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hATTR Compass™

Map Your Genetic Journey

Guide for Patients, Caregivers and Families

No-cost, confidential genetic testing and confidential genetic counseling for patients who are clinically suspected of having hereditary ATTR amyloidosis with polyneuropathy as well as individuals with a family history of hereditary ATTR amyloidosis

A Guide for Patients, Caregivers and Families to the hATTR Compass™ Genetic Testing Program

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About the hATTR Compass™ Program

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Akcea Therapeutics and Ambry Genetics are partnering to offer **no-cost, confidential genetic testing and confidential genetic counseling** to patients through the hATTR Compass Program who are clinically suspected of having hereditary ATTR amyloidosis with polyneuropathy as well as individuals with a family history of hereditary ATTR amyloidosis.

For family members, **genetic testing for hereditary ATTR amyloidosis may be the first stop on the diagnostic pathway** and will help you understand your future risk for this condition. It allows you to monitor for signs and symptoms of hereditary ATTR amyloidosis with polyneuropathy so that you can work with your doctor to make a healthcare management plan and treat the condition before it potentially gets worse. For patients with symptoms of hereditary ATTR with polyneuropathy, **genetic testing can be the final step on your diagnostic journey**.

The hATTR Compass Program is designed to:

- **Help** accelerate or confirm the diagnosis of hereditary ATTR amyloidosis with polyneuropathy
- **Provide** support and resources to patients, caregivers and healthcare professionals throughout the genetic testing process
- **Empower** patients and their healthcare professionals to make informed decisions about their health care

Who can get genetic testing?

- Patients 18 years and older who have a family history of hereditary ATTR amyloidosis
- Patients 18 years and older who have symptoms consistent with hereditary ATTR amyloidosis with polyneuropathy

Questions about genetic testing?

Genetic counselors are available at no-cost to speak with you on the phone before and after your tests.

- Before your test, a genetic counselor can review your goals, speak with you about any concerns you may have, and help you decide if genetic testing is right for you.
- After your test, a genetic counselor is available to discuss your results, help you plan your next steps, and answer any questions you may have.
- To learn more, ask your doctor to connect you with a genetic counselor at a third-party genetic counseling service working with the hATTR Compass Program.

How do I order hATTR Compass Program genetic testing and counseling?

1. If you are interested in joining, you or your doctor can sign up online. To sign up and order your free hATTR Compass Program genetic testing kit, visit **www.hATTRCompass.com**

   Tip: Don't forget to order confidential genetic counseling.
2. Next, you'll be asked to provide a blood or saliva sample that you or your doctor will submit for genetic testing.
3. Your doctor will receive your test results within 2-4 weeks after you send it in and will subsequently share the results with you.
4. You'll be able to work with your doctor to make a healthcare management plan based on your test results. For those individuals with a family history of hereditary ATTR amyloidosis, the hATTR Compass Program is the first stop on the diagnostic pathway to treat the condition.
5. For family members with a positive genetic test, you can work with your doctor to identify the red-flag symptoms of hereditary ATTR amyloidosis with polyneuropathy as soon as they manifest and potentially execute your healthcare management plan before the condition gets worse.

We're here to help you every step of the way. If you have any questions about the hATTR Compass Program, contact us at **+1 (949) 900-5500**.

The hATTR Compass Program is available in the United States, Canada and Puerto Rico. While Akcea provides financial support for this program, all tests and services are private and performed by independent third parties.

At no time does Akcea receive information about you or your test results.

To participate in the hATTR Compass Program, visit www.hATTRCompass.com

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What does hereditary ATTR amyloidosis mean for you and your family?

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Hereditary diseases are genetic disorders where a **gene change (called a genetic mutation) is passed down through family members**. It is the passed down mutation that can cause disease. In hereditary ATTR amyloidosis, a gene mutation changes the structure of the transthyretin (TTR) amyloid protein, causing it to fold incorrectly, stick together and build-up throughout the body.[1]

If hereditary ATTR amyloidosis runs in my family, what are the chances that my children will have the condition?

