



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

Dysproteinemia for the Nephrologist

Raad B. Chowdhury, MD, FASN

Medical Director, Onconeurology

Associate Program Director (APD), BWH-MGH Combined Renal Fellowship

Division of Renal Medicine, Brigham and Women's Hospital

Department of Medical Oncology, Dana Farber Cancer Institute

Instructor of Medicine, Harvard Medical School



Raad B. Chowdhury, MD, FASN

- ▶ MD @Windsor University School of Medicine
- ▶ Medicine Residency @ OhioHealth: Riverside Methodist Hospital
- ▶ Nephrology Fellowship @ University of Pittsburgh
- ▶ Onconeurology Fellowship @ Mayo Clinic, MN
- ▶ Medical Director, Onconeurology @ BWH/ DFCI
- ▶ APD Mass Gen Brigham – Renal Fellowship



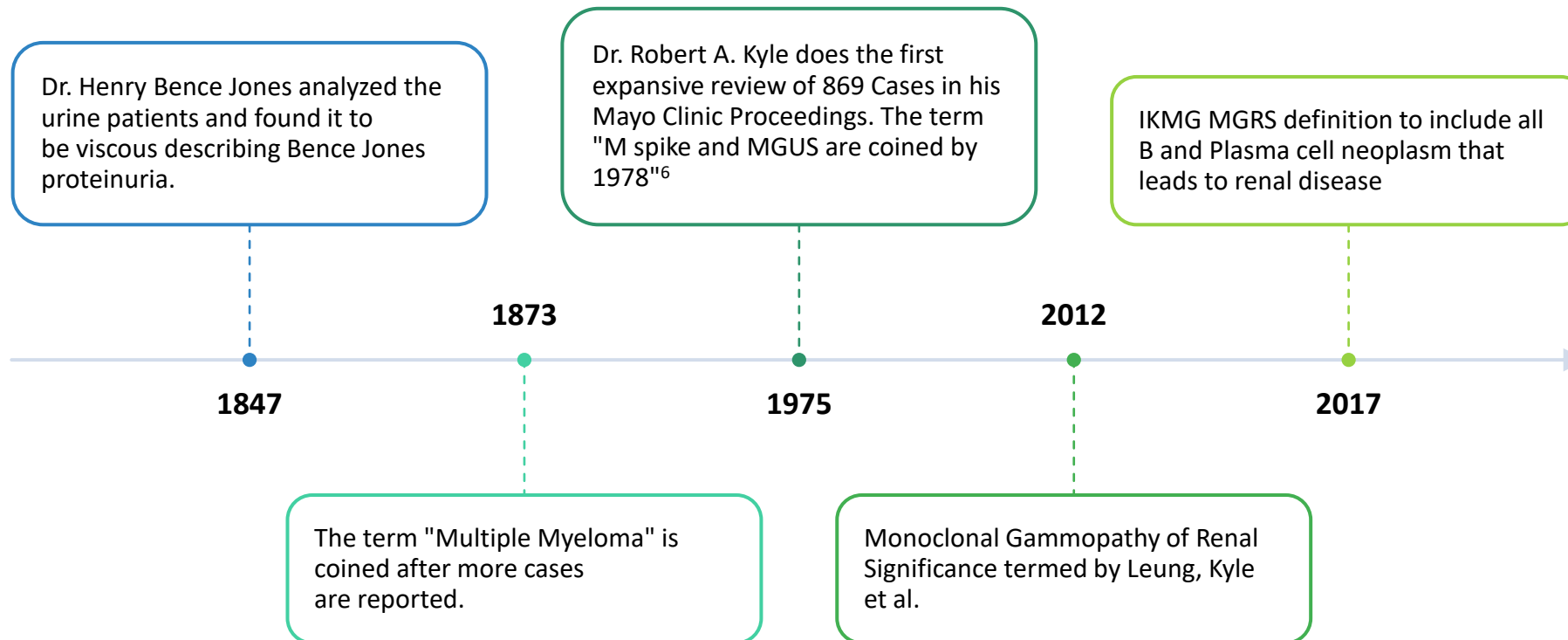
DISCLOSURES

- ▶ Nothing to disclose.

