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Clinical Outcomes of Molecular Tumor Boards: A Systematic Review

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Clinical Outcomes of Molecular Tumor Boards: A Systematic Review

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review articles

abstract

PURPOSE We conducted this systematic review to evaluate the clinical outcomes associated with molecular tumor board (MTB) review in patients with cancer.

METHODS A systematic search of PubMed was performed to identify studies reporting clinical outcomes in patients with cancer who were reviewed by an MTB. To be included, studies had to report clinical outcomes, including clinical benefit, response, progression-free survival, or overall survival. Two reviewers independently selected studies and assessed quality with the Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group or the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies depending on the type of study being reviewed.

RESULTS Fourteen studies were included with a total of 3,328 patients with cancer. All studies included patients without standard-of-care treatment options and usually with multiple prior lines of therapy. In studies reporting response rates, patients receiving MTB-recommended therapy had overall response rates ranging from 0% to 67%. In the only trial powered on clinical outcome and including a control group, the group receiving MTB-recommended therapy had significantly improved rate of progression-free survival compared with those receiving conventional therapy.

CONCLUSION Although data quality is limited by a lack of prospective randomized controlled trials, MTBs appear to improve clinical outcomes for patients with cancer. Future research should concentrate on prospective trials and standardization of approach and outcomes.

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INTRODUCTION

Precision medicine, specifically testing tumor tissue for mutations with next-generation sequencing (NGS) and using these results to guide therapy, is a major advance in the treatment of cancer and is considered standard of care (SOC) for many cancer types, including lung cancer. Receiving a targeted therapy yields substantial benefit for patients, since randomized, controlled trials have demonstrated that they are more effective, less toxic, and improve quality of life compared with cytotoxic cancer treatments.[1]

Despite the availability of clinical and affordable NGS, targeted therapies, and insurance coverage, the use of precision medicine remains low often because of insufficient support to guide clinicians in interpreting and acting on NGS results.[2-4] As a response, many medical centers have instituted molecular tumor boards (MTBs) as a means to educate, interpret, and facilitate the use of precision medicine for oncology patients.[5] Most MTBs consist of a multidisciplinary team of medical oncologists, surgeons, genetic counselors, pharmacists, pathologists, radiologists, and basic scientists.[6] This broad range of expertise allows for accurate and up-to-date confirmation of diagnoses and identification of actionable mutations and associated drugs, along with the ability to pair patients with open clinical trials. It can additionally identify potential germline mutations that would require further genetic testing and counseling for patients and their family members.

Many institutions have published descriptions of their MTBs outlining their aims, patient populations, and types of actionable mutations; however, data supporting the clinical utility of MTBs are lacking.[7-9] Therefore, we focus on reports that also include clinical outcomes such as clinical benefit (CB), response, and/or progression-free survival (PFS). The purpose of this systematic review is to evaluate the effect of MTBs on clinical outcomes in patients with cancer.

METHODS

This review was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic reviews.[10]

ASSOCIATED CONTENT

Appendix

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

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CONTEXT

Key Objective

What is the impact of a molecular tumor board on clinical outcomes?

Knowledge Generated

Molecular tumor boards reporting clinical outcomes had consistent structure and function. They are usually interdisciplinary, function as a consult service, and appear to improve clinical outcomes, including response and progression-free survival; however, studies are heterogeneous and data quality is limited.

Relevance

As the number of targetable mutations continues to increase and cancer care becomes even more complex, consultation with an interdisciplinary molecular tumor board can help guide therapy selection for patients with cancer.

Search Strategy and Inclusion and Exclusion Criteria

A PubMed search was conducted on April 1, 2020, using the following query: molecular tumor board [All Fields]. Further publications were found through additional means including a bibliography screen of all selected articles. Articles were excluded if they were not in English, were reviews, described MTBs for pediatric patients, or did not contain data about CB or survival. All remaining articles were screened for relevancy, and any duplicates were removed.

Data Analysis

Data extraction was performed by two researchers (K.L.L. and J.M.K.) for all publications examined. Any disagreement was discussed between the researchers, and a conclusion was reached. Because of data diversity and differences in study setup, a meta-analysis was not performed, and instead, data will be discussed using a description of the findings.

