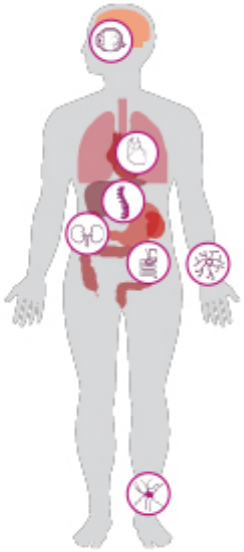


Understanding hATTR Amyloidosis:

Clinical Presentation, Patient Journey, and Treatment Landscape for This Rare Disease

Key Objectives

- Define ATTR amyloidosis and subtypes
- Discuss pathophysiology of hereditary ATTR (hATTR) amyloidosis and various clinical presentations including early nonspecific symptoms
- Understand burden of illness and unmet need of the disease
- Showcase existing categories of innovative medications used to treat hATTR amyloidosis

Definition of Transthyretin (TTR) Amyloidosis and Subtypes

What Is Transthyretin (TTR) Amyloidosis?

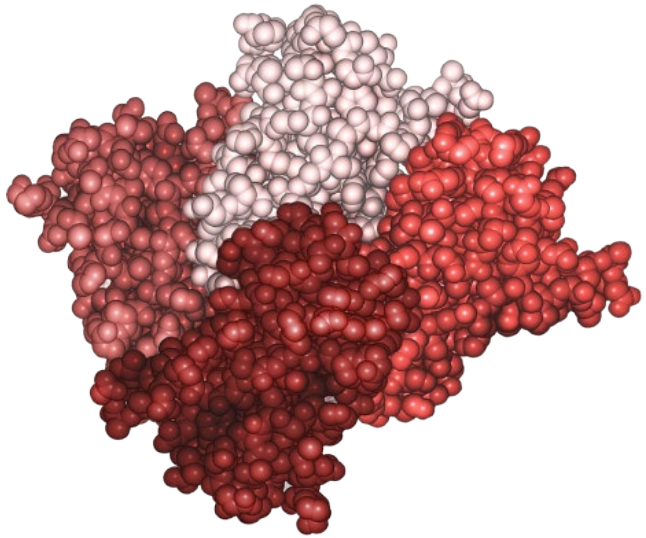
- **Amyloidosis** (plural: amyloidoses) is the deposition of amyloid fibrils in tissues[1]
  - Amyloid fibrils are formed from normally soluble proteins that misfold and then assemble to **form insoluble fiber aggregates**[2]
  - These proteins form elongated fibers with spines consisting of β-sheets[2]
  - Disease course for each specific amyloidosis can **vary dramatically**

Amyloidosis	Protein Origin
Amyloid Serum A Protein (AA amyloidosis)[3]	SAA protein produced by liver in large amounts due to pre-existing conditions
Amyloid Light Chain (AL amyloidosis)[4]	Plasma cells in bone marrow produce abnormal immunoglobulin protein
Amyloid Transthyretin (ATTR amyloidosis)[5]	Transthyretin protein produced in liver

*Based on a study of UK patients

1. Amyloidosis Foundation. 2016. Amyloidosis Information A General Overview for Patients. Available at: http://www.amyloidosis.org/wp-content/uploads/2016/11/2016-patient-overview.pdf. Accessed August 15, 2019; 2. Rambaran RN et al. *Prion*. 2008;2(3):112-117; 3. Real de Asúa D et al. *Clin Epidemiol*. 2014;6:369-377; 4. Desport E et al. *Orphanet J Rare Dis*. 2012;7:54; 5. Hawkins P et al. *Ann Med*. 2015;47:625-638.

In ATTR Amyloidosis, TTR Forms Amyloid Fibrils



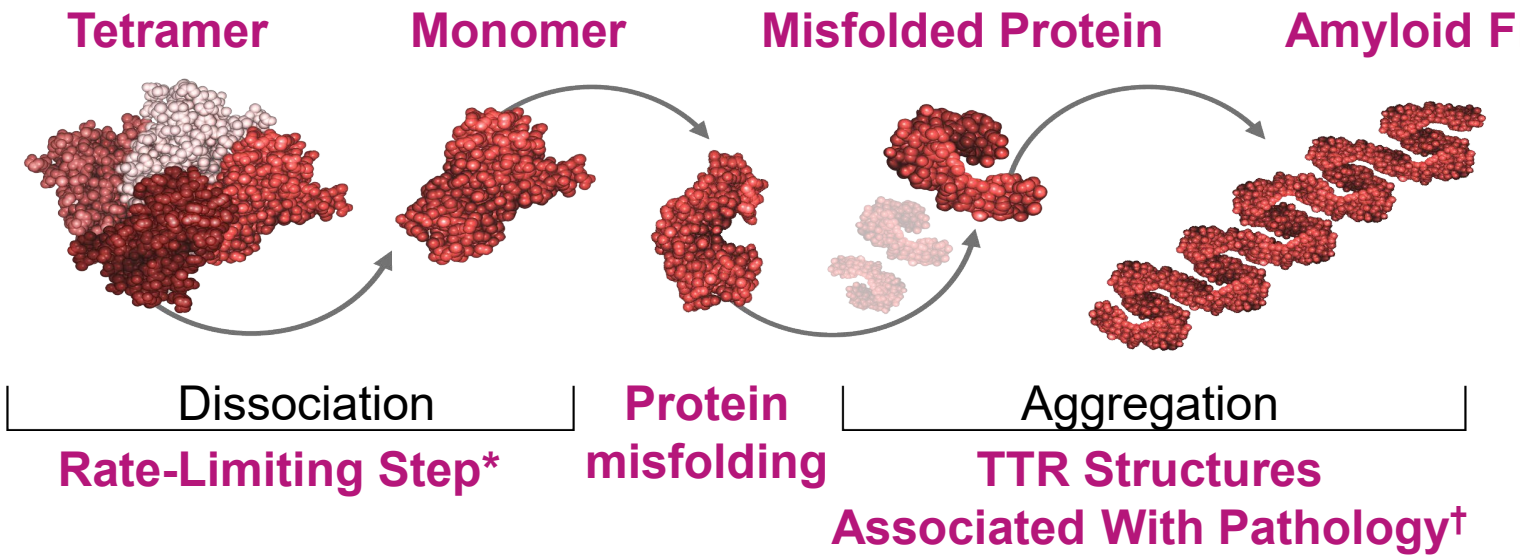
TTR protein

- The amyloidogenic precursor in ATTR amyloidosis is transthyretin protein (previously termed prealbumin)[1]
- Transthyretin (TTR) is involved in the **TRANS**port of **THYR**oxine and **RET**inol[2-4]
- The majority of TTR protein is **produced in the liver** (>95%)[2,3]
  - <5% of TTR protein is produced by the choroid plexus of the brain, retinal pigmented epithelium in the eye, and α cells in the pancreas
- Normally, TTR exists as a tetramer[1]

ATTR, amyloid transthyretin

1. Saraiva MJ. *FEBS Lett.* 2001;498:201-203; 2. Ueda M, Ando Y. *Transl Neurodegener*. 2014;3:19; 3. Misumi Y et al. *Liver Transpl*. 2016;22(5):656-664; 4. Coelho T et al. *A Guide to Transthyretin Amyloidosis*. 2018. http://amyloidosis.org/wp-content/uploads/2019/05/2018-ATTR-guide.pdf. Accessed August 15, 2019.

hATTR Amyloidosis Causes TTR Protein Destabilization, Leading to Amyloid Formation and Deposition



- In **hereditary ATTR amyloidosis**, mutations in the *TTR* gene are thought to disrupt the tetrameric structure of TTR resulting in weaker interactions between monomer subunits[1-3]
- Weakened interactions promote dissociation into monomers that misfold and have a greater propensity for aggregation[1-3]
- It is thought that amyloid fibrils cause damage through direct compression, obstruction, and local blood circulation failure[4]
    - Studies also show that monomers and other forms of TTR induce cytotoxicity

ATTR, amyloid transthyretin; TTR, transthyretin.
*Rate-limiting step involves dissociation of tetrameric TTR to a pair of dimeric TTR proteins that rapidly progress to monomeric TTR. †Misfolded protein can form a variety of toxic intermediates, including amyloid fibrils (shown here), as well as small oligomers and amorphous aggregates.
1. Saraiva MJ. *FEBS Lett*.2001;498:201-203; 2. Hou X et al. *FEBS J*. 2007;274:1637-1650; 3. Bulawa CE et al. *Proc Natl Acad Sci U S A*. 2012;109:9629-9634; 4. Sekijima Y. *J Neurol Neurosurg Psychiatry*. 2015;86(9):1036-1043.

ATTR Amyloidoses Are Differentiated Through Genetic Testing

Wild-Type[1-4]

- Develops with age (acquired), where normal TTR tetramers destabilize
- Patients are typically aged >60 years, white, and male
- 100,000 estimated patients in US
- Characterized mainly by cardiac manifestations, but symptoms can also include carpal tunnel syndrome and lumbar spinal stenosis

Hereditary[2,3,5-8]

- Autosomal dominant **inheritance** with variable penetrance, where mutations in *TTR* gene lead to abnormal proteins
- Age of **onset typically in 3rd to 5th decade of life**
- 3,000-3,500 estimated patients in the US
- Characterized by **peripheral sensorimotor neuropathy, autonomic neuropathy, cardiomyopathy, carpal tunnel syndrome**, and other symptoms

Carpal tunnel syndrome is characteristic of both types

ATTR, amyloid transthyretin; TTR, transthyretin

1. Brunjes DL et al. *J Card Fail*. 2016; 22(12):996-1003; 2. Coelho T et al. *A Guide to Transthyretin Amyloidosis*. 2018. http://amyloidosis.org/wp-content/uploads/2019/05/2018-ATTR-guide.pdf. Accessed August 15, 2019; 3. Hawkins P et al. *Ann Med*. 2015;47:625-638; 4. Inserro A. *AJMC*. 2019 May 6. https://www.ajmc.com/newsroom/pfizer-gets-fda-approval-for-tafamadis-for-attrcm. Accessed August 20, 2020. 5. Coelho T et al. *Curr Med Res Opin*. 2013;29:63-76; 6. Ando Y et al. *Orphanet J of Rare Dis* 2013,8:31; 7. Benson MD et al. *Amyloid*. 2018;25(4):215-219. 8. Mickle K, et al. *J Manag Care Spec Pharm*. 2019;25(1):10-15.

