

Collaborative, Multidisciplinary Evaluation of Cancer Variants Through Virtual Molecular Tumor Boards Informs Local Clinical Practices

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PURPOSE The cancer research community is constantly evolving to better understand tumor biology, disease etiology, risk stratification, and pathways to novel treatments. Yet the clinical cancer genomics field has been hindered by redundant efforts to meaningfully collect and interpret disparate data types from multiple high-throughput modalities and integrate into clinical care processes. Bespoke data models, knowledgebases, and one-off customized resources for data analysis often lack adequate governance and quality control needed for these resources to be clinical grade. Many informatics efforts focused on genomic interpretation resources for neoplasms are underway to support data collection, deposition, curation, harmonization, integration, and analytics to support case review and treatment planning.

METHODS In this review, we evaluate and summarize the landscape of available tools, resources, and evidence used in the evaluation of somatic and germline tumor variants within the context of molecular tumor boards.

RESULTS Molecular tumor boards (MTBs) are collaborative efforts of multidisciplinary cancer experts equipped with genomic interpretation resources to aid in the delivery of accurate and timely clinical interpretations of complex genomic results for each patient, within an institution or hospital network. Virtual MTBs (VMTBs) provide an online forum for collaborative governance, provenance, and information sharing between experts outside a given hospital network with the potential to enhance MTB discussions. Knowledge sharing in VMTBs and communication with guideline-developing organizations can lead to progress evidenced by data harmonization across resources, crowd-sourced and expert-curated genomic assertions, and a more informed and explainable usage of artificial intelligence.

CONCLUSION Advances in cancer genomics interpretation aid in better patient and disease classification, more streamlined identification of relevant literature, and a more thorough review of available treatments and predicted patient outcomes.

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THE CURRENT STATE OF PRECISION ONCOLOGY

Clinical decision making requires rapid integration of multiple data streams (eg, symptoms, signs, imaging) and choice of appropriate therapy. Although this process has not changed much over time, the data streams have evolved to include patient-reported outcomes, biometrics and data from wearable devices, radiographs, and genomic molecular profiles. Furthermore, the rapid development of next-generation sequencing (NGS) technologies and computing systems has had a tremendous impact on clinical research, particularly in the understanding of underlying physiologic mechanisms of diseases and identifying key altered pathways susceptible to molecular targeted or immunologic therapies.¹ Although such high-throughput strategies are often not necessary in determining clinical action (ie, *HER2* amplification can

be treated with trastuzumab), the adoption of NGS technologies in oncology enables the customization and matching of therapies to a patient's molecular profile, especially if the patient has experienced progression on multiple lines of therapy, thereby reducing adverse effects as a result of unnecessary treatments.²

In 2019, nearly a third of early-stage oncology drugs or biologics and 91% of late-stage drugs from pharmaceutical companies involved the use of biomarker tests.³ In addition, over a third of drug approvals in 2019 included DNA-based biomarker(s) in their original US Food and Drug Administration (FDA) submissions.³ Concurrently, we have increased our understanding of the underlying pathophysiology of both the tumor and patient-tumor interactions through this omics data. For example, in most solid tumors, the pathogenic driver mutations that inform clinical management

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

We aimed to describe the current state of collaborative molecular tumor boards used to reveal the clinical relevance in cancer genomes and integration of these data into clinical practice.

Knowledge Generated

Characteristics of molecular tumor boards are highlighted and demonstrate a molecular tumor board workflow leveraging local expertise and crowd-sourced knowledge. Resources available for use by tumor boards and the utility of those resources are described. Challenges in genomic interpretation are highlighted.

