

# Precision medicine for genetic childhood movement disorders

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## PUBLICATION DATA

Accepted for publication 23rd February 2021.

Published online

## ABBREVIATIONS

AAV	Adeno-associated virus
ADCY5	Adenylyl cyclase 5
BBB	Blood–brain barrier
DBS	Deep brain stimulation
NPC	Niemann–Pick disease type C
PKAN	Pantothenate kinase-associated neurodegeneration
PKD	Paroxysmal kinesigenic dyskinesia

Increasingly effective targeted precision medicine is either already available or in development for a number of genetic childhood movement disorders. Patient-centred, personalized approaches include the repurposing of existing treatments for specific conditions and the development of novel therapies that target the underlying genetic defect or disease mechanism. In tandem with these scientific advances, close collaboration between clinicians, researchers, affected families, and stakeholders in the wider community will be key to successfully delivering such precision therapies to children with movement disorders.

## THE ERA OF PRECISION MEDICINE: ADDRESSING AN UNMET CLINICAL NEED

Precision medicine is commonly defined as the tailoring or customization of healthcare based on individual patient characteristics. Precision medicine is also sometimes used interchangeably with ‘personalized medicine’, although over time the latter has become less popular since the term ‘personalized’ can be misconstrued as novel attempts to craft treatments unique to each individual, when in fact doctors have always strived to treat patients on an individual and personalized basis.<sup>1</sup> Furthermore, the practice of medicine has always emphasized the importance of accurate clinical diagnosis in providing personalized and effective disease-specific treatments. These tenets continue to be the foundation of precision medicine. Technological advances in molecular genetics, health bioinformatics, and neuroimaging have facilitated the stratification of diseases based on specific disease characteristics thereby enhancing the ‘signs and symptoms approach’ to diagnostic classification. Next-generation genomic sequencing approaches have significantly improved diagnosis in childhood movement disorders, although the bottle neck in understanding the underlying disease mechanisms continues to hamper efforts in drug discovery and novel therapy development.

Precision medicine approaches aim to accelerate the development of effective therapies for patients based on

the underlying disease-specific characteristics. This is particularly important given that the vast majority of childhood movement disorders continue to have poor outcomes, with symptomatic relief or palliation being the major therapeutic goal rather than disease modification or cure. Better understanding of the underlying disease processes and pathways that are aberrant in such diseases will allow the identification of novel targets for therapeutic intervention. It is hoped that such targeted approaches will better address the underlying molecular deficits arising from gene defects, leading to improvement of symptoms, long-term disease modification, and even cure.

## EXPANSION OF DIAGNOSTIC TOOLS FOR PRECISION MEDICINE APPROACHES

### Genetics

Advances in genomic studies have transformed the diagnostic process for childhood movement disorders. Next-generation sequencing technologies such as whole-genome or whole-exome sequencing are increasingly becoming a cost-effective alternative to individual gene or multiple gene panel testing. This technology has allowed for a molecular diagnosis to be achieved more rapidly and in a larger proportion of patients in the clinical setting,<sup>2</sup> embedding itself earlier in the diagnostic process for childhood movement disorders<sup>3</sup> and reducing the need for multiple tests and invasive investigations.

## Neuroimaging

The increasing accessibility of large-scale neuroimaging data sets, availability of automated processing methods, and utility of machine learning are now being harnessed to accelerate translational research for personalized medicine approaches.<sup>4</sup> In adult neurodegenerative conditions, it has facilitated the development of neuroimaging biomarkers, improved the understanding of disease mechanisms, formulated survival predictions, and embedded quantitative techniques into clinical workflow.<sup>5</sup> In childhood movement disorders, the increasingly recognized characteristic patterns of structural changes evident on neuroimaging (e.g. in the cerebellum<sup>6</sup> and/or basal ganglia<sup>7</sup>) is helping clinicians to make an accurate genetic diagnosis sooner. Advances in neuroimaging techniques will also aid the interpretation of novel genetic variants, lending further supportive evidence of pathogenicity for certain genetic syndromes with classical/recognizable neuroimaging features.

## Biomarkers

Biomarker research is a rapidly expanding field, given their potential to aid clinical diagnosis, prognostication, and assessment of disease severity. As such, they are likely to be helpful in the evaluation of new precision medicine treatments. Many biomarkers for neurological disorders are now being identified (such as neurofilament light chain in disorders associated with axonal damage<sup>8</sup>) and even utilized clinically<sup>9</sup> (such as tau proteins and amyloid beta in Alzheimer disease and  $\alpha$ -synuclein in Parkinson disease).

## CHALLENGES IN DEVELOPING PRECISION MEDICINE FOR GENETIC MOVEMENT DISORDERS

It is well recognized that the development of personalized medicine approaches for genetic movement disorders of childhood presents with numerous challenges. In general, rare diseases are often subject to reduced interest from the scientific community and financial investment from industry due to the perceived lack of widespread impact. However, the reality is that although each individual condition is rare (defined as <1 in 2000) or even ultra-rare (<1 in 50 000), collectively as a whole they are not rare; indeed 1 in 17 people will suffer from one of the estimated 6000 rare diseases at some point in their lives. Furthermore, hypothesis-driven precision therapy clinical trials in rare monogenic genetic disorders (e.g. nusinersen in spinal muscular atrophy<sup>10</sup>) have the potential to have an impact on more individuals, not only because of the transformative effect of the treatment on individual patients, but also the scientific advances that result from these types of trials. This is arguably of greater impact than perhaps some of the larger-scale trials for more common adult neurological disorders where the significant clinical heterogeneity within the patient population and multifactorial/oligogenic disease aetiology can affect outcomes. Nevertheless, the difficulty in recruiting sufficient numbers and an inevitably small

### What this paper adds

- Precision medicine for genetic childhood movement disorders is developing rapidly.
- Accurate diagnosis, disease-specific outcome measures, and collaborative multidisciplinary work will accelerate the progress of such strategies.

target population could potentially discourage academia and industry from investing resources into clinical trials for these rare conditions. In the future, such issues may be circumvented by international global patient registries, increased rare disease awareness, and more detailed cost-benefit analyses of precision medicine investment in rare diseases.

