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# Unveiling the Digital Evolution of Molecular Tumor Boards

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## Abstract

Molecular tumor boards (MTB) are interdisciplinary conferences involving various experts discussing patients with advanced tumors, to derive individualized treatment suggestions based on molecular variants. These discussions involve using heterogeneous internal data, such as patient clinical data, but also external resources such as knowledge databases for annotations and search for relevant clinical studies. This imposes a certain level of complexity that requires huge effort to homogenize the data and use it in a speedy manner to reach the needed treatment. For this purpose, most institutions involving an MTB are heading toward automation and digitalization of the process, hence reducing manual work requiring human intervention and subsequently time in deriving personalized treatment suggestions. The tools are also used to better visualize the patient's data, which allows a refined overview for the board members. In this paper, we present the results of our thorough literature research about MTBs, their process, the most common knowledge bases, and tools used to support this decision-making process.

## 1 Introduction

Precision medicine is a rapidly growing discipline, in which patients' genomic data are employed and integrated in the decision-making process and treatment finding. It has been proven to make notable achievements and advances in many fields, especially in oncology. Personalized oncology stands as a pivotal approach in contemporary cancer treatment, predicated on the premise that genomic biomarkers hold the key to tailoring treatment recommendations for individual

patients [1]. These biological metrics not only enable the prediction of individual disease risks, but also facilitate earlier disease detection while enhancing the precision and personalization of treatment selection. The Human Genome Project stands out as a flagship initiative driving the identification and development of these biomarkers, amplifying the efficiency of gene mapping, sequencing, and data analysis [2, 3].

Underpinning this approach is the assumption that cancer originates from somatically acquired mutations, essentially

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## Key Points

Molecular tumor boards (MTBs) have similar workflows, yet differ in organizational structure, remuneration and specialization with regional differences.

A digitalized MTB workflow implements standardization for streamlined decision-making and data harmonization for future cases and sharing across institutes.

Current support tools improve the digitalization of different phases of an MTB workflow, ranging from automated annotation to the support of a traceable digital collaborative workflow reducing manual efforts.

characterizing cancer as a genomic disease. The advent of DNA sequencing technologies, particularly next-generation sequencing, has revolutionized the comprehensive exploration of cancer genomes [4]. However, the proliferation of clinical laboratories offering tests for genomic biomarkers, alongside the extraction and subsequent discussion of pertinent data and information, introduces a potential complexity in the treatment decision-making process for physicians [5, 6]. The increased accessibility to genomic data may add layers of intricacy to the selection of optimal treatment paths, thereby necessitating a more discerning and informed approach by healthcare providers.

One specific event in which this is crucial is the advent of molecular tumor boards (MTB) in routine care, in which advanced cases of patients with cancer are not responding to the standard cancer therapies (radiation, chemotherapy, etc.) are discussed and a genetic-based treatment is offered when possible. The MTB process is very complex and requires the involvement of interdisciplinary stakeholders, including oncologists, radiologists, pathologists, bioinformaticians, genetic counselors and others. Each patient's case is discussed individually, and the different opinions are shared and discussed in a regular conference.

In this paper, we address the topic of MTB processes, including their definition, members, and digitalization, and describe the workflow used to derive a treatment suggestion. We also list some of the longest established MTBs in Germany and worldwide. We proceed to outline the used knowledge bases, various genetic analysis methods, and different digitalized tools.

## 2 Definitions, Workflow, and Team Players

### 2.1 Definition and Examples

#### 2.1.1 Definition

An MTB is a regular interdisciplinary meeting held by experts from various clinical fields to discuss challenging, individual cases of patients with cancer that are not responding to standard-of-care therapies. The main aim of an MTB is to assist in providing accurate and timely clinical interpretations of complex genomic results for each patient. All potential therapeutic strategies based on genetic analysis, molecular drivers of carcinogenesis, and actionable therapeutic targets from somatic variants of the tumor in question are identified. Involved individuals such as molecular pathologists, genetic counselors, oncologists, and others confer in a multidisciplinary manner to derive recommendations based on multiple factors including specific molecular modifications and the features of a patient (performance, status, comorbidities, etc). The recommendations are used

as a basis for trial screenings and cost coverage applications. Moreover, MTBs are used to clarify conflicting interpretations of clinical variants, and as educational tools in teaching hospitals and university clinics [7]. Furthermore, the composition of the board can be adaptive, accommodating additional specialists tailored to the specific disease under consideration, all with a singular focus: devising the most optimal treatment strategy for the patient at hand based on all available evidence. This embodies the convergence of expertise and technological advancements in the pursuit of individualized patient care.

The establishment of MTBs in an increasing number of medical institutions has garnered attention for their pivotal role in optimizing patient care [8]. Defined by Rao et al. in [9] as a mechanism designed to "aid in the delivery of accurate and timely clinical interpretations of complex genomic results for each patient, within an institution or hospital network," MTBs serve a critical function by amalgamating diverse expertise to dissect intricate patient cases, leveraging genetic insights gleaned from sequencing data [6].

#### 2.1.2 MTB Examples in Germany and Worldwide

MTBs are becoming more adapted in all regions of the world. However, each institution uses different approaches, processes, and methods. The reimbursement structures for MTBs are dependent on the specific framework conditions of the healthcare systems and the regulations of the health insurance companies. In Germany, MTBs are reimbursed by statutory health insurers through case-based flat rates and additional payments using billing codes for MTB specific services varying by service scope and complexity. Furthermore, MTBs receive funding from research projects to support the development of new diagnostics and therapies. [10, 11]

The reimbursement structure of the MTB in Japan differs depending on the institution and the type of services provided. Large and university hospitals receive fixed fees from the national health insurance, ranging from 5000 to 10,000 yen (35 to 70 euros) per session [12]. Specialized hospitals receive around 30,000 yen (210 euros) per patient for comprehensive genetic testing and 50,000–100,000 yen (350–700 euros) for advanced molecular profiling respectively [12, 13].

Compensation structures for MTBs in the USA are complex and vary by region, institution, and the specific set-up of the board (Table 1). MTB members are compensated for their participation (100–500 US dollars [USD] per session) depending on the location. Genomic testing often costs thousands of dollars, with partial coverage provided by health insurance. Additional funding from the state and pharmaceutical companies through research and clinical trial grants

further supports the development of new diagnostics and treatment options [14, 15].

In the following sections we list examples of a selection of MTBs in Germany and worldwide. Both the MTB Freiburg and Heidelberg have already been established for many years, with the former being one of the few to have published specific evidence numbers to date similar to the MTB at the Tohoku University Hospital in Japan. The latter initiated the MASTER program as a central program for patient stratification across different institutions. Augsburg represents a smaller MTB currently transitioning to a fully digitalized workflow while evaluating support tools mentioned in Sect. 5. The MTBs from Italy were selected because of their network approach between regional MTBs including virtual components. Further, MTBs in Finland and Denmark showcase the workflow in smaller countries, with their specialized approaches targeting specific cancer types and different organizational structures respectively. In contrast to Germany, Japan, and Europe, the MTB at UCSF represents the focus on innovation and private funding of most MTBs in the USA.

