

Feasibility of Large-Scale Genomic Testing to Facilitate Enrollment Onto Genomically Matched Clinical Trials

Funda Meric-Bernstam, Lauren Brusco, Kenna Shaw, Chacha Horombe, Scott Kopetz, Michael A. Davies, Mark Routbort, Sarina A. Piha-Paul, Filip Janku, Naoto Ueno, David Hong, John De Groot, Vinod Ravi, Yisheng Li, Raja Luthra, Keyur Patel, Russell Broaddus, John Mendelsohn, and Gordon B. Mills

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All authors: The University of Texas MD Anderson Cancer Center, Houston, TX.

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Corresponding author: Funda Meric-Bernstam, MD, The University of Texas MD Anderson Cancer Center, 1400 Holcombe Blvd, Unit 455, Houston, TX 77030; e-mail: fmeric@mdanderson.org.

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A B S T R A C T

Purpose

We report the experience with 2,000 consecutive patients with advanced cancer who underwent testing on a genomic testing protocol, including the frequency of actionable alterations across tumor types, subsequent enrollment onto clinical trials, and the challenges for trial enrollment.

Patients and Methods

Standardized hotspot mutation analysis was performed in 2,000 patients, using either an 11-gene (251 patients) or a 46- or 50-gene (1,749 patients) multiplex platform. Thirty-five genes were considered potentially actionable based on their potential to be targeted with approved or investigational therapies.

Results

Seven hundred eighty-nine patients (39%) had at least one mutation in potentially actionable genes. Eighty-three patients (11%) with potentially actionable mutations went on genotype-matched trials targeting these alterations. Of 230 patients with *PIK3CA/AKT1/PTEN/BRAF* mutations that returned for therapy, 116 (50%) received a genotype-matched drug. Forty patients (17%) were treated on a genotype-selected trial requiring a mutation for eligibility, 16 (7%) were treated on a genotype-relevant trial targeting a genomic alteration without biomarker selection, and 40 (17%) received a genotype-relevant drug off trial. Challenges to trial accrual included patient preference of noninvestigational treatment or local treatment, poor performance status or other reasons for trial ineligibility, lack of trials/slots, and insurance denial.

Conclusion

Broad implementation of multiplex hotspot testing is feasible; however, only a small portion of patients with actionable alterations were actually enrolled onto genotype-matched trials. Increased awareness of therapeutic implications and access to novel therapeutics are needed to optimally leverage results from broad-based genomic testing.

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INTRODUCTION

The increasing availability of next-generation sequencing combined with the availability of molecular therapeutics targeting genomically defined populations has created a growing interest in using multiplexed genomic profiling for routine cancer care and, in particular, for directing patients to relevant clinical trials. However, implementation of genomically informed therapy requires not only access to genomic profiling, but also the availability of molecularly targeted therapies matched to the genomic testing results. Availability of clinical trials may not only differ from institution to institution, but may also differ between tumor types. Enrollment onto clinical trials is also

limited by trial eligibility criteria, as well as availability of slots.

As a result of growing physician and patient demand for genomic profiling at The University of Texas MD Anderson Cancer Center, we initiated a prospective clinical study where physicians were able to enroll patients who they felt would benefit from multiplex genomic testing and where patients were likely to consider enrollment onto therapeutic clinical trials. Patients with any malignancy were eligible for the study and underwent genomic testing on a Clinical Laboratory Improvement Amendments (CLIA) –compliant platform after informed consent. Here, we report the experience with the first 2,000 patients who underwent testing on the genomic testing protocol, including the

frequency of actionable alterations across tumor types, subsequent enrollment onto clinical trials, and the challenges for subsequent trial enrollment.

PATIENTS AND METHODS

Patient Selection and Enrollment

Patients were enrolled onto an institutional review board–approved prospective protocol for genomic profiling, Molecular Testing for the MD Anderson Cancer Center Personalized Cancer Therapy Program (NCT01772771), after informed consent. The study was piloted in the Nellie B. Connally Breast Center and the GI Center through research nurse/coordinator identification of patients with metastatic breast and colorectal cancer. After 5 months, patient identification was transitioned to the treating oncologists, and patients perceived as likely to benefit from genomic characterization were enrolled. The majority of patients had metastatic, inoperable locally advanced or locally recurrent disease or were otherwise considered high risk. Patients were mainly accrued in disease centers with genomically relevant trials; also enrolled were patients with diseases for which there were no disease-specific trials but the treating physicians expressed interest in referring patients for phase I trial enrollment. Notably, patients with diseases for which multiplex genomic testing is accepted as standard of care (eg, lung cancer) were often tested without protocol enrollment and are under-represented.

We reviewed the first 2,000 patients who underwent genomic profiling; clinical information was collected from electronic medical records and prospective databases. Data acquisition was locked on August 26, 2014.

Genomic Analysis

Samples were evaluated using hematoxylin and eosin staining for tumor cellularity. DNA was extracted, purified, and quantified. Genomic analysis was performed by mass spectroscopy–based multiplex assay to assess the mutational status of hotspot regions in 11 genes (first 251 patients) or with next-generation sequencing using the Ion Ampliseq Cancer Panel (Life Technologies, Grand Island, NY) to assess hotspot mutations in 46 genes (Appendix Table A1, online only). In the last few months, testing expanded to 50 genes by adding *EZH2*, *IDH2*, *GNA11*, and *GNAQ* (33 patients, Appendix Table A1).

Sequence alignment and base calling were performed by Torrent Suite software V2.0.1 (Life Technologies) with Human Genome Build 19 (Hg19) as reference. Torrent Variant Caller software V1.0 (Life Technologies) was used for variant detection, and the Integrative Genomics Viewer (<http://www.broadinstitute.org/igv/>) was used to visualize variants. OncoSeek software was used to integrate the data.¹ Routine germline testing was not performed. Germline variants were defined based on relative prevalence within the MD Anderson Cancer Center patient population and by comparing the data with dbSNP v.138 (<http://www.ncbi.nlm.nih.gov/projects/SNP/>) global minor allele frequency numbers where available, as previously described.² Variants classified as likely to be germline are listed in Appendix Table A2 (online only).

Analysis

Alterations potentially targetable with established or investigational therapeutics directly or indirectly (eg, inhibiting downstream signaling) were considered actionable. The actionable genes are designated by asterisks in Appendix Table A1. The therapeutic implications of potentially actionable genes are listed in Appendix Table A3 (online only).

Categorical variables were summarized in frequency tables. Mutation rates were calculated based on the tested samples. The association between the presence or absence of actionable mutations and enrollment onto a clinical trial after the genomic testing was assessed using a Pearson χ^2 test.

RESULTS

From March 2012 to July 2013, 2,601 patients were enrolled; 601 patients (23%) did not undergo testing as a result of inadequate tissue or DNA quantity or quality. Two thousand patients underwent testing, 251 by an 11-gene Sequenom panel (Sequenom, San Diego, CA) and 1,716 by the 46-gene and 33 by the 50-gene Ampliseq panel. Of these 2,000 patients, 84 had already undergone sequencing of one or more genes for standard of care (eg, *BRAF* V600 melanoma) or for clinical trial eligibility testing for specific trials.

Median age was 55 years (range, 3 to 95 years). The most common cancer types tested are shown in Figure 1A. The most frequently mutated genes (with likely somatic mutations) are shown in Figure 1B.