Calculations

The frequency of cases reviewed by each molecular tumor board (MTB) was calculated using the following formula:

$$(\text{number of patients reviewed}/\text{number of patients referred}) \times 100.$$

The frequency of actionable mutations was calculated using the following formula:

$$(\text{number of patients with an actionable mutation}/\text{total number of patients reviewed by the MTB}) \times 100.$$

The frequency of patients who received MTB-directed targeted therapy was calculated using the following formula:

$$(\text{number of patients that received MTB-directed therapy}/\text{number of patients with actionable mutations}) \times 100.$$

Outcomes were reported by the authors. For all cross-sectional cohort studies, CB, if not explicitly provided, was calculated by adding the number of patients who achieved stable disease, partial response, or complete response (CR). Overall response rate (ORR), if not explicitly provided, was calculated by summing the number of patients who achieved partial response or CR. To calculate rates regarding outcomes, the following formula was used:

$$(\text{number of patients with CB or ORR}/\text{number of patients receiving MTB-directed therapy}) \times 100.$$

Finally, the outcomes if the trial employed and intention-to-treat design were calculated using the following formula:

$$(\text{number of patients with CB or ORR, respectively}/\text{total number of patients referred to the MTB}) \times 100.$$

Quality Assessment and Bias Determination

Quality assessment of the reviewed articles was performed using either the Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group or the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies depending on the type of study being reviewed.[11] Each of the above tools were created and validated by the National Institutes of Health and were developed to determine the concepts that are necessary for critical review. Responses were yes, not reported (NR), or not applicable. Two researchers (K.L.L. and J.M.K.) performed the assessments independently, and any disagreements were discussed and resolved.

Additionally, the same researchers (K.L.L. and J.M.K.) reviewed the studies for risk using the tool To Assess the Risk of Bias in Cohort Studies validated by the Cochrane Institute.[12] Each study was rated as definitely yes, probably yes, probably no, and definitely no with the risk of bias increasing from yes to no.

RESULTS

A total of 71 articles were retrieved through a PubMed search. Titles and abstracts of 31 studies were reviewed for inclusion criteria. Ten articles were selected for a full

review, and four more were added after a screen of bibliographies and other additional resources. Fourteen total articles were reviewed for this systematic analysis (Fig 1).

Study Characteristics

For inclusion in this systematic review, the studies had to report CB, response rate, or survival among patients receiving MTB-recommended therapies. All studies were observational, and the majority were retrospective. About half of the studies screened fewer than 100 patients with a range of 34-2,579 for all studies. The majority of studies used large (more than 300 genes) commercial or in-house panels, with two using in-house whole-exome sequencing and one using a small (37 gene) panel. All studies took place in the United States,[13-22] France,[23-25] or the Netherlands[26] with the majority being single institution studies at academic medical centers. Eleven of the articles outlined MTBs that had reviewed patient cases for more than 1 year with only one reviewing for less than 1 year and two not reporting duration of review.

The authors for all publications analyzed similar aims for each of their tumor boards with one or all of the following stated:

1. To investigate the rate of mutations and examine their clinical utility,
2. To breakdown complex genomic reports and guide treatment,
3. To increase access to up-to-date precision medicine treatment options and clinical trials, and
4. To determine the efficacy of a precision medicine program.

The MTBs generally employed a consistent structure and operations, composed of an interdisciplinary team of clinicians and scientists, and operated essentially as a consult service, making recommendations to the treating physician rather than managing patients. Inclusion of a genetics counselor was common, but not universal. In most cases, treating physicians ordered NGS testing and then referred patients to the MTB for evaluation. In one study, the MTB was responsible for approving NGS, and in another study, all patients were enrolled in a prospective sequencing study with only a fraction of cases reviewed by the MTB (Tables 1 and 2). All MTBs, with one exception, made recommendations on the basis of pathogenic or likely pathogenic mutations, but one also included variants of unknown significance (Appendix Table A1).

Characteristics of the Patient Populations

Most of the MTBs described reviewed cases for multiple solid tumors with the exceptions of Kaderbhai et al[23] and Koopman et al[26] (non–small-cell lung cancer only), Parker et al[17] (breast cancer only), and Rodriguez-Rodriguez et al[20] (gynecologic malignancies only). The mean and median patient age for all studies (with the exception of Tafe et al,[21] which did not report age for their patients) was in the range of 50-68 years. The study population and/or eligibility requirements for MTB review were similar across all studies. The majority of patients had advanced-stage

