

Prospective Decision Analysis Study of Clinical Genomic Testing in Metastatic Breast Cancer: Impact on Outcomes and Patient Perceptions

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PURPOSE To evaluate the impact of targeted DNA sequencing on selection of cancer therapy for patients with metastatic breast cancer (MBC).

PATIENTS AND METHODS In this prospective, single-center, single-arm trial, patients with MBC were enrolled within 10 weeks of starting a new therapy. At enrollment, tumor samples underwent next-generation sequencing for any of 315 cancer-related genes to high depth (> 500x) using FoundationOne CDx. Sequencing results were released to providers at the time of disease progression, and physician treatment recommendations were assessed via questionnaire. We evaluated three prespecified questions to assess patients' perceptions of genomic testing.

RESULTS In all, 100 patients underwent genomic testing, with a median of five mutations (range, 0 to 13 mutations) detected per patient. Genomic testing revealed one or more potential therapies in 98% of patients (98 of 100), and 60% of patients (60 of 100) had one or more recommended treatments with level I/II evidence for actionability. Among the 94 genomic text reports that were released, there was physician questionnaire data for 87 patients (response rate, 92.6%) and 31.0% of patients (27 of 87) had treatment change recommended by their physician. Of these, 37.0% (10 of 27) received the treatment supported by genomic testing. We did not detect a statistically significant difference in time-to-treatment failure (log-rank $P = .87$) or overall survival ($P = .71$) among patients who had treatment change supported by genomic testing versus those who had no treatment change. For patients who completed surveys before and after genomic testing, there was a significant decrease in confidence of treatment success, specifically among patients who did not have treatment change supported by genomic testing (McNemar's test of agreement $P = .001$).

CONCLUSION In this prospective study, genomic profiling of tumors in patients with MBC frequently identified potential treatments and resulted in treatment change in a minority of patients. Patients whose therapy was not changed on the basis of genomic testing seemed to have a decrease in confidence of treatment success.

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ASSOCIATED CONTENT

Data Supplement

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

Accepted on October 26, 2019 and published at ascopubs.org/journal/po on November 18, 2019; DOI <https://doi.org/10.1200/P0.19.00090>

ClinicalTrials.gov identifier: NCT01987726

INTRODUCTION

Among patients diagnosed with breast cancer, approximately 30% eventually develop metastatic breast cancer (MBC),¹ and the estimated 150,000 patients living in the United States with stage IV breast cancer are relatively understudied.²⁻⁷ Evaluating multiple somatic mutations in MBC may identify mechanisms of resistance, prognostic genomic biomarkers, or molecular targets to exploit.⁸⁻¹⁰ Personalized cancer medicine—tailoring medical decisions by integrating clinical features and demographic factors with genetic information—is promising but its value remains unclear for malignancies such as breast cancer, which harbor few truly predictive genomic alterations.^{8,10,11}

Most of our understanding of somatic genomic alterations in breast cancer comes from studies of primary

breast cancer,¹²⁻¹⁴ but our understanding of genomic data on MBC are not nearly as well developed.¹⁵ In the largest clinico-genomic analysis of MBC to date, 1,918 tumors prospectively underwent targeted DNA panel sequencing.¹⁵ Mutations in frequently altered genes were similar to those in primary cancers, such as *TP53* in triple-negative breast cancer (TNBC) and *PIK3CA* and *CDH1* in hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative patients.¹⁵ In HR-positive/HER2-negative patients, the total number of alterations was only moderately higher in MBC tumors compared with primary tumors.¹⁵ Recent evaluation of genomic targets in breast cancer suggests there are nine alterations with level I/II evidence for actionability¹⁶: *ERBB2* amplifications (level IA), germline pathogenic *BRCA1* or *BRCA2* mutations

CONTEXT

Key Objective

DNA sequencing is increasingly incorporated into clinical care for metastatic breast cancer (MBC). How targeted panel DNA sequencing impacts cancer therapy selection and patient perception of care remains unclear. This study provides a prospective analysis of physician decision making and outcomes of patients receiving tumor sequencing as part of MBC clinical care.

Knowledge Generated

Genomic testing revealed that most patients (60%) had at least one recommended treatment with level I/II evidence for actionability; however, only a subset of patients were given a recommendation for a change in treatment, and even fewer actually changed therapy on the basis of genomic testing results. Patients whose therapy did not change on the basis of genomic testing had a decrease in confidence of treatment success.

Relevance

Even though standard of care is improving, relatively few patients with MBC changed therapy on the basis of genomic testing in this prospective study. This suggests a need to better understand barriers to implementation of mutation-directed therapy as well as a need for improved understanding of patient perception of somatic genomic testing.

(IA), *PIK3CA* hotspot-activating missense mutations (IA), microsatellite instability (IC), *NTRK* fusions (IC), *ESR1* hotspot-activating missense mutations (IIA), *PTEN* loss (IIA), *AKT1* mutations (IIB), and *ERBB2* hotspot-activating missense mutations (IIB).¹⁶

Although genomic testing is promising for improving treatment efficacy, it is unclear how frequently it changes choice of treatment.¹⁷⁻¹⁹ Complex interactions between genomic testing and patient perception of care make it imperative to understand the impact of genetic sequencing in clinical oncology.^{17,20,21} To date, we have little understanding of how patients perceive the value or accuracy of genomic testing, and whether changes in treatment recommendation based on genomic testing affect patients' perceptions of care. There are discrepancies between cancer patient and physician expectations of therapy efficacy; patients demonstrate greater optimism about therapy efficacy.²²⁻²⁵ Expectations of patients with MBC and their motivations for undergoing somatic genetic testing have not yet been explored.