Of the 2,000 patients, 789 (39%) had at least one mutation in a potentially actionable gene, 414 (21%) had a presumed somatic mutation in a gene that was not actionable, 205 (10%) had a likely germline variant, and 592 (30%) had no mutations/variants identified (Fig 2A). Notably, most alterations considered as likely germline noted on this panel were not known functional polymorphisms or pathogenic germline mutations and were not considered actionable. One hundred forty-five patients (7.3%) had two or more potentially actionable alterations. It should be noted that for this analysis, we considered *TP53*, *IDH1*, and *IDH2* mutations not actionable because of lack of genotype-matched trials for solid tumors during that time period, and we considered *KRAS* actionable because of availability of trials targeting *MEK1*, with or without *KRAS* selection. If *KRAS* was also considered not actionable, 627 patients (31%) had a mutation in a potentially actionable gene (Fig 2B). If *TP53*, *IDH1*, and *IDH2* were considered potentially actionable, 1,156 patients (58%) had a mutation in a potentially actionable gene (Fig 2C). For the likely somatic mutations identified, only six genes were present at greater than 5% (with not all of these being druggable), six genes were present at a frequency of between 1% and 5%, and the remainder were present at less than 1% (Fig 1). On the basis of the mutation spectrum assessed, the percentage of patients with potentially actionable alterations varied from 5% to 79% by tumor type (Figs 2A to 2C). As we transitioned from the 11-gene Sequenom panel to the 46- and 50-gene Ampliseq panels, there were only modest increases in patients with potentially actionable alterations (Data Supplement).

The frequency of mutations in specific genes is shown for different tumor types where 20 patients or more were tested (Table 1). In addition to the expected common disease-mutation associations (eg, *KRAS*–colon cancer, *EGFR*–lung cancer), we identified a set of potentially actionable genes frequently mutated in specific diseases but also uncommonly mutated in other cancer types (eg, *BRAF*, *PIK3CA*). Furthermore, some genes had a low incidence of mutations across several tumor types (eg, *ERBB2*; Fig 3).

Enrollment Onto Clinical Trials

Five hundred nineteen patients (26%) enrolled onto therapeutic clinical trials at MD Anderson Cancer Center after genomic testing results were available (Fig 4A). Patients with mutations in potentially actionable genes were marginally more likely to be treated on therapeutic clinical trials after test results were available than those without actionable mutations (28.4% v 24.4%, respectively; $P = .0445$; Fig 4B).

Among the 789 patients with potentially actionable alterations (defined as shown in Fig 2A), 83 (11%) went on genotype-matched

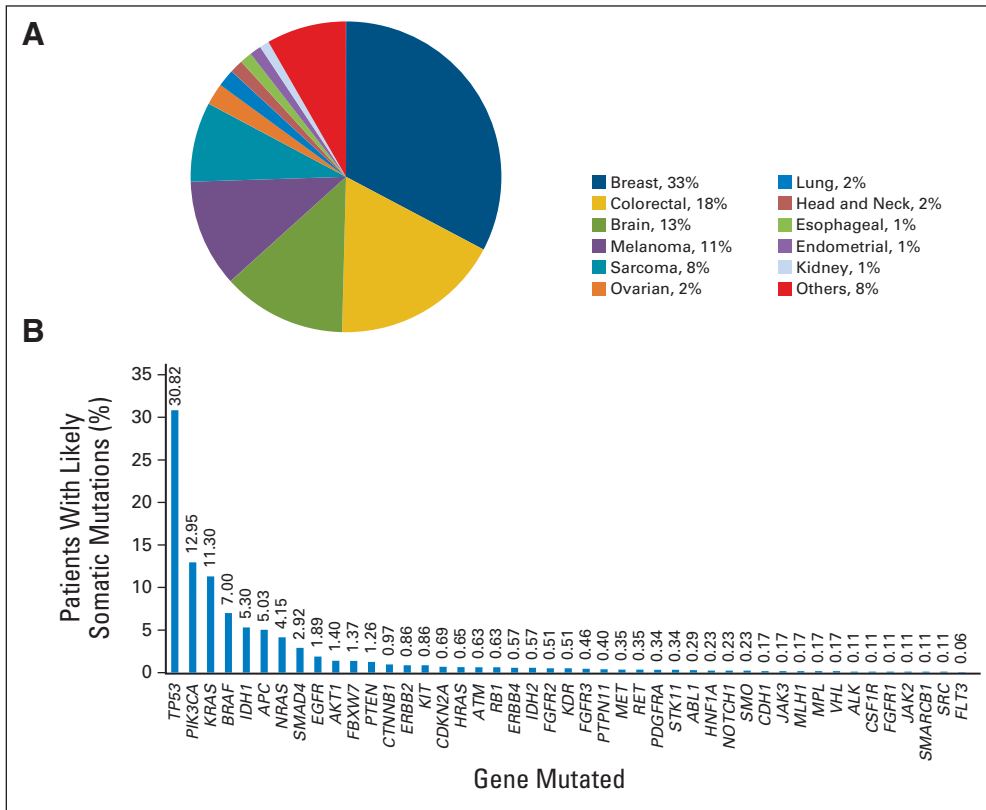


Fig 1. (A) The most common cancer diagnosis for patients who underwent genomic testing. Each diagnosis consisted of a variety of different histologic subtypes. (B) The most common (likely somatic) mutations observed in the overall cohort.

trials after genomic testing; 54 (7%) were treated on a genotype-selected trial (requiring a mutation for eligibility), and 29 (4%) were treated on a genotype-relevant trial (ie, a trial without biomarker selection but with an agent that targeted the gene product or downstream signaling). In addition, 121 patients (15%) were treated on other clinical trials (Fig 3C). Figure 4D demonstrates the key genomic alterations of patients who were enrolled onto genotype-matched trials. The right panel in Figure 4D depicts the key genomic alterations of patients who were enrolled onto genotype-matched trials excluding 24 patients who had alterations detectable by standard-of-care assays (*EGFR* in lung cancer, *BRAF* in melanoma, and *KRAS* in colon cancer).

To gain insights into obstacles for trial enrollment, we reviewed the records of the 429 patients with *PIK3CA/ACT1/PTEN/BRAF* mutations. The median time from CLIA test results to last follow-up was 257 days (range, 4 to 749 days for patients who returned to clinic). Surprisingly, 199 (46%) of 429 patients with *PIK3CA/ACT1/PTEN/BRAF* mutations did not undergo a new regimen of therapy at our institution after testing (Fig 5A); 75 (17%) of 429 patients did not return to the institution after testing, 55 (13%) returned but elected to be treated elsewhere (usually locally; ie, closer to home), 26 (6%) did not initiate new treatment as a result of declining performance status, and 43 (10%) did not start new treatment for other reasons (eg, stable disease). Of the 230 patients who received a new treatment at MD Anderson Cancer Center, 40 (17%) were treated on genotype-selected trials after testing, 16 (7%) were treated on genotype-relevant trials, 35 (15%) were treated on other trials, and 40 (17%) received a genotype-relevant drug (as standard of practice or off protocol) after testing (Fig 5B). In addition, eight patients (2%) had been treated on a genotype-

relevant trial before testing, and 12 patients (5%) received a genotype-relevant drug off protocol before testing. Thus, of the 230 patients with *PIK3CA/ACT1/PTEN/BRAF* mutations who received subsequent therapy at MD Anderson Cancer Center, 116 (50%) received a genotype-matched drug (96 patients after testing, 42%).

The clinical course of the 429 patients with *PIK3CA/ACT1/PTEN/BRAF* mutations is shown in Figure 5C. Of the 354 patients who returned to the institution after testing, 230 went on to subsequent new regimens. One hundred fifty-eight (68%) of 230 patients had the genomic testing result noted in the transcribed clinical notes, 106 (46%) had documentation of discussion of genotype-matched trials, and 61 (27%) were enrolled onto a genotype-matched trial (Fig 5C). Trials were discussed with 45 patients who subsequently were not treated on a genotype-matched trial but rather elected noninvestigational therapy, a non-genotype-matched trial, or treatment elsewhere or received genotype-relevant drug off protocol. In addition, slots could not be identified for four patients, four patients had too poor performance status, 11 patients were ineligible for trials for other reasons, and one patient had insurance denial for trial participation.

Also of note, 13 patients ultimately went on more than one genotype-matched trial after genomic testing. Fourteen patients had more than one actionable genomic alteration, and two patients went on trials simultaneously targeting two alterations (one patient with *KRAS* and *PIK3CA* and the other with *KIT* and *PIK3CA*).

