original reports abstract

Implementation of a Molecular Tumor Registry to Support the Adoption of Precision Oncology Within an Academic Medical Center: The Duke University Experience

Michelle F. Green, PhD[1]; Jonathan L. Bell, MD[1]; Christopher B. Hubbard, BS[1]; Shannon J. McCall, MD[1]; Matthew S. McKinney, MD[2]; Jinny E. Riedel, MS[3]; Carolyn S. Menendez, MD[3,4]; James L. Abbruzzese, MD[3,5]; John H. Strickler, MD[3,5]; and Michael B. Datto, MD, PhD[1]

PURPOSE Comprehensive genomic profiling to inform targeted therapy selection is a central part of oncology care. However, the volume and complexity of alterations uncovered through genomic profiling make it difficult for oncologists to choose the most appropriate therapy for their patients. Here, we present a solution to this problem, The Molecular Registry of Tumors (MRT) and our Molecular Tumor Board (MTB).

PATIENTS AND METHODS MRT is an internally developed system that aggregates and normalizes genomic profiling results from multiple sources. MRT serves as the foundation for our MTB, a team that reviews genomic results for all Duke University Health System cancer patients, provides notifications for targeted therapies, matches patients to biomarker-driven trials, and monitors the molecular landscape of tumors at our institution.

RESULTS Among 215 patients reviewed by our MTB over a 6-month period, we identified 176 alterations associated with therapeutic sensitivity, 15 resistance alterations, and 51 alterations with potential germline implications. Of reviewed patients, 17% were subsequently treated with a targeted therapy. For 12 molecular therapies approved during the course of this work, we identified between two and 71 patients who could qualify for treatment based on retrospective MRT data. An analysis of 14 biomarker-driven clinical trials found that MRT successfully identified 42% of patients who ultimately enrolled. Finally, an analysis of 4,130 comprehensive genomic profiles from 3,771 patients revealed that the frequency of clinically significant therapeutic alterations varied from approximately 20% to 70% depending on the tumor type and sequencing test used.

CONCLUSION With robust informatics tools, such as MRT, and the right MTB structure, a precision cancer medicine program can be developed, which provides great benefit to providers and patients with cancer.

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INTRODUCTION

Comprehensive genomic profiling of patients with advanced-stage cancer is becoming increasingly common, fueled by rapid advances in next-generation sequencing (NGS) technologies.[1] At the same time, an increasing number of biomarker-directed therapies are becoming available, through both new US Food and Drug Administration (FDA) approvals and investigational clinical trials. Since 2017, dozens of new FDA-approved oncology therapies have included an associated biomarker,[2-14] whereas an estimated 39% of current oncology clinical trials include a biomarker requirement for enrollment.[15] Although these advances may result in better outcomes for patients with cancer, they can be challenging to implement in oncology practice. In many instances, the use of tumor sequencing has outpaced available clinical evidence, and guidelines for the appropriate use of these tests is lacking. Multiple surveys have indicated that oncology providers sometimes encounter difficulties in interpreting tumor sequencing results and making informed treatment decisions, while there are additional concerns related to test reimbursement and access to targeted therapies, including difficulties in obtaining targeted therapies off-label and access to biomarker-specific clinical trials.[16-18] Molecular Tumor Board (MTB) programs have been established at several institutions to aid in the adoption of precision oncology and can serve as an important physician education and support mechanism.[19-22] These programs assemble multidisciplinary teams for manual review of submitted cases. However, as the volume of NGS testing increases, it can become increasingly difficult to provide administrative support for these programs, including the manual annotation of molecular alterations and generation of just-in-time personalized clinical recommendations. Furthermore, as the field of precision oncology is rapidly evolving, there is a need to analyze tumor-sequencing results longitudinally as new molecular targets are discovered and therapies become available. Thus, there is an unmet need to develop informatics platforms to organize and

ASSOCIATED CONTENT

Appendix

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

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CONTEXT

Key Objective

Comprehensive genomic profiling is becoming increasing common in the care of patients with advanced cancer, but informatics systems are needed to organize and store molecular data and make it available for timely physician support.

Knowledge Generated

We present here a unique system that leverages genomic testing results from multiple commercial vendors, which are then stored in an internal database, to foster precision oncology within our institution. This includes enabling analysis of genomic testing patterns, facilitating therapy and clinical trial matching, and guiding Molecular Tumor Board case reviews.

Relevance

Our model can be implemented at any institution, even those without comprehensive genomic profiling capabilities, to assist in the delivery of precision medicine to oncology patients.

store genomic testing results and provide timely physician support.

We present here our experience implementing a centralized molecular tumor registry to address these challenges and foster adoption of precision medicine within our institution. Our model is unique in that we leverage comprehensive genomic testing results from multiple commercial vendors, which are normalized and stored in our internal database. This system can be implemented at any institution, even those without internal molecular profiling capabilities, and has allowed us to broadly analyze the molecular landscape of tumors sequenced at our institution, provide therapy and clinical trial matching to our providers, and identify cases for review at our weekly MTB meetings. Furthermore, this system has allowed us to scale our MTB program to accommodate our increasing NGS test volume.

PATIENTS AND METHODS

Patient Selection and Genomic Testing

Comprehensive genomic profiling tests were ordered at the discretion of oncology providers as a component of routine cancer care. Genomic profiling tests were performed by Clinical Laboratory Improvement Amendments–accredited vendors approved by the Duke University Health System (DUHS) Diagnostic Technology Committee. Tumor tissue was primarily analyzed using FoundationOne F1 and CDx panels, which include DNA-based sequencing of more than 300 genes (Foundation Medicine Inc, Cambridge, MA).[23] In cases where gene rearrangements were expected, the FoundationOne Heme or Caris MI panels (Caris Life Sciences, Irving, TX), which include both RNA and DNA sequencing, was used. For liquid biopsy tests, the Guardant 360 (Guardant Health Inc, Redwood City, CA)[24] and FoundationOne Liquid panels were used. All solid tumor patients who receive comprehensive genomic profiling are reviewed by the MTB. For our analysis of outcomes associated with patients reviewed at MTB meetings, additional clinical characteristics including treatment history and disease status were collected through chart review and maintained using REDCap software (Research Electronic Data Capture, Vanderbilt, TN).[25] Approval for this retrospective review of patient records was granted from the Duke University Medical Center Institutional Review Board (Pro00104398).

The Molecular Registry of Tumors

An overview of the Duke University comprehensive genomic profiling workflow is presented in Figure 1A. Briefly, all genomic profiling results ordered within DUHS are stored within the electronic medical record (EMR), as well as an internally developed data warehouse solution called The Duke Molecular Registry of Tumors (MRT). MRT uses a normalized, relational SQL database that maintains tables for variants, variant types, pathogenicities, biomarkers, transcripts, chromosomes, genes, body sites, diagnoses, orderable test names, trials, clinical events, and other associated data elements that are used to define a genomic result. Users can normalize these data elements using a comprehensive suite of data curation tools. Users can also map results to action items including automated notification of users when a result is uploaded that makes a patient eligible for enrollment into a specific trial or a candidate for a specific therapy. Users interact with the MRT database through a web-based portal written in HTML5, Asp.net, C# for server side computing, and JavaScript. Additional data elements are imported from the EMR data warehouse including patient race, ethnicity, vital status, and last contact date. Approval for the establishment of MRT as a clinical and research data repository was granted by the Duke University Medical Center Institutional Review Board (Pro00085260). An additional protocol approved the use of MRT for clinical trial matching and included a waiver of informed consent (Pro00102329). For patients who enrolled in clinical trials, informed consent was obtained separately in accordance with each trial protocol.

