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Reclassification of clinically-detected sequence variants: Framework for genetic clinicians and clinical scientists by CanVIG-UK (Cancer Variant Interpretation Group UK)

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ABSTRACT

Purpose: Variant classifications may change over time, driven by emergence of fresh or contradictory evidence or evolution in weighing or combination of evidence items. For variant classifications above the actionability threshold, which is classification of likely pathogenic or pathogenic, clinical actions may be irreversible, such as risk-reducing surgery or prenatal interventions. Variant reclassification up or down across the actionability threshold can therefore have significant clinical consequences. Laboratory approaches to variant reinterpretation and reclassification vary widely.

Methods: Cancer Variant Interpretation Group UK is a multidisciplinary network of clinical scientists and genetic clinicians from across the 24 Molecular Diagnostic Laboratories and Clinical Genetics Services of the United Kingdom (NHS) and Republic of Ireland. We undertook surveys, polls, and national meetings of Cancer Variant Interpretation Group UK to evaluate opinions about clinical and laboratory management regarding variant reclassification.

Results: We generated a consensus framework on variant reclassification applicable to cancer susceptibility genes and other clinical areas, which provides explicit recommendations for clinical and laboratory management of variant reclassification scenarios on the basis of the nature of the new evidence, the magnitude of evidence shift, and the final classification score.

Conclusion: In this framework, clinical and laboratory resources are targeted for maximal clinical effect and minimal patient harm, as appropriate to all resource-constrained health care settings.

Introduction

Variant interpretation

Genomic sequence analysis is typically undertaken with the aim of identifying the genetic basis of a patient's disease. For any sequence variant detected, an interpretation is required as to whether the variant is pathogenic (P) (disease-causing) or benign (B). Variant interpretation typically integrates different types of evidence, such as predicted protein impact, clinical data, functional assays, and population variant frequency data, often requiring laborious reference to numerous data sources and literature. To reduce erroneous assignation of variant pathogenicity and between-laboratory

Lucy Loong and Alice Garrett contributed equally.

*Correspondence and requests for materials should be addressed to Clare Turnbull, Division of Genetics and Epidemiology, The Institute of Cancer Research, 15 Cotswold Road, Sutton, SM2 5NG, United Kingdom. *E-mail address:* clare.turnbull@icr.ac.uk

A full list of authors and affiliations appears at the end of the paper.

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variability, there have been concerted efforts within the clinical-laboratory community to produce consensus frameworks for variant interpretation, such as that of the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) put forward in 2015.[1]

The ACMG/AMP framework was formally adopted by the UK Association for Clinical Genomic Science in 2016. To deliver training in the use of the ACMG/AMP framework and subspecialty specification of the framework, national subgroups comprising National Health Service (NHS) clinical scientists and genetic clinicians were established for rare disease, cancer, cardiac, and cholesterol genetics. Established in 2017, the Cancer Variant Interpretation Group UK (CanVIG-UK) is a multidisciplinary network of >220 clinical scientists, clinical geneticists, and genetic counselors, with representation from each of the 24 Molecular Diagnostic Laboratories and Clinical Genetics Services of the United Kingdom (NHS) and Republic of Ireland.[2] The group holds a monthly national multidisciplinary meeting for review of problematic clinically-detected cancer susceptibility gene (CSG) variants, has developed detailed United Kingdom specification for CSGs of the ACMG/AMP framework (https://www.cangene-canvaruk.org/canvig-uk-guidance), and has developed a digital platform for sharing of variant-level resources, United Kingdom laboratory data, and interim clinical classifications (CanVar-UK, https://www.canvaruk.org/). Additional bimonthly national multidisciplinary meetings are held jointly by CanVIG-UK and the British Society of Genomic Medicine (BSGM) Cancer Genetics Group (UK-CGG) to review topics relating to clinical patient management in cancer susceptibility genetics.[3]

Evidence scoring in variant classification

In the ACMG/AMP framework, evidence items across different categories are awarded 1 of 4 strengths: supporting, moderate, strong, or very strong.[1] Tavtigian et al[5,6] undertook mapping of these to a Bayesian framework in which evidence points are combined with a prior probability of pathogenicity to produce a posterior probability of pathogenicity, which determines the variant pathogenicity classification.[4-6] If the prior probability of a variant being P is 10%, variants with ≥10 evidence points have a >99% posterior probability of being P and are classified as P; similarly, 6 to 9 evidence points and 90% to 99% probability are classified likely pathogenic (LP); 0 to 5 evidence points and 10% to 90% probability are classified as variant of uncertain significance (VUS); –1 to –6 evidence points and 0.1% to 10% probability are classified likely benign (LB); ≤ –7 evidence points and <0.1% probability are classified benign (B).

