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21-Gene recurrence score testing among Medicare beneficiaries with breast cancer in 2010–2013

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Purpose: We evaluated national patient-level utilization of the 21-gene recurrence score (21-gene RS) test among Medicare beneficiaries with breast cancer. We analyzed clinical, demographic, and regional factors that predict testing.

Methods: Using 2010–2013 Medicare claims, we conducted a retrospective study of breast cancer patients. The outcome variable was whether the patient underwent testing. Independent variables expected to predict testing were age, gender, race, Medicaid status, clinical characteristics, and hospital referral region (HRR).

Results: From 2010 to 2013, the number of test orders increased by 23.0%. Of the 256,818 patients identified in 2011–2012 claims, 25,352 (9.9%) underwent the 21-gene RS test. Estrogen receptor–positive status was the strongest positive predictor of testing (odds ratio (OR) 2.58, 95% confidence interval (CI) 2.48–2.69). White patients were more likely to be tested than minorities (OR 1.46, 95% CI 1.39–1.52). Secondary cancer was the strongest negative predictor. Medicaid recipients were less likely to be tested (OR 0.74, 95% CI 0.71–0.78). The likelihood of testing decreased with increasing age and comorbidities.

Conclusions: Despite widespread implementation of the 21-gene RS test, minorities and Medicaid recipients had less access to testing. Many patients with serious comorbidities or advanced age were tested even though the risk algorithm may not have been applicable to them.

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Key Words: breast cancer; genomic testing, 21-gene test; hospital referral region; Medicare

INTRODUCTION

Three million women in the United States live with breast cancer. One-third are Medicare beneficiaries.[1] The median age of diagnosis is 61 years, and 40% of newly diagnosed cases are women over age 64 years.[2,3] Approximately 96,000 Medicare beneficiaries are diagnosed yearly. The incidence rate has increased slowly, from 4.4% in 2003 to 5.4% in 2012.[1] For women over age 69, the incidence rate is expected to increase from 24 to 35%.[4] This trend has contributed to delays in care and increased costs.[5,6] These dynamics illustrate the need for tools that stratify patients by risk so that clinicians can identify and prioritize patients who require aggressive treatment versus patients who may avoid or delay treatment.

One tool that stratifies patients by risk is the 21-gene recurrence score test (trade name, Oncotype DX Breast Cancer Assay) developed and conducted by Genomic Health (Redwood City, CA). The test measures tumor gene expression (16 cancer-related, including *HER2*, *ER* and *PR*, and 5 normative) to quantify the likelihood of distant recurrence at 10 years.[7] Tumors are categorized as low-, moderate-, and high-risk, with an average recurrence risk of 7, 14, and 31%, respectively. These risk scores are used to predict the benefit from adjuvant chemotherapy after surgery for women with early-stage, lymph node–negative (LN-), estrogen receptor–positive (ER+), human epidermal growth factor receptor 2–negative (HER2-) breast cancer patients.[8,9] The 21-gene test has been included in American Society of Clinical Oncology and National Comprehensive Cancer Network (NCCN) guidelines for treatment of stage I to IIA ER+/LN- tumors since 2007 and 2008, respectively.[10,11] More recently, it has been included in NCCN guidelines for certain stage IIA–IIIB breast cancers with LN micrometastases.[11] Preliminary results of the large TAILORx trial of more than 11,000 HR+/HER2-/LN- patients showed that patients with a low-risk score had remarkably low rates of recurrence with hormonal therapy alone.[12] In 2016, the American Joint Committee on Cancer (AJCC) incorporated the Oncotype DX test in the Eighth Edition of the AJCC Cancer Staging Manual.[13]

Medicare coverage of the 21-gene test began in 2008.[14] A retrospective analysis of Surveillance, Epidemiology, and End Results (SEER) data from 2005 to 2009 demonstrated that the 21-gene recurrence score influenced receipt of chemotherapy among Medicare beneficiaries.[15]

Several studies have analyzed the clinical utility and cost-effectiveness of the 21-gene test.[16,17] However, few studies have analyzed national, patient-level utilization. The aims of this study were to identify and characterize Medicare beneficiaries who underwent the test in 2011–2012, analyze factors that

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predict the likelihood to undergo testing, and evaluate concordance with guidelines.

MATERIALS AND METHODS

Data sources

We conducted a retrospective study using secondary data analysis methods. The primary data source was Medicare claims, including 2010–2013 100% inpatient MedPAR, Part B, and outpatient files. Additional data sources included the denominator file (100%), the hierarchical condition categories (HCC) risk score file (developed by RTI International), the Provider of Service file, the Health Resources and Services Administration Area Health Resource file,[18] and the Dartmouth Atlas Hospital Referral Region (HRR) database.[19]

We used validated algorithms to identify incident breast cancer cases using Medicare claims data.[20,21] We created a variable to indicate the year when a claim for breast cancer treatment was first submitted. Beneficiaries identified in 2010 claims included prevalent cases from previous years; we eliminated those patients from subsequent analysis. Beneficiaries who had initial claims in 2011 through 2013 represented newly identified cases. We analyzed and reported data for beneficiaries identified in 2011 to 2013 claims. However, our previous research revealed that approximately half the claims for the 21-gene tests were ordered more than 30 days after the surgical pathology procedure.[22] Consequently, patients identified in 2013 claims may have had claims for testing in 2014 that were not available in our dataset. We therefore restricted multivariate and regional analysis to years 2011 and 2012.

