Translation of genomics into routine cardiological practice. ESC Munich 24032023

ATTR Cardiac Amyloidosis

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CENTRE DE RÉFÉRENCE AMYLOSES CARDIAQUES

RÉSEAU AMYLOSE MONDOR–FILIÈRE CARDIOGEN

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maladies rares

cardiogen

filière nationale de santé maladies cardiaques héréditaires ou rares

COI

- Alexion, Alnylam, Akcea, Ionis, Pfizer, Neurimmune

Plan

- Physiopathology
- Genomic and diagnostic
- Treatment and genetic
- Genomic and treatment…

Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases

Pablo Garcia-Pavia [1,2,3]*, Claudio Rapezzi[4,5], Yehuda Adler[6], Michael Arad[7], Cristina Basso [3,8,9], Antonio Brucato [10], Ivana Burazor [11], Alida L.P. Caforio [3,12], Thibaud Damy [3,13], Urs Eriksson [14], Marianna Fontana [15], Julian D. Gillmore [15], Esther Gonzalez-Lopez[1,3], Martha Grogan[16], Stephane Heymans[17,18,19], Massimo Imazio [20], Ingrid Kindermann[21], Arnt V. Kristen [22,23], Mathew S. Maurer[24], Giampaolo Merlini [25,26], Antonis Pantazis[27], Sabine Pankuweit[28], Angelos G. Rigopoulos[29], and Ales Linhart [30]

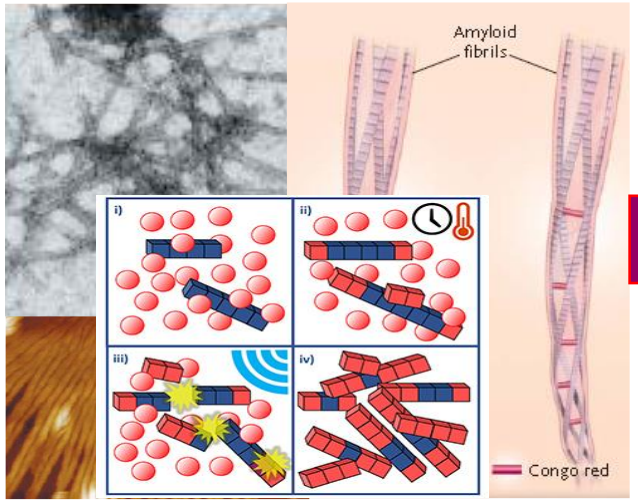
ESC European Society of Cardiology

European Heart Journal (2021) **00**, 1–15
doi:10.1093/eurheartj/ehab072
Garcia-Pavia P et al , 2021, 00, 1-15

SPECIAL ARTICLE
Heart Failure and Cardiomyopathies

Amyloidosis: Definition and physiopathology

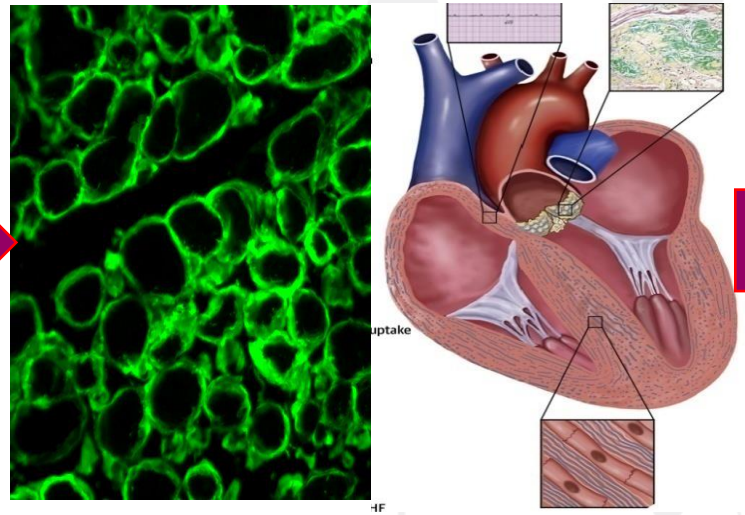
Amyloid Fibrills



Amyloid fibrills : >36 Proteins
Non Immunogenic++++
Associated with Aging-Process

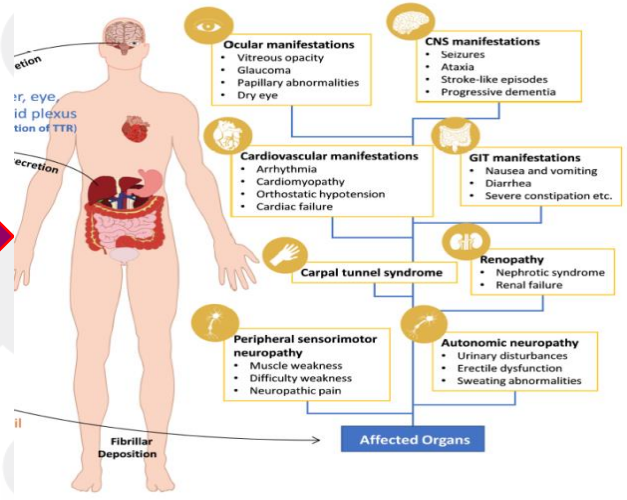
Dynamic progress+++

Organs infiltration



Extracellular infiltration
↗ Cellular death
↗ Stiffness : CMR
↗ Thickness : LVH
↘Stroke volume
↘Cardiac Output

