Knowledge about the clinical implications of individual genetic variants, genes, and genomics is growing rapidly. As a result, interpretations that were made at one time may later turn out to be incorrect. Awareness of these changes in results can occur in two ways. In the first case, the laboratory initially identified and reported a variant, assigning it some level of disease causation ranging from pathogenic to uncertain significance to benign. Subsequently acquired knowledge then reveals that the variant that was reported is now understood to have a different interpretation, most frequently more benign. In the second case, the laboratory may need to examine the original sequence data to identify variants that had not previously been reported but that have subsequently been classified as likely pathogenic or pathogenic. In either case, someone (whether the provider or the lab) must re-examine the original results.

Labs and clinicians are already reinterpreting and returning revised results to patients. Many commentators have sought to define how much effort, if any, ethically should be devoted to searching for and communicating the updated information to the individual to whom it pertains. These authors do, however, acknowledge that the boundaries of these ethical duties are not well defined. Other groups suggest that patients have significant roles to play in this process, having some obligation to seek reinterpretation or at least to provide updated clinical and contact information. Importantly, however, these ethical proposals are not in and of themselves enforceable as legal requirements.

The goal of this paper is not to engage in this ethical debate but rather to discuss the state of the law regarding the reinterpretation of genomic tests that were originally obtained for a clinical indication, such as a concerning family history or current symptoms, for the patient. By contrast with ethical analysis, the law asks a much narrower question: what must people do at the risk of liability or other penalty? In this context, for example, if a patient asks a laboratory to reinterpret a test result, must the lab do so? In answering these questions, the law often asks what it is reasonable for actors to do in light of the costs entailed and other potentially conflicting obligations.

In addressing this question, we will focus primarily on the common law of negligence and the particular case of medical malpractice. These two causes of action share the same elements—breach of a duty that proximately causes compensable harm—but differ in some important ways in terms of both the standards applied and the procedures by which the claims proceed. Negligence is founded on the notion that one should not be careless in a way that harms others, a standard that a jury can decide on its own, sometimes with the help of expert witnesses. In medical malpractice, by contrast, the provider’s duty is based on a specific relationship that arises out of contract, but whose obligations are defined by fiduciary duty and state medical licensure statutes and other regulations. Once undertaken, it can continue unless (1) the provider specifically states at the outset that the relationship is limited in time and scope; (2) the provider specifically terminates it, which may entail a requirement to refer to another provider to avoid abandonment; or (3) enough time has passed without contact that the relationship ceases as a legal matter.

The provider’s obligations in malpractice cases are generally shaped by the practice of other reasonably prudent, similarly situated practitioners, the so-called professional standard of care, and so generally require expert testimony to prove breach. However, a minority but growing number of states are recognizing a “general reasonableness” standard in malpractice cases, which can protect physicians whose actions depart from customary practice but are provably reasonable under the circumstances. Importantly, people who feel that they have been harmed often have a longer period of time to bring lawsuits based on negligence as compared with medical malpractice.

Some statutes and regulations also bear on the existence of legal duties and their scope, including CLIA regulations, and New York and Washington State requirements for CLIA-exempt labs. Nongovernmental standards issued by organizations such as the College of American Pathologists (CAP), American College of Medical Genetics and Genomics (ACMG), and the Joint Commission are also pertinent to the extent that they inform standards of clinical practice, although all states treat professional guidelines as only some, but not conclusive, evidence of the standard of care.

The short answer to our question is that there are no cases, statutes, or regulations at present that support a legal duty to reinterpret clinical genomic tests and return any new analyses, a point with which other commentators concur. To demonstrate the ways in which this situation could change, we address three questions: (1) how likely are the data needed for reinterpretation to be available, (2) when and how does reinterpretation occur at present, and (3) what are the probable legal consequences of future practices regarding reinterpreting and communicating
HOW LIKELY ARE THE DATA NEEDED FOR REINTERPRETATION TO BE AVAILABLE?

