XI Reunión. Estado del Arte en
INSUFICIENCIA CARDIACA
PRÁCTICA CLÍNICA Y MODELOS ORGANIZATIVOS
Sede: Hotel Meliá MaríaPita, A Coruña
A CORUÑA 27-28 SEPTIEMBRE 2024

XI Meeting. State of the Art in
HEART FAILURE
CLINICAL PRACTICE AND ORGANIZATIONAL MODELS
Venue: Hotel Meliá MaríaPita, A Coruña
# ACoruñaHF2024
A CORUÑA 27-28 SEPTEMBER 2024

# 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*

# WHAT TO LOOK FOR?

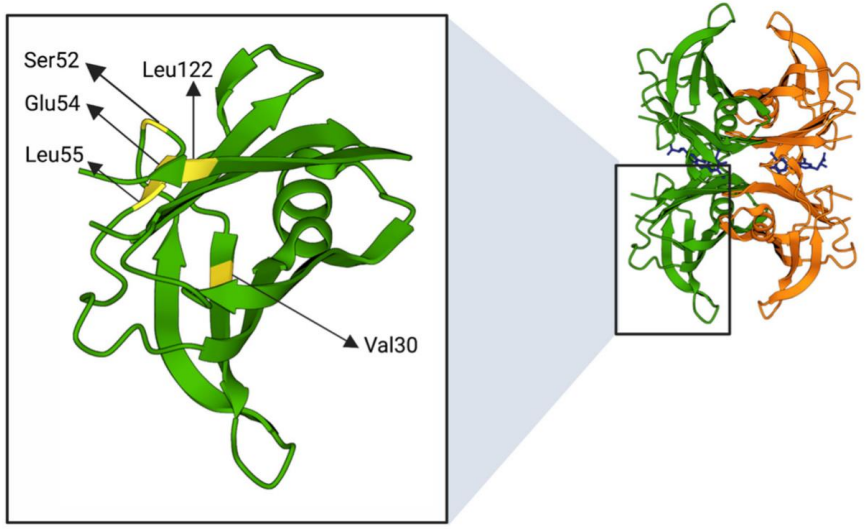
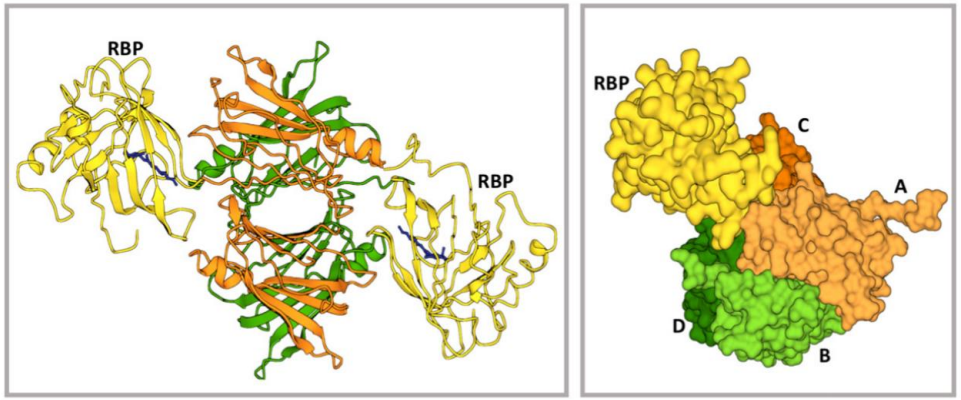



**Figure 4.** Positions of amino acids (highlighted in yellow) subjected to mutations described in Table 1. The figure was created through "www.rcsb.org" and "biorender.com" web sites (license agreement number KJ247URGZS), access date 22 June 2022.

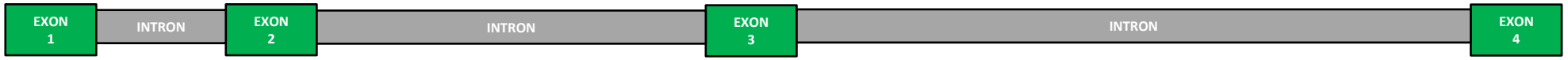
- **Human TTR** is a protein encoded by a single gene located on chromosome 18q.
- **Mature protein has 127 amino acids**. Pro-TTR monomers have 147 amino acids (including a 20-amino acid signal peptide). The current nomenclature, according to the Human Gene Organization, includes this peptide.
- **ATTRv**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

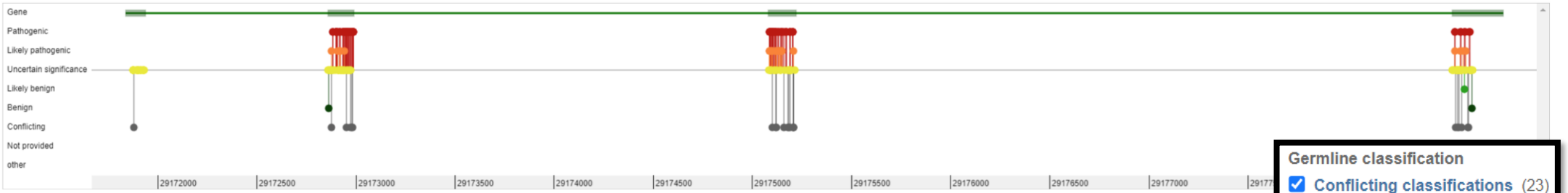





*Sanguinetti, Chiara et al. Biomedicines vol. 10,8 1906. 6 Aug. 2022 // Sekijima Y, Nakamura K. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.*

