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RESEARCH ARTICLE

Certainty in uncertainty: Determining the rate and reasons for reclassification of variants of uncertain significance in haematological malignancies

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Abstract

Introduction: Variants of uncertain significance (VUS) are commonly reported in cancer with the widespread adoption of diagnostic massive parallel sequencing. The rate of reclassification of VUS in patients with haematological malignancy is not known and we evaluated this retrospectively. We also investigated whether re-evaluating VUS in 12–24 months or greater than 24 months post-initial classification was significant.

Method: A retrospective audit of patients with haematological malignancies referred to the Molecular Medicine Department at the John Hunter Hospital in Newcastle, Australia between September 2018 and December 2021. Data was analysed for VUS, which was then re-analysed in standard software using current somatic variant guidelines. Proportions of VUS at baseline were compared to post-re-analysis.

Results: The most common diagnoses in the patient cohort ($n = 944$) were acute myelogenous leukaemia (41%), myelodysplastic syndrome (31%), and chronic myelomonocytic leukaemia (7%). A total of 210 VUS were re-analysed. The most common VUS were in the TET2 (20%), RUNX1 (10%) and DNMT3A (9%) genes. A total of 103 were re-analysed at 24–39 months post-initial classification and 107 variants were re-analysed between 12 and 24 months post-initial classification. Of these, 33 (16%) of VUS were re-classified at 24–39 months and 12 (11%) were re-classified at 12–24 months post-initial classification. The most common variants that were re-classified in both groups were CSF3R (32%), TET2 (29%), ASXL1 (11%) and ZRSR2 (11%).

Conclusion: This study on reclassification of VUS in blood cancers demonstrated that one in seven VUS were re-classified 12 months post initial classification. This can inform practice guidelines and potentially impact the prognosis, diagnosis and treatment of haematological malignancies.

KEYWORDS
haematological malignancy, leukaemia, massive parallel sequencing, reclassification, variants of uncertain significance

1 | INTRODUCTION

The recent increase in the availability and utility of Massive Parallel Sequencing (MPS) has enabled more sensitive and efficacious genetic testing in cancer [1, 2]. As a result, the need for guidelines standardising the interpretation of genetic variants has become vital [3]. Changes are generally detected by comparing DNA samples to large population databases such as the Genome Aggregation Database (gnomAD). In addition, scoring systems help assign variants based on the strength of evidence for disease association. The paradox of MPS is that, while it enables the sequencing of hundreds of variants, a large proportion of those will be classified as variants of uncertain significance (VUS) [4–6]. In studies sequencing breast and ovarian cancer variants, on average, 40%–50% are classified as VUS [7, 8]. There is limited literature regarding the average proportion of VUS in haematological malignancy genomic databases. Whilst the European Leukemia-NET guidelines aid with more common variations observed in certain blood cancers such as acute leukaemia, interpretation of less common variants including VUS is more challenging [9]. Most relevant to assessing VUS in haematological malignancies are the AMP-ASCO-CAP Guidelines for somatic variants, developed in 2017 by the American College of Molecular Genetics (ACMG) and the Association for Molecular Pathology (AMP), the College of American Pathologists (CAP) and American Society for Clinical Oncology (ASCO). Distinct from interpreting germline variants, where the focus is on oncogenicity, in the AMP-ASCO-CAP Guidelines, the focus is on clinical implications [3]. More recently, a structured point-based system for variant review has been suggested to make the classification more objective [10]. Despite the increasing clarity in these guidelines, there is still ambiguity as to variant re-evaluation and re-classification. The guidelines indicate that, given the monumental task of interpreting the clinical significance of variants and the wide range of evidence that can be considered relevant, molecular scientists and pathologists should exercise independent clinical judgment in the context of the evidence as to whether variants should be re-classified [3].

A combination of population, cancer-specific and other disease databases, as well as internal databases are recommended for use in the initial classification of MPS data [3]. However, it is usually laboratory-specific with each laboratory having its own preferred method, policy and protocol on how VUS should be re-assessed.

