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Unlocking the potential of Molecular Tumor Boards: from cutting-edge data interpretation to innovative clinical pathways

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ABSTRACT

The emerging era of precision medicine is characterized by an increasing availability of targeted anticancer therapies and by the parallel development of techniques to obtain more refined molecular data, whose interpretation may not always be straightforward. Molecular tumor boards gather various professional figures, in order to leverage the analysis of molecular data and provide prognostic and predictive insights for clinicians. In addition to healthcare development, they could also become a tool to promote knowledge and research spreading. A growing body of evidence on the application of molecular tumor boards to clinical practice is forming and positive signals are emerging, although a certain degree of heterogeneity exists. This work analyzes molecular tumor boards' potential workflows, figures involved, data sources, sample matrices and eligible patients, as well as available evidence and learning examples. The emerging concept of multi-institutional, disease-specific molecular tumor boards is also considered by presenting two ongoing nationwide experiences.

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1. Introduction

Over the last two decades, advances in basic science have been moving oncology practice towards a more personalized, molecular-driven approach. The advent of targeted anticancer therapies has been a milestone in the current era of precision medicine. At the same time, the rapid development of next generation sequencing (NGS) techniques results in an intricate flow of data, requiring a deep and complex knowledge in molecular biology.

To keep pace with these innovations, molecular tumor boards (MTBs) have been introduced, in which multiple professional figures share their own experience and contribute to the overall decision-making process (La Mantia et al., 2023). The main goal of MTBs is to exploit molecular and genetic data to provide prognostic and predictive insights for clinicians, offering a multidimensional, holistic characterization of each individual's disease. Yet, their application is limited by practical caveats, regarding its composition, as the interaction of different healthcare professionals is required, knowledge resources, which imply a need for constant updating of datasets and professional skills, and dedicated infrastructures (Luchini et al., 2020; Mano et al., 2022; Russo et al., 2022; Love et al., 2022).

In addition to healthcare development, MTBs are a valid tool to promote knowledge and research, as they frequently integrate outcome registries that can catalyze exploratory studies and journal clubs to review literature and update policies and standard procedures (Burkard et al., 2017; Gebbia et al., 2021). (Fig. 1)

The aim of this review is to analyze potential MTB workflows and to describe their principal actors, data sources, sample matrices and eligible patients, also by leveraging ongoing multi-institutional experiences and learning examples.

2. Board composition

The ideal composition of MTBs is still debated and a formal consensus has not been reached yet. Based on currently published and ongoing experiences, a basic roster should include at least medical oncologists, molecular pathologists, clinical molecular biologists, geneticists and bioinformaticians (Koopman et al., 2021; van der Velden et al., 2017). However, the continuous expansion of knowledge urges the need for additional clinical professionals (e.g., radiologists/nuclear physicians, radiotherapists, clinical chemists, laboratory technicians, pharmacologists/pharmacists, clinical pharmacologists, bioethicists), as well as patient representatives and study coordinators (van der Velden et al., 2017; Danesi et al., 2021; Miteva-Marcheva et al., 2020; Lesslie and Parikh, 2017).

2.1. Medical oncologist

Medical oncologists represent the most direct line for patients; they should provide them with appropriate educational resources and adequate information about available targeted treatments and enrolling clinical trials, as well as the potential implications of secondary findings (Sarfati et al., 2016). Moreover, they report on the patient's overall health, comorbidities and current treatments and check MTB eligibility criteria (Shirdarreh et al., 2021). However, due to the constant advancement of knowledge, sub-specialties should be respected, therefore only medical oncologists who can better dissect the growing complexity of specific disease settings shall be involved. This should be considered when setting up an MTB and coordinating the various professional figures involved.

2.2. Molecular pathologist

Molecular pathologists assess samples' quality and integrate conventional morphological and bio-molecular investigations with the most advanced molecular technologies (Alessandrini et al., 2018). They also contextualize potential preanalytical caveats and suggest the most appropriate technology, while maintaining turnaround time monitored (Matias-Guiu et al., 2020).

2.3. Clinical molecular biologist

Clinical molecular biologists perform genomic assays, detect and

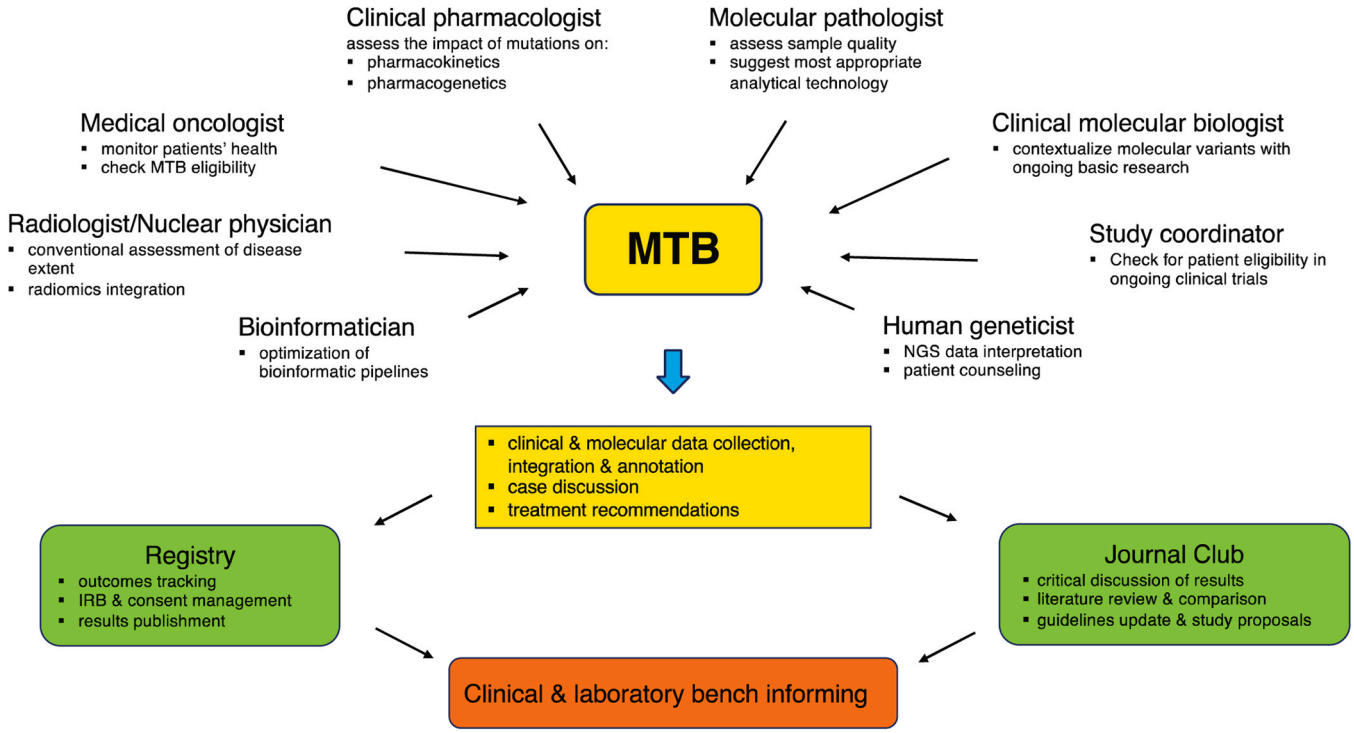

Fig. 1. The ideal workflow of a general molecular tumor board (MTB): professionals involved and their roles and contributions.

