Biol Blood Marrow Transplant 25 (2019) 989–994

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Supportive Care

Hematopoietic Cell Transplantation and Utilization of Fertility Preservation Services

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Article history:
Received 7 August 2018
Accepted 1 January 2019

Keywords:
Fertility preservation
HCT
Survivorship
Utilization
Longitudinal
Late effects

A B S T R A C T

Conditioning regimens for hematopoietic cell transplantation (HCT) are harmful to reproductive function, but national utilization of fertility preservation (FP) before HCT has not been studied. The primary aim of this descriptive retrospective analysis is to understand FP utilization in the HCT population of patients between ages 18 and 40 years, whereas the secondary aim is to describe temporal trends in FP before HCT. Key dates, procedures codes, and diagnosis codes were extracted from administrative and health services commercial claims data, which were obtained from FAIR Health's national claims database, to construct 29 patient-specific clinical journey timelines detailing the time from diagnosis to FP and to HCT. Patient characteristics studied include sex, age, HCT type (autologous and allogeneic), and census region. Key findings from primary and secondary analyses were that 7% of the HCT cohort had claims for FP services, FP utilization before HCT decreased with increasing age, there were 102 days (median) between FP and HCT procedure date, and 7 of 29 patients who received FP services had a nonmalignant primary indication for HCT. More research is needed to understand the barriers to FP before HCT so that targeted tools can be used to increase utilization and improve quality of life for HCT survivors.

INTRODUCTION

Hematopoietic cell transplantation (HCT) is a potentially curative treatment for patients with blood cancers and nonmalignant conditions such as sickle cell disease and other inherited metabolic disorders. Conditioning regimens for HCT typically include chemotherapy, radiation, or both, which can be highly toxic, potentially causing loss of or reduced reproductive function [1,2]. Myeloablative regimens containing some combination of cyclophosphamide, melphalan, busulfan, and total body irradiation have been cited as posing substantial risk to patients' fertility but are required to optimally treat aggressive hematologic malignancies in younger patients. The impact of reduced-intensity conditioning on fertility is unknown but probably significant as well [3-8]. Iatrogenic infertility is characterized by loss of reproductive function resulting from medical intervention that can compound the financial and emotional stress surrounding a life-threatening diagnosis and referral for transplant [9,10].

Current American Society of Clinical Oncology fertility preservation (FP) guidelines for cancer patients state that mature oocyte, embryo, and sperm cryopreservation are standard of care methods of FP. The American Society of Clinical Oncology practice guidelines recommend addressing fertility risk and preservation options as soon as possible after diagnosis and before gonadotoxic treatment [11,12].

As a result of lack of access, financial toxicity and negative psychosocial sequelae can lead to poor quality of life in transplant survivors [13,14]. Studying utilization is one way to start defining the current state of FP access before HCT and will help inform the development of future research studies and policy work in this space. As such, the primary aim of this study was to describe the utilization of FP before HCT among patients between the reproductive ages of 18 and 40 years. The secondary aim was to explore the timeline from diagnosis to FP and HCT to elucidate temporal trends associated with getting FP before HCT. To our knowledge, there have been no studies conducted to investigate the utilization of FP before HCT.

METHODS

Data Source

Administrative claims data are commonly used for estimating patterns of utilization and have the advantage of being more reflective of "real-world" patterns than data collected for research, which can be highly selective [15]. The FAIR Health, Inc. National Private Insurance Claims database is the nation's largest collection of private medical claims and is composed of medical and pharmaceutical administrative claims from over 60 health plans collectively representing over 150 million commercially insured patients across the United States [16]. Our dataset included claims from January 1, 2014 to June 30, 2017 for 30,045 adults who had an International Classification of Disease, 9/10th revision diagnosis for which autologous or

Financial disclosure: See Acknowledgments on page 993.
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https://doi.org/10.1016/j.bbmt.2019.01.005
1083-8791/

allogeneic HCT could have been chosen as a possible treatment. This research was considered exempt by the National Marrow Donor Program Institutional Review Board.

