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Is there a duty to reinterpret genetic data? The ethical dimensions

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The evolving evidence base for the interpretation of variants identified in genetic and genomic testing has presented the genetics community with the challenge of variant reinterpretation. In particular, it is unclear whether an ethical duty of periodic reinterpretation should exist, who should bear that duty, and what its dimensions should be. Based on an analysis of the ethical arguments for and against a duty to reinterpret, we conclude that a duty should be recognized. Most importantly, by virtue of ordering and conducting tests likely to produce data on variants that cannot be definitively interpreted today, the health-care system incurs a duty to reinterpret when more reliable data become available. We identify four elements of the proposed ethical duty: data storage, initiation of reinterpretation, conduct of reinterpretation, and patient recontact, and we identify the parties best situated to implement each component. We also consider the reasonable extent and duration of a duty, and the role of the patient's consent in the process, although we acknowledge that some details regarding procedures and funding still need to be addressed. The likelihood of substantial patient benefit from a systematic approach to reinterpretation suggests the importance for the genetics community to reach consensus on this issue.

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INTRODUCTION

In recent years, dramatic advances in sequencing technologies and the elimination of gene patents for clinical diagnostics have enabled clinical laboratories to provide increasingly comprehensive and less costly genetic testing. With the growing ease of data generation, the primary challenge is now accurate interpretation of identified variants. However, the knowledge base for variant interpretation is not static. As new cases are reported, additional population data become available, and as computational tools evolve, the classification of variants can change. In this paper, we consider the ethical implications of potential changes in variant classification, including whether an ethical duty exists to undertake such reinterpretation and the likely dimensions of such a duty.

A number of factors are driving the possibility for reinterpretation of previously analyzed variants. Variant databases such as ClinVar[1] have improved the reliability of interpretation, and expert working groups are resolving discrepancies across laboratories. More clinical laboratories are depositing data in ClinVar, with some insurers refusing to pay laboratories that do not deposit variant data publicly. Powerful new variant interpretation tools, such as Eigen[2] and Combined Annotation–Dependent Depletion (CADD),[3,4] have improved classification of variants using advanced computational algorithms, including a support vector machine (SVM) to integrate multiple sources of data into pathogenicity scores.[3] Due at least in part to these trends, data from multiple groups have shown that the clinical yield of exome sequencing (ES) increases by between 10% and 22% when ES data are reanalyzed (e.g., refs. [5–8]).

A primary motive for reinterpretation of genetic data is the presence of variants of uncertain significance (VUS), i.e., variants for which existing data do not allow classification as either pathogenic/likely pathogenic or benign/likely benign. VUS introduce uncertainty for both patients and clinicians[9] and can confuse decision making for both. Clinical sequencing for hereditary cancer, currently the most common reason for clinical sequencing, often results in high rates of VUS. Reported overall VUS frequencies from several large cohorts ranged from 34% to 41% for cancer panels.[10–12] Anecdotal reports exist of patients undertaking prophylactic interventions, including surgery, on the basis of VUS results only to learn subsequently that the variant was actually benign.[13] Most data on rates of reclassification derive from cancer-related testing, including *BRCA1/2* genes (12.4% of all variants and 14.8% of VUS[14]) and mixed hereditary cancer genes

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(8.4% of all variants and 21.7% of VUS,[15] 6.4% of all variants and 7.7% of VUS,[16] and 3.6% of all variants and 11.3% of VUS[17]).

