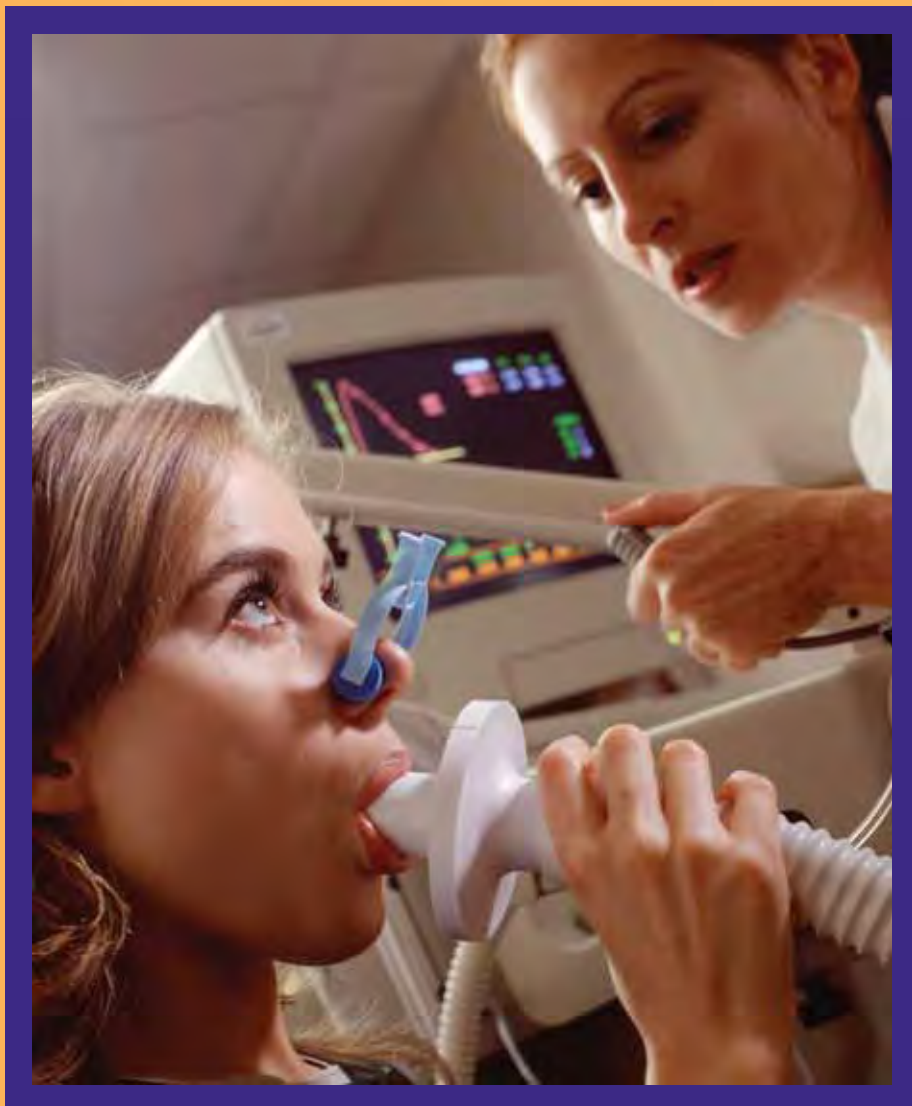




Alpha-1 Antitrypsin Deficiency Healthcare Provider's Guide



FOREWORD

Alpha-1 Antitrypsin Deficiency (Alpha-1) is one of the most common serious hereditary disorders. Alpha-1 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), 1-3% 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 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 Alpha-1 Antitrypsin (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

A 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 physician information packet are designed to educate physicians, their staff members, and patients about AAT Deficiency and available resources. An Education 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, such as bioethicists, physicians and nurses, and educators who contribute their expertise. AAT deficient individuals are also members of the Working Group to ensure that the patient point of view is incorporated. Acknowledgment is made to all of these individuals and the many other people who have provided insightful and helpful editorial comments. Also available are additional educational materials for your patients, including:

What is Alpha-1?

A Guide for the Recently Diagnosed Individual

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



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." The liver makes most of the circulating AAT in the blood. AAT protects the tissues of the body from being damaged by proteolytic enzymes (substances that break down proteins), especially neutrophil elastase (substance released by white blood cells in response to lung irritation or

What is Alpha-1 Antitrypsin Deficiency?