**MTB Freiburg (Germany)** In the context of the Comprehensive Cancer Center Freiburg (CCCF), a total of 22 interdisciplinary tumor boards have been established, each playing a pivotal role in orchestrating the precise and tailored therapeutic interventions required for patients [16–19]. Presently, the MTB at the CCCF comprises a complement of 35 proficient physicians and scientists. The attending physician plays a pivotal role as the facilitator in this framework, determining the eligibility of a patient for inclusion within the MTB. For prospective participants, the sole requisite is the provision of informed consent, thereby permitting the utilization of their clinical data for deliberations.

Predominantly, patients who gain admission to the MTB at the CCCF either

- have nearly exhausted conventional guideline-based therapies,
- exhibit limited tolerance to standard therapeutic options,
- or are afflicted by rare tumor entities, where established guideline-directed therapies are conspicuously absent.

In cases wherein patients are referred to the MTB, a comprehensive evaluation is undertaken by contributors within a span of 14 days, alongside an exploration of extant clinical options.

After this preliminary evaluation, the case is subjected to further assessment within the precincts of the MTB. Biomaterial samples are collected, and their molecular characteristics assessed. An incisive analysis is conducted to ascertain the congruence between the genetic mutations specific to the individual patient and the potential therapeutic modalities.

**Table 1** Differences between the individual MTBs in terms of structure and remuneration in the USA, Japan, Germany, Finland, Denmark and Italy

	USA	Japan	Germany	Finland	Denmark	Italy
Structure	Decentralized, variable by institution	Centralized, in large hospitals	Integrated into the health-care system	National network of cancer centers	Advisory, national network of cancer centers	Regionalized, network of cancer centers
Remuneration	Private insurance, various models	National health insurance, fixed fees	Statutory health insurance, flat rates per case	Public financing, uniform fees	Public health insurance, fixed fees	Regional health services, mixed financing
Evidence levels	–	C-CAT levels	NCT levels (Heidelberg, Augsburg)	–	Own	ESCAT, OncoKB
Tools	cBioPortal	ClinVar, OncoKB, gnomAD, COSMIC, CIViC	cBioPortal/MIRACUM-Pipe (Augsburg, Freiburg), Knowledge Connector (Augsburg, Heidelberg)	–	Locally populated knowledge databases	OncoKB
Meetings	Bi-monthly (MTB)	Weekly	Weekly	Weekly (+ ad hoc)	Bi-weekly/Weekly	Weekly–monthly

*C-Cat* center for cancer genomics and advanced therapeutics, *NCT* national center for tumor diseases, *ESCAT* european society for medical oncology scale for clinical actionability of molecular targets, *COSMIC* catalogue of somatic mutations in cancer, *CIViC* clinical interpretation of variants in cancer

The analysis workflow consists of many steps, starting with sequencing, a preprocessing phase, alignment, variant calling and annotation, analysis, and finalizing report generation and export to an external support tool (cBioPortal) [16, 19]. This process can extend over a period of up to 3 months.

Between 2015 and 2020, the MTB at CCCF has provided its guidance to a total of 1400 patients, encompassing almost 3000 distinct clinical cases over the 5-year period [20]. The multidisciplinary team of specialists has been able to provide 53% of the MTB patients with various personalized therapeutic recommendations, ranging from off-label therapy (61%), in-label (23%) to clinical studies (16%). Notably, these recommendations often venture into the realm of off-label usage, wherein approved pharmaceutical agents are repurposed within a divergent clinical context. An empirical analysis of patient outcomes from this approach has indicated a favorable response rate, with 8% of patients exhibiting positive responses to the recommendations [20].

**MTB Heidelberg (Germany)** The MTB Heidelberg is considered one of the most advanced in Germany. Two interdisciplinary tumor conferences are held on a weekly basis with experts from various medical disciplines, including thoracic surgery, pneumology, thoracic oncology, pathology, radiology, and radiotherapy [21–25]. These MTBs discuss various oncological disorders, such as dermatological, gastrointestinal, gynecological, and neurological tumors and many others [24]. Notably, Heidelberg features state-of-the-art molecular pathology methodologies, including next-generation sequencing (NGS), multiplex analysis, and liquid biopsy, with the aim to identify distinctive molecular alterations within patient samples. The identification of rare and unique genetic anomalies, on a case-by-case basis, presents an opportunity to furnish specialized therapeutic interventions either within the framework of clinical trials or through the off-label application procedure [23, 24].

At the National Center for Tumor Diseases (NCT) Heidelberg and Dresden, German Cancer Research Center (DKFZ), and the German Cancer Consortium (DKTK in Berlin, Essen/Düsseldorf, Frankfurt/Mainz, Freiburg, Munich, and Tübingen), the central program Molecularly Aided Stratification for Tumor Eradication Research (MASTER) was initiated. The main goal of this multidisciplinary platform is to stratify and classify patients with advanced rare cancers or incurable common tumors at early ages [22, 23]. An interdisciplinary team is involved, including physicians, biologists, study nurses, molecular oncologists, pathologists, documentalists, clinical, geneticists, investigators, and bioinformaticians. This team discusses registered patients' cases to identify novel treatment approaches based on whole-genome or exome sequencing (WGS/WES), RNA sequencing (RNA-seq) and DNA methylation profiling.

The MASTER program [26–31] is structured modularly:

1. **Fundamentals of clinical research and evidence-based practice:** This module introduces scientific methodologies, study designs, and the hierarchy of evidence.
2. **Systematic reviews and meta-analyses:** It covers the methodology for conducting and interpreting systematic reviews and meta-analyses, providing insights into how to aggregate and assess evidence.
3. **Critical appraisal and evidence synthesis:** Participants learn techniques for critically evaluating scientific literature and synthesizing findings to develop evidence-based guidelines.
4. **Special topics:** These are in-depth studies focusing on specialized areas such as pharmacology, oncology, and cardiology offering a detailed exploration of specific fields.

NCT derives treatment recommendations for the MTB discussions based on the tumor entity and four evidence levels as described in Table 2 to associate molecular biomarkers in patients' samples to drug responses [23].

During an MTB discussion, each patient case is presented individually and conferred in 8–10 min. The clinical history and the molecular alterations of the patient are first presented respectively by the handling physician as well as a clinical bioinformatician. Following the guidelines of the MASTER program, a level of evidence is assigned, a set of treatment options is concluded by the corresponding molecular oncologist, and the called variants are finally evaluated and classified by clinical geneticists taking into consideration the patient's personal and family history. At the end of the discussion, a report is generated containing a summary of treatment recommendations, disease course and previous therapy, alongside all supporting and opposing evidence [23].

