# ARC RESEARCH ROUNDTABLE MEETING

Amyloidosis Research Consortium

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# INTRODUCTION


## About the ARC Research Roundtable Meeting

The Amyloidosis Research Consortium (ARC) Research Roundtable was held with the goal of identifying and aligning efforts to address the most critical needs facing the amyloidosis research community. In January 2018, ARC held a two-day inaugural Research Roundtable Meeting in Miami, Florida, focused on key themes including basic and translational research, improved diagnosis, evidence development, clinical trial design, market access, and health care systems optimization with twenty multidisciplinary amyloidosis experts. The resulting white paper, "Advancing Amyloidosis: A Research Roadmap" (2019) represents the consensus vision and research priorities of the amyloidosis research community, with an aim of helping increase the pace and efficiency of amyloidosis research that improves the lives of patients with amyloidosis.

Given the significant advancements made in the diagnosis, treatment, and management of AL and ATTR amyloidosis since that time, experts reconvened to reset priorities for the field during the second ARC Research Roundtable, held in Miami, Florida, in January 2024. Almost 40 global experts from the fields of hematology, cardiology, neurology, nephrology, basic and translational research, statistics and health outcomes, and the drug development industry met over 3 days. The meeting was led by two Co-Chairs, Dr. Ashutosh Wechalekar, Professor of Medicine and Haematology at University College London, and Dr. Sarah Cairns-Smith, Former Senior Advisor at Boston Consulting Group, who also serves as the Chair of the ARC Board of Directors. The meeting focused on the following key themes: (1) basic and translational research, (2) advancing the science of clinical trials in AL and

ATTR amyloidosis, and (3) improving clinical care. Meeting attendees participated in oral sessions facilitated by experts in their respective fields, which allowed the opportunity for several speakers to present their topics followed by a question-and-answer period. In addition, attendees participated in pre-assigned discussion groups focused on priority topics including basic and translational science, shortening the time to diagnosis, achieving unified staging systems for AL amyloidosis, addressing current challenges and exploring future potential for imaging, and data sharing through a federated approach.

This white paper summarizes advancements in the field, key challenges, and consensus priorities for the amyloidosis research community that were identified and discussed by attendees of the 2024 ARC Research Roundtable Meeting. The information presented in this paper represents the opinions and outlooks of the global amyloidosis experts.


Amyloidosis Research Consortium

## About ARC

ARC has a simple vision — make a significant impact on the curability of amyloidosis. Created in 2015 as a patient-founded, patient-focused non-profit organization, ARC harnesses the power of collaboration and innovation to advance science, and both improve and extend the lives of those with amyloidosis. Despite significant progress in recent years, patients continue to experience high unmet need, and too few treatments option exist. ARC aims to shift this paradigm.

# WHAT HAS CHANGED OVER THE PAST 5 YEARS

The 2024 Research Roundtable meeting provided attendees with the opportunity to reflect on the momentous progress that has been made in the diagnosis and management of light chain (AL) and transthyretin (ATTR) amyloidosis since the prior meeting, and to celebrate these significant achievements as well as to discuss new challenges that have emerged.

## Improvements in Diagnosis

Significant advancements have been made in the diagnosis of both ATTR and AL amyloidosis since 2018. In ATTR, there has been a notable "left shift" in diagnosis, meaning patients are now diagnosed earlier in their disease course. This is primarily due to the emergence of scintigraphy, which allows for noninvasive definitive diagnosis of transthyretin amyloid cardiomyopathy (ATTR-CM) without the need for a biopsy. Additionally, increased awareness and education have led to earlier recognition and intervention. Standard heart failure (HF) therapies have also improved, however require reevaluation to align with evolving guidelines.

Similarly, in AL amyloidosis, the average time to diagnosis from symptom onset has improved significantly, reduced from 10 months to 6 months, leading to better patient outcomes. Advances in diagnostic testing and newly published guidelines have further streamlined the diagnostic process, contributing to earlier detection and management.

