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A Road Map for Precision Medicine in the Epilepsies

EpiPM Consortium

Summary

Technological advances have paved the way for accelerated genomic discovery and are bringing precision medicine clearly into view. Epilepsy research in particular is well-suited to serve as a model for the development and deployment of targeted therapeutics in precision medicine because of the rapidly expanding genetic knowledge base in epilepsy, the availability of good *in vitro* and *in vivo* model systems to efficiently study the biological consequences of genetic mutations, the ability to turn these models into effective drug screening platforms, and the establishment of collaborative research groups. Moving forward, it is critical that we strengthen these collaborations, particularly through integrated research platforms to provide robust analyses both for accurate personal genome analysis and gene and drug discovery. Similarly, the implementation of clinical trial networks will allow the expansion of patient sample populations with genetically defined epilepsy so that drug discovery can be translated into clinical practice.

I. Introduction

In the decades after the initiation of the Human Genome Project, the idea that treatments could be targeted to genetically-defined subgroups of individuals has often been espoused but rarely realized. The advent of next-generation sequencing has promoted a new wave of enthusiasm, and a new name to go with it – precision medicine. In this Personal View, precision medicine refers to the scientific basis that underpins the personalization of medical care (cf[1], “Moving toward precision medicine”, NRC committee report, 2011), particularly in the context of treatments targeted towards the precise molecular causes of disease. The realization of precision medicine is perhaps best illustrated in the specialty of cancer, in which mechanism-based treatments have successfully moved from bench to bedside.[2] However, in most therapeutic areas, particularly in neurological disease, precision medicine remains aspirational.

Here we argue that, after cancer, epilepsy offers one of the most compelling opportunities to achieve precision medicine for the following fundamental and synergistic reasons: the rapid progress in epilepsy gene discovery; the existence of good animal and in-vitro models

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Author’s Contributions

All authors provided sections of text covering their area of expertise and participated in the development of the perspectives presented. DBG and ELH compiled the manuscript, and all authors reviewed, edited, and approved the final version.

allowing the development of medications tailored to genetically defined subtypes of epilepsy, largely because neuronal excitability underlies epilepsy phenotypes and can often be accurately modelled *in vitro*; and the ability to assess efficacy of experimental targeted treatments in cost-effective, small, brief clinical trials. To realize the potential of precision medicine in epilepsy, however, many distinct areas of basic and translational research must coalesce into coherent and collaborative programmes. Here we outline a strategy for the development of an integrated programme for precision medicine in epilepsy, including the expansion of cohorts for research, the development of *in vitro* and *in vivo* animal models of disease, and strategies to perform genetically stratified clinical trials. We conclude that fostering integrated research teams to advance precision medicine in the epilepsies will improve health care that epilepsy could serve as a model for other therapeutic areas.

II. Precision Genetics for Precision Medicine

Molecular genetics research in epilepsy began more than 20 years ago and has entered a phase of rapid progress. This suggests that in the near future, at least some of the important genetic risk factors contributing to epilepsy will be identified in a substantial proportion of individuals with non-acquired epilepsy. Analyses of the genes implicated to date further indicate that genetically resolved epilepsies will eventually be grouped into larger sets that share common underlying biological causes or pathways.

Findings from traditional heritability studies[3–7] and more recent genomic heritability analysis[8] unequivocally show the important role of genetics in epilepsy risk. Before the development of next-generation sequencing, both linkage analyses and targeted candidate gene studies identified a number of epilepsy genes.[9–21] Although these discoveries represented a substantial advance and illuminated novel aspects of disease pathophysiology, collectively these genes underlie epilepsy in only a small proportion of individuals with the disorder.

The role of common variation in epilepsy has also been assessed, both with candidate genes[22] and comprehensive genome-wide association studies (GWAS) with generally limited findings.[23–26] In parallel, chromosome microarrays have been used to identify copy-number variants that confer substantial risk of epilepsy.[27–30] Although each copynumber variant confers significant risk, none is sufficient to cause epilepsy alone,[27,31] and all variants are associated with several neuropsychiatric diseases.[32,33] Collectively, these findings led researchers to focus on rare variants in epilepsy precisely when developments in next-generation sequencing facilitated the comprehensive interrogation of genomes.

The most common application of next-generation sequencing is to investigate the “exome,” or the set of nearly all protein-coding regions of the genome. Trio sequencing, in particular, in which the genomes of the individual with epilepsy and both parents are sequenced, is a successful method to identify new risk factors for the epileptic encephalopathies (panel),[34,35] as well as for other neuropsychiatric diseases, including intellectual disability and autism spectrum disorders.[36–40] In the EEs alone, trio-based analyses have led to the identification of *ALG13*,[34] *GABRB3*,[34] *DNM1*,[35] *HCN1*,[41] *GRIN2A*,[42–44] *GABRA1*[45] *GNAO1*,[46] KCNT1,[47] *SCN2A*,[48] *SCN8A*,[49,50] and *SLC35A2*[51] as genes associated with

epilepsy. Interestingly, and not surprisingly, many of the proteins encoded by these genes are involved in synaptic transmission.[35] The characterization of the specific effects of mutations in these genes will help to resolve the precise biological pathways within synaptic transmission that are disrupted in epilepsy.[52]

