Title
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Permalink
https://escholarship.org/uc/item/0q77q613

Journal
Epilepsia open, 3(2)

ISSN
2470-9239

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Publication Date
2018-06-01

DOI
10.1002/epi4.12112

Peer reviewed
Epilepsy as a dynamic disease: A Bayesian model for differentiating seizure risk from natural variability

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Epilepsia Open, 3(2):236–246, 2018
doi: 10.1002/epi4.12112

SUMMARY

Objective: A fundamental challenge in treating epilepsy is that changes in observed seizure frequencies do not necessarily reflect changes in underlying seizure risk. Rather, changes in seizure frequency may occur due to probabilistic variation around an underlying seizure risk state caused by normal fluctuations from natural history, leading to seizure unpredictability and potentially suboptimal medication adjustments in epilepsy management. However, no rigorous statistical approach exists to systematically distinguish expected changes in seizure frequency due to natural variability from changes in underlying seizure risk.

Methods: Using data from SeizureTracker.com, a patient-reported seizure diary tool containing over 1.2 million recorded seizures across 8 years, a novel epilepsy seizure risk assessment tool (EpiSAT) employing a Bayesian mixed-effects hidden Markov model for zero-inflated count data was developed to estimate changes in underlying seizure risk using patient-reported seizure diary and clinical measurement data. Accuracy for correctly assessing underlying seizure risk was evaluated through a simulation comparison. Implications for the natural history of tuberous sclerosis complex (TSC) were assessed using data from SeizureTracker.com.

Results: EpiSAT led to significant improvement in seizure risk assessment compared to traditional approaches relying solely on observed seizure frequencies. Applied to TSC, four underlying seizure risk states were identified. The expected duration of each state was <12 months, providing a data-driven estimate of the amount of time a person with TSC would be expected to remain at the same seizure risk level according to the natural course of epilepsy.

Significance: We propose a novel Bayesian statistical approach for evaluating seizure risk on an individual patient level using patient-reported seizure diaries, which allows for the incorporation of external clinical variables to assess impact on seizure risk. This tool may improve the ability to distinguish true changes in seizure risk from natural variations in seizure frequency in clinical practice. Incorporation of systematic statistical approaches into antiepileptic drug (AED) management may help improve understanding of seizure unpredictability as well as timing of treatment interventions for people with epilepsy.

KEY WORDS: Seizure risk, Bayesian inference, Epilepsy, Hidden Markov model, Mixed effects, Natural history, Seizure diary data, Tuberous sclerosis complex, Zero-inflated Poisson.
Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous disorder affecting approximately 1/5,000–10,000 live births. For patients with TSC, epilepsy is among the most common neurological manifestations, often developing by early infancy or childhood. Seizure unpredictability plays a large role in the burden of epilepsy for patients with TSC and other forms of epilepsy. Current monitoring and treatment decision-making in epilepsy is based on the observed number of seizures: increases in seizure frequency are interpreted as disease worsening, and typically lead to antiepileptic drug (AED) dose escalation or changes. However, monthly changes in seizure count may not necessarily reflect changes in underlying seizure risk but expected probabilistic variation around an unchanged seizure risk state (Figure 1). For example, 18.7% of TSC patients initially identified as drug-resistant go on to achieve epilepsy remission for at least 1 year, suggesting that defining drug-resistance based on observed seizure counts may not accurately reflect the underlying probability of future seizures.

Seizure unpredictability plays a large role in the burden of epilepsy for patients with TSC and other forms of epilepsy. Current monitoring and treatment decision-making in epilepsy is based on the observed number of seizures: increases in seizure frequency are interpreted as disease worsening, and typically lead to antiepileptic drug (AED) dose escalation or changes. However, monthly changes in seizure count may not necessarily reflect changes in underlying seizure risk but expected probabilistic variation around an unchanged seizure risk state (Figure 1). For example, 18.7% of TSC patients initially identified as drug-resistant go on to achieve epilepsy remission for at least 1 year, suggesting that defining drug-resistance based on observed seizure counts may not accurately reflect the underlying probability of future seizures.