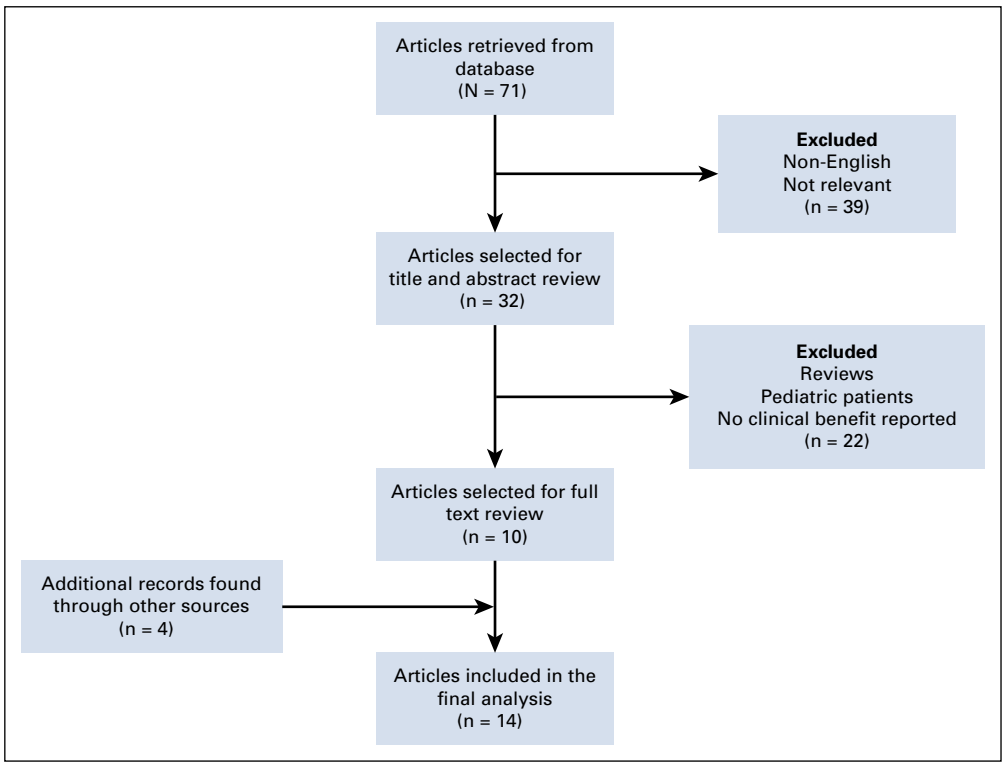

FIG 1. Study schema.

