Memorial Sloan Kettering Cancer Center

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The Rockefeller University

# Unmasking the "Great Masquerader" Presenting Elusive Real-World Cases of AL Amyloidosis


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# Objectives

- What is AL amyloidosis?
- What are the clues to the diagnosis, when to suspect?
- How does one diagnose it?
- Why is it important to make the diagnosis promptly?
- What is the current treatment approach and what are the goals of care?

# Patient #1: RS

- 58F, came to medical attention with progressive myalgias and intermittent paresthesia (over years)

2009 - 2011

- Elevated ESR → Polymyalgia rheumatica
  - Tx steroids w some improvement

Mid - 2011

- Exertional chest pain.
  - ECG: NSR, low voltage QRS
  - ECHO: mild LVH (IVSd 1.3cm), LVEF 50-55%, moderate diastolic dysfunction
  - Exercise stress test: non-specific ectopy, no ischemia

March 2012

- LE edema → Nephrosis
  - Renal biopsy: lambda light chain amyloidosis involving the glomeruli and blood vessels

June 2012

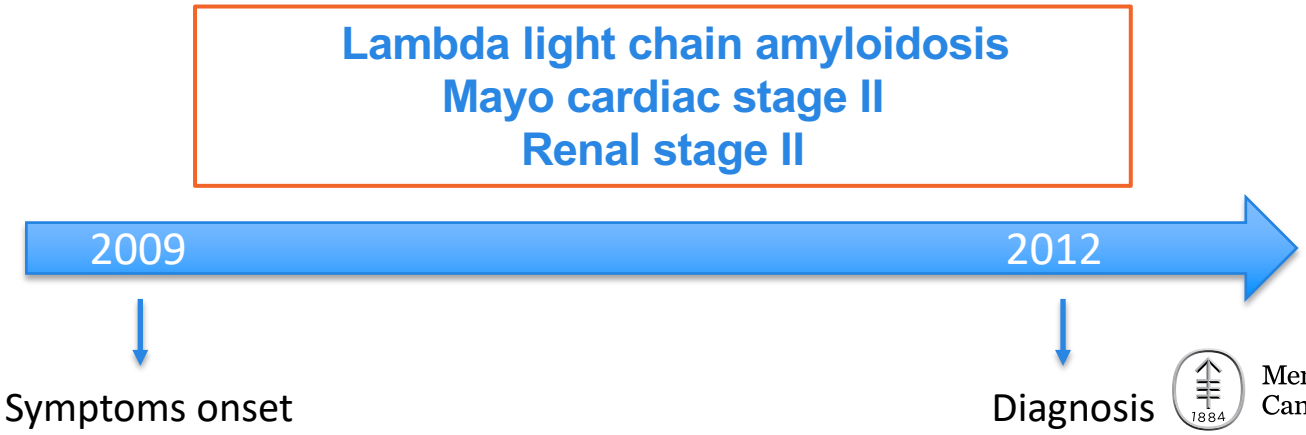
# RS came to MSK

July 2012

- CBC normal, Cr 0.8, ALB 3.3
- Free kappa 0.42mg/dl, free lambda 7.38mg/dl, k:l 0.06,
- SPEP neg, IFE neg
- BNP 269, TROP neg
- 24hr Urine TP: 5.1 g/24 hrs

- Cardiac MRI: Diffuse late gadolinium enhancement suggestive of amyloid.

- Bone marrow: 10% lambda restricted PCs, amorphous eosinophilic deposits + Congo red.

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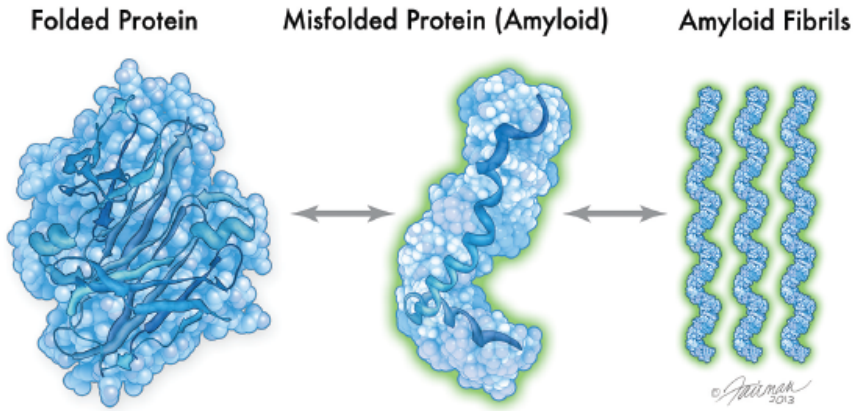
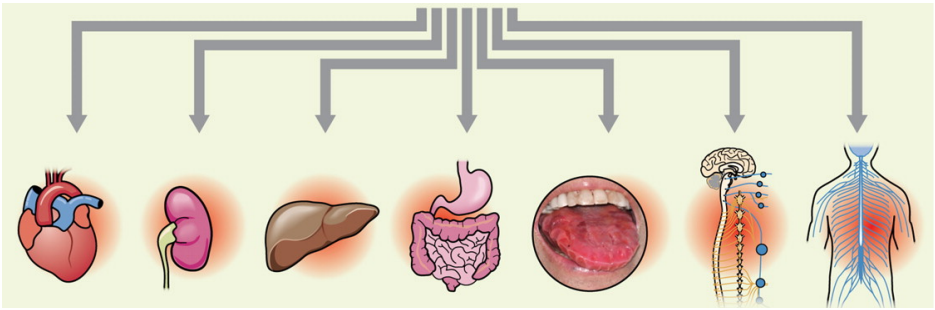
# What is Amyloidosis?

- *Amylum* – starch (Latin)
- Protein misfolding disorder



Merlini Blood 2012;119:4343-4345

# Types of Amyloid: Over 30 amyloidogenic proteins

| Amyloid protein | Precursor | Distribution | Syndrome |
|---|---|---|---|
| **AL** | **Immunoglobulin light chain** | Systemic/localised | Primary/myeloma associated |
| **AH** | **Immunoglobulin heavy chain** | Systemic/localised | Primary/myeloma associated |
| **AA** | **Serum amyloid A** | Systemic | Secondary |
| **A$\beta_2$ Microglobulin** | **$\beta_2$ Microglobulin** | Systemic | Secondary |
| **ATTR** | **Transthyretin** | Systemic | Senile systemic/familial |
| **AANF** | **Atrial natriuretic factor** | Localised | Atrial isolated |
| **AApoA-I** | **Apolipoprotein A-I** | Localised/systemic | Aortic/familial |
| AApoA-II | Apolipoprotein A-II | Systemic | Familial |
| **Amed** | **Lactadherin** | Localised | Aortic |
| Agel | Gelsolin | Systemic | Familial |
| Alys | Lysozyme | Systemic | Familial |
| Afib | Fibrinogen α chain | Systemic | Familial |
| Acys | Cystatin C | Systemic | Familial |
| Aβ | Aβ Protein precursor | Localised | Alzheimer's disease, aging |
| AprP | Prion protein | Localised | Spongiform encephalopathies |
| Abri | ABri protein precursor | Localised | Familial dementia |
| Acal | (Pro)calcitonin | Localised | Thyroid tumours derived from C cells |
| AIAPP | Islet amyloid polypeptide | Localised | Langerhans islets, insulinomas |
| Apro | Prolactin | Localised | Prolactinomas, pituitary in elderly |
| Ains | Insulin | Localised | Iatrogenic |
| Aker | Kerato-epithelin | Localised | Familial, cornea |
| Alac | Lactoferrin | Localised | Familial, cornea |

Proteins involved in the cardiovascular system are in bold.

Kholova I, J Clin Path 2005

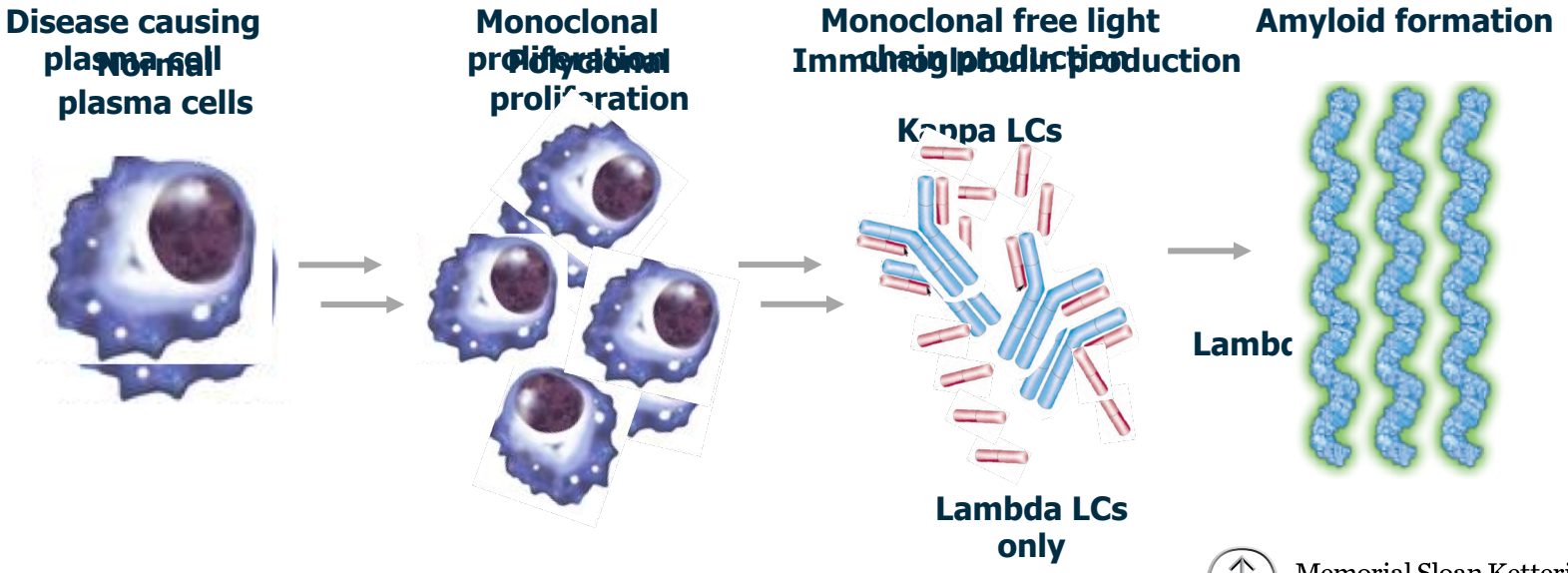
# Amyloid subtype classification

| TYPE OF AMYLOIDOSIS | PRECURSOR PROTEIN | USUAL AGE AT ONSET | MAIN ORGANS INVOLVED | AVERAGE SURVIVAL TIME IN UNTREATED PATIENTS | SPECIFIC TREATMENT |
|---|---|---|---|---|---|
| AL or light chain (primary) | Abnormal immunoglobulin light chains | 50+ | All except central nervous system; heart involved in 50% of cases | Determined by extent of cardiac disease; varies from 3 mos - >10 yrs | Chemotherapy aimed at plasma cells |
| Familial ATTR | Mutant TTR | 20-70+ (partially dependent on mutation) | Peripheral and autonomic neuropathy; heart | 7 to 10 years for neuropathy | Liver transplantation; Agents to stabilize TTR (tafamidis) or suppress its production |
| Wild-type ATTR | Wild-type TTR | 70+ | Heart, soft tissue (carpal tunnel syndrome) | 5 to 7 years | Agents to stabilize TTR (tafamidis) or suppress its production |
| AA (secondary) | Serum amyloid A (SAA), inflamm-atory protein | Teens upward | Liver, kidney; heart rarely | 10+ years | Treatment of underlying inflammatory condition |

Adapted from Falk and Hershberger. Chapter 77. Braunwald's 11th edition.

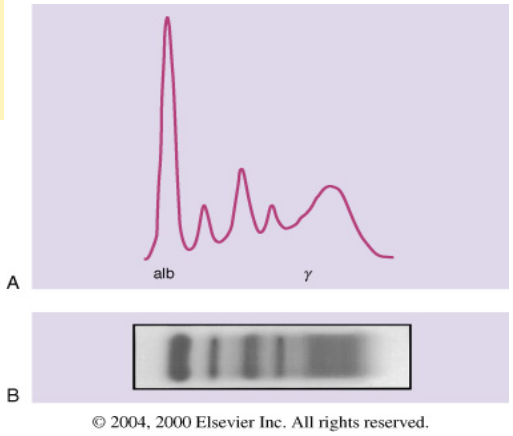
# AL (light chain) Amyloidosis
# What causes it?

- Plasma cell disorder
  - Pathologic plasma cells arise in the bone marrow
- Disease causing protein: Light chains (LC)
  - Monoclonal – meaning the light chains are identical and can be traced back to a single, original diseased plasma cell



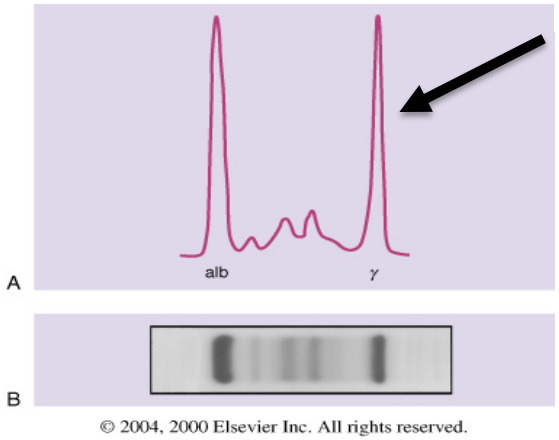
# Monoclonal gammopathy evaluation

- Serum and urine protein electrophoresis (SPEP + UPEP)