## Advances in Treatment

The treatment landscape for ATTR amyloidosis has evolved significantly with the approval of multiple therapies including inotersen, patisiran, vutrisiran, and eplontersen for transthyretin amyloid polyneuropathy (ATTRv-PN), revolutionizing patient care. Early initiation of therapy has been shown to provide the most clinical benefit, and upcoming prevention trials could further shift the paradigm toward preemptive intervention.

For AL amyloidosis, the approval of daratumuab in combination with bortezomib, cyclophosphamide, and dexamethasone (CyBorD) has changed the outlook for patients by providing the first regimen shown to significantly improve hematologic response rates and survival outcomes. This regimen is now the standard first-line treatment for newly diagnosed and relapsed daratumumab-naïve AL patients. Additionally, ongoing studies on chimeric antigen receptor (CAR) T-cells and bispecific antibodies suggest that deeper remissions may be achievable.

## Emerging Challenges

Despite these important advances in the diagnosis and management of patients with amyloidosis, several new challenges have emerged. Noninvasive imaging techniques has allowed for earlier diagnosis in ATTR amyloidosis but have also emerged as a leading source of misdiagnosis and mistyping. While patients with ATTR benefit from earlier diagnosis and greater access to treatments, there isn't a clear understanding of how to effectively manage patients diagnosed at an early stage, especially among those who initially present with few symptoms. Additionally, the next generation of clinical trials is moving away from placebo-controlled designs, requiring innovative approaches to assess efficacy. The need for continuous innovation in diagnostics and therapeutics remain critical areas of focus for future research and clinical practice.

# OVERARCHING THEMES

It is important to acknowledge that a new era is beginning for the management of amyloidosis, characterized by improved diagnostic tools, increased disease recognition, and several different treatment options for both ATTR and AL amyloidosis. However, there are broader challenges in key areas that must be addressed by the amyloidosis research community to ensure that all patients receive optimal care, regardless of their specific type of amyloidosis.

## Diagnosis

Early diagnosis is essential to improving patient outcomes, as symptoms often appear long before a definitive diagnosis is made. Delayed detection can lead to disease progression, reducing quality of life and limiting treatment options. Many physicians, even those likely to encounter amyloidosis, may not recognize the disease or order the appropriate tests. Enhancing awareness, leveraging artificial intelligence (AI)-driven diagnostic tools, and integrating electronic health record (EHR)-based alerts could help ensure earlier testing, reducing diagnostic uncertainty and improving care. Imaging plays a crucial role in diagnosis, yet challenges like delayed access to advanced imaging and the lack of standardized protocols hinder early detection.

As diagnostic capabilities improve, healthcare systems will face increased early referrals, placing pressure on resources. More patients are being identified at older ages with comorbidities, raising concerns about treatment initiation and cost-effectiveness.

## Advancing Imaging Technologies

Non-invasive imaging, particularly cardiac scintigraphy for ATTR-CM, has transformed amyloidosis diagnosis, but current modalities remain imprecise and lack strong links to treatment outcomes. Positron emission tomography (PET) imaging shows promise in differentiating amyloid subtypes, but high costs and infrastructure requirements limit widespread adoption. Research is needed to improve early disease detection, assess the accuracy and comparability of different tracers, and develop AI-driven tools for risk stratification using electrocardiogram (ECG) and echocardiography. Increasing access to standardized imaging techniques is essential for broader use.

## Data Sharing

Collaboration is crucial in basic and translational research, especially within the pre-competitive drug environment. Strong connections between scientists and clinicians are key to sharing knowledge, resources, and data. Systems must be organized to facilitate the sharing of longitudinal patient samples from clinical trials through virtual or traditional tissue repositories, enabling more effective joint research efforts.

