

Alpha-1 Antitrypsin Deficiency Healthcare Provider's Guide



Addressing the need for providing up-to-date information about screening, diagnosis, and treatment of this disorder



Foreword

Alpha-1 Antitrypsin Deficiency (AAT Deficiency) is one of the most common serious hereditary disorders. AAT Deficiency has been identified in virtually all populations but is most common in individuals of Northern European (Scandinavian and British) and Iberian (Spanish and Portuguese) descent. Among patients with Chronic Obstructive Pulmonary Disease (COPD), up to 3% are predicted to have AAT Deficiency. It can also cause life threatening liver damage in adults and children and liver cancer in adults. Despite its prevalence, patients and healthcare providers have been poorly informed about the disorder. For this and other reasons, the overwhelming majority of individuals with AAT Deficiency have not been detected. Of the more than 100,000 individuals in the United States estimated to have AAT Deficiency, less than 10% have been diagnosed, leaving more than 90,000 affected individuals undetected.

The discovery of AAT Deficiency by Laurell and Erickson in 1963 provided a foundation for current thinking about the pathogenesis of pulmonary emphysema. Although AAT Deficiency has become one of the best-understood genetic disorders at a molecular and cellular level, many questions about the clinical disorder remain unanswered.

The Alpha-1 Foundation, the National Institutes of Health (NIH) and pulmonary and liver disease experts are working aggressively to develop patient management and clinical treatment guidelines for working with patients affected by AAT Deficiency.

Healthcare Provider's Guide

This *Healthcare Provider's Guide to Alpha-1 Antitrypsin Deficiency* is a response by the Alpha-1 Foundation to the need for providing up-to-date information about screening, diagnosis, and treatment of this disorder. Materials in this document are designed to educate physicians, their staff members, and patients about Alpha-1 Antitrypsin Deficiency (AAT Deficiency) and the resources that are available for affected individuals, their family members and healthcare providers. An Educational Materials Working Group assists the Foundation's Medical and Scientific Advisory Committee (MASAC) in identifying, producing, and reviewing educational and training materials. The Working Group is comprised of a wide range of professionals, including bioethicists, physicians, nurses and educators, all contributing their expertise. Individuals with AAT Deficiency are also included in the Working Group membership to add their personal expertise. Acknowledgment is made to all of these individuals and the many others who have provided insightful and helpful editorial comments. The Foundation also has educational materials for your patients, several available in multiple languages, including:

What is Alpha-1 Antitrypsin Deficiency?

A Guide for the Recently Diagnosed Individual

What Does It Mean to Be an Alpha-1 Carrier?

The Liver and Alpha-1

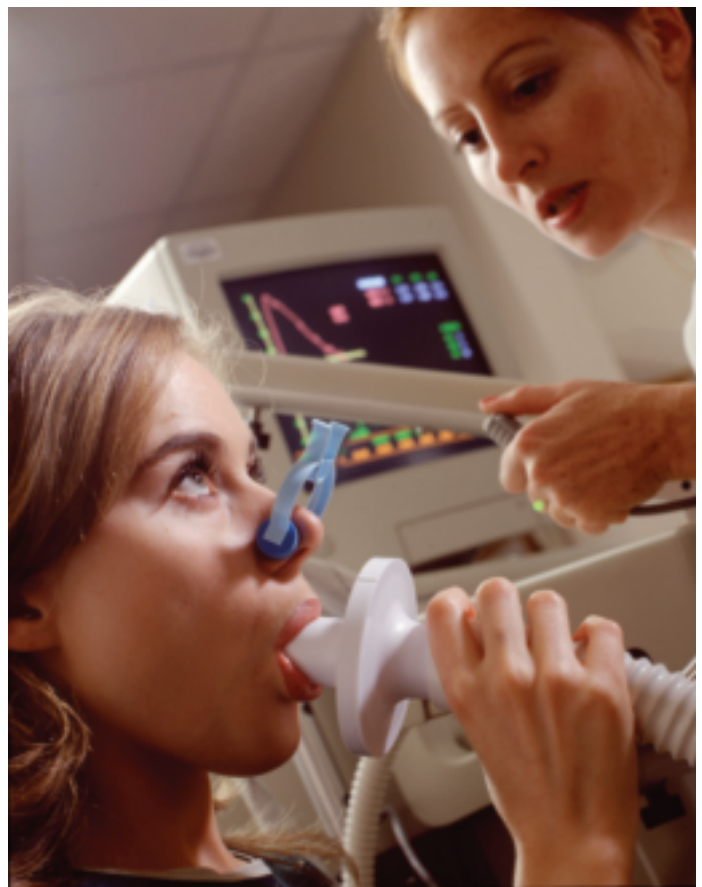
Overview and Disorder Description

What Is Alpha-1 Antitrypsin?

Alpha-1 antitrypsin (AAT) is a protein that circulates in the blood. Some scientists also call it "alpha1-proteinase inhibitor" or A1PI. The liver makes most of the circulating AAT in the blood. AAT protects the tissues of the body from being damaged by proteolytic enzymes (enzymes that break down proteins), especially neutrophil elastase, an elastin-degrading proteolytic enzyme released by neutrophils (acute inflammatory white blood cells) in response to an inflammatory stimulus.

What is Alpha-1 Antitrypsin Deficiency?

Alpha-1 Antitrypsin Deficiency (AAT deficiency) is a genetic disorder characterized by the production of an abnormal AAT protein. In most cases, the liver cells cannot secrete the abnormal AAT protein, which often accumulates within the cells and results in marked reductions of circulating AAT levels. Although the mechanisms are not completely known, it is believed that the retained abnormal AAT protein over time leads to liver injury in some affected persons. In the lungs, low-levels of AAT allow for the destructive effects of neutrophil elastase to go unchecked, which results in damage to the delicate gas exchange region of the lungs (alveoli), eventually leading to emphysema in individuals as young as 30 years of age. Thus, persons with AAT Deficiency are at high risk of developing life-threatening liver and lung disease. There are a number of other clinical conditions that have been associated with AAT Deficiency as well.



Epidemiology of AAT Deficiency

AAT Deficiency is the most prevalent potentially fatal genetic disorder of adult Caucasians in the U.S., and occurs approximately equally in men and women. The incidence of AAT Deficiency in the general Caucasian population is estimated between 1/2500 and 1/3000 in the U.S.; as a comparison, Cystic Fibrosis (CF) has an incidence in whites of 1/2500. Continuing the comparison with CF, because of the greater lifespan of well-treated AAT deficient individuals compared with CF, the prevalence of AAT Deficiency is more than three-fold that of CF.

Untargeted screening studies of large populations have revealed a variable prevalence of AAT Deficiency, depending upon the race and ethnicity of the study population. In addition, there have been several reports of screening studies in smaller populations of targeted individuals. These individuals have included adults with emphysema, chronic bronchitis, COPD, bronchiectasis, and asthma, as well as children with chronic liver disease. These targeted populations were identified based on the increased prevalence of these conditions among persons with AAT Deficiency.

