

ALPHA-1 FOUNDATION GUIDANCE:

TESTING FOR ALPHA-1 ANTITRYPSIN DEFICIENCY IN SPECIFIC SETTINGS

The Alpha-1 Foundation (Foundation) is excited and encouraged by advancements in the detection of Alpha-1 Antitrypsin Deficiency (Alpha-1). Such detection entails the need for guidance regarding the best testing practices given a variety of clinical situations. These guidelines are intended to assist individuals, the medical community, and industry to understand how testing should be conducted, to ensure that the most appropriate and efficient testing methodology is employed, and to protect patient rights and confidentiality. This document was approved by the Medical and Scientific Advisory Committee (MASAC) on November 19, 2011 and reflects the position of the Alpha-1 Foundation on testing for Alpha-1 Antitrypsin Deficiency.

The diagnosis of severe Alpha-1 Antitrypsin Deficiency relies on one or more of a) the demonstration of low plasma concentration b) the observation of a deficient variant of the protein alpha-1 antitrypsin (AAT) by protease inhibitor typing (Pi-typing; formerly known as phenotyping), and c) genotyping, or the detection of mutations in both copies of SERPINA1, the gene encoding AAT. In general, at least two of these methods should be employed, depending on the setting, and a positive result should be confirmed by additional testing. The Foundation encourages primary genotyping, which will identify not only individuals who are homozygous for the most common abnormal AAT genes, but also those who are heterozygous, i.e., those who carry a single abnormal AAT gene or who have two different deficient genes. Concurrent measurement of an AAT serum level is strongly recommended. Modern AAT genotyping generally enables detection of common abnormal genotypes and an AAT level using a finger stick to acquire a blood sample. This may be easier than venipuncture for healthcare professionals to perform in outpatient settings.

The Foundation is mindful of a number of ethical issues raised by Alpha-1 testing:

- Testing poses risks and offers benefits, and it is appropriate to address these. Identifying a genetic basis for an individual's medical condition can lead to appropriate therapy and might identify family members at risk. However, many genetic conditions, including Alpha-1 Antitrypsin Deficiency, do not always lead to the development of disease. Still, some insurers and employers believe that the presence of genetic risk factors (including carrier status) inevitably leads to medical issues and a shortened life. Some patients with genetic risk factors may be denied insurance, or lose their jobs. While the U.S. Genetic Information Non-discrimination Act (GINA) is intended to prevent discrimination in employment and health insurance, this law is untested, and in any event does not prevent genetic discrimination in access to life insurance.
- Independent of any risk of discrimination, genetic testing raises a number of privacy and confidentiality issues. The Foundation is emphatic that physicians, allied health professionals, screening event sponsors and others involved in the process follow the letter and spirit of all applicable state and federal privacy laws governing the communication, disclosure, storage, protection and analysis of biological material/information.
- Testing can have psychological consequences and might affect family dynamics, especially for otherwise healthy individuals.

- The role of industry in testing – and indeed in health care in general – continues to pose difficult challenges. The guidance below refers in a number of places to “free branded tests” provided by for-profit corporations. It is preferable to use non-branded testing whenever possible. Further, the presence of industry representatives in clinics and at testing events should be limited to the extent possible, and their actions should be monitored.

The Foundation’s specific guidance, sorted by setting, follows:

Physician Office or In-Hospital – Individual Patient Test

Physicians may order Alpha-1 testing in a variety of clinical situations. Distinctions must be made with respect to the degree of information and discussion required when one is doing testing to work up an unexplained illness versus screening a healthy family member, for example:

Patient confidentiality must be a priority. Please note that for all testing, except that provided by the Foundation’s Alpha-1 Coded Testing (ACT) trial, results can be expected to appear in the patient’s medical record.

Depending on the setting as mentioned above, benefits and risks of testing should be discussed with the patient prior to testing and the usual practice for that setting regarding documentation should be followed.

Sample Collection:

Bloodspot: A Qualified Healthcare Professional should collect the blood sample following instructions in the testing kit being used for the testing. Instructions include precautions in collecting the sample (i.e. pricking the finger and correctly filling the blood spot), correctly labeling the specimen, and drying before mailing it.

Venipuncture: If blood is being collected by venipuncture for AAT testing, appropriate techniques should be used. The sample should be correctly labeled and stored appropriately for pickup. **If a diagnosis code is required, the correct ICD-10 code for Alpha-1 Antitrypsin Deficiency is E88.01. If augmentation therapy is being prescribed the correct J-code for emphysema should be added, most commonly J43.1 for panlobular emphysema.**

Test results should be sent to the physician’s office and/or the hospital record for in-office or in-hospital testing. Once the results are received, the patient’s Qualified Healthcare Professional should explain the results to the patient and provide counseling and information about available network resources, depending on the results. A Qualified Healthcare Professional should make therapeutic recommendations to the patient, depending on the specifics of each case.

NOTE: A Qualified Healthcare Professional is a physician, nurse or nurse practitioner, physician assistant, genetic counselor or other professional authorized to discuss medical genetic issues with patients and/or order a genetic test.

