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Review

Proceedings from the multistakeholder EURO-NMD workshop on multisystemic ATTRv treatments, Paris, 8-9 December 2025

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Abstract

Hereditary transthyretin amyloidosis (ATTRv) is a rare, progressive, multisystem disorder characterised by marked phenotypic heterogeneity, delayed diagnosis, and major inequities in access to specialist care and disease-modifying therapies. Therapeutic innovation has transformed the outlook for many patients but has also introduced new uncertainties in diagnosis, treatment selection, sequencing, monitoring, and reimbursement. This manuscript summarises the outputs of

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a multistakeholder workshop convened by ERN EURO-NMD in Paris on 8-9 December 2025. Clinicians, researchers, patient representatives, methodologists, health technology assessment experts, and industry partners were invited to move beyond general consensus statements toward an implementation-focused roadmap. Three domains were prioritised: patient unmet needs and integration of patient perspectives; harmonised diagnostic pathways, including genetic testing, cascade screening, and pre-symptomatic monitoring; and minimal standards for treatment availability, delivery, and longitudinal follow-up across heterogeneous health systems. Participants emphasised that ATTRv should be managed as a systemic disease with frequent cardiac involvement, that current diagnostic tools are insufficient for early transition from carrier status to disease detection, and that refined risk stratification is needed for asymptomatic carriers. Evidence gaps in therapeutic decision-making, including first-line treatment choice, treatment switching and combinations, and management of special populations such as women of childbearing age were identified. A central outcome was the proposal for a European collaborative platform built around an EURO-NMD-aligned registry that supports prospective real-world data collection, biomarker validation, clinical trial readiness and health technology assessment. The current roadmap defines short-, medium-, and long-term priorities for implementing a healthcare system for ATTRv amyloidosis across Europe.

Keywords
hereditary transthyretin amyloidosis, ATTRv, polyneuropathy, cardiomyopathy, genetic testing, registry, real-world evidence, treatment sequencing, patient-reported outcomes

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1. Introduction

European Reference Networks were established to improve care for patients with rare and complex diseases by linking specialist centres, research groups, and patient organisations across countries. Within this framework, ERN EURO-NMD has identified a persistent gap between rapid scientific advances in rare neuromuscular disorders and their practical implementation across diverse healthcare systems. ATTRv amyloidosis exemplifies this gap. It is now possible to diagnose and treat the disease earlier than in previous decades, but access to timely diagnosis, expert multidisciplinary care, genetic counselling, and therapy remains uneven across Europe and globally.

ATTRv amyloidosis is no longer adequately conceptualised as a single-organ neuropathy. It is a systemic disorder with peripheral and autonomic neuropathy, cardiomyopathy, cardiac conduction disease, gastrointestinal manifestations, ocular disease, renal involvement, musculoskeletal manifestations, and, in selected patients, central nervous system involvement. The same TTR variant can be associated with neuropathy-predominant, cardiomyopathy-predominant, or mixed disease, and marked intrafamilial variability can occur. This creates major challenges for counselling, prognostication, monitoring, and treatment selection.

Therapeutic progress has intensified the need for practical guidance. TTR stabilisers remain relevant, particularly in selected early-stage presentations, while gene-silencing therapies have shown strong effects on neuropathy and emerging

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benefit in cardiomyopathy. Next-generation antisense oligonucleotides, longer-acting siRNA therapies, gene editing, and amyloid-depleting antibodies are rapidly changing the research landscape. These advances raise new questions: how early should therapy start, which treatment should be chosen first, when should therapy be switched, and when - if ever - should combinations be used? The workshop was designed to address these questions in a pragmatic way, integrating scientific evidence with patient priorities and health-system feasibility.

The full detailed summaries of the individual presentations and round-table discussions are provided in Supplementary File 1 along with the supporting bibliography. The extended implementation and working group structure tables are provided in Supplementary File 2. The present main manuscript distils the workshop outputs into a concise roadmap for clinical implementation, collaborative research, and policy alignment (Tables 1–3).

2. Workshop scope and approach

The workshop, held in Paris on 8-9 December 2025, brought together neurologists, cardiologists, internists, geneticists, researchers, patient advocates, methodologists, health technology assessment experts, and industry representatives active in ATTRv amyloidosis (see Table 4, in the final section of this manuscript). The goal was not to produce a formal guideline or an evidence-graded recommendation document. Instead, the objective was to define an actionable agenda that could be implemented through ERN EURO-NMD and partner networks.

The meeting was structured around three objectives. First, participants sought to clarify patients' unmet needs and expectations, including diagnostic delay, information at diagnosis, psychosocial impact, caregiver burden, and disparities in access. Second, they aimed to propose a common diagnostic workflow covering clinical suspicion, genetic testing, cascade testing, pre-symptomatic monitoring, and the role of emerging biomarkers. Third, they aimed to define minimal standards for the availability, delivery, and follow-up of treatment, acknowledging that healthcare systems differ substantially in reimbursement rules, specialist capacity, and diagnostic infrastructure.

The process deliberately included broad stakeholder engagement. Patient representatives' and caregivers' perspectives were integrated throughout the discussion, rather than confined to a single session. Industry participants contributed to discussions on feasibility, data sharing, post-marketing evidence, and access, but the proposed roadmap is framed around independent scientific governance and patient-centred priorities.

3. ATTRv as a multisystem disease: implications for early diagnosis

A recurring theme was the need to abandon rigid organ-based framing. ATTRv may present through neuropathic, cardiac, gastrointestinal, autonomic, ocular, renal, musculoskeletal, or central nervous system features. Even patients initially labelled as having neuropathy-predominant disease may have subclinical or overt cardiac involvement, while variants classically associated with cardiomyopathy may have neurological manifestations. Multisystem assessment is therefore a diagnostic requirement rather than an optional add-on.

Phenotypic variability is shaped by TTR variant, fibril composition, age at onset, disease duration, and modifying genetic or environmental factors. The distinction between fibril types has clinical relevance, particularly in relation to biopsy sensitivity and bone scintigraphy uptake, but current knowledge is largely derived from selected variants and should not be overgeneralised. Participants agreed that the same variant can produce different organ involvement within a family, making individualised longitudinal phenotyping essential.

Table 1. Workshop objectives and implementation-oriented outputs.

Workshop objective	Implementation question	Main output
Patient unmet needs	How can care pathways reflect what patients and caregivers identify as most important?	Earlier diagnosis, better information at diagnosis, holistic support, caregiver recognition, and systematic patient-reported outcomes.
Diagnostic workflow	How should suspected patients, relatives, and asymptomatic carriers be identified and monitored?	Integrated clinical, genetic, tissue/imaging, biomarker, and multidisciplinary assessment; structured counselling and cascade testing.
Treatment and follow-up standards	What minimum level of therapy access and monitoring should be expected across systems?	Multidimensional monitoring every 6-12 months; predefined core outcomes; registry-based evidence generation; equitable access strategy.

Table 2. Proposed minimum monitoring dataset with optional research layer.

Domain	Minimum dataset	Enhanced dataset/research layer
Genetics and family history	TTR variant, age, sex, ancestry, family history, proband age at onset, counselling status	Variant classification updates, parental transmission, penetrance modelling, reproductive counselling outcomes
Neuropathy	Symptoms, neurological examination (NIS or equivalent), functional/disability scale, nerve conduction studies and sudomotor assessment, where available	QST, Sudoscan/autonomic tests, skin biopsy, intraepidermal nerve fibre density, amyloid deposition, neurofilament light chain (Nfl) assay, nerve ultrasound, muscle MRI
Cardiac	ECG, echocardiography, NT-proBNP/troponin, rhythm history, heart failure status, anticoagulation/pacing status	Bone scintigraphy quantification, cardiac MRI, MIBG cardiac scintigraphy, atropine challenge, detailed arrhythmia burden
Systemic and supportive care	Weight/BMI, gastrointestinal and autonomic symptoms, pain, mobility, falls, ocular/renal screening as indicated	Nutrition metrics, rehabilitation outcomes, caregiver burden, socioeconomic measures
Treatment response	Therapy, dose, start/stop/switch dates, adverse events, patient preference, adherence/treatment burden	Serum TTR, NfL and stored biosamples, biomarker-response modelling, PROM/PREM longitudinal trajectories

Cardiac involvement received specific emphasis because it is frequent, can be clinically silent, and strongly influences prognosis. Standard cardiology assessments based on symptoms alone are insufficient in ATTRv because neuropathy can limit exercise tolerance and confound functional classification. ECG, echocardiography, natriuretic peptides, bone scintigraphy, cardiac MRI in selected cases, rhythm monitoring, and autonomic evaluation should be considered within a structured cardiac assessment pathway. Cardiac dysautonomia and conduction disease may precede overt infiltrative cardiomyopathy and should not be ignored in early disease.

Neuropathy diagnosis also requires refinement. ATTRv polyneuropathy is typically length-dependent and axonal, often beginning with small-fibre and autonomic involvement. Pain, thermal sensory disturbance, orthostatic symptoms, gastrointestinal dysmotility, erectile dysfunction, unexplained weight loss, and bilateral carpal tunnel syndrome should trigger consideration of amyloid neuropathy, especially when progression is rapid or when a presumed inflammatory neuropathy does not respond as expected. Skin biopsy, quantitative sensory testing, autonomic testing, neurophysiology, and emerging biomarkers can all contribute, but their optimal combination and timing remain unresolved.

Central nervous system involvement was recognised as an increasingly visible complication as survival improves. Leptomeningeal disease, haemorrhage, seizures, cognitive decline, ataxia, and stroke-like presentations may be misdiagnosed as more common neurological disorders. Current liver-directed and peripherally acting therapies may not address CNS TTR production, making systematic case collection and CNS phenotyping an important registry priority.

Table 3. Implementation roadmap.

Timeframe	Operational priorities	Expected deliverables
0-12 months	Create working groups; define registry objectives; agree on minimal dataset; establish governance; pilot data collection; build secure digital workspace.	Core protocol, pilot case report form, governance charter, participating-centre list, first pilot dataset.
1-3 years	Scale to multiple centres; validate PROMs; implement data-sharing agreements; launch targeted modules for CNS disease, pregnancy, rare variants, and biomarker studies.	Interoperable registry, PROM/PREM module, first real-world analyses, harmonised monitoring protocol, prospective sub-study protocols.
>3 years	Enable registry-based and hybrid clinical studies; support HTA and reimbursement evidence; maintain continuous data quality improvement; expand international collaborations.	Trial-ready platform, historical control cohorts, comparative effectiveness analyses, HTA-ready datasets, sustainable European ATTRv research ecosystem.

Table 4. Participants' list, contributions and conflict-of-interest disclosures.

Name	Affiliation/country	Workshop role	Writing/review role	COI/details
João Agostinho	ULSSM, CAML, Lisbon; PT	Presenter, Round table	Presentation; Internal reviewer	Yes - Received speaker and consulting fees from Pfizer, Alnylam, AstraZeneca and Bayer
Vincent Algalarrondo	Hôpital Bichat CRMR CERAMIC Cardio Paris; FR	Moderator, Round table	Moderation; Internal reviewer	Yes - Received speaker and consulting fees from Pfizer, Alnylam, AstraZeneca and Bayer
Filipe Assoreira	Purpose Pharma; PT	Participant, Round table	Internal reviewer	Yes - Purpose Pharma employee
Antonio Atalaia	Assistance Publique-Hopitaux de Paris/ERN EURO-NMD; FR	Moderator, Round table	Lead writer; Internal reviewer	No
Alexia Bakdache	Anylam France; FR	Participant, Round table	Internal reviewer	Yes - Alnylam employee
Gengshi Chen	AstraZeneca	Participant, Round table	Internal reviewer	Yes - AstraZeneca employee
Joao Costa	Faculty of Medicine, University of Lisbon; PT	Moderator, Round table	Moderation and writer; Internal reviewer	Yes - Chair GPG EAN
Aurora Maria Barreto Gomes da Costa	Unidade Local de Saúde Braga; PT	Participant	Internal reviewer	No
Francesco Daddoveri	Azienda Ospedaliero Universitaria Pisana; IT	Participant	Internal reviewer	No
Mário Rui Dias Almeida	Global Medical Affairs, BioPharmaceuticals Medical, AstraZeneca, Gothenburg, Sweden;; SW	Presenter; Round table	Internal reviewer	Yes - AstraZeneca employee
Isabel Conceição	ULSSM, CAML; Faculty of Medicine, Lisbon University; PT	Presenter, Round table, Moderator	Presentation and lead writer; Internal reviewer	Yes – Received consultancy and speaker fees from Alnylam, Akcea Therapeutic, Astra Zeneca, and Pfizer. PI in clinical trials promoted by Pfizer Inc., Alnylam Pharmaceuticals, Ionis Pharmaceuticals, Inc. and Eidos Therapeutics, Inc.
Andoni Echaniz-Laguna	Bicêtre University Hospital; FR	Participant, Round table	Internal reviewer	Yes - Received fees from Alnylam, Pfizer, Astra Zeneca, Intellia, BridgeBio
Teresinha Evangelista	Assistance Publique-Hopitaux de Paris/ERN EURO-NMD; FR	Participant	Internal reviewer	No
Jocelyn Ewuti Nonga	Neuro-Psycho-Pathological Center of the University of Kinshasa; CD	Participant, Round table	Internal reviewer	No

(continued)

Table 4. (continued)

Name	Affiliation/country	Workshop role	Writing/review role	COI/details
Lucía Galan Davila	Hospital Clínico San Carlos; ES	Presenter; Round table	Presentation; Internal reviewer	Honoraria for lectures and advisory boards from Pfizer, Alnylam, Akcea, argenx, AstraZeneca, Alexion, Grünenthal, Sanofi Genzyme, Sobi, and UCB. Travel support from Pfizer, Alnylam, Akcea, AstraZeneca, and Sobi. Research grant from Alnylam. Principal investigator in the APOLLO-A, HELIOS-A, and NeuroTTRansform clinical trials.
Juan Gonzalez Moreno	Hospital Son Llatzer; ES	Presenter; Round table	Presentation; Internal reviewer	Yes - Received fees from Alnylam, Pfizer, Astra Zeneca, Purpose
David Gregory	Amyloidosis Alliance; UK	Presenter; Round table	Presentation; Internal reviewer	No
Katrin Hahn	Department of Neurology with Experimental Neurology, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität Zu Berlin, Charitéplatz 1, Berlin 10117, Germany; DE	Presenter; Round table	Presentation; Internal reviewer	Yes - KH received financial reimbursement for consulting, advisory board activities, speaker fees and/or contributions to congresses and travel support to attend scientific meetings by Akcea Therapeuticals Inc., Alnylam Pharmaceuticals Inc., Amicus, AstraZeneca, Bayer Vital GmbH, BridgeBio, GSK, Hormosan, Takeda Pharmaceutical Inc., Pfizer Pharmaceuticals Inc., Purpose Pharma, Swedish Orphan Biovitrum Inc and ViiV Healthcare GmbH. KH further received research funding by the foundation Charité (BIH clinical fellow and digital accelerator), Alnylam Pharmaceuticals Inc., Amicus, AstraZeneca, Hormosan and Pfizer Pharmaceuticals
Catarina Hoff Falcão de Campos	Serviço de Neurologia, ULS Santa Maria; MUHCRI e Centro de Estudos Egas Moniz, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal; PT	Presenter; Round table	Presentation; Internal reviewer	Yes - Received fees from Alnylam, Astra Zeneca, Pfizer, Akcea, Purpose Pharma
Emmanuel Jammes	Amyloidosis Alliance; FR	Presenter; Round table	Presentation; Internal reviewer	No
Kleopas A. Kleopa	The Cyprus Institute of Neurology and Genetics; CY	Participant, Round table	Internal reviewer	Yes - Speaker honorarium from Alnylam, Travel support for participation in meetings from Genesis Pharma

(continued)

Table 4. (continued)

Name	Affiliation/country	Workshop role	Writing/review role	COI/details
Thirusha Lane	Purpose Pharma; UK	Participant, Round table	Internal reviewer	Yes - Consultant for Purpose Pharma International AB
K. H. Vincent Lau	Alnylam Pharmaceuticals; US	Participant, Round table	Internal reviewer	Yes - Employee of Alnylam Pharmaceuticals
Anna Mykytiuk	Kyiv Regional Children's hospital; UA	Participant	Internal reviewer	No
Laura Piera Obici	IRCCS Fondazione Policlinico San Matteo; IT	Presenter; Round table	Presentation; Internal reviewer	Speaker and/or consulting honoraria from Alnylam, AstraZeneca, Bayer, BridgeBio, Intellia, Novo Nordisk, Purpose Pharmaceutical, Pfizer.
Hanna Palahuta	Uzhhorod National University, Department of Neurosurgery, Neurology and Psychiatry; UA	Participant	Internal reviewer	No
Davide Pareyson	Fondazione IRCCS Istituto Neurologico Carlo Besta; IT	Presenter; Round table	Presentations and lead writer; Internal reviewer	Participation in Advisory Board: Alnylam, Akcea, Arvinas, Inflectis, Augustine Tx, DTx, Novartis, AnnJi Support for participation in International Meetings: AstraZeneca Speaker honorarium: Alnylam, AstraZeneca Local PI in clinical trials: Alnylam, Ionis, Applied Therapeutics, NIDO Biosciences
Jean-Philippe Plançon	EPODIN/Alliance Maladies Rares (FR); FR	Participant	Internal reviewer	No
Marie Violaine Plante-Bordeneuve	Université Paris Est Créteil-Hopital Henri Mondor, Assistance Publique-Hopitaux de Paris; FR	Presenter; Round table	Presentation; Internal reviewer	Pfizer and Alnylam supported expenses with travel and attendance to scientific meetings, consultancy for Alnylam, AstraZeneca, Purpose pharma, has spoken on behalf Alnylam at scientific meetings and received financial compensation
Maud Raimbault	AFM-Téléthon; FR	Participant	Internal reviewer	No
Mary Reilly	UCL Queen Square Institute of Neurology; UK	Presenter; Round table	Presentation and writer; Internal reviewer	Received fees form Alnylam and Bridgebio
Sofia Alexandra Reis Marques	ULS Tâmega e Sousa; PT	Participant	Internal reviewer	No
Kateryna Savinova	Kyiv Regional Children's hospital; UA	Participant	Internal reviewer	No
Natascha Schoenhart	Purpose Pharma	Participant, Round table	Internal reviewer	Yes - Purpose Pharma employee
Michel Slama	Centre de Reference CERAMIC Assistance Publique Hopitaux de Paris; FR	Presenter; Round table	Presentation; Internal reviewer	No
Tanya Stojkovic	Institute of Myology; FR	Moderator; Participant	Moderation; Internal reviewer	No

(continued)

Table 4. (continued)

Name	Affiliation/country	Workshop role	Writing/review role	COI/details
Ivailo Tournev	Expert hTTRA Center, Clinic of Nervous Diseases, University Hospital Aleksandrovska, Department of Neurology, Medical University-Sofia; BG	Participant, Round table	Internal reviewer	No
Jonas Wixner	Public Health and Clinical Medicine, Medicine, Norrland's University Hospital/Umeå University; SW	Participant, Round table	Internal reviewer	Yes - Received consulting fees from Pfizer, Alnylam, AstraZeneca, Purpose Pharma, BridgeBio, Intellia and Bayer
Yang Xu	AstraZeneca	Participant, Round table	Internal reviewer	Yes - Employee of AstraZeneca

4. Genetic testing, cascade screening, and asymptomatic carriers

TTR genetic testing is central to ATTRv care. It is not only confirmatory; it determines whether relatives require cascade testing, informs prognostic discussion, and may influence monitoring strategy. Testing should be considered early in patients with compatible neuropathy, autonomic dysfunction, bilateral carpal tunnel syndrome, infiltrative cardiomyopathy, conduction disease, unexplained multisystem features, or relevant ancestry. Importantly, genetic testing should not be omitted in patients initially labelled as wild-type ATTR, because a pathogenic variant may be found and has implications for family members.

