

# American Thoracic Society Documents

## American Thoracic Society/European Respiratory Society Statement: Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency

THIS JOINT STATEMENT OF THE AMERICAN THORACIC SOCIETY AND THE EUROPEAN RESPIRATORY SOCIETY WAS APPROVED BY THE ATS BOARD OF DIRECTORS, DECEMBER 2002, AND BY THE ERS EXECUTIVE COMMITTEE, FEBRUARY 2003

### CONTENTS

#### Executive Summary

|   |     |
|---|-----|
| Introduction . . . . .  | 820 |
| Goals, Organization of the Project, and Timeline . . . . .  | 820 |
| Summary of Main Recommendations Regarding<br>Diagnosis and Management by the Alpha-1<br>Antitrypsin Deficiency Task Force . . . . . | 820 |
| Clinical Recognition of AAT Deficiency . . . . .  | 820 |
| Genetic Testing for AAT Deficiency . . . . .  | 821 |
| Liver Disease . . . . .   | 821 |
| Other Conditions . . . . .  | 822 |
| Efficacy of Augmentation Therapy . . . . .  | 822 |
| General Management of Obstructive Lung Disease . . . . .  | 822 |
| References . . . . .  | 822 |

#### Lung Disease

|   |     |
|---|-----|
| Preparation of This Document . . . . .  | 823 |
| Introduction . . . . .  | 823 |
| Epidemiology . . . . .  | 823 |
| Pathophysiology of AAT Deficiency . . . . .   | 823 |
| Laboratory Tests . . . . .  | 825 |
| Identification of Individuals with AAT Deficiency . . . . .                                   | 826 |
| Pathology . . . . .   | 827 |
| Symptoms . . . . .  | 827 |
| Physical Findings . . . . .   | 828 |
| Lung Function Tests . . . . .   | 828 |
| Radiology, Including Computed Tomography<br>and Ventilation-Perfusion Scan . . . . .          | 828 |
| Parameters of Progression: FEV <sub>1</sub> , Desmosine,<br>and Computed Tomography . . . . . | 829 |
| Risk Factors . . . . .  | 830 |
| Natural History . . . . .   | 831 |
| Risks of the MZ and SZ Phenotypes for the<br>Development of Emphysema and COPD . . . . .      | 832 |
| Prognosis . . . . .   | 834 |
| Prevention of Lung Disease . . . . .  | 834 |
| Nonspecific Medical Treatment . . . . .   | 834 |
| Augmentation Therapy . . . . .  | 835 |

|   |     |
|---|-----|
| Surgical Procedures . . . . .   | 836 |
| Special Situations . . . . .  | 837 |
| Future Directions of Research in AAT Deficiency . . . . .   | 837 |
| Some Specific Research Needs in AAT Deficiency . . . . .  | 838 |
| Appendix 1. Primary Evidence Table: Summary<br>of Studies Addressing Clinical Features of PI*ZZ<br>Alpha-1 Antitrypsin Deficiency . . . . .         | 840 |
| Appendix 2. General Population-based Studies:<br>Prevalence of PI Variants and Risk of Associated<br>Lung Disease . . . . .                         | 841 |
| Appendix 3. Chronic Obstructive Pulmonary Disease<br>Population Studies: Prevalence of PI Variants and<br>Risk of Associated Lung Disease . . . . . | 842 |
| Appendix 4. Serial Case Studies in PI*ZZ: Risk<br>Categories Evaluated . . . . .  | 843 |
| Appendix 5. Studies That Address the Risk of a<br>COPD Family History to PI*MZ Individuals . . . . .  | 845 |
| Appendix 6. Smoking as a Risk Factor for Lung<br>Disease in PI*MZ Individuals . . . . .   | 845 |
| Appendix 7. Environmental Risks of Lung Disease<br>in PI*MZ Individuals . . . . .   | 846 |
| Appendix 8. PI*MZ Phenotype May Be a Risk Factor<br>for Atopic Disease . . . . .  | 846 |
| Appendix 9. Primary Evidence of Risk of Emphysema<br>in Individuals with PI*SZ Phenotype . . . . .  | 847 |
| Appendix 10. Primary Evidence Table: Summary<br>of Studies Regarding the Efficacy of Augmentation<br>Therapy . . . . .                              | 848 |
| References . . . . .  | 849 |

#### Liver and Other Diseases

|   |     |
|---|-----|
| Liver Disease . . . . .   | 856 |
| Introduction . . . . .  | 856 |
| Methods . . . . .   | 856 |
| Results . . . . .   | 857 |
| Description of Studies: Number and Types of<br>Reports and Individual Studies . . . . . | 857 |
| Risk of Liver Disease in PI*ZZ Children . . . . .                                       | 857 |
| Clinical Manifestations in PI*ZZ Childhood<br>Liver Disease . . . . .                   | 858 |
| Risk of Liver Disease in PI*ZZ Adults . . . . .   | 859 |
| Risk of Liver Disease in Adult PI*Z<br>Heterozygotes . . . . .                          | 862 |
| Role of Additional Factors for Liver Disease<br>in AAT Deficiency . . . . .             | 863 |
| Risk of Primary Liver Cancer in AAT Deficiency . . . . .                                | 863 |
| Risk of Liver Disease in Non-PI*Z Deficiency<br>States . . . . .                        | 864 |
| Diagnosis and Management . . . . .  | 864 |
| Follow-Up . . . . .   | 865 |

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|  |     |   |     |
|--|-----|---|-----|
| Remarks on the Accuracy of Diagnosis of AAT Deficiency: Isoelectric Focusing versus Hepatocytic PAS-D Inclusions . . . . . | 865 | Penetrance and Prevalence of AAT Deficiency–related Clinical Disease . . . . .  | 877 |
| Some Research Goals in AAT Deficiency–related Liver Disease . . . . .  | 866 | Pulmonary Disease . . . . .   | 877 |
| Some Specific Clinical Research Needs in AAT Deficiency–related Liver Disease . . . . .                                    | 866 | Liver Disease . . . . .   | 877 |
| Systemic Vasculitis and Renal Disorders . . . . .  | 866 | Necrotizing Panniculitis . . . . .  | 880 |
| Multiorgan Vasculitides . . . . .  | 866 | Multisystemic Vasculitis . . . . .  | 880 |
| Nephropathy . . . . .  | 867 | Clinical Impact of AAT Deficiency . . . . .   | 881 |
| Aneurysmal and Related Diseases . . . . .  | 867 | Pulmonary Disease . . . . .   | 881 |
| Abdominal Aortic Aneurysms . . . . .   | 867 | Liver Disease . . . . .   | 882 |
| Intracranial Aneurysms, Extracranial and Intracranial Arterial Dissections, and Fibromuscular Dysplasia . . . . .          | 868 | Necrotizing Panniculitis . . . . .  | 882 |
| Dermatologic Manifestations . . . . .  | 868 | Multisystemic Vasculitis . . . . .  | 882 |
| AAT Deficiency–associated Panniculitis . . . . .   | 868 | Efficacy of Therapeutic Measures . . . . .  | 882 |
| Skin Involvement in Systemic Necrotizing Vasculitides in Severe AAT Deficiency . . . . .                                   | 869 | Pulmonary Disease . . . . .   | 882 |
| Other Skin Disorders in Which AAT Deficiency Plays a Role . . . . .  | 869 | Liver Disease . . . . .   | 883 |
| Miscellaneous Conditions . . . . .   | 869 | Necrotizing Panniculitis . . . . .  | 883 |
| Exocrine Pancreatic Disease . . . . .  | 869 | Accuracy of Genetic Tests for AAT Deficiency . . . . .  | 883 |
| Endocrine Pancreatic Disease . . . . .   | 869 | Efficacy of Providing Genetic Risk Information about Changing Health-related Behaviors: Preventive Measures . . . . .                             | 885 |
| Celiac Disease . . . . .   | 869 | Cigarette Smoking . . . . .   | 885 |
| References . . . . .   | 869 | Change of Occupation in Response to Receipt of Genetic Information . . . . .  | 886 |
| <b>Genetic Testing for Alpha-1 Antitrypsin Deficiency: Genetics, Psychosocial, Ethics, and Economics Issues</b>            |     | Psychological Effects of Genetic Testing . . . . .  | 886 |
| Introduction . . . . .   | 874 | Symptomatic Individuals . . . . .   | 886 |
| Specific Question to Be Addressed . . . . .  | 874 | Asymptomatic Individuals at High Risk . . . . .   | 886 |
| Methods . . . . .  | 874 | Screening . . . . .   | 888 |
| Data Sources and Search Strategy . . . . .   | 874 | Adverse Social Effects: Discrimination/Stigma . . . . .   | 888 |
| Alternative Method of Developing Recommendations . . . . .   | 875 | Economic Costs . . . . .  | 889 |
| Background: Genetics of AAT Deficiency . . . . .   | 876 | Ethical Issues Involved with Genetic Testing . . . . .  | 889 |
| Systematic Reviews of the Evidence for the Efficacy of Genetic Testing . . . . .   | 876 | The Requirement for Informed Consent . . . . .  | 889 |
| Diagnostic Detection Testing . . . . .   | 876 | Overarching Principles . . . . .  | 889 |
| Predispositional Testing of Asymptomatic Individuals at High Risk . . . . .  | 876 | Testing of Children . . . . .   | 890 |
| Screening Programs . . . . .   | 877 | Do Physicians Have an Ethical and/or Legal Duty to Disclose the Availability of Predictive Genetic Testing to Asymptomatic Individuals? . . . . . | 891 |
| Systematic Reviews of the Individual Issues Relevant for Genetic Testing . . . . .   | 877 | Research Context . . . . .  | 891 |
| Prevalence of AAT Deficiency . . . . .   | 877 | Confidentiality of Genetic Information . . . . .  | 891 |
|  |     | Disclosure to Relatives . . . . .   | 891 |
|  |     | Recommendations for Genetic Testing . . . . .   | 891 |
|  |     | Diagnostic Detection Testing . . . . .  | 892 |
|  |     | Predispositional Testing . . . . .  | 895 |
|  |     | Carrier Testing in the Reproductive Setting . . . . .   | 895 |
|  |     | Screening . . . . .   | 896 |
|  |     | References . . . . .  | 896 |
|  |     | <b>Membership of the Alpha-1 Antitrypsin Deficiency Task Force</b>  |     |

# ATS/ERS: Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency

## EXECUTIVE SUMMARY

### Introduction

Since the first American Thoracic Society statement regarding the diagnosis and management of severe alpha-1 antitrypsin (AAT) deficiency in 1989 (1) and the initial Canadian Thoracic Society standards statement in 1992 (2) (which was updated in 2001) (3), significant advances in understanding the cell and molecular biology of AAT and the diagnosis, natural history, and treatment of individuals with AAT deficiency have occurred. These new developments, including completion of several large, longitudinal studies in both Europe and North America and a small randomized controlled trial of augmentation therapy, have provided important new insights that have impacted the clinical management of individuals with severe deficiency of AAT.

In the context of these new developments, a need was felt to reexamine recommendations for optimal management of AAT deficiency, to synthesize current knowledge of diagnosis and management for practicing clinicians, and to identify key remaining questions in need of further investigation. With these purposes in mind, a Task Force to develop a new standards document regarding the diagnosis and management of individuals with severe AAT deficiency was formed in 1998 under the auspices of the American Thoracic Society and the European Respiratory Society, with additional sponsorship and support by the Alpha-1 Foundation, the American College of Chest Physicians, and the American Association for Respiratory Care. Under a contractual arrangement, the Veterans Administration Technology Assessment Program, Office of Patient Care Services, Veterans Health Administration provided education regarding preparing an evidence-based document and support in conducting literature searches.

In keeping with current standards for developing evidence-based recommendations for optimal care, the current Task Force has undertaken a systematic review of current literature regarding AAT deficiency. Every effort was made to identify the scientific evidence for positions taken and to identify where there was little or no evidence. In the absence of ratable evidence, consensus among members of the Task Force determined the recommendation.

This summary document briefly describes the organization and preparation of the Task Force's report and provides an executive summary of key clinical recommendations. The three following sections are the full systematic reviews prepared by the three individual writing groups that comprised the AAT Deficiency Task Force.

### Goals, Organization of the Project, and Timeline

The goal of the AAT Deficiency Task Force was to prepare and present for the medical and interested lay communities the reasoned, current views of a large international group of experts regarding the current diagnosis and management of individuals with AAT deficiency, using a systematic review and the evidence-based approach. The Task Force undertook to evaluate the full clinical and management dimensions of this multisystem illness, including lung, liver, and other organ manifestations. Also, issues relating to the ethical, legal, social, psychological, and economic implications of genetic testing for AAT deficiency were addressed.

A planning group was assembled in the Fall of 1997, when sponsorship and funding by the major sponsors—the American Thoracic Society, the European Respiratory Society, and the Alpha-1 Foundation—was finalized. Additional support from

the Alpha-1 Foundation, the American College of Chest Physicians, and the American Association for Respiratory Care allowed the Planning Committee to assemble the full membership of the Task Force and to proceed.

As presented in Figure 1, the AAT Deficiency Task Force consisted of an Executive Committee, three individual Writing Groups comprising international experts, and a Steering Committee (composed of the Executive Committee and the Chairs of each of the three Writing Groups). Preparation of the systematic review was aided by members of the Health Care Technology Assessment Program of the Department of Veterans Affairs, who provided ongoing input and guidance to the project regarding literature searches and evidence-based medicine methods. Administrative assistance was provided by the American Thoracic Society.

The membership of the Task Force was fully constituted by September 1998, at which point Writing Groups began to review literature and to draft documents for subsequent review by the Steering Committee. The Steering Committee conducted a number of conference calls and five face-to-face meetings between Fall 1998 and Fall 2001 to review the evolving documents. Individual Writing Group documents were finalized by Fall 2001 for final editing by the Executive Committee and subsequent submission to the sponsoring organizations. Reviews were received in June 2002 and the revised document was resubmitted in Fall 2002 for final approval. Approval was granted by the American Thoracic Society in December 2002, when an additional review of salient literature led to a final update of the document.

While the Executive Committee has attempted to minimize overlap between the three documents, the Task Force's stated goal of preparing three individual documents, each complete and with its own emphasis, references, and supportive tables and figures, will inevitably lead to some overlap.

Finally, in the context that research is ongoing and that current understanding of AAT deficiency and optimal management is evolving, the Task Force recognizes the need for periodic review and updating of management recommendations.

### Summary of Main Recommendations Regarding Diagnosis and Management by the Alpha-1 Antitrypsin Deficiency Task Force

*Clinical recognition of AAT deficiency.* Available evidence suggests that PI\*ZZ AAT deficiency is frequently underrecognized or misdiagnosed by clinicians. The following features should prompt suspicion by physicians that their patient may be more likely to have AAT deficiency:

- Early-onset emphysema (age of 45 years or less)
- Emphysema in the absence of a recognized risk factor (smoking, occupational dust exposure, etc.)
- Emphysema with prominent basilar hyperlucency
- Otherwise unexplained liver disease
- Necrotizing panniculitis
- Anti-proteinase 3-positive vasculitis (C-ANCA [anti-neutrophil cytoplasmic antibody]-positive vasculitis)
- Family history of any of the following: emphysema, bronchiectasis, liver disease, or panniculitis
- Bronchiectasis without evident etiology (*see below*)

Notably, in recognizing the discordance of studies concerning whether bronchiectasis is specifically associated with AAT deficiency, the Task Force recommends discussing AAT testing with individuals who have bronchiectasis without evident etiology, with the understanding that testing could reasonably be accepted or declined.

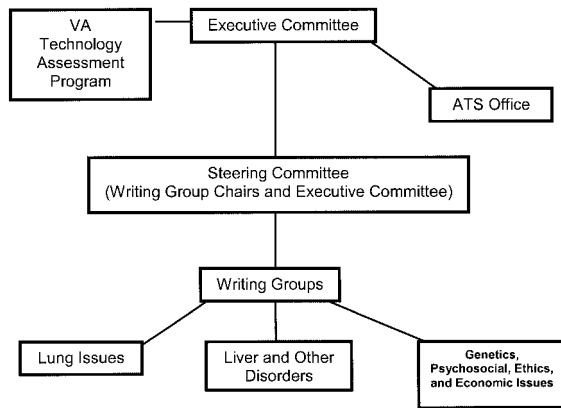


Figure 1. Structure of the Alpha-1 Antitrypsin Deficiency Task Force.

*Genetic testing for AAT deficiency.* Recognizing that identifying individuals as having AAT deficiency can expose them to risks (e.g., of psychologic burden or genetic discrimination), the Task Force recommends that clinicians weigh these risks and discuss them with those for whom testing (by serum level or phenotype) is being considered. In evaluating the strength of the Task Force's recommendation to test various individuals for AAT deficiency, the Task Force recognized four clinical purposes for which testing for AAT deficiency might be undertaken: (1) diagnostic testing (i.e., to identify symptomatic or otherwise affected individuals), (2) predispositional testing (i.e., to identify asymptomatic individuals who may be at high risk of having AAT deficiency), (3) assessment of carrier status in relation to reproduction, and (4) population screening.

Recommendations for genetic testing in specific situations were graded from type A to type D (see Table 1). Each recommendation type was based on the level of supportive evidence for each issue regarding testing (e.g., the penetrance of AAT deficiency, population prevalence of AAT deficiency, clinical impact, accuracy of genetic testing, efficacy of treatment, psychologic and social effects, and economic costs) and the weighing by the Task Force of the issues for or against testing. In the context of this grading scheme, recommendations for the four types of genetic testing are as follows.

#### 1. Diagnostic testing.

A type A recommendation for diagnostic testing was made in the following settings:

- Symptomatic adults with emphysema, chronic obstructive pulmonary disease (COPD), or asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators. (Notably, in populations where the prevalence of AAT deficiency is known to be much lower than the general North American and Northern European prevalence, a Type B recommendation for diagnostic testing in this setting is offered.)
- Individuals with unexplained liver disease, including neonates, children, and adults, particularly the elderly
- Asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors (e.g., cigarette smoking, occupational exposure)
- Adults with necrotizing panniculitis

A type B recommendation for diagnostic testing was made in the following settings:

- Adults with bronchiectasis without evident etiology
- Adolescents with persistent airflow obstruction
- Asymptomatic individuals with persistent airflow obstruction and no risk factors
- Adults with C-ANCA-positive (anti-proteinase 3-positive) vasculitis

TABLE 1. CLASSIFICATION OF RECOMMENDATIONS FOR GENETIC TESTING

| Type | Recommendation  |
|------|---|
| A    | Genetic testing is recommended  |
| B    | Genetic testing should be discussed and could reasonably be accepted or declined              |
| C    | Genetic testing is not recommended (i.e., testing should not be encouraged)                   |
| D    | It is recommended that genetic testing not be performed (i.e., testing should be discouraged) |

The recommendation type was determined by the Task Force's subjective weighing of all the issues that either supported or opposed genetic testing. The weight attributed to each issue is dependent on the level of evidence supporting each issue. Accordingly, the recommendation for genetic testing is informed by both the evidence of each issue and the consensus of experts on how strongly each issue supports or opposes testing.

This classification of recommendations should not be confused with schemes for grading the quality of evidence, which, as used in other documents (although not here), may also use letter designations.

A type C recommendation for diagnostic testing was made for

- Adults with asthma in whom airflow obstruction is completely reversible

#### 2. Predispositional testing.

A type A recommendation was made for:

- Siblings of an individual with AAT deficiency

A type B recommendation was made for:

- Individuals with a family history of COPD or liver disease not known to be attributed to AAT deficiency
- Distant relatives of an individual who is homozygous for AAT deficiency
- Offspring or parents of an individual with homozygous AAT deficiency
- Siblings, offspring, parents, or distant relatives of an individual who is heterozygous for AAT deficiency

A type D recommendation was made for:

- Predispositional fetal testing

#### 3. Assessment of carrier status in relation to reproduction.

A type B recommendation was made for:

- Individuals at high risk of having AAT deficiency-related diseases
- Individuals who are not at risk themselves of having AAT deficiency but who are partners of individuals who are homozygous or heterozygous for AAT deficiency

#### 4. Population screening.

A type D recommendation was made for:

- Population screening of either neonates, adolescents, or adults

That is, population screening is not recommended currently. However, a possible exception (type B recommendation) regarding population screening may apply in countries satisfying three conditions: (1) the prevalence of AAT deficiency is high (about 1/1,500, or more); (2) smoking is prevalent; and (3) adequate counseling services are available.

A type C recommendation was made for:

- Population screening of smokers with normal spirometry

*Liver disease.* Regarding the occurrence of liver disease in individuals with AAT deficiency, the Task Force offers the following findings and recommendations:

- Liver disease is a complication of the intrahepatocytic accumulation of unsecreted, polymerized AAT that forms characteristic periodic acid–Schiff-positive inclusions in individ-

uals with the Z allele and several others (e.g., S<sub>iiyama</sub>, M<sub>malton</sub>). Other deficiency alleles (e.g., null variants, S) do not predispose to liver disease.

- Serum phenotyping by isoelectric focusing performed by a reliable laboratory is the accepted “gold standard” for diagnosing AAT deficiency. Liver biopsy is not indicated for purposes of establishing the diagnosis of AAT deficiency; the role of liver biopsy is confined to staging of liver disease in individuals with clinically overt liver disease. The incidental finding of periodic acid–Schiff-positive globules in a liver biopsy should prompt suspicion of the Z allele or other rare deficiency alleles associated with intrahepatocyte inclusions.
- Most PI\*ZZ AAT-deficient individuals are clinically healthy throughout childhood but have liver enzyme abnormalities in early life. The PI\*ZZ phenotype is a common cause of neonatal cholestasis. Despite spontaneous resolution in a majority of such individuals, AAT deficiency is a frequent indication for liver transplantation in childhood. Cirrhosis in PI\*ZZ AAT-deficient individuals may become clinically apparent at any age, with the peak incidence occurring in elderly never-smokers who have survived without developing severe emphysema.
- Aside from low plasma AAT levels, laboratory and other clinical features of affected individuals are indistinguishable from those with cirrhosis of any etiology.
- Male sex appears to confer an increased risk for developing cirrhosis in PI\*ZZ AAT-deficient individuals, but firm evidence supporting other risk factors such as viral hepatitis or alcohol use does not exist.
- In heterozygotes carrying the Z allele, there is a much smaller risk for cirrhosis, for which toxic liver injury from alcohol and viruses (especially hepatitis C) may be risk factors.
- In heterozygotes with active liver or vasculitic disease, the plasma AAT level is frequently normal; performing isoelectric focusing is required for diagnosing such individuals who may be PI\*Z heterozygotes.
- Other than liver transplantation for individuals with advanced AAT deficiency-related liver disease, specific therapy for liver disease is not currently available; notably, intravenous augmentation therapy with  $\alpha_1$ -antiprotease does not confer benefits for liver disease.
- In the absence of firm evidence regarding optimal follow-up and preventive strategies, the Task Force suggests that clinical management of individuals with AAT deficiency-related liver disease should include the following: hepatitis A and B vaccinations, regular assessment by physical examination, liver function tests, and ultrasound examination. In older individuals (e.g., 50 years of age or more) with decompensated cirrhosis due to AAT deficiency and increased risk for hepatoma, periodic computed tomography imaging of the liver is recommended because of the insensitivity of other tests (e.g.,  $\alpha$ -fetoprotein measurement).
- Regular assessment of simple liver function tests is recommended in elderly individuals with AAT deficiency who lack liver symptoms.

*Other conditions.* Beside the conditions of emphysema and chronic liver disease, available evidence suggests a relationship between AAT deficiency, necrotizing panniculitis, and C-ANCA-positive vasculitis (e.g., Wegener’s granulomatosis); available evidence does not confirm suggested associations with other vascular conditions (e.g., intracranial aneurysms, abdominal aortic aneurysms), pancreatitis, or celiac disease.

#### *Efficacy of augmentation therapy.*

- Recognizing that supportive evidence of efficacy comes from concordant observational studies but not from a randomized controlled clinical trial, the Task Force recom-

mends intravenous augmentation therapy for individuals with established airflow obstruction from AAT deficiency. Evidence that augmentation therapy confers benefit (e.g., slowed rate of FEV<sub>1</sub> decline and decreased mortality) is stronger for individuals with moderate airflow obstruction (e.g., FEV<sub>1</sub> 35–60% predicted) than for those with severe airflow obstruction. Augmentation therapy is not currently recommended for individuals without emphysema, and benefits in individuals with severe (e.g., FEV<sub>1</sub>  $\leq$  35% predicted) or mild (e.g., FEV<sub>1</sub>  $\geq$  50–60% predicted) airflow obstruction are less clear.

- Insufficient evidence regarding the benefits of augmentation therapy in patients who have undergone lung transplantation for AAT deficiency precludes a firm recommendation. However, it has been observed that inflammation results in free elastase activity in epithelial lining fluid in individuals who have undergone lung transplantation (e.g., during acute rejection and infection). In the context of available data regarding this issue, this observation leads the Task Force to favor augmentation therapy for lung transplant recipients during such episodes.

*General management of obstructive lung disease.* Optimal management of stable individuals with AAT deficiency should include many of the interventions recommended for AAT-replete individuals with emphysema, including:

- Inhaled bronchodilators
- Preventive vaccinations against influenza and pneumococcus
- Supplemental oxygen when indicated by conventional criteria, including during commercial air travel
- Pulmonary rehabilitation for individuals with functional impairment
- Consideration of lung transplantation for selected individuals with severe functional impairment and airflow obstruction
- During acute exacerbations of COPD, management should again include usual therapies for AAT-replete individuals (e.g., brief courses of systemic corticosteroids, ventilatory support when indicated). However, in the context that acute infection poses the threat of increased elastolytic burden in individuals with AAT deficiency, the Task Force favors early antibiotic therapy for all purulent exacerbations

The scant evidence regarding the efficacy of lung volume reduction surgery (with possible resection of lower lobes) in individuals with AAT deficiency suggests that improvement in dyspnea, lung function, and functional status is possible. However, well-studied, robust selection criteria for ideal candidates remain elusive and the duration of lung volume reduction surgery benefit appears shorter than in individuals with AAT-replete COPD.

#### References

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# Lung Disease

## PREPARATION OF THIS DOCUMENT

This document was prepared by an international committee with representatives of the American Thoracic Society, the European Respiratory Society, and the American College of Chest Physicians. It is intended to be an authoritative guide to physicians and others working in health care, to indicate current understanding of alpha-1 antitrypsin (AAT) deficiency, and the methods for diagnosis and therapy.

The literature search involved published work since 1963. For information concerning clinical manifestations, including radiologic characteristics, risk factors, and therapy, studies with the largest cohorts of patients were selected. The evidence for clinical characteristics, risk factors, and therapeutic recommendations was graded as to quality according to the U.S. Preventive Services Task Force (*see* Table 1) (1).

## INTRODUCTION

AAT deficiency is a recently discovered hereditary condition, first described in 1963 (2). Intense research over the past 40 years has led to a detailed understanding of the structural genetic abnormalities, pathophysiology of associated pulmonary emphysema, and liver disease and therapeutic approaches for treating the deficiency and managing the associated diseases.

The severe deficiency of this protein in serum and in tissues, including lung, occurs as a result of the inheritance of two protease inhibitor deficiency alleles from the AAT gene located on chromosome segment 14q31-32.3 (3, 4). Of the deficiency alleles, PI\*Z, is most common and in the homozygous form (PI\*ZZ) results in low serum concentrations of AAT protein, usually below 50 mg/dl (less than 11  $\mu$ M) (5). Pulmonary emphysema of the panacinar type is the most prevalent clinical correlate of this deficiency and is the major cause of disability and death (6). The second most frequent clinical complication is liver disease, usually presenting in infancy as cholestasis, which usually resolves by adolescence (7, 8). However, the most recent data indicate that cirrhosis and carcinoma of the liver affect about 30–40% of patients with AAT deficiency over the age of 50 years and are a significant cause of death in nonsmoking individuals with the PI\*ZZ phenotype (9–11).

AAT is the protease inhibitor most prevalent in serum. It normally circulates in serum in concentrations of 120–200 mg/dl and was named for its ability to inhibit trypsin. However, its major biological role is to inhibit neutrophil elastase (NE), an enzyme that degrades elastin but also basement membrane and other matrix components (12, 13).

AAT is synthesized by hepatocytes and belongs to the serpin family (*serine protease inhibitors*). The Z variant of the molecule, which is the phenotype most frequently associated with lung disease, results in normal mRNA and rate of synthesis of antitrypsin, but only 15% is released into the circulation. The deficiency occurs because about 85% of synthesized AAT is blocked in the terminal secretory pathway of the hepatocyte (14) and can be seen as large intracellular inclusions in hepatocyte cytoplasm. In the null variants of AAT deficiency, where no AAT protein is produced, there are no inclusions and liver disease is not reported.

Through the technique of isoelectric focusing, about 100 genetic variants of AAT have been identified to date. The alphabetical designation to these variants is based on their mobility in an electrophoretic field at alkaline pH. The rapidly migrating variants are designated by the early letters of the alphabet and

those migrating more slowly by the later letters, with the Z variant being slowest. The predominant normal phenotype is PI\*MM (medium mobility), present in 94–96% of Caucasians (15, 16). Approximately 2–3% of the Caucasian population are heterozygous (PI\*MZ). AAT deficiency has been reported in the Far East and Africa, but is relatively rare (17, 18).

On the basis of a large survey of studies regarding the occurrence of AAT deficiency worldwide, de Serres estimates that worldwide, 117 million individuals have the PI\*MS and PI\*MZ phenotypes and that 3.4 million individuals have the PI\*ZZ, PI\*SZ, or PI\*SS phenotype (19).

## EPIDEMIOLOGY

The low frequency of the PI\*ZZ phenotype in the general normal population makes firm data collection with respect to prevalence of affected individuals difficult to obtain. However, a number of screening studies have been undertaken (*see* APPENDIX 2).

The prevalence of AAT deficiency in newborns has been estimated from large population studies, with a screening of all newborns in Sweden in 1972–1974 being the most comprehensive (20). Of 200,000 children in that study, 127 had the PI\*ZZ phenotype, yielding a prevalence of approximately 1 in 1,600 newborns. Other studies from Oregon (21), St. Louis (22), and New York (23) have estimated the prevalence to be 1 in 5,097, 1 in 2,857, and 1 in 3,694, respectively.

Studies from various regions of Europe have shown a large variation in frequency of the Z gene in different countries (24). The gene frequency for PI type Z is highest on the northwestern seaboard of the European continent and the mutation seems likely to have arisen in southern Scandinavia (24). In the United States, therefore, Z gene frequencies are highest in individuals of northern and western European descent (25). The distribution of S types is quite different; the gene frequency is highest in the Iberian Peninsula and the mutation is likely to have arisen in that region (*see* Table 2). (24).

Studies of the prevalence of PI\*ZZ, PI\*SZ, and PI\*MZ patients among patients with a diagnosis of chronic obstructive pulmonary disease (COPD) are summarized in APPENDIX 3. The range of this prevalence is generally low and variable, depending on the patient population studied, but for PI\*ZZ it is 1 to 4.5% and for MZ it can be as high as 17.8%.

## PATHOPHYSIOLOGY OF AAT DEFICIENCY

AAT is a 52-kD single-chain glycoprotein composed of 394 amino acid residues and 3 asparagine-linked complex carbohydrate side chains. The AAT gene spans 12.2 kb on human chromosome 14q31-32.3 and is organized in three noncoding (1a, 1b, and 1c) exons and four (2, 3, 4, and 5) coding exons. The active site of the protein is a single peptide bond, Met<sup>358</sup>–Ser<sup>359</sup>, of the AAT sequence and is encoded within exon 5. Hepatocytes are the primary source of AAT but other cells, including mononuclear phagocytes and intestinal and lung epithelial cells, may synthesize the protein. The major function of AAT is to inhibit a variety of serine proteinases, but kinetic studies have shown that the preferential target is neutrophil elastase (NE), an omnivorous 29-kD extracellular endopeptidase. Inhibition occurs by forming stable 1:1 equimolar complexes in which the proteinase binds to the AAT active site (26) (*see* Figure 1, which depicts the molecular interactions of inhibition).

The human neutrophil also contains and secretes a second potent elastase called proteinase-3 (PR-3). Also a serine prote-

TABLE 1. GRADES OF EVIDENCE

| Grade | Description   |
|-------|---|
| I     | Evidence obtained from at least one properly designed randomized controlled trial   |
| II-1  | Evidence obtained from well designed controlled trials without randomization  |
| II-2  | Evidence obtained from well designed cohort or case-control analytic studies, preferably from more than one center or research group  |
| II-3  | Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence |
| III   | Opinions of respected authorities based on clinical experience, descriptive studies, and case reports   |

Adapted from the U.S. Preventive Services Task Force (1).

Notably, other rating schemes for grading levels of evidence (e.g., WHO/NHLBI GOLD Reports; see <http://www.goldcopd.com/workshop/intro.html>) are available.

ase, PR-3 degrades elastin *in vitro* and causes emphysema when administered intratracheally to hamsters (27). The NH<sub>2</sub>-terminal amino acid sequence of PR-3 is identical to that of the target antigen of the anti-neutrophil cytoplasmic autoantibodies associated with Wegener's granulomatosis, also called antiproteinase-3-positive vasculitis in accompanying documents (28). Proteinase-3 is inhibited by AAT and by  $\alpha_2$ -macroglobulin but not by secretory leukoprotease inhibitor (28).

AAT is a highly pleiomorphic protein, thus reflecting a pleiomorphic gene locus, with roughly 100 alleles having been identified to date. Variants are codominantly inherited and are classified according to the protease inhibitor (PI) system, as defined by plasma isoelectric focusing.

AAT genotypes that confer an increased risk for developing pulmonary emphysema are those in which deficiency or null alleles are combined in homozygous or heterozygous states, which encode AAT plasma levels below a protective threshold, that is, 11  $\mu\text{mol/L}$  (29). On the basis of plasma levels and function of AAT, variants are categorized into the following:

**Normal:** Common M types, accounting for 95% of those found in Caucasian individuals, and characterized by normal plasma levels (more than 20  $\mu\text{mol/L}$ )

**Deficiency:** Characterized by plasma levels less than 20  $\mu\text{mol/L}$ .

Z variant AAT is the commonest deficient variant, with plasma levels among homozygotes of about 5–6  $\mu\text{mol/L}$ , whereas the S variant is more frequent in the Mediterranean area and is associated in homozygotes with plasma levels about 60% of normal. Other, rare, deficient variants are grouped within the terms "M-like" or "S-like" types

**Null:** Rare variants associated with no detectable circulating AAT in the plasma

**Dysfunctional:** For example, the AAT Pittsburgh converted from an elastase inhibitor to a thrombin inhibitor (30), or the PI\*F variant where the association with elastase is markedly reduced (31)

The gene or protein sequences of most variants have been characterized. The mechanism of the commonest AAT deficiency is related to conformational changes of the Z AAT, which spontaneously transforms its reactive loop into a  $\beta$ -sheet polymer under physiological conditions (32). Polymers with identical appearance have been isolated from the liver of a Z AAT homozygote.

The pathogenesis of pulmonary emphysema in AAT deficiency and as a consequence of cigarette smoking in individuals with normal levels of AAT has been postulated to be caused by a protease–antiprotease imbalance.

The protease–antiprotease imbalance hypothesis proposes that pulmonary emphysema in AAT deficiency occurs because of an imbalance between the antielastase defenses of the lung and the relatively excessive action of leukocyte elastase, leading to degradation of elastin and other extracellular matrix components of the lower respiratory tract. This hypothesis is based on evidence that AAT is a major antielastase defense in the alveolar spaces, and that severely AAT-deficient subjects have little or no AAT in their alveoli and are prone to develop destructive emphysema (33). Such evidence has been corroborated over the years by a range of experimental data.

Surveys of large series of patients have clearly shown that

TABLE 2. ESTIMATED GENE FREQUENCIES AND PREVALENCE FOR THE S AND Z ALLELES AND PHENOTYPES IN EUROPE AND THE UNITED STATES

| Allele         | Estimated Gene Frequency (per 1,000) |               | Estimated Prevalence (%) |                           |               |                           |
|----------------|--------------------------------------|---------------|--------------------------|---------------------------|---------------|---------------------------|
|                | Europe                               | United States | Europe                   |                           | United States |                           |
|                |                                      |               | Homozygous               | Heterozygous <sup>§</sup> | Homozygous    | Heterozygous <sup>¶</sup> |
| S*             | 1–9                                  | 2–4           | 0.01–2                   | 4–11                      | 0.05          | 3–8                       |
| Z <sup>†</sup> | 2–24 <sup>‡</sup>                    | 1–2           | 0.02–0.06                | 2–5 <sup>¶</sup>          | 0.02–0.04     | 2–4 <sup>¶</sup>          |

Data from references 22, 25, and 297.

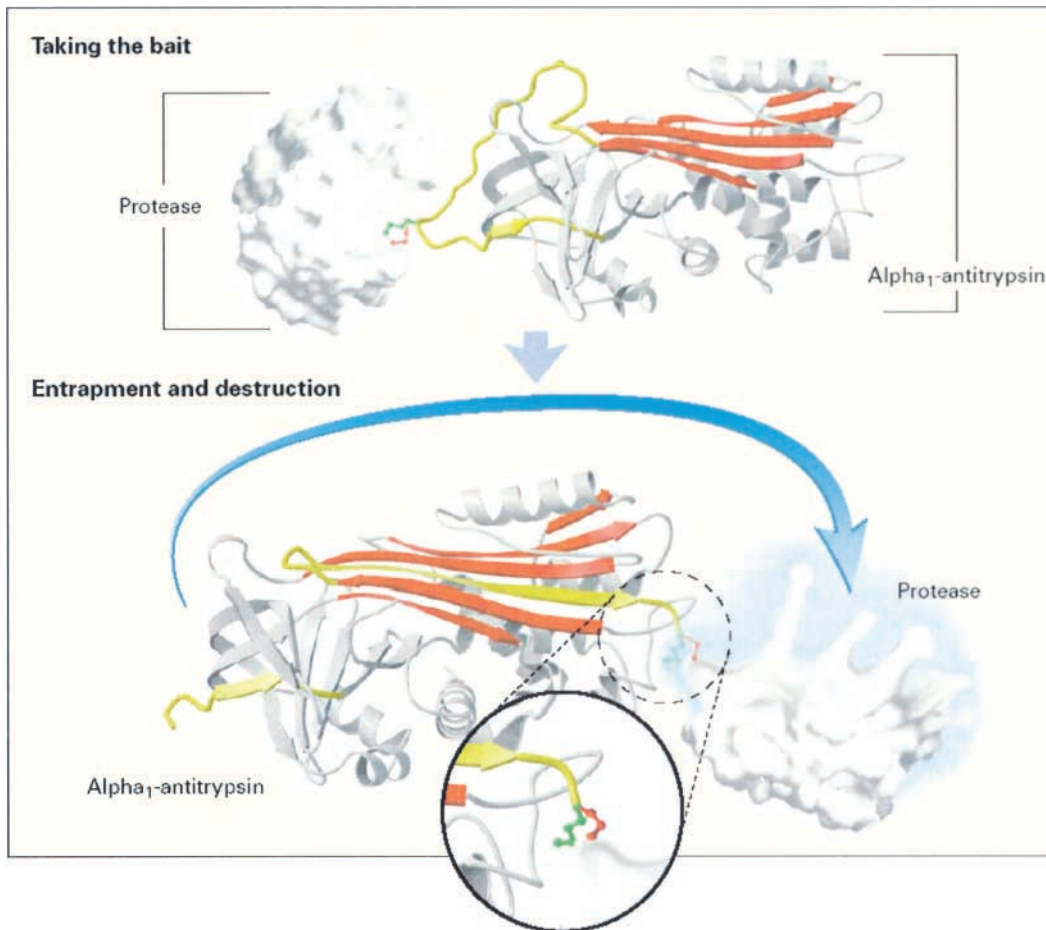
\* In Europe, S gene frequencies are highest in Iberia and lowest in Scandinavia. In the United States, S gene frequencies are highest in local Hispanic populations.

<sup>†</sup> In Europe, Z gene frequencies are highest in northwestern Europe and lowest in Eastern Europe and Iberia. In the United States, gene frequencies are highest in local populations of Northern and Western European descent.

<sup>‡</sup> Z gene frequency is virtually zero in Laplanders and Basques.

<sup>§</sup> SZ phenotype prevalence is reported as 0.2% in local populations in the United States and as 0.02 to 0.3% in Europe.

<sup>¶</sup> Higher prevalence than allele frequency because of ascertainment bias from chronic obstructive pulmonary disease populations.



**Figure 1.** Mechanism of inhibition of neutrophil elastase by the alpha-1 antitrypsin (AAT) inhibitor. Elastase attacks the reactive center loop (yellow) of AAT with the active serine of the elastase (small red side chain), forming a link to the amino acid at the base of the reactive center (small green side chain) of AAT. The resulting cleavage of the reactive loop allows it to snap back into the main  $\beta$  sheet (red ribbon with arrows) of the AAT. This spring-like movement flings the tethered elastase to the opposite end of the AAT molecule, distorting its active site and altering its structure so that it can be destroyed. The center of the active site of the AAT molecule is Met<sup>358</sup>. When Met<sup>358</sup> is oxidized to methionine sulfoxide or sulfone, the association rate constant of the inhibition of neutrophil elastase by AAT is markedly reduced. Oxidants in the lower respiratory tract arise from cigarette smoke, environmental oxidants, as well as neutrophils and macrophages. Modified by permission from Carrell and Lomas (295).

fewer than 60% of individuals with severe AAT deficiency develop significant airflow limitation (6). This suggests that in many cases, AAT deficiency alone is not enough to induce emphysema (34). It has also been suggested that pulmonary emphysema develops when elastin fiber repair mechanisms are overwhelmed by a massive attack of elastases from inflammatory reactions (35).

A major pathogenic factor is cigarette smoke, which contains oxidants capable of inactivating AAT by converting active site Met<sup>358</sup> to methionine sulfoxide, with the association constant for NE being reduced about 2,000-fold. In addition, it has been shown that Z AAT inhibits NE at a slower rate than does M AAT (4.5 versus  $9 \times 10^6 \text{ M}^{-1} \text{ second}^{-1}$ ) (36). Furthermore, AAT polymers can be detected in the bronchoalveolar lavage fluid, as demonstrated in two of five subjects with emphysema related to PI\*ZZ AAT deficiency (37). Because polymerization obscures the AAT reactive loop, the conformational transition may impair the inhibitory activity. Therefore, in AAT deficiency, oxidants contained in cigarette smoke may further impair a quantitatively and qualitatively less functional AAT. In addition, cigarette smoke and proteinases may both work to impair lung elastin resynthesis in the animal model of elastase-induced emphysema (38).

Cigarette smoke also recruits inflammatory cells. In AAT deficiency, more neutrophils are found within air spaces than in emphysematous lungs of individuals with normal AAT plasma levels. This contributes to a greater NE load (39). This phenomenon might be attributable to the presence of neutrophil chemotactic factors, mainly leukotriene B<sub>4</sub> released from alveolar macrophages (40).

In addition, neutrophils and macrophages may release a vari-

ety of metalloproteinases with the potential to degrade extracellular matrix components (41). A role for a human collagenase in alveolar injury in experimental emphysema has also been demonstrated (42). Metalloproteinases are not inhibited by AAT and may even inactivate it by limited proteolysis near the active site (41). The C-terminal fragments of AAT released during proteolytic inactivation are potent neutrophil chemotactic factors (43, 44).

## LABORATORY TESTS

Observation of a reduced or absent  $\alpha_1$ -globulin band on routine plasma protein electrophoresis should arouse suspicion of AAT deficiency and should be confirmed quantitatively and qualitatively (see Table 3).

**TABLE 3. RANGE OF SERUM LEVELS\* OF ALPHA-1 ANTITRYPSIN ACCORDING TO PHENOTYPE**

| Units         | Phenotype |        |         |        |       |
|---------------|-----------|--------|---------|--------|-------|
|               | PI*MM     | PI*MZ  | PI*SS   | PI*SZ  | PI*ZZ |
| $\mu\text{M}$ | 20–48     | 17–33  | 15–33   | 8–16   | 2.5–7 |
| mg/dl         | 150–350   | 90–210 | 100–200 | 75–120 | 20–45 |

Data from references 14, 47, and 298.

\* Serum levels given are measured using a typical commercial standard (mg/dl) and the purified standard ( $\mu\text{M}$ ) used in the U.S. Registry. A level of less than 11  $\mu\text{M}$  is associated with an increased risk for emphysema.



### Quantitative Tests

Plasma AAT levels are usually determined by rocket immunoelectrophoresis, radial immunodiffusion, or, more recently, by nephelometry. Commercially available standards, especially those used for radial immunodiffusion, tend to overestimate the AAT concentration by as much as 35–40% (45). To discriminate between historic values obtained using the nonpurified standard and those obtained with the pure standard developed by the U.S. National Institutes of Health, the former are expressed as milligrams per deciliter (mg/dl), and the latter in micromolar units ( $\mu\text{mol/L}$  or  $\mu\text{M}$ ). The two units are, however, often used interchangeably in many continental European countries, irrespective of the standard used. Moreover, nephelometry may also overestimate AAT levels, because of interference with lipids or hemoglobin. Also to be considered is that AAT is an acute-phase reactant, and inflammatory conditions may augment the steady state plasma AAT levels in Z heterozygotes. It should be noted that a “protective” threshold level of 11  $\mu\text{mol/L}$  previously maintained corresponds to 80 mg/dl if measured by radial immunodiffusion and to 50 mg/dl if measured by nephelometry (see Table 4). This protective threshold has evolved from the observation that patients with heterozygote phenotypes whose levels of AAT exceed this level are usually free from emphysema (29).

### Qualitative Tests

The most widely used method for identifying AAT variants is their separation based on the isoelectric point by means of thin-layer isoelectric focusing (IEF). This technique, commonly referred to as “phenotyping,” requires skill and experience and should be performed in reference laboratories. The IEF specificity may be further enhanced by coupling it with an immunoblot or by using an immobilized pH gradient IEF gel (46). Phenotyping may be performed on serum or plasma samples. Some laboratories perform IEF on “dried blot spot” samples, using a blood drop absorbed on special paper, allowing for easier transport of samples. This method is suitable for screening purposes, but the identification of a deficient variant should be confirmed on serum or plasma samples.

Diagnosis at a molecular level (“genotyping”) is performed on genomic DNA, extracted from circulating mononuclear blood cells. Known mutations may be detected by allele-specific amplification or analysis. Lack of recognition of a known mutation may imply the presence of a new variant. In this case, a gene scan should be performed by means of direct sequencing, or denaturing gradient gel electrophoresis (47). Molecular level diagnosis has been made easier by the commercial availability of test kits capable of detecting S and Z alleles in whole blood or mouthwash samples. However, available kits will miss null alleles and plasma levels of AAT may also be necessary.

## IDENTIFICATION OF INDIVIDUALS WITH AAT DEFICIENCY

### Early Detection: Prenatal

PI\*ZZ deficiency is inherited as an autosomal codominant gene. The risk of a homozygous offspring is 1 in 4 for each birth if

both parents are carriers of the Z allele. If one parent is PI\*ZZ and the other heterozygous, then all children are either carriers or affected (PI\*ZZ).