Clinical tumor genomic analyses typically rely on targeted next-generation sequencing (NGS) of a panel of specific, typically actionable cancer-related genes to analyze somatic gene alterations from biopsy specimens. Most commercial targeted panel sequencing approaches, including FoundationOne CDx (Foundation Medicine, Cambridge, MA) in this study, provide treatment suggestions that are based on genomic alterations and available clinical literature.²⁶ We hypothesized that prospective implementation of FoundationOne CDx testing into clinical care for patients with MBC will identify patient-specific approaches that offer improved patient outcomes and perceptions of care. In this study, patients with MBC received FoundationOne CDx testing when a new treatment was initiated and genomic testing results released to the provider at the next progression

event. The primary objectives of this study were to assess the proportion of patients whose subsequent cancer-related therapy was based on the FoundationOne CDx test results (FoundationOne CDx-supported treatment change), to evaluate time-to-treatment failure (TTF) and overall survival (OS) in patients whose therapy was genomically directed versus not, and to assess patient perceptions of genomic testing.

PATIENTS AND METHODS

Study Population

This was a prospective, single-site, single-arm trial at a National Cancer Institute–designated cancer center. Patients with MBC who were within 10 weeks of starting their current line of therapy and who had an estimated survival of 3 or more months were included in this study. Included patients needed to have a tumor sample (primary or metastatic) available for genomic testing. The study was approved by The Ohio State University Institutional Review Board and informed consent was obtained from all patients.

NGS

Testing was performed by using FoundationOne CDx, which used NGS on patients' formalin-fixed paraffin-embedded tumor tissue. The test provides information on alterations in 315 cancer-related genes and 28 selected rearrangements (Data Supplement). The selected genes sequenced by FoundationOne CDx have implications in cancer biology, prognosis, and availability of therapy that targets gene products. Genes with more than one alteration were counted once. The FoundationOne CDx report, which is based on detected genomic alterations, includes potential treatment options, such as therapies approved to treat specific tumor types, therapies approved in another tumor type, or therapies evaluated in a clinical trial that

target a specific alteration. Patients were observed until disease progression or intolerance of therapy. The FoundationOne CDx results were then released to the provider.

Survey Measures

Physicians received a five-item questionnaire after the FoundationOne CDx report was released to assess whether their treatment recommendation should be changed on the basis of those results. The questionnaire asked how the physician used the FoundationOne CDx test (multiple choice) and what else they would like to see in the report (multiple choice plus an open-ended “other” option). Patients completed a pretest (before genomic testing) questionnaire at study entry and a post-test questionnaire at the end of the study. Attitudes toward FoundationOne CDx testing were assessed with three items: (1) “By having the test, I will feel more confident of my treatment’s success”, (2) “I will trust the test results”, and (3) “I think the test results will be accurate”. Patient motivation and expectations for study participation were assessed with 15 questions using a five-point Likert scale that ranged from strongly disagree to strongly agree (Data Supplement). Because of small numbers in each group, these questions were assessed as a three-level outcome (agree v neutral v disagree) and as a binary outcome (agree v neutral and disagree).

Statistical and Survival Analyses

McNemar’s test of agreement (2 level or 3 level) was used to compare pre- and post-test survey responses and pre-versus post-test survey agreement by FoundationOne CDx–supported treatment change results from the physician questionnaire. We used McNemar’s nonparametric test because of the limited sample size and non-normal data. TTF was defined as the time from the release of the FoundationOne CDx report to the off-study date. The off-study date was defined as the date of the patient’s second progression (first while on study), second treatment change (first while on study), death, or loss to follow-up. Patients for whom the off-study date was missing were excluded from the TTF analysis. OS was defined as time from the date of study enrollment to death or loss to follow-up. Patients still alive on December 18, 2018, were censored as of this date. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.4.1, and survival curves were created using the packHV package.²⁷

RESULTS

Study Population

A total of 142 patients with MBC provided consent and were assessed for eligibility (Fig 1). Patients were excluded from analysis if there was no available tissue, insufficient tissue, or poor DNA quality (n = 21), died before the FoundationOne CDx report was released (n = 13), did not receive FoundationOne CDx testing within 10 weeks of starting their current line of therapy (n = 4),

were lost to follow-up (n = 2), withdrew consent (n = 1), or had a biopsy that revealed no metastatic disease (n = 1). A total of 100 patients had successful FoundationOne CDx NGS testing and were evaluable for analysis. Of these samples, 71% (71 of 100) were metastatic biopsies and 29% (29 of 100) were primary tumors (breast or axillary lymph node). The most common sites of metastatic biopsy were liver (n = 24), bone (n = 12), and skin/chest wall (n = 10). Most patients’ tumors (63%) were positive for estrogen receptor (ER) and/or progesterone receptor (PR) and negative for HER2. Genomic testing was performed from September 2013 through October 2015, and FoundationOne CDx reports were released to treating physicians starting in December 2013. The study population was predominantly age 55 years or older, white, and college-educated with a high income (Table 1).

