Is there a duty to routinely reinterpret genomic variant classifications?

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ABSTRACT

Multiple studies show that periodic reanalysis of genomic test results held by clinical laboratories delivers significant increases in overall diagnostic yield. However, while there is a widespread consensus that implementing routine reanalysis procedures is highly desirable, there is an equally widespread understanding that routine reanalysis of individual patient results is not presently feasible to perform for all patients. Instead, researchers, geneticists and ethicists are beginning to turn their attention to one part of reanalysis—reinterpretation of previously classified variants—as a means of achieving similar ends to large-scale individual reanalysis but in a more sustainable manner. This has led some to ask whether the responsible implementation of genomics in healthcare requires that diagnostic laboratories routinely reinterpret their genomic variant classifications and reissue patient reports in the case of materially relevant changes. In this paper, we set out the nature and scope of any such obligation, and analyse some of the main ethical considerations pertaining to a putative duty to reinterpret. We discern and assess three potential outcomes of reinterpretation—upgrades, downgrades and regrades—in light of ongoing duties of care, systemic error risks and diagnostic equity. We argue against the existence of any general duty to reinterpret genomic variant classifications, yet we contend that a suitably restricted duty to reinterpret ought to be recognised, and that the responsible implementation of genomics into healthcare must take this into account.

INTRODUCTION

The introduction of next generation DNA sequencing technologies into clinical practice has been transformative but double edged. On the one hand, while whole-exome and whole-genome testing produce significantly more molecular diagnoses compared with previous methods of DNA sequencing, absolute numbers are less encouraging. Close to half of those who undergo whole-exome or whole-genome testing today remain without a diagnosis, rising to over two-thirds for rare conditions. And while an initial test remains a more sustainable manner, this has led some to ask whether the responsible implementation of genomics in healthcare requires that diagnostic laboratories routinely reinterpret their genomic variant classifications and reissue patient reports in the case of materially relevant changes. In this paper, we set out the nature and scope of any such obligation, and analyse some of the main ethical considerations pertaining to a putative duty to reinterpret. We discern and assess three potential outcomes of reinterpretation—upgrades, downgrades and regrades—in light of ongoing duties of care, systemic error risks and diagnostic equity. We argue against the existence of any general duty to reinterpret genomic variant classifications, yet we contend that a suitably restricted duty to reinterpret ought to be recognised, and that the responsible implementation of genomics into healthcare must take this into account.

A further complicating factor is that our understanding of the clinical significance of genetic variants is subject to change, sometimes within short timeframes. In 2015, the American College of Medical Genetics and Genomics (ACMG) introduced a standard classification system on which genomic variants are classified regarding their pathogenicity (ie, as pathogenic (P), likely pathogenic (LP), of uncertain significance (VUS), likely benign (LB) or benign (B)). What at one point is a VUS may, upon the discovery of new evidence, warrant reclassification as a pathogenic variant, or perhaps as benign. A rare variant might at first thought be likely pathogenic, only to turn out (on greater population sequencing rates) to be more highly prevalent than previously understood, rendering it likely benign. At the same time, the underlying genetic data possess a peculiar and perhaps unique diagnostic durability, such that if patient data are stored over time then (pending rare mutations) a valid diagnosis can be obtained from initial data indefinitely, without having to retest the patient. As such, while an initial test remains unlikely—all else being equal—to result in a molecular diagnosis, subsequent reanalysis of test data may well do so. Not only this, but even where a molecular diagnosis is achieved, this may not prove the end of that patient’s ‘diagnostic odyssey’, if a causally relevant pathogenic variant is later revised down.

This status quo raises pressing questions regarding the responsible implementation of genomics in healthcare. On the assumption that NGS technologies will continue to become cheaper and more widely used, especially as first-line tests, those funding and delivering genomic medicine and research should be planning now for how they can best deliver on the promise of NGS technologies for patients. And here the question of regular or routine reanalysis of patient data is especially pertinent, not least because multiple studies have already shown that periodic reanalysis of patient data delivers significant increases in overall diagnostic yield. Further, there is widespread consensus among clinical geneticists that routine reanalysis of patient data is highly desirable.

However, at the same time, there is an equally widespread understanding that routine individual patient reanalysis is not presently feasible at scale.

