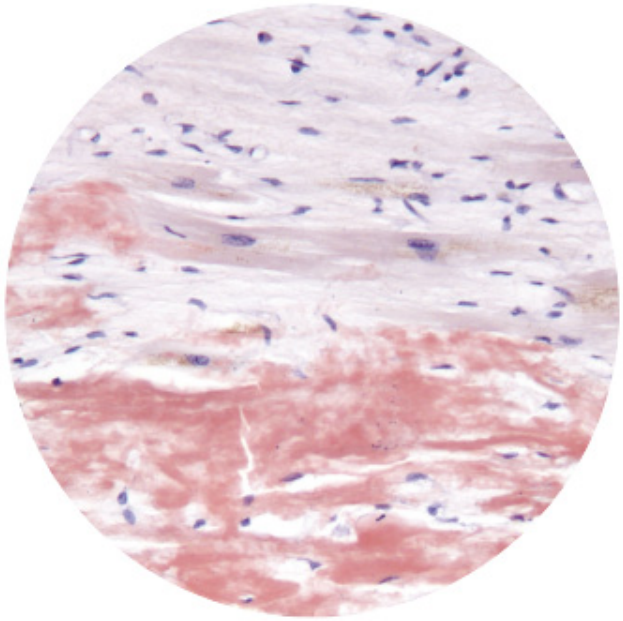
AEEA AhTTR

Asociación Española
Enfermedad de Andrade
(Amiloidosis Hereditaria por Transtirretina)

# II JORNADAS AMILOIDOSIS HEREDITARIA por TRANSTIRRETINA (AhTTR)



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Hospital Son Llàtzer (Salón de Actos)
Palma de Mallorca

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# EARLY DIAGNOSIS IN hATTR AMYLOIDOSIS: A MULTISYSTEMIC DISEASE

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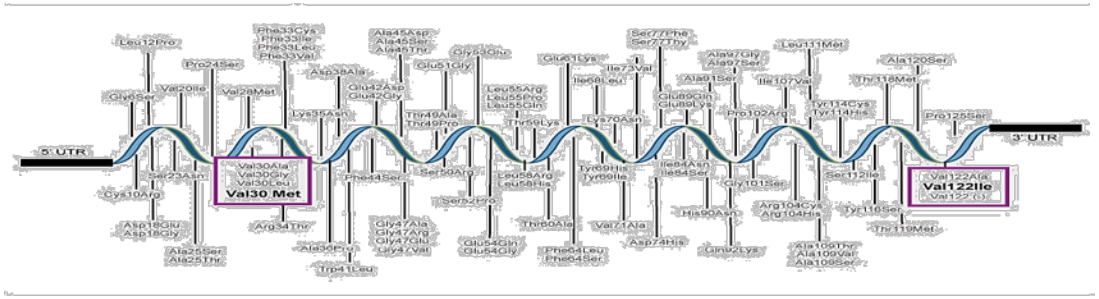
- Serves on the THAOS scientific advisory board, financial support from Pfizer

# hTTR-Amyloidosis

- An autosomal-dominant, adult-onset disorder associated with over 130 different mutations in the transthyretin (TTR) gene



