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Cervical cancer geographical burden analyzer: An interactive, open-access tool for understanding geographical disease burden in patients with recurrent or metastatic cervical cancer

Tara Castellano [a], Kathleen Moore [b], Jie Ting [c], Christina Washington [b], Yasin Yildiz [d], Andy Surinach [e], Kalyani Sonawane [f,g], Jagpreet Chhatwal [h], Turgay Ayer [i,j,*]

[a] Louisiana State University, Department of Gynecologic Oncology, New Orleans, LA, USA
[b] Stephenson Cancer Center at the University of Oklahoma HSC, Oklahoma, City, OK, USA
[c] Seagen Inc., Bothell, WA, USA
[d] Value Analytics Labs, Boston, MA, USA
[e] Genesis Research, Hoboken, NJ, USA
[f] Department of Public Health Sciences, College of Medicine, Medical University of South Carolina, Charleston, SC, USA
[g] Hollings Cancer Center, Medical University of South Carolina, Charleston, SC, USA
[h] Massachusetts General Hospital Institute for Technology Assessment, Harvard Medical School, Boston, MA, USA
[i] Georgia Institute of Technology, Department of Industrial and Systems Engineering, Atlanta, GA, USA
[j] Emory School of Medicine, Atlanta, GA, USA

HIGHLIGHTS

- There is variation in the geographic distribution of recurrent/metastatic cervical cancer burden.
- The online, interactive Cervical Geo-Analyzer identifies regions with high disease burden and could inform interventions.
- More studies are needed to clarify local risk factors for disease burden and local health disparities in cervical cancer.

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ABSTRACT

Objective. Cervical cancer (CC) disproportionately affects women based on socioeconomic status and racial/ethnic background. There is limited research in quantifying and visualizing whether substantial geographical disparities in the US exist with respect to CC burden, and especially with respect to recurrent or metastatic CC (r/mCC) disease burden. Identifying regions with higher r/mCC burden may help inform effective healthcare resource allocation and navigating patients to appropriate care.

Methods. We conducted a retrospective analysis of the 2015–2020 MarketScan® Commercial and Supplemental Medicare claims data; r/mCC burden was estimated as the number of patients initiating r/mCC systemic therapy over CC-diagnosed patients for each of the 410 metropolitan statistical areas (MSAs) considered. We developed a public, web-based tool, the Cervical Cancer Geographical Disease Burden Analyzer (Cervical Cancer Geo-Analyzer, http://www.geo-analyzer.org), that allows users to visualize r/mCC burden across MSAs over multiple years.

Results. There was considerable variation in r/mCC burden across MSAs, with a range of 0–83.3%. Burden increased in Boston-Cambridge-Newton, MA (r/mCC to CC ratio: 41% in 2018 to 50% in 2020), and Sacramento-Roseville-Arden-Arcade, CA (33% in 2018 to 50% in 2020). On the other hand, while r/mCC burden remained high, it decreased in Grand Rapids, MI (55% in 2018 to 31% in 2020) and San Francisco-Oakland-Hayward, CA (40% in 2018 to 26% in 2020). There were regions with sparse or no data, suggesting a need for more representative data capture.

Conclusion. The Cervical Geo-Analyzer is a tool to visualize areas with high need for CC interventions. It also

* Corresponding author at: Georgia Institute of Technology, Department of Industrial and Systems Engineering, H. Milton Stewart School of Industrial and Systems Engineering, 755 Ferst Drive, NW, Atlanta, GA 30332, USA.
E-mail addresses: tcaste@lsuhsc.edu (T. Castellano), kathleen-moore@ouhsc.edu (K. Moore), jting@seagen.com (J. Ting), christina-washington@ouhsc.edu (C. Washington), yyildiz@valueanalyticslabs.com (Y. Yildiz), andy@genesisrg.com (A. Surinach), sonawane@musc.edu (K. Sonawane), JagChhatwal@mgh.harvard.edu (J. Chhatwal), ayer@isye.gatech.edu (T. Ayer).

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builds the foundation for further work to understand local risk factors of disease burden, identify populations of interest, characterize health disparities of CC or r/mCC and inform targeted interventions.