Our analytic sample met the following criteria:

1. Were beneficiaries of Medicare fee-for-service who had at least one inpatient claim with a breast cancer diagnosis code (International Classification of Diseases, ninth revision (ICD-9), diagnosis codes 174.0–175.9) within MedPAR or two or more outpatient or Part B claims on separate dates with a breast cancer diagnosis code.
2. Had a short-term or specialty hospital stay in a physician office, inpatient or outpatient hospital, or ambulatory surgical center.
3. Sought breast cancer treatment in 2011–2013, defined as having a breast biopsy and/or a breast surgery (ICD-9 procedure codes 85.11–85.48) claim in MedPAR, or breast biopsy (CPT/HCPCS codes 10021–10022; 19100–19103; 76942), surgical pathology analysis (88305, 88307, 88309), or a complex diagnostic test (83890–98; 83900–14; 83950–51; 86215; 86225; 86294; 86300–05; 86316; 87149; 88371–72) in outpatient or Part B files.

We restricted our analysis to claims that had breast cancer listed as the line item or principal diagnosis code. MedPAR, outpatient, and Part B claims were placed in a patient-level analytic file that became the basis for the study.

Variables

The unit of observation was the patient. The outcome variable was whether the patient had a claim for the 21-gene test. This was coded as 1 if the claim was identified as Genomic Health's Clinical Laboratory Improvement Amendment (CLIA) 05D1018272. Independent variables expected to predict testing included patient demographics (age, gender, race), Medicaid status, clinical characteristics (ER status, LN status, secondary cancer, end-stage renal disease (ESRD), HCC score, inpatient stay for breast surgery, other molecular tests), and regional characteristics. We also analyzed the correlation between undergoing the 21-gene test and undergoing a similar genomic test for breast cancer. This was identified by a claim with the CLIA number for Agendia (Irvine, CA), the supplier of the Symphony suite of microarray-based assays for clinical management of breast cancer. These include the 70-gene signature test (MammaPrint) and TargetPrint and BluePrint. MammaPrint is used for selection of breast cancer patients unlikely to benefit from adjuvant chemotherapy.[23] TargetPrint provides a quantitative assessment of tumor receptor status by measuring messenger RNA expression levels of three markers (*ER*, *PR*, and *HER2*). The BluePrint test identifies the molecular subtype for breast cancer–based expression patterns of 80 genes and refines the prognostic ability of MammaPrint. In this analysis, the existence of a claim with Agendia was treated as an independent variable.

Patient demographic variables and postal codes of residence were obtained from the Medicare Denominator enrollment file. Postal code was used to characterize the region in which the patient lived (county, HRR, Urban Influence Code, and distance from a National Cancer Institute (NCI) cancer center).

Clinical characteristics obtained from claims data included ER status (V86.0-V86.1), LN status (196.0–196.9), secondary cancers (197.0–198.9), and ESRD (585.6). Secondary cancers and ESRD diagnoses were included to identify patients who were inappropriate candidates for the test. Each patient's health insurance claim number was used to obtain the weighted average HCC score, which served as a proxy to identify the patient's health status. This number is derived from a patient's prior year of claims to predict future costs. It represents the relative expenditures that are likely to be incurred for a patient, based on factors such as age, sex, Medicaid status, and individual disease groups.[24] Patients with lower HCC scores are considered healthier.

Most independent variables, including the HRR, were dichotomous; others such as age and HCC score were continuous. Age was measured in years. Distance was measured in miles. HCC score was measured in increments of 0.001.

Statistical analysis

Statistical analysis was performed using Stata software (version 12.0; StataCorp, College Station, TX). We conducted univariate and bivariate analyses and obtained descriptive statistics for all

variables. As appropriate, group differences were tested using the chi-square test of independence for categorical variables and *t*-tests or ANOVA for continuous variables. We performed multivariate logistic regression to identify characteristics associated with a claim for the 21-gene test. We performed sensitivity analysis to ensure that the observed effects were not attributable to an artifact of modeling.

RESULTS

Claims and payments

Between 2010 and 2013, we identified 50,873 claims for the 21-gene test (**Table 1**). The number of claims per year increased by 23%, from 10,988 in 2010 to 13,517 in 2013. The mean Medicare payment for the test remained stable at approximately $3,311, and the total expenditures amounted to $168,418,052 over the 4-year period. There were fewer claims for the 70-gene signature and other tests from Agendia. However, the number of claims for Agendia tests increased more than fourfold, from 308 in 2010 to 1,356 in 2013.

We identified 383,070 patients who had a new claim for breast cancer biopsy, surgery, complex laboratory diagnostic tests, or surgical pathology procedure from 2011 to 2013 for breast cancer diagnosis or treatment. Bivariate analysis identified several demographic, clinical, and regional characteristics associated with a claim for the 21-gene test. **Table 2** summarizes patient characteristics by testing status from 2011 through 2013.

Demographic and clinical characteristics of patients tested

Of the 256,818 patients identified in 2011 through 2012, 25,352 (9.9%) had a claim for the 21-gene test. Patients tested were younger than those not tested (mean = 69.2 years, SD = 6.9 for tested; mean = 73.0, SD = 10.0 for not tested). The highest percentage of patients tested (16.0%) were 65–69 years of age. Women were more likely to be tested than men (9.9 vs. 7.5%). Analysis of testing across race/ethnicities revealed that among non-Hispanic whites who underwent breast cancer treatment, 10.4% were tested compared to 6.8% of Hispanics and 7.0% of non-Hispanic blacks. There was a negative association between Medicaid status and testing. Only 7.4% of Medicaid recipients were tested, compared with 10.4% of those who did not receive Medicaid.

