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Perspective

Individualized antisense oligonucleotide treatment eligibility of patients living with neurodevelopmental diseases

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SUMMARY

With advances in genetic diagnostic tools, pathogenic variants in patients with genetic diseases are being identified at an accelerated pace. For a subset of these patients, individualized genetic interventions such as antisense oligonucleotides (ASOs) would address the disease cause. These individualized, or n-of-1, ASOs are currently being clinically applied in dozens of cases but mainly in patients with neurodegenerative diseases. For neurodevelopmental disorders, however, several questions arise: (1) Are they treatable? (2) What is the appropriate time window? (3) Does the treatment effect justify the burden and risks of treatment? In this consensus statement, we argue for the case to consider the development of individualized ASO treatment for individuals living with neurodevelopmental diseases and discuss which aspects need to be taken into consideration.

INTRODUCTION

Rare diseases, in aggregate, affect ~6%–8% of the population, and the majority of diseases have a genetic origin.[1] With advances in genetic analysis techniques, more and more patients receive a genetic diagnosis. At the same time, developments in therapeutic approaches to address the genetic cause of the disease at the transcript or gene level create therapeutic opportunities for an increasing number of patients. For prevalent genetic conditions, gene-targeted therapies have been developed that have received regulatory marketing authorization, e.g., the gene therapy Zolgensma and the antisense oligonucleotide (ASO) therapy nusinersen for spinal muscular atrophy patients.[2] However, the majority of genetic diseases has an extremely low prevalence, and downscaling therapy development from a larger scale to a very small, or even individual scale, is not commercially viable under current regulatory frameworks.[3] Often, ASO and gene editing approaches are variant specific; so, even for more common rare diseases, usually only a small subset of patients would be benefited.

For patients eligible for ASO intervention with nanorare variants (less than 30 cases worldwide), initiatives to facilitate the development of individualized ASO treatments have been established in a not-for-profit fashion, such as N-lorem and the N=1 collaborative, or within an academic setting, such as 1 Mutation 1 Medicine (1M1M) and the Dutch Center for RNA therapeutics.[3–8] Individualized genetic treatment development started with an ASO for an ultra-rare variant that caused Batten's disease (milasen, targeting CLN7 transcripts),[9] leveraging information from nusinersen. Currently, there are also examples of individualized gene therapy and base editing treatments that have been clinically applied.[10,11] The development of individualized ASOs, however, has especially taken off, and there are currently many more individualized ASOs than there are ASOs with

marketing authorization. To date, the FDA has reviewed 49 n-of-1 investigational new drug (IND) applications, encompassing 35 unique ASOs, for the intended treatment of 82 patients (CDER, November 2025).[4]

The development of individualized treatments has specific challenges that have been outlined by the International Rare Disease Research Consortium (IRDIRC) N=1 taskforce.[12] One important step is the careful assessment of patients' eligibility for individualized treatment development based on scientific, clinical, and ethical considerations. This is an aspect already discussed in the milasen publication[9] and should be done objectively based on prespecified criteria. 1M1M has produced a best practice, multidimensional framework to assess the eligibility of patients with neurological diseases for individualized ASO development,[5] and additional considerations have been described in other publications.[7,13] These publications describe that to assess the eligibility for personalized ASO therapy development, three main aspects have to be taken into account: the pathogenic variant, the disease, and the individual patient.[5] For each aspect, the main question is whether it can be expected that the patient will benefit from the treatment and that this benefit will outweigh the burden of the treatment. For the variant aspect, ASOs should target the molecular cause of the disease. ASOs can decrease the abundance of transcripts (e.g., for toxic gain-of-function diseases) or modulate splicing (e.g., to restore or increase protein production that is abolished due to a cryptic splicing variant). Guidelines on how to assess if and which ASO modality would apply to a specific pathogenic variant have been produced by the N=1 collaborative.[13] For the disease aspect, there should be unmet medical need, and the disease severity should justify the burden of treatment (e.g., repeated intrathecal delivery). Furthermore, the symptoms and their tissue origin have to be taken into account. Individualized treatment development leverages what is known for ASOs approved for larger groups of individuals. This means that the options for delivery are limited to tissues where efficient ASO delivery has been proven and clinical benefit has been reported: liver (systemic treatment using GalNAC conjugates), eye (via intravitreal injection), and the central nervous system (via intrathecal delivery). Thus, individualized ASO development is considered only when the main symptoms of the disease involve these tissues. Finally, the individual patient needs to be considered, as development of these ASOs takes time (usually 1–3 years), and clinical benefit from the treatment should still be expected at the time when the ASO is available. Additionally, an individual may have co-morbidities that preclude treatment (e.g., intrathecal delivery is not possible in individuals with severe scoliosis), or the disease burden may be so high that the added burden of treatment with an experimental therapy is not justified. Furthermore, the ability of a patient or family to cope with uncertainty inherent to experimental treatments may shift during the ASO development process. These aspects are all critically important, and very often, the answer is not a clear "yes" or "no." A framework to establish eligibility in a stepwise manner is essential and was generated by 1M1M.[5]

