A Review of the Many Facets of Standardized Variant Interpretation

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CANCER REMAINS THE leading cause of death worldwide, with the most common types being breast, lung, colorectal, prostate, skin, and gastric.[1] Although research has led to better screening, earlier detection, healthier lifestyles, and an overall decrease in cancer mortality rate, cancer is currently estimated to account for an average of about 1,670 deaths per day in the United States alone.[2] Therapies targeting the molecular mechanisms driving tumor development and growth provide hope that cancer patients with unresectable tumors can be treated successfully and bring down this astonishing number of cancer-related deaths. The number of FDA-approved therapies with companion diagnostics (CDx) has grown from one (trastuzumab for breast cancer patients with Her2-expressing tumors) to 154 in 25 years, with 93 percent of these approvals happening since 2010.[3] In fact, biomarker-driven precision medicine is now a hallmark of cancer therapy, accounting for nearly 90 percent of agents in the pharmaceutical pipeline aimed at late-stage cancer.[4]

Driving this trend to more precise testing is the now routine use of next-generation sequencing (NGS) to investigate patient tumor molecular profiles. Moving from single gene tests to hotspot panels to comprehensive cancer panels and even whole exome and genome sequencing, NGS has opened the door to develop these precision assays to enable physicians to provide personalized cancer therapy. A study reports that since 2017, oncologists have been routinely using NGS to guide therapy decisions.[5] While the tests performed and the methods applied to these tests have now been largely standardized, there remains a gap in variant interpretation.[6] The routine finding of previously uncharacterized variants introduces uncertainty to the molecular scientists and pathologists interpreting the data and inconsistency to the clinical reports (**Figure 1**).

With accurate variant interpretation in the context of cancer diagnosis, off-label therapies and clinical trials become available to the set of patients most likely to respond to the specified therapy. A study reports that while around 20 percent of screened non-small-cell lung cancer (NSCLC) patients harbor an EGFR variant for which there is an on-label therapy, the number of patients eligible for off-label personalized therapy more than doubles with proper evidence-based variant interpretation.[7] Similarly, the National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) study of personalized therapy in patients with refractory cancer reports identifying an actionable alteration in more than 37 percent of enrolled patients who underwent successful molecular profiling. Of these patients, 18 percent were assigned to a treatment arm.[8] This number is high because it allows alterations with both on-label and off-label therapies to be assigned to treatments.

The success of personalized medicine depends on accurate and standardized means to evaluate the impact and implications of detected variants; the success of precision medicine means selecting the best drugs (one or more) to treat that variant genotype. For somatic cancer, there are two classifications to consider for each

variant, namely pathogenicity (oncogenicity) and clinical actionability. For many variants, it remains challenging to determine the most fitting interpretation and to define the evidence required to make that call.

Variant actionability

As part of a collaboration, the Association for Molecular Pathology (AMP), the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) collectively published a set of guidelines in 2015 for the reporting of somatic variants.[9] These guidelines lay out a structure for laboratories to categorize variants into one of four tiers based on their prognostic, diagnostic, or therapeutic value. The four suggested tiers consist of variants with strong clinical significance (Tier 1), potential clinical significance (Tier 2), uncertain clinical significance (Tier 3), and likely benign and benign variants (Tier 4).

Variants are further differentiated by the level of evidence (LOE) found to support their clinical significance. For example, LOE A represents variants for which there is an FDA-approved therapy or those included in professional guidelines. LOE B is defined by the biomarker/variant being tested in well-powered studies with its therapeutic/prognostic/diagnostic significance having consensus from experts in the field. LOE C is again for FDA-approved therapies, but in an indication other than the patient's tumor or multiple small studies with consensus that the biomarker/variant is significantly associated with response/resistance, prognosis, or diagnosis. Finally, LOE D represents variants/biomarkers with only preclinical evidence or lacking consensus in the field. LOE A and B are placed in Tier I, levels C and D in Tier II, and Tier III (VUS) and IV (benign variants) lack LOEs (see **Table 1**).

