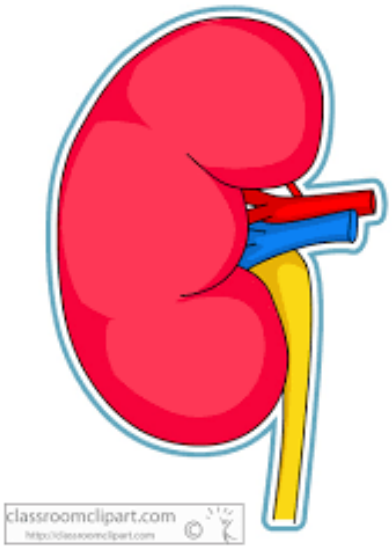
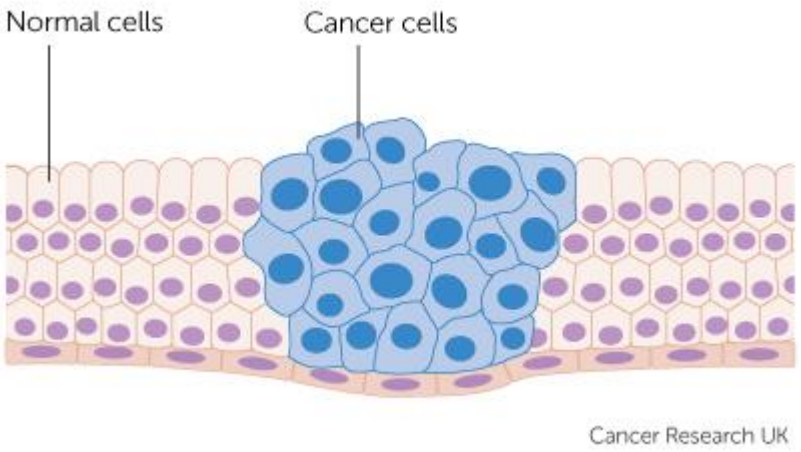
Onco-Nephrology

An invitation to a new field

Connection





Monoclonal Gammopathy of Renal Significance

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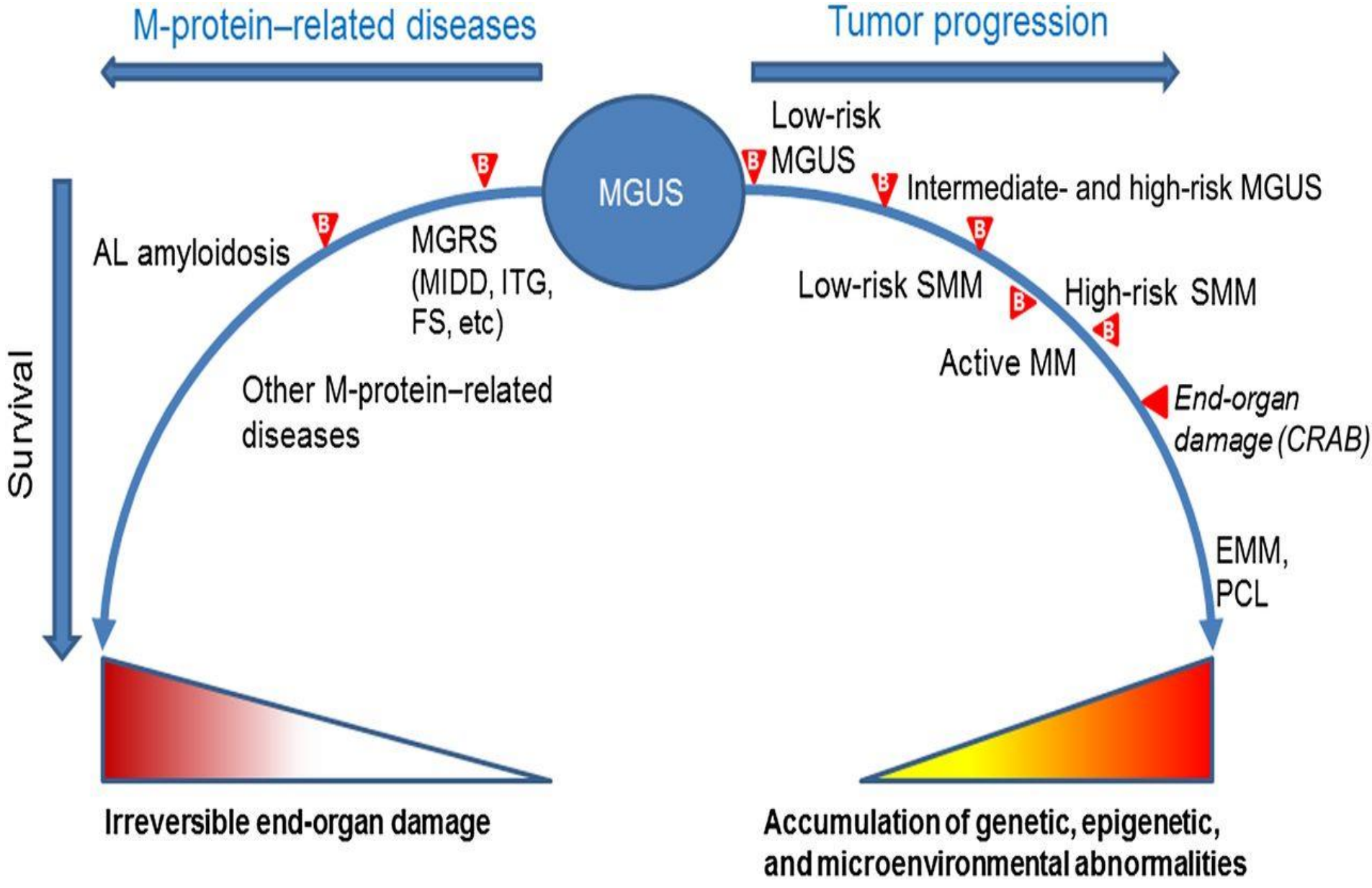

