When aTTR gets on your nerves: A primer on ATTR neurological involvement for Cardiologists

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Disclosures

- Consulting services for the following companies: Mitsubishi Tenabe Pharma America, Sanofi Genzyme, AL-S Pharma, AB Sciences, Biogen, Novartis, CSL Behring, Anavex, Avexis, Alexion, Wave life sciences, Revalesio, Roche, Cytokinetics, Orion, Akcea, Clene and Bayshore
- Participates as CRU medical director, PI or sub-PI on trials sponsored by the following companies: AB Sciences, AL-S Pharma, Acceleron, Amicus, Alnylam, Bioblast, Biogen, BMS, Boston Biomedical, Cytokinetics, Sanofi Genzyme, Grifols, Ionis, Lily, Mallinckrodt, Medimmune, Novartis, Orion, Orphazyme, Pfizer, Ra Pharmaceuticals, Roche, Teva, UCB,

ATTR Amyloidosis Is a Rare, Progressive, and Fatal Disease

- Characterized by deposition of amyloid fibrils, formed from misfolded transthyretin (TTR), in multiple organs[1]

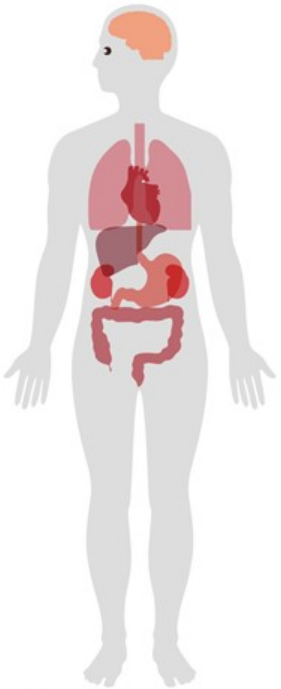
Two Main Types of ATTR Amyloidosis[1-3]

Hereditary

Deposition of misfolded mutant TTR in multiple organ systems

Wild-Type

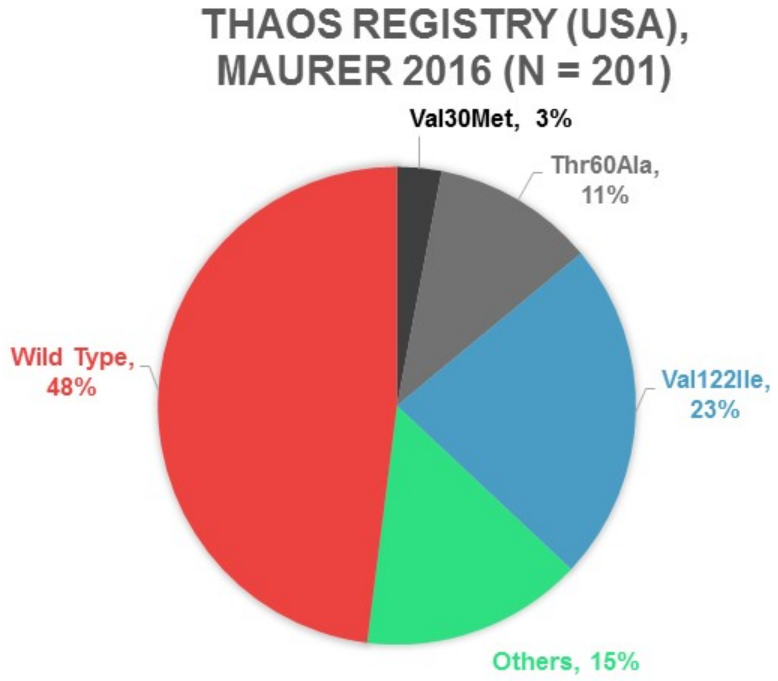
Deposition of wild-type misfolded TTR primarily in the heart of patients typically >60 years of age



TTR, transthyretin; ATTR, amyloid transthyretin

1.Hawkins P et al. *Ann Med*. 2015; 47:625-638; 2. Ando Y et al. *Orphanet Journal of Rare Diseases* 2013, 8:31; 3. Coelho T, et al. A physician's guide to transthyretin amyloidosis. Research Gate Amyloidosis; Foundation, 2008. https://www.researchgate.net/publication/265490881_A_Physician's_Guide_to_Transthyretin_Amyloidosis_Authored_by. Accessed January 3, 2018

Val122Ile, Thr60Ala, and Val30Met Are the Most Common Mutations in the United States[1]

