Archives of Epilepsy

Review

Precision Medicine and Pediatric Epilepsy

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Cite this article as: Ünalp A, Adalıoğlu E. Precision medicine and pediatric epilepsy. *Arch Epilepsy.* 2022;28(2):48-52.

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Received: October 6, 2021 **Accepted:** December 13, 2021 **Available Online:** April 2022

DOI: 10.54614/ArchEpilepsy.2022.05657

Abstract

Recently, it is time to shift from a reactive attitude that treats patients after the onset of seizures to a proactive one integrated into a broader "P4 medicine" approach in the treatment of epilepsy. Personalized, predictive, preventive, and participatory, this P4 approach puts patients at the center of their care and ultimately aims to prevent the onset of epilepsy. This goal will be achieved by tailoring epilepsy treatments not only to a particular syndrome but also to a particular patient and moving from the usual anti-seizure treatments to individualized treatments designed to target specific etiologies. In this review, we present the current state of this ongoing revolution, highlighting the emergence of the concepts of precision medicine and individualized medicine and its impact on clinical practice in pediatric epilepsies.

Keywords: pediatric epilepsy, precision, personalized, preventive, medicine

INTRODUCTION

There has been a rapid increase in the knowledge of the genetics of epilepsy in a few years. There are many genetic tests that can be used for diagnostic purposes in clinical practice. Especially, next generation sequencing (NGS) method to detect the genetic mutations leading to epilepsy is very effective in one-third of patients. This development also resulted in giving an idea about the pathophysiology of epilepsy and, as a result, paved the way for precision medicine defining potential therapeutic targets.[1] In this article, we shall explain what precision and individualized medicine are, what is the origin of these terms, what should pediatricians and neurologists know about this issue, and finally we will try to inform them about the age of precision medicine in patients with epilepsy.

The main purpose of the study of Alonso et al[2] is to investigate available predictive, personalized, preventive, participatory medicine research studies in telemedicine and e-health.

Most of these publications demonstrate how P4 medicine (personalized, predictive, preventive, and participatory) developed in the world and the benefits of P4 medicine to patients with different disorders. P4 medicine is crucial to ameliorate the medical services. One of the main benefits of studies is to provide an insight into how P4 medicine is applicable in telemedicine and e-health and also to prevent and predict diseases for the future. [2]

Precision medicine is defined apart from the concept of adapting tests and treatments from ancient times or ambiguously defined to an individual patient. Actually, in order for individual-level therapies to be performed on patients and to become a new paradigm, the use of -omic (e.g., genomic, proteomic, epigenomic markers) is required. This is used to divide cohorts into genetic groups instead of clinical, laboratory, or physiological findings. However, the necessary rules of evidence-based medicine still apply.[3]

Personalized medicine, precise medicine, P-medicine, and personalized genomic medicine are frequently used interchangeably. Personalized medicine can be considered as individualized health services to patients, at the right time and with the right drug doses including prevention of diseases. Besides, it can be considered as an adaptation of the patient to the individual, environmental, and genetic characteristics, needs, and preferences during the diagnosis, treatment, and follow-up phase.[4] Due to these and many other features, the concept of personalized medicine is frequently used in the media. However, it appears that the concept is used to express different situations. The future of medicine requires many changes, including making an advanced diagnosis for diseases, detecting genetic predisposition to diseases earlier, gene therapy, and supporting pharmacogenetics for personalized drugs. The fundamentals of this change began with the Human Genome Project. Functional genomic studies are designed to contribute to the development of more effective drug therapy with two main aspects. First, functional genomic approaches will help determine the most appropriate targets for drug treatments. Second, pharmacogenomics will help in determining why patients react differently to drugs. Genetic models that describe these reactions are defined and developed and aimed to use drugs more effectively.[5] This approach

also provides personalized/precision medical treatment possibilities. Today, personalized medicine is a developing field, using diagnostic tests to determine which medical treatments will work best for each patient. Gronowicz[6] explained personalized medicine as "broadly trying to identify genetic, phenotypic, or environmental factors that affect a person's health risks." Personalized medicine can offer the option of trying treatment with less damage to the body, with fewer or no side effects, rather than relying solely on known drugs for the treatment of a particular patient.