Analysis of clinical characteristics illustrated substantial undercoding of ER status, LN status, and potentially secondary cancers. These variables are needed to identify the eligible patient population. ER status was missing from claims for 68.5% of patients. LN+ disease was coded for only 12.1% of patients, and secondary cancer was coded for 6.1% of patients; these rates were substantially lower than the prevalence of LN+ and metastatic breast cancers in cancer registries.[25]

The 21-gene test is specifically designed for ER+ patients. Accordingly, ER+ patients were much more likely to be tested than ER- patients (21.4 vs. 2.0%). LN+ patients were more likely to be tested than those who did not have a code for LN+ disease (13.6 vs. 9.4%). Only 2.6% of patients with a secondary cancer diagnosis were tested, which was expected because the test is recommended for early-stage breast cancer patients. Analysis of the HCC score revealed that patients with fewer comorbidities were more likely to be tested. The mean HCC score of patients tested was 0.72 (SD = 0.56) compared to 0.97 (SD = 0.82) for patients not tested. Yet, some patients with serious conditions such as ESRD were still tested. Having an inpatient stay was negatively associated with testing. Undergoing other molecular tests was positively associated with undergoing the 21-gene test. Patients who underwent another breast cancer genomic test supplied by Agendia were almost twice as likely to undergo the 21-gene test.

Regional characteristics

We conducted several analyses to measure the association between residence and testing status. The number and percentage of patients tested varied widely by state (as shown in **Supplementary Table S1** online). New Mexico had the highest percentage (14%) of patients tested, and Rhode Island and the Commonwealth of Puerto Rico had the lowest percentage (each at 4–5%). We also analyzed the association between patient proximity to an NCI cancer center and testing status. In contrast to our previous research analyzing lung cancer molecular testing,[26] distance to an NCI cancer center was not significant. There was also no association between testing status and county-level income or education level. There was little variability in testing between various metropolitan and nonmetropolitan areas, which were classified according to Urban Influence Codes[27] (**Supplementary Table S2** online).

We then considered the association between HRR and testing status. Some HRRs were positively associated with testing, whereas others were negatively associated. The distribution of

Table 1 Claims for 21-gene and 70-gene breast cancer tests among Medicare beneficiaries in 2010 and 2013

	Year					
	2010	2011	2012	2013	Total	Percent change
21-gene RS test	10,988	12,976	13,392	13,517	50,873	23.0
Mean payments	$3,323	$3,302	$3,324	$3,296	$3,311	-0.8
Total payments	$36,508,894	$42,849,866	$44,513,830	$44,545,463	$168,418,052	22.0
Agendia tests[a]	308	436	856	1,356	2,956	340.3
Mean payments	$3,411	$3,647	$3,014	$3,348	$3,302	-1.8
Total payments	$1,050,588	$1,590,092	$2,579,984	$4,539,888	$9,760,552	332.1

[a]Agendia breast cancer tests identified in claims include MammaPrint, TargetPrint, and BluePrint.

Data from RTI International's analysis of Medicare claims 2010 through 2013.

Table 2 Characteristics of patients who underwent the 21-gene RS test in 2011–2013