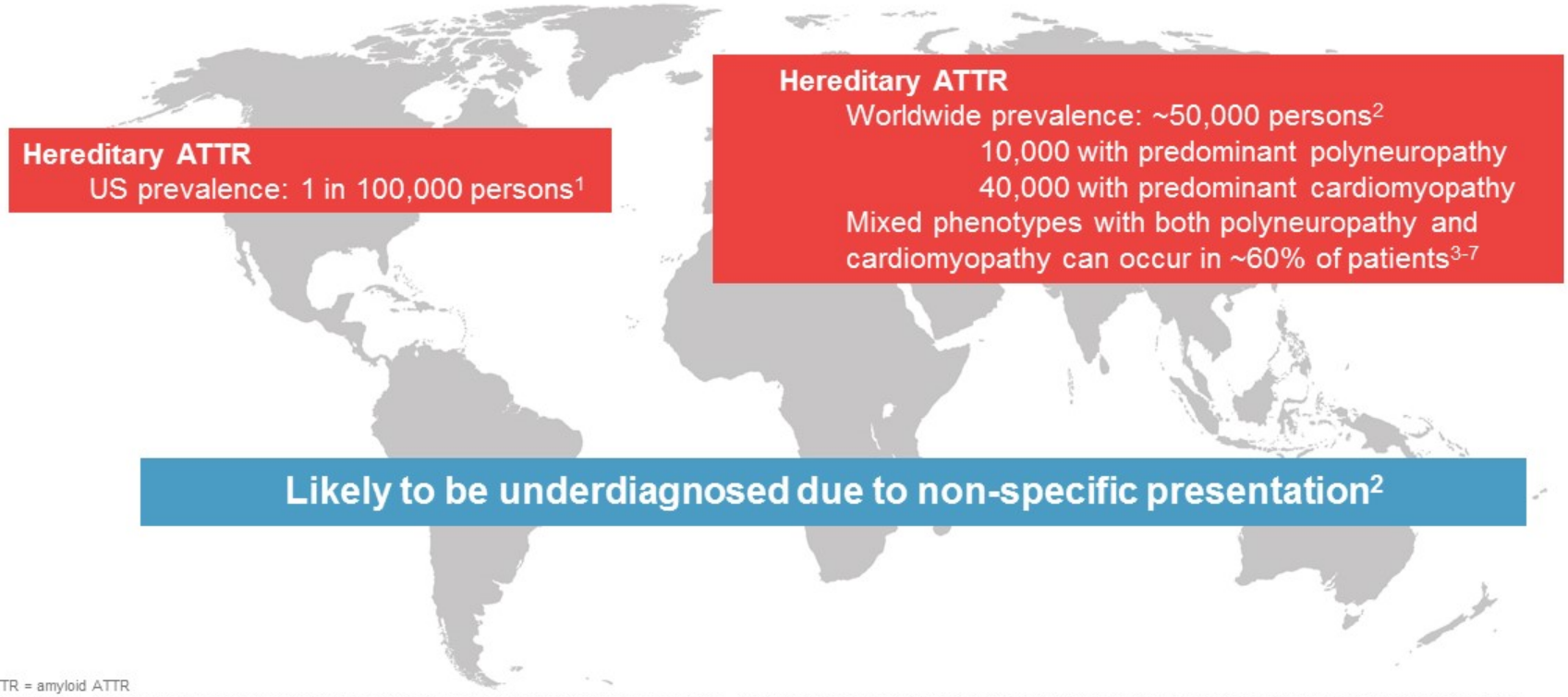


- *Val122Ile* is the most common mutation in patients with cardiomyopathy, but a significant proportion also present with **mild sensory neuropathy**[2,3]
- *Thr60Ala* is predominantly a disease of the heart and **autonomic nerves,** but many also present with **peripheral neuropathy**[4]
- *Val30Met* is the most common mutation in patients with **polyneuropathy**[2,3]

hATTR, hereditary amyloid transthyretin; TTR, transthyretin

1. Maurer MS et al. J *Am Coll Cardiol*. 2016;68(2):161-172; 2. Coelho T, Maurer M, and Suhr O. *CMRO*. 2013; 29:63-76; 3. Hawkins P et al. Ann Med. 2015;47:625-638; 4. Sattianayagam PT et al. *Eur Heart J*. 2012;33(9):1120-1127

Rare, but Most Likely Underdiagnosed



Hereditary ATTR
US prevalence: 1 in 100,000 persons[1]

Hereditary ATTR
Worldwide prevalence: ~50,000 persons[2]
10,000 with predominant polyneuropathy
40,000 with predominant cardiomyopathy
Mixed phenotypes with both polyneuropathy and cardiomyopathy can occur in ~60% of patients[3-7]

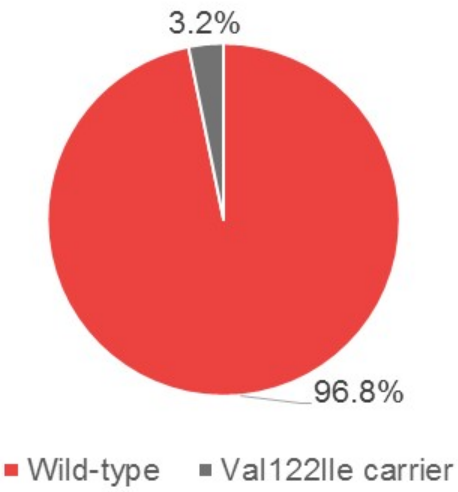
Likely to be underdiagnosed due to non-specific presentation[2]

