

Towards a treatment for genetic prion disease: trials and biomarkers



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Summary

Prion disease is a rare, fatal, and exceptionally rapid neurodegenerative disease. Although incurable, prion disease follows a clear pathogenic mechanism, in which a single gene gives rise to a single prion protein (PrP) capable of converting into the sole causal disease agent, the misfolded prion. As efforts progress to leverage this mechanistic knowledge toward rational therapies, a principal challenge will be the design of clinical trials. Previous trials in prion disease have been done in symptomatic patients who are often profoundly debilitated at enrolment. About 15% of prion disease cases are genetic, creating an opportunity for early therapeutic intervention to delay or prevent disease. Highly variable age of onset and absence of established prodromal biomarkers might render infeasible existing models for testing drugs before disease onset. Advancement of near-term targeted therapeutics could crucially depend on thoughtful design of rigorous presymptomatic trials.

Introduction

Prion disease is a rare, fatal neurodegenerative disease caused by misfolding of prion protein (PrP).¹ Most cases of prion disease in humans arise spontaneously and are not diagnosed until advanced dementia is present.^{2,3} Severe physical and mental impairment and rapid decline in health of the symptomatic patients have posed challenges for clinical trials.^{4,5} Genetic prion disease, which accounts for about 15% of cases,⁶ offers an unexplored opportunity for early therapeutic intervention to delay or prevent disease.

Exploration of this opportunity will require creativity in clinical trial design. Trials in presymptomatic individuals are unlikely to be able to show clinical benefit directly because of disease rarity and variability in age of onset.⁷ Secondary prevention strategies based on prodromal pathology will also likely be infeasible due to absence of an established prodrome before onset of genetic prion disease.^{8–10} However, alternative approaches could be designed on the basis of the well established pathophysiology of prion disease. Congruent lines of evidence from biochemistry, human genetics, and mouse models support the central role of PrP in prion disease.¹ Preclinical proof of concept studies suggest that a reduction in PrP concentration in the brain could delay disease onset in individuals with pathogenic PrP mutations.^{11–14} Ongoing development of antisense oligonucleotides for prion disease¹⁵ suggests that the therapeutic goal of PrP reduction might soon become clinically actionable.

Given the well established and singular role of PrP in prion disease, quantitative demonstration of reduced PrP concentration in the CNS via an appropriately qualified pharmacodynamic biomarker is likely to predict clinical benefit in prion disease. We therefore present a proposal made to scientists at the US Food and Drug Administration (FDA)'s Center for Drug Evaluation and Research that PrP load in human CSF merits evaluation as a surrogate endpoint in the context of the Accelerated Approval programme. Such an approach could enable, for the first time, rigorously controlled trials in presymptomatic individuals

with genetic prion disease mutations, with the aim of preserving full quality of life.

Pathogenesis of prion disease

All subtypes of human prion disease, including Creutzfeldt-Jakob disease, fatal familial insomnia, and Gerstmann-Straussler-Scheinker disease, share a common molecular mechanism—misfolding of native PrP, encoded by the prion protein gene (*PRNP*). The misfolded protein, known as a prion, can induce misfolding of other PrP molecules. Through such templated misfolding, prions spread in a conformational cascade, recognised for decades as the molecular mechanism driving PrP's gain-of-function in disease.^{1,16}

The true annual incidence of human prion disease is about two deaths per million population,¹⁷ or about one in 6000 deaths.^{6,18} Although prion disease is infamous for the small minority (<1%) of cases acquired through infection,¹⁹ most (about 85%) cases, termed sporadic, occur spontaneously, with no known environmental or genetic trigger. The remainder (about 15%) arise from dominant, gain-of-function, protein-altering variants in *PRNP*.⁶ Some of these variants are highly penetrant, with lifetime risk approaching 100%, and three such variants account for most genetic cases.⁶ Age of onset is highly variable and not well predicted by *PRNP* genotype.⁷

Among neurodegenerative diseases, prion disease is notable for its exceptionally rapid clinical course. Patients with symptomatic prion disease progress from first symptom to death in about five months.²⁰ Although about a quarter of genetic cases correspond to mutations that progress more slowly, most patients with genetic prion disease die within a year from first symptoms.⁷ In this short time, patients rapidly descend into advanced dementia, typically spending the last weeks of life in a state of akinetic mutism. Throughout the disease, the brain is the epicentre of destruction. Diagnosis is challenging because of the rapidity of decline and heterogeneity of early symptoms, which can be cognitive, motor, autonomic, or psychiatric in nature.²¹ On average, patients with prion disease do not

