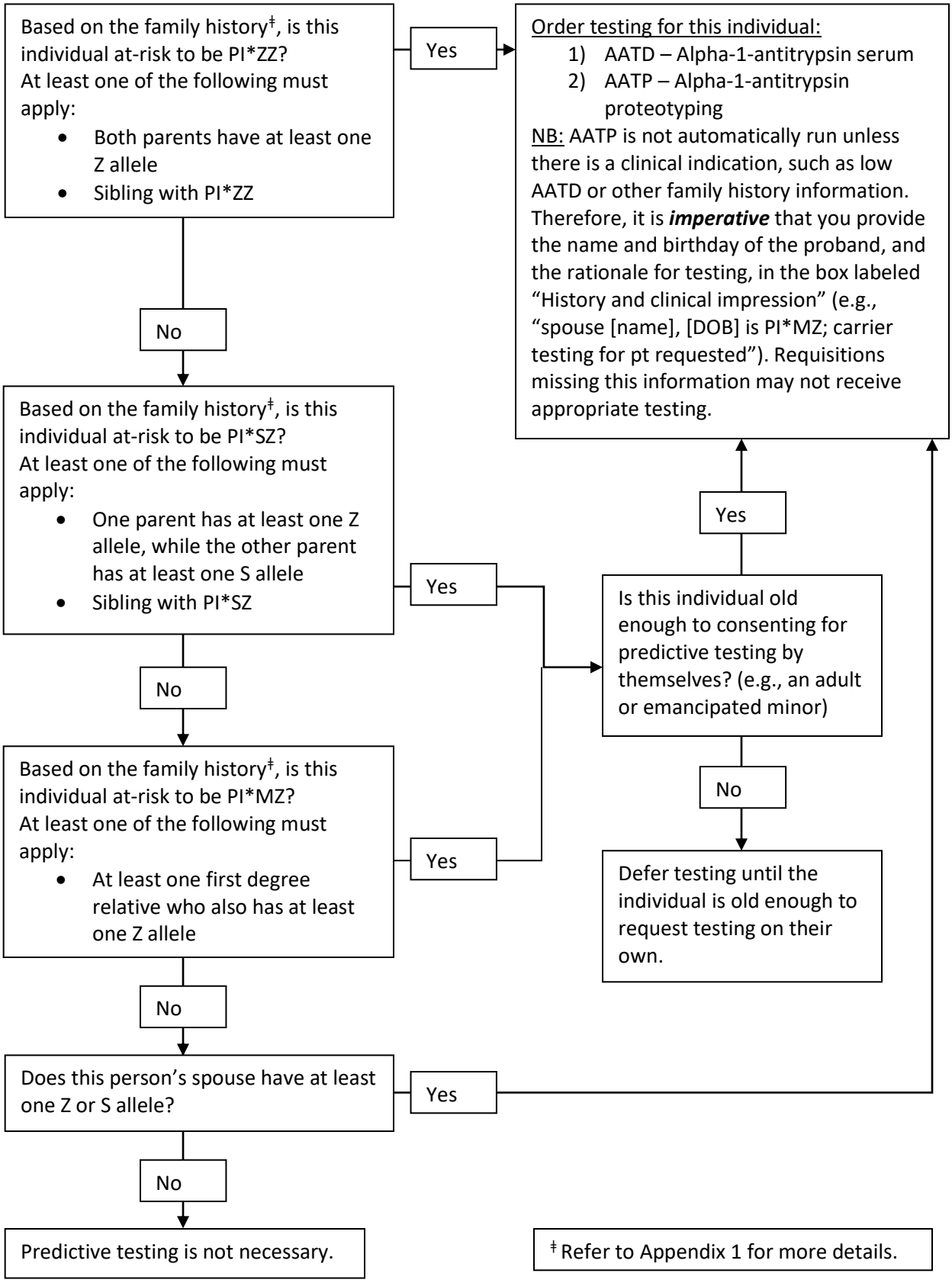
Manitoba Recommendations For Testing Alpha-1-Antitrypsin Deficiency In Asymptomatic Individuals



Alpha-1-Antitrypsin: Information For Primary Care Practitioners

Salient Features

Alpha-1-antitrypsin deficiency (AATD) is characterized by an increased risk of chronic obstructive pulmonary disease (e.g., emphysema sometimes with bronchiectasis, airflow obstruction, etc) in adults, liver disease in children and adults, panniculitis, and c-ANCA positive vasculitis. The penetrance is very high, but depends on various factors such as age and environmental exposures.

