ATTR Screening and Carrier Management

MED-US-DZSTATE-2400024

February 17, 2024

ATTR Disease State Slide Deck

- This resource provides information about ATTR.
- This resource is intended to be viewed in its entirety to support scientific exchange and is not intended as recommendations for clinical practice.
- This resource may contain hyperlinks that are not functional in this format.
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Screening and Carrier Management

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Pre-symptomatic Monitoring for TTR Variant Carriers

Recommendations to support early diagnosis

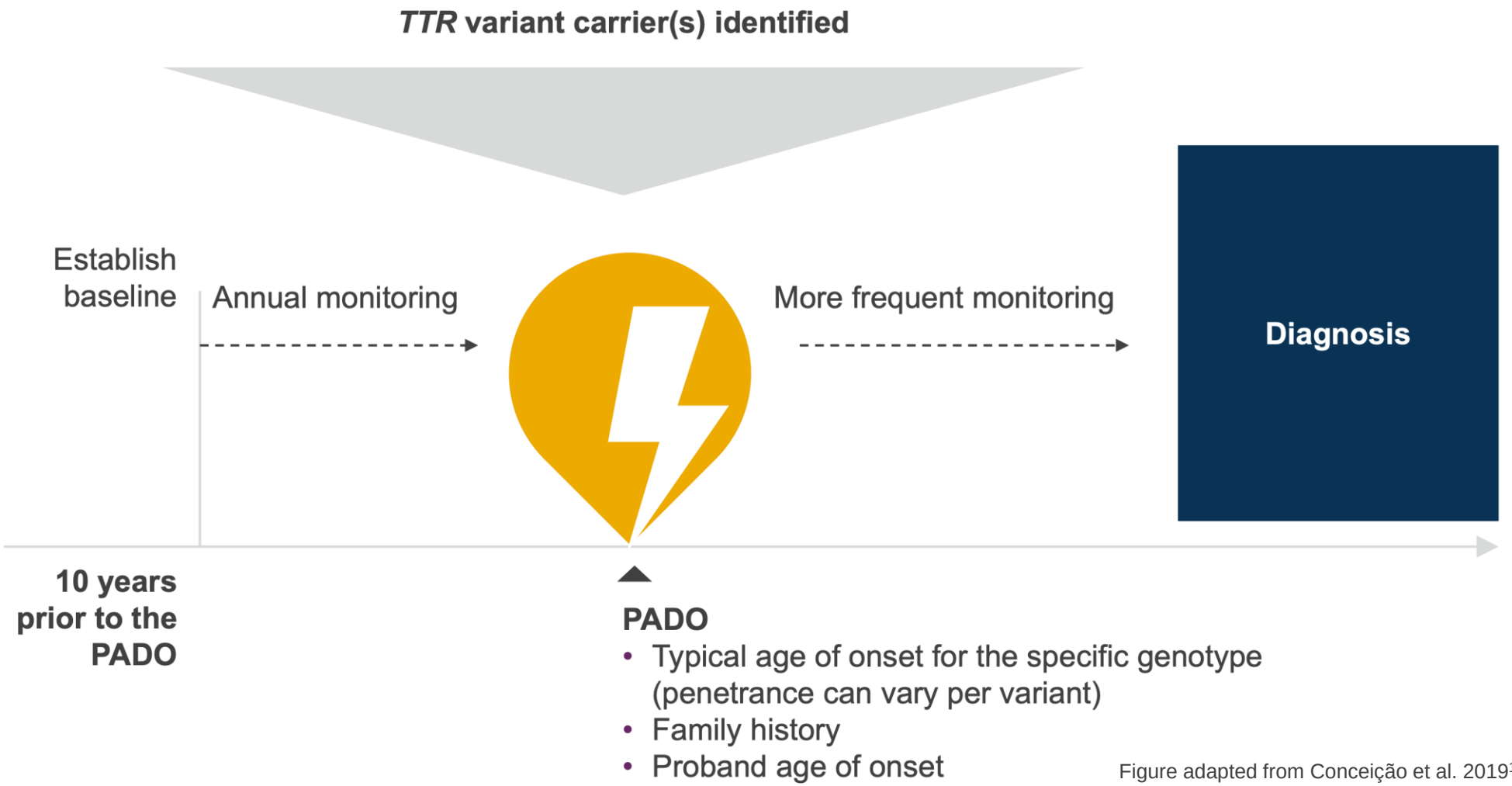

Figure adapted from Conceição et al. 2019[1]

PADO, predicted age of onset of symptomatic disease; TTR, transthyretin.

