Modeling the Impact of Improved Diagnosis and Treatment with Silencers on Disease Progression in Hereditary Transthyretin Amyloidosis with Polyneuropathy (ATTRv-PN)

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Objectives

Use a microsimulation model to assess the impact of improved diagnosis and treatment on disease progression in hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN) in the US.

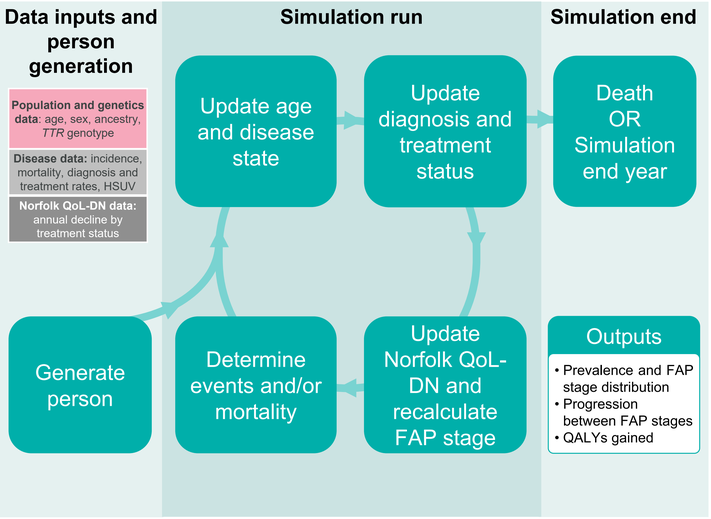
Introduction

- ATTRv-PN is a progressive autosomal dominant disorder that leads to sensorimotor polyneuropathy and autonomic dysfunction [1].
- Left untreated, ATTRv-PN can cause profound morbidity, particularly in later familial amyloidotic polyneuropathy (FAP) stages of disease [1].
- Phenotypic heterogeneity in ATTRv-PN results in delayed diagnosis, treatment, and increased severity [2].
- Improving time-to-diagnosis may delay disease progression, improve quality of life and reduce mortality.

Methods

- The microsimulation model incorporates US-specific (or proxy where unavailable) data to create a representative cohort of patients with ATTRv-PN in the US (Figure 1).
- Individuals were followed in annual cycles from 2025 to 2034, during which they could develop the disease, experience disease progression, receive diagnosis and/or treatment, or die.
  - A pre-simulation was used to establish the starting population.
- FAP stage progression is characterised by annual Norfolk Quality of Life Diabetic Neuropathy (Norfolk QoL-DN) decline derived from trial data [3], with Norfolk QoL-DN scores being mapped to FAP stage based on a mapping algorithm [4]:
  - Norfolk QoL-DN scores of ≥ 2.6 and < 54 correspond to FAP stage 1, Norfolk QoL-DN of ≥ 54 and < 91 correspond to FAP stage 2 and scores ≥ 91 correspond to FAP stage 3.
- A current practice and intervention scenario were run and compared (Figure 2).

Methods



FAP, Familial Amyloidotic Polyneuropathy; HSUV, Health state utility value; Norfolk QoL-DN, Norfolk Quality of Life Diabetic Neuropathy; QALYs, Quality-adjusted life years

Figure 1. Schematic of the microsimulation model

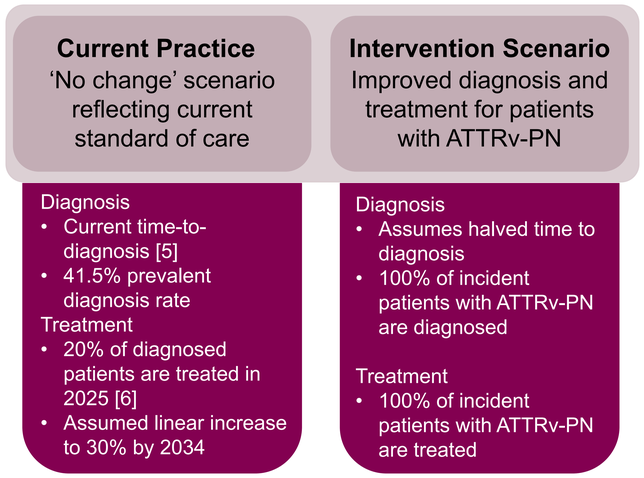


Figure 2. Specifications for the current practice and intervention scenarios

Results

Diagnosis and treatment over time

- In current practice, 42.1% of patients with ATTRv-PN are expected to be diagnosed in 2034 (totalling 1,665 patients). Of those diagnosed, 500 patients (30%) are treated with a silencer.
- In the intervention scenario, 69.5% of patients with ATTRv-PN are diagnosed by 2034 (an additional 1,213 patients) compared with the current practice scenario. Of those diagnosed, 2,365 (82.2%) are treated with a silencer (Figure 3).