FoundationOne CDx Genomic Testing Results

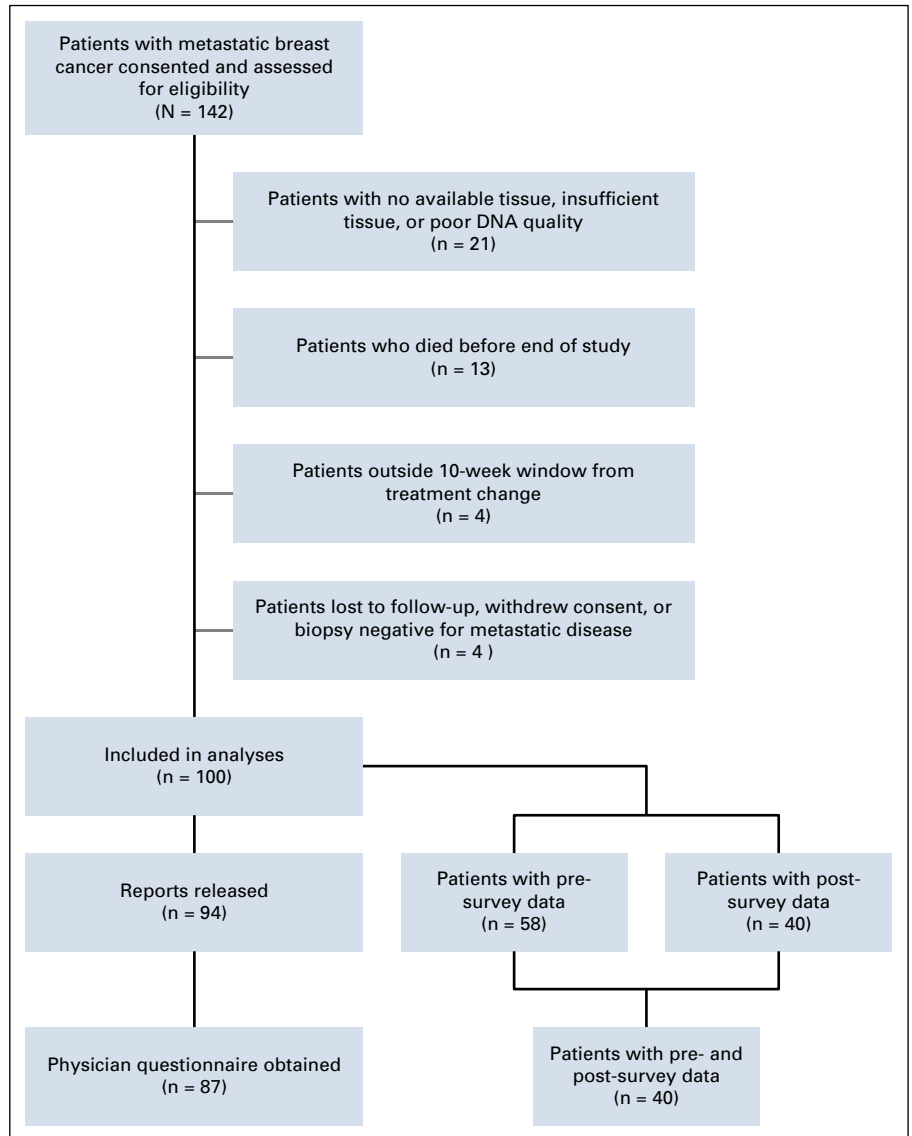
Among the 100 patients with successful FoundationOne CDx NGS testing, the number of mutations identified per patient ranged from 0 to 13 with a median of five mutations (Data Supplement). As anticipated, the most common mutations were missense or frameshift mutations in *TP53* (n = 49) and *PIK3CA* (n = 40) or amplification of *MYC* (n = 20; Fig 2A). Mutations in *TP53* were most common among patients with TNBC. Among ER-positive/HER2-negative patients, 10 (16.7%) of 63 harbored an *ESR1* mutation.

In terms of therapy recommendations, 98 (98.0%) of 100 patients had at least one potential therapy identified on FoundationOne CDx testing, with a median of nine potential treatments (range, 0 to 35 potential treatment; Fig 2B). The most commonly recommended therapy based on a genomic alteration was an mTOR inhibitor (everolimus or temsirolimus) for *PIK3CA* mutations (Data Supplement). Among all patients, 60 (60%) of 100 had at least one recommended treatment with level I/II evidence (not including *ERBB2* amplifications),¹⁶ with a median of one potential treatment with level I/II evidence (range, 0 to 2 potential treatments; Fig 2B).

Potential Germline Alterations in Somatic Tumor Testing

A known challenge in somatic tumor sequencing is potential identification of germline alterations.²⁸⁻³² Among the 100 total patients, 14 had alterations identified in *BRCA1* (n = 4), *BRCA2* (n = 8), or *PALB2* (n = 2). Of these, eight (57.1%) of 14 had previous knowledge of germline alterations but six (42.8%) of 14 did not. Of patients with no prior knowledge of germline alterations, five of six had no first-degree relatives with breast or ovarian cancer (Data Supplement). Of these six patients with no prior knowledge of germline mutations, two had germline alterations confirmed (one *BRCA1* and one *BRCA2*) and one underwent germline testing in which no alterations were identified (presumed somatic *BRCA2* mutation). Three patients did not undergo germline genetic testing; two patients were notified of FoundationOne CDx results and received

FIG 1. CONSORT diagram.



a referral for genetic testing; one patient died before release of the FoundationOne CDx results. After consultation with the medical ethics committee, that patient's family was notified of the results.