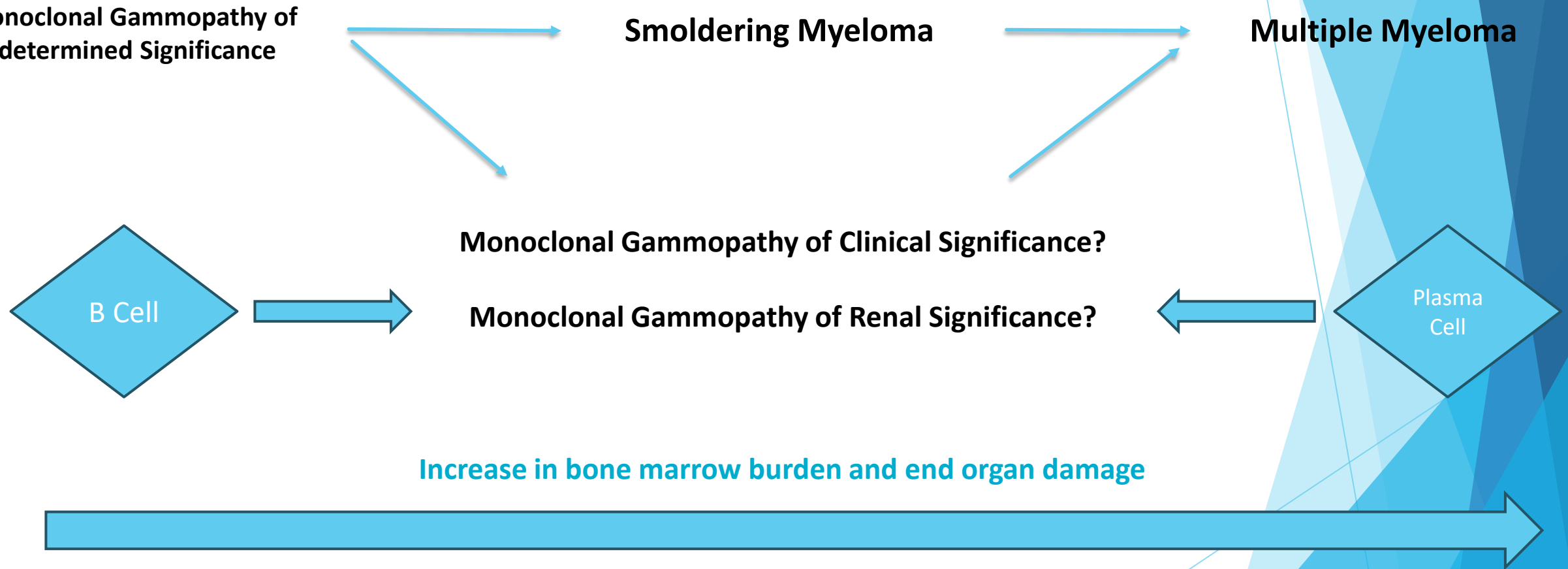
Objectives:

- ← 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)