Study Population and Patient Selection

The FAIR Health National Private Insurance Claims database was queried to identify men and women ages 18 to 40 who were diagnosed with a condition that could represent an indication for either autologous or allogeneic HCT between January 1, 2014 and June 30, 2017 (N = 30,045). Diagnoses included adrenoleukodystrophy, amyloidosis, aplastic anemia, β-thalassemia major, congenital thrombocytopenia, familial erythrophagocytic lymphohistiocytosis, Hurler syndrome, Krabbe disease, leukemia, metachromatic leukodystrophy, multiple myeloma, myelodysplastic syndrome, myelofibrosis, lymphoma, paroxysmal nocturnal hemoglobinuria, severe combined immunodeficiency disease, sickle cell disease, and Wiskott-Aldrich syndrome. Of the 30,045 patients with an HCT-compatible diagnosis, 447 patients were identified as having a procedure code for HCT (Figure 1) and were selected to comprise the HCT study population (before applying exclusion criteria). For reference, there have been approximately 5559 allogeneic HCT patients and 3814 autologous HCTs in the United States since 2014 [17]. Adults over age 40 years were excluded because of clinical evidence that shows declining efficacy of assisted reproductive technologies in this population [18,19]. The same age cut-offs were applied to both sexes in this study to eliminate any potential for case selection bias between sexes.

Details on patient selection and exclusion criteria are provided in Figure 1. The final HCT cohort was established by applying exclusion criteria to ensure patients had a diagnosis before transplant and to confirm that patients were of adult reproductive age (18 to 40 years) on the date of transplant. Applying exclusion criteria reduced the original HCT study population by 36 patients (447 to 411 patients).

To identify patients within the cohort who received FP services, we assessed whether patients had a diagnosis (International Classification of Disease, 9/10th revision, Clinical Modification) for FP counseling (V26.42, Z31.62) or procedure (V26.82, Z31.84) or a Current Procedure Terminology code for cryopreservation (89258, 82959, 89337) before transplant but after the first HCT compatible diagnosis.

Analysis

In our primary analysis we explored the demographics of the HCT cohort and the subgroup of HCT patients who underwent FP services before HCT. Demographic variables such as age and sex were assessed as well as type of HCT. Geographic variation was also evaluated by observing the US census region where HCT occurred. The timeframe between patients' first claim in the analysis window and their HCT was explored to account for lack of enrollment information in the dataset.

In secondary analyses clinical journey timelines were created for the subgroup of patients who underwent FP counseling or procedure before HCT. The timelines included the date of first and last claim in the dataset (regardless of diagnosis), date of HCT, dates of service for each diagnosis category, and date of each FP service claim (Figure 2). The clinical journey timelines were reviewed with a clinician to assign the likely primary diagnosis. After clinician review the timelines were used to summarize and describe when the FP occurred in relation to primary diagnosis and transplant date. Type of FP services and quantity of FP claims per patient were also evaluated.

SAS Enterprise Guide V7.1 (SAS Institute Inc., Cary, NC, USA; Microsoft Corporation, Redmond, WA, USA) was used to apply selection criteria, conduct primary analysis, and identify dates for clinical journey timelines. Microsoft Visio was used to create clinical journey timeline visuals, and Microsoft Excel was used for secondary analysis of timeline intervals including figures.

RESULTS

Primary Analysis

The HCT cohort included 411 patients, of whom only 29 (7.1%) had claims for FP services before transplant. The overall HCT cohort was primarily men (n = 235, 57%) and older (age $\geq$ 30, n = 211, 51%). In contrast, the subgroup of patients who had an FP service claim before transplant were predominantly women (n = 18, 62%) and younger (age $\leq$ 26, n = 20, 69%). No patients in the oldest age range (ages 35 to 40 years) had FP claims before HCT (Table 1).

The FP subgroup had a higher percentage of allogeneic HCT (n = 19, 66%) than the overall HCT cohort (n = 242, 59%). Geographically, most transplants took place in the West (44%) and Northeast (26%) regions, but FP was significantly overrepresented in the Northeast (45% of those receiving FP) and South (just 18% of transplants but 28% of FP recipients). The West and Midwest accounted for 44% and 13% of transplants but only 24% and 3% of FP claims, respectively.