Although the evidence score comprises a discrete number of evidence points (typically –7 to +12) and the likelihood (posterior probability) of pathogenicity is a percentage (0%-100%), clinical actionability is in effect a binary entity. Variants classified as P/LP are actionable in that they are used to inform clinical management, eg, eligibility for preventative surgery, intensive/invasive disease surveillance programs, reproductive interventions, and cascade testing of relatives. P and LP variants are treated equivalently in terms of clinical management. Variants of other classes are not used in patient management. Thus, there is effectively a binary cut-off for medical intervention at the threshold between the VUS and LP variant classifications (hereafter termed the actionability threshold). Identification of multiple B/LB variants is a frequent occurrence in genetic testing, particularly if a large set of genes is analyzed.

Evolution of evidence for variant classifications

The evidence base informing variant classifications is highly dynamic with regular emergence of novel databases, functional assays, predictive tools, and platforms for the sharing of clinical data. Furthermore, our understanding of how best to weight and combine evidence items is evolving, resulting in changes to the frameworks by which evidence is scored and combined. The interpretation and classification of a variant on the basis of the totality of available data may therefore change over time. Variant reinterpretation is defined as the practice of re-evaluating all the evidence available about the pathogenicity of a genetic variant and taking into account any new evidence that is made available since the previous interpretation.[7]

Implications and consequences of variant reclassification

Variant reinterpretation is typically reactive, triggered in response to clinical events, eg, a new clinical presentation, availability of new family history information, or a proposed medical/surgical/prenatal intervention in a patient with the variant. However, in such a reactive model, outdated variant classifications will inform patient management until such a trigger arises. When variant reinterpretation results in reclassification to the other side of the actionability threshold, this may have implications for patients regarding their clinical management. Delay in updating to a revised classification of P/LP, may result in perceived harm if the patient has in the meantime developed a cancer that might have been mitigated by risk-reducing surgery or enhanced surveillance. Conversely, when a variant previously ascribed as P/LP is down-classified, there may also be perceived harm regarding previously performed risk-reducing surgery or invasive surveillance, particularly when associated with a complication or suboptimal outcome. In contrast to such a reactive model for triggering of variant reinterpretation, a more regular proactive model may be advantageous, but would have significant resource implications for both laboratory and clinical workloads. In addition, a highly dynamic evidence base may result in

some variants hovering around or repeatedly crossing the actionability threshold, which has the potential to cause confusion and inconsistency (ie, management of a patient based on an erroneous or outdated variant classification).[8]

Research seeking views on recontacting of patients in clinical genetics practice suggested that UK patients tend to value recontact as an important means to access in a timely fashion the clinical (eg, prevention of disease) and psychological benefits of new information (eg, variant reclassifications).[9]

Existing practice for variant reclassification

In 2019, the European Society of Human Genetics (ESHG) published principles and broad recommendations on a range of scenarios relating to recontact of patients by clinical genetics services.[7] In the same year, the ACMG published points to consider in the re-evaluation and reanalysis of genomic test results and subsequent patient recontact after revision of genomic test results.[10,11] Both groups acknowledged that proactive/regular variant reinterpretation was unlikely to be feasible for health care services and advocated prioritization of reclassification scenarios where clinical impact was likely.[7,10] US-led research relating to the ethical, economic, legal, and clinical implications of variant reinterpretation has been performed in tandem.[10,12,13] A survey of United Kingdom genetic clinicians and clinical scientists in 2016 suggested practice is variable and ad hoc. There is currently no United Kingdom guidance or standardized practice for United Kingdom clinical-laboratory services regarding initiation of variant reinterpretation or the process for recontact of patients when variant reclassifications across the actionability threshold occur.[14] There have been numerous calls for more defined, specific professional guidance regarding patient recontact, including from within the CanVIG-UK network.[7,15,16]

Materials and Methods

We sought to leverage the comprehensive national representation of cancer genetics clinicians and laboratory clinical scientists within CanVIG-UK and UK-CGG to develop and ratify a guidance framework for clinical and laboratory management of variant reclassifications (Supplemental Table 1). The framework development process comprised the following:

1. A premeeting survey about management of different variant classes and reclassification scenarios (emailed to registrants ahead of the joint BSGM UK-CGG/CanVIG-UK clinical cancer genetics preliminary national scoping meeting) (Supplemental Table 2)
2. Within meeting polls regarding proposed approaches to reclassification scenarios (undertaken live during the joint BSGM UK-CGG/CanVIG-UK preliminary national scoping meeting) (Supplemental Table 3)
3. Provisional framework drafted by a working subgroup (from outputs of the joint BSGM UK-CGG/CanVIG-UK preliminary national scoping meeting)
4. Review of the draft output at a second national meeting (CanVIG-UK national meeting)
5. Circulation and ratification of the final output by the CanVIG-UK membership

Details of attendee and respondent numbers are captured in Supplemental Table 1.