# WHAT TO LOOK FOR?

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Filters activated: Conflicting classifications, Benign, Likely benign, Uncertain significance, Likely pathogenic, Pathogenic, Missense. Clear all to show 42

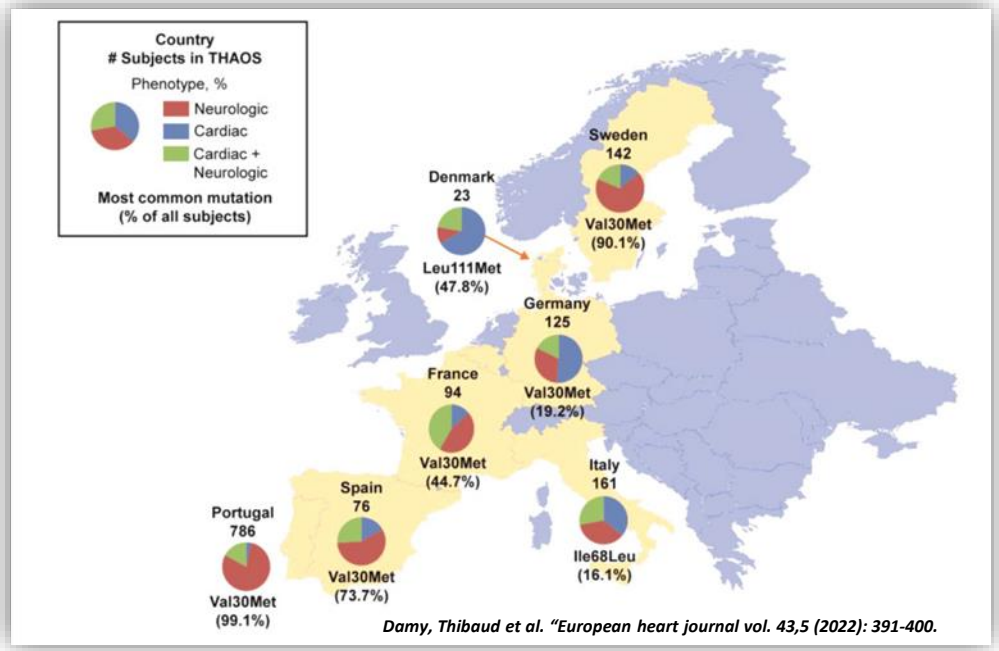
**216 missense variants in TTR (ClinVar)**

Germline classification
- Conflicting classifications (23)
- Benign (2)
- Likely benign (3)
- Uncertain significance (81)
- Likely pathogenic (54)
- Pathogenic (83)

| | | | | | |
|---|---|---|---|---|---|
| ☐ | 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 ★★ |

# ATTRv around the world

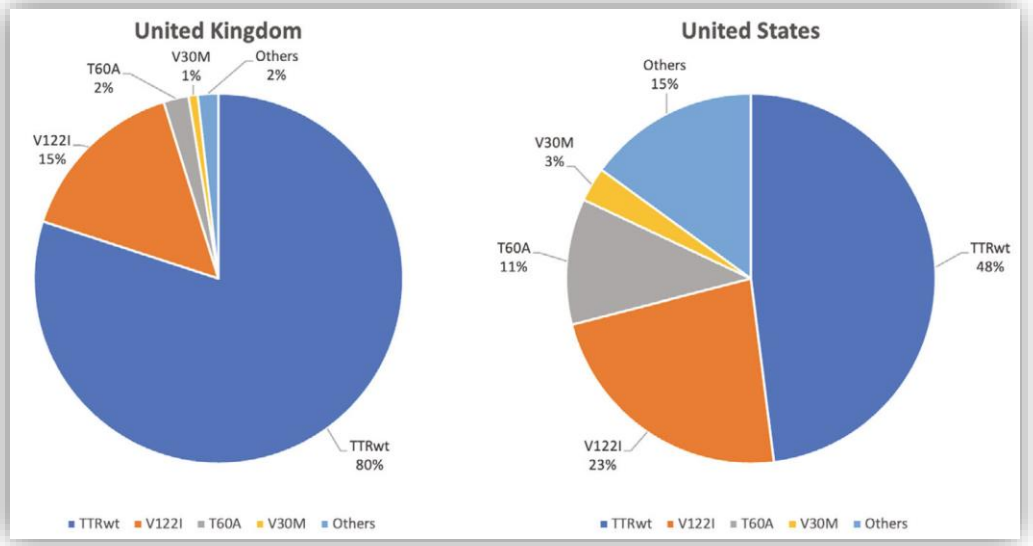
- Estimated **prevalence** of **1/1.000.000**.
- **Endemic foci**: Portugal (almost 1/500), Sweden, Brazil, Japan and 2 regions in Spain (Mallorca and Huelva).
- **Typical phenotype** for specific **variants**, but **geographical area** also matters.




