

AMYLOIDOSIS CENTER

Non-Immunoglobulin Renal Amyloidosis

Vaishali Sanchorawala, MD
Professor of Medicine

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**BOSTON
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Amyloidosis Center
Boston University Chobanian & Avedisian
School of Medicine

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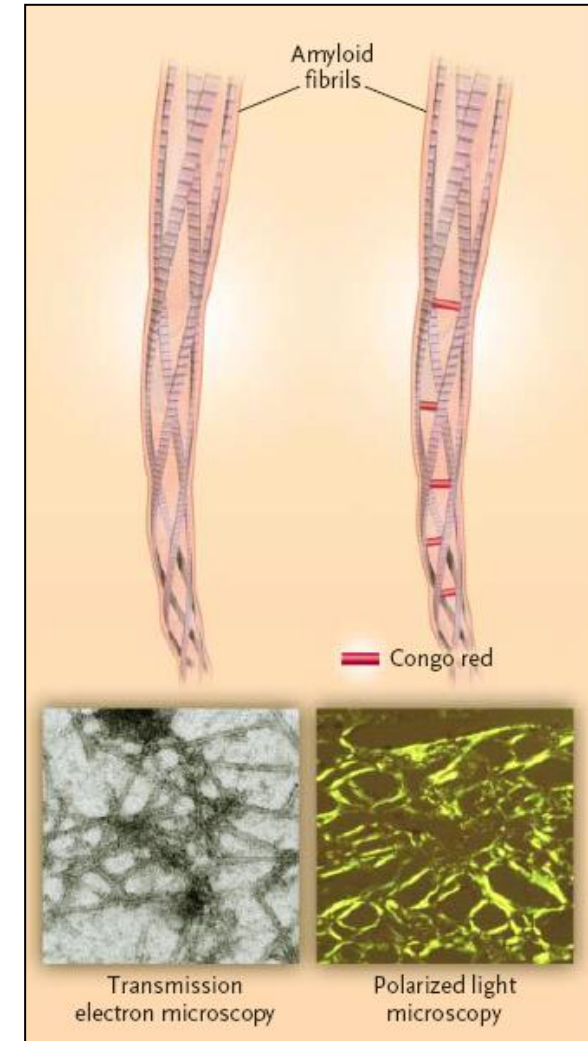
Learning Objectives

By the end of this presentation, participants will be able to:

- **Recognize the major types and clinical presentations of non-immunoglobulin renal amyloidosis**
- **Apply a diagnostic approach to accurately identify and type amyloid**, including the role of kidney biopsy, mass spectrometry, and genetic testing
- **Describe current and emerging treatment strategies and their implications for renal outcomes**

The systemic amyloidoses

- Group of diseases characterized by shared pathologic process
- Extracellular deposition of insoluble fibrillary proteins in organs and tissues
- Protein misfolding leads to amyloid fibril formation
- Amyloid fibrils are composed of beta-pleated sheet protein aggregates

