Hidden in Plain Sight: Cardiac Amyloidosis as a Cause of Heart Failure

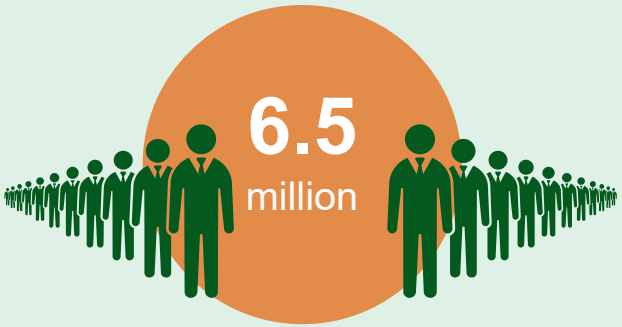
Rahul Deo, MD, PhD
Chief Data Scientist at One Brave Idea
Associate Physician, Brigham and Women's Hospital
Faculty Member in the Department of Medicine at Harvard Medical School

PP-R1D-USA-0595

IMPORTANT INFORMATION

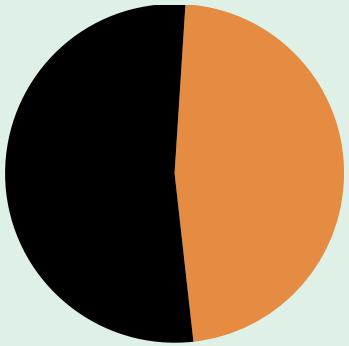
- This is a Pfizer-sponsored nonpromotional program. Moderators have been engaged by Pfizer to share their personal and professional experiences related to population health improvement initiatives within their respective institutions.
- This program does not offer continuing medical education (CME) credit.
- This program will not involve discussion of treatment pathways or specific pharmaceutical products. Any questions about specific Pfizer medications should be directed to your Pfizer account management team at another time. Questions related to certain business operations, health care institution operating expenses, or reimbursement/financial metrics are beyond the scope of this program and will not be discussed.
- Speaker Disclosures:
  - Consultant: Pfizer, Novartis
  - Research funding: Astra-Zeneca, Quest Diagnostics, Verily, Novo Nordisk, Apple, GE Healthcare, Nestle, American Heart Association, NIH/NHLBI

Heart failure (HF) remains the second highest cause of hospital admissions in patients over the age of 65, after septicemia[1]

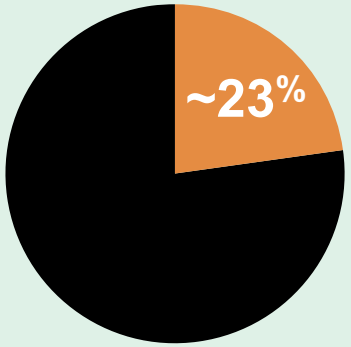


6.5 million people are living with HF in the United States, and this number is expected to rise by 46% by 2030[2,3,*]

The annual cost of HF in the United States is estimated at **$30.7 billion**…[2,3,†]



…over half of which was spent on hospitalizations[2-5]



Approximately **23% of Medicare patients** with a diagnosis of HF were readmitted within 30 days[6]

*American Heart Association (AHA) estimate. †Cost estimates include both direct and indirect costs for treatment and care of patients with HF. Direct costs were estimated to be 68% of total HF costs.[2] Direct costs were estimated using the 2004-2008 Medical Expenditure Panel Survey (MEPS). Indirect costs were estimated based upon per capita work loss and home productivity loss costs, which were attributable to HF based upon estimates from the 2001-2008 MEPS data and a negative bimodal model for annual days of work missed and annual days in bed attributable to illness or injury as a function of HF or other comorbid conditions.[3]

1. McDermott KW, Elixhauser A, Sun R. Trends in hospital inpatient stays in the United States, 2005–2014. HCUP statistical brief #225. 2017. Agency for Healthcare Research and Quality website. www.hcup-us.ahrq.gov/reports/statbriefs/sb225-Inpatient-US-StaysTrends.pdf. Accessed April 2019. **2.** Benjamin EJ, Blaha MJ, Chiuve SE, et al; for the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2017 update: A report from the American Heart Association. *Circulation*. 2017;135(10):e146-e603. **3.** Heidenreich PA, Albert NM, Allen LA, et al; for the American Heart Association Advocacy Coordinating Committee. Forecasting the impact of heart failure in the United States: A policy statement from the American Heart Association. *Circ Heart Fail*. 2013;6(3):606-619. **4.** Go AS, Mozaffarian D, Roger VL, et al; for the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation*. 2013; 127(1):e6-e245. **5.** Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;128:e240-e327. **6.** Dharmarajan K, Wang Y, Lin Z, et al. Association of changing hospital readmission rates with mortality rates after hospital discharge. *JAMA*. 2017;318(3):270-278.

