Closing the Personalized Medicine Information Gap: HER2 Test Documentation Practice

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Background: Uncertainty about human epidermal growth factor receptor-2 (HER2) testing practice in Canada continues to hinder efforts to improve personalized medicine. Pathologists routinely perform HER2 assessment for all tumors > 1 cm, and pathology is reported centrally to the provincial cancer registry.

Objectives: To understand patterns of HER2 test documentation for early-stage breast cancer (BC) patients in Ontario's centralized pathology reporting system.

Study Design: Retrospective cohort study of central HER2 test documentation in early-stage BC patients diagnosed in 2006-2007.

Methods: Cohort and staging information was derived from cancer registry and admissions data. Linkage across administrative databases provided data on surgical and radiologic treatment, sociodemographic factors, diagnosis setting, and comorbidities. Pathology reports from the provincial cancer registry were reviewed for HER2 testing, hormone receptor, and grade. Unadjusted and adjusted odds ratios were calculated to determine factors related to HER2 documentation.

Results: A HER2 test was documented for 66% of 13,396 patients. HER2 documentation was associated with stage, hormone receptor, and tumor grade documentation. Higher stage and grade at diagnosis were also associated with HER2 documentation. All models suggested variable regional documentation patterns. Documentation did not differ by sociodemographic factors, presence of comorbidities, or surgical procedure.

Conclusions: Despite a universal testing policy, the rate of centralized HER2 test documentation was lower than expected and related to disease severity. Differences in regional reporting likely reflect ascertainment bias inherent to centralized pathology reporting rather than testing access. Improved HER2 reporting is encouraged for cancer registration, quality-of-care measurement, and program evaluation.

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For author information and disclosures, see end of text.

Breast cancer (BC) is the most frequently diagnosed cancer among Canadian women, with a projected incidence of 23,400 in 2011.[1] Early diagnosis and adjuvant treatment provide significant gains in life expectancy for women diagnosed with early-stage disease.[2] Recent advances in treatment focus on using genetic information to target treatments to patients who are likely to respond. One example is the human epidermal growth factor receptor-2 (HER2) oncogene and protein, first noted as predictors of overall survival and time to relapse in BC.[3] Amplification of the HER2 oncogene in 20% of cancers is associated with poor prognosis, aggressive tumor proliferation, and poorer response to chemotherapy.[3,4] Trastuzumab therapy has demonstrated significant improvements in disease-free survival and mortality in patients whose tumors overexpress HER2.[5,6] Testing for HER2 to identify treatment candidates is typically conducted by immunohistochemistry (IHC) or in situ hybridization techniques, most commonly fluorescence (FISH).[7,8] Differences in test accuracy and cost prompted the development of testing guidelines[7] to ensure efficient and accurate diagnosis of HER2-positive patients. Although less expensive, IHC is also less accurate.[7] Quantification of HER2 gene overexpression by FISH is more accurate, but also more expensive and difficult to conduct. Guidelines recommend the use of either IHC or FISH to detect HER2 overexpression and promote reflex FISH testing to clarify the HER2 status of IHC-equivocal tumors.[7,8]

Accurate identification of HER2-positive patients is crucial given the high cost of adjuvant trastuzumab therapy and the potential exposure of false-positive patients to cardiotoxic side effects. Adjuvant treatment guidelines recommend that all incident patients with invasive disease receive a HER2 workup.[9] Economic evaluations of HER2 testing and treatment demonstrate the clinical and economic costs of failure to accurately classify IHC-equivocal patients.[10-12] Studies of HER2 testing in the early days of metastatic therapy in the United States suggested an information gap[13] in HER2 documentation for 48% of eligible patients. More information is needed to gauge the quality of current practice and to establish a foundation for assessing the optimal use of personalized medicine in the real world. Without this information, it is difficult for administrators or researchers to understand issues related to access to testing, appropriateness of treatment, and cost-effective care. HER2 testing practice in Canada remains largely unreported in the

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Population-based analysis indicated that tumor pathology for human epidermal growth factor receptor-2 (HER2) testing was not consistently reported to the central registry, despite universal access to HER2 testing in the Ontario public healthcare system.