We also evaluated the time required for genomic testing. Of the 429 patients with *PIK3CA/ACT1/PTEN* or *BRAF* mutations enrolled onto the study, 103 patients already had CLIA genomic testing (usually single-gene testing) done before multiplex testing. For the other 326 patients, time from consent to test results was an average of 31 days

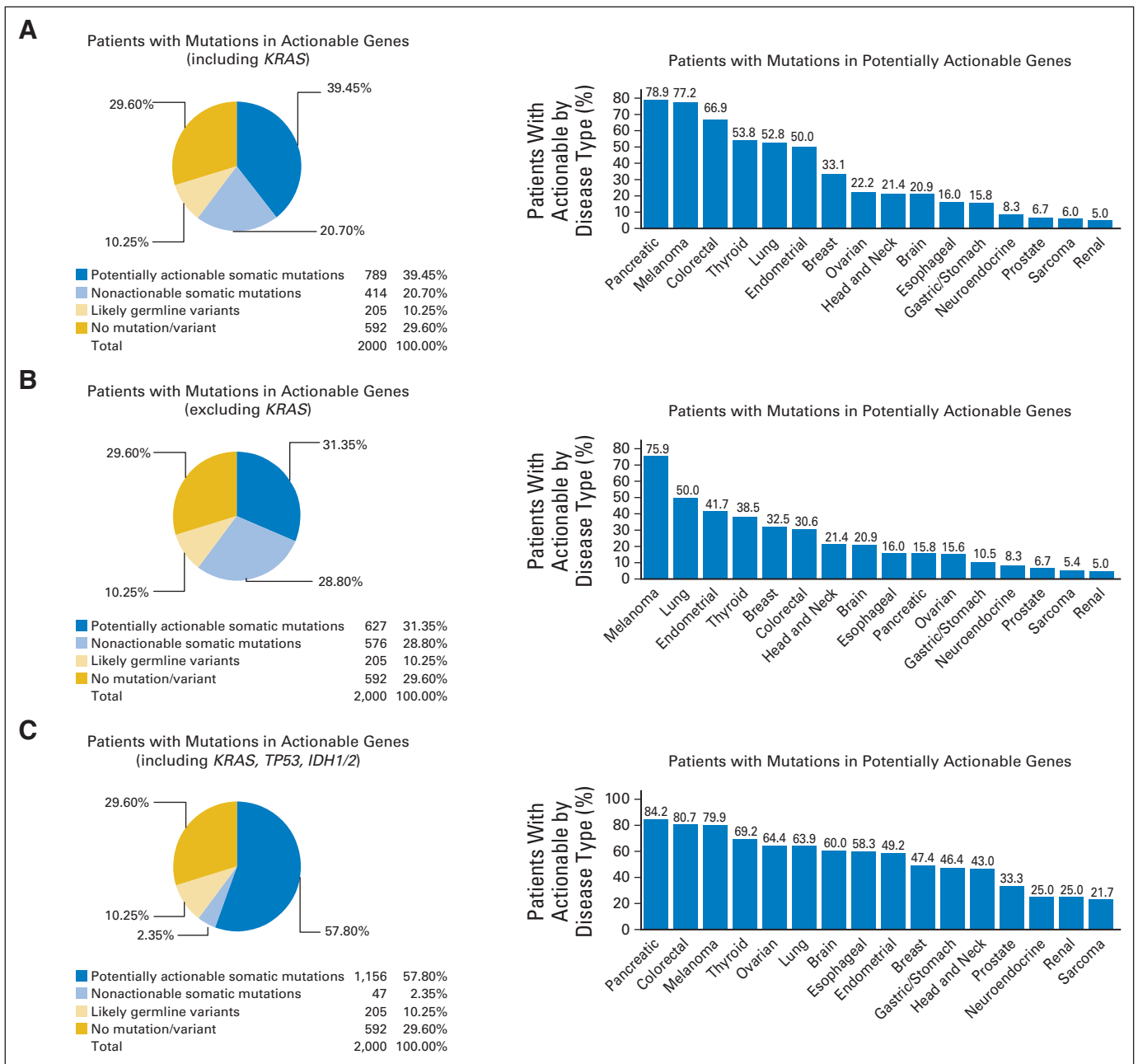


Fig 2. Frequency of actionable alterations. (A) Frequency of potentially actionable alterations among the 2,000 patients tested (left panel). For this analysis, patients were classified into mutually exclusive categories based on the highest category of alteration (actionable somatic mutation > nonactionable somatic mutation > germline variant; reporting each patient once). For the analysis, *TP53*, *IDH1*, and *IDH2* were considered not actionable, and *KRAS* was considered actionable. Frequency of potentially actionable alterations by tumor type among tumor types with 10 or more patients tested (right panel). (B) Frequency of potentially actionable alterations with *KRAS* as well as *TP53*, *IDH1*, and *IDH2* considered not actionable (left panel). Frequency of potentially actionable alterations by tumor type with this classification (right panel). (C) Frequency of potentially actionable alterations considering *KRAS*, *TP53*, *IDH1*, and *IDH2* actionable (left panel). Frequency of potentially actionable alterations by tumor type with this classification (right panel).

and median of 26 days. Notably, 102 patients (23.8%) with *PIK3CA*/*AKT1*/*PTEN*/*BRAF* mutations had another treatment started before test results were received; 13 of these were genotype-relevant choices.

DISCUSSION

Broad implementation of multiplex hotspot testing across an institution is feasible. However, overall, only a small portion of patients

with actionable alterations were enrolled onto genotype-matched trials. Notably, 46% of patients with *PIK3CA*, *AKT*, *PTEN*, or *BRAF* alterations did not receive subsequent treatment at the institution; however, of patients who received subsequent treatment, 23% were treated on a genotype-matched trial after genomic testing. One hundred fifteen (48%) of 242 patients who received additional treatment after multiplex testing received a genotype-relevant drug. Thus, for patients who receive additional treatment,