There is currently no systematic established approach for estimating a patient’s underlying seizure risk while teasing out variations in seizure frequency due to natural variability. However, the pattern of seizure remission and recurrence in epilepsy suggests that parameter-driven statistical models, compared to observation-driven models, may be better at separating true improvements in seizure burden from probabilistic deviations. Additionally, seizures are thought to occur when the level of ictogenicity surpasses the seizure threshold. These considerations support a concept of epilepsy natural history based on changes in underlying seizure risk rather than observed seizure frequencies.

In this paper, we propose a novel Bayesian statistical epilepsy seizure risk assessment tool (EpiSAT) for distinguishing expected changes in seizure frequency due to natural variability from changes in underlying seizure risk. This allows for a concept of “seizure control” based on the stability of the underlying seizure risk state rather than observed seizure counts.

To capture the underlying seizure risk state, we propose a hierarchical model for seizure predisposition based on latent (unobserved) variables. Observed seizures are modeled through a hidden Markov model (HMM) as the observed manifestation of the unobserved seizure risk state. HMMs have been successfully utilized to model unobserved states in several applications, including bronchiolitis obliterans, antibiotic resistance, multiple sclerosis, comparative genomics hybridization cancer data, and functional magnetic resonance imaging (fMRI). Utility for modeling seizure counts has also shown promise. Empirical evidence that seizure durations and interseizure intervals cluster around distinct modes is consistent with a generative model of seizure occurrence in which seizures emit

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**Key Points**

- No rigorous statistical method exists to distinguish expected changes in seizure frequency due to natural variability from changes in underlying seizure risk.
- This study develops a new statistical method for estimating underlying seizure risk from patient-reported seizure diary data on the individual patient level.
- Simulation studies indicate that quantitative model-based approaches for seizure risk assessment lead to different and potentially more accurate assessment of seizure risk.
- This statistical method may be beneficial to both clinical practice and clinical trial interpretation.

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**Abbreviations**

- DIC: deviance information criterion
- ILAE: International League Against Epilepsy
- MCMC: Markov Chain Monte Carlo
- TSC: tuberous sclerosis complex
- ZIP: zero-inflated Poisson

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**Figure 1.** Example of the issue of probabilistic variation in interpreting seizure count data: Monthly seizure diary from a patient with TSC from SeizureTracker.com. In month 6, the patient reported a decrease from 6 (red circle) to 5 (red cross) monthly seizures. However, the standard deviation of monthly seizures was 5.1. Therefore, the decrease from 6 to 5 seizures falls within an expected probabilistic deviation, suggesting it may not be representative of a true improvement in the risk of another seizure. Similarly, the increase from 6 to 8 seizures in month 50, shown in blue, also falls within an expected probabilistic deviation, underscoring the importance of distinguishing between probabilistic variation and true changes in seizure risk.
from an underlying seizure risk state with a given statistical distribution. From a statistical point of view, HMMs are also better suited for modeling long-term dependence than finite-order Markov chains when the length of relevant history affecting the current seizure risk state is unbounded.\textsuperscript{13} This consideration is particularly relevant given the complexity of seizure count data, in which multiple mechanisms may affect seizure risk,\textsuperscript{12} and the ability to account for error in recorded patient logs.

However, there are several aspects lacking in current HMM models for seizure counts. Existing models do not allow for inference on the unobserved seizure predisposition state on the individual patient level, due to methodological issues involving the increase in parameters involved in patient-level estimation. Several important aspects of seizure count data, such as zero-inflation (prolonged periods where zero seizures are observed), are furthermore not accounted for. Our proposed Bayesian statistical approach addresses these considerations. We propose a new Bayesian mixed-effects hidden Markov model for zero-inflated count data as an epilepsy seizure assessment tool (EpiSAT), which allows for systematic estimation of underlying seizure risk states at the individual patient level, while accounting for the influence of clinical characteristics on transitions between states. A simulation study is performed to evaluate accuracy for seizure risk assessment. Using seizure diaries from TSC patients collected by SeizureTracker.com, a patient-reported seizure diary tool containing over 1.2 million recorded seizures across 8 years, we demonstrate the clinical utility of an approach which assesses worsening or improvements in individual seizure risk rather than seizure frequencies.