Participants emphasised substantial heterogeneity across countries in access to genetic testing, test turnaround time, referral requirements, panel composition, and counselling infrastructure. The expansion of broad gene panels and direct-to-consumer or non-traditional testing creates additional challenges: TTR variants may be discovered incidentally in patients with atypical phenotypes, and results may reach patients without appropriate counselling. The workshop therefore favoured a structured approach that links test interpretation to phenotype, family history, variant knowledge, and formal genetic counselling.

Cascade testing should be offered to adult first-degree relatives through a stepwise process that includes pre-test counselling, informed consent, post-test disclosure, and structured follow-up. Counselling must communicate uncertainty. Penetrance is variant-dependent and population-dependent; age at onset can vary widely even within the same family; and anticipation-like patterns have been reported. The Predicted Age of Disease Onset (PADO) framework is useful as a pragmatic starting point but should not be treated as a rigid rule. Monitoring should be individualised according to variant, family history, parental transmission, patient preferences, and emerging evidence from biomarkers and imaging.

The preclinical phase was described as an 'iceberg': tissue amyloid deposition, small-fibre abnormalities, autonomic dysfunction, or biomarker changes may precede overt symptoms by several years. Defining the threshold at which an asymptomatic carrier becomes a patient remains one of the most important practical and ethical questions in the field. Early detection is only useful if linked to clear counselling, access to expert follow-up, and evidence-based decisions about treatment initiation.

5. Patient and caregiver priorities

Patient representatives highlighted that the central gaps in amyloidosis care extend beyond access to disease-modifying drugs. Diagnostic delay remains the most visible and damaging unmet need. Many patients experience a prolonged period of nonspecific symptoms, repeated consultations, emergency visits, or hospitalisations before diagnosis. These delays are particularly problematic because ATTRv is now treatable and because earlier intervention is likely to preserve function.

Information delivery at diagnosis was identified as inadequate in many settings. Patients and relatives need clear explanations of inheritance, variable penetrance, organ involvement, treatment options, monitoring expectations, reproductive implications, and the impact of results on family members. Communication should be staged and supported rather than delivered as a single technical disclosure.

The workshop also emphasised psychosocial and socioeconomic burden. ATTRv can reduce autonomy, disrupt employment, impose financial stress, and generate substantial caregiver burden. Current models of care are often centred on pharmacological treatment and do not consistently integrate the holistic support patients need, including physiotherapy,

nutrition, pain management, autonomic symptom management, psychological support, social work, and caregiver support. Patient-reported outcome measures and patient-reported experience measures should therefore be integrated into routine care and research infrastructure.

6. Treatment landscape and decision-making

The therapeutic landscape now includes TTR stabilisers and gene-silencing therapies, with additional strategies in development. Stabilisers act by reducing tetramer dissociation and may be particularly relevant in selected early-stage presentations, although the response is incomplete and varies across patients. Gene silencers reduce hepatic TTR production and have shown strong effects on neuropathy outcomes, with growing evidence of cardiac benefit that varies by disease stage and study population. Next-generation antisense and siRNA agents aim to improve dosing convenience, safety, and durability. Gene editing could offer long-term suppression after a single intervention but requires careful safety surveillance. Antibody-mediated amyloid clearance is attractive because it targets existing deposits rather than only preventing new deposition.

Treatment selection cannot currently be reduced to a simple algorithm. Phenotype, genotype, disease stage, rate of progression, cardiac involvement, autonomic involvement, CNS risk, patient preference, route of administration, monitoring burden, pregnancy plans, reimbursement rules, and local availability all influence choice. The workshop did not attempt to rank therapies universally. Instead, participants converged on principles for decision-making: treat early when disease is clinically or biologically evident; avoid single-organ thinking; reassess phenotype over time; document baseline status rigorously; and use multidimensional monitoring to detect progression.

Switching therapy is increasingly common, particularly from stabilisers to gene silencers when progression is documented. Evidence from observational cohorts suggests that progression may slow after switching in selected patients, but robust comparative data are limited. Switching between gene silencers may be appropriate to improve safety, tolerability, or treatment burden. Combination therapy has a strong mechanistic rationale because stabilisation, silencing, editing, and clearance target different steps in the amyloid cascade. However, current evidence is insufficient to justify routine combination therapy, particularly given cost and uncertainty about additive benefit. Investigator-led trials and registry-based comparative analyses are needed.

Special populations require dedicated attention. Women of childbearing age are underrepresented in trials, and current therapies lack adequate pregnancy safety data. Treatment interruption may risk disease progression, while alternative strategies require careful multidisciplinary discussion. A pregnancy-exposure registry was identified as a priority. Patients with CNS involvement, advanced cardiac disease, or aggressive multisystem variants also require structured case collection because conventional trial endpoints may not capture their trajectories.

7. Monitoring and minimal standards of care

Monitoring is the bridge between therapeutic innovation and personalised care. Participants agreed that treatment response or failure should not be inferred from a single variable. A multidimensional approach should include clinical examination, disability or functional scales, neurophysiology when feasible, autonomic assessment, cardiac biomarkers and imaging, patient-reported outcomes, weight and nutritional status, and treatment-specific laboratory monitoring. In most stable patients, assessments every 6-12 months are pragmatic; more frequent review is justified in rapidly progressive disease, advanced cardiac disease, early post-treatment periods, or when switching therapy is being considered.

Neurological measures remain essential but imperfect. Clinical stages based on walking capability, such as Familial Amyloid Polyneuropathy (FAP) and Polyneuropathy Disability (PND) scores, are easy to assess and relevant for disease-modifying treatments (DMT) prescription. NIS in clinical practice and modified NIS+7 in clinical trials are widely used yet are nonlinear measures and difficult to implement consistently. RODS provides linear scaling and may be useful for functional follow-up. Nerve conduction studies offer objective assessment of large-fibre involvement and are among the most reproducible tools for tracking neuropathy progression. Skin biopsy, muscle MRI, nerve ultrasound, and quantitative sensory testing can provide objective information but vary in accessibility. Sudomotor function testing, including "Sudoscan", adds value by evaluating autonomic small-fibre involvement, a core feature of ATTRv. Neurofilament light chain is promising as a marker of axonal injury and may help distinguish conversion or progression, but it is not disease-specific and must be interpreted in clinical context. Serum TTR levels can document biological response to silencing therapy but do not yet reliably predict clinical outcome.

Cardiac monitoring is somewhat more established but still incomplete for early disease. NT-proBNP, troponin, ECG, echocardiography, rhythm monitoring, bone-tracer scintigraphy with SPECT, and cardiac MRI can support staging and follow-up. However, arrhythmias, conduction abnormalities, autonomic dysfunction, and anticoagulation decisions are not

fully captured by structural criteria used in major trials. Patients with mixed phenotypes should be managed by teams that can integrate neurology and cardiology decisions rather than treating each organ in isolation.

The workshop, therefore, proposes a minimum feasible monitoring dataset rather than an exhaustive ideal dataset. The minimum should be implementable in reference centres and adaptable to resource-limited settings. Centres with access to advanced tools should collect additional data in harmonised formats to support biomarker validation. Where biomarkers are not yet routinely available, storing samples for future analysis should be considered if local governance allows.

8. European collaborative platform and registry

A central workshop output was the proposal for a European collaborative platform centred on a sustainable ATTRv registry aligned with ERN infrastructure. The registry should be designed as a pragmatic, scalable, interoperable, and modular tool serving multiple purposes: real-world evidence generation, post-marketing surveillance, trial readiness, historical control development, biomarker research, health technology assessment, and equitable access advocacy.

The registry must avoid the common failure mode in rare-disease databases: excessive complexity that discourages participation and results in incomplete data. A minimal core dataset should therefore be defined first, with optional modules for advanced phenotyping, CNS disease, pregnancy, rare variants, biobanking, and treatment sequencing. Interoperability with existing academic registries, ERN registries, industry-sponsored observational programmes, and national datasets should be prioritised over the creation of duplicative structures. FAIR data principles and GDPR-aligned governance are essential.

Governance should separate scientific decision-making from external stakeholder interests while maintaining structured collaboration. Neurology, cardiology, gastroenterology, genetics, rehabilitation, methodology, patient organisations, and industry partners all have legitimate roles. Patient organisations should contribute to outcome selection, communication strategy, and engagement. Methodologists should support core outcome selection, registry design, missing-data strategies, and comparative effectiveness analyses. Industry collaboration can be valuable for post-marketing surveillance and data sharing, provided that independence and transparency are protected.

The registry should also be able to support sub-studies that address immediate knowledge gaps. Priority modules include CNS involvement, pregnancy exposure, rare variants, including homozygous or compound-heterozygous cases, biomarker validation, outcome-measure harmonisation, and real-world treatment sequencing. Digital interfaces could facilitate the collection of patient-reported data and reduce clinician workload, but implementation should be carefully tested in pilot centres before scale-up.

9. Research priorities and implementation roadmap

The workshop marks a strategic shift from consensus generation to data generation. Participants identified research questions that are directly linked to clinical decisions and policy needs. First, the field needs better predictors of disease conversion among asymptomatic carriers and of treatment response among symptomatic patients. Second, it needs standardised outcome measures that are clinically meaningful, sensitive to change, and feasible in routine care. Third, it needs comparative effectiveness data to inform first-line therapy, switching, sequencing, and combinations. Fourth, it needs structured evidence for special populations and rare phenotypes. Fifth, it needs health-economic models that reflect long-term outcomes, treatment burden, and access disparities.

The roadmap is phased. In the short term, the community should establish working groups, define registry objectives, agree on a minimal dataset, select pilot centres, and develop shared digital infrastructure. In the medium term, the registry should scale across European centres, validate patient-reported outcomes, formalise data-sharing agreements, and launch targeted sub-studies. In the long term, the platform should support registry-based trials, hybrid trial designs, historical controls, health technology assessment, and continuous learning across the care pathway.

10. Consensus recommendations

1. Recognise ATTRv as a systemic disease in all patients, regardless of initial neuropathic or cardiac presentation.
2. Perform TTR genetic testing in all suspected ATTR cases, including patients initially considered to have wild-type cardiomyopathy when hereditary disease has not been excluded.
3. Offer cascade testing to adult relatives through structured genetic counselling that explicitly addresses uncertainty, penetrance, family communication, and psychological impact.
4. Monitor asymptomatic carriers with an individualised approach that uses predicted age of onset as a guide but not as an absolute rule.

5. Define early disease using multidimensional evidence rather than a single clinical, imaging, pathological, or biomarker threshold.
6. Use multidisciplinary care pathways integrating neurology, cardiology, genetics, rehabilitation, supportive care, and patient organisations.
7. Assess treatment response through longitudinal, multidimensional monitoring, with progression confirmed across domains where possible before switching therapy, unless rapid deterioration requires earlier action.
8. Develop and validate a core outcome set within 1-2 years, harmonised across clinical trials and real-world care.
9. Establish registry modules for pregnancy exposure, CNS involvement, rare variants, biomarker validation, and treatment sequencing.
10. Align diagnostic expansion with treatment access strategies so that patients are not identified without a realistic pathway to care.

11. Discussion

The workshop identified a central paradox in ATTRv amyloidosis: therapeutic innovation has outpaced the systems needed to deliver it equitably and evaluate it over the long term. The field now has several disease-modifying therapies, with more in development, yet clinicians lack robust comparative evidence to inform many decisions encountered in routine practice. At the same time, patients continue to experience diagnostic delays, fragmented care, insufficient information, and variable access to treatment.

Implementation requires a balance between ambition and feasibility. A comprehensive ideal dataset may be scientifically attractive but unsustainable. Conversely, a minimal dataset that is overly narrow may fail to address the key questions affecting treatment access and patient outcomes. The proposed two-layer model - a core dataset plus optional advanced modules - is intended to resolve this tension. It allows broad participation while preserving the capacity for deep phenotyping where expertise and resources exist.

Patient-centredness must be operational rather than rhetorical. Patient and caregiver priorities should influence outcome selection, registry interface design, communication materials, and health policy metrics. Diagnostic delay, information quality, treatment burden, autonomy, employment, caregiver strain, and access barriers should be measured and addressed alongside traditional clinical endpoints.

The roadmap also has implications for regulators and payers. Evidence for early intervention, switching, and combination therapy will likely come from a combination of trials, open-label extensions, natural history cohorts, and high-quality real-world data. A registry aligned with ERN EURO-NMD infrastructure could help generate the evidence needed for health technology assessment while also supporting scientific discovery. To be credible, however, it must maintain transparent governance, uphold data quality standards, and remain independent of commercial interests.

Several limitations should be acknowledged. The workshop outputs reflect expert and stakeholder discussion rather than a systematic guideline process. Evidence was not formally graded. Some therapeutic and diagnostic areas are evolving rapidly, and recommendations may require updating as new trial and real-world data become available. Nevertheless, the practical value of the workshop lies in its focus on implementable steps that can be taken now while stronger evidence is generated.

12. Conclusions

ATTRv amyloidosis has entered a phase in which the main challenge is no longer only therapeutic discovery but equitable, evidence-generating implementation. The workshop proposed a shift from static consensus statements to a learning healthcare system built on multidisciplinary care, patient-centred outcomes, harmonised monitoring, and interoperable real-world data. Immediate priorities include defining a minimal dataset, launching a pilot registry activity, standardising counselling and monitoring, integrating PROMs, and establishing targeted modules to address the most urgent evidence gaps. Over the longer term, a European collaborative platform can support registry-based trials, biomarker validation, health technology assessment, and more equitable access to innovation.

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Data Availability Statement

All data presented in the review are cited in referenced articles in Supplementary File 1.

Trial registration

Not applicable as it is not a clinical trial.

Supplemental material

Supplemental material for this article is available online.

Supplementary File 1

Detailed workshop presentation summaries and round-table discussions

Understanding Disease Evolution and the Diagnostic Window

Pathogenesis and phenotypic variability in ATTRv: Neuropathy, cardiomyopathy, and overlap syndromes – I. Conceição

Isabel Conceição (IC), from the Hereditary Amyloidosis Reference Centre at ULSSM-Santa Maria Hospital in Lisbon, Portugal, presented on the pathogenesis and phenotypic variability of ATTRv amyloidosis, including neuropathy, cardiomyopathy, and overlap syndromes.

ATTRv amyloidosis demonstrates significant inter- and intrafamilial phenotypic variability, even among family members carrying the same mutation. More than 150 pathogenic TTR mutations have been identified, each with distinct stability profiles and clinical behaviours. The disease manifests as a multisystemic disorder affecting the peripheral and autonomic nervous systems, the heart, the gastrointestinal tract, the kidneys, the eyes, the musculoskeletal system, and the central nervous system, underscoring the complexity of its clinical presentation and management.

Important clinical distinctions exist between wild-type and ATTRv amyloidosis. Wild-type ATTR predominantly involves cardiac and musculoskeletal manifestations, with neuropathy and renal disease being less common (1,2). In contrast, hereditary ATTR more frequently presents with neuropathy, autonomic dysfunction, and ocular, gastrointestinal, and renal involvement (3) Notably, family history is often absent in non-endemic areas, complicating early recognition of hereditary cases.

In contrast, hereditary ATTR more frequently presents with neuropathy, autonomic dysfunction, and ocular, gastrointestinal, and renal involvement (3) Notably, family history is often absent in non-endemic areas, complicating early recognition of hereditary cases.

From an epidemiological perspective, hereditary ATTRv amyloidosis shows distinct geographic clustering in endemic regions, including Portugal, Sweden, Japan, and Brazil. Mutation distribution varies geographically and continues to evolve as disease awareness improves and genetic testing expands. While the p.V50M mutation dominates in endemic areas, the p.V142I variant is increasingly recognised in Western Europe and among Afro-Caribbean populations, reflecting both improved diagnostic capacity and genuine population-specific prevalence patterns (4,5).