Clinical Importance of NGS Results

Of the 100 evaluable patients, 94 had FoundationOne CDx reports released, and 87 had corresponding physician questionnaire data (physician response rate, 92.6%). The six patients whose FoundationOne CDx reports were not released remained on their initial therapy without progression as of September 1, 2018; five of these patients had ER-positive/HER2-negative and one had ER-positive/HER2-positive breast cancer. Of the 87 patients with physician data, 27 (31.0%) were given a recommendation to change treatment as a result of the FoundationOne CDx results. Of these, 10 (37.0%) of 27 underwent this recommended treatment change. Across the study population,

10 (10.0%) of 100 total patients or 10 (11.5%) of 87 patients with physician questionnaire data experienced a treatment change supported by FoundationOne CDx data. Physicians described not changing treatment because the patient could not be enrolled on a clinical trial (ie, the recommended trial closed, the patient did not want to enroll, or the patient was ineligible; $n = 10$), patient hospitalization ($n = 3$), insurance denied treatment charges ($n = 2$), patient transferred care to other provider ($n = 1$), or patient pursued a non-recommended trial ($n = 1$; Data Supplement).

Genomic Alterations and Survival

Among 76 patients evaluable for TTF analysis, there was no significant difference in TTF (log-rank $P = .87$) by FoundationOne CDx-supported treatment change status (Fig 3A). Among the 87 patients evaluable for OS analysis, the median follow-up time was 14.3 months; there was no significant difference in OS (log-rank $P = .71$) by

TABLE 1. Patient and Clinical Characteristics

Characteristic	No.	%
Age, years		
< 45	17	16.8
45-54	29	28.7
55-64	31	30.7
≥ 65	24	23.8
Subtype		
ER and/or PR positive, HER2 positive	64	64.7
HER2 positive	6	6.1
TNBC	29	29.3
ECOG status		
0, fully active	55	54.5
1, restricted	44	43.6
2, ambulatory	2	2.0
Race		
Nonwhite	12	12.4
White	85	87.6
Education		
Less than a high school education	2	4.4
High school diploma or GED	2	4.4
Some college, technical school, or associate's degree	21	46.7
Bachelor's degree or higher	20	44.4
Income, \$		
< 30,000	7	15.6
30,000-49,999	4	8.9
50,000-69,999	7	15.6
70,000 or more	27	60.0
Median No. of previous therapies for metastatic disease (range)	1 (0-11)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; GED, General Educational Development test; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; TNBC, triple-negative breast cancer.

FoundationOne CDx-supported treatment change status (Fig 3B). By subtype, there were significant differences in OS (log-rank $P = .01$); patients who had TNBC had worse OS than ER-positive/HER2-negative patients, as anticipated (Data Supplement).

Among genomic alterations, we evaluated several mutations known to be prognostic (*ESR1* mutations) or potentially predictive of outcomes (*PIK3CA*). In MSK-IMPACT (a targeted tumor-sequencing assay developed at Memorial Sloan Kettering Cancer Center [MSK] termed "Integrated Mutation Profiling of Actionable Cancer Targets" [IMPACT]), there was evidence that patient response to aromatase inhibitor therapy was significantly worse for patients whose tumors harbored one of several alterations.¹⁵ Among

ER-positive/HER2-negative patients, we noted that the presence of an *ESR1* mutation was not significantly associated with OS (Fig 3C). Despite a high frequency of mutation, there was no significant difference in OS by *PIK3CA* mutation status among ER-positive/HER2-negative patients ($P = .18$) or TNBC patients ($P = .66$), or when evaluating alterations that could activate the PI3K pathway (*PIK3CA* mutation, *PTEN* loss, or *AKT1* mutation) among ER-positive/HER2-negative patients ($P = .60$) or TNBC ($P = .81$) patients (Data Supplement). In the MSK-IMPACT study (ClinicalTrials.gov identifier: [NCT01775072](https://clinicaltrials.gov/ct2/show/study/NCT01775072)), ER-positive/HER2-negative patients with detected tumor mutations in *ESR1*, MAP kinase pathway, or *MYC* or other transcription factors genes had a worse response to aromatase inhibitor therapy than patients without these alterations.¹⁵ We evaluated the association of these alterations with OS and found no significant difference among the four groups (Fig 3D).

Patients' Perceptions of Genetic Testing

A total of 58 (58.0%) of the 100 evaluable patients completed at least a portion of the survey at enrollment (pretest), and 40 (40.0%) completed at least a portion of the survey at study conclusion (post-test). We evaluated three pre-specified questions to assess patients' perceptions of treatment success, trust of genomic testing results, and accuracy of the results (Table 2). In the pretest survey, most patients strongly agreed or somewhat agreed that by having the genetic testing they would feel more confident in their treatment's success (36 [65.5%] of 55), whereas at study completion, a minority of patients (12 [30.8%] of 39) felt more confident in their treatment's success by having the genetic testing. We used a paired test among patients who completed both the pretest and post-test and found a statistically significant decrease in confidence for both 3-level (agree v neutral v disagree; McNemar's test of agreement $P = .003$) and 2-level (agree v neutral/disagree; McNemar's test of agreement $P = .002$) analyses. There was no significant difference in patients' trust of test results or thinking the results were accurate (McNemar's $P = .06$ for both questions).