**Methods**

**Patients**

Four hundred sixty-four patients with TSC recorded seizure and clinical data on SeizureTracker.com between December 1, 2007, and February 25, 2016. Records with invalid entry dates, dates of birth, or nonpositive seizure durations were excluded. To increase accuracy of longitudinal estimates, patients with <365 days between the first and last seizure entries were excluded. A full description of data cleaning is in Appendix S1. A total of 44,697 seizures from 105 patients with TSC were included, spanning seizure diary entries over a median of 927 days (range 365–3,003 days). Additional demographics are in Table 1.

**Data preprocessing**

Seizure duration was set to zero on days where no seizures were recorded. Three main seizure categories were considered (original SeizureTracker.com terminology in parentheses when different from revised 2017 terminology\textsuperscript{14}): (1) focal aware (previously “aura” or “simple partial”), focal impaired awareness (previously “complex partial”), focal emotional (previously “gelastic”); (2) atonic, clonic, myoclonic, myoclonic cluster, focal-to-bilateral tonic–clonic (previously “secondarily generalized”), tonic–
tonic–clonic, unknown onset infantile spasms (previously “infantile spasms”); and (3) typical and atypical absence. Morning (6 a.m.–12 p.m.), evening (12 p.m.–11 p.m.), or nocturnal (11 p.m.–6 a.m.) seizure start times were considered, due to electrocorticographic evidence of circadian seizure regulation. Total monthly seizure duration was also considered. Overall, the following covariates were included: sex; age; number of seizures per category; number of morning, evening, or nocturnal seizures; and total monthly duration of seizure.

Research on focal seizures has suggested that seizure durations cluster around distinct modes within patients, implying that seizure duration follows reproducible patterns. Random forests is an approach well-suited for imputing missing data due to nonreliance on distributional assumptions and accommodation of nonlinear relationships. For days on which ≥1 seizure was observed, if the duration of seizure was not reported, missing values were imputed using random forests. Number of seizures of each category and the number of morning, evening, or nocturnal seizures were similarly imputed (Appendix S2).

Proposed Bayesian mixed-effects hidden Markov model for zero-inflated counts

Herein we briefly describe the concepts behind our proposed statistical model, referred to as EpiSAT. Figure S1 provides a schematic overview. Appendix S3 provides a complete mathematical description.

We propose that a patient’s seizure frequency at any given time is the observed manifestation of a time-varying hidden (unobserved) seizure risk state. Our proposition is based on the theory that epilepsy stems from a multifactorial basis involving seizure threshold, epileptogenic abnormalities, and precipitating factors. Seizure threshold is the propensity for a seizure to occur and likely has a genetic basis, but may vary over time due to pathological, physiological, or pharmacological conditions. Epileptogenic abnormalities may be time-invariant, including genetic mutations or structural lesions; or time-varying, such as electrolyte status or lesion progression. Finally, precipitating factors determine when seizures occur and include internal and external factors, such as emotional or environmental stressors. To mathematically model the concept that seizures occur as the observed manifestation of the unknown seizure risk state, we impose an emission distribution on observed seizure counts; that is, conditional on the patient’s current underlying seizure risk state, seizures occur according to some probability distribution. We model zero seizures as an observed manifestation of a low seizure risk state rather than a separate no-risk state, as people with epilepsy are presumed to always have at least some probability of having a seizure. As the true underlying conditional probability distribution is unknown, our specification of emission distribution depends on several considerations: (1) seizure count data are empirically overdispersed relative to that expected under a generic Poisson process, with the variance exceeding the mean; and (2) seizure occurrence patterns exhibit dependence over time. To account for these considerations, we employ a zero-inflated Poisson (ZIP) process for the seizure emission distribution. Seizure count data are often zero-inflated, that is, patients often exhibit prolonged periods during which no seizures are observed, producing a larger number of zeros than expected under a simple Poisson process. The ZIP distribution models these excess zeros. An important note is that utilizing a ZIP process as the emission distribution does not imply that seizure counts follow a zero-inflated Poisson marginal distribution. Rather, the convolution of multiple zero-inflated Poisson conditional probability distributions is equivalent to a mixture of zero-inflated Poisson distributions, allowing for flexibility in accounting for overdispersion.

