



Brigham and Women's Hospital
Founding Member, Mass General Brigham

Dysproteinemia for the Nephrologist

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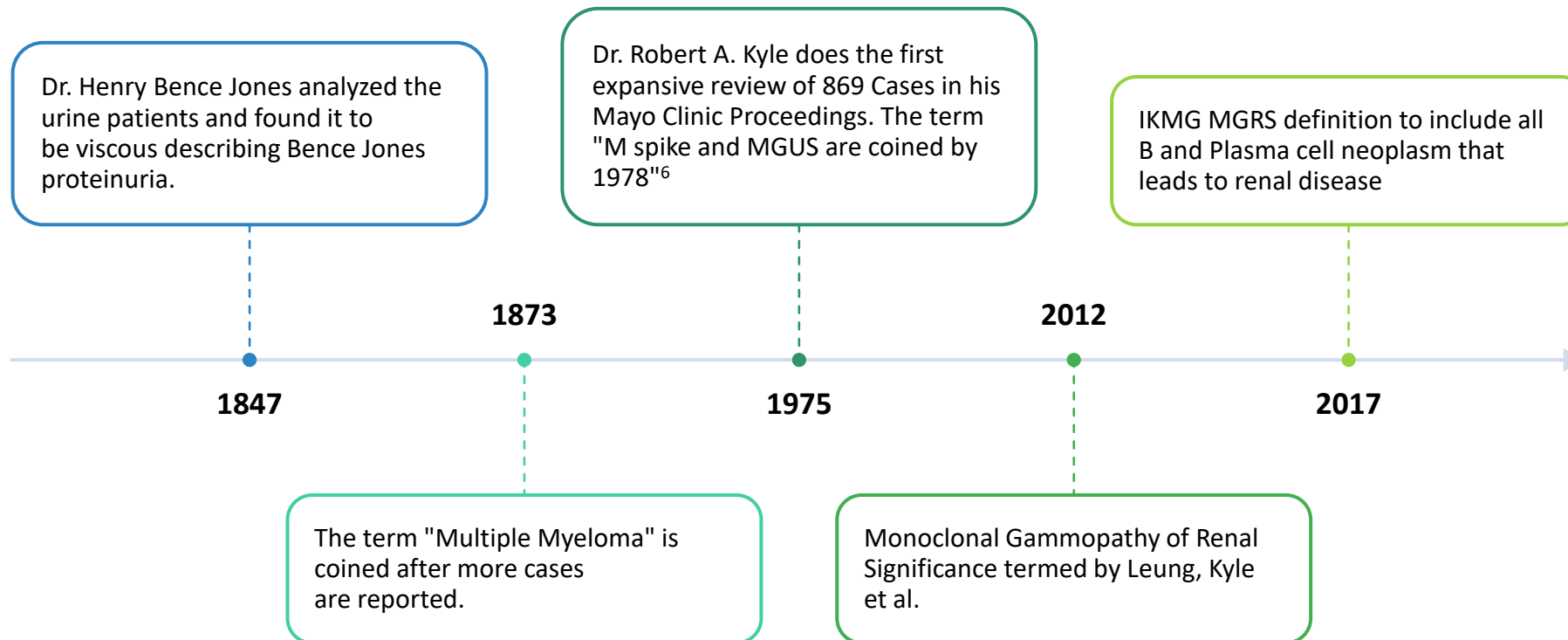
DISCLOSURES

- ▶ Nothing to disclose.