	2011			2012			2013			Two years (2011–2012)			
	All patients	Tested	Percent tested	All patients	Tested	Percent tested	All patients	Tested	Percent tested	All patients	Tested	Percent tested	*P* value*
Total	**132,754**	**12,458**	**(9.4)**	**124,064**	**12,894**	**(10.4)**	**126,252**	**11,025**	**(8.7)**	**256,818**	**25,352**	**(9.9)**	
Demographic characteristics													
Age (in years), mean (SD)	73.5 (10.0)	69.3 (6.9)		72.5 (10.0)	69.2 (6.8)		71.5 (9.8)	69.2 (6.8)		73.0 (10.0)	69.2 (6.9)		
Age group													<0.001
0–54	4,394	428	(9.7)	4,477	465	(10.4)	4,641	384	(8.3)	8,871	893	(10.1)	
55–59	3,284	330	(10.0)	3,365	377	(11.2)	3,572	282	(7.9)	6,649	707	(10.6)	
60–64	12,274	1,218	(9.9)	14,885	1,247	(8.4)	18,157	918	(5.1)	27,159	2,465	(9.1)	
65–69	29,554	4,670	(15.8)	29,962	4,844	(16.2)	33,680	4,349	(12.9)	59,516	9,514	(16.0)	
70–74	24,199	3,320	(13.7)	21,833	3,405	(15.6)	21,736	2,939	(13.5)	46,032	6,725	(14.6)	
≥75	58,307	2,461	(4.2)	48,636	2,499	(5.1)	43,408	2,104	(4.8)	106,943	4,960	(4.6)	
Missing	742	31	(4.2)	906	57	(6.3)	1,058	49	(4.6)	1,648	88	(5.3)	
Sex*													<0.001
Female	130,230	12,307	(9.5)	121,440	12,695	(10.5)	123,449	10,837	(8.8)	251,670	25,002	(9.9)	
Male	1,782	120	(6.7)	1,718	142	(8.3)	1,745	139	(8.0)	3,500	262	(7.5)	
Missing	742	31	(4.2)	906	57	(6.3)	1,058	49	(4.6)	1,648	88	(5.3)	
Race/ethnicity													<0.001
Unknown	406	39	(9.6)	634	55	(8.7)	1,122	63	(5.6)	1,040	94	(9.0)	
White (non-Hispanic)	111,336	10,987	(9.9)	103,494	11,379	(11.0)	104,326	9,735	(9.3)	214,830	22,366	(10.4)	
Black (non-Hispanic)	14,535	984	(6.8)	13,449	964	(7.2)	13,815	783	(5.7)	27,984	1,948	(7.0)	
Other	1,697	130	(7.7)	1,715	155	(9.0)	1,749	122	(7.0)	3,412	285	(8.4)	
Asian/Pacific Islander	1,773	129	(7.3)	1,738	127	(7.3)	1,927	123	(6.4)	3,511	256	(7.3)	
Hispanic	1,745	105	(6.0)	1,659	127	(7.7)	1,745	107	(6.1)	3,404	232	(6.8)	
North American Native	520	53	(10.2)	469	30	(6.4)	510	43	(8.4)	989	83	(8.4)	
Missing	742	31	(4.2)	906	57	(6.3)	1,058	49	(4.6)	1,648	88	(5.3)	
Medicaid status													<0.001
No Medicaid	109,077	10,840	(9.9)	101,720	11,134	(10.9)	104,723	9,578	(9.1)	210,797	21,974	(10.4)	
Medicaid	22,935	1,587	(6.9)	21,438	1,703	(7.9)	20,471	1,398	(6.8)	44,373	3,290	(7.4)	
Missing	742	31	(4.2)	906	57	(6.3)	1,058	49	(4.6)	1,648	88	(5.3)	
Clinical characteristics													
ER status													<0.001
ER- (V86.1)	5,475	124	(2.3)	5,096	92	(1.8)	4,976	82	(1.6)	10,571	216	(2.0)	
ER+ (V86.0)	34,142	6,916	(20.3)	32,608	7,355	(22.6)	33,207	6,546	(19.7)	66,750	14,271	(21.4)	
Both	1,836	238	(13.0)	1,657	201	(12.1)	1,250	168	(13.4)	3,493	439	(12.6)	
ER missing	91,301	5,180	(5.7)	84,703	5,246	(6.2)	86,819	4,229	(4.9)	176,004	10,426	(5.9)	
Lymph node													<0.001
Negative or not coded	115,662	10,369	(9.0)	110,125	10,768	(9.8)	109,736	9,023	(8.2)	225,787	21,137	(9.4)	
Diagnosis of lymph node–positive	17,092	2,089	(12.2)	13,939	2,126	(15.3)	16,516	2,002	(12.1)	31,031	4,215	(13.6)	
Secondary cancer													<0.001
Negative or not coded	122,950	12,247	(10.0)	118,078	12,696	(10.8)	117,223	10,824	(9.2)	241,028	24,943	(10.3)	
Diagnosis of secondary cancer	9,804	211	(2.2)	5,986	198	(3.3)	9,029	201	(2.2)	15,790	409	(2.6)	
ESRD													0.002
No ESRD diagnosis	131,867	12,389	(9.4)	123,273	12,835	(10.4)	125,425	10,986	(8.8)	255,140	25,224	(9.9)	
Diagnosis of ESRD	887	69	(7.8)	791	59	(7.5)	827	39	(4.7)	1,678	128	(7.6)	
HCC risk score, mean (SD)	0.99 (0.82)	0.72 (0.57)		0.95 (0.81)	0.71 (0.55)		0.89 (0.74)	0.71 (0.57)		0.97 (0.82)	0.72 (0.56)		
Inpatient status													<0.001
No inpatient stay	100,334	9,785	(9.8)	93,013	10,396	(11.2)	98,735	9,049	(9.2)	193,347	20,181	(10.4)	
Inpatient stay	32,420	2,673	(8.2)	31,051	2,498	(8.0)	27,517	1,976	(7.2)	63,471	5,171	(8.1)	
Other molecular test													<0.001
No molecular tests billed	107,172	7,449	(7.0)	99,507	7,809	(7.8)	103,044	6,645	(6.4)	206,679	15,258	(7.4)	
At least 1 other molecular test	25,582	5,009	(19.6)	24,557	5,085	(20.7)	23,208	4,380	(18.9)	50,139	10,094	(20.1)	
Other genomic test for recurrence risk (Agendia)[a]													<0.001
No Agendia tests billed	132,350	12,418	(9.4)	123,529	12,769	(10.3)	125,467	10,914	(8.7)	255,879	25,187	(9.8)	
At least 1 Agendia test	404	40	(9.9)	535	125	(23.4)	785	111	(14.1)	939	165	(17.6)	

ER, estrogen receptor; ESRD, diagnosis of end-stage renal disease; HCC, hierarchical condition categories.

[a]Agendia breast cancer tests identified in claims include MammaPrint, TargetPrint, and BluePrint. **P* values relate to the comparisons between all patients and those tested over the 2-year period (2011-2012).

Date from RTI Internationals' analysis of Medicare claims 2011 through 2013.

21-gene RS testing among HRRs is presented in **Figure 1**. Data used to create the figure are presented in **Supplementary Table S3** online. There was an eightfold difference between HRRs with the highest and the lowest levels of testing, ranging from 2.9% in Ogden, Utah, to 23.6% in Terre Haute, Indiana.

Prediction model

The relationship between several independent variables and the likelihood of undergoing the 21-gene test persisted in multivariate logistic regression analysis. **Table 3** summarizes the results of the logistic regression model.

Several demographic characteristics predicted testing. A yearly increase in age decreased the likelihood of testing by 4.0% (odds ratio (OR) 0.96, confidence interval (CI) 0.95–0.96). Non-Hispanic white patients were more likely to be tested (OR 1.46, CI 1.39–1.52). Medicaid recipients were less likely to be tested (OR 0.74, CI 0.71–0.78).

