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Navigating the Landscape of Personalized Treatment in Pediatric Epilepsy: A Review of Precision Medicine Strategies

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Abstract

As epilepsy treatment becomes more comprehensive and integrates into a "P4 medicine" strategy, it is time to move away from a reactive approach that treats patients after seizures occur and toward a proactive one. This P4 approach—which centres care around the patient and eventually attempts to prevent the onset of epilepsy—is personalized, predictive, preventive, and participatory. Achieving this goal will need switching from the standard anti-seizure medicines to customized treatments targeted at particular etiologies and customizing epilepsy treatments to fit both a given patient and a given syndrome. The current status of this ongoing revolution is presented in this review, with particular attention paid to the rise of the ideas of personalized and precision medicine as well as their implications for clinical practise.

Introduction

In a matter of years, the field of epilepsy genetics has seen a sharp rise in understanding. For diagnostic reasons in clinical practice, a variety of genetic tests are available. Particularly, in one-third of individuals, the next-generation sequencing (NGS) approach is highly effective in identifying the genetic abnormalities causing epilepsy. The pathophysiology of epilepsy was also shed light on by this advancement, which opened the door for precision medicine by identifying possible treatment targets[1]. This article aims to educate paediatricians and neurologists on the topic of precision and tailored medicine. It will also explain the meaning of these terms, their historical context, and the current state of precision medicine for epileptic patients.

The main purpose of the study of Alonso et al [2] is to look into research projects on participative, personalized, predictive, and preventive medicine that are now available in telemedicine and e-health.

The majority of these papers show how P4 medicine—which stands for personalized, predictive, preventive, and participatory medicine—developed globally and how it helps patients with various conditions. To improve medical services, P4 medicine is essential. A primary advantage of research is its ability to provide light on the applications of P4 medicine in telemedicine and e-health, as well as on the prevention and prognosis of future illnesses [3].

Using antiquated or inaccurate diagnostic and treatment techniques on a single patient is not synonymous with precision medicine. In fact, the administration of individual-level medications to patients and the establishment of new paradigms depend on the use of -omic (genomic, proteomic, and epigenomic) markers. This is used to group cohorts into genetic categories instead of utilizing clinical, laboratory, or physiological data. All the same, the basic rules of evidence-based medicine still apply [4]. These and many other characteristics make the idea of individualized medicine popular in the media. It seems, nonetheless, that the idea is applied to convey many circumstances. The field of medicine will need to undergo numerous changes in the future, such as improving disease diagnostics, identifying genetic predispositions to diseases early, enabling gene therapy, and promoting pharmacogenetics for customized medication. The Human Genome Project served as the catalyst for much of this transformation. There are two basic ways that functional genomic studies aim to advance the creation of more efficacious pharmacological therapy. Firstly, the most suitable targets for pharmaceutical treatments will be identified with the aid of functional genomic techniques. Second, the understanding of why patients respond to medications differently will be aided by pharmacogenomics. The definition, development, and application of genetic models that depict these responses aimed to use drugs more effectively.

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Offers options for precise and individualized medical care. With the use of diagnostic testing, customized medicine is a young area that aims to match patients with the most effective medical therapies [6]. Gronowicz outlined the general goal of personalized medicine as "identifying genetic, phenotypic, or environmental factors that affect a person's health risks." Instead than depending just on well-known medications to treat a specific patient, personalized medicine can provide the opportunity to attempt treatments that cause less harm to the body and have fewer or no side effects.

Access to healthcare, an individual's genetic and genomic structure, tissue biomarkers, environmental influences, behaviour and personality traits, and epigenetic changes are the parts of personalized medicine that Goetz and Schork categorized as needing to be integrated and analyzed [7].

While many scholars claim that there are some significant but small differences between "precision medicine" and "personalized medicine," it is crucial to note that many also use the words interchangeably [8].

In his 2009 book The Innovator's Prescription: A Disruptive Solution for Health Care, Christensen et al. introduced the idea of "precision medicine." Still, this phrase did not become widely accepted and used until the US National Research Council (NRC) released a report in 2011 titled "Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease" [9, 10].