- Locally performed HER2 tests were documented for 66% of patients at the centralized registry.
- Although HER2 test documentation was unrelated to income or urban residence, it was related to documentation of other pathology factors and disease severity measured by stage and tumor grade.
- Without improved or mandatory HER2 reporting to the central registry, program evaluation and health quality improvement studies are limited.

literature, particularly with respect to how testing is documented, what tests were performed, test results, and whether reflex testing is conducted. A sample of early-stage patients in Nova Scotia suggests that 81% of patients received a HER2 test, but provides no insight into the type of test(s) used.[14]

We aimed to describe centralized HER2 test documentation and testing patterns in Ontario and to gain insight into how to use and interpret these data. Our specific objectives were to (1) assess the availability of data to evaluate HER2 testing practices from a centralized source in a real-world setting; (2) describe reporting system, clinical, or sociodemographic factors associated with HER2 documentation in Ontario; and (3) describe HER2 test utilization with respect to test type and test sequencing.

METHODS

Study Design and Setting

A retrospective cohort design was used to study patients diagnosed with early-stage BC between 2006 and 2007 in the Canadian province of Ontario. This time frame allowed 6 months of lag time subsequent to the approval of adjuvant trastuzumab therapy in mid-2005.[15] The associated treatment guideline and relevant policies were implemented province-wide under the auspices of Cancer Care Ontario (CCO). As the provincial cancer agency, CCO is involved in screening, diagnostic, treatment, recovery, and palliative services to all patients diagnosed with cancer in the publicly funded Ontario healthcare system. The New Drug Funding Program of CCO administers the reimbursement of new, expensive systemic therapies, including trastuzumab. At the time of this study, adjuvant trastuzumab treatment was available to patients with HER2-positive tumors larger than 1 cm that were previously treated with chemotherapy.[9,15] Ontario's policy is to follow Canadian testing guidelines "…to test all patients with invasive breast cancer for HER2/*neu* at the time of diagnosis."[7,8] Testing was funded by the Ontario Ministry of Health and Long-term Care and routinely performed by pathologists irrespective of other clinical or pathologic factors. Tumor pathology should be reported centrally to the provincial cancer agency for maintenance of the cancer registry. Reimbursement for trastuzumab requires evidence of a positive HER2 test, but this is provided separately from registry reporting.

Research ethics board approval was obtained from St. Joseph's Healthcare Hamilton. The protocol was also approved by the privacy committees of CCO and the Institute for Clinical Evaluative Sciences. These agencies provided access to provincial and national administrative health data, and facilitated record linkage across data sources using anonymous patient identifiers. This manuscript was reviewed by CCO, the Institute for Clinical Evaluative Sciences, and the Ministry of Health and Long-term Care.