Hereditary ATTR (hATTR) Amyloidosis Is Transmitted in an Autosomal Dominant Manner With Variable Penetrance[1,2]

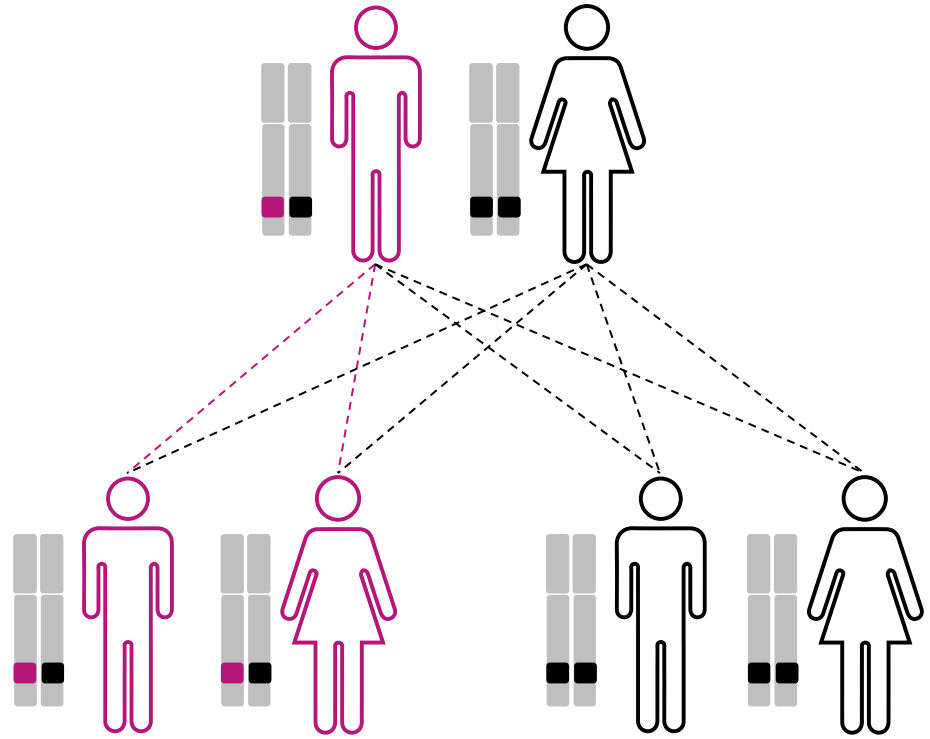


Image reproduced with permission from US National Library of Medicine Genetics Home Reference

- The disease-causing mutation has a 50% chance of being transmitted from affected individuals to their children[3]
- Variable penetrance means the disease may not manifest even if the mutation is present[2]
  - Patients with a known mutation should be monitored closely to detect early signs and symptoms
  - **Carriers may live to an advanced age with no symptoms, but still see their children develop symptoms**

Children of carriers have a 50% chance of inheriting a mutation. It is important for family members to understand the disease, symptoms, and testing options for hereditary ATTR.

ATTR, amyloid transthyretin.

1. Coelho T et al. *Curr Med Res Opin*. 2013;29:63-76; 2. Ando Y et al. *Orphanet J Rare Dis*. 2013;8:31; 3. National Center for Advancing Translational Sciences: Genetic and Rare Disease Information Center. https://rarediseases.info.nih.gov/diseases/6611/hereditary-amyloidosis#ref_11872. Accessed December 5, 2018.

Founder Effects Lead to Increased Prevalence Among Populations of Shared Ancestry

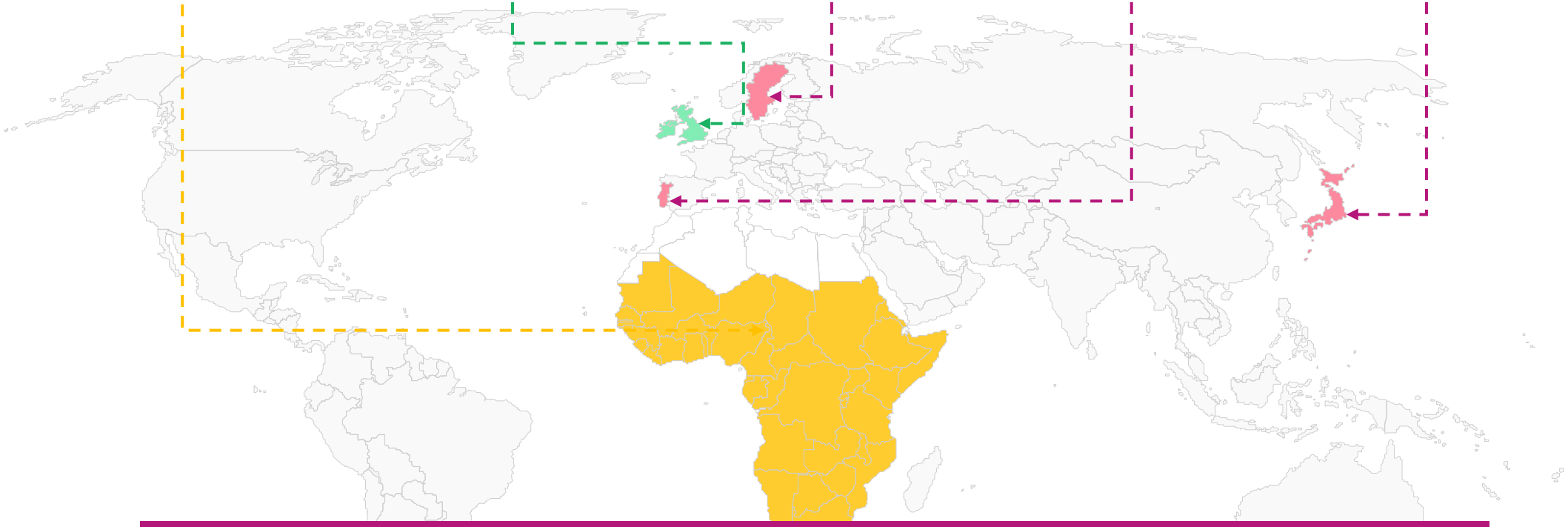
Western and Sub-Saharan Africa[1-3]
Val142Ile
(formerly Val122Ile)

UK and Ireland[1,2]
Thr80Ala
(formerlyThr60Ala)

Sweden[1,2]
Val50Met
(formerly Val30Met)

Portugal[1,2]
Val50Met
(formerly Val30Met)

Japan[1,2]
Val50Met
(formerly Val30Met)



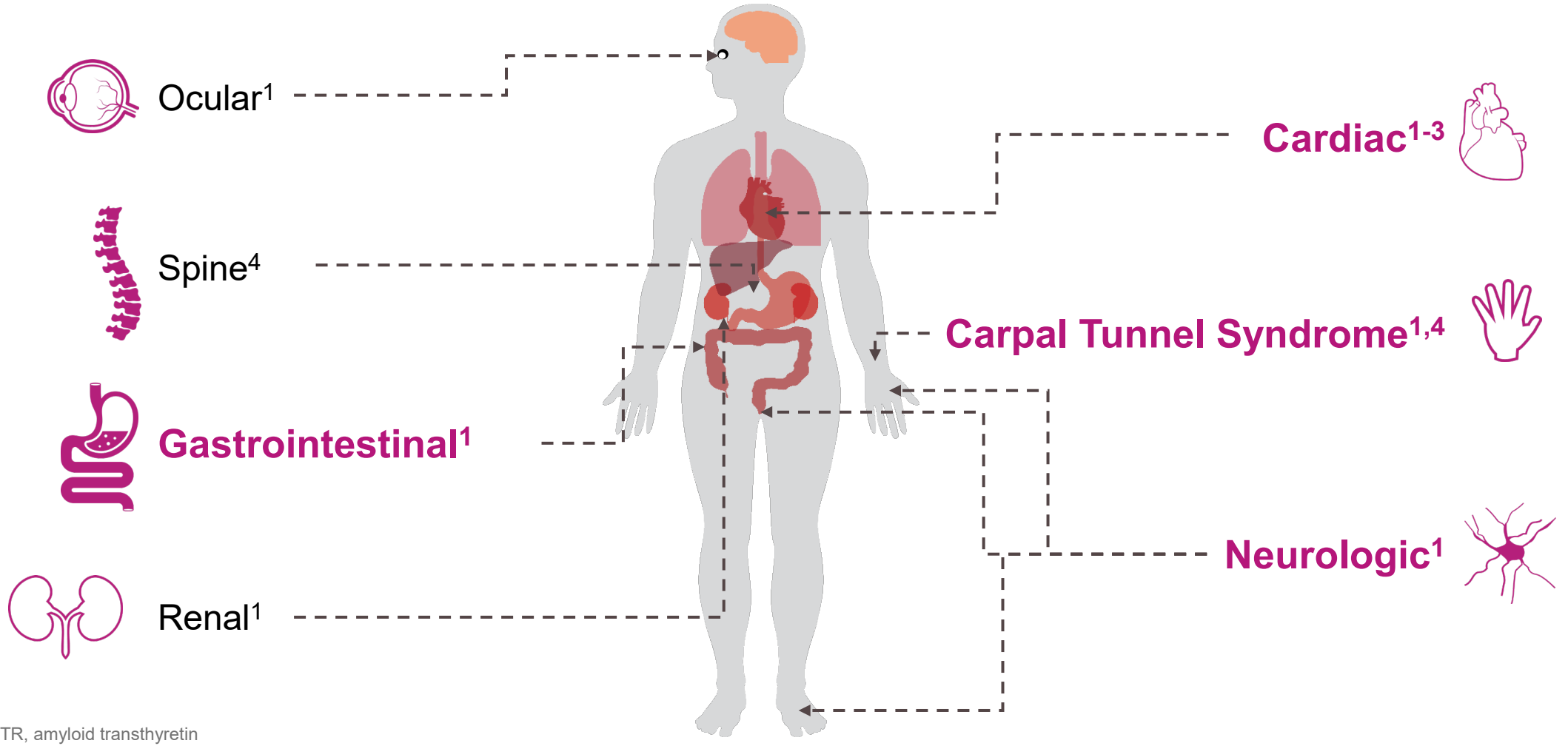
Persons from these specific backgrounds have an increased prevalence of hereditary ATTR amyloidosis mutation[1-3]

ATTR, amyloid transthyretin

1. Ruberg FL et al. *Circulation*. 2012;126(10):1286–1300; 2. Carr AS et al. *J Neurol Neurosurg Psychiatry*. 2016;87(6):620-627; 3. Jacobson DR et al. *Mol Genet Genomic Med*. 2016;4(5):548-556.