Results

The detailed CanVIG-UK consensus framework for recommended clinical and laboratory actions in response to reactive variant reclassification is presented in Table 1. There were 10 overarching principles agreed during the framework development process to be key to current United Kingdom variant reclassification practices:

1. There is dynamic evolution of evidence contributing to variant interpretation and how this evidence is weighted and combined. Patients should be made aware at the time of consenting for genetic testing that variant reclassification may occur.
2. Regular proactive and/or systematic variant reinterpretation by individual United Kingdom laboratories is not currently feasible. Variant reinterpretation will typically be reactive and triggered by clinical events.
3. Clinicians should be advised to routinely request variant reinterpretation before initiation of new clinical actions (eg, risk-reducing surgery, new cancer surveillance programs, cascade testing of relatives) when undertaken ≥12 months after the initial ascertainment of a variant in a family.
4. As genetics is mainstreamed, it is important that clinicians outside of the specialty of clinical genetics are made aware of points 1 to 3.
5. Reissuing of a report or need for communication with a patient/family after a variant has been reclassified will depend on the perceived significance and robustness of the new classification, as assessed by the following:
   - Size of shift in evidence points
   - Proximity of new classification to the actionability threshold
   - Nature of shift in evidence points (fresh evidence, new conflicting data, or new evidence weighting)
6. National multidisciplinary review is recommended for down-classification of variants from P/LP across the actionability threshold. This will allow full oversight and aggregation of the national data before implementation of the down-classification.
7. In cases in which a variant reclassification to a score just above or below the actionability threshold

Table 1 CanVIG-UK consensus framework for recommended clinical and laboratory actions in response to reactive variant reclassification

	Reclassification				Laboratory Management			Clinical Management		
Clinical Actionability	Nature of Evidence	Change in Evidence Score	Direction of Reclassification	New Classification	Multicenter MDT Review Recommended	Urgent National Reclassification Alert	Reissue of Laboratory Report	Proactive Recontact[a] of Historic[b] Patients and Their Clinicians/GP	Management of New Family Members From Historic Families	Management of Prospectively Identified New Probands
Reclassifications that cross the actionability threshold	New evidence is (1) substantive, nonconflicting, publicly available data or (2) locally available data[c]	Any	Upgrade	LP, P (ES: ≥6)	No	Yes	Yes	Yes	Standard P/LP	Standard P/LP
			Downgrade	B, LB, VUS (ES: ≤5)	Yes	Yes	Yes	Yes	Advise of down-classification; as standard for VUS/LB/B: no clinical action	As standard for VUS/LB/B: no clinical action
	New evidence is publicly available data that is conflicting with prior evidence[d] or revision to evidence strengths in variant classification framework with no new evidence	1-3 points	Upgrade	Upper-end LP (ES: 8)	No	Yes	Yes	Yes	Standard LP	Standard LP
			Upgrade[e]	Lower-end LP (ES: 6-7)	No	Yes	Yes; "potentially changeable classification at the actionability threshold"	Yes	Cautious LP management	Cautious LP management
			Downgrade[e,f]	"Warm"/"hot" VUS (ES: 4-5)	Yes	Yes	Yes; "potentially changeable classification at the actionability threshold"	Immediate systematic proactive recontact not recommended; reactive approach only recommended for initial period[g,h]	Advise of changeable down-classification; supply of information as standard for VUS	As standard for VUS: no clinical action
			Downgrade	"Tepid" VUS (ES: 3)	Yes	Yes	Yes	Yes	Advise of down-classification; as standard for VUS: no clinical action	As standard for VUS: no clinical action
		4 or more points	Upgrade	Upper-end LP, P (ES: ≥8)	No	Yes	Yes	Yes	Standard P/LP	Standard P/LP
			Upgrade	Lower-end LP (ES: 6-7)	No	Yes	Yes	Yes	Cautious LP management	Cautious LP management
			Downgrade	"Warm"/"hot" VUS (ES: 4-5)	Yes	Yes	Yes	Yes	Advise of down-classification; as standard for VUS: no clinical action	As standard for VUS: no clinical action
			Downgrade	B, LB, "ice cold"/"cold"/"cool"/"tepid" VUS (ES: ≤3)	Yes	Yes	Yes	Yes	Advise of down-classification; as standard for VUS/LB/B: no clinical action	As standard for VUS/LB/B: no clinical action

(continued)

Table 1 Continued

	Reclassification				Laboratory Management			Clinical Management		
Clinical Actionability	Nature of Evidence	Change in Evidence Score	Direction of Reclassification	New Classification	Multicenter MDT Review Recommended	Urgent National Reclassification Alert	Reissue of Laboratory Report	Proactive Recontact[a] of Historic[b] Patients and Their Clinicians/GP	Management of New Family Members From Historic Families	Management of Prospectively Identified New Probands
Reclassifications that DO NOT cross the actionability threshold	Any	Any	Upgrade from B, LB, "ice cold"/"cold"/"cool"/"tepid" VUS (ES: ≤3)	Upgrade to "warm"/"hot" VUS (ES: 4-5)	No	No	No	No	As standard for VUS: no clinical action	As standard for VUS: no clinical action
			Downgrade from "warm"/"hot" VUS (ES: 4-5)	Downgrade to B, LB, "ice cold"/"cold"/"cool"/"tepid" VUS (ES: ≤3)	No	No	Only if a "warm"/"hot" VUS report has previously been issued	No; exception: communication to patients of down-classification can be considered when patients are known to have previously been informed of the VUS (written communication likely sufficient)	Advise of down-classification; as standard for VUS/LB/B: no clinical action	As standard for VUS/LB/B: no clinical action

Scenarios are separated into reclassifications that cross the actionability threshold and those that do not. Reclassification scenarios that cross the actionability threshold are further separated by nature of evidence that led to reclassification and size of change in evidence score.