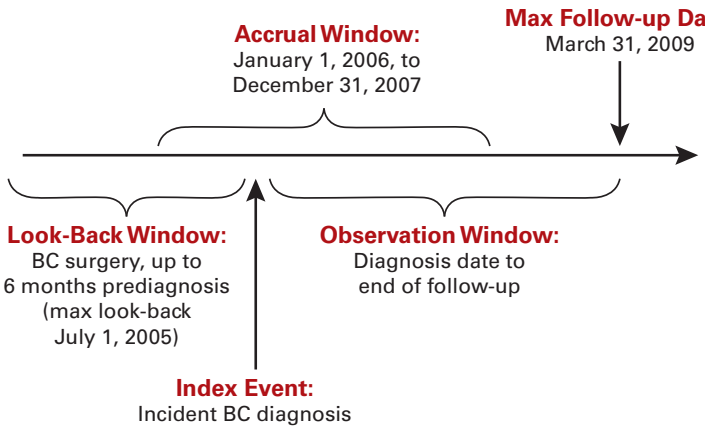
Participants

All female patients who were diagnosed with early-stage, invasive BC between January 1, 2006, and December 31, 2007, and were treated with surgery (modified radical or partial mastectomy, lumpectomy) within 6 months of diagnosis were eligible for the study. Patients with BC (*International Classification of Diseases, Ninth Revision* code 174) were identified from the Ontario Cancer Registry (OCR). The early-stage cohort was identified by eliminating metastatic and miscoded noninvasive carcinoma (stage 0) patients per clinical staging data.[16] Patients with metastatic disease were additionally eliminated if either of the following were identified: (1) metastatic treatment protocols in New Drug Funding Program records or (2) advanced cancer diagnosis on inpatient admission records within 4 months of incident diagnosis. Finally, the cohort was limited to patients who received surgical treatment within 6 months of diagnosis per inpatient, ambulatory care, and health insurance billing records. Surgery was defined as modified radical mastectomy, partial mastectomy, or lumpectomy with the exclusion of needle biopsies or lymph node excision alone. Surgical treatment was limited to 6 months following diagnosis to allow for sufficient access to HER2 testing in patients who were diagnosed in late 2007. These exclusions isolated a patient population indicated for HER2 testing and potentially eligible for adjuvant trastuzumab treatment in Ontario (**Figure 1**). All follow-up was captured through administrative health data or medical records.

Variables, Sources, and Measurement

We collected variables measuring clinical, demographic, and healthcare system factors likely to influence HER2 test documentation or test usage. Administrative data were de-

■ **Figure 1.** Time Frame Definitions for Selection of the Early-Stage Breast Cancer Cohort and Follow-Up Data Collection



BC indicates breast cancer.

rived from several sources: (1) inpatient and outpatient procedures and diagnoses from Canadian Institute for Health Information Same Day Surgery,[17] National Ambulatory Care Reporting System,[17] and Discharge Abstract Databases[18]; (2) professional and procedure billing codes from the Ontario Health Insurance Program database; and (3) demographic information from the Institute for Clinical Evaluative Sciences Physician and Registered Persons databases.[19] Incident diagnosis, institution of diagnosis, staging, laterality, and vital status were obtained from the OCR. Pathology reports submitted to CCO for OCR purposes were reviewed for HER2 testing, estrogen or progesterone receptor status, tumor grade, and testing laboratory. Whenever possible, we derived exclusion variables from multiple data sources to reduce the impact of nonreporting biases associated with a single data source. For example, surgical procedures were derived from Same Day Surgery, National Ambulatory Care Reporting System, and Ontario Health Insurance Program databases.

Data on the primary outcome, HER2 test documentation, were collected from pathology reports. We considered a patient to have HER2 test documentation when there was evidence in the pathology report that a HER2 test was requested or conducted. Detailed information was collected to document the type of test provided and sequencing. Testing was documented as IHC or FISH when any prespecified keyword (Table 1) was found in the report. A HER2 test was recorded as unknown when evidence of a HER2 test was present but the type was not distinguishable. The date of each HER2 test was recorded.

Potential predictors of documentation included age at diagnosis, income, laboratory type, diagnosing physician specialty, and tissue source. Income was categorized into quintiles according to Statistics Canada methodology, which uses postal code–derived census data to estimate household size–adjusted family income.[20,21] The specialty of the treating physician was derived from chemotherapy billing records. Finally, laboratory type and tissue source predictors were drawn from pathology reports. We considered urbanicity, treatment setting, and comorbidity as potential confounders of HER2 test documentation. Urbanicity was defined using postal code–derived census data.[22] The institution of diagnosis assigned in the OCR was used to determine the local health integration network (LHIN) diagnosis setting. LHINs are health authorities responsible for providing, planning, integrating, and funding all public healthcare within a defined geographic region. Charlson Comorbidity Index scores were computed from inpatient diagnosis codes[23-25] to categorize patients as having no prior comorbidities or 1 or more prior comorbidities in the 3 years prior to incident diagnosis. Hormone receptor status and histologic tumor grade were determined from pathology reports. This 3-year look-back window was chosen to maximize capture of patients with prior comorbidities, particularly cardiac conditions, that might not be identified in a single year prior to diagnosis via inpatient codes. Our a priori clinical reasoning was that trastuzumab therapy would be more likely to be contraindicated in patients with comorbidities, which might introduce a systematic bias against HER2 testing in the cohort. Stage at diagnosis was captured from the OCR. Finally, we collected several other clinical indicators to describe the cohort. Breast-conserving (partial excision, partial mastectomy, tumor excision, with or without reconstruction) or nonconserving (modified radical mastectomy, modified radical excision, with or without reconstruction) surgical procedures were determined from billing or inpatient/outpatient procedure codes. Radiation treatment was captured from billing records. Tumor laterality and vital status were determined from the OCR.

