Alnylam Act®: Effectiveness of Genetic Testing in Establishing a Diagnosis in Patients with Suspicion of Hereditary Transthyretin Amyloidosis

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Conclusions

- **A genetic testing program is an effective approach for confirming diagnosis in patients suspected of hereditary transthyretin amyloidosis (hATTR)**
- **Single gene tests for variants in the transthyretin (TTR) gene had the highest positivity rate**
- **hATTR was most prevalent among Black or African American individuals, the majority of whom had the V142I TTR variant**
- **Older patients were found to have the highest rates of TTR positivity**
- **Heart disease was the most common presentation among TTR-positive patients, including among those with the V142I variant**
- **TTR positivity rate was highest in patients referred by providers specializing in genetics or cardiology, possibly a result of increased pre-test selection modalities including the use of technetium cardiac imaging and cardiac biopsy**

Background & Rationale

- Transthyretin amyloidosis (ATTR) is a progressive and fatal disease caused by accumulation of toxic TTR amyloid fibrils in multiple tissues and organs, including the peripheral nerves and heart[1–3]
- There are two types of ATTR: wild-type ATTR, caused by deposition of toxic wild-type TTR, and hATTR, caused by variants in the TTR gene[1]
- To facilitate earlier diagnosis, Alnylam Pharmaceuticals and Invitae® have partnered to offer Alnylam Act®, a no-charge genetic testing and counseling program for individuals suspected of having hATTR

Objective

- Describe the effectiveness of genetic testing in identifying patients suspected of hATTR and the impact of patient baseline and disease characteristics, provider specialties, and test types performed

Methods

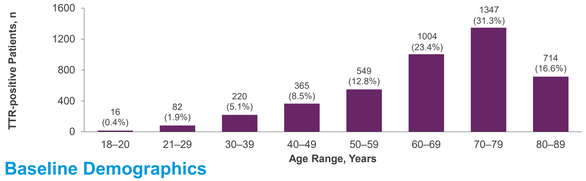
- Testing was offered to individuals ≥18 years with either suspected diagnosis or confirmed family history of hATTR
- Testing was performed using three gene panels, alone or in combination:
  - Neuropathies panel of 82 genes (including TTR)
  - Cardiomyopathies panel of 102 genes (including TTR)
  - Single-gene test for TTR gene variants
- Descriptive analyses were performed on data collected between August 2017 and May 2023

Results

- Overall, 89,760 individuals were tested
  - 12.4% (n=11,149) were positive for any gene
  - 4.8% (n=4297) were specifically TTR positive for a pathogenic or likely pathogenic DNA variant in TTR
- Of TTR-positive patients, 82.2% (n=3533) were probands with suspected hATTR diagnosis vs 17.8% (n=764) with only family history of hATTR
- The highest rates of TTR positivity were observed among those aged 60–69 (23.4%) and 70–79 years (31.3%; **Figure 1**)

Results (continued)

Figure 1. TTR Positivity by Age Range



Baseline Demographics

- Despite Black or African American individuals representing only 14.3% of the overall population who were tested, of those testing positive for variants in the TTR gene, 61.4% were Black or African American (**Table 1**)
  - 98.1% (n=2590) of Black or African American TTR-positive patients had the V142I variant

Table 1. Baseline Demographics

Characteristic	Total (N=89,760)	*TTR*-positive (N=4297)
Age, years, mean (SD)	60.5 (16.5)	65.6 (14.8)
Male[a], n (%)	51,219 (57.1)	2482 (57.8)
Race,[b] n (%)		
White	57,384 (63.9)	866 (20.2)
Black or African American	12,816 (14.3)	2640 (61.4)
Hispanic	3099 (3.5)	183 (4.3)
Confirmed family history, n (%)	2372 (2.6)	764 (17.8)
TTR variant, n (%)		
V142I	—	3299 (76.8)
T80A	—	292 (6.8)
V50M	—	271 (6.3)
V142I, V50M	—	1 (0.0)
Other	—	434 (10.1)

[a]3 individuals were recorded with unknown gender; [b]Self-reported.

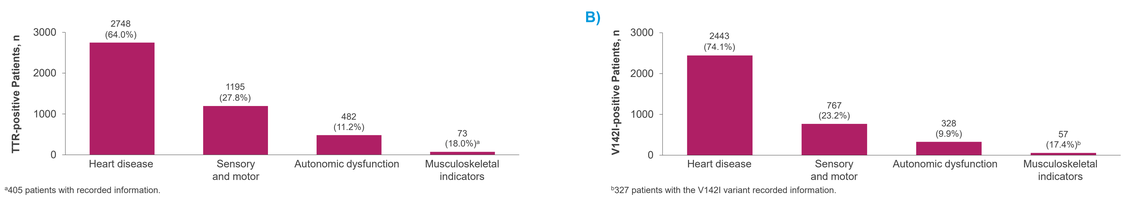
Presenting Signs and Symptoms

- Heart disease was the most common presentation among TTR-positive patients, including among patients with the V142I variant (64.0% and 74.1%, respectively; **Figure 2A and B**)

Alnylam Act® Provider Specialties

- Test providers specializing in neurology were the most common type of provider (31.5%; **Figure 3A**), but the patients they referred had the lowest TTR positivity rate (1.1%; **Figure 3B**)
- Patients referred for testing by providers specializing in genetics or cardiology had the highest TTR positivity rates (**Figure 3B**)

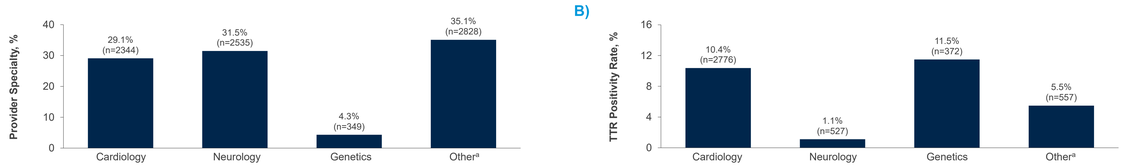
Figure 2. Presenting Signs and Symptoms. A) Presentation among TTR-positive Patients, and B) Patients with the V142I Variant



[a]405 patients with recorded information.

[b]327 patients with the V142I variant recorded information.

Figure 3. Alnylam Act® Provider Specialties. A) Number of Providers by Specialty, and B) Patient TTR Positivity Rate by Specialty

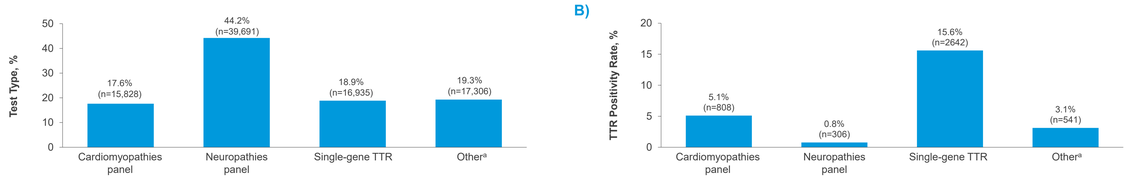


[a]Other specialties included oncologists, primary care physicians, obstetricians, gynecologists, pathologists, surgeons, and emergency medicine physicians.

Test Types Performed

- The neuropathies panel was the most performed test (44.2%; **Figure 4A**), but had the lowest TTR positivity rate (0.8%; **Figure 4B**)

Figure 4. Test Types Performed. A) Number of Tests Performed by Type, and B) TTR Positivity Rate by Test Type



[a]Combinations of the three tests.

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