**Re-classification 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’, that is as likely pathogenic or pathogenic, clinical actions may be irreversible, such as risk-reducing surgery or prenatal interventions. Variant re-classification up or down across the ‘actionability threshold’ can therefore have significant clinical consequences. Laboratory approaches to variant re-interpretation and re-classification vary widely.

##### Methods

Cancer Variant Interpretation Group UK (CanVIG-UK) is a multidisciplinary network of clinical scientists and genetic clinicians from across the 24 Molecular Diagnostic Laboratories and Clinical Genetics Services of the UK (NHS) and Republic of Ireland. We undertook surveys, polls and national meetings of CanVIG-UK to evaluate opinion regarding clinical and laboratory management regarding variant re-classification.

##### Results

We generated a consensus framework on variant re-classification applicable to cancer susceptibility genes and other clinical areas, which provides explicit recommendations for clinical and laboratory management of variant re-classification scenarios based on 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 impact and minimal patient harm, as appropriate to all resource-constrained healthcare 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 (disease-causing) or benign. 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 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/Association of Molecular Pathology (ACMG/AMP) put forward in 2015[1].

The ACMG/AMP framework was formally adopted by the UK Association for Clinical Genomic Science (ACGS-UK) in 2016. In order to deliver training in the use of the ACMG/AMP framework and sub-speciality specification of the framework, national subgroups comprising 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 counsellors, with representation from each of the 24 Molecular Diagnostic Laboratories and Clinical Genetics Services of the UK (NHS) and Republic of Ireland [2]. The group (i) holds a monthly national multidisciplinary meeting for review of problematic clinically-detected cancer susceptibility gene (CSG) variants (ii) has developed detailed UK specification for CSGs of the ACMG/AMP framework (https://www.cangene-canvaruk.org/canvig-uk-guidance) and (iii) has developed a digital platform for sharing of variant-level resources, UK laboratory data and interim clinical classifications (CanVar-UK http://www.canvaruk.org/). Additional bimonthly national multidisciplinary meetings are jointly held 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.

##### Evidence scoring in variant classification

In the ACMG/AMP framework, evidence items across different categories are awarded one of four strengths: supporting, moderate, strong or very strong. Tavtigian *et al.* undertook mapping of these to a Bayesian framework whereby evidence points are combined with a prior probability of pathogenicity to produce a posterior probability of pathogenicity, which determines the variant pathogenicity classification [3-5]. If the prior probability of a variant being pathogenic is 10%, variants with ≥ 10 evidence points have a >99% posterior probability of being pathogenic and are classified as pathogenic (P); 6-9 points, 90-99% probability, likely pathogenic (LP); 0-5 points, 10-90% probability, variant of uncertain significance (VUS); (-1) to (-6) points, <5% probability, likely benign (LB); ≤ (-7) points, <0.1% probability, benign (B).

Whilst 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 classed as Pathogenic/Likely Pathogenic (P/LP) are ‘actionable’ in that they are used to inform clinical management, for example eligibility for preventative surgery, intensive/invasive disease surveillance programmes, reproductive interventions and cascade testing of relatives. P and LP variants are treated equivalently in terms of clinical management. The other variant 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 analysed.

##### 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 based on the totality of available data may therefore change over time. Variant re-interpretation 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 made available since the previous interpretation[6].

##### Implications and consequences of variant re-classification

Variant re-interpretation is typically reactive, triggered in response to clinical events, for example 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. Where variant re-interpretation results in re-classification 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, where a variant previously ascribed as pathogenic is down-classified, there may also be perceived harm regarding previously performed risk-reducing surgery or invasive surveillance, particularly where associated with a complication or suboptimal outcome. In contrast to such a reactive model for triggering of variant re-interpretation, a more regular proactive model may be advantageous but would have significant resource impact for both laboratory and clinical workloads. Additionally, a highly dynamic evidence base may result in some variants hovering around or repeatedly crossing the actionability threshold [7], which has the potential to cause confusion and clinical errors (ie management of a patient based on an erroneous or outdated variant classification).

Research seeking views on re-contacting of patients in clinical genetics practice, suggested that UK patients tend to value re-contact as an important means to access in a timely fashion the clinical (eg prevention of disease) and psychological benefits of new information (eg variant re-classifications) [8].