**MTB Augsburg (Germany)** The Comprehensive Cancer Center Augsburg (CCCA) comprises 29 clinics, institutes, and establishments of the University Hospital Augsburg (UKA). It constitutes one of six pillars of the Bayerisches Zentrum für Krebsforschung (BZKF; others are Erlangen, two locations in Munich, Regensburg and Würzburg), as well as one of the four pillars of CCC and NCT WERA (Würzburg, Erlangen, Regensburg, and Augsburg). The MTB in Augsburg was created in 2018, and its structure was conceptualized based on MTB Freiburg. The conference takes place weekly on Wednesday, in which a multidisciplinary team consisting originally of four to five, and currently 10 to 15 specialists (molecular pathology, presenting physician, oncologists, human genetics, documentation, IT) discuss registered patients with cancer. On average, 230 patients are admitted each year following these criteria:

**Table 2** This table shows the NCT evidence levels with m1 (in the same entity), m2 (in various entities), m3 (preclinical), and m4 (biological rationale).

Evidence level	Description
Level 1 (m1)	Genetic variants with high evidence, mostly supported by clinical studies conducted in the same tumor entity. Variants that are recognized as relevant biomarkers for certain types of cancer through clinical studies or extensive scientific research. This information is usually anchored in national or international guidelines
Level 2 (m2)	Genetic variants with middle evidence. Variants that have been identified as potentially relevant in several studies but are not yet fully established in clinical practice
Level 3 (m3)	Genetic variants with lowest evidence. Variants that have been described as potentially relevant in individual studies or case reports but still require further research to confirm their clinical significance
Level 4 (m4)	In-depth molecular analysis of tumors, leading to the identification of new biomarkers and mutations that may be relevant for targeted therapies or experimental treatments

More information can be added to m1 and m2 evidence using suffixes (A: prospective study or meta-analysis, B: retrospective cohort or case-control study, and C: case study or single unusual responder) [23]

- malignant diseases (solid tumors and hematological neoplasms) with an absence of further standard therapeutic options,
- malignant diseases with no established therapy options,
- rare tumors or unusual tumor progress,
- young patients with cancer.

The MTB in Augsburg uses the Knowledge Connector for collaborative case preparation and the identification of biomarkers and cBioPortal for data sharing for external partners. Further, both tools are currently in evaluation for future usage. The classification of the patients and the therapy recommendations follow the evidence level guideline set by the MASTER program (Table 2).

**University of California (USA)** The MTB assembly at the University of California, San Francisco (UCSF) involves a diverse selection of healthcare providers, with clinical practitioners, researchers, graduate students, postdoctoral fellows, clinical fellows, and residents [32]. Moreover, healthcare providers affiliated with UCSF-affiliated hospitals are accorded opportunities for active participation in regularly scheduled MTB meetings, thereby fostering a cross-institutional discourse.

Patients eligible for enrollment in the MTB must have received a cancer diagnosis, accompanied by molecular profiling of their tumor specimen. It is noteworthy that the MTB's purview extends to pediatric cases, inclusive of malignancies across all age cohorts and spanning a spectrum of tumor types, even those characterized by an elusive primary origin. UCSF uses NGS panels, comprising over 500 genes, which includes germline analysis, microsatellite instability testing, and the evaluation of tumor mutational burden.

Within the MTB's operational framework, the UCSF tumor board convenes to deliberate upon a select subset of three to seven patient cases during each meeting. In

preparation for these deliberations, the requesting physician generates a concise clinical summary employing a standardized slide template disseminated by the MTB team. Subsequently, the pertinent test results are subjected to oral examination; in cases involving UCSF500 [33] results, the molecular pathologist responsible for endorsing the patient's report offers insights into the findings. Subsequently, one of the MTB's clinical experts expounds upon the clinical implications and utility of the findings, with a particular emphasis on addressing specific clinical queries. Following this presentation, the case is open for comprehensive discussion among the meeting attendees. Subsequently, a formal recommendation report is prepared and typically disseminated within a week of the MTB meeting.

**Tohoku University Hospital (Japan)** A retrospective observational study from September 2018 to January 2022 was conducted, focusing on Comprehensive Genomic Profiling (CGP) in patients afflicted with advanced solid tumors at Tohoku University Hospital and its affiliated medical institutions. The primary objective of this investigation was to extract comprehensive and granular data pertaining to patient demographics, a catalog of genetic alterations, and subsequent therapeutic recommendations. [13].

Patients enrolled in this study were those harboring advanced solid tumors or individuals anticipated to complete therapy after undergoing standard treatment regimens. Additionally, patients afflicted by rare neoplastic pathologies or those diagnosed with cancers of unknown primary origin (CUP), who had no recourse to established standard therapies, were deemed eligible for CGP testing before initiating treatment, thus rendering them suitable candidates for inclusion in this study.

The CGP tests administered were executed using approved in vitro diagnostic devices, grounded in NGS technology. By subjecting both normal and malignant tissues to the sequencing of 114 genes and discerning genetic

variations, the NCC Oncopanel was conceived in Japan. This innovative panel allows for the concurrent identification of somatic gene mutations, while also facilitating the confirmation of germline mutations.

It is noteworthy that the Japanese healthcare regulatory framework necessitates those cases undergoing CGP testing be subjected to deliberation within an MTB forum prior to the treating physician communicating the results to the patient. This requirement is met through the convening of a weekly MTB meeting at the originating institution, wherein a diverse cohort of at least ten oncology specialists convene. The attendees are made up from different subspecialties, including gastroenterology, breast oncology, urology, gynecology, and pediatrics. Furthermore, geneticists, genetic counselors, bioinformaticians, and other experts contribute their insights to these sessions. Although the attendance of attending physicians is mandatory, it is noteworthy that more than 50 physicians from external institutions also actively participate in these deliberations.

Within the MTB meetings, the treating physicians expound upon the patients' medical histories and general clinical conditions, paving the way for a comprehensive discourse regarding the potential therapeutic recommendations and the prospect of enrollment in clinical trials. Importantly, the MTB extends therapeutic recommendations to cases characterized by genetic alterations classified at level D or higher. Level D corresponds to cases wherein clinical reports have demonstrated therapeutic efficacy irrespective of the cancer type. Level E pertains to the preclinical stage of genetic alterations, whereas Level F denotes genetic variations with known implications in the realm of oncogenesis.

**MTB Italy** Italy currently hosts a total of 16 distinct active MTBs, representing a comprehensive network aimed at facilitating precision oncology initiatives. Notably, with a single exception, these MTBs have opted for a versatile approach, employing a mixed model that encompasses both virtual and face-to-face components, augmenting their accessibility and outreach [7].

Ciliberto et al. [34] published a commentary in 2022 summarizing a survey on different MTBs in Italy, conducted by the Alliance Against Cancer (ACC). It is evident that the ACC-MTB initiative is strategically evolving towards the establishment of a virtual MTB network characterized by a network topology akin to nodes and spokes. This network configuration mirrors non-redundant and cost-effective organizational paradigms commonly observed in healthcare management, optimizing resource utilization, and enhancing the dissemination of molecular oncology expertise.

More than half of the ACC members are engaged in the management of a diverse spectrum of solid and hematologic malignancies. Additionally, more than a third of these

members are responsible for addressing neoplastic conditions manifesting at various anatomic sites. Notably, the average MTB is composed of 9 staff members, with the majority, precisely 13 MTBs, with an attendance of more than 10 staff members during their meetings with permanent presence from medical oncologists. Their pivotal role encompasses the presentation of clinical cases, either following deliberations within organ-specific multidisciplinary panels or through direct clinical case presentations.

