Research Article

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Pharmacogenomics

Analysis of outpatient HER2 testing in New York state using the statewide planning and research cooperative system

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Aim: HER2 testing is necessary in the context of therapy with trastuzumab, pertuzumab, lapatinib and neratinib. There is a paucity of reports describing the utilization rates of HER2 testing in large outpatient populations. **Methods:** The Statewide Planning and Research Cooperative System (SPARCS) was used to examine HER2 testing across the state of New York (USA) during the 2012–2016 period. **Results:** There was a linear increase in HER2 testing ($r = 0.91$, $p = 0.030$). There were increases in HER2 testing observed among minorities, including 0.5-fold and 3.5-fold increases in individuals identified as black and Asian, respectively. Major state population centers showed the highest HER2 testing. **Conclusion:** This study establishes a platform to further evaluate clinical utility, outcomes and equity of access for 'precision oncology' testing.

First draft submitted: 18 July 2018; Accepted for publication: 3 October 2018; Published online: 6 November 2018

Keywords: breast cancer • CPT code • HER2 • HercepTest • lapatinib • New York state • pharmacogenomics • SPARCS database • trastuzumab

HER2 testing is used to guide therapy with drugs targeting the HER2 receptor. These drugs include trastuzumab (Herceptin®), pertuzumab (Perjeta®) lapatinib (Tykerb®) and neratinib (Nerlynx®). The clinical use of these drugs in the breast cancer setting represents a mature example of 'precision oncology' [1,2]. HER2 is a protein encoded by the *HER2* gene (official gene name: *ERBB2*), an oncogene that is overexpressed in approximately 20% of breast cancers [3–5]. The overexpression of HER2 in biopsies of breast tumors is often examined utilizing immunohistochemical or FISH approaches [6]. Clinical HER2 testing in the USA has been available since 1998, when HerceptTest™ (Dako) was approved by the US FDA as an aid for breast cancer therapy with trastuzumab. The use of trastuzumab since the early 2000s has contributed to significant improvements in breast cancer survival. For example, trastuzumab-containing regimens lowered the mortality of women with advanced disease by 20%, and have allowed >30% of patients with early stage disease to be cured [7]. The analysis of HER2 overexpression in tumor biopsies is also performed to guide therapy with Lapatinib (Tykerb™). Lapatinib is a small-molecule tyrosine kinase inhibitor that is used in combination with other antineoplastic agents for the therapy of HER2-positive metastatic breast cancer [8]. Other agents have since come on the market that target HER2 in breast cancer.

There is a paucity of reports describing the patterns of utilization of 'precision oncology tests' in relatively large and 'natural' populations. Studies in 'natural' populations often involve the analysis of datasets derived from a diverse array of healthcare facilities servicing millions of individual users from a distinct geographic area. A recent study by Lynch *et al.* utilized this type of approach. The authors examined nationwide precision medicine utilization among Medicare beneficiaries using large database analysis. They found that pharmacogenomic (PGx) tests were frequently billed, and that breast cancer was among the most common indications for testing [9]. The analysis of data from 'natural' populations can yield essential information to assess the clinical utilization of 'precision

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oncology' applications like HER2 testing from a broad healthcare perspective. Thus, the objective of this study was to analyze the utilization of HER2 testing in the state of New York (NY), the fourth most populous state in the US. Data from the Statewide Planning and Research Cooperative System (SPARCS) of NY were used to examine the utilization of HER2 testing during the years 2012–2016. Data from SPARCS include an average of approximately 20 million individual patients from over 390 clinical sites per year living in metropolitan, micropolitan and rural areas across NY. In this study, the SPARCS database was used to examine overall HER2 utilization, geographical distribution of HER2 testing and demographic characteristics of individuals receiving HER2 testing in NY.

Methods

Overview of the SPARCS database

The utilization of HER2 testing in outpatient clinical institutions from NY was examined using an ecological approach based on the analysis of population-level data from the SPARCS outpatient database. The University at Buffalo Institutional Review Board and the NY Department of Health (NYSDOH) approved this research. Access to the SPARCS database was obtained following the application process (www.health.ny.gov/statistics/sparcs/), and data were supplied on digital video discs in .DAT file format.

