ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

Session 2: Susceptibility to Amyloidoses and Screening Approaches

Chairs: Kevin Alexander, Taxiarchis Kourelis, Efstathios Kastritis

Faculty: Paolo Milani, Martha Grogan, Raymond Comenzo, Yoshiki Sekijima, Andrea Cortese, Frederick Ruberg, Justin Grodin, Lukas Weberling

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Early *rule in* in hematology

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Fondazione IRCCS Policlinico San Matteo

Sistema Socio Sanitario

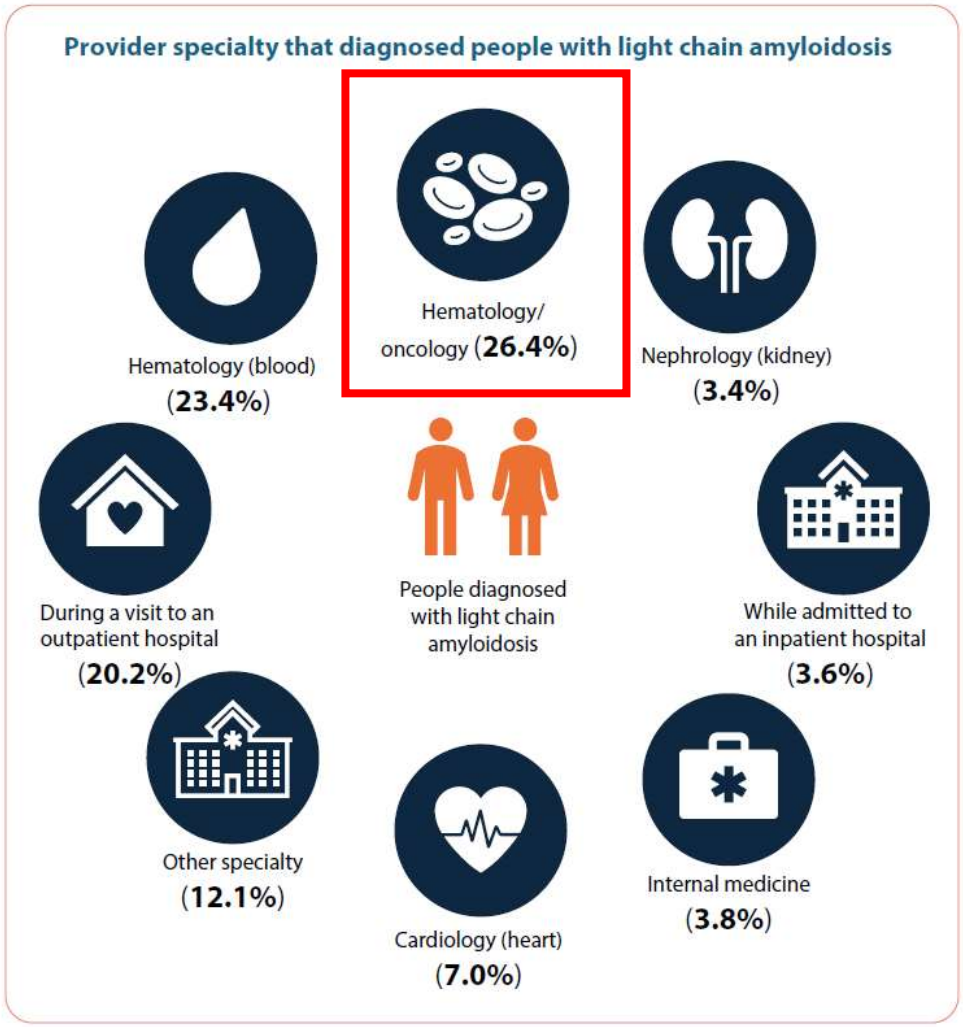
Regione Lombardia

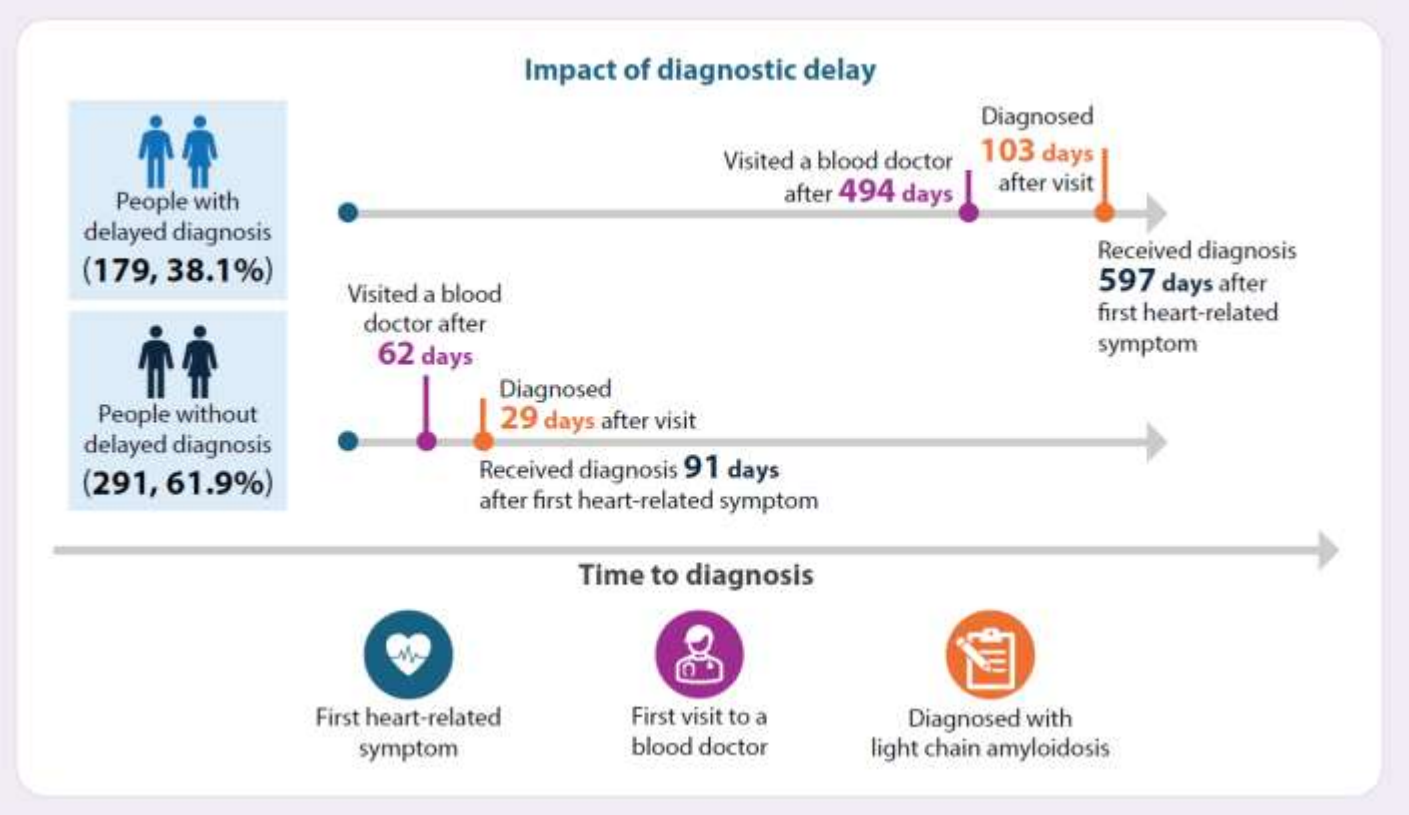
UNIVERSITÀ DI PAVIA

Disclosures

- Jannsen-Cilag (Honoraria)
- Siemens (Advisory Board)
- Pfizer (Honoraria, research grant)
- Prothena (Honoraria)
- Sebia (Honoraria)
- Bayer (Advisory Board, honoraria)

AL amyloidosis: The journey to Diagnosis





In the 2 years before being diagnosed with light chain amyloidosis, 72% of people visited heart doctors.

Lyons, et al. Future Cardiol 2025

2023 ACC Expert Consensus Decision Pathway

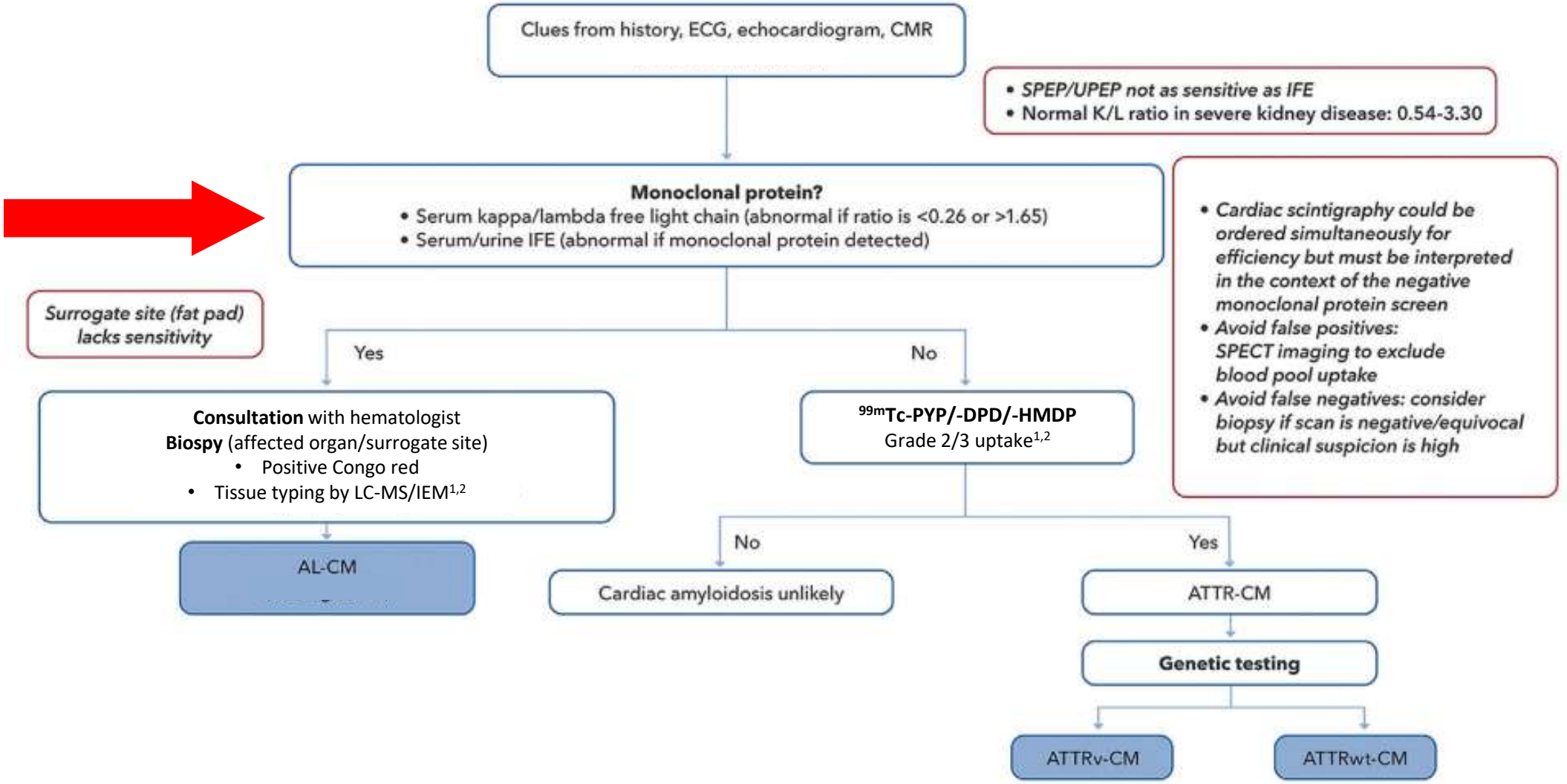
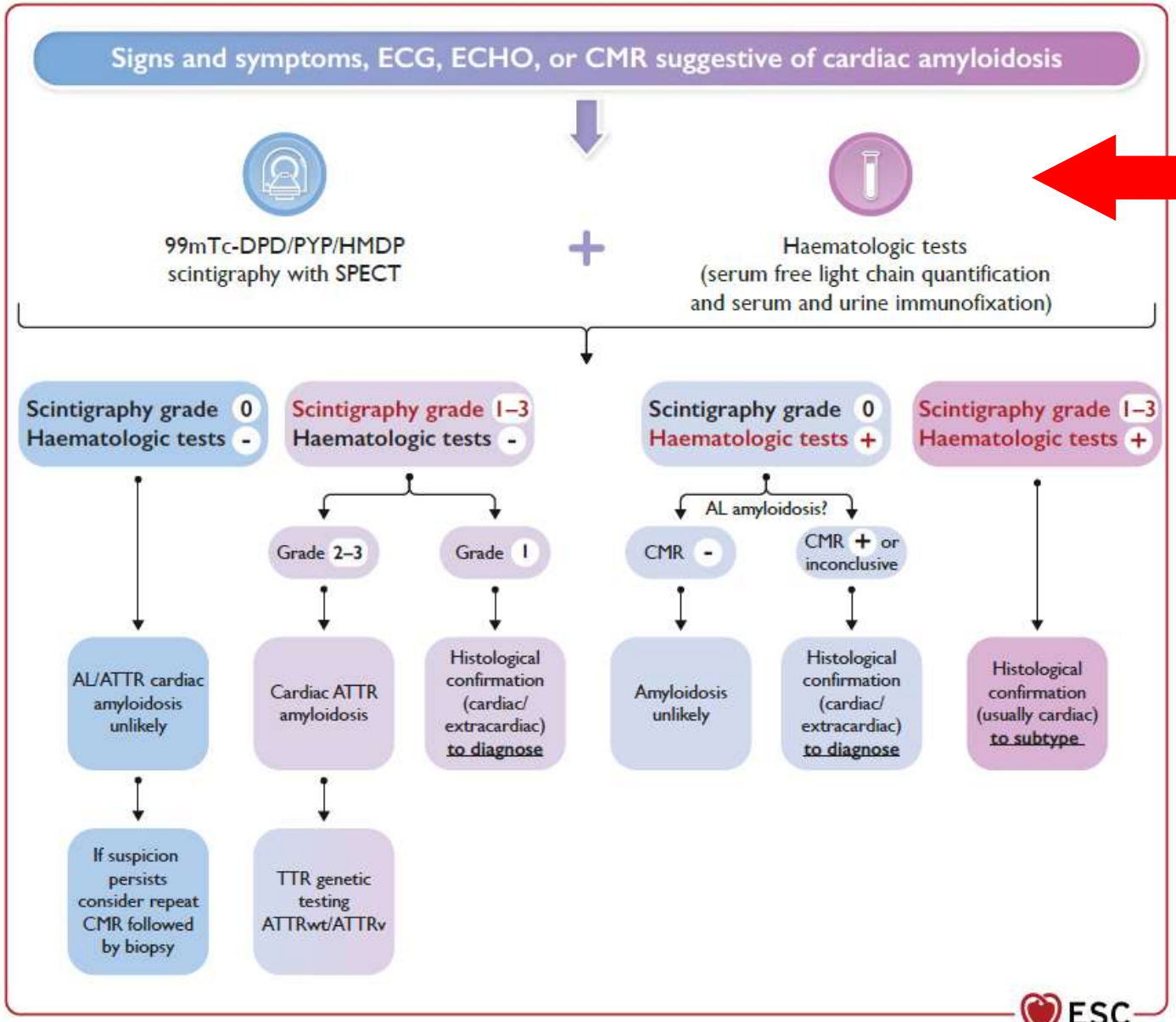


Image adapted from Kittleson MM, et al. JACC 2023

2023 ESC Guidelines for the management of cardiomyopathies



Arbelo, et al. Eur Hearet J 2023

Sequence of testing is essential!

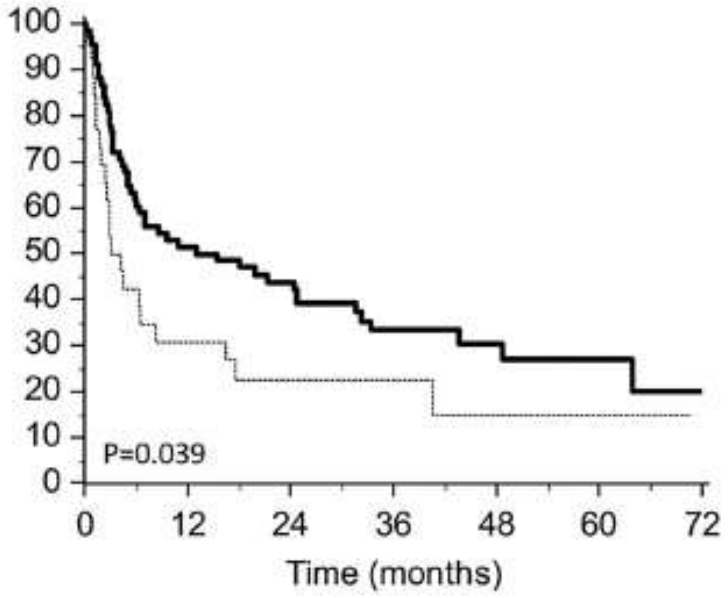


Figure 1. Survival of 94 patients with isolated cardiac AL amyloidosis according to the time interval between first clinical suspicion and M-LC studies. Bold line: patients that underwent M-LC studies <6 weeks after suspicion. Dotted line: patients that underwent MC-studies >6 weeks after suspicion.

Non-Biopsy Diagnosis of ATTR Cardiac Amyloidosis
The four Essential Criteria

1

APPROPRIATE CLINICAL SUSPICION

Common features: Heart failure, bilateral carpal tunnel syndrome, biceps tendon rupture, spinal stenosis, arrhythmias, conduction system disease, orthostatic hypotension, peripheral or autonomic neuropathy (hereditary ATTR)

Demographic clues: Typically, >60 years old (wild-type) and more common in individuals of African-Caribbean ancestry with hereditary variants (e.g., V122I).

Red flags: Disproportionate wall thickening without hypertension, low voltage on ECG despite increase wall thickness

2

CHARACTERISTIC FINDINGS ON CARDIAC IMAGING

Echocardiogram:

- Increased LV wall thickness (>12 mm)
- Small LV cavity size
- Diastolic dysfunction
- Apical sparing ("bulls-eye") strain pattern
- Biatrial enlargement

Cardiac MRI findings:

- Diffuse late gadolinium enhancement
- Abnormal myocardial nulling
- Elevated extracellular volume (ECV) fraction

3

POSITIVE CARDIAC SCINTIGRAPHY[1]

Planar uptake grade ≥2,

H/CL[2] ≥1.5 (1hr)or ≥1.3 (3hr)

AND

Confirmed myocardial uptake by SPECT imaging

Cardiac Biopsy should be considered if typical imaging findings are absent or high clinical suspicion with negative cardiac scintigraphy

[1]Bone-avid tracers: DPD, PYP, HMDP image according to current society guidelines, which are evolving. Some centers no longer perform planar imaging.

[2]Heart to Contralateral Chest ratio

4

ABSENCE OF A MONOCLONAL PROTEIN

Required tests: Serum FLC[3] assay, serum and urine **immunofixation**[4]

Hematology input recommended for test interpretation

Diagnosis of CA ATTR via cardiac scintigraphy **is invalid** if a monoclonal protein is detected - tissue biopsy required

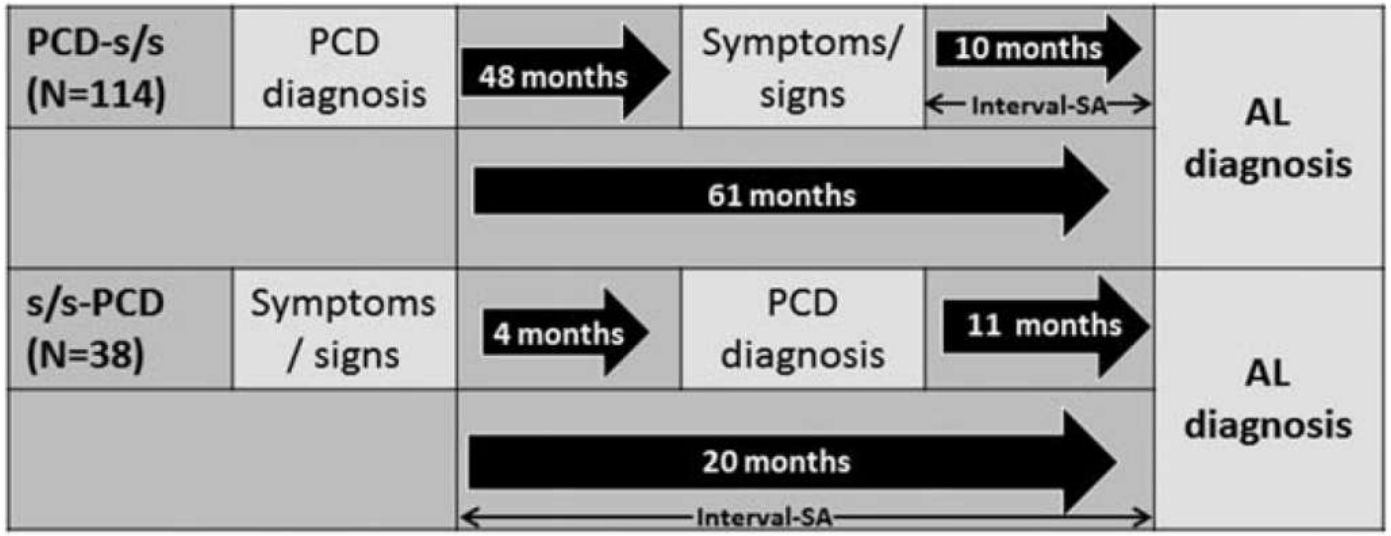
[3]Free light chain

[4]Protein electrophoresis alone or with "reflex" immunofixation is not adequate

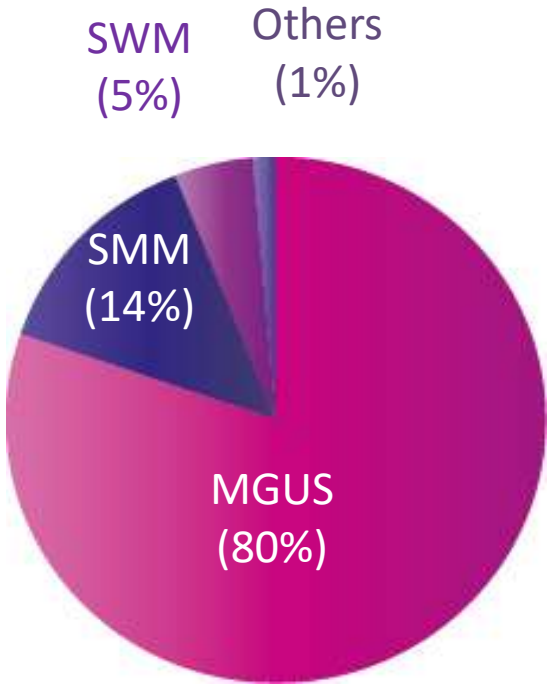
Milani, et al. Amyloid 2024

Muchtar, et al. Amyloid 2025

AL amyloidosis: The journey to Diagnosis



PCD: plasma cell dyscrasia, **AL:** Immunoglobulin light chain amyloidosis.
Interval SA : interval between symptoms/abnormal laboratory values and amyloid



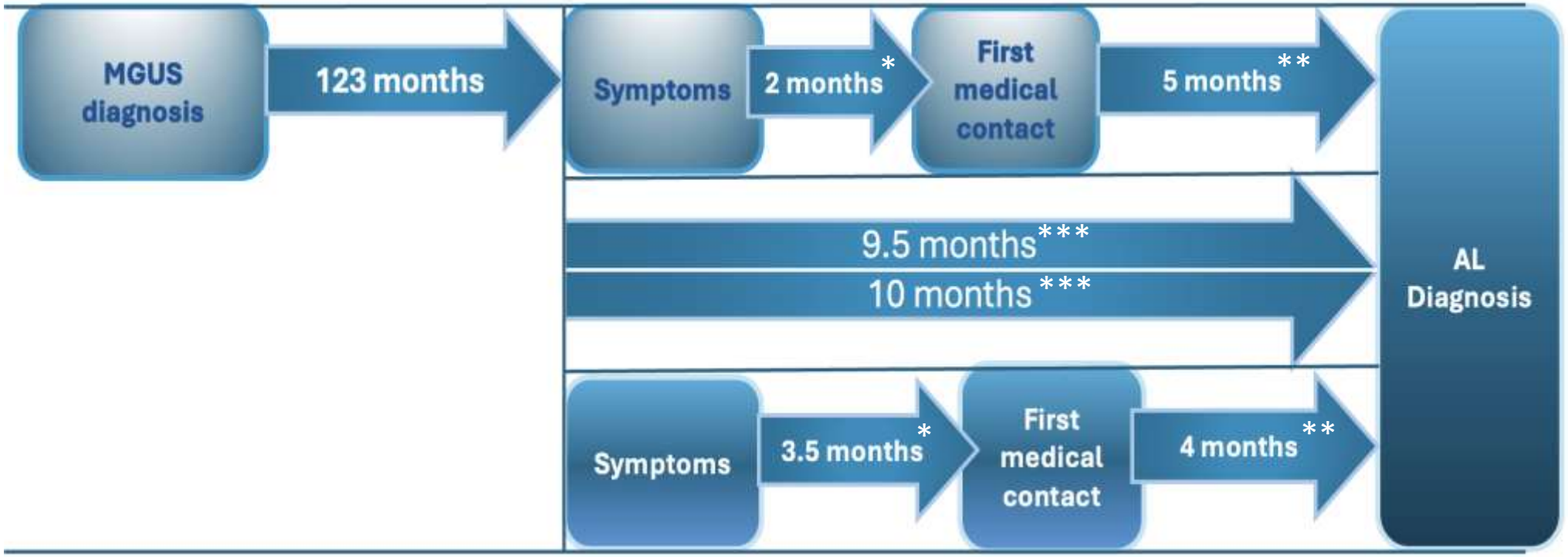
152 pts with monoclonal gammopathy

AL amyloidosis is diagnosed late also in patients with a known monoclonal gammopathy followed by a hematologist

Kourelis et al. Am J Hematol 2014

AL amyloidosis: The journey to Diagnosis

Pavia Amyloidosis center cohort of 937 patients diagnosed from 2016 to 2023



*P<0.001
** P =0.987
***P=0.754

Manuscript in preparation, do not post

Is screening possible for early rule in strategy?

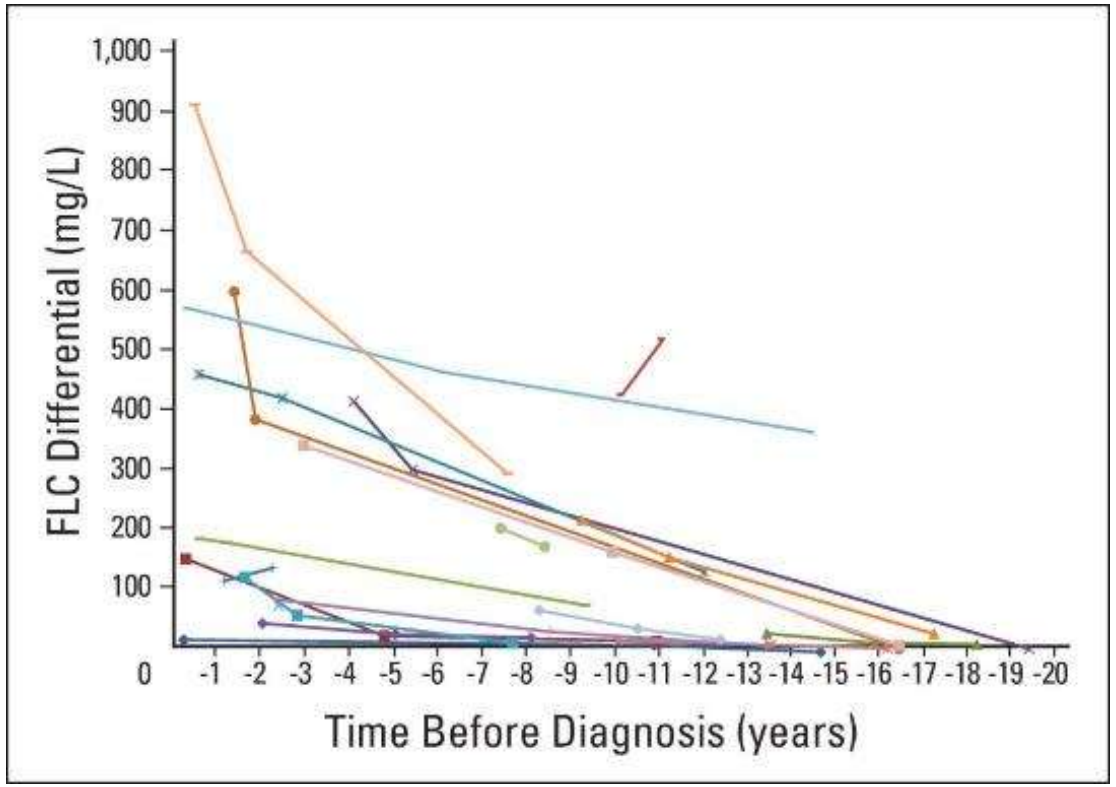
Populations at risk

- Lambda isotype (~80%)
- LC germline gene: IGLV6-57 (kidney), IGKV1 (soft tissue), IGLV1-44 and IGLV3 (heart)
- N-glycosylation of kappa LC in specific regions
- 98% of patients with a known pre-existing MGUS have abnormal FLCR

Comenzo, et al. Blood 2001
Perfetti, et al. Blood 2002
Prokaeva, et al. Arthritis Rhem 2007
Prokaeva. Amyloid 2010

Perfetti, et al. Blood 2012
Merlini & Palladini.Hematology 2012
Kumar et al. Leukemia 2017
Nevone et al. Leukemia 2022

Is screening possible for early rule in strategy?



The M-Ig was present in 100%, 80%, and 42% of cases at less than 4 years, 4 to 11 years, and more than 11 years before diagnosis, respectively.

The median FLC differential (FLC-diff) was higher in cases compared with controls at all time periods

The FLC-diff was greater than 23 mg/L in 85% of cases and 0% of controls (P<0.001).

The FLC-diff level increased more than 10% per year in 84% of cases compared with 16% of controls (P<0.001)

Weiss et al. JCO 2014

Is screening possible for early rule in strategy? → IGLV gene use et al.

British Journal of Cancer Research
2024; 7(1): 681- 686. doi: 10.31488/bjcr.193

Research article

Seeking Amyloidosis Very Early: Free light Chain Differentials and IGLV Gene Use as Screening Variables for Light-chain Amyloidosis in λ Monoclonal Gammopathies

Ping Zhou[1], Mahesh M Mansukhani[2], Raymond Yeh[2], Jiesheng Lu[2], Hongai Xia[2], Lahari Koganti[2], Jiuhong Pang[2], Denis Toskic[1], Stephanie Scalia1, Xun Ma[1], Nancy Coady Lyons[3], Teresa Fogaren[1,3], Cindy Varga[4], Raymond L Comenzo[*1,3]

[…] we show that in patients with λ MGUS or SMM the use of two variables, a dFLC > 23mg/L and the presence of an AL-related IGLV gene, may enable early diagnosis of AL […]

Journal of Clinical Medicine
MDPI

Article

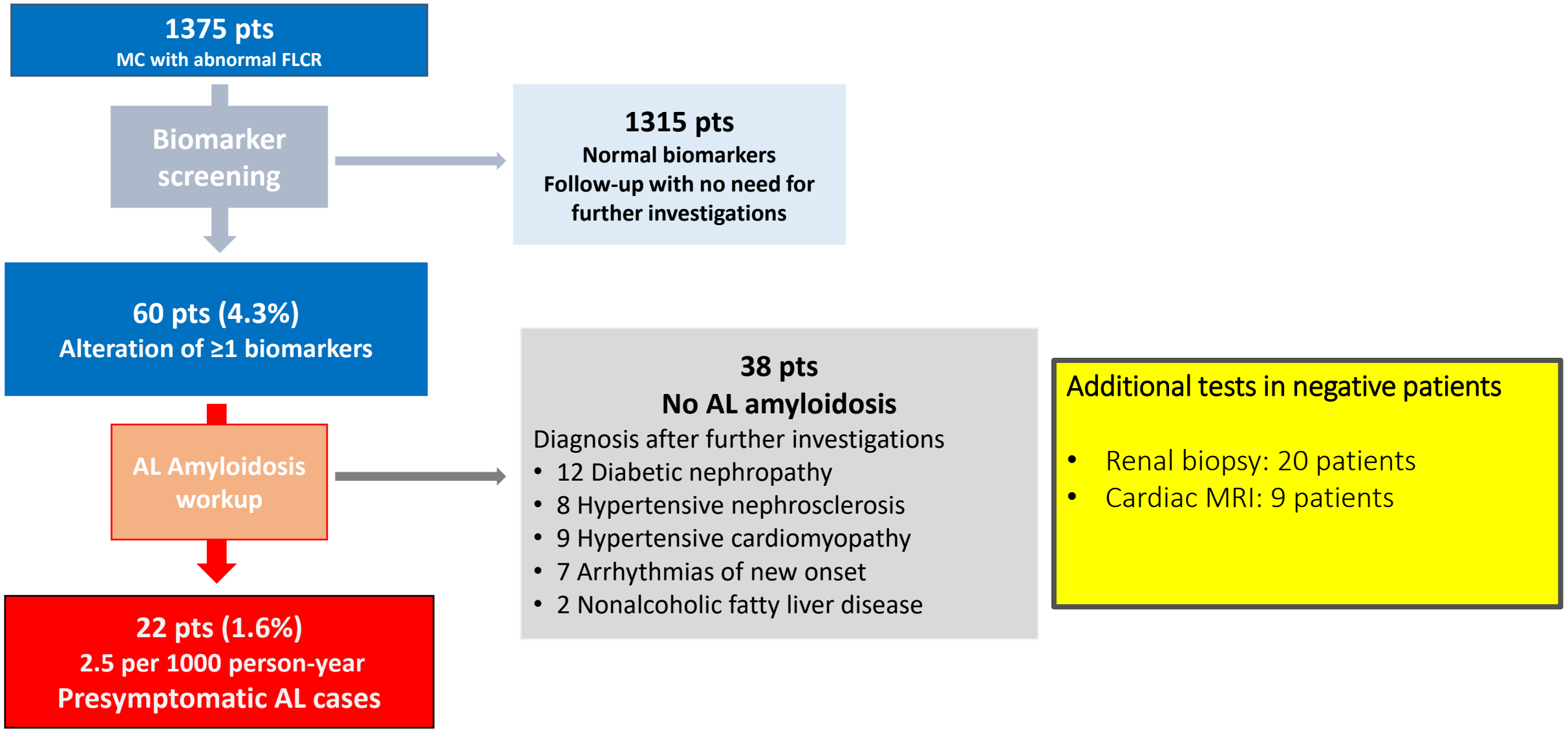
Screening for Systemic Light-Chain Amyloidosis in Patients Over 60 with λ Monoclonal Gammopathies

Ping Zhou [1], Mahesh M. Mansukhani [2], Raymond Yeh [2], Jiesheng Lu [2], Hongai Xia [2], Lahari Koganti [2], Jiuhong Pang [2], Denis Toskic [1], Stephanie Scalia [1], Xun Ma [1], Lisa X. Lee [3], Sandy W. Wong [4], Alfred Chung [4], Sascha A. Tuchman [5], Terry Fogaren [1,6], Nancy Coady Lyons [1,6], Cindy Varga [1,6], Suzanne Lentzsch [7] and Raymond L. Comenzo [1,6,*]

[…] we used age, the FLC criterion of a dFLC > 23 mg/L, and the presence of AL-related IGVL genes to evaluate the screening results for the presence of AL in patients with λ SMM and MGUS […]

[…] These results justify a larger study screening for AL in SMM to develop a likelihood algorithm for AL […]

Is screening possible for early rule in strategy? → biomarker based



Mangiacavalli et al. Am J Hematol 2024

Conclusions

- Early detection of monoclonal protein is fundamental in patients with suspected systemic amyloidosis
- The correct sequence of testing is crucial for avoiding critical delays
- In patients with known MGUS, should we suggest a screening program (?)

Acknowledgments

Amyloidosis Research and Treatment Center

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Cancer Research UK

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Screening and early diagnosis of AL amyloidosis

Early rule out in cardiology

Martha Grogan, MD

Founder and Director, Cardiac Amyloid Clinic

Mayo Clinic, Rochester, MN

Screening and early diagnosis of AL amyloidosis
Early "rule in or out" of AL in cardiology

Martha Grogan, MD

Founder and Director, Cardiac Amyloid Clinic

Mayo Clinic, Rochester, MN

63-Year-Old Female, Diagnosis of ATTR-WT
On Tafamidis two Years, referred ? GI amyloid

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- No prior cardiac history, no HTN; presented with AF with RVR
  - Echo- septal thickening, abnormal strain, consistent with amyloid
  - CMR – suggestive of amyloid
  - PYP- grade 2 uptake, c/w ATTR; screening for AL negative
  - DNA TTR - negative
- Tafamidis started two years ago
- GI – biggest problem, alternating diarrhea, constipation, bloating
- Colonoscopy elsewhere negative, stains for amyloid not done

63-Year-Old Female, Diagnosis of ATTR-WT

On Tafamidis two Years, referred ? GI amyloid

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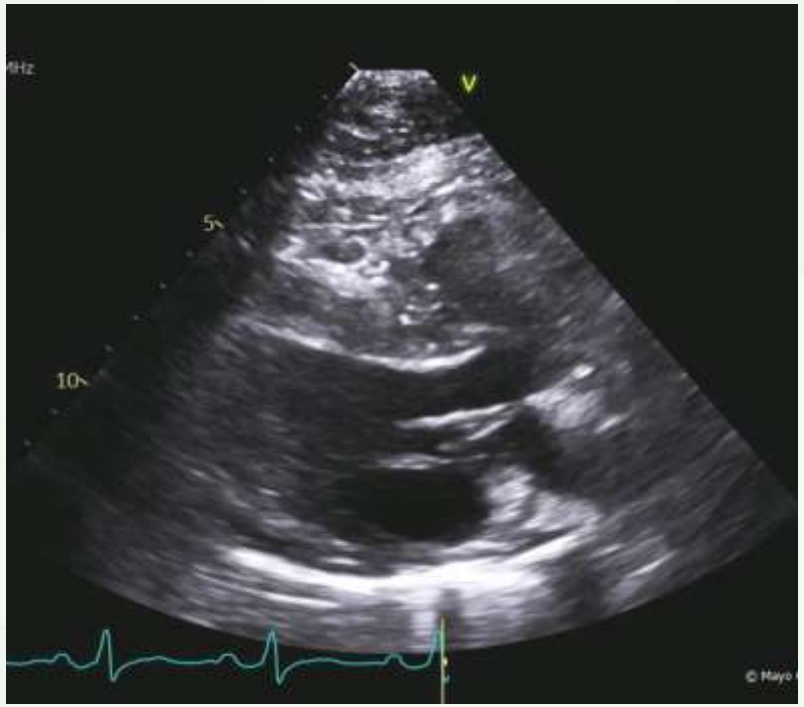

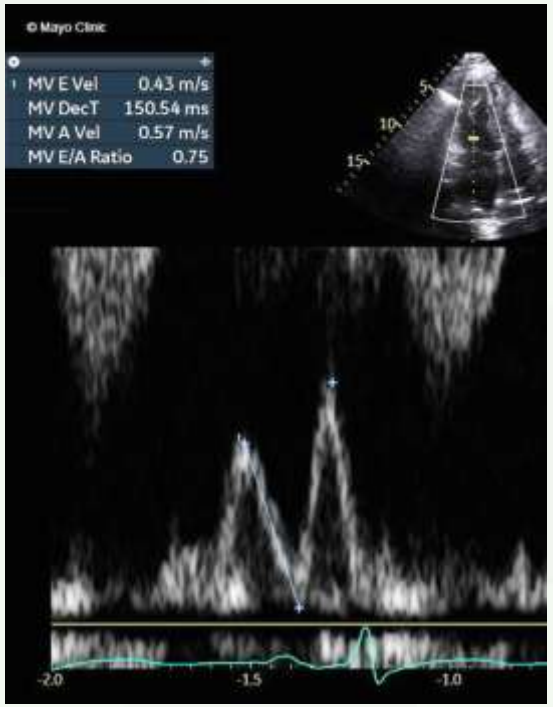

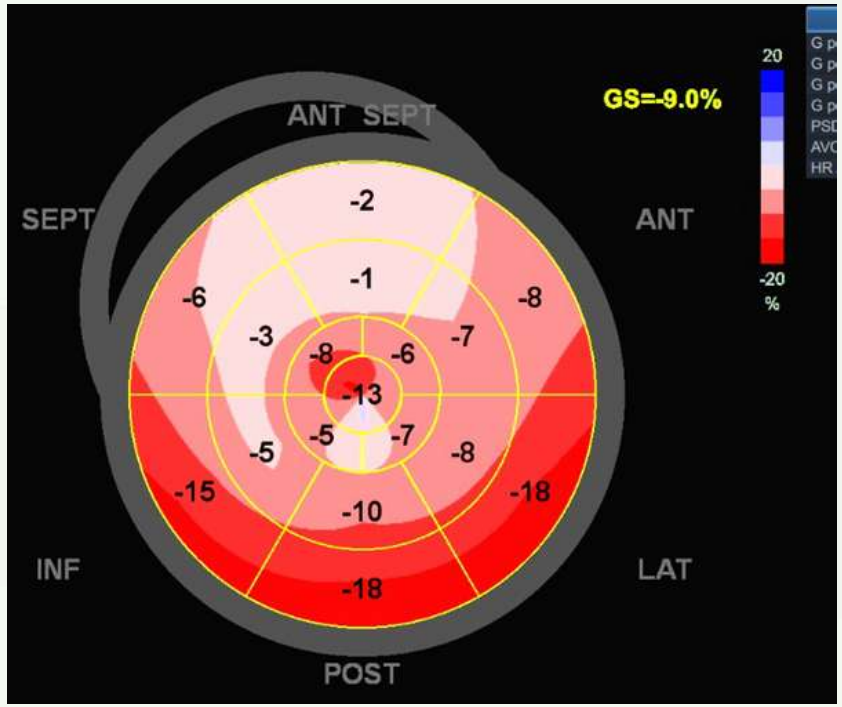

63-YEAR-OLD FEMALE, DIAGNOSIS OF ATTR-WT

YOUR NEXT STEP?

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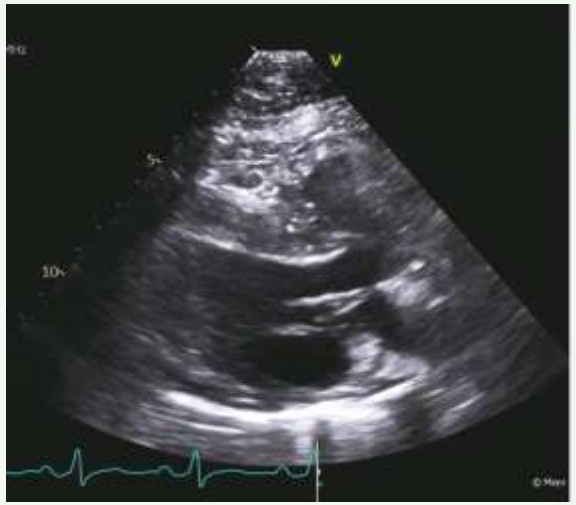
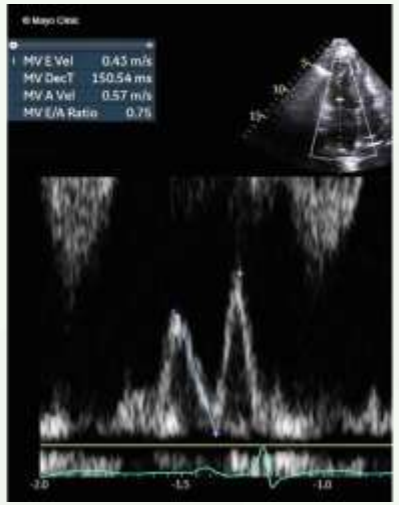
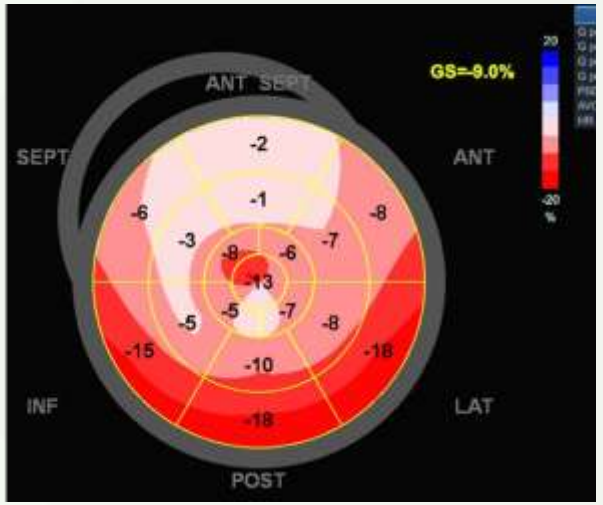
1. Repeat CMR
2. Cardiac Biopsy
3. Repeat PYP
4. ECG
5. Something else







63-YEAR-OLD FEMALE, DIAGNOSIS OF ATTR-WT

YOUR NEXT STEP?