Clinical Presentation of hATTR

hATTR Affects Multiple Organs, Tissues, and Anatomic Structures



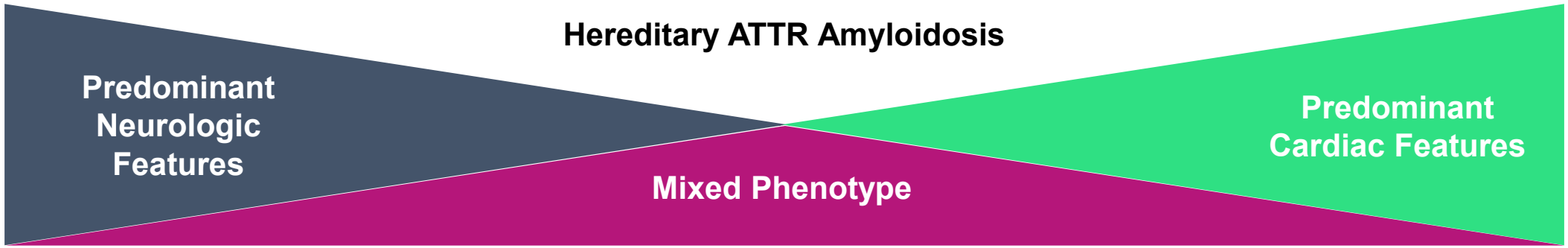
ATTR, amyloid transthyretin

1. Conceição I et al. *J Peripher Nerv Syst*. 2016;21(1):5-9. 2. Gertz MA. *Am J Manag Care*. 2017;23(suppl 7):S107-S112 3. Coelho T 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; 4. Rubin J et al. *Amyloid*. 2017 Dec;24(4):226-230.

There Is Substantial Overlap in the Clinical Features of hATTR Amyloidosis and Many Patients Have a Mixed Phenotype[1–3]

V50M Early Onset | **C30R** | **R54T** | **G67A** | **F84L** | **L78H** | **E109Q** | **I127V** | **S43N** | **L131M** | **I88L**

F53L | **S70R** | **S97Y** | **A56P** | **T69A** | **V50M** Late Onset | **W61L** | **H108R** | **T80A** | **V142I**



Due to the systemic nature of hereditary ATTR amyloidosis, it is imperative to perform a neurologic assessment in patients you suspect might have cardiac amyloidosis.

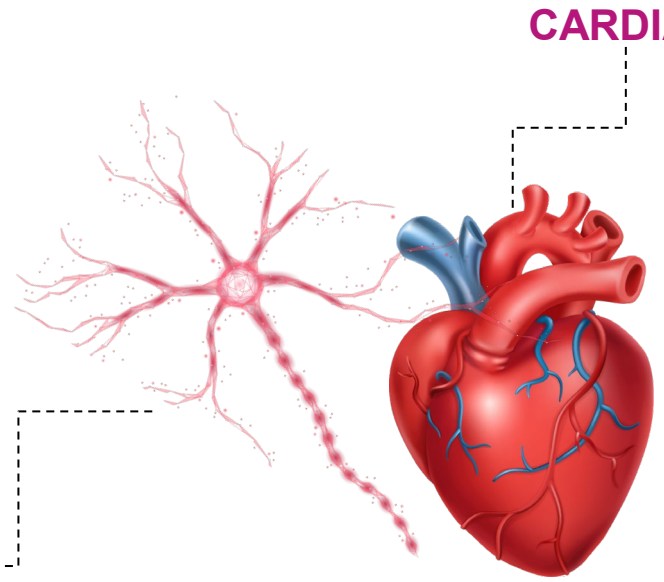
Note that the genotype nomenclature reflects the protein variant including the 20-aa signal peptide.

1. Benson MD, Uemichi T. *Amyloid*. 1996;3:44-56; 2. Rapezzi C et al. *Eur Heart J*. 2013;34:520-528. 3. Coelho T et al. *Curr Med Res Opinion*. 2013l29:63-76.

Patients With Cardiomyopathy From hATTR Amyloidosis May Also Have Neuropathy

Mixed phenotypes can occur

V142I is classically considered cardiomyopathy dominant, but up to **~30%** and **~18%** present with clinical signs of **peripheral and autonomic neuropathy** at diagnosis, respectively[1]



T60A is another mutation also dominated by cardiac amyloidosis, but **54%** and **75%** present with clinical signs of **peripheral and autonomic neuropathy** at diagnosis, respectively[2]

Autonomic neuropathies can also affect the heart[3]

- Life-threatening arrythmias and **sudden death** can occur
- These patients commonly experience **orthostatic hypotension**

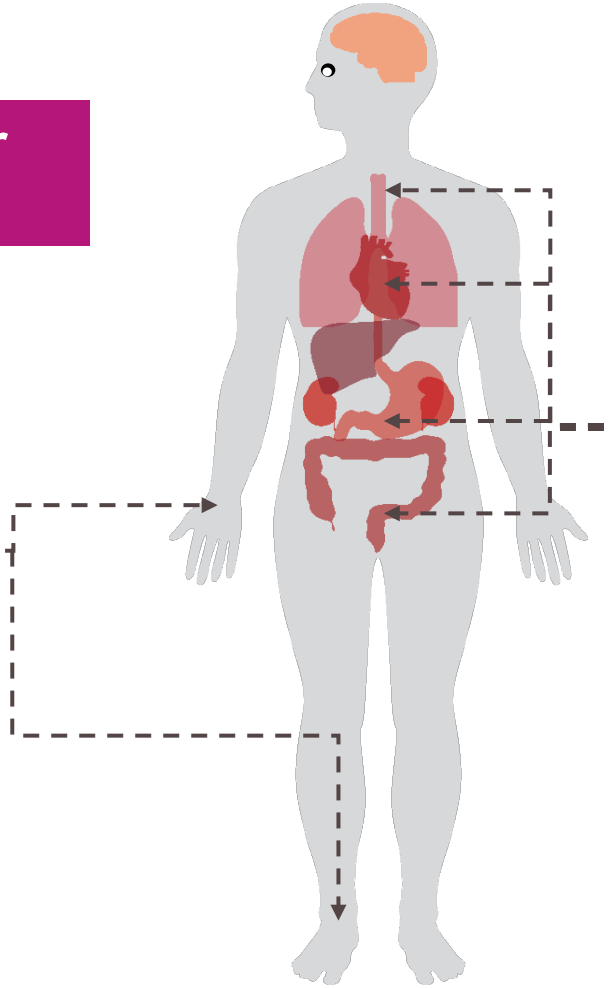
ATTR, amyloid transthyretin.

1. Swiecicki PL et al. *Amyloid*. 2015;22(2):123-131; 2. Sattianayagam PT et al. *Eur Heart J*. 2012;33:1120-1127; 3. Gonzalez-Duarte A. *Clin Auton Res*. 2019;29(2):245-251.

Polyneuropathy in hATTR Amyloidosis Includes Autonomic Neuropathy Symptoms and Sensorimotor Symptoms

Peripheral Sensorimotor Neuropathy[1-3]

- Numbness, tingling, swelling, burning, and other abnormal feelings in hands and feet
- Neuropathic pain
- Walking disability
- Loss of balance



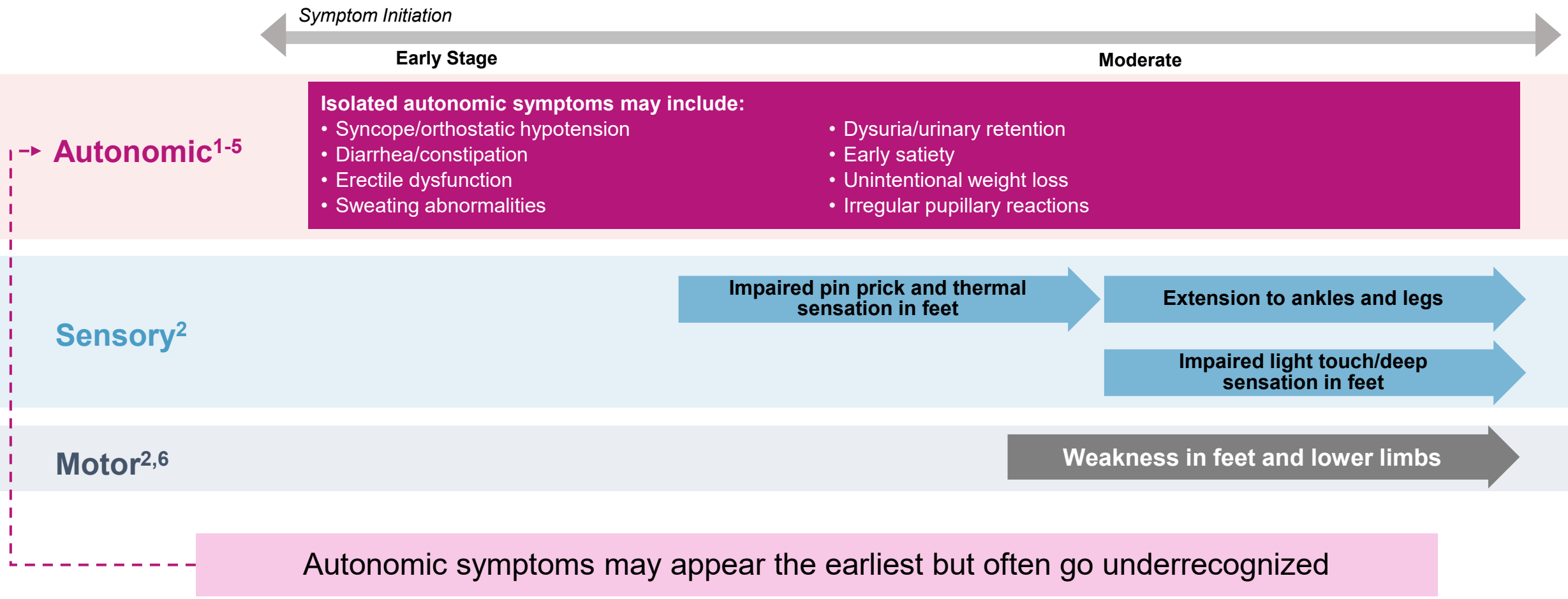
Autonomic Neuropathy[1-3]