Considering all claims that occurred before HCT, patients had an average of 1.9 different diagnoses for which HCT is a

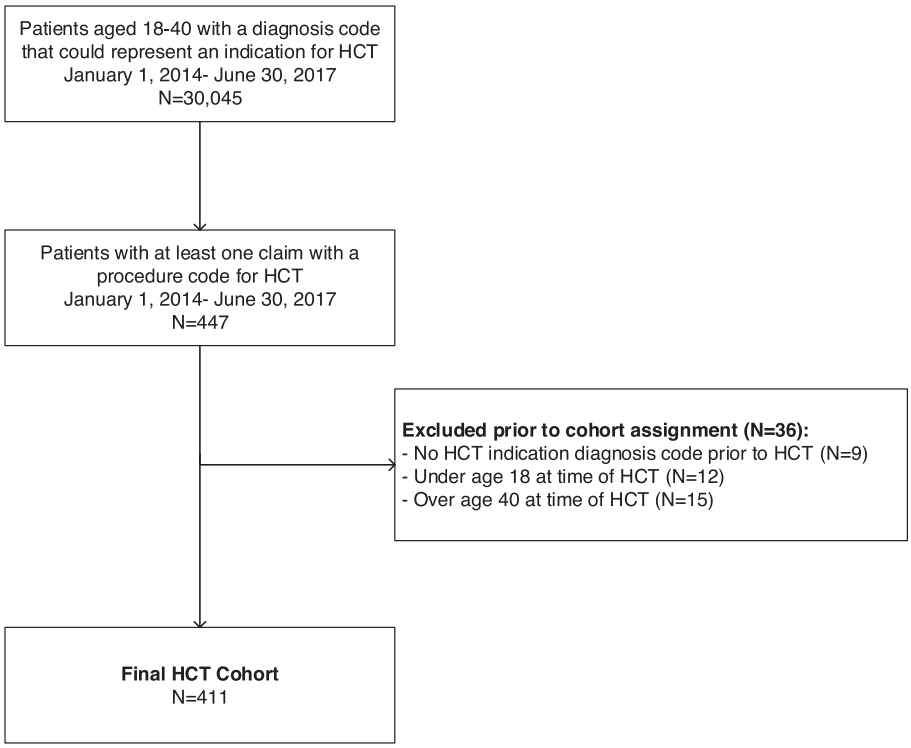

Figure 1. Patient selection and exclusion criteria.

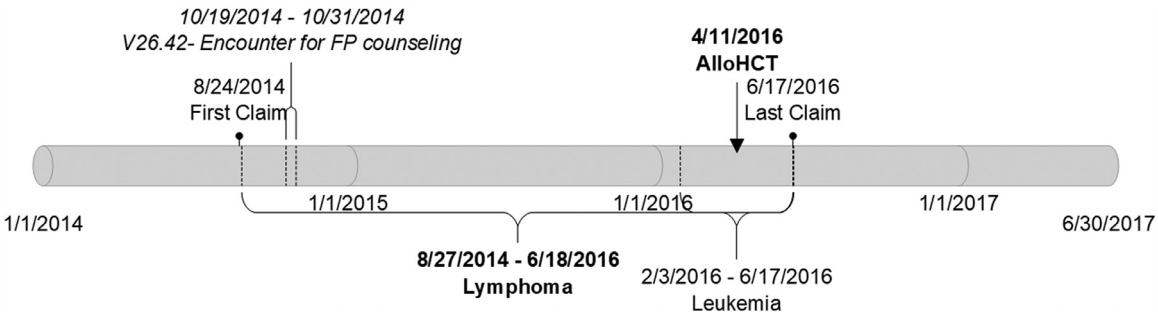

Figure 2. Sample clinical journey map. Includes first and last claim in the analysis window, range of dates of service for each HCT indication, range of dates of service for FP services, and HCT date.

possible treatment (range, 1 to 5). Aplastic anemia, leukemia, and lymphoma were the most frequent HCT indications seen in claims preceding transplant for both the HCT cohort and the FP subgroup (Table 2).

Secondary Analysis: FP Subgroup

Of the patients who had claims for FP services before transplant, 14% (n = 4) had claims for both counseling and procedure, 38% (n = 11) had procedure alone, and 48% (n = 14) had counseling alone. Of the 4 patients with both counseling and procedure, 3 had a counseling visit before the FP procedure. Although most patients (n = 19, 66%) had only 1 claim for FP services, some patients had multiple claims for FP services (range, 1 to 7). This implies some variability in the number of FP services used per patient. For patients with more than 1 FP claim, the average duration from first claim to last claim was 17.7 days (range, 1 to 32).