This framework was made to evaluate individual patients on a case-by-case basis, not to prioritize patients. However, the focus of the 1M1M framework publication was on patients with progressive diseases, and it did not specifically consider neurodevelopmental disease patients, which we focus on in this consensus statement.

Neurodevelopmental diseases are a group of conditions that disrupt processes of normal neurodevelopment, such as neuronal proliferation, migration, differentiation, synaptogenesis, and/or network maturation. Symptoms typically manifest prenatally or in early childhood and result in persistent impairments of brain structure, function, and connectivity, leading to long-lasting cognitive behavioral motor or social deficits. Examples include autism spectrum disease, learning disorders, developmental and epileptic encephalopathies, and intellectual disability.

When considering ASO treatment for genetic neurodevelopmental disorders, several questions arise: (1) are they treatable? (2) what is the appropriate time window? (3) does the treatment effect justify the burden and risks of treatment? In this consensus statement, we argue that there is a case to consider individuals living with neurodevelopmental diseases for the development of individualized ASO treatment (summarized in Figure 1). In a workshop organized by the n=few treatment work package (WP12) of the ERDERA project, consensus statements were conceived, and these are presented here as well with illustrative examples.

A CASE FOR INDIVIDUALIZED ASO DEVELOPMENT FOR PATIENTS WITH NEURODEVELOPMENTAL DISORDERS

At a molecular level, using ASOs to specifically restore production of a protein or reduce expression of a toxic protein will ideally correct aberrant cellular pathways. However, pathogenic genetic variants in individuals with neurodevelopmental disorders may impact brain function in complex ways, and some specific considerations of potential treatment effects are needed.

Firstly, differential spatiotemporal expression patterns of disease genes may have important implications. For instance, pathogenic variants in human genes encoding proteins important for early steps in the development might lead to abnormal generation of brain cells, brain circuitry, circuit function, or circuit plasticity/remodeling. Each specific biological disruption may result in a different critical therapeutic window, outside which any treatment would be expected to have little effect. Additionally, regional expressional differences of the gene of interest may require that ASO delivery should be optimal to the brain regions most strongly affected by the disorder.

Complicating the considerations for these first-order processes, the effect of a particular pathogenic variant causing neurodevelopmental disability may have secondary effects that are difficult to predict. These could be downstream consequences of disruption of cellular pathways or protein interaction networks of brain structures. For example, neuronal pathology may be further complicated by non-neuronal cellular pathology through inflammation and/or glial dysfunction (e.g., abnormal myelination). In another example, abnormal circuit wiring may cause activation of compensatory circuit networks. For any given condition, it is possible that these secondary processes could normalize with treatment of the root cause of disease, but they could have additional, difficult-to-predict effects as well. These could potentially make therapeutic correction more difficult.