##### Existing practice for variant re-classification

In 2019 the European Society of Human Genetics (ESHG) published principles and broad recommendations on a range of scenarios relating to re-contact of patients by clinical genetics services [6]. In the same year, the ACMG published points to consider in the re-evaluation and re-analysis of genomic test results and subsequent patient re-contact after revision of genomic test results [9, 10]. Both groups acknowledged that proactive/regular variant re-interpretation was unlikely to be feasible for healthcare services and advocated prioritisation of re-classification scenarios where clinical impact was likely [6, 9]. US-led research relating to the ethical, economic, legal and clinical implications of variant re-interpretation is being performed in tandem [9, 11, 12]. A survey of UK genetic clinicians and clinical scientists in 2016 suggested practice is variable and ad hoc. There is currently no UK guidance or standardised practise for UK clinical-laboratory services regarding initiation of variant re-interpretation, or the process for re-contact of patients when variant re-classifications across the actionability threshold occur [13]. There have been numerous calls for more defined, specific professional guidance regarding patient re-contact, including from within the CanVIG-UK network [6, 14, 15].

## Materials and Methods

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

1. a pre-meeting survey about management of different variant classes and re-classification scenarios (emailed to registrants ahead of the Joint BSGM UK-CGG/ CanVIG-UK clinical cancer genetics preliminary national scoping meeting) (Supplementary Table 2)
2. within meeting polls regarding proposed approaches to re-classification scenarios (undertaken live during the Joint BSGM UK-CGG/ CanVIG-UK preliminary national scoping meeting) (Supplementary 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 Supplementary Table 1.

## Results

The detailed CanVIG-UK consensus framework for recommended clinical and laboratory actions in response to reactive variant re-classification is presented in Table 1. There were ten overarching principles agreed during the framework development process to be key to current UK variant re-classification 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 re-classification may occur.
2. Regular proactive and/or systematic variant re-interpretation by individual UK laboratories is not currently feasible. Variant re-interpretation will typically be reactive and triggered by clinical events.
3. Clinicians should be advised to request as routine variant re-interpretation prior to initiation of new clinical actions (eg risk-reducing surgery, new cancer surveillance programmes, cascade testing of relatives) when undertaken ≥12 months following the initial ascertainment of a variant in a family.
4. As genetics is mainstreamed it is important that clinicians outside of the speciality of clinical genetics are made aware of points 1 - 3.
5. Re-issuing of a report, or communication with a patient/family after a variant has been re-classified will depend on the perceived significance and robustness of the new classification, as assessed by:
   1. Size of shift in evidence points
   2. Proximity of new classification to the ‘actionability-threshold’
   3. Nature of shift in evidence points (fresh evidence, new conflicting data or new evidence weighting)
6. In cases where a variant re-classification to a score (i) just above or below the actionability-threshold has resulted from (ii) new evidence which is conflicting with pre-existing evidence and/or a change to evidence weighting, which (iii) causes only a modest change to total evidence points, the variant classification may be considered a “potentially changeable classification at the actionability threshold” (Scenarios highlighted by the red box in the re-classification framework and the red box in Figure 1). In such circumstances:
   1. where the variant is down-classified across the actionability-threshold, we do not recommend immediate systematic re-contact 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.
   2. where a variant is up-classified across the actionability-threshold, caution and detailed patient discussion are advised when considering irreversible clinical actions.
7. Systematic re-contact of relevant historic families is recommended where re-interpretation of a variant has resulted in **stable** re-classification across the actionability-threshold (ie re-classification scenarios NOT considered “potentially changeable”).
8. Where variant re-interpretation leads to re-classification of a variant across the actionability-threshold, this should be communicated between laboratories. Development of a national infrastructure for systematic notification is a key priority.
9. A key future aim will be to evolve local/national laboratory infrastructure and automatized approaches to allow systematic proactive variant re-interpretation.

## Discussion

CanVIG-UK here offers a detailed framework recommending laboratory and clinical actions following variant re-classification. The recommended workflows are intended to be pragmatic and sustainable in a resource-constrained healthcare setting, via proportionate approaches in which we have sought to optimise clinical utility for the clinical and laboratory resource consumed.