Human Disease

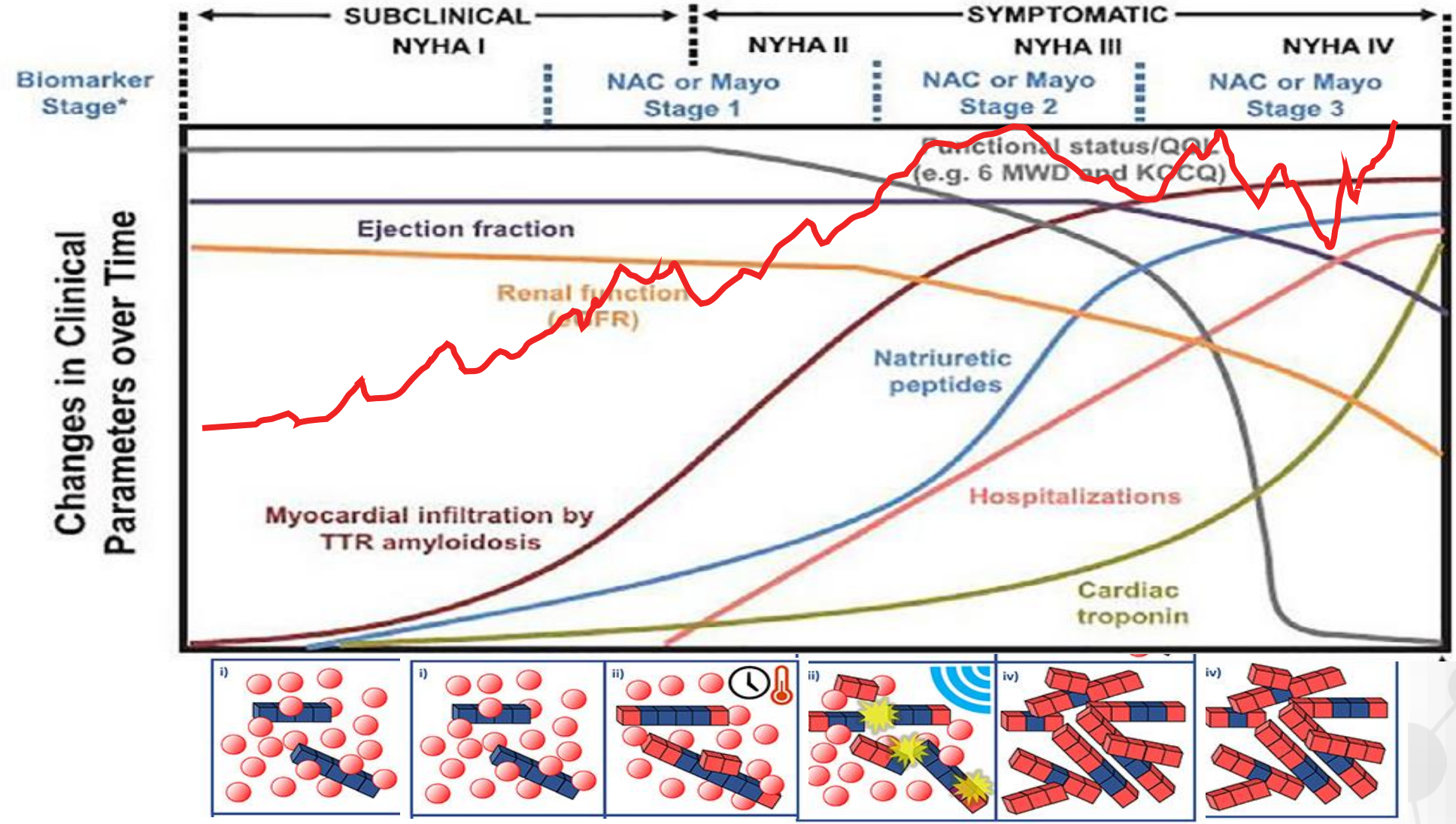


Extracardiac Sd

Heart Failure
Conduction D
Rhythm D
Death

Merlini, NEJM 2003
Ternacle J, JACC 2019

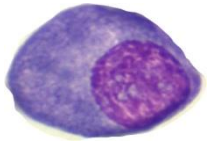
ATTR-CM Natural history of the disease before Tafamidis in