A similar, but more granular approach was adopted by N-of-One, now Qiagen Clinical Insights Precision Insights (QCI PI), following the publication of the AMP/ASCO/CAP guidelines where the same four tiers are used. However, the LOE B/C is added to account for variants with expert consensus to predict sensitivity to a therapy but lacking well-powered studies, and LOE C/D to account for case reports or small studies including exceptional responders indicating therapy sensitivity. QCI PI also includes Tier C.1 and C.2 to distinguish between biomarkers included in therapy approval for a different indication (C.1) and biomarkers included as inclusion criteria in clinical studies (C.2). QCI PI customers have the option to place B/C variants in Tier 1 with LOE A and B variants or in Tier 2 with LOE C and D variants (**Table 1**).

> Although research has led to sweeping changes in legislation and lifestyle, resulting in better screening, earlier detection, healthier lifestyles, and an overall decrease in cancer mortality rate, cancer is currently estimated to account for an average of about 1,670 deaths per day in the United States alone.

In 2018, the European Society for Medical Oncology (ESMO) published a Scale for Clinical Actionability of molecular Targets, the ESCAT, adding to the 'standard' ways variants can be interpreted.[10] This scale is more detailed than that of the AMP/ASCO/CAP framework and is composed of six tiers based on clinical LOE for variants that impact patient care. In this scale, Tier I variants (those that have been associated with improved clinical outcome in targeted drug trials) are divided into distinct categories based on LOE. For example, IA is reserved for alteration/drug combinations tested in prospective randomized studies with survival as the end point. Trastuzumab for ERBB2-amplified breast cancer is an example of a Tier IA combination. While most scales would place a ROS1 fusion in non-small-cell lung at Tier I LOE A, the ESCAT framework places it at IB due to it being tested in prospective non-randomized studies. The IC designation is for drugs that have been shown to have efficacy across multiple tumor types, with pembrolizumab given as an example for tumors exhibiting mismatch repair deficiency.

A major distinction between the ESCAT and other guidelines is repeated use of the A/B/C designations. While the AMP/ASCO/CAP guidelines, as well as QCI PI, use A and B only for Level 1 and C and D for Level 2 variants, ESCAT has IA as well as IIA, IIIA, and so on (**Table 1**). Some of the stated rationale behind the ESCAT guidelines is to provide rules that span all drug approval agencies by highlighting the specifics of the clinical studies rather than agency drug approval and accessibility, which may differ between countries. Using the ASCO/AMP/CAP criteria, the Tier 1A classification is reserved for therapies approved by the FDA based on the presence of the variant/biomarker, making this seem less relevant for laboratories outside of the US.

Countless additional laboratories, consortia, and companies have taken one or more of these guidelines and adapted them as they see fit. Two examples include the Comprehensive Cancer Center Freiburg in Germany and the Commission of Personalized Medicine (ComPerMed) panel of experts in Belgium.[11,12] The group in Freiburg takes an approach similar to that of ESCAT. They define Tier 1 variants by the demonstrated clinical effectiveness of the biomarker in a biomarker-stratified cohort analysis of well-powered prospective study (m1A) or in a retrospective cohort or case-control study (m1B) in the cancer indication. Levels m2A and m2B of this scale follow the same logic, but for a different type of cancer (**Table 1**).

The ComPerMed guidelines, however, follow a system similar to that of AMP/ASCO/CAP, but with Belgian-specific rules. For example, Tier 1 variants include those that predict response (or resistance) to a reimbursed therapy available in Belgium, or variants included in professional guidelines to have prognostic or diagnostic value and with consensus by ComPerMed experts (**Table 1**). Numerous online knowledgebases including CIViC, OncoKB, JaxCKB, and others, have additionally adapted the AMP/ASCO/CAP guidelines.[13,14,15,10] However, the manner and degree of guideline modification is not always transparent. In fact, a study comparing six well-cited databases of characterized somatic cancer variants has indicated a high degree of disparity in methods used for determining variant oncogenicity.[16] To address this challenge, Wagner and the Variant Interpretation for Cancer Consortium (VICC) developed their own algorithm and procedure for combining and

Table 1: Alignment of oncology variant tiers with LOE used by different guidelines

