Utility of Genetic Testing in Patients with ATTR-CM

Subjects: Cardiac & Cardiovascular Systems

Contributor: Ana-Maria Merino-Merino, Jorge Labrador-Gomez, Ester Sanchez-Corral, Pedro-David Delgado-Lopez, Jose-Angel Perez-Rivera

Transthyretin amyloid cardiomyopathy (ATTR-CM) is an increasingly diagnosed condition. Although wild-type transthyretin amyloidosis (ATTRwt) is the most common ATTR-CM, hereditary transthyretin amyloidosis (ATTRv) may also occur. Genetic testing for transthyretin pathogenic variants is recommended for patients with a confirmed clinical diagnosis of ATTR-CM. In fact, confirmation of this autosomal dominant pathogenic variant prompts genetic counselling and allows early identification of affected relatives. Additionally, in the presence of an ATTR-CM-associated polyneuropathy, specific drugs targeting transthyretin can be used.

Keywords: transthyretin amyloidosis ; genetics ; family screening

1. Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is an increasingly diagnosed condition causing heart failure. Although wild-type transthyretin amyloidosis (ATTRwt) is the most frequent form of ATTR-CM, hereditary transthyretin amyloidosis (ATTRv) can also occur [1]. ATTR is a rare disease resulting from the extracellular deposition of transthyretin (TTR) amyloid fibers. TTR is a transport protein produced especially in the liver but also in the retina and the choroid plexus. ATTRv is an autosomal dominant inherited disease that can occur as a result of more than 130 different mutations of the TTR gene [2]. The p.Val50Met mutation (previously p.Val30Met) was firstly identified, and it is the most common variant in Europe, whereas the p.Val142Ile mutation remains more prevalent among African Americans [3].

The exact prevalence of ATTRwt is unknown and likely underdiagnosed. It is estimated that around 13% of patients older than 60 years old have heart failure with preserved ejection fraction [4]. Recent evidence indicates that ATTR-CM is frequently disregarded as a source of prevalent cardiovascular diseases among elderly individuals, despite higher occurrence rates in cases of heart failure with preserved ejection fraction, low-flow aortic stenosis, and other circumstances involving augmented wall thickness [5]. Moreover, autopsy data have indicated that 25% of adults aged 80 years or older have significant TTR amyloid deposits in the myocardium [6]. Although ATTRwt has traditionally been viewed as a disease affecting older individuals, recent reports have indicated diagnosis in patients as young as 47 years of age [7].

The prevalence of ATTRv is much smaller (1/100,000 people) [8] and varies across countries and races. The penetrance of the disease is variable. Some of the variants are more prevalent in certain geographic areas due to the *founder effect*, like the p.Val50Met variant, especially prevalent in Portugal, Sweden, Japan, and the island of Majorca in Spain [9][10].

Currently, it is widely accepted that a non-invasive diagnosis of ATTR amyloidosis can be accomplished through imaging and nuclear tests. Specifically, a grade 2 or 3 cardiac uptake confirmed by diphosphonate scintigraphy, negative serum free light chains, and negative serum and urine immunofixation, when combined with echocardiographic or magnetic cardiac resonance criteria, serve as key factors in this diagnosis [1]. Signs and symptoms are known as “red flags” (**Table 1**).

Table 1. Main cardiac and extracardiac red flags for ATTR amyloidosis.

Localization	Type	Red Flag	Amyloidosis Where It Is Most Frequently Found
Extracardiac	Clinical	Ruptured biceps tendon	ATTRwt
		Carpal tunnel syndrome	ATTRwt and ATTRv
		Deafness	ATTRwt
		Lumbar spinal stenosis	ATTRwt
		Polyneuropathy	ATTRv
		Vitreous deposits	ATTRv
		Family history	ATTRv
Cardiac	Clinical	Heart failure	ATTRwt and ATTRv
		Atrial fibrillation	ATTRwt and ATTRv
	ECG	Pseudoinfarct pattern	ATTRwt and ATTRv
		Low QRS voltage	ATTRwt and ATTRv
	Laboratory	Disproportionally elevated NT-proBNP and troponin	ATTRwt and ATTRv
	Echocardiogram	Granular sparkling of myocardium	ATTRwt and ATTRv
		Increased right ventricular wall thickness	ATTRwt and ATTRv
		Increased valve thickness	ATTRwt and ATTRv
		Pericardial effusion	ATTRwt and ATTRv
	Cardiac magnetic resonance	Reduced longitudinal strain with apical sparing pattern	ATTRwt and ATTRv
		Abnormal gadolinium kinetics	ATTRwt and ATTRv
		Elevated native T1 values	ATTRwt and ATTRv
		Increased extracellular volume	ATTRwt and ATTRv