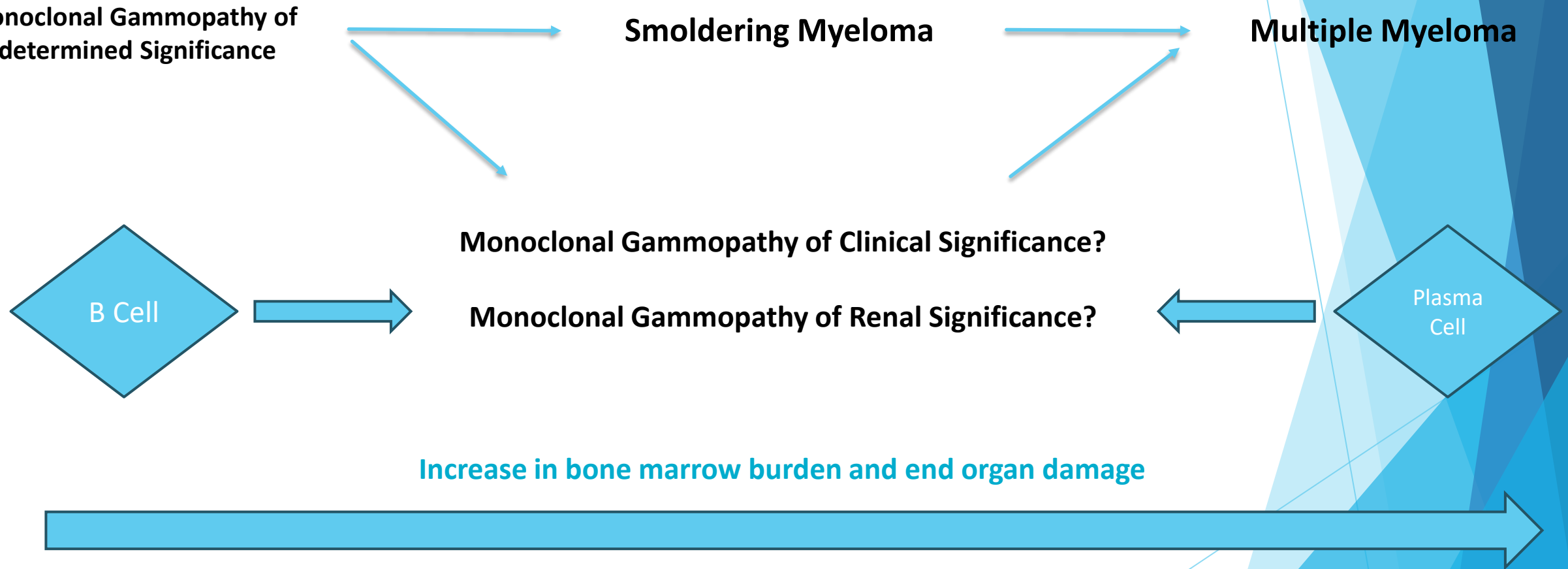
Objectives:

- ← Nomenclature
- ← Approach to Diagnostics
- ← Select Few Renally Significant Disorders

A Brief History:



Spectrum: What's In A Name?



Epidemiology

Monoclonal Gammopathy of
Undetermined Significance
(MGUS)

3% of general population over 50
years

10% chance of progressing

Multiple Myeloma (MM)

- 1-2% of all cancers (SEERS, 2020)
- 50% will experience AKI or CKD
- 10% of patients will require HD (Courant et al. NDT, 2021)