The ACMG emphasises the importance of re-evaluating individual patient's genetic data to ensure databases are up to date [11]. They recommend that laboratories should have policies and protocols on re-evaluation that balance the burden of re-evaluation with the importance of accurate data and suggest re-evaluation should occur in response to external requests or new evidence [11]. Where new evidence includes: community resources that assess population-based variant frequency (e.g. gnomAD), variant assessment methodologies, and gene-disease relationship or mechanism of disease evidence [11].

Taking into account the impracticalities of individual laboratories re-evaluating entire local databases due to financial and time constraints, the ACMG suggest that re-evaluation should prioritise maximum clinical impact, and VUS or likely oncogenic classifications should be reviewed more often than likely benign variants because they have greater potential implications on clinical management [11].

This study determined the rate of reclassification of VUS in patients with haematological malignancy. We also aimed to investigate whether re-evaluating VUS in 12–24 months or greater than 24 months post-initial classification was significant enough to warrant continuing periodic reviews.

2 | METHODS

2.1 | Design and data sources

A retrospective audit was conducted using medical records and genetic data of patients referred to the Molecular Medicine Department, NSW Health Pathology, John Hunter Hospital (JHH) in Newcastle, Australia between September 2018 and December 2021. Patients were referred from hospitals across New South Wales (NSW) following a positive bone marrow biopsy result for haematological malignancy.

Participants' results were included if they were diagnosed with a haematological myeloid malignancy classified as per the World Health Organisation (WHO) 2016 classification of tumours of hematopoietic and lymphoid tissues [12]. Included diagnoses were haematological malignancies including acute lymphoblastic leukaemia (ALL), acute myelogenous leukaemia (AML), myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPN). There were no limits on demographic characteristics such as age or gender. Additionally, participants were not excluded if they were deceased. Samples sent for germline testing were excluded from the analysis. All samples were run on the Illumina platform (MiSeq or NextSeq 550) using the SOPHiA myeloid panel (SOPHiA genetics).

The rate of reclassification of VUS as either benign or malignant in a 12–24-month period from initial classification compared to more than 24 months post-initial classification (i.e., 24–39 months) was also assessed [3]. Reclassifications were assessed in multidisciplinary team (MDT) meetings, informed by population frequency, available data and/or published literature, and by applying published criteria. The reclassification was undertaken when there was consensus amongst the MDT based on those criteria using information from the bioinformatic pipeline Agilent Alissa (using CGC, CIViC ClinVar, COSMIC and functional effect prediction) as shown in Figure 1. In addition, pipelines such as Mastermind, Varsome, Franklin and SOPHiA were used to interrogate variants further. The pipelines were similar at initial diagnosis and reanalysis apart from updates that occurred in the time gap.

Data for patients with VUS was collated to include demographic information, date sample collected, type of sample, diagnosis, clinically significant variants, percentage of blasts, number of VUS, type of variation, gene, cDNA, protein, variant allele frequency, depth, chromosome and effect. The reasons for reclassification were described for each variant.