ATTRwt, wild-type transthyretin-related amyloidosis; ATTRv, variant transthyretin-related amyloidosis. Modified from [1].

At the cardiac level, a diagnosis of left ventricular wall thickness greater than or equal to 12 mm and the presence of “red flags”, such as heart failure or aortic stenosis, particularly in individuals over 65 years old, are indicative of potential cardiac issues. **Figure 1** shows the diagnostic algorithm for cardiac amyloidosis.

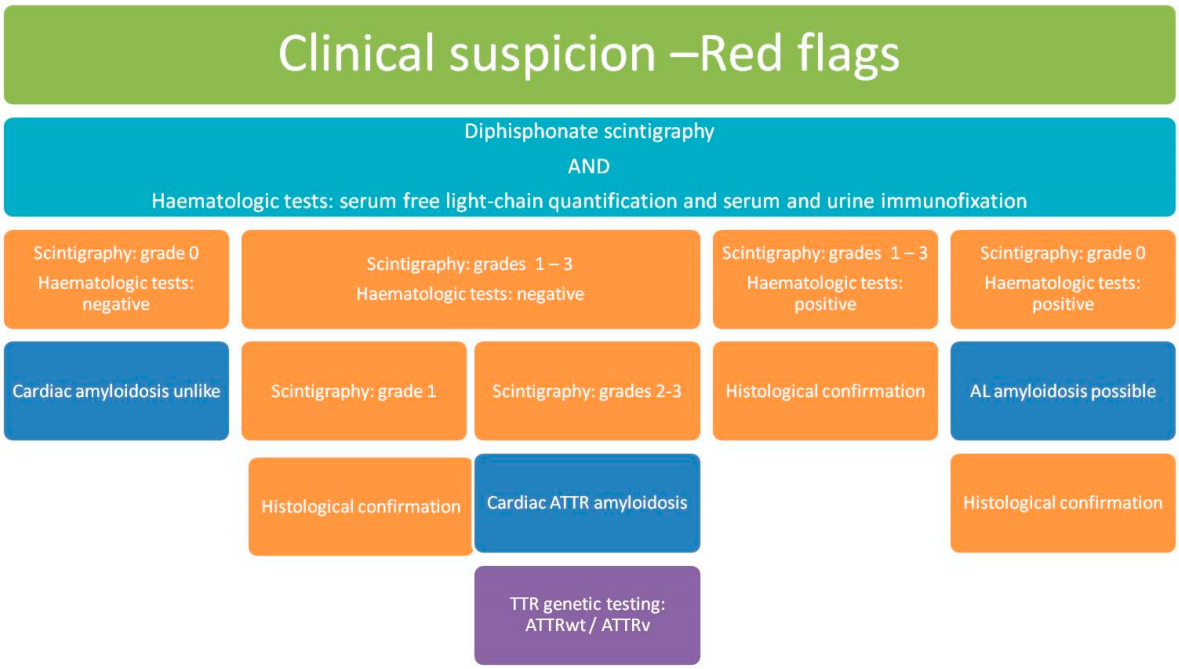

Figure 1. Diagnostic algorithm for cardiac amyloidosis. ATTR, transthyretin amyloidosis; ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; AL, light-chain amyloidosis; TTR, transthyretin. Adapted from: [4].