Several clinical characteristics positively predicted testing. Patients coded with ER+ breast cancer were almost four times as likely to undergo the 21-gene test (OR 3.90, CI 3.79–4.02). Patients who underwent another breast cancer molecular test were also more likely to undergo the 21-gene test (OR 2.80, CI 2.72–2.89). Clinical characteristics that were negative predictors of testing included secondary cancer diagnosis (OR 0.16, CI 0.14–0.17), ESRD diagnosis (OR 0.82, CI 0.67–0.99), and inpatient stay (OR 0.89, CI 0.86–0.92). Poor health status, as measured by HCC score, was also a negative predictor of testing. To interpret the OR (0.68, CI 0.66–0.69) of HCC score (which is measured in increments of 0.001), we obtained the logit coefficient. For every 0.10-point increase in HCC score, there was a 4.8% decrease in likelihood of being tested.

HRRs were both strong positive and negative predictors of testing. After adjusting for other demographic and clinical characteristics included in the model, patients most likely to be tested lived in McAllen, Texas (OR 2.84, CI 1.95–4.12). Patients who lived in Ogden, Utah, were least likely to be tested (OR 0.20, CI 0.09 to 0.44). Overall, there were 54 HRRs that were positive predictors of testing and 57 HRRs that were negative predictors.

DISCUSSION

This is the first study to analyze utilization of the 21-gene test among all Medicare beneficiaries with breast cancer. Several studies have analyzed test utilization among smaller groups of patients.[28–30] One study of 7,375 patients from 2006 to 2008 found disparities in access to testing among black patients and those with lower education levels.[31] Two larger studies of 70,802 and 44,044 patients in the SEER registry data linked to Medicare claims found a fourfold increase in testing from 2005 through 2009 and reported little variability in testing across SEER regions or by patient demographics.[15,32] Our population-level analysis of 256,818 Medicare patients found variations in access according to age and health status, which is consistent with clinical guidelines. However, in contrast to the study by Dinan et al.,[32] our study identified income, racial, and regional variations in access to the 21-gene test. In bivariate analyses,

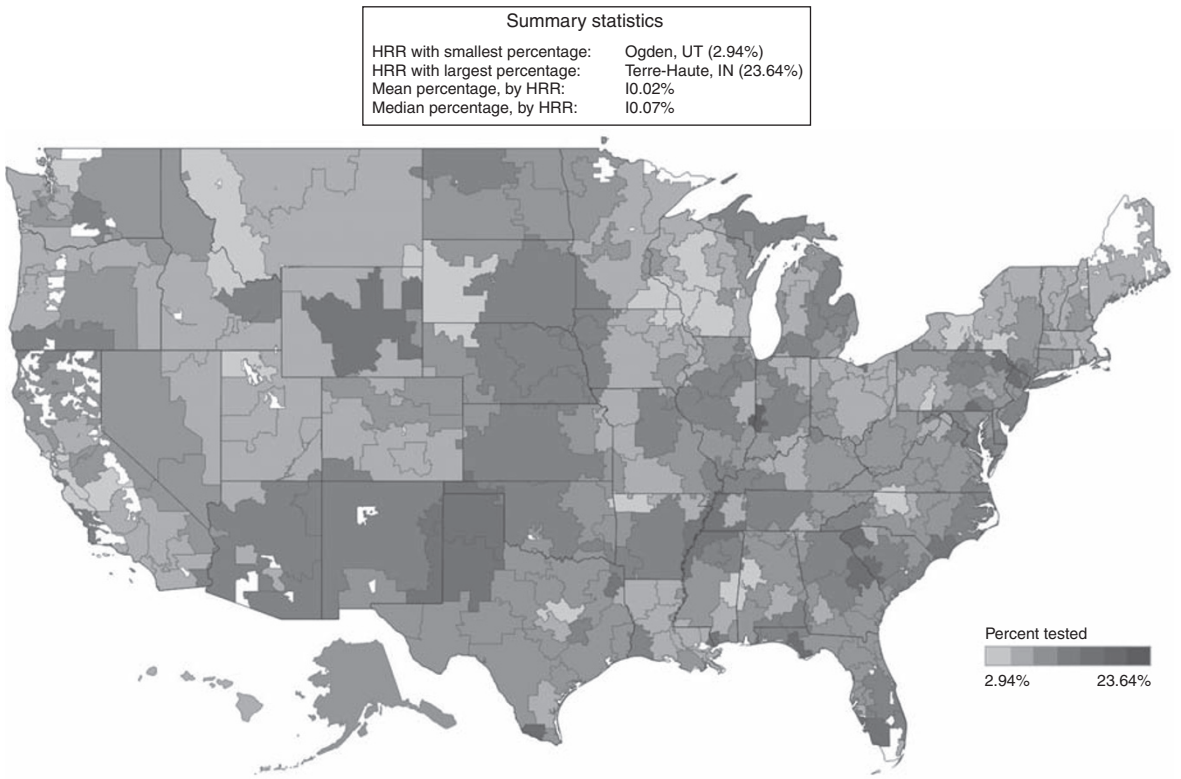

Figure 1 Distribution of 21-gene RS testing by Hospital Referral Region in 2011–2012. The denominator is the number of patients who had breast tissue analyzed.