> **Collaboration is crucial in basic and translational research, especially within the pre-competitive drug environment.**

Clinical trial design and drug development are increasingly complex due to the evolving treatment landscape and earlier disease diagnoses. Learning from completed clinical trials is essential, but sharing patient-level data in a competitive environment is challenging due to practical and legal barriers. Federated analytics offers a solution, allowing institutions to retain data control while participating in local analyses. This approach has shown effectiveness in evaluating biomarkers like N-terminal pro brain natriuretic peptide (NT-proBNP) and could support under-researched populations, refine surrogate endpoints, and enhance collaborative research.

## Patient Engagement Across the Research Continuum

Adopting a patient-centered approach aligns clinical trials with the real-world priorities and improves clinical care through meaningful and tangible outcomes. Involving patients as active partners results in improved trial recruitment, retention, and relevance.

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Researchers, clinicians, and patients also greatly benefit from inclusion of patient-reported outcomes (PRO) measures in clinical trial designs, which is another key aspect of patient-centered care. PROs provide much-needed insights into patients' subjective experiences from their own perspectives, including their quality of life (QOL), symptom burden, and functional status which cannot be obtained from objective clinical measurement alone. While PROs like the Kansas City Cardiomyopathy Questionnaire (KCCQ), Norfolk Quality of Life- Diabetic Neuropathy (Norfolk QOL-DN), and Short Form-36 Health Survey (SF-36) are commonly used in ATTR and/or AL amyloidosis clinical trials and observational studies, they were developed and validated for use as general health status measures (e.g., SF-36) or as disease-specific measures (e.g. heart failure, diabetic neuropathy), and were not intended for either type of amyloidosis. The Transthyretin Amyloidosis Quality of Life (ATTR-QOL) Questionnaire and the ITALY Questionnaire have been developed for ATTR amyloidosis.  While

these ATTR-specific measures have now been included in several studies, further validation of these measures are required for broader adoption in research and clinical practice. Consensus priorities for these measures include generating robust evidence supporting their content and psychometric validity, further testing among diverse, real-world populations, evaluation of clinical meaningfulness, and ultimately integration into standard clinical practice. In AL amyloidosis, two general health QOL measures, the SF-36 and Patient Reported Outcomes Measurement Information System (PROMIS)-29 Profile, have been incorporated into clinical trials. A disease-relevant PRO measure for AL amyloidosis, the AL-PROfile, was developed based on the PROMIS-29 and has been initially validated, however requires further validation as described for the ATTR-specific measures cited above.

## Health Equity

Health equity remains a prominent issue within the amyloidosis landscape, with significant racial and socioeconomic disparities impacting patient outcomes. For instance, in the U.S., the V122I variant of ATTR amyloidosis present in approximately 4% of African Americans which is notably underrepresented in clinical trials. This gap restricts treatment data and knowledge for this demographic, posing a barrier to equitable care. Acknowledging this disparity, the FDA has called for greater inclusivity in clinical trials to ensure safety and efficacy across diverse patient groups.

Several key imperatives were identified to address health equity challenges. First, specialists must actively engage with underserved populations, enhancing awareness, screening, and diagnostic access. Amyloidosis centers can spearhead actions by offering targeted education and specialized expertise to bridge gaps in access, while working directly with community healthcare providers to strengthen screening practices and improve trial recruitment inclusivity. Furthermore, the high cost of amyloidosis treatment presents a financial barrier for many patients. Treatment access should be based on clinical need, not financial capability, as no patient should be forced to choose between life-saving therapy and financial stability.

> **“No patient should be forced to choose between life-saving therapy and financial stability.”**

By fostering connections between health care providers (HCPs) in underserved areas and specialized amyloidosis centers, improvements can be made to patient outcomes, and a more inclusive research environment will emerge. This collaborative framework can advance clinical care equity and support the development of therapies that are accessible, safe, and effective for diverse patient groups.