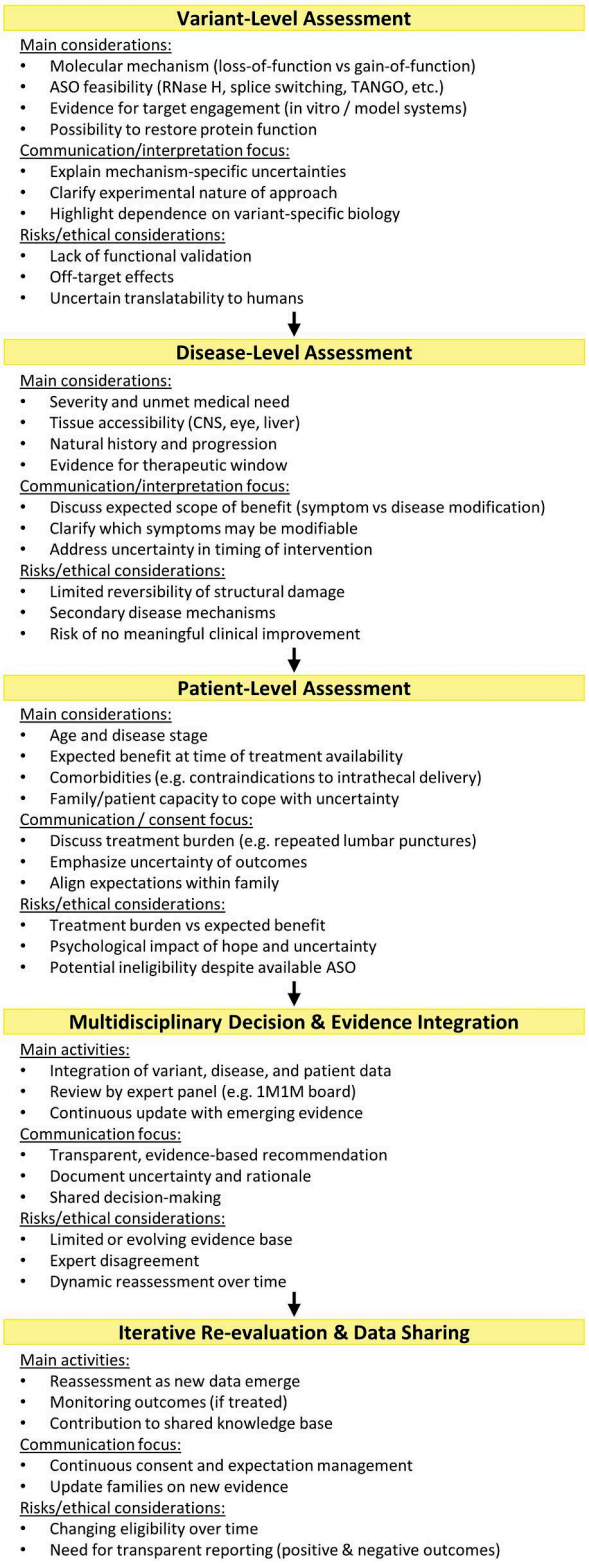

Figure 1. Schematic outline of steps and considerations to assess patient eligibility for individualized treatment development

One can even imagine scenarios where they could result in unintended consequences of genetic intervention making brain function paradoxically worse. These, at least theoretical possibilities are worth bearing in mind when assessing risk-benefit for interventional trials in neurodevelopmental disorders.

Caveats notwithstanding, there is convincing evidence from preclinical and clinical trials suggesting that treating individuals with neurodevelopmental disabilities can lead to successful outcomes. The first example is Angelman Syndrome (OMIM# 105830), a disease characterized by developmental delay, intellectual disability, motor and communication deficits, and seizures. This disease is caused by loss-of-function mutations in the maternally inherited copy of *UBE3A*. This gene is subjected to an imprinting mechanism, whereby the paternal copy of the *UBE3A* allele is not normally transcribed due to the expression of a long non-coding RNA, UBE3A-AST, which silences the paternally inherited *UBE3A* copy. There are various approaches in clinical development, including an ASO (rugonersen), that aim to prevent or knockdown the expression of UBE3A-AST, thus allowing the paternal expression of *UBE3A* and restoring the production of functional UBE3A.

