

# Building a Collaboration Network in Transthyretin Cardiac Amyloidosis: Challenges and Opportunities

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**Updates in Cardiac Amyloidosis: CME Conference**  
**Mayo-ASU Health Futures Center**  
**14 January 2023, Phoenix, Arizona**

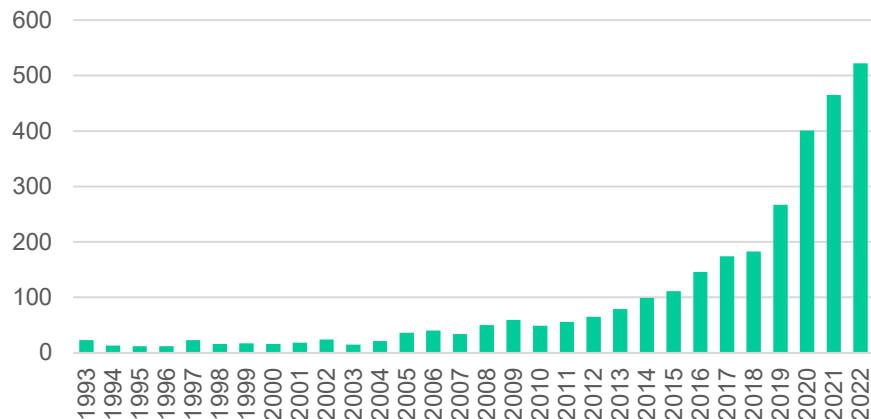
# **Transthyretin Cardiac Amyloidosis (ATTR-CA)**

- **higher prevalence than previously recognized in patients with HFpEF (ATTRwt / ATTRv)**
  - **under-diagnosed, under-treated**
- **often long delay between symptoms onset and definitive diagnosis**
  - **high utilization of health services in interval before diagnosis**
- **poor prognosis if untreated**
  - **median survival (2.5-3yr ATTRv : 3-5 yrs ATTRwt)**
- **expansion of Rx options**
  - **TTL silencers and stabilizers (ATTR-CM and ATTR-PN)**
- **Rx most effective before progression to NYHA class III-IV**
  - **reinforces priority for early detection**

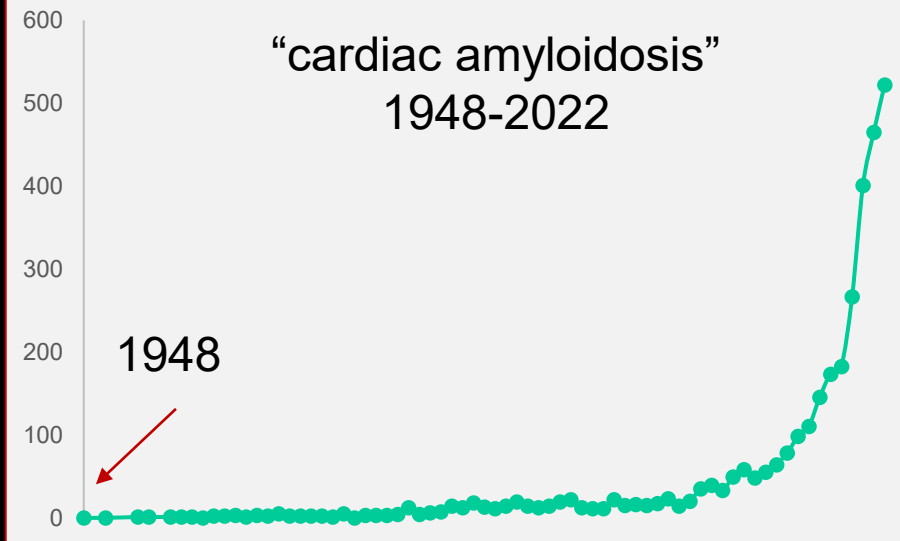
# ATTR-CA: *The publication tsunami*

PubMed Search Term (*italics*) results by year, quotations represent exact phrase