VUS are a particular issue for ethnic and racial minority populations,[18] who may be most likely to benefit from valid reinterpretation. In the past, *BRCA1/2* VUS frequencies have been as high as 7–15%[19] overall, but with significantly higher frequencies in minority populations: 22% in Hispanics in 2002 and 46% in African Americans in 2005.[20] More recently, VUS frequencies in *BRCA1/2* were 4.4% in Caucasians, but 8.9% in African Americans and 8.0% in Hispanics.[21] For larger panels of hereditary cancer genes, one laboratory reported VUS frequencies of 22.1% in Caucasians, 30.3% in African Americans, and 24.9% in Hispanics.[22] The higher frequency of VUS in ethnic and racial minority populations is attributable, in part, to persistent racial disparities in access to and utilization of genetic services, as well as lower rates of participation in genomic research.[13] The limited genetic data for minority patients results in significantly higher VUS frequencies, making test results less informative, potentially deterring minority patients from pursuing testing, and further exacerbating health-care disparities.

The desirability of accurate reclassification of variants, especially VUS, has led to increasing discussion of systematic approaches to variant reinterpretation. Several questions need to be resolved if this is to occur, including: Is there an ethical duty to undertake routine variant reinterpretation? If so, on whom should the responsibility be placed for reinterpretation? How long should the duty last? How frequently should reinterpretation be done? What should trigger it? Should all reanalysis results be returned or only a subset that might impact clinical care? Who should pay for it? To whom should results be communicated (e.g., patient, surviving family members, providers)? Who should communicate those results? What practical challenges need to be anticipated (e.g., locating treating physicians or patients)?

Despite a substantial literature in which these and similar questions have been raised,[23] clarity about the existence, nature, and scope of a duty to reinterpret is still lacking.[24] Recent "points to consider" from the American College of Medical Genetics and Genomics (ACMG) may be helpful, but lack detailed recommendations needed to implement a duty.[25] Surveys have been undertaken of practices in the UK,[26] Europe,[27] and the United States[28] showing considerable practice variability in the absence of clear-cut guidelines. Notwithstanding the reality that many of these questions have practical components, underlying them are significant, as yet not sufficiently addressed, ethical concerns.

Below, we articulate the elements of a potential duty to reinterpret genetic and genomic data in clinical settings, each of which may fall on different parties to discharge. (Questions about a duty to reinterpret and recontact in the research context have recently been addressed elsewhere.[29]) We then consider the ethical arguments for and against recognition of this duty, who should bear each of the elements of the duty, and the possible dimensions of a duty in practice. Our goal is to lay out an approach to these questions, stimulating debate and ultimately, we hope, moving toward consensus on these issues.

ELEMENTS OF THE DUTY TO REINTERPRET

Although much of the previous literature has characterized this issue as involving a "duty to recontact,"[19] and recent European guidelines focus exclusively on that task,[30] we suggest that recontact is merely the final stage of a more complex set of obligations that we subsume under the rubric of a "duty to reinterpret." Under this approach, the ethical duty to reinterpret genetic variants can be conceptualized as including four elements:

- Data storage—Without ongoing access to the original genetic test data, reinterpretation would not be possible. Laboratories are the most likely entities to store data currently, but other approaches could be imagined, including transferring the data to the patient to retain.
- Initiation of reinterpretation—Something or someone must trigger the process of reinterpretation. That could be the passage of a certain period of time, the accumulation of a particular number of changes in interpretation, or the decision of a stakeholder in the process, whether a laboratory director, clinician, or patient, to begin the process.
- Reinterpretation of the data—The process of reinterpretation requires both a data analytic pipeline and the application of human judgment with regard to interpretation of variants. Although data analysis is increasingly driven by algorithms, clinical knowledge is currently indispensable, with the time required implying potentially substantial costs to the entity doing the reinterpretation.
- Recontact of the patient—If new findings are identified, someone needs to reach out to the patient who was tested, convey the results, and indicate the implications—if any—for the patient's health and behavior. The ease of contacting the patient and communicating this information will vary, but (as with the other elements in this list) there will be real costs in time and effort that need to be considered.

Having identified the likely components of a duty, we now consider the ethical arguments in support of and opposed to recognition of such a duty.