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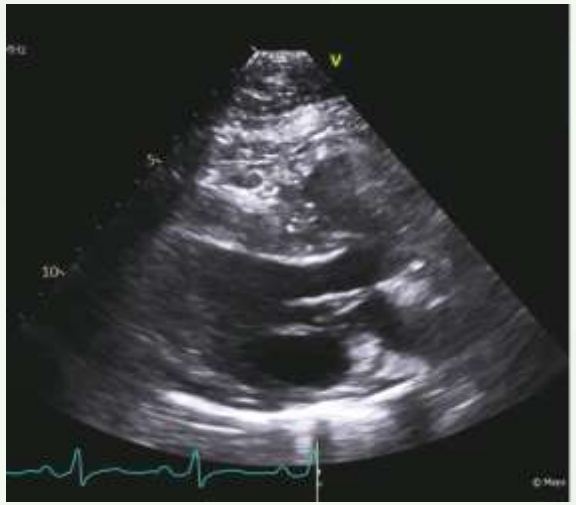

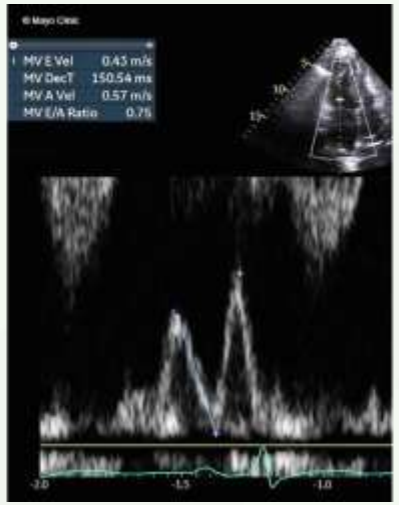

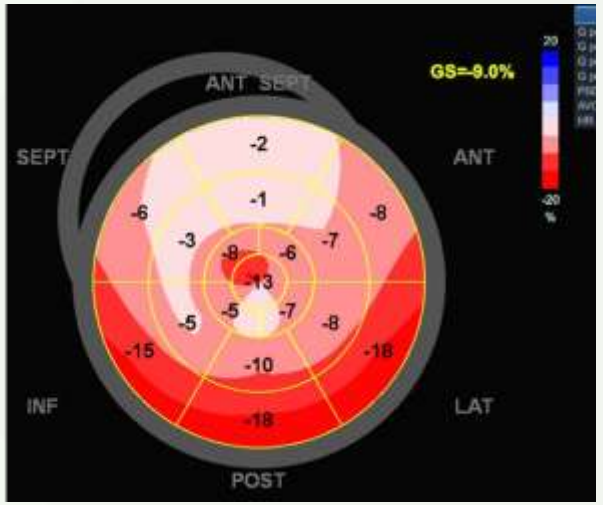

ECG

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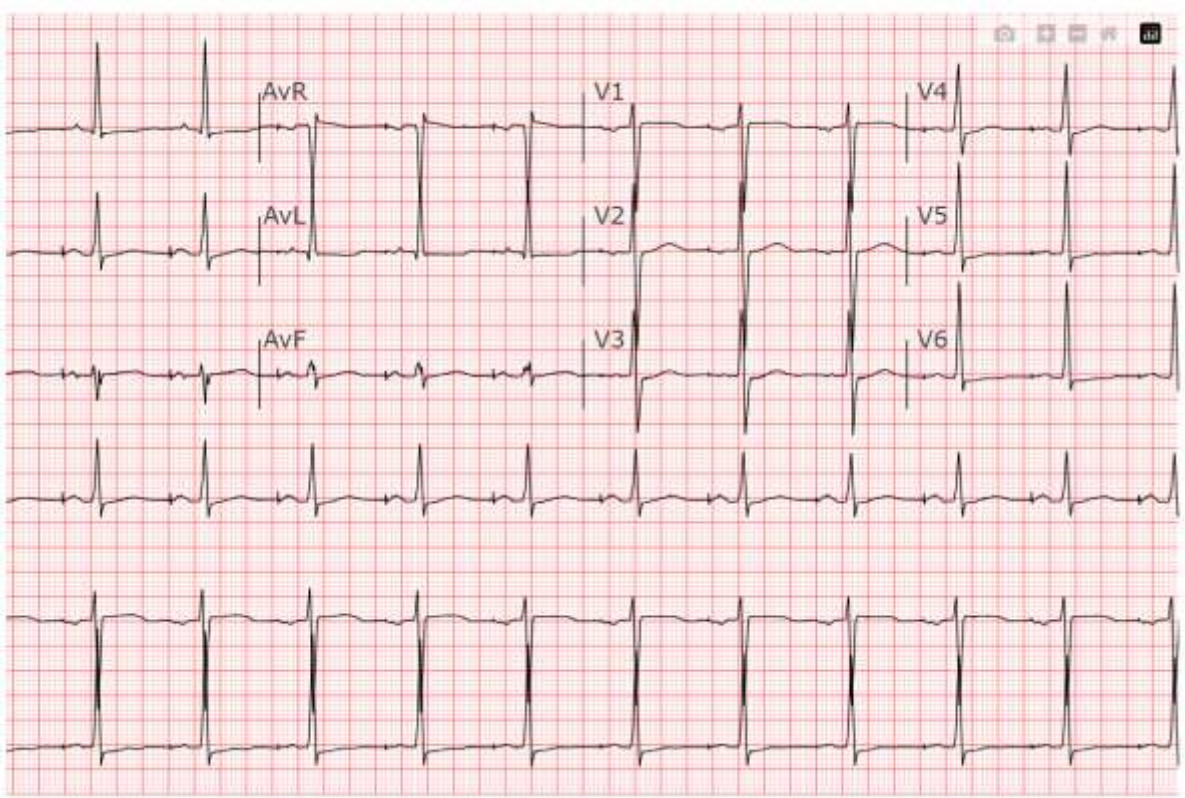

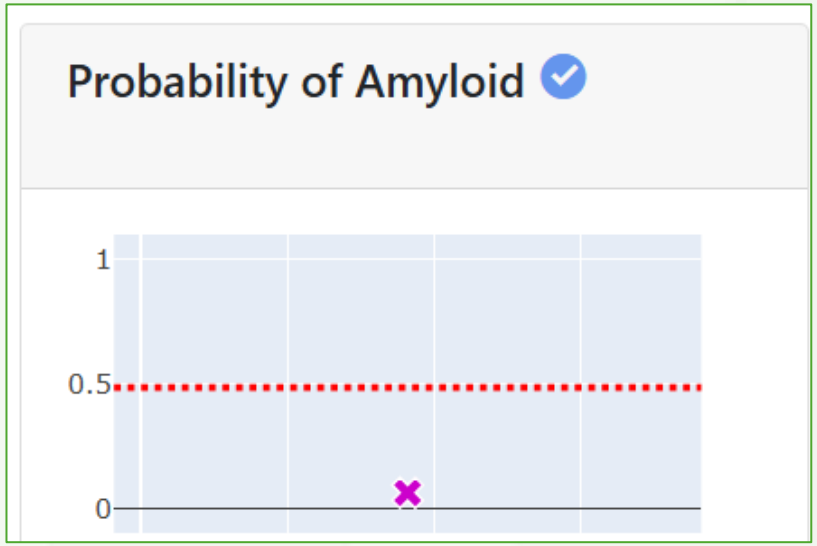

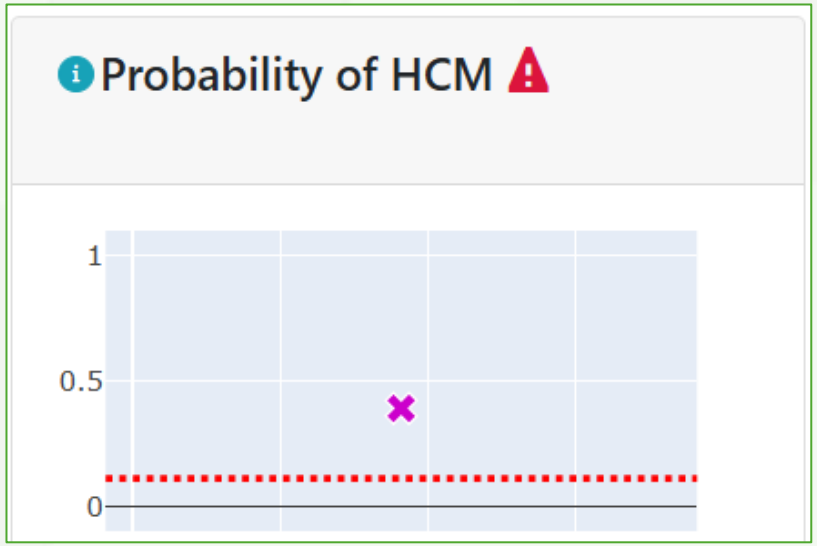

Genetic testing for TTR – negative
Panel showed MHY7 variant

Mayo PYP Negative
What else would you like to see?

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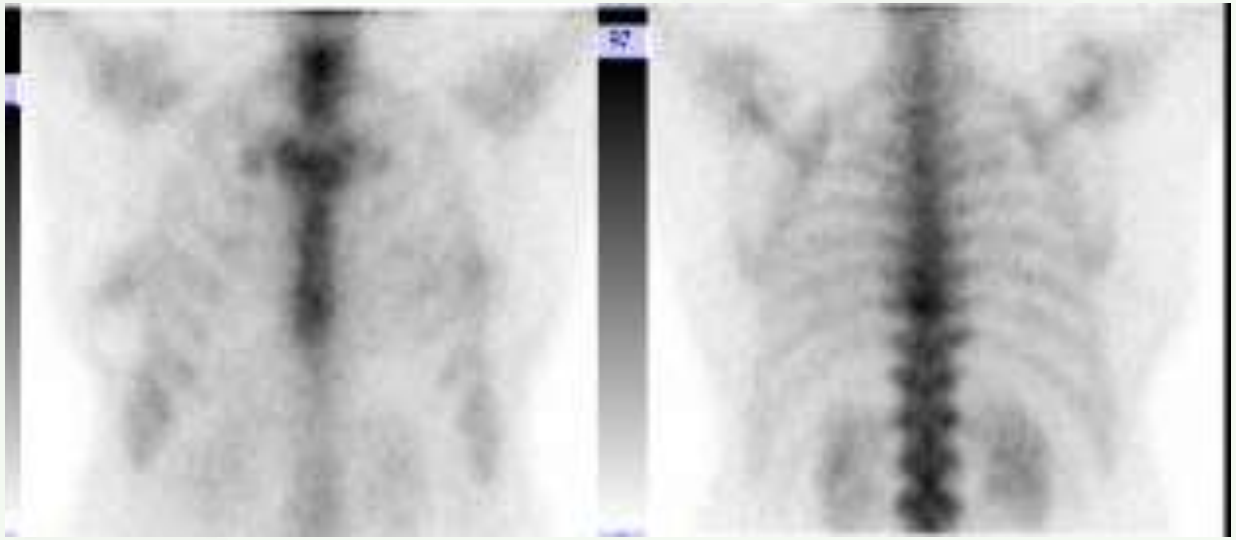
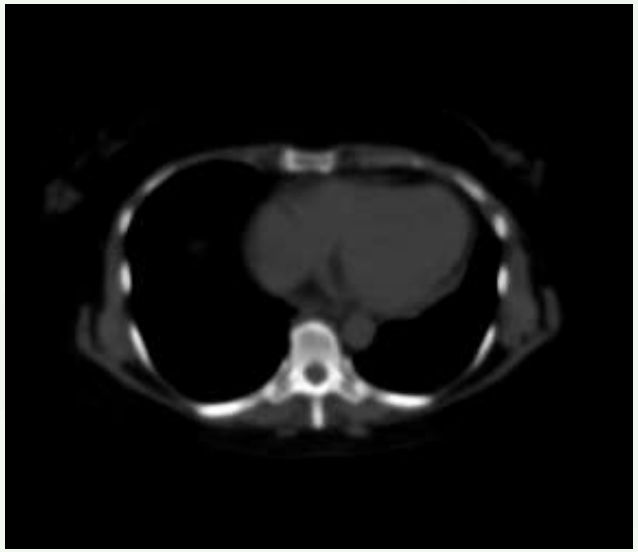
PYP 2.5 years ago





Pearl: PYP may become negative on stabilizer treatment without regression of disease, always review pre-treatment images

DIAGNOSIS: NON-OBSTRUCTIVE HCM DUE TO MHY7 VARIANT

56-Year-Old Male, elevated NT-BNP on insurance Exam

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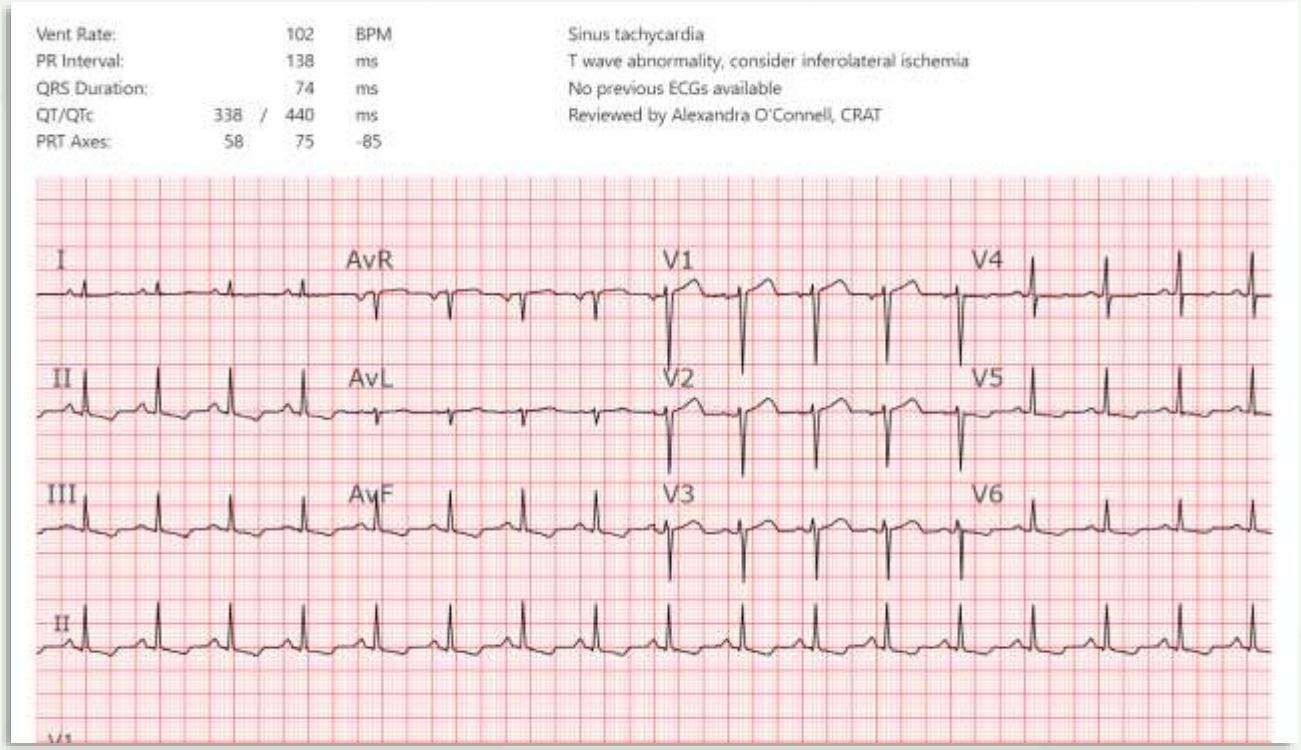

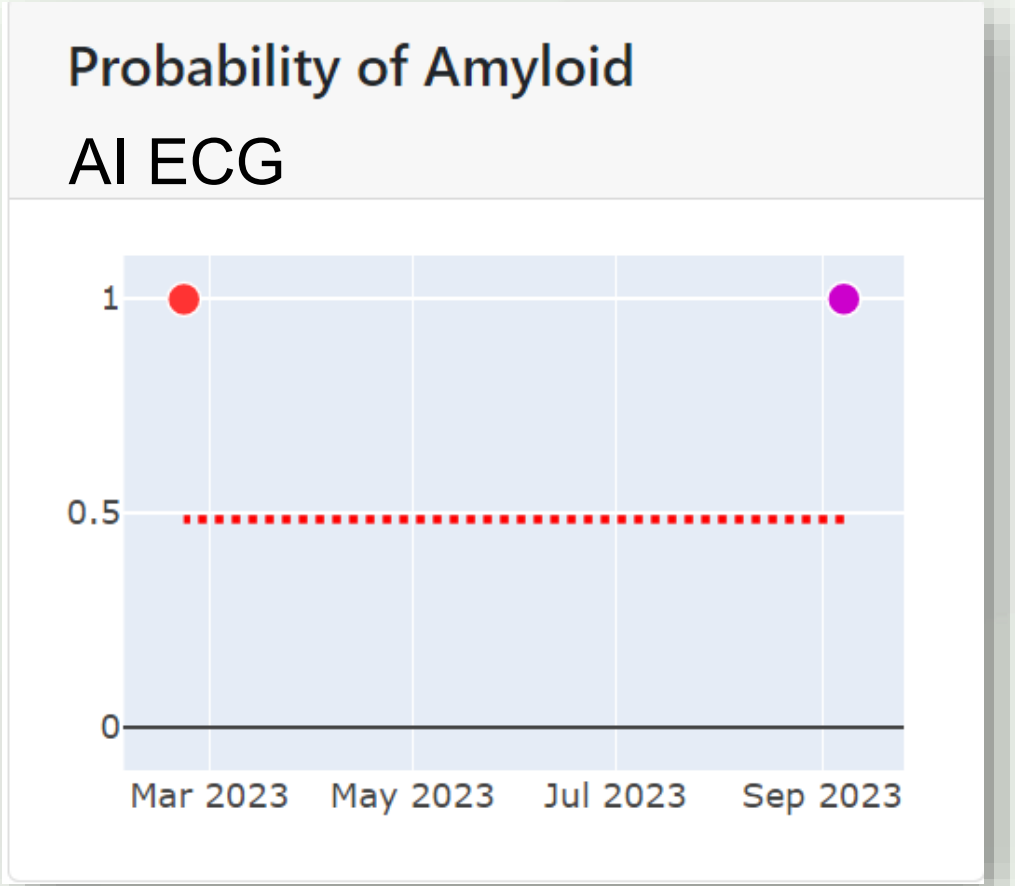

60-Year-Old Male, 3rd opinion - pulmonary

Small pleural effusions, hair loss, **Normal echo 6 months ago**

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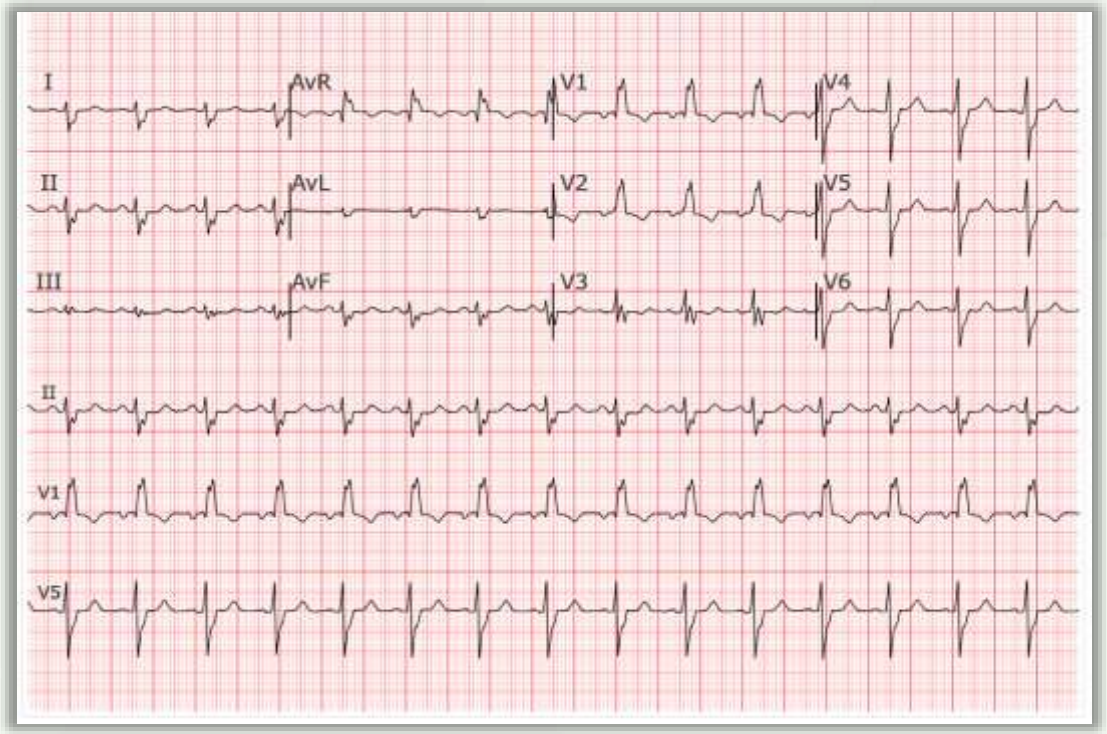
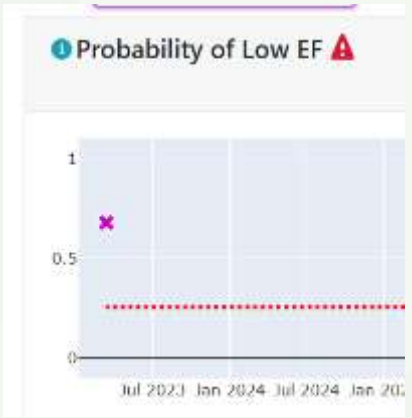
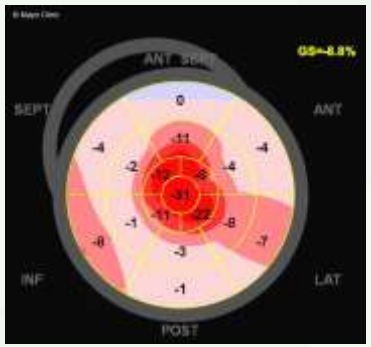
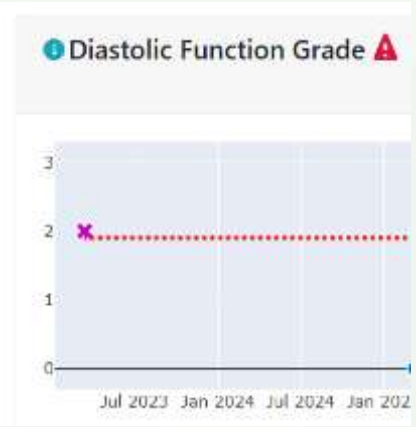
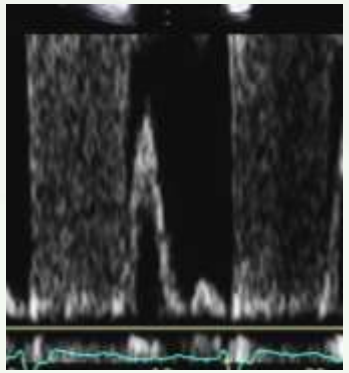




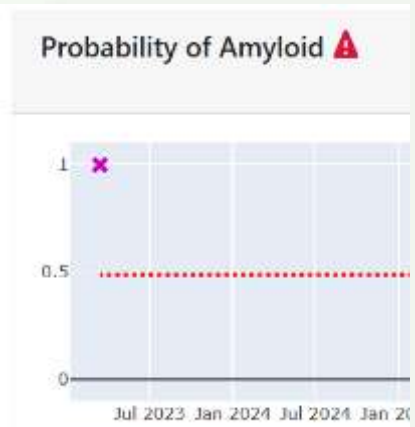


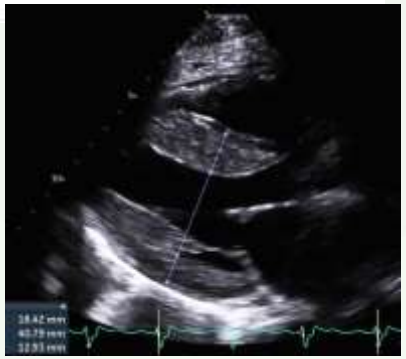
Strain -8%,
CI 2.0 l/min/m²
SVI = 20 ml





Restrictive Filling
Decel time 110 ms





Septal Thickness,
18 mm

Dx = Rapidly Progressive Cardiac, Renal AL

Rx = Daratumumab, Cy-Bor-D, Dramatic response

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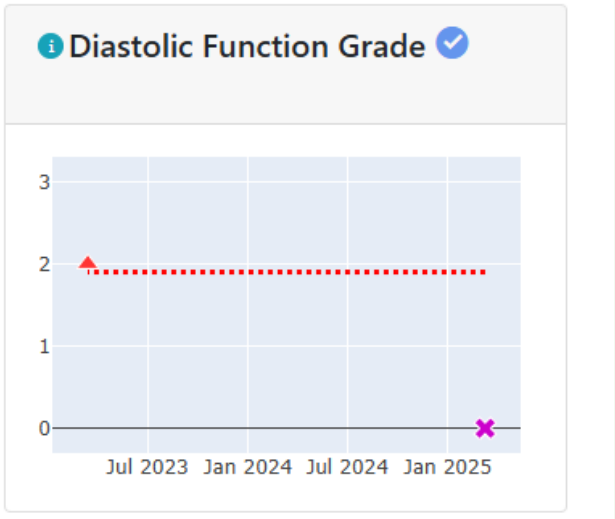
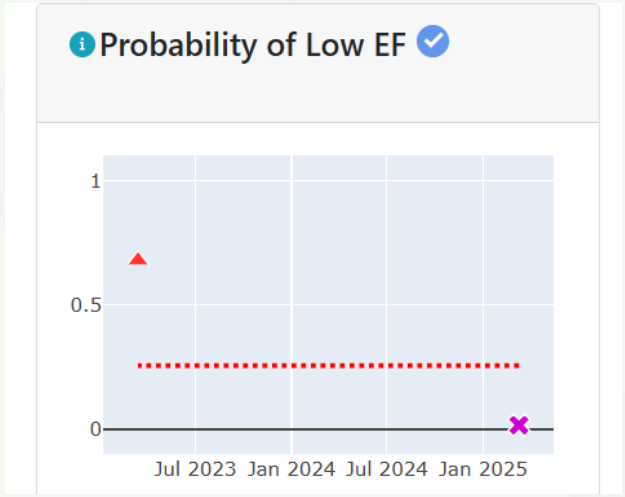
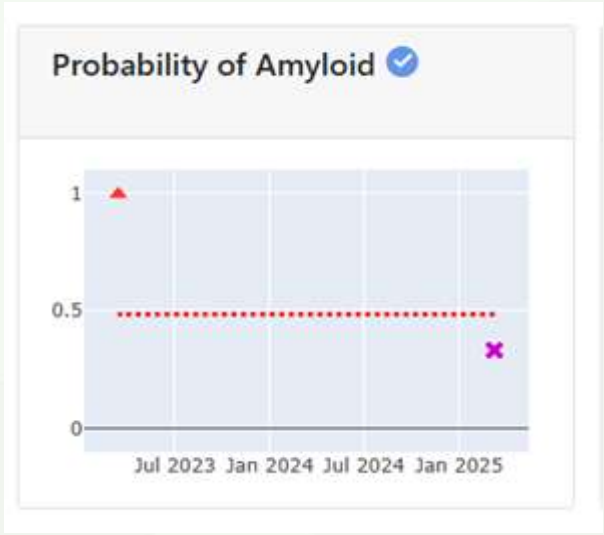
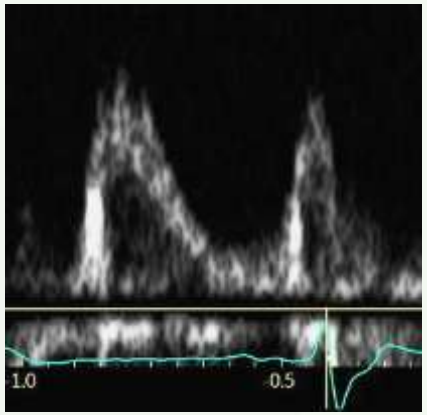
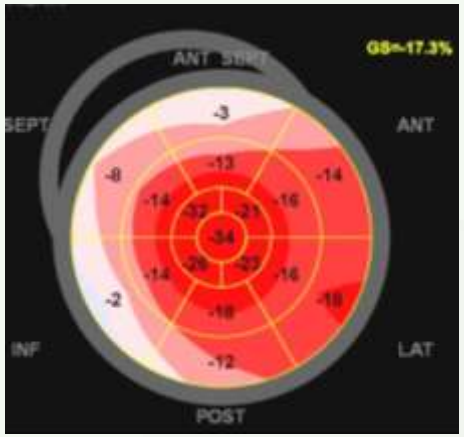




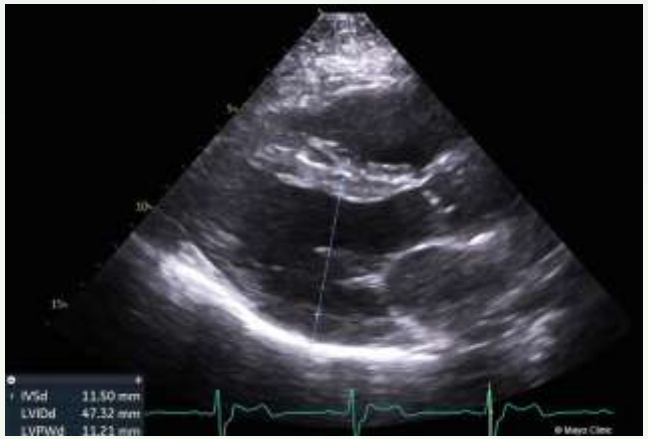




Decel = 233 msec



Strain -17%, CI = 2.5
SVI = 35 ml



Septum = 12 mm

Newly diagnosed Myeloma
Outside echo: Hypertrophic Cardiomyopathy (HCM)

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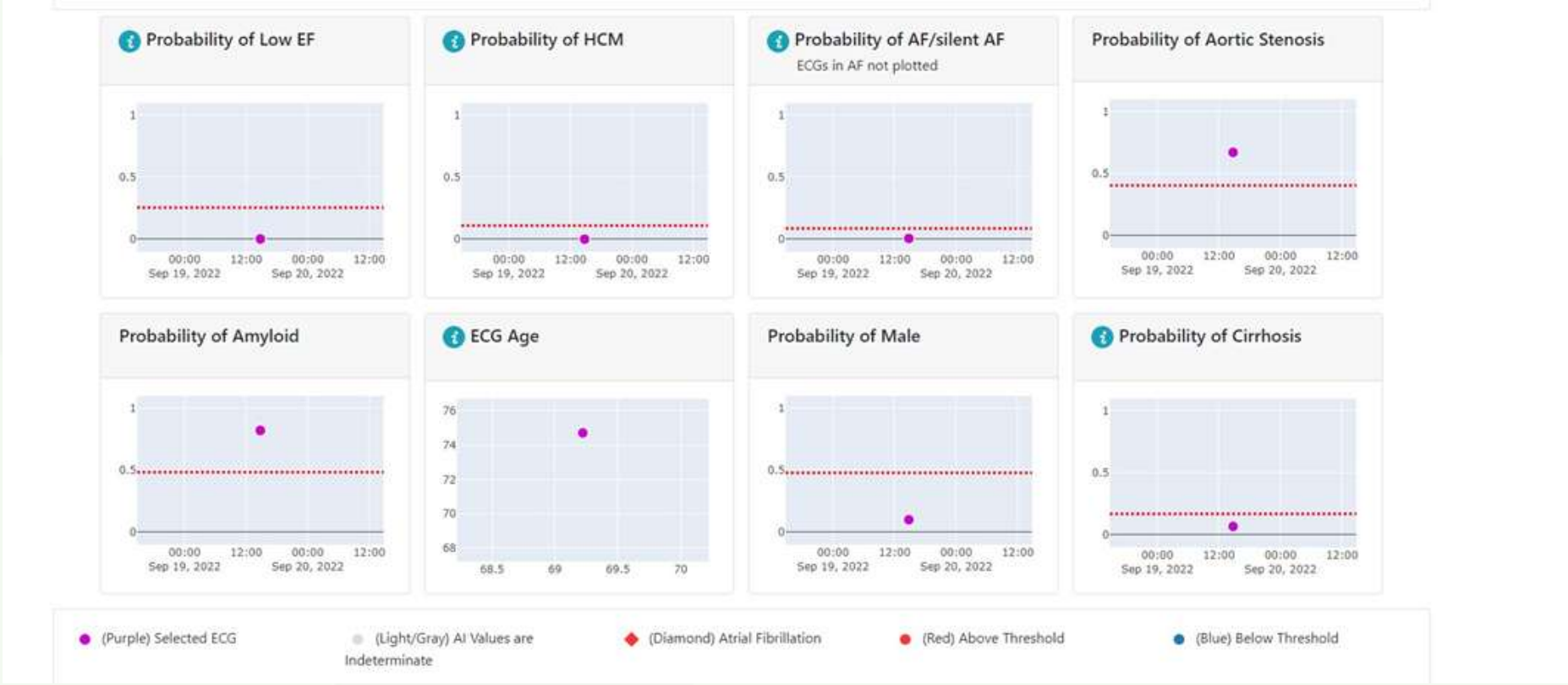
Mayo Cardiac MRI :

Consistent with HCM

How common is HCM?



HARNESSING THE POWER OF AI ECG TO PROMOTE EARLY DIAGNOSIS

AI APPLIED TO: MEDICAL RECORD, BLOOD TESTS, ECG, CARDIAC IMAGING, PATHOLOGY

Challenges:

Prevalence Uncertain

Positive Predictive Value

True Negative Controls

Gold Standard is not easy

Why Use AI-Enhanced ECG?

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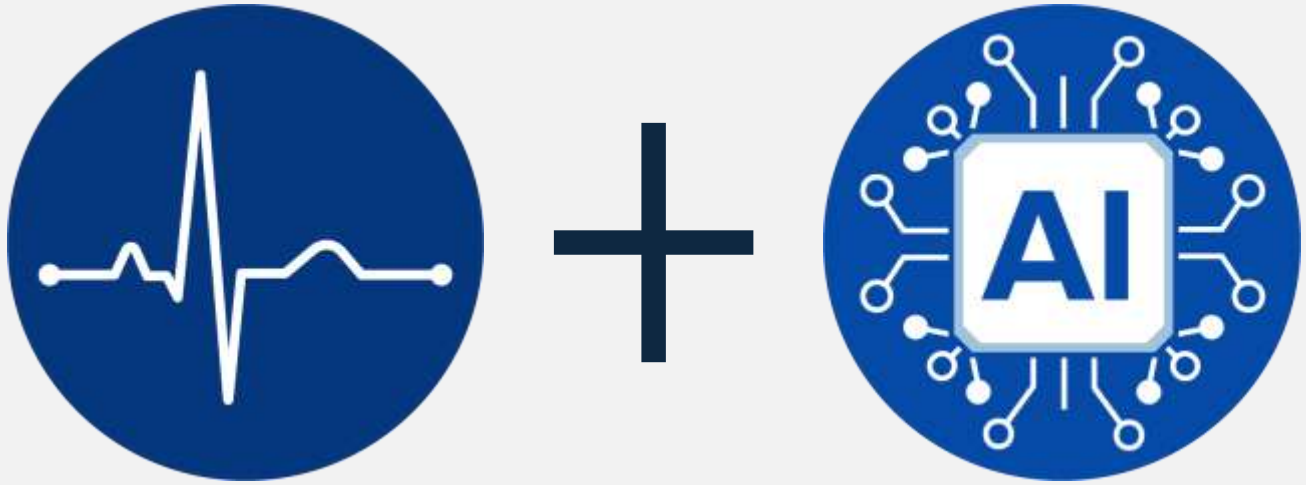
- 

Most patients have an ECG performed early in their diagnostic journey

- Often when amyloidosis has not yet been considered

THIS TOOL WORKS GREAT IN AMYLOID CLINIC

WHAT IS THE PROBLEM?

Despite a high negative predictive value (99%), the low prevalence of amyloidosis results in a low positive predictive value in unselected populations (8% Mayo Clinic ECGs positive)

Non-amyloid providers could be overwhelmed by false positive results

CONFUSION MATRICES FOR THE 12-LEAD AI-ECG AMYLOID MODEL AT DIFFERENT THRESHOLDS AND PREVALENCE.

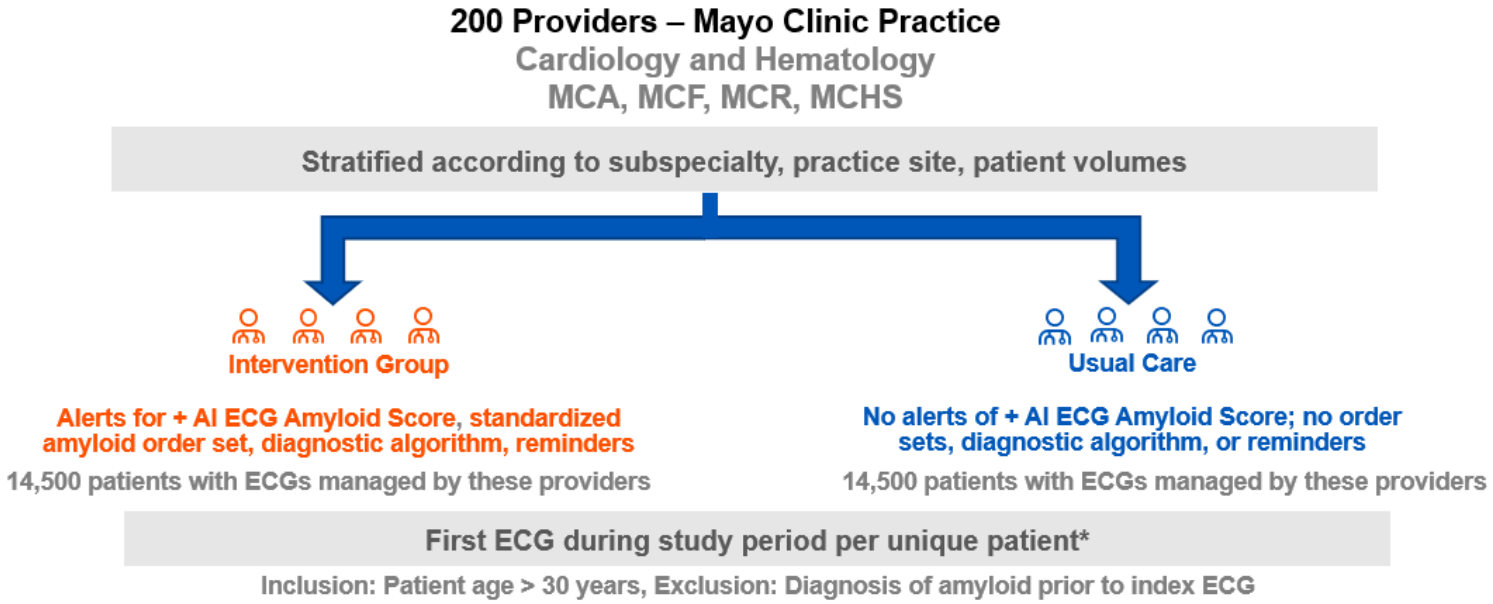
Scenario	Threshold	Prevalence %	Sensitivity	Specificity	PPV	NPV
1	0.485	51	81	89	89	82
2	0.485	15	81	89	57	96
3	0.8	51	60	97	95	70
4	0.8	15	60	97	76	93
5	0.8	5	60	97	49	98
6	0.3	5	90	72	15	99

PPV, positive predictive value; NPV, negative predictive value

WHY A PRAGMATIC CLINICAL TRIAL?

Pragmatic trials are designed to evaluate the effectiveness of interventions in real-life routine practice conditions

The AI ECG algorithm won't be useful if providers don't use it

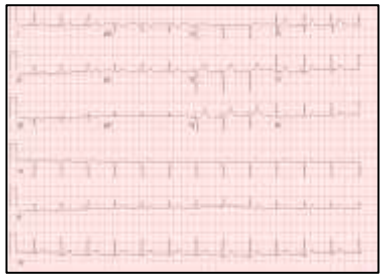


Randomize Providers to Intervention (Algorithm Alerts, amyloid order sets, Amyloid Content) or No Intervention

Primary Outcome:
Rate of Diagnosis of Cardiac Amyloid within six months

Secondary Outcomes:
- Stage at diagnosis
- Utilization of diagnostic tests for amyloidosis
- Provider satisfaction

Aim 1



AI EKG algorithm

Satisfies threshold for positive

Model

Aim 2

Augmented
AI EKG algorithm

Prospective clinical application in Pragmatic Trial

Electronic health record

NLP symptoms,
ICD codes,
Imaging, blood, urine

Machine learning

Identify important variables and phenotypes

Internal validation

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Welcome to the PREDICT-AMY webpage!

The A3E score** has been calculated based on additional clinic data, limited laboratory results and complete Echo results.

The A3E score shows a decreased probability relative to the original AI ECG score that your patient has cardiac amyloidosis.

**The A3E score is an augmented model adding available clinical, lab, ECHO data to the ECG score. It will be rerun daily for two weeks and you will be notified of significant change. To see values included, click HERE.

(pdf)

- How to Explain Amyloid and the AI ECG Algorithm to your patients (video) (pdf)

PREDICT-AMY - enhanced modeling to predict risk of Amyloid

Below are the inputs needed to calculate the full A3E (augmented AI ECG) score. Values shown are the most recent / most complete data available at the time of calculation.

Age	56	
Gender	F	
Height (cm)	150.0	05/25/2023
Weight (kg)	43.8	05/23/2023
AI ECG score	0.746	05/22/2023

Echo data	05/23/2023
Systolic BP (mmHg)	114
Diastolic BP (mmHg)	72
Heart Rate	59
Intraventricular Septum d (mm)	7
PW thickness d (mm)	8
LV Relative wall thickness	0.33
Left Ventricle Dimension d (mm)	49
LVOT TVI (cm)	20.5
AV TVI (cm)	29.2
AV Valve area (velocity) (cm2	2.54
Cardiac Output (l/min)	4.190
A velocity (m/sec)	0.6
Medial annulus e' velocity (m/sec)	0.06
Medial E/e' (m/sec)	6.70

Most Recent Vitals	05/31/2023
Systolic BP (mmHg)	106
Diastolic BP (mmHg)	66
Heart Rate	59

Blood labs

Hemoglobin	10.9	07/07/2023
Hematocrit	37	07/07/2023
MCV	88.0	07/07/2023
Platelets	260	07/07/2023
Leukocytes	6.2	07/07/2023
Neutrophils (x10(9)/L)	3.4	07/07/2023
Lymphocytes	2.0	07/07/2023
Serum Sodium (mmol/L)	138	07/10/2023
Total bilirubin (mg/dL)	0.3	07/07/2023
Serum Creatinine (mg/dL)	1.7	07/10/2023
Calcium (mg/dL)	9.0	07/10/2023
Fasting Glucose (mg/dL)		
Alkaline Phosphatase (U/L)	82	07/07/2023
Serum Albumin (g/dL)	4.1	07/07/2023
Serum Kappa FLC (mg/dL)	12.00	FLC date 05/18/2023

Using available data, the **A3E score** shows a decreased probability relative to the original AI ECG score that your patient has cardiac amyloidosis.

