Barriers to the Use of Personalized Medicine in Breast Cancer

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Abstract

Purpose: Personalized medicine—the use of genomics and molecular diagnostics to direct care decisions—may improve outcomes by more accurately individualizing treatment to patients. Using qualitative research, we explored care delivery barriers to the use of personalized medicine for patients with breast cancer using examples of *BRCA* and gene expression profile testing.

Methods: We conducted 51 interviews with multidisciplinary stakeholders in breast cancer care: clinicians ($n = 25$) from three academic and nine nonacademic organizations, executives ($n = 20$) from four major private insurers, and patient advocates ($n = 6$).

Results: Barriers were common to the *BRCA* and gene expression profile tests and were classified under two categories: poor coordination of tests relative to treatment decisions and

reimbursement-related disincentives. Perception of specific barriers varied across groups. Difficulty coordinating diagnostics relative to decisions was the most frequent concern by clinicians (60%), but only 35% of payers and 17% of advocates noted this barrier. For 60% of payers, drug- and procedure-based reimbursement was a significant barrier, but only 40% of clinicians and none of the advocates expressed the same concern. The opinion that patient out-of-pocket expenses are a barrier varied significantly between advocates and clinicians (83% v 20%, $P < .007$), and advocates and payers (83% v 15%, $P < .004$). Barriers were reported to result in postponement or avoidance of tests, delayed treatment decisions, and proceeding with decisions before test results.

Conclusion: Poorly coordinated diagnostic testing and the current oncology reimbursement model are barriers to the use of genomic and molecular diagnostic tests in cancer care.

Introduction

Personalized medicine—the use of genomics and molecular diagnostics to direct care decisions—has become a priority in health care^{1,2} and an important component of cancer care.^{3,4} ASCO recognizes the importance of personalizing care for all cancer stages, from early disease to end of life, both in the broader context of individualizing care decisions⁵ and in the specific sense of applying genomic technologies in care.^{6,7}

Integration of personalized medicine in care is challenged by significant obstacles,^{4,8,9} with some key barriers arising from care delivery.^{3,10-12} Experts have called for research to understand and address these barriers in cancer care.¹¹ Understanding barriers is increasingly important given the proliferation of genomic and molecular diagnostic tests: since 2006, more than 100 new genomic tests have been introduced in oncology.¹³ Other studies have identified delivery barriers to genetic and molecular diagnostics in oncology, including testing logistics and reimbursement.¹⁴⁻¹⁶ Our objective was to better define the delivery and reimbursement barriers to the use of personalized medicine in cancer treatment, using examples of two breast cancer tests: *BRCA-analysis* (Myriad Genetics, Salt Lake City, UT), as used for newly diagnosed patients, and the 21-gene assay *Oncotype DX* (Genomic Health, Redwood City, CA). Both technologies are recommended by clinical guidelines^{6,7,17} but are underused for eligible patients.^{18,19}

Methods

We used the framework approach of qualitative research²⁰ as the method for this exploratory study. Qualitative research is effective in identifying health care, policy, and clinical practice issues^{21,22} and has been used to explore barriers to adoption of personalized medicine.¹⁰ This study was conducted under a protocol approved by Northwestern University's institutional review board.

Sampling

Study informants were identified by using purposive sampling²² and recruited through a Chicago-based collaboration of medical centers, patient advocates, and payers, facilitated by Northwestern University and focused on integrating personalized medicine in oncology. We estimated that the initial number of informants in each group (clinicians, advocates, and payers) of 20, 15, and five, respectively, would allow elucidation of diverse perspectives within each information group, and we recruited our initial cohort on the basis of these numbers. As we conducted and analyzed the interviews, we used thematic analysis within and across groups to determine if we had reached a saturation point (ie, when the key themes become repetitive).²³ We then used the snowball approach (a method for locating data-rich informants by querying the initial cohort) to recruit additional interviewees,²² until we reached the saturation point within and across the clinician, payer, and advocate informant groups, and until no new themes were contributed by additional informants.

We selected clinicians with self-reported knowledge and experience in ordering and interpreting the tests, and payers with self-reported experience in developing policies for the tests. When several physicians from the same site were recruited, they represented separate practices within their organization and had independent processes and approaches for ordering and using *BRCAAnalysis* and *Oncotype DX*. In one practice, we interviewed three clinicians, but they had distinct roles in ordering, using, and interpreting the tests. All study informants were interviewed individually.