AMP	A	B	—	—	—	C	—	C	D	—
QCI PI	A	B	B/C	B/C	—	C.1	C.2	C/D	D	—
ESCAT	A	B	C	A	B	A	B	A	A	B
CCCF	m1A	m1B	—	—	—	m2A	m2B	m2C	m3	m4
CPM	Level1	—	—	Level2A	—	Level2B	Level3	Level3	—	—

This table is intended to provide a general comparison of these different scales with the acknowledgement that they are not one-to-one comparable. CCCF=Comprehensive Cancer Center Freiburg; CPM=ComPerMed; Letters=LOE; blue=Tier 1; purple=Tier 1 or 2 (user discretion); red=Tier 2; yellow=Tier 3; green=Tier 4.

systematizing interpretations from these separate sources, adding to the number of published options for "standardized" variant interpretation.

While the AMP/ASCO/CAP guidelines provide the first and necessary step toward standardizing somatic variant interpretation for prognosis, diagnosis, and therapeutic actionability, the many iterations of these and other guidelines lead to continued inconsistency in interpretation with potential negative impact on patients at the point-of-care. In fact, a recent study has found differing opinions on variant classification among experts to be as high as 28 percent.[17] This number reflects the complexity of somatic variant interpretation. Not only must the interpreter find and have access to the appropriate information to adequately judge the data and correctly classify variants into tiers, but this data must be viewed in a specific disease context and the biological effect of the variant must also be judged and classified. Only when the variant oncogenicity and actionability have been correctly assessed can a patient be optimally treated.

Variant oncogenicity

In 2015, the American College of Medical Genetics and Genomics (ACMG) in collaboration with the AMP and CAP published recommendations for the interpretation of variants found in Mendelian disorders, including mitochondrial variants. The group established five categories – pathogenic, likely pathogenic, uncertain, likely benign, and benign; these categories are based on levels of evidence, including data from population studies, computational studies, functional studies, and segregation studies.[18] Known as the "ACMG guidelines", this tiered framework uses a defined set of rules to classify variants into one of the five categories.

For example, for a variant to be classified as pathogenic, it must either fully meet the PVS1 criteria (nonsense, frameshift, canonical splice alteration, affect start codon, or be a single or multi-exon deletion in a gene where loss of function is a known mechanism of disease) or meet two or more criteria supporting pathogenicity, such as co-segregating with disease and be a novel missense change at an amino acid where a different amino acid change has previously been found to be pathogenic. Rules like PP2 (missense alteration in a gene with a low rate of benign missense alterations) or PP3 (multiple lines of computational evidence supporting a deleterious effect) can be used as supporting evidence to strengthen a pathogenic or likely pathogenic assessment (see **Table 2** for some example criteria).

Table 2: Alignment of example variant oncogenicity/pathogenicity scores used by different groups.

ACMG	QCI	ClinGen	Rule
PVS1	PVS1	OVS1 (8pts)	Null variant in tumor suppressor gene
not present	PVS7	OS3 (4pts)	Cancer hotspot with 50+ reports
PS1	PS1	OS1 (4pts)	Amino acid change support oncogenic effect
PS3	PS3	OS2 (4pts)	Functional studies support oncogenic effect
not present	PS7	OM3 (2pts)	Cancer hotspot with fewer than 50 reports
PP3	PP3	OP1 (1pt)	Computational evidence supports oncogenic effect
BP4	BP4	SPB1 (-1pt)	Computational evidence suggests no effect

This table is intended to provide a general comparison of these different scales with the acknowledgement that they are not one-to-one comparable.

This scale of pathogenicity, while intended for constitutional (germline) variants, has been widely used and adapted for both hereditary and somatic variant classification. For example, Qiagen's QCI platform bases the pathogenicity call on a set of rules stemming from the ACMG guidelines, but with additional rules developed from research and experience in hereditary and somatic testing. For example, QCI adds the PA1 rule (confers sensitivity to an approved drug) to the somatic workflow and PA2 (established common pathogenic founder mutation) to the hereditary workflow, and factors them into the computed call for pathogenicity in the respective workflows (**Table 2**).