There is no routinely available method developed for the prenatal diagnosis of the condition. Amniocentesis or chorionic villus sampling (48, 49) provides the material on which genetic testing can be performed. Requests for prenatal diagnosis may be based on a history of perinatal liver disease in a previous sibling, in which case the risk of developing liver disease may rise substantially (9, 50). Several techniques of prenatal gene identification have been reported and are available in limited cases. All require techniques of DNA amplification and use specific probes to provide adequately specific diagnostics (51, 52). However, financial and practical considerations limit their usefulness.

Postnatal detection of AAT deficiency depends on a high level of suspicion. The technology for rapid screening techniques is available and utilizes DNA amplification from heel blood samples (53). Postnatal detection may occur in the setting of neonatal hepatitis or a strong family history. Otherwise, most cases remain undetected unless emphysema, liver disease, or rare complications develop. Although AAT deficiency is one of the most common codominant disorders to affect Caucasians, routine screening is not performed.

### Detection in Adults

It is recognized that nonsmoking individuals with the homozygous Z phenotype have a remarkably delayed onset of symptoms and some may have an almost normal life span (54). Thus, the exact prevalence of AAT deficiency in most populations remains unknown and many afflicted individuals remain undiagnosed. Large-scale screening programs of the newborn or adult populations in the United States and Europe (except for Sweden) have not been undertaken because of cost and issues of personal vulnerability related to the presence of an inherited abnormality. Because there is presently no cure for the disease, subjects and their families must withstand the emotional stress of living with this knowledge at a time when they may be totally asymptomatic. Also, identification of the abnormality could compromise an individual's status with respect to insurability and employment. Because avoidance of smoking and exposure to hazardous respiratory environments may benefit the prognosis of individuals who have AAT deficiency, there is some medical justification for early detection. However, in recognition of the positive and negative factors related to detection, informed consent for performing the diagnostic tests should be obtained from the subject by the attending physician after a thorough explanation of the issues involved.

Three categories of genetic testing have been specified (see the GENETICS, PSYCHOSOCIAL, ETHICS, AND ECONOMIC ISSUES section). The first type is labeled “diagnostic” testing and refers to the testing of individuals with symptoms and/or signs consistent with an AAT deficiency-related disease.

The second type of testing is labeled “predispositional” test-

**TABLE 4. METHODS USED FOR QUANTITATIVE DETERMINATION OF PLASMA ALPHA-1 ANTITRYPSIN, THEIR NORMAL RANGES, AND PROTECTIVE THRESHOLD VALUE**

| Method                 | Normal Range           | Protective Threshold          |
|------------------------|------------------------|-------------------------------|
| Radial immunodiffusion | 150/200–350/400 mg/dl* | 80 mg/dl*                     |
| Nephelometry           | 83/120–200/220 mg/dl*  | 50 mg/dl*; 11 $\mu\text{M}$ † |

Data from references 14, 45, and 299.

\*Value obtained by commercially available standards.

†Value obtained by the NHLBI standard.

ing, which refers to identifying asymptomatic individuals who may be at high risk of having AAT deficiency. The third type of testing is labeled “screening,” which refers to programs designed to search in populations for persons possessing certain inherited predispositions to disease. The hallmark of screening is that there should be no previous suspicion that any given individual has the condition being tested. Specific recommendations and associated recommendation grades for testing in specific groups of individuals are given in Table 8 of the GENETICS, PSYCHOSOCIAL, ETHICS, AND ECONOMIC ISSUES section.

Subjects with abnormal blood levels should be investigated further to provide a qualitative evaluation of their AAT disorder. Even subjects with a borderline normal AAT plasma level (12–35  $\mu\text{mol/L}$  or 90–140 mg/dl) and their first-degree relatives should undergo qualitative testing, because these levels may correspond to an intermediate level phenotype (SZ, SS, MZ) and a relative with asymptomatic or misdiagnosed AAT deficiency may be uncovered within the family.

Beside occasional observation of a reduced or absent  $\alpha_1$ -globulin band on electrophoresis, an AAT level is particularly important in patients with early-onset pulmonary emphysema with or without a history of cigarette smoking. Testing should also be performed in siblings of AAT-deficient individuals and considered for offspring and when there is familial aggregation of symptoms of shortness of breath and chronic cough. Furthermore, it is recommended that all subjects with COPD or asthma characterized by incompletely reversible airflow obstruction should be tested once for quantitative AAT determination (see Table 5) (55). Also, individuals with evidence of cirrhosis of the liver with no known etiology should be tested for candidate phenotypes (e.g., PI\*ZZ, PI\*MZ, PI\*M<sub>malton</sub>) and testing should be considered in individuals with the syndrome of Wegener’s granulomatosis (antiproteinase-3 vasculitis), where a high prevalence of the PI\*ZZ and PI\*MZ phenotypes has been reported and antibodies to proteinase-3 have been implicated (9), and in adults with bronchiectasis without evident etiology.

## PATHOLOGY

At autopsy, panacinar emphysema with basal predominance is seen in all adult patients with severe AAT deficiency (56). Even in an 11-year-old girl who died from intraabdominal hemorrhage due to cirrhosis, uniform panacinar emphysema was found at autopsy (57). On occasion, minimal centrilobular emphysema is observed in the upper lobes. In 2 of 14 autopsies, where descriptions from inflation-fixed specimens are available, cylindrical bronchiectasis has been reported (56).

Descriptions of bronchiolar and bronchial histology in individuals with AAT deficiency are sparse in the literature. The Reid Index, reflecting bronchial gland hypertrophy, was reported as normal in one case, with mild gland enlargement noted in another case. Also, loss of muscle and elastic fibers in small bronchi was noted. In lung tissue resected from patients with severe emphysema due to AAT deficiency and undergoing lung volume reduction surgery, changes at the level of bronchioli (bronchiolitis obliterans, bronchiolectasia, acute and chronic bronchiolitis, bronchiolitis with organizing pneumonia) were more frequently observed compared with emphysema patients without AAT deficiency (58). On occasion, large bullae, preferentially in the basal parts of the lungs, are described at autopsy, in surgical specimens, or as seen by X-ray.

## SYMPTOMS

(See APPENDIX 1.) Symptomatic obstructive lung disease in AAT deficiency usually presents at a mean age between 32 and 41 years in individuals with a history of smoking (6, 59–63). Considerable variability in the time of onset of symptoms has been described, but symptoms rarely present before age 25 years. Although severe symptoms are most often seen in current or previous cigarette smokers, some smokers and many nonsmokers develop no symptoms at all (64, 65).

The largest cohort of patients ( $n = 1,129$ ) queried with a standardized symptom questionnaire (66) were participants in the National Heart, Lung, and Blood Institute (NHLBI) Registry of Individuals with Severe Deficiency of AAT (67). This registry included individuals with an AAT serum level  $< 11 \mu\text{M}$  and included some subjects ascertained through family screening (20%), often in the absence of symptoms. The most frequent symptom elicited was dyspnea on exertion (in 84% of participants). Self-reported wheezing during respiratory tract infections was prominent (76%), although wheezing independent of infections was also common (65%).

A cough was usually present in 42% of participants in the NHLBI Registry. Increased cough and phlegm for at least 3 weeks in a year were described by 50% of individuals (67) and may present as early as age 18 years (68). Other studies have described a chronic productive cough for 3 months in at least two successive years, consistent with chronic bronchitis in 8–40% of AAT-deficient patients (68–70). A chronic cough with or without sputum production has been seen in association with radiographic features of cylindrical bronchiectasis (70).

The presence of episodic wheezing and dyspnea consistent with a diagnosis of asthma has been noted in AAT deficiency.

**TABLE 5. RECOMMENDATIONS FOR QUANTITATIVE TESTING OF ALPHA-1 ANTITRYPSIN: DECREASING LIKELIHOOD OF FINDING DEFICIENCY\***

| No. | Recommendation  |
|-----|---|
| 1   | Confirmation of absent alpha-1 antitrypsin peak on serum protein electrophoresis                  |
| 2   | Early-onset pulmonary emphysema (regardless of smoking history)                                   |
| 3   | Family members of known alpha-1 antitrypsin-deficient patients                                    |
| 4   | Dyspnea and cough occurring in multiple family members in same or different generations           |
| 5   | Liver disease of unknown cause  |
| 6   | All subjects with chronic obstructive pulmonary disease   |
| 7   | Adults with bronchiectasis without evident etiology should be considered for testing <sup>†</sup> |
| 8   | Patients with asthma whose spirometry fails to return to normal with therapy                      |
| 9   | Unexplained panniculitis and anti-proteinase-3 vasculitis   |

\* See Table 11 of the GENETICS, PSYCHOSOCIAL, ETHICS, AND ECONOMIC ISSUES section for specific grading of these recommendations.

<sup>†</sup> As presented in Table 11 of the GENETICS, PSYCHOSOCIAL, ETHICS, AND ECONOMIC ISSUES section, diagnostic testing for AAT deficiency in individuals with bronchiectasis without evident etiology should be considered (Type B recommendation). This level of recommendation recognizes that AAT deficiency is underdiagnosed, that bronchiectasis occurs frequently in individuals with AAT deficiency in some series, but that the association of bronchiectasis with AAT deficiency has not been firmly established.

In a study evaluating the presence of wheezing, bronchodilator responsiveness, atopy, and increased serum IgE, three or more of these markers for asthma were found in 22% of AAT-deficient patients compared with 5% of COPD patients without AAT deficiency (69). Allergic rhinitis was common even when airway obstruction was not present. In the NHLBI Registry, 35% of participants self-reported a history of asthma and more than 50% demonstrated a significant postbronchodilator reversal of airflow obstruction (more than 12% and 200 ml) on serial testing (67, 69). In this registry, the mean age at which the first symptom, wheezing, manifested itself was 31 years.

No study of a population-based cohort has adequately addressed the prevalence of catastrophic disease in AAT deficiency. The best data available come from the NHLBI Registry (67), in which a majority (72%) of deaths were due to emphysema. A chest illness in the past 3 years that kept the patient off work, indoors at home, or in bed was self-reported by 68% of patients. Thirty percent of NHLBI Registry participants reported medical disability at a mean age of 46 years, indicating the significant morbidity associated with AAT deficiency (67). In summary, the respiratory symptoms of patients with AAT deficiency are striking in their early age of onset.

## PHYSICAL FINDINGS

No physical finding is sensitive or specific enough to be clinically useful in detecting the AAT-deficient individual. Wheezing is common; yet, the absence of wheeze on examination can occur in severe emphysema. Progressive disease is associated with signs of chest hyperinflation, reduced breath sounds at the bases, and muscle wasting. Because the most common alternative misdiagnosis is asthma, spirometry should supplant physical findings in patient evaluation; spirometric measures should return to normal in most patients with adequately treated asthma.

## LUNG FUNCTION TESTS

Pulmonary function testing should include spirometry (pre- and postbronchodilator), lung volume measurements by helium dilution or by body plethysmography, and single-breath CO-diffusing capacity (71, 72).

Spirometry is the pulmonary function test that is most often performed in AAT-deficient individuals because it is reproducible and reflects an important aspect of the lung disease. The spirometric abnormalities include reduction in the forced expiratory volume in 1 second (FEV<sub>1</sub>) and a normal or reduced forced vital capacity (FVC). The obstructive impairment (reduced FEV<sub>1</sub>/FVC ratio) is primarily due to loss of elastic recoil from parenchymal disease (emphysema) with dynamic collapse of otherwise normal airways. The flow-volume curves usually show a marked decrease in flow with decreasing lung volumes, typically evidenced by concavity of the expiratory portion of the flow curve.

The reduced elastic recoil results in increased lung compliance, which allows for hyperinflation with increases in residual volume (RV) and total lung capacity (TLC). Due to areas of lung that are poorly ventilated (air trapping), static lung volumes measured by body plethysmography are usually greater than those measured by dilution of an indicator gas.

Emphysema of the lung parenchyma also impairs gas exchange with reduction in the diffusing capacity and a widening of the alveolar-arterial gradient for oxygen. Although they are often different aspects of the same pathological process (emphysema), reduction in expiratory flow (FEV<sub>1</sub>) and reduction in the diffusing capacity are not always well correlated (73, 74), and both should be determined when assessing the overall severity

of pulmonary impairment in AAT-deficient individuals. In addition, arterial oxygen tension adds information about disturbed ventilation-perfusion relationships.

In more advanced pulmonary disease, the effect of emphysema on muscle activity of the thorax and diaphragm muscles can be assessed by measuring maximal inspiratory and expiratory mouth pressure. Predictive values have been published (75).

The cardiopulmonary status can also be assessed by exercise testing. While in normal individuals the Pa<sub>O<sub>2</sub></sub> may not change, or even increase, on exercise, AAT-deficient individuals may show markedly decreased Pa<sub>O<sub>2</sub></sub> and an increased alveolar-arterial oxygen difference. Individuals with AAT deficiency have increased respiratory rates at rest, and on mild exercise rapidly reach more than 80% of their predicted maximal voluntary ventilation, indicating that ventilation may become a limiting factor at higher work levels (76).

Although symptoms suggesting airway hyperresponsiveness such as cough and wheezing are present in an appreciable proportion of AAT-deficient individuals and some are initially diagnosed as having asthma, the reversibility in airflow obstruction after an aerosol bronchodilator is usually moderate (69).

## Conclusions

Optimal clinical practice would indicate that full lung function testing including spirometry, static lung volumes, arterial blood gas analysis, and gas transfer should all be assessed at baseline to fully document the physiologic status of patients with obstructive pulmonary disease (77, 78).

Because AAT-deficient individuals mainly develop fixed airflow obstruction, it does not seem justified to assess variability of airflow obstruction by peak expiratory flow monitoring in most subjects with AAT deficiency. However, follow-up of patients should include spirometry at yearly intervals.

## RADIOLOGY, INCLUDING COMPUTED TOMOGRAPHY AND VENTILATION-PERFUSION SCAN

### Emphysema

Chest roentgenography in early disease is usually normal. In advanced disease, hyperinflation and increased radiolucency of the lungs, particularly in the lower lung segments, are evident. Diaphragms are low and flat, and exaggerated verticality of the heart, increased anterior-posterior diameter of the chest, and widening of the retrosternal space are present. Of these criteria, diaphragmatic flattening in the lateral projection is probably the most specific. Vascular markings are decreased, mainly in the lower zones, in contrast to the preponderance of upper zone disease in non-AAT deficiency emphysema (63, 79-83). Concomitant enlargement of the hilar pulmonary arteries is evidence of possible pulmonary hypertension.

Computed tomography is much more sensitive than plain chest radiography or pulmonary function tests for the presence of emphysema (74, 83, 84). High spatial frequency reconstruction of images (high-resolution computed tomography [HRCT]) is more sensitive for detecting morphologic changes such as bullous disease and bronchiectasis. On HRCT, emphysema is characterized by the presence of areas of abnormally low attenuation, which can be contrasted with surrounding normal lung parenchyma if a sufficiently low window level (-600 to -800 Hounsfield units [HU]) is used. In AAT deficiency, the classic finding is panacinar emphysema in terms of uniform abnormally low attenuation of lobules, and predominant lower lobe distribution. Pulmonary vessels in the affected lung appear fewer and smaller than normal (85), but mild and even moderately severe panacinar emphysema can be subtle and difficult to detect radiographically (86). Whereas focal areas of emphysema usually lack distinct

walls, bullae, by definition are sharply demarcated by a thin wall and measure 1 cm or more in diameter. Bullae are more common in usual (non-AAT deficiency) emphysema (79).

### Bronchiectasis

Despite the well recognized association between AAT deficiency and the early development of emphysema, only a limited number of studies have assessed the association between AAT deficiency and bronchiectasis. In Eriksson's original patients, bronchiectasis was reported in 2 of 23 patients (59). Guest and Hansell observed bronchial wall thickening and/or dilation in 7 of 17 patients (41%) with AAT deficiency (82) and King and coworkers found evidence of bronchiectasis in 6 of 14 patients (43%) with AAT deficiency (87). Cuvelier and coworkers reported that the frequency of AAT deficiency alleles is not increased among patients with bronchiectasis, whereas other studies suggest bronchiectasis is more common in Hispanic patients (88). The study by Cuvelier and coworkers suggests that bronchiectasis is more a result of emphysematous changes in the parenchyma than of AAT deficiency per se (88).

### Lung Density Evaluation

Pixel values of CT images represent tissue density, which makes it possible to calculate densitometric parameters from frequency histograms of pixels within the lung. These densitometric parameters provide a quantitative assessment of the extent of emphysema. Various methods for calculating densitometric parameters have been reported in the literature. The "density mask" method enhances areas of abnormally low attenuation, using a computer program to highlight pixels to create a density mask within any desired range. The density mask parameter is defined as the percent area of lung highlighted relative to the total lung area. Highlighting all pixels with attenuation values below -910 HU correlates with pathologic scores and is comparable to that obtained by visual assessment (89). The "percentile" method assesses the extent of emphysema by the cutoff point that defines a given percentile of the histogram (e.g., the tenth percentile is extracted from the histogram as the density value, in Hounsfield units, at which 10% of the pixels have lower densities) (90). A third possibility is to assess the extent of emphysema by "mean lung density" (91).

Ventilation-perfusion scanning may be a useful tool in detection of early changes associated with AAT deficiency, as even individuals with relatively normal lung function may have abnormal scans (63, 76, 92-95). Typically, the ventilation scan shows symmetric distribution of xenon-133 throughout all zones of the lung during the equilibrium phase followed by a symmetric delay in washout, most prominent in the lung bases and midzones. A symmetric loss of pulmonary arterial perfusion is also found, most marked in the bases.

In summary, a chest X-ray should be performed as an initial test for incidental lung lesions or possible identification of localized bullous disease. However, CT scanning, including thin slices for morphology and thick slices for densitometry, is presently the most definitive technique to detect and quantify the presence of emphysema in AAT deficiency.

### PARAMETERS OF PROGRESSION: FEV<sub>1</sub>, DESMOSINE, AND COMPUTED TOMOGRAPHY

The standard method for monitoring the progress of emphysema is by pulmonary function tests, and rate of decline of FEV<sub>1</sub> is by far the most commonly used measurement in longitudinal studies. However, spirometry has shortcomings in assessing patients with emphysema. Because airway obstruction is due mainly to dynamic collapse, the results of spirometry are heavily dependent

on the cooperation and effort of the individual. Slow vital capacity is usually greater than FVC and, similarly, the FEV<sub>1</sub> can be greater with a submaximal than with a maximal effort.

It is an advantage of spirometry that it is simple to perform and can be easily repeated frequently. However, it has been shown that frequent measurements less than 3 to 6 months apart are not worthwhile, because measurements at short intervals will add little extra information to measured changes over the longer term (96).

FEV<sub>1</sub> is considered to be quite reproducible. In several large multicenter studies (97), spirometry of high technical quality, performed on separate days, had a standard deviation of about 100 ml. However, this measurement error is large in comparison with the annual decline in FEV<sub>1</sub>, which in normal adults is about 30 ml and in AAT-deficient individuals is about 60 ml. The measurement error implies a standard error of at least 100 ml/year when estimating the slope of decline in FEV<sub>1</sub> in individual subjects who have been monitored for no more than 1 year. The standard error is inversely proportional to the observation period (i.e., with an observation period of 10 years, the standard error of the slope reduces to 10 ml/year, which is still quite large).

The variability of repeated measurements of the single-breath diffusing capacity is greater than the variability of FEV<sub>1</sub> measurements, and therefore the diffusing capacity has less potential as a progression parameter. Although blood gas composition and diffusing capacity for carbon monoxide are frequently measured in the course of managing patients with AAT deficiency, studies have not been published demonstrating their effectiveness as follow-up parameters.

From a conceptual point of view, densitometric parameters derived from repeated CT scans could be sensitive and specific markers of the emphysematous process, and as Flenley suggested more than a decade ago, the progression of emphysema may be assessed more accurately by repeated quantitative CT than by measuring the FEV<sub>1</sub> (98, 99).

### Radiology

The principal source of variation of lung density measurements is the level of inspiration. Ranging from full inspiration to full expiration, lung densities more than double (100-102). The volume of air in the lung can be derived from CT images, that is, CT lung density histograms (102-104). Half the lung density is composed of blood in the microvascular circulation (105). When a deep breath is taken, not only is the volume of air increased but also blood is sucked into the lung, which makes the relation between inspiratory level and lung density more complicated.

The belief of some investigators that spirometric control of ventilation during scanning improves the reproducibility and accuracy of density measurements (106-108) has been complicated by the recognition that patients with COPD are less able to successively reproduce levels of full expiration and inspiration to allow standardization (109, 110).

Analysis of repeated CT scans at various levels of inspiration has revealed the relationship within an individual between lung density and volume. On the basis of this relationship, densitometric parameters can be standardized by log-transformed lung volume, which corrects for differences in lung volume between scans and eliminates the need for spirometrically controlled CT (111). Using a broad range of pixel percentiles from the 10th to the 30th (corresponding to densities ranging from -950 to -890 HU), the annual decline was found to be 2 HU, corresponding to a loss of lung tissue of 2 g/L lung volume (111). CT quantitation of emphysema by densitometric parameters seems to be a more sensitive measure of the progress of emphysema as compared with pulmonary function tests (e.g., FEV<sub>1</sub>) (98, 112, 113). Inspiratory CT was superior to expiratory CT for longitudinal estima-

tion of structural abnormalities caused by aging and smoking (113) and the pixel percentile was more robust than the pixel index for monitoring the progress of emphysema (111).

In a randomized clinical trial of AAT augmentation therapy over a period of 3 years with 56 patients, the sensitivity to measure the progression of emphysema by the percentile method proved two- to threefold higher than any parameter measured by spirometry or CO-diffusing capacity. This implies that new drug trials using CT as any outcome parameters are feasible with a fivefold lower number of patients (112).

Because it has been shown that CT lung density is influenced by age, normal CT attenuation values for the lung by age should be established (101, 113–116). Furthermore, pixel attenuation values fluctuate with the position in the thorax and change with aging of the X-ray tube (117).

A problem related to the use of CT for monitoring the progress of emphysema is radiation exposure. Limiting the examination to a single slice 5 cm below the carina would markedly reduce the radiation dose and results derived from calculations based on a thin slice were similar to results based on a volume scan of the whole lung (111). Also, a reduction of the electrical current (mA) to levels 10 times below standard settings has little influence on lung density measurements (118, 119).

### Biochemical Markers

Because it is widely accepted that lung damage in individuals with AAT deficiency results from an imbalance between neutrophil elastase (NE) and AAT, it is reasonable to suppose that factors related to the activity of NE and/or to turnover of lung extracellular matrices could be indicators of lung destruction (120). The former (active NE and the NE-specific fibrinogen-derived A $\alpha$  peptide) (121) are indirect markers, whereas the latter (desmosine/isodesmosine [DES/IDES] and elastin-derived peptides) are direct markers of elastin degradation and are therefore more closely linked to the true clinical outcome of emphysema (122). Elastin-derived peptides may be measured immunologically in plasma or urine, and have been found to be significantly increased in individuals with COPD compared with control subjects by direct measurement (123) and by radioimmunoassay (124); however, the incomplete biochemical characterization of the immunoreactive material raises concerns about its suitability for controlled clinical trials.

DES and IDES are cross-linked amino acids unique to mature elastin that are contained in elastin-derived peptides in the bloodstream and excreted in urine. Urinary DES levels are higher in smokers with a rapid decline of lung function indices than in those with slow decline (125). In addition, they are as high in subjects with AAT deficiency as in subjects with usual, AAT-replete COPD (123). Preliminary evidence that AAT augmentation therapy decreases urinary DES excretion in AAT-deficient subjects (126) prompted investigators to design clinical trials of short-term supplementation therapy with the primary end point being reduction of the urinary rate of excretion of DES/IDES. Results of one of these trials could not confirm the preliminary finding (127). Taken together, studies thus far support urinary DES/IDES as potential candidates for monitoring progression of lung disease and efficacy of therapy in AAT-deficient subjects, but further evidence is needed to demonstrate methodologic reliability and clinical relevance to progression.

In summary, there are adequate data to suggest that FEV<sub>1</sub> and CT densitometry are reliable methods to detect progression of emphysema in AAT deficiency. Spirometry should initially be performed on an annual basis until it is clear that progression is not rapid when a reduction in frequency of assessment can be initiated.

### RISK FACTORS

A number of studies have demonstrated the role of various risk factors for the development of COPD in patients who have the PI\*ZZ phenotype (see Table 6 and APPENDICES 3 and 4). It is clear that smoking is the most important risk factor for the development of emphysema in AAT deficiency of the PI\*ZZ type. The annual decline of FEV<sub>1</sub> in smokers with AAT deficiency is about 130 ml, and 70 ml in ex-smokers (67, 128–130). However, a later series (131) has shown mean declines of 70 ml/year in current smokers, 47 ml/year in never-smokers, and 41 ml/year in ex-smokers, indicating similar decline rate in nonsmokers and ex-smokers. To study other environmental and intrinsic factors contributing to the decline in lung function, nonsmoking status of participants must be assured to avoid the confounding effects of active smoking. In Sweden, Denmark, and the North American registries, large numbers of patients are available for follow-up studies.

Three reports have addressed the issue of impact of environmental factors on lung function decline based on self-reported exposures. In a series of 225 nonsmoking PI\*ZZ individuals in Sweden with an FEV<sub>1</sub> of 84  $\pm$  28% predicted (mean  $\pm$  SD), the history of occupational exposure for at least 3 months to gas, fumes, or dust; the frequency of annual colds; and the number of attacks of pneumonia were analyzed as possible risk factors in lung function (132). Increasing age, male sex, and symptoms of wheezing were identified as independent determinants of FEV<sub>1</sub> decline. Among men over 50 years old, wheeziness and occupational exposure to airway irritants were independent determinants of lung function. A subsequent report concerning the same patients showed that self-reported passive smoking had increased risk for chronic bronchitis and that the use of kerosene heaters and employment for more than 10 years in an agricultural environment were independent correlates of decreased lung function (133). With respect to passive smoking, other studies have also demonstrated a detrimental association with pulmonary symptoms (34, 68). A prospective study of 103 Swedish children with AAT deficiency detected at birth showed that they had normal lung function when they reached adulthood, indicating that childhood respiratory infections are not a major factor for development of emphysema (134). In a Danish study on never-smoking nonindex cases of PI\*ZZ, no abnormalities in lung function could be identified (135). In addition to the Swedish studies, Seersholm and Kok-Jensen described 27 index cases and 48 nonindex cases and could not find an effect of passive smoking on the development of emphysema (136). Further analysis of the data from the Danish AAT Deficiency Registry showed that the beneficial effect of smoking cessation was due to a decreased decline in FEV<sub>1</sub> among the quitters (128). The mean overall decline in FEV<sub>1</sub> was 81 ml/year with a decline of 132 ml/year among the smokers, 58 ml/year in the group of patients who quit smoking during the study period, and 86 ml/year in never-smokers. It was also found that the rate of decline according to initial FEV<sub>1</sub>% predicted was U-shaped, with the most rapid decline in the group of patients with an initial FEV<sub>1</sub>% predicted between 30 and 64%.

The North American NHLBI Registry monitored 1,129 patients with severe AAT deficiency for 3.5 to 7 years (137). The mean FEV<sub>1</sub> decline was 54 ml/year, with more rapid decline in males, those aged 30–44 years, current smokers, those with FEV<sub>1</sub> 35 to 79% predicted, and those who ever had a bronchodilator response.

In one report, Mayer and coworkers (138) studied 128 individuals with AAT deficiency of the PI\*ZZ phenotype to examine the relationship between chronic respiratory symptoms, airflow limitation, treatment requirements, and semiquantitative esti-

TABLE 6. RISK FACTORS FOR LUNG DISEASE IN PI\*ZZ INDIVIDUALS

| Risk                                    | Outcome                 | Reference              | Level of Evidence | Comment  |
|---|-------------------------|------------------------|-------------------|--|
| COPD and death                          | Overall high prevalence | APPENDIX 2             | II-1              | The initial population study (59) indicates the high risk of COPD and an autopsy study (10) confirms early mortality in smokers, whereas nonsmokers have low risk for COPD and almost normal life expectancy but high liver disease risks. There is no increased risk for COPD up to age 20 yr |
|   | Overall high prevalence | APPENDICES 2 and 4     | II-1              | High prevalence of PI*ZZ and PI*MZ in COPD populations (APPENDIX 3) and early onset and increased severity of COPD in case studies (APPENDIX 4)  |
| Smoking                                 | Survival                | APPENDIX 2             | II-1              | Autopsy series (11) confirms decreased survival of smokers   |
|   | Symptoms                | APPENDICES 3 and 4     | II-3              | Many studies show earlier onset of symptoms, lower FEV <sub>1</sub> , and more rapid decline in FEV <sub>1</sub> in smokers  |
| Sex                                     | Prevalence increase     | APPENDICES 2, 3, and 4 | II-3              | Mixed conclusions regarding increased male risk for COPD because of confounding factor of smoking. Some studies suggest increased male risk due to increased occupational or environmental exposure  |
| Occupational and environmental exposure | Prevalence increase     | APPENDIX 4             | II-3              | Studies in nonsmokers confirm the increased risk for respiratory symptoms from gas, fumes, and dust, but all studies were hampered by retrospective analysis and confounding factors (smoking, age, sex, and familial)   |
| Familial                                | Prevalence increase     | APPENDICES 2, 3, and 4 | II-2, II-3        | Familial increase in COPD, particularly in siblings of index cases with COPD   |
| Atopy                                   | No prevalence increase  | APPENDIX 2             | II-1              | Suggestion of asthma increase in Swedish longitudinal studies, but not statistically significant   |
|   | Prevalence increase     | APPENDICES 3 and 4     | II-2, II-3        | "Asthma diagnosis" and bronchodilator response prominent in many biased population studies. Only one study with control subjects suggests significant association with asthma (69)   |

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

mates of occupational exposure to dust fumes, smoke, and gas. Increased prevalence of chronic cough and having left a job because of breathlessness were seen in individuals with high mineral dust exposure compared with individuals with no exposure. Subjects with high mineral dust exposure had a significantly lower FEV<sub>1</sub> (31% predicted) compared with individuals with no exposure (40% predicted). Personal tobacco use was a significant risk factor for most outcome measures but no interaction with occupational exposure was seen.

In summary, besides active cigarette smoking, a history of wheezing and some specific environmental exposures such as indoor kerosene heating and agricultural occupation accelerate the development of emphysema in male subjects over 50 years of age. Also, occupational inhalational exposures are independently associated with respiratory symptoms and airflow limitation. The weight of evidence also indicates that exposure to passive smoking is detrimental (34, 68, 133).

## NATURAL HISTORY

Of 200,000 children screened in Sweden, 127 had the PI\*ZZ phenotype and have been monitored prospectively since birth, both clinically and with liver and lung function measurements. During the first two decades of life, lung function remained normal in the Swedish cohort (139). Studies of the natural history of AAT deficiency have indicated that emphysema leading to early death usually begins in the third and fourth decades of life. In a study of life expectancy of 246 subjects by Larsson, the median age at death for smokers was estimated to be about 40 years and 65 years for never-smokers (6). A study of a referral population of 124 AAT-deficient patients by Brantly and coworkers showed a cumulative probability of survival to age 50 years of 52% and only a 16% chance of surviving to 60 years of age (63). However, both studies were based on patients selected from hospital records identified because of pulmonary symptoms and, to a certain degree, the estimate of life expectancy

was probably too pessimistic because of selection bias. Data from the Danish Registry (140), from which 347 patients were included, indicated that FEV<sub>1</sub> was the most important predictor of survival. Median survival for patients with FEV<sub>1</sub> less than 25% predicted was 6.3 years, which increased to 10.5 and 14.2 years for those with FEV<sub>1</sub> above 25 and 50% predicted, respectively.

Tobin and coworkers studied the clinical course and survival of 166 patients with AAT deficiency, of whom 40 were nonindex cases, that is, ascertained through family studies (141). A much lesser degree of pulmonary symptoms was found in the nonindex group than in the index group and, in the nonindex group, none died compared with 23 in the index group. The study suggests a highly variable clinical course of the disease that cannot be explained only by differences in smoking history. In studying pulmonary function in 22 index cases and 30 nonindex cases, Silverman and coworkers also found large variations in pulmonary function between the two groups, and some subjects in the nonindex group did not have any pulmonary symptoms at all (34). It was concluded that other familial factors might contribute to a severe clinical course.

To obtain further insight into the natural history of AAT deficiency with particular focus on the nonindex cases, the Danish AAT Deficiency Registry was initiated in 1978 (54). Patients with AAT deficiency are reported by all Danish physicians, a family record is obtained, and family members are PI typed. By December 1998, the registry contained 695 subjects with AAT deficiency PI type ZZ or Z-null, of whom more than 200 were identified by family studies.

With the data in this registry, it has been possible not only to repeat the analysis of life expectancy conducted by Larsson in 1978 (6), but also to analyze the life expectancy of a large number of nonindex patients who did not have pulmonary symptoms (54). The nonindex smoking patients had a median life expectancy of 49 years whereas the median life expectancy of nonsmoking patients was 69 years, not statistically significantly

different from that of the normal Danish population. Further analysis of the data with control for lifetime tobacco consumption showed that the difference in life expectancy between index cases and nonindex cases could not be explained by differences in smoking history only, and some smokers never develop severe emphysema (54).

Risk factors other than smoking could be genetic or environmental factors such as exposure to dust and fumes, frequent pulmonary infections, or asthma (34, 68, 142–144). The possibility that bronchial hyperresponsiveness may increase FEV<sub>1</sub> loss over time has been incompletely explored in AAT deficiency (137). The most obvious approach would be to study the clinical course and prognosis of never-smokers with AAT deficiency, but only a few such studies exist, and they have a limited number of patients and follow-up time.

In a Swedish study of 225 self-reported never-smoking PI\*ZZ individuals, most have normal lung function until 50 years of age, and only a few of them were identified because of respiratory symptoms. Above 50 years of age, there were great differences in lung function between individuals, and the mean values (expressed as a percentage of predicted normal) declined significantly with age. Men were at greater risk of lung function deterioration than women, and asthmatic symptoms and occupational exposure to airway irritants appeared to constitute additional risk factors (132). In a report in which changes in FEV<sub>1</sub> was analyzed in 211 never-smokers, in 354 ex-smokers, and in 46 current smokers with the PI\*ZZ phenotype, the adjusted mean annual change in FEV<sub>1</sub> in never-smokers was 47 ml/year, 41 ml/year in ex-smokers, and 70 ml/year in current smokers. In never-smokers, a greater rate of decline in FEV<sub>1</sub> was found after 50 years of age than before and no sex differences were found in the rate of FEV<sub>1</sub> decline (128).

A British study (145) found an overall FEV<sub>1</sub> decline of 55 ml/year with no effect of smoking cessation. In that study, a slower decline in patients with a low initial FEV<sub>1</sub> was also found; this finding was probably due to a survivor effect, that is, of patients with low initial FEV<sub>1</sub>, only those with a slow decline survived long enough to generate sufficient data for calculation of the FEV<sub>1</sub> decline. A joint American and Swedish study (146) estimated the FEV<sub>1</sub> decline to be 100 ml/year, and a study by Janus and coworkers (147) found a FEV<sub>1</sub> decline of 316 ml/year in smokers and 80 ml/year in never-smokers. The two latter studies did not evaluate the effect of smoking cessation.

It has been clear from certain studies that determinants of the deterioration in lung function in an individual may be related to factors other than cigarette smoking (32). Data from longitudinal studies of patients with COPD and normal levels of AAT indicate that bronchial hyperreactivity is a strong prognostic indicator for FEV<sub>1</sub> loss over time (137). The presence of concomitant bronchial asthma may therefore increase the likelihood for FEV<sub>1</sub> loss by increasing airway inflammation unopposed by the antiinflammatory properties of AAT. Several studies have reported the association between asthma and AAT deficiency (69). Although studies demonstrating the benefits of antiinflammatory therapy to slow FEV<sub>1</sub> decline in AAT deficiency patients are unavailable, we currently recommend that those with AAT deficiency and asthma should be treated aggressively with agents that reduce airway hyperreactivity and the potential for uncontrolled airway inflammation.

Saccular and cylindrical bronchiectasis has been associated with AAT deficiency (87), either with or without concomitant emphysema, and the condition seems more common in Hispanic patients (148).

#### Vasculitis and Other Organ Manifestations

As discussed in the LIVER AND OTHER DISEASES section, a variety of other conditions have been reported as associated with AAT

deficiency. These include systemic vasculitides such as anti-neutrophil cytoplasmic antibody-positive Wegener's granulomatosis and necrotizing panniculitis (149–152), peripheral neuropathy (153), and cerebral or peripheral artery aneurysms (154). The latter report has not been substantiated by larger studies (155). Some report amelioration of signs of vasculitis with  $\alpha_1$  antiprotease treatment (149, 156). It is notable that results from the NHLBI Registry of 1,129 patients failed to reveal an association of death with any condition other than lung and liver disease (137).

#### Necrotizing Panniculitis

A rare complication of PI\*ZZ is the development of necrotizing panniculitis (157, 158). This condition is an inflammatory response to an unknown stimulus with typical necrotic lesions in the subcutis and the dermis, which can be extensive.

#### Liver Disease

Only 2.5% of newborns diagnosed with PI\*ZZ die because of acute liver failure. Patients over 50 years of age can also develop hepatocellular carcinoma and liver cirrhosis (9). However, the most impressive finding in more recent studies (10, 11) is the predominant role of cirrhosis-related mortality, especially in elderly never-smokers. Cirrhosis and its complications were the main cause of death in 12 of 41 patients and occurred in 14 of 41 patients, but in only 2 of 23 smokers as compared with 12 of 17 never-smokers ( $p < 0.001$ ). Hepatocellular carcinoma occurred in five cirrhotic livers but was not seen in any noncirrhotic livers.

The prevalence of cirrhosis in AAT deficiency has been underestimated. The figure of 5% maintained in a World Health Organization report (56) now seems too low. The total lifetime risk of cirrhosis is more realistically in the range of 30–40% (9, 10).

Polymerization of AAT protein is thought to be involved in the pathogenesis of these liver diseases, but the exact mechanism of the pathogenesis is unknown.

#### RISKS OF THE MZ AND SZ PHENOTYPE FOR THE DEVELOPMENT OF EMPHYSEMA AND COPD

There has been some uncertainty as to whether individuals who are heterozygous for the MZ or MS phenotypes are more susceptible than those with MM phenotypes to develop pulmonary emphysema and COPD. After the first reports correlating PI\*ZZ, AAT deficiency, and emphysema, an attempt was made on many fronts to determine the natural history of patients with PI\*MZ phenotypes. Unfortunately, a properly powered population-based screening study to find PI\*MZ individuals properly matched for age, sex, occupation, and smoking with a control cohort, and monitored by serial testing of airway function and airway hyperresponsiveness, has not been done. Instead, a wealth of data has been accumulated from smaller case-control and population-based studies that address individual risk factors for the development of obstructive lung disease in the PI\*MZ individual (see Table 7).

#### MZ Prevalence in Patients with COPD

The first body of evidence suggesting that PI\*MZ deficiency carries a risk for chronic obstructive pulmonary disease was found when phenotypes were determined for patients with established respiratory disease, and PI\*MZ patients were found to be more prevalent than would be expected by the gene frequency in the population (159–168). A few studies have suggested that this relationship does not exist (169–172).

TABLE 7. RISK FACTORS FOR LUNG DISEASE IN PI\*MZ INDIVIDUALS

| Risk Factor              | Reference                       | Level of Evidence | Comment  |
|--------------------------|---------------------------------|-------------------|--|
| Family history of COPD   | APPENDIX 5                      | II-1              | Will never have a randomized controlled trial  |
| Smoking                  | APPENDIX 6                      | II-1              | Will never have a randomized controlled trial  |
| Occupational risk        | APPENDIX 7                      | II-2              | Further science to stratify risk by degree and type of inhalational exposure needed                              |
| Atopy                    | APPENDIX 8                      | II-3              | Remains controversial with conflicting studies   |
| Non-child-bearing status | Horne and coworkers, 1992 (300) | II-3              | Differences found in subtle spirometric tests but not in FEV <sub>1</sub> . Single study has not been reproduced |

For definition of abbreviation see Table 6.

### Familial Influences

Many of these initial studies were performed by identifying a PI\*MZ cohort by their relationship to symptomatic PI\*ZZ patients. When obstructive abnormalities were found in this patient population (173–176), these studies were criticized because the airway obstruction might represent genetic or environmental factors other than AAT deficiency. In fact, the clustering of COPD in families without AAT deficiency mandated the study of individuals from generalized populations rather than relatives of symptomatic patient populations (see APPENDIX 2).

The largest trial to date evaluating PI\*MZ patients, conducted by Seersholm and coworkers, demonstrated that 9% of Danish hospitalizations for COPD exacerbations ( $n = 17,061$ ) occurred in PI\*MZ individuals (177). Compared with PI\*MM patients, the PI\*MZ phenotype carried a relative risk of hospitalization for COPD of 2.2 (95% confidence interval, 1.5–3.0). Furthermore, this excess risk was concentrated in 40- to 79-year-old first-degree relatives of PI\*ZZ index cases, confirming the familial tendency to develop COPD in PI\*MZ heterozygotes. It is noteworthy that a high prevalence of the PI\*MZ phenotype was found in individuals with cor pulmonale. Further studies of familial clustering of COPD in PI\*MZ individuals are included in APPENDIX 5.

### Cigarette Smoking and COPD in PI\*MZ Patients

Smaller population-based studies have been performed to determine whether PI\*MZ individuals have an excess prevalence of COPD when matched for the presence of cigarette smoking. These studies have suggested similar FEV<sub>1</sub> values between PI\*MM and PI\*MZ patients (178–186), with a few exceptions (187–189).

However, subtle abnormalities of lung function have been seen in PI\*MZ patients. Lung recoil pressures, mean forced expiratory flow during the middle half of the FVC (FEF<sub>25–75%</sub>) (173, 174, 181, 190, 191), frequency dependence of total pulmonary resistance (192), frequency dependence of dynamic compliance (173), ventilation inhomogeneity (192), and arterial oxygen tension have been found to be different in PI\*MZ patients than in PI\*MM patients. Most authors have suggested that these minor abnormalities have no clinical importance.

Population-based autopsy studies have also been at variance. One postmortem study has shown an increased prevalence of emphysema in MZ patients, although there was no association of premorbid symptoms or premature death (193). Another showed no difference in emphysema prevalence compared with PI\*MM patients (194).

To reconcile these studies and further analyze the covariate influence of cigarette smoking on airway obstruction, Silverman and coworkers (195) constructed regression equations for FEV<sub>1</sub> and FEF<sub>25–75%</sub> versus cigarette pack-years for PI\*MZ relatives of PI\*ZZ cases to demonstrate that PI\*MZ patients do have an increased risk of airflow obstruction that is intermediate between that of patients with the PI\*MM and PI\*ZZ phenotypes. An-

other population-based longitudinal study by Eriksson and coworkers (196) monitored FEV<sub>1</sub> serially for 6 years in a cohort of PI\*MZ individuals. The FEV<sub>1</sub> decline among smokers, 75 ml/year, was greater than that among PI\*MZ nonsmokers, 40 ml/year ( $p < 0.05$ ).

Additional data from the NHLBI Lung Health Study indicate the risk of the MZ phenotype in the smoking population. Among the 5,887 male and female smokers recruited into the NHLBI Lung Health Study, 283 subjects with the fastest decline in FEV<sub>1</sub> ( $\Delta$ FEV<sub>1</sub> =  $-154 \pm 3$  ml/year) and 308 who had no decline ( $\Delta$ FEV<sub>1</sub> =  $+15 \pm 2$  ml/year) were genotyped for polymorphisms in the AAT protein, microsomal epoxide hydrolase, vitamin D-binding protein, and tumor necrosis factor genes. Rapid decline of FEV<sub>1</sub> was associated with the MZ genotype of the AAT gene (odds ratio [OR], 2.8;  $p = 0.03$ ). This association was stronger for a combination of a family history of COPD with MZ (OR, 9.7;  $p = 0.03$ ). These data suggest that the MZ genotype results in an increased rate of decline in lung function and interacts with other familial factors. The microsomal epoxide polymorphisms were, like PI\*MZ AAT, associated with a more rapid decline in lung function. In this study, the AAT S and 3' polymorphisms, vitamin D-binding protein isoforms, and tumor necrosis factor (TNF- $\alpha$  200304467oc G308A and TNF- $\alpha$ -A252G) polymorphisms were not associated with an accelerated rate of decline in lung function (197). Overall, many studies have solidified the understanding that cigarette smoking is a risk for COPD in PI\*MZ individuals (see APPENDIX 6).

### Environmental Risks for COPD in PI\*MZ Patients

Some PI\*MZ population-based cohorts have been shown to have more breathlessness (198) and wheezing than do PI\*MM patients, particularly if subjected to the stresses of environmental dust or smoking. Others have not shown aspects of these findings in large populations (178, 182, 198–201).

The influence of the work environment has been evaluated in cotton mill workers at risk for byssinosis and the PI\*MZ phenotype was found to be a risk factor for symptoms by multivariate analysis, in which endotoxin levels were also measured and controlled for (202, 203). Although other studies have found no association between PI\*MZ patients and byssinosis symptoms (204, 205), these studies did not control for the stronger risk factor of endotoxin exposure. Other dusty occupations associated with risk may include grain working (206) and mining (207). Current studies addressing environmental air quality as a risk factor for COPD in PI\*MZ individuals are listed in APPENDIX 7.

### Influence of PI\*MZ Phenotype on Atopic Disease

A less complete database has been assembled for atopic diseases (see APPENDIX 8). Although the PI\*MS heterozygote may have an increased risk of asthma (208, 209), PI\*MZ gene prevalence may (186) or may not (201, 210–212) be higher than in the general population of patients with asthma. Other studies have reported an increase in PI\*MZ prevalence in populations with



aspirin-sensitive asthma (213), nasal polyposis, and sinusitis (214, 215).

Other respiratory diseases that have been reported as occurring more frequently among PI\*MZ individuals include community-acquired pneumonia (216), rheumatoid interstitial lung disease (217), and Wegener's granulomatosis (10).

### Summary

The influence of the PI\*MZ phenotype on respiratory disease appears to be established with an increased risk of chronic obstructive pulmonary disease. From the available studies, the concept of a multifactorial genetic, smoking, and environmental interaction has been established for PI\*MZ patients. The usual PI\*MZ individual who smokes has mild spirometric abnormalities that manifest later in life. A more substantial risk for symptomatic COPD may occur during the stresses of environmental and occupational challenge in heavy cigarette smokers, particularly in relatives of patients with obstructive lung disease.

### The SZ Phenotype

Studies have indicated that smoking imposes a major risk for the development of pulmonary emphysema, but in the absence of smoking the risk of developing emphysema is negligible (218–220) (*see* Table 8 and APPENDIX 9). However, the effects of smoking are profound and produce reduction in pulmonary function, which is often as marked as in PI\*ZZ smokers. Although no studies have been done to assess the effects of occupational and environmental pollutants on individuals with the SZ phenotype, it is reasonable to conclude that they are as vulnerable as individuals with the PI\*ZZ phenotype.