Another challenge in developing precision medicine for childhood movement disorders is the achievement of appropriate brain targeting. The existence of the blood-brain barrier (BBB), a multicellular structure that acts as a barrier between the central nervous system and peripheral blood circulation, poses a further hurdle to surmount in brain drug delivery. As such, precision medicine must be able to cross this barrier to reach the intended target. Otherwise, the BBB must be bypassed through a different administration route, such as intrathecal, intraventricular, or intraparenchymal delivery. Bypassing the BBB commonly requires neurosurgical intervention, with the associated increased risk of general anaesthesia, infection, and haemorrhage. Emerging new technologies, such as nanotechnology<sup>11</sup> and magnetic resonance-guided focused ultrasound, are being developed to allow for non-invasive penetration of the BBB to facilitate drug delivery. Magnetic resonance-guided focused ultrasound, which allows for accurate and temporary penetration of the BBB, has been trialled in amyotrophic lateral sclerosis.<sup>12</sup>

Diagnostic uncertainty is another key challenge in the field of precision medicine. Although next-generation sequencing technologies have revolutionized how patients are diagnosed, there are several pitfalls that may hinder the confirmatory diagnosis. First, the importance of a detailed and accurate assessment by a clinician with movement disorder expertise cannot be understated, particularly since non-inherited causes of movement disorders (including drug-induced conditions, functional movement disorders, and perinatal events) can look very similar to inherited diseases. It can also help to better delineate movement disorder semiology,<sup>3</sup> which may direct future investigations; indeed, if a genetic cause is suspected, the specialist in movement disorders may be able to narrow the differential diagnosis based on specific clinical aspects. The expertise of a clinical geneticist may also be valuable in interpreting whole-exome or whole-genome sequencing data, especially for novel, previously unreported genetic variants that can often be difficult to interpret and are often diagnostically reported as variants of uncertain significance. Again, the clinician with movement disorders expertise can provide a vital role since their careful delineation of the child's phenotype may help corroborate or refute genetic findings. Rarely, where diagnostic or research functional assays are

available (e.g. aromatic L-amino acid decarboxylase plasma activity for aromatic L-amino acid decarboxylase deficiency, cerebrospinal fluid neurotransmitter analysis for tyrosine hydroxylase deficiency), it may be possible to further investigate the effect of a novel variant on protein function. However, this is not always possible, leading to diagnostic doubt, which could deprive a patient of a potentially effective treatment. Over time, the development of more sophisticated genetic interpretation tools and improved functional assays will address this shortfall.

Another major challenge is the clinical heterogeneity and phenotypic pleiotropy observed in some genetic childhood movement disorders. Frequently patients with the same genetic condition (and even the same genetic variant) may manifest different clinical phenotypes of variable severity. Furthermore, for a particular individual, there are often natural fluctuations within the disease time course, with phases of relative stability and periodic exacerbations or rapid decline at other times. Depending on when a treatment is being tried in the disease course, these natural fluctuations could give a false impression of therapeutic efficacy. Detailed natural history studies of these genetic diseases will undoubtedly facilitate our understanding of the disease course and the effect of precision treatments at different disease stages.

The lack of reliable and objective outcome measures is another important challenge in precision medicine and can potentially hamper the development of effective treatments. The question of how one measures therapeutic success is both philosophical (which out of quality of life of the patient, quality of life of the carers, symptom relief, discernible motor and cognitive progress, and prevention of death is the most important measure?) and scientific (clinical rating scales vs quantifiable biomarkers). In fact, for most genetic movement disorders there are no established biomarkers or other objective measures that correlate accurately with disease progression. Without an objective measure, how would it be possible to determine if a proposed treatment has made a difference or not to the disease trajectory? Furthermore, the fluctuating and paroxysmal nature of some symptoms means that an assessment at a single time point will often not be enough. Moreover, existing validated scales, which although excellent for measuring specific areas (like tone or development), are often too generic and not specific enough to capture the global disease impact of most childhood genetic movement disorders. This is particularly true for genetic childhood movement disorders that have a combination of neurological features (e.g. axial hypotonia with peripheral spasticity and intermittent dystonia), systemic features (e.g. cardiac involvement, respiratory symptoms), and non-linear disease progression (e.g. gradual decline with stepwise regression during intercurrent infections). Again, natural history studies will help gauge the 'typical disease course' for a particular disorder; advances in multi-omics tools will also facilitate the development of blood, urine, and cerebrospinal fluid biomarkers for future use in clinical trials.

## PRECISION MEDICINE APPROACHES FOR GENETIC CHILDHOOD MOVEMENT DISORDERS

In this section, we discuss different precision medicine approaches for genetic childhood movement disorders (Fig. 1 and Table S1, online supporting information), focusing on those that are currently available and those that may become available in the near future. The categories are broad and while not an exhaustive list, several salient examples will be used to exemplify each approach.

### Reduction of accumulating toxic molecules

#### **Copper chelation and zinc salts for Wilson disease**

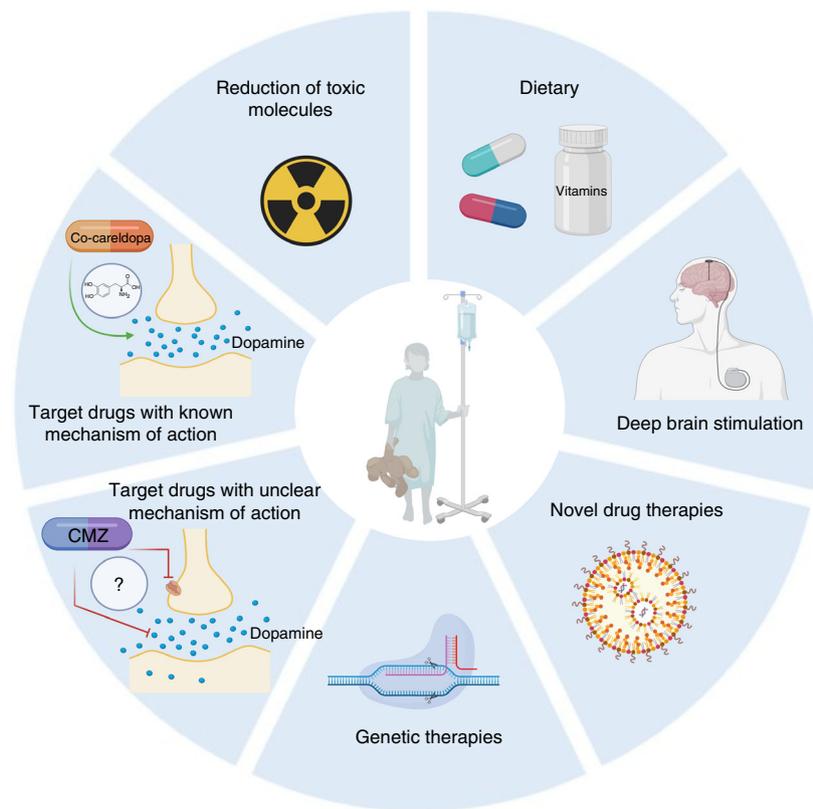
Recessive *ATP7B* mutations in Wilson disease lead to failure of biliary copper excretion, abnormal copper homeostasis, and toxic copper accumulation in various organs, most notably the liver and nervous system.<sup>13</sup> Neurologically, this classically manifests as tremor, dystonia, parkinsonism, dysarthria, and/or dysphagia. If diagnosed early before the development of advanced liver disease or brain injury, increasing urinary copper excretion through chelation therapy (D-penicillamine and trientine dihydrochloride) and reducing copper absorption through zinc salts can result in neurological improvement in up to 60% of patients over 1 to 3 years.<sup>13</sup>

