

Reimbursement Policy

Testing for Alpha-1 Antitrypsin Deficiency

[POLICY DESCRIPTION](#) | [INDICATIONS AND/OR LIMITATIONS OF COVERAGE](#) | [APPLICABLE STATE AND FEDERAL REGULATIONS](#) | [APPLICABLE CPT/HCPCS PROCEDURE CODES](#) | [EVIDENCE-BASED SCIENTIFIC REFERENCES](#) |

I. Policy Description

Alpha 1-antitrypsin deficiency (AATD) is a genetic disease that causes deficient or defective production of the alpha-1 antitrypsin (AAT) protease inhibitor that can affect the lungs, liver, and skin (Stoller, 2024). AAT deficiency results in unbalanced rapid breakdown of proteins, especially in the supporting elastic tissue of the lungs (NORD, 2024a).

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

- 1) For individuals who are suspected of having alpha-1 antitrypsin (AAT) deficiency, serum quantification of alpha-1 antitrypsin (AAT) protein **and** AAT phenotyping **or** AAT proteotyping (see Note 1) **MEETS COVERAGE CRITERIA** once per lifetime in **any** of the following situations:
 - a) For symptomatic individuals 18 years or older with emphysema, COPD, or asthma.
 - b) For individuals with unexplained liver disease (e.g., chronic hepatitis with or without cirrhosis, chronically elevated aminotransferase levels, portal hypertension, primary liver cancer).
 - c) For individuals with persistent obstruction on pulmonary function tests without identifiable risk factors (e.g., cigarette smoking, occupational exposure).
 - d) For individuals 18 years or older with necrotizing panniculitis.
 - e) For the siblings of an individual with known alpha-1 antitrypsin (AAT) deficiency.
 - f) For individuals with anti-proteinase three-positive vasculitis (C-ANCA [anti-neutrophil cytoplasmic antibody]-positive vasculitis).
 - g) For individuals with bronchiectasis without evident etiology.
 - h) For individuals with neonatal cholestasis.
- 2) For individuals who have negative genotype results for common variants or who have discordant results between AAT serum levels and proteotype, but for whom a clinical suspicion of AAT deficiency remains, isoelectric focusing/phenotyping **MEETS COVERAGE CRITERIA**.

Reimbursement Policy

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

- 3) For all other situations not described above, testing for AAT deficiency **DOES NOT MEET COVERAGE CRITERIA.**

NOTES:

Note 1: AAT phenotyping should be performed using isoelectric focusing. AAT proteotyping (Pi-typing or protease inhibitor typing) for Z and S alleles should be performed using liquid chromatography-tandem mass spectrometry.

III. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <http://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration

On November 17, 2017, the FDA approved Grifols' (Grifols, 2017) *SERPINA1* Variant Detection System as a qualitative in vitro molecular diagnostic system used to detect variants in *SERPINA1* gene in genomic DNA isolated from human specimens. On November 7, 2019, the FDA approved Grifols' AlphaID™, a cheek swab that can screen patients with COPD for alpha-1 antitrypsin deficiency. It “utilizes an FDA-approved genotyping assay to screen for the 14 most prevalently reported genetic mutations associated with Alpha-1, including the S, Z, F, I alleles, as well as rare and null alleles, helping detect patients who are at risk for this treatable condition” (Grifols, 2019).

On April 6, 2017 the FDA approved (FDA, 2017) the 23andMe PGS Genetic Health Risk Report for Alpha-1 Antitrypsin Deficiency (AATD) which determines if a person has variants associated with a higher risk of developing AATD-associated lung or liver disease. This report is based on a qualitative genetic test for single nucleotide polymorphism detection of the PI*Z (rs28929474) and PI*S (rs17580) variants in the *SERPINA1* gene by using the 23andMe Personal Genome Service.

