Discordance in Recommendation Between Next-Generation Sequencing Test Reports and Molecular Tumor Boards in India

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ABSTRACT

PURPOSE Accurate understanding of the genomic and transcriptomic data provided by next-generation sequencing (NGS) is essential for the effective utilization of precision oncology. Molecular tumor boards (MTBs) aim to translate the complex data in NGS reports into effective clinical interventions. Often, MTB treatment recommendations differ from those in the NGS reports. In this study, we analyze the discordance between these recommendations and the rationales behind the discordances, in a non–high-income setting, with international input to evaluate the necessity of MTB in clinical practice.

METHODS We collated data from MTB that were virtually hosted in Chennai, India. We included patients with malignancies who had NGS reports on solid tissue or liquid biopsies, and excluded those with incomplete data. MTB forms and NGS reports of each clinical case were analyzed and evaluated for recommendation concordance. Concordance was defined as an agreement between the first recommendation in the MTB forms and the therapeutic recommendations suggested in the NGS report. Discordance was the absence of the said agreement. The rationales for discordance were identified and documented.

RESULTS Seventy MTB reports were analyzed with 49 cases meeting the inclusion criteria. The recommendation discordance was 49% (24 of 49). Discordant recommendations were mainly due to low level of evidence for the drug (75% of cases).

CONCLUSION The discordance between MTB and NGS vendor recommendations highlights the clinical utility of MTB. The educational experiences provided by this initiative are an example of how virtual academic collaborations can enhance patient care and provider education across geographic borders.

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INTRODUCTION

Comprehensive genomic profiling (CGP) using next-generation sequencing (NGS) of tumors in patients with advanced cancers helps identify genomic alterations that may be targeted with medications.[1] This led to the advancement of precision oncology where sequencing-directed therapy (SDT) resulted in personalized treatment and improved clinical response. Over time, the use of SDT in oncology has grown.[2]

NGS generates complex and massive data that are often difficult to analyze and interpret. The promise of precision therapeutics hinges on the accurate interpretation of this complex data.[3] The substantial variations in the sample evaluated, reference databases used, postprocessing and recommendation algorithms, cost-effectiveness of tests, and the test-reporting pattern generated by commercial laboratories involved further contribute to the complexity. An accurate understanding of the data provided by NGS is essential for the effective utilization of precision oncology.[4]

Molecular tumor boards (MTBs) are a potential solution to this conundrum. MTBs aim to translate the complex information presented in these reports into effective clinical interventions through collaboration among a multidisciplinary team. It facilitates discussions among clinicians, scientists, bioinformaticians, and geneticists where they evaluate available patient data including personal information, performance status, oncological history, and

CONTEXT

Key Objective

The primary objective of this study was to analyze the discordance between therapeutic recommendations proposed in next-generation sequencing reports and those advocated during molecular tumor board (MTB) discussions within a non–high-income setting.

Knowledge Generated

The observed discordance in recommendations was determined to be 49% (24 of 49 cases). Notably, the predominant rationale for discordance was attributed to a low level of evidence, accounting for 75% of the cases.

Relevance

These findings underscore the clinical significance of MTB and advocate for the integration of MTB reviews into the standard practices of all tertiary institutes.

diagnostic and imaging investigation results to suggest potential therapeutic strategies for the patients.[1]

At times, treatment recommendations suggested by the MTB may differ from those suggested by the NGS reports.[1] Although there are reports on the utility and effectiveness of MTB and NGS, there are no global guidelines on the conduction or incorporation of MTB into clinical practice or on the harmonization of reporting of NGS assays.[5] There is a paucity of studies that have evaluated differences in recommendations of MTB and NGS reports. Hence, in this study, we aimed to analyze the discordance between these recommendations and the rationales behind the discordances, in a non–high-income setting. Thereby, we aim to evaluate the necessity of a MTB in clinical practice.

METHODS

In this single-center retrospective study, MTB consensus reports were assessed for discordance between the MTB recommendations and the recommendations suggested in the NGS reports.

We collated data from MTB that were virtually hosted from the city of Chennai in India. The cases awaiting MTB are communicated to the specialists the day before the meeting. MTBs are attended by medical, surgical, and radiation oncologists, pathologists, molecular oncologists, and other specialties relevant to the cases discussed. The patients' clinical history, questions for the MTB, and answers to the questions are recorded electronically in standardized MTB consensus report forms. NGS is done by various commercial laboratories from different regions of India and the United States.