- Constipation and diarrhea that often alternate
- Nausea and vomiting
- Early satiety
- Orthostatic hypotension
- Urinary incontinence and retention
- Sweating abnormalities
- Sexual dysfunction

ATTR, amyloid transthyretin

1. Ando Y et al. *Orphanet J Rare Dis*. 2013;8:31; 2. Conceição I et al. *J Peripher Nerv Syst*. 2016;21(1):5-9; 3. Gertz MA et al. *J Am Coll Cardiol*. 2015;66(21):2451-2466.

Early Signs of Neuropathy in hATTR Amyloidosis



ATTR, amyloid transthyretin

1. Gonzalez-Duarte A. *Clin Auton Res*. 2019;29(2):245-251; 2. Ando Y et al. *Orphanet J Rare Dis*. 2013;8:31; 3. Wixner J. Gastrointestinal disturbances in hereditary transthyretin amyloidosis [dissertation]. Umeå, Sweden: Umeå University; 2014; 4. Chao CC et al. *Ann Neurol*. 2015; 78(2):272-283; 5. Koike H et al. *J Neurol Neurosurg Psychiatry*. 2012;83(2):152-158. 6. Adams D. *Ther Adv Neurol Disord*. 2013;6(2):129-139.

hATTR Amyloidosis With Polyneuropathy Can Be Identified Earlier Using a Cluster of Red-Flag Signs or Symptoms

PROGRESSIVE, SYMMETRIC SENSORIMOTOR POLYNEUROPATHY

+

ONE OR MORE OF THE FOLLOWING RED-FLAG SIGNS AND SYMPTOMS[1-3]

Family history of hereditary ATTR amyloidosis

Cardiovascular manifestations
- Peripheral edema
- Congestive heart failure
- Syncope

Autonomic conditions
- Orthostatic hypotension
- Incontinence and recurring urinary tract infection
- Erectile dysfunction
- Sweating abnormality

Bilateral carpal tunnel syndrome

Debilitating and uncontrolled GI symptoms
- Chronic diarrhea
- Constipation
- Alternating diarrhea and constipation
- Unexplained weight loss

Renal abnormalities

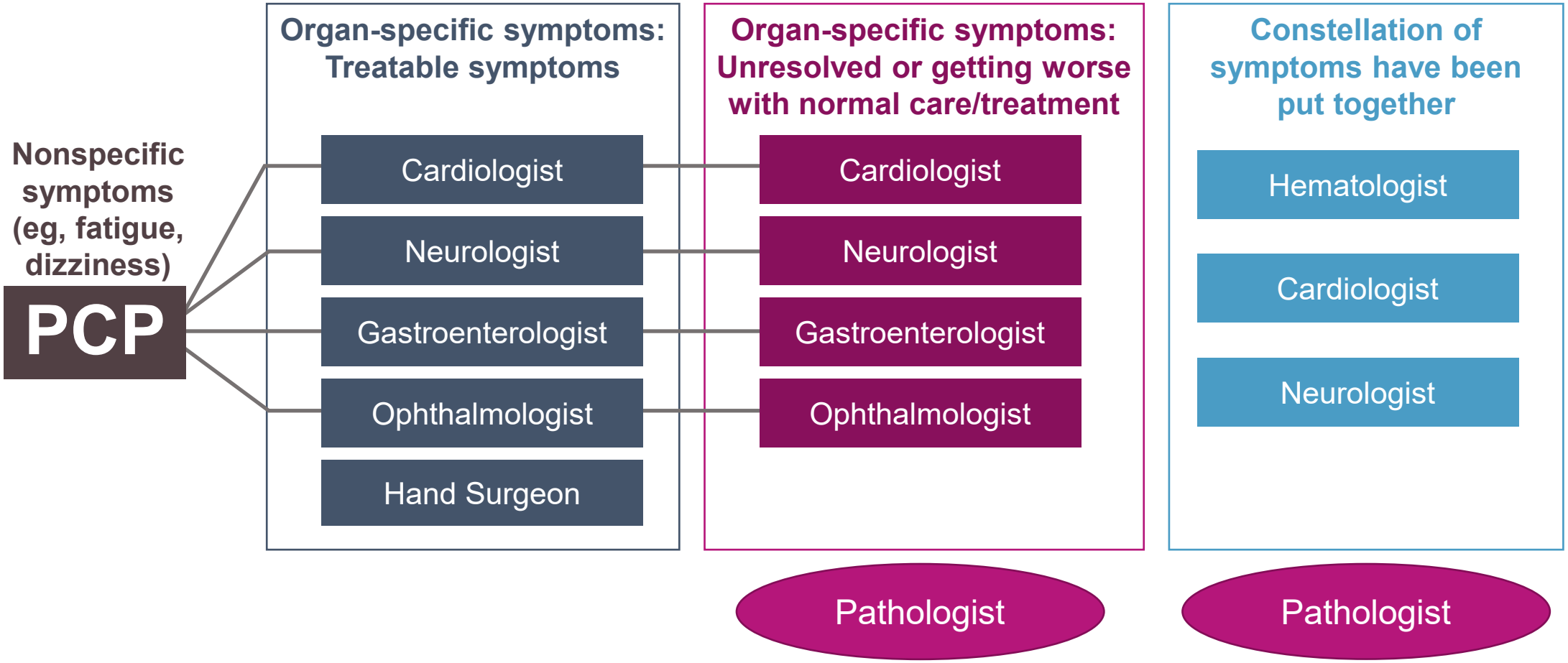
Vitreous opacities

Additional Alert Signs
- Rapid disease progression
- Failure of response to prior therapies

TTR, transthyretin

1. Conceição I et al. *J Peripher Nerv Syst*. 2016;21(1):5-9; 2. Ando Y et al. *Orphanet J Rare Dis*. 2013;8:31; 3. Coelho T et al. *Curr Med Opin*. 2013;29(1):63-76.

Patients Have As Many As 6 or More Physician Office Visits Before hATTR Amyloidosis Diagnosis



PCP, primary care physician.
Adapted from: Amyloidosis Foundation. Understanding the patient voice in hereditary transthyretin-mediated amyloidosis (ATTR amyloidosis). http://amyloidosissupport.org/support_groups/fam_isabell_attr.pdf. Accessed February 6, 2019.

Misdiagnoses of hATTR Amyloidosis With Polyneuropathy is Common

- Patients with hereditary ATTR amyloidosis experience a **median onset of signs or symptoms several decades earlier** than those with wild-type ATTR amyloidosis (39.0 to 53.9 years vs 71.4 years, respectively)[1,2]
  - Misdiagnosis is common, with **45% to 57%** of patients with hereditary ATTR amyloidosis being initially misdiagnosed, and average time to a correct diagnosis is **2 to 4 years**[3-5]

Typical characteristics of hereditary ATTR amyloidosis with polyneuropathy

- Axonal, symmetric, distal polyneuropathy that typically begins in lower limbs and progresses to upper limbs[7]

But due to nonspecific, atypical, sporadic presentation, and rarity…

Common Misdiagnoses[6]

- Idiopathic axonal polyneuropathy
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Charcot-Marie-Tooth neuropathy
- Diabetic or alcoholic neuropathy
- Motor neuron disease

1. Bensom ME, et al. *N Engl J Med.* 2018;379(1):22-31. 2. Coelho T, et al. *Curr Med Res Opin.* 2013;29(1):63-76. 3. Amyloidosis Foundation. Understanding the patient voice in hereditary transthyretin-mediated amyloidosis (ATTR amyloidosis). Amyloidosis Support Groups website. http://amyloidosissupport.org/support_groups/fam_isabell_attr.pdf. Accessed May 16, 2019; 4. Lousada I, et al. *Orphanet J Rare Dis.* 2017;12(suppl 1):P7. 5. Plante-Bordeneuve V, et al. *Neurology.* 2007;69(7):693-698. 6. Adams D et al. *Curr Opin Neurol.* 2016;29 (suppl 1):S14-26; 7. Gertz MA et al. *J Am Coll Cardiol.* 2015;66(21):2451-2466.

hATTR Amyloidosis Burden of Illness

hATTR Amyloidosis With Polyneuropathy Can Progress Rapidly



FAP Staging and Description	**FAP Stage 1**	**FAP Stage 2**	**FAP Stage 3**
	• Disease limited to lower limbs • Walking without help • Slight weakness in big toes	• Motor signs progression in lower limbs • Hand muscles weakened • Disabled but can move with help	• Patient confined to wheelchair or bed • Generalized weakness and areflexia
PND Scoring and Description	**PND I**	**PND II**	**PND III** / **PND IV**
	• Sensory disturbances in extremities • Preserved walking capacity	• Difficulty walking but no need for walking stick	**PND IIIa**: • One crutch/ stick required **PND IIIb**: • Two crutches/ sticks required	• Confined to a wheelchair or bed
Average Duration	5.6 ± 2.8 years	4.8 ± 3.6 years	2.3 ± 3.1 years

