Utility and User Experience of a Free Genetic Testing and Counseling Service for Hereditary ATTR (hATTR) Amyloidosis

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Background and Introduction

Hereditary ATTR (hATTR) Amyloidosis

- hATTR amyloidosis is an autosomal dominant, rapidly progressive, life-threatening disease[1-3]
  - Caused by a mutation in the transthyretin (TTR) gene that results in misfolded TTR proteins accumulating as amyloid fibrils in multiple tissues including the nerves, heart, and gastrointestinal tract[1,4,5]
  - More than 120 amyloidogenic TTR mutations have been described **(Figure 1)**[6]

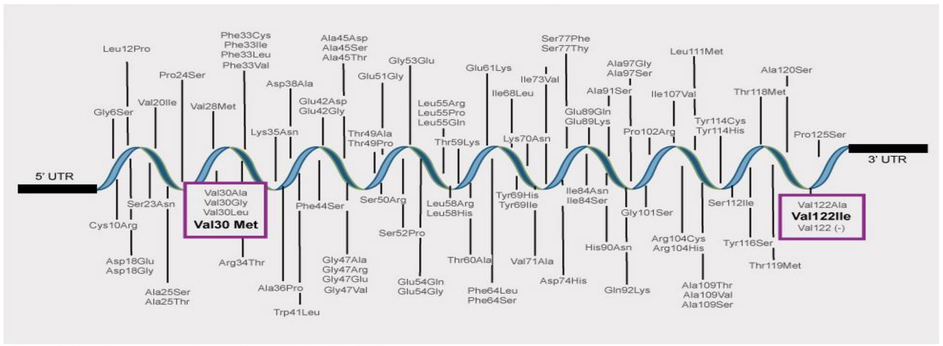


Figure 1. Select examples of variants identified in the TTR gene (www.alnylam.com)

- hATTR amyloidosis is a multisystemic disease with a heterogeneous clinical presentation
  - Includes sensory and motor, autonomic (e.g., diarrhea, erectile dysfunction, hypotension), and cardiac symptoms[2,7,8]
  - Can lead to significant morbidity, disability, and mortality within 2 to 15 years[1-3,9]
- hATTR amyloidosis is often misdiagnosed due to its constellation of symptoms[10]
- Since the etiology of hATTR amyloidosis is different from that of other types of polyneuropathy and cardiomyopathy, misdiagnosis could lead to ineffective or possibly detrimental treatment[7,9]

Free Third-Party Genetic Screening and Counseling

- As a means of facilitating potential earlier diagnosis, Alnylam Pharmaceuticals introduced a free, independent third party genetic screening program within the US in 2014 for individuals at risk to harbor a TTR gene variant associated with hATTR amyloidosis
- Samples are referred for testing by their treating physician and genotyped through Sanger sequencing of the TTR gene at an independent laboratory. The results are sent to the physician's clinic in 2-3 weeks.
  - Test results that have identified a pathogenic variant, are provided directly to the physician so that they can communicates the results to the individual
  - Genetic counseling can be initiated by either the patient or physician before and/or after genetic testing is complete
- As the sponsor of the program, Alnylam receives reports from an independent laboratory on the number of healthcare professional accounts set up as well as the number of patients tested and a de-identified breakdown on the pathogenic variants found through the program
- Pathogenicity of the variants are determined by a searching the comprehensive registry for variants and phenotypes in hATTR amyloidosis genes at *www.amyloidosismutations.org*
- In 2016, the program was expanded to include optional third-party genetic counseling via telephone for potential carriers and their at-risk family members. This service is also performed by an independent third party vendor

The aim of this report is to evaluate the utility and user experience of a free genetic testing and counseling service for hATTR amyloidosis.