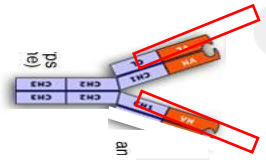
Atteinte Multisystémique

Modified from Griffin JM and Maurer M, Trends in Cvar Medicine 2019

AL -CA: Gammopathy and myeloma

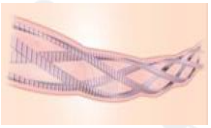


Lymphocyte

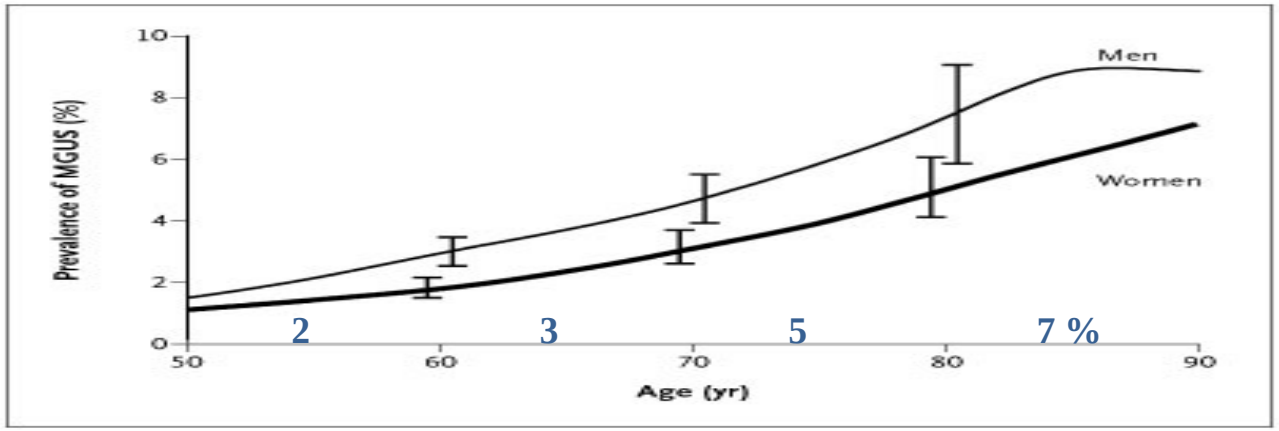


CLL

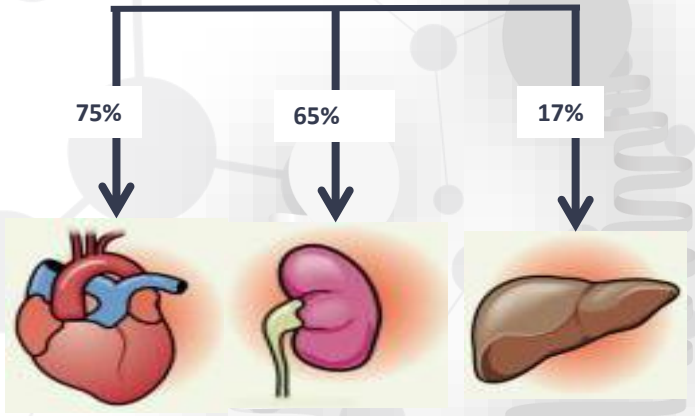
Lambda>kappa



Fibrilles amyloïdes

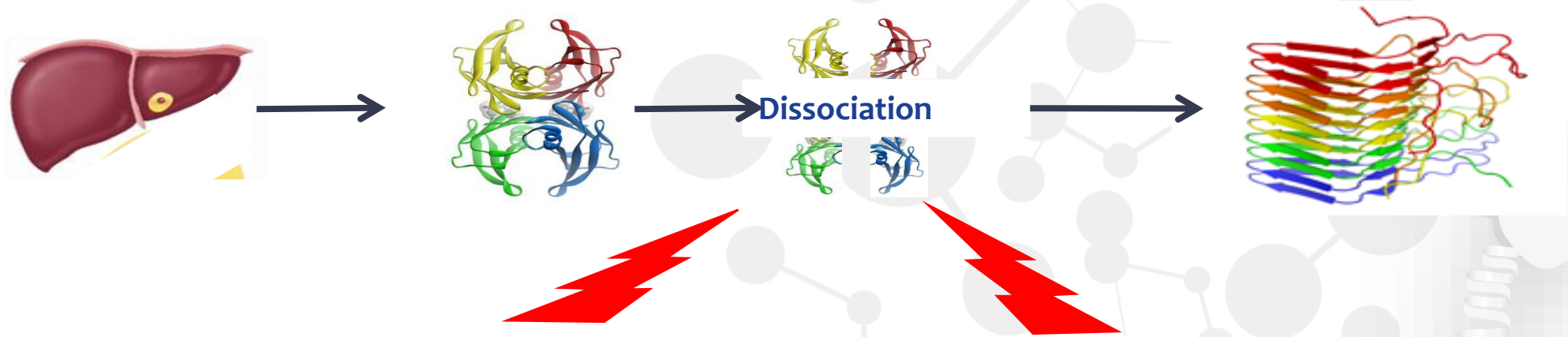


Prevalence of Monoclonal Gammopathy of Undetermined Significance
RA. Kyle et al New Engl J Med 2006



- AL-Amyloidosis: Over production of one type of light chain (Lambda>Kappa) by Lymphocytes
- AL-CA with HF symptoms without treatment = DEATH in 6months
- AL-CA = EMERGENCY! ; PROGNOSTIC = MAYO STAGING

Transthyretin CA
Definition and Physiopathology



Hereditary : **ATTRv (Variant)**

Autosomal dominant

120 mutations

HEART>>>nerve

Mean age at diagnosis in cardiac mutations

≈75 years old

Senescence or Wild-Type : **ATTRwt**

« Cardiac Alzheimer »