Relevance

Oncologists, molecular pathologists, clinician scientists, and genomic scientists can better contextualize the breadth of resources and guidelines available to support molecular tumor board activities.

remain the same between primary and metastatic (secondary) tumor sites.^{4,5} However, secondary tumors may develop additional genomic signatures that are associated with disease progression and/or resistance to specific targeted therapies.^{6,7} National trials⁸⁻¹⁰ that pair patient tumors with specific genomic alterations to targeted medications represent the first step in this paradigm shift. However, the interpretation of NGS-based test results in oncology remains the critical bottleneck in translating these data into effective treatment strategies.¹¹

Now more than ever, there is a need for multidisciplinary approaches in cancer care because no one person can be an expert in all required fields, including but not limited to the clinical domain, genomic profiles, disease etiology, drug sensitivity and resistance, clinical trials, and emerging scientific evidence for targeted treatments. In addition, it is paramount to understand the breadth of available resources and forums for the clinical interpretation of molecular data in cancer care. In this article, we review the landscape of genomic interpretation tools and knowledgebases, as well as guidelines that support the clinical interpretation and application of NGS data within the context of multidisciplinary molecular tumor boards (MTBs) and the potential application of virtual MTBs (VMTBs) that may complement MTB activities. See the glossary of terms provided in the Appendix.

MTBs

To support the wider integration of precision medicine in cancer, several academic medical centers and community clinics have established multidisciplinary MTBs, generally composed of oncologists, molecular pathologists, clinician scientists, genomic scientists, genetic counselors, bioinformaticians, and other experts in cancer and/or genetics within an institution to discuss the utilization of cancer NGS results in patient treatment decisions.^{12,13} MTB workflows typically focus on one or more cancer types and include the use of multiple variant interpretation knowledgebases, a software to input clinical and genomic test results, and custom algorithms to match patient characteristics to treatment and clinical trial recommendations.¹⁴ However, not all institutions have access

to appropriate expertise, time, and resources to conduct regular MTB discussions, which may result in insufficient utilization of relevant NGS test results and ultimately suboptimal patient care, especially in challenging cancer situations.^{12,15} In such scenarios, VMTBs provide a route of communication, information sharing, and data provenance by connecting genomic scientists and clinicians from multiple cancer centers and community clinics globally¹⁶ (Fig 1).

In a VMTB setting, case submission typically requires sharing de-identified patient information, including medical, treatment, and family history; radiology, pathology, and molecular profiling results from a spectrum of assays (eg, immunohistochemistry [IHC], fluorescent in situ hybridization, NGS); and other useful information for interpreting genomic results or recommending treatment. The case is then discussed via a Health Insurance Portability and Accountability Act-compliant Web conferencing software, thereby providing a means to share knowledge from experts at multiple institutions and their cumulative genomic resources for variant interpretation. VMTBs also provide a setting agnostic of physical and geographic constraints, allowing expansive crowd-sourced participation to better discuss cancer variant interpretation in the context of clinical data available. Although results from germline testing are important, somatic variant testing data are most often discussed in a VMTB forum. Several publicly or commercially available genomic variant interpretation resources and software are used within VMTBs and are indispensable for determining clinical relevance (diagnosis, prognosis, and therapeutic propensity) of variants within the context of a patient's disease and pathology. Furthermore, patient cases evaluated in MTBs can often benefit from being referred to a VMTB.¹⁷ VMTB participation can help resolve conflicting clinical variant interpretations, as well as train clinicians and clinical researchers to properly interpret genomic data in a clinical context. Several international efforts are ongoing, including but not limited to the VMTB forums conducted by the Variant Interpretation for Cancer Consortium (VICC), Vanderbilt-Ingram Cancer

