XII Meeting. State of the Art in

HEART FAILURE

CLINICAL PRACTICE AND ORGANIZATIONAL MODELS

Venue: Hotel Meliá María Pita, A Coruña

A Coruña 26-27 September 2025

A Coruña Heart Failure Academy

#ACORUÑAHF2025

Genetic testing: what to look for, when to do it and what it brings to clinical management.

Esteban Martín Álvarez || *Complexo Hospitalario Universitario A Coruña*

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WHAT TO LOOK FOR?

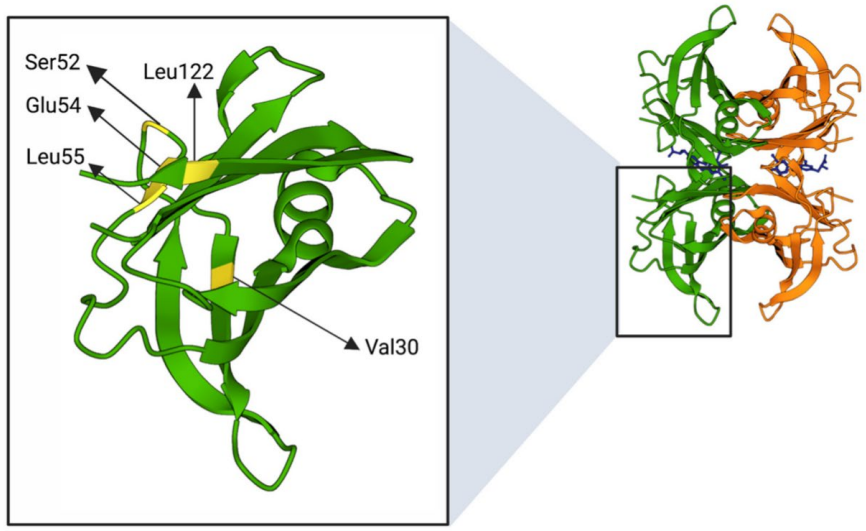
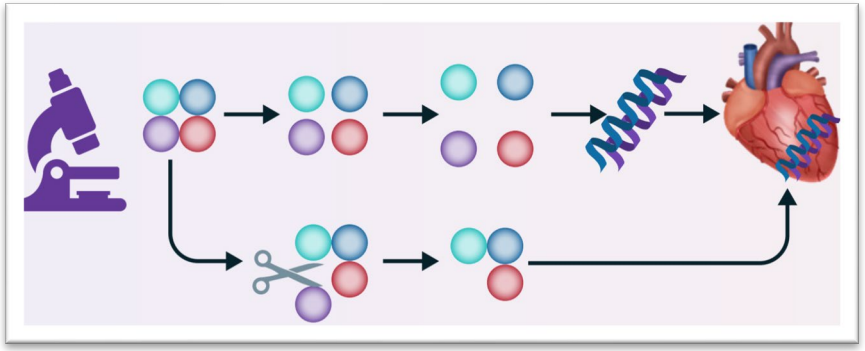
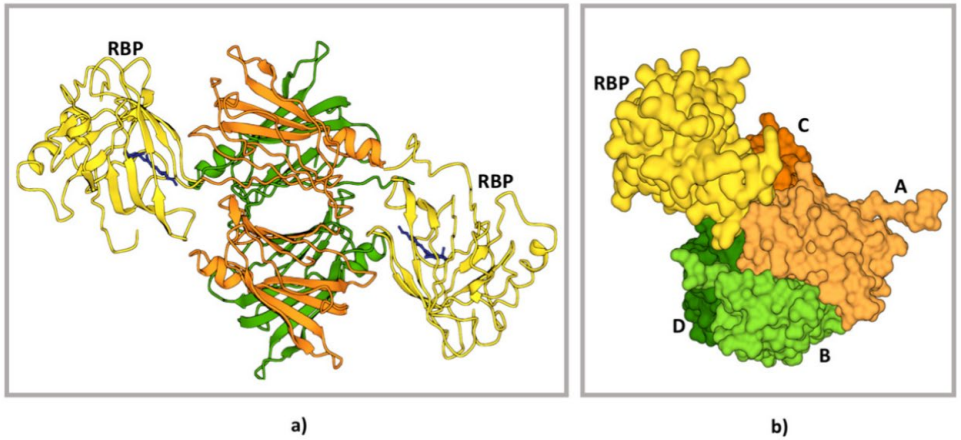


Figure 4. Positions of amino acids (highlighted in yellow) subjected to mutations described in Table 1. The figure was created through "www.rcsb.org" and "biorender.com" web sites (license agreement number KJ247URGZS), access date 22 June 2022.

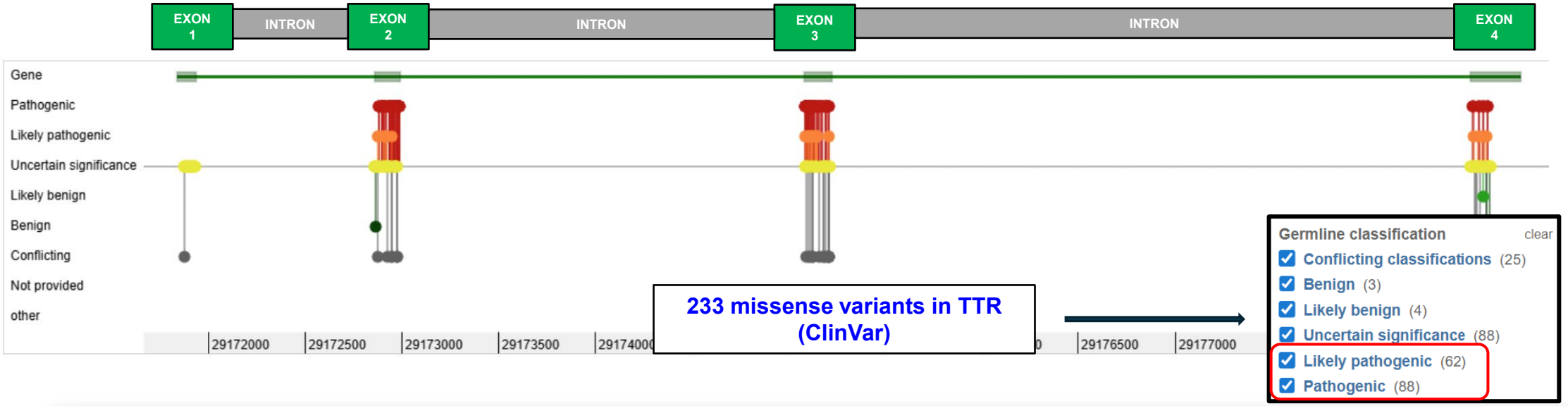
- **Human TTR** is a protein encoded by a single gene located on chromosome 18q.
- **Mature protein has 127 amino acids**. Pro-TTR monomers have 147 amino acids (including a 20-amino acid signal peptide). The current nomenclature, according to the Human Gene Organization, includes this peptide.
- **ATTRv** is caused by **pathogenic variants** in the **TTR gene** that **reduce stability** of the TTR tetramer, leading to **easier dissociation** in pro-amyloidogenic monomers.





Sanguinetti, Chiara et al. Biomedicines vol. 10,8 1906. 6 Aug. 2022 // Sekijima Y, Nakamura K. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.

WHAT TO LOOK FOR?