CLIA requires that laboratories retain enough data from genetic sequencing to permit reanalysis of a patient’s results for at least 2 years,13,16 and there is little information about whether laboratories keep them for a longer period, or which and how many data files (e.g., FASTQ, BAM, or VCF) they retain.17,18 The duration is important for a number of reasons. If the data exist, the Health Insurance Portability and Accountability Act of 1996 (HIPAA) usually permits patients to obtain them.19 How often patients exercise this option with clinical sequencing by commercial laboratories is unclear, but access requests appear relatively uncommon. Patients’ window to access and preserve their data is limited by laboratory retention practices since HIPAA only requires access to data a laboratory “maintains.”20 Otherwise, laboratories cannot reinterpret data they no longer have. What laboratories retain matters because clinicians and health-care institutions at present generally do not store original data, in part because the files are so large.

By contrast, clinicians are required to retain reported laboratory results for a defined period of time under state medical records laws, the conditions and extent of which vary from state to state.21 Test reports sent to clinicians, however, usually contain only a small fraction of the variant information generated during sequencing and would not generally support reinterpretation. Many clinicians and health-care institutions make reported results available to patients through mechanisms such as HIPAA-compliant portals. It should be noted, however, that genomic test results are not readily accessible in most electronic health records or patient portals because they are not typically delivered in machine readable formats.22 Nonetheless, if clinicians or patients know that the results are there, they can be found.

WHEN AND HOW DOES REINTERPRETATION OCCUR AT PRESENT?

Patients may reach out to laboratories to ask them to reinterpret data, but while HIPAA allows patients to obtain existing reports and the underlying data, it does not give them the right to require the laboratory to reinterpret the data or provide counseling. Indeed, most laboratories ask the patient to have the ordering physician submit a request for re-examination if desired.

At present, physicians generally request reinterpretation from laboratories only because of an intervening event, such as the development of new symptoms. This is especially true when the patient is young, perhaps even an infant, at the time of testing and “grows into the diagnosis” as additional features develop and are recognized over time. Alternatively, the family history may have changed, or new information is discovered. More up-to-date information may be desired to inform decisions about medical interventions, particularly those that are invasive or expensive. Without a recognized legal duty to reinterpret or recontact, most physicians seek updates only when they believe that the interpretation may have changed in a way that affects clinical management. Moreover, clinicians have no duty to review all their patients’ records to look for clues that may previously have been overlooked, especially in the absence of some other clinical reason to do so. Notably, such clinical indications may well expand as more people have broad genomic testing and as the understanding of the pertinence of particular genetic variants for clinical care increases.

Some have suggested, moreover, that new data analytics may make it possible for electronic record systems to review variants and/or medical records routinely to identify cases in which signals had previously been missed or a new interpretation might be relevant,23,24 and push potentially actionable results to clinicians for further testing and intervention. Were this to occur, it would be necessary to determine who will decide which analyses should be undertaken and under what circumstances, how clinicians should be informed, what decision support should be provided, and what actions clinicians should be expected to take—all issues that have potential legal implications.

Laboratory practices are also complex. Consider the following example. Laboratory personnel who are examining a new sample recognize that the patient has a variant that current evidence suggests is pathogenic, even though previously its significance had been uncertain. Such new interpretations may lead labs to go back to reports that had previously been issued for other patients (although laboratories vary in the situations in which they undertake such re-examinations) and to issue revised reports for those patients.25 Whether the laboratories should have a legal obligation to return such new interpretations to patients is contested, as is how hard they would have to try to ensure that the patient receives the new result. Yet the more common the practice becomes, the greater the potential for liability.26,27 Under-taking duties that law does not strictly require can nevertheless influence the standard of care.

