Received: 17 October 2024 | Revised: 27 December 2024 | Accepted: 16 January 2025

DOI: 10.1111/epi.18285

Epilepsia®

COMMENTARY

Embracing the future: Neonatal screening for epileptic syndromes

Rima Nabbout[1,2] | **Mathieu Kuchenbuch**[1,3]

[1]Reference centre for rare epilepies, department of Pediatric Neurology, Necker Enfants Malades hospital, APHP, member of ERN EpiCARE, Universite Paris cité, Paris, France

[2]Institut Imagine, INSERM UMR 1163, translational research on neurological diseases, Université Paris cité, Paris, France

[3]Université de Lorraine, CHRU-Nancy, Service de Pédiatrie, Reference centre for rare epilepsies, member of ERN EpiCARE, Nancy, France

Correspondence
Rima Nabbout, Department of Pediatric Neurology, Reference Centre for Rare Epilepsies, Necker Enfants Malades Hospital, 149 rue de Sèvres, 75015 Paris, France.
Email: rima.nabbout@aphp.fr

Funding information
Chair Geen-DS funded by FAMA fund hosted by Swiss Philanthropy Foundation; Agence Nationale de la Recherche, Grant/Award Number: ANR-10-IAHU-01 and ANR-23-RHUS-0002

Since Guthrie's pioneering work in 1963 on phenylketonuria, the spectrum of diseases addressed in neonatal screening programs has broadened. Ethical considerations regarding the conditions qualifying for neonatal screening were raised as early as the 1960s.[1,2] In 1968, the World Health Organization established recommendations for identifying disease candidates that could benefit from such an approach.[3] The main criteria outlined in this report include the importance of the impact of the disease on health, the understanding of its natural history, and the availability of suitable diagnostic tests and of acceptable treatment. In many high-income countries, national committees have been established to determine the diseases candidate to be included in neonatal screening programs.[4] The number of conditions in newborn screening currently spans from 2 (Bosnia and Herzegovina) to 40 (Italy) in Europe,[5] and from 33 (Montana and Louisiana) to 74 (Connecticut) in the United States.[6]

The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) founded in the United States to advise the Secretary of Health and Human Services on this topic developed, in 2006, an instrument to assess the suitability of disorders for inclusion in newborn screening programs (Figure 1).[7] This score enabled the distinction between high-scoring conditions (e.g., congenital hypothyroidism and galactosemia, scoring at or above 1200), low-scoring conditions (e.g., X-linked adrenoleukodystrophy and fragile X syndrome, scoring below 1000), and a middle group scoring between 1000 and 1199 (e.g., congenital toxoplasmosis and malonic acidemia). Using this score, 29 conditions with high scores were identified for inclusion in the recommended uniform screening panel (RUSP), whereas an additional 25 were selected from the middle group due to their relevance in the differential diagnosis of the core panel conditions.[7] Progressively, this number increased to include 37 conditions in the core panel and 26 conditions in the secondary panel, that is, "conditions that are part of the differential diagnosis of a core panel condition."[8] The inclusion of spinal muscular atrophy (SMA) in this core panel in 2018, mainly due to the revolution of its treatment landscape with the implementation of gene and antisense oligonucleotide (ASO) therapies, marked a significant milestone as it represents one of the first instances of genetic screening being integrated into routine newborn screening programs.

Recently, patients' advocacy groups and physicians highlighted to the committee that the nomination process for the RUSC is arduous and overlooks major factors valued by the families.[9] Consequently, the committee has chosen to suspend nominations of new conditions

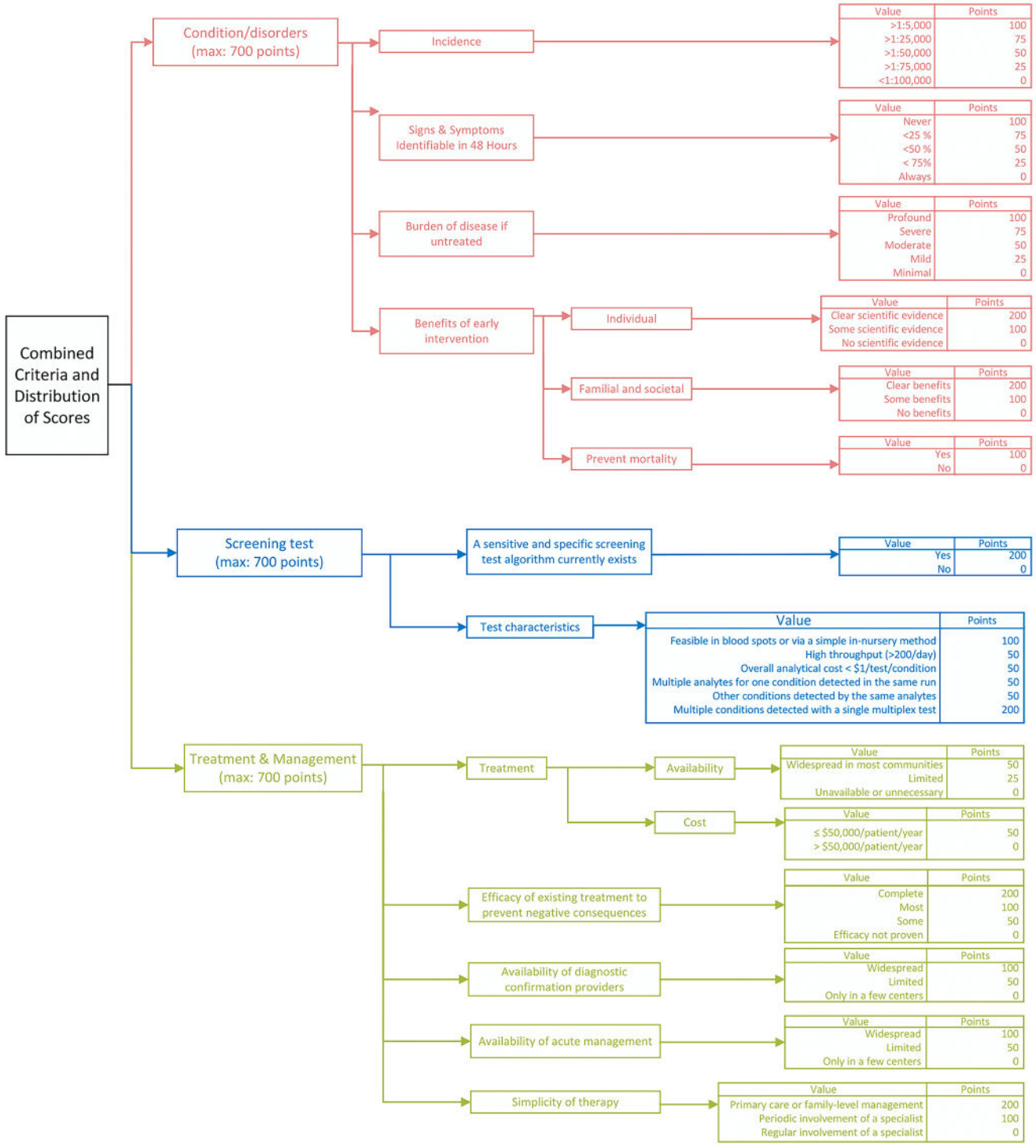

FIGURE 1 Combined criteria and distribution of scores in the data collection instrument adapted from Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) Criteria.[7]