ETHICAL CONSIDERATIONS IN SUPPORT OF A DUTY TO REINTERPRET

A number of principles appear to support the recognition of an ethical duty. These include respect for patient autonomy (i.e., the provision of new information may empower patients to make decisions about their situation), beneficence (i.e., patients may benefit from reinterpreted information either medically—as by taking prophylactic measures or initiating

treatment—or psychologically, if the data provide an explanation for their condition), and nonmaleficence (i.e., harm to patients may be avoided by provision of information that replaces ineffective or deleterious clinical management with more beneficial approaches).[25] All of these principles would support recognition of a duty; without further specification, however, they do not necessarily clarify its scope, who should bear the duty, or how it should be discharged.

In addition to these standard justifications, we suggest that the intrinsic features of contemporary genetic testing may create a duty related to reinterpretation that does not exist in other widely used clinical testing. Next-generation sequencing, whether at the exome/genome level or focused on a single gene or panel of genes, has the capacity to identify variants with unknown medical significance. Unlike most other medical tests, the variant data from genetic testing will remain stable over the course of a patient's life, but the interpretation of those data may change, a process inherent in the current practice of genetic testing.[31] As genetic knowledge increases, some proportion of those VUS will be susceptible to reinterpretation as either pathogenic or benign, with consequent implications for patients' physical and psychological well-being.[7,32,33] Data on the outcome of VUS reinterpretation tend to vary depending on the date of the study, type of testing, and disorders included; however, available data indicate that most VUS that are reinterpreted will be downgraded to benign/likely benign. Several studies show that 75–90% of reinterpretations will be downgraded,[16,17] with only a minority upgraded to pathogenic/likely pathogenic (e.g., 8.7% of unique variants and 3% of all variants in one study[29]). In addition, albeit much less frequently, variants already designated as (likely) pathogenic or (likely) benign may be reinterpreted as belonging to the other category.[28,29] Because new disease-related genes are still being discovered, reinterpretation of nondiagnostic exomes/genomes has a significant yield (e.g., one recent study found an increase in diagnostic yield from 25% to 47% after 5–6 years[6]) but requires comprehensive reanalysis of potentially hundreds to thousands of variants from a list of filtered variants, the vcf file, or raw data.

Thus, we suggest that by virtue of ordering and conducting a test that is likely to produce data on variants that cannot be definitively interpreted today—but may be subject to reliable interpretation in the future—the medical care system incurs a duty to reinterpret when a more reliable interpretation is available. Failure to do so may constitute a breach of a duty to the patient to continue the clinical relationship while ongoing care is indicated, equivalent to the traditional concept of abandonment. Having undertaken to provide genetic testing to the patient and knowing that interpretations may change over time, we believe, those involved assume the obligation to modify the interpretation and communicate the new information to the patient. We consider below on whom the elements of a duty might most reasonably be placed and its dimensions.

ETHICAL CONSIDERATIONS OPPOSING A DUTY TO REINTERPRET

Although existing literature suggests a number of ethical principles that might militate against a duty to reinterpret—such as the possibility of causing psychological distress to the patient, which would implicate the principle of nonmaleficence—the consensus appears to be that the strongest argument against such a duty is based on its practical consequences and their ethical implications.[19] Thus, to the extent that implementation of routine reinterpretation would utilize clinician or laboratorian time and scarce health-care dollars, its relative priority compared with other uses of those resources needs to be considered. Assessing this issue will require comparing the potential benefits of reinterpretation with the potential benefits of alternative health-care activities. A full assessment would include consideration of who bears the duty to reinterpret; the extent and duration of the duty, as discussed below; and the potential alternatives if a duty were deemed not to exist.

We agree that practical considerations and their consequences are the strongest arguments against the existence of an ethical duty or for limiting its scope. Although we grant that, in practice, those considerations may militate against imposing a duty to reinterpret, we suggest that these concerns are outweighed by the duties of respect for autonomy, beneficence, nonmaleficence, and avoidance of abandonment discussed above. However, we also note that these practical considerations are likely to change over time, as systems that can automatically trigger reinterpretation and notification (e.g., when new data are published on a given variant) are developed and refined,[34] and as the process of reinterpretation itself is increasingly automated—although we recognize that for the foreseeable future expert human involvement will be required. Thus, it seems likely that, over time, the arguments against imposing a duty to undertake new interpretations or for restricting its scope will become weaker, and the balance will shift even more strongly in the direction of recognizing a duty.

