Optimizing the Quality of Breast Cancer Biomarker Use at Duke Cancer Institute

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Abstract

Advances in identifying biomarker profiles in patients with early-stage breast cancer have improved 5-year curative rates. Identification of the HER2 receptor provides valuable information that has been shown to extend survival in adjuvant and metastatic settings. Current clinical guidelines discuss when confirmatory testing may be inappropriate. Using a quality improvement approach, the team at Duke Cancer Institute determined HER2 ordering practices in a large academic cancer center. HER2 ordering using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) was abstracted from the charts of 314 patients with early-stage breast cancer. Qualitative responses to current clinical practices were obtained from clinicians. Of the patients included, duplicate IHC was performed for 36% and in triplicate for 6%; repeat testing resulted in clinically significant change in HER2 status for approximately 20%. Repeat biomarker testing on metastatic biopsy sites "all of the time" was favored by the surveyed physicians. FISH was ordered for each grade of IHC: 0+ (>20% of cases), 1+ (>20%), 2+ (99%), 3+ (54%). Most physicians "strongly" or "somewhat" favored solutions that integrate order sets and care pathways into the electronic medical record. This quality improvement project identified root causes and solutions to practice variance in breast cancer biomarker ordering and interpretation. Further investigations are planned to standardize best practices while appreciating the clinical challenges posed by discordant test results. (*J Natl Compr Canc Netw* 2014;12[Suppl 1]:S21–S24)

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In 2012, more than 200,000 women in the United States were diagnosed with invasive breast cancer. Despite the high incidence, 5-year curative rates for early-stage cancer exceed 85%, reflecting remarkable progress over the past 3 decades in tailoring antineoplastic approaches.[1] One such advancement is identification of a breast cancer biomarker profile for all cancers, which results from regular testing of hormone receptors alongside other predictive and prognostic markers. In combination with patient characteristics, these profiles ensure that targeted therapies are selectively applied in delivering patient-centered care. A shining example of this has been the incorporation of trastuzumab for cancers that overexpress HER2, the use of which has dramatically extended survival in both the adjuvant[2] and metastatic settings.[3]

Breast cancer biomarker ordering and measurement are guided by several national recommendations of best practice based on clinical and pathologic scenarios.[4,5] These guidelines also highlight when testing may not be appropriate, such as when unnecessary confirmatory measures are ordered to validate a previously positive test. Especially in situations in which additional information rarely changes the clinical approach, systematic evaluations of the frequency of such "low value" practices should routinely occur. Quality improvement interventions can then be designed and tested in local organizations to identify solutions that simultaneously support both patient-centered and resource-efficient care.

Using the Standards for Quality Improvement Reporting Excellence (SQUIRE) framework,[6] this article describes a directed quality improvement project to address ordering variance of HER2 testing at the Duke Cancer Institute (DCI). Pilot data demonstrated special

cause variance in practice that was not easily attributable to patient- or disease-related causes. The team at DCI planned to target this to reach the following specified stated aims statement:

> Over the next 2 years, the multidisciplinary breast program at the DCI will establish standardized practices for biomarker ordering, receipt, and interpretation that apply to 90% of early-stage breast cancer patients.

Methods

The team incorporated a mixed-methods approach using quantitative and qualitative methods. Quantitative data originated from Duke University's enterprise-wide data warehouse, the NCCN Breast Cancer Registry at Duke, the Duke Tumor Registry, and chart abstraction by experienced research abstractors. The team incorporated qualitative data through 2 methods: a convenience sample focus group and an electronic survey of members of the Duke multidisciplinary breast program. The 18-element survey queried elements of current practice and acceptable future solutions from all members of the DCI team, including medical, surgical, and radiation oncologists; nursing professionals; pathologists; and radiologists.

Basic descriptive statistics were calculated. The Duke University Institutional Review Board approved the project.

Results

The research team abstracted 314 clinical cases of in situ or invasive breast cancer. As expected, most cases were lymph node–negative (66%), estrogen-receptor–positive (80%), HER2-nonoverexpressed (71%) cancers (Table 1). Twelve clinicians participated in the focus group. Twenty-three clinicians responded to the electronic survey invitation, yielding a response rate of 33%.

The research team first determined the prevalence of multiple HER2 testing on samples from the same patient and found that 42% (95% CI, 36%–48%) of patients had HER2 immunohistochemistry (IHC) performed at least twice; approximately 6% (95% CI, 3%–10%) underwent triplicate or quadruplicate testing. Repeat testing resulted in a clinically significant change in HER2 status approximately 20% of the time, confirming the utility of this practice. The electronic survey responses showed a strong agreement that HER2 testing should be run on most samples available to confirm results before treatment. For example, 69% of those surveyed stated that repeat biomarker testing should occur on metastatic biopsy sites "all of the time."