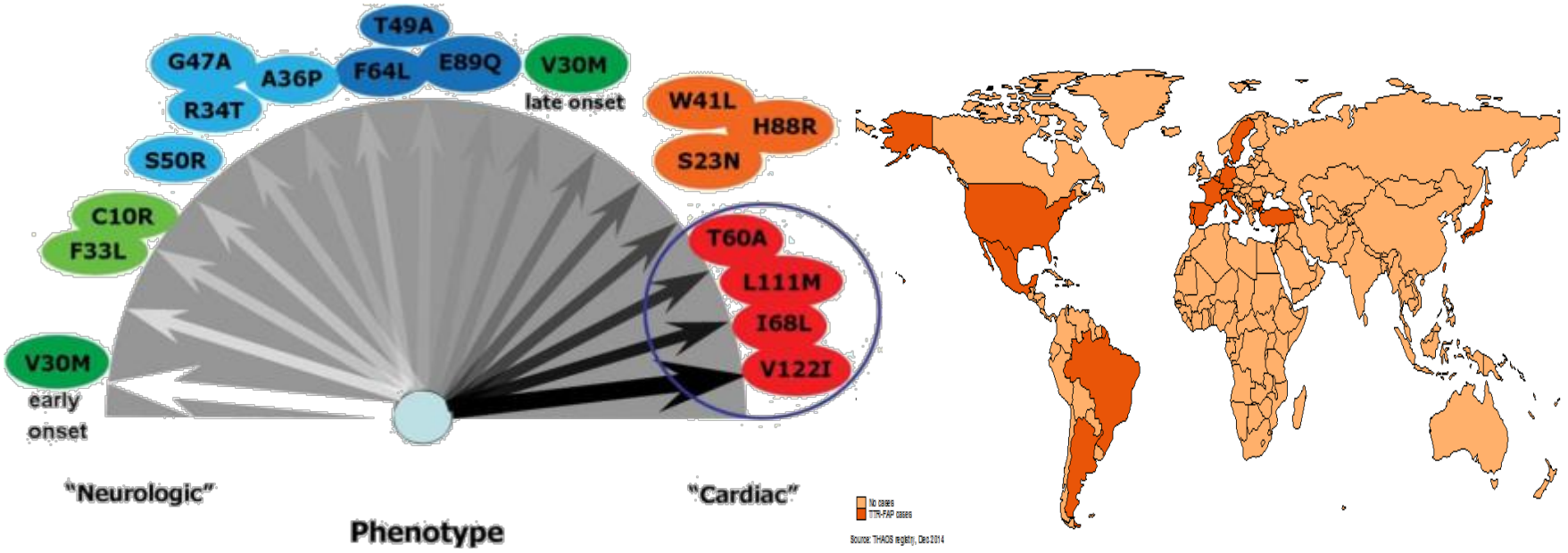

- TTR protein deposits as amyloid in peripheral and autonomic nerves, heart, gastrointestinal (GI) tract, kidneys, eyes, and connective tissue of the transversal carpal ligament[1,2,3]

- This results in progressive organ dysfunction as a multisystemic disease leading to death within an average of 10 years[1]

1-Ando et al., 2013; 2-Rowczenio et al., 2014; 3- Sekijima, 2015

# hATTR Amyloidosis

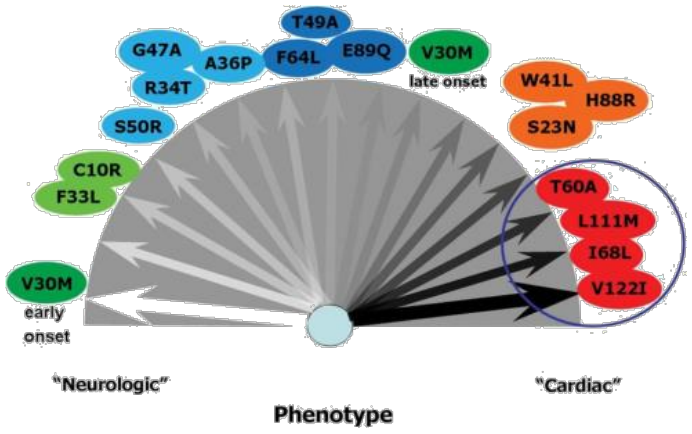
- The low prevalence of hTTR Amyloidosis worldwide and the high variation in both genotype and phenotypic expression of the disease can lead to difficulty in identifying symptoms outside of a specialized diagnostic environment.