2. Utility of Family Screening

An early diagnosis of ATTRv is crucial for the patient and relatives. Early signs of the disease can be anticipated and monitored, and decisions regarding personal and family plans can be optimized and better informed [11]. All adult individuals at risk who may wish to undergo testing should be provided with updated and pertinent information to enable them to make a knowledgeable and self-determined decision. Pre-test counselling must encompass not just the complete process of testing but also the follow-up that occurs after the testing [12]. Genetic sequence analysis detects more than 99% of the causal mutations among patients carrying the ATTRv variant. However, no pathogenic variant can be detected by gene-targeted deletion/duplication analysis [13].

3. Utility of Genetic Testing in Clinical Characterization and Anticipation of Symptoms

Genetic counselling in the context of presymptomatic testing for late-onset diseases poses ethical and psychological issues that include the psychological stress of a patient who knows that they carry a pathogenic variant of the disease as well as the potential impact of this information on the reproductive and professional life of the patient and on his/her family relationships [11]. Once a specific mutation has been identified in a patient, a predicted age of disease onset can be estimated for their relatives [14].

For relatives considered to be at-risk, two pre-test counselling sessions are generally recommended. This is especially important for patients testing positive and approaching the expected date of onset and for those already presenting with mild symptoms [15]. In fact, the anticipation phenomenon is more common among patients inheriting mutations from the mother’s lineage [16].

In order to monitor asymptomatic TTR carriers, several protocols have been proposed [17]. The European Network for Transthyretin Familial Amyloid Polyneuropathy has identified five areas of assessment, including clinical examination, sensorimotor function, autonomic dysfunction, cardiac evaluation, and renal function [11].

Certain variants, like the p.Val50Met mutated subtype, usually produce neurological symptoms, whereas others, like p.Val142Ile, provoke late-onset cardiomyopathy with mild or no neurological involvement. However, most variants are associated with a mixed phenotype with both cardiac and neurological manifestations [18]. Globally, the ATTRv variant

usually presents more as cardiomyopathy than polyneuropathy [11]. Despite that some variants have a predominant cardiac phenotype, they can also affect peripheral nerves, and expert neurologic assessment is recommended in all cases. **Figure 2** shows the differences in symptoms between ATTRwt and ATTRv.

