CLINICAL RESEARCH STUDY

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Testing Patterns and Disparities for Alpha-1 Antitrypsin Deficiency

Leonard Riley, MD,[a] Aryaman Sriram,[b] Mark Brantly, MD,[c] Jorge Lascano, MD[c]

[a]Department of Internal Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, Kansas City Veterans Affairs Medical Center, Mo; [b]University of Florida, Gainesville; [c]Department of Internal Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, University of Florida College of Medicine, Gainesville.

ABSTRACT

BACKGROUND: Alpha-1 antitrypsin deficiency is an under-recognized genetic cause of chronic lung and liver disease; it remains unclear what the testing frequency and disparities are for alpha-1 antitrypsin deficiency.

METHODS: This is a retrospective cohort study of people with newly diagnosed chronic obstructive pulmonary disease and liver disease identified at the University of Florida between January 1, 2012 and December 31, 2021. We performed incidence and prevalence analysis for alpha-1 antitrypsin (AAT) testing and point-biserial correlation analysis for tobacco use and AAT testing. We evaluated characteristics with AAT testing using adjusted multivariable logistic regression.

RESULTS: Among 75,810 subjects with newly diagnosed chronic obstructive pulmonary disease and liver disease between 2012 and 2021, 4248 (5.6%) were tested for AAT deficiency. All subjects had an AAT level performed, while 1654 (39%) had phenotype testing. Annual incidence of testing increased for subjects with newly diagnosed chronic obstructive pulmonary disease or liver disease from 2.8% and 5.4%, respectively, in 2012 to 4.1% and 11.3%, respectively, in 2021. Adjusted multivariable regression analysis showed factors favoring AAT testing were White race, and concomitant chronic obstructive pulmonary disease and liver disease. Increasing age, non-White race, current tobacco use, and being a male with chronic obstructive pulmonary disease had lower odds of AAT testing.

CONCLUSION: Although slowly improving, testing for AAT deficiency continues to have a low uptake in the clinical setting despite guidelines recommending broader testing. Individuals of White race and those with concomitant chronic obstructive pulmonary disease and liver disease are more likely to be tested, while older subjects, individuals of non-White race, current tobacco use, and men with chronic obstructive pulmonary disease are less favored to be tested.

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KEYWORDS: Alpha-1 antitrypsin; Alpha-1 antitrypsin deficiency; Testing disparities

INTRODUCTION

Alpha-1 antitrypsin deficiency is an under-recognized genetic condition due to a mutation in the SERPINA1 gene that produces alpha-1 antitrypsin (AAT), which is a protease inhibitor of elastase, trypsin, chymotrypsin, and thrombin.[1,2] In AAT deficiency, there are unopposed levels of alveolar neutrophil elastase, which carries an increased risk of emphysema and bronchiectasis. In genotypes associated with pathologic polymerization of the AAT protein, the variant AAT is unable to be excreted from the liver, leading to intrahepatic accumulation of the misfolded protein and ultimately, cirrhosis. AAT deficiency is inherited in an autosomal codominant pattern, meaning both alleles are expressed, and each version makes a different protein.[2] The normal allele is termed "M," whereas the most common pathologic allelic variants are "Z" and "S." The allelic homozygous variation "ZZ" accounts for approximately

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Requests for reprints should be addressed to Leonard Riley, MD, Department of Internal Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, Kansas City Veterans Affairs Medical Center, 4801 Linwood Blvd, Kansas City, MO 64128.