Post-zygotic (somatic) *de novo* mutations (panel) that are present in only a subset of cells have also been identified as the cause of malformation syndromes associated with severe epilepsy. Recent examples include somatic mutations in *AKT3*, *MTOR* and *PICK3CA* as the cause of hemimegalencephaly and intractable seizures,[53–55] and somatic mutations in *DCX*, *LIS1*, *FLNA*, and *TUBB2B* as the cause of double cortex syndrome, periventricular nodular heterotopia, and pachygyria.[56]

To date, progress has been modest in understanding less severe forms of epilepsy, almost certainly owing to a combination of very high locus and allelic heterogeneity and the possibility that combined effects of variants in multiple genes underlie susceptibility (Figure 1). We anticipate that larger sample sizes will soon be available to facilitate discovery in these more genetically complex epilepsies. These epilepsies might also depend on more subtle regulatory variants, requiring application of genomic and transcriptomic approaches, an emerging area of focus in common diseases including epilepsy. We note that epilepsies that occur in response to precipitating factors such as traumatic brain injury or brain tumours, although having some genetic component, will probably be less tractable targets for precision medicine than epilepsies whose aetiology is largely genetic.

Despite the progress towards the identification of epilepsy risk genes, precision medicine depends on the identification of mutations that contribute to disease in individual patients. This represents a distinct and more difficult challenge than the simple determination that a gene is involved in risk of epilepsy at the population level. The development of methods to quantitatively assess the degree of confidence that specific mutations contribute to disease in particular individuals is therefore a priority in epilepsy precision medicine. One recently developed approach to help pinpoint pathogenic mutations involves comparison of the patterns of genetic variation, including both types of mutations and their frequencies, between the general population and the population of individuals with disease. These analyses indicate that disease genes, particularly genes associated with neuropsychiatric disorders, tend to have less common functional variation in the general population than expected given the overall predicted mutability of the genes.[64,65] Indeed, bioinformatic signatures that integrate such “gene level” scores with established variant level scores have been shown to be predictive of causative mutations in the genomes of individuals with severe early-onset diseases.[65,66] A key focus of emerging efforts in epilepsy precision medicine will be to develop new statistical genetic approaches to expand these research areas, including analyses in diverse ethnic groups, and analyses of mutation patterns in non-coding genomic regions. In view of the need for expanded sample sizes, both for gene discovery and to facilitate accurate interpretation of individual genomes, genetic data generated in different locations must be integrated as much as possible. Importantly, data are being collected in commercial genetic testing laboratories that do exome sequencing on a fee-for-service basis, but these data are largely unavailable for research at this time. To make more effective use of these data, the epilepsy community has come together to

establish the Epilepsy Genetics Initiative (EGI) to integrate clinical data collected in medical centers and to allow the integration of clinical data with research data. EGI has created a database to house the clinically sequenced exomes (and, in due course, sequenced genomes) and phenotypic data of individuals with epilepsy, one unique purpose of which is to allow on-going iterative reassessment of unsolved cases. Thus, EGI is a resource that brings together people with epilepsy, clinicians, and researchers in a mutually beneficial effort to advance precision diagnostics and epilepsy research. Central to these discussions is the perspective of families living with epilepsy (TJD-S, unpublished). Taken together, developments in gene discovery, bioinformatic prioritization of putative pathogenic mutations, and large-scale genetic data integration suggest that the genetic basis for precision medicine in epilepsy is now within reach. As an illustration, the list of known epilepsy genes that can form the initial basis for epilepsy precision medicine is growing (Figure 2).

Precision medicine in the epilepsies also has an equally important role in facilitating avoidance of adverse reactions as in maximising efficacy, as illustrated by a number of recent examples. In some cases, improved diagnostics will enable avoidance of adverse reactions, as is the case for patients with epilepsy due to *POLG1* mutations who might develop fatal hepatic failure when treated with valproate.[67] In other cases the risk factors for a severe adverse reaction will be independent of factors responsible for the disease; for example, the HLA-B*15:02 allele is highly predictive of carbamazepine-induced Stevens-Johnson syndrome, a severe hypersensitivity reaction, in patients of Asian origin.[68]

III. Functional Modeling

Translation of genetic causes into new or more targeted treatments depends on effective model systems that illuminate the underlying biology and contribute to the development of new drug-screening protocols. Importantly, advances in the functional assessment of epilepsyassociated mutations in the past two decades have shown a remarkable ability to dissect disease mechanisms using both single cell and whole animal models.

There are multiple interrelated motivations for the Thorough characterization of the effects of identified mutations at the RNA, protein, cellular, tissue, and whole organism levels. First, a mechanistic understanding of how mutations confer risk provides new directions for drug development. Second, it is increasingly clear that *in vitro* functional readouts for individual mutations can provide important information about pathogenic mechanisms (e.g., gain vs. loss-of-function), prognosis, and in some cases, treatment choices.[69] The enthusiasm to model genetic epilepsies, and the need to model them well, as illustrated by the rapidly growing number of family foundations focused on funding specific genetic epilepsies (Figure 2).