In a very elegant study using a mouse model where expression from the maternal *Ube3a* copy could be activated at chosen time points, Silva-Santos et al. showed that there is a therapeutic window for the restoration of various pathological aspects.[14] When *Ube3a* expression was activated at conception, motor function, behavioral deficits, and anxiety were restored. However, when gene expression was activated in newborn (0 days old) or juvenile mice (3 weeks of age), only the motor deficits were restored. For animals where expression was induced at adolescence (6 weeks of age), only partial improvement of motor deficits was seen, while no improvement was seen when expression was induced in adulthood (14 weeks of age). This study clearly reveals that there is a critical treatment window where the behavioral deficits arise during embryogenesis and are not amenable to postnatal treatment, while for motor deficits, the treatment window closes between 3 and 6 weeks of age in mice. This sort of research gives important insights into what can and cannot be expected from treatment postnatally, although one always has to bear in mind that findings in animal models may not fully translate to the human situation.

Results from a phase 1 clinical trial with rugonersen in children with Angelman syndrome showed a dose-dependent, partial normalization of electroencephalogram (EEG) abnormalities and signals of clinical improvement that have not been seen in natural history.[15]

A second example is Dravet syndrome, a severe developmental and epileptic encephalopathy caused by pathogenic variants in *SCN1A* that cause haploinsufficiency and reduced levels of the $Na_v1.1$ sodium channels. Patients present with a spectrum of symptoms, including epilepsy, cognitive deficits, communication and behavioral impairments as well as autistic traits. The gene *SCN1A* produces high amounts of non-productive transcripts, which contain an exon that prevents protein translation. Zorevunersen is a splice-switching ASO that causes the skipping of this exon, thus increasing the amount of $Na_v1.1$. channel produced in patients with Dravet syndrome. A study in animal models revealed a reduction in seizures and improved function

and survival when treatment was given at postnatal day 2, but not when administered on day 14.[16] A clinical trial in children with Dravet syndrome showed a reduction in seizure frequency and duration—functional improvement according to clinical scales and caregiver reports for the majority of patients.[17] Notably, while preliminary, these findings suggest that the treatment window, which appeared to be lost between day 2 and day 14 in mice, persisted into adolescence in humans. A phase 3 clinical trial including a placebo group is currently ongoing.

Another example is related to myotonic-atonic epilepsy, caused by pathogenic variants of *SCL6A1* (OMIM# 616421). The likely disease mechanism is haploinsufficiency due to loss-of-function variants, and affected individuals typically present with intellectual disability, motor deficits, seizures, and autism spectrum disorder-like symptoms. Guo et al. showed partial improvement of symptoms in mouse models for *Scl6a1*-related disorders.[18] Neonatal treatment of *Scl6a1*-heterozygous or -homozygous knockout mice showed normalization of EEG patterns. There was also an improvement in some, but not all, behavioral phenotypes observed in the homozygous knockouts, such as fear conditioning and nest building. Treatment on day 5 in the homozygous knockouts restored nest building but did not improve EEG, while in the heterozygous mice, EEG patterns were restored. This shows that, depending on residual protein levels, the treatment window can vary.

The *MECP2* duplication syndrome is associated with developmental delay, intellectual disability, motor disfunction, anxiety, epilepsy, and autism spectrum disorder. The disease is caused by an increased amount of MECP protein due to a gene duplication. ASO-induced reduction of *Mecp2* over-expression in adult mouse models of duplication syndrome rescued various behavioral deficits and motor function and reduced seizures.[19,20]

