INTRODUCTION

Sequencing technology is rapidly improving, and costs are decreasing to the point that using genomic results in routine clinical decision making is becoming practical and increasingly widespread. However, the clinical impact of genomics is limited by clinicians’ ability to interpret this growing and rapidly changing information, specifically, to determine which alteration(s) impact gene function and to identify appropriate therapy. Unfortunately, approximately 22% of physicians at a major cancer center reported low confidence in their ability to interpret genomic results. Low physician confidence was associated with decreased anticipated use of genomic testing to drive clinical decision making.¹

Studies demonstrating success using targeted therapy for the treatment of cancer have increased in the past decade. Examples of these include the use of epidermal growth factor receptor (EGFR) inhibitors in patients with EGFR-mutated lung cancer,² BRAF and MEK inhibitors in those with BRAF V600E-mutant unresectable or metastatic melanoma,³,⁴ and human epidermal growth factor receptor 2 (HER2)-targeting agents in patients with HER2-positive metastatic breast cancer.⁵ These successes have fueled the drive to identify new molecular targets, which may improve outcomes for patients whose tumors harbor specific alterations. The presence of alterations in these novel targets may sensitize the tumors whose tumors harbor specific alterations. The presence of alterations in these novel targets may sensitize the tumors.
harboring them to treatment with targeted therapy. We have noted a rapid transition from single-gene testing into larger panel testing covering a larger number of genes and exons.

Although some alterations may not affect protein function, others may change function significantly. Furthermore, when an altered gene is believed to provide a useful target for treatment, the physician must be aware of currently available therapies and clinical trials.

The clinical impact of genomic testing may be limited by a clinician’s ability to appropriately order testing and correctly interpret the results. As use of genomics in medicine continues to grow, we must understand more fully how these changes are affecting physicians and the treatment that they are able to offer to their patients. We sought to understand physician perceptions regarding: 1) the clinical impact of the availability of genomic testing; and 2) the effect on patient satisfaction resulting from the addition of genomic testing (as perceived by the physician). This information may suggest areas in which resources and services can be provided to support physicians in their application of targeted therapy to maximize benefit to patients.

MATERIALS AND METHODS

Patients

Patients with metastatic or inoperable locally advanced or recurrent cancer, who were perceived as being likely to benefit from somatic genomic characterization, were enrolled on an institutional review board-approved prospective protocol for genomic profiling (ClinicalTrials.gov identifier NCT01772771).

Genomic Sequencing

Genomic sequencing was performed as described by Boland et al. Briefly, hematoxylin and eosin-stained archival tissue sections with >20% tumor cellularity were analyzed. Tumor DNA was tested in a Clinical Laboratory Improvement Amendments (CLIA) environment examining hotspot mutations in 46 or 50 genes using an Ion Torrent Personal Genome Machine Sequencer (Thermo Fisher Scientific, Waltham, Massachusetts). Only those alterations designated as likely somatic were considered for this questionnaire.

Determination of Actionability

Genomic alterations were annotated to determine actionability based on known or potential functional and/or therapeutic significance of the variant, and the availability of genomically matched therapies, as established by the Precision Oncology Decision Support (PODS) team at The University of Texas MD Anderson Cancer Center (MDACC), and previously described. First, it was determined whether or not the gene and type of alteration (ie, mutation, copy number change, or fusion) were actionable. Although a gene may be actionable if it is a biomarker of risk or diagnostic or prognostic, we focused on genes that were actionable due to therapeutic implications. Several of the factors considered in making gene-level calls included the availability of drugs targeting the gene/pathway either directly or indirectly, published literature suggesting that the gene may play a role in driving tumorigenesis, and the use of the gene as selection criteria for enrollment on a clinical trial. Our actionable gene list used for the current study has been previously published.

Once the actionability of the alteration type was determined, it was considered whether the specific variant was actionable based on information from the published literature, a functional genomics platform, and the location of the alteration within the gene and proximity to functional domains. Based on the findings, variants were grouped into one of the following classifications of actionability: “yes” (literature based or inferred [inferred loss of function mutations in tumor suppressors]), “potentially,” “unknown,” and “no.” For the purposes of this analysis, alterations having actionability calls of “yes” or “potentially” were considered to be in agreement with physicians who believed an alteration was actionable. In cases in which a patient had >1 actionable alteration identified, perceptions of actionability were compared with the alteration with the highest actionability level for each patient.