Table 1. Keywords Used in Determination of IHC or FISH Test Documentation From Pathology Reports

IHC Keywords	FISH Keywords
% Positive cells	FISH
A0485 (antibody)	Fluorescence in situ hybridization
ABC IHC technique	HER2/CEP 17
CB11 (antibody)	HER2/neu gene amplification
HER2/neu protein overexpression	HER2/neu oncogene amplification
HER2/neu oncoprotein overexpression	PathVysion
HercepTest	
Immunohistochemical testing	
IHC	
LSAB	
Polymeric IHC technique	
SP3 (antibody)	
TAB250 (antibody)	

FISH indicates fluorescence in situ hybridization; HER2, human epidermal growth factor receptor-2; IHC, immunohistochemistry.

Collection of Tumor Pathology From Medical Records

All OCR-related pathology reports available for the cohort were reviewed for HER2 test, tumor grade, and hormone receptor data using a study-specific protocol adapted from the 2009 College of American Pathologists guidelines.[26] Pathology report extraction was completed as a patient-level analysis by prioritizing the most aggressive tumor in multifocal cases for consistency with clinical decision making. Synoptex software (Artificial Intelligence in Medicine[27]) was used to assist in data capture from pathology reports. The software was used in a semiautomated way, whereby a study-specific data entry form was initially populated using customized algorithms adapted for this study. The data capture was then evaluated and either accepted or corrected by trained reviewers. Pathology reports were reviewed on an individual basis, although patients with 3 or more documented HER2 tests were subject to a holistic review of all pathology reports to reduce duplicate reporting of HER2 tests. The pathology review incorporated reports with and without linkage to the patient record in the cancer registry in an effort to reduce any reporting or system-related factors that might bias HER2 documentation.

Statistical Analysis

A minimum of 160 patients were required to detect a 0.05% deviation in HER2 test documentation with 80% power. Descriptive statistics were used to review the distribution of all variables. The relationship between each variable and the primary outcome was first analyzed by univariate odds ratios (ORs) and χ^2 tests. Adjusted ORs were estimated by multiple logistic regression. Variables were selected for inclusion in logistic models based on the significance of univariate ORs at the $P = .10$ level. We prespecified the inclusion of urbanicity and income variables in each model to address sociodemographic questions of access.

Documentation of HER2 testing was modeled from 2 perspectives to account for variability due to reporting system or clinical factors. From the system perspective, we assessed whether HER2 test reporting to the OCR was associated with reporting of other pathology factors by regressing HER2 test documentation against the documentation of other pathology variables (eg, histologic tumor grade documented vs undocumented). From the clinical perspective, we examined whether HER2 documentation was related to clinical factors such as disease severity by regressing HER2 documentation against clinically defined categories for relevant variables (eg, histologic tumor grade 2 or 3 vs 1). An alpha level of .05 indicated statistical significance in multivariable analysis.