Another reason for reinterpretation is physician request, which may require comparing the reported variant to reference databases, which at least theoretically could be done by anyone with the lab report, or examining the underlying sequence data to detect new variants, the latter of which would largely be within the purview of laboratories. In either case, the laboratory may choose to charge a new interpretation fee unless that cost was explicitly included in the original test. This may be a challenge for many patients, since insurance coverage of initial genomic testing remains quite limited, and insurers would likely apply strict criteria for coverage of reinterpretation.26,27

Notably, as is the case with clinicians, laboratories at present do not routinely re-examine prior results28 or use routine phenotype alerts to trigger re-examination. For example, they do not routinely re-examine all data from specimens that had previously been submitted for testing for predisposition to cancer or channelopathies. Finally, laboratories often analyze data for purposes other than the care of a specific patient, such as quality assurance/control (QA/QC), on the one hand, or for research, on the other—uses that fall outside the scope of this paper because they raise different ethical and legal issues.

WHAT ARE THE PROBABLE LEGAL CONSEQUENCES OF FUTURE PRACTICES REGARDING REINTERPRETING AND COMMUNICATING RESULTS?

For this analysis, several factors matter. The first is whether the new interpretation of a previously reported variant is at issue or whether re-examination of the underlying genomic data is required. The former can be accomplished at least in part by comparing the prior result to databases such as ClinVar, while the latter necessitates more specific analytic skills.

Patients who have their own results could attempt to reinterpret them on their own, although they have no legal obligation to do so. They could also submit the data to third-party interpreters, such as Promethease,28,29 which to date have not been subject to federal regulation30 but which have been reported to generate many errors.31 Patients may take such interpretations to their health-care providers, who may face challenges addressing them.32,33

Clinicians’ obligations to reinterpret results are defined by the standard of care, which is influenced by the practices of their colleagues and the recommendations of professional organizations, as illustrated by the related case of the ACMG’s
practices,38 perhaps requiring an additional fee and perhaps requests reanalysis since the laboratory would follow its usual patient pays any required fee for the service.11 The laboratory laboratories to do additional analyses or to provide counseling laboratories are required by HIPAA to return reports and under-may not exist.37 Yet while the lab may know more about the patients, thereby undertaking a duty of care, which otherwise might undertake to return reinterpreted results directly to patients. As noted above, this might occur when a variant is reanalyzes a result without a prior request on behalf of that patient. As noted above, this might occur when a variant is identified in and interpreted for another patient, and the laboratory decides to re-examine prior reports of the same variant in other patients. Laboratories vary in their practices about returning such results.25

If the laboratory decides to return these revised results to the ordering physician, several challenges are foreseeable.26,28 The physician who initially ordered the test may no longer be caring for the patient, which is particularly common when the clinician was a consultant who saw the patient on a limited basis. For example, a patient may have been seen by a physician who specializes in assessing whether the person has a genetic predisposition to a disorder, such as cancer or an arrhythmia, which often involves a limited encounter. Even if a clinician had been providing ongoing care, he or she may have moved to a different institution, or the patient may have chosen in the meantime to transfer care to a different provider. These scenarios raise issues about whether the earlier physician–patient relationship had been appropriately terminated.

If the physician–patient relationship was not formally concluded and the physician is notified by a testing laboratory that a previous interpretation of a patient’s genetic variant has changed in a way 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 may not be feasible, due to patient loss to follow up and limited provider resources.6,8 Efforts to contact may include telephone calls, messaging through patient portals, and sending certified letters to the patient’s last known address. Failure to make reasonable attempts to return the new results may lead to liability even though no such cases have arisen to date.

CONCLUSION

To date, no courts have imposed liability for failure to reinterpret genetic results. Yet, as knowledge about the impact of particular variants on individual phenotypes increases, there is growing interest by physicians and laboratories in re-assessing prior genomic test results and interpretations. Physicians and laboratories, however, working with their professional organizations need to think seriously about how fully to embrace this practice and what disclosures about limitations to make, especially given the challenges of ensuring that patients receive and understand the new results and the ensuing potential legal consequences.

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