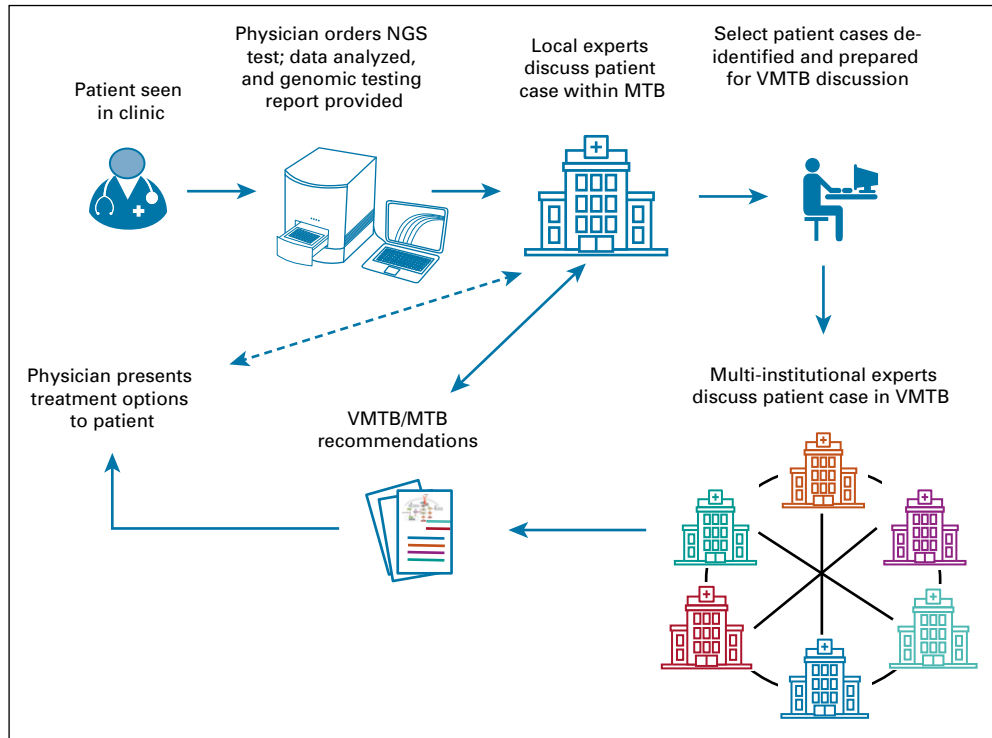


FIG 1. Incorporation of molecular tumor board (MTB) and virtual molecular tumor board (VMTB) workflows into clinical reporting practices. After a patient consults with a clinician and provides a tumor specimen, the clinical next-generation sequencing (NGS) testing is ordered. The clinical laboratory performs the NGS assay and sequencing and reports genomic variants of clinical relevance. The MTB leverages local expertise and available resources to interpret the clinical significance of genomic data. Because MTBs operate locally, there is often opportunity for adding insight directly from the physician and patient that can help guide and/or prepare clinical recommendations. When local expertise is insufficient to make appropriate clinical recommendations, variants are prioritized and patient data are de-identified before VMTB submission. VMTB members from multiple institutions use their cumulative genomic resources and expertise to evaluate an NGS case and to discuss consensus recommendations for the patient.

Center, and Cancer Core Europe to leverage global sharing of genomic expertise in clinical practice.

GUIDELINES AND STANDARDS TO DETERMINE THE CLINICAL SIGNIFICANCE OF GENOMIC DATA AND EXPERT KNOWLEDGE CURATION

Clinical-grade genomic variant interpretation is a well-documented pain point in translating tumor NGS test results into clinical action.¹¹ Clinicians and molecular pathologists must order NGS tests from Clinical Laboratory Improvement Amendments–certified genomic testing laboratories to ensure high-quality results to make clinical care decisions. Several professional societies around the world have developed guidelines to help molecular pathologists and clinical genomics scientists interpret multigene cancer panel sequence variants and determine their clinical significance in a standardized manner. For example, biomarkers relevant to disease predisposition are typically evaluated in a germline context and are classified under the American College of Medical Genetics and Genomics (ACMG)/ Association for Molecular Pathology (AMP) guidelines for interpretation of sequence variants.¹⁸ Biomarkers relevant

to prognosis and therapeutic response are typically evaluated in a somatic context under AMP, ASCO, and College of American Pathologists (CAP) guidelines for the reporting of cancer somatic variants¹⁹ in the United States. The European Society for Medical Oncology (ESMO) also recommends the ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) variant classification guidelines.²⁰

The AMP/ASCO/CAP and ESCAT guidelines slightly differ from each other. The ESCAT highest level of clinical significance (Tier I) differentiates between randomized (Tier IA), nonrandomized (Tier IB), and basket trials (Tier IC), whereas AMP does not. AMP considers somatic variants that predict response to FDA-approved therapies or recommended by professional societies like the National Comprehensive Cancer Network (NCCN) as the highest level of clinical significance (Tier IA). In addition, somatic variants that predict response to cancer therapies based on well-powered studies with expert consensus, but not yet included in professional guidelines, are also considered as having high-level clinical significance (Tier IB).¹⁹ Furthermore, AMP accounts for evidence from multiple case reports to

determine the clinical significance of cancer variants, whereas ESCAT does not. Molecular pathologists and genomic scientists must be cautious of these seemingly subtle differences in guidelines, which introduce subjectivity and discordance in the interpretation and reporting of cancer variants between clinical laboratories.²¹