for a period of 6 months (from December 2023 to May 2024) to ensure a consistent and standardized pathway, thereby preventing inconsistencies in the nomination processes. The updated process, introduced in May 2024, simplifies the nominations by implementing a two-step approach, starting with a lighter preliminary form to assess appropriateness before requiring a full nomination package. In addition to reducing the initial burden, the updated process allows an improved review involving different stakeholders and necessitating multidisciplinary consensus validation.[10] The patients' advocacy groups underscored the extension of the role of neonatal screening, beyond disorders with available cure, to the reduction of diagnostic odyssey, early access

to innovative therapies as soon as they become available, and the ability to plan for the child's future needs. However, it is worth noting that, to date, no monogenic epilepsies, mainly no developmental and epileptic encephalopathy (DEE), is included in these various official screening panels.

We are witnessing a significant shift in the field of epilepsy classification, adding to well-defined electroclinical syndromes a precision classification based on etiologies, particularly for monogenic and metabolic diseases. This shift is supported by the rise of precision medicine and disease-modifying therapies, along with a deeper understanding of the substantial social, societal, and economic impacts of early-onset epilepsies.

This urges the need to evaluate epilepsies and epileptic syndromes that are strong candidates for neonatal screening or may be close to meeting the inclusion criteria of these screening panels.

1 | GROUPS OF EPILEPSY SYNDROMES FOR NEWBORN SCREENING

We have chosen to categorize epilepsy and epilepsy syndromes based on the potential impact that neonatal screening may have on the outcomes trajectories of affected individuals. This classification allows for tailoring the screening and treatment strategies according to the specific characteristics of each group, thereby optimizing early intervention.

1.1 | Group 1: Syndromes with available "actionable" targeted therapies

The first group encompasses rare epilepsies that have available precision therapies targeting molecular pathways or mechanisms. It currently includes epilepsies associated with metabolic disorders that have substitution therapies, as well as epilepsies linked to an overactivation of the mechanistic Target Of Rapamycin (mTOR) signaling pathway.[11] In these disorders, diagnostic tests are available and early management improves the outcome. For instance, giving pyridoxine or pyridoxal phosphate supplementation within the first 6 months of life, or at birth, for people with pyridoxine-dependent epilepsy, is associated with seizure control and an improved neurodevelopmental outcome.[12] Similarly, the age at introduction of the ketogenic diet in individuals with glucose transporter 1 deficiency (GLUT1DS) was correlated with seizure control and improvement of the developmental outcome.[13,14] These two rare forms of genetic DEEs were identified by a panel of experts as the primary candidates for inclusion in future newborn screening programs focused on genetic epilepsy.[15] Available specific therapies in this group pave the way for presymptomatic interventions. For instance, the symptoms of pyridoxine-dependent DEE (PD-DEE) are often neonatal but they may appear later in the first weeks of life, leaving a possible window for presymptomatic treatment.[16] In individuals with GLUT1DS, the first symptoms may appear also beyond the neonatal period during the first months or years of life. The ketogenic diet, a targeted treatment for this disease, may be initiated during the neonatal period and has the potential to improve clinical outcomes.[17] The replacement therapy with early recombinant human tripeptidyl peptidase introduction, has shown significant improvement in the survival and other outcomes in individuals with neuronal ceroid lipofuscinosis type 2 (CLN2),[18,19] a neurodegenerative lethal disease in early infancy.[20] The treatment administered presymptomatically for siblings of patients with CLN2 significantly improved the outcome, with mild developmental delay at 4 years of age and no other manifestations of the disease such as epilepsy, sleep disorders, cerebral atrophy on magnetic resonance imaging (MRI), or abnormal electroretinography.[20] Another example of presymptomatic treatment may be the use of mTOR inhibitors (rapamycin and everolimus) as targeted therapies for tuberous sclerosis complex (TSC). Indeed, approximately 80 % of individuals with a TSC pathogenic variant in *TSC1* or *TSC2* will present epilepsy, mainly in the first 2 years of life.[21] In clinical trials, everolimus has shown effectiveness for hamartomas (ocular, renal, cutaneous, and cerebral) and epilepsy.[22,23] According to different studies, response rates for mTOR inhibitors in this population ranged from 30% to 71%.[24] Of interest, treatments identified as effective in this condition also seem to exert an inhibitory effect on the mTOR pathway, as seen with vigabatrin, ketogenic diet, and cannabidiol.[24] A common characteristic in patients with TSC is the frequent latency period for epilepsy of a few months, which creates a window of opportunity for the implementation of the presymptomatic treatment. The long-term, prospective study evaluating clinical and molecular biomarkers of epileptogenesis in a genetic model of epilepsy – Tuberous Sclerosis Complex (EPISTOP) study was the first to support effective preventive strategy for epilepsy in TSC.[25] In the preventive group, treated before epilepsy onset by vigabatrin, none experienced epileptic spasms at the age of 2 years, compared to 40% in the conventional treatment group, who received vigabatrin after the onset of seizures. In addition, the occurrence of drug-resistant epilepsy at 2 years was halved (28% vs 60%). However,

this approach did not substantially influence the incidence of autism spectrum disorder or developmental delay evaluated at 2 years. The substantial impact of epilepsy on individuals with TSC and their families[26] may support this presymptomatic use.[26] Currently, prenatal diagnosis of TSC is based on identification of cardiac rhabdomyoma or brain tubers or subependymal nodules on prenatal ultrasound, or on genetic testing in pregnancies with a family history of TSC. Between 2010 and 2020, prenatal diagnosis rates for TSC increased from ~33% before 2010 to 80% for those born during that period.[27] Neonatal diagnosis will capture the remaining 20%[25,28] (or more depending on the antenatal ultrasound expertise), enabling electroencephalography (EEG) follow-up to guide presymptomatic therapy and establish the recommended follow-up for hamartoma.[29] Indeed, the EEG monitoring schedule is well established,[30] and neonatal screening will improve epileptic outcome and possibly developmental outcomes.[31] A recent randomized study (PREVeNT) has confirmed a delay of the onset of spasms in infantile epileptic spasms syndrome (IESS) and a reduction of its overall prevalence in the TSC group treated preventively with vigabatrin.[32]