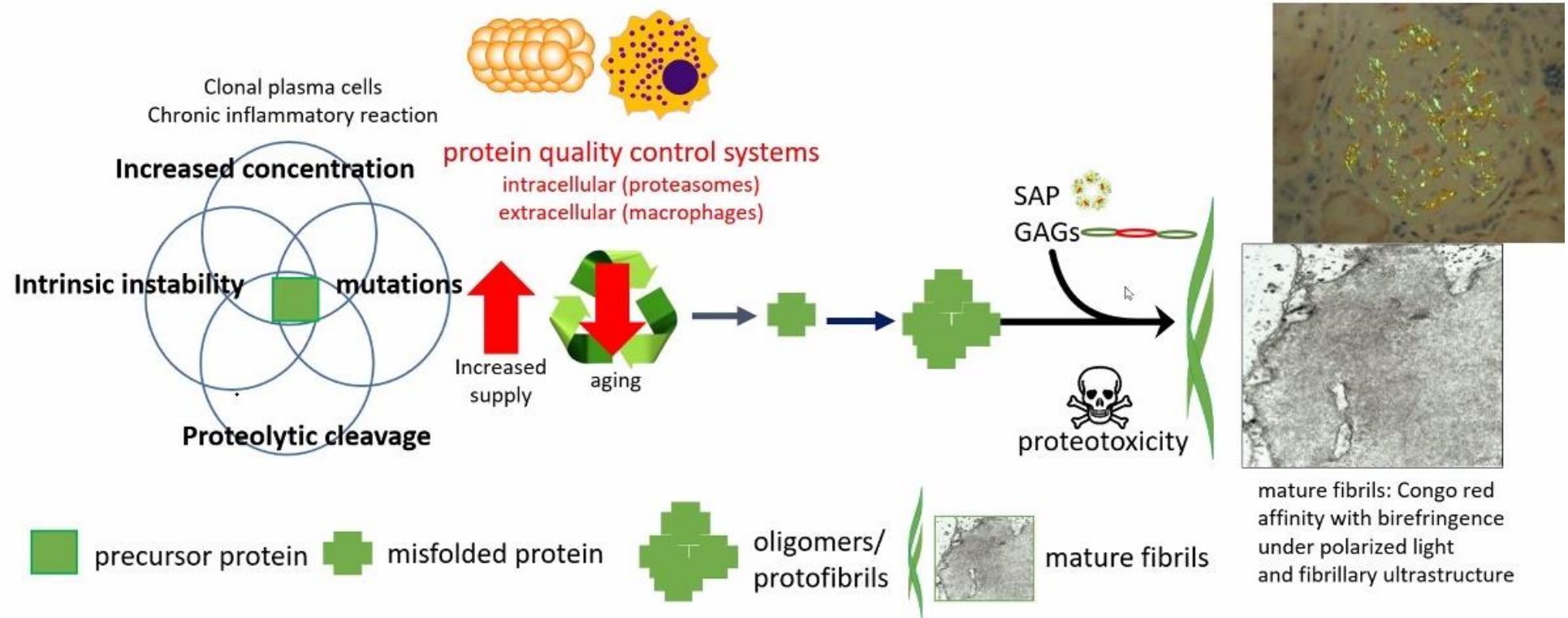


Classification

Table 1. Types of amyloidosis

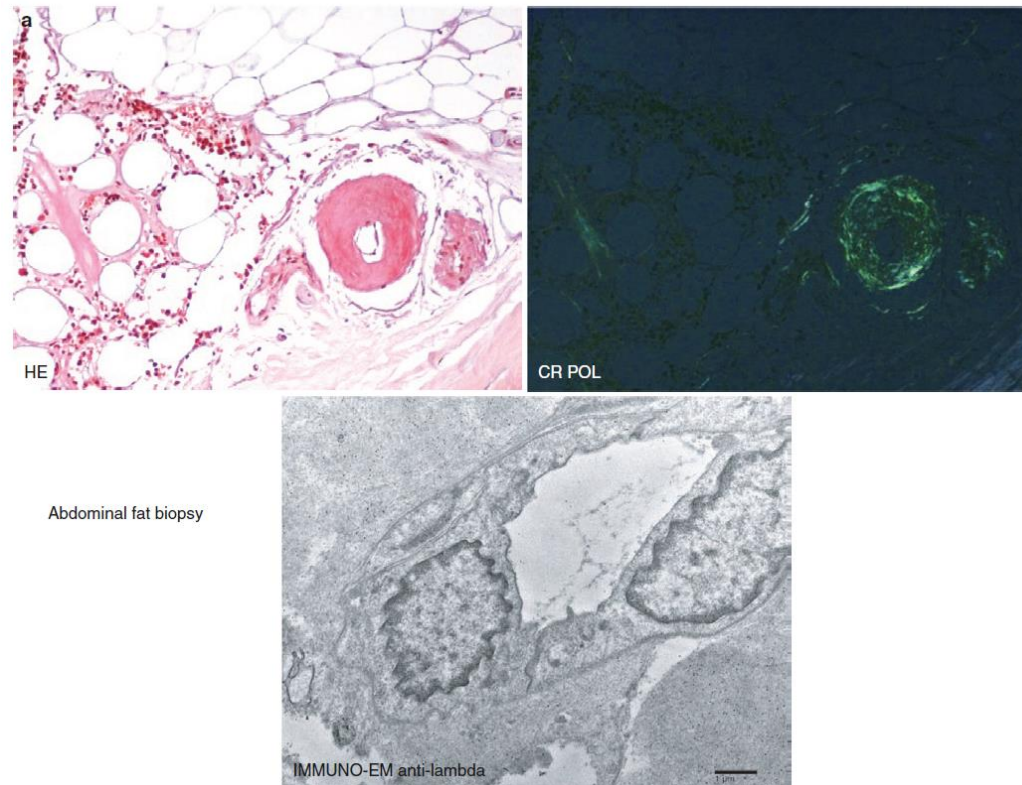
Disease	Precursor protein	Amyloid protein	Organ involvement
Systemic forms			
AL amyloidosis	Immunoglobulin light chain	AL	Kidney, heart, liver, GI tract, spleen, nervous system, soft tissue, thyroid, adrenals
AA amyloidosis	Serum amyloid A (SAA)	AA	Kidney, liver, GI tract, spleen, autonomic nervous system, thyroid
Familial amyloidosis	Transthyretin, apolipoprotein AI, apolipoprotein AII, fibrinogen A α chain, lysozyme, gelsolin, cystatin C	ATTR, AApoAI, AApoAII, AFibA, ALys, AGel, ACys	Varies with amyloid protein and mutation. Kidney affected in TTR, ApoAI, Apo AII, FibA α , and Lys disease
Senile systemic amyloidosis	Transthyretin (wild-type)	ATTR	Heart, soft tissue
Dialysis-related amyloidosis	Beta-2 microglobulin	A β 2M	Periarticular tissue, bone
Localized forms			
Localized AL	Immunoglobulin light chain	AL	Tracheobronchial tree, bladder, ureter
Alzheimer's disease	A β protein precursor	A β	Brain
Creutzfeldt-Jakob disease	Prion protein	APrP	Brain
Type 2 diabetes mellitus	Islet amyloid polypeptide	AIAPP	Pancreas

Pathogenesis of amyloid fibrillogenesis



Identifying amyloidosis

- **Diagnostic hallmark:** green birefringence on Congo red-stained tissue viewed under cross-polarized light microscopy



Surrogate tissue biopsies in the diagnosis of amyloidosis

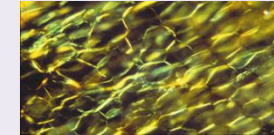
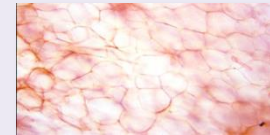
- In the absence of easily accessible involved organ, abdominal fat pad aspiration is a useful surrogate tissue for biopsy.
- Often the first diagnostic test when clinical suspicion for amyloidosis is high. This is quick, simple and safe!
- Diagnostic sensitivity varies by amyloidosis type:
 - AL: 75-90%
 - AA: 50-65%
 - ATTRwt: ~25%
- Both **false negatives** and **false positives** can occur.



Diagnosis requires two steps

1. Tissue biopsy of target or surrogate site and Congo red staining

- ✓ Abdominal fat (75-80%)
- ✓ Bone marrow (~70%)
- ✓ Minor salivary gland (~80%)



2. Accurate identification of amyloid precursor protein

- ✓ Appropriate treatment
- ✓ Assess prognosis
- ✓ Genetic counseling (when appropriate)