HF can be classified by its impact on cardiac ejection fraction[1]

HF Classification Definitions[1]

Classification	Classification Criteria
HF with reduced ejection fraction **(HFrEF)***	When left ventricular ejection fraction is **less than 40%**
HF with preserved ejection fraction **(HFpEF)†**	When left ventricular ejection fraction is **greater than 50%**

The prevalence of HF characterized as HFpEF appears to be increasing.[2]
Currently, HFpEF is present in approximately half of HF hospitalizations.[2]

*Previously termed systolic heart failure.[1] †Previously termed diastolic heart failure.[1]

1. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;128:e240-e327. **2.** Benjamin EJ, Muntner P, Alonso A, et al; for the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2019 update: A report from the American Heart Association. *Circulation*. 2019;139:e56-e528.

There May Be Underlying Causes of Heart Failure[1]

Common causes of/risk factors for heart failure may include but are not limited to[1,2]:

- Hypertension
- Cardiomyopathy, such as hypertrophic cardiac myopathy (HCM)
- Aging
- Diabetes
- Atrial fibrillation (as a trigger)
- Other, such as cardiac amyloidosis

Most HF patients are in the aging population.[3,*,†]
Patients over 65 with HF present with 6.5 comorbidities on average.
This may complicate presentation, disease course, and treatment.[2]

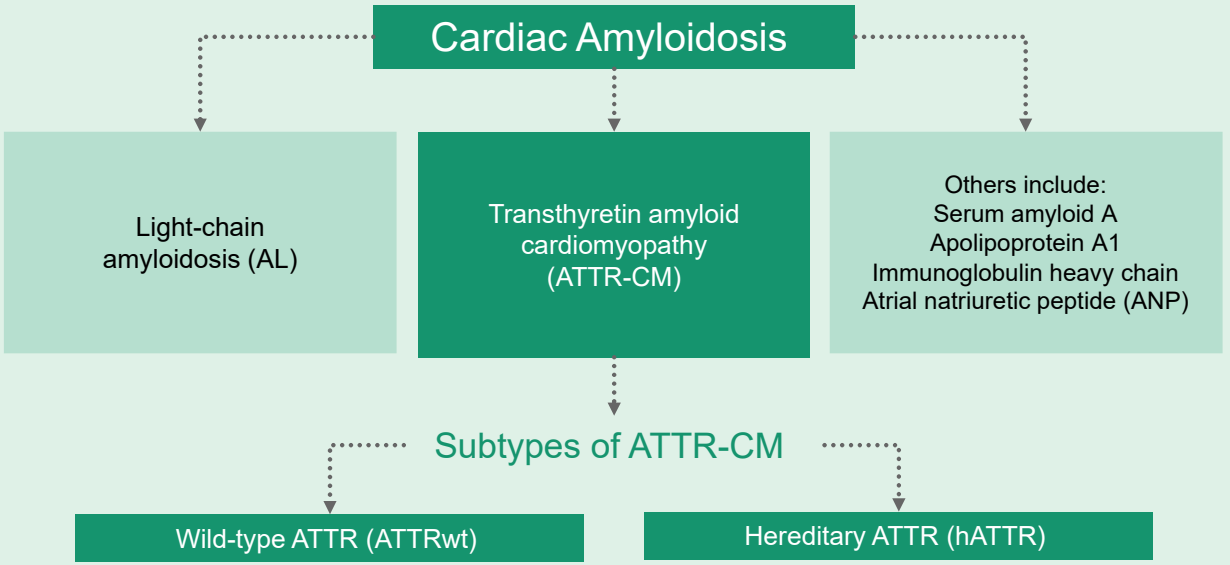
*Up to 80% of patients affected by HF are in the aging population.[3] †Aging population is defined as patients 65 years and older.[3]

1. Witteles RM, Bokhari S, Damy T, et al. Screening for transthyretin amyloid cardiomyopathy in everyday practice. *JACC Heart Fail*. 2019;7(8):709-716. **2.** Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;128:e240-e327. **3.** Hunt SA, Abraham WT, Chin MH, et al. 2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119:e391-e479.

Cardiac amyloidosis (CA) is a rare, fatal, and underdiagnosed group of diseases that lead to HF[1-3]

- CA is an infiltrative cardiomyopathy that occurs due to extracellular deposition of misfolded proteins, known as amyloid fibrils[4,5]
- CA typically presents as HFpEF, eventually progressing to HFrEF[6]