Goetz and Schork[7] classified the elements of personalized medicine that need to be integrated and evaluated as access to health care, genetic and genomic structure of the individual, tissue biomarkers, environmental factors, behavior and personality traits, and epigenetic modifications.

Although many researchers use the terms "personalized medicine" and "precision medicine" interchangeable, it is worth noting that many also argue that there are some important but subtle differences between them.[8]

The concept of "precision medicine" was first featured by Christensen et al[9] 2009 in his book *The Innovator's Prescription: A Disruptive Solution for Health Care*. However, this term did not gain widespread acceptance and use until a report titled "Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease" was published by the US National Research Council (NRC) in 2011.[10] Instead of a symptom-based classification system, the report laid out some recommendations for disease ontology based on causal genetic variants or molecular information content in the genomic information form. The first focus of precision medicine has been on the genetic and genomic basis of diseases. For example, a pre-definition of "Precision medicine, personalized service tailored to each patient's own genetic profile, and medical history" was given by the Institute of Precision Medicine.[11] But it is quite difficult to distinguish the main differences between precision medicine and personalized medicine.

Precision medicine includes predictive, preventive, pharmacotherapeutics, and patient participatory medicine. Current traditional medicine aims for treatment after the onset of the disease, based on the population comparison model. Precision medicine, on the other hand, involves the prevention of potential diseases that may occur, by examining the genotype.

Precision medicine stated that medical treatment is tailored to the personal characteristics of each patient. Rather than literally creating drugs or medical devices specific to a patient, precision medicine means classifying individuals into subpopulations that differ in their susceptibility to a particular disease, biological diseases, and/or prognosis. Although the concept of "personalized medicine" is also used to convey this meaning, it is misinterpreted as implying that unique treatments can be designed for each individual. Therefore, the NRC stated that the term "P-Medicine" was preferred to the term "personalized medicine" to convey the meaning stated in this report.[10,12]

"Personalized" medicine is a model of N-of-1, in which each patient is considered the only patient treated. "Precision" medicine, on the other hand, resembles the 1-in-N model, allowing a more traditional western medicine approach to conducting research on groups and subgroups and treating the patient's specific subgroup. It is also stated that "personalized" medicine is based on the individual N-of-1 model; "precision" medicine uses the 1-in-N model based on the widely used biostatistical data analysis and "big data" analytical tools. "Precision" medicine can best be defined as a mixture of "personalized" medicine, modern and traditional medicine. This illustrates the taxonomic relationship between precision and personalized medicine.[13,14]

While the same drug can have serious, even life-threatening, side effects in one person, in another, negative effects are less common and treatment may be favorable, or an anticancer drug can downsize the tumor in one person, while in another person it cannot. One of the most important reasons for this difference is the diversity in people's genomes, and even small changes can affect how the body reacts to certain drugs. Pharmacogenetics is a science that examines how genetic changes in individuals affect their response to drugs. Pharmacogenetics is a sub-branch of pharmacogenomics. Pharmacogenomics is a part of precision medicine. Pharmacogenomics is the study of how a person's unique genetic structure (genome) affects the response to drugs.[15] All this has led to new approaches to drug discovery, a personalized application of treatment, and new ideas on disease prevention. Today, the approach in drug therapy is to treat large patient populations as groups, regardless of potential individual and genetically based differences in drug response. In contrast, pharmacogenomics can help to focus on effective treatment in smaller patient subpopulations characterized by different genetic profiles, although the same phenotype of disease is seen.[16] The genes are encoded from DNA found in all human cells and may affect the individual response to drugs. DNA is mainly an important part of our chemical operating system in the body and determines how the body behaves and interacts at the cellular level. For example, a patient may have a genetic variation that allows the drug to remain in the body longer than usual, causing serious negative effects, or another person may have a variation that makes the drug less effective.[17]

Pharmacogenomics, like pharmacogenetics, have genomic technologies that have a high potential to positively influence the field of medicine.[18] It is thought that pharmacogenomic applications can improve patient safety and health outcomes, reduce healthcare costs, and thus give the right drugs to the right patients.[17]