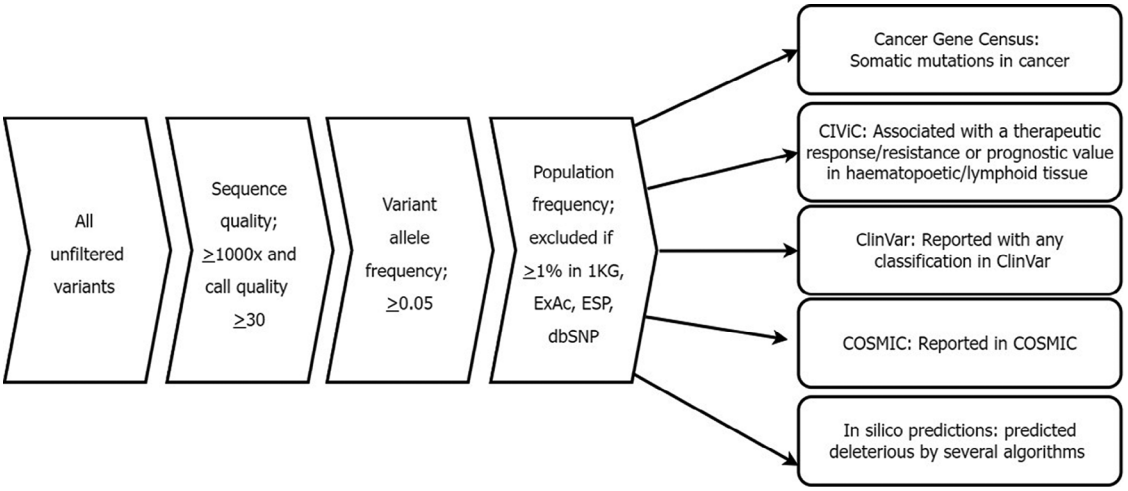

FIGURE 1 Showing the somatic pipeline algorithm that was used to classify variants.

2.2 | Analysis

All VUS were reanalysed using genomic databases and medical literature through the above-mentioned bioinformatic pipelines. The information provided in the above pipelines was used to re-evaluate the status of the VUS as either VUS, benign or oncogenic. VUS were classified according to the AMP-ASCO-CAP Guidelines. Following reclassification, descriptive summaries were presented for the study population. All VUS reclassifications were discussed and agreed upon at a multidisciplinary team meeting comprised of at least two scientists and two haemato-pathologists.

2.3 | Ethics

Ethics approval was granted by the Hunter New England (HNE) Human Research Ethics Committee on 28 September 2021 (AU202109-19) and the University of Newcastle's Human Research Ethics Committee (HREC).

3 | RESULTS

One hundred and fifty-three participants (16%) were identified as having VUS out of a total of 944 patients were analysed. The median age at bone marrow sampling was 66 years old (93 males and 60 females). The three most common diagnoses were AML (41%), MDS (31%) and chronic myelomonocytic leukaemia (CMML) (7%).

3.1 | Re-analysis of VUS

Two hundred and ten VUS (n = 210) from the 944 patients were re-analysed. The VUS were divided into those re-analysed at greater than 24 months post-initial classification (n = 103) and 12–24 months post-initial classification (n = 107). Overall, 173 VUS (82%) remained classified as VUS and 37 VUS were re-classified (16%). Sixteen variants (5%) were reclassified as benign, and seven variants (2%) were reclassified as likely benign. Four variants (1%) were reclassified as oncogenic, and six variants (2%) were reclassified as likely oncogenic. Four variants (1%) could not be reclassified as they were identified as requiring further investigation, that is, no consensus could be achieved (see Table 1).

TABLE 1 Distribution of variants of uncertain significance (VUS) that were re-classified.

Final verdict	2018/19	2020	Total	Percentage total
Benign	11	5	16	7.62%
Likely Benign	3	4	7	3.33%
VUS	84	89	173	82.38%
VUS but requires further investigation	1	3	4	1.90%
Likely oncogenic	2	4	6	2.86%
Oncogenic	2	2	4	1.90%

Abbreviation: VUS, variants of uncertain significance.

The three most common diagnoses received by participants with reclassified VUS were AML (39%), MDS (29%) and CMML (6%) (Figure 2A). All other diagnoses accounted for 3% or less. The 33 variants reclassified were made up of ten genes. The two most common genes requiring reclassification were CSF3R (32%) and TET2 (26%) followed by ASXL1 and ZRSR2 (Figure 2B).

The reasons for reclassification included changes in population frequency (64%), internal population data (15%), changing interpretation of available information (21%) or new published literature (6%). Several [16] reclassified VUS had multiple reasons for reclassification (Figure 3).

