

## RESEARCH ARTICLE

# Characterizing the treatment gap in the United States among adult patients with a new diagnosis of epilepsy

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## Abstract

**Objective:** Epilepsy is largely a treatable condition with antiseizure medication (ASM). Recent national administrative claims data suggest one third of newly diagnosed adult epilepsy patients remain untreated 3 years after diagnosis. We aimed to quantify and characterize this treatment gap within a large US academic health system leveraging the electronic health record for enriched clinical detail.

**Methods:** This retrospective cohort study evaluated the proportion of adult patients in the health system from 2012 to 2020 who remained untreated 3 years after initial epilepsy diagnosis. To identify incident epilepsy, we applied validated administrative health data criteria of two encounters for epilepsy/seizures and/or convulsions, and we required no ASM prescription preceding the first encounter. Engagement with the health system at least 2 years before and at least 3 years after diagnosis was required. Among subjects who met administrative data diagnosis criteria, we manually reviewed medical records for a subset of 240 subjects to verify epilepsy diagnosis, confirm treatment status, and elucidate reason for non-treatment. These results were applied to estimate the proportion of the full cohort with untreated epilepsy.

**Results:** Of 831 patients who were automatically classified as having incident epilepsy by inclusion criteria, 80 (10%) remained untreated 3 years after incident epilepsy diagnosis. Manual chart review of incident epilepsy classification revealed only 33% (78/240) had true incident epilepsy. We found untreated patients were more frequently misclassified ( $p < .001$ ). Using corrected counts, we extrapolated to the full cohort (831) and estimated <1%–3% had true untreated epilepsy.

**Significance:** We found a substantially lower proportion of patients with newly diagnosed epilepsy remained untreated compared to previous estimates from administrative data analysis. Manual chart review revealed patients were frequently misclassified as having incident epilepsy, particularly patients who were not

Barbara M. Decker and Colin A. Ellis are co-first authors due to equal contribution to the article.

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treated with an ASM. Administrative data analyses utilizing only diagnosis codes may misclassify patients as having incident epilepsy.

#### KEYWORDS

epidemiology, epilepsy, health services research, treatment gap

## 1 | INTRODUCTION

Epilepsy is a potentially life-threatening disease that affects one in 26 people in the United States during their lifetime.<sup>1</sup> Epilepsy is largely treatable with antiseizure medication (ASM). Two thirds of patients achieve seizure freedom with medical treatment,<sup>2,3</sup> and antiseizure therapy has been associated with improved quality of life.<sup>4</sup> Nonetheless, delays in treatment of epilepsy are prevalent due to a range of factors, including heterogeneity of clinical presentations, variable access to specialists and diagnostic testing, disease-related social stigma, and the difficulties of navigating complex health care systems.<sup>5-7</sup>

The epilepsy treatment gap, or the proportion of people with active seizures who are not appropriately treated, has been most commonly associated with care in under-resourced countries.<sup>8</sup> Recent analyses using administrative claims data have suggested that many patients with an incident epilepsy diagnosis remain undertreated or untreated in the United States<sup>5,7</sup>; Kalilani et al.<sup>7</sup> found one third of adult patients with incident epilepsy in the United States remained untreated 3 years after diagnosis. Furthermore, there may be important consequences of inadequate treatment, such as increased risk of adverse medical events and higher health care utilization as compared to treated patients.<sup>7</sup>

Although administrative claims data are invaluable for population-level inferences regarding health care delivery, in such studies consideration of key clinical details and understanding of patient–physician decision-making remain limited. Specifically, we hypothesized that the treatment gap could be overestimated if some patients were misclassified as having untreated epilepsy, or if some patients were untreated for clinically appropriate reasons (e.g., rare focal aware seizures only). The risk of misclassification is particularly problematic when studying the treatment gap, because many rigorous claims-based definitions of epilepsy include ASM prescription,<sup>9-11</sup> which cannot be used as an inclusion criterion when the goal is to identify untreated individuals. To test our hypothesis, we applied the same incident epilepsy diagnosis criteria as the Kalilani et al.<sup>7</sup> study to patients in our health system, and then we performed chart reviews for manual validation, in which we identified the frequency and causes of

### Key Points

- Recent national administrative claims data estimate one third of newly diagnosed adult epilepsy patients remain untreated up to 3 years after diagnosis
- We aimed to verify this treatment gap in incident epilepsy using granular clinical detail from the electronic health record of a large US academic health care network
- We applied validated administrative claims criteria and required absence of an antiseizure medication prescription preceding the diagnosis to identify cases
- Our estimates showed untreated incident epilepsy was significantly lower than reported claims data, <1%–3%, within this academic health care network
- Significant discrepancies of the treatment gap may be attributed to the misclassification of patients as having true incident epilepsy using claims criteria

misclassification and calculated a revised estimate of the epilepsy treatment gap.