### PROGNOSIS

Several studies have shown that FEV<sub>1</sub> is the most important predictor of survival of patients with emphysema due to AAT deficiency. In the Danish AAT Deficiency Registry, the 2-year survival was normal as long as the FEV<sub>1</sub> was above 35% predicted. For individuals with a FEV<sub>1</sub> below 35% predicted the 2-year mortality increased exponentially with decreasing FEV<sub>1</sub> (221). However, to date, the natural course of AAT deficiency is not fully clear because of the limited number of prospective studies. In smokers who cannot stop smoking, life expectancy is less than 20 years after the diagnosis of AAT deficiency is established. The decline in FEV<sub>1</sub> is most rapid when this value is between 30 and 65% of the predicted value (222). In follow-up studies of up to 19 years, the crude mortality rate was 41% (223). Among probands with impaired lung function, two studies could not show a significant difference in slopes of decline in FEV<sub>1</sub> between current smokers and ex-smokers, but ex-smokers had improved survival (223, 224). In a group of 282 PI\*ZZ patients, 2-year survival was calculated with mortality as a function of FEV<sub>1</sub>. In a simple exponential relationship, almost 100% survival was found until FEV<sub>1</sub> fell below one-third of predicted.

Two-year mortality of 50% occurred at an FEV<sub>1</sub> of 15% of predicted (224). Among nonindex patients who are never-smokers, a normal life expectancy was observed (135, 221).

### PREVENTION OF LUNG DISEASE

Preventing the development of emphysema is dependent solely on the success of techniques to curtail cigarette smoking and to eliminate environmental pollutants. Evidence from the Lung Health Study shows that the rate of FEV<sub>1</sub> decline is significantly less in those who quit successfully (225). Early cessation of smoking is particularly important in those with the homozygous phenotype. Unfortunately, young adults are least responsive to these messages. A variety of pharmacologic aids to quitting are now available and should be used by the smoker committed to stopping. Control of respiratory infections and bronchial hyperreactivity is theoretically advantageous in lessening neutrophil burden in the lungs and airways. Exposure to respiratory irritants such as second-hand tobacco smoke, dusts, and fumes should be minimized. A change of job may be desirable in those working in occupations where such exposure occurs frequently.

Preventive strategies such as influenza and pneumococcal vaccination are recommended. In view of the potential for liver disease, we recommend testing for hepatitis serology. With respect to hepatitis vaccination in AAT deficiency, where the subject has no overt disease or lung disease alone, we favor following the recommendations to the general population of the respective country. However, vaccination against hepatitis B is recommended for patients with AAT deficiency with overt liver disease. Because no cases have been reported among patients receiving augmentation therapy, the Task Force suggests that it is not mandatory to immunize against hepatitis B before the beginning of AAT augmentation therapy in those without liver disease.

### NONSPECIFIC MEDICAL TREATMENT

The guidelines for therapy of patients with COPD not related to deficiency of AAT have been well outlined in prior publications and are applicable to pulmonary disease associated with AAT deficiency (77, 78).

Most patients with AAT deficiency and obstructive lung disease find symptomatic benefit from bronchodilators even though objective bronchodilator responsiveness may be lacking. Many use these agents to lessen the dyspnea accompanying exertion, but overuse is common and leads to tremulousness and anxiety. Patients should be encouraged to remain active yet not reach a stage of exercise leading to hyperventilation and air trapping. Those with evidence of bronchial hyperreactivity may be given an inhaled steroid with the presumption that a decrease in bronchial inflammation may reduce the loss in FEV<sub>1</sub> over time. A study has suggested benefit of inhaled steroids in some patients

TABLE 8. SUMMARY OF RISK FACTORS FOR LUNG DISEASE IN THE PI\*SZ PHENOTYPE

| Risk Factor   | Level of Evidence Suggesting Risk | Comments   |
|---|-----------------------------------|--|
| Smoking   | II-2                              | Greater radiologic evidence of emphysema. Greater airflow obstruction in smokers significantly correlated to pack-years compared with PI*ZZ. Smaller proportion of PI*SZ smokers develop emphysema compared with PI*ZZ |
| PI*SZ itself and/or other environmental genetic factors | II-3                              | Radiologic emphysema and airflow obstruction in occasional, nonsmokers   |
| Serum AAT level   | II-3                              | More self-reported cough and wheeze with a serum level of > 11 μM. Overall, serum levels do not correlate with lung function   |

with AAT deficiency-related lung disease, although it is not clear which patients benefit (226).

Antibiotics should be used in patients with evidence of bronchitis or upper respiratory infection. Although no studies have adequately explored the impact of neutrophilic inflammation from infections on lung function, an aggressive approach appears justified. Macrolides in particular may reduce neutrophil inflammation (227). However, development of bacterial resistance to macrolides requires the use of  $\beta$ -lactams or quinolones. Those with bronchiectasis require more prolonged antibiotic treatment.

Oxygen should be used in patients with desaturation during exercise. Supplemental oxygen increases exercise capacity in those patients who desaturate but has not been shown to have a significant effect on quality of life or conditioning over and above pulmonary rehabilitation itself (228, 229). If severe hypoxemia is present, long-term oxygen should be started according to the criteria of the American Thoracic Society and the European Respiratory Society (76, 77).

Oral corticosteroids are useful in those with a clear asthmatic component to their disease, but should be used with caution over the long term because of their effects on bone loss (230). Loss of spine height contributes to loss of lung volume and disability from spinal pain.

Depression occurs frequently in patients with chronic lung disease and those with AAT deficiency are no exception. Early signs of depression such as loss of appetite should be recognized and treated aggressively. Tricyclic antidepressants may be poorly tolerated in those with chronic sputum production, but may be useful to induce sleep in some patients. The newer selective serotonin reuptake inhibitors are effective.

Panic is also a common disorder in patients with emphysema (231, 232) and may be managed pharmacologically with short-acting benzodiazepines. However, side effects in some patients may limit their usefulness. Buspirone, the 5-hydroxytryptamine receptor partial agonist, is particularly effective if used in a high enough dosage. More recently, selective serotonin reuptake inhibitors have been recognized as being useful in anxiety disorders (233). Some patients find nonpharmacologic relaxation techniques such as yoga helpful.

Pulmonary rehabilitation combines a multimodality therapeutic regimen involving the development of cardiovascular fitness, self-confidence, and stress control (234). Most authorities agree that rehabilitation improves endurance, reduces dyspnea, and reduces the number of hospitalizations (234). Many of the published regimens appear to work and the exact makeup of the program appears less important than a structured setting, a motivated therapist, and exercise performance. However, the training effect diminishes with time once the therapy is completed. Because AAT-deficient patients are usually younger and suffer from fewer comorbid conditions than most with COPD, higher exercise work rates are well tolerated. As most patients are still employed, many can afford to purchase home exercise equipment and monitor oxygen saturation with portable pulse oximeters.

Weight loss and malnutrition are common problems in emphysema (235) and are thought to be due to increased metabolism from the increased work of breathing (236). As a practical approach, however, intensive nutritional support has largely been unsuccessful in restoring ideal body weight, although smaller, more frequent, meals may reduce dyspnea by reducing abdominal bloating.

## AUGMENTATION THERAPY

The major focus of therapy for patients with emphysema due to severe AAT deficiency has been on correcting the deficiency

state. If deficiency could be abolished, further lung destruction might be prevented and the disease stabilized. Potential treatment options for AAT deficiency include (1) intravenous, human plasma-derived augmentation therapy, (2) augmentation therapy by inhalation, (3) recombinant AAT augmentation therapy, and (4) synthetic elastase inhibition (*see* Table 9 and APPENDIX 10) (237).

### Intravenous Human Plasma-derived Augmentation Therapy

Intravenous administration of purified human AAT concentrate was shown to increase lung levels of AAT in AAT-deficient individuals in the early 1980s (238, 239). Antineutrophil elastase capacity in the lung epithelial lining fluid, obtained by bronchoalveolar lavage increased to 60–70% of normal in homozygous AAT-deficient individuals who received human plasma-derived AAT once weekly at a dose of 60 mg/kg body weight. On the basis of these studies, a purified preparation of AAT concentrate derived from fractionated plasma (Prolastin) was manufactured and shown to be biologically effective (240, 242). Other preparations of pooled human plasma antiprotease are also available (241), and recombinant technology-based drugs are under development.

Results of these studies formed the basis for U.S. Food and Drug Administration approval in the United States in 1988, followed thereafter by approval by regulatory agencies in Canada, Germany, Spain, and Italy. To date, only a single randomized placebo-controlled trial has been done to determine whether augmentation therapy attenuates the development of emphysema (112). Such trials are difficult and expensive to mount because of the large number of patients and prolonged time needed to adequately power such a study. Recommendations regarding the use of augmentation therapy have been issued by the American Thoracic Society earlier (243) and by the Canadian Thoracic Society (244, 245).

Two reports have addressed the issue of clinical efficacy of augmentation therapy in concurrently controlled observational studies, a German–Danish study (246, 247) and the NHLBI Registry in the United States (137). The aim of the former study was to compare the decline in FEV<sub>1</sub> between Danish patients who had never received augmentation therapy and German patients treated with weekly infusions of AAT. The yearly decline in FEV<sub>1</sub> in the treated group (–53 ml) was significantly lower than in the untreated group (–75 ml) ( $p = 0.02$ ). Notably, the two groups differed with respect to sex and initial FEV<sub>1</sub>. In comparing the different degrees of functional impairment, a significant effect of the treatment was demonstrated only in the group of patients with an initial FEV<sub>1</sub> of 31–65% predicted. The authors concluded from this nonrandomized study that weekly infusion of human AAT in patients with moderately reduced lung function may slow the annual decline in FEV<sub>1</sub>.

In the NHLBI Registry, 1,129 subjects with severe deficiency of AAT (serum levels less than 11  $\mu$ M) were registered. They were monitored for 3.5 to 7 years. The 5-year mortality rate was 19%. In a multivariate analysis, the mortality rate was lower in those receiving augmentation therapy as compared with those not receiving therapy (OR, 0.79;  $p = 0.02$ ). The mean FEV<sub>1</sub> decline was 54 ml/year and there was no overall difference between those receiving augmentation therapy and nonrecipients. However, among those in the subgroup with moderate emphysema (i.e., American Thoracic Society Stage II emphysema with FEV<sub>1</sub> 35–49% predicted), the rate of FEV<sub>1</sub> decline was significantly slower in subjects receiving augmentation therapy ( $p = 0.03$ ).

These two observational studies suggest that progression of emphysema may be slowed in patients with moderate emphysema (FEV<sub>1</sub> 31–65% predicted). Moreover, mortality may be decreased in patients with a lower FEV<sub>1</sub>.

**TABLE 9. SUMMARY EVIDENCE TABLE: AUGMENTATION THERAPY FOR ALPHA-1 ANTITRYPSIN DEFICIENCY: INDICATION AND PERFORMANCE**

| Procedure             | Value   | Level of Evidence | Comments   |
|-----------------------|---|-------------------|--|
| Laboratory testing    | Alpha-1 antitrypsin serum level < 11.0 $\mu$ M                      | II-2              | Indication for treatment is independent of the phenotype and based on level and presence of obstructive lung disease   |
| Lung function testing | FEV <sub>1</sub> (postbronchodilation) between 30 and 65% predicted | II-2              | Subjects with normal or nearly normal pulmonary function can be treated, if they experience a rapid decline in lung function ( $\Delta$ FEV <sub>1</sub> > 120 ml/yr). Patients with very poor lung function, already treated, should be kept on treatment |
| Dosing and frequency  |   | II-3              | Serum level should exceed the 35% predicted threshold, that is, be above 15 $\mu$ M on Day 7 immediately before the next infusion. If the fourfold dosage of Prolastin is given monthly, the patient is unprotected for several days                       |

To extend the assessment of augmentation therapy efficacy, a small randomized clinical trial including 26 Danish and 32 Dutch patients has been performed (112). Active treatment involved monthly infusion of 250 mg of AAT per kilogram; placebo was albumin. The 2-year study was too small to show any difference in the slope of decline of lung function, but loss of lung density by CT showed a trend in favor of the actively treated group (50% reduction in decline,  $p = 0.07$ ). This study portends the value of lung density measurements by CT as an end point for efficacy.

Adverse reactions to AAT concentrate when given intravenously have been rare. Between February 1989 and December 1995, about 58,000 infusions were administered to 443 patients in one series (247). One hundred and twenty-four mild adverse reactions (fever, chills, dyspnea) were reported in 65 patients. Three patients terminated treatment with AAT concentrate because of repeated chills and fever immediately after infusion. In four patients, an anaphylactic reaction occurred, but in all cases complete recovery was obtained. An IgE-mediated anaphylactic reaction following the third intravenous infusion has been published (248). Because no viral transmission has been observed, this group does not consider immunization for hepatitis B to be essential before beginning therapy.

### Aerosol Augmentation Therapy

Aerosol application of AAT in patients with AAT deficiency increases AAT concentration and antielastase activity in the lower respiratory tract in a dose-dependent fashion (249). Deposition of radioactively labeled AAT showed more peripheral deposition in patients with mild emphysema compared with central deposition in those with advanced emphysema (250). No bronchospasm has been reported. Preliminary data suggest that once or twice daily administration of aerosolized AAT may produce sustained antielastase protection of the lungs.

### Recombinant AAT Augmentation Therapy

A number of recombinant forms of AAT have been developed as well as recombinant secretory leukoprotease inhibitor (251). Human AAT genes have been transferred into sheep embryos, resulting in the secretion of mannose-glycosylated AAT into the milk of these animals (252).

### Synthetic Inhibitors

Currently several synthetic, low molecular weight elastase inhibitors are being evaluated, but their clinical efficacy and safety have not been reported.

### Summary

In the context that no randomized controlled trial has definitively demonstrated the clinical efficacy of augmentation therapy, the weight of available studies of the clinical efficacy of AAT aug-

mentation therapy indicates a lowered overall mortality and a slower rate of FEV<sub>1</sub> decline in augmentation therapy recipients with FEV<sub>1</sub> values of 35–65% of predicted. Use of high-resolution CT scans to measure lung tissue density shows great promise for providing a practical, quantitative way to assess the efficacy of augmentation therapy in future studies.

### SURGICAL PROCEDURES

Lung transplantation (LT) has become an option for many patients with end-stage lung disease. Approximately 12% of all LTs are performed for emphysema secondary to AAT deficiency (253). Because of the lack of donor organs, most LTs are performed as a single LT, although a double lung transplant offers a better functional outcome.

The actuarial 5-year survival rate following LT is about 50% (254) and significant differences have been observed in actuarial survival at 1, 2, and 3 years posttransplantation between single versus double lung transplant recipients. Functional results have been good (254), but bronchiolitis obliterans remains the major cause of death after LT.

Posttransplantation augmentation therapy with AAT concentrate has generally not been recommended. One study has determined the proteinase-antiproteinase balance by bronchoalveolar lavage after lung and heart-lung transplantation in AAT deficiency (255). During periods of clinical stability, the AAT-deficient recipient did not have detectable free elastase activity in the bronchoalveolar lavage fluid. During periods of respiratory illness, some AAT-deficient recipients had measurable free elastase activity. Thus, AAT augmentation may be considered during episodes of respiratory tract inflammation and possibly during chronic rejection because of the presence of chronic inflammation in the respiratory tract of AAT-deficient lung transplant recipients (256).

Lung volume reduction surgery (LVRS) entails the resection of 20 to 30% of the most severely involved areas of emphysema with poor perfusion ("target areas"). Target areas can be preoperatively demarcated by CT or perfusion lung scanning and intraoperatively by "air trapping" (257). Patients with far advanced emphysema and incapacitating dyspnea despite optimal medical and rehabilitative treatment are considered candidates for the procedures. When properly selected, LVRS improves exercise capacity and relieves dyspnea in patients with usual emphysema. It is less clear, however, whether LVRS similarly improves lung function in patients with emphysema due to AAT deficiency.

In one prospective study, the intermediate-term functional outcome was studied in 12 consecutive patients with advanced AAT deficiency emphysema and in 18 patients with "smoker's emphysema." All underwent bilateral LVRS. Before surgery, there were no statistically significant differences between the two groups in the 6-minute walking distance, dyspnea score,

respiratory mechanics, or lung function data, except for the FEV<sub>1</sub>, which was lower in the AAT deficiency group (24 versus 31% predicted,  $p < 0.05$ ). In both groups, bilateral LVRS produced significant improvements in dyspnea, 6-minute walking distance, lung function, and respiratory mechanics. In the AAT-deficient group, however, the functional measurements (except the 6-minute walk test) returned to baseline at 6 to 12 months postoperatively and showed even further deterioration at 24 months (258).

The functional status of the usual emphysema group remained significantly improved over this period. The Task Force concludes that LVRS offers only short-term benefits for most patients with AAT deficiency emphysema and, pending additional studies that demonstrate the efficacy of LVRS in AAT-deficient individuals that permit better patient selection, does not currently recommend this procedure for this subgroup (258–264).

### SPECIAL SITUATIONS

Published information suggests that the AAT deficient patient does not differ from the COPD patient of similar severity in most respects. For instance, there is no evidence that pneumothorax risk is different between the two populations. Nevertheless, the persuasiveness of the biochemical constructs that define this disease suggests that any excess neutrophil burden should be avoided. Whether pulmonary function is more likely to decline after bronchitis, pneumonia, or rare episodes of acute respiratory distress syndrome remains unknown.

Evidence suggests that pregnancy remains problematic for some patients with PI\*ZZ AAT deficiency (265). Case series have noted an increased frequency of miscarriage and stillbirth that totaled 29% of 38 pregnancies in 8 patients (266). Case reports of pneumothorax during pregnancy have occurred in patients with preexisting bullae (267). Nevertheless, patients with severe emphysema have had successful term pregnancies (266).

Airline travel for patients with emphysema should prompt a specific preflight assessment. In patients without hypoxemia at sea level, the impact of cabin pressure during air travel on arterial oxygen levels can be estimated. Arterial blood gas results at sea level can be used in regression equations to predict the oxygen tension at cabin pressure (268). If predicted oxygen tension is in the hypoxic range (i.e., less than 55 mm Hg), 1 to 2 L of oxygen by nasal cannula during the flight is recommended to prevent hypoxemia-induced pulmonary hypertension (269). Patients who are already known to have hypoxemia at sea level and who receive oxygen are advised to increase their flow rate by 1 or 2 L/min. Efforts should be made to prevent arterial oxygen tension falling below 55 mm Hg (7.0 kPa).

From the surgical experience for lung transplantation and lung volume reduction, it is clear that anesthesia can be tolerated in patients with an FEV<sub>1</sub> less than 1.0 L. During anesthesia for upper abdominal surgery and in the immediate postoperative recovery period, it is important to ventilate with a prolonged expiration time. Postoperative mucous clearance is important. Indications for postoperative mechanical ventilation are respiratory acidosis, severe hypoxemia, atelectasis, and pneumonia (270). Urologic, gynecologic, and colorectal procedures should be performed under local or epidural anesthesia whenever possible.

### FUTURE DIRECTIONS OF RESEARCH IN AAT DEFICIENCY

Many avenues of research must be more fully developed to achieve effective therapies for AAT deficiency and its associated

diseases. With respect to the inherited deficiency, correction of the genetic abnormality could be curative. Gene therapy necessitates effective and efficient methods to transfer enough genetic material to target cells. Thus far, gene transfer strategies have utilized retroviruses, adenoviruses, and nonviral vectors to the target cells: lymphocytes, fibroblasts, hepatocytes, and respiratory epithelial cells.

Retroviruses are RNA viruses that gain entrance into the cell through specific receptors. Reverse transcriptase carried by the virus converts RNA to DNA and the double-stranded DNA virus inserts into the cell genome, using information carried in the 5' and 3' long terminal repeats. As a vehicle for gene therapy, the retrovirus is modified so that it cannot produce infectious virus after entering the cell (271). This technique has been used to produce a clonal population of mouse fibroblasts capable of secreting normal human AAT protein (272). This study demonstrated the feasibility of producing human AAT protein in cells other than hepatocytes, but the amounts were small and implantation of fibroblasts into tissue sites could lead to local fibrosis.

Other studies have utilized hepatocytes that have been isolated from resected liver lobes. In animal studies, 10–15% of hepatocytes have been infected and human AAT protein has been maintained for more than 6 months (273). This technique would require hepatectomy and reinfusion of modified hepatocytes. The use of allogeneic hepatocyte transplantation would have the disadvantage of immunologic rejection and the need for immunosuppression.

The direct infusion of recombinant retroviruses containing AAT cDNA into the portal vein is another approach, which has produced AAT protein beyond 6 months, but in subtherapeutic amounts (273).

T lymphocytes have been directly transplanted into the lung, producing local but subtherapeutic amounts of AAT (274). Retrovirus-based vectors have also been used to target lung epithelial cells but inefficient transfection has been noted, because retroviruses require replicating cells and epithelial cells replicate slowly.

Adenoviruses are double-stranded DNA viruses that are tropic for respiratory epithelium (275). Unlike the retrovirus, adenoviral DNA functions in an extrachromosomal manner, which removes the theoretical possibility of mutagenesis occurring after insertion. However, it should be noted that adenovirus-mediated gene therapy would then have to be given periodically as the genetic modification of the target cells is not transmitted to its progeny.

Also, the adenovirus does not necessitate host cell replication for gene transfer and expression. In one study, adenoviral vectors were transmitted directly to respiratory epithelium in cotton rats, both *in vitro* and *in vivo*. Human AAT was detected in respiratory epithelium after *in vivo* tracheal administration and levels were measurable in the epithelial lining fluid for 1 week (276). Other attempts at adenovirus-mediated gene therapy have targeted liver and peritoneum (277, 278) and these transfers have approached therapeutic levels of AAT (279).

Conceivably, the alveolar epithelium of the human lung could be targeted for transfer of AAT producing cDNA, but this might not be protective against degradation of matrix components beneath the epithelial layer.

Song and coworkers (280) have transduced DNA for human AAT into murine muscles, using a cytomegalovirus virus vector. Results were promising in that sustained concentrations of human AAT at levels of over 800  $\mu\text{g/ml}$  could be achieved for over 15 weeks.

The use of non-virus-mediated gene therapy systems for AAT deficiency, utilizing liposomes or molecular conjugates, is theoretically possible. A plasmid containing the AAT cDNA and a

cytomegalovirus promoter complexed to cationic liposomes has been given intravenously and by aerosol to rabbits (281). AAT protein was detectable by immunohistochemical staining in the pulmonary endothelium after intravenous administration and in the alveolar epithelial cells after aerosol administration. It is questionable whether aerosol administration of such liposome systems would prove protective against degradative processes in the lung parenchyma.

Molecular conjugates as another nonviral transfer system for transferring AAT cDNA have utilized a plasmid DNA complexed to polylysine and a molecule that targets the DNA complex to a specific cellular receptor. At present, however, these systems seem less efficient at transfer than viral vectors and would require further development (282). Kren and coworkers (283) have used chimeric molecules to effectively alter single nucleotides in episomal and genomic DNA in cell culture as a strategy for gene repair of hepatic genetic diseases such as AAT deficiency.

Thus far, experimental studies *in vitro* and *in vivo* have demonstrated that AAT cDNA can be transmitted to various cell types in the lung. Taking this strategy to human studies will require further evaluation of gene transfer methods in relation to (1) the invasiveness and risks of gene therapy as compared with existing intravenous AAT augmentation or possible aerosol AAT augmentation techniques, (2) how efficacy of gene transfer therapy can be established, and (3) the practicality and necessity of using gene transfer as a therapy for AAT deficiency, which may depend on the future availability and effectiveness of less invasive modes of therapy.

Two avenues of research deserve further exploration as potential therapies for emphysema in AAT deficiency and COPD in general. Hyaluronan aerosol has been shown to limit the development of experimental emphysema induced by intratracheal elastases (284) and has been shown to protect lung elastin from elastase degradation *in vitro* (285), thus offering the prospect of preventing progression of emphysema once initiated in the human lung.

Also, use of all-*trans*-retinoic acid in rats with elastase-induced emphysema has been shown to increase numbers of alveoli (286) and in the adult tight-skinned mouse to partially rescue failed alveolar septation induced by glucocorticoids (287).

With the recognition that loop-sheet polymerization occurs in the AAT protein of the Z phenotype as a result of lysine substitution for glutamic acid at position 342, new insights have been achieved concerning abnormal folding of the protein in hepatocytes (32). This recognition has encouraged the study of potential therapeutic agents that may counteract the abnormal folding and polymerization of the molecule, which could aid secretion of the molecule from hepatocytes and prevention of AAT globules in hepatocytes, which are implicated in the development of hepatic cirrhosis.

Because of the wide range of biological effects of neutrophil elastase, future therapy for patients with severe AAT deficiency may well require a safe and effective synthetic neutrophil elastase inhibitor beyond naturally occurring AAT. Neutrophil elastase has a wide range of biological effects that can be pathogenic beyond elastolysis. Such reactions include activation of complement, cleaving and complexing with AAT, and stimulation of epithelial cells to produce and secrete interleukin-8 (288) and macrophages to release leukotriene B<sub>4</sub>. Also, elastase may reduce the secretion of secretory leukoprotease inhibitor by airway cells (289). Such effects could perpetuate inflammation in airways by increased amounts of neutrophil elastase unopposed by a natural inhibitor. Cleavage of immunoglobulins by elastase could result in reduced ability of globulin proteins to bind bacteria and thereby reduce effective opsonophagocytosis of bacteria

(290). Neutrophil elastase may reduce ciliary beat frequency and increase mucous secretion, which would reduce mucociliary clearance. In bronchiectasis, with and without cystic fibrosis, elastase is often detectable in bronchial secretions on a continuing basis (291). An antiprotease could therefore be useful in such conditions.

A natural neutrophil elastase inhibitor or synthetic agent could be useful as a pulse therapy for acute exacerbations, or even more chronically if safety of such agents can be established.

Synthetic protease inhibitors, however, could have detrimental effects, because neutrophil elastase may have an important role in certain cellular defense mechanisms. Neutrophils may require neutrophil elastase to penetrate tissue during migration (292). Protease inhibitors might impair chemotactic responses, which depend on protease activity (293). Protease inhibitors that can enter cells could alter neutrophil differentiation to produce cells without neutrophil elastase activity. For these reasons, protease inhibitors may be best administered to local areas and for short intervals.

Recognizing that the homozygous Z allele leads to a misfolding of the AAT molecule and polymerization, which prevents normal secretion of AAT from the hepatocyte, Burrows and coworkers (294) have performed studies attempting to correct the misfolding. They showed that several "chemical chaperones" that can reverse this misfolding and mislocalization of the protein mediate an increase in secretion of AAT from the hepatocyte. Specifically, 4-phenylbutyric acid was particularly effective in causing a significant increase in Z phenotype AAT in a cell culture system. Carrell and Lomas (295) have indicated the breadth of the problem of conformational abnormalities leading to disease. Correction of this conformational abnormality is a fertile area of research to increase deficient levels of AAT.

Another area for future development in the care of patients with AAT deficiency is early detection of the disease to interdict smoking or exposure to toxic atmospheres. In this regard, efforts have been made with programs of targeted screening of adults (20) and, in some areas, neonatal screening programs (20, 296). Thus far, the broad use of neonatal screening programs has not been widely accepted. However, expanded efforts are worthwhile to increase awareness of primary care and subspecialist physicians to screen for AAT deficiency as a disease to be detected early.

Much more needs to be learned concerning the mechanisms leading to pulmonary emphysema in individuals with severe AAT deficiency. Because a variable proportion of individuals with the PI\*ZZ phenotype develop emphysema if they are non-smokers, we need to understand what the risk-minimizing factors are for the development of pulmonary emphysema. This requires a deeper understanding of the role of neutrophil and macrophage proteases and the possible protective role of inhibitors other than the AAT in such patients.

Similarly, we need a deeper understanding of the factors that predispose to severe liver dysfunction in some patients with the PI\*ZZ phenotype.

#### SOME SPECIFIC RESEARCH NEEDS IN AAT DEFICIENCY

1. A more detailed description of the pathology of the lung in AAT deficiency emphysema, including the parenchyma and bronchi, with particular attention to the inflammatory state of bronchi, bronchioles, and the blood vessels, and the influence of bronchial disease in disease progression
2. More definitive evaluation of the frequency and type of bronchiectasis occurring in association with AAT deficiency, along with clinical and physiological manifestations
3. Identification of risk factors other than cigarette smoking

- for the development of lung disease in AAT deficiency. These factors may include infection, atopy, familial factors, as well as environmental pollutants
4. Implementation of a placebo-controlled clinical trial of intravenous augmentation therapy. Such a trial should include the measurement of elastin degradation peptides in blood or urine, along with HRCT to evaluate efficacy. Part of this trial could include determination of optimal therapeutic regimens in terms of dose and frequency of administration of AAT
  5. Determination of the specific role of AAT augmentation after lung transplantation
  6. Evaluation of the potential therapeutic efficacy of aerosol AAT preparations
  7. Investigation of the basic mechanisms of liver disease in AAT deficiency, with an evaluation of the role of antioxidant therapy to prevent liver disease. In the evaluation of liver disease, the role of viral hepatitis infections as a cause of cirrhosis and hepatocellular carcinoma should be determined. Also, the efficacy and advisability of vaccination against hepatitis B and, possibly, when a vaccine becomes available, against hepatitis C
  8. Epidemiologic studies to determine the gene frequency of AAT deficiency alleles in various races and cultures, including the developing world. Such studies would provide guidance in the costs and benefits of population screening as a prelude to neonatal screening programs for AAT deficiency

## APPENDICES

## APPENDIX 1. PRIMARY EVIDENCE TABLE: SUMMARY OF STUDIES ADDRESSING CLINICAL FEATURES OF PI\*ZZ ALPHA-1 ANTITRYPSIN DEFICIENCY

| First Author, Year (Ref.) | Number of Subjects | Study Design  | Types of Symptoms  | Age at Symptom Onset                                  | Radiographic Features (Chest Film)  | Baseline Lung Function (FEV <sub>1</sub> , % predicted)        | Rate of Decline of Lung Function (FEV <sub>1</sub> )                                  | Mortality Experience  |
|---------------------------|--------------------|---------------|--|---|---|--|---|---|
| Eriksson, 1965 (59)       | 33                 | Retrospective | Dyspnea (60%); severe cough and phlegm (51%); peptic ulcer (30%) | 60% of patients younger than 40 yr                    | Emphysema more marked in lower zones; small cystic bronchiectasis in two patients | Less than 50% in 46% of patients                               | Not done  | Not reported  |
| Rawlings, 1976 (62)       | 20                 | SCS           | Dyspnea (95%); cough (55%); sputum (50%); wheezing (80%)         | Not done  | Not done  | FEV <sub>1</sub> /FVC, 43.8%                                   | Not done  | Not done  |
| Larsson, 1978 (6)         | 246                | SCS           | Dyspnea (44%); sputum (16%)                                      | Median age at onset of dyspnea: 53 yr (NS), 40 yr (S) | Not done  | Not done   | Not done  | Smokers: At age 50 yr, 30% CPS; at age 60 yr, 15% CPS. Nonsmokers: At age 50 yr, 90% CPS; at age 60 yr, 60% CPS   |
| Janus, 1985 (61)          | 69                 | L             | Dyspnea  | 32 ± 2 yr (CS); 51 ± 3 yr (NS) (mean ± SEM)           | —   | NS, 77.2 ± 9.6 (n = 13); CS, 37.5 ± 7.7 (n = 22) (mean ± SEM)  | NS, 79.6 ± 38.2 ml/yr (n = 7); CS, 316.8 ± 80 ml/yr (n = 6)                           | Not done  |
| Brantly, 1988 (63)        | 120                | SCS           | Dyspnea  | 25 to 40 yr   | Bullae, 49%; basilar localization, 72%  | 34 ± 22  | 51 ± 82 ml/yr   | CPS at age 50 yr, 52%; at age 60 yr, 16%  |
| Wu, 1988 (222)            | 158                | Retrospective | Not done   | —   | —   | NS, 60.2 ± 32.4; CS, 49.4 ± 26.1 (mean ± SD)                   | NS, 60 ± 100 ml/yr (n = 18); CS, 60 ± 170 ml/yr (n = 40)                              | 5-yr mortality rate: 59% (FEV <sub>1</sub> < 30%pred), 19% (FEV <sub>1</sub> 30–65%pred), 11% (FEV <sub>1</sub> > 65%pred)  |
| Seersholm, 1995 (128)     | 161                | L             | Not done   | —   | —   | Not reported   | NS, 86 ± 107 ml/yr (n = 18); CS, 132 ± 105 ml/yr (n = 43); ES, 58 ± 80 ml/yr (n = 90) | Not done  |
| Piitulainen, 1997 (132)   | 225 (all NS)       | SCS           | Dyspnea; wheezing  | Breathlessness, 52 yr; wheeziness, 45 yr              | —   | NS, 84 ± 28 (n = 225)  | Not done  | Not done  |
| Seersholm, 1998 (136)     | 75 (all NS)        | L             | Dyspnea; cough; phlegm   | Not done  | —   | Index case, 54 ± 25 (n = 27); nonindex case, 100 ± 21 (n = 40) | Not done  | Index cases: 12 died of emphysema (total deaths, n = 15). SMR: 8.8 (95% CI, 5.0 to 14). Nonindex cases: 1 died of emphysema (total deaths, n = 5). SMR: 0.96 (95% CI, 0.3 to 2.3) |

Definition of abbreviations: CPS = cumulative probability of survival; CS = current smokers; ES = ex-smokers; L = longitudinal; NS = never-smokers; PB = population based; RCT = randomized controlled trial; SCS = serial cross-sectional; SMR = standardized mortality ratio.

Studies were eligible for inclusion if they satisfied the following design features: representative cohorts of patients well defined by phenotype, pulmonary function, and radiography.

**APPENDIX 2. GENERAL POPULATION-BASED STUDIES: PREVALENCE OF PI VARIANTS AND RISK OF ASSOCIATED LUNG DISEASE**

| First Author, Year (Ref.) | Level                       | Population   | Control Subjects                                     | PI*ZZ  | PI*SZ                                    | PI*MZ                                   | Other                  | Risk Factors Addressed   |
|---------------------------|-----------------------------|--|--|--|--|---|------------------------|--|
| Eriksson, 1965 (59)       | I-2                         | 6,995; cross-section of 70% of community                   | 0  | 4  | —  | —                                       | —                      | All PI*ZZ nonsmokers, yet two had emphysema and one had chronic bronchitis; indicates marked risk for COPD. The oldest, a 69-yr-old man, was healthy, indicating risk not 100%   |
| Morse, 1977 (180)         | I-2 for PI*Z, I-1 for PI*MZ | 2,944; cross-section of 3,685 non-Mexicans                 | 2,637 PI*MM  | 2  | 6  | 88                                      | 208 PI*MS              | No lung disease in PI*ZZ and PI*SZ because of low mean age of 27 yr, but no PFT data reported. MZ and MS versus MM: no significant increase in COPD symptoms even for smokers > 40 yr  |
| Buist, 1980 (301)         | I-1                         | 107,000 neonates; longitudinal to age 5 yr (range, 3–7 yr) | 22 PI*MM   | 19   | 3  | —                                       | —                      | No FRC or V <sub>max</sub> difference in age, sex, height, weight-matched control subjects   |
| Wall, 1990 (65)           | I-1                         | 107,000; longitudinal to age 15.1 yr (range, 12–18 yr)     | 130 for questionnaire but not PFT                    | Known: 25<br>Studied: 18                             | 4<br>4                                   | —<br>—                                  | —<br>—                 | Normal PFT, but two PI*SZ sibs with asthma with normal PFT post-BD. Fewer smokers than among control subjects (p = 0.02)   |
| Sveger, 1979 (302)        | I-2                         | 11,128; cross-section 18-yr-old military inductees         | Total: 22<br>Smokers: 5<br>Bronchitis: 6             | Total: 5<br>Smokers: 3<br>Bronchitis: 2              | Total: 10<br>Smokers: 5<br>Bronchitis: 2 | Total: 3<br>Smokers: 3<br>Bronchitis: 0 | 2: 1 PI*M–,<br>1 PI*FM | No statistical analysis as n too small   |
| Sveger, 1984 (303)        | I-2                         | 200,000 neonates; longitudinal to age 8 yr                 | 0  | 117  | 49                                       | —                                       | 3: 2 PI*ZZ, 1 PI*SS    | 13 (8%) with asthma, with only 2.7% reported in 8-yr-old Swedes but not considered comparable population   |
| Sveger, 1994 (139)        | I-1                         | 200,000 neonates; longitudinal to age 16 yr                | Total: 50<br>Asthma: 2<br>Smokers: ?                 | Total: 103<br>Asthma: 11<br>Smokers: 3               | Total: 45<br>Asthma: 3<br>Smokers: 1     | —<br>—<br>0                             | 1 PI*ZZ<br>1 PI*SS     | Asthma: Difference not significant (p = 0.33)<br>Fewer smokers: significance less  |
| Browne, 1996 (304)        | I-2                         | 27 million deaths (1970–1991)                              | All COPD deaths                                      | 1,930 AAT deficiency; Dx assumed to be PI*ZZ         | —  | —                                       | Not phenotyped         | Mortality rate increased from 0.43/million in 1979 to 0.80/million in 1991. Expected: 0.54 to 1.34/million, indicating AAT deficiency underdiagnosed yet AAT deficiency in 2.7% of COPD deaths among those aged 35 to 44 yr, but in only 0.1% of all COPD deaths. AAT deficiency in 1.2% of all childhood liver deaths |
| Sveger, 1997 (305)        | I-1                         | 200,000 neonates; longitudinal to age 18 yr                | Total: 61<br>Age/sex matched: 41<br>Lung symptoms: 1 | Total: 61<br>Age/sex matched: 41<br>Lung symptoms: 7 | —  | —                                       | —                      | Significant difference in number with lung symptoms: 7 versus 1 (p < 0.05). No significant difference for other, no lung symptoms  |
| Pitulainen, 1998 (68)     | I-2                         | 200,000; longitudinal to age 18 yr                         | 0  | 88   | 40                                       | —                                       | —                      | FEV <sub>1</sub> lower in 13 smokers than never-smokers (p < 0.05), but no non-AAT deficiency control subjects. Smokers versus nonsmokers: FEV <sub>1</sub> lower (p < 0.05), more phlegm (p < 0.05), and FEV <sub>1</sub> lower if parents smoke (p < 0.05)   |
| Eriksson, 1999 (11)       | I-1                         | 96,600 autopsies (1962 to 1992), Malmö, Sweden             | 0  | Expected: 58<br>Identified: 41<br>Autopsied: 37      | —  | —                                       | —                      | M/F, 20/21; S/NS, 23/18 (22/15 autopsied); mean age at death: S, 56 yr; NS, 73 yr. Cause of death: emphysema in 17 of 23 S but in only 3 of 17 NS; 1 child, 2 of 22 S, and 12 of 17 NS died of cirrhosis   |

*Definition of abbreviations:* BD = bronchodilator; COPD = chronic obstructive pulmonary disease; FRC = functional residual capacity; M/F = male/female; NS = nonsmoking; PFT = pulmonary function testing; S = smoking; V<sub>max</sub> = maximum expiratory flow.



**APPENDIX 3. CHRONIC OBSTRUCTIVE PULMONARY DISEASE POPULATION STUDIES: PREVALENCE OF PI VARIANTS AND RISK OF ASSOCIATED LUNG DISEASE**

| First Author, Year (Ref.) | Risk Category | Level | Population  | PI*ZZ     | PI*SZ | PI*MZ                              | Other   | Risk Factors Addressed   |
|---------------------------|---------------|-------|---|-----------|-------|------------------------------------|---------|--|
| Fagerhol, 1969 (306)      | CB, AS, E     | II-3  | 196 patients with COPD from among 503 hospitalized pulmonary patients. Control subjects: 2,830 blood donors           | 3         | 1     | 5                                  | 3       | Highly significant increase in COPD in PI*ZZ and in combined PI*ZZ + PI*SZ + PI*SS (p < 0.01). No increase with other pulmonary diseases. Suggest increase in PI*SS and PI*MS among patients with asthma |
| Lieberman, 1969 (307)     | E, F          | II-3  | 66 VA hospital patients with emphysema, no control subjects   | 7         | —     | 10 (presumed with mild deficiency) | —       | Based on TIC levels. Marked increase in PI*ZZ and PI*MZ. Increased pulmonary disease in family, in both PI*ZZ and PI*MZ  |
| Hepper, 1969 (308)        | A, S, F, COPD | II-2  | COPD, 43 yr (?n of population)<br>FHx COPD  | 14        | —     | —                                  | —       | Estimate at least 25% PI*ZZ in COPD patients < 43 yr of age  |
|                           |               |       |   | 16        | —     | —                                  | —       | 2 PI*ZZ and 3 PI*MZ of 18 COPD patients with FHx of COPD   |
| Lieberman, 1986 (168)     | A, COPD, F    | II-3  | 965 COPD<br>1,380 control subjects  | 18        | 3     | 74                                 | 3 PI*SZ | Significant increase in PI*ZZ and PI*MZ (p < 0.005); PI*ZZ younger than PI*MM (56 versus 65 yr) (p < 0.001)  |
|                           |               |       |   | 0         | 5     | 34                                 | 1 PI*SS |  |
| Kueppers, 1969 (309)      | A, sex, E     | II-2  | 103 emphysema<br>Control subjects:<br>100 (age 36 yr)<br>88 (age 59 yr)   | 5         | —     | 25 (23 S)                          | —       | Highly significant increase in PI*ZZ and PI*MZ (p < 0.01); reduced PI*MZ in older men (1 of 39) suggests increased risk in males   |
|                           |               |       |   | 0         | —     | 14                                 | —       |  |
| Kueppers, 1977 (310)      | COPD, F       | II-2  | 114 COPD (FEV <sub>1</sub> < 70%)<br>114 matched control subjects (FEV <sub>1</sub> > 85%)<br>from 1,933 blood donors | 3         | 0     | 9                                  | —       | Significant increase in PI*ZZ and PI*MZ (p < 0.01); significant increase in COPD in siblings but not parents of patients with COPD (p < 0.001)   |
|                           |               |       |   | 0         | 0     | 6                                  | 1 PI*SS |  |
| Cox, 1976 (162)           | A, COPD, E    | II-2  | 1,441 parents and sibs<br>163 COPD<br>45 emphysema<br>721 control subjects  | 0         | 0     | 5                                  | —       | Highly significant increase in PI*ZZ, PI*MZ, PI*ZZ younger than PI*MM (49 versus 59 yr); 56% PI*ZZ less than 45 yr   |
|                           |               |       |   | 8 (4.5%)  | 0     | 8 (4.8%)                           | —       |  |
|                           |               |       |   | 8 (17.8%) | 0     | —                                  | —       |  |
|                           |               |       |   | 0         | 0     | 14 (1.9%)                          | —       |  |

*Definition of abbreviations:* A = age; AS = asthma; CB = chronic bronchitis; COPD = chronic obstructive pulmonary disease (AS + CB + E); E = emphysema; F = familial; FHx = family history; I = index; S = smoking; TIC = trypsin inhibitory concentration; VA = Veterans Affairs.