## Management of Frail Patients

Patients with amyloidosis often experience significant frailty due to advanced disease, comorbidities, and age, which can restrict treatment options. Insights from treating frail multiple myeloma patients may inform strategies for frail AL amyloidosis patients, as the combination of daratumumab with elotuzumab has shown promise in this population, despite the absence of current data for AL amyloidosis. Additionally, the potential use of daratumumab with bispecific antibodies raises concerns

about infection-related morbidity, necessitating careful consideration of frail patients' tolerance to treatment. In ATTR-CM frailty — defined as a clinically recognized state of increased vulnerability resulting from age-related declines in physiological reserve and function across multiple systems, compromising the ability to manage daily or acute stressor—remains a critical issue, with indicators such as low grip strength, diminished energy levels, slowed walking speed, reduced physical activity, and unintentional weight loss.

Promoting the inclusion of frail patients in clinical trials is essential, ensuring that efficacy and safety endpoints reflect patient priorities, including functional measures (e.g., six-minute walk test and Short Physical Performance Battery) and health-related QOL assessments. Understanding the timeline for therapeutic benefit and identifying when to discontinue ineffective treatments are crucial for optimizing care in this vulnerable population. Moreover, addressing the mechanisms of progression in advanced amyloidosis and variability in patient responses to therapy is vital for improving outcomes.

## Remote Care

The concept of remote healthcare gained significant momentum during the COVID-19 pandemic, driven by the urgent need for accessible and safe medical services in the face of widespread public health restrictions. This paradigm shift not only facilitated the continued provision of care while minimizing the risk of virus transmission but also highlighted the potential of telemedicine to enhance healthcare delivery across diverse populations. As the demand for virtual consultations surged, healthcare providers adapted rapidly, embracing technology to ensure continuity of care, improve patient outcomes, and expand access to services. This evolution presents a critical opportunity to establish telemedicine as a permanent fixture in healthcare, addressing existing barriers to access and promoting a more integrated, patient-centered approach to medical care.

## Summary of Overarching Priorities

Continued improvement of early and accurate diagnosis is crucial. New tools and AI/NLP models should be explored, while supportive infrastructure (education, testing, access to care) is established

Standardization and dissemination of imaging protocols, along with adoption in Phase 3 clinical studies/sub-studies

Evaluation of what changes seen over time with therapy mean across different imaging modalities

Employ federated analytics as a strategy to overcome challenges in data sharing and unlocking new insights into under-researched populations and surrogate endpoints

Integrate disease specific PROs into clinical trial design and clinical practice, generating data to understand patient perspectives

Improve health equity through targeted and improved inclusion of V122I patients in ATTR amyloidosis clinical trials, connecting HCPs in underserved areas with expert amyloidosis centers, and building expertise in the next generation of HCPs

Inclusion of frail patients in clinical trials

Advocate for the coverage/implementation/authorization of telemedicine across state lines to improve access to care for patients with amyloidosis

# BASIC AND TRANSLATIONAL RESEARCH

## KEY QUESTIONS AND PRIORITIES

Despite significant advances in the diagnosis and management of ATTR and AL amyloidosis, several critical questions remain unanswered in the basic and translational knowledge of the diseases. To accelerate progress, the following gaps must be addressed by the amyloidosis research community across multiple areas of disease research and clinical management.

### Deciphering Amyloid Fibril Structure and Pathogenesis

Understanding how fibril structure drives disease progression is essential for targeted drug development. In AL amyloidosis, it is understood that fibrils arise from light chain variable domains with destabilizing mutations, but it is not clear which mutations specifically drive fibril formation, and how they influence disease phenotype. Similarly, in ATTR amyloidosis, fibril morphology remains consistent across patients, and it's not understood how genetic mutations impact disease expression. It is imperative to answer these questions, as they will be pivotal in designing mutation-specific therapies.

### Unraveling the Role of Accessory Proteins

Amyloid fibrils do not form in isolation — other proteins are involved, potentially influencing disease onset and progression. These accessory proteins may serve as novel therapeutic targets, yet their precise roles remain unclear. Additionally, the surrounding tissue environment appears to contribute to disease development. Further research is needed to determine how these factors interact and how they might be leveraged for intervention.