E-mail address: elmer.riley2@va.gov

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95% of severe AAT deficiency and significantly increases the risk for severe lung disease.[2] In the setting of tobacco use, the heterozygous "MZ" allelic combination increases the severity of lung disease, compared with "MM" individuals.[3,4] Treatment of AAT deficiency is similar to usual chronic obstructive pulmonary disease with bronchodilators, immunizations, and avoidance of inhaled antigens. A specific treatment for severe AAT deficiency is the infusion of pooled human AAT, termed "augmentation therapy," which may slow the decline of lung function evaluated by pulmonary function tests or computed tomography densitometry.[5-8]

In order to identify these individuals, the American Thoracic Society (ATS) and the World Health Organization recommend testing all persons with chronic obstructive pulmonary disease and unexplained liver disease for AAT deficiency; however, there is low uptake of this in clinical practice.[9-11] Failure to implement these guidelines has been attributed to inadequate awareness of AAT deficiency, unclear results, cost, testing takes too much time, requiring a referral to a specialist, and the perception that testing will not impact clinical care.[11,12] In practice, clinicians use the known age predilection and family history of chronic obstructive pulmonary disease to guide a more directed screening approach rather than employing the broad ATS and World Health Organization recommendations.[11] Although these intentions may be informed, logical, and well-intended, it lacks consistency and leads to variable practices, which potentially introduces disparities in testing certain groups of people. In this study, we aim to describe testing frequency for AAT deficiency, and we hypothesize that patient characteristics influence who is tested.

CLINICAL SIGNIFICANCE

- Testing for alpha-1 antitrypsin deficiency has low uptake in practice.
- Alpha-1 antitrypsin deficiency is tested in 5.6% of eligible subjects.
- Tobacco use influences alpha-1 antitrypsin testing.
- White race and concomitant chronic obstructive pulmonary disease and liver disease favor testing.
- Increasing age, non-White race, and tobacco use have lower odds of testing.

MATERIALS AND METHODS

Study Population and Clinical Characteristics

This was a retrospective cohort study at the University of Florida (UF) for the period from January 1, 2012 through December 31, 2021 and approved by the institutional review board (IRB202200998). In accordance with the ATS guidelines for AAT testing, subjects who had either newly diagnosed chronic obstructive pulmonary disease or unexplained liver disease as documented by either International Classification of Disease (ICD)-9 codes 491, 492, 496, or 571 or ICD-10 codes J41-44 or K70-K77 during the study period were included. Subjects with liver disease attributed to abscess of liver, central hemorrhagic necrosis of liver, hepatic venoocclusive disease, infarction of liver, peliosis hepatis, and phlebitis of portal vein were excluded. Subjects who had undergone AAT testing prior to the study period were also excluded. Data were collected retrospectively by the UF Integrative Data Repository, which is a clinical data warehouse derived from various clinical and administrative information systems, including the health record system. Data regarding sex, race, ethnicity, and tobacco use were self-reported at the time of registration.

Study Outcomes

The primary outcome in this study was testing for AAT; defined as when a subject had either a serum AAT level or phenotype performed. Determination of which subjects had AAT testing was retrieved from the reported labs in the electronic health record. AAT testing performed and reported outside of UF health system were not available for review. In cases where a subject had multiple AAT phenotype tests, their characteristics were reported in a descriptive manner. The earliest AAT test date was used in statistical analysis. Describing AAT phenotypes was not performed due to the low number of phenotypes reported and the inability to confirm the technique, methodology, and standardization of AAT testing at the numerous labs performing and reporting results over the study period. To examine the differential for testing, we selected the covariates sex, race, ethnicity, tobacco use history, presence and age of diagnosis of chronic obstructive pulmonary disease, and presence and age of diagnosis of liver disease.

Statistical Analysis

Data are presented in a descriptive manner with median and 25^{th} and 75^{th} percentiles (interquartile range) for continuous variables and frequencies with percentages for categorical variables. Incidence of AAT testing over the study period was calculated by dividing the number of subjects tested for AAT by the number of new cases of chronic obstructive pulmonary disease and liver disease. Annual incidence was calculated by dividing the number of subjects tested for AAT by the number of new cases of chronic obstructive pulmonary disease and liver disease during the calendar year. To evaluate the relation between AAT testing and the number of years a subject used tobacco, we performed a point-biserial correlation analysis. Multivariable binary logistic regression analyses were performed for the outcome of AAT deficiency testing for subjects newly diagnosed with either chronic obstructive pulmonary disease or liver disease during the study period and adjusted for sex, race (White or non-White), ethnicity (Hispanic or non-Hispanic), presence of chronic obstructive pulmonary disease and age of diagnosis, presence of liver disease and age of

