

The Huntington's Disease Society of America (HDSA) appreciates the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) August 20, 2026 Draft Background and Scope for ifezuntrigene inilparvovec (AMT-130) for Huntington's disease (HD).

HDSA appreciates that the draft scope recognizes the profound, multidimensional impact on people living with HD, their families, and caregivers. In particular, ICER appropriately recognizes that HD affects far more than motor function, including cognitive, psychiatric, behavioral, and functional changes that affect daily life, relationships, employment, independence, and family well-being. It also recognizes HD as a "family disease and experience" and that caregiving needs increase substantially as the disease progresses.

HDSA also appreciates that ICER has included caregiver and family impact, health-related quality of life, need for long-term care, patient and caregiver productivity, and other indirect costs. These are important steps toward a more complete understanding of treatment value for HD. However, HDSA believes the patient experience reflected in the draft scope should be substantially strengthened.

1. The patient experience must reflect the most current evidence from people living with HD.

The draft scope states that ICER incorporated publicly available patient testimonials, including an FDA Voice of the Patient report from 2016. That report remains valuable historical evidence, but should not be treated as the most current or comprehensive representation of the HD patient experience.

In November 2024, HDSA convened an FDA-recognized EL-PFDD meeting focused on people with pre-symptomatic, early-, and mid-stage adult-onset HD. FDA currently lists that meeting and its Voice of the Patient Report¹ among its condition-specific patient-experience resources. The meeting captured contemporary patient and caregiver perspectives on the symptoms and impacts that matter most and their experiences with treatment, with substantial patient and family engagement. HDSA strongly recommends that ICER review and incorporate the complete report, including patient and caregiver narratives and community-generated information about what matters most to people living with HD.

This is particularly important for a potential disease-modifying therapy. From the perspective of people living with HD, the question is whether treatment changes what they experience as disease progresses: their ability to remain independent, work, communicate, participate in family life, make decisions, maintain relationships, and remain the person they recognize themselves to be.

2. ICER should distinguish "impacts" from "outcomes."

HDSA recommends that ICER broaden its terminology and framework from a focus on outcomes to a focus on impacts.

Traditional clinical outcomes are necessary, but they do not fully describe what matters to people living with HD and their families. A patient-centered impact can include an outcome, but also consequences that may not fit neatly into a conventional clinical endpoint, including loss of employment or income, caregiver burden, disrupted family relationships, inability to participate in meaningful activities, changes in family roles, out-of-pocket costs, lost educational or career opportunities, and the time and emotional burden of caregiving.

The National Health Council's Patient-Centered Core Impact Set (PC-CIS) Blueprint² was developed specifically to address this gap. A PC-CIS is a patient-derived and patient-prioritized list of the most important impacts a disease and/or its treatments have on patients, families, and caregivers. It is intentionally broader than health outcomes and can include economic burden, work and career loss, caregiver and family stress, and other consequences.

HDSA is applying this framework to HD through its Huntington's Disease Patient-Centered Core Impact Set (HD PC-CIS) initiative. The effort began with patient and caregiver input through the HDSA HD Symptoms and Treatment Impact Survey, the 2024 EL-PFDD meeting, and qualitative data in 2025. The next phases focus on prioritizing and defining impacts identified by the HD community to be completed in Q2/2027.

The HD PC-CIS work is directly relevant because it asks a question conventional outcomes frameworks often fail to answer: What consequences of HD matter to patients, caregivers, families, and society? HDSA encourages ICER to engage with the initiative as it progresses and, where appropriate, use its patient-derived framework to inform the assessment.

3. Quality-adjusted life years do not capture the full impact of HD.

The draft scope appropriately proposes to examine QALYs and other measures of health gain, while also considering patient and caregiver productivity and other indirect costs in a separate societal analysis. However, HDSA urges ICER not to assume these additional impacts can simply be translated into QALYs or treated as secondary adjustments to a health-based model. QALYs measure health-related quality and quantity of life; they do not, by themselves, capture the full impact of HD on a person's life, family, or society.