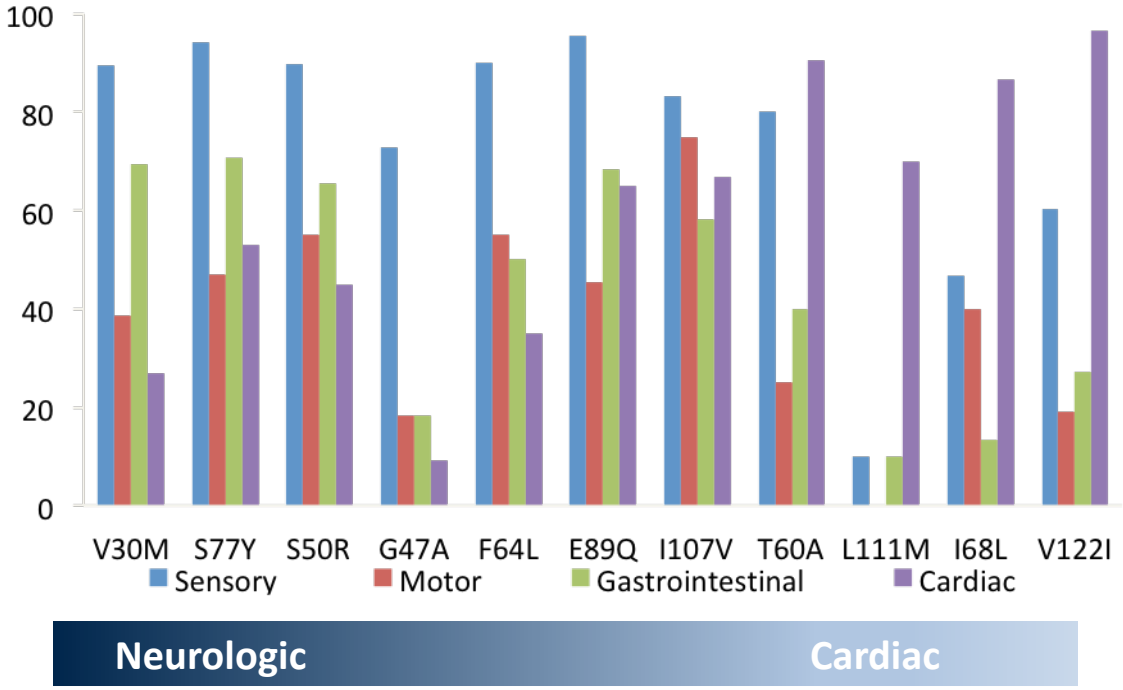



**References:** Adams et al. Current opinion in Neurology 2016;29(1); Rapezzi and al European Heart Journal 2013; 34, 520–528

# Hereditary ATTR amyloidosis

- A clear cut-off point for the diagnosis of active disease is usually difficult to achieved due to some confounding factors:
  - Genotype/phenotype variability
  - Phenotype variability within the same mutation




*Transthyretin Amyloidosis Outcomes Survey (THAOS) is financially supported by Pfizer
Wixner et al. *Orphanet J Rare Dis* 2014;9:61

Rapezzi and al European Heart Journal 2013; 34, 520–528

# hATTR-Amyloidosis: misdiagnosis

- In sporadic or scattered cases, the lack of awareness among physicians of variable clinical features and limited access to diagnostic tools can contribute to high rates of misdiagnosis.

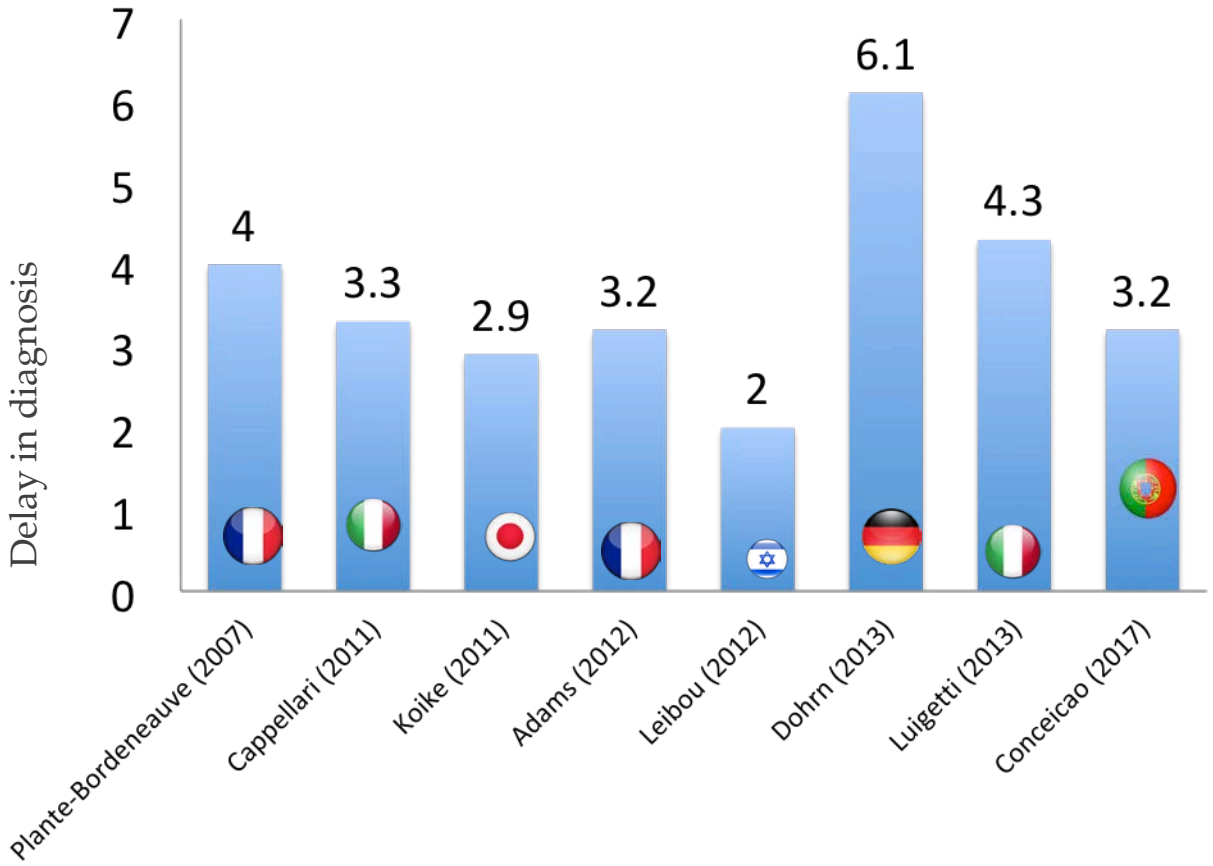
- In general, early and late-onset variants of hATTR-Amyloidosis, found within endemic and nonendemic regions, present several additional diagnostic challenges