Patients with cancer who had NGS reports of tissue or liquid biopsies and were evaluated in MTB were included, regardless of their age, sex, tumor type, location, or NGS platform used. We removed patients with incomplete MTB forms or missing NGS results.

Each clinical case's MTB forms and NGS reports were examined and analyzed for recommendation discordance. Concordance was defined as agreement between the MTB's first suggestion (if other alternatives were recorded) and any therapeutic recommendation suggested in the NGS report. The absence of the said agreement was referred to as discordance.

The rationale for each clinical case was characterized into categories as follows:

1. Low level of evidence
2. Progression on current regimen or on agents in a similar class
3. Alternative standard-of-care therapies available
4. Alternative targeted therapies available
5. Others—molecular target identified on another test, on appropriate targeted therapy, primary/secondary resistance mechanism present, tolerability concerns, wild-type resistance biomarkers

The primary objective was to determine the discordance between the recommendations of MTB and NGS reports to evaluate the clinical benefit of MTB in cancer care.

RESULTS

Seventy MTB forms were analyzed. Seventeen clinical cases discussed in MTBs had NGS reports that did not provide any treatment recommendations and those were excluded. We also eliminated duplicate MTB discussions on the same clinical case (Fig 1). Finally, 49 MTB forms assessing NGS reports of 49 unique patients were included in the study (Table 1). The cohort had a median age of 54 years (32-82 years). The most common cancers studied were lung cancer (28%), breast cancer (15%), and stomach cancer (10%). The recommendation discordance rate was 49% (24 of 49). Low

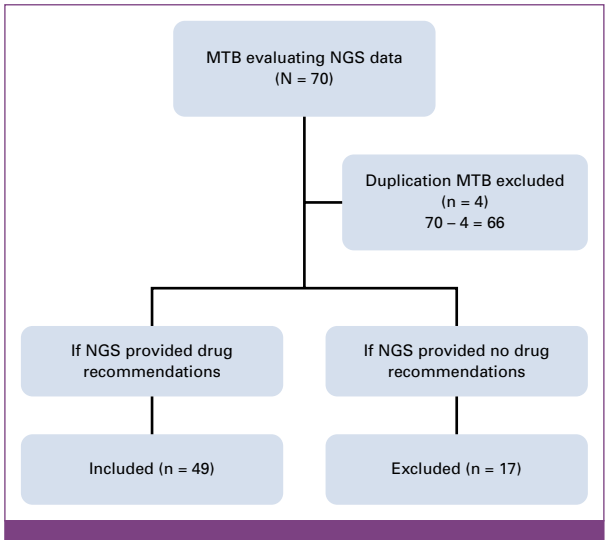

FIG 1. Study profile. Seventy MTBs between April 1, 2021 and December 1, 2021 were evaluated. Forty-nine MTBs were included in the study. Seventeen did not provide any treatment recommendations and hence were excluded. Four were discussions on the basis of NGS reports previously discussed in an MTB that was already included in the study, hence were excluded (duplication MTB). MTBs, molecular tumor boards; NGS, next-generation sequencing.

level of evidence (75% cases) was the most common rationale for discordance.

DISCUSSION

NGS, previously used only in cancers refractory to standard conventional treatment or in rare cancers, has now advanced integration into the standard of care. The cost-effectiveness of any intervention must be measured to determine its intrinsic value with only high-valued measures being integrated into routine clinical practice.[6] Upon retrospectively evaluating 221 patients who underwent CGP in India, Mathew et al found that 10% received a treatment that targets their genomic mutations and 4% (among 221 patients tested) derived any clinical benefit from the test.[7] CGP may add to the financial burden of patients with cancer. This is especially important for cancer care in India where financial toxicity has been reported in almost 54% of the patient population.[8]

Hence, potential overuse and the resultant economic burden of molecular profiling must be dealt with before they can be used on a larger scale. Despite these challenges, for hundreds of individual patients, CGP and SDT may improve survival outcomes and provide a good quality of life. To fully realize the potential of this innovation in limited-resource settings, we must focus our efforts on improving the reliability, precision, and affordability of precision oncology and practice careful utilization.

MTBs have a substantial role in improving the clinical utility of CGP. A recent study reported that doctors complied with MTB recommendations to make changes in treatment plan for 58% of the patients studied (N = 138).[9] To our knowledge, our study is the first from a non–high-income country to investigate the discordance between NGS treatment recommendations and MTB recommendations. We found the discordance to be 49% with low level of evidence listed as the most common discordance rationale (75%) in our study.