Model Completeness

Model	AL	ATTR
ECG + Echo results, full	☑	☑
ECG + Echo results, reduced	☑	☑
ECG + Vitals + Lab results, full	☑	☐
ECG+ Vitals + Lab results, reduced	☑	NA

AI ECG

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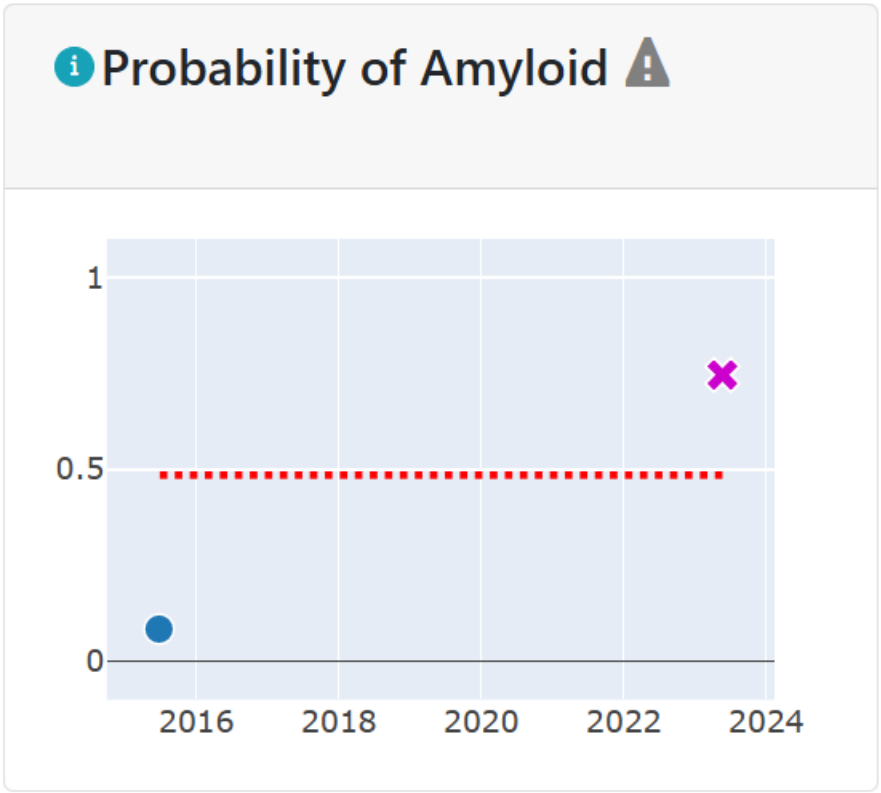

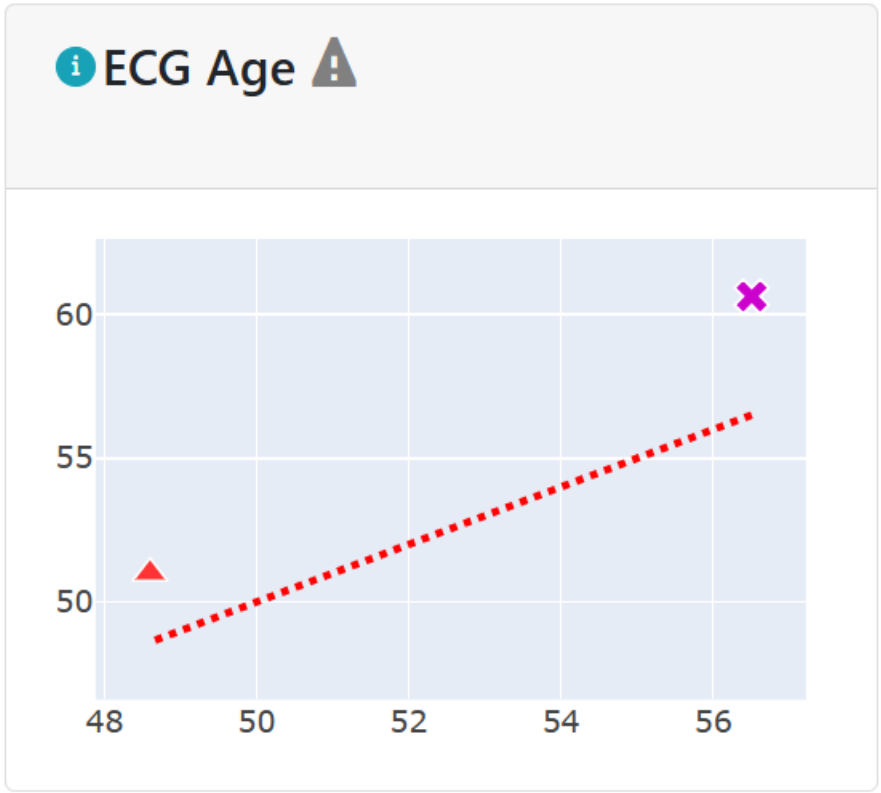

AI ECG “corrected” for false sex

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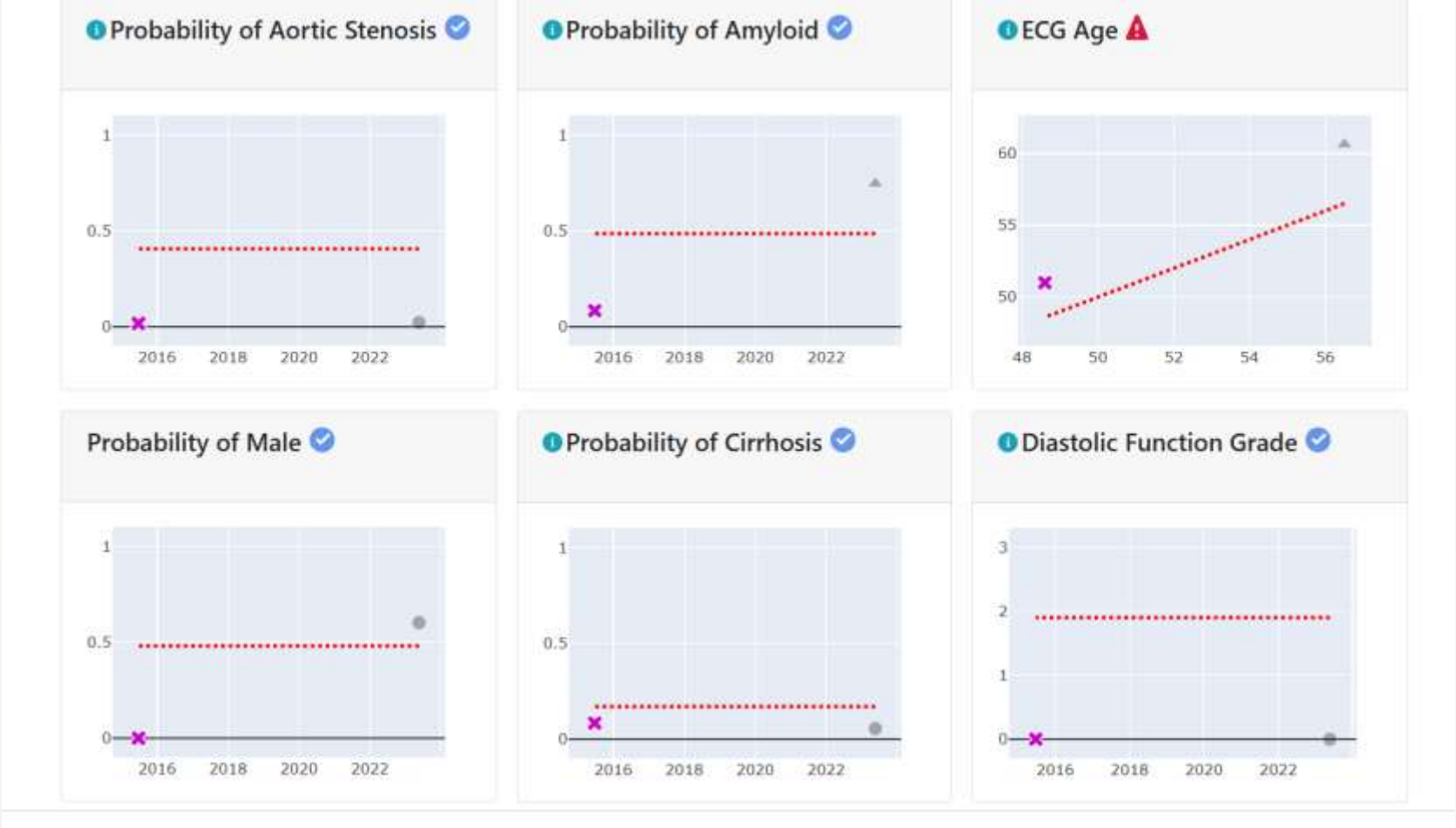


ASNC 2025

30th Annual Scientific Session and Exhibition of the American Society of Nuclear Cardiology

A Tale of Two Tracers – A Qualitative Comparison of the PET and SPECT Amyloid-Imaging Agents, ^{124}I-evuzamitide (AT-01) and ^{99m}Tc-p5+14 (AT-05), that are Derived from the Same Synthetic Amyloid-Binding Peptide, p5+14

THE UNIVERSITY of TENNESSEE GRADUATE SCHOOL OF MEDICINE

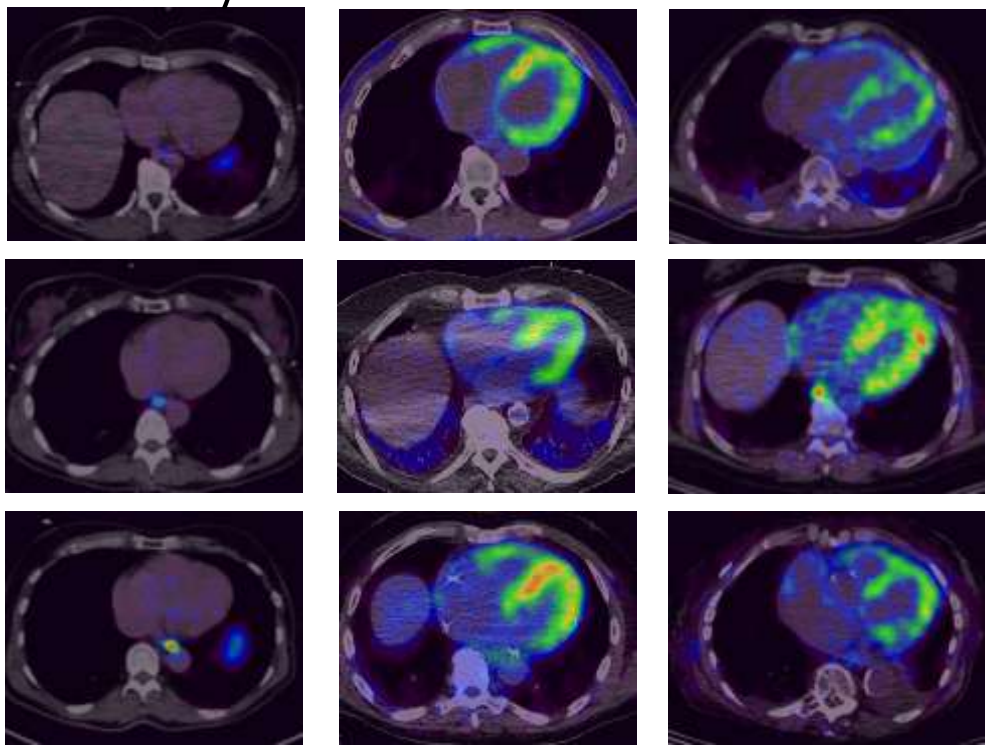
Jon Wall

jwall@utmck.edu

Cardiac Uptake of Radiolabeled p5+14

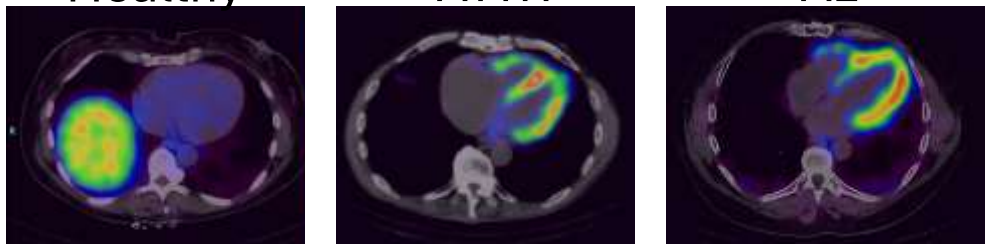
a

^{124}I-evuzamitide 5 h pi

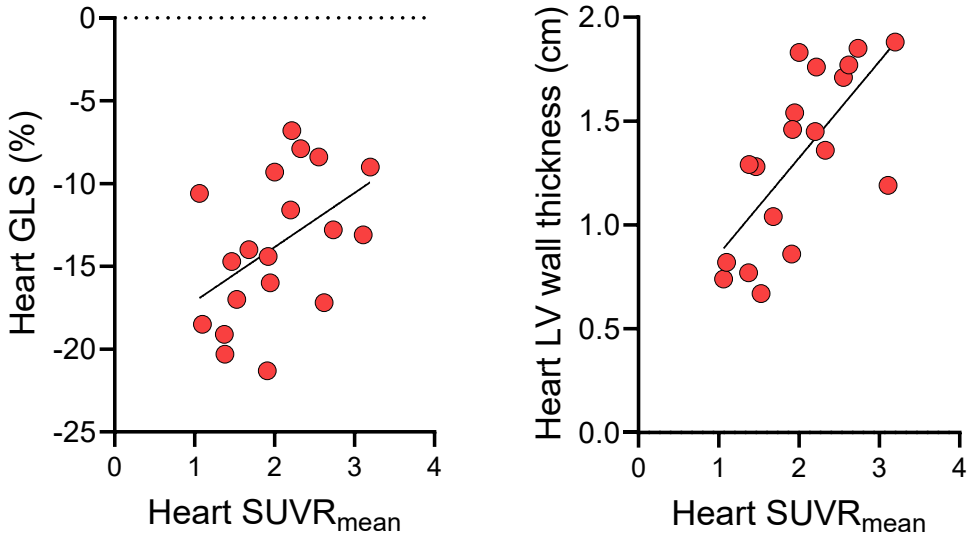


b

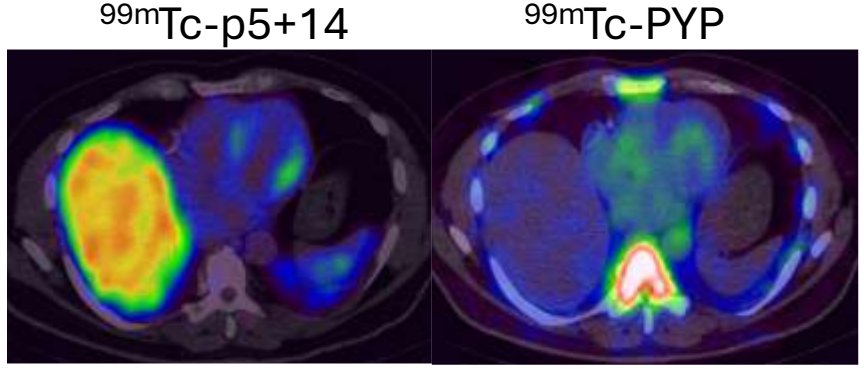
^{99m}Tc-p5+14 1 h pi



Uptake of ^{124}I-evuzamitide Correlates with Measures of Cardiac Function and Structure and QoL



Uptake of ^{99m}Tc-p5+14 (1 h pi) may Detect Early Cardiac Amyloid



EARLY RULE OUT (RULE IN) OF AL CARDIAC AMYLOIDOSIS

SUMMARY

1

AI MODELS RAPIDLY BEING DEVELOPED

Multimodal: clinical, lab, imaging– most important to suggest the diagnosis when not yet considered

2

NEW IMAGING AGENTS PLAY A KEY ROLE

PET and SPECT tracers and improved diagnostics fusing AI to complement traditional diagnostics: echo, MRI, path

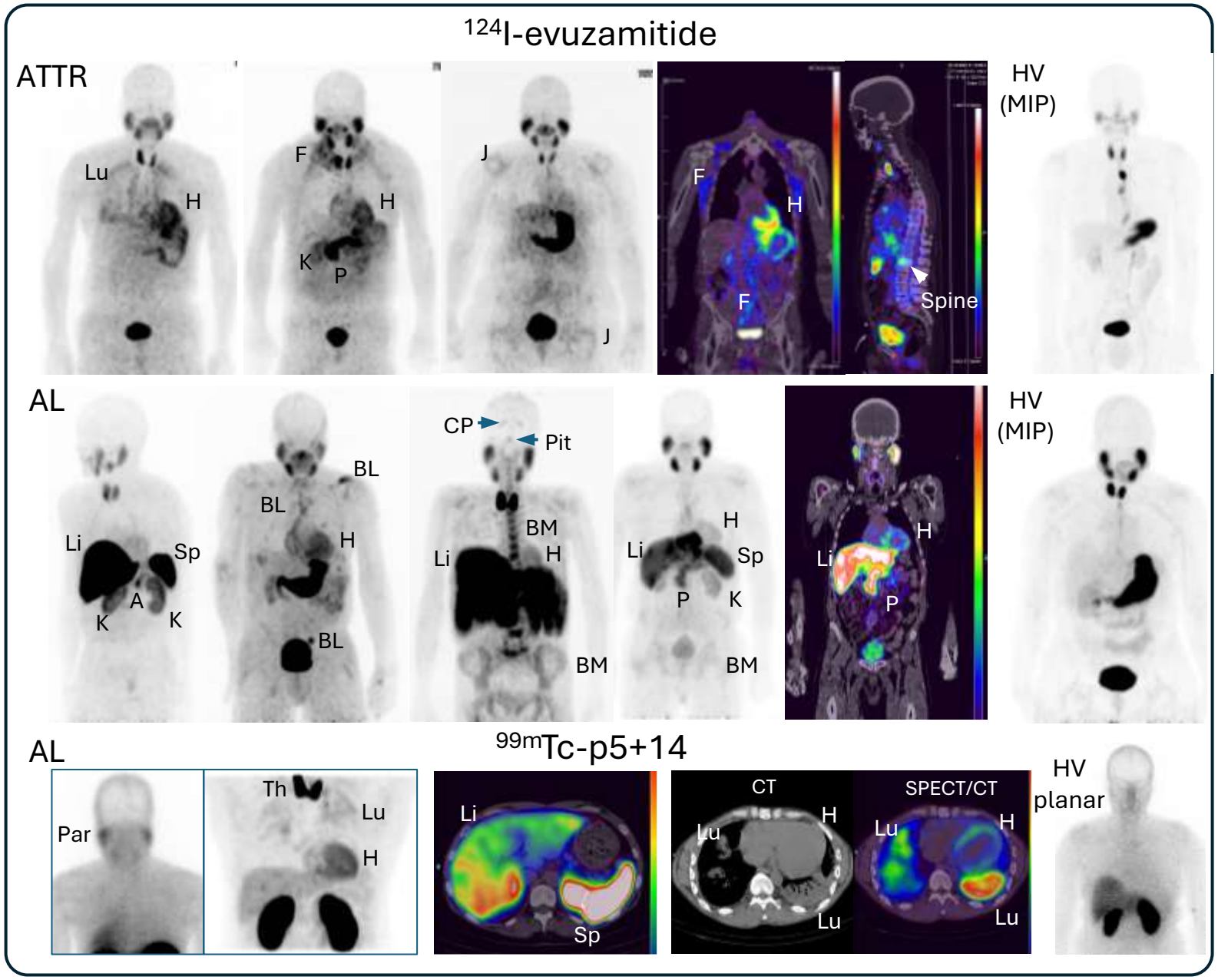
3

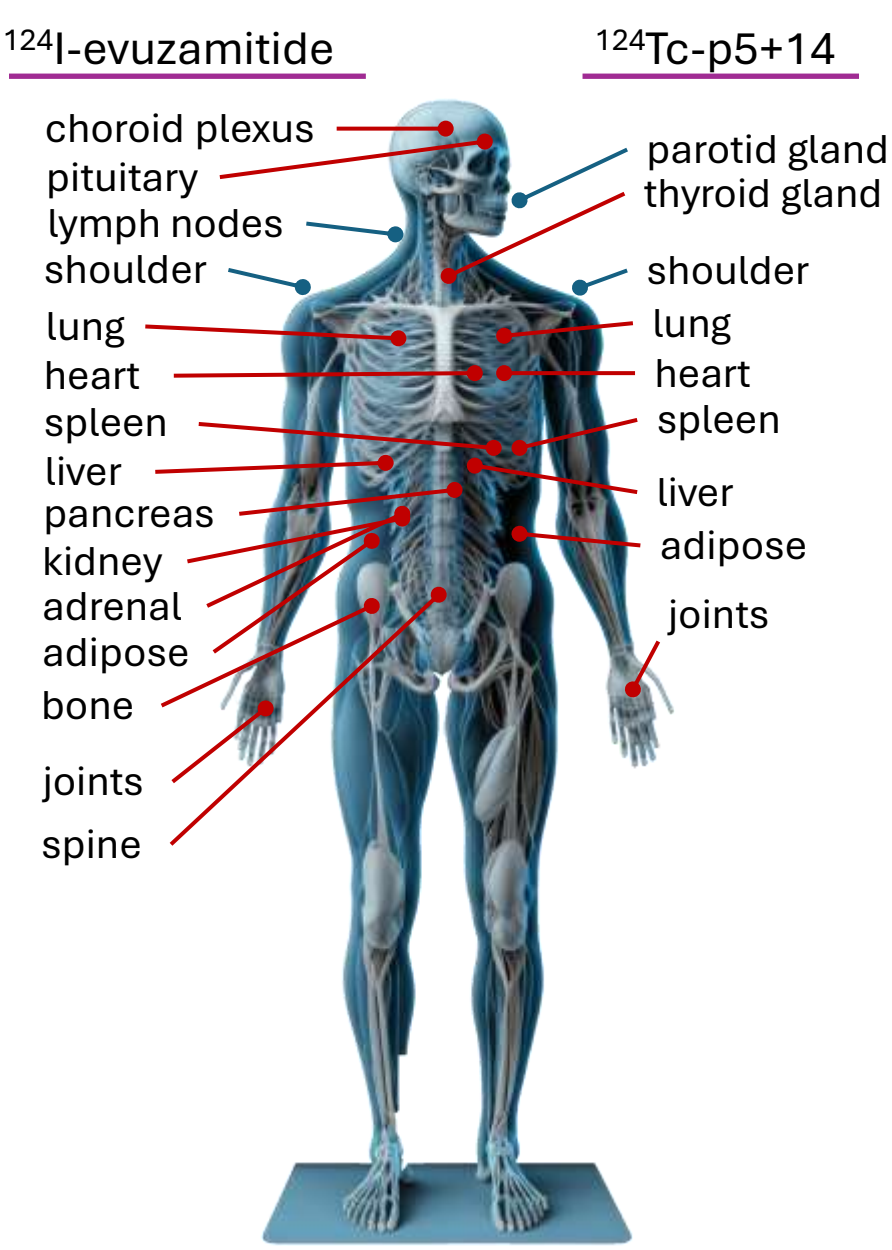
HEMATOLOGISTS NEED TO LEARN ATTR (AND HCM!) JUST AS CARDIOLOGISTS LEARN AL

Summary

- **^{124}I-evuzamitide (PET)**:
  - *High resolution and quantitative imaging*. Enabling accurate assessment of early focal as well as diffuse amyloid deposits.
  - *High sensitivity*. Demonstrated ~96% cardiac detection in AL and ATTR patients with amyloidosis, with uptake observed in multiple organs.
  - *Therapy monitoring*. Quantitative PET/CT imaging may allow tracking changes in organ-specific amyloid load in response to therapy.
  - *Whole-body imaging*. PET/CT can survey all organs in one study that can be rapidly performed.
  - *Regulatory support*. BTD has been granted by the US FDA. Orphan drug designation has been granted for AL and ATTR, both in the US and European Union. The Phase 3 REVEAL study is underway with results expected in early 2026 (NCT06788535). – Dr. Dorbala and Spencer Guthrie.
- **^{99m}Tc-p5+14 (SPECT)**:
  - *Accessibility*. Technetium-99m is generator-produced and radiotracer synthesis is rapid. Kits can be developed allowing widespread adoption; SPECT cameras are ubiquitous.
  - *Rapid imaging workflow*. Scans at 1 h post-injection fit routine practice.
  - *Pan-amyloid binding*. Like ^{124}I-evuzamitide, it binds and images both AL and ATTR amyloid.

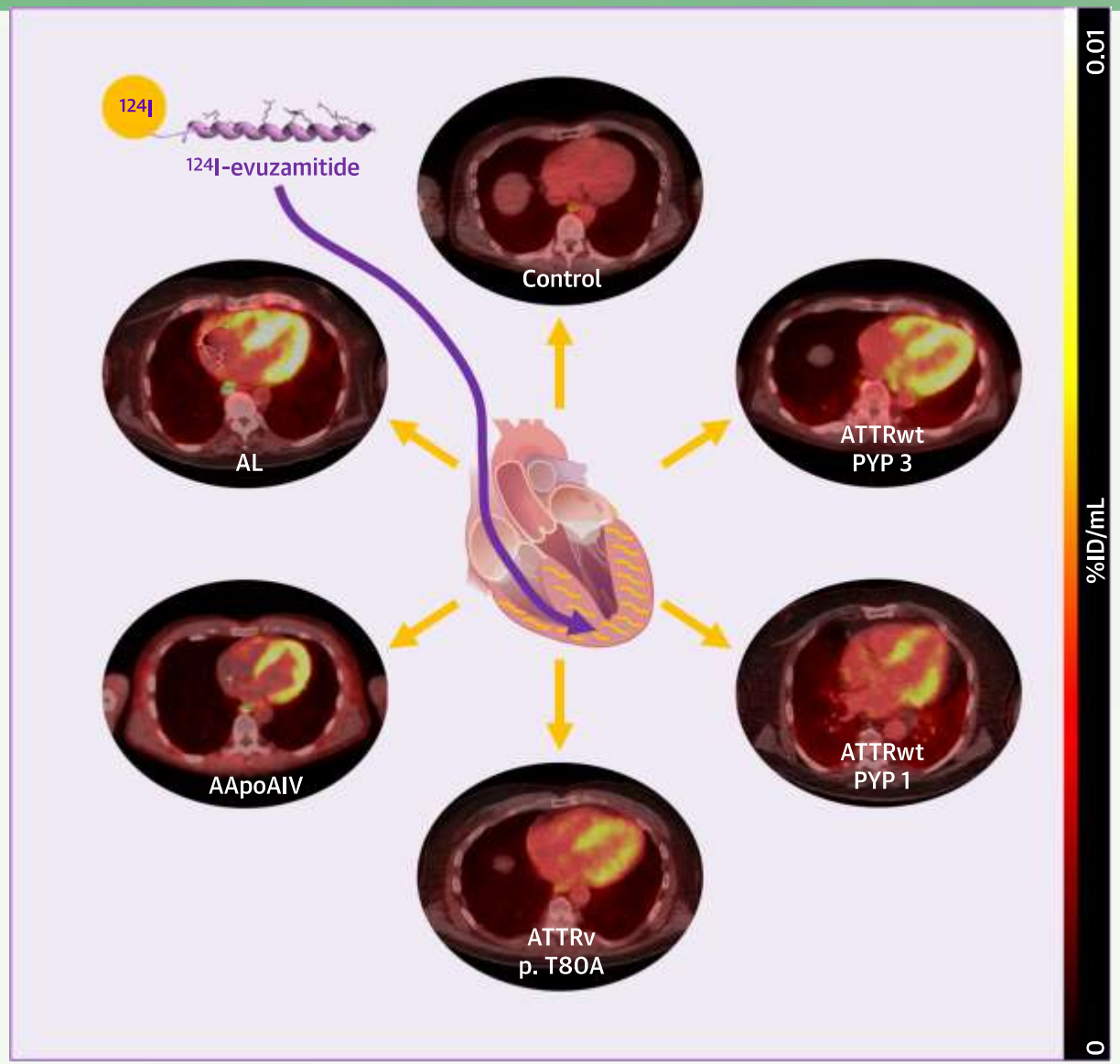
Extracardiac Uptake of Radiolabeled p5+14





ATTR Diagnostic mAb
124I-Evuzamitide (AT-01) in Amyloidosis

^{124}I-Evuzamitide PET/CT Imaging in Multiple Types of Amyloid CM



- AApoAIV, apolipoprotein A-IV amyloidosis; AL, light-chain amyloidosis; CT, computed tomography; %ID, percentage injected dose; PET, positron emission tomography; PYP, pyrophosphate.
- Clerc OF, et al. JACC Cardiovasc Imaging. 2023;16:1419-1432.

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Defining the Risk of Developing AL Amyloidosis

Raymond L. Comenzo, MD

Professor of Medicine, Tufts University School of Medicine

Director, The Tufts Medicine Myeloma and Amyloid Program

Tufts Medical Center

Boston, Massachusetts USA

Disclosures

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

- Research Funding
  - NIA/NIH
  - NCI/NIH
  - Janssen
  - Lloyd Foundation
  - Sidewater Family Fund
  - MacKenzie's Mission
  - Alexion
- Consultant/Advisor
  - Alexion
  - Janssen
  - Sanofi
  - Nexcella

Screening Studies

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- **The goal is to detect disease or risk of disease in asymptomatic subjects**
- ***Seeking AL Amyloidosis Very Early (SAVE)***
- ***SAVE 1(unfunded):*A Pilot Study Seeking AL Amyloidosis Very Early by Identifying Clonal λ Light-chain Genes in Patients at Risk**
  - **λ MGUS and λ SMM with dFLC > 23mg/L**
  - ***IGLV* genes amplified from peripheral blood**
  - **Screen subjects with *IGLV* genes enriched in AL**
- ***SAVE 2 (R21):*Screening for Systemic Light-Chain Amyloidosis in Patients Over 60 with λ Monoclonal Gammopathies (2021-2023)**

Clin Lymp Myel Leuk 2012;12(1):49-58.
J Clin Oncol 2014; 32(25):2699-704.
Br J Cancer Res 2024; 7(2):681-686.
J Clin Med 2025,14(12),4146;https://doi.org/10.3390/jcm14124146

Updated AL-Base IGVL Germline Genes Enriched in AL

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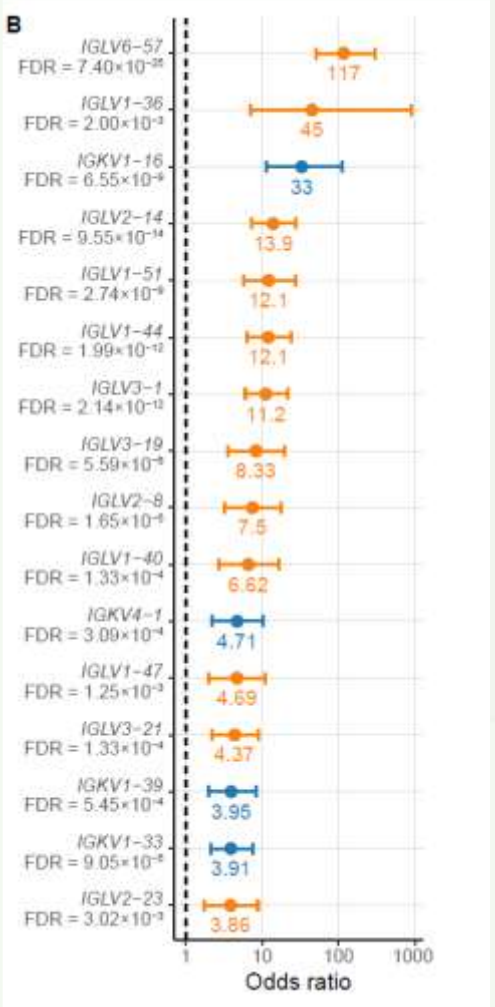
- **AL-Base**
  - **2163 sequences from PC diseases**
- **Compared germline gene use in AL, MM and polyclonal immune repertoire from the Observed Antibody Space**
- **16 germline genes enriched in AL**
  - **12 λ, 4 κ**
- **9/12 λ genes used in SAVE 1 and 2**



Amyloid 2025;32(2):129-138.

SAVE 1 (NCT02741999) Pilot Study Results

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We enrolled 21 patients, 19 SMM and 2 MGUS.

We identified IGLV genes in 86% (18/21) of cases. Four of the 18 IGLV genes were not enriched in AL and 3 of these 4 progressed to myeloma requiring therapy; the 4th was screened for amyloid and was negative.

Fourteen with genes enriched in AL had comprehensive evaluations and two with SMM had AL. The gene in both cases was LV 2-14.

Br J Cancer Res 2024; 7(2):681-686

SAVE 1 (NCT02741999) Pilot Study Results

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Characteristic	Patient One	Patient Two
Age/Gender	56/F	58/F
Months with SMM	9	99
λ FLC (mg/L) (5.7-26.3)	133	124.4
κ/λ Ratio (0.26-1.65)	0.09	0.05
M-protein (g/dL)	IgGλ 1.7	IgAλ 0.48
NT-proBNP (pg/mL)	221	412
Troponin I (ng/mL)	0.01	0.03
Creatinine (0.6-1.2 mg/dL)	0.9	0.69
Albumin (3.5-5.5 g/dL)	3.8	3.8
Alkaline Phosphatase (20-140 IU/L)	43	64
Biopsy Sites Positive	Fat, marrow, GI	Heart

SAVE 2 (NCT04615572)
A Multicenter Screening Study

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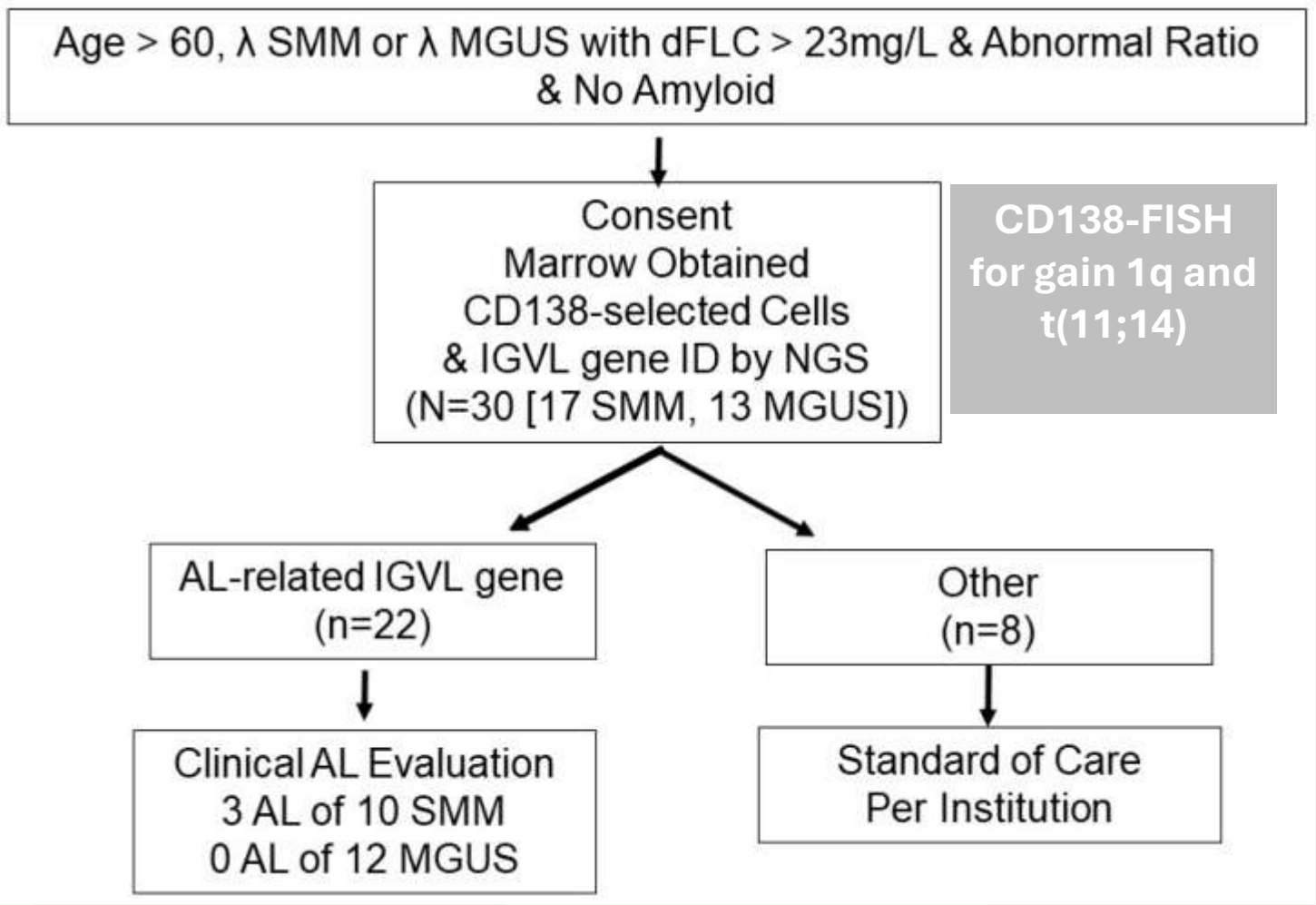

NGS (CUIMC) SMM Marrow MNC Adequate CD138-selection Not Needed

SMM IGVL	NCT04615572 (*n* = 17 SMM)	GenBank #
LV1-44	2	OQ912884 OQ912876
LV1-47	2	OQ884472 OR506910
LV2-8	3	OQ912883 OQ912886 OQ912887
LV2-11	1	OQ912882
LV2-14	1	OQ912877
LV2-23	2 (1 AL)	OR506909 OQ912881
LV3-1	3 (2 AL)	OQ819165 OQ912879 OQ912885
LV3-12	1	OQ912875
LV3-21	2	OQ912880 OQ912878

J Clin Med 2025;14:4146 https://doi.org/10.3390/jcm14124146

SAVE 2

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From 2021 to 2023, we enrolled 30 subjects (19 M) with a median age of 68.5 years (IQR 64.3–73), 17 SMM and 13 MGUS, with a median of 6% marrow plasma cells (3.5–40).

Eleven SMM and 4 MGUS cases had t(11;14) or gain 1q; 10/17 SMM and 12/13 MGUS had genes enriched in AL.

AL was confirmed by tissue biopsy in 3 with SMM.

SAVE 1 + SAVE 2
AND t(11;14) AND GAIN 1Q

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- Five AL in 36 SMM cases
- Zero AL in 15 MGUS cases
- Eight patients with SMM progressed
  - 7 to MM requiring therapy
  - 1 to glioblastoma
- In SAVE 2 SMM, AL *IGVL* genes,and t(11;14) or gain 1q were found in 6 SMM subjects, including the 3 with AL.
- In SMM 23% of patients are CCND1-positive with t(11;14)and 30% have gain 1q (J Clin Oncol. 2013;31(34):4325-32; Blood Adv. 2018;2(12):1470-9; Blood Cancer J. 2021;11(4):83)
- In a series of 133 AL patients whose marrow plasma cells were evaluated for clonal cytogenetic abnormalities, 83 (62%) had t(11;14) and 35 of 130 (27%) had gain 1q (J Clin Oncol. 2015;33(12):1371-8).
- In another series of 140 AL patients, 59% had t(11;14) and 20% had gain 1q (Blood. 2016;128(4):594-602).

SAVE 3 (NCT06365060)

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

Screening for AL Amyloidosis in Smoldering Multiple Myeloma

Clinicaltrials.gov # NCT06365060
NCI grant # R01CA279808

NIH NATIONAL CANCER INSTITUTE

Tufts Medical Center

AIM 1

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- **Creating a network to enroll patients on a collaborative study requiring marrow and blood specimens, to collect data for a training set of likelihood statistics and to plan a future validation study.**
- **Variables we are using to construct the algorithm: SMM, dFLC > 23, *IGVL* germline donor, presence of t(11;14) or gain 1q, and NT-proBNP > 332 pg/ml.**
- **We will evaluate 340 SMM patients > 40 years old who pass FLC criteria using standard of care tests including NT-proBNP and clinical marrow specimens evaluated for the presence of t(11;14) and gain1q.**
- **Marrow cells will be processed by NGS for clonal *IGVL* gene identification.**

AIM 2

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- **Validating an NGS assay that identifies *IGVL* genes in clonal plasma cells.**
- **Creation and validation of a laboratory developed test in a precision medicine laboratory that is certified under regulations of the Clinical Laboratory Improvement Amendments of 1988 (CLIA).**
- **Approval for this laboratory developed test for both κ and λ *IGVL* genes will permit providers, patients and researchers to use the test in decision-making to care for MG patients.**

Participating Centers
(13 of 15 Planned)

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Site Name	Name of Site PI (s)
Tufts Medical Center	Raymond Comenzo, MD
Columbia University Medical Center	Suzanne Lentzsch, MD, PhD Mahesh Mansukhani, MD
The Ohio State University Comprehensive Cancer Center	Naresh Bumma, MD
University of California, San Francisco	Alfred Chung, MD
UNC Lineberger Comprehensive Cancer Center	Sascha Tuchman, MD
University of Utah, Huntsman Cancer Hospital	Amandeep Godara, MD
Memorial Sloan Kettering Cancer Center	Heather Landau, MD
University of Alabama Hospital	Susan Bal, MD
Atrium Health Levine Cancer Institute (Hematology)	Cindy Varga, MD
Boston University School of Public Health	Vaishali Sanchorawala, MD Gheorghe Doros, PhD Gareth Morgan, PhD
VCU Medical Center	Hashim Mann, MD
Cedars-Sinai Medical Center	Robert A. Vescio, MD
Cleveland Clinic Florida, Weston Hospital	Chakra Chaulagain, MD

SAVE 3 (NCT06365060)

Data as of 9/1/25

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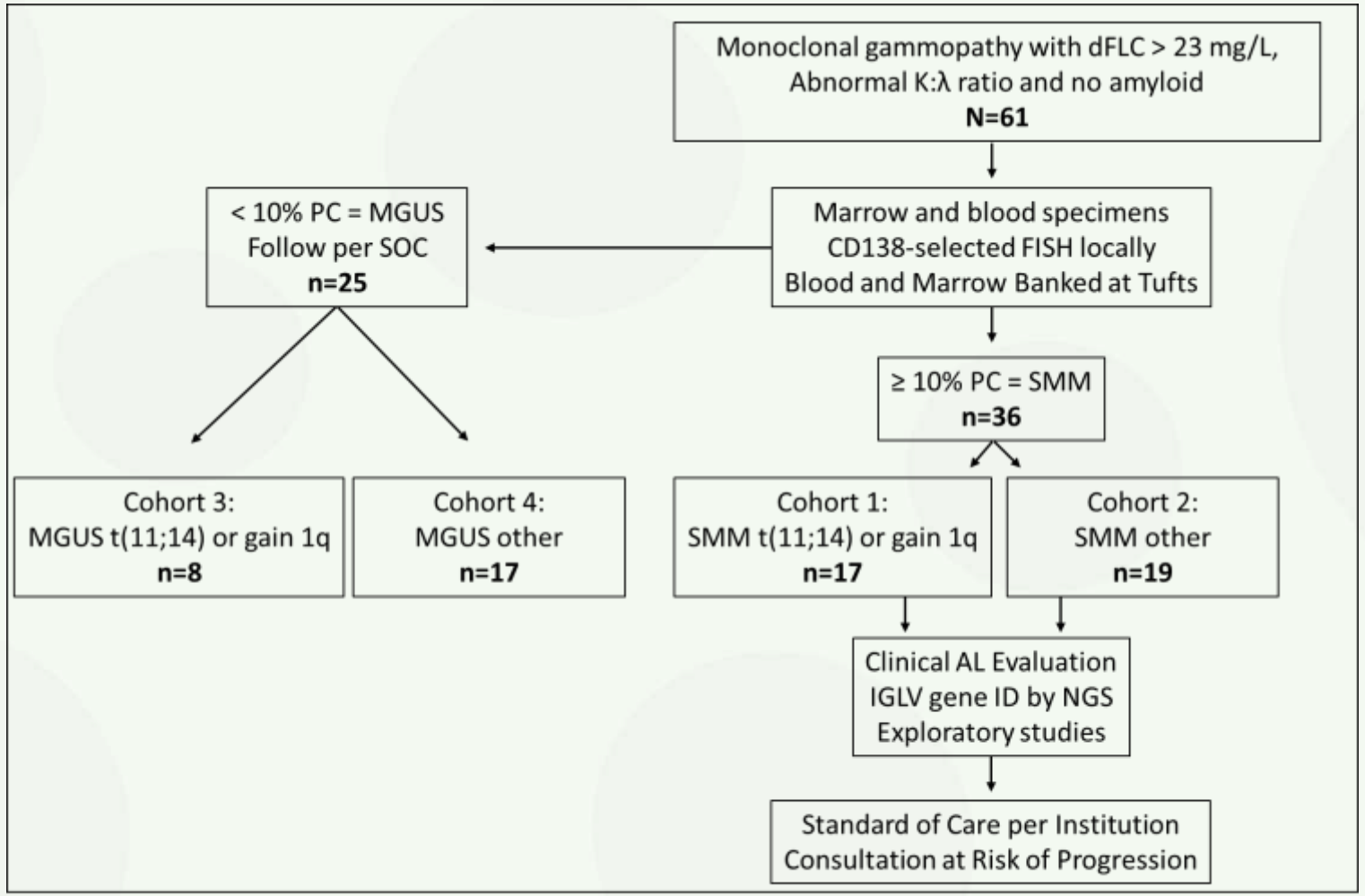

MGUS = monoclonal gammopathy of undetermined significance; IGVL = immunoglobulin variable region light chain; ID = identification; NGS = next generation sequencing; PC = plasma cells; SMM = smoldering multiple myeloma

Acknowledgements

Demarest Lloyd Jr Foundation

The Amyloidosis Foundation

Werner and Elaine Dannheiser Fund for Research on the Biology of Aging of the Lymphoma Foundation

The Sidewater Family Fund

The Amyloidosis and Myeloma Research Fund

MMRF

The Cam Neely and John Davis Myeloma Research Fund

Janssen

Laboratory

Ping Zhou, PhD, MD

Xun Ma, PhD, DMD

Stephanie Scalia, MA

Denis Toskic

Xia (Yaya) Wu, MD

Colin Kloock, MD

Aaron Feinstein, PhD

Neely Center for Clinical Cancer Research

MaryAnn Weitz, NP

Terry Fogaren, NP

ISA Workshop
Amyloidosis from Bench to Bedside and Back Again
2025.10.13 – 14 @ Collegio Ghislieri, Pavia, Italy

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Follow-up Standards for Carriers

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Department of Medicine (Neurology and Rheumatology)
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Disclosures

Yoshiki Sekijima

Lecture Honoraria, Advisory Board

Alnylam Pharmaceuticals, Alexion, Pfizer Inc.

Research Grants

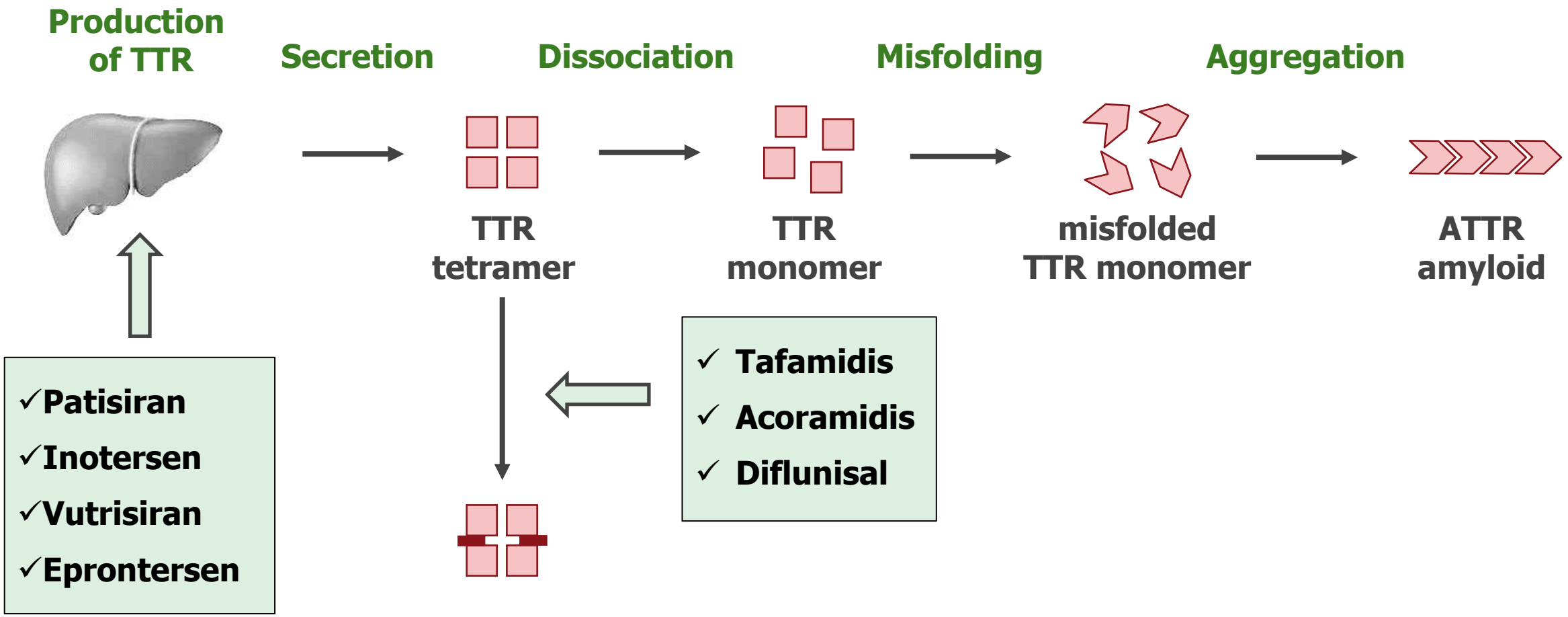
Alnylam Pharmaceuticals, Pfizer Inc.