WHO SHOULD BEAR THE FOUR ELEMENTS OF THE DUTY?

Assuming the existence of an ethical duty to reinterpret, the identity of the duty-holder(s) is critical. Three possibilities exist, i.e., the various components of a duty could be placed on the patient, a clinician (the primary care physician, a referring specialist, or the clinician who ordered the test, if different), or the laboratory. Considerations of justice suggest that the duty is best placed on the person or entity for whom discharging it effectively would constitute the least burden. We organize this analysis according to the four elements of the duty that we identified above.

Data storage

The most basic prerequisite to reinterpretation is that the data from the initial genetic analysis be retained and made accessible for reinterpretation. For single genes and gene

panels, variant data will usually be sufficient to allow reinterpretation. However, for exomes and genomes, application of advances in data analytic techniques, allowing the identification of copy-number or structural variants, complex insertions/deletions, variants in repetitive regions, and mosaicism will require access to the original data (i.e., BAM or FASTQ files). The laboratory that conducted the original test would seem to be the most reasonable locus for this element of the duty, given that it already possesses the information. However, data storage is not without costs, and as the number of test results retained increases, at some point it may no longer be appropriate to expect the laboratory to bear that burden. This determination may also be affected by the duration of the duty (see discussion below). We note that patients could also be asked to shoulder the burden of storage (e.g., given the option of downloading their data from a cloud location). However, that seems like a less desirable alternative, given the risks of neglect, hacking, loss, or destruction.

Initiation of reinterpretation

Access to up-to-date genetic information (i.e., knowing that revised data affecting a previously interpreted variant now exist) would appear to be a prerequisite to knowing when to trigger a reinterpretation. Although there have been suggestions that patients should be expected to inquire periodically whether new information exists that would alter the interpretation of their genetic tests,[35,36] and some patients assert their willingness to do so,[37] patients would appear to be the party least likely to have access to the genetic information necessary to discharge this element of the duty in an efficient manner. Primary care clinicians, who have the highest probability of being in ongoing contact with patients, are similarly unlikely to be aware of new data on variant reinterpretation, although they too have been suggested as bearers of this element of the duty.[23] Specialists, whether geneticists or other specialists (e.g., cardiologists, neurologists, oncologists), may be somewhat more likely to know of new data resulting in specific changes in variant interpretation or new reasons—such as the development of new treatments—why an updated genetic diagnosis is important, but nonetheless the probability that they will follow such changes in a systematic manner is small. In contrast, laboratories that perform genetic testing must monitor genetic databases for revised interpretations, which are crucial to the accuracy of their test results.

Thus, the party that would bear the least burden of initiating routine reinterpretation and be able to do so most effectively is almost certainly the laboratory that conducted the testing. Indeed, we are aware that many laboratories will update their interpretations when new, major data sets are released or important changes in classification are adopted. Other triggers may include when a laboratory identifies a variant again in a new patient and a substantial period of time (e.g., >12 months) has elapsed since it was previously interpreted,[28] new gene–disease relationships and/or mechanisms of disease are identified, or new methods of variant interpretation are developed.[21]

We note, though, that circumstances may exist in which parties other than laboratories become aware of the desirability of reinterpretation (e.g., the patient learns that a pathogenic variant was identified in a family member, or a treating physician either recognizes that reclassification could have significant consequences for patient management or is made aware of a new variant that has been characterized as likely pathogenic). In those cases, they should have the ability to trigger reinterpretation as well.