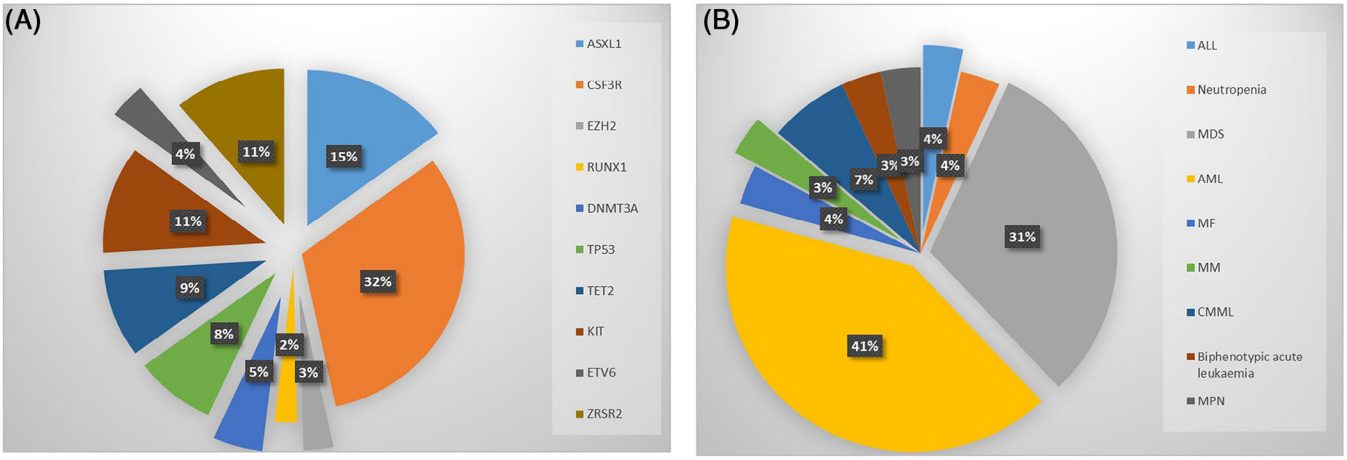

FIGURE 2 (A) Distribution of genes and their frequency. (B) Diagnostic categories in the reclassified variants of uncertain significance (VUS) cohort. Footnote: ALL, acute lymphoblastic leukaemia; MDS myelodysplasia; AML, acute myeloid leukaemia; MF, myelofibrosis; MM, multiple myeloma; CMML, chronic myelomonocytic leukaemia; AITL, angioimmunoblastic leukaemia; MPN, myeloproliferative neoplasm.

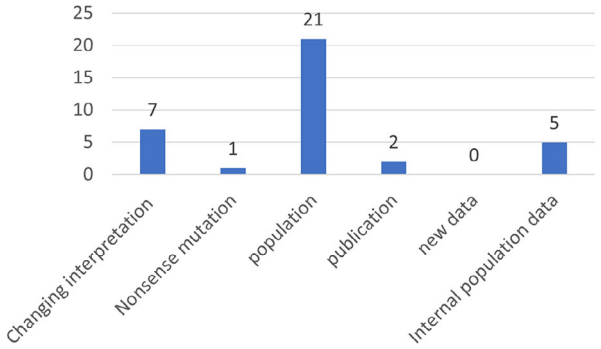

FIGURE 3 Reasons for reclassification of the variants of uncertain significance (VUS) variants.

3.2 | VUS reclassified between 12 and 24 months

Fifteen VUS were reclassified at 12–24 months post-initial classification. This group was made up of 14 participants, with seven (50%) male and seven (50%) female participants. The median age was 63.5. Of the 15 variants reclassified, five were reclassified as benign and four as likely benign. Two were reclassified as oncogenic and four as likely oncogenic. Three were identified as requiring further investigation and could not be reclassified.

The two most common diagnoses that correlated to reclassified VUS were MDS (36%) and AML (29%). The 15 reclassified variants included eight genes. The two most common genes were CSF3R (27%) and ASXL1 (20%). The third most common were both TET2 (13%) and TP53 (13%).

3.3 | VUS reclassified after 24 months

Eighteen VUS were reclassified at greater than 24 months. This group was made up of 17 participants, with seven (41%) male and 10 (59%) female participants. The median age was 63.