Factors influencing the decision on predictive genetic testing

- ✓ Availability of effective disease-modifying therapy
- ✓ Severity of the disease (particularly presence or absence of cognitive impairment)

	No cognitive impairment	Mild cognitive impairment	Sever cognitive impairment
Disease-modifying therapies available	Hereditary ATTR amyloidosis		Alzheimer disease
Effective symptomatic therapies available		Parkinson disease	
No effective therapy available	Charcot-Marie-Tooth disease	Spinocerebellar degeneration	Huntington disease

Disease Modifying Therapies for ATTR Amyloidosis



The availability of disease modifying therapies for ATTR amyloidosis with maximal efficacy in the early stages supports the use of predictive genetic testing to identify asymptomatic carriers and enable timely intervention.

Predictive Genetic testing for at risk ATTRv family members

- ✓ Predictive testing is indicated for adults aged 18 or older, because ATTRv is an adult-onset disease.
- ✓ To ensure an informed and autonomous decision, comprehensive information on disease natural history and long-term management should be provided.
- ✓ It is also important to provide anticipatory guidance, asking clients to imagine what life would be like if their test results were positive.
- ✓ Predictive testing should be performed after genetic counseling by qualified professionals.

Genetic counselors

Genetic counseling room

Predictive Genetic testing for at risk ATTRv family members

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Genetic counselors

Genetic counseling room

Recommended evaluations

- ✓ Clinical questionnaire/medical interview addressing positive and negative sensory symptoms, autonomic symptoms (gastrointestinal, genitourinary, orthostatic hypotension), heart failure symptoms, and ocular symptoms
- ✓ Neurological examination assessing small and large nerve fibers
- ✓ Cardiac investigations including ECG, blood biomarkers (NT-proBNP or BNP and cardiac troponin), and echocardiography
- ✓ Assessment of nutritional status according to mBMI and serum TTR
- ✓ Biopsy (abdominal fat, gastroduodenal mucosa)
- ✓ Amyloid imaging (bone scintigraphy, etc)

When to start the evaluations ?

Early-onset (< 50) family

(ATTRV30M families in endemic foci)

Annual evaluation should begin as soon as a pathogenic variant is identified

Late-onset (≥ 50) family

(most families in non-endemic foci)

Annual evaluation should begin approximately 10 years before the predicted age of onset

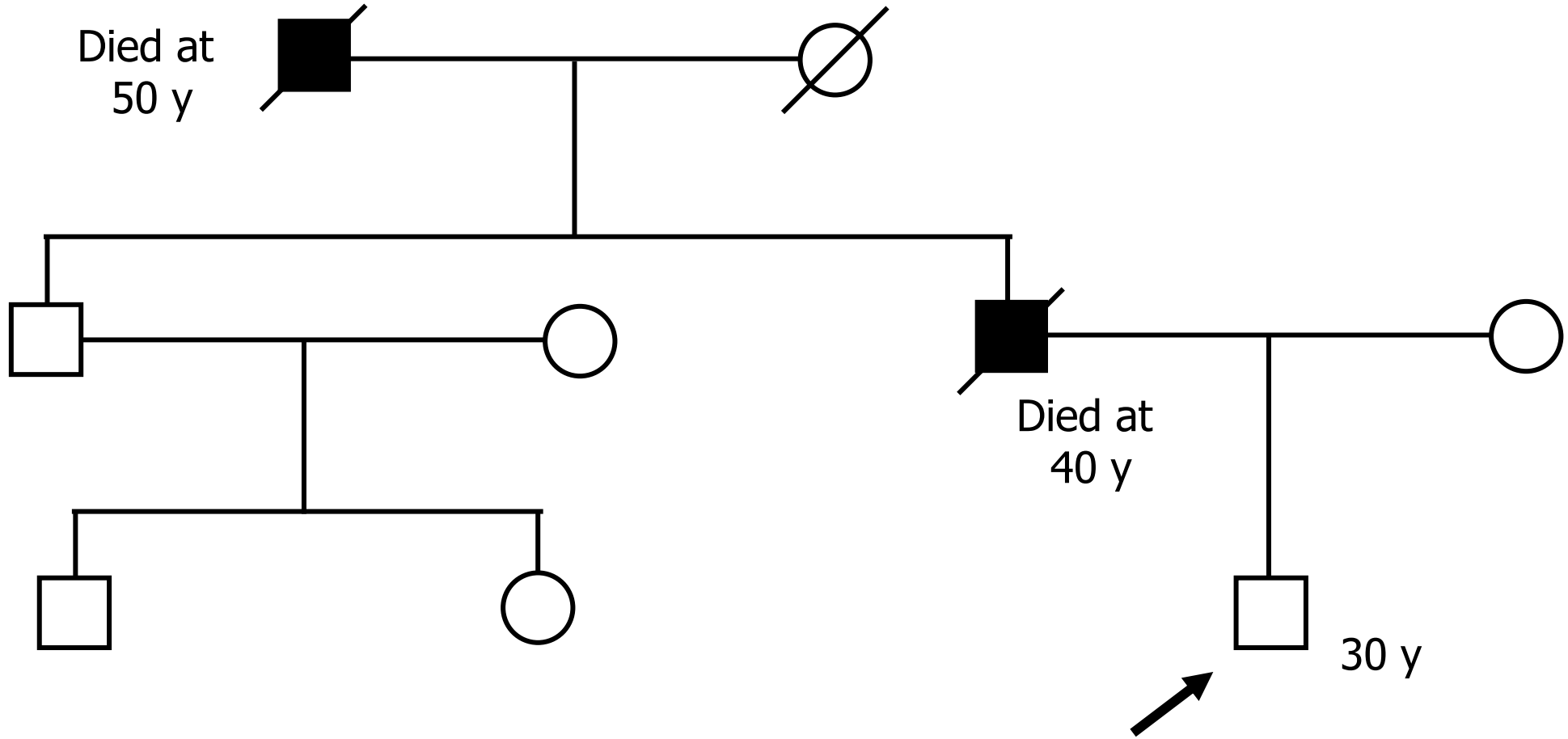
Females develop the disease approximately 5 years later and show lower penetrance rate compared to male even within the same family

Client: 30 y.o. Male

Past history: None

Family history: ATTRv amyloidosis with V30M (p.V50M) variant (father, grandfather)

Originated from an endemic focus in Nagano prefecture



Client: 30 y.o. Male

Present illness:

30 y.o. Visited the genetic counseling department of Shinshu University Hospital hoping to take predictive genetic testing.

Predictive genetic testing was performed after genetic counseling.

→ *TTR* gene V30M (p.V50M) variant heterozygote

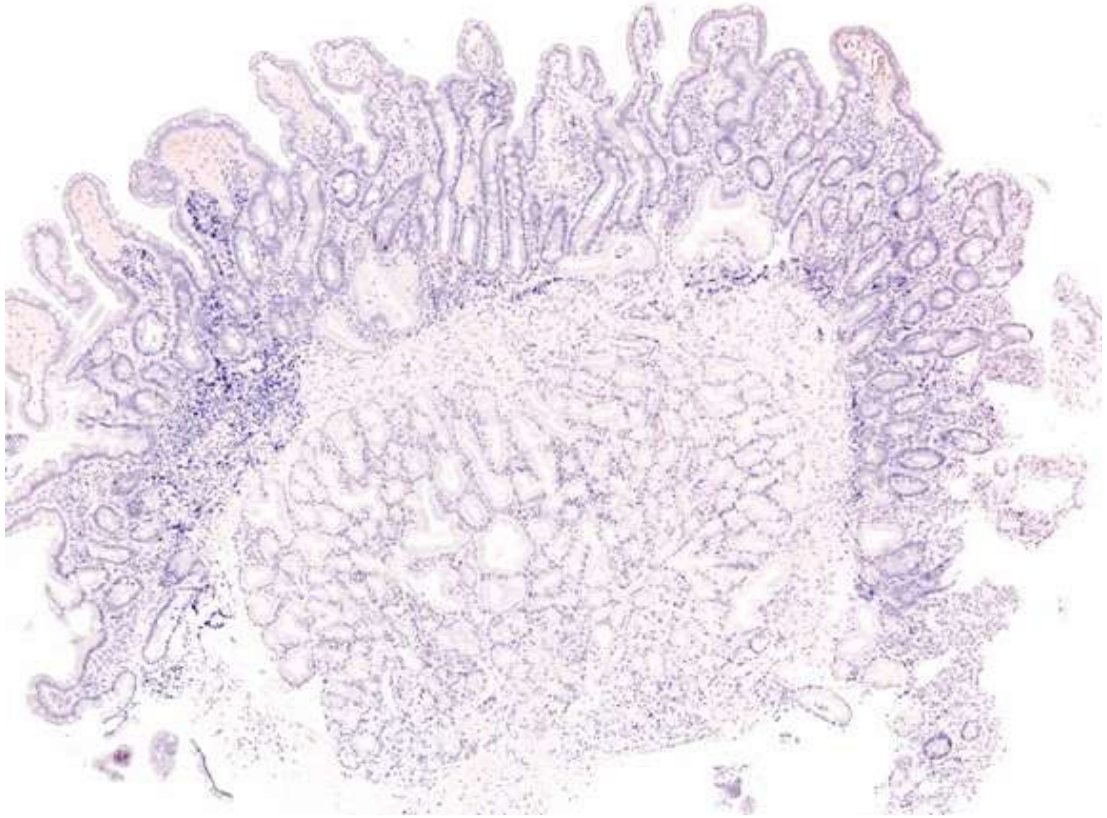
Annual follow-up counseling & evaluation

31 y.o. No symptoms, no amyloid deposition

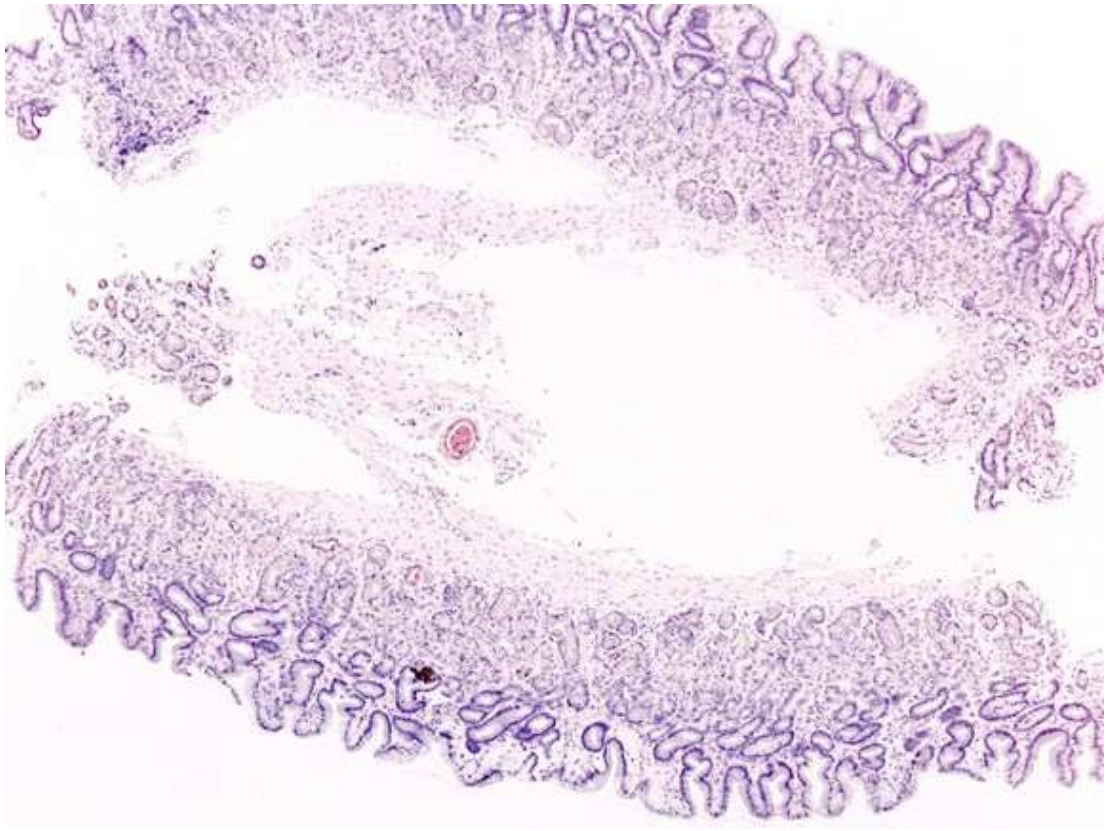
32 y.o. No symptoms, no amyloid deposition

33 y.o. Amyloid deposition was confirmed by gastroduodenal biopsy, although no symptoms or signs related to ATTRv were observed.

Gastroduodenal biopsy



Congo red staining

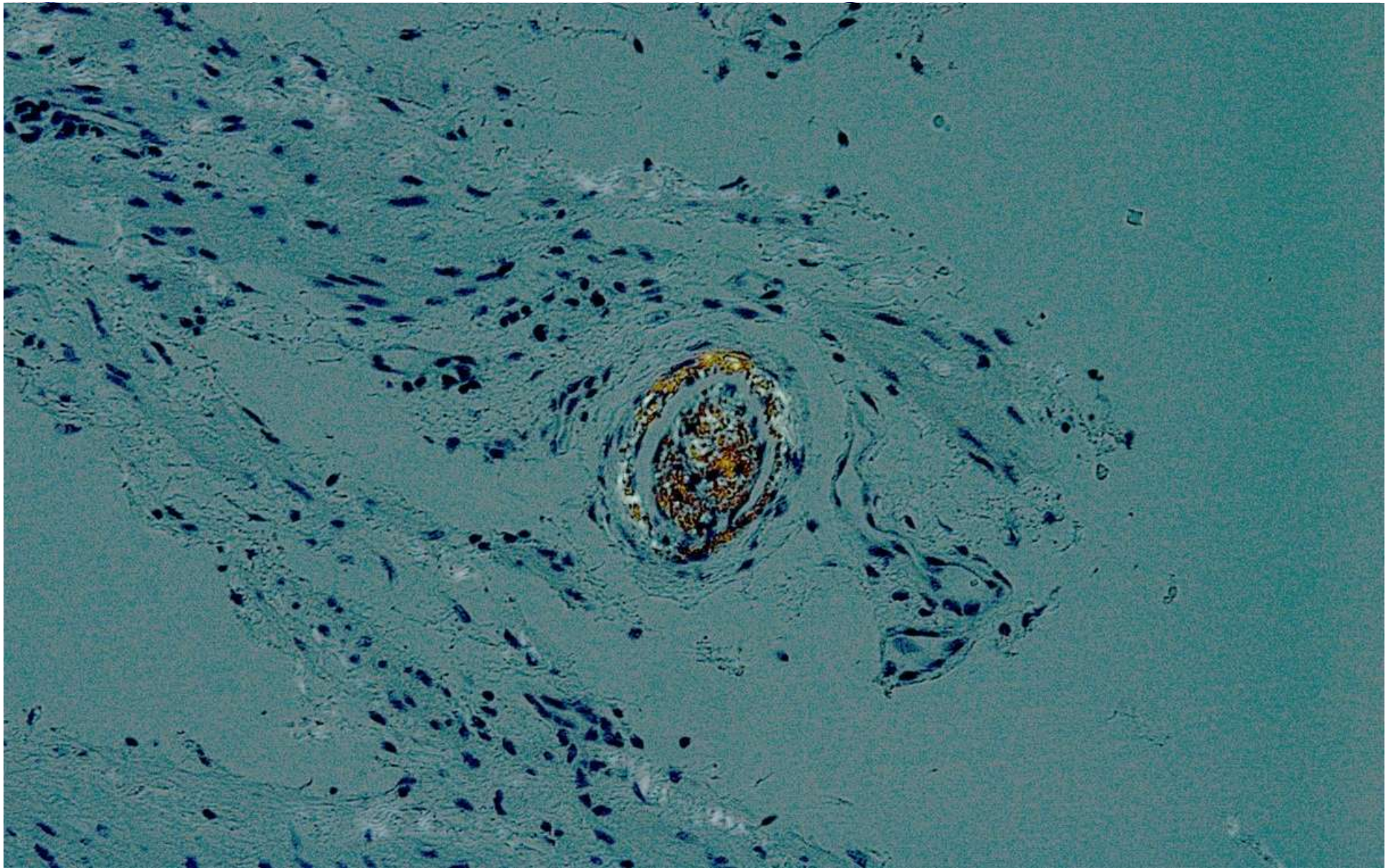


Congo red staining

Amyloid deposition was detected in 2 out of 6 specimens of gastroduodenal biopsy

(Amyloid was negative in 4 biopsied specimens)

Gastroduodenal biopsy

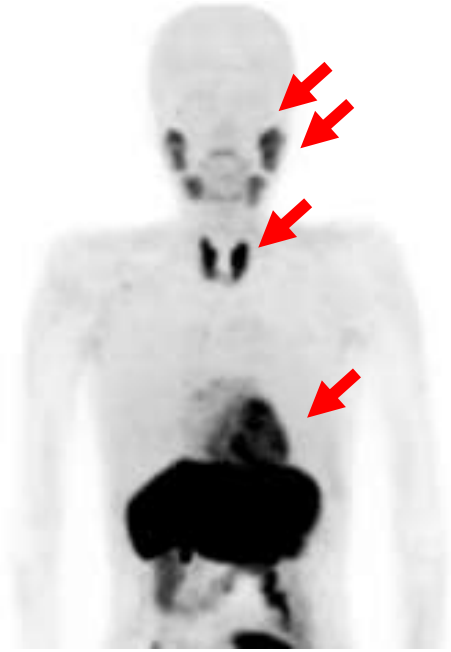


Recently developed clinical tests may detect asymptomatic amyloid neuropathy

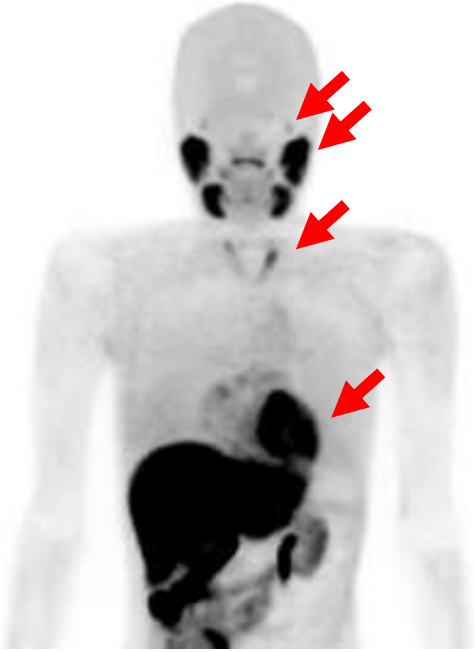
- ✓ Plasma/serum neurofilament light chain (NfL)
- ✓ Intraepidermal nerve fiber density (IENFD)
- ✓ Quantitative sensory testing
- ✓ Electrochemical skin conductance using Sudoscan® device
- ✓ Laser-evoked potentials
- ✓ Sympathetic skin responses
- ✓ High-resolution magnetic resonance neurography

Whole body PiB-PET

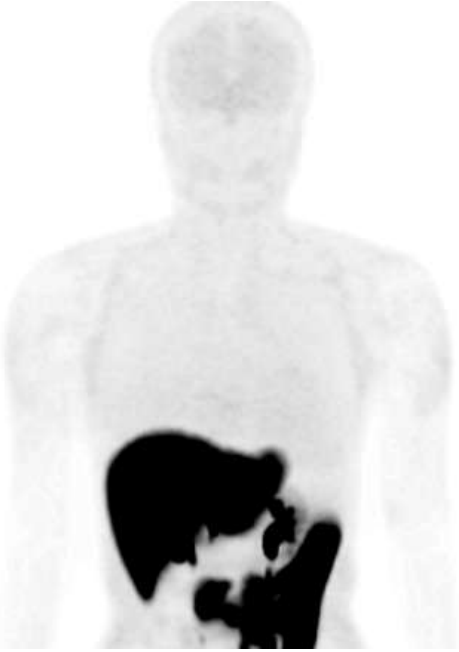
- ✓ PiB-PET can detect whole body amyloid deposition very clearly
- ✓ Amyloid PET may be useful for early diagnosis of asymptomatic variant carriers



ATTRv amyloidosis
43 y.o. Male



ATTRv amyloidosis
43 y.o. Male



Healthy control
39 y.o. Male

*PET has low sensitivity to type A amyloid fibers

Ezawa et al., Eur J Nucl Med Mol Imaging 45: 452-61, 2018

Ultimate Goal: Prevention!

Intervene with disease modifying drugs before onset and prevent the disease from developing

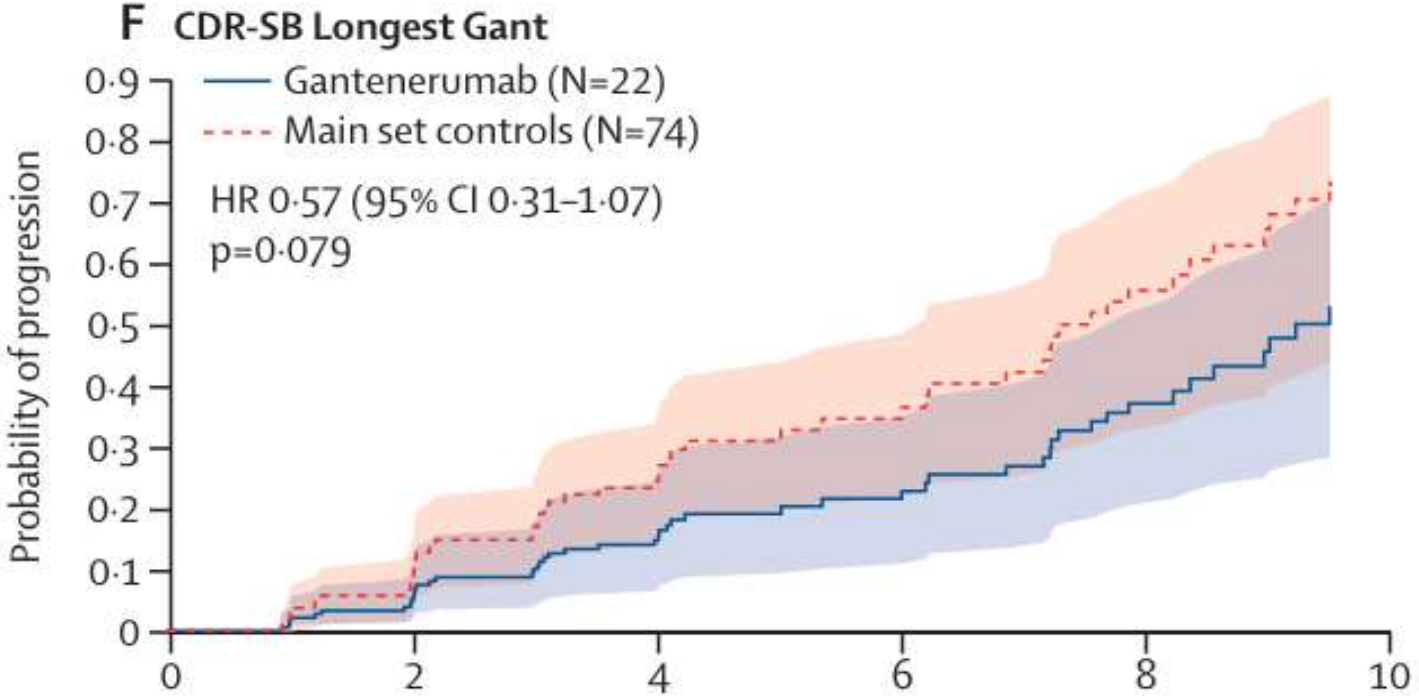
ACT-EARLY (https://clinicaltrials.gov/study/NCT06563895)

- ✓ Phase 3, randomized, placebo-controlled trial of Acoramidis
- ✓ Enroll 600 asymptomatic carriers
- ✓ Primary endpoint: time to onset of ATTR-CM or ATTR-PN

DIAN Preventive Intervention Study

Safety and efficacy of long-term gantenerumab treatment in dominantly inherited Alzheimer's disease: an open-label extension of the phase 2/3 multicentre, randomised, double-blind, placebo-controlled platform DIAN-TU trial.

Lancet Neurology 24:316–30, 2025



First Proof of Concept of Alzheimer disease Prevention

In a clinical trial of Gantenerumab (anti-Aβ antibody) targeting asymptomatic carriers of familial Alzheimer's disease, the incidence of dementia onset was significantly reduced in the long-term gantenerumab treatment group.

Take Home Messages

- ✓ Genetic counseling and predictive genetic testing are very important for early diagnosis of at-risk family members in ATTRv amyloidosis.
- ✓ Annual follow-up counseling & evaluations are necessary for asymptomatic carriers.
- ✓ The ultimate goal is to intervene with disease modifying drugs before onset and prevent the disease, and a phase 3 clinical trial targeting asymptomatic carriers will soon begin.

Thank you very much for your attention

Matsumoto Castle

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

Screening and early diagnosis of ATTR amyloidosis
Genetic predisposition

Prof. Andrea Cortese, MD, PhD

Queen Square Institute of Neurology – University College London, London

University of Milano, C. Besta Neurological Institute, Milan

Gene structure

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18q11.2-12.126

TTR

- The first exon contains **signal peptide** of 20 amino acids along with the first 3 amino acid residues of the mature protein.
- Depending on inclusion on 20AA signaling peptide, **147aa or 127aa** (mature) protein

Ingenbleek Y, Annu Rev Nutr, 1994

Gene function

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- RBP-vit A and T4 transporter
- Neuroprotection
  - in basal condition:
    - TTR KO mice show mild cognitive and behavioural phenotype
  - After injury:
    - PNS: TTR KO impaired axon regeneration after nerve crush
    - CNS: TTR KO increased ABeta accumulation (AD) – in vitro and animal models and impairs regeneration in stroke – models and humans
- Possible role in placenta and human foetal development

Feming CE, Saraiva MJ, Sousa MM. J Neurochem. 2007;103(2):831-839.
Brouillette J, Quirion R.. Neurobiol Aging. 2008;29(11):1721-1732.
Buxbaum JN, Proc Natl Acad Sci U S A. 2008
Buxbaum JN, Neuroscience. 2014

TTR variation in healthy controls (Gnomad)

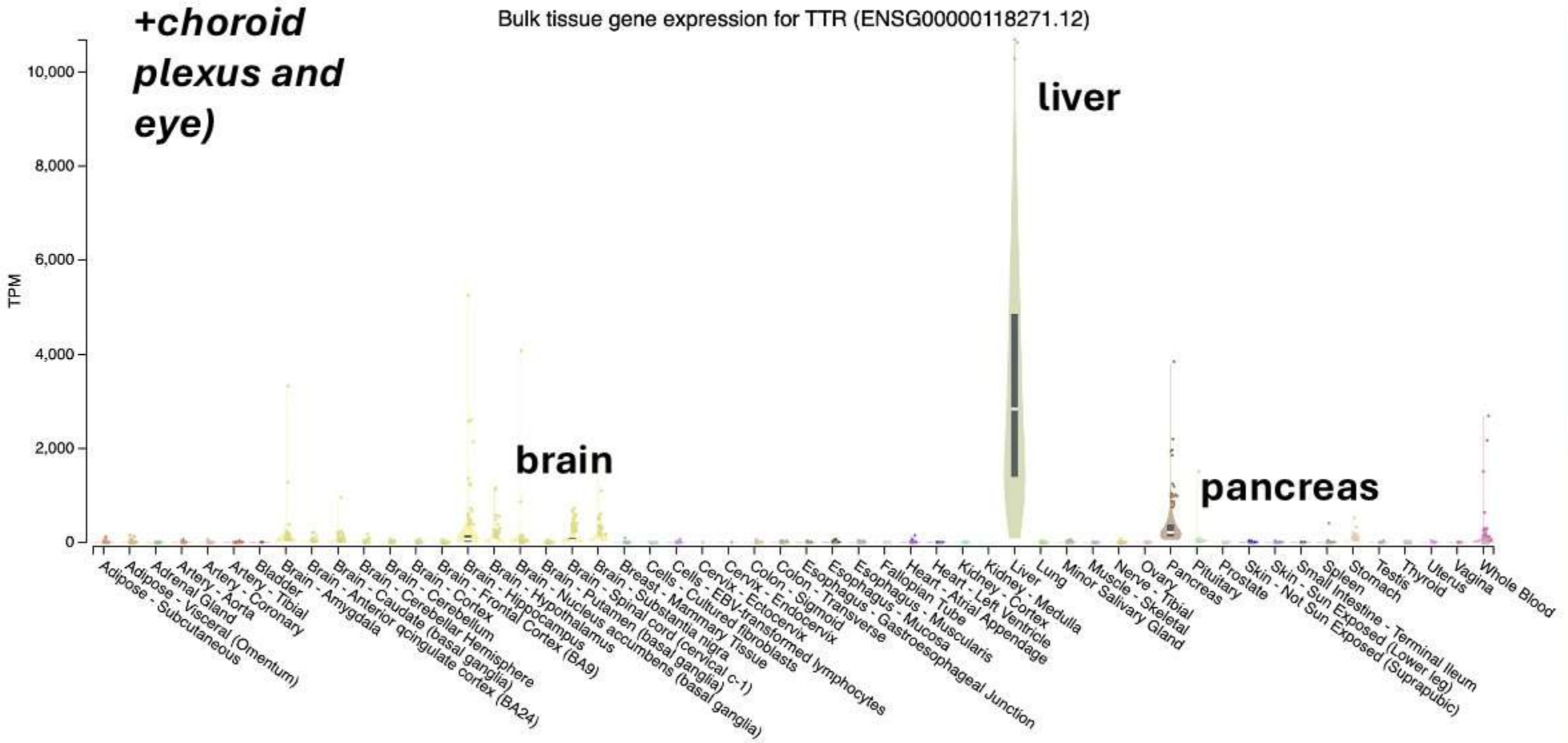
ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

- However no biallelic Loss of function observed in humans
- Heterozygous truncating variants are tolerated

Variant ID	Source	HGVS Consequence	VEP Annotation	LoF Curation	Germline classification	Flags	Allele Count	Allele Number	Allele Frequency	Number of Homozygotes
18-31591900-A-G	E G	c.-1-2A>G †	splice acceptor		Conflicting classifications ...	LC pLoF	20	1614086	1.24e-5	0
18-31591901-G-A	E	c.-1-1G>A †	splice acceptor			LC pLoF	1	1614144	6.20e-7	0
18-31591972-G-A	E G	c.69+1G>A	splice donor		Uncertain significance		2	1614122	1.24e-6	0
18-31592895-G-A	E	c.70-1G>A	splice acceptor		Uncertain significance		2	1613842	1.24e-6	0
18-31592910-CAA-C	E	p.Lys29ValfsTer29	frameshift				2	1614004	1.24e-6	0
18-31592911-A-T	E	p.Lys29Ter	stop gained		Uncertain significance		1	1614016	6.20e-7	0
18-31592942-CT-C	E	p.Val40SerfsTer46	frameshift				1	1614124	6.20e-7	0
18-31592942-C-CAG	E	p.Arg41SerfsTer46	frameshift				7	1614124	4.34e-6	0
18-31592943-T-TCCTCGG...	E	p.Val40ProfsTer50	frameshift				7	1614170	4.34e-6	0
18-31592947-C-T	E	p.Arg41Ter	stop gained		Uncertain significance		4	1614032	2.48e-6	0
18-31592977-CAT-C	E	p.His51ArgfsTer7	frameshift				1	1614108	6.20e-7	0
18-31593027-G-A	E	c.200+1G>A	splice donor				1	1613790	6.20e-7	0
18-31593027-G-T	E	c.200+1G>T	splice donor				1	1613790	6.20e-7	0
18-31595144-G-GC	E	p.His76ProfsTer6	frameshift				3	1614178	1.86e-6	0
18-31595155-CA-C	E	p.Thr80LeufsTer6	frameshift				1	1614136	6.20e-7	0
18-31595215-G-A	E	p.Trp99Ter	stop gained		Uncertain significance		1	1614174	6.20e-7	0
18-31598606-C-A	E	p.Tyr125Ter	stop gained				1	1614230	6.19e-7	0
18-31598670-G-T	E	p.Glu147Ter	stop gained		Conflicting classifications ...		24	1614152	1.49e-5	0

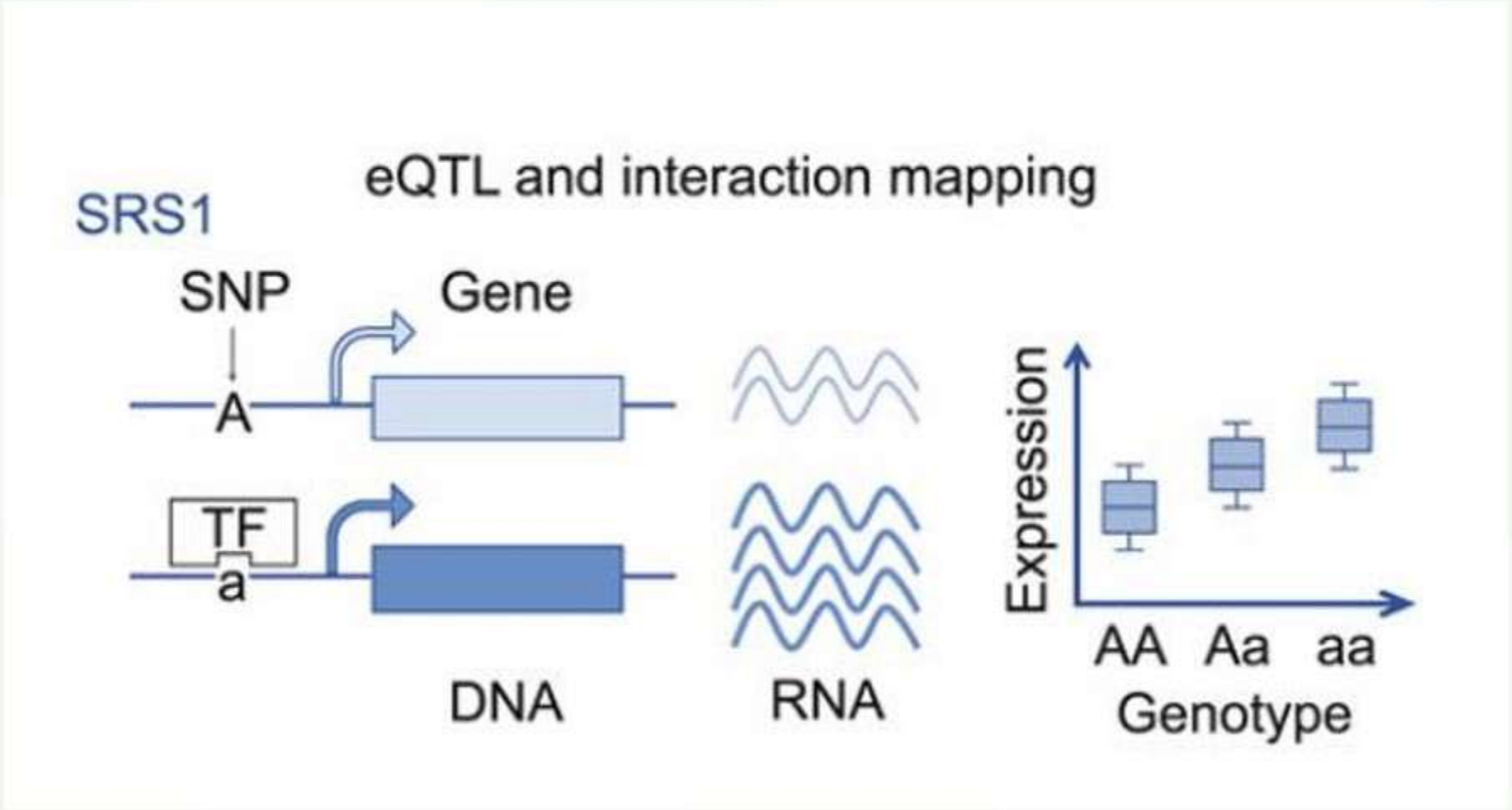
TTR expression (GTEx)

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS



Genetic regulation of gene expression

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS



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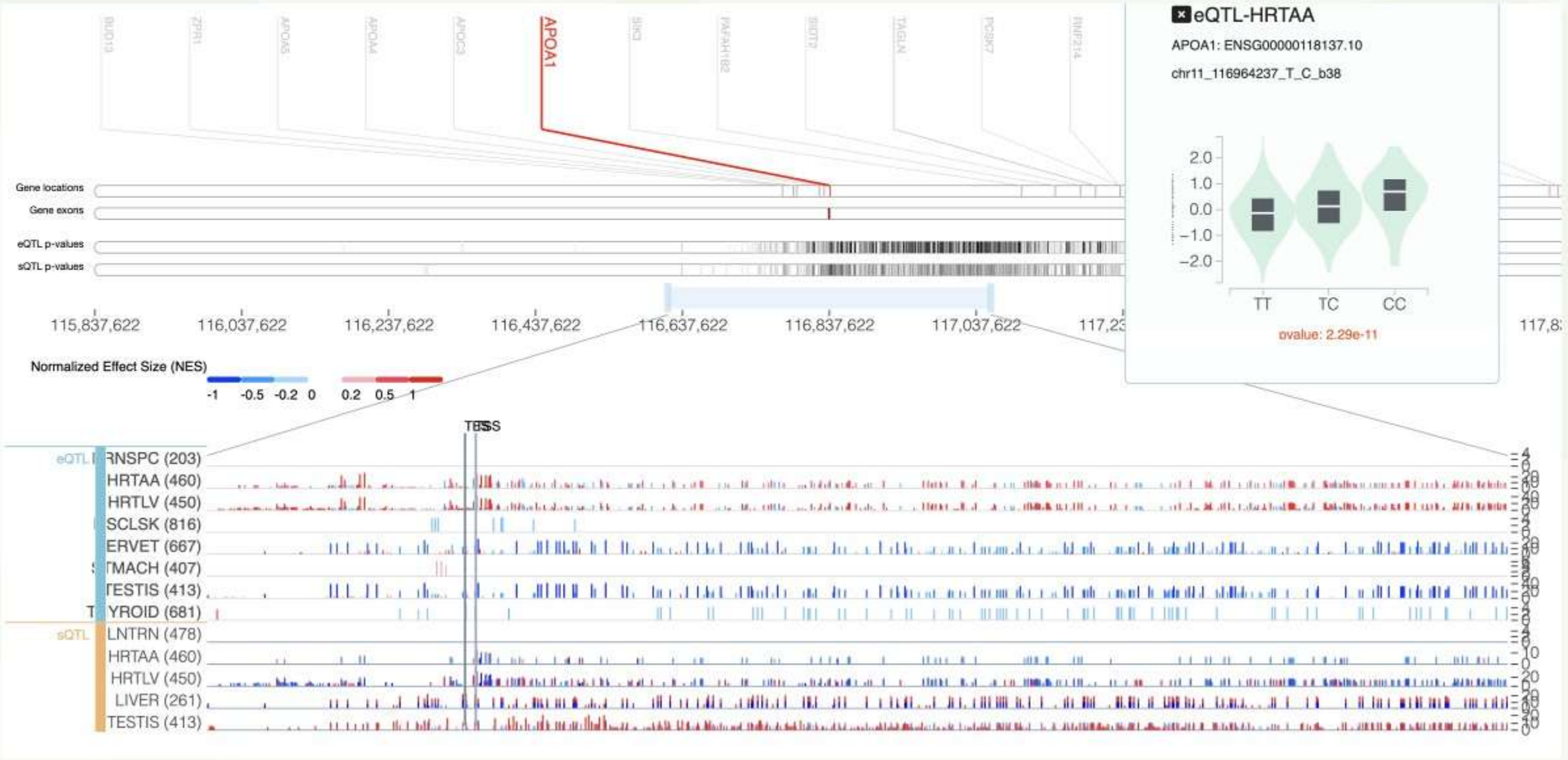
ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS



Genetic architecture of TTR locus

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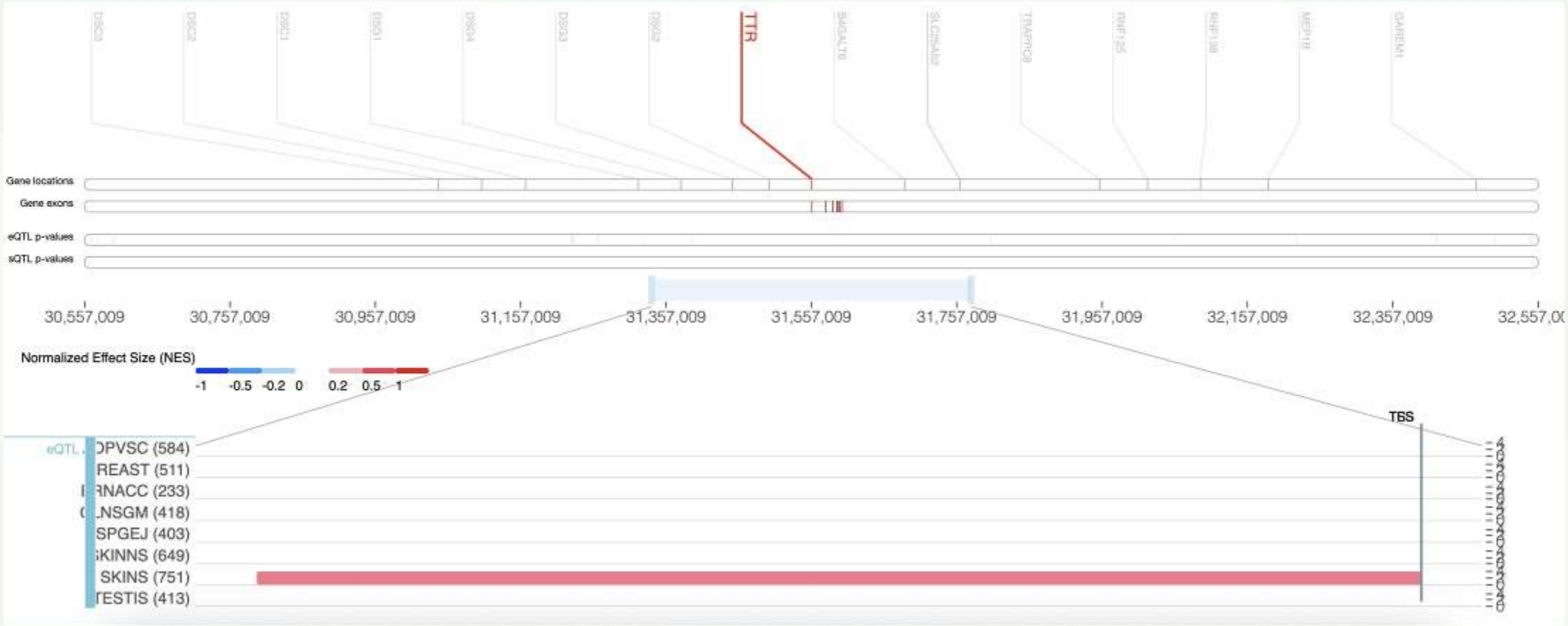

Regulation from cell-specific transcription factors (eg *hepatocyte nuclear factors (HNF)* in liver