ATTR = amyloid ATTR

1. Ando Y, et al. *Orphanet J Rare Dis* 2013;8:31; 2. Hawkins PN et al. *Ann Med* 2015;47(8):625-638; 3. Gertz MA. *Am J Manag Care*. 2017;23:S107-S112; 4. Benson. *Am J Pathol*. 1996 Feb;148:351-354; 5. Rapezzi et al. *Eur Heart J*. 2013 Feb;34:520-528; 6. Connors et al. *Amyloid*. 2003 Sep;10(3):160-84; 7. Wixner J et al. Orphanet J Rare Dis. 2014;9:61.

Val122Ile hATTR Is Thought to Be Significantly Underdiagnosed

Frequency of Val122Ile Allele in US African-Americans Quarta 2015 (n=3856)[1]



African-Americans ≥65 years old account for ~1% of the overall US population = 3.5 million people (using US census data from 2000 and 2016)

This translates to **~100,000 Val122Ile carriers age 65+** (as also estimated by Ruberg and Berk, 2012)[2]

Quarta et al. (2015) estimated **1.4 million carriers in the US, which will increase to 2.5 million by 2060, at an increased risk for heart failure** (consistent with an estimate by Ruberg and Berk (2012): 1.5 million Val122Ile carriers)[1,2]

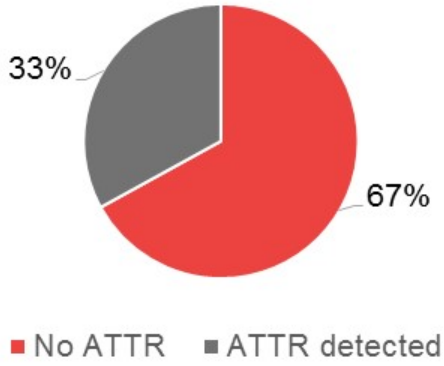
While the clinical penetrance of this mutation is currently undefined,[1] Val122Ile is "almost certainly underrecognized as a cause of heart failure"[3]

hATTR, hereditary amyloid transthyretin

1. Quarta et al. *N Engl J Med*. 2015 Jan 1;372(1):21-9. (article and letter to editor correspondence); 2. Ruberg and Berk. *Circulation*. 2012 Sep 4;126(10):1286-300; 3. Maurer, et al. *Circulation*. 2017 Apr 4;135(14):1357-1377

ATTR Can Be an Underlying Cause of Lumbar Spinal Stenosis

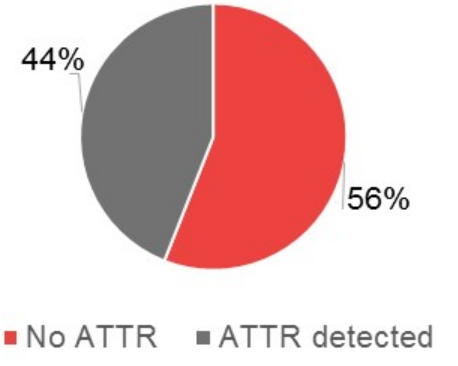
Lumbar Spinal Stenosis (Westermark 2014, n=15)



Amyloid detected in 81% (21/26) of samples

Methods: Congo red staining, immunohistochemistry

Lumbar Spinal Stenosis (Sueyoshi 2011, n=36)

