**LETTER OF MEDICAL NECESSITY**

**TTR GENETIC TESTING**

Date: Date of Service/claim

To: Utilization Review Department

Insurance Company Name, Address, City, State

Re: Patient Name, DOB, ID #

ICD-10 Codes:

This letter is regarding my patient and your subscriber, referenced above, to request full coverage of medically indicated genetic testing for hereditary transthyretin amyloidosis (hATTR) amyloidosis testing via TTR analysis to be performed by Ambry Genetics Corporation.

ATTR amyloidosis is a rare, progressive, and fatal disease characterized by deposition of amyloid fibrils in multiple organs and body systems (eg, heart and nervous system)1,2. Genetic testing is recommended for confirmation of the diagnosis and detection of specific of TTR gene mutations1,5,15. Sequence analysis detects nearly all mutations in the TTR gene13.

As amyloid protein builds in the body, symptoms are typically progressive and can impact many different organ symptoms with different signs and symptoms from patient to patient, even within the same family3,5. Making a clinical diagnosis is complicated by the fact that the nonspecific symptoms overlap with common disorders and hinder recognition of amyloidosis5. The average time to diagnosis is 2-3 years (regardless of family history) and in one study, diagnosis took over 6 years after the onset of symptoms for 1 in 10 patients14.

**Significant aspects of my patient’s personal and/or family medical history that suggest inherited hATTR are below5,8-11:** [check all that apply]

* Positive PYP scan showing deposition of TTR
* Family history of amyloidosis
* Ocular manifestations, including dark floaters, glaucoma, abnormal blood vessels in the eye, and pupillary abnormalities
* Spinal stenosis
* Central Nervous System manifestations such as progressive dementia, headache, seizures, spastic paresis, stroke-like episodes, loss of voluntary muscle control
* Gastrointestinal manifestations such as nausea and vomiting, early satiety, diarrhea, severe constipation, unintentional weight loss
* Bilateral carpal tunnel syndrome
* Cardiovascular manifestations such as aortic stenosis, arrhythmias, conduction blocks, congestive heart failure, ventricular wall thickening with preserved ejection fraction and absence of left ventricular dilation
* Nephropathy
* Peripheral sensory-motor neuropathy
* Autonomic neuropathy such as orthostatic hypotension, recurrent urinary tract infections, sexual dysfunction, sweating abnormalities
* Other: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**The American College of Cardiology (ACC), the American Heart Association (AHA),** **and the** **Heart Failure Society of America (HFSA) have all recognized the clinical utility of genetic testing for hereditary transthyretin amyloidosis and support it as standard of care**.16,17,18

Identification of a mutation through genetic testing confirms a diagnosis of hATTR. Genetic testing also informs prognosis, risk stratification, screening and treatment options, prevention efforts and genetic counseling, which can vary depending on the specific gene implicated in the disease.Specifically for this patient, the impact of testing may include: [check all that apply]

* Genetic testing could allow immediate management and treatment including drugs that inhibit synthesis of amyloidogenic TTR and stabilize native TTR tetramers13
* Genetic testing could assist in long-term management and monitoring of suspected disease progression based on the results of the testing including neurologic, cardiac, CNS, ophthalmologic, and renal monitoring13
* Genetic testing will lead to changes in diagnostic procedures such that more potentially invasive alternative procedures could be avoided, reducing unnecessary tests and cost
* Genetic testing will lead to informed decisions for other family members with similar conditions, or that may be at risk for similar conditions
* Other: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Based on the screening, lifestyle, and treatment modifications indicated above, this test has clinical utility for my patient. ATTR amyloidosis is a fatal disease that results in a progressive decline in quality of life severely impacting activities of daily living. Due to the availability of interventions available to reduce these risks, **I am requesting coverage for this testing as medically necessary care.**

Thank you for your time and please don’t hesitate to contact me with any questions.

Sincerely,

Ordering Clinician Name

**Test Details**

Test Name: TTR gene analysis

CPT codes:

Laboratory: Ambry Genetics Corporation (TIN 33-0892453 / NPI 1861568784), a CAP-accredited and CLIA-certified laboratory located at 7 Argonaut, Aliso Viejo, CA 92656

**References**

1. Hawkins PN, Ando Y, Dispenzeri A, Gonzalez-Duarte A, Adams D, Suhr OB. Evolving landscape in the management of transthyretin amyloidosis. Ann Med. 2015;47(8):625-38. doi: 10.3109/07853890.2015.1068949. Epub 2015 Nov 27. PMID: 26611723; PMCID: PMC4720049.

2. Suhr O, Danielsson A, Holmgren G, Steen L. Malnutrition and gastrointestinal dysfunction as prognostic factors for survival in familial amyloidotic polyneuropathy. J Intern Med. 1994 May;235(5):479-85. doi: 10.1111/j.1365-2796.1994.tb01106.x. PMID: 8182405.

3. Ando Y, Coelho T, Berk JL, Cruz MW, Ericzon BG, Ikeda S, Lewis WD, Obici L, Planté-Bordeneuve V, Rapezzi C, Said G, Salvi F. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013 Feb 20;8:31. doi: 10.1186/1750-1172-8-31. PMID: 23425518; PMCID: PMC3584981.