Questionnaires

Questionnaires were distributed to physicians with information regarding their patient provided in prepopulated fields (see Supporting Information). Relevant information provided to physicians included patient medical record number, name, the date the test was completed, and the alterations that were identified. Questionnaires were conducted through REDCap (Research Electronic Data Capture) and were sent to the physicians of these patients via a link contained within an e-mail. Questions in the questionnaire followed a pattern in which the physicians first were questioned regarding whether they considered the alterations identified to be actionable. They subsequently were asked if they were aware of targeted therapy available at MDACC for the identified alterations and were allowed the opportunity to describe any genotype-matched treatments considered. The next set of questions
included whether the patient received treatment based on the sequencing results and if so, what type of therapy was administered. A drop-down menu provided the options that could be selected (clinical trial, off label, or standard of care) and a free text field allowed physicians to type the name(s) of the therapy given. The last set of questions pertained to physician perceptions of the value added to the care provided as well as to the perceived effect of genomic testing on patient satisfaction with regard to care received as a result of the genomic testing.

RESULTS

Questionnaires were sent to 69 physicians regarding 288 patients to gain an understanding of physician perceptions regarding the actionability of alterations identified in potentially actionable genes, knowledge of genotype-matched therapy available at MDACC, clinical use of genomic testing results, and the perceived value of genomic testing. Of the 288 questionnaires sent, 250 were completed (87% response rate) by 64 individual physicians from 13 different departments and/or disease centers. The number of questionnaires completed by each physician ranged from 1 to 29, with the median being 2 questionnaires per physician.

Physicians regarded 168 of the 250 patients as having an actionable alteration (Fig. 1) (see Supporting Information Table 1). PODS annotators considered 165 of these 168 patients (98%) to have an actionable or potentially actionable alteration. Three of the 168 patients who were considered to have actionable alterations by their physicians had variants classified as being of “unknown significance” by PODS annotators (see Supporting Information Table 2).

Of the 168 patients who physicians believed had at least 1 actionable alteration, we asked how often physicians were aware of genotype-matched therapy available for these alterations at MDACC. For the 168 patients, 119 physicians were aware of genotype-matched therapy available (71%), whereas 49 (29%) were not. Using both the physician responses provided as well as manual review, we determined that of the 119 patients whose treating physician was aware of genotype-matched therapy at MDACC, 48 (40%) went on to receive matched therapy and 71 (60%) did not. As shown in Figure 2A, the altered genes most frequently acted on to receive targeted therapy were phosphatidylinositide 3-kinase (PIK3CA) (32%), BRAF (30%), phosphatase and tensin homolog (PTEN) (10%), NRAS (10%), and ERBB2 (6%). Alterations that were acted on in this patient population most frequently would have been classified as actionable based on either published literature (82%), inferred actionability (6%), or being potentially actionable (10%) (Fig. 2B). As shown in
of the patients who went on to receive genotype-matched treatment, patients most frequently went into a clinical trial (58%) with standard of care being the second most frequent treatment (36%), followed by off-label use of targeted therapy (6%).

To understand why 71 of the 119 patients whose physician was aware of genotype-matched therapy options did not go on to receive genotype-matched treatment, we used both physician comments in the questionnaires as well as manual review of patient clinic notes. Table 1 summarizes the reasons that we observed for why patients did not continue on to genotype-matched therapy. The most frequent reason, noted for 25 of the 71 patients, was the patient’s choice to receive treatment closer to home due to an unwillingness or inability to travel. Other common reasons reported were election to be treated with nontargeted therapy in 13 of 71 patients (18%), ineligibility for a matched clinical trial in 11 of 71 patients (15%), and poor performance status in 8 of 71 patients (11%). These reasons are consistent with our previous findings of common barriers to clinical trial enrollment, which were assessed by retrospective review rather than through a prospective questionnaire.10

In 79 of the 250 completed questionnaires, physicians believed that the specific alterations found in the potentially actionable genes were not truly actionable. We found that the PODS team would have classified at least 1

