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SUPPLEMENT ARTICLE

Epilepsia®

# Precision Medicine: Academic dreaming or clinical reality?

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**Abstract**

Precision medicine can be distilled into a concept of accounting for an individual's unique collection of clinical, physiologic, genetic, and sociodemographic characteristics to provide patient-level predictions of disease course and response to therapy. Abundant evidence now allows us to determine how an average person with epilepsy will respond to specific medical and surgical treatments. This is useful, but not readily applicable to an individual patient. This has brought into sharp focus the desire for a more individualized approach through which we counsel people based on individual characteristics, as opposed to population-level data. We are now accruing data at unprecedented rates, allowing us to convert this ideal into reality. In addition, we have access to growing volumes of administrative and electronic health records data, biometric, imaging, genetics data, microbiome, and other "omics" data, thus paving the way toward phenome-wide association studies and "the epidemiology of one." Despite this, there are many challenges ahead. The collating, integrating, and storing sensitive multimodal data for advanced analytics remains difficult as patient consent and data security issues increase in complexity. Agreement on many aspects of epilepsy remains imperfect, rendering models sensitive to misclassification due to a lack of "ground truth." Even with existing data, advanced analytics models are prone to overfitting and often failure to generalize externally. Finally, uptake by clinicians is often hindered by opaque, "black box" algorithms. Systematic approaches to data collection and model generation, and an emphasis on education to promote uptake and knowledge translation, are required to propel epilepsy-based precision medicine from the realm of the theoretical into routine clinical practice.

**KEYWORDS**

big data, epilepsy, machine learning, personalized medicine, precision medicine

## 1 | A TYPICAL CLINICAL CASE

Epileptologists at a specialized center face the following clinical scenario: A 30-year-old right-handed man with drug-resistant epilepsy has a 12-year history of weekly focal impaired awareness hyperkinetic seizures. He also has focal to bilateral tonic-clonic seizures occurring twice per year. He has failed to respond to adequate doses of carbamazepine, clobazam, and lamotrigine. The patient also has Attention-Deficit/Hyperactivity Disorder (ADHD) and depression with suicidal ideation, requiring treatment with antidepressants and hospitalization. His brother and maternal uncle also had epilepsy, not further specified. Relevant investigations include a normal structural magnetic resonance imaging (MRI), interictal electroencephalography (EEG)

demonstrating bifrontal spikes, and video-EEG monitoring demonstrating seizures originating broadly in the right frontal region. Functional imaging including single-photon emission computerized tomography (SPECT) and positron emission tomography (PET) scanning is noncontributory, and voxel-based morphometry MRI shows a relative decrease in white matter in the mesial prefrontal regions. Neuropsychological testing reveals mild to moderate deficits in executive function. Intracranial EEG recordings show bifrontal seizure onset with higher amplitude of ictal discharges on the right, but no regional or focal onset can be identified. This large amount of complex data is presented at the multidisciplinary case conference for discussion, aiming to arrive at a management consensus that can lead to informed decision-making by the patient and his family.

As this case illustrates, although we glean much information from currently available clinical and laboratory investigations, the findings often do not lead to an accurate or precise localization of the epileptogenic zone, or to the identification of a surgical target. Not only are the tools imprecise, but our ability to integrate all the data is limited.

That we need better and more precise therapies for patients with epilepsy is undeniable. Consider the proportion of patients whose seizures are controlled with medications. This has remained unchanged at about 60% for decades, notwithstanding the advent of dozens of new antiseizure medications (ASMs) with different modes of action.[1] Epilepsy surgery has fared similarly. Although patients with more complex epilepsies now undergo surgery, seizure-freedom after surgery overall remains stubbornly at about 60% despite tremendous technical advances.[2,3]

Fast forward a few years and envision what investigations could be available for the patient we described. He could have a 7T MRI and extensive connectivity and functional MRI (fMRI) studies with detailed parcellation and network analyses; detailed electrophysiological analyses of ripples and fast ripples as well as EEG-fMRI; high-resolution whole brain metabolomics; post-processing imaging studies; his entire electronic health record would be readily available; he would have whole genome sequencing as well as pharmacogenomic, microRNA (miRNA) and epigenetic studies; his microbiome and metabolomic profile would be available; in addition, access would be available to extensive longitudinal data from his multiple wearable physiologic sensors, as well as portable continuous seizure detection data coupled with seizure videos and biometric data obtained at home; and his environmental data and exposome would be obtainable. In addition, terabytes of raw EEG signal data and linked imaging data would be available for analysis. Furthermore, complex automated algorithms would be available that could purportedly unveil brain abnormalities, and analytical algorithms could be used to calculate various indices of brain function and dysfunction. It is notable that these data can also be used to convey risks of surgery in a more nuanced manner. Satisfaction with treatment comprises the perception of effectiveness, side effects, and convenience.[4] Use of high-density EEG arrays and sophisticated source localization combined with machine learning applied to fMRI and diffusion tensor imaging can identify critical cortical and subcortical regions, helping to avoid eloquent areas and providing a precise probability of postoperative deficits. Finally, using these data, surgical satisfaction scales can be derived and modeled on large populations of patients, which can then be applied to point-of-care conversations when counseling a patient about how satisfied they may be with a specific surgical procedure.

More could be added to the list of potential future data modalities and techniques.