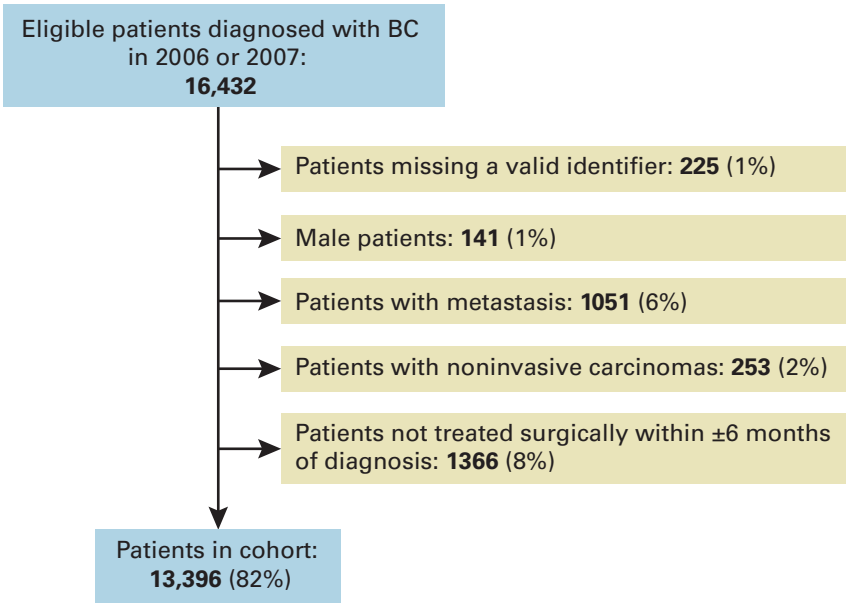
The significance of regional variation was estimated for LHINs as a group by using the global likelihood ratio test for each model. The robustness of model conclusions was tested in sensitivity analyses examining alternative modeling scenarios: (1) all clinically important and statistically significant predictors; (2) all clinically important and statistically significant predictors, excluding variables with >25% missingness; (3) only statistically significant predictors; (4) only clinically significant predictors. The preferred final model was the one that maximized the χ^2 likelihood ratio and pseudo R^2 values while also having clinical face validity. Final models were then used to examine prespecified interaction terms selected by systems or clinical reasoning. Finally, documentation of IHC and FISH tests was analyzed descriptively. All analyses were performed with STATA version 10 (StataCorp, College Station, Texas).

RESULTS

Cohort

A total of 16,432 patients diagnosed with incident BC in 2006 and 2007 were identified from the OCR. After application of exclusion criteria (**Figure 2**), the final analytic data set

Figure 2. Flow Diagram of Patient Exclusions From the Cohort and Pathology Reports Reviewed[a]



BC indicates breast cancer.
[a]Percentages shown were calculated on the basis of eligible patients diagnosed with breast cancer.

consisted of 13,396 patients. We reviewed 29,764 reports of breast tissue. At baseline, the cohort was similar to the Ontario BC population on the basis of age, stage at diagnosis, laterality, radiation usage, and vital status[28] as of March 2009 (Table 2). The vital status of all patients was known at the end of follow-up.

HER2 Documentation

HER2 test documentation was noted for 66% of the cohort (n = 8854). Age at diagnosis, LHIN, and documentation of other pathology variables were significant predictors of HER2 test documentation after adjusting for other predictors in the reporting system perspective (Table 3). Increasing age at diagnosis was associated with lower odds of having a documented HER2 test. Documentation of other tumor pathology factors was associated with higher odds of having a documented HER2 test; in the extreme case, patients with documented hormone receptor status had 12.5 times higher odds of having a documented HER2 test than those without hormone receptor status documentation. Practice varied significantly by regional LHIN (global likelihood ratio test P <.001; data not shown). The presence of comorbidities was a significant predictor in univariate analysis, but was not associated with HER2 test documentation after adjusting for other predictors. Sociodemographic factors were not associated with HER2 test documentation in the cohort. We excluded treating physician specialty and laboratory variables from models because of high proportions of missing values (47% and 84%, respectively). The direction and significance of all variables were robust to all sensitivity analysis (data not shown).

Clinical-perspective results (Table 4) were similar to reporting-system results. After accounting for regional LHIN variation (global likelihood ratio test P <.001; data not shown), sociodemographic factors and comorbidity were not associated with HER2 documentation. Older patients had lower odds of HER2 test documentation. Clinical indicators suggest that disease severity was associated with higher odds of HER2 test documentation. Patients diagnosed with clinical stage II and III disease had 1.45 and 1.83 times higher odds of HER2 documentation, respectively, than patients diagnosed with stage I disease. Similarly, patients diagnosed with histologic tumor grades 2 and 3 had 1.25 and 1.51 times higher odds of HER2 documentation, respectively, than patients diagnosed with grade 1. The direction and significance of all predictors remained consistent in sensitivity analyses (data not shown). From the clinical perspective, we also investigated interactions between urbanicity and income, age and stage, age and comorbidity, and stage and grade (capturing aggressive disease); none was significant (data not shown).