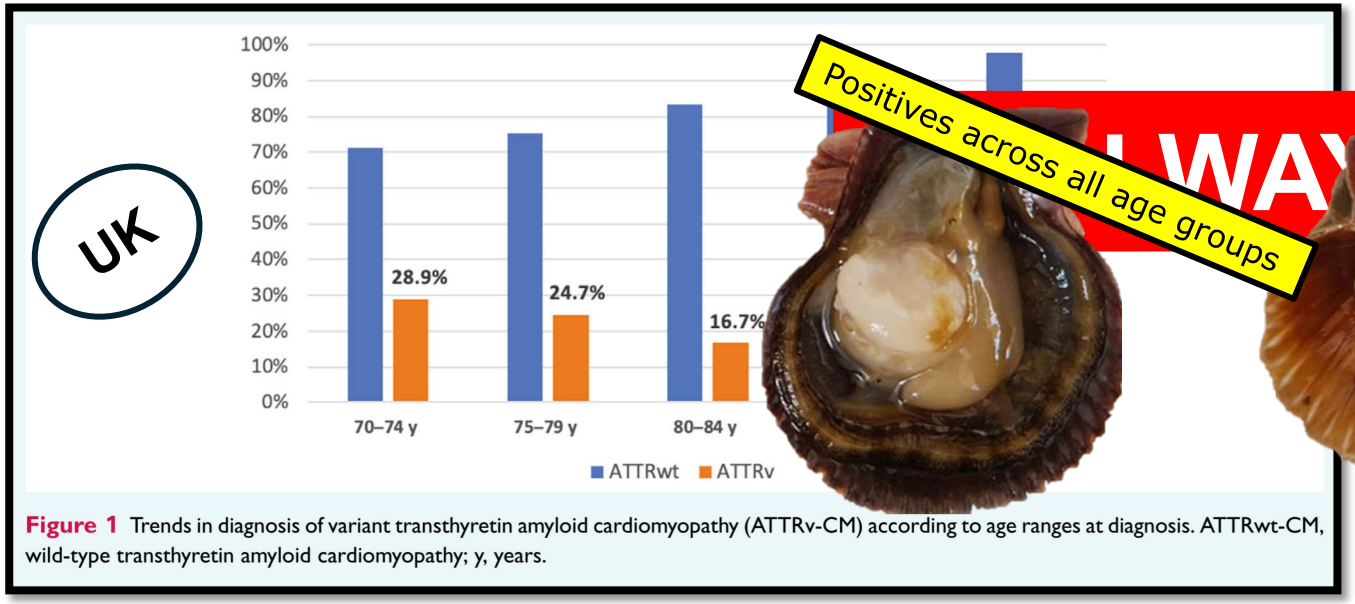


NM_000371.4(TTR):c.133G>T (p.Ala45Ser)	TTR (A45S)	Single nucleotide variant (missense variant)	Cardiovascular phenotype	G	Likely pathogenic ★
NM_000371.4(TTR):c.148G>T (p.Val50Leu)	TTR (V50L)	Single nucleotide variant (missense variant)	Familial amyloid neuropathy	G	Pathogenic ★
NM_000371.4(TTR):c.148G>C (p.Val50Leu)	TTR (V50L)	Single nucleotide variant (missense variant)	Cardiovascular phenotype +2 more	G	Pathogenic ★★
NM_000371.4(TTR):c.148G>A (p.Val50Met)	TTR (V50M)	Single nucleotide variant (missense variant)	Cardiovascular phenotype +7 more	G	Pathogenic ★★
NM_000371.4(TTR):c.149T>G (p.Val50Gly)	TTR (V50G)	Single nucleotide variant (missense variant)	Familial amyloid neuropathy	G	Pathogenic ★
NM_000371.4(TTR):c.149T>C (p.Val50Ala)	TTR (V50A)	Single nucleotide variant (missense variant)	Familial amyloid neuropathy	G	Pathogenic ★★
NM_000371.4(TTR):c.155T>C (p.Val52Ala)	TTR (V52A)	Single nucleotide variant (missense variant)	Cardiovascular phenotype +1 more	G	Likely pathogenic ★★

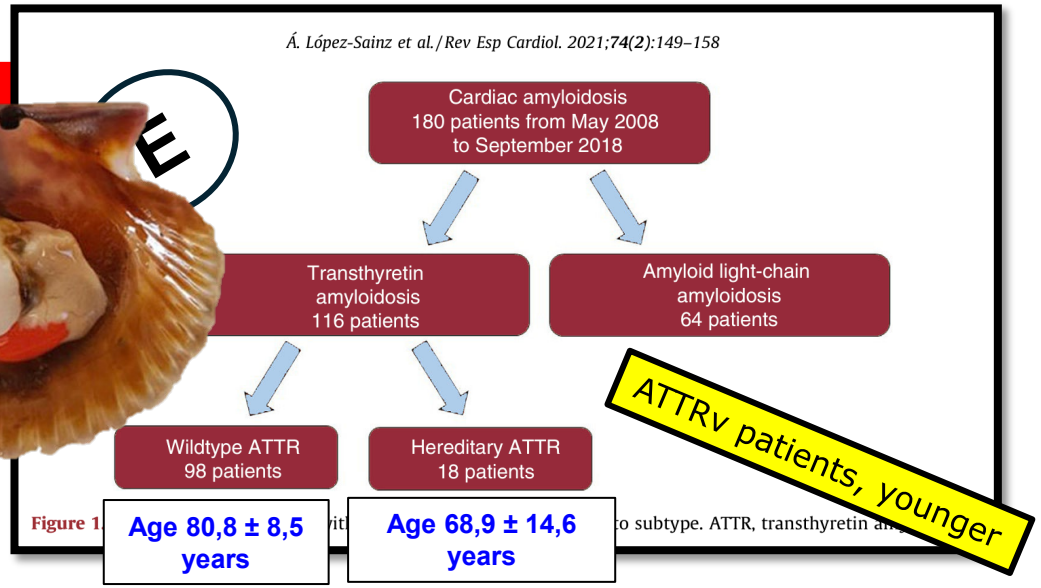
WHEN TO DO A GENETIC TEST?

- As soon as **ATTR-CM** has been confirmed, the presence of **pathogenic variants** in the TTR gene should be evaluated and **genetic counseling** should be given.
- **ATTRv** and **ATTRwt** are two different diseases. **100% of ATTRwt affect the heart**, but **not all ATTRv do so** (30-100%).
- Genetic testing should be done **regardless of age**.

ATTRv ≠ ATTRwt



Porcari, Aldostefano et al. "Prevalence, characteristics and outcomes of older patients with hereditary versus wild-type transthyretin amyloid cardiomyopathy." European journal of heart failure vol. 25,4 (2023): 515-524.



López-Sainz, Ángela et al. "Clinical profile and outcome of cardiac amyloidosis in a Spanish referral center." Revista española de cardiología (English ed.) vol. 74,2 (2021): 149-158.

Gentile, Luca et al. "A 15-year consolidated overview of data in over 6000 patients from the Transthyretin Amyloidosis Outcomes Survey (THAOS)." Orphanet journal of rare diseases vol. 18,1 350. 10 Nov. 2023

- Genetic testing should be done **regardless of age**.