#### **Manganese chelation for hypermanganesemia with dystonia**

There are two inherited disorders of hypermanganesemia associated with neurotoxicity type 1 (due to mutations in *SLC30A10* – dystonia, polycythaemia, and chronic liver disease) and type 2 (due to mutations in *SLC39A14* – rapidly progressive dystonia without polycythaemia or chronic liver disease). Both diseases have characteristic brain magnetic resonance imaging (MRI) changes (T2 hypointensity of the globus pallidus and T1 hyperintensity of the globus pallidus and white matter with pathognomonic sparing of the ventral pons).<sup>14</sup> Manganese chelation with intravenous sodium calcium edetate (for 5–8d every 4wks) along with oral iron supplementation, which reduces manganese absorption by being a competitive ligand on the manganese transporter, is the current mainstay of treatment.<sup>14</sup> Treatment can reduce manganese accumulation, avoid progression of liver disease (in hypermanganesemia associated with neurotoxicity type 1), and treat the neurological symptoms.<sup>14</sup>

#### **Iron chelation for pantothenate kinase-associated neurodegeneration**

Pantothenate kinase-associated neurodegeneration (PKAN) is a type of neurodegeneration characterized by iron accumulation in the brain caused by autosomal recessive mutations in *PANK2*. PKAN can be rapidly progressive with onset in early childhood (<6y, mean age at onset=3y in classic PKAN) or progress more slowly with onset in older children (>6y in atypical PKAN).<sup>15</sup> Progressive dystonia predominates in classic PKAN whereas parkinsonism and neuropsychiatric features are prominent features in atypical PKAN.<sup>15</sup> For most patients, there is a distinctive pattern seen on brain MRI with a central hyperintense signal



**Figure 1:** Precision medicine approaches in childhood genetic movement disorders. CMZ, carbamazepine. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

surrounded by hypointense signal in the globus pallidus on T2-weighted images, also known as the ‘eye of the tiger’ sign.<sup>15</sup> Iron chelation therapy in the form of oral deferiprone (which crosses the BBB) has been recently trialled in patients with PKAN. The results of the double-blind, randomized controlled trial with open-label extension showed that oral deferiprone was well tolerated and lowered the iron content in the basal ganglia, as measured on R2\*-MRI.<sup>16</sup> It appeared to slow disease progression (as assessed by the Barry–Albright Dystonia Scale), although this did not achieve statistical significance at the end of the 18-month trial period nor in the additional 18-month extension study.<sup>16</sup> Interestingly, in the subgroup analysis, patients with atypical PKAN had a statistically significant ( $p=0.019$ ) improvement on their Barry–Albright dystonia score.<sup>16</sup> The study results suggest that while iron accumulation is an important factor in PKAN pathogenesis, it is still a secondary phenomenon downstream of the primary molecular defect; this may explain the limited benefit observed with chelation in this trial.

### **Miglustat for Niemann–Pick disease type C**

Niemann–Pick disease type C (NPC) is a rare lysosomal storage disorder due to autosomal recessive mutations in the *NPC1* or *NPC2* genes, with visceral, neurodegenerative,

and/or psychiatric manifestations. Characteristic neurological features include vertical supranuclear saccadic palsy and gelastic cataplexy.<sup>17</sup> Other common neurological manifestations include ataxia, dysarthria, dysphagia, dystonia, and cognitive impairment.<sup>17</sup>

Miglustat is a disease-specific therapy approved for NPC that acts by inhibiting the glucosylceramide synthase enzyme, addressing the lipid trafficking defect in patients with NPC; it is thought to reduce the neurotoxic effects of excess GM2 and GM3 gangliosides and unesterified cholesterol.<sup>18</sup> Miglustat has been shown to stabilize neurological symptoms and delay disease progression, as assessed by neuropathological markers, quantitative neuroimaging, clinical assessment, and survival.<sup>18</sup>

### **Chenodeoxycholic acid for cerebrotendinous xanthomatosis**

Cerebrotendinous xanthomatosis is a rare lipid storage disease due to autosomal recessive mutations in *CYP27A1*. Deficiency of this mitochondrial enzyme sterol 27-hydroxylase prevents cholesterol from being converted to the bile acid chenodeoxycholic acid and upregulates an alternative pathway, resulting in excess cholesterol and cholestanol.<sup>19</sup> This excess lipid accumulates in various tissues, including muscle tendons, eye lenses, and arteries, and also results in

neuropathological abnormalities of the central and peripheral nervous system.<sup>19</sup>

Supplementation of exogenous chenodeoxycholic acid exerts a negative feedback effect that reduces the production of cholestanol.<sup>19</sup> It can improve or stabilize motor function, electrophysiological parameters, and brain structure, particularly if given during a therapeutic window before (or within 25y) of the onset of neuropsychiatric features.<sup>20</sup>