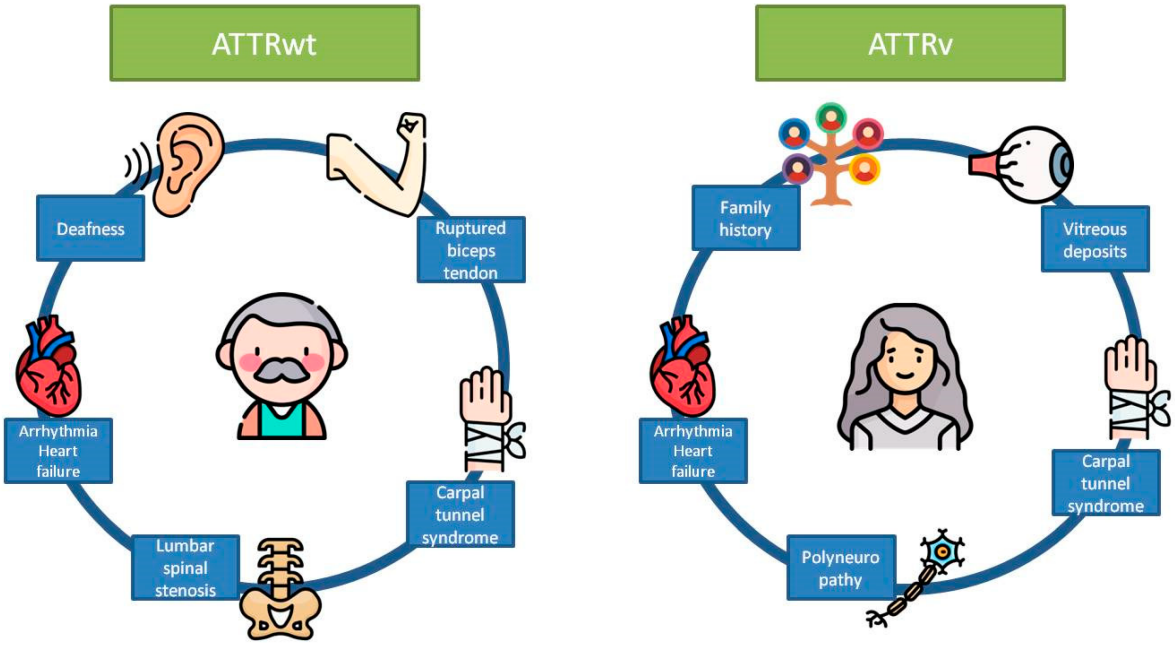

Figure 2. Major manifestations of the two subtypes of transthyretin-related cardiac amyloidosis. ATTRwt, wild-type transthyretin-related amyloidosis; ATTRv, variant transthyretin-related amyloidosis. Icons: Freepik fom https://www.flaticon.com/. Accessed on 1 November 2023.

4. Utility of Genetic Testing for the Initiation of a Specific Treatment

There is an increasing availability of novel, effective, and targeted therapeutic options for ATTRv, as well as for ATTRwt. As therapy is more effective in the early stages of the disease, a prompt diagnosis is key to enable the timely management of neurological, cardiac, and other systemic manifestations. The objective of such therapies is to decrease the production of overall and mutated TTR or to stabilize the circulating TTR molecule by preventing the dissociation of the molecule into amyloidogenic fragments [1].

Treatment alternatives vary according to the variant (ATTRwt versus ATTRv) and are also different within ATTRv patients, depending on the presence of cardiomyopathy, polyneuropathy, or both.

Tafamidis, a benzoxazole derivative without nonsteroidal anti-inflammatory activity, is a stabilizing molecule that selectively binds to the thyroxine-binding sites of TTR and inhibits the dissociation of tetramers into monomers. In the ATTR-ACT study, tafamidis was associated with a lower all-cause mortality than placebo and a lower rate of cardiovascular-related hospitalizations. It was also associated with a lower rate of decline in distance for the 6 minutes walk test and a lower rate of decline in the Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score [19]. Rapezzi et al. further analysed data from the ATTR-ACT in an attempt to determine whether the treatment effects were different between the ATTRv and ATTRwt groups. In fact, they found that the reduction in all-cause mortality following treatment with tafamidis compared with placebo was not different in the ATTRwt and ATTRv groups. In addition, tafamidis was associated with a similar reduction in the 6 min walk test distance and the KCCQ-OS score in both groups [20]. At present, tafamidis can be readily considered the agent of choice in both ATTRwt and ATTRv patients with a reasonable life expectancy who present with cardiac manifestations or stage 1 polyneuropathy [19]. Acoramidis is a new TTR stabilizer. Two phase 3 studies are ongoing to evaluate the efficacy and safety of acoramidis in patients with ATTR-CM (NCT03860935 and NCT04622046).

Ribonucleic acid (RNA) interference is an innate mechanism used to regulate gene expression. This process leads to the fragmentation of specific messenger RNA (mRNA) targets through the interaction of small interfering RNAs bound to the RNA-induced silencing complex. The genetic silencers decrease the production of transthyretin by targeting the transthyretin mRNA, causing the catalytic degradation of TTR mRNA in the liver. Patisiran and inotersen are two approved genetic silencers for ATTRv patients with polyneuropathy.

Patisiran is an interfering RNA encapsulated in a lipid nanoparticle that is delivered to the intracellular compartments of hepatocytes by intravenous infusion [21]. Patisiran has shown to improve multiple clinical manifestations of ATTRv. The favorable impacts of patisiran therapy on polyneuropathy and overall quality of life remained consistent across all primary subgroups, including age, gender, race, region, genotype, initial neuropathy impairment score, familial amyloid polyneuropathy stage, prior use of TTR stabilizers, and cardiac involvement, as observed in the APOLLO-A study [22].

Patisiran has also demonstrated that it is safe and effective in improving both the neurological and cardiovascular symptoms of ATTRv amyloidosis, and it can help patients maintain a good quality of life, regardless of the disease stage or the specific mutation involved [23].

