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AKCEA THERAPEUTICS

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hATTR Compass™

Map Your Genetic Journey

Guide for Healthcare Professionals

No-cost, confidential genetic testing and confidential genetic counseling for patients suspected of having or clinically diagnosed with hATTR amyloidosis with polyneuropathy

A Healthcare Professional's Guide to the hATTR Compass™ Program

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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 suspected of having or clinically diagnosed with hereditary transthyretin amyloidosis (hATTR) with polyneuropathy through the hATTR Compass Program.

Early genetic testing is a key part of the diagnostic pathway to ensure an accurate diagnosis of hATTR amyloidosis with polyneuropathy. It allows you to **watch out for signals and symptoms of hATTR amyloidosis with polyneuropathy** sooner so that you can make a healthcare management plan and treat the condition before it potentially gets worse.

The hATTR Compass Program is designed to:

- **Help** accelerate or confirm the diagnosis of hATTR 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 the most informed decisions about their health care

Who is Eligible?

The hATTR Compass Program is available for patients who are 18 years and older and who have a family history of or are experiencing symptoms of hATTR amyloidosis.

What genes are tested?

The following genetic tests are available through the hATTR Compass Program to confirm a diagnosis of hATTR amyloidosis with polyneuropathy. For assistance in identifying which test is appropriate for your patient, contact **+1 (949) 900-5500**.

- **hATTR Amyloidosis Test:** Single-gene test for TTR
- **CardioNext:** 85-gene panel targeting patients who have mixed phenotypes, including hATTR amyloidosis. Select this test for a comprehensive genetic assessment of patients with a mixed phenotype.
- **NeuropathySelect:** 80-gene panel targeting patients with hereditary neuropathies, including hATTR amyloidosis (available at select centers)

Genetic counselors are available at no-cost to consult with your patient through pre- and post-test counseling. Genetic counselors at PWNHealth, the third-party, independent partner working with the hATTR Compass Program, are trained to help patients navigate the social and emotional aspects of genetic testing. During pre-test counseling, a genetic counselor will be available by phone to discuss the benefits, limitations and implications of genetic testing with your patient. During post-test counseling, a genetic counselor will be available by phone to help your patient interpret their results and the potential implications for them and their families. If requested, genetic counselors can review treatment options available and provide additional resources. If your patient is interested in this confidential service, make sure to indicate on the ordering form whether your patient would like to have pre- and/or post-test counseling. If indicated, a customer service representative will contact your patient to schedule the designated counseling session(s).

How do I enroll my patient?

1. **Order Online:** If you have a patient who is interested in participating, order your free hATTR Compass Program kit at **www.hATTRCompass.com**

   Tip: Be sure to indicate whether your patient would like to receive confidential genetic counseling on the order form.

2. **Collect Samples:** Use the hATTR Compass Program kit provided to you by mail or an Ambry representative to collect your patient's blood or saliva DNA samples. Complete the Test Requisition Form provided with the kit.

3. **Submit for DNA Analysis:** Submit the hATTR Compass Program kit for DNA analysis with the completed Test Requisition Form using the mailing instructions provided in your kit.

4. **Receive Results:** Your patient's results will be sent to you within 2-4 weeks

   Tip: Ambry Genetic Counselors are available to help you interpret the test results. For assistance, contact **+1 (949) 900-5500**.

5. **Make a Plan:** Work with your patient to make a healthcare management plan based on their test results. The hATTR Compass Program is the first stop on the diagnostic pathway to treat the condition.

6. **Watch out for Symptoms:** With a confirmed diagnosis, you can work with your patient to identify the red-flag symptoms of hATTR amyloidosis with polyneuropathy as soon as they manifest and potentially execute your healthcare management plan before the condition gets worse. If you'd like to learn more about hATTR amyloidosis, start here at **www.hATTRGuide.com**

   Tip: To find an hATTR amyloidosis specialist in your area, visit **https://www.myamyloidosispathfinder.org/**

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 confidential and performed by independent third parties.