Lancet Neurol 2020; 19: 361–68

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For the Accelerated Approval programme see <https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval>

Panel 1: Evidence that PrP is integral to prion disease pathophysiology

Biochemical

Prions are composed of PrP,²⁴ prion strains are encoded in distinct conformations of PrP;^{25–27} prion infectivity can be generated in vitro from purified PrP^{28–31}

Animal genetics

PrP is required for prion propagation;³¹ PrP is required for prion neurotoxicity;³² PrP dosage and incubation time are inversely associated;³² PrP amino acid sequence governs the species barrier³³

Human genetics

All families with genetic prion disease carry protein-altering variants in PRNP;³⁴ certain missense variants in PRNP confer protection against prion disease^{35–37}

PrP=prion protein.

course. In the most commonly used experimental paradigm, intracerebral inoculation of wild-type animals with prions leads to fatal disease after a highly predictable incubation time. Experiments in these models have provided some of the most compelling evidence of the importance of PrP in prion disease. PrP knockout confers complete resistance to prion disease,³¹ and prion neurotoxicity only affects cells expressing PrP.³² Moreover, PrP gene dosage is associated with pace of disease across a wide range of expression levels,³² with heterozygous PrP knockout mice surviving prion infection 2·5 times as long as wild-type mice (figure 1). Similarly, in transgenic mouse models expressing PrP with mutations that cause genetic prion disease in humans, PrP dosage is inversely associated with age of onset of spontaneous illness.³⁸

Previous therapeutic efforts

No disease-modifying treatment exists for prion disease. Of drugs tested clinically, none had strong preclinical evidence from animal models, and most have been assessed only in case reports or observational studies in a few symptomatic patients.³⁹ Three existing drugs—flupirtine, quinacrine, and doxycycline—have been tested in randomised controlled trials^{4,5,40} in patients with symptomatic prion disease with cognitive or survival endpoints. Previous observational studies reporting survival increase from quinacrine and doxycycline were not supported by these randomised studies, highlighting the importance of adequately controlled trials. However, these studies also show the challenges of conducting trials in a population with advanced, rapidly progressive disease. In the doxycycline trial,⁵ for example, nearly as many patients died awaiting random group assignment as were ultimately enrolled.

Future therapeutic advances could increase awareness of prion disease among neurologists and facilitate early diagnosis. However, available preclinical data from animal models provide additional perspective on the limitations of evaluating therapeutic efficacy only at a symptomatic disease stage. Some small molecules and sulphated sugar polymers identified in the past 15 years have shown convincing anti-prion activity in animals. Although none have prospects for clinical advancement, owing to either inefficacy against human prion strains^{41–44} or inadequate brain distribution,^{45,46} these molecules have provided important insights into the time dependence of therapeutic efficacy. In all instances when different animal model treatment timepoints have been compared, effectiveness of the compound decreased the later it was administered.^{43,45,47,48} None of these compounds have shown efficacy after onset of symptoms. For example, the most thoroughly studied molecule, IND24, quadrupled time to disease onset when administered before prion infection, increased survival time by about 70% when administered between infection and symptom onset, and lost all efficacy if administered as symptom onset approached (figure 2).