1. Introduction

Despite the availability of human papillomavirus (HPV) vaccination, screening, and effective treatment for cervical dysplasia, an estimated 14,100 invasive cervical cancer (CC) cases will be diagnosed in the US in 2022, with an estimated 4280 deaths [1]. Approximately 16% of women with CC have metastatic disease at diagnosis [1], and even among those presenting with an earlier stage at diagnosis, up to 61% will recur with metastatic disease within the first 2 years following completion of therapy [2].

While historically a devastating diagnosis with limited treatment options and poor disease response [3,4], the recurrent or metastatic CC (r/mCC) treatment landscape is actively evolving, with new treatment options being approved or investigated in first-line, second-line or later r/mCC settings [5–13]. To better understand the unmet need in the r/mCC population against the backdrop of changing treatment landscape, it is necessary to equip researchers, policy decision-makers, and patient advocacy groups with tools to visualize areas with high need for r/mCC intervention in the US.

Although there have been previous studies of US epidemiologic or geographic clusters of cervical cancer, these are typically state-based, such as the Kaiser Family Foundation database, and most are focused mainly on the number of new invasive cervical cancer diagnoses. Lastly, if they were conducted among late-stage CC patients, it was prior to the availability of modern treatments for r/mCC [14–17]. From these national cancer registry reports, many important insights were gained, including the fact that there has been an overall increase in the proportion of CC cases diagnosed at a later stage from 2005 to 2014 [14–16], and that there have been substantial changes in the distribution of late-stage CC across states over time [14–16]. These findings further confirm the need to examine contemporary distribution of disease burden at the local level.

An MSA represents a small geographical region consisting of a city and surrounding communities that are linked by social and economic factors, and is formally defined as one or more counties with a city of ≥50,000 inhabitants or containing a Census Bureau-defined urbanized area with total population of ≥100,000 (≥75,000 in New England) [18]. Because of the way they are constructed, MSAs are helpful for small area analyses to identify potential disparities in health outcomes and provision of health services. In addition, the use of administrative claims data of privately- and publicly-insured patients is an increasingly popular way to enable better understanding of the contemporary patient journey. This data is increasingly important to capture in rare clinical settings such as r/mCC and according to MSA, where specialized resources, research, and expertise may need to be allocated.

The present study aims to understand and quantify the recent geographical distribution of CC and r/mCC burden in the US at the metropolitan statistical area (MSA)-level, using commercial claims databases and data visualization methodologies. Findings from this study may help to quantify and visualize any geographical disparities with respect to CC and r/mCC disease burden. These findings might subsequently lead to hypothesis generation for pinpointing the areas with high need for improved access and targeted interventions.

2. Methods

This study utilized a cross-sectional design and visualization analytics methods to examine the burden of CC and r/mCC in the general US population during 2015–2020 across MSA regions. For this purpose, we conducted a retrospective analysis of the IBM MarketScan® Commercial and Supplemental Medicare claims database.

2.1. Data

The MarketScan® database consists of de-identified Commercial and Supplemental Medicare claims of >203 million unique patients across the US. The database consists of member enrollment and demographic information, including age, sex, geographic location, health plan enrollment/disenrollment dates, and medical and prescription drug claims files. While most of the MarketScan® enrollees are from large US employer insurance plans, data from insurers for small and mid-size employers have seen increased representation in recent years. Enrollees' MSA were identified based on their residential address. There are a total of 421 MSAs in the US, of which 410 are captured in MarketScan.

2.2. Inclusion and exclusion criteria

Adult women with CC and r/mCC were identified from the database using a previously validated methodology [19]. Briefly, CC cases were defined by one or more inpatient, or two or more outpatient claims of malignant neoplasm of the cervix (International Classification of Diseases, 9th and 10th Revisions, Clinical Modification Codes 180.xx and C53.xx) in 2015–2020. From these patients, r/mCC cases were defined as those with one or more claim for a systemic treatment listed by the National Comprehensive Cancer Network guidelines for treatment of CC, which were not associated with surgery or radiation. Eligible patients had to have been continuously enrolled in a plan for ≥12 months of the measurement year (with a 30-day allowable gap).