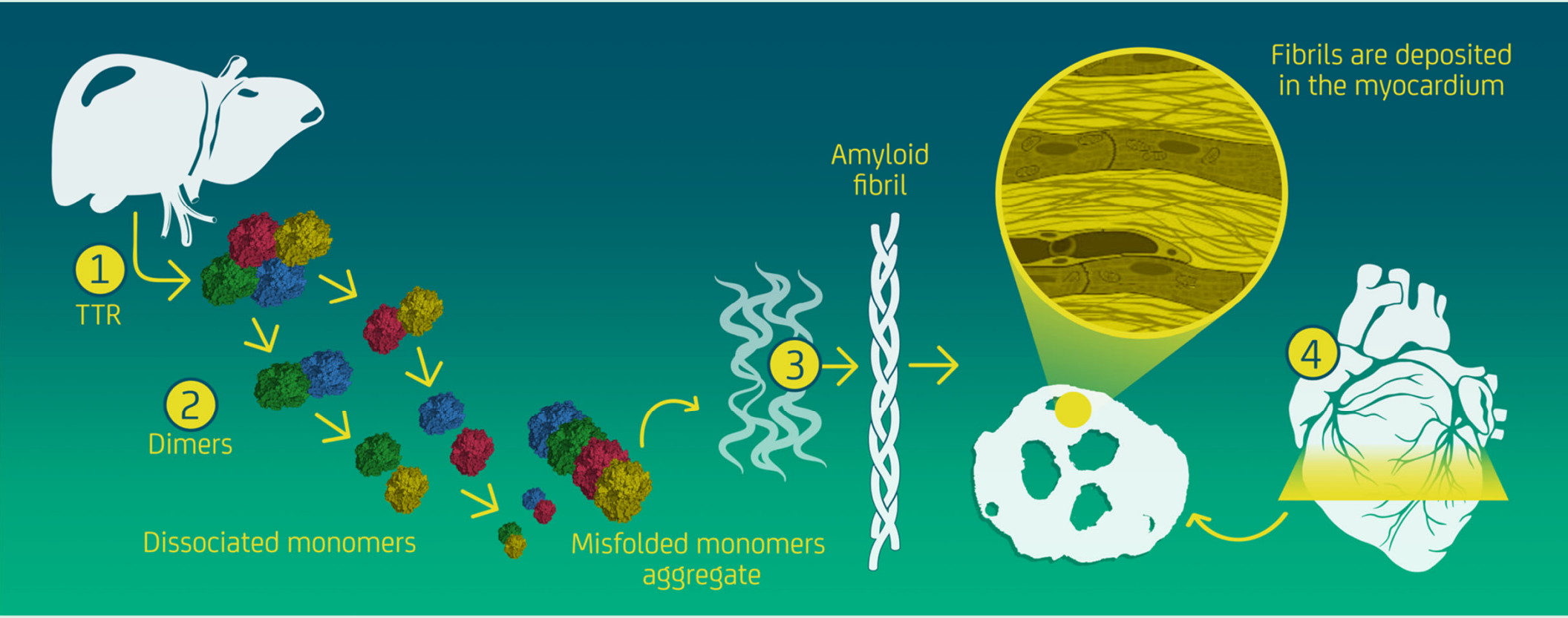
Main types of CA[7-9]



AL and ATTR-CM account for ~95% of all CA diagnoses.[7,8]

1. Kourelis T, Gertz M. Improving strategies for the diagnosis of cardiac amyloidosis. *Expert Rev Cardiovasc Ther*. 2015;13(8):945-961. **2.** Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;128:e240-e327. **3.** Bokhari S, Morgenstern R, Weinberg R, et al. Standardization of 99m technetium pyrophosphate imaging methodology to diagnose TTR cardiac amyloidosis. *J Nucl Cardiol*. 2018;25(1):181-190. **4.** Siddiqi OK, Ruberg FL. Cardiac amyloidosis: an update on pathophysiology, diagnosis, and treatment. *Trends Cardiovasc Med*. 2018;28(1):10-21. **5.** Halwani O, Delgado DH. Cardiac amyloidosis: an approach to diagnosis and management. *Expert Rev Cardiovasc Ther*. 2010;8(7):1007-1013. **6.** Castano A, Drachman BM, Judge D, Maurer MS. Natural history and therapy of TTR-cardiac amyloidosis: emerging disease-modifying therapies from organ transplantation to stabilizer and silencer drugs. *Heart Fail Rev*. 2015;20(2):163-178. **7.** Donnelly JP, Hanna M. Cardiac amyloidosis: an update on diagnosis and treatment. *Cleve Clin J Med*. 2017;84(12 suppl 3):12-26. **8.** Rapezzi C, Lorenzini M, Longhi S, et al. Cardiac amyloidosis: the great pretender. *Heart Fail Rev*. 2015;20:117-124. **9.** Gonzalez-Lopez E, Lopez-Sainz A, Garcia-Pavia P. Diagnosis and treatment of transthyretin cardiac amyloidosis. Progress and hope. *Rev Esp Cardiol*. 2017;70(11):991-1004.

Pathophysiology of ATTR-CM[1]



1. Donnelly JP, Hanna M. Cardiac amyloidosis: an update on diagnosis and treatment. *Cleve Clin J Med*. 2017;84(12 suppl 3):12-26.