The scope of MTBs extends to cases undergoing NGS profiling as part of standard therapeutic regimens, thereby engendering a higher caseload. Consequently, the range of cases discussed within MTBs is broad and diverse. All MTBs undertake the administration of targeted NGS panels, with three MTBs further extending their diagnostic repertoire to encompass whole-exome sequencing and/or RNA sequencing methodologies.

In terms of diagnostic reporting and evidence-based frameworks, ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) [35] and/or OncoKB evidence levels assume prominence in the diagnostic reporting process. Notably, the majority of MTBs, specifically 11, offer a comprehensive written diagnostic report within a stringent time frame of 15 days conveyed to the patient by the attending oncologist.

**Finland tumor board** A multidisciplinary functional precision medicine tumor board (FPMTB) approach was implemented for acute myeloid leukemia (AML) patients [36]. Meetings involved comprehensive assessments, incorporating clinical history, diagnostic workup, ex vivo drug-sensitivity testing, whole-exome sequencing, and transcriptomics. Treatment recommendations primarily relied on drug-sensitivity testing, supplemented by clinical history and routine molecular diagnostics. The diverse FPMTB team convened regularly to analyze clinical, molecular, and functional aspects of consecutive AML patients, assigning risk groups, evaluating treatment options, and making recommendations for clinical trials.

FPMTB meetings embraced a comprehensive strategy encompassing thorough clinical patient history, diagnostic workup involving laboratory values, cytogenetics, and clinical mutation data, ex vivo drug-sensitivity testing with a panel of 515 anticancer drugs, whole-exome sequencing, and transcriptomics sequencing data.

Treatment recommendations by the FPMTB were predominantly grounded in drug-sensitivity testing outcomes, complemented by clinical history and routine molecular diagnostics, including flow cytometry, cytogenetics, FLT3-ITD, NPM1, IDH1/2, and WT1 mutation status. Genomic and transcriptomic data were utilized when available to enhance precision.

The FPMTB comprised the AML tumor group chair, clinicians managing the patients, clinical laboratory specialists, translational scientists knowledgeable in functional assays and multiomics data, bioinformaticians, study nurses, and a genetic counselor for actionable germline variants, available by referral. Meetings were scheduled weekly, with ad hoc sessions as needed, ensuring timely discussions within one week of patient sampling.

The FPMTB's primary objective was to comprehensively evaluate clinical, molecular, and functional characteristics of consecutively diagnosed or relapsed/refractory (R/R) patients with AML. This included risk stratification, assessment of standard-of-care options, initiation of relevant clinical trials, and ongoing analysis of treatment responses. For R/R AML cases, the board evaluated candidate drugs for on- or off-label treatment, based on drug sensitivity and resistance testing (DSRT) and other profiling data. The FPMTB also played a crucial role in recommending bridging to allogeneic hematopoietic stem cell transplantation (alloHSCT).

**Danish MTB** Established in the year 2013, the Danish National Molecular Tumor Board (DN-MTB) operates with the utilization of comprehensive molecular data, including information derived from whole exome/genome somatic DNA sequencing, copy number alterations (CAs), and RNA expression and sequencing. A minority of cases undergo analysis using expansive commercial gene panels, ranging from 161 to over 500 gene coverage [37].

The primary objective of the DN-MTB is to provide expert advice on tailored treatment strategies based on the unique molecular profiles of individual patients with cancer. Furthermore, the DN-MTB aims to propose supplementary molecular analyses deemed relevant for a comprehensive understanding of the patient's condition, such as germline investigations. Also, the DN-MTB serves as a platform for the exchange of experiences among experts, fostering discussions on druggable genomic variants/profiles and targeted treatments. It is explicitly outside the scope of the DN-MTB to offer recommendations or priorities for standard treatments, recognizing the focus on personalized therapeutic approaches. Also, the DN-MTB does not engage in the conclusive decision-making process for individual patients' treatment plans. Instead, it functions in an advisory capacity, leaving the final decisions to the treating medical professionals.

## 2.2 Members and Roles

Given the complexity of cancer diseases, fostering interprofessional exchange beyond the confines of individual medical specialties is imperative to gain fresh insights and offer

patients the best possible care. Luchini et al. [7] describe the current state of MTBs globally through a systematic review-based approach using 40 studies with 6303 MTB cases. Using the gained information, they were able to provide a list of different professional figures that should contribute to MTB discussions. The evaluation showed that in any case oncologists and pathologists must participate in the MTB process. Further, geneticists make an important contribution to the discussion and result finding. Bioinformaticians can play an important role, especially if germline mutations are also to be considered. As soon as large amounts of molecular data are to be interpreted, the support of molecular biologists is useful. The expertise of oncology pharmacists, bioethicists, or scientists/physicians with a solid molecular background can also be supportive. If drugs are proposed or recommended for clinical trials at the end of the MTB process, the participation of a research/clinical trials coordinator may be beneficial [7].

In general, due to the usage of NGS, the inclusion of participants from increasingly technical disciplines is required. Therefore, van der Velden et al. [38] recommend five groups of members of an MTB. Depending on the case and cancer type this comprises clinicians, e.g., oncologists, hematologists, from the appropriate various disciplines. Similar to the MTB study as described above, the second member group describes pathologists and molecular pathologists respectively. The third group includes clinical molecular biologists. It is stated that the corresponding gathered sequencing data determines the necessity of the fourth group, geneticists, and the fifth group, bioinformaticians. Both are usually required when conducting germline testing, their interpretation and subsequently developing experimental treatment options.

Further, additional training is recommended for involved parties regarding the usage of genetic and sequencing techniques. Schickhardt et al. and Merry et al. [39] state that an MTB meeting requires a predefined leader or moderator who acts as a supervisor, organizer, and spokesperson for third parties. The leader should be responsible for the selection of MTB members and their areas of responsibility while factoring in a level of trust in the results of each participant. The patient's physician is responsible for the inclusion of the patient in the MTB, e.g., through a presentation of the case in the MTB meeting. Yet, while communicating and staying informed about MTB meetings and their decisions, it is stated that they should not be a direct participant of the MTB, since their understanding of each discipline is limited and therefore dependent on the decision [39, 40]. Physicians interested in this collaborative approach can engage in individual interactions through the network's diverse service offerings or participate in a wide range of training and educational events.

Toward the culmination of the MTB process, wherein drug recommendations or clinical trial proposals are

deliberated, the involvement of a research/clinical trials coordinator can be instrumental in facilitating seamless transitions from discussions to actionable plans. Luchini et al.'s comprehensive study emphasizes the indispensability of this multifaceted expertise, highlighting the intricate interplay of various specialized roles within MTBs, ultimately fostering comprehensive and informed decision-making in precision oncology [7].