While some neurodevelopmental diseases are due to genetic defects that cause both epilepsy and directly alter neurodevelopment, for other neurodevelopmental diseases, such as *SCN8A* encephalopathy, the epileptic seizures further disrupt normal brain development. *SCN8A* encephalopathy is a disease characterized by developmental delay, drug-resistant epileptic seizures, and cognitive impairment. The disease is caused by toxic gain-of-function variants of *SCN8A*. In an inducible *Scn8a*-knockin mouse model, ASO-induced reduction of expression delayed the onset of seizures and improved survival when treatment was given either before onset of symptoms[21] or after onset of symptoms.[22]

EVALUATION OF DISEASE SUITABILITY FOR NEURODEVELOPMENTAL DISEASES

In summary, this collection of pre-clinical and clinical research shows that partial reversal of symptoms, especially the frequency and severity of debilitating seizures, is often possible for neurodevelopmental diseases. However, when ASO treatment is stopped, seizures return, which confirms that this treatment effect is due to the effect of the ASOs on protein production.[23]

While there is evidence that there is some development-related therapeutic window for several neurodevelopmental diseases, it is presently unclear if that window fully closes and if the treatment window differs for different genetic etiologies.

Evidence from mouse studies suggests that this aspect varies not only across gene targets and related disease but even for the different symptoms associated with a single genetic disease. This makes it challenging to predict the expected benefit of an individualized ASO treatment, and whether the treatment offsets expected and unknown risks and burdens, thus complicating family counseling. Some extrapolation may be possible between ASOs targeting genes in similar pathways. However, even for patients that require the same individualized ASO, there will be uncertainty due to the timing of the intervention.

To facilitate assessment of the eligibility for individuals with neurodevelopmental diseases, a group of multidisciplinary content experts met during a meeting that was organized by specialists in the field of individualized treatment work package (WP12) of ERDERA. Consensus statements were proposed and discussed and are presented here.

APPROACH TOWARD CONSENSUS STATEMENTS

To assess whether consensus was reached, the 5-finger consensus methodology was used.[24] Here, a statement is presented, and participants vote using 1–5 fingers, where 1 indicates strong disagreement and inability to support, 2 indicates disagreement, 3 indicates willingness to go along with the group's decision, 4 indicates agreement, and 5 indicates strong agreement. When only 3, 4, and 5 are shown, consensus is considered to have been reached. When participants vote using "1" or "2," those individuals explain why they disagreed and make recommendations to change the statement in such a way that it is acceptable to them. Then, this new statement is voted on. If needed, several rounds of reiteration occur until consensus is achieved.

The meeting was done in a hybrid setting and included preclinical researchers, clinical geneticists, clinicians, researchers involved in individualized ASO development, an expert with regulatory background, and an ethicist with expertise in achieving consensus via the Delphi method, who was purposefully attentive during the process to ensure rigor. People could vote online via chat (giving a number between 1 and 5) or in person (by showing fingers). Individuals were allowed to vote only when they felt they had the required background and expertise.

CONSENSUS STATEMENTS

The consensus statements are shown in Box 1. Voting iterations and how final statements were shaped from original statements are outlined in the supplemental data. We, here, discuss the statements and also give illustrative examples. The first statement centers on evidence to assess the likelihood and magnitude of functional benefit and possible treatment-induced harm. In the dynamic research fields of antisense therapeutics and neurodevelopmental disorders, evidence evolves continuously. This underlines the critical importance of early sharing of research results and data, which is one of the cornerstones of the N=1 collaborative. Only then are individuals able to make a judgment based on all available evidence. It also underlines that assessments may change with time, both positively or negatively, when new research data and evidence arise.

Finally, the statement acknowledges that, especially in very rare diseases, there is no, or a paucity of, available evidence. In these cases, a multidisciplinary expert panel, such as the 1M1M treatment board,[5] could instead provide an estimate of the expected benefit or harm.