Reimbursement Policy

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

IV. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
82103	Alpha-1-antitrypsin; total
82104	Alpha-1-antitrypsin; phenotype
82542	Column chromatography, includes mass spectrometry, if performed (eg, HPLC, LC, LC/MS, LC/MS-MS, GC, GC/MS-MS, GC/MS, HPLC/MS), non-drug analyte(s) not elsewhere specified, qualitative or quantitative, each specimen
83789	Mass spectrometry and tandem mass spectrometry (eg, MS, MS/MS, MALDI, MS-TOF, QTOF), non-drug analyte(s) not elsewhere specified, qualitative or quantitative, each specimen

Current Procedural Terminology© American Medical Association. All Rights reserved.

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

V. Evidence-based Scientific References

- AlphaID. (2024). AlphaID. <https://www.alphaid.com/en/hcp/home>
- Ashenhurst, J. R., Nhan, H., Shelton, J. F., Wu, S., Tung, J. Y., Elson, S. L., & Stoller, J. K. (2022). Prevalence of Alpha-1 Antitrypsin Deficiency, Self-Reported Behavior Change, and Health Care Engagement Among Direct-to-Consumer Recipients of a Personalized Genetic Risk Report. *Chest*, 161(2), 373-381. <https://doi.org/10.1016/j.chest.2021.09.041>
- ATS/ERS. (2003). American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med*, 168(7), 818-900. <https://doi.org/10.1164/rccm.168.7.818>
- Balcar, L., Scheiner, B., Urheu, M., Weinberger, P., Paternostro, R., Simbrunner, B., Hartl, L., Jachs, M., Bauer, D., Semmler, G., Willheim, C., Pinter, M., Ferenci, P., Trauner, M., Reiberger, T., Stättermayer, A. F., & Mandorfer, M. (2022). Alpha-1 antitrypsin Pi*Z allele is an independent risk factor for liver transplantation and death in patients with advanced chronic liver disease. *JHEP Rep*, 4(11), 100562. <https://doi.org/10.1016/j.jhepr.2022.100562>
- Barrecheguren, M., Monteagudo, M., Simonet, P., Llor, C., Rodriguez, E., Ferrer, J., Esquinas, C., & Miravittles, M. (2016). Diagnosis of alpha-1 antitrypsin deficiency: a population-based study. *Int J Chron Obstruct Pulmon Dis*, 11, 999-1004. <https://doi.org/10.2147/copd.s108505>