Physician Office – Multiple Patient Testing Days

Patient confidentiality must be a priority. Please note that for all testing, except that provided by the Foundation’s Alpha-1 Coded Testing (ACT) trial, results can be expected to appear in the patient’s medical record.

There should be a physician of record responsible for the event.

Any invitation sent to an individual to attend a testing date, should come from the physician's office and not from a commercial entity. The invitation should provide some information on the reason(s) for providing such an event as well as a disclosure regarding risks and benefits for Alpha-1 testing.

On the day of the event, a Qualified Healthcare Professional should discuss with each individual the risks and benefits of Alpha-1 testing. Written information, including benefits and risks, can be provided at any time to the individual before the sample collection. The Qualified Healthcare Professional should make sure, on an individual basis, that the individual understands the information and that the individual consents to the test. The Foundation recommends that this consent should be documented either by patient signature, or as a note in the patient's chart, or by the patient completing the form on a test kit. Minimal demographic information should be kept for each individual tested so that future contact can be ensured if the tested individual does not already have a medical record on site.

Sample Collection:

Bloodspot: A Qualified Healthcare Professional should collect the blood sample following instructions in the testing kit being used for the testing. Instructions include precautions in collecting the sample (i.e. pricking the finger and correctly filling the blood spot), correctly labeling the specimen, and drying before mailing it.

Venipuncture: If blood is being collected by venipuncture for AAT testing, appropriate techniques should be used. The sample should be correctly labeled and stored appropriately for pickup. **If a diagnosis code is required, the correct ICD-10 code for Alpha-1 Antitrypsin Deficiency is E88.01. If augmentation therapy is being prescribed the correct J-code for emphysema should be added, most commonly J43.1 for panlobular emphysema.**

Test results should only be sent to the physician's office.

Once the results are received, the patient's Qualified Healthcare Professional should explain the results to the patient and provide counseling and information about available network resources, depending on the results. A Qualified Healthcare Professional should make therapeutic recommendations to the patient, depending on the specifics of each case.

If an individual who attends the testing event does not have a medical record, the physician's office should open the appropriate medical record according to state law requirements, and include the date the patient testing was done and the results of his or her test, as well as documentation that the results were explained to the patient either verbally or by letter (include the letter, if one was used).

Industry representatives/employees may assist in sponsoring physician based testing days and provide branded free test kits, but may not have access to patients, their personal information, specific individual test results or provide additional incentives for testing.

Alpha-1 antitrypsin deficient patients identified during physician office testing days and their treating physicians should not be obligated to use any specific commercial product, regardless of the sponsorship of a given event. Therapeutic recommendations should conform to the prescribing information contained in the commercial package information as well as approved guidelines for the management of Alpha-1 Antitrypsin Deficiency.

Specialized Health Care Events

Respiratory Rally, COPD Education Days, and support group sponsored screening days are examples of these types of events.

Patient confidentiality must be a priority. Please note that for all testing, except that provided by the Foundation's Alpha-1 Coded Testing (ACT) trial, results can be expected to appear in the patient's medical record.

A Qualified Healthcare Professional should inform participants about the risks and benefits of Alpha-1 testing and obtain appropriate consent before genetic testing. The Foundation recommends this consent be documented either as a written consent signed by the patient, as a signature on a consent list, or by the patient completing the form on a test kit.

Testing should be done in a private setting away from the exhibits or registration area.

Sample Collection:

Bloodspot: A Qualified Healthcare Professional should collect the blood sample following instructions in the testing kit being used for the testing. Instructions should include precautions in collecting the sample (i.e. pricking the finger and correctly filling the blood spot) and drying before mailing it.

Venipuncture: If blood is being collected by venipuncture for AAT testing, appropriate techniques should be used. The sample should be correctly labeled and stored appropriately for pickup. **If a diagnosis code is required, the correct ICD-10 code for Alpha-1 Antitrypsin Deficiency is E88.01. If augmentation therapy is being prescribed the correct J-code for emphysema should be added, most commonly J43.1 for panlobular emphysema.**

Results must remain confidential and preferably sent to the individual's physician or the physician of record for the event. If sent to the individual, specific instructions to contact their physician must be included.

Industry representatives/employees may assist in sponsorship of these types of testing days and provision of free branded test kits, but may not have access to the tested individuals' names, personal information, or test results and may not provide additional incentives for testing.

Once the results are received, the patient's Qualified Healthcare Professional should explain the results to the patient and provide counseling and information about available network resources, depending on the results. A Qualified Healthcare Professional should make therapeutic recommendations to the patient, depending on the specifics of each case.

Alpha-1 antitrypsin deficient individuals identified during these events and their treating physicians should not be obligated to use any specific commercial product, regardless of the sponsorship of a given event. Therapeutic recommendations should conform to the prescribing information contained in the commercial package information as well as approved guidelines for the management of Alpha-1 Antitrypsin Deficiency.