FAP, familial amyloid polyneuropathy; PND, polyneuropathy disability.
Note: These staging systems are not applicable to autonomic or cardiac symptoms.
Adapted from Adams D. *Ther Adv Neurol Disord*. 2013;6(2):129-139.

hATTR Amyloidosis With Polyneuropathy Leads to Premature Death

Early management of the disease is paramount, as the median survival after diagnosis is approximately

4.7 years*[1]

Causes of Death May Include[2,3]

- Cardiac failure
- Sudden cardiac death
- Cachexia
- Renal failure
- Infection

FAP, familial amyloid polyneuropathy; ATTR, amyloid transthyretin; PND, polyneuropathy disability.
*Figure includes patients with hereditary ATTR amyloidosis regardless of the presence of polyneuropathy

1. Swiecicki PL et al. *Amyloid*. 2015;22(2):123-131; 2. Coelho T et al. 2016. *A Guide to Transthyretin Amyloidosis*. Available at: http://www.amyloidosis.org/wp-content/uploads/2017/05/2017-ATTR-guide.pdf. Accessed April 15, 2019; 3. Sekijima Y et al. *Orphanet J Rare Dis*. 2018;13(1):6;

Burden and Prognosis of hATTR Amyloidosis Compares With ALS

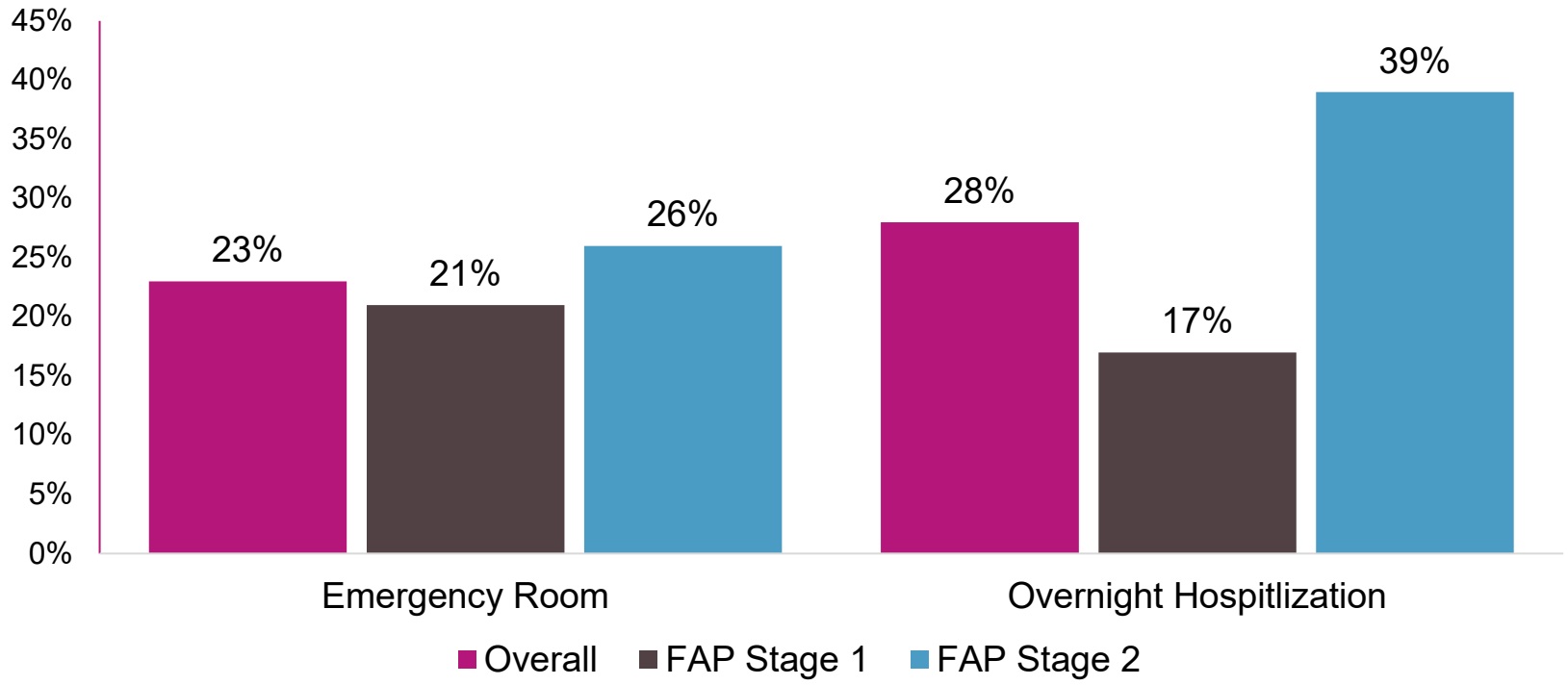
	Hereditary ATTR Amyloidosis[1]	Amyotrophic Lateral Sclerosis (ALS)[2]
Natural History	• Polyneuropathy can progress to **inability to work or get dressed, walking with a cane, then wheelchair** • Hereditary ATTR amyloidosis can cause other complications in addition to polyneuropathy, such as cardiomyopathy	• Progression includes weakness, wasting, and **paralysis of the muscles** of the limbs and torso and those that control vital functions such as **speech, swallowing, and breathing**
Age of Onset and Life Expectancy	• Between **mid-20s and mid-60s** • Life expectancy averages **4-5 years** from time of diagnosis	• Between ages **40 and 70** • Life expectancy is **2-5 years** from time of diagnosis
Initial Symptoms	• Initially, **peripheral neuropathy, carpal tunnel syndrome** • **Autonomic neuropathy** can present as loss of balance, **uncontrollable GI** (alternating diarrhea and constipation, vomiting)	• Early symptoms involve **muscle weakness** or stiffness

ATTR, amyloid transthyretin; GI, gastrointestinal; TTR, transthyretin

1. All information from hATTR Change the Course, https://www.hattrchangethecourse.com/, 2. All information from ALS Association, http://www.alsa.org/ .

ER Visits and Hospitalizations Associated with Patients with hATTR Amyloidosis

- An analysis of 225 patients in a phase 3 study found increased ER visits and hospitalizations in more severe stages

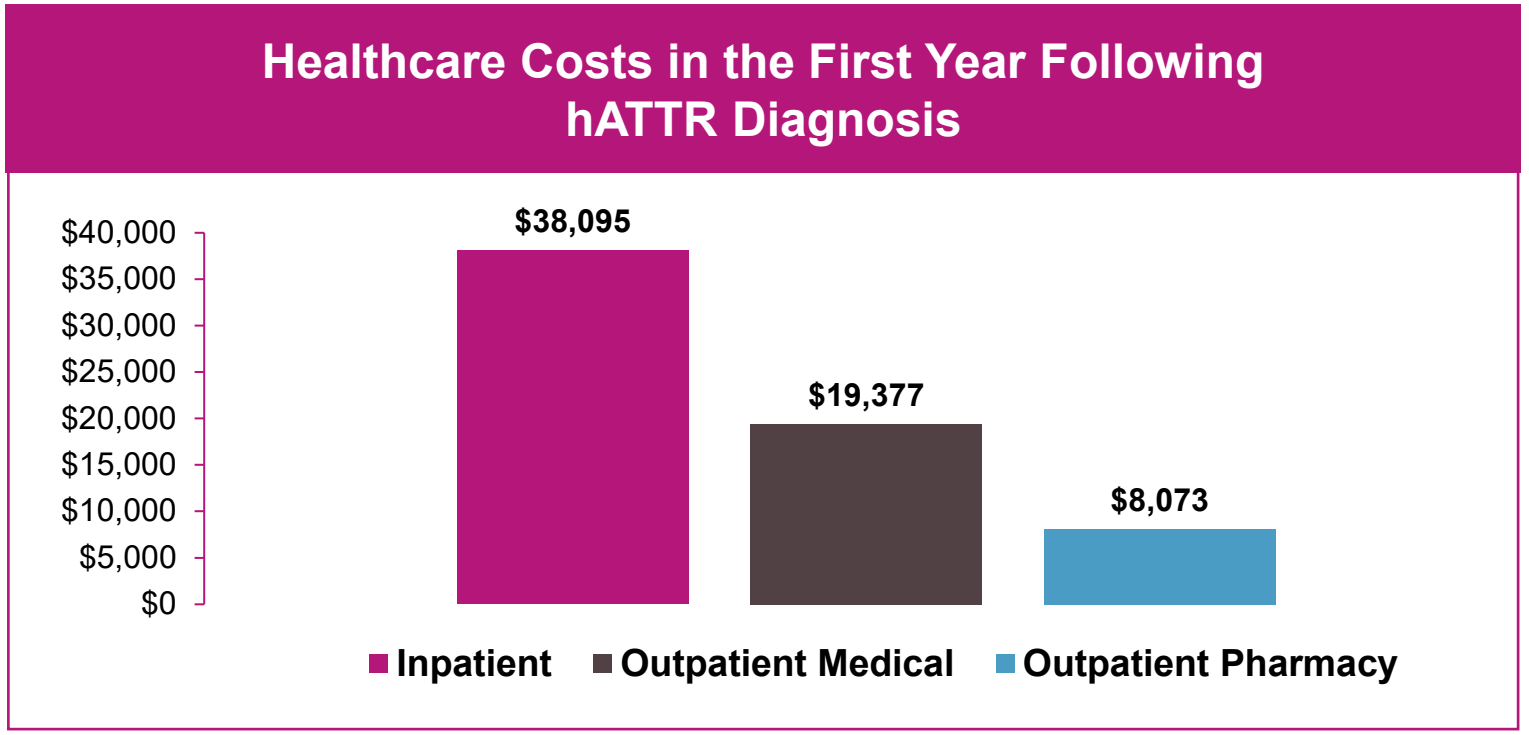


ER, emergency room; FAP, familial amyloid polyneuropathy.

Schmidt H, et al. Impact of hereditary transthyretin-mediated amyloidosis on use of health care services: an analysis of the APOLLO study. Poster presented at: The 16th International Symposium on Amyloidosis (ISA). March 26-29, 2018; Kumamoto, Japan.