It is estimated that reanalysing existing patient data in Australia alone would take 70 years, given the specialist and labour-intensive nature of the task. While innovations such as artificial intelligence (AI) are expected to play an increasingly
significant role in reanalysis, this will not help in the near term and the eventual role that AI will play remains speculative and uncertain. Instead, researchers, geneticists and ethicists are beginning to turn their attention to one part of reanalysis—variant classification reinterpretation—as a means of achieving increased diagnostic yields comparable to detailed individual reanalysis but in a more sustainable manner. In particular, it has been asked whether the responsible implementation of genomics in healthcare requires that diagnostic laboratories routinely reinterpret their genomic variant classifications and reissue patient reports in the case of materially relevant changes. As we go on to describe, reinterpretation of variant classifications is one of the key mechanisms by which the reanalysis of patient data is found to increase diagnostic yield. However, unlike other reanalysis mechanisms, variant reinterpretation occurs at the level of genomic variant classes, rather than the level of individual patient DNA sequences. The thought, then, is that the routine reinterpretation of variant classifications may be feasible in a way that large-scale individual reanalysis is not. And, if so, are diagnostic laboratories under a moral obligation to do so, as part of the responsible implementation of genomics in healthcare?

The aim of this paper is to set out the nature and scope of an obligation to routinely reinterpret variant classifications. We do so in three parts. First, we establish the contours of a duty to reinterpret variant classifications by distinguishing reinterpretation from reanalysis, and routine or active reinterpretation from ad hoc or reactive reinterpretation. Second, we consider the value of three potential outcomes of variant reinterpretation: upgrades, in which variants previously deemed as benign or uncertain are reclassified to pathogenic; downgrades, in which previously pathogenic variants are reclassified to benign or uncertain; and what we call regrades, in which variants of previously uncertain clinical significance are regraded to benign. Finally, we consider three grounds for mandating the active reinterpretation of variant classifications: ongoing duties of care, systemic error risk and diagnostic equity. While we argue against the existence of any general duty to reinterpret genomic variant classifications, we contend that a suitably restricted duty to reinterpret ought to be recognised.

A DUTY TO REINTERPRET?

In this debate, it is first important to establish terminology. We will follow Robertson et al in regarding reanalysis as an umbrella term describing ‘[t]he process of re-examining existing genomic data from an individual’ (our emphasis). Reanalysis has several components, including reinterpretation, which involves the re-evaluation and potential reclassification of genetic variants regarding their pathogenicity. Here re-evaluation is ‘the detailed reassessment of a variant in light of new/updated evidence... through the use of guideline frameworks’; while reclassification is the change of a variant’s previous classification on the basis of the results of re-evaluation. In a recent review of the efficacy of various mechanisms of reanalysis, variant reinterpretation was found to account for 26% of new diagnoses secured through reanalysis.

Although reinterpretation is typically conducted as one part of patient reanalysis, the practice of reinterpretation itself has distinct moral concerns. This is because reinterpretation, unlike other mechanisms of reanalysis, often involves a change in information previously relied on in clinical reporting. This distinct moral salience is exemplified by the European Society for Human Genetics (ESHG) in their Guidelines for diagnostic next-generation sequencing. The ESHG writes that,

[a] diagnostic laboratory should not become overloaded with requests to analyze ‘old’ data in the view of new findings and progress in the fields. A diagnostic request is a contract at a certain point in time. A laboratory will only be able to offer what is known, and validated, at a given point in time.

In light of this, they conclude that ‘[t]he laboratory is not expected to re-analyze old data systematically and report novel findings, not even when the core disease gene panel changes’. Yet, having said this, the ESHG also remarks that,

[O]n the other hand, if at a particular moment, it is decided – by the lab or by the community of experts in the disease – to change a variant from one class to another, the lab is responsible for reanalyzing the available data, re-issuing a report on the basis of the novel evidence, and also re-contacting referring clinicians for the patients that are possibly affected by the new status of the variant.

As we see it, the ESHG attributes a distinct moral importance to changes in variant classification arising specifically from the practice of reinterpretation. For while the ESHG explicitly absolves diagnostic laboratories from any responsibility to reanalyse patient data in light of ‘new findings and progress’, it charges laboratories with the responsibility of reanalysing patient data, as well as reissuing reports and recontacting clinicians, precisely when reinterpretation leads to a change in variant classification. This responsibility exceeds contractual obligations to analyse patient data, which extend only to ‘a certain point in time’, and also considerations of feasibility (avoidance of ‘overload’). Insofar as responsibilities that exceed legal and practical obligations are characteristically moral responsibilities, we understand the ESHG to regard the reanalysis of patient data following reinterpretation as a moral duty.