diagnosis, and tobacco history. We included all possible predictors in the final models, as they all represent possible confounders between the diagnosis of chronic obstructive pulmonary disease and liver disease and the decision of testing for AAT deficiency. Odds ratios with 95% confidence intervals were reported for logistic regression models. The significance level for all tests was an alpha of < .05. Analyses were performed with R Statistical Software, version 4.1.2 (R Foundation for Statistical Computing).

RESULTS

Study Cohort

A total of 75,810 subjects were identified by our criteria. Table 1 displays the subject characteristics in the entire cohort as well as grouped by AAT untested (n = 71,562) and tested (n = 4248). Of the 4248 subjects tested for AAT deficiency, all subjects had serum AAT levels and 1654 (39%) had phenotype testing. The median AAT level was 149 mg/dL (interquartile range 128-177 mg/dL). There were 273 (6.4%) subjects with a serum AAT level <100 mg/dL, and 30 (0.7%) subjects had a level <57 mg/dL. There were 22 subjects who had repeated AAT phenotype testing, and subjects with isolated liver disease were most frequently retested (n = 11), followed by combined chronic obstructive pulmonary disease and liver disease (n = 10), then isolated chronic obstructive pulmonary disease (n = 1). All repeated AAT testing yielded identical phenotypes except for one subject who had isolated liver disease and resulted SS then MM, which we suspect is the result of a liver transplant rather than lab error.

Incidence of AAT Testing

Throughout the study period, the incidence of AAT testing was 5.6%, or roughly 1 of 18 eligible subjects. Among subjects with newly diagnosed chronic obstructive pulmonary disease, the incidence of AAT testing was 3.3%, or 1 of 30 eligible subjects, whereas subjects with newly diagnosed liver disease had an incidence of AAT testing of 8.4%, or 1 of 12 eligible subjects. The annual incidence of testing for subjects newly diagnosed with chronic obstructive pulmonary disease or liver disease are depicted in Figures 1 and 2, respectively. For subjects with chronic obstructive pulmonary disease, the annual incidence of testing increased from 2.8% in 2012 to 4.1% in 2021. For subjects with liver disease, the annual incidence of testing increased from 5.4% in 2012 to 11.3% in 2021.

Clinical Characteristics and AAT Testing

There was an inverse correlation between AAT testing and how many years a subject reported using tobacco ($r = -0.06$, 95% CI -0.07 to -0.05, $P < .001$), indicating that the longer an individual smoked, the less frequently they were to be tested for AAT. Separate multivariable analyses were performed to examine the outcome of AAT testing in subjects with either a new diagnosis of chronic

Table 1 Subject Characteristics With Comparisons Between the Untested and Tested Cohorts

Variable	Entire Cohort	Untested Cohort	Tested Cohort
Total subjects	75,810	71,562	4248
Sex (male)	37,881 (50%)	35,804 (50%)	2077 (49%)
Race			
White	59,744 (79%)	56,276 (79%)	3468 (82%)
Black	9527 (13%)	9119 (13%)	408 (10%)
Asian	772 (1%)	722 (1%)	50 (1%)
Multiracial	353 (0.5%)	321 (0.4%)	32 (0.8%)
American Indian	160 (0.2%)	151 (0.2%)	9 (<0.1%)
Pacific Islander	12 (<0.1%)	12 (<0.1%)	0 (0%)
Other	3412 (5%)	3189 (4%)	223 (5%)
Unknown	1830 (2%)	1772 (2%)	58 (1%)
Ethnicity			
Non-Hispanic	70,099 (92%)	66,206 (93%)	3893 (92%)
Hispanic	3628 (5%)	3350 (5%)	278 (6.5%)
Unknown	2083 (3%)	2006 (3%)	77 (2%)
Presence of COPD (yes)	40,173 (53%)	38,841 (54%)	1,332 (31%)
Age diagnosed with COPD (year)	64 (56-73)	64 (56-73)	58 (51-66)
Presence of liver disease (yes)	43,763 (58%)	40,072 (56%)	3691 (87%)
Age diagnosed with liver disease (years)	56 (44-66)	56 (44-66)	54 (42-63)
Tobacco use status			
Current	17,784 (23%)	16,998 (24%)	786 (19%)
Former	30,181 (40%)	28,522 (40%)	1659 (39%)
Never	23,375 (31%)	21,696 (30%)	1679 (40%)
Passive	352 (0.5%)	324 (0.5%)	28 (0.7%)
Unknown	4118 (5%)	4022 (6%)	96 (2%)