The SPARCS database is a comprehensive all-payer data reporting system established in 1979 as a result of cooperation between the healthcare industry and the NY government. SPARCS was initially created to collect information on discharges from all Article 28 facilities, which are NYSDOH accredited public health facilities that include hospitals, diagnostic treatment centers and nursing homes. In 2011, SPARCS began to collect outpatient clinical data from all Article 28 facilities in NY. An outpatient visit includes all ambulatory surgery, emergency department services and outpatient services rendered by hospital extension clinics. As of 2017, the SPARCS outpatient database included 394 reporting facilities throughout the state.

SPARCS currently collects all payer claim level data on patient characteristics, diagnoses, treatments, services and charges from reporting outpatient facilities. Patient characteristics include variables such as age, sex, race, ethnicity and markers of socioeconomic status. Hospital-specific covariates are available including type of clinical institution and hospital location as well as identifiers for the patient's primary care provider. Up to 25 diagnostic codes are recorded according to the International Classification of Diseases Clinical Modification, Ninth Revision, and up to 15 procedure codes are be recorded as well. This database has been used extensively for research purposes, both on its own and as part of the Healthcare Cost and Utilization Project [10].

Reporting healthcare facilities in NY are required to submit data to SPARCS in electronic, computer readable format through NYSDOH's secure electronic network. Data must be submitted on a monthly basis and 95% of the facility's SPARCS data must be submitted within 60 days and 100% of data must be submitted 180 days following the patient visit. Data submitted to SPARCS go through a multiphase review process that involves both the submitting entity and SPARCS quality control. This minimizes reporting errors and duplication of patient records.

Demographic characteristics, including age, race and gender, were reported in the database in most cases. There are instances of individuals who do not report race or gender. These individuals were excluded from the demographic analysis. The racial groups reported in the SPARCS database are: white; black; Native American/Alaskan (including those identified as Aleut, Eskimo and Inuit); Asian (including east Asian and south Asian groups); Hawaiian or Pacific Islander (including those who are identified as Samoan, Guamanian and Chamorro); and other race (including multiracial individuals, those with an unknown race and those identifying as races not represented in the database). The geographical locations of individuals receiving HER2 testing were inferred from 5-digit zip codes present in the database. Individuals not reporting a complete zip code or living outside NY were excluded from geospatial analysis.

Study design

The current procedural terminology code for HER2 testing 88360 was considered a surrogate marker to determine the utilization of the test in NY in a 5-year time frame from 2012 to 2016 [11]. The main outcome variable was the incidence rate for HER2 testing. Annual incidence rates of HER2 testing were determined using the number of HER2 tests as the numerators and total outpatient visit estimates from the NYSDOH SPARCS database estimates of outpatient utilization as the denominators. Incidence rates are presented as HER2 tests per 100,000 total outpatient visits. Data analysis was performed with SAS version 9.4 (SAS Institute, Inc., NC, USA), Microsoft Excel 2016 (Microsoft Corporation, WA, USA) and GraphPad Prism version 7 (GraphPad Software,

Table 1. Breakdown of HER2 testing in the state of New York Statewide Planning and Research Cooperative System database from 2012 to 2016.

Patient characteristics	2012	2013	2014	2015	2016	r	p-value[†]
Total patients observed	1.93×10^7	1.99×10^7	2.01×10^7	2.06×10^7	2.71×10^7	0.80	$p > 0.05$
Total HER2 tests	5358	6108	6804	7914	9816	0.97	$p < 0.05$
Total tests per 100,000 individuals	28	31	34	39	36	0.91	$p < 0.05$
Tests in men per 100,000 individuals	1	2	3	4	4	0.95	$p < 0.05$
Tests in women per 100,000 individuals	26	29	31	34	33	0.90	$p < 0.05$
Mean age of individuals receiving HER2 test (years)	60.59	53.00	52.29	58.75	61.02	0.25	$p > 0.05$

[†] Two-tailed Pearson product-moment test.