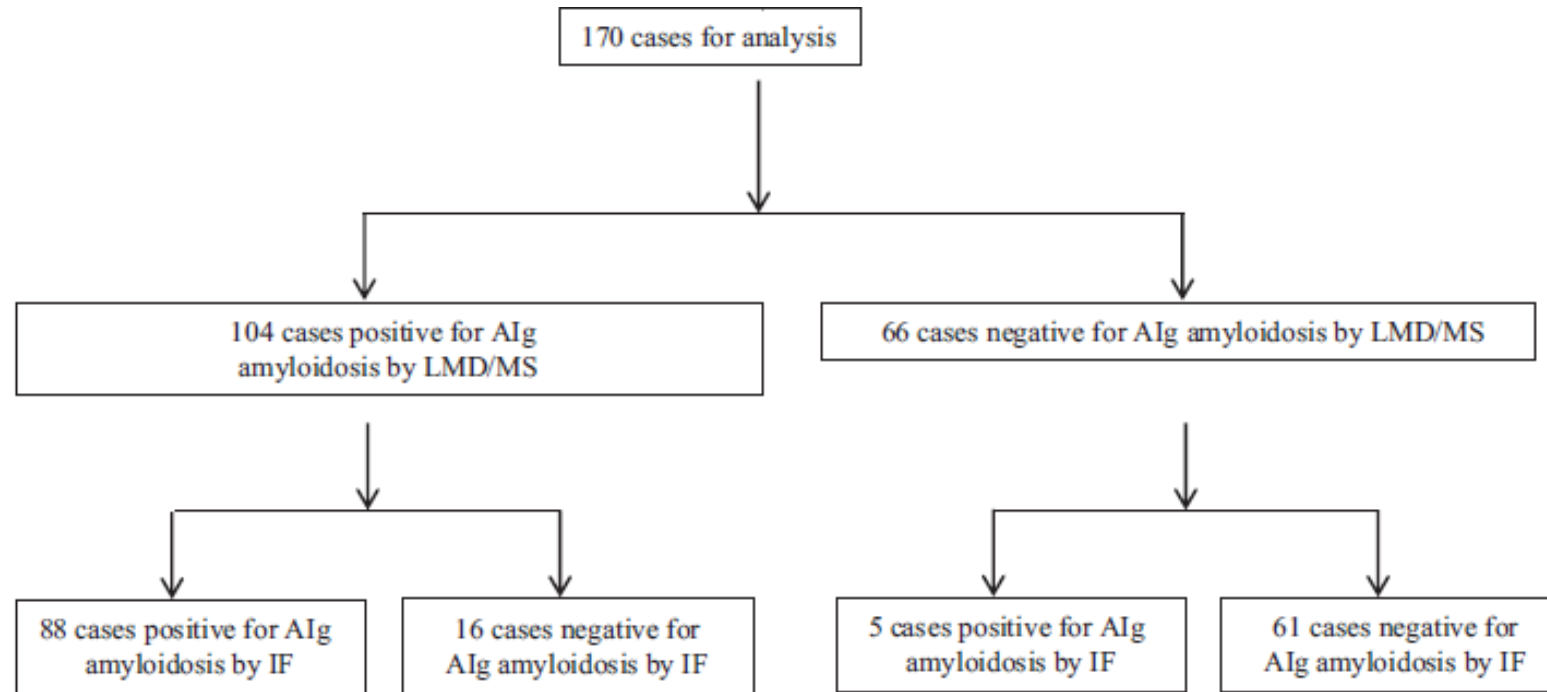
Options for typing amyloid deposits:

- ✓ Immunohistochemistry (unreliable with commercial antibodies)
- ✓ Ultrastructural (EM) immunohistochemistry (specificity 99% even with commercial antibodies)
- ✓ Mass spectrometry based proteomics (gold standard, LCMD or MudPIT, not antibody dependent)

Accurate amyloid typing

TABLE 2 Characteristics of Cardiac Amyloid Histological Typing Techniques					
	Requirements	Yield	Strengths	Limitations	Availability and Costs
IHC	• FFPE cardiac samples • Antibody-based method	• Dependent on sensitivity and specificity of antibodies • Unable to classify samples depending on center's expertise and era (6%-80% inconclusive findings reported)	• Availability • Affordable • Short time to results	• Low specificity for AL • Possible lack of staining and multiple reactions with various antibodies • Background staining and false-positive cases • Lack of availability of antibodies for all CA subtypes • Potential for assigning an incorrect amyloid type • Requires training and expertise from technicians and pathologists	• Widely available • Small cost
IEM	• Antibody-based method • Modified Karnovsky's solution for sample fixation • FFPE samples also possible • Electron microscopy	• 80% sensitivity and 100% specificity in abdominal fat aspirate • Close to 100% sensitivity and specificity in EMB	• Detection of small deposits • Minimizes background staining • High specificity using commercial antibodies	• Tiny deposits could be missed • Dependent on good tissue fixation • Lack of availability of antibodies for all CA subtypes • Requires training and expertise from technicians and pathologists	• Very limited availability • Intermediate cost (high-cost infrastructure)
LC-MS/MS	• FFPE cardiac samples • Laser microdissection • Liquid chromatography • Tandem mass spectrometry • Bioinformatics	• Gold-standard for amyloid typing • Very high sensitivity and specificity	• Objective and unambiguous • Tiny amounts of tissue required • All amyloid types can be identified • Able to distinguish between wild-type and hereditary forms	• Multiple-step and complex process • Longer time to results • Requires training and expertise from technicians and pathologists	• Limited availability • High cost
AL = light chain amyloidosis; CA = cardiac amyloidosis; EMB = endomyocardial biopsy; FFPE = formalin-fixed and paraffin-embedded; IEM = immunoelectron microscopy; IHC = immunohistochemistry; LC-MS/MS = liquid chromatography and mass spectrometry.					

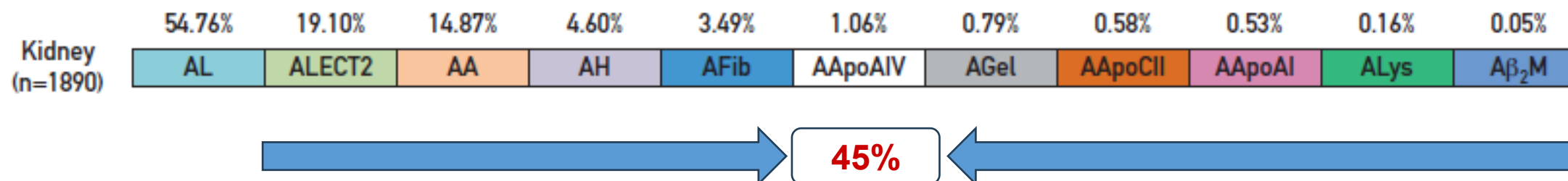
Diagnostic accuracy of renal biopsy immunofluorescence for AL amyloidosis



- Renal biopsy IF: **sensitivity 84.6%; specificity 92.4%**
- IF misclassified immunoglobulin-derived vs. non-immunoglobulin-derived amyloidosis in **12.3%** of renal amyloidosis cases
- Reference standard: laser microdissection with mass spectrometry