Table 3 Characteristics that predict use of the 21-gene RS test for breast cancer patients

Independent variables		OR	*P* value	95% CI		
Clinical and demographic characteristics						
	Age (per year)	0.96	0.00	0.95	–	0.96
	Non-Hispanic white (versus all other)	1.46	0.00	1.39	–	1.52
	Medicaid recipient (versus nonrecipient)	0.74	0.00	0.71	–	0.78
	Coded as ER+ breast cancer	3.90	0.00	3.79	–	4.02
	Lymph node+ cancer	0.96	0.07	0.93	–	1.00
	Coded with secondary cancer	0.16	0.00	0.14	–	0.17
	ESRD diagnosis	0.82	0.04	0.67	–	0.99
	Weighted average HCC score (per 0.001 increase)	0.68	0.00	0.66	–	0.69
	Inpatient surgery	0.89	0.00	0.86	–	0.92
	Receipt of another molecular test	2.80	0.00	2.72	–	2.89
HRR: state - city						
	TX – McAllen	2.84	0.00	1.95	–	4.12
	IN - Terre Haute	2.77	0.00	1.81	–	4.25
	OH – Elyria	2.61	0.00	1.74	–	3.92
	LA – Slidell	2.28	0.00	1.39	–	3.73
	NJ – Morristown	2.26	0.00	1.77	–	2.89
	SC – Greenville	2.15	0.00	1.68	–	2.74
	TX – Longview	2.02	0.00	1.31	–	3.11
	PA – York	2.01	0.00	1.44	–	2.79
	PA – Lancaster	1.99	0.00	1.48	–	2.68
	LA - Lake Charles	1.96	0.00	1.28	–	2.99
	GA – Augusta	1.85	0.00	1.39	–	2.46
	KY – Covington	1.83	0.00	1.25	–	2.67
	NY - East Long Island	1.82	0.00	1.52	–	2.20
	AL – Dothan	1.82	0.00	1.30	–	2.55
	Washington, DC	1.82	0.00	1.49	–	2.22
	CA - Santa Cruz	1.80	0.01	1.18	–	2.74
	MD - Takoma Park	1.75	0.00	1.29	–	2.36
	NJ – Newark	1.74	0.00	1.35	–	2.23
	MS – Tupelo	1.73	0.00	1.22	–	2.44
	SC – Florence	1.72	0.00	1.22	–	2.43
	IN – Munster	1.70	0.01	1.17	–	2.46
	NM – Albuquerque	1.69	0.00	1.34	–	2.13
	MO - Cape Girardeau	1.64	0.01	1.11	–	2.44
	FL - Panama City	1.64	0.02	1.07	–	2.51
	IL - Blue Island	1.63	0.00	1.26	–	2.11
	MI – Saginaw	1.63	0.00	1.25	–	2.12
	TX – Bryan	1.62	0.05	1.00	–	2.65
	NJ – Paterson	1.61	0.01	1.12	–	2.33
	PA – Scranton	1.58	0.01	1.11	–	2.24
	PA – Sayre	1.55	0.05	1.01	–	2.40
	IN – Gary	1.54	0.01	1.13	–	2.10
	TN – Memphis	1.53	0.00	1.23	–	1.90
	AZ – Tucson	1.53	0.00	1.19	–	1.96
	MI – Flint	1.52	0.01	1.12	–	2.06
	VA – Arlington	1.51	0.00	1.20	–	1.91
	MI – Dearborn	1.51	0.01	1.09	–	2.10
	NJ – Hackensack	1.51	0.00	1.18	–	1.92
	MI - Ann Arbor	1.48	0.00	1.16	–	1.89
	OH – Cincinnati	1.47	0.00	1.16	–	1.87
	HI – Honolulu	1.47	0.01	1.11	–	1.94
	TX- Amarillo	1.46	0.03	1.04	–	2.05
	NJ – Ridgewood	1.46	0.03	1.03	–	2.07
	MI – Detroit	1.44	0.00	1.15	–	1.80
	MI- Lansing	1.43	0.02	1.05	–	1.95
	NC – Wilmington	1.39	0.03	1.03	–	1.87
	AL – Mobile	1.38	0.03	1.03	–	1.84
	NY - New York	1.38	0.00	1.13	–	1.67
	IL - Melrose Park	1.37	0.01	1.08	–	1.75

Reference groups: race, Medicaid status, and clinical characteristics were dichotomous variables. Patients in the reference group included all other patients. The reference group for HRR is Birmingham, Alabama, which had the median percentage of patients tested (10.07%).

CI, confidence interval; ER, estrogen receptor; ESRD, end-stage renal disease; HCC, hierarchical condition categories; HRR, Hospital Referral Regions; OR, odds ratio.

Data from RTI International's analysis of 2011-2013 Medicare claims data.