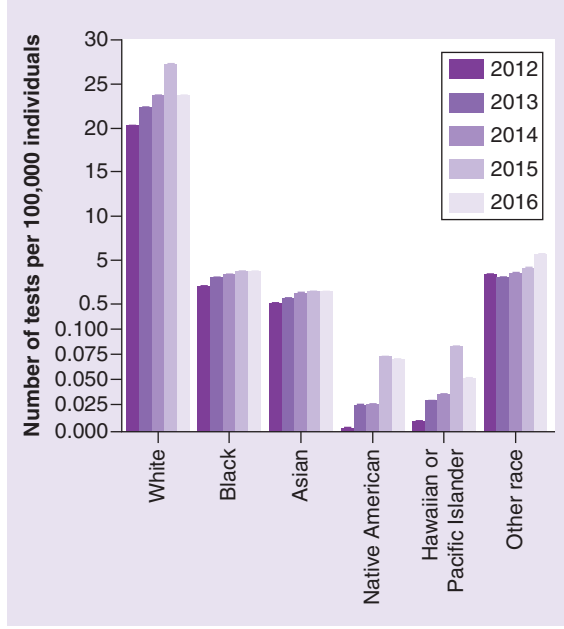

Figure 1. HER2 testing in the state of New York from 2012 to 2016 after stratification by racial categories as defined by Statewide Planning and Research Cooperative System. Individuals could choose from up to five races or an 'other race' option (see Methods).

Inc., CA, USA). Geospatial mapping of individuals receiving HER2 testing in NY was performed with Tableau 10.2.0 (Tableau Software, WA, USA). Normality of datasets was determined using the Kolmogorov–Smirnov test. Correlation analysis was performed using Pearson's product-moment test. Statistical significance was considered with a $p < 0.05$.

Results

The overall utilization of HER2 testing in NY was 27 tests per 100,000 individuals (2012) and 36 tests per 100,000 individuals (2016), as shown in Table 1. There was a linear increase in HER2 testing during the 2012–2016 period (Pearson r = 0.91, p = 0.03). The mean number of HER2 tests performed for the 2012–2016 period was 33 ± 4.2 tests per 100,000 individuals. The reporting rate for gender, age and race was >99% for all groups. Gender group analysis revealed that, for all years, the majority of individuals (>90%) receiving HER2 testing in NY were women (Table 1). From 2012 to 2016, an average of 91.1 ± 3.6% of reporting individuals receiving HER2 testing in NY were females. Table 1 shows linear increases in the number of HER2 tests in females (Pearson r = 0.91, p = 0.03) and males (Pearson r = 0.94, p = 0.016) during the 2012–2016 period. The mean ages of individuals receiving HER2 testing in NY are shown in Table 1. The mean age of individuals receiving HER2 testing in NY during the 2012–2016 period was 57.1 ± 4.1 years.

Figure 1 shows a breakdown of HER2 testing in NY according to racial categories as defined by SPARCS. Whites received more HER2 tests during the 2012–2016 period compared with the other racial groups. In 2012, 75% of the total reported HER2 tests were performed in individuals identified as white. That number declined to 66% in

10.2217/pgs-2018-0120

Table 2. Racial Breakdown of HER2 testing in the state of New York Statewide Planning and Research Cooperative System database from 2012 to 2016.[†]

Reported race	2012	2013	2014	2015	2016	r	p[‡]
White	20.72	22.66	24.17	27.63	24.08	0.73	$p > 0.05$
Black	2.51	3.46	3.83	4.17	4.11	0.91	$p < 0.05$
Asian	0.57	1.02	1.64	1.83	1.83	0.94	$p < 0.05$
Native American	0.0026	0.025	0.025	0.073	0.070	0.93	$p < 0.05$
Native Hawaiian or Pacific Islander	0.010	0.030	0.035	0.082	0.052	0.80	$p > 0.05$
Other race	3.77	3.40	3.97	4.47	6.00	0.86	$p > 0.05$

[†] Per 100,000 individuals.
[‡] Two-tailed Pearson product-moment test.