### 2.3 Workflow

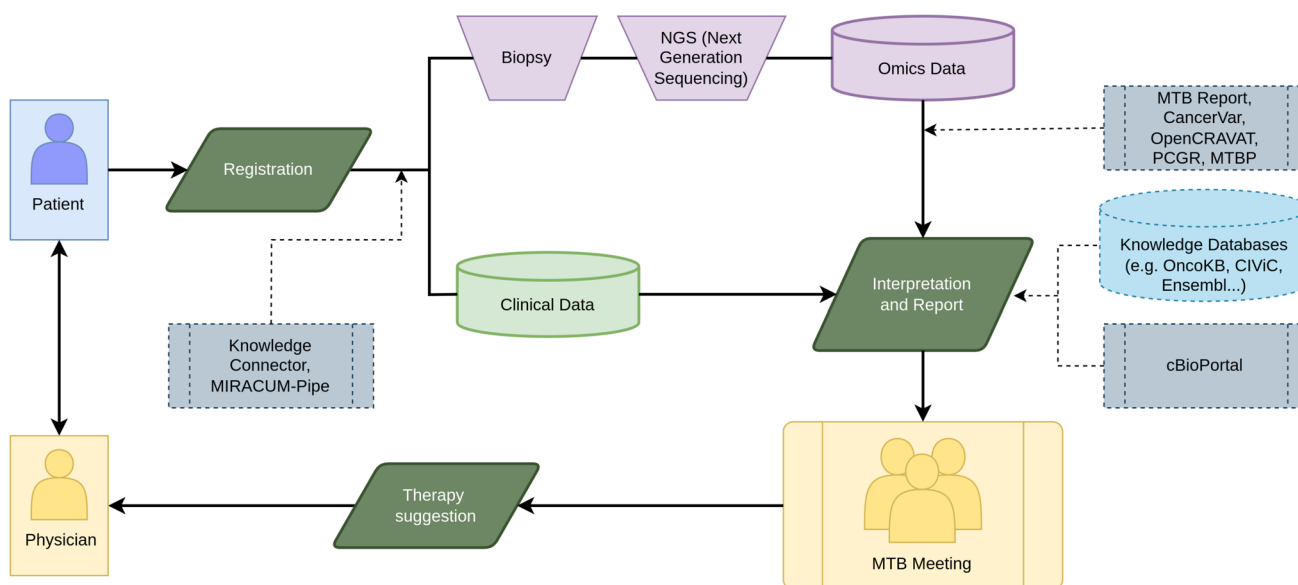
A simple MTB workflow (see Fig. 1). consists of the following steps [41]:

1. Eligibility screening.
2. Registration of a patient in the MTB, directly or through the handling physician. Patient's personal and family history are shared with the MTB.
3. A tumor biopsy is taken from the patient, and the DNA is extracted.
4. An NGS method is used to identify characteristic modifications.
5. Specific variants of the analyzed NGS data are called.
6. Resulting information is interpreted and associated with potential treatments and clinical trials.
7. A comprehensive clinical report containing all findings is created.

8. MTB is held to discuss the case and suggest a specific treatment.
9. The suggestion is exchanged with the handling physician and carried out.
10. Follow-up

The workflow delineated by Rao et al. in [9] elucidates the intricate process underlying MTBs and their virtual counterparts (VMTBs). Initially, following an initial eligibility screening, a tumor sample procured by the treating physician serves as the foundation for a clinical next-generation sequencing (NGS) assay conducted by the clinical laboratory. Subsequently, the results are shared and evaluated in conjunction with local expertise and available resources. Should local expertise prove insufficient for robust clinical recommendations, genomic variants of clinical significance are prioritized, and patient data undergo de-identification. This de-identified data is then shared among VMTB members from multiple institutions, who leverage their collective resources and expertise to collectively formulate recommendations tailored to the patient's needs.

Nevertheless, the influx of information poses a significant challenge for stakeholders engaged in both the MTB and VMTB processes, impeding the ability to sift through and discern crucial insights. To address this challenge, supplementary methodologies, including natural language processing (NLP) and machine learning, are being employed to extract and summarize clinically relevant information



**Fig. 1** The classic MTB workflow. A patient is first registered directly or through a handling physician to an MTB. A biopsy is taken from the patient, from which the DNA is extracted and sequenced. Results are analyzed, annotated, and presented alongside patient's clinical data to the MTB board. A therapy is suggested to the handling physician. The presented tools and knowledge databases in Sects. 3 and 5

with their corresponding starting points in the workflow are shown in gray and light-blue respectively. The Knowledge Connector and the MIRACUM-Pipe aim to integrate the complete workflow, while the knowledge databases, cBioPortal, and the other tools are mainly used for interpretation and report generation, with the latter focusing on pipelines

from biomedical literature. Further, Hamamoto et al. and Rodriguez Ruiz et al. suggest models for the prediction of significance for genetic abnormalities, continual learning, in addition to supervised and unsupervised learning approaches for disease onset predictions and patient stratification respectively [9, 12, 42]. Rao et al. underscore the potential of machine learning in integrating information effectively into clinical decision-making, advocating its use in constructing predictive models to identify personalized therapies for individual patients. These models encompass potential targets for modulating disease states, thereby influencing drug production [43].

### 3 Knowledge Databases

The objective behind the systematic profiling of characteristic genetic alterations in cancer is personalized medicine. For example, individual patient-oriented therapy decisions can be made from genetic mutations to treat the disease in a targeted manner. In addition, side effects are also to be avoided. Thus, in personalized medicine, genomic data are generated using methods such as NGS, which are subsequently discussed and debated at MTBs to determine a targeted therapy [44, 45]. Some of these MTBs use tools that use different knowledge bases (see Table 3), which will now be presented.

#### 3.1 OncoKB

OncoKB is a curated database developed and maintained at the Memorial Sloan Kettering Cancer Center for Precision Oncology. It includes the biological and clinical implications of genetic variants in cancer as a clinical decision support system. Their annotations include therapeutic, diagnostic, and prognostic significance of somatic molecular alterations and, therefore, provide detailed information about biological and potential oncogenic effects of specific gene changes found in cancer cells. Furthermore, OncoKB supplies treatment implications based on the level of evidence of specific molecular alterations. All available information is organized hierarchically by gene, alteration, tumor type, and clinical significance and uses a newly developed classification system of evidence level. The levels of evidence are derived from US Food and Drug Administration (FDA) labeling, scientific literature, expert group recommendations, and National Comprehensive Cancer Network (NCCN) guidelines. OncoKB currently lists over 7500 genetic variants in over 800 cancer-associated genes from over 130 tumor types. Those resources are accessible through their openly accessible web resources, queries to their API, or integration into cBioPortal. OncoKB is available as a commercial, and open-source license for academic use [46].