Hereditary ATTR amyloidosis is an autosomal dominant condition, meaning an individual needs to inherit **only one copy of the mutated gene from one parent** to develop the disease.[2] If one parent has hereditary ATTR amyloidosis, there is a **50% chance** their child will inherit the mutation.

Inheriting a mutated copy of the TTR gene does not always lead to disease or symptoms. However, even without symptoms, a parent with an altered copy of the gene is a carrier and still has a 50% chance of passing on the mutation.

- **More than 130** different TTR gene mutations have been discovered.
- **The most common mutations** in the United States are **Val142Ile, Thr80Ala and Val60Met**[1]

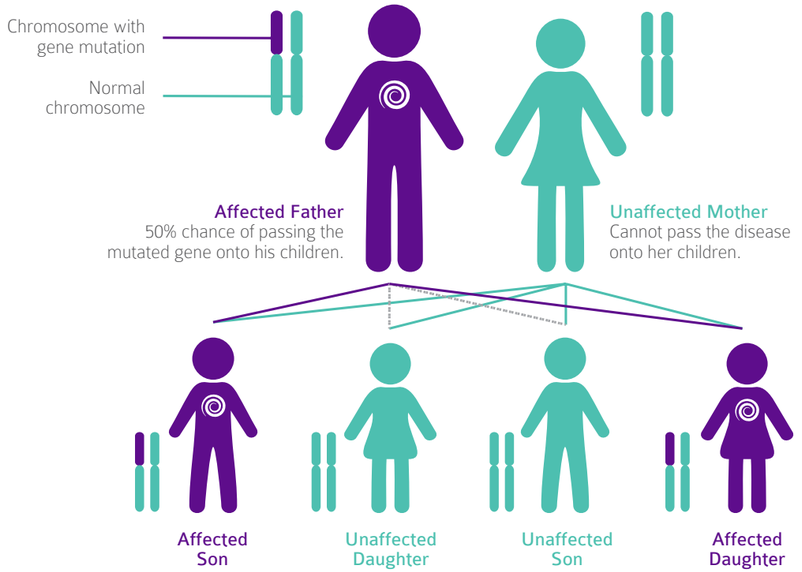
1. Gertz MA. Hereditary ATTR amyloidosis: burden of illness and diagnostic challenges. Am J Manag Care. 2017;23(suppl 7):S107-S112. 2. Coelho T, Maurer MS, Suhr OB. THAOS—The Transthyretin Amyloidosis Outcomes Survey: initial report on clinical manifestations in patients with hereditary and wild-type transthyretin amyloidosis. Curr Med Res Opin. 2013;29(1):63-76. 3. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013;8:31.

Hereditary ATTR amyloidosis is a severe, rare and life-threatening disease which negatively affects quality of life.

TTR amyloid fibrils form when the structure of a normally dissolvable TTR protein misfolds.[1]

The misfolded proteins are **sticky and clump together** in tissues and between the body's cells to **form amyloid deposits**.[3]

Amyloid deposits cause disease by damaging the structure and the function of the organs where they are found. They can **affect almost any body system** including the nerves, heart and GI tract.[3]



It is the mutated version of the TTR gene that is passed down through family members, which can lead to disease.

It is not always easy to determine whether a condition in a family is inherited. If you have a family history of hereditary ATTR amyloidosis, consider whether genetic testing through the hATTR Compass Program is right for you. The hATTR Compass Program is a **no-cost, confidential genetic testing and confidential genetic counseling program** designed to test patients who are clinically suspected of having hereditary ATTR amyloidosis with polyneuropathy as well as individuals with a family history of hereditary ATTR amyloidosis.

