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EPIDEMIOLOGY

Shared-patient physician networks and their impact on the uptake of genomic testing in breast cancer

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Abstract

Background Factors influencing the adoption of genomic testing are poorly understood, which may lead to inequitable and suboptimal treatment in cancer patients. Oncotype DX (ODX) is one of the first and most widely used genomic assays to stratify risk in women with early-stage breast cancer (BC). Physician networks have emerged as a significant and modifiable driver of emerging medical technology adoption.
Objective To investigate the association between physician network connections and the use of ODX testing.
Methods A retrospective study of women diagnosed with BC using SEER-Medicare from 2008 to 2012 was used. Medical oncologists were "connected" if they shared two or more patients during the early-adoption period (2008–2009). Parallel physician- and patient-level analyses employed logistic mixed models to determine the impact of being "connected" to an early-adopting oncologist on ODX use in 2011–2012.
Results 24,463 women met study criteria; 12,874 were diagnosed with BC in the early-adoption time period. 2129 medical oncologists treated these patients from 2008 to 2009. Medical oncologists had a median number of peer connections of 4 (IQR: 2–7). Peer connection to an early-adopting provider in 2008–2009 was associated with a 1.7-fold increase in providers' adopting ODX (95% CI: 1.1–2.6) and a 1.5-fold increase in their patients receiving ODX (95% CI: 1.1–2.0) in 2010–2012.
Conclusions Peer connectedness to an early-adopting physician predicts ODX adoption in both physician-level and patient-level analyses. Provider networks may provide a potent and modifiable means to modulate the diffusion of emerging medical technologies. Efforts to increase testing, where appropriate, may benefit from peer-to-peer-based connection strategies.

Keywords Provider network · Breast cancer · Oncotype DX · Genetic testing

Introduction

Oncotype DX® (ODX), a 21-gene assay used in early-stage breast cancer (BC), assigns a recurrence score (RS) representing the likelihood of cancer recurrence as low, intermediate, or high, which may be used to guide treatment decisions. ODX is the most common and most studied BC assay used in the United States, and is currently guideline-recommended for patients with ER-positive, HER2-negative lymph node-negative breast cancer [1, 2]. Despite recommendations, more than 10 years after its initial approval within Medicare carriers in 2006 ODX is still used in fewer than half of eligible women with BC [3, 4]. Prior work has shown that receipt of ODX may be associated with characteristics of the primary oncologic provider, suggesting a need for more detailed evidence of how providers make decisions with respect to genomic testing [5]. The focus of this study is to examine one potential avenue for ODX diffusion in the cancer care community: prescribing provider's peer networks.

Provider networks, or groupings of providers who likely interact, are increasingly studied in healthcare, and long thought to be an important mechanism underpinning the diffusion of medical technology [6–9]. Recently, a number of studies have studied physician networks that are defined by patient sharing using insurance claims records linked to

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cancer treatment and outcomes [9–12]. This early evidence suggests that patient-sharing networks do link strongly to treatment decisions, which ultimately may affect patient outcomes.

Because physician networks have the potential to be influenced by policies or other interventions, they provide a promising, potentially modifiable source of influence on genomic test adoption. However, they have not been previously examined in this context. In this study, we investigate the relationship between peer physician networks, defined by shared patients, and ODX prescribing/use.

Methods

To study the influence of network connections on ODX use, we created two analytic time periods: an early-adoption ODX period (2008–2009), and a subsequent period from 2010 to 2012. In the early period, we identified medical oncologists prescribing ODX, labeling them 'early adopting.' Our goal is to understand whether providers and the patients they serve who are *not* 'early adopting' are likely to start ODX testing if 'connected' to those who already use ODX. We created connections between providers using 'shared' patients, and tracked the number of distinct connections specifically to early-adopting peers as defined above. The later period is used to examine use of ODX among those patients treated by medical oncologists who were not classified as early adopting. More details on each of these elements are provided below.

Study population

SEER-Medicare linked claims data from 2008 to 2012 were used to identify the early (diagnosed 2008–2009) and late (2010–2012) cohorts of women identified with ER+, invasive, non-metastatic BC (site codes: 500–506, 508, 509). We required at least one BC diagnosis in the Medicare claims (ICD-9 diagnosis codes: 174.x, 233.0) as well as surgical resection of the breast tumor within four months of diagnosis via either mastectomy or lumpectomy (CPT codes: 19,120, 19,125, 19,126, 19,301–19,302, 19,160–19,162, 19,303–19,307, 19,180–19,240). All women in the sample were continuously enrolled in Medicare fee-for-service Part A and B one year prior to and one year following diagnosis or until death. We excluded women whose BC cancer diagnosis was made at autopsy or death, or if a diagnosis of cancer at a site other than breast was made in the year before BC diagnosis. Individual patient characteristics are retained from the combined registry and claims files.