For example, an individual with HD who can no longer work because of cognitive or behavioral symptoms may lose wages, retirement contributions, career advancement, professional identity, and financial independence. A caregiver may reduce working hours, leave employment, or forgo educational and career opportunities. Families may also incur costs for transportation, home modifications, assistive equipment, respite care, legal services, and long-term care planning. These are real-life impacts of HD.

The draft scope acknowledges that the majority of people with HD stop working within several years of diagnosis and recognizes the substantial burden on caregivers. Yet these consequences can be understated if ultimately reduced to a health utility weight.

The HD PC-CIS framework provides an important foundation for avoiding this problem. It explicitly distinguishes the broad universe of patient-identified impacts from downstream measures. HDSA therefore recommends that ICER present patient-identified impacts separately and transparently from health outcomes and QALYs. The assessment should make clear which impacts are captured by QALYs, which are captured elsewhere in the model, and which remain unmeasured or incompletely captured.

4. The full economic burden must include the patient and caregiver.

HDSA supports ICER's proposal to consider a modified societal perspective. However, this analysis should not be limited to productivity as traditionally defined or triggered only when societal costs are sufficiently large to change the incremental cost-effectiveness ratio by a specified threshold. At minimum, these should include:

- Loss of income and employment by the person living with HD;
- Reduced employment, lost employment, or career changes by caregivers;
- Lost retirement and other employment-related benefits;
- Unpaid caregiving time;
- Out-of-pocket expenses associated with HD;
- Home modifications and assistive equipment;
- Transportation and travel associated with HD care;
- Respite and long-term care costs;
- Time spent navigating insurance, disability benefits, and other systems;
- Financial consequences of reduced independence; and
- Broader effects on family members' education, employment, and family responsibilities.

These impacts should not be treated as peripheral considerations. They are central to the lived experience of HD and should be incorporated wherever credible data permit.

5. HDSA Centers of Excellence should be incorporated into the patient-experience and access assessment.

HDSA also recommends that ICER engage directly with HDSA Centers of Excellence (COEs) as an important source of patient-centered expertise. The draft scope appropriately recognizes the importance of access to specialized HD care, noting that only a minority of people with HD receive specialty neurological care and an even smaller proportion receive care at an HD Center of Excellence. It also recognizes the importance of multidisciplinary care.

HDSA COEs are uniquely positioned at the intersection of patient experience, multidisciplinary care, caregiver support, and the practical realities of living with HD. Their teams routinely see consequences that may not be visible through conventional outcomes: changes in employment, caregiver strain, family dynamics, loss of independence, social isolation, financial stress, and challenges navigating complex care systems. COEs can also provide insight into the practical implications of a new therapy, including treatment burden, access barriers, caregiver requirements, travel, follow-up, and the infrastructure necessary to deliver specialized care.

HDSA recommends that ICER include HDSA COE representatives in stakeholder engagement and seek their input when refining the patient-experience and value-assessment components of the review.

Conclusion

HDSA appreciates ICER's recognition that Huntington's disease has profound consequences for patients, caregivers, families, and society. The draft appropriately moves beyond a narrow focus on motor symptoms to acknowledge cognitive, psychiatric, functional, caregiver, employment, and family impacts.

First, it should incorporate the 2024 HDSA EL-PFDD meeting FDA-posted Voice of the Patient Report, rather than relying primarily on the 2016 Voice of the Patient report.

Second, ICER should explicitly distinguish patient-identified impacts from conventional clinical outcomes. The distinction matters because the consequences of HD extend far beyond what can be captured through clinical measures or health utility weights.

Third, ICER should engage with HDSA's emerging HD PC-CIS as a resource for understanding and prioritizing the impacts that matter most to people living with HD, their families, and caregivers.

Finally, ICER should ensure that its economic assessment reflects the full societal impact of HD, including lost income and career opportunities for patients and caregivers, unpaid caregiving, out-of-pocket costs, and other consequences identified by the HD community.