Reimbursement Policy

- BC Guidelines. (2024). Chronic Obstructive Pulmonary Disease (COPD): Diagnosis and Management. <https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/copd#diagnosis>
- Bellemare, J., Gaudreault, N., Valette, K., Belmonte, I., Nuñez, A., Miravittles, M., Maltais, F., & Bossé, Y. (2021). The Clinical Utility of Determining the Allelic Background of Mutations Causing Alpha-1 Antitrypsin Deficiency: The Case with the Null Variant Q0(Mattawa)/Q0(Ourém). *Chronic Obstr Pulm Dis*, 8(1), 31-40. <https://doi.org/10.15326/jcopdf.8.1.2020.0168>
- Belmonte, I., Nunez, A., Barrecheguren, M., Esquinas, C., Pons, M., Lopez-Martinez, R. M., Ruiz, G., Blanco-Grau, A., Ferrer, R., Genesca, J., Miravittles, M., & Rodriguez-Frias, F. (2020). Trends in Diagnosis of Alpha-1 Antitrypsin Deficiency Between 2015 and 2019 in a Reference Laboratory. *Int J Chron Obstruct Pulmon Dis*, 15, 2421-2431. <https://doi.org/10.2147/COPD.S269641>
- Campos, M. A., Wanner, A., Zhang, G., & Sandhaus, R. A. (2005). Trends in the diagnosis of symptomatic patients with alpha1-antitrypsin deficiency between 1968 and 2003. *Chest*, 128(3), 1179-1186. <https://doi.org/10.1378/chest.128.3.1179>
- Carreto, L., Morrison, M., Donovan, J., Finch, S., Tan, G. L., Fardon, T., Wilson, R., Furrie, E., Loebinger, M., & Chalmers, J. D. (2020). Utility of routine screening for alpha-1 antitrypsin deficiency in patients with bronchiectasis. *Thorax*, 75(7), 592-593. <https://doi.org/10.1136/thoraxjnl-2019-214195>
- Clark, V. C., Marek, G., Liu, C., Collinsworth, A., Shuster, J., Kurtz, T., Nolte, J., & Brantly, M. (2018). Clinical and histologic features of adults with alpha-1 antitrypsin deficiency in a non-cirrhotic cohort. *J Hepatol*, 69(6), 1357-1364. <https://doi.org/10.1016/j.jhep.2018.08.005>
- Corda, L., Medicina, D., La Piana, G. E., Bertella, E., Moretti, G., Bianchi, L., Pinelli, V., Savoldi, G., Baiardi, P., Facchetti, F., Gatta, N., Annesi-Maesano, I., & Balbi, B. (2011). Population genetic screening for alpha1-antitrypsin deficiency in a high-prevalence area. *Respiration*, 82(5), 418-425. <https://doi.org/10.1159/000325067>
- de Serres, F. J., Blanco, I., & Fernandez-Bustillo, E. (2003). Genetic epidemiology of alpha-1 antitrypsin deficiency in North America and Australia/New Zealand: Australia, Canada, New Zealand and the United States of America. *Clin Genet*, 64(5), 382-397.
- de Serres, F. J., Blanco, I., & Fernandez-Bustillo, E. (2007). PI S and PI Z alpha-1 antitrypsin deficiency worldwide. A review of existing genetic epidemiological data. *Monaldi Arch Chest Dis*, 67(4), 184-208. <https://doi.org/10.4081/monaldi.2007.476>
- Eriksson, S., Carlson, J., & Velez, R. (1986). Risk of cirrhosis and primary liver cancer in alpha 1-antitrypsin deficiency. *N Engl J Med*, 314(12), 736-739. <https://doi.org/10.1056/nejm198603203141202>
- FDA. (2017). *Decision Summary for 23andMe PGS Genetic Health Risk Report*. U.S. Food and Drug Administration Retrieved from https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN160026.pdf
- Fromme, M., Schneider, C. V., Pereira, V., Hamesch, K., Pons, M., Reichert, M. C., Benini, F., Ellis, P., K, H. T., Mandorfer, M., Burbaum, B., Woditsch, V., Chorostowska-Wynimko, J.,