1.2 | Group 2: Syndromes with emerging precision medicine approaches

In the second group, targeted therapies are not yet implemented, although some precision medicine approaches may be available. Channelopathy-associated epilepsies are a good example of this group. These disorders account for ~25% of rare genetic epilepsies. Timely identification of underlying genetic etiologies through neonatal screening would enable close monitoring, reduce diagnostic odyssey, and significantly improve therapeutic management. Identifying these diseases at birth will allow the avoidance of precipitating factors and propose presymptomatic therapy that may prevent, at least partly, the development of the severe phenotype of these disorders. For instance, a retrospective study on encephalopathy related to pertussis vaccination showed that 11 of the 14 individuals reported in this study had a pathogenic variant of sodium voltage-gated channel alpha subunit 1 gene (*SCN1A*). Pathogenic variants in this gene, with loss of function, mainly result in two phenotypes: Dravet syndrome (DS) and a milder form known as genetic epilepsy with febrile seizures plus (GEFS+). The two key predictors of DS are the *SCN1A* pathogenic variant genetic score and the age at seizure onset.[33] In individuals with a *SCN1A* pathogenic variant, vaccination may trigger earlier epilepsy onset.[34,35] A retrospective multicenter cohort study revealed that the prophylactic use of benzodiazepines is associated with a substantial reduction in the recurrence of post-vaccination seizures, with a remarkable 30-fold reduction in the likelihood of seizures.[36] A case report of two siblings with a novel pathogenic *SCN1A* variant underscored the importance of individualized management, revealing the severe outcome in the index case and the successful preventive measures, based on regular prophylactic sodium valproate and additional clobazam post-vaccination, used for the sibling.[36] Similar to TSC, we could hypothesize that the discovery of early predictive biomarkers for this group will allow timely and personalized neonatal or presymptomatic interventions. In the case of DS, the identification of *SCN1A* pathogenic variants at birth will also limit contraindicated anti-seizure medications (ASMs) and facilitate a tailored selection of appropriate ones. The worsening effect of sodium channel blockers in patients with DS exacerbates seizures but appears to have also a worsening impact on long-term neurodevelopmental outcome when used during the first 5 years of life.[37] Conversely, in cases of *SCN2A* and *SCN8A* gain-of-function mutations, sodium channel blockers are recommended as first-line therapies.[38–40] The same may apply to potassium channel–related DEEs associated with gain-of-function and the use of potassium blockers medications.[41] One may argue that targeted ASM therapy may be adequately guided by rapid genetic testing performed after the first seizure onset. Therefore, we may question the added value of neonatal screening. However, the rapid development of gene and assimilated therapies in these monogenic rare epilepsies will necessitate re-addressing the neonatal screening soon. The presymptomatic period between birth and the onset of the first seizure, existing in many monogenic epilepsies, may be an opportunity window to consider. Approaches based on ASOs are currently under development, primarily for gain-of-function channelopathies (sodium voltage-gated channel alpha subunit 2 gene (*SCN2A*),[42] sodium voltage-gated channel subunit 8 gene (*SCN8A*),[43] potassium sodium-activated channel subfamily T member 1 (*KCNT1*[44])) but also for loss-of-function types (*SCN1A*[45]). Trials for patients with *SCN1A*[45] and *SCN2A*[46] pathogenic variants are even undergoing phase 1/2 studies with promising results. Along the same line, other monogenic disorders with DEEs are also progressing, with significant results in the preclinical studies and a prompt translation to humans (syntaxin binding protein 1 gene (*STXBP1*),[47] synaptic ras GTPase activating protein 1 gene (*SYNGAP1*),[47] *SCN1A*,[48] cyclin-dependent kinase-like 5 (*CDKL5*)[49]...). Additional major challenges in this group concern the pathogenicity of the variants discovered with numerous variants of uncertain significance (VUS) and the identification of the patient's most probable phenotype and prognosis. These uncertainties pose a challenge in clinical decision-making and in the information provided to the family. However, a better understanding of the impact of different variants is currently developing, as well as major

research for specific prognosis markers that may delineate the phenotype and patient's outcome with a high level of certainty.

1.3 | Group 3: Syndromes excluded from neonatal screening

The third category of epileptic syndromes should, at this time, be omitted from the neonatal screening list. Several key reasons, often combined, justify the exclusion of these syndromes. First, certain epilepsy syndromes lack diagnostic biomarkers in the neonatal period, including genetic, biochemical, EEG, or imaging markers. For instance, idiopathic generalized epilepsy (20%–30% of all epilepsy syndromes) is presumed to have a polygenic etiology (polygenic risk score).[50] In addition, no specific alterations on EEG, imaging, or in biochemical markers have been reported during the neonatal period. Second, some monogenic conditions elude detection in the peripheral blood due to their somatic nature, such as pathogenic variants in *GNAQ* causing Sturge–Weber syndrome,[51] or because they involve a complex combination of genetic predisposition (first hit) and somatic mutations occurring during brain development, as seen in cortical focal dysplasia.[52] Third, certain epilepsy syndromes are self-limited, such as self-limited epilepsy with centro-temporal spikes.[53] Because these self-limited epilepsies typically resolve spontaneously without significant developmental impact, neonatal screening may not contribute significantly to improved patient management and outcome. Other syndromes may have acquired postnatal causes, such as post-infectious or clastic lesion, as seen in infantile spasms and Lennox–Gastaut syndromes. Finally, syndromes with immune-mediated etiologies (e.g., new-onset refractory status epilepticus, Rasmussen syndrome, febrile infection-related epilepsy syndrome [FIRES], and hemiconvulsion–hemiplegia–epilepsy syndromes) are difficult to propose for such screening due to a lack of clear neonatal biomarkers to date.[54,55] The prevention of these syndromes relies primarily on primary prevention measures, such as improving neonatal care practices and enhancing the diagnosis and treatment of central nervous system infections.[11] In summary, the complexity of these syndromes, coupled with the lack of clear monogenic, underlying mechanisms and biomarkers, currently excludes them from the neonatal screening candidates' list.

Although neonatal screening offers promise for some epileptic syndromes that have targeted therapies and clear biomarkers, the complexity of other syndromes creates significant challenges for effective screening implementation. Therefore, a careful assessment of the risk–benefit ratio is essential when deciding on the appropriateness of neonatal screening for such conditions.

We attempted to estimate the Combined Criteria and Distribution of Scores, based on the scoring system developed in 2006 by the ACHDNC, for epilepsy syndromes and etiology related epilepsy syndromes[7] based on the 2022 classification and terminology[50,53,56,57] (Figure 2). Of interest, the median scores were 1410 (ranging from 1525 for GLUT1DS to 1280 for TSC) for the first group, 1062.5 (ranging from 1165 for DS with *SCN1A* pathogenic variant to 980 for potassium voltage-gated channel subfamily Q member 2 DEE (*KCNQ2*-DEE) for the second group, and 488 (ranging from 870 for epilepsy in infancy with migrating focal seizure [EIMFS] to 400 for Rasmussen syndrome) for the third group. Using the same scoring system, the score for SMA is estimated at 1475. This highlights that the first group meets the current criteria for neonatal screening.