Adams et al. Current Opinion in Neurology: Volume 29 Supplement 1 February 2016

# hATTR-Amyloidosis

Early and accurate diagnosis of TTR-FAP represents one of the major challenges faced by physicians when caring for patients with idiopathic progressive neuropathy.

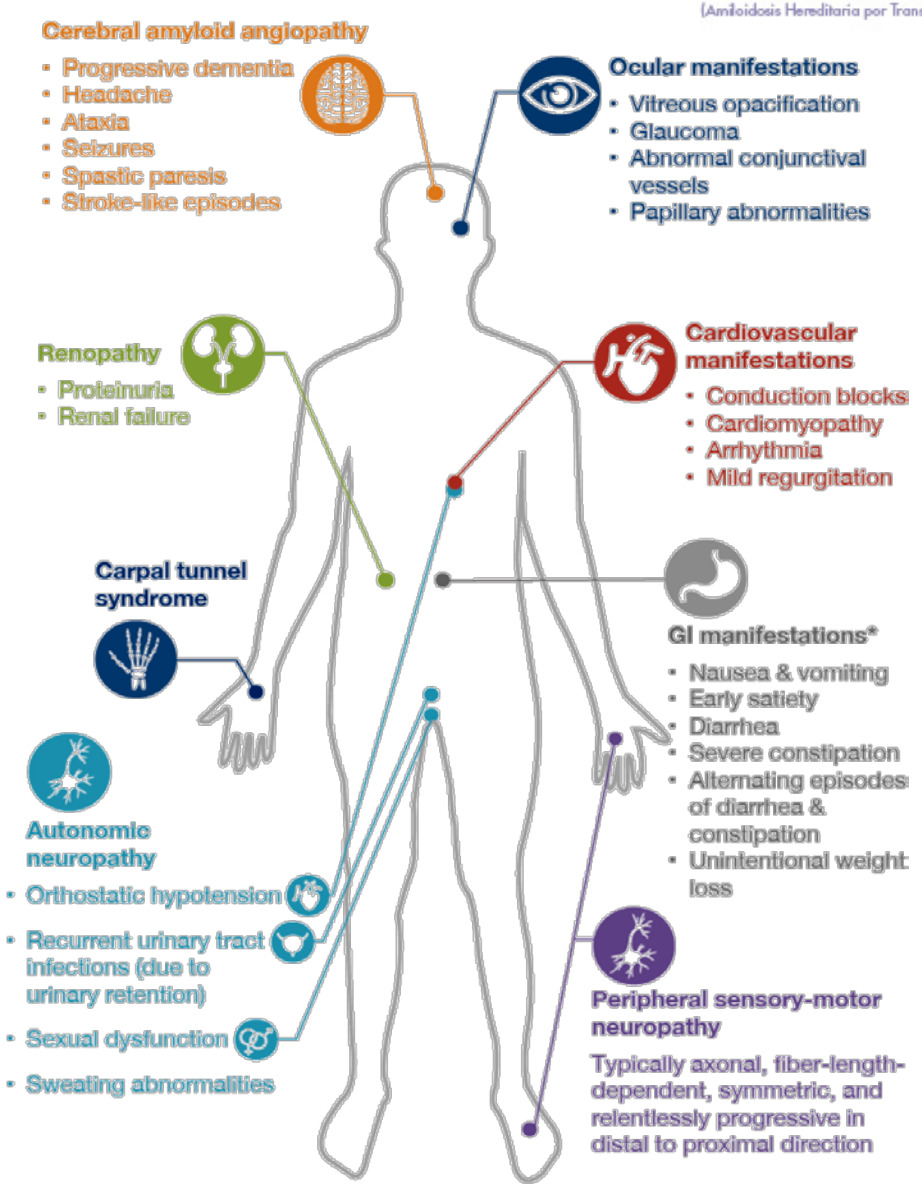
Accurate diagnosis of TTR-FAP is often delayed for years[1–4]




1-Adams et al., 2014; 2-Dohrn et al., 2013; 3-Koike et al., 2011; 4- Planté-Bordeneuve et al., 2007; 5-Coelho et al., 2013; 6-Ericzon et al., 2015

# hATTR-Amyloidosis

- An heterogeneous disease associated with a wide range of clinical manifestations, which leads to the phenotypic heterogeneity that characterizes the disease.