Prevalence of ATTR-CM is unknown, but it is believed to be significantly underdiagnosed[1]

Your health system may be underdiagnosing ATTR-CM

50% of patients with HF have HFpEF[2,3]

In 2 studies of older patients with HFpEF, ATTRwt deposits were identified in the hearts of 13%-17% of patients[3,4]

1. Maurer MS, Elliott P, Comenzo R, Semigran M, Rapezzi C. Addressing common questions encountered in the diagnosis and management of cardiac amyloidosis. *Circulation*. 2017;135(14):1357-1377. **2**. Halwani O, Delgado DH. Cardiac amyloidosis: an approach to diagnosis and management. *Expert Rev Cardiovasc Ther*. 2010;8(7):1007-1013. **3.** Gonzalez-Lopez E, Gallego-Delgado M, Guzzo-Merello G, et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J*. 2015;36(38):2585-2594. **4.** Mohammed SF, Mirzoyev SA, Edwards WD, et al. Left ventricular amyloid deposition in patients with heart failure and preserved ejection fraction. *JACC Heart Fail*. 2014;2(2):113-122.

Missed, delayed, and incorrect diagnosis of rare diseases may lead to an inefficient use of resources[1]

Challenges for Diagnosis

Primary care providers (PCPs) are often first to see patients with rare conditions. PCPs may lack the knowledge and confirmatory tests when addressing overlapping patient symptoms, making proper diagnosis of rare conditions difficult[2]

Suboptimal Disease Management

Failure to recognize the correct diagnosis may result in prescription of inappropriate medications and not receiving disease-appropriate medications[1,3]

Frequent Care Points

The average patient with a rare disease requires more than 9 health services, which includes hospitalizations, over a 2-year period[4]

Hospitalizations remain a main driver of direct and indirect health care costs[5]

Rising Costs and Resources

Proper diagnosis and management of a rare disease requires flexibility, personalization, and coordination through a multidisciplinary treatment approach.[4,6]

1. Sarkar U, Bonacum D, Strull W, et al. Challenges of making a diagnosis in the outpatient setting: a multi-site survey of primary care physicians. *BMJ Qual Saf.* 2012;21(8):641-648. **2.** Gainotti S, Mascalzoni D, Bros-Facer V, et al. Meeting patients' right to the correct diagnosis: ongoing international initiatives on undiagnosed rare diseases and ethical and social issues. *Int J Environ Res Public Health.* 2018;15:2072. **3.** Falk RH. Diagnosis and management of the cardiac amyloidoses. *Circulation.* 2005;112:2047-2060. **4.** Castro R, et al. Bridging the Gap between Health and Social Care for Rare Diseases: Key Issues and Innovative Solutions. In: Posada de la Paz M, Taruscio D, Groft SC (eds) *Rare Diseases Epidemiology: Update and Overview*, 2nd ed. Advances in Experimental Medicine and Biology, vol 1031. Cham, Switzerland: Springer Nature; 2017: 604-627. **5.** Shafie AA, Tan YP, Ng CH. Systematic review of economic burden of heart failure. *Heart Fail Rev.* 2018;23:131-145. **6.** Elliot EJ, Zurynski YA. Rare diseases are a 'common' problem for clinicians. *Aust Fam Physician.* 2015;44(9):630-633.

A sample patient affected by wild-type ATTR (ATTRwt) who presents to the clinic for evaluation and treatment*

Chief Complaint
A 68-year-old Caucasian male reports **dyspnea on exertion** that has been getting progressively worse over the last 3 years. He thought he was just "slowing down."

Past Medical History: **History of atrial fibrillation**, 4 years ago

Past Surgical History: **Carpal tunnel release**, about 10 years ago; **left knee total replacement**, 4 years ago

Medications: Daily vitamin, baby aspirin

Allergies: No known drug allergies

Review of Systems: No headaches, reports no chest pain, **notes some weakness in his hands bilaterally**, no change in sleeping, normal stooling and voiding

Vitals: BMI 31, **mildly hypotensive**, heart rate of 75

During the clinical encounter, various signs and symptoms can raise suspicion for ATTR-CM, many of which are signs of HF.[1]