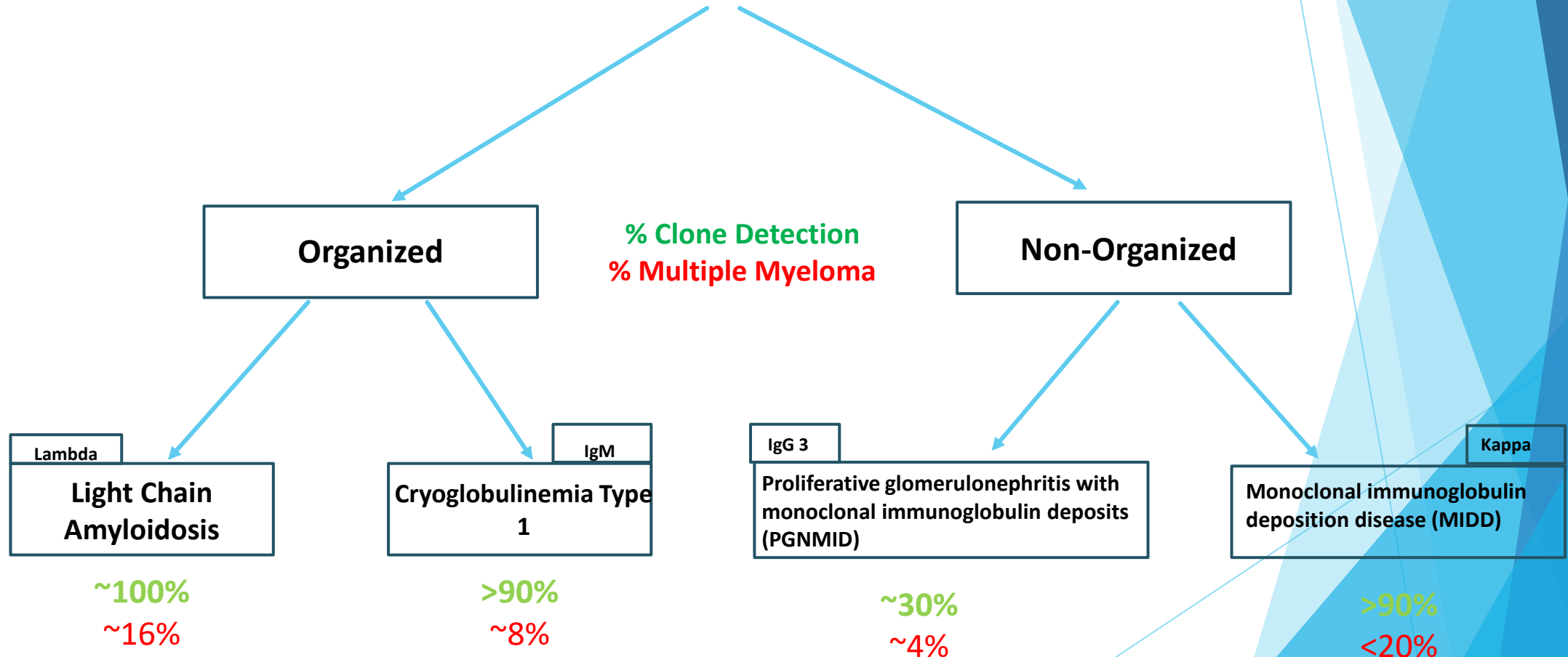
Monoclonal Gammopathy of Renal
Significance (MGRS)

Variable

A Rose By Any Other Name?



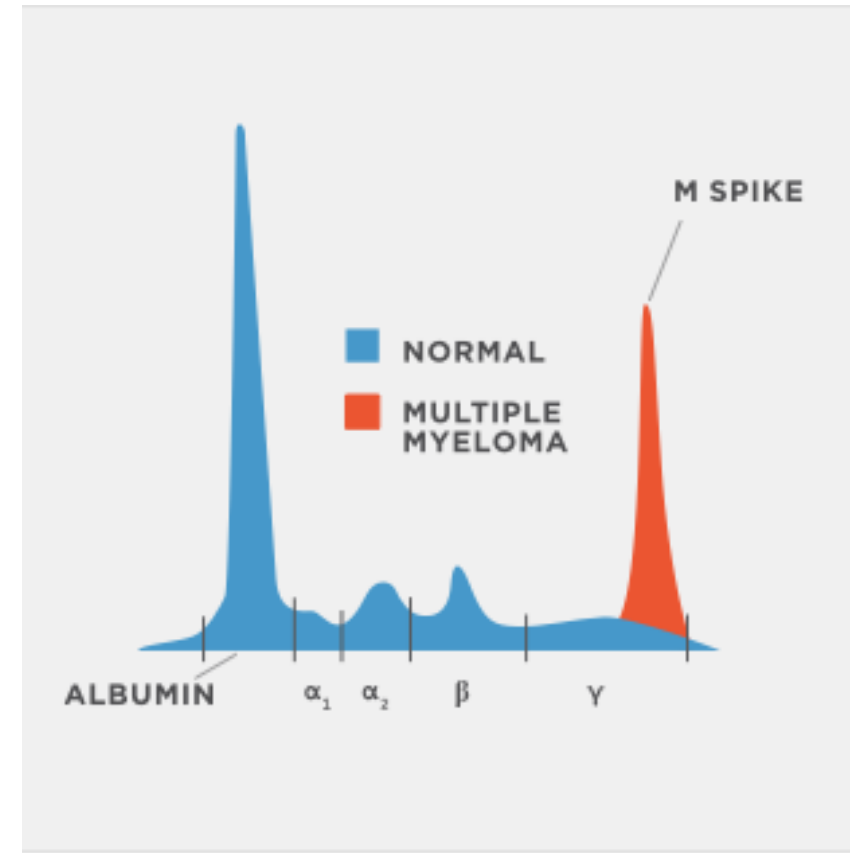
Monoclonal Gammopathy of Renal Significance



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)