The research presented several proposals for illness ontology based on causative genetic variations or molecular information content in the genomic information form, as an alternative to a symptom-based classification system. The genetic and genomic causes of disease have been the primary focus of precision medicine. An initial definition of precision medicine, which involves personalized care based on an individual's medical history and genetic profile, was provided by the Institute of Precision Medicine [11]. However, differentiating between customized care and precision medicine can be challenging.

Predictive, preventive, Pharmacotherapeutics, and patient participatory medicine are all included in precision medicine. While current traditional medicine uses a population comparison model to treat patients after a disease has already started, precision medicine looks at genotypes to prevent potential diseases before they arise.

According to the concept of precision medicine, each patient's medical care is customized to their unique needs. Precision medicine refers to grouping people into subpopulations based on differences in their susceptibility to specific diseases, biological conditions, and/or prognosis, as opposed to actually developing medications or medical equipment tailored to a patient. Although this idea is also expressed by the term "personalized medicine," it is incorrectly understood to suggest that each individual can have a custom treatment plan created for them. Consequently, in order to communicate the concept presented in this study, the NRC declared that the word "P-Medicine" was chosen above the term "personalized medicine" [10, 12]

"Personalized" medicine follows the N-of-1 model, where each patient is treated as if they are the only one. The 1-in-N model is more similar to "precision" medicine, which enables a more conventional western medical approach to group and subgroup research as well as patient treatment tailored to the patient's particular subgroup. Furthermore, the individual N-of-1 model is said to be the foundation of "personalized" medicine; the 1-in-N model is utilized in "precision" medicine and is based on commonly used analytical methods for "big data" and biostatistical data analysis. Modern and traditional medicine combined to create "personalized" medicine is the best way to describe precision medicine. This demonstrates how precision and customized treatment are related taxonomically [13, 14].

An anticancer medication may shrink a tumor in one person while it cannot in another, or a drug may have major, even life-threatening, side effects in one while having less frequent adverse effects and a more favourable course of treatment in another. The diversity of people's genomes is one of the main causes of this variation, since even little variations can have an impact on how the body responds to particular medications. The scientific field of pharmacogenetics studies how a person's genetic makeup influences how they react to medications. One subfield within pharmacogenomics is pharmacogenetics. A component of precision medicine is pharmacogenomics. Pharmacogenomics is the study of how an individual's distinct genome (genotype) influences how they react to medications [15]. All of this has produced novel methods for the discovery of new drugs, tailored approaches to treatment, and innovative concepts for illness prevention. Large patient populations are now treated as groups in medication therapy, regardless of possible individual and genetic variations in drug response. However, even when the disease phenotype is the same, pharmacogenomics can assist in concentrating on effective treatment in smaller patient subpopulations with distinct genetic profiles [16]. Genes can impact an individual's reaction to medications since they are encoded from DNA, which is present in every human cell. Primarily, DNA is a crucial component of our body's chemical operating system, governing cellular behaviour and interactions. Genetic variations can result in major side effects, such as a patient's drug remaining in the body longer than usual due to a variation, or another person's variant reducing the treatment's effectiveness [17].

Similar to pharmacogenetics, pharmacogenomics has genomic technologies that could greatly advance medical research [18]. Pharmacogenomics applications are believed to improve patient safety and health outcomes, lower healthcare costs, and enable patients to receive the appropriate medications [17].

Thanks to the availability of both in vitro and in vivo model systems, the rapidly growing body of genetic knowledge regarding epilepsy is well-suited for the development and implementation of targeted treatments in precision medicine. Forming collaborative research groups is essential going forward, particularly to fortify these alliances in order to deliver precise personal genome analysis as well as studies for gene and medicine discovery. Likewise, the utilization of clinical research networks could facilitate the enlargement of patient cohorts with epilepsy that is genetically characterized, hence facilitating the translation of drug discovery into clinical settings [19].

Children's Epilepsy and Precision Medicine

With neurobiological and psychological components, epilepsy is the most prevalent disorder among children. While there was once greater ignorance regarding the etiology of epilepsy, with the advent of new technological instruments and diagnostics, juvenile epilepsy is poised to enter the era of precision medicine [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.

Over the past twenty years, the majority of hereditary forms of epilepsy, including some focal and lesional forms, developmental encephalopathies, and epilepsy syndromes, have been linked to single-gene defects in ion channels or neurotransmitter receptors. A genetic etiology has been identified in over half of all epilepsies.