¼ of 80yrs old with TTR amyloid deposits in the heart

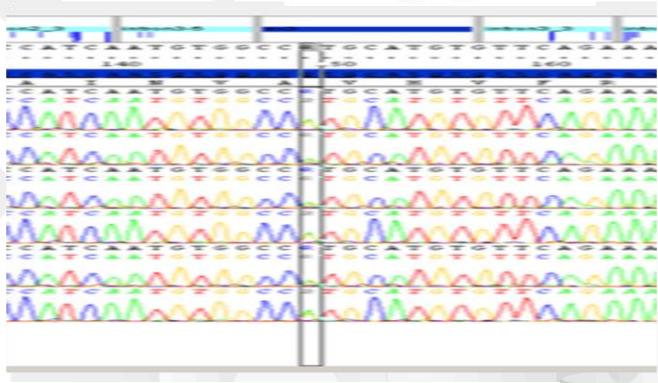
Mean age at diagnosis

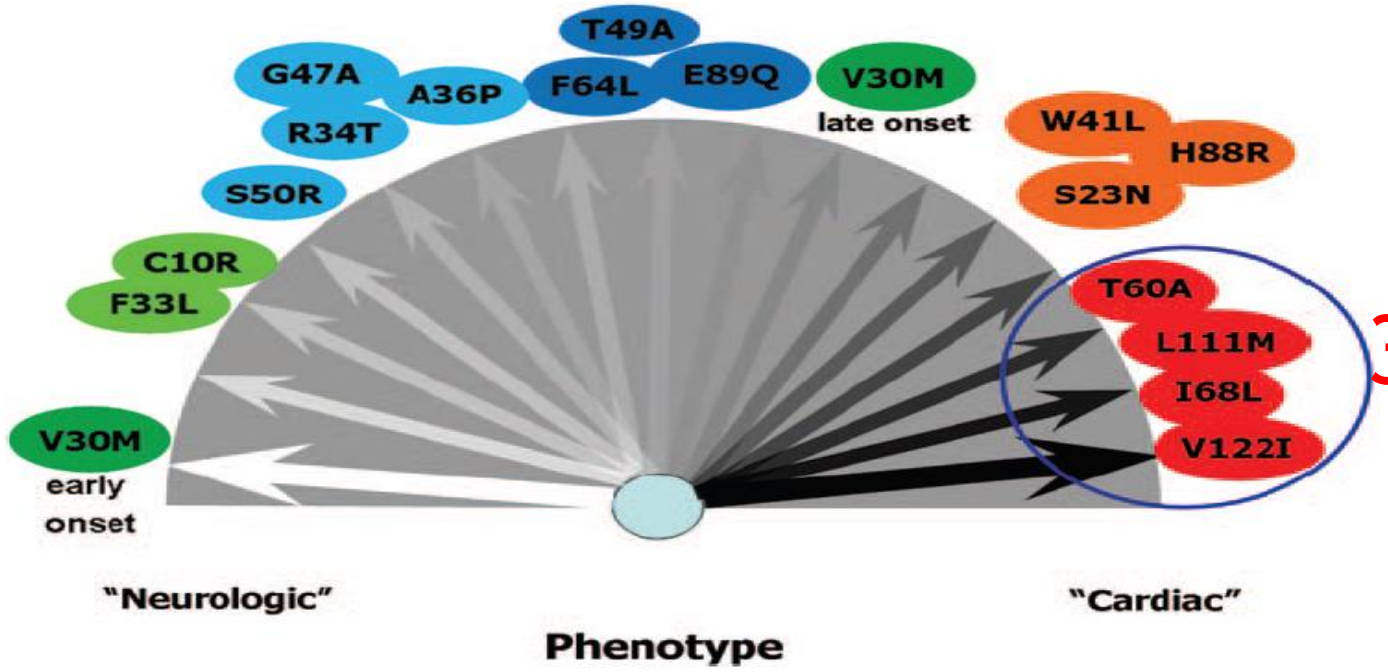
≈83 years old

mTTR-CA: Hereditary TTR-CA

- Transthyretin gene *(Chromosome 18; 4 exons).*
- Autosomal Dominant
- >100 mutations

Genetic sequencing





3.6% of Africans-Americans!

VAL122ILE

Rapezzi C et al, Eur Heart J 2013

Prevalence of ATTR and AL in Cardiac Diseases

	HF-PEF	AS+TAVI	HCM
ATTRwt	13%	6-16%	?
ATTRv	?	?	7.6%>65y old
AL	?	?	?
Rares A	?	?	?

ATTRwt

Gonzales-Lopez et al EHJ 2015;
Damy et al EHJ 2015;
Castano A, Eur Heart J 2017;
Cariou E et al Amyloid 2017

Cardiac amyloidosis

ESC Myocardial WG position paper

Réseau Amylose

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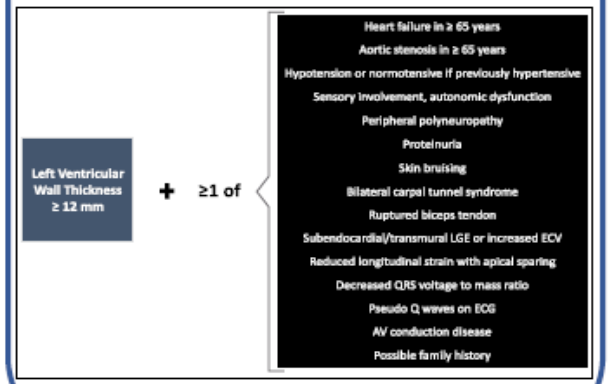
SUSPECT

Screen if

Left ventricle wall thickness ≥ 12 mm
&
≥ 1 Red Flag or Clinical Scenario



DIAGNOSIS

Diagnostic criteria

Invasive (all types)	Non-Invasive (only for ATTR)
Cardiac Biopsy positive for amyloid or Extracardiac Biopsy positive for amyloid + Echocardiographic/CMR criteria	Grade 2 or 3 cardiac uptake at diphosponate Scintigraphy + Negative serum free light chains & negative serum and urine immunofixation (SPIE & UPIE) + Echocardiographic/CMR criteria

Diagnostic algorithm

^{99m}Tc-DPD/PYP/HMDP Scintigraphy with SPECT & Haematologic tests (serum free-light chain quantification & serum and urine immunofixation)

Diagnosis made or proceed to **CMR and/or biopsy** according to results

TREATMENT

Cardiac complications and comorbidities

- Heart Failure
- Thromboembolism
- Atrial fibrillation
- Conduction disorders
- Ventricular arrhythmias
- Aortic stenosis

Disease modifying treatment

- **ATTR**: genetic silencers, stabilizers and removers.
- **AL**: chemotherapy and ASCT.
- **AA**: anti-inflammatory, anti-infective and immunosuppressive drugs.