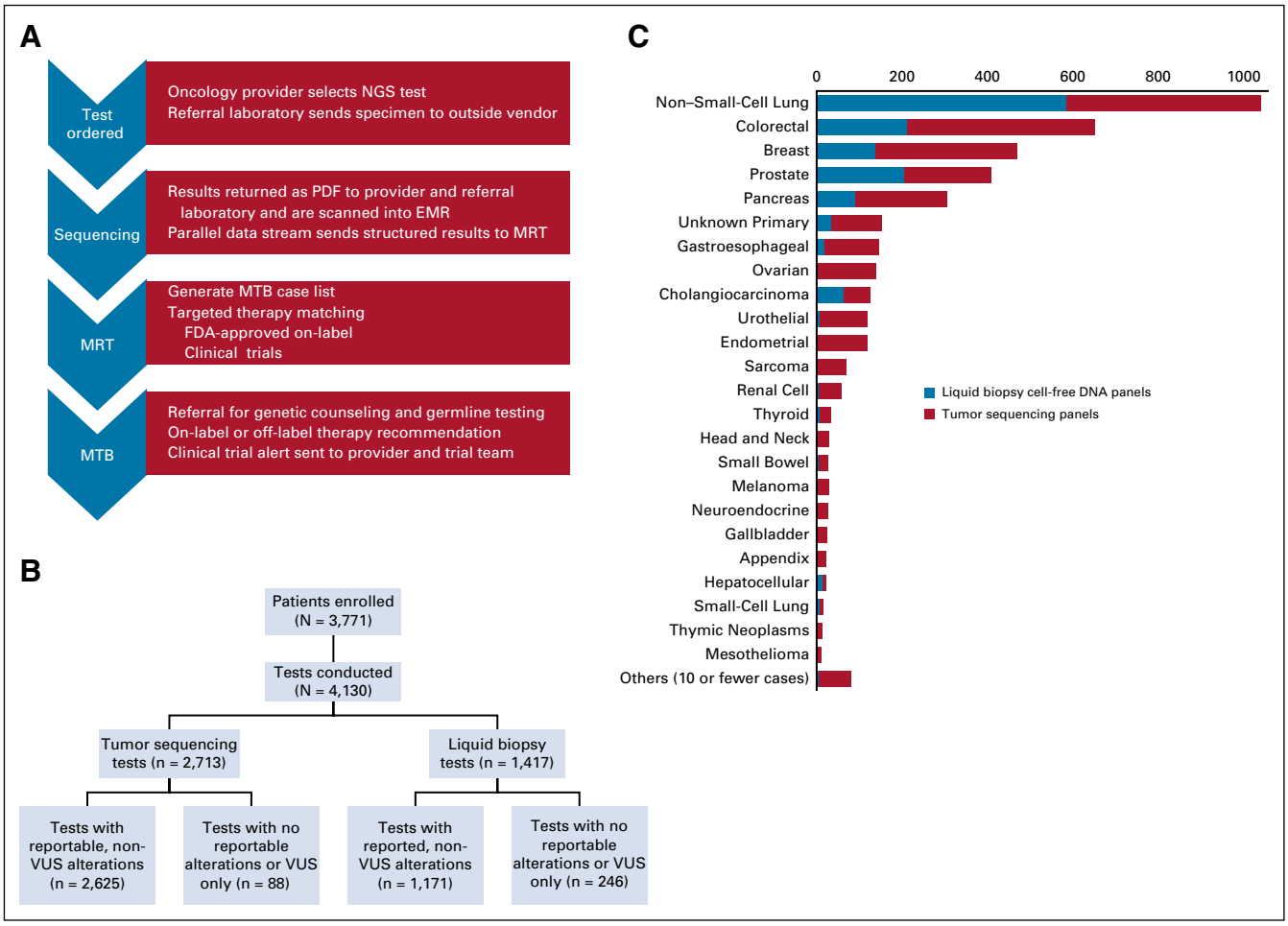


FIG 1. Overview of the Duke MRT workflow and solid tumor genomic profiling cohort. (A) Oncology providers select patients to receive NGS testing as part of routine cancer care. Tumor NGS testing is performed at an outside reference laboratory and results are returned to the oncology provider, the Duke Referral Lab, and to the MRT database. The MRT database is used to generate weekly MTB patient lists and to match patients to on-label targeted therapies and actively enrolling institutional clinical trials. (B) Number of patients and tests in the solid tumor genomic profiling cohort, which included both tumor tissue and liquid biopsy-based assays. A successful test was defined by the identification of at least one reported, non-VUS alteration. (C) Total number of liquid biopsy and tumor sequencing profiles separated by cancer type. For more information, see Appendix Table A1. EMR, electronic medical record; FDA, US Food and Drug Administration; MRT, Molecular Registry of Tumors; MTB, Molecular Tumor Board; NGS, next-generation sequencing; VUS, variant of uncertain significance.

MTB Organization

MRT is used to identify patients for MTB discussion. The MTB program coordinator, medical oncology coleaders, and a genetic counselor review all NGS test results from the previous week, and select cases for review. Cases are selected if they have actionable findings, atypical or unexpected results, germline implications, or make the patient eligible for a biomarker-directed clinical trial(s). Additional cases are discussed at the request of oncology providers. Multidisciplinary MTB meetings are held weekly and include medical oncologists, pathologists, medical geneticists, genetic counselors, clinical trial coordinators, basic scientists, bioinformaticians, and various trainees. During MTB meetings, MRT is used to display each patient's comprehensive genomic profiling results in a concise, standardized view including matching therapies and clinical trials. Discussion notes are recorded and sent to the ordering provider through secure e-mail within 24 hours.

Definition of Clinical Significance

The clinical significance of therapeutic sequence variants was classified according to guidelines jointly proposed by the Association for Molecular Pathology, ASCO, and College of American Pathologists with a few modifications.[26] Briefly, evidence level A includes variants associated with response to FDA-approved therapies in a specific tumor type and evidence level B includes variants associated with therapy response based on well-powered studies and expert consensus. Evidence level C was split into separate categories with level C1 indicating inclusion criteria for a clinical trial and C2 indicating a biomarker-specific therapy approval in a different tumor type. For the purposes of this study, only

DUHS clinical trials were considered, although the MTB also advised the ordering provider if a clinical trial was available outside of the institution. If a variant fulfilled criteria for both C1 and C2, it was classified as C1. As preclinical evidence was rarely used for clinical decision making, level D also includes alterations qualifying for clinical trial inclusion in another tumor type. Sequence variants associated with therapy resistance were classified as level A if they are included in professional guidelines, as level B if they have been identified in well-powered studies or repeatedly confirmed in multiple smaller studies, and as level C if they have only been reported in a small number of case series.

Data Analysis

Data were analyzed using Tableau software (Tableau Software LLC, Seattle, WA). Statistical analysis was performed using Statgraphics 18 software (Statgraphics Technologies Inc, The Planes, VA).