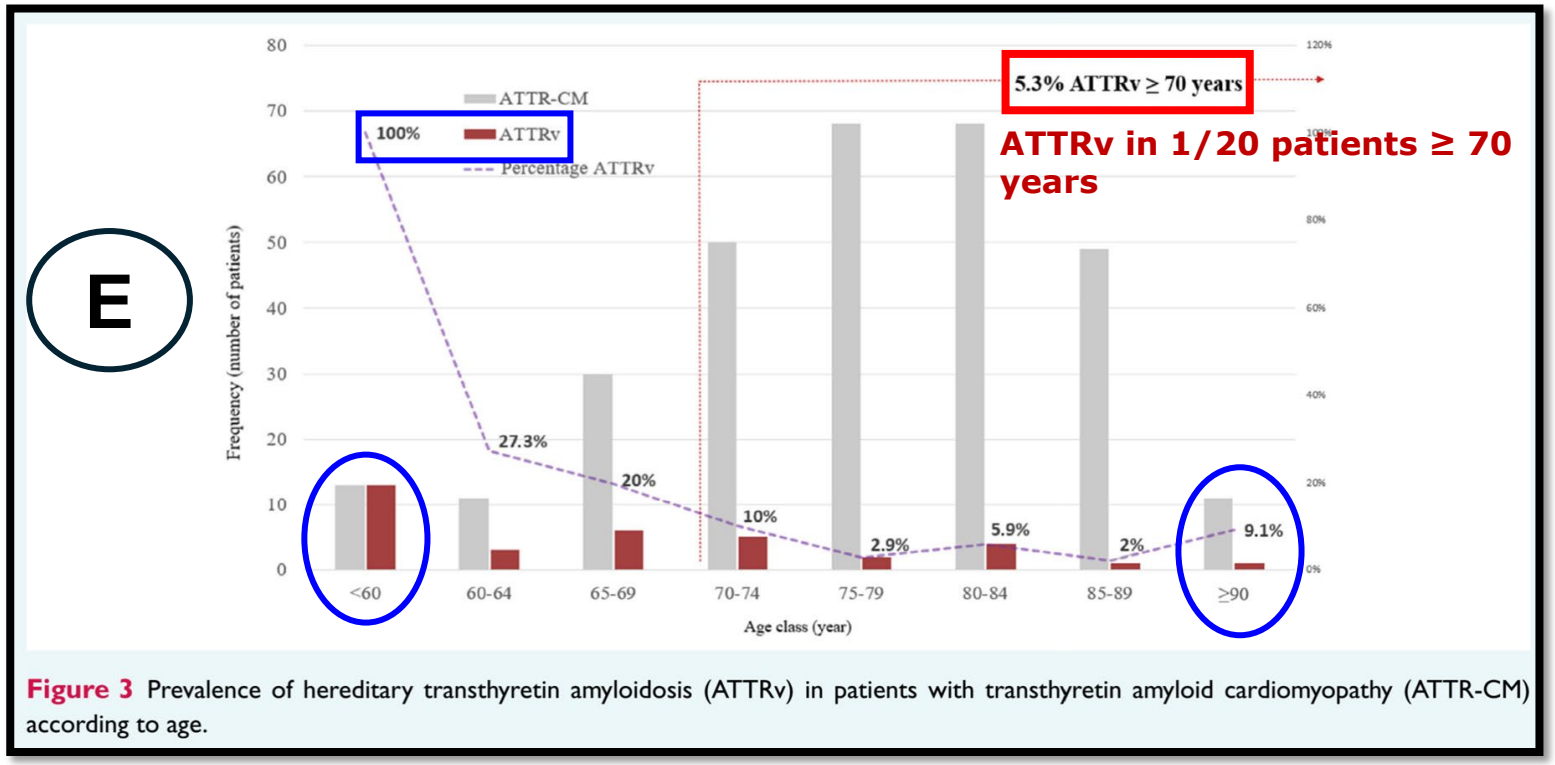
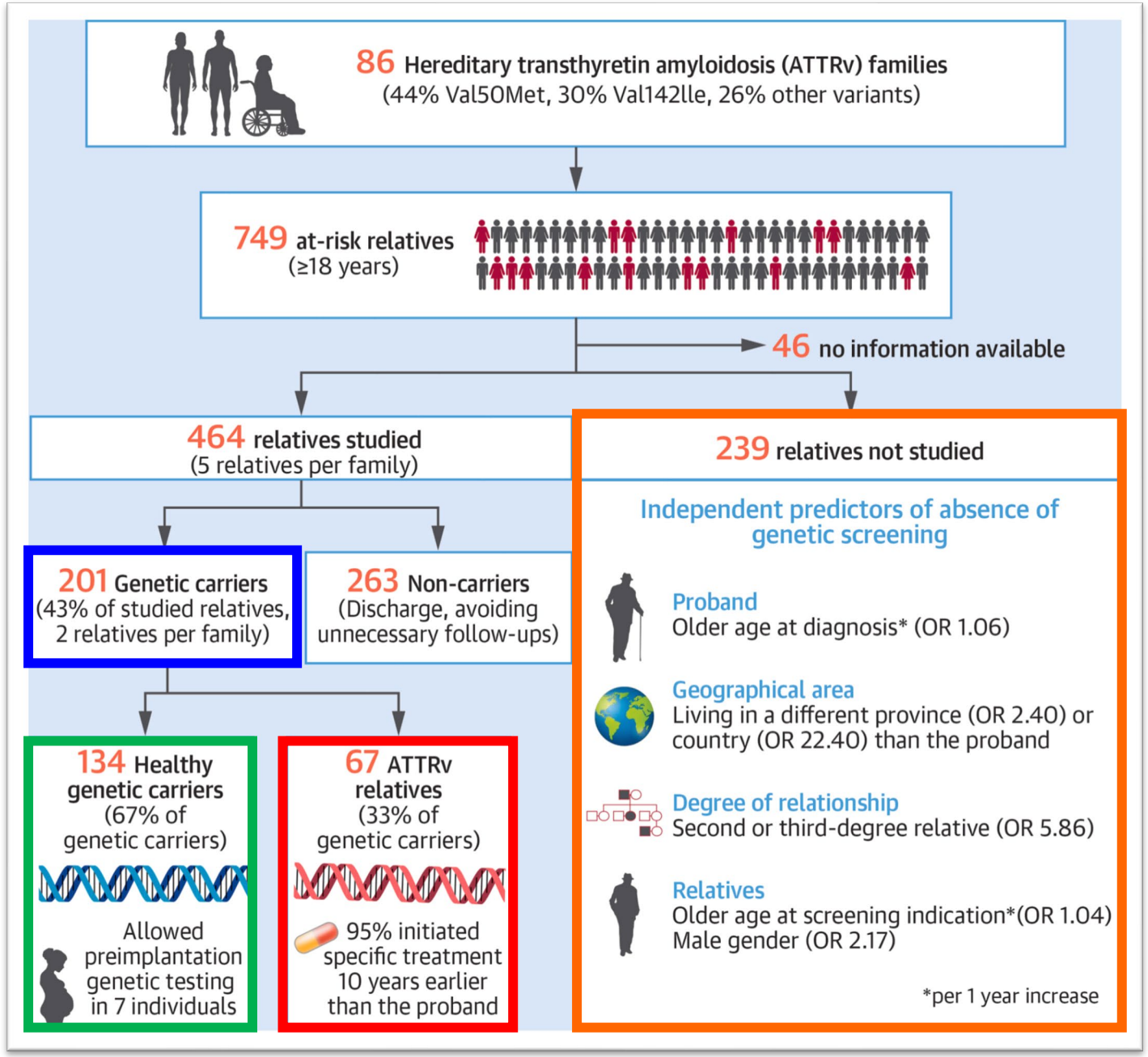


Figure 3 Prevalence of hereditary transthyretin amyloidosis (ATTRv) in patients with transthyretin amyloid cardiomyopathy (ATTR-CM) according to age.

- **Overall**, the prevalence of **ATTRv** among 300 patients with ATTR-CM was **12%**.
- In the cohort of ATTR-CM patients **≥ 70 years**, 13/246 had **ATTRv** (**5.3%**).
- Prevalence of **ATTRv** among **elderly female** patients with ATTR-CM was **13%**.
- Oldest ATTRv patient was 93-year-old Caucasian female with the p.Val142Ile variant
- Prevalence in <60 years was 100%.
- Implications of ATTRv diagnosis: **transthyretin-specific** drug treatment, genetic screening in **relatives**, identification of **asymptomatic carriers.**

Maestro-Benedicto, Alba et al. "Frequency of hereditary transthyretin amyloidosis among elderly patients with transthyretin cardiomyopathy." European journal of heart failure vol. 24,12 (2022): 2367-2373.



- Almost **half of studied relatives** were genetic **carriers**.
- Genetic carriers:
  - **2/3 healthy carriers**.
  - **1/3 ATTRv**.
- **1/3** of **at-risk** relatives **not studied**.

Early diagnosis

Reproductive planning

Early treatment

Mora-Ayestarán, Nerea et al. "Impact of Genetic Testing Family Screening in Hereditary Transthyretin Amyloidosis." JACC. CardioOncology, S2666-0873(25)00283-2. 13 Aug. 2025

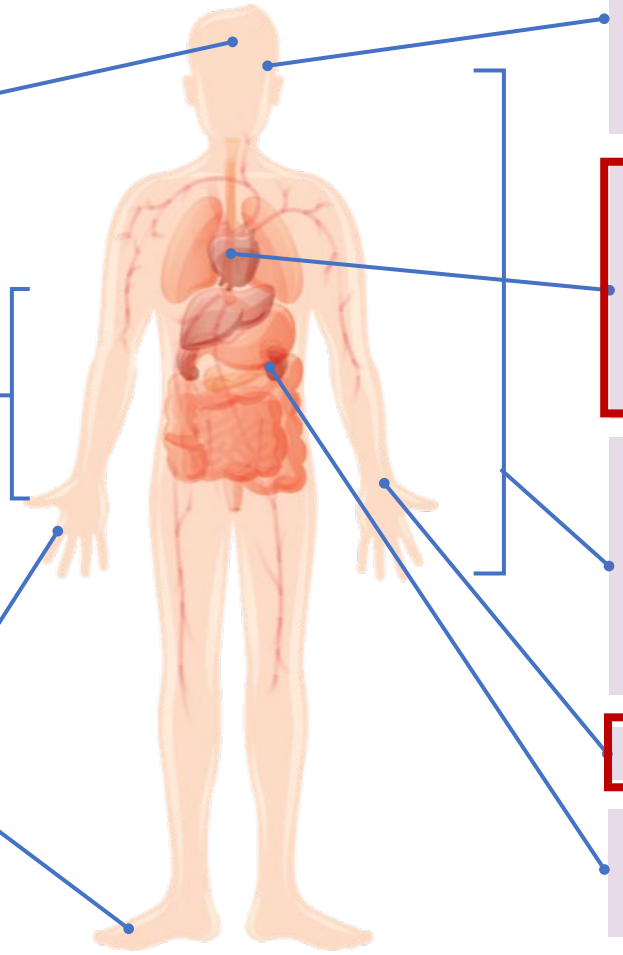
RELEVANCE IN CLINICAL MANAGEMENT

ATTRv ≠ ATTRwt

Manifestations in the CNS
- Progressive dementia
- Headache
- Ataxia
- Seizures
- Spastic paresis
- Thrombotic episodes

Gastrointestinal (GI) manifestations
- Nausea and vomiting
- GI motility changes (i.e., diarrhea, constipation, gastroparesis, early satiety)
- Unintentional weight loss

Sensory-motor polyneuropathy
- Neuropathic pain
- Altered sensation (changes in sensitivity to pain and temperature)
- Numbness and tingling
- Muscle weakness
- Balance disturbances
- Difficulty walking



Ocular manifestations
- Vitreous opacity
- Glaucoma
- Abnormalities of the blood vessels of the conjunctiva. Pupillary alterations

Cardiovascular manifestations
- Conduction block
- Cardiomyopathy
- Tachycardia and arrhythmia
- Mild regurgitation
- Dyspnea
- Oedema

ATTRwt and ATTRv

Autonomic neuropathy
- Orthostatic hypotension
- Recurrent urinary tract infections due to urinary retention
- Sexual dysfunction
- Sweating abnormalities
- Vasomotor dysfunction