contextualize molecular alterations and define the best technological strategies, in order to identify alterations that warrant confirmation by alternative methods (e.g., large rearrangements, chimeric transcripts, etc.). These laboratory specialists should be involved in MTBs to carefully integrate hypotheses-generating results with data from basic research.

2.4. Human geneticist

As NGS data can inform on multiple incidentally identified variants, both somatic and germline, human geneticists should be able to identify appropriate candidates for germline testing and to discuss with them the implications on the risk of inheritance. Proper criteria to refer patients to genetic counseling are needed, although they may be difficult to standardize, often requiring personalization (Yang et al., 2018).

2.5. Bioinformatician

Bioinformatic pipelines are usually optimized for specific diagnostic settings, so bioinformaticians are needed to minimize analytical misinterpretations and to distinguish at best the real signal from false positives and "background noise" (Oliver et al., 2015; Roy et al., 2018). Tailored software for interpretations and discussion of NGS panel results are also being developed and integrated specifically within the context of MTBs (Kahraman et al., 2022).

2.6. Radiologist/Nuclear physician

Imaging professionals assess the extent of the disease and evaluate the response to treatment, primarily based on RECIST criteria (Schwartz et al., 2016). In this context, the integration of radiomics and artificial intelligence (AI) is expected to provide a powerful tool to improve diagnostic, prognostic, and predictive accuracy (Lambin et al., 2017; Bera et al., 2022).

2.7. Clinical pharmacologist

Clinical pharmacologists are emerging health professionals, who critically assess the druggability of identified variants, while pointing out potential treatment strategies, as well as pharmacological differences within a drug class. Their expertise in pharmacogenetic testing and therapeutic drug monitoring could also prove useful to evaluate pharmacological interactions. NGS data could be employed to highlight genetic biomarkers potentially linked to altered drug exposure, toxicity or response to cancer treatments (Morganti et al., 2019; Hertz and Rae, 2015).

2.8. Study coordinator

Clinical study coordinators facilitate the process of intercepting patients who meet inclusion criteria for clinical trials; once a patient is deemed eligible, they should inform the other MTB members, so they can consider all the available strategies and come to a decision accordingly. Their role is becoming tougher, as multiple trial options are available, and attendance by multiple clinical study coordinators may be an impractical solution. Besides, available evidence have highlighted that screening for clinical trial eligibility is often performed considering active onsite studies only: as a result, a significant share of patients will be denied trial participation (Unger et al., 2019). Recommendations have been made to implement supporting algorithms and external tools, which may help matching patients' clinical and molecular features to suitable clinical trials and could benefit MTBs discussions by increasing patients' likelihood of trial participation (Fleury, 2024).

3. Variant annotation

Computational pipelines allow for the processing of raw sequencing data through the so-called "variant calling" procedure. The general workflow includes a pre-processing step, followed by a careful variant evaluation and a post-filtering phase (Xu, 2018). The main somatic variant callers analyze matched tumor-normal samples, although more recent alternatives have been developed to rely only on tumor samples (Xu, 2018; Zverinova and Guryev, 2022). Each variant caller has different settings and criteria, with a differential impact on the resulting variant call; as a consequence, the comparison of different variant callers based on sensitivity, precision, and F-Score (i.e., the harmonic mean of sensitivity and positive predictive value) has resulted in worrying inconsistent performances up to now (Xu et al., 2014; Sandmann et al., 2017; Dodani et al., 2022).

Attributing clinical significance to genetic alterations is paramount in the workflow of MTBs, considering the increasing availability of molecular and sequencing data. Genetic variants are annotated according to international standards and available evidence, dividing them into 5 categories (Lappalainen et al., 2019; Richards et al., 2015). (Table 1)

Variant annotation resources can be classified as databases and knowledge bases. Databases are defined as "data repositories that store, organize, validate, and make accessible the core data related to a particular system or systems", while knowledge bases are "warehouses that accumulate, organize, and link growing bodies of information related to core datasets" (Cambrosio et al., 2020). Beyond the formal definitions, overlapping areas still exist.

3.1. Databases

Benchmarks based only on a single reference set may provide an incomplete picture, so the integration of multiple tools is recommended (Jaksik et al., 2021). Based on the results of eight different databases, a meta-database was developed, that substantially improved overall sensitivity and positive predictive value. In addition, a precise pipeline definition allowed the experimenters to distinguish artifacts from polymorphisms and mutations (Sandmann et al., 2018).

3.2. Knowledge bases

3.2.1. Biological classification knowledge bases

Biological classification knowledge bases have been developed to collect data submitted by clinical testing and research laboratories, expert panels, and other groups, each of them giving possible clinical interpretations to identified genetic variants. The most famous example is ClinVar, created and supported by the National Institute of Health. This tool was originally intended for germline mutations only, but lately it has been applied successfully to cancer genome analysis (Landrum et al., 2018). Data retrieved can also be integrated with VarSome, a supplementary tool that provide information about the predicted variant effect, the frequency of the mutated allele within different populations and the associated pathogenic score (Kopanos et al., 2019). Meta-bases tools are in development, relying on different pipelines and allowing an easier, more manageable use of these data (Borchert et al., 2021).

Some limitations must be underlined. First, submissions by different users can lead to discordances in the meanings attributed to the same variant. In addition, similar tools may disagree with one another, making evaluations even trickier (Gradishar et al., 2017; Katsoulakis et al., 2020). Finally, although many scientists can contribute, the whole process is still manually performed, creating a temporal gap that may enhance the risk of having divergent interpretations.

Possible solutions to the aforementioned problems could be offered in the context of MTBs, particularly by the integration of journal clubs, a constantly updated source of information on the most recent findings, and the inclusion of basic scientists, in a two-way collaboration between

Table 1
Genetic variant annotation rules and class division according to clinical significance (criteria adapted from Richards S et al (Richards et al., 2015).).