To permit our model to capture temporal dependencies between seizures, we model temporal dependency between unobserved seizure risk states using a hidden Markov model. This is based on our hypothesis that temporal dependence between seizure frequencies results from dependence in the underlying three basic factors producing epilepsy. Although studies have investigated the duration of temporal dependency between seizures, with estimates ranging from 30 min to 40 days, the temporal dependency structure between unobserved underlying seizure risk states is unclear. There are likely to be multiple mechanisms with different lag lengths underlying the true temporal dependency between seizure risk states. A first-order HMM provides a useful approximation, and it is straightforward to derive extensions of the model to permit higher order processes. The 4th-order HMM assumes that, given the seizure risk history in the most recent k time epochs, the current seizure risk state is independent of all seizure risk states prior to those k time epochs. This does not imply that the current seizure risk state is independent of all history prior to the preceding k time epochs, but conditionally independent given the preceding k epochs.

Finally we allow external clinical measurement data to affect the probability that a patient will worsen/improve to a higher/lower seizure risk state. It is natural to hypothesize that clinical factors, such as age, electrolyte status, or cortisol level at the present time point, affect the probability of worsening/improving in seizure risk at the next time point, and are of particular interest given the advent of wearable biosensors for collecting physiologic measurements. Seizure activity may also modify functional brain configurations, differentially increasing the risk for future seizures for different seizure types. We model the effect of clinical measurements on future seizure risk by allowing the transition probabilities of the hidden Markov process to follow a multinomial logit distribution.

Derivations of full conditional distributions and Markov Chain Monte Carlo (MCMC) implementation in Appendix S4. Code was written in R version 3.1.3 (R Core Team, Vienna, Austria).
Simulation study
To validate our model, we tested our algorithm on simulated data for N = 100 patients. Validation on simulated data is standard in statistical methodology research to assess accuracy of new methods under known conditions. Model performance was assessed through the error rate and projected medication impact, as detailed below. As the true generative process for seizures is unknown, data were simulated for various levels of zero-inflation, overdispersion, and seizure emission rates. Seizure counts were generated from underlying seizure risk assuming that our model’s generative seizure process was misspecified according to a negative-binomial process different from the generating distribution assumed by the model. Simulation study details are in Appendix S5.

To provide practical context for incorporating a systematic statistical approach for seizure risk estimation into clinical practice, a quantitative comparison to current clinical practice is needed. However, literature review failed to yield any established quantitative approach employed in clinical practice. Therefore, we compare our model’s performance to two quantitative approaches, referred to as QUANT-GROUP and QUANT-PATIENT, which assess seizure risk based solely on the observed number of seizures. QUANT-GROUP is an algorithm analogous to a clinician who considers all of his/her other patients’ seizure count behaviors when making risk assessments for a given patient. QUANT-PATIENT is an algorithm analogous to a clinician who considers each patient’s seizure pattern as unique to them, and therefore only considers the risk state based on the history of that specific patient. To allow for fair comparison, thresholding for QUANT-GROUP and QUANT-PATIENT was chosen by thresholding into quantiles based on the true number of underlying risk states. Table 2 summarizes the clinical simulation approaches.

Accuracy of EpiSAT, QUANT-GROUP, and QUANT-PATIENT was compared based on (1) error rate, calculated as the proportion of incorrectly identified seizure risk states, and (2) projected medication impact, calculated as the number of medication adjustments that would be made under each approach, relative to the optimal number of medication adjustments if the true seizure risk state were known. Optimal timing of medication adjustments was defined to correspond to true increases/decreases in seizure risk. Similarly, timing of medication adjustments made in practice was defined as occurring every time EpiSAT, QUANT-GROUP, or QUANT-PATIENT detected an increase/decrease in seizure risk.