Patients had a median of 181 days (6 months) between primary diagnosis and HCT. The time from diagnosis to FP ranged from 3 to 685 days, with a median of 43 days. The time from FP to transplant ranged from 8 to 541 days, with a median of 102 days (Figure 3). Generally, patients undergoing autologous HCT had longer intervals between the 2 time points. This is particularly true for the time from FP to HCT. Of the 7 patients falling outside the interquartile range (>208 days from FP claim to HCT claim), 5 were autologous transplants.

After clinician review to assign a primary diagnosis, lymphoma and leukemia were the most common primary diagnoses, collectively making up 65% (n = 19) of the patients who had FP services before HCT (Table 3).

Three patients in the FP subgroup had claims before HCT with additional codes indicative of laboratory procedures during assisted reproductive technology cycles as defined by the

Table 1
Demographics and Transplant Type for HCT Cohort and Subgroup Who Received FP Counseling or Procedure before HCT

	HCT Cohort (n = 411)		FP Subgroup (n = 29)	
	No. of Cases	Percent	No. of Cases	Percent
Sex				
Male	235	57	11	38
Female	176	43	18	62
Age (at first transplant)				
18-21 yr	65	16	10	34
22-25 yr	78	19	10	34
26-29 yr	57	14	4	14
30-34 yr	87	21	5	17
35-40 yr	124	30	0	0
Transplant				
Autologous only	167	41	10	34
Allogeneic only	242	59	19	66
Autologous and allogeneic	2	0	0	0
Census region*				
South	73	18	8	28
West	180	44	7	24
Midwest	53	13	1	3
Northeast	106	26	13	45

* One patient had 2 transplant claims on the same date in 2 regions. Census regions are defined as follows: South (Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, West Virginia), West (Alaska, Arizona, California, Colorado, Hawaii, Idaho, New Mexico, Montana, Nevada, Oregon, Utah, Washington, Wyoming), Midwest (Indiana, Illinois, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, Wisconsin), and Northeast (Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont).

Table 2
Patients with at Least 1 Diagnosis in Each Diagnosis Category*

	Diagnosis Category	No. of Cases	Percent
HCT cohort (n = 411)	Aplastic anemia	213	52
	Leukemia	215	52
	Lymphoma	200	49
	Multiple myeloma	40	10
	Myelofibrosis	35	9
	Myelodysplastic syndrome	34	8
	Paroxysmal nocturnal hemoglobinuria	7	2
	Sickle cell disease	7	2
	Amyloidosis	5	1
	Familial erythrophagocytic lymphohistiocytosis	4	1
	Severe combined immunodeficiency disease	3	1
	Congenital thrombocytopenia	2	0
	Wiskott-Aldrich syndrome	1	0
FP subgroup (n = 29)	Aplastic anemia	19	66
	Lymphoma	16	55
	Leukemia	12	41
	Myelofibrosis	4	14
	Myelodysplastic syndrome	4	14
	Paroxysmal nocturnal hemoglobinuria	1	3
	Severe combined immunodeficiency disease	1	3
	Wiskott-Aldrich syndrome	1	3
	Multiple myeloma	0	0
	Sickle cell disease	0	0
	Amyloidosis	0	0
	Familial erythrophagocytic lymphohistiocytosis	0	0
	Congenital thrombocytopenia	0	0

Includes all diagnoses preceding HCT.

* Diagnosis category frequencies are not mutually exclusive from each other and will not add up to 100%. This means patients may have had 1 or more of the listed diagnoses in the table and would thus be counted more than once.