*Damy, Thibaud et al. "European heart journal vol. 43,5 (2022): 391-400.*

**p.Val50Met**

- Most common pathogenic variant worldwide
- Most frequent in Europe, South America and Japan.
- **Early-onset** phenotype in endemic areas in Japan and Portugal. **Late-onset** in the rest.




*Porcari, Aldostefano et al. European journal of heart failure vol. 25,4 (2023): 515-524.*

**p.Val142Ile**

- Most frequent in USA y UK, mainly in people with black ancestry.
- Predominantly cardiac phenotype.



*Adams, David et al. Journal of neurology vol. 268,6 (2021): 2109-2122 // Gentile, Luca et al. Orphanet journal of rare diseases vol. 18,1 350. 10 Nov. 2023. // Sekijima Y, Nakamura K. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.*

# ATTRv in Spain

| *Mutaciones* | |
|---|---|
| Val50Met | 120 (67,8) |
| Val142Ile | 22 (12,4) |
| Glu109Lys | 14 (7,8) |
| Ser97Tyr | 6 (3,4) |
| Val122Del | 4 (2,2) |
| Ser43Asn | 2 (1,1) |
| Asp38Asn | 2 (1,1) |
| Val71Ala | 1 (0,5) |
| Glu89Gln | 1 (0,5) |
| Ala65Thr | 1 (0,5) |
| Thr80Ala | 1 (0,5) |
| Leu32Pro | 1 (0,5) |
| Glu74Gln | 1 (0,5) |
| Ala128Val | 1 (0,5) |




The most frequent variant in **Spain** is **p.Val50Met**, not only in the two endemic areas, but in the others.

The typical form in Spain is the **late-onset phenotype** (vs Portugal).



*Álvarez Rubio, Jorge et al. "Characterization of hereditary transthyretin cardiac amyloidosis in Spain." Revista española de Cardiología (English ed.) vol. 75,6 (2022): 488-495.*

# 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**.

**ALWAYS**

UK

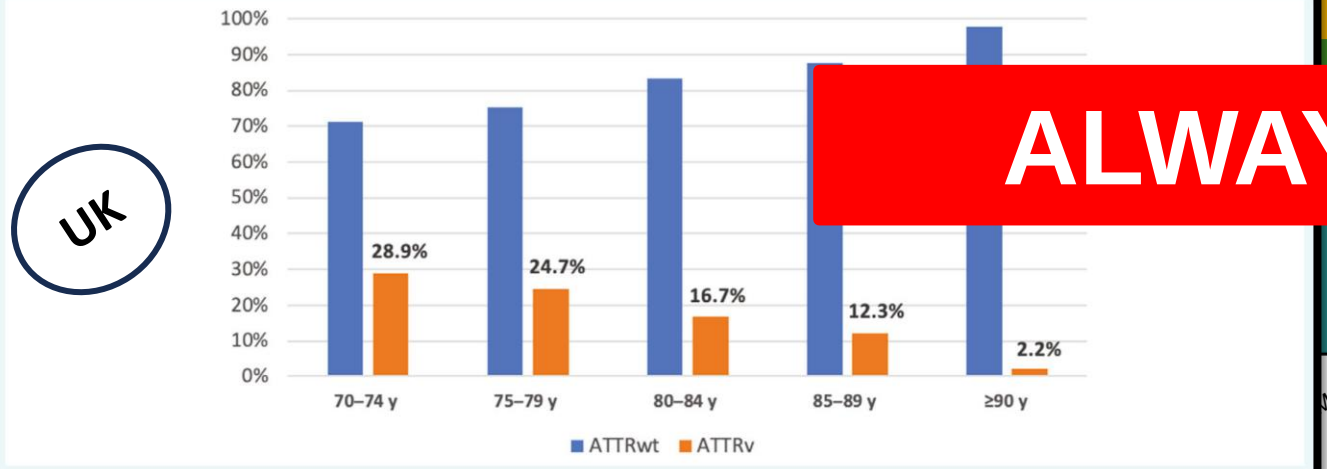



**Figure 1** Trends in diagnosis of variant transthyretin amyloid cardiomyopathy (ATTRv-CM) according to age ranges at diagnosis. ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; y, years.