Features of an ideal pre-clinical model of genetic epilepsy include the following: 1) efficient expression of the genetic risk factors identified in human beings; 2) accurate Representation of fundamental disease mechanisms, and pharmacosensitivity in human beings; 3) sufficient “scalability” to enable high-throughput screening of compounds; and 4) the ability to represent the full pathological consequences of mutations, including both the effect of the

primary molecular defect and the emergent disease pathways. No single model will satisfy all criteria, which is why we suggest an integrated approach across models. As an illustration, the fastest throughput in experimental screening will probably still be *in-vitro* models, whereas faithful reflection of the developmental consequences of epilepsy mutations will inevitably be lacking. Although many approaches to modelling epilepsy mutations exist, we discuss three broad classes of functional models that together meet the above criteria. This focus is not meant to imply that there is no value in other model systems, but rather that the application of the classes of models discussed will probably serve as a general approach for precision medicine in epilepsy.

Single-cell models

In the simplest models, the mutated gene is incorporated into a cell line that does not normally express that gene,[70] allowing for functional assessment of the mutant gene product in isolation. By far the most commonly used cell-types have been the human–derived HEK293 cell line and *Xenopus* oocytes. These cell-based platforms have been successfully applied to study voltage-gated and ligand-gated ion channels. Additionally, these systems permit multiple assays of molecular trafficking and processing of gene products. Studies of GABA receptor mutations found in human epilepsies exemplify how these systems have been used.[71–74]

Although artificial when compared to an *in situ* neuron, these simple models provide efficient ways to reveal functional mechanisms. These systems are also amenable to optimization for high-throughput screening. For these reasons, heterologous expression systems will continue to be a mainstay for modeling ion channel and transporter mutations.

Network scale models—A major limitation of single cell systems is the absence of network and support cell environments. As we suspect that many genetic causes of epilepsy result in non-cell-autonomous defects, the pathogenic consequences of many epilepsy mutations will probably be apparent only in the context of a neuronal network. Moreover, treatments that control epilepsy through indirect compensation of mutation effects can only be discovered only if many neuronal processes are represented in the model. To address these needs, *in vitro* models of interacting neurons are necessary.

Brain slices from rodent models provide a ready source of neuronal networks to assess disease mechanism and drug action. Acute and organotypic brain slices have been used in epilepsy research,[75] and although desirable because they retain many of the large-scale features of the brain regions from which they are derived, brain slices are not amenable to scaling sufficiently to allow effective screening.

A promising new direction is the use of cultured neural networks (CNNs). The large-scale assessment of CNNs is facilitated by advances in non-invasive approaches to monitor activity in these networks. The development of multi-well, plate-based multi-electrode arrays (MEA) allows for screening of hundreds of networks per day. With the recent introduction of optophysiological and optogenetic approaches[76] that can detect small and rapid changes in neuronal electrical state and can selectively stimulate neuronal populations, high-resolution interrogation of cultures has become possible. The use of CNNs, however, to

study genetic epilepsy requires some form of manipulation of the cells in culture. Several approaches are possible. Most simply, CNNs can be developed by harvesting neuronal cells directly from mouse genetic models, allowing higher throughput screening than is possible *in vivo*. CNNs can also be developed directly using human cells from individuals with epilepsy, reprogramming those cells to become induced pluripotent stem cells (panel), and then differentiating them into appropriate cells, such as neurons and glia. An alternative approach is to introduce the mutation by genome editing using CRISPRCas (panel) or other editing approaches in a controlled isogenic line of induced pluripotent stem cells, followed by differentiation into relevant cell type(s). These approaches involving induced pluripotent stem cells provide an expandable source of cells to study humanspecific phenotypes and a human cellular model for replicating single-gene epilepsies. Both approaches have methodological challenges, particularly with respect to the development of sufficiently homogeneous populations of neuronal or glial cells. Neurons derived from induced pluripotent stem cells do not fully recapitulate mature neurons, but further elaborations on the horizon will allow more realistic in vitro models. These include cerebral organoids that develop more tissue-like cortical structure and lamination patterns[77] and are amenable to so-called slice recording approaches. In principle, CNNs have all the advantages of a model that efficiently captures multiple aspects of the disease biology and pharmacology, and provide a direct pathway to the incorporation of human brain cells into the drug-discovery process.