Data Collection

The interviews were conducted between October 2008 and December 2009. We developed a semistructured interview guide based on the objectives of our study and review of the literature; pilot tested it with two providers, two payers, and one advocate not participating in the study; and adjusted it for clarity on the basis of their feedback. The interview guide contained short clinical scenarios for each test and questions regarding the use of the test, related barriers, and consequences of barriers (Appendix Table A1, online only).

The interviews were conducted over the phone by two investigators, lasted between 30 and 60 minutes, and were transcribed. All participants provided informed consent, and none reported a conflict of interest. No participants were compensated for their time. The interview questionnaire was shared with informants in advance of the interview.

Data Analysis

Interviews were analyzed by two separate investigators, functioning independently, following the five steps of the framework approach of qualitative research.^{20,23,24} The first three analytic steps—familiarization with interview data; identifying a thematic framework; and indexing, or coding, data based on the thematic framework—were conducted concurrently with data collection to determine the point of saturation, as described in the Sampling section above. The two remaining analytic steps—data charting according to the thematic framework, and data mapping and interpretation—were conducted after completion of the interviews. Disagreement was resolved by discussion and consensus. Simple frequencies and Fisher's exact test computing the two-sided *P* value by summing small *P* values were used to analyze the coded data.

BRCAAnalysis and Oncotype DX Tests

We selected *BRCAAnalysis* and *Oncotype DX* tests for this study because together they allow examination of an array of challenges along the continuum of care for patients with breast cancer. *BRCAAnalysis* identifies *BRCA1/2* germline mutations that indicate risk of breast and ovarian cancers. For patients with breast cancer, *BRCA* mutation is associated with an increased risk of contralateral breast cancer,²⁵⁻²⁸ and bilateral mastectomy and/or bilateral salpingo-oophorectomy may be appropriate treatment options.²⁹ Although there is a debate about using the test at diagnosis to inform the definitive surgery decision,³⁰⁻³² and related long-term outcome data are not avail-

able, preoperative *BRCA* testing influences patients' surgical decision making^{16,33} and is one of the appropriate scenarios for use of this test.⁷ We explored this scenario because it provides a useful example of barriers to the utilization of personalized medicine in cancer care.^{15,16} *BRCAAnalysis* is currently the only *BRCA1/2* mutation test available in the United States. It is performed on a blood or oral specimen that is sent to the Myriad Genetics central laboratory, with a typical result turnaround time of 2 weeks.³⁴

Oncotype DX is one of several available gene expression profile tests for patients with early-stage breast cancer.³⁵ We examined *Oncotype DX* rather than competing tests (eg, MammaPrint; Agendia, Amsterdam, the Netherlands) because it is most commonly used. *Oncotype DX* determines the risk of cancer recurrence and the likelihood of benefit from adjuvant chemotherapy³⁶⁻⁴¹ and is included in treatment guidelines for estrogen-positive, node-negative breast cancers.^{6,17} The test is performed on a paraffin-embedded tumor specimen, typically after the definitive surgery, when the node status is known. The specimen is sent to the Genomic Health central laboratory, with typical result turnaround time of 7 to 10 days from specimen receipt.⁴²

Results

The interviews were conducted with 51 individuals (Table 1): clinicians providing breast cancer care (*n* = 25) from three academic and nine nonacademic institutions, representatives from four major health plans (*n* = 20), and representatives from a single national advocacy group for patients with breast cancer (*n* = 6). Payer interviewees were senior executives from three major national health plans with a combined membership of more than 63 million, and from one leading regional health plan with a membership of 3 million. Five of the six advocates were breast cancer survivors; all six were peer counselors on the advocacy group's patient hotline. Response rates were 76%, 74%, and 86% for clinicians, payers, and advocates, respectively (Table 1).

Identified Barriers and How They Affect Care

Our theme analysis identified two mutually influencing categories of barriers to using *BRCAAnalysis* and *Oncotype DX* in breast cancer care (Table 2): (1) poor timing and sequencing of tests relative to the care decisions they are intended to guide (timing category), and (2) provider reimbursement and patient benefits create counterincentives to the use of tests (reimbursement category).

