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Yevgeniy Brailovsky

Indranee Rajapreyar

Rene Alvarez

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GUEST EDITOR'S PAGE



TTR Amyloidosis

Current State of Affairs and Promise for the Future



Yevgeniy Brailovsky, DO, MSc, Indranee Rajapreyar, MD, Rene Alvarez, MD

Transthyretin amyloidosis (ATTR) is instigated when a transthyretin (TTR) protein, which is normally produced by the liver, pathologically misfolds, aggregates into amyloid fibrils, and deposits in various tissues causing irreversible damage. Cardiac ATTR has historically been considered a medical zebra. It was thought to be a rare disease that required invasive testing for diagnosis and was associated with poor outcomes without specific therapies. Incredible recent advances in the field of ATTR now allow for rapid noninvasive assessment in most patients, and we can offer specific disease-modifying treatments, leading to improved functional outcomes and prolonged survival.

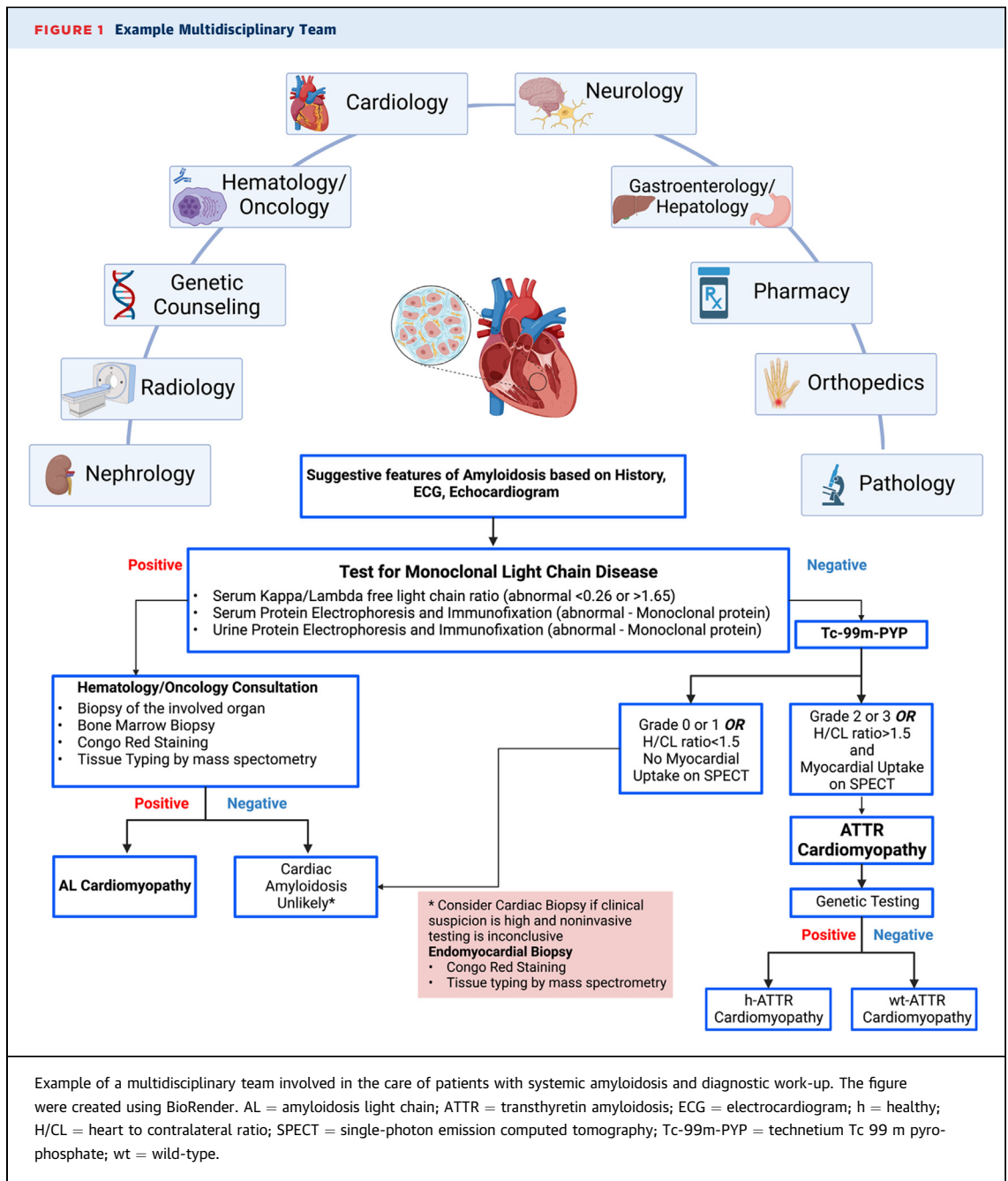
Once thought to be uncommon, we now recognize that cardiac ATTR occurs in up to 14% of patients with heart failure with preserved ejection fraction,^{1,2} 16% of patients with aortic stenosis undergoing transcatheter aortic valve replacement,³ and 19% of patients with severe mitral regurgitation undergoing mitral transcatheter edge-to-edge repair.⁴ Additionally, many patients with bilateral carpal tunnel syndrome (10%-16%) and lumbar spinal stenosis (13%-21%) have amyloidosis in the surgical specimens and will develop cardiac involvement.⁵⁻⁷ More so, 3%-4% of African Americans are carriers of the most common sequence variant (Val142Ile) and are at risk for developing ATTR.⁸ Wild-type ATTR is probably more common than we thought, with 25% of patients over 80 years of age having evidence of amyloid deposits on autopsy.⁹