Whole-animal models

Many model organisms have contributed to advances in epilepsy gene research, including rodents, flies, fish and invertebrates,[78–83] with the mouse being the most successful and widely used. Experiments with mice have contributed substantial insights into epilepsy pathogenesis,[84,85] and specific gene discoveries in the mouse have often anticipated later findings in human beings.[83,86–88] Explicit gene targeting[89–92] and editing[84] now noticeably enhance the use of mice in precision medicine approaches. Whole animal models provide excellent behavioural and electroclinical correlates of seizure activity in the absence and presence of drugs. Because scalability in the whole animal model is a concern for *in vivo* screening, the use of lower organisms such as Caenorhabditis elegans (worm) or Danio rerio (zebrafish) afford improved throughput has also been undertaken. However, the advantage of scalability of lower organisms may be offset by the cost of losing the ability to evaluate some comorbid symptoms, including depression, anxiety, movement disorders, intellectual disability, and other cognitive impairments. Moreover, the identification of a drug that rescues a phenotype in a fish, worm, or fly will likely require validation in mice or *in vitro* human cell models before moving to clinical trials in human beings, although some promising therapeutic directions have emerged from studies in these organisms.[93] Thus, mouse models of genetic epilepsy continue to be crucial as they fulfil several of the above criteria, including the provision of a ready source of neurons for ex-vivo single-cell and network analyses, most readily bridging clinically relevant spatiotemporal scales through sufficient behavioural complexity at the organism level. Importantly, use of mouse models allows screening for adverse effects on other organ systems.

Treatment modalities

Several factors must be considered in the search for candidate treatments for genetic subtypes of epilepsy, including potential toxicities of the treatment and the severity and prevalence of the disorder. Development strategies should be informed, to the extent possible, by the genetic and biological causes of the disease. The EEs illustrate all of these considerations most clearly since they often result from highly penetrant mutations in genes with at least partially elucidated biological roles in epileptogenesis.

To facilitate the development of new treatments for genetic epilepsies, a clear functional readout of the mutations that is both related to how the mutation causes disease and whether it is amenable to screening is essential. Once such information is available, assessment of drugs approved for other indications that revert the phenotype of interest (so-called "repurposing") is an obvious priority. However, the fortuitous coincidence that an effective compound for a particular genetic epilepsy is already clinically available cannot be relied upon, and systems amenable to high-throughput screens for a range of new compounds should be a major priority.

A key first consideration in any screening effort is the "druggability" of the relevant gene product. Some researchers suggest that only 5% of human genes are both druggable and disease relevant.[94] Although new small molecule strategies might increase the number of druggable targets, the development of alternative drug discovery approaches that rely on targeting alternative proteins in the same disease networks and pathways will be essential. For example, treatment of epilepsy caused by a loss-of-function mutation might be limited to treatment with compounds that activate compensatory mechanisms. Although a mutation can be appropriately expressed, some *in vitro* models may not have enough complexity to enable the assessment of compounds that compensate for deficiencies created by mutant proteins. However, we expect that the assessment of drug effects in CNNs, human cells, and mouse models in concert will be able to overcome these limitations.

In cases for which no active drugs are known and the screening of approved drug libraries fails to identify new treatments, consideration must be given to screening new chemical entities. Bioactive peptides from venom libraries[95] are a rich source of molecules biologically selected to act on nervous system targets. Anti-sense oligonucleotides, currently in clinical trials for various disorders,[96] can cause long-term knockdown of specific genes and are therefore compatible with gain-offunction mutations, and could potentially be applied in an allele-specific manner. Small molecule drug screening can provide a longer-term strategy for delivery of novel drugs using single cell and network assays as primary screens. Finally, viral delivery of genes or knockdown oligonucleotides has shown promise in mouse models,[97,98] and efforts to target, "de-target," and ensure the safe delivery of these products in human beings are on the horizon. These methods could prove to be particularly useful for loss-of-function mutations for which Replacement strategies may be the only approach. We note that drug discovery efforts within this framework will not be limited to academic research. In fact, pharmaceutical companies are showing interest in pursuing treatments for genetic conditions, as emphasized by the development of genetically targeted treatments for cystic fibrosis (CFTR), and by many drug development efforts inspired by

human genetics (eg, PCSK9). Importantly, pharmaceutical companies are also much better equipped than academic laboratories to rapidly screen for potential adverse reactions to candidate therapeutic compounds not yet tested in human beings.

The availability of multiple avenues of treatment development, in combination with the emerging high-throughput efficacy screening methods in cellular models, makes tractable treatments for genetic epilepsies an increasingly realistic goal for the near future.

Frameworks for testing genetically targeted Therapies—Although precision diagnostics in the clinical management of epilepsy is not new,[99–101] advances in genetics suggest that the possibility of considerably improved targeting of treatments to precise underlying causes will not only control seizures, but also improve neurodevelopmental outcomes. However, there are practical barriers to clinical implementation of precision medicine that need to be overcome. Access to clinical genetic testing needs to be increased and should be widely available for epilepsies such as the epileptic encephalopathies, for which abundant evidence suggests that the current diagnostic yield could be 15–20%,[35,58,59,102–105] and the rate of gene discovery suggests that this proportion will continue to increase. Making such diagnostic evaluation available to all individuals with epilepsy, even in resource-poor environments, is crucial. Dedicated multidisciplinary epilepsy clinics with expertise in genetic epilepsy, not currently available to all patients, will be required to facilitate early expert clinician involvement in diagnosis and optimization of treatment; such clinics would be ideally placed to act as clinical trial centers. Furthermore, application of precision diagnostics and treatment has ethical, legal, and social implications of genetics for people with epilepsy and their family members; consideration of individual preferences, psychosocial impacts, and equity of access should be a priority.