TABLE 1. Reasons Patients Whose Physician Was Aware of Genotype-Matched Therapy Options Did Not Go on to Receive Genotype-Matched Treatment

| Reason for Not Receiving Treatment                                      | N=71 |
|------------------------------------------------------------------------|------|
| Elected local treatment                                                | 25   |
| Elected nontargeted therapy                                            | 13   |
| Ineligible                                                             | 11   |
| Previous no. of treatments                                             | 1    |
| No measurable disease                                                   | 3    |
| Other comorbidities                                                    | 7    |
| Poor performance status                                                | 8    |
| Eligible but no available openings                                      | 2    |
| Not financially cleared/insurance declined coverage                     | 3    |
| Already receiving targeted therapy                                      | 5    |
| Not interested in clinical trials                                       | 3    |
| Stable disease/surveillance                                            | 1    |
alteration in 36 of these 79 patients (46%) as either actionable or potentially actionable (Fig. 1) (see Supporting Information Table 3). For this analysis, we considered KRAS alterations present in a patient with a diagnosis of colorectal cancer to be considered as not actionable.11 However, KRAS alterations were categorized as theoretically actionable for other diagnoses. Figure 2D shows that differences were most frequently observed for KRAS alterations in tumor types other than colorectal cancer (27%), followed by alterations in NRAS (17%). For these 36 patients, approximately 73% of these alterations would have been classified as actionable (either inferred or literature based) and 27% would have been classified as potentially actionable based on the PODS team’s definition of actionability.

For 27 of 36 patients (75%) with actionable or potentially actionable alterations that the physician deemed not actionable, there was a clinical trial open at MDACC that was either selecting for alterations in an altered gene or using a drug relevant for one of the altered genes present. Full screening for eligibility could not be performed. However, based on the genotype and clinical disease type, patients were considered a “match.” At the time of the questionnaire, there were very few trial options for patients with KRAS/NRAS mutations, making these alterations more “theoretically” rather than “practically” actionable through targeted therapy.

Figure 1 summarizes the physician-perceived value added to the care that was provided to the patient as a result of the genomic profiling. When physicians were asked whether they believed that use of next-generation sequencing (NGS) platforms improved the “quality of care” that they were able to provide to the patient, 175 (70%) responded that it did improve the quality of care, whereas 75 physicians (30%) believed that it did not. When asked whether or not the physician perceived NGS as having improved patient satisfaction with efforts to personalize treatment options, 222 physicians (89%) responded that it did improve patient satisfaction and 28 (11%) believed that it did not. It is interesting to note that when physicians believed that NGS improved the quality of care that they were able to provide, they also were found to be more likely to perceive the patient as having improved satisfaction with efforts to personalize treatment options (P<.0001).

DISCUSSION
The high response rate of 87% noted in the current study suggests that physicians are actively engaged and willing to discuss the clinical impact of genomic testing. We observed that treating physicians and genomic annotators were in agreement with regard to the actionability of genomic alterations. Specifically, in 67% of patients with an alteration identified in a potentially actionable gene, physicians identified at least 1 alteration as actionable. Within this group, the physician call on actionability agreed with the classifications of the PODS team approximately 98% of the time.

However, of the 79 patients whose physician did not recognize any actionable alterations, 46% had an alteration that the PODS team classified as either “actionable” or “potentially actionable.” This suggests an area in which decision support services may have clinical usefulness. Another opportunity lies in the ability of decision support teams to offer treatment “match” options to physicians so that they have all the information provided when deciding on the next best treatment option. We found that physicians were aware of genotype-matched therapy for only 71% of patients who believed to have an actionable alteration, once again suggesting an important role for decision support to help physicians interpret results and recognize when targeted therapy options are available for their patients.

Patients whose tumors harbored alterations in BRAF, PIK3CA, PTEN, NRAS, and ERBB2 were most likely to receive targeted therapy. This suggests that physicians may be more inclined to act on alterations about which more information is available. It is interesting to note that several of the alterations were only theoretically actionable due to a lack of trials, emphasizing the importance of having a suite of applicable clinical trials to realize the promise of targeted therapy for cancer. This discordance between theoretical and actual actionability partly suggests that studies that only examine theoretical actionability may overestimate the clinical usefulness of genomic testing. Conversely, some of the alterations classified as nonactionable by physicians were potentially actionable. Both false-positive and false-negative findings in interpretation can decrease the clinical usefulness of genomic testing; thus, there is a need for decision support to help physicians optimally use targeted therapy. This challenge will become more acute as larger panels, whole-exome, or even genome testing become widely available. The importance of decision support is supported further by the previously reported lack of physician confidence in interpreting genomic testing results.1

One limitation to the questionnaire in the current study is that, in cases in which a patient had >1 alteration identified in a potentially actionable gene, we could not gather alteration-specific perceptions of actionability. For example, if a patient had 1 alteration that the PODS team would have classified as “unknown actionability” and
another that would been classified as “actionable,” it is impossible to know which alteration the physician was referring to as actionable unless the patient received therapy targeted toward a specific alteration. Another limitation is that the current study was conducted in a single academic center. In the community practice setting, there may exist greater discordances between clinician and annotator interpretations, which may be due to a lower perception of actionability as a consequence of decreased access to investigational therapeutics at the site. To address this issue, it will be important to consider ways in which we can have a broader impact and assist physicians and treatment centers outside of MDACC by providing access to decision support on the ever-changing actionability classification of genes as it relates to new scientific evidence and the offering of novel targeted therapies in the clinical trial setting. Support also should be given to ensure that physicians feel confident to suggest a visit to one of the centers in which these targeted therapies are available for further evaluation of eligibility.