Some of these data may seem far-fetched, but they are not that distant. Genetic techniques for different types of diagnostic sequencing (eg, genome wide association, exome, epigenetics, miRNA), and genetic engineering techniques such as CAR (chimeric antigen receptor T cells) and CRSPR (clustered regularly interspaced short palindromic repeats) are revolutionizing clinical genetics and moving closer to the clinical coalface. The rise of various molecular "omics" (eg, metabolomic, proteomic, microbiomic) in clinical medicine is an increasing reality. For example, research continues to turn up remarkable links between gut microbiota, brain disease, and behavior,[5] and there is evidence of a mediation effect of gut microbiota on the antiseizure effect of the ketogenic diet.[6] In epilepsy surgery, data complexity is well illustrated by a recent review of the changing concepts in presurgical evaluation.[7]

Add the fact that genetic studies are becoming increasingly available, and one could foresee that these will be a

**Key Points**

- Precision medicine is a tool by which we can predict outcomes on an individual patient, rather than population-level, basis
- There is great potential for precision medicine in epilepsy due to rich multimodal clinical, biometric, genetic, and ancillary data
- Collating and integrating data sources while adhering to patient confidentiality remains a challenge
- Current models are at risk of overfitting, misclassifying due to a lack of ground truth, and often fail external validation
- Systematic approaches and an emphasis on medication education are required to realize the potential of precision medicine in epilepsy

regular and prominent element of patients' clinical records. As the cost of gene sequencing plummets, it is estimated that in the future, companies might offer sequencing services at very low cost or even free in exchange for the purchase of other services, such as genetic interpretation, much like mobile business models operate at present.[8]

The question is, how do we make sense of a growing volume of data from an increasing type and number of sources, how do we judge its relative value, how do we turn these vast amounts of data into meaningful knowledge and clinical wisdom, and how can it help us make more precise diagnoses and personalized management decisions. This is the world of big data and the promise of precision medicine.

## 2 | WHAT IS PRECISION MEDICINE?

*Precision medicine* has been defined in a variety of ways. The National Institutes of Health's (NIH's) precision medicine initiative emphasizes genetic information, and defines precision medicine as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."[9] The scope of the definition has evolved from earlier constructs that emphasized genomics almost exclusively as the basis for precision medicine.

The closely related concept of *personalized medicine* shares the targeted approach of precision medicine and is embedded within the precision concept, but emphasizes evidence-based decision-making, consideration of individual circumstances, and clinical skills of health care providers.[10]

The United States National Research Council[11] emphasizes the inappropriate misconstruing of the term "personalized medicine" as signifying that each person receives a specific model created using their own data, rather than the actual approach in which algorithms are generated from large data sets and then applied to individual patients with high degrees of accuracy. Hence, we use the term 'precision medicine" throughout the text in the broadest sense, to encompass multiple data types and sources, and to inform more precise decision-making at numerous levels, ranging from the individual to the health system (Figure 1).

The Centers for Disease Control and Prevention (CDC) takes a more holistic approach and defines *Precision Public Health* as "the ability to prevent disease, promote health and reduce health disparities in populations by: (a) applying emerging methods and technologies for measuring disease, pathogens, exposures, behaviors, and susceptibility in populations; and (b) developing policies and targeted public health programs to improve health."[12]

Enlarging the scope of precision medicine to public health is a necessary extension of the concept, given the enormous