Examples of effective precision therapy in genetic epilepsies are already emerging. The first is in glucose transporter deficiency syndrome, generally caused by mutations in the *SLC2A1* gene and treated with a ketogenic diet.[99] The second is for pyridoxine-dependent epilepsy, typically caused by mutations in the *ALDH7A1* gene and treated with pyridoxine (vitamin B6).[99,101] These treatments became established through decades of anecdotal treatments, case reports, and case series rather than randomized controlled trials. Currently, diagnosis of these and other potentially treatable disorders[100] is still often delayed because of wide phenotypic variability leading to delay in testing. This delay will be rectified only by large-scale comprehensive genomic testing across the epilepsies.

Several genetic epilepsies now amenable to prompt genetic diagnosis[106] are candidates for controlled trials of potentially effective, disease-modifying precision therapies. In some instances, suggestions of targeted therapies have been based on the results of elegant *invitro* studies showing reversibility of underlying functional defects and suggesting application in human cases.[102] These cases include individuals with *KCNT1* mutations treated with quinidine,[107,108] children with KCNQ2 mutations treated with ezogabine (retigabine),[109] individuals with GRIN2A mutations treated with memantine,[110,111] and patients with so-called mTORopathies treated with everolimus.[112–114] Epilepsies with these mutations can present in infancy with encephalopathy and seizures, can be diagnosed with targeted gene panels or exome sequencing, often do not respond to currently available treatments, and are

obvious candidates for organized, multi-center clinical and translational research initiatives. Although it is far from clear that these initial candidate therapies will prove to be safe and effective, they illustrate a precedent for the use of appropriate functional models to identify new, targeted treatments for assessment in the clinic.

An initial step to improve the evidence base for epilepsy precision treatment is a curated registry of therapeutic trials for rare genetic epilepsies. A registry is a key requirement and will facilitate the development of appropriately powered clinical trials to assess treatment effects. It is inevitable that some targeted treatments of genetic epilepsies will take place outside of multi-center, controlled trials as these are often disorders with devastating consequences, and families might be unwilling to wait for the results of properly designed trials. Such registries, when combined with careful phenotyping data about specific genes and functional profiling of mutations, will provide information on dosing and side effects and generate hypotheses for more rigorous trials. A platform such as EGI, for example, will provide a phenotype and genotype data repository and could be expanded to include data on successful and unsuccessful precision treatments, side effects, and other consequences. A registry such as this would provide a portal for analysis of the evidence for a personalized treatment choice for each disorder.

In addition to registries, multi-center, randomized, controlled trials are needed – and are feasible. The high seizure burden in genetic EEs, combined with the potential for a rapid therapeutic effect of some precision treatments,[108] makes the cross-over trial design, lasting 2–6 weeks and comparing precision therapy with placebo or conventional therapy, a valid and robust study design to assess short-term efficacy. Long-term efficacy, safety, and neurodevelopmental outcomes can be assessed with open-label extensions of the initial controlled trials. On the basis of early case reports,[108] the therapeutic effect could be rapid and pronounced, and as few as 10–20 study participants might be sufficient to assess some precision therapeutics in a controlled trial. For epilepsies or investigational compounds needing a trial of longer duration, controlled trials are still possible with careful attention to inclusion and exclusion criteria as well as outcome measures. Multi-center collaborations using EGI, the Pediatric Epilepsy Research Consortium (PERC) (http://www.pediatricerc.com/), and the US National Institutes of Health NeuroNEXT trial network present an opportunity for future research initiatives. Moreover, extending these networks to allow input from global networks of clinicians will enable more rapid accrual of outcomes and inform improvements in clinical care. Non-profit epilepsy advocacy groups and social media will be vital in raising awareness of trials and in directing potential participants to study sites. In some cases, drugs being investigated might have broader therapeutic implications and pharmaceutical companies could be sponsors or valuable partners. In other cases, just as with quinidine to treat individuals with *KCNT1* mutations, the drug might be widely available as a generic drug with little profit potential, so support for trials from government and non-profit organizations will be needed.

Since specific mutations in epilepsy genes (i.e., mutations causing gain- or loss-of-function) can have profound implications for precision therapeutics, a clinical trial network will ideally be directly linked to a collaborative group of geneticists and experts in *in vitro* functional models. All newly identified mutations in known epilepsy genes must be

analyzed expeditiously to determine their *in vitro* pathological effects and potential for therapeutic correction. As knowledge of epilepsy gene pathways, such as the mTOR pathway, evolves, the prospect of treatments that target the pathways could be assessed in a similarly collaborative way. Since the underlying molecular mechanisms of the genetic epilepsies and potential therapeutic targets converge on specific homeostatic pathways, such as disruption in cell signaling, cell growth, vesicle fusion and release, and ion channel function, the molecular mechanisms behind genetic epilepsies become tangible and targetable. Therefore, an organized effort to characterize mutations and assess possible treatments is of great interest to clinicians, academic basic scientists, the pharmaceutical industry, and most of all individuals with epilepsy and their families.

