Patisiran & Vutrisiran, in Development for the Treatment of Transthyretin-Mediated Amyloidosis

RNAi ROUNDTABLE 2020

September 3, 2020

Alnylam® PHARMACEUTICALS

Agenda

Welcome
- Christine Lindenboom – Senior Vice President, Investor Relations & Corporate Communications

Introduction and Overview of ATTR Amyloidosis
- Eric Green – Senior Vice President, General Manager, TTR Program

Cardiac Amyloidosis: A New Paradigm
- Nitasha Sarswat, M.D., Director, Infiltrative Cardiomyopathy Program, University of Chicago Hospital

RNAi Therapeutics in Development for ATTR Amyloidosis with Cardiomyopathy
- John Vest, M.D. – Vice President, Clinical Research

Alnylam's TTR Franchise Opportunity
- Rena Denoncourt – Senior Director, Program Leader, Vutrisiran Program

Q&A Session

Reminders

Event will run for approximately 60 - 75 minutes

Q&A session at end of presentation

- Questions may be submitted at any time via the ‘Ask a Question’ field on the webcast interface

Replay, slides and transcript available at www.alnylam.com/capella

Alnylam Forward Looking Statements

This presentation contains forward-looking statements, within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward-looking statements. These important factors include: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic, such as the scope and duration of the outbreak, government actions and restrictive measures implemented in response, material delays in diagnoses of rare diseases, initiation or continuation of treatment for diseases addressed by our products, or in patient enrollment in clinical trials, potential supply chain disruptions, and other potential impacts to our business, the effectiveness or timeliness of steps taken by us to mitigate the impact of the pandemic, and our ability to execute business continuity plans to address disruptions caused by the COVID-19 or any future pandemic; our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates; pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies; delays, interruptions or failures in the manufacture and supply of our product candidates, including lumasiran, and our marketed products; intellectual property matters including potential patent litigation relating to our platform, products or product candidates; our and our partner's ability to obtain regulatory approval for our product candidates, including lumasiran and inclisiran, and our ability to maintain regulatory approval and obtain pricing and reimbursement for products, including ONPATTRO® (patisiran) and GIVLAARI® (givosiran); our progress in continuing to establish a commercial and ex-United States infrastructure; our ability to successfully launch, market and sell our approved products globally, including ONPATTRO and GIVLAARI, and achieve net product revenues for ONPATTRO within our further revised expected range during 2020; our ability to successfully expand the indication for ONPATTRO in the future; competition from others using similar technology and developing products for similar uses; our ability to manage our growth and operating expenses within the reduced ranges of guidance provided by us through implementation of further discipline in operations to moderate spend and our ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; our ability to establish and maintain business alliances; our dependence on third parties, including Novartis, for the development, manufacture and commercialization of inclisiran, Regeneron, for development, manufacture and commercialization of certain products, including eye and CNS products, Ironwood, for assistance with the education about and promotion of GIVLAARI, and Vir for the development of ALN-COV and other potential RNAi therapeutics targeting SARS-CoV-2 and host factors for SARS-CoV-2; the outcome of litigation; and the risk of government investigations; as well as those risks and other factors more fully discussed in our most recent annual, quarterly and current reports filed with the SEC. If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.

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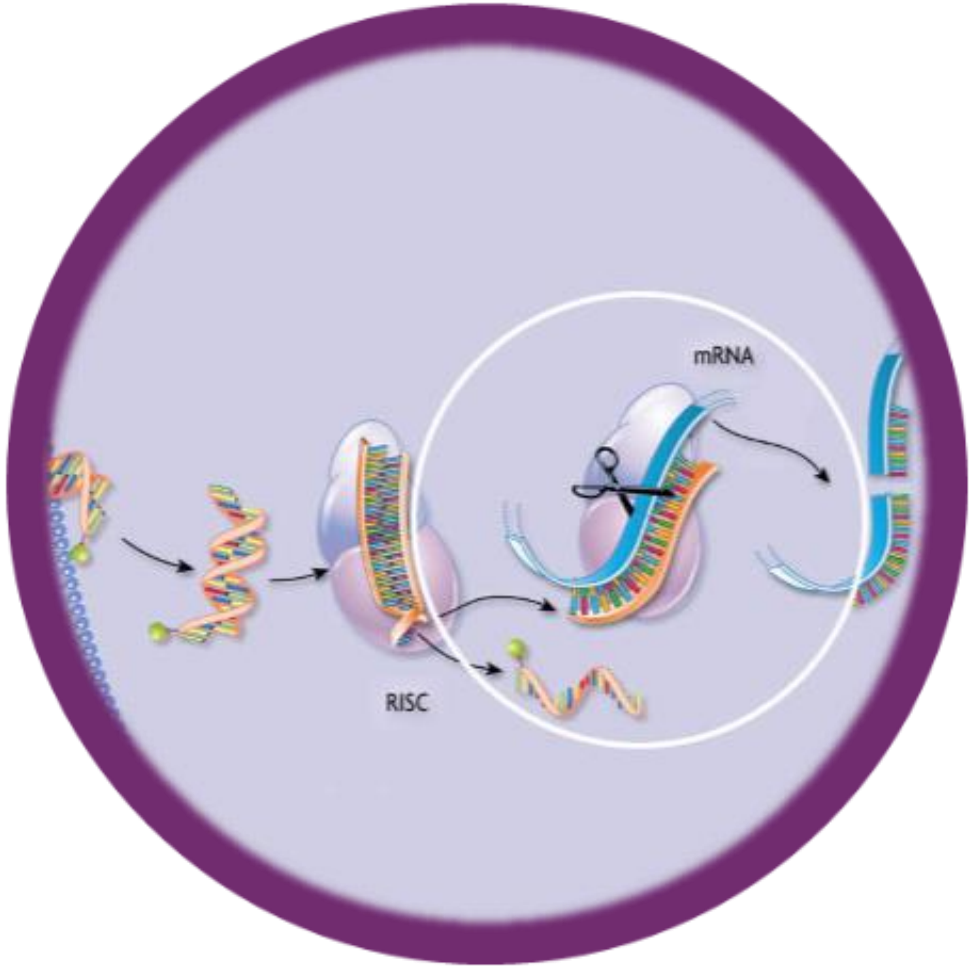
RNAi Therapeutics: New Class of Innovative Medicines

Clinically Proven Approach with Transformational Potential

- **Nobel Prize-winning science**
- **Silence any gene in genome**
- **Potent and durable mechanism of action**
- **Product engine for sustainable innovation**
- **Multiple products impacting patients globally**



Alnylam Commercial Products and Late Stage Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Infectious Diseases
- CNS/Ocular Diseases

		BREAKTHROUGH DESIGNATION	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION	COMMERCIAL	COMMERCIAL RIGHTS
onpattro (patisiran) lipid complex injection 10 mg/5 mL	*hATTR Amyloidosis*[1]	●			●	Global
GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL	*Acute Hepatic Porphyria*[2]	●			●	Global
Lumasiran	*Primary Hyperoxaluria Type 1*	●		●		Global
Inclisiran	*Hypercholesterolemia*			●		Milestones & up to 20% Royalties[3] **(Novartis)**
Patisiran	*ATTR Amyloidosis Label Expansion*		●			Global
Fitusiran	*Hemophilia and Rare Bleeding Disorders*		●			15-30% Royalties **(Sanofi)**
Vutrisiran	*ATTR Amyloidosis*		●			Global

[1] Approved in the U.S. and Canada for the polyneuropathy of hATTR amyloidosis in adults, in the EU, Switzerland and Brazil for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy

[2] Approved in the U.S. for the treatment of adults with acute hepatic porphyria (AHP), and in the EU for the treatment of AHP in adults and adolescents aged 12 years and older

[3] As part of Blackstone strategic financing collaboration, 50% of inclisiran royalty revenue will be payable to Blackstone

As of September 2020

Alnylam Early Stage Clinical Development and 2020 IND Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Infectious Diseases
- CNS/Ocular Diseases

		HUMAN POC[1]	BREAKTHROUGH DESIGNATION	2020 IND CANDIDATES	EARLY STAGE *(Phase 1-Phase 2)*	COMMERCIAL RIGHTS
Cemdisiran	*Complement-Mediated Diseases*	✓			●	50-50 **(Regeneron)**
Cemdisiran/Pozelimab Combo[2]	*Complement-Mediated Diseases*				●	Milestone/Royalty **(Regeneron)**
ALN-AAT02 (DCR-A1AT)[3]	*Alpha-1 Liver Disease*	✓			●	Ex-U.S. option post-Phase 3 **(Dicerna)**
ALN-HBV02 (VIR-2218)	*Hepatitis B Virus Infection*	✓			●	50-50 option post-Phase 2 **(Vir)**
ALN-AGT	*Hypertension*	✓			●	Global
ALN-HSD	*NASH*				●	50-50 **(Regeneron)**
ALN-COV (VIR-2703)	*COVID-19*			○		50-50 option post-Phase 2 **(Vir)**

2-4 *INDs per year planned from organic product engine*

[1] POC, proof of concept – defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies
[2] Cemdisiran is currently in Phase 2 development and pozelimab is currently in Phase 1 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics
[3] Dicerna is leading and funding development of ALN-AAT02 and DCR-A1AT and will select which candidate to advance in development

As of September 2020

Alnylam Commercial Products and Late Stage Clinical Development Pipeline

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As of September 2020

Cece
Living with hATTR Amyloidosis

ATTR Amyloidosis

Rare, Progressively Debilitating, and Often Fatal Disease

Description

Caused by misfolded TTR protein that accumulates as amyloid deposits in multiple tissues including heart, nerves, and GI tract[1]

Hereditary ATTR (hATTR) Amyloidosis

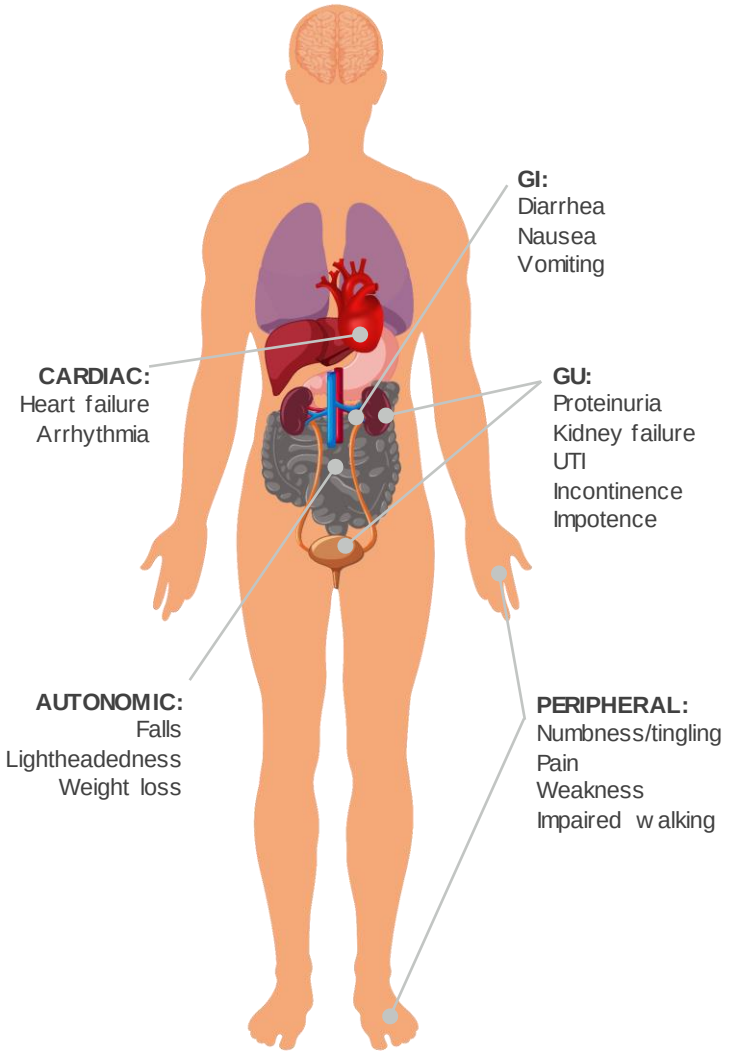
~50,000

patients worldwide*

Wild-Type ATTR (wtATTR) Amyloidosis

~200,000 – 300,000

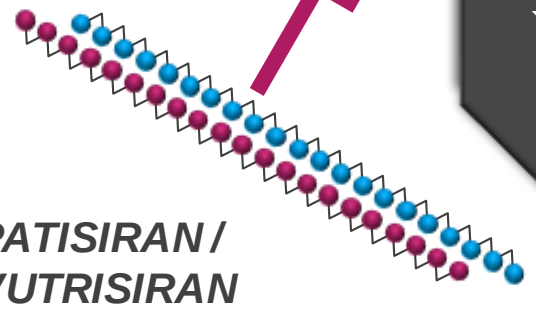
patients worldwide



1 Coelho T, et al. N Engl J Med. 2013;369(9):819-829
* Ando, et al. Orphanet J Rare Dis, 2013; Ruberg, et al. Circulation, 2012

RNAi Therapeutic Hypothesis in ATTR Amyloidosis

Silencing TTR Gene Expression Can Potentially Address Underlying Cause of Disease



PATISIRAN / VUTRISIRAN

siRNA sequences selected to silence both mutant and wild-type TTR

Production of mutant and wild-type TTR in liver*

Reduce
circulating TTR

Prevent or clear
tissue amyloid deposits

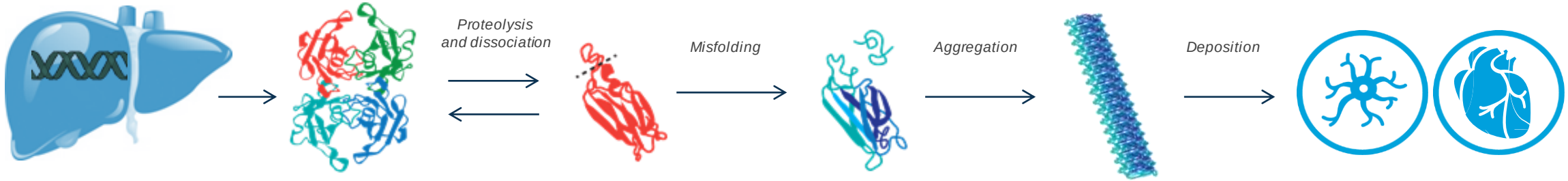
Halt or improve
progressive manifestations of disease

* >95% of TTR in circulation produced in liver

Current or Potential Therapy Options for ATTR Amyloidosis

ONPATTRO and Vutrisiran Silence the Source of the Disease

ATTR Amyloidosis Disease Cascade and Therapies



***TTR* gene expressed in liver**

TTR tetramer

TTR fragments and full-length monomers

Misfolded, aggregation-prone monomer and fragments

Amyloid oligomers and fibril formation

Amyloidosis disease state

Eliminate production of mutant TTR:
- Orthotopic liver transplant

Suppression of TTR synthesis (gene silencing):
- **RNAi (patisiran, vutrisiran)**
- Antisense oligonucleotides

Prevent dissociation of TTR tetramer:
- TTR stabilizers

Remove existing amyloid:
- Monoclonal antibodies

Alnylam's TTR Amyloidosis Franchise

Approved Treatment Option and Investigational Programs

onpattro® (patisiran) lipid complex injection 10 mg/5 mL

ONPATTRO® (patisiran) is an **Approved** RNAi Therapeutic for Treatment of Polyneuropathy of hATTR Amyloidosis*

- Favorable efficacy and safety profile in APOLLO study
- Improvement in neuropathy impairment in majority of patients
- Improvement in quality of life in majority of patients

About ONPATTRO

- RNAi therapeutic targeting transthyretin (TTR)
- IV administration, once every 3 weeks
- Patisiran also in clinical development as potential treatment for ATTR amyloidosis patients with cardiomyopathy‡

Vutrisiran

Vutrisiran is an **Investigational** RNAi Therapeutic for Potential Treatment of ATTR Amyloidosis†

- Potential treatment for hATTR amyloidosis with polyneuropathy (HELIOS-A study)
- Potential treatment for ATTR amyloidosis with cardiomyopathy (HELIOS-B study)

About Vutrisiran

- RNAi therapeutic targeting transthyretin (TTR)
- Subcutaneous administration, once every 3 months
  - Exploring biannual dosing regimen
- Pre-filled syringe (PFS) presentation

* ONPATTRO is approved in the U.S. and Canada for the polyneuropathy of hATTR amyloidosis in adults, in the EU, Switzerland and Brazil for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy; ‡ Patisiran has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population;
† Vutrisiran is an investigational agent and has not been approved by the FDA, EMA, or any other regulatory agency and no conclusions can or should be drawn regarding its safety or effectiveness

The first RNAi therapeutic is

APPROVED IN U.S., EU, CANADA, JAPAN, SWITZERLAND & BRAZIL

onpattro® (patisiran) lipid complex injection 10 mg/5 mL

onpattro® 2 mg/mL concentrate for solution for infusion patisiran

オンパットロ® パチシランナトリウム注射液2mg/mL

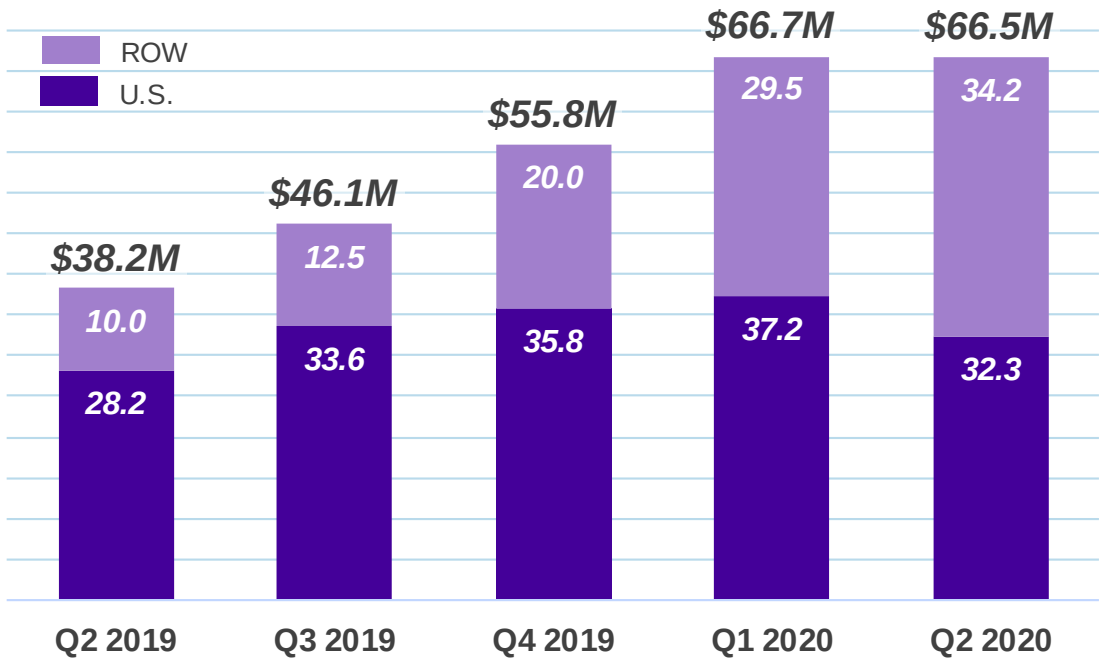
onpattro® (patisirana) solução para infusão intravenosa

ONPATTRO® (patisiran) Launch Update: Q2 2020

Strong Performance with Steady Growth in Patients Worldwide on Commercial ONPATTRO

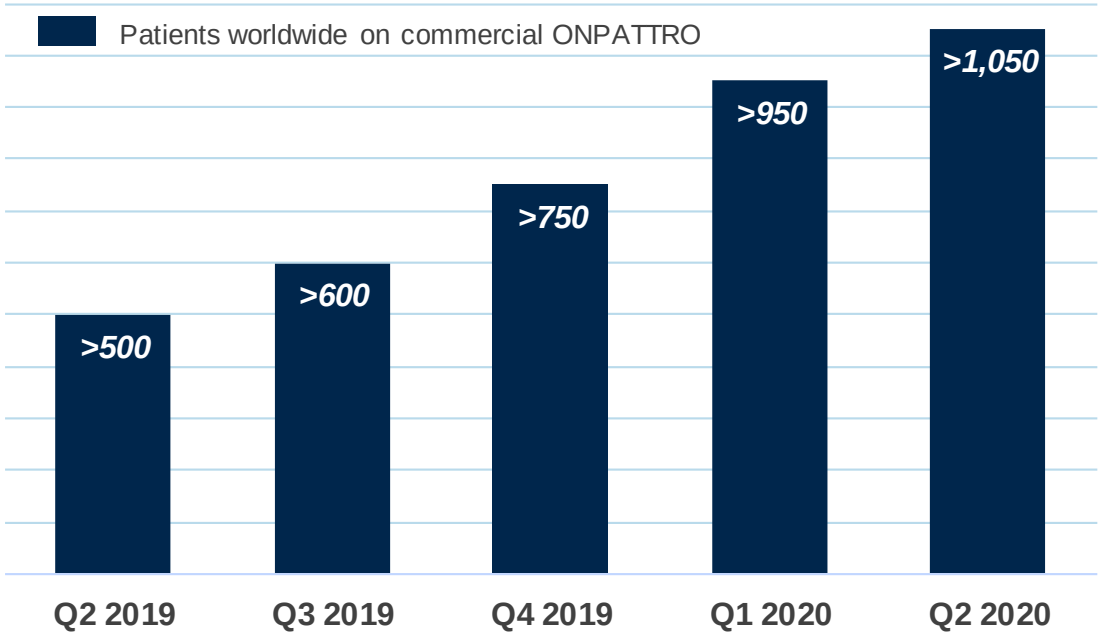
$66.5M

ONPATTRO Global Q2 Net Product Revenues



>1,050

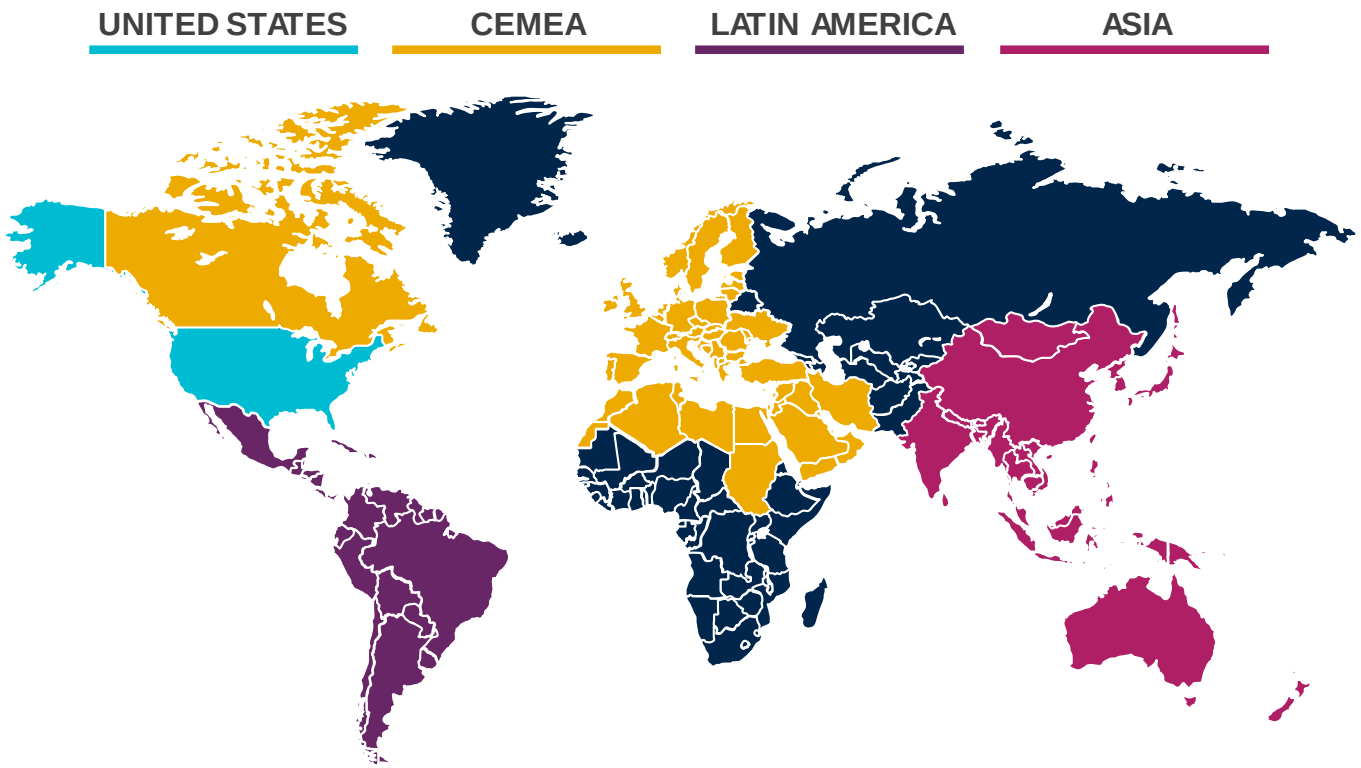
Patients Worldwide on Commercial ONPATTRO at end of Q2 2020