TABLE 1. Clinical Outcome of MTBs—Cross-Sectional Cohort Studies

Reference	Study Design	Scope of MTB	Sequencing Method	Tumor Types	Age (range), Years	Prior Lines of Therapy, Mean (range)	Patients Referred to MTB	Frequency Reviewed by MTB	Frequency of Actionable Mutations	Frequency of Receiving MTB Recommended Therapy	Outcomes If Received MTB Treatment	Outcomes If ITT
Bryce et al[13]	Prospective	Consult Multidisciplinary Treatment recommendations	Commercial panels In-house whole exome	Solid and hematologic	53 (1.5-86)	NR	165	141 of 165 (85%)	92 of 141 (65%)	31 of 92 (34%)	CB: 13 of 31 (42%)	CB: 13 of 165 (8%)
Burkard et al[14]	Prospective	Consult Multidisciplinary Treatment recommendations	Commercial panels In-house panels Single gene	Solid	57 (33-88)	2 (0-5)	38	38 of 38 (100%)	32 of 38 (84%)	9 of 32 (28%)	CB: 4 of 9 (44%) ORR: 2 of 9 (22%)	CB: 4 of 38 (11%) ORR: 2 of 38 (5%)
Harada et al[16]	Retrospective	Consult Multidisciplinary Treatment recommendations Approved testing	Commercial panels Panels at another university	Solid	57 (range NR)	NR	191	132 of 192 (69%)	48 of 132 (36%)	15 of 48 (31%)	CB: 8 of 15 (53%) ORR: 3 of 15 (20%)	CB: 8 of 191 (4%) ORR: 3 of 191 (2%)
Kaderbhai et al[23]	Retrospective	Consult Oncologist and molecular biologists Treatment recommendations	In-house panel	NSCLC	61 (42-78)	2.3[a] (1-7)	50	48 of 50 (96%)	29 of 48 (60%)	9 of 29 (31%)	CB: 7 of 9 (78%)[b] ORR: 4 of 9 (44%)	CB: 7 of 50 (14%) ORR: 4 of 50 (8%)
Koopman et al[26]	Retrospective	Consult Multidisciplinary Treatment recommendations	In-house panel	NSCLC	68 (36-89)	NR 68% with 0 32% with ≥ 1	129	110 of 129 (85%)	76 of 110 (69%)	25 of 76 (33%)	CB: 17 of 21[c] (81%) ORR: 14 of 21 (67%)	CB: 17 of 129 (13%) ORR: 14 of 129 (11%)
Rodriguez-Rodriguez et al[20]	Prospective	Consult Multidisciplinary Treatment recommendations	Commercial panels	Gynecologic	61 (22-80)	NR but only rare or refractory included	69	68 of 69 (99%)	64 of 68 (94%)	25 of 64 (39%)	CB: 16 of 25 (64%) ORR: 10 of 25 (40%)	CB: 16 of 69 (23%) ORR: 10 of 69 (14%)
Schwaederle et al[18]	Retrospective	Consult Multidisciplinary Treatment recommendations	Commercial panels	Solid	56 (29-75)	3[a] (1-13)	34	34 of 34 (100%)	33 of 34 (97%)	12 of 33 (36%)	CB: 7 of 12 (58%) ORR: 3 of 12 (25%)	CB: 7 of 34 (21%) ORR: 3 of 34 (9%)
Tafe et al[21]	Retrospective	Consult Multidisciplinary Treatment recommendations	In-house panel	Solid	NR	2[a] (1-7)	35	35 of 35 (100%)	18 of 35 (51%)	2 of 18 (11%)	CB: 2 of 2 (100%) ORR: 1 of 2 (50%)	CB: 2 of 35 (6%) ORR: 1 of 35 (3%)
Trédan et al[25]	Prospective	Consult Multidisciplinary Treatment recommendations	Small in-house panel (ION torrent PGM)	Solid and hematologic	58 (44-63)	NR but only advanced disease	2,579	1,980 of 2,579 (77%)	1,032 of 1,980 (52%)	163 of 1,032 (15%)	CB: 80 of 182[d] (43%) ORR: 23 of 182 (13%)	CB: 80 of 2,579 (3%) ORR: 23 of 2,579 (0.0%)
Trivedi et al[22]	Retrospective	Consult Multidisciplinary Treatment recommendations	Commercial panels	Solid	64 (37-82)	2.4 (1-6)	54	54 of 54 (100%)	54 (100%)	12 of 54 (22%)	CB: 9 of 12 (75%) ORR: 0 of 12 (0%)	CB: 9 of 54 (17%) ORR: 0 of 54

Abbreviations: CB, clinical benefit; ITT, intention to treat; MTB, molecular tumor board; NR, not reported; NSCLC, non–small-cell lung cancer; ORR, overall response rate.

[a]Median.

[b]Progression-free survival of 3 months considered stable disease.

[c]Outcomes of four individuals on clinical trials NR.

[d]Some pateints got more than one MTB-recommended therapy.

TABLE 2. Clinical Outcome of MTBs—Before-After Studies

Reference	Study Design	Scope of MTB	Sequencing Method	Tumor Types	Ages (range), Years	Prior Lines of Therapy, Mean (range)	Patients Referred to MTB	Frequency Reviewed by MTB	Frequency of Actionable Mutations	Frequency of Receiving MTB-Recommended Therapy	Outcomes If Received MTB Treatment	Outcomes If ITT
Dalton et al[15]	Retrospective	Consult Multidisciplinary Treatment recommendations	Commercial panels	Solid	59 (17-73)	2 (0-10)	155	155 of 155 (100%)	132 of 155 (85%)	28 of 132 (22%)	Median PFS (n) MTB (22): 5 months, 95% CI, 2.9 to NR Conv. (54): 3 months, 95% CI, 2.4 to 5 6-month PFS probability (n) MTB: 43%, 95% CI, 26 to 71 Conv.: 20%, 95% CI, 11 to 35	NA
Parker et al[17]	Retrospective	Consult Multidisciplinary Treatment recommendations	Commercial panels	Breast	59 (range NR)	3[a] (1-13)	43	43 of 43 (100%)	40 of 43 (93%)	17 of 40 (43%)	CB: 7 of 17 (41%) ORR: 5 of 17 (29%) PFS ratio ≥ 1.3 in 7 of 17 (41%)	CB: 7 of 43 (16%) ORR: 5 of 43 (12%)
Radovich et al[19]	Prospective	Consult Multidisciplinary Treatment recommendations	Commercial panels	Solid	55 (range NR)	4[a] (2-6)	168	168 of 168 (100%)	NR	44 of NR	PFS ratio ≥ 1.3 MTB: 19 of 44 (43%) Conv.: 3 of 57 (5%) $P < .0001$ Median PFS MTB: 86 days Conv.: 49 days HR = 0.55 (95% CI, 0.38 to 0.84)	NA
Réda et al[24]	Prospective	Consult Multidisciplinary Treatment recommendations	In-house WES but recommendations limited to panel	Solid	65 (24-94)	2[a] (1-8)	506	386 of 506 (76%)	342 of 506 (68%) (included VUS)	79 of 342 (23%)	PFS ratio ≥ 1.3 MTB: 12 of 48 (25%) Conv.: 23 of 89 (26%) NS $P = .8$ (χ^2 test)	NA