TTRv amyloidosis arises from TTR tetramer destabilisation and proteolytic cleavage, leading to monomer misfolding, accelerated fibril formation, and tissue amyloid deposition (6). Two distinct fibril types have been characterised with important clinical implications. Type B fibrils consist of full-length TTR, exhibit homogeneous tissue deposition, and are typically associated with early-onset p.V50M mutation, neuropathic phenotype, positive biopsy findings, and low DPD uptake on bone scintigraphy using ^{99m}Tc-DPD, a nuclear medicine scan used to detect cardiac transthyretin amyloid deposition. In contrast, Type A fibrils contain a mixture of full-length TTR and fragments, show patchy tissue deposition, and correlate with late-onset and cardiac-dominant phenotypes, higher DPD uptake, and increased risk of false-negative biopsies (7). Critically, amyloid deposition is a dynamic and self-propagating process once initiated, underscoring the importance of early intervention (8).

The mechanisms underlying neuropathy in ATTRv amyloidosis differ substantially based on age of onset. Early-onset disease is characterised by small-fibre predominance, prominent autonomic dysfunction, Schwann cell toxicity, and a dying-back neuropathy pattern. In contrast, late-onset neuropathy involves vascular endothelial injury, large-fibre involvement, and presents as a mixed sensorimotor neuropathy, frequently leading to misdiagnosis as chronic inflammatory demyelinating polyneuropathy (CIDP). These distinct pathophysiological mechanisms have important implications for clinical recognition and diagnostic approach (9,10).

Cardiac involvement is very common in ATTRv amyloidosis, even in patients initially labelled as having predominantly neuropathic disease. Manifestations include conduction abnormalities and infiltrative cardiomyopathy. Importantly, cardiac involvement represents the major driver of mortality in ATTR amyloidosis, underscoring the need for systematic cardiac screening and monitoring regardless of the initial phenotype (11).

Central nervous system (CNS) involvement is increasingly recognised as patient survival has improved with modern therapies. CNS manifestations are highly heterogeneous and include leptomeningeal disease, haemorrhage, seizures, cognitive decline, and balance disorders. These presentations are often misdiagnosed as stroke, epilepsy, autoimmune encephalopathy, or dementia. CNS involvement is likely under-recognised in clinical practice, but CSF biomarkers may help differentiate ATTR-related cognitive impairment from Alzheimer's disease (12,13).

Prognosis in ATTR amyloidosis varies widely depending on mutation type and phenotypic presentation. Earlier diagnosis and timely initiation of treatment have been shown to significantly improve outcomes (14). Notably, the same mutation can manifest as neuropathy-only, cardiac-only, or mixed disease, highlighting the unpredictable nature of phenotypic expression and reinforcing the importance of comprehensive multisystem evaluation in all patients.

In summary, the presentation addressed ATTRv amyloidosis as a highly heterogeneous, multisystem disease with marked variability in phenotype, genotype-phenotype correlation, age of onset, organ involvement, and prognosis. The speaker emphasised that amyloid type, fibril composition (type A vs type B), mutation stability, age of onset, and modifying genetic and environmental factors all shape clinical presentation. Although historically viewed as a neuropathy, ATTRv is now clearly recognised as a mixed disease with frequent cardiac involvement, which is the main determinant of survival. Diagnostic delays remain substantial, especially in cardiomyopathy, negatively affecting outcomes. Increasing survival due to modern therapies has revealed central nervous system involvement, adding further complexity. Overall, understanding phenotypic variability is critical for early recognition, accurate diagnosis, individualised prognostic assessment, and timely selection and sequencing of disease-modifying therapies within a multidisciplinary care framework.

Clinical and Research Implications

The presentation and subsequent discussion generated several key recommendations for clinical practice and future research directions. In clinical practice, participants emphasised the critical importance of amyloid typing before initiating management decisions. Systematic cardiac screening should be performed in all ATTRv patients, including those presenting primarily with neuropathy, given that cardiac involvement is the major determinant of mortality. Clinicians should maintain a low threshold for suspecting CNS involvement, particularly in long-term survivors and post-liver transplant patients. The discussion highlighted the need to avoid rigid age-of-onset assumptions when counselling asymptomatic carriers and instead implement individualised longitudinal phenotyping strategies. Participants also cautioned against common misdiagnoses, including CIDP, diabetic neuropathy, vasculitis, stroke, and dementia.

Regarding diagnostic approaches, the workshop emphasised the need to interpret negative biopsies carefully, especially in suspected Type A fibril disease, where patchy deposition increases the risk of false-negative results. Clinicians should recognise the limitations of DPD scintigraphy in early-onset and Type B fibril disease, where uptake may be low despite active disease. For patients with suspected CNS involvement, CSF analysis should be considered in the workflow to sort out ATTRv-related cognitive impairment from other neurodegenerative diseases.

In the context of genetic counselling and follow-up, participants stressed that counselling must emphasise the inherent uncertainty and phenotypic variability observed even within families carrying the same mutation. Close monitoring of asymptomatic carriers is justified despite predicted late onset, given the unreliability of age-of-onset predictions and the potential for earlier-than-expected disease manifestation.

Several research priorities emerged from the discussion. There is a need for expanded fibril-type studies beyond the p.V50M mutation to better understand the relationship between fibril composition and clinical phenotype across the full spectrum of TTR variants. Better characterisation of modifier genes, epigenetic factors, and environmental influences is essential to explain the marked phenotypic variability observed. Finally, variant-specific natural history data are needed to inform precision treatment strategies and improve prognostic counselling.

Discussion and Participant Perspectives

The presentation generated substantial discussion among participants, highlighting several areas of evolving understanding and ongoing uncertainty. Regarding the mutation landscape, VA noted an increasing number of p.V142I cases in France and among populations of Arabian origin, suggesting that current mutation distribution maps may be outdated. IC agreed, emphasising that the distribution of mutations continues to evolve as disease awareness increases and access to genetic diagnostics expands.

The relationship between fibril type and phenotype emerged as a topic of debate. KH questioned whether the association between Type A fibrils and neuropathy versus Type B fibrils and cardiomyopathy represents an oversimplification of the true complexity. IC acknowledged that the evidence base is predominantly derived from p.V50M studies and that mixed phenotypes dominate in clinical practice. While fibril type may influence early disease manifestations, its impact on long-term

outcomes remains unclear. AA added that outside of early-onset p.V50M disease, most studied variants demonstrate Type A fibrils and mixed phenotypes, with limited data available for comprehensive analysis.

The management of asymptomatic carriers generated considerable discussion, with participants highlighting the ethical and clinical dilemma inherent in counselling carriers when the predicted age of onset is often unreliable. There was strong consensus that close follow-up of all carriers is warranted, as deferring monitoring based on average age-of-onset data is not clinically safe given the wide variability observed in clinical practice.

Intra-familial phenotypic variability emerged as a key concern, with participants describing cases of the same mutation within the same family resulting in different patterns of organ involvement. The mechanisms underlying this variability remain unknown, representing an important gap in current understanding.

CNS involvement generated particular interest among participants. Cases of aggressive CNS ATTR were discussed, presenting with haemorrhage, cognitive decline, and seizures, with CSF biomarker profiles differing from those seen in Alzheimer's disease. Participants raised the diagnostic challenge of distinguishing ATTR-related cognitive decline from Cerebral Amyloid Angiopathy, Alzheimer's disease, or vascular dementia in clinical practice. There was consensus that CNS disease, while rare, is highly heterogeneous, frequently misdiagnosed, and increasingly recognised as patient survival improves with disease-modifying therapies.

Genetic Testing, Variant Interpretation, and Management of Asymptomatic Carriers in ATTRv Amyloidosis – V. Planté-Bordeneuve

Following the discussion on phenotypic variability and disease evolution in ATTRv amyloidosis, Violaine Planté-Bordeneuve, from the Neuropathies Expert Centre at Henri-Mondor Hospital in Créteil, Paris, France, discussed the role of genetic testing, variant interpretation, and the increasingly important challenge of managing asymptomatic gene carriers in the era of disease-modifying therapies.

Expanding Disease Spectrum and Implications for Testing

The presentation began by situating hereditary transthyretin amyloidosis within its broader clinical spectrum. ATTR amyloidosis includes both wild-type disease—often affecting older men with mainly cardiac symptoms and limited life expectancy—and the hereditary form (ATTRv), characterised by autosomal dominant inheritance, a wide age range of onset from the third to the ninth decade, incomplete and age-dependent penetrance, and significant intrafamilial phenotypic variability. Late-onset cases often lack a clear family history, which leads to ongoing diagnostic delays. With the advent of well-tolerated, disease-modifying therapies that aim to prevent or decrease transthyretin amyloid build-up, early diagnosis has become essential. This change in therapy has fundamentally shifted the importance of genetic testing, especially in asymptomatic relatives of affected individuals (15).

Technical Aspects of TTR Genetic Testing

The transthyretin (TTR) gene is small, comprising four exons and three introns, and has been routinely analysed for decades. Classical Sanger sequencing remains a reliable and appropriate diagnostic method. However, next-generation sequencing (NGS) panels for neuropathies and cardiomyopathies increasingly include TTR, though panel composition is not standardised across centres or countries.

Significant heterogeneity in access to genetic testing persists across Europe. In some settings, testing requires referral to specialised genetics services and may involve prolonged turnaround times. Industry-sponsored genetic programs have broadened access to testing globally and generated valuable epidemiological data, including confirmation of the high prevalence of the p.Val142Ile variant and reclassification of certain variants of uncertain significance. Nonetheless, these initiatives lack harmonisation, underscoring the need for standardised recommendations regarding TTR testing strategies and interpretation (16).

More than 140 TTR variants have been identified, most of them amyloidogenic. Although traditional models categorise variants as predominantly neuropathic (e.g., p Val50Met), cardiac (e.g., p.Val142Ile), or mixed, systematic evaluation reveals that most variants are associated with multisystem involvement. Genotype–phenotype correlations are influenced by tetramer stability: highly destabilising variants (e.g., p.Leu75Pro) are associated with early onset, severe multisystem disease, and short survival, whereas milder variants (e.g., p.Glu81Lys) are associated with later onset and slower progression. Protective variants

such as p. p. Thr139Met, which increase tetramer stability, provided the mechanistic basis for the development of TTR stabilisers.

Homozygosity for p.Val142Ile has been reported to be a modifier of disease severity, with earlier onset and more severe cardiac involvement compared with heterozygous individuals.

Indications for Genetic Testing in Clinical Practice

Genetic testing was emphasised as both a diagnostic and prognostic tool. In patients presenting with neuropathy, TTR testing should be considered early in the presence of red-flag features such as length-dependent axonal neuropathy with early autonomic involvement, bilateral carpal tunnel syndrome, rapid progression, or poor response to immunotherapy when misdiagnosed as chronic inflammatory demyelinating polyneuropathy. In cardiology settings, TTR testing should be integrated into the diagnostic algorithm for hypertrophic or infiltrative cardiomyopathy, particularly in individuals of African ancestry, given the high prevalence of p.Val142Ile (17).

Importantly, TTR testing should not be omitted in patients initially labeled as having wild-type ATTR, as identification of a pathogenic variant has implications for prognosis and enables cascade family screening.

Cascade Testing and Genetic Counselling

Cascade genetic testing has become a cornerstone of modern ATTRv management. Once an index case is identified, adult first-degree relatives should be offered predictive testing within a structured genetic counselling framework. Although legal and ethical frameworks vary by country, in many European systems, patients may need to inform at-risk relatives, with physician support when needed.

Predictive testing involves a stepwise process that includes pre-test counselling, informed consent, and structured post-test follow-up. Testing is generally offered to adults aged 18 and over, prioritising siblings and then offspring.

Predictive Age of Disease Onset (PADO) and Monitoring

Management of asymptomatic carriers represents one of the most challenging areas in contemporary ATTRv care. The concept of the Predicted Age of Disease Onset (PADO), introduced in a 2021 expert consensus, integrates genotype-specific average age at onset, family history, and the proband's age at onset to guide monitoring. Baseline evaluation and annual follow-up are recommended beginning 10 years prior to the predicted onset (18). However, this approach had substantial limitations. Penetrance studies have demonstrated marked variability across populations—for example, in ATTR associated with p.Val50Met, penetrance is incomplete in Swedish families but approaches near-complete levels in Portuguese families. Age at onset is highly variable even within the same pedigree, and anticipation phenomena—particularly with maternal transmission—have been reported, with earlier onset observed in offspring, especially sons of affected mothers (19)(20).

Importantly, penetrance variability is not restricted to p.Val50Met and differs substantially across other TTR variants. Low penetrance has been documented in families carrying p.Val142Ile and p.Ile127Val, whereas high penetrance is observed in families with variants such as p.Thr69Ala and p.Glu109Gln. These observations underscore that penetrance is strongly variant-dependent and may be further influenced by geographic, genetic, and possibly epigenetic modifiers.

Collectively, these data indicate that a uniform monitoring strategy based solely on predicted age of onset may be overly simplistic. More refined risk-stratification models that incorporate variant-specific penetrance, parental transmission patterns, and emerging early biomarkers are needed to optimise surveillance and the timing of therapeutic intervention in asymptomatic carriers.

The Preclinical "Iceberg" Phase

Retrospective analyses indicate that subclinical abnormalities—including small fibers sensory and autonomic dysfunction and tissue amyloid deposition—may precede overt symptoms by several years (21). This "iceberg" model highlights the existence of a prolonged presymptomatic phase whose duration likely varies by genotype and modifying factors. Improved characterisation of this phase may ultimately allow earlier therapeutic intervention.

Clinical Illustrations

Two family cases demonstrated the real-world impact of cascade testing. In an early-onset Portuguese p.Val50Met family, identifying asymptomatic carriers enabled close monitoring and early treatment of affected children. In a late-onset, mixed-phenotype family with no obvious initial family history, retrospective genealogical research uncovered previously misdiagnosed cases of amyloidosis, leading to early diagnosis and treatment of a sibling at a less advanced stage of the disease than the proband.

Discussion

The workshop discussion underscored several key points:

1. TTR genetic testing is essential in all suspected ATTR cases, including those presenting with cardiomyopathy.
2. Access to testing and to panel standardisation remains uneven across Europe.
3. Cascade testing, supported by structured genetic counselling, is central to reducing diagnostic delay and improving outcomes.
4. The PADO framework provides a pragmatic monitoring strategy but requires refinement given variable penetrance, anticipation, and phenotypic heterogeneity.
5. Better characterisation of the preclinical phase is a priority to inform optimal timing of treatment initiation.

Overall, genetic testing has evolved from a confirmatory diagnostic step to a central tool in precision medicine for ATTRv amyloidosis, shaping prognosis, guiding family management, and enabling earlier therapeutic intervention.

Cardiac Involvement in Hereditary Transthyretin Amyloidosis: Diagnostic Challenges, Prognostic Implications, and Therapeutic Considerations – Michel S Slama

Professor Michel S. Slama provided the cardiologist's perspective on cardiac involvement in hereditary transthyretin amyloidosis (ATTRv), emphasising its frequency, prognostic impact, diagnostic complexity, and implications for treatment decisions in patients with ATTRv polyneuropathy (22).

Evolving Understanding of Cardiac Involvement

The earliest descriptions of ATTR neuropathy in the 1950s concentrated on severe early-onset neuropathic phenotypes, and cardiac involvement was not initially recognised. In hindsight, many patients probably succumbed to advanced neuropathy before cardiac features were systematically evaluated (23). It is now widely accepted that ATTR amyloidosis is a multisystem disease affecting the heart, nerves, eyes, and musculoskeletal system (24). For example, carpal tunnel syndrome and spinal stenosis often appear before obvious cardiac or neurological symptoms and can serve as early warning signs (25).

Historically, the outlook was poor once symptomatic cardiac disease emerged, with a median survival of around 3 years in untreated patients, as reported in large referral cohorts (26). Nonetheless, the scientific landscape has shifted significantly over the past twenty years (24), marked by a sharp rise in amyloidosis-related publications and, more crucially, the advent of disease-modifying therapies (27,28). This progress highlights the importance of recognising cardiac involvement earlier, given its strong link to adverse outcomes, and the advantages of initiating treatment sooner.

Frequency of Cardiac Involvement in ATTRv

Cardiac involvement may occur across the entire phenotypic spectrum of ATTRv. Even patients classified as having "neuropathic" forms may exhibit subclinical or overt cardiac disease, while variants traditionally associated with cardiomyopathy may demonstrate neurological features.

Clinical trial data illustrate this overlap. In major studies of ATTRv polyneuropathy treated with SiRNA (27,28), approximately 50–60% of participants met criteria for cardiac disease despite not being selected for cardiomyopathy.

In a cohort of asymptomatic ATTRv carriers followed longitudinally, cardiac amyloid deposition was identified in approximately 16% of individuals with otherwise normal neurological evaluations (21). This finding is clinically significant, as detection of cardiac amyloid can influence the decision to initiate disease-modifying therapy.

Pathophysiology and Clinical Spectrum

Cardiac involvement in ATTRv reflects infiltration of multiple cardiac structures that has been characterised using advanced imaging modalities (29)(30). The phenotype includes:

- Infiltrative/restrictive cardiomyopathy with preserved ejection fraction,
- Conduction system disease (atrioventricular block, bundle branch block),
- Atrial fibrillation,
- Cardiac dysautonomia.

Cardiac denervation and autonomic dysfunction, commonly overlooked, may precede structural infiltration, myocardial thickening and conduction abnormalities, representing an early manifestation of disease.

Defining Cardiac Involvement: Limitations of Current Criteria

Diagnostic criteria used in landmark cardiomyopathy trials (e.g., ATTR-ACT (31), APOLLO-B (32)) rely on combinations of imaging findings (septal thickness ≥12 mm), elevated natriuretic peptides, history of heart failure, and scintigraphic or biopsy confirmation. However, these criteria do not capture the full spectrum of the disease, as they do not account for arrhythmias, conduction abnormalities, or autonomic dysfunction.

Importantly, reliance on advanced structural changes likely identifies patients at a relatively late stage. If overt myocardial thickening, elevated biomarkers, and heart failure symptoms are present in a patient with known ATTRv, this suggests delayed recognition.

Clinical Assessment and Functional Evaluation

Clinical assessment alone is insufficient. NYHA classification is unreliable in ATTRv patients with coexisting neuropathy, as ambulation may be limited by neurological impairment rather than cardiac symptoms (33,34). The NYHA classification is also known to have poor reproducibility, and reclassification based on six-minute walk testing provides a more accurate functional staging, more sensible management decisions, treatment assessment in clinical trials, and is now used as a follow-up tool.