## 2 | MATERIALS AND METHODS

### 2.1 | Standard protocol approvals, registrations, and patient consents

The University of Pennsylvania Institutional Review Board approved this study, and subject consent was waived.

### 2.2 | Clinical context: University of Pennsylvania Health System

The University of Pennsylvania Health System is comprised of six acute care hospitals and hundreds of outpatient facilities, serving Pennsylvania and New Jersey. There were >6.5 million outpatient visits, 129 000 adult

inpatient admissions, and 337 000 emergency department visits reported within the 2021 fiscal year.<sup>12</sup> This health care network serves patients with a spectrum of socioeconomic and demographic backgrounds, living in a large metropolitan area as well as some rural settings.

### 2.3 | Study population identified by automated classification

To first identify study subjects using similar criteria to the Kalilani et al. study, we queried the health system electronic health record (EHR) from 2012 to 2020 using automated classification of incident epilepsy (i.e., by diagnosis code criteria). We applied a validated administrative claims data definition for epilepsy that requires two encounters (spaced 30 days to 2 years apart) with diagnoses of epilepsy/seizures (International Classification of Diseases [ICD]-9345, ICD-10G40), or one encounter with a diagnosis of epilepsy/seizures and one encounter with a diagnosis of convulsions (ICD-9780.3, ICD-10 R56). This definition of epilepsy, composed of two encounters with qualifying diagnoses within 2 years, has a reported positive predictive value of 89%.<sup>9</sup> Additionally, to identify incident epilepsy cases, we required the absence of ASM prescription in the 2 years preceding the first qualifying diagnosis. ASM prescriptions and dates of entry were abstracted from the EHR medication list throughout the study period. We considered all adult inpatient, outpatient, and emergency department (ED) encounters that included evaluation and management (E/M) coding with a qualifying diagnosis. We excluded patients who resided outside of Pennsylvania, New Jersey, or Delaware to reduce the risk of sampling patients with incomplete data capture (i.e., those who were treated incidentally within the health system but who likely received the bulk of their health care elsewhere). Similarly, we excluded patients with insufficient engagement with the health system over the study period; all patients were required to have at least one inpatient, outpatient, or ED encounter at least 2 years prior to their first qualifying diagnosis (baseline or washout period) and at least one inpatient, outpatient, or ED encounter at least 3 years following their second qualifying diagnosis (follow-up period to capture primary outcome). This baseline period to establish an incident epilepsy diagnosis matched the Kalilani et al. study and other prior administrative claims studies.<sup>7,13</sup>

### 2.4 | Outcomes and variables

The primary outcome in this study was whether patients were treated for epilepsy. Patients were considered

untreated if no ASM was initiated by 3 years after their first qualifying diagnosis encounter.

We queried patient demographics including age, sex, race, ethnicity, primary language spoken, and state of residence. Comorbidities were collected from the baseline period (2 years prior through the first qualifying diagnosis). Neurologic comorbidities included stroke, traumatic brain injury, dementia, brain tumor, migraine, syncope, and intellectual/developmental disability. Psychiatric comorbidities included psychotic disorder, anxiety, depression, psychogenic nonepileptic spells (PNES), and substance abuse (see Table S1 for definitions). Elixhauser comorbidities were queried from the EHR and defined via the R package “comorbidity.”<sup>14</sup> Diagnostic tests were collected from a patient's first qualifying diagnosis through 3 years of follow-up and included electroencephalogram (EEG), brain magnetic resonance imaging (MRI), and head computed tomography. We also considered the occurrence of neurology consultation and location of the qualifying encounters (inpatient vs. outpatient).

### 2.5 | Treatment status confirmation and diagnosis verification by chart review

Using manual chart review, we confirmed treatment status and defined treatment in relation to the study period (2 years prior to the qualifying diagnoses through 3 years subsequent to the qualifying diagnoses) using the following categories (Table 1): Untreated (no ASM throughout study period), Treated (first ASM started within study period), or Pretreated (found on manual chart review to have already been prescribed ASM prior to study period, although the ASM prescription was not automatically captured).