2 | EPILEPSY IN ONGOING RESEARCH ON GENETIC NEWBORN SCREENING

The advances in genetics, making genomic sequencing faster (from months to few days) and more affordable (from $1000 to $500 for a genome between 2014 and 2024), have paved the way for genetic newborn screening.[58] These developments have spurred the initiation of several international genomic newborn screening studies. To date, eight studies[59–66] have proposed newborn screening gene panels, ranging from 14 to 954 genes (Table 1). The common goal of these studies is to implement and evaluate the utility of genomic sequencing for screening of "actionable" genes in newborn. They also aim to examine the ethical implications and value of utilizing genomic data generated at birth as a lifelong health care asset.

However, the fact that none of the genes associated with epileptic syndromes appear in all eight panels of neonatal screening highlights the difficulty in constructing these panels. For instance, GLUT1DS, present in 7 out of 8 panels, and pyridox(am)ine 5′-phosphate deficiency (P5PD)-DEE, identified in 6 out of 8, were the most represented syndromes, consistent with our proposition and our estimated score. Despite the market authorization of a precision therapy, cerliponase alpha, for type 2 neuronal ceroid lipofuscinosis (NCL2) giving, is a significant positive impact in presymptomatic individuals,[20] the search for pathogenic variants in tripeptidyl peptidase 1 gene (*TPP1*) was only included in half of the neonatal screening panel. Similarly, PD-DEE and *TSC* genes were excluded from over 50% of the panels. The rationale behind this decision warrants further

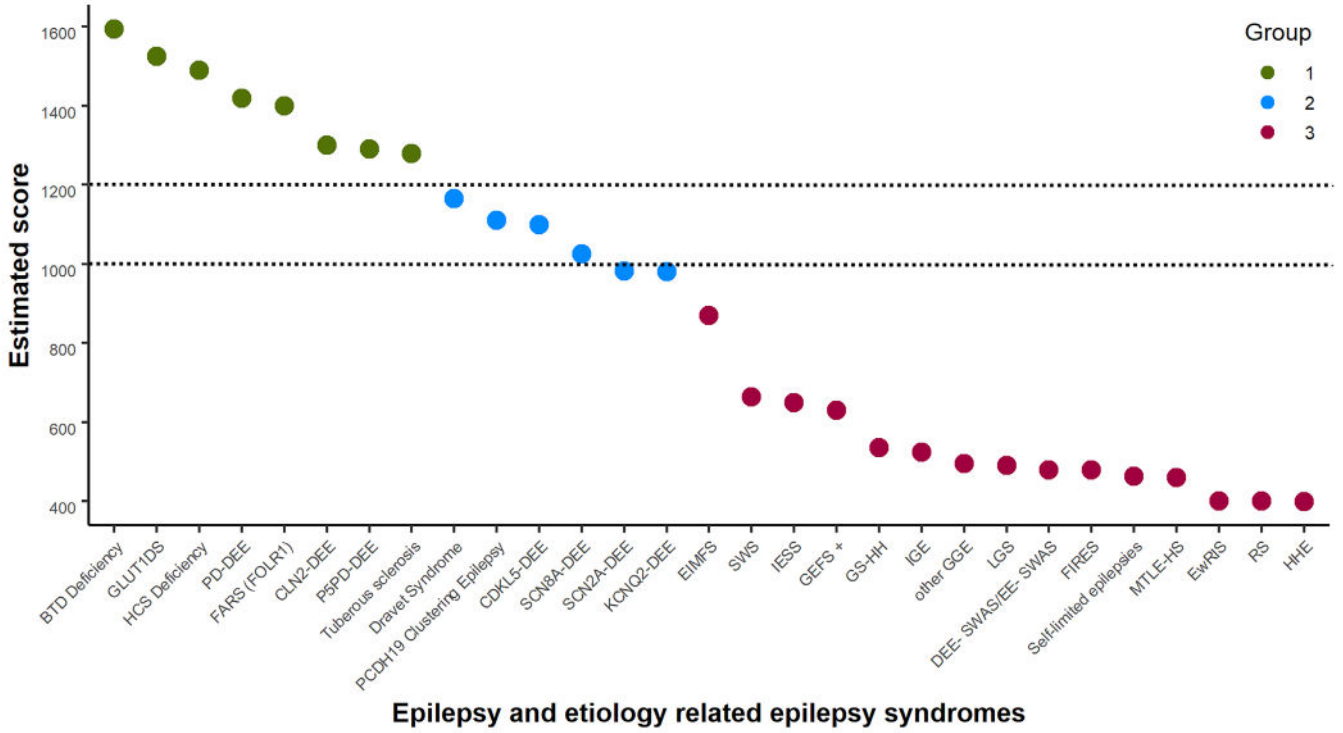

FIGURE 2 Estimation of score distribution for epilepsy and etiology related epilepsy syndromes based on Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) Criteria.[7] BTD, biotinidase deficiency; CLN2, neuronal ceroid lipofuscinosis type 2; DEE, developmental and epileptic encephalopathy; DS, Dravet syndrome; EE, epileptic encephalopathy; EIMFS, epilepsy in infancy with migrating focal seizure; EwRIS, epilepsy with reading-induced seizures; FARS, folinic acid–responsive seizures; FIRES, febrile infection–related epilepsy syndrome; GGE, genetic generalized epilepsy; GEFS+, generalized epilepsy with febrile seizures +; GS-HH, gelastic seizures–hypothalamic hamartoma syndrome; GLUT1DS, GLUT1 deficiency syndrome; HCS, holocarboxylase synthetase; HHE, hemiconvulsion–hemiplegia–epilepsy syndrome; IESS, infantile epileptic spasms syndrome; IGE, idiopathic generalized epilepsy; LGS, Lennox–Gastaut syndrome; MLTE-HS, mesial temporal lobe epilepsy with hippocampal sclerosis; PD, pyridoxine-dependent epilepsy; P5PD, pyridox(am)ine 5′-phosphate deficiency; SWAS, spike wave activation In sleep; SWS, Sturge–Weber syndrome; TSC, tuberous sclerosis complex.

investigation, acknowledging that this exclusion may also reflect the existence of a separate screening panel for metabolic diseases, including PD-DEE, established in these institutions or regions.