Application to tuberous sclerosis complex
The proposed approach was applied to seizure diaries from patients with TSC from SeizureTracker.com. Seizure risk states were estimated and the expected duration of each risk state (mean sojourn time) computed as the mean number of months that the Markov chain remained in each given state. The number of states was selected based on minimization of the deviance information criterion. Hyperparameters, MCMC settings, and convergence diagnostics were as in Appendix S6.

Results

Simulation study
We found that a model explicitly including hidden states into seizure risk assessment led to significant differences when evaluating which changes in seizure frequency reflected true changes in underlying seizure risk versus natural variability. Our EpiSAT model consistently estimated seizure risk with greater accuracy than approaches that relied solely on observed seizure frequencies (QUANT-GROUP and QUANT-PATIENT), even in simulation scenarios intentionally generated not to correspond to the assumed model (Figure 2). For all tested approaches, error was lower in simulation scenarios involving fewer months with zero seizures (ie, less zero inflation or $p = 0.001$) or patients with higher seizure emission rates (ie, $\lambda = 120,100$). An example seizure diary, as well as the estimated underlying seizure risk states using the three risk-evaluation approaches, is shown in Figure 3. In comparison to our model-based approach, approaches relying only on observed seizure frequencies had more false positives and false negatives in identifying changes in underlying risk (Figure 3C,D). These findings indicate that explicit statistical modeling of underlying seizure risk results in different clinical conclusions, compared to non–model-based approaches where hidden states are not considered.

As an example, we illustrate the potential impact of incorporating a systematic approach to seizure risk identification into clinical AED management. Figure S2 shows the percentage reduction in unnecessary medication adjustments projected in a scenario where a medication adjustment is made every time a true change in underlying seizure risk is

| Table 2. Clinical practice simulation approaches for evaluating seizure risk |
|-----------------------------------------------|
| **Scenario** | **Method** |
| QUANT-GROUP | Provider compares each individual patient’s seizure rate to an overall rate stratification drawn from the population (patient is compared to other patients in the provider’s practice) Estimate seizure risk state based on quantiles of seizure counts for all patients |
| QUANT-PATIENT | Provider compares each individual patient’s seizure rate to only that patient’s own seizure history (patient is compared only to him/herself) Estimate seizure risk state based on individual patient quantiles of seizure counts |
detected. As shown, our approach consistently resulted in fewer unnecessary medication adjustments compared to both QUANT-GROUP and QUANT-PATIENT, an effect greater in seizure patterns with less overdispersion.

Finally, we explored the effect of seizure diary unreliability on our method’s performance. To do so, we evaluated our model’s accuracy under situations where patients fail to report a certain percentage $X$ of their seizures. Figure 4 shows the effect of an increasing percentage $X$ of missing seizures on our model’s performance. As expected, larger proportions of unreported seizures led to decreased accuracy of underlying seizure risk evaluation.

**Application to tuberous sclerosis complex**

EpiSAT was applied to seizure diary data recorded by 105 patients with TSC from SeizureTracker.com. Figure S3 in Appendix S7 shows the estimated underlying seizure risk based on the seizure diary of a randomly selected patient with TSC, as well as the patient’s estimated probabilities of worsening/improving to a higher/lower seizure risk state during the first month of seizure diary recordings. Four underlying seizure states were identified in the TSC sample: a low seizure risk state averaging one seizure every 1.77 months, a low-medium seizure risk state averaging 5.03 seizures per month, a high-medium seizure risk state averaging 20.69 seizures per month, and a high seizure risk state averaging 78.09 seizures per month (Table S1).