*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.*

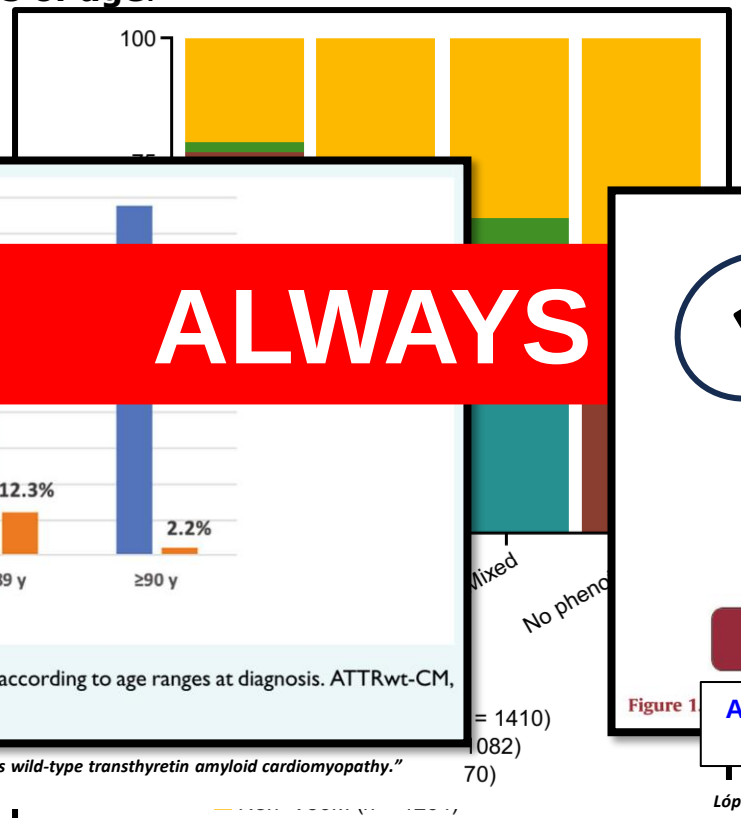
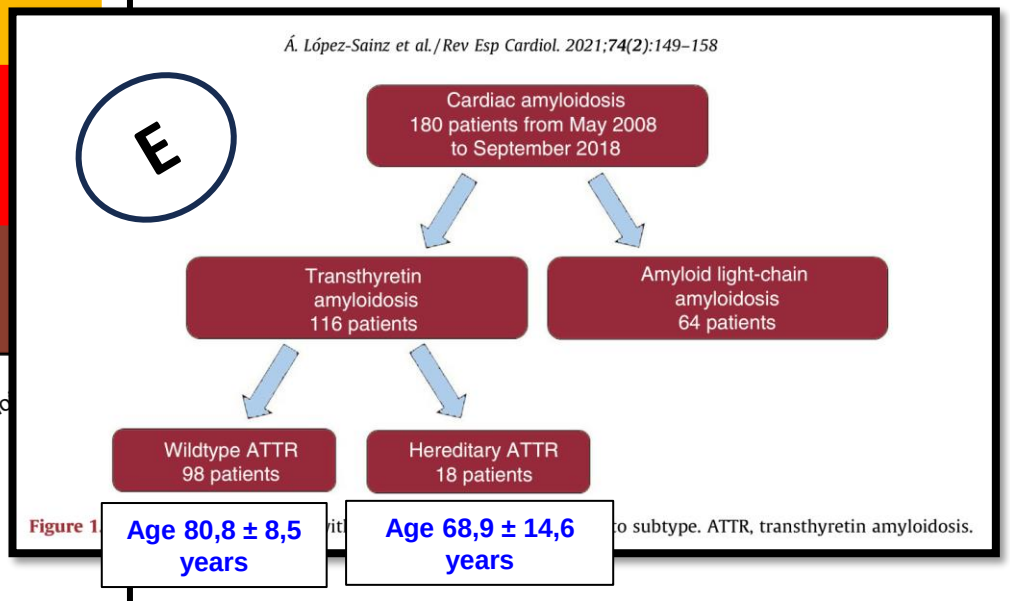



**Fig. 4** Distribution of phenotype at enrollment in symptomatic patients according to genotype category. The proportions of patients with each phenotype are shown by genotype. ATTRwt amyloidosis = wild-type transthyretin amyloidosis

E




*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.*



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*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**.