Class	Clinical significance	Definition	Main criteria
I	Benign	Variant not considered as the cause of the patient's disease	a. Benign stand-alone criteria met b. ≥ 2 benign strong criteria met
II	Likely benign	Variant not likely to be the cause of the patient's disease (> 90% of chances, still a degree of uncertainty exists)	a. 1 benign strong and 1 benign supporting criteria met b. ≥ 2 benign supporting criteria met
III	Variants of Unknown Significance (VUS)	Likely independent disease-causing variant according to its characteristics, but insufficient or conflicting evidence available	a. Other criteria not fully met b. Contradictory criteria met
IV	Likely pathogenic	Variant likely to be the cause of the patient's disease (> 90% of chances, still a degree of uncertainty exists)	a. Pathogenic very strong and 1 pathogenic moderate criteria met b. 1 pathogenic strong and 1–2 pathogenic moderate criteria met c. 1 pathogenic strong and ≥ 2 pathogenic supporting criteria met d. ≥ 3 pathogenic moderate criteria met e. 2 pathogenic moderate and ≥ 2 pathogenic supporting criteria met f. 1 pathogenic moderate and ≥ 4 pathogenic supporting criteria met
V	Pathogenic	Variant considered to be the cause of the patient's disease	a. Pathogenic very strong and EITHER ▪ ≥ 1 pathogenic strong criteria met OR ▪ ≥ 2 pathogenic moderate criteria met OR ▪ 1 pathogenic moderate and 1 pathogenic supporting criteria met OR ▪ ≥ 2 pathogenic supporting criteria met b. ≥ 2 pathogenic strong criteria met c. 1 pathogenic strong and EITHER ▪ ≥ 3 pathogenic moderate criteria met OR ▪ 2 pathogenic moderate and ≥ 2 pathogenic supporting criteria met OR ▪ 1 pathogenic moderate and ≥ 4 pathogenic supporting criteria met

preclinical and clinical professionals (Muia and Casari, 2016). (Fig. 1)

3.2.2. Clinical classification knowledge bases

Associating molecular alterations with matching targeted treatments is of crucial importance in MTBs therapeutic decision-making. To optimize this process, a number of open-label, easily accessible knowledge bases have been created, reporting all available relevant information on the clinical actionability of cancer mutations (Borchert et al., 2021; Banck et al., 2021). (Fig. 2)

3.2.2.1. CiViC. CiViC (Clinical Interpretation of Variants in Cancer) is an expert-crowdsourced knowledge base, which integrates the direct contribution of its community with other knowledge bases. Data are filtered by an expert commission and concomitantly associated with an evidence level range. Variants are classified as predictive, prognostic, diagnostic and/or predisposing for cancer (Griffith et al., 2017).

3.2.2.2. OncoKB. OncoKB is a comprehensive, publicly available precision oncology knowledge base, comprising both individual somatic mutations and germline structural alterations. It discriminates clinically actionable variants according to Food and Drug Administration (FDA) labeling and National Comprehensive Cancer Network (NCCN) guidelines. To date, more than 3000 alterations in 418 cancer genes have been annotated and stratified into four levels of evidence (Chakravarty et al., 2017).

3.2.2.3. JAX-CKB. JAX-CKB (Jackson Laboratory Clinical Knowledge Base) enables dynamic curation of data, including the connection of genetic variants to phenotype and protein effects, as well as therapeutic relevance and potential treatment approaches. Each specific alteration is annotated via a standardized variant nomenclature. In addition, JAX-CKB facilitates data analysis through customized queries (Patterson et al., 2019).

3.2.2.4. PMKB. PMKB (Precision Medicine Knowledge Base) requires associations with gene-variant, tumor-type and tissue-type descriptions. The tool is based on a deep interaction among all users, who can have three different privilege levels (guest, standard user, and high-level approver) (Huang et al., 2017).

3.2.2.5. The VICC meta-knowledge base. As different knowledge bases are now available, their alignment is a tough challenge that implies a high risk of having numerous "knowledge silos" that do not communicate with one another. Despite the existence of international guidelines, heterogeneous modalities of variant representation are used, often leading to misjudgment and discordances among reports from different groups. To overcome this hindrance and reach a consensus in genomic data sharing and reporting, the Variant Interpretation for Cancer Consortium (VICC) developed a vast "meta-knowledge base" that integrates information about genes, variants, diseases, drugs and available evidence from six different knowledge bases (CGI, CIViC, JAX-CKB, Molecular Match [MMatch], OncoKB, PMKB). It also allows the implementation of clinically significant findings (Wagner et al., 2020; Pallarz et al., 2019).

3.3. Clinical trial registries

Information about ongoing clinical trials is usually collected into large registries. In the frame of MTBs, they help increase the chance of a patient being enrolled in a clinical trial and possibly receiving new treatment options; this becomes particularly valuable in disease contexts where no other drugs proved effective. Furthermore, data collected can support existing and future research projects. *ClinicalTrials.gov* is the largest and best known among clinical trial registries, but other helpful sources are available in Europe (*ClinicalTrialsRegister.eu*) and in more restricted national contexts (Zarin et al., 2016). Supporting algorithms and external tools, some of them AI-based, are also currently being implemented, in order to allow for site-agnostic clinical trial screening and matching (Fleury, 2024).