At no time does Akcea receive patient identifiable information.

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

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What does **hereditary ATTR amyloidosis** mean for your patient?

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Hereditary transthyretin amyloidosis (hATTR) is a **rare, progressive and deadly disease**[1,2] which robs people of their independence and dignity.

hATTR amyloidosis was previously known as transthyretin **familial amyloid polyneuropathy (TTR-FAP)** or **familial amyloid cardiomyopathy (TTR-FAC)** deriving its name from the most predominant clinical presentation.[3,4]

hATTR amyloidosis is an autosomal dominant disease with variable penetrance. Amyloid deposition or symptomatic disease typically occurs in adults ranging from 30 to 70 years of age, depending on mutation.[4]

- **More than 120** different TTR gene mutations have been identified. The most common mutations in the United States are **Val122Ile, Thr60Ala and Val30Met**[4]
- Although some mutations are more predominantly associated with polyneuropathy or cardiomyopathy, **many patients with hATTR amyloidosis have mixed clinical phenotypes** including neurologic, cardiac, GI, and other signs and symptoms[4-6]
- hATTR amyloidosis symptomatology can have variable penetrance which **can differ among affected family members' hATTR amyloidosis**[4]

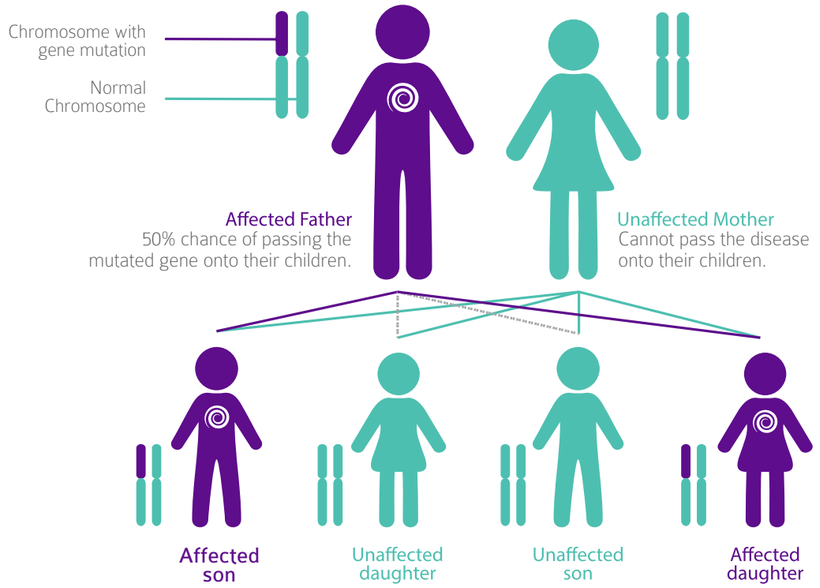
1. Adams D, Amitay O, Coelho T. Patients with hereditary ATTR amyloidosis experience an increasing burden of illness as the disease progresses. Orphanet J Rare Dis. 2015;10(suppl 1):P58. 2. Conceição I, González-Duarte A, Obici L, et al. "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy. J Peripher Nerv Syst. 2016;21(1):5-9. 3. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013;8:31. 4. Gertz MA. Hereditary ATTR amyloidosis: burden of illness and diagnostic challenges. Am J Manag Care. 2017;23(suppl 7):S107-S112. 5. 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. 6. Hawkins PN, Ando Y, Dispenzeri A, Gonzalez-Duarte A, Adams D, Suhr OB. Evolving landscape in the management of transthyretin amyloidosis. Ann Med. 2015;47(8):625-638. 7. Coelho T, Ericzon B-G, Falk R, et al. A guide to transthyretin amyloidosis. Amyloidosis Foundation. http://www.amyloidosis.org/wp-content/uploads/2017/05/2017-ATTR-guide.pdf. Accessed February 14, 2018. 8. Johnson SM, Connelly S, Fearns C, Powers ET, Kelly JW. The transthyretin amyloidosis: from delineating the molecular mechanism of aggregation linked to pathology to a regulatory agency approved drug. J Mol Biol. 2012;421(2-3):185-203.

hATTR amyloidosis is a systemic disorder characterized by the extracellular deposition of transthyretin (TTR) protein, which misfolds and aggregates into amyloid fibrils. These amyloid fibrils then accumulate in multiple organs throughout the body, leading to both polyneuropathies and cardiomyopathies.