COPD = chronic obstructive pulmonary disease.

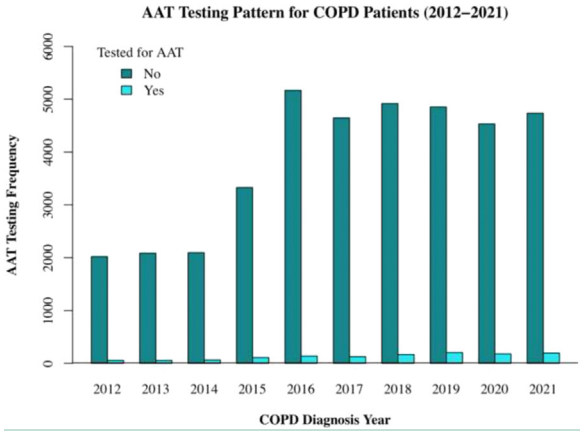

Figure 1 Annual incidence of alpha-1 antitrypsin (AAT) testing for patients with chronic obstructive pulmonary disease (COPD) from 2012 through 2021.

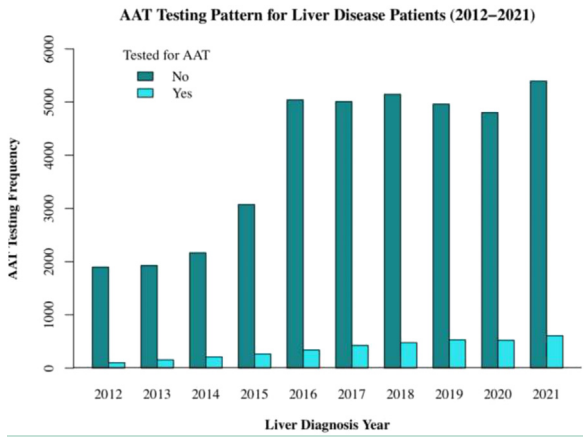

Figure 2 Annual incidence of alpha-1 antitrypsin (AAT) testing for patients with liver disease from 2012 through 2021.

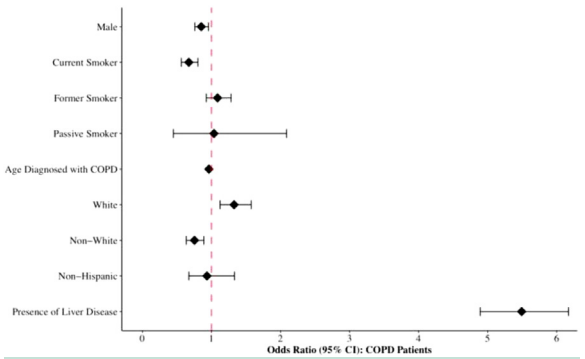

Figure 3 Odds ratios for alpha-1 antitrypsin (AAT) testing in subjects with chronic obstructive pulmonary disease (COPD) according to specified variables. A nominal, multivariable logistic regression model was performed for the outcome of AAT testing adjusted for age of diagnosis with COPD, sex, race (White vs Non-White), ethnicity, presence of liver disease, and tobacco history (never smoker control). CI = confidence interval.