Significant Healthcare Utilization and Costs Among Patients with hATTR

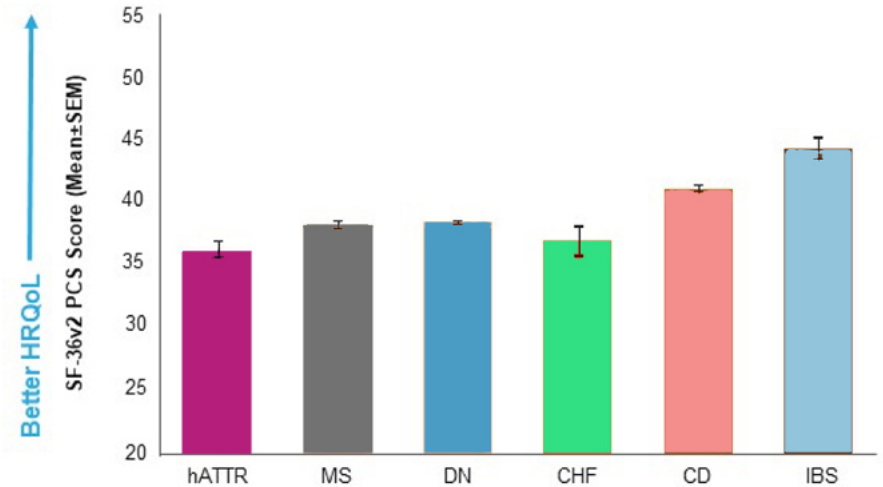
- A retrospective US claims analysis of newly diagnosed hATTR patients over a 5-year period (2012-2016) estimates **over $65,000 in healthcare costs during the first year** following diagnosis



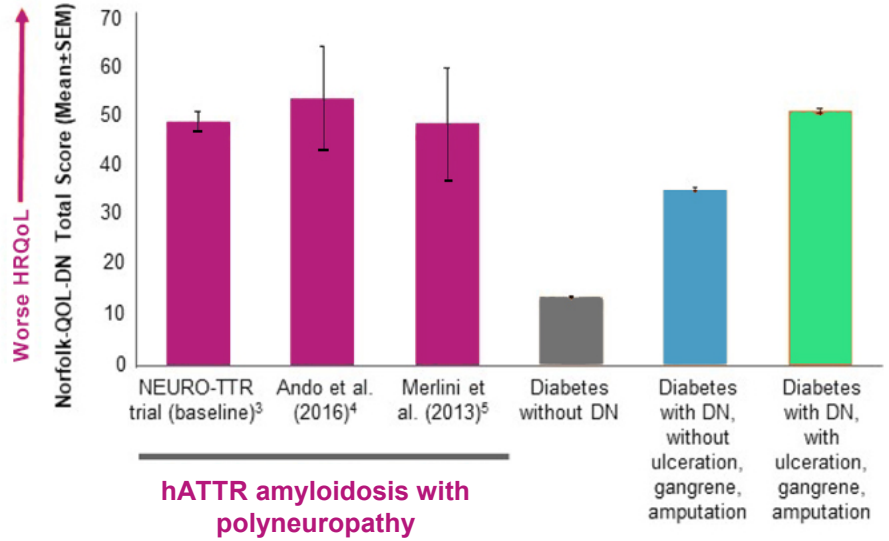
Claims databases included Truven Health Analytics MarketScan® Commercial and Medicare Supplemental databases and the IQVIA™ Real-World Data Adjudicated Claims – US Databases.
Guthrie S, Reddy SR, Tieu R, et al. Healthcare utilization and costs among patients with hATTR. Poster presented at ISPOR; May 19-23, 2018; Baltimore, MD.

hATTR Amyloidosis With Polyneuropathy Can Have a Devastating Impact on Patients' Quality of Life

Patients with hATTR amyloidosis with polyneuropathy have a higher physical burden of disease than do patients with diabetic neuropathy, Crohn's disease, or IBS[1]



Neuropathy-related quality of life for patients with hATTR amyloidosis is similar to that of the most severe diabetics with neuropathy accompanied by ulceration, gangrene, or amputation[2]

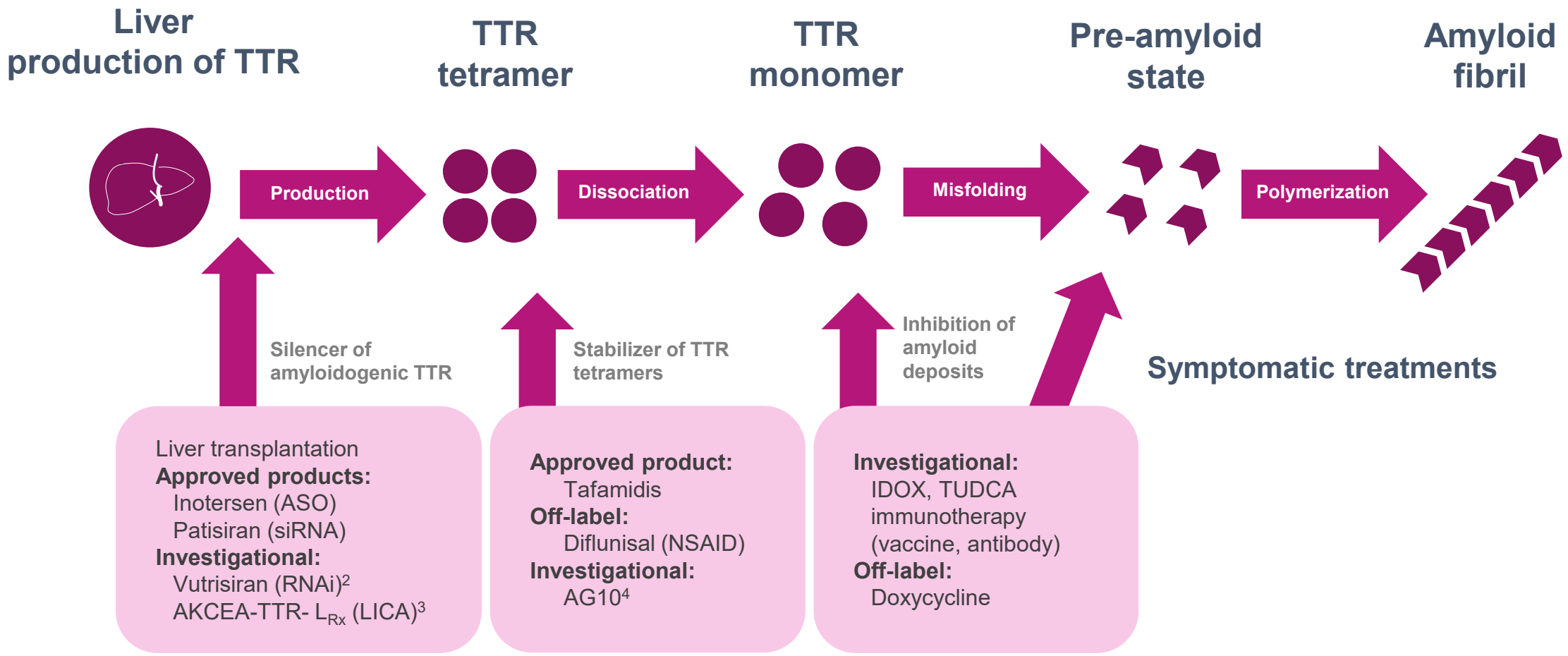


CD, Crohn's disease; CHF, congestive heart failure; hATTR, hereditary transthyretin amyloidosis; DN, diabetic neuropathy; HRQoL, health-related quality of life; SF-36 Health Survey; IBS, irritable bowel syndrome; MS, multiple sclerosis; PCS, physical component summary; QoL-DN, quality of life-diabetic neuropathy; SEM, standard error of the mean

1. Lovely A et al. The Burden of Hereditary Transthyretin Amyloidosis on Health-related Quality of Life. Presented at ISPOR Annual Meeting, May 19-23, 2018. May 2018, Baltimore, MD, USA; 2. Yarlas A et al. Disease Burden as Assessed by the Norfolk Quality of Life Scale in Hereditary Transthyretin Amyloidosis Relative to Diabetic Neuropathy. Presented at AMCP Managed Care and Specialty Pharmacy Annual Meeting. April 23-26, 2018, Boston, MA, USA; 3; Benson MD et al. *N Engl J M*ed. 2018;379(1):22-31; 4. Ando Y et al. *J Neurol Sci*. 2016;362-:266-271; 5. Merlini G et al. *J Cardiovasc TranslRes*. 2013;6:1011-20.

hATTR Treatment Landscape

Approved and investigational products target different stages in the pathogenesis of ATTR amyloidosis[1]



ASO, antisense oligonucleotide; IDOX, 4'-iodo-4'-deoxydoxorubicin; LICA, Ligand Conjugated Antisense; siRNA, small interfering RNA; TUDCA, tauroursodeoxycholic acid.

1. Adapted from Gertz M. *Am J Manag Care*. 2017;23:S107-S112; 2. Vutrisiran. https://www.alnylam.com/wp-content/uploads/pdfs/Vutrisiran-Fact-Sheet.pdf. Accessed August 19, 2020. 3. https://akceatx.com/our-programs/pipeline/. Accessed August 19, 2020. 4. http://ir.eidostx.com/news-releases/news-release-details/eidos-therapeutics-initiates-attribute-cm-phase-3-study-ag10. Accessed, August 19, 2020.