Genetics

The gene encoding alpha-1-antitrypsin is called *SERPINA1*. However, testing of the *SERPINA1* gene is usually not required for to identify individuals at-risk or carriers for AATD. Inferences regarding the individual's genotype can be made by measuring serum levels of alpha-1-antitrypsin and proteotyping, i.e., testing for the two most common disease-associated variants, S and Z. The M allele is the most common allele and is considered benign. The S and Z variants are the most common disease-associated variants. Most individuals who have clinically-significant AATD are homozygous for the Z allele (written as PI*ZZ); individuals who are homozygous also have the greatest risk for lung disease and liver disease. The S variant is only associated with disease when it is *in trans* with the Z variant; individuals who are PI*SZ have an increased risk for lung disease, but not for liver disease.

Allele Combinations With Clinically-Significant Impacts On Lung and Liver Disease

- PI*MZ: These individuals are usually ***not*** considered at increased risk for the symptoms of AATD. However, a subset of these individuals may still be at increased risk for clinical emphysema, especially if they are smokers. There may be elevated liver enzymes or liver inclusions on biopsy. These individuals are not at increased risk for clinically-significant childhood-onset liver disease, but PI*MZ heterozygotes have been slightly overrepresented in adults with chronic liver failure than in the general population (8.4% vs 3%).
- PI*SZ: These individuals have a slightly increased risk for adult-onset lung disease, especially if there is a smoking history of history of other exposures. They are not at increased risk for clinically-significant liver disease, but there may be elevated liver enzymes or liver inclusions on biopsy.
- PI*ZZ: These individuals have a significantly greater risk for adult-onset lung disease. Childhood-onset lung disease has been reported, but is especially rare. They also have an increased risk for childhood-onset liver disease (around 18% have clinically-recognized liver abnormalities, but only 2% with severe liver disease). There is also an increased risk of adult-onset liver disease irrespective of whether childhood-onset liver disease was present. This risk increases with age. There may also be a risk of hepatocellular carcinoma that also increases with age.

Refer to Appendix 2 for a summary of this information.

Lifestyle Implications

While the genotype plays a strong role in clinical presentation and disease risks, there is also a very strong environmental component. For instance, smoking history (or other exposures to pollutants) is associated with higher penetrance and earlier age of onset for lung disease. Therefore, depending on the individual's genotype and the associated health risks, individuals who are PI*MZ, SZ, or ZZ may be recommended to:

If at-risk for lung disease:

- Avoid exposure to environmental pollutants (e.g., complete smoking cessation including exposure to second hand smoke, avoid occupational exposures to dust or other irritants, avoid outdoor activities during times of poor air quality, etc)

- Keep up-to-date with yearly influenza and pneumococcus vaccinations

If at-risk for liver disease:

- Minimize alcohol consumption
- Vaccinate against hepatitis A and B

Testing For ***Asymptomatic*** Individuals In Manitoba

Testing for AATD (via alpha-1-antitrypsin serum measurements and proteotyping) can be done if the individual has a family history of AATD, or if their spouse has a personal history of at least one pathogenic allele. The main purpose of testing AATD for asymptomatic individuals is to:

1) Identify if the individual or their relatives are at-risk for an adult-onset lung disease, or
2) Identify if the individual or their relatives are at-risk for a pediatric-onset liver disease.