At least one barrier in the timing category was noted by a majority of clinicians (80%) and advocates (83%), but by less than half of payor interviewees (40%; Table 2). Interviewees described that for either test, ordering, obtaining insurance authorization, sending the specimen to an outside laboratory, receiving results, and discussing results with patients could be a lengthy and complex process. If the tests are not ordered with adequate lead time, results are not available for the relevant decisions: definitive surgery for *BRCAAnalysis* and adjuvant chemotherapy for *Oncotype DX*. Interviewees reported that as a

Table 1. Informant Characteristics

Informant Group	No. of Individuals Invited	No. of Individuals Participating	Participation Rate (%)
Total informants	67	51	76
Clinicians	33	25	76
Specialty			
Breast surgery	7	5	71
Oncology	13	10	77
Genetics and psychology	5	4	80
Nursing	8	6	75
Practice setting			
Academic	13	12	92
Nonacademic	18	13	72
Payers (from four major plans)	27	20	74
Role			
Medical director (including four oncologists)	12	10	83
Benefits management	7	4	57
Provider management	8	6	75
Patient advocate	7	6	86

consequence, decisions are made without test results: the *BRCA* status results may arrive after the surgery or after the appointment when the surgical decision has been made and the operating room scheduled. In either case, the surgery is performed without considering *BRCA* mutation status. Similarly, it was reported that the *Oncotype DX* recurrence score may arrive after the consultation at which the adjuvant treatment plan is developed; thus the consultation is postponed, resulting in additional appointments or in treatment without the test result.

The majority of clinicians (80%), payers (80%), and advocates (83%) noted at least one barrier under the reimbursement category. Informants reported that the reimbursement barriers create disincentives for both physicians' and patients' use of *BRCAAnalysis* before definitive surgery and *Oncotype DX* testing for adjuvant chemotherapy decisions. As a result, the test may be postponed (eg, *BRCA* testing is postponed by surgeons

until after surgery when the medical oncologist may order it) or avoided altogether.

Barriers Related to Poor Timing of Tests Relative to Treatment Decisions

Four specific barriers to effective timing of diagnostics relative to decisions were reported (Table 3). Difficulty coordinating and planning diagnostics relative to decisions was the barrier most commonly noted by clinicians (60%) and payers (35%) in the timing category. This was also the barrier most noted by clinicians across both timing and reimbursement categories. Both academic and nonacademic clinicians noted this barrier. The majority of payers who noted this barrier were medical directors. The interviewees commented that it is difficult to time tests relative to decisions because of the complexity of the testing process; because ordering is often done outside of the physician's office (eg, pathology department, genetic counseling); and because ordering physicians lack tools to coordinate the various participants, such as insurers or outside laboratories.

Two specific components of the testing process were noted as barriers to effective coordination of tests relative to treatment decisions: prior authorization and time required for working with patients on test-related decisions. A sizable minority of clinicians noted these two barriers (36%, 32%), whereas few payers (0%, 10%) and few advocates (17%, 17%) reported them as factors. Notably, there was a statistically significant variance in clinician and payer opinions on prior authorization as a barrier ($P < .002$). Specifically among clinicians, prior authorization was a more commonly noted by support staff—nurses, genetic counselors, and psychologists (50%)—than physicians (27%). Prior authorization is required by many insurers for *BRCAAnalysis* and *Oncotype DX* and was described as an additional step, often involving staff outside of clinician offices, over whom the ordering physician has little control. It was also reported that *BRCAAnalysis* and *Oncotype DX* tests require more discussion time with patient than other tests because they entail complex shared decisions regarding both whether to order the test and how to proceed with interventions

Table 2. Summary of Identified Barriers

Category and Barrier	Informant Group Noting at Least One Barrier in Category	Consequences of Barriers (found for both <i>BRCAAnalysis</i> and <i>Oncotype DX</i>)
Poor timing of tests relative to decisions	Clinicians (80%)	Test is avoided
Difficulty coordinating tests relative to treatment decisions	Payers (40%)	
Prior authorization delays test ordering	Patient advocates (83%)	
Time spent working with patients on test decisions results in treatment delay		Test is ordered but is not used in the treatment decision
Physicians assume patient priorities and preferences for pace of treatment		
Provider reimbursement and patient benefits	Clinicians (80%)	Test is postponed
Test may reduce drug or procedure reimbursement	Payers (80%)	
Time spent working with patient on test decisions is not well reimbursed	Patient advocates (83%)	
Supportive and genetic services are not reimbursed		Treatment decision and/or treatment is delayed
Patient out-of-pocket costs for tests		