Amyloid Typing by Mass Spectrometry in Clinical Practice: a Comprehensive Review of 16,175 Samples

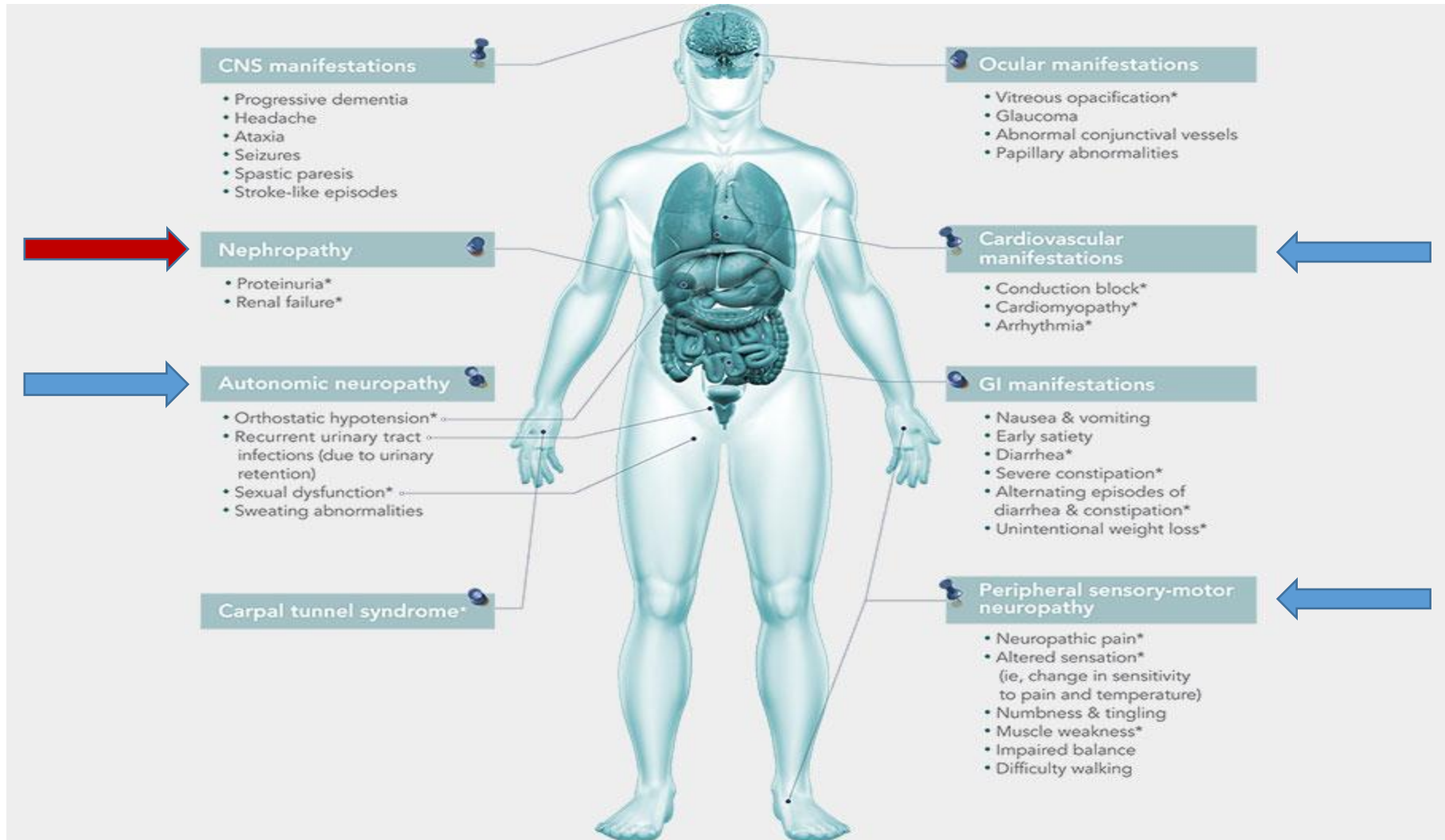
Surendra Dasari, PhD; Jason D. Theis, BS; Julie A. Vrana, PhD; Karen L. Rech, MD; Linda N. Dao, MD; Matthew T. Howard, MD; Angela Dispenzieri, MD; Morie A. Gertz, MD; Linda Hasadsri, MD, PhD; W. Edward Highsmith, PhD; Paul J. Kurtin, MD; and Ellen D. McPhail, MD



Transthyretin-related (ATTR) amyloidosis

- Originates from either an **inherited variant** in the transthyretin protein gene (ATTRv) or from **acquired instability** of the wild-type transthyretin protein with aging (ATTRwt)
- These forms commonly manifest with cardiomyopathy, neuropathy, spinal stenosis, carpal tunnel syndrome, trigger finger, biceps tendon rupture

Clinical presentations of ATTR amyloidosis



Renal involvement in ATTR amyloidosis

- More common than previously recognized
- Prevalence of CKD (defined as eGFR <60 mL/min/1.73²):
 - ~30% of patients with symptomatic hereditary ATTRv amyloidosis
 - >50% of patients with ATTRwt amyloidosis
- Kidney dysfunction may result from direct renal amyloid deposition and/or cardiorenal mechanisms

Clinical presentation of renal involvement in ATTR amyloidosis

- Albuminuria/proteinuria is a common manifestation
 - ATTRv amyloidosis (n=232):
 - eGFR <60 mL/min/1.73m²: **31%**
 - Proteinuria: **20%**
 - ESKD: **10%**
 - ATTRwt amyloidosis:
 - CKD is the most common noncardiac comorbidity
 - Kidney dysfunction has historically been attributed to heart failure, but intrinsic renal involvement is gaining recognition

ATTR amyloidosis: the forgotten kidney amyloidosis

Lobato *et al*, Nephrol Dialy Transplant 2003

N=74; V30M ATTRv amyloidosis

- Symptomatic patients
 - Microalbuminuria: **40.6%**
 - Nephropathy: **28%**
 - ESKD: **9.4%**
- Asymptomatic carriers
 - Microalbuminuria: **36.6%**
 - Nephropathy: **13.6%**
 - ESKD: **4.5%**
- Typical progression:
 - Microalbuminuria develops **~5 years** after neuropathy
 - Overt nephropathy **~2 years** after microalbuminuria
 - ESKD **~5 years** after onset of microalbuminuria