Therapeutic Options for ATTR Amyloidosis*

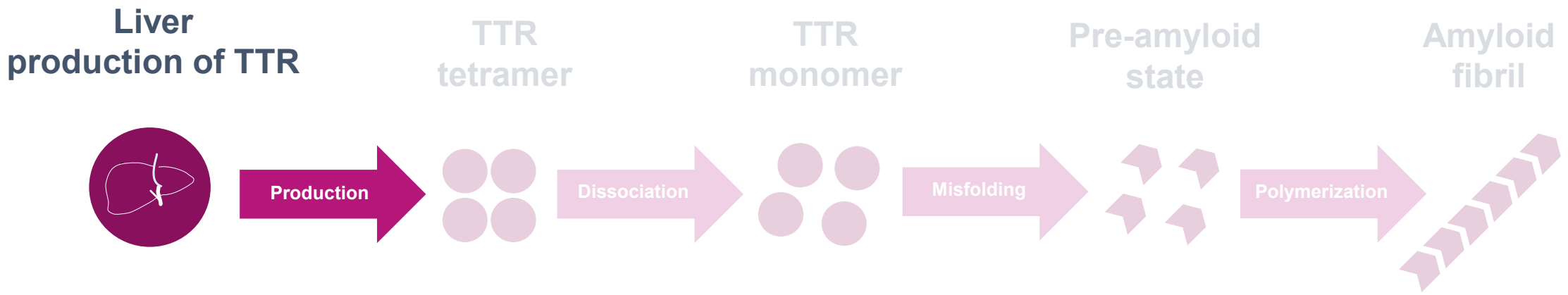
	Inotersen[1]	Patisiran[3]	Tafamidis[7]
Indication	Treatment of the polyneuropathy of hATTR in adults	Treatment of the polyneuropathy of hATTR in adults	Treatment of CM of wtATTR or hATTR in adults to reduce CV mortality and CV-related hospitalization
Route of administration	Subcutaneous injection	Intravenous infusion	Oral
Benefit design	Pharmacy benefit	Medical benefit	Pharmacy benefit
Site of administration	Home, self-administered	Infusion center or home infusion, administered by HCP[4,5]	Home, self-administered
Distribution network	Exclusive distribution network[2]	Limited distribution (N=2)[6]	Limited distribution (N=8)[8]
REMS program	Yes	No	No

*** There have been no head-to-head studies for these products; therefore, cross-trial comparisons should not be made.**

CM, cardiomyopathy; CV, cardiovascular; REMS, Risk Evaluation and Mitigation Strategy.

1. TEGSEDI [package insert]. Boston, MA: Akcea Therapeutics. 2. Ionis Pharmaceuticals. 2018 October 5. https://ir.ionispharma.com/news-releases/news-release-details/akcea-announces-its-access-and-distribution-strategy-tegseditm. Accessed August 20, 2020. 3. ONPATTRO [package insert]. Cambridge, MA: Alnylam Pharmaceuticals, Inc. 4. Onpattro (patisiran). Find an infusion center. https://www.onpattrohcp.com/infusion-center-directory. Accessed August 20, 2020. 5. Onpattro (patisiran). https://www.onpattro.com/sites/default/files/pdfs/ONPATTRO-Home-Infusion-Brochure.pdf. Accessed August 20, 2020. 6. Alnylam. https://www.onpattrohcp.com. Accessed August 20, 2020. 7. VYNDAQEL/ VYNDAMAX [package insert]. New York, NY: Pfizer Inc. 8. Pfizer. https://www.vyndalink.com. Accessed August 20, 2020.

Treatment of Polyneuropathy of hATTR Amyloidosis in Adults: Inotersen[1,2]



Indication: Treatment of polyneuropathy of hATTR in adults

Route of administration	Subcutaneous injection
Benefit design	Pharmacy benefit
Site of administration	Home, self-administered
Distribution network	Exclusive distribution network
REMS program	Yes

REMS, Risk Evaluation and Mitigation Strategy.

1. TEGSEDI [package insert]. Boston, MA: Akcea Therapeutics. 2. Ionis Pharmaceuticals. 2018 October 5. https://ir.ionispharma.com/news-releases/news-release-details/akcea-announces-its-access-and-distribution-strategy-tegseditm. Accessed August 20, 2020.

Tegsedi Important Safety Information

- **WARNING: THROMBOCYTOPENIA AND GLOMERULONEPHRITIS**
  - **<u>Thrombocytopenia</u>**
    - **TEGSEDI causes reductions in platelet count that may result in sudden and unpredictable thrombocytopenia, which can be life-threatening. One clinical trial patient died from intracranial hemorrhage.**
    - **Tegsedi is contraindicated in patients with a platelet count below 100 x 10^9/L.**
    - **Prior to starting TEGSEDI, obtain a platelet count. During treatment, monitor platelet counts weekly if values are 75 x 10^9/L or greater, and more frequently if values are less than 75 x 10^9/L.**
    - **If a patient develops signs or symptoms of thrombocytopenia, obtain a platelet count as soon as possible. The patient should not receive additional TEGSEDI unless a platelet count is determined to be interpretable and acceptable by a medical professional.**
    - **Following discontinuation of treatment for any reason, continue to monitor platelet count for 8 weeks, or longer if platelet counts are less than 100 x 10^9/L, to verify that platelet counts remain above 75 x 10^9/L.**

Please see additional boxed WARNING information on the following slide and full Prescribing Information available at this presentation.

Tegsedi Important Safety Information (cont.)

- **WARNING: THROMBOCYTOPENIA AND GLOMERULONEPHRITIS**
  - **Glomerulonephritis**
    - **TEGSEDI can cause glomerulonephritis that may require immunosuppressive treatment and may result in dialysis-dependent renal failure. One clinical trial patient who developed glomerulonephritis and did not receive immunosuppressive treatment remained dialysis-dependent. In clinical trials, cases of glomerulonephritis were accompanied by nephrotic syndrome, which can have manifestations of edema, hypercoagulability with venous or arterial thrombosis, and increased susceptibility to infection.**
    - **TEGSEDI should generally not be initiated in patients with urinary protein to creatinine ratio (UPCR) of 1000 mg/g or higher.**
    - **Prior to starting TEGSEDI, measure the serum creatinine, estimated glomerular filtration rate (eGFR), urine protein to creatinine ratio (UPCR), and perform a urinalysis. During treatment, monitor serum creatinine, eGFR urinalysis, and UPCR every 2 weeks. TEGSEDI should not be given to patients who develop a UPCR of 1000 mg/g or higher, or eGFR below 45 mL/minute/1.73 m^2, pending further evaluation of the cause.**
    - **If a dose is held, once eGFR increases to ≥45 mL/minute/1.73 m^2, UPCR decreases to below 1000 mg/g, or the underlying cause of the decline in renal function is corrected, weekly dosing may be reinitiated. In patients with UPCR of 2000 mg/g or higher, perform further evaluation for acute glomerulonephritis, as clinically indicated. If acute glomerulonephritis is confirmed, TEGSEDI should be permanently discontinued.**

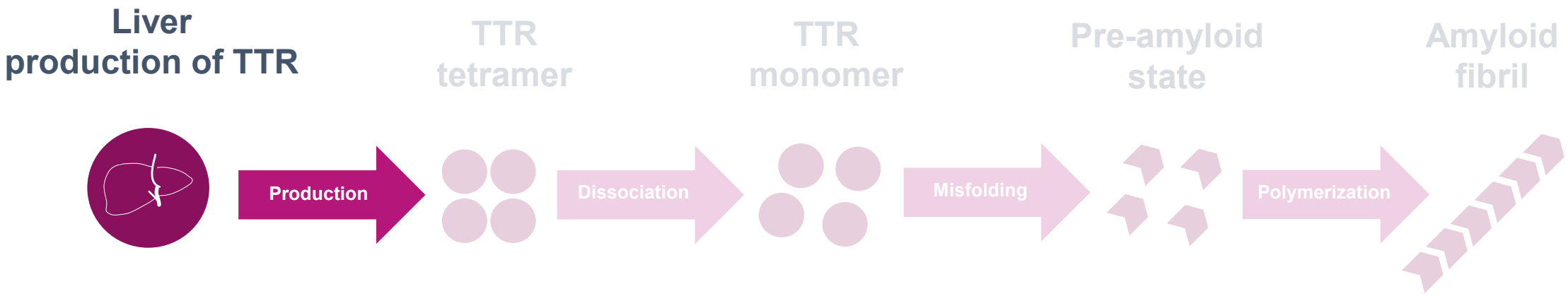
Please see additional boxed WARNING information on the following slide and full Prescribing Information available at this presentation.

Tegsedi Important Safety Information (cont.)

- **WARNING: THROMBOCYTOPENIA AND GLOMERULONEPHRITIS**
  - **<u>TEGSEDI REMS Program</u>**
    - **Because of the risks of serious bleeding caused by severe thrombocytopenia and because of glomerulonephritis, both of which require frequent monitoring, TEGSEDI is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the TEGSEDI REMS Program.**

Please see additional Important Safety Information later in this presentation and full Prescribing Information available at this presentation.

Treatment of Polyneuropathy of hATTR Amyloidosis in Adults: Patisiran[1,2]



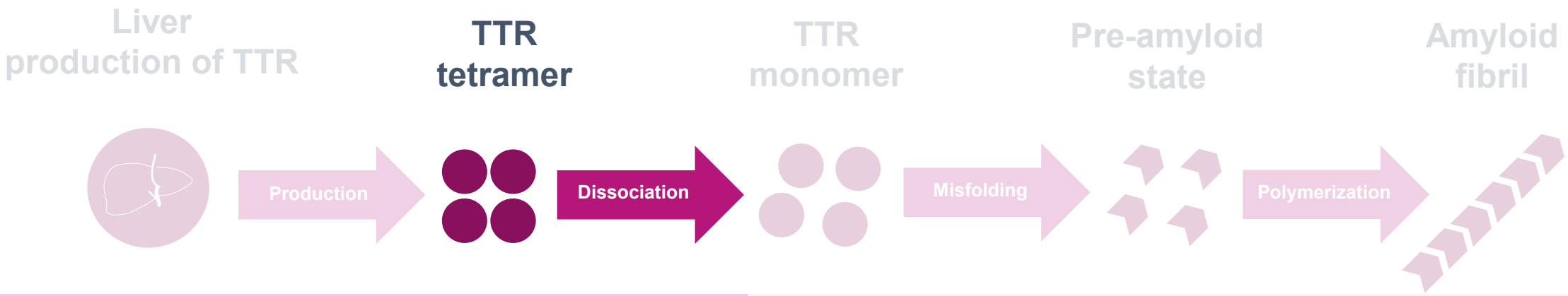
Indication: Treatment of polyneuropathy of hATTR in adults

Route of administration	Intravenous infusion
Benefit design	Medical benefit
Site of administration	Infusion center or home infusion, administered by HCP[1-3]
Distribution network	Limited distribution (N=2)[4]
REMS program	No

REMS, Risk Evaluation and Mitigation Strategy.