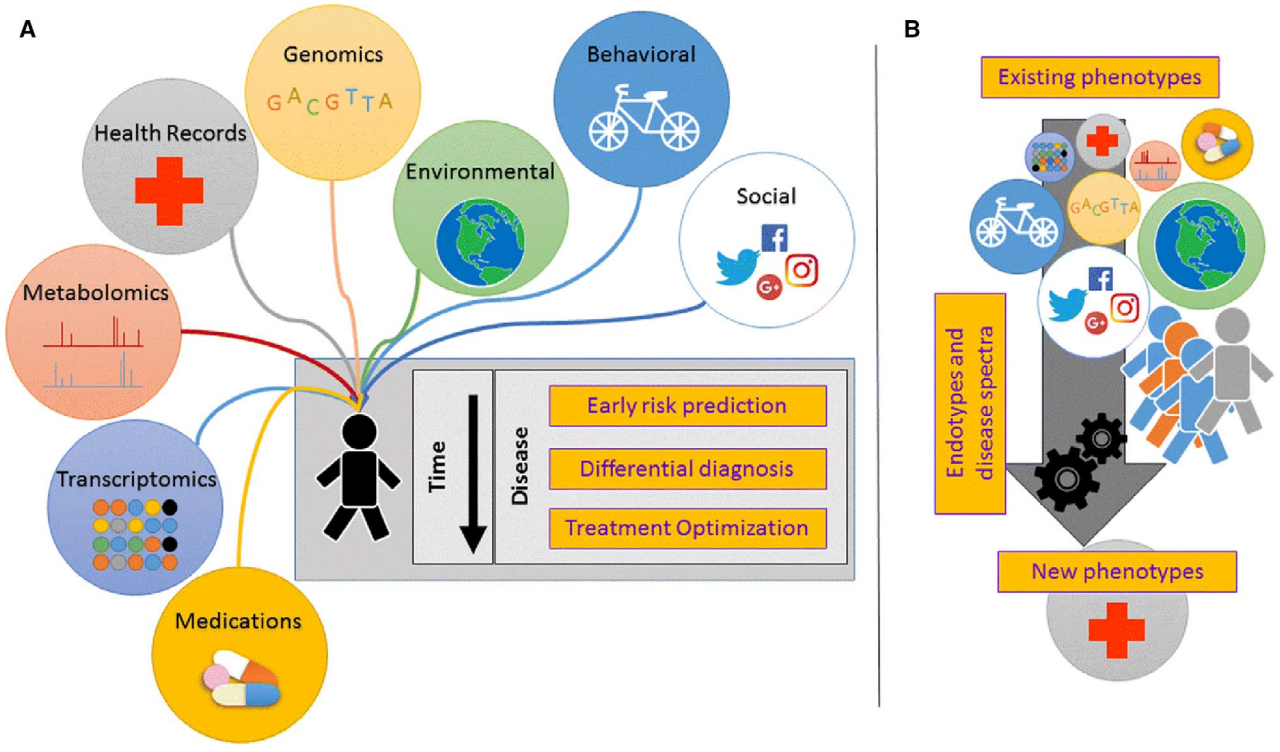


**FIGURE 1** Precision medicine across the continuum of care, from prevention to diagnosis and treatment. It involves dynamic risk assessment and optimization of current and future health status through immutable (eg, genetic) and actionable (eg, behavior) factors (unmodified from[13])

impact that targeted public health interventions have had on global health. Most of the success in reducing morbidity and death over the last five decades has been due to earlier detection of disease, public health measures, and wide application of efficacious interventions for primary and secondary prevention.[10] This broader concept is helpful because it emphasizes that precision medicine is more than genes or molecular biomarkers, spanning the continuum of care (Figure 2).[13]

## 3 | WHAT IS ALL THE PRECISION MEDICINE HYPE ABOUT?

To be sure, clinicians have been practicing precision medicine for a long time, with precision improving as knowledge accrues. For example, long before precision medicine was in vogue, we selected ASMs for specific types of seizures or epilepsy, targeted surgery as precisely as possible, and treated comorbidities such as depression with specific medications. Yet, the prominence of precision medicine has steadily climbed in the last decade, as shown by the growth in publications (Figure 3), increased funding allocated to this field, and in the United States, a presidential initiative focused on precision medicine, among others.

At least three factors explain the ascent to prominence of precision medicine: (a) the unprecedented accrual and availability of individuals' digital data including omics, health records, and data from wearables; (b) advances in and ready access to high-performance computing; (c) and the application of artificial intelligence and machine learning algorithms in medicine.

### 3.1 | The data Tsunami

The volume of longitudinal information in an individual is now so intensive, that researchers are proposing the concept of the "epidemiology of one" in which a single individual is viewed as an entire population of observations that can be analyzed for self-monitoring and forecasting by adapting statistical methods to individual-level data.[14] In addition, systems biology, which aims at comprehensively studying molecular diversity, identifying general principles and patterns and integrating biological knowledge in complex models,[15] is likely to become increasingly applied in epilepsy.[16] An illustration of this approach is the analysis in patients investigated for epilepsy surgery of complex correlations among brain tissue metabolomics (high-resolution magnetic resonance spectroscopy), genomics (RNA microarray analysis), histopathology (cellular interactome, neovascularization, and newly found microlesions), and electrocorticographic data (spiking rate in different cortical regions).[17] Researchers derived accurate biomarkers of epileptogenesis, which, pending validation, could be used noninvasively.

Because resources are scarce, researchers need to identify minimum data quality standards and cost-effective data sources and models. For example, granular data from electronic health records and multi-center registries may justify

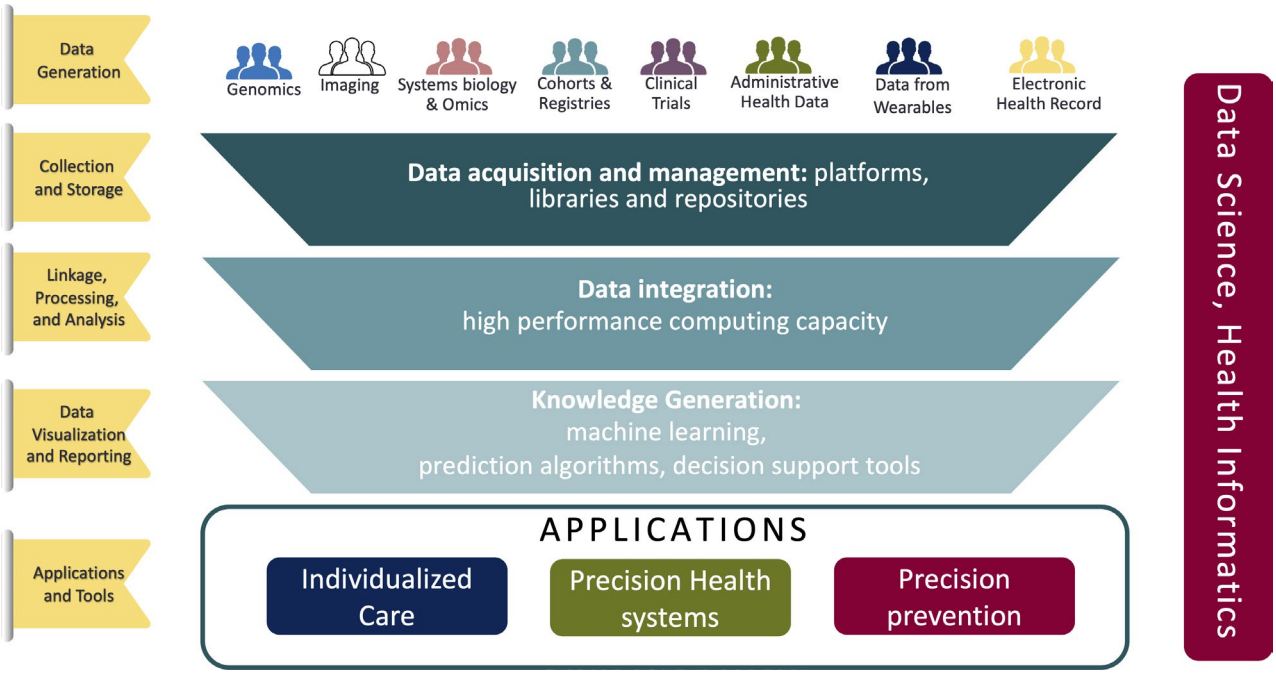


**FIGURE 2** Incorporating data of different types and sources, using high-performance computing and machine learning methods, to inform more precise decision making at different levels, ranging from the individual patient to the health system