Solignac *et al*, Clin Kid J 2022

N=103; ATTRv amyloidosis

- Renal involvement at diagnosis
 - CKD: **16.5%**
 - Proteinuria: **16.1%**
 - Nephrotic syndrome: **1.7%**
- Renal involvement at last assessment
 - CKD: **30.4%**
 - Proteinuria: **20.3%**
 - ESKD: **2.5%**

Renal pathology in ATTR amyloidosis

- Amyloid deposits can involve **all renal compartments**: glomeruli, tubulointerstitium, arterioles, and arteries
- Compared with AL and AA amyloidosis, **ATTRv nephropathy** demonstrates more prominent **tubulointerstitial involvement**, including medullary deposits (77% vs. 33-44% in AL/AA)
- In **ATTRwt amyloidosis**, amyloid deposition within the **renal papilla** has been described

Renal pathology in ATTR amyloidosis

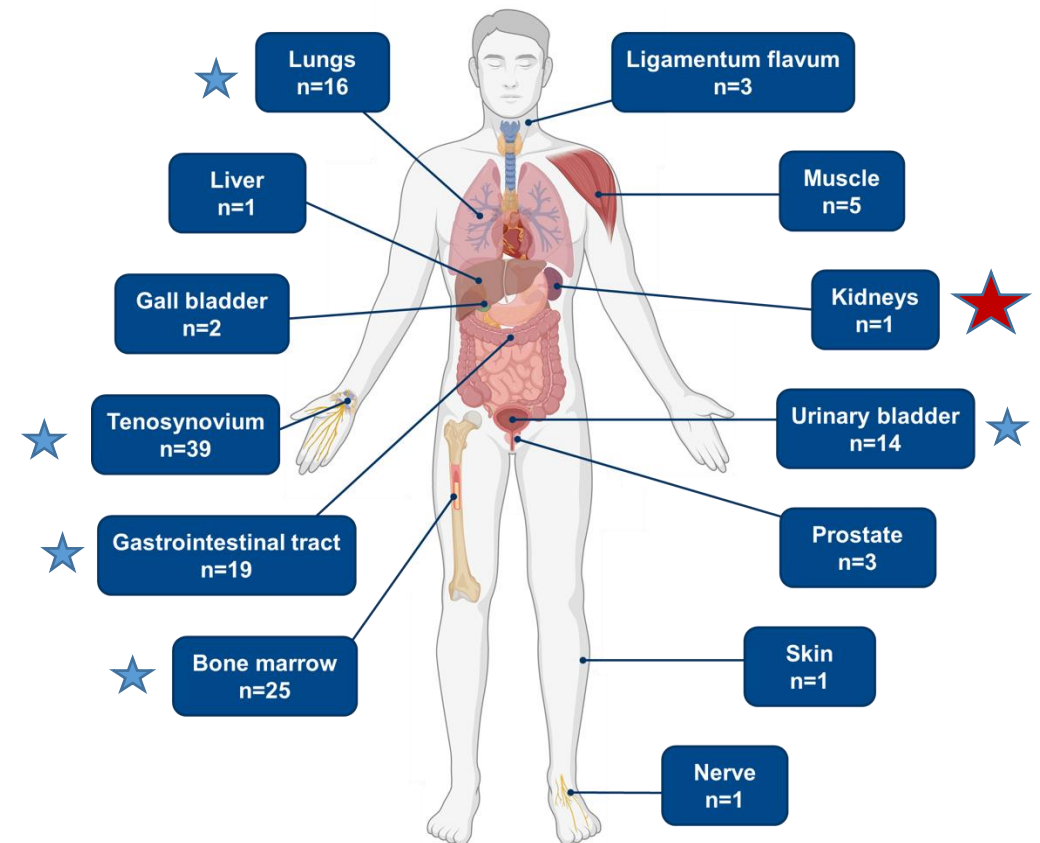
- At least **15 ATTR** variants have been associated with nephropathy:
 - **Val30Met (V30M)**: Best characterized; more glomerular and arteriolar deposition with relatively preserved eGFR
 - **Val122Ile (V122I)**: Associated with faster eGFR decline and worse renal outcomes
 - Other nephropathic variants include Val30Ala, Phe33Cys, Gly47Glu, Ser77Tyr, and Ser50Arg