For more information on genetic testing and genetic counseling, please visit www.hATTRCompass.com

Hereditary ATTR amyloidosis symptom checklist

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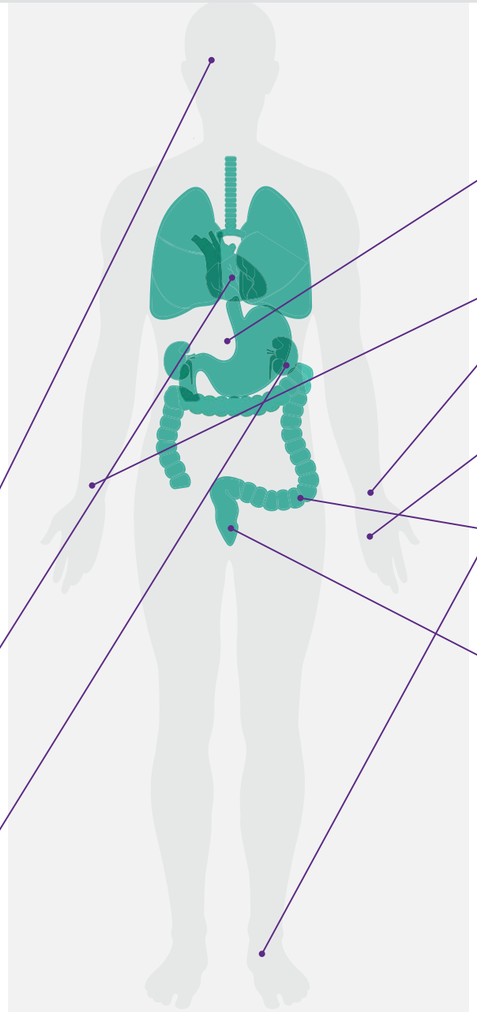
Since hereditary ATTR amyloidosis can manifest itself in many ways and with a broad range of symptoms, it can be hard for doctors and patients to recognize. Patients often present with a cluster of two, three or more red-flag symptoms.

If you are experiencing two or more symptoms related to hereditary ATTR amyloidosis, consider whether **genetic testing through the hATTR Compass Program is right for you**. The hATTR Compass Program is a **no-cost, confidential genetic testing and confidential genetic counseling program** for patients who are clinically suspected of having hereditary ATTR amyloidosis with polyneuropathy as well as individuals with a family history of hereditary ATTR amyloidosis.



Ocular[1,2] ☐

Symptoms related to the eyes, often causing visual changes

- Dark floaters ☐
- Glaucoma ☐
- Abnormal blood vessels in eye ☐
- Eyelid swelling and inflammation ☐

Cardiovascular[1,2,6-8] ☐

Symptoms related to the heart, blood vessels and circulation

- Irregular heart beat ☐
- Increasing fatigue ☐
- Shortness of breath ☐
- Leg swelling (peripheral edema) ☐
- Thickening of ventricular walls ☐
- Aortic stenosis ☐

Nephropathy[1,2,9] ☐

Damage to kidneys

- Renal failure ☐
- Protein in urine ☐

☐ Spinal Stenosis[3-5]

Pain, tingling or numbness of the legs and buttocks caused by pressure of the nerves in the spine due to narrowing of spinal cavity

☐ Carpal Tunnel Syndrome[1,3,6,10]

Numbness and tingling in the hands and arms caused by a pinched nerve in the wrists

☐ Peripheral Sensory-Motor Neuropathy[9,11,12]

Weakness, numbness and pain from nerve damage

- ☐ Nerve damage beginning in feet and legs that can progress to the hands and to the central part of the body

☐ Gastrointestinal[1,2]

GI tract including stomach issues. GI issues are often caused by autonomic nerve damage.

- ☐ Nausea and vomiting
- ☐ Loss of appetite
- ☐ Diarrhea, constipation, or alternating diarrhea and constipation
- ☐ Unintentional weight loss

☐ Autonomic Neuropathy[1,2,9]

Damage to the nerves that manage everyday body functions

- ☐ Sexual dysfunction
- ☐ Sweating abnormalities
- ☐ Alternating diarrhea and constipation
- ☐ Dizziness from low blood pressure
- ☐ Recurrent urinary tract infections (due to urinary retention)