obstructive pulmonary disease or liver disease during the study period and adjusted with the covariates sex, race (White or non-White), ethnicity (Hispanic or non-Hispanic), tobacco use history, presence of chronic obstructive pulmonary disease, presence of liver disease, and corresponding age of diagnosis. For subjects with newly diagnosed chronic obstructive pulmonary disease during our study period, higher odds for AAT testing were found in subgroups of individuals of White race and individuals with concomitant liver disease (Table 2, Figure 3). Lower odds of AAT testing were seen in subgroups of men, individuals of non-White race, current tobacco use, former tobacco use, and with increasing age. For subjects with newly diagnosed liver disease during the study period, higher odds for AAT testing were found in subgroups of individuals of White race, former smokers, and concomitant chronic obstructive pulmonary disease (Table 3, Figure 4). Lower odds of AAT testing were noted in older patients, individuals of non-White race, and those with current tobacco use.

DISCUSSION

The results of our study suggest that the rate of AAT testing continues to be low in clinical practice despite guidelines for the last 20 years recommending broader testing. Also, a serum level was the preferred testing method, and specific populations have characteristics that influence testing.

Based on population genetics and newborn screening, we understand that AAT deficiency affects 1%-2% of those with chronic obstructive pulmonary disease, and occurs in 1 of 1600-5000 individuals in the general population.[2,13-15] In the United States there is an estimated 15 per 1000 persons with a Z allele and 62,820 subjects with homozygous "ZZ," although only approximately 10,000 subjects with "ZZ" have been diagnosed.[16] These findings raise the questions of why so few have been identified and whether low testing may be contributing to detection. Studies reviewing the frequency of testing chronic obstructive pulmonary

Table 2 Odds Ratios for AAT Testing in Subjects With COPD According to Specified Variables

Variable	OR (95% CI)	*P* Value
Age, years	0.96 (0.96-0.97)	< .001
Sex (male)	0.85 (0.76-0.96)	< .001
Race (White)	1.33 (1.12-1.58)	< .001
Race (Non-White)	0.75 (0.63-0.89)	< .001
Ethnicity (Non-Hispanic)	0.93 (0.67-1.33)	.70
Presence of liver disease	5.49 (4.89-6.17)	< .001
Tobacco history (current smoker vs never smoker)	0.13 (0.08-0.20)	< .001
Tobacco history (former smoker vs never smoker)	0.21 (0.14-0.32)	< .001

AAT = alpha-1 antitrypsin; CI = confidence interval; COPD = chronic obstructive pulmonary disease; OR = odds ratio.

A nominal, multivariable logistic regression model was performed for the outcome of AAT testing adjusted for age of diagnosis with COPD, sex, race (White vs Non-White), ethnicity, presence of liver disease, and tobacco history (never smoker control).

Table 3 Odds Ratios for AAT Testing in Subjects With Liver Disease According to Specified Variables

Variable	OR (95% CI)	*P* Value
Age, years	0.99 (0.99-0.99)	< .001
Sex (male)	1.05 (0.98-1.13)	.15
Race (White)	1.40 (1.28-1.54)	< .001
Race (Non-White)	0.71 (0.65-0.78)	< .001
Ethnicity (Non-Hispanic)	0.94 (0.82-1.08)	.38
Presence of COPD	1.35 (1.23-1.48)	< .001
Tobacco history (current smoker vs never smoker)	0.88 (0.79-0.97)	.01
Tobacco history (former smoker vs never smoker)	1.12 (1.03-1.22)	< .001

AAT = alpha-1 antitrypsin; CI = confidence interval; COPD = chronic obstructive pulmonary disease; OR = odds ratio.

A nominal, multivariable logistic regression model was performed for the outcome of AAT testing adjusted for age of diagnosis with liver disease, sex, race (White vs Non-White), ethnicity, presence of COPD, and tobacco history.