In an attempt to standardize the application of variant interpretation and reporting guidelines, collaborative efforts such as the Clinical Genome (ClinGen) Resource program²² have organized working groups (WGs) of multidisciplinary experts in various clinical domains including somatic and hereditary cancers. These clinical domain WGs oversee multiple gene-disease specific variant curation efforts, called Gene Curation Expert Panels or Variant Curation Expert Panels (VCEPs).²³ ClinGen germline VCEPs recommend a standardized approach to apply the ACMG/AMP guidelines to interpret germline variants using an FDA-recognized process.²⁴ An analogous somatic VCEP process is currently under development by the ClinGen Somatic Cancer WG. Such multi-institutional endeavors address gaps in existing variant classification guidelines, ensure consistency and transparency in the clinical interpretation of genomic variants between knowledgebases, and subsequently inform MTB and VMTB recommendations.

LANDSCAPE OF GENOMIC DATA RESOURCES AND KNOWLEDGBASES THAT INFORM TUMOR BOARD DISCUSSIONS

The large-scale adoption of NGS-based testing in clinical oncology underscores the need for standardized variant interpretation and reporting procedures across clinical laboratories. When evaluating cancer genomic biomarkers, clinicians, molecular pathologists, and clinical genomic scientists primarily reference knowledgebases with human-curated collections of biomedical evidence supporting assertions on the clinical significance of genomic variants in a disease context.²⁵ For example, the contextualized interpretation of a variant may be predisposing (eg, *BRCA1/2* variants increase predisposition to develop breast or ovarian cancers in the germline context and can also predict therapeutic response to poly [ADP-ribose] polymerase [PARP] inhibitors in breast or ovarian cancers in the somatic tumor context), prognostic (eg, *TP53* mutations predict poor outcome in chronic lymphocytic leukemias), diagnostic (eg, *PCM1-JAK2* fusions are exclusionary criteria for a diagnosis of chronic myelomonocytic leukemia with evidence of eosinophilia), or predictive (eg, patients with *BRAF* V600E-mutant melanomas benefit from combination therapy with RAF and MEK inhibitors). [Table 1](#) presents a survey of clinically relevant knowledgebases.^{23,26-39}

Knowledgebases vary considerably in both data structure and content. Consequently, genomic scientists must select a subset of resources for their clinical analysis and reporting workflows to reduce the intellectual investment needed to

apply relevant knowledgebase information to a patient case. The VICC represents a collaborative effort between many knowledgebase leaders to improve interoperability and accessibility of curated content across resources adopting standards for data representation.⁴⁰ Although cancer variant knowledgebases are useful in providing clinical assertions, they often fall short in the ability to interpret rare or poorly studied cancer variants, resulting in discordant or nonoverlapping assertions between knowledgebases or VMTB entities.⁴⁰ In such cases, *in silico* prediction algorithms⁴¹⁻⁴⁴ applied to the genomic findings in a cancer profile can predict which variants are oncogenic. However, the results produced by these methods, especially for benign variants, are frequently discordant and may need validation based on their structural⁴⁵ or functional⁴⁶ impacts. Population databases (eg, gnomAD, dbSNP) determine whether a variant is present in the general population and therefore less likely to be oncogenic. Large data sets, such as in The Cancer Genome Atlas, International Cancer Genome Consortium, Catalogue of Somatic Mutations in Cancer, or cBioPortal, identify whether a variant has been consistently observed within disease cohorts but absent or rare in controls.⁴⁷ Although *in silico* models, population databases, and large data sets cannot replace human expert-curated knowledgebases, these resources are essential for the scientist to interpret genomic data and predict oncogenicity. Furthermore, efforts are ongoing to automate the current variant interpretation processes with artificial intelligence (AI) strategies to integrate resources automatically and make interpretation processes scalable.