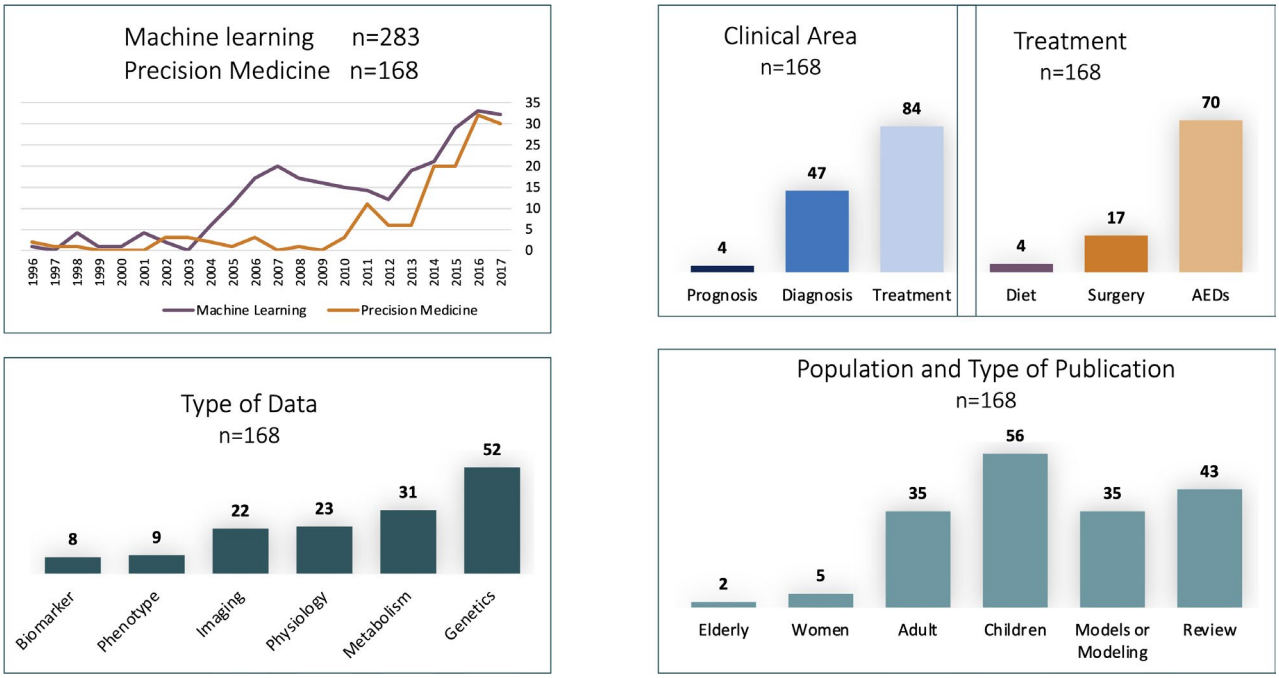


**FIGURE 3** Publications in precision medicine and machine learning related to epilepsy up to 2017

the platform, personnel, and analytic costs as they allow for individual-level predictions. However, these data are often of insufficient value on their own, yielding models with moderate capacity for discrimination.[18-21] Multimodal data (eg, MRI, EEG, and genetics) can improve performance, but at incremental financial and logistical costs and greater threats to patient confidentiality due to complex linkage schemes. Empirical approaches incorporating information theory, such as Akaike information criterion and Bayesian information criterion, and cross-validation can help establish minimal data sets that populate models with simplicity and efficiency. This area should be a research priority to avoid drowning in the digital tsunami.

### 3.2 | High-performance computing keeps getting higher

Compute power keeps growing at astounding rates. Electronic Numerical Integrator and Computer (ENIAC), the first computer built in 1946 in the United States, weighing 27 tons, was capable of performing 3 square roots per second. By comparison, SUMMIT, the fastest computer in the world in 2018 could perform 200 quadrillion calculations per second, and only 2 years later, this was superseded by the Fugoka cluster, which is almost three times faster.[22] This level of computing power makes it possible to handle large, complex clinical data sets and apply advanced analytics with increasing speed, a key component of precision medicine.

### 3.3 | Artificial intelligence

The human capacity to store and process information is limited. By various accounts, our brain can handle from 4 to 10 "chunks" of information at any one time.[23] Traditionally, clinicians have dealt with this by thinking in groups; rounding on cases or discussing at case conferences helps us manage problems too difficult for any single mind to solve. Yet, medical decisions have become vexingly complex and every patient is a big-data challenge. On the other hand, computer algorithms capable of dealing with complex data are increasingly used to find clinical patterns, predict clinical outcomes, and help choose among clinical interventions. This ability to more precisely identify patterns and prognoses is at the core of precision medicine. The application of validated computer algorithms in clinical medicine is a reality to which clinicians are learning to adapt.[24,25] Ongoing involvement of clinicians at various levels of training and speciality will facilitate this transition in an egalitarian fashion that balances efficiency, productivity, and accessibility.