##### Applicability of re-classification framework

Although evolved by CanVIG-UK, a national UK-based group of clinical scientists and genetic clinicians focused on cancer susceptibility genes, this re-classification framework is applicable in any healthcare setting and to variants relating to other disease areas. The re-classification 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, 16]. Additionally, the re-classification framework is fully consistent with the ACMG position statements regarding (i) the principles of patient re-contact and (ii) reevaluation and reanalysis of genomic test results as well as (iii) the ESHG position statement regarding principles of patient re-contact [6, 9, 10]. The aim of 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 re-classification framework are designed to instruct clinical practice: deviation would of course be anticipated following 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 re-interpretations will influence clinical practice. Mersch *et al.* reported the number of unique variants re-classified for individuals who had a CSG test at a single commercial laboratory in the US between 2006 and 2016. The laboratory studied engaged in proactive and partly automated variant re-interpretation. Re-classification 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 re-classified (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 sequence data in multiple ethnic groups, revealing the population frequency for many variants as too high to be pathogenic. Most variants were observed in more than one individual, meaning that 24.9% of all reported VUS were re-classified [17].

Within a resource-constrained healthcare service, the resources required for variant re-interpretation need to be balanced with capacity for care of future patients. The proactive regular re-interpretation 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 re-classification framework has therefore been designed to fit a reactive approach to variant re-interpretation which is consistent with current practice in the NHS, most laboratories in Europe and many laboratories in the US [15]. Furthermore, we concentrate recommended clinical and laboratory actions to scenarios in which re-classifications are across the actionability-threshold and thus may affect clinical management [6, 10].

##### Proximity to “actionability-threshold” and “potentially changeable” classifications.

Amongst participating clinicians and laboratory clinical scientists, confidence in re-classifications varied according to the new evidence score, magnitude of new evidence, nature of the new evidence/rescoring and proximity of the evidence score to the actionability threshold. There was lower confidence in re-classifications based on 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 re-classifications based on new non-contradictory evidence (eg a new robust functional assay) and/or provision of new evidence not publicly available (eg substantial local familial, segregation and/or tumour data for a MMR gene variant). There was lower positivity amongst participating clinicians in offering irreversible medical interventions for “likely pathogenic” variants which were closer to the actionability threshold, compared to those with greater evidence (Supplementary Table 2). Fewer clinicians favoured patient re-contact when variants were down-classified to the upper end of the VUS evidence range compared to the lower end (Supplementary Tables 2,3).

Accordingly, in the re-classification framework, we make distinction between low-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 ‘hot’ VUS (4-5 evidence points), compared to a ‘tepid’ (3 evidence points) or ‘cold’ VUS (0-2 evidence points), terms as per the ACGS variant interpretation specification [18]. Of note, whilst subclassifications of VUS (cold/tepid/hot) and LP (low-end/upper-end) are useful for internal discussions amongst 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 re-classification framework scenarios which (i) are based on evidence perceived as less robust (ii) involve small changes in evidence score AND (iii) are close to the actionability-threshold. We define these re-classifications 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 low-end LP (6-7 evidence points). For example, based on risk-benefit considerations, some participating clinicians advocated risk reducing post-menopausal bilateral salpingo-oophorectomy (BSO) but not bilateral mastectomy for a woman with a BRCA1/BRCA2 variant (re-) classified as low-end LP (6-7 evidence points).

Both ESHG and ACMG consider that there needs to be better discussion about the possibility of re-classification of their results with patients and indeed amongst clinicians. As part of this discussion patients need to be informed how they might seek and update, and that they might be re-contacted by a service. Advising patients to ensure their contact details are up-to-date is an important part of this discussion [6, 9].

##### National consistency and collaboration

There was strong consensus in favour of national communication of clinically important re-classifications, in particular 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 re-classification, as well as to ascertain whether there is any additional evidence held locally in any participating laboratories (e.g. segregation, phenotypic, functional data) that should be incorporated into the re-classification [7, 17]. CanVIG-UK infrastructure would also be key for ongoing monitoring and management of downgraded variants labelled as "Potentially changeable classification at actionability threshold”. We also define the re-classification scenarios for which the re-classification should routinely be shared nationally.

It was agreed that a central national repository was required for documentation and sharing of the evidence behind the re-classification. Within CanVIG-UK we have developed a national platform for sharing of clinical variant data and local variant interpretations (http://www.canvaruk.org/): this was agreed as the appropriate national repository for communicating and storing variant re-classifications, 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 re-interpretation.

