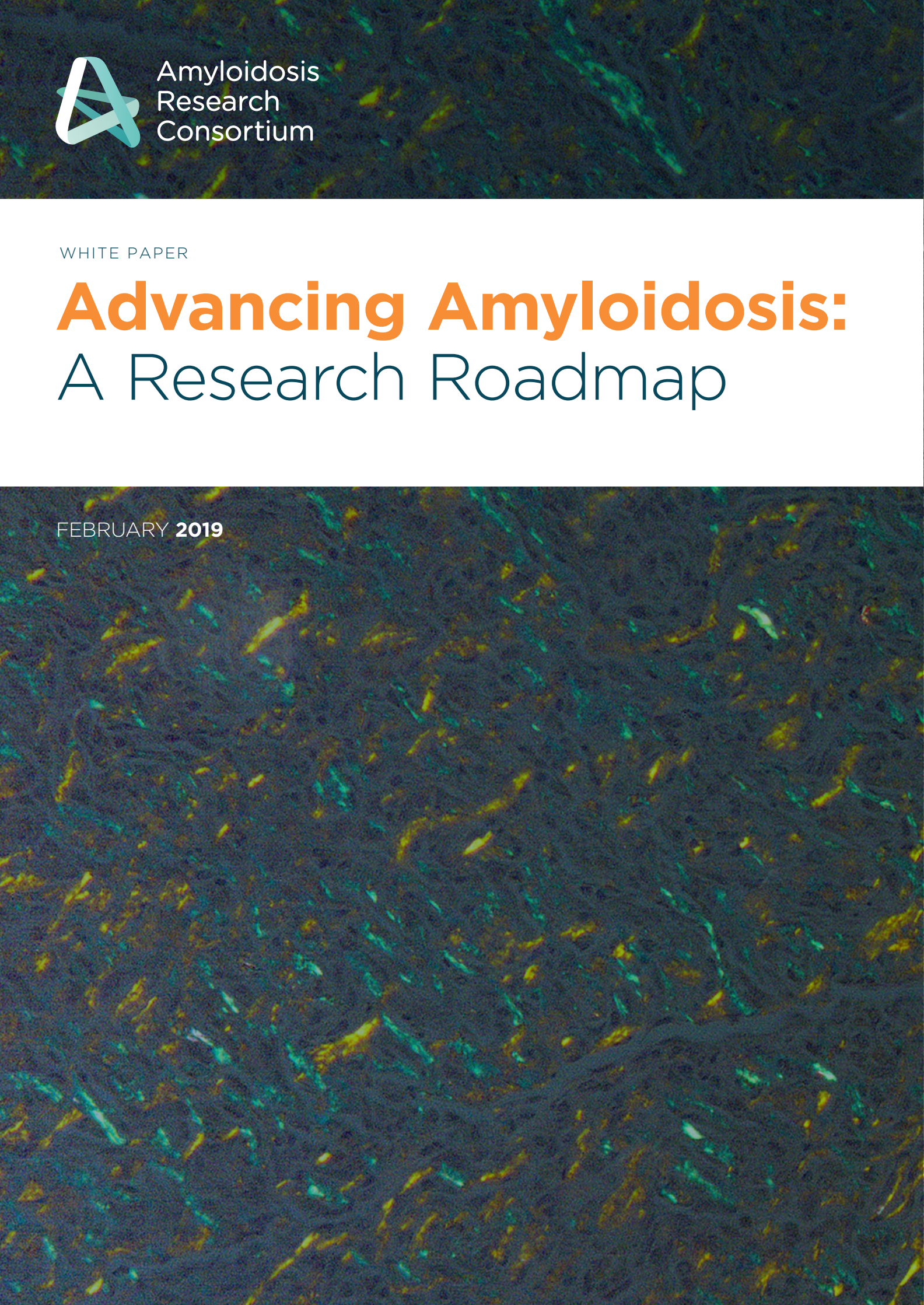


WHITE PAPER

Advancing Amyloidosis: A Research Roadmap

FEBRUARY **2019**

OBJECTIVE

To summarize 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.

PREFACE

This research blueprint is intended to be used by all those conducting amyloidosis research, as well as by funders, policy makers, health technology assessment (HTA) and reimbursement agencies, and service delivery professionals. This approach of publishing a consensus document, drawn from a broad array of amyloidosis stakeholders, might also be useful for other rare disease and innovation communities.

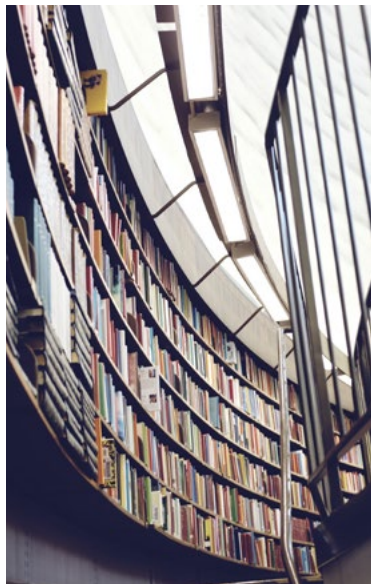
This document highlights priorities in multiple domains of amyloidosis research, including basic research, translational research, diagnosis, clinical research, and health systems and market access. To help drive success in these domains, each section describes what success in that domain should look like.

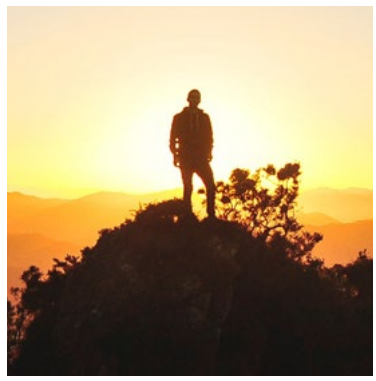
To reflect the opinions of the greater amyloidosis community, great care was taken to draw the goals and priorities outlined in this document from a broad array of amyloidosis stakeholders. Patients should hold the amyloidosis community accountable for achieving the goals outlined herein.

It is important to note that each priority has different timelines and challenges and that each should be implemented and assessed differently for success.