## APPENDIX 4. SERIAL CASE STUDIES IN PI\*ZZ: RISK CATEGORIES EVALUATED

| First Author, Year (Ref.) | Risk Category                     | Study Level | Population  | Control Subjects    | Number PI*ZZ              | M/F                  | S/NS                | Index/Nonindex         | Comment Supporting Risk Category Data  |
|---------------------------|-----------------------------------|-------------|---|---------------------|---------------------------|----------------------|---------------------|------------------------|--|
| Eriksson 1965 (59)        | A, sex, F, AS, COPD, S            | II-2        | Hospital and families   | 0                   | 33                        | 23/10                | 10/23               | 24/9                   | 23 with COPD; risk ratio for COPD, 15; M/F = 15/8; S/NS = 10/13; 6 of 10 without COPD < 40 yr; 11 had family history of COPD   |
| Hepper, 1969 (308)        | A, S, F<br>COPD                   | II-2        | COPD, 43 yr (?n of population)<br>FHx COPD                                  | 0<br>0              | 14<br>16                  | 14/0<br>13/3         | All S<br>All S      | All index<br>All index | Estimate at least 25% PI*ZZ in COPD 43 yr<br>2 PI*ZZ and 3 PI*MZ of 18 COPD patients with FHx of COPD  |
| Keuppers, 1974 (311)      | A, O, AB, S, G, CB, E, F, O, S    | II-3        | COPD patients from 17 references  | 0                   | 84 S<br>30 NS             | 60/24<br>16/14       | 84 S<br>30 NS       | All<br>Index           | Mean age of onset, 35 yr; predominance of males suggests other factors, possibly occupational.<br>Mean age of onset, 44 yr. 7 with no Sx < 40 yr. 24 NS > 40 yr abnormal FEV <sub>1</sub>  |
| Rawlings, 1976 (62)       | A, COPD, S, AB                    | II-2        | Hospital outpatients and families (7)                                       | 0                   | 20                        | 10/10                | 18                  | 13/7                   | Marked decrease in FEV <sub>1</sub> with age. Nonindex younger (38 versus 47 yr). NL PFTs only in two young nonsmokers   |
| Larsson, 1978 (6)         | A, S, E, COPD, S                  | II-2        | Hospitals and families  | 0                   | 246                       | 141/105              | 151/95              | ?                      | % COPD, S/NS = 86/57%; age at onset, S/NS = 40/53 yr. No p values but survival markedly decreases with age and smoking. Less than 10% reach age 60 yr. PI*ZZ NS, 60% reach age 60 yr   |
| Black, 1978 (312)         | A, O, S, E, COPD                  | II-1        | Lung (17), liver (2) patients and families (3); all never-smokers           | 36 PI*ZZ smokers    | 22                        | 13/9                 | 0/22                | 19/3                   | COPD variable but similar to smokers. Age at onset lower: S/NS = 37/51 yr, 4 < 29 yr; no COPD in 18, age 49 to 79 yr. Suggests factors other than smoking to explain variability   |
| Tobin, 1983 (141)         | A, S, E, COPD, sex, F, O, S       | II-2        | Chest clinic and families   | 0                   | 126<br>40                 | 82/44<br>17/23       | 108/18<br>24/16     | 126/40                 | Multiple regression versus FEV <sub>1</sub> : S, A, and sex significant. Age S/NS = 56 versus 48 yr (p < 0.01). High M/F, I versus NI (p < 0.025). High M/F, S versus NS (p < 0.01). Concludes high M/F due to S, not sex                                  |
| Janus, 1985 (147)         | A, S, sex, E COPD                 | II-2        | Referrals to hospital   | 0                   | 69 identified, 33 studied | NA<br>16/17          | NA<br>22/11         | NA<br>33/0             | Marked S/NS difference: FEV <sub>1</sub> %pred = 77/37 (p < 0.01). FEV <sub>1</sub> decline, 80/316 ml/yr (p = 0.02). No sex difference. Age of onset: S/NS = 43/59 yr (p < 0.02)  |
| Brantly, 1988 (63)        | A, E, COPD, S                     | II-2        | Referred ZZ patients  | 0                   | 120                       | 80/40                | 112/8               | 120/0                  | Mostly ex-smokers showing marked decrease in survival to age 60 yr: 16% in S PI*Z versus 85% expected in NS without alpha-1 antitrypsin deficiency   |
| Silverman, 1989 (34)      | A, AS, F, sex, O, S, COPD, AB, CB | II-2        | COPD patients, 22; liver patients, 4; families, 20; population screen       | 0                   | 52                        | 35/17                | 40/12               | 26/24                  | Univariate analysis: for FEV <sub>1</sub> < 66%: S pack-years, p = 0.002; age, p = 0.009; occupational gas or fumes, p = 0.074; occupational dust, NS; passive smoke, p = 0.074; sex, NS; asthma, p = 0.018. Ascertainment bias greatest factor            |
| Seersholm, 1995 (128)     | A, S, sex, F, COPD, CB, AS        | II-2        | Danish Registry: index, 335; 2,500 families, 277; longitudinal studies, 161 | 0                   | 161 > 25 yr               | 66/47<br>16/32       | 106/7<br>37/11      | 113/48                 | Decline in FEV <sub>1</sub> versus NI not significant. Current S versus ex-S, 132 versus 52 ml/yr (p < 0.01). Never S = 86 ml/yr not significant FEV <sub>1</sub> 30–65% versus > 65% (p < 0.01). Sex not significant                                      |
| 1. Wu, 1988 (222)         | A, AB, COPD, S                    | II-1        | 1. Swedish Registry 1963–1988; longitudinal                                 | 0                   | 158                       | —                    | 72% smokers         | —                      | Increased mortality: smokers and low initial FEV <sub>1</sub> (p = 0.005); 3-yr mortality: FEV <sub>1</sub> < 30%, 40%; FEV <sub>1</sub> 30–65%, 7%. Decline in FEV <sub>1</sub> greater in smokers by cross-section analysis but not by longitudinal data |
| 2. Eriksson, 1990 (313)   | A, AB, COPD, S                    | II-1        | 2. Swedish Registry 1963–1988; longitudinal                                 | 0                   | 158                       | —                    | —                   | —                      |  |
| Eden, 1997 (69)           | A, AS, COPD, F, S                 | II-2        | Patients, 38<br>Families, 5   | PI*MM with COPD, 22 | 38<br>5                   | 24/14<br>1/4<br>16/6 | 31/7<br>20/2<br>1/4 | 38, I<br>5, NI<br>—    | Asthma %: index = 22%, control subjects = 5% (p = 0.05). Atopy %: index = 48%, control subjects = 27% (not significant). Conclusion: Asthma more common in AAT deficiency  |

Continued

## APPENDIX 4. CONTINUED

| First Author, Year (Ref.)            | Risk Category                    | Study Level | Population  | Control Subjects | Number<br>PI*ZZ | M/F            | S/NS  | Index/<br>Nonindex | Comment Supporting<br>Risk Category Data   |
|--------------------------------------|----------------------------------|-------------|---|------------------|-----------------|----------------|---|--------------------|--|
| Seersholm, 1998 (136)                | A, AB, C, S, COPD, sex, O, F, AS | II-2        | Danish Registry and family longitudinal death analysis of never-smokers | 0                | 75              | 12/15<br>17/31 | All nonsmokers  | 27 = I<br>48 = NI  | SMR: for all 75 = 3.0 (CI, 1.9–4.0). Index = 8.8 (CI, 5–14). Nonindex = 0.96 (CI, 0.3–2.3). FEV <sub>1</sub> %, I/NI = 54/100 (p < 0.001) (only 3 NI had FEV <sub>1</sub> ) (70%). Sex not significant. Occupational exposure to dust and chemicals, not significant. Age at diagnosis: I versus NI: 56 versus 46 yr (p < 0.01)                                    |
| Piitulainen, 1997 (132)              | A, C, sex, O, S, F, COPD, AS     | II-2        | Swedish Registry and family, 665 total                                  | 0                | 225             | 107/118        | All nonsmokers  | 172/53             | FEV <sub>1</sub> %, M/F, 80/88% (p = 0.028). Occupational exposure versus no exposure to gas, fumes, or dust and > 50 yr. M + F, FEV <sub>1</sub> % = 76 versus 63% (p = 0.032). Males only, FEV <sub>1</sub> % = 69 versus 54 (p = 0.017). Conclusion: male sex, A > 50 yr, O, and A are significant risks  |
| McElvaney, 1997 (67)                 | A, C, sex, AB, AS, COPD, E, S    | II-2        | NIH Registry  | 0                | 1,129           | 627/502        | 902/227   | 816/313            | Normal FEV <sub>1</sub> and DL <sub>CO</sub> versus FEV <sub>1</sub> < 80%: Univariate analysis for: Age, 37 versus 47 yr (p = 0.001). % Male = 40 versus 57 (p = 0.01). I versus NI, 79 versus 11 (p = 0.001). Smoking, pack-years, 3.1 versus 19.8 (p = 0.001). Lung Sx (p = 0.001). Multivariate analysis: Age, S, and AB all p = 0.0001 as predictors for COPD |
| Piitulainen, 1998 (133)              | A, AS, sex, COPD, S, EV, O       | II-2        | Swedish Registry and family studies of never-smokers                    | 0                | 205             | 95/110         | All nonsmokers  | 160/45             | (1) CB with passive smoke: expected OR, 1.6; (2) wheezing and dyspnea > with agriculture workers: OR, 1.8 with > 10 yr of agricultural work; FEV <sub>1</sub> % = 59 versus 89% (p = 0.01); (3) kerosene in home (not gas stoves): FEV <sub>1</sub> %, 55 versus 88% (p = 0.05)  |
| NIH Registry Study Group, 1998 (137) | A, S, E, COPD, sex, AB, EV, AS   | II-2        | NIH Registry > 18 yr; total, 1,129                                      | 0                | 927             | 55.3% M        | 78.7% smokers   | 71.4% index        | (1) Univariate analysis of decline in FEV <sub>1</sub> : (a) > males, p = 0.001; (b) > current smokers, p = 0.001; (c) > BD response, p = 0.001; (2) multivariate analysis for survival: age > 65 yr, risk ratio, 5.61 (CI, 3.3–9.7); education < 12 yr, risk ratio, 2.7 (CI, 1.5–5.1); (3) (AB) not significant   |
| Miravittles, 1998 (314)              | A, S, AB, COPD                   | II-2        | Spanish National Registry   | 0                | 223             | 73% M          | 31% nonsmokers  | 83% index          | Index cases: older, 49 versus 35 yr (p = 0.001); lower FEV <sub>1</sub> %pred = 40 versus 96% (p = 0.001); more S, 85 versus 47% (p = 0.01)  |
| Piitulainen, 1999 (131)              | A, COPD, sex, S                  | II-2        | 698 in Swedish Registry   | —                | —               | —              | 211 never-smokers<br>351 ex-smokers<br>46 current smokers | —                  | FEV <sub>1</sub> decline, ml/yr (CI): 47 ml/yr (CI, 41–53), greater decline after age 59 yr; 41 ml/yr (CI, 36–48), decline proportional to cigarette consumption; 70 ml/yr (CI, 58–82), no sex differences   |
| Mayer, 2000 (138)                    | A, sex, AS, COPD, O, S, CB       | II-2        | Patients from Denver clinic, 101; AAT deficiency meeting, 62            | 0                | 128 studied     | 55% M          | 76% smokers   | ? All index        | Occupational exposure to dust, gas, or fumes in 69% of studied group. After adjusting for age, smoking, and infection: Increased cough: odds ratio, 4.69 (CI, 1.6 to 13.7). Exposure = high, low, some; FEV <sub>1</sub> % = 31%, 36%, 40% (p = 0.032). Smoking a risk factor independent of exposure  |

*Definition of abbreviations:* A = age; AAT = alpha-1 antitrypsin; AB = ascertainment bias; AS = asthma; CB = chronic bronchitis; CI = confidence interval; COPD = chronic obstructive pulmonary disease (AS + CB + E); E = emphysema; EV = environmental; F = familial; FHx = family history; I = index; NA = not available; NI = nonindex; NL PFTs = normal pulmonary function tests; NS = nonsmoking; O = occupational; OR = odds ratio; S = smoking; SMR = standardized mortality ratio; Sx = symptoms.

**APPENDIX 5. STUDIES THAT ADDRESS THE RISK OF A COPD FAMILY HISTORY TO PI\*MZ INDIVIDUALS**

| First Author, Year (Ref.) | n      | n (PI*MZ)      | Population        | Findings   |
|---------------------------|--------|----------------|-------------------|--|
| Larsson, 1970 (315)       | 242    | 26 in MZ range | SCS               | Airflow obstruction in control cohort correlated with family history of COPD and not AAT concentrations  |
| Lam, 1979 (316)           | 32     | 32             | SCS, PB           | 5/13 PI*MZ relatives of COPD patients had abnormal lung function compared with 5/19 PI*MZ without a family history ( $p = \text{NS}$ )   |
| Madison, 1981 (176)       | 163    | 67             | SCS, longitudinal | Male PI*MZ individuals with a family history of lung disease had more rapid decline in FEV <sub>1</sub> over 6 yr than PI*MZ patients without family history ( $p < 0.05$ )  |
| Khoury, 1986 (317)        | 1,787  | —              | SCS               | Smoking pack-years, family history of COPD, and blood group A found to be risk factors for airway obstruction (but not PI*MZ phenotype) in multiple regression analysis  |
| Silverman, 1990 (143)     | 169    | 85             | SCS               | Parents of PI*ZZ subjects with COPD ( $n = 9$ ) had lower FEV <sub>1</sub> than parents of PI*ZZ subjects without COPD ( $n = 12$ ) ( $p = 0.05$ )   |
| Seersholm, 2000 (177)     | 17,061 | 1,551          | SCS, PB           | Hospital discharges for obstructive lung disease more likely in PI*MZ subjects than in PI*MZ control subjects (relative risk, 2.2; 95% CI, 1.5–3.0). Risk concentrated in age 40- to 79-yr-old first-degree relatives of PI*ZZ index cases |

*Definition of abbreviations:* COPD = chronic obstructive pulmonary disease; PB = population based; SCS = serial cross-sectional.

**APPENDIX 6. SMOKING AS A RISK FACTOR FOR LUNG DISEASE IN PI\*MZ INDIVIDUALS\***

| First Author, Year (Ref.) | n     | n (PI*MZ) | Population       | Findings  |
|---------------------------|-------|-----------|------------------|---|
| Horton, 1980 (185)        | 56    | 28        | PB, longitudinal | FEV <sub>1</sub> decline over 7 yr in PI*MZ cohort higher for smokers than for nonsmokers but no different from PI*MM individuals   |
| Mittman, 1973 (318)       | 164   | 18        | SCS              | PI*MZ patients with COPD had fewer smoking pack-years than PI*MM COPD patients ( $p < 0.05$ ).  |
| Cooper, 1974 (319)        | 123   | 54        | SCS              | Smoking additive to PI*MZ phenotype in producing lower Pa <sub>o2</sub> and less elastic recoil than in PI*MM nonsmokers ( $p < 0.005$ )  |
| Klayton, 1975 (187)       | 291   | 27        | SCS, PB          | Smoking PI*MZ individuals > age 40 yr were more likely to have COPD than were nonsmoking PI*MZ individuals ( $p < 0.005$ ) or smoking PI*MM individuals ( $p < 0.01$ )  |
| Morse, 1977 (297)         | 2,944 | 88        | PB               | Smoking PI*MZ patients had steeper slope of age-related FEV <sub>1</sub> compared with nonsmokers, although not different from PI*MM individuals  |
| Larsson, 1977 (190)       | 78    | 39        | PB               | Smoking 50-yr-old PI*MZ men have higher residual volume, loss of elastic recoil, and increased closing capacity compared with nonsmoking PI*MZ individuals  |
| Gulsvik, 1979 (200)       | 1,268 | 55        | PB               | FEV <sub>1</sub> % predicted lower in smoking PI*MZ individuals than in nonsmoking PI*MZ individuals at age > 55 yr   |
| Lam, 1979 (316)           | 32    | 32        | SCS, PB          | Correlation of smoking with abnormal specific airway conductance ( $p < 0.05$ ) but not FEV <sub>1</sub> /FVC in PI*MZ individuals over age 30 yr   |
| de Hamel, 1981 (320)      | 592   | 29        | PB, longitudinal | No difference in any measure of respiratory health between PI*MZ and PI*MM individuals over 3 yr. Smoking status, smoking duration, and smoking quantity not found to be a risk for lung disease ( $p = \text{NS}$ )      |
| Eriksson, 1985 (196)      | 63    | 32        | PB, longitudinal | PI*MZ smokers had FEV <sub>1</sub> decline of 75 ml/yr over 6 yr compared with 40 ml/yr in PI*MZ nonsmokers ( $p < 0.05$ )  |
| Sutinen, 1985 (194)       | 186   | 15        | PB               | No excess of emphysema independent of smoking status in 15 consecutive PI*MZ autopsies  |
| Khoury, 1986 (317)        | 1,787 | —         | SCS              | Smoking pack-years, family history of COPD, and blood group A found to be risk factors for airway obstruction (but not PI*MZ phenotype) in multiple regression analysis   |
| Laros, 1988 (321)         | 1,850 | 49        | PB, SCS          | Relative risk = 1.6 for PI*MZ smokers to develop decreased lung elasticity compared with PI*MZ nonsmokers   |
| Silverman, 1992 (195)     | 167   | 85        | SCS              | Correlation of pack-years and FEV <sub>1</sub> for PI*MZ first-degree relatives of PI*ZZ subjects, $r = 0.42$ ( $p < 0.01$ )  |
| Horne, 1992 (300)         | 544   | 22        | PB               | Serial cohort of women found independent risks of PI*MZ phenotype and smoking on subtle spirometric tests of airflow obstruction but not FEV <sub>1</sub> ( $p < 0.01$ )  |
| Sandford, 1999 (189)      | 266   | 12        | SCS              | Serial cohort of lung cancer resections found that 12/12 (100%) PI*MZ patients had obstruction versus 181/254 (71%) PI*MM patients ( $p = 0.04$ by age, sex, and smoking intensity adjusted logistic regression analysis) |

*Definition of abbreviations:* COPD = chronic obstructive pulmonary disease; PB = population based; SCS = serial cross-sectional.

\*All studies with 10 or more MZ individuals that objectively address the risk of smoking.

## APPENDIX 7. ENVIRONMENTAL RISKS OF LUNG DISEASE IN PI\*MZ INDIVIDUALS\*

| First Author, Year (Ref.) | n     | Population       | Findings   |
|---------------------------|-------|------------------|--|
| Chan-Yeung, 1978 (204)    | 1,138 | PB               | 31 PI*MZ individuals from sawmills and grain elevators, all with normal FEV <sub>1</sub> , despite smoking in 14 individuals   |
| Stjernberg, 1984 (205)    | 518   | PB               | PI*MZ gene frequency 12.8% in PI*MZ sulfite pulp workers with chronic bronchitis versus 8.4% in normal workers (p = NS)  |
| Horne, 1986 (206)         | 56    | SCS              | 28 PI*MZ grain workers were case matched to 28 PI*MM grain worker control subjects, finding lower FEV <sub>1</sub> in PI*MZ patients   |
| Pierre, 1988 (207)        | 871   | PB, longitudinal | No difference in baseline lung function or symptoms in heavily exposed miners with similar smoking history. Five-year FEV <sub>1</sub> /FVC decline greater in PI*MZ individuals than in control subjects (p < 0.05)         |
| Brandslund, 1993 (202)    | 226   | SCS              | Same population as Sigsgaard modeling AAT and endotoxin levels showing additive risk for byssinosis  |
| Sigsgaard, 1994 (203)     | 226   | SCS              | PI*MZ individuals exposed to cotton dust more likely to develop byssinosis 3/8 (38%) than PI*MM individuals 25/187 (13%). OR, 5.8 (CI, 1.1–30) in logistic regression model controlling for endotoxin, tobacco, sex, and age |

*Definition of abbreviations:* CI = confidence interval; OR = odds ratio; PB = population based; SCS = serial cross-sectional.

\*All studies to specifically address environmental risk with more than five PI\*MZ individuals.

## APPENDIX 8. PI\*MZ PHENOTYPE MAY BE A RISK FACTOR FOR ATOPIC DISEASE\*

| First Author, Year (Ref.) | n     | n (PI*MZ) | Population | Findings  |
|---------------------------|-------|-----------|------------|---|
| Schwartz, 1977 (210)      | 410   | 44        | PB, SCS    | No difference in PI*MZ gene frequency in children with asthma (p = NS)  |
| Vance, 1977 (191)         | 224   | 37        | PB         | Asthma present in 11% of PI*MZ versus 6% PI*MM children (p = NS)  |
| Buist, 1979 (183)         | 102   | 27        | PB         | Physician-diagnosed (before age 12 yr) asthma found more frequently in PI*MZ individuals, 6/34 compared with control subjects, 2/68 (p = 0.05)  |
| Hoffman, 1981 (322)       | 512   | 13        | SCS        | PI*MZ individuals had more frequent high-titer RAST scores than did PI*MM individuals   |
| Kabiraj, 1982 (211)       | 65    | 31        | PB         | Methacholine responsiveness identical in 31 PI*MM and 34 PI*MZ individuals (p = NS)   |
| Monteseirin, 1984 (323)   | 93    | 10        | SCS        | PI*MZ gene frequency (9/55) higher than expected in atopic dermatitis cohort compared with control subjects (1/38) (p < 0.005)  |
| Portenko, 1989 (215)      | 1,738 | 22        | PB         | PI*MZ gene frequency higher (3.4%) in individuals with polypoid rhinosinusitis than in healthy control subjects (0.79%)   |
| Townley, 1990 (209)       | 489   | 34        | SCS        | PI*MS (n = 36) but not PI*MZ (n = 34) individuals had more methacholine responsiveness and skin test positivity than PI*MM control subjects   |
| Lindmark, 1990 (212)      | 172   | 11        | SCS        | No difference in PI*MZ gene frequency among children with asthma compared with control subjects (OR, 1.3; 95% CI, 0.76–2.6) (p = NS)  |
| Silverman, 1990 (143)     | 169   | 85        | SCS        | IgE levels no different between PI*MM (n = 22) and PI*MZ relatives (n = 85); but IgE higher in those PI*MZ individuals age < 25 yr with PI*ZZ relative with COPD compared with PI*MZ individuals < 25 yr with PI*ZZ relative without COPD (p = 0.015) |
| Sigsgaard, 1994 (203)     | 226   | 8         | SCS        | PI*MZ patients self-report familiar allergy (50%) more commonly than PI*MM individuals (12%) (OR, 2.8; CI, 1.3–5.9)   |
| Maune, 1995 (214)         | 308   | 19        | SCS        | Chronic polypoid sinusitis found to have PI*MZ gene frequency five times that of control (p < 0.01)   |
| Prados, 1995 (213)        | 242   | 9         | SCS        | PI*MZ gene frequency higher than control subjects for patients with intrinsic asthma (p < 0.001), nasal polyposis (p = 0.001), family history of atopy (p < 0.001), and intolerance to nonsteroidal agents (p = 0.001)                                |

*Definition of abbreviations:* CI = confidence interval; OR = odds ratio; PB = population based; SCS = serial cross-sectional.

\*All studies with > 5 PI\*MZ individuals that evaluate clinical aspects of allergy, rhinitis, or asthma.

## APPENDIX 9. PRIMARY EVIDENCE OF RISK OF EMPHYSEMA IN INDIVIDUALS WITH PI\*SZ PHENOTYPE

| First Author, Year (Ref.) | Study Type  | Identification     | Number of Subjects | Control subjects                                    | Risk of Emphysema   | Comment   |
|---------------------------|---|--------------------|--------------------|---|---|---|
| Larsson, 1976 (220)       | Observational   | Identification IEF | 7                  | Historical and healthy nonsmokers                   | Increased   | Abnormalities in nitrogen washout, regional ventilation, and lung mechanics found in three nonsmoking asymptomatic individuals                          |
| Gishen, 1982 (79)         | Multicenter survey: blinded CXR study                                       | SGE or IEF         | 25 (14 index)      | 165 with PI*ZZ                                      | No increase   | Radiographic signs of emphysema were more generalized and occurred only in PI*SZ smokers, whereas these occurred in 65% of PI*ZZ nonsmokers             |
| Hutchison, 1983 (219)     | Multicenter survey: observational   | SGE or IEF         | 25 (14 index)      | Historical  | No increase   | Age at symptom onset in index cases was no different from that of historical control subjects. No emphysema in nonsmoking nonindex cases                |
| Turino, 1996 (218)        | Registry  | IEF                | 50 (25 index)      | 965 with PI*Z                                       | No increase in nonsmokers; less severe emphysema in smokers compared with those with PI*Z | Pulmonary function relatively normal in nonsmokers; symptoms, CXR, and pulmonary function test abnormalities less severe compared with those with PI*ZZ |
| Sandford, 1999 (189)      | Case-control genotyping study of those undergoing resection for lung cancer | PCR amplification  | 266                | 73 with no airway obstruction                       | No increase   | Prevalence of S allele was no higher in those with airway obstruction   |
| Seersholm, 1998 (324)     | Registry mortality study  | IEF                | 94 (28 index)      | SMR for study group compared with Danish population | Increased risk in a small fraction of those with PI*SZ                                    | No increase in SMR in nonindex cases, but possible in respiratory deaths  |

*Definition of abbreviations:* CXR = chest X-ray; IEF = isoelectric focusing; PCR = polymerase chain reaction; SGE = slab gel electrophoresis; SMR = standardized mortality ratio.

## APPENDIX 10. PRIMARY EVIDENCE TABLE: SUMMARY OF STUDIES REGARDING THE EFFICACY OF AUGMENTATION THERAPY

| First Author, Year, Country (Ref.)                   | Level of Evidence | Type of Study   | Design of Study   | Number of Patients   | Mean Age/Sex                | Main Findings   | Conclusions   | Comments  |
|--|-------------------|---|---|--|-----------------------------|---|---|---|
| Seersholm, 1997, Denmark/Germany (246)               | II-2              | Prospective, controlled, nonrandomized                  | Comparison between untreated Danish and treated German patients with PI*ZZ and lung emphysema in ex-smokers. Weekly infusion with 60 mg Prolastin/kg body weight. Inclusion criteria: alpha-1 antitrypsin serum level $\leq$ 11 $\mu$ M           | n = 295: 97 control subjects, 198 treated. All PI*ZZ                                       | 45.7 yr; 67% male           | 1. The decline in lung function in the treated group was significantly lower than in the untreated group (FEV <sub>1</sub> = 53 versus 75 ml/yr, p < 0.002)<br>2. Stratification by initial lung function showed a significant influence of the treatment in patients with moderately advanced emphysema (FEV <sub>1</sub> = 31–65%pred) only | Weekly infusions with 60 mg Prolastin/kg bw may slow the progress of the disease in patients with moderately reduced lung function due to alpha-1 antitrypsin deficiency  | Both groups were comparable concerning smoking habits, age, sex, lung function, and selection criteria  |
| Wencker, 1998, Germany (247)                         | II-3              | Prospective, noncontrolled, nonrandomized               | Comparison between treated patients and historical data. Infusion with 60 mg Prolastin/kg body weight. Inclusion criteria: alpha-1 antitrypsin serum level $\leq$ 11 $\mu$ M  | n = 443: 89% PI*ZZ, 7% PI*SZ   | 47.0 yr, 66% male           | 1. Replacement therapy had few serious adverse reactions (5 in 58,000 infusions). No death or viral transmission was observed<br>2. The decline in lung function was lower in the treated group compared with historical data (FEV <sub>1</sub> = 64 ml/yr versus 101 ml/yr in a Swedish study and 111 ml/yr in a U.S. study)                 | Long-term treatment with alpha-1 antitrypsin intravenous augmentation in severely deficient patients is feasible and safe. The decline in lung function seems to be lower in treated patients compared with historical data | The study was primarily designed to investigate the feasibility and toxicity of long-term augmentation therapy, not to prove clinical efficacy  |
| AAT Deficiency Registry Study Group, 1998, USA (137) | II-3              | Prospective, noncontrolled, nonrandomized               | Comparison of lung function and mortality in treated versus untreated patients within the Alpha-1 Antitrypsin Deficiency Registry. Inclusion criteria: alpha-1 antitrypsin level $\leq$ 11 $\mu$ M  | n = 927; 227 treated versus 650 untreated; FEV <sub>1</sub> = 49%pred; phenotype not known | 46 yr, 55% male             | 1. Mortality decreased in patients on therapy compared with untreated (p < 0.02)<br>2. The decline in lung function was significantly lower in treated patients with moderately decreased lung function (FEV <sub>1</sub> = 35–49%pred): FEV <sub>1</sub> = 66 ml/yr versus 93 ml/yr (p = 0.003)  | Augmentation therapy in moderately advanced emphysema due to severe alpha-1 antitrypsin deficiency can reduce mortality and slow disease progress   | 1. Indications for augmentation therapy were left to the treating physician<br>2. Augmentation therapy varied between "always"/"partly" and "weekly"/"biweekly"/"monthly"<br>3. No information on smoking status available                        |
| Dirksen, 1999, Danish Study Group (112)              | I-1               | Double-blind, randomized, prospective multicenter study | Comparison of treatment with 250 mg alpha-1 antitrypsin concentrate at 4-wk intervals and albumin (625 mg/kg body weight) for at least 3 yr in patients with PI*ZZ. End points were pulmonary function tests measured daily and CT thorax changes | n = 56 ex-smokers; FEV <sub>1</sub> = 48%pred  | 47 yr, 51% male, 100% PI*ZZ | 1. There was no significant difference in decline of lung function expressed as FEV <sub>1</sub> per year between both arms<br>2. The loss of lung tissue estimated from changes in lung density, obtained by CT, also did not show statistically significant differences, although there was a clear trend (p = 0.07)                        | Although there was no statistically significant difference between both arms, CT follow-up might prove a better tool for further studies  | 1. Because of the monthly treatment regimen, on several days of the month patients were below the protective serum level<br>2. A larger trial with 130 patients would probably have proven efficacy on the basis of serial CT scans of the thorax |

Definition of abbreviation: CT = computed tomography.

Inclusion criterion: prospective studies with more than 50 subjects.

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# Liver and Other Diseases

## LIVER DISEASE

### Introduction

Harvey Sharp and associates first described cirrhosis in alpha-1 antitrypsin (AAT) deficiency in 10 children from six different kindreds (1). In 1971, Sharp also described intrahepatocyte periodic acid–Schiff diastase (PAS-D)-resistant globules or inclusions, the result of polymer formation by mutant PI\*Z protein in the endoplasmic reticulum (2). Individuals manifesting this intrahepatocytic aggregation are at increased risk of developing cirrhosis. This section, prepared by the Liver and Other Diseases Writing Group of the Alpha-1 Antitrypsin Deficiency Task Force, presents a systematic analysis of the strength of association among various forms of severe and intermediate AAT deficiency and liver disease in the various age groups.

The pathophysiology of liver disease in AAT deficiency is different from that of lung disease. Although a variety of theories have been proposed to explain liver injury in individuals with homozygous PI\*ZZ AAT deficiency, the most widely accepted explanation, and the only one supported by significant experimental evidence, is the “accumulation theory” (reviewed in references 3 and 4). This theory states that liver injury in AAT deficiency results from accumulation of mutant, AAT Z protein molecules within the endoplasmic reticulum (ER) of hepatocytes. Large quantities of mutant AAT Z protein are synthesized in the liver of PI\*ZZ individuals, but about 80–90% of the Z protein synthesized appears to be retained within hepatocytes rather than being efficiently secreted. Intracellular processes, known as the quality control apparatus, recognize that the nascent mutant AAT Z polypeptide is abnormal during biogenesis and direct it to a pathway of retention within the ER rather than allowing export from the hepatocyte. The quality control apparatus of the cell involves “molecular chaperone” proteins that are members of the heat shock protein family.

The accumulation theory of liver injury in AAT deficiency is supported by several lines of evidence. First, reports concerning various experimental mice transgenic for the human AAT Z gene have shown the accumulation of AAT Z protein within hepatocytes. Furthermore, the patterns of liver injury, including neonatal liver disease, hepatic fibrosis, and late hepatocellular carcinoma, are similar to the human disease (5–7). Although the results of the AAT Z transgenic mouse experiments have been criticized for their variability, which could result from environmental or other mouse genetic factors, they do completely rule out the possibility that the liver injury is due to low circulating levels of AAT in the serum. This is because these mice have normal levels of endogenous antielastases as directed by their intact murine antielastase genes.

Other evidence for the accumulation theory has come from investigations of the intracellular processing of AAT Z protein within the ER. Studies have shown that the majority of PI\*ZZ individuals are “protected” from liver injury by efficient mechanisms for the intracellular degradation of the AAT Z protein retained within the ER. However, patients susceptible to liver injury appear to have inefficient intracellular degradation mechanisms, leading to a net increase in the ER accumulation of the retained AAT Z protein (8). Host-specific genetic or environmental differences in the hepatocellular response to AAT Z intracellular accumulation may explain the clinical observation that only a subpopulation of PI\*ZZ individuals develop significant liver injury.

Interestingly, the AAT Z molecule has an increased tendency

to form polymers by the so-called loop–sheet insertion mechanism (9). Molecular structural studies have suggested that a single amino acid substitution in the Z mutant and some other deficient proteins results in insertion of the loop of one Z molecule into the A sheet of another, so that long interlocking polymers form. However, it is unclear whether the ER retention signal for AAT Z occurs at a step proximal to the formation of polymers or whether polymerization itself triggers a retention signal within the cell.

The exact relationship between AAT Z polymerization and hepatocellular injury remains unclear. Although polymerization of AAT Z has been proven to occur *in vivo*, the exact links to the pathophysiology of the human disease remain undefined. Studies of environmental factors that could predispose AAT deficiency patients to liver injury have so far yielded conflicting results. Suggestions that breast-feeding might be protective against the development of liver disease in children have not been consistent across all reports (10, 11). Some studies have suggested an increase in the prevalence of viral hepatitis infection in heterozygous PI\*MZ adults with liver disease; other studies in adults have not found such a correlation (12, 13). However, a theory supports the possibility that AAT deficiency–associated liver disease can be exacerbated by viral hepatitis, because both hepatitis B and hepatitis C viruses express proteins that are selectively retained in the ER of hepatocytes (14). It has been suggested that whatever cellular injury results from the ER retention of proteins could be compounded by the additional retention of these viral proteins. However, it is clear that nearly all PI\*ZZ children and adults with liver disease are free from hepatitis B and C infections, and that PI\*MZ individuals do not develop AAT deficiency–associated liver disease during their childhood years (15).

Alpha-1 antitrypsin deficiency (AAT deficiency) PI\*ZZ predisposes to liver disease, often presenting as jaundice in early infancy. In countries with a high prevalence of AAT deficiency, it is a common cause of neonatal cholestasis. Alpha-1 antitrypsin deficiency is also a common metabolic disease in children with end-stage liver disease for whom liver transplantation is performed.

The association of liver disease with AAT deficiency in adults is less clear than in children. In particular, the association between intermediate AAT deficiency (PI\*MZ, PI\*SZ) and liver disease has been controversial. Although many studies on the association between AAT deficiency and chronic liver disease (CLD) have been reported, variations in approach and study results preclude a clear understanding. The current systematic review and metaanalysis was undertaken to analyze evidence in the literature regarding the causal link between AAT deficiency and CLD in children and adults.

### Methods

**Study objectives.** The purpose of this review was to thoroughly review and evaluate the literature linking AAT deficiency with CLD in children and adults and to assess the strength of the causal association. Attempts were also made to delineate laboratory or clinical findings that may be helpful in identifying this subset of patients and to identify risk factors related to liver dysfunction. Concerning the epidemiology of CLD in childhood, special attention was paid to the spectrum of CLD in individuals 0–18 years of age, the frequency of AAT deficiency as a cause of neonatal cholestasis (synonymous with neonatal hepatitis syndrome), and the frequency of AAT deficiency as a cause of end-stage CLD requiring transplantation.

**Review material.** To evaluate the full spectrum of disease associa-

tions with AAT deficiency, several literature searches were conducted in both MEDLINE and HealthSTAR databases for the years 1963–2000, using the index terms *AAT deficiency* and *liver disease*, and *AAT deficiency* and *vasculitic disorders, glomerulonephritis, panniculitis, skin disorders, aneurysmal diseases, and pancreatic and celiac diseases*. In addition, reference lists of research reports and reviews were systematically screened. Full reports published in peer-reviewed journals in the English language (but not abstracts) were retained for review. Articles tabulated (Tables 1–4) (7, 8, 10, 13) in this review are shown in the reference section along with material that provides additional information.

Over the interval during which this document was under review (through Fall 2002), the text was amended to reflect the impact of selected newer references that were deemed to affect the insights and conclusions offered.

**Review process.** All articles reporting observational case series and epidemiologic data that were retrieved by January 2000 were assessed by the authors by means of a checklist, shortened versions of which are shown in Tables 1–13.

**Statistically significant associations.** Results in available reports were reported as rate ratios (prevalence odds ratios or risk ratios) with 95% confidence intervals (95% CI), when possible. An estimated risk ratio exceeding 1 was considered to show a statistically significant positive association, provided the lower 95% CI exceeded 1.0 or if  $p < 0.05$ . The reported results on adult heterozygotes were also scrutinized for the association between etiologic subgroups of CLD (cryptogenic, alcoholic, autoimmune, and viral), when such analyses were available. These results were then reported as “+” (yes) for a statistically significant association or as “–” (absence of a statistically significant association). When analyzing the association between the heterozygous state and primary liver cancer (PLC), the same approach was used.

The quality of the evidence supporting clinical characteristics, risk factors, and therapeutic recommendations was graded according to the U.S. Preventive Services Task Force (*see* Table 1 in the LUNG DISEASE section).

**Other study characteristics.** In the analysis, close attention was paid to methods used for diagnosing AAT deficiency. Isoelectric focusing (or crossed immunoelectrophoresis and starch gel electrophoresis in early reports) was considered the “gold standard” for phenotyping. Hepatocytic PAS-D-positive inclusions were considered surrogate markers of the PI\*Z allele (and some other, rare variants).

The following limitations were applied to reports of childhood liver disease chosen for analysis:

- In studies of the occurrence of clinical and subclinical liver abnormalities, analysis was restricted to reports identifying 100 or more AAT-deficient children.
- In studies of the occurrence of AAT deficiency in individuals with neonatal cholestasis or in recipients of liver transplants for end-stage liver disease, more than 50 individuals were required.

In analyzing the occurrence of CLD in adult homozygotes, observational case series providing information about sex, age, clinical characteristics, laboratory features, and putative additive factors were accepted for analysis despite limited information concerning the representativeness of the sample. Case reports and smaller case series ( $n < 8$ ) were not included unless providing important new information that was biologically or clinically relevant.

When analyzing the occurrence of CLD in adult heterozygotes, analysis was restricted to larger samples ( $n > 300$ ) of patients with CLD. The PI\*Z allele frequency in these samples was compared with that in the general background population.

## Results

**Description of studies: number and types of reports and individual studies.** Regarding childhood CLD, a total of 21 articles spanning 1974–1999 (listed in Tables 1–4) were identified. Only one study (16) is a population-based epidemiologic study, the remaining being observational case series collected at referral centers.

Regarding adult CLD, 24 articles (listed in Tables 7 and 8) were identified, 13 dealing with PI\*Z homozygotes and 11 dealing mainly with PI\*Z heterozygotes. The studies spanned the years 1972–2000, with 8 articles published in the 1970s, 6 in the

**TABLE 1. CLINICAL SYMPTOMS OF LIVER DISEASE AND LIVER TEST ABNORMALITIES IN 127 PI\*ZZ CHILDREN IDENTIFIED IN THE SWEDISH NEONATAL SCREENING STUDY**

| Main Finding  | Percent |
|---|---------|
| Clinical signs of neonatal liver disease              | 17      |
| Healthy infants with abnormal liver tests at age 3 mo | 52      |
| Risk of liver cirrhosis before adolescence            | 3       |

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1980s and 10 in the 1990s and 2000. Of the 24 retained articles, the majority were case series collected at referral hospitals and lacking data on representativeness of the background population. In data from homozygotes (Table 7), only three reports (17–19) used epidemiologic methodology; the first two were case-control studies and the third (19) was a nationwide, multiple-cause mortality study. In adult AAT-deficient individuals, no true population-based reports were available. The two Swedish case-control studies (17, 18) based on autopsies include the majority of expected PI\*Z homozygotes in a defined population of about 250,000 during 30 years. Therefore, these studies are considered to approach representativeness and provide minimum figures for the incidence of CLD. Similarly, the two autopsy studies (20, 21) in Table 8 may be regarded as population-representative, although they use PAS-D staining as a surrogate marker of the PI\*Z allele. Twelve additional reports on PLC in AAT deficiency were included in Table 10.

**Risk of liver disease in PI\*ZZ children.** The Swedish neonatal screening study of 200,000 infants fulfilled the criteria for the definition of liver abnormalities in AAT-deficient subjects (16). One in about 1,600 infants had severe AAT deficiency and 127 AAT-deficient children (Table 1) were monitored prospectively from birth through 18 years of age (16, 22). Clinical signs of liver disease found in the PI\*ZZ infants included 11% who suffered from neonatal cholestasis and 6% who had other clinical symptoms of liver disease without jaundice (16). Four of the children with liver disease in infancy died: two died of liver cirrhosis, one had aplastic anemia with autopsy indicating liver cirrhosis, and one child died in an accident, with the autopsy showing a mild increase in peripheral fibrous tissue in the liver. In those with cholestasis, serum bilirubin normalized within 6 months. Through age 18 years, all surviving children with neonatal liver disease were clinically healthy (22).

In early childhood, more than half of the healthy PI\*ZZ infants had abnormal liver test results (22). At age 12–18 years, almost all had normal or at most marginally increased liver enzyme concentrations. None of them had any clinical symptoms of liver disease (22). Rough estimates of the risk that a PI\*ZZ sibling of a proband with severe liver disease will follow a similar course were 40% in a Canadian series, 21% in a U.S. series, and 67% in a U.K. series (23).

The most common cause of neonatal cholestasis is extrahepatic biliary atresia, often accounting for about 50% of the cases. Studies of neonatal cholestasis, extrahepatic biliary atresia being excluded, are summarized in Table 2 (23–28). Depending on the PI\*Z gene frequency in the population and the referrals to the liver units, the percentage of AAT-deficient cases varies between 7 and 18%.

As summarized in Table 3 (29–31), AAT deficiency-related liver disease, which progresses to end-stage liver disease and liver transplantation, accounts for 14–46% of children transplanted for CLD (biliary atresia being excluded).

In conclusion, most AAT-deficient individuals (83%) are clinically healthy throughout childhood and most will have liver



TABLE 2. STUDIES OF NEONATAL CHOLESTASIS OR NEONATAL HEPATITIS SYNDROME

| First Author, Country, Year of Publication (Ref.) | Type of Study                 | n*  | % PI*ZZ |
|---|-------------------------------|-----|---------|
| Cottrall, UK, 1974 (23)                           | Retrospective referral center | 45  | 16      |
| Deutsch, Australia, 1985 (24)                     | Retrospective referral center | 123 | 7       |
| Danks, Australia, 1977 (25)                       | Retrospective referral center | 94  | 9       |
| Henriksen, Norway, 1981 (26)                      | Retrospective referral center | 56  | 14      |
| Mowat, UK, 1976 (27)                              | Epidemiologic referral center | 135 | 18      |
| Odievre, France, 1981 (28)                        | Retrospective referral center | 103 | 17      |

\*Those with biliary atresia are excluded.

enzyme abnormalities in early life. The PI\*ZZ phenotype is a common cause of neonatal cholestasis and is often encountered in children in need of liver transplantation.

*Clinical manifestations in PI\*ZZ childhood liver disease.* Data describing the epidemiology of PI\*ZZ childhood liver disease, obtained with the search criteria defined above, are powerful in their ability to define the incidence of individuals with clinically significant disease and the gene frequency. However, clinical descriptions of more than 500 pediatric patients with AAT deficiency have been published in a variety of case report formats and consideration of these cases, with the appropriate objectivity, can also be useful in understanding the wide variability of liver disease observed in PI\*ZZ children. Table 4 (1, 10, 32–40) summarizes retrospective clinical reports, each describing 10 or more pediatric patients with PI\*ZZ-associated liver disease. Taken together, the clinical course of 480 PI\*ZZ children is discussed.

Review of these reports confirms that the presentation of pediatric PI\*ZZ disease (Table 5) can range widely from rare, severe, fatal liver failure in infancy to asymptomatic healthy children without detectable biochemical or physical abnormalities (1, 10, 16, 22, 32–42). If present, liver dysfunction is often first noted at 1 or 2 months of life because of prolonged jaundice or hepatomegaly. Laboratory analysis often reveals moderately elevated conjugated bilirubin levels and elevated serum transaminase activity. Several authors suggest that the diagnosis of PI\*ZZ AAT deficiency should be considered in all infants with evidence of conjugated hyperbilirubinemia, elevated serum transaminases, “neonatal hepatitis syndrome,” or any other evidence of liver disease. Often, elevated serum transaminase levels can be documented to persist for years, even though minimal clinical signs of liver disease remain beyond infancy (1, 10, 22, 32–40). Small numbers of infants with AAT deficiency initially came to medical attention as a result of a coagulopathy manifested by episodes of gastrointestinal bleeding, bleeding from the umbilical stump, easy bruising, or rarely a central nervous system hemorrhage. This bleeding diathesis usually represented vitamin K deficiency in the setting of mild to moderate liver dysfunction, and timely supplemental vitamin K administration to these patients was thought to be life-saving.

On other occasions, an infant with little clinical evidence of

liver disease, but who presented with failure to thrive, possibly with mild hepatomegaly, was found to have AAT deficiency. A small proportion of affected infants developed progressive hepatosplenomegaly, ascites, and liver synthetic dysfunction, sometimes compounded by poor feeding and poor growth (1, 10, 13, 32–40). Fulminant hepatic failure in infancy appears to be rare, but has been described (4, 43). Another rare presentation in infancy is the syndrome of cholestatic pruritis and hypercholesterolemia, in which histologic examination of the liver shows a nonspecific paucity of intrahepatic bile ducts (14). On occasion, AAT deficiency was found to coexist with other infantile conditions such as biliary atresia and cystic fibrosis, although it is likely that these reports are only coincidental occurrences (44).

Regarding hepatic presentations of AAT deficiency later in childhood, during adolescence, and in adulthood, reports indicate that patients may present with hepatosplenomegaly, ascites, upper gastrointestinal bleeding resulting from esophageal varices, chronic hepatitis, cirrhosis, or hepatic failure (16, 37, 40). The presentation of AAT deficiency may appear similar to other chronic liver diseases, including autoimmune hepatitis, drug-induced hepatitis, chronic viral hepatitis, and Wilson’s disease (1, 10, 17, 32–40, 45). The weight of these reports suggests that patients with any unexplained features of chronic liver disease should be evaluated for AAT deficiency. Some reports encourage and we recommend testing first-degree family members of newly diagnosed patients with AAT deficiency, in conjunction with appropriate patient education and counseling, because many affected individuals of all ages have been identified through family studies.

Several of the retrospective studies have attempted to identify clinical prognostic indicators of severity in AAT deficiency-associated liver disease. The accumulated findings are listed in Table 6. Although the limitations of retrospective analysis and the bias in ascertainment must be recognized, the information may be useful when applied to patients already identified with disease in a referral population.

Consideration of these factors could be useful in clinical decisions about the timing of liver transplantation, although experienced clinicians use these and many similar factors when evaluating the severity of many chronic liver diseases. However, it has been noted in several reports that many PI\*ZZ children with

TABLE 3. LIVER TRANSPLANTATION STUDIES OF CHILDREN AND ADOLESCENTS WITH CHRONIC LIVER DISEASE

| First Author, Country, Year of Publication (Ref.) | Type of Study                 | n*  | % PI*ZZ |
|---|-------------------------------|-----|---------|
| Adrian-Casavilla, USA, 1994 (29)                  | Retrospective referral center | 82  | 46      |
| Esquivel, USA, 1987 (30)                          | Retrospective referral center | 123 | 18      |
| Migliazza, Spain, 2000 (31)                       | Retrospective referral center | 115 | 14      |

\*Those with cirrhosis due to biliary atresia are excluded.

**TABLE 4. OBSERVATIONAL REPORTS ON LIVER DISEASE ASSOCIATED WITH PI\*ZZ ALPHA-1 ANTITRYPSIN DEFICIENCY IN CHILDREN**

| First Author, Country, Year of Publication (Ref.) | Type of Study                 | No. of Cases of PI*ZZ | Main Findings   |
|---|-------------------------------|-----------------------|---|
| Burk, USA, 1976 (32)                              | Retrospective referral center | 10                    | Disease presentations highly variable.  |
| Ghishan, USA, 1988 (33)                           | Retrospective referral center | 18                    | Male predominance, cholestasis, suggests poor prognosis   |
| Ibarguen, USA, 1990 (34)                          | Retrospective referral center | 98                    | Elevated transaminases, bilirubin prothrombin time suggests poor prognosis; no effect of breast-feeding |
| Labrune, France, 1989 (35)                        | Retrospective referral center | 72                    | Neonatal cholestasis suggests poor prognosis; no effect of sex or breast-feeding                        |
| Moroz, Canada, 1976 (36)                          | Retrospective referral center | 18                    | Liver biopsy not predictive of short-term prognosis   |
| Nebbia, France, 1983 (37)                         | Retrospective referral center | 45                    | Elevated transaminases, bilirubin, and hard hepatomegaly indicate poor prognosis                        |
| Nemeth, Sweden, 1982 (38)                         | Retrospective referral center | 13                    | Documented severe disease without preceding cholestasis   |
| Odievre, France, 1976 (39)                        | Retrospective referral center | 20                    | Disease presentations highly variable; lack of diseases in MZ, MS, SZ                                   |
| Psacharopoulos, UK, 1983 (40)                     | Retrospective referral center | 136                   | Reported concordance of disease in sibling; no sex predilection   |
| Sharp, USA, 1969 (1)                              | Retrospective referral center | 10                    | Identified pediatric liver disease association with PI*ZZ   |
| Udall, USA, 1985 (10)                             | Retrospective referral center | 40                    | Breast-feeding protection from severe disease   |

evidence of portal hypertension, elevated serum transaminases, or prolongation of prothrombin time may remain stable for many years without the need for liver transplantation (4, 22, 43). The decision to proceed to liver transplantation must take into account many individual factors about the patient and the family, and assumes a progressive deterioration in the patient's liver disease (4, 43, 46–49). There appears to be no causal relationship between viral hepatitis, including hepatitis C, and childhood liver disease associated with AAT deficiency (43, 46, 50, 51). In families in whom a previously affected child has had severe liver disease, the chance that a second PI\*ZZ child will follow a similar course is increased (47) (Table 6).

Regarding liver disease in Z heterozygotes, although transiently elevated serum transaminases have been described in a small minority of PI\*MZ newborns, clinically significant health problems in PI\*MZ heterozygous individuals do not appear to develop in childhood. Therefore, in children, a PI\*MZ type should not be regarded as sufficient explanation for unexplained liver disease (15, 43, 46, 47). The PI\*SZ type has, in some case reports, been associated with pediatric liver disease identical to PI\*ZZ disease, although other large series have failed to show this association, making conclusions about causality unclear (38, 43, 47, 52).

*Risk of liver disease in PI\*ZZ adults.* Reports in the 1970s (Table 7) (17–19, 45, 53–61) established a link between AAT deficiency in adults and cirrhosis. Characteristic findings were a predominance of elderly nonalcoholic and hepatitis B-negative males with cirrhosis, portal hypertension, and PLC whose prognosis was gloomy, but the strength of association between AAT deficiency and cirrhosis remained obscure.