Garcia-Pavia P et al , 2021, 00, 1-15

Plan

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- Treatment and genetic
- Genomic and treatment…

Biomarqueurs, ECG et Imageries Cardiaques

Réseau Amylose

Centre de référence Amyloses cardiaques
Réseau Amylose Monodor-Filière Cardiogen

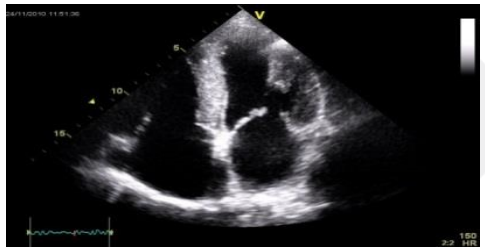
ECG

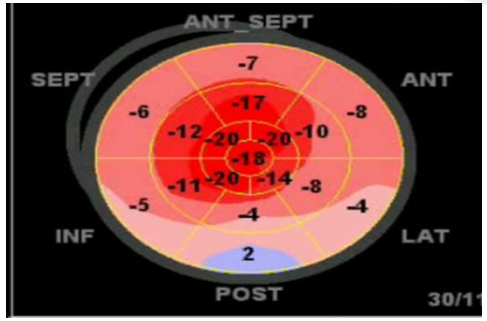
- Microvoltage
- Onde Q

Biomarqueurs

- NTproBNP
- Troponine

ECHO

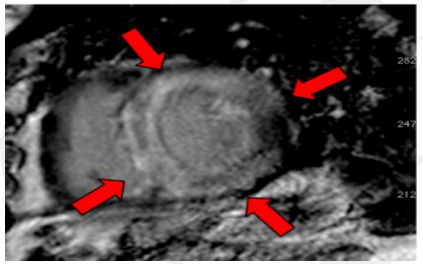




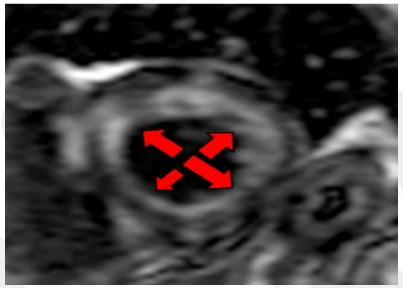
- Hypertrophie biventriculaire
- Profil restricitf
- Anomalie du Strain global
- Aspect « apical sparing »