RESULTS

Patient and NGS Testing Characteristics

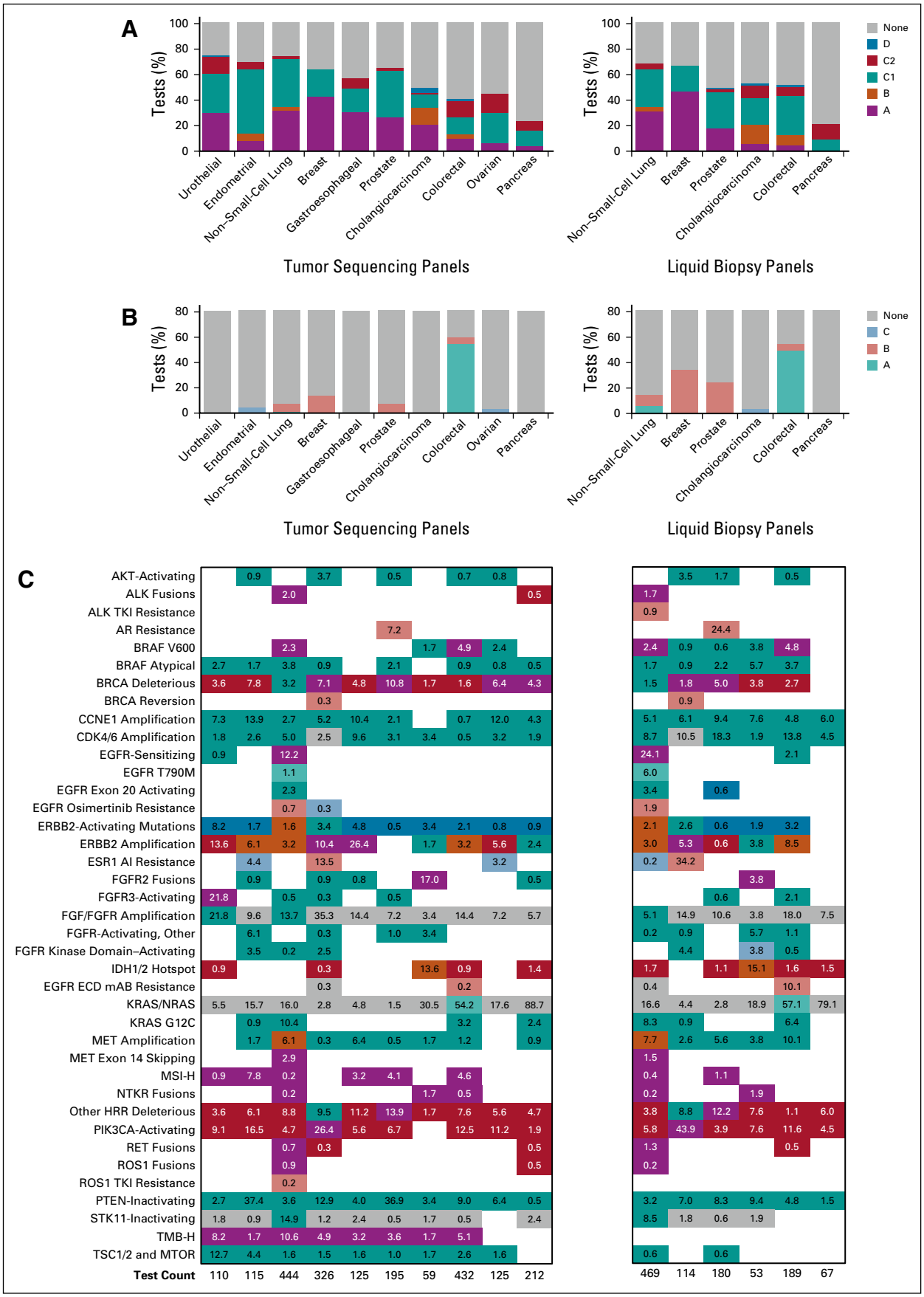
Before the implementation of the MRT database in March 2018, genomic testing results were returned directly to oncology providers as PDFs that were manually scanned into the EMR. This presented a challenge, as genomic data were not stored in a structured, easily searchable format. Following the launch of MRT, all genomic profiles generated by outside vendors dating back to 2013 were retrospectively uploaded, while secure data feeds supplied subsequent test results in real time. To better understand our genomic testing patterns, we performed an analysis of profiles from all solid tumors (excluding central nervous system tumors and hematologic malignancies) generated at our institution between June 1, 2013, and July 1, 2020. Patient characteristics are listed in Table 1. Our population included a diverse assortment of solid tumors, with the majority of profiles derived from common tumor types such as lung, breast, colorectal, and prostate carcinoma (Fig 1C; Appendix Table A1). Molecular profiling included a combination of tumor tissue– and liquid biopsy–based sequencing tests, with 309 patients receiving multiple profiles (Fig 1B). A test was considered successful if it returned at least one non–variant of uncertain significance alteration, with success rates of 96.8% and 82.6% for tumor tissue– and liquid biopsy–based testing, respectively. The total number of alterations detected varied by test type, with an average of 17 alterations detected by tumor sequencing tests and five detected by liquid biopsy.

TABLE 1. Characteristics of Solid Tumor Patients With Comprehensive Genomic Profiling Results (N = 3,771)

Characteristic	No. of Patients	Median (range)
Age at testing, years		64 (3-100)
Sex		
Female	1,962	
Male	1,809	
Race		
Caucasian or White	2,749	
Black or African American	697	
Unknown or declined	145	
Asian	80	
Other	40	
Two or more races	31	
American Indian or Alaskan Native	23	
Native Hawaiian or Other Pacific Islander	6	
Ethnicity		
Not Hispanic or Latino	3,398	
Not reported or declined or unavailable	315	
Hispanic Other	25	
Hispanic Mexican	21	
Hispanic Puerto Rican	8	
Hispanic Cuban	4	
Vital status		
Alive	1,727	
Deceased	2,044	
Time between testing results and death, days		213 (–50 to 1,993)

Landscape of Detected Alterations and Therapeutic Matching

We next examined the frequency of alterations that predict sensitivity or resistance to targeted therapies in our most commonly profiled tumor types (Figs 2A-2C). The percent of patients who could potentially qualify for an FDA-approved targeted therapy varied from approximately 40% in breast cancer to < 5% in pancreatic cancer (Figs 2A and 2C), whereas alterations associated with therapeutic resistance were most common in colorectal cancer (Figs 2B and 2C). The analysis above was performed with currently available targeted therapies, but as the number of targeted therapies has increased over time, it likely overestimates the number of patients who had a targeted therapy available during their cancer treatment. It can be challenging for oncology providers to identify patients who may benefit from a newly approved therapy based on previously obtained test results. To address this problem, starting in 2019 with the approval of erdafitinib for fibroblast growth factor receptor (FGFR)-altered urothelial carcinoma,[9] we performed a search of the MRT database to identify patients with previously detected alterations that may qualify for treatment with a newly approved targeted therapy (Fig 3A). We then notified oncology providers of these matches. While several patients with