In an analysis of a nationwide Swedish cohort ascertained through hospital admissions, Larsson (45) found evidence of cirrhosis in only 2% of 104 PI\*ZZ homozygotes between 20 and

50 years of age, but in 19% of 142 patients over 50 years of age. The importance of age as a determinant of risk for CLD in adults was also emphasized in a Canadian study (53), where the risk for cirrhosis was estimated at 15% in males between 50 and 60 years of age. A similar predominance of elderly males was noted in one U.S. study (19) and in a retrospective analysis of 94 Swedish postmortem cases ascertained nationwide (54). In the latter study, cirrhosis was present in 37% and PLC as present in 15%. Among the patients with cirrhosis, the mean age at death was 66 years compared with 54 years for the noncirrhotic patients ( $p < 0.01$ ). Never-smokers survive longer and therefore have “more years” to develop cirrhosis. In a multiple-cause mortality analysis (55) of the Malmö series, this concept was strengthened; cirrhosis was the main cause of death in 12 of 17 never-smokers (mean age at death, 73 years) versus only 2 of 23 smokers ( $p < 0.01$ ) (mean age at death, only 56 years). Conversely, as expected, smokers died predominantly of emphysema. In a large nationwide U.S. multiple-cause mortality study (19) covering the interval 1979–1991 and including 413 PI\*Z cases (male-to-female ratio, 1.35), 1.2% of all deaths among children aged 1–14 years was ascribed to AAT deficiency. A mortality peak was also seen in deficient individuals aged 65–84 years, but deficiency was reported in fewer than 0.1% of persons who died of hepatic disease in this age group.

Reports on diagnostic testing for AAT deficiency in consecutive CLD patients seen at referral centers permit calculation of an estimate of the strength of association between homozygosity and CLD (see Table 8) (12, 20, 21, 62–69). Overall, the observed prevalence of PI\*ZZ homozygotes among series of patients with CLD is 20-fold higher than would be expected from the population prevalence of PI\*ZZ individuals. Specifically, in the series presented by Fisher and coworkers (62)  $5/469 \times 100 = 1\%$  were homozygotes; in the Carlson and Eriksson series (64) the

**TABLE 5. CLINICAL FEATURES SUGGESTING PI\*ZZ ALPHA-1 ANTITRYPSIN DEFICIENCY IN CHILDHOOD**

| Clinical Feature  | Grade of Evidence |
|---|-------------------|
| Infant with increased level of transaminase and/or bilirubin    | II-2              |
| Infant with neonatal hepatitis syndrome                         | II-2              |
| Child or adolescent with hepatomegaly and/or hepatosplenomegaly | II-2              |
| Infant with failure to thrive                                   | II-2              |
| Infant with vitamin K-deficient coagulopathy                    | II-2              |
| Child or adolescent with symptoms of chronic liver disease      | II-2              |
| First-degree relative of PI*ZZ individual                       | II-2              |

**TABLE 6. FACTORS INDICATING POTENTIALLY MORE SEVERE PROGNOSIS IN PI\*ZZ CHILDHOOD LIVER DISEASE**

| Risk Factor   | Grade of Evidence |
|---|-------------------|
| PI*ZZ relative with liver disease                         | II-2              |
| Neonatal cholestasis                                      | II-2              |
| Male sex  | II-2              |
| Persistent hyperbilirubinemia                             | II-2              |
| Hard hepatomegaly   | II-2              |
| Early splenomegaly  | II-2              |
| Prolonged prothrombin time                                | II-2              |
| Persistently elevated $\gamma$ -glutamyltransferase level | II-2              |

TABLE 7. LIVER DISEASE IN ADULT PI\*ZZ HOMOZYGOTES (INCLUDING CASE SERIES WITH MORE THAN EIGHT SUBJECTS)

| First Author, Country, Year of Publication (Ref.) | No. of PI*ZZ Cases; M/F Ratio | Mean Age; Range (yr) | Type of Study   | Main Findings   | Clinical and Laboratory Features   | Comments   |
|---|-------------------------------|----------------------|---|---|--|--|
| Berg, Sweden, 1972 (56)                           | 13; –                         | 59; –                | Hospital-based autopsy series   | 5 adults (> 50 yr) had cirrhosis, 3 PLC, majority had E   | Cirrhosis and PLC only in patients > 50 yr of age  | Liver disease and E linked to the same genetic defect  |
| Eriksson, Sweden, 1975 (54)                       | 9; 6/3                        | 62; 50–83            | Hospital-based autopsy series   | All > 50 years of age; cirrhosis in all; PLC in 6/9   | Portal hypertension and E in majority; alcohol, HB,Ag, and autoimmune markers absent; no neonatal hepatitis      | 7/9 cases identified during 10 yr in a population of 240,000; poor prognosis after diagnosis |
| Triger, UK, 1976 (57)                             | 9; 4/5                        | 41; 16–73            | Hospital-based referrals  | Macronodular cirrhosis in majority  | Nonspecific LFT abnormalities; HB,Ag, alcohol, and autoimmune markers absent                                     | Variable course; mean age relatively low; only 1 PLC   |
| Larsson, Sweden, 1978 (45)                        | 246; 141/105                  | > 20; –              | Hospital-based referrals; Sweden, 1963–1977                             | Cirrhosis in 2% but in 19% above 50 yr of age; PLC in 25% of cirrhotic cases  | Alcoholism in 3/32 cirrhotics; neonatal hepatitis in only 1 cirrhotic case                                       |  |
| Cox, Canada, 1983 (53)                            | 112; –                        | 47; 20–76            | Mixed ascertainment referral and screening cases                        | Cirrhosis in 3.5%; cirrhosis in 6.2% men 41–50 yr of age and in 15.4% of men 51–60 yr of age                                | Prealbumin level sensitive indicator of liver disease  | Risk of cirrhosis in men increases with age; ascertainment bias; few cases                   |
| Eriksson, Sweden, 1987 (58)                       | 94; 65/29                     | 58 (at death)        | Hospital-based referrals; autopsies, 1963–1982                          | Cirrhosis in 37% (27 males, 10 females); PLC in 15% (10 males, 4 females)   | Portal hypertension in majority; cirrhotics, mean age 65 yr, versus noncirrhotics, mean age 58 yr ( $p < 0.01$ ) | Bias with respect to sex; laboratory features nonspecific; slight ALP elevation              |
| Rakela, USA, 1987 (59)                            | 8; 7/1                        | 58;                  | Hospital-based referrals  | Cirrhosis in 8 homozygotes at age 58 yr; PLC in 2/8   | Portal hypertension; nonspecific laboratory findings; HB,Ag negative in 7  |  |
| Larsson, Sweden, 1977 (60)                        | 10; 5/5                       | 46; 24–66            | Random sample of hospital-based referrals; cross-sectional study of LFT |   | Normal transferases, $\gamma$ -GT, albumin, prealbumin, and quantitative LFT in all                              | Majority had normal lung function  |
| Von Schonfeld, Germany, 1996 (61)                 | 27; 17/10                     | 48; 30–72            | LFT in patients with emphysema  | LFT normal in 17; modest elevation of $\gamma$ -GT in 30% and of transferases in 19%; galactose elimination abnormal in 6/7 |  |  |
| Eriksson, Sweden, 1986 (17)                       | 17; 9/8                       | 64 (at death)        | Case-control study; autopsies in defined population, 1963–1982          | Relative risk: OR, 7.8 (CI, 2.4–24) and 20 (CI, 3.5–114) for cirrhosis and PLC, respectively                                | Majority have decompensated cirrhosis; HB,Ag negative  | 2/3 of expected cases medically recognized; risks significant only for males                 |
| Elzouki, Sweden, 1996 (18)                        | 30; 15/15                     | 65 (at death)        | Case-control study; autopsies in defined population, 1963–1994          | Relative risk: OR, 8.3 (CI, 3.8–18.3) and 5.0 (CI, 1.6–15.8) for cirrhosis and PLC, respectively                            | Alcoholism absent as well as viral markers (hepatitis B and C)   | Majority of expected PI*ZZ cases recognized; risks significant for both sexes                |
| Browne, USA, 1996 (19)                            | 413; 1.35*                    | —                    | Multiple-cause mortality, USA, 1979–1991                                | 1.2% of all deaths among children aged 1–14 yr ascribed to AAT deficiency   | Percentage of descendents with hepatic disease highest in 1–25 and 55–84 yr groups                               | Low detection rate; heterozygotes not excluded   |
| Eriksson, Sweden, 2000 (55)                       | 40; 19/21                     | 63 (at death)        | Multiple-cause mortality, City of Malmö, Sweden, 1962–1997              | Cirrhosis main cause of death in 12/17 never-smokers versus 2/23 smokers; age at death 73 versus 56 yr ( $p < 0.01$ )       | Emphysema main cause of death in ex-smokers  | High detection and autopsy rates (70 and 88%, respectively)                                  |

Definition of abbreviations: ALP = alkaline phosphatase; CI = confidence interval; E = emphysema;  $\gamma$ -GT =  $\gamma$ -glutamyltransferase; HB,Ag = hepatitis B surface antigen; LFT = liver function test; M/F = male/female; PLC = primary liver carcinoma.

\*Includes children.

estimate was  $4/861 \times 100 = 0.4\%$ ; in the series examined by Bell and coworkers (65) the estimate was  $3/365 \times 100 = 0.9\%$ ; in the Propst and coworkers series (12) the estimate was  $9/1,865 \times 100 = 0.5\%$ ; in the series presented by Eigenbrodt and coworkers (67) the estimate was  $3/683 \times 100 = 0.4\%$ , in Czaja's series (69) the estimate was 0%; and in the Graziadei and coworkers series (68) the estimate was  $14/599 \times 100 = 2.3\%$ . Taking all these seven series together, the mean prevalence of PI\*ZZ homozygotes (0.8%) is 20-fold higher than the population prevalence of PI\*ZZ homozygotes, estimated at 1/2,500 or 0.04%, suggesting that the homozygous state confers a 20 times higher risk of CLD.

Results from repeated autopsy-based case-control studies from Malmö, Sweden provide evidence for an increased propensity of adult homozygous AAT-deficient individuals to develop cirrhosis or PLC and, in addition, allow an estimate of relative

risks. The latest case-control study from 1996 (18) comprised 31 adult homozygous patients (3 adults with incomplete autopsies and 1 child with cirrhosis were excluded), who were compared with 124 birth date- and sex-identical control subjects from the same autopsy register. Mean age at death was 64 years in the PI\*ZZ group and 67 years ( $p = \text{NS}$ ) in the non-PI\*ZZ control group. The relative risks of cirrhosis and PLC, estimated in terms of odds ratios ( $\text{OR}_{\text{mh}}$ ) with the Mantel-Haenszel procedure for matched case-control studies with four control subjects per case, were 8.3 (95% CI, 3.8–18.3) and 5.0 (95% 1.6–15.8), respectively. A total of 43% of the cases in this series developed cirrhosis and 28% developed PLC. The cirrhotic homozygotes (18) all lacked hepatitis B virus markers and anti-hepatitis C virus (HCV) antibodies were absent in all sera (the majority) that were tested. Autoimmune markers were absent in accordance

**TABLE 8. RISK OF CHRONIC LIVER DISEASE IN ADULT PI\*Z HETEROZYGOTES**

| First Author, Country, Year of Publication (Ref.)                                | Study Population; Control Subjects   | Random Sampling                               | Type of Study                              | PI*ZZ Identification   | Main Findings   | Significant RR (95% CI)    | Significance of Association with Subgroup* |             |         | Comments  |
|--|--|---|--|--|---|----------------------------|--|-------------|---------|---|
|  |  |   |  |  |   |                            | Crypto-genic                               | Auto-immune | Viral   |   |
| <b>A. Population based-Autopsy Studies</b>                                       |  |   |  |  |   |                            |  |             |         |   |
| Eriksson, Sweden, 1975 (20)  | 700 consecutive necropsies, 1973   | Yes   | Case series compares PAS-D (pos/neg)       | PAS-D  | 26 cases (3.7%) PAS-D positive; 3/26 cirrhosis and 3 fibrosis versus 2/674 PAS-D negative                               | p < 0.002                  | -  | -           | -       | Small but population representative study, PAS-D stain underestimates PI*Z heterozygotes and is not 100% specific |
| Blenkinsopp, UK, 1977 (21)   | 4,895 consecutive necropsies, 1961-1975; 64 cases of cirrhosis versus 110 control subjects | Selects cirrhosis                             | Case series compares PAS-D (pos/neg)       | PAS-D plus immuno-histochemical staining                                       | 10/64 (15.6%) cirrhotics PAS-D positive versus 4/110 (3.6%) control subjects  | 4.30 (1.29-14.34)          | -  | -           | -       | PAS-D plus immuno-histochemical staining not 100% specific  |
| <b>B. Case Studies (n &gt; 300) of Chronic Liver Disease at Referral Centers</b> |  |   |  |  |   |                            |  |             |         |   |
| Fisher, UK, 1976 (62)  | 469 CLD; 98 control subjects (hospital personnel)  | Consecutive cases during 6 mo                 | Case series                                | PI typing (starch gel electrophoresis) in those with subnormal AAT levels only | 4.7% abnormal phenotypes in CLD versus 6.1% in control subjects   | NS                         | -  | -           | -       | Series underestimation of PI*Z; children not excluded   |
| Hodges, UK, 1981 (63)  | 1,055; control subjects (general population), 3%   | Selects PAS-D-positive cases                  | Prospective liver biopsy series, 1975-1979 | PAS-D plus immunohistochemical staining; IEF in PAS-D-positive cases           | 23 (2.4%) PAS-D positive; 17 (9.2%) of 195 cirrhosis are MZ; 8 (24%) of 34 CAH are MZ; 8 (24%) of 28 cryptogenic are MZ | NS; 3.1 (1.60-4.50)        | +  | -           | - (HBV) | PAS-D and immuno-histochemical staining underestimates PI*Z; M/F ratio not given; PI*ZZ not given                 |
| Carlson, Sweden, 1985 (64)   | 861; control subjects (general population), 4.8%   | Consecutive cases during 5 yr                 | Case series compares PI*Z (pos/neg)        | PI*Z heterozygotes by PI*Z spec.; monoclonal, IEF                              | 64 (7.6%) are PI*Z heterozygotes; 14/64 (21.8%) PI*Z-heterozygotes are cryptogenic versus 3/128 (2.3%)                  | 1.58 (1.21-1.95)           | +  | -           | - (HBV) | Only 50% of PI*Z heterozygotes have subnormal AAT levels; M/F ratio = 2.03; 4 (0.4%) PI*ZZ                        |
| Bell, Norway, 1990 (65)  | 365; control subjects (blood donors), 2.9%   | Consecutive cases, 1978-1988                  | Case series                                | IEF  | 11 (3.3%) are PI*Z heterozygotes; 2/18 cryptogenic cases are MZ   | 1.13 (0.52-2.28)           | -  | -           | - (HBV) | M/F ratio not given; 3 (0.9%) PI*ZZ   |
| Propst, Austria, 1992 (12)   | 1,865; control subjects (general population), 3.2%   | Consecutive cases, 1987-1990                  | Case series compares MZ with/without LD    | IEF  | 155 (8.3%) PI*Z heterozygotes; of 51 cirrhotics, 62% HCV- and 33% HBV-positive  | 2.87 (1.56-4.19)           | -  | -           | +       | In PI*Z heterozygotes without LD none had PI*ZZ; M/F ratio = 1.56; 9 (0.5%) PI*ZZ                                 |
| Elzouki, Sweden, 1997 (66)   | 709; control subjects (general population), 4.8%   | Consecutive cases                             | Case series, liver biopsy                  | PI*Z heterozygotes by monoclonal antibody, IEF                                 | 44 (6.2%) PI*Z heterozygotes  | 1.29 (0.92-1.66), p < 0.05 | ND   | ND          | ND      | M/F ratio = 2.66  |
| Eigenbrodt, US, 1997 (67)  | 683 OLT candidates; control subjects (general population), 2.8%                            | Consecutive cases, 1990-1996; Caucasians only | Case series                                | IEF  | 53 (7.8%) PI*Z heterozygotes  | 3.1 (1.9-5.0)              | +  | +           | +       | OR for being PI*Z: heterozygote, 4.0 (95% CI, 1.0-3.7) for women; 3 (0.5%) PI*ZZ                                  |
| Graziadei, USA, 1998 (68)  | 599 OLT candidates; control subjects (general population), 3%                              | Consecutive cases, 1985-1996; Caucasians only | Case series                                | IEF  | 49 (8.2%) PI*Z heterozygotes  | 2.7 (2.0-3.56)             | +  | -           | -       | M/F ratio = 1.33; 14 (2.2%) PI*ZZ   |
| Czaja, USA, 1998 (69)  | 484; control subjects (general population), 3.6%   | Consecutive cases; Caucasians only            | Case series                                | IEF  | 155 (8.3%) PI*Z heterozygotes   | 1.72 (1.16-2.28)           | +  | -           | -       | None had PI*ZZ  |

Definition of abbreviations: AAT = alpha-1 antitrypsin; CAH = chronic active hepatitis; CI = confidence interval; CLD = chronic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; IEF = immunoelectrophoresis staining; LD = liver disease; M/F = male/female; ND = not determined; NS = not significant; OLT = orthotopic liver transplantation; OR = odds ratio; PAS-D = periodic acid-Schiff diastase; pos/neg = positive/negative; RR = risk ratio.

\* + = present; - = absent.

with other studies. Alcoholism was not a major contributing factor to the development of cirrhosis in any patient.

At present, the repeated Swedish case-control studies, although small (Table 7), provide the best available epidemiologic evidence for an increased risk of developing end-stage AAT-related liver disease in adults. These case-control studies cover a long time interval (from 1963 to 2000) and a population of 250,000, served by one university hospital and one department of pathology where standardized autopsies have been performed on a majority of the deceased residents. As of 1997 (35-year study period), 40 residential PI\*ZZ patients had been identified (no referrals from outside the city of Malmö were included). This means that, considering the established homozygote frequency of 1/1,666 in Sweden, approximately two-thirds of the expected deficient individuals have been medically identified before death. This figure, as well as a male-to-female ratio close to 1, strongly argues against any important ascertainment bias. The risk of cirrhosis in individuals more than 50 years of age is considerable, and is particularly high in never-smoking individuals, who will not develop severe smoking-related emphysema, and therefore will survive longer (reference 55 in Table 7). There is, however, a lack of consistent data from other geographic areas.

In the U.S. multiple-cause mortality study, although a mortality peak was seen in AAT-deficient individuals aged 55–84 years, AAT deficiency was seen in fewer than 0.1% of persons who died of hepatic disease in this age group (reference 19 in Table 7). The discrepancy with other reports may be ascribed to underreporting of AAT deficiency. Furthermore, heterozygotes were not excluded from the analysis.

In conclusion, AAT deficiency-related cirrhosis in adults is a complication of older persons, predominantly occurring in those AAT-deficient individuals who have never smoked, and who have therefore survived without developing severe emphysema. Cirrhosis in AAT deficiency may become clinically apparent at any age, but the peak incidence is to be expected in the elderly never-smoker. Aside from low plasma AAT levels, laboratory and other clinical features are indistinguishable from those of decompensated cirrhosis of any etiology. Prognosis is generally grave, with a mean survival of 2 years after diagnosis. Emphysema was present in most ex-smokers and occasionally in never-smokers. In the Swedish series all cases of PLC appeared in cirrhotic livers, but PLC can also occur in the absence of cirrhosis (reference 83 in Table 10).

*Risk of liver disease in adult PI\*Z heterozygotes.* At present, there is no population study that explores the risk of liver disease in an adult individual patient with heterozygous AAT deficiency. Table 8, which is based on an aggregate of more than 14,000 patients, offers an overview of the main published studies concerning liver disease in heterozygotes. It also provides information about coexisting risk factors presented as subcategories of CLD. The risk of developing CLD in heterozygotes in case series of more than 300 patients is shown as OR and 95% CI. Because of the heterogeneity of the published data, an overall calculation of a common OR is impossible. In most of the more recent studies, the OR ranges from 1.8 to 3.1. The conclusions of these studies differ in their interpretation of whether heterozygous AAT deficiency is sufficient for the development of CLD or whether additional risk factors are important. In most reports of CLD in heterozygotes, there is an excess of males over females.

Early studies (20, 21) of autopsy materials suggested an increased risk for developing liver disease in heterozygotes. Although access to larger liver specimens from autopsy material increases the sensitivity of PAS-D stain as a surrogate marker of the PI\*Z allele, 100% sensitivity or specificity will not be reached (*see below*). These studies, therefore, offer relatively

weak evidence in favor of an association between PI\*Z heterozygosity and CLD. A similar weakness affects the 1981 study performed by Hodges and coworkers (63). Here, the presence of PAS-D inclusions is used as a first step in recognizing the MZ phenotype. This procedure, applied to ordinary liver biopsies, will result in an about 20% underestimation of the PI\*Z allele according to data provided by Clausen and coworkers (70). The study by Fisher and coworkers from 1976 (62), is invalidated by the biased selection of sera with subnormal AAT levels alone for heterozygosity, resulting in an underestimate of about 50%, as clearly shown in the 1985 report by Carlson and Eriksson (64).

Despite underestimating the MZ phenotype in the study by Hodges and coworkers (63), it was the first to find a higher risk of developing cryptogenic liver cirrhosis and hepatitis B-negative cirrhosis with features of chronic active hepatitis (*see* Table 8). The distribution of patients with the MZ phenotype was 20.5% in non-B chronic active hepatitis and 21% in cryptogenic cirrhosis compared with only 3.5% in alcoholic cirrhosis and 2.6% in other kinds of cirrhosis. An overrepresentation of cryptogenic CLD was also reported in the study by Carlson and Eriksson (64). The high prevalence of “cryptogenic” disease in these two studies, published before hepatitis C tests became available, cannot entirely be ascribed to such an infection. Most of the more recent studies support the finding of an excess of cryptogenic cases among PI\*Z heterozygotes (Table 8).

In only one of the studies cited in Table 8 (67) was alcohol abuse suggested as a significant additional risk factor for end-stage CLD in PI\*Z heterozygotes, although earlier, small studies by French and Canadian investigators had also suggested such an association. Morin and coworkers (71) could not find an excess of the MZ phenotype, determined by isoelectric focusing (IEF), in 132 patients with alcoholic cirrhosis, nor could Roberts and coworkers (72) in a series of liver biopsies from 155 alcoholics diagnosed by PAS-D inclusions.

None of the reports in Table 8 supports an association between autoimmune CLD and the PI\*Z heterozygote, in agreement with the 1976 report from Kueppers and coworkers (73), which included both chronic active hepatitis and primary biliary cirrhosis.

Most studies (Table 8) have excluded hepatitis B infection as an additive risk factor. In contrast, controversial data have been presented regarding the role of hepatitis C virus infection in the development of liver disease in heterozygotes. A high prevalence of hepatitis C virus infection was found in a series of 164 patients (128 heterozygotes) with evidence of CLD; none of the heterozygotes without liver disease had hepatitis C virus infection (12). A smaller study could not confirm this high prevalence of hepatitis C virus infection in heterozygotes with liver disease (66). A French case-control study (74) compared the MZ prevalence in hepatitis C virus-infected patients with and without cirrhosis (84 versus 484, respectively); the MZ prevalence was identical, 2%, in each group.

In another study, the prognosis and life expectancy of 160 patients with AAT deficiency was investigated (75). After a follow-up of 15 years, the estimated life table analysis of mortality was retrospectively calculated. Life expectancy for patients with AAT deficiency and CLD was significantly lower than for patients with AAT deficiency without CLD. No difference in life expectancy for AAT-deficient individuals without liver disease was found in comparison with that of the normal population; 78% of 54 patients with chronic liver disease showed viral markers positive for additional viral infection.

The lack of prospective population-based studies is an obvious limitation of an attempt to estimate the propensity of heterozygotes to develop CLD. Another weakness is the use of PAS-D

inclusions as a surrogate marker of the PI\*Z allele in early reports (*see below*). This approach will result in modest underestimation of the true prevalence of heterozygotes, and also inclusion of some "false positives" (some of them, however, are probably M-like variants). Inclusions cannot replace IEF as the gold standard for diagnosis of PI\*Z heterozygosity but provides a rough estimate of its prevalence. False positives can be avoided by use of Z-specific monoclonal antibodies (76).

The retrospective analysis of heterozygotes in cohorts with CLD seen at referral centers (Table 8) is also open to criticism, but referral bias as an explanation of the results is probably negligible. Referring physicians are often unaware of the patient's heterozygosity for several reasons. The plasma AAT levels in heterozygotes with CLD are often normal or only slightly subnormal (64, 66, 68) and phenotyping is not a routine screening test. Liver transplantation centers (43) capture virtually all patients with liver failure who are reasonable candidates for transplantation, regardless of etiology. Consequently, the findings in the reports summarized in Table 8 provide evidence for an increased risk of developing cirrhosis (or end-stage CLD) in PI\*Z heterozygotes. However, the risk appears small, perhaps 3% compared with 30% or more in elderly homozygotes. A rough estimate of the strength of the association between the heterozygous state per se and the risk of end-stage CLD can also be obtained from the liver transplant series (Table 8) (68). At the Mayo Clinic, 14 homozygotes were transplanted over 10 years. The heterozygote prevalence in the referral population was 3%. Because heterozygotes are 120 times more prevalent than homozygotes, the homozygote prevalence in the referral population is calculated as  $1/4,000$ . Had the risk of end-stage CLD been identical in hetero- and homozygotes,  $14 \times 120$  or 1,680 heterozygotes would have been expected to be referred. The actual figure was 50. Hence, the relative risk for end-stage CLD in heterozygotes was  $50/1,680 \times 100 = 3\%$  or one-tenth, 10%, of the risk in homozygotes, that is estimated at 30%. When additional risk factors (alcohol and chronic viral infections) were present (67), this figure increased to 17%.

*Role of additional risk factors for liver disease in AAT deficiency.* In all reports (Tables 7 and 8) in which sex ratios are presented, there is an excess of males with AAT-related CLD. This is true both for homo- and heterozygotes, except in the case-control series. In these studies, the sex ratio is close to 1, as expected in a population-based study. A high male-to-female ratio cannot be explained solely on the basis of a diagnostic bias by clinicians because male predominance in the context of abnormal liver function tests is seen already in the neonatal period. Elevated serum transaminase levels in homozygous children, with a male-to-female ratio of 2:1, suggests male sex to be a contributory factor (16) in the development of CLD in AAT deficiency.

The possession of a second genetic trait, which is prevalent in the population, could interact, additively or synergistically, with the Z allele and promote development of CLD in AAT deficiency. Several case reports describe the concomitant occurrence of AAT deficiency and genetic hemochromatosis, a common metabolic disorder. In one series (77), 3 (4.5%) of 67 consecutive patients with hemochromatosis were found to be PI\*Z homozygotes, but the prevalence of PI\*Z heterozygotes was not increased. Only one report, by Rabinovitz and coworkers (78), found an association between heterozygous AAT deficiency and genetic hemochromatosis. No association was seen by others (79–81).

Other, hitherto unidentified genetic traits may contribute to the development of liver injury in a subpopulation of AAT-deficient children and adults. Using transduced skin fibroblasts, Wu and coworkers (8) showed a selective lag in degradation of

**TABLE 9. SUMMARY OF STUDIES EXAMINING RISK FACTORS FOR CHRONIC LIVER DISEASE IN ADULTS WITH ALPHA-1 ANTITRYPSIN DEFICIENCY**

| Risk Factor          | Phenotype and Level of Evidence |           | Comments         |
|----------------------|---------------------------------|-----------|------------------|
|                      | PI*ZZ                           | PI*MZ, SZ |                  |
| Male sex             | II-2                            | II-3      |                  |
| Neonatal hepatitis   | 0                               | 0         |                  |
| Other genetic traits | II-3                            | 0         | Hemochromatosis* |
| HAV                  | No data                         | No data   |                  |
| HBV                  | 0                               | II-3      |                  |
| HCV                  | 0                               | II-2      |                  |
| Alcohol              | 0                               | II-3      |                  |
| Autoimmune disease   | 0                               | 0         |                  |
| Occupational         | No data                         | No data   |                  |

*Definition of abbreviations:* HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus.

\* See text.

mutant Z-AAT from three unrelated PI\*ZZ individuals with CLD. These data provide evidence that other genetic traits that affect the fate of the abnormal Z molecule may, at least in part, determine susceptibility to CLD.

There are obvious difficulties in retrospective studies in excluding the possibility that subtle exogenous factors such as moderate alcohol consumption or occupational exposure might be important in promoting the slow development of cirrhosis in men. However, as summarized in Table 7, published data do not support alcohol abuse as an important cofactor in at least homozygotes. Only 3 of 32 patients with cirrhosis in Larsson's study (reference 45 in Table 7) were alcoholics, and alcoholism was virtually absent from the Swedish case-control studies (Table 7). Concerning heterozygotes (Table 8), only one of seven studies (67) identified alcohol as a cofactor. In the report by Carlson and Eriksson (64), with its excess of males over females, the number of alcoholics was less than expected.

There is no evidence that hepatitis B or C infection plays any role in the development of CLD in homozygous AAT deficiency, either in children or in adults, although data on hepatitis C are relatively sparse (reference 18 in Table 7). However, there is increasing evidence (references 12 and 67 in Table 8) that in heterozygotes, CLD will develop only when another factor such as a virus or a toxic injury serves as a trigger and promoter for the process. A surprisingly high prevalence of seropositivity for HCV (62–75%) was found in the series presented by Propst and coworkers (12). It has been suggested (82) that an HCV infection could unmask a heterozygous deficiency by constantly stimulating the hepatocytes to produce mutant AAT that accumulates in the ER, and by competing with molecular chaperones necessary for the posttranslational processing of AAT.

In conclusion, as summarized in Table 9, there are no known factors, endogenous or exogenous, other than male sex, that have been identified as risk factors for development of CLD in adults or children with homozygous AAT deficiency. There is emerging evidence that cofactors such as viruses, particularly HCV, and toxic injuries as from alcohol, are necessary to promote CLD in heterozygotes.

*Risk of primary liver cancer in AAT deficiency.* The association of cirrhosis and primary liver cancer (PLC) in adult PI\*ZZ persons was first observed in the early 1970s (*see references 54 and 56 in Table 7*). In Larsson's study (45), 8 of 29 (28%) patients with cirrhosis had PLC, verified at necropsy. In Eriksson's study from 1987 (58) comprising 94 Swedish autopsied ZZ adults, cirrhosis was seen in 37 (39%). Primary liver cancer was present

**TABLE 10. FREQUENCY OF PI\*Z HETEROZYGOTES AMONG PATIENTS WITH PRIMARY LIVER CANCER\***

| First Author, Year, Country (Ref.) | PLC (n) | Method       | Percent PI*Z Heterozygotes <sup>†</sup> | Significant Association (+/-) |
|------------------------------------|---------|--------------|---|-------------------------------|
| Berg, 1972, Sweden (56)            | 78      | PAS-D        | 8.9 (4.7)                               | +                             |
| Palmer, 1976, USA (86)             | 21      | PAS-D + imm. | 23.8 (3.0)                              | +                             |
| Blenkinsopp, 1977, UK (21)         | 15      | PAS-D + imm. | 26.6 (3.6)                              | +                             |
| Reintoft, 1979, Denmark (87)       | 56      | PAS-D + imm. | 17.8 (4.7)                              | +                             |
| Kelly, 1979, UK (88)               | 42      | PAS-D + imm. | 4.2 (1.0)                               | -                             |
| Fargion, 1996, Italy (89)          | 47      | IEF          | 6.4 (2.0)                               | +                             |
| Cohen, 1982, South Africa (90)     | 58      | IEF          | 0 (0)                                   | -                             |
| Govindarajan, 1981, USA (91)       | 124     | IEF          | 4.0 (2.9)                               | -                             |
| Vergalla, 1983, South Africa (92)  | 80      | IEF          | 5.0 (1.9)                               | -                             |
| Sparos, 1984, Greece (93)          | 80      | IEF          | 0 (1.3)                                 | -                             |
| Rabinovitz, 1992, USA (94)         | 59      | IEF          | 1.7 (1.6)                               | -                             |
| Zhou, 1998, Germany (83)           | 164     | PI*Z - imm.  | 7.9 (2.4)                               | +                             |

Definition of abbreviations: IEF = isoelectric focusing; imm. = immunohistochemical staining; PAS-D = periodic acid-Schiff positive after diastase digestion; PLC = primary liver cancer.

\*Case series with 15 or more subjects.

<sup>†</sup> Figures within parentheses indicate frequencies in control subjects.

in 14 of these (38%, 10 males and 4 females). In the series studied by Rakela and coworkers (59), PLC was seen in two of eight PI\*ZZ adults (25%) with cirrhosis (seven men and one woman). Numerous case reports support the putative association between PI\*ZZ and PLC. In a majority, PLC has appeared in cirrhotic livers but its appearance in noncirrhotic liver has been reported (83). Dysplasia, cirrhosis, and PLC have been described in PI\*M<sub>malton</sub> (84). Histologically, most cases of PI\*ZZ-associated primary liver cancer have been described as hepatocellular, but cases of cholangiocellular carcinoma have been reported, even appearing in PI\*ZZ siblings (85).

The results from the Swedish autopsy-based case-control studies are shown in Table 7. Two studies (17, 18) provide evidence for an association between homozygous PI\*Z deficiency and PLC. The relative risk (odds ratio) of PLC in these reports was 20 (95% CI, 3.5-114) and 5.0 (95% CI, 1.6-15.8), respectively; the absolute risk of developing PLC in cirrhosis was 29 and 28%, respectively. This frequency is in agreement with other case series (see references 58-60 in Table 7). The increased risk of PLC was significant only for male homozygotes and there was no evidence that additive factors such as alcoholism or chronic viral hepatitis were important in the Swedish series (18). Consistent epidemiologic reports from other geographic areas are lacking. Reports on the prevalence of PLC in heterozygotes are summarized in Table 10 (21, 56, 83, 86-94).

Most early studies using PAS-D inclusions and immunohistochemical staining have probably overestimated the Z allele frequency in PLC, probably as a result of nongenetic, nonspecific retention of AAT in these cases. The majority of reports based on IEF cannot verify an association but, in general, case series are small. Males predominate in most of them. Some study samples (90, 93) are confounded by chronic hepatitis B virus-infected cases. A German study (83) identifying hepatic Z inclusions by a monoclonal Z-specific antibody found a high prevalence of heterozygotes in a consecutive series of 164 cases of liver cell carcinoma. In all 13 presumed PI\*Z cases, the carcinoma had developed in the noncirrhotic livers of elderly people (mean age, 63 years) lacking viral markers. In contrast, Propst and coworkers (95) studied the prevalence of PLC in 60 heterozygotes with established cirrhosis (male-to-female ratio, 37:24; mean age, 61 years). The risk of developing PLC was increased to the same extent as in other causes of cirrhosis and was considered to be due to the chronic liver disease and not the metabolic error itself. In this series, the prevalence of chronic hepatitis B

and C infection was 21 and 15%, respectively. Primary liver cancer occurred in 6 of 64 Swedish heterozygotes (10%) compared with 13 of 793 non-PI\*Z patients ( $p < 0.001$ ). Hepatitis B was absent in this series. Hepatitis C was not analyzed (64).

In conclusion, it appears that although the risk of PLC is relatively high in homozygotes with cirrhosis, the risk in heterozygotes is small. These findings were confirmed and extended in a larger study (96).

*Risk of liver disease in non-PI\*Z deficiency states.* Case reports describe the association of the rare phenotypes (PI\*M<sub>malton</sub>, M<sub>duarte</sub>) with hepatic fibrosis, cirrhosis, dysplasia, and hepatocellular cancer (84). These variants have a marked propensity for polymerization and formation of PAS-D-positive inclusions. The M-like alleles are 100 to 200 times rarer than the PI\*Z allele, which explains the absence of epidemiologic data for estimation of risk of developing CLD. No reports on liver disease in the S<sub>hiyama</sub> variant have been published.

The PI\*S variant is frequent in southern European populations. Although its polymerization propensity is relatively weak, it may occasionally be associated with PAS-D inclusions (97). In the Italian neonatal screening study (14), 456 PI\*MS children, of whom 135 could be evaluated with liver function tests, were identified. An apparently self-limiting hepatic dysfunction, comparable to that seen in PI\*MZ children, was observed: 15% of PI\*MS carriers had abnormal test results at 2 months of age, 7.4% at 5 months of age, and there were none at 12 months of age.

Three adult reports (Table 8) include data on PI\*S individuals. In only one of them (67) was PI\*MS overrepresented (OR, 2.1; 95% CI, 1.4-3.3); no significant difference from the background population was found in the two others (68, 69).

In conclusion, the evidence that the PI\*S variant predisposes to liver disease appears weak. The relative risk in M-like phenotypes and severe deficiency is unknown, but is probably similar to that of PI\*ZZ.

*Diagnosis and management.* As summarized in Table 11, CLD and cirrhosis in AAT deficiency may occur at any age; the peak incidence occurs in the elderly never-smoker. Signs and symptoms do not differ from other causes of liver disease except in homozygotes, who may develop clinically overt lung disease at the same time or before manifestation of chronic liver disease.

The diagnosis of homozygous PI\*ZZ AAT deficiency is made by identifying the phenotype of the AAT protein present in a patient's serum by isoelectric focusing. The result is sometimes

**TABLE 11. RELATIVE RISK\* OF CIRRHOSIS DEVELOPMENT IN VARIOUS AGE GROUPS WITH SEVERE (PI\*ZZ AND RARE VARIANTS) AND INTERMEDIATE (PI\*MZ, PI\*SZ) ALPHA-1 ANTITRYPSIN DEFICIENCY, AND ESTIMATED GRADE OF EVIDENCE**

| Age Group (yr)    | Severe AAT Deficiency |                   | Intermediate AAT Deficiency |                   |
|-------------------|-----------------------|-------------------|-----------------------------|-------------------|
|                   | Percent               | Grade of Evidence | Percent                     | Grade of Evidence |
| < 18              | 3                     | I                 | 0                           | II                |
| Between 18 and 50 | 2–5                   | III               | 2–5                         | III               |
| > 50              | 20–40 <sup>†</sup>    | II                | —                           | III               |

\* Percent.

<sup>†</sup> Mainly never-smokers.

confirmed by other electrophoretic methods or by phenotyping of family members. Determination of the level of total AAT protein present in a patient's serum should not be used as the sole basis for establishing the diagnosis. In heterozygotes, plasma levels are often normal and they may transiently increase even in PI\*ZZ patients during periods of systemic inflammation. The AAT level may provide useful supplemental information. However, especially in cases of compound heterozygotes, or in detecting carriers of M allelic variants such as M<sub>duarte</sub> (98), family studies are useful. DNA testing is used in prenatal diagnosis (chorionic villi biopsies). Diagnosis can also be performed on genomic DNA extracted from circulating mononuclear blood cells.

The diagnosis of AAT deficiency-associated chronic liver disease is made by clinical and laboratory examinations, including AAT phenotyping and abdominal ultrasound examination. Liver biopsy is not necessary to establish the diagnosis, as phenotyping is accepted as the gold standard in diagnosis of AAT deficiency. As in CLD of any cause, biopsy may be useful for staging severity. The validity of PAS-D inclusions in liver biopsy specimens as surrogate markers of the PI\*Z allele is discussed below. Other causes of chronic liver disease (e.g., viral infection, hemochromatosis, Wilson's disease, alcoholic and autoimmune liver disease) should be ruled out by laboratory examinations. In doubtful cases (e.g., coexistence of two or more risk factors for liver disease), biopsy may also be required. Treatment recommendations are summarized in Table 12.

*Follow-up.* Considering the high incidence of CLD in the elderly, we recommend regular checks of this group with simple liver function tests. Checks should be undertaken in both asymptomatic AAT-deficient individuals and in those with extrahepatic disease (lung, etc.) alone, whereas in this group, vaccinations against viral hepatitis are not indicated. In contrast, vaccination is recommended in children and adults with AAT deficiency and overt CLD. These patients should be monitored regularly by clinical, laboratory, and ultrasound examination. One-third of elderly patients with homozygous AAT deficiency die from complications of portal hypertension and PLC. Patients with cirrhosis are at the same risk for the development of PLC as is true for other causes of cirrhosis (e.g., chronic viral hepatitis). In these

patients, screening for PLC by computed tomography scan is recommended, because of the low sensitivity and specificity of serum  $\alpha$ -fetoprotein measurement.

Regarding the poorer prognosis of CLD patients with AAT deficiency and hepatitis B or C virus coinfection compared with patients without hepatitis viral coinfection, vaccination against hepatitis A and B is recommended by the World Health Organization. Although there is no evidence that alcohol consumption accelerates the progression of liver disease in patients with AAT deficiency, alcohol consumption should be kept below 60 g/day. In patients with overt CLD, cessation of alcohol intake is necessary. There are no data presenting any occupational risk factors for developing CLD for patients with AAT deficiency.

Liver transplantation is indicated for patients with end-stage CLD. Criteria for transplantation do not differ from other causes of CLD.

*Remarks on the accuracy of diagnosis of AAT deficiency: isoelectric focusing versus hepatocytic PAS-D inclusions.* The term AAT deficiency usually refers, when not otherwise stated, to classic PI\*ZZ AAT deficiency. The gold standard for diagnosis of phenotype in AAT deficiency is isoelectric focusing of sera in polyacrylamide gels (IEF), using a narrow pH gradient. In some older studies, the diagnosis is based on starch-gel or crossed immunoelectrophoresis; these provide identical information about PI type. Some early studies, included in the review, used PAS-D inclusions as a surrogate marker of the PI\*Z allele.

The finding of periodic acid-Schiff-positive inclusions after diastase digestion (PAS-D) in periportal hepatocytes is a characteristic finding in homozygous PI\*ZZ AAT deficiency (2). The presence of such inclusions, the result of entangled polymer formation or mutant Z AAT (9), was used as a marker of Z allele-associated AAT deficiency in early reports (Table 8). However, it gradually became apparent that these inclusions are neither 100% sensitive nor specific as surrogate markers of the Z allele. Although almost invariably seen in homozygous deficiency, they are less abundant in the heterozygous states and may be absent in the neonate (99–101). In the Carlson and Eriksson series (64), PAS-D-positive inclusions were seen in 28 of 43 liver biopsies (65%) from IEF-verified heterozygotes. In

**TABLE 12. TREATMENT OF CHILDREN, ADOLESCENTS, AND ADULTS WITH LIVER DISEASE DUE TO ALPHA-1 ANTITRYPSIN DEFICIENCY**

| Treatment                | Level of Supportive Evidence | Strength of Recommendation | Comments         |
|--------------------------|------------------------------|----------------------------|------------------|
| Hepatitis vaccination    | 0                            | A-B                        | Expert's opinion |
| Avoidance of alcohol     | 0                            | A-B                        | Expert's opinion |
| Intravenous augmentation | 0                            | D                          |                  |
| Liver transplantation    | I                            | A                          |                  |

Level of supportive evidence (see Table 1 in LUNG DISEASE) and strength of recommendation grades (see Table 1 in EXECUTIVE SUMMARY and Table 10 of GENETIC TESTING FOR ALPHA-1 ANTITRYPSIN DEFICIENCY) are shown. "D" indicates that intravenous augmentation should not be undertaken for liver disease.



one prospective series, liver biopsies from 600 patients were stained with PAS after diastase treatment and by indirect immunoperoxidase staining for AAT deposits (70) and phenotyping was performed by IEF. Alpha-1 antitrypsin inclusions larger than 3  $\mu\text{m}$  had a diagnostic specificity of 0.94, whereas AAT inclusions larger than 1  $\mu\text{m}$  had a specificity of 0.77. Only 47% of the biopsies from patients with the PI\*Z allele contained AAT inclusions larger than 3  $\mu\text{m}$ . Access to larger liver samples from autopsy or transplantation increases the sensitivity of the procedure; mild to moderate PAS-D-positive inclusions could be seen in 37 of 51 native liver specimens (73%) from heterozygotes (68). The immunoperoxidase method using PI\*Z monospecific antibodies against AAT improves sensitivity of inclusions as markers of the Z allele to 100% (102). The S variant is known to have a less pronounced polymerization tendency than the Z variant (103) and is only occasionally associated with PAS-D inclusions (97).

Three less frequent AAT mutants that favor polymerization are associated with PAS-D inclusions and plasma deficiency (PI\* M<sub>malton</sub> [84], M<sub>duarte</sub> [98], and S<sub>jiyama</sub> [104]). These rare phenotypes may be undetectable by routine isoelectric focusing. In one report (97), PAS-D-positive inclusions were detected in 17 (10%) of 171 hepatic excision specimens. Of these, only three homozygous PI\*Z patients and none of the PI\*Z heterozygotes had a preoperative diagnosis. Of the unrecognized cases, one was PI\*SS, 8 were PI\*MZ, and 4 were PI\*MM. The 4 PI\*MM patients had plasma AAT levels in the subnormal or low normal range, consistent with heterozygosity for hitherto undescribed alleles that electrophoretically colocalize with the normal M allele. Accordingly, the clinician should be alerted to the possibility of an unsuspected AAT abnormality in liver disease patients manifesting "unexplained" PAS-D inclusions. DNA sequencing and family investigations are required for correct diagnosis in such cases.

Inclusions may also be formed by the ordinary M protein when the biosynthetic rate overwhelms the secretory capacity of the hepatocytes, as in alcoholic or chronic viral hepatitis. Such nonspecific inclusions have been described in the elderly with highly active disease, in alcoholic cirrhosis hepatitis (105) and hepatoma (87). The "risk" that such inclusions will occur in the MM phenotype was estimated at 4% (106) but the possibility of unknown M-like alleles was not excluded in that report.

In conclusion, PAS-D inclusions are neither 100% sensitive nor specific as markers of the PI\*Z allele and cannot replace IEF as the gold standard for phenotyping. When they are found in routine liver specimens, the physician should be alerted to the possible presence of a genetic AAT variant and suspect first a PI\*Z allele and, if that is excluded, M-like variants (including unknown variants), PI\*S, or PI\*MM in that order.

*Some research goals in AAT deficiency-related liver disease.* AAT deficiency is an excellent model for a conformational disease (107). The basic defect is a markedly enhanced propensity of the mutant Z protein to undergo loop-sheet polymerization. The polymer chains are retained in the ER of hepatocytes, where they cause cytotoxicity and finally form inclusions in a dilated ER.

The mechanism behind the cellular injury caused by these abnormal protein conformers is largely unknown and should continue to attract attention.

A central goal for research would be to achieve a better understanding of polymer formation: rates of formation (108), degradation, interactions, and identification of factors other than concentration and temperature that promote polymerization (109).

The individual progression of liver cell damage in AAT deficiency is extremely variable. Factors, genetic or environmental, that promote a rapid progression in a subset of children compared with the slow progress leading to cirrhosis and carcinoma in the elderly should be defined. Animal studies, including the

use of transgenic mouse models (110) and of human fibroblasts engineered for expression of mutant Z AAT (111), are important tools in defining variability of progression of damage.

Research on therapeutic alternatives in AAT deficiency should be focused on prevention and reversion of the conformational abnormalities that lead to formation of pathogenic proteins (107). Gene therapy (*see* LUNG DISEASE section) has future potential in AAT deficiency.

In liver disease, the goal of gene therapy should be not only to achieve effective expression of the normal gene, but also to suppress expression of the Z protein, thereby preventing polymer formation. Such a dual approach has the potential to prevent both lung and liver disease (112).

The use of chemical chaperones is an attractive alternative. *In vitro* compounds such as trimethylamine *N*-oxide and citrate markedly retard the rate of AAT polymerization (107). Another promising approach is the use of butyric acid derivatives such as 4-phenylbutyrate. Its mechanism of action is largely unknown. It has been administered to patients with cystic fibrosis to normalize trafficking of the cystic fibrosis transmembrane conductance regulator, resulting in normalization of chloride transport. 4-Phenylbutyrate mediates an increased secretion of mutant Z AAT (113). It must be emphasized that a better understanding of the polymerization and transport processes in AAT deficiency is of central importance and opens exciting possibilities for rational drug design to block the protein-protein interaction and polymer formation and thus to prevent lung, liver, and other rare complications in AAT deficiency (114).