It is now feasible to sequence every encoder (whole exome) and non-encoder (whole genome) area of the human genome because to the wide range of genetic tests that are already available, including cutting-edge testing and focused studies.

New developments in technology have also led to genetic discoveries regarding epilepsy and improved our comprehension of the molecular mechanisms underlying many epileptic disorders. In certain cases, such as Dravet syndrome, pyridoxine-dependent epilepsy, and glucose transporter-1 deficiency syndrome, these discoveries have even provided targets for precision medicine. In order to diagnose most cases of idiopathic epilepsies and developing epileptic encephalopathy, genetic testing is now available and is an essential part of the diagnostic process. Genetic testing outcomes can also influence treatment planning, which enhances patient care. It is quite probable that in the coming years, the treatment of epilepsy will resemble "precision medicine" more than the current empirical approach, and that it will be accessible to a wider audience [21].

More than ever in the past ten years, developments in genetics, neuroimaging, and EEG have made it possible to identify the etiology of epilepsy earlier than ever. Simultaneously, advances in the study of experimental epilepsy models have led to a deeper comprehension of the fundamental mechanisms underlying the disorder and the discovery of medicines that specifically address its etiologies. We are currently seeing how these developments are affecting our day-to-day therapeutic work [22].

Over 70 million people worldwide suffer from epilepsy, a persistent neurological condition. Approximately one-third of epileptic patients experience drug-resistant seizures, despite the fact that there are over twenty anti-seizure medications (ASD) available for the symptomatic treatment of epileptic seizures. Due to the high risks of early death, damage, psychosocial dysfunction, and poor quality of life associated with this kind of drug-resistant epilepsy (DRE), there is an urgent clinical need to discover more effective treatments.

But complicated models of resistance, different forms of epilepsy, and seizures exacerbate the issue. Furthermore, the basic processes of DRE remain unclear despite recent studies starting to clarify our understanding.

The default mechanisms of drug resistance can be investigated, characterized, and challenged using the experimental models provided by DRE. Preclinical models of this kind play a crucial role in the creation of medicines capable of overcoming drug resistance.

A promising avenue for treatment for patients who are not yet resistant to ASD is the development of new multi-targeted ASDs for severe paediatric (monogenetic) epilepsies and acquired partial epilepsies. This is because preclinical and clinical research is helping to clarify the pathophysiological mechanisms that underlie epilepsies and drug resistance.

One of the main challenges in managing epilepsy is drug resistance. The knowledge currently available regarding the molecular, genetic, and structural multidisciplinary reviews of the mechanisms behind medication resistance in epilepsy are necessary, and studies with applications in precision medicine are required [23].

According to reports, over 70% of epileptic diseases—that is, conditions in which epilepsy manifests as a primary or comorbid symptom—are caused by or impacted by genetic anomalies.

Single-gene mutation-induced epilepsy is complex because distinct gene mutations can result in the same manifestation whereas single-gene mutations might produce various outcomes. Hereditary testing has become a crucial component of treating paediatric epilepsy, as syndromes like hereditary epilepsy typically manifest in early childhood or early adulthood.

In paediatric epilepsy, diagnostic techniques have evolved from narrowly applicable tools (e.g., single-gene testing and on-site fluorescent hybridization, or FISH) to tests like chromosomal microarray, whole-exome sequencing (WES), whole-genome sequencing (WGS), and multigene panels. Table 1 lists their benefits and drawbacks.

By identifying the diverse patterns that reveal these genes, next-generation sequencing (NGS) not only increases the number of genes linked to epilepsy but also helps forecast the pathophysiology of the condition, its possible pathogenicity, and ultimately its potential for therapeutic intervention.

The majority of research use WES or epilepsy gene panels. Epilepsy panels are becoming more and more gene-rich; currently, there is an epilepsy panel with mitochondrial gene testing that covers 553 genes in total [24]. After imaging, these genetic tests may be the next test of choice because of their rapidly declining costs for whole exome and genome testing.

The broad category of epigenetic factors includes DNA methylation, histone modification, and non-coding RNA, which are the most suc-

cessful in treating paediatric epilepsy. These variables can provide light on the disease's progression and symptoms, making them more useful for precise diagnosis.