Systemic involvement of the disease requires the expertise of multiple specialties to assess

and treat various manifestations. Some centers have elected to form multidisciplinary teams to promote awareness of the disease and help standardize the care of these complex patients (Figure 1). Unfortunately, such centers of excellence are still limited to large academic centers, and access to care for patients is still limited across the country.

TRAINING AND EDUCATION

Increased recognition of ATTR has placed a significant focus on clinical training to improve future patient care access. Because cardiac amyloidosis can manifest with heart failure, valvular heart disease, and arrhythmias, it is critical to incorporate ATTR into the clinical training of general cardiologists, electrophysiologists, advanced imaging specialists, interventional cardiologists, and advanced heart failure cardiologists. Without large randomized controlled trials to guide us in specific clinical scenarios, a multidisciplinary approach is helpful for diagnostic work-up and nuanced management strategies. The 2022 American College of Cardiology, American Heart Association, and Heart Failure Society of America heart failure guidelines, for the first time, include an expanded section on the diagnosis and management of ATTR cardiomyopathy.¹⁰ The editors of *JACC: Case Reports* have also recognized the significance of ATTR, and there have been more than 20 manuscripts dedicated to the unique challenges of diagnosing and managing patients with ATTR since the journal's inception. Increased awareness of the disease and educational campaigns have led to a substantial increase in the diagnosis of ATTR cardiomyopathy. Patients are now identified at an earlier stage of the disease when treatments could be more effective. The median duration of symptoms before diagnosis has



decreased from 36 months (2002-2006) to 12 months (2017-2021).¹¹

DIAGNOSIS

Diagnosis is often delayed because of a misconception that ATTR is a rare disease and heterogeneity of clinical presentation. Diagnosis relied on pathological examination of affected organs, but

this can be avoided in most patients in the current era. The introduction of advanced echocardiographic techniques, cardiac magnetic resonance, and excellent diagnostic performance of bone scintigraphy has allowed accurate identification of cardiac ATTR in most patients. We can reliably rule out light chain amyloidosis with highly sensitive serum-free light chain assays and protein immunofixation.¹²

One important caveat when using bone scintigraphy for diagnosing ATTR is that planar imaging must always be accompanied by single photon-emission computed tomography to verify myocardial uptake instead of uptake within the blood pool.¹³ Another vital consideration for accurate diagnosis is excluding light chain amyloidosis, which can have a similar symptomatic presentation but is associated with a significantly worse prognosis and requires chemotherapy-based treatment. Genetic testing should be performed to exclude variant type ATTR, which requires family screening and has therapeutic implications, as discussed herein. Overall, the diagnosis requires a high index of suspicion. Several systemic features may alert the clinician to assess for ATTR, such as heart failure with preserved ejection fraction, increased left ventricular thickness with disproportionately normal or low voltage on electrocardiogram, atrial arrhythmias, carpal tunnel syndrome, lumbar spinal stenosis, peripheral neuropathy, autonomic dysfunction, or unexplained gastrointestinal or genitourinary complaints (Figure 2).