Table 1. Frequency of Alterations in All Tested Genes by Tumor Type

Gene	Overall (N = 2,000)		Breast (n = 655)		CRC (n = 353)		Melanoma (n = 224)		Brain (n = 258)		Sarcoma (n = 166)		Ovary (n = 45)		Lung (n = 36)		Head and Neck (n = 28)		Esophageal (n = 25)		Endometrial (n = 24)		Kidney (n = 20)		
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	
Tested using Ion Torrent																									
	1,749		531		288		224		201		161		45		36		28		25		24		20		
ABL1	5	0.3	2	0.4	1	0.4	1	0.5	1	0.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0
AKT1*	28	1.4	23	3.5	3	0.9	1	0.5	0	0.0	0	0.0	0	0.0	0	0.0	1	3.6	0	0.0	0	0.0	0	0.0	0
ALK	2	0.1	0	0.0	1	0.4	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	4.2	0
APC	88	5.0	8	1.5	69	24.0	1	0.5	1	0.5	1	0.6	2	4.4	0	0.0	1	3.6	0	0.0	1	4.2	0	0.0	0
ATM	11	0.6	3	0.6	1	0.4	4	1.8	1	0.5	0	0.0	0	0.0	1	2.8	0	0.0	0	0.0	0	0.0	0	0.0	0
BRAF*	140	7.0	4	0.6	18	5.1	97	43.3	10	3.9	3	1.8	3	6.7	2	5.6	0	0.0	0	0.0	0	0.0	0	0.0	0
CDH1	3	0.2	0	0.0	2	0.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0
CDKN2A	12	0.7	1	0.2	0	0.0	5	2.2	2	1.0	1	0.6	0	0.0	0	0.0	0	0.0	1	4.0	0	0.0	0	0.0	0
CSF1R	2	0.1	0	0.0	0	0.0	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	4.2	0
CTNNB1	17	1.0	0	0.0	4	1.4	6	2.7	0	0.0	3	1.9	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	4.2	0
EGFR	33	1.9	2	0.4	1	0.4	3	1.3	10	5.0	0	0.0	1	2.2	11	30.6	1	3.6	1	4.0	0	0.0	0	0.0	0
ERBB2	15	0.9	5	0.9	5	1.7	0	0.0	0	0.0	1	0.6	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	4.2	0
ERBB4	10	0.6	1	0.2	5	1.7	3	1.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	4.0	0	0.0	0	0.0	0
FBXW7	24	1.4	0	0.0	0	0.0	2	0.9	0	0.0	1	0.6	0	0.0	1	2.8	1	3.6	0	0.0	5	20.8	0	0.0	0
FGFR1	2	0.1	1	0.2	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0
FGFR2	9	0.5	2	0.4	1	0.4	2	0.9	2	1.0	0	0.0	1	2.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0
FGFR3	8	0.5	1	0.2	2	0.7	2	0.9	0	0.0	0	0.0	0	0.0	0	0.0	1	3.6	0	0.0	0	0.0	0	0.0	1
FLT3	1	0.1	0	0.0	1	0.4	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0
GNAS*	13	0.7	0	0.0	5	1.4	4	1.8	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0
HNF1A	4	0.2	0	0.0	0	0.0	2	0.9	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	4.2	0	0.0	0
HRAS	12	0.7	5	0.9	1	0.4	3	1.3	0	0.0	0	0.0	0	0.0	0	0.0	2	7.1	0	0.0	0	0.0	0	0.0	0
IDH1*	106	5.3	1	0.2	1	0.3	3	1.3	92	35.7	5	3.0	0	0.0	1	2.8	0	0.0	0	0.0	1	4.2	0	0.0	0
JAK2	2	0.1	0	0.0	0	0.0	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0
JAK3	3	0.2	2	0.4	0	0.0	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0
KDR	9	0.5	0	0.0	1	0.4	5	2.2	1	0.5	0	0.0	0	0.0	1	2.8	0	0.0	0	0.0	0	0.0	0	0.0	0
KIT	15	0.9	1	0.2	0	0.0	10	4.5	1	0.5	2	1.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0
KRAS*	226	11.3	5	0.8	175	49.6	6	2.7	4	1.6	1	0.6	4	8.9	3	8.3	0	0.0	0	0.0	5	20.8	0	0.0	0
MET*	7	0.4	2	0.4	2	0.6	0	0.0	0	0.0	0	0.0	0	0.0	1	2.8	1	3.6	0	0.0	0	0.0	0	0.0	0
MLH1	3	0.2	1	0.2	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0
MPL	3	0.2	2	0.4	0	0.0	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0
NOTCH1	4	0.2	1	0.2	1	0.4	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0
NRAS*	83	4.2	4	0.6	15	4.3	57	25.5	1	0.4	1	0.6	1	2.2	0	0.0	0	0.0	1	4.0	0	0.0	0	0.0	0
PDGFRA	6	0.3	0	0.0	2	0.7	2	0.9	2	1.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0
PIK3CA*	259	12.9	168	25.7	56	15.9	1	0.5	18	7.0	1	0.6	2	4.4	1	2.8	2	7.1	2	8.0	5	20.8	0	0.0	0
PTEN	22	1.3	5	0.9	2	0.7	3	1.3	7	3.5	1	0.6	0	0.0	0	0.0	0	0.0	0	0.0	2	8.3	0	0.0	0
PTPN11	7	0.4	1	0.2	0	0.0	2	0.9	4	2.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0

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Table 1. Frequency of Alterations in All Tested Genes by Tumor Type (continued)

Gene	Overall (N = 2,000)		Breast (n = 655)		CRC (n = 353)		Melanoma (n = 224)		Brain (n = 258)		Sarcoma (n = 166)		Ovary (n = 45)		Lung (n = 36)		Head and Neck (n = 28)		Esophageal (n = 25)		Endometrial (n = 24)		Kidney (n = 20)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
<i>RB1</i>	11	0.6	0	0.0	3	1.0	1	0.5	2	1.0	1	0.6	0	0.0	1	2.8	0	0.0	2	8.0	0	0.0	0	0.0
<i>RET</i> ^a	7	0.4	0	0.0	2	0.6	1	0.5	1	0.4	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
<i>SMAD4</i>	51	2.9	6	1.1	30	10.4	1	0.5	3	1.5	0	0.0	1	2.2	0	0.0	0	0.0	0	0.0	1	4.2	0	0.0
<i>SMARCB1</i>	2	0.1	0	0.0	1	0.4	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
<i>SMO</i>	4	0.2	0	0.0	1	0.4	1	0.5	1	0.5	0	0.0	0	0.0	1	2.8	0	0.0	0	0.0	0	0.0	0	0.0
<i>SRC</i>	2	0.1	1	0.2	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
<i>STK11</i>	6	0.3	1	0.2	1	0.4	2	0.9	0	0.0	0	0.0	0	0.0	2	5.6	0	0.0	0	0.0	0	0.0	0	0.0
<i>TP53</i>	539	30.8	150	28.3	155	53.8	27	12.1	70	34.8	28	17.4	20	44.4	9	25.0	9	32.1	13	52.0	9	37.5	4	20.0
<i>VHL</i>	3	0.2	0	0.0	0	0.0	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	10.0

NOTE. Two thousand patient underwent testing overall, 1,749 patients on Ion Torrent platform and 251 patients on Sequenom platform. Thirty-three patients underwent *EZH2* and *GNAI1* mutation testing and 352 had *GNAQ* testing, and no mutations were found. In addition, 352 patients had *IDH2* testing, and two mutations were found (in brain tumors).

Abbreviation: CRC, colorectal cancer.
^aGenes that were on both Sequenom and Ion Torrent platforms. Information on these genes was available in all 2,000 patients. Frequency of mutations in all other genes was calculated based on the 1,749 patients tested.