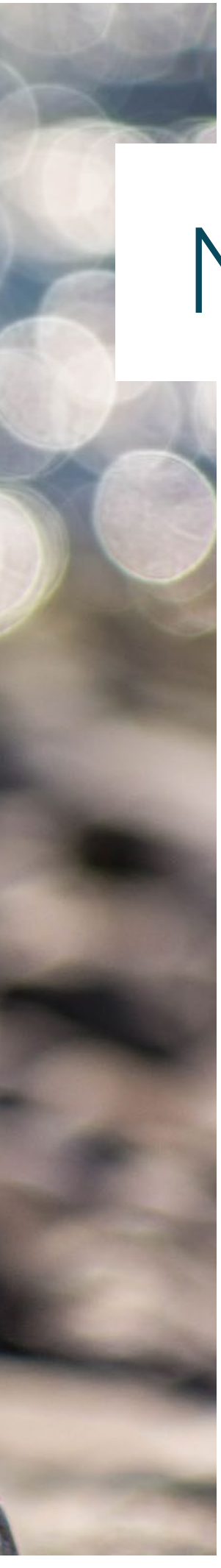
CONTENTS

ARC AMYLOIDOSIS WHITE PAPER
Advancing Amyloidosis: A Research Roadmap





Cover photo courtesy of Jonathan Wall



Methodology

Wide consultation was sought with international experts from academic, clinical, regulatory, patient advocacy, health policy, industry, and other key areas. They included basic and translational research scientists, hematologists, cardiologists, imaging experts, outcomes researchers, regulatory bodies, and industry.

Twenty multidisciplinary participants engaged in a 2-day roundtable meeting in Miami, Florida, in January 2018 that was organized by the Amyloidosis Research Consortium (ARC). The meeting was framed around the following specific themes: basic research, translational research, improved diagnosis, evidence development, clinical trial design, market access, and health systems optimization. Discussions around each theme were led by a panel of 4 to 5 experts appointed by ARC. Before the meeting, panel members consulted by teleconference and email to identify key questions and future direction related to their theme. Their collective views were summarized and presented by a nominated panel lead at the start of each session, followed by highly participatory facilitator-led discussions. A post-meeting summary document of research priorities and critical success factors was sent to meeting participants for review to clarify content and fidelity. The summary document was then circulated to a multidisciplinary group of 52 amyloidosis professionals from the broader expert community who did not attend the meeting for their review and input. As a result, additional priorities were identified and incorporated into each of the research themes. In total, the priorities listed herein were derived from the input of 78 experts representing 61 institutions from 13 countries (see Appendix for a complete list).

Although every priority identified has merit, inclusion of each one in detail is beyond the scope of this white paper. The basic and translational research sections required refinement to narrow the number of priorities. Contributors were asked to rank the importance of each priority through SurveyMonkey®. Those included in this white paper reflect the highest scoring ones and the overall consensus.

Any mention of our or we in this document therefore refers to the community who convened to agree on these priorities, not ARC.

A vision for **better research**

ARC's vision is of a reverse translational approach to amyloidosis research. In this model, patient needs drive the direction of research and discovery, with a circular bedside-to-bench-to-bedside approach that accelerates and increases the ultimate value of research to patients. Such a model underpins the key principles of ARC. The requirements for success are:

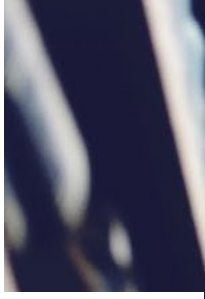
- Understand disease burden and needs from the patient perspective.
- Collaborate better with all stakeholders, especially regulators, HTA bodies, payers, industry, clinicians, researchers, and, most important, patients and patient groups.
- Use collaborative and partnership models for research and innovation, including the concept of "hybrid" research approaches.
- Recognize the different interests, incentives, and rewards across the community to find common goals for alignment.

Such a model will foster better research and will provide benefits for all stakeholders involved.

The need for a **research blueprint**

Much progress has been made across the many domains of amyloidosis research, yet the level of unmet needs remains high and few treatments exist. More progress is needed to ensure that amyloidosis is diagnosed earlier, there is a pathway to develop treatments, improve quality of life, and to ultimately find cures.

A new approach to research is necessary to make effective use of the scarce resources and expertise available in the field. Improved patient outcomes will be best achieved with research that moves forward in an efficient and planned way and with a patient-centric focus to support the diffusion of innovation into clinical practice so that all patients, no matter where they live, will benefit.



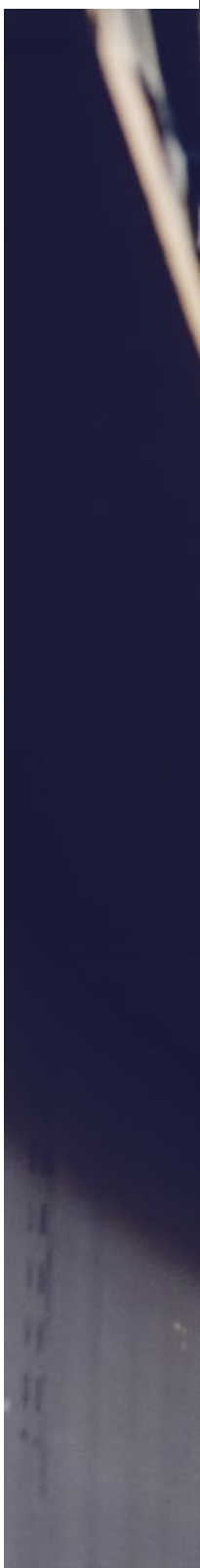
Research **priorities**

OVERARCHING THEMES

Investing in Research

To make progress and find solutions, we have to position amyloidosis research within relevant traditional funding bodies, such as the US National Institutes of Health (NIH). In particular, researchers should advocate for a "home" for amyloid transthyretin (ATTR) and amyloid light chain (AL) amyloidosis research at the NIH. Given that age is one of the greatest risk factors for amyloid diseases, it could be reasonably argued that the National Institute of Aging (NIA), a division within the NIH, is the right home for these diseases. Moreover, a number of parallels can be drawn between amyloidoses and other NIA-funded proteinopathies such as Alzheimer's disease, Parkinson's disease, and Huntington's disease, including the observation that amyloid deposits can accumulate for over a decade before symptoms emerge. Research successes achieved by the amyloidosis community appear to align with the interests of the NIA. Moreover, the development of a research home at the NIH will enhance public awareness, encourage the allocation of research funding, and fuel scientific consensus in the amyloidosis research community.

Furthermore, we should encourage venture philanthropy and industry support to establish more stable and predictable funding streams. With these in place, we can ensure promising research is advanced and expertise is built. It is especially important to excite young clinicians about amyloidosis so they will realize that a career in this arena can be fruitful, productive, and rewarding and to expand the number and breadth of amyloidosis programs. Further, collaboration is vital to increase specialty engagement among basic scientists, clinicians, and industry at all levels and across disciplines to fill the gap between experimental models and human aspects of the disease.



"A lot of questions could be addressed through harmonization of carefully monitored trials which would be very helpful to clinicians, patients and next sponsors."

Natural History

Robust, organized, and mature natural history data are lacking but are critical for better understanding of basic disease biology and for optimized clinical research. Natural history data should be sought from multiple sources, such as patient surveys, placebo-assigned patients in clinical trials, and electronic health records, with a focus on developing new disease-specific end points (eg, a time-to-progression scale). Understanding disease etiology through basic research must be complemented with the development of tools to improve the quality and speed of the clinical trial process and its relevance, to allow for earlier and more accurate diagnosis of disease, and to identify the best treatments for specific patient subgroups.