TTR level influenced by sex, age, inflammation, nutrition, TTR variant

TTR genotype spectrum

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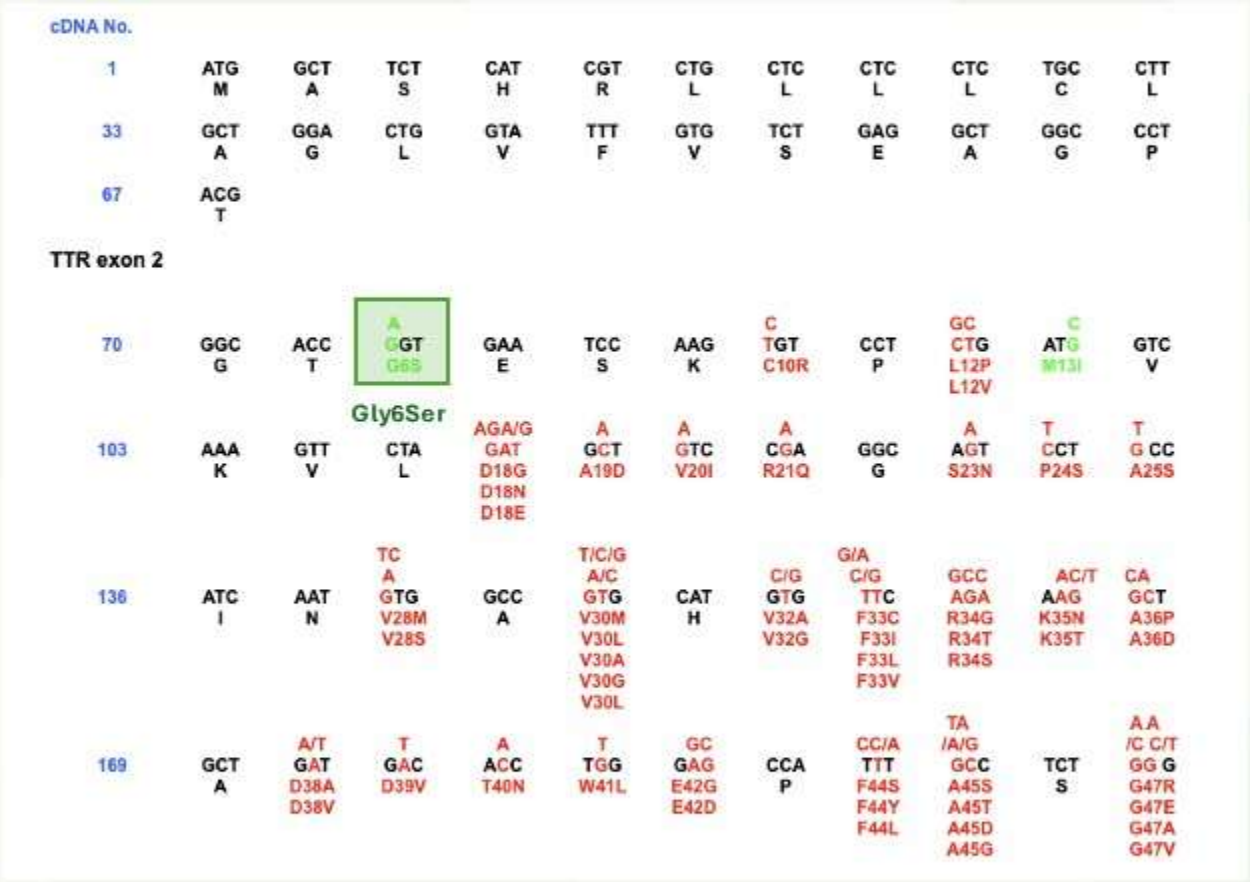
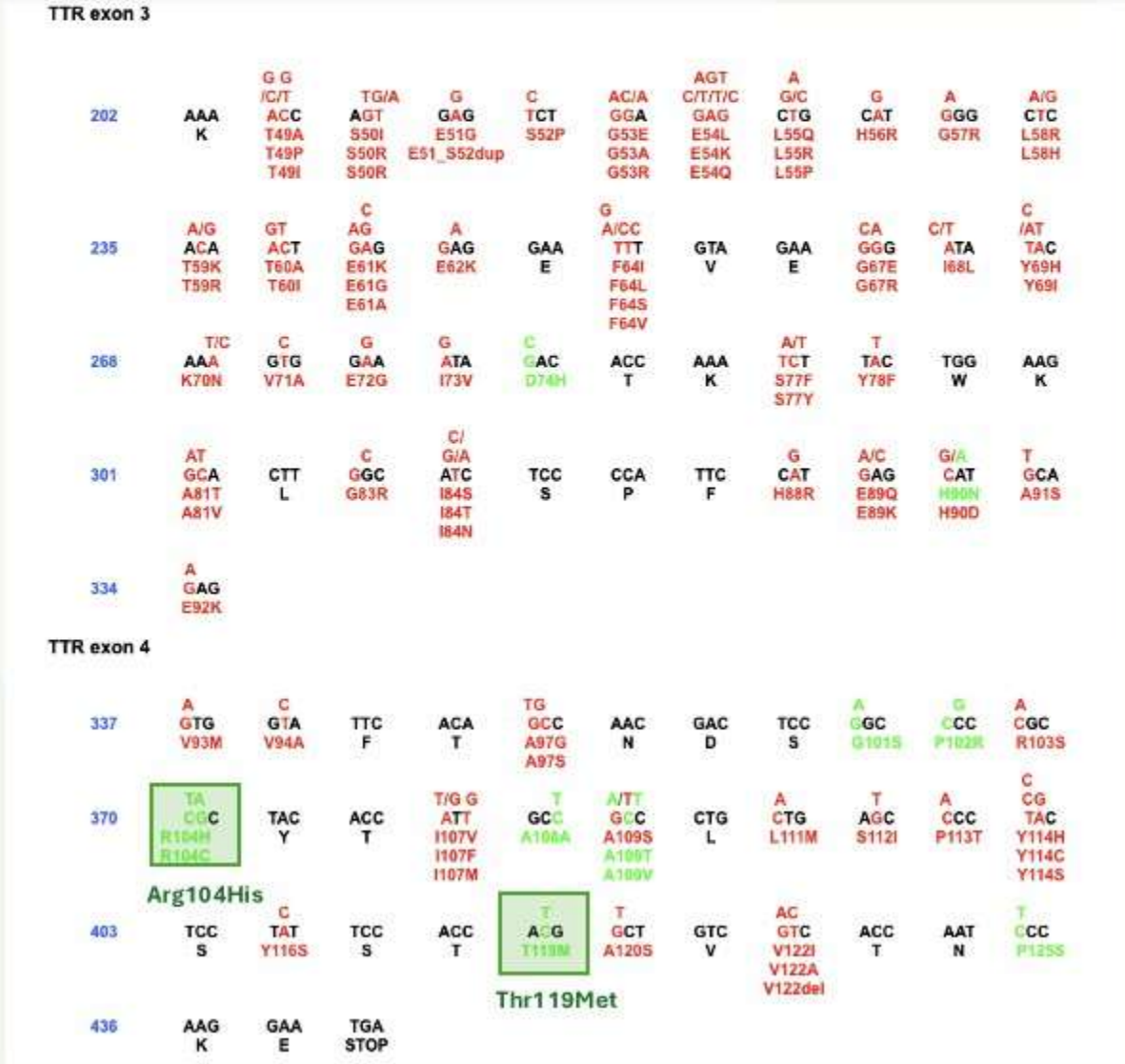


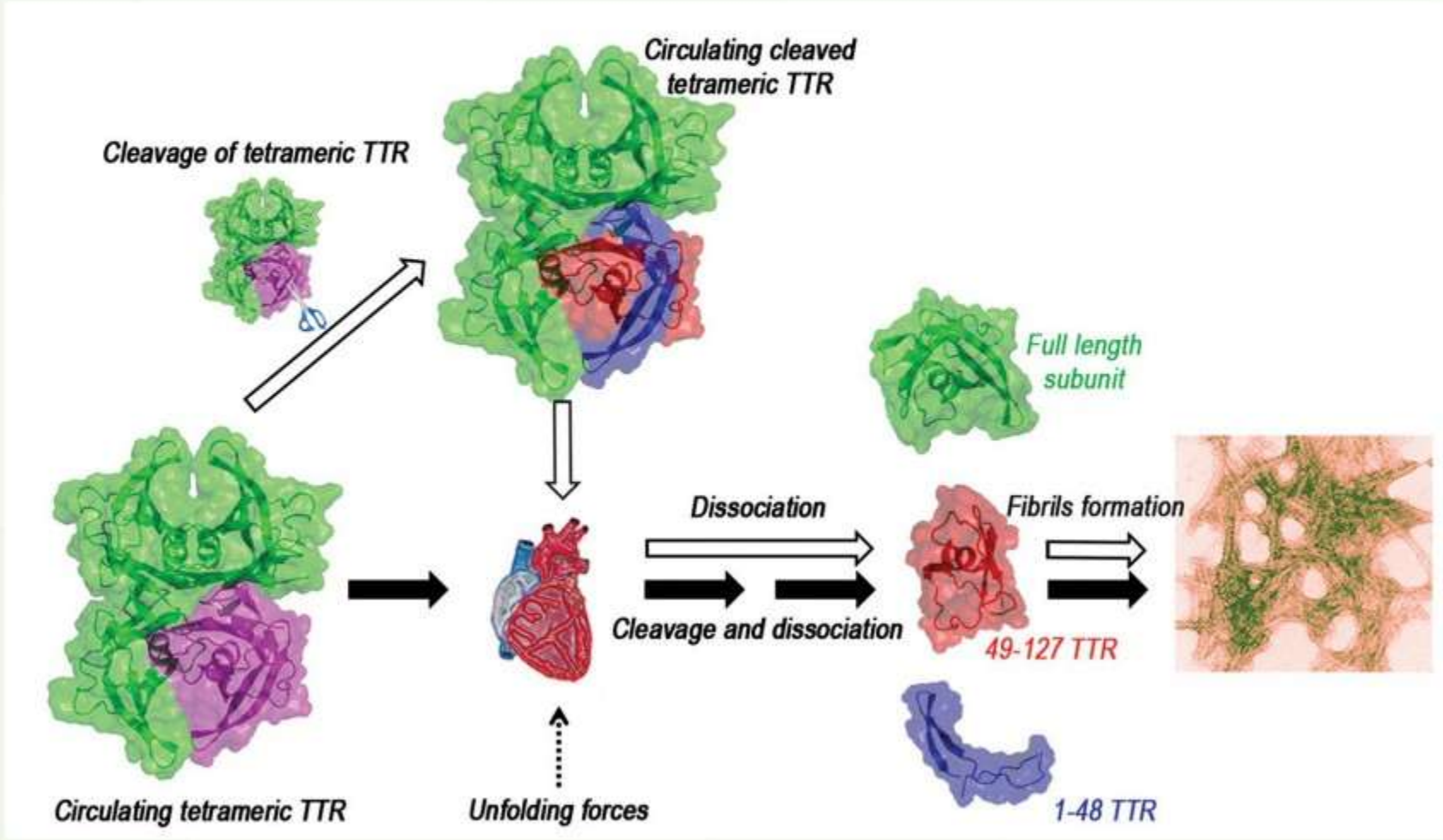


>150 TTR variants

http://amyloidosismutations.com/cdna-attr.html

Mechanisms of amyloidogenesis

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS



Julien Marcoux, EMBO Mol Medicine, 2015

Won Yee et al. Nat Comm 2019

Fibril composition

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Feature	Type A Fibrils (C-terminal fragment + full-length)	Type B Fibrils (Full-length only)
Fibril composition	Mixture of full-length TTR and C-terminal fragments (typically residues 49–127)	Exclusively full-length TTR (1–127)
Proteolytic cleavage	Cleavage at residues 48–49 generates amyloidogenic fragments; thought to promote aggregation	Minimal or absent cleavage; native tetramer misfolds without proteolysis
Associated genotypes	Late-onset V30M; most non-V30M variants (e.g., T60A, L111M, etc.); wild-type ATTR (ATTRwt)	Early-onset V30M (familial endemic Portuguese/Japanese cases)
Congo red staining	+	++
Fibril morphology (EM)	Shorter, thinner, and more granular fibrils; less ordered	Long, unfragmented, densely packed fibrils
Age at onset	Typically >50 years	Typically <50 years
Clinical course	Later onset, slower neuropathy, more cardiac involvement	Earlier onset, predominant neuropathy, minimal cardiac disease
Response to therapy (e.g. tafamidis, siRNA) and liver transpant	Some evidence of less complete regression after stabilization/silencing therapy	Better response in halting progression when treated early

T119M Protective effect

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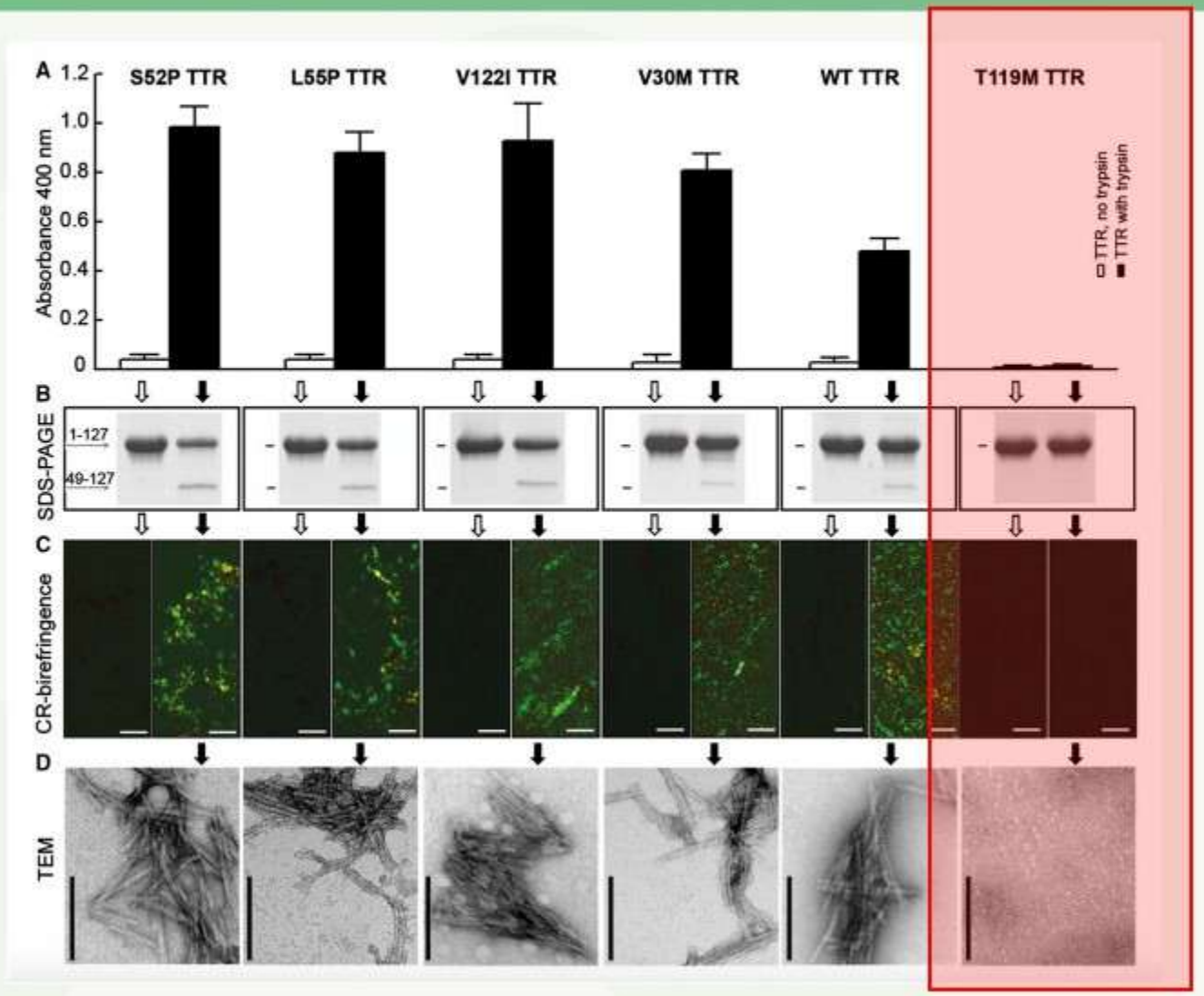

Julien Marcoux, EMBO Mol Medicine, 2015

Won Yee, Nat Comm, 2019

ATTRv clinical variability: TTR variant and phenotype

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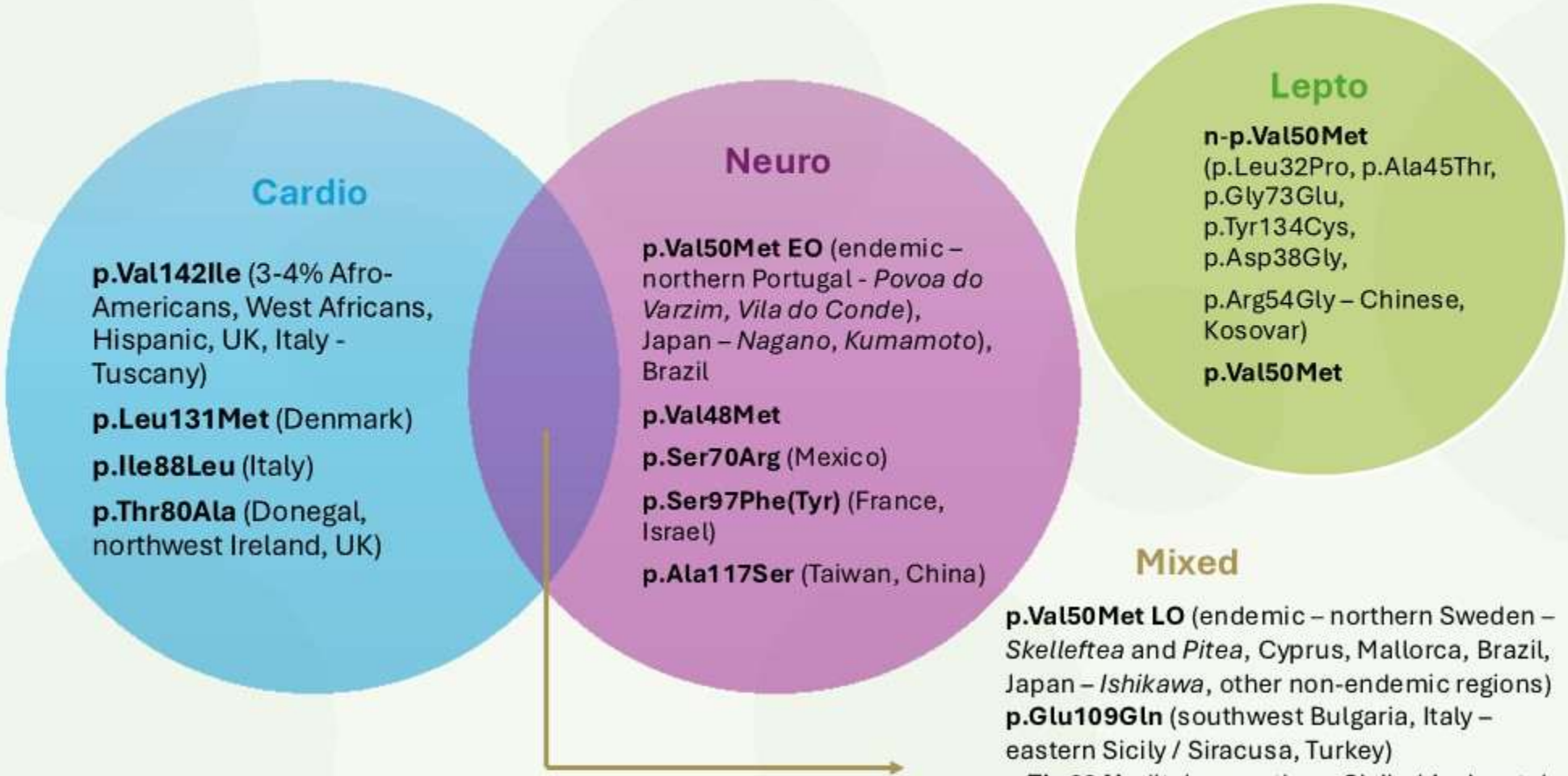


Mixed

p.Val50Met LO (endemic – northern Sweden – *Skelleftea* and *Pitea*, Cyprus, Mallorca, Brazil, Japan – *Ishikawa*, other non-endemic regions)
p.Glu109Gln (southwest Bulgaria, Italy – eastern Sicily / Siracusa, Turkey)
p.Thr69Ala (Italy – southern Sicily / Agrigento)
p.Phe84Leu (Italy – northern Sicily / Palermo)
p.Tyr98Phe (Italy – Lombardy/Bergamo)

ATTRv clinical variability: TTR variant and AOO

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

Table 1 Demographics of symptomatic patients according to genotype category

	Overall ($n = 4428$)	ATTRwt amyloidosis ($n = 1410$)	V30M early onset ($n = 1082$)	V30M late onset ($n = 670$)	Non-V30M ($n = 1264$)
Male, *n* (%)	3137 (70.8)	1315 (93.3)	565 (52.2)	433 (64.6)	822 (65.0)
Race/ethnicity[a], *n* (%)					
White	2450 (77.2)	1141 (94.1)	263 (68.3)	382 (83.2)	663 (59.5)
African descent	310 (9.8)	38 (3.1)	33 (8.6)	18 (3.9)	221 (19.8)
American Hispanic	17 (0.5)	1 (0.1)	10 (2.6)	1 (0.2)	5 (0.4)
Latino American	136 (4.3)	8 (0.7)	22 (5.7)	4 (0.9)	102 (9.1)
Asian	245 (7.7)	18 (1.5)	56 (14.5)	53 (11.5)	118 (10.6)
Other	14 (0.4)	6 (0.5)	1 (0.3)	1 (0.2)	6 (0.5)
Age at enrollment (years), mean (SD)	62.5 (17.22)	77.9 (7.14)	40.6 (9.44)	68.6 (7.94)	60.9 (13.22)
Age at onset of ATTR amyloidosis symptoms (years)	*n* = 4421	*n* = 1409	*n* = 1082	*n* = 670	*n* = 1259
Mean (SD)	56.6 (17.93)	72.3 (9.73)	33.8 (7.19)	63.3 (8.14)	55.0 (13.88)
Time from symptom onset to diagnosis (years)	*n* = 4069	*n* = 1337	*n* = 993	*n* = 596	*n* = 1142
Mean (SD)	4.0 (5.96)	4.6 (6.73)	2.8 (4.74)	3.7 (3.96)	4.4 (6.61)
Follow-up time[b] (years), mean (SD)	3.9 (3.20)	2.3 (1.94)	6.8 (3.29)	4.1 (3.03)	3.2 (2.61)

V30M early onset and late onset *n* based on all patients with available data for disease diagnosis

Symptom onset was the date of first occurrence of symptom(s) reported as definitely related to ATTR amyloidosis

ATTR amyloidosis transthyretin amyloidosis, *ATTRwt amyloidosis* wild-type transthyretin amyloidosis, *SD* standard deviation

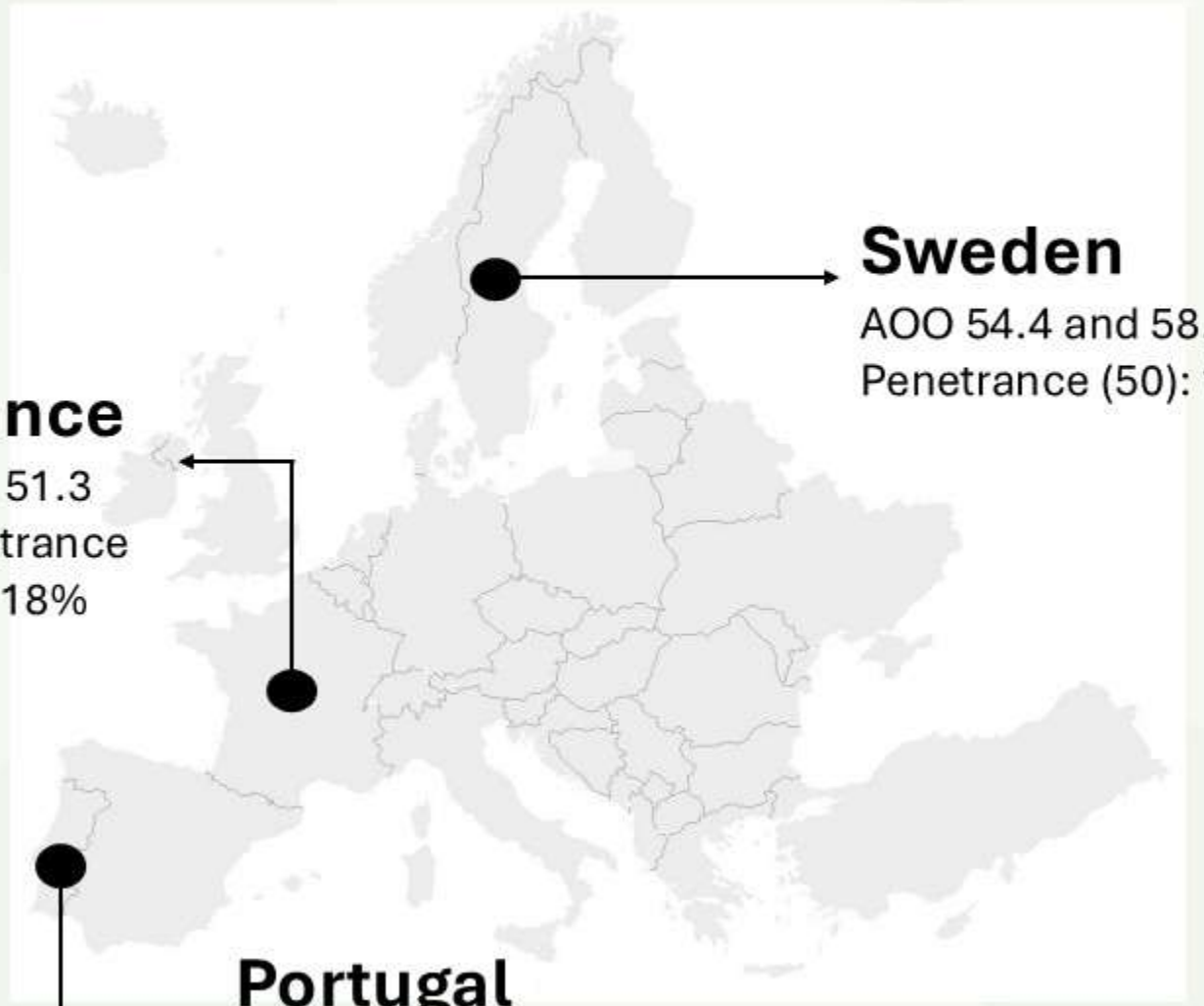
[a] Denominator for race/ethnicity is the total of non-missing records

[b] Follow-up time is based on all patients, from enrollment to last observation

L. Gentile et al. *Orphanet Journal of Rare Diseases*, 2023

ATTRv variability within TTR mutation: Geographic distribution

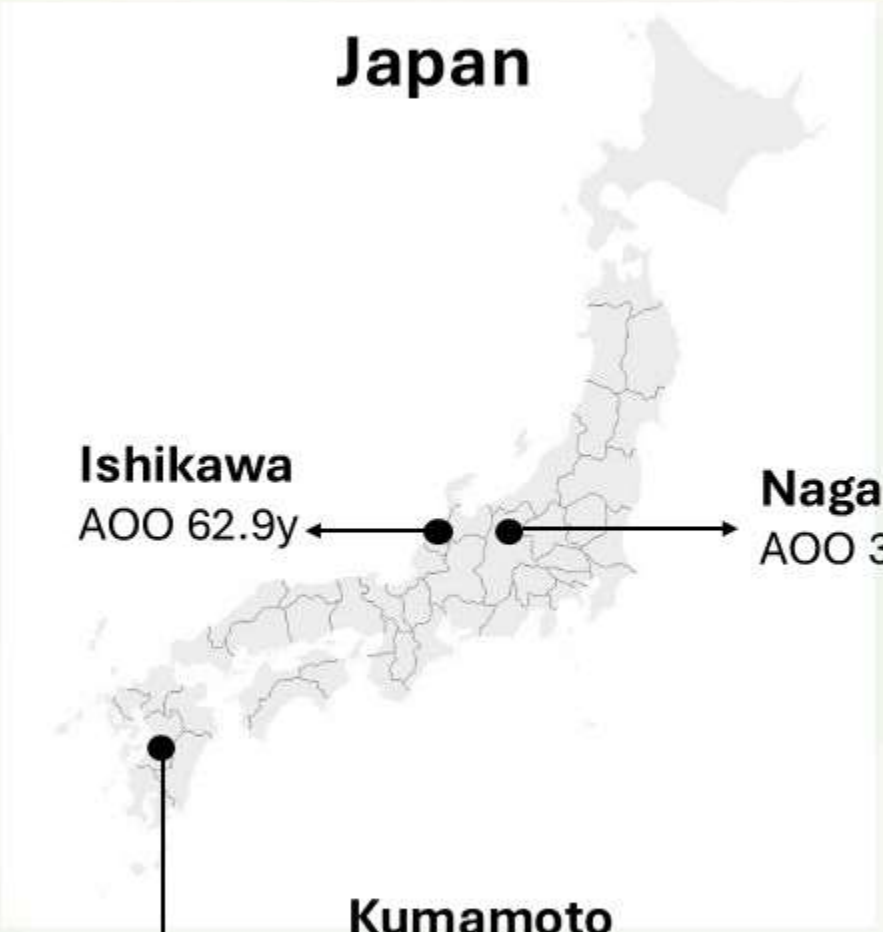
ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS



Sweden
AOO 54.4 and 58.8
Penetrance (50): 11%

France
AOO 51.3
Penetrance (50): 18%

Portugal
AOO 33.5y
Penetrance(50y): 60%



Ishikawa
AOO 62.9y

Nagano
AOO 33.1y

Kumamoto
AOO 35.6y

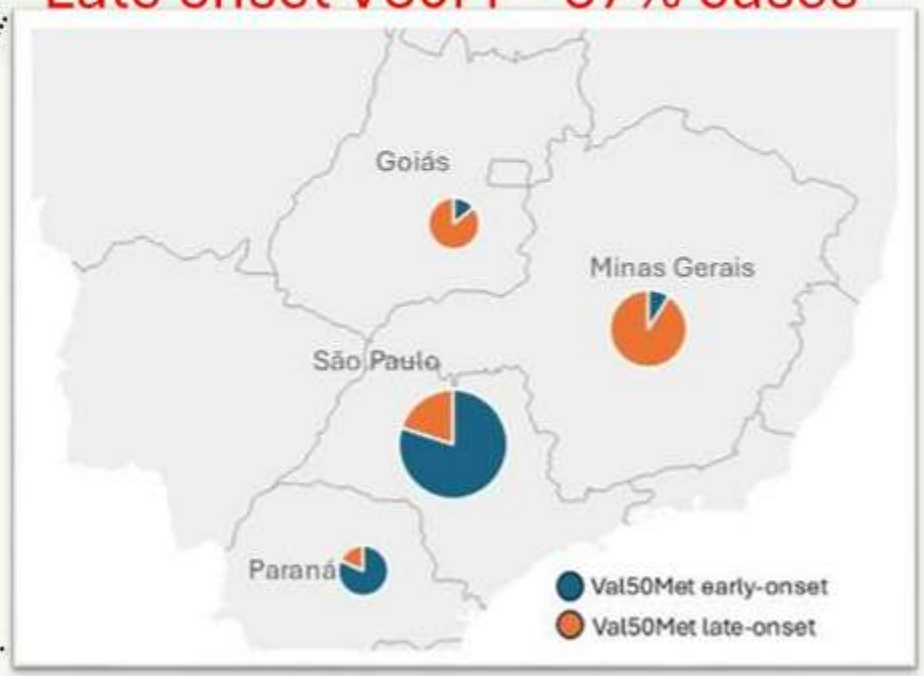
Planté-Bordeneuve and Said. Lancet 2011.

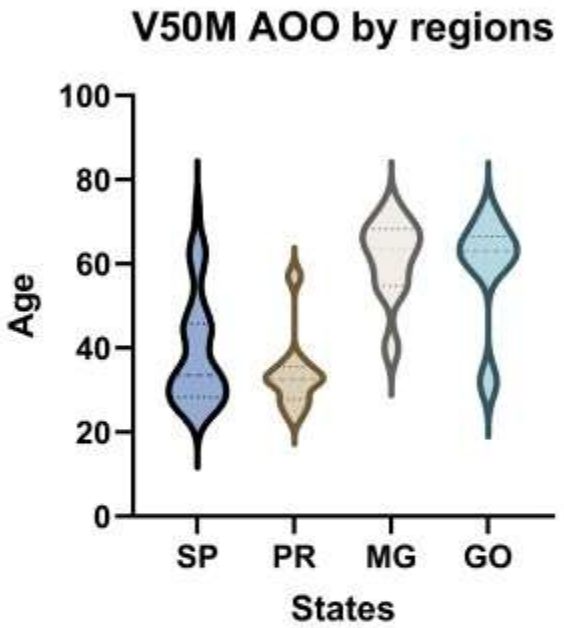
Carvalho et al., J. of Neurology 2024

EO and LO V30M ATTRv in Brazil

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

Late onset V30M = 37% cases





Saporta, Waddington-Cruz et al. Europ J. of Neurol. 2009

Maximiano-Alves, Gustavo; [...] Cortese, Andrea; Marques Jr, Wilson. under review

1:10,000 V30M carriers

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

SNV: 18-31592974-G-A(GRCh38)

Copy variant ID | Gene page | Dataset: gnomAD v4.1.0

	Exomes	Genomes	Total
Filters	Pass	Pass	
Allele Count	85	7	92
Allele Number	1461806	152292	1614098
Allele Frequency	0.00005815	0.00004596	0.00005700
Grpmax Filtering AF (95% confidence)	0.00004178	0.00005281	0.00004182
Number of homozygotes	0	0	0

External Resources

- dbSNP (rs28933979)
- UCSC
- ClinVar (13417)
- ClinGen Allele Registry (CA256790)
- All of Us

Feedback

Report an issue with this variant

Genetic Ancestry Group Frequencies

gnomAD | HGDP | 1KG | Local Ancestry

Genetic Ancestry Group	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
Remaining	14	62504	0	0.0002240
Middle Eastern	1	6062	0	0.0001650
Admixed American	5	60016	0	0.00008331
European (Finnish)	4	64014	0	0.00006249
European (non-Finnish)	62 62	1179988	0	0.00005254
East Asian	2	44886	0	0.00004456
South Asian	3	91078	0	0.00003294
African/African American	1	75034	0	0.00001333
Ashkenazi Jewish	0	29604	0	0.000
Amish	0	912	0	0.000
XX	48	812426	0	0.00005908
XY	44	801672	0	0.00005489
Total	**92**	**1614098**	**0**	**0.00005700**

3% Val122Ile carrier

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

SNV: 18-31598655-G-A(GRCh38)

Copy variant ID | Gene page

Dataset: gnomAD v4.1.0

	Exomes	Genomes	Total
Filters	Pass	Pass	
Allele Count	722	711	1433
Allele Number	1461852	152230	1614082
Allele Frequency	0.0004939	0.004671	0.0008878
Grpmax Filtering AF (95% confidence)	0.01633	0.01551	0.01619
Number of homozygotes	3	5	8

External Resources

- dbSNP (rs76992529)
- UCSC
- ClinVar (13426)
- ClinGen Allele Registry (CA214382)
- All of Us

Feedback

Report an issue with this variant

Genetic Ancestry Group Frequencies

gnomAD | HGDP | 1KG | Local Ancestry

Genetic Ancestry Group	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
African/African American	1273 1273	75018	8	0.01697
Admixed American	55	60022	0	0.0009163
Remaining	57	62508	0	0.0009119
Middle Eastern	4	6062	0	0.0006598
South Asian	13	91078	0	0.0001427
European (non-Finnish)	30	1180020	0	0.00002542
East Asian	1	44868	0	0.00002229
Ashkenazi Jewish	0	29608	0	0.000
European (Finnish)	0	63988	0	0.000
Amish	0	910	0	0.000
XX	806	812416	2	0.0009921
XY	627	801666	6	0.0007821
Total	**1433**	**1614082**	**8**	**0.0008878**

Sex

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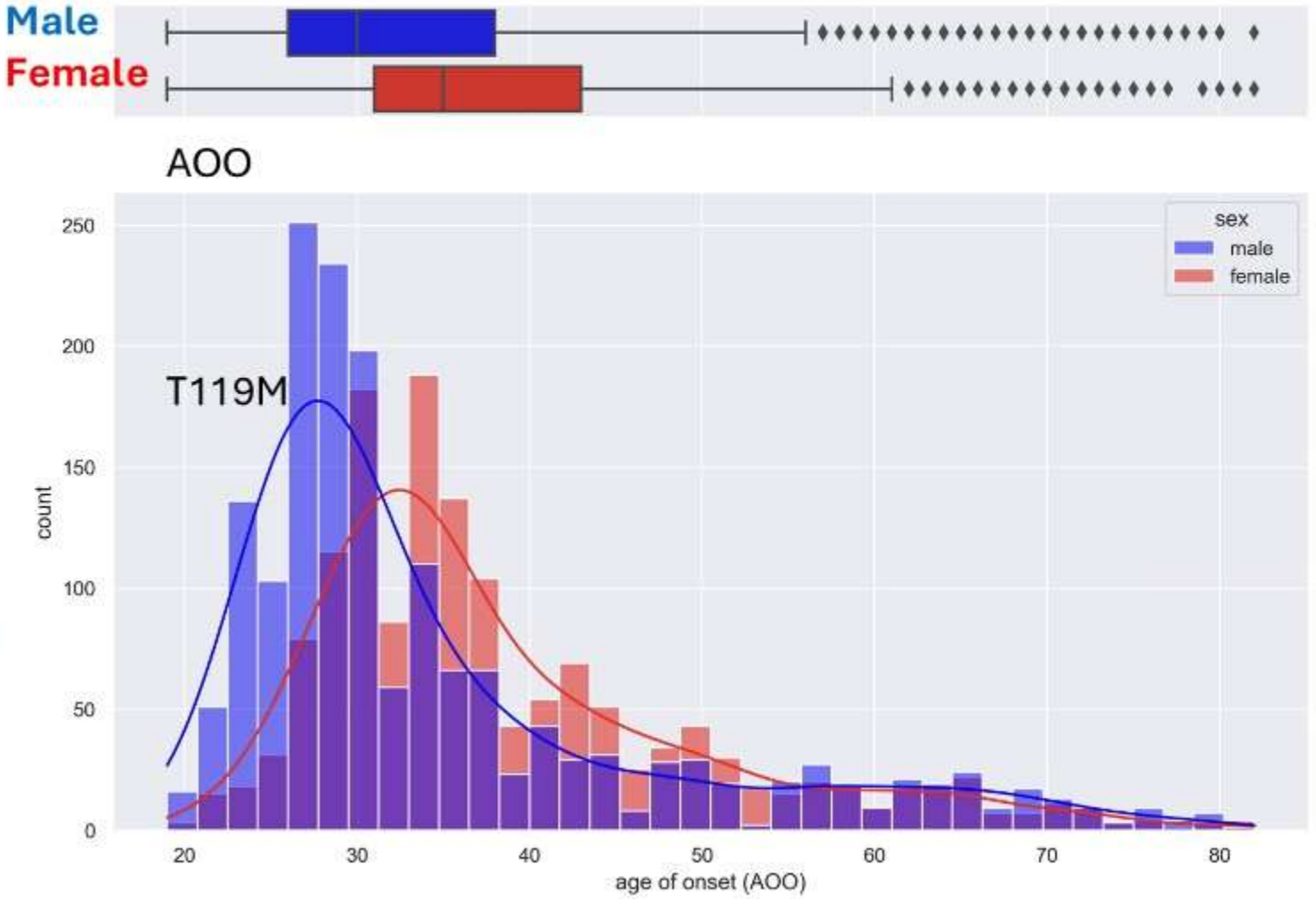

Figure 1. Age of disease onset (AOO) of all observed carriers. Results show symptomatic carriers AOO distribution. There is a difference close to five years for the peak of each distribution with male patients having a risk of presenting symptoms earlier. Mann–Whitney has a *p*-value result below .05, which shows there is a significant difference in AOO between genders.

M. Pedroto et al., Amyloid 2024

Anticipation and Transmitting parent

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

- **Anticipation** (=decrease of the AOO within each generation) reported for p.Val50Met kindreds from **Portugal, Sweden, Japan, Cyprus, Bulgaria**
  - Larger anticipation in offspring of affected mothers (**mother-son pairs**) in Portugal, Sweden, Japan and Bulgaria (up to 10.9 ys for p.Val50Met – Portugal and >20 ys for p.Glu109Gln – Bulgaria)
  - Possible **parental imprinting** and **mitochondrial involvement** (Sousa, Amyloid, 1991; Drugge, J Med Genetics, 1993; Gorram, Amyloid, 2021; Yamatomo, J. Med Genetics, 1998)

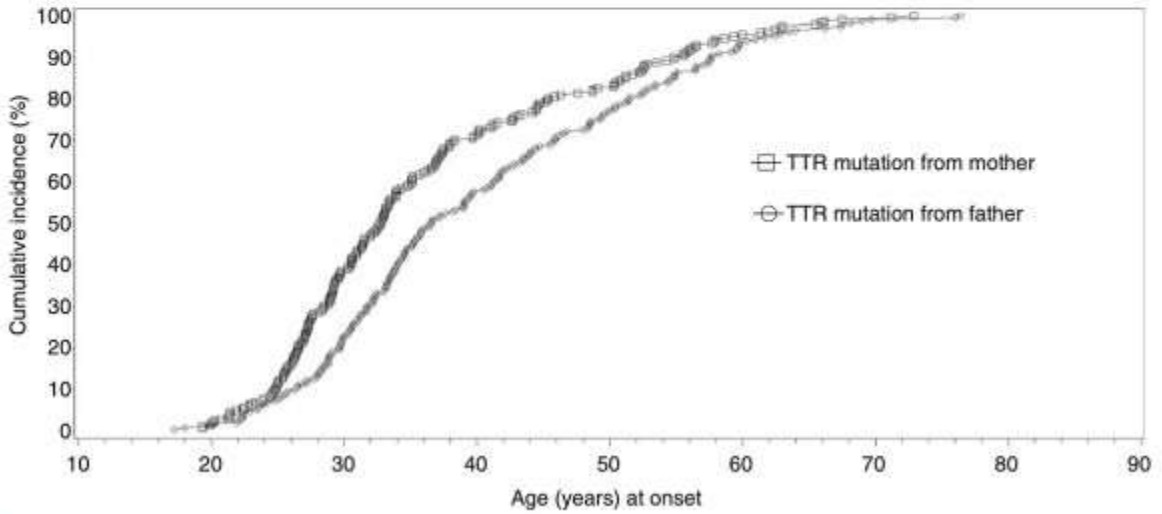

Figure 3. Disease onset in patients with hereditary transthyretin amyloidosis according to sex of affected parent. Onset of disease manifestations was earlier in patients with an affected mother ($n = 229$) than in those with an affected father ($n = 241$) ($p < 0.0001$, Wilcoxon Rank–Sum test).