Alpha-1 Antitrypsin (AAT) Deficiency is a genetic disorder characterized by the production of an abnormal AAT protein. The liver cells cannot secrete the abnormal AAT protein, which 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 as young as 30 years of age. Thus, persons with AAT Deficiency are at high risk of developing life-threatening liver and lung disease.

EPIDEMIOLOGY OF AAT DEFICIENCY

AAT Deficiency is the most prevalent potentially fatal genetic disorder of adult Caucasians in the U.S., which occurs 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 has an incidence in whites of 1/2500 at birth.

Untargeted screening studies of large populations have revealed a variable prevalence of AAT Deficiency, depending upon where the studies have been done. 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. However, more studies are needed to prove that AAT Deficiency is more prevalent in these targeted disease groups.

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 are non-smokers.

Liver disease related to AAT Deficiency can manifest at any age. In infancy, the liver disease commonly takes the form of “prolonged obstructive jaundice.” 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, chronic active hepatitis or “cryptogenic” cirrhosis. AAT Deficiency is the leading genetic cause of liver disease in infants and children and is the second most common indication for liver transplantation in this group in the U.S. The risk of hepatocellular carcinoma is increased in persons with AAT Deficiency. However, the rate of liver disease progression in affected individuals, even those with severe disease, may be relatively slow, so that AAT deficient individuals may lead a relatively normal life. Recent evidence suggests that there is some increased risk of liver and lung disease in persons with 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 many alleles for the protein and (2) that the clinical manifestations (lung and liver disease) result from

specific combinations of alleles.

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 circulation). AAT in the serum can be characterized by phenotyping (identifying the expressed AAT proteins in the body), which is accomplished by isoelectric focusing. There are more than 90 different allelic variants of AAT but many of these are quite rare.

Please note that phenotyping for AAT Deficiency is very complicated. When we refer to the “phenotype” in this disorder, we are referring to the protein TYPES. The most common variants of AAT Deficiency are discussed in detail below; there are also many other possibilities.

For this reason it is easier to group the variants into categories: (1) normal variants of AAT (those that produce and distribute AAT normally in the serum); and (2) deficient variants (those that produce reduced or no AAT levels in the serum) and which lead to an increased risk of AAT Deficiency-related lung and liver disease.

Common Alleles:

The family of the normal AAT alleles is referred to as 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 four identified variants of the M allele.

The most prevalent type of deficient allele associated with AAT Deficiency is the Z allele. More than 95% of individuals with AAT Deficiency have phenotype Pi Z (that is, express only the Z variant in the plasma); there are at least 20 other rare allele variants that comprise the rest of the 5% of the AAT deficient population.

The Z variant is subtly abnormal as an inhibitor of neutrophil elastase. However, the most striking abnormality in affected individuals is that circulating levels of the protein are only 10-15% of normal. When livers of these individuals are examined, the hepatocytes contain an abnormal accumulation of AAT. The Pi Z type of 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.

A Pi allele associated with mild AAT deficiency

is the S allele, producing the S variant protein. The S mutation is not associated with intracellular accumulation of the protein, and the S protein inhibits elastase nearly normally. The S allele is slightly more prevalent than the Z allele. 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 further below).

Another allelic variation is represented by the null alleles. The null alleles express no AAT in the blood. Note that in Pi Z individuals, isoelectric focusing reveals only an abnormally migrating Pi Z type 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. 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 may be a possibility that a null allele might be present. Family studies of the pattern of inheritance and further documentation are necessary to distinguish between the possibilities.

Common Heterozygotes:

Pi MS individuals have one normal allele and one S allele. They have nearly normal, and occasionally normal, 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 classical 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 may have an increased risk for developing lung or liver disease. At present, it seems prudent to reassure Pi MZ heterozygotes regarding their potential risk for developing lung or liver disease, and to counsel them about the risk of genetic transmission of the deficient allele. You should recommend that the patient avoid tobacco smoking.

Pi SZ individuals have one allele for the S variant and one for the deficient Z variant. Pi SZ heterozygotes are more common than those with Pi ZZ. Pi SZ individuals probably have some increased risk of lung or liver disease. As for persons who are Pi MZ,



Pi SZ individuals should be reassured regarding their potential risk for developing lung or liver disease, and counseled about the risk of genetic transmission of the deficient allele. Pi SZ individuals should also avoid tobacco smoking.