APPLICATIONS OF AI IN TUMOR BOARDS

The surge in clinically relevant molecular data accompanied by advances in AI and machine learning (ML) has enabled integration of information extracted from large data sets into clinical decision-making processes. For example, data from NGS-based molecular profiling and drug sensitivity experiments can help build predictive models to match an individual patient with the appropriate therapy. This is a key component of precision oncology, and although the universally applicable, unbiased models remain elusive, there have been some promising applications to optimizing enrollment in clinical trials.⁴⁸ Drug development is another area of translational research where ML has found success in terms of identifying potential druggable targets for modulating a disease state.⁴⁹

AI-based tools are in use or development for a number of tasks performed by MTBs and VMTBs, and as these efforts progress, more use of AI-driven technologies is inevitable. Biomedical literature remains a primary source of content to annotate and interpret cancer variants for supporting clinical decisions. However, it is impractical for biocurators, clinical researchers, and oncologists to keep up with the rapidly growing volume and breadth of information, especially those that describe the therapeutic implications of

TABLE 1. Selected Knowledgebases Containing Interpretations of Genomic Variants in Cancers

Resource Name	Primary Institute	VICC Member ^a	Cancer Focused ^b	Therapeutic Evidence	Predisposing Evidence	Diagnostic Evidence	Prognostic Evidence	Variant Emphasis	Data Access	Web Address
BRCA Exchange	GA4GH	X	X	X	X			Germline	Free	http://brcaexchange.org/
CanDL	Ohio State University/ James Cancer Hospital	X	X	X				Somatic	Free	https://candl.osu.edu/
CGI	Institute for Research in Biomedicine, Barcelona, Spain	X	X	X				Somatic	Free for noncommercial/research use	https://www.cancergenomeinterpreter.org/home
ClinGen Knowledge Base	ClinGen				X			Germline	Free	https://www.clinicalgenome.org/resources-tools/
CIVIC	Washington University School of Medicine	X	X	X	X	X	X	Majority somatic	Free	https://civcdb.org
ClinVar	National Center for Biotechnology Information			X	X			All variants	Free	http://www.ncbi.nlm.nih.gov/clinvar/
COSMIC Drug Resistance Curation	Wellcome Trust Sanger Institute	X	X	X				Somatic	Free for noncommercial/research use	http://cancer.sanger.ac.uk/cosmic/drug_resistance
Gene Drug Knowledge Database	Synapse	X	X	X		X		Somatic	Free	https://www.synapse.org/#/Synapse:syn2370773/wiki/62707
JAX CKB	The Jackson Laboratory	X	X	X	X	X	X	Somatic	Partial content free for noncommercial/research use	https://ckb.jax.org/
My Cancer Genome	Vanderbilt University		X	X	X	X		Somatic	Free for noncommercial/research use	https://www.mycancergenome.org/
OncoKB	Memorial Sloan Kettering Cancer Center	X	X	X				Somatic	Free for noncommercial/research use	http://oncokb.org/#/
Personalized Cancer Therapy Database	The University of Texas MD Anderson Cancer Center		X	X	X	X	X	Somatic	Free for noncommercial/research use	https://pct.mdanderson.org/#/home
PharmGKB	Stanford University			X				Germline	Free	https://www.pharmgkb.org/
PMKB	Weill Cornell Medical College	X	X	X	X	X	X	Somatic	Free	https://pmkb.weill.cornell.edu/
HGMD	Institute of Medical Genetics in Cardiff				X			Germline	Partial content free for noncommercial/research use	http://www.hgmd.cf.ac.uk

Abbreviation: CanDL, Cancer Driver Log; CGI, Cancer Genome Interpreter; CIVIC, Clinical Interpretation of Variants in Cancer; CKB, JAX Clinical Knowledgebase; COSMIC, Catalogue of Somatic Mutations in Cancer; GA4GH, Global Alliance for Genomics and Health; HGMD, The Human Gene Mutation Database; PharmGKB, Pharmacogenomics Knowledgebase; PMKB, Precision Medicine Knowledgebase; VICC, Variant Interpretation for Cancer Consortium.