Methods

- The number of genetic tests, variants, opened accounts, and counseling appointments are provided to the sponsor every other week. These reports contain no patient identifiers
- A 20 question survey was sent to account holders to better understand user experience
  - The survey was deployed by email through an online survey platform and responses remained anonymous
  - Questions ascertained respondents' demographics including medical practice setting (i.e., community or academic), and primary medical specialty
  - Additional questions asked of participants included multiple choice and free response questions on initiation, utility, and experience of physicians in testing their patients through the third-party testing program

Results

Utility of a Free Third-Party Genetic Screening and Counseling Program

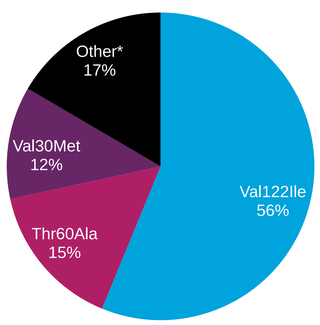
Genetic Testing†

- 209 healthcare professional accounts were set up and 1079 individuals tested
- Out of the 1079 individuals tested, a total of 173 pathogenic variants were identified. The most common pathogenic variant was a Val122Ile variant (n=95; 56%) followed by the Thr60Ala variant (n=26; 15%) and Val30Met variant (n=20; 12%)

Genetic Counseling†

- 51 physicians have signed up for the genetic counseling service and referred 31 patients for counseling

Distribution of Pathogenic Variants Identified Through the Program



*Represents 16 different pathogenic variants

†As of March 2017

Results

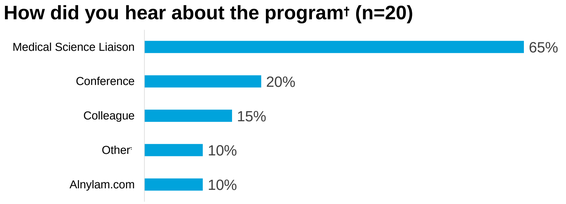
Free Third-Party Genetic Screening and Counseling Survey Results

Responder Demographics

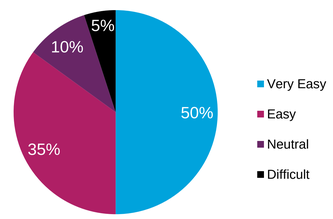
- In May 2016, a 20 question survey was sent out to 142 healthcare professionals with accounts set up at the time
- Of the 142 healthcare professionals that received the survey, 20 (14%) completed survey
- Respondents were from mostly from an academic practice (n=19; 95%) while only one healthcare professional was from a community practice (5%)
- Respondents described themselves as a cardiologist (n=10; 50%), neurologist (n=8; 40%), or hematologist (n=2; 10%).

User Experience

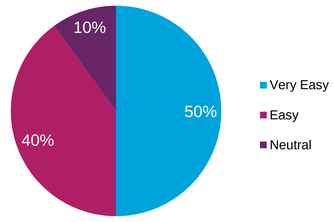
How did you hear about the program† (n=20)



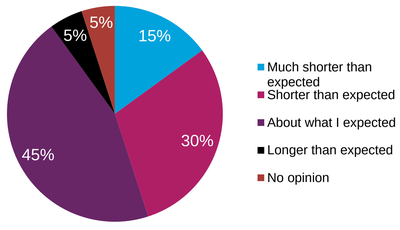
Ease of setting up an account (n=20)



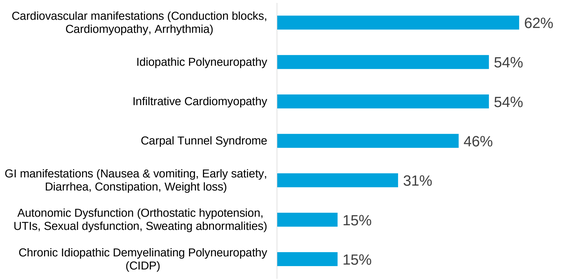
Ease of submitting samples for genotyping (n=20)



Timeliness of receiving blood draws (n=20)