ONPATTRO Global Commercialization

Increasing Access and Value Recognition

- Significant progress with global ONPATTRO availability
  - Recent launches in Spain and Italy
  - Reimbursement achieved in France
  - Access achieved in “big five” Western European markets, plus Portugal, Sweden, The Netherlands, and Belgium.
  - About 20 countries outside U.S. now selling ONPATTRO through direct reimbursement, named patient sales, or reimbursed expanded access
  - Uptake observed from both first-line treatment and switching from other products, including stabilizers
- Strength coming from Japan
  - Now represents second largest country for ONPATTRO revenue



onpattro® (patisiran) lipid complex injection 10 mg/5 mL

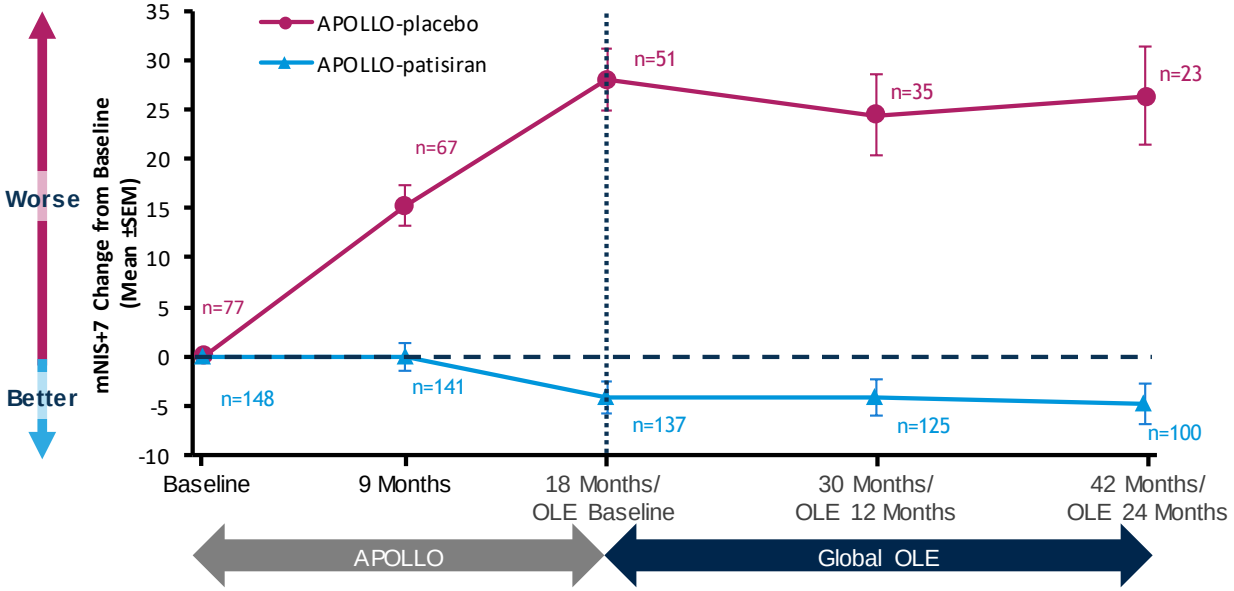
CEMEA: Canada, Europe, Middle East, North Africa

Patisiran Continues to Demonstrate Benefit for Patients

Multiple Presentations at 2020 PNS Virtual Event

- After an additional **24 months of treatment in the Global OLE**, patients treated with patisiran earlier in their disease continued to **demonstrate reversal of polyneuropathy by mNIS+7**

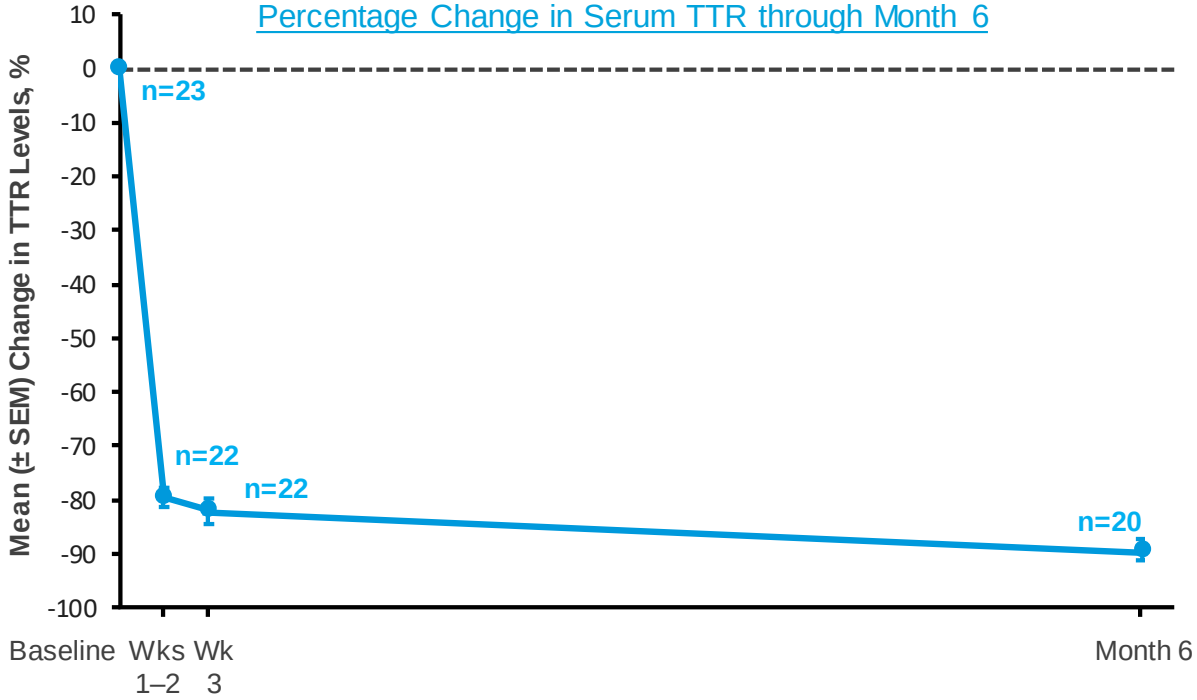
Integrated Change in mNIS+7 from APOLLO and Global OLE



- Similarly, patients treated with patisiran earlier in their disease demonstrated sustained and durable improvement from parent study baseline in quality of life by Norfolk QOL-DN
- No new safety concerns; the safety profile remained consistent with previous studies and patisiran continues to show a positive benefit:risk profile

- Patisiran **reduced serum TTR levels by >85%** through six months of treatment in patients with hATTR amyloidosis **with disease progression post-OLT**

Percentage Change in Serum TTR through Month 6



- After 6 months of patisiran treatment, the mean reduction from baseline in serum TTR levels was 89.2%
- To date, the safety profile remains consistent with the Phase 3 APOLLO study

Capella link for press release and all posters: https://www.alnylam.com/2020/07/10/pns-2020/

Vutrisiran HELIOS·A Phase 3 Study

Randomized, Open-Label Study in Hereditary ATTR Amyloidosis Patients

N ~ 160
Patient Population

- hATTR amyloidosis; any TTR mutation
- Neuropathy Impairment Score (NIS) of 5-130
- Prior tetramer stabilizer use permitted

3:1 RANDOMIZATION

Vutrisiran
SC q3M
25 mg

or

Reference Comparator
(patisiran)

9-Month Efficacy^

- Assessment vs. APOLLO placebo arm

18-Month Efficacy

- Assessment vs. APOLLO placebo arm

Open-Label Extension

ClinicalTrials.gov Identifier: NCT03759379

HELIOS·A

Efficacy Assessments vs. APOLLO placebo arm

Primary Endpoint at 9M

- Change in mNIS+7 from baseline

Secondary Endpoints at 9M

- Change in Norfolk QOL-DN from baseline
- 10-meter walk test

Secondary Endpoints at 18M include

- Change in mNIS+7 from baseline, change in Norfolk QOL-DN from baseline, 10MWT, mBMI, R-ODS

Exploratory Endpoints Include

- NT-proBNP
- Echo parameters
- Technetium (select sites only, change from baseline)

HELIOS-A Phase 3 study
enrollment complete

Topline results expected
early 2021

^ Primary endpoint for the study is at 9 months

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AT THE FOREFRONT

UChicago Medicine

Cardiac Amyloidosis: A New Paradigm

Nitasha Sarswat, MD

Director, Infiltrative Cardiomyopathy Program

Advanced Heart Failure, Mechanical Circulatory Support and Transplantation

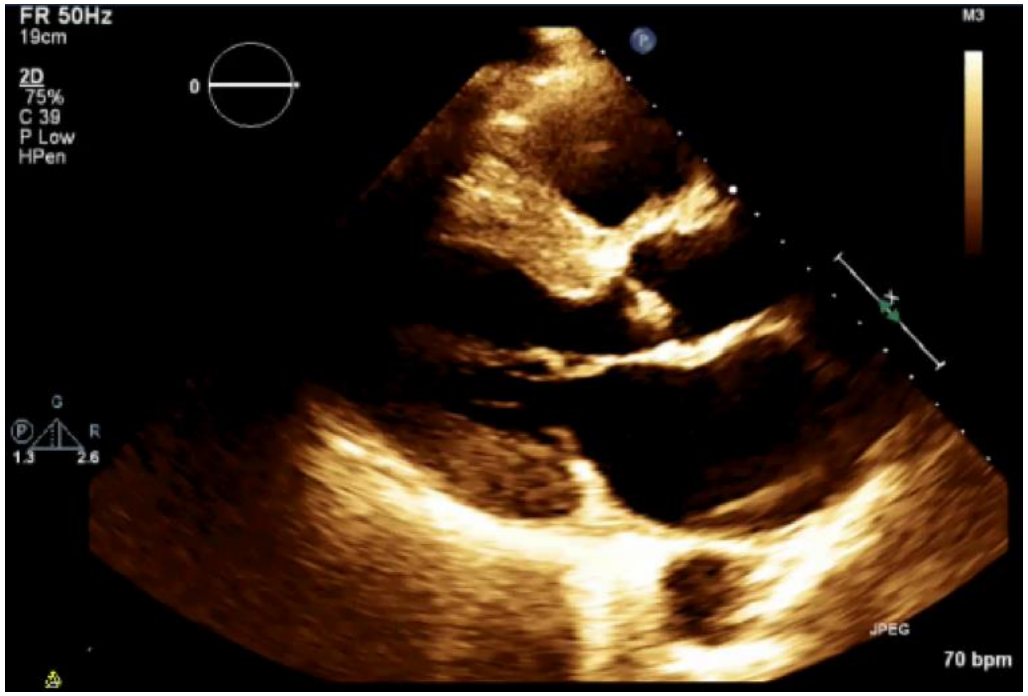
University of Chicago Hospital

Goals of Discussion

- Cardiac amyloidosis is more prevalent than previously thought
- Cardiac amyloidosis is challenging to diagnose, therefore you must have a high index of suspicion
- Cardiac amyloidosis carries a high morbidity and mortality and time to diagnosis and treatment is essential
- The field is exploding at an amazing pace given new diagnostic tools and the emergence of new therapies
- Treatments are available for all types of cardiac amyloidosis – imperative to understand which subtype is involved in order to effectively treat

Patient Case

- 53-year-old African American female
- Past medical history of hypertension and a family history of heart failure (father passed away in shock)
- Presented to clinic with worsening dyspnea with Zumba classes
- Found to in decompensated heart failure, admitted to our hospital for diuresis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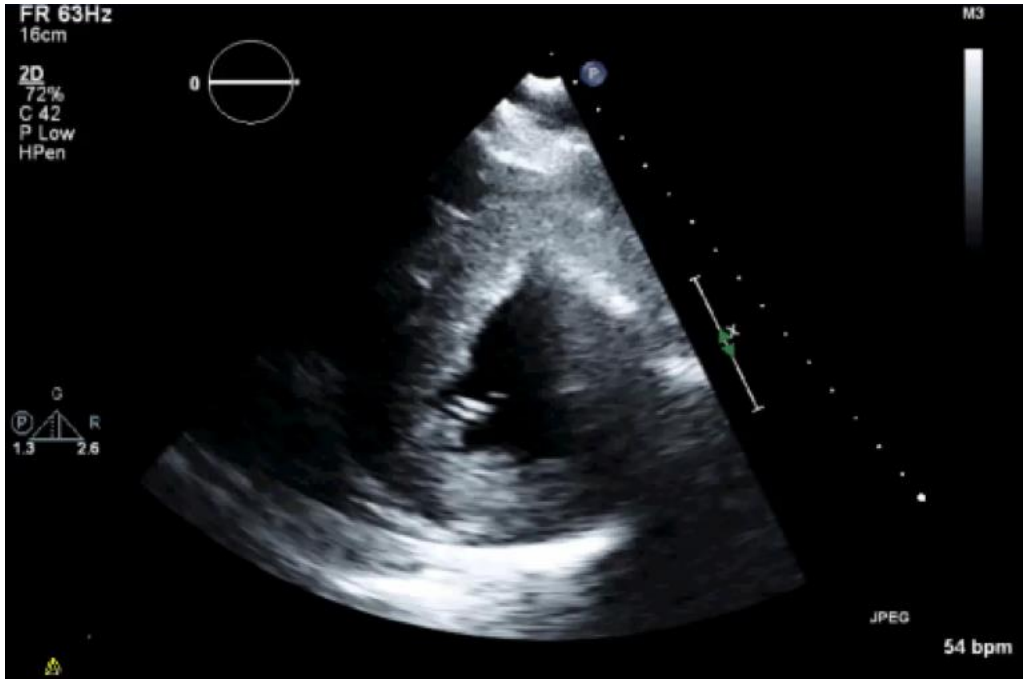
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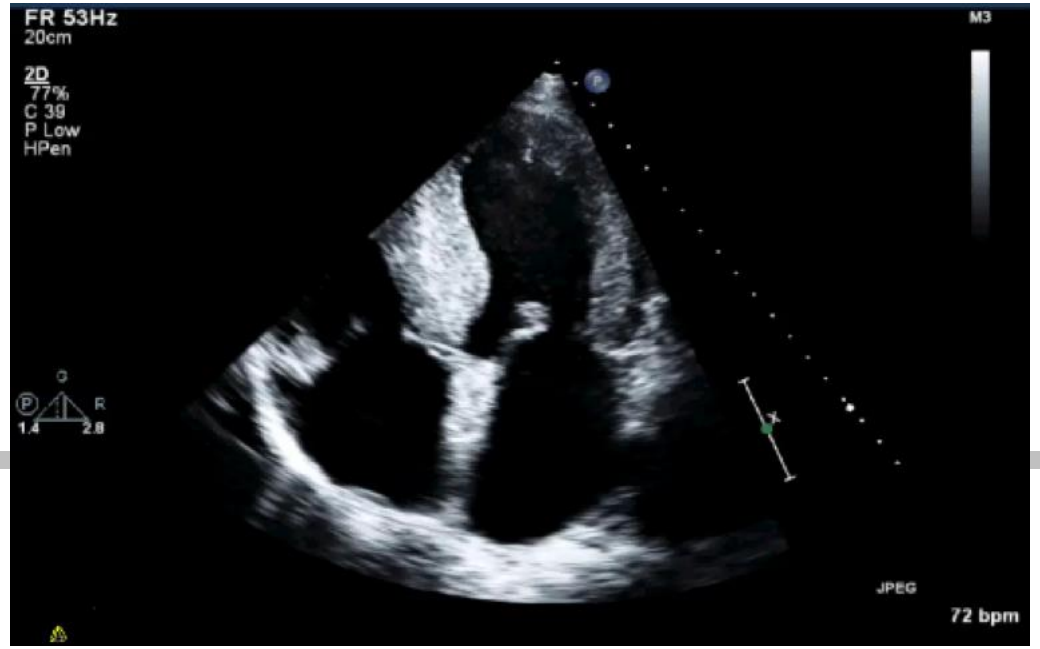
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C 39
P Low
HPen
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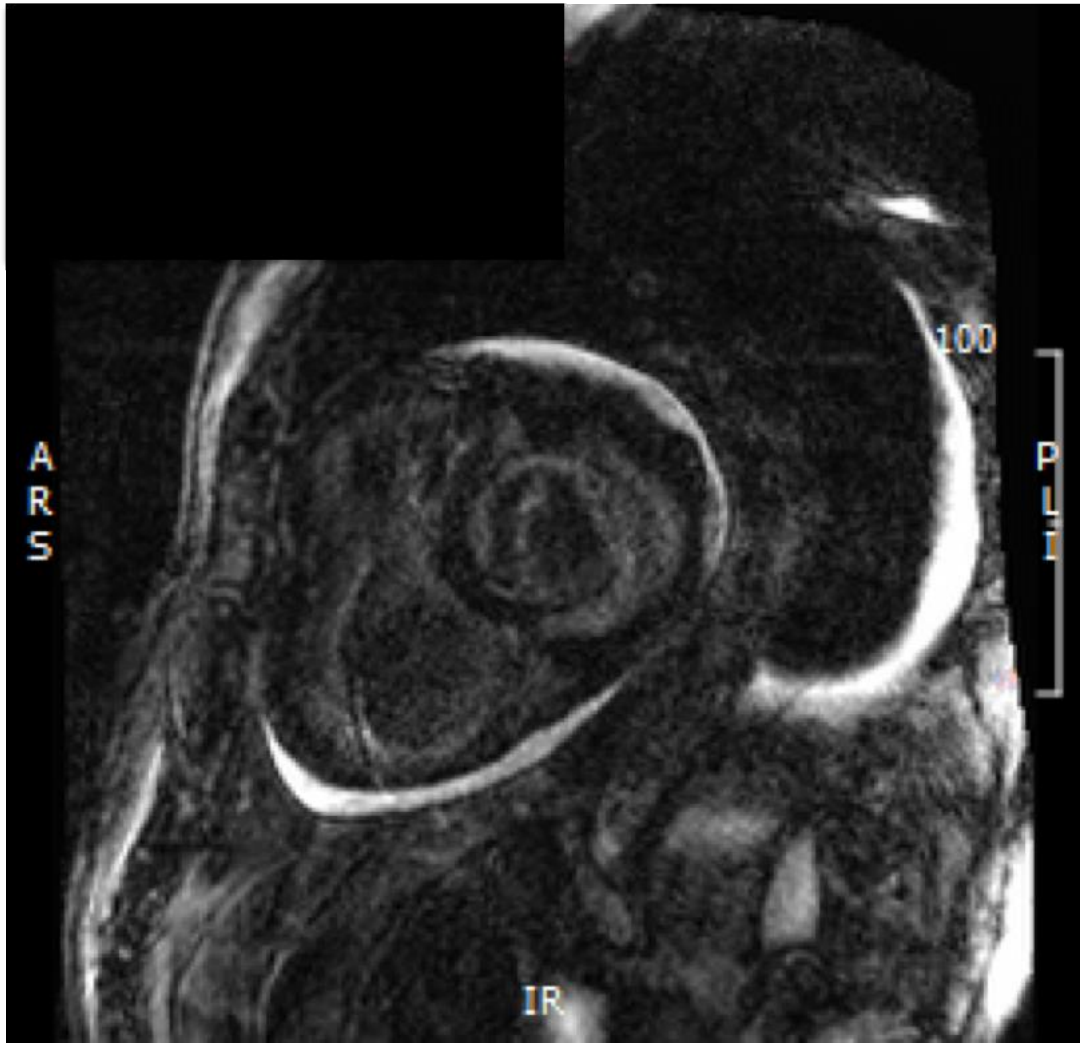
JPEG
72 bpm