AAT Deficiency can appear as a chronic lung disease (i.e., emphysema, chronic bronchitis, COPD, bronchiectasis, and asthma) in adults as early as the third decade of life, especially in smokers. Nevertheless, symptomatic AAT Deficiency can be diagnosed in adults in all decades. Finally, some persons with AAT Deficiency can live completely normal life spans without significant symptoms, especially if they reduce or eliminate risk factors such as cigarette smoke.

Liver disease related to AAT Deficiency can manifest at any age. In infancy, the liver disease commonly takes the form of neonatal cholestasis or liver failure. AAT Deficiency should be suspected in older children, adolescents and adults with elevated liver enzymes, prolonged clotting tests, enlarged liver and/or spleen, portal hypertension, esophageal varices, ascites, or “cryptogenic” cirrhosis. AAT Deficiency is the leading genetic cause of liver disease in infants and children and among the most common indications for liver transplantation in this group in the U.S. The risk of hepatocellular carcinoma is increased in adults with AAT Deficiency. However, the percentage of individuals with clinically significant liver disease in individuals with AAT Deficiency is relatively low. Recent evidence suggests that there is some increased risk of liver and lung disease in persons who are Z-allele heterozygotes (Pi MZ), although these issues are still under investigation.

Liver disease has not been identified in persons with the rare Pi null/null phenotype, who do not produce any AAT protein.

Genetics of AAT Deficiency

The accumulated knowledge about AAT Deficiency is the result of many studies conducted worldwide. The two most important genetic aspects of AAT Deficiency are: (1) the understanding that there are over 200 genetic mutations of the AAT gene identified and (2) the appreciation that a minority of the identified mutations cause AAT Deficiency; the rest are variants that don't appear to affect AAT levels or function.

A pair of alleles at the proteinase inhibitor (Pi) locus controls the synthesis of AAT. The genes are inherited as co-dominant alleles (products from both genes can be found in the blood). AAT in the serum can be characterized by Pi-typing (previously referred to as phenotyping) which identifies the expressed AAT proteins in the blood. “Pi” reflects the fact that AAT is a protease inhibitor and Pi-typing is usually performed by isoelectric focusing and requires an experienced eye for interpretation of the results.

Examples of Results Reported by Pi-Typing and their Meaning

Pi-type	What does it mean?
Pi Z (ZZ) (Homozygote)	Patient HAS severe Alpha-1 Antitrypsin Deficiency
Pi MZ (Heterozygote)	Patient has a heterozygote (carrier) for Alpha-1 Antitrypsin Deficiency and can pass an abnormal gene on to their children
Pi M (MM)	Patient doesn't NOT have Alpha-1 Antitrypsin Deficiency Pi-type

Please note that Pi-typing for AAT Deficiency is very complicated. The most common variants of AAT Deficiency are discussed in detail below; there are also many other possibilities.

More commonly, testing for AAT Deficiency relies on evaluating the DNA of the AAT gene (also called the SERPINA1 gene). Most commercial facilities rely on DNA probes specific for the two to four most common genetic variants. Thus, a result reflects whether, for each of the two AAT alleles, a Z or an S gene is present (see page 5 for a discussion of these alleles). If

neither is present, the gene is assumed to be normal (M). A growing number of laboratories are able to perform sequencing of the AAT gene. This type of evaluation, while expensive, can detect all known variants of the AAT gene and even identify new variants. Sequencing is currently quite expensive but the costs are dropping very rapidly.

Generally, AAT genotypes are separated into two categories: (1) normal variants of AAT (those that produce and distribute active AAT at normal levels in the blood and tissues); and (2) deficient variants (those that produce reduced or no AAT levels in the blood and tissues or produce a defective protein and which lead to an increased risk of AAT Deficiency-related disease).

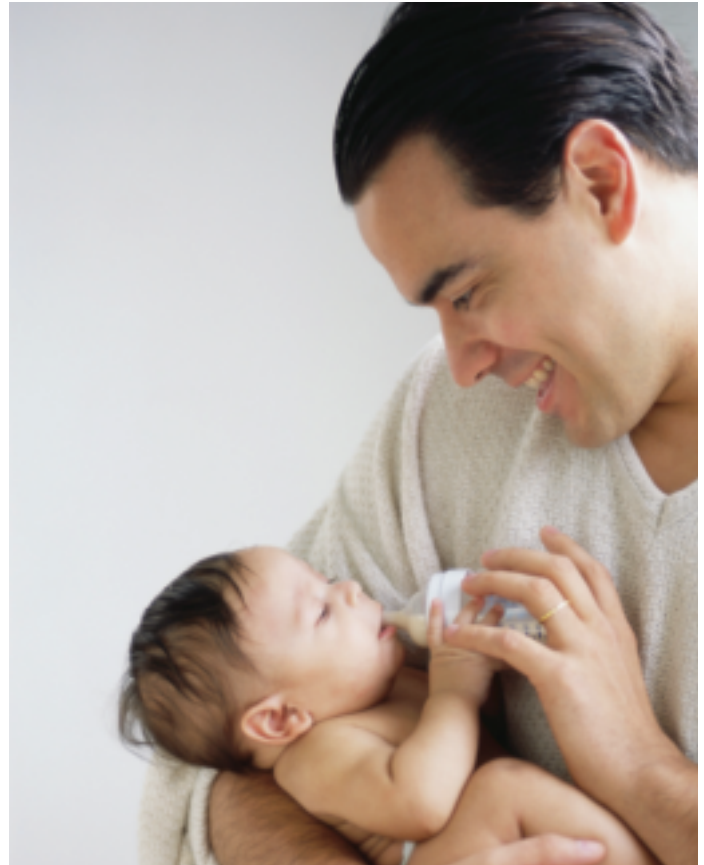
Common Alleles:

The family of the normal AAT alleles is referred to as M (or Pi M). The M alleles are the most common types of AAT gene and result in normal amounts and normal functionality of AAT in the blood. About 95% of the population of the United States has only M alleles. There are other normal alleles, and at least six identified variants of the M allele (usually labeled M1, M2, M3, etc.).

The most prevalent deficient alleles associated with AAT Deficiency are the S and Z alleles. Most individuals identified with AAT Deficiency have Pi-type Z (that is, express only the Z variant in the blood and presumably have two Z genes for AAT). The S allele is actually more prevalent than Z in the U.S. population. Since the S allele leads to a less severe depression of AAT levels, it causes less disease, and is therefore found less frequently. This is because most individuals who are found to have AAT Deficiency have been tested because of unexplained clinical symptoms.

The Z variant is less effective as an inhibitor of neutrophil elastase than the normal protein (M). However, the most striking abnormality in individuals with two Z alleles is that circulating levels of the protein are only 10-15% of normal. When livers of these individuals are examined, hepatocytes often contain an abnormal accumulation of polymerized AAT protein. This aggregated AAT cannot be released effectively from liver cells. As a result, the levels in the blood are decreased and the retained AAT may cause injury to the liver.