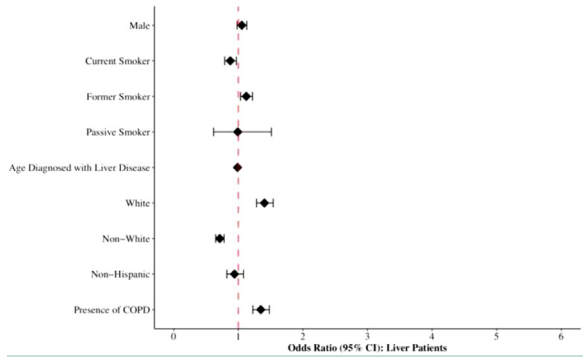

Figure 4 Odds ratios for alpha-1 antitrypsin (AAT) testing in subjects with liver disease according to specified variables. A nominal, multivariable logistic regression model was performed for the outcome of AAT testing adjusted for age of diagnosis with liver disease, sex, race (White vs Non-White), ethnicity, presence of chronic obstructive pulmonary disease (COPD), and tobacco history. CI = confidence interval.

disease subjects in the United States are limited, but low testing has been described in the United Kingdom and Spain. In a study by Soriano et al[17] of the Optimum Patient Care Research Database in the United Kingdom and comprising approximately 550 general practices, 2.2% of eligible subjects with chronic obstructive pulmonary disease under the age of 60 years were tested. Their analysis spanned from 1990 until 2013 and showed an increased annual incidence of AAT testing over time. However, these results may have been confounded by the development and subsequent tracking of electronic ordering that evolved during that time frame.[18] In Spain there are an estimated 14,500 subjects with AAT deficiency, and approximately 511 have been identified.[16,19] In a study by Calle Rubio et al,[20] they examined the AAT testing frequency for patients with chronic obstructive pulmonary disease at 57 hospitals. In 1 year's time, 4405 patients with chronic obstructive pulmonary disease were evaluated, and 995 (22.5%) patients had AAT testing. They also examined patient characteristics associated with testing, which found that individuals <55 years of age had higher odds of testing, similar to our study. We hypothesize that this finding is related to the awareness that individuals with severe AAT deficiency have an earlier onset of obstructive lung disease compared with usual chronic obstructive pulmonary disease. In the National Heart, Lung, and Blood Institute registry of 1129 subjects with severe AAT deficiency, the mean age was 46 ± 11 years, as compared with the sixth and seventh decades of life seen in usual chronic obstructive pulmonary disease.[21] However, individuals with chronic obstructive pulmonary disease and "MZ" AAT deficiency present at a different age. For example, the COPDGene, ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints), and LTRC (Lung Tissue Research Consortium) showed that "MZ" subjects have a mean age of 60.56−65.91 years, not unlike those with usual chronic obstructive pulmonary disease.[4]

In addition to this age discrepancy, these databases also found that "MZ" have an average of 36.70-51.34 pack years of smoking, which was similar to "MM" subjects.[4] Subjects with "MZ" and "SZ" also have high odds of being current smokers when compared with "ZZ" patients.[22] Our findings showed individuals with more years of tobacco use were tested less frequently, current smokers were tested less, and conflicting testing patterns for former smokers. For unclear reasons, this suggests a patient's tobacco history influences the decision to test for AAT deficiency and opens the door to potentially not detecting patients with AAT deficiency. Because it is known that tobacco is the most important risk factor for developing chronic obstructive pulmonary disease, we question if a proportion of patients with AAT deficiency with less severe symptoms or milder pulmonary function test (PFT) changes are victims of search satisficing bias, which is the tendency to stop searching for a cause once another explanation is found.[23,24] For example, when a patient with chronic obstructive pulmonary disease has a history of tobacco use, it provides a readily explainable reason to call a physician off from investigating for another process, such as AAT deficiency. In support of testing individuals actively using tobacco, we know that the subject's awareness of an AAT deficiency diagnosis has a significant impact on their tobacco cessation. Subjects with AAT deficiency have 3.3 times higher odds of quit attempts compared with nondeficient individuals, and "ZZ" subjects have a 92% quit rate.[25,26]