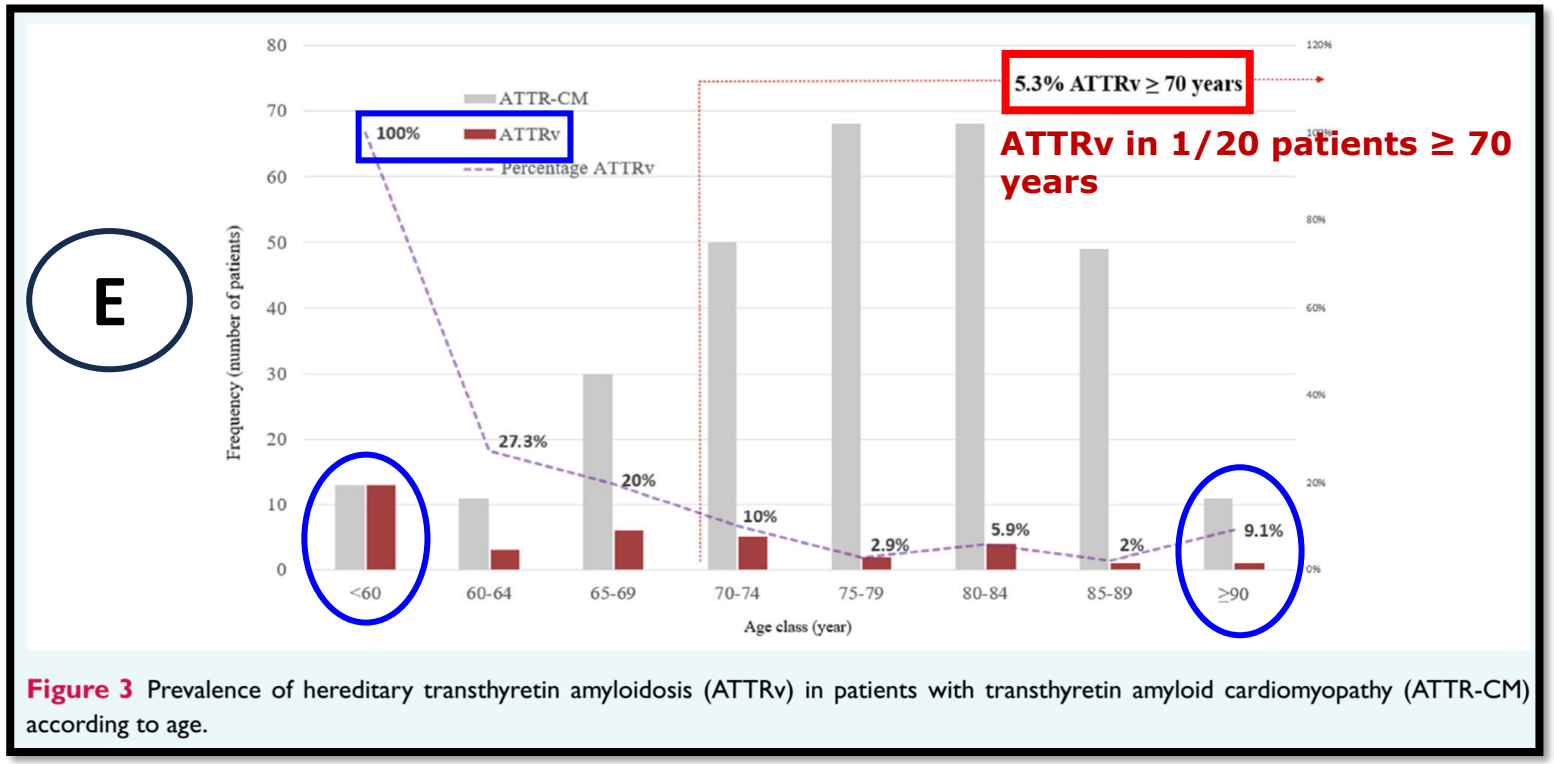



**Figure 3** Prevalence of hereditary transthyretin amyloidosis (ATTRv) in patients with transthyretin amyloid cardiomyopathy (ATTR-CM) according to age.

- **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%**.
- Eldest 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.*