## 4 | WE NEED MORE PRECISE MEDICINE

### 4.1 | Population vs individual level predictions

Conventional research depends on drawing samples and extrapolating the results back to the whole population.

This approach allows us to make inferences about the general population from which patients were sampled and provides an estimate of how the average patient will respond to an exposure of interest. Using data from these studies we can counsel patients with incident epilepsy that they have an ~47% chance of responding to their first ASM.[26] However, if one were to delve deeper, we can only be 95% confident that the average patient has between a 42% and 52% chance of responding. Individual patients may reasonably wonder where in this range they lie, and if they could be an outlier whose probability exceeds these boundaries. They may also ask whether the type, etiology, anatomic location of their seizure focus, or genetic profile would make them more or less likely to respond. Finally, an obvious question is whether specific ASMs would alter their anticipated chance of responding. These fundamental questions are not unique to medications. On average, 63% of patients will become seizure-free after temporal lobe surgery.[27] However, we can only be 95% confident that the probability for the average patient is between 46% and 79%. We again face questions about whether a patient's baseline characteristics and type of surgery could shift this range and by how much.

Precision medicine is both a laudable and inevitable aim in medicine. However, the process by which we can achieve high degrees of precision and accuracy for individual patients presents major challenges to researchers and clinicians. The fundamental problem, analogous to the "epidemiology of one," is how to stratify all available variables to only those expressed by the patient at hand while accruing longitudinal person-level data with sufficient volume to preserve statistical power.[14] Stratifying to such a degree requires immense sample sizes, to avoid predictor (p) vs number (n) problems.[28] Furthermore, intricate combinations of multimodal data, combined with the required complex algorithms to handle disparate information require using high-performance computing paradigms. The advent and convergence of all three prerequisites (sufficient data, diverse data, and advanced analytics) has created the foundations required to start advancing this mission with aplomb.

## 4.2 | Key established data sources

Large data sources are no longer esoteric curiosities available only at selected centers. *Electronic health records (EHRs) and administrative health care records (AHR)* can be rapidly queried using validated case definitions[29,30,31,32] in order to extract large cohorts of patients with epilepsy. Previously Read Codes, and now structured clinical ontologies, such as Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT), in addition to International Classification of Diseases (ICD) terminology, are being expeditiously incorporated into EHRs to facilitate health informatics.[33] Currently 38 countries have endorsed SNOMED CT as the preferred reference terminology for EHR systems (https://www.snomed.org/our-customers/members). Application of validated nomenclature systems for epilepsy can yield cohorts in the tens of thousands with varying degrees of granular clinical data.[34] Use of these data alone has yielded important insights into premature mortality[35] and potential interventions to reduce risk,[36] bidirectional relationships between psychiatric disease and epilepsy,[34,37] and prediction models for individualized risks of psychiatric adverse effects from levetiracetam[19] and drug-resistant epilepsy[38].

*Biometric neurophysiologic data*, such as those derived from EEG and MRI recordings, have also been applied to improve precision approaches to epilepsy. These have been exploited in attempts to produce individualized automated seizure detection algorithms,[39] and have been proposed as a means of predicting individual response to ASMs[40] and surgery.[41]

*Genetic studies* have benefited from the advent of next-generation sequencing. Genome-wide association studies and whole exome sequencing are now feasible and realistic for routine use in research and clinical settings. Identification of single gene mutations can have individualized treatment implications for those affected by GLUT1 deficiency (ketogenic diet)[42] and *SCN1A* mutations (avoidance of sodium channel blocking ASMs for specific mutations).[43] Whole exome sequencing, performed in triplicate with the proband's biological parents, has identified risk factors for epileptic encephalopathies with the obvious potential that identified genes and their associated RNA and protein products, could serve as targets for intervention.[44] However, these hopes are currently tempered by the lack of statistical modeling required to demonstrate that identified genetic variants are indeed causative at an individual level.[44] Pharmacogenomics embody immense promise to predict skin and mucosal side effects, thus improving patient quality of life[45] and decreasing morbidity and mortality.[46,47] Identification of genetic markers for severe ASM-related tegmental and mucosal adverse effects, for example, *HLA-B*1502* and Stevens-Johnson syndrome,[48] highlight how pharmacogenomics can be deployed for precision medicine. Incorporating these in predictive models could change patient care beyond reducing seizure frequency.

## 4.3 | Selected emerging data sources

Emerging sources of large data include w*earable seizure detection* and *implantable devices*. To date, these have yielded promising results, but few have been rigorously validated[49] and their application to precision epilepsy remains in a nascent stage. These include wrist accelerometers that detect rhythmic motions consistent with bilateral tonic-clonic seizures,[50] and electromyography, applied as small patches on the skin, that employ machine learning algorithms in attempt to distinguish ictal muscle activity from

