Emerging Diagnosis and Treatment Options for Neuromuscular Diseases

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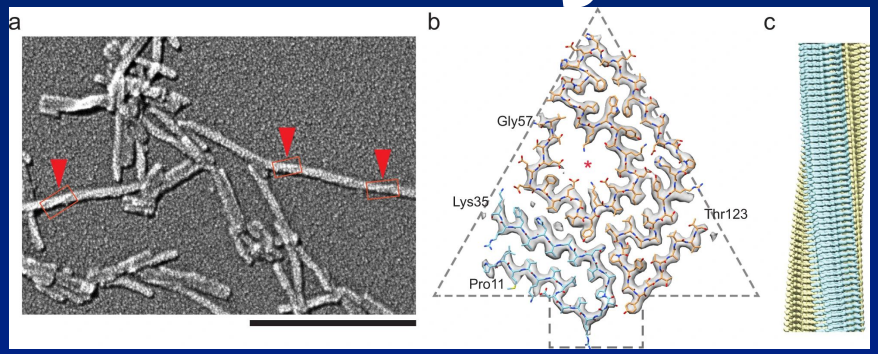
Disclosures

Contracted Research (Principal Investigators must provide information, even if received by the institution)
Edgewise Therapeutics

Objectives:

1) Discuss rare neuromuscular disorders that have newer treatment options
2) Review available treatment options
3) Discuss past and present clinical trials

Could this be Amyloid?



Steinebrei, M., Gottwald, J., Baur, J. *et al.* Cryo-EM structure of an ATTRwt amyloid fibril from systemic non-hereditary transthyretin amyloidosis. *Nat Commun* **13**, 6398 (2022). https://doi.org/10.1038/s41467-022-33591-4

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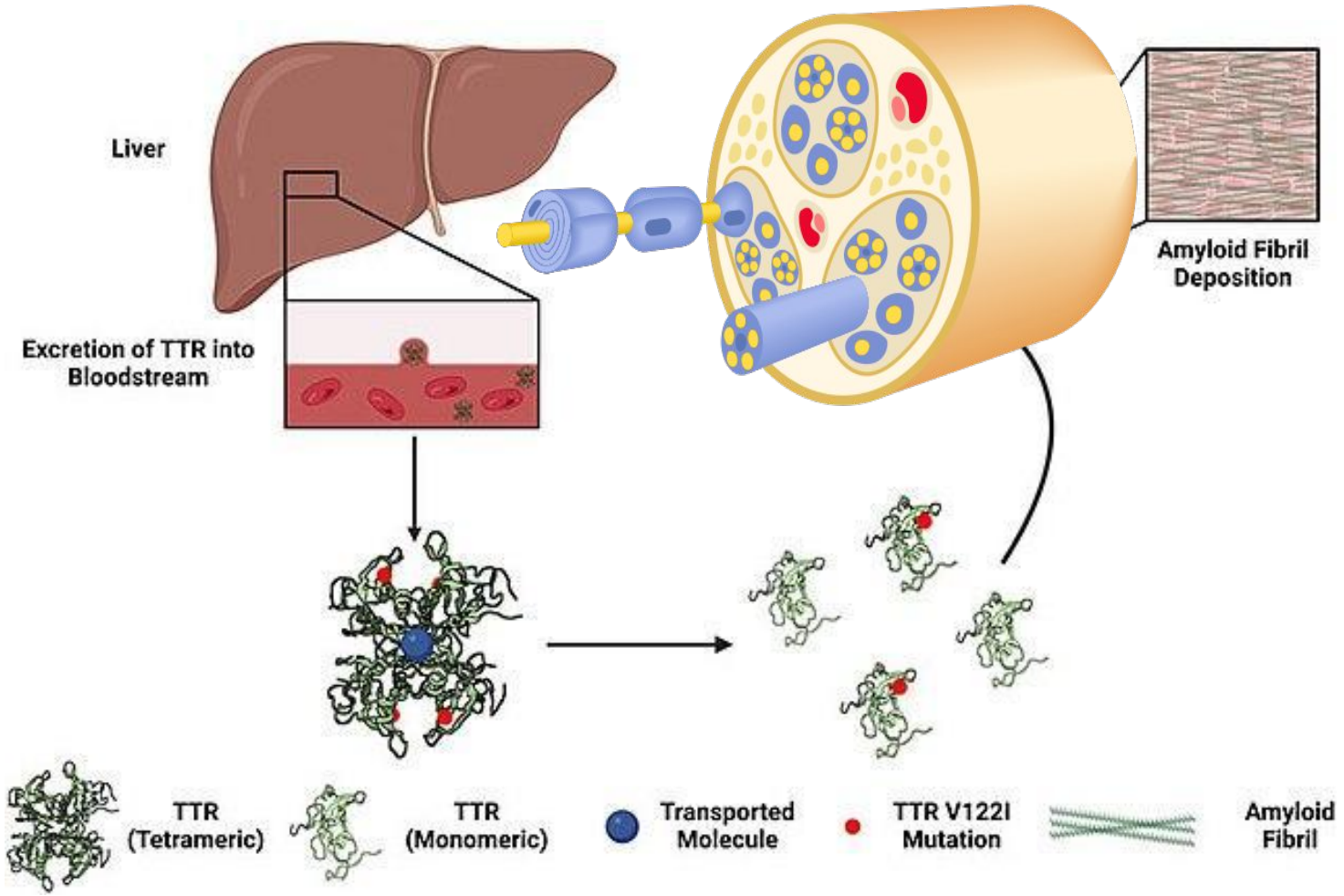
TTR Amyloidosis