Normal SPEP

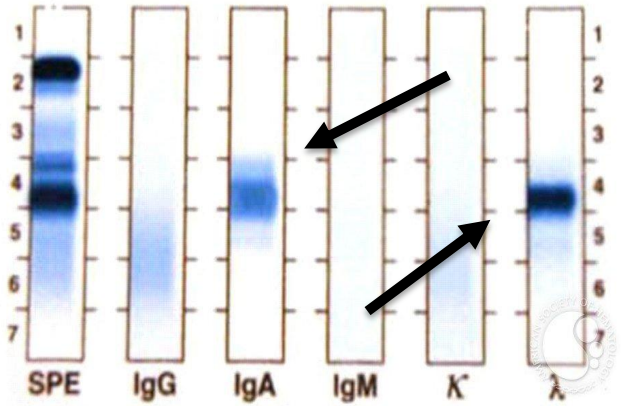




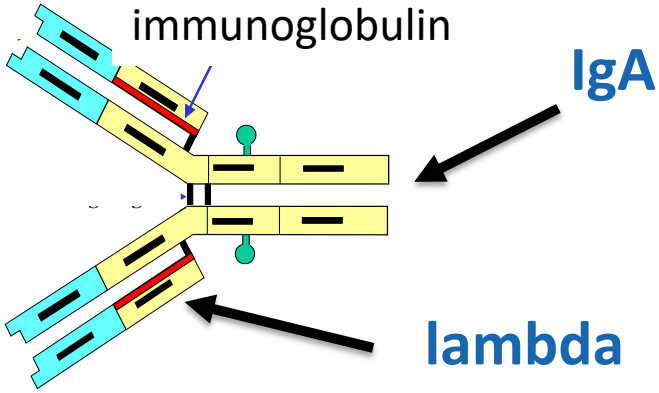
Abormal SPEP

M spike

- Immunofixation




Disease causing immunoglobulin

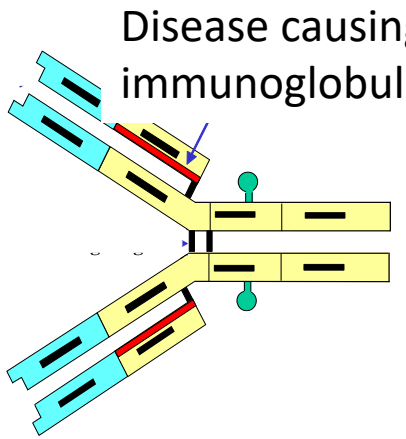


IgA

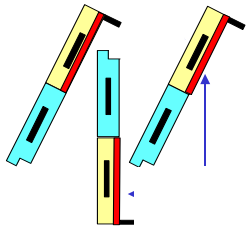
lambda

# Monoclonal gammopathy evaluation

- **Multiple myeloma**
- **AL Amyloidosis**




**Intact immunoglobulin**
**Detected by SPEP**



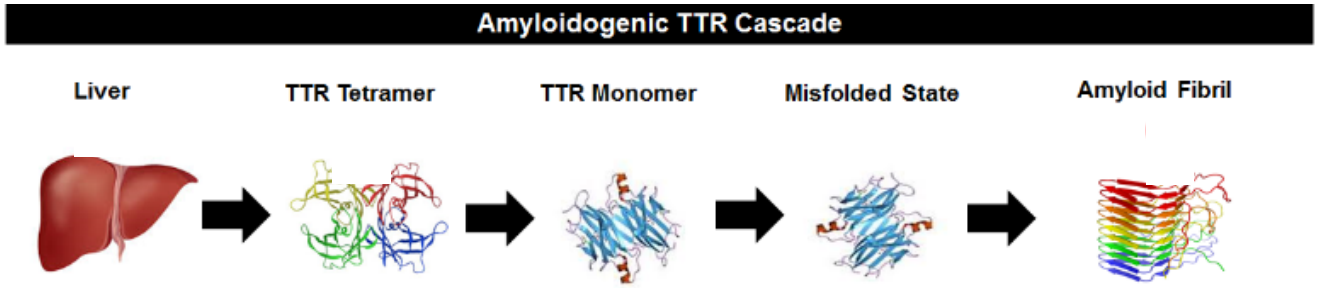
**Freely circulating LCs**

## Serum free light chain assay:

Over-production of one light chain type (kappa or lambda) as measured by an elevated free light chain level and abnormal k:l ratio

# ATTR Amyloidosis

## Precursor Protein: Transthyretin




Castano, Mauer ACC 2015

| TYPE OF AMYLOIDOSIS | PRECURSOR PROTEIN | USUAL AGE AT ONSET | MAIN ORGANS INVOLVED | AVERAGE SURVIVAL TIME IN UNTREATED PATIENTS |
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| Wild-type ATTR | Wild-type TTR | 70+ | Heart, soft tissue (carpal tunnel syndrome) | 5 to 7 years |
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Falk and Hershberger. Chapter 77. Braunwald's 11th edition

# Important to distinguish AL from ATTR Amyloidosis

- **Monoclonal gammopathy of undetermined significance (MGUS)**
  - Occurs in 3% of the white population > 50 years
  - Incidence increases with age ( ~10% in patients 80 years or older)
- **ATTR**
  - True incidence and prevalence unknown
  - 80-89 year olds make up 50% of those diagnosed with wild-type ATTR
- **BU study:** Among 226 patients with biopsy-proven ATTR, including wild-type (N = 155 ) and hereditary (N = 71), MGUS was found in 39% and 49%, respectively

**Different amyloidosis subtypes require different therapies**

# Patient #2: FR

- 52F, presenting with progressive cough, dyspnea and decreased effort tolerance over 1 year.

Early 2014

- Extensive work-up:
  - allergist, GI and ENT consultation. No definitive etiology found.
  - Stress test showing reduced exercise capacity; unremarkable otherwise

2014 - 2015

- Worsening symptoms with DOE after one block

- Syncope after getting out of the car and walking in the parking lot. Admitted to the hospital, work-up:
  - ECG: sinus rhythm with 1st degree AV block and low voltage
  - Echo: concentric LV hypertrophy. No wall motion abnormality
  - Stress test: chronotropic incompetence; drop in HR during exercise with near syncope
  - Cardiac MRI: circumferential delayed enhancement c/w an infiltrative cardiomyopathy

Mid/ late 2015

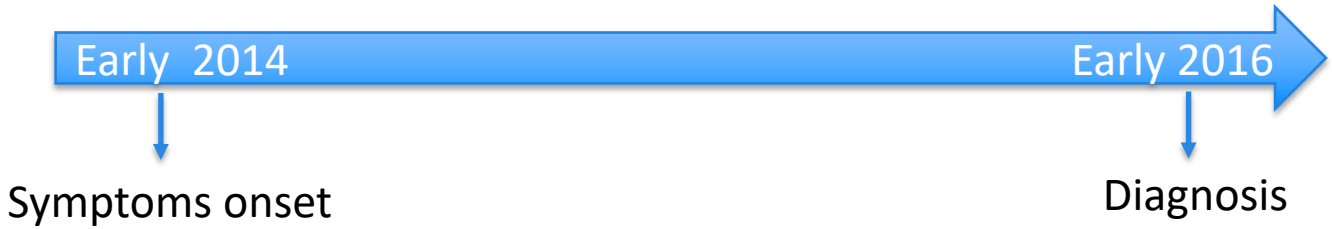
# Patient #2 FR

Early 2016

- **Labs:**
  - Free lambda 9.93mg/dl, free kappa 1.39mg/dl, kappa/lambda ratio 0.14
  - SPEP no monoclonal protein, serum + urine IFE + lambda light chain
  - BNP 923; troponin negative; Cr. 1.1; albumin 4.3

- **Tissue biopsy**
  - Bone marrow biopsy showed < 5% plasma cells, lambda light chain restricted; amyloid seen in a vessel wall
  - Fat Pad biopsy negative for amyloid
  - Endomyocardial biopsy showed congo red positive for amyloid deposition

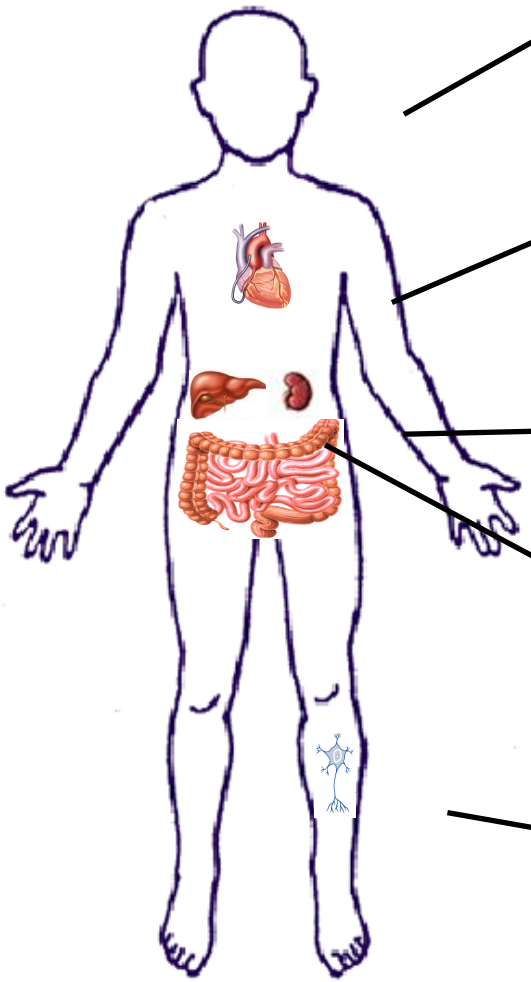
**Lambda light chain amyloidosis with cardiac involvement**
**Mayo Stage II Disease**



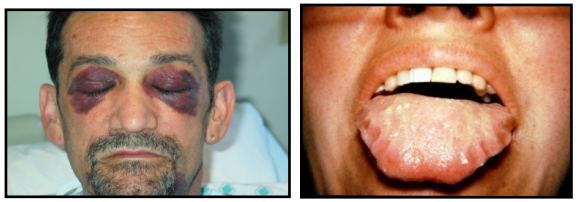
# What are the clues to the diagnosis?

# When to suspect?

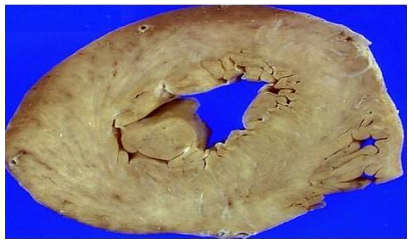
# AL Amyloidosis: Multi-Organ System Involvement



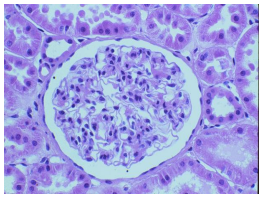
**Soft Tissue Involvement**
- periorbital ecchymosis,
- macroglossia: pathognomonic of AL



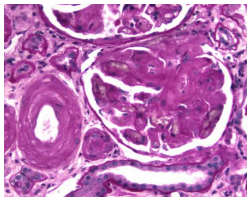
**Cardiac Involvement (>50%)**
- heart wall thickening
- congestive heart failure
- restrictive cardiomyopathy



**Renal Involvement (>50%)**
- glomerulus deposition
- nephrotic range proteinuria
- edema

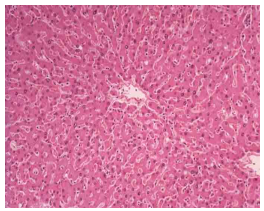


Normal Kidney

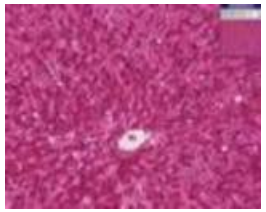


Amyloid in glomerulus

**GI Involvement**
- occult/overt bleeding
- impaired motility
- hepatic infiltration



Normal Liver



Amyloid in liver sinusoids

**Neuropathy**
- sensory: pain, numbness, tingling
- autonomic: orthostasis, gastric dysmotility

# Clinical Presentation: Common Signs/Symptoms

- Fatigue
- Dizziness/syncope
- Weight loss
- Paresthesias
- Edema
- Dyspnea
- Carpal tunnel syndrome
- Hoarseness
- Mucocutaneous lesions
- Hepatomegaly
- Cardiac dysrrhythmias
- Alternating constipation and diarrhea
- Orthostasis
- Bleeding tendency
- Frothy urine

**Diagnosis often delayed due to multisystemic presentations.**

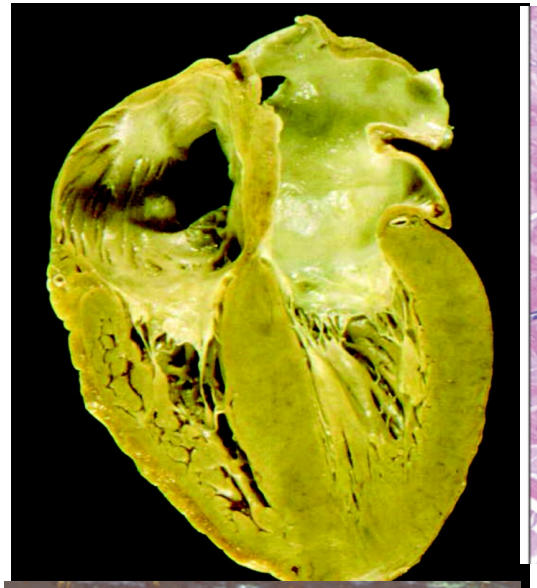
**4 = average number of MDs seen before diagnosis**

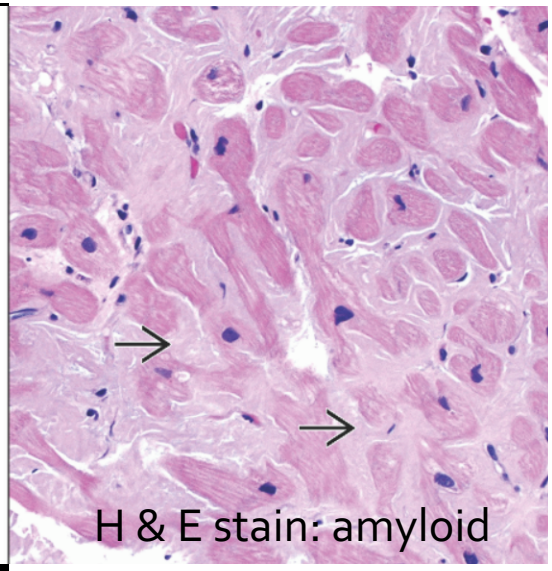
**> 1/3 of patients are diagnosed >1 year after the onset of symptoms**