The rapidly expanding genetic knowledge base in epilepsy is well suited for the development and dissemination of targeted therapeutics in precision medicine due to the availability of in vitro and in vivo model systems. Establishing joint research groups is critical going forward, especially strengthening these collaborations to provide both accurate personal genome analysis and analyses for gene and drug discovery. Similarly, the application of clinical research networks may enable the expansion of patient populations with genetically defined epilepsy so that drug discovery can be translated into clinical practice.[19]

Precision Medicine in Pediatric Epilepsy

Epilepsy is the most common disease with neurobiological and psychosocial aspects in children. While our knowledge of the etiology of epilepsy was more limited in the past, today we are about to enter the age of precision medicine in pediatric epilepsy with new technical tools and tests.[20]

Epilepsy includes a number of medical conditions in which recurrent seizures are the common feature. A large number of different types of syndromes and seizures, as well as highly variable interpersonal responses to therapies, often complicate the management of this condition.

In the last two decades, a genetic etiology has been revealed in more than half of all epilepsies, and single-gene defects in ion channels or neurotransmitter receptors have been associated with most hereditary forms of epilepsy, including some focal and lesional forms, as well as developmental encephalopathies and epilepsy syndromes.

A variety of genetic tests are now available, including revolutionary tests and targeted analyses making it possible to sequence all encoder (whole exome) and non-encoder (whole genome) regions of the human genome.

These latest technological advances have also led to genetic discoveries in epilepsy and increased our understanding of the molecular mechanisms of many epileptic disorders and eventually provided targets for precision medicine in some syndromes such as Dravet syndrome, pyridoxine-dependent epilepsy, and glucose transporter-1 deficiency syndrome. Today, genetic testing is available for most developmental epileptic encephalopathy and idiopathic epilepsies and plays a crucial role in the diagnosis of these complex conditions. In addition, the results of genetic testing can affect treatment management and therefore improve patient care. The most likely scenario in the next years is that epilepsy treatment will be very different from the empirical approach at the moment and will ultimately be a "precision medicine" approach that can be applied on a large scale.[21]

In the last decade, advances in genetics, neuroimaging, and EEG have led to earlier identification of the etiology of epilepsy ever than before. At the same time, progress in the research of experimental epilepsy models provided a better understanding of the underlying mechanisms of the condition and the identification of treatments targeting specific etiologies. We are now witnessing the impact of these advances on our daily clinical practice.[22]

Epilepsy is a chronic neurological disease that affects more than 70 million people worldwide. Although there are more than twenty anti-seizure drugs (ASD) for symptomatic treatment of epileptic seizures, about a third of patients with epilepsy have drug-resistant seizures. Patients with this type of drug-resistant epilepsy (DRE) have risks of premature death, injury, psychosocial dysfunction, and poor quality of life, so the development of more effective treatments is an urgent clinical need.

However, various types of epilepsy and seizures and complex models of resistance complicate the problem. Furthermore, although recent studies have begun to shape our understanding more clearly, the underlying mechanisms of DRE are not fully understood.

DRE's experimental models offer opportunities to explore, characterize, and challenge the default mechanisms of drug resistance. In addition, such preclinical models are important in the development of treatments that can overcome drug resistance.

Encouragingly, better clarification of pathophysiological mechanisms that explain epilepsies and drug resistance through preclinical and clinical efforts suggests that the long-awaited breakthrough in treatment for patients who are not yet resistant to ASD is a viable goal, with new multi-targeted ASDs for severe pediatric (monogenetic) epilepsies and acquired partial epilepsies.

Drug resistance constitutes a major difficulty in epilepsy management. The current understanding of the molecular, genetic, and structural mechanisms of drug resistance in epilepsy must be reviewed multidisciplinarily, and studies with precision medicine applications are needed.[23]

Genetic abnormalities reportedly cause or affect more than 70% of epileptic conditions (i.e., to say, conditions where epilepsy occurs as a core or associated symptom).

Epilepsy caused by single-gene mutation is complicated because single-gene mutations may cause variable phenotypes, and different-gene mutations may cause the same phenotype. Syndromes such as genetic epilepsy tend to occur in infancy or childhood, and genetic testing has become an integral part of pediatric epilepsy.

Due to the evolution of diagnostic techniques, from narrowly applicable tools [e.g., on-site fluorescent hybridization (FISH) and single-gene testing] to the tests such as multigene panels, whole-exome sequencing (WES), whole-genome sequencing (WGS), and chromosomal microarray have been used in pediatric epilepsy. Table 1 demonstrates their advantages and disadvantages.