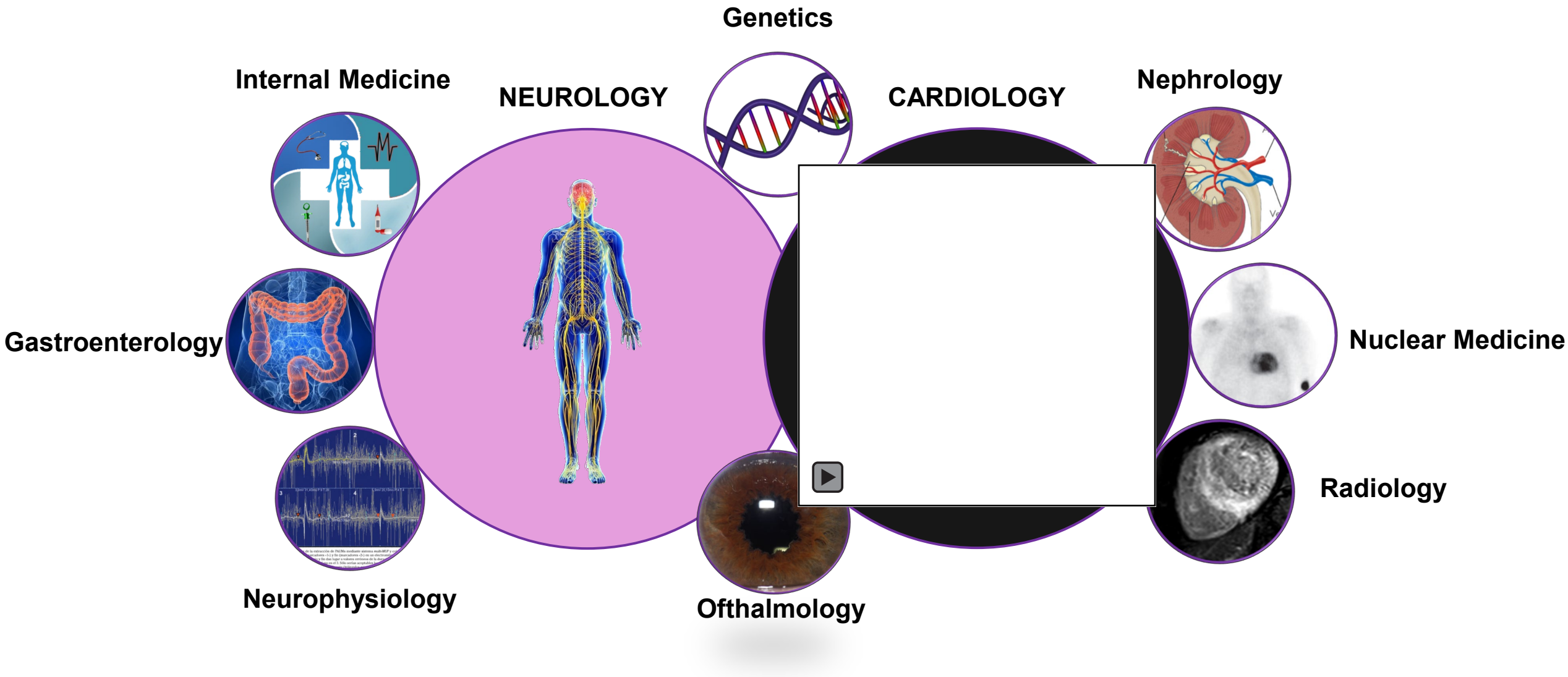
Bilateral carpal tunnel syndrome

ATTRwt and ATTRv

Nephropathy
- Proteinuria
- Kidney failure

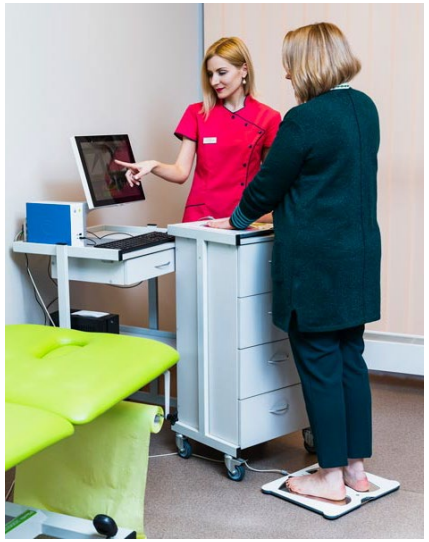
Conceição I et al. "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy. J Peripher Nerv Syst. 2016;21:5-9; 2. Gonzalez-Duarte A. Autonomic involvement in hereditary transthyretin amyloidosis (hATTR amyloidosis). Clin Auton Res. 2019; 29(2):245-251

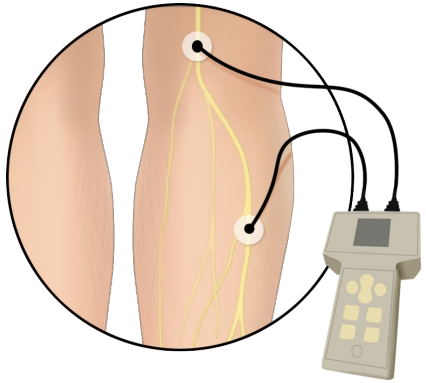
ATTRv: Multidisciplinary management



ATTRv: Multidisciplinary management

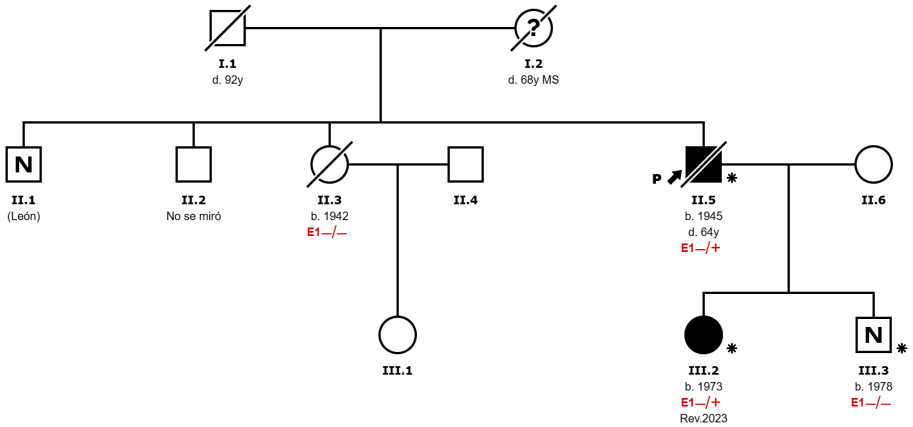
Sudoscan

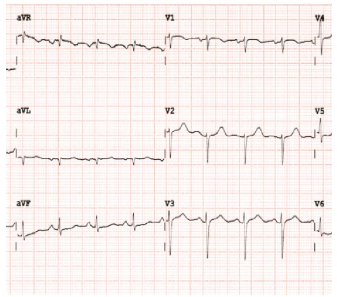


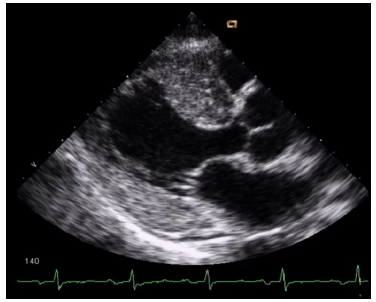


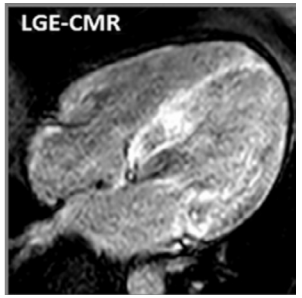
nerve conduction study(NCS)

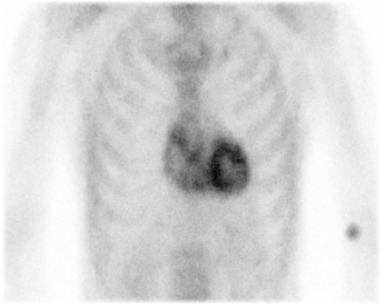
BIOMARKERS (TnI, NT-proBNP) RENAL FUNCTION, uACR











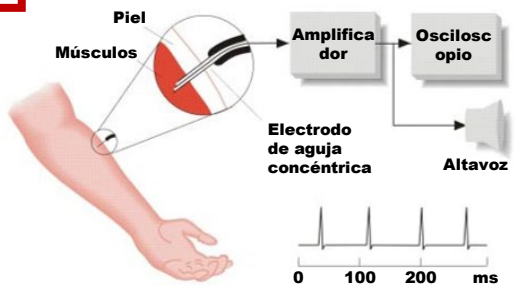
Medical & Science

NIS

means

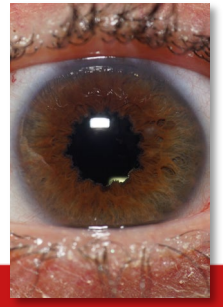
Neuropathy Impairment Score

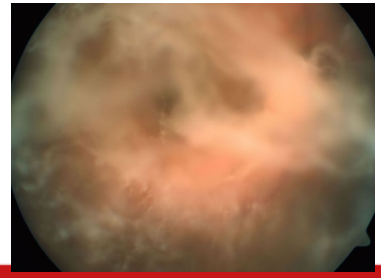
by acronymsandslang.com

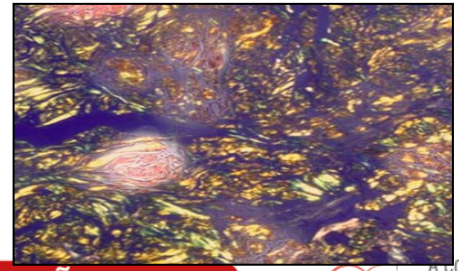


Electromyography (EMG)