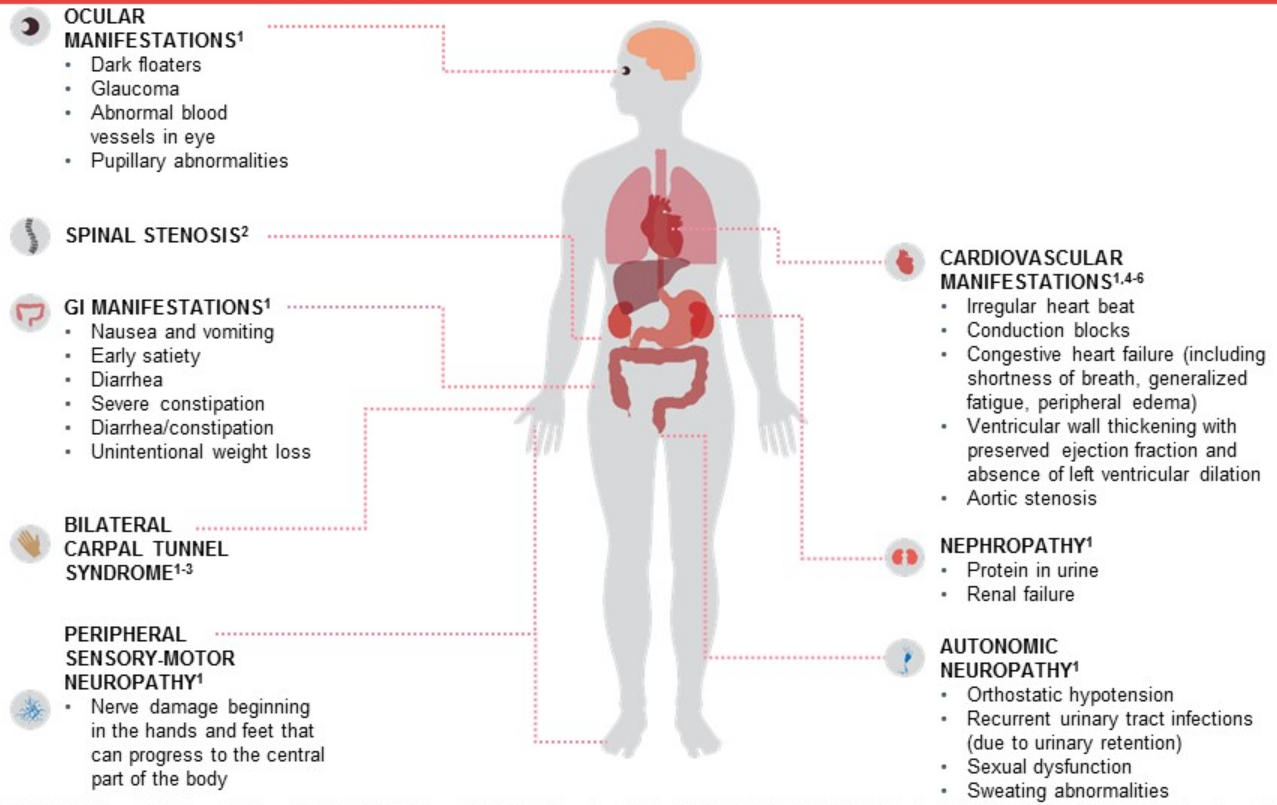


All samples obtained from patients at Kumamoto University Hospital, Japan

Methods: biopsy of affected area (yellow ligament), Congo red staining, immunohistochemistry

Both studies mainly involved patients with wild-type ATTR
ATTR, amyloid transthyretin
Westermark P, Westermark GT, Suhr OB, Berg S. Upsala Journal of Medical Sciences 2014; 119(3): 223-8; Sueyoshi T, Ueda M, Jono H, et al. *Human Pathology* 2011; 42(9): 1259-64

Hereditary ATTR Amyloidosis is a Systemic, Multi-organ Disease



GI, gastrointestinal.

1. Conceição I, et al. J Peripher Nerv Syst. 2016;21(1):5-9; 2. Donnelly JP, Hanna M. Cleve Clin J Med. 2017;84(12 suppl 3):12-26; 3. Ikram A, et al. J Card Fail. 2017;23(8):S11-S12 (P021); 4. Coelho T, et al. A physician's guide to transthyretin amyloidosis. Research Gate Amyloidosis; Foundation, 2008. https://www.researchgate.net/publication/265490881_A_Physician's_Guide_to_Transthyretin_Amyloidosis_Authored_by. Accessed January 3, 2018; 5. Gertz MA. Am J Manag Care. 2017;23(7 suppl):S107-S112; 6. Galat A, et al. Eur Heart J. 2016;37(47):3525-31.

hATTR amyloidosis Has a Variable Natural History

- Median age of onset can vary, depending on geographic location[1]
  - United States: 68 years
  - Portugal: 32 years
  - Sweden: 52 years
  - Most common *TTR* mutation in both Portugal and Sweden is Val30Met, whereas in the US, Val122I is the most common mutation.
- But, even in similar geographic locations, the age range of patients can be fairly wide[2]
- Val30Met Early-onset (age <50 years)[3]
  - Progressive sensory-motor and autonomic neuropathy leading to cachexia and death in ~11 years.
- Val30Met Late-onset (age ≥50 years)[3]
  - More rapid progression of sensory and motor ability
  - Median survival is shorter than early-onset at ~7 years

PN, polyneuropathy; hATTR, hereditary amyloid transthyretin

1. Coelho T, Maurer M, and Suhr O. CMRO. 2013; 29:63-76; 2. Parman Y, et al. Curr Opin Neurol. 2016, 29 (suppl 1):S3–S13; 3. Adams D. Ther Adv Neurol Disord. 2013. 6(2): 129–139

Confounding Findings for hATTR-PN

Characteristics of ATTR-PN

- Symmetric, distal polyneuropathy[2]
- Axonal polyneuropathy[2]