The testing patterns at our institution favored White individuals. There is significant variability of AAT deficiency among different racial and ethnic groups. The most common severe allelic combination, "ZZ," is reported to occur in 1/4472 White Americans, 1/11,954 Hispanic Americans, 1/153,000 Black Americans, and virtually nonexistent in Asian American populations.[27] The lower odds of testing non-White races may align with reported epidemiological prevalence, but this finding, as well as the age and tobacco disparities, force us to look inward and question how much implicit and explicit bias is present as well.

From an explicit bias standpoint, the classical understanding of an AAT deficiency patient reflects a "ZZ" clinical picture, which is a younger White individual with liver or lung disease and disproportionally lower tobacco exposure. The testing patterns shown in our study support this perception; yet, AAT deficiency patients have a broader clinical presentation. Emerging evidence demonstrates that the "MZ" allelic combination is associated with lung disease that is distinct from both "MM" and "ZZ" subjects.[3,4] This raises the suggestion of redefining our perception of an AAT deficiency patient and improving testing rates to identify them.

Improvement in testing rates has been achieved in the form of population-based screening, case-finding, and targeted detection methods. Newborn screening studies performed in Oregon, New York, and Sweden demonstrated detection rates for severe AAT deficiency in approximately 1 in 1600-5000 infants.[13,14,28] Nevertheless, AAT testing

has not been included in newborn screening, in part due to the risk−benefit ratio of newborn testing, increased psychosocial stress in patients and families, and the operational costs and logistics of testing.[29] Studies have also focused on targeting populations with obstruction on PFTs by educating respiratory therapists to offer AAT testing and annotating PFT reports to recommend AAT testing, which increased testing from 6% to 13%.[30-32] Using the electronic medical record to generate an alert for those patients with qualifying obstructive lung disease has also increased testing rates from approximately 5% to 68%.[33-35] When Calle Rubio et al evaluated subjects with chronic obstructive pulmonary disease and testing patterns, they found that subjects who had management at a specialized center also had higher odds of testing.[20]

There are a number of limitations with this study, including the singular institution practices on our specific population. Also, the rates of testing may be an underestimation, because subjects may have had testing at a laboratory outside of our institution or through direct-to-consumer genetic testing (eg, 23andMe, South San Francisco, Calif).[36] There is also an AAT deficiency detection program based in our catchment area, and upon review, approximately 800 subjects completed AAT deficiency testing in this catchment area. These subjects were not included for 2 reasons. Firstly, the aim of the study was focused on individuals receiving care at the institution and not in a specific geographic area. Secondly, we could not calculate testing incidence for the geographic area because it is unknown how many subjects with newly diagnosed chronic obstructive pulmonary disease or liver disease did not receive care at our institution. A point could also be made that testing rates may be overestimated due to the presence of a large detection program, which raises awareness for the disease. Although chronic obstructive pulmonary disease and unexplained liver disease account for the majority of subjects eligible for testing, other indications do exist, for example, panniculitis and vasculitis. These indications were not included because their presumed small sample size would not be powered to detect differences among the variables. Lastly, there may also be unaccounted factors that influence a health care provider's decision to test, such as family history of AAT deficiency, PFT results, chest imaging, functional status, psychosocial support, and subject preference, which were not readily available for review.

CONCLUSION

Although slowly improving, testing for AAT deficiency continues to have a low uptake in the clinical setting. White subjects and those with concomitant chronic obstructive pulmonary disease and liver disease are more likely to be tested, while older subjects, individuals of non-White races, current tobacco use, and men with chronic obstructive pulmonary disease are less likely to be tested. These findings continue to support further investigation and improvement in AAT testing and detection.

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