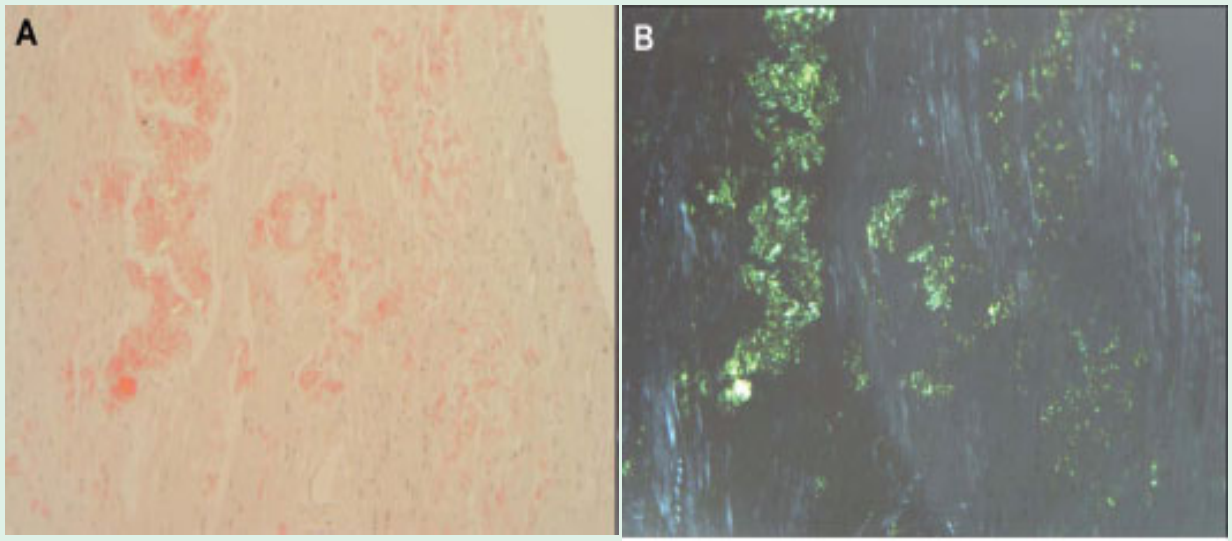
*Representative case for illustrative purposes only.

1. Tuzovic M, Yang E, Baas AS, et al. Cardiac amyloidosis: diagnosis and treatment strategies. *Curr Oncol Rep*. 2017;19(7):1-11.

Confirming Suspicion of ATTR-CM: Invasive Techniques[1-3]

Cardiac Tissue Biopsy

- Document the extent of amyloid infiltration
- Provide definitive etiologic classification of the amyloidogenic protein
- Achieve a definitive classification to help rule out AL amyloidosis



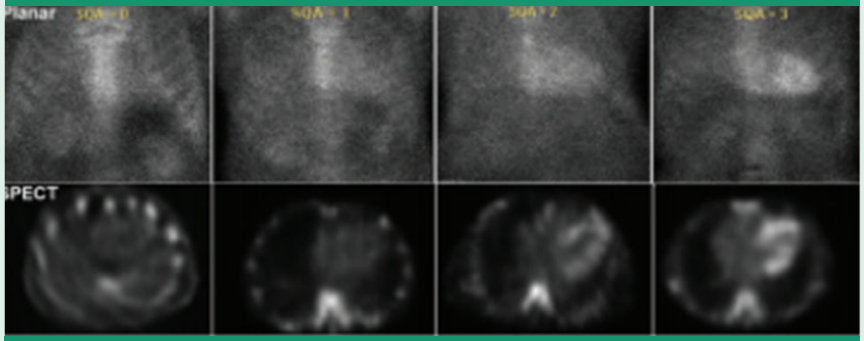
Reprinted with permission from Ruberg FL and Berk JL. Transthyretin (TTR) cardiac amyloidosis. *Circulation.* 2012;126(10):1286-1300. https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.111.078915. Published by American Heart Association.[3]

1. Maurer MS, et al. Circulation. 2017;135:1357-1377. **2**. Gillmore JD, et al. Circulation. 2016;133:2404-2412. **3.** Ruberg FL and Berk JL. Circulation. 2012;126:1286-1300.

ASNC Practice Points highlight the importance of PYP cardiac imaging in diagnosing ATTR-CM noninvasively for select patients[1]

Nuclear scintigraphy is a highly sensitive diagnostic imaging technique that displays increased cardiac uptake of a radiotracer, indicating the presence of ATTR[2,3]

Grading ^{99m}Tc-PYP Uptake on Planar and SPECT Images[1]