# 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**.

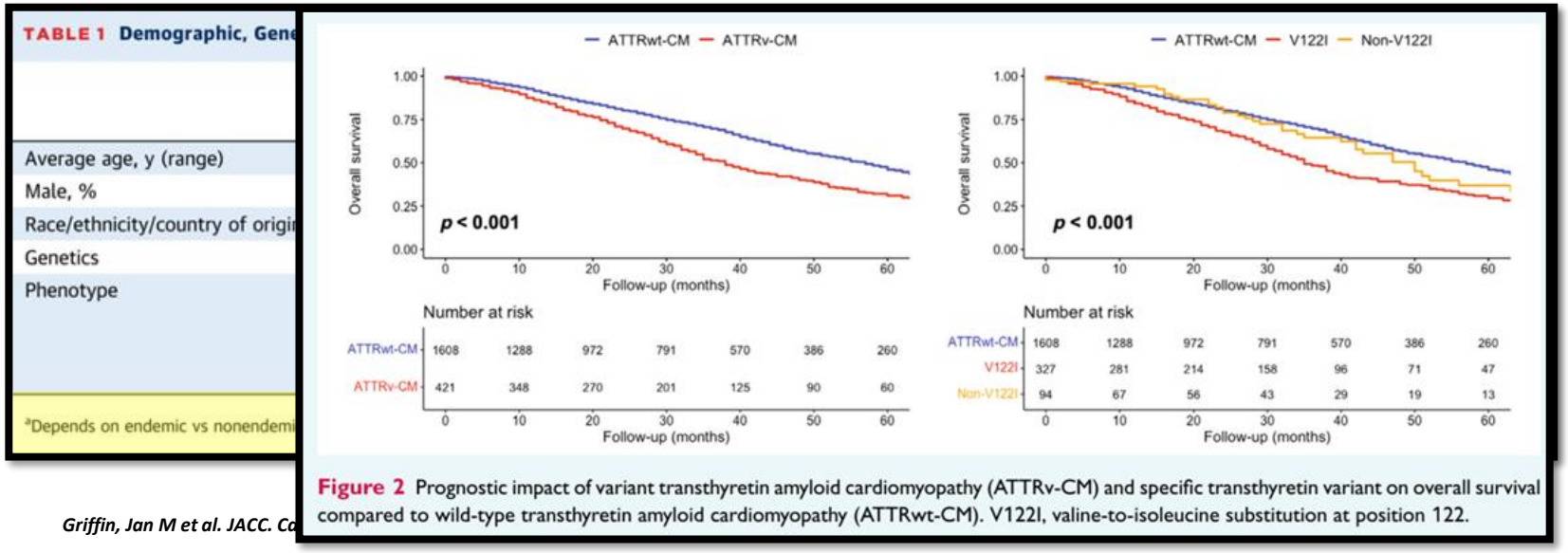
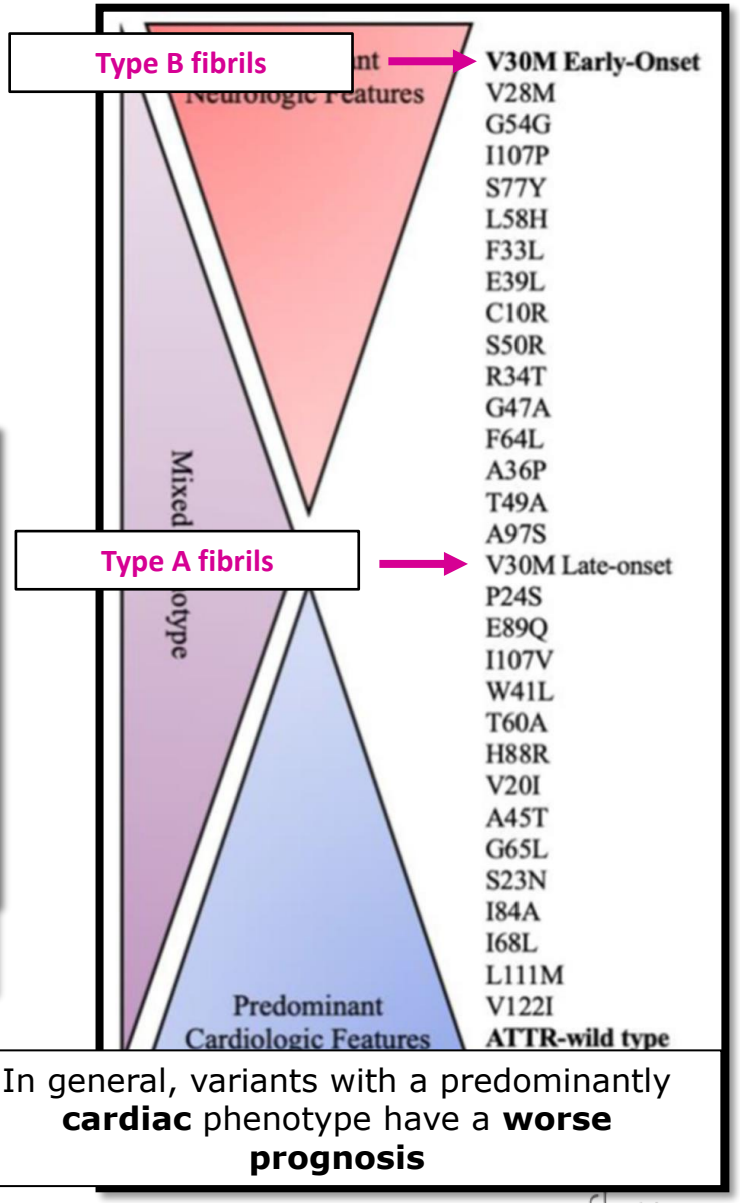



**Figure 2** Prognostic impact of variant transthyretin amyloid cardiomyopathy (ATTRv-CM) and specific transthyretin variant on overall survival compared to wild-type transthyretin amyloid cardiomyopathy (ATTRwt-CM). V122I, valine-to-isoleucine substitution at position 122.

*Griffin, Jan M et al. JACC. Ca*

*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.*




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



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*Poli, Loris et al. "Hereditary transthyretin amyloidosis: a comprehensive review with a focus on peripheral neuropathy." Frontiers in neurology vol. 14 1242815. 5 Oct. 2023*