IRM

Diffuse enhancement



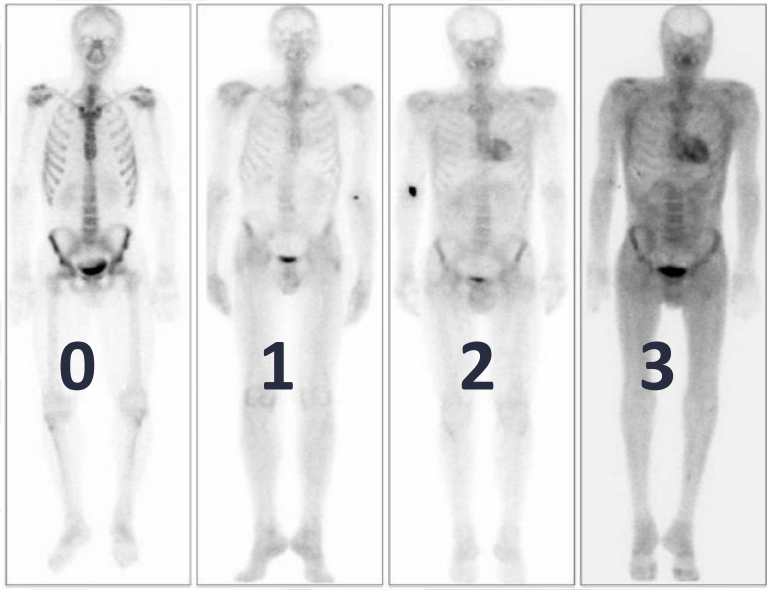
Subendocardial enhancement



- Réhaussement

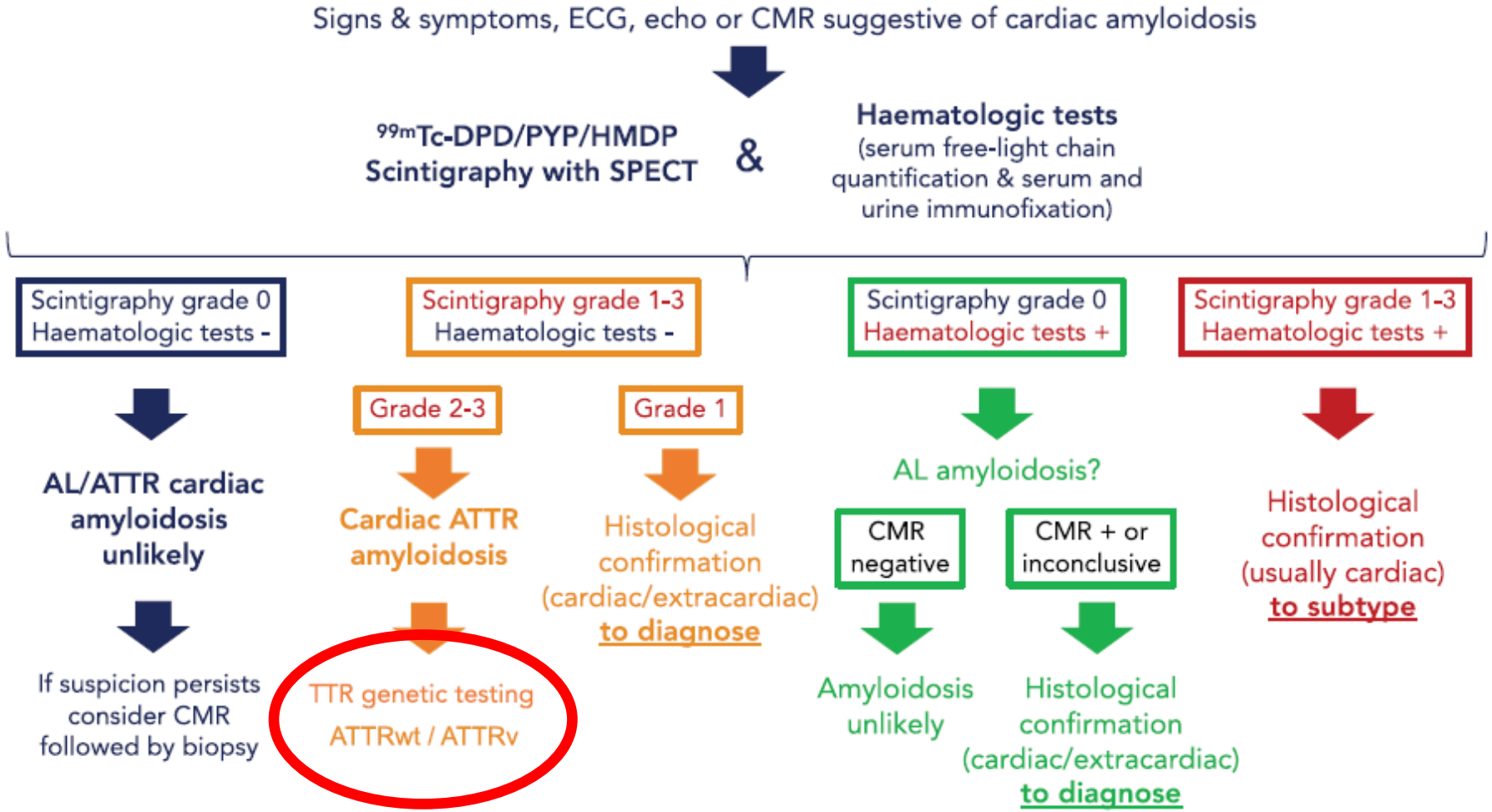
Tardif diffus ou circonferenciel

Scintigraphie



- Fixation cardiaque avec Score Visuel de Perrugini ≥ 2 = Amylose TTR
- Absence de Fixation : Ne permet pas d'éliminer une amylose AL

Diagnosis algorithm



Other rare type of amyloidosis

↓

BIOPSY

↓

MASS SPEC

↓

NGS Amyloidosis

The only way to diagnose ATTRv or ATTRwt is to perform the genetic testing; False idea : « He is old, it is a ATTRwt… »
20% of ATTR older than 70years old have ATTRv

Garcia-Pavia P et al , 2021, 00, 1-15

Porcari A et al, Eur J HF Janv 2023

Colombat M et al Haematologica. 2022 Dec 1;107(12):2983-2987.

Several ways to the genetic diagnosis of ATTR in real life

- ATTR gene full sequencing (sanger)
  - Not available in all cardiac centers ≈ 6 centers in France:
  - Results in 1 to 3 months
- Next Generation Sequencing (NGS) Cardiomyopathy :
  - Results in 1 year?
  - Several centers include it…something misleading results if GLy6Ser, Val122Ile, Thr119Met
  - Not all NGS included ATTR gene analysis
- NGS Amyloidosis :
  - 1 center (CHU Mondor)
  - Results several months
- Whole-genome sequencing (WGS) : rarely used in cardiology and in amyloidosis

Pitfalls of ATTRv Genetic Diagnosis

- Providers and patients often fail to recognize the hereditary nature of clinical traits : “he is old, so it is a wild-type ATTR”.
- Genetic results are returned several weeks to months following the initial disease presentation and typically long after major clinical decisions have been made…and the results is lost…
- Limited interpretation and interpretability of cardiologic and genetic data :
  - ATTR Ser26Gly : polymorphism ; ATTR Thre119Met : protective
  - ATTR Val122Ile in Afro caribbean : 3.6%...penetrance
  - NGS identified mutation…but sometimes the “amyloidosis process” has not started…= unrelated to the actual diagnosis.

Genetic counceiling

- Need to be done by experts in the fields
- Most geneticians don’t know the penetrance of the disease, and do not adapt the information to each mutation.
- Genetic testing is the first examen to be done (consent…)
- Some ask for an echocardiography (as in sarcomeric HCM) before the genetic testing.
- The cardiologic checking is performed only in subject with a pathogenetic mutation and 10 years before their sibiling started the disease.