**In a survey of 443 patients**
**220 cardiologists missed the diagnosis**

http://www.amyloidosis.org/facts

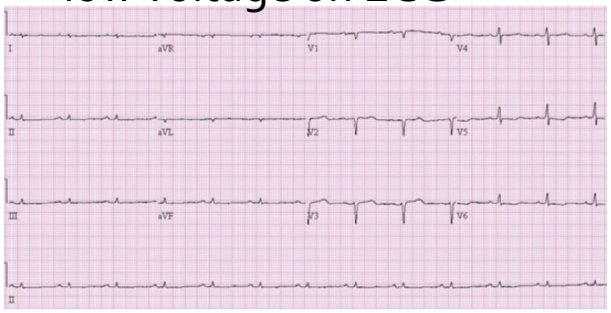
# Cardiac Amyloidosis

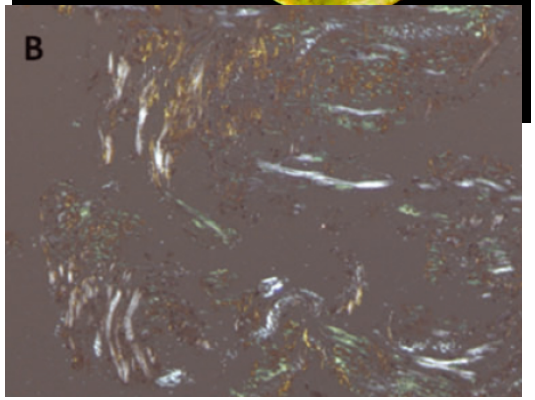




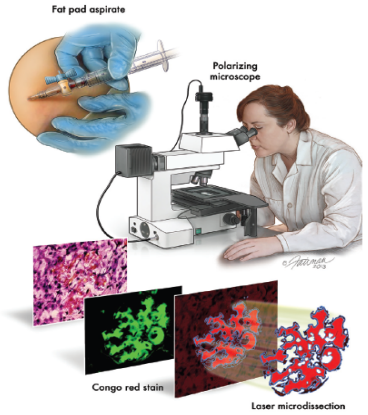
H & E stain: amyloid

low voltage on ECG






Congo red stain




Mass Spectroscopy:
AL vs. TTR

# Cardiac Amyloidosis: Clinical Manifestations

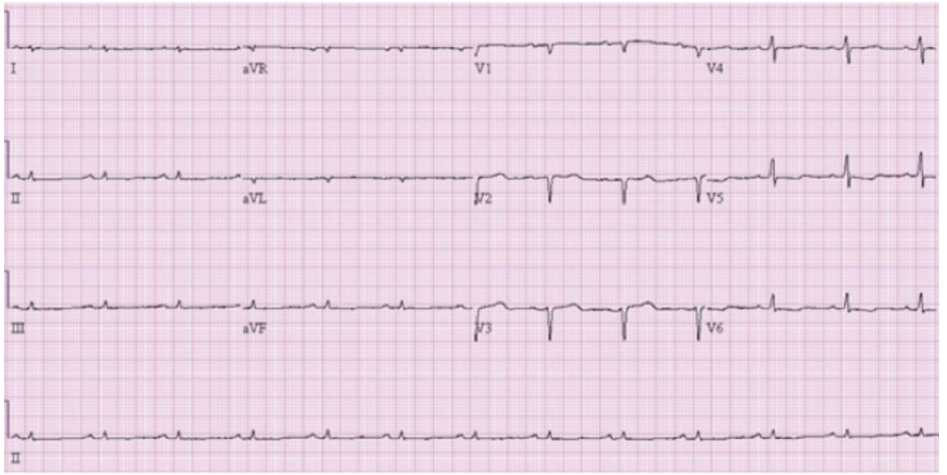
- Heart failure
  - Restrictive cardiomyopathy with predominant right heart failure symptoms
- Angina
  - Amyloid infiltration of intramyocardial and microvessels
- Syncope
  - Exertional syncope due to low and fixed cardiac output
  - Postural hypotension due to autonomic neuropathy
  - Tachyarrhythmias
    - Atrial fibrillation/cardioembolic stroke
    - Ventricular arrhythmia
  - Bradyarrhythmia/AV block
- Sudden death
  - Asystole, PEA, ventricular arrhythmia

# Cardiac Amyloidosis
# When to Suspect: Clues to Diagnosis

**ECG: Low voltage in the limb leads and pseudo-infarct pattern in the precordial leads**

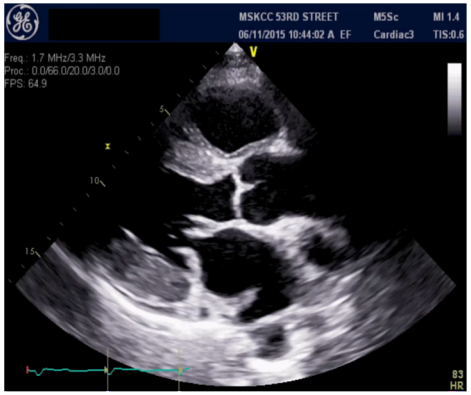
127 AL amyloid patents with biopsy proven cardiac involvement

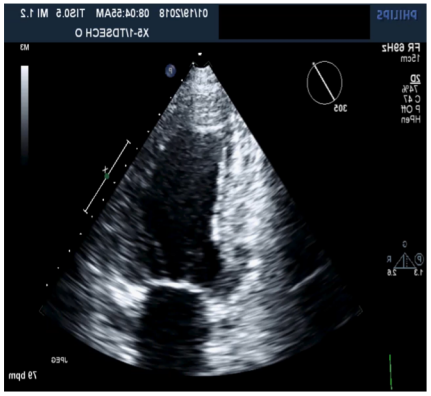
- Low voltage - 45%
- Pseudoinfarct – 47%
- Atrial fibrillation – 10%
- LVH - 7%

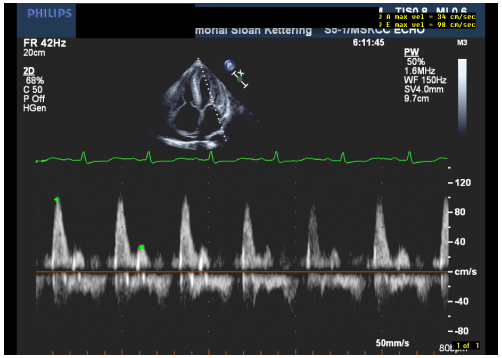


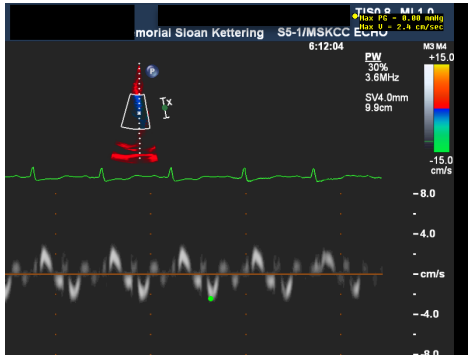

Murgah B, AJC 2005

# Cardiac Amyloidosis
# Clues to Diagnosis – When to Suspect
## Cardiomyopathy with unexplained "hypertrophy on echo"





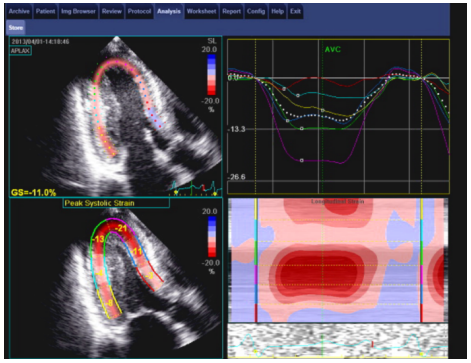

E/A >2, DT<150 msec

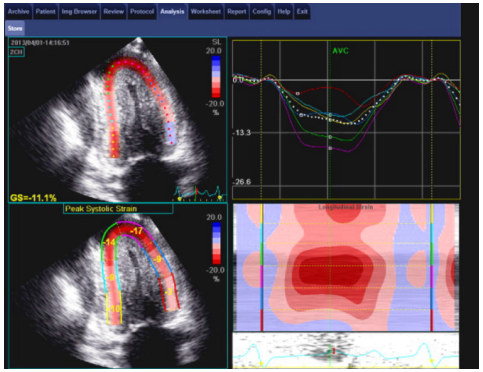
Typical Features:

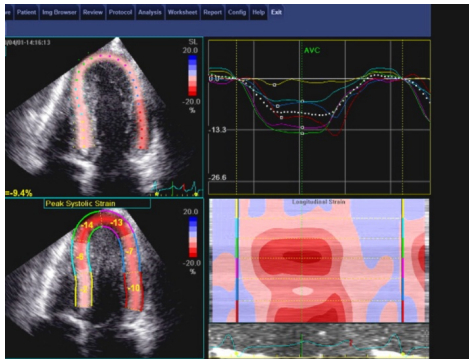
- Increased wall thicknesses with decreased LV end-diastolic volume
- Granular/sparkling appearance of the LV myocardium
- Typically preserved or mildly reduced LV EF
- Valve thickening and pericardial effusion
- Increased right and left atrial volumes; reduced atrial function
- RV thickening, reduced RV myocardial velocities
- Diastolic dysfunction with restrictive LV filling pattern

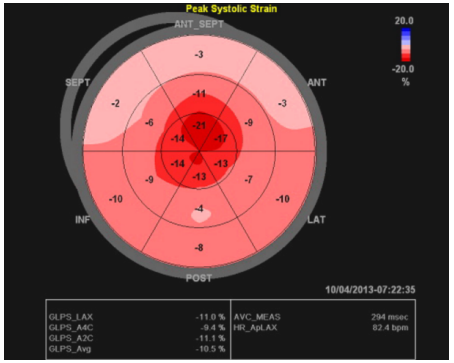
# Cardiac Amyloidosis
# Clues to Diagnosis – When to Suspect

## Global Longitudinal Strain



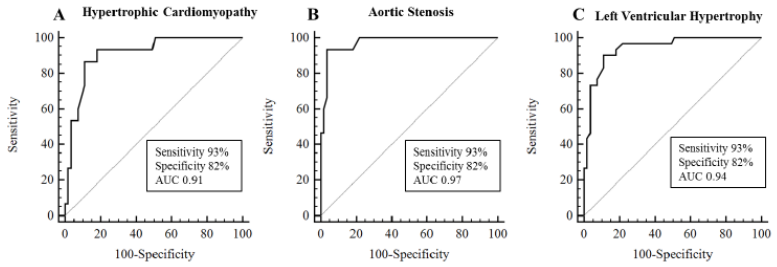




- Impaired GLS with normal LVEF; worse at the base and mid ventricular regions compared to the apex - "apical sparing" pattern
- Sensitive and specific for diagnosis of cardiac amyloidosis

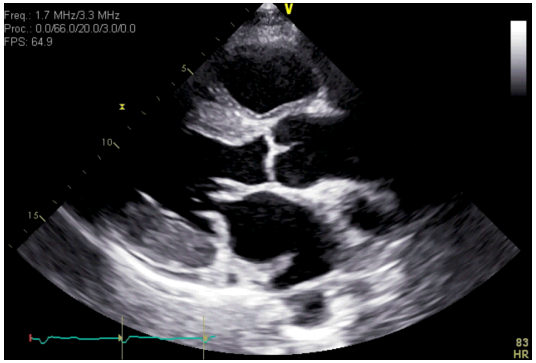
**Difference in Relative Regional Longitudinal Strain between Groups.**

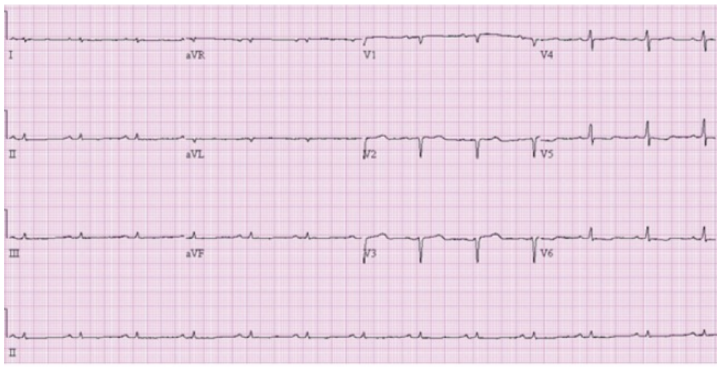
$$\text{Relative apical LS} = \frac{\text{Average apical LS}}{\text{Average basal LS} + \text{Average mid LS}} \geq 1$$

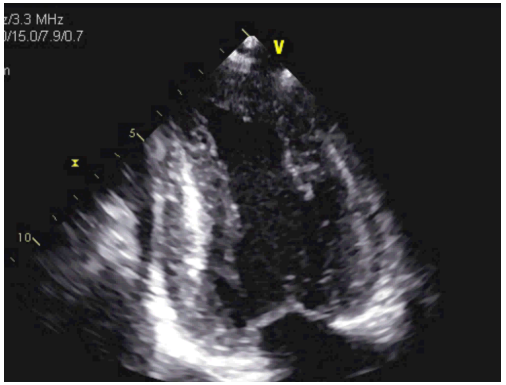


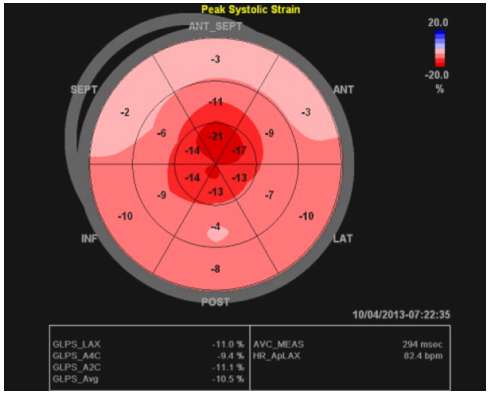

Phelan D. CV Imaging Heart 2012

# Cardiac Amyloidosis: Clues to Diagnosis
# Disconnect between 'LVH' + low voltage



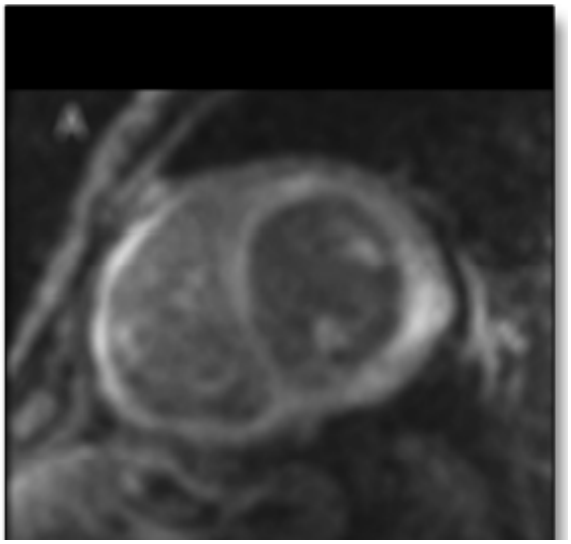





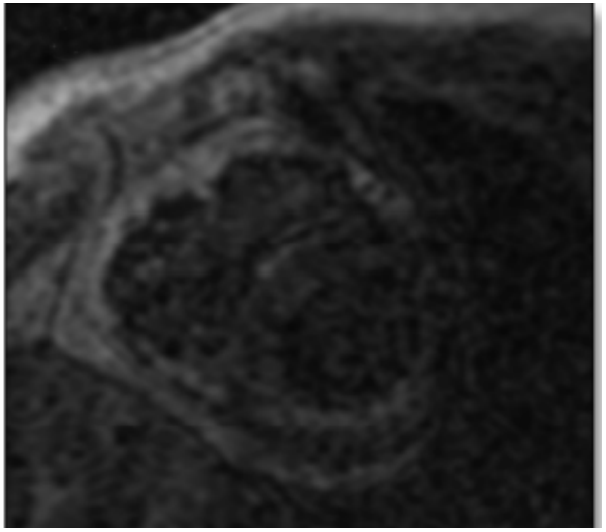

- Unexplained "hypertrophy" on echo
- Normal LVEF with low GLS, particularly with an apical sparing pattern