MEDICAL CARE

There has been a tremendous advancement in therapeutic options available for patients with ATTR. In the last 5 years, we went from no available treatments to several US Food and Drug Administration (FDA)-approved therapies with specific ATTR targets to improve functional outcomes and prolong survival (Figure 3). Clinical trials were conducted based on specific organ involvement, such as polyneuropathy or cardiomyopathy. U.S. FDA approval of these drugs is particular to the organ system for which the drug was tested. Tafamidis, a TTR stabilizer, was evaluated in patients with cardiac ATTR amyloidosis (wild-type and variant) and demonstrated a significant reduction in mortality (HR: 0.70; 95% CI: 0.51-0.96) and reduced cardiovascular-related hospitalization (risk ratio: 0.68; 95% CI: 0.56-0.81).¹⁴ Another stabilizer, acromadis (AG10), is currently being investigated for ATTR cardiomyopathy.¹⁵ Liver transplantation has historically been the only option to reduce TTR production and alter the course of the disease. RNA silencers work by inhibiting TTR production in the liver and largely supplanted the need for liver transplantation. Multiple agents were evaluated in patients with hereditary ATTR-associated polyneuropathy. Inotersen, patisiran, and vutrisiran all demonstrated significant improvement in neuropathy impairment scores and are all U.S. FDA approved for hereditary ATTR-

associated polyneuropathy.¹⁶⁻¹⁸ Gene editing technology, CRISPR-CAS9, is a Nobel Prize-winning technology that is quickly gaining attention as a potential game changer for otherwise incurable genetic diseases. NTLA 2001 (Intellia Therapeutics and Regeneron Pharmaceuticals) is a CRISPR-CAS9-based in vivo gene editing platform that has shown promise as a possible cure in phase 1 clinical trial of patients with ATTR polyneuropathy.¹⁹