IV. Conclusions

The considerations and examples outlined above make it clear that precision medicine could transform clinical care in epilepsy, and in so doing will establish a new paradigm in the treatment of the epilepsies (Figure 3). Precision medicine in epilepsy will probably emerge first in epilepsies that are most strongly determined by single mutations of major effect that can be accurately modeled in vitro, in particular the EEs (Figure 2). Although this prediction could seem to imply that only the strongly genetic epilepsies will benefit from precision medicine, it is worth appreciating that some targeted treatments for genetic epilepsies might find wider applications in other epilepsies. Although this nascent specialty already has a number of successful examples of genetics guiding therapy, the development of precision medicine in epilepsy needs a broad range of tools, techniques, and approaches that are never present in single laboratories and are often difficult to assemble without the appropriate mechanisms and structures.

A systematic approach to precision medicine in epilepsy will require the following: 1) large cohorts of individuals with epilepsy who have been carefully characterized phenotypically and genomically; 2) standardized functional characterization of mutations in each of the epilepsy genes and careful co-interpretation of functional readouts for studied mutations incorporating information about the frequency of mutations and mutation types in cases and controls; and 3) the initiation of well-designed clinical trials when functional work identifies new targeted therapeutics. Meeting these goals depends on the development of collaborative and integrated research groups that bring together researchers with clinical, genetic, and biological expertise.

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In September 2014, 100 scientists, clinicians, and representatives from lay organizations, industry, and government assembled for the *Epilepsy Genetics in the Era of Precision Medicine* Meeting in Half Moon Bay, California to map out to develop a strategy for the advancement of precision medicine in epilepsy. This perspective reflects the discussions from the two day conference. The meeting was organized by Dan Lowenstein and was funded by John and Barbara Vogelstein, Ron and Sanne Higgins, The Joseph and Vera Long Foundation, Richard Thalheimer, Citizens United for Research in Epilepsy (CURE), Epilepsy Foundation, Ambry Genetics, GeneDx, Biogen, and Lundbeck. All of the authors participated in the meeting. We would like to thank all participants for their insight and contributions to the meeting.

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Conflicts of Interest

Dr. Berkovic reports personal fees from Bionomics and Athena in the past. Dr. Berkovic also has a patent for DEPDC5 testing applied for by University of South Australia and University of Melbourne pending, and a patent for SCN1A testing held by Bionomics Inc. and licensed to various diagnostic companies.

Dr. Goldstein reports personal fees from LabCorp, Clarus Ventures, Astra Zeneca, Johnson & Johnson, Takeda, Teva, and Eli Lilly.

Dr. Mefford reports personal fees from SFARI Gene Advisory Board and Sera Prognostics.

Dr. Petrou reports personal fees from Bionomics Limited in the past and patents for SCN1A testing held by Bionomics Limited and licensed to various diagnostic companies.

Dr. Scheffer reports personal fees from UCB, Athena Diagnostics, Transgenomics, GlaxoSmithKline, Sanofi, Eisai. In addition, Dr. Scheffer has a patent Diagnostic and Therapeutic Methods for EFMR (Epilepsy and Mental Retardation Limited to Females) with royalties paid.

Dr. Traynelis reports personal fees from NeurOp Inc. and Janssen. In addition, Dr. Traynelis is a co-inventor on US Patents 7,375,136 and 8,420,680 licensed to NeurOp Inc, and is a co-founder of NeurOp Inc., a pharmaceutical company developing NMDA receptor modulators for the treatment of neurological diseases.

Glossary of Terms

CRISPR-Cas system	A novel gene-editing system derived from a prokaryotic immune system that confers resistance to foreign genetic elements. The system delivers the Cas9 protein and appropriate guide RNAs into a cell, allowing the organism''s genome to be cut at any desired location and edited to include specific sequences of interest.
Cultured neural networks (CNNs)	Cultures of neurons and support cells used to create an in-vitro model of communicating neurons. Cultured neural networks provide a controlled environment in which to investigate neuronal activity and the effect of mutations on that activity. The behaviour of cultured neural networks can be monitored with non-invasive approaches, including multielectrode array technology and optogenetic approaches.
De-novo mutation	Agenetic mutation present in a child that is not present in either parent (ie, not detectable by conventional means of assaying DNA from leucocytes) and usually arises in an individual as a result of a germ-cell (egg or sperm) mutation in one of the parents.
Druggability	The extent to which a particular protein can be modulated by a drug acting on that target (ie, largely on the basis of how drugs work).
Epileptic encephalopathies	Severe forms of epilepsy, generally beginning in childhood, typically associated with intellectual disability, where the epileptic progress may contribute to severe cognitive and behavioural impairments.
HEK293 cell line	A cell line originally derived from human embryonic kidney (HEK); HEK293 cells are easy to grow in culture and have been

	used widely for gene expression studies and heterologous gene studies.
Induced pluripotent stem cells (iPSCs)	Cells that are reprogrammed into a state that is capable, in theory, of differentiating into any type of human cell with the right types of stimulation.
Locus heterogeneity and allelic heterogeneity	Locus heterogeneity relates to the number of genes that can affect a trait. Allelic heterogeneity relates to the number of different alleles at a locus that can affect a trait.
Multi-electrode array (MEA)	A system to monitor non-invasively the electrical activity of cultured neural networks. This system is typically used in single-well or multiwell (12–96 wells per plate) formats with embedded electrodes, which monitor the action potentials of a small subset of the neurons in each of the cultured neural networks.
Optogenetics	In the context of this Personal View, optogenetics is a method that uses rhodopsin proteins to allow optical control and monitoring of neuronal membrane potentials.
Precision diagnostics	The use of genomic and related technologies to determine the precise cause of epilepsy in individual patients.
Precision medicine	While precision medicine generally refers to the scientific basis that underpins the personalization of medical care the term here is primarily used in the context of targeting treatments to the precise molecular and physiological causes of disease