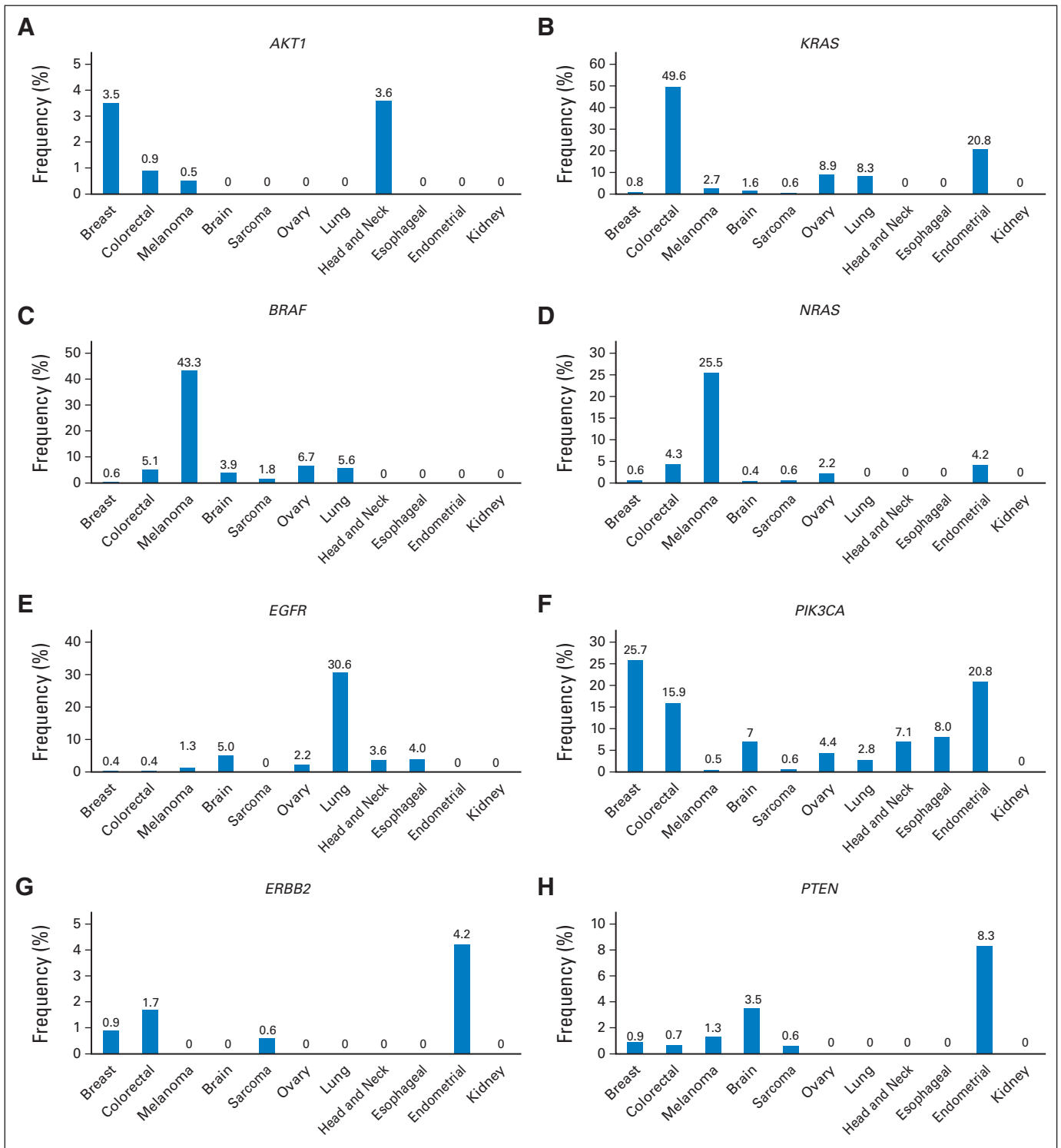


Fig 3. Frequency of selected alterations in different tumor types. Frequency of (A) *AKT1*, (B) *KRAS*, (C) *BRAF*, (D) *NRAS*, (E) *EGFR*, (F) *PIK3CA*, (G) *ERBB2*, and (H) *PTEN* mutations in breast cancer, colorectal cancer, melanoma, brain tumors, sarcoma, ovarian cancer, lung cancer, head and neck cancer, esophageal cancer, endometrial cancer, and kidney tumors.

multiplex testing was used to drive genomically informed clinical decision making.

Seven hundred eighty-nine patients (39%) had a mutation in a potentially actionable gene. However, the frequency of actionable

alterations differs widely (from 5% to 79%) between different tumor lineages; thus, the utility of this platform may differ based on tumor type. Furthermore, likely actionable mutations at a frequency of greater than 5% were present in only four genes, and likely actionable

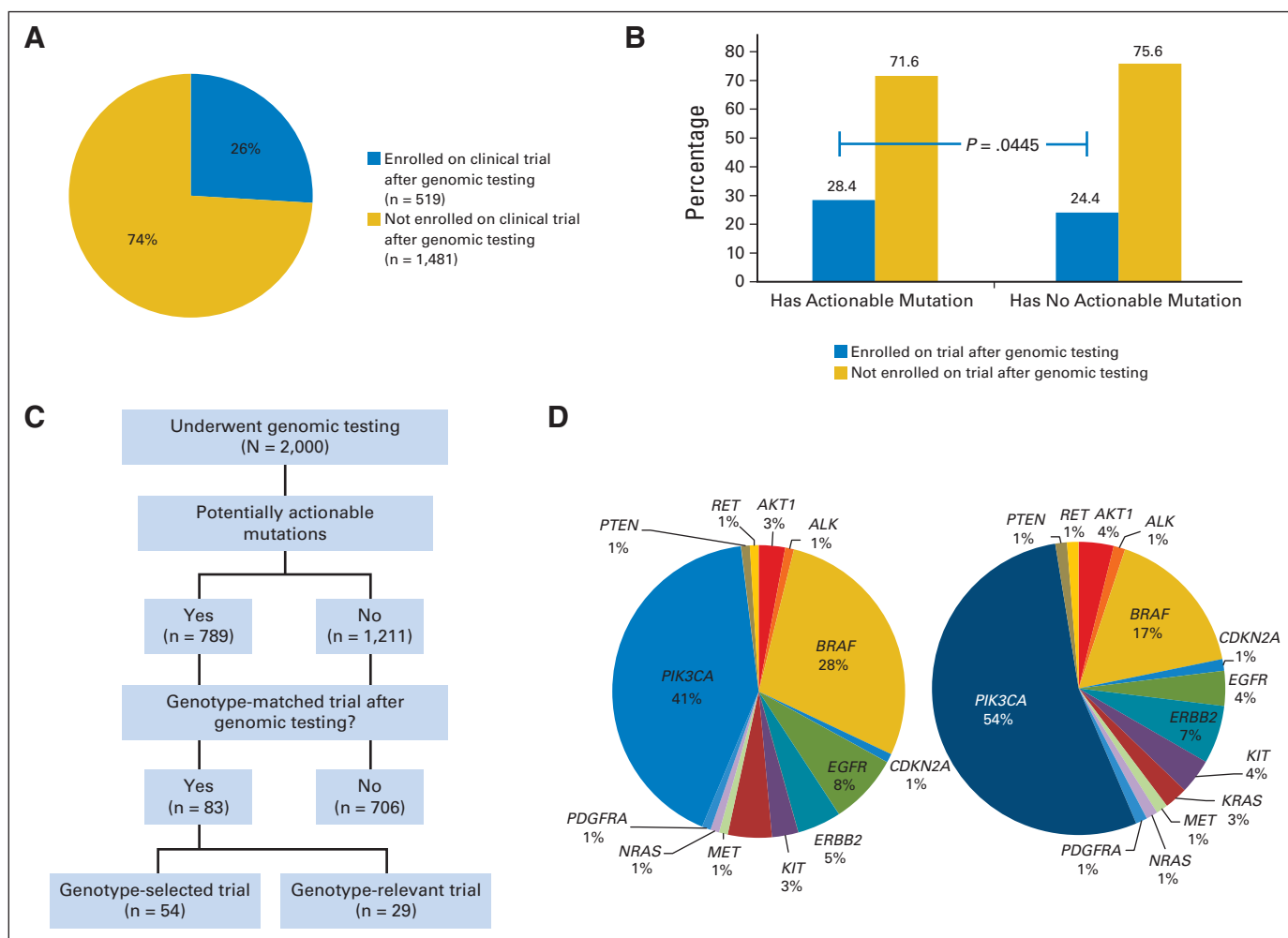


Fig 4. Clinical trial enrollment. (A) Proportion of patients enrolled onto a therapeutic clinical trial after results of genomic testing were available. (B) Proportion of patients enrolled onto a therapeutic clinical trial among patients with actionable mutations and those without actionable alterations (28.4% v 24.4%, respectively; $P = .0445$). (C) CONSORT diagram of patients who went on genotype-matched trials. (D) Key genomic alterations of patients who were enrolled onto genotype-matched trials (left panel). The right panel depicts the key genomic alterations of patients who were enrolled onto genotype-matched trials excluding alterations detectable by standard-of-care assays (*EGFR*, $n = 5$; *BRAF*, $n = 16$; and *KRAS* mutant, $n = 3$).

mutations at a frequency between 1% and 5% were also present in only four genes. The low frequency of mutations in most actionable genes could present a challenge for validating the actionability of the targets. In addition, to identify sufficient patients for genotype-selected trials, it will be necessary to test large numbers of patients with multiplexed testing.

