Joint Position Statement on Heparan Sulfate as a Primary Disease Activity Biomarker for Neuronopathic MPS

Issued by the International MPS Network (IMPSN) and MPS Society UK

The global MPS community is united in one urgent message: **time is our most precious resource, and we cannot afford to waste it.**

For individuals affected by neuronopathic mucopolysaccharidoses (MPS), **early diagnosis and timely access to treatment is not just beneficial it's a lifeline.** Earlier intervention leads to significantly better outcomes, particularly for neurological symptoms. **Delaying treatment in these irreversible neurodegenerative diseases is no longer acceptable.**

At the recent *Heparan Sulfate Global Biomarker Meeting*, co-hosted by the International MPS Network (IMPSN) and MPS Society UK, and chaired by Professor Simon Jones and Professor Maurizio Scarpa, a global group of scientific, clinical, regulatory, industry, and patient experts came together to build momentum toward a shared goal: the formal recognition of **cerebrospinal fluid (CSF) heparan sulfate (HS)** as a **Primary Disease Activity Biomarker** in neuronopathic MPS.

Why CSF Heparan Sulfate Matters
In many rare pediatric genetic diseases of metabolism, the biomarker is not only a diagnostic tool but the very **toxic substrate driving the disease.** This is especially true in MPS III (Sanfilippo syndrome), where **brain heparan sulfate accumulation** is both the **primary inciting factor** and the **most proximate, quantifiable indicator of disease progression and therapeutic response**.

CSF HS reduction reflects active engagement with brain pathology and is **more accurate than serum enzyme levels**, making it a **reliable surrogate for clinical benefit**. As supported in the FDA's March 2020 guidance on single enzyme defect disorders, CSF HS must be embraced as:

- A **primary pharmacodynamic biomarker**
- A **reasonably likely surrogate marker** of clinical benefit
- A **primary clinical endpoint** in trials, particularly when aligned with complementary biomarkers such as brain volume stabilization or cognitive outcomes

The Cost of Delay

- **Treating pre-symptomatic children offers the best chance to prevent irreversible decline**, but early diagnosis through **newborn screening (NBS)** is currently limited by a lack of approved therapies.
- Families often learn too late that their child is **too advanced** to qualify for a clinical trial—an avoidable tragedy.
- **Stabilization** in brain volume, cognition, and communication must be recognized as a **meaningful clinical outcome** in progressive, irreversible diseases.
- Clinical trial failure is devastating not because of safety concerns, but because of **regulatory and funding barriers** that delay or deny treatment access.
- **Without reform, children and families continue to bear the burden of regulatory inaction.**

Our Position
As two leading voices in the global MPS community, the **International MPS Network (IMPSN)** and the **MPS Society UK** jointly call for:

- **Formal Recognition** of heparan sulfate as a primary biomarker in the diagnosis, monitoring, and therapeutic evaluation of neuronopathic MPS.
- **Regulatory Alignment**: Integration of CSF HS into accelerated approval pathways when supported by complementary biomarker and clinical outcome data.
- **Standardization of Measurement**: Harmonization of laboratory methods to ensure data comparability across institutions and regions.
- **Inclusion in Clinical Guidelines**, to embed CSF HS into routine clinical and research practices globally.
- **Investment in Ongoing Research** to support innovation in detection techniques and combination biomarker strategies.
- **Greater Flexibility in Outcome Measures**: Enable clinical trial designs that reflect the true nature and urgency of these diseases, with stabilization recognized as meaningful and relevant.

Our community is not asking for shortcuts. We are demanding smarter, faster, and more ethical pathways that prioritize what matters most—giving children with neuronopathic MPS a fighting chance.

CSF HS is not just a biomarker. It is the disease. And reducing it is our clearest path to hope.

The time to act is now. Every second matters.

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