Because it can control gene expression and functioning that alters the associated disease (e.g., KCNQ3, SCN3A, and GABRB2, respectively), DNA methylation is an epigenetic marker for many genetic epilepsy-related diseases, including Dravet, benign familial new born seizures, and epileptic neurodevelopmental disorders. Epigenetic biomarkers are also starting to be significant in etiopathogenesis, in addition to NGS.

A clinician's list of obstacles when selecting metabolic or genetic testing includes determining which tests to run in what order, selecting a screening test type, accounting for test costs, and evaluating laboratory test quality.

The majority of the time, the first stages involve confirming the illness, determining the kind of epilepsy based on the clinical history, doing an EEG, and using neuroimaging to identify the structural reasons of epilepsy. The patient will determine which metabolic or genetic tests to perform next in order to determine the etiology.

Every epilepsy diagnosis should be followed by a treatment trial in order to identify a curable cause of the condition. Once the etiology of epilepsy is identified, controlling seizures will only be viable in certain circumstances. Even if you have tried it, try taking pyridoxine, folinic acid, and biotin.

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] discovered that the best diagnostic results at the lowest cost came from the early use of WES in conjunction with metabolic testing. This work clearly indicates that in epileptic patients, gene panels, WES, or WGS should be used with great precision for diagnosis.

Beginning with a thorough history and physical examination, the use of innovative diagnostic techniques can yield crucial information in uncovering the reason of childhood epilepsy. Additionally, choosing tests and interpreting test results require this information.

The benefits of the advancements in laboratory diagnosis are greatest for these groups. We can now make precise diagnoses much more often because to the laboratory tests that are already available. Diagnostic techniques for genetic and metabolic disorders are more numerous and more advanced.

For doctors treating adults and children with epilepsy, the proliferation of novel testing poses a problem. Healthcare professionals must make tough decisions. Knowing how much the testing will cost is one of these decisions. Treatment for epilepsy and other related diseases is complicated by the diverse genesis of the condition, the wide range of syndromes and seizure patterns, and the individual diversity in responsiveness to pharmaceutical medicines. A genetic diagnosis can aid in obtaining support from other affected individuals or families, as well as providing information regarding prognosis and comorbidity risk, even though it is not yet useful for therapy. Finally, it can be crucial for genetic

Table 1: Genome sequencing tests [21].

Genetic tests	Method	Types and technical differences	Advantages	Disadvantages
Comprehensive gene testing: Multigene panels	Sequences group 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. • 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.
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 be analyzed.	• Generates a large number of variants of unknown significance. • Cannot detect imprinting errors, uniparental heterodisomy, nucleotide repeats, pseudo genes, non-coding regions, mitochondrial genes, mosaic changes, large copy number variation, or chromosome rearrangements.
Genome sequencing	Sequence 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.	• 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)	• Has the same advantages as exome sequencing - Less arduous sample preparation. • Can identify structural variants and chromosome breakpoints in non-coding regions.	• Does not analyse all exomes or genome. • Does not sequence genes in the targeted regions analyzed.

Table 2: Treatable epilepsies in paediatric epilepsy.

Type of epilepsy	Gene	Treatment
Cerebral folate deficiency	Folate receptor defect or folate receptor antibody	Folinic acid and methyl folate
Pyridoxine – responsive epilepsy	*ALDH7A1/alpha* aminoadipic semi aldehyde	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*	

counselling and supporting healthy reproduction, which includes future pregnancies where prenatal or preimplantation diagnosis is made. [21]

According to one study, genetic testing should be done as soon as possible to diagnose all children with DRE and early epileptic encephalopathy. New techniques for structural, metabolic, and genetic identification have allowed us to treat epilepsy with more effective means. Precision medicine can be used to treat the conditions included in Table 2 that are associated with epilepsy.

The most severe epilepsies that affect children may be treated with new medications, gene therapy, protein replacement, and many more promising approaches if the exact cause of epilepsies is identified. There will likely be advancements in the localization of the anatomical and developmental alterations that lead to focal epilepsy. It's an extremely accurate moment for medicine, and one of the most thrilling times in epilepsy.

In order to make an early and correct diagnosis, we believe that professionals should become more knowledgeable about ordering the appropriate tests, interpreting the results, and using the information.

Declaration of Interests

The authors state that there was no conflict of interest in this study.l.

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Conflict of Interest

None.

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