(Conceição et al., 2015; Sekijima, 2015)

# "Red Flag" Symptom Cluster Recommended for hATTR Amyloidosis Presenting with Polyneuropathy



**Progressive symmetric sensory motor neuropathy**

+ **≥1 of**

- **Family history**
- **Early autonomic dysfunction**
- **GI complaints**
- **Unexplained weight loss**
- **Cardiac hypertrophy, arrhythmias, ventricular blocks, or cardiomyopathy**
- **Renal abnormalities**
- **Vitreous opacities**

**Additional alert signs:**

- Rapid disease progression
- Lack of response to prior therapies

Based on Conceicao et al. *J Peripher Nerv Syst* 2016;21:5–9

# TTR-FAP THE NEUROPATHY…



## "EARLY-ONSET (<50 Y) V30M

- **Length dependent progressive sensory-motor and autonomic neuropathy**
  - First, small fiber involvement (decrease in pain and temperature sensation + neuropathic pain)
  - Larger fiber involvement occur later in disease (decrease in proprioception + motor weakness)
- **Autonomic neuropathy** can be the clinical presentation

## LATE ONSET DISEASE (>50 Y)

- **Male predominance** and an apparently sporadic disease presentation.
- **NEUROPATHY -** characterized by relative preservation of unmyelinated nerve fibers
  - **Larger fibers** more rapidly affected than in early onset cases
  - **Sensory and motor neuropathy symptoms of both upper and lower extremities** may appear within a short period or even simultaneously
  - Impaired superficial and deep sensation
  - Severe neuropathic pain
  - Early distal motor involvement,
- **Mild autonomic symptoms**

*Violaine Planté-Bordeneuve, Gerard Said . Lancet Neurol* 2011; 10: 1086–97; *Andrade, 1952; Coutinho et al., 1980;* Koike et al., 2004; Conceição and De Carvalho, 2007; Koike et al., 2011; Misu et al., 1999; Sobue et al., 2003

# hATTR amyloidosis- initial clinical manifestations

| Phenotype | Neuropathic symptoms | | Bilateral CTS | Autonomic | GI | Cardiac | |
|---|---|---|---|---|---|---|---|
| | Positive | Negative | | | | Conduction/rhythm disturbances | Cardiomyopathy |
| Val30M early onset | +++ | ++ | ± | +++ | +++ | ++ | ± |
| Val30M late onset | + | ++ | + | ± | ± | ++ | +++ |
| Non V30M/Cardiac Phenotype | ± | ± | + | + | ± | ++ | +++ |
| Mixed phenotype | + | + | ± | + | + | + | + |