Prognostic staging systems incorporating estimated glomerular filtration rate and NT-proBNP provide risk stratification, particularly in variants such as p.Val142Ile, but remain imperfect.

Electrocardiography and Echocardiography

Electrocardiographic findings are nonspecific. Low voltage in the presence of increased wall thickness is suggestive but occurs in only about half of patients. Conduction abnormalities and atrial arrhythmias are common but not commonly used as diagnostic tools in clinical trials, although they are in “real life”. The electrocardiographic–echocardiographic dissociation pattern was described in large cohorts of ATTR (26).

Echocardiography typically demonstrates:

- Increased left ventricular wall thickness,
- Restrictive filling pattern,
- Bi-atrial enlargement,
- Right ventricular involvement,
- Left ventricular strain imaging shows characteristic abnormalities in the basal LV segments, with relative apical sparing.

However, these findings generally represent established disease.

Advanced Imaging: The Role of Bone Scintigraphy

Bone scintigraphy with DPD (or HMDP or PYP) has become a cornerstone of non-invasive diagnosis. The Perugini grading system and heart-to-lung ratio provide a semiquantitative assessment. Large cohorts have demonstrated high diagnostic accuracy, although real-world specificity may vary (32).

Age and genotype affect uptake (35,36). In p.Val50Met, DPD positivity is more common in late-onset disease than in early-onset forms, indicating that the length of exposure to amyloidogenic TTR may impact detectability.

DPD positivity is also prognostically relevant: even low-grade uptake is associated with increased cardiac events and mortality. Patients with normal echocardiography and normal scintigraphy have an excellent prognosis, whereas DPD positivity markedly increases mortality risk.

Cardiac MRI is valuable in ambiguous cases and in the early stages of the disease, particularly with T1 mapping and extracellular volume quantification, but is less specific and less accessible in routine practice than scintigraphy.

Cardiac Dysautonomia

Cardiac autonomic dysfunction represents an early and under-recognised feature. Two diagnostic tools were highlighted (37)(25):

- Atropine challenge testing: blunted heart rate response reflects parasympathetic denervation.
- MIBG scintigraphy: reduced heart-to-mediastinum ratio indicates sympathetic denervation.

Both measures carry prognostic value and may precede overt structural changes. Cardiac denervation may be the earliest cardiac manifestation in ATTRv.

Genetic Testing in Cardiomyopathy

A significant proportion of elderly patients diagnosed with ATTR cardiomyopathy (ATTR-CM) harbour pathogenic TTR variants. Approximately 20% of patients over 70 years with apparent ATTR-CM may have hereditary disease. Therefore, TTR genetic testing should be systematically performed even when wild-type disease is suspected (38).

Natural History of Cardiac Involvement in p.Val50Met

In a large cohort of p.Val50Met carriers, cardiac involvement increased with age and disease duration. While early-onset patients historically appeared to have less cardiac disease, long-term survivors develop cardiac manifestations at rates comparable to late-onset patients. This observation challenges earlier assumptions and underscores the need for long-term cardiac surveillance in all genotypes.

Therapeutic Considerations

- Symptomatic Management

  Management of heart failure in ATTR differs from conventional paradigms:

  - Diuretics remain the mainstay.
  - Beta-blockers and ACE inhibitors are poorly tolerated in patients with chronotropic incompetence or hypotension for instance, but may be appropriate in selected contexts (e.g., coronary disease, rapid atrial fibrillation).
  - Increasing diuretic requirement and recurrent hospitalizations portend poor prognosis.

  Implantable cardioverter-defibrillators have not demonstrated clear survival benefit, as many deaths occur from electromechanical dissociation rather than ventricular arrhythmia. Pacemaker implantation may be necessary in selected patients with conduction disease.

  Liver transplantation is contraindicated in advanced heart failure.

- Disease-Modifying Therapy
  - Tafamidis reduced mortality and cardiovascular hospitalizations in ATTR cardiomyopathy. However, subgroup analyses in ATTRv populations were underpowered and did not demonstrate statistically significant mortality benefit, although trends favored treatment.
  - RNA-silencing therapies (patisiran, vutrisiran) have demonstrated improvements in survival, cardiac biomarkers and structural parameters in ATTR-CM cohorts that included a vast majority of patients with wild type amyloidosis. While not all trials were powered for mortality endpoints, reductions in NT-proBNP and troponin and decreased DPD uptake suggest beneficial cardiac effects (39)(40).
  - Evidence supporting combination therapy using stabilisers and silencers remains limited and inconclusive; current data do not demonstrate a clear additive survival benefit.
  - Early initiation of therapy, even before overt heart failure, appears associated with improved outcomes, though dedicated studies are ongoing.

Key Conclusions

Professor Slama concluded with several key messages:

- Cardiac involvement significantly worsens prognosis in ATTRv.
- All patients with ATTRv polyneuropathy may harbor mixed cardiac involvement.
- Cardiac assessment should begin early—ideally before 60 years of age and approximately 10 years before predicted disease onset.
- Multimodal evaluation is essential: clinical assessment alone is insufficient; ECG and echocardiography must be complemented by bone scintigraphy, cardiac MRI when needed, and autonomic testing.
- Cardiac dysautonomia may precede structural cardiomyopathy.
- Genetic testing should be performed in all cases of suspected ATTR cardiomyopathy.
- Disease-modifying therapy should be considered early, with careful longitudinal monitoring using clinical status, biomarkers (NT-proBNP), weight, and imaging.
- Overall, the presentation reinforced that cardiac involvement in ATTRv is common, heterogeneous, and prognostically critical. Early detection through systematic and multimodal evaluation is central to optimizing timing and selection of therapy in this multisystem disease.

Discussion Following the Presentation on Cardiac Involvement

- **Diagnostic Uncertainty and the “Grey Zone”**

The discussion opened with a comment highlighting an important parallel between cardiology and neurology: despite advances in imaging and biomarkers, the exact onset of organ involvement remains uncertain. Participants acknowledged that bone scintigraphy (DPD) is widely used but incompletely understood. The biological basis for variable tracer uptake—particularly across genotypes and disease stages—remains unclear, reinforcing the presence of a diagnostic "grey zone."

There was consensus that ATTRv should be approached as a systemic disease rather than as isolated neuropathy or cardiomyopathy. This perspective has implications for how early disease is defined and when treatment should be initiated.

- **Incidental Genetic Findings and Gene Panel Expansion**

An important issue raised concerned incidental findings from broad gene panels. Cases were described in which young patients with suspected sarcomeric hypertrophic cardiomyopathy were found to carry a p.Val142Ile TTR variant. This posed complex interpretative challenges, particularly when phenotypes were atypical of amyloidosis.

The discussion underscored the need for:

- Careful genotype–phenotype correlation.
- Improved interpretation frameworks for incidental TTR findings.
- Possible refinement of gene panels in specific clinical contexts to reduce diagnostic ambiguity.

Participants noted that as whole-genome and panel testing become more widespread, such scenarios are likely to increase.

- **Early Diagnosis and Reimbursement Implications**

A question from the audience addressed how emerging early diagnostic tools—particularly structured clinical tools such as standardized neurological assessment frameworks—could influence reimbursement policies.

It was acknowledged that many healthcare systems currently restrict access to disease-modifying therapies to patients with clearly symptomatic disease. The challenge is demonstrating that earlier biological markers (e.g., imaging abnormalities, biomarkers, autonomic dysfunction, skin amyloid deposition) reliably predict clinical progression.

Participants emphasised that reimbursement decisions will likely require:

- Prospective validation of early biomarkers.
- Evidence that these markers predict symptomatic conversion.
- Data demonstrating that early intervention improves long-term outcomes.

Without such predictive validation, payers may remain reluctant to authorise treatment in pre-symptomatic or minimally symptomatic individuals.

- **Systemic Disease Concept and Organ-Based Licensing**

A broader conceptual concern emerged regarding the current regulatory framework, in which therapies are licensed separately for neuropathy or cardiomyopathy despite identical pathophysiology. Several participants expressed concern that organ-specific licensing risks fragmented care and may delay treatment in patients with mixed or evolving phenotypes.

The discussion reinforced the importance of multidisciplinary collaboration and comprehensive monitoring across organ systems.

- Monitoring and Multimodal Assessment

There was agreement that neither cardiology nor neurology currently has a definitive answer regarding:

- The earliest detectable marker of disease.
- The optimal schedule for surveillance in gene carriers.
- The relative utility of imaging versus circulating biomarkers.

Participants acknowledged that different centres possess expertise in different modalities (e.g., DPD imaging, skin biopsy, neurofilament assays, MRI), and few studies systematically compare these approaches head-to-head in the same population.

The importance of collaborative, prospective, multimodal studies was emphasised as a vital research priority.

Emerging diagnostic and monitoring tools for ATTRv neuropathy – Mary M. Reilly

ATTRv peripheral neuropathy: phenotype and diagnostic challenges

Mary M. Reilly is Professor of Neurology and Head of the Department of Neuromuscular Diseases at the UCL Queen Square Institute of Neurology, London. She is an internationally recognised expert in inherited peripheral neuropathies and amyloid neuropathies, with a longstanding focus on the clinical characterisation, diagnosis, and natural history of hereditary transthyretin amyloidosis. In her presentation "Emerging diagnostic and monitoring tools for ATTRv neuropathy", she addressed emerging diagnostic tools for ATTRv neuropathy, emphasising early detection across the disease spectrum—from asymptomatic gene carriers to treated patients—and highlighted the role of advanced neurophysiology, skin biopsy, biomarkers, and imaging in refining diagnosis and monitoring disease progression in this multisystem condition.

ATTRv-PN was discussed as a length-dependent, predominantly axonal neuropathy with early small-fibre involvement, frequently accompanied by autonomic dysfunction. Neuropathic pain, altered thermal and pain perception, sensory loss, imbalance, and progressive weakness were highlighted as typical features, often preceded or accompanied by autonomic symptoms such as orthostatic hypotension, gastrointestinal dysmotility, erectile dysfunction, and weight loss. Importantly, carpal tunnel syndrome—particularly when bilateral—was emphasised as a frequent early manifestation, sometimes preceding overt neuropathy by several years.

The diagnostic complexity of ATTRv-PN was illustrated through several clinical scenarios, including undiagnosed neuropathy, early symptomatic disease in known gene carriers, and neuropathy developing in patients initially presenting with ATTRv cardiomyopathy (e.g., T80A or V142I variants). Red flags prompting consideration of amyloid neuropathy include painful small-fibre onset, autonomic involvement in the absence of diabetes, prior carpal tunnel syndrome, cardiomyopathy with conduction disease or arrhythmia, unexplained weight loss, family history, and specific ethnic backgrounds.

Current diagnostic practice remains heterogeneous. In selected contexts—such as early-onset p.V50M with a typical phenotype and strong family history—tissue confirmation may not always be required. In contrast, in later-onset disease, mixed phenotypes, or in patients with confounding comorbidities (e.g., diabetes), demonstration of amyloid deposition (most commonly via skin biopsy) was emphasised as critical to diagnostic certainty.

Tools for early and pre-symptomatic detection

A major focus of the presentation was the challenge of detecting neuropathy at its earliest stages, particularly in asymptomatic or minimally symptomatic TTR variant carriers. Traditional clinical scales (e.g. NIS, CMTNS) and nerve conduction studies remain central but may lack sensitivity for early disease. Quantitative sensory testing (QST), autonomic function testing, and skin biopsy were discussed as complementary tools, particularly for identifying small-fibre and autonomic involvement.

Skin biopsy data presented showed that reduced intraepidermal nerve fibre density is highly prevalent even at very early stages, and that intracutaneous amyloid deposition in presymptomatic carriers is associated with subsequent deterioration in nerve conduction parameters (41).

Blood biomarkers were highlighted as an attractive, minimally invasive approach. Neurofilament light chain (NfL) levels correlated with disease severity and stage across multiple ATTRv cohorts, with proposed thresholds distinguishing asymptomatic carriers from symptomatic individuals and predicting conversion over time (42). However, the lack of disease specificity of NfL - now known to be elevated in numerous neurological conditions - was underscored, necessitating cautious interpretation and use in conjunction with clinical and other biomarker data.

Advanced imaging techniques are emerging as additional objective markers. Quantitative muscle MRI demonstrates progressive fatty infiltration in length-dependent neuropathies, including ATTRv-PN (43). Nerve MRI and ultrasound reveal nerve enlargement and signal abnormalities in both symptomatic patients and carriers. These modalities may offer valuable tools for longitudinal monitoring, although their precise role in routine clinical practice remains to be defined.

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ATTRv as a systemic disease: implications for CNS involvement

Beyond peripheral nerve involvement, ATTRv amyloidosis was consistently emphasised as a systemic disorder with potential CNS manifestations, including progressive cognitive impairment, seizures, ataxia, spasticity, and stroke-like episodes. These features, although less common than peripheral neuropathy or cardiomyopathy, highlight the limitations of a purely peripheral or cardiac disease model. The persistence of CNS amyloid deposition despite liver-targeted therapies was noted as a key biological consideration, reinforcing the need for vigilance regarding neurological symptoms beyond the peripheral nervous system.

Future directions and unmet needs

Key unanswered questions include the optimal screening schedule and combination of tools for early diagnosis in TTR variant carriers, the relative value of skin biopsies versus blood biomarkers and imaging, and whether diagnostic strategies should be tailored to specific genotypes or populations. Additionally, as disease-modifying therapies are increasingly used earlier, defining reliable markers of treatment response and indicators for therapy escalation remains a priority.

Round Table 1: Patient unmet needs and expectations regarding diagnosis and treatments – accelerating early and accurate diagnosis across Europe

Round Table 1 focused on the challenges and unmet needs related to the diagnosis, genetic testing, and long-term management of transthyretin amyloidosis (ATTR), with the explicit aim of informing a workshop paper on future research. The discussion was framed around three overarching objectives: clarifying patient needs and expectations, proposing a shared diagnostic workflow applicable across Europe, and defining minimal standards for treatment and follow-up.

The session was opened by Davide Pareyson, who outlined the scope of the workshop and highlighted key areas for discussion, including patient-centred expectations, the role of national genomic screening programs, cascade family testing, diagnostic guidelines, and structured systems to raise clinical suspicion. He identified three priority areas requiring further work: clear definitions and standards for genetic counselling, optimal monitoring strategies for asymptomatic carriers, and the potential role of biomarkers such as neurofilament light chain in early detection and follow-up.

Mary Reilly raised concerns about an emerging and increasingly common scenario: patients arriving at specialist clinics with a genetic diagnosis obtained through direct-to-consumer or non-traditional testing pathways, often without appropriate medical supervision or counselling. This shift challenges established diagnostic pathways and raises questions about how healthcare systems should adapt to ensure clinical interpretation, counselling, and follow-up are not bypassed.

The discussion then addressed who should initiate genetic testing. While neurologists have traditionally served as gatekeepers, some participants argued that other specialists—such as hand surgeons who encounter amyloid deposits during carpal tunnel surgery—could play a role in initiating testing, provided that appropriate patient information and referral pathways are in place. This led to recognition of substantial heterogeneity across countries. For example, in some settings, neurologists must refer patients to specialised genetics departments for predictive testing, whereas cardiologists may operate under different regulatory frameworks.

Genetic counselling emerged as a central theme. It was emphasised that counselling is a process of communication, not merely a technical step linked to testing. Concerns were raised about the inappropriate use of diagnostic test kits—particularly if provided without structured counselling—for cascade testing within families, which may generate conflict or distress when results are shared without adequate support. The role of pre-implantation genetic diagnosis was also discussed, reflecting evolving therapeutic landscapes and ethical considerations.

From the patient's perspective, issues related to family testing, psychological burden, and potential implications for insurance and employment were discussed. While several clinicians noted that insurability concerns appear to be diminishing as ATTR becomes a treatable disease, the need for clear guidance and reassurance for patients and families was acknowledged.

A persistent and unresolved challenge highlighted during the discussion was the diagnosis of sporadic cases. Participants noted that diagnostic delays in ATTR have changed little over decades, underscoring the need for improved education beyond neurology and cardiology, particularly among gastroenterologists and primary care physicians. Screening strategies based on carpal tunnel syndrome were debated extensively. Given the very high volume of carpal tunnel surgeries performed annually in some countries, universal screening was considered impractical, and it was stressed that the presence of amyloid in tissue does not automatically equate to systemic amyloidosis.

Antonio Atalaia proposed leveraging federated learning approaches and registries to link disparate data sources, enabling large-scale phenotype analysis without compromising data privacy. It was also noted that ongoing guideline initiatives from major neurological societies should be closely aligned with any recommendations emerging from this workshop to avoid fragmentation.

The round table concluded with a discussion of homozygous ATTRv patients, during which contrasting experiences were reported. Some cohorts, such as Swedish patients with homozygous p.Val50Met, were described as not showing clearly increased disease severity, whereas other populations appeared to exhibit more aggressive phenotypes. This variability was identified as an important area for future collaborative research. Final points addressed the management of incidental genetic findings, particularly in younger individuals, and the need for age-adapted recommendations for monitoring carriers.

In closing, key action points were summarised:

- Improving approaches to pre-symptomatic diagnosis
- Systematic collection of homozygous, compound heterozygous, and heterozygous case data.
- Development of a minimal core dataset for early diagnosis and longitudinal follow-up.
- Creation of a standardised, implementable "common core" protocol for participating centres.
- Exploration of federated learning strategies to integrate registry data.
- Formulation of monitoring recommendations for young individuals identified as TTR mutation carriers.
- Patient-centred strategies to accelerate accurate diagnosis and optimise care across Europe.

Overview of Current Therapies and Indications

The role of Stabilisers: evidence base, indications and limitations – Juan Gonzalez Moreno

Dr Juan González-Moreno is an Internal Medicine Physician based in Mallorca, Spain, with recognised expertise in hereditary transthyretin amyloidosis (ATTRv). His clinical and academic work focuses on the diagnosis, longitudinal management, and phenotypic characterisation of patients with TTR-related neuropathy, with particular attention to early detection strategies and genotype–phenotype correlations. He presented a structured overview of transthyretin (TTR) stabilisers in hereditary transthyretin amyloidosis (ATTRv), focusing on mechanistic rationale, clinical trial evidence, responder profiles, safety considerations, and therapeutic positioning within the evolving treatment landscape.