Biomarkers

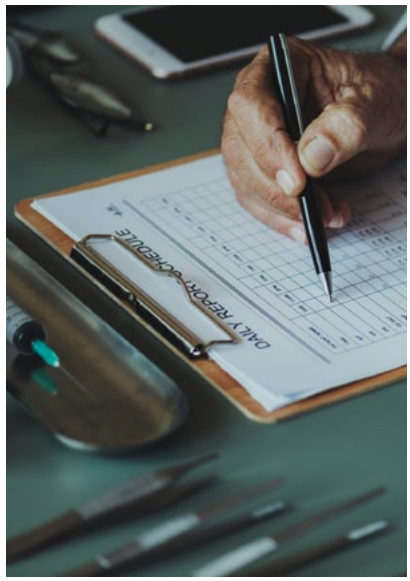
Fundamental to this is the identification of different sets of biomarkers that may indicate who is at risk for disease and the disease type, disease stage, and patient prognosis and that may guide the selection of treatment and the assessment of response to therapy. These biomarkers often emerge from basic research, but they should be scrutinized in patient populations so that their appropriateness for use in academic- and industry-sponsored clinical trials and their acceptance within the regulatory, payer, and HTA bodies, and ultimately in the real-world setting, can be determined. Importantly, we must develop a biomarker strategy to identify the roles of existing biomarkers and how they should best be used. This will enable identification of other needed markers and clarify whether additional evidence is required for existing biomarkers.

Data Sharing

Although there are a number of large, carefully curated amyloidosis databases across the academic community, they were established in isolation from each other, and the broader community cannot access or learn from them. To best use all data created within the amyloidosis community, we have to develop a strategic and global database and biobanking approach that incorporates the establishment of standardized data sets, database, collection and assay techniques, and virtual tissue banking. Such an endeavor will follow best practices for balancing patient privacy with research needs and will guarantee that a framework is incorporated to enhance access and ensure data and materials are used to help answer critical research questions. Establishment of these elements is critical to confirm resources and related metadata are accessible to researchers and collaboration is readily achieved and will increase the efficiency and relevancy with which disease biomarkers and druggable targets are identified and tested.

Clinical Trials

Clinical trials should be designed with novel approaches and end points and with allocation schemes that provide access to active therapy for as many patients as possible, take less time, and include an open-label extension. Patients' needs should be understood and incorporated; we should seek and include input from advocacy groups and patients during the design of clinical trials to understand what end points are most important to them, ensure that we are conducting trials that are relevant, and decide what improvements can be made. It is also important to make the data from all clinical trials—successful or otherwise, investigator-sponsored or industry-sponsored—published and available for the benefit of all.



Focusing our attention on certain priorities in basic, translational, and clinical research and on improved methods of diagnosis and increased access to the best treatments will be critical in driving better quality of life (QoL) and future cures for patients with amyloidosis.

BASIC RESEARCH

Background and Rationale

Our understanding of the basic science of amyloidosis has expanded rapidly in recent years. Although in vitro studies have deepened our understanding of areas such as the amyloidogenicity of proteins, protein misfolding dynamics, and the structure of amyloid fibrils, there remains a lack of understanding on the development and evolution of almost all forms of amyloidosis in animal models and an almost complete lack of detail regarding amyloid formation in human patients. Further research is needed to address the gaps in our understanding and to develop systems that increase the relevance of laboratory models to the pathological and clinical experience in patients with amyloidosis.

Barriers to Basic Research

Further advancing our understanding of the mechanisms of amyloidosis depends on overcoming specific research barriers. In particular, we lack experimental models that accurately and generally represent the human phenotype of disease and that can help answer specific questions related to amyloidogenesis. Additionally, many scientific questions remain hampered by poor access to samples from human patients, a situation exacerbated by the rare nature of the disease; overcoming this critical barrier will require development of physical, or more likely virtual, tissue repositories. Furthermore, questions related to early disease processes are hindered by inadequate imaging agents and biomarkers that can sensitively and specifically detect disease.

Research Priorities

The basic research priorities we have identified can be divided into 2, albeit interrelated, categories:

- Those related to the underlying mechanism of the disease – how it starts and progresses both at the molecular level and in different tissues
- Those related to individual patient variation and disease progression over time – how different persons are more or less susceptible to disease and how this impacts their symptoms and outcomes once disease starts

Here we outline the consensus priorities and indicate how pursuing these priorities may spur new avenues for treatment. Understanding the mechanism of disease enables scientists to identify new drug targets and treatment strategies. These are the points where drugs might be able to stop the disease process or reduce its effects. Understanding the heterogeneity of a disease and how it progresses over time helps identify the patient populations who have slightly different underlying disease mechanisms and the resultant need for different drugs. This understanding also helps determine where a patient is in the disease process, thereby enabling treatment to be tailored more effectively. Over the longer term, our understanding of individual variation could also inform disease prevention strategies.

Underlying Mechanism of Disease

Several priorities relate to the basic biochemistry of amyloidogenesis or protein aggregation—how the precursor protein shifts from being a single molecule to misassembled multiple molecule chains, or fibrils, that characterize disease and how aberrantly shaped single molecules, as well as misfolded oligomers and fibrils, cause toxicity in patient tissue. Goals here include:

- Understand the structure-proteotoxicity relationships for the amyloidoses. In other words, determine the cytotoxic/organ-toxic effects that monomeric proteins, misfolded proteins, oligomers, and fibrils have that lead to dysfunction and how the distribution of a misshapen protein may be influenced by different genetic mutations.
  - Determining which conformers/aggregates cause toxicity and whether their removal reduces organ degeneration would indicate high priority molecular targets for treatment and indicate potential assays to evaluate whether drugs are having the desired effects.

- Determine the relative importance of seeding/propagation in amyloidoses and the mechanisms underlying this process.
  - This is important for understanding whether seeding is a central part of disease etiology. In other words, do individual amyloid molecules create a "seed" that can serve as a building block for the growth of new amyloid fibrils. If so, what factors impact this process? The involvement of rogue cells in this process merits investigation.
  - Determine what is the role of the protein homeostasis network, including autophagy in disease, what drives proteostatic imbalance, and what causes dysregulation of proteostasis.
  - Understanding how the natural mechanisms the body uses to reduce the buildup of amyloid could enable the identification of new drug targets.
  - Understanding how patients vary with respect to these mechanisms could also enable the identification of important pathways and targets.

- Understand the mechanisms underlying organ tropism and the role of the extracellular matrix and tissue-specific bioforces that favor unfolding/misfolding of amyloidogenic proteins.
  - Amyloidoses exhibit different tissue involvement, and this defines a patient's prognosis and treatment options; understanding how different organs are impacted enables more effective intervention, including new targets for drug design that could reduce susceptibility of specific organs to amyloid buildup.