### **Dietary intervention**

#### ***Ketogenic diet for glucose transporter 1 deficiency syndrome due to SLC2A1***

Heterozygous mutations in *SLC2A1* were originally described in patients with early-onset intractable seizures and developmental delay associated with a low fasting cerebrospinal fluid glucose to plasma glucose ratio (<0.4).<sup>21</sup> Subsequently, the phenotype expanded to include patients with paroxysmal exercise- or fasting-triggered movements without epilepsy.<sup>21,22</sup> The classical ketogenic diet (or the better-tolerated modified Atkins/ketogenic diet<sup>23</sup>) is an established effective treatment for this disorder since the ketone bodies produced can cross the BBB via the monocarboxylic acid transporter, thereby bypassing the defective glucose transporter 1 to provide an alternative energy source for brain metabolism, thereby improving seizures, movement disorder, and head growth.<sup>21</sup>

#### ***Oral supplementation and dietary restrictions***

The inborn error of metabolism glutaric aciduria type 1 is an organic aciduria due to recessive mutations in the *GCDH* gene. If left untreated, it can lead to acute encephalopathic crises (often triggered by intercurrent infection), which result in acute bilateral striatal brain injury and a resultant complex hyperkinetic movement disorder. If managed presymptomatically (such as those identified through newborn screening or from older siblings) with a strict low-lysine diet, carnitine supplementation, and emergency regime for intercurrent illness, the neurological outcome is much improved and the movement disorder can even be prevented.<sup>24</sup>

A similar approach is used for creatine deficiency syndromes like guanidinoacetate methyltransferase deficiency where patients can have pathological signal intensities in the basal ganglia on brain MRI; some (approximately 30%) also have movement disorders.<sup>25</sup> Creatine monohydrate and high-dose L-ornithine supplementation along with an arginine-restricted diet are associated with improvement or stabilization of symptoms.<sup>25</sup>

#### ***Vitamin and trace element supplementation***

A number of genetic movement disorders are related to inherited defects in vitamin/trace element transport or metabolism, including cerebral folate deficiency,<sup>26</sup> ataxia due to vitamin E deficiency,<sup>27</sup> thiamine transporter defects,<sup>28</sup> and hypomanganesemia glycosylation type II.<sup>29</sup> Many of these can be treated successfully with replacement strategies, which commonly lead to both biochemical improvements and clinical benefit (Table S1).

### **Target drugs with known mechanisms of action**

#### ***Levodopa for dopa-responsive dystonia***

Dopa-responsive dystonia is a clinically and genetically heterogeneous group of disorders that are characterized by dystonia that often begins in the limbs, fluctuate diurnally, and have a sustained response to levodopa treatment.<sup>30</sup> The archetypal condition in this group is caused by guanosine 5'-triphosphate cyclohydrolase I deficiency due to autosomal dominant mutations in *GCHI* (also known as Segawa disease or dystonia 5a). There are several other genetic dopa-responsive dystonia conditions (e.g. sepiapterin reductase deficiency, tyrosine hydroxylase deficiency) where it would be prudent to diagnose early given that there is an effective treatment that targets the disease mechanism, although levodopa-derived clinical benefit is commonly less dramatic than that seen in guanosine 5'-triphosphate cyclohydrolase I deficiency. For tyrosine hydroxylase deficiency, levodopa-induced dyskinesia that can develop (precipitated by increments in levodopa dosages, febrile illness, or stress) is usually amenable to amantadine.<sup>31</sup> By acting as a weak, non-competitive N-methyl-D-aspartate receptor antagonist (increasing dopamine release and preventing dopamine reuptake), amantadine can be introduced when dyskinesia develops to allow for further increases in levodopa as required.<sup>31</sup> Of note, there are also other dopamine-deficient neurotransmitter disorders, such as aromatic L-amino acid decarboxylase (AADC) deficiency where levodopa may be useful but for only a small proportion of patients; in this case, the majority of patients rely on dopamine agonists as well as serotonergic therapies (e.g. monoamine oxidase inhibitors).

#### ***Caffeine in adenylyl cyclase 5 dyskinesia***

Heterozygous mutations in adenylyl cyclase 5 (*ADCY5*) result in a hyperkinetic movement disorder classically characterized by generalized chorea and dystonia that tend to be more prominent in the upper body, with a propensity to paroxysmal exacerbations. Paroxysmal exacerbations typically occur with regard to drowsiness or transitions in the sleep-wake cycle. Anecdotal reports of response to caffeine have emerged.<sup>32</sup> This condition is thought to be due to a gain-of-function effect of the *ADCY5* enzyme predominantly expressed in the striatum and activated through adenosine A2A receptors.<sup>32</sup> Caffeine is an adenosine A2A receptor antagonist and, as a result, may have inhibitory effects on *ADCY5* protein function. The effect of caffeine in *ADCY5*-related disorders is currently being investigated in larger studies.<sup>33</sup> In a recent case report, a patient with *ADCY5*-related disease responded to treatment with istradefylline, a selective adenosine A2A receptor antagonist.<sup>34</sup>

#### **The role of deep brain stimulation**

Deep brain stimulation (DBS) involves utilizing electrical impulses to alter neural signals in specific subcortical parts of the brain through the implantation of electrode leads that are connected to a pacemaker. In paediatrics, DBS was initially considered only in pharmacoresistant cases of

childhood dystonia. Over time, it is increasingly being used as an early option for a number of monogenic inherited dystonias where DBS is emerging as a highly efficacious treatment modality.<sup>35</sup> DBS is effective in children with DYT1 dystonia due to mutations in the *TOR1A* gene,<sup>36</sup> DYT6-related disease due to dominant mutation in the *THAP1* gene,<sup>37</sup> *GNAO1*-associated hyperkinesia,<sup>38</sup> and *KMT2B*-related dystonia,<sup>39</sup> and provides effective symptom palliation in PKAN.<sup>36</sup> The sustained benefits of DBS range from improvement in gross motor function,<sup>35</sup> prevention of life-threatening hyperkinesia events,<sup>38</sup> reduction in dystonia,<sup>36,37,39,40</sup> and even restoration of independent ambulation.<sup>39</sup>