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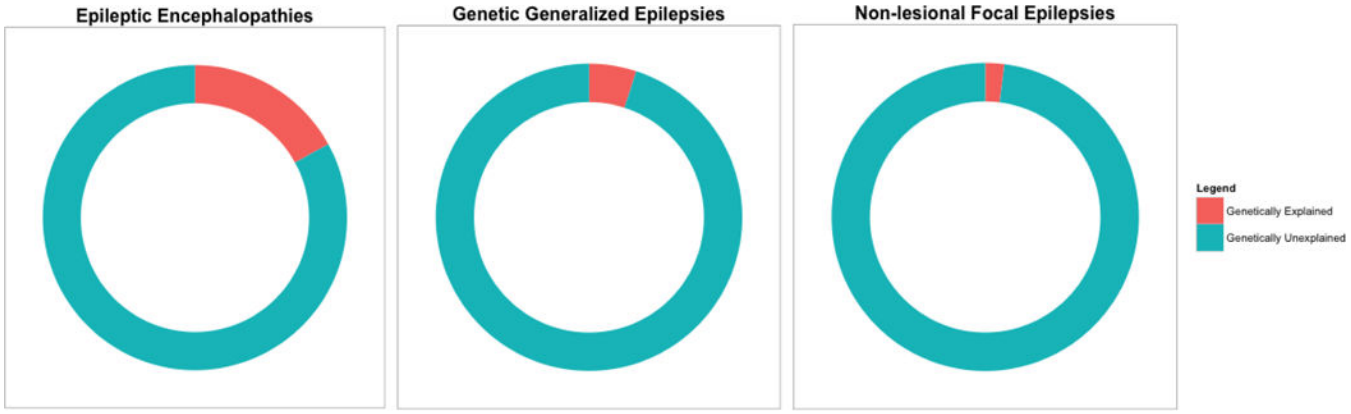

Figure 1.

Estimated proportion of individuals with different types of epilepsy who carry a strong-acting, single mutation that either contributes substantially to or causes epilepsy.

Source: Kalachikov et al (2002),[14] EuroEPINOMICS-RES Consortium, Epilepsy Phenome/Genome Project, Epi4k Consortium (2014),[35] Epilepsy Phenome/Genome Project Epi4K Consortium (2015),[57] Mefford et al (2011),[58] Olson et al (2014),[59] Dibbens et al (2013),[60] Ishida et al (2013),[61] Picard et al (2014),[62] and Thomas et al (2014).[63]

A.

ALDH7A1'	CHRNA2'	DEPDC5'	GNAO1'	IER3IP1'	KCNT1'	PNKP'	SCN1A'	SLC13A5'	SRPX2'	SZT2'
ALG13'	CHRNA4'	DNM1'	GOSR2'	KCNA2'	KCTD7'	PNPO'	SCN1B'	SLC25A22'	ST3GAL3'	TBC1D24'
ARHGEF9'	CHRNB2'	EEF1A2'	GRIN1'	KCNB1'	LGI1'	PRICKLE1'	SCN2A'	SLC2A1'	STRADA'	WWOX'
ARX'	CLN8'	EPM2A'	GRIN2A'	KCNC1'	MEF2C'	PRICKLE2'	SCN8A'	SLC35A2'	STX1B'	,
ASAH1'	CNTNAP2'	GABRA1'	GRIN2B'	KCNMA1'	NHLRC1'	PRRT2'	SCN9A'	SLC6A1'	STXBP1'	,
CDKL5'	CPA6'	GABRB3'	HCN1'	KCNQ2'	PCDH19'	RELN'	SIAT9'	SNIP1'	SYN1'	,
CHD2'	CSTB'	GABRG2'	HNRNPU'	KCNQ3'	PLCB1'	SCARB2'	SIK1'	SPTAN1'	SYNGAP1'	,