Finally, the rationale behind the selection of certain genes in the list of neonatal screening panels may be debated. For instance, the inclusion of some progressive myoclonic epilepsies as ceroid lipofuscinosis neuronal 3 gene (*CLN3*), *CLN5*, and *CLN6*, a group of neurodegenerative epilepsy syndromes, characterized by drug-resistant epilepsy, myoclonia with severe neurological prognosis, and early death, may be puzzling because of the lack of available therapies. Lafora-causing genes are also present in the large 928-gene panel, although the trials for this progressive myoclonus epilepsy are only initiating in humans.[67] Finally, calcium voltage-gated channel subunit alpha1 A gene (*CACNA1A*), a gene causing a wide range of phenotypes—such as type 2 episodic ataxia, DEEs, including Lennox–Gastaut syndrome (LGS) and EIMFS, as well as familial hemiplegic—presents a significant challenge because of the known high variability of the phenotypes, even within the same family.[69–70] Furthermore, acetazolamide, a targeted therapy for *CACNA1A*-related disorders, has shown benefits in some limited cases, but further research is needed.[71]

3 | CHALLENGES IN DEVELOPING NEONATAL EPILEPSY SCREENING

In addition to the technical and ethical considerations,[58,72,73] the implementation of a neonatal screening program for epilepsy requires the establishment of a robust infrastructure to ensure timely diagnosis confirmation and intervention. The establishment of dedicated tertiary centers for rare epilepsies with a network of laboratories with expertise in epilepsy genetic testing would be pivotal in providing an effective framework for neonatal screening for epilepsy in France. These centers

TABLE 1 Overview of epilepsy-related genes in the eight-gene panel proposed for newborn screening.

Name of study			Guardian	Babyseq	Beginngs	Early Check	Generation	Baby Detect	BabyScreen+	ScreenPlus
Reference			66	62	65	64	63	67	69	68
Country			USA	USA	USA	USA	UK	BE	AUS	USA
Number of genes implemented			234	954	458	210	250	126	622	14
Targeted population			100 000	1000	>2000	10 000	100 000	40 000	1000	100 000
Epilepsy syndrome	Gene	Group								
Biotinidase Deficiency	*BTD*	1	+	+	+	+	+	+	+	
GLUT1DS	*SLC2A1*	*1*	+	+	+	+	+	+	+	
HCS deficiency	*HLCS*	*1*	+	+	+	+	+	+	+	
PD-DEE	*ALDH7A1*	*1*	+		+	+	+	+		
PD-DEE	*PLPBP*	*1*			+	+	+	+	+	
FARS	*FOLR1*	*1*					+	+	+	
PME/NCL 2	*TPP1*	*1*	+	+				+		+
P5PD-DEE	*PNPO*	*1*	+	+	+	+	+	+	+	
TSC	*TSC1*	*1*		+	+	+				
TSC	*TSC2*	*1*		+	+	+				
DS	*SCN1A*	*2*	+	+	+	+	+			
PCDH19-clustering epilepsy	*PCDH19*	*2*								
CDKL5-DEE	*CDKL5*	*2*	+	+		+				
DEE	*SCN8A*	*2*	+		+		+			
DEE	*SCN2A*	*2*	+		+		+			
KCNQ2-DEE	*KCNQ2*	*2*			+		+			
PME/NCL 3	*CLN3*	*2*		+						
PME/NCL 5	*CLN5*	*2*		+						
PME/NCL 6	*CLN6*	*2*		+						
DEE	*STXBP1*	*3*	+	+						
DEE	*CACNA1A*	*3*		+						
EIMFS	*KCNT1*	*3*			+					
PME/Lafora disease	*NHLRC1*	*3*		+						
PME/Lafora disease	*EPM2A*	*3*		+						

Abbreviations: ALDH7A1, Aldehyde Dehydrogenase 7 Family Member A1; BTD: Biotinidase; CACNA1A, Calcium Voltage-Gated Channel Subunit Alpha1 A; CE, clustering epilepsy; CDKL5, Cyclin-Dependent Kinase-Like 5; CLN, Ceroid Lipofuscinosis Neuronal; DEE, developmental and epileptic encephalopathy; DS, deficiency syndrome; DS, Dravet syndrome; EIMFS, epilepsy of infancy with migrating focal seizures; EPM2A, Epilepsy Progressive Myoclonus 2A; FARS, folinic acid–responsive seizures; FOLR1: Folate Receptor 1; GLUT1DS, GLUT1 deficiency syndrome; Group, proposed group; HCS, holocarboxylase synthetase; KCNT1, Potassium Sodium-Activated Channel Subfamily T Member 1 NCL, neuronal ceroid lipofuscinosis; NHLRC1, NHL Repeat Containing 1; P5PD, pyridox(am)ine 5′-phosphate deficiency; PCDH19, Protocadherin 19; PD, pyridoxine-dependent; PLPBP, Pyridoxal Phosphate Binding Protein; PME, progressive myoclonus epilepsy; PNOP, Pyridoxamine 5′-Phosphate Oxidase; SCN1A, Sodium Voltage-Gated Channel Alpha Subunit 1; SCN2A, Sodium Voltage-Gated Channel Alpha Subunit 2; SCN8A, Sodium Voltage-Gated Channel Alpha Subunit 8; SLC2A1, Solute Carrier Family 2 Member 1; STXBP1, Syntaxin Binding Protein 1; TSC, tuberous sclerosis; TPP1, Tripeptidyl Peptidase 1.

would facilitate the rapid validation of pathogenic variants, thereby ensuring that newborns receive appropriate therapies through a streamlined care pathway. The readiness of a multidisciplinary team, including pediatric epileptologists, geneticists, psychologists, rehabilitation specialists, and care coordinators and nurses, with the option of national consensus meetings for complex cases, should be established and supported. The work achieved by neuromuscular pediatricians and their existing networks for the care of newborns screened with the survival motor neuron 1(*SMN1*) pathogenic variant may serve as a valuable model.

The development of therapies for rare diseases is frequently expensive due to various factors, including the intricate nature of the treatments and the clinical trials, which are often lengthy and costly. This is exemplified by the development of therapies for SMA. It is anticipated that the costs of these therapies will decline over time, with advances in therapy modalities and production pipelines and the development of methodologies in clinical trials adapted for rare diseases with smaller numbers of patients. Therefore, it is imperative that individuals with rare epilepsies who are eligible for targeted therapies (Group 1) do not face delays in access to precision therapies beyond what is currently actionable. Furthermore, delayed treatment exposes patients to the higher costs of managing disease complications frequently affecting neurodevelopment in these disorders. The identification of additional accurate biomarkers will facilitate optimal patient selection, particularly in individuals with epilepsy syndromes that are amenable to emerging precision medicine approaches (Group 2). Once the potential for significant improvements in both quality of life and survival is demonstrated by these therapies, the cost–benefit ratio will favor neonatal screening and early treatment and neonatal screening.