We then assessed whether pretest and post-test survey results were associated with treatment change on the basis of FoundationOne CDx results in patients who completed both the pretest and post-test survey questions of interest. For treatment confidence, we found that patients who did not have a treatment change supported by FoundationOne CDx data were significantly more likely to change their response from agree to neutral or disagree (McNemar's test of agreement $P = .001$; Fig 4). There was no significant change in perceptions of the group who had treatment change supported by FoundationOne CDx data (McNemar's test of agreement $P = .32$).

To understand patients' motivations and expectations, we assessed 15 questions from the survey administered before

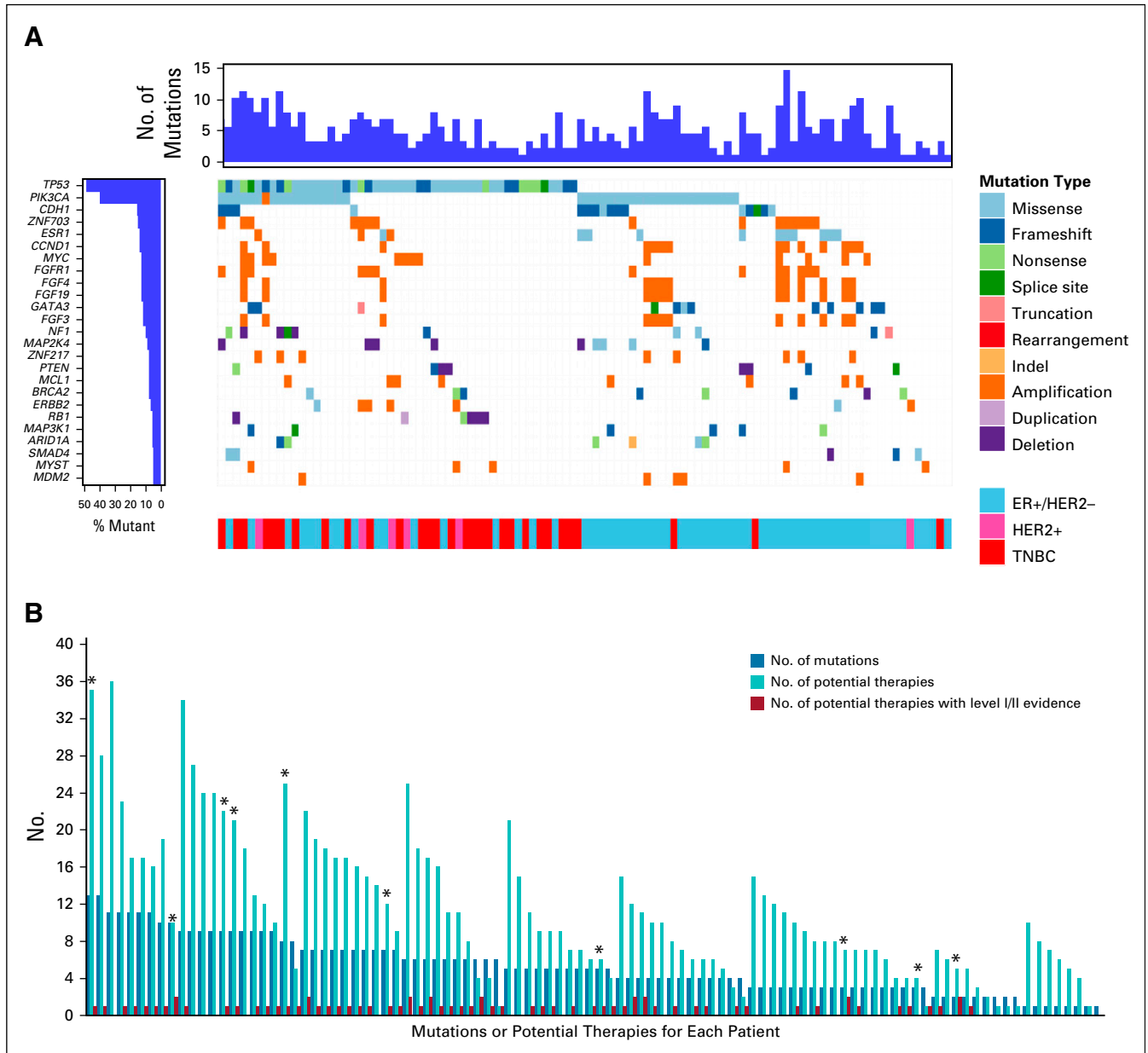


FIG 2. Genomic alterations and therapeutic implications. (A) Patient-level (n = 100) mutation plot of the 25 most frequently altered genes in the study population. Left: frequency of the alteration in each gene; top: number of detected mutations per patient; bottom: receptor subtype. CoMut plot created by using the GenVisR package.⁴⁷ (B) For each patient (n = 100), the graph shows number of detectable mutations, number of potential therapies identified, and number of potential therapies with level I/II evidence for actionability in breast cancer based on Condorelli, et al.¹⁶ (*) Indicates patients whose treatment was changed based on genomic testing results.