There remains, however, a further distinction to be drawn, pertinent to the question of a putative duty to reinterpret genomic variant classifications. This is between active and reactive reinterpretation. According to El Mecky et al the reactive reinterpretation of genomic variants originates from an ‘external trigger’ such as a patient or third-party request or finding. A simple example of reactive reinterpretation is when a patient or their clinician requests the reanalysis of a patient’s test results. Here any reinterpretation that occurs as part of this reanalysis is reactive. A more complicated example is when the identification of a genetic variant in a new patient, B, prompts the re-evaluation and reclassification of that variant within a laboratory’s database, which in turn prompts the reanalysis of that variant in an existing patient, A. Here, patient B’s analysis includes an interpretation of variant pathogenicity, while patient A’s reanalysis includes a reactive reinterpretation of the same.

Active reinterpretation, by contrast, describes a situation in which a laboratory routinely re-evaluates either all or some of the variants in their database and reclassifies as appropriate. Such active reinterpretation may occur at a predetermined time interval, or when a body of evidence reaches some predetermined threshold. What makes this sort of reinterpretation active rather than reactive is that the laboratory pre-emptively decides to reinterpret their variant classifications or a subset therein.

When the ESHG requires that diagnostic laboratories reanalyse patient data following variant reinterpretation, we suppose that they have reactive reinterpretation in mind. For they speak of laboratories deciding to conduct reinterpretation ‘at a particular moment’ as opposed to ‘systematically’, which...
suggests a specific prompt, and they refer to the reinterpretation of a variant by a ‘community of experts in the disease’ as an appropriate external trigger for conducting reanalysis. As such, while the ESHG recognises that laboratories have a moral duty to conduct reanalysis of patient data following reinterpretation, they do not appear to recognise a moral duty to actively reinterpret genomic variants, so as to pre-emptively discover changes in variant classifications, independent of patient requests or shifts in expert opinion.

Indeed, to the best of our knowledge, no professional guidelines currently require that clinical laboratories actively reinterpret their variant classifications. The current (2019) ACMG re-evaluation and reanalysis guidelines, for instance, state that the ‘routine reevaluation of a clinical laboratory’s entire internal database of variant classifications is likely to be impractical’. Instead, the ACMG leaves the question of active reinterpretation to the discretion of clinical laboratories, citing situations in which re-evaluation of variant classifications ‘may be considered’. These include when new resources become available (eg, new variant databases), when new variant assessment methodologies are adopted and when new evidence emerges as to gene–disease relationships and/or mechanisms of disease. Yet it remains the case that the ACMG places no requirement on laboratories to actively reinterpret their variant classifications, whether totally or partially.

Despite not being required to actively reinterpret variant classifications, the question of whether laboratories ought to establish protocols for the routine reinterpretation of variant classifications is a salient one among laboratory geneticists and clinicians. Here there are calls for laboratories to move away from a strictly contractual understanding of their relationship to patients—something still emphasised by the ESHG—on which they provide services on request, towards a model on which laboratories assume significant further responsibilities to those whom they provide testing services to. The strongest of these charge laboratories with a moral duty to actively reinterpret variant classifications that is independent of practical impediments, and which ought to guide both policymaking and practice.

For instance, Appelbaum et al assert that ‘[h]aving 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’, and that ‘[f]ailure 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’. By linking the supposed ‘failure’ to actively reinterpret variant classifications to patient abandonment, Appelbaum et al argue that testing laboratories owe a moral duty of care to patients beyond that of ensuring that their initial interpretation is accurate and up to date. Because laboratories have provided a service in the knowledge that a valid interpretation may become invalid within a relatively short space of time, and because they are (on the authors’ reasoning) well placed to conduct a reinterpretation, laboratories are morally obligated to actively reinterpret variant classifications for as long as ‘ongoing care is indicated’. Appelbaum et al distribute the responsibility for patient care across laboratories, genomic specialists (if relevant) and referring clinicians, yet they place responsibility for the active reinterpretation of variant classifications specifically on laboratories.

Before we consider the possible outcomes of reinterpretation and examine Appelbaum et al’s claim in further depth, we need to make two further overarching remarks to situate our argument. The first regards the concern voiced by the ACMG, and shared by others, that active reinterpretation, even if feasible, is presently too onerous to implement in an ethically responsible manner. As Appelbaum et al state: to the extent that [the] implementation of routine reinterpretation would utilize clinician or laboratory 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.

In our view, time intervals will play an important role here. What is too resource intensive to justify repeating every 6 months is less resource intensive at 18-month intervals, and even less so every 3 years. In general, we suppose that where there is a duty to reinterpret variant classifications, a point in time can be found where the relative benefits of reinterpretation will justify the requisite allocation of resources vis-à-vis alternative health-care activities.