1. ONPATTRO [package insert]. Cambridge, MA: Alnylam Pharmaceuticals, Inc. 2. Onpattro (patisiran). Find an infusion center. https://www.onpattrohcp.com/infusion-center-directory. Accessed August 20, 2020. 3. Onpattro (patisiran). https://www.onpattro.com/sites/default/files/pdfs/ONPATTRO-Home-Infusion-Brochure.pdf. Accessed August 20, 2020. 4. Alnylam. https://www.onpattrohcp.com. Accessed August 20, 2020.

Treatment of Cardiomyopathy of wtATTR or hATTR Amyloidosis in Adults: Tafamidis[1,2]



Indication: Treatment of cardiomyopathy of wtATTR or hATTR in adults to reduce CV mortality and CV-related hospitalization

Route of administration	Oral
Benefit design	Pharmacy benefit
Site of administration	Home, self-administered
Distribution network	Limited distribution (N=8)[2]
REMS program	No

CM, cardiomyopathy; CV, cardiovascular; REMS, Risk Evaluation and Mitigation Strategy.

1. VYNDAQEL/ VYNDAMAX [package insert]. New York, NY: Pfizer Inc. 2. Pfizer. https://www.vyndalink.com. Accessed August 20, 2020.

Tegsedi Important Safety Information (continued)

- **CONTRAINDICATIONS**
  - TEGSEDI is contraindicated in patients with
    - Platelet count below 100 x 10^9/L
    - History of acute glomerulonephritis caused by TEGSEDI
    - History of hypersensitivity reaction to TEGSEDI
- **WARNINGS AND PRECAUTIONS**
  - **Thrombocytopenia**
    - TEGSEDI causes reductions in platelet count that may result in sudden and unpredictable thrombocytopenia that can be life-threatening. In Study 1, platelet counts below 100 x 10^9/L occurred in 25% of TEGSEDI-treated patients compared with 2% of patients on placebo. Platelet counts below 75 x 10^9/L occurred in 14% of TEGSEDI-treated patients compared with no patients on placebo. One patient in a clinical trial experienced a fatal intracranial hemorrhage. Do not initiate TEGSEDI in patients with a platelet count below 100 x 10^9/L. Follow recommended monitoring and treatment recommendations for platelet count.
    - Symptoms of thrombocytopenia can include unusual or prolonged bleeding (eg, petechiae, easy bruising, hematoma, subconjunctival bleeding, gingival bleeding, epistaxis, hemoptysis, irregular or heavier than normal menstrual bleeding, hematemesis, hematuria, hematochezia, melena), neck stiffness, or atypical severe headache. Patients and caregivers should be instructed to be vigilant for symptoms of thrombocytopenia and seek immediate medical help if they have concerns.

Please see additional Important Safety Information below and full Prescribing Information, including boxed WARNING regarding the risk of thrombocytopenia and glomerulonephritis, available at this presentation.

Tegsedi Important Safety Information (continued)

- **WARNINGS AND PRECAUTIONS (CONTINUED)**
  - **Glomerulonephritis and Renal Toxicity**
    - TEGSEDI can cause glomerulonephritis that may result in dialysis-dependent renal failure. In Study 1, glomerulonephritis occurred in 3 (3%) TEGSEDI-treated patients compared with no patients on placebo. One patient did not receive immunosuppressive treatment and remained dialysis-dependent. If glomerulonephritis is suspected, pursue prompt diagnosis and initiate immunosuppressive treatment as soon as possible. Follow recommended monitoring and treatment recommendations for renal parameters. TEGSEDI should generally not be initiated in patients with a UPCR of 1000 mg/g or greater. If acute glomerulonephritis is confirmed, TEGSEDI should be permanently discontinued.
- **TEGSEDI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the TEGSEDI REMS Program because of risks of serious bleeding caused by severe thrombocytopenia and because of glomerulonephritis.**

Please see additional Important Safety Information below and full Prescribing Information, including boxed WARNING regarding the risk of thrombocytopenia and glomerulonephritis, available at this presentation.

Tegsedi Important Safety Information (continued)

- **WARNINGS AND PRECAUTIONS (CONTINUED)**
  - **Stroke and Cervicocephalic Arterial Dissection**
    - TEGSEDI may cause stroke and cervicocephalic arterial dissection. In clinical studies, 1 of 161 (0.6%) TEGSEDI-treated patients experienced carotid artery dissection and stroke. Educate patients on the symptoms of stroke and central nervous system arterial dissection. Instruct patients to seek help as soon as possible if symptoms of stroke or arterial dissection occur.
  - **Inflammatory and Immune Effects**
    - Inflammatory and immune changes are an effect of some antisense oligonucleotide drugs, including TEGSEDI. In clinical studies, serious inflammatory and immune adverse reactions occurred in TEGSEDI-treated patients, including immune thrombocytopenia and glomerulonephritis, as well as a single case of antineutrophil cytoplasmic autoantibody (ANCA)–positive systemic vasculitis.

Please see additional Important Safety Information below and full Prescribing Information, including boxed WARNING regarding the risk of thrombocytopenia and glomerulonephritis, available at this presentation.

Tegsedi Important Safety Information (continued)

- **WARNINGS AND PRECAUTIONS (CONTINUED)**
  - **Liver Injury**
    - In clinical studies, 8% of TEGSEDI-treated patients had an increased alanine aminotransferase (ALT) at least 3 times the upper limit of normal (ULN) compared with 3% of patients on placebo; 3% of TEGSEDI-treated patients had an ALT at least 8 times the ULN compared with no patients on placebo. Monitor ALT, aspartate aminotransferase, and total bilirubin at baseline and every 4 months during treatment with TEGSEDI. If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction, promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with TEGSEDI, as appropriate.
  - **Liver Transplant Rejection**
    - In a clinical study, cases of liver transplant rejection were reported 2-4 months after starting TEGSEDI in patients whose liver allografts had previously been clinically stable (for over 10 years) prior to starting TEGSEDI. In these cases, the patients clinically improved and transaminase levels normalized after glucocorticoid administration and cessation of TEGSEDI.
    - In patients with a history of liver transplant, monitor ALT, AST, and total bilirubin monthly. Discontinue TEGSEDI in patients who develop signs of liver transplant rejection.

Please see additional Important Safety Information below and full Prescribing Information, including boxed WARNING regarding the risk of thrombocytopenia and glomerulonephritis, available at this presentation.

Tegsedi Important Safety Information (continued)

- **WARNINGS AND PRECAUTIONS (CONTINUED)**
  - **Hypersensitivity Reactions/Antibody Formation**
    - TEGSEDI can cause hypersensitivity reactions. In clinical studies, 6 of 161 (4%) TEGSEDI-treated patients stopped treatment because of a hypersensitivity reaction. These reactions generally occurred within 2 hours of administration of TEGSEDI. Antibodies to TEGSEDI were present when the reactions occurred. If a hypersensitivity reaction occurs, discontinue administration of TEGSEDI and initiate appropriate therapy. Do not use in patients who have a history of hypersensitivity reactions to TEGSEDI.
  - **Uninterpretable Platelet Counts: Reaction Between Antiplatelet Antibodies and Ethylenediaminetetraacetic acid (EDTA)**
    - In Study 1, 23% of TEGSEDI-treated patients had at least 1 uninterpretable platelet count caused by platelet clumping compared with 13% of patients on placebo. If there is suspicion of EDTA-mediated platelet clumping, perform a repeat platelet count using a different anticoagulant (eg, sodium citrate, heparin) in the blood collection tube. Recheck the platelet count as soon as possible if a platelet measurement is uninterpretable. Hold TEGSEDI dosing until an acceptable platelet count is confirmed with an interpretable blood sample.

Please see additional Important Safety Information below and full Prescribing Information, including boxed WARNING regarding the risk of thrombocytopenia and glomerulonephritis, available at this presentation.

Tegsedi Important Safety Information (continued)

- **WARNINGS AND PRECAUTIONS (CONTINUED)**
  - **Reduced Serum Vitamin A Levels and Recommended Supplementation**
    - TEGSEDI treatment leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance of vitamin A is advised for patients taking TEGSEDI. Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (eg, night blindness).
- **ADVERSE REACTIONS**
  - The most common adverse reactions that occurred in at least 20% of TEGSEDI-treated patients and more frequently than in those on placebo were injection site reactions, nausea, headache, fatigue, thrombocytopenia, and fever. Serious adverse reactions were more frequent in TEGSEDI-treated patients (32%) than in patients on placebo (21%).
- **DRUG INTERACTIONS**
  - Because of the risk of thrombocytopenia, caution should be used when using antiplatelet drugs (including nonprescription products that affect platelets) or anticoagulants concomitantly with TEGSEDI. Because of the risk of glomerulonephritis and renal toxicity, caution should be used when using nephrotoxic drugs and other drugs that may impair renal function concomitantly with TEGSEDI.

Please full Prescribing Information, including boxed WARNING regarding the risk of thrombocytopenia and glomerulonephritis, available at this presentation.

Key Takeaways

- Hereditary ATTR amyloidosis is a **progressive and fatal disease** that is underdiagnosed
- Early signs and symptoms of hereditary ATTR amyloidosis can include **carpal tunnel syndrome** and **peripheral and autonomic polyneuropathy**, red flag symptoms that may aid in diagnosis and treatment before rapid progression occurs
- hATTR amyloidosis generally progresses to **multisystem complications and death** from causes that include cardiac failure, renal failure, infection, and severe cachexia
- hATTR amyloidosis is associated with **high healthcare resource utilization and increased costs**
- There are 3 currently approved therapies in the category for adults: 2 for treatment of polyneuropathy in hATTR amyloidosis, and 1 for treatment of cardiomyopathy of wtATTR or hATTR
- The **products under investigation** used to treat ATTR amyloidosis include follow on and novel agents for patient-specific needs

Questions?

Thank You