The research team then analyzed HER2 fluorescence in situ hybridization (FISH) ordering according to various HER2 IHC results. Consistent with guidelines,[4,5] HER2 FISH was ordered 99% of the time in cases of IHC 2+. Interestingly, the team observed that HER2 FISH was ordered in more than 35% of IHC 0/1+ cases and in 70% of IHC 3+ cases. Insight into this practice stems from another important finding. The team found 4 cases of discordance between IHC and HER2 results that led to meaningful changes in clinical approaches (eg, negative to positive or positive to negative clinical HER2 status). These observed variations in biomarker ordering practice are indicative of occasional clinician uncertainty with the results.

The research team also explored how variations in HER2 biomarker results affect clinician decision-making (Table 2). In 5 clinical scenarios, various HER2 IHC positivity results were coupled with positive, negative, or equivocal HER2 FISH results. These results confirmed an understanding of the

Table 1 Descriptive and Clinical Cancer Characteristics

Total abstracted charts, N	314
Median age, y (range)	56 (23–93)
Lymph node status, N (%)	
Positive	75 (24)
Negative	206 (66)
Not assessed[a]	33 (10)
Hormone receptor status, N (%)	
ER-positive	251 (80)
ER-negative	60 (19)
Missing	3 (1)
HER2 overexpression status, N (%)	
Overexpressed	41 (13)
Nonoverexpressed	223 (71)
Not assessed	50 (16)
Tumor histology, N (%)	
Ductal	271 (86)
Not ductal	43 (14)

[a]Lymph node status not assessed in ductal carcinoma in situ.

Table 2 Clinician Responses Regarding Clinical HER2 Status

Question	Patient is HER2-Positive	Patient is HER2-Negative	Patient is Neither HER2-Positive or -Negative	Unsure	Depends on the FISH Ratio	Total Responses
1. IHC: HER2 0+ FISH: positive	10	1	0	1	2	14
2. IHC: HER2 1+ FISH: positive	11	1	0	1	1	14
3. IHC: HER2 1+ FISH: equivocal	0	6	3	0	5	14
4. IHC: HER2 2+ FISH: equivocal	1	4	2	2	5	14
5. IHC: HER2 3+ FISH: positive	6	4	0	0	4	14

Abbreviations: FISH, fluorescence in situ hybridization; IHC, immunohistochemistry.

challenges faced by clinicians when findings are discordant. For example, in one hypothetical case of a patient with HER2 1+ by IHC and equivocal FISH, 43% of survey respondents answered that the patient is "clinically HER2-negative," whereas 36% said, "it depends on the centromere ratio." In another case of HER2 IHC 3+ and FISH negativity, responses were approximately equally distributed among HER2 "positive," "negative," and "depends on the centromere ratio."

Finally, clinicians were asked about their acceptance of potential interventions to standardize the biomarker testing approach at DCI. Most respondents (80%) said that they "strongly" or "somewhat" favored potential solutions that integrate order sets and care pathways into the electronic medical record. Most also endorsed the idea of a portfolio of initiatives that span a continuum, from creating a portfolio of policies to creating electronic guidance and point-of-care decision support.

Discussion

The study goal was to identify areas of variation within practice, explore their root causes, conduct stakeholder analyses to develop a short list of acceptable solutions, and then test those interventions through small, repeated quality improvement cycles. The data present background information to inform the multidisciplinary conversations needed to brainstorm a portfolio of interventions to implement, test, and sustain. The research team was encouraged that almost 100% of clinical cases recommended for HER2 testing did, in fact, receive testing. Furthermore, DCI is an academic medical center with a large portfolio of clinical trials using targeted anti-HER2 agents; clinicians demonstrated frequent sample retesting to identify potential false-negative cases. Importantly, these data demonstrate a discordance rate of approximately 20% during repeat HER2 testing. This finding aligns with those of other groups comparing primary tumor biomarker profiles with those of recurrence sites.[7,8]

These findings also demonstrate a local culture that prioritizes continuous improvements to optimize breast cancer care. The team incorporated a mixed methods approach into this series of projects, integrating expertise in continuous quality improvement and health services research methods to rigorously investigate processes that produce excellence in dependable and regular ways. The results are reported using the SQUIRE Framework, which establishes best practices in reporting quality improvement results that assist in translating methods and findings across institutions. As quality assessment and improvement continue to integrate into the health care landscape, approaches will be increasingly needed that leverage the interests and expertise of a multidisciplinary team of clinicians and administrators. This ensures that the institution, patients, and caregivers can continue to experience world-class, patient-centered breast cancer care that responds to the ever-changing landscape of evidence and best practices.

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