Separately, we created a cohort of medical oncologists as the group of physicians treating the cohorts of women defined above, listed on a BC-related claim during the study period. To create a cohort of actively practicing providers, we excluded medical oncologists with fewer than two separate claims for BC-related services in the period defined as early adoption (2008–2009). For more detailed individual provider characteristics, we merged Medicare claims to the AMA Physician Master File using National Provider Identifiers (NPI).

Outcome: receipt of ODX

The primary outcome of interest is receipt of ODX in the later time period (2010–2012) among patients seen by medical oncologists who were not early adopters. Because of the non-specific procedure codes used to bill for ODX in Medicare claims during this time period, we employed the following algorithm to identify receipt of ODX: (1) CPT code 84,999 (non-specific); AND (2) claim reimbursement of exactly $3414 (unchanged during this time period); AND (3) performing NPI = M000953637 (all tests administered by a single lab in this time period: Genomic Health) [5].

Physician–patient connections

Connections to an early-adopting peer and ODX prescribing were our primary exposure of interest. In our primary analyses, we looked at connections between medical oncologists (Fig. 1). Two medical oncologists are considered 'connected' if they share at least two breast cancer patients diagnosed in the early-adoption period (i.e., are listed as provider on a claim for the same patient in 2008 or 2009) [13]. We use the full SEER-Medicare cohort of BC patients to define connections between providers (i.e., any woman diagnosed with BC during the time period, $N = 135{,}351$). Specifically, sharing "two" patients was chosen as the minimum threshold for a connection to ensure a level of connectedness between providers (varied in sensitivity analyses). The number of early-adopting medical oncologists connected to a non-early-adopting medical oncologist forms the primary independent study variable of interest. To explore a potential dose response, we categorize this number as having three levels: no connections to early adopters, 1 connection to an early adopter, or connections to 2 or more early adopters (Fig. 1). Patients are assigned a 'primary' medical oncologist using the modal (most frequent) medical oncologist on the insurance claim post diagnosis. To account for a common alternative connection structure, in sensitivity analyses we also consider connections between pairs of medical oncologists that occur because both share patients with the same surgeon (Supplemental Figure S1).

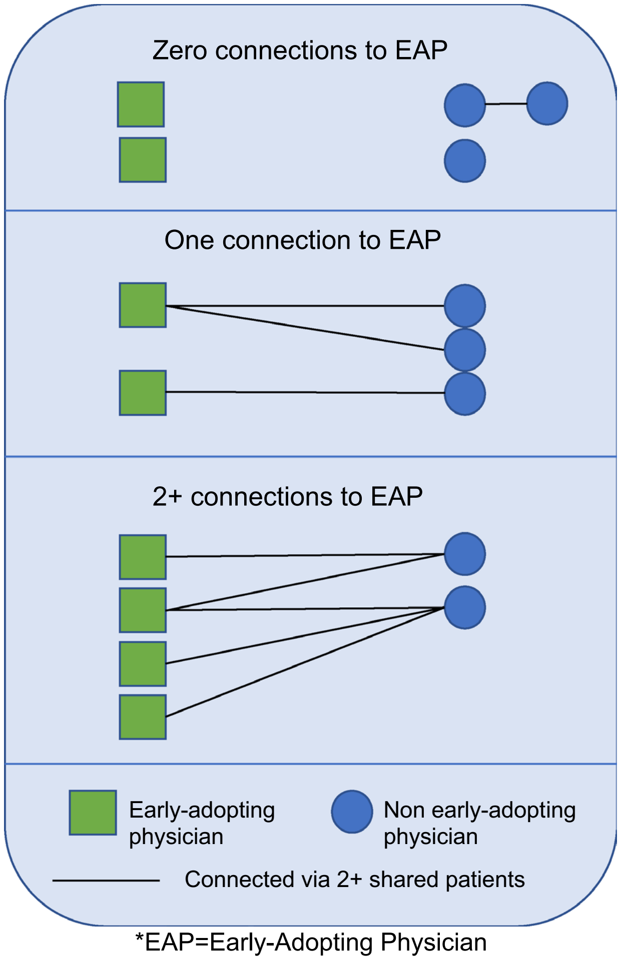

Fig. 1 Shared-patient connections between medical oncologists

Analyses

Two parallel analyses are used to understand ODX adoption and its association with shared-patient provider networks: one at the provider level, and one at the patient level. Both analyses use generalized linear mixed models (GLMM) with a binomial distribution, a logit link function, Laplace parameter estimation, and a random intercept effect at the hospital referral region (HRR) level to account for correlation between observations within hospital region.