As mentioned above, the S allele produces the S variant AAT protein and is associated with mild AAT Deficiency. The S mutation is not associated with intracellular accumulation of the protein, and the



S protein inhibits elastase nearly normally. Individuals with Pi S phenotype do not appear to be at an increased risk for lung or liver disease (Pi S individuals who are heterozygous with the Z allele are discussed on page 6).

Another variation is represented by the null alleles. The null alleles are a group of AAT mutations that express no AAT protein in the blood. Note that in Pi Z individuals, Pi-typing reveals only an abnormally migrating Pi Z type of AAT. These individuals may be either Pi ZZ homozygotes or Pi Z/null heterozygotes, since no AAT attributable to the null genes can be found in the circulation. Of interest, commercial genotyping may identify a Z/null heterozygote as Pi MZ, because in the absence of an S or Z allele, most laboratories will assume the second allele is M. There has been no evidence of liver disease in the Pi null/null population. Also, in cases of Pi M phenotypes associated with low levels of AAT, there is the possibility that a null allele might be present. Family studies of the pattern of inheritance and more sophisticated testing are necessary to distinguish between these possibilities. When paternity (or maternity) issues arise during family testing for AAT Deficiency, many times these are explained by the presence of an unappreciated null allele.

Common Heterozygotes:

Pi MS individuals have one normal allele and one S allele. They usually have normal or slightly decreased levels of AAT. They do not appear to be at an increased risk for lung or liver disease. Pi MZ individuals have one normal allele and one Z variant (the most commonly identified deficiency variant). They usually have decreased levels of AAT in their circulation; however, their levels can fall within the normal range. Although this issue remains under investigation, recent studies suggest that Pi MZ heterozygotes have a slightly increased risk for developing lung or liver disease compared to the general population with normal AAT genes. At present, it seems prudent to educate Pi MZ heterozygotes regarding their potential risk for developing lung or liver disease and recommend avoiding risk factors for lung and liver disease, especially tobacco smoke. Counseling about the risk of genetic inheritance of the deficient allele should also be considered.

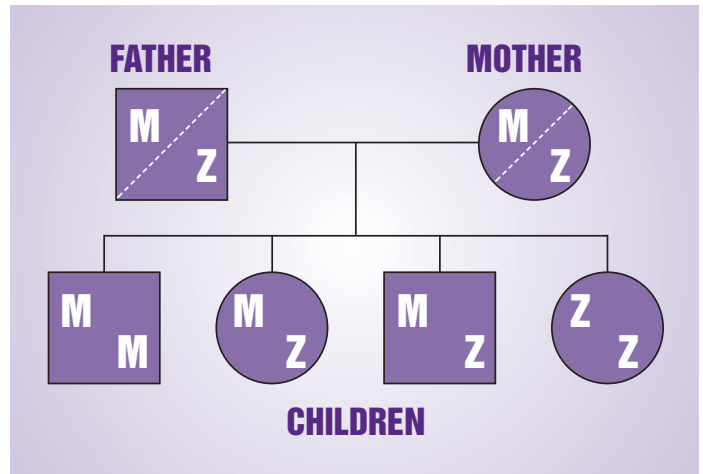
Pi SZ individuals have one allele for the S variant and one for the deficient Z variant. Pi SZ heterozygotes are statistically more common than those with Pi ZZ but are less frequently identified because their risk for disease is considerably less than for PiZZ individuals. Pi SZ individuals have some increased risk of lung or liver disease. As for persons who are Pi MZ, Pi SZ individuals should be educated regarding their potential risk for developing lung or liver disease, and counseled about the risk of genetic inheritance of the deficient alleles. Pi SZ individuals should also avoid risk factors such as tobacco smoke.

Genetic Inheritance:

Genetic inheritance of AAT Deficiency follows simple Mendelian principles. Individuals with AAT Deficiency have two deficient alleles for the protein (e.g. Z, S, null and/or rarer alleles). Thus, the deficiency is inherited similarly to an autosomal recessive condition. Brothers and sisters of deficient individuals have a significant chance of also having the condition. Children of deficient individuals are usually heterozygous (a “carrier”) for the deficiency (assuming the patient’s spouse is a Pi M). Among U.S. Caucasians, approximately 3-6% are carriers. These people often have reduced levels of the protein, but have minimal excess risk of lung or liver disease. Pi typing or genotyping is necessary to reliably detect carriers, since AAT levels of normal individuals and carriers can overlap.

EXAMPLE:

AAT Deficiency is a genetic disorder. Look at the figure below to see the possible outcomes for children if both parents are carriers of an abnormal AAT gene.



Normal	(MM)	Does not have the disorder and does not carry any altered AAT genes.
Carrier	(MZ)	Mild to moderate AAT Deficiency — may develop disease symptoms and does carry an altered AAT gene.
Carrier	(MS)	One altered AAT gene (most studies do not indicate an increased risk for disease).
AAT deficient	(ZZ or SZ)	Moderate to severe deficiency — could develop disease and does carry two altered AAT genes.
AAT deficient	(SS)	Two altered AAT genes (most studies do not indicate an increased risk for disease).

Diagnosis

Family History:

A positive family history of AAT Deficiency is the greatest risk factor for AAT Deficiency. The implications for finding ALL family members who may be carriers or severely deficient are of great importance.

Identification of Patients:

You should test adult patients with the following problems, as recommended by current standards and guidelines:

- COPD
- Chronic Asthma
- Family history of AAT Deficiency
- Chronic liver disease

Other conditions possibly indicating an increased risk for AAT Deficiency include:

- Bronchiectasis
- Necrotizing Panniculitis
- Unexplained vasculitis, particularly granulomatosis with polyangiitis
- Hepatocellular carcinoma

It is important to understand that if these conditions are seen in non-smokers of any age, or if COPD occurs at an early age (under 55 years) in smokers, the likelihood of AAT Deficiency is increased.

Patients with unexplained liver disease should also be considered for testing. Here is a list of common symptoms that may indicate the presence of liver disease:

- Increased abdominal swelling or edema of the extremities
- Coughing up or vomiting bright red blood
- Blood in toilet or diaper
- Blackish, purplish or dark colored stools
- Acholic (pale) stools in neonates
- Confusion, crankiness, unusual crying, disorientation, lethargy
- Little or no urine
- Dark (tea or cola-colored) urine
- Lack of energy, easily fatigued
- Fever
- No appetite/refusal to eat or drink
- Itching or increased itching
- Jaundice



Evaluation of AAT Deficient Patients:

After confirming the AAT Deficiency status of your patient, you may want to consider the following baseline assessments:

Baseline Examination

- Physical Exam
- Posteroanterior (PA) and Lateral Chest X-Ray or a high resolution CT of the lungs
- Pulmonary function test, including:
 - Spirometry (before and after inhaled bronchodilator)
 - Lung volumes
 - Diffusion capacity
 - Oximetry or arterial blood gases
- Liver function test, including:
 - AST
 - ALT
 - Total and Direct bilirubin
 - Albumin
 - INR
 - Liver ultrasound examination