T. Coelho et al., CRMO 2012

Additional genetic modifiers

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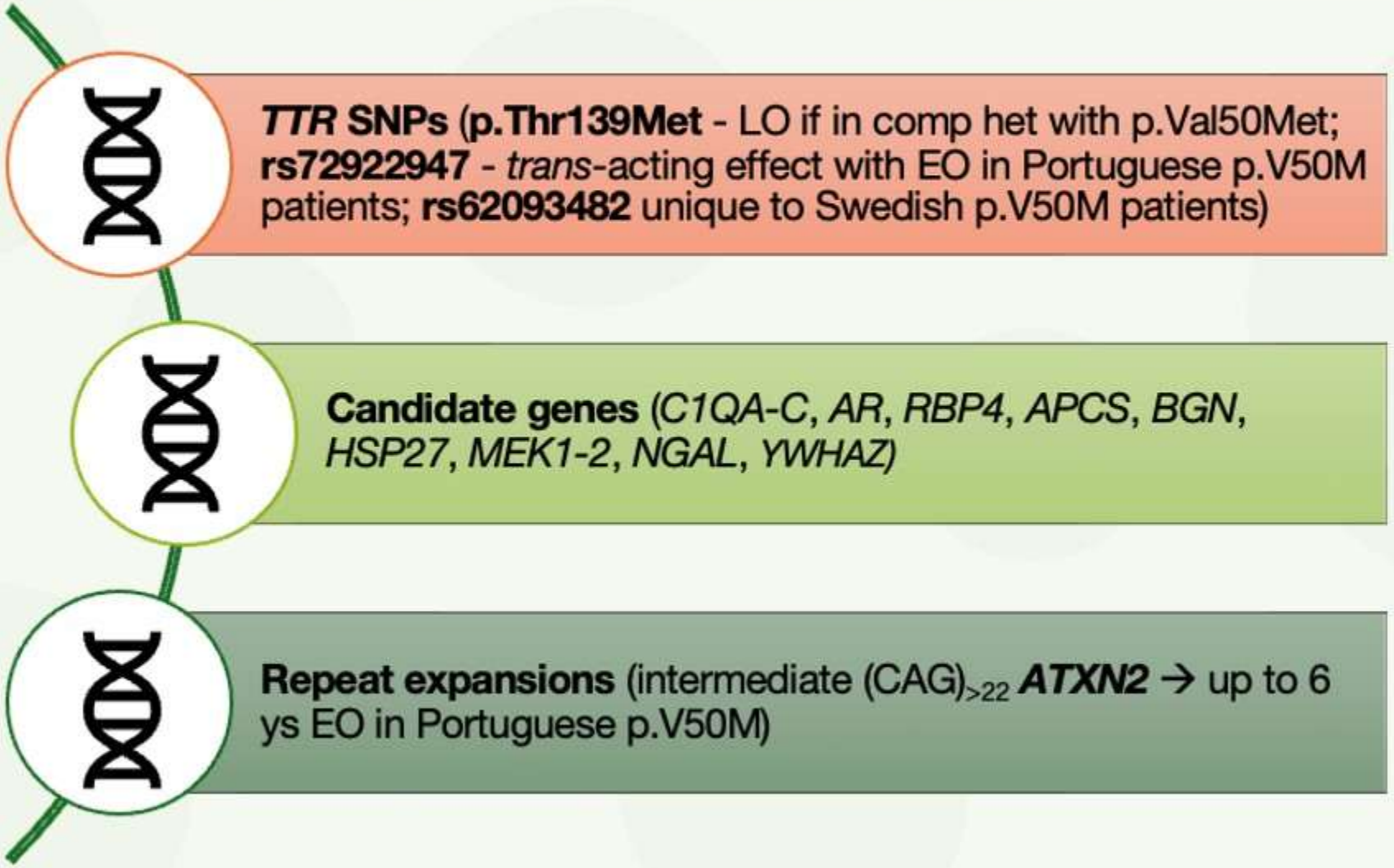

See also Carvalho et al., J. of Neurology 2024

Clinical and genetic modifiers

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Factors	References
***TTR* pathogenic variant**	Reilly. J Neurol Neurosurg Psychiatry; 2005; Koike. Arch Neurol, 2002; Mariani. Ann Neurol, 2015; Buxbaum. Genet Med, 2017; Pinto. J Neurol Sci, 2019; Gospodinova. J Cardiovasc Med, 2020; Waddington-Cruz. Neurol Ther, 2021; Gentile. Cardiol Ther, 2021
Age-of-onset	Ikeda. Brain, 1987; Misu. Brain, 1999; Sousa. Hum Hered, 1993; Holmgren. 1994; Sousa. Am J Med Genet, 1995; Bittencourt. 2005; Conceição. 2007; Andreou. Amyloid, 2018; Yamashita. J Neurol, 2018; Dispenzieri. Orphanet J Rare Dis, 2022
Gender and parent-of-origin	*Sousa. Amyloid, 1991; Drugge, J Med Genetics, 1993; Coelho. J Med Gen. 1994; Yamatomo, J. Med Genetics, 1998; Planté-Bordeneuve. Lancet Neurol 2011; Waddington-Cruz. Amyloid. 2017; Buxbaum. Gent Med. 2017; Adams. Nat Rev Neurol 2019; Cisneros-Barroso. Amyloid. 2020; Caponetti. JACC Heart Fail, 2021; Gorram, Amyloid, 2021*
Non-coding variants	*Soares.* Eur J Hum Genet, 2004; *Polimanti. Amyloid, 2014; Iorio.* Eur J Hum Genet, 2017; Alves-Ferreira. Mol Neurobiol, 2018; Alves-Ferreira. Amyloid, 2021
Fibril composition (type A – C-ter fragment + full-length TTR *vs* type B – full-length TTR only)	*Bergstro. J of Pathology, 2005; Ihse. J of Pathology, 2008; Marcoux, MBO Mol Med, 2015*
Epigenetic (e.g., DNA methylation, histone modification) and **environmental factors**	*Yordanova. Gene 2019; Ruzhansky. J Clin Neuromuscul Dis, 2014; Saporta. Amyloid, 2009; Holmgren. J Intern Med, 2004, Munar-Ques. J Med Genet, 1999; Polimanti. Clin Epigenetics, 2020; Polimanti. Circ Genom Precis Med; 2021*
Others (e.g., somatic mosaicism, monoallelic expression)	*Federico. Hum Gen, 2017; Yordanova. Gene, 2019*

Our study – GWAS approach

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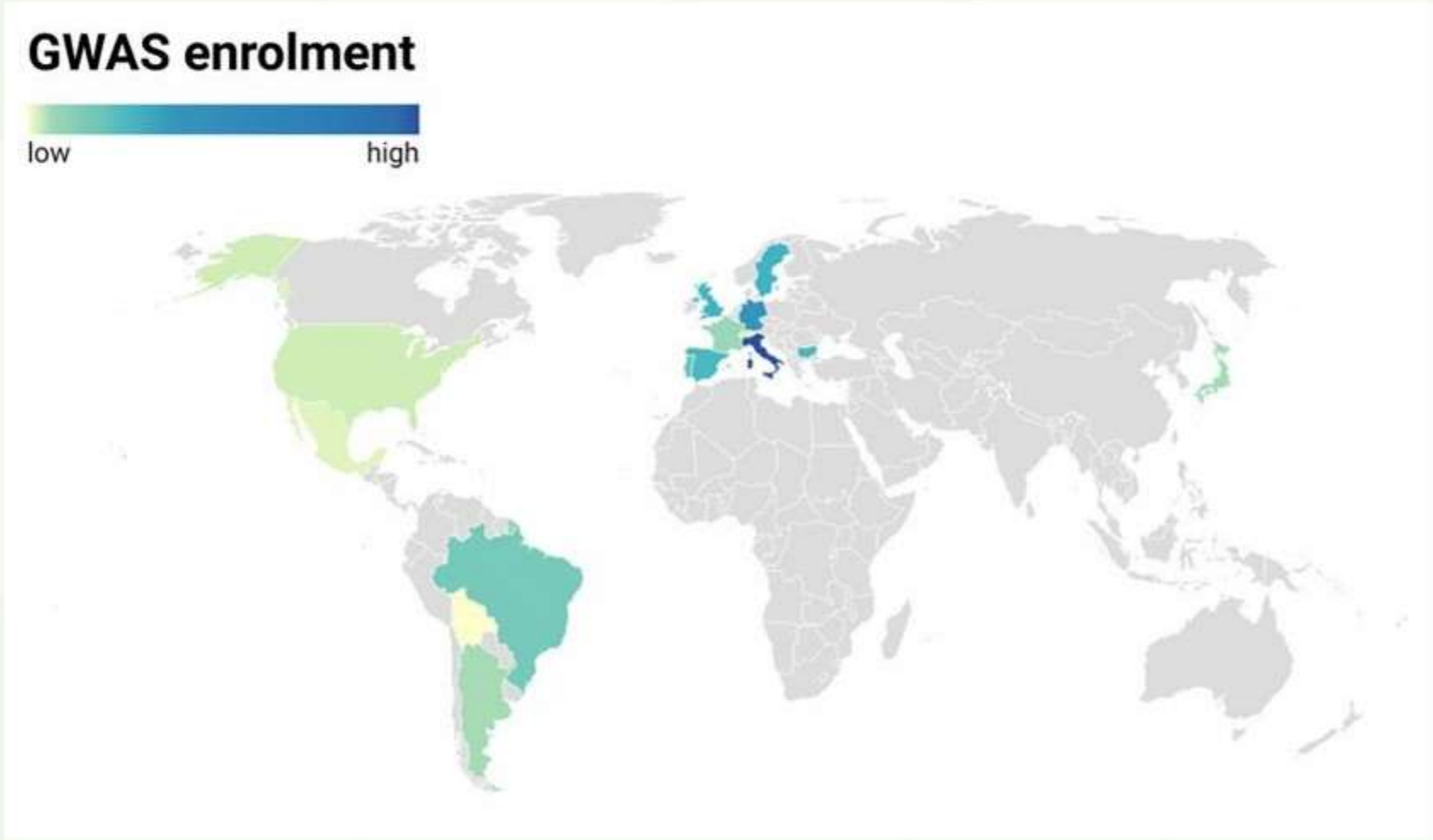


16 Countries / 42 Centres

Europe: Italy, France, Spain, Portugal, Germany, UK, Cyprus, Bulgaria, Sweden, Switzerland

America: USA, Brasil, Argentina, Mexico, Bolivia

Asia: Japan

Fondazione Regionale per la Ricerca Biomedica

Pfizer

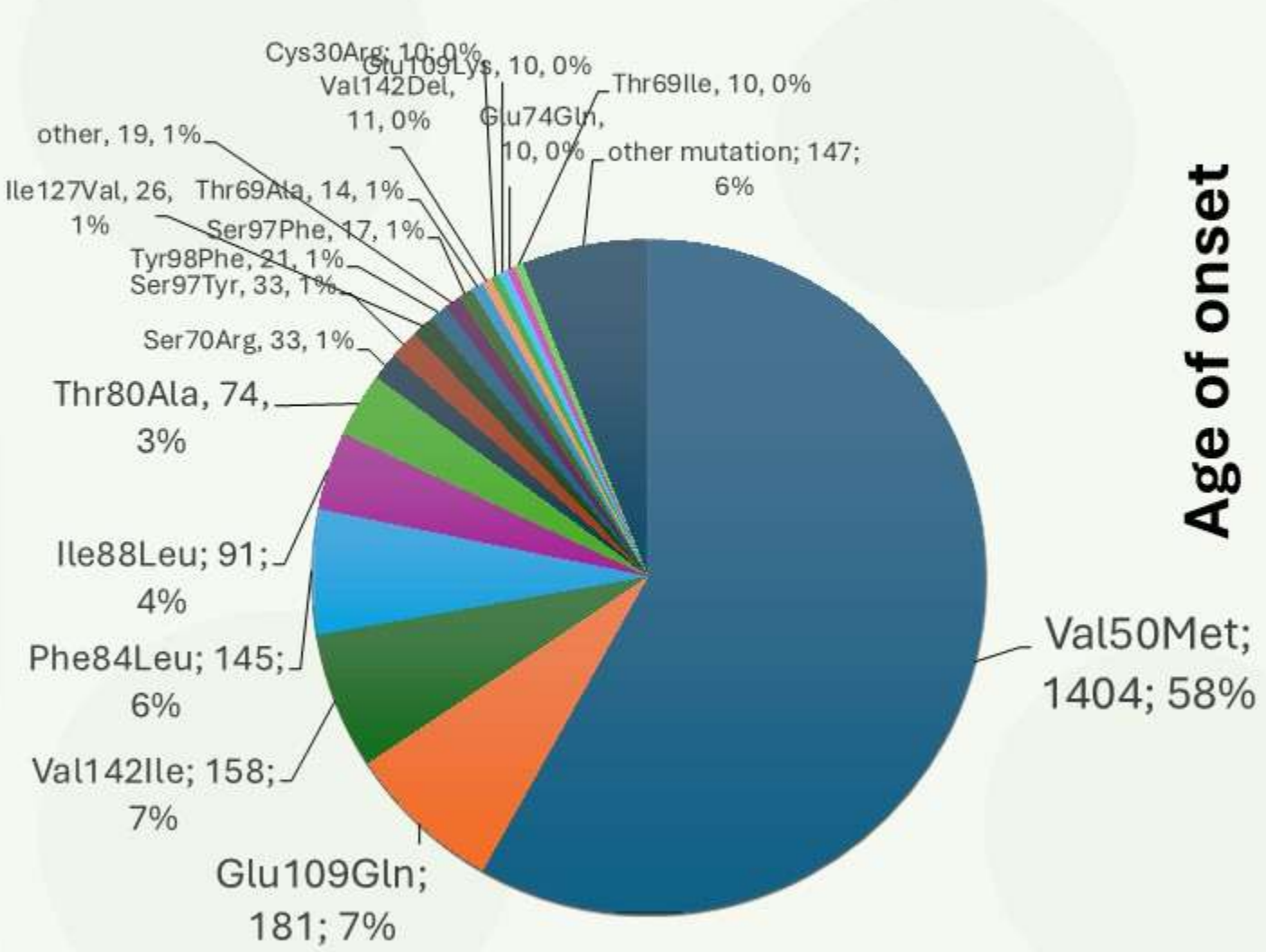
GWAS genetic modifier of ATTRv

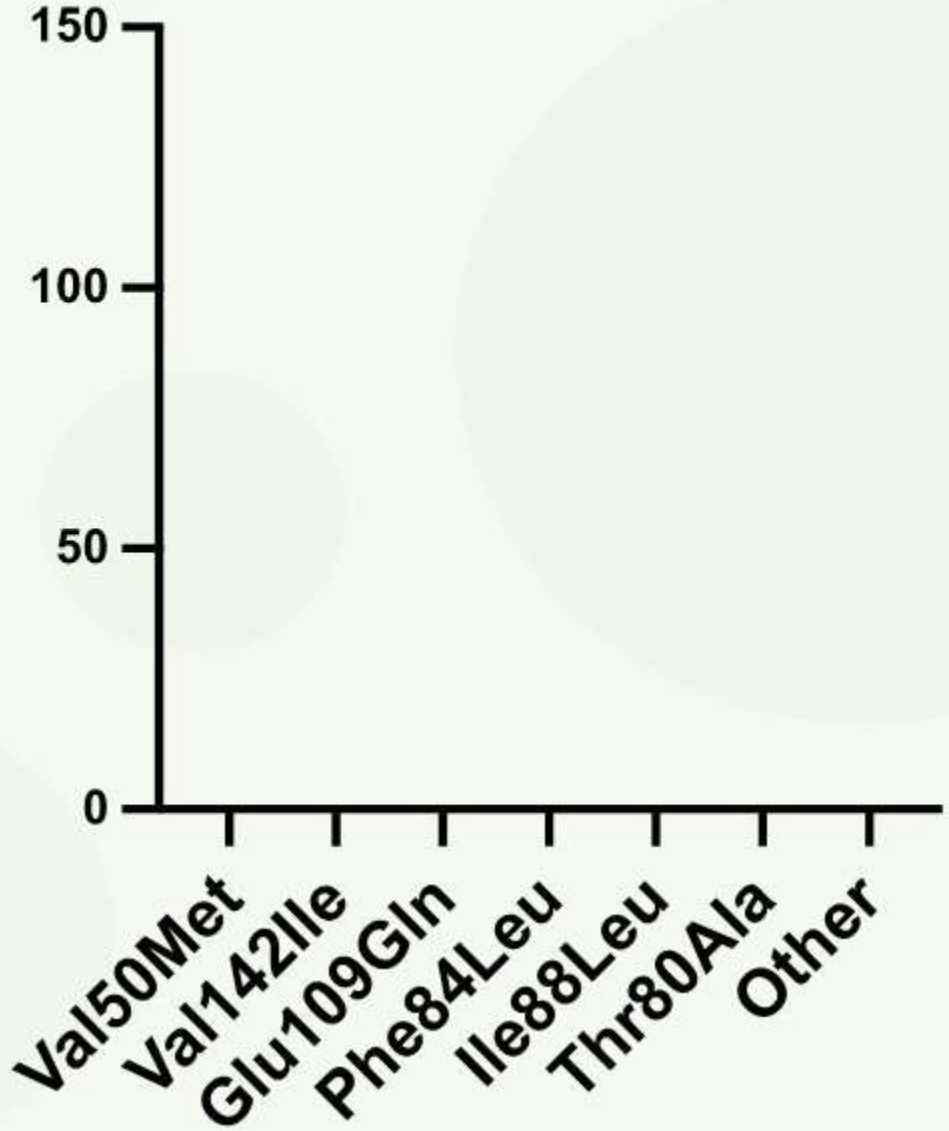
ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

	ATTRv		ATTRwt	Controls	Total
	V30M	nV30M			
DNA samples received	2769		1673	504	4946
	1529	1240			
DNA samples with available clinical data	2420		1492	504	4416
Symptomatic ATTRv patients	2316		NA	NA	
Genotyped samples	1745		1457	504	3706

GWAS genetic modifier of ATTRv

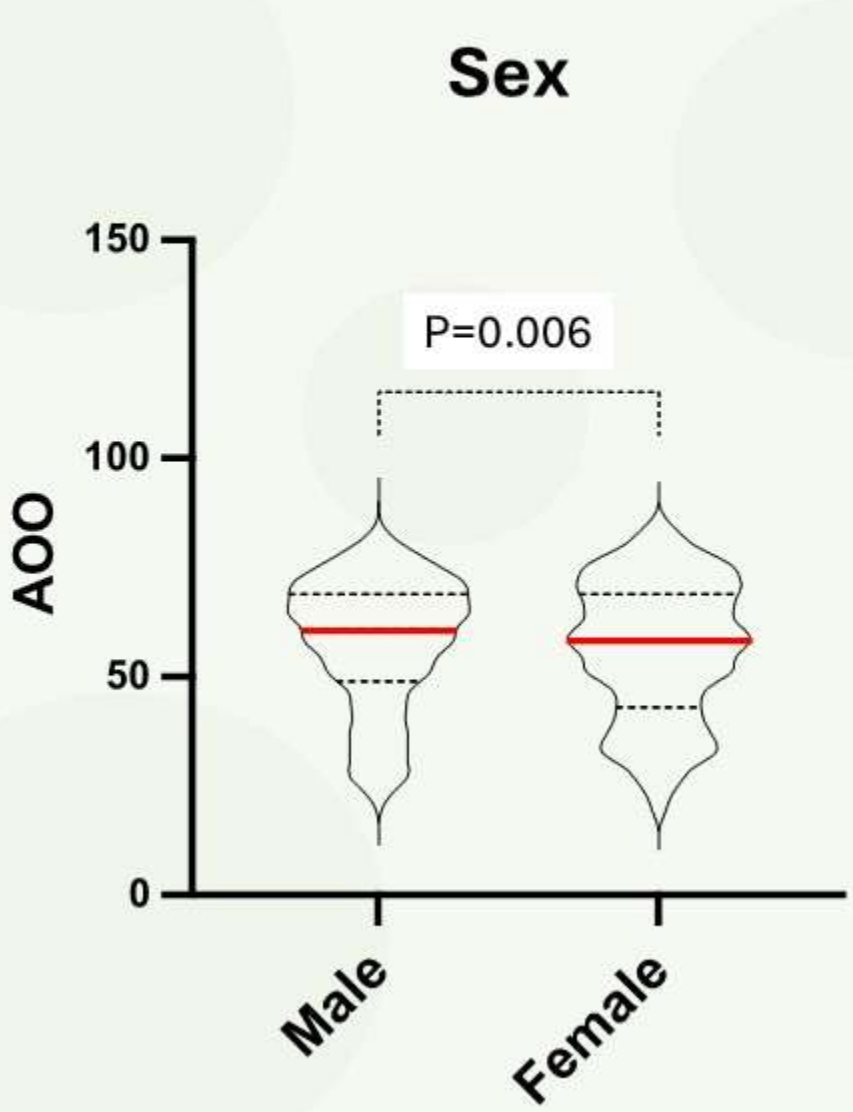
ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

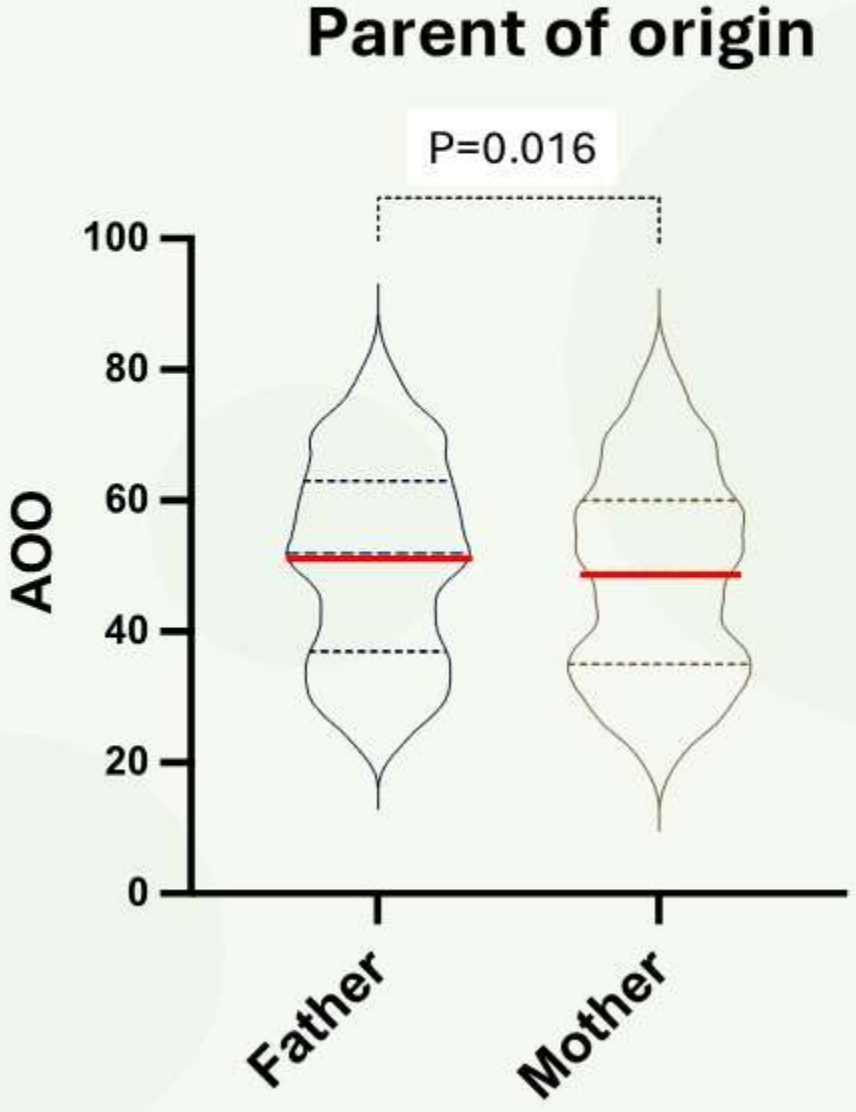




GWAS genetic modifier of ATTRv

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS





GWAS genetic modifier of ATTRv

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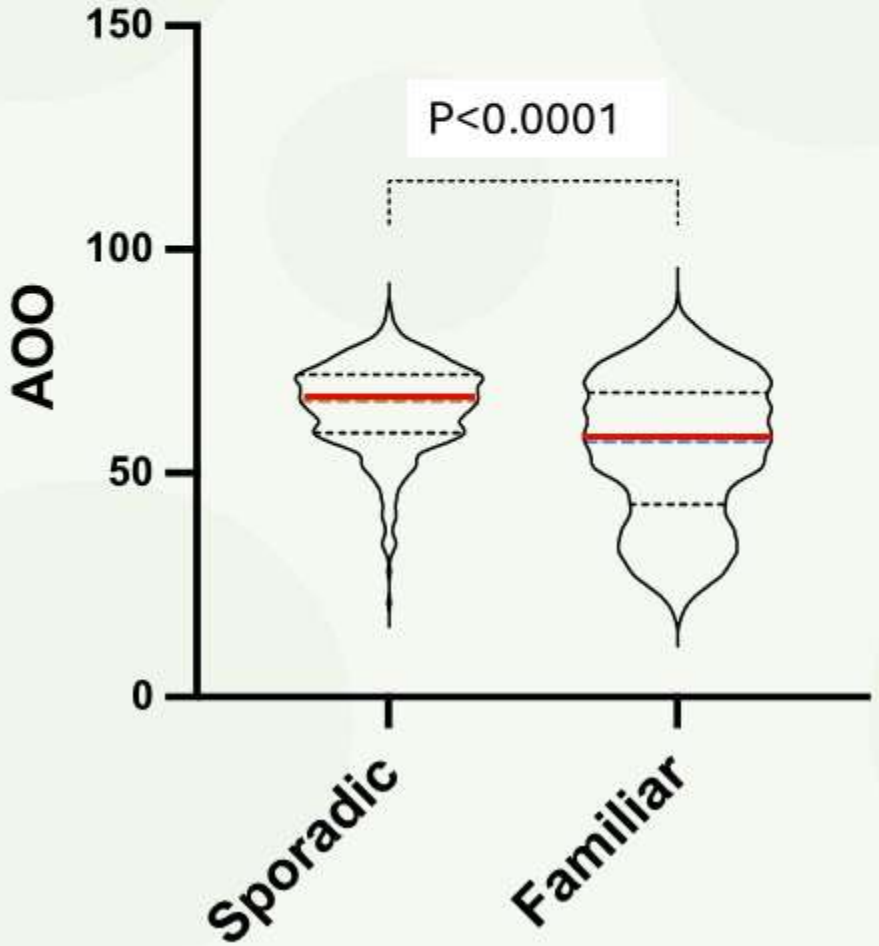
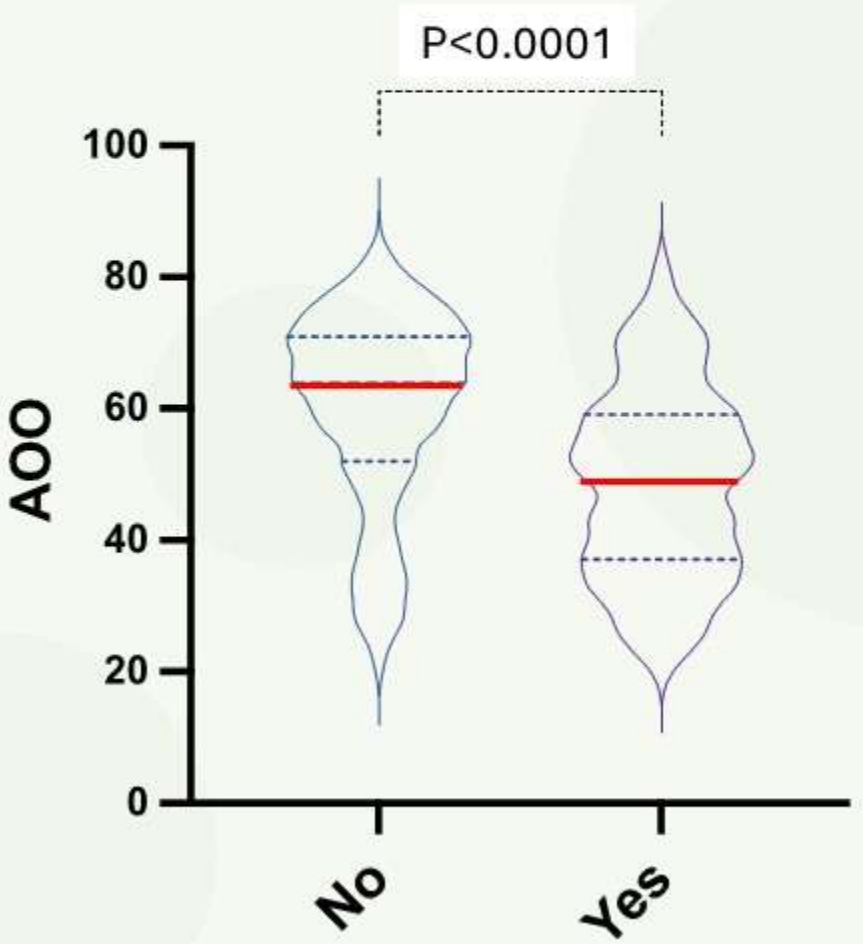
Family history vs sporadic



Monitoring of presymptomatic



Principal component analysis

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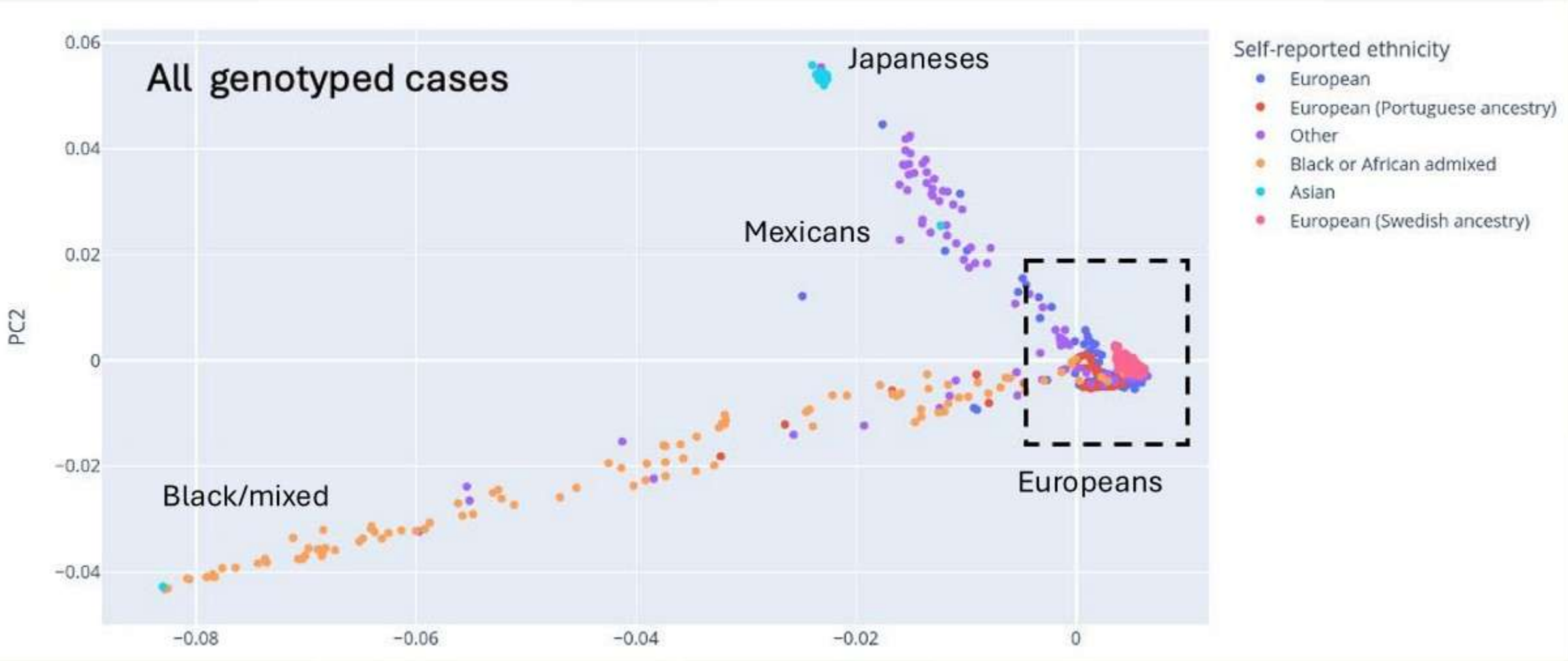
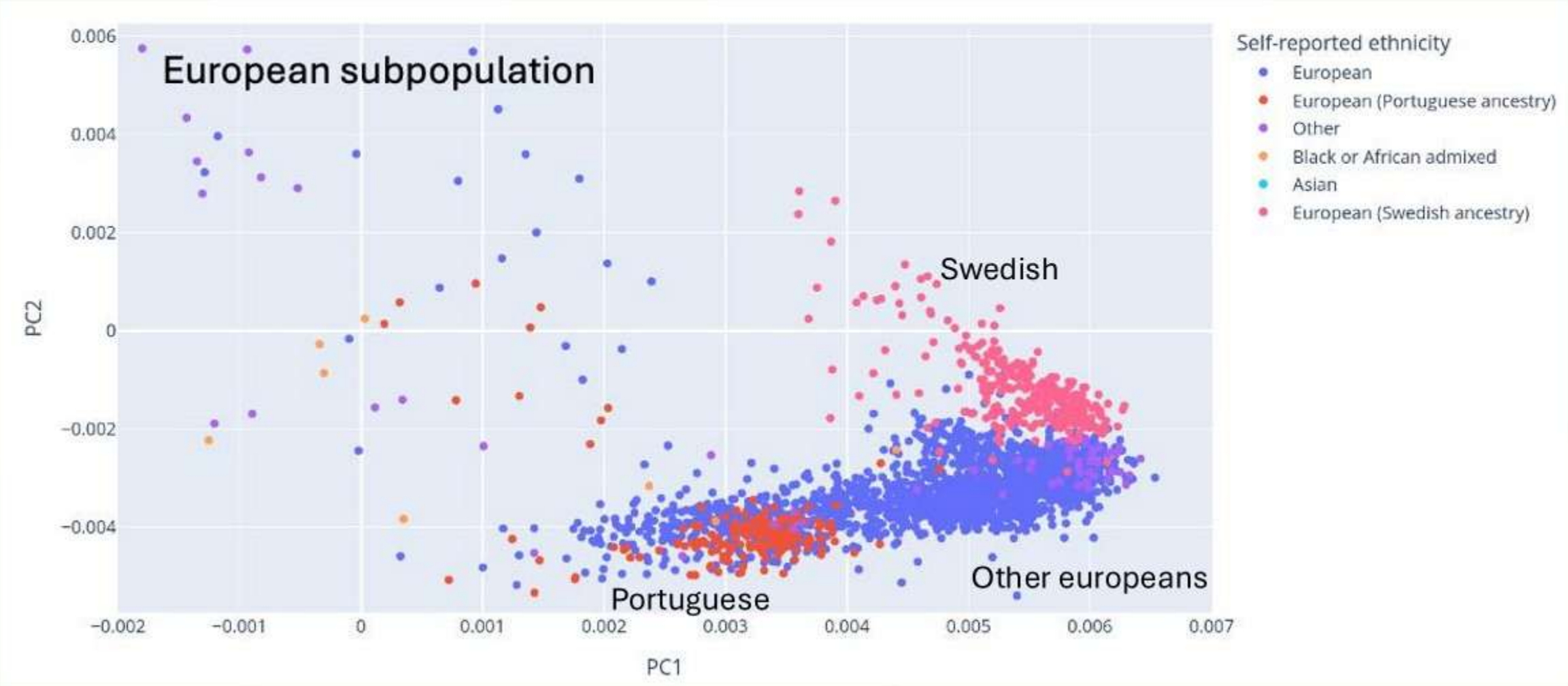


Principal component analysis

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS



Twin studies

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Table 2 Four pairs of monozygotic twins with FAP-I

Origin	*Indonesia*[22]	*Sweden*[23]	*Majorca*	*Portugal*
Sex	Female	Male	Male	Male
Symptoms of FAP-I	Both	Only one	Both	Both
Difference in onset age (y)	4	? (>7)	12	4
Different clinical expression:	Yes	NA	Yes	Yes
in sensorimotor syndrome	Yes	NA	Yes	Yes
in digestive disturbances	Yes	NA	Yes	Yes
in renal involvement	Yes	NA	Yes	NP
in vitreous deposits	NP	NA	Yes	NP
in cardiac involvement	Yes	NA	NP	Yes
Probability of monozygosity	Presumed	Presumed	99.03%	99.99%

Role of environment and epigenetics (eg Allele specific expression)

Munar-Ques. J of Med Gen, 1999

Aknowledgments

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

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Ilaria Quartesan
Natalia Dominik
Riccardo Curró
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Cyprus
- Nicosia: Kleopa

France
- Creteil: Valentine Perrain and V Planté-Bordeneuve

Germany
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- Heidelberg: U Hegenbart, S Schoenland

Italy
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- Verona: Tagliapietra and Fabrizi
- Messina: Mazzeo
- Rome: Leonardi and Antonini and Luigetti
- Naples: Tozza and Manganelli
- Florence: Argiro and Cappeli
- Milan: Pareyson
- Padova: Salvalaggio and Briani
- Genoa: Mandich
- Palermo:Di Stefano
- Bologna: Guaraldi

Portugal
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- Porto: Carolina Lemos and Teresa Coelho

Switzerland
- Lausanne: Theaudin

Spain
- Barcelona: Morales and Casasnovas, Sanchez-Tejerina, Rojas-Garcia
- San Sebastian: Fernandez and Arregui
- Zaragoza: Menao
- Bilbao: Solange Garcia
- Valencia: Sevilla
- Huelva: Gragera
- Palma: Cisneros

Sweden
- Umea: Anan Intissar

United Kingdom
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- London UCL: Mary Reilly, Henry Houlden

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- Buenos Aires Britanico Hospital: Reisin

Bolivia
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Brazil
- Ribeirao Preto: Wilson Marques
- Rio de Janeiro: Márcia Cruz

Mexico
- Mexico City: Karla Soto

USA
- Boston: Berk

Asia

Japan
- Kumamoto: Tasaki and Mitt
- Matsumoto: Kiccho and Sekijima

Fondazione Regionale per la Ricerca Biomedica
Pfizer
NAF National Ataxia Foundation
erc
MRC Medical Research Council
CMTA Charcot-Marie-Tooth Association
Muscular Dystrophy UK
fondazione CARIPLO
AFMTELETHON INNOVER POUR GUERIR

Screening and early diagnosis of ATTR amyloidosis: Demographic Factors

Frederick L. Ruberg, MD

Thomas J. Ryan Professor and Chief, Cardiovascular Medicine

Boston University Amyloidosis Center

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Boston, MA USA

Disclosures

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

- Research support from NIH (R01 HL139671 and R01HL177670, Anumana, Pfizer, AstraZeneca/TriNetX, BridgeBio
- Consulting income from eMyosound, Attralus

Overview of Topics Reviewed

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

1.	**Demography of age and sex at diagnosis**
2.	**Demography of race and ethnicity in relation to ATTRwt and ATTRv**
3.	**Active ascertainment vs. referral populations**

ATTR deposits associated with age

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

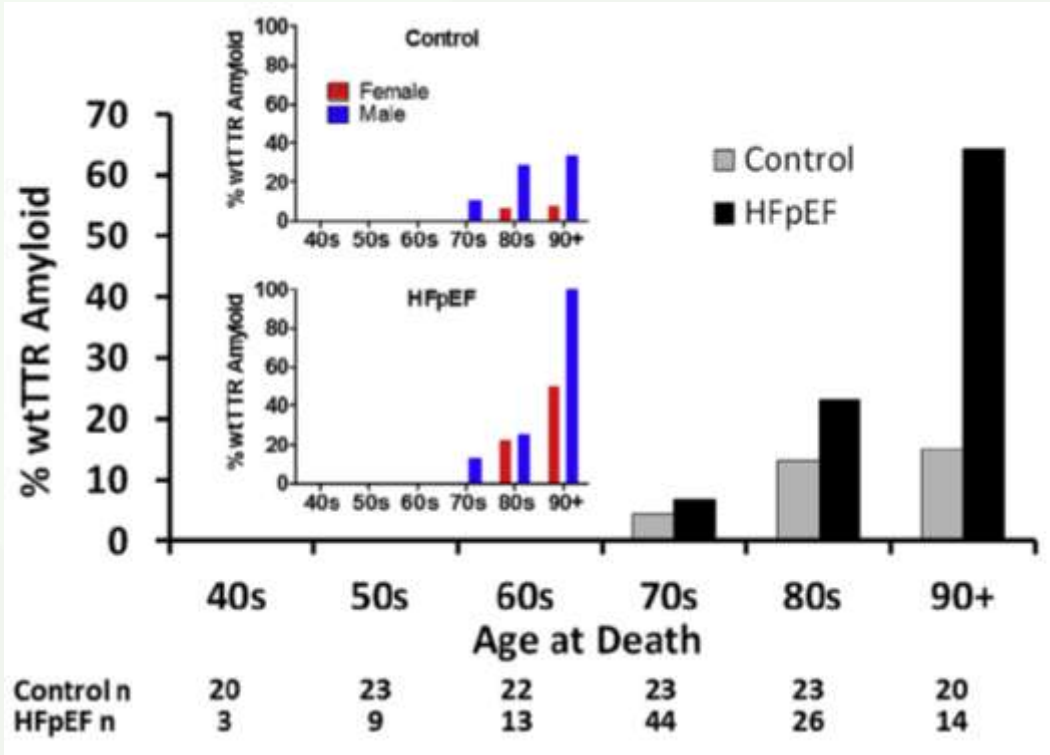
- Myocardial TTR amyloid accumulation is demonstrable in approximately 25% of hearts in patients over age 80-85y
  - Deposits vs. amyloidosis
  - Amyloidosis more common in males
  - Associated with HFpEF

Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in *alpha2-macroglobulin* and *tau*: A population-based autopsy study

MAARIT TANSKANEN[1], TERHI PEURALINNA[2], TUOMO POLVIKOSKI[3], IRMA-LEENA NOTKOLA[4], RAIMO SULKAVA[5], JOHN HARDY[6], ANDREW SINGLETON[6], SARI KIURU-ENARI[2,7], ANDERS PAETAU[1], PENTTI J. TIENARI[2,7] & LIISA MYLLYKANGAS[8]

Table Ia. The study subjects stratified by age at death, gender, and grade of senile systemic amyloidosis.

		Age at death (years)			
	SSA grade (0–3)	85–89.9	90–94.9	95–99.9	≥100
Men	3	1	2	1	0
	2	0	0	1	0
	1	0	7	2	0
	0	10	11	7	0
Women	3	0	1	1	1
	2	1	3	2	0
	1	9	16	11	4
	0	44	87	31	3



Frequency similar by sex, men more severe

Tanskanen, *Ann Med,* 2008; Cornwell, *Am J Med,* 1983; Mohammed, *JACC HF,* 2014

pV142I excess risk at defined age thresholds

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

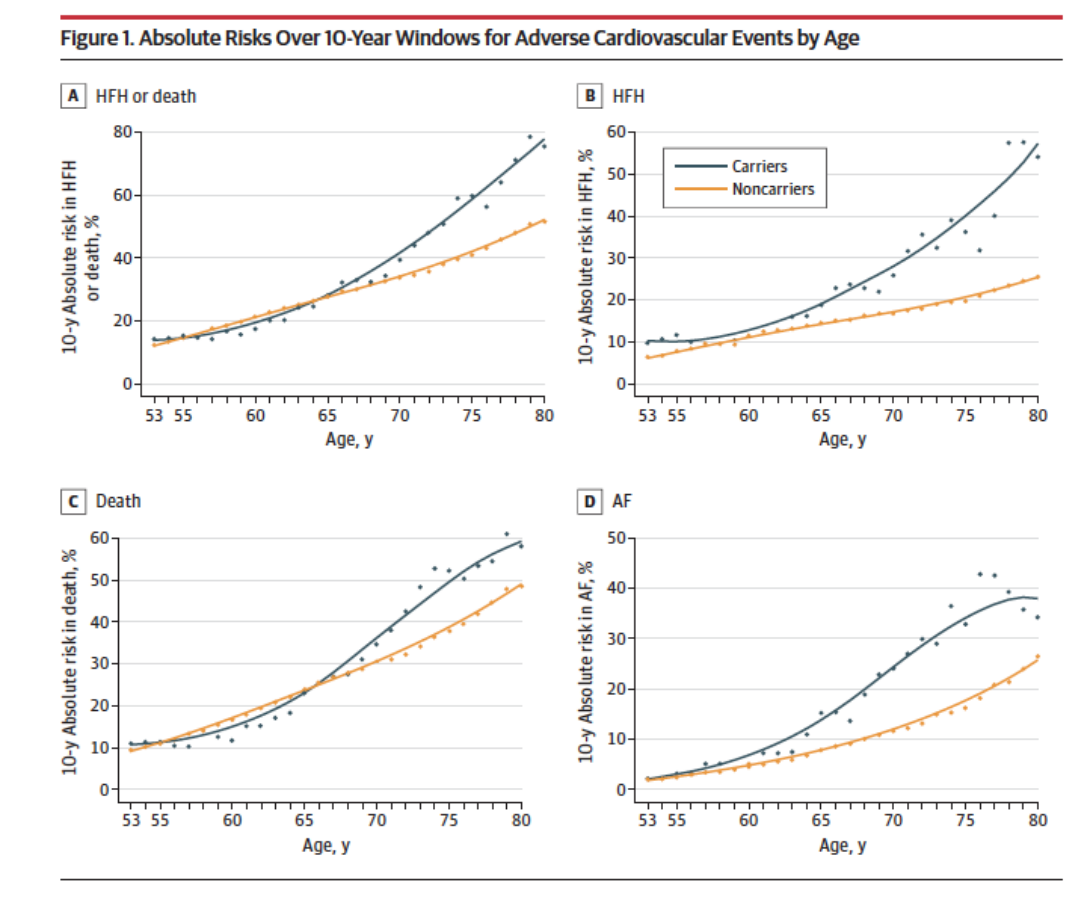
JAMA Cardiology | Brief Report

Age Dependency of Cardiovascular Outcomes With the Amyloidogenic *pV142I* Transthyretin Variant Among Black Individuals in the US

Senthil Selvaraj, MD, MS, MA; Brian L. Claggett, PhD; C. Cristina Quarta, MD; Bing Yu, PhD; Riccardo M. Inciardi, MD; Joel N. Buxbaum, MD; Thomas H. Mosley, PhD; Amil M. Shah, MD, MPH; Sharmila Dorbala, MD, MPH; Rodney H. Falk, MD; Scott D. Solomon, MD

- 65y for Atrial Fib.
- 70y for Heart Failure
- 75y for Death

- **430,000 pV142I carriers > 50 years of age projected to lose ~ 1M years of life**
- **? Proportion with ATTRv-CM**



Selvaraj, *JAMA Cardiol* 2023: Selvaraj, JAMA 2024

ATTR age at diagnosis – Cohort Studies

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

Reference	Number of subjects	ATTR genotype	Median age at diagnosis (years)	% Male
Pinney, *J Am Heart Assoc* **2013**	102	100% ATTRwt	73	89
Connors, *Circulation* **2016**	121	100% ATTRwt	75	98
Gonzalez-Lopez, *Eur Hear J* **2017**	108	100% ATTRwt	79	81
Lane, *Circulation* **2019**	711	100% ATTRwt	79	94
Lane, *Circulation* **2020**	205	100% ATTRv pV142I	77	71
Campbell, *Cardiol Ther* **2022**	1386	100% ATTRwt	80 females, 78 males	N/A

Age of diagnosis ≥ 75 years, highly enriched for males

ATTR age at diagnosis – Active ascertainment

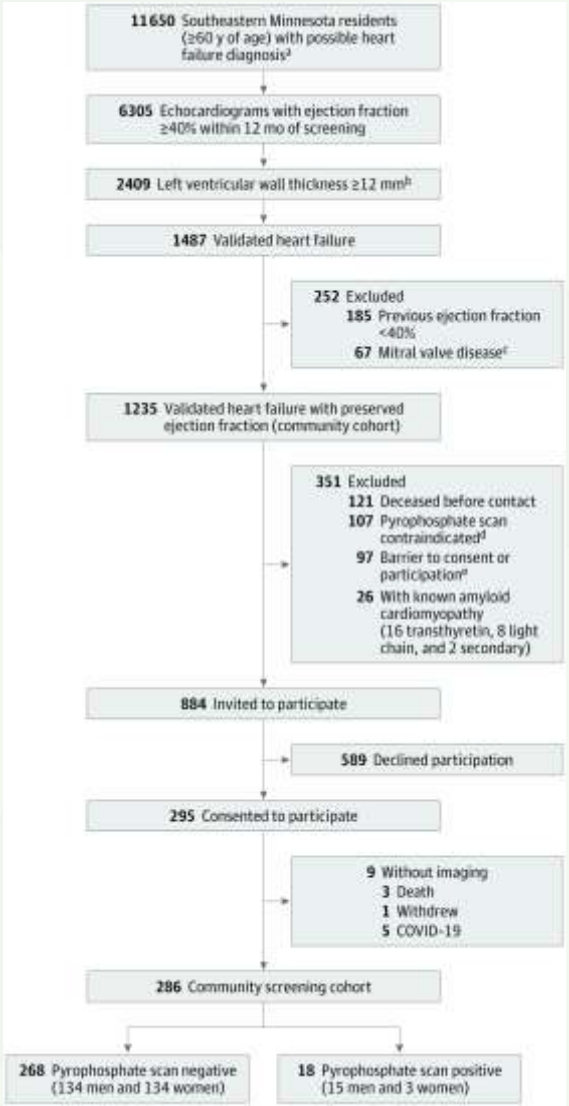
ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

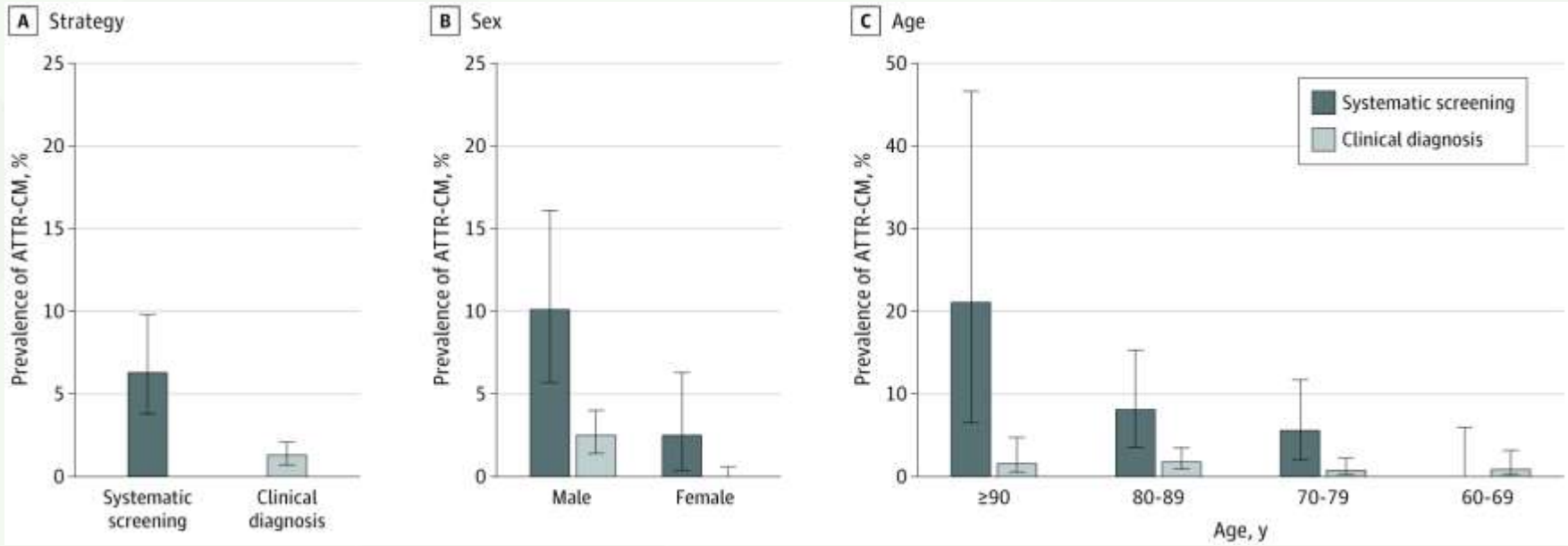
Reference	Indication	Genotype	Number of Subjects	Median age (years)	% Male
Gonzalez-Lopez, *Eur Hear J* 2015	• HFpEF • LVWT ≥12 mm • ≥60 years	ATTRwt 100%	120	82	41
AbouEzzedine, *JAMA Cardiol* 2021	• LVEF ≥40% • LVWT ≥12 mm • ≥60 years	ATTRwt 100%	286	78	50
Ruberg, *JAMA Cardiol* 2025	• HF • Black or Hispanic • ≥60 years • LVWT ≥12 mm	ATTRwt 56% and ATTRv 44%	646	80	61

Median age is not different from retrospective cohorts

Percentage of males vs. females IS different from retrospective cohorts

Community screening – Mayo study



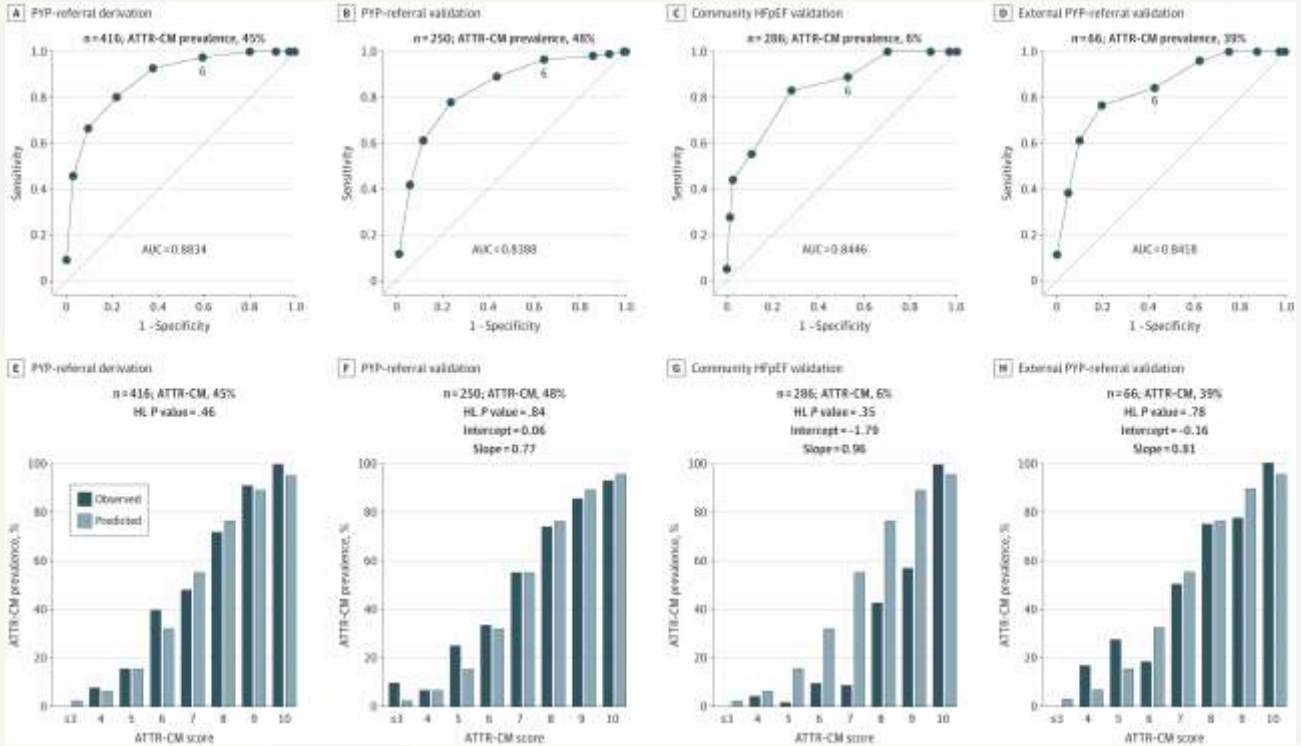


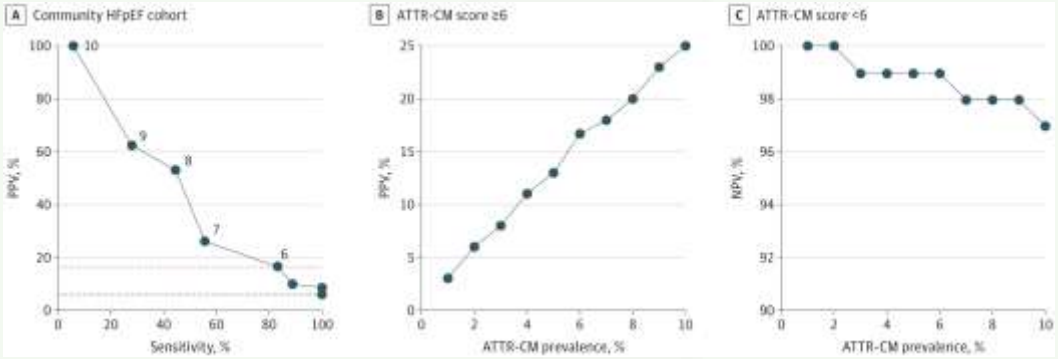
AbouEzzedine, *JAMA Cardiol* 2021

Importance of Age and Sex - Mayo

Clinical variable	Value	Points[a]
Age, y	If 60-69	+2
	If 70-79	+3
	If ≥80	+4
Sex	Male	+2
Hypertension diagnosis	Present	−1
Ejection fraction	<60%	+1
Posterior wall thickness	≥12 mm	+1
Relative wall thickness[b]	>0.57	+2
High-risk score ≥6		

Transthyretin Amyloid Cardiomyopathy score (TCAS)
80 year old man = 6 points!