Case

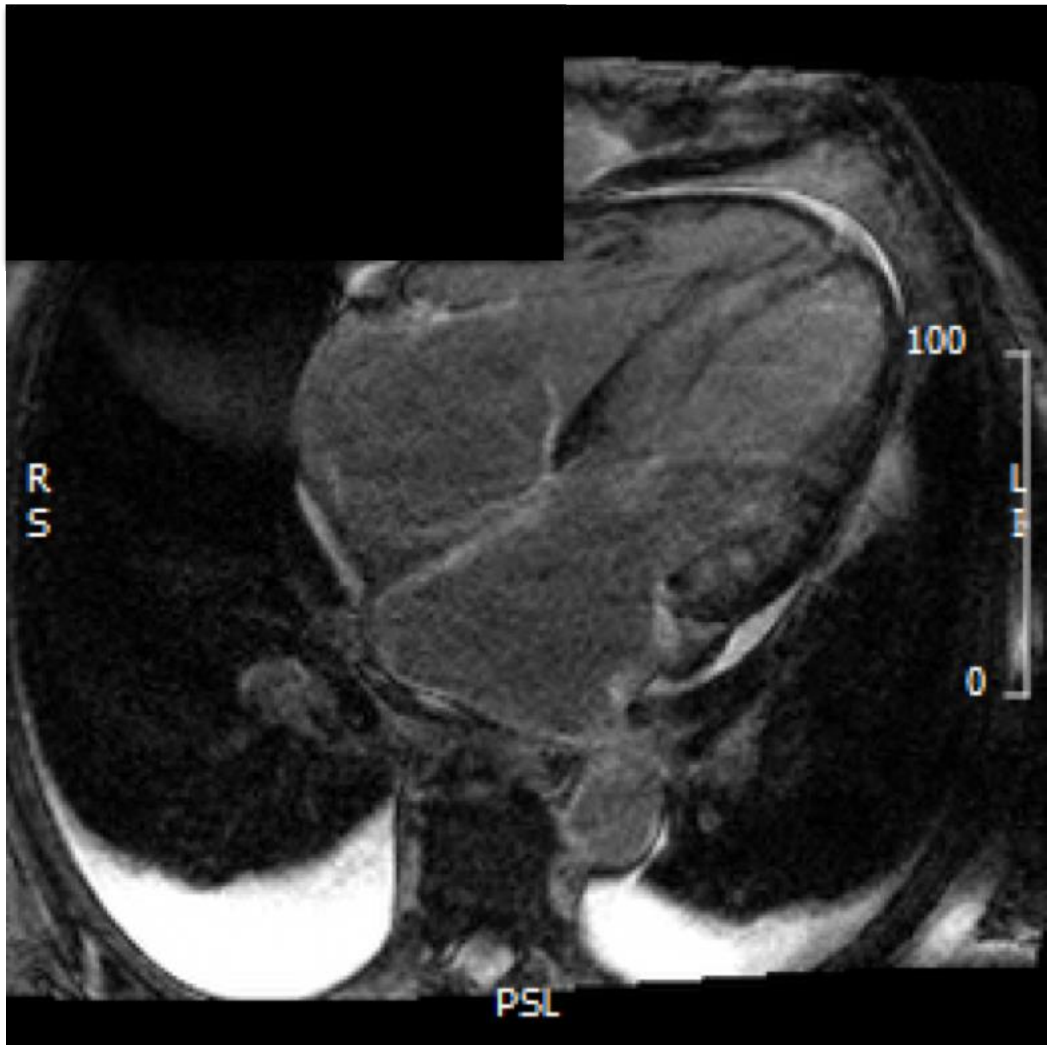
- Suspicion of infiltrative disease
- More discussion of patient's history reveals bilateral carpal tunnel syndrome, chronic diarrhea and 10 lb overall weight loss
- Sent for a cardiac MRI

Cardiac MRI



Diffuse subendocardial enhancement of LV and RV

Cardiac MRI



Diffuse enhancement in septum and subendocardium

Interatrial septum and atrial wall enhancement

Pleural effusions

Pericardial effusion

Case

- Suspicion of cardiac amyloidosis
- Lab work sent: SPEP, UPEP, light chains and all were normal
- PYP scan ordered and showed grade 3 uptake in the heart, no myocardial biopsy was performed

Case

- Felt to have likely TTR amyloidosis
- TTR genetic test sent
- Diuresed but had worsening renal function
- Right heart catheterization with restrictive filling pattern, diuresis guided by swan-ganz catheter
- Volume status stabilized; renal function improved
- Discharged to home

Case

- Followed closely in amyloidosis clinic and was found to have V122I mutation
- Genetic counseling performed; family screened
- Currently on tafamidis and patisiran therapy
- Intracardiac pressures closely followed with CardioMems
- Able to resume her Zumba

What's Amazing About the Case

- The patient was able to turn around quickly and survive and to have a reasonable-quality of life once the disease was recognized and the hemodynamics understood

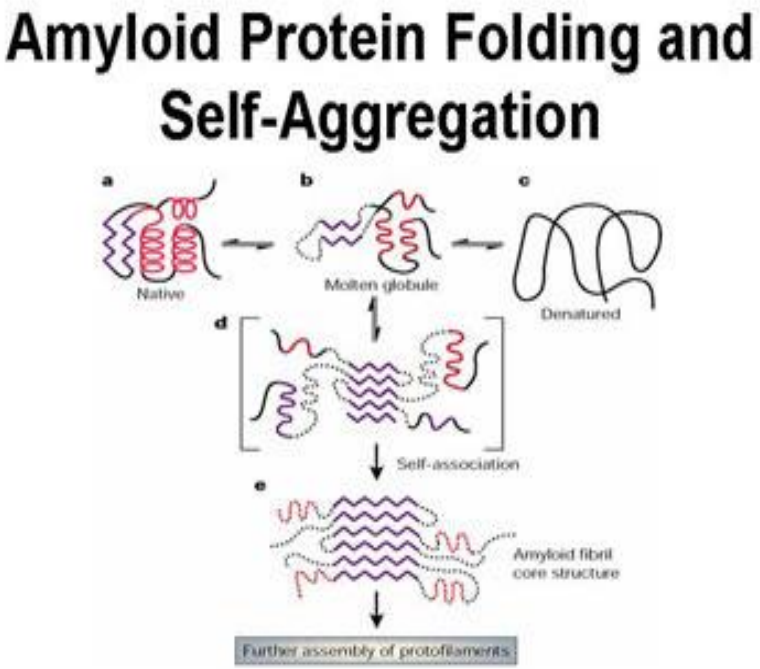
- A novel imaging technique in PYP allowed an essentially non-invasive diagnosis

- New therapies were able to be offered to "attack" the disease from multiple venues

Pathophysiology of TTR Amyloidosis

Caused by extracellular deposits of amyloid protein in an abnormal insoluble beta-pleated sheet fibrillary conformation

(as amyloid fibrils)

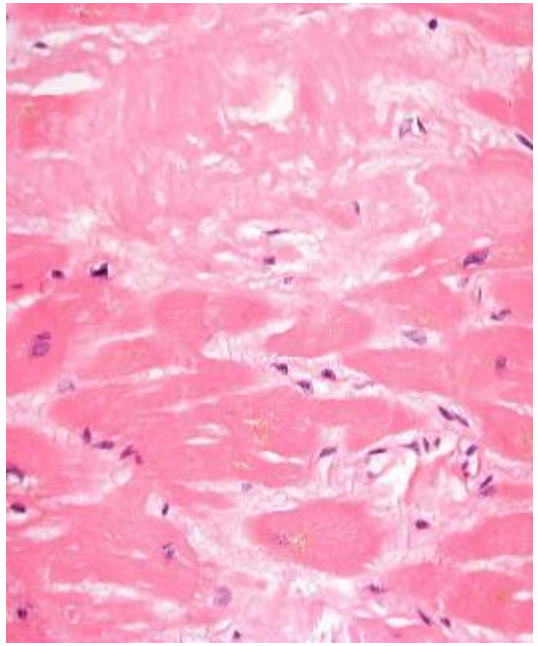


Transthyretin is a tetramer and serves mainly as a transporter protein for thyroxine and the retinol-binding protein.

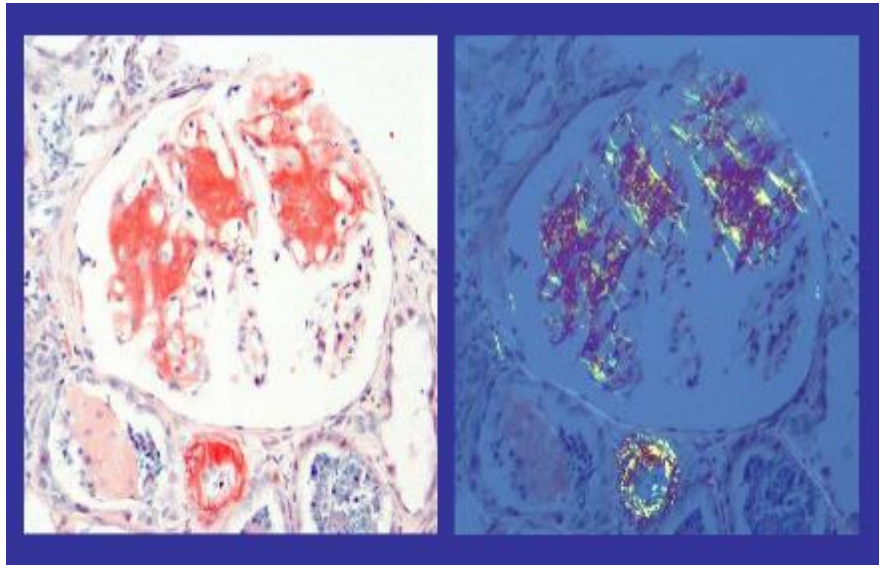
Primary Systemic Amyloidosis
JH Nyirady, https://emedicine.medscape.com/article/1093258-overview#showall

Pathology

High magnification micrograph of cardiac biopsy showing evidence of wild-type ATTR amyloidosis on H&E stain. The micrograph shows amyloid (extracellular fluffy pink material) and abundant lipofuscin (yellow granular material).



Fibrils bind Congo red stain -> classic apple-green birefringence under polarized light microscopy

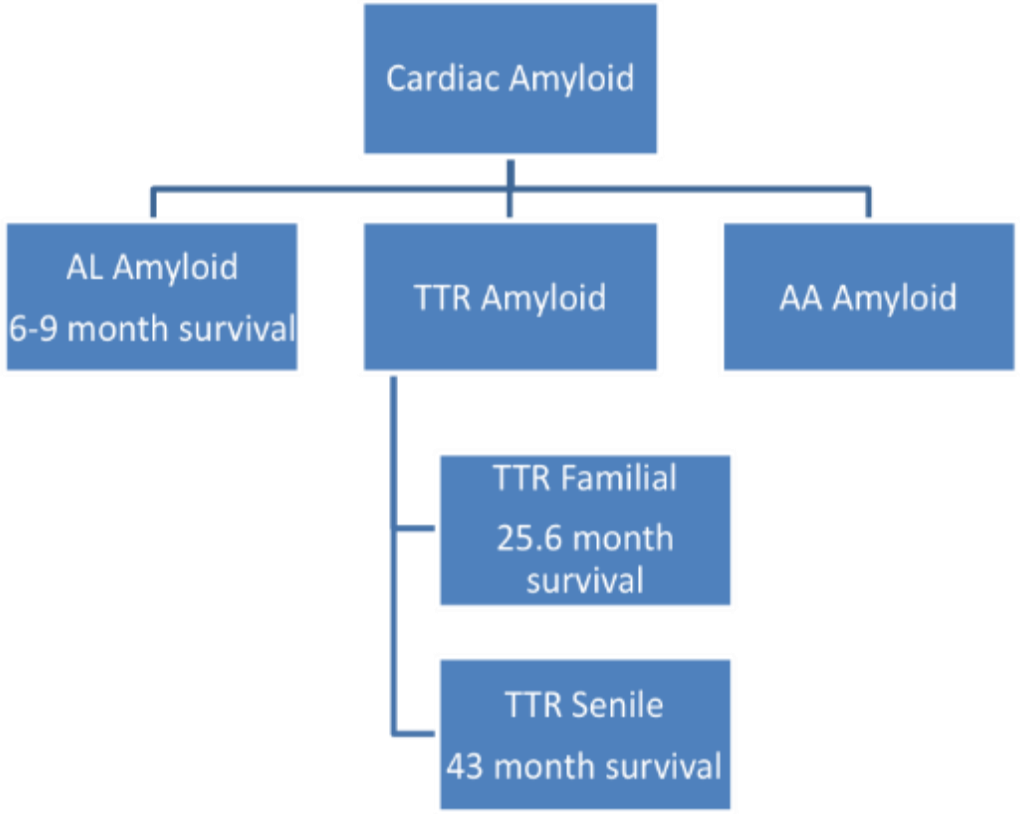


Immunohistochemical staining for precursor proteins identifies the type of amyloidosis

Ultimately, immunogold electron microscopy and mass spectrometry confer the greatest sensitivity and specificity for amyloid typing

Types of Cardiac Amyloidosis and Prognosis

A systemic disease that may present as a type of infiltrative cardiomyopathy



- hATTR is also known as TTR familial
- wtATTR is also knows as senile

What is the mortality with modern treatment?

1. Grogan M, Dispenzieri A. Natural history and therapy of AL cardiac amyloidosis. Heart Fail Rev 2015; 20: 155-62
2. Grogan et al. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: TRACS. Am Heart J 2012 Aug; 164(2):222-228.

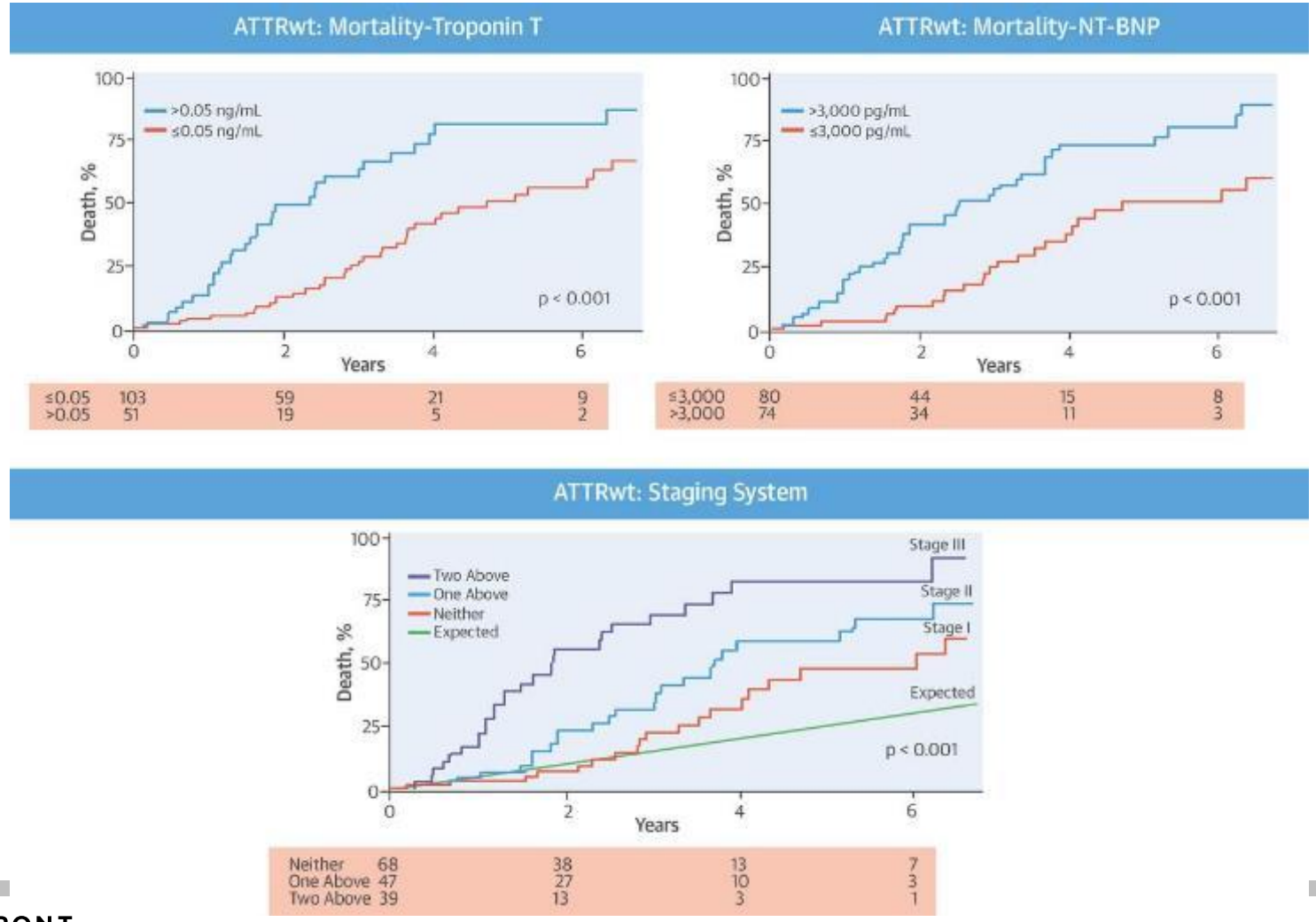
Are TTR Fibrils Myo-Toxic?

- Tetramer breaks down into monomers which misfold and produce oligomers
- Oligomers are deposited in tissues along with the mature amyloid fibrils
- Oligomeric deposition has been shown to produce toxic apoptotic cell death
- Still unclear whether oligomer deposition produces cardiac toxicity independent of the damage caused by the amyloid fibrils

AND/OR

Deposition of fibrils from either wild-type (ATTRwt) or mutated TTR (ATTRm) disrupt tissue architecture causing diastolic dysfunction, heart failure, eventual systolic dysfunction, and death

Staging System: Mayo Clinic



Martha Grogan et al. JACC 2016;68:1014-1020

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JACC

A New Staging System from the UK

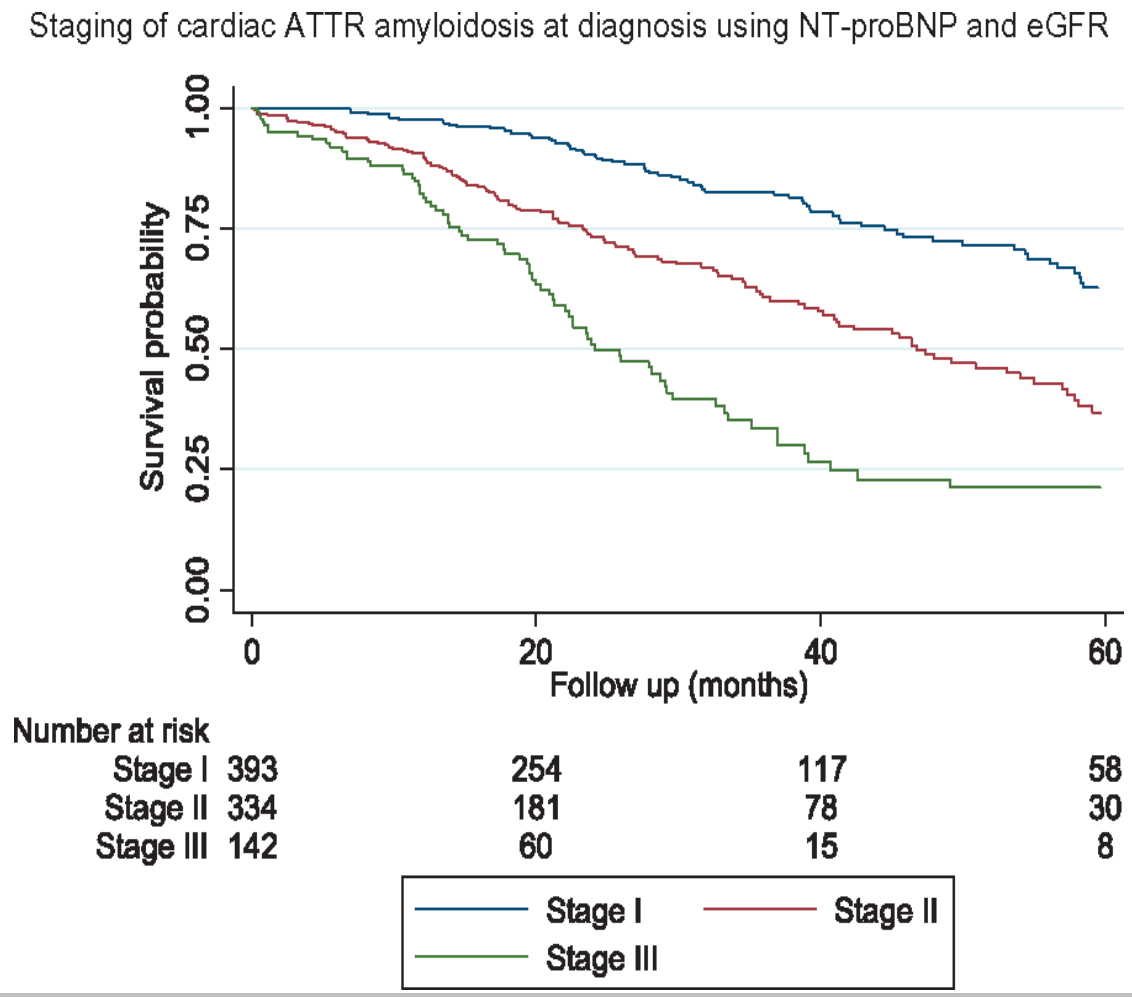
ESC European Society of Cardiology

Survival probabilities in 869 patients with cardiac transthyretin amyloidosis stratified by disease stage:

Stage I patients had a median survival of **69.2 months**

Stage II patients had a median survival of **46.7 months**

Stage III patients had a median survival of **24.1 months**



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But amyloidosis is a zebra, right?

Prevalence

- Autopsy study[1]:
  - 25% of patients >80 years old had TTR deposition
  - 2/3 of those had left ventricular involvement -> significant cardiac involvement in 8-16% of people >80 years old

- Recent study of 151 patients undergoing TAVR for aortic stenosis: 16% of the patients[2] were PYP+

- Emerging data using nuclear scintigraphy has suggested that 13% (95% confidence interval, 7.2% -19.5%) of patients hospitalized with heart failure with preserved ejection fraction may have ATTR with cardiac involvement[3]

1. Cornwell et al. Am J Med. 1983;75:618–623.
2. Castano et al. Eur Heart J. 2017 Oct 7;38(38):2879-2887.
3. Gonzalez-Lopez et al. Eur Heart J. 2015 Oct 7;36(38):2585-94.

Prevalence Data from THAOS

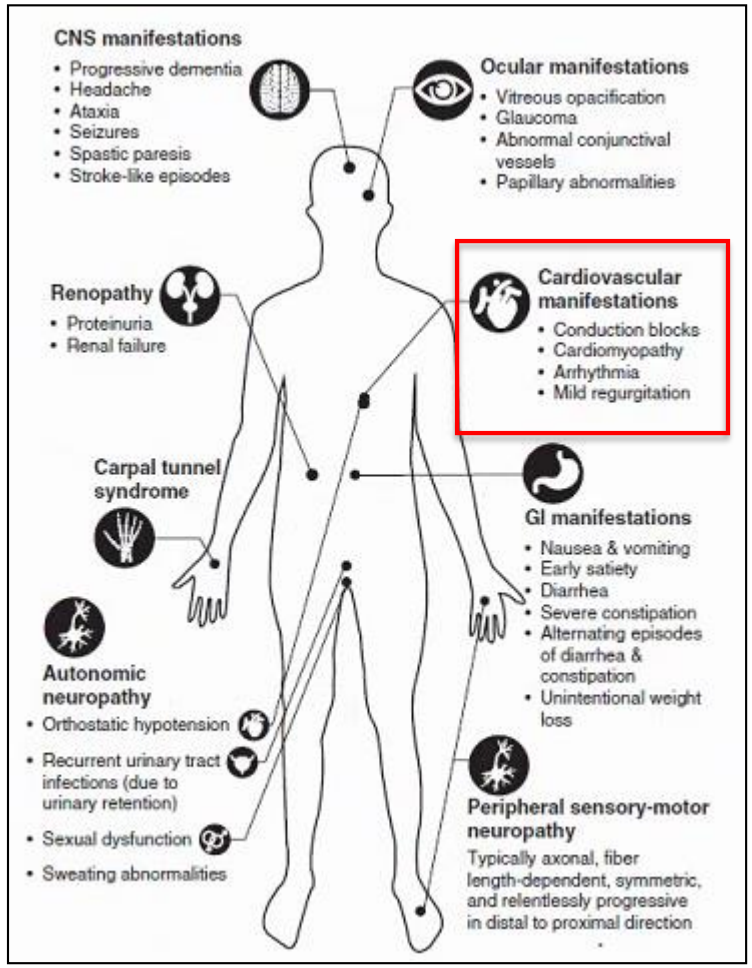
THAOS data in U.S.:

- 50% of patients with ATTR-CA have ATTRwt
- Patients with ATTRm, 34 different mutations
  - 45% due to a valine to isoleucine substitution at position 122 (Val122Ile), a mutation present almost exclusively in African Americans with an allele frequency of ~4%
- Most commonly encountered CA subtypes in elderly adults is ATTRwt, followed by ATTRm, and light-chain (AL)

1. Maurer et al, Thaos investigators. Genotype and Phenotype of Transthyretin Cardiac Amyloidosis: Transthyretin Amyloid Outcome Survey). JACC 2016 Jul 12; 68(2):161-72
2. Ruberg et al. Transthyretin Amyloid Cardiomyopathy. JACC 2019 Jun 11; 73(22):2872-2891

What are signs and symptoms of the disease?