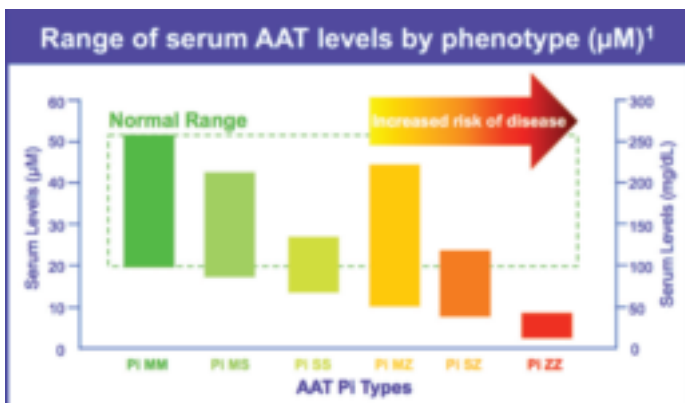
Testing:

In general, testing for AAT consists of an assay for AAT levels followed by genotyping or Pi-typing. Genotype or Pi-typing should be performed:

1. If the level AAT is abnormal, and/or,
2. If there is a known family history of AAT Deficiency, and/or,
3. If there is otherwise unexplained liver disease or emphysema.

Individuals found with a serum level of $11\mu\text{M}$ (= 58 mg/dL) or less, or a deficient Pi-type or genotype are considered to have AAT Deficiency.

Genotype/Pi-type & AAT Deficiency:



Modified from D. Waldrop

- μM result can be derived from mg/dL by multiplying by 0.19; mg/dL can be derived from μM by multiplying by 5.3

Treatment



There are several forms of treatment listed in this brochure for the confirmed AAT deficient patient, including these four major areas: Behavioral & Lifestyle Modification, Medical Treatment, Augmentation Therapy and Surgical Options.

The Alpha-1 Foundation is an important resource for the physician with an AAT deficient patient. The Foundation:

- Provides a list of Clinical Resource Centers (CRCs) and physicians who specialize in the care of AAT deficient patients. It may be of value to have your patient seen once a year at a CRC to monitor their AAT Deficiency and coordinate their care with you. Many CRCs have available specialized tests that can serve as a valuable tool in detecting disease and monitoring its progression.
- Provides regular updates on AAT Deficiency research activities and announcements on newly approved treatment products and options.

- Provides access to its Clinical Director for consultation, information, and referral.
- Gives the patient an opportunity to get involved in their personal treatment, by talking with and meeting other Alphas through support groups, social media and telephone calls. Contact (and refer your patients to) the resources listed at the end of this guide for more information and for support and advice for your patients in making important lifestyle changes.

Behavioral & Lifestyle Modification

Individuals with AAT Deficiency should ELIMINATE personal and second-hand tobacco smoke from their lives. Evidence shows that smoking tobacco products significantly increases the risk and severity of emphysema in AAT Deficiency and may decrease life span by ten years or more. Exercise and nutritional plans also contribute to maintaining a healthier body, which places less stress on the lungs. These issues are explored in further detail below:

1. Smoking Cessation

This is the first priority in managing patients with AAT Deficiency. Lifelong non-smokers will have a good chance of avoiding lung disease, even with AAT Deficiency. Current smokers should stop smoking upon diagnosis, since the most severe lung function impairment is seen in current or former smokers. It is well documented that secondhand smoke can be just as important a risk to AAT Deficient patients, especially parental smoking during childhood.

Smoking attracts neutrophils and macrophages to the lungs in large numbers and speeds the development of lung disease. The lungs in individuals with AAT Deficiency do not have the normal defenses against these cells and especially neutrophil elastase.

2. Avoid Environmental Pollution

Case controlled studies have shown it is advisable for Alphas (persons with AAT Deficiency) to avoid inhaled occupational exposures to dust, fumes, and second-hand tobacco smoke. These substances can cause further irritation of the lungs and worsen the current condition of individuals with lung or liver disease.

Avoid both indoor and outdoor air pollution, especially particulates smaller than 10 μm (found in higher industrialized urban regions) and exposure to aerosolized sprays. It is also important to realize that pollutants and infections may be encountered both at home and at work, thus we recommend precautions in both places.

In the Workplace

Patients should avoid exposure to inorganic or organic dust, (i.e., coal, hay, etc.) or irritating gasses (i.e. chlorine, isocyanates, etc.). Your patients should seek the healthiest possible work environment, and demand clean indoor air, with proper ventilation and filtration systems and avoid second-hand tobacco smoke whenever possible. Wear protective clothing, i.e., gloves, etc., when handling any type of chemical compounds since they may be absorbed through the skin and could further damage an already compromised liver. Read labels carefully and be aware of potential dangers from these agents.

In the Home

Advise your patients to avoid certain household chemicals, such as:

- Respiratory irritants
- Chlorine and ammonia (found in common household cleaning products)
- Pesticides

Since bacterial and viral infections are harmful to the lungs, recommend that your patients try to avoid contact with sick or infectious people. Hand washing with an antibacterial soap is the single most effective way to avoid both contracting and spreading infectious diseases.

3. Development of an Exercise Program

Routine exercise can improve mental outlook, stamina and physical well-being. Exercise is essential to all Alphas.

- Supervised aerobic and strength exercises should begin as soon as possible after diagnosis.



- Walking programs (particularly in climate controlled areas such as indoor shopping malls), strolling, swimming, and biking are all excellent forms of exercise, which may be beneficial in improving lung function and endurance.
- It is important for all Alphas to have personally tailored exercise programs carefully monitored by you and/or an exercise specialist. Patients should start exercising slowly and increase levels of exercise over time, as the patient's tolerance for exercise increases. Some physicians recommend the use of a portable oximeter during exercise.

A Pulmonary Rehabilitation Program is highly recommended for Alphas. Pulmonary Rehab, as it is commonly called, can help an individual with pulmonary disease through exercise, breathing retraining, education, smoking cessation, and nutrition counseling. You should recommend a program tailored to your patient's specific needs.

4. Alcohol Consumption

Alcoholic beverages can damage the liver even in normal people. Many authorities recommend low, infrequent or no alcohol consumption for ZZ patients. Patients with any indications of AAT Deficiency-related liver damage should probably avoid alcohol completely.

5. Development of a Nutrition Program

Although there is a lack of formal research regarding the effects of specific nutritional recommendations,

proper eating habits may help to preserve lung and liver function.

It is important for your patient to maintain an ideal body weight, whether he/she has lung/liver disease or not. Since scientific research indicates that people with lung disorders need to consume more calories than "lung-healthy" people, this affects the manner in which your patient should approach nutrition.

Nutritional needs in those patients exhibiting liver complications due to AAT Deficiency are highly individualized. Since sodium and protein intake may become a concern in patients with liver failure, good nutritional advice is recommended. In the AAT deficient individual who exhibits signs of liver complications, fat absorption may be altered; therefore the physician may recommend supplementing the diet with Vitamins A, D, E, and K.

It is very important to inform the individual to carefully read the labels on over-the-counter medications and to be certain to inform the healthcare provider if alternative medicine (i.e., Milk Thistle) or vitamin supplements are being taken.