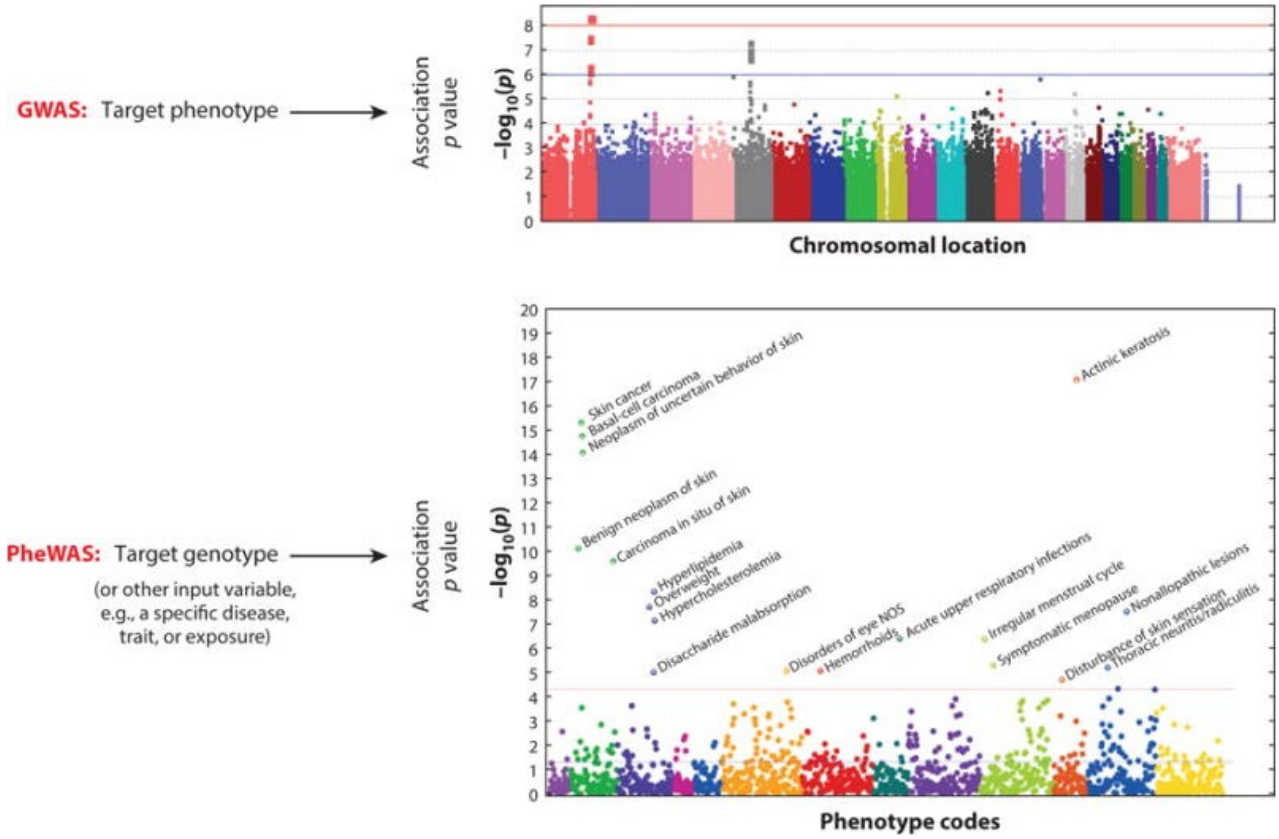


**FIGURE 4** Phenome-wide association studies as contrasted with genome-wide association studies. This paradigm can be adapted to epilepsy to include epilepsy and seizure characteristics, comorbidities, biometric and genetic markers, and response to antiseizure medications and surgery (unmodified from[54])

physiological activation.[51] Combined devices, integrating various permutations of accelerometers, electromyography, electrodermal activity, and heart rate sensors now exist[49] offering unprecedented access to vast amounts of raw physiological data that can be readily applied to machine learning and artificial intelligence algorithms for individualized precision medicine. *Implantable responsive neurostimulation* can also record immense amounts of neurophysiological data. The device is designed to monitor neural activity and, in conjunction with physician input, "learn" the individual patient's ictal patterns.[52] Although the purpose of an implantable responsive neurostimulator is to abort seizures using closed-loop stimulation, the potential exists to extract interictal, ictal, and electrocorticography (ECoG) data. Currently, data are limited and lack granularity and anatomical extent, and the devices have suboptimal storage capacity.[53] However, it is highly likely these issues will eventually be circumvented, unleashing the clear potential of these data sources for individual-level predictions.

### 4.4 | Phenome-wide association studies

Integration of these multidimensional sources of data leads the way to one of the ultimate aims of precision medicine, the phenome-wide association study. These studies adapt the classic genotype-phenotype paradigm in genetic studies to real world multimodal data. Every form of data we use, including but not limited to clinical, EHR and AHR codes, biometric, and genetic, can be considered part of an individual's unique phenotype. Contrary to a conventional genome-wide association studies, the approach to phenome-wide is to start with a target genome and then map the degree to which specific features within biobanked EHR, AHR, registry, and biometric data associate with it.[54,55] In addition, the input need not include genetic data, and could include any metric, or the complete phenotype itself can be used to identify unique clusters of patients who are amenable to precision-based treatment approaches (Figure 4).[45,54,56] Parsing patients into increasingly discrete clusters with identical phenotypes will, by nature, catalyze tailored treatments specific to individual, rather than population-level, traits.

## 5 | WHERE ARE WE NOW?

### 5.1 | The "hype cycle"

A precision model, if well designed, clinically informed, robust, and externally validated, can be used at point-of-care,