1. Conceição et al. *Amyloid.* 2019;26:3–9.

Management of TTR Variant Carrier[1,2]

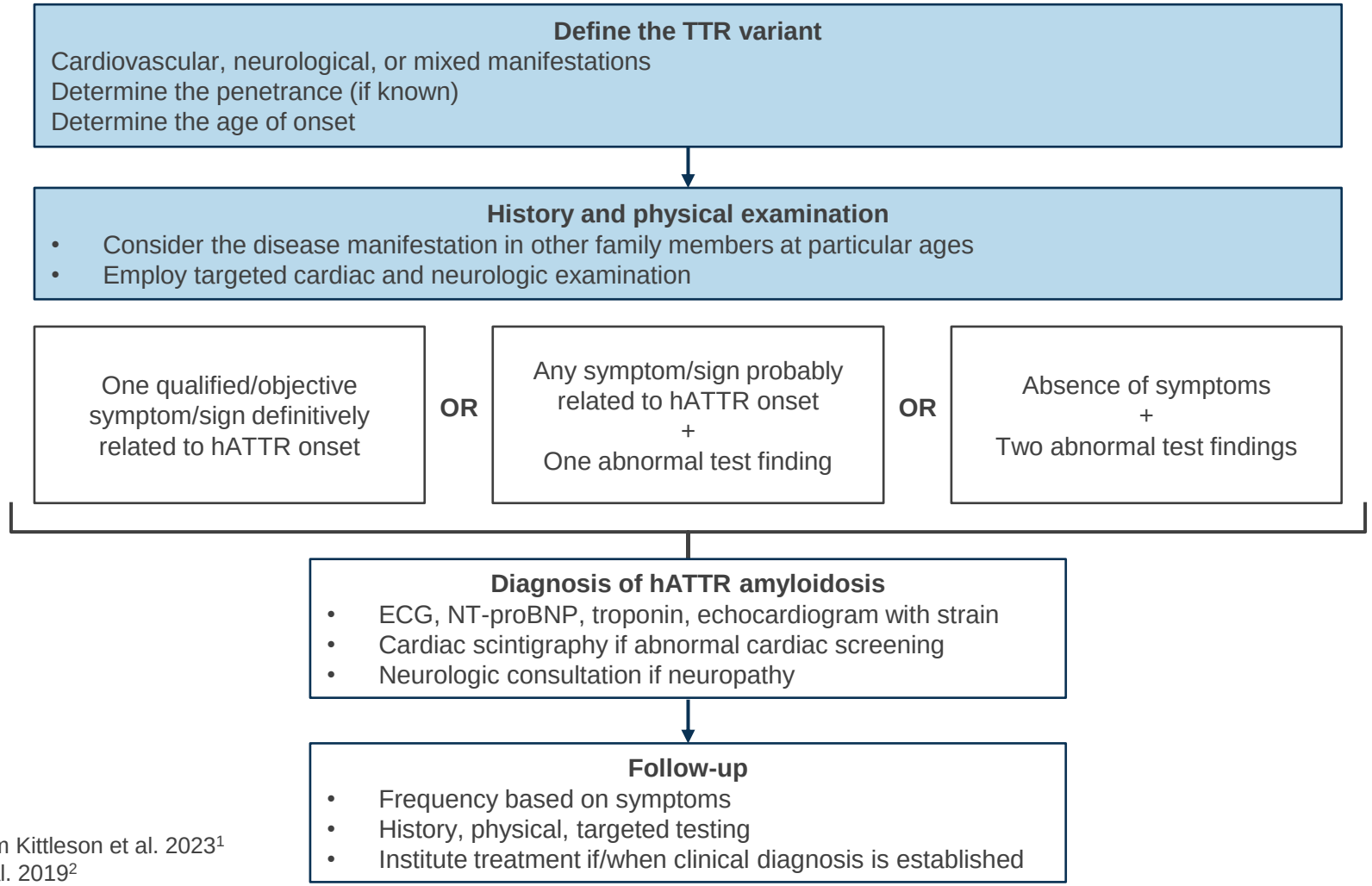

Figure adapted from Kittleson et al. 2023[1] and Conceição et al. 2019[2]

hATTR, hereditary ATTR; ECG, electrocardiogram; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TTR, transthyretin.