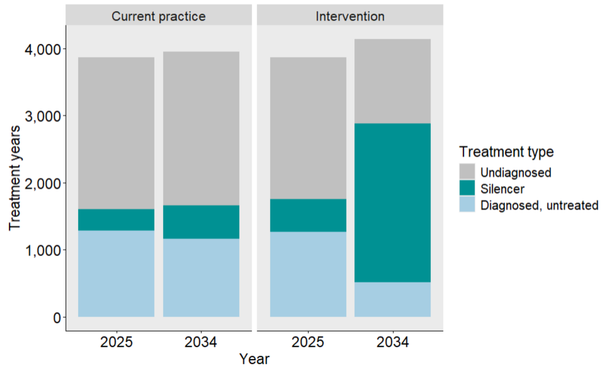


Figure 3. Diagnosis and treatment rates in the two scenarios

FAP stage distribution

- In current practice, 2,915 patients with ATTRv-PN are estimated to be in FAP stage 1, 397 in stage 2, and 560 in stage 3 in 2025. By 2034, an additional 120 patients are projected to be in FAP stage 1, with 16 and 25 fewer patients in stages 2 and 3, respectively (Figure 4).
- In the intervention scenario, 546 additional patients in FAP stage 1 are projected in 2034 compared to current practice. 157 fewer patients in FAP stage 2 compared with current practice, and 202 fewer patients in FAP stage 3 are projected, representing a 41.2% and 37.7% decrease, respectively (Figure 4).

Quality-adjusted life years (QALYs) gained in the intervention scenario

- Over the 10-year period, a total of 1,222 QALYs are gained in the intervention scenario compared with the current practice, driven by the reduction in FAP stage 2 and 3 patients by 2034.

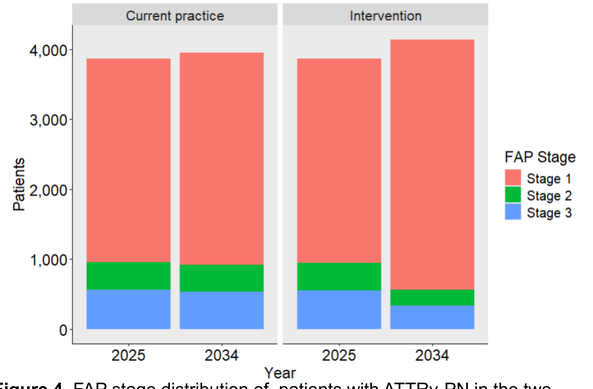


Figure 4. FAP stage distribution of patients with ATTRv-PN in the two scenarios

Cumulative disease progression avoided in the intervention scenario

- Over the 10-year period, a 34.1% reduction in progression to more severe FAP stages is projected under the intervention scenario; with 696 fewer patients progressing from FAP stage 1 to FAP stage 2, and 421 fewer patients progressing from FAP stage 2 to FAP stage 3 (Figure 5).

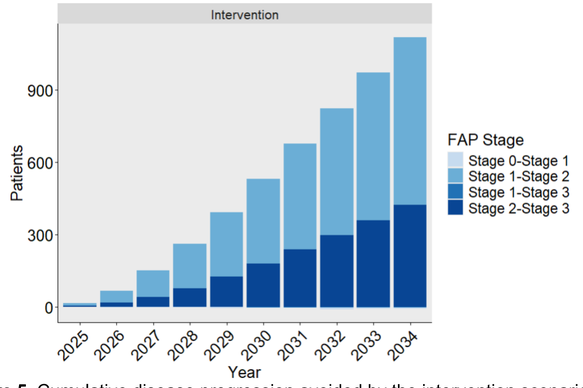


Figure 5. Cumulative disease progression avoided by the intervention scenario

Conclusion

- Earlier diagnosis and treatment with silencers are projected to slow ATTRv-PN progression by 34.1% and reduce prevalence of severe disease by 40% by 2034.
- This reduction in disease severity is associated with an estimated 1,222 QALYs gained, reflecting patients' longer lives and better health-related quality of life.
- These findings underscore the importance of timely diagnosis and treatment in patients with ATTRv-PN.

References: [1] Adams, D., et al., *Expert Consensus Recommendations to Improve Diagnosis of ATTR Amyloidosis with Polyneuropathy.* Journal of Neurology, 2021. **268**(6): p. 2109-2122. [2] Wang, T.-W., et al., *Updates on Hereditary Transthyretin Amyloidosis Polyneuropathy:* Journal of the Formosan Medical Association, 2026. [3] Coelho, T., et al., *Eplontersen for Hereditary Transthyretin Amyloidosis With Polyneuropathy.* Jama, 2023. **330**(15): p. 1448-1458. [4] Faria, R., et al., *Tafamidis for Transthyretin Familial Polyneuropathy (TTR-FAP) Evidence Review Group assessment of manufacturer submission.* 2012. p. 1-187. [5] Anderson, L., et al., *Early Clinical Manifestations and Time-To-Diagnosis in Patients with ATTR Amyloidosis With Mixed Phenotype - Results From the OverTTuRe Study,* in *European Society of Cardiology Heart Failure (ESC-HF) Congress 2025.* 2025: Belgrade, Serbia. [6] Bazell, C., et al., *Descriptive characteristics of patients diagnosed with transthyretin amyloidosis (ATTR) in the Medicare fee-for-service and commercial populations,* in *International Symposium of Amyloidosis 2024.* 2024: Rochester, MN.

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