treatment (Data Supplement). A total of 58 patients completed most or all of these questions. Most patients (61.8%) did not believe the FoundationOne CDx test would have a negative impact on their family. Most patients (80.0%) believed the FoundationOne CDx test would give them a better understanding of the chance of success for their treatment option, and 59.3% believed the test would tell them about their genetic future. About half the patients (49.1%) believed the test would tell them what medications to take. Most patients (67.9%) believed the test results

would tell them their children’s risk of disease. Most patients (91.1%) believed that their participation would help researchers. To evaluate potential nonresponse bias, given the response rates, we compared patients who completed the pretest survey with those who did not. We found no significant differences between these two groups in age, cancer subtype, Eastern Cooperative Oncology Group status, race, and number of genetic mutations. Similarly, we did not find significant differences in these demographics between patients who completed both surveys

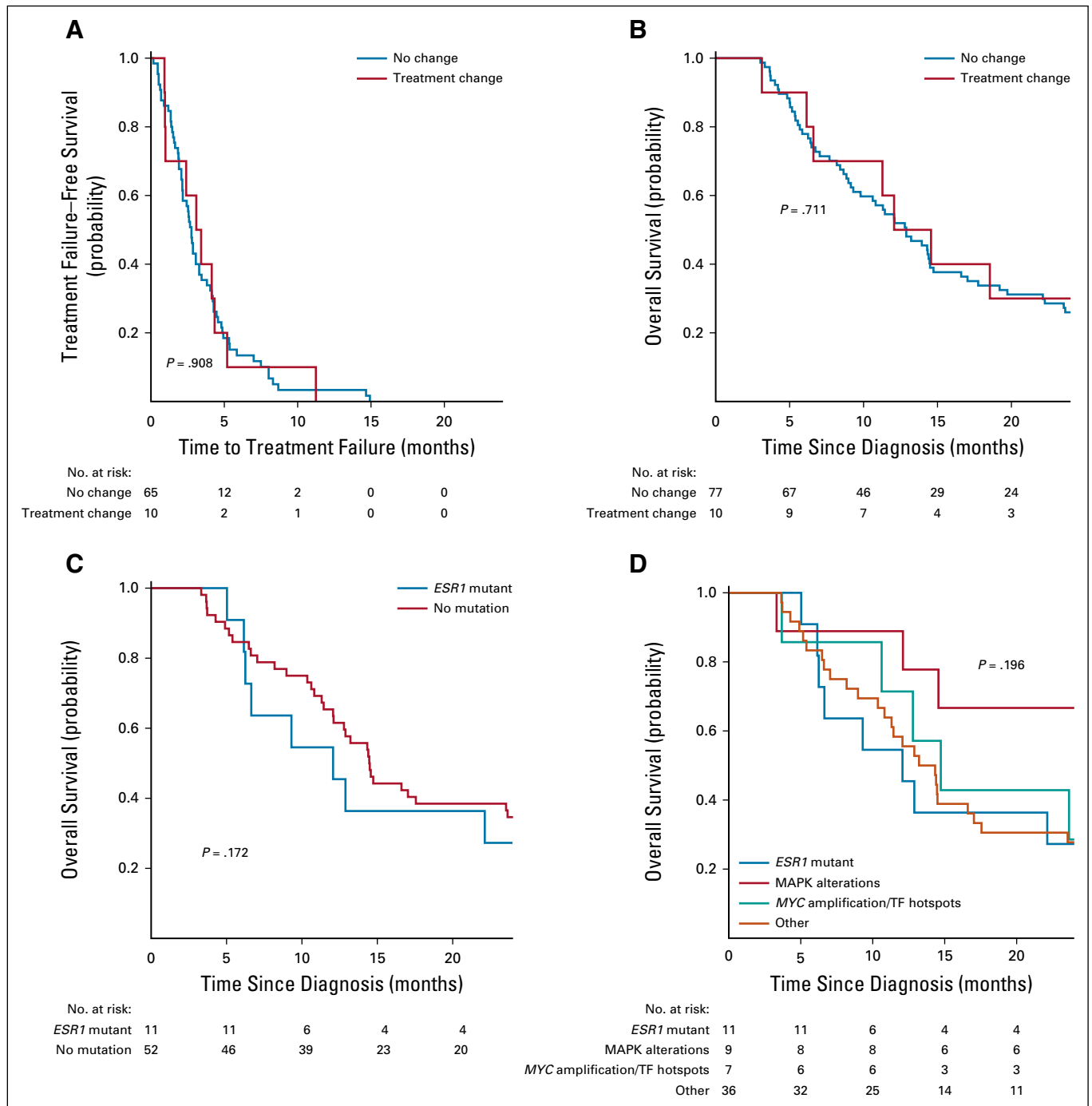


FIG 3. Cohort survival analyses by receptor and genomic features. Kaplan-Meier plots with log-rank test P value. (A) Kaplan-Meier plot of time to treatment failure stratified by patients with treatment change based on genomic testing (red line) v no treatment change. Time to treatment failure defined as time from release of FoundationOne CDx results to the off-study date, defined as date of second progression or treatment change (first during the study period), death, or loss to follow-up. (B) Kaplan-Meier plot of overall survival by receptor status. Overall survival is defined as the period of time from the date of study enrollment to death or loss to follow-up. Patients who were still alive on December 18, 2018, were censored on this date. (C) Kaplan-Meier plot of overall survival for patients with estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer, stratified by presence or absence of mutation in *ESR1*. (D) Kaplan-Meier plot of overall survival for patients with ER-positive/HER2-negative metastatic breast cancer stratified by presence or absence of *ESR1* mutation, MAPK pathway alteration, *MYC* amplification, transcription factor (TF) alteration, or other, as defined by Razavi, et al.¹⁵