## Defining Disease Onset and the Potential for Prevention

Early intervention is critical, yet fundamental uncertainties remain. It is still unclear when amyloidosis truly begins — whether it starts with amyloid deposition or only once symptoms manifest. As prevention trials are planned, we must establish a new disease definition that aligns with emerging therapeutic approaches. Understanding the optimal timing for intervention could transform patient outcomes and shift the paradigm from treatment to prevention.

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## Understanding Protein Aggregation and Stability

Despite its inherent stability, wild-type TTR protein is prone to aggregation, a process that remains poorly understood. Identifying the mechanisms that drive TTR aggregation is crucial to designing novel therapeutic strategies that prevent amyloid formation at its source.

## Uncovering the Role of the Immune System in Disease Progression and Regression

The immune system's role in amyloidosis is an emerging area of study, particularly in wild-type ATTR amyloidosis, where age-related immune dysfunction may contribute to disease onset. Recent clinical observations suggest that spontaneous amyloid regression can occur, possibly mediated by immune responses. However, fundamental mechanisms remain poorly understood. The processes by which the immune system recognizes and clears amyloid deposits, the specific cells involved, and the role of antibodies in facilitating amyloid degradation are still being elucidated. Gaining clarity on these mechanisms could unlock powerful immunotherapeutic strategies.

## Assessing Toxicity Beyond Amyloid Deposits

Soluble light chains exhibit direct cardiotoxicity in AL amyloidosis, yet it remains unclear whether TTR protein is similarly toxic. If toxicity is a key driver of disease, there may be a need to shift therapeutic focus from solely reducing amyloid burden to also targeting toxic protein species. Investigating whether wild-type and mutated TTR proteins have different toxic properties is a critical next step.

## Addressing the Unmet Needs of CNS and Ocular Involvement

Amyloid deposition in the eye and central nervous system (CNS) remains a significant challenge. Current pharmacological treatments do not effectively target ocular amyloid, and as patients live longer, CNS involvement is becoming more prevalent. Understanding the mechanisms driving CNS amyloid accumulation, and how it progresses from early-stage biochemical changes to debilitating neurological symptoms, is essential for developing effective interventions.

## The Path Forward

Addressing these critical gaps requires a collaborative, multidisciplinary approach, leveraging advances in structural biology, immunology, and biomarker research. By defining disease onset, improving early diagnosis, identifying new therapeutic targets, and developing innovative treatment strategies, the amyloidosis community can move toward a future where amyloidosis is not only better managed but potentially prevented. The time to act is now — through sustained research efforts and strategic investments, we can transform the landscape of amyloidosis treatment and improve the lives of patients worldwide.

## Future Priorities for Basic and Translational Research

- Learn from other protein misfolding diseases (e.g., Alzheimer's Disease)
- Identify toxic protein species and their role in disease progression
- Investigate amyloid clearance mechanisms and immune system involvement
- Develop a standardized, cross-institutional biorepository
- Advance biomarker and assay development to detect toxic amyloid species and track disease progression
- Conduct pan-amyloid studies to uncover universal disease mechanisms
- Enhance understanding of imaging modalities
- Establish a consensus definition of amyloidosis, including asymptomatic amyloid deposition

# AL AMYLOIDOSIS

## KEY QUESTIONS AND PRIORITIES IN CLINICAL RESEARCH AND CARE

In AL amyloidosis, several research priorities have been identified to build on the progress made since 2018. By addressing these critical research gaps, the fields of AL amyloidosis can continue to refine treatment strategies, improve long-term outcomes, and ensure that emerging therapies are effectively integrated into patient care.


### Advancing Treatment Goals

The primary goal in AL amyloidosis treatment remains achieving a deep and rapid hematologic response, ideally complete response (CR), with minimal toxicity. A CR is predictive of long-term benefits, yet current therapies achieve this in only 60% of patients. Beyond hematologic response, long-term outcomes such as amyloid clearance and organ function recovery remain critical. The development of new biomarkers for early organ response assessment is a priority, moving beyond late-stage indicators like dialysis or heart transplantation.