### Target drugs with unknown mechanism of action

#### **Carbamazepine for paroxysmal kinesigenic dyskinesia**

Paroxysmal kinesigenic dyskinesia (PKD) is one of the most common paroxysmal movement disorders; attacks are typically short (<1min), without loss of consciousness and pain. It is triggered by sudden voluntary movements ('kinesigenic' trigger).<sup>41</sup> Heterozygous *PRRT2* gene mutations are a major cause of PKD. *PRRT2* clearly exemplifies phenotypic pleiotropy, which is reported in association with benign familial infantile seizures, hemiplegic migraine, and PKD.<sup>41</sup> In those with *PRRT2*-related PKD, low-dose carbamazepine is highly effective with complete response and cessation of triggered episodes observed in more than 95% of patients.<sup>41</sup> The exact mechanism of carbamazepine efficacy in PKD has not yet been fully elucidated but may relate to its voltage-gated sodium channel blockage properties or possibly to inhibition of dopamine neurotransmission from increased striatal acetylcholine concentrations.<sup>42</sup>

### Novel drug therapies

There are several novel compounds designed specifically to target disease mechanisms that are actively being studied in clinical trials. Results so far suggest that such targeted therapies can be challenging in the clinic. In PKAN, fosmetpantotenate replacement therapy aims to bypass the enzymatic block in the vitamin B<sub>5</sub>-coenzyme A pathway. Despite promising preclinical data,<sup>43</sup> it has not been shown to be effective in patients with PKAN in the Fosmetpantotenate Replacement Therapy trial.<sup>44</sup> Another vitamin B<sub>5</sub> intermediary metabolite (coenzyme A-Z), which targets a different part of the vitamin B<sub>5</sub>-coenzyme A pathway has shown promising results in the mouse model of PKAN<sup>45</sup> and is currently being studied in a phase II clinical trial.<sup>46</sup> Building on the work on a *Drosophila* model of *PLA2G6*-associated neurodegeneration (PLAN), RT001 (a deuterated homologue of linoleic acid that aims to make polyunsaturated fatty acids resistant to lipid peroxidation) is currently being evaluated in an ongoing clinical trial.<sup>47</sup> Although huge progress is being made in this area, it is likely that improvements in preclinical data sets, better brain targeting, and accurate dosing studies will further advance the efficacy of such novel targeted therapeutic compounds.

## GENETIC THERAPIES

Advances in genetic technologies have meant that there are now multiple therapeutic approaches either in trial or being developed for genetic disorders (Fig. 2).

### Adeno-associated viral vector-related gene therapy

Adeno-associated viruses (AAVs) were first discovered in the 1960s; as early as the 1980s, recombinant AAVs were vectorized for in vitro gene delivery.<sup>48</sup> Recombinant AAVs have the same capsid sequence and structure as wild-type AAVs but all the AAV protein-coding sequences are replaced by therapeutic gene expression cassettes.<sup>48</sup> In the 2000s, the AAV toolbox was greatly expanded by the discovery of a new set of primate AAV serotypes, such that today it is the leading platform for gene therapy delivery<sup>48</sup> (Fig. 2) and is being utilized in clinical trials. In spinal muscular atrophy type 1 (a rapidly progressive neuromuscular disease with early mortality in infancy), due to lack of a functional survival motor neuron 1 gene, a single-dose intravenous administration of onasemnogene abeparvovec (an AAV serotype 9 vector containing the human *SMN* gene that can cross the BBB) has resulted in improved outcomes in survival, motor function, and motor milestone achievement.<sup>49</sup> In aromatic L-amino acid decarboxylase deficiency (an inherited neurotransmitter disorder), a recombinant AAV cassette containing L-dopa decarboxylase complementary DNA has been delivered with targeted stereotactic neurosurgery into either the bilateral putamen or substantia nigra pars compacta and ventral tegmental area of affected children resulting in sustained improvements in motor function, reduction/ablation of dystonic attacks and oculogyric crisis, and improvement in autonomic dysfunction.<sup>50–52</sup>