Second, we take it for granted that the responsible implementation of genomics in healthcare will require broad cooperation between clinicians, laboratories, researchers and patients, as well as the sharing of specific responsibilities. This said, as regards the reinterpretation of variant classifications, we agree with Appelbaum et al that diagnostic laboratories are best placed to both perform and communicate the significance of reinterpretation, and therefore that insofar as a duty to reinterpret exists, the responsibility for discharging this duty should, prima facie, fall primarily to them. This being the case, our analysis of a putative duty to reinterpret considers the demands placed specifically on laboratories and sets aside any responsibilities that might arise for clinicians as distinct from laboratory geneticists (while recognising that the same person might act in both roles).

As a consequence, our analysis excludes an in-depth consideration of any obligation to recontact patients with information arising from reinterpretation. We expect this can be prospectively addressed with good consent arrangements, informed by previous debates on recontact in the context of single-gene genetic conditions. For our purposes, it suffices to say that if any information relevant to clinical management of patients arises from active reinterpretation of variant classifications, then laboratories have a prima facie (but also defeasible) obligation to communicate this information to clinicians (who in turn interpret this information and potentially pass it to patients), and that this obligation requires that communication channels are planned for and established pre-emptively.

THE VALUE OF REINTERPRETATION
To determine whether diagnostic laboratories have an obligation to actively reinterpret their variant classifications we will first consider the value of three different possible outcomes of reinterpretation. These are upgrades, in which previously benign or uncertain variants (ie, VUS/LB/B) are reclassified to pathogenic variants (ie, P/LP); downgrades, in which previously pathogenic variants (P/LP) are reclassified to benign or uncertain variants (VUS/LB/B); and what we can call regrades, in which variants of previously uncertain clinical significance (VUS) are regraded to

In saying this, we appreciate that such laboratories will operate under different organisational structures and funding models and that this must be taken into account when considering the existence and applicability of a duty to reinterpret.
benign (LB/B) in light of further evidence. We will consider each in turn.\textsuperscript{18}

**Upgrades**

While NGS technologies have vastly improved diagnostic yields over traditional sequencing methods, almost half of those who undergo genomic testing remain without a diagnosis, rising to over two-thirds for rare diseases.\textsuperscript{13} Furthermore, whole-genome and whole-exome testing typically return a large fraction of VUS. VUS prevalence varies, but rates as high as 41% have been observed in large cohort studies for cancer panels.\textsuperscript{24}

There is, therefore, a relatively high likelihood that the majority of patients undergoing genome sequencing will be left without a diagnosis after the initial analysis of their results, and perhaps with more unanswered questions than prior to testing.

This said, studies have found that reanalysis of genomic data significantly increases diagnostic yield. A recent literature review by Tan et al found a median 15% new diagnosis rate via reanalysis, across a median reanalysis timeframe of 22 months, for patients who had initially received no diagnosis.\textsuperscript{3} Further studies show increases of up to 47% over 6 years.\textsuperscript{15} Some of this increased diagnostic yield can be attributed to the reprioritisation of previously unanalysed sections of a patient’s genome, and some to the discovery of novel gene–disease connections. However, the re-evaluation and reclassification of prior non-pathogenic variant categorisations also plays a significant role in improving diagnostic yield.\textsuperscript{8,17}

Securing a diagnosis allows for informed prognosis, for better clinical management and potentially for management of recurrence risk. Therefore, classification upgrades through active variant reinterpretation have the potential to provide substantial benefits to patients for whom genomic testing initially results in no diagnosis. And even in cases where an eventual diagnosis is of no benefit to the patients themselves (eg, patients who have since died), the knowledge generated through diagnosis can benefit their surviving relatives, for example, by informing later reproductive decisions, or through providing knowledge of susceptibility to genetic conditions, in particular those where an intervention is available to mitigate risk.

**Downgrades**

Patients who receive a diagnosis from genomic testing also stand to benefit from the active reinterpretation of variant classifications when variants previously classified as pathogenic or as likely pathogenic are downgraded to either VUS, LB or B. The frequency of downgrades from pathogenic to non-pathogenic has reduced significantly following the implementation of the ACMG guidelines for the standardisation of variant interpretation in 2015.\textsuperscript{22} Still, there is cause for concern.