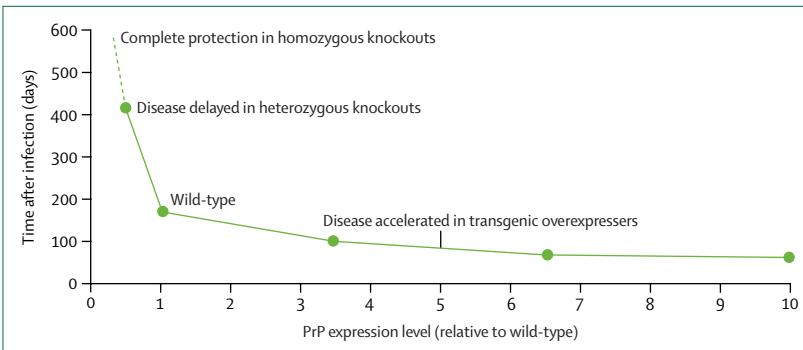


Figure 1: Prion disease incubation time and PrP expression level

Time to terminal disease in transgenic prion-infected animals is shown as a function of PrP expression level. Wild-type mice intracerebrally inoculated with prions develop fatal disease in 5–6 months. Transgenic mice producing extra PrP develop disease more rapidly than wild-type mice, while heterozygous knockout animals producing half the normal amount of PrP remain healthy more than twice as long as wild-type mice. Homozygous knockout animals cannot propagate prions and never develop prion disease. Plotted on the basis of data reported by Fischer and colleagues.³² PrP=prion protein.

receive a diagnosis until two-thirds of the way through the short symptomatic course,² at which point they are severely debilitated. Detection of prion seeding activity in CSF using real-time quaking induced conversion (RT-QuIC) now offers excellent sensitivity and specificity,²² but prion disease is typically not suspected until about three months from first symptom onset.²³

Despite its rarity and variability in clinical presentation, prion disease is well understood at the molecular level, with all lines of evidence pointing to the central role of PrP in prion disease. PrP forms a naturally transmissible proteinaceous pathogen devoid of nucleic acid,¹⁶ and biochemical, human genetic, and model organism approaches support the notion that PrP is required for prion disease (panel 1).

Many mammals are natural hosts of prion disease, and accordingly, the study of prion disease benefits from use of animal models that faithfully recapitulate the disease

These results could reflect fundamental differences in the molecular stage of disease. Following prion infection of animals, prion titres in the brain rise during a clinically silent incubation phase, with prion accumulation rate corresponding to the animal's PrP expression level. Some evidence indicates that increase in prion titre might slow or halt by the time symptoms emerge.^{16,49} If so, therapies that inhibit prion replication without affecting prion neurotoxicity might be highly effective prophylactics, with less clear molecular basis for efficacy at symptomatic stages.

These observations suggest that development of anti-prion drugs has two complementary needs moving forward. In addition to identifying molecules worth testing in humans, the field would be served by investigating new clinical paradigms.

Emerging therapeutic directions

Although the aforementioned drug discovery efforts were not targeted towards discovery of drugs with any single mechanism of action, genetics has long provided a strong therapeutic hypothesis in prion disease: reduction of native PrP. The importance of PrP in prion disease is well established, and genetic proof-of-concept studies show a dose-dependent protective effect of lowering PrP expression. Experimentally, this protective effect has been recapitulated using conditional and constitutive knockout systems.^{13,14} Substantial evidence also suggests that reducing PrP expression should be well tolerated. PrP knockout mice are viable, fertile, have normal lifespans, and exhibit normal behaviour, initially defying efforts to identify a knockout phenotype.⁵⁰ In the peripheral nervous system, PrP undergoes proteolytic cleavage to release a signalling peptide that promotes myelin maintenance.⁵¹ PrP knockout mice develop a slowly progressing demyelinating polyneuropathy, which leads to mild sensorimotor deficits late in life.⁵² Heterozygotes are unaffected.⁵² No native function has yet been identified in the CNS. Knockout cattle⁵³ and naturally occurring knockout goats^{54,55} are described as phenotypically normal. Although truncating variants late in the human *PRNP* coding sequence are known to give rise to a secreted protein, early truncating variants appear to convey true loss of function of PrP. Such variants have been observed in a heterozygous state in healthy middle-aged and older individuals with no syndromic or neurological health concerns.^{6,56} As such, a reduction in *PRNP* gene dosage appears to be well tolerated in humans.