##### 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. Whilst 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 non-genetic factors. Genetic testing came of age when the single gene explanations for rare phenotypes were discovered and this too can create an impression, amongst 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 on clinical testing. Such discussions are sometimes reduced, for example, to ‘is there a duty to re-classify regularly/ re-contact proactively?’ but we suggest the answers to these questions will do little to improve clinical practices. If a clinician knows that a patient has been told 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. Re-contact 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. Would health professionals involved in variant interpretation be remiss if they did not do this? Almost certainly yes, although they will also need to weigh in the balance plausible clinical benefit for that patient against just use of resources for other patients. ‘The UK Joint Committee of Genomics in Medicine (JCGM) guidance on Consent and Confidentiality in Genomic Practice’ provides a more detailed consideration of the relevant ethical and legal factors relating to patient consent. In the UK there is currently no statute law requiring variant re-interpretation. It is likely that future practice will be influenced by case law, just as the Montgomery ruling following a perinatal intervention has influenced disclosure practices regarding what level of risk should be included within “informed consent” , or the ABC ruling regarding medical disclosure to family members of genetic risk of Huntington Disease has delineated a duty to weigh competing disclosure factors [20-22].

## Conclusion

Variant re-interpretation and re-classification is a growing clinical problem, with evidence of disparate practice between UK centres and broad clinical anxiety regarding the practical, ethical and legal aspects [13] [14]. Variant re-interpretation and re-classification is also a fact of 21st century genomic practice and requires a shift in the verbal discourse and written lexicon about genetic testing, both with patients and other clinical professionals. There is a need for greater consistency in approach to the management of variant re-classification 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 re-classifications, consistent with principles articulated by the ACMG and ESHG [6, 9, 10]. In this we offer a feasible approach to variant review, the re-issue of reports, patient re-contact and national communication, in which the nature and likely stability of the re-classification is taken into account.

## Data Availability

Poll and survey questions and responses are included in Supplementary Tables 2 and 3. No other datasets were generated or analysed during the current study.

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## Ethics Declarations

No identifiable data from human patients/subjects are used. Survey data from medical professionals only is presented. Therefore IRB approval was not required.

## Disclosure

The authors declare no conflicts of interest.

## Legends

**Table 1**: CanVIG-UK consensus framework for recommended clinical and laboratory actions in response to reactive variant re-classification. Scenarios are separated into re-classifications that cross the actionability-threshold, and those that do not. Re-classification scenarios that cross the actionability threshold are further separated by nature of evidence which led to re-classification and size of change in evidence score. The red box highlights re-classification scenarios which produce 'Potentially changeable classifications at the actionability threshold' which are re-classifications resulting from conflicting evidence OR from revision to evidence strengths in the variant classification framework AND where the change in evidence score is ≤3 AND the new classification is close to the actionability-threshold (ES 4-6).

P, Pathogenic; LP, Likely Pathogenic; VUS, Variant of Uncertain Significance; LB, Likely Benign; B, Benign; ES, Evidence Score

1Substantive new publicly available evidence (e.g. functional assay, multifactorial analysis) or locally available evidence (e.g. segregation data, RNA analysis) in the absence of previous evidence of that type. 2New publicly available evidence conflicting with previous data of the same type (e.g. 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. 3Definition of “Proactive re-contact” requires further specification. Suggestion: letter explaining situation, proactive scheduling of appointment slot with one further attempt to re-contact if original appointment not attended. 4Historic patients refers to all current and former patients who have been identified to have the re-classified variant, including former patients, seen in the past, discharged from care, and no longer in an ongoing relationship with the specific healthcare professional involved. 5Where sufficient national infrastructure exists, these down-classified variants should remain under active national review. 6Where infrastructure exists for active national review, systematic contact of historic patients may be considered in the absence of further fluctuation in variant class over the subsequent ≥1 years.

**Figure 1.** Example scenarios for variant re-interpretation 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 (benign), LB (likely benign), VUS (variant of uncertain significance), LP (likely pathogenic), and P (pathogenic). For VUS, subclassifications ‘cold’, ‘tepid’ and ‘hot’ are shown. For LP, subclassifications ‘low-end’ and ‘upper-end’ are shown. Double-headed arrows represent changes in variant interpretation scores of 3 evidence points. The red arrows are those re-interpretations which result in a re-classification across the actionability-threshold, represented as a dark red vertical line. \*“Potentially changeable classifications at actionability threshold” as they satisfy the three 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).

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