The robust use of molecular profiling and targeted therapies has led to increasingly small cohorts of patients for whom supportive data are available. Insufficient data often pose a challenge in confidently extrapolating results to a specific case.[4] This explains the high documentation of low level of evidence as the rationale for discordance. The second most common recorded rationale for discordance was progression on current regimen or on an agent of similar class (12.5%), which reflects a lack of clinical context. Unlike the commercial laboratories performing NGS assays, MTBs have access to additional patient data such as clinical profile and comorbidities, the social and economic background, diagnostic results, and biopsy reports. This helps the MTBs to conduct a holistic assessment of the patient and to arrive at a treatment strategy that is tailored toward the needs of the patient. Moreover, the clinical acumen and expertise of the tumor board panel can contribute to improved decisions on patient management.[4] This combination of personal clinical expertise, access to patient data, and real-time assessment of current literature in a MTB discussion helps fill gaps in knowledge as well as algorithms. MTBs have also been associated with increased access to genetic counseling and improved patient education.[10]

Virtual MTBs provide a setting removed of physical and geographical constraints, which is a means to combine expertise and genomic resources across institutions and borders. International virtual collaboration across the globe can further boost its clinical utility. This is especially true in low- or middle-income countries with resource constraints and a lack of adequate access to expert opinion. A study conducted among 422 patients with neuroblastoma from 32 countries assessing the benefit of such collaborations reported that they resulted in altering the treatment strategy in almost 70% of the sample population.[11]

Along with the patients, clinicians benefit from MTB. It provides them with a better understanding of indications as well as the deficiencies of molecular profiling, thus resulting in their judicious utilization. It improves the doctors' confidence in precision oncology, resulting in its increased acceptability as well as prevents increased dependence on the reports of commercial NGS platforms.[12]

Numerous studies have attempted to quantify the benefit of MTB. The analysis of five systematic reviews published between 2007 and 2018 by Larson et al[13] demonstrated the positive effect of MTB on patient management and its

TABLE 1. Discordance Between NGS Test Vendor Recommendations and MTB Recommendations

No.	Age, Years	Cancer Type	Alterations Identified	NGS Recommendations	MTB Recommendations	Discordance
1	67	Colorectal cancer	KRAS KMT2D APC TP53	FOLFOX + bevacizumab	Regorafenib + pembrolizumab	Yes[a]
2	50	Carcinoma of unknown primary	ERBB2 amplification AURKA amplification MYC amplification ARFRP1 amplification GNAS amplification RAD21 amplification SRC amplification TP53 L264fs*81 ZNF217 amplification	T-DM1	T-DM1	No
3	48	Breast	ERBB2 amplification PIK3CA G1049R CDK12 rearrangement intron 1 MYC amplification—equivocal[b] NSD3 (WHSC1L1) amplification TP53 splice site 559 + 2T>C	Immunotherapy or anti-HER2 therapy	Alpelisib + trastuzumab	Yes[b]
4	45	Ovary	PIK3CA N345K TSC2 splice site 3815-2A>G ARID1A Q185* CTCF T204fs*26	Everolimus	Tazemetostat	Yes[b]
5	60	Rectum	PIK3CA APC PBRM1 TP53	FOLFOX + bevacizumab	FOLFOX + bevacizumab	No
6	60	Breast	ERBB2 S310F D769Y TBX3 P134S	Neratinib	Neratinib	No
7	74	Lung	EGFR A763_Y764insFQEA (exon 20 insertion) GNAS R201C	Afatinib	Afatinib	No
8	70	Carcinoma of unknown primary	ARID1A p.Trp2048Ter PIK3CA p.Gln546Arg MET amplification	PARP inhibitor	Immunotherapy + PARP inhibitor	Yes[c]
9	49	Cervix	PD-L1 (22c3) KMT2C PIK3CA	Pembrolizumab	Pembrolizumab	No
10	41	Lung	NF1 C1367 PDGFRB Y562C—subclonal PIK3CA E542K—subclonal NFE2L2 G81A RICTOR amplification FGF10 amplification FGF12 amplification MLL2 R4238C MUTYH Q400 SF3B1 K666N TP53 L194R	Selumetinib	Selumetinib	No

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TABLE 1. Discordance Between NGS Test Vendor Recommendations and MTB Recommendations (continued)