TTR is a tetramer made up of 4 single-chain monomers. TTR gene mutations are thought to destabilize the protein and cause tetramer dissociation into monomers[3,4,7,8]

The TTR monomers aggregate into amyloid fibrils, which accumulate in multiple organs throughout the body[3,4,7,8]

Amyloid deposits cause illness by damaging the structure and the function of the organs where they are found. They can **affect almost any part of the body** including the nervous system, heart, kidney, and GI tract.[3-8]



Due to the familial nature of hATTR amyloidosis, **if you have a patient who is aware of a family history of the disease, consider whether genetic testing is right for them through the hATTR Compass Program.** The hATTR Compass Program is a **no-cost, confidential genetic testing and confidential genetic counseling program** for patients suspected of having or clinically diagnosed with hATTR amyloidosis with polyneuropathy.

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

hATTR amyloidosis
symptom checklist

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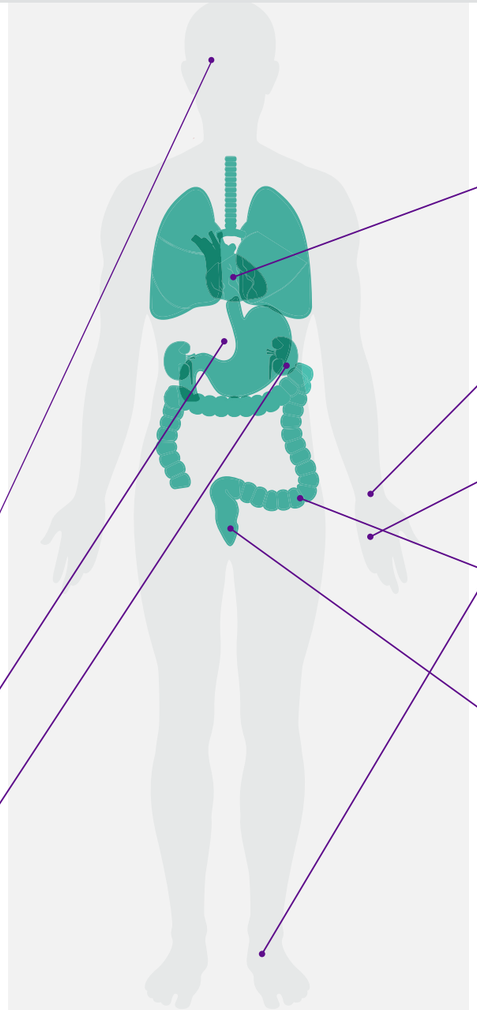
Identifying hATTR amyloidosis is complicated, due to nonspecific symptoms which can resemble other conditions. Patients often present with a cluster of one, two, three or more red-flag symptoms. This often results in patients seeing physicians across multiple specialties before receiving an accurate diagnosis of hATTR amyloidosis.[1]

It's especially important to watch out for **early signs of polyneuropathy symptoms.** For example, **tingling in the hands and feet** that can progress to the central part of the body or **trouble with balance and coordination. If you have a patient who is experiencing** at least two clinical symptoms or manifestations related to hATTR amyloidosis, consider **whether genetic testing is right for them** through the hATTR Compass Program. The hATTR Compass Program is a **no-cost, confidential genetic testing and confidential genetic counseling program** for patients suspected of having or clinically diagnosed with hATTR amyloidosis with polyneuropathy.