Another approach is taken by the ComPerMed panel of experts in cancer diagnostics in Belgium.[12] Rather than strictly modeling after the framework laid out by the ACMG guidelines, this panel developed a comprehensive list of consensus pathogenic variants (CPV) and their own system of scoring those variants not on the CPV list as likely pathogenic, unknown, likely benign, or benign. While it is recognized that some of these calls are partially dependent on the preceding pipeline, as well as some differences in the population being tested, the ComPerMed guidelines serve as a standard scoring system throughout Belgium. Yet another group published a method of applying a Bayesian framework to calculate a point system for application of the ACMG/AMP guidelines.[19] These and numerous additional adaptations have been put into practice around the world, suggesting a new scale aimed specifically toward somatic variant interpretation may be needed to help standardize the field.

To answer this need for international standardization of oncogenicity interpretation for somatic variants, the ClinGen/Cancer Genomics Consortium (CGC)/VICC Guidelines (referred to here as ClinGen guidelines) were published in 2022.[20] The language chosen for the first two of the five variant categories – namely oncogenic and likely oncogenic – highlighted the

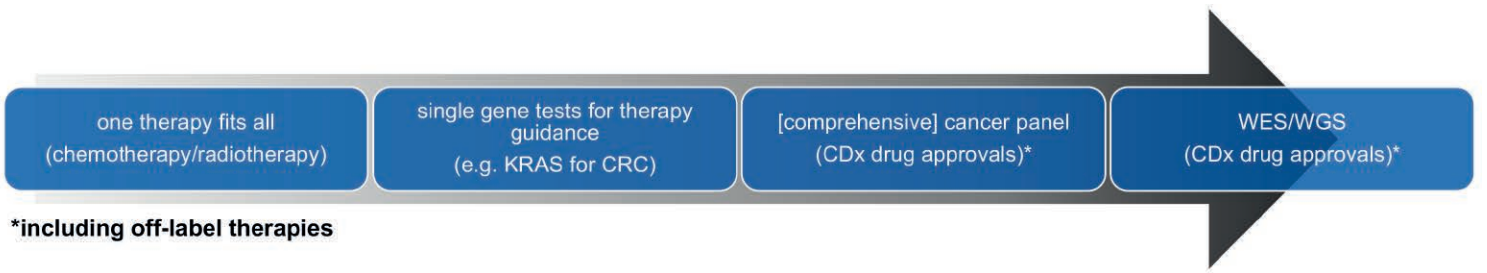

Figure 1: Evolution of personalized therapy
In the past decade, therapy decisions have moved from a one-size-fits-all framework to therapy selection based on single gene analysis to multigene hotspot analysis to comprehensive cancer panels and now extending to whole exome and whole genome sequencing (WES/WGS). Companion diagnostic (CDx) approvals drive this process and extend therapy relevance to off-label indications, including off-label variants and disease indications. The blue boxes indicate this trend toward larger data sets used to inform therapy decisions. The arrow in the back indicates the increased requirement of disease-specific variant interpretation as these molecular tests and approvals expand, and the level of uncertainty in how to achieve adequate interpretation at scale.

different intent of these guidelines from that of the ACMG guidelines. Likewise, the guidelines are strictly intended for somatic variants and not germline cancer predisposition variants; however, guidelines for handling of somatic variants potentially driving oncogenicity in genes with variants associated with germline cancer were also established.

Additionally, these guidelines are limited to single nucleotide variants and insertions/deletions and do not extend to CNVs, fusions, or other rearrangements. Importantly, these ClinGen guidelines take disease context into consideration as mutations in some genes are known to play different roles depending on the biological context. Finally, these guidelines are intended to be used together with the ASCO/AMP/CAP guidelines for clinical actionability tiering.

The ClinGen guidelines use "oncogenicity" to define variant pathogenicity in context of cancer and other neoplastic diseases. The standard operating procedure (SOP) defines a scale ranging from below -7 to 10 and above. On this scale, oncogenic variants have positive scores and benign variants have negative scores. Variants of uncertain significance (VUS) comprise the middle ground with scores ranging from slightly negative to slightly positive. Again, the purpose of this SOP is to avoid inconsistency in clinical interpretation by providing a clear and defined procedure for cancer variant classification and are of particular use in classifying Tier I variants. Numerous factors go into the ClinGen variant score, and, like the rules established by Qiagen's QCI platform, elaborate on the rules established by the ACMG guidelines (**Table 2**).