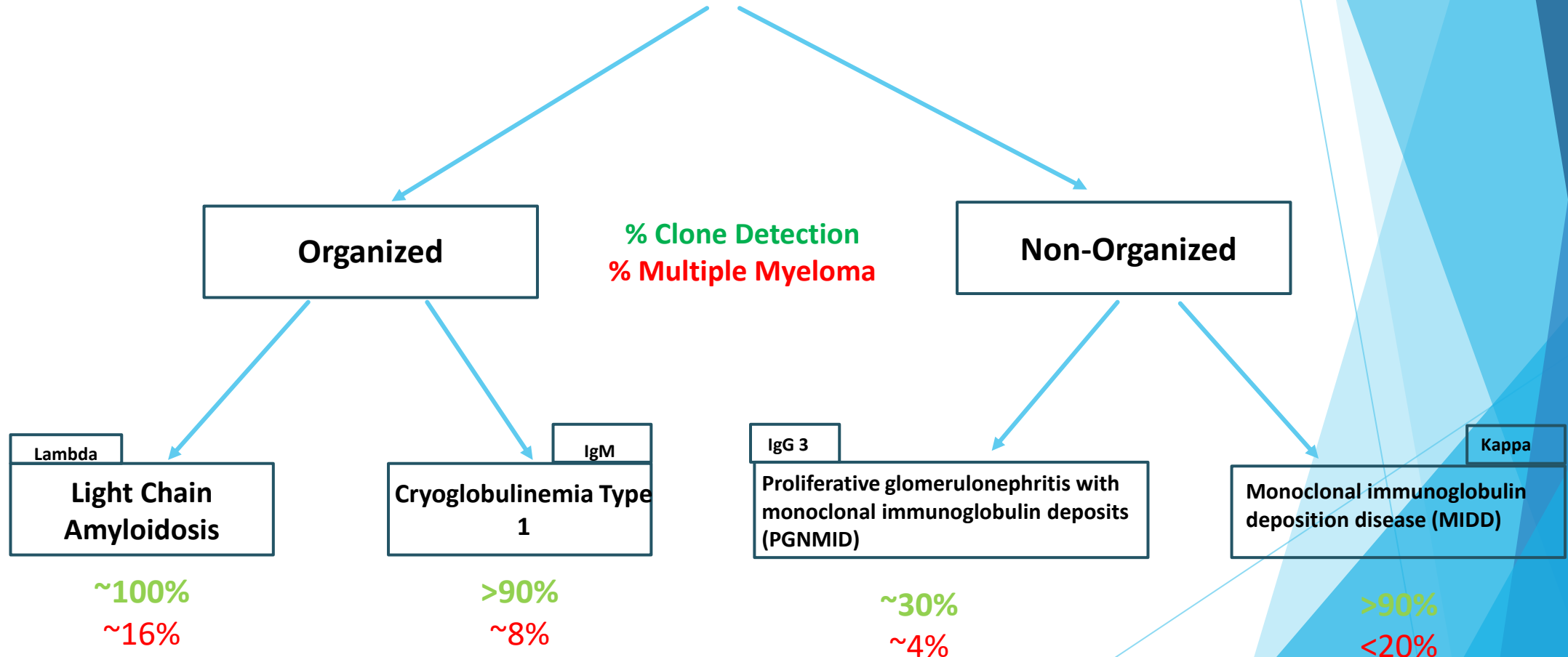
Monoclonal Gammopathy of Renal
Significance (MGRS)

Variable

A Rose By Any Other Name?



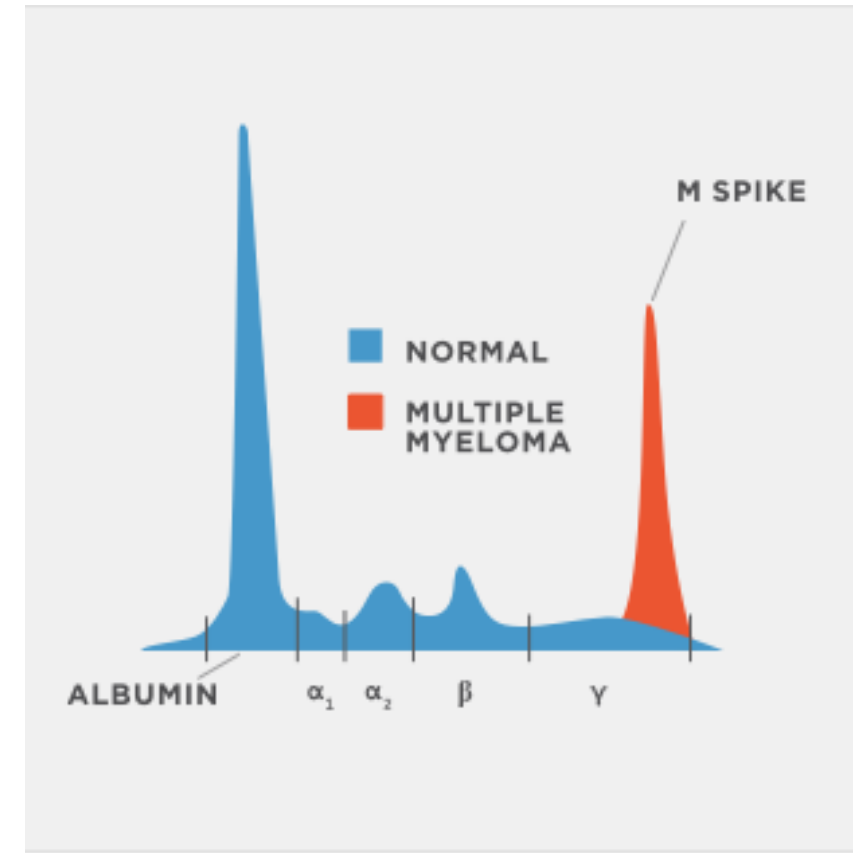
Monoclonal Gammopathy of Renal Significance



