



**BlueCross BlueShield
of Oklahoma**

If a conflict arises between a Clinical Payment and Coding Policy (“CPCP”) and any plan document under which a member is entitled to Covered Services, the plan document will govern. If a conflict arises between a CPCP and any provider contract pursuant to which a provider participates in and/or provides Covered Services to eligible member(s) and/or plans, the provider contract will govern. “Plan documents” include, but are not limited to, Certificates of Health Care Benefits, benefit booklets, Summary Plan Descriptions, and other coverage documents. BCBSOK may use reasonable discretion interpreting and applying this policy to services being delivered in a particular case. BCBSOK has full and final discretionary authority for their interpretation and application to the extent provided under any applicable plan documents.

Providers are responsible for submission of accurate documentation of services performed. Providers are expected to submit claims for services rendered using valid code combinations from Health Insurance Portability and Accountability Act (“HIPAA”) approved code sets. Claims should be coded appropriately according to industry standard coding guidelines including, but not limited to: Uniform Billing (“UB”) Editor, American Medical Association (“AMA”), Current Procedural Terminology (“CPT”), CPT® Assistant, Healthcare Common Procedure Coding System (“HCPCS”), ICD-10 CM and PCS, National Drug Codes (“NDC”), Diagnosis Related Group (“DRG”) guidelines, Centers for Medicare and Medicaid Services (“CMS”) National Correct Coding Initiative (“NCCI”) Policy Manual, CCI table edits and other CMS guidelines.

Claims are subject to the code edit protocols for services/procedures billed. Claim submissions are subject to claim review including but not limited to, any terms of benefit coverage, provider contract language, medical policies, clinical payment and coding policies as well as coding software logic. Upon request, the provider is urged to submit any additional documentation.

Testing for Alpha-1 Antitrypsin Deficiency

Policy Number: CPCPLAB061

Version 1.0

Enterprise Clinical Payment and Coding Policy Committee Approval Date: July 17, 2023

Plan Effective Date: November 1, 2023

Description

BCBSOK has implemented certain lab management reimbursement criteria. Not all requirements apply to each product. Providers are urged to review Plan documents for eligible coverage for services rendered.

Reimbursement Information:

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**) **may be reimbursable** in **any** of the following situations:
 - a. For symptomatic individuals 18 years of age or older with emphysema, COPD, or asthma
 - b. For individuals with unexplained liver disease
 - 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 of age 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
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 **may be reimbursable**.
3. For all other situations not described above, testing for alpha-1 antitrypsin (AAT) deficiency **is not reimbursable**.

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.

Procedure Codes

The following is not an all-encompassing code list. The inclusion of a code does not guarantee it is a covered service or eligible for reimbursement.

Codes
82103, 82104, 82542, 83789

References:

Agusti, A., Celli, B. R., Criner, G. J., Halpin, D., Anzueto, A., Barnes, P., Bourbeau, J., Han, M. K., Martinez, F. J., Montes de Oca, M., Mortimer, K., Papi, A., Pavord, I., Roche, N., Salvi, S., Sin, D. D., Singh, D., Stockley, R., Lopez Varela, M. V., . . . Vogelmeier, C. F. (2023). Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. *Am J Respir Crit Care Med*, *207*(7), 819-837. <https://doi.org/10.1164/rccm.202301-0106PP>

Ashenurst, 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>

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>

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>

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., Furrrie, 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>

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>

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

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*. <http://www.grifols.com/en/web/international/view-news/-/new/fda-approval-of-genetic-test-for-alpha-1-deficiency-and-ema-approval-of-fibrin-sealant>

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>

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>

Matrix Clinical Labs, & (2022). AlphaID. <http://www.biocerna.com/alphaid>

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 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. (2022). Alpha-1 Antitrypsin Deficiency. <https://rarediseases.org/rare-diseases/alpha-1-antitrypsin-deficiency/>

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. (2022a, 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. (2022b, 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., 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>

Vogelmeier, C. F., Criner, G. J., Martinez, F. J., Anzueto, A., Barnes, P. J., Bourbeau, J., Celli, B. R., Chen, R., Decramer, M., Fabbri, L. M., Frith, P., Halpin, D. M., Lopez Varela, M. V., Nishimura, M., Roche, N., Rodriguez-Roisin, R., Sin, D. D., Singh, D., Stockley, R., . . . Agusti, A. (2017). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary. *Respirology*, 22(3), 575-601. <https://doi.org/10.1111/resp.13012>

WHO. (1997). Alpha 1-antitrypsin deficiency: memorandum from a WHO meeting. *Bull World Health Organ*, 75(5), 397-415. https://apps.who.int/iris/bitstream/handle/10665/55120/bulletin_1997_75%285%29_397-415.pdf?sequence=1&isAllowed=y

Policy Update History:

7/17/2023	Document updated with literature review. Reimbursement Information revised for clarity. References revised.
11/1/2022	New policy