The provider analyses test whether, among providers not using ODX in the early period, connections, via shared patients, to an early-adopting peer increase the likelihood of using ODX in the later period. The provider model controls for provider-level characteristics including sex, years of practice, practice census region, US/non-US medical training, as well as patient volume tertile.

The patient analysis tests whether patients diagnosed in the later period and whose primary medical oncologist (defined as the modal provider) is connected to an early-adopting peer are more likely to receive ODX than those whose primary medical oncologist is not connected to an early-adopting peer. Like the provider analysis, patient models are restricted to women whose primary medical oncologist is non-early adopting. In addition to covariate adjustment for provider characteristics, the patient models additionally adjust for differences in patient case-mix via patient characteristics, not accounted for in provider models. Additional patient-level covariates include characteristics related to the surgeon/surgery, clinical characteristics related to the tumor, patient comorbidity, and patient demographics such as age, sex, race, census tract, education, marital status, and poverty status.

As additional sensitivity analyses, we tested an alternative connection structure (described above), increased the number of required shared patients to five from two (increasing the 'strength' of the connection between providers [13]), limited the patient sample to younger Medicare beneficiaries (< 76 years), based on evidence of extremely rare ODX use in women aged 76 + [5], and repeated all analyses using complete case to test for the effect of missingness on results. All analyses were conducted using SAS 9.4®. The study was approved by the Duke University Institutional Review Board.

Results

After applying study criteria, there were 2129 primary medical oncologists who treated 24,463 women in our sample. 703 medical oncologists were classified as early adopting (prescribed ODX in 2008–2009), leaving 1426 non-early-adopting oncologists to form the group for primary provider analyses. Compared to non-early-adopting medical oncologists, early adopters were more likely to be female, less likely to be practicing in the Midwest, and more likely to be US-trained (Table 1). Medical oncologists treated a median of 71.0 [IQR: 28.0, 124.0] patients (both early and late time periods), and were connected to a median of 4.0 [IQR: 2.0, 7.0] other medical oncologists, early or late adopting (at least 2 required). The median number of patient connections to an early-adopting peer was 6.0 [IQR: 4.0, 9.0]. 330 of the 1426 non-early-adopting physicians (23%) subsequently prescribed ODX in the later period (between 2010 and 2012).

Provider-level analysis of the association between connection to an early-adopting provider ODX in the later period demonstrated increased likelihood of ODX prescribing associated with one or multiple connections to early-adopting providers (Table 2). One connection to an early-adopting provider is associated with an increased odds of 1.66 (95% CI: 1.08, 2.57); 2 + connections to an early-adopting provider is associated with an increased odds of 1.44 (95% CI: 0.96, 2.15), both compared to having no connections. We

Table 1 Characteristics of medical oncologists by early ODX adoption

Variable	Non-early adopter	Early RS adopter	*p* value
N	1426	703	
Medical oncologist characteristics			
Sex			.03
Missing	130 (.)	16 (.)	
Female	335 (25.8%)	210 (30.6%)	
Male	961 (74.2%)	477 (69.4%)	
Practicing > 5 years			.14
Missing	163 (.)	32 (.)	
No	211 (16.7%)	95 (14.2%)	
Yes	1052 (83.3%)	576 (85.8%)	
Region			< .001
Northeast	169 (11.9%)	77 (11.0%)	
Midwest	132 (9.3%)	15 (2.1%)	
Missing	292 (20.5%)	157 (22.3%)	
South	341 (23.9%)	201 (28.6%)	
West	492 (34.5%)	253 (36.0%)	
US trained			< .001
Missing	130 (9.1%)	16 (2.1%)	
1	834 (58.5%)	483 (68.8%)	
0	462 (32.4%)	204 (29.1%)	
Patient count, median (Q1, Q3)	48.0 (16.0, 101.0)	111.0 (70.0, 159.0)	< .001
Connection count, median (Q1, Q3)	4.0 (2.0, 7.0)	6.0 (4.0, 9.0)	< .001

*Connections require at least 2 shared patients

also observe, similar to prior studies, that longer tenured physicians have significantly lower odds of prescribing ODX and that patient volume is a strong predictor of use [5].