Reimbursement Policy

- Verbeek, J., Nevens, F., Genesca, J., Miravittles, M., Nuñez, A., Schaefer, B., . . . Strnad, P. (2022). Hepatobiliary phenotypes of adults with alpha-1 antitrypsin deficiency. *Gut*, *71*(2), 415-423. <https://doi.org/10.1136/gutjnl-2020-323729>
- GOLD. (2024). GLOBAL STRATEGY FOR PREVENTION, DIAGNOSIS AND MANAGEMENT OF COPD: 2024 Report. <https://goldcopd.org/2024-gold-report/>
- Greulich, T., Nell, C., Herr, C., Vogelmeier, C., Kotke, V., Wiedmann, S., Wencker, M., Bals, R., & Koczulla, A. R. (2016). Results from a large targeted screening program for alpha-1-antitrypsin deficiency: 2003 - 2015. *Orphanet J Rare Dis*, *11*(1), 75. <https://doi.org/10.1186/s13023-016-0453-8>
- Grifols. (2017). FDA approval of genetic test for alpha-1 deficiency and EMA approval of fibrin sealant. <https://www.grifols.com/documents/3627767/3632483/np-20171117-en.pdf>
- Grifols. (2019, November 7). *Grifols introduces AlphaID™, a free cheek swab to screen for Alpha-1, the most common genetic form of COPD*. Retrieved April 11 from <https://www.grifols.com/en/view-news/-/news/grifols-introduces-alpha1d-a-free-cheek-swab-to-screen-for-alpha-1-the-most-common-genetic-form-of-copd>
- Hamesch, K., Mandorfer, M., Pereira, V. M., Moeller, L. S., Pons, M., Dolman, G. E., Reichert, M. C., Schneider, C. V., Woditsch, V., Voss, J., Lindhauer, C., Fromme, M., Spivak, I., Guldiken, N., Zhou, B., Arslanow, A., Schaefer, B., Zoller, H., Aigner, E., . . . Strnad, P. (2019). Liver Fibrosis and Metabolic Alterations in Adults With alpha-1-antitrypsin Deficiency Caused by the Pi*ZZ Mutation. *Gastroenterology*, *157*(3), 705-719.e718. <https://doi.org/10.1053/j.gastro.2019.05.013>
- Kwo, P. Y., Cohen, S. M., & Lim, J. K. (2017). ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. *Am J Gastroenterol*, *112*(1), 18-35. <https://doi.org/10.1038/ajg.2016.517>
- Lin, H. C., Kasi, N., & Quiros, J. A. (2019). Alpha-1-Antitrypsin Deficiency: Transition of Care for the Child With AAT Deficiency into Adulthood. *Curr Pediatr Rev*, *15*(1), 53-61. <https://doi.org/10.2174/1573396314666181113094517>
- Marciniuk, D. D., Hernandez, P., Balter, M., Bourbeau, J., Chapman, K. R., Ford, G. T., Lauzon, J. L., Maltais, F., O'Donnell, D. E., Goodridge, D., Strange, C., Cave, A. J., Curren, K., & Muthuri, S. (2012). Alpha-1 antitrypsin deficiency targeted testing and augmentation therapy: a Canadian Thoracic Society clinical practice guideline. *Can Respir J*, *19*(2), 109-116. <https://doi.org/10.1155/2012/920918>
- Mattman, A., Gilfix, B. M., Chen, S. X., DeMarco, M. L., Kyle, B. D., Parker, M. L., Agbor, T. A., Jung, B., Selvarajah, S., Barakauskas, V. E., Vaags, A. K., Estey, M. P., Nelson, T. N., & Speevak, M. D. (2020). Alpha-1-antitrypsin molecular testing in Canada: A seven year, multi-centre comparison. *Clin Biochem*, *81*, 27-33. <https://doi.org/10.1016/j.clinbiochem.2020.05.001>
- Miravittles, M., Dirksen, A., Ferrarotti, I., Koblizek, V., Lange, P., Mahadeva, R., McElvaney, N. G., Parr, D., Piitulainen, E., Roche, N., Stolk, J., Thabut, G., Turner, A., Vogelmeier, C., & Stockley, R. A. (2017). European Respiratory Society statement: diagnosis and treatment