COMPASS 31



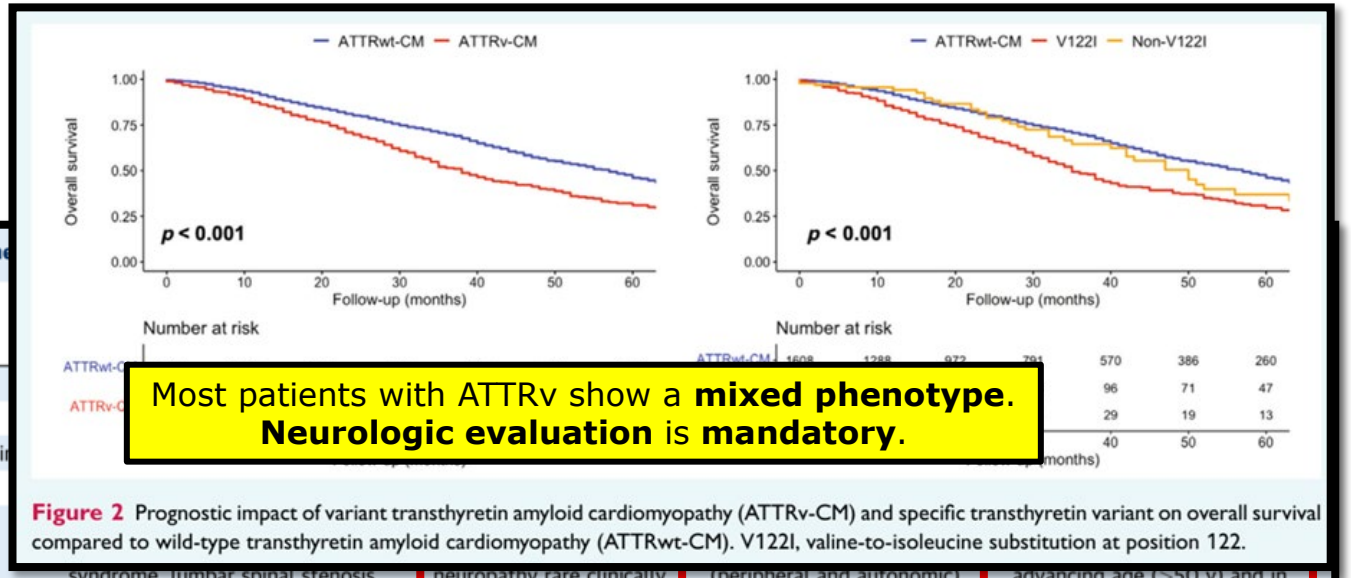




RELEVANCE IN CLINICAL MANAGEMENT

ATTRv is a **multisystem autosomal dominant disease**. **Phenotypic expression** differs between different **variants**, and even for the **same variant** (**early-onset p.Val50Met** vs. **late-onset p.Val50Met**)

*"**Cardiac variants**": **Val142Ile**, Leu131Met, Thr80Ala, Ile88Leu*



Most patients with ATTRv show a **mixed phenotype**. **Neurologic evaluation** is **mandatory**.

Figure 2 Prognostic impact of variant transthyretin amyloid cardiomyopathy (ATTRv-CM) and specific transthyretin variant on overall survival compared to wild-type transthyretin amyloid cardiomyopathy (ATTRwt-CM). V122I, valine-to-isoleucine substitution at position 122.

Porcari, Aldostefano et al. "Prevalence, characteristics and outcomes of older patients with hereditary versus wild-type transthyretin amyloid cardiomyopathy." European journal of heart failure vol. 25,4 (2023): 515-524.

TABLE 1 Demographic, Gene

Average age, y (range)
Male, %
Race/ethnicity/country of origi
Genetics
Phenotype

[a]Depends on endemic vs nonendemic areas, early vs late age onset. [b]Age of disease penetrance is later in women than in men

Griffin, Jan M et al. JACC. CardioOncology vo

In general, variants with a predominantly **cardiac** phenotype have a **worse prognosis**

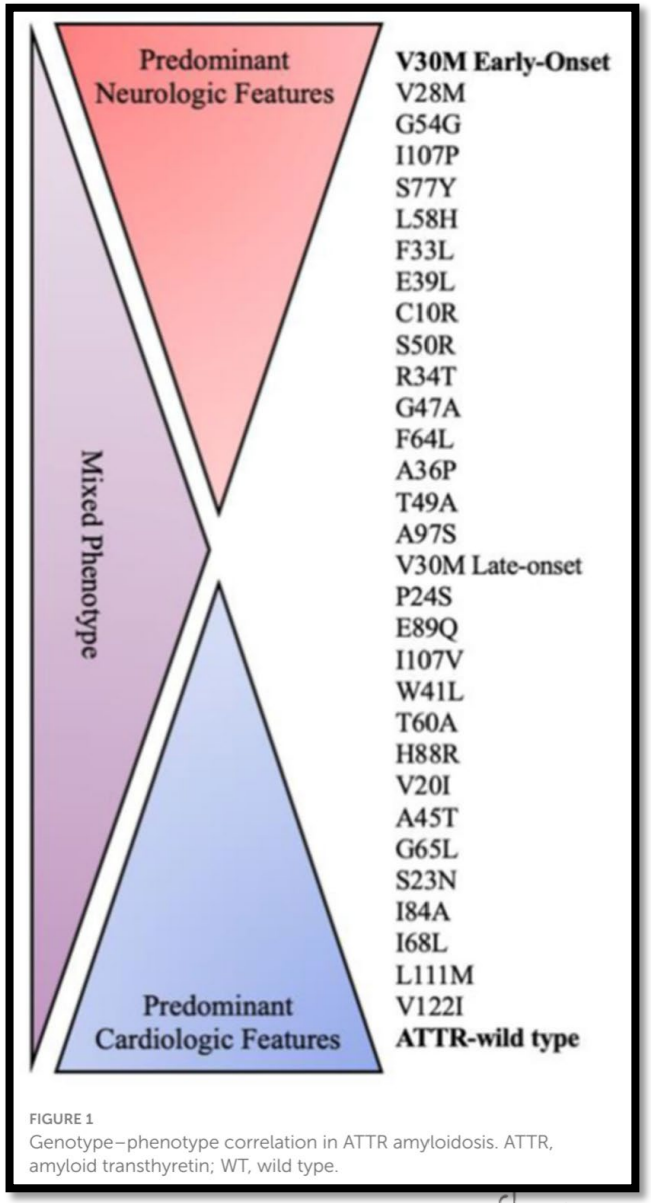


FIGURE 1
Genotype–phenotype correlation in ATTR amyloidosis. ATTR, amyloid transthyretin; WT, wild type.

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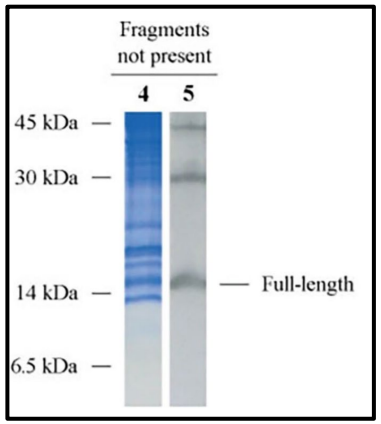
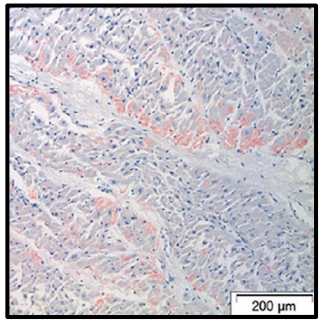
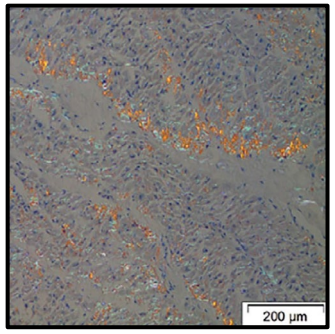
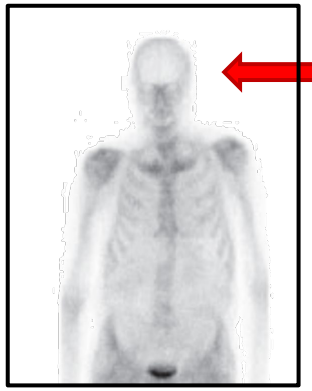