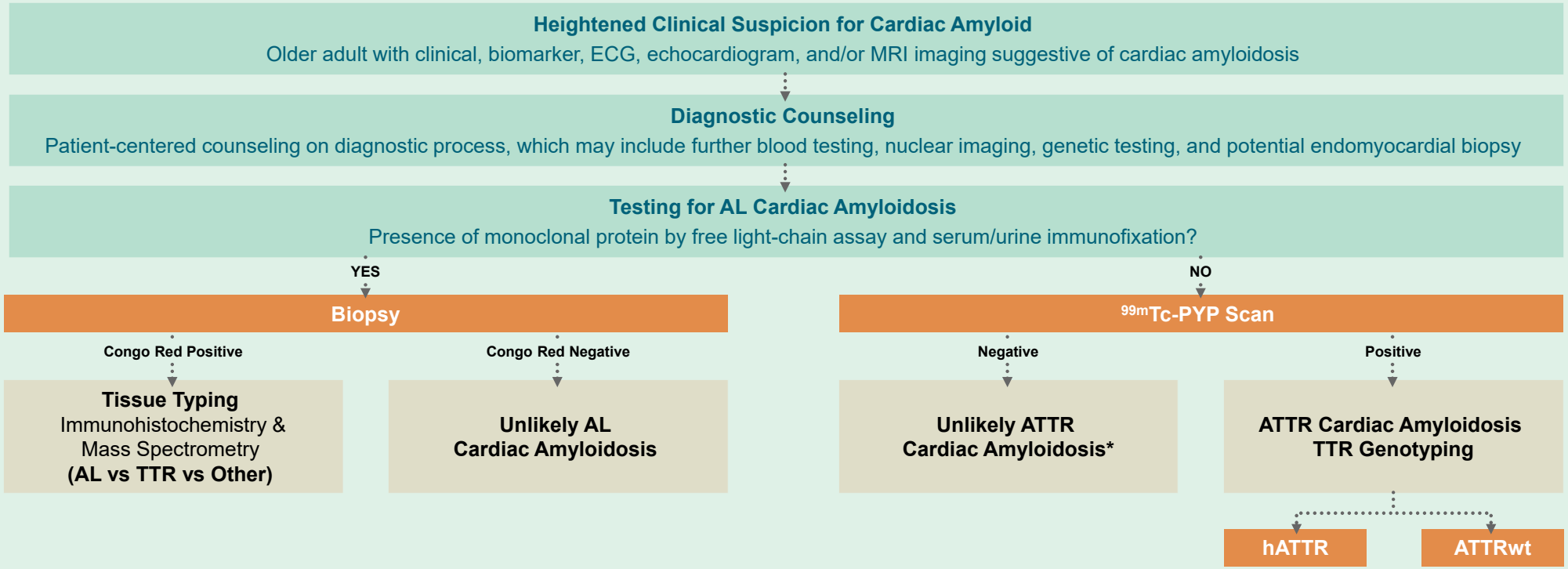


Grade 0: Myocardial uptake absent
Grade 1: Myocardial uptake < rib
Grade 2: Myocardial uptake = rib
Grade 3: Myocardial uptake > rib

Both planar and SPECT imaging should be reviewed and interpreted using visual and quantitative approaches, irrespective of the timing acquisition. SPECT imaging is necessary for studies that show planar myocardial uptake because it can help differentiate myocardial uptake from blood pool or overlying bone uptake.

1. Dorbala S, Bokhari S, Miller E, et al; for the American Society of Nuclear Cardiology. 99m technetium-pyrophosphate imaging for transthyretin cardiac amyloidosis. ASNC Practice Points. Available at: https://www.asnc.org/files/19110%20ASNC%20Amyloid%20Practice%20Points%20WEB(2).pdf. Updated February 2019. Accessed April 2019. **2.** Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation*. 2016;133:2404-2412. **3.** Castano A, Haq M, Narotsky DL, et al. Multicenter study of planar technetium 99m pyrophosphate cardiac imaging: predicting survival for patients with ATTR cardiac amyloidosis. *JAMA Cardiol*. 2016;1(8):880-889.

A diagnostic algorithm that provides an invasive and noninvasive diagnostic approach[1]



*If clinical suspicion remains for cardiac amyloidosis despite negative ^{99m}Tc-PYP scan, biopsy may be considered to evaluate for other types of infiltrative cardiomyopathy (eg, AA).

1. Brunjes DL, Castano A, Clemons A, et al. Transthyretin cardiac amyloidosis in older Americans. *J Card Fail.* 2016;22(12):996-1003.

Suspecting and diagnosing ATTR-CM allows patients and HCPs to choose an appropriate management plan

MOA of current and investigational pharmacological agents to address the underlying protein misfolding disorder[1]

TTR Stabilizers	TTR Silencers	Fibril Disruptors
Stabilize the TTR protein, which slows breakdown and formation of fibrils	Target the liver to prevent the production of the TTR protein[2]	Break up ATTR amyloid fibrils that have been deposited

Another option in select patients may include heart or heart/liver transplantation

1. Donnelly JP, Hanna M. Cardiac amyloidosis: an update on diagnosis and treatment. *Cleve Clin J Med*. 2017;84(12 suppl 3):12-26. **2.** Dubrey SW, Davidoff R, Skinner M, Bergethon P, Lewis D, Falk RH. Progression of ventricular wall thickening after liver transplantation for familiar amyloidosis. *Transplantation*. 1997;64(1):74-80.