Table 1 Continued on next page

Table 3 Continued

Independent variables		OR	*P* value	95% CI	
	TN – Nashville	1.36	0.00	1.10	– 1.68
	NJ – Camden	1.36	0.00	1.12	– 1.65
	OK - Oklahoma City	1.35	0.01	1.08	– 1.69
	MD – Baltimore	1.30	0.01	1.05	– 1.59
	GA – Atlanta	1.25	0.02	1.04	– 1.51
	PA – Philadelphia	1.21	0.05	1.00	– 1.46
	FL – Jacksonville	0.77	0.03	0.60	– 0.98
	NC – Asheville	0.74	0.03	0.56	– 0.98
	MI - Grand Rapids	0.73	0.03	0.55	– 0.97
	WI – Milwaukee	0.73	0.00	0.58	– 0.90
	CA - San Bernardino	0.72	0.02	0.54	– 0.96
	CA - Los Angeles	0.71	0.00	0.59	– 0.87
	IN - Fort Wayne	0.71	0.05	0.50	– 1.00
	IN - South Bend	0.71	0.05	0.50	– 0.99
	CA - San Jose	0.69	0.03	0.50	– 0.96
	MO - Kansas City	0.68	0.00	0.54	– 0.85
	CA - Santa Rosa	0.68	0.05	0.46	– 1.00
	AK – Anchorage	0.67	0.05	0.46	– 0.99
	IL – Evanston	0.67	0.00	0.52	– 0.88
	MO – Springfield	0.67	0.01	0.49	– 0.90
	ME – Bangor	0.66	0.03	0.45	– 0.96
	MN – Minneapolis	0.66	0.00	0.53	– 0.82
	MA – Boston	0.65	0.00	0.53	– 0.79
	OR – Eugene	0.64	0.02	0.44	– 0.93
	NY- Syracuse	0.64	0.01	0.47	– 0.87
	CA - Palm Springs/Rancho Mirage	0.62	0.03	0.40	– 0.95
	CA - Contra Costa County	0.62	0.02	0.41	– 0.92
	UT - Salt Lake City	0.61	0.00	0.46	– 0.81
	ME - Portland	0.61	0.00	0.47	– 0.80
	NY - Rochester	0.61	0.01	0.43	– 0.86
	CA - San Francisco	0.60	0.00	0.43	– 0.84
	CA - Orange County	0.60	0.00	0.47	– 0.77
	KY - Louisville	0.56	0.00	0.44	– 0.72
	MT - Billings	0.55	0.00	0.38	– 0.81
	CO - Colorado Springs	0.54	0.00	0.38	– 0.78
	WI - Wausau	0.54	0.05	0.30	– 0.99
	IA - Mason City	0.53	0.03	0.30	– 0.95
	WI - Marshfield	0.52	0.01	0.32	– 0.86
	OR - Salem	0.51	0.02	0.29	– 0.90
	CA - Salinas	0.51	0.02	0.29	– 0.89
	AL - Tuscaloosa	0.50	0.01	0.29	– 0.87
	VT - Burlington	0.50	0.00	0.35	– 0.73
	ID – Boise	0.50	0.00	0.35	– 0.72
	GA – Albany	0.48	0.01	0.26	– 0.86
	RI - Providence	0.47	0.00	0.34	– 0.65
	NC - Winston-Salem	0.45	0.00	0.33	– 0.62
	WA - Seattle	0.45	0.00	0.35	– 0.57
	CA – Fresno	0.44	0.00	0.30	– 0.66
	WI - Madison	0.44	0.00	0.32	– 0.60
	NC - Hickory	0.42	0.00	0.26	– 0.66
	NC - Greensboro	0.41	0.00	0.29	– 0.60
	CA - San Mateo County	0.41	0.00	0.26	– 0.64
	CO - Grand Junction	0.40	0.00	0.24	– 0.65
	AR - Springdale	0.37	0.00	0.22	– 0.62
	SD - Rapid City	0.34	0.00	0.18	– 0.65
	TX – Waco	0.34	0.00	0.18	– 0.61
	MN - Rochester	0.34	0.00	0.18	– 0.62
	MT - Missoula	0.31	0.00	0.19	– 0.51
	WA – Everett	0.30	0.00	0.19	– 0.47
	WI - La Crosse	0.29	0.00	0.16	– 0.56
	MS – Meridian	0.27	0.00	0.13	– 0.57
	FL – Clearwater	0.26	0.00	0.16	– 0.44
	UT – Ogden	0.20	0.00	0.09	– 0.44

Reference groups: race, Medicaid status, and clinical characteristics were dichotomous variables. Patients in the reference group included all other patients. The reference group for HRR is Birmingham, Alabama, which had the median percentage of patients tested (10.07%).

CI, confidence interval; ER, estrogen receptor; ESRD, end-stage renal disease; HCC, hierarchical condition categories; HRR, Hospital Referral Regions; OR, odds ratio.

Data from RTI International's analysis of 2011-2013 Medicare claims data.

Hispanics and blacks were tested less often than non-Hispanic whites. In multivariate analyses, non-Hispanic whites were 1.5 times more likely to be tested than non-whites. Higher rates of ER- and triple-negative breast cancer among black and Hispanic women may explain some differences. If ER status was reliably coded in the claims, then we could have analyzed this, but ER status was missing in most cases. Also, we cannot exclude that testing may have positively affected reporting of ER+ status because the test is covered only for ER+ patients. By contrast, Medicaid status was a reliable indicator of poverty, and Medicaid recipients were much less likely to undergo testing, illustrating income disparities in access to genomic medicine.