Recently, Xiang et al selected 217 P/LP variants from ClinVar.\textsuperscript{21} Of these they found that 24% ought to be downgraded to VUS, LB or B, rising to 40% when variants were submitted prior to 2014.\textsuperscript{21} These variants had been submitted by laboratories rather than curated by expert panels, yet each was without conflicting interpretations. Especially notable here is that 47% of the original variants selected (102/217) were submitted to ClinVar without any documentation of collection methods or rationale for categorisation, of which 71% were downgraded.\textsuperscript{23} While 10% of the variants that were either downgraded to VUS/LB/B or changed to risk factors rather than causes of disease (9/92) were correctly interpreted as per their supporting documentation but incorrectly submitted to ClinVar as P/LP.\textsuperscript{23} It is not especially surprising that low-quality variant classifications should lack conflicting interpretations when the reasons for those classifications are undocumented. Yet numerous studies document a tendency towards inflation of pathogenicity even among well-documented submissions to public databases.\textsuperscript{22,24,25}

It is reasonable to expect that some currently pathogenic variants will be downgraded as further evidence becomes available as to population and disease allele frequencies. What at one point in time seems causal may turn out not to be so. Still, the prevalence of downgrades in public repositories suggests a significant degree of ascertainment bias as well.\textsuperscript{24,25} This is a problem as there are many harms that might arise from inflated pathogenicity claims. False positives may lead to ineffective or deleterious treatment, they may erroneously assign risk to relatives and they might influence reproductive decisions needlessly.\textsuperscript{26} To the extent that active reinterpretation of variant classifications promises to detect false positives in a timely manner then these harms might be avoided. Yet even when irreversible medical decisions have been made on account of a false positive diagnosis (eg, prophylactic mastectomies), downgrades of inflated variant classifications have the potential to benefit future patients, as well as temper ongoing anxiety or worry.

**Regrades**

The last outcome to consider is when variants of previously uncertain clinical significance (VUS) are regraded to benign (LB/B) in light of further evidence. A recent review of 571 850 classifications submitted to ClinVar found that the most common self-submitted reclassification type is a regrade from VUS to either LB or B.\textsuperscript{26} This occurred in 42.8% of such cases. This is to be expected given the high prevalence of VUS, but it also means that any benefits of regrades are likely to be well distributed among patient populations. VUS cause difficulties for both patients and clinicians. Uncertainty as to the clinical significance of a variant can lead patients to undergo irreversible yet ultimately unnecessary clinical intervention.\textsuperscript{27} Similarly, such uncertainty creates further uncertainty as to what information clinicians should report.\textsuperscript{1} Although regrades are in one sense non-diagnostic, the regrading of VUS promises peace of mind through the resolution of diagnostic uncertainties to the negative (ie, benign). Insofar as the active reinterpretation of variant classifications promises to regrade significant numbers of VUS in a timely manner it could produce widespread benefits through removal of ongoing worry and health system/payer savings through avoidance of ongoing clinical surveillance.

**MORAL GROUNDS FOR ACTIVE REINTERPRETATION**

Each of the outcomes above—upgrades, downgrades and regrades—itself provides a reason to implement the active reinterpretation of variant classifications. The question, however, is whether there is a moral imperative for diagnostic laboratories to actively reinterpret the variant classifications in their databases on account of the potential benefits of these outcomes. Here we consider three grounds for mandating active reinterpretation of variant classifications: ongoing duties of care; systemic error risk; and diagnostic equity.

**Ongoing duty of care**

We noted above that Appelbaum et al contend that the ‘failure to [actively reinterpret variant classifications] 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.\textsuperscript{13} This contention can be reframed as holding that diagnostic laboratories—on behalf of the healthcare system—have an ongoing duty of care to patients that extends beyond any explicit legal duties of care, and beyond current standard practice (which could ground an implicit legal duty of care), and that actively reinterpreting variant classifications is essential to discharging this duty, such that not actively doing so constitutes a moral failure akin to patient abandonment.\textsuperscript{15,17}

Central to Appelbaum et al\textquoteright s argument is that whole-genome and whole-exome testing are known by healthcare providers as ‘likely to produce data on variants that cannot be definitively interpreted today—but [that] may be subject to reliable interpretation in the future’,\textsuperscript{15} namely VUS. Furthermore, Appelbaum et al point out that genomic data possess what we have above called ‘diagnostic durability’, where—excluding rare mutations—genomic data retain its diagnostic validity for as long as it is stored.\textsuperscript{1} As such, it follows that a reliable future interpretation of presently uninformative variant data can still be used to generate a valid diagnosis merely through reinterpretation, without retesting a patient. In light of this, Appelbaum et al suggest that by virtue of ordering and conducting [such] a test … those involved assume the obligation to modify the interpretation and communicate the new information to the patient.\textsuperscript{15}