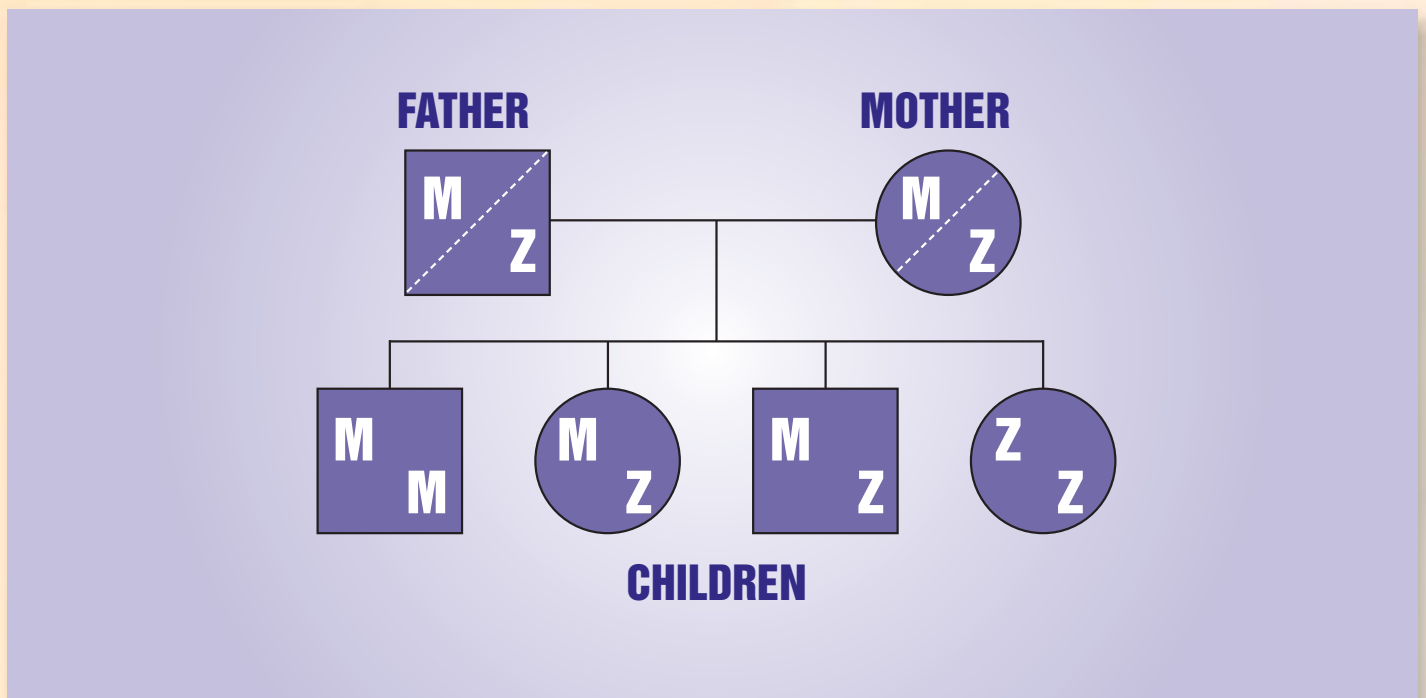
Genetic Transmission:

Genetic transmission of AAT Deficiency follows simple Mendelian principles. Individuals with AAT Deficiency have two deficient alleles for the protein (e.g. Z and/or null allele). Thus, the deficiency is inherited similar 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% are carriers. These people often have reduced levels of the protein, but have minimal excess risk of lung or liver disease. Phenotyping is necessary to reliably detect carriers, since AAT levels of normal individuals and carriers overlap to some extent.

For 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)	It is unclear whether there is a risk for developing disease symptoms but does carry an altered AAT gene (though most studies do not indicate an increase risk for disease).
AAT Deficiency	(ZZ) (SZ)	Moderate to severe deficiency – could develop disease and does carry two altered AAT genes.
AAT Deficiency	(SS)	It is unclear whether there is a risk for developing disease symptoms but does carry two altered AAT genes (though most studies do not indicate an increase 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 are of great importance.