Understanding Patient Variation (heterogeneity) and Disease Progression Over Time

- Identify potential drivers of disease through whole genome sequencing and identify genetic and proteomic signatures that can predict the likely onset of disease.
  - This is a fundamental area of work that examines the genetic and biochemical factors related to disease onset and progression, allowing the potential for earlier diagnosis and treatment before the buildup of amyloid causes organ deterioration. It can also contribute to our understanding of disease mechanisms, be a potential source of drug target information, and will provide a platform for biomarker discovery.

- Understand the change in stress-responsive signaling, including the unfolded protein response (UPR), that occurs with aging.
  - The UPR controls protein homeostasis in the secretory pathway. Determining the mechanisms that lead to increased accumulation of misfolded proteins inside and outside cells will help identify novel targets for treatment.

"Understanding the heterogeneity of a disease and how it progresses over time helps identify the patient populations who have slightly different underlying disease mechanisms and the resultant need for different drugs."

- Understand the mechanism of ATTR and AL precursor protein destabilization and dissociation, including what age-related factor(s) and post-translational modifications make some patients more susceptible to wild-type transthyretin dissociation and AL-forming immunoglobulin light chain misfolding, and aggregation in both cases, and how they are similar to or distinct from the influence of aging on destabilizing pathogenic mutations.
- Defining mechanisms other than destabilizing amino acid mutations will improve the understanding of ATTRwt and offer insight into treatments specifically tailored for this patient population
- Understand the genetics and epigenetics of ATTRwt and AL.
  - We know that certain mutations in ATTR are associated with a higher risk for disease, but many patients do not have these common mutations; therefore, this analysis may help us identify genetic and epigenetic factors that may drive ATTRwt to aggregate. This may help predict disease risk and may allow earlier intervention in susceptible patients.
  - Knowledge of genetic, epigenetic, and proteomic signatures predictive of AL amyloidosis may enhance early detection of disease.
- Explore the basis of sex and race disparities in both the hereditary and the spontaneous amyloidoses.
  - We see different presentations of disease in women and men and different responses to the established disease-modifying strategies. By establishing the sex-specific presentations of amyloidosis, we can determine whether outcomes and interventions require sex-specific consideration.

What Does Success Look Like?

Development of experimental cellular, mammalian, nonmammalian, murine, and computation models to address specific research questions will accelerate our understanding of the mechanisms of amyloidosis. More general models that replicate the disease will support discovery of novel treatments. Sharing of longitudinal patient samples, either through virtual or traditional tissue repositories, will allow a greater number of researchers to conduct patient-centric research. Sensitive and quantitative imaging and biomarker technologies will detect lower levels of amyloid burden. Scholarship programs will grow, encourage, and help retain a key workforce.

"We see different presentations of disease in women and men and different responses to the established disease-modifying strategies."

Amyloidosis Research Consortium

Key Priorities for Basic Research

KEY PRIORITY TOPIC

UNDERLYING MECHANISMS OF DISEASE	Structure-proteotoxicity relationships of monomeric proteins, misfolded proteins, oligomers, and fibrils
	Relationship of seeding and propagation on disease etiology
	Protein homeostasis and intrinsic mechanisms of amyloid clearance
	Drivers of organ tropism
PATIENT VARIATION AND DISEASE PROGRESSION	Genetic and proteomic signatures associated with ATTR and AL onset
	Age-related changes to stress-responsive signaling and protein accumulation
	Factors involved in increased susceptibility to transthyretin dissociation, to AL-forming immunoglobulin light
	Genetics and epigenetics of ATTRwt and of AL
	Sex and race disparities in disease presentation and treatment response chain misfolding, and to destabilization in both cases

TRANSLATIONAL RESEARCH

Background and Rationale

Translational and basic research are closely linked. Translational research represents the bridge between basic research and the clinic, where advancements made in the laboratory will be readily applicable to patients. In this realm, the community has so far identified and validated a prognostic biomarker for advanced stages of cardiac dysfunction in AL and ATTR amyloidosis and has developed imaging tracers to identify certain types of TTR amyloid in the heart, liver, and spleen. Similar tools for other organs and amyloid types and for use earlier in the disease process are needed to improve accurate diagnosis, accelaerate clinical trials, and enhance the evaluation of treatments.

Barriers to Translational Research

A general lack of understanding of disease pathogenesis and multidomain disease progression hinders the development of tools to speed diagnosis and prognosis for improvements in clinical practice. We also lack early disease biomarkers and consensus about which assays, reagents, and technologies to use. Forming connections between clinicians and researchers to foster the sharing of knowledge and resources will help break this barrier. Moreover, standardization of imaging, quantitative proteomics, and staining techniques across laboratories will improve the quality and quantity of available data. Disparate data exist now in many different places, requiring improved collaboration and standardization so that these data may be used to speed relevant biomarker identification and development. Scholarship and fellowship programs to ensure this research continues. A lack of amyloidosis awareness in funding bodies hinders financial support.

Translational Research Priorities

Understanding disease etiology through basic research must be complemented with the development of tools to accelerate diagnosis, improve quality of care, and speed clinical trials.

- Biomarkers often emerge from basic research but must be scrutinized in patient populations to enable use in regulatory and clinical settings. We have to translate biomarkers to the clinic for use in screening, diagnosis, stratification of prognosis, and response to treatment. Particular attention should be paid to those biomarkers specific for CNS or ocular involvement, gastrointestinal involvement, peripheral nerve injury, and irreversible organ damage.
- Expert and regulatory validation of biomarkers will accelerate drug development, improve diagnosis, and aid evaluation of prognosis and response to treatment. Imaging techniques to

quantify amyloid must also be developed.

  - Establishing such techniques will improve diagnosis and allow clinicians to assess whether amyloid load reduces in response to disease-modifying treatments to inform drug development and efficacy.

- Better and more comprehensive diagnostics are needed, including specific assays and tools to diagnose and detect TTR destabilization and dissociation of serum TTR tetramers in order to diagnose patients as quickly as possible
- Making best use of existing tools or developing new ones to assess specific organ involvement and abnormal TTR will lead to earlier and more accurate diagnoses.
- Understand the different mechanisms of myocardial damage and correlation with mortality (sudden cardiac death vs heart failure progression).
  - Greater understanding of these mechanisms is key to identifying new drug-treatable targets, developing assays or electrophysiological tools to evaluate them, and improving response to treatment.

What Does Success Look Like?