M-protein–related diseases
Tumor progression
Survival
MGUS
Low-risk MGUS
Intermediate- and high-risk MGUS
AL amyloidosis
MGRS (MIDD, ITG, FS, etc)
Other M-protein–related diseases
Low-risk SMM
High-risk SMM
Active MM
End-organ damage (CRAB)
EMM, PCL
Irreversible end-organ damage
Accumulation of genetic, epigenetic, and microenvironmental abnormalities

EXPERT CONSENSUS DOCUMENT

The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group

The term **MGRS** applies specifically to any B cell or plasma cell clonal lymphoproliferation with both of the following characteristics:

- ✓ One or more kidney lesions that are related to the produced monoclonal immunoglobulin
- ✓ The underlying B cell or plasma cell clone does not cause tumor complications or meet any current haematological criteria for specific therapy

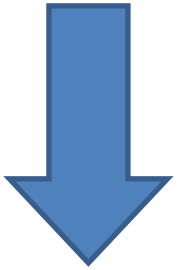
MGRS vs MGUS

	MGUS	MGRS
Serum M-spike	< 3 g/dl	< 3 g/dl
Clonal BM Plasma Cells	< 10%	< 10%
C_AB	Absent	Absent
Renal Disease (not cast nephropathy)	Not attributable to the monoclonal gammopathy	Attributable to the monoclonal gammopathy

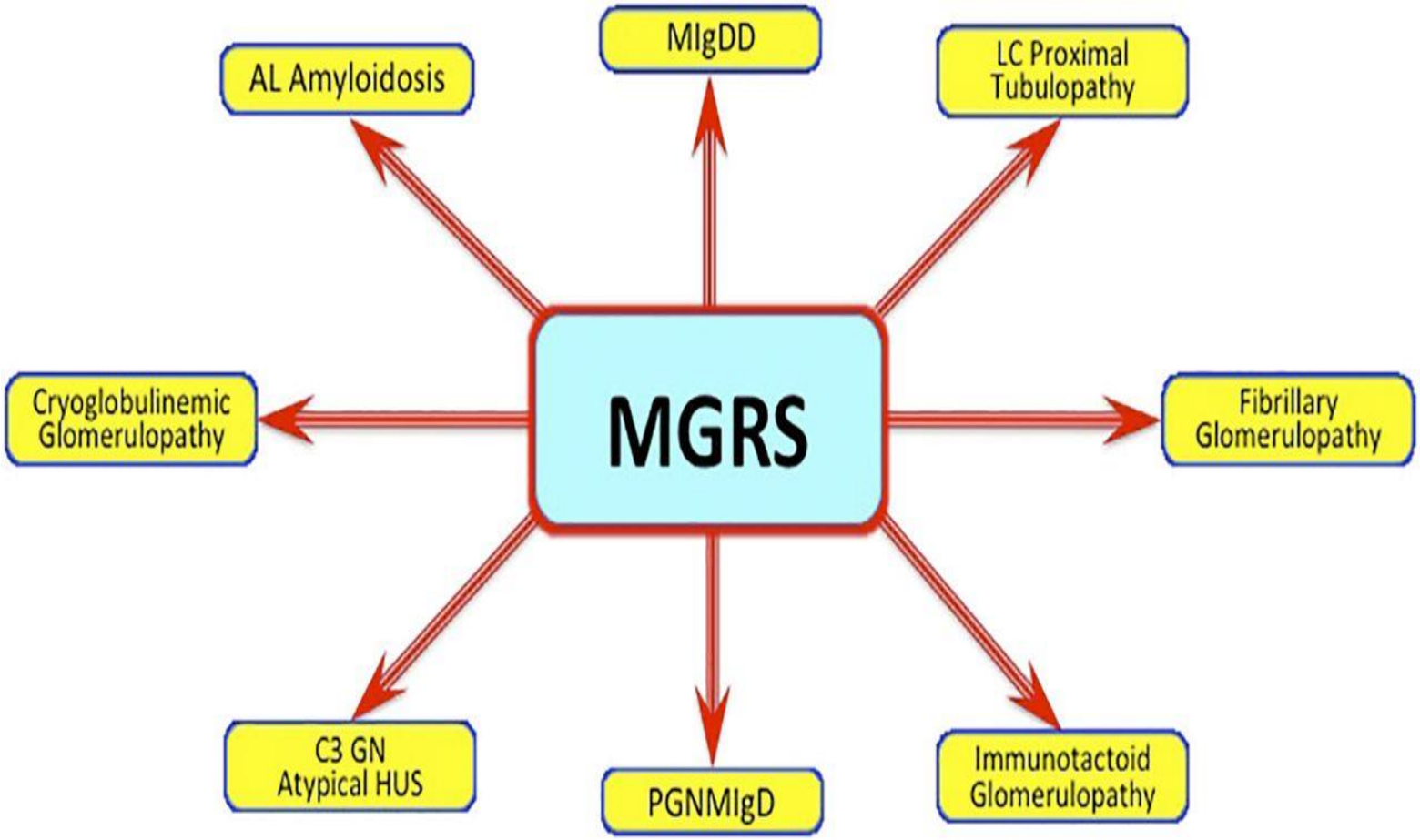
- ***MGRS*** represents a group of kidney disorders caused by a monoclonal immunoglobulin that is caused by a nonmalignant or premalignant B cell or PC clone