1. Gertz MA. Hereditary ATTR amyloidosis: burden of illness and diagnostic challenges. Am J Manag Care. 2017;23(suppl 7):S107-S112. 2. Coelho T, et al. A physician's guide to transthyretin amyloidosis. Amyloidosis Foundation, 2008. https://www.researchgate.net/publication/265490881_A_Physician's_Guide_to_Transthyretin_Amyloidosis; 3. Nakagawa M, et al. Carpal tunnel syndrome: a common initial symptom of systemic wild-type ATTR (ATTRwt) amyloidosis. Amyloid. 2016;23(1):58-63.; 4. Cortese A et al. Diagnostic challenges in hereditary transthyretin amyoidosis with polyneuropathy: avoiding misdiagnosis of a treatable hereitary neuropathy. Journal of Neurology, Neurosurgery, and Psychiatry 2017; 88(5): 457-8; 5.Yanagisawa A et al. Amyloid deposits derived from transthyretin in the ligamentum flavum as realted to lumar spinal canal stenosis. Modern Pathology 2015; 28(2): 201-7; 6. Donnelly JP, Hanna M. Cardiac amyloidosis: an update on diagnosis and treatment. Cleve Clin J Med. 2017;84(12 suppl 3):12-26; 7. Ikram A, et al. Carpal Tunnel Syndrome and Amyloid Cardiomyopathy. J Card Fail. 2017;23(8):S11-S12(P021); 8. Galat A, et al. Aortic stenosis and transthyretin cardiac amyloidosis: the chicken or the egg? Eur Heart J. 2016;37(47):3525-31; 9. Adams D, Coelho T, Obici L, et al. Rapid progression of familial amyloidotic polyneuropathy: a multinational natural history study. Neurology. 2015;85(8):675-682; 10. Lousada I et al. Amyloidosis research consortium cardiac amyloidosis survey: results from patients with ATTR amyloidosis and their caregivers. Orphanet Journal of Rare Diseases 2017;12(Suppl 1): 165 (P7); 11. Ando Y et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet Journal of Rare Diseases 2013, 8:31; 2; 12. Conceição et al. "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy. Journal of the Peripheral Nervous System. 2016; 21:5-9

Why participate in genetic testing?

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Initial symptoms of hereditary ATTR amyloidosis typically appear between the mid-20s to the mid-60s, involve multiple tissues and organs and are often seemingly unrelated. Because symptoms aren't always specific and may be confused with more common conditions, hereditary ATTR amyloidosis can be hard to diagnose.[1]

- It often takes **more than 4 years** from symptom onset to a diagnosis[2]

It is not always easy to determine whether a condition or disease in a family is passed down from parent to child and genetic tests can help. Genetic testing uses laboratory methods to look for mutations, or changes, in your genes. Genetic tests help to identify increased risks of health problems or help to choose the best treatment.

Through genetic testing, you can learn if you carry gene changes known to be associated with hereditary ATTR amyloidosis.

For family members, genetic testing for hereditary ATTR amyloidosis may be the first stop on the diagnostic pathway and will help you understand your future risk for this condition. It allows you to monitor for signs and symptoms of hereditary ATTR amyloidosis with polyneuropathy so that you can work with your doctor to make a healthcare management plan and treat the condition before it potentially gets worse. For patients with symptoms of hereditary ATTR amyloidosis with polyneuropathy, genetic testing can be the final step on your diagnostic journey.

Overall, benefits of genetic testing include:

- Diagnose disease
- Identify gene changes that are responsible for an already diagnosed disease
- Guide doctors in deciding on the best medicine or treatment to use for certain individuals
- Identify gene changes that may increase the risk to develop a disease
- Identify gene changes that could be passed on to children
- Treat the condition

Where can I find more information about genetic testing?

- **Your Doctor**
- **Genetic Counselor**
- **Amyloidosis Research Consortium (www.ARCI.org)**
- **Amyloidosis Support Group (www.amyloidosissupport.org)**
- **Akcea Patient Advocacy (email: patientadvocacy@akceatx.com)**

As with any disease, especially with hereditary diseases, early diagnosis is key. The hATTR Compass Program was developed to fulfill an unmet need, providing best-in-class genetic testing for patients who wish to know if they have the mutated TTR gene. Providing access to **no-cost, confidential genetic testing and confidential genetic counseling** will allow you and your family to make more informed decisions about your health care.