Reimbursement Policy

- of pulmonary disease in alpha1-antitrypsin deficiency. *Eur Respir J*, 50(5).
<https://doi.org/10.1183/13993003.00610-2017>
- Murray, J. D., Willrich, M. A., Krowka, M. J., Bobr, A., Murray, D. L., Halling, K. C., Graham, R. P., & Snyder, M. R. (2021). Liquid Chromatography-Tandem Mass Spectrometry-Based alpha1-Antitrypsin (AAT) Testing. *Am J Clin Pathol*, 155(4), 547-552.
<https://doi.org/10.1093/ajcp/aqaa149>
- NICE. (2019, July 26). *Chronic obstructive pulmonary disease in over 16s: diagnosis and management*. <https://www.nice.org.uk/guidance/ng115/chapter/Recommendations>
- NORD. (2024a). Alpha-1 Antitrypsin Deficiency. <https://rarediseases.org/rare-diseases/alpha-1-antitrypsin-deficiency/>
- NORD. (2024b, 01/25/2024). *Neonatal Cholestasis*. <https://rarediseases.org/rare-diseases/idiopathic-neonatal-hepatitis/>
- Sandhaus, R. A., Turino, G., Brantly, M. L., Campos, M., Cross, C. E., Goodman, K., Hogarth, D. K., Knight, S. L., Stocks, J. M., Stoller, J. K., Strange, C., & Teckman, J. (2016). The Diagnosis and Management of Alpha-1 Antitrypsin Deficiency in the Adult. *Chronic Obstr Pulm Dis*, 3(3), 668-682. <https://doi.org/10.15326/jcopdf.3.3.2015.0182>
- Snyder, M. R., Katzmann, J. A., Butz, M. L., Wiley, C., Yang, P., Dawson, D. B., Halling, K. C., Highsmith, W. E., & Thibodeau, S. N. (2006). Diagnosis of alpha-1-antitrypsin deficiency: An algorithm of quantification, genotyping, and phenotyping. *Clin Chem*, 52(12), 2236-2242.
<https://doi.org/10.1373/clinchem.2006.072991>
- Soriano, J. B., Lucas, S. J., Jones, R., Miravittles, M., Carter, V., Small, I., Price, D., & Mahadeva, R. (2018). Trends of testing for and diagnosis of alpha1-antitrypsin deficiency in the UK: more testing is needed. *Eur Respir J*, 52(1).
<https://doi.org/10.1183/13993003.00360-2018>
- Sorroche, P. B., Fernandez Acquier, M., Lopez Jove, O., Giugno, E., Pace, S., Livellara, B., Legal, S., Oyhamburu, J., & Saez, M. S. (2015). Alpha-1 Antitrypsin Deficiency in COPD Patients: A Cross-Sectional Study. *Arch Bronconeumol*, 51(11), 539-543.
<https://doi.org/10.1016/j.arbres.2015.01.008>
- Stoller, J. (2023, September 13). *Clinical manifestations, diagnosis, and natural history of alpha-1 antitrypsin deficiency*. <https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-natural-history-of-alpha-1-antitrypsin-deficiency>
- Stoller, J. (2024, July 6). *Extrapulmonary manifestations of alpha-1 antitrypsin deficiency*. <https://www.uptodate.com/contents/extrapulmonary-manifestations-of-alpha-1-antitrypsin-deficiency>
- Stoller, J. K., & Aboussouan, L. S. (2012). A review of alpha1-antitrypsin deficiency. *Am J Respir Crit Care Med*, 185(3), 246-259. <https://doi.org/10.1164/rccm.201108-1428CI>
- Stoller, J. K., Sandhaus, R. A., Turino, G., Dickson, R., Rodgers, K., & Strange, C. (2005). Delay in diagnosis of alpha1-antitrypsin deficiency: a continuing problem. *Chest*, 128(4), 1989-1994. <https://doi.org/10.1378/chest.128.4.1989>
- Strnad, P., Buch, S., Hamesch, K., Fischer, J., Rosendahl, J., Schmelz, R., Brueckner, S., Brosch, M., Heimes, C. V., Woditsch, V., Scholten, D., Nischalke, H. D., Janciauskiene, S.,

Reimbursement Policy

- Mandorfer, M., Trauner, M., Way, M. J., McQuillin, A., Reichert, M. C., Krawczyk, M., . . . Trautwein, C. (2019). Heterozygous carriage of the alpha1-antitrypsin Pi*Z variant increases the risk to develop liver cirrhosis. *Gut*, 68(6), 1099-1107. <https://doi.org/10.1136/gutjnl-2018-316228>
- Teckman, J., Rosenthal, P., Hawthorne, K., Spino, C., Bass, L. M., Murray, K. F., Kerkar, N., Magee, J. C., Karpen, S., Heubi, J. E., Molleston, J. P., Squires, R. H., Kamath, B. M., Guthery, S. L., Loomes, K. M., Sherker, A. H., & Sokol, R. J. (2020). Longitudinal Outcomes in Young Patients with Alpha-1-Antitrypsin Deficiency with Native Liver Reveal that Neonatal Cholestasis is a Poor Predictor of Future Portal Hypertension. *J Pediatr*, 227, 81-86.e84. <https://doi.org/10.1016/j.jpeds.2020.07.031>
- Teckman, J., Rosenthal, P., Ignacio, R. V., Spino, C., Bass, L. M., Horslen, S., Wang, K., Magee, J. C., Karpen, S., Asai, A., Molleston, J. P., Squires, R. H., Kamath, B. M., Guthery, S. L., Loomes, K. M., Shneider, B. L., & Sokol, R. J. (2023). Neonatal cholestasis in children with Alpha-1-AT deficiency is a risk for earlier severe liver disease with male predominance. *Hepatol Commun*, 7(12). <https://doi.org/10.1097/hc9.0000000000000345>
- WHO. (1997). Alpha 1-antitrypsin deficiency: memorandum from a WHO meeting. *Bull World Health Organ*, 75(5), 397-415. <https://www.ncbi.nlm.nih.gov/pubmed/9447774>