Translational success is defined when a person who experiences symptoms is promptly and accurately diagnosed, typed, and staged based on a greater understanding of the disease process and an availability of new assessment criteria across multiple organs and systems. Clinical trial end points will be based on validated biomarkers or other novel end points, and timelines to new treatments will be shortened. For translational research success, a clinician will also be able to identify whether a treatment is working in terms of alleviating symptoms, removing tissue amyloid, or slowing, halting, and reversing the underlying disease biology.

Amyloidosis Research Consortium

Key Priorities for Translational Research

KEY PRIORITY TOPIC

Validate biomarkers from the laboratory in the clinic
Develop diagnostic tools for earlier and more comprehensive diagnosis of organ involvement
Use imaging methods to quantify amyloid load for diagnosis and treatment response
Understand mechanisms of cardiac damage and their impact on mortality

IMPROVING DIAGNOSIS

Background and Rationale

There is clear consensus that treatment should be initiated as early as possible, yet most patients have advanced disease at diagnosis, and as a result may not benefit from treatment. To improve patient outcomes, we must raise clinical suspicion and make diagnoses earlier and more accurately.

Barriers to Diagnosis

Often the symptoms of amyloidosis are nonspecific and are associated with disorders that are much more common, rendering early and accurate diagnosis a challenge. Lack of appreciation for the systemic nature of amyloidosis is compounded by a general lack of communication between specialists and between clinical centers. Suspicion is further impeded by the fact that a diagnosis of amyloidosis is missing from many guidelines of relevant societies.

Diagnostic tools are increasingly available. Although there are commonly used pathways for diagnosis, there is no single, consistently used algorithm. Additionally, with no single test, making the diagnosis can be challenging. Biopsies and histological testing can produce incorrect results and can be misinterpreted.

Priorities to Improve Diagnosis

At the core of facilitating a rapid and correct diagnosis is improving awareness among clinicians. The focus of education cannot be only on hematologists, neurologists, and cardiologists but must extend to other specialists, including pathologists and gastroenterologists. Consensus priorities to improve diagnosis are as follows:

- Specialists typically only look for symptoms relevant to their organ of interest. Patients must be evaluated in a "whole body" manner. Moreover, a risk scoring system must be developed in which red flag symptoms are a central part of a clinician visit.
  - It is important to identify the multiple red flags, combine them into predictive algorithms, and develop tools to assist with earlier diagnosis of amyloidosis.
- Better understanding is needed of the common symptoms associated with amyloidosis and the diagnostic approaches to treat it. We must establish a framework for educational awareness and a unified, strategic approach across the community for educational programs and awareness opportunities.
  - Awareness will aid in raising suspicion and making earlier diagnoses.
- There are several diagnostic tools of varying availability for amyloidosis, among them free light chains, cardiac and renal biomarkers, nuclear scintigraphy, proteomics, and genetic testing. However, these tools often go unused because amyloidosis is not suspected, or, if they are used, they are too frequently used incorrectly. The easiest and most immediate initiatives will aim to improve accurate adoption and diffusion of available diagnostic tools. In particular, it is essential to increase and correct the use of nuclear scintigraphy/DPD/HMDP imaging as an alternative to cardiac biopsy for patients with suspected ATTR.
  - Proper use and understanding of diagnostic tools will aid in making accurate diagnoses once suspicion is raised.

What Does Success Look Like?

Early detection of amyloidosis will lead to improved patient outcomes. When patients receive diagnoses earlier, they have a greater chance to benefit from personalized treatment. Accurate diagnoses will enable the right treatment choices for the underlying disease etiology, thereby increasing survival and QoL.

Amyloidosis Research Consortium

Key Priorities for Diagnosis

KEY PRIORITY TOPIC

- Create a risk-scoring system for suspicion of amyloidosis with unexplained multisystem symptoms and signs and syndromes
- Establish a framework for educational awareness
- Improve adoption and understanding of existing diagnostic tools

CLINICAL RESEARCH

Background and Rationale

Clinical trials in amyloidosis have increased. Two new treatments have recently been approved for hereditary ATTR amyloidosis, a disease for which treatment options had been limited. Although the approval of new products will result in improvements in standards of care and survival rates, they will also give rise to additional challenges for future research: trials that risk becoming lengthier and a lack of clear criteria for approval that will limit progress. Payers, regulatory bodies, and academia often have different priorities and requirements for trials.

There is a critical need to include patients in all stages of clinical trial development, identify patient-relevant end points that serve as acceptable trial outcomes, and increase disease-related research and data sharing to avoid inefficiencies and delays in delivering critical treatments to patients with amyloidosis.

All downstream decision-makers should be involved in the process of designing and executing clinical trials, with patient needs at the forefront. The current approach to clinical development programs must change to get stakeholder alignment across patients, payers, clinicians, regulators, and regions, without creating substantial delays to the development of new treatments.

Barriers to Research

AL amyloidosis and ATTR amyloidosis are rare diseases with diverse clinical presentations and patient subtypes, making patient selection for successful clinical trials challenging. These distinct patient subgroups have different phenotypic features, requiring distinct assessment end points. In addition, in trials of new treatments, failure to consider what is of most value and relevance to patients as well as to HTA and payer groups can lead to lead to upstream challenges. Trial designers often pose research questions that are too limited in scope

or that are unable to adequately address patient concerns. Failure to consider patient needs and viewpoints can also slow recruitment and lead to high discontinuation rates, limiting the usefulness of trials. Restrictions on inclusion criteria in clinical trials are linked to attempts to meet the needs of regulatory bodies and payers, which can slow the process as trials struggle to recruit sufficient numbers of appropriate patients. Lack of collaboration between stakeholders, including industry, regulatory bodies, and academia, as well as competing interests also lead to data being collected in isolation, reducing the opportunity to analyze large and rich data sets that may provide valuable clinical and scientific data that could inform future trials.

"Placebo data from industry trials is a unique and valuable resource. In a rare disease it is an ethical imperative and each company's responsibility to share this with the community."

Clinical Research Priorities

Given that the clinical landscape of disease includes two main amyloidosis types of different etiologies and needs, we have broken the clinical research priorities into general priorities, priorities specific to AL amyloidosis, and priorities specific to ATTR amyloidosis.

General Considerations (both AL and ATTR amyloidosis)

Use of existing data to inform future trials:

A key approach to optimizing future trials is to examine which data are available. It is necessary to be able to combine and draw clinical data from existing data sets from both investigator-initiated and industry-initiated trials. An overall priority is to create a data catalog to identify gaps and the possible need for prospective studies to address those gaps. Assessment of existing data, particularly correlations between biomarker, functional, and QoL data, will help determine which end points are most clinically relevant and patient relevant. Placebo group data or patient data from a study group, including those for which results are negative, must also be analyzed to better understand the natural history of the disease, along with pathology data, which can inform epidemiology and biomarker analyses. Studying data on supportive treatments in amyloidosis may also enhance understanding of the patient perspective and unmet needs. It is imperative that all studies be published, whether the findings are positive or negative, in order to further research. That their data will be used to inform research should be part of an implicit agreement with patients.