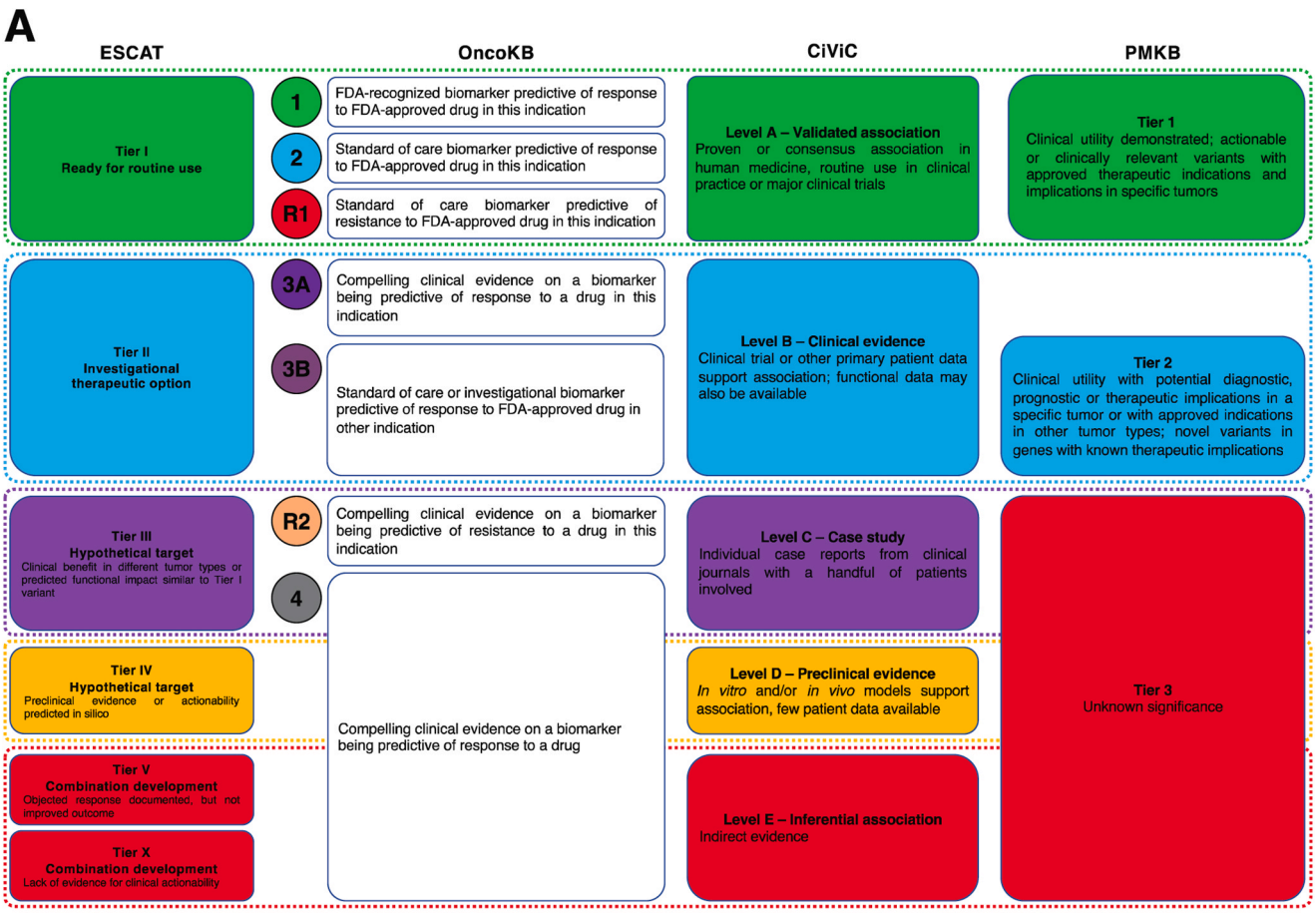

Fig. 2. **(A)** A comparison of levels of evidence across different knowledge bases (OncoKB, CiViC and PMKB), which are put in the framework of the ESCAT tier system. **(B)** JAX-CKB presents a more structured system of variant annotation and attribution of a corresponding level of evidence, which is based on the combination of three parameters.

4. Sample matrices

4.1. Tissue vs liquid biopsy

A consideration of the biological sample matrix on which molecular and genetic data are analyzed should be paramount, when discussing cases presented to MTBs. Tissue biopsies have long been considered the gold standard in cancer diagnostics, but their use is limited by several potential risks (e.g., technical failure, procedure-related complications, delays in the results' delivery) (Massard et al., 2017; Ahlborn et al., 2019). Moreover, they provide good information on the genomic landscape of the specific site where it was performed, but fail to capture tumor heterogeneity (Mattos-Arruda et al., 2014; Gerlinger et al., 2012; Ng et al., 2012).

On the other hand, liquid biopsy is emerging as a powerful informative tool: it is, in fact, a very simple, minimally invasive and easy-to-repeat procedure, well tolerated by patients and with quicker turnaround times (Mohanty et al., 2021; Saini et al., 2018; Bayle et al., 2022). Thanks to its high reproducibility, this technique has first been developed to allow for dynamic disease monitoring, depicting a more precise temporal portrait of cancer biology. In addition, it can be performed even in patients with difficult-to-reach lesions, overcoming a limitation of tissue biopsies; results can inform on the primary tumor as well as other distant sites, mitigating spatial heterogeneity (Eslami-S et al., 2020; Voigt et al., 2020). While often intended as the research of DNA fragments in the blood stream, many other components can be exploited, like circulating tumor cells, extracellular vesicles and tumor educated platelets (Poulet et al., 2019).

4.2. Caveats of liquid biopsy

Although liquid biopsy is gradually gaining traction, it still has technical limitations and potential caveats. In addition, harmonizing the power to detect potentially targetable variants between tissue and liquid biopsy is still an unmet need (Rolfo et al., 2018; Bianchini et al., 2020; Russo et al., 2023).

4.2.1. Clonal hematopoiesis

Clonal hematopoiesis (CH) is a para-physiological cellular process, which acts in the natural process of aging by the accumulation of somatic mutations and the expansion of hematopoietic stem cells. Up to 10% of CH mutations detected are listed as "oncogenic" in OncoKB datasets and 13% of them are indicated for either an approved targeted therapy or a treatment under clinical trial (Razavi et al., 2019; Xu et al., 2021).

Some typical features can discriminate circulating tumor DNA (ctDNA) from CH sequences, such as mutations in genes associated with hematological malignancies (e.g., *DNMT3A*, *TET2*, *ASXL1* and *JAK2*), specific lengths of DNA fragments deriving from apoptotic or necrotic cancer cells, specific nucleotide alterations (e.g., the transition cytosine-thiamine through spontaneous deamination of methylated cytosine, typically associated with aging) and epigenetic biomarkers (e.g., DNA methylation levels in CpG sites) (Bellosillo and Montagut, 2019; Underhill et al., 2016; Chan et al., 2020; Gai and Sun, 2019).

4.2.2. Incidental germline mutations

Criteria to define the germline origin of mutations still lack standardization. While commercial laboratories commonly consider DNA mutations having mutant allele fractions (MAFs) $\geq$ 25% as putatively germline, most studies included only variants with MAFs between 40% and 60%; as a result, a lower prevalence is observed (Slavin et al., 2018).

In a cohort of 828 patients with advanced breast, ovarian, prostate and pancreatic cancer, routine plasma-based genotyping revealed the emergence of polyclonal reversion *BRCA* mutations in 9 of 42 patients initially harboring germline variants and treated with poly(ADP-ribose) polymerase (PARP) inhibitors, contributing to the development of resistance to both PARP inhibitors and platinum-based therapy (Vidula et al., 2020).

On the other hand, patients carrying a germline variant should be carefully evaluated, as reversion mutations may be detected in blood samples while being absent in tissue samples of the primary tumor (Weigelt et al., 2017; Lin et al., 2019).

5. Eligible patients

In the hierarchical organization of modern health care systems, MTBs should be considered as second-level structures, intended for complex cases where a standard of care (SoC) treatment lacks or a decision is not straightforward. A consensus on the elements that make a patient suitable for discussion has not been reached yet; however, some eligibility criteria have been proposed, with the general aim to include those who are more likely to show a clinical benefit.

