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Does the law require reinterpretation and return of revised genomic results?

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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 reexamine the original results.

Laboratories 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

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whom it pertains.¹⁻⁴ Appelbaum, et al., for example, have argued that laboratories have an ethical duty to store and reinterpret genomic data, while the ordering physician has an ethical duty to recontact the patient with updated results, reasoning that these actors are best able to fulfill these roles.⁵ 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.² 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 in 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.⁶⁻⁸ 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 clinician specifically states at the outset that the relationship is limited in time and scope, 2) the clinician 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.⁹

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.^{10,11} 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.¹²

Some statutes and regulations also bear on the existence of legal duties and their scope, including the Clinical Laboratory Improvement Amendment (CLIA) regulations, and New York and Washington State requirements for CLIA-exempt labs. Non-governmental 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.¹³

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.^{2,14} 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 results? At each of these steps, we address the responsibility (and limits thereof) of three separate sets of actors: 1) patients 2) clinicians, and 3) laboratories.

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,^{15,16} 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, 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 reexamination 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,^{9,23,24} 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 reexaminations) and to issue revised reports for those patients.²⁵ Whether the laboratories should have a legal obligation to return such new interpretations to patients² 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.^{6,8} Undertaking 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 reexamine prior results²⁵ or use routine phenotype alerts to trigger reexamination. For example, they do not routinely reexamine 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 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 reexamination 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,¹⁴ 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 promulgation of guidelines regarding testing for secondary findings in genomic testing.³⁴⁻³⁶ The standard may vary depending on the initial reason for testing and the clinician's specialty. As noted above, physicians do not generally reinterpret previously reported results on their own or in consultation with other physicians or the laboratory in the absence of some clinical reason to do so or some other notification that prior interpretations may have changed. Less commonly, some do ask laboratories to reexamine sequence data from an earlier test.

Some practices are changing in ways that may open the door more widely for liability in genomic medicine. Some clinicians, mostly specialists, are reexamining and reinterpreting their patients' results more routinely. Because clinicians can be held liable for failing to meet the standard of care defined by the practices of their colleagues, they should realize that this standard will rise as their peers do more.¹³ This is particularly important for clinicians who frequently utilize genetic testing in general or for certain disorders, who may face greater exposure because they are more likely to be aware of advances in genomics that may be clinically pertinent, such as new therapies for specific conditions. If a large enough number of such clinicians begin to seek reinterpretation as a matter of course, these practices could influence the standard of care.

In the event that reanalysis becomes established practice, Marchant et al.^{6,8} have argued that physicians may have a duty to ensure that this occurs. If a clinically meaningful change in interpretation is made, the physician will need to try to communicate it to the patient, with whom the clinician likely has an ongoing relationship. As noted earlier, some states recognize a general reasonableness standard for malpractice suits,^{10,11} and when this is the case, it would be left to the jury to decide whether, given the new information available to physicians, it would have been reasonable to order a reinterpretation.

Laboratories are the best situated to reexamine both previously reported results and the underlying genomic data to the extent that they retain them.⁶ In response to direct *patient request*, while laboratories are required by HIPAA to return reports and underlying data they have, this statute explicitly does not require the laboratories to do additional analyses or to provide counseling unless the laboratory and the patient mutually agree and the patient pays any required fee for the service.¹¹ The laboratory might undertake to return reinterpreted results directly to patients, thereby undertaking a duty of care, which otherwise may not exist.³⁷ Yet while the lab may know more about the variant than a clinician does, it will likely have incomplete knowledge about the patient and so may lack other pertinent information about the patient's situation that could influence reinterpretation. Thus, the laboratory would be well advised to specify the limits of its interpretation as well as any counseling it may provide and what it will charge for these services, and to recommend that the patient identify a clinician to whom the results could be sent.

The situation is clearest when the original *ordering clinician* requests reanalysis since the laboratory would follow its usual practices,³⁸ perhaps requiring an additional fee and perhaps working with the clinician to obtain more information to ensure that the most informative result is returned. In most cases, the patient will have sought or at least be aware of this exploration and, if he or she had previously been appropriately counseled, would be as prepared as possible to receive revised results.

By far the most complicated situation arises when the *laboratory* 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 reexamine 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.^{2,6,8} 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 reassessing 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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