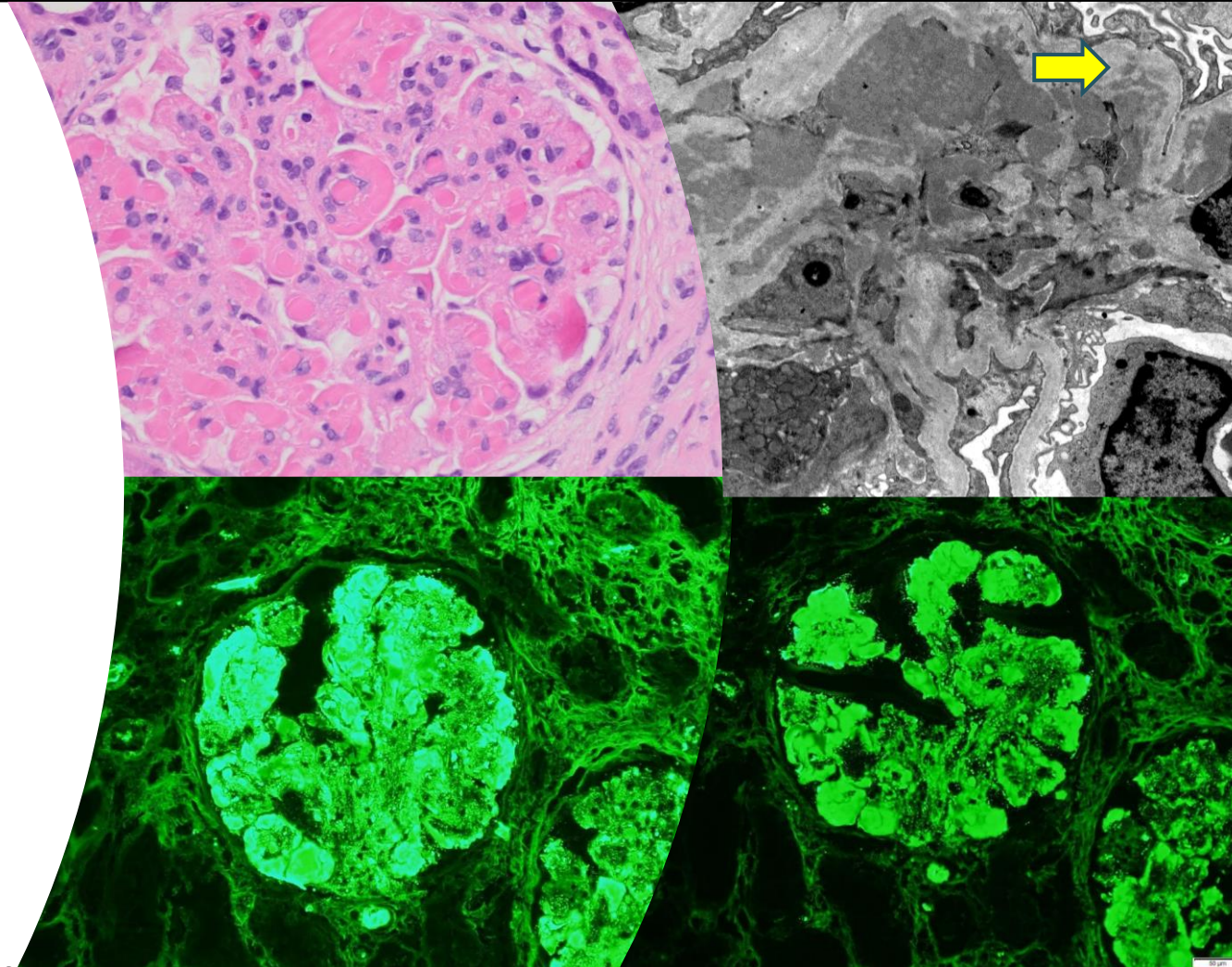
Source: [Understand and Track Your Multiple Myeloma Lab Tests \(ninlaro.com\)](https://www.ninlaro.com/understand-and-track-your-multiple-myeloma-lab-tests)

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% O2 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)