NOT ALL MGRS ARE CREATED EQUAL

Diagnostics: Initial Screening

- ▶ **Serum Protein Electrophoresis (SPEP)**
 - ▶ Detect monoclonal protein and quantify
 - ▶ Assess response to treatment
- ▶ **Serum Immunofixation (SIFX)**
 - ▶ Identify type of monoclonal protein
- ▶ **Free Light Chains (FLC)**
 - ▶ Identify "non secretory" and non-heavy chain monoclonal protein
 - ▶ Assess response to treatment
- ▶ Sensitivity >97% when all three combined (Katzmann et al. Clinical Chem, 2009)



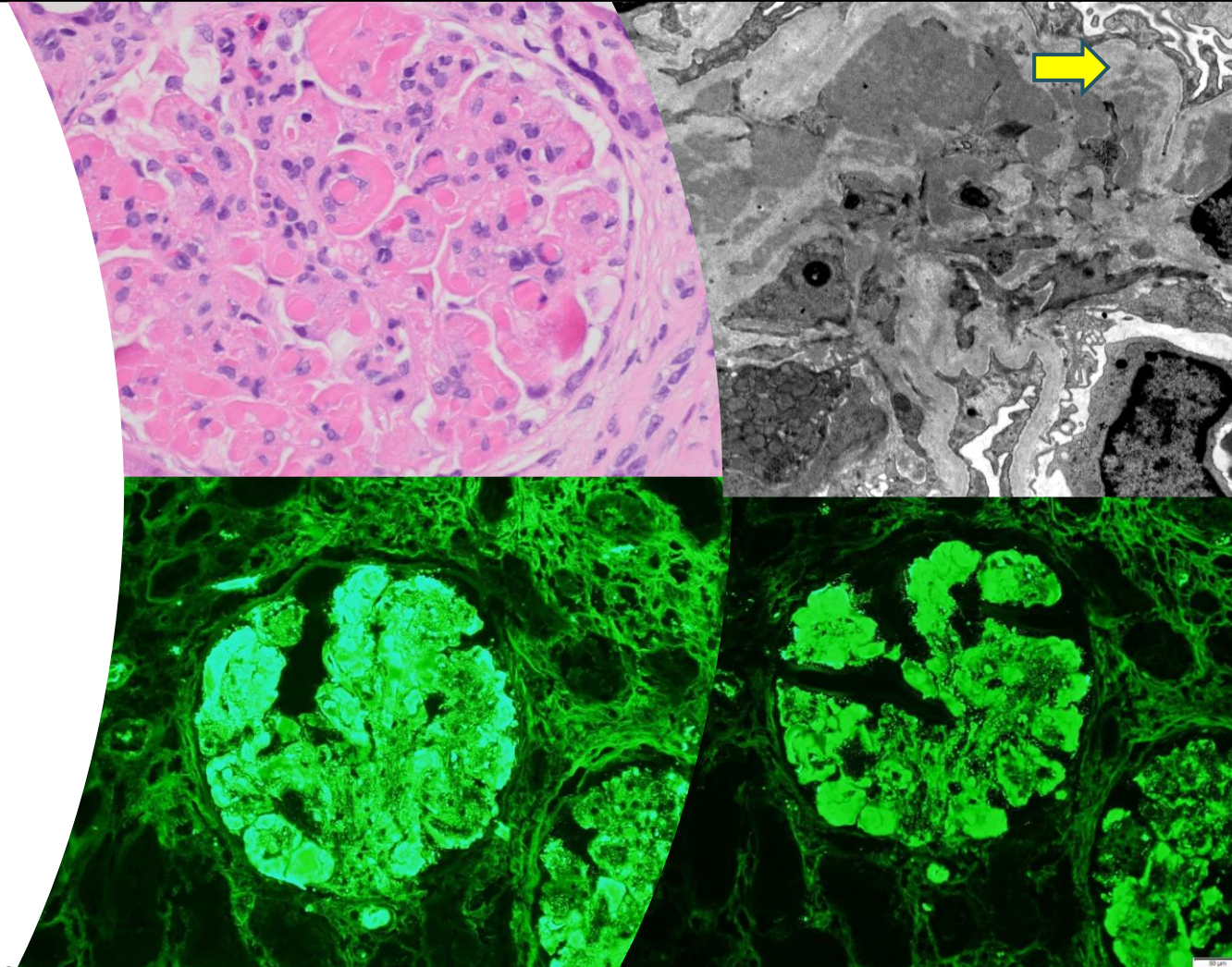
Source: [Understand and Track Your Multiple Myeloma Lab Tests \(ninlaro.com\)](https://www.ninlaro.com/understand-and-track-your-multiple-myeloma-lab-tests)