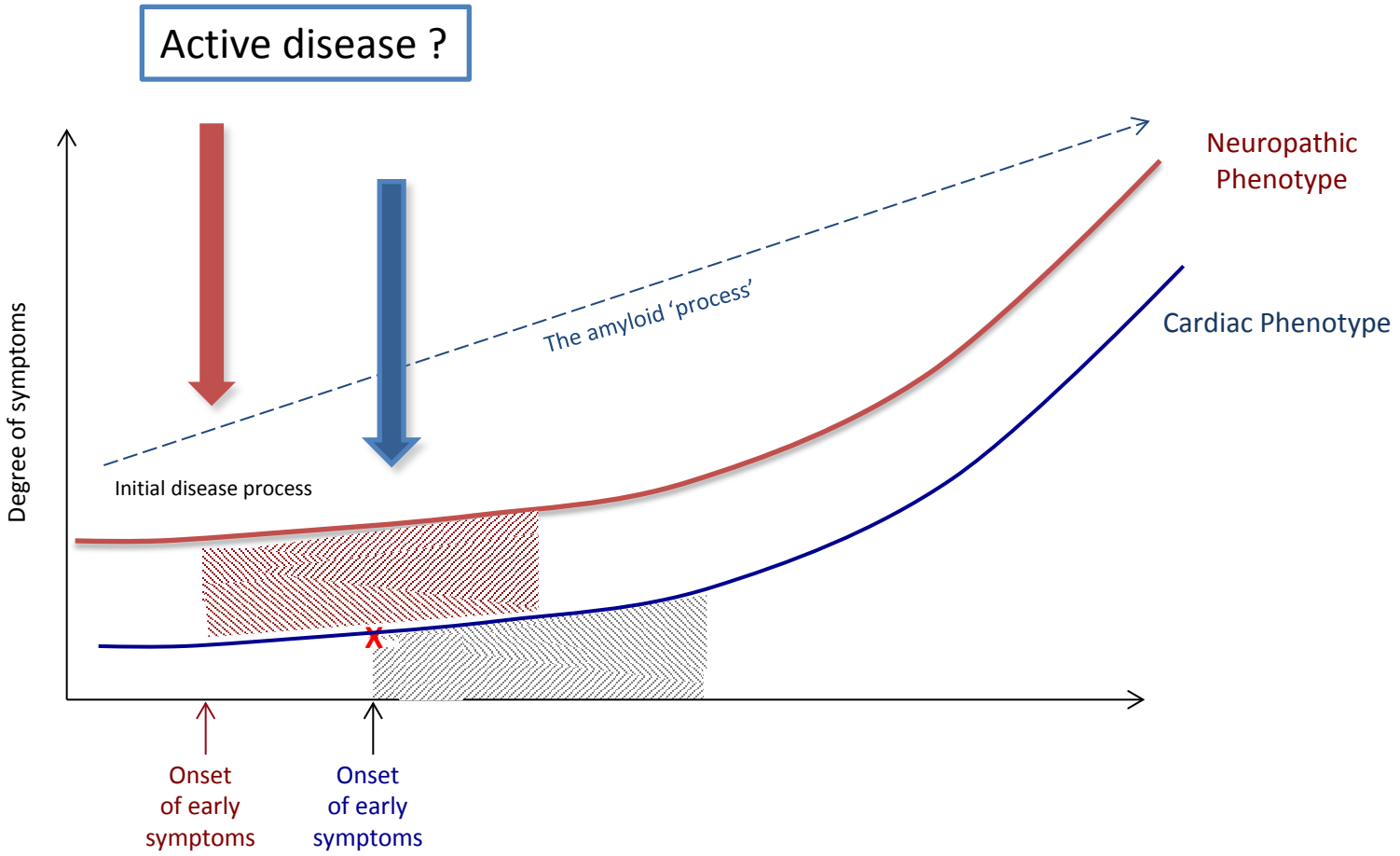
# hTTR-Amyloidosis: diagnosis

- Diagnosis of symptomatic disease in TTR gene mutation carriers should occur upon manifestation of the earliest detectable disease sign/symptom[1]

- Diagnosis in the early stages of disease is essential to allow for timely treatment to prevent or delay disease progression.
  - Pre-symptomatic treatment of gene mutation carriers is not an accepted indication at this time[2]

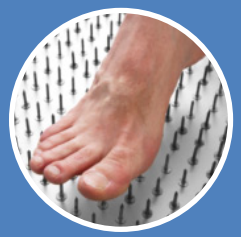
- Due to the highly heterogeneous, multi-systemic nature, and nonspecific symptoms of TTR-FAP, to define a gene carrier as symptomatic can occasionally be a challenge[2]

**REFERENCES**: 1-Conceicao IM, et al. J Peripher Nerv Syst 2016;21:5–9; 2-Schmidt HH, et al Muscle Nerve. 2016 Sep;54(3):353-60.

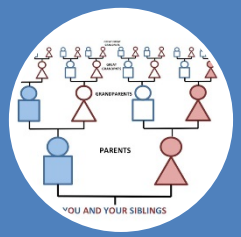



adapted from - Arbustini E, Merlini G. JACC Cardiovasc Imaging. 2014 May;7(5):511-4.

# Assessments to support diagnosis of hATTR amyloidosis[1,2]



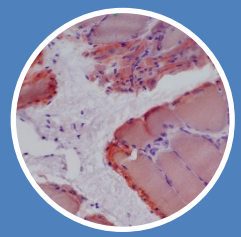
**Clinical Assessment (Onset of symptoms and/or signs)**




**Family history**

**TTR genotyping**

**Changes in neurophysiologic tests vs baseline**



**Biopsy evidence of amyloid**

**Confirmation of diagnosis is by TTR genotyping[3] alone or with tissue biopsy[4]**

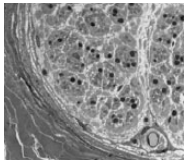
1. Adams et al. Rev Neurol (Paris) 2016;172:645–52; 2. Ruberg & Berk. Circulation 2012;126:1286–1300;
3. Obici et al. *Curr Opin Neurol* 2016;29(Suppl. 1):S27–35; 4. Adams et al. Curr Opin Neurol 2016;29 (Suppl 1):S14–26

# Clinical Tools for Diagnosis and Monitoring of hATTR Amyloidosis: Invasive Tests



## Sensitivity of biopsy can vary significantly by biopsy site and center

| Biopsy site | Sensitivity |
|---|---|
| Abdominal fat pad biopsy | 20–83%[1–4] |
| Salivary gland biopsy | 75–91%[5,6] |
| Nerve biopsy | 55–92%[1,2,7,8] |
| Cardiac biopsy | ~100%[9] |