Vutrisiran, a novel RNA interference agent, reduces serum TTR levels by curtailing TTR synthesis, and it has been recently approved for the treatment of ATTRv amyloidosis-related polyneuropathy in adults. This molecule is targeted to the liver, the primary site of TTR synthesis, by binding to a triantennary N-acetylgalactosamine ligand that attaches to the asialoglycoprotein receptor on hepatocyte surfaces. This binding design incorporates an enhanced stabilization chemistry, which enhances its potency and metabolic stability, thereby enabling subcutaneous injections once every three months [24].

Antisense oligonucleotides (ASOs) are single-stranded amphipathic molecules that bind to proteins present in serum, on cell surfaces, and within cells. Within the nucleus of the target cell, ASOs bind to the target mRNA, initiating mRNA degradation [25].

Inotersen, a 2′-O-methoxyethyl–modified antisense oligonucleotide inhibitor, specifically targets the hepatic production of the transthyretin protein. Studies have indicated its ability to enhance the course of neurological disease and improve the quality of life in patients with hereditary transthyretin amyloidosis. These improvements were observed independently of the disease stage, mutation type, or the presence of cardiomyopathy [1][26]. Inotersen has also demonstrated a stabilization effect on the disease progression of ATTR cardiomyopathy patients [27]. Inotersen is a reasonable option for ATTRv patients with early-stage polyneuropathy involvement (stages 1 or 2 polyneuropathy) [21]. Gene silencers are only indicated for patients with ATTRv. The cost of these drugs, along with the cost of the genetic test, makes it difficult to generalise the use of these drugs for all healthcare systems.

Eplontersen represents a new generation of antisense oligonucleotide inhibitors that are linked to triantennary N-acetyl galactosamine. This linkage enhances uptake by hepatocytes, reducing immunogenic reactions and facilitating a reduction in TTR gene expression. Currently, a phase 3 study is underway to assess its effectiveness and safety in patients diagnosed with ATTR-CM (NCT04136171).

The application of genomic editing through CRISPR Cas9 is a promising therapeutic approach in managing ATTR amyloidosis. This technique involves using a nuclease (Cas9) combined with a single-stranded RNA, leading to the irreversible suppression of the TTR gene. A phase 1 clinical trial is ongoing in patients affected by ATTRv polyneuropathy, ATTRv, and ATTRwt CM (NCT04601051) [28].

Overall, patients diagnosed with stage 1 polyneuropathy survive longer [29]. Although therapy can delay disease progression, the recovery of established neurological deficits should not be expected [2]. At present, there is no consensus on what is considered the minimum level of organ damage needed to initiate treatment. This is important because classifying a carrier as affected usually prompts treatment initiation [2][11]. In general, disease-modifying therapies, like tafamidis, have significantly improved the survival of amyloidosis-affected patients [30].

5. Utility of Genetic Testing in Prognosis Assessment

The prognosis for ATTR amyloidosis exhibits variability based on factors such as mutation type, phenotype, and the delay in diagnosis [7]. Advances in diagnostic imaging, alongside the emergence of novel therapies targeting TTR, are contributing to an improved prognosis for ATTR-CM. In cases of ATTRwt and ATTRv with cardiac involvement, whether associated with neurological symptoms or not, the disease typically progresses, resulting in heart failure and mortality within approximately 10 years from the disease's onset. However, in ATTRv patients with a pure neurological phenotype, the overall survival tends to be longer [31]. Specifically, the median survival time for untreated patients experiencing cardiomyopathy or a mixed cardiac-neurological presentation is estimated at 2.5 years for ATTRv and 3.6 years for ATTRwt [19].