Of the 18 variants reclassified, 11 were reclassified as benign and three as likely benign Two were reclassified as oncogenic and two as likely oncogenic. One variant was identified as requiring further investigation and could not be reclassified. The most common genes included CSF3R (38%), TET2 (38%), ZRSR2 (19%) and ETV6 (6%). No reclassification was observed in several genes such as IDH1, KIT, WT1, KRAS, DNMT3A, SF3B1 and SRSF2 (Figure 4A). The distribution of clinically significant variants (oncogenic and likely oncogenic), in patients with confirmed myeloid disease ($n = 103$), in the study period is also shown (Figure 4B). The frequency of TET2, as expected, also had a higher frequency amongst the clinically significant variants diagnosed in the same period; the frequency of other clinically significant gene variants, where VUS reclassification rates were high, was lower or absent in the study cohort.

The 23 variants that were reclassified as either benign or likely benign were made up of five genes. The two most common genes were CSF3R (43%) and TET2 (35%). The remaining genes were ASXL1 (9%), ZRSR2 (9%) and KIT (4%). The nine variants that were reclassified as either oncogenic or likely oncogenic were made up of eight genes. The most common genes were TP53 (22%) and DNMT3A (22%) The remaining seven genes (ETV6, EZH2, BRAF and RUNX1) accounted for 11% each (see Figure 2). ASXL1 was the only gene represented in both groups.

4 | DISCUSSION

Various studies have attempted to establish the appropriate timing for efficient variant re-classification programs. One study re-evaluated VUS 20 months after initial analysis in patients with neurologic/neurodevelopmental conditions and found 10% of variants could be reclassified [13]. In another study, genetic data from 1.9 million participants with hereditary cancers was reviewed over a 20-year period, with 68% of participants identified as having a variant that was reclassified and 4.7% of unique variants being reclassified [14]. In a

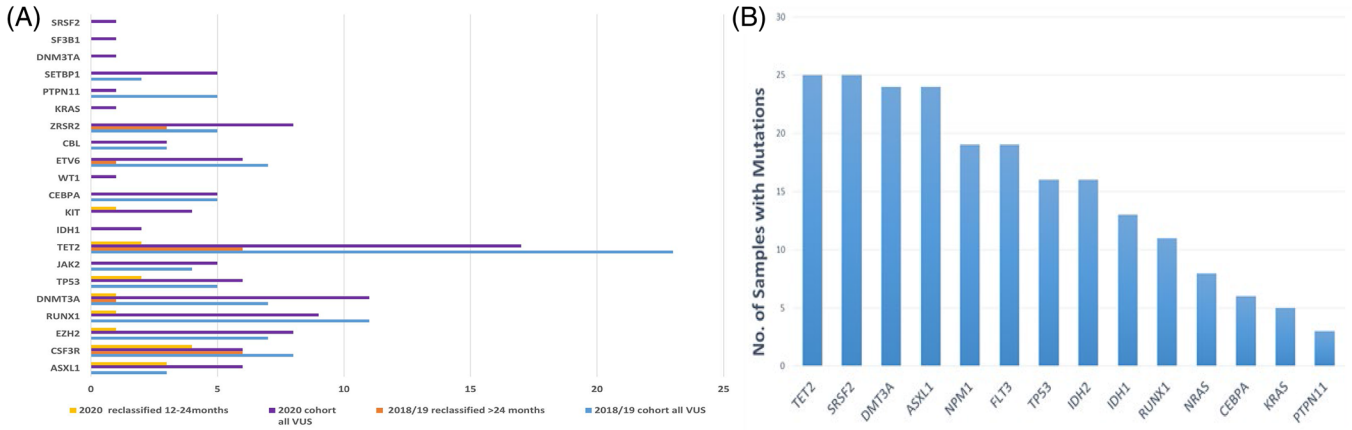

FIGURE 4 (A) Initial and reclassification frequencies for the variants of uncertain significance (VUS) cohort in this study. (B) Distribution of clinically significant variants with confirmed diagnoses of myeloid disease in the same time period as VUS subjects ($n = 103$).

third study of 1,103 participants with breast and/or ovarian cancer, 5% of variants were reclassified within a 5-year period, with most reclassifications being from 'VUS' to 'likely benign' [15]. In a fourth study of 1.45 million participants, 7.7% of variants were reclassified over a 10-year period [16]. The re-classification in all studies [13, 15–17] except one [14] was based on clinical judgement and information; in the other study, re-classification was based on population frequency databases and literature [14].