Identification of Patients:

You should test adult patients with the following problems, as recommended by the World Health Organization (WHO):

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

Other conditions not specifically recommended by WHO, but possibly indicating increased risk for AAT Deficiency include:

- Bronchiectasis
- Panniculitis
- Unexplained vasculitis, particularly of Wegener's granulomatosis type
- Hepatocellular carcinoma
- Any evidence of unexplained liver disease

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 (age 30 to 55) in smokers, the likelihood of AAT Deficiency is increased.

Testing At-Risk Patients:

After confirming the AAT Deficiency status of your patient, you may want to consider the following tests for collecting baseline data:

Baseline Examination

- Physical Exam
- Postero-Anterior (PA) and Lateral Chest X-Ray or a high resolution CT of the lungs
- Pulmonary function test, including:
 - Spirometry curves (before and after inhaled bronchodilator)
 - Lung volumes
 - Diffusion capacity
 - Arterial blood gases
- Liver function test, including:
 - AST/ALT
 - Alkaline Phosphatase
 - Total and Direct bilirubin
 - Albumin, clotting studies (PT, INR, PTT)
 - Liver ultrasound examination
 - Alpha Fetoprotein

Testing:

In general, testing for AAT consists of an immunoassay for AAT levels followed by phenotyping.

Phenotyping is 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 μ M or less or a deficient phenotype are considered to have AAT Deficiency. Newer testing methods utilize a finger stick test that measures both AAT levels and genotype (type of AAT gene in DNA).

Phenotype & AAT Deficiency Risk:

μ M result can be derived from mg/dl by multiplying mg by 1923.

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, Drug Therapy for Lung Problems, Specialized Therapy for AAT Deficiency, 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 over 50 Clinical Resource Centers (CRC's) 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 Center to monitor their AAT Deficiency and coordinate their care with you. Many CRC's 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 Medical Director for consult, information, and referral.
- Gives the patient an opportunity to get involved in their personal treatment, by talking and meeting other Alphas through computer and telephone access. 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 these important lifestyle changes.

Behavioral & Lifestyle Modification

Individuals with AAT Deficiency should NEVER smoke. Evidence shows that smoking tobacco products significantly increases the risk and severity of emphysema in AAT deficient individuals and may decrease their 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 three 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 serious 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.

Smoking attracts white blood cells to the lungs in large numbers and speeds the development of lung disease. The lungs in AAT deficient patients do not have the normal defenses against the white blood cells and neutrophil elastase.

2. Avoiding Environmental Pollution

Although formal studies are lacking, it is probably advisable for Alphas (persons with AAT Deficiency) to avoid occupational and environmental pollutants that can be inhaled (including pollen, dust, areas with high levels of air pollution, and second-hand tobacco smoke). These substances can cause further irritation of the lungs and worsen the current condition of the patients with disease.

Avoid both indoor and outdoor air pollution such as particulates smaller than 10 μm (found in higher industrialized urban regions) and exposure to aerosolized sprays. It is also important to realize that your patient(s) may encounter pollutants and infections at both home and at work, thus 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 secondhand 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

Although formal studies are lacking, 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 local indoor shopping malls), strolling, swimming, and/or biking can facilitate 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 Exercise Program (PREP) is highly recommended for Alphas. PREP can help an individual with pulmonary disease through exercise, breathing retraining, education, smoking cessation, and nutrition counseling. You should recommend and discuss 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-related liver damage should 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.

Supportive 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 patient 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. A special formula is often recommended for an infant experiencing feeding difficulties, showing poor growth and a failing to thrive.

Recommend to your patients that they should establish or maintain good eating habits. 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 appropriate, individualized nutritional plan.

5. Reducing Stressors

Persons with AAT Deficiency (Alphas) report benefits with stress reduction techniques. There are



many relaxation 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.

Drug Therapy for Lung Problems

This is among the most important type of medical therapy for the newly diagnosed individual with AAT Deficiency.

1. Vaccinations (influenza/pneumonia)

It is important for your patient to have a yearly influenza vaccine and a Pneumovax[®] shot every five to six years. 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. Effective vaccines are available for hepatitis A and B. These are especially important in patients with established liver disease.

Recommendations:

- Annual influenza vaccine
- Administration or confirmation of Pneumovax vaccine (consider every five to six years)
- 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
- Changes in color of phlegm

Because the lungs attract more leukocytes when an infection is present, and the leukocytes release

neutrophil elastase, it is important to control lung inflammation. Antibiotics may help to speed recovery.