In the current study, when physicians believed that an actionable alteration was present and also were aware of matched therapy targeting the alteration, approximately 40% of patients went on to receive genotype-matched therapy (48 of 119 patients). It is interesting to note that the type of treatment received was most commonly experimental as in a clinical trial (58%) or an off-protocol use (6%), whereas standard-of-care therapy comprised slightly more than one-third of genotype-matched therapy received (36%). The most common reasons patients did not receive genotype-matched treatment were similar to those previously reported, with the most frequent reason being patient preference for being treated closer to home (35%). Other factors limiting treatment with genotype-matched therapy was the election to be treated with alternate therapy (18%), ineligibility for the clinical trial being considered (15%), and poor performance status (11%). The trial enrollment rate of 40% that we observed, when physicians both perceived a patient as having an actionable alteration and were aware of available treatment, is in line with what others have noted. The Lung Cancer Mutation Consortium found a 28% rate of enrollment onto matched-therapy trials in patients who had an oncogenic alteration identified, similarly, the SAFIR-01 breast cancer trial found that 28% of patients with a targetable alteration went on to receive matched therapy.

Physicians who believed that a patient had an actionable alteration were more likely to perceive that genomic testing improved the quality of the care that they were able to provide to the patient (82% vs 43%). However, it is interesting to note that the overall perception of improved patient satisfaction as a result of genomic testing was not different between the patients whose physician believed they had actionable alterations versus those who did not (89% for both). This suggests that whether or not the physician deems an alteration actionable, they perceived that genomic testing improved patient satisfaction.

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**CONFLICT OF INTEREST DISCLOSURES**

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AUTHOR CONTRIBUTIONS

Conceptualization: Lauren L. Brusco, Kenna R. Mills Shaw, and Funda Meric-Bernstam. Methodology: Lauren L. Brusco, Chetna Wathoo, Kenna R. Mills Shaw, Vijaykumar R. Holla, Elmer V.Bernstam, and Funda Meric-Bernstam. Software: Vijaykumar R. Holla, Ann M. Bailey, Amber M. Johnson, Yekaterina B. Khotskaya, Nora S. Sanchez, Jia Zeng, Elmer V. Bernstam, Mark J. Routbort, and Funda Meric-Bernstam. Validation: Lauren L. Brusco, Chetna Wathoo, Vijaykumar R. Holla, Ann M. Bailey, Amber M. Johnson, and Funda Meric-Bernstam. Formal analysis: Lauren L. Brusco, Chetna Wathoo, Kenna R. Mills Shaw, and Funda Meric-Bernstam. Writing original draft: Lauren L. Brusco, Chetna Wathoo, Kenna R. Mills Shaw, Vijaykumar R. Holla, and Funda Meric-Bernstam. Writing review and editing: All authors. Resources: Elmer V. Bernstam, Gordon B. Mills, John Mendelsohn, and Funda Meric-Bernstam. Data curation: Lauren L. Brusco, Chetna Wathoo, Kenna R. Mills Shaw, Vijaykumar R. Holla, and Funda Meric-Bernstam. Writing original draft: Lauren L. Brusco, Chetna Wathoo, Kenna R. Mills Shaw, Vijaykumar R. Holla, and Funda Meric-Bernstam. Writing review and editing: All authors. Visualization: Lauren L. Brusco, Chetna Wathoo, Kenna R. Mills Shaw, Vijaykumar R. Holla, and Funda Meric-Bernstam. Supervision: Kenna R. Mills Shaw, Elmer V. Bernstam, Gordon B. Mills, John Mendelsohn, and Funda Meric-Bernstam. Project Administration: Kenna R. Mills Shaw, Elmer V. Bernstam, Gordon B. Mills, John Mendelsohn, and Funda Meric-Bernstam. Funding acquisition: Elmer V. Bernstam, Gordon B. Mills, John Mendelsohn, and Funda Meric-Bernstam.

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