- ***Renal damage*** is the result of monoclonal immunoglobulin deposits or its activity as autoantibodies, which can compromise any nephron area

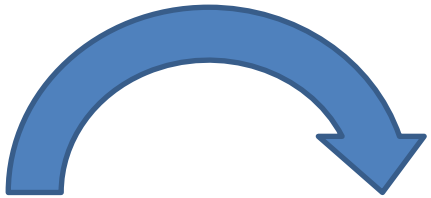
Small But Dangerous Clones



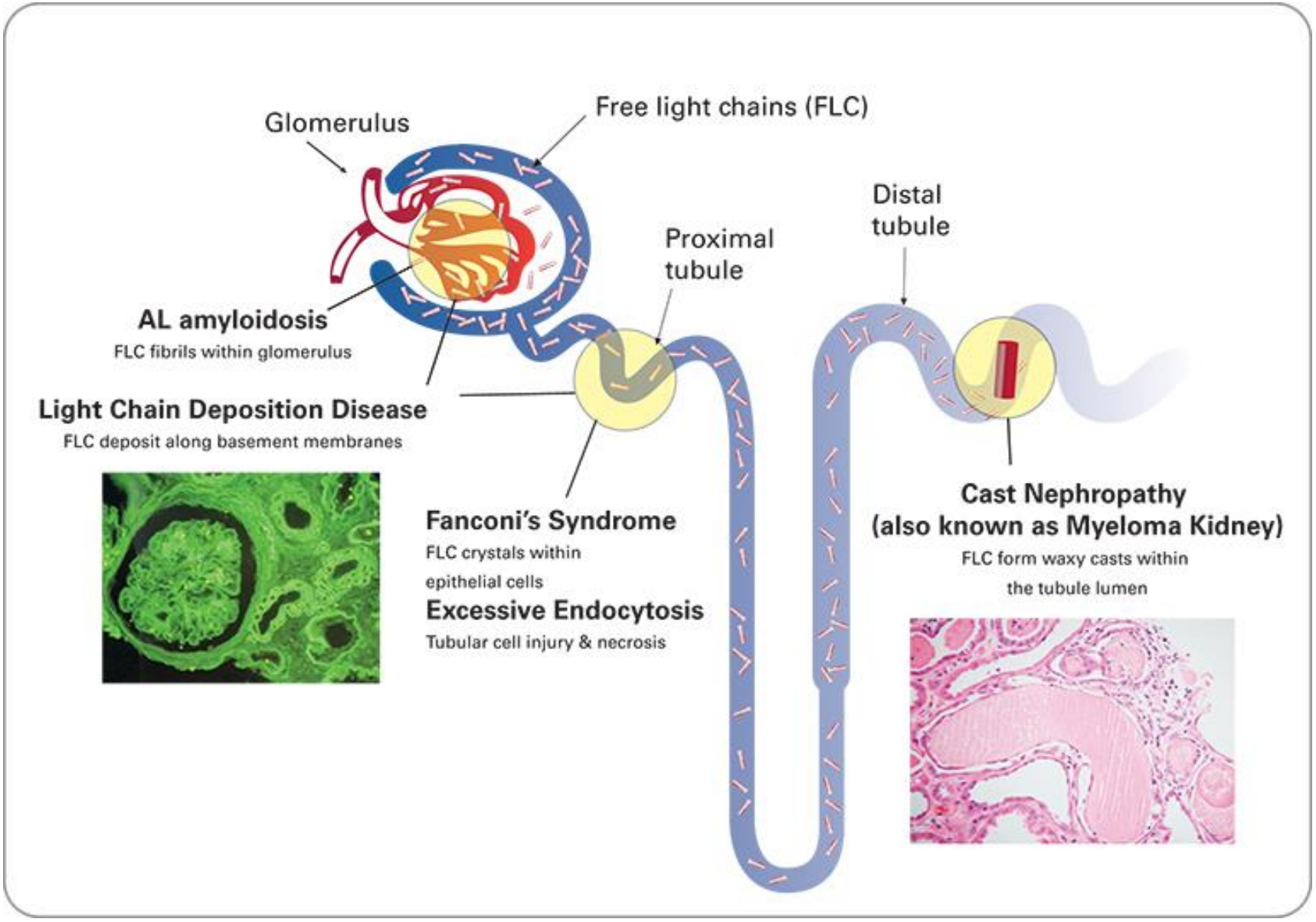
- Clone does not fulfill criteria for malignancy
- Nephrotoxic Monoclonal Immunoglobulines
- Kidneys are involved