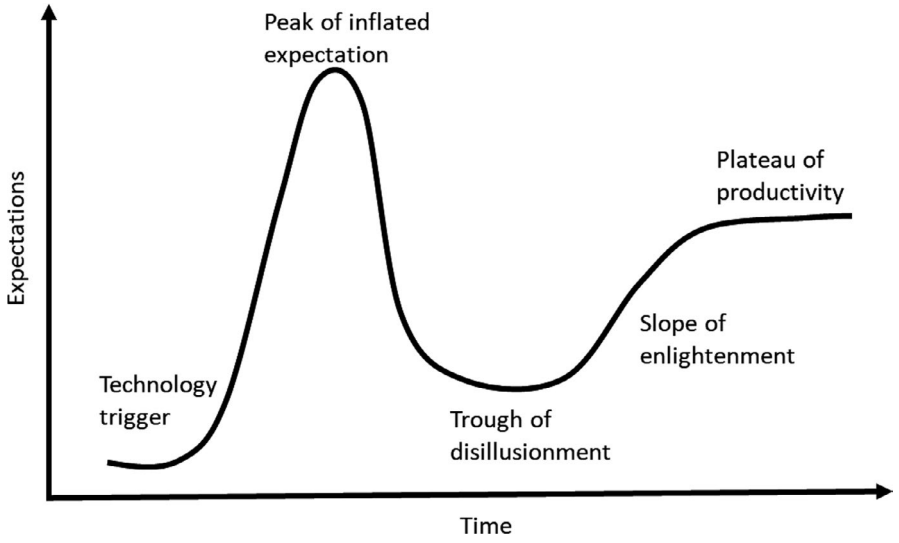


**FIGURE 5** The five phases of the Gartner Hype Cycle (unmodified from[78])

ideally through EHRs or a web-based interface that amalgamates all requisite sources of data, to produce a quick, accurate, and precise estimate of a unique patient's likelihood of developing a specific outcome. However, precision medicine, like all emerging technologies is susceptible to the "hype cycle" (Figure 5). Breakthroughs in high-performance computing, cloud-based storage, medical ontologies, and advances in machine learning and artificial intelligence led to prolific interest in academic journals[57-60] and the media, thus stoking enthusiasm without actually having yet delivered a clinically viable product. This leads to a peak of inflated expectations about what the technology can truly deliver. The unfortunate consequence of unrequited expectations is disillusionment and a tendency to eschew the novel technology due to unfettered skepticism. Those who are dedicated to the idea may then enter a phase of gradual enlightenment, refining and revising the data, models, and deployment platforms in efforts to iteratively improve the product in an effort to restore faith in its initial promise. With increasing adaptation, we enter the fifth and final stage, whereby the technology is gradually rolled out into mainstream use following validation of performance and usability. This phase levels off at a plateau that lies between the original peak of inflated expectations and the trough of disillusionment.[61]

## 5.2 | Where is the hype?

In our view, epilepsy precision medicine currently resides between phases 2 and 3. There continues to be hope and hype about the potential of precision medicine. However, there is growing fatigue and attrition when it comes to developing precision medicine models. Conventional and advanced prediction algorithms frequently perform poorly in clinical practice, a phenomenon that can actually lead to patient harm.[62] Small sample sizes, choice of statistical model, and failure to replicate results independently in external populations are among the reasons underlying this phenomenon. This leads to research waste[63]; it is estimated that up to two-thirds of models in cardiovascular disease go unvalidated in external populations and, of those that do, only one-fifth are by independent investigators.[64] Good models are lost in the noise, further adding to skepticism and disillusionment in the general medical community. The field of epilepsy is not immune. Few validation-only studies exist. The few studies published by independent groups that have externally validated individual level prediction models have demonstrated declines in discriminative capacity and poor calibration.[21,65,66] In addition, even in derivation models, overall discrimination and performance measures have been modest,[19-21,67] since most are defined by low dimensionality, small sample sizes, and lack of comprehensive and granular data on patient demographics, seizure and epilepsy characteristics, comorbidities, neurophysiologic, imaging, genetics, and omics data.

## 5.3 | Caveat emptor

These are not trivial critiques. Caveat emptor is still the recommended approach. Small study sizes, limited effect sizes, and increasingly fluid approaches to model generation all can lead to publication bias and proliferation of inflated models.[68] Overfitting remains an issue. This arises when models fit the data so well that it perfectly predicts outcome within the sample population yet has limited applicability to external populations. Such overfitted algorithms model both signal and random noise (ie, exhibit high model *variance*), and their performance varies widely when applied to other populations. On the other hand, if not tuned adequately, the model has poor predictive value, leading to high *bias,* and is unsuited to any population. Thus performance of the model is

skewed irrespective of the population on which it is derived or validated. We are currently mired in a state that leans both ways on the bias-variance trade-off. Many prediction models are restricted to single-center populations and are underpowered. This promotes overfitting through an imbalance of predictors to sample size.[28] This tendency is compounded by the fact that there are an no reliable means estimating a priori power for many advanced prediction models.[69]

At the other end of the spectrum, we may underfit models due to lack of high-dimensional data. Conventional statistics aim to create parsimonious models, although biological systems do not often conform to this assumption.[69] Mechanisms underlying epilepsy are rarely independent nor do they exist in isolation. Complex algorithms, including machine learning, artificial intelligence, and neural networks can handle these interconnected complexities by comprehensively assessing for a vast array of permutations and interactions between input variables. Deep learning, neural networks, and advanced machine learning can handle featurized multidimensional data that are intrinsic to biological systems. If one remains vigilant for issues of collinearity, as well as tolerant to model complexity and interpretability, use of these algorithms is feasible and may yield more accurate estimations of response. Note that vast amounts of data are required, which are frequently lacking. Large multinational collaborations are now emerging to address this need. For instance, the ENIGMA (http://enigma.ini.usc.edu/ongoing/enigma-epilepsy/), Epi25k (http://epi-25.org/), and PGP/Epi4K (https://www.epgp.org/index.html) consortia have been created for this purpose. Researchers can access data from population-based EHRs of up to 100 000 patients with epilepsy.[34] Schemes, such as the UK Biobank, can link these records to biometric data.[70] Efforts to engage general practitioners and neurologists to leverage their expertise and access granular, multimodal data have been successful in smaller scale registries.[71] Adaptation of these strategies may yet yield data sets of sufficient volume and variety for "data-hungry" algorithms as we aim to move into phase 4 of the "hype cycle."