^aVICC members are collaborating knowledgebases in the design and analysis of standards for representing interpretation knowledge.

^bCancer focused indicates that the knowledgebase primarily or exclusively describes interpretations of cancers.

biomarkers. The intrinsic complexity of biomedical text and vocabulary necessitates the use of sophisticated approaches including natural language processing (NLP) and ML to mine and biocurate clinically relevant information on drugs, genes, diseases, and therapeutic opportunities. A selected list of NLP and ML tools to aid in annotation and interpretation of cancer genomic variants is presented in [Table 2](#).⁵⁰⁻⁵⁷

Advancement of publicly available AI tools and the development of commercial software have the potential to propel VMTBs significantly. It is important to note that the exact nature of commercial systems is proprietary and that the degree to which they use NLP or other AI technologies cannot be verified in the public domain. However, AI text mining and data analysis are fundamental components of commercial sector curation of cancer variant knowledge, both for databases kept in-house by large laboratories and commercially available products. AI has also been deployed in systems that match a patient's genetic test results to eligibility for clinical trials, using NLP to mine databases such as the National Institute of Health's ClinicalTrials.gov, which rapidly updates information on > 300,000 clinical trials.⁵⁸

BARRIERS TO THE UTILIZATION OF NGS DATA AND AI APPLICATIONS IN VMTBs

Experts participating in VMTBs often communicate with oncologists to help determine appropriate treatment options for patients based on current scientific knowledge associated with their tumor molecular profile. Defining the clinical actionability of variants is perhaps the foremost challenge in the use of VMTBs. Randomized controlled trials (RCTs) remain the gold standard for proving treatment efficacy. However, it is impossible to conduct RCTs individually for all biomarker-treatment-cancer type combinations as a result of the tremendous overhead and small sample sizes. This has led to a number of new trial designs.⁵⁹ Umbrella trials, such as the I-SPY2 trial in breast cancer⁹ and the LUNG-MAP trial in lung cancer,⁶⁰ use a master protocol for a single tumor tissue type but multiple biomarkers and treatments. While the I-SPY2 trial uses gene expression array testing, the LUNG-MAP trial considers NGS and IHC biomarkers. Basket or bucket trials, in contrast, consider a biomarker-drug pair and multiple tumor types, such as the imatinib B2225 trial, which considered 40 malignancies with activation of specific tyrosine kinases and led to FDA approval for 4 of them.⁶¹ The MyPathway multiple basket trial showed that the combination treatment of pertuzumab and trastuzumab may prove to be beneficial in patients with *HER2*-amplified colorectal cancer, and this treatment is now included in the NCCN guidelines.⁶² The National Cancer Institute (NCI) MATCH and Pediatric MATCH trials have been described as hybrids between umbrella and basket trials because they consider multiple tumor types, biomarkers, and drugs.^{63,64} Thus, it is essential that results from these novel

designs be discussed in VMTBs as well as between researchers trained in the systematic review/evidence-based medicine paradigm and those trained as bioinformaticians or biocurators.⁶⁵

Several commercial entities market the prediction of clinically actionable mutations without the need for interpersonal dialog between genomic scientists and clinicians for routine patients.⁶⁶⁻⁶⁸ Moreover, novel clinical trial design and streamlined application of interpretation guidelines to assess the clinical actionability of cancer variants are insufficient when the variants are either too rare or there is no evidence for their match to a specific therapy. For example, only 17% of the first 5,963 patients in the NCI MATCH trial had an actionable mutation of interest (aMOI),⁶⁹ whereas only 29% of the first 422 patients in the NCI Pediatric MATCH trial had an aMOI.⁷⁰ One approach to address this issue is to assess variants in genes or proteins that are downstream of oncogenic alterations in a systematic, evidence-based way, thereby increasing the number of patients who may potentially benefit from targeted therapies.⁷¹ With larger gene panels and complete genome sequencing for each patient on the horizon, available curated resources may not provide the most sustainable variant interpretation. We may need to leverage more algorithmic approaches to alter the way we interact with variant interpretation resources.⁷²