To verify the automated classification of patients as having incident epilepsy via application of diagnosis code-based definition, we manually reviewed the medical records of all patients classified as having untreated incident epilepsy and reviewed a randomly selected subset of patients classified as having treated incident epilepsy, using the R statistical software (v4.1.2; R Core Team, 2021) pseudorandom number generator to select charts for review. Charts were reviewed by one board-certified epileptologist (C.A.E.) and one neurology resident (C.V.K.-S.). Reviewers were informed of the dates of encounters with qualifying diagnoses. For each patient, reviewers applied a rubric to manually verify the diagnosis as one of the following five categories (see Table 1): Incident Epilepsy, Chronic Epilepsy, Resolved Epilepsy, Not Epilepsy, and Indeterminate. The category Not Epilepsy was coded when the patient had a confirmed alternate diagnosis to

explain the symptoms that led to the epilepsy diagnosis code; subcategories included PNES, provoked seizures only, a single unprovoked seizure without additional risk factors for epilepsy, and other diagnoses such as syncope and migraine. The category Indeterminate was coded when there was missing information, such as no clinical details in the note to explain the associated epilepsy diagnosis code, or when there was clinical ambiguity, such as unexplained altered mental status or unexplained loss of consciousness with no clear diagnosis and/or documented uncertainty about the diagnosis. As a sensitivity analysis, we performed a secondary analysis in which we assumed all patients with an Indeterminate diagnosis actually had epilepsy.

**TABLE 1** Classification system for manual chart review.

Category	Definition
1. Treatment status	
A. Untreated	No ASM throughout study period
B. Treated	First ASM started within the study period
C. Pretreated	Already prescribed ASM prior to study period (i.e., prior to washout period)
2. Epilepsy diagnosis	
A. Incident epilepsy	Onset within 2 years of first diagnosis code date
B. Chronic epilepsy	Onset >2 years before first diagnosis code date
C. Resolved epilepsy	Diagnosis code is being used to reflect a childhood/remote diagnosis
D. Not epilepsy	Nonepileptic events, provoked seizures only, single unprovoked seizure without additional risk factors, other
E. Indeterminate	Unable to determine whether the participant has epilepsy due to missing data or clinical ambiguity

Abbreviation: ASM, antiseizure medication.

**TABLE 2** Study population by automated classification.

Inclusion/exclusion criteria	<i>n</i>
1. Any qualifying diagnosis code, outpatient, inpatient, or ED	26 140
2. First qualifying diagnosis 2012–2020	19 235
3. >2 years health system care preceding first qualifying diagnosis code	9980
4. Second qualifying diagnosis 30 days to 2 years after first qualifying diagnosis	3796
5. >3 years health system care after second qualifying diagnosis	1776
6. No ASM prescriptions preceding first qualifying diagnosis	831

Abbreviations: ASM, antiseizure medication; ED, emergency department.

## 2.6 | Statistical analysis

Patient demographics, comorbidities, and relevant health care utilization are presented as categorical frequencies. Categorization as treated versus untreated and as incident epilepsy versus other is presented as categorical frequencies. Characteristics of automatic classification of treated versus untreated groups were compared by Fisher exact tests. Differences in manually verified diagnoses between treated versus untreated cohorts were tested with a chi-squared test and Fisher exact test. Confidence intervals around binomial proportions were calculated with the Jeffreys interval method.<sup>15</sup> Although we planned to analyze predictors of untreated incident epilepsy, there were too few untreated cases for meaningful analysis.

## 3 | RESULTS

### 3.1 | Study cohort by automated classification

From 154 457 encounters representing 26 140 unique patients with a qualifying diagnosis in our health system, 831 met criteria for incident epilepsy (Table 2). Of these 831 patients, 80 (10%) had no ASM prescription during the 3-year follow-up period. Characteristics of the cohort are shown in Table 3. Patients classified as untreated by automated classification were more likely to be female (Fisher exact test,  $p = .003$ ), more likely to be Black ( $p = .01$ ), and less likely to have an EEG or MRI (both  $p < .001$ ) compared to patients automatically classified as treated. Other variables in Table 3 did not differ between the two groups.

### 3.2 | Treatment status confirmation by chart review

To verify the automated classifications, we manually reviewed the charts of all 80 patients classified as untreated incident epilepsy, plus 160 (~20%) randomly selected patients classified as treated incident epilepsy. Overall,