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 (they are often infectious or exposed to infections).

3. Aggressive Evaluation of Liver Complications

It is important for parents, caregivers or significant others to be aware and advised of any indication of complications related to liver disease.

Here is a list of common symptoms that may require therapy:

- 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
- 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
- Peripheral edema
- Change in or the appearance of jaundice

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.

4. 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.

5. Corticosteroids

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

6. Supplemental Oxygen

For people who need supplemental oxygen, it has been shown to be lifesaving. 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 and/or sleep.

Supplemental oxygen is also recommended during exercise. For some Alphas, it is especially important when traveling by air, because cabin pressure changes with altitude.

7. Specialized Therapy for AAT Deficiency

There is a specific treatment for AAT Deficiency called augmentation therapy. Augmentation therapy increases the lung levels of AAT. Augmentation therapy is not a cure; it will not reverse the lung damage that has occurred 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.

Augmentation Therapy

Augmentation therapy, a derivative of human plasma, is the only currently available treatment for AAT Deficiency. It is used to increase the concentration of AAT in the blood and lungs. However, long-term controlled clinical trials have not been done to show that augmentation therapy alters the course of lung disease.



Clinical Criteria for Use

- Currently, augmentation therapy can 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 AAT Deficiency patients with phenotypes Pi Z, Pi Z/null, Pi null null, and/or patients who have AAT serum levels $< 11 \mu\text{M}$. It should not be given to those individuals who do not have AAT Deficiency or to individuals with mildly deficient phenotypes.
- Augmentation therapy can be administered in the physician's office or in a facility where intravenous infusions are routinely given for other indications. Home administration is also an option; several companies offer home infusion services.
- Some patients infuse themselves or have a spouse, relative, or friend perform the infusion.

Safety of Augmentation Therapy

Augmentation therapy is prepared from pooled human plasma that has been screened for Hepatitis A, B and C and tested for human immunodeficiency virus. As an additional precaution against transmission of infectious agents, the product is heat-treated during the manufacturing process. For further protection, administration of the hepatitis B vaccine is recommended prior to therapy.

Known Side Effects

- There are relatively few side effects reported: headaches, myalgias, arthralgias, 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 IgA deficiency can develop acute anaphylaxis when given augmentation therapy. Therefore, these patients should NOT receive augmentation therapy.

Surgical Options

As the patient's physician, you determine the rationale for use of surgery.

There are two major types of surgery for those patients with AAT Deficiency:

- Lung Volume Reduction Surgery (LVRS)
- Organ Transplantation of Lung or Liver:
Lung/liver transplantation is becoming a viable

option for some patients. As experience with new surgical techniques (particularly single lung transplantation) increase, lung transplantation may become more attractive to AAT deficient patients with end-stage lung disease. Utilization of this therapy is only for patients with end-stage lung or liver disease. The option of living-related liver transplantation is available at some transplant facilities.

Large volume paracentesis (LVP) may become necessary in end stage liver disease when diuretic therapy is inadequate in the treatment of ascites. Portal vein decompression utilizing surgical shunts has long been known to be effective means of relieving intractable cirrhotic ascites and 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. The TIPS (transjugular intrahepatic portosystemic shunt) procedure has also been effective in controlling bleeding from esophageal or gastric varices, as well as controlling cirrhotic ascites. 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 for the extent to which there will be improvement of medical condition. Please consult with your patient about these options, if appropriate.

■ With AAT Deficiency, one of the last options is organ transplantation. Utilization of this therapy is for those patients who:

- Do not respond to more conservative therapy.
- Have extensive damage of the lungs or liver.

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
3. Employment
4. Reimbursement/Insurance claims
5. Confidentiality.

1. Psychosocial/Family Support

The most useful steps the patient 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 patient can speak and even 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 console him/her. Getting actively involved with the overall treatment of the patient, which will extend into other aspects of the patient's life, is of utmost importance.

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

A: We recommend that, after discussion with you about the discriminatory issues surrounding AAT Deficiency that they suggest to blood relatives to 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. Those who have symptoms, as noted in the WHO recommendations, should be encouraged 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 that patients may ask:

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

A: It may. The extent to which it specifically affects health insurance (continuing and acquiring new policies) depends upon their current insurance coverage status.