Reinterpretation of the data

With what are likely to be rare exceptions, the laboratory that conducted the testing initially will be in the best position to undertake the reanalysis and reinterpretation. Of course, patients should have the option of requesting a reanalysis of their data from another laboratory, although in that case, the costs may fall to the patient. We note that additional options exist for patients to access updated information on the pathogenicity of specific variants, for example the freely accessible ClinVar database[1] and third-party interpretation services that allow people to upload their genetic information for automated analysis.[38]

Recontact of the patient

Either the laboratory or the ordering clinician could be assigned the responsibility of reaching out to the patient to convey the reinterpreted results. A stronger case for the laboratory bearing this element of the duty would exist if it had genetic counselors available to help the patient understand the implications of the findings. If a reinterpretation were sent to a patient without that kind of support, though some patients would seek assistance in understanding it, there is a substantial risk that the findings would be misinterpreted or simply ignored. Moreover, laboratories will typically not have patients' clinical information (although the ACMG recently suggested that laboratories could request such information[21]) or know how to contact them, and in some cases there may be regulatory constraints on their contacting patients directly. Thus, the ordering clinician is likely in a better position to contact and counsel the patient with regard to the implications of the reinterpretation, assuming the result is conveyed to the physician by the laboratory. We recognize, however, that many tests are ordered by specialists who are consulted in a time-limited way and do not have an ongoing relationship with the patient. Although it may be burdensome to ask them to reach out to attempt to contact a patient who they do not know well and have not seen for several years to convey the results, that nonetheless may be the best means of communicating the implications of the findings and recommendations for follow-up.

Parameters of a duty

Even if we accept the foregoing analysis, many questions about the scope of the ethical duty described above remain

unanswered. These include the extent of the duty (i.e., the variants to which it applies), the duration of the duty, the effect on the duty of the (un)availability of resources to pay the costs of implementation, and the efforts required to carry out the elements of the duty. We offer preliminary thoughts on each of these below, although they vary in the extent to which ethical concerns are likely to be determinative in resolving the issues.

Extent of the duty

Insofar as likely benefit and avoidance of harm motivate the duty to reinterpret variants, the relevance of the duty increases with the penetrance of the variant, the severity of the condition involved, and its preventability or treatability. Thus, the more penetrant, severe, and preventable or treatable the condition, the greater applicability of the duty described here. The duty is greatest when a variant related to such a condition is reclassified from another category to pathogenic/likely pathogenic. Of note, however, a reclassification from pathogenic or VUS to benign could have important consequences for patient management—e.g., justifying discontinuation of surveillance provided to people at higher risk—so in these circumstances would also have priority for return. Insofar as it may not be possible in advance to identify the nature of the change that would result from reinterpretation, these considerations may apply to recontact of the patient but not to initiation of the reinterpretation process. Further deliberation will be required by groups representing laboratories doing genetic testing and genetic professionals to define the specific parameters of a duty to reinterpret.

Duration of the duty

How long the duty should continue will depend in part on empirical factors that are not clear at this point. As genetic knowledge increases, the value of periodic reinterpretation should increase, as more variants that were previously identified as VUS can be definitively interpreted and errors in other interpretations can be revised. At the point at which this knowledge is substantially incorporated into the pipelines for analysis of genetic samples, the additional yield from reinterpretation will begin to diminish. At some point—although perhaps not for several decades—the cost–benefit ratio of reanalysis will tilt against an ongoing duty—or will make it such that there is no longer any need to speak of such a duty.

An alternative approach to determining the duration of a duty to reinterpret is based on passage of a fixed period of time, e.g., 5 years after testing. Considerations of fairness toward the laboratory or clinician bearing one or more of the elements of the duty appear to be at play here. Particularly in the absence of an ongoing relationship with the patient (for clinicians) and given the accumulation of a large number of patients for whom the duty may apply (for both laboratories and clinicians), there seems to be a strong case for recognizing a definite endpoint. However, even if one accepts the argument that a fixed duration of the duty should be set, data on the yield over time of reinterpretation will need to be taken into account in determining what that duration should be, i.e., at some point the yield will be sufficiently low as to no longer warrant the cost of reinterpretation.