The general belief is that ideal patients should be adults aged $\geq$ 18 years with good life expectancy (at least 12 weeks), who have expired or are resistant to available SoC anticancer drugs; or have rare pathologies or histological types with limited therapeutic options; or whose unusual clinical history may benefit from a non-routine molecular profiling, with possible clinical implications; or whose family history may suggest the presence of a hereditary mutation.

MTBs could also represent a way to offer targeted therapies to patients who will otherwise have no other therapeutic option (Neugut and Prigerson, 2017). While being an opportunity to gather more data on the management of trial-ineligible patients, a preliminary discussion about their current clinical situation, all possible clinical evolutions and what could realistically be achievable must always come first. Patients' personal beliefs and desires must also be respected in the overall decision-making process (Tang and Lee, 2022; Pennell et al., 2019; West, 2018).

6. Available evidence on MTBs

6.1. Positive experiences

Some preliminary experiences have tried to describe the utility and potential benefits of implementing complex genomic data through MTBs. (Table 2)

A multicenter comparison of eight Dutch MTBs highlighted a high degree of heterogeneity in the composition, the data- and knowledge bases used for variant calling and/or interpretation, the online resources available, the scientific literature, the guidelines and trial registries considered. Furthermore, each center received 10 complex clinical cases and had to suggest a treatment strategy: interestingly, after reading the statements of other groups, some changed their minds, suggesting the need for a wider sharing of knowledge and for constantly updated information (Koopman et al., 2021).

A prospective trial was conducted on 200 patients with metastatic breast cancer (mBC); among them, 64 were treated according to MTB recommendations and 53 were evaluable for response. In this cohort, a 40% clinical benefit rate (CBR, 21/53) was reached, with 15% partial responses (8/53) and 25% stable diseases (13/53). Moreover, 30% of evaluable patients (16/53) had their second progression-free survival (PFS) improved by at least 30% compared with their first PFS, even though they were receiving a second line treatment and therefore had a higher disease burden (Hlevnjak et al., 2021).

A recent publication (Bayle et al., 2023) presented the French STING trial, which represents the largest prospective cohort analyzed to date. In this trial, 1772 patients with locally advanced, unresectable, or metastatic solid tumors underwent a liquid biopsy-driven genomic test. Of note, results were available in a median turnaround time of 12 days, significantly shorter compared with tissue profiling analyses (frequently $>$ 30 days) (Massard et al., 2017). 1658 patients (93.6%) returned informative ctDNA results, with at least one actionable target detected in

Table 2
Summary of the main features, as well as reported survival and response outcomes, of available previously published MTB experiences.

Study reference	Study features & timeframe	Patients' features	Survival outcomes	Response outcomes
(Hlevnjak et al., 2021).	Prospective precision oncology program Single center June 2017 – March 2019	▪ 200 with metastatic breast cancer ▪ 128 discussed (64%), of which 64 treated according to MTB recommendations ▪ 53 evaluable for response (26.5%)	*PFSr > 1.3, evaluable cohort*: ▪ 30% (16/53)	*Evaluable cohort* (n = 53): ▪ CBR: 40% (21/53) ▪ best responses: 8 PR and 13 SD
(Bayle et al., 2023). (NCT04932525)	Prospective precision oncology study Single center December 2020 – November 2021	▪ liquid biopsy-driven, patients with metastatic solid tumors ▪ 1772 included, of which 1658 ctDNA-profiled (93.6%) ▪ 1059 with ≥ 1 actionable target (64% of all profiles), of which 597 with ≥ 1 treatment recommendation ▪ 122 treated with M therapy, 107 of which evaluable for response	*Patients with M therapy* (n = 122): ▪ mPFS (months): 4.7 (95% CI 2.7–6.7) ▪ mOS (months): 8.3 (95% CI 4.7–11.9)	*Evaluable cohort* (n = 107): ▪ ORR: 37% (39/107) ▪ CBR: 62% (66/107) ▪ best responses: 4 CR, 35 PR and 27 SD
(Kato et al., 2020).	Retrospective case series Single center December 2012 – September 2018	▪ 715 with various advanced or metastatic solid tumors ▪ 429 evaluable for therapy after MTB discussion (60%) ▪ 265 M to ≥ 1 recommended therapy ▪ 164 received UM/low-M PC treatment ▪ stratified according to MS: high (≥ 50%, n = 125) vs low (< 50%, n = 304)	*Fully M vs UM PC therapy*: ▪ PFS: HR 0.68 (95% CI 0.51–0.90) ▪ OS: HR 0.69 (95% CI 0.49–0.98) *HM vs LM*: ▪ PFS: HR 0.63 (95% CI 0.50–0.80) ▪ OS: HR 0.67 (95% CI 0.50–0.89)	*CBR* (HM vs LM): ▪ 52.1% vs 30.3%
(Rodon et al., 2019). (NCT01856296)	Prospective navigation trial Multi institutional April 2013 – December 2015	▪ 303 with metastatic solid tumors, of which 107 received treatment according to MTB recommendations (35.3%) ▪ navigated according to fresh biopsy-derived DNA sequencing (arm A, n = 69) or RNA expression (arm B, n = 38)	*PFSr > 1.5*: ▪ 22.4% overall (24/107) ▪ 20.3% arm A (14/69) ▪ 26.3% arm B (10/38) *mPFS & mOS* (months): ▪ mPFS: 2.01 overall; 1.94 arm A; 2.43 arm B ▪ mOS: 5.9 overall; 5.1 arm A; 7.4 arm B	*Evaluable cohort* (n = 107): ▪ ORR: overall 11.2% (12/107); arm A 13.0% (9/69), arm B 7.9% (3/38) ▪ CBR: overall 26.2% (28/107); arm A 23.2% (16/69), arm B 31.6% (12/38)
(Sicklick et al., 2019). (NCT02534675)	Prospective navigation trial Two centers February 2015 – June 2017	▪ 149 with previously treated metastatic cancers ▪ 83 treated (55.7%), of which 73 with ≥ 1 M therapy ▪ 69 evaluable for response, 53 patients evaluated for PFSr ▪ stratified according to MS: high (> 50%, n = 28) vs low (≤ 50%, n = 55)	*HM vs LM*: ▪ mPFS: 6.5 vs 3.1 months ▪ mOS: NR vs 10.2 months *PFSr ≥ 1.3, evaluable cohort* (n = 53): ▪ 45.3% overall (24/53) ▪ 75.0% with HM (9/12) ▪ 36.6% with LM (15/41)	*DCR, evaluable cohort* (n = 69): ▪ overall: 30.4% (21/69) ▪ HM: 50.0% (10/20) ▪ LM: 22.4% (11/49)
(Sicklick et al., 2021). (NCT02534675)	Prospective navigation trial Two centers February 2015 – November 2019	▪ 145 with treatment-naïve, unresectable or metastatic cancers ▪ 133 had ≥ 1 theoretically targetable alteration (91.7%) ▪ 76 treated (52.4%), of which 54 with ≥ 1 M therapy ▪ 68 evaluable for response ▪ stratified according to MS: high (≥ 60%, n = 27) vs low (< 60%, n = 49)	*HM vs LM*: ▪ mPFS: 11.6 vs 2.8 months ▪ mOS: 18.7 vs 11.6 months	*DCR, evaluable cohort* (n = 68): ▪ overall: 44.1% (30/68) ▪ HM: 68.0% (17/25) ▪ LM: 30.2% (13/43)
(Tourneau et al., 2015). (NCT01771458)	Prospective, randomized, open-label, phase II trial Multicenter October 2012 – July 2014	▪ 741 with any recurrent or metastatic solid tumor screened ▪ 496 had a complete genomic profile (66.9%) ▪ 293 (40%) with ≥ 1 alteration matching an available agent ▪ 195 (26%) randomized (1:1) to receive M targeted agent vs PC UM treatment	*mPFS* (months): ▪ 2.3 (95% CI 1.7–3.8) M arm (n = 99) ▪ 2.0 (95% CI 1.8–2.1) PC arm (n = 96)	*ORR, evaluable cohort* (n = 187): ▪ M arm: 4.1% (4/98) ▪ PC arm: 3.4% (3/89)