Insofar as an obligation to reinterpret variant classifications obtains simply ‘by virtue of ordering and conducting’ genomic testing, it follows that not actively reinterpreting VUS after having ordered and conducted genomic testing is to abandon patients for whom more could knowingly be done to either secure a diagnosis (through upgrades) or bring peace of mind (through regrades). Indeed, Appelbaum et al maintain that such a duty exists for at least so long as reinterpretation continues to significantly increase in informational yield (through either upgrades or regrades of VUS) across patient populations.\textsuperscript{15}

We agree with Appelbaum et al that the healthcare system has an ongoing duty of care to patients who receive genomic testing; both to those who receive a diagnosis and those who do not. This said, we do not believe that the active reinterpretation of VUS is essential to discharging this duty. We have two reasons for taking this position. First, while healthcare providers do knowingly provide tests that are likely to produce variant data which cannot presently be reliably interpreted but that could be in the future, this knowledge is conditioned by other knowledge. For instance, NGS technologies are offered to patients in the knowledge that whole-genome and whole-exome testing produce far superior diagnostic yields to gene panel testing.\textsuperscript{1} This is a reason for offering NGS alongside traditional methods as second-line test, but also as a first-line test in situations where more comprehensive initial testing is the most appropriate for determining further clinical pathways.\textsuperscript{22} In other words, there are often good reasons to offer NGS despite knowing that more comprehensive testing is more likely to produce variant data that cannot presently be reliably interpreted, but which may so in the future. This being the case, it is too strong to claim that simply ‘by virtue of ordering and conducting’ such tests diagnostic laboratories incur an obligation to actively reinterpret variant classifications.

For if the potential gains of offering an NGS-based test outweigh the potential harms of uncertainty, as is arguably most often the case, then test providers can knowingly provide such tests without incurring an obligation to actively reinterpret uncertain variants. This position holds insofar offering such tests is in the best interests of the patient, all things considered.

It might be objected here that this argument only serves to absolve diagnostic laboratories from actively reinterpreting VUS with the intent to provide patients with peace of mind following regrades (ie, from a VUS to B or LB) but not from upgrades of VUS to LP or P. Here we respond that we ought to distinguish between duties of care owed to individuals and those owed to populations. This is significant because while the probability that reinterpretation will increase the diagnostic yield for a patient population is high, the likelihood that reinterpretation will secure a diagnosis for any particular individual within that population is low.\textsuperscript{16} As such, we contend that it is better, in general, to prepare patients for the high likelihood that whole-genome or whole-exome testing will produce results that are uncertain, and that are statistically unlikely to become clinically relevant in the future, than to hold out hope of a statistically unlikely diagnosis through regular variant reinterpretation. So long as such counselling is offered both before and after testing then any ongoing duties of care have been discharged, subject to the following exceptions.

The first exception is that VUS are not a blanket category. Some laboratories draw a further distinction among VUS according to their estimated likelihood of being either upgraded or downgraded with additional evidence. For instance, distinctions are drawn between VUS(a) which are uncertain yet potentially clinically relevant, VUS(b) which are of unknown clinical relevance and VUS(c) which are of low clinical relevance.\textsuperscript{3}

In the case that a laboratory classifies a VUS as being of potential clinical relevance on the discovery of additional evidence (ie, VUS(a)) then we believe that the laboratory has a duty to routinely re-evaluate that variant and to reclassify as appropriate, and that this duty obtains for as long as the variant is considered to remain VUS(a).

Second, in those instances where laboratories are either funded or otherwise compensated to actively reinterpret VUS then they have an ongoing duty of care to do so. We only intend our considerations above to apply in general, and we happily acknowledge that there may be situations in which duties of care include a duty to reinterpret all VUS pertaining to a particular patient or patient population. We note also that there can be good reasons to fund the active reinterpretation of all VUS in a laboratory’s database in the absence of any moral obligation to do so. For instance, if active reinterpretation of all VUS turns out to be more cost-effective than alternative diagnostic pathways then healthcare providers ought to fund the establishment of such reinterpretation programmes.\textsuperscript{28} Still cost-effectiveness is a pragmatic imperative, not a moral one, and does not—of itself—establish a duty to reinterpret all VUS, whether to secure diagnoses or to achieve peace of mind.