Recommend to your patients that they should establish or maintain good eating habits. Being overweight or underweight presents risks to individuals with AAT Deficiency. If your patient has lung and/or liver problems, it may help to work closely with a nutritionist or registered dietician, who will be able to set up an individualized nutritional plan.





6. Reducing Stress

Persons with AAT Deficiency (Alphas) report benefits with stress reduction techniques. There are many techniques that help in reducing stress. Here are a few:

- Breathing exercises
- Muscle relaxation
- Biofeedback
- Visualization
- Hypnotherapy
- Positive thinking
- Improving sleep patterns
- Yoga
- Meditation

Information on these relaxation techniques is available at local libraries and bookstores or through the resources listed at the end of this guide.

Medical Treatment

1. Vaccinations (influenza/pneumonia/hepatitis)

It is important for your patient to have a yearly influenza vaccine and a pneumococcal vaccine at recommended intervals. Since his/her lungs are vulnerable to pollutants and infections, the use of these prophylactic vaccinations is of the utmost importance. Furthermore, your patient may find this the easiest and most convenient type of therapy available.

Hepatitis may increase the risk or severity of liver disease in those with AAT Deficiency. Effective vaccines are available for preventing hepatitis A and B and should be administered to all with AAT Deficiency. A vaccine against hepatitis C may be available by the time you read this.

Recommendations:

- Yearly influenza vaccine
- Administration or confirmation of current pneumococcal vaccination
- Hepatitis A vaccine
- Hepatitis B vaccine

2. Aggressive Treatment of Lung Infections

Prompt and aggressive treatment of infections is recommended due to the increased neutrophil elastase burden during infection. It is important for you to recommend to your patients that they notify you immediately when they suspect a lung infection. Here is a list of common symptoms they should be advised about:

- Fever
- Increased shortness of breath
- Increased coughing (may not be productive)
- Chills with fever
- Darkening of color of phlegm or sputum
- Increase in quantity of phlegm or sputum

Because the lungs attract more white blood cells when an infection is present, and the neutrophilic white blood cell releases neutrophil elastase, it is important to control lung inflammation. Early and prolonged antibiotics may help to speed recovery and prevent additional lung injury in AAT Deficiency.

Another piece of preventive advice for the patient should be:

- Avoid people who are sick (infected individuals).
- Avoid children less than five years of age (who are often infectious or exposed to infections).

3. Bronchodilators

Bronchodilators may be useful in relieving the symptoms of AAT Deficiency. Depending on the specific medical history and present condition of the patient, you may advise the use of bronchodilators. Long acting beta-agonists, long acting anticholinergics, and short acting rescue inhalers have all been used with good effect in appropriate AAT Deficient individuals to improve symptoms and decrease exacerbations. In general, the indications are the same as their use in non-AAT deficient COPD.

4. Corticosteroids

Inhaled corticosteroids can be useful as a preventative treatment for AAT Deficiency and oral corticosteroids may be helpful during exacerbations.

5. Supplemental Oxygen

For people who need supplemental oxygen, it has been shown to be life-prolonging. Oxygen can be important for individuals with low blood oxygen levels, during active infections and/or with progressive destruction of the lung tissue. Supplemental oxygen may be needed during exercise, with sleep, and, as lung disease worsens, at rest. Oxygen therapy needs to be guided by oximetry or arterial blood gases performed at various levels of activity and during sleep. For some Alphas, supplemental oxygen is needed when traveling by airplane and airlines should allow individuals to carry approved portable oxygen concentrators for use during flights.

6. Specialized Therapy for AAT Deficiency

There is a specific treatment for lung disease due to AAT Deficiency referred to as augmentation therapy (see next section).

Augmentation Therapy

Augmentation therapy, AAT protein purified from the plasma of healthy human donors, is the only currently available specific treatment for the lung disease associated with AAT Deficiency. It is used to increase the concentration of AAT in the blood and lungs. Augmentation therapy is not a cure; it will not reverse lung damage already present nor treat or prevent AAT Deficiency-related liver problems. Contact the resources listed at the end of this guide for the latest standard of care related to the use of augmentation therapy.

Clinical Criteria for Use

- Currently, augmentation therapy should only be prescribed for patients with AAT Deficiency-related emphysema. This is not a treatment option for AAT Deficiency related liver disease. Augmentation therapy cannot be recommended for individuals with normal lung function. It should be reserved for those with severe AAT Deficiency, usually those with Pi Z, Pi Z/null, Pi null/null, Pi SZ, individuals with other, rarer genotypes with low levels of AAT (< 11 μ M) or individuals with dysfunctional AAT protein

(currently those with Pi F or Pi Pittsburgh genotypes). It should not be prescribed to individuals who do not have AAT Deficiency or to individuals with mildly deficient genotypes.

- Most patients receive their augmentation therapy in the home using a home infusion service. Others have their therapy administered in the physician's office, a freestanding infusion facility, or a hospital infusion facility.
- Some patients infuse themselves or have a spouse, relative, or friend perform the infusion. Special training is required for these methods of infusion.

Safety of Augmentation Therapy

- Augmentation therapy is prepared from pooled human plasma that has been screened for a variety of viruses, including hepatitis, HIV, and West Nile. As an additional precaution against transmission of infectious agents, augmentation therapy undergoes sterilization and viral exclusion and elimination steps during the manufacturing process. At various times during the manufacturing process and after packaging, the medication is tested for infectious agents. Over the more than 25 years since augmentation therapy was first introduced, the safety record of these drugs has been very good.

Known Side Effects

- There are relatively few side effects reported: headache, myalgia, arthralgia, and low back pain are most frequent complaints by patients on therapy, but require no treatment or occasional analgesic use. For patients with severe COPD or heart failure, worsening of shortness of breath may occur.
- It is important to be aware that patients who have both AAT Deficiency and severe IgA deficiency can develop acute anaphylaxis when given augmentation therapy. Therefore, these patients should NOT receive augmentation therapy.
- Other allergic types have been seen but are quite rare.

Surgical Options

Depending on the type and severity of disease, there are two major types of surgery available for those with AAT Deficiency:

- Lung Volume Reduction Surgery
- Organ Transplantation of Lung or Liver. Organ transplantation is reserved for those with end-stage lung or liver disease.

Lung volume reduction surgery (LVRS) has proved beneficial for selected patients based on the experience provided by the National Emphysema Treatment Trial (NETT). Unfortunately, many of the criteria that indicate a beneficial outcome of LVRS are absent in those with lung disease due to AAT Deficiency. In particular, most individuals with emphysema due to AAT Deficiency have diffuse, panlobular disease, two characteristics that predict a poor outcome for LVRS. Recently, non-surgical, bronchoscopic lung volume reduction procedures have been gaining acceptance. These include miniature one-way valves and metal coils. It remains to be seen whether some people with AAT Deficiency might benefit from these procedures.

Lung transplantation has relatively poor survival statistics compared with other organ transplants. On the other hand, individuals with AAT Deficiency who require a lung transplant have among the best survival statistics of any group of lung disease sufferers. Therefore, those with end-stage lung disease from AAT Deficiency should be encouraged to evaluate lung transplant as an option.