### Optimizing Daratumumab-Based Therapy

The ANDROMEDA trial revolutionized AL amyloidosis treatment, establishing daratumumab-based regimens as the standard of care for newly diagnosed and relapsed (daratumumab naïve) patients. However, critical questions remain, including the inclusion of cyclophosphamide in treatment regimens, understanding the efficacy of other agents, and the optimal treatment duration. The high efficacy of daratumumab sets a new benchmark, making future Phase 3 trials more challenging due to the need for larger patient populations and extended study durations. Given the rarity of AL amyloidosis, collaboration with regulatory agencies is crucial to ensure promising therapies are not overlooked due to underpowered studies.

### Addressing Unmet Needs Beyond Daratumumab

Despite the success of daratumumab, substantial gaps remain. Up to 50% of patients do not achieve CR, 20% fail to reach very good partial response (VGPR), and 45% do not experience organ response. Early mortality in the ANDROMEDA trial remains high, raising concerns about treatment-related toxicity, particularly from bortezomib and steroids. Further research is needed to refine

treatment regimens, optimize steroid dosing, and develop strategies for managing daratumumab non-responders. Emerging therapies including bispecifics and CAR-T cellular therapy offer promising alternatives, but their role in treatment sequencing, retreatment strategies, and long-term efficacy requires further study.

## Expanding Treatment Options and Prioritizing Clinical Trials

A robust pipeline of novel therapies, including targeted plasma cell agents, cellular immunotherapy, and anti-amyloid antibodies, is emerging. Given the small patient population, prioritization of clinical trials is critical to ensure the most impactful therapies progress efficiently. Additionally, rather than waiting for data from multiple myeloma trials, the field must advocate for the direct evaluation of novel therapies in AL amyloidosis.

## Managing High-Risk Stage IIIb Patients

Patients with stage IIIb disease have a poor prognosis, with nearly half dying within the first year. Rapid hematologic and early cardiac responses are key determinants of survival, yet there are no approved therapies for this population. These patients are often excluded from clinical trials due to assumptions of limited benefit; an approach that must be reconsidered as novel therapies emerge. Research priorities include identifying high-risk subgroups, optimizing treatment modifications to balance efficacy and toxicity, and re-evaluating the role of heart transplantation and cardiac devices in management.

## Redefining Disease Progression and Staging

Current definitions of disease progression remain inadequate for both clinical trials and real-world management. A new, simplified framework incorporating difference in free light chain (dFLC) thresholds and organ progression markers is needed. In addition, staging systems may need to be reevaluated in the daratumumab era, integrating biomarkers, imaging modalities, and functional assessments beyond cardiac involvement. A refined staging system should incorporate new biomarkers and weigh multiple risk factors to guide treatment decisions more effectively. It is also important to look at parameters beyond just the heart – for example, renal staging is an important part of risk assessment. Although this would add to the complexity of a new staging system, It may well be that "weighting" of the components will be required, as not all are of equal usefulness. Finally, the world of basic and translational research will likely identify new biomarkers that may be critical to staging systems. Identifying stage II/IIIa patients at high risk of early mortality is an urgent priority, as 10–15% die within the first six months.

# Future Priorities for AL Amyloidosis Clinical Research and Care

## Clinical Research

- Establish a clear, simplified definition of disease progression, potentially incorporating dFLC thresholds
- Integrate emerging biomarkers into staging system refinements, with a planned reassessment in two years
- Develop improved markers for assessing organ response to therapy
- Engage with regulatory agencies to address the challenges of Phase 3 trial designs based on outdated survival data, ensuring adequate study power and feasibility
- Prioritize global clinical trials to optimize research efforts and accelerate therapeutic advancements

## Management/Treatment

- Accelerate the introduction of effective therapies, such as bispecific antibodies, into first- and second-line treatment
- Improve management strategies for advanced cardiac patients and collaborate to update device recommendations
- Identify predictors of early mortality (10–15%) in stage II and IIIa patients to facilitate timely interventions
- Develop risk stratification methods to identify stage IIIb patients at highest risk of death within the first year
- Implement robust safety monitoring frameworks to assess early mortality associated with novel therapies
- Enhance supportive care strategies to reduce early mortality in therapy-naïve patients