1. Kittleson et al. *JACC.* 2023; 81(11):1076–176; 2. Conceição et al. *Amyloid.* 2019;26:3–9.

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Biomarkers for ATTR (1/2)

Troponin T and I

Structure of troponin[1]

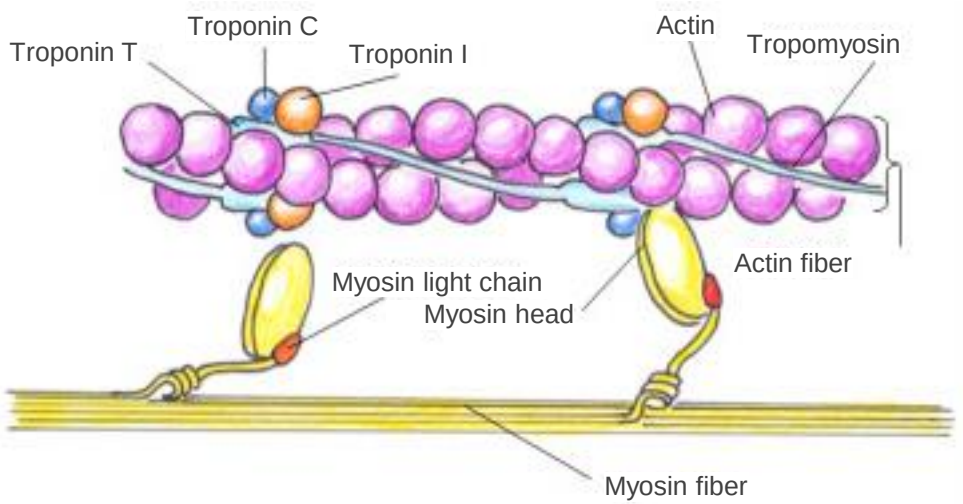


Image taken from Danek et al. 2017[1]

	Normal values[2]	ATTR effect on biomarker levels[2-4]
Troponin T	<0.01 µg/L	↑
Troponin I	<0.01 µg/L	↑

- **Cardiac troponin T and I** are both sensitive and specific biomarkers of myocardial injury and are both associated with heart failure and cardiovascular disease death[5,6]
- **Elevated cardiac troponin T and I** have been shown to support ATTRdiagnosis and contribute to prognosis estimates[2,3]
  - The THAOS registry found that ATTR patients with higher levels of troponin T/I presented with a greater disease severity, evidenced by a lower Karnofsky index score and mBMI, as well as a decline in renal function[2]

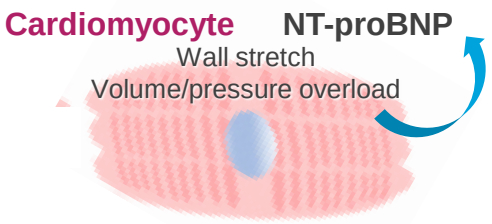
ATTR, transthyretin amyloidosis; mBMI, modified body mass index; THAOS, Transthyretin Amyloid Outcome Survey.

1. Danek et al. *Cor et Vasa.* 2017;59(3):e229–34; 2. Kristen et al. *PLoS One.* 2017; 12(4):e0173086; 3. Maurer et al. *Circ Heart Fail.* 2019;12(9):e006075; 4. Takashio et al. *ESC Heart Fail.* 2018:5(1):27–35; 5. Welsh et al. *Circ.* 2019;139(24):2754–64 ; 6. Pregenzer-Wenzler et al. *JACC.* 2020;8(9):701–11.

Biomarkers for ATTR Amyloidosis (2/2)

NT-proBNP and eGFR

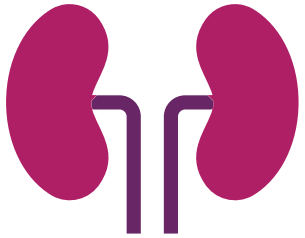
Release of NT-proBNP[1,2]



	Normal values[3,4]	ATTR effect on biomarker levels[5,6]
NT-proBNP	≤125 ng/L	↑

- **NT-proBNP** is a widely used diagnostic biomarker for HF and cardiac dysfunction[7]
- In patients with ATTR, NT-proBNP correlated with echocardiographic parameters, and higher levels predicted reduced survival[8,9]

eGFR



	Normal values[10]	ATTR effect on biomarker levels[11]
eGFR	≥90 ml/min/1.73m^2	↓

- **eGFR** measures the extent of a patient's kidney filtration ability and is commonly used as a diagnostic for chronic kidney disease[10]
- In both hATTR-CM and wtATTR-CM, eGFR is used in clinical staging, with lower levels corresponding to worsened survival[11]
  - The UK National Amyloidosis staging system established an eGFR **<45 mL/min/1.73m^2** (with >3000 ng/L for NT-proBNP) to be associated with death

ATTR, transthyretin amyloidosis; hATTR, hereditary ATTR with cardiomyopathy; wtATTR-CM, wild-type ATTR with cardiomyopathy; eGFR, estimated glomerular filtration rate; HF, heart failure; NT-proBNP, N-terminal-prohormone brain natriuretic peptide.