To identify the geographic, MSA-level distribution of CC burden, we calculated the prevalent number of patients with CC diagnosis in proportion to the number of adult female enrollees ≥18 years of age for each MSA each year. Data were stratified by age group (18–21 years, 22–64 years, and 65 years and above) to allow estimation of age-adjusted point prevalence. Since women younger than 21 are not likely to receive screening, we considered women in the 18 to 21-year-old age group as a separate category. For each age group, geographic distribution of r/mCC burden was estimated as the number of patients initiating r/mCC systemic therapy in proportion to CC-diagnosed patients for each MSA each year. We also compared the trends in treatment utilization for r/mCC over time to understand temporal changes in disease burden at the individual MSA level. Women without MSA information were excluded from the analysis.

2.3. Cervical geo-analyzer: an online, interactive tool to analyze r/mCC geographical burden

We visualized our findings and made them publicly available using an online, interactive tool, the Cervical Geo-Analyzer (http://www.geo-analyzer.org). The Cervical Geo-Analyzer enables users to quantify r/mCC disease burden across MSAs over multiple years (2015–2020). Users can filter the results by year, age group, and minimum number of CC diagnoses at the MSA level. The user interface was constructed using ReactJS, a Java-based free and open-source software [20].

3. Results

The estimated annual prevalence of CC among MarketScan® Commercial and Supplemental Medicare enrollees with MSA data was 0.048% (range: 0–0.72%) patients, with a total of 2144 (2015), 2817 (2016), 2322 (2017), 2553 (2018), 2184 (2019), and 2332 (2020) patients diagnosed annually (Table 1).

In 2020 (the latest year available in the database), the estimated CC prevalence was highest in women ≥65 years (0.080%) and lowest in women 18–22 years (0.0006%). In the same year, estimated r/mCC incidence rate was 0.013% and was generally highest in patients ≥65 years.

In contrast to the most recently reported year of 2020, the overall CC burden among women was highest in the 23 to 64-year age group across multiple years and MSAs (Fig. 1). However, many MSAs also reported high or increasing CC burden among older women ≥65 years over time (e.g., Chicago-Naperville-Elgin, St. Louis, and New York-Newark-Jersey City). Similar to CC, r/mCC burden was also relatively greater in the 23–64 year-old age group during 2014–2019. However, the number of MSAs reporting any r/mCC burden in the ≥65 age group was much fewer than that in the younger age group and decreased over time, except for the New York-Newark-Jersey City MSA showing persistent r/mCC burden in older women.

The geographical distribution of r/mCC burden relative to number of CC-diagnosed cases in the latest available year (2020) is visualized in Fig. 2.

Significant geographical variation is observed across MSAs (range: 0–83.3%). Among MSAs with ≥10 CC-diagnosed patients, the average r/mCC burden between 2018 and 2020 was generally >30% in the top 10 MSAs with the highest r/mCC burden (Table 2).

R/mCC burden was on an increasing trajectory in Boston-Cambridge-Newton, MA (41% in 2018 to 50% in 2020) and Sacramento-Roseville-Arden-Arcade, CA (33% in 2018 to 50% in 2020). On the other hand, although r/mCC disease burden remained high, it was on a decreasing trajectory in Grand Rapids, MI (55% in 2018 to 31% in 2020) and San Francisco-Oakland-Hayward, CA (40% in 2018 to 26% in 2020). In the remaining top 10 MSAs, the r/mCC burden fluctuated over time but was consistently >15% for any given year. Interestingly, we observed that some MSAs with the lowest average r/mCC rates (<20%) share the same state as those with the highest rates, such Lakeland-Winter Haven in FL (16%) and Greenville-Anderson-Mauldin in SC (18%).

4. Discussion

To our knowledge, this is one of the first studies to examine contemporary geographical distribution of r/mCC burden in the US. We found large geographic variation with respect to CC and r/mCC burden, with a disproportionally greater number of MSAs in the South, Northeast, and Midwest regions with high r/mCC burden. We also identified specific MSAs with persistently high or increasing disease burden across time, which can inform future activities geared toward providing a geographically targeted approach to medical and research resource distribution and allocation. Our publicly available tool, the Cervical Geo-Analyzer, can help visualize areas with high need for future investigations into whether that particular MSA would benefit from further CC expertise, education and/or intervention.