TTR Amyloidosis

Tafamidis:

- Stabilizes TTR to prevent dissociation into monomers then misfolding.
- Reduces build up in heart and nerves.

Patisiran:

- siRNA targets and degrades TTR RNA, reducing protein production.

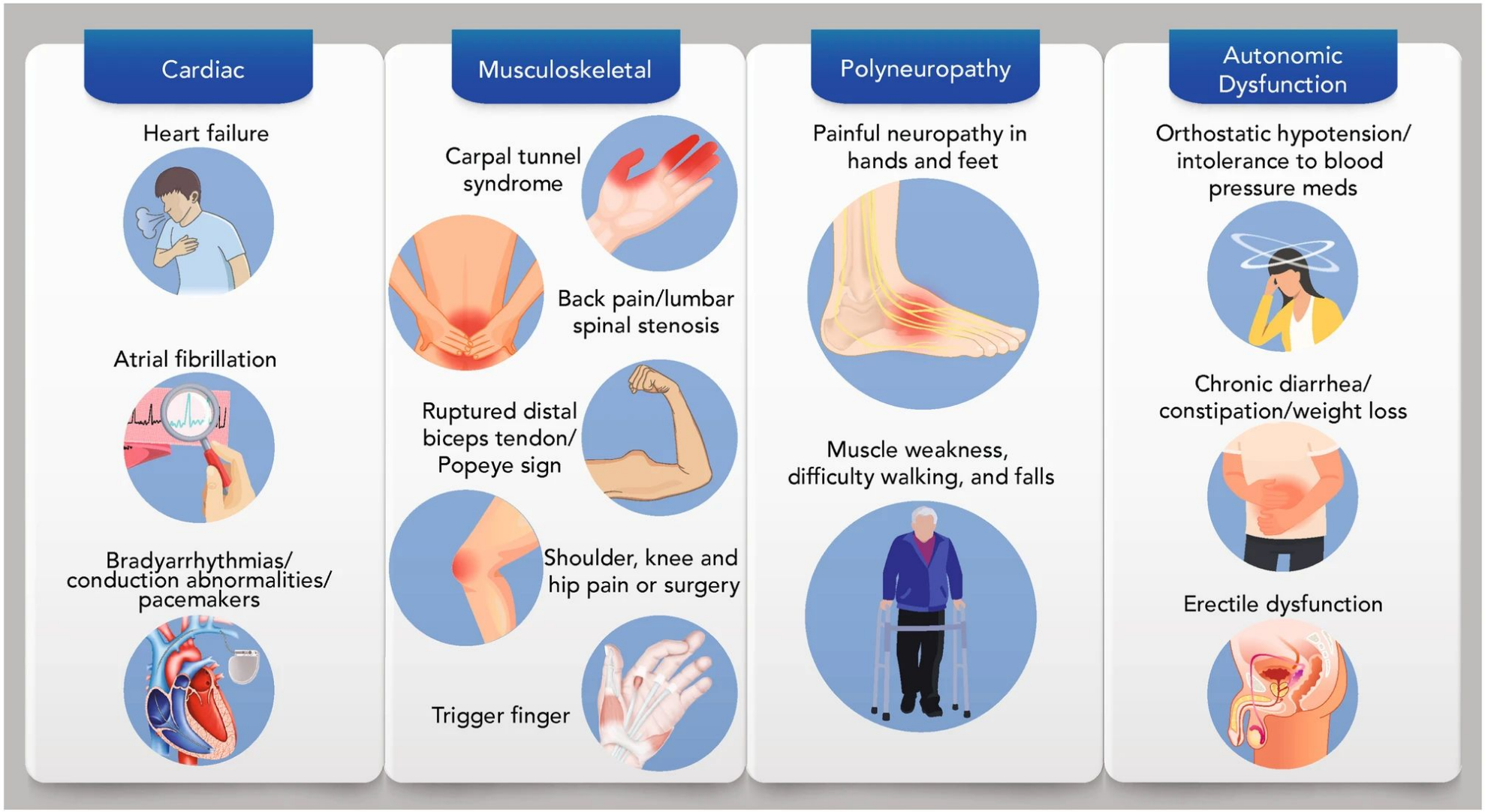
Inotersin:

- An antisense oligonucleotide that binds to TTR mRNA, resulting in the degradation of the mRNA and a subsequent decrease in the production of TTR protein.

Diflunisal:

- NSAID that stabilizes the TTR tetramer

When to Suspect TTR?



Nativi-Nicolau, J.N., Karam, C., Khella, S. et al. Screening for ATTR amyloidosis in the clinic: overlapping disorders, misdiagnosis, and multiorgan awareness. Heart Fail Rev 27, 785–793 (2022). https://doi.org/10.1007/s10741-021-10080-2

Second Question:

Have the Porphyrins returned yet?

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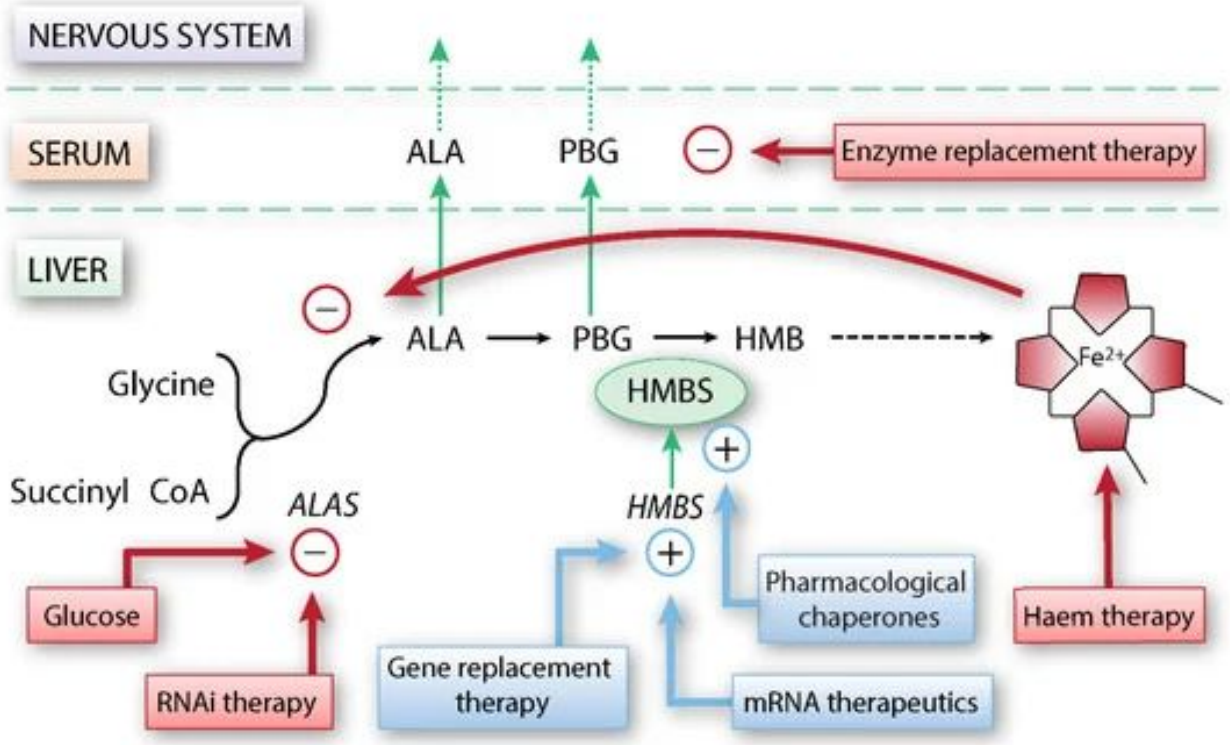
Porphyria

Givosiran (2019):

- siRNA blocks ALAS synthesis leading to reduced ALA and PBG.
- 70% reduction in attacks.
- Monthly SQ injection.