My Approach

- ❑ **Know the type of proteinuria** (total proteinuria vs albuminuria)
- ❑ **Know the bone marrow** (what % involvement B or Plasma)
- ❑ **Know the clone** (IgG, IgM, Lambda vs Kappa)

Case # 1

- ▶ A 65-year-old male with a 6-month history of weight loss is admitted for Acute Kidney Injury (AKI) with worsening Cr of 6.6 mg/dl (baseline 2mg/dl). His major complain is blurry vision, leg swelling, and intermittent headaches.
- ▶ **Vital Signs:** 180/90s HR 105 96% 02 RA
- ▶ **Workup:**
 - pr/cr of 2.8 mg/mg uACR 1.5 mg/mg UA with hematuria
 - Low C3/C4
 - SPEP M spike of 1.2 g/dl SIFX with IgM K
 - BM biopsy lymphoplasmacytic pattern kappa restriction
 - positive for MYD 88 mutation
 - PET/CT with mediastinal lymphadenopathy and FDG uptake.



Case #1: Cryoglobulinemia Type 1

- **Plasmapheresis**
 - 2A Recommendation Clinical Apheresis (Connelly-Smith et al. Clinical Apheresis, 2023)
 - 2-3 Sessions with goal reduction of 30-60% (Castillo et al. 2015, Blood)
- **Clone Directed Therapy**
 - Bortezomib plus Dexamethasone (BDR +/- Cyclophosphamide)
 - Rituximab (once IgM <4000mg/dl)