\textsuperscript{1}We wish to remain agnostic as to the meta-ethical nature of this duty, that is, whether it is derived from the beneficial consequences of providing ongoing patient care, or whether it is a primary fact of the caregiving relationship between providers and patients. Our concern here is whether the routine reinterpretation of variant classifications is necessary to discharge this duty, and our answer is neutral as to the nature of the duty itself.

\textsuperscript{2}To be clear, genomic data may lose its diagnostic validity when the sequencing methods used to generate those data are superseded. What the diagnostic durability of genomic data refer to is the fact that genomic data do not decay over time.

\textsuperscript{28}As per Tan et al, there is a 15% median new diagnosis rate from reinterpretation after 22 months, 26% of which (as per Robertson et al) is attributable to reinterpretation, which amounts to a 3.75/100 prior likelihood that any individual will receive a new diagnosis through variant reinterpretation.
Lastly, as to the question of whether laboratories have an ongoing duty of care to actively reinterpret P/LP variants in case of a possible downgrade, we hold that so long as there is no reason to think that the laboratory has been negligent in classifying variants as P/LP, then there is no moral obligation to actively reinterpret variant classifications on the grounds of an ongoing duty of care. Our rationale here is that best practice healthcare provision ought to morally indemnify healthcare providers from liabilities for errors that are outside their control—but see immediately below.

Systemic error risk

We have argued that there is no moral duty for diagnostic laboratories to actively reinterpret P/LP variants in their databases because of an ongoing duty of care to patients. Assuming no error in classification, laboratories ought to be considered to have discharged their duties of care after providing pathogenic or likely pathogenic results that—to the best of their knowledge and abilities—are accurate and up to date. This said, while best practice healthcare provision ought to morally indemnify healthcare providers from liabilities for errors that are outside their control, there are what we call ‘systemic error risks’ peculiar to genomic testing that we believe generate a moral obligation to actively reinterpret some variant classifications.

More specifically, interpretation of data obtained from genomic testing relies on large-scale data generation and sharing efforts in order to synthesise and use the immense amounts of information gathered on great numbers of sequence variants. Central repositories for variant classifications such as ClinVar, PanelApp and Shariat play an invaluable role in disseminating information as to variant pathogenicity, yet, as seen in the ‘Downgrades’ subsection, such services come with an inherent risk that classifications of pathogenicity are inflated either through ascertainment bias or simple error. As such, attempts at diagnosis must be seen to come with an inherent systemic error risk given the especially information-intensive nature of this medical field.

We assume that laboratories take appropriate care to guard against such systemic error risks when identifying, interpreting and reporting on sequence variants in any particular instance. Still, to the extent that such risks are inherent to openly sourced variant classification schemes we believe that diagnostic laboratories are obligated to actively reinterpret instances of variant classification that are more likely susceptible to systemic error risk. For instance, variant classifications in ClinVar are ranked according to the quality of the evidence in support of their classification.30 We suggest that when laboratories either rely on poorer quality submissions to classify a variant as P or LP—or are themselves the only source of a P/LP classification—then they have duty to actively reinterpret that variant classification until such time as there is a majority consensus as to a P/LP interpretation. Likewise, if a laboratory is one of only two sources as to a contested variant classification (whether P, B or VUS) then they ought to actively reinterpret that variant classification until there is a majority consensus as to their interpretation, whether pathogenic or non-pathogenic. Otherwise, where a laboratory classifies a variant as P or LP in opposition to majority consensus, expert opinion or practice guidelines, then the laboratory ought to actively reinterpret that variant classification in their database, as such attestations of pathogenicity ought to be seen as carrying a high inherent risk of error, despite good faith attestations and best clinical practice.

Diagnostic equity

Above we argued that diagnostic laboratories are not morally obligated to actively reinterpret genomic variant classifications merely on the basis that genomic testing is currently very likely to generate VUS. Still, it is possible to distinguish between the intrinsic high likelihood of a test returning VUS on account of its comprehensive nature, and the extrinsic high likelihood of the same test returning VUS on account of outside limitations on the initial data set. For instance, as noted above, VUS are prevalent among all populations. But they are especially prevalent among ethnic and racial minority populations.14 15 24 The heightened prevalence of VUS among such populations can be explained by relatively limited data sets, which in turn can be at least partly explained by disparities in access to genetic services, lower rates of utilisation and lower participation rates in research.

At the same time, while the initial data sets for racial and ethnic minority populations are relatively limited, we note again that genomic data possess a peculiar diagnostic durability. As such, and so long as genomic databases themselves are being revised to become more representative, the active reinterpretation of VUS classifications pertaining to minority populations has the potential to help reduce disparities in diagnosis through more accurate variant classifications. And here, insofar as reducing VUS rates has the potential to decrease inequities in diagnosis rates between populations, considerations of diagnostic equity require laboratories to actively reinterpret all VUS pertaining to patients from racial and ethnic minority populations.