Because only the PI*ZZ variant combination is associated with pediatric-onset illness, predictive testing for asymptomatic children is *only* recommended if the child is at-risk for this genotype. Otherwise, to support the autonomy of children and the right to make their own decision about testing for genetic conditions, testing for asymptomatic individuals at-risk for other genotypes can deferred until they are old enough to consent for testing on their own.

Appendix 1: Recommendations for Predictive and/or Carrier Screening for Alpha-1-Antitrypsin Deficiency

(Adapted from Table 3 in Hogarth and Rachelefsky, 2008[‡])

Affected individual's PI* phenotype/proteotype	**Relative to the affected**	**Recommendations**	**Rationale**
ZZ	Siblings	Testing is recommended	Siblings have a 25% chance of also being PI*ZZ, and likely 50% chance of being PI*MZ
ZZ	Offspring	Testing should be discussed Also consider testing the individual's spouse	Offspring have at least PI*MZ. They may be PI*ZZ only if the other parent is at least PI*MZ.
ZZ	Parents	Testing should be discussed	Parents are expected to at least have one Z allele.
MZ	Siblings	Testing should be discussed	Siblings have a 50% chance of also being PI*MZ.
MZ	Offspring	Testing should be discussed Also consider testing the individual's spouse	Offspring have a 50% chance of being PI*MZ. If both parents are PI*MZ, then offspring have a 25% chance of being PI*ZZ
MZ	Parents	Testing should be discussed	At least one parent is likely PI*MZ
SZ	Siblings	Testing should be discussed	Siblings have a 25% chance of also being PI*SZ
SZ	Offspring	Testing should be discussed Also consider testing the individual's spouse	Offspring have a 50% chance of being either PI*MZ or PI*MS. They may be at risk of PI*ZZ or PI*SZ if the other parent is PI*MZ or PI*MS.
SZ	Parents	Testing should be discussed	At least one parent is likely PI*MZ

[‡] Some of the risk percentages provided in the original table were incorrect; these have been corrected here. The original table also did not provide recommendations for family members of PI*SZ individuals.

Appendix 2: Relationship of AAT Protein Variants to Serum AAT Levels, Lung Disease Risk in Adults, and Liver Disease Risk

(Adapted from Table 3 in Stoller et al., 2006)

AAT protein variants	"True level" mean (5^{th}–95^{th} centile) (µmol/L)	Commercial standard median (5^{th}–95^{th} centile) (mg/dL)	Lung disease risk (adults)	Liver disease risk (children)*	Liver disease risk (adults)*
MM	33 (20-53)	147 (102-254)	Background	Background	Background
MS	33 (18-52)	125 (86-218)	Background	Background	Background
MZ	25.4 (15-42)	90 (62-151)	Background, although a subset may have an increased risk	Background	Background
SS	28 (20-48)	95 (43-154)	Background	Background	Background
SZ	16.5 (10-23)	62 (33-108)	20-50%	Background	Background
ZZ	5.3 (3.4-7)	≤ 29 (≤ 29-52)	80-100%	18%; 2% with severe disease	Up to 40% based on autopsy studies
Null-null	0	0	100%	Background	Background

* Individuals with at least 1 Z allele may have liver inclusions or elevated liver enzymes, without clinically-significant liver disease. A greater percentage of PI*MZ heterozygotes are seen in adults with chronic liver failure compared to the general population, but longitudinal studies are required to characterize this risk.

References

Hogarth, D. K. and G. Rachelefsky. 2008. Screening and familial testing of patients for α1-antitrypsin deficiency. Chest 133:981–988.

Stoller, J. K., F. L. Lacbawan, and L. S. Aboussouan. Alpha-1-antitrypsin deficiency. 2006 (Updated January 19, 2017). In: M. P. Adam, H. H. Ardinger, R. A. Pagon, et al., Eds. Genereviews (Internet). Seattle WA: University of Washington, Seattle, 1993-2020. Retrieved January 23, 2020 from: https://www.ncbi.nlm.nih.gov/books/NBK1519