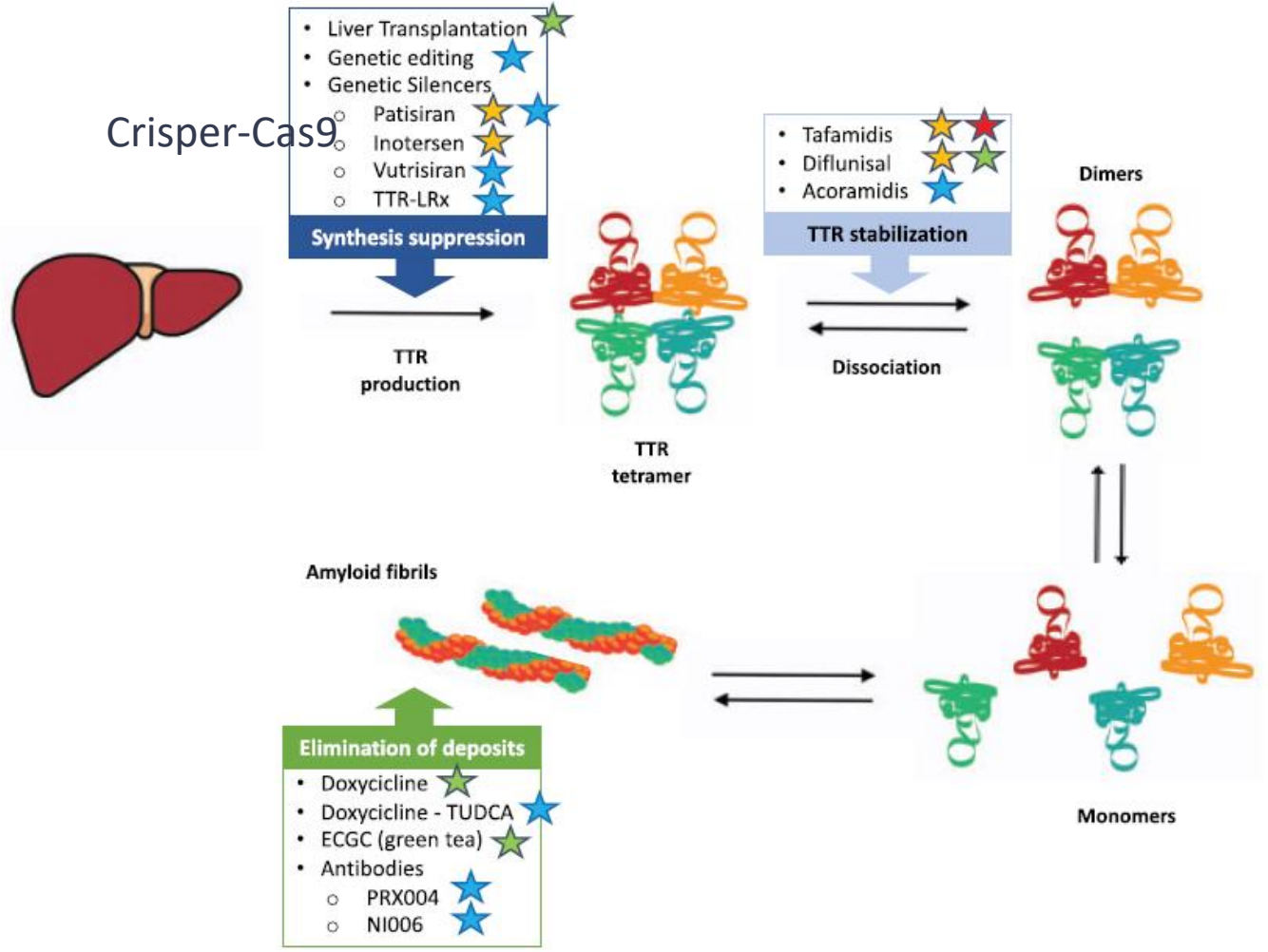
Early diagnosis of ATTR amyloidosis through targeted follow-up of identified carriers of TTR gene mutations.Conceição I, Damy T, Romero M, Galán L, Attarian S, Luigetti M, Sadeh M, Sarafov S, Tournev I, Ueda M.Amyloid. 2019 Mar;26(1):3-9. doi: 10.1080/13506129.2018.1556156. Epub 2019 Feb 22.PMID: 30793974

Plan

- Physiopathology
- Genomic and diagnostic
- Treatment and genetic
- Genomic and treatment…

Available and future disease-modifying therapies in transthyretin amyloidosis (ATTR).

Crisper-Cas9

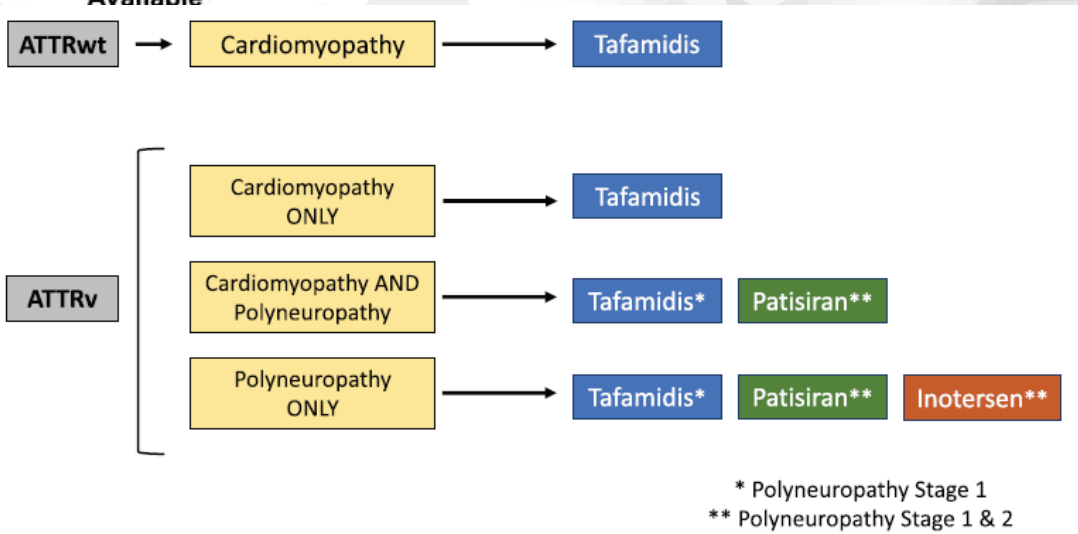


Effective in ATTRv Neuro clinical trials

Effective in ATTR Cardiac clinical trials

Ongoing ATTR clinical trials

Available



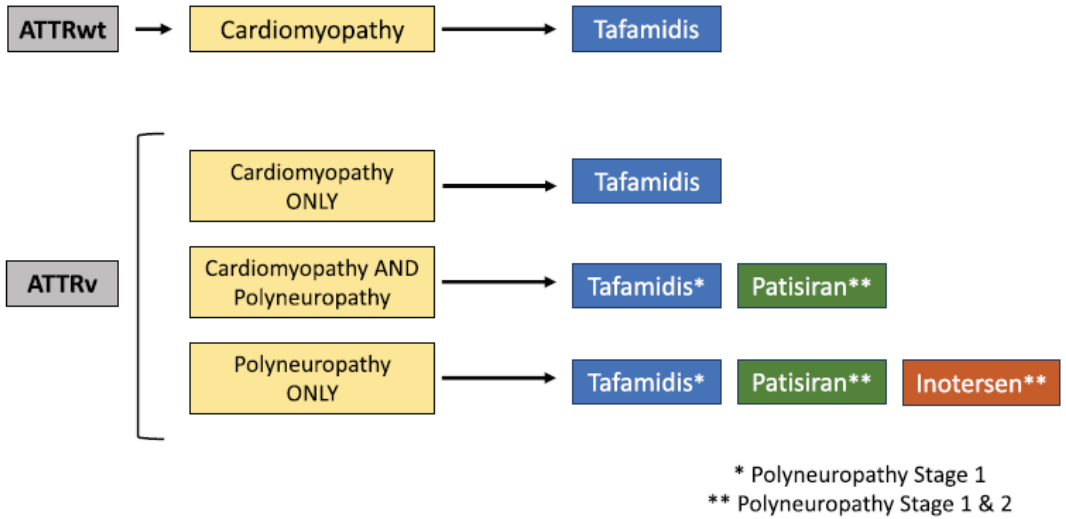
* Polyneuropathy Stage 1
** Polyneuropathy Stage 1 & 2