# Family Study and Asymptomatic Carriers of Pathogenic Variants

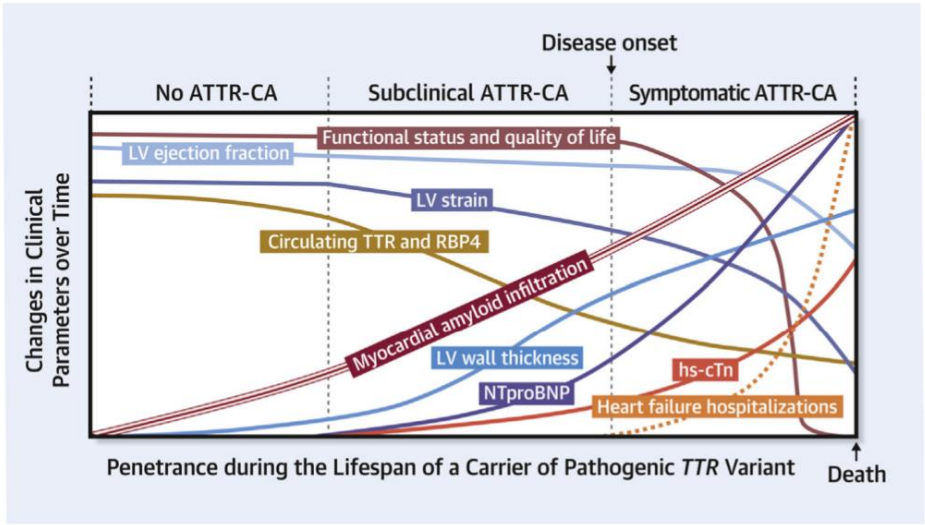
- In hereditary TTR amyloidosis, we do not see isolated patients, but **families**.
- The **age of presentation**, **phenotype**, **penetrance**, and **progression** depend on the particular variant.
- To decide when to initiate penetrance assessment in carriers, we are guided by the **specific variant**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