Ocular Manifestations[2] ☐
- Dark floaters ☐
- Abnormal blood vessels in eye ☐
- Glaucoma ☐
- Pupillary abnormalities ☐

Spinal Stenosis[3] ☐

Nephropathy[2] ☐
- Renal failure ☐
- Protein in urine ☐

Cardiac Manifestations[1-2,4] ☐
- ☐ Irregular heart beat
- ☐ Conduction Blocks
- ☐ Ventricular wall thickening with preserved ejection fraction and absence of left ventricular dilation
- ☐ Congestive heart failure (including shortness of breath, generalized fatigue, peripheral edema)

Bilateral Carpal Tunnel Syndrome[2-3] ☐

Peripheral sensory-motor neuropathy[2] ☐
- ☐ Nerve damaging beginning in the hands and feet that can progress to the central part of the body
- ☐ Peripheral neuropathy generally initiates as a small fiber neuropathy with more motor involvement as the disease progresses

Gastrointestinal Manifestations[2] ☐
- ☐ Nausea and vomiting
- ☐ Diarrhea
- ☐ Early satiety
- ☐ Severe constipation

Autonomic Neuropathy[2] ☐
- ☐ Sexual dysfunction
- ☐ Orthostatic hypotension
- ☐ Sweating abnormalities
- ☐ Recurrent urinary tract infections (due to urinary retention)
- ☐ Alternating bouts of diarrhea and constipation

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

1. Gertz MA. Hereditary ATTR amyloidosis: burden of illness and diagnostic challenges. Am J Manag Care. 2017;23(suppl 7):S107-S112. 2. Conceição I, González-Duarte A, Obici L, et al. "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy. J Peripher Nerv Syst. 2016;21(1):5-9. 3. Donnelly JP, Hanna M. Cardiac amyloidosis: an update on diagnosis and treatment. Cleve Clin J Med. 2017;84(12 suppl 3):12-26. 4. Coelho T, Ericzon B-G, Falk R, et al. A guide to transthyretin amyloidosis. Amyloidosis Foundation. http://www.amyloidosis.org/wp-content/uploads/2017/05/2017-ATTR-guide.pdf. Accessed February 14, 2018.

Why should your patients participate in the hATTR Compass Program?

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For hATTR amyloidosis patients, the journey to diagnosis can be challenging

hATTR amyloidosis can be a physically debilitating disease that can cause a **decline in quality of life and negatively affect activities of daily living.** The speed at which hATTR amyloidosis progresses is unpredictable, but left untreated, can be fatal within a few years of initial clinical presentation.[1] This underscores the importance of a helping your patients receive a timely diagnosis.

Often, patients with hATTR amyloidosis experience

- Substantial delays between initial symptoms and diagnosis[2,3]
- Visits to multiple physicians, often 5 or more, across a broad range of clinical specialties before receiving a diagnosis[2,3]

The hATTR Compass Program was created to:

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

Through the hATTR Compass Program, your patient can learn if they carry a gene mutation known to be associated with hATTR amyloidosis. For patients seeking an accurate diagnosis, genetic testing results can provide a sense of relief from uncertainty. Results can help patients and their families determine the risk for developing the disease. It can also help accelerate your patient's path to diagnosis, enabling you and your patient to make informed decisions about their health care.

1. Gertz MA. Hereditary ATTR amyloidosis: burden of illness and diagnostic challenges. Am J Manag Care. 2017;23(suppl 7):S107-S112. 2. Nakagawa M, et al. Carpal tunnel syndrome: a common initial symptom of systemic wild-type ATTR (ATTRwt) amyloidosis. Amyloid. 2016;23(1):58-63. 3.Lousada I, et al. Patient experience with hereditary and senile systemic amyloidoses: a survey from the Amyloidosis Research Consortium. Presented at: the First European Congress on Hereditary ATTR Amyloidosis. November 2015; Paris, France.

Early genetic testing is a key part of the diagnostic pathway to ensure an accurate diagnosis of hATTR amyloidosis with polyneuropathy. It allows you to watch out for signals and symptoms of hATTR amyloidosis with polyneuropathy sooner so that you can make a healthcare management plan and treat the condition before it potentially gets worse.