A
Tests (%)
100
80
60
40
20
0
Urothelial
Endometrial
Non-Small-Cell Lung
Breast
Gastroesophageal
Prostate
Cholangiocarcinoma
Colorectal
Ovarian
Pancreas
Tumor Sequencing Panels
Liquid Biopsy Panels
None
D
C2
C1
B
A
B
C
B
A
AKT-Activating
ALK Fusions
ALK TKI Resistance
AR Resistance
BRAF V600
BRAF Atypical
BRCA Deleterious
BRCA Reversion
CCNE1 Amplification
CDK4/6 Amplification
EGFR-Sensitizing
EGFR T790M
EGFR Exon 20 Activating
EGFR Osimertinib Resistance
ERBB2-Activating Mutations
ERBB2 Amplification
ESR1 AI Resistance
FGFR2 Fusions
FGFR3-Activating
FGF/FGFR Amplification
FGFR-Activating, Other
FGFR Kinase Domain–Activating
IDH1/2 Hotspot
EGFR ECD mAB Resistance
KRAS/NRAS
KRAS G12C
MET Amplification
MET Exon 14 Skipping
MSI-H
NTKR Fusions
Other HRR Deleterious
PIK3CA-Activating
RET Fusions
ROS1 Fusions
ROS1 TKI Resistance
PTEN-Inactivating
STK11-Inactivating
TMB-H
TSC1/2 and MTOR
Test Count
110 115 444 326 125 195 59 432 125 212
469 114 180 53 189 67

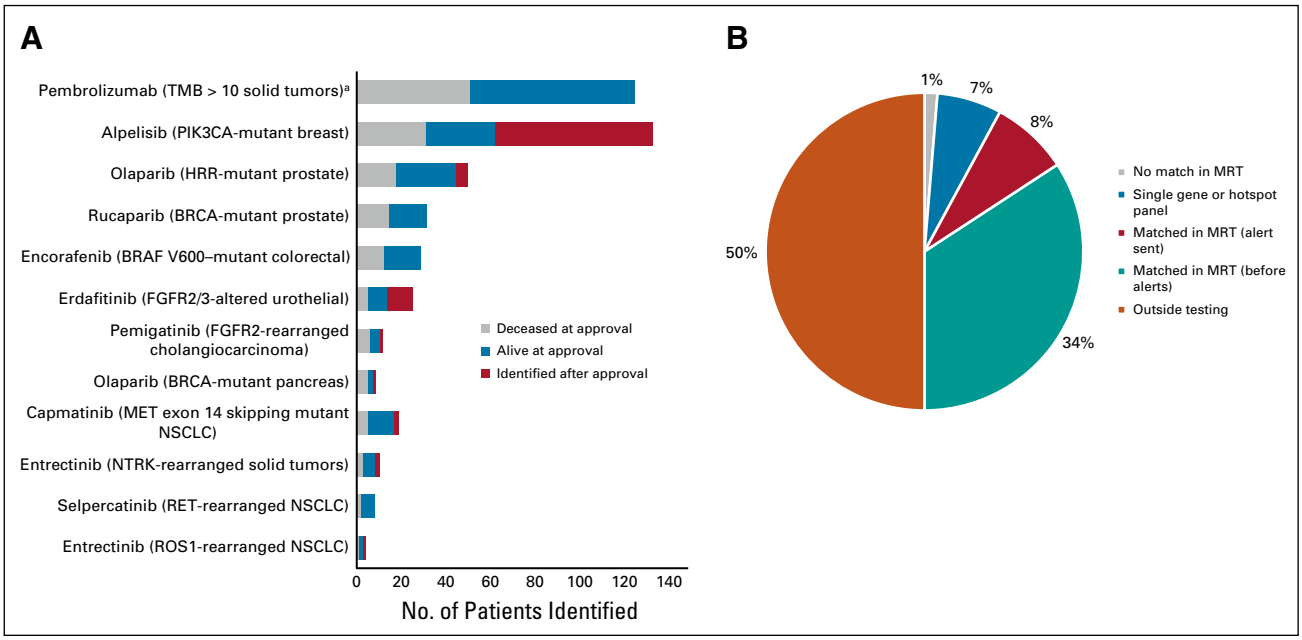


FIG 3. Newly approved therapy alerts and clinical trial matching. (A) Newly approved therapies are listed on the left, with the number of patients identified stratified by vital status and if the alteration was detected before or after the US Food and Drug Administration approval. (B) Sources of genomic profiling results for 76 patients enrolled on 14 biomarker-specific trials. [a]NSCLC, urothelial, and melanoma cases with TMB > 10 were excluded as use of pembrolizumab in these indications is dictated by other clinical and molecular diagnostic considerations, including programmed death-ligand 1 positivity. HRR, homologous recombination repair; MRT, Molecular Registry of Tumors; NSCLC, non–small-cell lung carcinoma; TMB, tumor mutational burden.

qualifying mutations were found to be deceased at the time of approval, between two and 71 patients were identified who could potentially benefit from each new therapy.

Clinical Trial Enrollment

For the tumor types examined above, the most frequently detected actionable alterations were those associated with clinical trial eligibility. Starting in September of 2019, molecular eligibility criteria for all DUHS biomarker-specific clinical trials were curated in the MRT database and matched to patients based on the presence of a qualifying alteration in the appropriate disease context. Trial matches were displayed during MTB meetings and notifications were sent to the ordering provider and clinical trial research staff when appropriate. We next examined the ability of the MRT database to identify patients who successfully enrolled and received treatment on biomarker-specific clinical trials. We identified 14 interventional clinical trials curated in the MRT database that required a biomarker predominately identified through genomic profiling tests for enrollment. As of Jul 1, 2020, 76 patients have successfully enrolled and received treatment on these trials, with 42% (32 of 76) matched in the MRT system either before or after notifications were implemented, 7% (5 of 76) identified through internal single-gene or hotspot panels not currently in the MRT database, and 50% (38 of 76) identified through external testing initiated at other institutions (Fig 3B). For the single case that was not matched in the MRT database, we found that the diagnosis of pancreatic adenocarcinoma associated with the NGS test was inaccurate. While the specimen had features consistent with a pancreaticobiliary primary, correlation with additional clinical findings resulted in a final diagnosis of cholangiocarcinoma. For the 38 internal cases with available data, the median time between return of genomic profiling results and start of treatment on a clinical trial was 117 days (range 21-691 days).

MTB Reviews

Since its launch, the MRT database has been used to identify patients with recent comprehensive genomic

FIG 2. Frequency of actionable alterations detected across common tumor types. Genomic profiling results from successful profiles from the 10 cancer types given across the top were stratified by the alteration with (A) maximal sensitizing or (B) resistant therapeutic significance according to modified Association for Molecular Pathology, ASCO, and College of American Pathologists joint guidelines. The results from tumor sequencing tests are on the left, whereas the liquid biopsy results are on the right. (C) Overall frequencies of actionable alterations found in the same tumor types as above are given for tumor sequencing and liquid biopsy panels, with the functional variant group on the left hand side. The total number of successful tests is given below. Evidence levels are colored coded as in (A) and (B). AI, aromatase inhibitor; ECD, extracellular domain; HRR, homologous recombination repair; mAB, monoclonal antibody; MSI-H, microsatellite instability–high; TKI, tyrosine kinase inhibitor; TMB-H, tumor mutational burden–high.