No.	Age, Years	Cancer Type	Alterations Identified	NGS Recommendations	MTB Recommendations	Discordance
11	61	Colorectal cancer	KRAS G12D IDH1 R132C HGF amplification—equivocal[b] MYC amplification BCORL1 E1567* NRAS wildtype SMAD4 C363S TP53 H193Y	Ivosidenib	No actionable mutation	Yes[b]
12	50	Rectum	NRAS Q61K BARD1 R378S TP53 F270S MAP3K4 R157Hfs*11 TRPM1 T1423A CNTNAP4 F746S AURKA I57V	Immunotherapy	Regorafenib	Yes[b]
13	53	Stomach	ATM DNMT3A ERBB2 (HER2/Neu) KMT2D TMB high	Pembrolizumab	Anti-HER2 therapy	Yes[c]
14	60	Breast	CCND1 FGF3 FGF4 FGFR1 PIK3CA TP53 TMB Proteins—IHC—ER, PR, AR, PD L1 22c3, PD L1 sp142, PTEN-neg, ERBBS equivocal 2+, 10%	Pembrolizumab or endocrine therapy + everolimus	Endocrine therapy + metronomic chemotherapy	Yes[b]
15	82	Urothelial carcinoma	FBXW7 splice site 950_985 + 6del42 PIK3CA E545K BAP1 D225H BRD4 Q1017fs*50 CUL3 Y320fs*1 SMARCA4 P18fs*25 TERT promoter-124C>T TP53 R306* IHC—AR, PD-L1 22c3, sp142, PTEN	Immunotherapy	Chemotherapy	Yes[a]
16	34	Colorectal cancer	BRAF PIK3CA PTEN	Cetuximab + encorafenib	BRAF inhibitor + MEK inhibitor; but no disease now, therefore wait and watch	No
17	45	Stomach	PD-L1 22c3	Immunotherapy	Immunotherapy	No
18	46	Lung	RET gene rearrangement—CCDC6—RET fusion	Selpercatinib	Selpercatinib on progression	No
19	62	Stomach	PD-L1 (22c3) RNF43 TP53	Pembrolizumab	FOLFIRI + pembrolizumab	No

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TABLE 1. Discordance Between NGS Test Vendor Recommendations and MTB Recommendations (continued)

No.	Age, Years	Cancer Type	Alterations Identified	NGS Recommendations	MTB Recommendations	Discordance
20	46	Lung	EGFR p. (L858R)c.2573T>G	Osimertinib	Osimertinib	No
21	68	Hepatocellular carcinoma	A variant was detected in CTNNB1	Sorafenib	Sorafenib	No
22	47	Cholangiocarcinoma	FGFR2-BICC1 fusion, BICC1-FGFR2 noncanonical fusion PIK3CA E545K, MDM2 amplification—equivocal, MUTYH M1I	FGFR inhibitors	FGFR inhibitors on progression	No
23	43	Stomach	BRCA1 inversion exons 22-23 PTEN loss FGFR1 amplification—equivocal[b] APC E1540* CIC S183* FAS loss SMAD4 Q334* TP53 H193R	Immunotherapy	Immunotherapy + chemotherapy	No
24	61	Breast	Deletion of exon 3-5 of the PMS2 gene Extended NGS: BRIP1 p.(R798*) c.2392C>T (tier IIC) TP53 p.(P151S) c.451C>T (tier IIC), BRCA2 deletion (tier IIC), RAD52 p.(S346*) c.1037C>A (tier IIC)	PARP inhibitor	Chemotherapy + immunotherapy	Yes[b]
25	64	Lung	EML4-ALK fusion	ALK inhibitor	ALK inhibitor	No
26	62	Rectum	KRAS wildtype NRAS wildtype ERBB2 R678Q FBXW7 R465C APC D1394fs*21 GRM3 R465* TP53 R306*	Anti-HER2 therapy	Do not recommend anti-HER2 therapy	Yes[b]
27	52	Lung	EML4-ALK fusion PIK3CA542	ALK inhibitor	Chemotherapy + bevacizumab Stop lorlatinib	Yes[a]
28	48	Colorectal cancer	None	Anti-EGFR therapy	Anti-EGFR therapy	No
29	55	Lung	STK11 CDK4	MTOR inhibitor CDK 4/6 inhibitor	MTOR inhibitor CDK 4/6 inhibitor	No
30	52	Carcinoma of unknown primary	mTOR ICC-positive VEGFA ICC-positive MYC amplification (seven copies)	MTOR inhibitor/bevacizumab	Chemotherapy	Yes[b]
31	57	Lung	ERBB2	Afatinib or trastuzumab	Chemotherapy; afatinib when stable	Yes[b]
32	46	Breast	GATA3 TP53 IHC PDL1, PTEN, ER, PR, HER2:triple-negative AR IHC+	Bicalutamide, PARP inhibitor	Immunotherapy	Yes[b]
33	36	Breast	TP53. PD-L1 (SP142), PD-L1 (22c3), ER/PR/HER2/Neu triple-negative	PARP inhibitor	Observation Do not recommend PARP inhibitor. Chemotherapy + immunotherapy on recurrence	Yes[b]
34	64	Cholangiocarcinoma	FGFR2 Y375C ARID1A Q1333* BAP1 K38fs*50 CDKN2A/B CDKN2A loss, CDKN2B loss	Erdafitinib Pazopanib	Pembrolizumab + lenvatinib or chemotherapy	Yes[b]
35	32	Metastatic SPEN pancreas	FANCJ loss 1 copy	PARP inhibitor	Tamoxifen	Yes[b]