**FIGURE 2** Proposed Natural History of Penetrance in Carriers of Pathogenic *TTR* Variants




*Griffin, Jan M et al. JACC. CardioOncology vol. 3,4 488-505. 19 Oct. 2021*

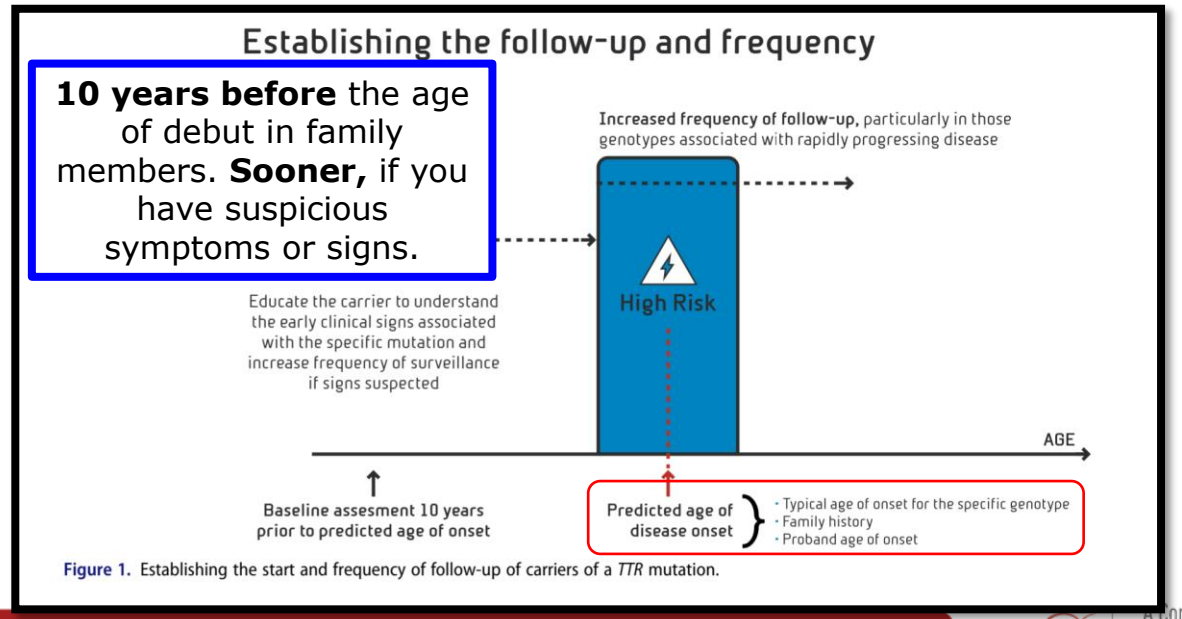



**Figure 1.** Establishing the start and frequency of follow-up of carriers of a *TTR* mutation.

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

# Genetics are a must in ATTR!!

**CARRIERS**

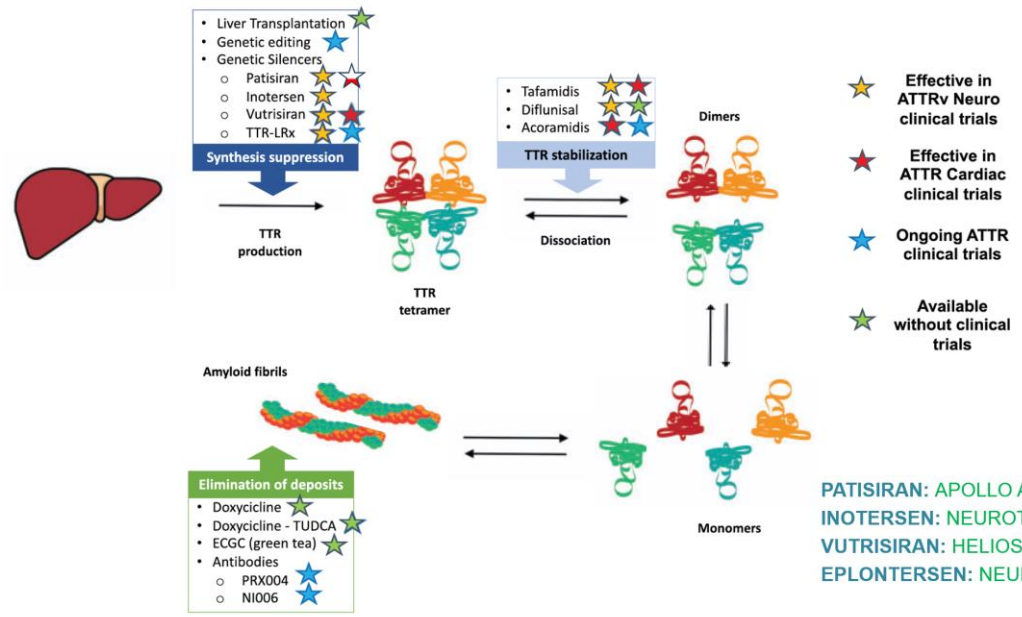
**DIAGNOSIS (ATTRv vs ATTRwt)**

**PROGNOSIS**

**TREATMENT**

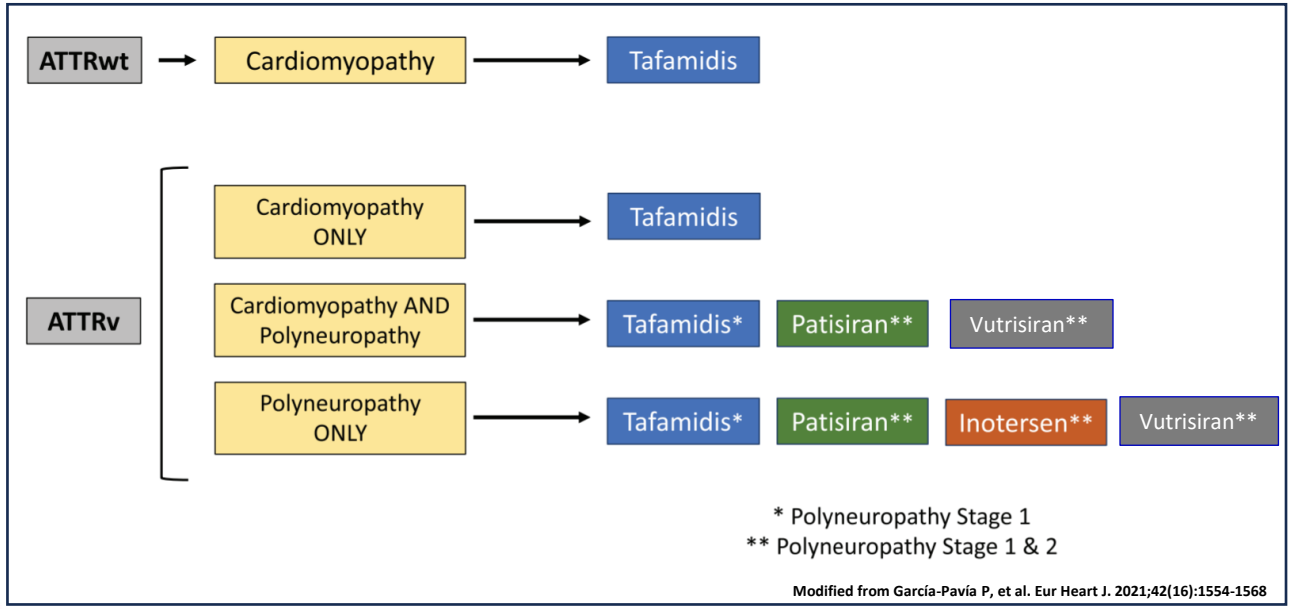
**FOLLOW-UP**

**GENETIC COUNSELING**




PATISIRAN: APOLLO A / B
INOTERSEN: NEUROTTR
VUTRISIRAN: HELIOS A / B
EPLONTERSEN: NEURO / CARDIO-TTRansform

Modified from García-Pavía P, et al. Eur Hear J. 2021;42:1554-1568.

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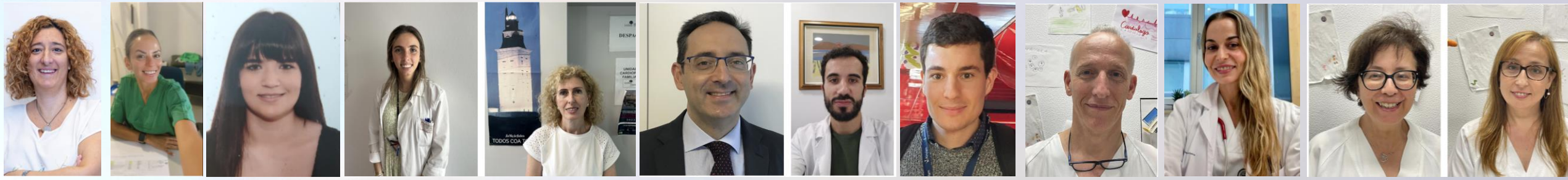

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