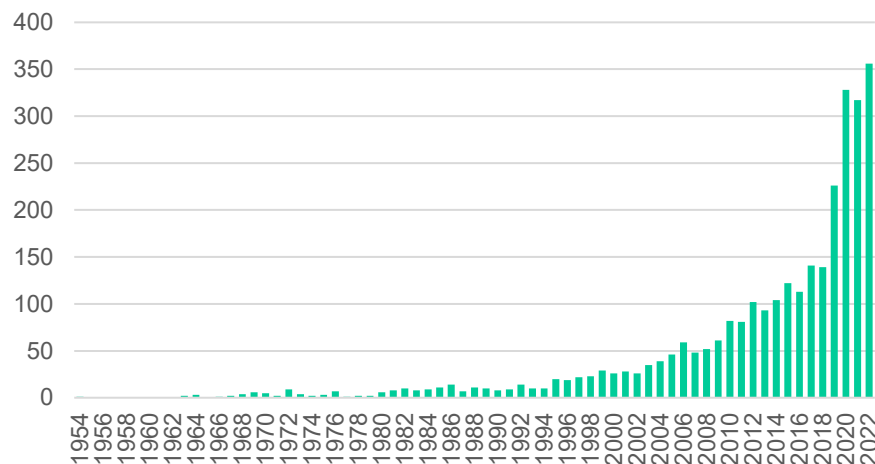
"cardiac amyloidosis"  
1993-2022



"cardiac amyloidosis"  
1948-2022



"cardiac amyloidosis therapy"



# **Transthyretin Cardiac Amyloidosis (ATTR-CA):**

- **limited Arizona-specific data**
  - **prevalence/incidence across age, gender, ethnicity, geography, SDoH**
  - **treatment patterns and outcomes**
- **majority of national/international data from hospitalized patients and specialized amyloid clinics in academic medical centers**
- **limited data on Hispanic populations and none on Native American populations**

# **Transthyretin Cardiac Amyloidosis (ATTR-CA)**

- **transition from invasive endomyocardial biopsy to non-invasive scintigraphic imaging**
- **development of multi-parameter phenotypic risk scores to select patients for scintigraphic diagnosis versus economically unrealistic imaging of all HFpEF / NP cases**
  - **clinical, ECG, echocardiographic, ICDs, claims data, non-cardiac predictors (neuropathies, carpal tunnel, synovitis/tenosynovitis, spinal stenosis)**
  - **new ML/AI algorithms**
  - **need for validation of risk score metrics across cohorts with variable ATTR-CA prevalence rates**

# **Issues in Transthyretin Cardiac Amyloidosis: Diagnosis and Clinical Management**

- **improve broader clinical recognition and awareness beyond specialized amyloid centers**
- **paucity of validated low-cost biomarkers from easily acquired biospecimens (blood, urine)**
  - **expand cost-effective screening for earlier detection and Rx initiation**
  - **prognosis and prediction of PN to CM progression risk**
  - **evaluation of Rx efficacy**
  - **disease progression monitoring and correlation with functional metrics and QOL**
  - **screening of asymptomatic ATTRv cohorts for late onset disease due to incomplete mutation penetrance**