TABLE 2. Patient Perception of Genomic Testing Accuracy, Results, and Treatment Success

Patient Questionnaire Item	Pretest Results						Post-Test Results						Agree v Neutral/ Disagree P	Agree v Neutral v Disagree P
	Disagree		Neutral		Agree		Disagree		Neutral		Agree			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%		
By having the test, I will feel more confident of my treatment's success.	4	7	14	25	37	67	11	28	16	41	12	31	.002	.003
I will trust the test results.	2	4	9	16	44	80	3	8	10	25	27	68	.06	NA
I think the test results will be accurate.	2	4	8	15	45	82	1	3	8	21	30	77	.06	NA

Abbreviation: NA, not applicable.

and those who completed only the presurvey, suggesting that nonresponse bias is minimal.

DISCUSSION

NGS is increasingly common in MBC care and has significant potential value for physicians and patients when making cancer treatment decisions.³³⁻³⁵ Despite this evidence, the role of NGS for patients with MBC remains fluid, and patient perception, motivation, and expectations are poorly understood. We prospectively evaluated the impact of NGS on MBC treatment decisions and potential associations with patient outcomes and their perceptions of genomic testing.

In this study, more than 60% of patients had a genomic alteration associated with level I or II evidence for actionability (not including HER2 amplification) based on a recent consensus panel¹⁶—an impressive number that emphasizes the potential for widespread use of NGS. The 31% of evaluable patients in this prospective study for whom a change in treatment was recommended on the basis of somatic NGS findings is similar to the frequency seen in large retrospective cohorts.¹⁵ Of the patients for whom a different treatment was recommended by their provider on the basis of the FoundationOne CDx results, only 37% (11.5% of total) proceeded with the recommendation to

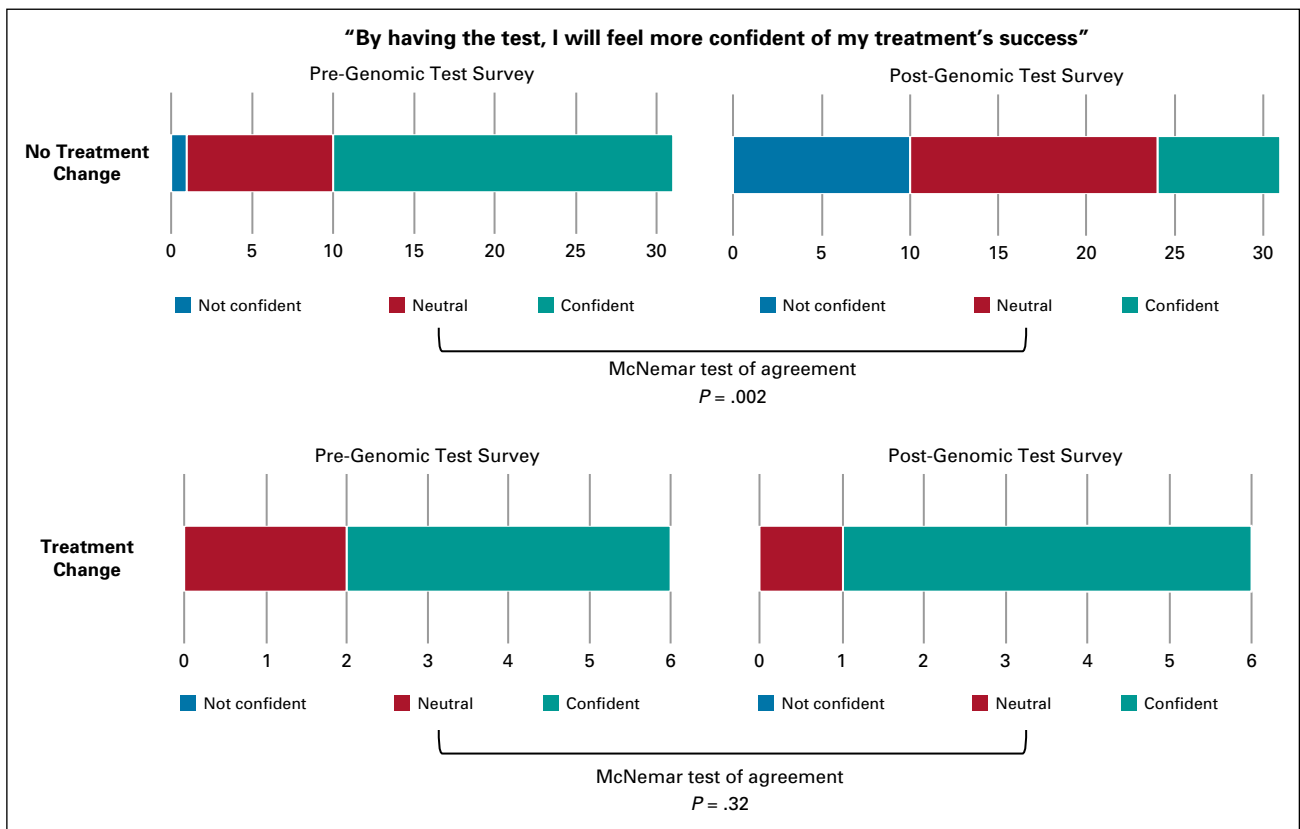


FIG 4. Patient confidence in treatment success before and after genomic testing. Enrolled patients were surveyed regarding their perception of genomic testing: “By having the test, I will feel more confident of my treatment's success.” A total of 37 patients answered the question both before (pre-genomic test survey) and after (post-genomic test survey) genomic test results were shared with physicians. Number of patients who were not confident, neutral, or confident are indicated.