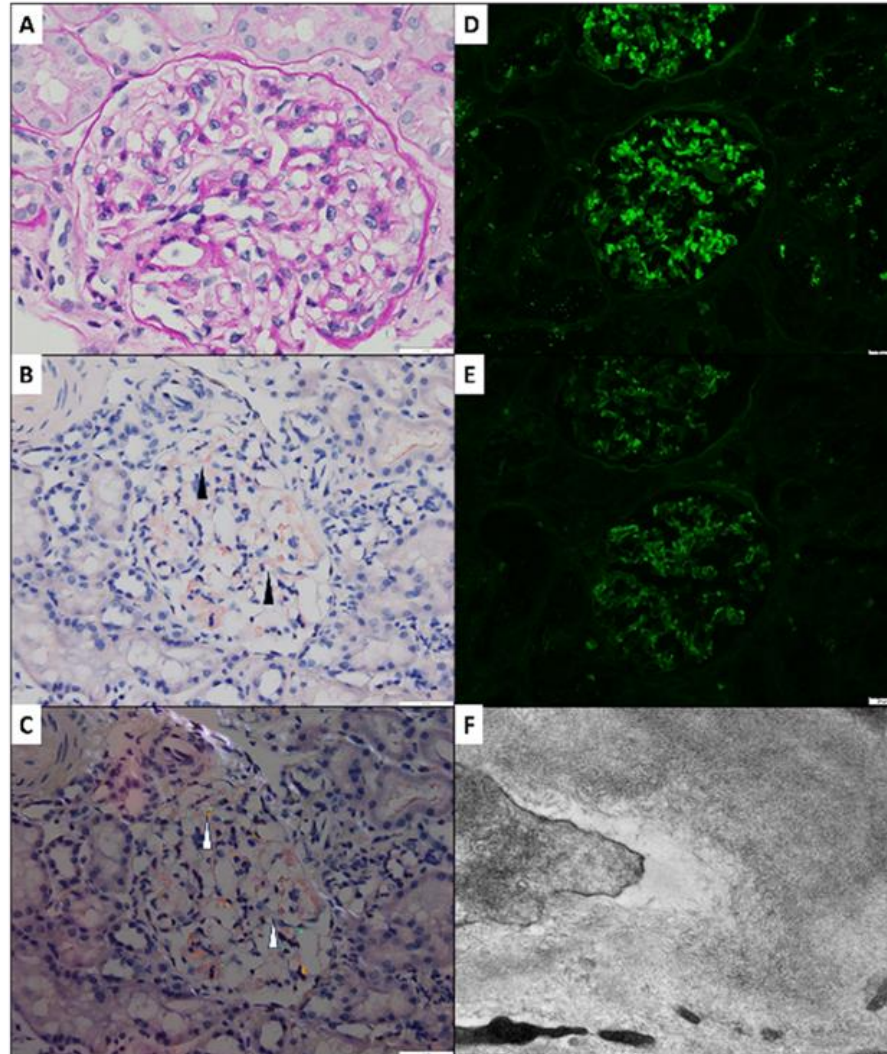


Case #2

- 67-year-old female presents for worsening diarrhea, pulmonary nodules, and new onset nephrotic syndrome. Extensive workup over 2 years for diarrhea and pulmonary nodule has been unrevealing, and there are plans for biopsy and colonoscopy.
 - 2022: 2400g/day proteinuria. 2024 7g/day of proteinuria and 5g/day of albumin
 - ANA + 1: 40
 - C3/C4 Normal
 - SPEP/SIFX/FLC: No M spike Lambda 322 mg/L Kappa 7.7mg/L R 0.02
 - BMBx: unrevealing



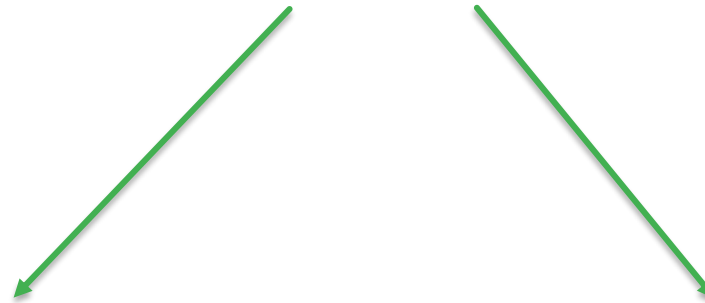
Kidney Biopsy



Light Chain Amyloidosis

- ▶ 50-70% will have renal involvement, 40% will have nephrotic syndrome
- ▶ Plasma cell clone produce pathogenic light chain > protein misfolding, fibril formation, organ deposition
- ▶ Lambda chains and mutations in N terminus of V region increase "amyloidogenicity" (Merlini et al. NEJM, 2003)