# **Issues in Clinical Management of ATTR-CM: Treatment**

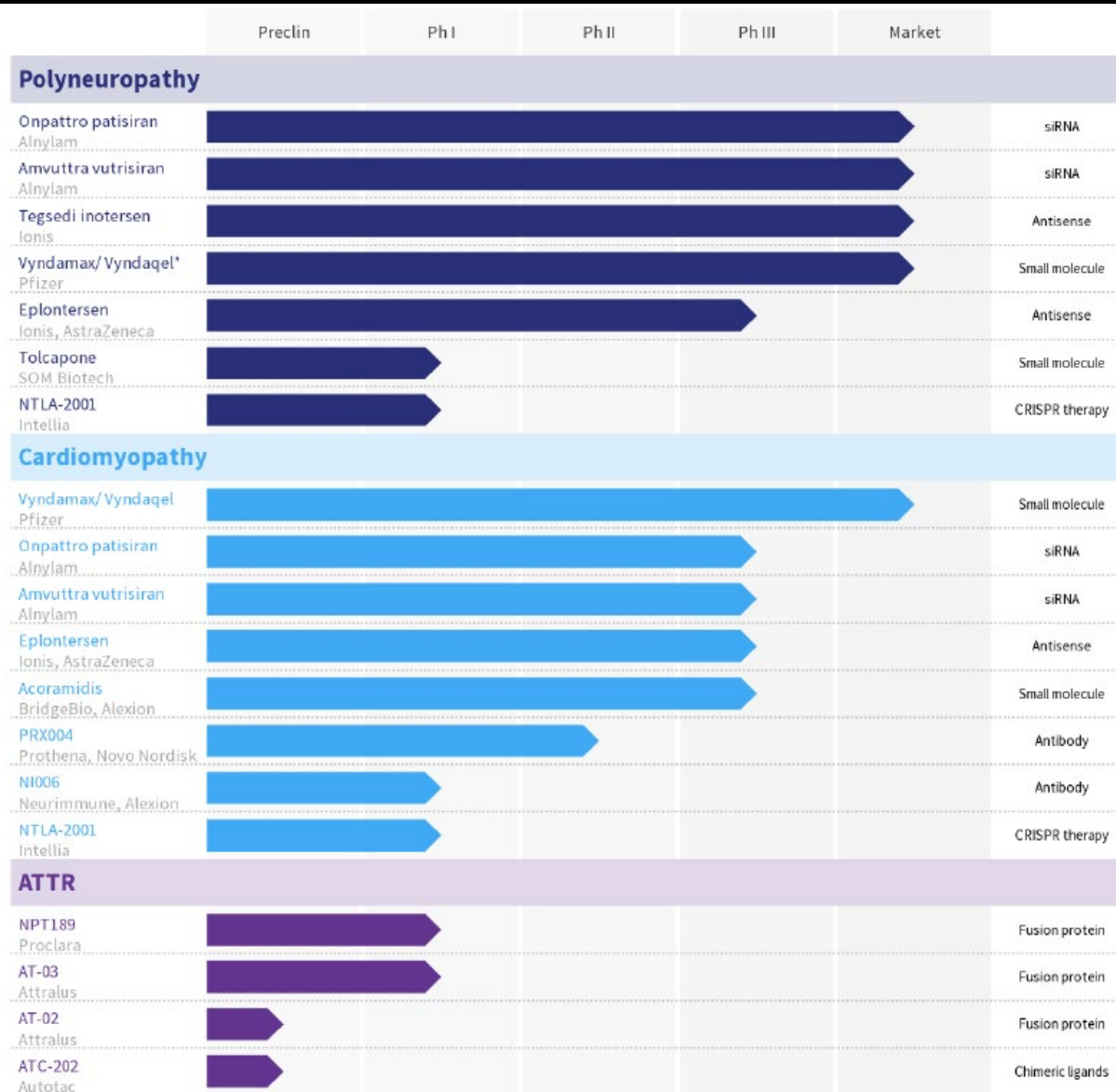
- **comparative efficacy of TTR stabilizers and silencers?**
- **value of combination Rx**
  - **additive/synergistic; no benefit; new AE risks?**
  - **when to transition from monotherapy?**
  - **agent dose titration, dosing frequency and order of administration?**
  - **economic feasibility given high cost of individual agents?**
- **are there thresholds for irreversible progression and lack of Rx efficacy?**
- **is ATTR-CM reversible (microfibril clearance agents)?**

# **Disease-Modifying Agents in Transthyretin Amyloidosis: Treatment Cost**

- **currently approved Rx require life-long therapy**
- **high annual cost of approved Rx (\$225-500K)**
- **age-related prevalence and significant OOP spend for older patients under Medicare-Part D**
  - **influence on adoption rates and Rx adherence**
- **substantial reduction in list price for existing Rx to achieve cost-effective QALY thresholds of \$50-150K**



# The ATTR Therapeutics Pipeline



Source: Company websites and [BCIQ](#) • \* Not approved for ATTR-PN in the U.S.

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# **Transthyretin Cardiac Amyloidosis: A Pending Therapeutic Paradigm Shift?**

- **currently approved agents require lifelong therapy**
- **transition from Rx disease modification to curative intervention?**
  - **CRISPR-cas9 TTR gene editing knockout (Intellia/Regeneron: NTLA-2001)**
  - **initial efficacy studies in hereditary amyloid polyneuropathies and ongoing expansion to ATTR-CM**
  - **encouraging duration of reduced TTR expression levels (6-12 months) but clinical benefit to be demonstrated**
  - **threshold of hepatocyte transduction efficiency required for long term efficacy?**
  - **monitoring off-target effects (often delayed)?**

**The Challenges and Opportunities in TTR-Amyloidosis  
Reflect Many of the Same Elements  
Shaping Biomedical R&D and Healthcare Delivery At Large**

# **The Contemporary Environment for Biomedical R&D and Healthcare Delivery**

- **aging populations, economically unsustainable chronic disease burden and major unmet clinical/social needs**
- **public and political expectations of constant innovation to improve access, availability and quality of care, lower cost, clinical outcomes and QOL**
- **multiOmics stratification of major diseases into subtypes with distinct molecular pathologies (precision medicine)**
- **high Rx prices for smaller market of size of subtype-specific Rx (proliferation of 'orphan status' designations)**
- **need for companion Dx in disease subtype Rx selection**

# **The Contemporary Environment for Biomedical R&D and Healthcare Delivery**

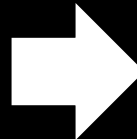
- **escalating scientific and clinical complexity (staying current)**
  - **pace and diversity of innovation: new concepts; new technologies**
  - **burgeoning large-scale data sets**
- **fusion of previously largely separate domains**
  - **biomedicine, engineering, computing**
  - **new combination products: Dx-Rx-device-Ix algos**
- **accelerated adoption of ML/AI technologies**
  - **regulatory validation (SaMD)**
- **new regulatory and pharmacoeconomic requirements: efficacy, safety and **VALUE****