**Amyloid deposition can be missing in biopsy sample, due to patchy deposition[3,10]**

- **A positive biopsy confirms the presence of systemic amyloidosis**
- **A negative finding should not exclude the diagnosis**

1. Cappellari et al. *J Peripher Nerv Syst* 2011;16:119–129; 2. Luigetti et al. *Neurol Sci* 2013;34:1057–1063; 3. Ikeda et al. *Amyloid* 2011;18:211–215; 4. Van Gameren et al. *Arthritis Rheum* 2006;54:2015–2021; 5. de Paula Eduardo et al. 2017;38:311–318; 6. Do Amaral et al. *Amyloid* 2009;16:232–238; 7. Leibou et al. *Ist Med Assoc J* 2012;14:662–665; 8. Dohrn et al. *J Neurol* 2013;260:3093–3108; 9. Ruberg, Berk. *Circulation* 2012;126:1286–1300; 10. Hawkins et al. *Annals Med* 2015;47:625–638

# Clinical Tools for Diagnosis and Monitoring of hATTR Amyloidosis: Non-invasive Tests



## Genetic Molecular Test

- Full sequence of TTR gene

## Neuropathy assessment

- Compass31; Norfolk QOL
- NIS assessment
- Electromyography with Nerve Conduction Studies
- Sudomotor tests (Sudoscan; Sympathetic Skin Response; QSART)
- Quantitative Sensory Tests (QST)
- Postural blood pressure, HRdB

## Cardiac assessment

- ECG and echocardiography
- CMRI
- Nuclear scintigraphic imaging
- Serum cardiac biomarkers

HRdb, heart rate during deep breathing.

Ikeda et al. *Amyloid* 2011;18:211–215; Hawkins et al. *Annals Med* 2015;47:625–638; Adams et al. Curr Opin Neurol 2016;29(Suppl 1):S14–26

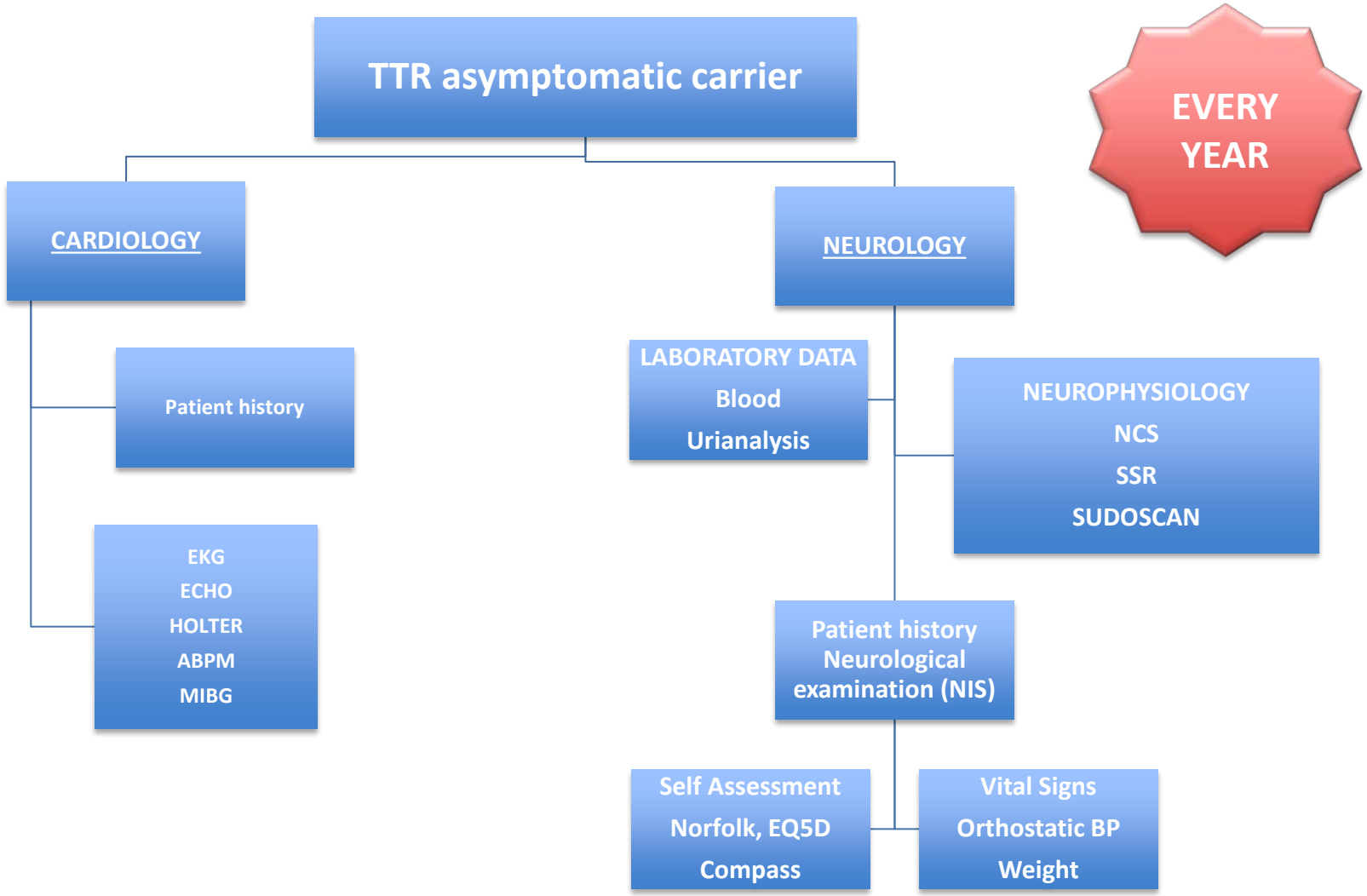
# Clinical Tools for Diagnosis of hATTR Amyloidosis