Liver transplantation is a highly successful treatment for end-stage liver failure and many infants, children, and adults with AAT Deficiency have had their life changed for the better by an appropriate liver transplant. Of interest, liver transplantation “cures” AAT Deficiency in the sense that a successful liver transplant from a healthy donor with two normal AAT genes will synthesize and export normal levels of Pi M AAT into the blood. All other cells of the body retain their abnormal genes, so the recipient of a successful liver transplant can still pass on one of these genes to their offspring.

Before transplant there are a number of surgical approaches to liver disease that may be used. Paracentesis may become necessary in end stage liver disease with ascites that doesn't respond to diuretic therapy. Portal vein decompression utilizing surgical shunts has long been known to be of benefit in the treatment of portal hypertension when there is evidence of esophageal varices. The portocaval shunt surgical procedure, either side-to-side or end-to-side

is often used if more conservative measures utilized in controlling bleeding, such as sclerotherapy or band ligation, are ineffective and the patient is not a candidate for liver transplant. Surgical treatment options are highly individualized to each patient, as is the decision as to the timing of liver transplantation.

As with all surgery, outcomes depend on a number of issues specific to each person. There are no guarantees regarding the success at treating or improving any individual's medical condition. Please consult with your patient about these options, if appropriate.

Other Issues

Once your patient is diagnosed as having AAT Deficiency, he/she may feel overwhelmed and have many questions. To provide a more comprehensive approach to talking with your patient about the ramifications of an AAT Deficiency diagnosis beyond a purely medical discussion, it may be helpful to review the following material.

The purpose of this section is to give you several scenarios that may arise when dealing with an AAT deficient patient. Each scenario is merely a starting point. Contacting the resources at the end of this guide will provide you and your patient(s) with more in-depth support and strategies for addressing each situation, from the perspective of a person living with AAT Deficiency. These topics include:

1. Psychosocial/Family support
2. Health insurance/Life insurance
3. Employment
4. Reimbursement/Insurance claims
5. Confidentiality

1. Psychosocial/Family Support

Among the most useful steps an individual can take to reach out for support is to contact one of the resources listed at the end of this guide. These organizations exist to help people with AAT Deficiency all over the country. The individual can speak with and meet other people with AAT Deficiency who can provide support and additional information.

Remember to reassure your patient that you are here to assist them along the way, and will answer any questions that will educate, counsel, and console him/her. Getting actively involved with the overall treatment of the individual, which will extend into other aspects of the patient's life, is of utmost importance.

Q: What should I tell my patients about informing their family members?

A: We recommend that, after discussion with you about the potential for genetic discrimination surrounding a diagnosis of AAT Deficiency, they discuss family testing with blood relatives suggesting they learn about this genetic condition and seek testing, because of the genetic nature of the disorder.

Q: Should I encourage my patient to discuss AAT Deficiency testing with other family members?

A: Yes. It is advisable to encourage your patient to inform his or her family members about the genetic aspects of AAT Deficiency and encourage them to seek genetic counseling. You should encourage those who have symptoms to be tested. Other family members should be urged to educate themselves about the disorder and be vigilant for the development of symptoms.

EXAMPLE:

If both parents are carriers, each child has a chance of inheriting AAT Deficiency, a chance of being a carrier of AAT Deficiency, or a chance of having both normal genes.

2. Health Insurance/Life Insurance

Insurance is a major issue for patients diagnosed with AAT Deficiency. Here are some questions you might be asked:

Q: Will the AAT Deficiency diagnosis affect my health insurance?

A: It shouldn't. Both GINA (the Genetic Information Non-discrimination Act) and the Affordable Care Act prevent discrimination based on a genetic diagnosis and exclusion due to pre-existing medical conditions.

If your patient is currently insured:

Instruct your patients to educate themselves regarding:

- Specific insurance benefits regarding coverage and reimbursement.
- Lifetime maximum benefits, if any. The Affordable Care Act is designed to eliminate these lifetime caps on benefits.
- State laws concerning mandatory coverage.

If your patient is currently uninsured:

You may direct your patient to seek professional advice and recommend that they familiarize themselves with the insurance regulations in their state of residence.

While GINA prevents genetic discrimination in health insurance and employment, it does not cover life insurance. Thus someone with AAT Deficiency, even

a carrier of a single gene, can be denied life insurance under current laws and regulations.

3. Employment

Q: Can your patient continue to work?

A: The answer to this question usually depends on two conditions:

- The present state of your patient's health
- The possibility of unwanted airborne exposures (i.e., dust, fumes or other environmental hazard) at work

It is good for individuals with AAT Deficiency to work! Please discuss with your patient his/her health status and assess the possibility of occupational exposure to dust and fumes. If your patient is in acceptable health and has no occupational exposure to dust and fumes, then they can continue to work. Otherwise, you may suggest the possibility of changing jobs to reduce these exposures.

Please note that continuation of health insurance coverage, if your patient changes jobs after diagnosis, may vary from state to state.

Q: What role does disability insurance have?

A: If your patient's physical condition does not allow him/her to work, it is important to discuss the availability of disability insurance with your patient. Disability insurance will help pay for your patient's medical care; however, it may severely limit your patient's ability to work in the future.

4. Reimbursement/Insurance Claims

Each individual diagnosed with AAT Deficiency should contact his/her insurance company concerning insurance coverage and reimbursement issues. If augmentation therapy is recommended, a service of the Alpha -1 Foundation is to assist in the preparation of supporting documentation requested from the patients by the insurance company regarding the use of augmentation therapy and/or other options (see Treatments).

Most health care insurance companies will cover the drug and administration costs of augmentation therapy. However, benefits may vary depending upon where the therapy is administered (i.e., in your office, a hospital, a separate infusion clinic, or at home).

5. Confidentiality

Establishing and maintaining confidentiality in the doctor-patient relationship is always the best way to promote the trust of your patients. Breaching this trust

can produce devastating results. You should discuss the following confidentiality issues with your patient:

Q: Who will know the patient's AAT Deficiency diagnosis?

A: The results of the test will be included in a patient's medical record. Although generally treated as confidential, inform the patient that insurance companies, healthcare facilities, and other professionals may access this information.

Q: To whom should (or must) the patient disclose the AAT Deficiency diagnosis?

A: Patients must make their own decisions about disclosing this information. However, it is highly recommended that patients tell their blood relatives about the risk and urge them to seek testing. Patients should inform future healthcare providers, and may have to inform insurance companies, if there is a change in policy.

Note: Finding out about an AAT Deficiency diagnosis can be an overwhelming and upsetting experience. It is important for the patient to share this information with his/her family, and to seek professional psychological counseling, if necessary.

Each newly diagnosed patient should be encouraged to seek more information and support. It is recommended that your patient get more information as soon as possible after diagnosis by talking with persons living with AAT Deficiency and identify support for himself/herself and family members. (The end of this guide includes a list of resources.)