MGRS
MIgDD
AL Amyloidosis
LC Proximal Tubulopathy
Cryoglobulinemic Glomerulopathy
Fibrillary Glomerulopathy
C3 GN Atypical HUS
PGNMIgD
Immunotactoid Glomerulopathy

MGRS



AKI, NS, Nephritic syndrome, RPGN, …


Glomerulus
Free light chains (FLC)
Distal tubule
Proximal tubule
AL amyloidosis
FLC fibrils within glomerulus
Light Chain Deposition Disease
FLC deposit along basement membranes
Fanconi's Syndrome
FLC crystals within epithelial cells
Excessive Endocytosis
Tubular cell injury & necrosis
Cast Nephropathy (also known as Myeloma Kidney)
FLC form waxy casts within the tubule lumen

Investigation

Looking for a clone

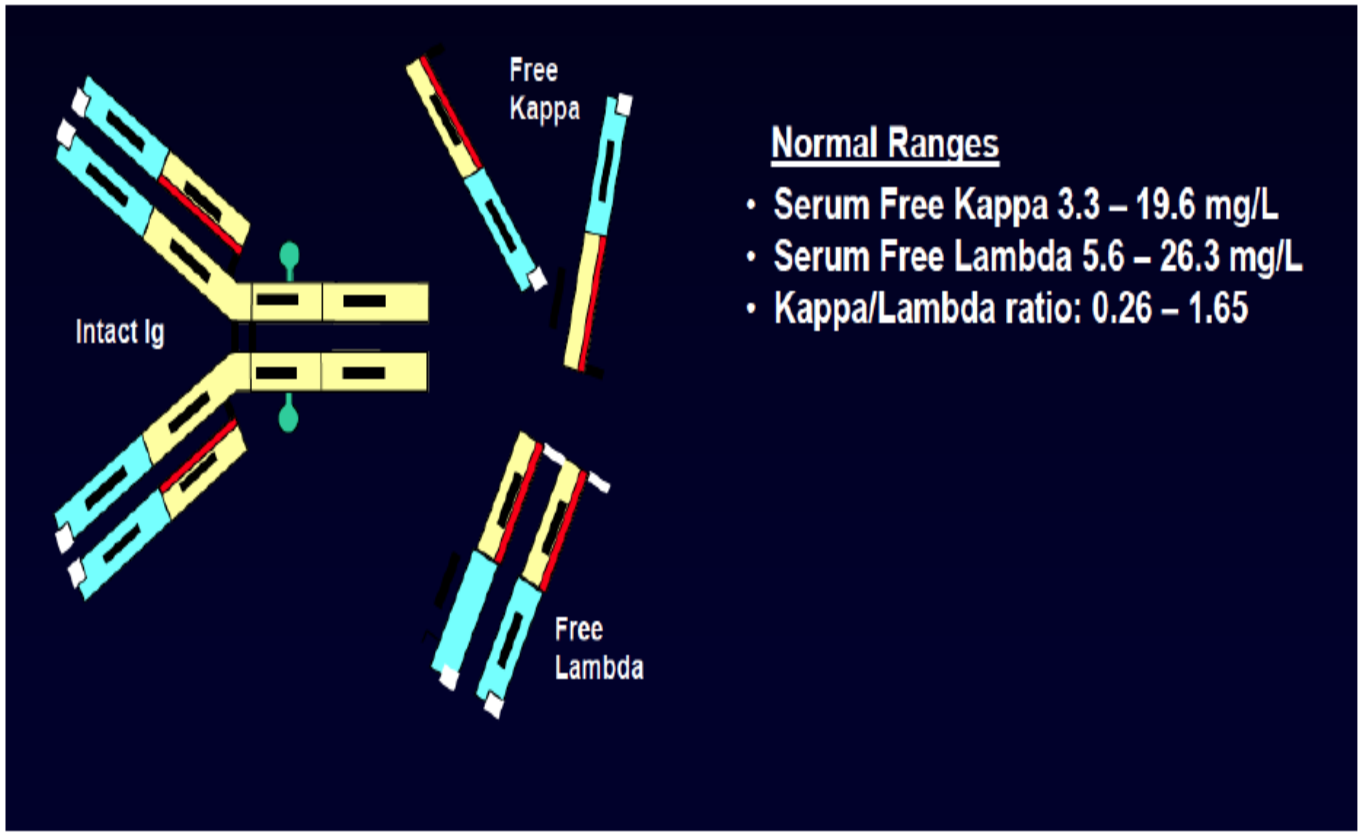
Serum free Light Chain

Serum & Urine protein electrophoresis & IFE

A negative IFE does not rule out clonal pathology

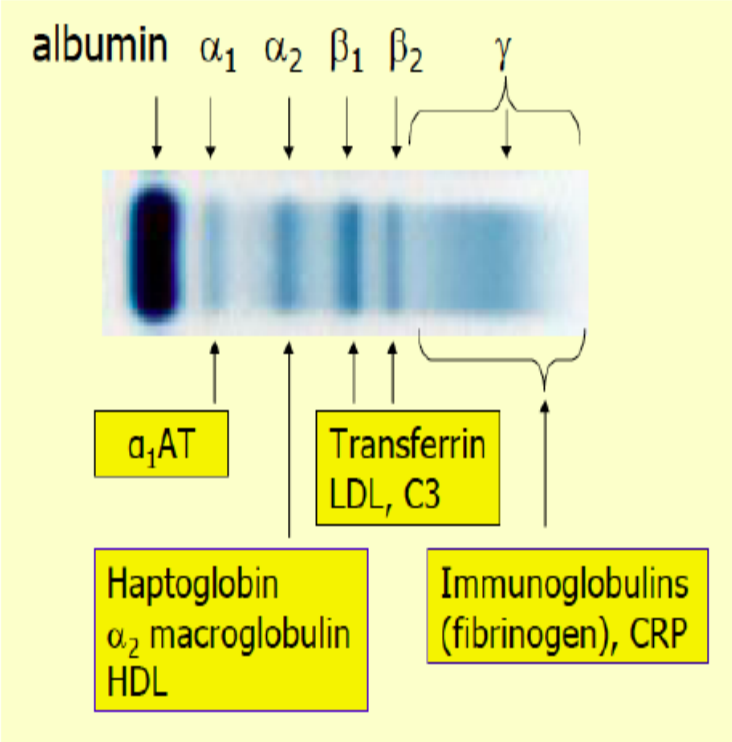
Western blot (protein immunoblotting)/ low MIG levels and Ig-G subclass