**Table 3** An overview of knowledge databases including their access methods, updates, and the number of entries

Database	Developer/Institution	Access	Entries	Maintenance
OncoKB	Memorial Sloan Kettering Cancer Center	<a href="https://www.oncokb.org/">https://www.oncokb.org/</a>	> 7500 variants	Regular (06/2024)
CIViC	WUSM, St. Louis	<a href="https://civicdb.org/">https://civicdb.org/</a>	> 3500 variants	Regular (06/2024)
Ensembl	EBI	<a href="https://www.ensembl.org/">https://www.ensembl.org/</a>	> 10 million variants (structural)	Regular (05/2024)
Reactome	OICR, NYULMC, EMBL-EBI	<a href="https://reactome.org/">https://reactome.org/</a>	> 2700 human pathways	Regular (06/2024)
My Cancer Genome	Vanderbilt–Ingram Cancer Center	<a href="https://www.mycancergenome.org/">https://www.mycancergenome.org/</a>	> 16,800 biomarkers	No update since 2021
TARGET	Dana–Farber Cancer Institute	Commercial platform	> 135 manually curated genes	Regular
GDKD	Fred Hutchinson Cancer Research Center, Seattle	Not public	> 700 gene–drug interactions	Not updated since 2015
ClinVar	NCBI	<a href="https://www.ncbi.nlm.nih.gov/clinvar">https://www.ncbi.nlm.nih.gov/clinvar</a>	> 1.5 million variants	Regular
BRCA Exchange	ENIGMA consortium	<a href="https://brcaexchange.org/">https://brcaexchange.org/</a>	> 27,400 BRCA 1/2 variants	Regular (01/2024)
GnomAD	ExAC	<a href="https://gnomad.broadinstitute.org/">https://gnomad.broadinstitute.org/</a>	> 730,947 exomes/ > 76,215 genomes	Regular (05/2024)
NCBI SNP Database	NCBI	<a href="https://www.ncbi.nlm.nih.gov/snp/">https://www.ncbi.nlm.nih.gov/snp/</a>	> 2 billion submitted SNP	Regular

WUSM Washington University School of Medicine, NCBI National Center for Biotechnology Information, EBI European Bioinformatics Institute, OICR Ontario Institute for Cancer Research, NYULMC New York University Langone Medical Center, EMBL European Molecular Biology Laboratory, ExAC Exome Aggregation Consortium

### 3.2 CIViC

Clinical Interpretation of Variants in Cancer (CIViC) is an expert-led and crowd-sourced knowledge base that provides clinical interpretation of cancer variants developed and maintained by the Washington University School of Medicine St. Louis (WUSM). The therapeutic application and predisposing significance of inherited and somatic variants of all types are informed by open-source code, freely available content, public application programming interfaces (APIs), and provenance of evidence. The goal is to ensure the transparent generation of up-to-date and accurate variant interpretations for use in precision medicine in cancer [47, 48]. It is freely available and accessible through the official website [49].

### 3.3 Ensembl

Ensembl is a freely available database of genomic data and annotation created and maintained by the European Bioinformatics Institute (EBI). The database provides annotations on genome assemblies from public archives, including genes, regulatory regions, variants, and comparative data for scientific research and genome interpretation in various species. Ensembl released a new website for genomic data research. With it, the aim is to create a regularly updated handbook, available alongside the website [50], describing the data available and how to access it. The data can be directly accessed on the website, through an API, or downloaded as files [50–52].

### 3.4 Reactome

Reactome is an open source, freely accessible database in which the pathways and relationships of signaling and metabolic molecules are organized as biological pathways and processes developed by a collaboration of the Ontario Institute for Cancer Research, Cold Spring Harbor Laboratory (OICR), New York University School of Medicine (NYULMC), and the EBI. It is an online, open-source, curated database containing knowledge on metabolic and signaling pathways and reactions in human biology [53]. Reactions are considered basic units, consisting of reactants and products (proteins, nucleic acids, complexes, small molecules, etc.). Reactome also offers a set of bioinformatics tools, such as the Pathway Browser. It enables visualization, interpretation, and analysis of this knowledge for basic and clinical research, genome analysis, modeling, systems biology, and education [54, 55].

### 3.5 My Cancer Genome

My Cancer Genome is designed for precision cancer medicine for physicians, patients, caregivers, and researchers by the Vanderbilt-Ingram Cancer Center. This knowledge resource contains, in addition to available clinical studies, information on the therapeutic effects of mutations that promote cancer growth, which were not updated since 2021. It provides manually curated and maintained content on genes and alterations, diseases, drugs, and pathways [56]. My Cancer Genome matches tumor mutations with therapies, making information conveniently accessible [57]. For all genetic variant and expression biomarkers, individual biomarker pages are generated and linked to other entries, such as diseases, curated clinical trials, and therapeutic assertion [56].

### 3.6 TARGET

Therapeutically Applicable Research to Generate Effective Treatments (TARGET) is a commercial database from the Dana–Farber Cancer Institute that contains genes somatically altered by cancer and the corresponding direct clinical impact. TARGET genes are linked to open-source resources to derive rules such as clinical and biological relevance of somatic variants, additional biologically significant pathways and gene sets, and demotion of variants based on uncertain significance. In addition, response or resistance to therapy can be predicted, prognosed, and/or diagnosed [58].

### 3.7 GDKD

Gene Drug Knowledge Database (GDKD) is a structured database with standardized terminology and linkage to PubMed identifiers. Tumor types, genes, variants, and drug response/resistance patterns are described in GDKD. Predictive biomarker-drug associations are described that are linked to drugs or that are described in national guidelines associated with specific therapies. These associations are then classified hierarchically [59].

### 3.8 ClinVar

Maintained by the National Center for Biotechnology Information (NCBI) within the National Library of Medicine (NLM) at the National Institutes of Health (NIH), ClinVar is a freely available archive containing human genomic variants and interpretations of their conditions and diseases' relationships [60]. It describes relationships between human variations and phenotypes with reports. The database contains variants from patient samples, claims about their clinical significance, information about the submitter. It relies on data submissions, and its scope is limited to variants that have been interpreted for clinical or functional significance,

not merely observed. The submission follows special criteria and regulations both on the submitter and the data. It currently holds more than 3 million submitted records and over 1,5 million variants and can be accessed through their official website [61].

### 3.9 BRCA Exchange

The BRCA Exchange database project [62] provides information on cataloged BRCA1 and BRCA2 genetic variants by combining information from existing databases. By default, it shows variants that have been curated and classified by the ENIGMA consortium, to assess their pathogenicity. Optional settings allow the user to look at unclassified variants. In most cases, these variants are awaiting expert review, and their pathogenicity has not yet been established. [63]

#### 3.9.1 gnomAD

The Genome Aggregation Database (gnomAD) [64] is a database established by an international consortium of researchers known as the Exome Aggregation Consortium (ExAC). Its primary aim is to aggregate and standardize exome and genome sequencing data from a broad spectrum of extensive sequencing initiatives including allele frequency, per-base expression levels, constraint scores, and variant co-occurrence [64]. The v4 data set (GRCh38) available on this website contains 730,947 exome sequences and 76,215 whole-genome sequences derived from unrelated individuals of diverse ancestral backgrounds. These sequences were obtained through various disease-specific and population genetic studies [64].