Effect of resource limitations

Neither laboratories nor clinicians are usually expected (except, for the latter, in the case of emergencies) to provide services without reimbursement. Laboratories could build the projected cost of reinterpretation into the initial price of the test, assuming this can be successfully negotiated with payers, which would obviate the need to approach either insurers or patients for reimbursement at the time of reinterpretation. To the extent that clinicians are involved either in triggering the reinterpretation (which presumes time spent identifying patients for whom reinterpretation is needed) or in tracking down patients to discuss the results with them, reimbursement from insurers would be appropriate. However, the logistics of this may be complicated—including situations in which the clinician is not in-network for the patient's current insurer. Resolving reimbursement issues goes beyond the area where ethical analysis is likely to be helpful, except insofar as the existence of strong ethical support for a duty to reinterpret would suggest that a solution must be found.

Efforts to recontact

Regardless of whether this last element of the duty falls on the laboratory or more likely on a clinician, the question of the efforts required to discharge it must be addressed. In some cases, this will be straightforward, e.g., when a clinician receives reinterpreted results from a laboratory for a patient who continues to be under the clinician's care, in which case even skeptics of a duty would agree that clinicians must attempt recontact.[39] When patients are no longer under the care of a particular clinician, however, tracking them down so that they can be offered the results will involve additional effort. To the extent that the duty to reinterpret is to be meaningful, at least some efforts to contact the patient would seem to be required and might be facilitated at the health system level by ensuring that contact information of patients undergoing testing is updated when it changes and includes contact information for someone who is likely to know how to reach them if the information in their record is no longer current. Creation of a centralized (i.e., regional or national) registry where patient contact information could be entered (with their consent) and updated could simplify the task of tracking down patients to provide reinterpretations, but whether patients would make the effort to keep such information up-to-date remains to be determined. Even so, the exact dimensions of the recontact element of the duty—beyond the obvious conclusion that it should not be overly burdensome—would need to be determined.

CONSENT TO REINTERPRETATION

Patients should be told about the possibility of uncertain test results as part of an informed consent process to genetic

testing. If a duty to reinterpret variants becomes generally accepted, the possibility of being recontacted should also be part of the consent process, as well as being noted on initial laboratory reports, so that patients are not taken by surprise if that occurs. Currently, only a minority of consent forms for clinical genomic testing include such information and, when they do, the content varies significantly.[40] Whether patients should be offered the opportunity at the time of initial consent to opt out of reinterpretation is an open question, although our sense is that few would do so, since patients generally want the most accurate interpretation possible of their results, especially if it may affect their clinical care.

For similar reasons, we believe that patients whose consent to testing did not include specific notice of the possibility of reinterpretation should not be precluded from benefiting from new interpretations. In such cases, a specific consent to reinterpretation per se should not be required. However, over time patients' conditions may change and legitimate reasons may arise why further reinterpretations are not desired. Hence, mechanisms should exist for patients to decline to receive reinterpreted results and to opt out of additional reinterpretation if they so desire.

CONCLUSION

The growing use of genetic testing, and particularly next-generation sequencing technologies, has brought to the forefront of clinical genetics the question of whether variant reinterpretation should be undertaken on a routine basis. We believe that an ethical duty to reinterpret variants should be recognized, although we acknowledge that some aspects of such a duty, such as its precise dimensions and duration and the funding mechanism, will need to be worked out over time. Development of common practices with regard to reinterpretation, perhaps deriving from guidelines adopted by professional organizations, will reduce the risk of inequities resulting from inconsistent practices across laboratories and clinicians. Such a duty comports with the health-care system's traditional obligations toward patients and with the special obligations that may arise from the use of a technology that has a high likelihood of generating uncertain and other results that will change over time.

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