Abbreviations: CB, clinical benefit; conv., conventional; HR, hazard ratio; ITT, intention to treat; MTB, molecular tumor board; NA, not applicable; NR, not reported; NS, not significant; ORR, overall response rate; PFS, progression-free survival; VUS, variants of unknown significance; WES, whole-exome sequencing.

[a]Median.

TABLE 3. Quality Assessment of Before-After Studies

Quality Criteria	Dalton et al[15]	Parker et al[17]	Radovich et al[19]	Réda et al[24]
Clearly stated question or objective	No	No	Yes	No
Study eligibility clearly described	Yes	No	Yes	Yes
Participants' representative	Yes	Yes	Yes	Yes
All eligible patients enrolled	Yes	NR	NR	NR
Sample size sufficient	No	No	Yes	No
Intervention clearly described	Yes	Yes	Yes	Yes
Outcomes clearly defined, valid, reliable, and assessed consistently	No	No	Yes	No
Outcome assessors blinded	No	No	No	No
Loss to follow-up ≤ 20%	Yes	Yes	NR	Yes
Statistical methods provide *P* for pre- to postchanges	No	Yes	Yes	No
Outcome measures taken multiple times before and after intervention	NA	NA	NA	NA
Statistical analysis for group to individual effect	NA	NA	NA	NA

Abbreviations: NA, not applicable; NR, not reported.

disease and had received several prior therapies with most having exhausted all SOC options.

Quality Assessment

Study quality was analyzed using the quality assessment tools provided by the National Institutes of Health.[11] If the main outcomes of a study included comparing survival on an MTB-directed treatment with patients' prior treatment, the study was classified as before-after, and quality was assessed with Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group (Table 3). All other studies were classified as cross-sectional cohort studies, and quality was assessed with Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (Table 4). Most groups reported similar eligibility requirements or described their patient populations, and almost all patients were followed until progression on MTB therapy, and therefore used an appropriate timeframe to measure patient outcomes. Physician or patient choice, insurance, geographic location of clinical trials, and waiting to exhaust SOC options were the main reasons for not accepting MTB recommendations.

Bias analysis was performed using the tool from the Cochrane Institute.[12] Nine of the 14 studies did not include a matched control, neither a cohort of untreated patients nor by comparing MTB-recommended therapies with the patients' prior therapy. This resulted in those studies receiving the lowest score in that category, but the overall level of bias was low (Table 5).

Genetic Testing and Actionable Mutations

The types of sequencing varied among studies and within studies. The majority of samples were sent to commercial Clinical Laboratory Improvement Amendments laboratories with the most common being FoundationOne. Some researchers used on-site clinical laboratories to perform all DNA extraction and sequencing. The types of testing used included whole-exome sequencing, gene panels, and comparative genomic hybridization. Each study defined an actionable mutation differently with four[18-20,22] of the 14 studies not defining actionability at all. Those studies that used on-site clinical laboratories also varied in their decision making in regard to somatic calls, using different databases, and publications, to determine each patient's mutation profile. We calculated actionability rates for each study that provided sufficient data as described in methods. The frequency of actionable mutations ranged from 36% to 100%. Of note, the only MTB that considered tumor mutation burden an actionable mutation was the most recently published.[24] We diagrammed these actionability rates along each study timeline in Appendix Figure A1 (for those studies that included the timeframe of data collection). In general, rates of actionability increased over time, likely because of new targets and drug approvals. Exceptions were Koopman et al,[26] who only evaluated lung cancer, where the most common targetable driver mutations have been known for decades, and Parker et al[17] and Rodriguez-Rodriguez et al,[20] who focused on breast and gynecological malignancies, respectively, where new targetable have been slow to be identified.