TABLE 2. Molecular Tumor Board Patient Characteristics (N = 215)

Characteristic	No. of Patients	Median (range)
Age at testing, years		65 (27-91)
Sex		
Female	124	
Male	91	
Metastatic disease at the time of NGS testing?		
Yes	193	
No	19	
Unknown	3	
NGS test type		
Liquid biopsy	46	
Tumor tissue	169	
Time between order and test result, days[a]		
Liquid biopsy		9 (7-14)
Tumor tissue		13 (8-94)
Time between result and MTB meeting, days[b]		
Liquid biopsy		5.5 (3-17)
Tumor tissue		6 (3-45)
Time between MTB meeting and therapy change, days[a]		
Liquid biopsy	9	16 (0-39)
Tumor tissue	27	84 (1-409)
Specimen type (tumor testing only)		
Metastatic lesion	86	
Primary lesion or local recurrence	80	
Unspecificed	3	
Cancer type		
Breast	47	
Non–small-cell lung	43	
Colorectal	32	
Prostate	18	
Gastroesophageal	13	
Uterine	12	
Pancreas	12	
Urothelial	10	
Cholangiocarcinoma	8	
Small bowel	4	
Ovarian	3	
Unknown primary	3	
Appendix	2	
Skin	2	
Sarcoma	2	
Cervix	1	
Salivary gland	1	
Thymus	1	
Thyroid	1	
Total	215	

Abbreviations: MTB, Molecular Tumor Board; NGS, next-generation sequencing.

[a]A significant difference between liquid biopsy and tissue testing as determined by a two-sided P value $< .05$ based on the Mann-Whitney test.

[b]No significant difference as determined by a two-sided P value $> .05$ based on the Mann-Whitney test.

profiling results to be discussed at weekly MTB meetings. To better understand the influence comprehensive genomic profiling had on the treatment of patients with cancer within our institution, we performed a chart review of 215 patients discussed at MTB meetings over a six-month period between April and September of 2019. Characteristics for these patients are presented in Table 2. Among these cases, 176 actionable therapeutic alterations and 15 resistance alterations were identified (Figs 4A and 4B). The time between test order and result was slightly faster for liquid biopsy as compared with tissue testing (9 *v* 13 days), but there was no significant difference in time between test result and MTB discussion (Table 2). While patients discussed at MTB meetings were biased toward those with actionable alterations, there was a higher frequency of therapeutically sensitizing and potential germline alterations identified using tissue sequencing tests as compared with liquid biopsy tests (Fig 4E). However, a higher frequency of resistance alterations were detected using liquid biopsy tests. For patients with sensitizing alterations, therapy changes were made in 17% (36 of 215) of cases (Fig 4D). The median time between MTB discussion and treatment change was 14 days for liquid biopsy versus 84 days for tumor testing. For the 11 patients who received off-label therapies, the median time on treatment was 160 days, ranging from 12 to 589 days (Appendix Fig A1). Of note, 27% (3 of 11) of patients receiving off-label therapies would have qualified for targeted-therapies based on subsequent FDA approvals.

Alterations with potential germline significance were identified in 51 cases, with 31 of these patients receiving an evaluation by the Duke Hereditary Cancer Clinic (Fig 4C). Among the 20 patients who were not evaluated, seven passed away shortly after receiving comprehensive genomic test results, five were lost to follow-up, three had variant of uncertain significance alterations, and one was a potential MUTYH carrier.

DISCUSSION

The primary goal of our MTB program is to foster the adoption of precision medicine within our institution. This includes support for clinical decision making, enabling access to state-of-the art molecular testing, and facilitating high-impact clinical research. However, a major challenge to accomplishing these goals was a lack of access to molecular genetic data, which were typically stored in the EMR as a PDF. To overcome this challenge, we developed a centralized molecular tumor registry. Our system is unique as compared with others described in the literature in that it incorporates genomic testing results from multiple sources, which are then stored and normalized in an internal database.[27-32] This model allows our providers access to a range of high-quality, innovate tests offered through commercial partners, but also makes structured data available to our internal MTB team. Our model allows for implementation at any oncology practice, even those not