If your patient is currently insured:

Instruct your patients to educate him/herself regarding:

- Specific insurance policy and benefits regarding coverage and reimbursement.
- Lifetime maximum benefits, if any.
- The laws in your patient's state regarding mandatory coverage.

If your patient is currently uninsured:

AAT Deficiency is considered a pre-existing condition, and future insurance companies may not be obligated to cover costs for this specific condition for some period of time. You may direct your patient to seek professional advice and recommend that they familiarize themselves with the insurance regulations in their state of residence. In general, your patients are obligated to inform an insurance company of any pre-existing condition when they apply for coverage.

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 Alpha patients 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 your patient can continue to work. Otherwise, you may suggest the possibility of him/her 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. The issue of disclosure of this diagnosis may also affect the benefit status of future coverage.

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 payments 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 the augmentation therapy. However, benefits may vary depending upon when and 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 have 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 discussing this information. However, it is highly recommended that the patient tells his/her 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.

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 for you to be 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, giving test results and explaining the various aspects of an AAT Deficiency diagnosis.

Promoting Screening

Setting: In-Office Visit

Objective: Request Blood Sample

“As one of my patients with the diagnoses 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 as many as 100,000 people in the US alone, making it one of the most common genetic disorders in this country. Since AAT Deficiency was only recently discovered, there is much to learn about its frequency, severity, treatment and prevention. I am advising you to consider this test because this information will be important to help me take better care of you as a patient. By taking the test, you will learn whether or not you have the genetic disorder called AAT Deficiency. Early detection of AAT Deficiency is very important because there are medical interventions I can prescribe that may help to prevent or prolong the time before the damage to your lungs occurs. I can discuss these interventions with you.

The only way to be tested for AAT Deficiency is to have a blood test. This test will only take a few minutes and uses a finger stick. The results generally require a two-week period of time to receive. Once the test results are back, I will contact you by telephone to come in for a follow-up visit to discuss your results.

There may be some mild physical discomfort and risk of an infection from obtaining the finger stick blood sample for the blood test. You may experience slight discomfort at the needle site and there is a risk of a bruise.

There are ways your life could be affected by learning information that may be discovered by genetic testing. There may be additional risks, 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 are free to refuse to be tested at any time.”

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 Antitrypsin Deficiency? Should I Be Tested?”

Giving Test Results

Alternative A

Setting: Office Visit

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

“After reviewing the results of the blood test we performed at your last visit to determine if you had the inherited genetic disorder AAT Deficiency, I am pleased to inform you that the results were negative. This means that you have enough alpha1-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

Setting: Office Visit

Objective: Explain a Carrier Test Result (PI MZ or Pi MS) for AAT Deficiency

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

“Heterozygotes (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 yourself appears to be low.” There have been published research findings that have indicated that there may be a higher risk for developing chronic liver disease in the adult PI MZ population either alone or in combination with other liver diseases.”

“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. 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, and a chance of having both 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 secondhand. At this point, you can provide the patient with the brochure “A Guide for the Recently Diagnosed Carrier” and the Alpha-1 Research Registry questionnaires for family members.

Alternative C

Setting: Office Visit

Objective: Explain a Positive Test Result (Pi Z) for AAT Deficiency and its consequences

Adult Patient — Pulmonary Disease

“After reviewing the results of the blood test we performed at your last visit, to determine if you had the inherited genetic disorder AAT Deficiency, I must inform you that the results were positive for the disorder. The amount of alpha1-antitrypsin in your blood is low, and the alpha1-antitrypsin in your blood 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, due to the impact that having this disorder may have on your health. However, with behavioral and lifestyle modifications such as not smoking, exercise, nutrition, drug therapy, medical treatments, specialized therapy for AAT Deficiency, and preventive measures, Alpha patients 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 Alpha1 at the present.”