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TABLE 1. Discordance Between NGS Test Vendor Recommendations and MTB Recommendations (continued)

No.	Age, Years	Cancer Type	Alterations Identified	NGS Recommendations	MTB Recommendations	Discordance
36	49	Ovary	PIK3CA E542K ARID1A P452fs*168 CTNNB1 G34V	MTOR inhibitor	Chemotherapy	Yes[b]
37	63	Breast	FGFR1 PIK3Ca TP53 IHC—ER+	Alpelisib	Alpelisib	No
38	51	Carcinoma of unknown primary	ARID1A	PARP inhibitor	PARP inhibitor	No
39	67	Colorectal cancer	KRAS PIK3CA	Use alpelisib	Continue chemotherapy + bevacizumab ± everolimus	Yes[d]
40	72	Lung	MEt-MET MET exon 14 skipping	Capmatinib	Capmatinib	No
41	65	Lung	BRAF, p.V600E ERBB2, exon 20 insertion (p.Y772_A775dup)	BRAF inhibitor or anti-HER2 therapy T-DM1 Afatinib	Do not recommend BRAF inhibitor, T-DM1, or afatinib	Yes[b]
42	32	Lung	EGFR—exon 19 deletion	EGFR inhibitor	EGFR inhibitor	No
43	53	Cervix	BRCA1 rearrangement intron 2 CCND2 amplification KRAS amplification MTAP loss PTEN loss ARFRP1 amplification—equivocal[b] CDKN2A/B CDKN2A loss, CDKN2B loss FGF23 amplification FGF6 amplification KDM5A amplification SRC amplification TP53 R175H	PARP inhibitor	Chemotherapy + immunotherapy	Yes[b]
44	55	Lung	MET, p.T1010I, MET (14) [NM_001127500.3]	Crizotinib/cabozantinib	Chemotherapy	Yes[b]
45	57	Periampullary carcinoma	ATM splice site 7090-1G>A CCND1 amplification—equivocal[b] RAF1 amplification MDM2 amplification MTAP loss exons 2-8CDKN2A/B loss ERBB3 amplification—equivocal[b] FGF19 amplification—equivocal FGF3 amplification—equivocal FGF4 amplification—equivocal SMAD2 D450N	PARP inhibitor	PARP inhibitor	No
46	53	Gallbladder	CNVs ERBB2 amplification, TP53 (Y234C)	Anti-HER2 therapy	Anti-HER2 therapy	No
47	65	Pancreas	KRAS—p.G12D (MAF 2.91% at 107477X) TP53 KRAS G12D NF2 K99* TP53 P278A TP53 R65Efs*58	Trametinib	Trametinib	No

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TABLE 1. Discordance Between NGS Test Vendor Recommendations and MTB Recommendations (continued)

No.	Age, Years	Cancer Type	Alterations Identified	NGS Recommendations	MTB Recommendations	Discordance
48	59	Breast	ERBB2 amplification PIK3CA G1049R AKT1 amplification MYCN amplification GABRA6 T113M KEL splice site 924 + 1G>T REL amplification TP53 R248Q	Alpelisib	Alpelisib	No
49	54	Lung	EGFR exon 19 deletion (E746_T751>IP) ATM S2134fs*1 IDH1 R132C DNMT3A splice site 2597 + 1G>A, K276fs*4, S770L	PARP inhibitor	Chemotherapy	Yes[b]

NOTE. Rationales for discordance between the MTB recommendations and NGS recommendations are denoted by the superscripts.