## 5.4 | Teaching the machine

Quantity is important, but so is veracity. Due to the nature of the disease, epilepsy continues to find itself mired in subjectivity. This lack of a "ground truth" impedes the ability to apply conventional statistical and supervised machine learning algorithms to precision medicine problems in epilepsy. As a field, we are growing better at agreeing on some aspects of semiology, yet such consensus is not perfect, especially for nonepileptic attacks.[72] Even experts only demonstrate fair agreement when deciding on individual interictal discharges[73] and seizures[74] on scalp EEG, or ictal-onset patterns on intracranial EEG.[75] This is critically important because models rely on human input for correct application of labels to input features and outcome classes. For precision medicine purposes, predicting comorbidities and death on an individual level is relatively immune to this issue. However, if the intention is for the algorithm to include anything other than raw, unlabeled electrophysiological data, then we are at risk of trying to "run before we can walk." Erroneous designation of the inputs and classes will inevitably lead to spurious results with effects that could harm patients and set the field back by exacerbating the disillusionment of phase 3 of the "hype cycle."

## 5.5 | Deciphering the enigma

Even with large amounts of accurate multimodal data, evidence-based systematic approaches to model selection remains elusive. Often, there is a trial and error approach to selecting the final algorithm. At an overarching level, general categories of models are applied based on the question and data structure. Typically, algorithms are divided into supervised, unsupervised, and reinforcement learning depending on the problem at hand. Supervised machine learning problems involve features (independent variables) and a labeled class (dependent variable). Unsupervised algorithms look for patterns in data without the need for labeled classes. Reinforcement learning primarily involves optimizing a system without a need for labeled classes. No algorithm is universally accurate, implementable, or interpretable.[76] Often an inverse relationship exists between these factors, especially accuracy and interpretation. Models that can handle high-dimensional, multimodal data, such as deep learning, exhibit high degrees of accuracy when fed sufficient data, but the underlying processes by which the prediction is reached remain opaque.

This is problematic in medicine, since clinicians are unlikely to embrace models that they themselves cannot parse or dissect into familiar indices such as odds, risks, and hazards.[77] Efforts to overcome this include preferential selection of interpretable models, concerted medical education dedicated to precision medicine, and application of post hoc tools such as Local Interpretable Model-Agnostic Explanations (LIME). Over the short term, interpretable models and medical education are the most tractable approaches. Models such as regularized logistic regression, which produces odds ratios, and linear kernel support vector machines, which produce coefficients that can be arranged in order of importance, provide clinicians insight into how the algorithm behaves. Dedicated time reserved to precision medicine is increasingly becoming a fundamental part of medical school and resident training. The focus of these sessions should include the importance of local feasibility and performance of algorithms in representative populations. Even "black box" algorithms can be accepted if trainees are comprehensively informed of the benefits, limitations, and risks of these models when applied to individual patients. Over the medium to

long term, LIME represents a promising tool for communicating results in an accessible manner. By definition it is model agnostic, although to date it has been applied primarily to deep learning algorithms employed to classify images. By focusing on a specific (local) point of an image, and then perturbing inputs to the model, LIME is capable of analyzing how the output varies. With this knowledge, we can then weight inputs, create linear models that approximate original model function within that specific region, and then use this to extrapolate specific features that influence the algorithm's decision within this specific region. However, depending on model complexity, to be broadly applicable this process will have to be repeated within multiple regions to understand how deep learning or artificial neural networks behave across all phenotypes. Such a task requires extensive computing power and until efficiency is improved, is not yet ready for immediate deployment into routine clinical settings.

## 6 | WHERE NEXT?

Initial progress has been made in precision medicine in epilepsy. As the foundations are built, a systematic approach is needed in research so that sufficiently accurate and externally validated models can be derived and tested in clinical settings before routine use as point-of-care tools. First, we need to support and develop existing large collaborative multi-center research networks, many of which remain in nascent stages. Cloud-based systems will be essential to promote rapid integration and distribution of patient-level multimodal anonymized or pseudonymized data sets. Specific questions must be asked that are clinically relevant and likely to impact patient care. Once these are decided, efforts must be made toward cleaning and featurizing data, a central and critical element because reliable models are entirely dependent on their inputs. Feature engineering encompasses variable selection, data imputation, adjusting and accounting for outliers, manipulating and reformatting (eg, normalizing and standardizing) input variables, and determining their impact on predictive performance. These processes will have to be tailored to each clinical question. Concurrently, we must work on "ground truth," making concrete efforts to standardize definitions for inputs and outcomes (such as formally defining interictal and ictal neurophysiologic activity), to increase reliability between centers, as well as to ensure construct validity for precision models. Incorporating these standards into the production of interpretable and intuitive models, as well as dedicated medical education that instills health care providers with the resources needed to understand the benefits and limitations of artificial intelligence and "black box" algorithms, will promote uptake and knowledge translation. Finally, ideally such algorithms will be published in nonproprietary, open-source formats, to promote global uptake with no limitations on software or digital platforms. Precision medicine has unprecedented potential to revolutionize individual-level management of people with epilepsy. Following systematic and empirical steps forward will help clinicians and patients realize its full potential, moving us steadily toward phase 5, or the "plateau of productivity," for patient-level, point-of-care decision tools.

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## CONFLICTS OF INTEREST

All authors declare that they have no conflicts of interest.

## ETHICAL PUBLICATION STATEMENT

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.

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