**TABLE 3** Study cohort by automated classification.

Characteristic	Treated, <i>n</i> = 751	Untreated, <i>n</i> = 80	Total, <i>N</i> = 831
Age, mean (SD)	46.3 (18.4)	39.9 (16.2)	45.7 (18.3)
Female sex	434 (57.8%)	60 (75.0%)	494 (59.4%)
Race			
American Indian	4 (.5%)	0 (0%)	4 (.5%)
Asian	15 (2.0%)	2 (2.5%)	17 (2.0%)
Black	280 (37.3%)	42 (52.5%)	322 (38.7%)
White	421 (56.1%)	33 (41.2%)	454 (54.6%)
Other	19 (2.5%)	1 (1.2%)	20 (2.4%)
Unknown	12 (1.6%)	2 (2.5%)	14 (1.7%)
Ethnicity			
Hispanic/Latino	28 (3.7%)	3 (3.8%)	31 (3.7%)
Non-Hispanic/Latino	715 (95.2%)	77 (96.2%)	792 (95.3%)
Patient declined	8 (1.1%)	0 (0%)	8 (1.0%)
Primary language			
English	741 (98.7%)	80 (100%)	821 (98.8%)
Spanish	7 (.9%)	0 (0%)	7 (.8%)
French	1 (.1%)	0 (0%)	1 (.1%)
Russian	1 (.1%)	0 (0%)	1 (.1%)
Creole	1 (.1%)	0 (0%)	1 (.1%)
State			
Delaware	12 (1.6%)	0 (0%)	12 (1.4%)
New Jersey	55 (7.3%)	5 (6.2%)	60 (7.2%)
Pennsylvania	684 (91.1%)	75 (93.8%)	759 (91.4%)
Neurologic comorbidities			
Stroke	69 (9.2%)	2 (2.5%)	71 (8.5%)
Traumatic brain injury	15 (2.0%)	3 (3.8%)	18 (2.2%)
Dementia	16 (2.1%)	1 (1.2%)	17 (2.0%)
Brain tumor	30 (4.0%)	2 (2.5%)	32 (3.9%)
Migraine	60 (8.0%)	12 (15.0%)	72 (8.7%)
Syncope	40 (5.3%)	5 (6.2%)	45 (5.4%)
Intellectual/developmental disability	24 (3.2%)	5 (6.2%)	29 (3.5%)
Psychiatric comorbidities			
Psychotic disorder	11 (1.5%)	0 (0%)	11 (1.3%)
Anxiety	60 (8.0%)	11 (13.8%)	71 (8.5%)
Depression	70 (9.3%)	10 (12.5%)	80 (9.6%)
PNES	2 (.3%)	1 (1.2%)	3 (.4%)
Substance abuse	75 (10.0%)	11 (13.8%)	86 (10.3%)
Elixhauser comorbidity score, mean (SD)	2.19 (1.81)	2.38 (1.51)	2.20 (1.79)
EEG	452 (60.2%)	30 (37.5%)	482 (58.0%)
Brain MRI	444 (59.1%)	27 (33.8%)	471 (56.7%)
Brain CT	308 (41.0%)	19 (23.8%)	327 (39.4%)
Neurology consult	244 (32.5%)	23 (28.8%)	267 (32.1%)
Inpatient [vs. outpatient] first epilepsy diagnosis	100 (13.3%)	11 (13.8%)	111 (13.4%)
Inpatient [vs. outpatient] second epilepsy diagnosis	101 (13.4%)	13 (16.2%)	114 (13.7%)

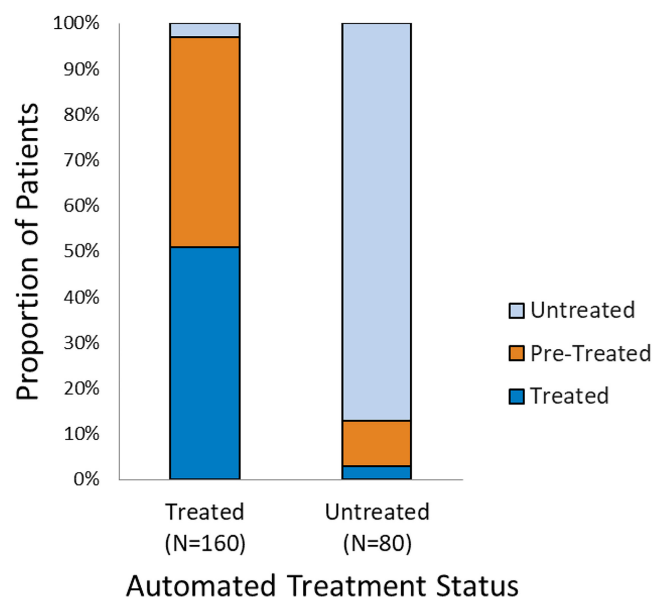
Abbreviations: CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging; PNES, psychogenic nonepileptic spells.