Documented HER2 Testing Patterns

The quality and consistency of HER2 test documentation varied widely, but test type was distinguishable for 96% and 95% of first and second tests, respectively. Among tested pa-

Table 2. Characteristics of Cohort Patients Diagnosed With Early-Stage Breast Cancer in 2006 or 2007[a]

Characteristic	Cohort, % (n)	HER2 Test Documentation, % (n)	
		Undocumented	Documented
All patients	100 (13,396)	34 (4542)	66 (8854)
Age at diagnosis, y[b]			
<50	23 (3034)	21 (961)	23 (2073)
50-59	25 (3376)	25 (1117)	26 (2259)
60-69	24 (3149)	23 (1063)	24 (2086)
70-79	18 (2449)	19 (859)	18 (1590)
≥80	10 (1388)	12 (542)	10 (846)
Diagnosis year[b]			
2006	49 (6622)	48 (2162)	50 (4460)
2007	51 (6774)	52 (2380)	50 (4394)
Vital status			
Alive at end of follow-up	95 (12,704)	95 (4319)	95 (8385)
Urbanicity[b]			
Urban	87 (11,706)	85 (3876)	88 (7830)
Rural	13 (1684)	15 (665)	12 (1019)
Stage at diagnosis[b]			
I	35 (4712)	38 (1710)	34 (3002)
II	32 (4319)	28 (1258)	35 (3061)
III	10 (1358)	8 (347)	11 (1011)
Unknown	22 (3007)	27 (1227)	20 (1780)
Hormone receptor status[b]			
Positive	50 (6660)	19 (866)	65 (5794)
Negative	12 (1599)	3 (157)	16 (1442)
Unknown	38 (5137)	77 (3519)	18 (1618)
Histologic tumor grade[b]			
1	13 (1668)	11 (486)	13 (1182)
2	27 (3594)	18 (804)	31 (2790)
3	19 (2601)	10 (468)	24 (2133)
Unknown	41 (5533)	61 (2784)	31 (2749)
Laterality[b]			
Left	44 (6137)	40 (1818)	49 (4319)
Right	47 (5948)	38 (1721)	48 (4227)
Bilateral	2 (302)	1 (60)	3 (242)
Unknown	8 (1009)	21 (943)	1 (66)
Breast-conserving surgery	60 (8048)	60 (2717)	60 (5331)
Radiation treatment[b]	67 (8966)	62 (2832)	69 (6134)
Income			
Income quintile 1 (lowest)	17 (2334)	17 (771)	18 (1563)
Income quintile 2	19 (2577)	20 (910)	19 (1667)
Income quintile 3	20 (2649)	19 (879)	20 (1770)
Income quintile 4	21 (2812)	21 (956)	21 (1856)
Income quintile 5 (highest)	22 (2991)	22 (1014)	22 (1977)
Comorbidity[b]			
Charlson Comorbidity Index score ≥1	7 (988)	8 (367)	7 (621)

HER indicates human epidermal growth factor receptor-2.
[a]Numbers may not add to 100% due to rounding. Follow-up to March 31, 2009.
[b]Statistically significant differences between documented and undocumented patients at the $P = .05$ level per Pearson's χ^2 test.

■ **Table 3.** Unadjusted and Adjusted Odds Ratios for HER2 Documentation in Centrally Held Pathology Reports of Patients Diagnosed With Early-Stage Breast Cancer in 2006 or 2007: Reporting-System Perspective[a]

Reporting-System Variable	HER2 Test Documentation	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age at diagnosis, y		
50-69 vs <50	0.92 (0.84-1.01)	0.88 (0.78-0.99)[b]
≥70 vs <50	0.81 (0.73-0.89)[b]	0.74 (0.65-0.85)[b]
Income quintile		
Quintile 1, 2, 3, or 4 vs quintile 5	1.00 (0.92-1.09)	1.00 (0.90-1.12)
Urbanicity		
Rural vs urban	0.76 (0.68-0.84)[b]	0.90 (0.77-1.04)
Stage documentation		
Documented vs undocumented	1.47 (1.35-1.60)[b]	1.58 (1.42-1.77)[b]
Hormone receptor documentation		
Documented vs undocumented	15.38 (14.09-16.80)[b]	12.54 (11.36-13.85)[b]
Histologic tumor grade documentation		
Documented vs undocumented	3.52 (3.26-3.79)[b]	2.18 (1.98-2.41)[b]
Comorbidity		
Charlson Comorbidity Index score ≥1 vs 0	0.86 (0.75-0.98)[b]	1.02 (0.85-1.22)