# ATTR AMYLOIDOSIS

## KEY QUESTIONS AND PRIORITIES IN CLINICAL RESEARCH AND CARE

As described previously, significant advancements in the diagnosis and management of ATTR amyloidosis since 2018 have greatly improved patient outcomes. The observed rise in ATTR amyloidosis diagnoses reflects not only earlier detection but also a broader recognition and diagnosis of the disease, driving heightened interest and engagement among all relevant stakeholders. Addressing the following critical research questions and challenges have been identified as key priorities for the amyloidosis research community.

### A Shifting Patient Population

Advances in diagnostic tools and increased awareness have led to earlier detection of ATTR amyloidosis, fundamentally altering the patient population. The adoption of cardiac scintigraphy for non-invasive diagnosis has shifted diagnoses to earlier disease stages, particularly in ATTR-CM, compared to traditional biopsy-based methods. As a result, patients entering clinical trials now are generally healthier, younger, and requiring longer study durations and larger sample sizes to capture meaningful clinical events. ATTR-CM predominantly impacts older adults and there is a critical need to refine strategies for the identification and inclusion of high-risk patients in clinical trials. From a clinical practice standpoint, we need to assess how comorbidities, frailty, and age-related changes should influence treatment decisions, including when to initiate or discontinue disease-modifying therapy.

### Understanding the Extra-cardiac Involvement of ATTRwt

While much attention has been given to the cardiac involvement of ATTRwt, there remains a critical need to better understand the extent and impact of extra-cardiac involvement, particularly in terms of peripheral neuropathy, orthopedic manifestations, and other systemic complications. In elderly patients with comorbidities, distinguishing these symptoms from normal age-related changes or other common age-associated conditions becomes particularly difficult. Orthopedic symptoms, such as carpal tunnel syndrome, and other musculoskeletal issues, can overlap with common age-related degenerative conditions, complicating both diagnosis and monitoring. The heterogeneous nature of the disease, coupled with the overlapping features of aging, makes it challenging to accurately assess disease progression. Therefore, further research into these extra-cardiac features, particularly in the elderly population, is essential for improving diagnostic accuracy, disease monitoring, treatment and ultimately, patient outcomes.

## Defining Disease Progression

A clear understanding of disease progression is critical for both clinical care and trial design. Existing progression markers are complex, operator-dependent, and not universally applicable. There is an urgent need for simple, widely available biomarkers that capture clinically meaningful changes. NT-proBNP is being evaluated for ATTR-CM, but further research is necessary to develop standardized progression criteria that integrate both biological markers and PRO measures.

## Rethinking Clinical Trial Endpoints

Improved diagnosis and expanded treatment options make it increasingly difficult to use traditional endpoints such as survival and hospitalization in clinical trials. More sensitive and predictive markers must be developed, incorporating clinical assessments (e.g., NYHA class, frailty scores), biomarkers (e.g., NT-proBNP, troponin), and PROs. It is crucial to determine what changes in these measures are most meaningful to patients and whether composite endpoints provide a more accurate assessment of treatment efficacy.

## Optimizing Treatment Strategies and Future Directions

The current treatment landscape offers multiple options for ATTR amyloidosis, including silencers (inotersen, patisiran, vutrisiran, eplontersen) and stabilizers (tafamidis, acoramidis). Ongoing trials will further shape the treatment paradigm, but key questions remain that may be best addressed by comparative effectiveness research (CER). For example, questions related to understanding the best treatment options for patients (e.g., whether silencers are a more effective treatment option for neuropathy and stabilizers are more effective for cardiac disease). Additionally, understanding why some patients fail to respond to stabilizers and the role of anti-amyloid antibodies in treatment sequencing and combination therapy must also be clarified.