A comparison of the ClinGen rules and those used QCI Interpret for Oncology found that all of the 43 variants classified by ClinGen rules as oncogenic/likely oncogenic were also classified as pathogenic/likely pathogenic by QCI Interpret; using another dataset, the results were similar.[21] When discrepancies in classification did arise, QCI Interpret criteria consistently 'upgraded' the variant compared with ClinGen. For example, a variant called benign by ClinGen either received the same call by QCI Interpret or was classified as VUS; likewise, a VUS by ClinGen SOP was either also a VUS by QCI Interpret or called likely pathogenic. This is desired behavior for such decision support software, as the user can ensure potentially relevant variants are not overlooked in the assessment.

What to choose and what to avoid: How decision support software can help

With so many different established and emerging methods to classify both the oncogenicity and clinical relevance of neoplastic variants, it can become daunting for clinical scientists and pathologists to know the best way to proceed. The various interpretation methods all highlight the utility of bioinformatic tools to assist in the prioritization of variants, especially as the number of genes tested on a routine basis increases. But the question remains – what differentiates the variety of bioinformatics tools and knowledgebases, all with slightly different methods of variant prioritization and/or interpretation. Thus, there is a need to validate these tools.

A recent independent study underscores how one such tool, QCI Interpret for Oncology, can aid in standardizing variant interpretation of tumor molecular profiles.[17] In this study, the quality assessment organization GenQA recruited eight European laboratories to compare their standard methods of variant interpretation with those of QCI Interpret. Overall, there was 91 percent agreement in variant classification between QCI Interpret and the laboratories or expert panel. We posit that, had the laboratories been allowed to implement their own set of rules as part of the study, which is possible in this software, this number may have approached 100 percent.

> Thus, there is a need for these multiple variant interactions to be properly and consistently classified in order to bring the best and most relevant therapy options to the treating physician, including options that should be avoided based on evidence.

This level of agreement far exceeds that of other studies. For example, a report comparing three different commercial clinical decision software platforms found only 4-28 percent concordance in classification of Tier 1A and 1B variants.[22] Another study compared the implementation of the ASCO/CAP/AMP guidelines in different institutions and found an overall concordance in variant classification of 58 percent.[23] However, comparisons need to be made against a standard, which is often lacking in such studies.[7] In the study cited in the previous paragraph, QCI was used as a standard with a panel of experts chosen to dispute discrepencies.

What the GenQA study shows is that evidence-powered clinical decision support software (CDSS) can provide an objective measure of the accuracy, consistency, and reliability in somatic variant interpretation for both oncogenicity and actionability. The right CDSS can additionally incorporate any institutional, governmental, or individual nuances to classification and reporting rules, allowing the user to meet required standards and regulations and scale interpretations to large gene or exome/genome panels at high-volume throughput.

A caution regarding CDSS is that some tools lack appropriate transparency and traceability, resulting in a lack of accountability. Tools that rely on crowdsourcing and/or artificial intelligence (AI) may be lacking in data, or biased by data selection, or even by the nature of the algorithms, and hence are prone to systematic mistakes. For example, public data contributions often contain inconsistencies in transcripts, genetic nomenclature, gene name, and typos that can result in missing or inappropriate associations.[7] Another study has found a gross inconsistency in public resources with regard to references used to support interpretation.[16]

Likewise, AI has been reported to introduce errors that then become amplified with further use and to lack transparency, making it difficult to impossible to trace the rationale behind a clinical therapy suggestion.[7] What differentiates the most reliable CDSS systems are the ones that combine machine learning technology with manual curation and expert interpretation. This combination can thoughtfully and consistently tackle the multi-faceted questions that arise in clinical laboratories, such as emerging resistant mutations, correct interpretation of fusions, and calling out interactions with therapeutic, prognostic, or diagnostic significance – and incorporate the latest and most relevant data from the overwhelming wave of daily publications – to provide trustworthy interpretative reports at scale.