Mechanistic considerations

The presentation emphasised that tetramer dissociation is the rate-limiting step in TTR amyloidogenesis. Stabilisers act by binding to the thyroxine-binding sites of the TTR tetramer, thereby preventing dissociation into amyloidogenic monomers (44).

Key mechanistic insights included:

- Occupation of a single thyroxine-binding site can be sufficient to stabilise the tetramer.
- Clinical efficacy depends not only on intrinsic binding potency but also on relative affinity for TTR versus albumin and on achieved plasma concentrations.
- Tafamidis 20 mg achieves approximately 96% plasma TTR stabilisation, although interindividual variability in drug exposure has been observed. Monitoring of plasma levels may become clinically relevant in the future.
- Tafamidis appears to increase circulating native TTR rather than total TTR, consistent with a pharmacological chaperone effect.
- Diflunisal has lower intrinsic potency, but this is compensated by higher dosing. It lacks central nervous system (CNS) penetration; however, its safety profile has proven manageable.
- Acoramidis demonstrates high intrinsic potency but requires twice-daily dosing due to its shorter half-life and bioavailability profile.

Neuropathy phenotype

Tafamidis

The 2012 pivotal neuropathy trial (45) demonstrated that tafamidis slowed disease progression as measured by Neuropathy Impairment Score (NIS), modified BMI, and quality-of-life endpoints. However, disease progression was not halted, and a proportion of patients transitioned to liver transplantation during follow-up.

Benefit was most pronounced in early-onset p.Val50Met disease and in patients with low baseline NIS. Late-onset V30M patients showed attenuated response.

Real-world data (46) suggest a consistent response distribution, with approximately one-third of patients classified as full responders, one-third as partial responders, and one-third as non-responders. Predictors of better response include female sex, early disease stage, and baseline NIS <15.

Dose considerations were discussed. While 20 mg remains the approved neuropathy dose, some data suggest that higher exposure (61 mg) may be necessary in certain variants or in male patients. Tafamidis 20 mg—the neuropathy dose—was shown to slow but not halt progression, with the strongest effects in early-onset p.Val50Met disease and in women with low baseline NIS. Real-world data suggest that only ~30–40% of patients are full responders, with another third partial responders. The question of dose optimisation remains open (47).

Diflunisal

The diflunisal trial (48), which enrolled an older, more advanced cohort than the tafamidis study, demonstrated slowed progression comparable to that of tafamidis. These findings support its utility even in later-stage disease.

Real-world safety data confirm acceptable tolerability:

- Renal function declines comparable to placebo in controlled studies.
- Low gastrointestinal complication rates when co-administered with proton pump inhibitors (PPIs).

Acoramidis

Although acoramidis is a potent stabiliser, neuropathy-specific clinical data are not yet available. Its role in ATTRv neuropathy, therefore, remains to be defined.

CNS and Ocular phenotypes

Tafamidis has been shown to penetrate cerebrospinal fluid (CSF) and vitreous humour at concentrations theoretically sufficient for stabilisation. Case reports indicate increased CSF-to-serum TTR ratios following treatment. However, the clinical relevance of this finding remains uncertain. The potential benefit of higher dosing for CNS manifestations remains hypothetical.

Diflunisal does not meaningfully penetrate the CNS.

Tolcapone was discussed as a potential future option for leptomeningeal variants due to its CNS penetration, although further clinical evidence is required.

Positioning of stabilisers in the therapeutic algorithm

The expert discussion addressed the role of stabilisers relative to TTR gene silencers.

Points raised included:

- Limited CNS engagement remains a concern for currently available stabilisers.
- Some participants expressed caution regarding global TTR silencing, given TTR's physiological functions in retinol and thyroxine transport.
- Stabilisers may be particularly appropriate in:
    - Very early p.Val50Met disease.
    - Selected asymptomatic carriers with documented systemic deposits.
    - Mixed phenotypes, as reported in Swedish clinical experience.
- The presence of motor involvement or more aggressive variants should prompt consideration of gene-silencing therapies.

Conclusions

Dr González-Moreno concluded that TTR stabilisers remain an important therapeutic option in ATTRv, particularly in early-stage disease and selected genotypes. Their principal limitations include incomplete arrest of progression, interindividual variability in response, and limited CNS engagement.

Outstanding questions include optimal dosing strategies, identification of responders, potential combination approaches, and the role of next-generation or CNS-penetrant stabilisers.

The session reinforced that stabilisers continue to occupy a defined but phenotype-dependent position within the contemporary ATTRv treatment framework.

Gene silencers: efficacy, safety, and eligibility by phenotype – Isabel Conceição

Gene silencers (patisiran, vutrisiran, inotersen, eplontersen)

In the discussion on gene-silencing therapies for transthyretin amyloidosis (ATTR), Dr Isabel Conceição emphasised that these agents act upstream in the disease process by directly reducing hepatic transthyretin (TTR) production. Since the liver produces the vast majority of circulating TTR, suppressing TTR mRNA markedly lowers the substrate available for amyloid formation.

Particular attention was given to the different delivery platforms used to achieve gene silencing. Lipid-nanoparticle–delivered siRNA, exemplified by patisiran, was presented as the first effective RNA-interference therapy, achieving substantial TTR knockdown but requiring intravenous infusions and premedication. Newer approaches rely on GalNAc-conjugated siRNA, which enables targeted uptake by hepatocytes after subcutaneous administration. The leading example, Vutrisiran, demonstrated robust TTR reduction and strong clinical efficacy while offering a convenient dosing schedule of one subcutaneous injection every three months. It is now approved for both hATTR polyneuropathy and ATTR cardiomyopathy.

The workshop also addressed antisense oligonucleotide therapies. While inotersen proved effective in slowing neuropathy progression, its use has been limited by the need for regular platelet and renal monitoring due to safety concerns. A next-generation antisense therapy, eplontersen, incorporates GalNAc targeting and appears to avoid these complications, potentially improving the practicality of this class. In the NEURO-TTRansform trial, eplotersen halted disease progression and improved quality of life.
Overall, gene silencers were presented as highly effective therapies, consistently achieving high TTR reductions via a mechanism distinct from that of tafamidis. In indirect comparisons, they generally show stronger effects on neuropathy outcomes, although the magnitude of cardiac benefit appears to depend on the stage of cardiomyopathy at the time of treatment initiation.

Choosing between stabilisers and silencers

Experts debated whether stabilisers should still be used in very early p.V50M disease (including asymptomatic carriers with documented deposits), while silencers should be preferred once any motor involvement appears. On the other hand, effective treatment could be considered "delayed" by the time motor findings emerge. Both genotype and phenotype were emphasised as crucial determinants. Some clinicians highlighted good outcomes with tafamidis, even in mixed phenotypes, while others questioned the mutation-specific stability and cleavage properties that may limit the stabilisers' efficacy.

Treatment response monitoring: clinical and paraclinical tools – Davide Pareyson

Davide Pareyson reviewed existing proposals for standardised monitoring of ATTRv (49–55). Due to therapy-modified disease trajectories, defining progression and non-response remains challenging. NIS and modified NIS+7 remain core measures but are affected by nonlinearity, unlike RODS, which provides linear scaling. Neurophysiological, skin biopsy, and imaging assessments (muscle MRI, peripheral nerve ultrasound) provide objective measures but vary in accessibility. Biomarkers—particularly serum TTR levels and NfL—are emerging as vital tools for tracking biological responses. Cardiac monitoring benefits from more established frameworks and biomarkers. Experts agreed on the need for a minimal, globally harmonised monitoring protocol, ideally with evaluations every 6–12 months, tailored to the aggressiveness of the mutation.

The session ended by highlighting the need to unify treatment algorithms, re-evaluate phenotype-based drug positioning, and define meaningful change thresholds for both clinical practice and research.

Round Table 2: Optimising therapy selection in real-life patients

Round Table 2 addressed the practical challenges clinicians face when selecting and monitoring therapy for hereditary transthyretin amyloidosis (ATTRv) in routine practice. The discussion focused on treatment sequencing, monitoring strategies, and the development of a robust registry infrastructure to support long-term outcome analyses across Europe. Two key clinical questions guided the exchange: how to determine the most appropriate first-line therapy and how best to monitor disease progression, particularly in patients with polyneuropathy.

At the beginning of the session, the moderator highlighted the significant uncertainty still surrounding therapeutic decision-making in ATTRv. The choice of treatment depends on various factors, including phenotype, genotype, disease stage, and differences in drug availability and reimbursement across countries. Although upcoming EAN/PNS guidelines are expected to provide structured recommendations, current clinical practice remains varied, and expert consensus remains vital for guiding real-world decisions.

Monitoring strategies formed a central part of the discussion. Participants highlighted the need to define a minimal core monitoring protocol that could be implemented across centres regardless of resources. Particular attention was given to circulating transthyretin levels and neurofilament light chain as potential biomarkers for patients receiving gene-silencing therapies. In centres where these measurements are not yet routinely available, speakers recommended storing biological samples to allow future retrospective analysis as biomarker assays become more widely accessible. The importance of multidisciplinary follow-up—integrating neurological, cardiological, and systemic assessments—was repeatedly underscored.

A substantial portion of the session addressed the role of real-world registries in improving understanding of long-term treatment outcomes. The moderator proposed that the ERN registry could serve as a platform for harmonised data collection extending beyond reference centres, potentially incorporating biorepositories to support biomarker research. However, participants acknowledged that registry participation imposes a significant workload on high-volume centres and stressed that any expansion must be accompanied by clearly defined objectives and incentives to maintain engagement.

Industry representatives confirmed that several real-world initiatives are currently underway, including observational programmes such as MaesTTRo and retrospective analyses such as OverTTuRe. Nevertheless, speakers noted the absence of coordinated post-marketing surveillance systems for disease-modifying therapies outside clinical trial extensions. This gap limits the ability to assess long-term effectiveness and safety, reinforcing the need for registries built around a small set of standardised core data fields to enable meaningful comparison and federated analyses across datasets.

The discussion also addressed data interoperability across European Reference Networks. Participants highlighted that ERN registries already share a set of common European Commission–defined variables and follow FAIR data principles, allowing data exchange and federated analysis even when disease-specific registries differ in structure. However, speakers argued that the community must first identify a limited set of high-priority scientific questions—such as predictors of disease conversion or early markers of treatment response—before deciding whether existing registries are sufficient or new infrastructure is required.

Later in the session, complex clinical cases were presented to illustrate the heterogeneity of ATTRv. One case involved a patient with extensive systemic amyloid deposition and severe central nervous system involvement who developed acute encephalitis-like deterioration during treatment. The discussion highlighted the difficulty of distinguishing disease progression from potential treatment-related complications and underscored the limitations of current monitoring tools in patients with aggressive multisystem phenotypes. Participants agreed that structured case reporting remains essential for improving awareness and informing future guideline development in such rare presentations.

The session concluded with a brief reflection on terminology in ATTRv classification. Participants noted the ambiguity associated with terms such as “primary” and “secondary” manifestations and suggested that phenotype-based descriptors—such as neuropathy-predominant, cardiomyopathy-predominant, or leptomeningeal-predominant disease—might provide greater clarity and align with classification approaches used in other forms of amyloidosis.

Overall, the round table highlighted several priorities for the field: establishing a feasible consensus monitoring protocol, strengthening participation in real-world registries, improving interoperability across ERN databases, and developing the infrastructure needed for future biomarker-driven and federated analyses. These efforts were widely viewed as essential steps toward optimising therapy selection and improving long-term management of patients with ATTRv in real-world clinical settings.

Sequencing of therapies, combination therapies and other novelties

The opening session of the second workshop day, moderated by João Costa and Mary Reilly, focused on the rapidly evolving therapeutic landscape for transthyretin (ATTR) amyloidosis, with emphasis on treatment sequencing, emerging therapeutic modalities, and the potential role of combination strategies.

Emerging therapies: ASO innovations, gene editing and antibodies – L. Obici

Next-Generation RNA Interference Therapies

Laura Obici reviewed the continued evolution of RNA interference–based therapies targeting hepatic production of transthyretin. While currently approved silencers have demonstrated robust reductions in circulating transthyretin levels, newer molecules aim to further improve potency, durability, and safety.

One example discussed was nucresiran, a next-generation siRNA currently in phase III clinical development. The molecule incorporates several incremental chemical modifications—including 2'-O-methyl and 2'-fluoro ribose substitutions as well as a phosphorothioate backbone—to enhance molecular stability and reduce susceptibility to nuclease degradation. These modifications also appear to reduce immunogenicity while allowing less frequent dosing. Preliminary data suggest that a 300 mg dose given every six months can maintain transthyretin suppression above 90% for at least 180 days. Two ongoing studies, TRITON-PN and TRITON-CM, are assessing the clinical effects of this agent in neuropathy and cardiomyopathy types. In these trials, vutrisiran is used as a biochemical comparator rather than a direct randomised control, reflecting the ethical issues associated with placebo-controlled designs in a therapeutic setting where disease-modifying treatments are already available (56).

Gene Editing Approaches

The presentation also addressed gene-editing therapies based on CRISPR/Cas9 technology, focusing on NTLA-2001, which targets the transthyretin gene within hepatocytes to achieve permanent suppression of protein production. Early phase clinical studies have demonstrated substantial and durable reductions in circulating transthyretin, with average suppression levels approaching 90%. Initial clinical observations suggested potential neurological improvement in some patients, raising the possibility that a single administration could provide long-term disease control. Such a strategy would represent a paradigm shift in the management of ATTR amyloidosis, transforming treatment from chronic therapy into a one-time intervention. However, recent safety concerns have significantly affected the development of this approach. Several cases of severe hepatic adverse events occurred during the MAGNITUDE trials, including one fatal case. These events appeared roughly four to five weeks after infusion, suggesting a delayed immune-mediated hepatic injury rather than immediate toxicity. As a result, the trials were suspended globally while regulatory and mechanistic reviews were conducted. This episode highlights both the transformative potential and the important safety considerations associated with permanent gene-editing therapies (57).

Antibody-Mediated Amyloid Clearance

Another emerging therapeutic strategy involves monoclonal antibodies that bind misfolded transthyretin and facilitate the removal of deposited amyloid fibrils. This approach aims not only to stop further deposition but also to reverse existing tissue damage.

Two antibodies were discussed in detail. Coramitug (PRX004) recognises both circulating misfolded transthyretin species and deposited fibrils. Early-phase clinical studies have shown stabilisation of neuropathy impairment scores along with signals of cardiac improvement (58). A second agent, Cliramitug (Alexion 2220), is highly selective for fibrillar transthyretin (59). Phase I data have shown significant reductions in myocardial amyloid burden, as measured by DPD scintigraphy and extracellular volume (ECV) metrics on cardiac MRI. The therapy has generally been well tolerated, although mild adverse events such as arthralgia and occasional thrombocytopenia have been observed.

Additional approaches in development include Atralus AT-02 (60), a peptide–antibody fusion molecule designed to broadly bind amyloid deposits and promote macrophage-mediated clearance. These strategies aim to address a core limitation of current therapies: although transthyretin production can be effectively suppressed, the removal of existing amyloid deposits remains slow and incomplete.

Discussion of Emerging Therapeutic Strategies

Following the presentation, participants engaged in an extended discussion focusing on scientific, clinical, and methodological challenges associated with novel therapies.

One major topic concerned the ethical complexities of placebo-controlled trials in ATTR cardiomyopathy. Because tafamidis is widely available as standard therapy, withholding treatment in randomised studies raises ethical concerns, prompting alternative trial designs that rely on historical controls or active comparators.

Another point of discussion was the interpretation of neurological outcomes within cardiomyopathy-focused trials. Many patients exhibit mixed phenotypes, making it difficult to determine whether neurological changes reflect true therapeutic effects or natural disease variability.

The issue of anti-drug antibodies (ADAs) was also raised. Some patients receiving biological therapies develop antibody responses that may increase circulating transthyretin levels or reduce therapeutic efficacy. These responses are sometimes transient but may complicate the interpretation of biochemical endpoints.

Participants also considered the capacity of antibody therapies to remove amyloid from peripheral nerves. Compared with the heart, peripheral nerves contain a lower amyloid burden and are protected by the blood–nerve barrier, which may limit antibody penetration. Consequently, the effectiveness of clearance strategies in neuropathic disease remains uncertain.

Concerns about the potential arrhythmogenic effects of rapid cardiac amyloid removal were also discussed. Although theoretically plausible, no clear safety signals suggesting increased arrhythmia risk have been observed in early clinical studies.

Finally, several experts emphasised the limited understanding of transthyretin physiology within the central nervous system. Most current therapies—including RNA silencers and experimental therapies like monoclonal antibodies—do not cross the blood–brain barrier. The potential consequences of removing amyloid from CNS structures, as well as the long-term effects of significant systemic transthyretin suppression, remain largely unknown.

Combination therapies: scientific rationale, feasibility, and potential synergy – K. Hahn

Background and Rationale

Combination therapy is emerging as a potential next step in the treatment of transthyretin (TTR) amyloidosis, given that different therapeutic classes act at distinct stages of the amyloid cascade. During the workshop, Katrin Hahn presented a pathophysiological framework illustrating how currently available and emerging therapies target complementary steps in disease progression.

Within this framework, therapeutic strategies can be categorised according to their mechanism of action:

1. Gene silencers and gene editing approaches reduce hepatic production of TTR protein.
2. TTR stabilisers prevent tetramer dissociation into monomers, a key step in amyloid formation.
3. Disruptors and antibody-based therapies aim to promote clearance of existing amyloid deposits.

The rationale for combining therapies is a result of clinical observations in trials of RNA interference–based silencers, in which approximately half of treated patients show clear neurological improvement, while others show only stabilisation or continued progression. This variability suggests that differences in the biological capacity to clear existing amyloid deposits may influence treatment response.

Consequently, combining production-reduction therapies with clearance-enhancing strategies may provide additional benefit in patients whose endogenous amyloid removal mechanisms are limited.