Serum Free Light Chain Assay

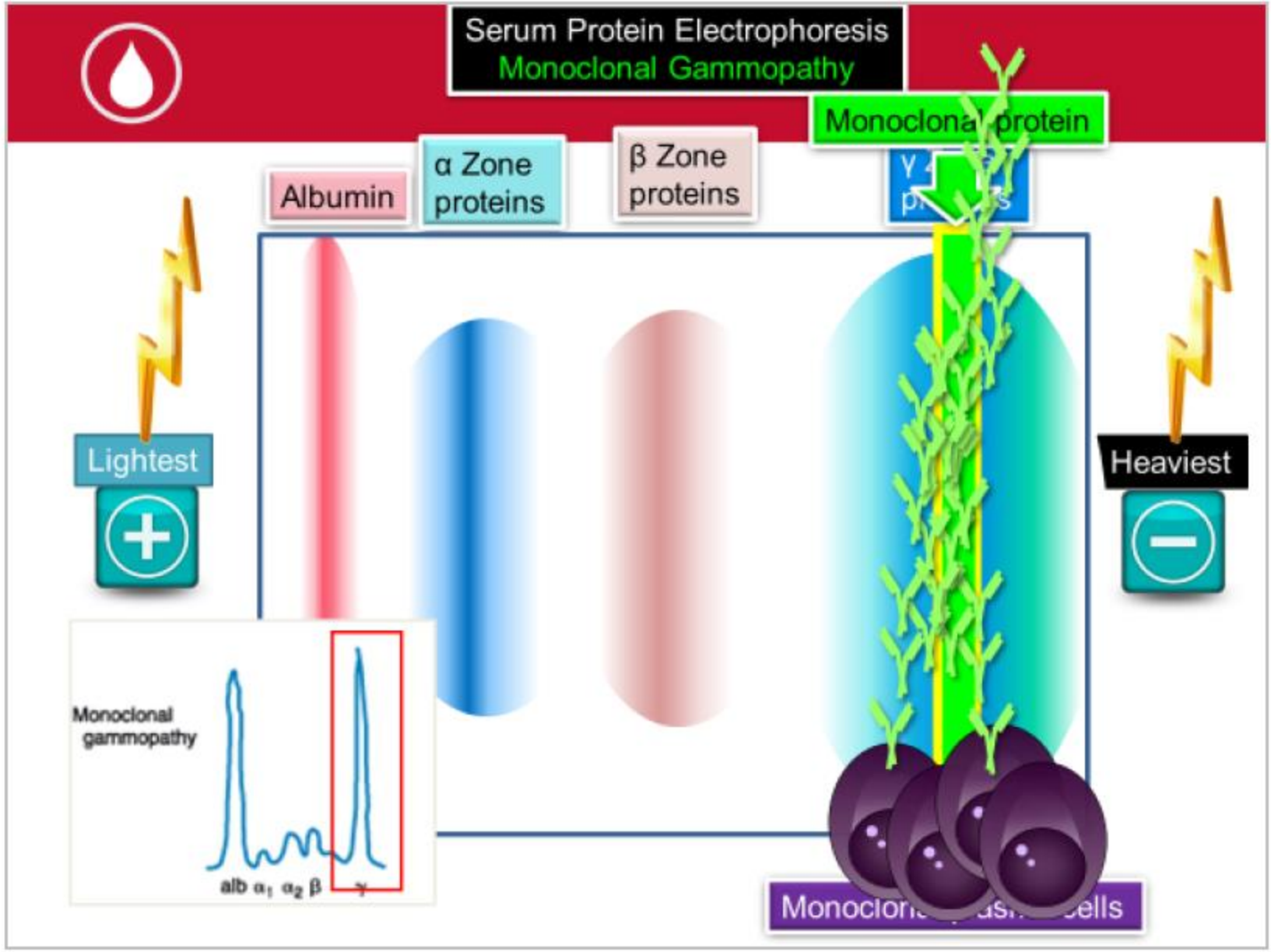


Katzmann et al Clin Chem. 2002;428-44

Serum Protein Electrophoresis (SPEP)



- Serum protein migrate into bands based on their size and charge
- Limitations:
  - Not sensitive when M-protein is small
  - Cannot classify type of M-protein

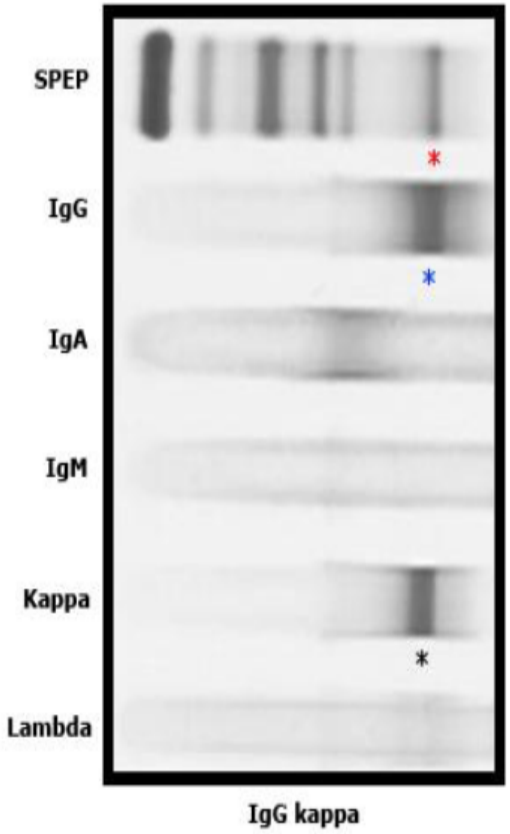

Serum Protein Electrophoresis
Monoclonal Gammopathy
Monoclonal protein
Albumin
α Zone proteins
β Zone proteins
Lightest
Heaviest
Monoclonal gammopathy
alb α1 α2 β γ

Beyond the SPEP

- If only SPEP is done – about 15% of myeloma /other disorders WILL BE MISSED because SPEP will be negative

- What can be done about this?
  - Urine Protein ElectroPhoresis (UPEP)
  - **Serum free light chain ratio (SFLCR)**