B, benign; *ES*, evidence score; *GP*, general practitioner; *LB*, likely benign; *LP*, likely pathogenic; *MDT*, multidisciplinary team; *P*, pathogenic; *VUS*, variant of uncertain significance.

[a]Definition of proactive recontact requires further specification; suggestion: letter explaining situation, proactive scheduling of appointment slot with 1 more attempt to recontact if original appointment not attended.

[b]Historic patients: all current and former patients who have been identified to have the reclassified variant, including former patients, seen in the past, discharged from care, and no longer in an ongoing relationship with the specific health care professional involved.

[c]Substantive new publicly available evidence (eg, functional assay, multifactorial analysis) or locally available evidence (eg, segregation data, RNA analysis) in the absence of previous evidence of that type.

[d]New publicly available evidence conflicting with previous data of the same type (eg, new functional assay conflicting with previous functional assay, new multifactorial analysis conflicting with previous multifactorial analysis); new evidence is of equivalent validity, thus nullifying existing data for that evidence class.

[e]Rows showing reclassification scenarios that produce "potentially changeable classifications at the actionability threshold" which are reclassifications resulting from conflicting evidence or from revision to evidence strengths in the variant classification framework and when the change in evidence score is ≤3 and the new classification is close to the actionability threshold (ES: 4-7).

[f]When sufficient national infrastructure exists, these down-classified variants to remain under active national review.

[g]A reactive approach in this context refers to advising historic patients of down-classification only when they come forward for new intervention.

[h]When national infrastructure exists for active variant monitoring and review, in the absence of further fluctuation in variant class, systematic recontact of historic patients may be considered after a period of ≥1 years.

occurs, resulting from new evidence that is conflicting with pre-existing evidence and/or a change to evidence weighting, and which causes only a modest change to total evidence points, the variant classification may be considered a "potentially changeable classification at the actionability threshold" (scenarios presented in the reclassification framework and the red box in Figure 1). In such circumstances,
   - when the variant is down-classified across the actionability threshold, we do not recommend immediate systematic recontact of historic families; where sufficient national infrastructure exists, these down-classified variants should remain under active national review and in the absence of further fluctuation in variant class over the subsequent ≥1 year, systematic recontact of historic patients may be considered and
   - when a variant is up-classified across the actionability threshold, systematic recontact of historic patients is recommended, but caution and detailed patient discussion is advised when irreversible clinical actions are under consideration.
8. Systematic recontact of relevant historic families is also recommended when reinterpretation of a variant has resulted in stable reclassification up or down across the actionability threshold (ie, reclassification scenarios not considered as potentially changeable).
9. When variant reinterpretation leads to reclassification of a variant across the actionability threshold, it should be communicated between laboratories. Development of a national infrastructure for systematic notification is a key priority.
10. A key future aim will be to evolve local/national laboratory infrastructure and automatized approaches to allow systematic proactive variant reinterpretation.

Discussion

CanVIG-UK, in this article, offers a detailed framework recommending laboratory and clinical actions after variant reclassification. The recommended workflows are intended to be pragmatic and sustainable in a resource-constrained health care setting, via proportionate approaches in which we have sought to optimize clinical utility for the clinical and laboratory resource consumed.

Applicability of reclassification framework

Although evolved by the CanVIG-UK, a national UK-based group of clinical scientists and genetic clinicians focused on CSGs, this reclassification framework is applicable in any health care setting and to variants relating to other disease areas. The reclassification framework uses the widely-accepted and internationally-applied 2015 ACMG/AMP variant classification framework, fully incorporating its subsequent transition from a categorical to a numeric scale.[1,6] In addition, the reclassification framework is fully consistent with the ACMG position statements regarding (1) the principles of patient recontact, (2) re-evaluation and reanalysis of genomic test results, and (3) the ESHG position statement regarding principles of patient recontact.[7,10,11] The aim of the CanVIG-UK was to provide a more explicit framework of management recommendations so as to reduce subjectivity in interpretation of said principles and increase consistency of practice. The recommendations within the reclassification framework are designed to instruct clinical practice; deviation would of course be anticipated after judgment of experienced clinical experts regarding an atypical scenario.