Counseling

The objectives of these materials are to increase physician awareness of AAT Deficiency and to promote screening of patients at risk. It is important that you are able to explain the disorder in a clear and concise manner and encourage testing of your patients at risk. Through a simple blood test, you can identify affected patients and receive results within two weeks.

Following are scenarios that were developed to assist you in encouraging screening, providing test results and explaining the various aspects of an AAT Deficiency diagnosis. All scenarios assume an in-office visit.

Promoting Screening

Objective: Request Blood Sample

"As one of my patients with the diagnosis of (emphysema, COPD, bronchiectasis, liver disease,



etc.) I am advising you to consider being tested for the genetic disorder AAT Deficiency."

"AAT Deficiency is believed to affect at least 100,000 people in the US alone, making it one of the most common genetic disorders in this country. Although AAT Deficiency was discovered in 1963, there is still much to learn about its frequency, severity, treatment and prevention. I am advising you to consider this test because the results will help us work together to maintain your health. By taking the test, we will learn whether or not you have AAT Deficiency. Early detection of AAT Deficiency is very important because there are medical interventions I can prescribe and lifestyle changes that you can make to prevent lung damage or prolong the time before the damage to your lungs occurs."

"The only way to be tested for AAT Deficiency is to have a blood test. This test will only take a few minutes and usually can be done with a simple finger stick. It can take up to two weeks to receive results. Once the test results are back, I will ask you to come in for a follow-up visit to discuss your results."

"There may be some mild physical discomfort and there is a minimal risk of an infection from obtaining the finger stick blood sample for the blood test. There is also a risk of a bruise. There may be additional risks from learning the test results, including emotional distress, which I cannot predict at this time. All of these issues should be carefully considered prior to being tested."

"Your choice to be tested is totally voluntary. You can refuse to be tested."

“Again, as your doctor, I would be happy to answer any questions concerning AAT Deficiency, and your possible risk.”

At this point, provide the patient with the brochure *What is Alpha-1? What you need to know about Alpha-1 Antitrypsin Deficiency*.

Giving Test Results

ALTERNATIVE A

Objective: Explain a Negative Test Result (Pi M) for AAT Deficiency

“After reviewing the results of the blood test we performed to determine if you have AAT Deficiency, I am pleased to inform you that the results were negative. This means that you have enough alpha-1 antitrypsin (AAT) in your blood, and indicates that you do not have the disorder.”

Despite the negative result, you should still advise patients that it is important to avoid all tobacco smoke, whether it is from directly smoking tobacco products or situations where it is inhaled secondhand.

ALTERNATIVE B

Objective: Explain a Carrier Test Result (Pi MZ or Pi MS)

“After reviewing the results of the blood test we performed to determine if you have the inherited genetic disorder AAT Deficiency, I must inform you that the results were positive for a special state of the disorder known as being a carrier.

For Pi MZ:

“Carriers have one normal gene and one gene for the disorder. This combination of genes does NOT typically cause health problems. Currently, the risk of lung or liver problems for you appears to be low. There have been published research findings that have indicated that there may be a higher risk for developing chronic liver and lung disease in adults with Pi MZ. The health effects of cigarette smoke on the lungs can be magnified in those with Pi MZ.”

For Pi MS:

“Carriers have one normal gene and one gene for the disorder. This combination of genes does NOT typically cause health problems. Currently, the risk of lung or liver problems for you appears to be low.”

For both carrier states:

“However, it is recommended that you should inform your blood relatives of the test result because of the genetic nature of the disorder. Since AAT Deficiency is

passed genetically from parents to child, it is possible that your blood relatives could be heterozygotes (carriers) such as yourself, or have AAT Deficiency (two abnormal genes). Another important aspect of this test result is that you can pass on the gene to your children.”

EXAMPLE:

If both parents are carriers, each child has a chance of inheriting AAT Deficiency, a chance of being a carrier of AAT Deficiency, or a chance of having two normal genes.

Most importantly, you should advise patients that it is important to avoid all tobacco smoke, whether it is from directly smoking tobacco products or situations where it is inhaled second-hand. At this point, you can provide the patient with the brochure *Am I an Alpha-1 Carrier?* and the Alpha-1 Research Registry application.

ALTERNATIVE C

Objective: Explain a Positive Test Result (Pi Z) to an Adult Patient with Pulmonary Disease

“After reviewing the results of the blood test to determine if you had the genetic disorder AAT Deficiency, I must inform you that the results were positive for the disorder. The amount of alpha1-antitrypsin or AAT in your blood is very low, and the AAT you do have is slightly different from the normal type. This test result explains some of the health problems that you are experiencing (or have experienced) including [symptoms specific to this patient, i.e., coughing, wheezing, shortness of breath].

“I know that this can be upsetting news. However, with lifestyle changes (including smoking cessation and avoidance, exercise and nutrition) and medical treatments including specialized therapy, people with AAT Deficiency can and do lead full lives and enjoy relatively stable lung function.

“Before we go into the explanation of what this means and the questions you may have, let me review the information we have about AAT Deficiency at the present.”

A. Explain

- The course of AAT Deficiency
- The progression of AAT Deficiency
- Consequences, including the genetic risk to the patient’s family

B. Review information in the manual A Guide for the Recently Diagnosed Individual

C. Schedule the next patient visit

D. Complete the Treatment Checklist

E. Provide information and an application for the Alpha-1 Research Registry.

ALTERNATIVE D

Objective: Explain a Positive Test Result (PiZZ) to the Parents of a Pediatric Patient with Liver Disease

“After reviewing the results of the blood test to determine if your child has the genetic disorder AAT Deficiency, I must inform you that the results were positive for the disorder. Your child’s liver complications are the result of misfolded alpha-1 antitrypsin or AAT protein that is trapped in your child’s liver. This backup of AAT in the individual liver cells causes damage to the liver.

“At this time, there is no specific treatment for liver disease associated with AAT Deficiency. Clinical care is primarily supportive management for any liver dysfunction and prevention of complications. Each child is an individual and treatment is highly individualized. Liver transplantation may be required. It is difficult to say if your child will definitely need a liver transplant. The majority of children diagnosed with AAT Deficiency have a low rate of disease progression and often their liver function returns to normal.”

A. Explain

- The course of AAT Deficiency
- The progression of AAT Deficiency
- Consequences, including the genetic risk to the family members

B. Review information in the manual A Guide for the Recently Diagnosed Individual

C. Schedule the next patient visit

F. Complete the Treatment Checklist (see below)

G. Provide information and an application for the Alpha-1 Research Registry

Make sure that you note your counseling discussion in your patient’s medical record.

Treatment Checklist for AAT Deficiency

Many patients will be upset and anxious about their diagnosis. It may be necessary to schedule an additional visit to discuss recommended medical treatment and lifestyle changes.

1. Initial Visit(s)

- Discuss baseline testing (with subsequent follow-up)
- Discuss requirement for lung function tests (FEV1, etc.)