AL Amyloid Risk Stratification



Cardiac

Mayo 2012	Median Survival (months)
Stage I	94.1
Stage II	40.3
Stage III	14.0
Stage IV	5.8

Renal

Palladini	2 Year Dialysis Risk
Stage I	<3%
Stage II	11-25%
Stage III	60-75%

Treatment

- ▶ 2018-2021 Phase 3 open-label RCT 388 patients
- ▶ Group B: 6 cycles of SQ Daratumumab, Cyclophosphamide, Bortezomib, Dexamethasone, then SQ Daratumumab monthly for 18 more cycles (total 24months).
 - Increased speed, frequency, and depth of hematological response
 - Cardiac and Renal responses nearly doubled
 - Median progression-free survival improved significantly
- **Summary: Dara-CyBorD showed a faster complete response, longer survival, and improved organ response**

Renal Amyloid

Renal amyloidosis suspected?

Initial Testing

- SPEP, SIF, sFLC, UIF
- Urine protein studies
- Ferritin, SAA, genetic studies*

Kidney biopsy

Evaluate

Congo RED+

- Light microscopy
- Immunofluorescence
- Electron Microscopy

<10 nm randomly arranged fibrils

Determine Amyloid Protein

LMD-MS

- Efficient
- Increases diagnostic accuracy
- Can identify multiple precursors

General Therapy: volume, hemodynamic, symptom management

Light Chain Amyloidosis

- ❖ clone directed therapy

AA Amyloidosis

- ❖ target inflammation

ALECT 2

- ❖ unclear

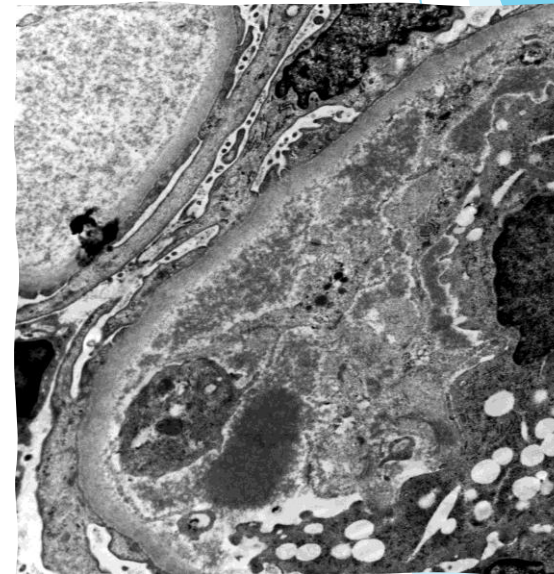
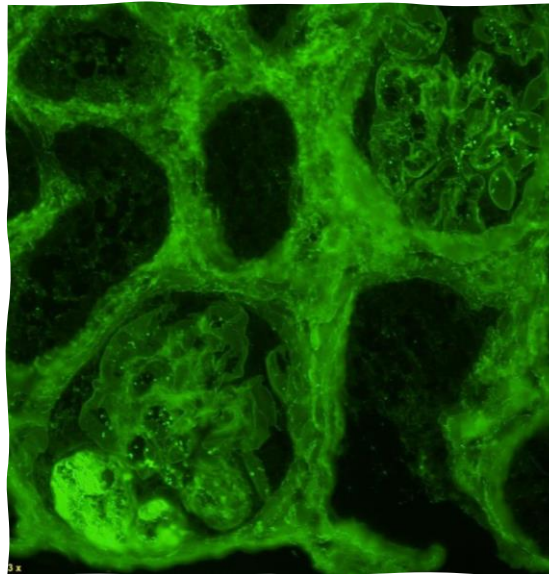
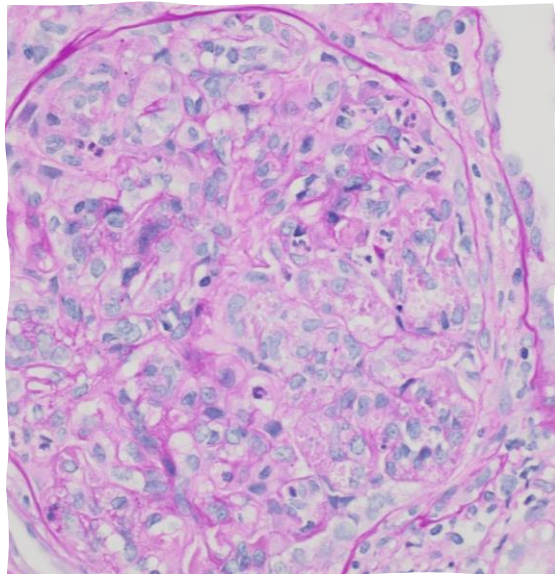
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- ❖ see Table 3