change treatment, which implies that there are significant barriers to pursuing NGS-supported treatments. This is consistent with a previous study that identified barriers such as trial ineligibility, distance to trial, and physical/emotional exhaustion.¹⁸ Treatment change was not significantly associated with TTF or OS; however, the small number of patients experiencing treatment change limits the conclusions that can be drawn from these analyses.

This is the first study to our knowledge to prospectively evaluate the influence of somatic NGS on patient perception of care and it provides important initial data, but the lower patient survey response rate limits definitive conclusions. When comparing study surveys at admission to surveys at conclusion, patients seemed less confident in their treatment, particularly those whose treatment was not changed by FoundationOne CDx results. This is consistent with other studies that suggest genetic testing may increase negative emotions in patients with metastatic cancer,¹⁸ although most studies evaluated effects from germline testing.³⁶⁻⁴⁰ Our data preliminarily suggests that there may be ramifications of somatic genomic testing for patients despite its known utility in selecting therapy for MBC. Because negative emotions are associated with decreased quality of life and potentially with survival,⁴¹⁻⁴⁴ the possible negative implications of broadly integrating NGS into clinical practice should be considered.

Furthermore, pretest survey data suggest that patients have misconceptions about what somatic mutation testing can inform. We found that patients had overly optimistic expectations for somatic tumor NGS: almost half believed the test would tell them which medication to take whereas only 11.5% of the total patients switched therapy on the basis of FoundationOne CDx reports. This is similar to previous studies that demonstrate that patients have greater optimism regarding treatment efficacy than physicians do,²⁴ possibly because physicians provide patients with more optimistic information than their true assessment.⁴⁵

In addition, most patients incorrectly believed the test would predict future genetic mutations, assess children's disease risk, or estimate treatment success, despite the informed consent stating that participants would rarely benefit personally or therapeutically from this study. Therefore, this supports further exploration of the readability of consent forms, an area currently under investigation.⁴⁶ We hypothesize that patients' limited knowledge of genetics

may explain their decreased confidence after genomic testing,¹⁷⁻¹⁹ and we also hypothesize that improved decision support for genomic testing for patients will improve confidence in their treatment, particularly in the context of increases in available targeted treatments for MBC.

There are known limitations to our study that prevent us from making definitive conclusions. Among survey data, we had a high physician survey response rate (> 90%) but a substantially lower response rate among evaluable participants: the response rate was 58% (58 of 100) for the pretest and 40% (40 of 100) for both pretest and post-test. Despite this, our findings provide preliminary insight into critical aspects of MBC care that warrant evaluation in a larger study. Furthermore, unlike the methodologies in the existing literature, we used a unique prospective and longitudinal methodology to evaluate patient perceptions. Future studies may benefit by including patient interviews to assess the experience of somatic NGS. The use of nonvalidated survey items and single site design in our study also support the need for further research. In addition, among all consented patients, 14.8% had no available tissue, inadequate tissue, or inadequate DNA quality. This is a realistic barrier to NGS that is infrequently captured in retrospective analyses. Furthermore, the potential treatments identified by FoundationOne CDx test results reflect drugs approved for any indication, not necessarily for MBC, and therapies available at the time of the test. For example, both everolimus and temsirolimus were reported as potential therapies for patients with alterations in *NF1*, *PTEN*, *AK1*, *PIK3R1*, *RPTOR*, *AKT3*, *FBXW7*, *KIT*, *PDGFRA*, *STK11*, and *VHL*; however, only everolimus is approved by the US Food and Drug Administration for MBC. In addition, since this study was completed, multiple new therapies approved by the US Food and Drug Administration have not been considered, suggesting that clinical implications of NGS should be assessed regularly.

In conclusion, our findings suggest that NGS by tools such as FoundationOne CDx may provide valuable insight for physicians and patients when determining the best treatment option for patients with MBC upon disease progression. There are clear clinical challenges involved with integrating NGS into the framework of MBC care, including barriers to preferred treatment options and complex interactions between genomic testing and patient perceptions, which warrant further study.

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EQUAL CONTRIBUTION

D.G.S. and R.E.R. contributed equally to this work.
B.R. and M.B.L. equally directed the work.

PRIOR PRESENTATION

Presented in part at the Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 9-13, 2014, and the Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 3-7, 2016.

SUPPORT

Supported by grants from Pelotonia (D.G.S, M.B.L.), the Stephanie Spielman Fund (D.G.S.), and Foundation Medicine.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/po/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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Patents, Royalties, Other Intellectual Property: MatchTX, a genomics software package that helps researchers, oncologists, and clinical trial managers identify the full set of biomarkers that collectively predict the outcome of patients with cancer to treatment

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Patents, Royalties, Other Intellectual Property: Patents via Foundation Medicine and via Seres Health on microbiome in non-neoplastic disease (I)

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No other potential conflicts of interest were reported.

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