CI indicates confidence interval; HER, human epidermal growth factor receptor-2; OR: odds ratio.
[a]All pathology variables were modeled as either documented or undocumented to assess reporting-system relationships. Adjusted odds ratios account for variability by local health integration network in addition to the variables shown. This model considered 13,363 observations (99.7% of cohort).
[b]Significant at the $P = .05$ level.

tients, 95% had 1 or more IHC tests and IHC tests accounted for 94% of all first tests. Conversely, 15% of tested patients had 1 or more FISH tests, and 2% received FISH as the first test. The majority of patients (73%) had a single test documented. Secondary tests were noted for 24% of tested patients, while the remainder received more than 2 tests (3%). The second test type was split almost evenly among IHC and FISH at 49% and 46%, respectively. A maximum of 6 tests were noted for a patient across multiple pathology reports, which could not be ruled as duplicate reporting.

DISCUSSION

This study addresses a knowledge gap about HER2 test documentation and testing patterns in the largest cohort of female early-stage BC patients reported in the literature to date. In this population-based cohort, we documented a HER2 test for 66% of patients from pathology reports held by the Ontario provincial cancer agency within the context of a universal access environment where HER2 testing was standard practice for all early-stage patients.

Test documentation was related to documentation of other pathology factors such as hormone receptor testing, tumor stage, and histologic grade. Similarly, clinical measures of tumor pathology indicated that patients with more aggressive disease (advanced stage and grade) were more likely to have HER2 test documentation. Higher odds for testing in stage II or III versus stage I disease were expected given that some stage I tumors were likely smaller than 1 cm and therefore not indicated for trastuzumab treatment or HER2 testing. We also found that hormone receptor–negative patients were less likely to have HER2 documentation. We would expect the opposite trend, with hormone receptor negative–patients having a higher rate of documentation, if the potential clinical need for trastuzumab were a determinant of HER2 documentation. These findings do not suggest that patients with less aggressive disease lacked access to HER2 testing, but rather suggest that completeness of centralized reporting or documentation might be related to disease severity. That is more likely to be a function of the registry reporting system than of the clinical need for trastuzumab, as HER2 reporting for trastuzumab reimbursement is provided independent of the registry. However, the potential for residual confounding in the cohort limits our ability to draw conclusions about the role of disease severity in HER2 documentation. In contrast, HER2 test documentation was not related to sociodemographic factors such as urbanicity

Table 4. Unadjusted and Adjusted Odds Ratios for HER2 Documentation in Centrally Held Pathology Reports of Patients Diagnosed With Early-Stage Breast Cancer in 2006 or 2007: Clinical Perspective[a]

	HER2 Test Documentation	
Clinical Variable	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Age at diagnosis, y		
50-69 vs <50	0.92 (0.84-1.01)	0.78 (0.66-0.93)[b]
≥70 vs <50	0.81 (0.73-0.89)[b]	0.60 (0.49-0.74)[b]
Income quintile		
Quintile 1, 2, 3, or 4 vs quintile 5	1.00 (0.92-1.09)	1.00 (0.85-1.17)
Urbanicity		
Rural vs urban	0.76 (0.68-0.84)[b]	0.92 (0.75-1.14)
Stage at diagnosis		
II vs I	1.39 (1.27-1.51)[b]	1.45 (1.25-1.69)[b]
III vs I	1.66 (1.45-1.90)[b]	1.83 (1.45-2.30)[b]
Hormone receptor status		
Negative vs positive	1.37 (1.15-1.64)[b]	1.44 (1.11-1.87)[b]
Histologic tumor grade		
2 vs 1	1.43 (1.25-1.63)[b]	1.25 (1.05-1.48)[b]
3 vs 1	1.87 (1.62-2.17)[b]	1.51 (1.24-1.86)[b]
Comorbidity		
Charlson Comorbidity Index score ≥1 vs 0	0.86 (0.75-0.98)[b]	1.19 (0.88-1.60)