Features Associated with ATTR Amyloidosis



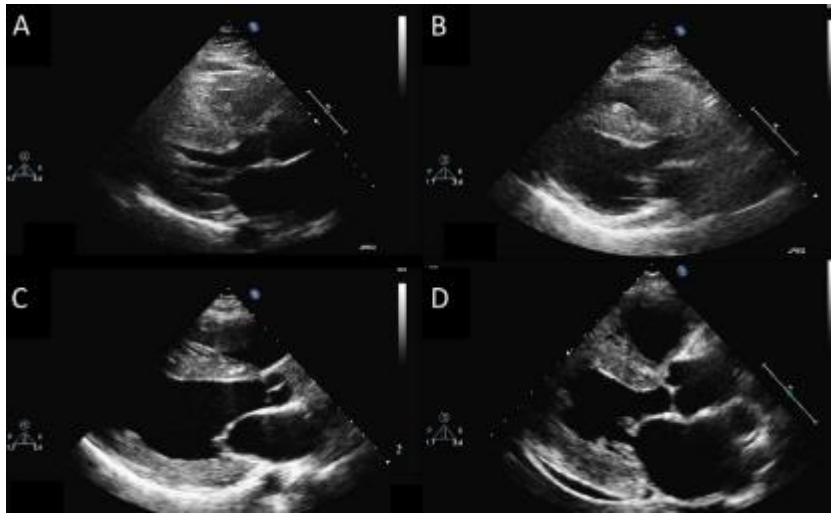
RED-FLAG SYMPTOMS

Heart failure: +

- Bilateral carpal tunnel syndrome
- Orthostatic hypotension
- GI problems: constipation or diarrhea

Conceicao; "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy; Journal of the Peripheral Nervous System 21:5–9 (2016)

ATTR Amyloidosis Can Be Misdiagnosed



Heightened Index of Suspicion

- Increased wall thickness without obvious cause
- HFpEF with concomitant right heart failure (+JVP, hepatomegaly, edema)
- Discordance of wall thickness and electrocardiographic voltage
- History of carpal tunnel syndrome, lumbar spinal stenosis, or spontaneous biceps tendon rupture
- Low flow, low gradient aortic stenosis
- Diffuse late gadolinium enhancement or increased extracellular volume of cardiac MRI
- Apical longitudinal strain preservation
- Natriuretic peptides elevated out of proportion to clinical syndrome
- Persistently positive troponin in the absence of acute coronary syndrome

Potential misdiagnoses based on cardiac signs/symptoms can include:

- Hypertrophic cardiomyopathy[1]
- Heart failure with preserved ejection fraction[2]

Can AI help us to “screen” for patients?

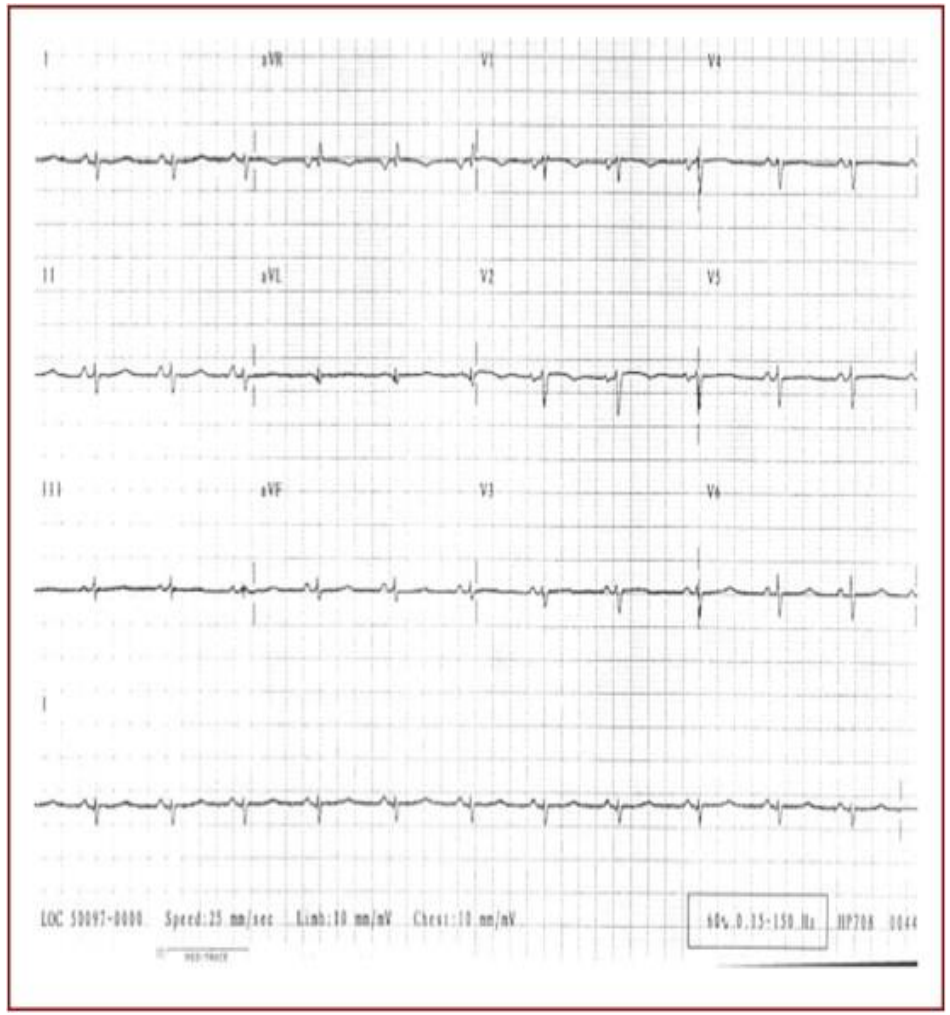
Rapezzi C et al. *Eur Heart J*. 2013;34:520-528; 2. Mesquita ET et al. *Arq Bras Cardiol*. 2017;109:71-80; 3. Hawkins PN et al. *Ann Med*. 2015; 47:625-638; 4. Cortese A et al. *J Neurol Neurosurg Psychiatry*. 2017;88:457-458.

Disease symptoms are vague, but this disease is not very rare and is deadly.

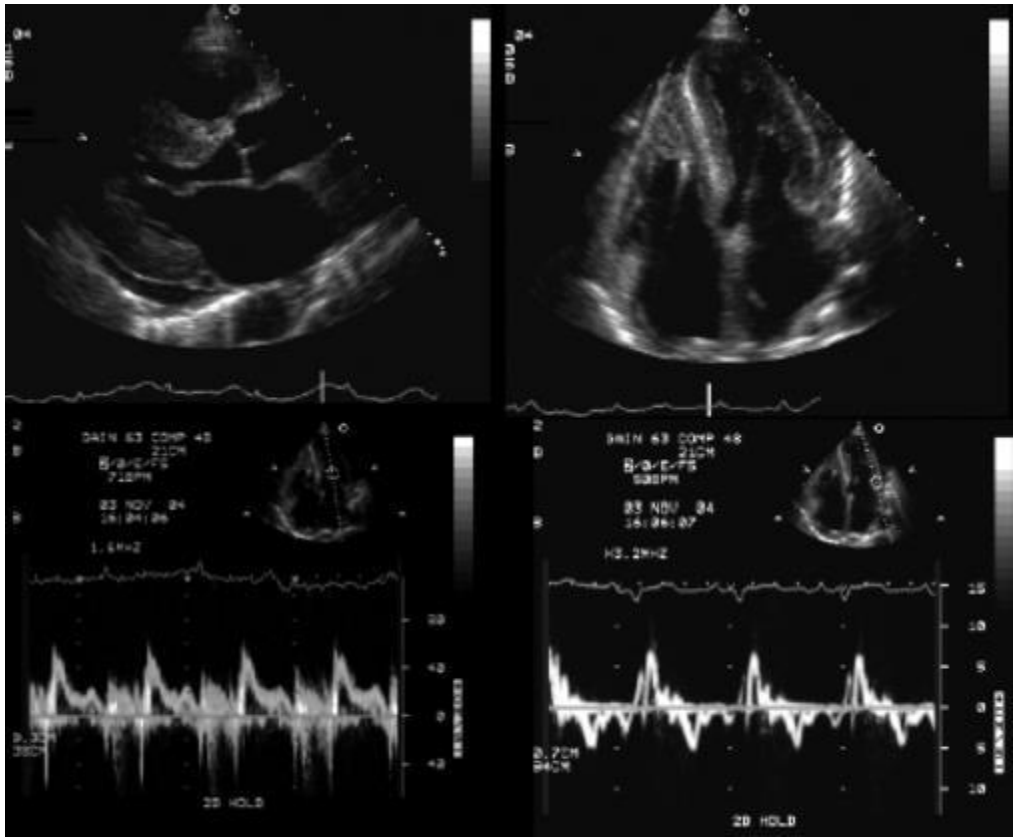
How do cardiologists diagnose this disease?

ECG

- Low QRS voltage
  - prevalence of low voltage varies with etiology, ranging from 60% in AL to 20% in ATTR amyloidosis
- Poor R wave progression
- Right bundle-branch block is uncommon
- Left bundle-branch block is very unusual unless it is a preexisting condition



Echocardiographic Findings in Patients with Cardiac Amyloidosis



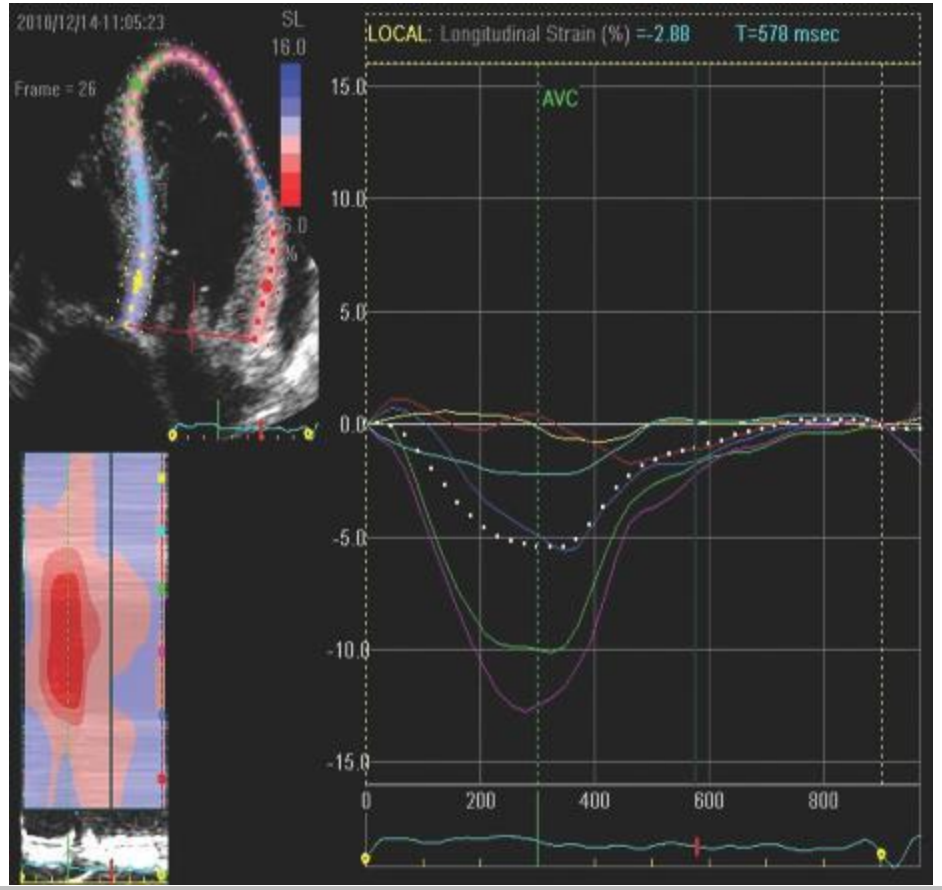
- LV and RV wall thickening
- bi-atrial enlargement
- thickening of the interatrial septum
- pericardial effusion
- diastolic dysfunction is common and often advanced restrictive filling pattern
- high early (E) and relatively low atrial (A) wave with an E/A ratio >2, and a short deceleration time
- myocardium may have a “granular sparkling” or “speckled” appearance

Rodney H. Falk Circulation. 2005;112:2047-2060

Transthoracic Echocardiogram with Speckle Tracking

Red and yellow lines represent longitudinal motion in the basal segments, whereas the purple and green lines represent apical motion.

- Detects changes in regional myocardial deformation specific to amyloid
- Impairments in strain may occur earlier than can be seen in 2-D TTE or by symptoms
- Compared to other LVH
- Significantly reduced longitudinal and radial strain
- Diminished global longitudinal strain (LS) in base/mid segments, preserved at apex



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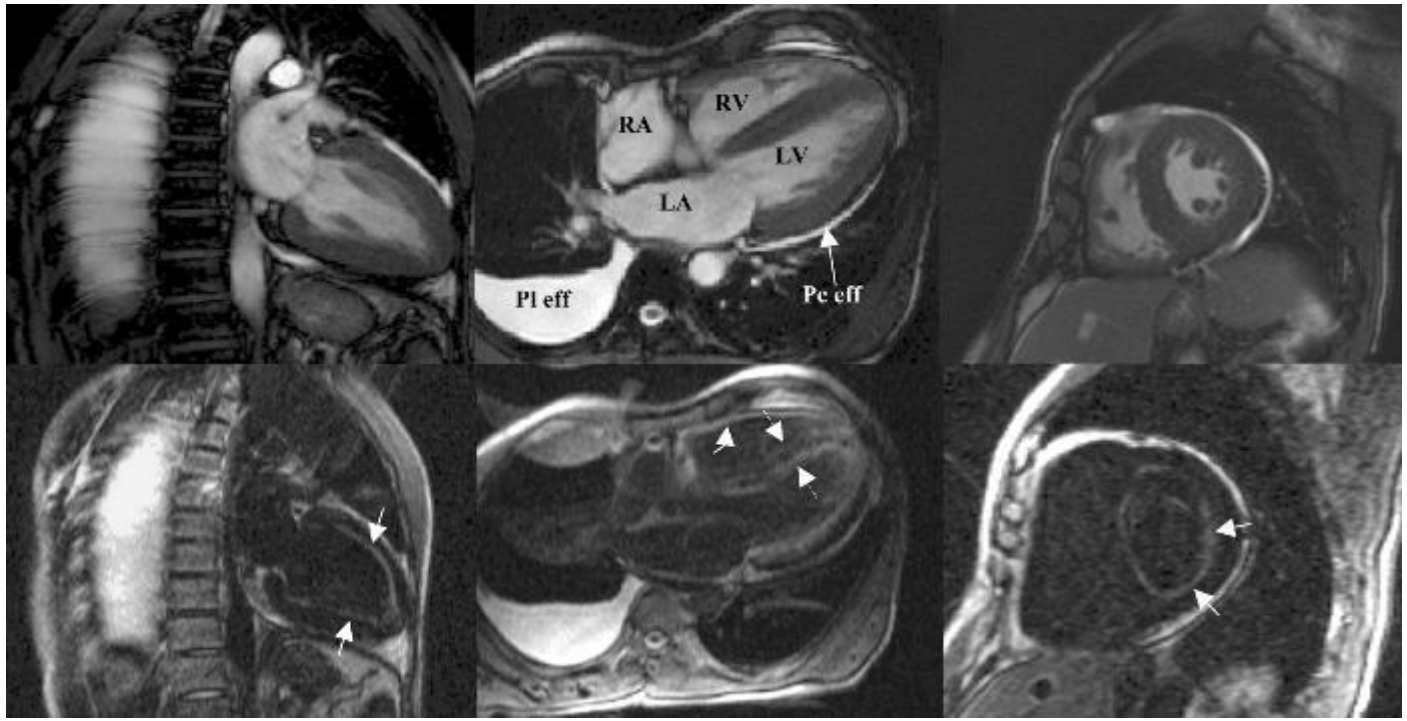
Sanjay M. Banypersad et al. J Am Heart Assoc 2012;1:e000364

Cardiac Magnetic Resonance (CMR) in a Patient with Systemic Amyloidosis

Top: Thickened LV, pleural and pericardial effusions
Bottom: Diffuse global subendocardial gadolinium enhancement



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Alicia Maria Maceira et al. Circulation. 2005;111:186-193

Cardiac MRI

- Characteristic patterns of LGE
  - Global subendocardial and transmural enhancement

- T1 mapping can analyze changes in myocardial longitudinal relaxation
  - help distinguish amyloid from HCM
  - pre-contrast and post-contrast T1 data can be used together to calculate the ECV
  - ECV: a measurement of interstitial expansion which is significantly elevated in patients with CA, due to interstitial amyloid deposition

- T2 mapping can represent myocardial edema
  - higher in untreated AL amyloidosis compared with treated AL and ATTR amyloidosis
  - predictor of prognosis in AL amyloidosis

- Meta-analysis of CMR: 85% sensitivity, 92% specificity

Kotecha et al. JACC 2018 Jun 26;71(25):2919-2931

Questions Left to be Answered

What is the best imaging modality to follow response to treatment?

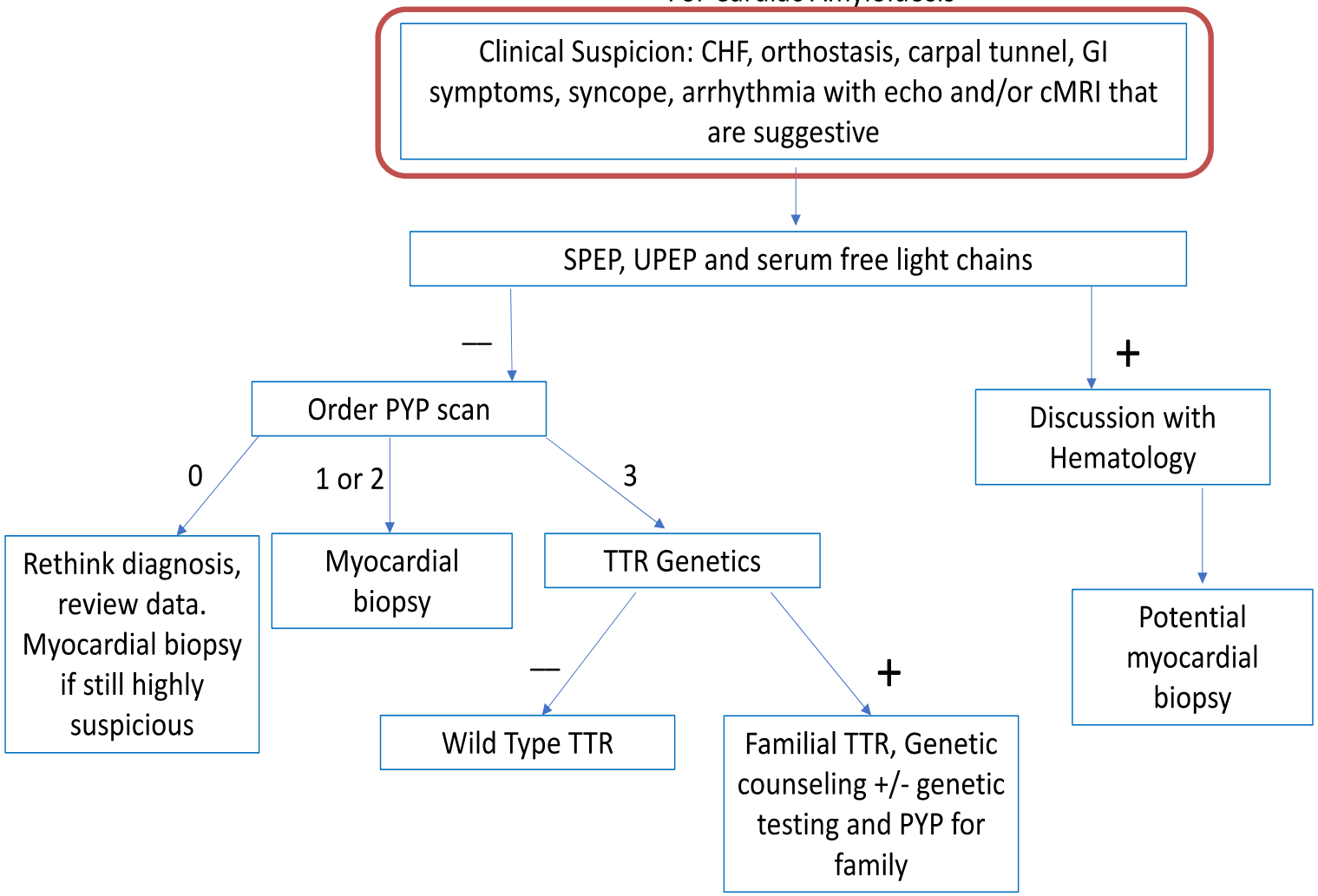
What causes the LGE in cardiac amyloidosis?

Can MRI help us understand if TTR fibrils are toxic?