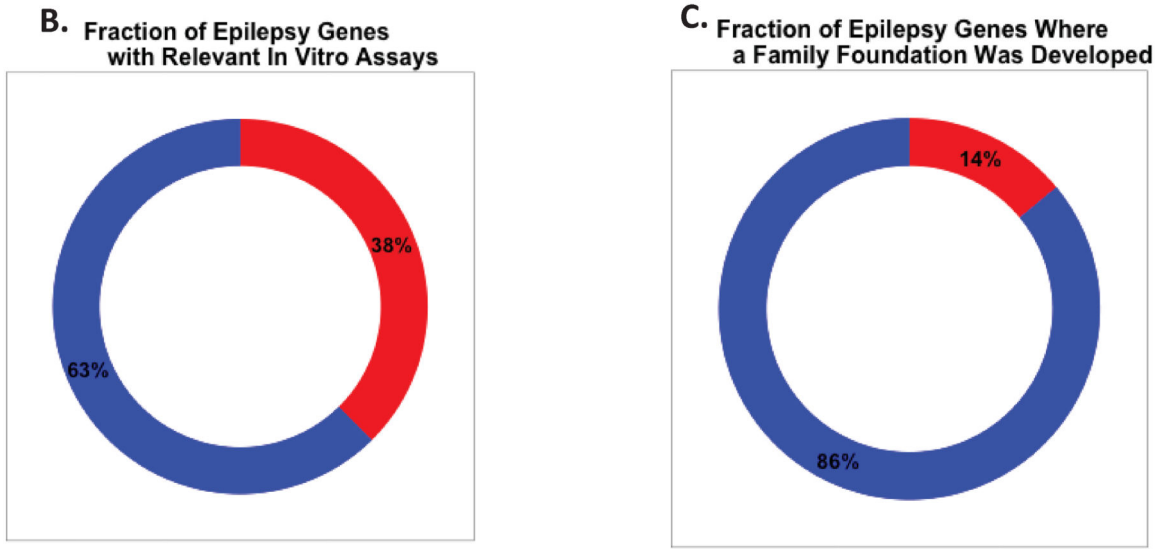

Figure 2.

Genes known to be associated with epilepsy, broken out by those with relevant in-vitro models and those with research support from family foundations (A) List of known epilepsy genes. (B) The estimated percentage of epilepsy genes for which an in-vitro assay is available to accurately assess the effects of mutations (in red). (C) The percentage of epilepsy genes for which research is actively being driven by family foundations (in red).

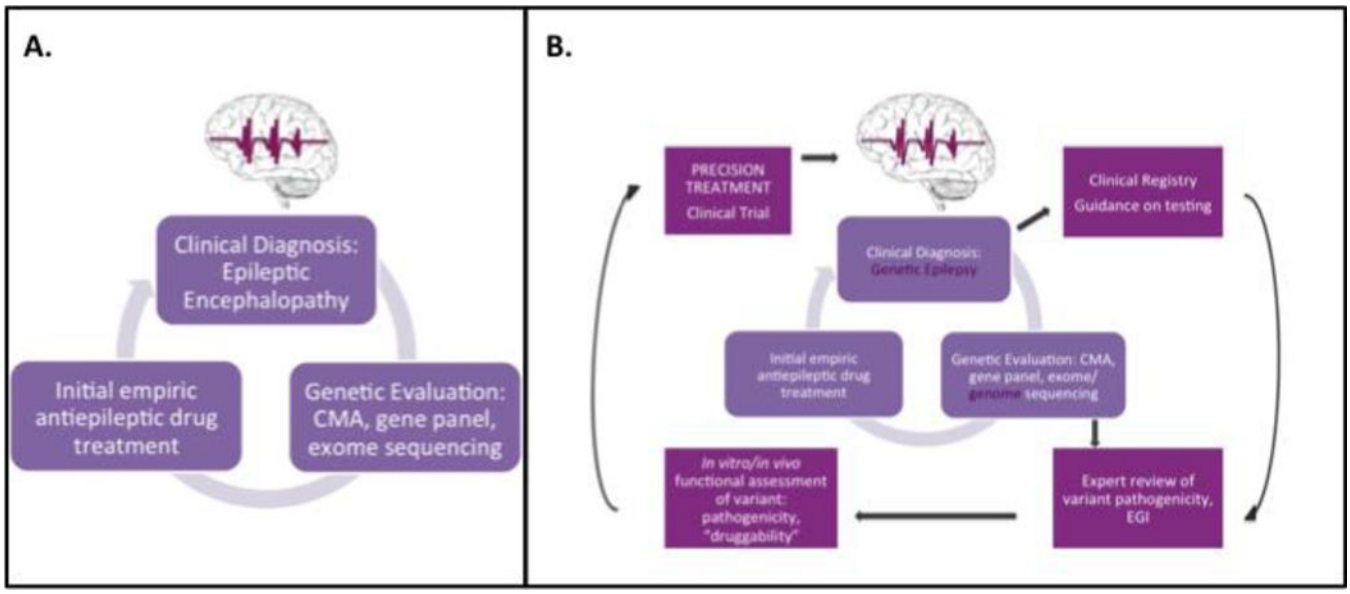

Figure 3.

Current practice for genetic diagnosis in epilepsy and the envisioned future of precision medicine in epilepsy (A) Current practice for genetic diagnosis in epilepsy. (B) New additions to the approach of precision medicine are highlighted in purple boxes. In the envisioned model of precision medicine in epilepsy, all types of non-acquired epilepsy will be assessed, and basic, clinical, and translational science will be closely integrated to drive the development of precision therapies.