In a 2021 retrospective cohort study of participants from the National Cancer Centre in Singapore, the authors re-analysed VUS over a 6-year period [18]. They found an 8.1% reclassification rate of VUS, with the majority being re-classified as benign or likely benign (94%) [18]. The median time to reclassification in this study was 1 year and the mean time for a VUS to be re-classified as oncogenic or likely oncogenic was shorter than re-classification as benign or likely benign [18]. The authors concluded that a routine re-analysis every 2 years was sufficient taking into account the burden of re-analysis with the clinical importance [18].

In our cohort, 14% of VUS were reclassified as either benign or oncogenic, 60% of which were reclassified 24 months post-initial classification and 40% reclassified 12–24 months post-initial classification. Out of the nine genes re-classified as oncogenic and/or likely oncogenic, four resulted in discernible clinical changes in disease classification, prognosis and potential treatment options (TP53, EZH2, RUNX1 and BRAF). While these changes may not always have a clinical impact at the time of reclassification, timely reanalysis of VUS will ensure genomic analysis remains clinically useful and that genomic analysis in the context of advances in haematological malignancies continues to be applied to individual patient care [19]. This means more accurate predictions of prognosis and treatment response [13, 15, 20], more information on the risk of relapse [13, 21, 22], improved knowledge of prognosis [23–28] and enabled the development of targeted treatment approaches [27, 29, 30]. In more recent studies, sub-tiering of VUS into those more likely to be pathogenic or more likely to be benign has been suggested for cancer variants with a suggestion of the use of terminology such as "ice cold," "cold," "cool," "tepid," "warm," and "hot" [31]. The "ice cold" end of the spectrum is more likely to be classified as benign in the future and "hot" likely to be more aligned with likely oncogenic.

Any local policy needs to take into consideration the stakeholders involved in the journey of variant reinterpretation (laboratory directors, scientists, pathologists, clinicians and patients/carers) to assess opinions on key issues, including initiation of reinterpretation, variants to report, termination of the responsibility to reinterpret, as well as consent, cost, and liability [32]. Whilst one may argue the ethical need for such variant reviews exists, the legal implications are likely to vary between jurisdictions and would be a very important consideration in such variant reassessments [33, 34].

Given the scale of variants being reported through MPS, and the large proportion of VUS, timely re-evaluation will ensure genomic analysis remains clinically useful, and in the context of advances in haematological malignancies, genomic analysis continues to be applied to individual patient care [11]. It is therefore essential that research seeks to inform this jurisdictional guideline or local policies by determining appropriate timeframes for re-analysing genetic data that is specific to haematological malignancies. Our study provides retrospective evidence, but prospective studies that explore differences in patient management based on variant reclassification would be important to establish the need and frequency for such a process. The frequency of the re-analysis and its clinical impact as well as health economic impact is uncertain given the small proportion of variants reclassified (16%).

Using artificial intelligence-based algorithms that can potentially be run at a clinically relevant pre-determined interval, such as 24 months as demonstrated in this study could pave the way to variant re-analysis through updated bioinformatic pipelines in order to make this achievable in clinical practice. Once this becomes available, implementing re-classification in a diagnostic setting may be more practical.

AUTHOR CONTRIBUTIONS

Anoop K. Enjeti conceived and provided overall direction to the project. Analysis of variants was done by Anoop K. Enjeti, Andrew Ziolkowski and David Mossman. The second review of variants was done by Oliver Fahey, Elizabeth Johnston, Hannah Legge-Wilkinson

and Nateika Ramsurrun and supervised by Anoop K. Enjeti and David Mossman. Anoop K. Enjeti, Oliver Fahey, Elizabeth Johnston, Hannah Legge-Wilkinson, Nateika Ramsurrun and Lisa F. Lincz wrote the manuscript. All authors reviewed the data and provided critical feedback. All authors reviewed the final version of the manuscript.