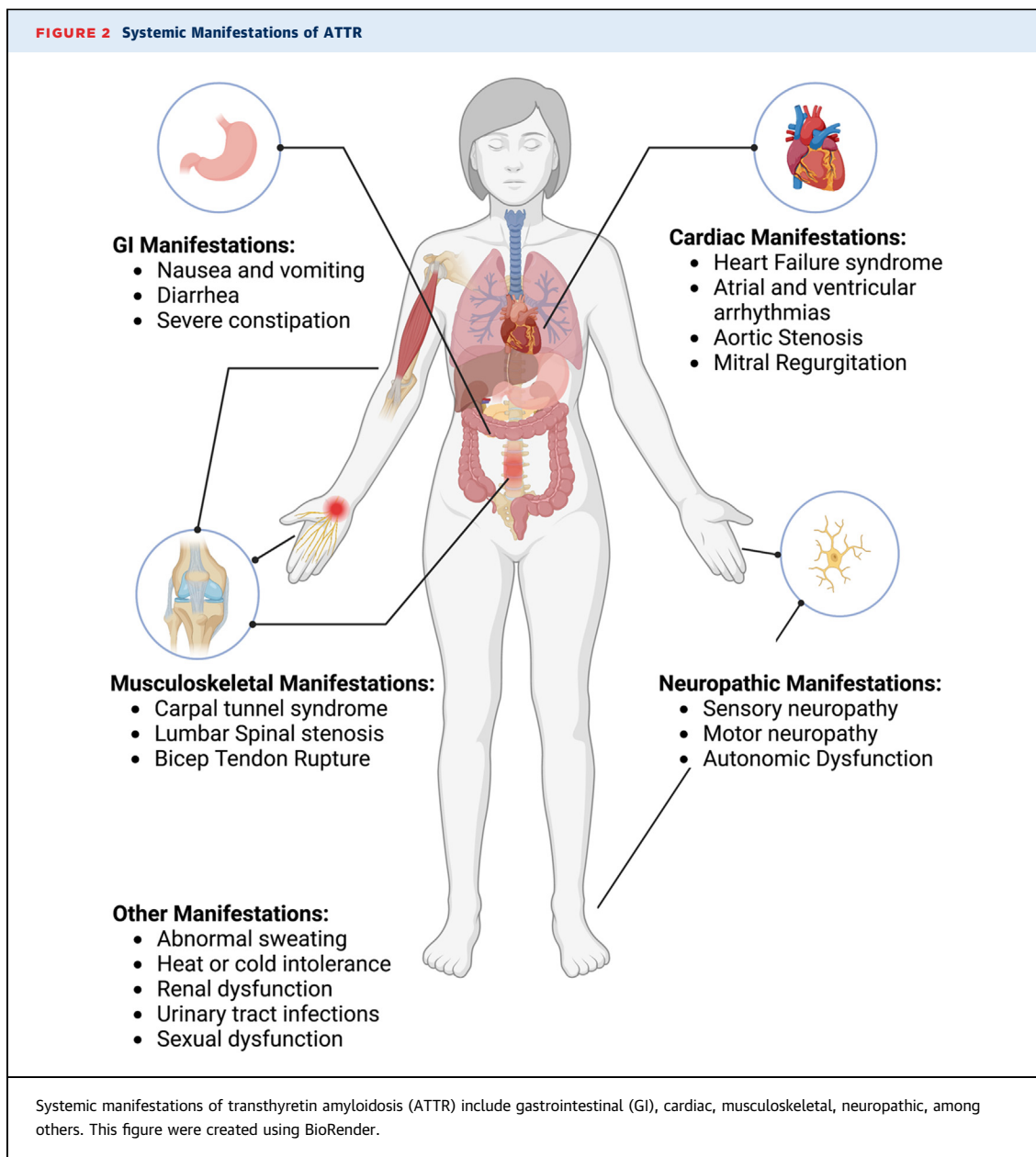
Available data suggest that patients with concomitant valvular disease and cardiac amyloidosis tend to benefit from transcatheter aortic valve replacement and transcatheter edge-to-edge repair.^{3,4} In selected patients with advanced cardiomyopathy without significant extracardiac manifestations, cardiac transplantation is associated with excellent outcomes.²⁰

FUTURE DIRECTIONS

Despite incredible advances in therapeutics, access remains an issue because of the high cost. The current price of tafamidis is \$225,000 per year, and the cost of RNA silencers are around \$450,000 per year.²¹ A recent cost analysis demonstrated that a 92.6% price reduction to \$16,563 per year would be necessary to make tafamidis cost-effective at \$100,000 per quality-adjusted life-year.^{21,22}

Whereas RNA silencers are only approved for ATTR-associated polyneuropathy, ongoing studies are evaluating RNA silencers for cardiac ATTR and are showing promise. Other therapies being evaluated are monoclonal antibodies against misfolded TTR protein, which can bind to monomeric and misfolded TTR, targeting them for degradation and thus inhibiting amyloid production.^{23,24}