If you are experiencing symptoms of hereditary ATTR amyloidosis with polyneuropathy or have a family history of hereditary ATTR amyloidosis, speak to your doctor about whether genetic testing is right for you.

The hATTR Compass Program allows you to Map Your Genetic Journey.

To participate in the hATTR Compass Program, visit www.hATTRCompass.com

1. Amyloidosis Foundation and Amyloidosis Support Groups. Understanding the patient voice in hereditary transthyretin-mediated amyloidosis (ATTR amyloidosis). Last Accessed May 25, 2018. http://amyloidosissupport.org/support_groups/fam_isabell_attr.pdf
2. Hawkins P et al. Ann Med. 2015;47:625-638

Talking with your family about genetic testing for hereditary ATTR amyloidosis

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It can be hard to talk with loved ones about genetic testing for hereditary ATTR amyloidosis. For some people, genetic test results serve as a relief, removing some of the uncertainty surrounding their health. For others, learning that you or someone in your family has or is at risk for a disease can be scary. Some people can also feel guilty, angry, anxious or depressed when they find out their results.

As with any serious family discussion, there are benefits and risks to discussing a serious topic, such as genetic testing.

Potential benefits of talking with your family about genetic testing include:

- Helping family members understand their risk for hereditary ATTR amyloidosis
- Helping family members watch out for signs of hereditary ATTR amyloidosis and start screening earlier
- Helping family members understand the need for tests or treatments
- Talking about your and your families' risk or diagnosis of hereditary ATTR amyloidosis can help release pent-up feelings

Potential risks to keep in mind when talking to your family about genetic testing:

- Learning that you or someone in your family has or is at risk for a disease can be scary
- Family members may find it upsetting to get genetic testing if other family members have hereditary ATTR amyloidosis
- Having a gene or passing the gene on to children can also lead to guilt or anger

Talking with your family about your family health history can help you stay healthy. Below are a few tips to get you started.

1. **Educate yourself on hereditary ATTR amyloidosis.**

   It is important to gain an in-depth understanding of the disease so you can discuss your potential symptoms and path to diagnosis with your family. The more you know about the condition the better you will be able to answer questions your family may have.
   Learn more at www.hATTRChangeTheCourse.com

2. **Collect information about your family health history of hereditary ATTR amyloidosis and share this information with other family members.**
   By sharing your family health history, you can help family members understand why your disease might affect them. Be sure to consult "What does hereditary ATTR amyloidosis mean for you and your family?" (page 5) for helpful information.

   Tip: Try to recall if any family member has one or more of the symptoms of hereditary ATTR amyloidosis, as this may help to diagnose the hereditary aspect of the disease.

3. **If you have received genetic testing,** be prepared to share your experience and results with your family. Knowing that you have been through the process can help family members in their decision about genetic testing. Refer to information about the hATTR Compass Program (page 3).

   Tip: Remember through the hATTR Compass Program, genetic counselors are available to talk about your genetic testing results and what they could mean for your family. Consider referring family members to speak with a genetic counselor or their doctor if they have questions or concerns about genetic testing that you can't answer.*

4. **If you are still considering genetic testing,** have an honest conversation with your family about what your genetic testing and results could mean for them. If possible, consider getting tested together as a family. Genetic testing can take an emotional toll and having the support of family is important.

Remember, although this may be a difficult conversation to have with your family, there are many resources, people and organizations that can help you through the process.

- **Your Doctor**
- **Genetic Counselor**
- **Amyloidosis Research Consortium (www.ARCI.org)**
- **Amyloidosis Support Group (www.amyloidosissupport.org)**
- **Akcea Patient Advocacy (email: patientadvocacy@akceatx.com)**

* The hATTR Compass Program will cover the cost of two genetic counseling sessions (pre- and post- testing). Any additional sessions will be the responsibility of the patient.