Current Evidence and Knowledge Gaps

Despite strong mechanistic justification, clinical evidence supporting combination therapy remains limited.

- ***Polyneuropathy***

At present, no randomised clinical trials have specifically evaluated combination therapy for transthyretin amyloid polyneuropathy (PNP). Most existing studies have examined single therapeutic classes in isolation.

- ***Cardiomyopathy***

Evidence from transthyretin amyloid cardiomyopathy studies provides preliminary insights. The HELIOS-B study (39) reported suggestive, non-randomised findings indicating potential incremental benefit from combining:

- Tafamidis (stabiliser)
- Vutrisiran (gene silencer)

The observed benefit appeared particularly notable in patients younger than 75 years. However, these findings should be interpreted cautiously because the combination therapy analysis was not randomised and may therefore be influenced by selection bias.

For completeness, some participants also mentioned the trial CARDIO-TTRansform, which includes more than 1,400 patients and evaluates eplontersen in a population representative of current clinical practice (61). The results, however, are still unpublished but seem encouraging.

- ***Central Nervous System Involvement***

A key theme of the presentation was the increasing recognition of central nervous system (CNS) involvement in transthyretin amyloidosis. Emerging evidence suggests that CNS pathology may occur earlier and more frequently than previously appreciated. A major limitation of current therapies is that RNA interference–based silencers do not cross the blood–brain barrier, leaving TTR production in cerebrospinal fluid (CSF) largely unaffected.

Among candidate agents capable of addressing this gap, Tolcapone was highlighted because it crosses the blood–brain barrier and has demonstrated TTR-stabilising properties within the CNS (62). Nevertheless, its clinical use is constrained by the risk of hepatotoxicity, necessitating careful safety monitoring.

Economic Considerations

While combination therapy offers a compelling mechanistic strategy, the associated costs represent a major barrier to widespread implementation. Current disease-modifying therapies for transthyretin amyloidosis are already among the most expensive treatments in neurology and cardiology. Combining two or more agents could result in annual treatment costs exceeding several hundred thousand euros per patient, depending on national pricing and reimbursement frameworks. This economic challenge highlights the need for cost-effectiveness modelling and healthcare policy planning if combination strategies are to become clinically feasible.

Extended Panel Discussion

The extended panel discussion that followed the presentation broadened the perspective on the future role of combination therapy.

- ***The importance of individualised treatment***

Clinicians emphasised the substantial heterogeneity observed among patients with transthyretin amyloidosis. Some individuals experience significant improvement with relatively modest TTR suppression, whereas others continue to deteriorate despite reductions in circulating TTR levels exceeding 80%.

These observations reinforce the need to identify biomarkers and clinical predictors of therapeutic response. Real-world datasets such as the MAESTRO Registry were highlighted as valuable tools for analysing treatment outcomes and understanding inter-patient variability.

- ***Investigator-led clinical trials***

A major obstacle to combination therapy research is the difficulty of coordinating trials involving drugs developed by different pharmaceutical companies. As a result, workshop participants emphasised the importance of investigator-initiated studies led by academic consortia. Proposed initiatives include a European randomised controlled trial comparing standard therapy with combination regimens, and trials specifically addressing CNS disease manifestations, including adjunctive therapies targeting central TTR production or stabilisation.

- ***Addressing the CNS treatment Gap***

CNS pathology represents a growing clinical challenge as patient survival improves with peripheral disease control. Because current silencers do not reach the central nervous system, patients may develop leptomeningeal amyloidosis or CSF TTR pathology despite effective suppression of hepatic TTR synthesis. Developing therapies capable of targeting CNS TTR production or stabilising TTR within the CSF was therefore identified as a priority research area.

Proposed Action Items

Participants identified several strategic priorities for advancing the field:

- Develop investigator-initiated European clinical trials evaluating combination therapy approaches, including silencer–stabiliser combinations and regimens incorporating CNS-active agents.
- Improve disease phenotyping and biomarker development to better understand amyloid clearance mechanisms and predict treatment response.
- Continue long-term safety monitoring of emerging gene-editing therapies, particularly following recent reports of hepatic adverse events.
- Accelerate research into therapies capable of penetrating the central nervous system, including repurposed agents such as tolcapone and next-generation stabilisers.
- Expand the use of real-world registries to analyse treatment patterns and outcomes associated with combination therapy.

- Develop health economic models to evaluate the long-term sustainability and global accessibility of multi-drug treatment strategies.

Conclusion

The workshop session highlighted a rapidly evolving therapeutic landscape in transthyretin amyloidosis, in which multiple drug classes—including gene silencers, gene-editing approaches, stabilisers, and antibody-based therapies—are converging toward potentially synergistic treatment strategies.

Although the biological rationale for combination therapy is compelling, the clinical evidence base remains limited. Key challenges include designing robust clinical trials, the high cost of multi-drug regimens, and the need to personalise treatment based on patient-specific disease mechanisms.

Participants concluded that meaningful progress will depend on collaborative, investigator-led research initiatives and a deeper understanding of amyloid-clearance biology and the central nervous system involvement in transthyretin amyloidosis.

Switching or combining treatments– C. Campos

Background and Rationale

Catarina Campos, from the Hereditary Amyloidosis Reference Centre at ULSSM-Santa Maria Hospital in Lisbon, outlined the principal clinical scenarios that prompt treatment switching in ATTR amyloidosis. These include:

- Inadequate clinical response, defined by continued disease progression despite therapy
- Adverse events or safety concerns
- Treatment burden and route of administration
- Evolution of disease phenotype (e.g., development of cardiac involvement in predominantly neuropathic disease)

These factors reflect the dynamic nature of ATTR amyloidosis and underscore the need for individualised, adaptive therapeutic strategies.

Evidence Supporting Switching Strategies

- ***From TTR Stabilisers to Gene Silencers***

Catarina Campos presented real-world evidence supporting the switch from tafamidis to patisiran in patients with ATTR polyneuropathy exhibiting disease progression. Data from two observational cohorts [France (63) and the Iberian Peninsula-Portugal and Menorca (64)] consistently demonstrated a significant reduction in the annual rate of progression of the Neuropathy Impairment Score (NIS) following transition to patisiran. In both studies, patients experienced slower neurological deterioration after switching, with additional improvements observed in specific clinical domains such as autonomic symptoms. These findings support the biological rationale that gene silencing, by reducing TTR production, may offer greater disease control in patients insufficiently responsive to TTR stabilisation.

- ***Switching between Gene Silencers***

Evidence was also presented for switching between gene-silencing agents. Data from clinical trials and extension studies indicate that:

- Transition from inotersen to eplontersen is associated with maintained neurological stability and improved safety, particularly with respect to thrombocytopenia and improved nutritional state (65)
- Switching from patisiran to vutrisiran preserves therapeutic efficacy while simplifying administration (66)

These findings highlight the potential advantages of second-generation gene silencers, including reduced treatment burden and improved tolerability, which may enhance adherence and long-term outcomes.

Role of Disease Phenotype Evolution

A key point emphasised during the presentation was that ATTR amyloidosis is a progressive and phenotypically evolving disease. A substantial proportion of patients develop mixed phenotypes over time, necessitating reassessment of therapeutic strategy. For example, patients initially presenting with isolated polyneuropathy may later develop cardiomyopathy, potentially

favouring a switch to therapies with broader indications (67). This reinforces the importance of continuous monitoring and a multidisciplinary approach to management.

Combination Therapy: Rationale and Current Evidence

The theoretical rationale for combining a TTR stabilizer with a gene silencer is compelling, given their complementary mechanisms of action. However, Campos highlighted that current clinical evidence remains limited and inconclusive.

Available data suggest(68)(69)(70):

- No clear superiority of combination therapy over gene-silencer monotherapy in small neuropathy cohorts
- Non-significant trends toward reduced mortality and cardiovascular events in long-term extension studies
- No significant mortality benefit after adjustment in real-world analyses

Importantly, combination therapy is associated with substantially higher costs, raising questions about its economic sustainability in the absence of a clear clinical benefit.

Monitoring and Decision-Making

During the roundtable discussion, participants emphasised that treatment decisions—particularly switching—should be based on comprehensive, longitudinal assessment rather than on isolated measures.

Current practice typically involves:

- Regular evaluations (approximately every six months)
- Use of multidimensional outcome measures, including neurological scores, neurophysiology, and patient-reported outcomes
- Confirmation of progression over time before modifying therapy

There was broad consensus on the need to define a standardised core set of outcome measures that are both clinically meaningful and feasible in real-world settings.

Special Populations: Women of Childbearing Age

An important unmet need identified during the discussion is the lack of safety data for ATTR therapies in pregnancy. Current treatments are generally contraindicated or require extreme caution, as women of childbearing potential are sometimes underrepresented in clinical trials.

This limitation complicates therapeutic decision-making in younger patients and highlights the need for dedicated data collection and post-marketing surveillance.

Global Access and Equity Considerations

A substantial portion of the discussion addressed disparities in access to diagnosis and treatment. Many regions lack not only advanced therapies but also basic diagnostic tools such as genetic testing.

Proposed strategies to address these gaps included:

- Expansion of genetic testing programs
- International collaborations and partnerships
- Engagement with patient advocacy groups such as the Amyloidosis Alliance
- Development of humanitarian access programs

Despite these efforts, significant structural and economic barriers remain, particularly in low-resource settings.

Toward Standardised Outcome Measures

João Costa highlighted a critical gap in the field: the absence of standardised outcome measures to address key clinical questions about treatment sequencing and combination strategies.

He emphasised that:

- Current endpoints may not adequately capture clinically meaningful changes
- Real-world data will be essential to identify optimal treatment pathways
- The ATTR community is uniquely positioned to harmonise outcome measures across trials and clinical practice

The session concluded with a call to develop a feasible, consensus-based core outcome set to guide both research and routine care.

Conclusions

This session underscored that switching therapies—particularly from TTR stabilisers to gene silencers—is supported by emerging evidence and represents an important strategy in patients with disease progression. Switching between gene silencers appears safe and may improve convenience and adherence.

In contrast, combination therapy remains investigational, with insufficient evidence to justify routine use given its cost implications.

Ultimately, early diagnosis, regular multidimensional monitoring, and individualised treatment decisions remain central to optimising outcomes in ATTR amyloidosis. Future efforts should focus on generating robust comparative data, improving global access, and establishing standardised outcome measures to better inform clinical practice.

Round Table 3: Scientific and Economic Feasibility of Treatment Sequencing

This section summarises key themes and agreements from an international expert roundtable led by Mary Reilly and João Costa, which focused on the feasibility and rationale for treatment sequencing and addressed several unresolved clinical and systemic challenges in hereditary transthyretin amyloidosis (ATTRv). The discussion addressed five major domains: (i) prediction of response to tafamidis and other therapies, (ii) management of women of childbearing age, (iii) monitoring strategies for treatment response, (iv) the development of a core set of outcome measures, and (v) global inequities in access to diagnosis and treatment. The following text synthesises these discussions into a set of consensus principles and actionable recommendations intended to guide clinical practice, research priorities, and health policy.

Introduction

Hereditary transthyretin amyloidosis (ATTRv) is a progressive multisystem disorder associated with significant morbidity and mortality, primarily driven by neuropathic and cardiac involvement. The therapeutic landscape has evolved substantially with the introduction of transthyretin stabilisers and gene-silencing therapies. However, this expansion has introduced new complexities in treatment selection, monitoring, and long-term management.

Clinicians are now confronted with questions that extend beyond treatment initiation, including how to identify responders, when to modify therapy, and how to integrate emerging therapeutic strategies into routine care. These challenges are compounded by the lack of standardised outcome measures and significant disparities in access to care across regions.

This consensus statement reflects the collective perspectives of clinicians, researchers, industry representatives, and patient advocates and aims to provide a framework for addressing these challenges.

Predicting Treatment Response

Current evidence and clinical experience suggest that patients with very early-stage p.Val50Met disease, particularly those with mild neuropathy, are more likely to benefit from tafamidis. Female sex and, in some cohorts, higher transthyretin levels have also been associated with improved response, especially in p.Val50Met disease. However, these associations remain insufficiently robust for individual-level clinical decision-making.

Importantly, although there are studies exploring the use of amyloid deposits, reduced intraepidermal nerve density in skin biopsies, and NFL levels to predict disease conversion in asymptomatic carriers, there is insufficient data and no current consensus on the best markers. There is also no consensus on how to reliably identify treatment failure in treated patients. Analyses of transthyretin levels have not demonstrated consistent predictive value, and the absence of biological markers limits the ability to personalise therapy.

This uncertainty has significant implications as treatment options expand, particularly when considering early initiation of therapy or the use of gene-silencing agents.

Treatment in women of childbearing age

The management of women of childbearing potential remains a major unmet need. All currently available disease-modifying therapies for ATTRv lack adequate safety data in pregnancy due to systematic exclusion of this population from clinical trials. As a result, treatment discontinuation is generally recommended in the context of planned or confirmed pregnancy.

This approach introduces clinical risk, as interrupting therapy may lead to disease progression. Alternative strategies, including liver transplantation, have been considered in selected cases, but the need for long-term immunosuppression during pregnancy poses risks that must be weighed against this option. Limited discussion also addressed the potential use of diflunisal in early pregnancy under careful monitoring, although its availability and applicability are context-dependent.

The absence of prospective data in this population represents a critical gap that must be addressed through structured data collection and registry-based approaches.

Monitoring and treatment optimisation

Monitoring practices across centres are broadly aligned but remain heterogeneous in implementation. Patients are typically assessed at six-to twelve-monthly intervals using a combination of clinical examination, functional scales such as the Neuropathy Impairment Score (NIS), neurophysiological studies, and patient-reported outcomes.

A key point of agreement is that treatment decisions should not rely on a single parameter but rather on a multidimensional assessment of disease progression. In practice, clinicians often require consistent evidence of deterioration across multiple domains over at least 1 year before considering treatment modification.

However, the feasibility of such comprehensive monitoring is limited by resource constraints in many settings. This has led to recognition of the need for a pragmatic and standardised approach that balances clinical rigour with real-world feasibility.

Core Outcome Measures and Real-World Evidence

A central conclusion of the round table was the urgent need to define a standardised core set of outcome measures applicable across both clinical trials and routine clinical practice. As João Costa emphasised, current outcome measures are not adequately aligned with the clinical questions practitioners face, particularly regarding treatment switching and combination strategies.

Furthermore, the discrepancy between trial-based outcome measures and those used in real-world practice limits the translation of evidence into clinical decision-making. The development of a core outcome set represents a unique opportunity for the ATTR community, given the recent expansion of therapeutic options.

Real-world data will be essential to this effort, particularly for identifying treatment modifiers, understanding long-term outcomes, and informing personalised treatment strategies.

Global Access and Ethical Considerations

Significant disparities in access to diagnosis and treatment persist across regions. In many countries, patients lack access to genetic testing, specialised diagnostic infrastructure, and disease-modifying therapies. These inequities reflect a combination of economic, logistical, and systemic barriers.

Efforts to address these challenges include initiatives to expand genetic testing, build diagnostic capacity, and develop international collaborations. Patient advocacy organisations, including the Amyloidosis Alliance, play a critical role in facilitating these efforts and in fostering partnerships between stakeholders.

At the same time, ethical concerns arise when patients are diagnosed in settings where treatment is not available. The group emphasised that strategies to improve diagnosis should be accompanied by parallel efforts to ensure access to care, rather than being pursued in isolation.

Consensus Recommendations

1. 1. Prediction of Treatment Response

1.1. There is an urgent need to identify and validate biomarkers capable of predicting treatment response and disease progression.

1.2. Clinical predictors such as disease stage and phenotype should be used cautiously and should be used alongside the development of biological markers.

1.3. Longitudinal real-world data should be systematically collected to refine predictive models.

2. 2. Management of Women of Childbearing Age

2.1. Pregnancy registries should be established to collect prospective safety data on all ATTR therapies.

2.2. Women of childbearing potential should receive standardised counselling regarding treatment risks and uncertainties.

2.3. Alternative management strategies should be individualised and discussed within multidisciplinary teams.

3. 3. Monitoring and Treatment Optimisation

3.1. Treatment response should be assessed using a multidimensional approach incorporating clinical, neurophysiological, and patient-reported measures.

3.2. A minimum observation period of approximately 12 months should be considered before defining treatment failure, unless rapid progression occurs.

3.3. A minimum feasible monitoring protocol should be defined to ensure applicability across diverse healthcare settings.

3.4 There is a need to identify and validate biomarkers of treatment response

4. 4. Core Outcome Measures

4.1. The ATTR community should prioritise the development of a standardised core outcome set within the next 1–2 years.

4.2. Outcome measures should be clinically meaningful, sensitive to change, and feasible in routine practice.

4.3. Harmonisation between clinical trials and real-world practice should be actively pursued.

5. 5. Role of Real-World Data

5.1. Registries and observational studies should be expanded to capture long-term outcomes and treatment patterns.

5.2. Real-world data should be used to inform decisions on treatment sequencing, switching, and combination strategies.

6. 6. Global Access to Diagnosis and Treatment

6.1. Efforts to expand genetic testing and diagnostic capacity should be prioritised globally.

6.2. Access to treatment should be addressed through collaborative models involving industry, healthcare systems, and advocacy organisations.

6.3. Humanitarian and partnership-based approaches should be explored to support underserved regions.

7. 7. Ethical Considerations

7.1. Diagnostic initiatives should be aligned with strategies to ensure access to care.

7.2. Ethical implications of diagnosing patients without treatment options should be explicitly considered in program design.

Supportive Care and Patient-Centred Management

This session was moderated by Davide Pareyson and addressed the non–disease-modifying dimensions of ATTR care: autonomic dysfunction, neuropathic pain, motor disability, cardiac complications, psychosocial needs, and caregiver burden.

Across all three talks, a unifying message emerged: disease-modifying therapies alone are insufficient. Optimising outcomes requires a holistic, multidisciplinary, patient-centred model that addresses symptoms, function, mental health, autonomy, communication, and caregiver well-being.