Mechanisms of kidney disease in ATTR amyloidosis

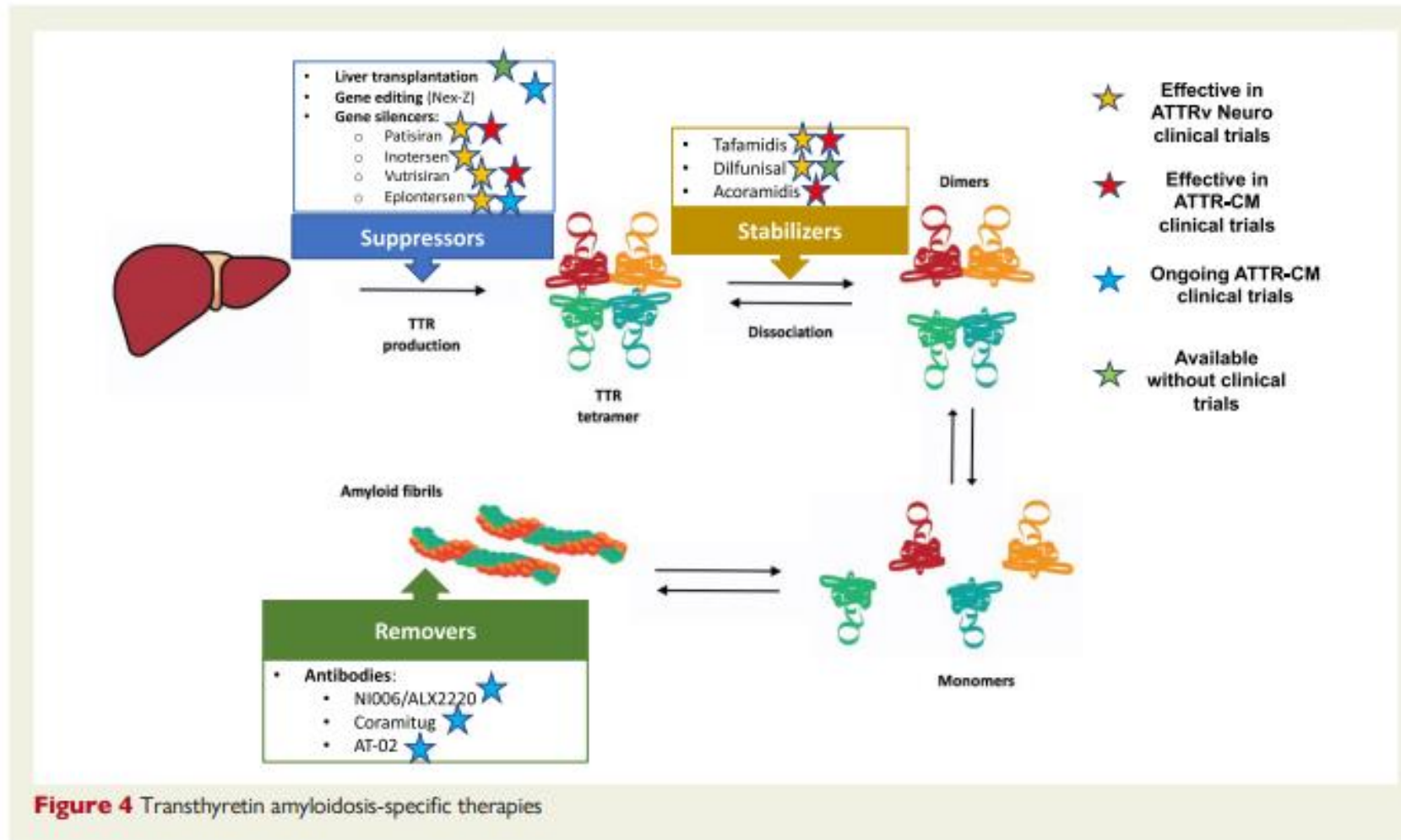
- **Direct amyloid deposition** causing structural kidney injury
- **Cardiorenal syndrome** due to ATTR cardiomyopathy with reduced renal perfusion
- **Autonomic neuropathy** leading to hemodynamic instability and impaired kidney perfusion
- **Potential bidirectional relationship:** CKD may further promote amyloidogenesis through reduced transthyretin monomer clearance, uremic protein modifications (e.g., lysine carbamylation), and protein destabilization within the renal papilla

ATTRwt amyloidosis in extracardiac tissues/organs

- 957 biopsy specimens analyzed (median 2 tissues/patient); **48% Congo red-positive**
- Highest diagnostic yield:
 - **Endomyocardium:** 99% (203/205)
 - **Abdominal fat pad:** 23% (123/534)
- Common extracardiac sites of involvement: **tenosynovium, bone marrow, GI tract, lungs, and urinary bladder**

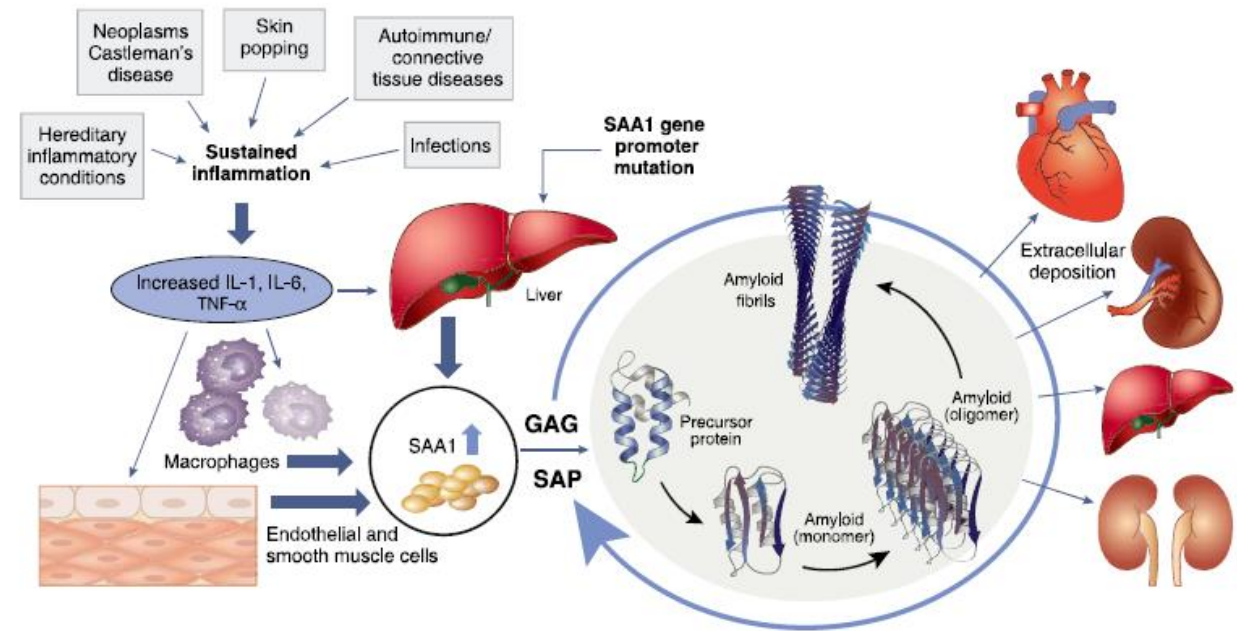


ATTR amyloidosis therapeutics



AA amyloidosis

- Second most common systemic amyloidosis globally
- Caused by deposition of **serum amyloid A (SAA)**, an acute-phase reactant overproduced in chronic inflammation
- Etiologies
 - Chronic inflammatory disease: rheumatoid arthritis, inflammatory bowel disease
 - Autoinflammatory syndromes: familial Mediterranean fever (FMF), TRAPS, CAPS
 - Chronic infection: tuberculosis, bronchiectasis, osteomyelitis
 - Injection drug use
 - Rare idiopathic cases
- **Clinical presentation:**
 - Albuminuria → nephrotic syndrome
 - Progressive CKD → ESKD



Treatment of AA amyloidosis

- **Colchicine:** highly effective for FMF-associated AA amyloidosis
- **TNF- α inhibitors** (etanercept, infliximab, adalimumab): for rheumatologic disorders
- **IL-1 blockade** (anakinra, canakinumab): effective in autoinflammatory syndromes (CAPS, TRAPS, FMF refractory to colchicine)
- **IL-6 blockade** (tocilizumab): increasingly used, including in cases without identifiable etiology
- **Kidney transplantation:** A contemporary French multicenter cohort (2008–2018) of 86 patients showed **5-year patient survival of 85.5%** and histologically proven **recurrence in only 5.8%**, supporting transplantation in well-controlled disease.