As you talk with your patient about whether or not genetic testing is right for them, they may have questions or concerns. Genetic testing and the results can be frightening and have an emotional impact regardless of the results. There are many resources, people and organizations that can help your patients through the process by providing support, guidance and additional resources.

Additional resources include:

- **Genetic Counselor (www.pwnhealth.com)**
- **Amyloidosis Research Consortium (www.ARCI.org)**
- **Amyloidosis Foundation (www.amyloidosis.org)**
- **Amyloidosis Support Group (www.amyloidosissupport.org)**
- **Akcea Patient Advocacy (email: patientadvocacy@akceatx.com)**
- **My Amyloidosis Pathfinder (https://www.myamyloidosispathfinder.org/)**

If you have a patient who has a family history of or is experiencing symptoms of hATTR amyloidosis, consider whether genetic testing and counseling is right for them. The hATTR Compass Program offers **no-cost, confidential genetic testing and confidential genetic counseling** for patients that qualify.

To learn more or participate in the hATTR Compass Genetic Testing Program, visit www.hATTRCompass.com

Talking with your patient about genetic testing for hATTR amyloidosis

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Whether your patient has a family history of or is experiencing symptoms of hATTR amyloidosis, the decision to talk with your patient about genetic testing for a hereditary condition can be challenging. It's important to remember that while you may encourage them to seek answers, not all patients - especially those who are presymptomatic - may want to know if they carry the genetic mutation known to be associated with hATTR amyloidosis.

Potential benefits of genetic testing include:

- Helping your patient understand their risk for specific diseases
- Empowering you and your patient to make informed decisions about future monitoring and treatment
- Fostering open communication between you and your patient
- Providing support resources and tools for patients to manage their disease

Potential risks of genetic testing to keep in mind:

- Introducing anxiety, guilt and emotional distress to your patient
- Telling a family member about a genetic risk that they do not wish to know about

If you choose to discuss genetic testing with your patient, below are a few tips to help prepare you to have an informed, understanding conversation:

1. **Educate yourself on hATTR amyloidosis.** It is important to have an in-depth understanding of the disease so you can discuss symptoms, path to diagnosis and potential treatment options with your patient. The more you know about the condition the better you will be able to answer questions your patient may have. Start here: **www.hATTRGuide.com**

2. **Be prepared to talk about the hereditary nature of hATTR amyloidosis.** By highlighting the hereditary nature of the condition, you can help your patient understand the condition and why they are at risk. Be sure to consult **www.hATTRGuide.com** for helpful information.

   Tip: Have your patient try to recall if deceased family members were affected by the symptoms of hATTR amyloidosis, as this may help to determine the hereditary aspect of the disease.

3. **If your patient has already received genetic testing,** be prepared to discuss the results and what they mean. Having a high-level understanding of the results and limitations of genetic testing can be helpful for your patient as they process the findings. Refer to the hATTR Compass Program overview (page 3).

   Tip: Genetic counselors through the hATTR Compass Program are available at no-cost to consult with your patient through pre-test and post-test counseling. Genetic counselors at PWNHealth, the third-party, independent partner working with the hATTR Compass Program, are trained to help patients navigate the social and emotional aspects of genetic testing.

4. **If your patient is still considering genetic testing,** have an honest conversation with your patient about what testing and results could mean for them. The hATTR Compass Program is a **no-cost, confidential genetic testing and confidential genetic counseling program** for patients suspected of having or clinically diagnosed with hATTR amyloidosis with polyneuropathy.

   Tip: Discuss the simple and easy genetic testing and confidential genetic counseling process offered through the hATTR Compass Program and resources available at **www.hATTRCompass.com**.

Remember, although discussing genetic testing with your patient may be difficult, there are many resources, people and organizations that can support you and your patient through the process by providing support, guidance and additional resources.

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

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