1. Reinmann & Meyer. *Cardiovasc Med.* 2020;23:w02095; 2. Taylor et al. *BMJ Open.* 2014;4:e004675; 3. Roche Pharmaceuticals. Elecsys proBNP II package insert. Updated November 2020. Accessed November 15, 2022. https://www.rochecanada.com/content/dam/rochexx/roche-ca/products/docs/package_inserts/ElecsysproBNPII-07027664190-EN-CAN.pdf ; 4. Ponikowski et al. *Eur Heart J.* 2016;37(27):2129–200; 5. Grogan et al. *JACC.* 2016; 68(10):1014–20; 6. Gilmore et al. *Eur Heart J.* 2018; 39(30):2799–806; 7. Cao et al. *Int J Mol Sci.* 2019;20:1820; 8. Kristen et al. *PLoS One.* 2017;12:e0173086; 9. Klaassen et al. *Am J Cardiol.* 2018;121:107–12; 10. National Kidney Foundation. Estimated Glomerular Filtration Rate (eGFR). Accessed November 4, 2022. https://www.kidney.org/atoz/content/gfr; 11. Gilmore et al. *Eur Heart J.* 2018; 39(30):2799–806.

Summary and Next Steps

- ATTR is is a multisystemic, rapidly progressive, debilitating, and fatal disease caused by misfolded TTR accumulating as amyloid deposits in multiple organs and tissues including nerves, heart, and GI tract [1-4]
  - Patients diagnosed with hATTR and wtATTR have a median survival of 4.7[5] and 2.5-5.5 years,[6-8] respectively
- ATTR remains underdiagnosed or misdiagnosed[4,9,10]
- Patients with ATTR experience substantial burden, including reduced QoL[11-14] and functional impairment[6,15]

There remains a need for health care professionals to:

1	2	3	4
Recognize the constellation of red-flag symptoms of ATTR [16,17]	**Collaborate with a multidisciplinary team for a potential diagnosis**[16,17]	**Employ the diagnostic algorithm and confirmatory diagnostic tools to verify diagnosis**[17-19]	**Assess progression of disease following treatment and provide patient with holistic care (mental, physical, and social support)**[20,21]

ATTR, transthyretin amyloidosis; hATTR, hereditary ATTR; wtATTR, wild-type ATTR; GI, gastrointestinal; QoL, quality of life; TTR, transthyretin.

1. Hanna. *Curr Heart Fail Rep.* 2014;11:50–7; 2. Mohty et al. *Arch Cardiovasc Dis.* 2013;106:528–40; 3. Adams et al. *Neurology.* 2015;85:675–82; 4. Maurer et al. *Circ Heart Fail.* 2019;12:e006075; 5. Swiecicki et al. *Amyloid.* 2015;22:123–31; 6. Lane et al. *Circulation.* 2019;140:16–26; 7. Aus dem Siepen et al. *Clin Res Cardiol.* 2018;107(2):158–69; 8. Givens et al. *Aging health.* 2013;9(2):229–35; 9. Hawkins et al. *Ann Med.* 2015;47:625–38; 10. Castano et al. *Heart Fail Rev.* 2015;20:163–78; 11. Coehlo et al. *Muscle Nerve.* 2017;55:323–32; 12. Vinik et al. *J Peripher Nerv Syst.* 2014;19:104–14; 13. Ines et al. *ISPOR Congress* 2015. Poster N21; 14. Obici et al. *Amyloid.* 2020;27:153–62; 15. Bolte et al. *Orphanet J Rare Dis* 2020;15:287; 16. Nativi-Nicolau et al. *Heart Fail Rev.* 2022;27(3):785–93; 17. Kittleson et al. *JACC.* 2023; 81(11):1076–176; 18. Namiranian and Geisler. *Am J Med.* 2022;135 Suppl 1:S13–19; 19. Ando et al. *Orphanet J Rare Dis.* 2013;8:31; 20. Adams et al. *Orphanet J Rare Dis.* 2021;16:411; 21. Obici et al. *BMJ Open.* 2023;13:e073130.