For this analysis, we categorized *TP53*, *IDH1*, and *IDH2* as not actionable, although *IDH*-targeted therapies are now in trials, and recently trials have started using *TP53* as a selection marker. Also notable is that we considered *KRAS* as an actionable gene, because there are *KRAS* genotype-selected trials. However, these trials may not be applicable for several tumor types, and available slots are limited; thus, this is an overestimation of true actionability. Although we categorized mutations as being in a potentially actionable gene, it should be noted that during clinical trial consideration, the level of evidence for the functional impact of each mutation also needs to be considered. Therefore, the frequency of actionable mutations may be less than the frequency of mutations in potentially actionable genes. Also of note, there is growing interest in using larger panels, such as

whole-exome sequencing or targeted full-length sequencing of actionable genes. These approaches not only cover nonhotspot alterations, but they may also yield copy number information and, depending on design, gene rearrangements. Such larger panels may demonstrate potentially actionable alterations in many more patients.³⁻⁶

We noted several challenges in linking genomic testing to genomically matched trials. First, 17% of patients did not return to MD Anderson Cancer Center after testing, and 13% elected to be treated closer to home. Therefore, in nearly a third of the patients, the genomic information from testing was likely not used for therapy planning. This is at least in part attributable to MD Anderson Cancer Center being a referral center. Although one option would be to limit testing to patients who are local, genomic testing remains an important tool to deliver the most informative consultations. However, before testing, it is important to determine whether the patient is interested in clinical trials. Second, 6% of patients did not initiate new treatment as a result of declining performance status, and several were ineligible for trials because of their performance status. It remains difficult to predict health deterioration in patients with advanced

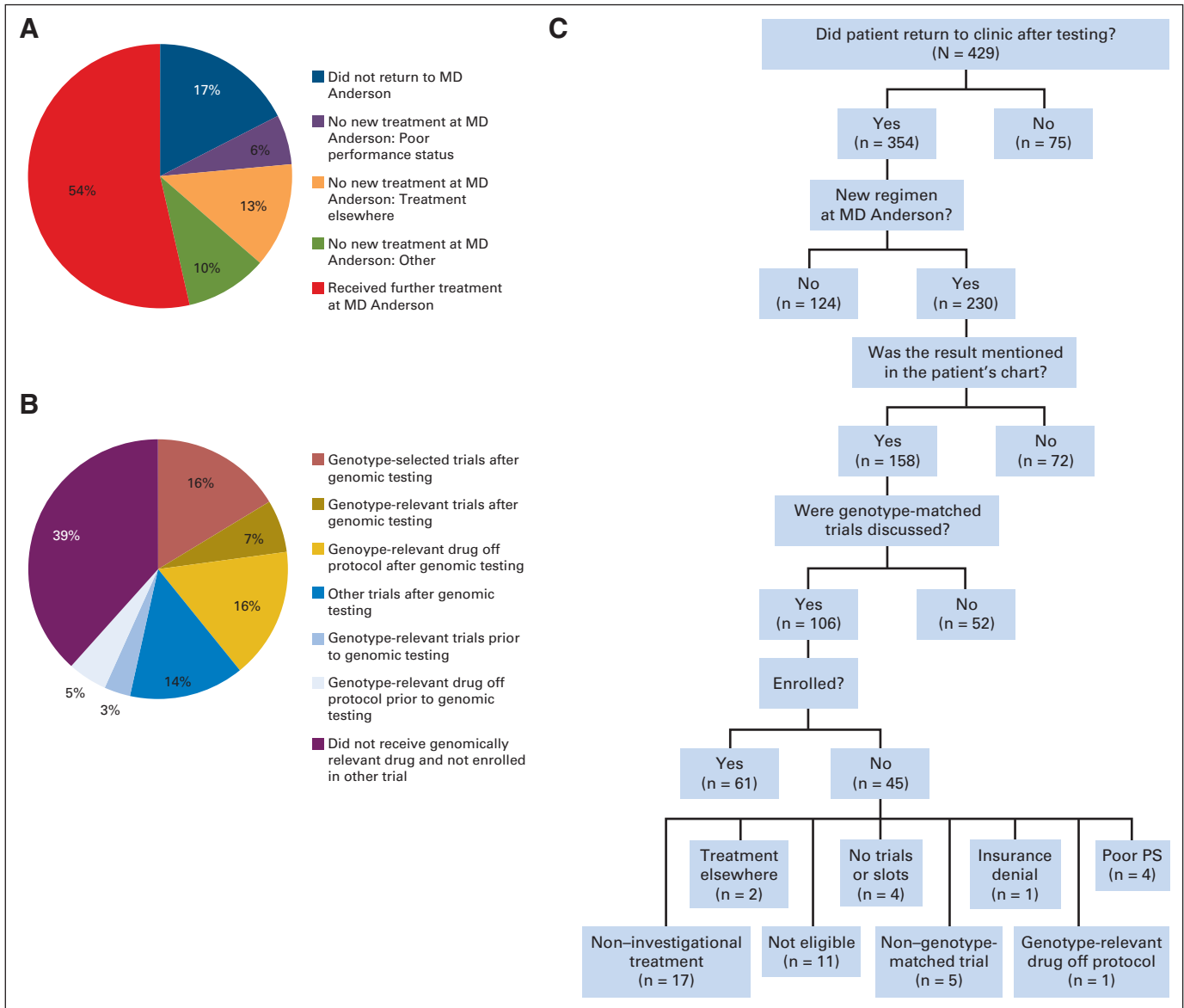


Fig 5. Genotype-matched trial enrollment in patients who had tumors with *PIK3CA/AKT1/PTEN/BRAF* mutations. (A) Subsequent treatment of 429 patients who had tumors with *PIK3CA/AKT1/PTEN/BRAF* mutations. (B) Treatments given to the 230 patients with *PIK3CA/AKT1/PTEN/BRAF*-mutant tumors who received a subsequent new treatment regimen at The University of Texas MD Anderson Cancer Center. (C) Reasons patients who had tumors with *PIK3CA/AKT1/PTEN/BRAF* mutations were not enrolled onto trials. PS, performance status.

cancer, and unfortunately, 105 patients (5%) died within 3 months of testing. Thus, careful assessment of performance status and comorbidities is needed. Testing for non-standard-of-care markers is most likely to benefit patients with adequate performance status to participate in clinical trials in the next two lines of treatment.

Many patients underwent genomic characterization to guide future treatments rather than point-of-care testing to decide on next-line therapy. This approach allows for the most expedited delivery of the next line of therapy but represents an opportunity lost for enrollment onto genotype-matched trials. In our study, time from consent to genomic report was a median of 26 days; this delay, at least in part, is attributable to the time to locate archival tissue blocks. Point-of-care tumor biopsies for molecular profiling or liquid biopsy approaches may not only immediately obtain samples for testing, but may also overcome potential challenges as a result of genomic evolution.

Even studies that have performed point-of-care testing have demonstrated the challenges to offering a genotype-matched treatment option to all patients. In the Lung Cancer Mutation Consortium, an oncogenic driver was found in 64% of patients who underwent genomic testing; however, only 28% of patients were enrolled onto a marker-selected trial.⁷ In the SAFIRO1 breast cancer trial, a targetable alteration was identified in 46% of patients and therapy was personalized in 13% of patients, with 28% of patients with a targetable alteration receiving a matched therapy.⁸ In the institutional series from Vanderbilt, Lovly et al⁹ reported that among 150 patients with melanoma who underwent SNaPSHOT testing, 60% had at least one mutation and 43% of patients harboring metastatic disease with actionable mutations were treated in genomically matched trials. In our study, genomic analysis was not point-of-care testing and was not linked to a prespecified treatment algorithm. Keeping that in mind,

with widespread implementation of genomic testing, enrollment of 11% of patients who underwent genomic testing onto genomically matched trials overall and nearly 40% of patients with *PIK3CA/AKT/PTEN/BRAF* mutations receiving genomically relevant drugs after testing establish the potential value of genomic testing for therapy selection. However, a major obstacle was the paucity of genomically matched trials, especially for less common tumor types and for the less commonly mutated genes. Tracking frequency of alterations (Table 1) can help determine feasibility of genotype-selected trials in each disease type.

Over the study period, there was a steady increase in number of genes for which we have genotype-selected trials. We have leveraged our genomic testing to design genotype-selected investigator-initiated trials. We have also recruited several industry-sponsored trials and activated genomically selected histology-independent basket trials. Novel trial approaches to explore antitumor efficacy in rare molecular subtypes and novel trial access mechanisms such as just-in-time trial access activating genomically matched trials appropriate for individual patient genotype are needed.