The goal is to reduce SAA to <10 mg/L, which is associated with stabilization or improvement of renal function

ALECT2 (Leukocyte Chemotactic Factor 2) amyloidosis

- Wild-type leukocyte chemotactic factor 2 (LECT2) protein; amyloid forms without gene mutation
- First described in **2008**
- **2nd or 3rd most common renal amyloidosis** in certain populations
 - Occurs in **non-Caucasian populations**: Hispanic, Egyptian, South Asian, others
 - 50% of renal amyloidosis in **Hispanic patients (Southwestern US)**
 - ~31% in **Egyptian cohorts**
- Median age at diagnosis: **~62 years**

ALECT2 (Leukocyte Chemotactic Factor 2) amyloidosis

- **Clinical presentation:** CKD with minimal proteinuria
 - Median eGFR: **~33 mL/min/1.73 m²**
 - Proteinuria: **~0.5 g/day**
- **Renal pathology:**
 - Predominantly **cortical interstitial amyloid deposition**
 - Medullary involvement in **~one-third** of cases
- **Clinical course:**
 - Indolent progression
 - eGFR decline: **~4.2 mL/min/year**
 - Median renal survival: **~8 years from diagnosis**

AFib (Fibrinogen A α -Chain) amyloidosis

Category	Key Features
Genetics	- Autosomal dominant FGA mutations - Common variants: E526V, R554L, P552H, T538K, frameshift mutations - Variable penetrance, family history often absent
Clinical presentation	- Median age at onset 51-58 yrs Proteinuria (93%), HTN (83%), renal failure (68%) - Extrarenal manifestations uncommon
Pathology	Massive glomerular enlargement with near-complete replacement by amyloid and minimal vascular/interstitial deposition
Prognosis	- Median time to ESKD: 4.6 years - Median overall survival: 15.2 years from presentation
Treatment and transplantation	- Kidney transplantation feasible – lower recurrence with E526V variant Combined liver-kidney transplantation curative

AApoAI (Apolipoprotein A-I) amyloidosis

Category	Key Features
Genetics	- Autosomal dominant APOA1 mutations - Variable phenotype by mutation (e.g., Leu75Pro, Glu34Lys)
Natural history and target organs	Kidney and liver predominantly affected Very slow progression (often decades)
Pathology	- Medulla and tubulointerstitium involvement - Glomeruli typically spared (key distinguishing feature)
Clinical presentation	- Defective urine concentrating ability, polyuria - Hepatic involvement (cholestasis) ~30% - Hypogonadism in ~68% of males (Leu75Pro cohort) - Retinal amyloid deposits (some variants) Low HDL cholesterol is a diagnostic clue
Genotype-phenotype	- Leu75Pro: TIN in 49%, dialysis in 13% - Glu34Lys: can involve glomeruli and retina
Treatment	- Kidney transplantation generally successful - Hepatorenal transplantation performed in selected cases
Prognosis	Median graft survival after kidney transplant: ~13.1 years

AApoAIV (Apolipoprotein A-IV) amyloidosis

Category	Key Features
Genetics	• Wild type, age related
Epidemiology	• Older men, mean age 63.5 years
Pathology	• Massive amyloid deposition restricted to renal medulla • Complete sparing of renal cortex
Clinical presentation	• Progressive chronic kidney disease • Absent proteinuria • Cardiac involvement rare occurrence but reported
Diagnostic insight	• Must distinguish from other medullary-predominant amyloidosis • Diagnosis may be missed without medullary sampling
Prognosis	• Limited data due to rarity • Generally slowly progressive CKD phenotype

AApoCII (Apolipoprotein C-II) amyloidosis

Category	Key Features
Genetics	• Novel hereditary amyloidosis (first described 2017) • Caused by mutations in APOC2 gene • Index mutation: E69V missense variant
Clinical presentation	• Predominantly renal disease, kidney-limited • Nephrotic syndrome (index case)
Pathology	• Nodular glomerular amyloid deposits
Proteomic signature	• Distinct amyloid proteome • Enrichment of complement pathway proteins

ALys (Lysozyme) amyloidosis

Category	Key Features
Genetics	• Rare autosomal dominant hereditary amyloidosis • Caused by mutations in LYZ (lysozyme) gene • Initially described in ~7 unrelated families
Clinical presentation	• Multisystem involvement: kidney, liver, and gastrointestinal tract • Occasional catastrophic bleeding
Diagnostic pitfall	• Frequently misdiagnosed as AL amyloidosis
Natural history	• Indolent, long disease course • Gradual organ dysfunction over decades
Treatment	• Kidney transplantation outcomes excellent • Median graft survival ~13.1 years

AGel (Gelsolin) amyloidosis

- Characterized by the triad:
 1. Corneal lattice dystrophy
 2. Cranial neuropathy
 3. Cutis laxa
- Nephrotic syndrome and CKD
- 20% with renal involvement in our series
- p.Asn211Lys (N211K) mutation appears to represent a **renal-limited form** without the classic triad



→ Alopecia

→ Facial nerve involvement:

- Frontalis muscle paralysis and lack of forehead crease

→ Decrease or absence of naso-labial folds

→ Cranial nerve involvements:

- Trigeminal - difficulty chewing
- Facial - orbicularis oris weakness with subsequent drooling