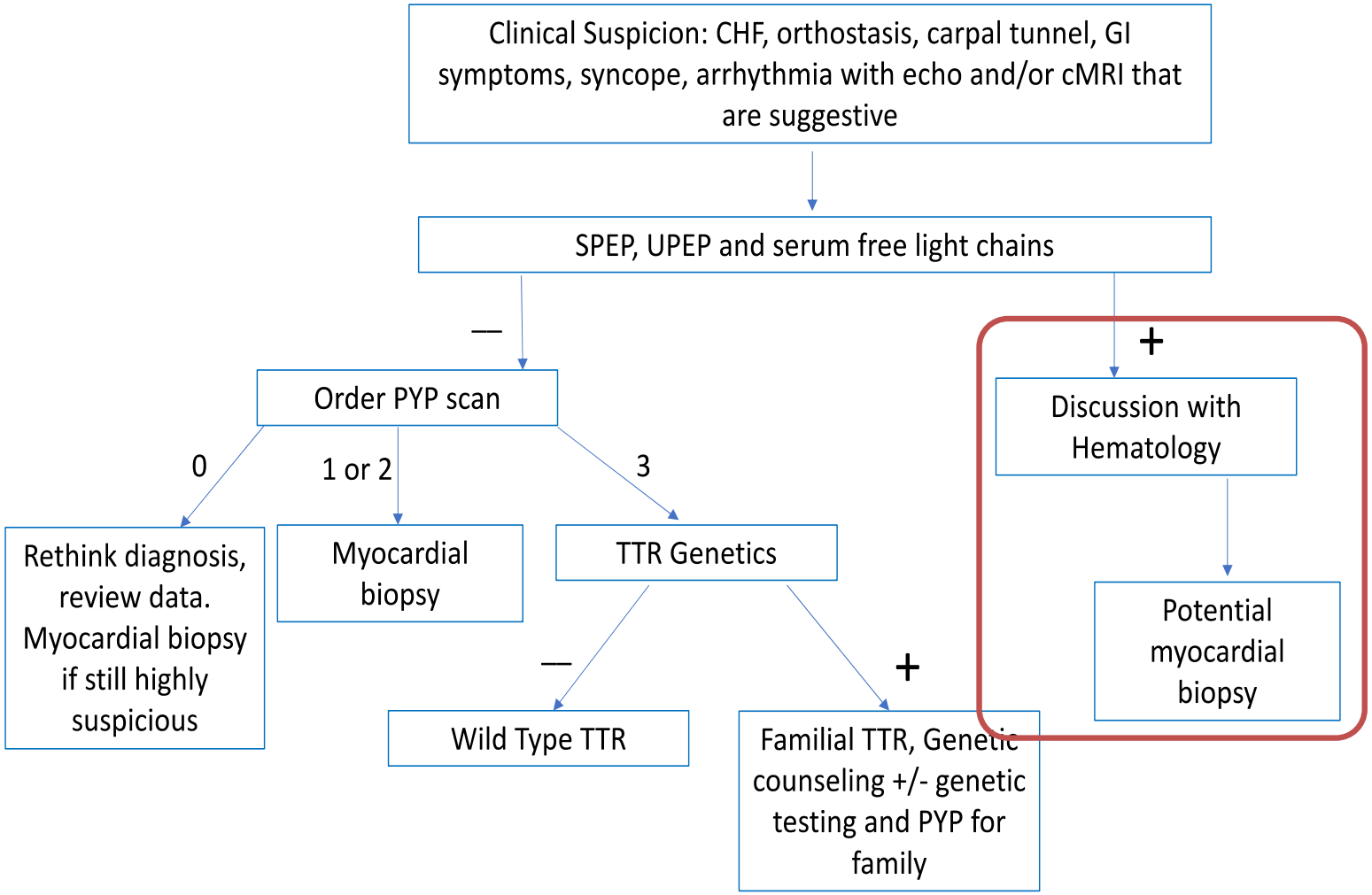
Which parameters are best for following treatment? T1/T2/ECV

We now have a high suspicion that the patient has cardiac amyloidosis, so how do we figure out which type?

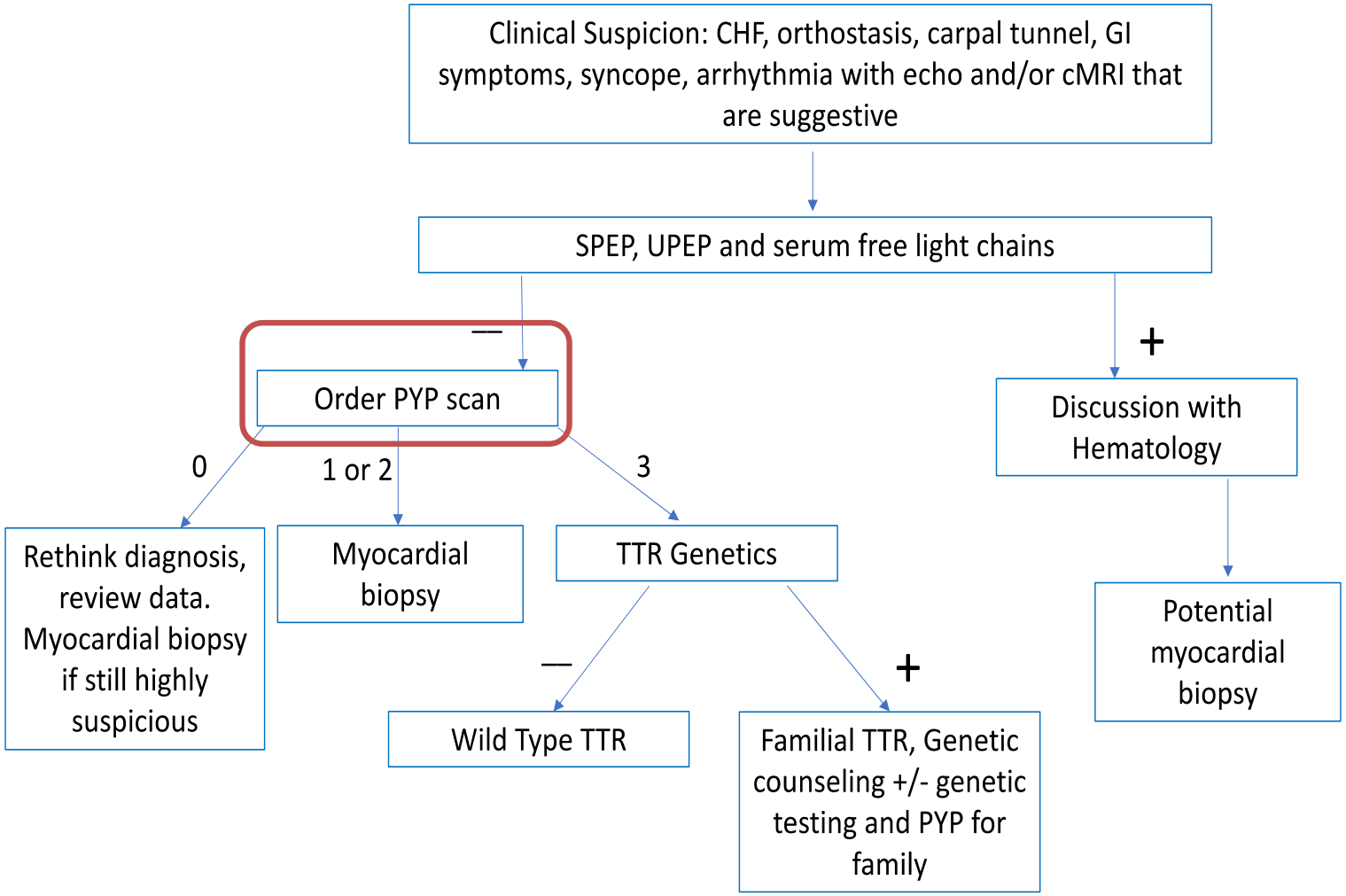
University of Chicago Diagnostic Algorithm
For Cardiac Amyloidosis



University of Chicago Diagnostic Algorithm
For Cardiac Amyloidosis



University of Chicago Diagnostic Algorithm
For Cardiac Amyloidosis



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Imaging with Nuclear Tracers

^{99m}Tc-DPD and PYP localizes cardiac amyloid deposits very sensitively

- Especially in patients with ATTR type
- Uptake of 99mTc-PYP occurs in about 1/3 of patients with cardiac AL amyloidosis
- Can help to distinguish AL from ATTR amyloidosis

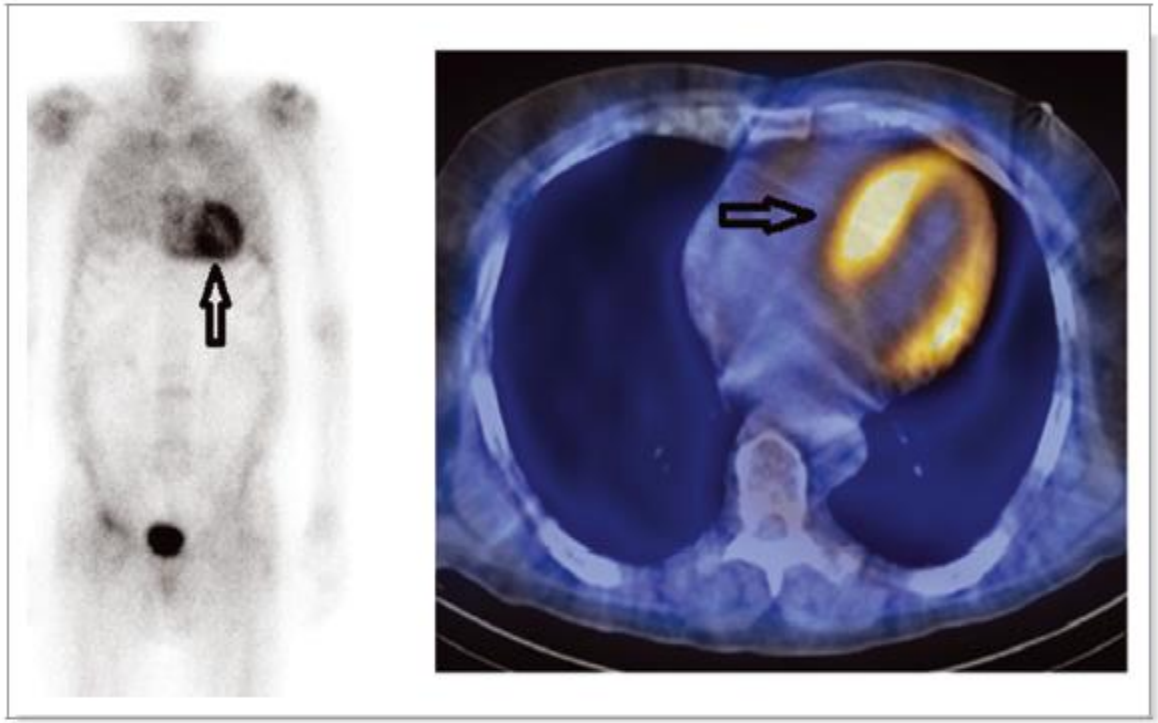


Figure 5. A positive 99mTc-DPD scan for TTR cardiac amyloid (left), showing uptake in the heart (arrow) and reduced bone uptake. The right-hand panel shows a fused CT/SPECT image showing myocardial uptake with greater uptake in the septum.

Asymptomatic cardiac ATTR deposits seen at an early stage when echocardiography, serum cardiac biomarkers, and perhaps even CMR remain normal

Imaging with Nuclear Tracers

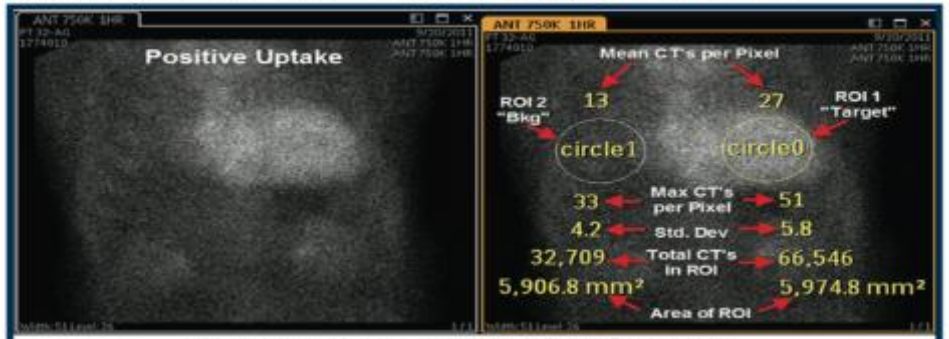
99^{m}Tc-PYP testing

- Can calculate a quantitative heart to contralateral lung ratio which correlates with prognosis
- Able to identify early-stage TTR-CM in asymptomatic carriers of variant transthyretin
- Able to diagnose TTR-CM without the complications that can arise with cardiac biopsy
- May be contributing to the increasing recognition of this disease

Table 2. Semi-quantitative Visual Grading of Myocardial ^{99m}Tc-PYP Uptake by Comparison to Bone(rib) Uptake

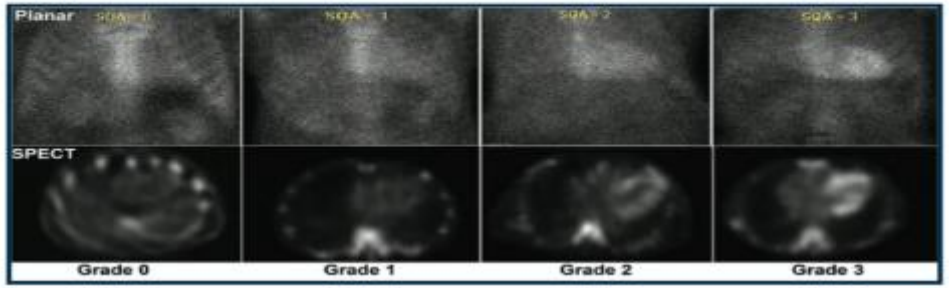
Grade	Myocardial ^{99m}Tc-PYP Uptake
Grade 0	no uptake and normal bone uptake
Grade 1	uptake less than rib uptake
Grade 2	uptake equal to rib uptake
Grade 3	uptake greater than rib uptake with mild/ absent rib uptake

Figure 1. Quantitation of Cardiac ^{99m}Tc-PYP Uptake Using Heart to Contralateral Lung (H/CL) Ratio



Biopsy proven ATTR with H/CL = 2.08

Figure 2. Grading ^{99m}Tc-PYP Uptake on Planar and SPECT Images



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PRACTICE POINTS

^{99m}Technetium-Pyrophosphate Imaging for Transthyretin Cardiac Amyloidosis

OVERVIEW

The purpose of this document is to identify the critical components involved in performing ^{99m}Technetium-pyrophosphate (^{99m}Tc-PYP) imaging for the evaluation of cardiac transthyretin amyloidosis (ATTR).

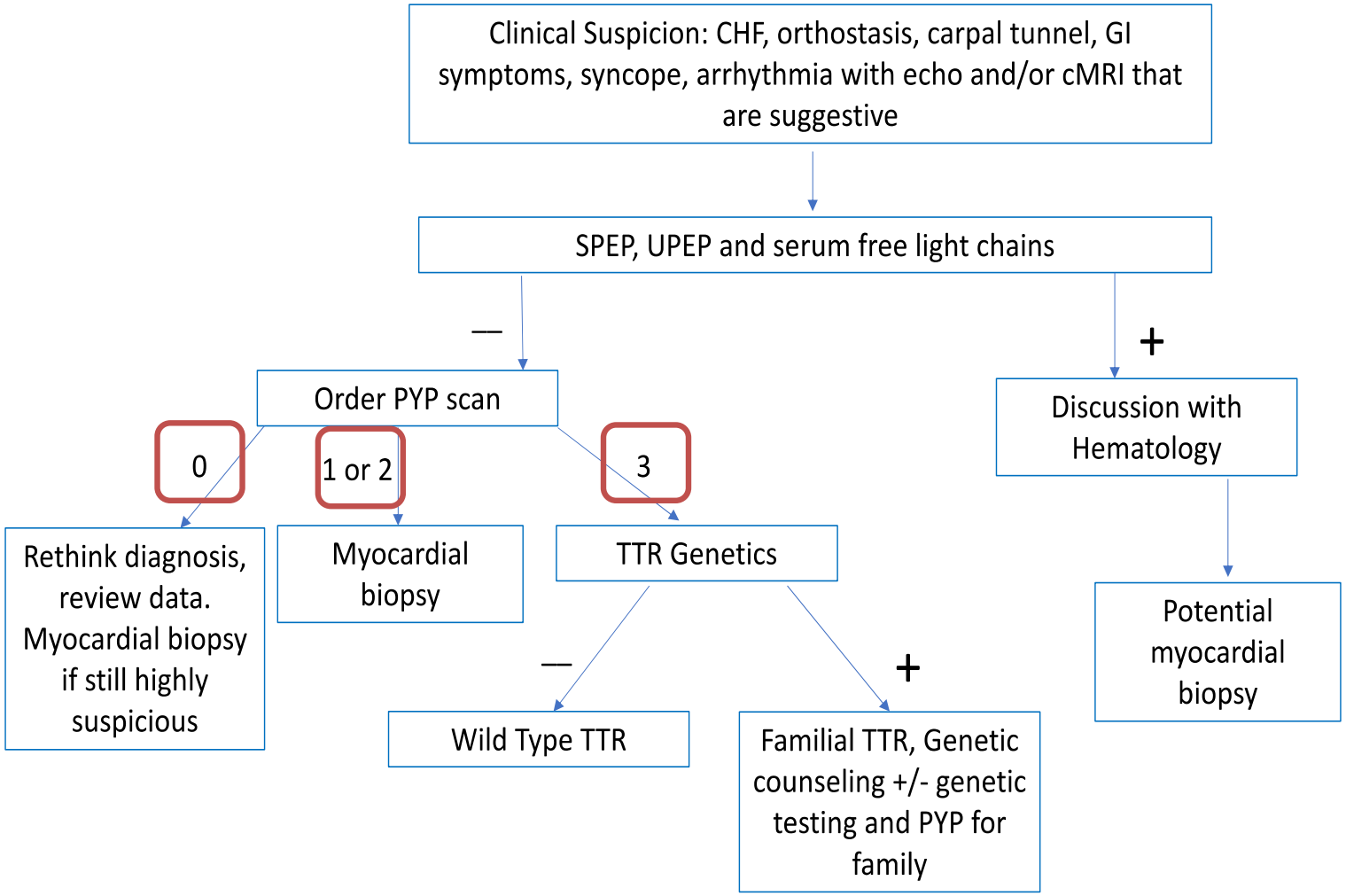
BACKGROUND

- The majority of individuals with cardiac amyloidosis have myocardial amyloid deposits formed from misfolded light chain (AL) or transthyretin (TTR) proteins. Diagnosis of amyloidosis and differentiation between the types is important for prognosis, therapy, and genetic counseling.
- Cardiac TTR amyloidosis, the focus of this practice points document, is an under diagnosed cause of heart failure.
- Amyloid derived from wild-type TTR results in a restrictive cardiomyopathy, most commonly presenting in men in their early 70's onwards, but occasionally seen as young as age 60. Although almost 1 in 4 males > 80 years have some TTR-derived amyloid deposits at autopsy, the clinical significance of a mild degree of deposition is unknown--generally clinical manifestations of heart failure occur once enough amyloid has been deposited to cause LV wall thickening (1).
- Approximately 3 – 4% among US African Americans have a common inherited mutation of the TTR gene (Val122Ile), which produces a restrictive cardiomyopathy in a minority, but may contribute to heart failure in a higher proportion (1).
- Cardiac amyloidosis should be suspected in individuals with heart failure and thickened ventricles with grade 2 or greater diastolic dysfunction on echocardiography or typical findings on cardiac magnetic resonance imaging (CMR; diffuse late gadolinium enhancement, ECV expansion or characteristic T-1 relaxation times); diagnosis is confirmed by endomyocardial biopsy and typing of amyloid fibrils as needed.
- Several studies confirm the high sensitivity and specificity of ^{99m}Tc-bone compound scintigraphy (^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) or PYP(2, 3)) for cardiac ATTR amyloidosis; recent studies highlight the value of DPD and/or PYP in differentiating cardiac ATTR from AL amyloidosis (4).
- A distinct advantage of ^{99m}Tc-PYP imaging, even when echocardiography and CMR are diagnostic for cardiac amyloidosis, is its ability to specifically identify ATTR cardiac amyloidosis non-invasively and thereby guide patient management (5).

PATIENT SELECTION

- Individuals with heart failure and unexplained increase in left ventricular wall thickness.
- African-Americans over the age of 60 years with heart failure, unexplained or with increased left ventricular wall thickness (>12 mm).
- Individuals over the age of 60 years with unexplained heart failure with preserved ejection fraction.
- Individuals, especially elderly males, with unexplained neuropathy, bilateral carpal tunnel syndrome or atrial arrhythmias in the absence of usual risk factors, and signs/symptoms of heart failure.
- Evaluation of cardiac involvement in individuals with known or suspected familial amyloidosis.
- Diagnosis of cardiac ATTR in individuals with CMR or echocardiography consistent with cardiac amyloidosis.
- Patients with suspected cardiac ATTR amyloidosis and contraindications to CMR such as renal insufficiency or an implantable cardiac device (5).