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All scientists and clinicians who were members of the haematology molecular MDT and contributed to variant curation.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

FUNDING INFORMATION

The authors received no specific funding for this work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Ethics approval was granted by the Hunter New England (HNE) Human Research Ethics Committee on 28 September 2021 (AU202109-19) and the University of Newcastle's Human Research Ethics Committee (HREC).

PATIENT CONSENT STATEMENT

Patient consent was not required as per the ethics waiver obtained for this retrospective study.

CLINICAL TRIAL REGISTRATION

The authors have confirmed patient consent statement is not needed for this submission.

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REFERENCES

1. Claussnitzer M, Cho JH, Collins R, Cox NJ, Dermitzakis ET, Hurles ME, et al. A brief history of human disease genetics. Nature. 2020;577(7789):179–89.
2. Strande NT, Berg JS. Defining the clinical value of a genomic diagnosis in the era of next-generation sequencing. Ann Rev Genom Hum Genet. 2016;17:303–32.
3. Li MM, Datto M, Duncavage EJ, Kulkarni S, Lindeman NI, Roy S, et al. Standards and guidelines for the interpretation and reporting of sequence variants in cancer: a joint consensus recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn. 2017;19(1):4–23.
4. Federici G, Soddu S. Variants of uncertain significance in the era of high-throughput genome sequencing: a lesson from breast and ovary cancers. J Exp Clin Cancer Res. 2020;39(1):46.
5. Morash M, Mitchell H, Beltran H, Elemento O, Pathak J. The role of next-generation sequencing in precision medicine: a review of outcomes in oncology. J Pers Med. 2018;8(3):30.
6. Pereira R, Oliveira J, Sousa M. Bioinformatics and computational tools for next-generation sequencing analysis in clinical genetics. J Clin Med. 2020;9(1):132.
7. Balmaña J, Digiovanni L, Gaddam P, Walsh MF, Joseph V, Stadler ZK, et al. Conflicting interpretation of genetic variants and cancer risk by commercial laboratories as assessed by the prospective registry of multiplex testing. J Clin Oncol. 2016;34(34):4071–78.
8. Henrie A, Hemphill SE, Ruiz-Schultz N, Cushman B, DiStefano MT, Azzariti D, et al. ClinVar Miner: demonstrating utility of a web-based tool for viewing and filtering ClinVar data. Hum Mutat. 2018;39(8):1051–60.
9. Döhner H, Estey EH, Amadori S, Appelbaum FR, Büchner T, Burnett AK, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood. 2010;115(3):453–74.
10. Horak P, Griffith M, Danos AM, Pitel BA, Madhavan S, Liu X, et al. Standards for the classification of pathogenicity of somatic variants in cancer (oncogenicity): Joint recommendations of Clinical Genome Resource (ClinGen), Cancer Genomics Consortium (CGC), and Variant Interpretation for Cancer Consortium (VICC). Genet Med. 2022;24(5):986–98.
11. Deignan JL, Chung WK, Kearney HM, Monaghan KG, Rehder CW, Chao EC, et al. Points to consider in the reevaluation and reanalysis of genomic test results: a statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2019;21(6):1267–70.
12. WHO. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC Press; 2017.
13. Wenger AM, Guturu H, Bernstein JA, Bejerano G. Systematic reanalysis of clinical exome data yields additional diagnoses: implications for providers. Genet Med. 2017;19(2):209–14.
14. Esterling L, Wijayatunge R, Brown K, Morris B, Hughes E, Pruss D, et al. Impact of a cancer gene variant reclassification program over a 20-year period. JCO Precis Oncol. 2020(4):944–54.
15. Macklin S, Durand N, Atwal P, Hines S. Observed frequency and challenges of variant reclassification in a hereditary cancer clinic. Genet Med. 2018;20(3):346–50.
16. Mersch J, Brown N, Pirzadeh-Miller S, Mundt E, Cox HC, Brown K, et al. Prevalence of variant reclassification following hereditary cancer genetic testing. JAMA. 2018;320(12):1266–74.
17. Bennett JS, Bernhardt M, McBride KL, Reshmi SC, Zmuda E, Kertesz NJ, et al. Reclassification of variants of uncertain significance in children with inherited arrhythmia syndromes is predicted by clinical factors. Pediatr Cardiol. 2019;40(8):1679–87.
18. Chiang J, Chia TH, Yuen J, Shaw T, Li ST, Binte Ishak ND, et al. Impact of variant reclassification in cancer predisposition genes on clinical care. JCO Precis Oncol. 2021;5:577–84.
19. Young AL, Challen GA, Birmann BM, Druley TE. Clonal haematopoiesis harbouring AML-associated mutations is ubiquitous in healthy adults. Nat Commun. 2016;7(1):12484.
20. Mrózek K, Marcucci G, Nicolet D, Maharry KS, Becker H, Whitman SP, et al. Prognostic significance of the European LeukemiaNet standardized system for reporting cytogenetic and molecular alterations in adults with acute myeloid leukemia. J Clin Oncol. 2012;30(36):4515–23.
21. Nikolova D, Damyanova V, Radinov A, Toncheva D. Molecular response in long-term monitoring of patients with chronic myelogenic leukemia (CML) on nilotinib therapy. Biotechnol Biotechnol Equip. 2021;35(1):650–56.
22. Zelent A, Greaves M, Enver T. Role of the TEL-AML1 fusion gene in the molecular pathogenesis of childhood acute lymphoblastic leukaemia. Oncogene. 2004;23(24):4275–83.
23. Campana D. Determination of minimal residual disease in leukaemia patients. Br J Haematol. 2003;121(6):823–38.
24. Faham M, Zheng J, Moorhead M, Carlton VE, Stow P, Coustan-Smith E, et al. Deep-sequencing approach for minimal residual disease detection in acute lymphoblastic leukemia. Blood. 2012;120(26):5173–80.
25. Garg R, Kantarjian H, Thomas D, Faderl S, Ravandi F, Lovshe D, et al. Adults with acute lymphoblastic leukemia and translocation