(*continued on next page*)

Table 2 (*continued*)

Study reference	Study features & timeframe	Patients' features	Survival outcomes	Response outcomes
			Potentially actionable alterations (n = 781):	
(Zhao et al., 2021). (NCT02534675)	Prospective precision oncology study Single center October 2016 – October 2019	▪ 1564 with advanced NSCLC, of which 1166 profiled (74.6%) ▪ 781 (49.9%) with ≥ 1 potentially actionable alteration ▪ 440 received a M targeted therapy (37.7%), of which 244 (20.9%) were enrolled in a clinical trial	▪ mPFS: 9.0 months (M), 4.9 months (UM) ▪ mOS: 3.9 years (M), 2.5 years (UM) *OncoKB level 1–2 alterations*: ▪ mPFS: 9.2 months (M), 5.2 months (UM) ▪ mOS: 3.9 years (M), 2.7 years (UM) *mPFS, ESCAT tier I/II* (n = 115):	Not reported
(Andre et al., 2022). (NCT02299999)	Prospective, randomized, open-label, phase II trial Multicenter April 2014 – October 2019	▪ 1462 with HER2⁻ metastatic breast cancer ▪ 646 with ≥ 1 targetable genomic alteration (44.2%) ▪ 594 discussed at MTB for therapeutic decision (40.6%) ▪ 238 randomized (2:1) to receive maintenance CT (n = 81) or a M targeted therapy (n = 157) ▪ 115 carried an ESCAT tier I/II variant	▪ 9.1 months (90% CI 7.1–9.8 months) M arm ▪ 2.8 months (90% CI 2.1–4.8 months) C arm *mPFS, overall cohort* (n =238): ▪ 5.5 months (95% CI 4.0–6.9 months) M arm ▪ 2.9 months (95% CI 2.3–4.8 months) C arm *PFSr ≥ 1.3, evaluable cohort* (n = 193):	Not reported
(Massard et al., 2017). (NCT01566019)	Prospective precision oncology study Single center December 2011 – March 2016	▪ 1035 adults with metastatic solid tumors ▪ 948 had successful biopsies performed (91.6%), with a molecular portrait obtained in 843 of them ▪ 411 with ≥ 1 actionable target (39.7%), of which 199 received a M therapy ▪ 194 evaluable for response, 193 evaluated for PFSr	▪ 32.6% overall (63/193) ▪ 37.0% with target treatment level of evidence A (10/27) Median PFS on M treatment: 2.3 months (95% CI 1.9–2.7 months) Median OS on M treatment: 11.9 months (95% CI 9.5–14.3 months)	*ORR, evaluable cohort* (n = 194): ▪ 11% (95% CI 7–17%) ▪ best responses: 2 CR, 20 PR and 100 SD

Abbreviations: C, control; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; CT, chemotherapy; ctDNA, circulating tumor DNA; DCR, disease control rate; ESCAT, European Society of Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets; HER2, human epidermal growth factor receptor 2; HM, high-matching; HR, hazard ratio; (m)OS, (median) overall survival; LM, low-matching; M, matched; MS, matching score; MTB, molecular tumor board; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; PC, physician's choice; (m)PFS, (median) progression-free survival; PFSr, progression-free survival ratio; PR, partial response; SD, stable disease; UM, unmatched.

1059 patients (64%). Reports were reviewed and discussed in a weekly MTB; at least one matched therapy was recommended for 597 patients (56%). In addition, a total of 819 orientations were emitted, mostly indicating the enrollment in a genotype-matched clinical trial (693 cases, 78%). Consequently, 122 patients received a ctDNA-matched therapy and 107 of them were evaluable for responses: overall, a 37% objective response rate (ORR, 39/107) and a 62% CBR (66/107) were reported.

Similarly, Kato et al. evaluated 429 patients presenting different advanced or metastatic cancers, most of whom had received at least two prior lines of treatment. After MTB discussion, 265 (62%) of them were recommended to at least one matched therapy, while the remaining 164 (38%) received a SoC physician's choice treatment, generally unmatched or low-matched. Improved PFS and overall survival (OS) were reported in the matched treatment group, as compared to the SoC group, with longer survival outcomes in patients who received MTB-recommended therapies with a high (≥ 50%) matching score (Kato et al., 2020). Two additional trials reported a general, although not statistically significant, trend towards improved survival outcomes (PFS-ratio, PFS and OS), particularly among patients receiving a highly matched therapy (Rodon et al., 2019; Sicklick et al., 2019, 2021).

6.2. Thought-provoking results

Some studies did not find any improvement in survival outcomes by the integration of MTBs (Tourneau et al., 2015). (Table 2) In particular, contrasting results were obtained among non-small cell lung cancer (NSCLC) patients (Kris et al., 2014; Hendriks et al., 2023). In a retrospective cohort of stage IIIB/IV or recurrent non-squamous advanced NSCLC patients, broad-based genomic sequencing was not associated with better survival than routine *EGFR* and/or *ALK* testing. Consistently, only 4.5% of patients who underwent broad-based genomic sequencing subsequently received a corresponding treatment for non-*EGFR* or *ALK* variants (Presley et al., 2018).