Of the 24,463 patients who met study criteria, 12,874 were diagnosed with BC in the early-adoption time period. 7622 of these women either (1) saw primary medical oncologists who were classified as early adopters, (2) saw a medical oncologist not practicing in the early period, or (3) did not see a medical oncologist at all, leaving 3967 with primary medical oncologists who were not early adopters as the primary analysis sample. Controlling for clinical and patient socio-demographics decreases the strength of the association between connections to an early-adopting provider and ODX receipt, compared to the provider-level analysis (Table 3 of selected covariates; full table contained in supplement). Still, both 1 and 2 + connections to an early-adopting provider are associated with an approximately 40–50% increase in the odds of ODX use.

Under a modified connection structure (connections built through surgeons), we observed similar results as in primary analyses when requiring a direct connection to the surgeon (Supplemental Tables S1–S2). Without requiring a direct connection to the surgeon, we see attenuated estimates, perhaps the result of a more distal network (Supplemental Table S3). Increasing the required number of shared patients to form a connection between providers from two to five produces qualitatively similar, but marginally larger associations between connectedness and ODX use. Having one connection with at least 5 shared patients increased the odds of ODX use in physician-level models by 2.46 (1.77, 3.41) and 1.63 (1.28, 2.01) in patient-level models (Supplemental Tables S4–S5). When restricting patient analyses to younger Medicare beneficiaries (< 76 years), connection to an early-adopting medical oncologist results in moderately smaller, but similar findings (1.23 and 1.46 for 1 and 2 + connections, respectively, Supplemental Table S6). Results were likewise similar when restricting to a complete-case analysis (Supplemental Table S7).

Discussion

In a retrospective cohort of older women diagnosed with early-stage BC, we found that peer connectedness to an early-adopting physician was a strong predictor of ODX adoption, both in physician- and patient-level analyses. Medical oncologists who had not yet adopted the technology were more likely to do so when ‘connected’ via shared patients to at least one early-adopting peer. In patient-level models, we see mildly attenuated, but more precise effect estimates (45% vs. 66% increased odds), likely a result of differences in patient mix and disease

Table 2 Physician-level analysis of association between connection to early adopter and adoption of ODX

Comparison	Odds ratio	95% CI	
Connection to early adopter			
No	Ref.	–	–
1 connection	1.66	1.08	2.57
2 or more connections	1.44	0.96	2.15
Sex			
Male	Ref.	–	–
Female	1.69	1.24	2.31
Years in practice			
< 5	Ref.	–	–
5 or more	0.34	0.23	0.50
Region			
West	Ref.	–	–
Midwest	1.20	0.77	1.86
Northeast	1.07	0.74	1.53
South	1.13	0.79	1.61
Trained in US			
No	Ref.	–	–
Yes	1.24	0.93	1.66
Tertile of patient volume			
1	Ref	–	–
2	3.56	2.17	5.84
3	9.37	5.53	15.89

Model is logistic with random intercepts at the hospital referral region level

*Sample is among providers who did not order ODX in early time period (2008–2009)

severity accounted for in patient models. The association is marginally stronger when we require a higher number of patients to define a provider connection—seen as a proxy for stronger connectedness. The association is generally consistent when we changing the connection from between medical oncologists to between medical oncologists and surgeons These results suggest that shared patients and/or shared experiences between physicians may speed or increase diffusion of new medical technologies.

These findings are consistent with a number of other studies that have demonstrated a positive association between connectedness (however defined) and technology uptake. Pollack et al. [10] create networks of 'social contagion' to estimate physician adoption of advanced imaging in breast cancer. Despite limited evidence of clinical benefit, the authors find strong network effects, suggesting MRI and PET use were associated with being connected to other using providers (OR = 2.47 and 2.04, respectively). In another similar study, authors test for the impact of provider networks on brachytherapy [9]. With a design similar to ours, the authors find the adoption of brachytherapy for those providers connected to early users nearly doubled—an increase of about four percentage points (8.0% vs. 4.1%).