Finally, we explored the expected duration of each identified underlying seizure risk state in our TSC patient sample, which is the expected amount of time that a patient with TSC could be expected to remain in each state before “exiting” that state. The expected duration of each underlying seizure risk state is of particular interest, since the 2009 ILAE Commission provided a practical definition of seizure freedom based on the minimum of three times the longest pre-intervention interseizure interval or 12 months, whichever is longer.36 If the expected duration of the low seizure risk state based on natural history were known for each seizure etiology, this would be useful in determining how long a clinician should reliably wait for the patient to stay in the low seizure risk state before assessing the patient to be reasonably seizure-free. In Markov processes such as the model proposed here, the “mean sojourn time” is an easily estimated quantity that yields the expected duration of each underlying seizure risk state. The mean sojourn time was <12 months for all identified seizure risk states, with a slightly longer mean (median) sojourn time of 8.16 (3) months for the low seizure risk state (Figure 5). The duration of the low seizure risk state was <12 months in 77% of cases (Figure 5A). As such, a 12-month seizure-free period may be hypothesized to be a reasonable indicator of a stable low seizure risk state for this patient population.

**Discussion**

In this article, we aim at introducing a rigorous statistical approach for estimating underlying seizure risk into clinical practice. We have developed a new epilepsy seizure assessment tool (EpiSAT) employing a Bayesian mixed-effects hidden Markov model for zero-inflated count data, which provides a way to differentiate changes in seizure risk from natural variability, while accounting for crucial aspects of seizure diary data, such as system memory, zero-inflation, and other clinical measurements that may be obtained from electronic health records (EHRs) or biosensors. Using simulation studies, we statistically validate the proposed new approach, and show that this method accurately distinguishes true changes in underlying seizure risk state from natural variations under model misspecification. Although further trials are needed to evaluate this method, our simulation studies suggest that use of EpiSAT in clinical practice leads to different assessment of seizure risk than when hidden states are not taken into account. Applied to seizure diary data collected by SeizureTracker.com from 105 patients with TSC, we found evidence of four underlying seizure risk states. The expected duration of each seizure risk state was <12 months for each state, providing novel data-based evidence supporting the current International League Against Epilepsy (ILAE) guideline of 12 months as a temporal marker for seizure freedom in patients with TSC.

While a mathematical model to systematically estimate underlying seizure risk has not been provided previously, our study shows that incorporation of rigorous statistical
approaches, such as latent variable models, into seizure risk evaluation leads to different conclusions about a patient’s seizure risk level than approaches based only on observed seizures. The potential for more accurate seizure risk assessment suggests that hidden Markov models are a potentially valuable systematic approach to thinking about seizure occurrence. Higher accuracy of EpiSAT may result from several factors not currently considered in day-to-day epilepsy management, including (1) inclusion of clinical measurement data in predicting the next seizure risk state, (2) explicit modeling of zero-inflation, and (3) a Bayesian inferential framework to provide more accurate estimation due to borrowing of information across time points as well as patients.

Because physicians generally utilize clinical judgment rather than a systematic quantitative approach to determine whether changes in seizure count are due to natural variability or true changes in underlying seizure risk, applications of our model to physician trial data are needed to evaluate whether the simulation results here extend to actual clinical practice. Given that accuracy of new statistical models can be assessed only when the true underlying seizure risk state is known, comparison to current clinical practice was possible only through simulations and an operational definition of clinical practice. Actual clinical decision-making is not systematic, and therefore it is likely to result in greater variance than the simulated constructs considered here.

Figure 3.
Validation study using simulated data: Seizure frequencies from a sample simulated seizure diary (A), along with the estimated underlying seizure risk states using EpiSAT (B) are shown. In comparison, approaches that estimated seizure risk relying only on observed seizure frequencies demonstrated significantly poorer performance in correctly identifying changes in underlying seizure risk (C–D). Red = true underlying seizure risk state; black = estimated underlying seizure risk state. $\lambda = (1, 10, 50); p = 0.1; \phi = 0.2$. 