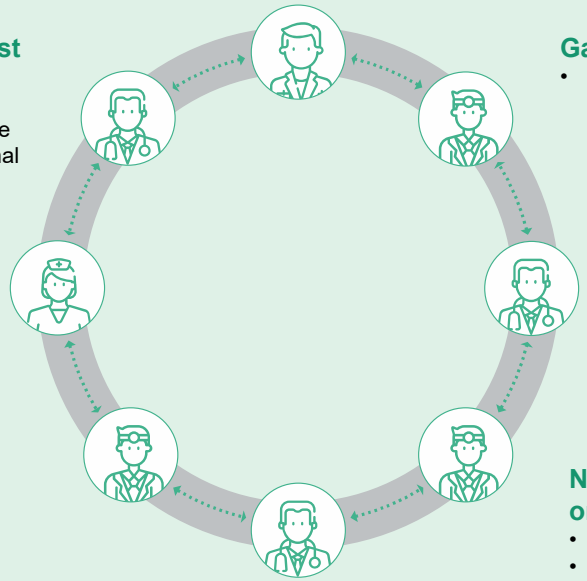
A multidisciplinary approach includes a variety of specialists across the care continuum to differentiate, diagnose, and manage ATTR-CM

Primary Care Physician
- Recognize the clinical presentation and signs and symptoms of ATTR-CM
- Refer to cardiologist for further evaluation

Orthopedist
- Recognize the noncardiac orthopedic clinical clues that may be present in patients with ATTR-CM (eg, carpal tunnel syndrome, hip/knee arthroplasty, biceps tendon rupture, lumbar spinal stenosis)

Gastroenterologist
- Recognize clinical presentation of common gastrointestinal symptoms that may be present in patients with ATTR-CM

Genetic Counselor
- Provide counseling to patients and families about genetic testing and screening



Cardiologist
- Recognize the clinical presentation and clinical clues of ATTR-CM
- Integrate PYP testing into the diagnostic algorithm for patients with suspected ATTR-CM after ruling out AL

Neurologist
- Awareness of the noncardiac neurologic clinical clues that may be present in patients with ATTR-CM (ie, autonomic neuropathy, orthostatic hypotension, peripheral neuropathy, and peripheral sensory motor dysfunction)

Nuclear Cardiologist, Nuclear Medicine Specialist, or Radiologist
- Recognize proper PYP cardiac imaging procedure
- Standardize testing protocols and reporting

Hematologist
- Recognize the diagnostic workup for ATTR-CM in patients referred with abnormal monoclonal protein
- Evaluate patients with abnormal monoclonal protein

Health systems may drive awareness, diagnosis, and management of ATTR-CM to advance health outcomes and quality of life for patients