*Some specific clinical research needs in AAT deficiency-related liver disease.*

1. A more detailed description of the pathology of the liver in AAT deficiency-related liver disease is needed, with special emphasis on the early stages and its relationship to both quantitative and qualitative aspects of the polymer status.
2. The high incidence of liver cirrhosis and carcinoma, particularly in the elderly never-smoker reported in Swedish series, needs confirmation in other geographic areas.
3. The recommendations to use simple liver function tests and regular ultrasound examination in follow-up of asymptomatic individuals with AAT deficiency or those with lung disease alone need validation in prospective investigations.
4. The putative interaction of AAT deficiency and chronic viral hepatitis, in particular the role of hepatitis C in heterozygotes, needs further exploration.
5. The efficacy and advisability of vaccination against chronic viral infections, in particular hepatitis C, when a vaccine becomes available, need evaluation.
6. The value and impact of periodic computed tomography scans of the liver in AAT-deficient individuals with resultant cirrhosis need evaluation in prospective studies.

## SYSTEMIC VASCULITIS AND RENAL DISORDERS

### Multigorgan Vasculitides

AAT deficiency has been shown to be involved in immune processes. For example, heterozygotes for the Z allele have been reported to be at increased risk of developing anterior uveitis and rheumatoid arthritis as well as a variety of collagen vascular diseases (115). Overall, these associations appear weak and often controversial and seem to lack impact on clinical management of the patient. Pheno- or genotyping of AAT in such patient cohorts may be motivated from a research point of view, but is rarely justified for clinical reasons. More important are a number of case reports linking the PI\*Z deficiency state to systemic

**TABLE 13. PI PHENOTYPES IN ANTI-PROTEINASE-3 (C-ANCA)-POSITIVE PATIENTS WITH VASCULITIC DISORDERS**

|                              | France | Sweden | Austria | Australia | UK  | Denmark |
|------------------------------|--------|--------|---------|-----------|-----|---------|
| No. of patients              | 37     | 105    | 32      | 31        | 99  | 44      |
| PI*ZZ                        | 3      | 1      | 2       | 1         | 1   | 0       |
| Z allele frequency           | 17.6   | 9      | 10.9    | 6.5       | 5.6 | 9.1     |
| Z allele in control subjects | 1.9    | 2.4    | 1.4     | 0.9       | 1.8 | 2.4     |

Modified from Esnault and coworkers (124).

vasculitis and glomerulonephritis (116–122). The results of two relatively small series reported in 1993 for the first time showed a possible relationship between the Z gene and the presence of C-ANCA (antineutrophil cytoplasm antibodies) (123, 124). Since then, numerous studies have confirmed a strong relationship between hetero- and homozygous PI\*Z AAT deficiency and small vessel-necrotizing vasculitides, in particular Wegener's granulomatosis and microscopic polyangiitis (125–131). As is evident from Table 13, the link between the PI\*Z allele and anti-PR-3 (antiproteinase-3 or C-ANCA) is convincing. As a rule, in each studied cohort of C-ANCA-positive patients at least one PI\*Z homozygote is identified. It means that about 2% of all patients with anti-PR-3-positive multisystemic vasculitis can be expected to be PI\*Z homozygotes, the remaining PI\*Z individuals being heterozygotes. In none of the reports in Table 13 has the smoking behavior of subjects been included. Proteinase-3 is a neutrophil elastase-like serine protease localized in the primary granules of the neutrophil. It possesses a potent tissue-destructive capacity. In the extracellular fluid, AAT is a major physiologic inhibitor of PR-3. It has been suggested (132) that the subnormal response of plasma AAT seen in vasculitic patients enhances the risk of fatal outcome, suggesting that AAT has a crucial function as a protective protein in vasculitic syndromes. Rather than being merely an etiologic risk factor, the PI\*Z variant for AAT deficiency may have an adverse accelerative effect on a vasculitic process once it starts.

Despite the firm association between Z allele-associated, C-ANCA-positive Wegener's granulomatosis, it is obvious that AAT deficiency is only a minor genetic risk factor for the development of vasculitic disease. However, the association attracts attention to the putative pathogenetic importance of a protease-antiprotease imbalance in these conditions (125). The relative lack of AAT could theoretically also promote the development of autoimmunity due to the exposure of a normally intracellular antigen, PR-3. Alternatively, the observations could be explained by a linkage disequilibrium phenomenon, in which immunologically important gene(s) tend(s) to be inherited with a particular AAT gene (130). Finally, the intrinsic properties of the mutant Z and S proteins, particularly their polymerization ability, could be pathogenetically important. Future clinical studies on PI\*Z-associated vasculitis in particular and other vasculitic syndromes in general should include attempts to analyze the pathogenetic role of smoking-induced AAT deficiency in these conditions. At present, available literature does not permit any meaningful analysis of the role of smoking in nephropathy or panniculitis.

Homozygotes and heterozygotes are overrepresented among patients with anti-PR-3-positive vasculitic syndromes (Table 13), which is why diagnostic testing for AAT deficiency is indicated for this group. Considering the low incidence of vasculitic disorders in the population, it is obvious that the relative risk of a particular PI\*Z heterozygote for developing a vasculitic complication is small. In heterozygotes with active disease, the AAT level is frequently normal (127), which is why quantitation alone

is insufficient. IEF is mandatory to exclude heterozygosity. There is a need for large prospective collaborative studies to confirm the possible adverse prognostic effects of AAT deficiency in this setting and for randomized controlled studies focusing on the effect of augmentation therapy.

An association between the PI\*S variant and C-ANCA-positive vasculitic disorders has been reported in only one study (125). In P-ANCA (anti-myeloperoxidase)-positive vasculitis, a slightly increased frequency of individuals with the PI\*S allele was reported in series from the UK and Italy (130, 133). In the latter study, the MZ phenotype was more prevalent among patients than control subjects (8 versus 1.5%), but with no significant difference between C-ANCA and P-ANCA. This report also describes subnormal AAT levels in the normal PI\*M phenotype during acute illness.

### Nephropathy

Various types of glomerulonephritis have been reported in AAT deficiency, predominantly in the pediatric age group (134). Specifically, there are three case reports (lacking ANCA data) of systemic vasculitis with glomerulonephritis in young adults with severe AAT deficiency (116, 118, 121). Glomerulonephritis alone in the elderly with severe PI\*ZZ deficiency seems to be rare (135). In the latter case, cirrhosis and emphysema were also present. One 30-year-old man with AAT deficiency with cirrhosis in early childhood developed IgA nephropathy and hypertension in adult life. He had no lung disease (136). In 20 children with AAT deficiency-associated liver disease, glomerular changes were seen in 79% versus only 43% in age-matched control subjects with hepatic failure not related to AAT deficiency. The glomerular changes were heterogeneous, with a high proportion of mesangiocapillary glomerulonephritis (134). In one study (137), five AAT-deficient children with end-stage liver disease and preoperative evidence of kidney pathology developed severe hypertension after liver transplantation. Dramatic improvement of renal function after liver transplantation in AAT deficiency has been reported (138).

In conclusion, when evaluating nephropathy in adults with AAT deficiency, an ANCA-positive vasculitic complication is the most probable explanation, whereas in children, an association with chronic liver disease is more likely. Nephropathy should be borne in mind, particularly in children, when patients are evaluated for liver transplantation.

## ANEURYSMAL AND RELATED DISEASES

### Abdominal Aortic Aneurysms

Biochemical data (139–141) support the concept of a systemic alteration in elastin metabolism in abdominal aortic aneurysms (AAAs). The inhibition of various proteolytic enzymes, such as neutrophil elastase by AAT, may have an important role in maintaining the integrity of connective tissue, including blood vessel walls. Furthermore, reports of familial aggregation of AAA (142, 143) and the male predominance in most cases (143)

suggest a significant genetic component in the pathogenesis of some aneurysms. Against this background, several authors have tried to establish a link between AAT deficiency and the formation of AAA. Early reports were based on isolated case presentations (144). The first large study on 47 patients with AAA suggested a higher frequency of AAT deficiency in patients with AAA (145). In contrast, in a case-control autopsy-based study (146) in 31 PI\*ZZ individuals, no increased frequency of AAA could be substantiated. More recently, no evidence for an association between AAT deficiency and AAA was found in larger, separate groups of patients from Pittsburgh, Pennsylvania, and from London, UK (147). There was also no evidence of association in a Swedish study of 102 consecutive patients with AAA (148). In the latter study, AAAs with a diameter of 40 mm or more were analyzed separately, but even then no increased PI\*Z allele frequency could be found. Furthermore, in patients with homozygous AAT deficiency, abdominal aortic diameter did not differ from that in non-PI\*Z control subjects (149). However, male individuals had significantly lower aortic stiffness values than did control subjects, a finding that might be compatible with an early vessel wall abnormality.

A German study (150) comprising 103 patients found heterozygous AAT deficiency to be of little or no importance for the development of AAA. In a later study (151), the authors found an increased prevalence of the rare phenotype PI\*MV. PI\*V is of unknown functional significance.

In conclusion, the evidence for a postulated link between AAT deficiency and AAA is weak. In clinical practice, screening of such patients for AAT deficiency is not warranted.

#### **Intracranial Aneurysms, Extra- and Intracranial Arterial Dissections, and Fibromuscular Dysplasia**

Several studies have focused on AAT deficiency as a possible risk factor for the development of intracranial aneurysms (IAs), but results are equivocal. Among 362 consecutive patients with AAT deficiency seen at the Mayo Clinic during a 10-year interval, 3 had suffered an aneurysmal subarachnoidal hemorrhage, which is considerably higher than would be expected by chance (152). Alpha 1-antitrypsin deficiency (PI\*MZ, MS, and ZZ) was found to be more frequent in patients with IA than in the general population (153), but other studies have failed to find a significant excess of AAT deficiency in patients with IA (154–156). Furthermore, the pattern of inheritance seen in familial IA does not fit any single Mendelian model, suggesting a genetic heterogeneity and possibly a strong influence of environmental gene interactions (157). It appears that AAT deficiency does not constitute a major genetic risk factor in IA formation. However, a possible pathogenetic role for a disturbed protease–antiprotease balance in formation and rupture of IAs has not been excluded and further study seems warranted. Screening for AAT deficiency as a marker for asymptomatic IA cannot be recommended.

One report (158) described elevated serum leukocyte elastase levels both in patients with ruptured and unruptured aneurysms. The elevated levels (the sum of free and complex elastase) correlated with degree of elastin degradation (154) in the superficial temporal arteries, suggesting a role for elastase in systemic elastin degradation including aneurysm formation. The presence of high elastase levels in patients with unruptured IA could not be confirmed in a smaller Japanese report (156). These authors suggested that the increased elastase levels in patients with ruptured aneurysms is attributable to the leukocytosis transiently occurring after a subarachnoidal hemorrhage. The small size of the study population, sex bias (156), and different methods for elastase assay may contribute to the conflicting results.

Another group of papers focuses on the putative role of acquired AAT deficiency in the development of IA. In formation

of multiple aneurysms, cigarette smoking is a definite risk factor (159). Reduced activity of AAT, because of oxidation of methionine in the reactive center, might explain the increased risk of IA rupture in smokers (160). Similarly, a reduced functional capacity of AAT may be due to low levels of antioxidants (161) and increase the risk of aneurysm bleeding.

Schievink and coworkers at the Mayo Clinic have repeatedly reported on the possible link between AAT deficiency and both intra- and extracranial arterial dissections and fibromuscular dysplasia. Their first case reports on these associations (162–164) have been extended more recently (165, 166). In four consecutive patients with subarachnoid hemorrhage due to spontaneous intracranial arterial dissection seen over 2 years, two were PI\*MZ, one was PI\*MS, and one was PI\*MM. In another study (166), AAT phenotyping was performed in three consecutive patients (all smoking females) who underwent bypass surgery for extracranial arterial dissection of the extracranial internal carotid artery. Two had the PI\*MZ phenotype. The authors suggest that this phenotype may predispose to the development of fibromuscular dysplasia. The figures are suggestive, but any causal link between these rare conditions and AAT deficiency must be considered conjectural until larger studies with adequate control subjects become available.

#### **DERMATOLOGIC MANIFESTATIONS**

##### **AAT Deficiency–associated Panniculitis**

Necrotizing panniculitis, characterized by inflammatory and necrotizing lesions of skin and subcutaneous tissue, represents the least common but well-recognized complication of AAT deficiency. The first case (probably an MZ individual) was published in 1972 (167). Rubinstein and coworkers reported two cases in PI\*ZZ individuals in 1977 (168). To date, about 40 cases (some of them reported more than once) have been reported (169). In two-thirds of the cases, severe deficiency, PI\*ZZ, has been present, but PI\*MZ, SS, and even MS phenotypes have been seen. Familial occurrence has been reported (170). Alpha-1 antitrypsin deficiency–associated panniculitis has sometimes (167, 168, 170) been referred to as Weber-Christian panniculitis, a condition characterized by relapses of a febrile, nonsuppurative panniculitis that may have numerous underlying causes. In contrast, AAT deficiency–associated panniculitis should be considered as a distinctive form of panniculitis, leading to spontaneous ulcerations and drainage of the lesions and having fairly distinct histopathological features.

Typically (171), the panniculitis starts with painful, hot, red, tender nodules on thighs and/or buttocks in a young adult, AAT-deficient individual (mean age, 40 years). There is an equal sex distribution of affected individuals. Subsequently, ulcerations occur with drainage of clear, yellow, oily, odorless fluid, sterile at culture. In approximately one-third of these patients, trauma may have precipitated the disease (171–173). For appropriate histopathological evaluation, deep excisional specimens, with a large amount of tissue, are required (171). Fat necrosis is frequent, as is the presence of normal-appearing fat juxtaposed to inflammatory and necrotic panniculitis. Fragmentation and loss of elastic tissue in areas of inflammation are frequently observed but vasculitis, except that resulting from necrosis, is infrequent (171, 172). The prognosis in these patients is variable and partly dependent on the presence of other AAT deficiency-related complications such as cirrhosis or emphysema. The panniculitis can be lethal.

Necrotizing panniculitis in AAT deficiency is an unusual complication. In a World Health Organization report (174), a prevalence of less than 1 case per 1,000 was mentioned. If the recommendation (174) to analyze plasma AAT levels in all cases of

biopsy-proven severe panniculitis is followed, particularly in factitious and necrotizing cases, this rate of prevalence may well increase considerably.

For obvious reasons, no controlled trials that provide a basis for clear treatment recommendation are available. Family screening and antismoking counseling are essential. Corticosteroids, antibiotics, or cytostatic drugs appear useless. Augmentation therapy with purified human AAT or fresh frozen plasma to restore plasma and local tissue levels of AAT appears rational, safe, and effective (175–178). Restoration of plasma AAT levels after liver transplantation led to permanent cure in one case (169). Dapsone, either alone in less severe cases, or combined with augmentation therapy, may be of additional value. Its mechanism of action in this setting is, however, unclear (175).

#### Skin Involvement in Systemic Necrotizing Vasculitides in Severe AAT Deficiency

In a 1996 report (179) of 14 cases (8 Swedish and 6 cases reported in the literature) of systemic necrotizing vasculitis in patients with severe AAT deficiency, skin involvement was present in all 14. In this cohort, characterized by multiple organ involvement (median number of organs affected was 8) and fatal outcome, the majority of patients had biopsy-proven microscopic polyangiitis or Wegener's granulomatosis. The cutaneous abnormalities were heterogeneous: erythematous or necrotizing papules, vesicles, palpable purpura, subcutaneous nodules, erythematous plaques, and relapsing ulcerative panniculitis. Necrotizing and leukocytoclastic vasculitis were the most frequent histopathological findings. A few reports of isolated cutaneous vasculitis in PI\*ZZ AAT deficiency have appeared. The first was that of a 2-year-old girl with generalized, nonpruritic eruption resistant to treatment (180). A case of persisting vasculitis in a 49-year-old PI\*ZZ male responded dramatically to administration of purified AAT (181).

#### Other Skin Disorders in Which AAT Deficiency Plays a Role

Studies of genetic markers in psoriasis led Beckman and coworkers (182) to phenotype AAT in 72 psoriatic patients. The frequency of the Z allele was found to be significantly ( $p < 0.001$ ) increased. Despite a relatively high risk (172, 173), the association would, however, explain only a minor part of the etiology of psoriasis. Their results were confirmed in several reports from the United States (183–185). MZ psoriatics had an earlier onset and a more severe disease than did non-Z individuals (185). Electron microscopic features suggested a defective inhibition of proteolytic activity in MZ psoriasis (186).

In 1975, Doeglas and Bleumink first published findings concerning 92 patients with various types of chronic urticaria (187) in whom decreased values of AAT were found. This phenomenon was particularly present in patients with cold urticaria and acquired idiopathic angioedema. Their findings were confirmed by several groups (188–190) but criticized by others (191, 192). However, in 1985 Doeglas and coworkers definitely confirmed their early findings (193) by phenotyping 281 patients with chronic urticaria. The MZ phenotype was significantly more frequent in the urticaria group. Again, the Z allele predominated in the groups with cold urticaria and acquired angioedema. The mechanism underlying this predisposition in carriers of the Z allele is unknown.

### MISCELLANEOUS CONDITIONS

#### Exocrine Pancreatic Disease

It seems reasonable to postulate a role for a serum protease inhibitor such as AAT in the prevention of proteinase-induced damage of the pancreas. Case reports have described acute pan-

creatitis in individuals with AAT deficiency (194, 195) and hemorrhagic pancreatitis has occurred after endoscopic retrograde cholangiopancreatography (196), but no significant excess of deficient phenotypes could be seen in a larger study including 31 patients with acute pancreatitis (197). Neither could these authors find a link between chronic pancreatitis and AAT deficiency (197). Such an association was first postulated in a South African study including 110 patients with chronic pancreatitis (198). There was a significant excess of the phenotype MZ in these patients, mostly alcoholics, but there was no association between the MZ phenotype and idiopathic chronic pancreatitis. Conflicting reports regarding the association between AAT deficiency and pancreatitis continue to appear. For example, Seersholm and Kok-Jensen (199) have reported an association between PI\*Z AAT deficiency and pancreatitis, whereas Witt and coworkers (200) have observed no association of AAT deficiency with chronic pancreatitis. In summary, the data relating exocrine pancreatic disease to AAT deficiency remain inconclusive.

#### Endocrine Pancreatic Disease

Islet cell hyperplasia is a universal feature of AAT deficiency (201). It has been postulated that an accumulation of aggregated Z AAT in islet cells may provoke a sequential development of such hyperplasia from benign to malignant tumors. Against this background, it is of interest that two endocrine pancreatic tumors, one benign and one malignant, were observed in the Malmö, Sweden series of individuals with AAT deficiency (202).

#### Celiac Disease

Alpha-1 antitrypsin immunoreactivity was demonstrated by immunofluorescence in epithelial cells of normal human small intestine (203). A case of AAT deficiency (probably PI\*Z) in an elderly man with emphysema, cirrhosis, and total intestinal mucosal atrophy was reported in 1975 (204), supporting earlier observations of AAT levels compatible with heterozygous AAT levels (no phenotyping) in children with celiac disease (205, 206). However, later and larger studies from Spain and Ireland refute an association between AAT deficiency and celiac disease (207, 208).

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# Genetic Testing for Alpha-1 Antitrypsin Deficiency

## Ethical, Legal, Psychological, Social, and Economic Issues

### INTRODUCTION

Alpha-1 antitrypsin (AAT) deficiency is a common genetic disorder, defined as an insufficient amount of serum AAT, a plasma protein with antiproteolytic activity. This genetic disorder predisposes to chronic obstructive airway disease, chronic liver disease, and rarely to skin and vasculitic disorders (*see LUNG DISEASE section and LIVER AND OTHER DISEASES section*).

There has been gathering interest in genetic testing for AAT deficiency for several reasons. First, AAT deficiency is perceived to be an "uncommon" cause of lung and liver diseases by health care providers and, hence, symptomatic individuals with AAT deficiency are undiagnosed or misdiagnosed. Consequently, such patients may undergo unnecessary testing and procedures and/or fail to receive appropriate therapy or counseling regarding preventive measures, for example, smoking cessation. Second, there is an interest in identifying asymptomatic individuals at high risk of having AAT deficiency so that they can be advised to lead healthier lifestyles that may prevent or delay the onset of disease (1). Finally, in populations where the prevalence of AAT deficiency may be high, some type of conditional, targeted population screening may be recommended.

To respond to the interest in genetic testing for AAT deficiency, a Genetics Writing Group was assembled under the auspices of the American Thoracic Society, the European Respiratory Society, the American College of Chest Physicians, the American Association for Respiratory Care, and the Alpha-1 Foundation, to develop recommendations for genetic testing. The Genetics Writing Group was composed of 12 members with backgrounds in medicine, philosophy, economics, law, genetics, and health care policy.

### SPECIFIC QUESTION TO BE ADDRESSED

The general charge to the Genetics Writing Group was to perform a systematic review to answer the following specific, focused clinical question: "Does genetic testing for AAT deficiency improve outcomes in individuals with AAT deficiency compared with no genetic testing?"

The Genetics Writing Group defined the scope of this clinically focused question by identifying the following categories of inclusion criteria:

#### Types of Genetic Testing

- a. Diagnostic detection testing
- b. Predispositional detection testing
- c. Screening

The Genetics Writing Group defined three types of genetic testing. The first two types of testing fall under the general category of "detection" testing. The first type is labeled "diagnostic" testing, defined as evaluating for the presence of AAT deficiency in a person with symptoms and/or signs consistent with an AAT deficiency-related disease. Essentially, diagnostic testing is undertaken for diagnosis of the underlying cause of a specific medical condition and the ethical imperative for such testing is similar to the testing performed in sorting out the differential diagnosis of any other medical condition.

The second type of detection testing is labeled "predispositional" testing, defined as identifying asymptomatic individuals who may be at high risk of having the genetic predisposition for

developing AAT deficiency-related diseases. Positive results on such testing do not necessarily mean that the disease will inevitably occur; rather, they replace the individual's prior risks based on population data or family history with risks based on genotype or phenotype (2).

The third type of genetic testing is labeled "screening," which refers to programs designed to search in populations for persons possessing certain inherited predispositions to disease. The hallmark of screening is that there be no previous suspicion that any given individual has the condition (3).

#### Types of Outcomes

- Medical benefits: Prevention or delay of disease, regression of disease already present, or delay in the progression of abnormalities already present
- Explanation of disease
- Psychologic effects, both adverse and beneficial
- Social discrimination/stigma
- Economic effects

#### Types of Individuals

##### *Symptomatic individuals.*

- Persistent obstructive pulmonary dysfunction
- Liver disease
- Necrotizing panniculitis
- Multiorgan vasculitis

##### *Asymptomatic individuals at high risk of having AAT deficiency.*

- Individuals with a family history of AAT deficiency
- Individuals with a family history of obstructive lung disease or liver disease
- Fetuses

##### *Carrier testing in the reproductive setting.*

- Individuals at high risk of having AAT deficiency
- Partners of individuals with AAT deficiency

##### *Asymptomatic individuals with no known higher risk of having AAT deficiency.*

- Targeted populations: newborn, adolescent, adult

### METHODS

#### Data Sources and Search Strategy

We searched the MEDLINE and HealthSTAR databases from their inception to the beginning of 2001. We used the terms *genetic test/genetic screening/mass screening, AAT deficiency, controlled study, randomized controlled trial, and meta-analysis*. We also applied these search terms to the genetics of any disease, as observations on the efficacy of genetic testing in diseases with similar characteristics (e.g., adult onset, availability of treatment, and/or preventive measures) may provide insight concerning potential outcomes of AAT genetic testing. Finally, we contacted leading clinicians and researchers in the field of AAT deficiency and obtained the database of the Alpha-1 Foundation to identify additional studies.

The initial search strategy yielded reports of two uncontrolled, nonrandomized neonatal screening programs for AAT deficiency (4, 5). No studies were found regarding the efficacy of genetic testing of symptomatic individuals or asymptomatic individuals at high risk of developing a genetic disease.

### Alternative Method of Developing Recommendations

Because of the scarcity of studies investigating the efficacy of genetic testing, we pursued an alternative strategy for developing recommendations for genetic testing. This strategy consisted of three parts:

1. First, we determined the individual issues that, in and of themselves, either supported or opposed genetic testing for AAT deficiency (6, 7). The relevant issues considered important for genetic testing included (a) the prevalence of AAT deficiency, (b) the penetrance of AAT deficiency-associated diseases, (c) the clinical impact or disease burden of AAT deficiency-associated diseases, (d) the accuracy of genetic testing, (e) the efficacy of augmentation therapy, (f) the efficacy of providing information about changing health-related behaviors, (g) the psychologic effects of genetic testing, (h) the social effects of genetic testing, (i) the economic costs of genetic testing, and (j) the ethical obligations and constraints regarding genetic testing (e.g., informed consent from adolescents).
2. The next step consisted of determining the weight of each issue, or how strongly each issue supports or opposes each type of genetic testing, by examining the level or strength of the evidence of each issue, via systematic review method. Essentially, systematic reviews of these individual issues would determine the implication that each issue had, in and of itself, for genetic testing, that is, whether it favors, detracts, or is neutral in supporting the case for testing. For example, the mere existence of augmentation therapy would strongly argue for recommending genetic testing for individuals with symptoms. But, if Grade I evidence is lacking for the efficacy of this treatment, then the potential implication of this issue for testing is downgraded.

The scientific evidence was evaluated, using the U.S. Preventive Services Task Force criteria (8) (Table 1). Tables of evidence were derived from systematic reviews of available studies.

Specific search strategies for the issues considered important in genetic testing for AAT deficiency included the following:

- a. What is the prevalence of AAT deficiency in the population?
- b. What is the penetrance of AAT deficiency-associated diseases, (i.e., percentage of AAT individuals that present with clinical disease: lung, liver, skin, vasculitis, etc.) and what is the prevalence of AAT deficiency-associated diseases in the general population?
- c. What is the clinical impact of AAT deficiency-associated diseases on individuals, that is, morbidity and mortality?
- d. What is the accuracy of genetic testing for AAT deficiency?
- e. Does intravenous augmentation therapy improve survival and/or physiologic lung function in individuals with AAT deficiency compared with no treatment?

- f. Does providing information about risks of developing these diseases to individuals favorably affect health-related behaviors (e.g., smoking cessation, change in occupations)?
- g. What are the psychologic effects of genetic testing for AAT deficiency and other similar chronic, genetically related diseases?
- h. What are the social effects of genetic testing for AAT deficiency and other similar chronic, genetically related diseases?
- i. What are the economic implications of genetic testing for AAT deficiency?
- j. What are the ethical implications of genetic testing for AAT deficiency?

To broaden the reach of the systematic reviews on the issues involving the efficacy of providing information about changing health-related behaviors, the psychologic effects of genetic testing, and the potential social discriminatory effects of genetic testing, we searched the literature for studies on other newborn or adult-onset chronic genetic disorders that are amenable to either preventive measures or specific medical treatments. These diseases included cystic fibrosis, breast cancer, hereditary hemochromatosis, hereditary nonpolyposis colon cancer, familial adenomatous polyposis, and familial hypercholesterolemia. We also performed systematic reviews of any studies evaluating the efficacy of genetic testing of symptomatic individuals, of asymptomatic individuals at high risk of developing a genetic disease, and of populations systematically screened for these other genetic conditions.

3. The final step in the development of recommendations consisted of subjectively weighing the issues relevant for each genetic testing scenario for each type of individual/group. For example, a genetic testing scenario would receive a recommendation for testing if many of the issues favorable for testing had large weights attached to them to the extent that they outweighed the weights attached to the issues that opposed testing.

The final recommendations were achieved by a consensus of the Genetics Writing Group. As relevant new evidence becomes available, our recommendations will need to be reevaluated.

It is important to emphasize that the various recommendations involving genetic testing reflect the informed judgment and deliberations of the Genetics Writing Group concerning whether the medical, psychologic, and ethical benefits of genetic testing (e.g., effects of treatment, enhancing efforts at changing health-related behaviors, or providing an explanation of disease) *outweighed in general and for the particular type of case* any psychologic or social harms, economic costs, or ethical concerns. In addition, it is critical to recognize that the Genetics Writing Group did not engage in some sort of utilitarian calculation in developing the recommendations, as many of the recommenda-

TABLE 1. GRADES OF EVIDENCE

| Grade | Description   |
|-------|---|
| I     | Evidence obtained from at least one properly designed randomized controlled trial   |
| II-1  | Evidence obtained from well designed controlled trials without randomization  |
| II-2  | Evidence obtained from well designed cohort or case-control analytic studies, preferably from more than one center or research group  |
| II-3  | Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence |
| III   | Opinions of respected authorities based on clinical experience, descriptive studies, and case reports   |

Adapted from U.S. Preventive Services Task Force (1).

tions reflect a balancing of competing rights and responsibilities—for example, balancing a patient's right of privacy against the physician's responsibility to promote health. Finally, we acknowledge that certain individual cases may present exceptional considerations that warrant a conclusion different from what we draw. The recommendations are therefore offered as a guide and not as a rule.

## BACKGROUND: GENETICS OF AAT DEFICIENCY

Deficiency of AAT is an autosomal, codominant genetic disorder and by itself is not a disease, but a predisposition to later development of a disease. Low serum levels of AAT, in conjunction with other genetically determined characteristics and environment influences, result in the development of a disease state (e.g., pulmonary or liver disease).

Reasonable evidence from epidemiologic studies suggests there is a serum threshold level above which the lung appears to be protected (9). This serum threshold lies at 11  $\mu\text{M}$ , about 35% of the average normal level. The AAT protein is an extremely polymorphic molecule; approximately 100 alleles of the AAT gene have been identified and categorized into an arrangement designated as the protease inhibitor (PI) system (10). Of these alleles, more than 30 genetic variants have been identified that lead to deficient levels of AAT. The normal and deficient AAT alleles can be identified by isoelectric focusing, the techniques currently used for definitive diagnosis (11), and are assigned a letter code (A to Z). AAT alleles are expressed in a codominant fashion and the AAT protein phenotype is described on the basis of these alleles, that is, it is referred to as the PI phenotype.

The most common allele is referred to as M; most individuals have a protein phenotype PI\*MM. AAT genotypes that confer an increased risk for developing lung disease are those in which deficiency or null alleles, combined in homozygous or heterozygous states, encode AAT levels below the protective threshold. The most frequent deficient AAT allele is the Z variant, and individuals who are PI\*ZZ homozygotes have plasma levels of AAT that are about 15% of the normal plasma concentration and are at the greatest risk for developing AAT deficiency-associated lung disease. The S variant is more frequent in the Mediterranean area and the homozygous form is associated with plasma levels about 60% of normal. The remaining frequent types of AAT phenotypes include PI\*SZ, PI\*MS, and PI\*MZ. Evidence from the literature (*see LUNG DISEASE* section) suggests that individuals with the SS, SZ, MS, or MZ phenotype are at increased risk of developing AAT deficiency-associated diseases.

The null alleles (homozygotes designated as PI QOOO) are associated with the most severe deficiency, producing no active AAT, or less than 1% of the normal amount of plasma AAT.

Suspicion of AAT deficiency can be confirmed quantitatively and qualitatively. Quantitative plasma AAT levels are usually determined by rocket immunoelectrophoresis, radial immunodiffusion, or, more recently, nephelometry (*see LUNG DISEASE* section). Subjects with abnormal blood levels should be investigated further to provide a qualitative evaluation of their AAT disorder. Even subjects with a borderline normal AAT plasma level (12–35  $\mu\text{M}$  or 90–140 mg/dl) should undergo qualitative testing, because these levels may correspond to an intermediate-level phenotype (SZ, SS, MZ, and MS). Also, a relative with asymptomatic or misdiagnosed AAT deficiency may be uncovered within the family.

## SYSTEMATIC REVIEWS OF THE EVIDENCE FOR THE EFFICACY OF GENETIC TESTING

### Diagnostic Detection Testing

We found no studies investigating the effectiveness of detection testing programs of symptomatic individuals for AAT deficiency or for other genetically related, chronic diseases. Studies of effectiveness of future detection testing programs should include the beneficial medical effects as well as the psychologic, social, and economic costs that may accrue from testing.

### Predispositional Testing of Asymptomatic Individuals at High Risk

The “gold standard” approach for evaluating testing in these individuals would be a randomized trial involving testing, surveillance, and treatment. However, such a trial would require a large number of participants, take many years to carry out, and be expensive. Accordingly, we found no controlled trials or observational studies comparing outcomes in asymptomatic individuals at high risk who were tested for AAT with individuals who were not tested. Studies of genetic testing for genetically related, chronic diseases were also not available.

In the absence of such studies, quantitative and/or semiquantitative decision analysis may be informative in assessing the efficacy of genetic testing. Two such decision analyses have been performed for breast cancer (12, 13), showing that genetic testing of individuals at high risk may be associated with improved outcomes (Table 2). This conclusion is conditioned on the efficacy of the preventive measures and the likelihood that individu-

**TABLE 2. EFFICACY OF GENETIC TESTING OF ASYMPTOMATIC INDIVIDUALS AT HIGH RISK OF DEVELOPING A GENETIC DISEASE**

| First Author, Year (Ref.) | Disease; Genetic Marker    | Study Design; Group                          | Length of Follow-up | Intervention                      | Outcome Variable       | Major Results   | Remarks           |
|---------------------------|----------------------------|--|---------------------|-----------------------------------|------------------------|---|-------------------|
| Tengs, 1998 (12)          | Breast cancer; BRCA1/BRCA2 | Decisional analysis; population and familial | NA                  | Bilateral mastectomy/oophorectomy | Life expectancy; QALYs | Vast majority of women in the population will not benefit from testing because their pretest risks are low and surgical prophylaxis is undesirable. Women who have family histories of early breast and/or ovarian cancer may gain up to 2 QALYs if genetic testing informs their decisions concerning treatment/preventive options | Theoretical study |
| Schrag, 1997 (13)         | Breast cancer; BRCA1/BRCA2 | Decisional analysis; familial                | NA                  | Mastectomy/oophorectomy           | Life expectancy        | Women who carry gene mutation gain from 2.9 to 5.3 yr of life expectancy from mastectomy and from 0.3 to 1.7 yr of life expectancy from oophorectomy  | Theoretical study |

Definition of abbreviations: BRCA = breast-ovarian cancer gene; NA = not available; QALY = quality-adjusted life-year.

als testing positive will undergo the preventive measures (e.g., surveillance and mastectomy or hormone treatment).

### Screening Programs

The initial search strategy yielded reports of two uncontrolled, nonrandomized neonatal screening programs for AAT deficiency (4, 5) (Table 3). No randomized, control study determining the efficacy of screening programs for AAT deficiency has been performed. One nonrandomized, noncontrolled study on neonatal screening for AAT was performed in Sweden (4). The experience with this neonatal screening program showed favorable long-term outcomes on smoking initiation rates and pulmonary function (14–18). The smoking rates of adolescents identified with AAT deficiency at birth were lower compared with those of age-matched control subjects (16) and the pulmonary function test results of AAT-deficient nonsmokers were significantly better than those of AAT-deficient smokers (18). Adverse psychologic effects from the receipt of genetic knowledge of having a potential to develop a future disease were not observed, as adolescents identified at birth with AAT deficiency had psychosomatic complaints that were similar to those of a matched control group (17). However, psychologic distress was experienced by the parents of these children and interactions between mother and child were problematic (19–25).

Another neonatal screening program conducted in Oregon also suggested favorable long-term results with such a program (5). Specifically, 22 adolescents with homozygous AAT deficiency had normal pulmonary function and, whereas smoking attitudes did not differ from control subjects, smoking initiating rates were significantly lower ( $p = 0.02$ ), suggesting that screening followed by family-based smoking intervention may lead to a nonsmoking lifestyle.

The efficacy of neonatal screening programs has been investigated in several studies involving cystic fibrosis (Table 3). Specifically, seven cystic fibrosis neonatal screening trials have been performed with follow-up periods ranging from 1 to 10 years. Two of these studies were randomized, controlled clinical trials that reported significant beneficial effects in the screened population (26–28). The five other reports were case-control trials that also showed beneficial medical effects in the screened population (29–34).

The AAT deficiency and cystic fibrosis neonatal screening experiences suggest the efficacy of instituting preventive measures in individuals identified early on as having a genetic condition. Although AAT deficiency and cystic fibrosis are similar in that preventive measures are available, they differ in that the onset of disease occurs later in AAT deficiency compared with cystic fibrosis. Accordingly, the success of preventive measures for cystic fibrosis may depend on identification of the genetic condition shortly after birth, whereas a later time period for the identification of AAT deficiency may be as effective as neonatal screening, for example, during the adolescent period.

## SYSTEMATIC REVIEWS OF THE INDIVIDUAL ISSUES RELEVANT FOR GENETIC TESTING

Tables of evidence (Tables 4–7) were constructed regarding the individual issues relevant for developing recommendations for genetic testing. Because many of the aforementioned issues are reviewed in the other sections of this statement, the reader is referred to those sections at the appropriate places for complete discussion and tables of evidence. Table 8 shows for each issue a summary of the conclusions from the evidence, the strength of the evidence, and the implications for testing.

### Prevalence of AAT Deficiency

Estimates of the prevalence of the PI\*ZZ phenotype in the general population have varied considerably, depending on the population used to derive the estimate (e.g., AAT deficiency occurs predominantly in Caucasians), the ethnic mix of the population, and the analytic method of phenotyping. On the basis of the newborn screening program in Sweden, the prevalence of AAT deficiency (PI\*ZZ phenotype) in Sweden is estimated at 1 in 1,575 (4, 35). Direct population screening studies in the United States indicate that the prevalence of individuals with AAT deficiency is between 1 in 2,857 and 1 in 5,097 (36–38). On the basis of a U.S. population of about 260 million, 80,000 to 100,000 individuals with AAT deficiency (symptomatic and asymptomatic) are expected. As only 3,000–4,000 individuals have been diagnosed with AAT deficiency, these figures suggest that AAT deficiency is presently undiagnosed or is not manifest by disease in a large proportion (about 95%) of individuals with this genetic condition. Hence, although AAT deficiency is considered a rare genetic condition, it is as common as cystic fibrosis, which has a prevalence rate in Caucasians from 1 in 1,700 to 1 in 6,500. These prevalence data, by themselves, provide moderate support for screening programs in European and North American countries, but lack relevance for ethnic populations where the frequency of an allele associated with AAT deficiency is low. Also, these prevalence data have no relevance for diagnostic or predispositional genetic testing programs (Table 8).

### Penetrance and Prevalence of AAT Deficiency-related Clinical Disease

**Pulmonary disease.** The penetrance of chronic obstructive pulmonary disease (COPD) among subjects with severe AAT deficiency is not properly known because many PI\*ZZ individuals are never identified. In a study of 54 individuals who were clinically healthy when AAT deficiency was identified, only one-third, almost all smokers, had developed COPD between 30 and 60 years of age (39). This suggests that the existence of AAT deficiency alone is not enough to induce lung disease.

Estimates of the absolute prevalence of AAT deficiency-related pulmonary disease in the general population are based on several reports demonstrating the yield of detection testing in populations of targeted individuals. In a sampling 965 patients with COPD, Lieberman and colleagues observed severe deficiency of AAT (PI\*ZZ phenotype) in 1.9% and intermediate deficiency (primarily MZ phenotype) in 8.0% (40). Testing performed by the AAT deficiency Detection Center in Salt Lake City on 16,748 individuals with chronic bronchitis, emphysema, or asthma, or with a family history of AAT deficiency, detected AAT deficiency in 3.1% of the total samples (1). Of these, one individual had the PI\*SZ phenotype and the remainder had the PI\*ZZ phenotype. Finally, a large number of heterozygotes was also detected; for example, 1.1% of the individuals were of the PI\*SZ phenotype. Extrapolating from the estimate of the U.S. National Health Interview Survey (41) that 2.1 million individuals have emphysema, emphysema caused by AAT deficiency is expected in about 40,000–60,000 persons.

These estimates for the penetrance of AAT deficiency and the absolute prevalence of AAT deficiency-associated pulmonary disease in the general population provide strong support for diagnostic detection testing for individuals who belong to an ethnic population for which there is, *a priori*, evidence that the frequency of the allele is not low (Table 8). These data have no relevance for predispositional testing or for screening.

**Liver disease.** Liver disease associated with AAT deficiency is less common than the prevalence of lung disease (*see* LIVER

TABLE 3. EFFICACY OF GENETIC TESTING IN SCREENED POPULATIONS

| First Author, Year (Ref.)                          | Disease | Study Design; Group   | Sample Size   | Length of Follow-up, yr | Intervention; Methods   | Outcome Variable   | Major Results   | Remarks   |
|--|---------|---|---|-------------------------|---|--|---|---|
| Sveger, 1994 (14)                                  | AAT     | Case-control; neonatal population   | 150 adolescents: 103 PI*ZZ, 1 PI*Z-, 1 PI*S-, 45 PI*SZ; 50 control subjects | 16                      | Antismoking advice  | Pulmonary function tests, clinical examination                                     | No differences found in physical examination or clinical signs of lung disease. The AAT PI type did not contribute to the variation in PFTs. Only four adolescents had smoked   | Children with AAT deficiency have a favorable prognosis and normal lung development up to 16 yr. Antismoking advice was found to be reasonably successful |
| Sveger, 1995 (15)                                  | AAT     | Case-control; neonatal population   | 87 PI*ZZ, 42 PI*SZ; 48 control subjects                                     | 18                      | No intervention; 0% of PI*ZZ, 8% of PI*SZ, 21% of control subjects were current smokers             | Pulmonary function, clinical examination   | No difference in lung disease symptoms. The AAT PI type contributed to the variation of DL <sub>CO</sub> and FEV <sub>1</sub> /VC%  | Deviations of pulmonary function tests results are marginal and of no clinical importance   |
| Thelin, 1996 (16)                                  | AAT     | Case-control; neonatal population   | 61 with AAT; 61 demographically matched control subjects                    | 18                      | No intervention; self-report  | Smoking rates  | AAT children reported smoking less than control subjects: 94% versus 83% (p < 0.05); AAT parents' smoking rates greater than those of control parents when children 5-7 yr old (p < 0.05), but no difference at 18 yr   |   |
| Sveger, 1997 (17)                                  | AAT     | Case-control; neonatal population   | 61 cases compared with 61 control subjects                                  | 18                      | No intervention; self-report  | Somatic symptoms, psychosomatic symptoms   | 12% of AAT-deficient individuals reported pulmonary symptoms compared with 2% of control individuals (p < 0.05); no difference in psychosomatic symptoms between AAT and normal individuals   |   |
| Piitulainen, 1998 (18)                             | AAT     | Comparison within group; neonatal population  | 88 PI*ZZ plus 40 PI*SZ; no control subjects                                 | 18                      | No intervention; analyzed effects of active and passive smoking on lung function in AAT individuals | Pulmonary function tests   | FEV <sub>1</sub> and FEV <sub>1</sub> /VC were lower in smokers (n = 13) compared with nonsmokers (n = 115) (p < 0.05). Mean FEV <sub>1</sub> /VC was lower for those presently exposed to parental smoking (p < 0.05). AAT-deficient nonsmokers had normal lung function | PFTs of AAT-deficient nonsmokers were not compared with those of individuals without AAT deficiency   |
| Wall, 1990 (5)                                     | AAT     | Case-control; neonatal population   | 22 adolescents with PI*ZZ; 130 control subjects                             | 16-18                   | No intervention   | Pulmonary function tests, smoking attitudes, smoking initiation rates              | All subjects had normal lung function studies; smoking attitudes similar to those of control subjects; smoking initiation rates were lower than those of control subjects (p = 0.02)  | Screening followed by family-based smoking intervention may lead to a nonsmoking life-style   |
| Fost, 1989 (26); Farrell, 1997 (27); Wisconsin RCT | CF      | Randomized control trial; neonatal population. All infants screened, but disclosure of results was subject to randomization | 56 cases compared with 40 control subjects                                  | 10                      | Treatment (not prophylactic antibiotics)  | Growth, lung status  | Children in disclosure arm had more favorable weights and heights (p = 0.003); no difference in prevalence and incidence rate of lung infections between the two groups   |   |
| Chatfield, 1991 (28); Wales/Midlands RCT:          | CF      | Randomized control trial; neonatal population screened-detected versus clinically detected                                  | 58 cases; 44 control subjects   | 4                       | Antibiotic treatment  | Hospital stay, growth, clinical score  | Screened group spend shorter time in hospital during the first year of life (p < 0.01); no differences in growth at the end of 4 yr   | Screened-detected patients were treated by general pediatricians with suboptimal antibiotic regimens  |
| Kuzemko, 1986 (29); East Anglia                    | CF      | Case-control  | 7 cases; 5 control subjects   | 1                       |   | Weight, antibiotic usage, X-ray score  | Screened-detected infants had better X-ray scores (p < 0.01)  | No difference in weight or antibiotic usage   |
| Mastella, 1988 (30); northeast Italy               | CF      | Case-control  | 144 cases; 75 control subjects  | 10                      |   | <i>Pseudomonas</i> colonization; Shwachman/Chrispin-Norman scores; ht/wt; survival | Screened-detected had better survival (p < 0.00001), better ht/wt (both p < 0.001), and better Shwachman/Chrispin-Norman scores (both p < 0.0001)   |   |
| Dankert-Roelse, 1989 (31); northeast Netherlands   | CF      | Case-control  | 23 cases; 27 control subjects   | 11                      |   | Survival   | Survival more favorable in screened infants (p = 0.05)  | Geographic bias because more of screened infants were treated in a specialized CF center  |
| Bowling, 1988 (32); Queensland                     | CF      | Case-control  | 28 cases; 23 control subjects   | 2                       |   | Antibiotics, weight  | Higher antibiotic usage compared with screened-detected (p < 0.025)   |   |
| Wilcken, 1985 (33); New South Wales I              | CF      | Case-control  | 34 cases; 48 control subjects   | 2                       |   | Hospitalization  | Screened-detected less hospitalizations (p < 0.0001)  |   |
| Waters, 1999 (34); New South Wales II              | CF      | Case-control  | 60 cases; 59 control subjects   | 10                      |   | Shwachman score, FEV <sub>1</sub> , FVC  | Screened-detected had higher Shwachman scores, higher FEV <sub>1</sub> , and higher FVC (all p < 0.05)  |   |

Definition of abbreviations: AAT = alpha-1 antitrypsin; CF = cystic fibrosis; ht/wt = height-to-weight ratio; PFT = pulmonary function test.