Our study was observational in design; we relied on retrospective assessment of impact of testing on treatment choices. Notably, only 69% patients had the genomic testing results acknowledged in the transcribed clinic notes, and 44% had documentation of discussion of genotype-matched trials. It is unclear whether test results were indeed not appreciated and trial options not discussed or whether these were simply not documented. However, it is possible that alerting treating physicians that genomic testing results are available may improve trial accrual. To facilitate this, we have activated a clinical trial alert system. Physicians now receive an e-mail alert when actionable genomic test results are received, with a list of genotype-matched trials. It has been recently reported that even oncologists at leading cancer centers have variable comfort levels with their knowledge of genomics.¹⁰ To assist in decision making, we have put together a Precision Oncology Deci-

sion Support Team. For common actionable genes, variant-level information on mutations that have been experimentally characterized based on published literature is included on our Web site PersonalizedCancerTherapy.org. We expect that by increasing education and streamlining decision making, we can improve the implementation of genomically informed cancer therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Funda Meric-Bernstam, Kenna Shaw, Yisheng Li, Keyur Patel, John Mendelsohn, Gordon B. Mills

Financial support: Funda Meric-Bernstam, John Mendelsohn, Gordon B. Mills

Administrative support: Funda Meric-Bernstam, Kenna Shaw, John Mendelsohn, Gordon B. Mills

Provision of study materials or patients: Funda Meric-Bernstam, Scott Kopetz, Michael A. Davies, Sarina A. Piha-Paul, Filip Janku, Naoto Ueno, David Hong, John De Groot, Vinod Ravi, Raja Luthra, Keyur Patel, Russell Broaddus

Collection and assembly of data: Funda Meric-Bernstam, Lauren Brusco, Chacha Horombe, Scott Kopetz, David Hong, Raja Luthra, Keyur Patel, Russell Broaddus

Data analysis and interpretation: Funda Meric-Bernstam, Lauren Brusco, Kenna Shaw, Scott Kopetz, Michael A. Davies, Mark Routbort, Sarina A. Piha-Paul, Filip Janku, Naoto Ueno, David Hong, John De Groot, Vinod Ravi, Yisheng Li, John Mendelsohn, Gordon B. Mills

Manuscript writing: All authors

Final approval of manuscript: All authors

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Feasibility of Large-Scale Genomic Testing to Facilitate Enrollment Onto Genomically Matched Clinical Trials

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Funda Meric-Bernstam

Honoraria: Genentech, Roche Diagnostics, Sysmex

Consulting or Advisory Role: Novartis, Roche, Genentech

Research Funding: Novartis (Inst), AstraZeneca (Inst), Taiho (Inst), Genentech (Inst), Calithera (Inst), Debiopharma (Inst), Bayer (Inst)

Lauren Brusco

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Kenna Shaw

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Chacha Horombe

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Scott Kopetz

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Research Funding: Roche, Amgen, GlaxoSmithKline, Sanofi, Sysmex, Biocartis, Guardant, Agendia

Michael A. Davies

Consulting or Advisory Role: GlaxoSmithKline, Genentech/Roche, Novartis, Sanofi

Research Funding: GlaxoSmithKline (Inst), Genentech/Roche (Inst), AstraZeneca (Inst), Merck (Inst), Oncothyreon (Inst), Myriad Genetics (Inst), Sanofi (Inst)

Mark Routbort

No relationship to disclose

Sarina A. Piha-Paul

No relationship to disclose

Filip Janku

No relationship to disclose

Naoto Ueno

No relationship to disclose

David Hong

No relationship to disclose

John De Groot

Consulting or Advisory Role: Deciphera Pharmaceuticals, Novartis, Roche/Genentech, Celldex, VBL Therapeutics, Foundation Medicine

Research Funding: Sanofi-Aventis, AstraZeneca, EMD-Serono, Eli Lilly, Novartis, Deciphera Pharmaceuticals

Vinod Ravi

No relationship to disclose

Yisheng Li

No relationship to disclose

Raja Luthra

No relationship to disclose

Keyur Patel

No relationship to disclose

Russell Broaddus

No relationship to disclose

John Mendelsohn

Leadership: Merrimack Pharmaceuticals-Director

Stock or Other Ownership: Merrimack Pharmaceuticals

Patents, Royalties, Other Intellectual Property: Royalties from University of California, San Diego

Gordon B. Mills

Honoraria: AstraZeneca/MedImmune, Critical Oncology Technologies, GlaxoSmithKline, Blend, Nuevolutino

Consulting or Advisory Role: AstraZeneca, Nuevolution, Critical Oncology Technologies

Research Funding: Critical Oncology technologies, GlaxoSmithKline, AstraZeneca/MedImmune

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Appendix

Table A1. Codons Tested on Sequenom 11-Gene Assay and the Ampliseq 46-Gene (CMS46) and 50-Gene (CMS50) Assays

Gene	Codons Tested in Sequenom Panel	Codons Tested in CMS46	Codons Tested in CMS50
<i>ABL1*</i>		237-260, 275-283, 303-319, 350-362, 387-412	232-260, 275-279, 314-360, 380-412
<i>AKT1*</i>	17,173, 179	16-59	16-52, 154-183
<i>ALK*</i>		1172-1177, 1259-1277	1172-1204, 1270-1279
<i>APC</i>		865-886, 1105-1122, 1289-1322, 1349-1382, 1430-1467, 1487-1509	860-891, 1089-1125, 1284-1326, 1342-1384, 1426-1471, 1483-1524, 1543-1582
<i>ATM*</i>		343-355, 395-412, 601-614, 837-862, 1307-1324, 1674-1693, 1733-1758, 1785-1802, 1935-1957, 2436-2445, 2650-2667, 2693-2715, 2721-2739, 2888-2891, 2937-2950, 2996-3016, 3037-3052	326-355, 407-412, 601-626, 834-865, 1292-1325, 1674-1707, 1726-1757, 1790-1815, 1926-1946, 2436-2454, 2650-2667, 2682-2711, 2718-2736, 2865-2891, 2933-2950, 2996-3026, 3041-3057
<i>BRAF*</i>	464, 466, 469, 594, 597, 600, 601	439-471, 581-605	439-473, 581-611
<i>CDH1</i>		69-92, 351-373, 395-415	65-96, 337-374, 380-408
<i>CDKN2A*</i>		51-76	51-90, 98-140
<i>CSF1R*</i>		299-318, 952-973	297-319, 953-973
<i>CTNNB1</i>		12-45	9-48
<i>EGFR*</i>		89-125, 280-297, 575-601, 698-722, 729-761, 766-790, 803-823, 830-866	96-123, 279-297, 575-601, 695-726, 729-796, 807-823, 855-875
<i>ERBB2*</i>		753-769, 772-797, 832-852, 875-883	752-797, 839-882
<i>ERBB4*</i>		136-141, 177-186, 234-247, 272-289, 303-322, 343-363, 588-619, 923-943	136-141, 167-186, 225-247, 254-290, 295-323, 333-367, 580-623, 919-948
<i>EZH2</i>			625-649
<i>FBXW7</i>		264-279, 381-400, 450-472, 478-506, 566-583	264-287, 378-403, 434-473, 478-509, 567-594
<i>FGFR1*</i>		121-139, 247-268	120-148, 247-273
<i>FGFR2*</i>		250-268, 297-313, 367-395, 546-558	250-275, 296-313, 362-399, 546-558
<i>FGFR3*</i>		247-268, 377-409, 634-653, 681-712, 790-807	247-277, 367-402, 631-653, 690-719, 771-807
<i>FLT3*</i>		441-458, 569-575, 589-613, 662-682, 828-846	437-466, 570-610, 663-685, 828-847
<i>GNA11*</i>			202-219
<i>GNAQ*</i>	209		206-245
<i>GNAS</i>	201	196-218	196-240
<i>HNF1A</i>		198-217, 253-282	192-221, 253-282
<i>HRAS*</i>		5-23, 48-79	5-35, 42-82
<i>IDH1</i>	132	118-134	101-135
<i>IDH2</i>	172		133-177
<i>JAK2*</i>		604-622	603-622
<i>JAK3*</i>		568-578, 709-729	128-140, 568-580, 709-733
<i>KDR*</i>		240-258, 267-280, 472-490, 872-892, 959-985, 1138-1161, 1192-1216, 1301-1321, 1336-1356	244-291, 471-480, 872-894, 961-988, 1135-1156, 1192-1221, 1283-1310, 1324-1357
<i>KIT*</i>		47-69, 501-514, 536-549, 550-585, 641-684, 714-728, 807-828, 836-854	23-58, 494-514, 525-587, 627-661, 664-684, 714-724, 802-828, 832-858
<i>KRAS*</i>	12,13,61,146	5-28, 40-67, 136-150	5-66, 114-150
<i>MET*</i>	375,848,988,1010,1112,1124,1248,1253,1268	160-187, 362-379, 992-1017, 1105-1126, 1247-1268	159-188, 339-378, 816-856, 981-1012, 1105-1132, 1246-1274
<i>MLH1</i>		373-393	373-415
<i>MPL*</i>		499-522	501-522