Next-generation sequencing (NGS) expands the list of epilepsy-related genes and also unveils the variable patterns that reveal these genes, predicting potential pathogenicity, disease pathophysiology, and may evolve into therapeutic targeting.

Most studies involve epilepsy gene panels or WES. The number of genes in epilepsy panels is increasing rapidly, and the epilepsy panel including mitochondrial gene testing covering a total of 553 genes is now available.[24] The cost of the entire exome and genome test is rapidly decreasing; these genetic tests could be the next choice of tests after imaging.

Epigenetic factors are very broad and DNA methylation, histone modification, and non-coding RNA are the most effective epigenetic factors in pediatric epilepsy. Such factors have a more detailed diagnostic value; they can clarify the symptoms and evolution of the disease.

DNA methylation is an epigenetic marker because it can regulate many genetic epilepsy-related diseases (e.g., Dravet, benign familial neonatal seizures, and epileptic neurodevelopmental disorders), gene expression, and functioning that modifies the associated disease (e.g., KCNQ3, SCN3A, and GABRB2, respectively). In addition to NGS, epigenetic biomarkers are also beginning to play an important role in etiopathogenesis.

When choosing metabolic or genetic tests, clinician awaits many challenges, such as deciding the order of tests, choosing the type of screening test, considering the cost of the tests, and comparing the quality of laboratory tests.

Confirming the disorder, the type of epilepsy according to the clinical history, and an EEG, neuroimaging to reveal the structural causes of epilepsy are the first steps in most cases. The next set of metabolic or genetic tests to identify etiology is variable according to the patient.

To determine a treatable cause of epilepsy, it should always be accompanied by a trial from treatment to diagnosis. Controlling seizures will only be possible in some cases when you find the cause of epilepsy. Try with pyridoxine, folinic acid, and biotin, even if you have tested it.

Table 1. Genome Sequencing Tests[21]

Genetic Tests	Method	Types and Technical Differences	Advantages	Disadvantages
Multigene panels	- Sequences groups of genes causing a phenotype	- Sequence analysis with/without deletion/duplication analysis	- May be able to detect mutations that are missed in comprehensive gene testing (e.g., ARX gene and SCN1A23) - Can design specific multigene panels - Generates fewer variants of unknown significance	- Tests only for the genes in the panel unless done as part of whole-exome sequencing
Comprehensive Gene Testing				
Exome sequencing	- Sequences protein-coding regions only	- Sequence enrichment - Single- or paired-end sequencing - Read depth - Accuracy of base calling - Family testing-trio sequencing	- More useful for hard-to-characterize epilepsy phenotypes - Sequencing has reported sensitivity. - Covers genes that may not be in multigene panels - Can identify variants of uncertain significance that may be pathogenic - Can be reanalyzed	- Generates a large number of variants of unknown significance - Cannot detect imprinting errors, uniparental heterodisomy, nucleotide repeats, pseudogenes, non-coding regions, mitochondrial genes, mosaic changes, large copy number variation, or chromosome rearrangements - Results may take four or more weeks to return
Genome sequencing	- Sequences all coding and non-coding regions	- Has similar laboratory limitations as listed for exome sequencing	- Has the same advantages as exome sequencing - Less arduous sample preparation - Can identify structural variants and chromosome breakpoints in non-coding regions	- Many of the same limitations as exome sequencing - Some exons may not be sequenced - More expensive than exome sequencing
Chromosome microarray	- Detects copy number deletions or duplications of variable sizes	- Oligonucleotide array (comparative genomic hybridization) - Polymorphism genotypic (single-nucleotide polymorphism)	- Available in many medical facilities - Covered by insurance and Medicaid	- Does not analyze all exomes or genome - Does not sequence genes in the targeted regions analyzed

Table 2 lists gene mutations for some treatable causes of epilepsy. Early diagnosis and treatment of these disorders are important to improve the long-term outcome.

However, a recent cost analysis community-based study reported by Howell et al[25] found that early use of WES, along with metabolic tests, provided the highest diagnostic efficiency at the lowest cost. This study strongly demonstrates the need for gene panels, WES, or WGS use with diagnostic precision in a patient with epilepsy.