Table 3. Specific Barriers to the Use of Personalized Medicine

Category and Barrier	Clinicians (%; n = 25)	Payers (%; n = 20)	Patient Advocates (%; n = 6)	Total Interviewees (%; N = 51)	P*
Poor timing of diagnostics versus decisions					
Difficulty coordinating tests relative to treatment decisions	60	35	17	45	.08 (clinicians to advocates)
Prior authorization delays test ordering	36	0	17	20	.002 (clinicians to payers)
Time for working with patients on test decisions delays treatment	32	10	17	22	NS
Physicians assume patient priorities and preferences for pace of treatment	20	5	67	20	.04 (clinicians to advocates), .004 (payers to advocates)
Provider reimbursement and patient benefits					
Test may reduce drug or procedure reimbursement	40	60	0	43	.01 (payers to advocates)
Time for working with patient on test decisions is not well reimbursed	36	45	0	35	.06 (payers to advocates)
Supportive and genetic services are not reimbursed	40	5	0	22	.01 (clinicians to payers)
Patient out-of-pocket costs for tests	20	15	83	25	.007 (clinicians to advocates), .004 (payers to advocates)

* Only variations that are statistically very significant, significant, or trending (not quite significant) are reported.
Abbreviation: NS, not significant.

based on test results. In the case of *BRCAAnalysis*, genetic counseling was reported to significantly prolong the timeline.

The fourth barrier—physicians' assumptions about patient priorities—was the most commonly noted timing barrier among advocates (67%) but the least commonly noted barrier among clinicians (20%), with statistically significant variance between advocates and clinicians ($P < .04$). None of the support staff informants noted this as a barrier. Among physicians, more surgeons than oncologists reported this factor, explaining that they often don't mention preoperative *BRCA* testing, even when clinically relevant, because they assume that patients prefer the speediest time to surgery and would prioritize it over preoperative testing. Oncologists noted that they assume patients are anxious to start chemotherapy, and they may not offer *Oncotype DX* or may recommend proceeding with chemotherapy before receiving results. Conversely, advocates reported that many patients they counsel may not prefer the speediest time to treatment (unless medically necessary) and would like the opportunity to consider all relevant test results in their decisions.

Provider Reimbursement and Patient Benefits Create Counterincentives to Using the Tests

Four specific barriers to the use of *BRCAAnalysis* before definitive surgery and *Oncotype DX* for adjuvant chemotherapy decisions were reported under the reimbursement category (Table 3). That use of the tests might result in reduced drug or procedure reimbursement was one of the barriers most commonly noted by clinicians (40%). Clinicians reported that a decision to forego chemotherapy based on *Oncotype DX* results reduces the revenue from drugs and therefore creates an incentive to avoid the test. Similarly, they commented that that preoperative *BRCA* testing may delay surgery, thus reducing surgical revenue during a given time period. Of interest, among clinicians, only

physicians, both academic and nonacademic, reported this barrier. The majority (60%) of payers—medical directors and provider management executives—also recognized this factor as a barrier to clinicians' use of the tests.

As a separate but related issue, clinicians (36%) and payers (45%) noted that clinicians' time required to work with the patient on test-related decisions is not reimbursed as lucratively as chemotherapy or surgery. They reported that as an incentive to minimize this activity and forego testing. Physicians noted this barrier more commonly than support staff (47% and 20%, respectively). Another service that was reported as necessary for the use of personalized tests, but not well reimbursed, was the delivery of supportive care, specifically psychosocial counseling, and genetic counseling. This barrier was noted by 40% of clinicians (33% of physicians and 50% of support staff), who explained that psychosocial counseling helps patients cope with decisions posed by *BRCA* and *Oncotype DX* testing, and genetic counseling is a guideline-recommended component of the *BRCA* testing process. However, these services are not directly reimbursed and are often offered at the expense of the patient, especially outside the academic setting. This creates an incentive for physicians to avoid offering the tests. Only one payer interviewee and none of the advocates reported this barrier.

