 N.W.2d 711 (Minn. 2004), where the court held that a physician had a duty to warn the mother of a child born with a genetic condition of the risk to a future child.

¹²⁹ The *Safer* case was decided pre-HIPAA.

¹³⁰ Rothstein, *supra* note 124, at 286.

¹³¹ Dep't of Health and Human Services, Modifications to the HIPAA Privacy, Security, Enforcement and Breach Notification Rules, *Federal Register* 78 (2013): 5565-5702, 5668, available at <<https://www.federalregister.gov/documents/2013/01/25/2013-01073/modifications-to-the-hipaa-privacy-security-enforcement-and-breach-notification-rules-under-the>>.

¹³² HHS, Under the HIPAA Privacy Rule, may a health care provider disclose protected health information about an individual to another provider, when such information is requested for the treatment of a family member of the individual?, Jan. 13, 2009, available at <<https://www.hhs.gov/hipaa/for-professionals/faq/512/under-hipaa-may-a-health-care-provider-disclose-information-requested-for-treatment/index.html>> (last visited Oct. 18, 2019).

¹³³ Wolf et al., *supra* note 72.

¹³⁴ See, e.g., Pennsylvania, *28 Pennsylvania Code § 115.29* (“Upon the death of a patient, the hospital shall provide, upon request, to the executor of the decedent’s estate or, in the absence of an executor, the next of kin responsible for the disposition of the remains, access to all medical records of the deceased patient.”); Louisiana, *West’s Louisiana Statutes Annotated: Revised Statutes, 40:1165.1* (“[A] patient or his legal representative, or in the case of a deceased patient, the executor of his will, the administrator of his estate, the surviving spouse, the parents, or the children of the deceased patient...shall have a right to obtain a copy of the entirety of the records in the form in which they exist, except microfilm, upon furnishing a signed authorization.”); Georgia, *Georgia Code Annotated, § 31-33-2* (“If the patient is deceased, such request may be made by the following persons: (A) The executor, administrator, or temporary administrator for the decedent's estate if such person has been appointed; (B) If an executor, administrator, or temporary administrator for the decedent's estate has not been appointed, by the surviving spouse; (C) If there is no surviving spouse, by any surviving child; and (D) If there is no surviving child, by any parent.”); New Hampshire, *New Hampshire Revised Statutes § 332-I:13* (“Where there is no estate administration, the surviving spouse or next of kin of the deceased is designated the personal representative of the deceased for the limited purpose of obtaining the medical records of the deceased.”); North Carolina, *North Carolina Administrative Code 10A.13B.3904* (“Upon the death of a patient, the executor of the decedent's estate, or in the absence of an executor, the next of kin responsible for the disposition of the remains, shall have access to all medical records of the deceased patient.”).

¹³⁵ Wolf et al., *supra* note 72, at 443.

¹³⁶ HIPAA applies for 50 years after a patient’s death, but a patient’s designated representative is authorized to consent on behalf of the patient. The issue of how a deceased patient’s personal representative is identified, and the rules applying to a deceased patient’s medical records, are mostly governed by state law.

¹³⁷ See *supra* note 125 and accompanying text.

¹³⁸ Many states have a history of requiring physician involvement in the DTC ordering process, although the FDA may be in favor of increased direct access. S. Hogarth, G. Javitt, and D. Melzer, “The Current Landscape for Direct-to-Consumer Genetic Testing: Legal, Ethical, and Policy Issues,” *Annual Review of Genomics and Human Genetics* 9, no. 1 (2008): 161-182, at 171; M. A. Allyse et al., “Direct-to-Consumer Testing 2.0: Emerging Models of Direct-to-Consumer Genetic Testing,” *Mayo Clinic Proceedings* 93, no. 1 (2018): 113-120, at 118 (arguing that the FDA has “signaled a regulatory approach that seeks to allow direct consumer access to some types of health-related genetic information while maintaining stricter regulatory oversight over what it considers to be diagnostic and other more clearly medical results.”). The appropriate degree of involvement by physicians, genetic counselors, and the patient or subject themselves is extensively debated. See, e.g., Allyse et al., at 113-120; E. Ramos and S. M. Weissman, “The Dawn of Consumer-Directed Testing,” *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* 178, no. 1 (2018): 89-97.

¹³⁹ American Society of Clinical Oncology, “American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility,” *Journal of Clinical Oncology* 28, no. 5 (2010): 893-901; S. Hogarth, G. Javitt, and D. Melzer, “The Current Landscape for Direct-to-Consumer Genetics Testing: Legal, Ethical, and Policy Issues,” *Annual Review of Genomics and Human Genetics* 9 (2008): 161-182; A. Hawkins and A. Ho, “Genetic Counseling and the Ethical Issues Around Direct to Consumer Genetic Testing,” *Journal of Genetic Counseling* 21, no. 3 (2012): 367-373.

¹⁴⁰ Since our focus here is on liability associated with clinical application of genomics, we do not consider the liability implications for the DTC company.

¹⁴¹ Clinician reliance on DTC testing has sparked substantial discussion and commentary. See, e.g., S. Tandy-Connor et al., “False-positive Results Released by Direct-to-consumer Genetic Tests Highlight the Importance of Clinical Confirmation Testing for Appropriate Patient Care,” *Genetics in Medicine*, 20, no. 12 (2018): 1515-1521; J. V. Schleit, L. M. Naylor, and F. Hisama, “First, Do No Harm: Direct-to-

consumer Genetic Testing,” *Genetics in Medicine*, 21, no. 2 (2019): 510-511; Ramos & Weissman, *supra* note 138, at 89-97.

¹⁴² See, e.g., S. Tandy Connor et al., *supra* note 137 at 1515 (“Our analyses indicated that 40% of variants in a variety of genes reported in DTC raw data were false positives.”); B. M. Kuehn, “Inconsistent Results, Inaccurate Claims Plague Direct-to-Consumer Gene Tests,” *JAMA* 304, no. 12 (2010): 1313-1315, at 1313 (“results for identical DNA samples varied between companies and, in some cases, conflicted with the medical status or family history of the individual who supplied the DNA.”).

¹⁴³ See *supra* note 34 and accompanying text.