Prognostic methods for cardiac amyloidosis patients include multiparametric biomarker scores and biomarker-based staging systems, primarily developed for AL and ATTR cardiac amyloidosis. Current scoring systems acknowledge several

presentation parameters [1]. Gilmore et al. described a score for ATTRwt and ATTRv using glomerular filtration (< or >45 mL/min/1.73 m^2) and NT-proBNP levels (< or >3000 pg/mL) [31]. Patients in stage 1 (zero parameters) had a median survival of 69.2 months, patients in stage 2 (one parameter) had a median survival of 46.7 months, and patients in stage 3 (two parameters) had a median survival of 24.1 months [1]. For the Mayo risk model [7], a group of ATTRwt patients underwent classification into three distinct prognostic stages determined by the levels of troponin T (>0.05 ng/mL) and N-terminal proB-type natriuretic peptide (>3000 pg/mL) biomarkers. Stage 1 comprised patients without elevated biomarkers, stage 2 included individuals with an elevation in one biomarker, and stage 3 encompassed those with elevations in both biomarkers. Patients in stage 3 exhibited a significantly poorer median survival compared to those in stage 1. The median survival times for patients in stages 1, 2, and 3 were 66, 40, and 20 months, respectively [32].

References

1. Garcia-Pavia, P.; Rapezzi, C.; Adler, Y.; Arad, M.; Basso, C.; Brucato, A.; Burazor, I.; Caforio, A.L.P.; Damy, T.; Eriksson, U.; et al. Diagnosis and Treatment of Cardiac Amyloidosis. A Position Statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur. J. Heart Fail. 2021, 23, 512–526.
2. Ando, Y.; Coelho, T.; Berk, J.L.; Cruz, M.W.; Ericzon, B.-G.; Ikeda, S.; Lewis, W.D.; Obici, L.; Planté-Bordeneuve, V.; Rapezzi, C.; et al. Guideline of Transthyretin-Related Hereditary Amyloidosis for Clinicians. Orphanet J. Rare Dis. 2013, 8, 31.
3. Ueda, M.; Ando, Y. Recent Advances in Transthyretin Amyloidosis Therapy. Transl. Neurodegener. 2014, 3, 19.
4. González-López, E.; Gallego-Delgado, M.; Guzzo-Merello, G.; de Haro-Del Moral, F.J.; Cobo-Marcos, M.; Robles, C.; Bornstein, B.; Salas, C.; Lara-Pezzi, E.; Alonso-Pulpon, L.; et al. Wild-Type Transthyretin Amyloidosis as a Cause of Heart Failure with Preserved Ejection Fraction. Eur. Heart J. 2015, 36, 2585–2594.
5. Maurer, M.S.; Elliott, P.; Comenzo, R.; Semigran, M.; Rapezzi, C. Addressing Common Questions Encountered in the Diagnosis and Management of Cardiac Amyloidosis. Circulation 2017, 135, 1357–1377.