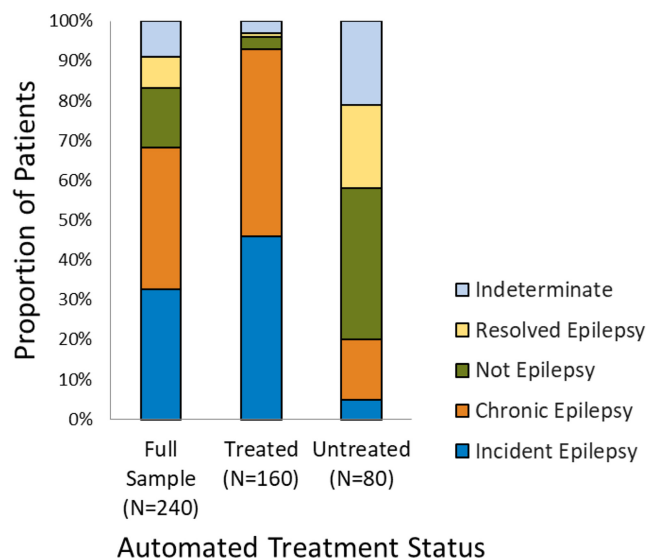
automated extraction of ASM treatment status (treated vs. untreated) was accurate in 224 of 240 cases (93%; Figure 1). The untreated classification was accurate in 70 of 80 (88%); misclassifications occurred when ASMs were prescribed by providers outside the health system. The treated classification was accurate in 156 of 160 (98%); four patients classified as treated were taking ASMs for indications other than epilepsy (e.g., topiramate for migraine or gabapentin for pain). Notably, in nearly half of the treated cases (74/156, 47%), ASM treatment was initiated prior to the study period (“Pretreated”), as these patients were found to have chronic rather than incident epilepsy. These misclassifications occurred when a patient with longstanding epilepsy, on chronic ASM treatment, initiated neurologic care in the health system, which thereby generated an unprecedented epilepsy diagnosis code.

### 3.3 | Diagnosis verification by chart review

Overall, the automated classification of Incident Epilepsy was accurate in 78 of 240 patients reviewed (positive predictive value for incident epilepsy of 33%). The other manually verified diagnoses were Chronic Epilepsy (87/240, 36%), Not Epilepsy (35/240, 15%), Resolved Epilepsy (19/240, 8%), and Indeterminate (21/240, 9%; Figure 2).



**FIGURE 1** Confirmation of treatment status by manual chart review. Charts were manually reviewed to confirm the treatment classification of the automated extraction algorithm. Manual classifications were defined as Untreated (no antiseizure medication [ASM] throughout study period), Treated (first ASM started within study period), or Pretreated (already prescribed ASM prior to study period).



**FIGURE 2** Verification of diagnosis by manual chart review. Charts were manually reviewed to confirm the epilepsy diagnosis classification of the automated extraction algorithm. Manual classifications were defined as Incident Epilepsy (onset within 2 years of first diagnosis code date), Chronic Epilepsy (onset more than 2 years before first diagnosis code date), Resolved Epilepsy (diagnosis code used to reflect a childhood/remote diagnosis), Not Epilepsy (nonepileptic events, provoked seizures only, single unprovoked seizure without additional risk factors, or other), and Indeterminate (unable to determine whether the participant has epilepsy due to missing data or clinical ambiguity).

Chronic epilepsy was misclassified as incident epilepsy by automated classification when a patient with longstanding epilepsy previously received care for other conditions within the health system and then newly sought care for epilepsy within the health system. The category of Not Epilepsy consisted of PNES (13/35, 37%), provoked seizures only (9/35, 26%), single unprovoked seizure without additional risk factors (8/35, 23%), and other nonepilepsy diagnoses (5/35, 14%) such as syncope, migraine, and cyclic vomiting syndrome. The Indeterminate category was due to missing information (13/21, 62%) and clinical ambiguity (8/21, 38%). There were no significant differences in sex or race between treatment categories assigned by manual classification (Fisher exact tests,  $p > .05$ ).

The distribution of manually verified diagnoses differed for patients automatically classified as treated versus untreated (Figure 2;  $\chi^2 [4] = 134.5, p < .0001$ ). Untreated patients were more commonly misclassified as having incident epilepsy than treated patients (76/80 [95%] vs. 86/160 [54%], Fisher exact test  $p < .001$ ). Among patients automatically classified as treated, Incident Epilepsy (74/160, 46%) and Chronic Epilepsy (75/160, 47%) were the most frequent manually verified diagnoses. Among patients automatically classified as untreated, the most frequent manually verified diagnoses were Not Epilepsy (30/80,

38%), Resolved Epilepsy (17/80, 21%), and Indeterminate (17/80, 21%). Only four of 80 patients (5%) who were automatically classified as untreated incident epilepsy actually had incident epilepsy after manual verification of diagnosis, and only three of 80 patients (4%) actually had untreated incident epilepsy after manual confirmation of treatment status (positive predictive value for untreated incident epilepsy of 4%), because one patient was misclassified as untreated but had an ASM prescription from an external provider.