Overview of the action sites of established and potential therapy options for AIP.
Bustad, H.J.; Kallio, J.P.; Vorland, M.; Fiorentino, V.; Sandberg, S.; Schmitt, C.; Aarsand, A.K.; Martinez, A
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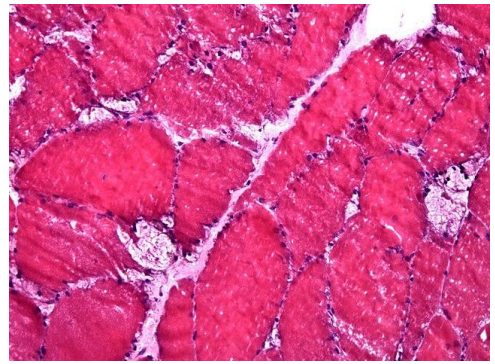
Key Points

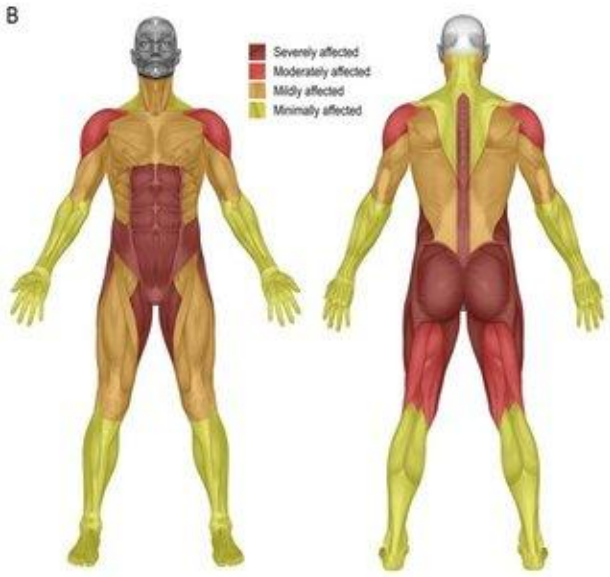
- Genetic mutation is common—1:1700.
- Constellation of abdominal pain, brain fog, proximal>distal weakness (arms), non-length dependent.
- Recurrent episodes frequently in luteal phase.
- Autonomic symptoms are common.
- Store urine in a jar wrapped in foil in the freezer.

Adult Onset Pompe



Key Points

- Incidence 1:40,000 but much higher in African-American and Southeast Asian.
- Mutation in GAA gene (recessive) leads to glycogen accumulation.
- CPK frequently elevated but can be normal.
- GAA blood spot or genetic testing.
- May present only with respiratory weakness.