Comprehensive meta-analysis of these data will inform future trial designs, including better understanding of different groups of patients and selection of appropriate end points along with standardized outcome measures that can be used across trials and centers.

Regulatory input and payer input are absolutely necessary to ensure that proposed outcome measures and end points are relevant and acceptable to both groups. These data will also help to broaden access after approval, when payers query the value to patients outside the trial participants.

Trial designs:

Academics, clinicians, industry, and the appropriate regulatory bodies should collaborate earlier in the clinical trial development process to enable a more comprehensive evaluation of potentially beneficial agents to mitigate regulatory constraints on trial design and subsequent evidence. This collaborative approach will ensure only those agents with validated clinical potential will move forward in clinical development, gain approval, and be available to the broadest number of patients worldwide.

The aim should be for future trials to be shorter and allow for greater flexibility. Umbrella

designs, which assess several different drugs versus one placebo arm and therefore minimize placebo exposure, and adaptive designs, which allow for the trial design to be altered in real time as data become available, are needed when relevant. Interim analyses and crossover designs should also be used where statistically possible to minimize patient time on placebo while still meeting thresholds for regulatory requirements. Trials in a space with approved treatments must always adopt the gold standard of a randomized controlled trial with a control group receiving standard-of-care treatment. Novel end points that are relevant and measurable, such as composite end points, should be considered in these settings.
We must also undertake prospective observational studies to gain further understanding of disease characteristics and to aid in identification of biomarkers and tools for stratification/staging and clinical end points. Such prospective trials incorporating active ascertainment components (carpal tunnel, imaging, genetic testing) will increase our understanding of the impact of early indicators and potentially lead to the development of trials in presymptomatic patients.

HRQoL measures:

Previously seen as of low priority, health-related QoL (HRQoL) measures are now a key part of clinical trials and must be incorporated as such. Progression-free survival is not predictive and should not replace HRQoL measures. However, further data are needed regarding which instruments and tools are best to

evaluate HRQoL, including which domains are most important for patients. This analysis should consider the requirements of regulatory, HTA, and payer bodies and what changes may have to be made to make HRQoL measures acceptable and meaningful as end points. A toolkit of different HRQoL measures to pull from must be developed given the heterogeneity of amyloidoses. Although some HRQoL measures have been evaluated for reliability and validity for use in studies involving patients with AL amyloidosis, no such effort has been made for patients with ATTR amyloidosis; therefore, and a comprehensive evaluation of currently available HRQoL measures must be conducted.

Measures of physiological function:
Standardized measures of physiological function should be used to assess the functional capacity, response to therapy and prognosis, and may include the Six-Minute Walk Test, the Short Physical Performance Battery, a Cardiopulmonary Exercise Test, Actigraphy, and the Neuropathy Impairment Score. These measures may provide earlier indication of the efficaciousness of an investigational treatment than can be gained from a typical study end point such as mortality or hospitalization. However, given that most measures of function were first developed for nonamyloid disorders, researchers must consider the validity of a given measure if applied to a patient with amyloidosis.

Patient involvement:
Patient involvement is crucial and should be incorporated throughout the trial process.

Several clinical trial elements were identified as critical to making trials more patient friendly and balanced with the needs of other stakeholders, including
the following:

- Shortest trial duration possible with a long-term extension
- Limited use of placebo arms or time on placebo
- Patient-relevant end points
- Open-label extension as a standard component for continued access to effective treatment
- Early access programs

"It is clear you have to start with an understanding of the impact of the disease on the people who have it, and what they value most in terms of alleviation before you set up a measurement and go forward with truly patient-focused drug development."

Optimal trial design should be facilitated through patient advisory boards at early stages during trial design to identify the most relevant end points acceptable to the regulatory bodies, obtaining detailed feedback from patients to assess what improvements can be made and partnering with patient advocacy organizations to facilitate the process. Regulatory agencies require education about the end points relevant to patients. The needs and views of a broad and diverse range of patients and decision-makers should be considered to ensure that trials are designed to maximize the availability of safe and effective treatments for as many patients as possible. Investigator-sponsored trials must help fill evidence gaps and can support regulatory processes if executed in a rigorous manner.
The practical aspects of a clinical trial, such as assessment timing and location, must accommodate the needs of often frail patients for whom travel imparts a considerable burden. Incorporating travel expense reimbursement (eg, for overnight stays) into the clinical trial design is also important to reduce the burden on patients. Designing clinical trials with the patient in mind will encourage enrollment and reduce dropout rates.

AL-Specific Considerations

Trials in different patient subsets:
Specific subsets of patients with AL amyloidosis can be defined at different severity stages; most of the population has moderate disease. Patients at both ends of the severity spectrum are often excluded from trials because of restrictive entry criteria and the need to evaluate drugs in more homogeneous populations. We should design trials for patients in the early stages of the disease, when treatment may be most beneficial, and for patients in the later stages of the disease, when there is significant unmet need, while mitigating the potential high risk for trial failure in these populations. Additionally, the concept of "measurable residual disease" merits study in the population of patients who have responded to light chain–targeted treatment but still have organ dysfunction.

Appropriate end points:
Trials should include end points that are appropriate to each patient subset and are acceptable to regulators for approval and reimbursable by insurance. Establishment of validated outcomes that relate to both pathology and QoL is important for clinical trials in earlier stages of the disease.
For patients who have had a response to light chain–targeted treatment but still have cardiac dysfunction, trial event rates are often slower, limiting the value of survival end points. For these patients, HRQoL, cardiac biomarkers, and midpoint and multimodal functional end points should be included.

For each subgroup of patients, appropriate trial end points and HRQoL measures should

be considered and discussed with regulatory agencies. It will also be important to evaluate correlations between improvement in HRQoL and improvements in organ function to validate HRQoL measures in AL amyloidosis. In addition, response criteria should be reevaluated and potentially updated.

ATTR-Specific Considerations

Appropriate end points and trial designs:
In hATTR amyloidosis, many patients have a mixed phenotype, including both cardiac and neurologic elements, often with greater predominance of one versus the other and with varying genetic subtypes. Therefore, clinical trials in hATTR should include reliable and appropriate cardiac and neurologic end points. Cardiac imaging end points may lead to shorter trial designs and accurately assess pathology; however, collaboration on training approaches is needed to ensure accurate assessment and interpretation of data. ATTRwt patients should also be specifically included in trials because less is known about these patients and the natural history of the disease.
A critical need in ATTR amyloidosis is the development of quick, simple, noninvasive tools that are appropriate in a clinical trial and in the real world to assess neurologic dysfunction and disease progression. These tools are necessary for monitoring of patients who are known to have ATTR mutations but who do not yet have symptoms to determine when treatment should be started and to assess in clinical practice whether a drug approved by the US Food and Drug Administration or the European Medicines Agency is working as it should.