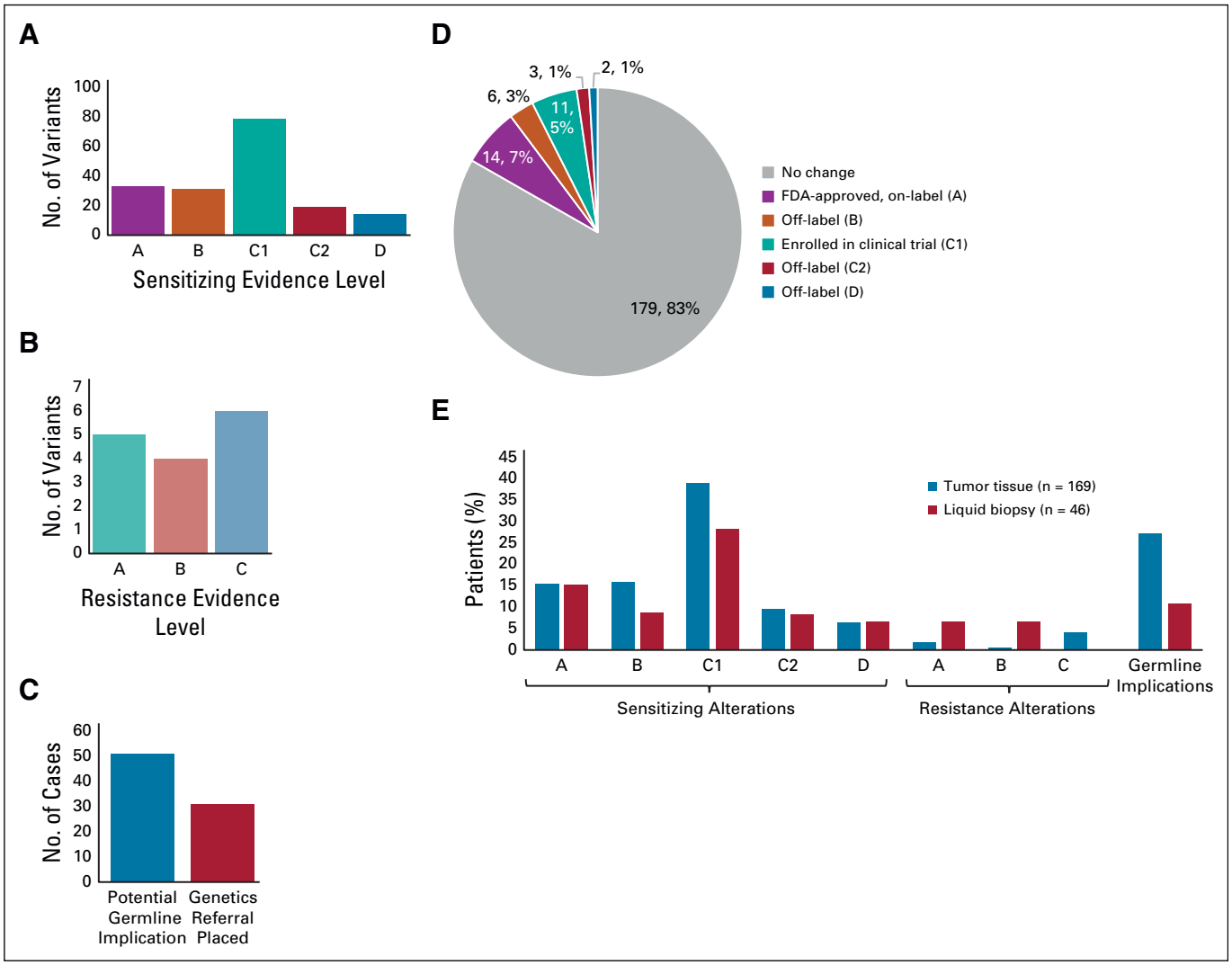


FIG 4. MTB patient outcomes. Variants discussed at MTB meetings were classified by the level of sensitizing (A) or resistant (B) clinical evidence. (C) Number of cases where NGS results identified an alteration with potential germline implications, and number of patients referred to our Hereditary Cancer Clinic for follow-up. (D) The number of patients where therapy changes were made based on NGS test results are shown, stratified by the clinical evidence level of the associated variant. Labels include the number and percentage of patients with therapy changes for each evidence level. (E) Percentage of patients receiving tumor tissue or liquid biopsy tests harboring actionable alterations. FDA, US Food and Drug Administration; MTB, Molecular Tumor Board; NGS, next-generation sequencing.

associated with academic centers capable of comprehensive genomic profiling. As reported here, this approach gives us the ability to support clinical decision making through several mechanisms. This includes the identification of patients who may benefit from discussion during our weekly multidisciplinary MTB meetings and systematic matching of patients to appropriate targeted therapies and biomarker-specific clinical trials. We are also able to search our database longitudinally and notify providers as new therapies become available. Finally, our MTB system also facilitates clinical research. We present here a broad analysis of our NGS testing characteristics and the molecular landscape of detected alterations. Other teams within our institution have also made use of our centralized tumor registry for clinical research projects,[33-35] and our database has enabled our participation in the American Association of Cancer Research Genomics Evidence Neoplasia Information Exchange data sharing initiative.[36]

Although we consider our MTB program successful based on our ability to achieve the goals discussed above, only 17% (36 of 215) of patients included in our MTB analysis received a matched targeted therapy. This is similar to other studies assessing the feasibility of using comprehensive genomic profiling to guide targeted therapy selection where actionable alterations were identified in 27%-75% of patients, but only 6%-23% went on to receive a targeted therapy.[37-42] The reasons for this are complex. In many cases, the evidence for molecularly targeted therapies may

be insufficient to replace standard-of-care chemotherapy regimens with proven clinical benefit and often the optimal sequencing of molecularly matched therapies is poorly defined. As an example of this, pembrolizumab was first approved for the treatment of refractory microsatellite instability–high or mismatch repair-deficient colorectal cancer in 2017 based on response rate and duration of response,[5] but data from the KEYNOTE-177 trial demonstrating superiority to standard of care chemotherapy in the first-line setting were not available until 2020.[43] Other elements that require optimization include selection of the most appropriate NGS test and guidelines for when these tests should be ordered during the course of cancer treatment. A recent analysis comparing the utility of tissue testing and liquid biopsy to facilitate enrollment of patients with gastrointestinal cancer on clinical trials found a shorter screening time and increased trial enrollment rate for patients who received liquid biopsy tests.[44] In our analysis, we found that liquid biopsy had a slightly faster turnaround time, but also detected a reduced number of sensitizing alterations. This difference was most likely a result of smaller panel size. For tumor sequencing results, the time between MTB discussion and therapy change was also highly variable, ranging from 1 to 409 days. This variability most likely results from the wide range of clinical scenarios where NGS testing is ordered, ranging from newly diagnosed metastatic disease to advanced, heavily treated patients. Finally, tolerability of molecular therapies can limit their use. In our patients with breast cancer, we identified PIK3CA mutations associated with alpelisib sensitivity in 30% of cases, but this therapy is associated with high rates of hyperglycemia that have limited its use at our institution.[4,45]

In summary, this study demonstrates the feasibility of a centralized molecular tumor registry to guide the adoption of precision oncology in an academic medical center. Our registry serves many functions, including enabling analysis of NGS testing patterns, facilitating therapeutic matching, and guiding MTB case reviews. We expect informatics solutions similar to ours will be a critical component in the delivery of precision medicine to oncology patients.

AFFILIATIONS

[1]Department of Pathology, Duke University Medical Center, Durham, NC
[2]Division of Hematologic Malignancies, Department of Medicine, Duke University Medical Center, Durham, NC
[3]Duke Cancer Institute, Duke University Medical Center, Durham, NC
[4]Department of Surgery, Duke University Medical Center, Durham, NC
[5]Division of Medical Oncology, Department of Medicine, Duke University Medical Center, Durham, NC

CORRESPONDING AUTHOR

Michael B. Datto, MD, PhD, Duke Health System Clinical Laboratories, Green Zone Duke South Hospital, Duke Medicine Circle, DUMC Box 3712, Room 353M, Durham, NC 27710; e-mail: michael.datto@duke.edu.

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AUTHOR CONTRIBUTIONS

Conception and design: Michelle F. Green, Christopher B. Hubbard, Shannon J. McCall, Matthew S. McKinney, Jinny E. Riedel, James L. Abbruzzese, John H. Strickler, Michael B. Datto
Financial support: Shannon J. McCall
Administrative support: Christopher B. Hubbard, Shannon J. McCall
Provision of study materials or patients: Christopher B. Hubbard, James L. Abbruzzese
Collection and assembly of data: Michelle F. Green, Jonathan L. Bell, Christopher B. Hubbard, Shannon J. McCall, Matthew S. McKinney, Jinny E. Riedel, Michael B. Datto
Data analysis and interpretation: Michelle F. Green, Christopher B. Hubbard, Matthew S. McKinney, Carolyn S. Menendez, James L. Abbruzzese, John H. Strickler, Michael B. Datto
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Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Brown NA, Elenitoba-Johnson KSJ: Enabling precision oncology through precision diagnostics. Annu Rev Pathol 15:97-121, 2020
2. Drilon A, Laetsch TW, Kummar S, et al: Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 378:731-739, 2018
3. Doebele RC, Drilon A, Paz-Ares L, et al: Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: Integrated analysis of three phase 1–2 trials. Lancet Oncol 21:271-282, 2020
4. André F, Ciruelos E, Rubovszky G, et al: Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. N Engl J Med 380:1929-1940, 2019
5. Marcus L, Lemery SJ, Keegan P, et al: FDA approval summary: Pembrolizumab for the treatment of microsatellite instability-high solid tumors. Clin Cancer Res 25:3753-3758, 2019