This said, any obligation here should be considered defeasible if the underlying reasons for lower rates of utilisation of genomic testing among minority populations—as well as lower participation rates in research—stem from legitimate concerns regarding cultures of medical surveillance. The reanalysis of genomic data is arguably one such form of medical surveillance, and thus any supposed obligation to actively reinterpret genomic variants pertaining to minority groups ought to be balanced against this concern. However, as we see things, this can be addressed through quality patient engagement, codesign and consent processes.

A second consideration concerning diagnostic inequity regards instances in which racial and ethnic populations are more likely to receive false positive test results due to a variant deemed pathogenic in one population being benign in another (less represented) population. For instance, Manrai et al demonstrated that the prevalence of genetic variants that had been causally linked to hypertrophic cardiomyopathy ranged from 0.01% to 1.5% among white Americans, yet from 1.5% to 14.9% among black Americans.24 As such, multiple patients with African heritage had been misdiagnosed as being at risk of hypertrophic cardiomyopathy on the basis of a pathogenic variant classification, when in fact the variant was simply more penetrant among that population, and ought to have been (and later was) classified as benign.

This instance of diagnostic inequity escapes the controls on systemic error risk we outlined above, as here an initial (yet incorrect) pathogenic classification would be in line with the majority (yet unrepresentative) opinion. Such cases are, however, likely to become more common as diversity among patient populations increases. Consequently, we believe that considerations of diagnostic equity demand that laboratories routinely reinterpret any pathogenic variants in their databases that are observed to produce high diagnosis rates in minority populations, relative to the general population.
CONCLUSION
When Appelbaum et al argue for a duty to reinterpret all VUS they do so with the expressed aim of ‘stimulating debate’ and ‘moving toward consensus’ on the question of whether the responsible implementation of genomics in healthcare requires that diagnostic laboratories routinely reinterpret their genomic variant classifications and reissue patient reports in the case of materially relevant changes. In the same vein, we have closely analysed three potential outcomes of active reinterpretation and have considered a number of moral grounds in favour of recognising a duty to actively reinterpret variant classifications.

Contra Appelbaum et al we do not recognise any general moral obligation to actively reinterpret all VUS for all populations, and we hold this regardless of the potential benefits of increased diagnostic yields through upgrades, or the peace of mind offered by regrades from VUS to benign classifications. VUS, to our mind, are an inherent part of next generation genomic sequencing and it is better to prepare patients for the high likelihood that genomic testing will not end their diagnostic odyssey, and to support them through any attendant uncertainties, than to hold out hope of an unlikely molecular diagnosis through the regular reinterpretation of variant classifications.

This said, we believe that ongoing duties of care constitute sufficient moral grounds to require that laboratories routinely reinterpret VUS that they estimate as likely to be of clinical relevance, given further evidence (ie, VUS(a), described above). Alongside this, we also recognise a defeasible moral obligation for laboratories to actively reinterpret all VUS pertaining to racial and ethnic minority populations with the aim of reducing diagnostic inequities. To this extent, we agree with Appelbaum et al that those planning, funding and delivering genomic medicine and genomic research should be planning for wider scale reinterpretation of VUS now.

In addition, we believe that there are strong moral grounds for diagnostic laboratories to actively reinterpret variant classifications that are at comparably higher risk of being false positives. Here we have outlined two such cases: pathogenic variant classifications that come with what we have called ‘systemic error risk’, and pathogenic variant classifications likely to generate diagnostic equity considerations between different populations.

In sum, we hold that the promise of genomics in healthcare has a double valence. There is the promise that we will be able to understand, treat and cure diseases which we previously had little insight into, and there is the promise that the implementation of genomic technologies—such as whole-exome and whole-genome sequencing—will be equitable, and will guard patients against systemic hazards. And here, while the duties of care owed to patients are significant, they do not extend to attempting to mitigate uncertainties attending the first promise through the routine reinterpretation of all VUS. Instead, when planning for the responsible implementation of genomics in healthcare, the promise of equitable and safe treatment ought to take precedence.

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GW and AJN contributed substantially to the manuscript. Both authors jointly conceived the idea for the manuscript. GW wrote the first draft and led the editing. GW and AJN then jointly critically reviewed the manuscript over several iterations and agreed on the final manuscript. GW is the author acting as guarantor.

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