(1;19) abnormality have a favorable outcome with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and high-dose cytarabine chemotherapy. Cancer. 2009;115(10):2147–54.
26. Genovese G, Kähler AK, Handsaker RE, Lindberg J, Rose SA, Bakhoum SF, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med. 2014;371(26):2477–87.
27. Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman PV, Mar BG, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med. 2014;371(26):2488–98.
28. Stams WA, den Boer ML, Beverloo HB, Meijerink JP, van Wering ER, Janka-Schaub GE, et al. Expression levels of TEL, AML1, and the fusion products TEL-AML1 and AML1-TEL versus drug sensitivity and clinical outcome in t(12;21)-positive pediatric acute lymphoblastic leukemia. Clin Cancer Res. 2005;11(8):2974–80.
29. Szczepański T, Orfão A, van der Velden VH, San Miguel JF, van Dongen JJ. Minimal residual disease in leukaemia patients. Lancet Oncol. 2001;2(7):409–17.
30. Kwok B, Hall JM, Witte JS, Xu Y, Reddy P, Lin K, et al. MDS-associated somatic mutations and clonal hematopoiesis are common in idiopathic cytopenias of undetermined significance. Blood. 2015;126(21):2355–61.
31. Loong L, Garrett A, Allen S, Choi S, Durkie M, Callaway A, et al. Reclassification of clinically-detected sequence variants: Framework for genetic clinicians and clinical scientists by CanVIG-UK (Cancer Variant Interpretation Group UK). Genet Med. 2022;24(9):1867–77.
32. Berger SM, Appelbaum PS, Siegel K, Wynn J, Saami AM, Brokamp E, et al. Challenges of variant reinterpretation: opinions of stakeholders and need for guidelines. Genet Med. 2022;24(9):1878–87.
33. Appelbaum PS, Parens E, Berger SM, Chung WK, Burke W. Is there a duty to reinterpret genetic data? The ethical dimensions. Genet Med. 2020;22(3):633–39.
34. Clayton EW, Appelbaum PS, Chung WK, Marchant GE, Roberts JL, Evans BJ. Does the law require reinterpretation and return of revised genomic results? Genet Med. 2021;23(5):833–36.

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