Antisense oligonucleotides

Studies have investigated various therapeutic modalities to lower PrP expression,^{57–60} but to date, no practical means to achieve this therapeutic goal in the human brain has been available. However, because of the strength of clinical advances in the application of antisense oligonucleotides (ASOs) to other neurological diseases,^{61,62} ASOs designed to target and degrade PrP RNA have emerged as a

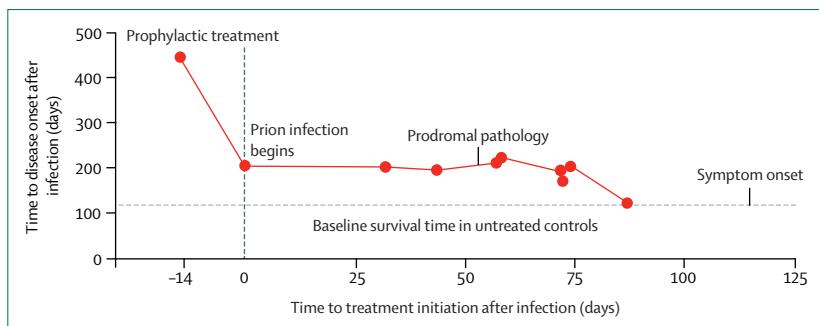


Figure 2: Treatment efficacy by time of administration in prion-infected mice

Efficacy of the anti-prion small molecule IND24, which inhibits prion replication by an unknown mechanism of action, depends on the timepoint at which treatment begins. When given prophylactically, it can quadruple time to disease of intracerebrally prion-infected mice. After prion infection begins, it increases time to disease onset by only about 70%. Beginning around 90 days post-infection, still before symptom onset, the IND24 molecule becomes ineffective. Plotted on the basis of data reported by Giles and colleagues.⁴³

plausible near-term therapeutic option and are now in preclinical development.¹⁵ ASOs are short (17–20 base) single-stranded oligonucleotides, chemically modified for pharmacokinetic stability, that specifically bind complementary target RNA. Following binding, ASOs can modulate their targets by various mechanisms; of particular interest for prion disease, they can trigger RNase H1-mediated degradation of the target RNA, reducing the amounts of encoded protein.⁶³

ASOs for neurological applications have been intensively studied, including the successfully completed phase 1, 2, and 3 trials of nusinersen in children with spinal muscular atrophy⁶⁴ and phase 1–2 trial of an anti-huntingtin antisense oligonucleotide (ASO-HTT Rx) in adults with Huntington's disease.⁶² Although nusinersen acts through splice modification, ASO-HTT Rx acts through degradation of *HTT* RNA, and has been shown to be capable of achieving a 40% reduction of mutant huntingtin protein in CSF of patients.⁶² Together, these and other programmes have compiled a wealth of knowledge regarding the behaviour of ASOs in the CNS (panel 2).

ASOs are uniquely modular drugs. Nucleotide sequences of ASOs specify target binding through Watson-Crick base pairing, yet these sequences are orthogonal to classes of backbone chemistry that determine many pharmacokinetic and pharmacodynamic parameters.⁶³ Considering this modularity, human data from other CNS antisense oligonucleotide programmes provide insights into potential properties of a PrP-reducing antisense oligonucleotide.

Trials in presymptomatic mutation carriers

Development of a plausible, genetically targeted therapy for prion disease lends urgency to the question of how clinical trials might be designed to give such a therapy its strongest chance to succeed. Although no method exists to identify patients with sporadic prion disease before clinical onset, genetic prion disease could offer a unique opportunity for presymptomatic intervention. Through predictive genetic testing, individuals carrying high-penetrance

Panel 2: Behaviour of ASOs in the CNS

Extensive preclinical and clinical testing of ASOs has delineated many pharmacological and toxicological parameters relevant to consideration of testing of PrP-lowering ASOs in individuals at risk for prion disease.

Delivery

ASOs delivered by intrathecal infusion or intrathecal bolus injection have achieved broad distribution across the CNS in non-human primates. Although ASOs are most potent in the cortex, activity is also seen in deep brain structures, with knockdown of target RNA reaching or exceeding 50% in regions including the cortex, hippocampus, spinal cord, pons, and cerebellum.^{65–67} Clinical studies of spinal muscular atrophy and Huntington's disease have relied on bolus delivery of ASO by intrathecal injection.^{61,62}

Safety and tolerability

In studies of intrathecally delivered ASOs for spinal muscular atrophy, Huntington's disease, and amyotrophic lateral sclerosis, treatment was not associated with safety or tolerability concerns, and no serious drug-related adverse events were reported in treated individuals.^{62,64,68}

Time to effect

ASO activity is reflected in target mRNA concentrations within 14 days of treatment in rodents and non-human primates;^{65,66,69} PrP has an estimated in-vivo half-life of 18 h,¹⁴ indicating that ASO-based mRNA depletion could quickly affect PrP at the protein level.