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As shown in our work, improved identification of seizure freedom in patients with epilepsy has important clinical consequences for improving understanding of the natural history of epilepsy. The current ILAE definition of seizure freedom utilizes a 12-month marker to identify patients as seizure-free (or three times the longest seizure-free interval). An important attribute of hidden Markov models is that they provide a straightforward method to estimate the expected amount of time that a patient will remain in a low seizure risk state. In our study, the expected sojourn time for the low seizure risk state in patients with TSC was 8.16 months, with a 77% probability that a low-seizure risk state would last for <12 months. Whereas the ILAE definition of seizure freedom was initially based on clinical consensus, our work offers preliminary data-driven support for this recommendation for the group in this investigation. In other words, if a patient with TSC remains seizure-free for at least 12 months, he/she would have exceeded the expected sojourn time of a low-risk state, suggesting high likelihood that he/she is seizure-free. Applications of our model to intracranial electrographic data, as well as to seizure diaries from other populations including patients with low seizure rates or other epilepsy etiologies, are straightforward and may illuminate additional understanding of natural history.

Usage of Seizure Tracker data in the development and assessment of EpiSAT allows for model testing based on one of the largest existing databases of patient-reported seizure events in the world. Studies comparing patient-reported events to electrographic seizures suggest that patient-reported seizure diaries may over-/underestimate the number of seizures depending on patient recognition of seizures, miscounting, or lack of recording. Although online and mobile access to Seizure Tracker mitigates the number of unrecorded events, patients may still be more (less) likely to record events during periods of worsened (improved) seizure burden. Application to patient-reported seizure diary data has its advantages and disadvantages. Use of seizure diary data allows for large-sample conclusions not possible through electrographic data, whereas electrographic data allow for smaller-scale verification of preliminary results discovered through seizure diary data. Therefore, application of our model to electrographically verified seizure count data is needed to confirm results of this work. However, outpatient clinic visits, as well as nearly all clinical trials, currently depend on patient-reported seizure diaries. Seizure clusters, which are broadly defined as “longer-than-normal” interseizure intervals according to various definitions, may be handled by inputting each seizure cluster as an individual seizure rather than multiple seizures. Physician verification of patient-reported data is needed to verify conclusions regarding mean sojourn time. Additional clinical and seizure covariates may also be useful to consider, such as medication levels and laboratory values, and are likely to improve predictive accuracy. Daily seizure count applications may also be of interest for inpatient interventions.

This study shows that a new view of seizure burden, based not on observed seizure counts but on statistical estimation of underlying seizure risk, is not only statistically more rigorous but may lead to decreased misidentification of normal fluctuations in natural history as reflective of changing seizure burden. Based on simulation studies, preliminary evidence suggests that incorporation of such statistical approaches into clinical practice may decrease...
unnecessary medication dose changes while attempting to achieve seizure control. The promising results of this work suggest that EpiSAT provides a potentially valuable approach to clinical evaluation of seizure occurrence. Future investigations may examine whether incorporating such a tool into clinical trial data may result in decreased adverse event rates without altering seizure control rates. If so, incorporation of systematic estimation of underlying seizure risk into routine clinical management may allow for improved treatment of people with epilepsy.

**Acknowledgments**

The authors would like to thank Dr. William H. Theodore and Dr. Gary W. Mathern for providing valuable insights to this work. Funding/support for this research was provided by (1) the National Library of Medicine Training Fellowship in Biomedical Informatics, Gulf Coast Consortia for Quantitative Biomedical Sciences (Grant #2T15-LM007093-21) (SC); (2) the National Institutes of Health (Grant #5T32-CA096529-07) (SC); the National Institutes of Neurological Disorders and Stroke, Intramural Research Division (DMG); (3) NIH-NINDS K23 Grant NS044936 (JMS); and (4) The Leff Family Foundation (JMS). Use of the data was facilitated by the International Seizure Diary Consortium (https://sites.google.com/site/isdchome/).

**Disclosure of Conflicts of Interest**

Robert Moss is the cofounder/owner of Seizure Tracker and has received personal fees from Cyberonics, UCB, and Courtagen, and grants from the Tuberous Sclerosis Alliance. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.
Appendix S1. Data cleaning of Seizure Tracker data.
Appendix S2. Random forests imputation.
Appendix S3. Bayesian mixed-effects hidden Markov model for zero-inflated count data.
Appendix S4. MCMC algorithm.

Appendix S5. Validation study.
Appendix S6. Hyperparameter settings.
Appendix S7. Case study example: seizure diary data on patient with TSC.