Clinical Outcomes

To assess clinical outcomes, studies were divided into before-after or cross-sectional cohort studies. For the cross-sectional cohort studies, the percentage of patients receiving MTB-recommended targeted therapies ranged from 11% to 39%. Although reasons for not receiving an MTB-directed therapy were not frequently reported, when reported, the most common reasons were lack of actionable mutations, rapidly progressive disease, and when clinical trials were recommended by the MTB, patients were unwilling to travel or ineligible.[14] The frequency of patients achieving a CB from MTB-directed therapies ranged from 42%[14] to 100%,[21] although one study[21]

TABLE 4. Quality Assessment of Cross-Sectional Cohort Studies

Quality Criteria	Bryce et al[13]	Burkard et al[14]	Harada et al[16]	Kaderbhai et al[23]	Koopman et al[26]	Rodriguez-Rodriguez et al[20]	Schwaederle et al[18]	Tafe et al[21]	Trédan et al[25]	Trivedi et al[22]
Clearly stated question or objective	No	No	No	No	No	No	No	No	No	No
Defined population	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Participation rate of ≥ 50%	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Participant recruited from the same population	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sample size justification	No	No	No	No	No	No	No	No	No	No
Exposures measured before the outcome	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sufficient timeframe	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Different levels or exposures examined	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Exposure measures clearly defined	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcome measures clearly defined	No	No	No	No	No	No	No	No	No	No
Outcome assessors blinded	No	No	No	No	No	No	No	No	No	No
Loss to follow-up ≤ 20%	Yes	Yes	Yes	NR	NR	Yes	NR	NR	NR	Yes
Compounding variables measured	No	No	No	No	No	No	No	No	No	No

Abbreviations: NA, not applicable; NR, not reported.

reported clinical outcomes for only two patients. Kaderbhai et al[23] and Koopman et al[26] reported excellent CB rates of 78% and 81%, respectively, in patients with non–small-cell lung cancer. ORRs ranged from 0% to 67% reported by Trivedi et al[22] and Koopman et al,[26] respectively, with none of the patients in Trivedi's study achieving a partial or CR.

For the before-after studies, the percentage of patients receiving MTB-recommended targeted therapies ranged from 22% to 43%. There were two prospective trials reported, the first by Radovich et al[19] who prospectively compared the PFS ratio and PFS for 168 patients referred to their MTB. Of these, 67 were lost to follow-up or had insufficient follow-up duration and were excluded. Of the remainder, 44 received a genomically targeted therapy and 57 received nontargeted therapy. Patients with an actionable mutation and receiving a targeted therapy had improved PFS (mean 86 days) compared with those not receiving genomic therapy (mean 49 days, hazard ratio: 0.55, 95% CI, 0.37 to 0.84). In addition, 43.2% of those with a targeted therapy achieved a PFS ratio of ≥ 1.3, compared with only 5.3% of those with nontargeted therapy, $P < .0001$. Réda et al[24] evaluated 506 patients who were referred for NGS and were able to perform sequencing on 386. The primary end point was feasibility of the approach, defined as proportion of individuals who received a recommendation on the basis of their genomic report. Overall, 79 received a recommended therapy; however, there was no difference proportion of patients achieving a PFS of ≥ 1.3 between genomically targeted and standard therapy.

DISCUSSION

Somatic genomic sequencing has added additional layers of complexity to diagnosing and treating cancer. Molecular tumor boards have been developed to assist with assessing and acting on genomic reports.[6,27] All the studies analyzed for this review stated similar aims for their molecular tumor boards, using them as an opportunity to break down the complexity of genomic testing and reporting, increase access to up-to-date treatments and clinical trials, and better understand the clinical utility of precision medicine in oncology.