A. Explain

- The course of Alpha-1 Antitrypsin Deficiency
- The progression of Alpha-1 Antitrypsin Deficiency
- Consequences, including the genetic risk to the patient’s family

B. Review information in the manual, “A Guide for the Recently Diagnosed Patient”

C. Schedule the next patient visit; and

D. Complete the Treatment Checklist

E. Provide information and questionnaires for each member from the Alpha-1 Research Registry.

Alternative D

Setting: Office Visit

Objective: Explain a Positive Test Result

Pediatric Patient — Liver Disease

“After reviewing the results of the blood test we performed at your last visit, to determine if your child had the inherited genetic disorder AAT Deficiency, I must inform you that the results were positive for the disorder. The amount of alpha1-antitrypsin in your child’s blood is low, and the alpha1-antitrypsin (AAT) in your child’s blood is slightly different from the normal type. However, your child’s liver disease is not due to this low level of AAT in the blood stream. Research studies indicate that these liver complications are the result of the misfolded protein not being secreted properly into the blood stream. 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 these children diagnosed with AAT Deficiency have a low rate of disease progression and lead a relatively normal life for extended periods of time.

A. Explain

- The course of Alpha-1 Antitrypsin Deficiency
- The progression of Alpha-1 Antitrypsin Deficiency
- Consequences, including the genetic risk to the patient’s family

B. Review information in the manual, “A Guide for the Recently Diagnosed Patient”

C. Schedule the next patient visit; and

F. Complete the Treatment Checklist

G. Provide information and questionnaires for each family member from the Alpha-1 Research Registry.

At this point, make sure that you note your counseling discussion in your patient’s medical record.

TREATMENT CHECKLIST FOR AAT DEFICIENCY

Many patients will experience emotional upset and anxiety due to their diagnosis. It may be necessary to schedule an additional visit in order to complete discussion about recommended medical treatment and behavioral changes.

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)
- Pneumovax®(every six years)
- Hepatitis A
- Hepatitis B
- Assess smoking status and give a strong message to quit if patients smoke any form of tobacco, including cigars and cigarettes
- Discuss risk of occupational and environmental exposures, including second-hand tobacco smoke and dusts
- 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 stressors
- Discuss referring patient to a counselor (if necessary)
- Contact and refer patients to the resources listed at the end of this guide

Subsequent Visit(s)

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

Alpha-1 Antitrypsin Deficiency Physician Resources

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 Alpha-1 Antitrypsin Deficiency (AAT Deficiency or Alpha-1). 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 Translational Research Laboratory** is devoted to characterizing the molecular mechanisms responsible for the development of liver and lung, disease in AAT Deficiency and to the development of new treatments.
- The **Alpha-1 Gene Therapy Program** is focused on the development of safer and more efficient vehicles for the delivery of therapeutic genes to the liver, lung, and other tissues.
- The **Alpha-1 DNA and Tissue Bank** serves the international scientific community with the largest single-disease collection of DNA and tissue samples for research studies in the United States.
- The **Bronchoscopy Research Procedure Unit** and the **Lung Cell Biology Laboratory** enable clinical studies on the fundamental process associated with lung injury in individuals with AAT Deficiency and determine the efficacy of new therapies.
- The **Alpha-1 Genetics Laboratory** is an International Reference Laboratory for AAT levels, phenotype, and genotype analysis. Testing is provided free of charge to patients throughout the world and includes:
 - Alpha-1 Antitrypsin Genotyping, Phenotyping and blood concentration
 - Follow-up and/or referral for specialized care
 - Genetic Counseling Referral
 - Alpha-1 Specific Patient Educational Resources

- The **Alpha-1 Florida Detection Program** is a state sponsored, statewide, targeted population screening for AAT Deficiency. The Alpha-1 Florida Detection Program targets Florida residents with Chronic Obstructive Pulmonary Disease (COPD) and liver disease. The Program is dedicated to raising awareness among Florida medical professionals, the media, and the public about AAT Deficiency. Through this Program, diagnostic testing for AAT Deficiency is offered free of charge, and appropriate referrals for education and clinical care are made.

For a free test kit and/or for more information on the programs and services of the University of Florida Alpha-1 Research Program contact:

University of Florida College of Medicine
Toll Free Telephone: 1-866-284-2708
Email: alpha1lab@medicine.ufl.edu
Website: www.alphaone.ufl.edu/

Community Organizations & Resources

There are a number of organizations, which help and support people with AAT Deficiency. Each of these organizations works with the AAT deficient individual in different ways.