Davies, *JAMA Cardiol* 2022

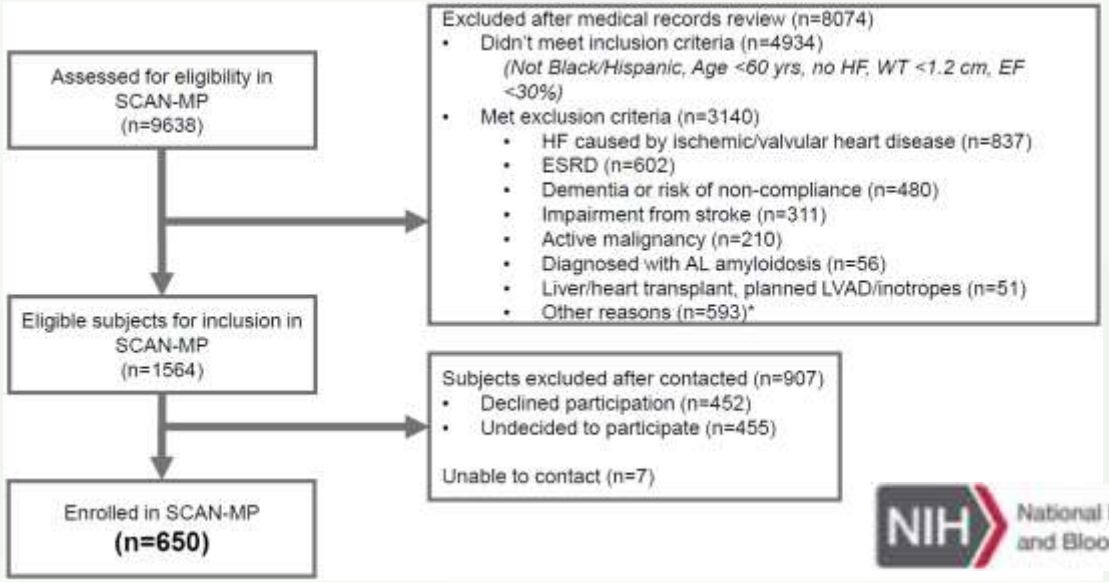
Community Screening – SCAN-MP

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

JAMA Cardiology | Original Investigation

Transthyretin Cardiac Amyloidosis in Older Black and Hispanic Individuals With Heart Failure

Frederick L. Ruberg, MD; Sergio Teruya, MD, MS; Stephen Helmke, MPH; Dia A. Smiley, MD; Denise Fine, MS; Damian Kurian, MD; Farbod Raiszadeh, MD, PhD; Tatiana Prokaeva, MD, PhD; Brian Spencer, MS; Sherry Wong, MS; Shivda Pandey, MD; William S. Blaner, PhD; Albert DeLuca, MD; Lynne L. Johnson, MD; Mona P. Kinkhabwala, MD; Jay Leb, MD; Akiva Mintz, MD; Michael P. LaValley, PhD; Andrew J. Einstein, MD, PhD; Elizabeth Cohn, PhD; Cesia Gallegos, MD, MHS; Gillian Murtagh, MD; Jeffery W. Kelly, PhD; Edward J. Miller, MD, PhD; Mathew S. Maurer, MD



Participants	Assessments
Longitudinal, observational, cohort study Multi-center - New York City, Boston, New Haven	*TTR* genotype TTR stability Cardiac Biomarkers RBP4/Vitamin A Prealbumin Genetic ancestry analysis
Age ≥ 60 years Black race or Caribbean Hispanic ethnicity	6-minute walk Short Physical Performance Battery
	KCCQ SF-12 Social determinants
Heart failure LV wall thickness ≥ 12 mm LVEF > 30%	Echocardiography
	Nuclear imaging

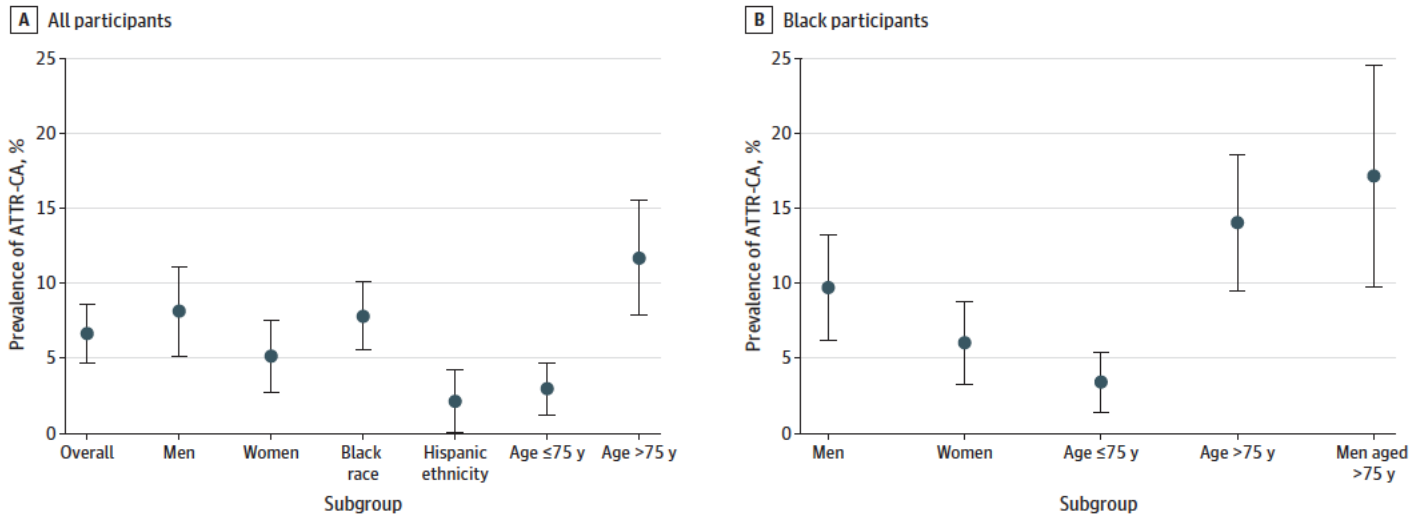
NIH National Heart, Lung, and Blood Institute · Boston Medical Center · Boston University · Columbia University · Yale-New Haven Hospital · NYC Health+ Hospitals | Harlem

Ruberg…Maurer, JAHA 2023 and *JAMA Cardiology 2025*

Community Screening – SCAN-MP

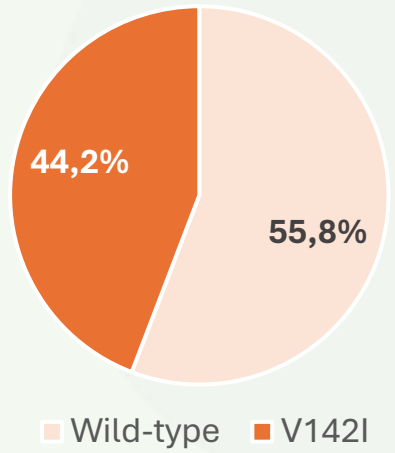
ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

Figure. Prevalence of Transthyretin Cardiac Amyloidosis (ATTR-CA)
Among All SCAN-MP Participants and Among Self-Identified Black SCAN-MP Participants



Characteristic	No. (%)[a] Overall (n = 43)	ATTRwt-CA (n = 24)	V142I ATTRv-CA (n = 19)	*P* value[a]
Age, mean (SD), y	80.3 (8.3)	82.5 (8.6)	77.6 (7.3)	.06
Sex				
Female	17 (39.5)	8 (33.3)	9 (47.4)	.35
Male	26 (60.5)	16 (66.7)	10 (52.6)	

ATTR Genotype in Positive Subjects



SCAN-MP

Ruberg…Maurer, *JAMA Cardiology 2025*

Earlier stage diagnosis but not younger

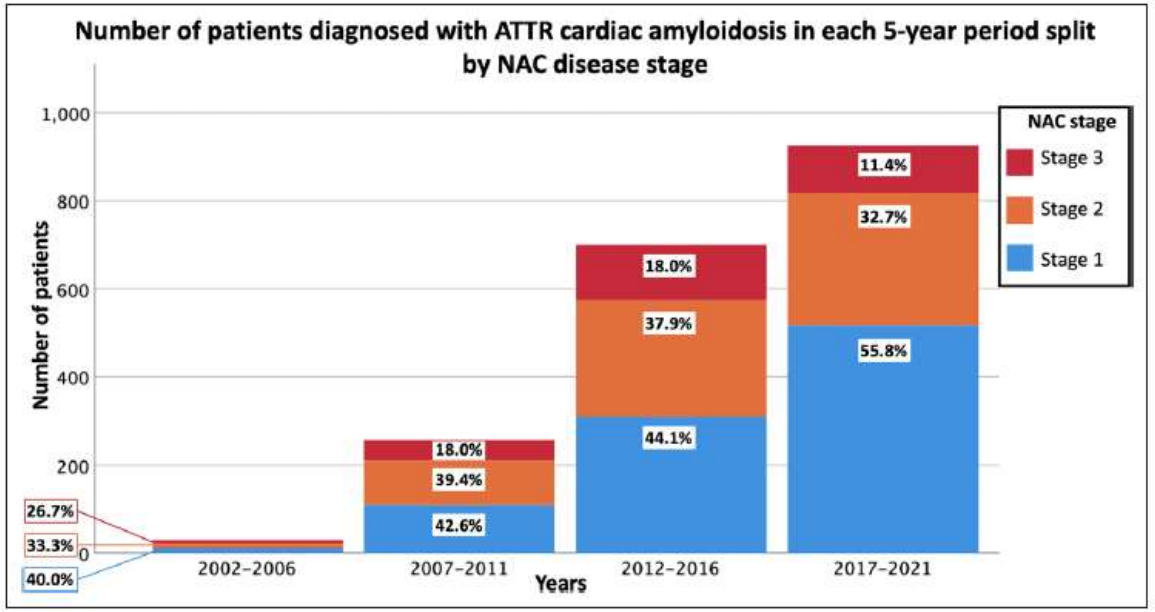
ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

ORIGINAL RESEARCH ARTICLE

Impact of Earlier Diagnosis in Cardiac ATTR Amyloidosis Over the Course of 20 Years

Adam Ioannou, MBBS, BSc*; Rishi K. Patel, MBBS, BSc*; Yousuf Razvi, MBChB, BSc; Aldostefano Porcari, MD; Gianfranco Sinagra, MD; Lucia Venneri, MD, PhD; Francesco Bandera, MD, PhD; Ambra Masi, MD; Georgina E. Williams, BSc; Sophie O'Beara, BSc (Hons); Sharmananthan Ganesananthan, BSc (Hons); Paolo Massa, MD; Daniel Knight, PhD; Ana Martinez-Naharro, PhD; Tushar Kotecha, PhD; Liza Chacko, MBBS, BSc; James Brown, MB, BChir; Muhammad U. Rauf, MBBS; Charlotte Manisty, MD, PhD; James Moon, MD, PhD; Helen Lachmann, MD; Ashutosh Wechelakar, MD; Aviva Petrie, MSc; Carol Whelan, MD; Philip N. Hawkins, MD, PhD; Julian D. Gillmore, MD, PhD†; Marianna Fontana, MD, PhD†

Era	n	Age (mean +/- SD)	Male sex (%)
2007-2011	260	74 +/- 7	86
2012-2016	704	76 +/- 7	87
2017-2021	968	76 +/- 9	86



Despite earlier stage patients identified in more contemporary cohorts, age remains the same

Ioannou, *Circulation* 2022

Earlier stage diagnosis but not younger

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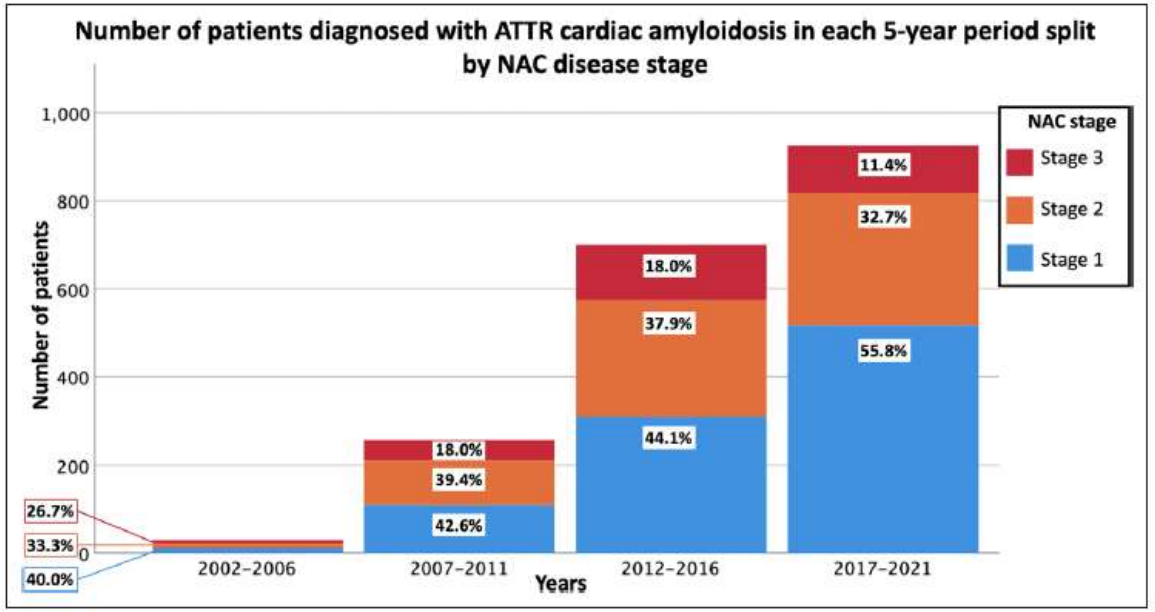
ORIGINAL RESEARCH ARTICLE

Impact of Earlier Diagnosis in Cardiac ATTR Amyloidosis Over the Course of 20 Years

Adam Ioannou, MBBS, BSc*; Rishi K. Patel, MBBS, BSc*; Yousuf Razvi, MBChB, BSc; Aldostefano Porcari, MD; Gianfranco Sinagra, MD; Lucia Venneri, MD, PhD; Francesco Bandera, MD, PhD; Ambra Masi, MD; Georgina E. Williams, BSc; Sophie O'Beara, BSc (Hons); Sharmananthan Ganesananthan, BSc (Hons); Paolo Massa, MD; Daniel Knight, PhD; Ana Martinez-Naharro, PhD; Tushar Kotecha, PhD; Liza Chacko, MBBS, BSc; James Brown, MB, BChir; Muhammad U. Rauf, MBBS; Charlotte Manisty, MD, PhD; James Moon, MD, PhD; Helen Lachmann, MD; Ashutosh Wechelakar, MD; Aviva Petrie, MSc; Carol Whelan, MD; Philip N. Hawkins, MD, PhD; Julian D. Gillmore, MD, PhD†; Marianna Fontana, MD, PhD†

Era	n	Age (mean +/- SD)	Male sex (%)
2007-2011	260	74 +/- 7	86
2012-2016	704	76 +/- 7	87
2017-2021	968	76 +/- 9	86



Despite earlier stage patients identified in more contemporary cohorts, age remains the same

Ioannou, *Circulation* 2022

Summary – Age and sex at diagnosis

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Redefining the epidemiology of cardiac amyloidosis. A systematic review and meta-analysis of screening studies

Alberto Aimo[1,2], Marco Merlo[3], Aldostefano Porcari[3], Georgios Georgiopoulos[1,4,5], Linda Pagura[3], Giuseppe Vergaro[1,2], Gianfranco Sinagra[3], Michele Emdin[1,2], and Claudio Rapezzi[6,7]*

HFpEF: 12%
(95% CI 6-20%)
M 73% (39-100%)
77 years (66-86)
AL-CA 10% (0-40%)

HFrEF/HFmrEF: 10%
(95% CI 6-15%)
M 100%
81 years (76-85)
AL-CA 0%

Prevalence: 10-12% in older patients with HF irrespective of EF
Age: 77-81 years
Sex: WT perhaps 2-3:1 males:females, but pV142I perhaps 1:1

Aimo, *Eur J HF* 2022

Age of enrollment in clinical trials

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Study	Age (years)	Male sex (%)	Black race (%)
ATTR-ACT	74	90%	14%
ATTRIBUTE-CM	77	90%	5%
HELIOS-B	77	92%	7%

- **Women under-represented**
- **Black race participants (pV142I or WT) under-represented**
- **We need to do better!**

Thank you for your attention

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@Amyloidosis_BU

BOSTON MEDICAL CENTER
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BOSTON UNIVERSITY

/frederick-l-ruberg-md

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Screening and early diagnosis of ATTR amyloidosis: Novel biomarkers

Justin L. Grodin, MD, MPH, FACC, FHFSA

Division of Cardiology, Department of Internal Medicine,

UT Southwestern Medical Center, Dallas, TX

Disclosures

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- **Consulting/Scientific Advisory Board:** Pfizer, Eidos/BridgeBio (Executive Steering Committee, ACT-EARLY), AstraZeneca, Alexion, Alnylam, Intellia, Novo Nordisk, Tenax Therapeutics (DSMC), Ultromics, and Lumanity
- **Research Funding:** Pfizer 67656485, Eidos/BridgeBio, Texas Health Resources Clinical Scholars Fund, and NHLBI R01HL160892 and R01HL172993

Why Consider Screening?

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1. *Amyloid fibril deposition is progressive*
2. *Therapeutic efficacy of ATTR treatment diminishes with disease progression*
3. *Carriers of pathogenic TTR alleles can have evidence of subclinical ATTRv*
4. *Screening can detect subclinical ATTRv*

Mechanism of Transthyretin Amyloidogenesis

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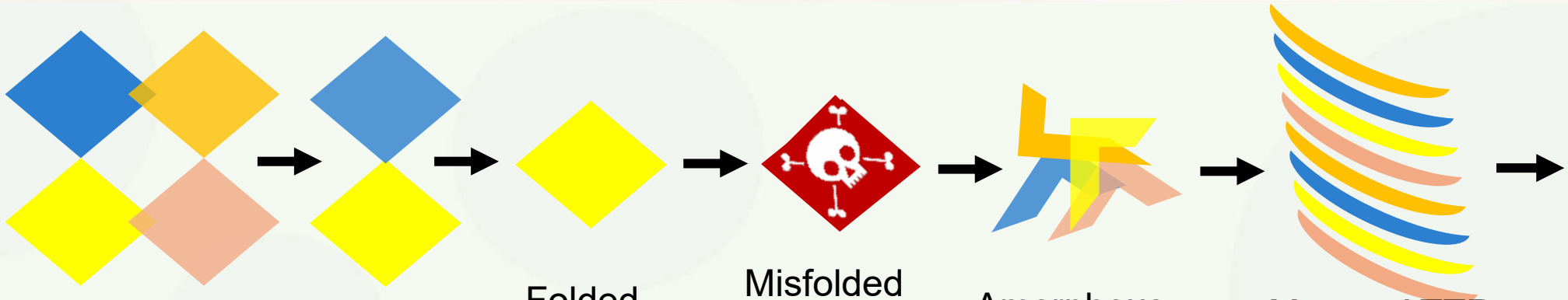


TTR tetramer

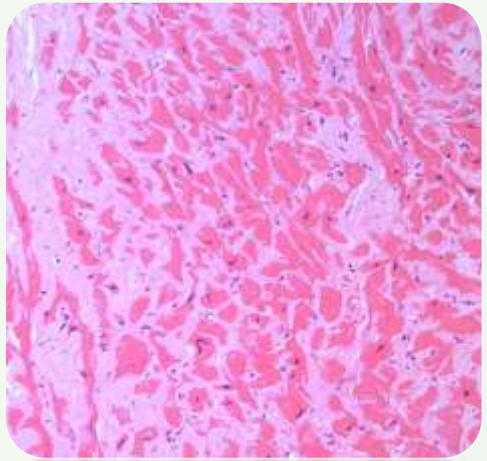
Folded dimer

Folded monomer

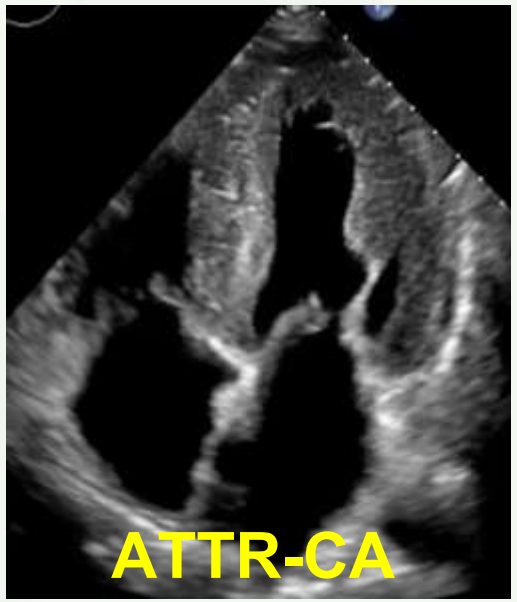
Misfolded amyloidogenic monomer

Amorphous ATTR oligomers

Mature ATTR fibrils



Myocardial infiltration



Transthyretin

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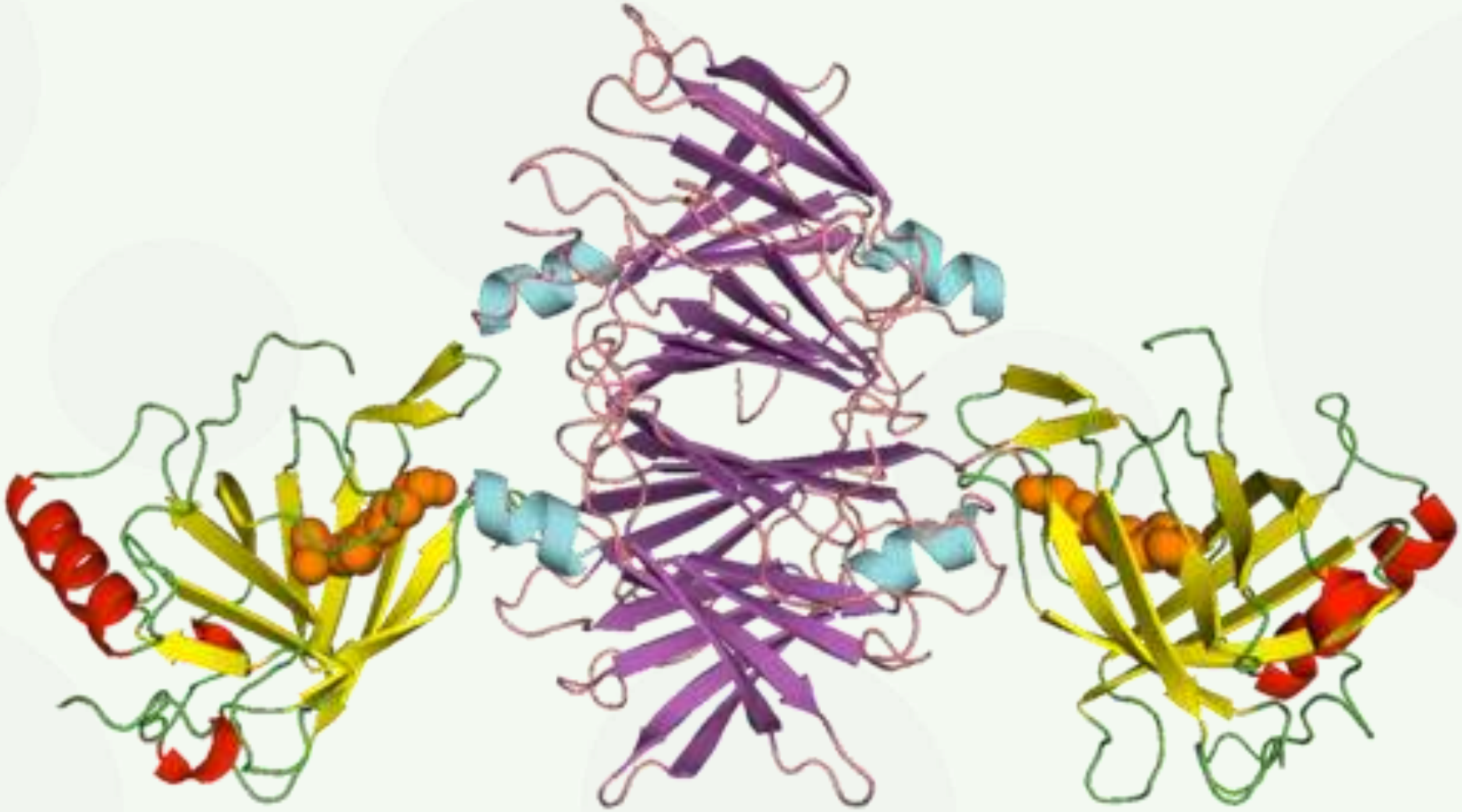

Circulating TTR in V122I (p.V142I) *TTR* Carriers

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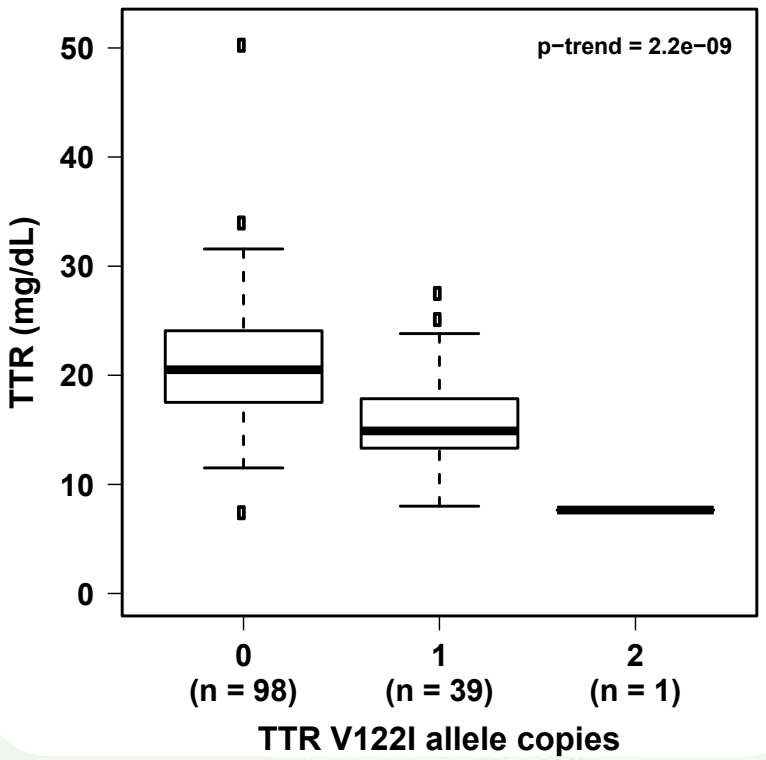
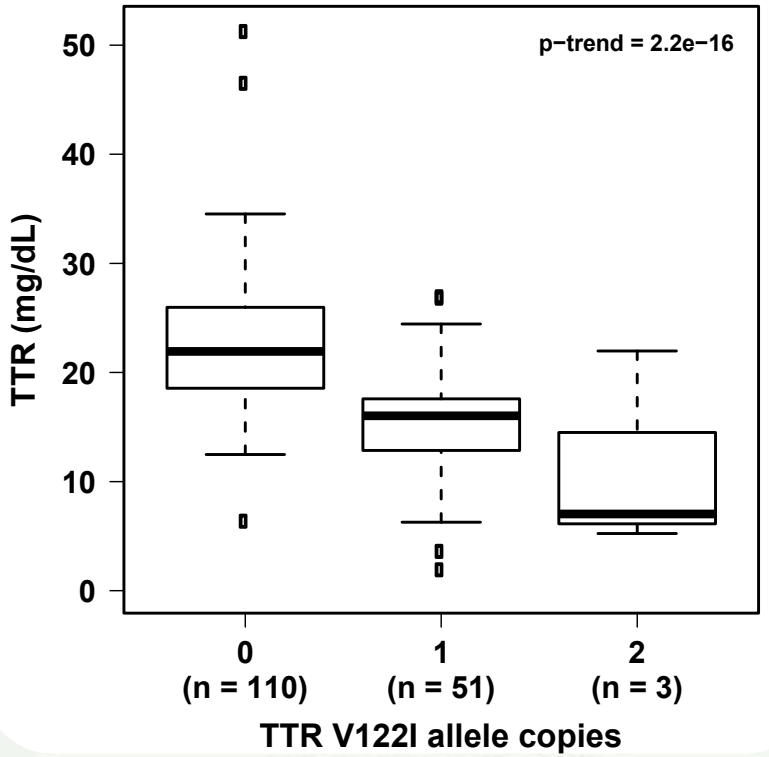
Dallas Heart Study Visit 1



Dallas Heart Study Visit 2



V122I carriers (hetero- and homozygotes) vs. age-, sex-, race-matched controls in general population

Hendren NS, Grodin JL, et al. Amyloid. 2024

Circulating RBP4 in V122I (p.V142I) *TTR* Carriers

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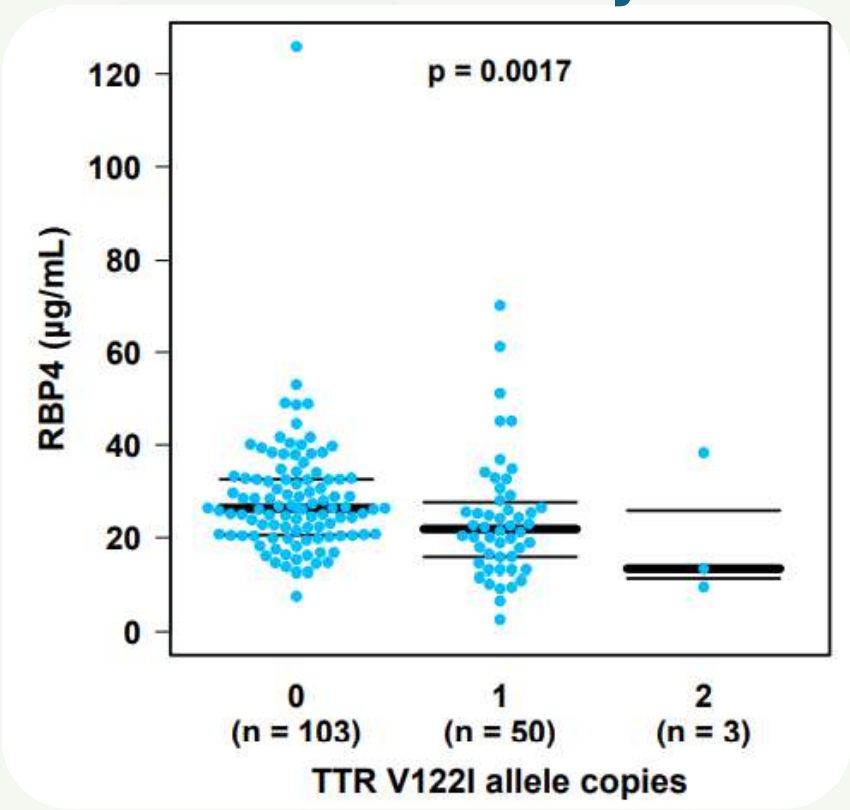
Dallas Heart Study Visit 2



V122I carriers (hetero- and homozygotes) vs. age-, sex-, race-matched controls in general population

Hendren NS, Grodin JL, et al. Amyloid. 2024

TTR Kinetic Stability Assessments

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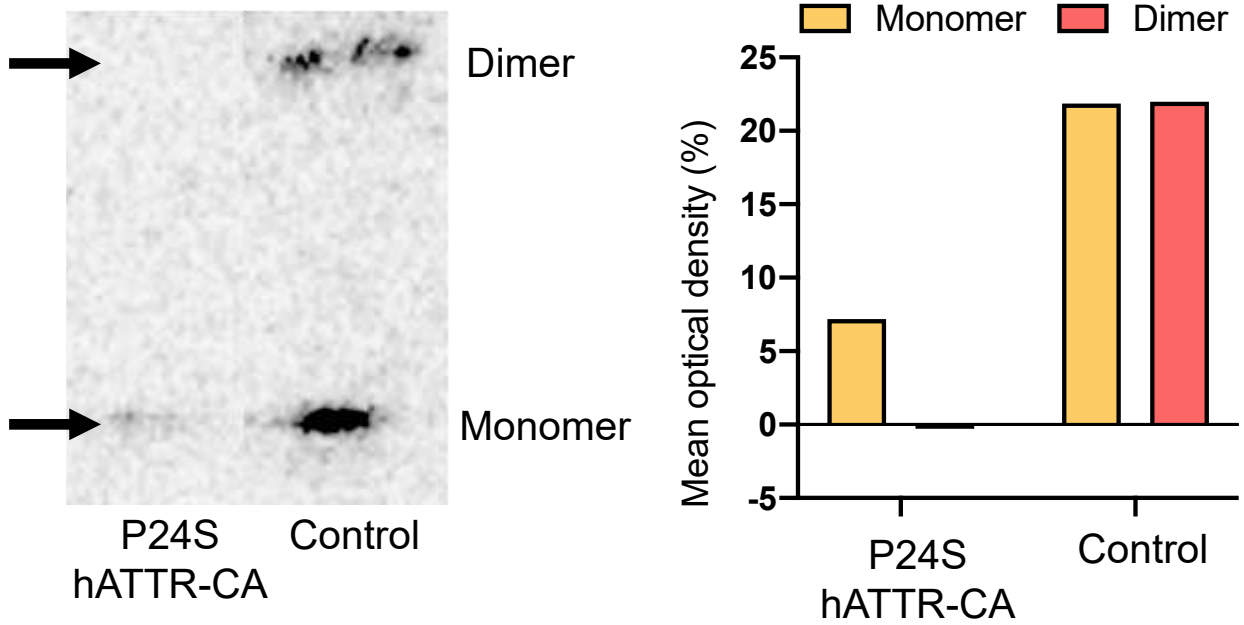
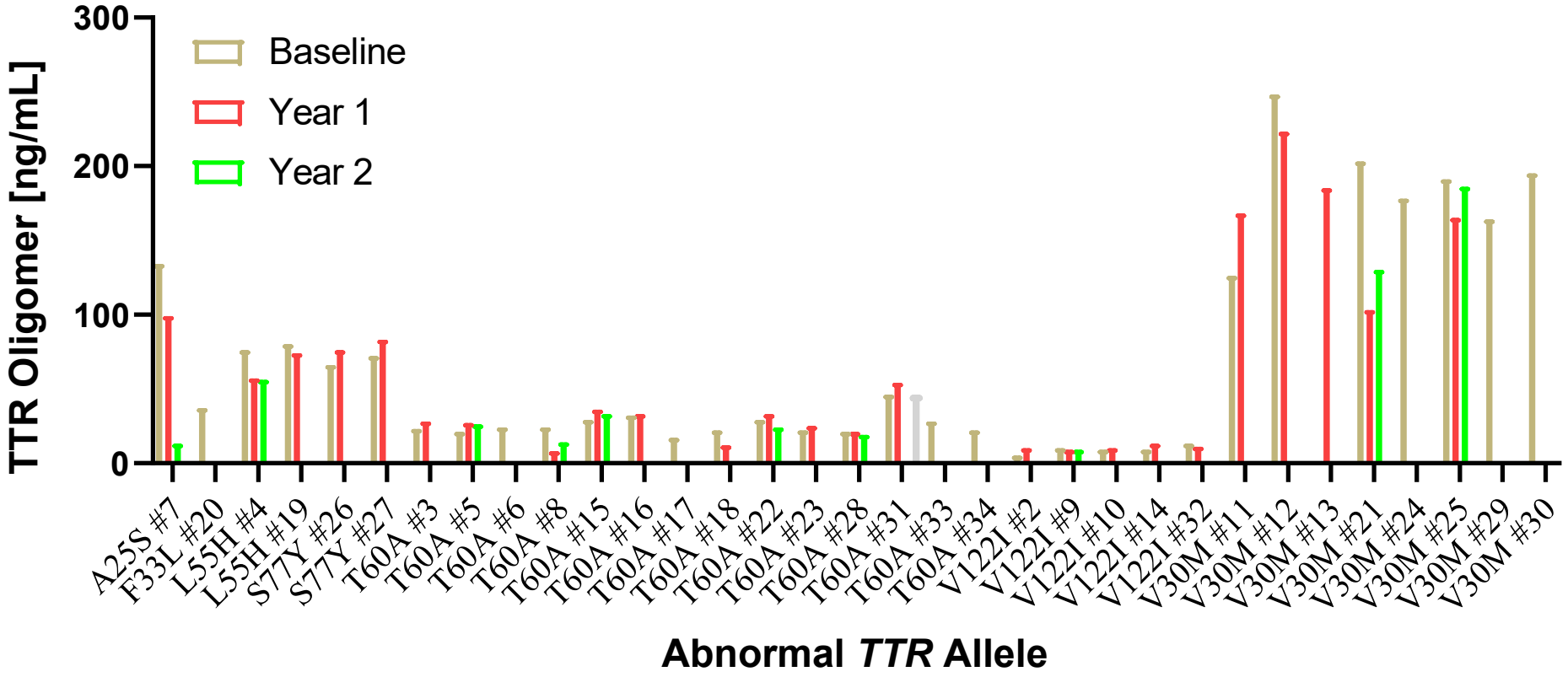
- Western blot analysis showing disproportionately higher signal of monomers than dimers in a patient with ATTRv-CM than a non-amyloid control indicative of lower kinetic stability



Western Blot of TTR dimers and monomers for a patient with P24S (p.Pro44Ser) hATTR-CA (arrows) compared with a non-ATTR-CA control patient run in the laboratory of Dr. Lorena Saelices Gomez. Note: the bands are faint for the P24S hATTR-CA patient because of lower circulating TTR.

Non-native TTR in Carriers of Pathogenic *TTR* Alleles Identify a Spectrum of TTR Amyloidogenic Activity



These are preliminary data from 30 carriers of abnormal *TTR* alleles enrolled in the MED-hATTR study (NCT03431896) collected and measured over 2 years.