Type B: Long and thick

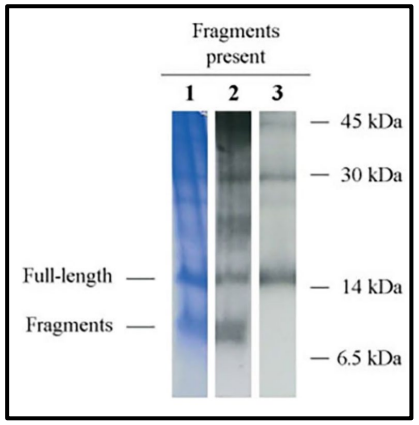
Small non myelinated fibres





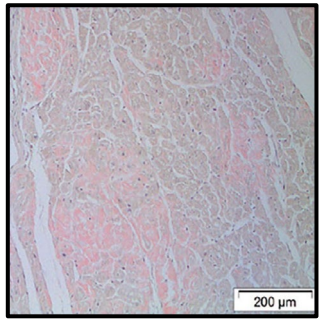


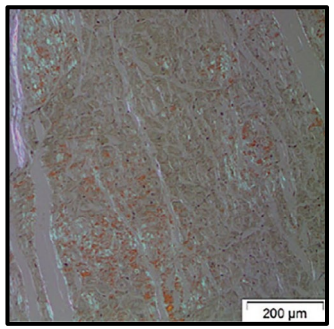
Some variants are associated with **false negatives on the 99mTc-DPD scintigraphy scan**, even in cases with cardiac involvement (**early-onset p.Val50Met**, p.Phe84Leu, p.Ser97Tyr).

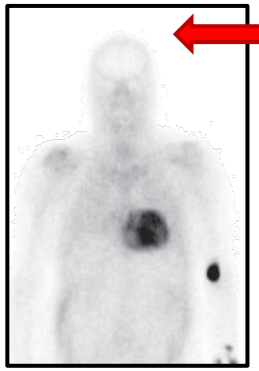


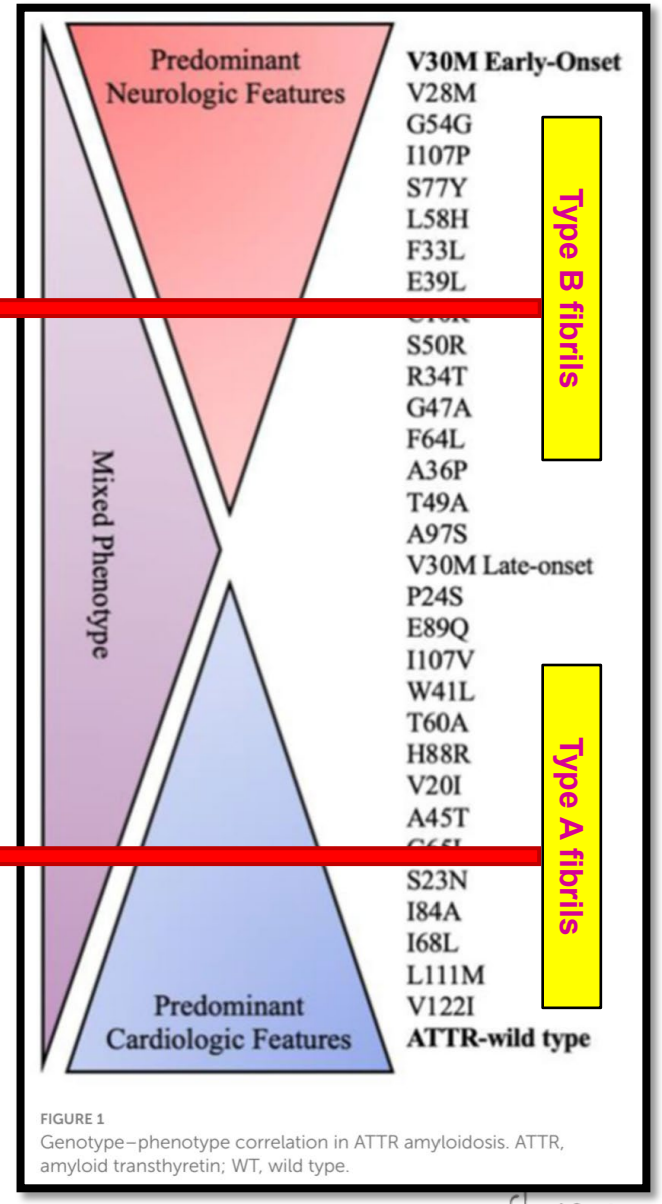
Type A: Short and thin

Large myelinated fibres









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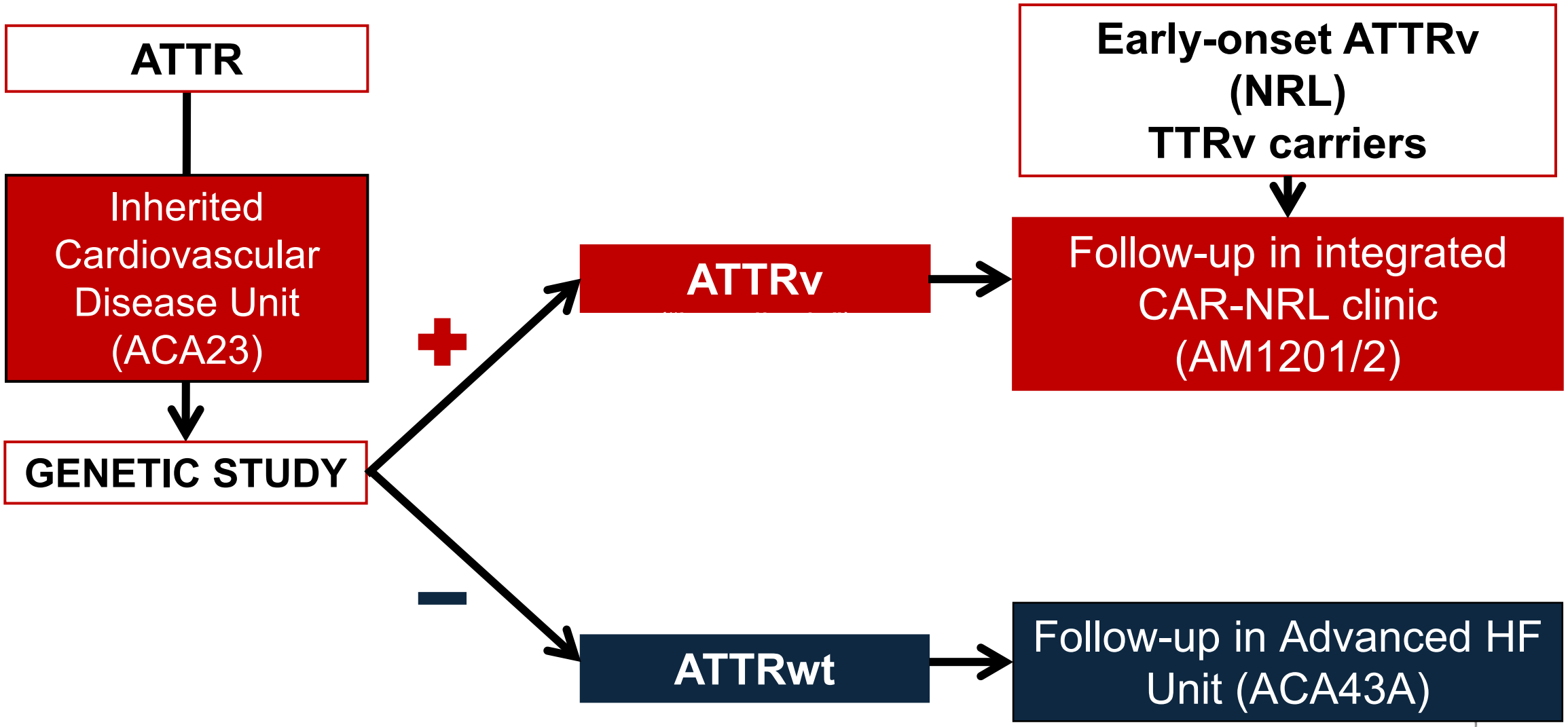
How do we do it?