University of Chicago Diagnostic Algorithm
For Cardiac Amyloidosis



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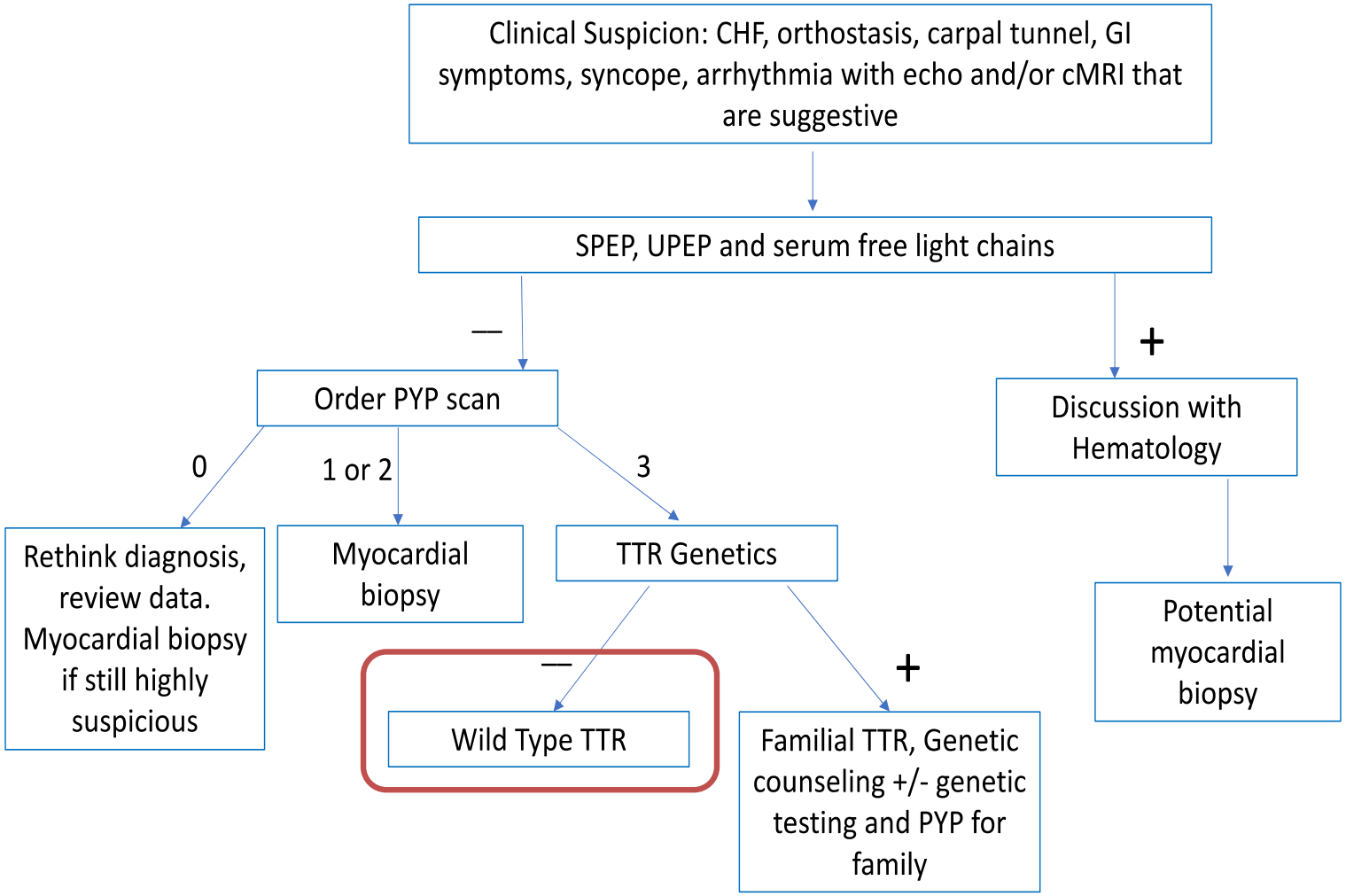
University of Chicago Diagnostic Algorithm
For Cardiac Amyloidosis



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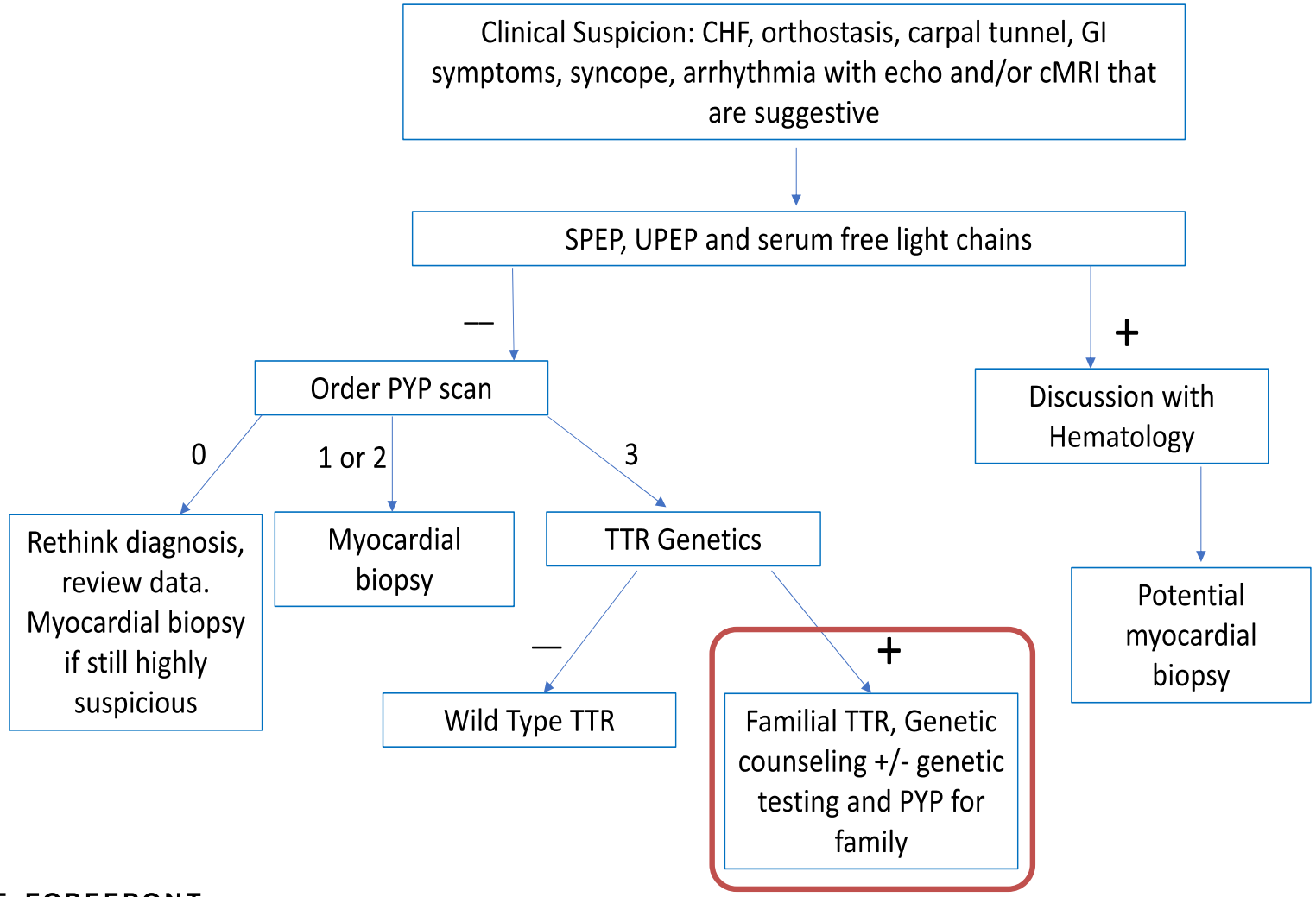
Wild Type TTR (formerly known as senile)

- Non-hereditary form
- Predominantly affects the heart + carpal tunnel, neuropathy is uncommon
- Can also present as spinal stenosis or biceps tendon rupture (often years before a cardiac presentation)
- Patients are usually >60 years old, male predominance
- May be a process of aging

University of Chicago Diagnostic Algorithm
For Cardiac Amyloidosis



Hereditary TTR

Over 100 known mutations

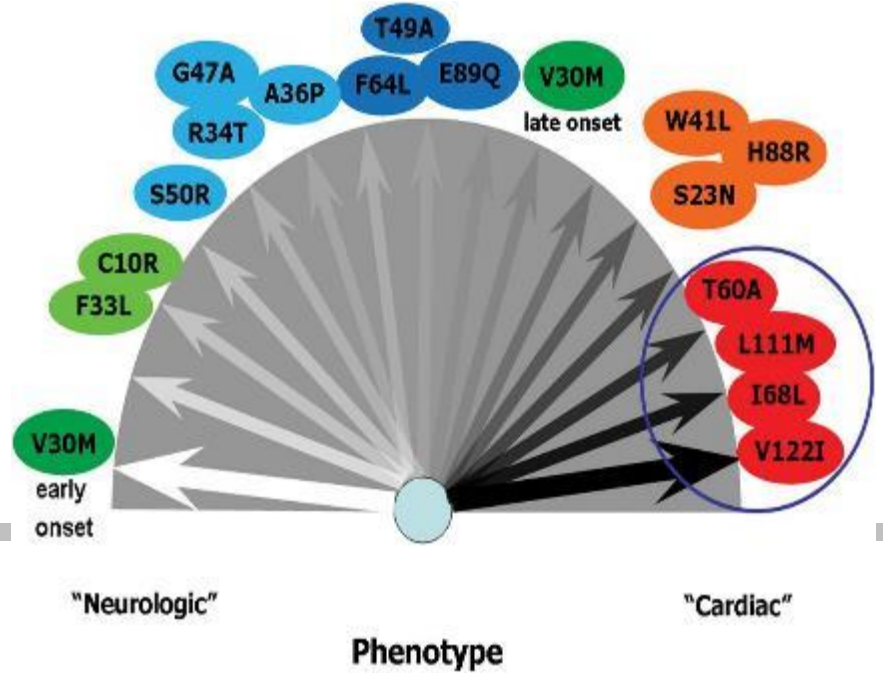
- 3 most common *TTR* mutations: Thr60Ala, Val30Met, Val122Ile

Patients with the Val122Ile variant are generally older and have a higher degree of cardiac infiltration than patients with the other two mutations

- 3.9% of African Americans and 23% of African Americans who have cardiac amyloidosis

Val30Met

- Most common mutation worldwide
- Neuropathy at presentation
- Development of cardiomyopathy later in the disease course



Rapezzi et al. European Heart Journal. 34 (7): 520-528

So now we know the patient has amyloid and what type, where do we go from here?

Treating hATTR Requires a Multi-disciplinary Team

Neurologist

Genetic Counselor

Cardiologist

Hematologist

Gastroenterologist

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Advanced Heart Failure Treatment

- LVAD: rarely done given small LV cavity, multi-organ involvement, chance of reoccurrence of disease and risk of infection

- Heart Transplant: controversial for AL, iCCAT. More clear for TTR
  - AL: Series of patients with OHT followed by either stem cell transplant or ongoing chemotherapy have reported outcomes comparable to other subjects with restrictive cardiomyopathies

  - 1-year survival post-OHT in UNOS for CA (including both AL-CA and ATTR-CA) from 2010 to 2012 was 81.6%.

  - Current guidelines endorse consideration of selected patients with either AL or ATTR-CA.

Therapeutic Approaches

1. Stabilize the TTR tetramer
   - Tafamidis
   - Diflunisal
   - AG10

2. Prevent TTR production
   - Patisiran
   - Vutrisiran
   - Inotersen

3. Breakdown TTR protein
   - Doxycycline + TUDCA (tauroursodeoxcholic acid)

Whom to Treat?

Any symptomatic patient

- HF requiring diuretics, hospitalization, dyspnea
- Neurological impairment

Asymptomatic but PYP grade 2 or 3 with a known mutation

Phenotype:

- Cardiac -> tafamidis
- Mixed -> patisiran and tafamidis[1]
    - inotersen and tafamidis[1]
- Neurologic: patisiran or inotersen

1. There have been no clinical trials conducted to formally evaluate the concomitant use of patisiran and tafamidis, or inotersen and tafamidis

Conclusions

TTR cardiac amyloidosis is a prevalent, deadly, underdiagnosed disease in our patient population

New nuclear imaging techniques allow less invasive diagnostics

Therapeutic options remain limited but hopeful new treatments exist

Thank you!

Agenda

Welcome
- Christine Lindenboom – Senior Vice President, Investor Relations & Corporate Communications

Introduction and Overview of ATTR Amyloidosis
- Eric Green – Senior Vice President, General Manager, TTR Program

Cardiac Amyloidosis: A New Paradigm
- Nitasha Sarswat, M.D., Director, Infiltrative Cardiomyopathy Program, University of Chicago Hospital

RNAi Therapeutics in Development for ATTR Amyloidosis with Cardiomyopathy
- John Vest, M.D. – Vice President, Clinical Research

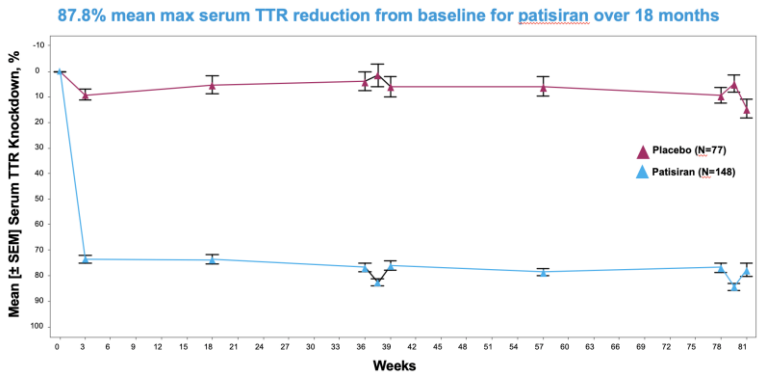
Alnylam's TTR Franchise Opportunity
- Rena Denoncourt – Senior Director, Program Leader, Vutrisiran Program

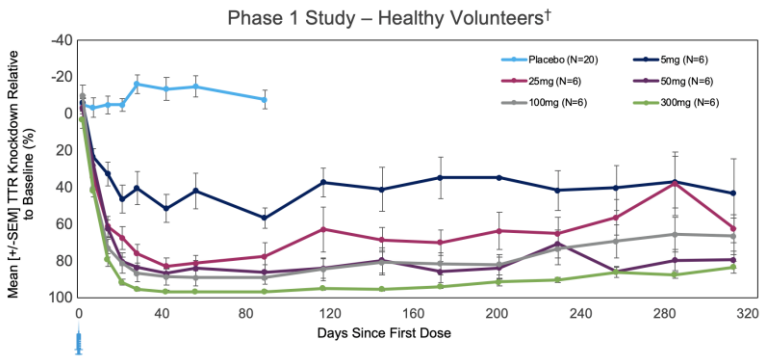
Q&A Session

RNAi: Proven Ability to Treat Polyneuropathy of hATTR Amyloidosis

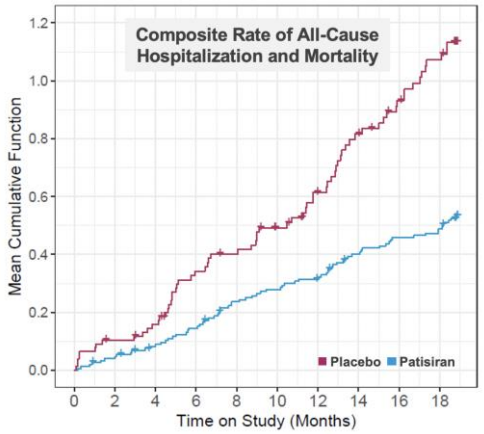
Encouraging Evidence to Provide Confidence in Potential for Success in ATTR-CM; Focus on Execution

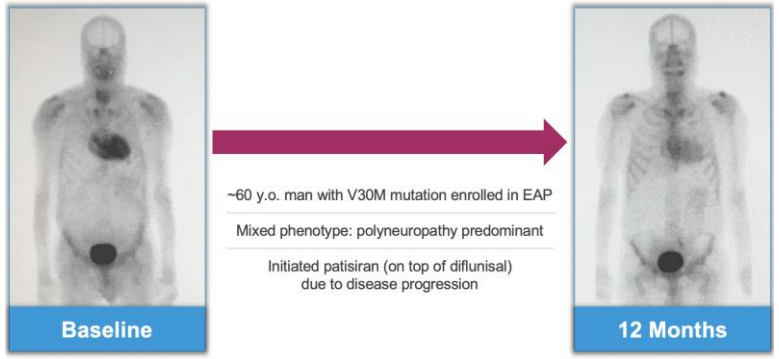
Known Reduction of TTR, Disease-Causing Protein



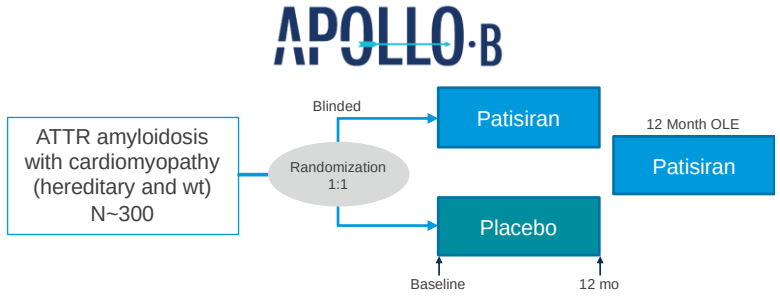


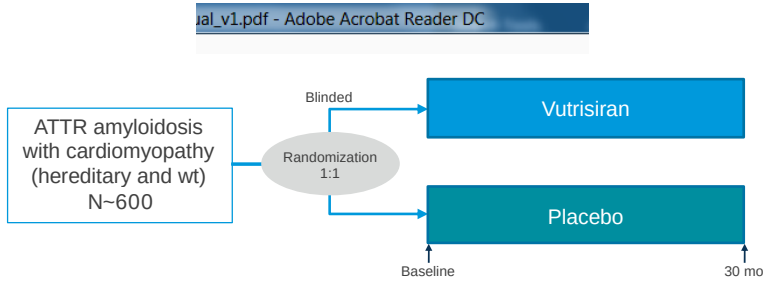
Exploratory Cardiomyopathy Clinical Data





Robust Clinical Program



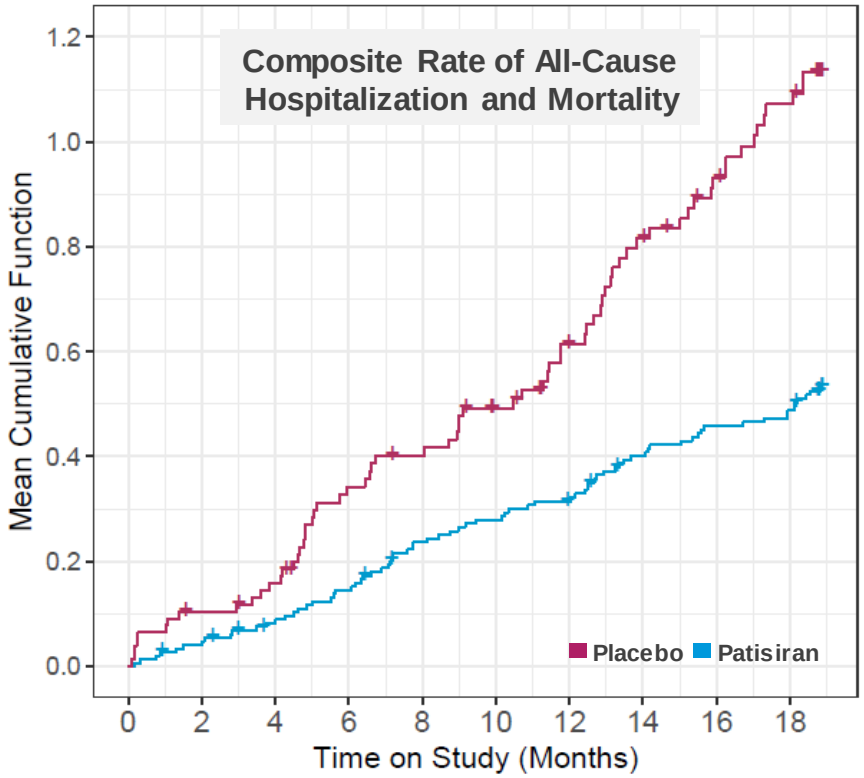


Adams D, et al. NEJM 2018; Solomon S, et al. Circulation 2018; Gillmore, OTS Munich 2019

APOLLO Phase 3 Study Results

Encouraging Evidence for Patisiran's Potential in ATTR Cardiomyopathy[1]

~50% **Reduction in all-cause hospitalization and mortality in post-hoc analysis***



Analysis of hospitalization/death data was conducted post-hoc based on data collected from AE CRFs; hospitalization/death events caused by SAEs within 28 days of last dose of study drug were included; hospitalization events caused by SAEs within SOC of cardiac disorder were classified as cardiac hospitalization

55% • Relative reduction in **NT-proBNP** vs. placebo†
  – Effect noted as early as 9 months

0.9mm • Mean reduction in **LV wall thickness** vs. placebo‡

-1.4% • Improvement in **global longitudinal strain** vs. placebo‡

0.35m/s • Improvement in **10-MWT** vs. placebo†

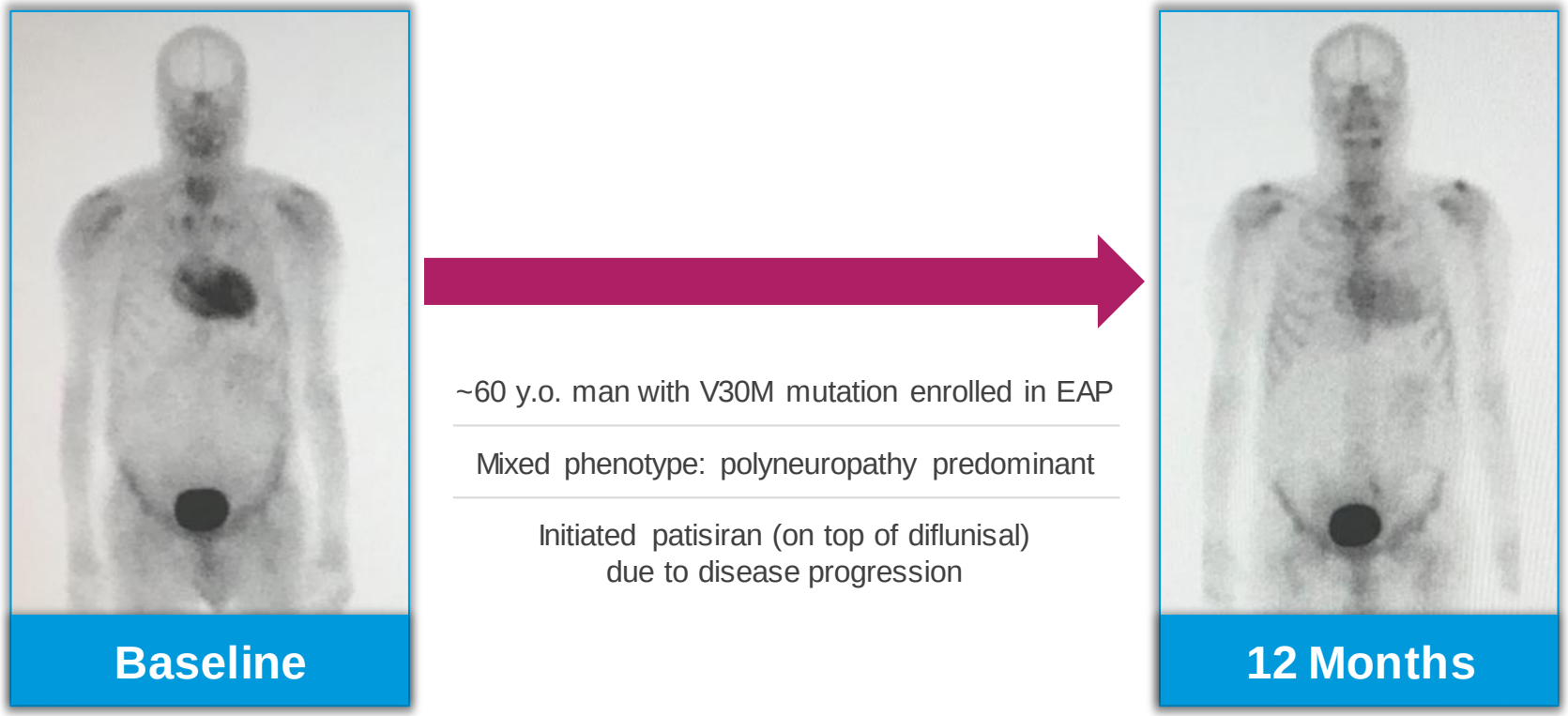
Cardiac Safety Data in Entire APOLLO Study Population:

	Placebo[2] (n=77)	Patisiran[2] (n=148)
Rates of Death/Hospitalization, per 100 py (95% CI)		
Death	6.2 (2.5 – 12.7)	3.2 (1.4 – 6.2)
All-cause hospitalization	69.7 (54.3 – 87.7)	32.9 (25.9 – 41.1)
Cardiac hospitalization	15.6 (9.0 – 24.9)	8.2 (5.0 – 12.6)
Hospitalization and/or death	71.8 (56.1 – 90.1)	34.7 (27.5 – 43.1)
Cardiac hospitalization and/or death	18.7 (11.4 – 28.8)	10.1 (6.4 – 14.9)

[1] Patisiran has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population
[2] For any hospitalization/death analysis: negative binomial regression rate ratio (RR) 0.49 [0.30, 0.79]; Anderson-Gill hazard ratio (HR) 0.48 [0.34, 0.69]
† nominal p<0.01; ‡ nominal p<0.05; Solomon S, et al. Circulation 2018

Patisiran Treatment of hATTR Amyloidosis

Evidence for Potential Cardiac Amyloid Regression[1]