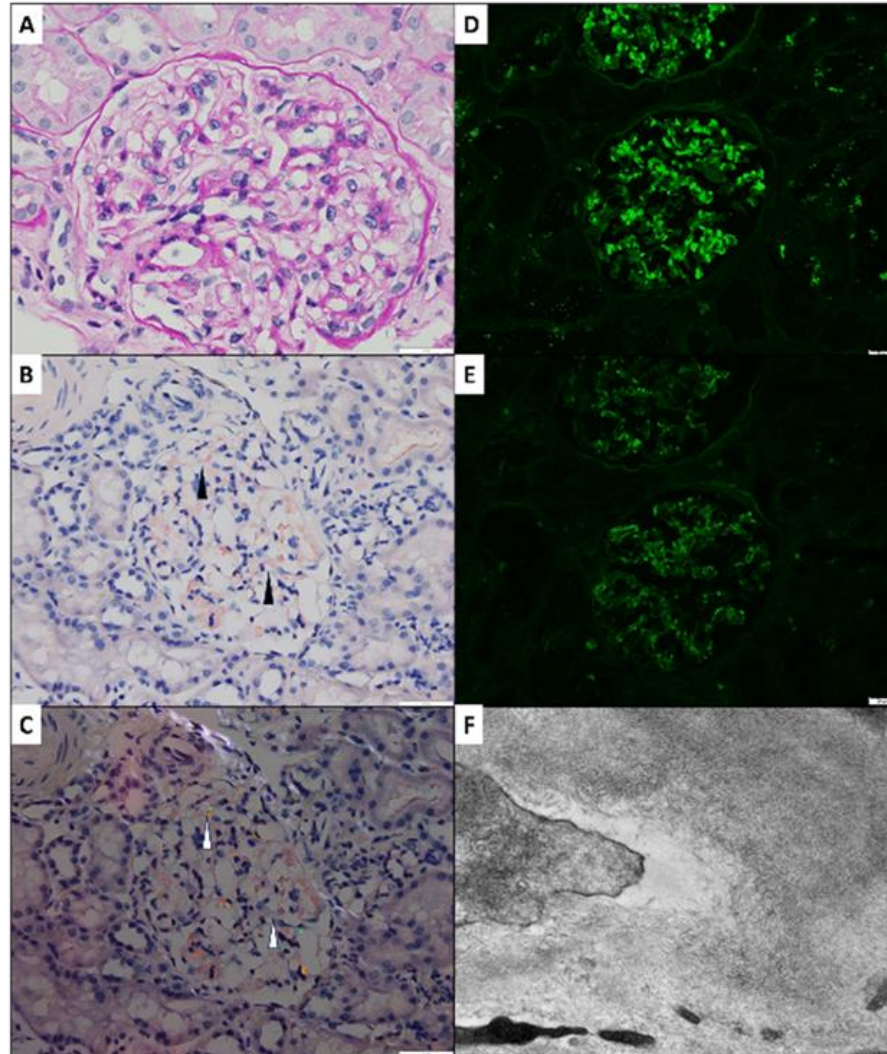


Case #2

- 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



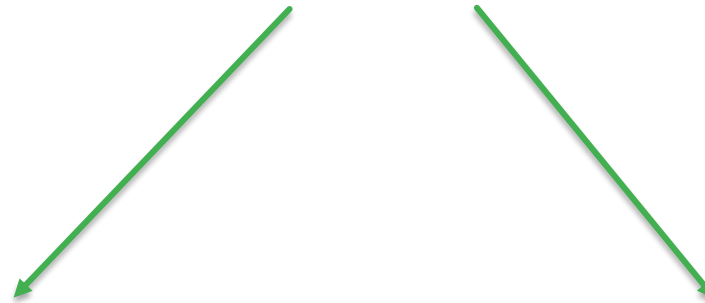
Kidney Biopsy



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" (*Chowdhury et al. Kidney 360, 2025*)