The second statement deals with the phenotypic aspects of the disease that should be considered with regards to whether they may be modifiable by an individualized ASO treatment. First, one should consider whether the damage is functional or structural. It may be possible to rescue dysfunction, while it is more difficult to rescue cell death. Secondly, one should consider which gene-related pathways are still active and relevant at the time the patient is being treated, e.g., neuronal maturation, synaptogenesis, refinement of synaptic circuitry, and myelination. Thirdly, the affected neural networks should retain plasticity at the time of treatment. Fourthly, one should consider which aspects of disease progression are due to molecular dysfunction (i.e., the aspect targeted by the ASO), and which aspects are driven by secondary mechanisms that drive pathology further—compensatory mechanisms or aging. Finally, if patients respond to symptomatic treatment, this suggests that the symptoms are of a dynamic and, thus, potentially modifiable nature.

These aspects are based on current understanding and knowledge and may change in the future with further accumulation of knowledge and evidence. This again underlines the importance of sharing knowledge. Furthermore, often, there will be no evidence on one or several aspects. In that case, an estimation should be made by experts, as outlined in statement 1.

ILLUSTRATIVE SCENARIOS

Scenario 1: An individual is not eligible because an alternative, effective treatment exists

An individual is identified with a genetic epilepsy for which antiseizure medication is an established and effective treatment and where the symptomatic burden is primarily driven by the seizures. The patient or family declines the standard therapy without ever trying it, in favor of an individualized ASO. The established antiseizure medication has a known benefit/risk ratio and is immediately available, while the ASO may not be effective or safe and has a higher delivery burden, but is not available yet. So, this patient would not be deemed eligible for ASO development. Our previously published ethical framework to assess patient eligibility also clearly specifies that only patients without an available treatment or those in which treatments have failed should be considered for individualized ASO development.[5]

Notably, for many genetic neurodevelopmental diseases, seizures are part of the symptoms but not per se the main driver of the disease burden. Here, ASOs could be considered as an alternative to address both seizures and the additional symptoms, which are not addressed by the antiseizure medication.

Scenario 2: A case is initially not eligible but becomes eligible when the pathomechanism becomes clear

SCN2A variants can be gain- or loss-of-function variants, where gain-of-function variants cause early-onset developmental and epileptic encephalopathy, while the loss-of-function variants cause later-onset epilepsy, for which alternative treatment options exist. RNase H ASOs can be a therapeutic option for symptoms caused by gain-of-function variants, while they are not a therapeutic option and might even exacerbate symptoms caused by loss-of-function variants. If, for new variants, it is not clear whether the pathomechanism is gain-of-function, then ASOs should not be considered as a therapeutic option, but functional studies in cell or animal models can be performed to elucidate the pathomechanism. A study by Wagner et al. illustrated this with a real-life example of a pre-term girl born with a *de novo SCN2A* variant and developmental epileptic encephalopathy. Voltage-clamp experiments confirmed impaired channel inactivation and increased persistent current, consistent with a gain-of-function variant.[25] An RNase H ASO targeting SCN2A transcripts that was in clinical development was provided for compassionate use. A combined treatment of the ASO via intrathecal delivery and sodium channel blockers resulted in sustained seizure reduction of over 60% during a follow-up period of 22 months.

Scenario 3: Uncertainty for estimating the effect size or benefit

For this scenario, we use an example from the neurodegenerative field, as an approved ASO treatment exists. Amyotrophic lateral sclerosis (ALS) is a severe progressive neurodegenerative disease, characterized by loss of motor neurons. A subset of ALS patients carry pathogenic variants in an increasing number of genes, where ASO treatment might be an option. Indeed, tofersen is approved for *SOD1*-mutated ALS, and jacifusen is in clinical development for *FUS*-mutated ALS.[26–28] However, there are many additional genes where pathogenic gain-of-function variants predispose an individual to ALS development—a case that would also be eligible for RNase H-mediated ASO treatment. For a hypothetical novel familial ALS case, preclinical evidence of ASO-mediated knockdown of the target transcript and protein is available in cell models. Now, a multidisciplinary board could reason that treatment initiation is ethically justifiable when a patient's physical condition is comparable to that of someone for whom tofersen treatment is indicated. However, the board would also explicitly acknowledge that for this new ASO, there is uncertainty, as clinical evidence with regards to the efficacy and safety of tofersen is lacking. This uncertainty needs to be transparently communicated to the patient.