Schonhoft JD, et al. Sci Transl Med. 2017

Structure-based Peptide Inhibitors to Detect ATTR

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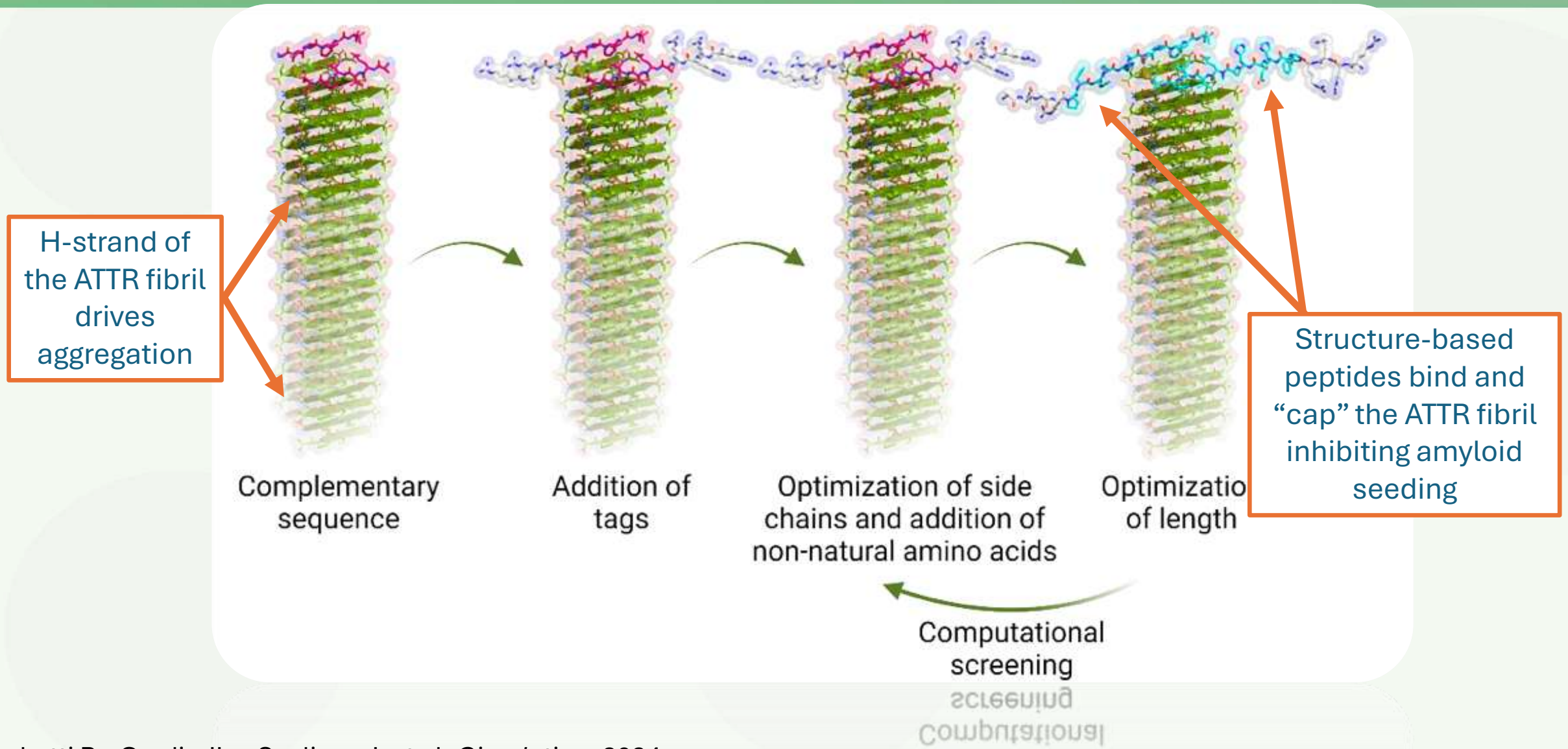
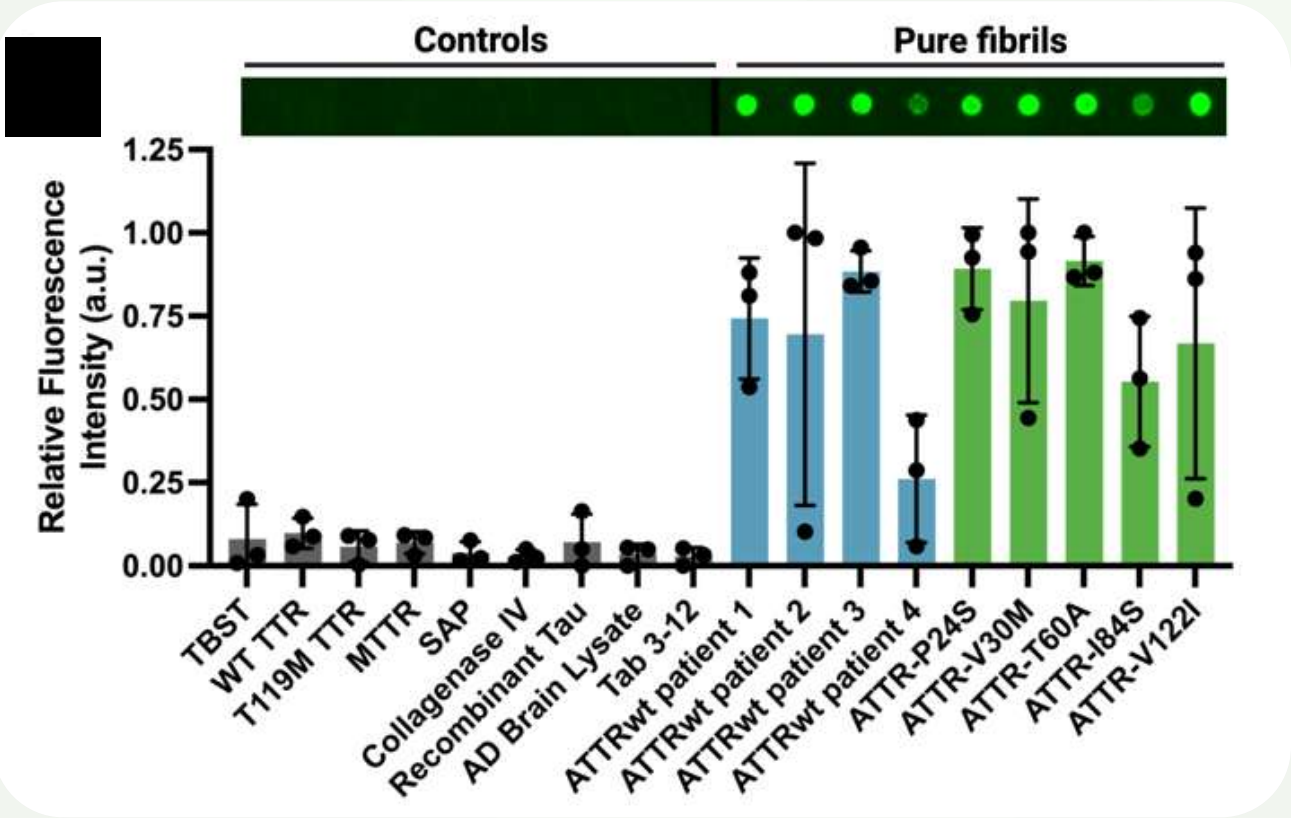
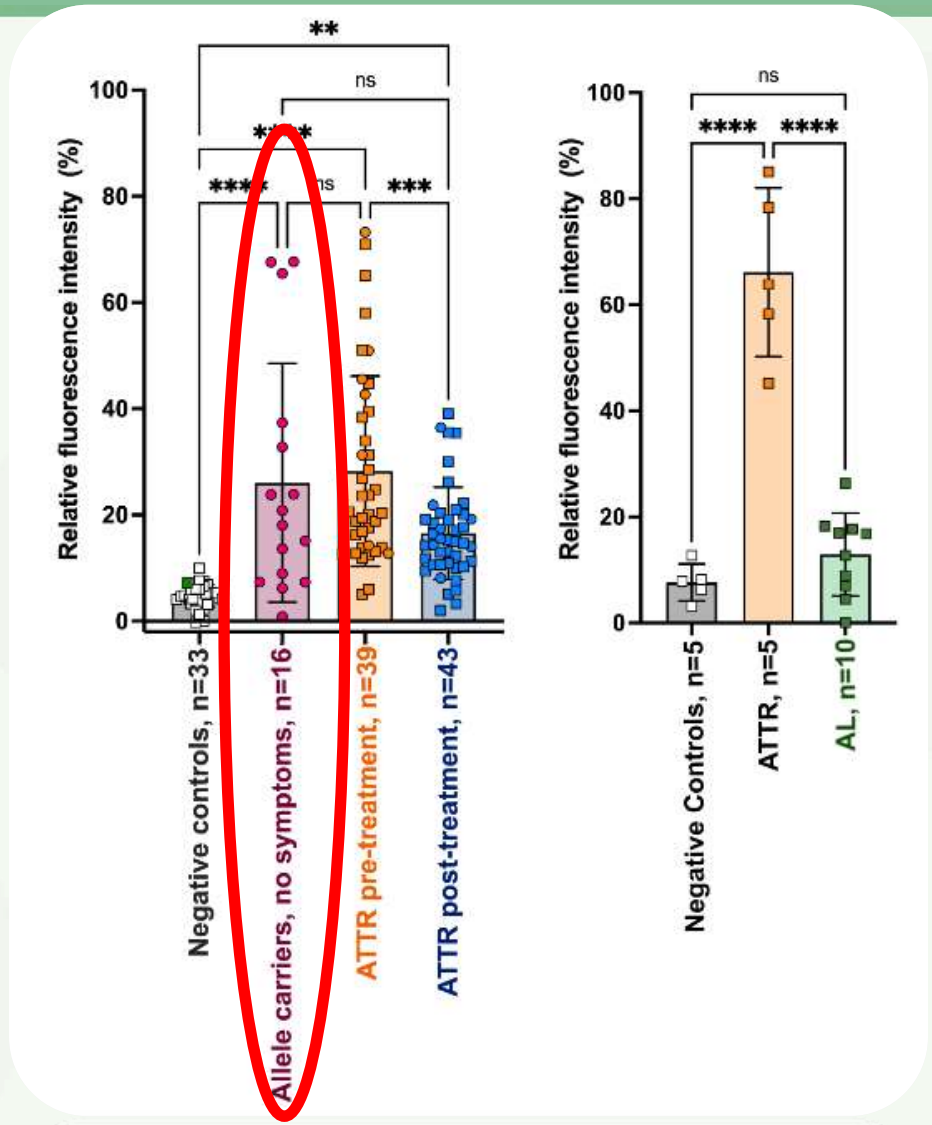


Pedretti R...Grodin JL... Saelices, L et al. *Circulation*, 2024

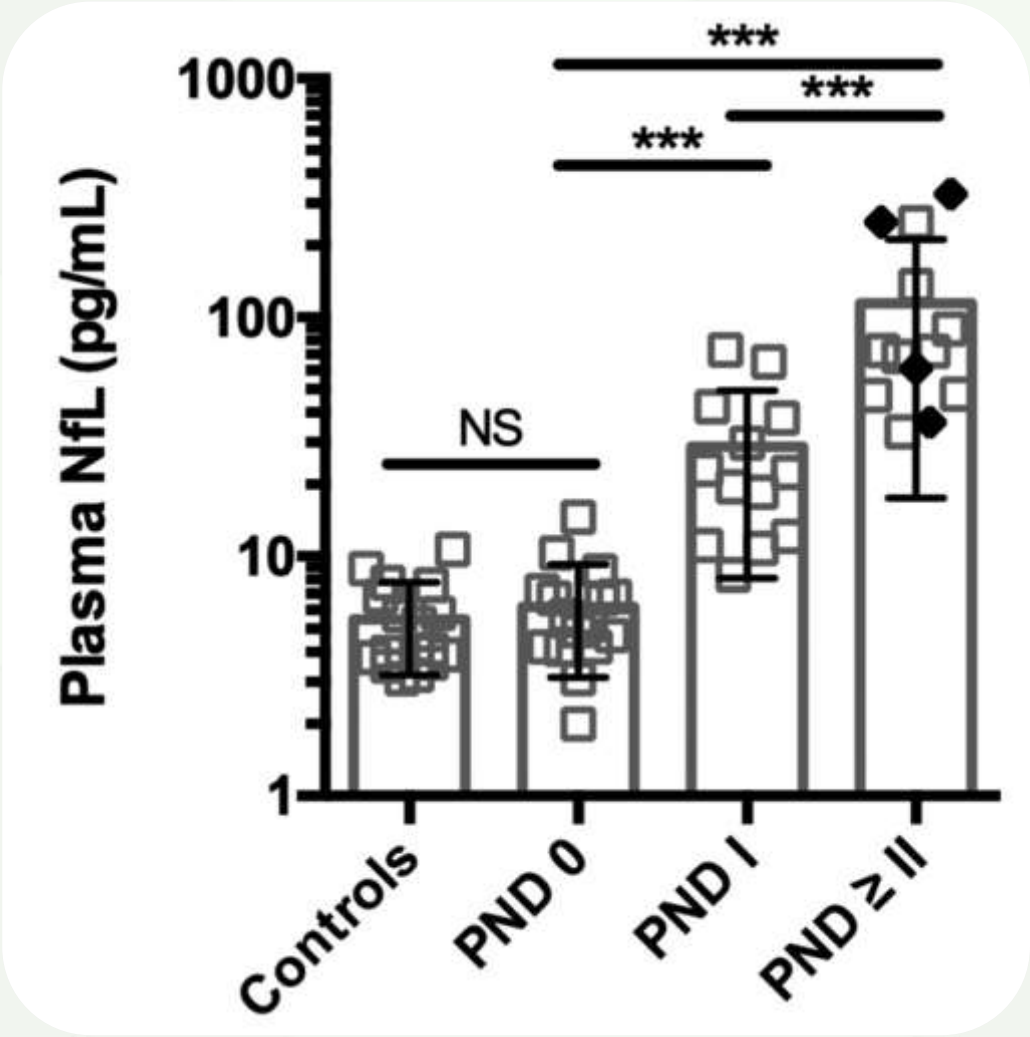
Highly Specific and Sensitive Peptide Probes (“TAD1”) Detect Circulating ATTR Aggregates in *TTR* Carriers





Pedretti R...Grodin JL... Saelices, L et al. Circulation, 2024

Plasma Neurofilament Light Chains (NfL) As A Marker Of ATTR Polyneuropathy Progression

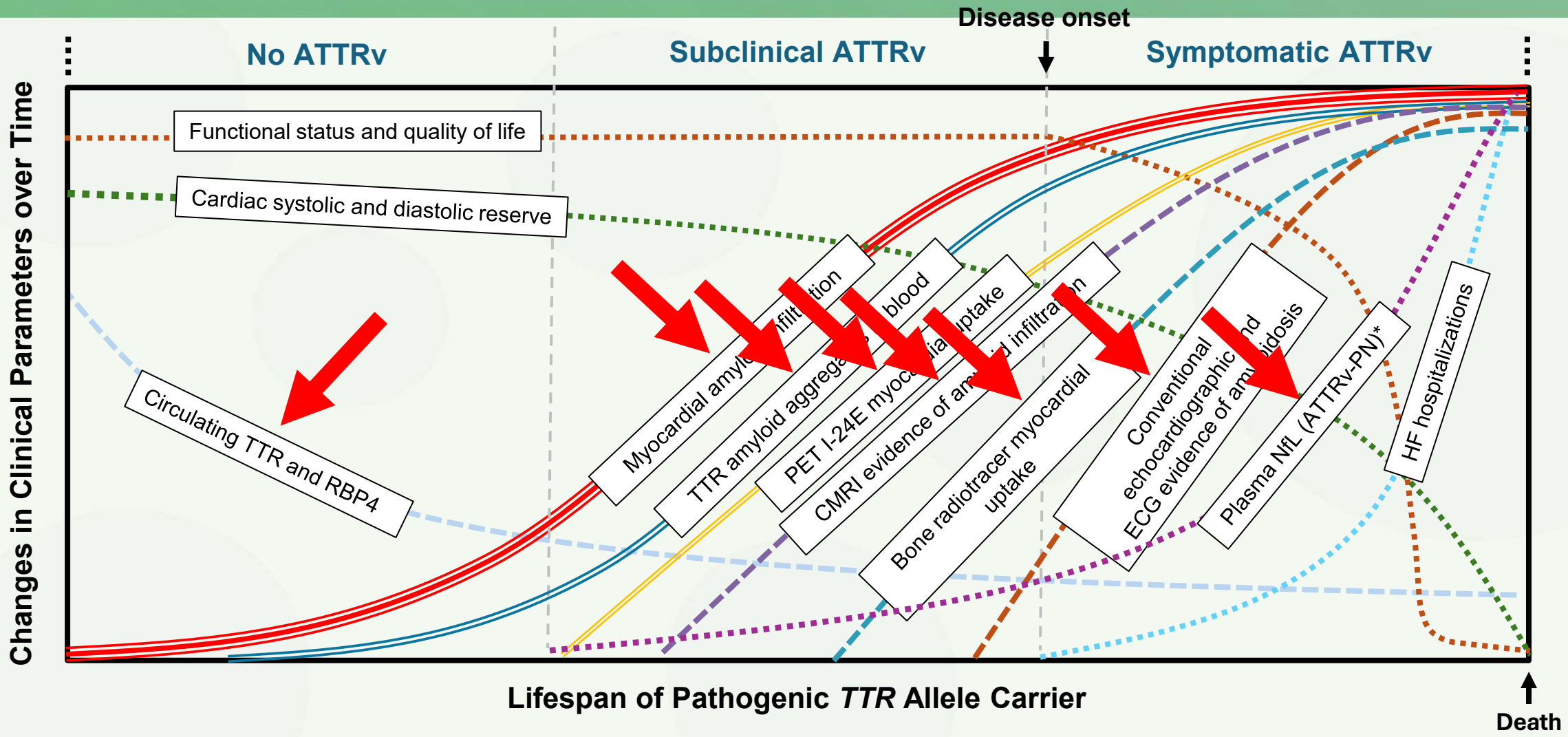


Plasma NfL

- Quantifies neuro-axonal damage in disorders of the peripheral and central nervous system
- “Neuron troponin”

Maia LF, et al. Amyloid 2020

Hypothesized Non-invasive Assessments to Detect Evidence of Subclinical ATTRv



Abbreviations: PET, positron emission tomography; I24E Iodine-124 evuzamitide; CMRI, cardiac magnetic resonance imaging; Nfl, neurofilament light chains; and ECG, electrocardiography

Conclusion

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Completely novel highly sensitive and specific ATTR biomarkers hold promise to detect early ATTRv

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Artificial Intelligence in the Screening and Early Diagnosis of Amyloidosis

Dr. Lukas D. Weberling, MD

Heidelberg University Hospital, Germany

Disclosures

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- Provision of free software licenses for research by Myocardial Solutions (Durham, NC, USA)
- Provision of Technical Equipment for research by Area 19 Inc (Québec, Canada)

Moravec‘s paradoxon

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“The hard problems are easy and the easy problems are hard”

IBM’s “Deep Blue” beats chess world champion Garri Kasparo, 1997

Tesla’s Robot “Optimus” pours a drink, 2024

(remote-controlled)

Data vs. Patient

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- What do you ask?
- What does he tell?
- What do you notice?

The patient pathway

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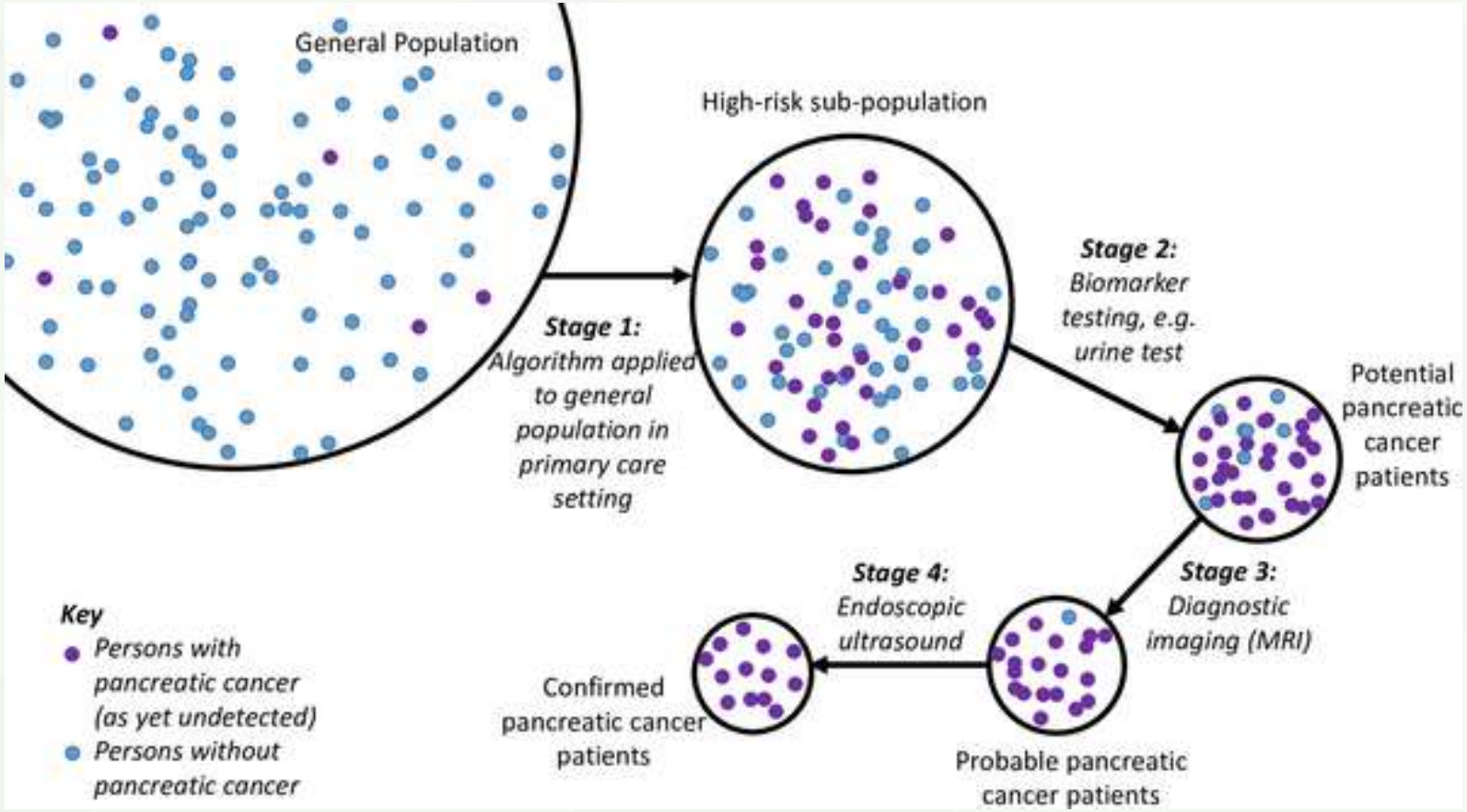

https://doi.org/10.1371/journal.pone.0251876

EstimATTR: A Simplified, Machine-Learning-Based Tool to Predict the Risk of Wild-Type Transthyretin Amyloid Cardiomyopathy

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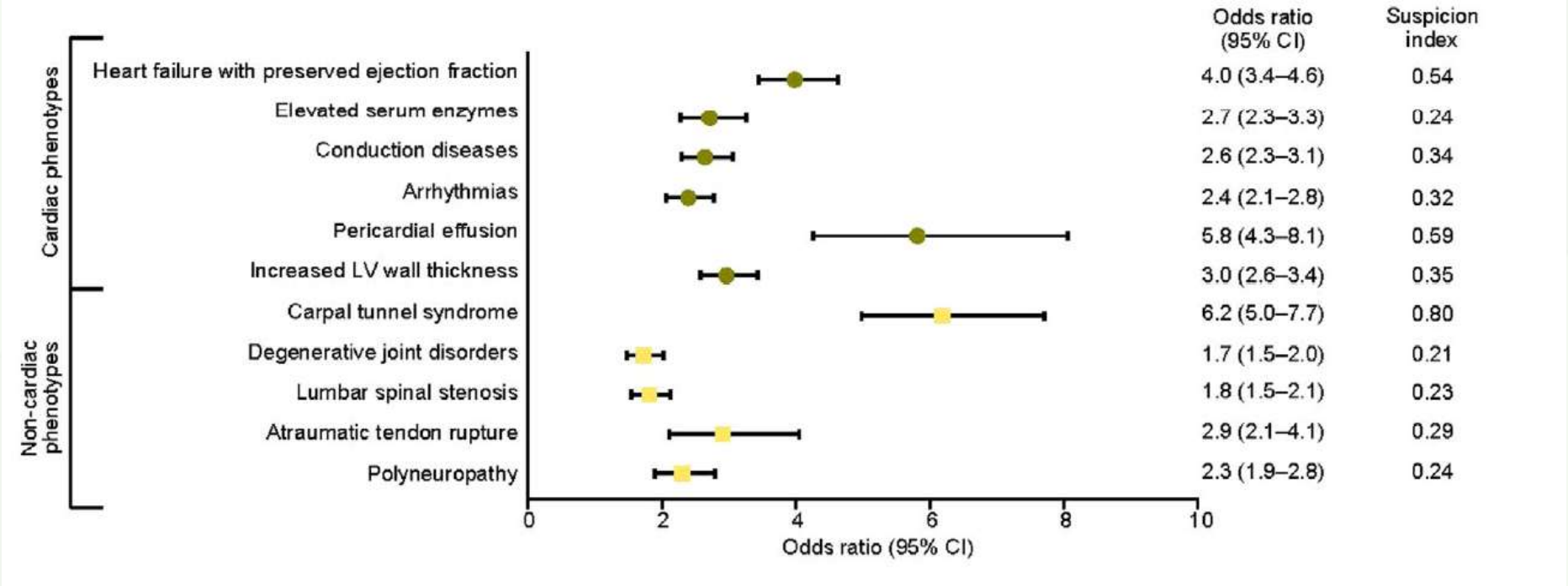
- Used medical health records
- Identifies ATTR in Heart Failure Patients
- AUC 0,82 / sensitivity 77% / specificity 72%



Castaño et al; Journal of Cardiac Failure 2024

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T-Amylo: Development and Validation of a Prediction Model and Score for Transthyretin Cardiac Amyloidosis Diagnosis

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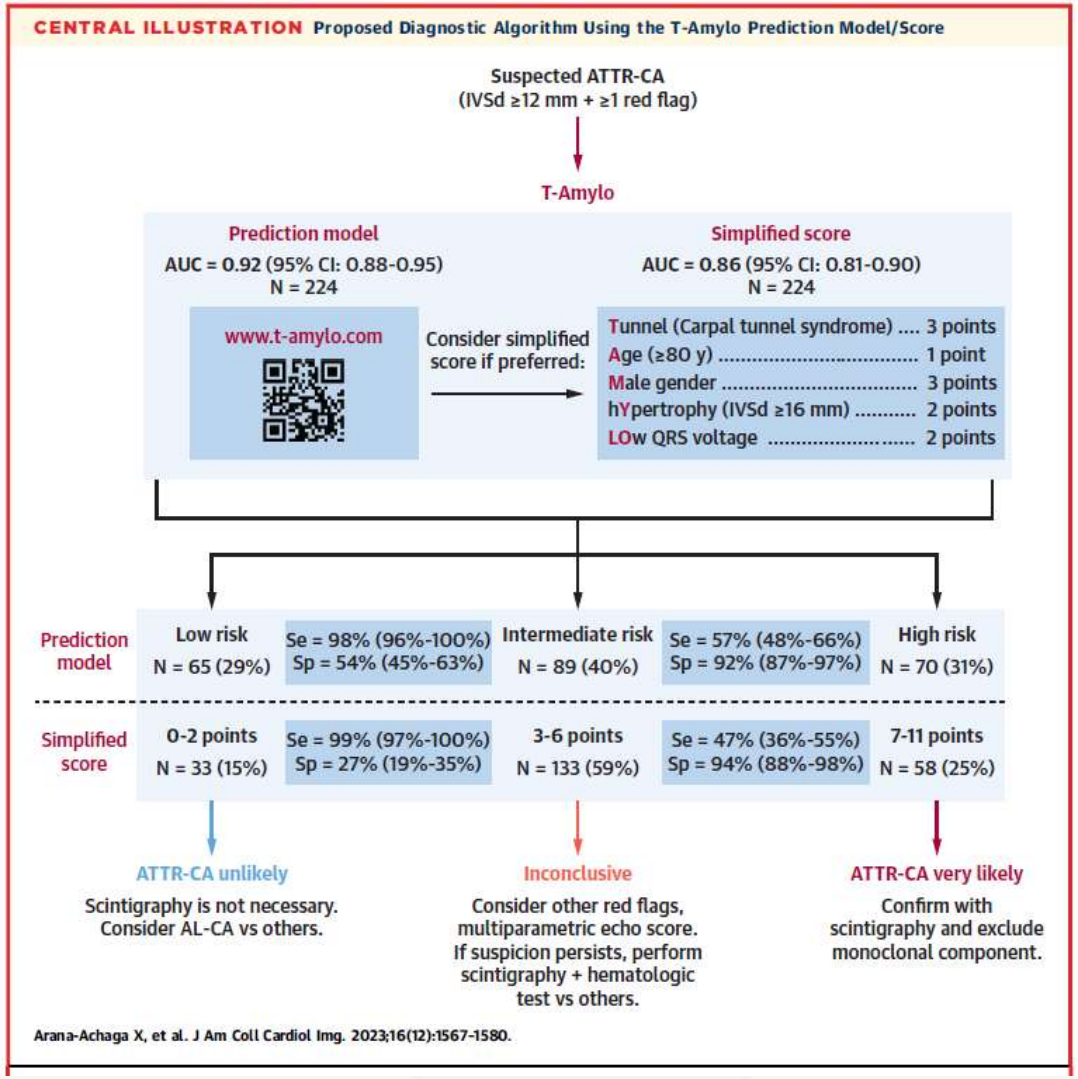

→AUC 0.84 / 0.82 in validation cohort (895 patients)

→Patients with scintigraphy

Arana-Achaga et al. JACC Cardiovascular Imaging 2023

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A machine learning model for identifying patients at risk for wild-type transthyretin amyloid cardiomyopathy

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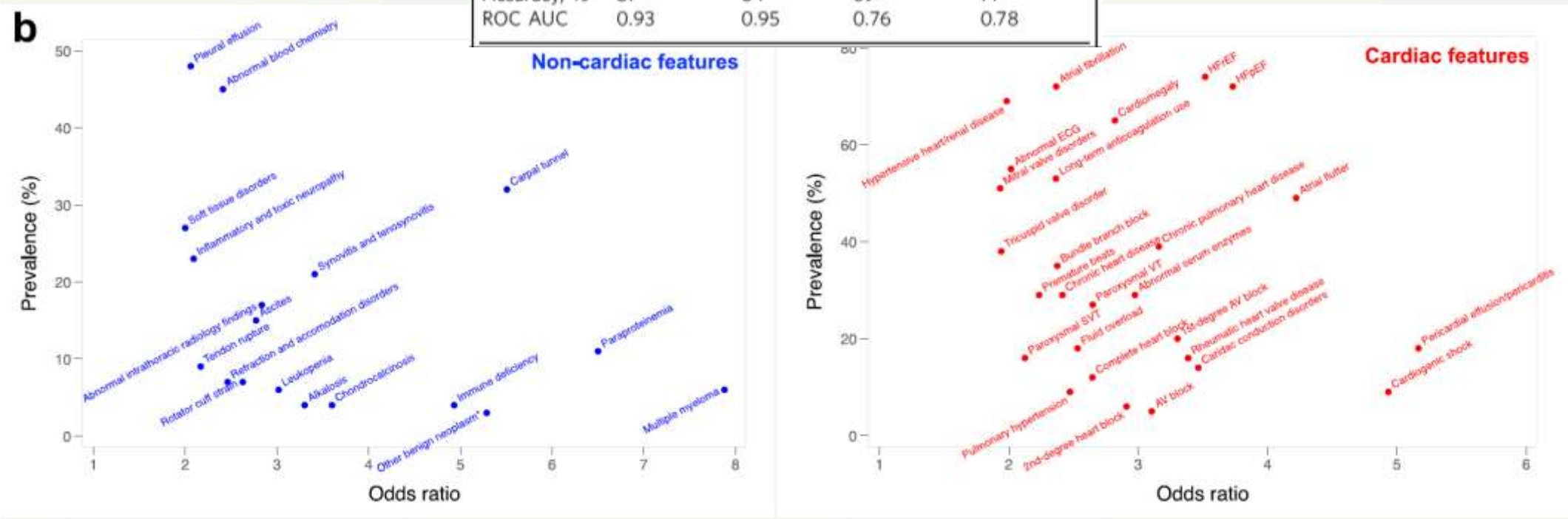
Metric	Validation cohort			
	Cohort 1: IQVIA holdout (ATTR-CM)	Cohort 2: Optum (ATTR-CM)	Cohort 3: IQVIA (cardiac amyloid)	Cohort 4: Optum (cardiac amyloid)
Sensitivity, %	87	90	56	61
Specificity, %	87	79	83	81
PPV, %	88	81	76	76
NPV, %	86	89	65	67
Accuracy, %	87	84	69	71
ROC AUC	0.93	0.95	0.76	0.78

→Medical claims data

→Only heart failure patients

→AUC 0.80 in non-matched validation cohort



Huda et al. Nature Comm 2021

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Cardiac amyloidosis detection from a single echocardiographic video clip: a novel artificial intelligence-based screening tool

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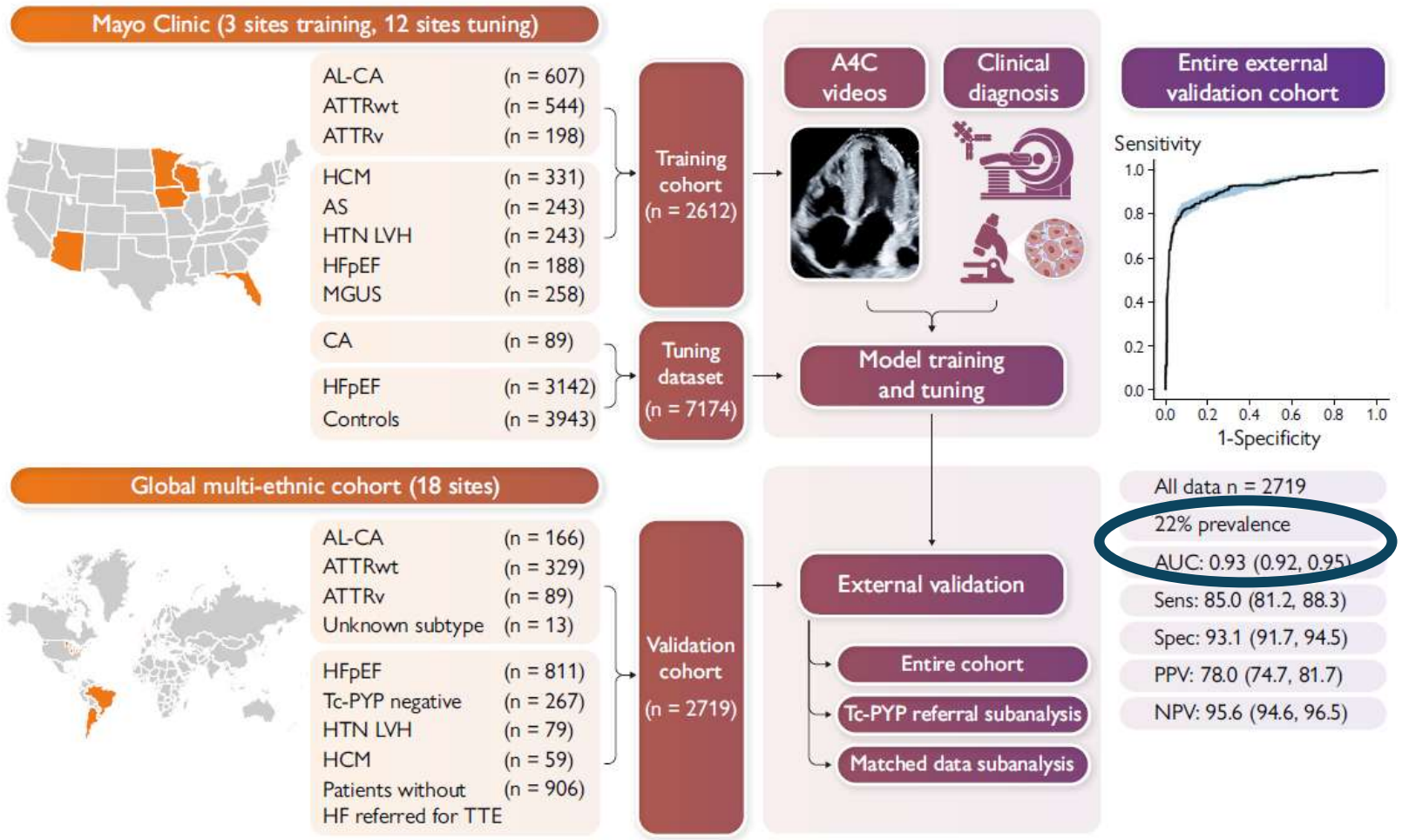

→Removal of uncertain AI predictions (13%)

Slivnick et al. European Heart Journal 2025

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CMR to differentiate AL, ATTR, HCM

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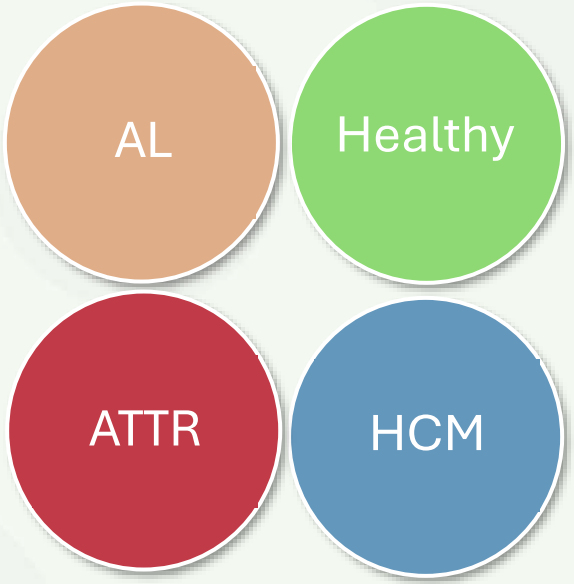
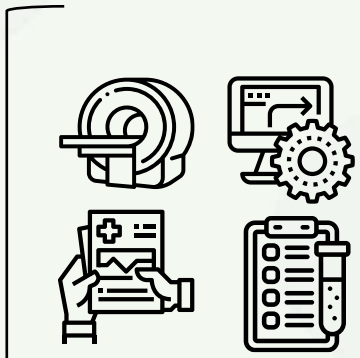
Retrospective, multi-vendor, multi-center CMR study



n = 400

51 referring CMR centers

Supervised/Corrected by two experienced readers (LW / AO)



Mostly automated CMR imaging data

Standard clinical information

Machine learning model to predict diagnosis

SCAN ME

CMR to differentiate AL, ATTR, HCM

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22 non-imaging parameters
185 imaging parameters

Selection of Imaging-derived group characteristics							
		Healthy	HCM	AL	ATTR	Healthy vs. Patient	HCM vs. Amyloidosis	AL vs. ATTR
Interventricular septum (mm)		8 [7; 10]	19 [17; 22]	16 [14; 17]	20 [17; 22]	p < 0.001	p = 0.06	p < 0.001
Asymmetric hypertrophy		2 (2.1%)	89 (94.7%)	23 (24.2%)	45 (38.8%)	p < 0.001	p < 0.001	p = 0.03
Pericardial fluid		3 (3.2%)	21 (22.3%)	62 (65.3%)	60 (51.7%)	p < 0.001	p < 0.001	p = 0.06
Left Ventricle								
	EDV, normalized (ml/m²)	84 [77; 94]	81 [69; 90]	74 [65; 83]	87 [76; 97]	p = 0.009	p = 0.6	p < 0.001
	Myocardial mass (g)	90 [76; 106]	156 [125; 184]	149 [114; 182]	188 [146; 215]	p < 0.001	p = 0.06	p < 0.001
	Ejection fraction (%)	58 [55; 61]	62 [57; 67]	56 [48; 62]	49 [41; 57]	p = 0.002	p < 0.001	p < 0.001
	GLS (-%)	18.9 [20.4; 17.7	14.1 [15.4; 11.9	12.3 [15.8; 9.0]	10.4 [12.5; 7.9]	p < 0.001	p < 0.001	p = 0.001
	GCS (-%)	19.2 [20.7; 18.4	18.4 [19.6; 16.7	16.3 [18.7; 14.5	13.9 [16.4; 11.1	p < 0.001	p < 0.001	p < 0.001
	GRS (%)	32.8 [30.3; 37.1	32.7 [28.5; 36.5	26.2 [21.8; 31.7	20.8 [15.2; 26.5	p < 0.001	p < 0.001	p < 0.001
Right Ventricle								
	EDV, normalized (ml/m²)	90 [81; 98]	75 [64; 87]	74 [65; 85]	91 [75; 103]	p < 0.001	p = 0.01	p < 0.001
	Ejection fraction (%)	56 [53; 60]	61 [56; 65]	55 [47; 63]	50 [40; 57]	p = 0.16	p < 0.001	p = 0.002
	GLS (-%)	24.1 [26.5; 21.9	25.6 [27.7; 21.7	18.6 [24.0; 14.1	17.4 [21.1; 13.6	p < 0.001	p < 0.001	p = 0.04
	GCS (-%)	16.5 [18.4; 13.8	17.6 [20.3; 15.1	16.8 [19.0; 13.4	15.1 [17.8; 13.0	p = 0.7	p < 0.001	p = 0.01
	GRS (%)	55.7 [47.0; 66.8	60.4 [44.2; 71.4	33.2 [21.5; 51.1	29.2 [20.9; 39.4	p < 0.001	p < 0.001	p = 0.03

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CMR to differentiate AL, ATTR, HCM

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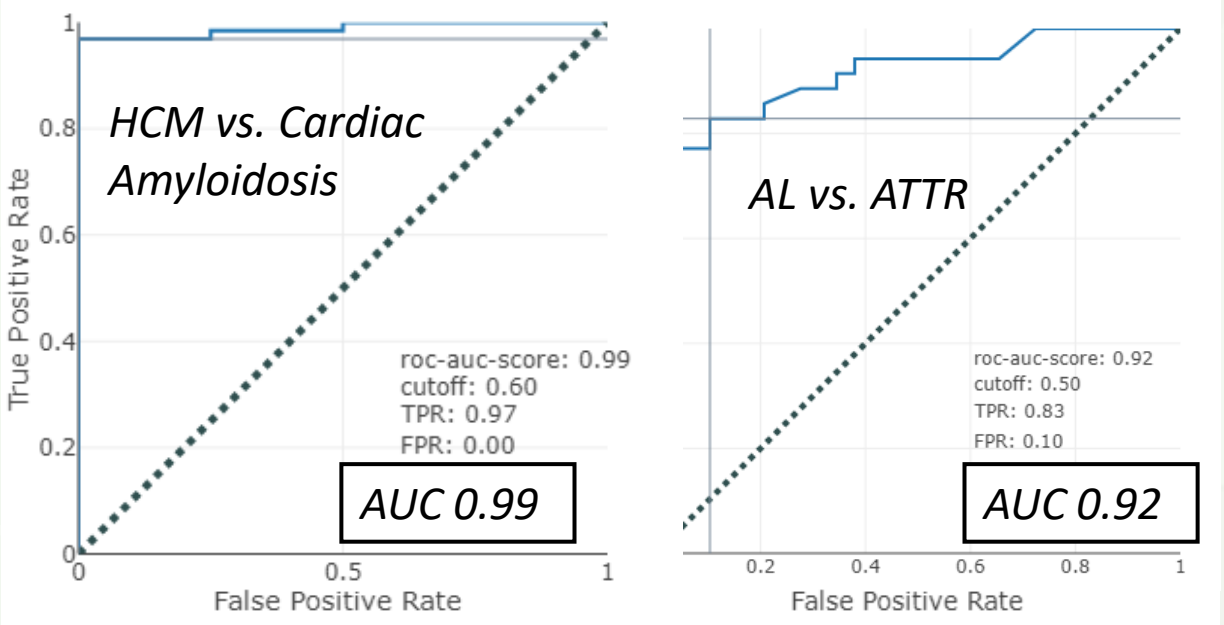
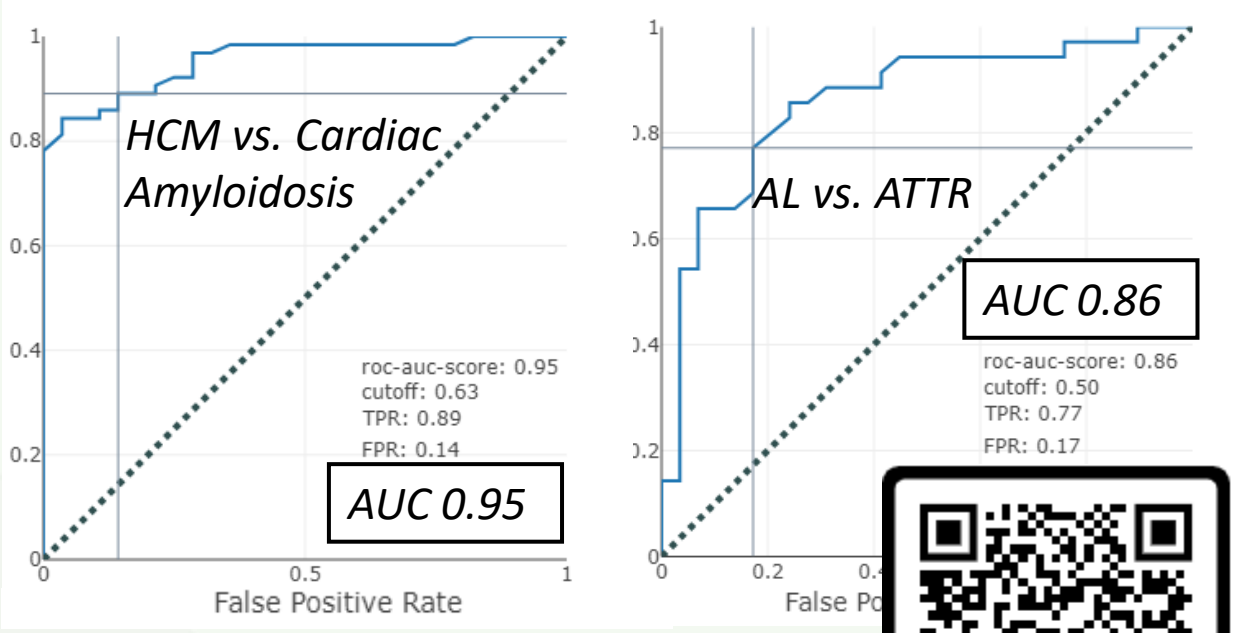
CMR and standard clinical information



Needle-free CMR without clinical information



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Conclusions

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- AI is data-driven not patient-centered
  - Great help for data it has access to, which is only a fraction
  - Great help if you ask the right questions
- AI is currently (!) not ready to screen an unselected general population
- CMR has a great potential for the future of amyloidosis imaging
  - 15min protocols without contrast agents
  - >200 imaging biomarkers readily available
  - Helps you even if the patient does not have amyloidosis

Thank you for your attention

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

"The hard problems are easy and the easy problems are hard" → Use it to your advantage!

Heidelberg University Hospital

www.ukhd.de/cmr

lukas.weberling@med.uni-Heidelberg.de / www.linkedin.com/in/weberlingld