Placebo data from ATTR neuropathy and cardiomyopathy trials have provided significant natural history data. Trials should move toward reducing the use of placebo and begin studying combination treatments in ATTR.

CNS and ocular involvement:
CNS (including dementia, focal neurologic symptoms, and cerebrovascular bleeding) involvement and ocular involvement in both wild-type and hereditary ATTR are less well understood; fewer specific treatments are available to address these manifestations. It is critical that reliable tools to assess CNS and ocular involvement and progression be developed.

What Does Success Look Like?

Data sharing and analysis, along with collaboration across academia, industry, clinicians, and regulatory bodies, will streamline the clinical trial process and, in turn, reduce time and costs lost to duplication of efforts or to avenues of research that are not clinically or scientifically relevant and from which future patients are unlikely to benefit. Involving patients and decision-makers in clinical trial planning from the earliest stages and keeping them at the center of the process will encourage recruitment and retention and improve the efficiency of trials. These approaches will lead to well-designed trials that facilitate the development of treatments suitable for and accessible to a broad range of patients and will increase knowledge about amyloidosis.

Amyloidosis Research Consortium

Overview of Key Priorities for Clinical Research

KEY PRIORITY TOPIC	
GENERAL PRIORITIES	Identify and leverage existing data sets where possible
	Standardize prospective data collection across centers
	Undertake a comprehensive review to compare and critique existing QoL tools
	Develop and monitor trials for patients at various disease stages
	Undertake prospective observational studies
PRIORITIES SPECIFIC TO AL AMYLOIDOSIS	Develop trials for different subsets of patients, including those at both ends of the severity spectrum
	Develop trials for “organ-refractory” patients
	Engage with regulatory bodies as a community to further discuss patient-reported outcomes, end points, and trial designs, leading to guidance documents for registrational trials
	Understand the role of measurable residual disease and light chain toxicity in patients with persistent organ dysfunction
PRIORITIES SPECIFIC TO ATTR AMYLOIDOSIS	Design mixed-phenotype studies incorporating both neuropathy and cardiac end points
	Develop studies that include ATTRwt amyloidosis
	Initiate combination therapy trials in ATTR
	Better focus on CNS and ocular involvement, including development of diagnostic tools, understanding progression, and development of treatments
	Develop quick, simple, and non-invasive neurological tools to follow yearly mutant TTR carriers and detect earlier disease onset as well as disease progression

HEALTH SYSTEMS AND MARKET ACCESS OPTIMIZATION

Background and Rationale

Although clinical development programs have historically sought feedback from a wide range of stakeholders, feedback from regulators has often been sought earlier and weighted disproportionately against those of HTA and payer bodies. These requirements are often different from those of HTA and payer bodies. Given that regulatory approval does not guarantee access, it is critical to provide HTA and payer bodies with the data they need to better understand the value of new treatments compared with the current standard of care. The value proposition of a new treatment in the rare disease space depends a great deal on the opinions of experts, patients, and caregivers regarding the burden of disease and the impact of treatment; therefore, the perspectives of these key stakeholders must also be captured, clearly understood, and communicated.

"There is a huge disconnect between the data needs in the regulatory enviroment and health technology assessment and reimbursement decision making."

Barriers to Market Access

Clinical development programs are almost always designed to achieve marketing authorization in the quickest time possible. Speed to market is positive but can result in suboptimal data for clinical and cost-effectiveness assessments. New treatments are coming to market with very high prices, but the relative magnitude of benefit is often uncertain. In the context of increasingly tight health care budgets, pricing and budget impact are increasingly important considerations and pose major barriers to patient access. There is a need to provide robust epidemiological data as well as data that quantify the amyloidosis disease burden and patient preferences to support appropriate pricing.

Health Systems and Market Access Optimization Priorities

Solutions must be geared toward better meeting the evidence requirements of HTA and payers. Market access and health systems research should be an essential, integral part of optimally designed clinical development programs.

Research to address uncertainties and support value creation

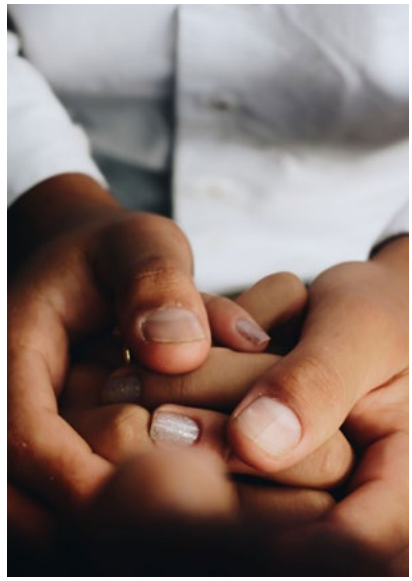
The types of research that could have substantial value for decision-making for market access and the adoption and diffusion of research results include:

- Localized epidemiological data to help payers understand the population who will benefit from and the budget impact of new treatments
- Current care patterns and associated outcomes across geographic regions and in clinically important subpopulations to inform relevant reference groups for health economic (cost-effectiveness, clinical, and budget impact evaluations)
- Quantitative description of disease progression, including extrapolation or modeling approaches to assess lifetime impacts
- Assessment of patient and caregiver utilities and preferences, QoL, comparative effectiveness against standard of care, societal benefits, natural history, and assessments in real-world relevant populations

Market access-oriented trial design

Payers need education, particularly in the case of rare diseases. Payers are unfamiliar with the patient perspective and trying to inform them at the time of an HTA meeting is too late. It is important to generate robust patient-level data that can be dispersed across a research and

development, regulatory, and payer approval continuum. Scientific peer-reviewed publications brokered by a patient advocacy group are required.



Appropriate end points that demonstrate value from both the patient and the payer perspective must be identified and incorporated into the design of trials to ensure that the right data are being collected at the right time.

Collaboration and knowledge sharing for market access

Collaboration across companies and academia is critical to efficiently address common gaps (ie, need for registries, development of health economic models to facilitate evidence generation), minimizing duplication of effort and costs.

An overall framework of market access approaches and priorities will help in mapping out early stakeholder engagement and ensuring we are filling the gaps required to bring new treatments to patients with amyloidosis in the most optimal way.

What Does Success Look Like?

Addressing the likely hurdles in the way of market access early on as part of a strategic approach to evidence development will ensure important amyloidosis treatments are adopted by health systems without the delays and barriers we are currently experiencing. Ensuring that clinical development programs are designed in way that, as far as possible, meets the demands of regulators, health technology assessment bodies, and payers in different countries will provide additional certainty and strengthen the value proposition of new treatments. Investment into and collaboration on the creation of additional evidence to improve knowledge of the disease burden and natural history of amyloidosis and the preferences and values of the patients with amyloidosis will improve the ability of the amyloidosis community to prioritize and optimize research.