Neuropathic pain, autonomic dysfunction, motor disability, and patient-reported outcomes in ATTRv amyloidosis – Lúcia Galán

Lucía Galán Dávila is a neurologist and coordinator of the Neuromuscular Unit at Hospital Clínico San Carlos, IdISSC, and Complutense University of Madrid, Spain. Her clinical and research work focuses on hereditary transthyretin amyloidosis, with particular emphasis on the symptomatic burden of ATTRv neuropathy. In her presentation, she addressed neuropathic pain, autonomic dysfunction, motor disability, physiotherapy integration, and patient-reported outcomes, highlighting the high prevalence and early impact of pain and dysautonomia, the limitations of current assessment tools, and the need for ATTRv-specific outcome measures to better capture patient experience and guide multidisciplinary care.

Neuropathic pain: prevalence, characteristics, and under-measurement

Neuropathic pain was identified as one of the most prevalent and impactful manifestations of ATTRv neuropathy. Data from the French Daily Impact Study, including over 600 patients with ATTR amyloidosis, demonstrated that pain is among the earliest symptoms, often present before diagnosis, and persists throughout disease progression. More than half of patients reported significant ongoing pain, with a major effect on daily activities, sleep, and overall quality of life.

Importantly, pain was shown to be common in late-onset ATTRv phenotypes, with prevalence approaching 60–70%, challenging the traditional view that these forms are relatively painless. Pain symptoms were also detectable in a subset of pre-symptomatic TTR variant carriers, supporting the concept that small-fibre involvement may precede clinically overt neuropathy. Clinically, pain was characterised by burning dysaesthesias, mechanical allodynia, and lancinating sensations, typically accompanied by thermal sensory impairment and loss of epidermal innervation.

Despite its clinical relevance, neuropathic pain remains insufficiently quantified in routine practice. Structured pain assessment tools such as numerical rating scales or neuropathic pain questionnaires are not consistently used, and pain evaluation often remains descriptive. This lack of standardisation limits longitudinal monitoring and hampers the interpretation of treatment effects.

Symptomatic treatment strategies largely rely on extrapolation from diabetic and other neuropathies. First-line agents such as duloxetine, pregabalin, gabapentin, and tricyclic antidepressants show only moderate efficacy and are frequently limited by autonomic side effects in ATTRv patients. Second-line options, including high-concentration capsaicin patches or opioid-based therapies, are supported by limited data, with no ATTRv-specific randomised trials available. A critical gap identified was the absence of dedicated pain endpoints in ATTR clinical trials. While some disease-modifying therapies have reported improvements in pain-related items or subdomains of broader questionnaires, pain has never been a primary or standalone outcome, limiting conclusions regarding analgesic benefit.

Autonomic dysfunction: early, disabling, and partially treatment-responsive

Autonomic dysfunction was presented as an early and frequent feature of ATTRv, affecting approximately 40–60% of symptomatic patients and often preceding overt polyneuropathy. Clinical manifestations include neurogenic orthostatic hypotension, gastrointestinal dysmotility, bladder dysfunction, sweating abnormalities, and cardiovascular autonomic failure. Pathophysiologically, amyloid infiltration of postganglionic sympathetic neurons leads to impaired norepinephrine release, with early cardiovagal dysfunction associated with disease progression and prognosis.

Assessment commonly relies on patient-reported tools such as the COMPASS-31 questionnaire, complemented by objective autonomic reflex testing and surrogate markers of nutritional status such as modified body mass index. Symptomatic management remains multimodal and largely supportive, combining non-pharmacological strategies with targeted pharmacological treatments for orthostatic hypotension, gastrointestinal dysfunction, and genitourinary symptoms.

Among disease-modifying therapies, RNA interference agents have shown the most consistent evidence of benefit on autonomic symptoms, with improvements in COMPASS-31 scores and stabilization of nutritional parameters reported in clinical trials. Antisense oligonucleotide therapies have also demonstrated improvements in autonomic domains in post-hoc analyses. However, the lack of autonomic-specific primary endpoints and limited long-term domain-specific data were highlighted as major evidence gaps

Motor disability, falls, and functional assessment

Motor impairment was discussed as a key driver of loss of independence in ATTRv neuropathy. Distal weakness, sensory ataxia, and gait instability contribute to reduced mobility and increased fall risk. However, balance impairment and falls are rarely measured systematically in either clinical practice or trials.

Among available disability scales, the Rasch-built Overall Disability Scale (RODS) was highlighted as particularly valuable due to its linear structure and patient-centred assessment of daily activities. In contrast, clinician-based impairment scores, while sensitive to motor deficits, were considered less reflective of the combined sensory and autonomic burden that characterizes ATTRv. The natural history of motor disability, particularly in treated populations, remains poorly defined, and ATTRv-specific validation data for commonly used scales are limited.

Emerging technologies, including wearable gait sensors and digital accelerometry, were discussed as promising tools for real-world monitoring of mobility, balance, and fall risk. However, the absence of ATTRv-specific datasets currently limits their clinical implementation.

Physiotherapy and rehabilitation: an under-studied but essential component

Physiotherapy was emphasised as a critical yet under-researched element of ATTRv management. Evidence supporting rehabilitation interventions is largely extrapolated from other hereditary and acquired neuropathies. Available data suggest that strength training, balance-focused interventions, orthotic support, and multifactorial fall-prevention programs can improve gait efficiency, postural control, and safety. Nevertheless, randomised controlled trials in ATTRv are scarce, intervention protocols are heterogeneous, and long-term outcomes remain largely unknown. These limitations are particularly relevant in healthcare systems where access to physiotherapy depends on out-of-pocket payment, underscoring the need for standardised, evidence-based rehabilitation pathways.

Patient-reported outcome measures and future directions

The presentation concluded with a critical evaluation of PROMs currently used in ATTRv research. Widely adopted instruments were noted to incompletely capture the multisystem nature of the disease. Neuropathy-focused quality-of-life measures can be difficult for patients to complete and rely on non-linear scoring, autonomic questionnaires do not fully reflect all dysautonomic manifestations, and cardiomyopathy-specific tools fail to address neurological disability.

RODS was again identified as a strong candidate for core disability assessment, while the development of an ATTR-specific quality-of-life instrument was highlighted as a major unmet need. Such a tool would ideally integrate pain, autonomic dysfunction, motor disability, and social participation, providing a unified framework for patient-centred assessment in both clinical care and trials.

Discussion and Participant Perspectives

The discussion following Lucia Galán's presentation highlighted several shared gaps and priorities in the symptomatic assessment and holistic management of ATTRv amyloidosis. Participants broadly agreed that neuropathic pain, while highly prevalent and impactful in daily life, is rarely quantified systematically in routine practice; clinicians acknowledged relying on qualitative questioning rather than structured tools. Simple instruments such as DN4 or numerical rating scales were discussed as feasible options, although concerns were raised about non-linearity and interpretability, reinforcing the need for consensus on a minimal, practical pain assessment set.

A second major theme was the lack of robust data on balance, ataxia, falls, and fall-risk progression, despite their clear relevance for patient safety, autonomy, and treatment decisions—particularly in the context of earlier diagnosis and treatment. Participants noted both practical barriers (time, clinic workflow, who should collect the data) and methodological challenges, and emphasised that fall risk should be prioritised as a longitudinal outcome, potentially supported by patient-reported or digital tools.

There was strong interest in unlocking subdomain-level data from completed clinical trials, with the view that fully anonymised datasets could yield important insights into pain, autonomic symptoms, and functional outcomes that remain underexplored. Complementing this, real-world registries were seen as essential to capture long-term symptomatic trajectories and treatment impact beyond trial settings.

The discussion also broadened to include psychological distress, caregiver burden, and communication at diagnosis, with consensus that anxiety, depression, and caregiver strain are likely under-recognised and insufficiently supported. Access to psychological care and the role of specialist nurses were highlighted as critical enablers of patient- and caregiver-centred care.

Finally, there was wide agreement on the urgent need for a holistic, ATTR-specific patient-reported outcome framework. While recognising that development and regulatory validation take time, participants converged on a pragmatic approach: using existing tools in combination. The Rasch-built Overall Disability Scale (RODS) was repeatedly endorsed as a core measure of autonomy and daily functioning, while emerging ATTR-specific quality-of-life instruments were viewed as promising candidates to integrate symptoms, impact, and quality of life across disease stages. Overall, the discussion underscored a clear shift toward outcomes that better reflect patients' lived experience and evolve across the ATTRv disease continuum.

Cardiac Management in Mixed Phenotype Cases – João Agostinho

João Agostinho is a cardiologist based in Lisbon with expertise in amyloid cardiomyopathy and multidisciplinary ATTR management. In his presentation, he outlined the principles of cardiac care in mixed phenotype ATTR amyloidosis, emphasising the importance of disease-modifying therapies, the complexity of heart failure management, the high prevalence and thrombotic risk associated with atrial fibrillation, and evolving strategies for conduction disease and pacing. His talk underscored the narrow therapeutic margins in these patients and the necessity for tailored, physiology-driven approaches.

Supportive Cardiac Care Begins With Disease Modification

A central concept of the presentation was that cardiac management in ATTR amyloidosis cannot be dissociated from disease-modifying therapy (DMT). Disease-modifying agents form the foundation of all supportive cardiac care, as they target the underlying transthyretin amyloid process that drives myocardial infiltration and dysfunction.

However, even in the era of DMTs, supportive cardiac strategies remain indispensable. These include the management of heart failure, arrhythmias, conduction system disease, and blood pressure instability. The interaction between these domains creates a highly dynamic clinical scenario requiring continuous reassessment and individualisation of therapy.

Heart failure management: navigating a narrow therapeutic window

Heart failure in ATTR cardiomyopathy is characterised by restrictive physiology, with stiff ventricles and reduced stroke volume. This results in a particularly narrow therapeutic window, where small changes in volume status can lead to significant clinical consequences.

Overdiuresis may precipitate hypotension and renal dysfunction, while insufficient diuresis leads to congestion and symptomatic deterioration. Achieving and maintaining euvolemia is therefore a central but challenging therapeutic goal.

Loop diuretics remain the cornerstone of treatment, although their use requires careful titration and close monitoring. Sodium–glucose cotransporter 2 (SGLT2) inhibitors have shown encouraging observational benefits, including potential reductions in diuretic requirements, although their use may be associated with an increased risk of urinary tract infections.

Conventional heart failure therapies, such as ACE inhibitors and beta-blockers, are frequently poorly tolerated due to baseline hypotension and limited cardiac output. In contrast, mineralocorticoid receptor antagonists, including spironolactone and finerenone, appear to offer the most consistent benefit in observational studies and have a more favourable tolerability profile in this population.

Atrial fibrillation: highly prevalent and intrinsically thrombogenic

Once atrial fibrillation (AF) is confirmed, anticoagulation is strongly recommended, regardless of the CHA_2DS_2-VASc score, given AF's inherent tendency to cause clots. Conversely, anticoagulation in patients who remain in sinus rhythm continues to be debated, especially considering the competing risks of bleeding, such as cerebral amyloid angiopathy and falls.

From a therapeutic perspective, rhythm control is generally preferred over rate control. This underscores the vital role of atrial contraction in ventricular filling in restrictive cardiomyopathy, where the “atrial kick” may contribute up to 30% of stroke volume. Additionally, rate-control agents are often poorly tolerated. Among antiarrhythmic options, amiodarone remains the most consistently safe and effective agent in this setting. Electrical cardioversion, previously considered high risk, is now regarded as safe even without routine transoesophageal echocardiography, with very low rates of embolic complications in modern practice.

Catheter ablation, although technically more complex due to the presence of non–pulmonary vein triggers, has demonstrated greater safety and efficacy than historically assumed. Early consideration of ablation was particularly encouraged in younger patients with hereditary ATTR, in whom maintaining sinus rhythm may confer significant functional benefits.

Conduction disease and pacing: anticipating progression

Conduction system disease is another key aspect of cardiac involvement in ATTR amyloidosis, with up to 45% of patients needing pacing during the disease course. Progression can be unpredictable and sometimes rapid, highlighting the importance of regular rhythm monitoring, including Holter assessments. Notably, disease-modifying therapies do not seem to considerably change the progression of conduction abnormalities, emphasising the need for proactive management strategies.

Traditional right ventricular pacing may worsen ventricular dyssynchrony and lead to functional decline. Consequently, alternative pacing strategies are becoming more popular in patients likely to need a high pacing burden. Cardiac resynchronisation therapy (CRT) and conduction system pacing techniques, particularly left bundle branch pacing (LBBP), were highlighted as preferable options when pacing dependency exceeds approximately 40%. LBBP, in particular, is emerging as a physiologically sound and potentially cost-effective strategy, capable of preserving ventricular synchrony and improving functional outcomes.

Discussion And Clinical Perspectives

The discussion following João Agostinho’s presentation underscored the complexity of cardiac management in mixed-phenotype ATTR amyloidosis and the need for highly individualised care strategies. Participants agreed that, despite advances in disease-modifying therapies, supportive cardiac management remains challenging due to the fragile haemodynamic balance and frequent treatment intolerance.

A key theme was the difficulty of applying conventional heart failure paradigms to ATTR cardiomyopathy. Clinicians highlighted the need for more disease-specific evidence, particularly regarding the role of SGLT2 inhibitors and mineralocorticoid receptor antagonists, as current practice is largely guided by observational data.

The management of atrial fibrillation generated significant discussion, particularly regarding anticoagulation in sinus rhythm and the optimal timing of rhythm control interventions. There was broad agreement that earlier and more proactive rhythm control, including ablation, may improve functional outcomes, although prospective data are still needed. The growing interest in conduction system pacing, especially LBBP, was seen as a major shift toward more physiological management.

Patient and caregiver needs: what is missing from current care – Amyloidosis Association (David Gregory, Emmanuel James)

We had the opportunity to hear from patients and caregivers. David Gregory is a diagnosed ATTRv patient who remains asymptomatic, and Emmanuel James acted as his father's carer and as project manager for the Amyloidosis Alliance. They gave us a different view of the same problem, focusing on what matters to those who suffer the limitations and stress imposed by the ATTRv multisystemic disease.

The central gap in amyloidosis care is not only medical

The Amyloidosis Alliance highlights that the main gaps in amyloidosis care extend far beyond purely medical management. While therapeutic advances are significant, patients continue to face substantial challenges, beginning with persistent delays in diagnosis that often lead to disease progression before appropriate care is initiated. At the time of diagnosis, many patients receive insufficient information, limiting their understanding of the disease and their ability to navigate care. The burden of amyloidosis also profoundly affects daily life, reducing autonomy, social participation, and the ability to maintain employment. In parallel, the impact on caregivers remains largely under-recognised, despite clear evidence of emotional and physical strain. These issues are further compounded by fragmented healthcare systems and marked disparities between countries in access to expertise, diagnostics, and treatment. In this context, the Alliance underscores that integrating patient-reported data is essential to fully capture these unmet needs and to guide more patient-centred, equitable models of care.

The AmiLife survey: a patient-centred evidence-based

The AmiLife survey provides a robust, patient-centred evidence base to better understand these gaps, drawing on responses from approximately 3,000 patients and 650–900 caregivers across more than 40 countries. Designed as a comprehensive, multilingual online questionnaire of around 150 items, it deliberately focuses on real-life experiences rather than clinical parameters, aiming to capture the lived reality of amyloidosis and inform both policy and care organisations. In line with the previously identified unmet needs, the Amyloidosis Alliance has developed this tool specifically to assess diagnostic delays, identify gaps in care and treatment, and evaluate their real-world consequences for patients and caregivers. Its findings clearly identify delayed and complex diagnosis as the primary unmet need. Although the average diagnostic delay is estimated at around 1.7 years, many patients report much longer trajectories, frequently exceeding a decade. Notably, nearly 40% required emergency care or hospitalisation before receiving a diagnosis, and about two-thirds experienced worsening symptoms during this period. These results reflect the nonspecific nature of early manifestations, such as fatigue and dyspnea, which often lead to misdiagnosis and are compounded by insufficient awareness among both patients and healthcare professionals. Altogether, this highlights substantial inefficiencies in healthcare pathways and underscores the avoidable morbidity associated with delayed recognition of the disease.

Lack of information at diagnosis

Another critical gap identified by the AmiLife survey concerns the lack of information provided at the time of diagnosis. Approximately 60% of patients report that they receive no informational material when their diagnosis is disclosed. As a result, many leave consultations without the necessary tools to understand their condition, its progression, or the available management options. This represents a major shortcoming in patient education and empowerment, particularly in a complex and multisystem disease such as amyloidosis. Importantly, this issue does not appear to stem from a lack of available resources, but rather from insufficient and inconsistent dissemination within healthcare pathways, highlighting the need for more systematic integration of patient-oriented information at the point of diagnosis.

Disease burden beyond clinical symptoms

Beyond its clinical manifestations, amyloidosis imposes a substantial burden on patients' everyday lives. More than two-thirds of individuals report experiencing "daily disability," reflecting a pervasive impact that extends well beyond physical symptoms. This burden significantly affects multiple dimensions of life, including social interactions, physical activity, and participation in leisure or travel, often leading to progressive withdrawal from previously valued activities. Such limitations not only reduce functional independence but also alter patients' sense of identity and role within their social environment. These findings underscore that amyloidosis should not be viewed solely as a medical condition, but rather as a profoundly life-altering disease with wide-ranging consequences on autonomy and social well-being.

Socioeconomic Impact

The AmiLife survey also highlights a substantial and often underestimated socioeconomic impact of amyloidosis. Approximately 63% of patients report having stopped working, either partially or completely, within the year preceding the survey. This finding reflects a significant loss of productivity and income, translating into a considerable economic burden not only for individuals and their families but also for society at large. Importantly, these data challenge the common misconception that amyloidosis predominantly affects older, non-working populations, as many patients are of working age, particularly in hereditary forms of the disease. This underscores the need to recognise amyloidosis as a condition with meaningful socioeconomic consequences and strengthens the case for prioritising it within health policy, including access to early diagnosis, effective treatments, and supportive care measures aimed at preserving functional capacity and employment.