Abbreviations: EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; HER2, human epidermal growth factor receptor 2; MTBs, molecular tumor boards; NGS, next-generation sequencing; PARP, poly (ADP-ribose) polymerase.

[a]Progression on current regimen or agent in a similar class.

[b]Low level of evidence.

[c]Alternate targeted therapies available.

[d]Alternate standard-of-care therapies available.

evolutionary trend. Various clinical end points examined were diagnosis and staging accuracy, quality of life, tumor recurrence and metastasis rates after surgical resection, survival, changes in patient management/clinical practices, adherence to evidence-based guidelines, implementation of MTB decisions, care coordination for professionals and patients, clinical and patients' satisfaction, visits to general practicioner, wait time from diagnosis to treatment, appropriate referral patterns, enrollment to tumor registries, and commitments to research and clinical trials.[13]

Walters et al[4] reviewed the MTB of the Advocate Aurora Health Oncology Precision Medicine program to document a discordance of 46% with "low level of evidence" as the most common rationale for discordance. The development of tissue-agnostic therapy recommendations, inaccessibility to the patient data and the ever-evolving literature on the drugs including resistance mechanisms and adverse events, and lack of expertise in clinical medicine were other contributors to high discordance. Some of the NGS-related concerns identified in a 2017 survey of oncologists in the United States are the lack of clinical guidelines for its use, the lack of expertise and resources to order and interpret NGS, the volume of genomic data, and the ambiguity of NGS reports.[14]

Our study assessed the impact of MTB on precision oncology by determining the recommendation discordance between MTB and NGS reports. However, our study is not without its limitations. First, our study demonstrates the recommendation discordance in a small sample size. Nevertheless, our study adds to the growing literature on the clinical benefit of MTBs and their various functions in cancer care by highlighting their role in improving the accessibility of targeted therapies. Second, we are unaware of the implementation of the MTB recommendations and the clinical outcomes of the study population. Hence, studies that monitor patient populations that adopt these recommendations may be beneficial. Third, the recommendation discordances were not stratified into the different NGS commercial laboratories involved. Finally, while the categorized rationales might offer some understanding of MTB's clinical decision making, it remains a subjective measure prone to bias, with potential to oversimplify the value of MTBs.

In conclusion, the discordance between MTB and NGS report recommendations and the corresponding rationales can be used to validate the clinical utility of MTBs. To enhance the benefits of the approach of precision oncology, we suggest incorporation of MTB reviews in all tertiary institutes, improved documentation of the MTB discussions in the electronic medical records along with concordance/discordance rationales, and an audit of response to targeted therapy after 6 months of treatment.

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Travel, Accommodations, Expenses: Boehringer Ingelheim, AstraZeneca, Roche, Bristol Myers Squibb, MSD, Pfizer, Lilly, Novartis, Takeda, Bayer, BeiGene, Guardant Health, Sanofi, EQRx
Uncompensated Relationships: British Thoracic Oncology Group, ALK, EGFR Positive UK, Roy Castle Lung Cancer Foundation

Aparna Raj Parikh
Consulting or Advisory Role: Checkmate Pharmaceuticals, Guardant Health, Foundation Medicine, AbbVie, Value Analytics Labs, Bayer, Taiho Oncology, Delcath Systems, Seagen, CVS, SAGA Diagnostics, Scarce, Illumina, UpToDate, Takeda, AstraZeneca, PMV Pharma, Pfizer, KAHR Medical, Xilio Therapeutics, Sirtex Medical
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Travel, Accommodations, Expenses: Karkinos Healthcare
Other Relationship: C2i genomics, Xact Robotics, Parithera, CADEX Genomics

Siddhartha Yadav
Research Funding: Repare Therapeutics (Inst), AstraZeneca (Inst)
Uncompensated Relationships: AstraZeneca
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Randeep Singh
Honoraria: Roche India, AstraZeneca

Deborah Mukherji
Honoraria: Merck, Bristol Myers Squibb, Pfizer, Astellas Pharma, AstraZeneca, Bayer, Janssen, BeiGene, MSD Oncology
Consulting or Advisory Role: MSD Oncology, Pfizer, Bristol Myers Squibb, Astellas Pharma
Research Funding: Bristol Myers Squibb (Inst), Merck Serono (Inst), Novartis (Inst), Pfizer (Inst)
Travel, Accommodations, Expenses: Amgen, Merck Serono

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