Disease Burden and Unmet Need

Increase awareness of ATTR-CM as an underdiagnosed and fatal cause of HF

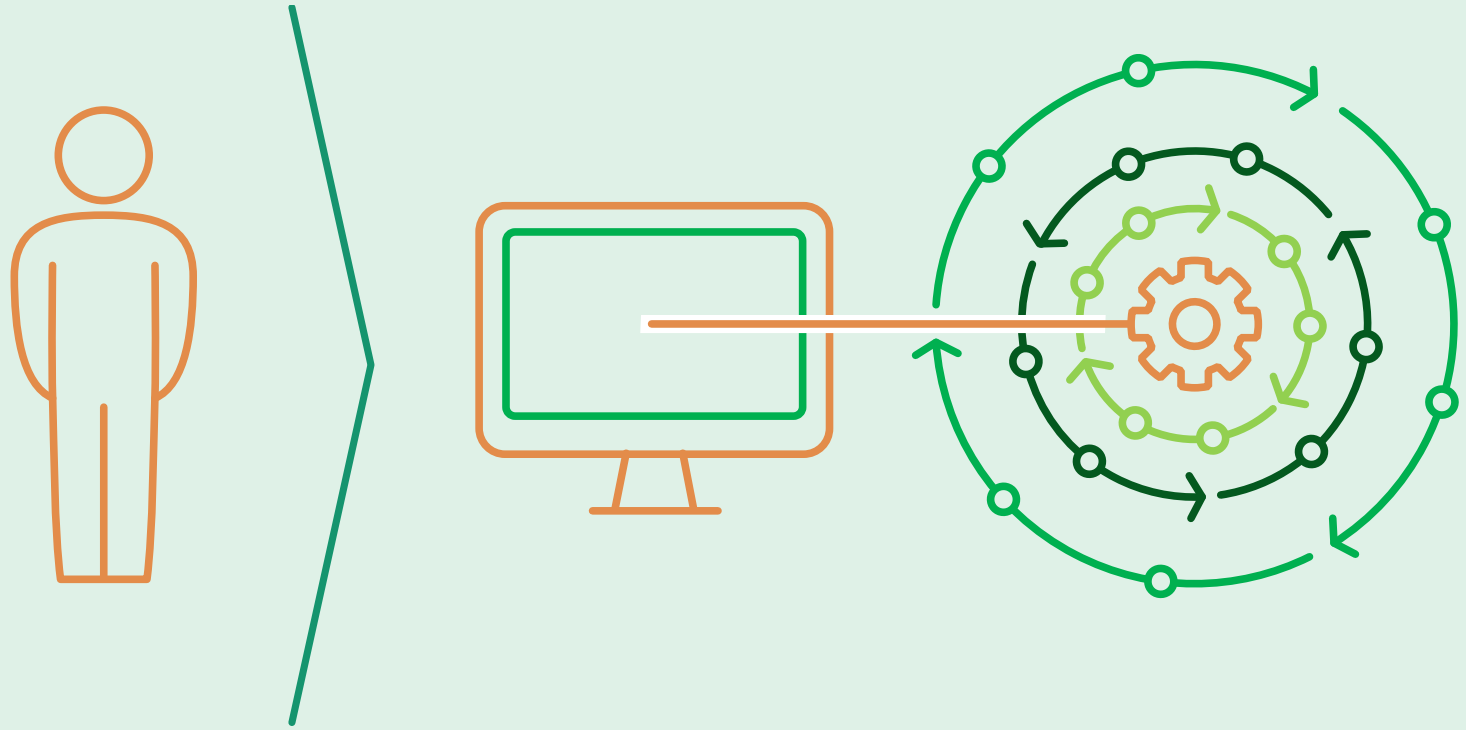
Suspicion and Diagnosis

Improve suspicion and diagnosis of ATTR-CM in a systemic manner within the organization

Management

Drive action by encouraging systemic ATTR-CM management to advance heart failure outcomes and quality measures

Rare Causes of Heart Failure: Can AI Technology Help?



1. Deo RC. Machine learning in medicine. *Circulation.* 2015;132:1920-1930

Can we build systems where providers have AI support to detect these diseases?

Input

- Diagnostic codes
- Structured data from ECG, echocardiogram
- Laboratory values
- ECG voltage tracing
- Echocardiogram images

Algorithm

- Decision tree
- Logistic regression
- Random forest
- Convolutional neural network (“deep learning”)

Output

- Probability of ATTR
- Probability of AL
- Joint probability of all cardiac amyloid
- Probability of HCM
- Probability of PAH

Decisions

- Follow-up diagnostic testing (eg, PYP, serum free light chains)
- Markers of cardiac risk (eg, NT-proBNP, TnI)

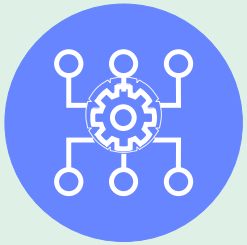
HCM, hypertrophic cardiomyopathy; PAH, pulmonary arterial hypertension; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; TnI, cardiac troponin I.

1. Deo RC. Machine learning in medicine. *Circulation.* 2015;132:1920-1930. **2.** Zhang J, Gajjala S, Agrawal P, et al. Fully automated echocardiogram interpretation in clinical practice: feasibility and diagnostic accuracy. *Circulation*. 2018;138:1623-1635. **3.** Tison GH, Zhang J, Delling FN, Deo RC. Automated and interpretable patient ECG profiles for disease detection, tracking, and discovery. *Circ Cardiovasc Qual Outcomes.* 2019;12(9):e005289. doi: 10.1161/CIRCOUTCOMES.118.005289.

Challenges with introducing automated systems

Input

- Is the input (eg, chest x-ray, echocardiogram) ordered frequently at an early treatable stage?
- Are the inputs consistent across institutions?
- Are there APIs to pull data (cost)?
- Can we access data without disrupting clinical workflow?



Algorithm

- How high of a positive predictive value do we need?
- How computationally demanding is preprocessing the data and deploying the model?
- Will models trained in one system generalize to another?

Output

- How should the results be presented?
- Does the provider need to see the “evidence” behind the recommendation?

Decisions

- Who will see the result?
- Do they have the expertise to make follow-up decisions?
- Can remote assistance be deployed to facilitate follow-up testing, prior authorizations?
- How to avoid adding to provider burnout generated by more pop-ups?

Upcoming!

Live Forum – March 26, 2020, in San Diego, CA

Rare Causes of Heart Failure: Can AI Technology Help?

An ATTR-CM Case Study

Rahul Deo, MD, PhD, cardiologist and data analytics expert from Brigham and Women's Hospital (a Harvard-affiliated Partners HealthCare hospital), will review transthyretin amyloid cardiomyopathy (ATTR-CM), a rare, fatal, and underdiagnosed disease that can lead to heart failure. Patients affected by ATTR-CM often go years without a diagnosis and may cycle through multiple physicians and health systems. Artificial intelligence (AI) may lead to new approaches to identify at-risk patients. Dr Deo will discuss how AI may be employed to help systems identify patients affected by rare diseases, like ATTR-CM. Following this discussion, attendees will participate in a Q&A session where Dr Deo will facilitate a discussion regarding potential approaches to leveraging technology to detect rare diseases within their health care systems.

Featuring:

Rahul Deo, MD, PhD
Associate Physician,
Brigham and Women's Hospital
Email: Rahul.c.deo@gmail.com
Phone: 617-732-8302