In the past several years, genomic testing has received considerable interest from the research and patient communities [14, 15]. Though relatively few such tests have been approved by the FDA (not a requirement for diagnostic testing, in general), there has been noticeable optimism surrounding an approach that treats gene expression, rather than a siloed site-based approach [16]. ODX, as one of the first available assays has been the most studied, though its indication is limited to ER + HER2—breast cancer, perhaps limiting its exposure and impact. Moreover, because ODX is a lab test that does not require purchasing equipment or capital resources, it may be particularly susceptible to network diffusion. In contrast, the newly expanded label for FoundationOne CDx includes an indication for any solid tumor, greatly increasing its potential to impact patients with any cancer type [17]. We believe the findings from this study are important to demonstrate how diffusion may work through provider networks for upcoming genomic tests, such as FoundationOne, and specifically to provide quantitative estimates of the association. Efforts to increase patient access may find success intervening on the supply side, leveraging existing physician networks for diffusion.

We interpret this study against several limitations. Firstly, limited by data in the claims, the models used in these analyses are of reduced form, and not intended to be structural. As such, we cannot comment on some of the specific mechanisms by which provider connectedness leads to increased ODX use. In designing ways to improve connectedness it will be important to understand the specifics of how networks function to improve diffusion. Still, we find the initial work to establish an association important for additional hypothesis generation and proof of concept. The choice of 'shared-patient' as the metric for network, in contrast to geo-location-based networks, may shed some light on one path to diffusion. We note that other factors may explain the association with adoption, in particular a shared context or residual confounding [18]. Second, our models are limited by what we can observe. While we control for a number of known factors associated with ODX use from prior work, it is impossible to claim we have eliminated all potential confounding factors in this relationship. Third, though the SEER-Medicare sample contains a broadly diverse sample of Medicare beneficiaries with cancer, many states and subpopulations may be underrepresented. Specifically, we are not able to make claims about the non-elderly population, or the non-FFS elderly, many of whom also would benefit from increased diffusion of ODX. Finally, we note that there are many ways to construct a network. Our choice of shared patients was made to provide a simple and intuitive structure with a high likelihood of provider interaction. Future work can and should use alternative definitions which may, as

Table 3 Patient-level analysis of association between medical oncologist connection to early adopter and receipt of ODX (selected coefficients)

Comparison	Odds ratio	95% confidence limits	
Medical oncologist connected to early adopter (ref = no)			
1 connection	1.45	1.06	1.98
2 + connections	1.52	1.15	2.02
Age at diagnosis (ref = 66–70)			
71–75	0.71	0.57	0.88
76–80	0.36	0.28	0.47
81 +	0.1	0.07	0.14
Male (ref = female)	0.66	0.27	1.64
Black (ref = non-black)	1.2	0.81	1.78
Married (ref = married)	1.27	1.05	1.53
Geographic region (ref = west)			
Midwest	1.25	0.81	1.94
NA	1.94	1.19	3.15
Northeast	2.21	1.44	3.38
South	1.36	0.88	2.08
Comorbid conditions (ref = 0)			
1	0.85	0.68	1.06
2 +	0.75	0.6	0.94
Histologic tumor grade (ref = I)			
II	1.3	1.05	1.63
III	1.34	1	1.79
IV	4.05	0.93	17.73
Unknown	0.9	0.53	1.54
Progesterone receptor status (ref = negative)			
Positive	0.92	0.71	1.2
Unknown/intermediate	1.13	0.28	4.58

*Sample is among patients with primary medical oncologists who did not order ODX in early time period (2008–2009). Model is logistic with random intercepts at the hospital referral region level

alluded to above, help to compare specific mechanisms for diffusion.

In this study, we found evidence that peer connectedness to an early-adopting physician is a strong predictor of ODX adoption in both physician-level and patient-level analyses. These results suggest that provider networks may provide a potent and modifiable means to modulate the diffusion of emerging medical technologies, and that genomic testing practices may be shared between oncologists. Efforts to increase guideline-recommended genomic testing, where appropriate, may benefit from peer-to-peer-based connection strategies, providing better access to risk information, and better, more targeted care for patients.

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Compliance with ethical standards

Conflict of interest Author Craig Pollack reports stock in Gilead Pharmaceuticals. All other authors report no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent The Duke University IRB determined this study as secondary data use to be exempt from individual informed consent, posing minimum to no risk.

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