| | Clinical Evaluation | | | Neurophysiology | | | | Biomarkers | | | Cardiac evaluation | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NIS | BP supine vs orthtostatic | BMI | NCS | Sudomotor (SSR/Sudoscan) | hRDB RR | QST | NT-proBNP | Troponin | Blood/Urine sample | Scintigraphy $^{99m}$Tc-DPD | MRI | Echo | ECG |
| Val30M early onset | + | + | + | + | + | + | + | + | - | + | - | - | + | + |
| Val30M late onset | + | + | + | + | ± | - | ± | + | + | + | + | - | + | + |
| Non V30M/Cardiac Phenotype | - | + | + | - | - | - | - | + | + | + | + | + | + | + |
| Mixed phenotype | + | + | + | + | + | + | + | + | - | + | - | - | + | + |

$^{99m}$Tc-DPD, technetium-99m-3,3-diphosphono-1,2 propanodicarboxylic acid; MRI, magnetic resonance imaging; NIS, Neuropathy Impairment Score; NT-proBNP, N-terminal pro-brain natriuretic peptide.

# The practical approach: asymptomatic carrier





# Proposed Diagnosis Criteria

**At least one quantified/objective sign or symptom definitely related to onset of ATTR amyloidosis disease**

- sensorimotor neuropathy (change from baseline)
- Autonomic neuropathy
- Cardiac involvement
- Renal or ocular involvement

**OR**

**Any symptom possibly related to ATTR amyloidosis disease in the absence of objective signs**

**+**

**at least 1 abnormal test finding**

**OR**

**Absence of symptoms possibly related to ATTR disease**

**+**

**at least 2 abnormal test findings**

# hATTR Amiloidosis : the early diagnosis

- Diagnosis of symptomatic hATTR amyloidosis and treatment initiation in gene mutation carriers should occur upon manifestation of the earliest detectable disease sign/symptom.
- Decision of first disease manifestation should be done based on a set of clinical symptoms and signs
- Objective evidence of neuropathy, such as a change from baseline, can be considered sufficient to reach a diagnosis of hATTR amyloidosis in gene carriers.

**REFERENCES:** 1. Obici L, et al. Curr Opin Neurol 2016;29(suppl 1):DOI:10.1097/WCO.0000000000000290

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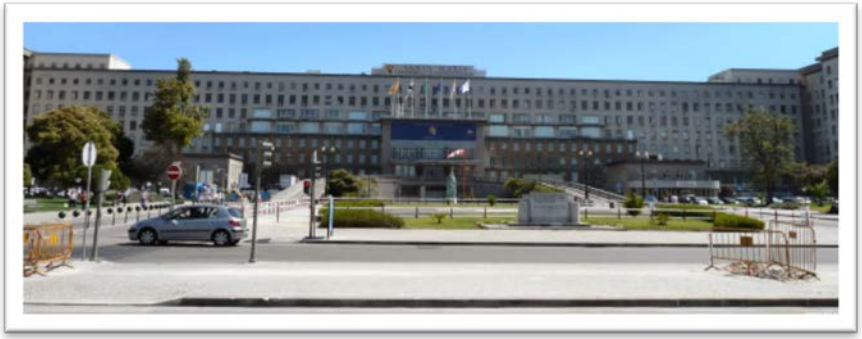

# THANK YOU