Nine of the 14 studies analyzed for this review had CB and/or response rate as the primary outcome. None of these studies were randomized nor were they controlled for non–MTB-directed outcomes, thus making it difficult to determine the effectiveness of molecular targeted therapies and the recommendations of their MTBs. ORRs in these

TABLE 5. Risk of Bias of All Studies

Bias Criteria	Bryce et al[13]	Burkard et al[14]	Dalton et al[15]	Harada et al[16]	Kaderbhai et al[23]	Koopman et al[26]	Parker et al[17]	Radovich et al[19]	Réda et al[24]	Rodriguez-Rodriguez et al[20]	Schwaederle et al[18]	Tafe et al[21]	Trédan et al[25]	Trivedi et al[22]
Selection of exposed and nonexposed cohorts drawn from the same population	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Confident in the assessment of exposure	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Confident that the outcome was not present at start of study	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Exposed and unexposed matched for all variables	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Confident in the assessment of the presence or absence of prognostic factors	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Confidence in the assessment of outcome	3	3	3	3	3	3	3	2	3	3	3	3	3	3
Follow-up of cohorts adequate	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Cointerventions similar between groups	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

NOTE. 1, definitely yes; 2, probably yes; 3, probably no; 4, definitely no.
Abbreviation: NA, not applicable.

studies ranged from 0% to 67%, which favorably compared with previously published ORRs of 5% in unmatched phase I trials[28] and 6% for all phase I trials in a single institution.[29] Trédan et al[22] not only had the largest patient cohort but also used the smallest gene panel for their NGS testing, resulting in a relatively low rate of patients with an actionable mutation. Koopman et al[26] reported a high CB in patients receiving an off-label drug, but the authors indicated stricter criteria for off-target therapies than other studies, denoting that mutations in downstream pathways were not considered for off-target therapies of an upstream protein.

The three studies that either used patients' PFS ratio or compared PFS between patient groups allowed for a more direct analysis of the efficacy of the MTB-directed therapies. Of these, one was positive,[19] one trended toward superiority,[15] and one found no difference.[24] Since PFS typically decreases with every subsequent therapy, a minor increase in PFS2 may be noteworthy in this population.[30]

Comparing outcomes across a wide variety of reports with different primary outcomes, patient populations, and criteria for recommendations makes definitive conclusions difficult; however, generally, positive benefits were seen. Outcomes reported in trials without a control arm did appear to be much better than in other salvage situations such as phase I trial responses from the era before targeted therapy.[29,30] Among those trials with a control arm, while not conclusive, MTBs provide CB and at least do no harm. In addition, overall impressions from the authors of each study were positive in regard to the utility of the MTBs at their respective institutions and suggested that each MTB helped to inform treatment decisions and increase access to genetic counseling for patients.

Although clinical trials comparing targeted therapies with standard therapies in those with a biomarker are almost universally positive, the reported benefit of NGS for the selection of therapy has been mixed. Several NCI-MATCH study arms demonstrate promising results. In arm H, patients with BRAFV600 mutations were treated with dabrafenib and trametinib. This arm met its primary end point, with an ORR of 33%.[31] The MOSCATO trial concluded that NGS improved outcomes, but only among a small subset of patients with targetable mutations.[32] The SHIVA trial was a

randomized phase II trial that included patients with a mutation in one of the three pathways, hormone receptors, PI3K, or RAF, and matched them to one of the 11 different targeted therapies. In this trial, there was no improvement in survival after treatment with targeted therapies.[33] The SHIVA trial has been criticized for its design, for both assigning therapies with unproven activity for the targets and using an algorithm that only considered mutations in the targeted arm, whereas physician discretion was allowed in the control arm. The number of patients eligible for targeted therapies increased between 2006 and 2018, likely because of more targeted therapy approvals every year, but that fewer than 7% actually benefitted, whereas only 16% were eligible.[34]

Advances in NGS technologies are also identifying additional patients with actionable mutations. High tumor mutation burden, an indication for pembrolizumab in any tumor type,[31] loss of heterozygosity, an indication for poly (ADP-ribose) polymerase inhibition for prostate cancer,[32] and certain RNA fusions, which confer sensitivity to specific targeted therapies, are now routinely reported on many NGS panels.[33] In addition, there is an increasing awareness of the ability of somatic mutation testing to identify potential germline mutations.[35] In addition to being targetable with small molecules, these germline mutations are clinically important to the patient's family members and support the need for inclusion of genetic counselors in the MTB team.

As the number of eligible patients continues to rise, it will become increasingly important for clinicians to accurately interpret complex genomic test results and to have increased access to therapies and clinical trials. Resources such as interprofessional MTBs can help clinicians navigate the complex world of precision medicine and provide these advanced treatments to their patients. Furthermore, as larger cohorts of data become available and shared, standardizing the components of an MTB, such as the definition of actionability, use of off-target drugs, and the types of sequencing will be imperative.