Co-occurring alterations: How appropriate CDSS can help

None of the variant interpretation guidelines adequately address a recommended standard classification of one variant based on the presence or absence of another variant in the same sample. While the ESCAT does acknowledge the need for interpretative scoring of co-occurring mutations in tumors, no clear instructions for doing so and no example interpretations are provided.[10] These interactions between (and among) different alterations occurring in the same cancer can have critical clinical implications, ranging from diagnostic stratification to therapy efficacy.[24] Thus, there is a need for these multiple variant interactions to be properly and consistently classified in order to bring the best and most relevant therapy options to the treating physician,

including options that should be avoided based on evidence.

As more tumors are sequenced and larger panels used, detection of relevant co-occurring variants has consequently increased. The NCI-MATCH study reports finding co-occurring actionable alterations in nearly 53 percent of successfully screened cancer patients, highlighting the prevalence and potential relevance of these alterations.[8] Professional clinical practice guidelines, such as those from the World Health Organization, European Leukemia Network, National Comprehensive Cancer Network, and ESMO, all note the relevance of specific co-occurring variant interactions with respect to prognosis, diagnosis, and therapy sensitivity/resistance. While such interactions are particularly prevalent in hematologic cancers, more data are emerging for solid tumors. What is missing is clear guidance about how to classify these interactions into tiers and assign LOE for optimized treatment approaches.

Although not necessarily highlighted in all guidelines, each laboratory faces co-occurring mutations on a routine basis and must decide how they are handled, or if they are addressed at all. The approach taken by QCI PI, which combines machine learning with expert curation, is to weigh the evidence of the interaction and assign an LOE that is dependent on the cancer diagnosis. For example, the presence of a MYC rearrangement together with a rearrangement in BCL6 in double hit lymphoma would receive a Tier 1B designation for prognosis based on multiple studies with consistent results and expert consensus. This same interaction would receive a Tier 1A designation for diagnosis, as it is present as a diagnostic marker in professional clinical practice guidelines. These tier designations would only apply if both variants were present and determined to be pathogenic or likely pathogenic.

Summary

Variant calling and classification of tiers has led to more arrows in precision medicine's quiver. Because tiering and LOE assignment for co-occurring variants in specific disease contexts requires a multi-faceted approach, it is not surprising that standardization is lagging. The complexity of standard interpretation for single variants alone is exemplified by the sheer number of attempts at standardization as described above. With today's improved CDSS capabilities and the recognized need to combine expert knowledge with these capabilities, it is now possible to appropriately score these variant interactions at scale. And with these advances, informative guidelines for variant interactions are likely just around the corner. PMQ

Summary Points

- There are many published guidelines describing rules and recommendations for assigning variant oncogenicity and/or actionability in the field of oncology.
- Putting these guidelines into practice is difficult and often results in minor or major adaptations of published standards.
- Clinical decision support software, when appropriately vetted and implemented, can reduce the variability and increase the scalability of appropriate somatic variant interpretation.
- What differentiates the most reliable CDSS systems are the ones that combine machine learning technology with manual curation and expert interpretation. This combination can thoughtfully and consistently tackle the multi-faceted questions that arise in clinical laboratories.