Importantly, insight from the Cervical Geo-Analyzer allows for hypothesis generation as to why certain regions are displaying contemporary and persistently high r/mCC burden, such as MSAs in Massachusetts, Florida, California, Michigan, and North Carolina. Even as these are not areas traditionally thought of as poor-resourced, they may represent places with the highest need of CC education, or places where standard up-front treatments are less likely to be accessed or more likely to fail. To adequately address the needs of r/mCC patients in these regions, however, we need to understand the area-level contextual risk factors associated with increasing or persistent r/mCC burden. For example, prior studies have noted a correlation between the number of oncologists, radiation services (including brachytherapy), and access to treatment in the context of disease burden based for various cancers [21]. Further analyses could characterize drivers of geographic disparity in r/mCC and help inform targeted intervention.

In this study, our observation of varying r/mCC burden across geographic areas over time reflects previous reports of continual changes in state- or county-level distribution of late-stage CC incidence rates [14–16]. Despite our Cervical Geo-Analyzer tool finding an increasing CC burden across most MSAs from 2015 to 2020, the number of MSAs with >40% of patients initiating r/mCC therapy relative to that of CC-diagnosed patients has generally decreased. One possible explanation is that cervical cancer screening and vaccination, as well as advancements in surgical and radiation techniques in the curative setting, may have led to an increasing number of CC cases detected in earlier stages and cured, leading to a corresponding decline in the number of women progressing to r/mCC and initiating systemic therapy.

However, a contradictory finding of an increasing trend in the proportion of CC cases diagnosed at a later stage (47% to 54% between 2005 and 2014) [16], and relatively little evolution of treatment landscape in the locally advanced setting [22] implies we may also see higher r/mCC burden post-2020, as more patients recur with metastatic disease. Additionally, disruption across the spectrum of cancer care due to the COVID-19 pandemic may have contributed to a relatively lower number of women initiating r/mCC systemic therapy in 2020 [23]. The ongoing pandemic and its strain on healthcare resources, combined with the known disparities observed in the CC and r/MCC population due to geography [25], further highlights the importance of dynamic data visualization tools such as the Cervical Geo-Analyzer to aid in understanding what types and where to focus evolving efforts for prevention, education, implementation and study of new treatment options, and overall allocation of healthcare resources.

The current study has a few advantages. Study findings and the Cervical Geo-Analyzer offers an easy way to visualize MSA-level geographic variation in CC and r/mCC burden across the US to a wider audience including researchers, policy decision-makers, and patient advocacy groups. Additionally, the validated algorithm used in this analysis to identify patients with CC and r/mCC provides for an intuitive metric to

Table 1
CC burden in the US, 2015–2020[a].

Sample flow	2015	2016	2017	2018	2019	2020
Women aged ≥18 years old in the calendar year	13,182,451	12,800,015	11,378,661	11,527,495	9,168,786	8,531,859
Continuously enrolled in health plan	9,854,271	9,890,421	8,571,008	8,394,255	6,478,462	6,464,482
Women diagnosed with CC[b]	2,144	2,817	2,322	2,553	2,184	2,332
Annual prevalence of CC[b]	0.0255%	0.0333%	0.0378%	0.0411%	0.0451%	0.0482%
Women with r/mCC[c]	854	980	769	778	652	647
Annual incidence rate of r/mCC[c]	0.0102%	0.0116%	0.0125%	0.0125%	0.0135%	0.0134%

CC, cervical cancer; r/mCC, recurrent or metastatic cervical cancer.
[a] CC and r/mCC data are collected for only patients with Metropolitan Statistical Area data.
[b] Identified via International Classification of Diseases, 9th and 10th Revisions, Clinical Modification Codes 180.xx and C53.xx.
[c] CC-diagnosed patients who initiated ≥1 systemic therapy for CC beyond surgery or radiation [19].