Resource implications

Next generation sequencing has enabled rapid expansion in clinical sequencing capacity, the number of patients tested, the number of genes tested per patient, and relatedly the cumulative number of variants held in diagnostic laboratories. Given the rapidly evolving evidence base and variant interpretation frameworks, it is challenging to predict how often variant reinterpretations will influence clinical practice. Mersch et al[17] reported the number of unique variants reclassified for individuals who had a CSG test at a single commercial laboratory in the United States between 2006 and 2016. The laboratory studied engaged in proactive and partly automated variant reinterpretation. Reclassification to a different clinical category for unique variants initially classified as P/LP or B/LB was infrequent (0.7% and 0.2% respectively), whereas for unique VUS, 7.7% were reclassified (91.2% downgraded and 8.7% upgraded). The higher proportion of down-classifications of VUS likely reflects emergence over that time period of large-scale population sequencing data from individuals with different ancestries, revealing the population frequency for many variants as too high to be pathogenic. Most variants were observed in >1 individual, meaning that 24.9% of all reported VUS were reclassified.[17]

Within a resource-constrained health care service, the resources required for variant reinterpretation need to be balanced with capacity for care of future patients. The proactive regular reinterpretation of all genetic variants by individual laboratories is therefore not considered feasible at this juncture, especially considering the current, still semi-manual nature of variant interpretation, limitations in laboratory information management systems, absence of a formal structure for remuneration of this activity, and restricted availability of clinical scientist and clinician time. Our reclassification framework has therefore been designed to fit a reactive approach to variant reinterpretation that is consistent with current practice in the NHS, most laboratories in Europe and many laboratories in the United States.[16] Furthermore, we concentrated recommended clinical and laboratory actions on scenarios in which

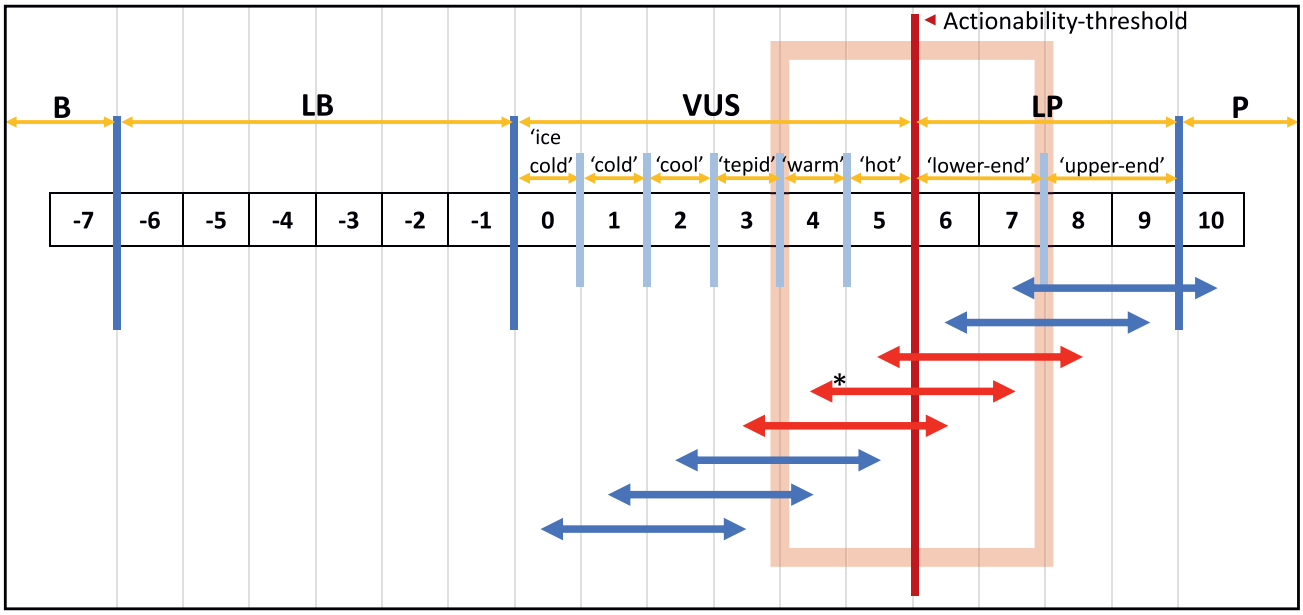

Figure 1 Example scenarios for variant reinterpretation involving new conflicting evidence or a revised variant interpretation framework. The scale (–7 to 10) represents total evidence points for a variant. Displayed above the scale are categorical variant classes: B, LB, VUS, LP, and P. For VUS, subclassifications "ice cold," "cold," "cool," "tepid," "warm," and "hot" are shown. For LP, subclassifications "lower-end" and "upper-end" are shown. Double-headed arrows represent changes in variant interpretation scores of 3 evidence points. The red arrows are those reinterpretations that result in a reclassification across the actionability threshold, represented as a red vertical line. *Indicates "potentially changeable classifications at the actionability threshold" because they satisfy the 3 criteria of (1) resulting from new conflicting evidence or from a revised variant interpretation framework, (2) having a change in evidence score of ≤3, and (3) the new classification and score is close to the actionability threshold (ES: 4-7, pale red box). B, benign; LB, likely benign; LP, likely pathogenic; P, pathogenic; VUS, variant of uncertain significance.