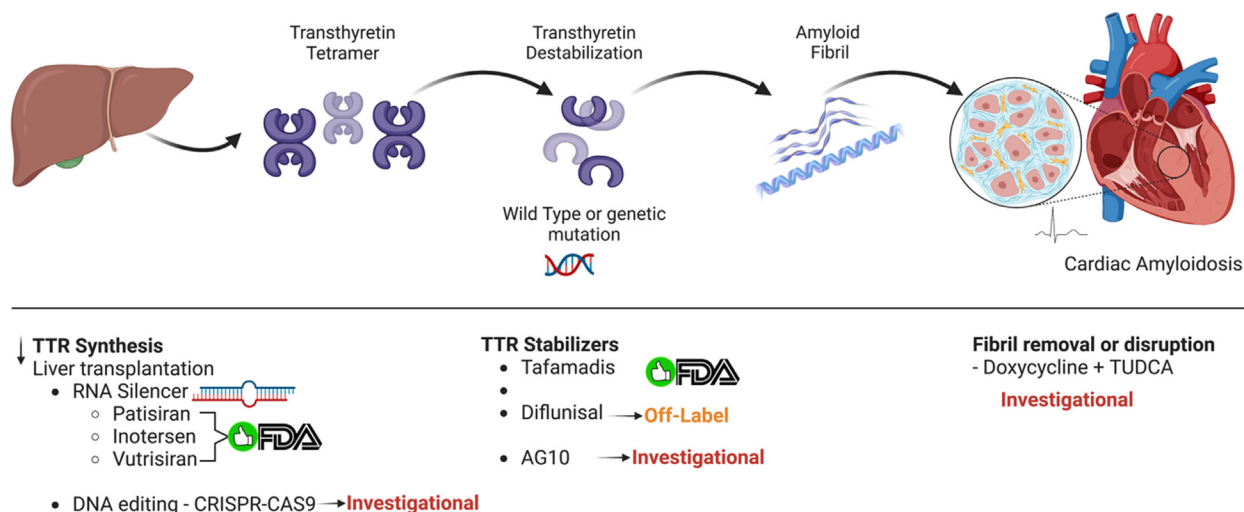
Currently, approved therapies are only available for patients with an established diagnosis of ATTR cardiomyopathy or polyneuropathy, but there is a substantial number of people who carry pathogenic mutations who are at risk of developing this debilitating disease. The goal is to initiate therapy early in the disease course when it is associated with the greatest benefit.¹⁴ The holy grail of therapy for ATTR is to initiate treatment before the phenotypic manifestations. The potential promise of CRISPR-CAS9 may offer a cure for patients with a genetic predisposition. We can also test already approved therapies in this patient population, but this may be limited by the current high cost and need for a large sample size to demonstrate effectiveness. Alternatively, diflunisal, which has shown benefit but is currently used off-label in patients with ATTR, can be tested in patients with a genetic predisposition. For other



patients, further work is needed to identify ATTR at an earlier stage of the disease. For example, orthopedic manifestations usually precede cardiac involvement by 5 to 10 years. Some centers routinely send specimens to pathology for Congo red staining and amyloid typing from carpal tunnel release surgery and lumbar spinal stenosis to identify ATTR, but unfortunately, this is not the standard of care.⁵⁻⁷ If we can identify the disease at that stage and initiate therapy, we can potentially prevent cardiac manifestations, but this remains to be proven in a prospective trial. Because of the increased prevalence of

ATTR in patients with heart failure with preserved ejection fraction, atrial fibrillation, aortic stenosis undergoing transcatheter aortic valve replacement, and severe mitral regurgitation undergoing transcatheter edge-to-edge repair, some centers are routinely screening these patients for ATTR cardiomyopathy, but this is not the standard of care. Perhaps we need to incorporate such recommendations into future societal guidelines. There is also emerging data on the use of machine learning to systematically identify cardiac amyloidosis in patients with heart failure.²⁵

FIGURE 3 Pathophysiology and Therapeutic Targets of Systemic ATTR



Pathophysiology and therapeutic targets of systemic transthyretin amyloidosis (ATTR) are shown. This figure were created using BioRender. TTR = transthyretin; TUDCA = tauroursodeoxycholic acid.

CONCLUSIONS

We once considered ATTR amyloidosis a medical zebra, but it is a horse dressed in zebra clothes. With expanded educational campaigns from multiple societies and advancements in noninvasive diagnostic strategies, we recognize that ATTR cardiac amyloidosis is more common than previously was thought. Approval of several disease-specific effective therapeutic agents makes diagnosing ATTR promptly and initiating therapy more important than ever.

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ADDRESS FOR CORRESPONDENCE: Dr Yevgeniy Brailovsky, Jefferson Heart Institute, Thomas Jefferson University Hospital, 833 Chestnut Street, Philadelphia, Pennsylvania 19107, USA. E-mail: Yevgeniy.brailovsky@jefferson.edu. Twitter: [@YevgeniyBr](https://twitter.com/YevgeniyBr).