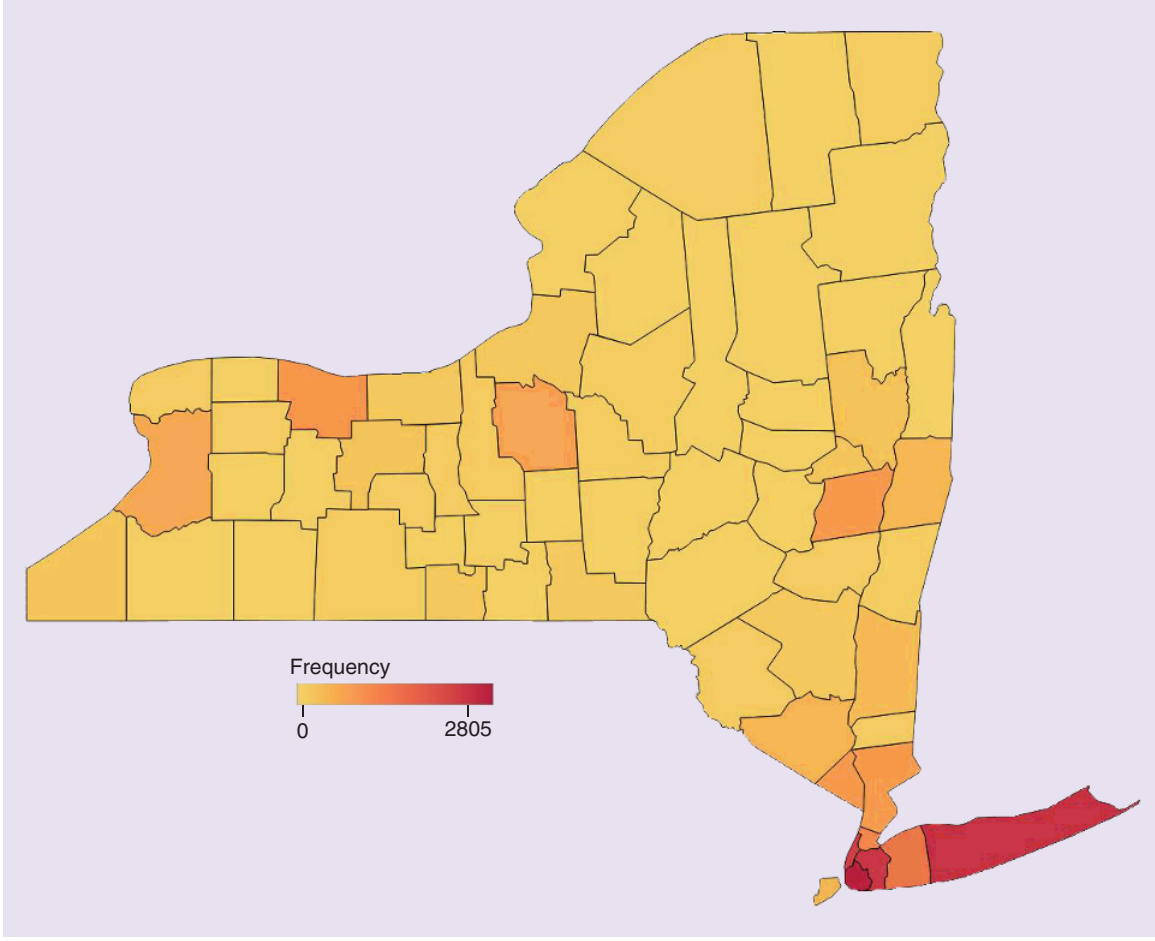

Figure 2. Geospatial county-by-county analysis of HER2 testing in the state of New York from 2012 to 2016. The light yellow color indicates relatively low HER2 testing rates while dark red indicates high HER2 testing rates (see text for details).

2016. In contrast, individuals identified as 'other race' increased from comprising 14% of those receiving HER2 testing in 2012 to 16% in 2016. In general, there were increases in HER2 testing utilization during the 2012–2016 period among individuals identified as Hawaiian or Pacific Islander, Asian, Native American or black (Table 2).