# Solutions for Major Unmet Medical Needs Require Sophisticated Integration of Multidisciplinary Expertise

## The S4 to M4 Paradigm Shift

### S4

- single discipline/speciality
- single institution
- subcritical resources
- slow (translation to practical benefit)



### M4

- multidisciplinary/specialities
- multiple institutions
- managing scale and integration logistics
- momentum (faster translation and adoption)

# Solutions for Major Unmet Medical Needs Require Sophisticated Integration of Multidisciplinary Expertise

## The S4 to M4 Paradigm

### S4

- single disciplinary/specialty
- single disciplinary/specialties
- single institution
- multiple institutions
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**SILOS SUBVERT SOLUTIONS**



# Arizona

- **third fastest growing US state (Tx, Fla, Az)**
- **metro-Phoenix: Maricopa County**
  - **now fifth largest US urban population (cf. Philadelphia, Houston comps)**
  - **second fastest population growth in US**
- **unique demographics**
  - **Hispanics (24%), Native Americans (5.6%)**
- **limited number of major healthcare provider systems facilitates development of clinical research collaboration network trials**
  - **Abrazo, Banner, Dignity (Common Spirit), Honor Health, Mayo, ValleyWise, VA**
  - **attraction to industry sponsors of turnkey networks to accelerate investigational trials (Dx, Rx, devices, Ix algos)**
- **rapid growth in university R&D**
  - **ASU, UA, NAU: \$1.5 billion annual grant revenues**



# **Network Arizona: Building State-Wide Consortium Networks**

- **Aegis Consortium (pandemic preparedness)**
- **ACCEL: Arizona Coalition for Comprehensive Evaluation of Long COVID**
- **Arizona Alzheimer's Consortium**
- **Arizona Telemedicine Council (platforms, policy)**
- **Arizona Emergency Medical Reserve System (pandemic and disaster preparedness, emergency supply chain management)**
- **WearTech Applied Research Center (sensors, remote health monitoring)**

# Exploration of New Biomarkers for ATTR-Amyloidosis to Facilitate Expanded Diagnostic Screening and Disease Progression Monitoring

Biobanks	New Biomarker Analytes	Analytic Platforms	Data Analytics
<ul style="list-style-type: none"> <li>● longitudinal registry paired with EHRs</li> <li>● ethnic diversity</li> <li>● disease stages</li> <li>● multi-organ amyloidosis               <ul style="list-style-type: none"> <li>- cardiac</li> <li>- non-cardiac</li> </ul> </li> <li>● blood, urine</li> <li>● biopsies</li> </ul>	<ul style="list-style-type: none"> <li>● multiOmics ATTRwt/v profiling               <ul style="list-style-type: none"> <li>- WES/WTs (WGS)</li> <li>- proteomics</li> </ul> </li> <li>● exosomes</li> <li>● ATTR structural biology</li> </ul>	<ul style="list-style-type: none"> <li>● NGS</li> <li>● mass spectrometry</li> <li>● hyperspectral microscopy</li> <li>● TTR subunit exchange assays</li> <li>● TTR peptide probes</li> <li>● cryoEM</li> </ul>	<ul style="list-style-type: none"> <li>● high performance computing</li> <li>● ML/AI               <ul style="list-style-type: none"> <li>- expanded multi-parameter risk scores</li> </ul> </li> <li>● pharmaco-economic analyses</li> </ul>

## **The Arizona Transthyretin Translational Research Network (ATTR-N)**

- **build state-wide network of research and clinical expertise for advances in the detection and treatment of ATTR-amyloidosis**
- **generate detailed epidemiological data on ATTR-amyloidosis prevalence in Arizona, clinical interventions and outcomes**
  - **age, gender, ethnicity, geography**
  - **new hereditary risk variants in Hispanic/native American populations**
- **analyze multi-level (patient, provider, payer) barriers and facilitators to implementation of EBP care protocols**
- **build additional scale via collaboration with other national/international COEs in ATTR-Amyloidosis**

# Disclosures



**Board of Directors (Oncology Therapeutics)**



**Board of Directors (Oncology Molecular Diagnostics)**



**Board of Directors (CAR-T Cell Therapy)**



**Board of Directors (Next Generation Nanopore Sequencing)**



**Scientific Advisory Board (Gene Editing)**



**Scientific Advisory Board (Infectious Disease Dx and Rx)**



**Co-Founder (ML/AI Computational Modeling of Immune Recognition Epitope)**

**Slides Available at: <https://casi.asu.edu/presentations/>**