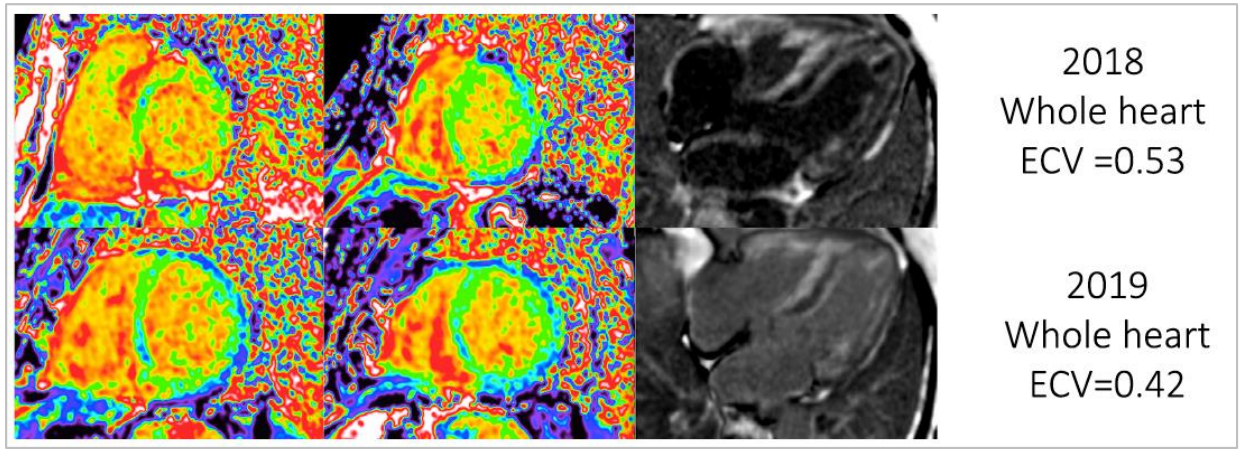
- Recent uncontrolled case series[2]
- Recently published similar findings by Nienhuis *et al*.[3]
- Patisiran treatment may be associated with cardiac remodeling and/or amyloid regression
- Cardiac effects to be further assessed in randomized, controlled trials

[1] Patisiran has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population
[2] Gillmore, OTS Munich 2019
[3] Mayo Clinic Proceedings, 2019

Further Evidence of Cardiac Amyloid Regression with Patisiran Treatment

Encouraging Data Recently Presented at ESC[1,2]

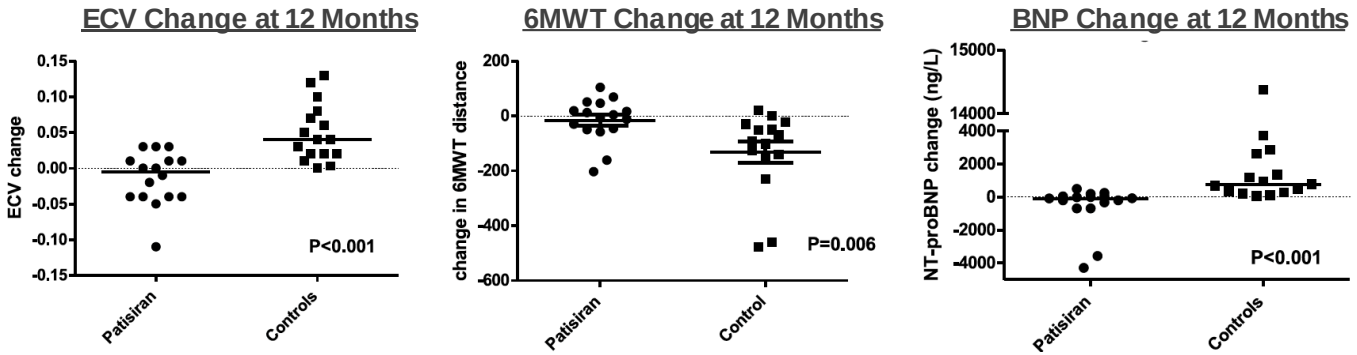
- 32 patients with hATTR amyloidosis with cardiomyopathy (n=16 patisiran, n=16 control)
- Non-randomized study
- Concomitant diflunisal allowed
- Assessments at baseline and one year:
  - Cardiac magnetic resonance (CMR)
  - 6-minute walk test (6-MWT)
  - NT-proBNP
  - Echocardiogram



Top panel shows a patient before treatment, and bottom panel shows regression in the same patient after one year of treatment with patisiran

Results

- Substantial reduction in cardiac amyloid burden in 45% of patients who received patisiran
- Patients treated with patisiran showed reduction in extracellular volume fraction (ECV) compared to an increase in ECV in the control group (p<0.001) at one-year follow up
- Improvement in 6-MWT and NT-proBNP at one year in patisiran-treated patients compared to control

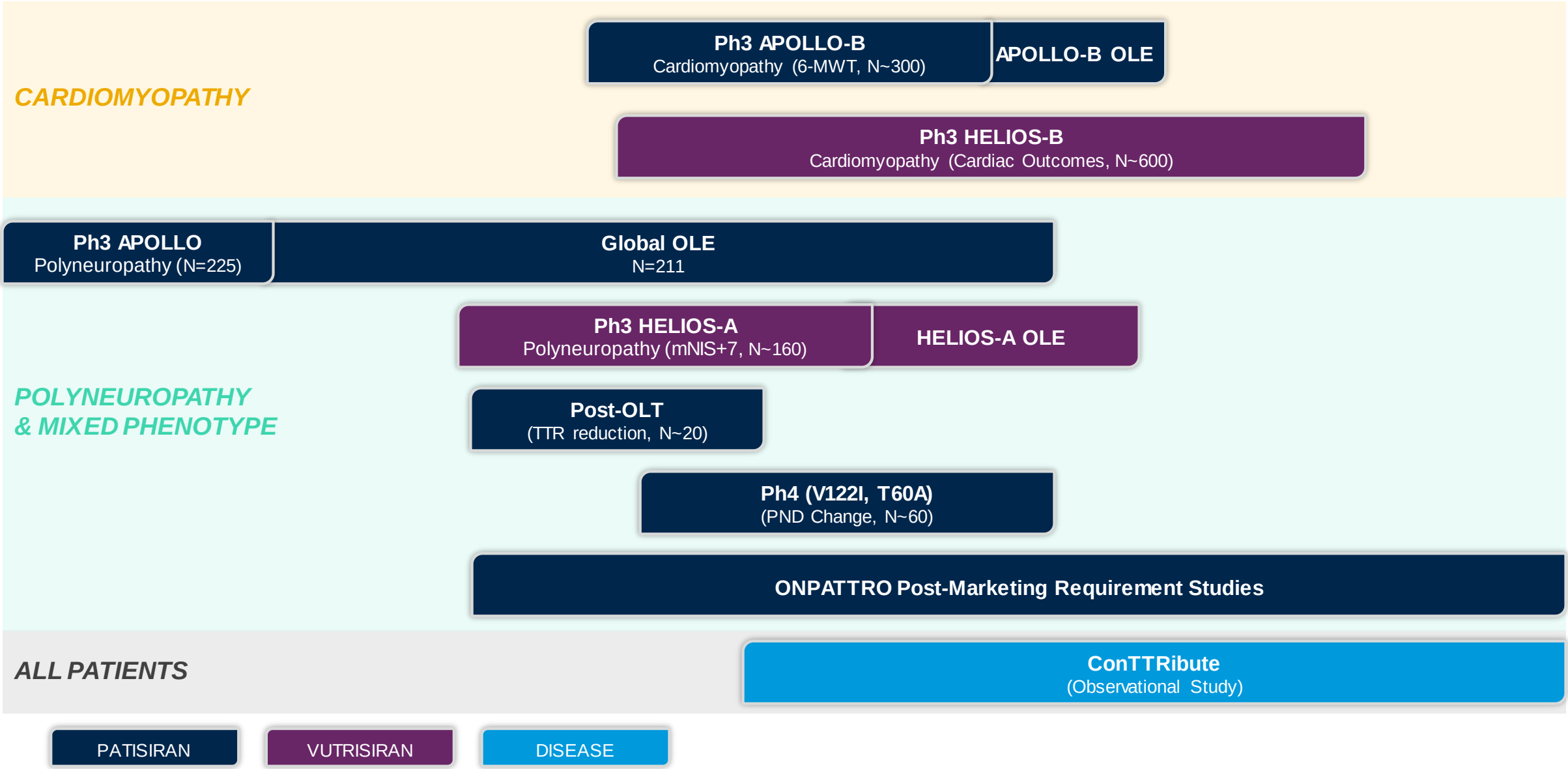


Change in assessments in patients receiving treatment with patisiran and controls, measured at baseline and one year

[1] Patisiran has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population

[2] Chacko, L et al. Regression of cardiac amyloid deposits with novel therapeutics: reaching new frontiers in cardiac ATTR amyloidosis. ESC 2020

Robust, Integrated Clinical Development Plan for ATTR Amyloidosis



Patisiran APOLLO-B Phase 3 Study

Randomized, Double-Blind, Placebo-Controlled Study in ATTR Amyloidosis Patients with Cardiomyopathy

N ~ 300
Patient Population

- ATTR amyloidosis; wild-type or any TTR mutation
  - TTR stabilizer naïve and/or TTR stabilizer progressor
- Confirmed cardiomyopathy and medical history of symptomatic heart failure
- NYHA ≤III; minimum walk and NT-proBNP limits at baseline

1:1 RANDOMIZATION

Patisiran
IV q3w†
0.3 mg/kg

or

Placebo
IV q3w†

Primary Endpoint

- Change in 6-MWT at 12 months

Key Secondary Endpoints

- Cardiomyopathy symptoms and health status
- Death and hospitalization outcomes
- Cardiac biomarkers

12-Month Treatment Extension

ClinicalTrials.gov Identifier: NCT03997383

APOLLO-B

Study initiated
September 2019

Enrollment completion expected
2021

Concomitant use of local standard of care allowed during study, including TTR stabilizer
† To reduce likelihood of infusion-related reactions, patients receive following premedication or equivalent at least 60 min. before each study drug infusion: 10 mg (low dose) dexamethasone; oral acetaminophen; H1 and H2 blockers
NYHA: New York Heart Association; NT-proBNP: N-terminal pro b-type natriuretic peptide; 6-MWT: 6-Minute Walk Test

Vutrisiran HELIOS·B Phase 3 Study

Randomized, Double-Blind Outcomes Study in ATTR Amyloidosis Patients with Cardiomyopathy

N ~ 600
Patient Population

- ATTR amyloidosis; wild-type or any TTR mutation
  - ≤ 30% tafamidis use at baseline
- Confirmed cardiomyopathy and medical history of symptomatic heart failure
- NYHA ≤ III; minimum walk and NT-proBNP limits at baseline

1:1 RANDOMIZATION

Vutrisiran
SC q3M
25 mg

or

Placebo
SC q3M

Primary Endpoint

- Composite outcome of all-cause mortality and recurrent CV events (when last patient reaches Month 30)

Select Secondary Endpoints

- 6-MWT distance
- Kansas City Cardiomyopathy Questionnaire (KCCQ OS) score
- Echocardiographic parameters
- All-cause mortality and recurrent all-cause hospitalizations and HF events
- All-cause mortality
- Recurrent CV events
- NT-proBNP

ClinicalTrials.gov Identifier: NCT04153149

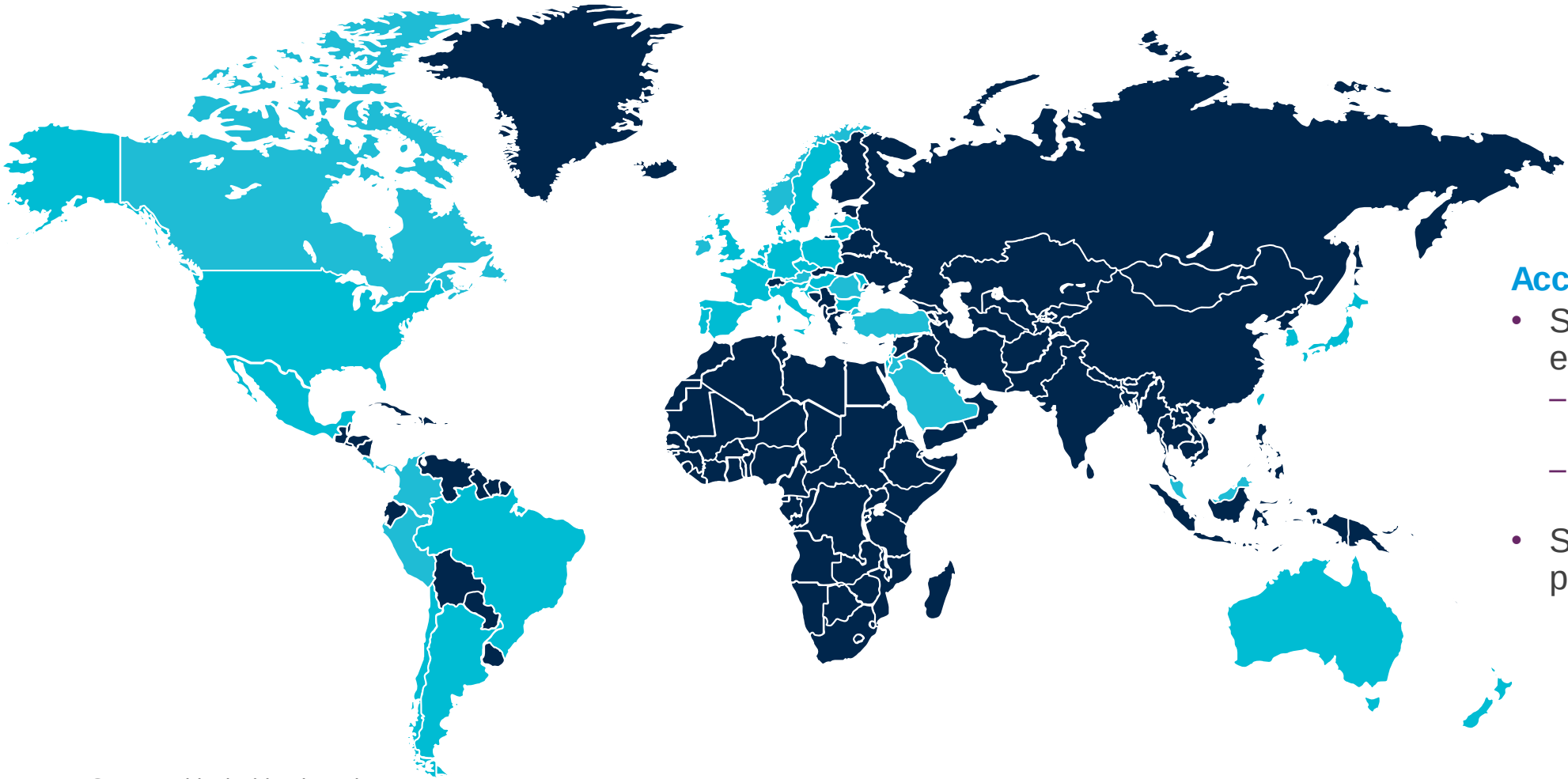
HELIOS·B

HELIOS-B Phase 3 study
now enrolling

Study includes optional interim analysis

APOLLO-B and HELIOS-B Utilizing Global Clinical Study Sites

Activating Sites in >40 Countries; Targeting >100 Clinical Sites



Country with site(s) selected for Cardiac Studies

Accelerating Enrollment

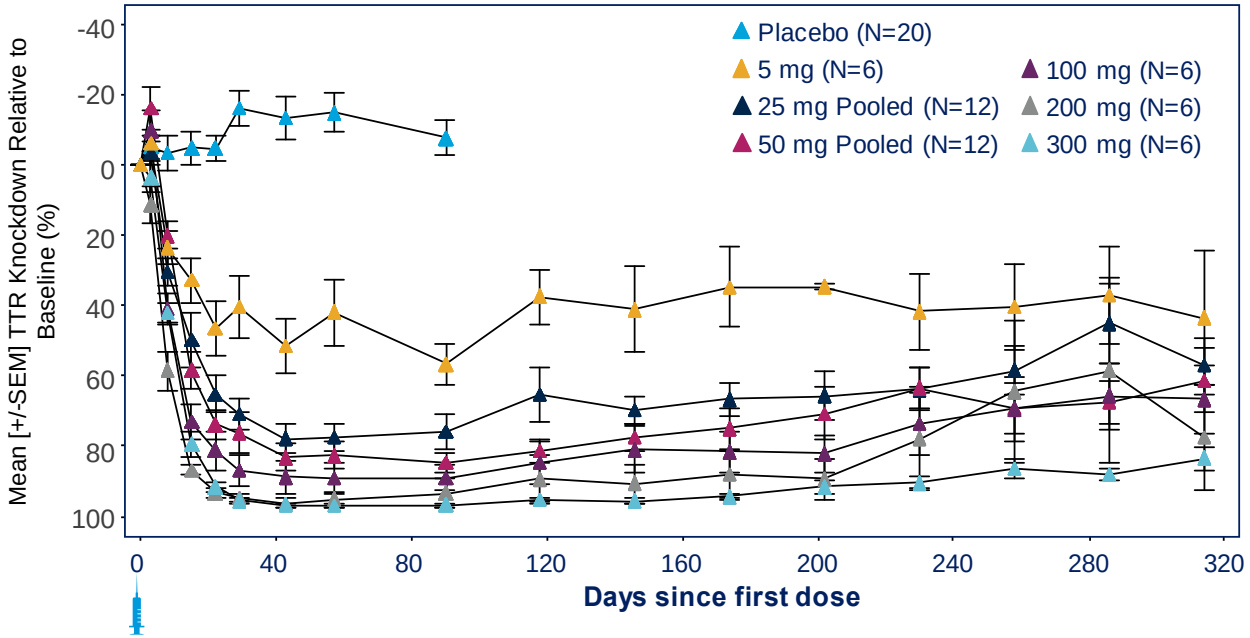
- Study footprints continue to expand
  - Opening more sites within activated countries
  - Expanding to new countries around globe
- Sites preparing for strong post-pandemic rebound

Opportunity for q6M Vutrisiran Dosing Regimen

Modeling Supports Potential Biannual 50mg Dosing Regimen in Addition to Quarterly 25mg Dosing Regimen

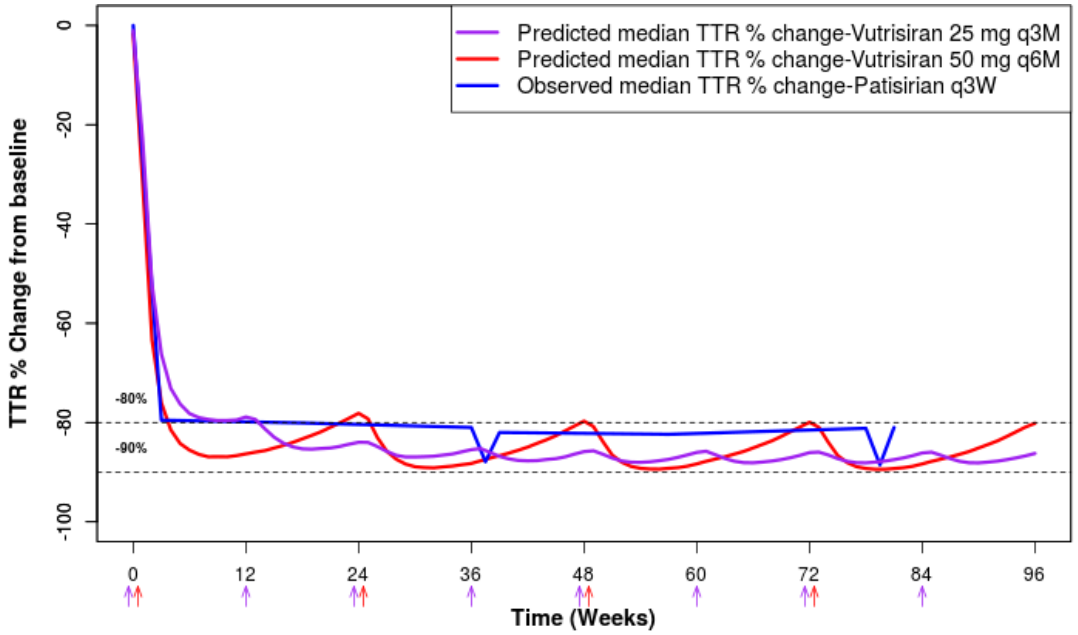
Phase 1 Study – Healthy Volunteers

- Mean max TTR reduction of >80% after single dose of either 25mg or 50mg†



Pharmacodynamic Modeling

- After repeat dosing, ~90% peak TTR reduction predicted with both 25mg q3M and 50mg q6M vutrisiran regimens
- 50mg q6M vutrisiran dosing predicted to have similar TTR reduction as 0.3mg/kg q3W patisiran
- Comparable average TTR reduction at steady state predicted for both 25mg and 50mg repeat dosing



† Taubel J, et al. Phase 1 Study of ALN-TTRsc02, a Subcutaneously Administered Investigational RNAi Therapeutic for the Treatment of Transthyretin-Mediated Amyloidosis. ISA 2018: XVIIth International Symposium of Amyloidosis; Kumamoto, Japan; March 2018 (poster)

q3M – dosing every three months
q6M – dosing every six months

Agenda

Welcome
- Christine Lindenboom – Senior Vice President, Investor Relations & Corporate Communications

Introduction and Overview of ATTR Amyloidosis
- Eric Green – Senior Vice President, General Manager, TTR Program

Cardiac Amyloidosis: A New Paradigm
- Nitasha Sarswat, M.D., Director, Infiltrative Cardiomyopathy Program, University of Chicago Hospital

RNAi Therapeutics in Development for ATTR Amyloidosis with Cardiomyopathy
- John Vest, M.D. – Vice President, Clinical Research

Alnylam's TTR Franchise Opportunity
- Rena Denoncourt – Senior Director, Program Leader, Vutrisiran Program