RNA Targeting and Gene Editing Strategies for Transthyretin Amyloidosis. Ioannou A, Fontana M, **Gillmore JD.** BioDrugs. 2023 Mar;37(2):127-142

European Heart Journal (2021) **00**, 1–15

siRNA : Indication for ATTRv with neurologic symptoms

- siRNA are indicated in patients with ATTRv and neuropathy
- Patients with ATTR needs to have the genetic testing with the diagnostic of ATTRv to get the treatment for the neuropathy.



Drugs	Patisiran	Vutrisiran	IONIS
Inclusion	ATTRv neuro	ATTRv neuro	ATTRv neuro
Trial	Phase 3 APPOLO	Phase 3 HELIOS	Phase 3 IONIS
Methodology	Phase 3 / Double blind	Phase 3 / Double blind	Phase 3 / Double blind
Administration	Intravenous	Subcutaneous	Subcutaneous

European Heart Journal (2021) **00**, 1–15

New treatments siRNA, Crisper Cas9

- Therefore, new « genetic » treatments are tested to treat both ATTRv and ATTRwt with cardiac amyloidosis.

Drugs	Patisiran	Vutrisiran	ION-682884	Cripser Cas 9
Inclusion	ATTR Cardiomyopathy	ATTR Cardiomyopathy	ATTR Cardiomyopathy	
Trial	Phase 3 APPOLO B	Phase 3 HELIOS B	Phase 3 CARDIO TTRansform	
Methodology	Phase 3 / Double blind	Phase 3 / Double blind	Phase 3 / Double blind	
Administration	Intravenous	Subcutaneous	Subcutaneous	
Where we are?	Inclusion started	Inclusion started	Inclusion pending	

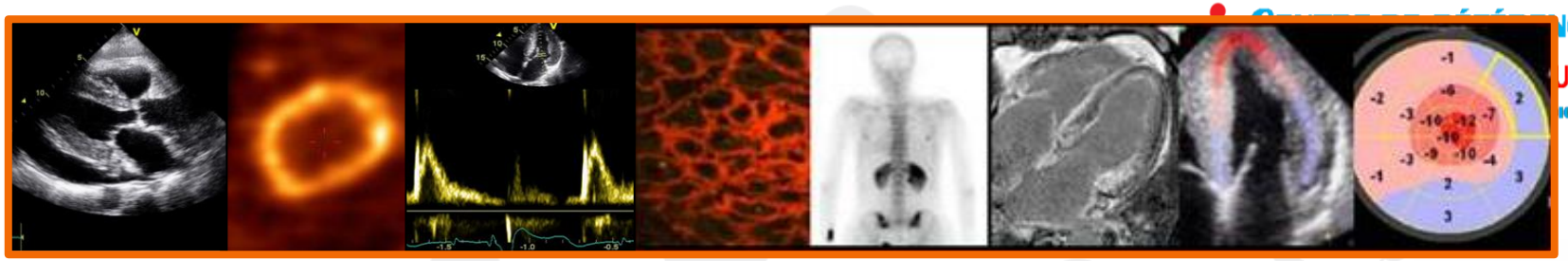
*Maurer MS et al, ISA Heidelberg meeting Abstract : **OPLB001 08_09_2022***

Conclusion

- ATTR amyloidosis are still under recognized in the field of genetic cardiomyopathy
- There is a limited access to genetic ATTR testing
- Genetic informations must be available in a timely fashion for those making medical decisions…and treatment.
- Interpretation and interpretability of genetic data need to be improved.
- Need to develop supporting resources and incorporate genetic data into guidelines, risk-assessment and clinical decision support
- Emergence of novel gene-silencing and gene-editing therapies have rapidly expanded the armamentarium of treatments available for all type of ATTR amyloidosis.

Réseau Amylose

RÉSEAU AMYLOSE MONDOR
CHU HENRI MONDOR



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Medicine

Cardiology: T Damy, S Guendouz, N Lellouche, L Hittinger, JL Dubois-Randé, N Elbaz, D Bodez, A Galat, S Rouffiac, G Abeshira, S Oghina, P Issaurat, V Ouazana
Neurology: V Planté-Bordeneuve, S Hayet
Psychology: J Pompougnac
Neuro-muscular disease: J Authier, G Bassez
Nephrology: V Audard, P Rémy, K El Karoui
Haematology: C Haioun, K Belhadj, J Dupuis, F Le Bras
Internal medicin: M Michel
Hepatology: C Duvoux
Dermatology L Allanore
Genetic: B Funalot

Surgery

Cardiac surgery: T Folliguet, JP Couetil, E Bergoend,
C Radu, M Hillion
Hepatic surgery : D Azoulay
Orthopedy : A Pidet

Clinical research

Cardiology : M Kharoubi

Administration

Coordination : C Henrion
Secretariat : I Vallat

Platforms

Haematology : O Wagner-Ballon
Electrophysiology : JP Lefaucheur
Pathology : A Moktefi, E Poullot
Sequencing : B Funalot, P Fanen, B Hebrard, C Mekki
Immuno-biology: V Frenkel
Radiology: JF Deux
Scintigraphy : E Itti, M Abelisi

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