Caregiver burden

The AmiLife survey further reveals that caregiver burden is significant yet often underestimated. Caregivers themselves report a greater impact on their physical health than patients recognise, as well as a markedly higher emotional burden than patients tend to admit. This discrepancy highlights the often-invisible strain experienced by those providing daily support. Caregivers, therefore, are a hidden, vulnerable group exposed to considerable psychological stress, potential deterioration of their own health, and a lack of structured support within current care models. These findings emphasise the need to better integrate caregivers into the care framework, not only as partners in patient management but also as individuals requiring recognition, monitoring, and targeted support interventions.

Pre-diagnostic delay

An important additional insight from the AmiLife survey concerns delays that occur even before patients enter the healthcare system. About 22% of respondents reported experiencing severe, disabling symptoms prior to seeking medical attention. This suggests that diagnostic delay is not solely due to healthcare processes but also reflects a lack of public awareness, with patients often normalising, minimising, or misattributing their symptoms. Consequently, valuable time is lost before the first clinical assessment. These data emphasise the need for improved awareness at the population level, encouraging earlier recognition of warning signs and promoting timely healthcare engagement, which is crucial for reducing overall diagnostic delay and improving outcomes.

Structural and systemic gaps

The findings also highlight significant structural and systemic gaps in how amyloidosis care is organised. Marked inequalities exist between countries, with notable differences in access to prompt diagnosis, availability of treatments, and care pathways, reflecting broader disparities in healthcare resources and infrastructure. In this context, the lack of standardised patient pathways further adds to the variation in care, as a universal "patient journey" cannot be defined across diverse healthcare systems. Beyond these structural issues, current models of care remain mostly centred on medical treatment, with inadequate integration of supportive interventions such as nutritional advice, physical activity programmes, and psychosocial support. Collectively, these gaps emphasise the need for more coordinated, multidisciplinary, and equitable approaches to amyloidosis care at both national and international levels.

Role of patient organisations and the AmiLife Survey

This survey was conducted by the Amyloidosis Alliance to amplify the voices of patients and caregivers, support national organisations—especially in underserved regions—promote early diagnosis and the dissemination of best practices, influence health policy and access to therapies, and foster international collaboration networks. The methodological limitations include reliance on self-reported data without clinical validation, potential selection bias with overrepresentation of more engaged or less severely affected patients, and the absence of linkage between questionnaire sections, which restricts cross-variable analyses. Additionally, cultural and linguistic differences across participating countries may have affected the interpretation of certain questions. Nevertheless, despite these limitations, the dataset offers highly valuable real-world insights into the lived experiences of those with amyloidosis and its impact on patients and caregivers.

Key takeaways for clinicians and stakeholders

1. Early diagnosis is the most critical unmet need
2. Information delivery at diagnosis is inadequate
3. Care must go beyond treatment to include holistic support
4. Caregiver impact is substantial and under-recognised
5. Amyloidosis has a major socioeconomic burden
6. Patient-reported outcomes should guide health system improvements

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Supplementary File 2

Towards a European Collaborative Platform for ATTRv

Round Table 4: Towards a European Collaborative Platform for ATTRv

This section summarises key themes and agreements from an international expert roundtable led by Davide Pareyson and João Costa. The focus was on advancing collaborative research and improving access to care for hereditary transthyretin amyloidosis (ATTRv) neuropathy across Europe.

Key priorities and outcomes

Emphasis on actionable strategies to enhance data collection, research quality, and clinical implementation
Development of a sustainable European registry
Integration of multidisciplinary stakeholders
Establishment of standardised protocols for genetic and clinical management

Table I – Key Priorities and Outcomes

Our key priorities and outcomes focus on advancing practical, actionable strategies to improve data collection, strengthen research quality, and facilitate effective clinical implementation. Central to these efforts is the development of a sustainable European registry that can support long-term data integration and analysis. Equally important is integrating multidisciplinary stakeholders to ensure collaboration across clinical, research, and policy domains. In parallel, the establishment of standardised protocols for both genetic and clinical management is essential to promote consistency, reliability, and improved patient outcomes.

The round table concluded with the formation of a structured working group and a clear roadmap for short-, medium-, and long-term objectives.

Strategic Shift: Consensus to Data Generation

A key conclusion of the round table was the need to prioritise implementation-oriented research.

Research Priorities

Future efforts should therefore focus on establishing robust research priorities, including prospective, multicentre data collection and the adoption of standardised outcome definitions. In addition, greater integration of real-world data with clinical trial findings is essential to enhance the relevance and applicability of research. Ultimately, these approaches should support the rapid translation of new insights into clinical practice, ensuring that advances benefit patients in a timely and effective manner.

The objective is to create a learning healthcare system for ATTRv that continuously integrates clinical care and research.

Research Priorities

Prospective, multicentre data collection
Standardised outcomes definitions
Integration of real-world and clinical trial data
Rapid translation of findings into clinical practice

Table 2 – Research Priorities

Short and medium-term feasible initiatives

Short- and medium-term initiatives should concentrate on practical, high-impact actions that enhance both data infrastructure and clinical practice. Essential objectives include implementing systematic CNS phenotyping through structured collection of CNS cases within dedicated registry modules, and expanding genotype–phenotype correlations by documenting rare genetic variants, including homozygous and compound heterozygous cases. Simultaneously, efforts should focus on standardising genetic

counselling by developing clear guidelines, especially regarding incidental findings and direct-to-consumer testing, along with harmonising communication strategies for disclosing presymptomatic diagnoses. Finally, establishing a comprehensive knowledge base on pregnancy and treatment exposure—via systematic collection of pregnancy outcomes in treated patients—will be vital, with registry modules and specialised working groups acting as primary frameworks to support these initiatives.

Objective	Task	Requirements
Systematic CNS Phenotyping	Systematic collection of CNS cases	Registry module
Expanded Genotype–Phenotype Correlation	Documentation of rare genetic variants, including homozygous and compound heterozygous cases	Registry module
Standardised Genetic Counseling	Development of genetic counselling guidelines, particularly for incidental findings and direct-to-consumer testing	Working Group
Tailored Communication	Standardisation of communication practices for the disclosure of presymptomatic diagnoses	Working Group
Pregnancy and Treatment Exposure knowledge base	Collection of pregnancy outcome data in treated patients	Registry module

Table 3 – Objectives, tasks and requirements for short and medium-term feasible initiatives

Complex Strategic Initiatives

Complex, strategic initiatives should focus on strengthening both research infrastructure and therapeutic approaches. Central to this is the development of a robust registry, underpinned by clearly defined research objectives, well-established core outcome measures, and a carefully delineated minimal dataset, alongside the integration of patient-reported outcome measures (PROMs) to capture patient perspectives. In parallel, efforts to optimise treatment strategies are essential and should include implementing updated genetic classification frameworks, exploring combination therapy approaches, and identifying patient subgroups most likely to respond to specific treatments, thereby enabling more precise and effective care.

Complex Strategic Initiatives

Key requirements for registry development
Clearly defined research objectives
Clearly defined outcome measures
Definition of a minimal dataset
Integration of patient-reported outcome measures (PROMs)
Treatment strategy optimisation
Exploration of combination therapy strategies
Identification of treatment-responsive patient sunbgroups

Table 4 – Complex Strategic initiatives

Registry design and infrastructure

The proposed registry should be conceived as a pragmatic, scalable, and interoperable platform designed to serve multiple complementary purposes across the ATTRv research and care continuum. Its primary objectives are to generate high-quality real-world evidence, support clinical trial design—including the development of robust historical control cohorts—enable post-marketing surveillance, and inform health technology assessment (HTA) and reimbursement decision-making.

To achieve these goals, the registry must be grounded in core design principles that ensure feasibility, sustainability, and scientific value. Central to this approach is the adoption of a minimal dataset, focusing on essential variables that maximise

participation, enhance data completeness, and reduce the burden on both clinicians and patients. This is particularly critical in rare diseases, where overly complex data collection frameworks often compromise long-term viability.

Equally important is ensuring interoperability while avoiding duplication. The registry should be carefully aligned with existing initiatives—including academic registries, industry-sponsored platforms, and the EURO-NMD registry infrastructure—and, wherever possible, leverage existing systems rather than recreate parallel structures. Such alignment will facilitate data harmonisation and integration, enabling more robust analyses at scale.

To enhance both data richness and patient engagement, the platform should incorporate direct patient input through digital tools, such as secure web-based interfaces or mobile applications. This will support the systematic collection of patient-reported outcome measures (PROMs) and longitudinal follow-up data, strengthening the patient-centred dimension of the registry.

The registry architecture should also remain flexible and modular, allowing iterative adaptation to emerging research priorities, evolving therapeutic landscapes, and advances in disease understanding. This flexibility is essential to ensure that the platform remains relevant over time and can support new study designs. In particular, the inclusion of standardised data elements will be critical to ensure trial readiness, enabling the registry to function as a reliable source of external or historical control data for future clinical studies.

From a technical and regulatory perspective, implementation should build upon existing European infrastructures. Leveraging the frameworks established by the European Reference Networks (ERNs), particularly EURO-NMD, provides a strong foundation for governance, coordination, and ethical oversight. Full compliance with the General Data Protection Regulation (GDPR) is mandatory, and the use of established data-sharing agreements can significantly accelerate deployment. Ensuring interoperability with both academic and industry platforms will be essential to enable data exchange, cross-validation, and large-scale collaborative research.

Finally, the long-term success of the registry will depend on the effective integration of a multidisciplinary stakeholder ecosystem. Close collaboration among neurologists, cardiologists, gastroenterologists, and genetic specialists is necessary to capture the multisystem nature of ATTRv. Coordination with initiatives such as ERN Guard-Heart will further strengthen the evaluation of cardiac involvement. The active participation of patient advocacy organisations is equally critical, particularly in shaping meaningful outcomes and promoting sustained engagement. In parallel, structured and transparent collaboration with industry partners should be established to align data-generation efforts while maintaining clear scientific independence and governance integrity.

Registry Governance and Stakeholder Integration

The successful execution of the registry relies on a robust, multilevel governance framework that brings together diverse expertise and perspectives. Four key stakeholder groups play critical roles in shaping the platform:

1. 1. Clinical Disciplines: Collaboration among specialists in neurology, cardiology, gastroenterology, and genetics ensures that the registry comprehensively addresses the multisystem nature of ATTRv.
2. 2. Patient Organisations: Involving patient advocacy groups in the co-design of outcomes and participation strategies helps align the registry with patient priorities and fosters greater engagement.
3. 3. Methodological Expertise: Input from biostatistics, epidemiology, and registry science experts is vital for ensuring methodological rigour and the generation of high-quality, reliable data.
4. 4. Industry Collaboration: Structured and transparent engagement with industry partners enables data sharing and effective post-marketing surveillance, while maintaining scientific integrity.

A clear separation between scientific governance and external stakeholders is essential to guarantee the registry's independence and credibility.

Implementation Roadmap

In the short term (0–12 months), the primary focus will be on laying the groundwork for the registry’s success. This includes forming a collaborative working group that brings together key stakeholders and building the necessary digital infrastructure. During this period, the registry’s objectives will be clearly defined, a minimal dataset will be established, and pilot data collection will begin in selected centers to test processes and workflows.

Over the medium term (1–3 years), the registry will expand its reach by scaling to multiple European centers. Efforts will concentrate on validating patient-reported outcome measures (PROMs) and integrating them into routine clinical practice,

establishing formal data-sharing agreements, and launching targeted sub-studies to address specific research questions, such as the involvement of the central nervous system and pregnancy outcomes.

In the long term (beyond 3 years), the registry will enable the conduct of registry-based clinical trials and hybrid study designs, providing a valuable resource for ongoing research. The goal is to generate robust datasets that can inform health technology assessments (HTA) and regulatory decision-making. Ultimately, these activities will help sustain a pan-European research ecosystem dedicated to advancing knowledge and improving care for individuals with ATTRv.

Implementation Roadmap

Short Term (0-12 months)
Establish collaborative working groups
and digital infrastructure
Define registries objectives and minimal dataset
Install pilot data collection in selected centres
Medium Term (1-3 years)
Scale registry across multiple European centres
Validate PROMs and integrate in routine workflows
Establis formal data data-sharing agreements
Lauch targeted sub-studies (e.g., CNS involvement, pregnancy outcomes)
Long Term (>3 years)
Enable registry-based clinical trials and study designs
Provide robust datasets for HTA and regulatory decision-making
Sustain a pan-European ATTRv resarch ecosystem

Table 5 – Implementation Roadmap

Key Challenges and Mitigation Strategies

The development and maintenance of a comprehensive, pan-European ATTRv registry is an ambitious endeavor that must address several significant challenges. To ensure the registry's effectiveness and sustainability, targeted mitigation strategies have been identified for each major obstacle:

Data heterogeneity arises when participating centres use varying data collection practices, making it difficult to compare or aggregate results. This challenge will be addressed through the adoption of a standardised core dataset and clear definitions, ensuring consistency and reliability across all contributors.

Limited participation can hinder the registry's reach and impact. By designing a minimal dataset and implementing intuitive digital tools, the registry will reduce the administrative burden on clinicians and encourage wider involvement from diverse sites.

Regulatory complexity is an inherent challenge, especially when navigating the legal requirements of different countries. Leveraging established frameworks such as the European Reference Networks (ERN) and ensuring full GDPR compliance will streamline regulatory processes and protect patient data.

Sustainability is crucial for the long-term success of the registry. Integrating registry activities seamlessly into everyday clinical workflows and securing funding from multiple stakeholders will help maintain momentum and institutional support over time.

Duplication of efforts can detract from the registry's value. By coordinating closely with existing registries and initiatives, resources can be used more efficiently, and the overall impact of collective research efforts can be maximised.

By proactively implementing these mitigation strategies, the ATTRv registry will be well-positioned to overcome obstacles and serve as a durable, high-quality resource for both research and patient care.

Key Challenges	Mitigation Strategies

Data heterogeneity	Standardised core dataset and definitions
Limited participation	Minimal dataset and digital tools
Regulatory complexity	Use of ERN and GDPR-aligned frameworks
Sustainability	Integration with clinical workfloes and multi-stakeholder funding
Duplication efforts	Coordination with existing registries

Table 6 – Key challenges and Mitigation Strategies

Consensus Recommendations

5. 1. Prediction of Treatment Response
6. 1.1. There is an urgent need to identify and validate biomarkers capable of predicting treatment response and disease progression.
7. 1.2. Clinical predictors such as disease stage and phenotype should be used cautiously and should not replace the development of biological markers.
8. 1.3. Longitudinal real-world data should be systematically collected to refine predictive models.
9. 2. Management of Women of Childbearing Age
10. 2.1. Pregnancy registries should be established to collect prospective safety data on all ATTR therapies.
11. 2.2. Women of childbearing potential should receive standardized counseling regarding treatment risks and uncertainties.
12. 2.3. Alternative management strategies, including treatment interruption or transplantation, should be individualised and discussed within multidisciplinary teams.
13. 3. Monitoring and Treatment Optimisation
14. 3.1. Treatment response should be assessed using a multidimensional approach incorporating clinical, neurophysiological, and patient-reported measures.
15. 3.2. A minimum observation period of approximately 12 months should be considered before defining treatment failure, unless rapid progression occurs.
16. 3.3. A minimum feasible monitoring protocol should be defined to ensure applicability across diverse healthcare settings.
17. 4. Core Outcome Measures
18. 4.1. The ATTR community should prioritise the development of a standardised core outcome set within the next 1–2 years.
19. 4.2. Outcome measures should be clinically meaningful, sensitive to change, and feasible in routine practice.
20. 4.3. Harmonisation between clinical trials and real-world practice should be actively pursued.
21. 5. Role of Real-World Data
22. 5.1. Registries and observational studies should be expanded to capture long-term outcomes and treatment patterns.
23. 5.2. Real-world data should be used to inform decisions on treatment sequencing, switching, and combination strategies.
24. 6. Global Access to Diagnosis and Treatment
25. 6.1. Efforts to expand genetic testing and diagnostic capacity should be prioritised globally.
26. 6.2. Access to treatment should be addressed through collaborative models involving industry, healthcare systems, and advocacy organisations.
27. 6.3. Humanitarian and partnership-based approaches should be explored to support underserved regions.
28. 7. Ethical Considerations
29. 7.1. Diagnostic initiatives should be aligned with strategies to ensure access to care.
30. 7.2. Ethical implications of diagnosing patients without treatment options should be explicitly considered in program design.

Working Group Formation

A collaborative working group was established with the following structure:

- Core Members: David Pareyson, Mary Reilly, Isabel Conceição, Katrin Hahn, Laura Obici, Antonio Atalaia
- External Advisors: João Costa (methodology), Jonas Wixner (gastroenterology), cardiologist representative
- Industry Liaison: One representative per pharmaceutical company
- Patient Advocacy: Patient association representatives
- Technical Support: PISA Centre for app development and platform integration

We have also collected the names of the workshop participants who would be interested in continuing to work with the collaborative working group.

Next Steps and Deliverables

Immediate Actions

- Establish shared digital workspace and communication channels
- Create a collaborative document repository for working group access
- Begin stakeholder outreach to other medical specialities and patient organisations

Medium-term Goals

- Develop a registry framework with clear research objectives
- Validate and implement patient-reported outcome measures
- Establish data sharing protocols with industry partners
- Create a governance structure for multi-ERN collaboration

Long-term Vision

- Publish workshop findings as a research roadmap rather than a consensus paper
- Establish a sustainable registry for real-world evidence collection
- Enable future clinical trial design with robust historical controls
- Support health technology assessment and treatment value evaluation

Conclusion

In conclusion, this round table marks a significant shift from consensus-building to coordinated action, outlining a clear and practical roadmap towards a European collaborative platform for ATTRv. By prioritising implementation-focused research, establishing a sustainable, interoperable registry, and encouraging multidisciplinary and multi-stakeholder collaboration, the proposed framework aims to bridge gaps between data collection and clinical care. The structured working group defined research priorities and a phased implementation approach, providing a strong foundation for a learning healthcare system capable of continuously incorporating real-world evidence into practice. Ultimately, these efforts are expected to accelerate innovation, enhance treatment strategies, and ensure more equitable access to high-quality care for patients with ATTRv across Europe.