#### 3.9.2 NCBI SNP database

The Single Nucleotide Polymorphism database (dbSNP) [65] is a variation database at the National Center for Biotechnology Information (NCBI). This repository of polymorphisms consists of single-nucleotide substitutions, small-scale insertions or deletions spanning multiple bases, and insertions of retroposable elements as well as microsatellite repeat variations, specifically short tandem repeats. Each entry within the dbSNP database is accompanied by detailed information including the sequence context of the polymorphism, the allele frequency of the polymorphism, and descriptions of the experimental methods, protocols, and conditions employed to detect and characterize the variation. dbSNP accepts submissions for variations in any species and from any part of a genome.

## 4 Data Analysis Methods

In order to perform precision oncology, various methods of analysis are used. In the field of individualized cancer treatment, revolutionary advances in genomics have opened new possibilities. Systematic profiling of characteristic genetic alterations in cancer is now possible. Mutated proteins can arise from these genomic alterations, which in turn provide the target for individualized targeted cancer therapy. Therefore, it is important for the treating physician to have knowledge of mutations, chromosomal rearrangements, copy number alterations, or epigenetic changes [66].

In the field of genomics, there are now many approaches and technologies so that characteristic changes in cancer can be detected. These include comparative genomic hybridization; chromatin immunoprecipitation, massively parallel sequencing, fluorescent in situ hybridization, immunohistochemistry, polymerase chain reaction, RNA sequencing, single-nucleotide polymorphism, targeted sequencing, whole-exome sequencing, and whole-genome sequencing [66, 67].

Initial approaches to cancer gene sequencing were performed by amplification of exonic regions of specific genes. For this purpose, the polymerase chain reaction (PCR) was used first, followed by capillary devices. Sanger sequencing is considered the gold standard of molecular diagnostics and is used to study gene mutations and insertions/deletions (indels). However, since it is insensitive to change, there are now newer sequencing technologies that offer higher sensitivity. For analysis, the entire coding sequence does not need to be interrogated to identify the major activating mutations. Technologies used for this purpose include mass spectrometric genotyping and allele-specific polymerase chain reaction. For the assessment of cancer driver events other technologies like array comparative genomic hybridization and fluorescent in situ hybridization have been implemented in clinical and molecular diagnostic laboratories. To have a technology that can identify all the plausibly actionable genetic alterations at once, powerful DNA sequencing technologies emerged since 2005. With these next-generation sequencing technologies, unprecedented depth and breadth of genomic interrogation is possible [66]. NGS data are stored in sequence alignment format (SAM) and its compressed counterpart (BAM). There is also the CRAM format as another compressed alternative to SAM/BAM [67].

## 5 Digitalization and Available Tools

### 5.1 Virtual Molecular Tumor Boards (VMTBs)

Virtual molecular tumor boards (VMTBs) represent the development of leveraging collaborative knowledge beyond the confines of individual local hospitals or institutions, facilitating information sharing and communication among diverse organizations as a clinical decision support system. In contrast to traditional MTBs, VMTBs are defined as “an online forum for collaborative governance, provenance, and information sharing between experts outside a given hospital network with the potential to enhance MTB discussions” by Rao et al. [9].

The data utilized within VMTBs are drawn from multiple sources, including crowd-sourced data, expert-curated genomic assertions, and the integration of artificial intelligence. This amalgamation encompasses information derived from both in-house repositories and publicly available resources such as knowledge bases, bioinformatics

tools, expert consensus criteria, or databases documenting ongoing clinical trials [68]. These diverse data sources are needed for supporting extended tasks within VMTB discussions, ranging from diagnosis to the exploration of therapeutic options. The harmonization of these varied data types into comparable datasets is pivotal, requiring standardization to ensure uniformity, as emphasized by the need for standardized similar units resulting in comparable datasets [9].

Data harmonization requires planning, either prospectively—predefining data collection and management protocols—or retrospectively merging data from disparate sources. Moreover, the interoperability of tools and systems is crucial for seamless execution, communication, and data exchange [69]. This interoperability enables the transformation of data from multiple sources, fostering the ability to query, view, and analyze comprehensive datasets.

In the following section, we present eight tools used to support MTB discussions and therapy finding. The selection of the following tools highly depends on established processes, data sharing options and integration into the

**Table 4** Overview of different MTB supporting tools. The table lists the most important information needed to use the various listed tools

Tool	Input	Processing	Knowledge bases	Output	URL	Refs.
cBioPortal	CNV, expressions, clinical data etc. as meta and data files (TSV)	MIRACUM-Pipe: processing of aligned omics data variant calling, annotation/ analysis	OncoKB CIViC MyCancerGenome	Visualization reports	<a href="https://cbioportal.org">https://cbioportal.org</a>	[70, 71]
KC	SNVs, indel, CNV, SV, gSmVs, Fusion, RNA, etc.	NGS collaboration	OncoKB CIViC Ensembl Reactome	Word document with an MTB report	–	[44, 72, 73]
MTB Report	SNVs, CNV, gene fusions, cancer type	Actionable variant filtering	GDKD CIViC TARGET	Actionable variants, gene–drug predictive associations	<a href="https://mtb.bioinf.med.uni-goettingen.de/mtb-report/">https://mtb.bioinf.med.uni-goettingen.de/mtb-report/</a>	[74–78]
MTBP	SNVs, small indels	Predictive relevance analysis, variant annotation	In-house DBs ClinVar BRCA-Exchange OncoKB CIViC	HTML report	<a href="https://mtbp.org">https://mtbp.org</a>	[1, 35, 79]
CancerVar	CNV, exon variants, indels	Map variants to genome, annotate variants/genes	OncoKB CIViC metaKB	Variant interpretation (clinical significance)	<a href="https://cancervar.wglab.org">https://cancervar.wglab.org</a>	[80]
OpenCravat	Unannotated VCF, TSV/CSV, dbSNP, 23andme	Annotation, mapping	ClinVar PharmGKB CIViC Multiple extensions	Visualization VCF	<a href="https://www.opencravat.org">https://www.opencravat.org</a>	[81]
PCGR	SNVs, indels, CNAs	Variant/allele-specific annotation, functional, prediction of MSI status, mutational signature estimation	DoCM DGIdb CIViC	Interactive HTML report	<a href="https://sigven.github.io/pcgr">https://sigven.github.io/pcgr</a>	[82]

CNV copy number variation, SNV single nucleotide variants, VCF variant call format, can copy number alteration, TSV tab separated values, CSV comma separated values

infrastructure. Table 4 also highlights the main information needed to use these tools, including input, output, processing method, and integrated knowledge databases.

## 5.2 Available Tools

### 5.2.1 cBioPortal

Using cBioPortal, an overview of genomic alterations in a number of patients and cancer types can be obtained, survival analyses can be performed, and group comparisons can be made. Own data can be analyzed with cBioPortal as well. cBioPortal uses OncoKB, CIViC, and MyCancerGenome to support decision-making participants in MTBs [70].

cBioPortal for Cancer Genomics is a tool for multidimensional cancer genomics datasets and can be explored interactively. In addition, cBioPortal provides access to molecular profiles, clinical features from large-scale cancer genomics projects, and visualizations. This allows the previously mentioned large datasets to be used clinically. cBioPortal curates data directly from the TCGA Data Coordinating Center and from literature. In addition, researchers are asked to provide additional data in special cases. For consistent annotation, mutation calls are processed through an internal pipeline with prior knowledge on variants and clinical utility [70].