People living with Huntington's disease are not simply seeking improvements in scores on clinical measures. They are seeking more time with independence, meaningful relationships, work, family, and the ability to participate in the lives they value. An assessment of a potential treatment for HD should therefore measure and communicate value in terms that reflect the full human experience of the disease.

HDSA encourages ICER to strengthen the final scope accordingly and looks forward to continued engagement throughout the assessment.

Sincerely,



Amy Gray
President and Chief Executive Officer

CITATIONS

¹[HDSA 2024 VOICE OF THE PATIENT REPORT](#). Huntington's Disease Society of America. (2025). *The voice of the patient: Huntington's disease – Externally-led patient-focused drug development meeting report*.

²[National Health Council](#). (2022). *A blueprint for developing patient-centered core impact sets (PC-CIS)*.



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September 11, 2026

Submitted via email to publiccomments@icer.org

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Thank you for the opportunity to comment on ICER's Draft Scoping Document for ifezuntrigene inilparvovec (AMT-130; uniQure N.V.) for Huntington's disease (HD). We appreciate ICER's longstanding commitment to rigorous, transparent evidence review in rare and serious neurological diseases, and we recognize the significant public health importance and methodological significance of a thorough assessment of emerging HD therapeutics for a disease in which no disease-modifying treatment has been approved and for which the full evidentiary and economic framework has never been established.

HD presents a distinctive cluster of methodological challenges for evidence synthesis: small and genetically defined patient populations; heterogeneity of clinical progression driven by CAG repeat length; stage of disease; and natural history databases (TRACK-HD, PREDICT-HD, and Enroll-HD) that remain an imperfect substitute for a randomized concurrent control. These features make deliberate, methodologically explicit scoping especially critical for producing an evidence report that is trustworthy and decision-relevant.

AMT-130 is a neurosurgically-administered single therapy that uses a vector as a vehicle to lead to continuous production of a huntingtin (both mutant and wild type) lowering epigenetic agent similar to the approach with antisense oligonucleotides in development for HD.

Prilenia respectfully requests ICER consider the following:

- **Adopt a Comprehensive, Validated Outcome Framework Consistent with HD's Multidimensional Burden Based on Disease Progression (HD-ISS)**
- **Prespecify Subgroup Analyses by Established HD Clinical and Pharmacological Effect Modifiers (concomitant antidopaminergic medication, ADM)**
- **Apply Evidence Uncertainty Ratings Commensurate with the Methodological Limitations of Natural History–Based Evidence**
- **Ensure Economic Model Captures Single Therapy–Specific Cost Drivers and Long-Horizon Uncertainty**



Adopt a Comprehensive, Validated Outcome Framework Consistent with HD's Multidimensional Burden Based on Disease Progression (HD-ISS)

HD is heterogeneous, presenting with a wide variation in symptoms, age of onset, and disease progression among different patients and families, even though the core genetic cause is the same. The **Huntington's Disease Integrated Staging System (HD-ISS)** classification helps navigate the massive heterogeneity and fluctuation of HD symptoms and categorizes progression into objective milestones. Because patients do not experience symptoms in the same order or with the same severity, this step-by-step structure provides a universal metric to determine exactly where a patient is in the disease course, normalizing the clinical noise as well as what are the clinical aspects that can be assessed.

HD simultaneously impairs motor, cognitive, and functional domains and the outcomes should reflect this. Consistent with the published HD outcome measurement literature, ICER should formally include the composite Unified Huntington's Disease Rating Scale (cUHDRS, combining TFC, TMS, SDMT, and SWR), Q-Motor measures, validated patient-reported outcomes (HD-PRO, HDQLIFE), caregiver productivity and burden costs, and CSF/plasma biomarkers as primary or co-primary elements of both the clinical and economic analyses. Patient advocacy organizations should be engaged to ensure that the outcome framework reflects the domains of function and well-being that matter most to people living with HD and their families.

Establishing a stage-anchored framework now ensures consistent comparison for AMT-130 versus potential future chronic non-invasive therapies (e.g., oral therapeutics). ICER should explicitly incorporate HD staging (e.g., ISS-2 and ISS-3) into the AMT-130 scope and align outcome measures to stage-specific treatment goals.