Another prospective study enrolled 1166 advanced NSCLC patients, of whom 781 had potentially actionable alterations. After excluding those who could receive standard targeted therapies, the remainders could receive either a matched therapy, via a clinical trial (244 patients) or an off-label request (196 patients), or a non-matched therapy (215 patients). Patients harboring potentially actionable alterations who were given a matched targeted therapy had a statistically higher median OS than those who received a non-matched treatment. However, when stratifying for clinical actionability according to OncoKB levels of evidence, statistical significance was kept only for mutations in levels 1 and

2 (Zhao et al., 2021).

Similarly, the SAFIR02-BREAST trial (Andre et al., 2022) tested the use of the European Society of Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets (ESCAT) as a framework to guide treatment decision-making in patients with human epidermal growth factor receptor 2 (HER2) negative mBC. 238 patients whose genomic profile returned at least one targetable alteration were randomized in a 2:1 fashion to receive either a maintenance chemotherapy regimen (81 patients) or a matched targeted therapy (157 patients). Among them, 115 patients carried an ESCAT tier I/II variant, which could extrapolate to OncoKB levels 1–3 A (Chakravarty et al., 2017). A significantly longer PFS was observed among patients who were offered a matched targeted therapy only in the latter subgroup; instead, no significant differences were reported in the overall

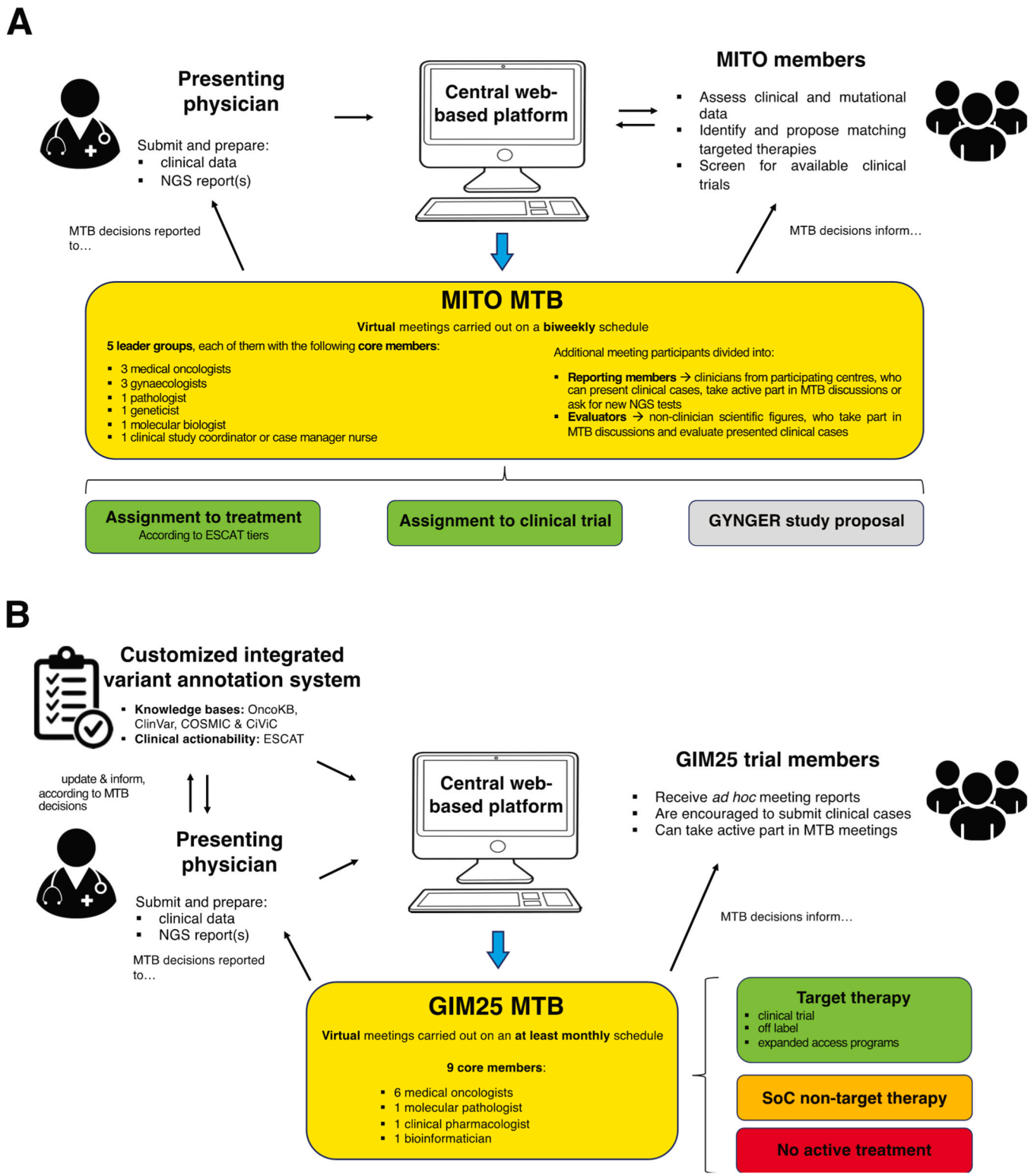

Fig. 3. The specific workflow of two multi-institutional disease-specific MTBs: **(A)** MITO-GYNGER; **(B)** GIM25-CAPT.

population. Such results suggest that molecular-driven treatments can improve patients' outcomes only in the presence of a highly-ranked drug/alteration match.

The MOSCATO-01 trial results are still being debated. Applying NGS techniques and setting up an MTB derived some benefit only in a small subgroup of patients with locally advanced or metastatic cancer. The reason why the improvement was so limited is not clear, with possible explanations owing to the patients' characteristics, as they were generally heavily pre-treated (a median of 4 prior lines of treatment was reported) and to the massive adoption of single-agent treatment strategies, even in the targeted therapy arm (Massard et al., 2017).

6.3. *The financial impact*

The economic impact of MTBs and molecular-guided treatment approaches on health care systems is also a frequent topic of concern. A recent position paper (Jager et al., 2024) strongly recommended routine implementation of large-panel NGS for every patient with advanced NSCLC. However, this strategy may not be easily applicable to more peripherical contexts, due to insufficient in-house expertise or limited availability of therapeutic options. Furthermore, large-panel NGS testing may be expensive for spoke hospitals, while a high sample volume is required for it to be considered cost-effective. Therefore, expert laboratories operating high-volume testing should be established as dedicated hub centers within regional oncology networks. Linked MTBs are also advised as the main, centralized structure for the interpretation and discussion of test results.