## Evaluating Combination Therapy

While combining stabilizers and silencers may have potential advantages, more evidence is required to demonstrate the benefits of combination therapy over monotherapy. The cost of combination therapy poses a significant barrier, and alternative approaches, such as using lower-cost stabilizers like diflunisal, require further investigation. The impact of background stabilizer therapy in silencer trials should also be critically evaluated.

## Addressing CNS and Ocular Involvement

The management of central nervous system and ocular involvement in ATTR amyloidosis remains poorly understood. ATTR-CM patients exhibit a higher prevalence of glaucoma, and subdural hematomas occur at a significantly higher rate than in the general population. As improved treatments extend patient survival, CNS manifestations will become increasingly relevant. Research should focus on identifying at-risk patients and determining whether current therapies penetrate the CNS effectively.

## The Case for Early Intervention and Prevention

The ability to detect disease earlier raises a critical question: When should treatment begin? Data indicate that early intervention leads to better outcomes, and patients rarely recover lost function once disease progression begins. The concept of preventive treatment—initiating therapy in individuals with genetic mutations or early amyloid deposits before symptom onset — warrants serious consideration. Screening strategies using family history, biomarker assessments, and advanced imaging could help identify candidates for early intervention. Lessons from Alzheimer's disease, where amyloid-targeting therapies are being tested in asymptomatic individuals, may provide valuable insights for ATTR amyloidosis.

# Future Priorities for ATTR Amyloidosis Clinical Research and Care

## Management/Treatment

- Address the progression of orthopedic manifestations, including carpal tunnel syndrome, spinal stenosis, and bicep tendon rupture, to enhance patient quality of life
- Gain consensus on the most appropriate heart failure therapy for patients with ATTR amyloidosis to ensure optimal treatment outcomes

## Clinical Research

- Investigate the tipping point of amyloid deposition prior to the onset of symptoms, potentially similar to other conditions like Alzheimer's disease
- Evaluate the effectiveness of combination regimens in treating amyloidosis to identify the most beneficial therapeutic strategies
- Examine the incidence, prevalence, and impact of neuropathy in ATTR wild-type amyloidosis and the effects of various treatment modalities
- Enhance the management of central nervous system and ocular involvement in variant populations, particularly in individuals with cardiomyopathy who are at higher risk for glaucoma and subdural hematomas
- Understand skeletal muscle involvement in ATTR wild-type amyloidosis
- Evaluate prevention studies
- Develop robust and reproducible criteria for assessing treatment response in ATTR amyloidosis

## Final Thoughts

The 2024 ARC Research Roundtable served not only as a forum to celebrate the significant advancements in both AL and ATTR amyloidosis research, diagnosis and management since 2018, but also as a catalyst for identifying the key challenges that remain. The discussions underscored the urgent need for continued collaboration, broader data and resource sharing, and a sustained focus on education across the amyloidosis community.

Moving forward, the responsibility lies with all members of the research ecosystem; clinicians, scientists, patients, and institutions, to work together and hold one another accountable in advancing the priorities identified. ARC remains committed to convening diverse stakeholders through initiatives like the Research Roundtable to monitor progress, and Amyloidosis Forum to address emerging challenges, and refine research priorities as needed.

Progress will be driven by the collective commitment to innovation, collaboration, and patient-centered research. Together, we can build a future where individuals living with amyloidosis can thrive.


## Acknowledgements

ARC extends its sincere gratitude to all attendees and facilitators of the 2024 Research Roundtable. Your time, insights, and expertise were instrumental in shaping this white paper and in advancing the conversation around critical research needs in amyloidosis.

We recognize and deeply appreciate your valuable contributions to the field. ARC will continue to support and foster collaborative efforts across the amyloidosis community, in alignment with our mission to harness the power of collaboration and innovation to accelerate scientific progress and improve patient outcomes.


> **The commitment to collaboration, innovation, and patient-centered research brings us closer to a reality where patients with amyloidosis lead full lives.**

# APPENDIX

## MEMBERS AND SPONSORS

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