CI indicates confidence interval; HER2, human epidermal growth factor receptor-2; OR, odds ratio.
[a]All pathology variables were modeled using clinical categorizations to address relationships between disease pathology and HER2 documentation. Adjusted odds ratios account for variability by local health integration network in addition to the variables shown. This model considered 6142 observations (45.8% of cohort).
[b]Significant at the $P = .05$ level.

or income, or to comorbidity, consistent with the policies of the Ministry of Health and Long-term Care. These observations were robust across different modeling perspectives and sensitivity analyses.

Our multivariable analysis results both support and challenge the findings of other studies. A report from Nova Scotia, Canada, found that untested patients tended to be older and have smaller tumors.[14] Similarly, a study in Swansea, Southwest Wales, also suggested that elderly patients were less likely to have HER2 testing.[29] These age-related differences in HER2 testing and documentation are consistent with the results of the current study. A study of Kaiser Permanente Northwest patients found that HER2 testing was more common among those also tested for estrogen receptor status.[30] That is consistent with documented practice in Canada, where HER2 and hormone receptor testing by IHC are typically conducted simultaneously in centralized laboratories.[31] However, HER2 testing in the Kaiser Permanente population was lower in patients with Medicare or Medicaid insurance.[30] This situation differs from that in Ontario, where HER2 testing is universally available, regardless of enrollment in either provincial or private insurance plans. Indeed, we demonstrated that sociodemographic factors did not play a role in test documentation. A recent analysis of early-stage BC in Aetna patients demonstrated a 97% rate of HER2 testing, and showed that documentation was not related to age, tumor pathology, or sociodemographic factors.[32] The contrasting rates of HER2 documentation between the Aetna study and this analysis underscore the regional reporting variation across Ontario LHINs. This variation provides an important caveat for researchers studying personalized medicine practice using a centralized, cancer registry–driven data source and provides support for the ongoing effort to adopt collaborative staging standards in Ontario.[33]

Incomplete HER2 test documentation in centrally held reports makes interpretation of these findings challenging, which in turn has implications for efforts to improve the quality of personalized medicine through research and monitoring. Recent calls for better evidence to evaluate personalized medicine practice have highlighted 2 challenges: (1) pricing-based reimbursement for diagnostic tests does not facilitate individual test identification in administrative data and (2) registries documenting testing and subsequent treatment decisions are lacking.[34]

We assessed the ability to document HER2 testing in Ontario across treatment settings and geographical locations, but found that HER2 status was not detailed in the OCR, and HER2 tests were not discernible from other diagnostics in billing data (despite being billed individually vs as a bundle). CCO's repository of OCR pathology submissions provided a central source for pathology reports, but we identified several deficiencies in this source. Although submission of pathology reports to CCO to inform cancer diagnoses and staging in the OCR is mandatory, HER2 testing was not required for reporting at the time of this study. Moreover, HER2 tests tend to be reported on addendum pathology reports, which may not be submitted centrally unless the addendum alters diagnosis or staging for registry purposes. Differential use of electronic systems to manage and submit pathology reports at the laboratory level may also account for variability. These system factors may explain the high missingness of HER2 and other pathology factors in the cohort. Pathology reports as a source of HER2 information are also highly variable in format, detail, and structure.

This study provides a baseline measure of HER2 test documentation using multivariable methods in the largest early-stage BC cohort reported in the literature. We have demonstrated the potential for biased reporting of more aggressive disease, which may be related to the capabilities of individual laboratory information systems or incentives to gain access to drug reimbursement. Information about testing practice can be used to independently assess testing guideline adherence, identify variations in testing practice across laboratories, and improve the consistency and quality of HER2 testing. However, improvements to the reporting system, or mandatory reporting of HER2 test results, are necessary to produce high-quality data for provincial assessment. Program evaluators and health services researchers need to be aware of potential ascertainment bias before using this information for quality improvement or policy development purposes.

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