4 | CONCLUSION

The severity of several epileptic syndromes and the potential for significant improvement with early therapeutic intervention justify the inclusion of biotinidase deficiency (*BTD*), folinic acid–responsive seizures related to *FOLR1* pathogenic variants and holocarboxylase synthetase deficiency (*HLCS*), PD-DEE (*ALDH7A1, PLPBP*), P5PD-DEE (*PNPO*), *GLUT1*DS (*SLC2A1*), and PME related to *CLN2* and TSC (*TSC1* and *TSC2*) in neonatal panel screening. In addition, a second group, including some channelopathies (*SCN2A*, *SCN8A*, *SCN1A*, *KCNQ2*) and PME (NCL 3, NCL 5, NCL 6, Lafora), might warrant inclusion in the neonatal screening panel due to emerging therapies and the potential for early intervention in the presymptomatic period, such as for *SCN1A*. In this last group, some challenges on the pathogenicity predictioner of the variants detected at birth remain to be resolved.

Despite the changes proposed by the ACHDNC, the previous scoring system may be a good first step in initiating a consensus proposal within the epilepsy community supported by the International League Against Epilepsy (ILAE) and other partners such as the European Reference Centre for Rare Epilepsies (EpiCARE)[74] involved in rare and complex epilepsies, emphasizing the roles of the medical and scientific experts, patient advocacy groups, and pharmaceutical industries. This will allow us to propose and update the list of epilepsy syndrome candidates for neonatal screening and their implementation in regional and national initiatives. However, we recognize that access issues for children born in low- and middle-income countries (LMICs) remain unresolved. In this setting, epilepsy diagnosis is often delayed or sometimes missed, and genetic testing is generally not available. However, such recommendations with a consensus list could support increased investments in diagnostic infrastructures to facilitate the diagnosis of rare epilepsy syndromes with actionable genetic etiologies in vulnerable populations. We hope that, with the identification of additional accurate biomarkers, a better understanding of underlying mechanisms, and the development of targeted therapies, other syndromes will be included as candidates for neonatal screening in the future.

ACKNOWLEDGMENTS

This work was supported by a government grant managed by the Agence Nationale de la Recherche under the 4th PIA, integrated into France 2030, with the reference ANR-23-RHUS-0002. RN is supported by the Chair Geen-DS funded by FAMA fund hosted by Swiss Philanthropy Foundation, ERDERA, RealiseD (Innovative Health Initiative) and Innov4-ePiK, France 2023.

FUNDING INFORMATION

R.N. is supported by the Agence Nationale de la Recherche under “Investissements d'avenir” program (ANR-10-IAHU-01) and Chair Geen-DS funded by FAMA fund hosted by Swiss Philanthropy Foundation. M.K. and R.N. are recipients of a grant managed by the Agence Nationale de la Recherche under the 4th PIA, integrated into France2030, with the reference ANR-23-RHUS-0002 (innov4-epiK).

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships

that could be construed as a potential conflict of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Rima Nabbout https://orcid.org/0000-0001-5877-4074
Mathieu Kuchenbuch https://orcid.org/0000-0002-5944-2204

REFERENCES

1. Holm VA, Deering WM, Penn RL. Some factors influencing the development of a voluntary PKU screening program: possible implication for other screening procedures for newborns. JAMA. 1970;212(11):1835–42.
2. Lesser AJ. Phenylketonuria and the Guthrie test. Pediatrics. 1963;32(5):940.
3. Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva: WHO: Public Health Papers; 1968.
4. Franková V, Driscoll RO, Jansen ME, Loeber JG, Kožich V, Bonham J, et al. Regulatory landscape of providing information on newborn screening to parents across Europe. Eur J Hum Genet. 2021;29(1):67–78.
5. Zetterström RH, Schielen PJCI. Dépistage néonatal en Europe Évolution au cours. Med Sci. 2021;37:441–56.
6. Newborn screening in your state | newborn screening. [Internet] Available from: https://newbornscreening.hrsa.gov/your-state. Accessed 24 Mar 2025.
7. Committee on Heritable Disorders in Newborns and Children. Newborn screening: towards a uniform screening panel and system. 2006.
8. Recommended Uniform Screening Panel | HRSA. [Internet]. Available from: https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp. Accessed 24 Mar 2025.
9. Health Resources and Services Administration. Nominate a condition | HRSA. [Internet]. Available from: https://web.archive.org/web/20240124210639/https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/nominate. Accessed 24 Mar 2025.
10. Advisory Committee on Heritable Disorders in Newborns and Children. Nominate a condition. Health Resources and Services Administration (HRSA). 2024 [Internet]. Available from: https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/nominate. Accessed 24 Mar 2025.
11. Nabbout R, Kuchenbuch M. Impact of predictive, preventive and precision medicine strategies in epilepsy. Nat Rev Neurol. 2020;16(12):674–88.
12. Coughlin CR, Tseng LA, Bok LA, Hartmann H, Footitt E, Striano P, et al. Association between lysine reduction therapies and cognitive outcomes in patients with pyridoxine-dependent epilepsy. Neurology. 2022;99(23):e2627–e2636.
13. Daci A, Bozalija A, Jashari F, Krasniqi S. Individualizing treatment approaches for epileptic patients with glucose transporter Type1 (GLUT-1) deficiency. Int J Mol Sci. 2018;19(1):122–32.
14. Barthold M, Jurkutat A, Goetz R, Schubring L, Spiegler J, Fries AS, et al. Timing of ketogenic dietary therapy (KDT) introduction and its impact on cognitive profiles in children with Glut1-DS—a preliminary study. Children. 2023;10(4):1–12.
15. Hess-Homeier DL, Cunniff C, Grinspan ZM. Priorities for newborn screening of genetic epilepsy. Pediatr Neurol. 2019;101:83–5.
16. Van Karnebeek CDM, Tiebout SA, Niermeijer J, Poll-The BT, Ghani A, Coughlin CR, et al. Pyridoxine-dependent epilepsy: an expanding clinical spectrum. Pediatr Neurol. 2016;59:6–12.
17. Olivotto S, Duse A, Bova SM, Leonardi V, Biganzoli E, Milanese A, et al. Glut1 deficiency syndrome throughout life: clinical phenotypes, intelligence, life achievements and quality of life in familial cases. Orphanet J Rare Dis. 2022;17(1):365.
18. Schulz A, Ajayi T, Specchio N, de Los Reyes E, Gissen P, Ballon D, et al. Study of intraventricular cerliponase alfa for CLN2 disease. N Engl J Med. 2018;378(20):1898–907.
19. Schulz A, Specchio N, Gissen P, de los Reyes E, Cahan H, Slasor P, et al. Persistent treatment effect of cerliponase alfa in children with CLN2 disease: a 3-year update from an ongoing multicenter extension study. In: Abstracts of the 45th Annual Meeting of the Society for Neuropediatrics. 2019.
20. Schaefers J, van der Giessen LJ, Klees C, Jacobs EH, Sieverdink S, Dremmen MHG, et al. Presymptomatic treatment of classic late-infantile neuronal ceroid lipofuscinosis with cerliponase alfa. Orphanet J Rare Dis. 2021;16(1):221.
21. Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. Lancet. 2008;372(9639):657–68.
22. Krueger DA, Care MM, Holland K, Agricola K, Tudor C, Mangeshkar P, et al. Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. N Engl J Med. 2010;363(19):1801–11.
23. Krueger DA, Wilfong AA, Holland-Bouley K, Anderson AE, Agricola K, Tudor C, et al. Everolimus treatment of refractory epilepsy in tuberous sclerosis complex. Ann Neurol. 2013;74(5):679–87.
24. Nabbout R, Kuchenbuch M, Chiron C, Curatolo P. Pharmacotherapy for seizures in tuberous sclerosis complex. CNS Drugs. 2021;35(9):965–83.
25. Kotulska K, Kwiatkowski DJ, Curatolo P, Weschke B, Riney K, Jansen F, et al. Prevention of epilepsy in infants with tuberous sclerosis complex in the EPISTOP trial. Ann Neurol. 2021;89(2):304–14.
26. Jansen AC, Vanclooster S, de Vries PJ, Fladrowski C, Beaure d'Augères G, Carter T, et al. Burden of illness and quality of life in tuberous sclerosis complex: findings from the TOSCA study. Front Neurol. 2020;11:1–11.
27. Pearsson K, Björk Werner J, Lundgren J, Gränse L, Karlsson E, Källén K, et al. Childhood tuberous sclerosis complex in southern Sweden: a paradigm shift in diagnosis and treatment. BMC Pediatr. 2023;23(1):1–11.
28. Nabbout R, Belousova E, Benedik MP, Carter T, Cottin V, Curatolo P, et al. Epilepsy in tuberous sclerosis complex: findings from the TOSCA study. Epilepsia Open. 2019;4(1):73–84.
29. Krueger DA, Northrup H, Krueger DA, Roberds S, Smith K, Sampson J, et al. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 international