# Diagnosis of Cardiac Amyloid by MRI Pattern of Delayed Gadolinium Enhancement: Diffuse to Patchy

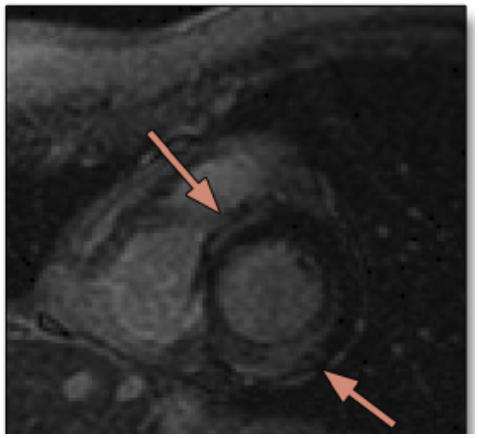
Diffuse Enhancement



Inability to null the myocardium



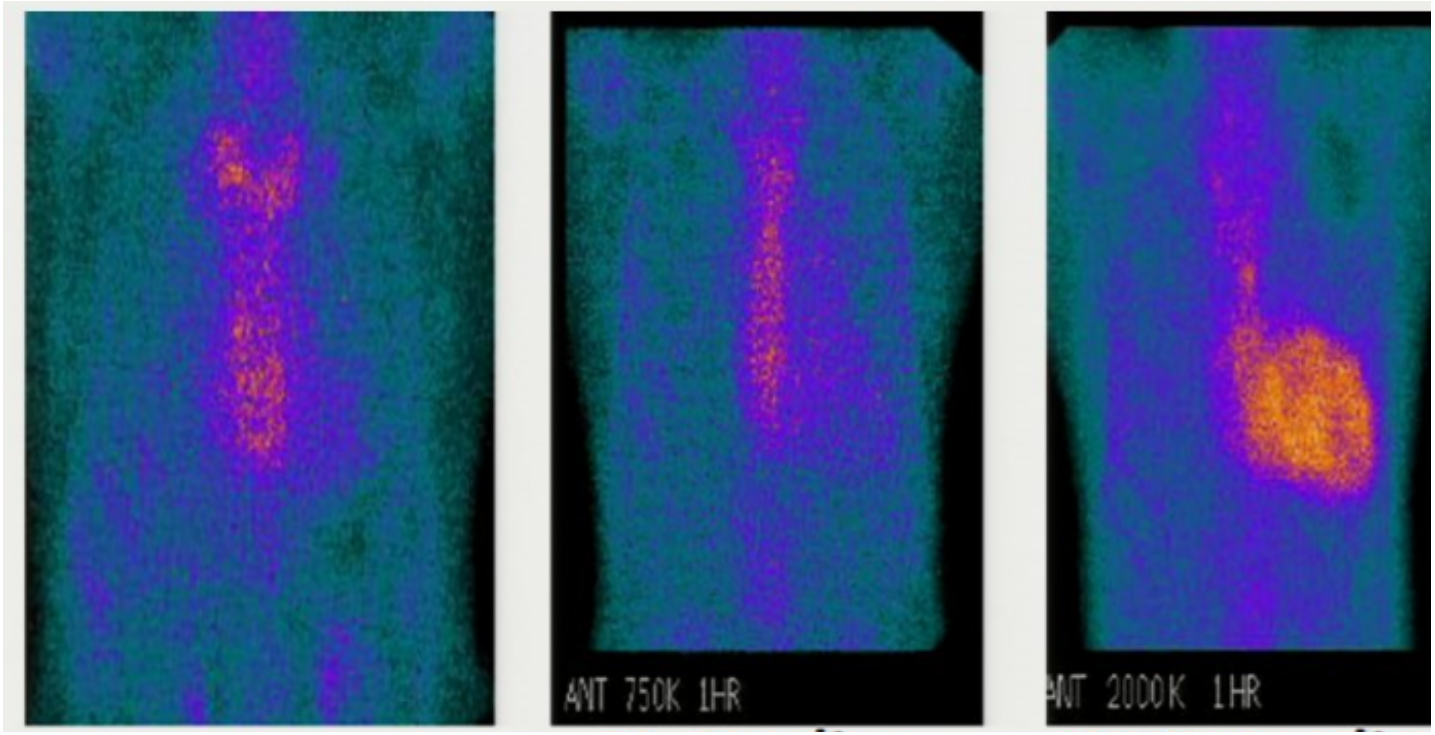
Focal Patchy



- ~ 90% sensitivity and specific
- PPV, NPV ~ 90-93%
- Negative scan does not exclude the diagnosis

Ruberg F, Berk J. Circulation 2012
Boynton , JACC CV Imaging 2016

# Technetium Pyrophosphate Scan Diagnosis of TTR Amyloidosis



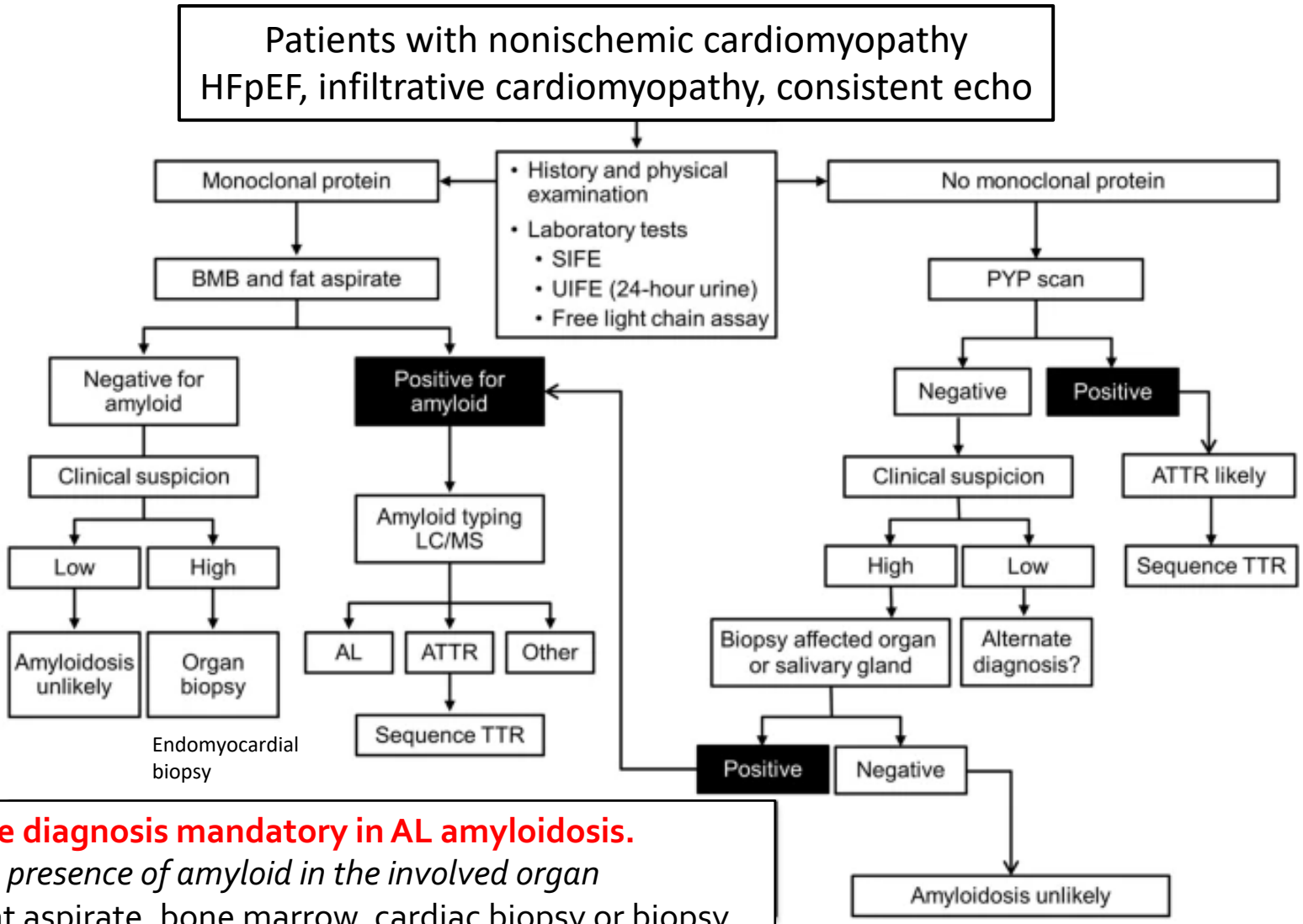

HFpEF

AL Cardiac Amyloid

ATTR Cardiac Amyloid

Bokhari et al, Circ Cardiovasc Imaging 2013

# Diagnostic Algorithm




**Tissue diagnosis mandatory in AL amyloidosis.**

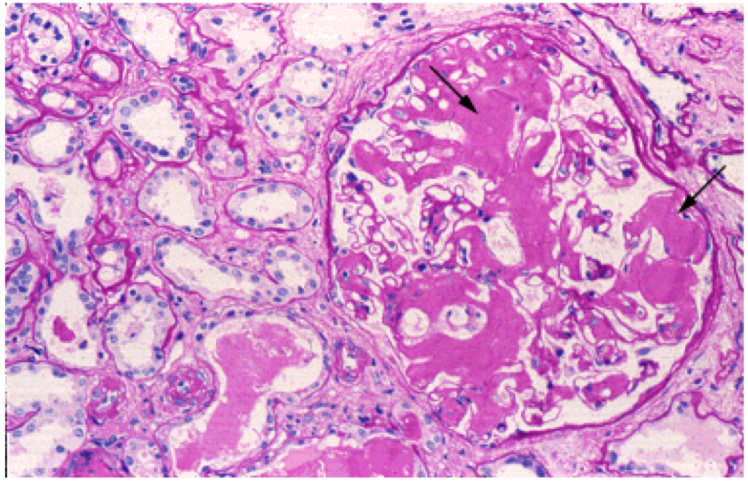
*Prove presence of amyloid in the involved organ*

- Fat aspirate, bone marrow, cardiac biopsy or biopsy of suspicious organ

Gertz M. Blood Cancer Journal 2021

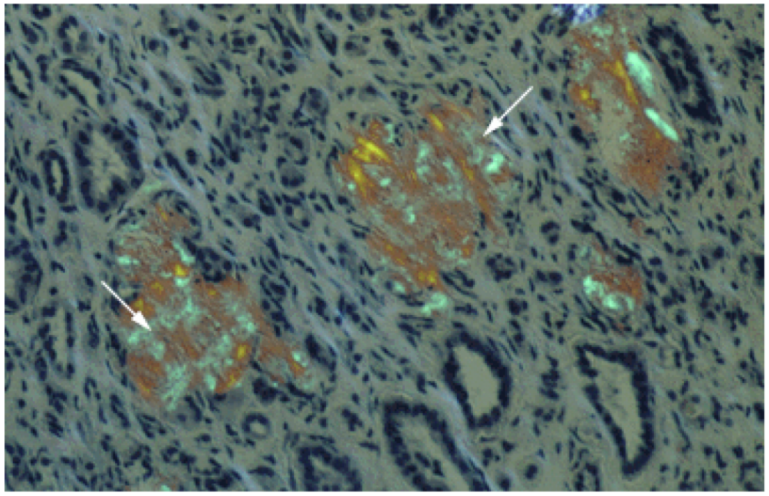
# Renal Involvement in AL Amyloidosis: Pathologic Features

**Light micrograph showing glomerular amyloidosis**



- Nodular amorphous material extending from the mesangium into the capillary loops, narrowing or closing the capillary lumen
- Appearing pale, light pink on H/E stain

**Congo red stain in amyloidosis**



- Green birefringence of interstitial amyloid deposits, viewed under polarized light

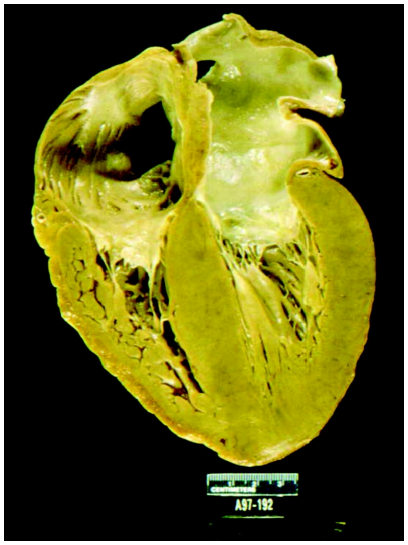
UpToDate Renal Amyloidosis

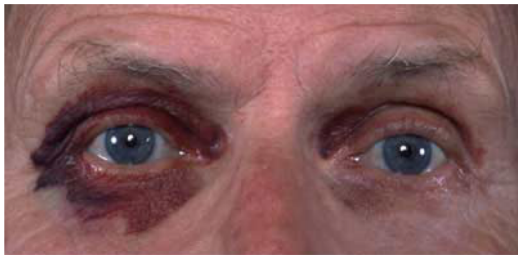
# Renal Involvement in AL Amyloidosis Clinical Manifestation

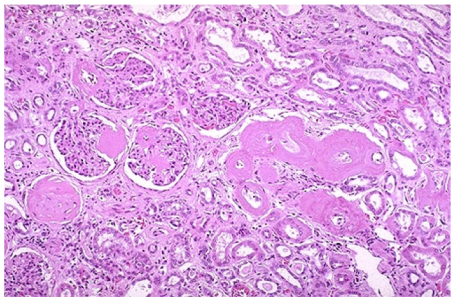
- Glomerular deposits
  - Proteinuria/nephrotic syndrome
  - ESRD in 20% of patients with nephrotic syndrome
- Vascular deposits
  - Leading to narrowing of the vascular lumen
  - Progressive chronic kidney disease w/ rise in Cr
- ESRD is associated with worse survival. Proteinuria >5 g/24 and eGFR <50 ml/min predict progression to dialysis best.

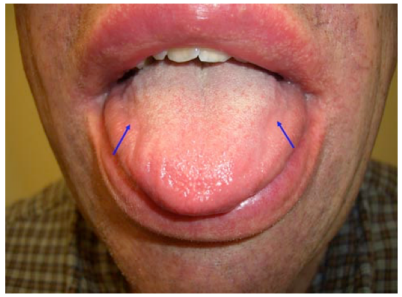
# AL Amyloidosis: Multi-organ system involvement

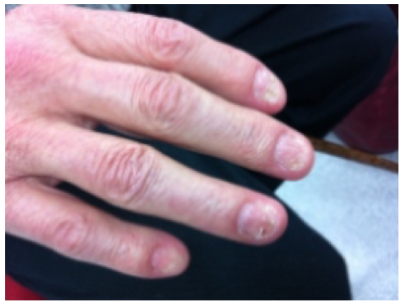
- Cardiac: HFpEF, arrhythmias, hypotension, ✓
- Renal: proteinuria/nephrotic syndrome, renal failure ✓
- Neurologic: peripheral neuropathy, autonomic dysfunction
- GI: dysphagia, malaborption, GI bleeding, liver dysfunction
- Soft tissue/ENT: macroglossia, periorbital purpura, carpal tunnel syndrome, nail changes.