Serum immunofixation



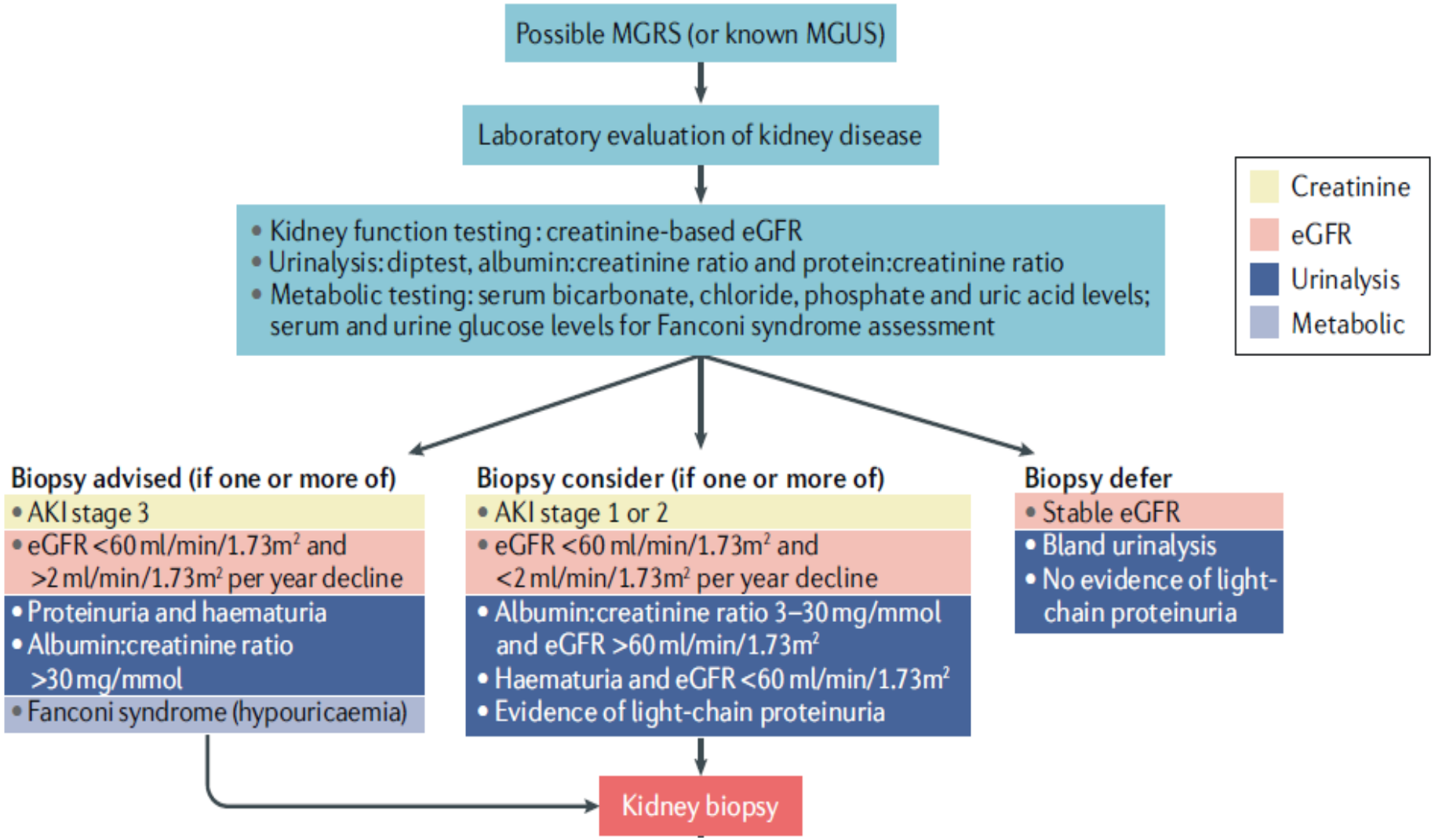
IgG kappa

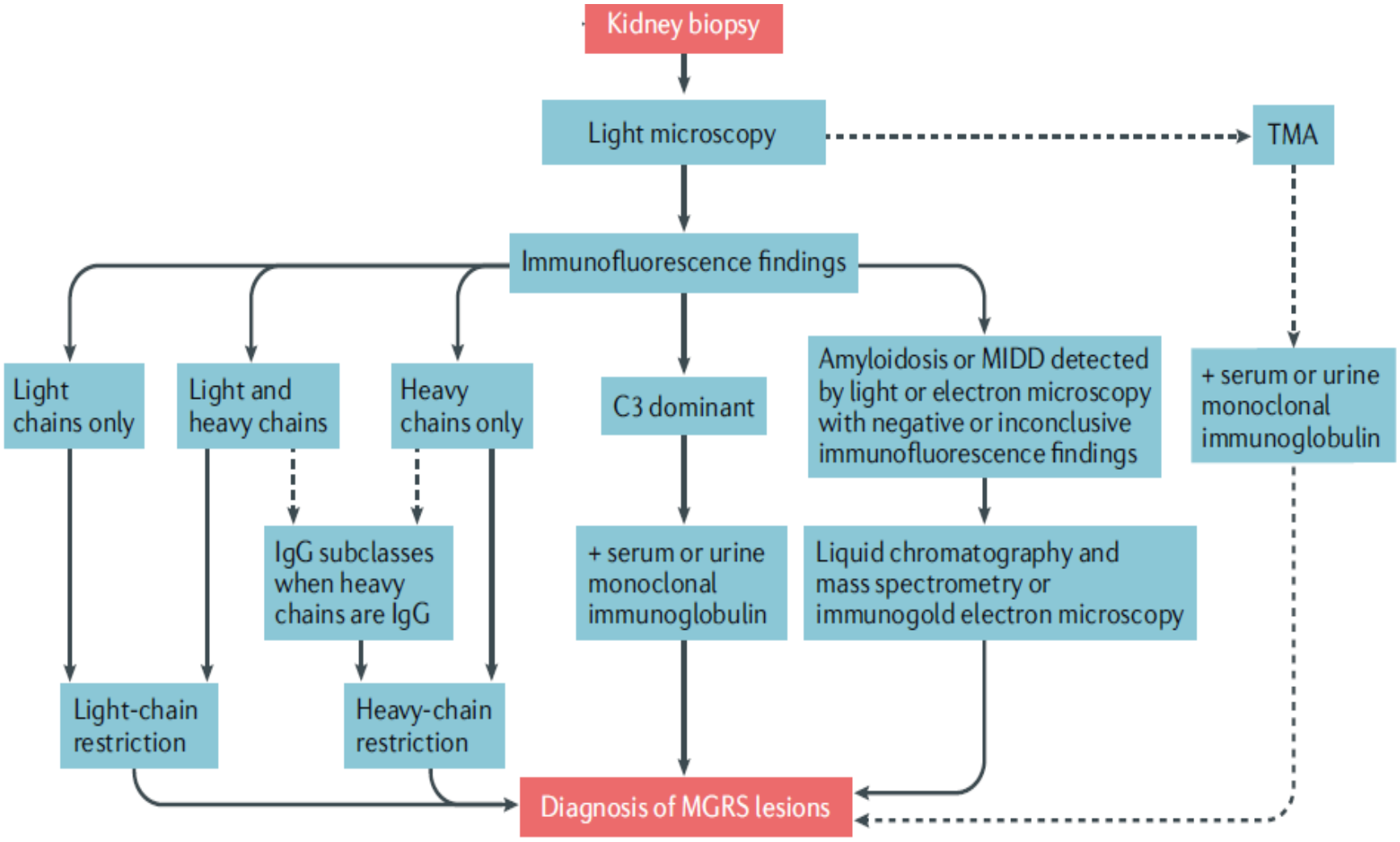
- Used to determine clonality
  - Monoclonal versus polyclonal
- Not able to quantitate the concentration of the M band
- Must be done in conjunction with the SPEP