(continued on following page)

Implementing Genomically Informed Therapy

Table A1. Codons Tested on Sequenom 11-Gene Assay and the Ampliseq 46-Gene (CMS46) and 50-Gene (CMS50) Assays (continued)

Gene	Codons Tested in Sequenom Panel	Codons Tested in CMS46	Codons Tested in CMS50
<i>NOTCH1</i> *		1566-1605, 1673-1697	1566-1602, 1673-1680, 2536-2476
<i>NPM1</i> *		283-295	283-295
<i>NRAS</i> *	12,13,61,146	6-22, 53-69	3-31, 43-69, 124-150
<i>PDGFRA</i> *		552-570, 647-688, 819-847	552-583, 644-668, 671-709, 819-854
<i>PIK3CA</i> *	60,88,110,111,345,405,418,420,453,539,542,545,546,909,1021,1025,1043,1046,1047,1049	77-98, 328-351, 418-422, 533-551, 688-716, 1019-1049, 1065-1069	54-90, 106-118, 316-351, 390-422, 449-468, 522-549, 677-720, 898-924, 1017-1051, 1065-1069
<i>PTEN</i> *		5-24, 55-70, 167-184, 212-222, 240-266, 282-300, 316-342	1-25, 55-70, 99-135, 165-184, 212-215, 231-267, 282-300, 312-342
<i>PTPN11</i> *		53-82, 486-506	46-82, 485-527
<i>RB1</i>		132-154, 195-203, 350-371, 549-565, 566-585, 655-680, 703-724, 743-765	130-159, 196-203, 314-345, 350-366, 452-463, 547-582, 655-691, 703-724, 743-770
<i>RET</i> *	918	609-627, 630-654, 762-774, 880-901, 914-931	608-654, 762-786, 875-924
<i>SMAD4</i>		109-128, 167-184, 228-247, 304-319, 330-363, 385-404, 444-472, 497-526	98-136, 142-146, 165-202, 242-263, 307-319, 326-365, 384-424, 443-474, 494-532
<i>SMARCB1</i>		39-55, 154-167, 182-203, 376-386	35-72, 144-206, 373-386
<i>SMO</i> *		186-218, 310-340, 399-418, 516-542, 626-646	186-228, 307-331, 391-419, 511-542, 608-646
<i>SRC</i> *		514-534	499-533
<i>STK11</i> *		30-62, 174-199, 253-281, 325-360	22-64, 155-181, 191-207, 253-285, 317-361
<i>TP53</i>		1-18, 81-114, 126-135, 149-181, 187-223, 230-253, 269-306, 332-344	1-20, 68-113, 126-138, 149-223, 225-258, 263-307, 332-367
<i>VHL</i>		88-110, 120-149, 147-175	78-108, 114-150, 155-174

*Genes considered actionable in the clinical trial enrollment analysis.

Table A2. List of Likely Germline Variants

Gene	Codon	Wild Type	Variant Type
<i>ABL1</i>	247	K	R
<i>APC</i>	870	P	S
<i>APC</i>	1317	E	Q
<i>ATM</i>	410	V	A
<i>ATM</i>	604	P	S
<i>ATM</i>	858	F	L
<i>ATM</i>	1309	A	T
<i>ATM</i>	1691	S	R
<i>FGFR3</i>	384	F	L
<i>JAK3</i>	132	P	T
<i>JAK3</i>	722	V	I
<i>KDR</i>	482	C	R
<i>KDR</i>	1356	V	A
<i>KIT</i>	541	M	L
<i>MET</i>	168	E	D
<i>MET</i>	362	M	T
<i>MET</i>	375	N	S
<i>MET</i>	1010	T	I
<i>MLH1</i>	384	V	D
<i>PIK3CA</i>	391	I	M
<i>STK11</i>	354	F	L
<i>TP53</i>	273	R	H

Table A3. Selected Therapeutic Implications of Potentially Actionable Genes on 50-Gene Panel

Gene	Potential Therapeutic Implications
<i>ABL1</i>	Treatment with ABL or BCR-ABL inhibitors
<i>AKT1</i>	Treatment with AKT or mTOR inhibitors
<i>ALK</i>	Treatment with ALK inhibitors
<i>ATM</i>	Treatment with PARP inhibitors
<i>BRAF</i>	Treatment with BRAF inhibitors
<i>CSF1R</i>	Treatment with CSF1R monoclonal antibody and inhibitors
<i>EGFR</i>	Treatment with EGFR inhibitors
<i>ERBB4 (HER4)</i>	Treatment with HER4 inhibitors
<i>FGFR1</i>	Treatment with FGFR1 inhibitors
<i>FGFR2</i>	Treatment with FGFR2 inhibitors
<i>FGFR3</i>	Treatment with FGFR3 inhibitors
<i>FLT3</i>	Treatment with FLT3 inhibitors
<i>GNA11</i>	Treatment with PKC and MEK inhibitors
<i>GNAQ</i>	Treatment with PKC and MEK inhibitors
<i>HRAS</i>	Treatment with MEK inhibitors
<i>JAK2</i>	Treatment with JAK inhibitors
<i>JAK3</i>	Treatment with JAK inhibitors
<i>KDR</i>	Treatment with KDR inhibitors
<i>KIT</i>	Treatment with KIT inhibitors
<i>KRAS</i>	Treatment with MEK inhibitors
<i>MET</i>	Treatment with MET inhibitors
<i>MPL*</i>	Treatment with JAK2 inhibitors
<i>NOTCH1</i>	Treatment with γ -secretase inhibitors
<i>NPM1</i>	Correlate with positive response to all- <i>trans</i> -retinoic acid therapy and chemotherapy in AML
<i>NRAS</i>	Treatment with MEK inhibitors
<i>PDGFRA</i>	Treatment with PDGFRA inhibitors
<i>PIK3CA</i>	Treatment with PI3K, AKT, or mTOR inhibitors
<i>PTEN</i>	Treatment with p110 β , AKT, or mTOR inhibitors
<i>PTPN11</i>	Treatment with MEK inhibitors
<i>RET</i>	Treatment with Ret inhibitors
<i>SMO</i>	Treatment with SMO inhibitors
<i>SRC</i>	Treatment with SRC inhibitors
<i>STK11</i>	Treatment with mTOR or AMPK inhibitors

NOTE. Genes were classified as potentially actionable if there is at least preclinical evidence suggesting genomic alteration may affect function and the gene can be targeted with an approved or investigational agent or if the gene is being used as an enrollment criterion for ongoing genotype-selected trials.

Abbreviations: AML, acute myeloid leukemia; EGFR, epidermal growth factor receptor; HER4, human epidermal growth factor receptor 4; mTOR, mammalian target of rapamycin; PARP, poly (ADP-ribose) polymerase; PDGFRA, platelet-derived growth factor receptor alpha; PI3K, phosphatidylinositol 3-kinase.

*Borderline classification as actionable.