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Data analysis and interpretation: Bin Huang, Heidi L. Weiss, Pam Hull, Philip M. Westgate, Rachel W. Miller, Susanne M. Arnold, Jill M. Kolesar
Manuscript writing: All authors
Final approval of manuscript: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

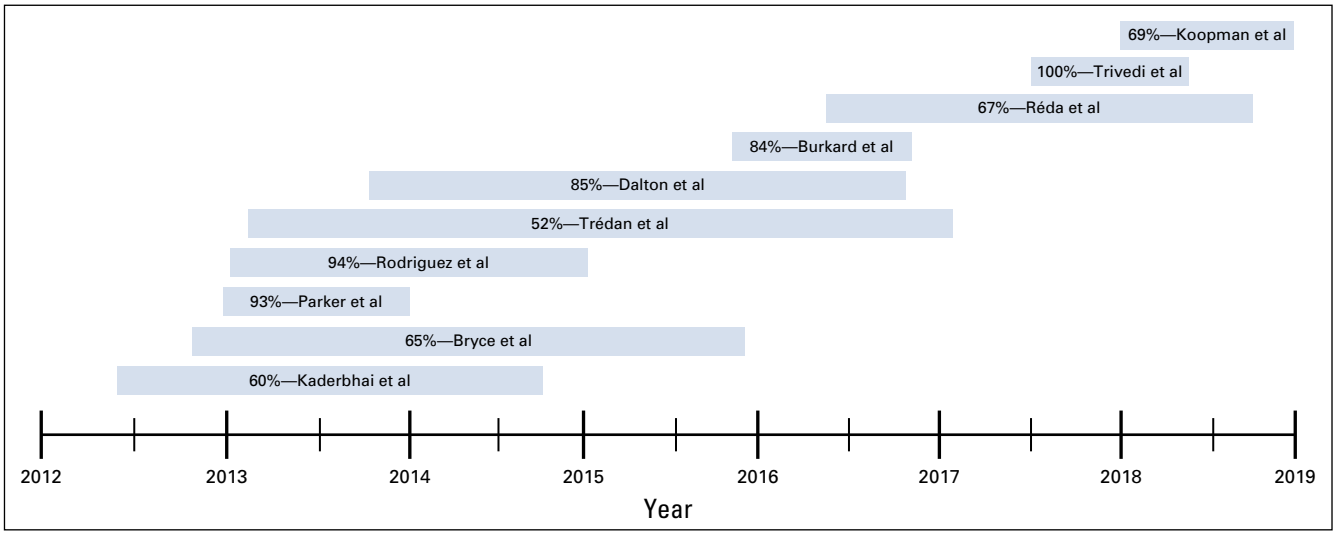

FIG A1. Actionability rates by year.

TABLE A1. Definitions of Actionability as Provided by the Authors

Reference	Definition of Actionability
Bryce et al[13]	An aberration with known functional significance that could be therapeutically targeted with an FDA-approved drug or clinical trial
Burkard et al[14]	Allowed for identification of a molecular-targeted clinical trial or off-trial treatment
Dalton et al[15]	Offered a target for a drug approved by the FDA, an FDA-approved drug off-label, a clinical trial, or was a potential germline mutation for a hereditary syndrome
Harada et al[16]	Variants classified as predictive or prognostic of any tumor types or have been reported in cancer and had available clinical trials
Kaderbhai et al[23]	Associated with FDA-approved drugs, potentially targetable when associated with a clinical trial or potential sensitivity to a drug
Koopman et al[26]	Tier 1 or 2 according to 2017 American College of Medical Genetics guidelines or existence of effective targeted therapy options
Parker et al[17]	An FDA-approved drug or in clinical trials that targeted at low nanomolar concentrations or was the primary target of an antibody
Radovich et al[19]	NR
Réda et al[24]	Class I-III variants with some class IV according to European Society of Medical Oncology Scale for Clinical Actionability of Molecular Tests guidelines, included some VUS
Rodriguez-Rodriguez et al[20]	NR
Schwaederle et al[18]	NR
Tafe et al[21]	Associated with available (approved, off-label, or experimental) targeting of the affected pathway
Trédan et al[25]	NR
Trivedi et al[22]	Linked as either a positive or negative biomarker for an approved therapy or enrollment criteria for an open clinical trial

Abbreviations: FDA, US Food and Drug Administration; NR, not reported; VUS, variants of unknown significance.