REFERENCES

- Hahn VS, Yanek LR, Vaishnav J, et al. Endomyocardial biopsy characterization of heart failure with preserved ejection fraction and prevalence of cardiac amyloidosis. *Heart Fail*. 2020;8(9):712-724.
- González-López 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.
- Castano A, Narotsky DL, Hamid N, et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J*. 2017;38(38):2879-2887.
- Elgendy IY, Elbadawi A. Transcatheter edge-to-edge repair of the MV among patients with cardiac amyloidosis: ready for prime time? *Cardiovasc Interv*. 2022;15(17):1759-1761.
- Godara A, Riesenburger RI, Zhang DX, et al. Association between spinal stenosis and wild-type ATTR amyloidosis. *Amyloid*. 2021;28(4):226-233.
- Westin O, Fosbøl EL, Maurer MS, et al. Screening for cardiac amyloidosis 5 to 15 years after surgery for bilateral carpal tunnel syndrome. *J Am Coll Cardiol*. 2022;80(10):967-977.
- Maurer MS, Smiley D, Simsolo E, et al. Analysis of lumbar spine stenosis specimens for identification of amyloid. *J Am Geriatr Soc*. 2022;70(12):3538-3548.
- Quarta CC, Buxbaum JN, Shah AM, et al. The amyloidogenic V122I transthyretin variant in elderly black Americans. *N Engl J Med*. 2015;372(1):21-29.
- Tanskanen M, Peuralinna T, Polvikoski T, et al. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: a population-based autopsy study. *Ann Med*. 2008;40(3):232-239.
- Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79(17):e263-e421.
- Ioannou A, Patel RK, Razvi Y, et al. Impact of earlier diagnosis in cardiac ATTR amyloidosis over the course of 20 years. *Circulation*. 2022;146:1657-1670.
- Gillmore JD, Maurer MS, Falk RH, et al. Non-biopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation*. 2016;133(24):2404-2412.

13. Poterucha TJ, Elias P, Bokhari S, et al. Diagnosing transthyretin cardiac amyloidosis by technetium Tc 99m pyrophosphate: A test in evolution. *J Am Coll Cardiol Img.* 2021;14(6):1221-1231.
14. Maurer MS, Schwartz JH, Gundapaneni B, et al, ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med.* 2018;379(11):1007-1016.
15. Judge DP, Heitner SB, Falk RH, et al. Transthyretin stabilization by AG10 in symptomatic transthyretin amyloid cardiomyopathy. *J Am Coll Cardiol.* 2019;74(3):285-295.
16. Adams D, Tournev IL, Taylor MS, et al, HELIOS-A Collaborators. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid.* Published online July 23, 2022. <https://doi.org/10.1080/13506129.2022.2091985>
17. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med.* 2018;379(1):11-21.
18. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med.* 2018;379(1):22-31.
19. Gillmore JD, Gane E, Taubel J, et al. CRISPR-Cas9 in vivo gene editing for transthyretin amyloidosis. *N Engl J Med.* 2021;385(6):493-502.
20. Griffin JM, Chiu L, Axsom KM, et al. Outcomes after heart transplantation for ATTR compared to ATTR cardiac amyloidosis. *Clin Transplant.* 2020;34(10):e14028.
21. Griffin JM, Rosenthal JL, Grodin JL, Maurer MS, Grogan M, Cheng RK. ATTR amyloidosis: current and emerging management strategies: JACC: CardioOncology State-of-the-Art Review. *J Am Coll Cardiol CardioOnc.* 2021;3(4):488-505.
22. Kazi DS, Bellows BK, Baron SJ, et al. Cost-effectiveness of tafamidis therapy for transthyretin amyloid cardiomyopathy. *Circulation.* 2020;141(15):1214-1242.
23. A Study of PRX004 in Subjects With Amyloid Transthyretin (ATTR) Amyloidosis. ClinicalTrials.gov. Accessed January 16, 2023. <https://clinicaltrials.gov/ct2/show/NCT03336580?term=NCT03336580&draw=2&rank=1>
24. First-in-Human Study of NI006 in Patients With Amyloid Transthyretin Cardiomyopathy. ClinicalTrials.gov. Accessed January 16, 2023. <https://clinicaltrials.gov/ct2/show/NCT04360434?term=NCT04360434&draw=2&rank=1>
25. Huda A, Castaño A, Niyogi A, et al. A machine learning model for identifying patients at risk for wild-type transthyretin amyloid cardiomyopathy. *Nat Commun.* 2021;12(1):2725.

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