Case #3

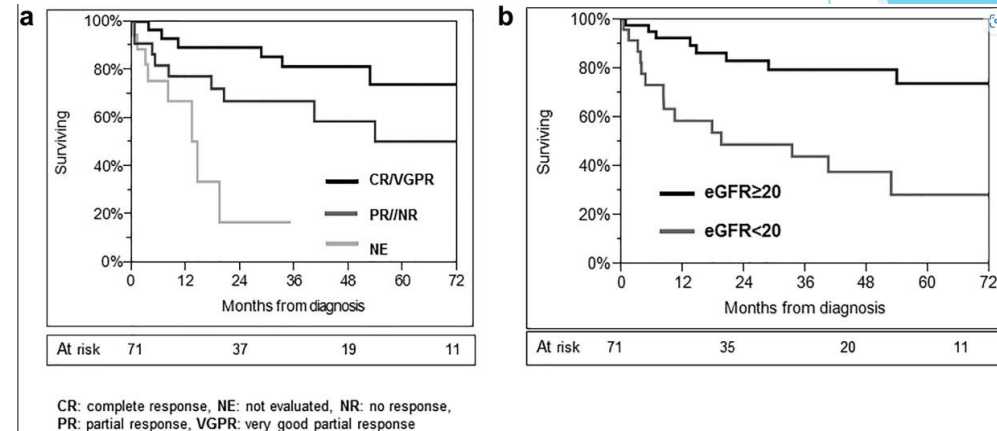
- ▶ A 55-year-old male with uncontrolled IDDM2 (~20 years), heart failure, and smoldering multiple myeloma is referred for worsening proteinuria of **12.0 g/day** (**7.5g albuminuria**) with baseline CKD Cr of **2.0-2.5 mg/dl** (eGFR 30 ml/min/m²).
- ▶ Workup:
- ▶ **A1C of 10%**
- ▶ SIFX/SIFE/FLC M spike 0.8g/dl, Kappa 75 mg/l
- ▶ BM: 40% Kappa restricted plasmacytosis

► To Biopsy or not to biopsy?



Monoclonal Immunoglobulin Deposition Disease

- ▶ 5-year overall survival (OS) and renal survival (RS) 67% vs 57%
- ▶ Mean RS prior to current therapy ~22 months (Lin et al. JASN, 2001)
- ▶ Management
 - ▶ ASCT or Bortezomib based regimen more likely to increase response
 - ▶ Complete response = Increased RS



eGFR better predictor of renal outcome, not proteinuria



-
- ▶ What about Proliferative Glomerulonephritis + MIDD = PGNMID?

PGNMID vs MIDD

PGNMID	MIDD
IgG 3 K IgM? IgA?	Light Chain most commonly
Low C3/ Low C4	Normal Complements
30 % Clone detection rate	~90% Clone detection rate
~40% progress to ESKD, median 7.5m	Variable, up to 5 years without Rx
Transplant: 50% within 6 months	Transplant: ~30% with treatment median 46 months
Viral, Autoimmune, B or Plasma Cell	B or Plasma cell
Consider Daratumumab vs Rituximab monotherapy	Clone directed therapy

My Approach

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CLINICAL TRIALS

Clinical Trials	Change in Management	
None Specific as this topic was a gross overview		