6. de Bono J, Mateo J, Fizazi K, et al: Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 382:2091-2102, 2020
7. Wolf J, Seto T, Han J-Y, et al: Capmatinib in MET exon 14–mutated or MET-amplified non–small-cell lung cancer. N Engl J Med 383:944-957, 2020
8. Drilon A, Oxnard GR, Tan DSW, et al: Efficacy of selpercatinib in RET fusion-positive non-small-cell lung cancer. N Engl J Med 383:813-824, 2020
9. Loriot Y, Necchi A, Park SH, et al: Erdafitinib in locally advanced or metastatic urothelial carcinoma. N Engl J Med 381:338-348, 2019
10. Abou-Alfa GK, Sahai V, Hollebecque A, et al: Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: A multicentre, open-label, phase 2 study. Lancet Oncol 21:671-684, 2020
11. Golan T, Hammel P, Reni M, et al: Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med 381:317-327, 2019
12. Kopetz S, Grothey A, Yaeger R, et al: Encorafenib, binimetinib, and cetuximab in BRAF V600e–mutated colorectal cancer. N Engl J Med 381:1632-1643, 2019
13. Abida W, Patnaik A, Campbell D, et al: Rucaparib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 gene alteration. J Clin Oncol 38:3763-3772, 2020
14. Marabelle A, Fakih M, Lopez J, et al: Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: Prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol 21:1353-1365, 2020
15. IQVIA: Global Oncology Trends 2019, 2019. https://www.iqvia.com/insights/the-iqvia-institute/reports/global-oncology-trends-2019
16. Razelle K, Colevas AD, Anthony O, et al: NCCN oncology research program's investigator steering committee and NCCN best practices committee molecular profiling surveys. J Natl Compr Canc Netw 13:1337-1346, 2015
17. Freedman AN, Klabunde CN, Wiant K, et al: Use of next-generation sequencing tests to guide cancer treatment: Results from a nationally representative survey of oncologists in the United States. JCO Precis Oncol 10.1200/PO.18.00169
18. Gray SW, Hicks-Courant K, Cronin A, et al: Physicians' attitudes about multiplex tumor genomic testing. J Clin Oncol 32:1317-1323, 2014
19. Knepper TC, Bell GC, Hicks JK, et al: Key lessons learned from Moffitt's molecular tumor board: The Clinical Genomics Action Committee experience. Oncologist 22:144-151, 2017
20. Schwaederle M, Daniels GA, Piccioni DE, et al: On the road to precision cancer medicine: Analysis of genomic biomarker actionability in 439 patients. Mol Cancer Ther 14:1488-1494, 2015
21. Dalton WB, Forde PM, Kang H, et al: Personalized medicine in the oncology clinic: Implementation and outcomes of the johns hopkins molecular tumor board. JCO Precis Oncol 10.1200/PO.16.00046
22. Luchini C, Lawlor RT, Milella M, et al: Molecular tumor Boards in clinical practice. Trends Cancer 6:738-744, 2020
23. Frampton GM, Fichtenholtz A, Otto GA, et al: Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. Nat Biotechnol 31:1023-1031, 2013
24. Lanman RB, Mortimer SA, Zill OA, et al: Analytical and clinical validation of a digital sequencing panel for quantitative, highly accurate evaluation of cell-free circulating tumor DNA. PLoS One 10:e0140712, 2015
25. Harris PA, Taylor R, Thielke R, et al: Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 42:377-381, 2009
26. Li MM, Datto M, Duncavage EJ, et al: Standards and guidelines for the interpretation and reporting of sequence variants in cancer: A joint consensus recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn 19:4-23, 2017
27. Tao JJ, Eubank MH, Schram AM, et al: Real-world outcomes of an automated physician support system for genome-driven oncology. JCO Precis Oncol 10.1200/PO.19.00066
28. Lindsay J, Del Vecchio Fitz C, Zwiesler Z, et al: MatchMiner: An open source computational platform for real-time matching of cancer patients to precision medicine clinical trials using genomic and clinical criteria. bioRxiv 10.1101/199489
29. Pishvaian MJ, Blais EM, Bender RJ, et al: A virtual molecular tumor board to improve efficiency and scalability of delivering precision oncology to physicians and their patients. JAMIA Open 2:505-515, 2019
30. Johnson A, Khotskaya YB, Brusco L, et al: Clinical use of precision oncology decision support. JCO Precis Oncol 10.1200/PO.17.00036
31. Tamborero D, Dienstmann R, Rachid MH, et al: Support systems to guide clinical decision-making in precision oncology: The Cancer Core Europe Molecular Tumor Board Oortal. Nat Med 26:992-994, 2020
32. Tao J, Eubank MH, Pamer E, et al: PRECISE: A clinical-grade automated molecular eligibility screening and just-in-time (JIT) physician decision support solution for molecularly-selected oncology trials. J Clin Oncol 36, 2018 (suppl; abstr 6507)
33. Watson CH, Broadwater G, Wong J, et al: Results and clinical utilization of foundation medicine molecular tumor profiling in uterine and ovarian cancers. Target Oncol 16:109-118, 2021
34. Tan I, Stinchcombe TE, Ready NE, et al: Therapeutic outcomes in non-small cell lung cancer with BRAF mutations: A single institution, retrospective cohort study. Transl Lung Cancer Res 8:258-267, 2019
35. Zhu J, Tucker M, Marin D, et al: Clinical utility of FoundationOne tissue molecular profiling in men with metastatic prostate cancer. Urol Oncol 37:813.e1-813.e9, 2019
36. AACR Project GENIE: Powering precision medicine through an international consortium. Cancer Discov 7:818-831, 2017
37. Meric-Bernstam F, Brusco L, Shaw K, et al: Feasibility of large-scale genomic testing to facilitate enrollment onto genomically matched clinical trials. J Clin Oncol 33:2753-2762, 2015
38. Le Tourneau C, Delord J-P, Gonçalves A, et al: Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): A multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. Lancet Oncol 16:1324-1334, 2015
39. Réda M, Richard C, Bertaut A, et al: Implementation and use of whole exome sequencing for metastatic solid cancer. EBioMedicine 51:102624, 2020
40. Trédan O, Wang Q, Pissaloux D, et al: Molecular screening program to select molecular-based recommended therapies for metastatic cancer patients: Analysis from the ProfiLER trial. Ann Oncol 30:757-765, 2019
41. Massard C, Michiels S, Ferté C, et al: High-throughput genomics and clinical outcome in hard-to-treat advanced cancers: Results of the MOSCATO 01 trial. Cancer Discov 7:586-595, 2017
42. Flaherty KT, Gray RJ, Chen AP, et al: Molecular landscape and actionable alterations in a genomically guided cancer clinical trial: National Cancer Institute molecular analysis for therapy choice (NCI-MATCH). J Clin Oncol 38:3883-3894, 2020
43. PD-1 inhibitor bests chemo for colorectal cancer. Cancer Discov 10:OF2, 2020

44. Nakamura Y, Taniguchi H, Ikeda M, et al: Clinical utility of circulating tumor DNA sequencing in advanced gastrointestinal cancer: SCRUM-Japan GI-SCREEN and GOZILA studies. Nat Med 26:1859-1864, 2020
45. Nunnery SE, Mayer IA: Management of toxicity to isoform α-specific PI3K inhibitors. Ann Oncol 30:x21-x26, 2019