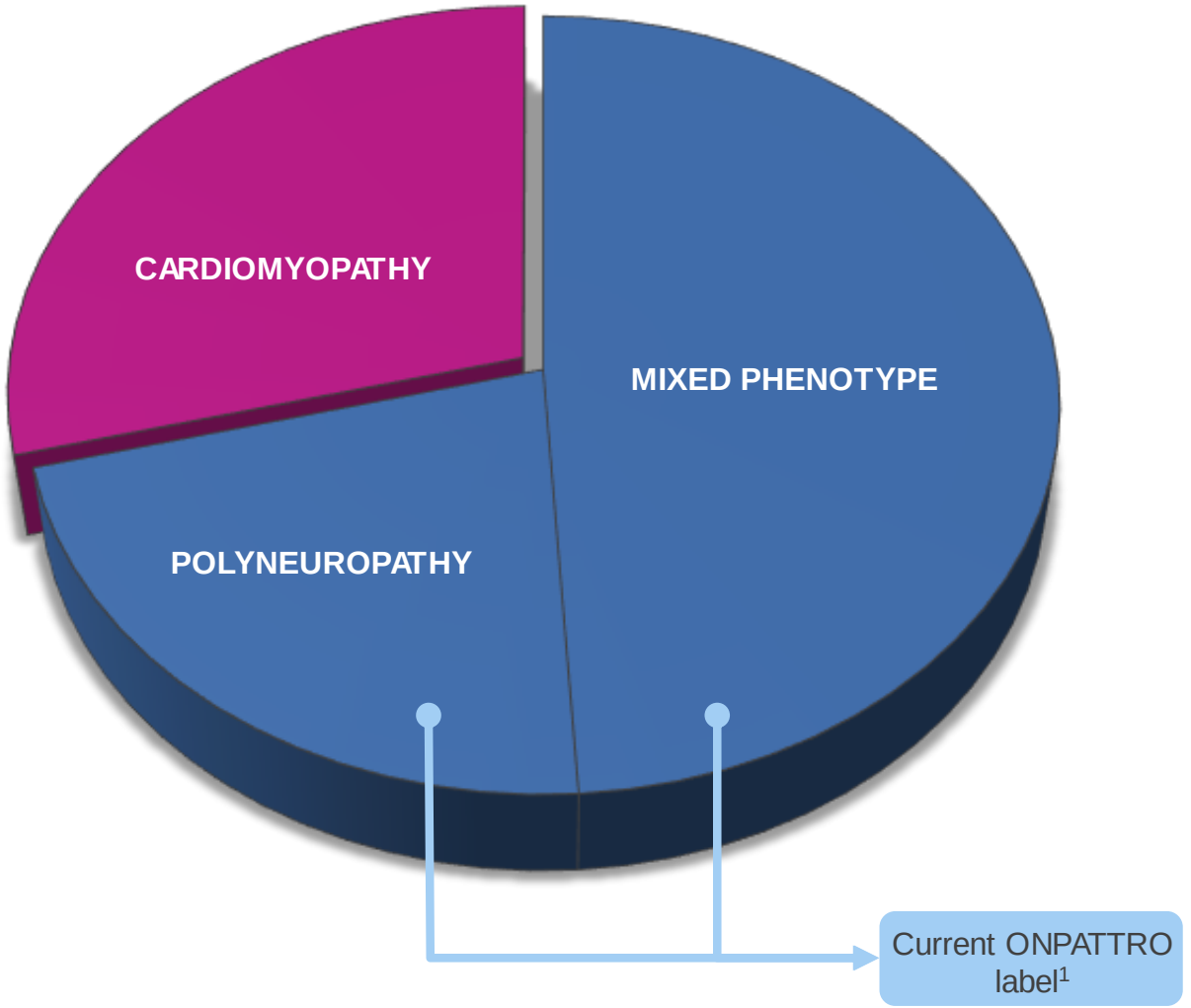
Q&A Session

Substantial Opportunity in hATTR Amyloidosis

ONPATTRO Creating Foothold; Vutrisiran Expected to Increase Share through HELIOS-A

Hereditary ATTR Amyloidosis

- Rare disease
  - Global prevalence ~50,000
- Genetic basis helps with diagnosis
  - Diagnostic rate 15-30% (varies by geography, patient population)
- Increasing awareness and diagnosis
- Multisystem involvement

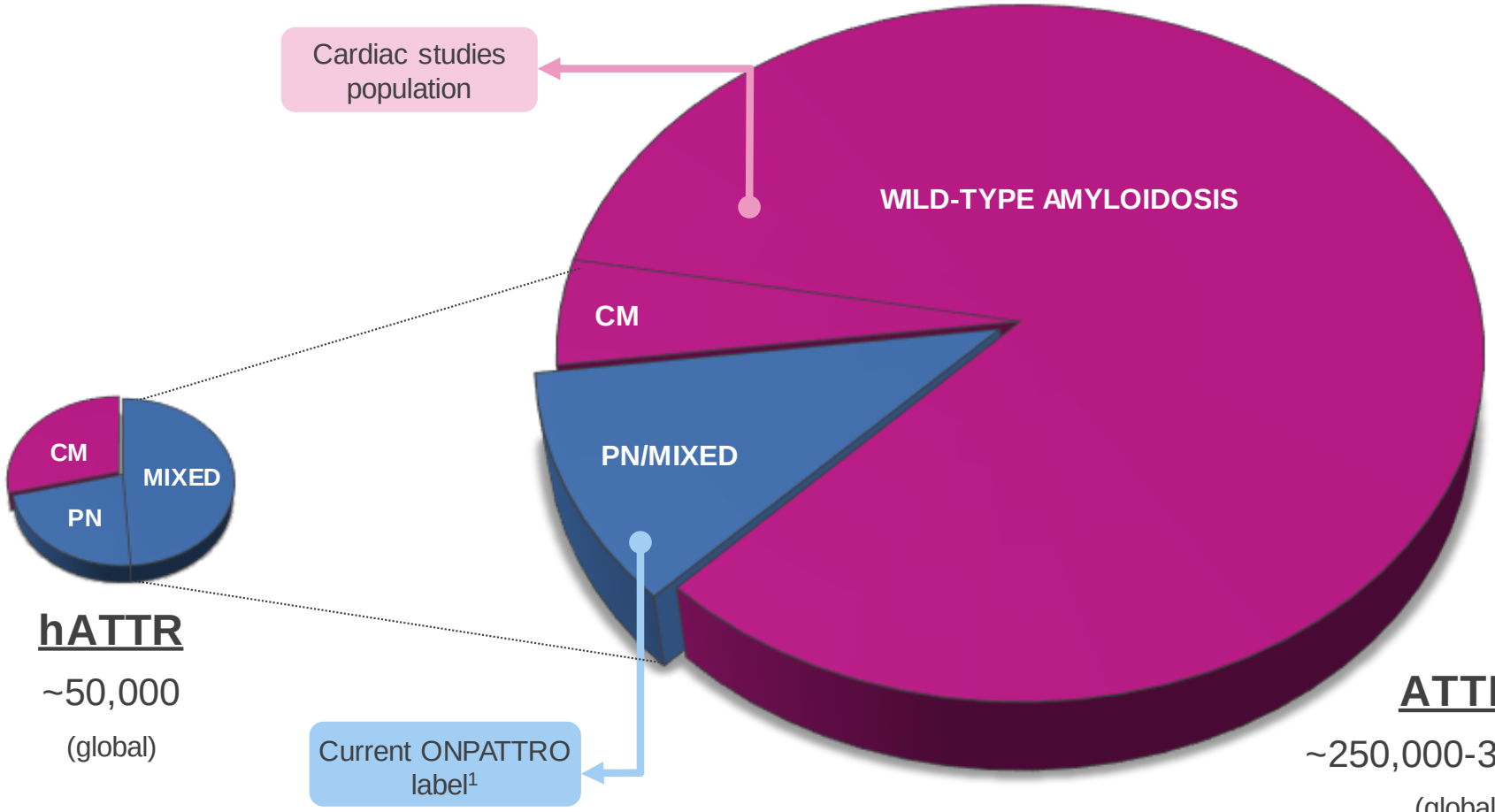


Illustrative, not meant to reflect exact estimates of the size of the patient population

[1] Approved in the U.S. and Canada for the polyneuropathy of hATTR amyloidosis in adults, in the EU, Switzerland and Brazil for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy

Expanding to Full ATTR Amyloidosis Represents Blockbuster Potential

APOLLO-B and HELIOS-B Providing Path to Wild-Type ATTR Amyloidosis



hATTR

~50,000

(global)

ATTR

~250,000-350,000

(global)

Wild-Type ATTR Amyloidosis

- Multisystem disease
  - Increasing awareness of extra-cardiac manifestations
- Increasing awareness and diagnosis
- Unmet need persists

Illustrative, not meant to reflect exact estimates of the size of the patient population

[1] Approved in the U.S. and Canada for the polyneuropathy of hATTR amyloidosis in adults, in the EU, Switzerland and Brazil for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy

Dynamic Time in ATTR Amyloidosis with Cardiomyopathy

Market Forces Align to Drive Significant Potential as Next Generation of Treatments are Advanced

Deeper Understanding of Disease Etiology

- Appreciation of heart failure as a broad category
- Awareness of infiltrative cardiomyopathy
- Better understanding of ATTR amyloidosis etiology

Greater Disease Awareness and Physician Attention

- Motivation to pursue definitive diagnosis
- Mainstream visibility and educational opportunities
- Multi-disciplinary care provided at centers of excellence

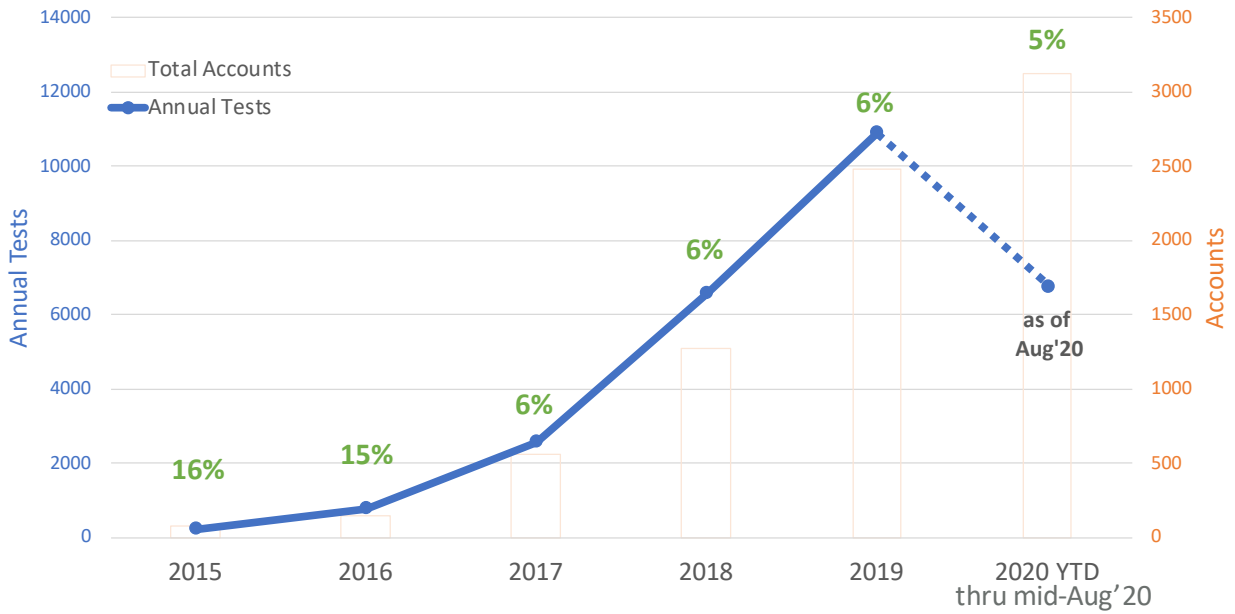
Advances and Availability of Diagnostic Tools

- Increased availability and utilization of imaging tools and genetic testing
- Technetium imaging emerging as best practice for diagnosis

Physician Interest in Genetic Testing for hATTR Amyloidosis Continues to Grow; Important Step for Definitive Diagnosis

Alnylam Act® – Seven Years of Improved Diagnoses and Support for Patients and Their Families

Annual TTR Alnylam Act Tests and Total Accounts



- Continued growth in accounts utilizing program
- Percentage of tests with positive mutations remaining steady as volume increases

Weekly TTR Alnylam Act Tests for 2020

- Testing volumes impacted by COVID-19 in 2020, but returning to pre-pandemic levels

Data as of Aug 2020; Alnylam Act volume is subject to minor change due to lab information adjustment

Non-invasive and Highly Specific Imaging for Diagnosis

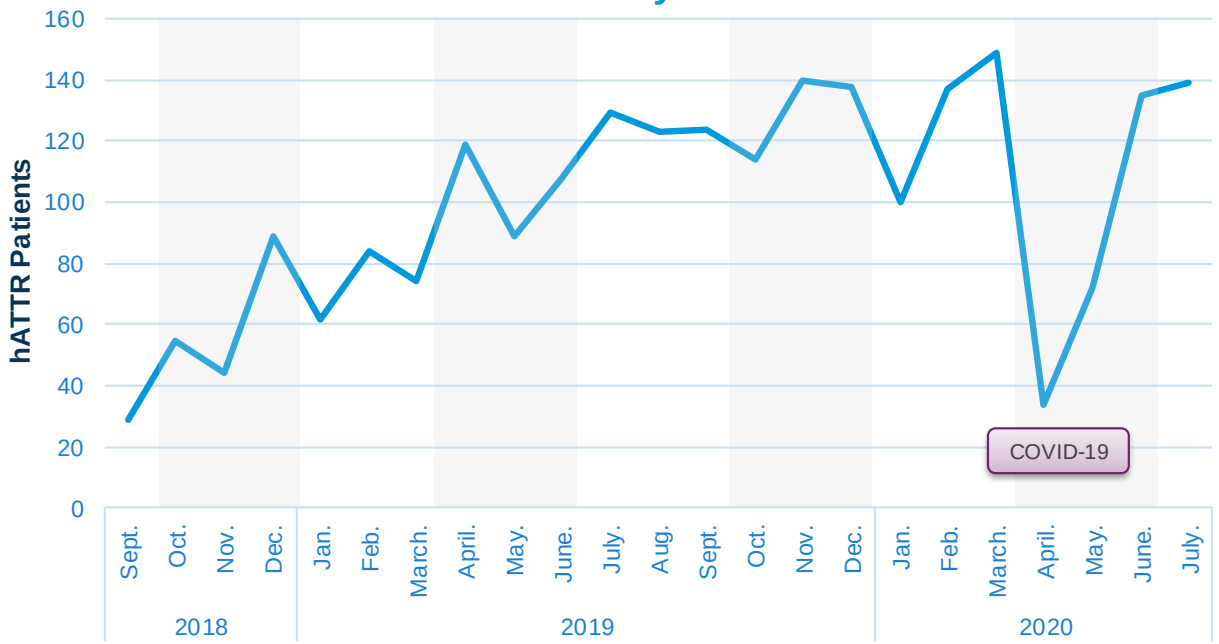
Technetium (^{99m}Tc-PYP) Scan Volume Has Significantly Increased Since 2018 in U.S.

Historical: Quarterly PYP Scan Volume

Data Source: Historical Komodo Claims data

1. All patients: Commercial, Medicare and Medicaid patients
2. Amyloidosis patients: All amyloidosis patients including hereditary, wild type and other amyloidosis patients
3. A list of procedural and diagnosis codes for PYP scans and TTR population are provided in appendix

Real Time: Monthly PYP Scan Volume



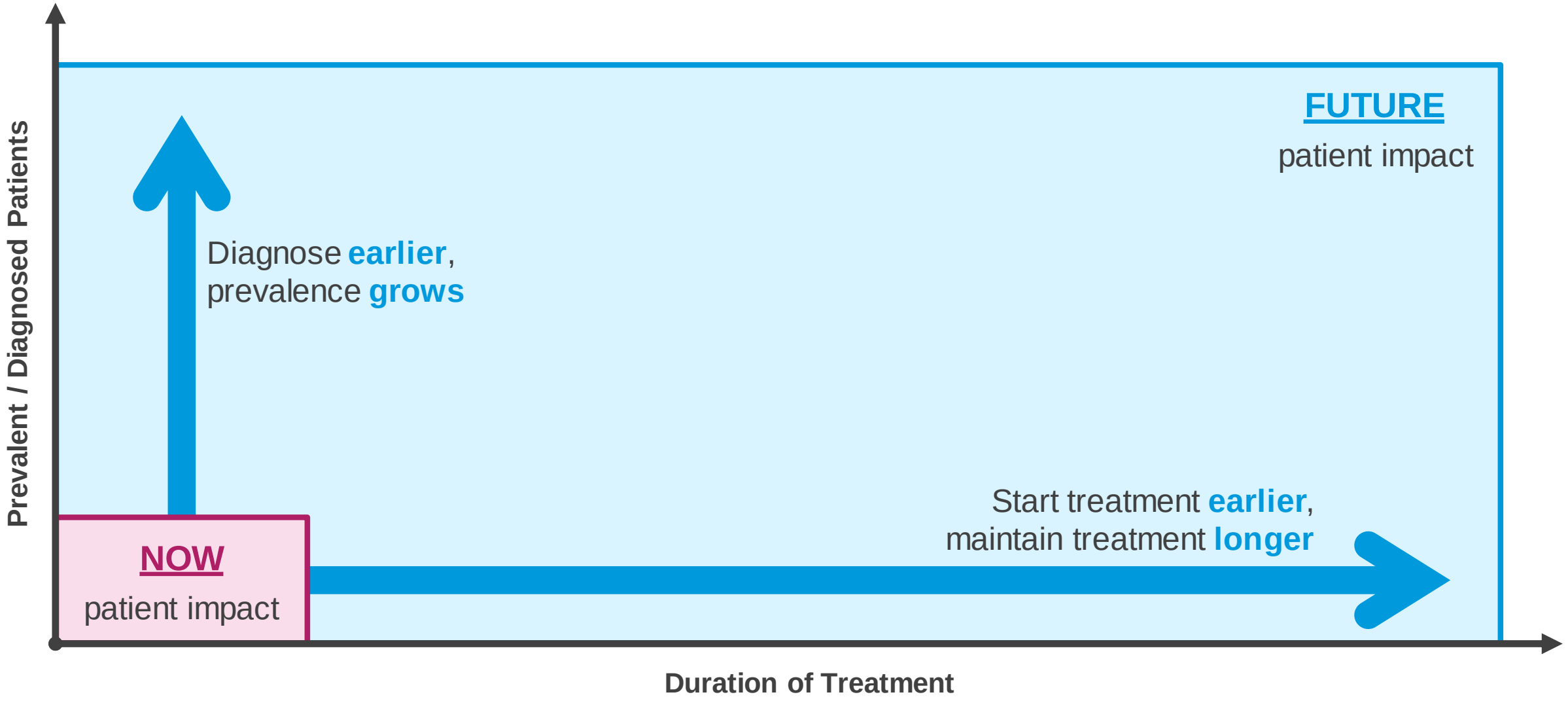
Data Source: Biweekly hATTR Pulse Claims data

1. hATTR patients: Pulse data is a subset of Komodo data. It is focused on hATTR Commercial patients
2. Data Lag: ~ 50% of medical claims data is captured within 2.5 weeks, 80% within 6 weeks; ~ 50% of pharmacy claims data is captured within 1.5 weeks, 87% within 2 weeks

Data as of August 2020

Find More Patients, Start Treatment Earlier, Maintain Longer

With Chronic Treatments, Number of Patients *and* Duration of Treatment Both Important



Building Leading TTR Franchise to Serve Patients for Years to Come

Vision: ONPATTRO® Establishes Strong Foundation; Vutrisiran Achieves Sustainable Market Leadership

Benefits of franchise

Product revenue supports continued investment and innovation in ATTR amyloidosis;

Continuous relationships with KOLs increases efficiency of clinical development;

Vutrisiran launch will utilize global footprint established with ONPATTRO

Patient and physician choice is key

Alnylam aims to provide options for patients and physicians to choose best treatment choice

ONPATTRO will remain an attractive option

Many patients and HCPs will be well served by ONPATTRO and will choose to continue therapy

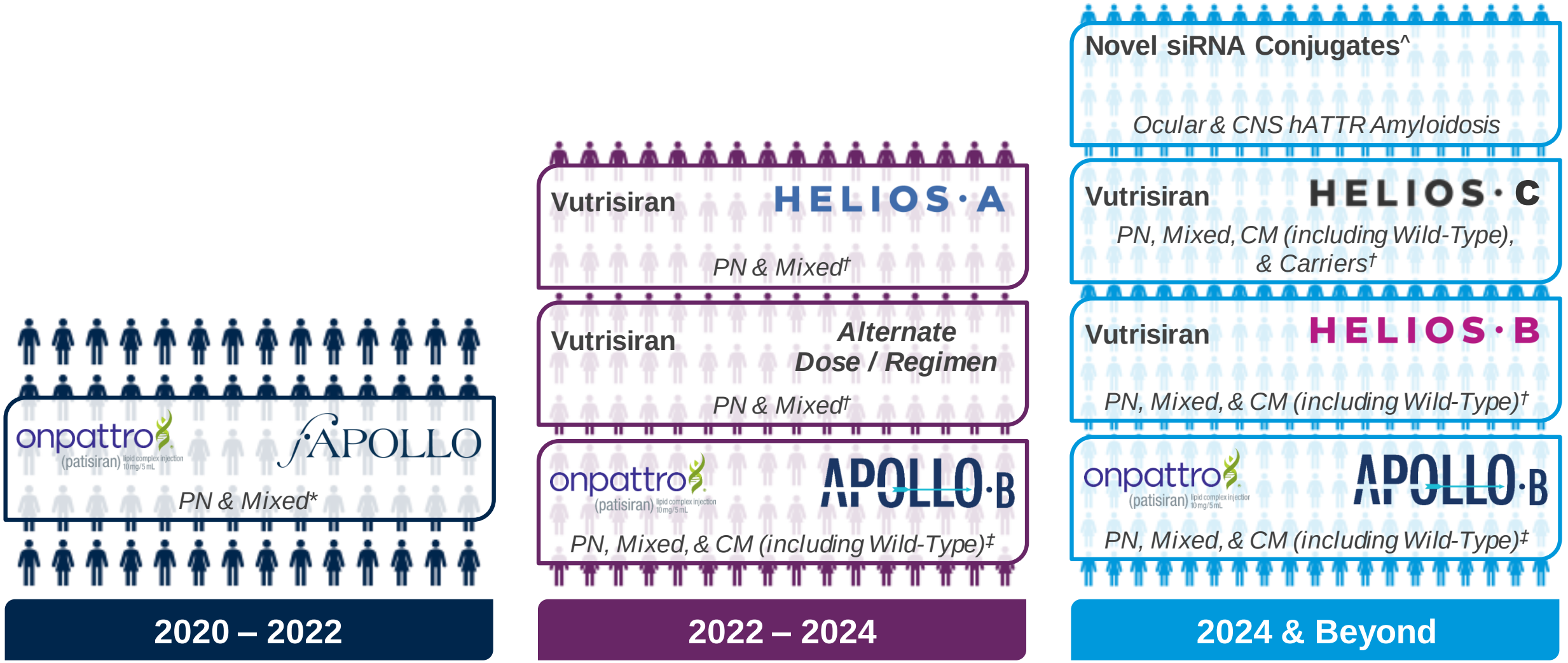
Vutrisiran target profile

Potential to have most competitive product profile (efficacy, safety, quarterly and biannual dosing) of current and emerging therapies

Ensure broad access via continued innovation with payers

Alnylam ATTR Amyloidosis Franchise

Potential to Expand Value to Patients Globally for Many Years to Come



* ONPATTRO is approved in the U.S. and Canada for the treatment of the polyneuropathy of hATTR amyloidosis in adults, in the EU, Switzerland and Brazil for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy; ‡ ONPATTRO has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population

† Vutrisiran is an investigational agent and has not been approved by the FDA, EMA, or any other regulatory agency and no conclusions can or should be drawn regarding its safety or effectiveness; additional studies and future development possible; ^Novel siRNA conjugate development candidates for ocular or CNS hATTR amyloidosis not yet selected.

Intended to be illustrative and not intended to represent specific estimates of patient numbers

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Q&A Session

Upcoming RNAi Roundtables

Givosiran, for the Treatment of Acute Hepatic Porphyria

- Monday, September 14, 1:30 pm ET

Additional details for upcoming RNAi Roundtables, including speakers, dates and times, will be provided on the Capella section of the Company's website, www.alnylam.com/capella

Alnylam PHARMACEUTICALS