TABLE 4. EFFICACY OF PROVIDING GENETIC RISK INFORMATION ABOUT HEALTH-RELATED BEHAVIORS

| First Author, Year (Ref.) | Disease; Behavior Studied   | Study Design  | Sample Size  | Intervention   | Outcome Variables  | Major Results  | Remarks  |
|---------------------------|---|---|--|--|--|--|--|
| Thelin, 1996 (16)         | AAT; prevention of cigarette smoking                                  | Case-control  | 61 children with AAT and their families compared with a demographically matched control group                      | Receipt of genetic information at birth  | Smoking habits assessed via interviews and questionnaires on two occasions: 5–7 yr after birth and 18 yr after birth             | <i>Children:</i> At 18–20 yr of age, smoking rates of AAT-deficient individuals were less than those of control subjects. <i>Never smoked:</i> AAT versus control, 88 versus 65% ( $p < 0.05$ ). <i>Smoker today:</i> AAT versus control, 6 versus 17% ( $p < 0.05$ ). <i>Parents:</i> At 5–7 yr, smoking rates among fathers of AAT children were higher than those of control subjects ( $p < 0.05$ ); at 18 yr, smoking rates were similar between the two groups | Results may not be applicable to smoking cessation efforts aimed at adolescents  |
| Wall, 1990 (5)            | AAT; prevention of cigarette smoking                                  | Case-control  | 22 children identified as PI*ZZ at birth compared with 130 control subjects  | Receipt of genetic information at birth  | Smoking initiation rates   | AAT-deficient children had lower rates of smoking compared with control subjects ( $p < 0.02$ )  | Same as above  |
| Lerman, 1997 (74)         | Smokers; quit rates of smokers  | Randomized controlled trial   | 165 male and 262 female smokers, ages 18–75 yr, who responded to advertisements for a free smoking cessation trial | Subjects randomized to (1) minimal-contact QSC, $n = 141$ ; (2) QSC plus EBF about carbon monoxide in exhaled breath, $n = 153$ ; (3) QSC plus EBF plus SBF about genetic susceptibility to lung cancer, $n = 133$ | 2-mo self-reported quit rates; perceived risk of lung cancer; perceived health benefits of quitting; fear arousal; quit attempts | No significant differences between the groups in quit attempts or smoking quit rates at 2 mo follow-up ( $p < 0.005$ ). SBF produced significantly greater effects on perceived risk, perceived quitting benefits, fear arousal than either QSC or EBF (all $p < 0.005$ )  | Genetic information may cause distress that could lead some smokers to deny or underestimate their smoking problem, which would increase resistance to behavior change |
| Audrain, 1997 (75)        | Smokers; quit rates of smokers  | Randomized control trial: 12 follow-up of Lerman and coworkers study on the impact of genetic susceptibility feedback on smoking behavior | 165 male and 262 female smokers, ages 18–75 yr, who responded to advertisements for a free smoking cessation trial | Subjects randomized to (1) minimal-contact QSC, $n = 141$ ; (2) QSC plus EBF about carbon monoxide in exhaled breath, $n = 153$ ; (3) QSC plus EBF plus SBF about genetic susceptibility to lung cancer, $n = 133$ | 12-mo self-reported quit rates; quit attempts; depression scale  | No significant differences between the groups in quit rates at 12 mo; significant impact of genetic feedback on the likelihood of a quit attempt, $p < 0.05$ ; initial increase in depression in the SBF group was not maintained over time  | Genetic risk information may enhance motivation to quit; it may need to be delivered within a more intensive smoking cessation treatment                               |
| Kash, 1992 (76)           | Breast cancer; mammography adherence and clinical breast examinations | Survey study; collection of cross-sectional data  | 217 first-degree relatives of breast cancer patients (i.e., at high risk for breast cancer)                        | None   | Surveillance behaviors; psychological distress   | 94% came in for regularly scheduled mammograms; 69% came in for regular clinical breast examinations. Increased cancer anxiety was associated with decreased regular clinical examinations ( $r = -0.65$ ) and predicted poor adherence to monthly breast self-examinations (multiple $r = 0.61$ )   | Higher anxiety was directly related to poor attendance at a clinical breast examination and poor adherence to monthly breast self-examination                          |
| Lerman, 1993 (77)         | Breast cancer; mammography adherence                                  | Survey study; collection of cross-sectional data  | 140 first-degree relatives of breast cancer patients (i.e., at high risk for breast cancer)                        | None   | Mammogram screening patterns; depression; stress impact; breast cancer worries   | Mammogram adherence varied by age: 76% adherence, age 35–39 yr; 86% adherence, age 40–49 yr; 63% adherence, age > 50 yr. Variables associated negatively with adherence included intrusive thoughts about breast cancer ( $p = 0.04$ ) and breast cancer worries ( $p = 0.004$ )   | Psychological distress may lead some individuals to avoid screening examinations   |

Continued

AND OTHER DISEASES section for a more detailed discussion). Two major distinct clinical entities have been identified: neonatal liver disease and adult-onset liver disease.

*Liver disease in newborns and children:* The Swedish newborn screening program demonstrated that about 70% of PI\*ZZ

newborns have abnormal liver function tests and about 10% develop clinically significant cholestasis (4). Approximately 2.5% of individuals with AAT deficiency die of cirrhosis by age 18 years (42).

*Liver disease in adults:* The natural history of liver disease in

TABLE 4. CONTINUED

| First Author, Year (Ref.) | Disease; Behavior Studied   | Study Design  | Sample Size   | Intervention | Outcome Variables  | Major Results   | Remarks  |
|---------------------------|---|---|---|--------------|--|---|--|
| Lerman, 1991 (79)         | Breast cancer; mammogram adherence  | Survey study with prospective analysis of factors associated with mammogram adherence | Members of HMO who were 50 yr of age or older: 121 with normal mammograms, 119 with low-suspicion mammograms, 68 with high-suspicion mammograms   | None         | Adherence to subsequent annual mammography; psychological responses 3 mo after mammogram | Women with high-suspicion mammograms had substantial mammography-related anxiety (47%) and worries about breast cancer (41%). For each variable, a consistent trend ( $p > 0.05$ ) was seen with degree of mammogram abnormality. All three groups had similar adherence rates to subsequent mammograms   | A substantial proportion of women with suspicious mammograms have psychological difficulties, but such sequelae do not appear to interfere with subsequent adherence   |
| Lerman, 1991 (78)         | Breast cancer; BSE frequency and intentions to obtain subsequent mammograms | Survey study  | 308 women, 50 yr old and older, approximately 3 mo after a screening mammogram. Subjects included women with suspicious abnormal mammograms, nonsuspicious abnormal mammograms, and normal mammograms | None         | BSE frequency; mammogram intentions; breast cancer worries                               | Women with suspicious abnormal mammograms exhibited significantly elevated levels of mammography-related anxiety and breast cancer worries. Women with moderate levels of impairment in mood or functioning were more likely to practice monthly BSE than women with either high or low levels of impairment. Breast cancer worries were associated with mammogram intentions |  |
| Senior, 1999 (80)         | FH  | Qualitative analysis of semistructured interviews                                     | Parents of 24 children who had received a positive test for FH at a neonatal screening program  | None         | Themes obtained from semistructured interviews   | When the test was seen as detecting a genetic problem, the condition was perceived as uncontrollable and, hence, more threatening than when the test was perceived as detecting raised cholesterol  | Responses vary according to perceptions of underlying cause of positive screening test. Assessing disease risks by DNA analysis may result in a sense of fatalism, adversely affecting motivation to change behavior to reduce risks |

Definition of abbreviations: BSE = breast self-examination; EBF = exposure biomarker feedback; FH = familial hypercholesterolemia; HMO = health maintenance organization; QSC = quit smoking counseling; SBF = susceptibility biomarker feedback.

adults is less well known than in children. Serial case-control and retrospective cohort studies (*see* Table 7 in LIVER AND OTHER DISEASES section) show that individuals with AAT deficiency have an increased risk for cirrhosis and hepatocellular carcinoma. These studies demonstrate the importance of sex and age as determinants of developing cirrhosis, as the risk of cirrhosis in AAT-deficient individuals is about 2% in individuals under the age of 50 years, but reaches a peak of 15–19% for elderly males greater than the age of 50 years (43, 44). Regarding prevalence of chronic liver disease in the general population, several reports have observed that the prevalence of PI\*ZZ in patients with chronic liver disease is about 0.8% (*see* Table 8 in LIVER AND OTHER DISEASES section).

Regarding primary liver cancer, several reports have shown that the risk of liver cancer is relatively high in homozygotes with cirrhosis, whereas the risk in heterozygotes is small (*see* LIVER AND OTHER DISEASES section).

These data provide strong support for diagnostic detection testing in patients with chronic liver disease (Table 8).

**Necrotizing panniculitis.** The frequency of necrotizing panniculitis in individuals with AAT deficiency is unknown, but is probably low (i.e., less than 0.1%) as only 1 patient in the National Heart, Lung, and Blood Institute (NHLBI, National Institutes of Health, Bethesda, MD) Registry ( $n = 1,129$ ) had necrotizing panniculitis (1). There are no data on the prevalence of

AAT deficiency in individuals with necrotizing panniculitis. The low prevalence of necrotizing panniculitis in individuals with AAT deficiency and the unknown prevalence of AAT deficiency in patients with necrotizing panniculitis do not provide support for or against detection testing (Table 8).

**Multisystemic vasculitis.** AAT deficiency has been shown to be involved in immune processes. PI\*Z heterozygotes have been reported to be at increased risk of developing uveitis, rheumatoid arthritis, and other collagen vascular diseases (*see* LIVER AND OTHER DISEASES section). There are reports linking the Z allele to systemic vasculitis and glomerulonephritis (45–47). Also, numerous studies have confirmed a strong relationship between hetero- and homozygous AAT deficiency PI\*Z and small vessel-necrotizing vasculitides, in particular, Wegener's granulomatosis and microscopic polyangiitis (48–53). As shown in Table 13 in the LIVER AND OTHER DISEASES section, the link between the PI\*Z allele and antiproteinase-3 (anti-PR-3 or antineutrophil cytoplasm antibodies [C-ANCA]) is convincing. In each studied cohort of C-ANCA-positive patients, at least one PI\*ZZ homozygote is identified; that is, about 2% of all patients with anti-PR-3-positive multisystemic vasculitis can be expected to be PI\*ZZ homozygous, the remaining PI\*Z individuals being heterozygotes. The evidence that homozygotes and heterozygotes are overrepresented among patients with anti-PR-3-positive vasculitic syndromes provides moderate support to diagnostic detection in individuals with vasculitis (Table 8). There is a need for

**TABLE 5. PSYCHOLOGICAL IMPACT OF PREDISPOSITIONAL TESTING ON ASYMPTOMATIC ADULTS AT HIGH RISK: OTHER CHRONIC GENETIC DISEASES**

| First Author, Year (Ref.) | Disease                     | Study Design   | Sample Size   | Outcome Measures  | Length of Follow-up                                      | Major Results  | Remarks  |
|---------------------------|-----------------------------|--|---|---|--|--|--|
| Croyle, 1997 (83)         | BRCA1                       | Carriers compared with noncarriers. Pretest and posttest scores compared           | 25 carriers/35 noncarriers; members of a large Utah-based kindred of northern European descent. In-person genetic counseling provided                   | General distress (State Anxiety Scale); test-related distress (IES that measures Intrusion and Avoidance) | Baseline and 1- to 2-wk follow-ups                       | General distress declined after testing, but less so with carriers compared with noncarriers. Carriers exhibited higher levels of test-related distress compared with noncarriers. Participants who were more anxious at baseline manifested more test-related distress at follow-up | Many of the participants had participated in genetic research before and, hence, their level of psychological distress may be less than the general population   |
| Lerman, 1996 (84)         | BRCA1                       | Prospective cohort study with baseline interview assessment of predictor variables | 96 men/women of families of BRCA1-linked HBOC who requested BRCA1 test results: 12 carriers, 103 noncarriers, compared with 44 who had declined testing | Depression; functional health status  | Baseline and 1-mo follow-up interview                    | Noncarriers exhibited significant reductions in depressive symptoms and functional impairment compared with carriers and those who declined testing. Carriers did not exhibit increases in depression and functional impairment  | BRCA1 test results were offered after an education and counseling session in a research setting  |
| Lerman, 1998 (85)         | BRCA1                       | Prospective cohort study with baseline assessment of predictor variables           | 327 male and female members of BRCA1- and BRCA2-linked hereditary breast and ovarian cancer families  | Depression  | Baseline, 1- and 6-mo follow-up                          | Among persons with high baseline levels of stress: depression rates decreased in noncarriers, no change in carriers, and increased in decliners (decliners versus noncarriers; $p = 0.004$ )   | Persons with high levels of cancer-related stress who decline testing may be at risk for depression  |
| Lynch, 1997 (86)          | HBOC                        | Cross-sectional study; carriers versus noncarriers                                 | 181 individuals from HBOC families; 78 carriers, 100 noncarriers, 3 ambiguous   | Qualitative data on emotional reactions   | ? Follow-up data collected at time of genetic counseling | 80% of noncarriers reported emotional relief, whereas more than one-third of carriers reported sadness, anger, or guilt  | No pretest comparison, results only at time of obtaining results; individuals received test results after genetic counseling   |
| Dudok de Wit, 1998 (92)   | HD, FAP, HBOC               | Prospective comparative study  | Individuals at 50% risk for either HD ( $n = 25$ ), FAP ( $n = 23$ ), or HBOC ( $n = 10$ )  | Psychological distress (IES)  | Baseline, 1 wk, and 6 mo                                 | Carriers of the disease genes showed unchanged levels of distress, whereas noncarriers showed a decrease   |  |
| Freyer, 1999 (87)         | Medullary-thyroid carcinoma | Prospective comparative study between carriers and noncarriers                     | 77 subjects   | HADS; SQLP  | ?  | SQLP scores were lower in Ret-mutation carriers. HADS scores were similar between carriers and noncarriers   | Study suggests a possible alteration in various aspects of the quality of life of the genetically predisposed individuals  |
| Aktan-Collan, 2000 (88)   | HNPCC                       | Prospective follow-up  | 271 high risk members of 36 families with HNPCC   | Questionnaires  | 1 mo and 1 yr  | 46% reported that the need for support had been greatest at the moment of test disclosure. Only a minority expressed need for posttest follow-up sessions  | A protocol that includes one comprehensive educational pretest counseling session and a test disclosure session, supplemented with the option of professional psychological support, seems to be sufficient                                  |
| Aktan-Collan, 2000 (89)   | HNPCC                       | Prospective follow-up  | 334 high risk members of families with HNPCC  | Questionnaires  | Baseline, 1 mo, and 1 yr                                 | More than 90% were fully satisfied with the decision to take the test  | High satisfaction with taking the test, which was considerably higher than in previously reported studies, was attributed to careful face-to-face individualized counseling, the health care system, and attitudes of the Finnish population |

*Definition of abbreviations:* BRCA = breast-ovarian cancer susceptibility; FAP = familial adenomatous polyposis; HADS = Hospital Anxiety and Depression Scale; HBOC = hereditary breast-ovarian cancer; HD = Huntington's disease; HNPCC = hereditary nonpolyposis colorectal cancer; IES = Impact of Event Scale; SQLP = Subjective Quality of Life Profile.

studies focusing on the potential effects of augmentation in this patient group.

### Clinical Impact of AAT Deficiency

Justification for genetic testing for a genetically related disorder is enhanced if the clinical burden (i.e., morbidity and mortality) is significant.

*Pulmonary disease.* (A detailed analysis of the evidence demonstrating the impact of AAT deficiency on the lung is provided in the LUNG DISEASE section.) The severity of airflow obstruction in AAT deficiency, age at presentation of respiratory symptoms, and physiologically demonstrable airflow obstruction vary widely. Briefly, lung function is generally well preserved in the first two decades of life (5, 14). Specifically, in follow-up studies



TABLE 6. PSYCHOLOGICAL IMPACT OF PREDISPOSITIONAL TESTING IN ASYMPTOMATIC CHILDREN AT HIGH RISK

| First Author, Year (Ref.) | Disease | Study Design    | Sample Size   | Outcome Measures  | Length of Follow-up | Major Results   | Remarks  |
|---------------------------|---------|-----------------|---|---|---------------------|---|--|
| Codori, 1994 (97)         | FAP     | Longitudinal    | Volunteer sample of 41 children, aged 6–16 yr, and their parents: 19 carriers, 22 noncarriers | Self-report inventories of depression, anxiety, behavior problems, and competence | 3 mo                | All psychological distress scores remained within normal limits after testing   | Predictive testing of children at risk for FAP did not lead to clinically significant psychological symptoms in tested children or their parents                       |
| Rosenberg, 1997 (95)      | FH      | Longitudinal    | 52 children aged 4–17 yr who presented for screening: 34 with FH and 18 without FH            | CBCL, CDI, STAIC  | 1 and 12 mo         | Children with hyperlipidemia (n = 34) had at 12 mo after testing higher mean CBCL scores than children without hyperlipidemia (n = 18)  | Children screened for hyperlipidemia may experience harmful psychological effects  |
| Tonstad, 1996 (96)        | FH      | Cross-sectional | 154 single parents or pairs of parents with 182 affected children aged 6–16 yr with FH        | Semistructured interviews   | NA                  | 8% of parents thought that their child's emotional or social life had been adversely affected; 10 and 28% of the children stated they had worries about cholesterol and heart disease, respectively | Most parents of children with FH do not report psychosocial problems in their offspring; thus screening and treatment need not be postponed for fear of these problems |

Definition of abbreviations: CBCL = Child Behavior Checklist; CDI = Children's Depression Inventory; FAP = familial adenomatous polyposis; FH = familial hyperlipidemia; NA = not available; STAIC = State-Trait Anxiety Inventory for Children.

of adolescents with PI\*ZZ identified at birth normal lung function or at most marginal deviations of no clinical importance were found (14, 15). A decline in pulmonary function may begin to occur in the third and fourth decades of life (see LUNG DISEASE section). Available estimates of yearly decline in FEV<sub>1</sub> among smokers range from as low as 42 ml/year to as high as 317 ml/year (see Appendix 1 in LUNG DISEASE section) (54–60).

Several series have reported early death among individuals with AAT deficiency-associated lung disease. In one study of 246 individuals, the median age at death for smokers was estimated to be about 40 years and 65 years for never-smokers (44). In a study evaluating survival among 120 PI\*ZZ individuals referred to the National Institutes of Health, Brantly and coworkers reported that the actuarial survival to age 60 years among PI\*ZZ subjects was 16% compared with an expected age-matched U.S. survival rate of 85% (61). Similar mortality rates have been observed in other series (57, 59, 62, 63). Ascertainment bias may have caused mortality rates in these studies to be overestimated. AAT deficiency is, however, also reported in elderly nonsmokers (64).

Enhanced morbidity and mortality due to the effects of AAT deficiency on the lung provide strong support for all types of testing (Table 8).

**Liver disease.** A detailed analysis of the clinical burden of liver disease due to AAT deficiency is provided in LIVER AND OTHER DISEASES (see Table 8 in that section). Briefly, of newborns with AAT deficiency, 17% have symptoms of liver disease in infancy, about 10% of newborns with AAT deficiency develop clinically significant hepatitis, whereas 2.5% die of cirrhosis by age 18 years. For adults, cirrhosis of the liver occurs in about 5–15% of AAT-deficient adults, with higher figures for the elderly, particularly among never-smokers, who escape severe emphysema. The overall risk of liver disease in adults is about 20-fold increased compared with the general population. The risk in heterozygotes is much smaller. The enhanced morbidity due to AAT deficiency-related liver disease provides strong support for all types of genetic testing (Table 8).

**Necrotizing panniculitis.** Necrotizing panniculitis is characterized by inflammatory and necrotizing lesions of the skin and represents the least common of the well-recognized complications of AAT deficiency, with about 40 cases reported in the literature as of 1999 (65). In a recent World Health Organization report, a prevalence of less than 1 case per 1,000 was mentioned. Typically, necrotizing panniculitis starts with painful, hot, tender nodules on thighs and/or buttocks in an individual with AAT deficiency (mean age, 40 years). The prognosis is variable and can be lethal. The clinical impact of necrotizing panniculitis provides strong support for genetic testing (Table 8).

**Multisystemic vasculitis.** (See references 48 and 49.) It has been suggested that the presence of an AAT deficiency state in vasculitic patients enhances the risk of fatal outcome (66). The clinical impact of multiorgan vasculitis provides strong support for genetic testing (Table 8).

#### Efficacy of Therapeutic Measures

**Pulmonary disease.** Approval for the use of pooled plasma alpha-1 antitrypsin concentrate (Prolastin; Bayer, West Haven, CT) for treatment of severe AAT deficiency was based on studies demonstrating the “biological efficacy” of intravenous augmentation therapy (67, 68).

Several studies suggest that augmentation therapy may improve survival or reduce the rate of decline in lung function (see Appendix 10 in LUNG DISEASE section). Briefly, two retrospective cohort studies (Grade II-2 level of evidence), a German-Danish study (69) and the NHLBI Registry (60), suggest that the annual decline of FEV<sub>1</sub> may be slowed in patients with moderate impairment (initial FEV<sub>1</sub> predicted < 65%). A multivariate analysis of subjects with severe impairment in the NHLBI Registry showed a decreased mortality rate in those receiving augmentation therapy as compared with those not receiving therapy (p = 0.02).

A prospective German study (70) involving 443 patients with severe AAT deficiency who received weekly intravenous infusions of AAT in addition to their regular medication showed

**TABLE 7. SCREENING: PSYCHOLOGICAL IMPACT OF GENETIC TESTING ON CHILDREN, PARENTS, AND PARENT-CHILD RELATIONSHIPS**

| First Author, Year (Ref.) | Disease | Study Design  | Sample Size   | Outcome Measures   | Length of Follow-up, yr                    | Major Results  | Remarks   |
|---------------------------|---------|---|---|--|--|--|---|
| Sveger, 1999 (19)         | AAT     | Case-control  | 61 adolescents, aged 18–20 yr, identified at birth with AAT compared with 61 matched control subjects   | Psychosomatic symptoms elicited via written-structured questionnaires  | 18   | No differences in psychosomatic complaints between the two groups  |   |
| Thelin, 1985 (20)         | AAT     | Case-control  | Parents of 61 healthy P1*ZZ children; 61 families of control children without AAT; 183 control families selected at random for demographic comparisons  | Qualitative impressions  |  | Initial reactions after obtaining screening results were negative (worry and anxiety) and long lasting. Most parents perceived the deficiency as representing an immediate, serious threat to the child's health. One-third felt relief after the first appointment with the specialist doctor   |   |
| McNeil, 1986 (104)        | AAT     | Case-control  | Parents of 61 healthy 5- to 7-yr-old P1*ZZ children; parents of 61 children without AAT   | Data (qualitative content and specific topics) from interviews with parents  | 5–7  | No significant differences in any of the survey items between the two groups   | Neonatal screening had no negative effects on parental attitudes and feelings toward the child        |
| McNeil, 1986 (25)         | AAT     | Case-control  | Parents of 53 healthy 5- to 7-yr-old children with AAT; 52 control children without AAT   | Observation of selected mother-child interactions  | 5–7  | AAT-deficient children had more problematic behavior in interacting with their mothers compared with control subjects  | Neonatal screening had long-term effects on mother-child interactions                                 |
| Thelin, 1985 (21)         | AAT     |   | Parents   |  |  | One half of mothers and one third of fathers were judged to have made a poor or very poor emotional adjustment to the child's AAT deficiency, as reflected in negative feelings toward the child's AAT deficiency and diverse consequences for the parents' relationships with other family members  |   |
| Helton, 1991 (105)        | CF      | Control study between parents of newborn screen group and parents of children diagnosed traditionally (i.e., at time of symptoms) | 62 parents of children diagnosed with CF by newborn screening; 30 parents of traditionally diagnosed children with symptoms   | Structured interviews evaluating subjective ratings of depressions and anxiety and parental perception of the impact of early diagnosis on parent-child relationship | Range of time since diagnosis: 4 days–5 yr | No significant differences found between the newborn screen group and the traditionally diagnosed group on parental focus or affect or subjective ratings of depression and anxiety. Parents reported intention to maintain their behavioral expectations and discipline of their child with CF. However, 35% of them felt they were more overprotective than they would be of a child without CF and 69% focused increased attention on physical symptoms because of the CF. Almost all felt emotionally closer to the child because of the CF and 27% felt that the diagnosis had actually led to enhanced family relationships with the spouse or with other children | No adverse psychological effects on parents of screened children. Potential enhanced family relations |
| Boland, 1990 (106)        | CF      | Case-control  | 16 mothers of asymptomatic children at the time of screening; 13 mothers of symptomatic children at the time of screening; 29 mothers whose children were diagnosed after the onset of symptoms | Parental Attitude Research Inventory Scale to measure protective attitudes; State Trait Anxiety Inventory Scale to measure anxiety                                   | NA   | No differences in either of the scales measuring protective attitudes and anxiety between the three groups   |   |
| Baroni, 1997 (107)        | CF      | Case-control  | 17 families of children diagnosed through newborn screening; 20 families of children diagnosed traditionally; 33 families of healthy children   | PSI designed to measure stress in the parent-child system  | NA   | No significant differences in PSI scores between all three groups. Of the screening group, 45% had "at-risk" Total scores and 50% had Child Demandingness scores warranting referral   |   |

Definition of abbreviations: AAT = alpha-1 antitrypsin; CF = cystic fibrosis; NA = not available; PSI = Parenting Stress Index.

that the mean decline in FEV<sub>1</sub> was approximately half the rate of decline previously reported for untreated index cases (54, 57, 63, 71). Finally, a randomized control study (Grade I level of evidence) showed a trend toward slower loss of lung tissue on computed tomography scanning in augmentation therapy recipients compared with control subjects ( $p = 0.07$ ), but no effect of intravenous augmentation therapy on decline in FEV<sub>1</sub> (67).

The available evidence on the efficacy of intravenous augmentation therapy provides mild support for the consideration of diagnostic genetic testing (Table 8). The efficacy of intravenous augmentation therapy is not relevant when considering the appropriateness of predispositional testing or screening, as individuals being tested are asymptomatic and without spirometric

changes and, hence, treatment modalities are not a consideration (Table 8).

*Liver disease.* Other than liver transplantation, there are no known treatments for AAT deficiency-induced liver disease.

*Necrotizing panniculitis.* Augmentation therapy appears safe and effective (*see* references 175–178 in LIVER AND OTHER DISEASES section). Dapsone, either alone in less severe cases, or combined with augmentation therapy, may be of additional value.

#### Accuracy of Genetic Tests for AAT Deficiency

As reviewed in the LUNG DISEASE section, available tests to determine both the serum AAT level and the phenotype are highly accurate. The availability of accurate testing techniques

**TABLE 8. RELEVANT ISSUES INVOLVED WITH GENETIC TESTING: CONCLUSIONS FROM THE EVIDENCE, IMPLICATIONS FOR TESTING, AND STRENGTH OF THE EVIDENCE**

| Relevant Issue  | Conclusions from the Evidence   | Implication for Testing* |                  |           | Strength of Evidence |
|---|---|--------------------------|------------------|-----------|----------------------|
|   |   | Diagnostic               | Predispositional | Screening |                      |
| <b>A. Prevalence of AAT deficiency</b>  | 1/1,575 in Sweden, 1/2,857–1/5,097 in United States. On the basis of a U.S. population of 250 million, 80,000–100,000 AAT-deficient individuals are expected. Studies may have selection bias and, therefore, may overrepresent the general population. Frequency of AAT deficiency is comparable to that of cystic fibrosis in the United States and is twice as common in Scandinavia and, hence, provides moderate support for screening. Prevalence data have no relevance for diagnostic or predispositional testing | §                        | §                | ++        | II-2                 |
| <b>B. Penetrance and population prevalence of AAT deficiency-associated disease</b> |   |                          |                  |           |                      |
| Obstructive lung disease  | The penetrance of COPD among subjects with severe AAT deficiency is not properly known because many Pi*ZZ individuals are never identified. In the United States, there are about 2.1 million individuals with emphysema and 2–3% of patients with COPD have AAT deficiency; accordingly, about 40,000–60,000 individuals with emphysema has AAT deficiency. These results provide strong support for diagnostic testing of individuals with COPD; no relevance for predispositional testing or screening                 | +++                      | §                | §         | II-3                 |
| Liver disease (cirrhosis/cancer)  | <i>Adults:</i> Cirrhosis of the liver occurs in about 5–15% of AAT-deficient adults; the figure is higher for the elderly, particularly among never-smokers, who escape severe emphysema. The overall risk of liver disease in adults is approximately 20-fold increased compared with the general population<br><i>Children:</i> Of newborns with AAT deficiency: 17% have symptoms of liver disease in infancy and 2.5% die of cirrhosis by age 18 yr. These figures provide strong support for diagnostic testing      | +++                      | §                | §         | II-2                 |
| Necrotizing panniculitis  | Fewer than 1/1,000 individuals with AAT deficiency have necrotizing panniculitis. These data and the unknown prevalence of AAT deficiency in individuals with necrotizing panniculitis do not provide support for or against detection testing  | ±                        | §                | §         | III                  |
| Multisystem vasculitis (anti-PR-3-positive vasculitis)                              | Penetrance and population prevalence are unknown. Evidence shows a strong link between the Pi*ZZ allele and anti-PR-3-positive vasculitis. These data provided moderate support for diagnostic testing  | ++                       | §                | §         | II-2                 |
| <b>C. Clinical impact of AAT deficiency</b>   |   |                          |                  |           |                      |
| Obstructive lung disease  | Greater decline in FEV <sub>1</sub> and greater mortality at earlier age compared with those with usual COPD  | +++                      | +++              | +++       | II-2                 |
| Liver disease   | Approximately 2.5% of infants identified at birth with AAT deficiency need liver transplantation or die in childhood. Increased risk of cirrhosis/carcinoma in adults with AAT deficiency, especially in elderly never-smokers  | +++                      | ++               | ++        | II-2                 |
| Necrotizing panniculitis  | Inflammatory and necrotizing lesions of the skin can be lethal.   | +++                      | ++               | ++        | III                  |
| Multisystem vasculitis (anti-PR-3-positive vasculitis)                              | AAT deficiency may enhance the risk of fatal outcome  | +++                      | ++               | ++        | II-2                 |
| <b>D. Efficacy of treatment</b>   |   |                          |                  |           |                      |
| Lung disease  | Efficacy augmentation therapy suggested in two retrospective studies and one prospective uncontrolled study. One randomized, control study showed augmentation therapy had no effect on FEV <sub>1</sub> decline, but there was a trend toward a decrease in the loss of lung tissue as measured by computed tomography (p = 0.07). These data on the efficacy of augmentation therapy provide mild support for detection testing   | ++                       | §                | §         | I                    |
| Liver disease   | There are no known treatments for AAT deficiency-induced liver disease  | –                        | §                | §         | —                    |
| Necrotizing panniculitis  | Augmentation therapy appears safe and effective. Dapsone, either alone or combined with augmentation therapy, may be of additional value  | +                        | §                | §         | III                  |
| Multisystem vasculitis (anti-PR-3-positive vasculitis)                              | There are no known treatments for AAT deficiency-induced vasculitis   | –                        | §                | §         | —                    |
| <b>E. Accuracy of genetic tests</b>   | Accurate: low false negative/low false positive   | +++                      | +++              | +++       | III                  |
| <b>F. Efficacy of providing information about changing-health related behaviors</b> |   |                          |                  |           |                      |
| Smoking prevention  | Two studies showed smoking initiation rates of adolescents identified at birth as having AAT were lower than rates among matched control subjects   | +                        | +                | ++        | II-2                 |
| Smoking cessation   | Studies show no effect of genetic information about smoking cessation programs  | ±                        | ±                | ±         | I                    |
| Change of occupation  | Theoretical benefit. No study shows that individuals change jobs in response to receipt of genetic information  | ∅                        | ∅                | ∅         | —                    |
| <b>G. Psychologic effects</b>   |   |                          |                  |           |                      |
| Symptomatic individuals   | Studies suggest positive and negative effects from knowledge of a positive test   | ±                        | §                | §         | III                  |
| Asymptomatic adults at high risk  | Can be variable. In the short term (posttesting), noncarriers have decreased distress, carriers have no change in prestress levels, and nontested individuals have increased stress. Long-term effects are similar between carriers and noncarriers. Studies suggest that posttest distress is more dependent on level of pretest stress than on the test itself  | §                        | ±                | §         | II-1                 |
| Asymptomatic children at high risk  | Data are limited and mixed  | §                        | ±                | §         | II-2                 |
| Family members  | Can create tensions in families; testing can also bring families together   | ±                        | ±                | ±         | II-3                 |
| Screening population  | Can have adverse effects on parents and parent-child relationship. No long-term effects on Swedish adolescents identified at birth  | §                        | §                | –         | II-3                 |
| <b>H. Social discrimination</b>   | Anecdotal data that insurance-/employment discrimination exists   | –                        | –                | –         | III                  |
| <b>I. Economic costs</b>  |   |                          |                  |           |                      |
| Costs of testing  | Minimal costs associated with testing, higher costs with screening due to increased numbers   | ++                       | ++               | +         | III                  |
| Costs of augmentation therapy   | Mean annual costs, \$40,123; incremental cost per year of life saved, \$40,301  | –                        | §                | §         | II-2                 |
| Costs of infrastructure for testing (e.g., counseling)                              | No data, but costs will be high   | –                        | –                | –         | —                    |

Definition of abbreviations: AAT = alpha-1 antitrypsin; COPD = chronic obstructive pulmonary disease.

Definition of symbols: ∅ = no evidence is available; § = no relevance for testing; – = negative support for testing; ± = neutral support for testing, as evidence is conflicting or implication of testing is individualized; + = mild support for testing; ++ = moderate support for testing; +++ = strong support for testing.

\* Implication for testing represents the significance that each issue has, in and of itself, for or against testing.

satisfies one of the important conditions in support for genetic testing for AAT deficiency (Table 8).

### **Efficacy of Providing Genetic Risk Information about Changing Health-related Behaviors: Preventive Measures**

Support for genetic testing for any adult-onset genetic condition increases to the extent to which there are behavioral risk factors that can be modified in response to detecting genetic mutations in individuals. Accordingly, to effect reductions in morbidity and mortality, individuals identified as having genetic mutations predisposing to future diseases will be advised to adhere to changes in lifestyle and frequent surveillance (72, 73). Psychologic factors, however, may prevent individuals from adopting preventive health behaviors.

For AAT deficiency, two major risk factors have been identified: cigarette smoking and environmental pollutants (*see LUNG DISEASE* section [Table 6 and Appendices 3 and 4] for an analysis of the evidence for these risk factors).

**Cigarette smoking.** Theoretically, the existence of cigarette smoking as a risk factor for developing or enhancing AAT deficiency-related disease would provide support for diagnostic testing, as a positive test can encourage individuals either to stop smoking or not to take up smoking. This risk factor also has potential implications for predispositional testing and screening, as a positive test can motivate individuals to avoid this risk factor. However, whether the receipt of genetic information concerning an enhanced risk of developing a disease will lead to a modification of health-related behaviors is not clear. The following summarizes the available data on the effects of the receipt of genetic information about cigarette smoking as well as other health-related behaviors that enhance the risk of other adult-onset, genetically related disorders.

**Smoking prevention.** Because of the powerful addictive properties of smoking (e.g., even with maximal support, smoking cessation occurs in only a small proportion of smokers [22% sustained quitters at 5 years in the Lung Health Study]), counseling nonsmokers not to smoke may be more successful than efforts aimed at smokers. Two studies (Table 4) have demonstrated the efficacy of providing genetic information about AAT deficiency to individuals identified at birth as having AAT deficiency on initiation rates of smoking. These investigations were cohort-controlled studies (Grade II-2 evidence) that observed lower frequency of adolescent smoking in individuals with AAT deficiency identified at birth compared with matched control subjects. Specifically, Thelin and colleagues showed that the smoking rate of adolescents (18–20 years old) previously found to have AAT deficiency during neonatal screening in Sweden was significantly lower than that of a demographically matched control group, that is, 6 versus 17% (16). Wall and coworkers observed that 22 individuals identified to be PI\*ZZ at birth had a lower rate of current smoking or of trying smoking cigarettes than did an age-matched cohort (5).

These data provide moderate support for screening programs aimed at newborns and adolescents, as well as for diagnostic and predispositional testing of adult nonsmokers (Table 8).

**Smoking cessation.** Institution of smoking cessation efforts in asymptomatic, current smokers identified with AAT deficiency may prevent or delay onset of disease or prevent progression of disease in symptomatic individuals. It is unknown, however, whether the quit rates of smokers with AAT deficiency-associated lung disease would be greater with the receipt of genetic information about having a genetic susceptibility to a lung disease compared with the standard information given about the adverse effects of smoking. Similarly, it is unknown whether asymptomatic smokers at high risk of having AAT deficiency would have higher quit rates after receiving genetic

risk information of developing AAT deficiency disease compared with just knowing that they might have a familial disposition to having AAT deficiency-associated disease.

No studies have investigated the effects of receiving genetic information about smoking quit rates in individuals with AAT deficiency. However, two studies (Table 4) have investigated the effects of providing individuals with genetic risk information of developing tobacco-induced carcinoma on their smoking quit rates. Lerman and coworkers showed that the quit rate of smokers 2 months after receiving minimal contact quit-smoking counseling and information that they had an inherited susceptibility to the carcinogenic agents in tobacco, obtained via genetic testing, were not higher than those of smokers who received only minimal contact quit-smoking counseling (74, 75). In a follow-up study, the lack of efficacy of genetic feedback on enhancing smoking rates persisted at 12 months (75). However, there was a significant impact of genetic feedback on the likelihood of a quit attempt at 12 months. Hence, genetic susceptibility feedback has the intended effects on motivation to quit and, therefore, its success may be dependent on a more intensive smoking cessation treatment for the heightened motivation to translate into smoking cessation. Also, the initial increases in depressive symptoms observed at the 2-month follow-up in the genetic susceptibility feedback group were not sustained at the 12-month follow-up.

These studies suggest that providing genetic information concerning the future risk of developing tobacco-induced lung disease is not efficacious in motivating individuals to quit smoking. It may be interesting to speculate that such genetic information may be only as efficacious as just receiving general information about the adverse effects of cigarette smoking. Accordingly, these data do not provide support for or against any of the types of genetic testing (Table 8).

Research is needed to investigate the impact of genetic testing on smoking cessation efforts for the AAT population. Such research can inform the development of clinical practice standards to ensure that the potential medical benefits of genetic testing are not outweighed by the psychologic costs. If patients' anxiety about their predisposition for future disease is not addressed adequately in the context of genetic counseling, they may be less likely to follow the screening and lifestyle recommendations they receive.

Regardless of whether the information from a genetic test encourages smoking cessation, some might argue that the information nevertheless confers greater responsibility on the patient for the negative consequences of (continued) smoking. Research is needed to investigate what impact such allegedly greater responsibility would have on health care and financing.

**Health-related behaviors that enhance the risk of other adult-onset genetic related disorders.** Several studies have explored the effects of receiving information about having a genetic predisposition for a future disease on other health-related behaviors. Two studies involving women who were at increased risk for developing breast cancer (one or more first-degree relatives with breast cancer) suggested that adherence to screening recommendations may be suboptimal due to psychologic distress (76, 77). In a study of women notified of an abnormal mammogram, those who experienced high levels of psychologic distress after notification were less likely to perform subsequent breast self-examination than those with moderate levels of distress (78). However, in another study involving women with normal, low-suspicion, and high-suspicion mammograms, although women with high-suspicion mammograms had substantial mammography-related anxiety and worries about breast cancer, all three groups had similar adherence rates to subsequent mammograms (79).

One other study analyzed the semistructured interviews of

parents of children who had received a positive screening test result, informing them that their child was at risk for having familial hypercholesterolemia. During the course of the interviews, it became apparent that not all parents were aware that their child had been screened for a genetic condition. When parents perceived the test as detecting a raised cholesterol level that reflected primarily a dietary phenomenon, the condition was perceived as controllable and less threatening. When the test was seen as detecting a genetic problem, the condition was perceived as uncontrollable and more threatening (80).

These studies support previous evidence showing the lack of efficacy of the receipt of genetic information in altering health-related behaviors (i.e., smoking cessation), and emphasize that how people think about disease, particularly the perceived controllability of a disease, is an important determinant of what they do about it (81).

*Change of occupation in response to receipt of genetic information.* Several studies suggest a role for environmental factors in the development of AAT deficiency-associated pulmonary disease (see LUNG DISEASE section). Accordingly, another potential preventive measure for AAT deficiency-related diseases includes occupational counseling to minimize breathing polluted air. Although it may be likely that individuals would change their occupations in response to receipt of genetic information about risk assessment of developing AAT deficiency-related diseases, no evidence is available to support this conclusion (Table 8).

### Psychologic Effects of Genetic Testing

Genetic tests are different from standard diagnostic tests in several ways. First, the tests differ in their relevance for the person's concept of self. Second, the tests differ in their relevance for the person's current health versus future health. A typical nongenetic, diagnostic test pertains to a person's current health and directs a specific course of medical treatment. A predictive genetic test pertains to future health and may or may not lead to any immediate treatment or changes in prevention behavior. Finally, genetic testing is distinct because the test result provides the basis for predictions not only about the individual tested but also about that individual's parents, siblings, and offspring. Hence, genetic testing has immediate implications for the entire family, implications that must be discussed and anticipated before testing. It is these differences that account for the unique psychologic issues and effects of testing that arise in the context of genetic testing for tested persons and their families. They also raise important ethical issues regarding confidentiality and privacy, and duty to disclose, which we discuss in ETHICAL ISSUES INVOLVED WITH GENETIC TESTING (see below).

Evidence of the psychologic impact of genetic testing comes from observational studies (Grade III evidence) and prospective studies comparing the effects between carriers and noncarriers (Grade II-2 evidence). These studies involved testing for AAT deficiency as well as for other genetic disorders: cystic fibrosis, hereditary hemochromatosis, familial hypercholesterolemia, and the hereditary cancer syndromes (breast-ovarian cancer susceptibility [BRCA1 gene], familial adenomatous polyposis, and hereditary nonpolyposis colorectal cancer). The results obtained from these other genetic disorders may or may not be relevant to genetic testing for AAT deficiency.

*Symptomatic individuals.* Theoretically, symptomatic individuals who test positive for a genetically related disease in which medical therapies are available may gain psychologic benefits from finding an explanation for their symptoms and from the knowledge that symptoms can be treated.

On the other hand, there may be potential adverse psychologic effects from a positive test. For example, there may be

difficulty maintaining a healthy concept of self caused by feelings that the seed of one's own destruction lies in one's predetermined biologic makeup. In addition, there may be feelings of guilt due to thoughts that one may have passed on the genetic condition to one's offspring.

Only limited evidence is available on the psychologic effects of genetic testing for symptomatic individuals with AAT deficiency (82). In a survey of individuals with AAT deficiency-associated diseases, equal numbers of respondents reported adverse and beneficial effects of having a genetic disease on their relationships and their marriages. However, it is not known whether any of the psychologic effects are due to knowledge of having a genetic disease or to having impaired health.

These data, in and of themselves, are of limited value in providing support either for or against diagnostic testing and are of no relevance for predispositional testing and screening (Table 8).

Further research is needed to investigate the psychologic effects from being tested positive or negative for AAT deficiency.

#### *Asymptomatic individuals at high risk.*

**Adults.** (See Table 5.) In contrast to studies involving symptomatic individuals, more information is available concerning the psychologic impact of predispositional testing on asymptomatic adult individuals at high risk of developing a genetically related disease that is amenable to preventive measures or specific treatment modalities. No studies determining the psychologic effects of predispositional testing in individuals at high risk for AAT deficiency have been performed. In the absence of such data, we decided to review the relevant data for genetic conditions that share common characteristics with AAT deficiency, for example, single-gene defect, adult onset, and the existence of preventive and therapeutic measures. As these diseases include the cancer syndromes, we do recognize, however, that data generated from individuals with cancer syndromes may not be generalizable to those with AAT deficiency.

Although it is readily recognized that receipt of a positive test result may be associated with adverse psychologic effects, such a testing result may also incur psychologic benefits by reducing uncertainty and providing an opportunity for appropriate planning.

Four prospective studies were identified that explored the psychologic reactions to genetic testing for breast cancer. Croyle and coworkers reported initial psychologic outcomes for 60 women, members of a large Utah-based kindred of northern European descent, who received genetic test results (83). These investigators examined levels of general distress (anxiety) and specific test-related distress (thoughts and feelings about the test results) 1–2 weeks after the women had received their test results, during an in-person visit with a genetic counselor and a psychologic counselor. In a follow-up telephone interview, the average level of general distress reported by the group of women declined, but carriers demonstrated more distress than noncarriers at the follow-up interview. Carriers exhibited higher levels of test-related distress compared with noncarriers. These data, however, are limited by the fact that all the study participants are members of one large, Utah-based kindred.

Lerman and coworkers reported the results of a larger and more diverse group of participants (84). Their findings were based on a 1- and 6-month follow-up interview assessment of 96 men and women who had received their BRCA1 mutation carrier results. In addition, the study included comparison data from 44 individuals who had been offered BRCA1 testing but had declined. Depression was assessed at baseline and follow-up, using the Center for Epidemiological Studies Depression Scale. Analyses of the findings revealed no increase in depressive symptoms in either carriers or noncarriers. Relative to those

who declined testing, the noncarriers manifested a decline in depression from baseline to follow-up. In addition, the noncarriers showed some improvement in self-reported sexual functioning and role impairment.

In another study involving 327 male and female members of BRCA1/2-linked hereditary breast and ovarian cancer families, Lerman and colleagues (85) observed that among persons who reported high baseline levels of stress, depression rates decreased in noncarriers, showed no change in carriers, and increased in decliners (decliners versus noncarriers,  $p = 0.004$ ). Finally, in an observational study involving 181 individuals from hereditary breast-ovarian carcinoma families who received BRCA1 testing, 80% of noncarriers reported emotional relief, whereas more than one-third of carriers reported sadness, anger, or guilt (86). No pretest comparison was performed in these individuals.

Studies investigating the psychologic effects of other hereditary cancer syndromes have shown various results and suggest that the results may be dependent on the type of counseling provided (87–89).

Although these studies provide important insights into psychologic responses to genetic risk testing, their selective sampling bias limits the generalizability of results. More specifically, these samples were not clinical cohorts of individuals seeking and/or referred for personal genetic cancer risk assessment, as they were derived from samples invited to participate in genetic epidemiologic research. As such, these samples differ from a clinic-attending sample of women seeking and/or referred for heritable ovarian cancer risk estimates.

In two of the studies involved with BRCA1 testing, it was found that psychologic adjustment to test results depends more on pretest psychologic adjustment than on the results themselves (83, 85). Finally, DudokdeWit and colleagues (90–92) observed that participants who were depressed before the test were more distressed after testing. Essentially, the test result did not additionally contribute to posttest distress.

The *prima facie* simple notion that the test result, as such, determines the distress experienced seems to be a misrepresentation of a more complex reality. Essentially, the psychologic impact of genetic testing may depend more on pretest psychologic distress than on the test result itself. Finally, there is evidence that individuals who choose to be tested are self-selected for a favorable psychologic response to testing, that is, these individuals feel that they are equipped to handle “bad news” (93). On the other hand, there may be individuals who avoid testing because they perceive themselves to be more vulnerable to adverse psychologic reactions. As these individuals’ experiences are not represented in studies investigating the psychologic reactions of testing, such studies showing that psychologic reactions to testing are far less than catastrophic may be overly optimistic.

A qualitative analysis of the data on the testing of asymptomatic individuals at high risk of having a genetic predisposition to a future disease shows that the psychologic reactions are at best mixed. Also, most of these studies are limited by modest sample sizes, uncontrolled research designs, and self-selected subject participation. However, most of the evidence shows that, in general, noncarriers and carriers differ significantly in terms of short-term, but not long-term, psychologic adjustment to test results. Also, the posttest psychologic reactions may be more dependent on the psychologic state of the individual before testing. Although the psychologic reactions to testing are probably individualized, these data do provide moderate support for genetic predispositional testing.

More research is needed on the psychologic reactions of adult, high-risk individuals to being tested for AAT deficiency, as the observations obtained from other genetic disorders may not be generalizable to AAT deficiency.