6. Tanskanen, M.; Peuralinna, T.; Polvikoski, T.; Notkola, I.-L.; Sulkava, R.; Hardy, J.; Singleton, A.; Kiuru-Enari, S.; Paetau, A.; Tienari, P.J.; et al. Senile Systemic Amyloidosis Affects 25% of the Very Aged and Associates with Genetic Variation in Alpha2-Macroglobulin and Tau: A Population-Based Autopsy Study. Ann. Med. 2008, 40, 232–239.
7. Grogan, M.; Scott, C.G.; Kyle, R.A.; Zeldenrust, S.R.; Gertz, M.A.; Lin, G.; Klarich, K.W.; Miller, W.L.; Maleszewski, J.J.; Dispenzieri, A. Natural History of Wild-Type Transthyretin Cardiac Amyloidosis and Risk Stratification Using a Novel Staging System. J. Am. Coll. Cardiol. 2016, 68, 1014–1020.
8. González-López, E.; López-Sainz, Á.; Garcia-Pavia, P. Diagnosis and Treatment of Transthyretin Cardiac Amyloidosis. Progress and Hope. Rev. Esp. Cardiol. (Engl. Ed.) 2017, 70, 991–1004.
9. Ohmori, H.; Ando, Y.; Makita, Y.; Onouchi, Y.; Nakajima, T.; Saraiva, M.J.M.; Terazaki, H.; Suhr, O.; Sobue, G.; Nakamura, M.; et al. Common Origin of the Val30Met Mutation Responsible for the Amyloidogenic Transthyretin Type of Familial Amyloidotic Polyneuropathy. J. Med. Genet. 2004, 41, e51.
10. Zaros, C.; Genin, E.; Hellman, U.; Saporta, M.A.; Languille, L.; Wadington-Cruz, M.; Suhr, O.; Misrahi, M.; Planté-Bordeneuve, V. On the Origin of the Transthyretin Val30Met Familial Amyloid Polyneuropathy. Ann. Hum. Genet. 2008, 72, 478–484.
11. Obici, L.; Kuks, J.B.; Buades, J.; Adams, D.; Suhr, O.B.; Coelho, T.; Kyriakides, T. European Network for TTR-FAP (ATTReuNET) Recommendations for Presymptomatic Genetic Testing and Management of Individuals at Risk for Hereditary Transthyretin Amyloidosis. Curr. Opin. Neurol. 2016, 29, S27–S35.
12. Manganelli, F.; Fabrizi, G.M.; Luigetti, M.; Mandich, P.; Mazzeo, A.; Pareyson, D. Hereditary Transthyretin Amyloidosis Overview. Neurol. Sci. 2022, 43, 595–604.
13. Sekijima, Y. Hereditary Transthyretin Amyloidosis. In GeneReviews®; Adam, M.P., Everman, D.B., Mirzaa, G.M., Pagon, R.A., Wallace, S.E., Bean, L.J., Gripp, K.W., Amemiya, A., Eds.; University of Washington, Seattle: Seattle, WA, USA, 1993.
14. Conceição, I.; Damy, T.; Romero, M.; Galán, L.; Attarian, S.; Luigetti, M.; Sadeh, M.; Sarafov, S.; Tournev, I.; Ueda, M. Early Diagnosis of ATTR Amyloidosis through Targeted Follow-up of Identified Carriers of TTR Gene Mutations. Amyloid 2019, 26, 3–9.
15. Sekijima, Y. Transthyretin (ATTR) Amyloidosis: Clinical Spectrum, Molecular Pathogenesis and Disease-Modifying Treatments. J. Neurol. Neurosurg. Psychiatry 2015, 86, 1036–1043.
16. Lemos, C.; Coelho, T.; Alves-Ferreira, M.; Martins-da-Silva, A.; Sequeiros, J.; Mendonça, D.; Sousa, A. Overcoming Artefact: Anticipation in 284 Portuguese Kindreds with Familial Amyloid Polyneuropathy (FAP) ATTRV30M. J. Neurol.