Notably, among the three cases of true untreated incident epilepsy, manual chart review elucidated that all three patients had infrequent focal aware seizures only, and all three were evaluated by neurologists who recommended no treatment.

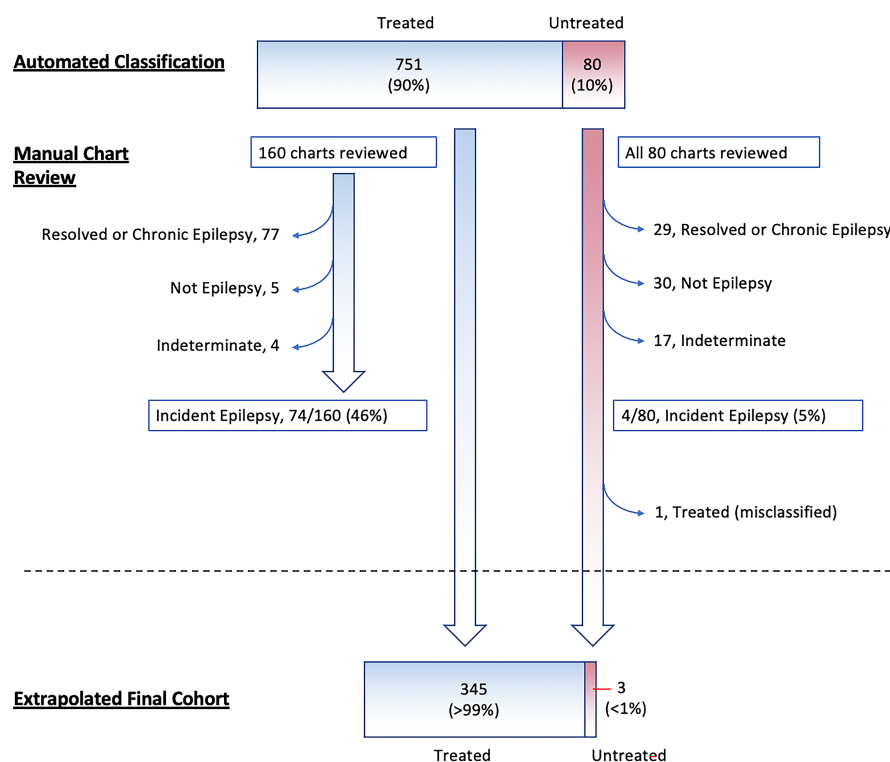
### 3.4 | Estimated proportion of untreated incident epilepsy

Given the low positive predictive value of automated incident epilepsy classification by diagnosis code definition as uncovered by our manual verification of incident epilepsy diagnosis, we sought to correct our initial estimate that 10% of patients with incident epilepsy remained untreated.

As discussed above, of the 80 patients automatically classified as untreated incident epilepsy, manual verification revealed only 4% had true incident epilepsy and were untreated. Of the patients automatically classified

as treated incident epilepsy, manual verification of 160 charts revealed that only 46% had true incident epilepsy (all had confirmed treatment with ASMs). Therefore, we extrapolate that 345 (46%) of the 751 patients initially classified as treated incident epilepsy truly had treated incident epilepsy, and three (4%) of the 80 patients initially classified as untreated epilepsy truly had untreated incident epilepsy (plus one additional patient was recategorized to treated incident epilepsy). Combining these estimates into a single final cohort, we approximate that only three of 349 (<1%, 95% confidence interval [CI] = 0%–2%) incident epilepsy cases were untreated (Figure 3).

As a sensitivity analysis to generate a proposed upper bound on the proportion of patients with incident epilepsy who remained untreated, we repeated our estimate assuming all patients with an Indeterminate diagnosis actually had epilepsy. Of the 21 Indeterminate patients, chart review confirmed the clinical episodes concerning for possible seizures preceded the study period for nine cases, and thus these patients would not qualify as “incident” epilepsy even if the episodes were seizures. Of the remaining 12 cases, eight were untreated and four were treated. Assuming these eight cases were all cases of true incident epilepsy, this would produce a final cohort of 11 untreated and 350 treated. This translates to an upper bound of 11 of 361 (3%, 95% CI = 1%–5%) of patients with incident epilepsy remaining untreated at 3 years.



**FIGURE 3** Estimated proportion of untreated incident epilepsy. After identifying the rate of misclassifications through manual chart reviews of a subset of the cohort, we extrapolated the rate of true untreated incident epilepsy in the full cohort.