But due to non-specific, atypical, sporadic presentation, and rarity…

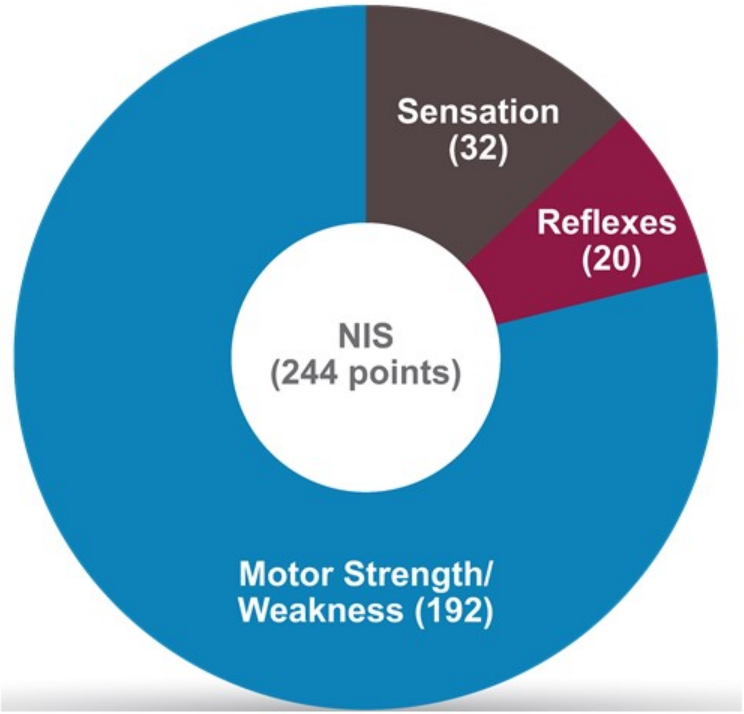
Common Misdiagnoses[1]

- Idiopathic axonal polyneuropathy
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Charcot-Marie-Tooth neuropathy
- Diabetic or alcoholic neuropathy
- Motor neuron disease

hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy

1. Adams, et al. *Curr Opin Neurol*. 2016 Feb;29 Suppl 1:S14-26; 2. Gertz, et al. *J Am Coll Cardiol*. 2015 Dec 1;66(21):2451-2466.

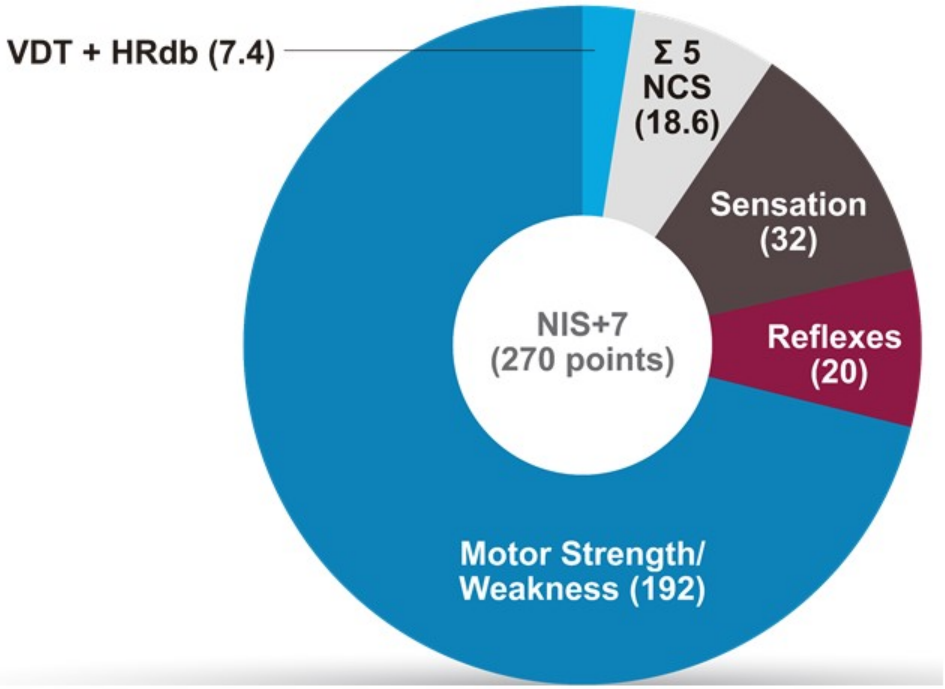
NIS



- NIS is a scoring system to evaluate global neuropathic impairments
  - Range: 0-244; higher score is worst neurologic deficit[1,2]
- NIS and its variants have been used in clinical trials and natural history studies as an outcome measure[3-6]

1. Adams D, et al. *Neurology* 2015;85(8):675-682; 2. Diabetic polyneuropathy in controlled clinical trials: Consensus Report of the Peripheral Nerve Society. *Ann Neurol* 1995;38(3):478-482; 3. Planté-Bordeneuve V, et al. J Neurol. 2017 Feb;264(2):268-276; 4. Berk JL, et al. JAMA. 2013 Dec 25;310(24):2658-67; 5. Benson MD, et al. N Engl J Med 2018;379:22-31; 6. Coelho T, et al. Muscle Nerve. 2017 Mar;55(3):323-332.