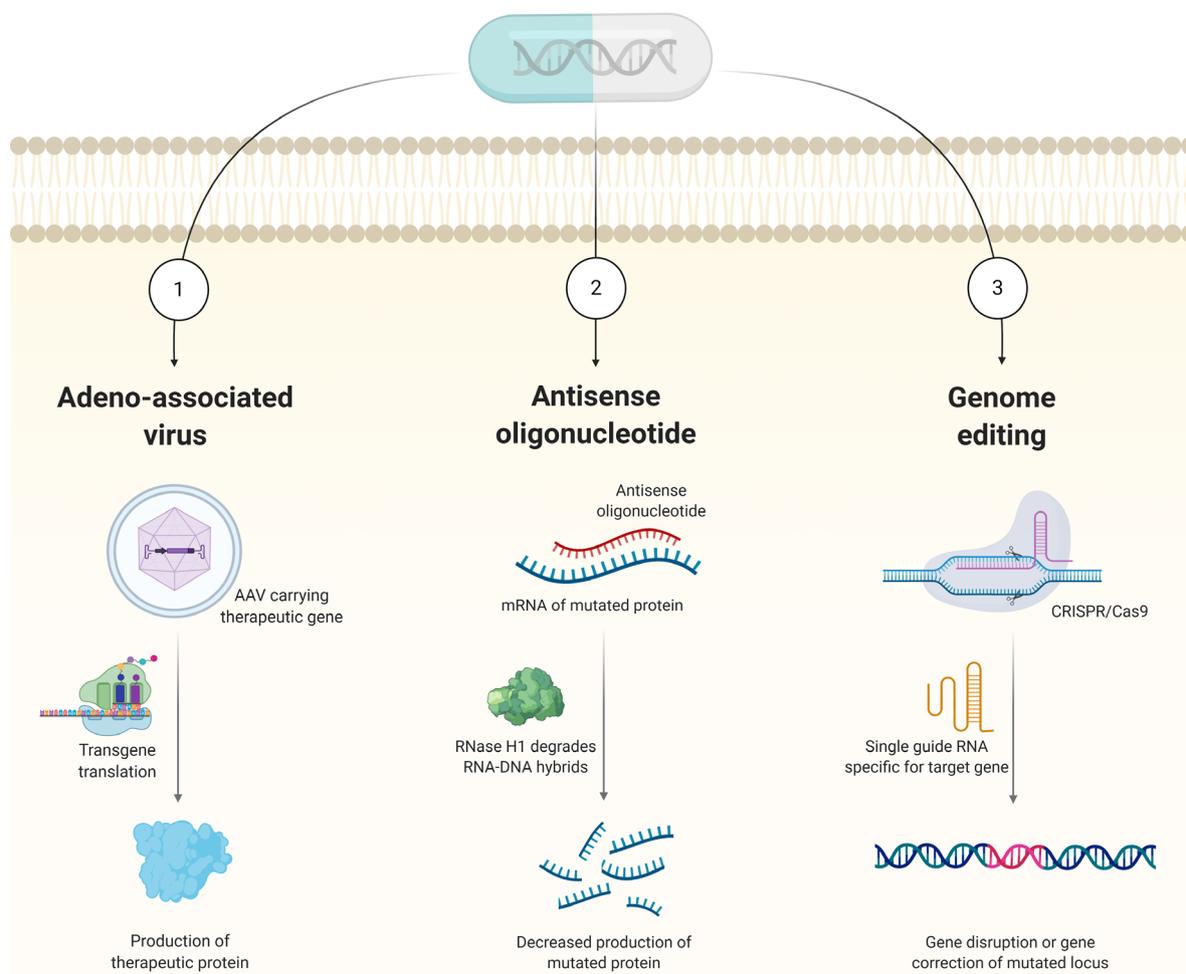
### Antisense oligonucleotides

Antisense oligonucleotides are single-stranded DNA sequences that are complementary to specific messenger RNA. This RNA–DNA hybrid can be used to target mutations that produce disease-causing protein, modulate splicing sites, block translation, or reduce protein levels by inducing RNA degradation (Fig. 2).<sup>53</sup> This elegant system has been used effectively in spinal muscular atrophy, by increasing the incorporation of exon 7 and functional SMN protein, and is in the advanced stages of testing for Huntington disease (by selectively lowering mutant huntingtin protein expression by targeting its RNA for destruction).<sup>53</sup> Recently, a customized antisense oligonucleotide was even designed for a child with ceroid lipofuscinosis neuronal subtype 7, also known as Batten disease (a rare genetic neurodegenerative condition), based on a specific mutation, resulting in neurological stabilization and seizure reduction.<sup>54</sup>

### Genome editing technology

The ability to perform increasingly accurate genome editing is continually evolving. By taking advantage of nature's DNA repair processes, the bacterial CRISPR–Cas9 system can be manipulated with a guide RNA to induce a double-stranded break (conventional genome editing) or a single-

## Genetic therapies for precision medicine



**Figure 2:** Genetic therapies for precision medicine. AAV, adeno-associated virus. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

strand break (base editing) by the Cas9 enzyme (Fig. 2).<sup>55</sup> However, these methods have issues (e.g. unwanted insertions and deletions at the point of the double-stranded breaks, off-target effects) and limitations (e.g. base editing only allows single-base repair). The latest addition to the gene editing toolbox, which bypasses these issues, is prime editing.<sup>56</sup> The most exciting and pertinent feature of prime editing for neuroscience research is that prime editing is possible in postmitotic, terminally differentiated primary cells (including neurons) with a much higher efficacy of edited DNA compared to conventional methods.<sup>56</sup>

### A PRAGMATIC APPROACH FOR ACCELERATION OF PRECISION MEDICINE

From the development of vaccines to next-generation sequencing technologies, medical history has shown that major scientific breakthroughs have the potential to completely revolutionize the entire field. As novel precision therapies emerge for genetic movement disorders, multidisciplinary collaborative working will be key to driving the process.

### The role of the clinician

Given the scientific advances in genomics, artificial intelligence, and automated processes, it is easy to overlook the importance of the clinician's role. However, we postulate that clinicians have never been more important since they are in the position to deliver and accelerate such precision medicine approaches. Careful clinical delineation of signs and symptoms to aid interpretation of genetic findings is essential to reach the right diagnosis. Furthermore, clinicians are important drivers of the necessary clinical trials for these novel therapies.

### The role of the scientist

Scientists are rising to the challenge of accelerating translational research, bringing advances from bench to bedside faster than ever. The team who developed and delivered a customized oligonucleotide therapy for the patient with ceroid lipofuscinosis neuronal subtype 7 (Batten disease) was able to do so within 1 year.<sup>54</sup> Increasingly, newer *in vitro* techniques, such as induced pluripotent stem cells

and three-dimensional models like neural organoids and minibrains for drug discovery,<sup>57</sup> are being harnessed to accelerate the translation of preclinical work in better humanized laboratory disease models. They have the potential to complement the necessary animal model work for elucidating disease mechanisms and driving drug development. They are also particularly useful for diseases where an animal model either does not exist or fails to accurately recapitulate the human disease.

### The role of the community and wider society

Many childhood genetic movement disorders are rare and the justification or applicability of research into rare diseases is often questioned. However, the rarity of disease can prompt global international collaborations with resource sharing (e.g. study consortiums, disease registries, biobanks). Moreover, the study and treatment of such rare but well-defined, homogenous groups of patients means that rare disorders often act as a stepping stone to further scientific advancement for the wider society, by providing insights into more common diseases that may have overlapping disease features and underlying mechanisms. For example, elucidation of the underlying genetic basis of early-onset and juvenile Parkinson disease revealed key pathways contributing to disease pathogenesis, such as mitophagy,  $\alpha$ -synucleinopathy, and clathrin-mediated endocytosis, which are also relevant in the understanding of the more common later-onset sporadic forms of the disease. Thus, it is likely that advances in precision medicine for rare disorders will also advance the field generally for the wider society.

Patient, parent, and lay public involvement is playing an increasing role in research. Given their first-hand experience of managing their child's movement disorder, families have unique and invaluable insights into these rare diseases. From helping to set research priorities and fundraising, to actively participating in research and raising awareness, parent organizations and patient and public

involvement and engagement groups are helping to accelerate further development of precision medicine.

In conclusion, genetic childhood movement disorders are being ushered into the exciting era of precision medicine, addressing a huge unmet clinical need. Increasingly, effective targeted precision medicine is either already available or in development for a number of conditions. Although there are many challenges in developing such precision medicine, anticipating and addressing the key issues (including ensuring that natural history studies are undertaken, robust biomarkers and good outcome measures are developed, strong preclinical data sets in multiple patient-relevant laboratory models are created that circumvent the BBB, and good trial design is implemented before clinical trials) will aid the development of efficacious therapies. In tandem with these scientific advances, close collaboration between clinicians, researchers, affected families, and stakeholders in the wider community will be key to successfully delivering such precision therapies.