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References

1. World Health Organization. Cancer Fact Sheet. Published February 3, 2022. https://www.who.int/news-room/fact-sheets/detail/cancer
2. American Cancer Society. 2022-cancer-facts-and-figures. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2022.html
3. Food and Drug Administration. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). FDA. Published online March 22, 2021.
4. IQVIA Institute for Human Data Science, Global Oncology Trends 2018. www.iqvia.com.
5. Freedman AN, Klabunde CN, Wiant K, et al. Use of next-generation sequencing tests to guide cancer treatment: Results from a nationally representative survey of oncologists in the united states. JCO Precision Oncology. 2018;(2). doi:10.1200/po.18.00169
6. Elkin S. Variability in Somatic Variant Interpretation: Can Software Help? Journal of Precision Medicine. Vol 8.; 2022.
7. Bungartz K, Lalowski K, Elkin S. Making the Right Calls in Precision Oncology, Nature Biotechnology; 2018. DOI: 10.1038/nbt.4214
8. Flaherty KT, Gray RJ, Chen AP, et al. Molecular landscape and actionable alterations in a genomically guided cancer clinical trial: National cancer institute molecular analysis for therapy choice (NCI-MATCH). Journal of Clinical Oncology. 2020;38(33). doi:10.1200/JCO.19.03010
9. Li MM, Datto M, Duncavage EJ, 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. Journal of Molecular Diagnostics. 2017;19(1). doi:10.1016/j.jmoldx.2016.10.002
10. Mateo J, Chakravarty D, R. Dienstmann, et al. A framework to rank genomic alterations as targets for cancer precision medicine: The ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). Annals of Oncology. 2018;29(9). doi:10.1093/annonc/mdy263
11. Hoefflin R, Lazarou A, Maria Elena Hess, et al. Transitioning the molecular tumor board from proof of concept to clinical routine: A german single-center analysis. Cancers. 2021;13(5). doi:10.3390/cancers13051151
12. Froyen G, Marie Le Mercier, Lierman E, et al. Standardization of somatic variant classifications in solid and haematological tumours by a two-level approach of biological and clinical classes: An initiative of the belgian compermed expert panel. Cancers. 2019;11(12). doi:10.3390/cancers11122030
13. Griffith M, Spies NC, Krysiak K, et al. CIViC is a community knowledgebase for expert crowdsourcing the clinical interpretation of variants in cancer. Nature Genetics. 2017;49(2). doi:10.1038/ng.3774
14. Chakravarty D, Gao J, Phillips S, et al. OncoKB: A precision oncology knowledge base. JCO Precision Oncology. 2017;(1). doi:10.1200/po.17.00011
15. Patterson SE, Statz CM, Yin T, Mockus SM. Utility of the JAX Clinical Knowledgebase in capture and assessment of complex genomic cancer data. npj Precision Oncology. 2019;3(1). doi:10.1038/s41698-018-0073-y
16. Wagner AH, Walsh B, Mayfield G, et al. A harmonized meta-knowledgebase of clinical interpretations of somatic genomic variants in cancer. Nature Genetics. 2020;52(4). doi:10.1038/s41588-020-0603-8
17. Fairley JA, Deans ZC, Rebecca, et al. An independent assessment of a commercial clinical interpretation software indicates that software can mitigate variation in human assessment. Journal of Molecular Pathology. 2022;3(3):125-139. doi:10.3390/jmp3030012
18. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in Medicine. 2015;17(5). doi:10.1038/gim.2015.30
19. Tavtigian SV, Harrison SM, Boucher KM, Biesecker LG. Fitting a naturally scaled point system to the ACMG/AMP variant classification guidelines. Human Mutation. 2020;41(10). doi:10.1002/humu.24088
20. Horak P, Griffith M, Danos AM, 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). Genetics in Medicine. 2022;24(5). doi:10.1016/j.gim.2022.01.001
21. Goverdhan A, Mullineaux L, Pryzbylski A, Teigen C, Elkin S, Pitel BA. A Comparative Analysis of Somatic Cancer Variant Interpretation Using the ClinGen/CGC/VICC Framework and QIAGEN Clinical Insight Decision Support Software. Association for Molecular Pathology 2022 Annual Meeting Abstracts. Abstract I005.
22. Perakis SO, Weber S, Zhou Q, et al. Comparison of three commercial decision support platforms for matching of next-generation sequencing results with therapies in patients with cancer. ESMO Open. 2020;5(5). doi:10.1136/esmoopen-2020-000872
23. Deepika Sirohi, Schmidt RL, Aisner DL, et al. Multi-institutional evaluation of interrater agreement of variant classification based on the 2017 association for molecular pathology, american society of clinical oncology, and college of american pathologists standards and guidelines for the interpretation and reporting of sequence variants in cancer. Journal of Molecular Diagnostics. 2020;22(2). doi:10.1016/j.jmoldx.2019.10.010
24. Ferdinandos Skoulidis, Heymach JV. Co-occurring genomic alterations in non-small-cell lung cancer biology and therapy. Nature Reviews Cancer. 2019;19(9). doi:10.1038/s41568-019-0179-8