Dosing regimen

The in-vivo half-life of nusinersen in CSF was estimated at 132–166 days;⁶⁴ clinically, following a series of loading doses, maintenance dosing of nusinersen is given every 4 months;⁷⁰ the ASO-HTT-Rx phase 1–2 study dosed once a month,⁶² and the ongoing phase 3 study administers drug every 2 or 4 months.⁷¹

ASO=antisense oligonucleotides. PrP=prion protein.

PRNP mutations can be identified years or decades before symptom onset.

A trial in individuals who are presymptomatic and at risk of disease can be designed in multiple ways. The trial could recruit healthy mutation carriers, randomly assign them to drug or placebo, and follow them up to see if treatment delays onset of symptoms. One such trial is being done in families with *PSEN1* mutation causing autosomal-dominant early-onset Alzheimer's disease, costing about US\$96 million (ClinicalTrials.gov, NCT01998841).⁷² For prion disease, this approach is infeasible because the disease is very rare and age of onset is very variable,⁷ both more so than for *PSEN1* variants. Furthermore, such a costly trial design would not be tenable in a rare disease with no prospects for off-label or expanded use of the drug once approved.

Prodromal biomarkers

In slowly progressing neurodegenerative diseases, prodromal imaging or biochemical tests can detect pathological changes well before symptoms manifest.^{73,74} Such prodromal biomarkers might offer opportunities for secondary prevention, enabling selective enrolment of individuals close to onset,⁷⁵ or allowing subclinical markers of disease to be tracked as outcome measures. However, no such markers exist for prion disease. Prospective studies of carriers of prion disease mutations have reported consistent neurological and neurophysiological signatures, including brain volumetric changes by MRI,⁹ regional hypometabolism by FDG-PET,⁸ and lower-limb sensory deficits,¹⁰ concurrent with, or shortly after, symptomatic onset, but not before onset. At most, suggestive changes were noted in single individuals about one year before symptom onset.^{8,9} In an ongoing natural history study of presymptomatic mutation carriers and control participants, we have measured two markers of neuronal damage, neurofilament light chain and total tau, as well as prion seeding activity²² in CSF, all markers that are highly diagnostic or prognostic, or both, in patients with symptomatic prion disease.^{22,76–82} Neurofilament light chain and total tau concentrations were within normal ranges in all presymptomatic carriers, indistinguishable from non-carrier control participants; seeding activity was observed in only one of 23 presymptomatic individuals, and any prognostic implication remains unclear.⁸³

This picture could change with further study, particularly in the minority of at-risk individuals whose mutations can predispose to a longer-than-average disease course. If prodromal changes can be identified in this population, change in such markers might provide supporting data for a drug development programme. Nonetheless, validating the prognostic value of such markers could take decades.^{7–10} More importantly, a focus on individuals with prodromal pathology would prohibitively limit the number of trial participants, and preclinical proof-of-concept studies such as those we have discussed suggest that this approach might specifically select for those individuals

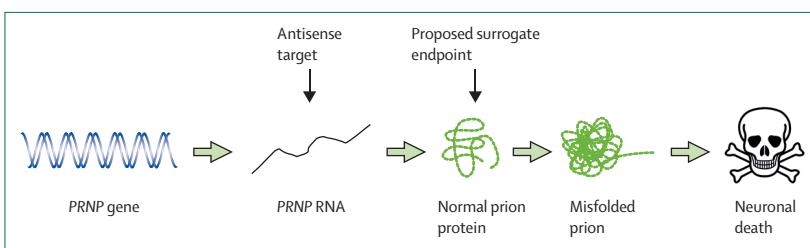


Figure 3: Drug target and proposed surrogate endpoint within the pathophysiological pathway of prion disease
 In this proposal, drug candidates, such as antisense oligonucleotides, designed to target the human *PRNP* RNA sequence, can be administered in clinical trials to healthy people at risk for genetic prion disease, before the disease process begins. These drugs are expected to engage their target, the *PRNP* RNA in the brain, reducing the overall amount of PrP in the brain. The anticipated drug-dependent change in PrP concentration in the brain can be measured in the CSF as a proxy sampling compartment. Because PrP lies directly on the main pathway of disease and is essential for disease development and progression, lowering PrP concentration in CSF is expected to predict clinical benefit. Thus, a demonstration of lowered concentration of CSF PrP in presymptomatic individuals at risk for genetic prion disease could potentially support an application for Accelerated Approval of a PrP lowering drug. Adapted with permission from Raymond et al.¹⁵ PrP=prion protein.

likely to benefit the least from a drug, as prion amplification and neuropathology would have already begun.