Neurosurg. Psychiatry 2014, 85, 326–330.

17. Adams, D.; Cauquil, C.; Theaudin, M.; Rousseau, A.; Algalarrondo, V.; Slama, M.S. Current and Future Treatment of Amyloid Neuropathies. Expert Rev. Neurother. 2014, 14, 1437–1451.
18. Reinés, J.B.; Vera, T.R.; Martín, M.U.; Serra, H.A.; Campins, M.M.C.; Millán, J.M.D.; Lezaun, C.G.; Cruz, M.R. Epidemiology of Transthyretin-Associated Familial Amyloid Polyneuropathy in the Majorcan Area: Son Llàtzer Hospital Descriptive Study. Orphanet J. Rare Dis. 2014, 9, 29.
19. Maurer, M.S.; Schwartz, J.H.; Gundapaneni, B.; Elliott, P.M.; Merlini, G.; Waddington-Cruz, M.; Kristen, A.V.; Grogan, M.; Witteles, R.; Damy, T.; et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N. Engl. J. Med. 2018, 379, 1007–1016.
20. Rapezzi, C.; Elliott, P.; Damy, T.; Nativi-Nicolau, J.; Berk, J.L.; Velazquez, E.J.; Boman, K.; Gundapaneni, B.; Patterson, T.A.; Schwartz, J.H.; et al. Efficacy of Tafamidis in Patients with Hereditary and Wild-Type Transthyretin Amyloid Cardiomyopathy: Further Analyses From ATTR-ACT. JACC Heart Fail. 2021, 9, 115–123.
21. Mathew, V.; Wang, A.K. Inotersen: New Promise for the Treatment of Hereditary Transthyretin Amyloidosis. Drug Des. Dev. Ther. 2019, 13, 1515–1525.
22. Adams, D.; Gonzalez-Duarte, A.; O'Riordan, W.D.; Yang, C.-C.; Ueda, M.; Kristen, A.V.; Tournev, I.; Schmidt, H.H.; Coelho, T.; Berk, J.L.; et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. N. Engl. J. Med. 2018, 379, 11–21.
23. Di Stefano, V.; Fava, A.; Gentile, L.; Guaraldi, P.; Leonardi, L.; Poli, L.; Tagliapietra, M.; Vastola, M.; Fanara, S.; Ferrero, B.; et al. Italian Real-Life Experience of Patients with Hereditary Transthyretin Amyloidosis Treated with Patisiran. Pharmacogenomics Pers. Med. 2022, 15, 499–514.
24. Habtemariam, B.A.; Karsten, V.; Attarwala, H.; Goel, V.; Melch, M.; Clausen, V.A.; Garg, P.; Vaishnaw, A.K.; Sweetser, M.T.; Robbie, G.J.; et al. Single-Dose Pharmacokinetics and Pharmacodynamics of Transthyretin Targeting N-Acetylgalactosamine-Small Interfering Ribonucleic Acid Conjugate, Vutrisiran, in Healthy Subjects. Clin. Pharmacol. Ther. 2021, 109, 372–382.
25. Griffin, J.M.; Rosenthal, J.L.; Grodin, J.L.; Maurer, M.S.; Grogan, M.; Cheng, R.K. ATTR Amyloidosis: Current and Emerging Management Strategies: JACC: CardioOncology State-of-the-Art Review. JACC CardioOncology 2021, 3, 488–505.
26. Benson, M.D.; Waddington-Cruz, M.; Berk, J.L.; Polydefkis, M.; Dyck, P.J.; Wang, A.K.; Planté-Bordeneuve, V.; Barroso, F.A.; Merlini, G.; Obici, L.; et al. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. N. Engl. J. Med. 2018, 379, 22–31.
27. Benson, M.D.; Dasgupta, N.R.; Rissing, S.M.; Smith, J.; Feigenbaum, H. Safety and Efficacy of a TTR Specific Antisense Oligonucleotide in Patients with Transthyretin Amyloid Cardiomyopathy. Amyloid 2017, 24, 219–225.
28. Monda, E.; Bakalakos, A.; Rubino, M.; Verrillo, F.; Diana, G.; De Michele, G.; Altobelli, I.; Lioncino, M.; Perna, A.; Falco, L.; et al. Targeted Therapies in Pediatric and Adult Patients With Hypertrophic Heart Disease: From Molecular Pathophysiology to Personalized Medicine. Circ. Heart Fail. 2023, 16, e010687.
29. Russo, M.; Gentile, L.; Di Stefano, V.; Di Bella, G.; Minutoli, F.; Toscano, A.; Brighina, F.; Vita, G.; Mazzeo, A. Use of Drugs for ATTRv Amyloidosis in the Real World: How Therapy Is Changing Survival in a Non-Endemic Area. Brain Sci. 2021, 11, 545.
30. Falcão de Campos, C.; Conceição, I. Updated Evaluation of the Safety, Efficacy and Tolerability of Tafamidis in the Treatment of Hereditary Transthyretin Amyloid Polyneuropathy. Drug Healthc. Patient Saf. 2023, 15, 51–62.
31. Gillmore, J.D.; Damy, T.; Fontana, M.; Hutchinson, M.; Lachmann, H.J.; Martinez-Naharro, A.; Quarta, C.C.; Rezk, T.; Whelan, C.J.; Gonzalez-Lopez, E.; et al. A New Staging System for Cardiac Transthyretin Amyloidosis. Eur. Heart J. 2018, 39, 2799–2806.
32. Obi, C.A.; Mostertz, W.C.; Griffin, J.M.; Judge, D.P. ATTR Epidemiology, Genetics, and Prognostic Factors. Methodist Debakey Cardiovasc. J. 2022, 18, 17–26.