reclassifications are across the actionability threshold and thus may affect clinical management.[7,11]

Proximity to actionability threshold and potentially changeable classifications

Among participating clinicians and laboratory clinical scientists, confidence in reclassifications varied according to the new evidence score, magnitude of new evidence, nature of the new evidence/rescoring, and the proximity of the evidence score to the actionability threshold. There was lower confidence in reclassifications on the basis of new evidence that was contradictory to previous evidence (eg, a new functional assay discordant with a previous functional assay) or revised weightings in evidence scoring (eg, down-weighting of the PM2 evidence item). There was greater confidence in reclassifications on the basis of new noncontradictory evidence (eg, a new robust functional assay) and/or provision of new evidence not publicly available (eg, substantial local familial, segregation, and/or tumor data for a mismatch repair gene variant). There was lower positivity among participating clinicians in offering irreversible medical interventions for LP variants that were closer to the actionability threshold than for those with greater evidence (Supplemental Table 2). Fewer clinicians favored patient recontact when variants were down-classified to the upper end of the VUS evidence range than when it was to the lower end (Supplemental Tables 2 and 3).

Accordingly, in the reclassification framework, we made distinction between lower-end LP (6-7 evidence points) and upper-end LP (8-9 evidence points). Likewise, in the framework, distinction is made between management when there is down-classification from P/LP to a "warm"/"hot" VUS (4-5 evidence points) compared with an "ice cold"/"cold"/"cool"/"tepid" VUS (0-3 evidence points), terms as per the Association for Clinical Genomic Science variant interpretation specification.[18] Of note, although subclassifications of VUS (ice cold/cold/cool/tepid/warm/hot) and LP (lower-end/upper-end) are useful for internal discussions among clinical scientists and genetic clinicians, because of their potential to cause confusion or concern for patients, it is recommended that such terms should not be used in the formal report, which should include instead the overall variant classification (P/LP/VUS/LB/B), the evidence criteria, and the evidence points.[18,19]

We also highlight specifically in the reclassification framework scenarios that (1) are based on evidence perceived as less robust, (2) involve small changes in evidence score, and (3) are close to the actionability threshold. We define these reclassifications scenarios as "potentially changeable classifications at the actionability threshold" to signify need for more considered clinical management.

Some participating clinicians also drew distinction between which clinical actions they would advocate for variants (re)classified as lower-end LP (6-7 evidence points). For example, on the basis of risk–benefit considerations, some participating clinicians advocated risk-reducing postmenopausal bilateral salpingo-oophorectomy but not bilateral mastectomy for a woman with a *BRCA1/BRCA2* variant (re)classified as lower-end LP (6-7 evidence points).

National consistency and collaboration

There was strong consensus in favor of national communication of clinically important reclassifications, in particular, for those crossing the actionability threshold. On account of the significant repercussions and potential for unnecessary psychological harm, if subsequently reversed, it was agreed that CanVIG-UK national multidisciplinary review was indicated first ahead of a proposed down-classification across the actionability threshold. This would be predicted to be a low-frequency event and would provide opportunity to both review the interpretation and reclassification and to ascertain whether there is any additional evidence held locally in any participating laboratories (eg, segregation, phenotypic, functional data) that should be incorporated into the reclassification.[8,17] CanVIG-UK infrastructure would also be key for ongoing monitoring and management of downgraded variants labeled as "potentially changeable classification at the actionability threshold". We also defined the reclassification scenarios for which the reclassification should routinely be shared nationally.

It was agreed that a central national repository was required for documentation and sharing of the evidence behind the reclassification. Within CanVIG-UK, we have developed a national platform for sharing of clinical variant data and local variant interpretations (https://www.canvaruk.org/); it was agreed as the appropriate national repository for communicating and storing variant reclassifications, with subsequent international submission to ClinVar. Defined responsibilities and reliable procedures are still required locally for review, dissemination, and actioning of clinical responses.

It is anticipated that with improved clinical-laboratory systems for data assimilation and integration, in time, more automated and thus proactive approaches will become possible, for which national coordination would still be of ongoing or increased value. Ongoing impact analyses will continue to be important, including study of the health economics of variant reinterpretation.

Ethical and legal considerations

It is interesting to observe that the public discourse about genetics and genomics remains one that anticipates clear cut answers from any testing—a blueprint that remains fixed throughout life. Although this may be (largely) true on the level of the sequence, such representation does little to encourage an understanding that interpretation of genetic variants may fluctuate depending on emerging evidence, but also exposition of their interplay with other genetic and nongenetic factors. Genetic testing came of age when the single gene explanations for rare phenotypes were discovered and this too can create an impression, among patients and professionals alike, that if we can only decipher our genetic sequence, the clinical consequences will be clear. An ethical priority therefore is to help foster more realistic discussions and understandings about what to expect from a variant detected in clinical testing. If a clinician knows that a patient has been told that their variant was on one side of the actionability threshold, yet evidence now clearly points to the other side, then professional practice would demand an honest discussion about this in a timely fashion.