Scenario 4: Anticipating benefit due to the pathomechanism involving cellular dysfunction rather than irreversible structural damage

Rett syndrome is caused by loss-of-function variants of *MECP2*, which is located on the X chromosome. The disease is characterized by progressive loss of cognitive and motor skills and the development of seizures. At a cellular level, the disease is characterized by neuronal dysfunction, rather than neuronal death, and the neuronal circuitry remains intact. This suggests that phenotypes likely can be substantially reversed by treatment that restores MECP2 function. Indeed, in adult *Mecp2*-deficient mice, reactivation of *Mecp2* expression rescued established deficits in motor function, anxiety-like behavior, epileptiform activity, EEG abnormalities, and thermoregulation. Additionally, morphological defects, including neuronal size

and dendritic complexity, were reversed by late *Mecp2* activation.[29] These findings indicated that, at least in mice, neural circuitry deficits arising from *Mecp2* deficiency are reversible and that benefit is possible after treatment when functional cellular dysfunction predominates over cell loss. For this example, we would like to stress that ASO therapy development to increase *MECP2* expression is at early stages in cell and mouse models and is not yet close to clinical application.[30]

Scenario 5: Anticipating no benefit due to the pathomechanism involving irreversible structural damage

LIS1 lissencephaly is a neurodevelopmental disease characterized by the absence or severe reduction of gyra in the cerebral cortex. Symptoms include developmental delay, spasms, seizures, and hypotonia. The disease is caused by *de novo* heterozygous variants of *PAFAH1B1*.[31] The PAFAH1B1 (LIS1) protein has functions in cytoskeletal dynamics, cellular division, and motility, and the pathogenic variants result in abnormal neuronal migration in weeks 9–13 of gestation.[32] Postnatal treatment would not be able to reverse the cortical architecture established early in embryonic development.

CONSIDERATIONS FOR PATIENTS TO BE TREATED WITH AN EXISTING INDIVIDUALIZED ASO

Individualized ASOs are developed initially for single individuals with a nanorare condition (less than 30 patients known worldwide who would benefit from the treatment). However, often, additional patients likely to benefit from the same ASO will be found in the future. This is especially the case for RNase H ASOs developed for nanorare diseases.[8] When these ASOs are not allele selective, in principle, they would apply to all other patients with similar pathogenic variants (i.e., same pathomechanism) in the same gene. For allele-selective RNase H ASOs, additional patients may be eligible if they carry the ASO target (pathogenic variant or single nucleotide polymorphisms). Likewise, the same ASO would apply to patients carrying different pathogenic variants for splice-switching ASOs, using the TANGO approach, where, for haploinsufficiency, the amount of protein produced is increased by targeting exons that prevent protein translation in non-productive transcripts.[16] For ASOs targeting a deep intronic variant that causes cryptic splicing, the likelihood of finding additional patients is smaller, but it is still a possibility in familial cases.

We stress that when patients are identified who carry eligible variants for which an ASO is already available, the newly identified patients are not automatically eligible for treatment. The preclinical and clinical information available for the ASO will help to reduce uncertainty. However, as different patients may present with different symptoms and may be in different disease stages, the justification of whether benefit is expected and whether this justifies the burden of the treatment needs to be evaluated on a case-by-case basis.

OUTLOOK

The field of individualized treatment offers hope to patients for whom there was no option available until now. However, at the same time, there are many uncertainties, which are inherent to individualized treatment development, as well as known limitations and burdens associated with the individualized treatments. Still, decisions have to be made to justify whether the anticipated benefit is balanced by the uncertainty of treatment effects and safety, and the burden of the treatment. Especially for neurodevelopmental diseases, these assessments are challenging and ethically complex and, rarely, will have a clear "yes" or "no" answer. We aim, through our publication and the consensus statements, to guide those making these decisions. Finally, in this field with significant uncertainty, the only way forward is to share all experiences (positive, negative, and uninformative) so that everyone can benefit from more informed decisions.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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