**Children.** (See Table 6.) The primary objection to predictive testing of children is that youngsters who learn they could or will incur a serious genetic condition later in life will experience devastating emotional damage. Because this information would come to them at a stage when their distinctive identity is emerging, several observers fear they would suffer a diminished sense of self-esteem and worth. Because children have a limited understanding of illness, they might come to view themselves as sick and damaged and might blame themselves for having inadvertently done something to alter their genes. Furthermore, a positive test may affect parent-child relationships, as parents may tend to regard their children as being sick, a child with the mutated gene may tend to identify only with the affected parent, and a noncarrier child may harbor feelings of guilt for not carrying the mutated gene. However, predictive testing of children can provide some with substantial emotional benefits. The most obvious benefit is to those who test negative, for they will experience reduced uncertainty and anxiety. Some children who test positive may also be relieved to have the uncertainty that has hovered over them resolved.

At present, there are a limited number of studies that have determined the effects of predispositional testing on adolescents. Codori and colleagues (94) evaluated the psychologic effect of predictive genetic testing through surveys of children at risk for familial adenomatous polyposis. Their psychologic state was assessed before testing and 3 months later. The main outcome measures were self-report inventories of depression, anxiety, behavior problems, and competence. The study population consisted of 41 children, aged 6 to 16 years. Nineteen children were carriers of the gene mutation and 22 were noncarriers. All psychologic distress scores remained within normal limits after testing.

Rosenberg and colleagues conducted a longitudinal study involving children, aged 4–17 years, screened for familial hyperlipidemia and observed that children with hyperlipidemia ( $n = 34$ ) had, 12 months after testing, higher mean scores on a behavioral assessment tool than did those without hyperlipidemia ( $n = 18$ ), suggesting that identification of hyperlipidemia may have harmful psychologic effects in children (95). Finally, Tonstad performed a cross-sectional interview study of 154 single parents or pairs of parents with 182 affected children, aged 6–16 years, with familial hyperlipidemia and observed that greater than 90% of the parents of children with familial hyperlipidemia did not report psychosocial problems in their offspring and only 10 and 28% of the children stated they had worries about cholesterol or heart disease, respectively (96). Thus, screening and treatment need not be postponed for fear of these problems.

These few studies are too incomplete to draw any definitive conclusions regarding the balance of harms and benefits of testing. Accordingly, these data are not helpful in providing any conclusions concerning support for or against predispositional testing. Any future testing of adolescents should be performed within a research setting that will assess the short-term as well as the long-term effects of such testing.

**Family relationships.** Findings reported to date have focused on the individuals tested rather than on their family relationships. Although individual psychologic functioning is an important outcome, evaluations that focus only on assessment of individual psychiatric sequelae (such as depression and anxiety inventories) can miss many of the important psychosocial consequences of genetic testing. Hence, patients who does not manifest clinically significant levels of depression or anxiety might nevertheless be faced with impaired relationships with their spouse, parents, or siblings. Siblings with different test results must often redefine the meaning of their relationship, as must parents and offspring who feel guilt, resentment, or envy concerning the test results

of family members. The psychosocial context of a particular family can influence the adaptation of individuals in ways that are difficult to measure and evaluate. Another concern is the effects of disclosure of genetic test results on marital discord and relationships with friends. In a survey performed on patients with AAT deficiency, respondents were mixed in their reports concerning the effects of testing on their marriages and relationships with friends (82). Studies of other genetic conditions have also observed mixed effects on marital relationships (93, 97–100).

Predictive testing, however, need not have only harmful consequences within families. It can provide families with the opportunity to foster closeness, honesty, and openness (93, 97, 99, 100). The risks of psychologic distress and family disruption are likely to be greater when testing is offered in clinical settings that do not provide adequate patient education, genetic counseling, informed consent, and follow-up.

These preliminary data demonstrate that psychologic effects on family members are probably individualized and, therefore, do not provide either support for or against predispositional testing.

**Screening.** (See Table 7.) General concern has been expressed concerning the potential adverse psychologic and social effects of screening healthy populations with no known previous genetic risk.

**Children.** The Swedish neonatal screening experience showed that the psychosomatic complaints of young adults, 18–20 years old, who were identified as having AAT deficiency at birth were similar to those of age-matched control subjects (17).

**Parents and parent-child bonding.** One concern with neonatal screening relates to the degree of parental stress and anxiety, as well as adverse effects on parent-child bonding, triggered by a positive result. In the nationwide neonatal screening for AAT deficiency in Sweden, longstanding adverse psychologic effects on mothers and on the mother-child relationship occurred (20–22, 25, 101–104). Such effects may have been due to the lack of counseling services available to families on notification of test results.

More evidence is available from the cystic fibrosis (CF) experience. For example, Helton and colleagues (105) found no significant differences in subjective ratings of depression and anxiety between parents of children identified at newborn screening and parents of children traditionally diagnosed. Also, most parents of infants with CF reported intentions to treat their child the same as they would a child without CF. Furthermore, almost all parents felt emotionally closer to the child because of the diagnosis of CF. Nevertheless, more than one-third of the same parents admitted to being overprotective and more than two-thirds of the parents felt they tended to focus attention heavily on physical symptoms.

Boland and Thompson compared the strength of overprotective child-rearing attitudes of 3 groups of mothers: (1) 16 mothers whose children were asymptomatic at the time of newborn screening, (2) 13 mothers whose children were symptomatic at the time of screening, and (3) 29 mothers whose children were diagnosed after the onset of symptoms. Results showed that newborn screening had not increased a mother's tendency to overprotect her child with CF and in some cases the tendency had decreased. Further, delay in diagnosis when screening was not conducted usually caused mothers considerable personal distress (106).

Preliminary data from the Wisconsin CF Neonatal Screening Project showed that parents of children diagnosed with CF through newborn screening did not show significantly higher stress scores than their healthy or "traditionally diagnosed" CF comparison families. They did, however, have high frequencies of "at-risk scores" warranting referral based on clinical cutoff

levels for Total Parenting Stress scores (45%) and Child Demandingness subscale scores (50%) (107).

One of the primary factors that has been suggested to impact on whether or not newborn screening affects the relationship between parent and child is follow-up communication and counseling. Grossman and colleagues (108) reported that families who received genetic counseling after screening for sickle cell anemia both gained and retained knowledge about the sickle cell trait and, therefore, experienced less anxiety about the unknown. The effectiveness of genetic counseling has been shown to be related to the parents' prescribed burden of the disease. The more accurate the interpretation of test results received by parents, the more accurate their perception of how the child's special needs would play a role in the family's life. Miscommunication and/or misunderstanding of the entire screening process may cause undue stress for parents, who generally have little personal knowledge about specific genetic disorders. An important consideration related to the possibility of mass newborn screening for any disease is the feasibility of providing professional follow-up counseling to all families to ameliorate the stress that early testing may cause.

These data provide support for a recommendation that newborn screening not be done unless adequate counseling is provided and early diagnosis is essential for the institution of preventive measures (Table 8).

#### **Adverse Social Effects: Discrimination/Stigma**

The sensitive nature of genetic information creates concerns with the potential for breaches of confidentiality and the subsequent risk of genetic discrimination by employers and insurers (health, life, and disability). Within the European Community, health insurance discrimination would be expected to be rare, as most countries have national health insurance. However, if AAT-deficient individuals decide to purchase supplemental private insurance, then they may be subject to practices like those that may be occurring in the United States. Regarding workplace discrimination, in the United States, where health insurance is usually provided by the employer, genetic screening of employees has more serious implications. A position in Great Britain is that genetic screening in the workplace is justified only by concerns for the safety of the involved individual or that of third parties. Evidence of discriminatory practices comes mainly from descriptive studies and case reports (Grade III level of evidence).

The actual prevalence of discrimination cases involving individuals with AAT deficiency is unknown. An American mail survey of patients with AAT deficiency-associated lung disease showed that 15.8% reported losing their jobs and 10.5% reported losing their health insurance after diagnosis (82). The survey, however, did not report details of the reasons for loss of health insurance coverage, which may or may not have been coincident with their job loss. An individual with AAT deficiency received a determination from the U.S. Equal Employment Opportunity Commission (EEOC) that she was fired by her employer because of her disability. The individual with AAT deficiency had filed under one of the three prongs of the Americans with Disability Act to get a determination from the EEOC. She filed under the second prong, that is, "regarded as disabled" (109, 110). Other individuals with AAT deficiency have claimed employment discrimination due to their genetic condition (111).

Concerning other genetic disorders, in a study of the perceptions of 332 members of genetic support groups with 1 or more of 101 different genetic disorders in the family, it was found that as a result of a genetic disorder, 25% of the respondents or affected family members believed they were refused life insurance, 22% believed they were refused health insurance, and 13% believed they were denied or let go from a job (112). Other

cases of alleged genetic discrimination by employers and insurers have been reported (113, 114). Billings and coworkers illustrated these possibilities in a review of 39 cases of insurance or employment discrimination (32 insurance, 7 employment) (113). They found discrimination against the asymptomatic ill—those with a genetic predisposition who remain healthy—who usually lost their insurance after undertaking preventive care. Overall, the problems encountered included difficulty in obtaining coverage, finding or retaining employment, and being given permission for adoptions. Finally, in a postal survey, Low and colleagues (115) observed that 33.4% of members of seven British support groups for families with genetic disorders had problems when applying for life insurance, compared with 5% of applicants who answered questions on applying for life insurance as part of an omnibus survey.

Insurance companies may deny insurance to those they consider to be at too great a risk for an illness or to those with preexisting conditions. On the other hand, insurers may have little interest in whether potential policyholders have a genetic predisposition for a disease, perhaps because of the high turnover rate in health insurance policies. In a survey of genetics services providers, Fletcher and Wertz (116) found that refusal of employment or insurance was generally not related to genetic testing. In a survey of health insurers, Hall and Rich (117) found no well-documented cases of health insurers either asking for or using presymptomatic genetic test results in their underwriting decisions.

Regarding discrimination in the workplace, the U.S. EEOC went to court to stop a company from testing its employees for genetic defects (118). The commission asked that Burlington Northern Santa Fe Railroad be ordered to halt such testing on blood taken from employees who have filed claims for work-related injuries based on carpal tunnel syndrome. The test seeks to identify a genetic defect that some experts believe can predispose a person to some forms of carpal tunnel syndrome. Accordingly, the belief is that if an employee tests positive for the genetic test, the employer may be able transfer responsibility for the development of carpal tunnel syndrome to the employee.

Although it is difficult to quantify the incidence of genetic discrimination, there is a real concern that as these tests become prevalent, this issue will loom larger for insurers (119). In addition to actual discrimination is the fear of discrimination and the way that people's choices are limited as a result of this fear. For example, individuals may refuse to obtain testing and thereby not receive a diagnosis because of the fear of losing insurance and/or employment (120).

In the United States, genetic discrimination has been addressed in specific states legislation (121). These laws, however, are ineffective and are preempted by federal regulations relative to self-employed individuals (two-thirds of Americans are self-employed). There is now some protection in the workplace for the asymptomatic ill. In 1995, the U.S. EEOC stated in its compliance manual that healthy people carrying abnormal genes will be protected against employment discrimination by the Americans with Disabilities Act (122). Several European countries have also enacted specific policies prohibiting the obtaining and use of genetic information by insurers (123).

### Economic Costs

Major determinants of the cost-effectiveness of screening are the prevalence and disease burden of AAT deficiency; the sensitivity and specificity of the genetic tests; the effectiveness of treatment and prevention measures in reducing the burden of disease; compliance with screening, diagnosis, and therapy; the costs of the administrative infrastructure needed to conduct the screening; and the costs of informed consent procedures, educational

services, and counseling services. The cost-effectiveness of population screening for AAT deficiency is largely unknown and challenging to determine because technology and treatment modalities are changing rapidly.

Several investigators have looked at the costs associated with intravenous augmentation therapy in individuals with AAT deficiency. In a study relying on self-reported data regarding health resource utilization, augmentation therapy incurred substantial additional costs (124). The mean annual cost was \$40,123 (U.S. dollars) for PI\*ZZ individuals receiving augmentation therapy compared with \$3,553 for those individuals not receiving such therapy. Several studies have used economic models to estimate the cost-effectiveness of augmentation therapy (125–127). For example, assuming a 30% therapy efficacy, Hay and Robin (125) estimated the cost per life-year saved ranged between \$50,000 and \$128,000, a value comparable to other widely used medical interventions. A more recent preliminary report of a cost-effectiveness analysis using a Markov chain model and data from the NHLBI Registry (60) shows that lifelong augmentation therapy (begun at age 46 years and with an FEV<sub>1</sub> of 49% predicted) costs \$312,511 per quality-adjusted life-year, and that augmentation therapy has a less favorable incremental cost-effectiveness ratio (i.e., exceeds \$100,000 [126]). These cost estimates for diagnostic testing, however, should be interpreted with caution, as the efficacy of augmentation has never been demonstrated in a randomized, controlled trial. The cost-effectiveness of a screening program would depend on whether the costs of screening, diagnosis, and therapy are justified by the compliance and effectiveness of preventive measures, and the effectiveness of therapeutic modalities.

## ETHICAL ISSUES INVOLVED WITH GENETIC TESTING

(See Table 9.)

### The Requirement for Informed Consent

*Overarching principles.* Informed consent has become an ethical standard in clinical care and human subject research. Genetic information can identify traits, predisposition to a disorder, and actual inheritance of a disorder. Although the obtaining of such information will help with the selection of treatment/preventive options in a relatively few genetic conditions, such information will undoubtedly have broader psychologic and social implications for almost all who consider undergoing such testing. Because of the unique issues related to genetic testing as opposed to routine testing, individuals have a right to receive the necessary information to make an informed choice regarding genetic testing. Correlatively, such a right imposes obligations on the health care profession to provide such information and to obtain the informed consent of individuals before testing. These rights and obligations are grounded in the principle of autonomy and the right to self-determination, based on the moral conviction that individuals ought to be able to shape their own plan of life, especially where sickness and health care are concerned. The informed consent process allows patients to weigh the benefits of testing against the possible risks and reduces misunderstanding.

The concept of informed consent in the realm of genetic testing has been broadly embraced by ethics task forces and commentators in the United States, Canada, Great Britain, and other European countries (128–133). Other commentators have written on theoretical concerns with implementing the principle of autonomy and conflicts with other principles regarding genetic testing (134, 135).

Regarding content, informed consent requires explaining to the patient, before the test, the nature and scope of the information to be gathered, the significance of positive test results, the



TABLE 9. ETHICAL ISSUES INVOLVED WITH GENETIC TESTING: CONCLUSIONS\*

| Ethical Issue   | Conclusions   |
|---|---|
| Informed consent  |   |
| Adults  | Patients should provide informed consent before genetic testing for clinical or research purposes.  |
| Children  | Genetic testing of children should proceed only if:<br>The adolescent is mature enough to understand the issues involved with testing<br>The adolescent gives his or her assent for testing, and the parents give their permission for such testing |
| Duty to disclose availability of predictive genetic testing |   |
| Adults  | Health care providers have an obligation to disclose the availability of predictive genetic testing to adults at increased risk of having AAT deficiency  |
| Children  | Health care providers should offer genetic counseling about AAT deficiency only on request of the parents of a healthy child  |
| Confidentiality   | Before any genetic testing, health care providers should inform their patients that a genetic test can reveal medical information about relatives, as well as about the patient   |
| Disclosure to relatives                                     | Physicians should inform patients of the importance/benefits of other family members knowing about the chance of increased risk   |

Definition of abbreviation: AAT = alpha-1 antitrypsin.

\* Normative claims.

nature of the disease in question, the presence and likely efficacy of treatment modalities, potential risks from social discriminatory practices, potential emotional impact on individuals and on family dynamics, and, if relevant, the risks involved in procreating (136). To this list may soon be added the duty to warn about the possible interests of insurers, employers, adoptive parents, or future marriage partners. The Swedish neonatal screening effort demonstrated that provision of important information is critical to the success of any genetic testing. Specifically, the incidence of adverse psychologic effects in parents of newborns testing positive for AAT deficiency was attributed to the manner with which parents were told about such testing and the absence of adequate psychologic support (22, 137). Furthermore, of the adolescents identified at birth as having AAT deficiency, 73% assessed the information they obtained about AAT deficiency as being satisfactory, 17% rated the information as being both good and bad, and 10% thought the information was unsatisfactory (17).

**The role of the physician in genetic counseling.** At present, the public's knowledge of genetic diseases and the implications of genetic testing is poor. Understanding genetic testing involves learning complex concepts such as test sensitivity, carrier status, patterns of inheritance, risk/probability, and genotype-phenotype correlations. These gaps in the public's genetic knowledge suggest that genetic testing programs must include educational and counseling components. Unfortunately, there is a severe scarcity of genetic professionals both in the United States and in Europe, so implementation of widespread genetic testing must rely heavily on primary care providers and specialists (138). In addition to the paucity of genetic specialists relative to the potential demand for genetic testing, other reasons warrant the involvement of nongenetic professionals in genetic testing. For example, health care professionals are in an excellent position to elicit risk information. Also, health care providers are best able to determine whether a high-risk situation is present, as few people have sufficient understanding of genetics to recognize whether or not they or their children are at increased risk of inherited disease (133). With proper training and adequate knowledge of test validity, disease, and mutation frequencies in the ethnic groups to whom they provide care, primary care providers, specialists, and other nongenetic health care providers can and should be the ones to offer predictive genetic tests to

at-risk individuals. Under some circumstances, for instance, when the family history is complicated or the symptoms in relatives do not point to a clear diagnosis, referral to a genetic specialist is appropriate before offering testing.

Despite the advantage of nongenetic providers being the gateway to genetic testing, there are some concerns. One is the limited knowledge of some of these individuals regarding genetics and genetic tests (139). Another concern is the tendency of nongeneticist providers to be directive in situations in which reproductive options to avoid the conception or birth of an infant with a serious disorder are considered (140). It has been recognized that nondirectiveness may not be achievable and may not always be desired by patients (141, 142). Another concern is whether primary care providers and specialists are able to devote sufficient time to informing patients about the risks and benefits of genetic testing, which has been estimated to exceed 1 hour (143). Recommendations have been made to address these issues (133).

*Conclusion: Health care providers must provide individuals with the necessary information so that an informed and voluntary decision can be made, and must receive the individual's informed consent before any genetic testing.*

*Testing of children.* Obtaining informed consent to genetic testing of children or adults who lack legal competency generally requires that a parent, surrogate, or guardian decide by proxy. In their joint statement, the American Society of Human Genetics and the American College of Medical Genetics recommended that "[t]imely medical benefit to the child should be the primary justification for genetic testing in children and adolescents," and that if the medical benefits "are uncertain" or will not accrue until a later time, genetic testing should generally be deferred (144). However, what constitutes a "timely medical benefit," what level of "certainty" should be required for the efficacy of a medical benefit, and what time period constitutes a "later time" are controversial issues (145, 146). Concerns about testing children have focused largely on the potential psychologic implications to the child, the impact on family relationships, the possibility of social discrimination, and the abrogation of the right of the child to make an autonomous choice about testing as adults. These concerns, however, include much empirical and conceptual uncertainty. Other factors that should be considered

in the decision to perform genetic testing on children include the likelihood of occurrence (e.g., the existence of a family history or the degree of penetrance), the severity of the illness, the level of maturity of the child, and the concerns, values, and objectives of the parents and of the children involved in the decision.

*Conclusion: Genetic testing of children should proceed only if:*

1. The adolescent is mature enough to understand the issues involved with testing.
2. The adolescent gives his/her assent for testing.
3. The parents give their permission for such testing.

*Do physicians have an ethical and/or legal duty to disclose the availability of predictive genetic testing to asymptomatic individuals?* An important issue involves whether physicians have an obligation to disclose the availability of genetic tests to asymptomatic individuals and the potential for liability for failure to inform patients about such tests. This issue is more controversial for disclosure of genetic tests to parents of healthy children, because of concern with the potential of creating psychologic distress for the child and/or disruption of family dynamics. Liability would probably exist only if beneficial treatment exists and/or preventive measures could be instituted and failure to test or to test in a timely manner would result in harm. Such a situation may be relevant to those with an increased risk of having AAT deficiency.

*Conclusion:*

1. Health care providers have an obligation to disclose the availability of predictive genetic testing to adults at an increased risk of having AAT deficiency.
2. Health care providers should offer genetic counseling about AAT deficiency testing only on the request of the parents of a healthy child.

*Research context.* Stringent informed consent procedures are required for genetic testing in research settings. The American Society of Human Genetics has issued guidelines for informed consent for genetic research (147).

### Confidentiality of Genetic Information

Genetic information is highly personal and can be associated with potential psychologic and social risks. Accordingly, ensuring the confidentiality of genetic information is an important principle.

Regarding social discrimination, there are fears that individuals may suffer from discrimination in relation to health insurance, life insurance, and employment. Breaches of confidentiality to health insurers are more of an issue in the United States, where universal health coverage does not exist. However, even in countries that provide their citizens with basic care, obtaining supplementary health insurance may be an issue if genetic information is not kept confidential.

*Disclosure to relatives.* The obligation of assuring confidentiality, however, is not an absolute principle in medical ethics. Such information may be disclosed, albeit only in exceptional cases involving the public interest or potential harm to third parties (128, 148). In the realm of genetic testing, the main ethical dilemma arises when an individual's genetic test results may have important implications for other family members. This possibility raises the question of whether such family members have a right to such information and, correlatively, whether there is an obligation on health care providers to disseminate such information. Some commentators would consider it a duty to warn relatives, on the basis of the concept that hereditary information is a family possession rather than simply a personal one (149). Others question why a mere biological link justifies an encroach-

ment on an individual's privacy (150, 151). Among health care providers, there is equal representation of both viewpoints—the desire to disclose and the desire to protect confidentiality (151). Commentators have suggested that disclosure should be considered if the following factors are present: there is a high likelihood that the relative has the genetic mutation at issue (this would limit disclosure to the nuclear family), the disease is serious or fatal, effective treatment is available, the disease is transmitted dominantly with high penetrance, there is evidence that disclosure of the information would prevent or ameliorate the serious risk, there is no other reasonable way to avert the harm, and attempts to elicit voluntary disclosure have failed (152–154).

The American Society of Human Genetics has issued a statement concluding that providers performing genetic testing services for their patients have a “privilege” to disclose genetic risk information directly to relatives of a patient if necessary to mitigate a serious risk of harm (155). The U.S. Task Force on Genetic Testing opined that health care providers must make clear that they will not communicate results to relatives, except under extreme circumstances, which the provider should define. Providers should be explicit in describing the extreme situations in which they would inform other relatives (133). Finally, in Great Britain, an emerging consensus is that only under exceptional cases may confidential information be conveyed to relatives (128). Case law in the United States provides little guidance on this issue, with one court case deciding that the duty of health care providers to warn is satisfied by telling their patients that they should inform their family members, whereas another court opined that a duty to warn may require a breach of confidentiality in some cases (156, 157).

*Conclusion: Before any genetic testing, health care providers should inform their patients that a genetic test can reveal medical information about relatives. Physicians should inform patients of the importance/benefits of other family members knowing about their chance of increased risks. If physicians contemplate that there may be extreme circumstances in which they believe they have an ethical obligation to reveal such information to family members, physicians should explicitly inform their patients of the nature of these extreme circumstances before testing.*

### RECOMMENDATIONS FOR GENETIC TESTING

(See Tables 10 and 11.) The different types of recommendations that could be given in testing situations is shown in Table 10. Recommendations of Types A and B entail a duty on physicians to disclose the availability of the test. Subsequently, testing should be performed only after informed consent is obtained from the patient. For recommendations of Types C and D, there is no duty to disclose the availability of the test.

The following recommendations are based on the weighting and the weighing of the individual issues important in the determination of genetic testing. The individual weights assigned to each issue were dependent on the assessment of the strength of the available evidence for each issue, whereas the weighing of these issues reflected a subjective balancing of these issues by the Genetics Writing Group. Hence, a recommendation of Type A signifies that many of the issues favorable for testing (e.g., high prevalence, large burden of disease, favorable evidence for treatment efficacy) had large weights attached to them and outweighed the issues that detracted from testing (e.g., potential for discrimination and costs). Lower grades of recommendations (e.g., recommendation Type B) reflected the following: (1) fair or poor evidence existed regarding the benefits to individuals; (2) weighing of the benefits and harms of testing were balanced; or (3) compelling issues involved with testing were more reflective of the different values and desires of individuals and their comfort level regarding genetic testing.

TABLE 10. RANGE OF RECOMMENDATIONS FOR GENETIC TESTING

| Recommendation | Description   |
|----------------|---|
| A              | Testing is recommended  |
| B              | Testing should be discussed, acknowledging that it could be reasonably accepted or declined |
| C              | Testing is not recommended (testing should not be encouraged)                               |
| D              | It is recommended that testing not be performed (testing should be discouraged)             |

The recommendation type was determined by the Task Force's subjective weighing of all the issues that either supported or opposed genetic testing. The weight attributed to each issue is dependent on the level of the evidence supporting each issue. Accordingly, the recommendation for genetic testing is informed by both the evidence of each issue and consensus of the experts on how strongly each issue supports or opposes testing.

This classification of recommendations should not be confused with schemes for grading the quality of evidence, which, as used in other documents (although not here), may also use letter designations.

## Diagnostic Detection Testing

### 1. Symptomatic adults with persistent obstructive defects on pulmonary function testing.

- a. Emphysema
- b. COPD
- c (i). Asthma in which airflow is incompletely reversible after aggressive bronchodilator treatment

#### **Recommendation Type A:** Testing is recommended.

**Rationale:** Recommendation of Type A is justified by the following reasons. First, the prevalence of lung disease due to AAT deficiency is not insignificant. Second, AAT deficiency-associated lung disease carries a significant clinical burden. Third, studies (albeit observational in nature) suggest that administration of intravenous augmentation therapy may potentially enhance survival and decrease the progression of pulmonary disease. Fourth, suggestions for changes in health-related behaviors can be made to prevent further progression of disease. It is not known, however, if providing knowledge of having a genetic disease can influence smoking quit rates. Fifth, beneficial psychologic effects may also be gained from testing, resulting mainly from receiving an explanation of the disease process. Adverse psychologic effects, however, may also occur. Finally, identification of individuals with AAT deficiency may provide important economic benefits, for example, elimination of unnecessary diagnostic tests and/or incorrect therapeutic strategies for individuals not known to have AAT deficiency and prevention of costly exacerbations of obstructive pulmonary disease. All these potential benefits outweigh potential adverse social discriminatory effects.

It should also be emphasized that testing should be considered more strongly when other factors are present, for example, symptoms of emphysema occurring in younger patients, or a rapid decline in FEV<sub>1</sub>, or if clinical symptoms are present in an individual with a strong family history of AAT deficiency. On the other hand, testing should be considered less relevant for members of ethnic groups in whom the frequency of AAT deficiency is known to be low, for example, western Pacific islanders. In settings where the prevalence of AAT deficiency is known to be much lower than in North America or Europe, a Type B recommendation for diagnostic testing is made.

Finally, a Type B recommendation for diagnostic detection testing is made for adults with bronchiectasis. On the one hand, AAT deficiency is underrecognized and bronchiectasis has been observed frequently in AAT-deficient patients in some series. On the other hand, available studies do not firmly establish the association between AAT deficiency and bronchiectasis.

The Genetics Writing Group recognizes the problem of identifying heterozygotes from testing, many of whom will not receive augmentation therapy, as their serum AAT levels will not be

severely depressed. Accordingly, these individuals will not reap the medical benefits of testing, although they may experience psychologic and/or social adverse effects. Further research is needed to determine the extent of the psychologic and social sequelae experienced by these individuals.

- c (ii). Asthma with completely reversible airflow obstruction

#### **Recommendation Type C:** Testing is not recommended.

**Rationale:** There is no evidence available showing that individuals with asthma characterized by completely reversible airflow obstruction have an increased prevalence of AAT deficiency. In one study involving Swedish individuals identified at birth, the frequency of asthma was not different from that of the general population (14). Hence, it is recommended that testing not be performed, as these individuals are not likely to have AAT deficiency.

### 2. Adolescents with persistent obstructive defects on pulmonary function testing.

**Recommendation Type B:** Testing should be discussed, acknowledging that it could be reasonably be accepted or declined.

**Rationale:** A recommendation of Type B is being made because (1) efforts at preventing risky health-related behaviors may be more successful with timely diagnosis in this age group (e.g., efforts at smoking prevention and occupational counseling efforts at a time when adolescents are actively choosing future career opportunities), and (2) adverse psychologic effects have not been well established in adolescents who receive genetic testing. A recommendation of Type A is not made because of (1) the low prevalence of lung disease in adolescents, (2) a theoretical concern with the future autonomy rights of adolescents, and (3) potential social discriminatory effects.

### 3. Asymptomatic individuals with a persistent obstructive defect on pulmonary function testing.

- a. No risk factors present for promoting AAT deficiency-related lung disease (i.e., nonsmokers and no exposure to environmental pollutants)

**Recommendation Type B:** Testing should be discussed, acknowledging that it could reasonably be accepted or declined.

**Rationale:** The existence of potential adverse psychologic and social discriminatory effects (including individuals identified as being heterozygous) coupled with the low likelihood of any medical benefits obtained from a positive test (augmentation therapy is unlikely to be given, as the presence of significant spirometric obstruction is unlikely; also, preventive measures will not be applicable because of the absence of risk factors) warrants that testing should be merely discussed, but not recommended.

- b. Smoking exposure

TABLE 11. RECOMMENDATIONS FOR GENETIC TESTING FOR ALPHA-1 ANTITRYPSIN DEFICIENCY

| Type of Genetic Testing  | Recommendation   | Rationale of the Recommendation   |
|--|--|---|
| <b>A. Diagnostic Testing</b>   |  |   |
| 1. Symptomatic adults with persistent obstructive defects on pulmonary function testing          |  |   |
| a. Emphysema   | Type A: Testing is recommended (In populations where the prevalence of AAT deficiency is known to be much lower than the prevalence in North America or Europe [e.g., << 1/3,000], a Type B recommendation is made.) | Prevalence of AAT deficiency in individuals with emphysema is not insignificant and observational studies suggest efficacy of augmentation therapy in such patients. In addition, preventive measures can be employed (e.g., smoking cessation and change of occupation). It is not known, however, if providing knowledge of having a genetic disease can influence smoking quit rates. Beneficial psychological effects may also be gained from testing, due mainly from having an explanation of the disease process. Finally, a diagnosis of AAT deficiency can have economic benefits, as a diagnosis of AAT deficiency can end further diagnostic testing for other diseases. These benefits most likely outweigh potential adverse social discriminatory effects |
| b. COPD  | Type A: Testing is recommended   | Same as above   |
| c. Bronchiectasis  | Type B: Testing should be discussed  | In the context of discordant studies about whether bronchiectasis is clearly associated with AAT deficiency, diagnostic testing should be considered because bronchiectasis occurs frequently in individuals with AAT deficiency and because AAT deficiency is clearly underrecognized  |
| d. Asthma  |  |   |
| i. Incompletely reversible airflow obstruction   | Type A: Testing is recommended   |   |
| ii. Completely reversible airflow obstruction  | Type C: Testing is not recommended   | No evidence that such individuals are more likely to have AAT deficiency  |
| 2. Adolescents with persistent obstructive pulmonary dysfunction                                 | Type B: Testing should be discussed  | Efforts at preventing risky health-related behaviors may be more successful in this age group, for example, efforts at smoking prevention and occupational counseling efforts at a time when adolescents are actively choosing future career opportunities; and adverse psychological effects have not been well established in adolescents. A Type A recommendation is not being made due to (1) low prevalence of persistent obstructive pulmonary disease in adolescents, (2) concern with the future autonomy rights of adolescents, and (3) potential social discriminatory effects  |
| 3. Asymptomatic individuals with persistent obstructive pulmonary dysfunction                    |  |   |
| a. No risk factors present for promoting AAT deficiency-related lung disease                     | Type B: Testing should be discussed  | Existence of potential adverse psychosocial effects (including individuals identified as being a heterozygote) coupled with low likelihood of any medical benefits obtained from a positive test warrants that testing should be merely discussed, but not recommended  |
| b. Smoking exposure  | Type A: Testing is recommended   | A positive test, in conjunction with the efforts of the clinical provider, may lead such individuals to stop smoking. One study, however, showed that although receipt of genetic risk information enhanced motivation to quit smoking, the smoking quit rates were not affected. More research is needed to explore the factors that influence smoking quit rates  |
| c. Occupational exposure   | Type A: Testing is recommended   | A positive test result may influence an individual to change occupation   |
| 4. Individuals with unexplained liver disease: newborns, children, adults                        | Type A: Testing is recommended   | Testing can provide explanation of disease, but must be weighed against potential adverse psychological and social effects  |
| 5. Adults with necrotizing panniculitis  | Type A: Testing is recommended   | Testing can provide an explanation of disease and potentially be treated with augmentation therapy  |
| 6. Adults with multisystemic vasculitis (anti-PR-3-positive vasculitis)                          | Type B: Testing should be discussed  | Studies show a convincing link between the PI*Z allele and anti-PR-3-positive vasculitis and one study showed that AAT deficiency in patients with vasculitis may signify an enhanced risk of fatal outcome. Effects of augmentation therapy, however, are unknown. Adverse psychosocial effects also need to be considered   |
| <b>B. Predispositional Testing</b>   |  |   |
| 1. Individuals (adults and adolescents) with a family member with AAT homozygosity (i.e., PI*ZZ) |  |   |
| a. Siblings  | Type A: Testing is recommended   | *Siblings have a 25% chance of being homozygous. This risk is higher if the parent(s) are homozygotes   |
| b. Offspring   | Type B: Testing should be discussed  | Offspring can be homozygous only if the other parent is at least heterozygous. This potentially low prevalence rate coupled with potential adverse psychosocial effects warrants that testing be discussed rather than be recommended, even if obstructive pulmonary dysfunction and/or risk factors are present  |
| c. Parents   | Type B: Testing should be discussed  | If the proband is homozygous for AAT deficiency, then either one or both of the parents is at least heterozygous. The evidence that even heterozygotes may be at risk for adverse health effects warrants a Type B recommendation   |
| d. Distant relative  | Type B: Testing should be discussed  | The low likelihood of a distant relative being homozygous coupled with potential adverse psychosocial effects warrants a Type B recommendation  |

Continued

TABLE 11. CONTINUED

| Type of Genetic Testing   | Recommendation  | Rationale of the Recommendation   |
|---|---|---|
| <b>2. Individuals (adults and adolescents) with a family member with AAT heterozygosity</b> |   |   |
| a. Siblings   | Type B: Testing should be discussed                     | Siblings have a 25% chance of heterozygosity if the tested individual is heterozygous for an AAT deficiency allele. The evidence that heterozygotes can be at risk for adverse health effects warrants a Type B recommendation.   |
| b. Offspring  | Type B: Testing should be discussed                     | Offspring of a parent who is heterozygous have a 25% chance of being heterozygous. The evidence that even heterozygotes may be at risk for adverse health effects coupled with this moderate prevalence rate warrants a Type B recommendation.  |
| c. Parents  | Type B: Testing should be discussed                     | The prevalence of having a deficient AAT allele is low, and if the proband is a heterozygote, then a parent can be either heterozygous or have normal alleles. However, the evidence that even heterozygotes may be at risk for adverse health effects warrants a Type B recommendation.  |
| d. Distant relative   | Type B: Testing should be discussed                     | Distant relatives of a heterozygous proband may be at most heterozygous or have normal AAT alleles. Although there is a low likelihood of being heterozygous, the evidence that even heterozygotes can be at risk for adverse health effects warrant a Type B recommendation.   |
| <b>3. Individuals with a family history of obstructive lung disease or liver disease</b>    |   |   |
| 4. Fetal testing  | Type D: It is recommended that testing not be performed | Studies have shown that the prevalence of PI*ZZ in individuals with lung disease or liver disease is less than 3 and 1%, respectively. The low likelihood of having AAT deficiency coupled with potential adverse psychosocial warrants a Type B recommendation. AAT deficiency-related diseases are not considered a serious enough disease to warrant genetic testing in the prenatal period, as such diseases occur in late-onset adulthood and the incidence of death among those children affected with AAT deficiency-related liver disease is low. Also, the level of interest among high-risk individuals for AAT genetic testing in the prenatal period is unknown. Finally, there is a concern that raising the issue of genetic testing may inadvertently suggest that abortion be considered. |
| <b>C. Carrier Testing in the Reproductive Setting</b>                                       |   |   |
| 1. Individuals at high risk of having AAT deficiency-related diseases                       | Type B: Testing should be discussed                     | Options for testing should be discussed as a negative test may relieve anxieties and a positive test may allow prospective parents to become emotionally prepared for parenting a child with AAT deficiency or consider options for adoption.   |
| 2. Partners of individuals with either AAT deficiency or carrier status                     | Type B: Testing should be discussed                     | Same as immediately above   |
| <b>D. Screening</b>   |   |   |
| 1. Newborn  | Type D: It is recommended that testing not be performed | Although the previous Swedish experience showed that adolescents identified at birth as having AAT deficiency had decreased smoking rates and no adverse psychologic effects, there were adverse psychological effects on parents and on mother-child bonding.  |
| 2. Adolescents  | Type D: It is recommended that testing not be performed | An adolescent screening program is potentially more logical than newborn screening, as preventive measures can be instituted at the time of testing and before onset of unhealthy lifestyle choices (e.g., smoking). However, other factors make the desirability of such a program problematic. For example, there is a concern with the potential of discriminatory effects and the cost-effectiveness of such a program. Also, the psychological effects from the knowledge that one is a heterozygote are unknown. Finally, the presence of adequate counseling may be problematic where testing may occur in a large population.   |
|   | Type B: Testing should be discussed                     | *In countries where the prevalence of AAT deficiency is high (e.g., about 1/1,500 or more), coupled with high smoking rates and the presence of adequate counseling services, a voluntary program would be acceptable.  |
| 3. Adults   | Type D: It is recommended that testing not be performed | There are concerns with the psychological effects of testing on healthy individuals without prior increased risk of having AAT deficiency, potential for social discriminatory effects, and the costs associated with such programs.  |
|   | Type B: Testing should be discussed                     | *In countries where the prevalence of AAT deficiency is high (e.g., about 1/1,500 or more), coupled with high smoking rates and the presence of adequate counseling services, a voluntary program would be acceptable.  |
| 4. Smokers with normal spirometry   | Type C: Testing is not recommended                      | Low prevalence of AAT deficiency (prevalence may be lower than in the general population as normal spirometry despite smoking history may indicate that such individuals may not have AAT deficiency), coupled with potential adverse psychosocial effects, makes such testing problematic.   |

Definition of abbreviations: AAT = alpha-1 antitrypsin; PR-3 = proteinase-3.

\* See text.

#### **Recommendation Type A:** Testing is recommended.

**Rationale:** A positive test, in conjunction with the efforts of the clinical provider, may lead such individuals to stop smoking. However, one study showed that receipt of genetic risk information enhances motivation to quit smoking, but that smoking quit rates are not enhanced.

- c. Occupational exposure

#### **Recommendation Type A:** Testing is recommended.

**Rationale:** A positive test may influence an individual to change occupation and prevent further decrements in pulmonary function.

4. *Individuals with unexplained liver disease: neonates, children, adults.*

#### **Recommendation Type A:** Testing is recommended.

**Rationale:** Testing can provide accurate diagnosis of the liver disease, as well as important prognostic information (e.g., the risk of liver cancer, which is increased in PI\*ZZ individuals). These benefits need to be balanced against potential adverse psychologic and social discriminatory effects from genetic testing.

5. *Adults with necrotizing panniculitis.*

**Recommendation Type A:** Testing is recommended.

**Rationale:** Testing may provide accurate diagnosis of an unexplained disease and case reports have suggested efficacy of augmentation therapy.

6. *Adults with multisystemic vasculitis: anti-PR-3-positive vasculitis.*

**Recommendation Type B:** Testing should be discussed, acknowledging that it could reasonably be accepted or declined.

**Rationale:** Testing can provide explanation of the disease process, as several studies have demonstrated a convincing link between the PI\*Z allele and anti-PR-3-positive vasculitis and one study showed that AAT deficiency in patients with vasculitis may signify an enhanced risk of fatal outcome. The effects of augmentation therapy in this setting, however, are unknown. Adverse psychosocial effects also need to be considered.

### Predispositional Testing

1. *Individuals (adults and adolescents) with a family member with AAT homozygosity.*

a. Siblings

**Recommendation Type A:** Testing is recommended.

**Rationale:** If a tested individual is homozygous for AAT deficiency (i.e., PI\*ZZ), then the sibling has a 25 to 100% chance of being a homozygote (these percentages depend on the genotypes of the parents; possibilities are PI\*MZ and PI\*MZ, PI\*MZ and PI\*ZZ, or PI\*ZZ and PI\*ZZ). If the affected child is PI\*ZZ, then the highest probability is that the parents are PI\*MZ and PI\*MZ, but the other two possibilities should not be discounted, especially in northern European populations, where the prevalence in isolated population subgroups may be high.

b. Offspring

**Recommendation Type B:** Testing should be discussed, acknowledging that it could be reasonably be accepted or declined.

**Rationale:** Offspring can be homozygous only if the other parent is at least heterozygous. This potentially low prevalence rate for homozygosity coupled with potential adverse psychosocial effects warrants that testing be discussed rather than be recommended, even if obstructive pulmonary dysfunction and/or risk factors are present.

c. Parents

**Recommendation Type B:** Testing should be discussed, acknowledging that it could reasonably be accepted or declined.

**Rationale:** If the proband is homozygous for AAT deficiency, then either one or both of the parents is at least heterozygous. The evidence that even heterozygotes may be at risk for adverse health effects warrants a Type B recommendation.

d. Distant relative of the proband

**Recommendation Type B:** Testing should be discussed, acknowledging that it could reasonably be accepted or declined.

**Rationale:** If the proband is homozygous, a distant relative may have normal AAT alleles, be heterozygous, or be homozygous (a low likelihood). The low likelihood of being homozygous coupled with potential adverse psychosocial effects warrants a Type B recommendation.

2. *Individuals (adults and adolescents) with a family member with AAT heterozygosity.*

a. Siblings

**Recommendation Type B:** Testing should be discussed, acknowledging that it could reasonably be accepted or declined.

**Rationale:** If an individual is heterozygous for an AAT deficiency allele, then his or her sibling has a 25% chance of being a heterozygote. The evidence that even heterozygotes may be at risk for adverse health effects coupled with the high prevalence of being at least a heterozygote for an AAT deficiency allele warrants a Type B recommendation.

b. Offspring

**Recommendation Type B:** Testing should be discussed, acknowledging that it could reasonably be accepted or declined.

**Rationale:** Offspring of a parent who is heterozygous has a 25% chance of being a heterozygote. The evidence that even heterozygotes may be at risk for adverse health effects coupled with this moderate prevalence rate warrants a Type B recommendation.

c. Parents

**Recommendation Type B:** Testing should be discussed, acknowledging that it could reasonably be accepted or declined.

**Rationale:** The prevalence of having a deficient allele is low, because if the proband is a heterozygote, then a parent can be either heterozygous or have normal AAT alleles. However, the evidence that even heterozygotes may be at risk for adverse health effects warrants at least a Type B recommendation.

d. Distant relative

**Recommendation Type B:** Testing should be discussed, acknowledging that it could reasonably be accepted or declined.

**Rationale:** Distant relatives of a heterozygote proband may be at most heterozygous or have normal AAT alleles. Despite this low likelihood of being heterozygous, the evidence that even heterozygotes can be at risk for adverse health effects warrants a Type B recommendation.

3. *Individuals with a family history of persistent obstructive lung disease or liver disease.*

**Recommendation Type B:** Testing should be discussed, acknowledging that it could reasonably be accepted or declined.

**Rationale:** Previous studies have shown that the prevalence of the PI\*ZZ phenotype in individuals with lung disease or liver disease is less than 3 and 1%, respectively. The low likelihood of having AAT deficiency coupled with potential adverse psychosocial effects warrants a Type B recommendation.

4. *Fetal testing for AAT deficiency.*

**Recommendation Type D:** It is recommended that genetic testing not be performed.

**Rationale:** AAT deficiency-related diseases are not generally considered serious enough diseases to warrant genetic testing in the prenatal period, as such diseases occur in late-onset adulthood and the incidence of death among those children affected with AAT deficiency-related liver disease is low. If severe progressive liver disease has occurred in the neonatal period in a previous child, the risk for a subsequent PI\*ZZ sibling to develop severe liver disease may be as high as 40% (158). Under these rare circumstances, the family should be informed about prenatal diagnosis as part of the genetic counseling endeavor.

### Carrier Testing in the Reproductive Setting

1. *Individuals at high risk of having AAT deficiency-related diseases who are planning a pregnancy or are in the prenatal period.*

**Recommendation Type B:** Testing should be discussed, acknowledging that it could reasonably be accepted or declined.

**Rationale:** Options for testing should be discussed, as a negative test may relieve anxiety and a positive test may allow prospective parents to become emotionally prepared for parenting a child with AAT deficiency or to consider options for adoption.

No data exist regarding the level of interest in AAT deficiency genetic testing in this group. An Office of Technology Assessment survey demonstrated that 83% of Americans said they would take a genetic test before having children if it would tell them whether their children would be likely to inherit a fatal genetic disease. Hence, it is likely that a majority of individuals at high risk of having AAT deficiency would not desire such genetic testing, as AAT deficiency confers individuals with a genetic predisposition to having a relatively late-onset disease, rather than to having a certain fatal disease.

2. *Individuals who are not at high risk themselves of having AAT deficiency, but are partners of individuals who are either homozygous or heterozygous for AAT deficiency.*

**Recommendation Type B:** Testing should be discussed, acknowledging that it could reasonably be accepted or declined.

**Rationale:** Same as above.

## Screening

### 1. Neonatal.

**Recommendation Type D:** It is recommended that genetic testing not be performed.

**Rationale:** Although the previous Swedish experience showed that adolescents identified at birth as having AAT deficiency had decreased smoking rates and no adverse psychologic effects, the demonstration of parental distress and adverse effects on the mother-child relationship, coupled with the potential of discriminatory effects and the unknown cost-effectiveness of such screening programs, warrants that newborn population testing not be performed at this time.

### 2. Adolescents: more than 11 years old.

**Recommendation Type D:** It is recommended that genetic testing not be performed.

**Rationale:** An adolescent screening program is potentially more logical than newborn screening, as preventive measures can be instituted at the time of testing and before onset of unhealthy lifestyle choices (e.g., smoking). However, other factors make the desirability of such a program problematic. For example, there is a concern with the potential of discriminatory effects and the cost-effectiveness of such a program. Also, the psychologic effects from the knowledge that one is heterozygous are unknown. Finally, the presence of adequate counseling may be problematic when testing involves a large population.

**Recommendation Type B:** Testing should be discussed, acknowledging that it could reasonably be accepted or declined.

In countries where the prevalence of AAT deficiency is high (e.g., about 1 in 1,500 or more), coupled with high smoking rates and the presence of adequate counseling services, a voluntary program would be acceptable.

### 3. Adults.

**Recommendation Type D:** It is recommended that genetic testing not be performed.

**Rationale:** As described above for adolescents. Recommendation Type B can also be made if similar conditions apply.

### 4. Smokers with normal spirometry.

**Recommendation Type C:** Genetic testing is not recommended.

**Rationale:** The low prevalence of AAT deficiency (prevalence may be lower than in the general population, as normal spirometry despite a history of smoking may indicate that such individuals may not have AAT deficiency), coupled with potential adverse psychosocial effects, makes such testing problematic.

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