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

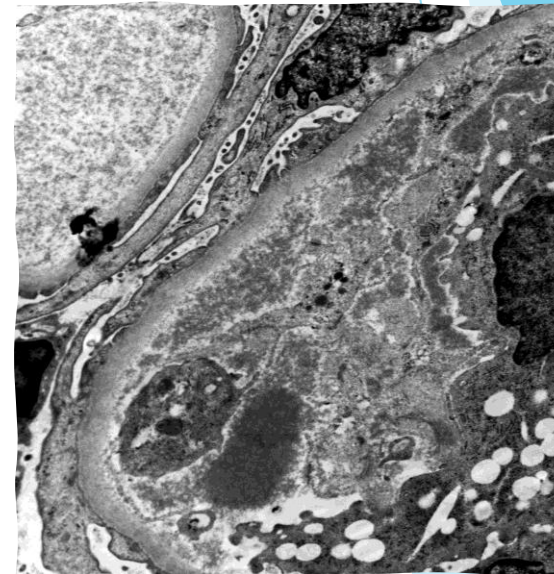
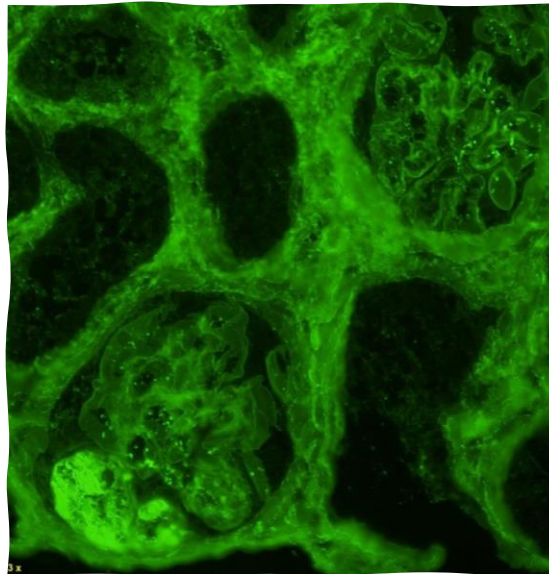
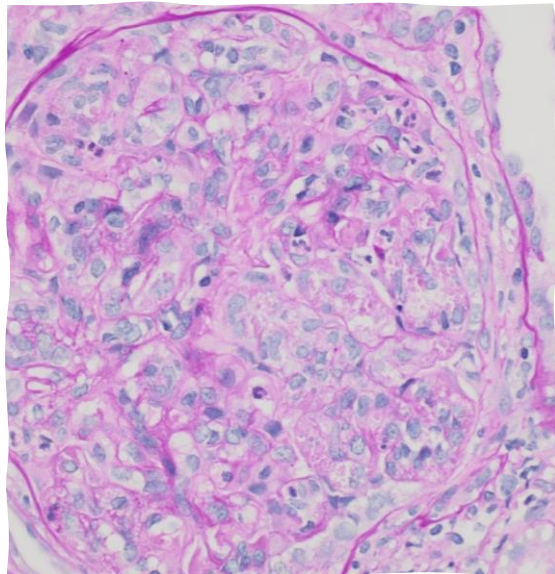
ATTR

- ❖ see Table 3

Case #3

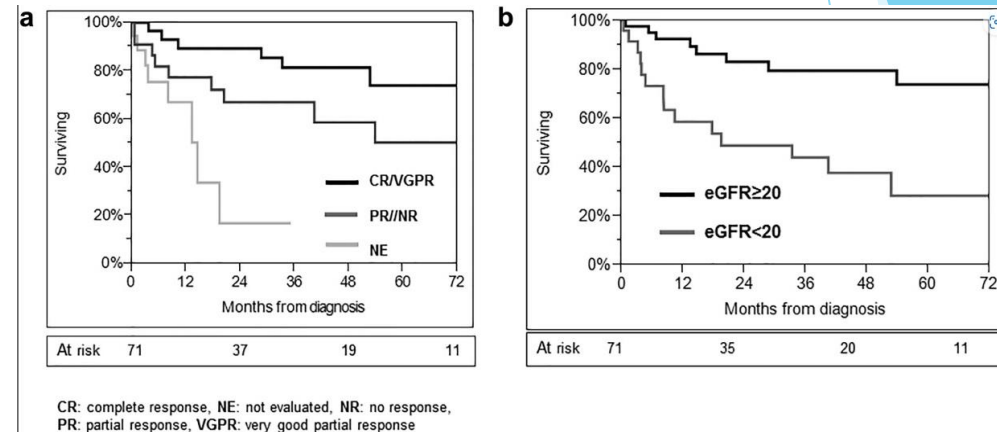
- ▶ A 55-year-old male with uncontrolled IDDM2 (~20 years), heart failure, and smoldering multiple myeloma is referred for worsening proteinuria of **12.0 g/day** (**7.5g albuminuria**) with baseline CKD Cr of **2.0-2.5 mg/dl** (eGFR 30 ml/min/m²).
- ▶ Workup:
- ▶ **A1C of 10%**
- ▶ SIFX/SIFE/FLC M spike 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
MPGN, glomerular limited IgG 3 K IgM? IgA?	Can affect tubular basement membrane. "Powdery deposits" Light Chain most commonly
Low C3/ Low C4	Usually 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

- **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)

CLINICAL TRIALS

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