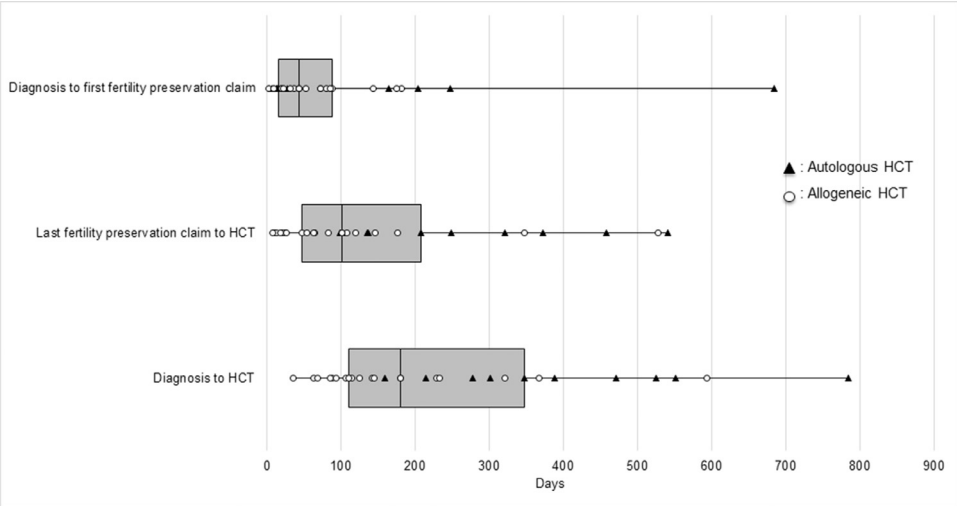

Figure 3. Days between intervals of interest including primary diagnosis to first FP claim, FP to HCT, and the complete interval from primary diagnosis to HCT.

American Society for Reproductive Medicine [20]. One of these patients had a biopsy of testis a year after FP counseling and a few weeks before HCT. The other 2 patients had cryopreservation of reproductive tissue oocytes, oocyte identification from follicular fluid, and follicle puncture for oocyte retrieval. Additionally, 1 of these 2 also had culture of oocyte(s)/embryo(s), less than 4 days.

Limitations

The FAIR Health, Inc. database is a valuable data source particularly due to its size, inclusion of multiple commercial payers, and nationwide breadth. Despite being the nation's largest collection of private medical claims, FAIR Health's database does not include all commercial payers. Additionally, the database does not include enrollment information; therefore, continuous enrollment could not be assessed or included as selection criteria, and as a result some claims may be missing. Furthermore, without expanding the scope of analysis beyond date of HCT, it is impossible to know what additional fertility procedures and treatments occurred after HCT, such as in vitro fertilization.

As with all administrative claims databases, data quality can be a concern. For example, our research identified a patient with claims for HCT on the same date in 2 different regions of the United States and patients with autologous and allogeneic HCT codes on the same date. Although theoretically possible, both of these scenarios are highly unlikely in the HCT population and could have been due to a documentation error on the claim. Furthermore, administrative data are limited in detail and do not necessarily portray the clinical or patient-level details required to draw conclusions from longitudinal analysis. Increasing the analysis window, ensuring continuous enrollment, linking claims data to another data source, and perhaps moving to a prospective design would improve the ability to make inferences supported by the data.

Relatedly, because this is a claims database, it is not possible to know with certainty how to interpret multiple diagnosis codes. Hence, in Table 2 our numbers add up to more than 411 patients, because our analysis captured all potentially relevant codes. There are myriad reasons why HCT patients could have more than 1 indication. For example, patients may have underlying conditions, such as myelodysplastic syndrome or paroxysmal nocturnal hemoglobinuria, that can transform into acute myeloid leukemia [21]. In such cases both diagnoses would be appropriately recorded. A person also could have multiple diagnoses if they have a history of lymphoma and then develop a therapy-related myeloid neoplasm. This could be acute myeloid leukemia, or it could be myelodysplastic syndrome and then acute myeloid leukemia [22]. An additional possibility is that a patient is assigned 1 code at an initial diagnosis, but after workup the diagnosis changes. For example, there is clinical suspicion for lymphoma, but a bone marrow biopsy demonstrates acute lymphoblastic leukemia. In this case the initial provider would document lymphoma as the first diagnosis but then change to acute lymphoblastic leukemia once the diagnosis is confirmed. Although this may obfuscate indications for transplant, the important finding of our study—that very few patients availed themselves of the opportunity for FP—remains unchanged.