### ACKNOWLEDGEMENTS

MAK is funded by a National Institute for Health Research (NIHR) professorship, the Jules Thorn Award for Biomedical Research and Rosetrees Trust. AKSS is funded by an NIHR Great Ormond Street Hospital Biomedical Research Centre PhD fellowship. The views expressed are those of the authors and not necessarily those of the NHS, NIHR, or the Department of Health.

### DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

### SUPPORTING INFORMATION

The following additional material may be found online:

**Table S1:** Examples of genetic childhood movement disorders with specific treatment

### REFERENCES

- McGrath S, Ghersi D. Building towards precision medicine: empowering medical professionals for the next revolution. *BMC Med Genomics* 2016; **9**: 23.
- Lionel AC, Costain G, Monfared N, et al. Improved diagnostic yield compared with targeted gene sequencing panels suggests a role for whole-genome sequencing as a first-tier genetic test. *Genet Med* 2018; **20**: 435–43.
- Brandsma R, Vanegmond ME, Tijssen MAJ, et al. Diagnostic approach to paediatric movement disorders: a clinical practice guide. *Dev Med Child Neurol* 2021; **63**: 252–8.
- Alfaro-Almagro F, Jenkinson M, Bangarter NK, et al. Image processing and quality control for the first 10,000 brain imaging datasets from UK Biobank. *Neuroimage* 2018; **166**: 400–24.
- Goodkin O, Pemberton H, Vos SB, et al. The quantitative neuroradiology initiative framework: application to dementia. *Br J Radiol* 2019; **92**: 20190365.
- Poretti A, Wolf NI, Boltshauser E. Differential diagnosis of cerebellar atrophy in childhood: an update. *Neuropediatrics* 2015; **46**: 359–70.
- Morales-Briceno H, Mohammad SS, Post B, et al. Clinical and neuroimaging phenotypes of genetic parkinsonism from infancy to adolescence. *Brain* 2020; **143**: 751–70.
- Gaetani L, Blennow K, Calabresi P, Di Filippo M, Parnetti L, Zetterberg H. Neurofilament light chain as a biomarker in neurological disorders. *J Neurol Neurosurg Psychiatry* 2019; **90**: 870–81.
- Polivka J, Polivka J Jr, Krakorova K, Peterka M, Topolcan O. Current status of biomarker research in neurology. *EPMA J* 2016; **7**: 14.
- Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N Engl J Med* 2017; **377**: 1723–32.
- Teleanu DM, Chircov C, Grumezescu AM, Volceanov A, Teleanu RI. Blood-brain delivery methods using nanotechnology. *Pharmaceutics* 2018; **10**: 269.
- Abraham A, Meng Y, Llinas M, et al. First-in-human trial of blood-brain barrier opening in amyotrophic lateral sclerosis using MR-guided focused ultrasound. *Nat Commun* 2019; **10**: 4373.
- Członkowska A, Litwin T, Dusek P, et al. Wilson disease. *Nat Rev Dis Primers* 2018; **4**: 21.
- Anagianni S, Tuschl K. Genetic disorders of manganese metabolism. *Curr Neurol Neurosci Rep* 2019; **19**: 33.
- Hayflick SJ, Kurian MA, Hogarth P. Neurodegeneration with brain iron accumulation. *Handb Clin Neurol* 2018; **147**: 293–305.
- Klopstock T, Tricta F, Neumayr L, et al. Safety and efficacy of deferiprone for pantothenate kinase-associated neurodegeneration: a randomised, double-blind,