Advocates reported only one reimbursement barrier, but by a majority (83%): patient out-of-pocket expenses related to *BRCAAnalysis* and *Oncotype DX* testing. Advocates explained that both tests are expensive (\$3,000), and under many benefit plans they are subject to in-network deductibles or larger out-of-network deductibles (when Myriad Genetics and Genomic Health are out-of-network providers). This entails large out-of-pocket expenses for some patients and creates an incentive for patients to postpone or avoid testing. Twenty percent of clinicians (13% of physicians and 30% of support staff) and 15% of payers (all benefit managers) also noted this as a barrier to

ordering the tests, with a statistically significant variance of responses by clinicians versus advocates ($P < .007$) and by payers versus advocates ($P < .004$).

Discussion

Complex Mix of Barriers Affects the Use of Personalized Medicine in Oncology, With Similar Barriers Across Tests

Our study explored the barriers to the use of personalized medicine in oncology care using the example of two breast cancer tests: *BRCA*Analysis and *Oncotype* DX. We found that the barriers to the use of these two tests were similar and could be classified under two mutually influencing categories: poor timing of testing relative to treatment decisions guided by the tests, and the disincentives arising from provider and patient reimbursement in oncology. We found that these barriers result in avoiding or postponing the tests, decisions that do not use the results of ordered tests, and delayed decisions and treatments. Our study revealed incongruent perceptions of specific barriers among clinicians, payers, and patient advocates, suggesting that clinicians and payers had low awareness of each other's concerns and that both groups had low awareness of patient concerns.

We confirmed the findings of Weitzel et al¹⁶ and Schwartz et al,^{15,33} and commentaries of others, that logistical delivery and reimbursement issues, including complexity and length of the testing process, prior authorization, and lack of reimbursement for genetic counseling, challenge the offering of *BRCA* preoperative testing.^{15,16,31,32} Our study also showed that barriers affecting the use of *BRCA* testing also affected the use of *Oncotype* DX, which is used in a different setting and a different clinical scenario. This may indicate that the issues are deep and broad enough to adversely affect adoption of other personalized medicine tests. As evidence is developed for expanded applications of *BRCA* and gene expression profile tests, they may be used in new settings (eg, *BRCA* testing in the future may guide therapy decisions^{32,43,44}), and their new use may be riddled with the same challenges. However, commonality of issues may also provide an opportunity for developing common solutions that address the adoption of a broad array of personalized medicine technologies across settings and utilization contexts.

In addition to confirming the barriers found by others, our study highlighted several other factors that impede adoption of personalized medicine in oncology. First, we found that physicians assume the pace of treatment and may not offer a test to the patient if it could cause care delay. Few interviewed organizations had a culture or process for ordering tests in advance of treatment decisions. This underscores the necessity to not only personalize treatment to genetic profile, but to also individualize the pace and sequence of care on the basis of patient preferences. Future studies should explore how to strike the difficult balance between timely care and providing patients with the full array of options. Second, we found that not only the lack of reimbursement for counseling and cognitive services,^{16,30,31} but also reimbursement for drugs and procedures constrain the timely use of personalized medicine tests, as using tests like

Oncotype DX may directly reduce provider revenue. Existing data support this finding: studies show that use of *Oncotype* DX on average decreases the use of chemotherapy,^{45,46} therefore presenting a provider disincentive to use the test. There is published evidence that drug-related reimbursement influences the choice of cancer drugs.^{47,48} We showed that it also impedes the use of tests that influence treatment decisions.

Collaborative Patient-Centered Solutions Will Require Mutual Awareness of Barriers Among Stakeholders and a Larger Role for Patient Advocates

The complex mix of barriers to using personalized medicine in oncology will require collaborations across multiple stakeholders to develop solutions.⁹⁻¹¹ A finding of our study—the incongruent views on barriers to personalized medicine among clinicians, payers and patient advocates—presents a challenge to developing collaborative solutions. Of specific concern are the findings that payers did not report some reimbursement-related hurdles, such as prior authorization and patient out-of-pocket contributions, as barriers, and that barriers perceived by advocates were not reported by clinicians or payers. Future efforts to develop solutions should not assume consistent awareness of challenges by key stakeholders and should first focus on mutual education and dialogue. Furthermore, in light of the current emphasis on developing patient-centered outcomes in health care,⁴⁹ it will be critical to increase the role of patient advocates in developing solutions.