Prespecify Subgroup Analyses by Established HD Clinical and Pharmacological Effect Modifiers (concomitant antidopaminergic medication, ADM)

Concomitant antidopaminergic medications (ADMs) are a pharmacologically important covariate. Independent analyses of natural history and real-world data (EHDN Registry, Enroll-HD) and of randomized placebo arms (PROOF-HD, GENERATION-HD1) consistently show that ADM use is associated with significantly faster decline on the functional and clinical scales used across HD trials, including TFC, TMS, SDMT, SWR, and the composite cUHDRS. A recent causal analysis of the PROOF-HD placebo arm confirmed this after adjusting for age, sex, CAG repeat length, disease stage, and baseline TFC, with participants on ADMs declining significantly faster across all five outcome measures than those off ADMs. In small sample size studies a chance imbalance in ADM use between groups can disproportionately shift group-level averages on functional scales, and limited statistical power constrains the ability to adjust for or stratify by ADM exposure, making it harder to distinguish a true treatment effect from an artifact of unbalanced background medication use. Because ADM use is prevalent, often unbalanced across studies, and independently worsens outcomes used to judge treatment effect, it warrants explicit consideration, alongside trial design and analytic adjustment, when comparing efficacy



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data across HD development programs. ICER should pre-specify subgroup analyses stratified by ADM use, CAG repeat burden (CAP score tertile or quartile), and TFC stratum for all treatments under review. consistent with established HD trial methodology and the clinical heterogeneity of the population.

Apply Evidence Uncertainty Ratings Commensurate with the Methodological Limitations of Natural History–Based Evidence

AMT-130's evidence relies on comparing treated patients to a propensity-matched group from Enroll-HD although the original design includes a 1-year placebo arm. While Enroll-HD is a strong registry, this type of natural-history comparison has built-in limits: important patient differences that can't be matched, such as caudate and putamen size (a key prognostic inclusion criterion absent from Enroll-HD), bias from who chooses to enter a surgical trial versus a registry, different visit schedules, possible behavior changes after surgery, and very small numbers of treated patients at longer follow-up. ICER should clearly assess how strong these comparisons are, apply its usual uncertainty grading, and distinguish this evidence from what would be expected from randomized trials.

Ensure Economic Model Captures Single Therapy–Specific Cost Drivers and Long-Horizon Uncertainty

Standard cost-effectiveness models don't naturally fit one-time or short-term treatments. For AMT-130, assumptions about how long the benefit lasts will heavily shape the results. The model faces structural issues: all costs happen upfront while long-term benefit is uncertain; the delivery procedure itself is expensive and risky; and a single-payment therapy doesn't align well with comparisons to chronic treatments paid for overtime. These challenges are even greater here because effects beyond four years are unknown, access is limited to a few neurosurgical centers (creating geographic inequities), and there is no retreatment data. ICER should clearly separate what is observed from what is modeled, run strong sensitivity tests on durability assumptions, and include scenario analyses with an oral disease-modifying comparator so results reflect the real future treatment landscape.

Prilenia thanks ICER for the opportunity to submit input at the scoping stage of this assessment. The recommendations, we believe, are grounded in the published HD trial literature and in ICER's own stated methodology. We offer them in the constructive spirit of strengthening an evidence report that will be consequential for patients, payers, and the HD field.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "H. Schuring", with a stylized flourish at the end.

Henk Schuring, Chief Regulatory & Commercialization Officer



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REFERENCES – provided for informational purposes; all references available upon request

ICER Draft Scoping Document:

- Ifezuntrigene Inilparvovec for Huntington's Disease. August 20, 2026.