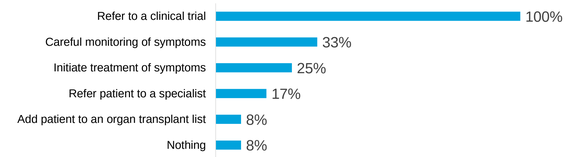


Diagnoses or symptoms identified prior to genotyping‡ (n=13)

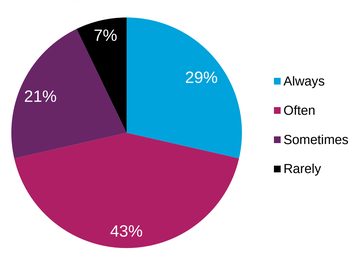


‡Respondents could make multiple selections

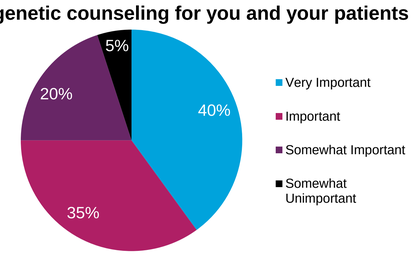
Next steps taken for individuals with a positive TTR pathogenic variant† (n=12)



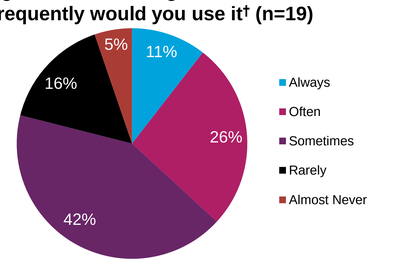
For individuals identified with a positive TTR pathogenic variant, how often have you tested their family members? (n=14)



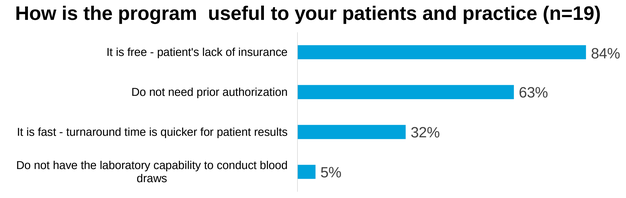
Importance of genetic counseling for you and your patients (n=20)



If a third-party, genetic counseling service was offered to patients, how frequently would you use it† (n=19)



How is the program useful to your patients and practice (n=19)



Would you recommend the program to a colleague

- 19 of 20 (95%) would recommend the program

Discussion and Conclusion

- The results of the survey demonstrate that a free third party genetic testing service is useful in diagnosing or ruling out hATTR amyloidosis in individuals at risk based on symptomology or family history
- As there may be barriers to receiving genetic testing, such as lack of (or inadequate) insurance coverage, the program has been able to help facilitate the diagnosis of individuals with a positive pathogenic variant associated with hATTR amyloidosis
- To date, HCP experience with the program suggests satisfaction with both the genetic testing and genetic counseling offerings

References and Disclosures

1. Hanna. *Curr Heart Fail Rep*. 2014;11(1):50-57. **2.** Mohty D et al. *Arch Cardiovasc Dis*. 2013;106(10):528-540. **3.** Adams et al. *Neurology*. 2015;85(8):675-682. **4.** Damy et al. *J Cardiovasc Transl Res*. 2015;8(2):117-127. **5.** Hawkins et al. *Ann Med*. 2015;47(8):625-638. **6**. Rowcenzio DM, et al. *Hum Mutat* 2014;35:E2403-12. **7.** Conceição et al. *J Peripher Nerv Syst*. 2016;21(1):5-9. **8.** Shin et al. *Mt Sinai J Med*. 2012;79(6):733-748 **9.** Castaño. *Heart Fail Rev*. 2015;20(2):163-178 **10.** Adams et al. *Curr Opin Neurol*. 2016;29(suppl 1):S14-S26.

The survey was conducted by Alnylam Pharmaceuticals. The free third-party genetic screening program referenced in this study is sponsored by Alnylam Pharmaceuticals.