APPENDIX

Patient	Cancer Type	Variant	Therapy
11	Breast carcinoma	ERBB2 extracellular domain–activating	Trastuzumab; trastuzumab plus endocrine therapy plus ERBB2 TKI
10	Prostate adenocarcinoma	BRCA-inactivating	Olaparib
9	Lung adenocarcinoma	Atypical MET-activating mutation	Cabozantinib; capmatinib
8	Lung adenocarcinoma	MET exon 14 skipping mutation	Crizotinib; capmatinib
7	Colorectal carcinoma	ERBB2 amplification	Pertuzumab/trastuzumab; ado-trastuzumab emtansine
6	Prostate carcinoma	BRAF V600 hotspot	Encorafenib/binimetinib
5	Prostate adenocarcinoma	BRCA-inactivating	Talazoparib
4	Lung adenocarcinoma	ROS1 fusion	Lorlotinib
3	Melanoma	NRAS G12 hotspot	Binimetinib
2	Cholangio-carcinoma	IDH1 hotspot	Ivosidenib
1	Gastric adenocarcinoma	BRCA-inactivating	Olaparib

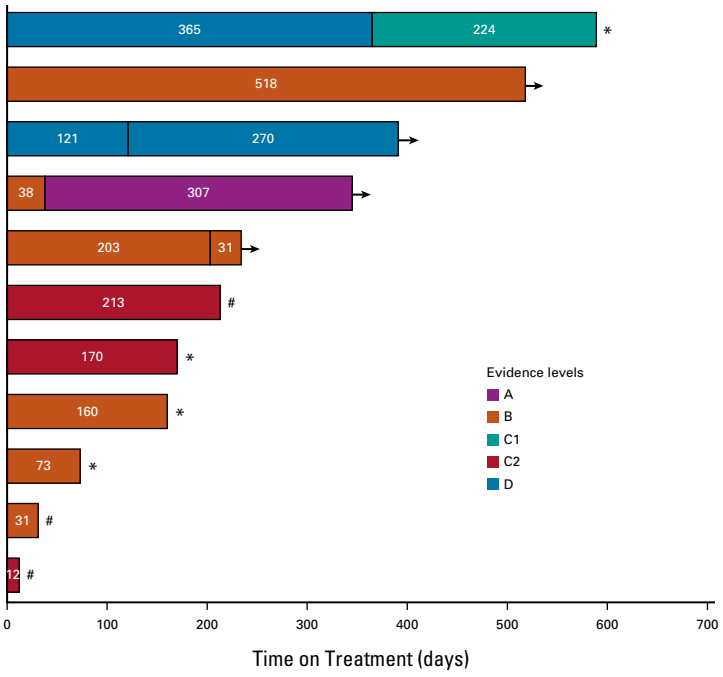

FIG A1. Outcomes of patients treated with off-label targeted therapies. The characteristics of patients treated off-label with targeted therapies are shown on the left, including cancer type, biomarker targeted, and the specific therapy. Patients 11, 9, 8, and 7 received multiple lines of targeted therapies. Time on therapy is included on the right, with colors correlating to the Association for Molecular Pathology/ASCO/College of American Pathologists joint guidelines therapeutic evidence level. The arrow (→) indicates treatment was ongoing at time of review, an asterisk (*) indicates the patient discontinued therapy because of progression, and the number sign (#) indicates the patient was on treatment at the time of death. TKI, tyrosine kinase inhibitor.

TABLE A1. Detailed Patient and Test Counts for the Solid Tumor Genomic Profiling Cohort Separated by Specimen Type, Diagnosis, and Test Success

		All Patients and Tests		Patients and Tests With Reported, Non-VUS Alterations	
Panel Type by Specimen	**Diagnosis Group Name**	**Patient Count**	**Test Count**	**Patient Count**	**Test Count**
Liquid biopsy cell-free DNA panels	Non–small-cell lung carcinoma	541	585	442	469
	Colorectal carcinoma	195	212	177	189
	Prostate carcinoma	195	205	174	180
	Breast carcinoma	131	137	109	114
	Pancreas carcinoma	86	91	67	67
	Cholangiocarcinoma	61	63	52	53
	Unknown primary cancer	33	35	27	28
	Gastroesophageal carcinoma	19	19	14	14
	Hepatocellular carcinoma	13	13	12	12
	Urothelial carcinoma	8	8	8	8
	Thyroid carcinoma	7	8	7	8
	Small-cell lung carcinoma	7	7	5	5
	Small bowel adenocarcinoma	5	6	5	6
	Renal cell carcinoma	6	6	3	3
	Appendix cancer	4	4	4	4
	Gallbladder carcinoma	3	3	2	2
	Thymic neoplasms	2	2	1	1
	Sarcoma	2	2	2	2
	Ovarian or fallopian tube carcinoma	2	2	1	1
	Melanoma	2	2	1	1
	Penile carcinoma	1	1	0	0
	Mesothelioma	1	1	1	1
	Head and neck cancers	1	1	0	0
	Gastrointestinal stromal tumor	1	1	0	0
	Chordoma	1	1	1	1
	Ampullary carcinoma	1	1	1	1
	Adrenal cortical carcinoma	1	1	1	1
	Total	1,328	1,417	1,117	1,171

(Continued on following page)

TABLE A1. Detailed Patient and Test Counts for the Solid Tumor Genomic Profiling Cohort Separated by Specimen Type, Diagnosis, and Test Success (Continued)

		All Patients and Tests		Patients and Tests With Reported, Non-VUS Alterations	
Panel Type by Specimen	**Diagnosis Group Name**	**Patient Count**	**Test Count**	**Patient Count**	**Test Count**
Tumor sequencing panels	Non–small-cell lung carcinoma	441	454	433	444
	Colorectal carcinoma	431	438	429	432
	Breast carcinoma	317	331	312	326
	Pancreas carcinoma	212	214	211	212
	Prostate carcinoma	198	203	191	195
	Ovarian or fallopian tube carcinoma	129	136	120	125
	Gastroesophageal carcinoma	125	127	124	125
	Unknown primary cancer	116	118	116	118
	Endometrial carcinoma	116	118	114	115
	Urothelial carcinoma	108	110	108	110
	Sarcoma	64	68	58	59
	Cholangiocarcinoma	61	62	58	59
	Renal cell carcinoma	51	52	45	46
	Head and neck cancers	29	29	27	27
	Neuroendocrine cancer	25	27	24	25
	Melanoma	26	26	25	25
	Thyroid carcinoma	25	25	25	25
	Small bowel adenocarcinoma	21	22	21	22
	Gallbladder carcinoma	22	22	22	22
	Appendix cancer	18	19	17	17
	Thymic neoplasms	10	10	7	7
	Sex cord stromal tumors	10	10	10	10
	Mesothelioma	9	10	8	8
	Cervical carcinoma	10	10	10	10
	Hepatocellular carcinoma	9	9	9	9
	Small-cell lung carcinoma	8	8	8	8
	Ampullary carcinoma	8	8	8	8
	Adenoid cystic carcinoma	8	8	7	7
	Urinary tract carcinoma, other	7	7	7	7
	Nonmelanoma skin cancer	7	7	5	5
	Gastrointestinal stromal tumor	5	6	4	5
	Vulva or vagina carcinoma	4	4	4	4
	Germ cell tumors	4	4	2	2
	Anal cancer	4	4	1	1
	Adrenal cortical carcinoma	3	3	2	2
	Penile carcinoma	2	2	2	2
	Hepatoblastoma	1	1	1	1
	Chordoma	1	1	0	0
	Total	2,639	2,713	2,572	2,625
Grand totals	Total	3,771	4,130	3,540	3,796

Abbreviation: VUS, variant of uncertain significance.