As AI and ML technologies evolve and more tasks associated with VMTBs are undertaken by AI systems, it is likely that cancer variant interpretation will become more automated. However, there is a large gulf between a decision-support system and one that makes fully executable clinical decisions. For the foreseeable future, AI systems will support, but not replace, human curators, laboratory professionals, and physicians in directing personalized cancer treatment. A key to the progress of automated systems will be developing the means to evaluate their clinical performance. Standards for data accuracy and clinical utility of systems need to be developed so that the efforts of AI developers are clinically useful. It will also become important to quantify the additional time and workflow demands of larger NGS data sets to prove utility and feasibility of new AI-assisted VMTB tools that automate or expedite variant interpretation.^{46,72} In addition, the need for innovative data visualization methods to improve usability of molecular diagnostic reports and enable a more interactive and effective cancer variant interpretation experience for end users will become critical.^{73,74}

FUTURE DIRECTIONS

A multitude of efforts are underway to advance precision oncology, including novel trial designs that match a patient to the most appropriate therapy based on their tumor molecular profile (eg, I-SPY,⁹ NCI MATCH,⁸ TAPUR,¹⁰ SMMART⁷⁵), large genomic data sharing initiatives across country borders (eg, ClinGen²²), data standards

TABLE 2. Selected List of Useful NLP and ML Tools to Aid in the Annotation and Interpretation of Genomic Variants in Cancer

Name of the Tool	Purpose of the Tool	Data Source	Tool Availability	Web Address
CIViCmine	Extract clinically relevant variants and key biologic relations between a variant and its closely related entities: genes, diseases, and drugs	PubMed abstracts and PubMed Central open access full-text papers	Free Web-based	http://bionlp.bogsc.ca/cvicmine/
DiMeX	Extract mutation to disease associations	PubMed abstracts	Free Web-based	http://biotm.cis.udel.edu/dimex/
eGARD	Extract relations between genomic anomalies and drug response	PubMed abstracts	Free Web-based	https://research.bioinformatics.udel.edu/itextmine/integrate
PubTator Central	Provides automatic annotations of biomedical entities: genes, mutations, diseases, chemical, and species	PubMed abstracts and PubMed Central open access full-text papers	Free Web-based	https://www.ncbi.nlm.nih.gov/research/pubtator/
Linguamatics NLP platform	Allows search and retrieval of multiple data types and key relations between the data types, including genes, variants, diseases, drugs, toxicities, clinical laboratory tests, and so on	Multiple data sources including open access full-text medical literature, electronic health records, patents, news feeds, clinical trials, and proprietary content	Commercial with fee for service	https://www.linguamatics.com/products/linguamatics-natural-language-processing-platform
LitGen	Retrieve papers for a particular variant and filter them by specific evidence types used by curators to assess for pathogenicity	PubMed abstracts and PubMed Central open access full-text papers	Code freely available on GitHub	https://github.com/windweller/ClinGenML
LitVar	Allows search and retrieval of variants and key biologic relations between a variant and its closely related entities: genes, diseases, and drugs	PubMed abstracts and PubMed Central open access full-text papers	Free Web-based	https://www.ncbi.nlm.nih.gov/CBBresearch/Lu/Demo/LitVar/#?query=
Mastermind Search Engine	Genomics search engine that retrieves disease, gene, and variant data from millions of scientific articles and prioritizes them based on clinical relevance of the article's content	PubMed abstracts, open access full-text papers, and supplemental data of medical literature	Commercial: BASIC version free; cost associated with professional and/or enterprise versions	https://www.genomenon.com/mastermind

Abbreviations: ML, machine learning; NLP, natural language processing

and interoperability tools (eg, Global Alliance for Genomics and Health,⁷⁶ Fast Healthcare Interoperability Resources,⁷⁷ Substitutable Medical Applications, Reusable Technologies⁷⁸), and emerging academic and commercial tumor board technologies.^{16,79,80} These efforts will be aided by guidelines and standards for genomic testing and clinical interpretation of cancer variants. These will continue to evolve with new discoveries of biomarkers and treatments, especially those involving combinations of immuno-oncology, targeted, and chemotherapeutic agents. As AI and ML models improve and more data become available, some current implementation challenges will be addressed, including overfitting of data and lack of external validation. These developments within informatics, alongside high