## 4 | DISCUSSION

In this study characterizing the treatment gap for adults with incident epilepsy within an academic health system in the United States, automated classification of patients with incident epilepsy using the same criteria as previous claims-based studies found that 10% of patients were untreated 3 years after initial diagnosis. However, manual review of the EHR revealed that the actual rate of untreated incident epilepsy was much lower. We found that automated identification of incident epilepsy had an accuracy of only 33%, and that misclassifications were especially common in the putatively “untreated” group; the majority did not have epilepsy. After accounting for misclassifications, we estimate <1%–3% of true incident epilepsy cases in our study cohort were untreated.

Administrative data studies employ validated claims-based disease definitions to identify populations of interest. Although most administrative data definitions of epilepsy include ASMs in addition to epilepsy diagnosis code criteria,<sup>9–11</sup> studies that seek to measure treatment status (ASM) as an outcome have the limitation that ASM cannot be an inclusion criterion. This leads to risk of misclassification, which we found to be substantial in our cohort. In our manual chart review, the automated classification of incident epilepsy using diagnosis code criteria alone was largely inaccurate at 33%. We found that untreated patients were even more likely to be misclassified as having incident epilepsy when they did not. Frequently, patients carried diagnosis codes for epilepsy when they did not actually have active epilepsy or epilepsy at all; for example, a diagnosis code may be carried forward for a patient with remote childhood epilepsy or a chart may contain an epilepsy code for a patient who actually has PNES. Additional epilepsy-mimicking conditions, such as provoked seizures, a single unprovoked seizure, syncope, or migraine, often generated epilepsy codes as well. Within the untreated cohort, nonepileptic events and remote seizures (e.g., childhood epilepsy now resolved but still documented as a diagnosis) accounted for >50% of inaccurate epilepsy diagnoses.

Taken in sum, our data suggest that application of a definition of epilepsy that does not require an ASM may be less rigorous. Our verified diagnoses for the treated cohort demonstrated that 93% had epilepsy (Incident Epilepsy 46% plus Chronic Epilepsy 47%), yet only 20% of the untreated cohort actually had epilepsy (Incident Epilepsy 5% plus Chronic Epilepsy 15%). This is not particularly surprising, as a clinical diagnosis of epilepsy nearly by definition warrants the initiation of an ASM and therefore a diagnosis of epilepsy without initiation of ASM hints at clinician suspicion of, or perhaps confirmation of, a different diagnosis. Although not possible to assess

with administrative claims data, using EHR data allowed us a deeper dive into patient clinical details and physician judgment. Furthermore, female and Black patients in our cohort were disproportionately likely to receive automated classifications of untreated incident epilepsy, although the final classifications by manual chart review did not differ by sex or race, raising the possibility of systematic biases in automated classifications that could perpetuate health care disparities.

The range of our estimate, <1%–3% (upper limit from sensitivity analysis), for patients with incident epilepsy remaining untreated 3 years after diagnosis is substantially lower than the previously published estimate of 37% presented in the 2019 Kalilani et al. paper. This 2019 study estimated untreated incident epilepsy from the Truven Health MarketScan database, an administrative claims dataset of insurance billing codes that comprehensively captures health care utilized by an individual during their enrollment. Although our study used data from our EHR in patients who experienced regular interface with our health network, which may miss health care utilization from outside health systems as well as those less engaged with medical care, the EHR has the advantage of more robust clinical information due to breadth of documentation (e.g., free text from clinical visit notes, telephone calls, portal messages) that allows for incident epilepsy diagnosis verification. Thus, we believe the most likely explanation for the large discrepancy in estimations of untreated incident epilepsy is the misclassification of patients as having incident epilepsy in administrative claims dataset analysis. Because we found that misclassification disproportionately affects untreated patients, this creates a bias toward overestimating the untreated group. This proposal is supported by the sensitivity analysis presented in the Kalilani et al. paper, in which their most stringent case definition (achieved by increasing the minimum number of epilepsy encounters to four) yielded an estimate of 4% untreated incident epilepsy at 3 years, similar to our estimate. The proportion of untreated incident epilepsy patients may be lower at an academic center than across the general population, but this consideration alone is unlikely to account for the full magnitude of the discrepancy. We acknowledge that the comparison to prior national claims-based studies is imperfect because we cannot capture all health care utilization, due to patients accessing health care outside our system and analyzing only E/M codes. Nonetheless, the concerning finding of our study—which should also be problematic in a longitudinal administrative national claims dataset—is the large proportion of verified untreated patients who were misclassified as having incident epilepsy but were found on manual review not to have epilepsy (30/80, 38%).



Importantly, our findings should not be extrapolated to other care environments, such as low- or middle-income countries.