Alpha-1 Foundation

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

Web Site: www.alpha-1foundation.org

The Alpha-1 Foundation is a not-for-profit organization founded by individuals diagnosed with Alpha-1 Antitrypsin (AAT) Deficiency. Its mission is to provide the leadership and resources that will result in increased research, improved health, worldwide detection and a cure for Alpha-1. This mission is achieved through the following programs and activities:

- The **Alpha-1 Research Grants and Award Program** has funded to date nearly \$39 million in research and programs at more than 70 institutions in the United States, Europe and Australia.
- The **Alpha-1 Research Registry** is a confidential database of AAT deficient individuals and Alpha-1 Carriers that provides the population base eligible for clinical trials and research studies. The Registry is administrated by the Medical University of South Carolina.
- **Alpha-1 DNA and 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 College of Medicine.

- The **Alpha-1 Research Network** provides support for and consultation with an international network of scientists who volunteer their time and expertise through service Boards, Committees and Working Groups. The network is also comprised of over 60 Clinical Resource Centers, 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.
- **Scientific Meetings, Conferences, Workshops, Working Groups and Symposia** focus on specialized topics to advance knowledge of AAT Deficiency and address critical issues in the areas of improved treatments, education, detection and ethical issues.
- An **Alpha-1 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.
- **Public Policy and Advocacy** government relations activities in Washington respond to the challenge of increasing research funding, addressing product shortages, ensuring blood safety, developing new therapies and advocating for access to care, which includes insurance reimbursement and genetic discrimination.
- **University of Florida at Gainesville, Alpha-1 Research Program** was established by the Foundation as a resource to the medical and scientific community.

AlphaNet

Toll Free: 800-577-2638 ■ www.alphanet.org

AlphaNet, a not-for-profit disease management company, currently employs more than 20 Alphas. AlphaNet provides a wide range of support services to patients, administers clinical trials involving Alpha-1 therapies, and has developed a comprehensive disease management program to enhance the quality of life for those affected by Alpha-1. Since its inception in 1995, AlphaNet has contributed over \$25 million to support Alpha-1 research and community programs.

Alpha-1 Association

Toll Free: 800-521-3025 ■ www.alpha1.org

The Alpha-1 Association is a not-for-profit, membership organization founded in 1991. The community of people who are affected by Alpha-1 governs this international organization. Its mission is “to identify those affected by Alpha-1 Antitrypsin Deficiency and to improve the quality of their lives through support, education, advocacy, and research.” That mission is fulfilled through an international network of support groups; a Peer Guide program to help newly diagnosed individuals, and an array of educational materials. The Alpha-1 Association advocates for the community on a host of issues including genetic privacy and discrimination, insurance issues, and product safety and availability. The Association also encourages research and supports the programs of the Alpha-1 Foundation.

American Liver Foundation

Toll Free: 800-465-4837 ■ 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.

American Lung Association

Toll Free: 800-548-8252 ■ www.lungusa.org

The American Lung Association (ALA) is a nationwide health organization. Since 1904, the American Lung Association has been fighting lung disease through education, community service, advocacy and research, seeking better treatments and cures. The ALA can also help you find information on smoking cessation programs that are available.

For Alpha-1 Registry enrollment information,
and for more information on the Alpha-1 DNA and Tissue Bank,
please contact:

The Alpha-1 Foundation
2937 SW 27th Avenue, Suite 302,
Miami, FL 33133
Telephone: (888) 825-7421 • Fax: (305) 567-1317
www.alpha-1foundation.org



The Alpha-1 Foundation thanks Ken and Pam Van Scoy of Virginia for allowing us to use their family photo on page 3.



Research for a Cure

About the Alpha-1 Foundation

The mission of the Alpha-1 Foundation is to provide the leadership and resources that will result in increased research, improved health, worldwide detection and a cure for Alpha-1 Antitrypsin Deficiency. The Foundation has invested nearly \$39 million to support Alpha-1 Antitrypsin Deficiency research in more than 70 institutions in North America, Europe and Australia. For more information, visit: www.alpha-1foundation.org.

About the Alpha-1 Association

The Alpha-1 Association is the leading national patient membership organization serving the Alpha-1 community since 1991. Its mission is to identify those affected by Alpha-1 Antitrypsin Deficiency and to improve the quality of their lives through support, education, advocacy and to encourage participation in research. Its programs include a national Support Network of about 70 Support Groups, Patient Hotline, national and educational programs, a Genetic Counseling Service and grassroots advocacy program. For more information, visit: www.alpha1.org.

ALPHA-1FOUNDATION.ORG

1 (888) 825-7421

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