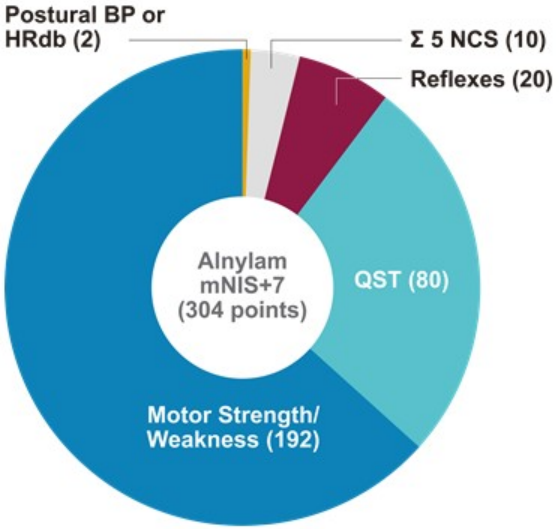
NIS+7

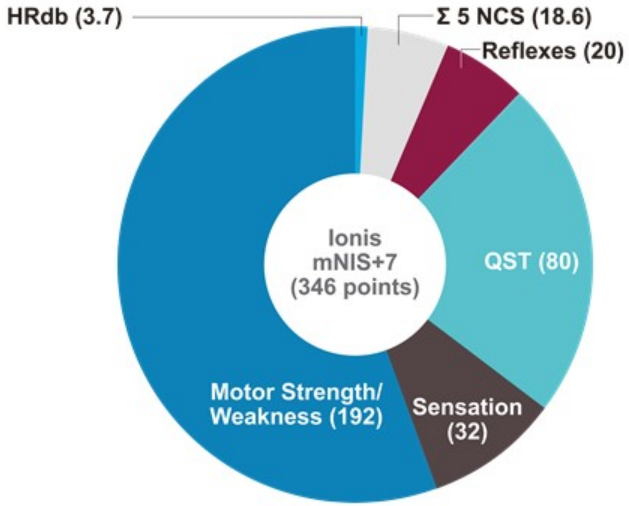


- Combines NIS with 5 nerve conduction study attributes from 3 lower extremity nerves, and other tests[1]
- Range: 0-270; higher score is worse neurologic deficit[1]
- NIS+7 has been shown to have some deficits in assessing sensation, autonomic dysfunction, and conduction abnormalities[2]