- Discuss need for baseline liver evaluation or referral to a GI/Liver specialist (Pediatric or Adult)
- Discuss need for baseline lung evaluation or referral to a pulmonologist (Pediatric or Adult)
- Discuss the use of drug therapy for lung problems
 - Use of bronchodilators
 - Use of corticosteroids
 - Aggressive treatment of lung infections
- Discuss aggressive treatment of liver complication symptoms
- Discuss need for vaccinations
 - Influenza (annual)
 - Pneumococcal vaccine
 - Hepatitis A
 - Hepatitis B
- Assess smoking status and give a strong message to quit if patients or family members smoke any form of tobacco, including cigars, pipes, and cigarettes
- Discuss risk of occupational and environmental exposures, including second-hand tobacco smoke, dusts, and fumes
- Avoid being around exposed individuals who are ill with the flu or a cold, etc.
- Discuss alcoholic beverage consumption
- Discuss developing an exercise program
- Discuss developing a nutrition program
- Discuss reducing stress
- Discuss referring patient to a counselor (if necessary)
- Contact and refer patients to the resources listed at the end of this guide

2. Subsequent Visit(s)

- Discuss requirement of follow-up visits
- Discuss augmentation therapy (specialized therapy for AAT Deficiency lung disease) if appropriate
- Discuss use of supplemental oxygen (if necessary)
- Discuss surgery options (if appropriate)
- Discuss referring patient to a counselor (if necessary)

Resources for Physicians

The **Alpha-1 Research Program at the University of Florida in Gainesville** was established by the Alpha-1 Foundation and is devoted to the study of lung and liver disease associated with AAT Deficiency. The resources and services offered by the Program are an important access point for the national and international medical and scientific communities. These resources include the Alpha-1 Genetics Laboratory, an International Reference Laboratory for AAT levels, Pi-typing, and genotype analysis. Testing is provided free of charge to patients throughout the world and includes genotyping, Pi-typing, and blood level testing. See alpha1lab@alphaone.ufl.edu

In addition, there are **Alpha-1 Foundation Clinical Resource Centers (CRCs)** throughout the U.S. and in Canada. These are centers designated by the Alpha-1 Foundation because of their interest and experience in treating individuals with AAT Deficiency. Many are at academic institutions and are involved in basic and clinical research. Others are clinical practices with particular expertise in AAT Deficiency. To find a CRC near you, visit alpha-1foundation.org/clinical-resource-centers/

Community Resources

There are a number of organizations that help and support people with AAT Deficiency. Each of these organizations works with AAT deficient individuals in different ways.

Alpha-1 Foundation

Toll Free: 877-2-CURE-A1 (228-7321)

Web Site: www.alpha1.org

The Alpha-1 Foundation is a not-for-profit organization founded by individuals diagnosed with Alpha-1. The Alpha-1 Foundation is committed to finding a cure for Alpha-1 Antitrypsin Deficiency and to improving the lives of people affected by Alpha-1 worldwide. Some of the Foundation's programs include:

- The **Alpha-1 Research Grants and Award Program** has funded \$76 million in a broad range of research grants and awards.

- The **Alpha-1 Research Registry** is a confidential database of AAT deficient individuals and Alpha-1 carriers that provides a population eligible for clinical trials and research studies. The Alpha-1 Foundation administers the Research Registry and everyone with AAT Deficiency is welcome to participate. The Research Registry also administers the Alpha-1 Coded Testing (ACT) trial that provides free confidential testing for AAT Deficiency. For more information, please call the Alpha-1 Foundation at 1-877-228-7321, ext. 252.
- The **Alpha-1 DNA & Tissue Bank** serves the international scientific community with the largest single disease collection of Alpha-1 DNA and tissue samples for research studies. It is located at the University of Florida.
- The **Alpha-1 Research Network** provides support for and consultation with an international network of scientists who volunteer their time and expertise serving on boards, committees and working groups. The network is also comprised of over 80 Clinical Resource Centers (CRCs), including pulmonary and liver centers where AAT deficient individuals are referred for expert care and have the opportunity to participate in clinical trials and research studies.
- **Educational materials** on a host of issues including genetic privacy and discrimination, insurance issues, and product safety and availability.
- The **Genetic Counseling Program** (1-855-476-1227) offers free phone-based confidential information and resources to Alphas, family members and medical professionals on the genetics of AAT Deficiency and provides information on testing options.
- The **Patient Information Line** (1-800-245-6809) is available free to anyone affected by AAT Deficiency and provides support and answers to topics such as Alpha-1 testing, emotional impact, and physician and support group referrals.

- **Public Policy and Advocacy** promotes government relations activities to respond to challenges such as limited research funds, product shortages, blood safety, developing new therapies and access to care, which includes insurance reimbursement and genetic discrimination.
- **Scientific Meetings, Conferences, Workshops, Working Groups and Symposia** bring scientists together to focus on special topics related to Alpha-1, to advance knowledge of the disorder and to work toward new therapies and a cure.
- The **Support Network** is comprised of 80 support groups nationwide that provide support and education to Alphas and family members, create awareness in local communities, and advocate for national and state issues that affect Alphas. To find a Support Group near you, visit www.alpha1.org.
- The **Targeted Detection Program** promotes worldwide awareness and the identification of AAT deficient individuals in population groups at high risk for AAT Deficiency, such as adults with chronic obstructive pulmonary disease (COPD), chronic asthma and/or chronic liver disease.

For more information on all of these programs, call toll-free, (877) 228-7321 or visit www.alpha1.org.

AlphaNet

Toll Free: 800-577-2638

Web Site: www.alphanet.org

AlphaNet, a not-for-profit disease management company, currently employs more than 45 individuals with AAT Deficiency and follows nearly 5,000 individuals with the condition. AlphaNet provides a wide range of support services to patients, administers clinical trials involving AAT therapies, and has developed a comprehensive disease management program to enhance the quality of life for those affected by Alpha-1. The **Big Fat Reference Guide to Alpha-1** (BFRG) and multiple **Skinny Little Reference Guides** (SLRG) are available online at BFRG.org or as a free Alpha-1 App for iPhone and iPad devices. Since its inception in 1995, AlphaNet has contributed nearly \$58 million to support research and community programs for AAT Deficiency. For more information, call (800) 577-2638 or email info@alphanet.org.

American Liver Foundation

Toll Free: 800-465-4837

Web Site: www.liverfoundation.org

The American Liver Foundation is a national, voluntary not-for-profit organization dedicated to the prevention, treatment, and cure of hepatitis and other liver diseases through research, education and advocacy.

The COPD Foundation

Toll Free: 866-316-COPD (2673)

Web Site: www.copdfoundation.org

The COPD Foundation was established to undertake initiatives that result in expanded services for COPD and improve the lives of individuals affected by COPD. The Foundation's activities focus on achieving these results through research, education and advocacy programs that will lead to prevention, and someday, a cure for this disease.

The Alpha-1 Foundation thanks Ken and Pam Van Scoy of Virginia for allowing us to use their family photo on page 7.



The Alpha-1 Foundation is committed to finding a cure for Alpha-1 Antitrypsin Deficiency and to improving the lives of people affected by Alpha-1 worldwide.

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