standards for validation among clinicians and researchers, are crucial if ML-based technologies are to benefit future cancer care. Innovative and integrated digital approaches that leverage these advances, including VMTBs, will become critical to enable knowledge sharing among different institutions and standardize the use of patient-derived genomic data in clinical decision making. VMTBs have the potential to increase the breadth of resources accessed to interpret a patient case, bring local expertise to a global stage, and supplement the work of traditional MTBs and disease-specific tumor boards with extramural expertise. The VMTB model reviewed here can be a valuable approach to address the genomic variant interpretation bottleneck in the clinical context of cancer care.

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APPENDIX

Glossary of Terms

Resource or tool: Any module either on screen or in print that aids in interpreting a genetic variant.

Clinical grade: Term used to describe a high caliber of sensitivity, specificity, and reproducibility needed to confidently use a laboratory assay to ascertain clinical relevance from characteristics of a patient specimen.

Interpretation: A cumulative assertion about a variant or set of variants made by taking into account several pieces of genomic evidence.

Molecular tumor board (MTB): A group of people that collaboratively share expertise (eg, pathology, informatics, genetics, oncology) to provide clinical suggestions based on the results of molecular oncology testing.

Virtual molecular tumor board (VMTB): A group of people that collaboratively share expertise (eg, pathology, informatics, genetics, oncology) across multiple institutions using conference calls and/or online interfaces to provide assertions based on the results of de-identified molecular oncology testing.

Evidence: Literature or other primary scientific source that supports an assertion about a genetic variant.

Assertion: A statement pertaining to the clinical relevance of a variant that is supported by genomic evidence.

Classification: The assignment of a genetic variant into an organized grouping using criteria determined by various guidelines outlined by governing professional associations.

Next-generation sequencing (NGS): A broad term to describe many modern genomic sequencing techniques that incorporate a high throughput of data and massive parallel sequencing.

Precision oncology: The practice of understanding and treating cancer based on the presence or absence of actionable mutations and/or biomarkers within a patient tumor.

Immunohistochemistry (IHC): A protein staining technique used to determine expression characteristics of tissue by using antibodies to selectively illustrate the presence of specific proteins in tissue.

Fluorescent in situ hybridization (FISH): A technique that uses fluorescent probes to illustrate their position or abundance in the genome at a single-cell level.

VMTB case submission: The act by which a de-identified patient case is recommended for interpretation in a VMTB. Many case submission processes are facilitated by virtual means to ensure adequate information is provided by the requester. As an example, we have provided a link to the Vanderbilt-Ingram Cancer Center's Hereditary and Oncologic Personalized Evaluation Molecular Tumor Board Case Submission Portal (<https://redcap.vanderbilt.edu/surveys/index.php?s=FHWRA3M3T7>).

Health Insurance Portability and Accountability Act (HIPAA) compliance: Protection of identifiable patient information by de-identification and sharing only the information that is relevant to interpreting genomic data as outlined by the HIPAA of 1996 (<https://www.govtrack.us/congress/bills/104/hr3103>).

Predisposing: Characteristic of a mutation that increases the risk of developing a specific disease.

Diagnostic: Characteristic of a mutation that is associated with a specific disease or subtype of a disease.

Prognostic: Characteristic of a mutation that is associated with a favorable or unfavorable clinical outcome.

Predictive: Characteristic of a mutation that is associated with a predicted response to a specific therapy.

Oncogenicity: The ability of a genomic variant to drive development of cancer.

Actionability: Characteristic of a variant that informs a therapeutic direction whether by describing a therapeutic target or by informing the diagnosis or prognosis in a way that alters treatment options (Carr TH, McEwen R, Dougherty B, et al: Nat Rev Cancer 16:319-329, 2016).

Artificial intelligence (AI): A term used to describe computationally driven logic; includes concepts such as natural language processing and machine learning.

Natural Language Processing (NLP): A branch of AI techniques that use human readable text as logic-based matching criteria and/or machine learning criteria.

Machine learning (ML): A branch of AI techniques that logically or algorithmically assign a set of rules to a data set to allow the computing system to function with more accuracy.