Several cost-analyses have also been published, reporting that MTBs seem to affect only a small share of the total cost of the patient journey ($\leq$ 6%), with the main cost drivers being drugs and hospitalizations. Overall, these results depict MTBs as new, cost-effective strategies, whose actual economic burden affects the patient's journey in a limited way (Pagès et al., 2017; Micheli et al., 2022).

7. multi-institutional disease-specific MTBs

7.1. *GIM25-CAPT*

The GIM25-CAPT phase II trial (NCT05266937) aims to evaluate a possible benefit from the addition of carboplatin to the combination of atezolizumab and nab-paclitaxel as first line therapy in patients with triple-negative, programmed death-ligand 1 (PD-L1) positive mBC. The study has also an ambitious exploratory aim to set up an MTB and assess its efficacy in defining the best subsequent therapy for enrolled patients. The MTB core team includes six medical oncologists, a molecular pathologist, a clinical pharmacologist and a bioinformatician. To optimize and standardize the process, all liquid biopsy data include both the annotation of significant variants and a corresponding clinical actionability assessment according to OncoKB (Chakravarty et al., 2017) and ESCAT (Mateo et al., 2018; Condorelli et al., 2019). Treatment recommendations are made, primarily suggesting the use of a targeted therapy, either via enrollment in a clinical trial or via off-label requests or national Expanded Access Programs. The MTB may also indicate the use of a SoC non-targeted therapy or even no anticancer treatment at all. Data are collected and managed using a REDCap® Cloud platform and an *ad hoc* annotation pipeline based on the combination of OncoKB, COSMIC, ClinVar and CiViC knowledge bases has been developed. (Fig. 3)

7.2. *GYNGER*

The GYNGER trial (NCT05733793) is a retrospective-prospective observational cohort study aimed to gather NGS data and to explore possible correlations with clinical outcomes in gynecological cancer patients, including rare subtypes. This trial is also linked to a larger MTB, composed by members of the Multicenter Italian Trials in Ovarian cancer and gynecologic malignancies (MITO) group, namely medical oncologists, gynecologists, pathologists, geneticists, molecular biologists and data managers. Virtual meetings are held on a biweekly schedule, involving nationwide experts. Data of discussed patients are submitted at least 72 hours before the meeting, via a shared virtual platform; after careful assessment of clinical and mutational data and a check of available targeted therapies and ongoing clinical trials, therapeutic proposals are made (Bartoletti et al., 2022). (Fig. 3)

8. Discussion and future perspectives

We believe that the implementation of MTBs could bring many advantages to current clinical practice. Previous experiences suggest a trend towards improved responses and survival outcomes by the use of MTB-recommended matched therapies, as compared to SoC non-matched options (Bayle et al., 2023; Kato et al., 2020). However, numbers are still limited in many cases and the observed benefit currently appears to be restricted to only few alterations with higher evidence of clinical actionability (i.e., ESCAT tier I/II or OncoKB level 1–3 A) (Zhao et al., 2021; Andre et al., 2022). On a financial standpoint, MTBs do not appear to have a negative impact on the overall patient journey, but they become more feasible and cost-effective when applied to broad oncology networks (Jager et al., 2024; Pagès et al., 2017). Nevertheless, MTBs implementation could represent a unique opportunity to increase collaboration between hub cancer research centers and peripherical spoke hospitals, with the aim to possibly get equal access to precision medicine tools, even to more unfavored local realities. Unanswered key questions remain, regarding MTBs composition, datasets and sample matrices to be used, as well as patients who could be offered this opportunity. Ongoing trials are expected to give further insights and help unravel the puzzle in the near future.

Regarding the sample matrices, liquid biopsy deserves a particular focus, as its use is currently limited to small disease subsets (Liebs et al., 2021; Rolfo et al., 2021; Fusco et al., 2021; Wang et al., 2016; Harada and Morlote, 2020; Cremolini et al., 2019; Knuever et al., 2020). However, data are emerging on its clinical utility. Preliminary results from the phase III PADA-1 study show that switching the endocrine therapy (ET) backbone from an aromatase inhibitor to fulvestrant, while keeping concomitant palbociclib, upon detection of a resistance mutation, particularly *ESR1* mutations, resulted in a doubled PFS in patients with estrogen receptor-positive (ER^+)/$HER2^-$ mBC (Berger et al., 2022; Jacobson, 2022). Besides, the recent FDA approval of elacestrant in the just mentioned patient group, after disease progression to at least one ET line, is based on the very use of a companion liquid biopsy-based test to identify *ESR1* mutations (Bidard et al., 2022). Similarly, the APPLE phase II trial tested whether an early switch from gefitinib to osimertinib, triggered by ctDNA detection of the *EGFR* T790M mutation, could be able to improve the PFS rate at 18 months compared to a standard switch after radiological evidence of disease progression in patients with *EGFR* mutated NSCLC (Remon et al., 2017). In Arm B of the study, a total of 47 patients initially receiving gefitinib were analyzed, of whom 17% (8/47) transitioned to osimertinib due to an emerging *EGFR* T790M mutation, while an additional 51% (24/47) of them made the change upon disease progression. The resulting PFS rate at 18 months of the 32 patients receiving osimertinib was 67.2% (84% CI 56.4–75.9%), meeting the primary endpoint of the study. Interestingly, a numerical-only better PFS rate was documented for patients switching upon molecular progression rather than those following the standard imaging criterion. Overall, serial ctDNA monitoring proved itself a feasible strategy to detect early molecular signs of disease progression, triggering a beneficial prompt switch in the treatment strategy (Remon et al., 2023). Finally, liquid biopsy methods to evaluate ctDNA are increasingly employed to assess and longitudinally monitor the molecular residual disease (MRD) across various cancer types and settings (Chin et al., 2019; Pellini et al., 2021).

9. Conclusion

MTBs represent a promising approach to personalize cancer care, enabling healthcare professionals to identify the most effective treatment for each individual patient based on its unique features. As new technologies, such as liquid biopsy and advanced variant annotation tools, are still developing, MTBs have the potential to become even more powerful in the years to come.

However, there are still many challenges to overcome in implementing MTBs, including issues around data privacy, funding, and access to expertise. Nevertheless, MTBs have the potential to play an increasingly important role in ongoing cancer research and innovation.

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Conception/Design: Riccardo Vida, Michele Bartoletti, Lorenzo Gerratana, Fabio Puglisi. **Collection and assembly of data:** Brenno Pastò, Riccardo Vida. **Data analysis and interpretation:** Brenno Pastò, Riccardo Vida, Michele Bartoletti, Lorenzo Gerratana, Fabio Puglisi. **Manuscript writing:** Brenno Pastò, Riccardo Vida, Michele Bartoletti, Lorenzo Gerratana, Fabio Puglisi. **Final approval of manuscript:** all authors.

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