Consider the diagnosis in pts presenting with HF associated with proteinuria and other systemic illnesses.

# Patient #3: QD

- 49M, previously physically active, developed dyspnea; stopped going to the gym

July 2019

- Hospitalized for asthma exacerbation + Pneumonia
  - Tx steroids, bronchodilators + diuresed

April 2020

- Unable to ambulate 20 yards→ cardiac evaluation
  - Nuclear stress test: LVEF 25%, no ischemia
  - Initiated on heart failure medications

August 2020

- Pulmonary evaluation → optimize asthma regimen
  - Thoracentesis with 1L clear fluid drained

October 2020

- Cardiology 2nd opinion
  - ECHO: severely increased LV wall thickness (IVSd 1.9cm), mild global hypokinesis, LVEF 47%. + diastolic dysfunction, GLS 6%.
  - ECG: NSR 91bpm, low voltage, poor R wave progression
  - Cardiac MRI: diffuse subendocardial LGE

Nov 2020

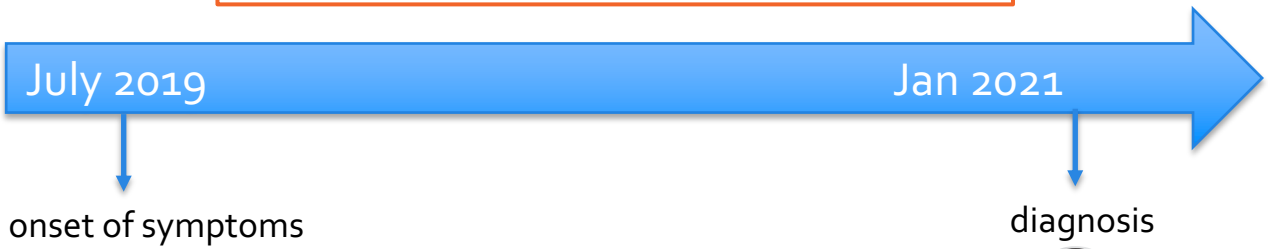
- **Labs:**
  - **CBC normal, BUN 21, Cr 1.1, ALB 4.1, ALK Phos 222**
  - **Free kappa 1.24mg/dl, free lambda 13.05mg/dl, k:l 0.10**
  - **SPEP neg, IFE neg**
  - **BNP 957, TROP 0.92**
  - **24hr Urine TP: none**

Dec 2020

Jan 2021

- **Bone marrow: 10% lambda light chain restricted PCs, No evidence of amyloidosis.**
- **Fat pad biopsy: negative**
- **Endomyocardial biopsy: lambda light chain amyloidosis**

**Mayo (2004) cardiac stage IIIB**
**Lambda light chain amyloidosis**

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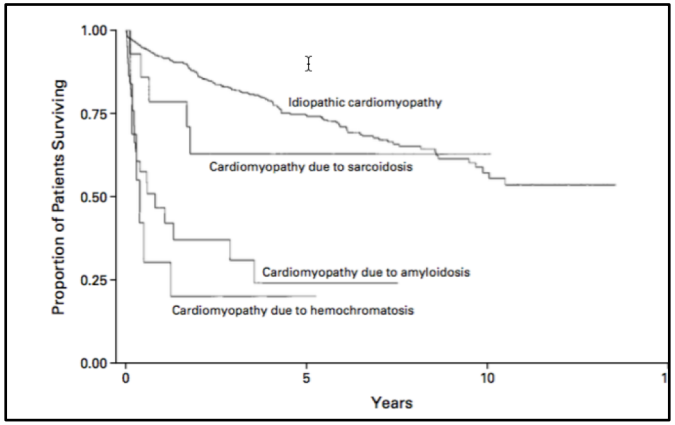
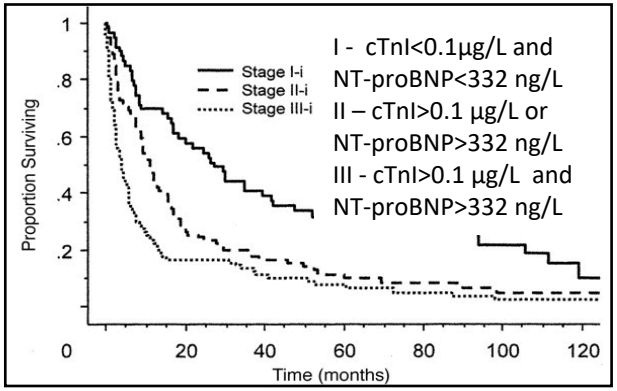
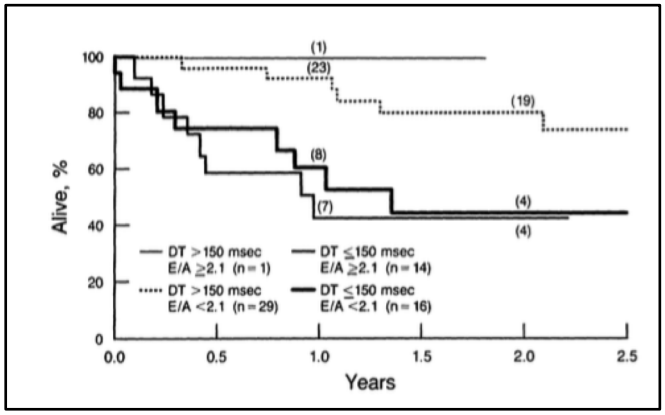
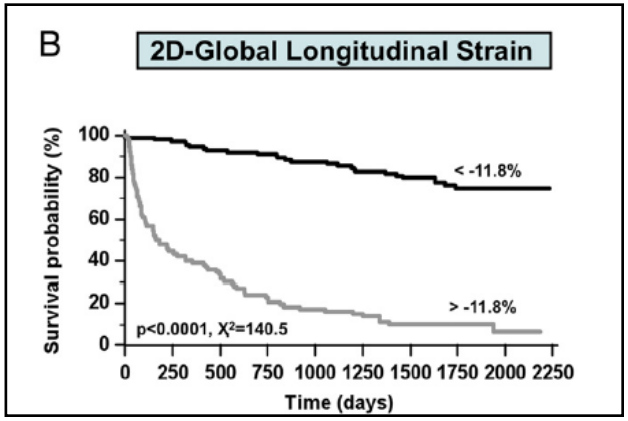
# Prognosis and Staging of AL Amyloidosis

# Predictor of Survival: Extent of Cardiac Involvement Importance of Timely Diagnosis




Klein et al. Circulation 1991
Felker et al. NEJM 2000
Dispenzieri et al. JCO 2004
Buss et al, JACC 2016

# Baseline Prognostic Staging Systems
# Cardiac Biomarker Based: Tn and NT-proBNP/BNP

| Models | Variables and cutoffs | Stages |
|---|---|---|
| Mayo2004 | • NT-proBNP, 332 ng/L (or BNP, 81 ng/L)<br>• cTnT, 0.035 ng/mL (or cTnI, 0.1 ng/mL) | Stage I: both variables below the cutoffs<br>Stage II: one variable above the cutoff<br>Stage III: both variables above the cutoffs |
| Mayo2004 European | Mayo 2004 stage III is divided into two groups according to<br>• NT-proBNP, 8500 ng/L (or BNP, 700 ng/L) | Stage IIIa: Mayo2004 stage III and NT-proBNP (or BNP) below the cutoff<br>Stage IIIb: Mayo2004 stage III and NT-proBNP (or BNP) above the cutoff |
| Mayo2012 | • NT-proBNP, 1800 ng/L<br>• cTnT, 0.025 ng/mL (or cTnI 0.1 ng/mL, or hs-cTnT 40 ng/L)<br>• dFLC, 180 mg/L | Stage I: all markers below the cutoffs<br>Stage II: one marker above the cutoffs<br>Stage III: two markers above the cutoffs<br>Stage IV: all markers above the cutoffs |

NT-proBNP, amino-terminal portion of pro-brain natriuretic peptide type B; BNP, natriuretic peptide type-B; cTnT, cardiac troponin T; cTnI, cardiac troponin I; hs-cTnT, high sensitivity cardiac troponin T; dFLC, difference between involved and uninvolved free light chain concentration.

Ability to Identify High Risk Patients

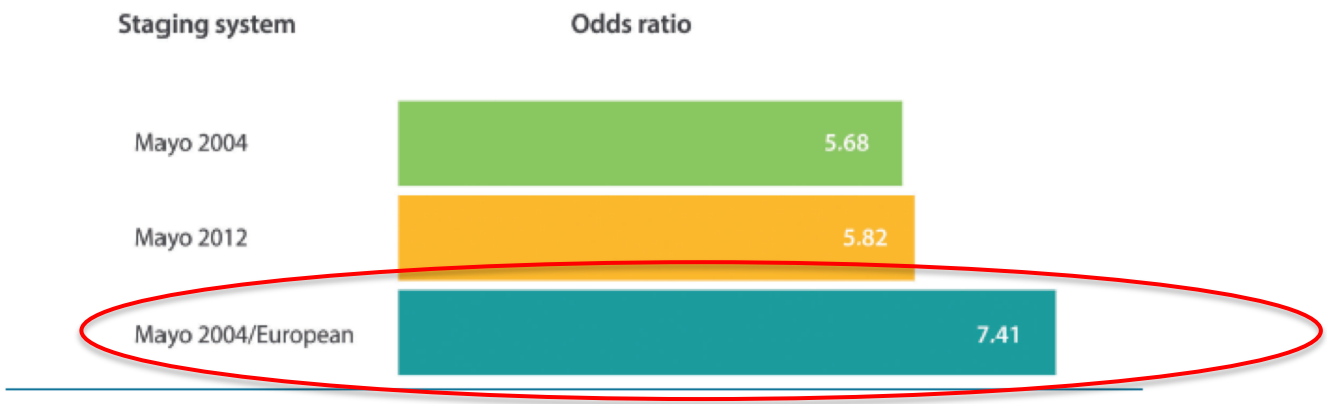
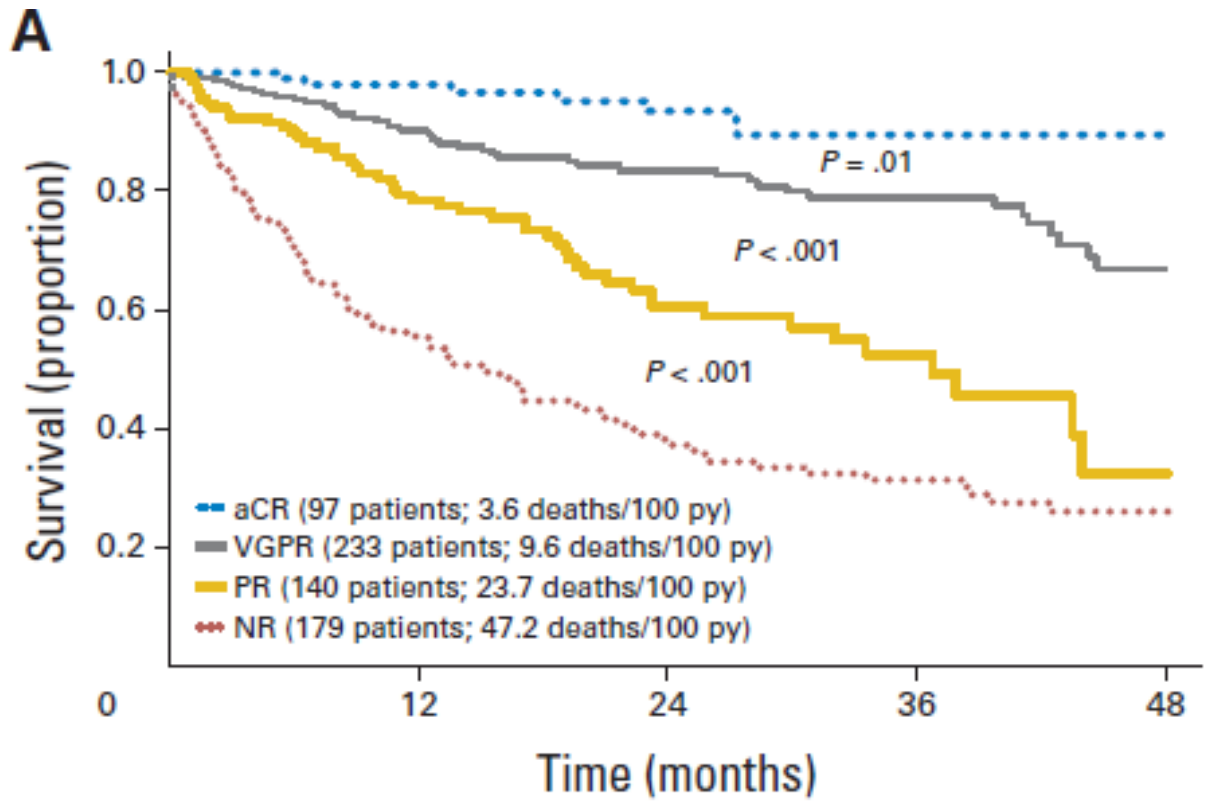



Figure 1. Odds ratio for very early death (within 6 months of diagnosis) of patients classified as being at highest risk by the three staging systems. Data from 1,065

Palladini G et al haematologica 2019

# Predictor of Survival: Hematologic Response to Treatment




- Hematologic response based on the serum free light chain assay in blood:

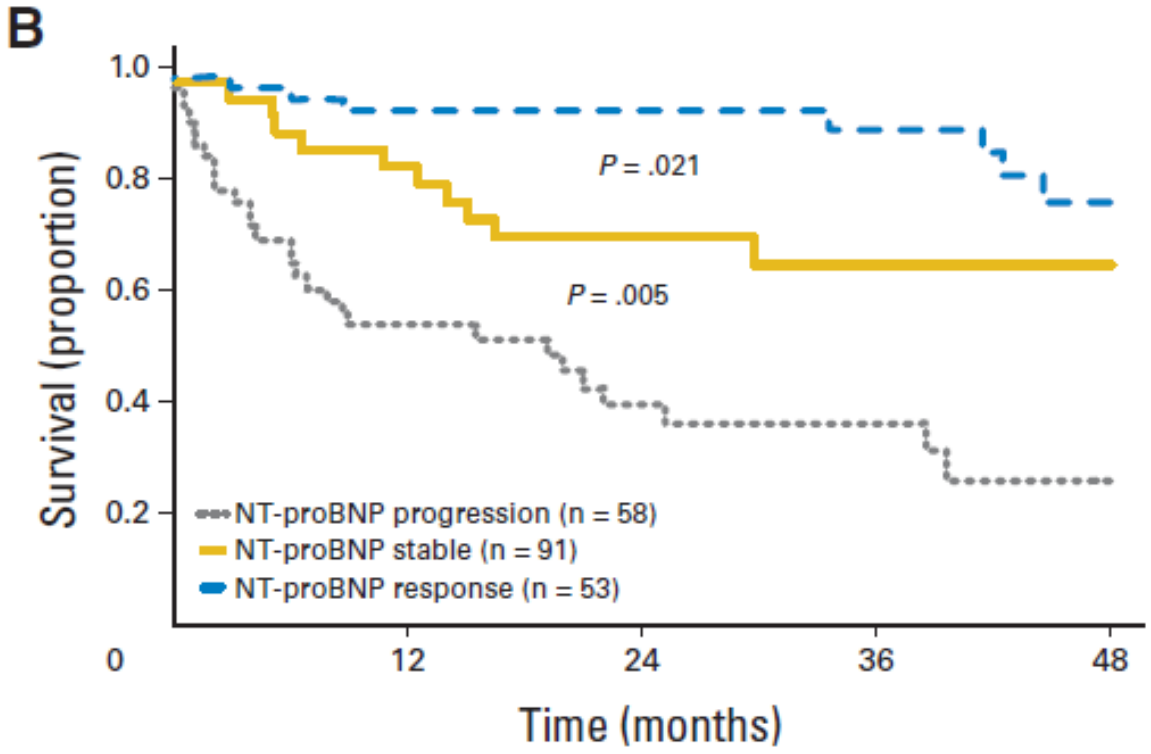
CR (complete remission) = negative serum and urine, and normal FLC ratio; VGPR (very good partial response) = dFLC <40 mg/L; PR(partial response) = dFLC decrease >50%; NR= no response

- **Hematologic response to therapy (VGPR and CR) is strongly associated with improved organ outcome**

Pallidini et al, J Clin Oncol 2012

# Predictor of Survival: Cardiac Response to Treatment

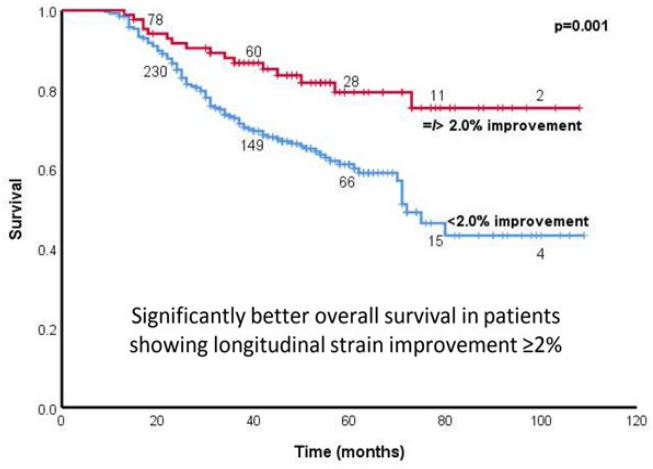
- NT-pro BNP Response: >30% and >300 ng/dl decrease
- BNP: ≥ 30% and ≥ 50 pg/ml decrease

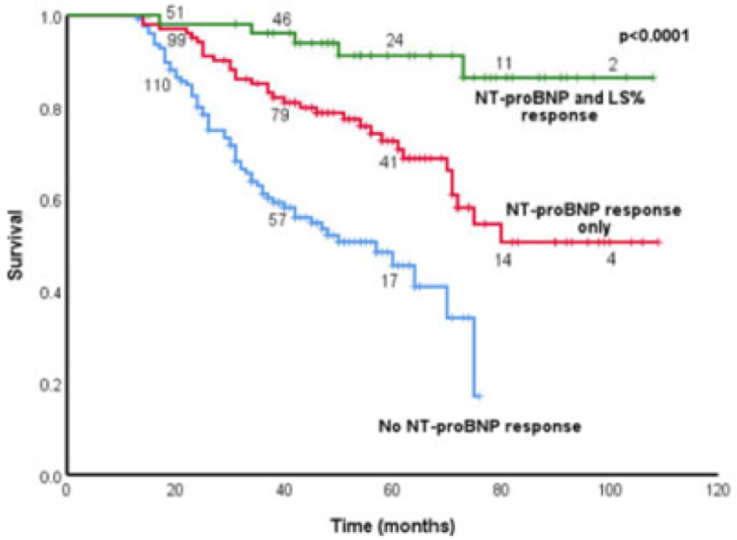



Palladini et al, JCO 2012
Lilleness et al, Blood 2019

# Predictor of Survival: Cardiac Response to Treatment

- Improvement in GLS is associated with better survival
- Pts with both NT-proBNP and GLS response showed best survival outcome



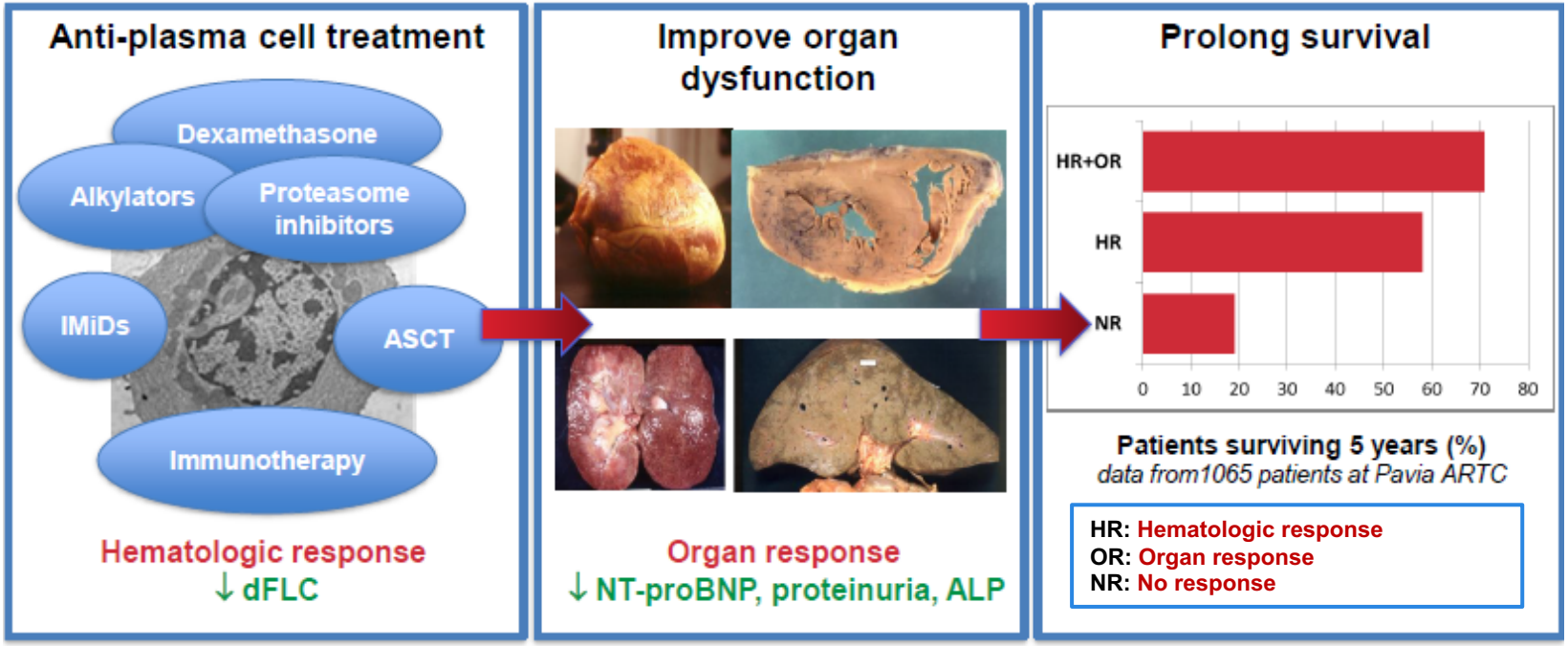

Cohen OC.et. Al Eur H J 2021

Memorial Sloan Kettering Cancer Center

# How is AL Amyloidosis treated?

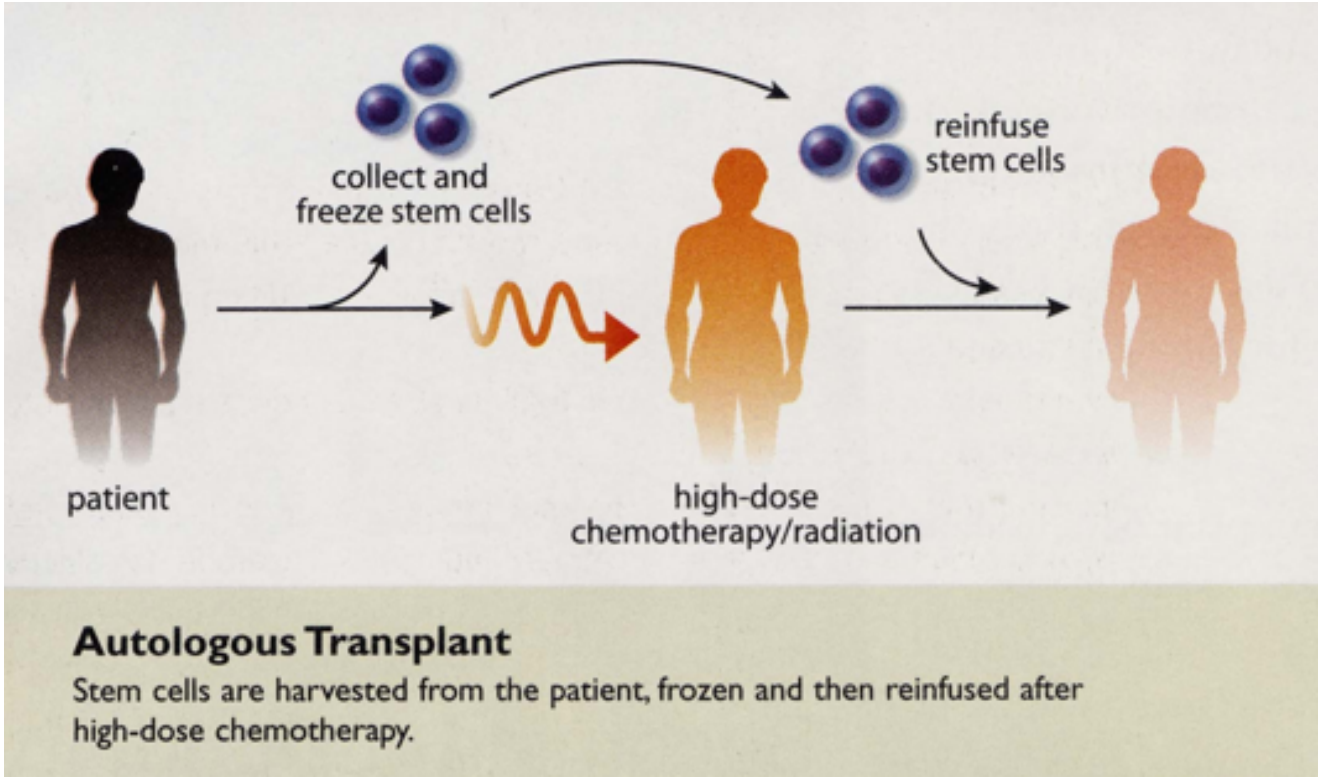
# What are the goals of therapy?

# Targeting the plasma cell to improve organ function and prolong survival




Palladini et al. 2018
Palladini et al. *JCO* 2012

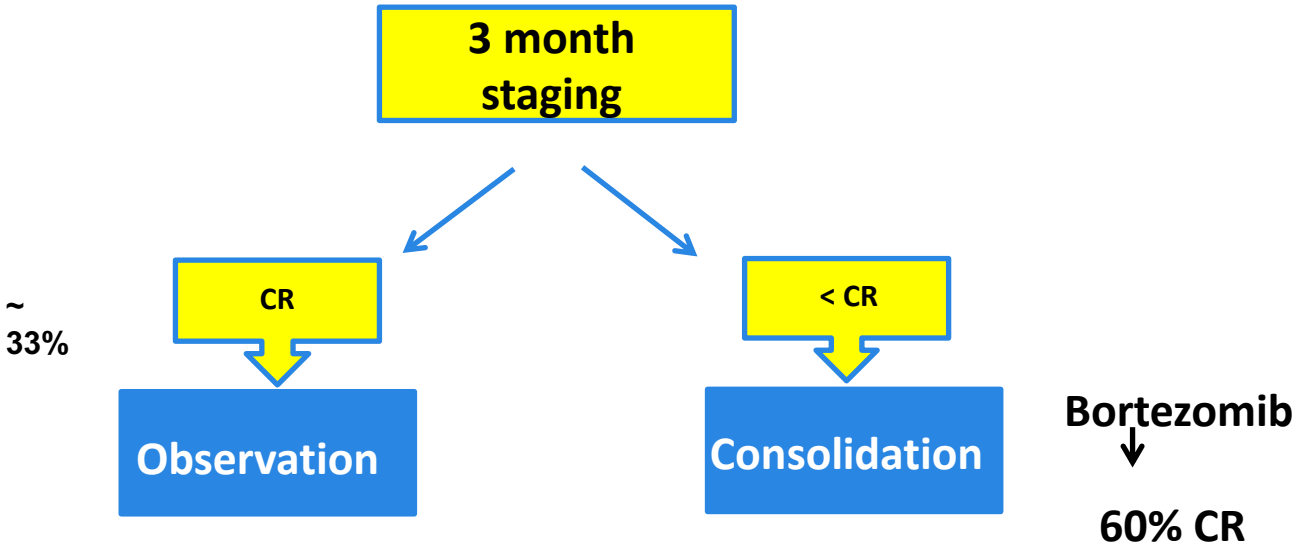
# High dose melphalan + autologous stem cell transplant for AL