Figure 2 shows the nonscaled geospatial distribution by county of individuals receiving HER2 testing in NY from 2012 to 2016. The reporting rate of five-digit zip codes was 60.4%. The top five counties exhibiting the highest numbers of reporting individuals receiving HER2 testing were Kings, New York, Suffolk, Queens and

Nassau (Figure 2 & Supplementary File 1). These counties also comprise or are in close proximity to the New York city metropolitan area. In the area of upstate New York, Albany, Monroe, Erie, Onondaga and Rensselaer counties had the highest number of reported HER2 tests during the years 2012–2016.

Discussion

This study provides a representative snapshot on the patterns of utilization of HER2 testing in an open and 'real-world' scenario such as NY. We summarized data on HER2 testing in a large, 'natural' population of approximately 20 million individuals by mining a professionally curated government healthcare database. Similar approaches based on procedure codes have been used to track various aspects of healthcare utilization [12]. The current study lays the foundation for establishing a baseline utilization rate of HER2 testing in outpatient institutions reporting to the SPARCS database in NY [13].

Geospatial mapping (Figure 2) indicated that major population centers generally demonstrated the highest rate of reported HER2 testing in NY. While the current study supports population as a key driver of HER2 testing, the rate of breast cancer diagnoses may influence HER2 testing. Querying the available data in the SPARCS database for initial breast cancer diagnoses upon clinic admission using ICD9 codes 174.9 and 175.9 showed that 66.0 ± 3.2% of diagnoses received HER2 testing from 2012 to 2014 (Supplementary File 2). While the admission diagnosis is not necessarily definitive and the number of reported diagnoses can fluctuate with the number of reporting facilities, it appears that breast cancer diagnoses may be impacting HER2 testing rates as documented in the SPARCS database. Other potential factors that may influence HER2 testing rates include prevalence of cancer-focused clinics that report to the SPARCS database in each county.

The availability of demographic data is the starting point for incorporating various socioeconomic metrics into the analysis of HER2 testing in the oncology clinic. These data may be useful to explore potential disparities in healthcare access or utilization in various socioeconomic categories. For example, incorporating covariates such as individual socioeconomic status based on payer (Medicaid versus private insurance), individual geospatial socioeconomic metrics and incidence of breast cancer in a particular area or group of individuals would be necessary to begin drawing conclusions regarding HER2 utilization differences. Similarly, more in-depth analysis of the differences seen in utilization of HER2 testing in male individuals versus female individuals requires incorporation of breast cancer prevalence and population metrics for each respective group. Exploring potential racial disparities using these data is a possibility, but pitfalls do exist. The first one is related to the fact that race is a social construct with fluid boundaries between racial categories. In this context, racial reporting is impacted by multiple confounding factors, including individual racial identity. For example, individuals that are perceived as being 'multiracial' may identify or report as a single race due to personal convictions or cultural factors. Further examination of potential racial disparities in HER2 testing would likely require prospective and controlled investigation by considering other socioeconomic variables to elucidate any potential differences, while also adjusting for estimates of breast cancer prevalence in each respective racial category.

While the current study considers HER2 testing, this methodology can be applied to ascertaining the utilization of other aspects of precision medicine and genome-guided pharmacotherapy. PGx testing is one aspect of personalized medicine that can be considered using the methodology outlined in this work. PGx tests can be used to improve the safety and efficacy of many drug regimens. Starting in 2012, specific current procedural terminology codes for many PGx tests have become available [11]. This may allow for a larger future study that considers the utilization of multiple classes of PGx tests across NY. Previous studies utilized the US Medicare database to explore precision medicine trends with success. While the Medicare database is a powerful repository of information, the SPARCS database is free to use for nonprofit state institutions (such as state universities). Smaller state-wide healthcare databases may represent a valuable and affordable source of information to conduct health-service research. There are potential pitfalls associated with the current study. First, scaling the data to relevant racial or gender populations will need to be performed prior to drawing specific conclusions with regards to potential utilization trends in specific racial or gender groups. Second, SPARCS receives data from approximately 394 outpatient facilities in NY; however, many outpatient facilities in the state do not report to SPARCS. It is not currently possible to account for HER2 testing performed in nonreporting facilities, therefore the current data underestimate the total rates of HER2 testing in NY.