The use of new diagnostic tools begins with a good anamnesis and physical examination and can provide very important information in

Table 2. Treatable Epilepsies in Pediatric Epilepsy[21]

Type of Epilepsy	Gene	Treatment
Cerebral folate deficiency	Folate receptor defect or folate receptor antibody	Folinic acid or methylfolate
Pyridoxine-responsive epilepsy	*ALDH7A1*/alpha aminoadipic semialdehyde	Pyridoxine and folinic acid
Pyridoxal 5'-phosphate-dependent epilepsy	*PNP0/PNP0* enzyme	Pyridoxal 5'-phosphate
Glucose transporter defect	*SLC2A1/*glucose transporter protein type 1	Ketogenic diet
Biotinidase deficiency	BTD/biotinidase	Biotin
Biotin-thiamine-responsive basal ganglia disease	SLC19A3/thiamine transporter protein	Thiamine and biotin
Serine synthesis defects	*PHGDH, PSPH, PSAT* genes	Oral L-serine
Creatine deficiency syndromes	*SLC6A8/GAMT*	Dietary arginine restriction and creatine- monohydrate and L ornithine supplementation
Riboflavin transporter deficiency	SLC52A2/RFVT2	Riboflavin
Molybdenum cofactor deficiency A	*MOCS1* and *MOCS2*	Purified cyclic pyranopterin monophosphate
Tuberous sclerosis	*TSC1* OR *TSC2*/hamartin	Vigabatrin mammalian target of rapamycin (mTOR) inhibitors: rapamycin, serolimus, and everolimus
POLG gene disorders	*POLG* genes	

This table shows the epilepsy list for which we have a specific treatment for the underlying abnormality that may be accompanied by seizures.
Some treatments do not completely correct the underlying disorder. Most metabolic diseases not listed in this table can be treated with dietary changes. Most of these can be detected by newborn testing.

revealing the cause of epilepsy in children. This information is also necessary to select tests and interpret test results.

In many infants and children, they do not have a feature in the history or physical examination to achieve a certain diagnosis, and these are usually patients with DRE (as mentioned above).

These are the groups that benefit the most from the improvements in laboratory diagnosis. The laboratory tests currently available have significantly improved our ability to make specific diagnoses. There are more and better-improved methods for identifying genetic and metabolic abnormalities.

The outburst of new tests presents a challenge for clinicians caring for epileptic children and adults. Clinicians have to make difficult choices. These decisions include knowing the cost of the tests. However, the heterogeneous etiology of epilepsy, many different syndromes and seizure types, and individual variability in response to pharmacological agents complicate the treatment of these diseases. However, although currently ineffective for treatment, a genetic diagnosis can provide information about prognosis, risk of comorbidities, and also facilitates support from other affected individuals or families. Finally, it can be extremely important for genetic counseling and to aid healthy reproduction, including prenatal or preimplantation diagnosis in future pregnancies.[21]

One study showed that all children with early epileptic encephalopathy and DRE deserve genetic examination in early diagnosis. Improved methods of structural, metabolic, and genetic identification have given us new tools to treat epilepsy. The disorders listed in Table 2 indicate the diseases that can be treated with precision medicine for epilepsy.

The precise definition of the cause of epilepsies will open the door to new drugs, protein replacement, gene therapy, and many other promising treatments for the most devastating epilepsies affecting children. Improvements in the localization of developmental/structural changes that cause focal epilepsy are also on the horizon. It's one of the most exciting times in epilepsy, a really precise medicine time.[23]

As a result, we think clinicians should increase their knowledge of requesting the right tests, interpreting the results, and using the information in order to make an early and accurate diagnosis.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.Ü., E.A.; Design - A.Ü., E.A.; Supervision - A.Ü.; Resources - A.Ü., E.A.; Materials - A.Ü.; Data Collection and/or Processing - A.Ü., E.A.; Analysis and/or Interpretation - A.Ü., E.A.; Literature Search - A.Ü., E.A.; Writing Manuscript - A.Ü., E.A.; Critical Review - A.Ü., E.A.

Declaration of Interests: The authors state that there was no conflict of interest in this study.

Funding: The authors declared that this study has received no financial support.

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