### 5.2.2 MIRACUM-Pipe

MIRACUM-Pipe is a workflow developed to analyze and annotate NGS data used in an MTB. It uses different individual tools to perform quality control and alignment, call variants, estimate copy number variation, evaluate complex markers, and detect RNA fusion. It acts as a standardized solution to support the different steps of an MTB including additional modules for data import, clinical analyses, visualization, and report generation [71]. Using the current model, three types of analysis are supported: WES, targeted NGS (tNGS), and tumor-only analysis. The workflow is dockerized (MIRACUM-Pipe-Docker) and therefore allows for a fast deployment. The report generated using the pipeline can be imported into cBioPortal and visualized. The pipeline can also be adapted for more individualized usage by integrating or merging future databases, analysis tools and workflows [71].

### 5.2.3 Knowledge Connector

The Knowledge Connector (KC) summarizes information on the effect of mutations on the protein, an assessment of oncogenicity, drugs targeting the specific variant or gene, and signaling pathways involving the gene [72]. The KC links genomic data with in-house clinical data and information from knowledge bases, such as CIViC, Ensemble,

OncoKB, and Reactome. In this way, the KC supports the MTB members in maintaining and exchanging the collected knowledge collaboratively. In addition to gene-based biomarkers, the KC can also be used to represent more complex biomarkers. This allows therapy recommendations to be documented and evidence-based evaluations to be concluded. All this information can be displayed in presentation mode as part of the MTB, and an MTB report can additionally be exported [73].

### 5.2.4 MTB-Report

MTB-Report is a platform for automated interpretation of genomic data and the reporting of treatment options based on public knowledge [74–77]. The application covers two areas. First, it provides a web interface to manually prepare patient data for an MTB. On the other hand, large data sets can be processed for further analysis. For MTB-Report, genomic input data are matched with databases such as GDKD, CIViC, OncoKB, or TARGET. These are specialized on cancer predictive biomarkers. MTB-Report also allows the results to be downloaded as a PDF or CSV report. It is important to note that MTB-Report does not provide treatment suggestions but serves solely as a reporting tool. The quality of the resulting information depends strongly on the quality of the databases provided [78].

### 5.2.5 MTBP

Unlike MTB-Report, the MTB-Portal is a clinical decision support system. MTB-Portal is used for clinical trials, including selection of candidates for the Basket of Baskets study, a modular, multi-arm study for genomically defined populations. The MTB-Portal automates the collection, interpretation, and reporting of “-omics” data by providing reports including annotations of the uploaded gene variants (single-nucleotide variants [SNVs] and indels) [1]. The results from the MTB-Portal are provided in a structured HTML report. Here, the variants are classified in three tables according to their functional relevance based on the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS). MTB-Portal uses several knowledge bases created by international initiatives and whose content is open to academic research. These are ClinVar, BRCA Exchange, OncoKB, and CIViC. However, the content of the knowledge databases is not updated automatically, as the content is always manually downloaded periodically [79].

### 5.2.6 CancerVar

CancerVar is a tool that utilizes statistical methods and machine learning to automatically analyze genetic changes in cancer cells. The platform provides detailed information

for variants, including all automatically generated criteria, supporting evidence, and predictive scores for clinical significance. Users can also manually adjust criteria and perform reinterpretation based on their prior knowledge or experience. CancerVar includes quality control for somatic variants, an adjustable scoring system for clinical evidence criteria, a semi-supervised deep-learning model, and the generation of reports. However, CancerVar has a few limitations. It depends on high-quality data and requires extensive integration with powerful hardware due to the integrated predictive models. While a few copy number alterations (CNAs) have emerged as important biomarkers for disease characterization, there is a lack of a specific database for clinically actionable somatic CNAs. It is also worth noting that CancerVar cannot interpret inversions or gene fusions, nor can it process indels due to the vast number of possible variations. [80]

### 5.2.7 OpenCRAVAT

The Open Custom Ranked Analysis of Variants Toolkit (OpenCRAVAT) is an open-source platform for genomic analysis. OpenCRAVAT acts as a central web-based platform with a graphical and command-line interface, which is extensible through modules for the integration of different databases and various genomic analyses including reference genomes. This allows for a more complete analysis of genomic data. Additionally, researchers have the ability to customize and develop their own modules and pipelines to their specific needs, providing a more efficient and effective analysis. While OpenCRAVAT is a powerful tool for genomic analysis, it may be subject to overload when handling large amounts of data. This can result in slower analysis times and a decrease in performance. [81]

### 5.2.8 PCGR

Personal Cancer Genome Reporter (PCGR) is a software package for annotation of somatic variants provided standalone and open-source by Nakken et al. PCGR enables not only variant sequence annotation, but also allele-specific annotation for precision oncology and functional and cancer-specific annotation of genes. This can end up with predictions of microsatellite instable (MSI) status, estimates of mutation signature contributions, and a comprehensive summary HTML report. [82]

## 6 Summary and Outlook

Despite the promising outlook regarding MTBs, the real-world evidence regarding their efficacy is still limited due to the lack of randomized controlled real-world studies.

Multiple studies have demonstrated or are currently in progress, that show an improvement in progression-free survival rate (PFS) [83]. The WINTHER trial (2019) [84] shows the usage of genomic and transcriptomic profiling in improving therapy recommendations, yet failed to meet its primary endpoint with a 22.4% PFS rate. Further, the SHIVA trial (2015) as the first randomized study for precision medicine found no improvement in PFS [85], which was later shown to apply only to certain cases [86]. However, real-world evidence of already published MTB trials [83, 87–89] show that matched recommendations from MTBs have longer PFS compared with unmatched therapies. Overall, while there is increasing evidence of the efficacy of MTBs, to ensure timely and increased access to recommended treatments for patients, standardization, broad biomarker analyses, and increased availability are key for the future use and development in precision medicine.

In this paper, we presented the current state of MTBs in Germany and worldwide with their workflows, support tools, and integrated knowledge databases. The institutions have either adopted or are in the process of implementing digitalized workflows of their respective MTBs to support collaborative work on cases among internal and external experts. Further, tools for the visualization, automated analyses of potential biomarkers, and scoring based on predefined evidence levels are developed and gradually implemented. Future works require the standardization of methodologies and exchange formats for consistency across different MTBs, enhancing data sharing and clinical studies. Furthermore, the integration of large language models (LLMs), especially for literature reviews, summaries, and trial matching supports case preparations to decrease the workload while retaining the best possible outcomes. The development of centralized expert-curated databases across multiple sites and the integration of follow-ups to prove the evidence and effectiveness of the MTB, as well as mirroring the data to cost bearers. Finally, addressing the coverage gaps in patient care by digitally integrating oncology centers will be crucial for equitable healthcare delivery.

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