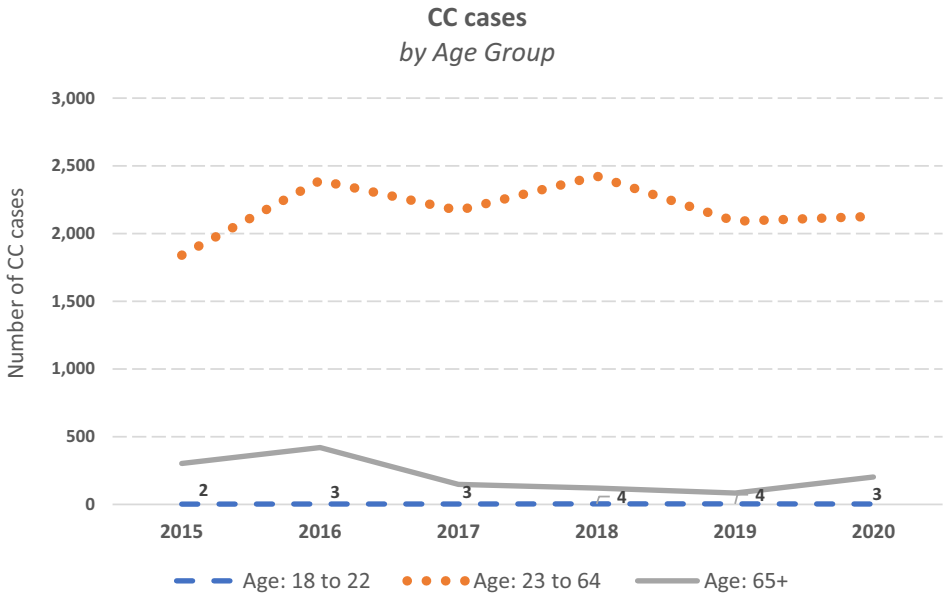

Fig. 1. Age-stratified CC disease burden at the national level.
CC, cervical cancer.

define disease burden, which can be easily updated in the tool as new data become available. Future directions include the Cervical Geo-Analyzer tool offering a platform where further analyses and insights can be made publicly available to benefit diverse stakeholders and inform ways to reduce health disparities and burden of r/mCC in the US.

The current study also provided insight into ways to improve upon the limitations of the tool's current applicability. First, our study population, those enrolled in a commercial or supplemental Medicare insurance plan, may limit the generalizability of our findings. Data from a prior study however suggests that privately insured women account for the majority of CC diagnoses in the US (47%) [24]. Second, r/mCC burden in our study is likely underestimated, due to (i) the necessity for patients with r/mCC in administrative claims to be identified by the initiation of systemic therapy [19], and (ii) only patients with r/mCC with MSA data were included in the Cervical Geo-Analyzer. Finally, because we identified patients with r/mCC based on administrative codes for treatment, we cannot rule out the possibility of misclassification of treatment assignment. Despite the inherent limitations of database studies, including missing and incomplete data, and the lack of facility/hospital based MSA data, we contend that administrative claims remain a resource with rich, contemporary real-world patient journey information. Future analyses should include nationally representative data.

5. Conclusion

There is substantial variation in the geographic distribution of CC and r/mCC burden at the MSA level. Our online, publicly available Cervical Geo-Analyzer tool identifies regions with disproportionately high disease burden and can be used to inform targeted interventions. Current findings, when used in context, can generate further exploration