→ Cutis laxa

Kidney transplantation across subtypes

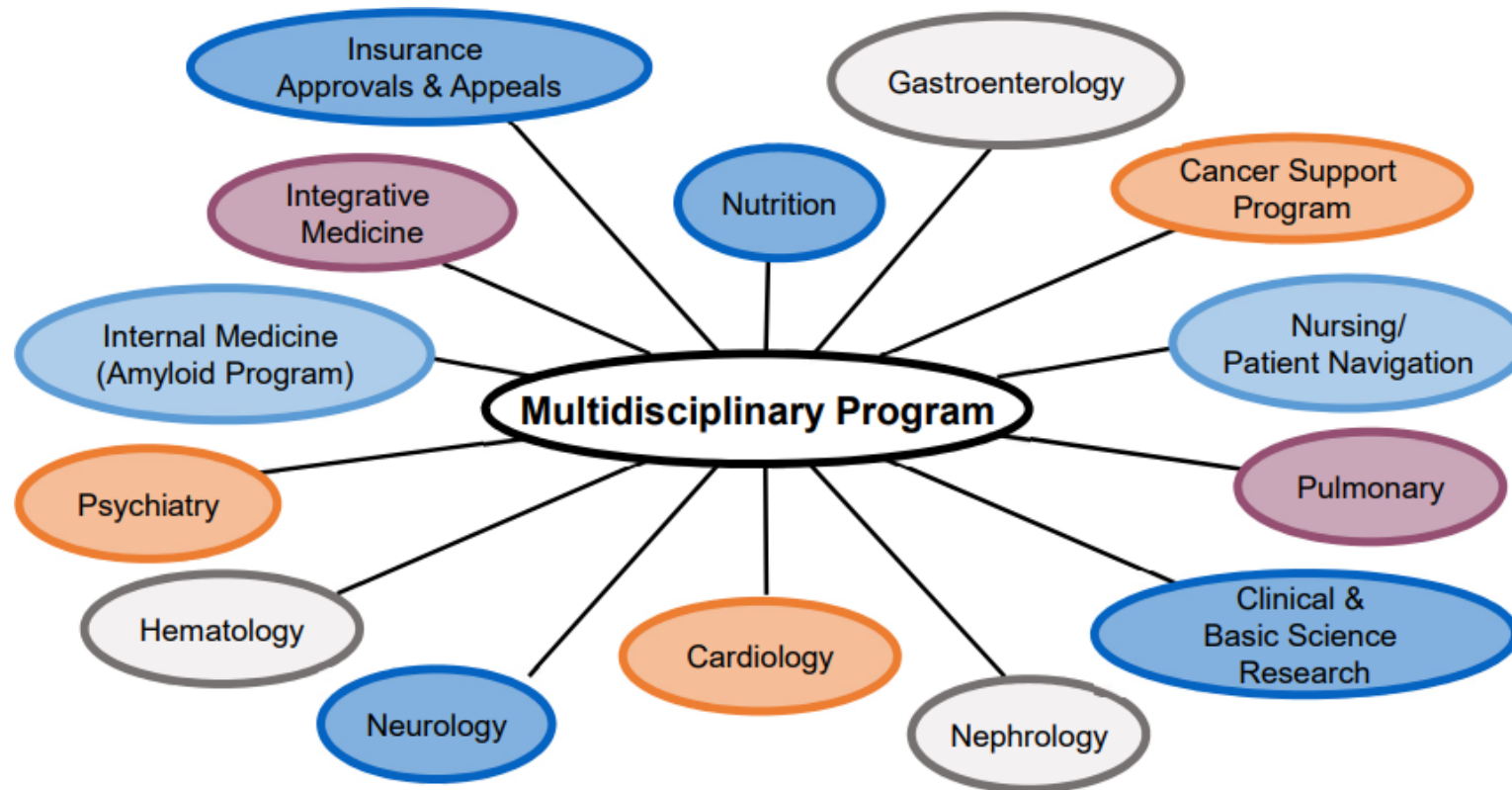
Type	Transplant strategy	Outcomes
ALys & AApoAI	- Kidney transplantation commonly performed - No disease-specific contraindication	89% of ESKD patients transplanted (UK NAC data) - Median graft survival: ~13.1 years
AA	Kidney transplantation after control of underlying inflammatory disease	5-year patient survival: 85.5% - Low recurrence (~5.8%)
AFib	- Kidney-only transplant for selected variants (e.g., E526V) - Combined liver-kidney transplant (LKT) for high-risk mutations	- Lower recurrence with E526V (22%) - Higher recurrence in non-E526V variants (up to 83%) - LKT is curative

Comparative summary of non-AL renal amyloidosis subtypes

Subtype	Precursor Protein	Inheritance	Typical Presentation	Predominant Renal Pathology	Key Treatment
AA	Serum amyloid A	Acquired	Nephrotic syndrome, CKD	Glomerular + vascular	Anti-inflammatory (anti-IL-1, anti-IL-6, anti-TNF)
ALECT2	LECT2 (wild-type)	Unknown/acquired	CKD, minimal proteinuria	Cortical interstitial	Supportive only
AFib	Fibrinogen A α -chain	AD	Proteinuria, hypertension, CKD	Massive glomerular obliteration	KT or LKT
ATTR	Transthyretin	AD or acquired (wt)	Proteinuria, CKD (often with cardiac/neuro)	All compartments, tubulointerstitial	TTR stabilizers, gene silencers, LKT
AApoAI	Apolipoprotein A-I	AD	Tubulointerstitial nephritis, low HDL	Medullary/interstitial (glomeruli spared)	Supportive, hepatorenal transplant
AApoAIV	Apolipoprotein A-IV	Acquired or AD	CKD, minimal proteinuria	Medullary (cortex spared)	Supportive
AApoCII	Apolipoprotein C-II	AD	Nephrotic syndrome	Nodular glomerular	Supportive
ALys	Lysozyme	AD	Renal, GI, hepatic, bleeding	Variable	Supportive, KT
AGel	Gelsolin	AD	Nephrotic syndrome $\pm$ classic triad	Glomerular	Supportive
Aβ2M	β 2-microglobulin	Acquired (dialysis)	Osteoarticular, rare renal	Variable	High-flux dialysis, KT

Multidisciplinary care model

Integrated care at specialized centers helps patients and physicians navigate the challenges of there rare diseases



Acknowledgements