Finally, the greatest limitation to using claims data for studying utilization of a traditionally noncovered service is that the population represented in claims is not generalizable enough to include those who are receiving the service despite lack of insurance coverage. The lack of generalizability of our study population is apparent when observing the small number of men (11/235, 4.7%) who had FP claims (Table 1), which may be attributed to lack of coverage and greater sperm cryopreservation and banking options available outside of a provider setting; this data cannot be captured in claims. Understanding this limitation is important; however, it does not preclude the value of examining the use of insurance to receive FP services given the importance of insurance as a mechanism to pay for healthcare.

Table 3
Primary Diagnosis of Patients with FP before HCT

Primary HCT Indication	No. of Cases	Percent
Lymphoma	10	34
Leukemia	9	31
Aplastic anemia	5	17
Myelodysplastic syndrome	2	7
Wiskott-Aldrich syndrome	1	3
Myelofibrosis	1	3
Severe combined immunodeficiency disease	1	3

DISCUSSION

Despite research showing that oncologists and HCT physicians are aware that infertility is a nearly universal effect of

HCT and is a significant concern to patients [23], we found that only 7.1% of HCT recipients of reproductive age had claims for FP services before their transplant. Our analysis showed that patients in the FP subgroup consisted of a higher proportion of younger women (Table 1). The high proportion of patients in the 2 youngest age groups suggests a relatively higher utilization of FP in the postpubescent, adolescent age group (includes ages 12 to 17 years), a group that was not investigated in this study.

The ability to track patients longitudinally proved valuable in understanding the clinical journey that patients experience from diagnosis to FP through HCT, which was the secondary aim of our study. One important finding from Figure 3 is that most patients who received FP services did so several months before transplant (median, 102 days). Additionally, autologous HCT patients generally had longer intervals between FP and HCT.

Secondary analysis of the FP subgroup also showed wide variation between the dates of the primary diagnosis and receipt of FP services (Figure 3) (range, 3 to 685 days). Because of the limitations of using dates of service associated with diagnoses, rather than actual date of diagnosis, this interval is likely underestimated. However, it speaks to variation in referral patterns, which could be improved through FP education materials and facilitated referrals. Patient and provider education materials around referral and treatment options are critical to ensure timely and appropriate referral, but currently these resources are limited [24,25].

To understand why the observed utilization of FP before HCT is so low in administrative claims data, future research should explore the use of FP services outside of insurance as well as the reasons HCT patients do not pursue FP. This study does not examine the referral practices of HCT physicians, but it may be an important next step to understand whether low uptake of these services is because of patient choice or other barriers, such as those related to socioeconomic or cultural factors. The financial coordinator model of transplant programs could be an ideal resource to assist patients with FP coverage issues before HCT.

FP insurance coverage mandates are 1 approach that could improve access for HCT patients [26]. Currently, Illinois, Maryland, Delaware, Connecticut, and Rhode Island have passed such legislation. Unfortunately, not every existing coverage mandate is inclusive of patients diagnosed with a nonmalignant diseases who are at risk for iatrogenic infertility; such is the case with legislation passed in Connecticut [27]. In our analysis we saw that 7 patients (24%) who had claims for FP services before HCT had primary diagnoses that were not cancers. Ongoing advocacy efforts should align with any diagnosis that could result in iatrogenic infertility [28] to provide access to FP uniformly across all patient populations.

In summary, although the American Society of Clinical Oncology and many other clinical and patient advocacy organizations consider FP services to be standard of care for patients at risk of iatrogenic infertility, our analysis showed that claims for FP services were uncommon among HCT patients between the ages of 18 and 40 years. This is the first study to assess FP in the HCT population using a multipayer administrative claims database. In addition to quantifying the utilization of FP in this population, the longitudinal link within the claims data facilitated the construction of patient-specific clinical journeys depicting FP before HCT. The findings presented here should inform future research efforts to identify and remove barriers facing HCT patients interested in FP.

ACKNOWLEDGMENTS

The authors thank Rachel Glissmann and Michelle SanCartier for review and Michelle Fendrich for assistance. Research for this article is based on healthcare charge data compiled and maintained by FAIR Health, Inc. The authors are solely responsible for the research and conclusions reflected in this article. FAIR Health, Inc. is not responsible for the conduct of the research or for any of the opinions expressed in this article.

Financial disclosure: The authors have nothing to disclose.

Conflict of interest statement: There are no conflicts of interest to report.

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