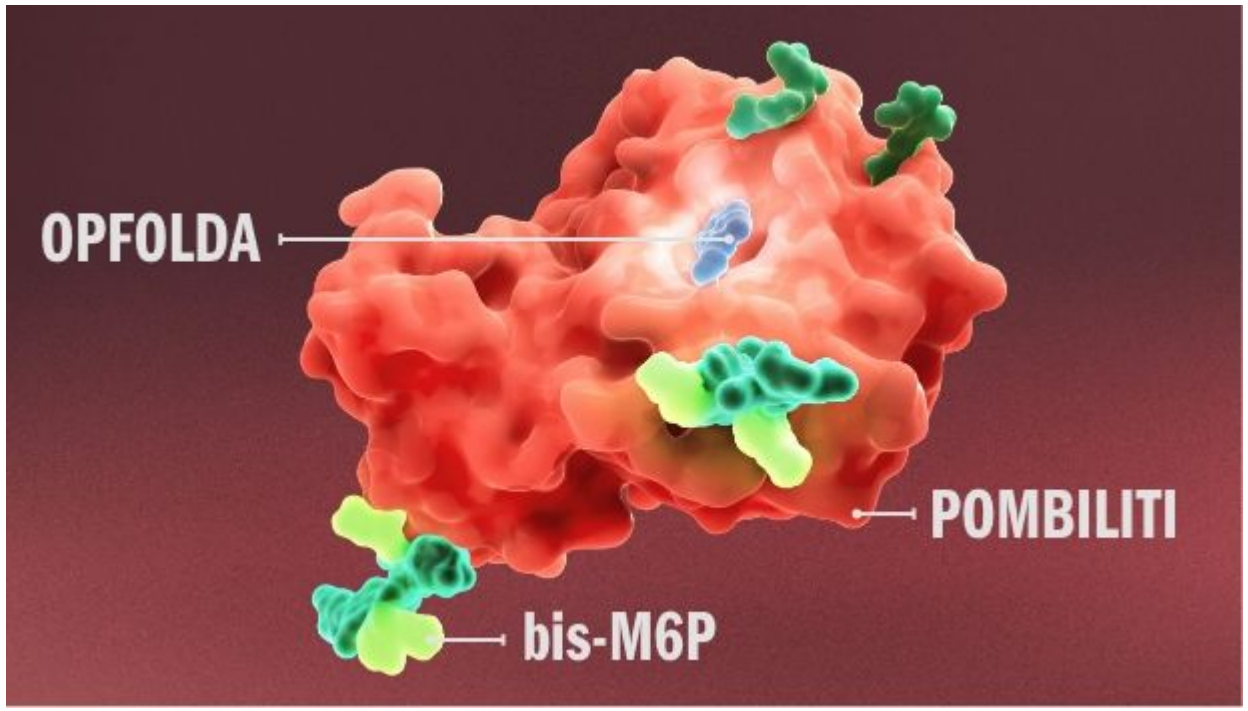


Beek, Nadine & Vries, Juna & Hagemans, Marloes & Hop, Wim & Kroos, Marian & Wokke, J.h.j & de Visser, Marianne & Van Engelen, Baziel & Kuks, Jan & van der Kooi, Anneke & Notermans, Nicolette & Faber, Karin & Verschuuren, Jan & Reuser, Arnold & Ans, Tina & Doorn, Pieter. (2012).

Treatment-Enzyme Replacement Therapy

- Alglucosidase Alfa (Myozyme 2006/Lumizyme 2010).
- Avalglucosidase Alfa (Nexviazyme 2021).

- Cipaglucosidase alfa (Pombiliti) in combination with miglustat (Opfolda) 2023.



Case Study

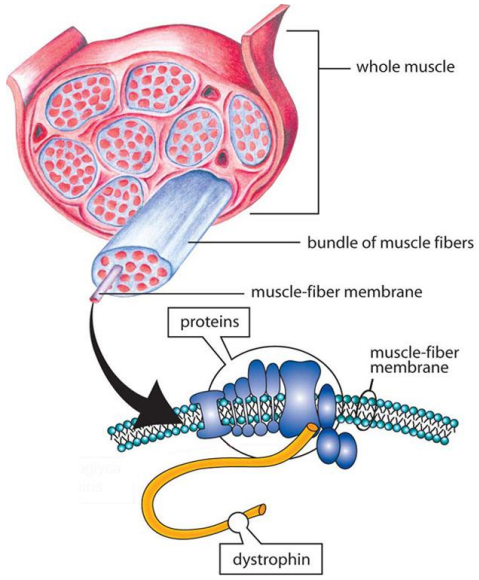
41 year-old man

- Trouble climbing stairs 4 years ago.
- Could not do a squat for flight physical.
- No other weakness noted.
- Aunt possibly had IBM.
- Exam:2/5 quads, 4/5 biceps, decreased arm reflexes, normal sensation.
- CPK 350
- EMG mild proximal myopathy.
- Quadriceps muscle biopsy-”rimmed vacuoles”

Clinical summary

A Pathogenic variant, Deletion (Exons 45-47), was identified in DMD.

Becker Muscular Dystrophy (BMD)



- Patients walk later but still develop disabling weakness.
- No approved treatments for BMD.
- Importance of natural history studies and clinical trials.

Current BMD Clinical Trials

Vamoralone: Dissociative Steroid approved for DMD.

EDG-5506: Myosin inhibitor.

Utrophin boosting?: Orphan drug designation.

Summary

- Rare disorders deserve our attention as we should not miss treatable conditions.
- Genetic testing is evolving and transforming the neuromuscular landscape.
- Natural history studies and clinical trials are paving the way for better treatment options.