# AL Amyloidosis: Eligible for ASCT

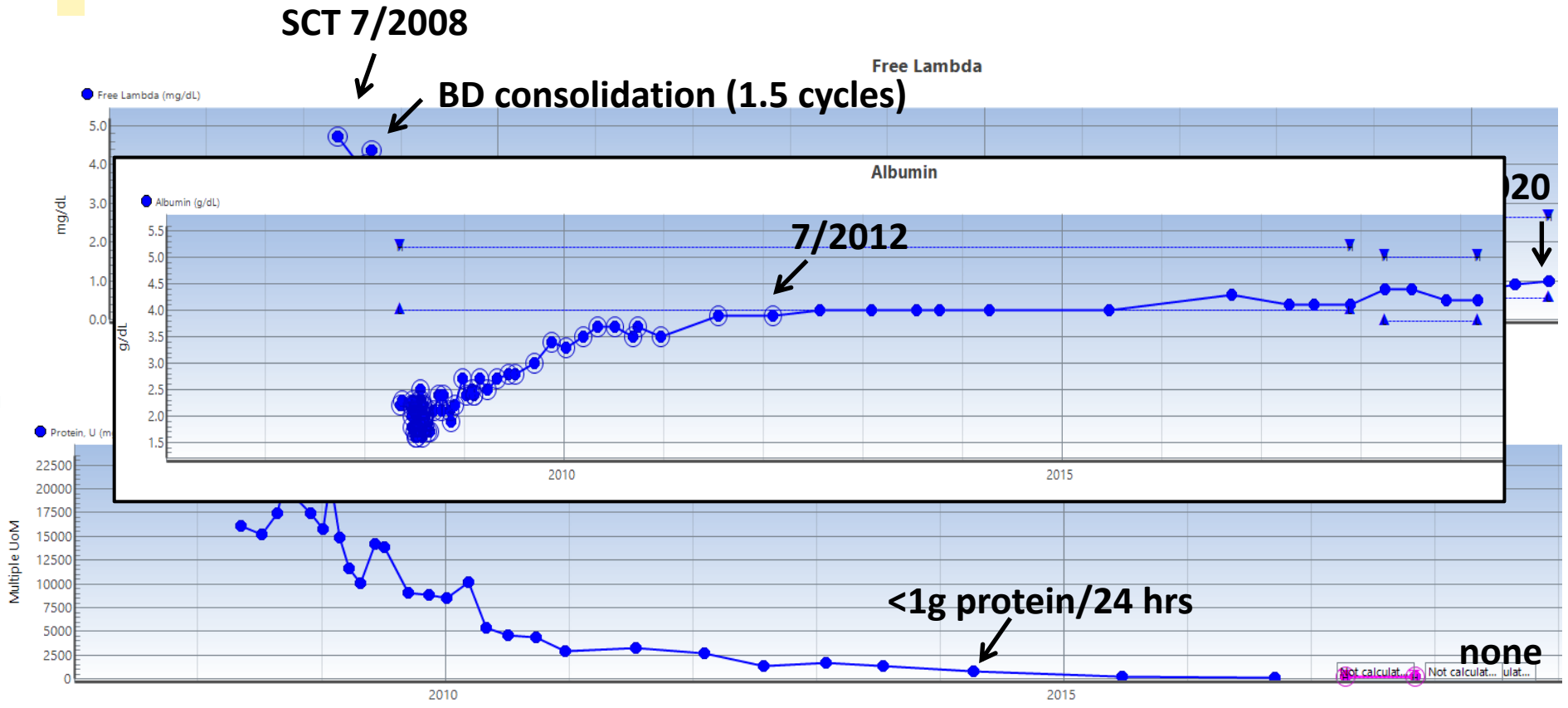
Risk-adapted MEL

| Age (years) | ≤ 60 | > 60 |
|---|---|---|
| No cardiac or renal compromise | MEL 200 | MEL 140 |
| With cardiac and/or renal compromise | MEL 140 | MEL 100 |




Landau et al. *Leukemia* 2013.

# Organ responses evolve over time



# Bortezomib-based therapy studied in variety of settings

- Bortezomib, cyclophosphamide & dexamethasone (VCd)
  - Stem cell sparing, preferred in renal compromise
  - Retrospective series (N= 230), heme ORR 60%, CR 23%
  - Organ response suboptimal/delayed, poor outcome in t(11;14)

Venner et al. *Blood* 2012.
Mikhael et al. *Blood* 2012.
Palladini et al. *Blood* 2015.

- Bortezomib, melphalan & dexamethasone (BMDex)
  - Prospective RCT BMDex (N=53) vs Mdex (N=56), BMDex ORR 81%, CR 23%
  - Prolonged PFS and OS, 50% reduction in mortality
  - Overcome poor outcome in t(11;14)

Kastritis et al. *JCO* 2020.

- Bortezomib-based induction prior to high dose melphalan
  - Lower relapse and improved PFS vs no induction

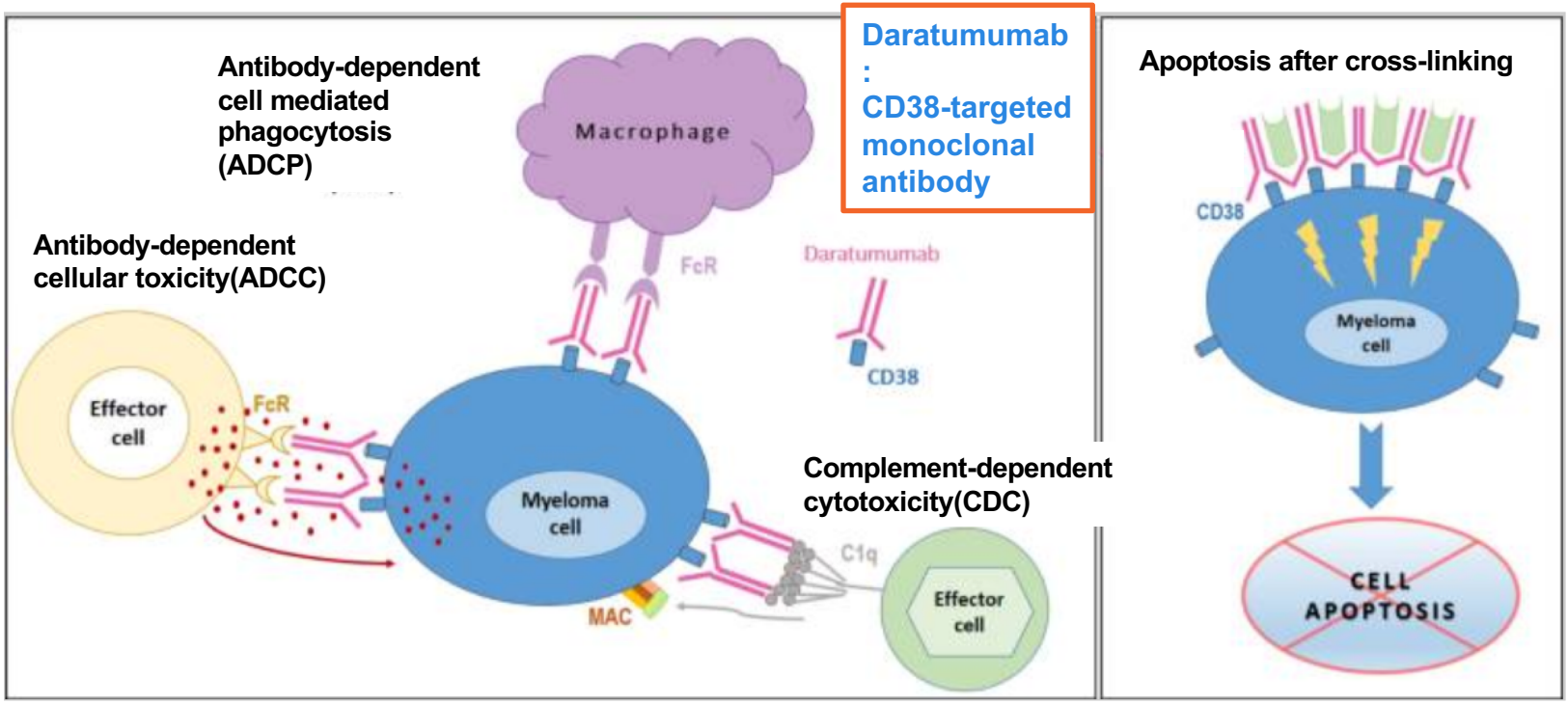
Cornell et al. *JCO* 2020.

- Attenuated bortezomib or low dose combinations
  - High risk patients (stage IIIb, NYHA class III or IV)

Jaccard et al. *Hematologica* 2014.

**Bortezomib-based induction = standard of care**

# Daratumumab approved as plasma cell directed therapy for multiple myeloma in 2015




Dima et al. 2020

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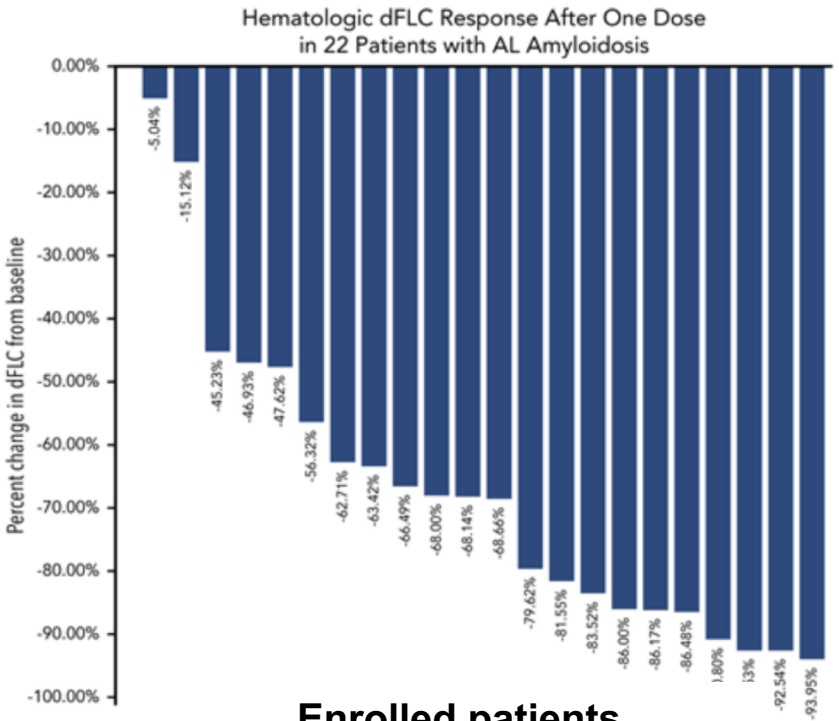
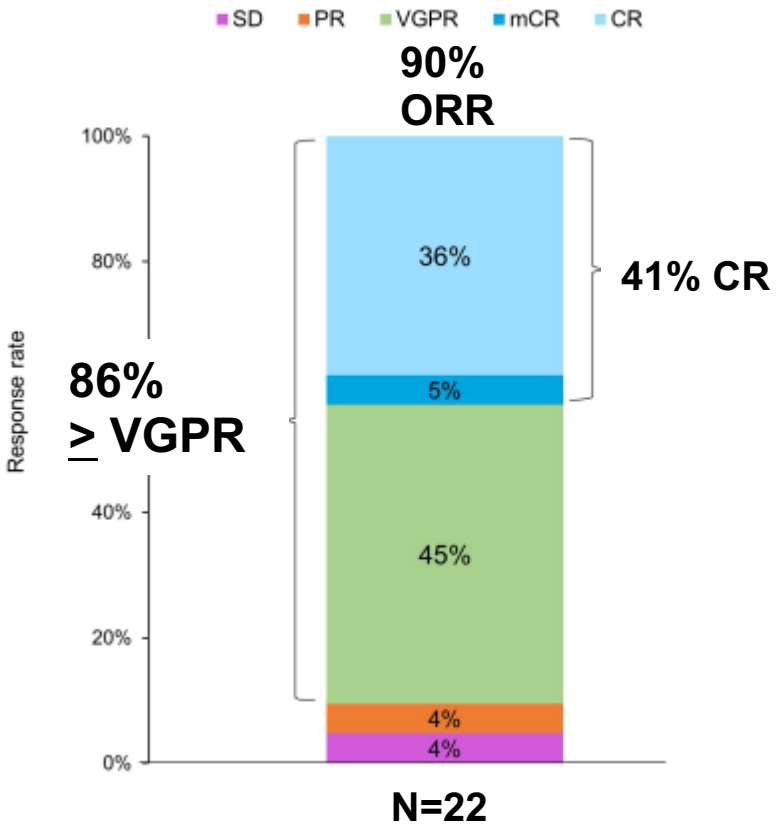
# Phase II study of daratumumab in relapsed AL

**Hematologic response after *one dose* of daratumumab**




**Enrolled patients (N=22)**




Sanchorawala et al. *Blood* 2019.

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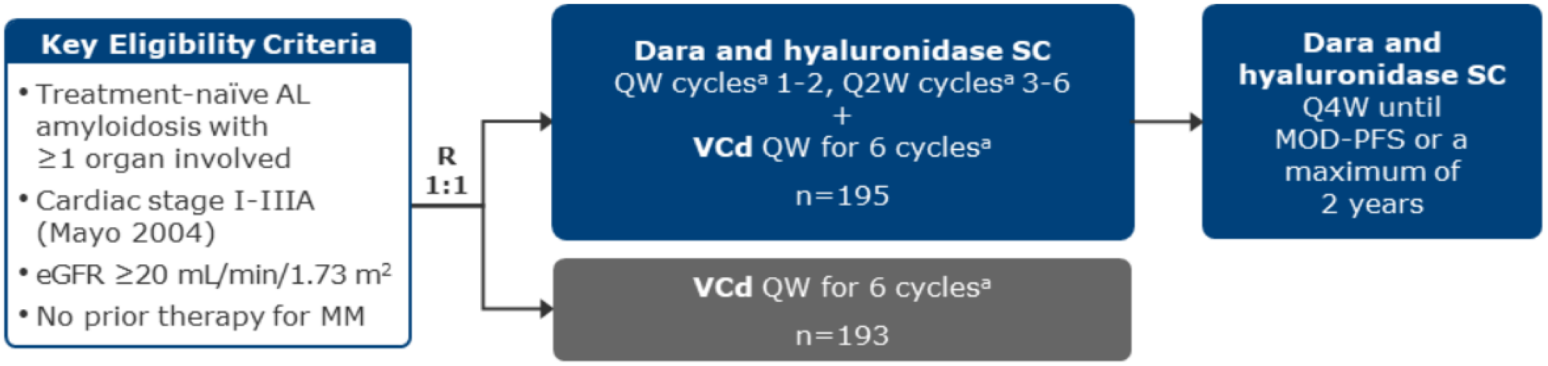
# ANDROMEDA trial: VCd vs VCd + Daratumumab in newly diagnosed patients with Primary AL Amyloidosis




**Stratification Criteria**

- Cardiac stage (I vs II vs IIIA)
- Transplant typically offered in local country (yes vs no)
- Creatinine clearance (≥60 vs <60 mL/min)

**Dose**

- **Dara and hyaluronidase SC:** Dara 1800 mg + rHuPH20 30,000 Units
- **Bortezomib:** 1.3 mg/m² SC
- **Cyclophosphamide:** 300 mg/m² PO or IV
  - 500 mg maximum weekly dose
- **Dexamethasone:** 40 mg PO or IV[b]
  - Patients >70 years old, underweight[c], or hypervolemic, or with poorly controlled DM, or prior intolerance/AEs with steroids: may be administered at a dose of 20 mg QW

**Endpoints**

- **Primary endpoint: Hematologic CR rate**
- **Secondary endpoints: MOD-PFS, organ RR, time to response, safety**

Kastritis et al. *NEJM* 2021.