Amyloidosis Research Consortium

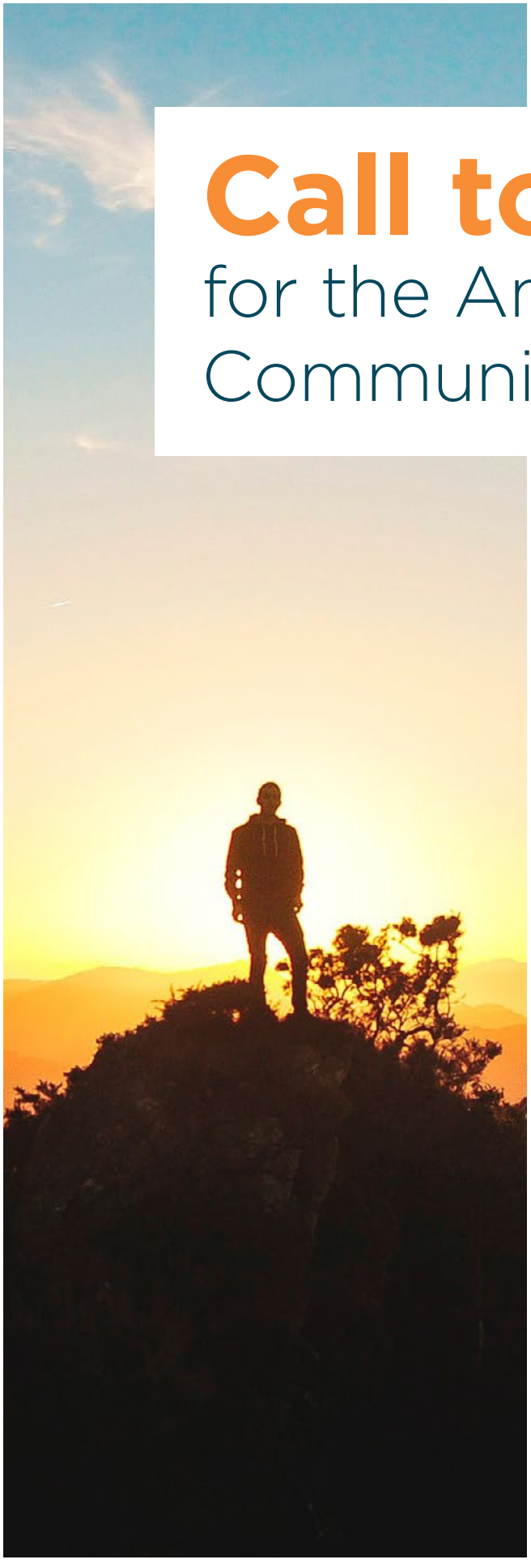
Overview of Key Priorities to Optimize Market Access

- Engage and partner with decision-makers early on clinical development programs
- Promote the complementary roles of commercial and academic research in generating the data needed to gain both regulatory and market access approval of new treatments
- Promote efforts to control excessive pricing of new treatments
- Conduct research to understand patients' and caregivers' perspectives on the benefits and risks of treatment and the desired clinical and personal outcomes
- Improve understanding of the prevalence, natural history, and disease burden of amyloidosis by analyzing and improving secondary real-world evidence sources
- Share knowledge within key stakeholder groups about market access and advocate for initiatives to bring about the most critical changes needed in the system
- Communicate with, and educate, regulatory and payer groups about relevant end points and patient needs

The research **blueprint**

From vision to reality

We have outlined a set of research priorities for basic, translational, clinical, and health economics and market research and a set of priorities to improve diagnosis. Importantly, these priorities should always be informed by patients. They should also include perspectives from regulatory agencies, payers and HTA bodies, and other decision-makers from the beginning to ensure the research is relevant. All stakeholders must work together to cross disciplines, share data, ensure research continuity, and ultimately pool limited resources to perform research that, whenever possible, matters to patients. ARC, as an honest broker, will hold working group meetings and advisory boards each year to review advances in research and consequently reevaluate these priorities. ARC will take ownership of and advance those priorities that have been identified through this process as best driven by ARC. ARC is also uniquely positioned to convene stakeholders to facilitate collaboration and monitor progress. It is the responsibility of all those working in the field to hold the community accountable to the research priorities most likely to improve survival and QoL for patients with amyloidosis.



Call to action
for the Amyloid Research Community

The amyloidosis research community is composed of many brilliant investigators who can accomplish much together. The commitment of this research community must be to communicate, to collaborate, and to keep a razor-sharp focus on improving the outcomes that matter most to patients with amyloidosis.

As a community, we have a responsibility to maximize scarce resources and to share knowledge of our successes and our failures to ensure that scientific progress can be made.

The broader amyloidosis community, including patients and patient advocates, must hold the research community accountable for advancing the key priorities as identified through the rigorous process that led to this research blueprint.

About **ARC**

WHO WE ARE

The Amyloidosis Research Consortium (ARC) is an independent 501(c) (3) nonprofit organization dedicated to accelerating the development of and access to new and innovative treatments by driving the research that will have the greatest impact on the length and the quality of life of patients with amyloidosis.

OUR VISION

Our vision is to make a significant, material contribution to the curability of amyloidosis. There is an urgent need to improve survival and quality of life in amyloidosis. We want amyloidosis to be a disease people live with rather than die from, and, despite significant steps forward in recent years, there is still so much more to do.

OUR FOCUS

ARC is focused on developing the critical research tools, assets and infrastructure needed to accelerate progress in amyloidosis research. Our research model is predicated on speed, efficiency, and excellence. We have a razor-sharp focus on delivering outcomes for patients within an acceptable time frame. We also build collaborations across industry, academic, regulatory, and other relevant stakeholders to align research strategies, ensuring that scarce research resources are optimized and directed to prioritized areas of research.

Ultimately, our work is dependent on the successful approval, adoption, and diffusion of new treatments and diagnostic tests in health systems around the world. Consequently, ARC is also focused on understanding the unmet needs of and the value of treatments to patients to ensure worldwide market access.

OUR LEADERSHIP

Isabelle Lousada, President and Chief Executive Officer, has been the driving force behind ARC, building successful collaborations and programs across the sectors to advance the science and understanding of the amyloidosis diseases.

Isabelle was diagnosed with AL amyloidosis and was one of the first patients to successfully undergo stem cell transplantation. For the past 20 years she has been committed to empowering other patients while serving on several boards and committees, speaking at leadership meetings and key events to encourage research, increase access, and support the critical and unmet needs of amyloidosis patients.

APPENDIX

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Amyloidosis Research Consortium

Accelerating the development of and access to new and innovative treatments for amyloidosis.

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