Despite the methodological concerns about automated case definition raised by our study, our findings are good news. Our most rigorous estimates and extrapolation of our health system data suggest there may be a very small treatment gap for patients with incident epilepsy within academic health systems in the United States. Moreover, for the three incident epilepsy cases reviewed that were untreated, all three patients had focal seizures with intact awareness and the choice was made not to treat. Therefore, it is plausible that the estimated <1%–3% of untreated incident epilepsy patients are often appropriately or purposefully not treated, rather than simply falling through the cracks of a complex health care system.

Although our diagnosis claim definition was grounded in a previously validated definition<sup>16</sup> and has been used for similar work,<sup>7</sup> the original validation performed by Reid et al. used a sample of outpatient visits to neurologists' practices in Canada. This definition may not perform as strongly in a different, broader population, in which epilepsy would be less prevalent and not all encounters are with neurologists. Although our dataset was not an administrative claims dataset, our findings should be considered in future research designs, as the choice of a case definition that includes ASM prescription may be preferable.

We recognize that our algorithm-based cohort will not capture every patient with incident epilepsy within our health system. In particular, the requirement of a 2-year “washout” period with no epilepsy diagnosis codes excludes people who were otherwise healthy, or did not access health care, prior to the onset of epilepsy. Prior studies have demonstrated the importance of a washout period for the identification of incident disease as well as the challenge of choosing the optimal washout period duration and timing.<sup>9,10</sup> Relaxing this threshold would capture more cases (increasing sensitivity) at the expense of many more false positives (decreasing specificity and positive predictive value) due to misclassifying as new onset what is actually chronic epilepsy. Our study demonstrates that misclassification may already be unacceptably high even with a 2-year washout period. Likewise, the 3-year follow-up period requires ongoing health care engagement and will exclude patients who received sparser care; this may potentially undercount untreated incident epilepsy. However, Kalilani et al. found the untreated cohort to have higher health care utilization. Moreover, this follow-up requirement is necessary to measure the relevant treatment outcome. These considerations for washout and follow-up apply

to both our study and to prior claims-based studies. For example, our requirement of 3 years of follow-up led to exclusion of about half of identified subjects; in the Kalilani et al. study, only 6.5% of the identified study cohort were still enrolled and assessed at 3 years of follow-up (personal communication, D. Friesen, UCB Pharma). It is possible that patients with less health care engagement are different than those with more health care engagement, including their likelihood of being treated for epilepsy, which could bias the estimated treatment gap. This limitation applies to all claims-based research, and to most retrospective research that relies on health outcomes documented through ongoing medical care. An additional limitation is that our study was conducted at a single academic center with a level 4 epilepsy center, which is not the only source of health care for residents within this geographic region. The proportion of patients with untreated incident epilepsy could be higher at other smaller hospitals, at hospitals without epilepsy center expertise, or in geographic locations in which access to care is more challenging, such as low- and middle-income countries. This study included adult patients; similar studies are needed for pediatric populations. Furthermore, the treatment gap can also encompass undertreated epilepsy. Although not within the scope of this analysis, future considerations to assess the impact of undertreated epilepsy should be considered.

## 5 | CONCLUSIONS

In conclusion, our study found that untreated incident epilepsy is uncommon within our health system—by our estimate, comprising only <1%–3% of patients with incident epilepsy. Moreover, these patients may be untreated due to thoughtful clinical consideration and/or patient choice. Our validation findings suggest administrative data analysis utilizing only diagnosis codes is likely overestimating the proportion untreated due to common misclassification of patients as having incident epilepsy. Further work could help clarify the prevalence of untreated incident epilepsy in other health care settings.

### AUTHOR CONTRIBUTIONS

**Barbara M. Decker:** Study concept/design; analysis/interpretation of data; drafting/revising manuscript for content. **Colin A. Ellis:** Study design; major role in acquisition of data; analysis/interpretation of data; drafting/revising manuscript for content. **Emily Schriver:** Study design; major role in acquisition of data; analysis/interpretation of data; drafting/revising manuscript

for content. **Kelly Fischbein:** Study design; interpretation of data; revising manuscript for content. **Debbie Smith:** Study design; interpretation of data; revising manuscript for content. **Jason T. Moyer:** Study design; interpretation of data; revising manuscript for content. **Catherine V. Kulick-Soper:** Major role in acquisition of data; revising manuscript for content. **Danielle Mowery:** Study design; analysis of data. **Brian Litt:** Study concept/design; interpretation of data; revising manuscript for content. **Chloe E. Hill:** Study design; analysis/interpretation of data; drafting/revising manuscript for content.

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## CONFLICT OF INTEREST STATEMENT

K.F., D.S., and J.T.M. are employees of UCB Pharma, Smyrna, Georgia, USA. None of the other authors has any conflict of interest to disclose.

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#### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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