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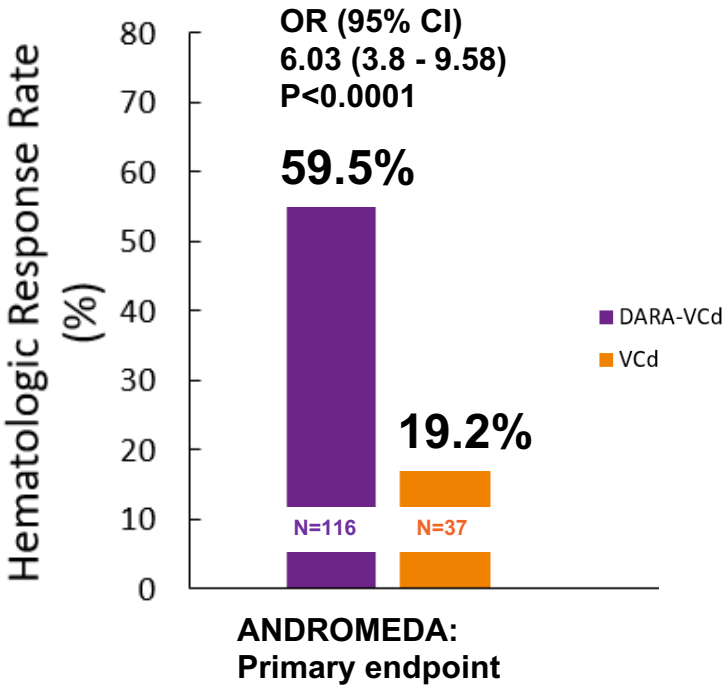
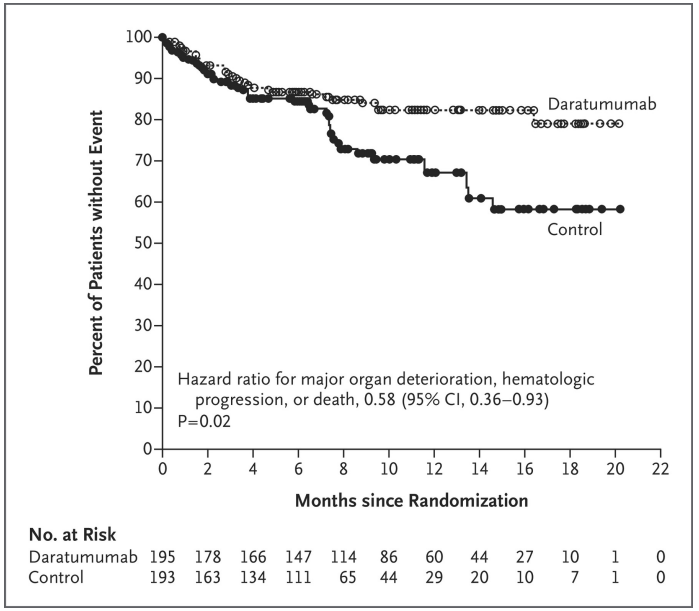
# ANDROMEDA trial:
# Primary and secondary endpoints

## Hematologic CR rate




ANDROMEDA:
Primary endpoint

## *Major organ deterioration (MOD)-PFS




*MOD-PFS defined by: death, cardiac deterioration, ESRD, hematologic progression

Comenzo et al. ASH 2020.
Kastritis et al. *NEJM* 2021.

# FDA Approves First and Only Treatment for AL Amyloidosis

**DARZALEX *FASPRO*®** (daratumumab and hyaluronidase-fihj) Becomes the First FDA-Approved Treatment for Patients with Newly Diagnosed Light Chain (AL) Amyloidosis

January 15, 2021

Memorial Sloan Kettering Cancer Center

# Choice of upfront therapy – since 2021

- CyBorD + Daratumumab

  Stem cell sparing, preferred in patients with renal compromise, favorable outcome in patients with t(11;14)

- High risk patients (stage IIIb, NYHA class III or IV) – single agent daratumumab with intensive supportive care

- Upfront AHCT

  < 10% PCs, ≤ 2 organ involvement, Mayo stage I/II cardiac disease

# Key Points (1)

- What is amyloidosis?
  - AL (light chain) amyloidosis, a plasma cell disorder producing monoclonal light chains that misfold, aggregate and deposit in tissues; leads to dysfunction of organs, often multi-systemic
  - ATTR (transthyretin) amyloidosis, arising from precursor protein produced in the liver, transthyretin; primarily involves heart and nervous system

- Diagnosis - clues and when to suspect?
  - Often elusive; presents with multisystemic signs/symptoms
  - Unexplained LV hypertrophy on echo, with low voltage on ECG, should raise suspicion for cardiac amyloidosis.
  - Diagnosis of AL amyloidosis:
    - elevated serum free light chains, clonal BM plasma cells, tissue biopsy positive for amyloidosis; mass spect showing lambda/kappa subtype

# Key Points (2)

- Prognosis
  - Extent of cardiac involvement = strongest determinant of survival
  - Cardiac biomarker (NT proBNP + troponin) staging predicts survival in newly diagnosed patients
  - Renal biomarkers (proteinuria + GFR) predict risk of progression to hemodialysis

- Treatment goals
  - Elimination of clonal plasma cells, reduction of circulating light chains + organ improvement
  - Hematologic complete remission (CR) is associated with organ improvement and better survival
  - Cardiac response defined by >30% and >300 ng/L decrease if baseline NT-proBNP≥ 650 ng/L

**THINK AMYLOIDOSIS!**

# QUESTIONS ?

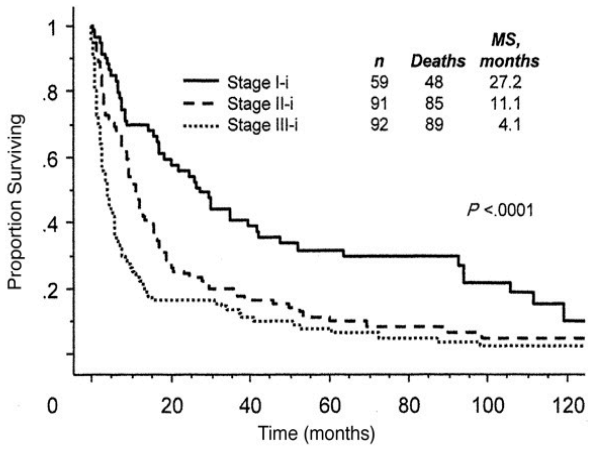
Thank You!

# Laboratory findings suggestive of AL amyloidosis

- Abnormal serum free light chain assay
- Screen for organ involvement
  - Cardiac: BNP, NT-ProBNP, Troponin
  - Renal: serum ALB, 24hr urine total protein
  - Liver: alkaline phosphatase
  - Coagulopathy: factor X

# Prognostic Staging Systems
# Cardiac Biomarker Based: Troponin and NT-proBNP

## Mayo Staging System



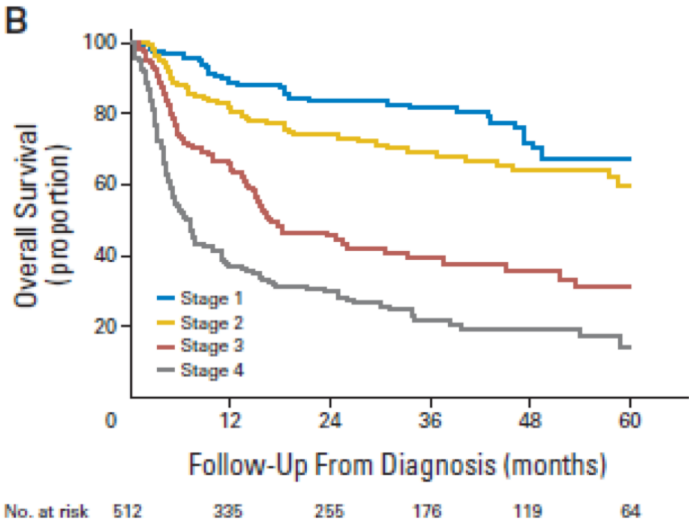

Stage I
- cTnI<0.1µg/L and NT-proBNP<332 ng/L

Stage II
- cTnI>0.1 µg/L or NT-proBNP>332 ng/L

Stage III
- cTnI>0.1 µg/L and NT-proBNP>332 ng/L

Dispenzieri, JCO 2004

## Revised Mayo Staging System




3 prognostic variables (cTnT ≥ 0.025 ng/mL, NT-proBNP ≥ 1,800 pg/ml or BNP >400, FLC-diff ≥ 18 mg/dL)

Stage I - score 0

Stage II – score 1

Stage III – score 2

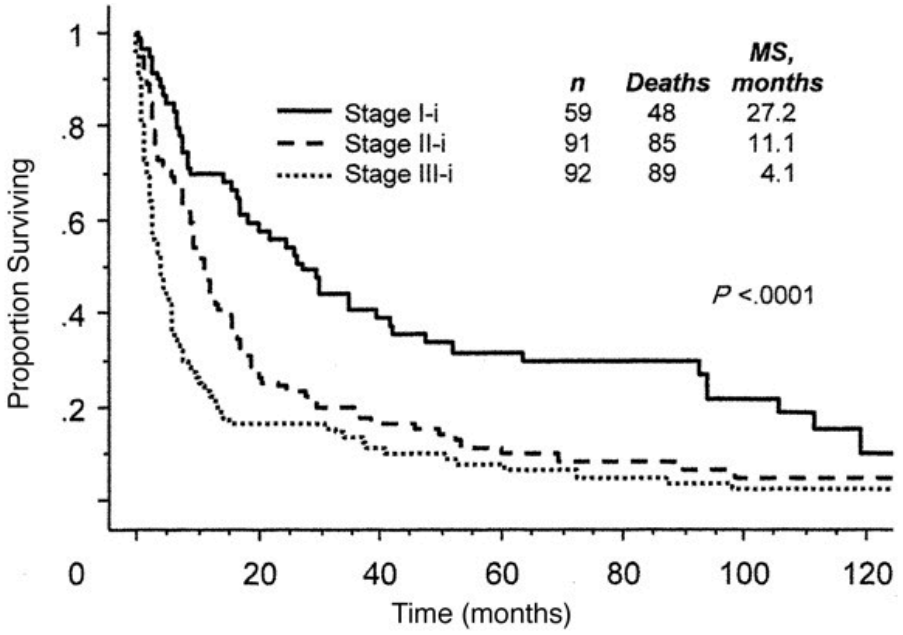
Stage IV – score 3

Kumar, JCO 2012

# Serum Cardiac Biomarker Based Staging System: Troponin and NT-proBNP

- Sensitive markers for the presence of cardiac amyloidosis
- Strongly prognostic in AL amyloidosis

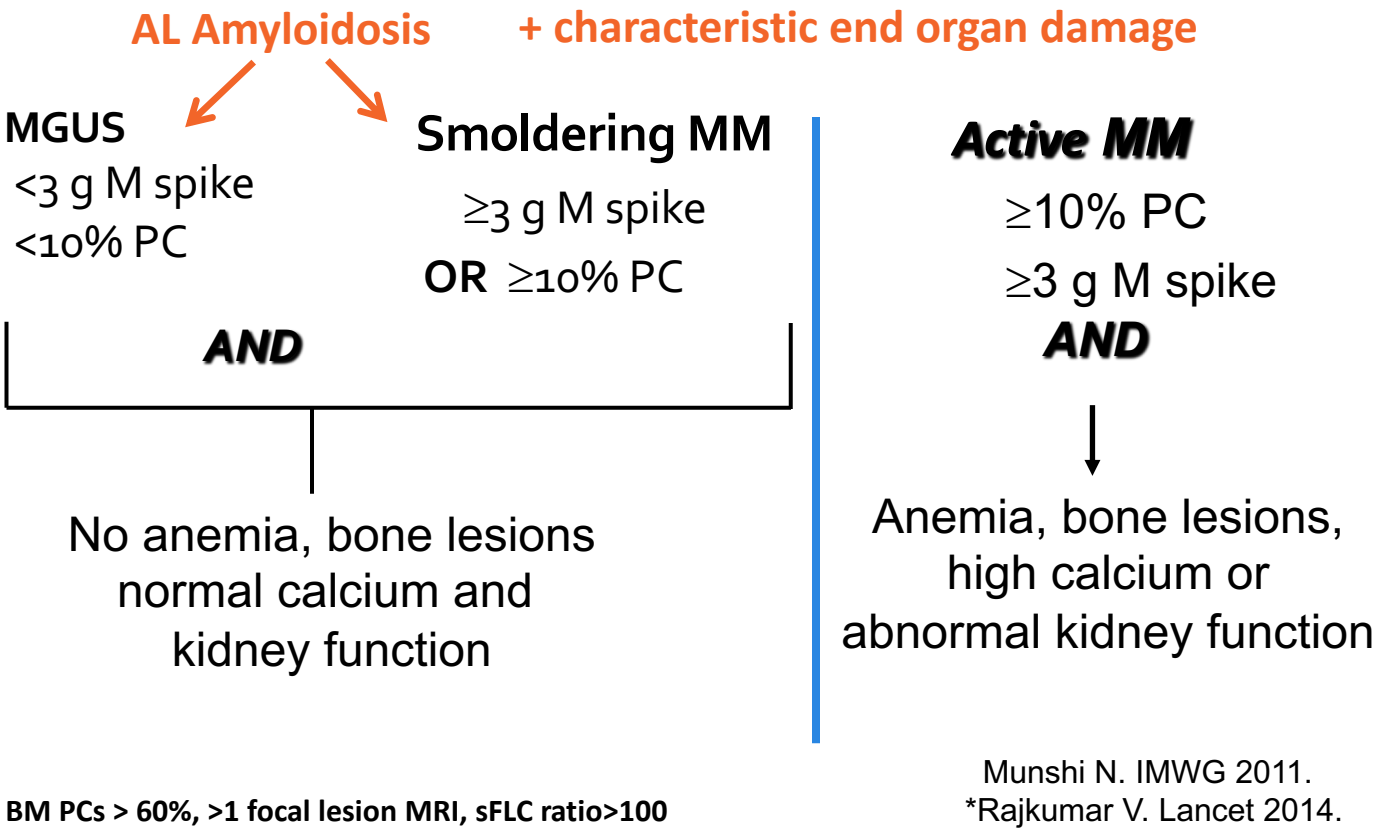
Mayo Staging System




Stage I - cTnI<0.1µg/L and NT-proBNP<332 ng/L
Stage II – cTnI>0.1 µg/L or NT-proBNP>332 ng/L
Stage III - cTnI>0.1 µg/L and NT-proBNP>332 ng/L

Dispenzieri, JCO 2004

# Plasma cell dyscrasias




* BM PCs > 60%, >1 focal lesion MRI, sFLC ratio>100

Munshi N. IMWG 2011.
*Rajkumar V. Lancet 2014.