Family Study and Asymptomatic Carriers of Pathogenic Variants

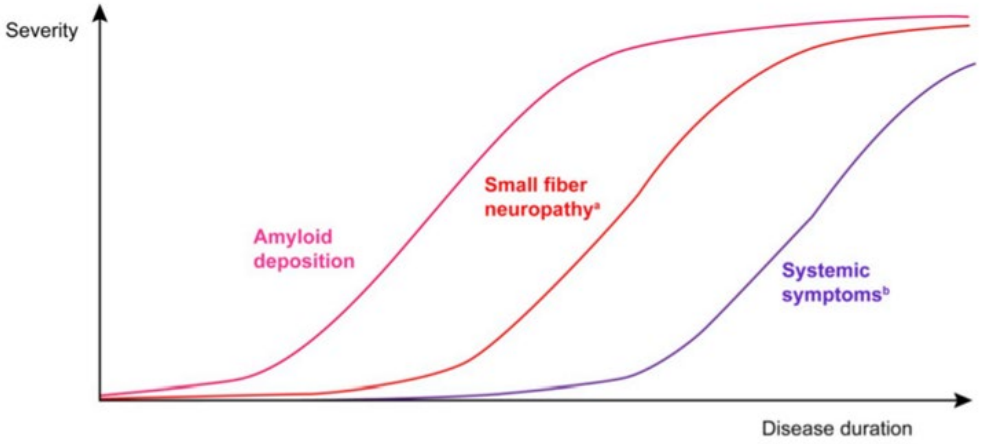
- In hereditary TTR amyloidosis, we do not see isolated patients, but **families**.
- The **age of presentation**, **phenotype**, **penetrance**, and **progression** depend on the specific variant.
- To decide when to initiate penetrance assessment in carriers, we are guided by the **specific variant** and the **age of onset in affected relatives** (**PADO**).

Table 2. Estimating the predicted age of disease onset in patients with ATTR amyloidosis.

Phenotype group	Genotype	Penetrance	Typical age of onset	Rate of progression
Neurologic	V30M early onset	>90%	<40 years	++++++
Neurologic/mixed	V30M late onset	>60%	>50 years	++++++
Cardiac	V122I	Unknown	55 years	++
	L111M	>90%	35–40 years	++
	T60A	>90%	55 years	++
	I68L	>90%	55 years	++
Mixed	S77Y	>90%	55 years	++++
	E89Q	>90%	50 years	++++
	G47E	>90%	30 years	++++++

The number of "+" provides an indication of how fast the disease progresses, with "+" representing slow progression of ATTR amyloidosis.

Amyloid deposition begins **before** the onset of symptoms**.** **Monitoring of carriers** is essential for early diagnosis.



Ueda, Mitsuharu et al. Journal of the neurological sciences vol. 414 (2020): 116813.

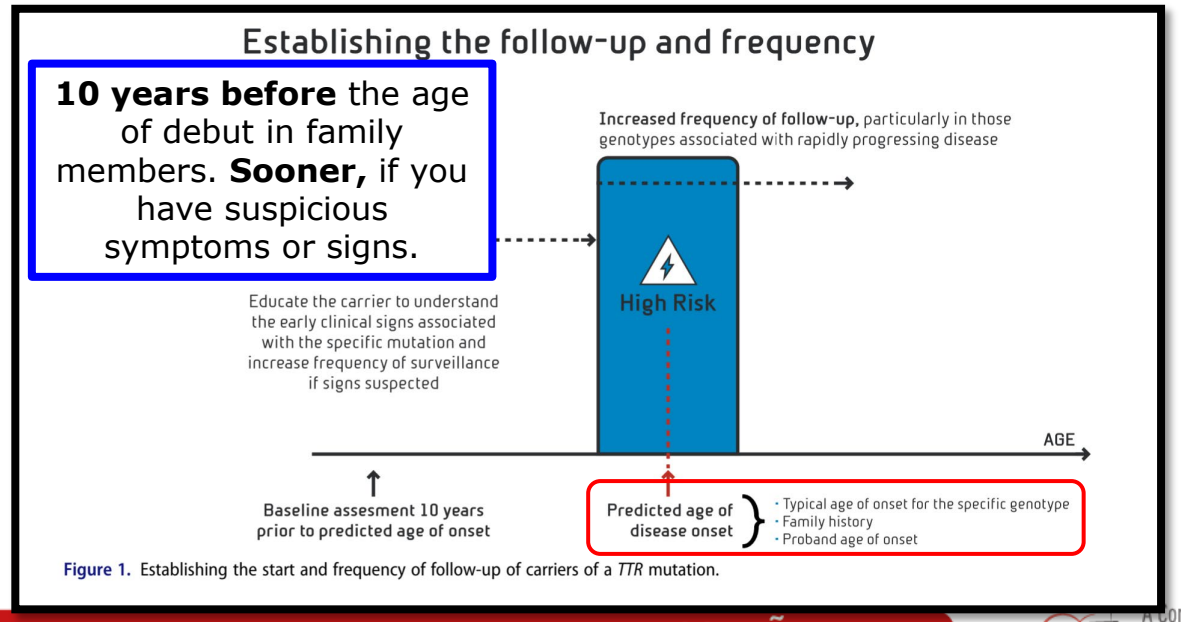


Figure 1. Establishing the start and frequency of follow-up of carriers of a *TTR* mutation.

Conceição, Isabel et al. the official journal of the International Society of Amyloidosis vol. 26,1 (2019): 3-9.

Follow-up of gene variant carriers

Evaluation	Frequency
Medical interview (sensation, movement, autonomic nerve function [orthostatic hypotension, gastrointestinal symptoms, and dysuria], weight loss, heart failure, arrhythmia, and eye symptoms)	**ANNUAL**
Physical examination (neurological, autonomic, cardiac, orthostatic test, NIS scales, mBMI)	**ANNUAL**
Neurological Evaluations: EMG/ENG and **Sudoscan**	**ANNUAL**
Ophthalmological examination	**ANNUAL**
Laboratory: NT-proBNP, Troponin, Creatinine, GFR, Albumin, Microalbuminuria.	**ANNUAL**
ECG	**ANNUAL**
Echocardiogram	**ANNUAL**
Holter-ECG	**Every 2 years**
DPD ± Cardiac MRI Scan **MIBG scan?**	**Every 3 years/if suspicion**
Biopsy (sural nerve, salivary gland, abdominal fat, skin, heart)	**If suspected and negative non-invasive diagnosis**
LIGHT-CHAIN NEUROFILAMENTS?	**ANNUAL?**

Asymptomatic ATTRv patients vs **asymptomatic TTRv carriers**

New tools in ATTRv

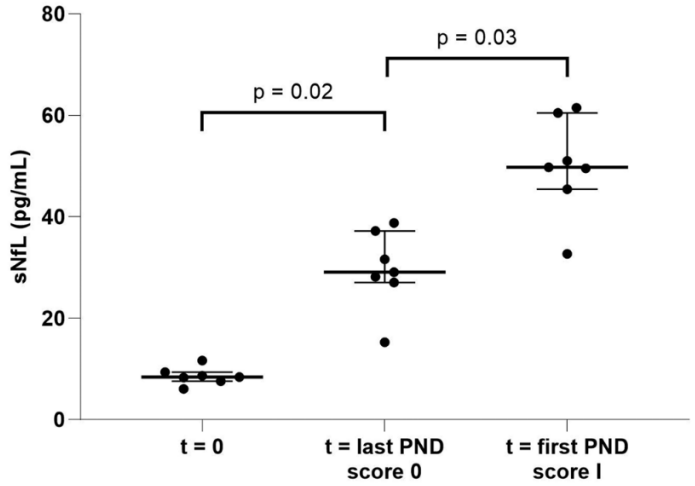
RESEARCH ARTICLE

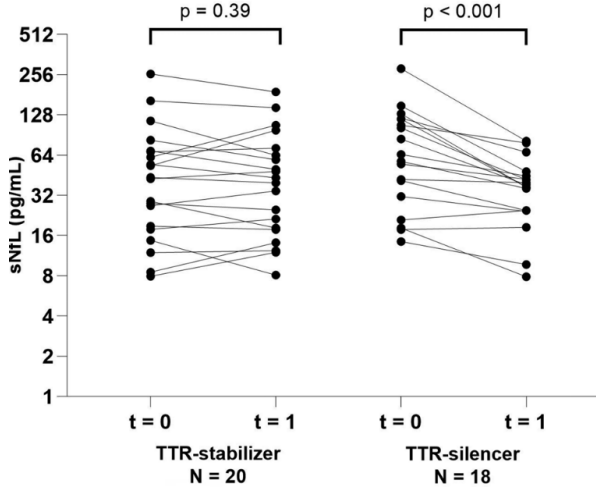
OPEN ACCESS

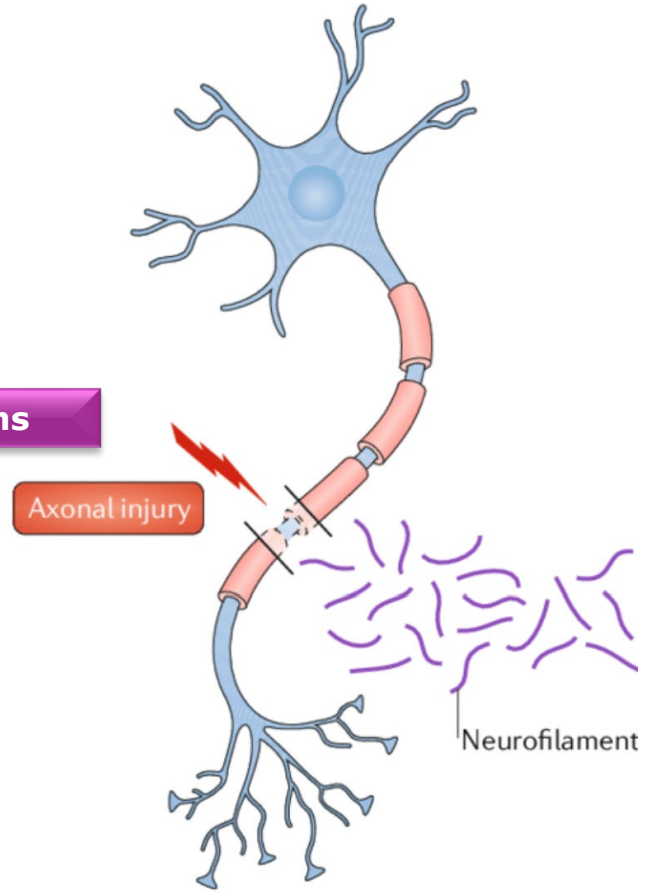
Check for upd

Longitudinal analysis of serum neurofilament light chain levels as marker for neuronal damage in hereditary transthyretin amyloidosis

- Elevated sNfL levels identify **asymptomatic ATTRv patients**.
- **Clinical progression** correlates with sNfL progression.
- **Stabilizers stabilize** sNfL; **silencers reduce** sNfL.