Analysis of regional factors that predict testing demonstrate that, although there has been widespread implementation of the 21-gene test, there is also a modest level of both underutilization and inappropriate utilization. A comparison of the 57 HRRs where patients were less likely to be tested and other benchmarking measures demonstrated that many of these regions also have lower acute-care hospital capacity than the national average. Constrained capacity to care for patients probably impacts delivery of guideline-concordant cancer genomics care. Interestingly, the second lowest rate of testing occurred in Rochester, Minnesota, the location of an important medical research facility (Mayo Clinic) that also has a large commercial reference laboratory. One explanation for the low utilization of the 21-gene test in the Rochester, Minnesota, HRR may be that the Mayo Clinic was testing patients as part of its Breast Cancer Genome Guided Therapy protocol (BEAUTY). Rochester, Minnesota, also has fewer acute-care hospital beds per 1,000 residents than the national average.[19]

In HRRs where patients had significantly higher ORs than the national average, there may be overutilization of testing. We identified patients who were tested despite having comorbid clinical conditions that put into question the clinical utility of the test. However, our prediction model revealed that patients with secondary cancers, ESRD, and higher HCC scores were less likely to be tested. Still, utilization among these patients was not zero. Clinical guidelines and Medicare reimbursement policies specify that testing should be applied only for ER+ patients with early-stage, predominantly LN- disease for whom test results impact clinical decisions. If chemotherapy is precluded as a treatment option by a patient's comorbid conditions, age, or stated declination of chemotherapy, then the test has no clinical utility. Furthermore, the recurrence-risk algorithm may not be applicable to patients with serious comorbid medical conditions such as ESRD or those at an advanced age. The life expectancy for ESRD patients is 7.9 years.[33] These patients are at greater risk for cancer and there are significant challenges in treating cancer patients with chemotherapy when they also have ESRD.[34] There is no evidence that the algorithm for the 21-gene test would be valid in a patient population with extensive comorbidities.

Consistent with other studies of regional variation in healthcare delivery, our results illustrate that use of cancer genomics is subject to local practice patterns. We conclude that clinicians who order other molecular tests are also likely to order the 21-gene test. Remarkably, patients who underwent the 70-gene genomic test, which has similar utility for selecting patients for adjuvant chemotherapy, were more likely to undergo the 21-gene test.

Reliance exclusively on claims data limited this analysis in several ways. It is not feasible to use claims data to conclusively identify newly diagnosed breast cancer cases. By eliminating the 2010 claims and restricting analysis to patients who had new claims for breast surgical pathology procedures in 2011–2012, we identified a cohort of mostly newly diagnosed patients who had tissue available for testing. However, we know from SEER data that there are approximately 96,000 newly diagnosed breast cancer cases per year among Medicare beneficiaries. Clearly, therefore, our denominator included some prevalent patients who may have been previously diagnosed and tested prior to their eligibility for Medicare. Undercoding of ER status, LN status, and HER2 status substantially impeded our ability to identify the appropriate patient population for testing and made it difficult to evaluate the level of concordance with clinical practice guidelines. We can develop estimates based on analysis of SEER data suggesting that 44% of newly diagnosed patients are ER+, LN-, and HER2- and may be eligible for the 21-gene test.[2] This approach suggests that approximately 126,720 patients (44% of (96,000 × 3)) may be eligible. However, if we restricted the denominator to Medicare beneficiaries based on age and comorbid conditions (selecting the patients for whom the test is most likely useful), then the eligible patient population would be much smaller. In 2011–2012 claims, we identified 148,227 patients younger than age 75. Based on SEER estimates, 65,220 (44%) were ER+, LN-, and HER2- patients. There were 20,304 patients younger than age 75 who had claims for the 21-gene test. If all these patients were ER+, LN-, and HER2-, then approximately 31% of guideline-recommended cases were tested. There are several reasons for believing that the market penetration of the test is even higher than 31%. The estimate of the ER+, LN-, and HER2- population does not consider the number of patients who have comorbid conditions that limit the clinical utility of the test. It also does not exclude patients whose stated preference is to forgo chemotherapy regardless of their risk score.

The 21-gene test is clinically most useful for young, healthy patients with newly diagnosed breast cancer. A definitive study analyzing population-level implementation of the 21-gene test in the United States would include private-payer claims data. However, data use agreements for aggregated private-payer claims prohibit researchers from identifying providers. This restriction impedes identification of the 21-gene test in private-payer claims. Ideally, third-party payers and researchers could use claims data to identify the population for whom guidelines recommend genomic testing.

Several studies have illustrated that the 21-gene test generates cost savings for third-party payers.[35] Other studies have demonstrated that the prognostic strength of a score derived from standard pathology findings can be comparable to that derived from the 21-gene test,[36–38] especially for patients with

high- and low-risk scores as opposed to intermediate-risk scores. The intermediate-risk category remains the most challenging for both genomics-based and conventional decision making. When the TAILORx trial is completed for all patient groups (projected for December 2017), the results may shed more light on the utility of the 21-gene test for this group of patients.[39]

In comparison to other genomics tests, the 21-gene test has achieved remarkable market penetration. Several factors may explain the successful translation of the test. There has been a long history of understanding the importance of tumor molecular biology for breast cancer diagnosis and treatment. Therefore, it is not surprising that breast cancer genomic tests were adopted more rapidly than lung cancer genomic tests. Early coverage and consistent inclusion of the 21-gene test across several clinical practice guidelines facilitated implementation. There are also several strong patient-advocacy groups for breast cancer that have an important role in patient education. The fact that some beneficiaries are undergoing multiple tumor gene expression tests may demonstrate consumer-based demand for testing.

Despite widespread diffusion of the 21-gene test, estimates of the eligible patient population suggest that there may also be underutilization of the test. With only 25,352 patients being tested in 2011–2012 and less access for minorities, Medicaid patients, and patients seeking care in 54 HRRs, there is clearly room for improvement. Our analysis has illustrated opportunities to expand appropriate use of genomic testing to improve risk stratification among Medicare beneficiaries diagnosed with breast cancer.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/gim

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DISCLOSURE

Genomic Health, Inc., is funding a clinical trial within the Veterans Healthcare Administration. J.A.L. is the principal investigator of the study, and B.B. worked on the study. The other authors declare no conflict of interest.

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