tuberous sclerosis complex consensus conference. Pediatr Neurol. 2013;49(4):255–65.
30. Northrup H, Aronow ME, Bebin EM, Bissler J, Darling TN, de Vries PJ, et al. Updated international tuberous sclerosis complex diagnostic criteria and surveillance and management recommendations. Pediatr Neurol. 2021;123:50–66.
31. Wang X, Ding Y, Zhou Y, Yu L, Zhou S, Wang Y, et al. Prenatal diagnosis and intervention improve developmental outcomes and epilepsy prognosis in children with tuberous sclerosis complex. Dev Med Child Neurol. 2022;64(10):1230–6.
32. Bebin EM, Peters JM, Porter BE, McPherson TO, O'Kelley S, Sahin M, et al. Early treatment with vigabatrin does not decrease focal seizures or improve cognition in tuberous sclerosis complex: the PREVeNT trial. Ann Neurol. 2023;95(1):15–26. https://doi.org/10.1002/ana.26778
33. Brunklaus A, Pérez-Palma E, Ghanty I, Xinge J, Brilstra E, Ceulemans B, et al. Development and validation of a prediction model for early diagnosis of SCN1A -related epilepsies. Neurology. 2022;98(11):e1163–e1174.
34. Ben-Menachem E. Vaccination and the onset of Dravet syndrome. Epilepsy Curr. 2011;11(4):120–2.
35. Scott RC, Moshé SL, Holmes GL. Do vaccines cause epilepsy? Review of cases in the National Vaccine Injury Compensation Program. Epilepsia. 2024;65 (2):293–321.
36. Deng L, Ma A, Wood N, Arden-Holmes S. Vaccination management in an asymptomatic child with a novel SCN1A variant and family history of status epilepticus following vaccination: A case report on a potential new direction in personalised medicine. Seizure. 2020;78:49–52.
37. de Lange IM, Gunning B, Sonsma ACM, van Gemert L, van Kempen M, Verbeek NE, et al. Influence of contraindicated medication use on cognitive outcome in Dravet syndrome and age at first afebrile seizure as a clinical predictor in SCN1A-related seizure phenotypes. Epilepsia. 2018;59(6):1154–65.
38. Castro MJ, Stam AH, Lemos C, De Vries B, Vanmolkot KRJ, Barros J, et al. First mutation in the voltage-gated NaV1.1 subunit gene SCN1A with co-occurring familial hemiplegic migraine and epilepsy. Cephalalgia. 2009;29(3):308–13.
39. Dilena R, Striano P, Gennaro E, Bassi L, Olivotto S, Tadini L, et al. Efficacy of sodium channel blockers in SCN2A early infantile epileptic encephalopathy. Brain Dev. 2017;39(4):345–8.
40. Boerma RS, Braun KP, van de Broek MPH, van Berkestijn FMC, Swinkels ME, Hagebeuk EO, et al. Remarkable phenytoin sensitivity in 4 children with SCN8A-related epilepsy: a molecular neuropharmacological approach. Neurotherapeutics. 2016;13(1):192–7.
41. Mulkey SB, Ben-Zeev B, Nicolai J, Carroll JL, Grønborg S, Jiang YH, et al. Neonatal nonepileptic myoclonus is a prominent clinical feature of KCNQ2 gain-of-function variants R201C and R201H. Epilepsia. 2017;58(3):436–45.
42. Li M, Jancovski N, Jafar-Nejad P, Burbano LE, Rollo B, Richards K, et al. Antisense oligonucleotide therapy reduces seizures and extends life span in an *SCN2A* gain-of-function epilepsy model. J Clin Invest. 2021;131(23):e152079. https://doi.org/10.1172/JCI155233
43. Lenk GM, Jafar-Nejad P, Hill SF, Huffman LD, Smolen CE, Wagnon JL, et al. Scn8a antisense oligonucleotide is protective in mouse models of *SCN8A* encephalopathy and Dravet syndrome. Ann Neurol. 2020;87(3):339–46.
44. Burbano LE, Li M, Jancovski N, Jafar-Nejad P, Richards K, Sedo A, et al. Antisense oligonucleotide therapy for KCNT1 encephalopathy. JCI Insight. 2022;7(23):e146090.
45. Stoke Therapeutics. Stoke therapeutics announces positive new safety & efficacy data from patients treated with STK-001 in the phase 1/2a studies (MONARCH & ADMIRAL) and the SWALLOWTAIL open-label extension (OLE) study in children and adolescents with Dravet syndrome – Stoke Therapeutics. [Internet]. Available from: https://investor.stoketherapeutics.com/news-releases/news-release-details/stoke-therapeutics-announces-positive-new-safety-efficacy-data/. Accessed 24 Mar 2025.
46. Embrave: a clinical trial of Prax-222, a novel antisense oligonucleotide, in pediatric participants with early-onset *SCN2A* developmental and epileptic encephalopathy. [Internet]. Available from: https://aesnet.org/abstractslisting/embrave-a-clinical-trial-of-prax-222-a-novel-antisense-oligonucleotide-in-pediatric-participants-with-early-onset-scn2a-developmental-and-epileptic-encephalopathy. Accessed 24 Mar 2025.
47. Marotta N, Boland MJ, Prosser BL. Accelerating therapeutic development and clinical trial readiness for STXBP1 and SYNGAP1 disorders. Curr Probl Pediatr Adolesc Health Care. 2024;54(8):101576. https://doi.org/10.1016/j.cppeds.2024.101576
48. Mora-Jimenez L, Valencia M, Sanchez-Carpintero R, Tønnesen J, Fadila S, Rubinstein M, et al. Transfer of SCN1A to the brain of adolescent mouse model of Dravet syndrome improves epileptic, motor, and behavioral manifestations. Mol Ther Nucleic Acids. 2021;25:585–602.
49. Medici G, Tassinari M, Galvani G, Bastianini S, Gennaccaro L, Loi M, et al. Expression of a secretable, cell-penetrating CDKL5 protein enhances the efficacy of gene therapy for CDKL5 deficiency disorder. Neurotherapeutics. 2022;19(6):1886–904.
50. Hirsch E, French J, Scheffer IE, Bogacz A, Alsaadi T, Sperling MR, et al. ILAE definition of the idiopathic generalized epilepsy syndromes: position statement by the ILAE Task Force on Nosology and Definitions. Epilepsia. 2022;63(6):1475–99.
51. Shirley MD, Tang H, Gallione CJ, Baugher JD, Frelin LP, Cohen B, et al. Sturge–weber syndrome and port-wine stains caused by somatic mutation in GNAQ. N Engl J Med. 2013;368(21):1971–9.
52. Ribierre T, Deleuze C, Bacq A, Baldassari S, Marsan E, Chipaux M, et al. Second-hit mosaic mutation in mTORC1 repressor DEPDC5 causes focal cortical dysplasia–associated epilepsy. J Clin Invest. 2018;128(6):2452–8.
53. Specchio N, Wirrell EC, Scheffer IE, Nabbout R, Riney K, Samia P, et al. International league against epilepsy classification and definition of epilepsy syndromes with onset in childhood: position paper by the ILAE Task Force on Nosology and Definitions. Epilepsia. 2022;63(6):1398–442.
54. Champsas D, Zhang X, Rosch R, Ioannidou E, Gilmour K, Cooray G, et al. NORSE/FIRES: how can we advance our understanding of this devastating condition? Front Neurol. 2024;15:1426051.
55. Leitner DF, Lin Z, Sawaged Z, Kanshin E, Friedman D, Devore S, et al. Brain molecular mechanisms in Rasmussen encephalitis. Epilepsia. 2023;64(1):218–30.
56. Zuberi SM, Wirrell E, Yozawitz E, Wilmshurst JM, Specchio N, Riney K, et al. ILAE classification and definition of epilepsy syndromes with onset in neonates and infants: position