Current Health Care Initiatives Should Include Considerations for Personalized Medicine

Advancement of personalized medicine coincides with a number of health care and oncology initiatives that may help address the barriers to adoption and use of personalized medicine tests. A recent article by the National Cancer Institute and Group Health Research Institute⁵⁰ outlined the role of information technology, patient-centered focus, and systems-based approaches in improving modern cancer care. Advanced information systems that help integrate the spectrum of care management tasks⁵¹ may help better connect the ordering physician, patient, payer, and outside laboratory and streamline the process of ordering and using diagnostic tests. Systems-based approaches, such as systems engineering, are advocated by Institute of Medicine for use in improving cancer care coordination.⁵² Enabled by information technology, these approaches may facilitate better timing of tests and treatment decisions across multidisciplinary providers within and across organizational walls. Patient-centered care, enabled by information technology, may facilitate capturing important patient perspectives and preferences,⁵⁰ including those related to genetic testing and the pace of treatment. Patient-accessible Web portals may help patients manage their care and educate them on their choices,⁵³ including the use of personalized medicine, to enable informed discussion with surgeons and oncologists.

In addition, new oncology payment models, such as episode-based payment and accountable care organization,^{54,55}

may help address reimbursement barriers to oncology personalized medicine by removing drug and procedure-based reimbursement. Such models may also provide incentives for important services, such as genetic counseling and care coordination.

These solutions will likely take years to implement. Thus individual provider and payor organizations may take steps now to improve the timing of tests and to better incorporate patient preferences for testing and pace of treatment.^{54-56,55}

Limitations

Our study involved national payers and patient advocates but was limited to providers in the Midwest. Future studies should examine barriers to personalized medicine in other US regions and nationwide. The interviews were conducted 2 to 3 years ago. However, our recent study of clinical data⁵⁷ and current research with 26 Chicago hospitals⁵⁸ indicate that the same barriers to personalized medicine persist. Finally, our cohort intentionally included clinicians and payers who reported that they were knowledgeable of BRCA^{Analysis} and Oncotype DX tests and clinical contexts explored in our study. We therefore did not explore potential barriers related to knowledge level and dissemination. Future studies should explore knowledge dissemination and compare self-reported versus actual knowledge among stakeholders.

Conclusion

Our study is an incremental step in developing the knowledge of and approaches to addressing barriers to personalized medicine in oncology. We found that poorly coordinated diagnostic testing and the current oncology reimbursement model are significant barriers to the use of genomic and molecular diagnostic tests in cancer care.

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Appendix

Table A1. Summary of the Interview Questions

The interviewer describes the scenario for the use of BRACAnalysis test, followed by questions. The interviewer then describes the scenario for the use of Oncotype DX, followed by the same set of questions
BRACAnalysis use scenario: Use of BRACAnalysis test for patients newly diagnosed with breast cancer at high risk for hereditary breast and ovarian cancer (BRCA mutation carrier) who are not otherwise indicated for bilateral mastectomy (based on stage and grade of tumor)
Oncotype DX use scenario: Use of Oncotype DX test for patients with early-stage (I or II), node-negative, ER-positive/HER2-negative breast cancer
Questions asked for each of the scenarios:
1. How is the test used in your practice? What have you observed regarding test use in your provider network? How have patients with breast cancer described using the test?
2. Who is responsible for ordering the test? What are the specific steps after the order? How is your practice/organization involved in each step? Who else is involved and how?
3. What are reasons the test is not ordered in the described scenario?
4. What is the timing of ordering the test? When is it typically ordered, when are results received, and when are results shared with patients?
5. What decisions does the test result impact?
6. How is the test reimbursed? What is the financial impact on the provider, payer, and patient?
7. What barriers, in addition to those you have already described, are there to using the test in making such decisions?
8. How do the barriers affect the use of this test for patients newly diagnosed with breast cancer?
9. What steps, if any, are you taking to address barriers to the test?

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.