HD-ISS (Huntington's Disease Integrated Staging System)

- Tabrizi SJ, Schobel S, Gantman EC, et al. "Huntington's Disease Integrated Staging System (HD-ISS): A Novel Evidence-Based Classification System For Staging." The system establishes a standard case definition based on HTT CAG expansion (≥ 40 repeats) and a formal staging system using well-established prognostic biological, clinical, and functional landmarks, with preliminary evidence that HD-ISS is a valid classification matching known HD natural history. (Lancet Neurology; preprint at medRxiv: <https://www.medrxiv.org/content/10.1101/2021.09.01.21262503v1>) [sciencedirect](#)
- HD Insights / Huntington Study Group summary of the HD-ISS: https://huntingtonstudygroup.org/hd-insights/vol27_hd-iss/

ADM (antidopaminergic medication) effect on decline / PROOF-HD placebo-arm causal analysis

- Anderson KE, Tan AM, Feigin A, et al. "Antidopaminergic Medications Are Associated with Faster Decline in Measures of Clinical Outcome in HD: Insights from PROOF-HD." <https://www.medrxiv.org/content/10.1101/2025.10.30.25339054v1>) [medrxivmedrxiv](#)
- Related Enroll-HD registry analysis showing ADM use linked to worsening functional/cognitive measures despite chorea benefit: <https://www.researchgate.net/publication/340287722> (Antidopaminergic treatment is associated with reduced chorea and irritability but impaired cognition in HD: Enroll-HD)
- PROOF-HD topline trial results (subgroup analysis excluding ADM users showed pridopidine benefit): <https://practicalneurology.com/news/proof-hd-trial-results-show-benefits-of-pridopidine-as-huntington-disease-treatment-in-those-not-taking-adms/2474032/>

AMT-130 / Enroll-HD propensity-matched comparison

- uniQure topline pivotal Phase I/II results (Sept 24, 2025): (<https://unique.gcs-web.com/news-releases/news-release-details/unique-announces-positive-topline-results-pivotal-phase-iii>) [gcs-webmedcentral](#)
- uniQure regulatory update on FDA-agreed use of ENROLL-HD, TRACK-HD/TRACK-ON, and PREDICT-HD as external control datasets: <https://www.biospace.com/press-releases/unique-provides-regulatory-update-on-amt-130-for-huntingtons-disease>



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- FDA shift away from Enroll-HD as sole comparator toward a concurrent standard-of-care control for the confirmatory study, June 2026) <https://www.medicaldaily.com/amt-130-huntington-disease-gene-therapy-fda-accelerated-approval-unique-june-2026-475714>

Outcome measures — cUHDRS, TFC, SDMT, SWR

- Schobel SA, et al. (2017), cUHDRS Roche RG6042 protocol, citing Schobel et al. 2017: https://cdn.clinicaltrials.gov/large-docs/69/NCT03842969/Prot_SAP_000.pdf
- Neurology, 2021 AAN abstract: https://n.neurology.org/content/96/15_Supplement/3024/neurology
- TFC as a validated global function measure: Roche protocol NCT03761849: https://cdn.clinicaltrials.gov/large-docs/49/NCT03761849/Prot_000.pdf

Patient-reported outcomes — HDQLIFE, HD-PRO

- Carlozzi NE, et al., "HDQLIFE: development and assessment of health-related quality of life in Huntington disease (HD)." <https://link.springer.com/article/10.1007/s11136-016-1386-3>
- HD-PRO-TRIAD validation study: <https://www.researchgate.net/publication/261841305>
- HDQLIFE and Neuro-QoL. <https://pubmed.ncbi.nlm.nih.gov/31724237/>

Single/short-term therapy (SST) economic modeling challenges

- ICER's Single/Short-Term Therapy (SST) framework <https://www.sciencedirect.com/science/article/pii/S1098301521015837>)
- <https://icer.org/wp-content/uploads/2020/11/ICER-Gene-Therapy-White-Paper-030317.pdf>
- ICER's updated durability-uncertainty approach. <https://www.biopharmadive.com/news/icer-gene-therapy-one-time-pricing-framework/567249/>)
- 2024 ICER/NEWDIGS durability assumptions: https://icer.org/wp-content/uploads/2024/04/Managing-the-Challenges-of-Paying-for-Gene-Therapy-_-ICER-NEWDIGS-White-Paper-2024_final.pdf