1. Berk JL, et al. *JAMA* 2013;310(24):2658-2667; 2. Suanprasert N, et al. *J Neurol Sci* 2014;344(1-2):121-128.

mNIS+7

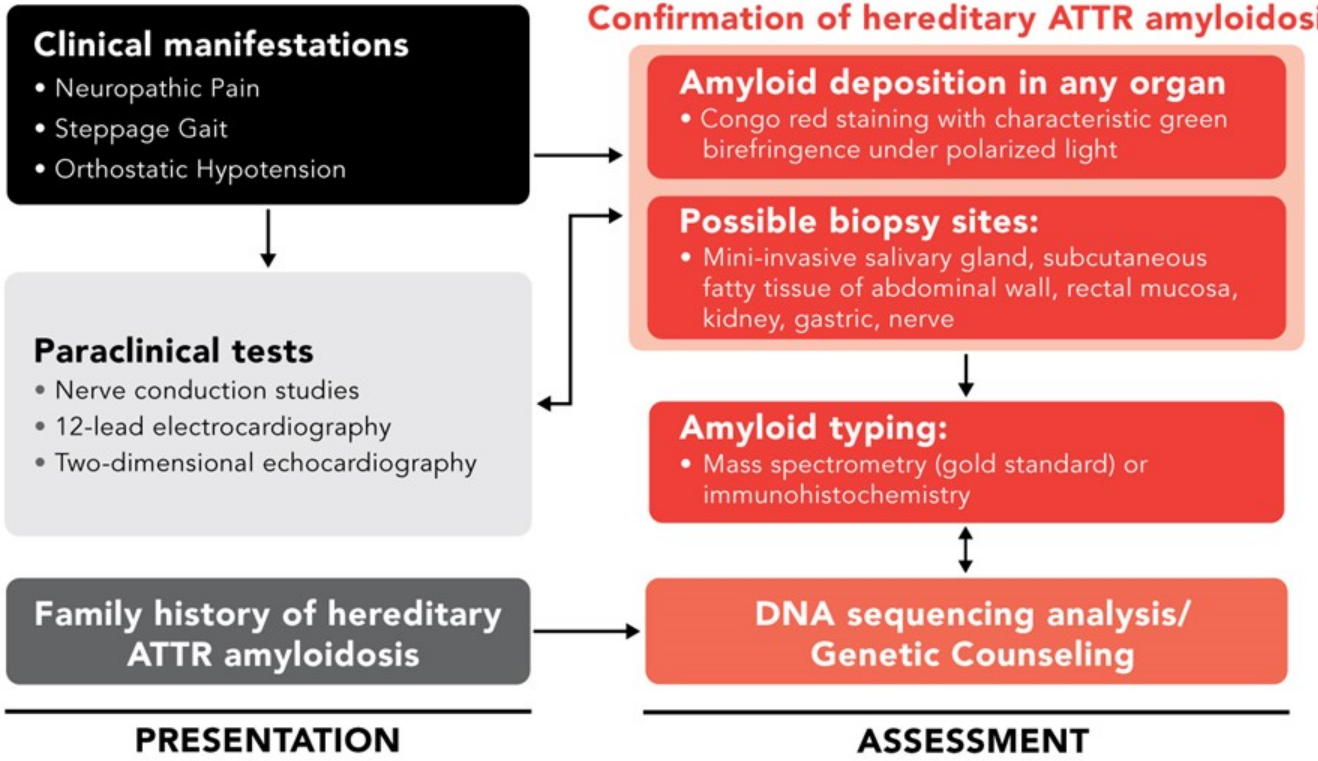




- Various different versions of mNIS+7 exist[1]
- Range:0 – >300; higher score is worst neurologic deficit[2]
- May improve characterization and quantification of symptoms compared to previous NIS tests[3]
- NIS can be used in clinical practice but NIS+7 and mNIS+7 require equipment and are time consuming[3]

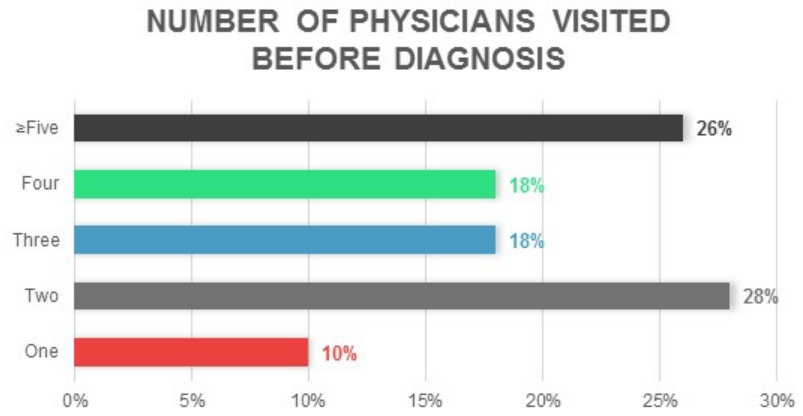
1. Bergemann R, et al. *Orphanet J Rare Dis* 2015;10(suppl 1):O22; 2. Adams, et al. *Neurology*. 2015 Aug 25;85(8):675-82; 3. Suanprasert N, et al. *J Neurol Sci* 2014;344(1-2):121-128.

Approach to Diagnosing ATTR-PN



ATTR, amyloid transthyretin
[a]Figure modified with permission from Carvalho A et al.
1. Carvalho A et al. *Liver Transplantation*. 2015;21:282-292.

Delays in Diagnosis Occur Often



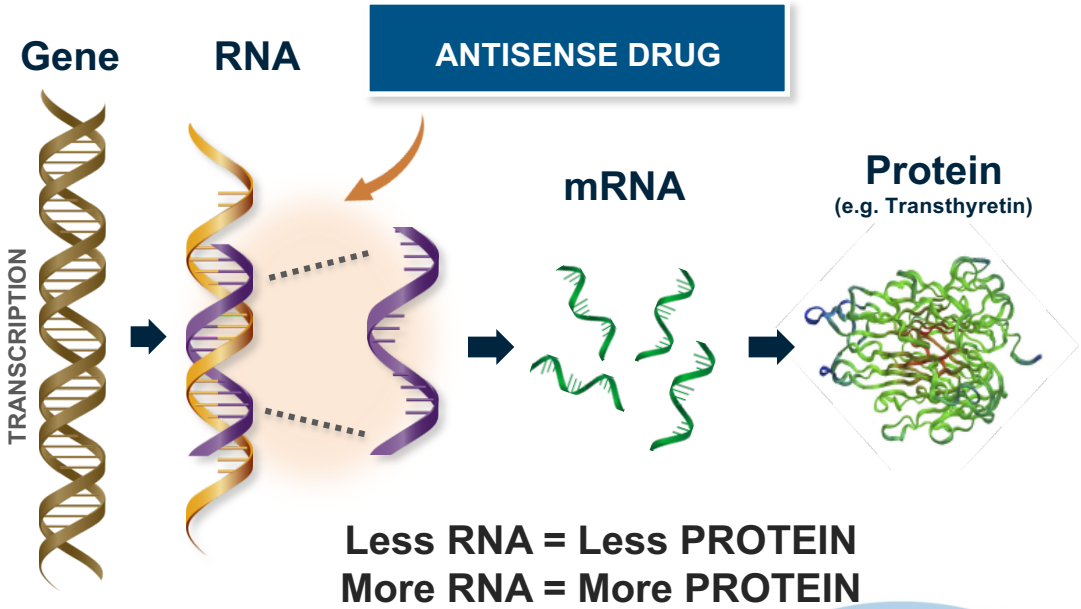
- 30% of patients had hATTR diagnosis delayed for 3 or more years