statement by the ILAE Task Force on Nosology and Definitions. Epilepsia. 2022;63:1349–97.
57. Riney K, Bogacz A, Somerville E, Hirsch E, Nabbout R, Scheffer IE, et al. International League Against Epilepsy classification and definition of epilepsy syndromes with onset at a variable age: position statement by the ILAE Task Force on Nosology and Definitions. Epilepsia. 2022;63(6):1443–74.
58. Vears DF, Savulescu J, Christodoulou J, Wall M, Newson AJ. Are we ready for whole population genomic sequencing of asymptomatic newborns? Pharmgenomics Pers Med. 2023;16:681–91.
59. Ceyhan-Birsoy O, Machini K, Lebo MS, Yu TW, Agrawal PB, Parad RB, et al. A curated gene list for reporting results of newborn genomic sequencing. Genet Med. 2017;19(7):809–18.
60. Conditions list | Genomics England. [Internet]. Available from: https://www.genomicsengland.co.uk/initiatives/newborns/choosing-conditions/conditions-list-generation-study. Accessed 24 Mar 2025.
61. Early check – home. [Internet]. Available from: https://earlycheck.org/. Accessed 24 Mar 2025.
62. Kingsmore SF, Smith LD, Kunard CM, Bainbridge M, Batalov S, Benson W, et al. A genome sequencing system for universal newborn screening, diagnosis, and precision medicine for severe genetic diseases. Am J Hum Genet. 2022;109(9):1605–19.
63. Conditions screened – guardian study. [Internet]. Available from: https://guardian-study.org/conditions-screened/. Accessed 24 Mar 2025.
64. Liste des maladies – Baby Detect. [Internet]. Available from: https://babydetect.com/liste-des-maladies/. Accessed 24 Mar 2025.
65. Overview | ScreenPlus | Albert Einstein College of Medicine. [Internet]. Available from: https://www.einsteinmed.edu/research/screenplus/. Accessed 24 Mar 2025.
66. Conditions screened – babyscreen+. [Internet]. Available from: https://babyscreen.mcri.edu.au/conditions-screened/. Accessed 24 Mar 2025.
67. Parihar R, Ganesh S. Lafora progressive myoclonus epilepsy: disease mechanism and therapeutic attempts. J Biosci. 2024;49:22.
68. Kessi M, Chen B, Pang N, Yang L, Peng J, He F, et al. The genotype–phenotype correlations of the *CACNA1A*-related neurodevelopmental disorders: a small case series and literature reviews. Front Mol Neurosci. 2023;16:1222321.
69. Angelini C, Van Gils J, Bigourdan A, Jouk PS, Lacombe D, Menegon P, et al. Major intra-familial phenotypic heterogeneity and incomplete penetrance due to a CACNA1A pathogenic variant. Eur J Med Genet. 2019;62(6):103530.
70. Nardello R, Plicato G, Mangano GD, Gennaro E, Mangano S, Brighina F, et al. Two distinct phenotypes, hemiplegic migraine and episodic ataxia type 2, caused by a novel common CACNA1A variant. BMC Neurol. 2020;20(1):1–7.
71. Le Roux M, Barth M, Gueden S, Desbordes de Cepoy P, Aeby A, Vilain C, et al. CACNA1A-associated epilepsy: electroclinical findings and treatment response on seizures in 18 patients. Eur J Paediatr Neurol. 2021;33:75–85.
72. Lynch F, Best S, Gaff C, Downie L, Archibald AD, Gyngell C, et al. Australian public perspectives on genomic newborn screening: risks, benefits, and preferences for implementation. Int J Neonatal Screen. 2024;10(1):6.
73. Stark Z, Scott RH. Genomic newborn screening for rare diseases. Nat Rev Genet. 2023;24(11):755–66.
74. ERN EpiCARE. [Internet]. Available from: https://epi-care.eu/. Accessed 24 Mar 2025.

How to cite this article: Nabbout R, Kuchenbuch M. Embracing the future: Neonatal screening for epileptic syndromes. Epilepsia. 2025;00:1–11. https://doi.org/10.1111/epi.18285