4. Coelho T, Maurer MS, Suhr OB. THAOS - The Transthyretin Amyloidosis Outcomes Survey: initial report on clinical manifestations in patients with hereditary and wild-type transthyretin amyloidosis. Curr Med Res Opin. 2013 Jan;29(1):63-76. doi: 10.1185/03007995.2012.754348. Epub 2012 Dec 13. PMID: 23193944.

5. Gertz MA. Hereditary ATTR amyloidosis: burden of illness and diagnostic challenges. Am J Manag Care. 2017 Jun;23(7 Suppl):S107-S112. PMID: 28978215.

6. Leung N, Nasr SH, Sethi S. How I treat amyloidosis: the importance of accurate diagnosis and amyloid typing. Blood. 2012 Oct 18;120(16):3206-13. doi: 10.1182/blood-2012-03-413682. Epub 2012 Sep 4. PMID: 22948045.

7. Conceição I, González-Duarte A, Obici L, Schmidt HH, Simoneau D, Ong ML, Amass L. "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy. J Peripher Nerv Syst. 2016 Mar;21(1):5-9. doi: 10.1111/jns.12153. PMID: 26663427; PMCID: PMC4788142.

8. Donnelly JP, Hanna M. Cardiac amyloidosis: An update on diagnosis and treatment. Cleve Clin J Med. 2017 Dec;84(12 Suppl 3):12-26. doi: 10.3949/ccjm.84.s3.02. PMID: 29257735.

9. Ikram A, et al. *J Card Fail*. 2017;23(8):S11-S12 (P021)

10. Coelho T, et al. A physician’s guide to transthyretin amyloidosis. Research Gate Amyloidosis; Foundation, 2008. https://www.researchgate.net/publication/265490881\_A\_Physician’s\_Guide\_to\_Transthyretin\_Amyloidosis\_Authored\_by. Accessed January 3, 2018

11. Galat A, Guellich A, Bodez D, Slama M, Dijos M, Zeitoun DM, Milleron O, Attias D, Dubois-Randé JL, Mohty D, Audureau E, Teiger E, Rosso J, Monin JL, Damy T. Aortic stenosis and transthyretin cardiac amyloidosis: the chicken or the egg? Eur Heart J. 2016 Dec 14;37(47):3525-3531. doi: 10.1093/eurheartj/ehw033. Epub 2016 Feb 22. PMID: 26908951.

12. Buxbaum JN, Ruberg FL. Transthyretin V122I (pV142I)\* cardiac amyloidosis: an age-dependent autosomal dominant cardiomyopathy too common to be overlooked as a cause of significant heart disease in elderly African Americans. Genet Med. 2017 Jul;19(7):733-742. doi: 10.1038/gim.2016.200. Epub 2017 Jan 19. PMID: 28102864; PMCID: PMC5509498.

13. Sekijima Y, Nakamura K. Hereditary Transthyretin Amyloidosis. 2001 Nov 5 [Updated 2024 May 30]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1194/

14. Amyloidosis Foundation. Understanding the patient voice in hereditary transthyretin-mediated amyloidosis (ATTR amyloidosis);

15. Alreshq R, Ruberg FL. Clinical approach to genetic testing in amyloid cardiomyopathy: from mechanism to effective therapies. Curr Opin Cardiol. 2021 May 1;36(3):309-317. doi: 10.1097/HCO.0000000000000841. PMID: 33605615; PMCID: PMC8221237.

16. Kittleson, M, Ruberg, F. et al. 2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient With Cardiac Amyloidosis: A Report of the American College of Cardiology Solution Set Oversight Committee. *JACC.*2023 Mar, 81 (11) 1076–1126.[**https://doi.org/10.1016/j.jacc.2022.11.022**](https://doi.org/10.1016/j.jacc.2022.11.022)

17. Kittleson MM, Maurer MS, Ambardekar AV, Bullock-Palmer RP, Chang PP, Eisen HJ, Nair AP, Nativi-Nicolau J, Ruberg FL; American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology. Cardiac Amyloidosis: Evolving Diagnosis and Management: A Scientific Statement From the American Heart Association. Circulation. 2020 Jul 7;142(1):e7-e22. doi: 10.1161/CIR.0000000000000792. Epub 2020 Jun 1. Erratum in: Circulation. 2021 Jul 6;144(1):e10. doi: 10.1161/CIR.0000000000000997. Erratum in: Circulation. 2021 Jul 6;144(1):e11. doi: 10.1161/CIR.0000000000000998. PMID: 32476490.

18. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, Fang JC, Fedson SE, Fonarow GC, Hayek SS, Hernandez AF, Khazanie P, Kittleson MM, Lee CS, Link MS, Milano CA, Nnacheta LC, Sandhu AT, Stevenson LW, Vardeny O, Vest AR, Yancy CW. 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. Circulation. 2022 May 3;145(18):e895-e1032. doi: 10.1161/CIR.0000000000001063. Epub 2022 Apr 1. Erratum in: Circulation. 2022 May 3;145(18):e1033. doi: 10.1161/CIR.0000000000001073. Erratum in: Circulation. 2022 Sep 27;146(13):e185. doi: 10.1161/CIR.0000000000001097. Erratum in: Circulation. 2023 Apr 4;147(14):e674. doi: 10.1161/CIR.0000000000001142. PMID: 35363499.