hATTR, hereditary amyloid transthyretin

Lousada, et al. Patient Experience With Hereditary and Wild-type Amyloidosis: A Survey from the Amyloidosis Research Consortium. Presented at: European Congress on Hereditary Amyloidosis 2015.

The Science of Antisense: Targeting RNA, Not Proteins

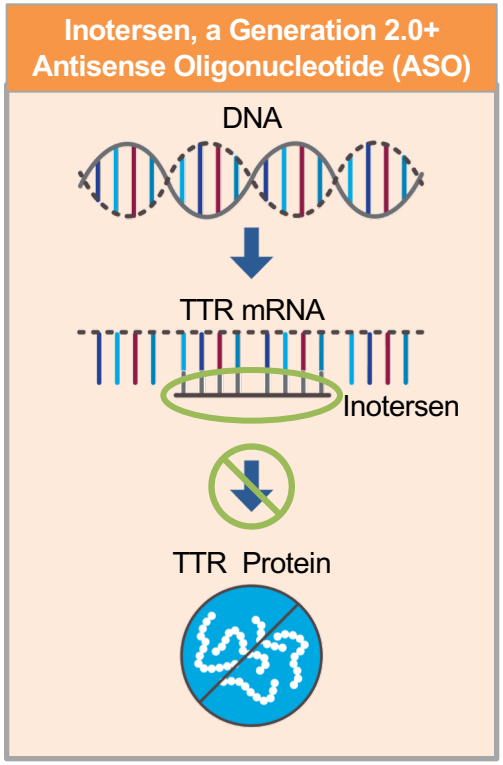
- Antisense technology **prevents the production of proteins** involved in disease
  - This results in a therapeutic improvement to patients
  - Potential to treat patients with a wide range of serious rare genetic diseases
- Typically, DNA is transcribed into messenger RNA (mRNA) and then translated into protein
- Antisense technology **binds to mRNA causing it to degrade**. With no mRNA to translate, there is no protein product



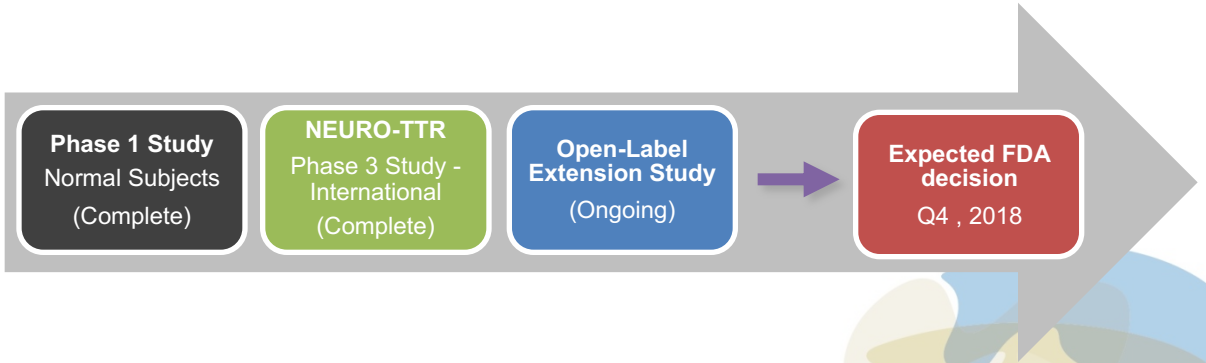
Inotersen in investigational and not approved

Inotersen (AKCEA-TTR$_{Rx}$)

An Antisense Approach to Treat TTR-related Amyloid Diseases



- Inotersen binds to TTR messenger RNA (mRNA) **reducing the amount of disease causing TTR protein**
  - Binds to TTR mRNA and all known mutations
  - Results in degradation of TTR mRNA and reduction of TTR protein production by the liver



Inotersen in investigational and not approved

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THANK YOU!

Clinical Research Unit
C.R.U.