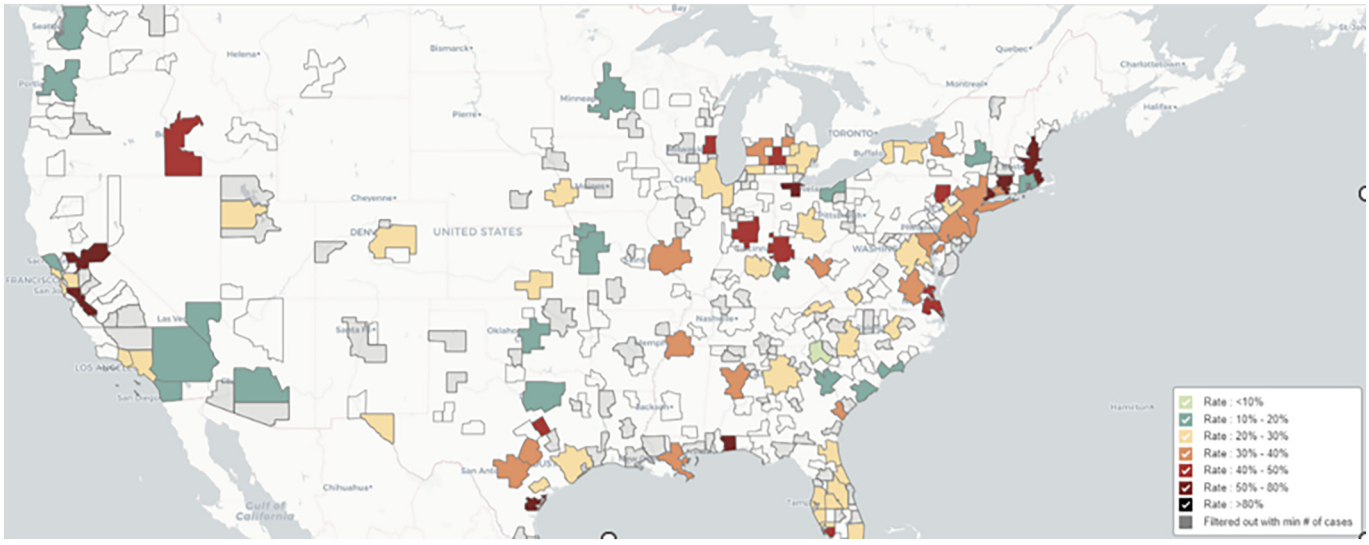

Fig. 2. Burden of r/mCC across MSAs in the US.
CC, cervical cancer; MSA, metropolitan statistical area; r/mCC, recurrent or metastatic CC.

Table 2
Top 10 MSAs with highest burden of r/mCC in the US[a,b].

MSA	2018	2019	2020	Average
Boston-Cambridge-Newton, MA-NH	41%	45%	50%	45%
Cape Coral-Fort Myers, FL	64%	31%	40%	45%
Sacramento-Roseville-Arden-Arcade, CA	33%	46%	50%	43%
Grand Rapids-Wyoming, MI	55%	36%	31%	41%
Raleigh, NC	47%	54%	20%	40%
Baltimore-Columbia-Towson, MD	39%	33%	38%	37%
Augusta-Richmond County, GA-SC	39%	50%	19%	36%
Virginia Beach-Norfolk-Newport News, VA-NC	38%	27%	40%	35%
San Francisco-Oakland-Hayward, CA	40%	36%	26%	34%
Birmingham-Hoover, AL	27%	43%	30%	33%

CC, cervical cancer; MSA, metropolitan statistical area; r/mCC, recurrent or metastatic cervical cancer.

[a] r/mCC burden defined as proportion of patients initiating systemic therapy for r/mCC over number of CC cases; top 10 rates included MSA with ≥10 cervical cancer cases per year.

[b] Only years 2018–2020 were included in Table 2 due to MSAs in the earlier periods having a higher degree of missing data.

into the underlying causes of geographic variation to uncover potential drivers of disproportionate r/mCC burden.

Author contributions

Tara Castellano, Kathleen Moore, Jie Ting: Conceptualization, Methodology, Investigation, Supervision, Validation, Writing-Original draft preparation, Reviewing and Editing. Christina Washington: Methodology, Validation, Writing-Reviewing and Editing. Andy Surinach, Kalyani Sonawane: Investigation, Data curation, Data analysis, Writing-Reviewing and Editing. Yasin Yildiz, Jagpreet Chhatwal, Turgay Ayer: Conceptualization, Methodology, Project administration, Validation, Visualization, Writing- Original draft preparation, Reviewing & Editing.

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Declaration of Competing Interest

Kathleen Moore has received consulting fees from Green Fire Bio, and payment or honoria from, and participated in data monitoring or advisory boards for Astra Zeneca, Aravive, Alkemeres, Addi, Blueprint pharma, Clovis, Elevar, Eisai, EMD Serono, GSK/Tesaro, Genentech/Roche, Hengrui, Immunogen, INxmed, IMab, Mersana, Merck, Myriad, Mereo, Novartis, OncXerna, Onconova, SQZ, Tarveda, VBL Therapeutics and Verastem, received support for attending meetings from Astra Zeneca, GSK/Tesaro and holds a leadership role with GOG partners; Jie Ting is an employee of, and holds stock in Seagen Inc.; Yasin Yildiz is a paid employee of Value Analytics Labs, which received funding from Seagen Inc. in connection with this study; Andy Surinach is an employee of Genesis Research, which received consulting fees from Seagen Inc. in connection with this study; Kalyani Sonawane has received consulting fees from, and has held a leadership role with Value Analytics Labs; Jagpreet Chhatwal is a co-owner of Value Analytics Labs, which received funding from Seagen Inc. in connection with this study, and he has received consulting fees and honoria from Novo Nordisk, and Bayer; Turgay Ayer is a co-owner of Value Analytics Labs, which received funding from Seagen Inc. in connection with this study. Tara Castellano and Christina Washington have no competing interests to disclose.

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