Other Special Situations:

Family Testing, Newborn Screening, Pre-natal Testing, Post-Mortem Testing, and Alpha-1 Coded Testing (ACT) are all considered specialized situations and have or will have their own specific guidance.

Individuals who fall within evidence categories B, C, or D in the testing guidance of the American Thoracic Society/European Respiratory Society Statement: Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency may be considered for testing. The significance of these levels of evidence usually reflects a lack of convincing data rather than an increased risk or increased cost to the individual.

Even within these special situations, confidentiality must be a priority.

Within these special situations, when appropriate and not done via written information (as in the ACT study) a Qualified Healthcare Professional should inform the patient or their legal representative about the risks and benefits of AAT testing and obtain consent before genetic testing (e.g., for Newborn Screening). This consent should be documented in a manner consistent with the type of testing being done.

Sample Collection:

Bloodspot: A Qualified Healthcare Professional should collect the blood sample following the instructions in the testing kit being used for the genotyping. Instructions should include precautions in collecting the sample (i.e. pricking the finger and correctly filling the blood spot) and drying before mailing it.

Venipuncture: If blood is being collected by venipuncture for AAT testing, appropriate techniques should be used. The sample should be correctly labeled and stored appropriately for pickup. **If a diagnosis code is required, the correct ICD-10 code for Alpha-1 Antitrypsin Deficiency is E88.01. If augmentation therapy is being prescribed the correct J-code for emphysema should be added, most commonly J43.1 for panlobular emphysema.**

Other methods of sample collection apply to pre-natal and post-mortem testing.

Depending on the setting results must remain confidential and be sent to the individual's physician, the physician of record for the event, or to the individual being tested (or their parent(s) or guardian as appropriate). If sent to an individual, specific instructions to contact a physician must be included.

Industry representatives/employees may assist in sponsorship of these types of testing but may not have access to the tested individuals' names, personal information, or test results and may not provide incentives for testing.

Results received by the physician should be explained to the patient or appropriate family member/guardian, and counseling and information about available network resources should be provided, depending on the results. A Qualified Healthcare Professional should make therapeutic recommendations to the patient, depending on the specifics of each case.

Alpha-1 antitrypsin deficient individuals identified during these programs and their treating physicians should not be obligated to use any specific commercial product, regardless of the sponsorship of a given program. Therapeutic recommendations should conform to the prescribing information contained in the commercial package information as well as approved guidelines for the management of Alpha-1 Antitrypsin Deficiency.

Standard Health Fair

It is generally not advised to screen for Alpha-1 Antitrypsin Deficiency at general Health Fairs that normally focus on screenings for blood pressure, diabetes, cholesterol, or other generalized tests, due to the complex nature of consenting and sensitivity surrounding genetic testing. Depending on the setting, exceptions to this recommendation can be made, such as testing targeted at individuals with lung problems or abnormal spirometry

A more appropriate presence in the Health Fair setting could be the provision of educational materials and referral to the ACT study, as appropriate. The goal would be to increase knowledge of Alpha-1 Antitrypsin Deficiency and to consider confidential testing for those at risk.

Industry representatives/employees may assist in sponsoring education at Health Fairs. Industry employed Patient Advocates can be present to assist with patient questions.

SPECIFIC RECOMMENDATIONS REGARDING TESTING LIMITATIONS

Limitations of genotyping:

Anyone performing or advising patients about genotyping for Alpha-1 Antitrypsin Deficiency should understand the limitations of this testing.

Genotyping, as currently performed, evaluates the DNA of the tested individual for the presence of a limited number of specific mutations on each of the pair of AAT genes all individuals have. If none is present, then the genotype is presumed to be PiM or normal. Therefore, genotyping is generally not capable of detecting rare deficient genotypes or Null genotypes (which would be identified as M by most genotyping methodologies). Since there have been at least 50 deficient mutations and 14 Null mutations of the AAT gene identified to date, this is not an insignificant issue, although non-S/non-Z deficient genotypes are very rare.

Some of these limitations can be overcome by performing concurrent AAT level testing. Individuals suspected of having a rare deficient genotype need to be tested by Pi typing and/or more complete DNA sequencing techniques. Several of the available testing programs will automatically perform DNA sequencing on samples with discordant results. Often, DNA sequencing is required to detect Null AAT genes.

Limitations of Serum Levels and/or Pi typing:

Anyone performing or advising patients about serum levels for AAT should understand the limitations of this testing, including the possibility of temporarily increased levels due to the role of AAT as an acute phase reactant.

Serum AAT level testing may not definitively identify individuals carrying a single abnormal AAT gene (a carrier) and may not detect certain rare deficient genotypes. Additional testing is required if these are suspected.

Pi-typing will not detect the presence of a Null gene unless the patient is PiNull/Null.

Pi-typing must be performed by very experienced laboratory personnel familiar with this specific methodology.

Please contact the Alpha-1 Foundation for any questions or concerns regarding these guidelines. If you are planning a testing event that is not outlined above, contact the Foundation for specific guidelines.