Surrogate endpoints

Another option exists for clinical research in pre-symptomatic mutation carriers: trials designed to support Accelerated Approval. Under this US FDA programme, trials can use a surrogate endpoint that is reasonably likely to predict clinical benefit. Developed in 1992 to address the AIDS crisis, Accelerated Approval served as a mechanism by which AIDS drugs could secure provisional approval on the basis of decreasing HIV viral load in patients. This approval process allowed new drugs to reach patients swiftly, without having to follow up participants in randomised controlled trials until death. The link between viral load and clinical outcome was considered biologically well established, and clinical benefit was subsequently confirmed post-approval. Since then, the US Congress has incorporated Accelerated Approval into law and has clarified that this mechanism is appropriate to consider when disease biology provides comparably predictive surrogate endpoints and if rareness and severity render other trial designs infeasible.⁸⁴

PrP lies directly on the sole pathway of prion disease pathophysiology (figure 3). All available lines of evidence agree that PrP is the pivotal molecule on this pathway, required for pathogen formation, disease initiation, and disease progression in a dose-dependent manner. Demonstration of target engagement for a PrP-lowering drug, a pharmacodynamic biomarker reflecting lowered brain PrP concentration, would therefore be reasonably likely to predict clinical benefit in prion disease. The conceptual resemblance between prion disease and infectious disease highlights the opportunity for PrP concentration to serve as a meaningful indicator, with some analogy to viral load in HIV.

PrP is abundant in human CSF and can be detected using commercially available ELISA kits.^{76,85} PrP is much less abundant in blood than in CSF, suggesting that detected PrP is primarily CNS-derived rather than blood-derived, and therefore reflects the tissue of interest.⁸⁶ Concentration of PrP in CSF is reduced in individuals with symptomatic prion disease compared with healthy controls or patients with other dementias,^{76,85–88} perhaps because of incorporation in plaques or intracellular accumulation. Crucially, however, this decline does not appear to be underway in presymptomatic individuals: an ongoing natural history study has confirmed the test-retest stability (mean coefficient of variation 7%) of CSF PrP in presymptomatic mutation carriers over the short (2–4 month) and medium (10–20 month) term.⁸³ Concentration of PrP in CSF was stable even in one presymptomatic individual with prion seeding activity in CSF. Thus, the pharmacodynamic effects of a PrP-lowering drug should be measurable in the CSF of presymptomatic individuals without confounding from disease state.

Panel 3: Paving the path for successful trials in genetic prion disease

Engaging carriers as part of our team

The best-laid therapeutic and clinical strategies still have no hope of advancing without another essential element: patients. One UK study⁸⁹ found that three-quarters of individuals at risk for genetic prion disease opt against predictive genetic testing. Many people are counselled against testing on the basis that the result is not actionable. However, some individuals might wish to know their status, and motivated individuals at risk could have an active and essential part in bringing a drug into existence. Natural history and biomarker studies lay groundwork for future trials, powered by donated samples and data. Registries showing an organised patient base inspire drug development partnerships. Trials depend on participants. Although no one choice regarding genetic testing will best serve everyone at risk, acknowledging the full spectrum of preference present in every genetic disease community is important, and being prepared to support, equip, and empower those who wish to pursue their genetic information is equally crucial.

Offering forward-looking counselling

Genetic counsellors and physicians who advise families at genetic risk have an important opportunity to set the tone for how these individuals will relate to their risk for the rest of their lives. As neurodegenerative diseases become meaningfully treatable, it is more important than ever to offer genetic counselling that encompasses pros as well as cons of predictive testing. Especially in a rapidly progressive disease such as prion disease, being able to make an informed decision in advance of symptoms could be essential to accessing and benefitting from plausible near-term therapeutics.