Recontact will be easier to initiate if it has been made clear that this might happen during discussions at the time of testing and decision-making regarding clinical interventions. Both ESHG and ACMG consider that there needs to be better discussion about the possibility of reclassification of their results with patients and indeed among clinicians. The UK Joint Committee of Genomics in Medicine guidance on consent and confidentiality in genomic practice provides a more detailed consideration of the relevant ethical and legal factors relating to patient consent. As part of this discussion, patients need to be informed on how they might seek an update and that they might be recontacted by a service. Advising patients to ensure their contact details are up-to-date is an important part of this discussion.[7,10]

Would health professionals involved in variant interpretation be remiss if they did not initiate patient recontact? Almost certainly yes in some scenarios, although for others they will also need to weigh the resources required to bring plausible clinical benefit for that patient, against use of resources for other patients.

In the United Kingdom, there is currently no statute law requiring variant reinterpretation. It is likely that future practice will be influenced by case law, similar to how the *Montgomery v Lanarkshire Health Board*[20] ruling after a perinatal intervention has influenced disclosure practices regarding what level of risk should be included within informed consent or the *ABC v St George's Healthcare NHS Trust*[21] ruling regarding medical disclosure to family members of genetic risk of Huntington disease has delineated a duty to weigh competing disclosure factors.[22-24]

Conclusion

Variant reinterpretation and reclassification are growing clinical challenges, with evidence of disparate practice between United Kingdom centers and broad clinical anxiety regarding the practical, ethical, and legal aspects.[14,15] A

shift in the verbal discourse and written lexicon about genetic testing is required both for patients and other clinical professionals. There is also a need for greater consistency in approach to the management of variant reclassification at laboratory, patient, and societal levels.

Incorporating surveys and consultation of a broad, national group of genetics clinicians, and laboratory scientists, on behalf of CanVIG-UK we present a detailed consensus framework for management of variant reclassifications, consistent with principles articulated by the ACMG and ESHG.[7,10,11] In this framework, we offer a feasible approach to variant review, the reissue of reports, patient recontact, and national communication, in which the nature and likely stability of the reclassification is taken into account.

Data Availability

Poll and survey questions and responses are included in Supplemental Tables 2 and 3. No other data sets were generated or analyzed during the current study.

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Author Information

Conceptualization: C.T., H.H., L.L., A.G., F.L., M.T., A.K., M.D., A.C., J.D., G.J.B., R.R.; Formal Analysis: H.H., L.L.; Funding Acquisition: C.T., M.T., D.M.E.; Project Administration: B.T., S.A.; Writing-original draft: L.L., C.T., A.L.; Writing-review and editing: L.L., A.G., S.A., S.C., M.D., A.C., J.D., G.J.B., R.R., B.T., I.R.B., A.J.W., D.M.E., S.E., E.B., D.G.E., E.R.W., A.K., F.L., M.T., A.L., H.H., C.T.

Ethics Declarations

No identifiable data from human patients/subjects were used. Survey data from medical professionals only is presented. Therefore Institutional Review Board approval was not required.

Conflict of Interest

The authors declare no conflicts of interest.

Additional Information

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Authors

Lucy Loong[1], Alice Garrett[1], Sophie Allen[1], Subin Choi[1], Miranda Durkie[2], Alison Callaway[3], James Drummond[4], George J. Burghel[5], Rachel Robinson[6], Beth Torr[1], Ian R. Berry[7], Andrew J. Wallace[5], Diana M. Eccles[8,9], Sian Ellard[10,11], Emma Baple[11,12], D. Gareth Evans[5,13], Emma R. Woodward[5,13], Anjana Kulkarni[14], Fiona Lalloo[5], Marc Tischkowitz[15], Anneke Lucassen[16,17], Helen Hanson[1,18], Clare Turnbull[1,19,*]; On behalf of the CanVIG-UK

Affiliations

[1]Division of Genetics and Epidemiology, The Institute of Cancer Research, Sutton, United Kingdom; [2]Sheffield Diagnostic Genetics Service, NHS North East and Yorkshire Genomic Laboratory Hub, Sheffield Children's NHS Foundation Trust, Sheffield, United Kingdom; [3]Wessex Regional Genetics Laboratory, Central and South Genomics Laboratory Hub, Salisbury NHS Foundation Trust, Salisbury District Hospital, Salisbury, Wiltshire, United Kingdom; [4]Cambridge Genomic Laboratory, East Genomic Laboratory Hub, Cambridge University Hospital NHS Foundation Trust, Cambridge, United Kingdom; [5]Manchester Centre for Genomic Medicine and North West Genomic Laboratory Hub, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom; [6]North East and Yorkshire Genomic Laboratory Hub, The Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom; [7]Bristol Genetics Laboratory, Southmead Hospital, North Bristol NHS Trust, Bristol, United Kingdom; [8]Cancer Sciences, Faculty of Medicine, University of Southampton, Southampton, United Kingdom; [9]Human Genetics and Genomic Medicine, Faculty of Medicine, University of Southampton, Southampton, United Kingdom; [10]Exeter Genomics Laboratory, South West Genomic Laboratory Hub, Royal Devon and Exeter NHS Foundation Trust, Exeter, United Kingdom; [11]University of Exeter Medical School, Exeter, United Kingdom; [12]Genomics England, London, United Kingdom; [13]Division of Evolution & Genomic Sciences, The University of Manchester, Manchester, United Kingdom; [14]Southeast Thames Regional Genetics Service, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [15]Department of Medical Genetics, National Institute for Health Research Cambridge Biomedical Research Centre, University of Cambridge, Cambridge,