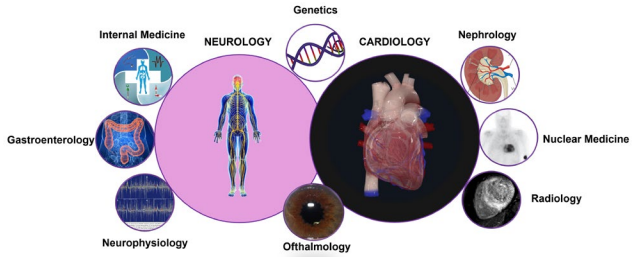
Berends, Milou et al. Amyloid : the international journal of experimental and clinical investigation : the official journal of the International Society of Amyloidosis vol. 31,2 (2024): 132-141.

Genetics are a must in ATTR!!

DIAGNOSIS (ATTRv vs ATTRwt)

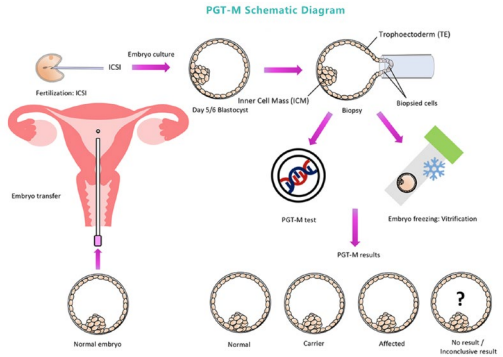
CARRIERS

FOLLOW-UP

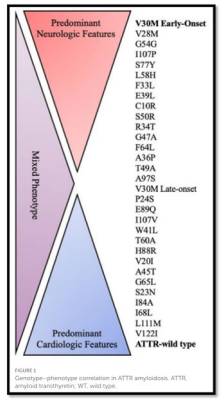


TREATMENT

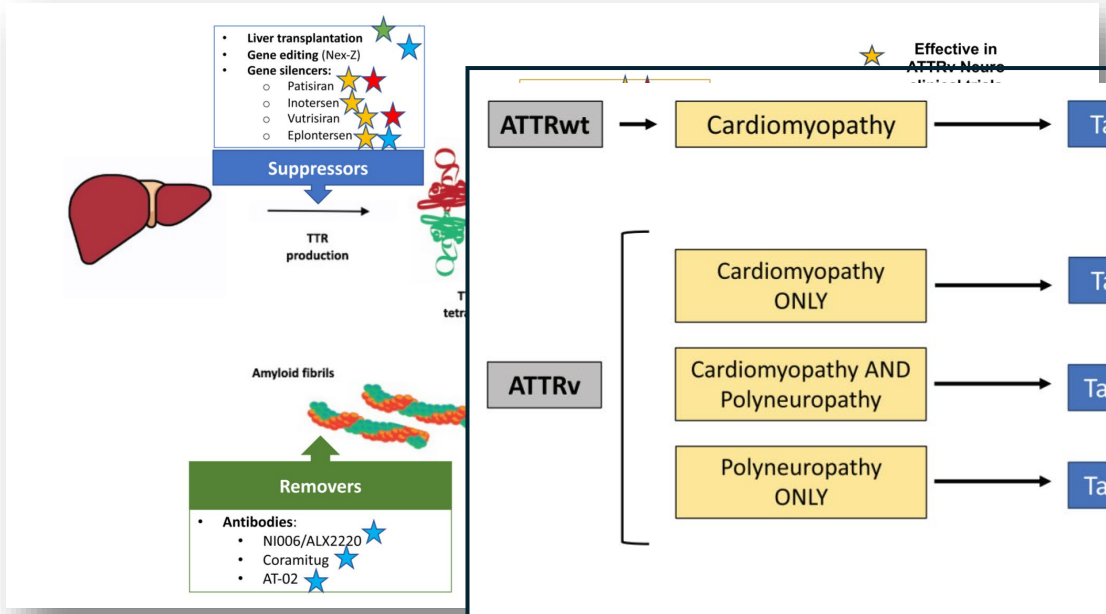
GENETIC COUNSELING/REPRODUCTIVE PLANNING



PROGNOSIS



Genetics are a must in ATTR!!

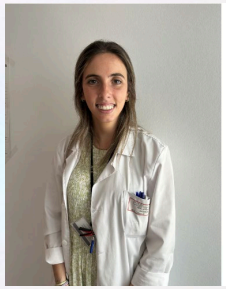


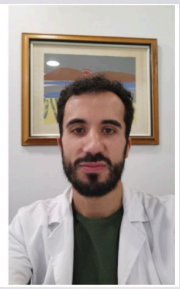
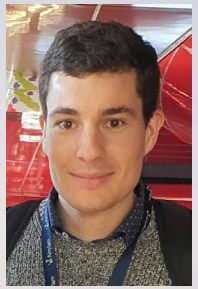
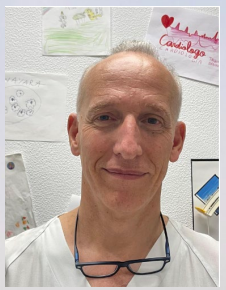
PATISIRAN: APOLLO A / B
NEUROTTR
: HELIOS A / B
N: NEURO / CARDIO-TTRansform*
S: ATTRibute-CM /ACT-EARLY*
-ZICLUMERAN: MAGNITUDE*

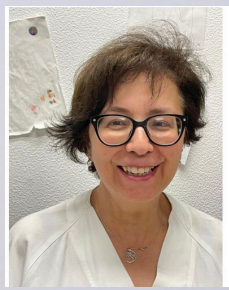
TREATMENT

Gonzalez-Lopez, Esther et al. "Transthyretin amyloid cardiomyopathy: a paradigm for advancing precision medicine." European heart journal vol. 46,11 (2025): 999-1013

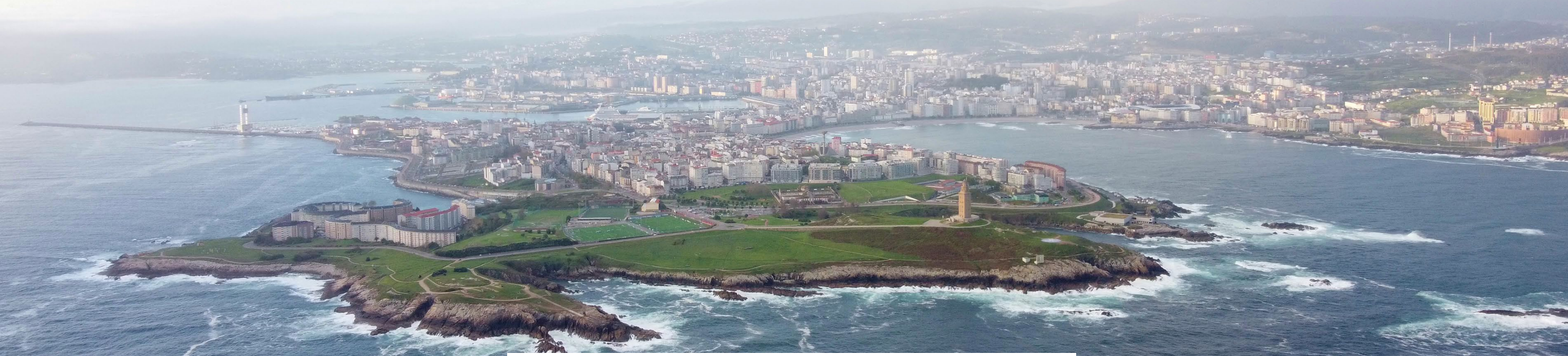







¡MUCHAS GRACIAS POR LA ATENCIÓN!



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Instituto de Salud Carlos III

SERVIZO GALEGO de SAÚDE

Complexo Hospitalario Universitario A Coruña

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