Referring mutation carriers to the Prion Registry

In July, 2017, in collaboration with patient organisations Creutzfeldt-Jakob Disease Foundation and Creutzfeldt-Jakob Disease International Support Alliance, we launched a simple online portal called the Prion Registry. The registry aims to be a location-agnostic, researcher-agnostic resource that provides information about research studies and trials to patients, carriers, and families on an opt-in basis, while also providing de-identified summary statistics to the research community. Referring at-risk individuals to this centralised platform will help to motivate drug development partners across sectors and to facilitate swift trial recruitment when required.

Additional considerations should be worked out as the therapeutic development of PrP-lowering ASOs advances. As in other CNS antisense oligonucleotide programmes,⁶² detailed pharmacodynamic modelling in non-human primate brains will crucially inform how reduction of CSF PrP concentration reflects knockdown across the brain. Corresponding studies in prion-infected rodents could illuminate how regional brain PrP knockdown translates into delaying clinical endpoints. As in other Accelerated Approval programmes, following biomarker-based provisional approval, clinical benefit would need to be confirmed in a post-marketing study. Under reasonable assumptions, a registry-based study of treated presymptomatic individuals, compared with historical controls, could provide an estimate of delay in disease onset within 5–15 years.⁷

For the Prion Registry see
<https://prionregistry.org>

Regulatory and community engagement

As we considered an Accelerated Approval strategy, we took advantage of the FDA's Critical Path Innovation Meeting mechanism to request an in-person meeting with FDA scientists regarding the prospects for

For the Critical Path Innovation Meeting see <https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/critical-path-innovation-meetings-cpim>

Search strategy and selection criteria

We searched Google Scholar and PubMed using the search terms "prion", "PrP", "Creutzfeldt-Jakob disease", "fatal familial insomnia", and "Gerstmann-Straussler-Scheinker disease" between Jan 1, 2014, and Dec 31, 2019. The search was restricted to English language articles and terms were included on the basis of their relevance to our strategies and considerations for prevention of genetic prion disease.

Accelerated Approval of a genetic prion disease drug on the basis of a demonstration of CSF PrP in asymptomatic mutation carriers, in light of the aforementioned considerations. In November, 2017, at the FDA's headquarters in Silver Spring, MD, USA, we had the opportunity to discuss the points we have outlined here with 25 of the agency's scientists. The FDA scientists were supportive of the concept, offered constructive questions and ideas about appropriate biomarker and preclinical data that would be needed, and generously offered to provide continued input. Although the FDA does not make commitments under the Critical Path Innovation Meeting mechanism, we felt the process was a model for regulatory partnership in rare-disease drug development, and we are continuing to work closely with the FDA as we gather further data in support of this biomarker and clinical strategy. Proactive consultation with non-US regulatory bodies, health insurance companies, and other payers is also an important near-term priority. Finally, engaging the community of presymptomatic carriers and building trial-ready cohorts will be crucial to enabling prevention in this population (panel 3).

Conclusions and future directions

No disease-modifying therapy exists for any adult-onset neurodegenerative disease. Calls are mounting for therapeutic efforts to aim for early points in the disease process,^{90,91} but the tractability of doing so varies across indications on the basis of disease biology and available tools. Genetic prion disease has unique assets: a single causal gene and protein, robust genetic proof-of-concept evidence supporting a knockdown therapeutic strategy, and established animal models in which this strategy can be honed. These insights and resources align to present a unique opportunity to shift therapeutic intervention upstream beyond early symptoms or preclinical pathology to genetically informed primary prevention. The unusual constraints of genetic prion disease make it an ideal test case for a concept with resonance well beyond this one rare indication: leveraging of predictive genetics to rewrite the future, and to keep healthy people healthy.

Contributors

SMV and EVM conceived and wrote the article with mentorship and guidance from SLS and ESL. SMV retrained as a biomedical researcher after learning, in 2011, that she had inherited a lethal, highly penetrant

PRNP variant (D178N) from her mother, who had died of a then-undiagnosed rapidly progressive dementia in 2010.

Declaration of interests

SMV and EVM report unrestricted charitable gifts from Charles River Laboratories and Ionis Pharmaceuticals, and non-financial support from Ionis Pharmaceuticals, outside the submitted work. EVM reports personal fees from Deerfield Management, outside the submitted work. All other authors declare no competing interests.

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