United Kingdom; [16]Wellcome Centre for Human Genetics/Centre for Personalised Medicine, University of Oxford, Oxford, United Kingdom; [17]Clinical Ethics and Law, Faculty of Medicine, University of Southampton, Southampton, United Kingdom; [18]Department of Clinical Genetics, St. George's University Hospitals NHS Foundation Trust, London, United Kingdom; [19]Cancer Genetics Unit, The Royal Marsden NHS Foundation Trust, London, United Kingdom

Members of CanVIG-UK

S. Abbs, M. Ahmed, S. Albaba, Z. Allen, K. Andrews, A. Ansari, C. Armstrong, E. Atkinson, K. Baker, D. Baralle, M. Bartlett, J. Barwell, T. Bedenham, S. Begum, C. Bowles, P. Brace, M. Bradford, K. Bradshaw, A. Brady, C. Brewer, C. Brooks, K. Brown, R. Brown, J. Bruty, J. Burn, L. Busby, S. Butler, C. Byrne, K. Cadoo, J. Callaway, J. Campbell, H. Carley, D. Chubb, K. Ciucias, C. Clabby, R. Cleaver, H. Clouston, V. Clowes, B. Coad, L. Cobbold, E. Cojocaru, R. Coles, L. Connolly, J. Cook, G. Corbett, C. Corbett, T. Cranston, L. Crookes, C. Crosby, E. Cross, S. Daniels, R. Davidson, P. Dean, J. Del Rey Jimenez, S. Dell, B. DeSouza, I. Doal, A. Donaldson, D. Donnelly, J. Dring, M. Duff, J. Field, T. Foo, I. Frayling, B. Frugtniet, J. Grant, K.L. Greenhalgh, S. Greville-Heygate, A. Hadonou, D. Halliday, S. Hardy, J. Harper, R. Harrison, R. Hart, L. Hawkes, S. Hegarty, M. Hegarty, S. Heggarty, H. Heppell, A.C. Hogg, J. Hoyle, L. Hughes, C. Husher, M. Huxley, A. Innes, L. Izatt, C. Jenkins, E. Johnston, C. Joyce, Z. Kemp, L. Kiely, R. Kirk, A. Kumar, C. Lawn, H. Lindsay, T. Linton-Willoughby, P. Logan, S. Mackenzie, S. MacMahon, S. MacParland, E. Maher, R. Martin, R. Martin, J. Mason, C. Maurer, P. May, V. McConnell, T. McDevitt, B. McIldowie, K. McKay Bounford, S. McKee, C. McKenna, F. McRonald, T. McVeigh, O. Middleton, R. Mitchell, K. Mokretar, K. Monahan, D. Moore, G. Mullan, B. Mullaney, K. Murphy, A. Murray, J. Murray, G. Nickless, D. Nocera-Jijon, R. Nyanhete, C. O'Brien, D. O'Sullivan, C. Olimpio, J. Oliver, M. Owens, J. Pagan, S. Palmer-Smith, F. Pelz, E. Petrides, L. Pierson, H. Powell, S. Prapa, K.-R. Ong, L. Rainey, A. Ramsay Bowden, D. Randhawa, E. Rauter, G. Rea, K. Reay, D. Reay, L. Reed, A.M. Reuther, S. Ribeiro, N. Roberts, A. Ross, K. Russell, F. Ryan, M. Ryten, K. Sahan, S. Samant, J. Sampson, L. Sarkies, F. Sava, M. Shanmugasundaram, A. Shaw, S. Shepherd, L. Side, M. Slean, K. Smith, M. Smith, K. Snape, E. Sofianopoulou, B. Speight, J. Spiers, D. Stobo, K. Stone, T. Tadiso, L. Taggart, S. Talukdar, P. Tarpey, K. Tatton-Brown, A. Taylor, A. Taylor-Beadling, J. Tellez, S. Tennant, H.J.W. Thomas, A. Timbs, J. Tolmie, I. Tomlinson, R. Tredwell, V. Tripathi, M. Tsang, J. VanCampen, L. Walker, L. Walker, Y. Wallis, M. Watson, C. Watt, J. Whitworth, J. Williams, H. Williamson, N. Woodwaer, L. Worrillow, R. Wright, L. Yarram, A. Znaczko

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