- controlled trial and an open-label extension study. *Lancet Neurol* 2019; **18**: 631–42.
17. Patterson MC, Mengel E, Vanier MT, Moneuse P, Rosenberg D, Pineda M. Treatment outcomes following continuous miglustat therapy in patients with Niemann-Pick disease type C: a final report of the NPC Registry. *Orphanet J Rare Dis* 2020; **15**: 104.
  18. Pineda M, Walterfang M, Patterson MC. Miglustat in Niemann-Pick disease type C patients: a review. *Orphanet J Rare Dis* 2018; **13**: 140.
  19. Nie S, Chen G, Cao X, Zhang Y. Cerebrotendinous xanthomatosis: a comprehensive review of pathogenesis, clinical manifestations, diagnosis, and management. *Orphanet J Rare Dis* 2014; **9**: 179.
  20. Amador MDM, Masingue M, Debs R, et al. Treatment with chenodeoxycholic acid in cerebrotendinous xanthomatosis: clinical, neurophysiological, and quantitative brain structural outcomes. *J Inherit Metab Dis* 2018; **41**: 799–807.
  21. Brockmann K. The expanding phenotype of GLUT1-deficiency syndrome. *Brain Dev* 2009; **31**: 545–52.
  22. Leen WG, Klepper J, Verbeek MM, et al. Glucose transporter-1 deficiency syndrome: the expanding clinical and genetic spectrum of a treatable disorder. *Brain* 2010; **133**: 655–70.
  23. Kass HR, Winesett SP, Bessone SK, Turner Z, Kossoff EH. Use of dietary therapies amongst patients with GLUT1 deficiency syndrome. *Seizure* 2016; **35**: 83–7.
  24. Boy N, Mengler K, Thimm E, et al. Newborn screening: a disease-changing intervention for glutaric aciduria type 1. *Ann Neurol* 2018; **83**: 970–9.
  25. Stockler-Ipsiroglu S, van Karnebeek C, Longo N, et al. Guanidinoacetate methyltransferase (GAMT) deficiency: outcomes in 48 individuals and recommendations for diagnosis, treatment and monitoring. *Mol Genet Metab* 2014; **111**: 16–25.
  26. Pope S, Artuch R, Heales S, Rahman S. Cerebral folate deficiency: analytical tests and differential diagnosis. *J Inherit Metab Dis* 2019; **42**: 655–72.
  27. El Euch-Fayache G, Bouhhal Y, Amouri R, Feki M, Hentati F. Molecular, clinical and peripheral neuropathy study of Tunisian patients with ataxia with vitamin E deficiency. *Brain* 2014; **137**: 402–10.
  28. Ortigoza-Escobar JD, Molero-Luis M, Arias A, et al. Treatment of genetic defects of thiamine transport and metabolism. *Expert Rev Neurother* 2016; **16**: 755–63.
  29. Park JH, Högrefe M, Fobker M, et al. SLC39A8 deficiency: biochemical correction and major clinical improvement by manganese therapy. *Genet Med* 2018; **20**: 259–68.
  30. Wijemanne S, Jankovic J. Dopa-responsive dystonia: clinical and genetic heterogeneity. *Nat Rev Neurol* 2015; **11**: 414–24.
  31. Pons R, Syrengelas D, Youroukos S, et al. Levodopa-induced dyskinesias in tyrosine hydroxylase deficiency. *Mov Disord* 2013; **28**: 1058–63.
  32. Méneret A, Gras D, McGovern E, Roze E. Caffeine and the dyskinesia related to mutations in the *ADCY5* gene. *Ann Intern Med* 2019; **171**: 439.
  33. Méneret A. Pilot study on caffeine efficiency in ADCY5-related dyskinesia (CAF-ADCY5) [Internet]. Bethesda, MD: National Institutes of Health, US National Library of Medicine, 2020. Available from: <https://clinicaltrials.gov/ct2/show/NCT04351360> (accessed 2 March 2021).
  34. Miyamoto R, Kawarai T, Takeuchi T, Izumi Y, Goto S, Kaji R. Efficacy of istradefylline for the treatment of *ADCY5*-related disease. *Mov Disord Clin Pract* 2020; **7**: 852–3.
  35. Tustin K, Elze MC, Lumsden DE, Gimeno H, Kaminska M, Lin J-P. Gross motor function outcomes following deep brain stimulation for childhood-onset dystonia: a descriptive report. *Eur J Paediatr Neurol* 2019; **23**: 473–83.
  36. Artusi CA, Dwivedi A, Romagnolo A, et al. Differential response to pallidal deep brain stimulation among monogenic dystonias: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2020; **91**: 426–33.
  37. Danielsson A, Carecchio M, Cif L, et al. Pallidal deep brain stimulation in *DYT6* dystonia: clinical outcome and predictive factors for motor improvement. *J Clin Med* 2019; **8**: 2163.
  38. Koy A, Cirak S, Gonzalez V, et al. Deep brain stimulation is effective in pediatric patients with *GNAO1* associated severe hyperkinesia. *J Neurol Sci* 2018; **391**: 31–9.
  39. Zech M, Lam DD, Winkelmann J. Update on *KMT2B*-related dystonia. *Curr Neurol Neurosci Rep* 2019; **19**: 92.
  40. Panov F, Gologorsky Y, Connors G, Tagliati M, Miravite J, Alterman RL. Deep brain stimulation in *DYT1* dystonia: a 10-year experience. *Neurosurgery* 2013; **73**: 86–93.
  41. Ebrahimi-Fakhari D, Saffari A, Westerberger A, Klein C. The evolving spectrum of *PRRT2*-associated paroxysmal diseases. *Brain* 2015; **138**: 3476–95.
  42. Rissardo JP, Caprara ALF. Carbamazepine-, oxcarbazepine-, eslicarbazepine-associated movement disorder: a literature review. *Clin Neuropharmacol* 2020; **43**: 66–80.
  43. Elbaum D, Beconi MG, Monteagudo E, et al. Fosmetpantotenat (RE-024), a phosphopantothenate replacement therapy for pantothenate kinase-associated neurodegeneration: mechanism of action and efficacy in nonclinical models. *PLoS One* 2018; **13**: e0192028.
  44. Klopstock T, Videnovic A, Bischoff AT, et al. Fosmetpantotenat randomized controlled trial in pantothenate kinase-associated neurodegeneration. *Mov Disord* 2020. <https://doi.org/10.1002/mds.28392>. (Online ahead of print).
  45. Jeong SY, Hogarth P, Placzek A, et al. 4'-Phosphopantetheine corrects CoA, iron, and dopamine metabolic defects in mammalian models of PKAN. *EMBO Mol Med* 2019; **11**: e10489.
  46. Gregory AM. CoA-Z in pantothenate kinase-associated neurodegeneration (PKAN) [Internet]. Bethesda, MD: National Institutes of Health, US National Library of Medicine, 2019. Available from: <https://clinicaltrials.gov/ct2/show/NCT04182763> (accessed 2 March 2021).
  47. Adams D, Midei M, Dastgir J, et al. Treatment of infantile neuroaxonal dystrophy with RT001: a deuterated ethyl ester of linoleic acid: report of two cases. *JIMD Rep* 2020; **54**: 54–60.
  48. Wang D, Tai PWL, Gao G. Adeno-associated virus vector as a platform for gene therapy delivery. *Nat Rev Drug Discov* 2019; **18**: 358–78.
  49. Al-Zaidy SA, Kolb SJ, Lowes L, et al. AVXS-101 (onasemnogene abeparvovec) for SMA1: comparative study with a prospective natural history cohort. *J Neuromuscul Dis* 2019; **6**: 307–17.
  50. Kojima K, Nakajima T, Taga N, et al. Gene therapy improves motor and mental function of aromatic l-amino acid decarboxylase deficiency. *Brain* 2019; **142**: 322–33.
  51. Chien Y, Lee N, Teng S, et al. Gene therapy with AGIL-AADC in children with AADC deficiency leads to de novo dopamine production and sustained improvement in motor milestones over 5 years. 47th Annual Meeting of the Child Neurology Society. *Ann Neurol* 2018; **84**: S281–S428.
  52. Pearson T, Gupta N, Viehoveer A, et al. Gene therapy for AADC Deficiency. 47th Annual Meeting of the Child Neurology Society. *Ann Neurol* 2018; **84**: S281–S428.
  53. Leavitt BR, Tabrizi SJ. Antisense oligonucleotides for neurodegeneration. *Science* 2020; **367**: 1428–9.
  54. Kim J, Hu C, Moufawad El Achkar C, et al. Patient-customized oligonucleotide therapy for a rare genetic disease. *N Engl J Med* 2019; **381**: 1644–52.
  55. Platt RJ. CRISPR tool modifies genes precisely by copying RNA into the genome. *Nature* 2019; **576**: 48–9.
  56. Anzalone AV, Randolph PB, Davis JR, et al. Search-and-replace genome editing without double-strand breaks or donor DNA. *Nature* 2019; **576**: 149–57.
  57. Farkhondeh A, Li R, Gorshkov K, et al. Induced pluripotent stem cells for neural drug discovery. *Drug Discov Today* 2019; **24**: 992–9.