Table 2 | **Consensus recommendations for the evaluation of MGRS-associated disorders**

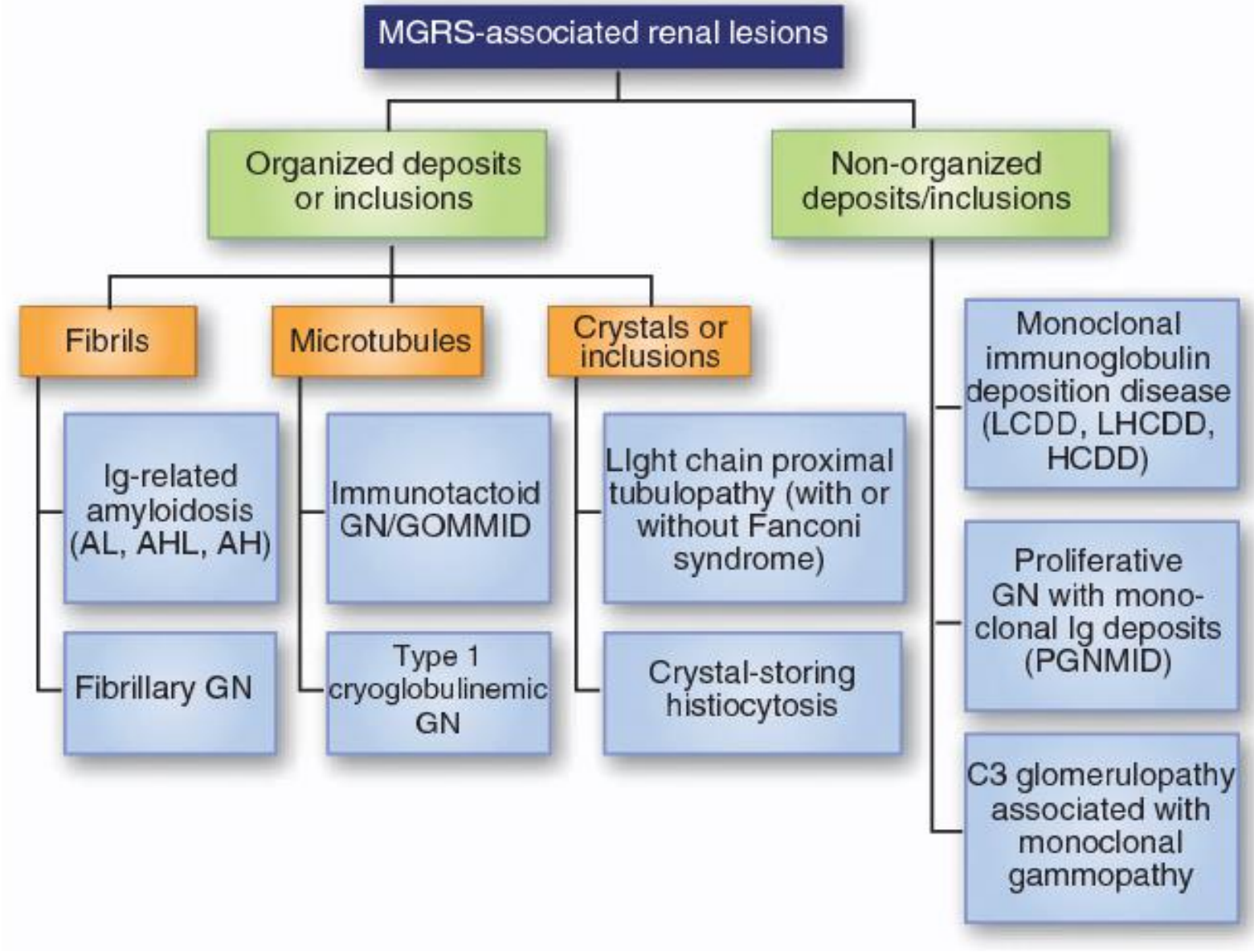
Modality	Recommendations	R
Kidney biopsy	Recommended in the following patients: • Those with monoclonal gammopathy and unexplained kidney disease • Those with known risk factors for chronic kidney disease but an atypical clinical course • Patients with kidney disease and monoclonal gammopathy aged <50 years	
Protease immunofluorescence on kidney biopsy	Recommended in the following scenarios: • When glomeruli are lacking in frozen tissue samples • In patients with suspected LCPT and other forms of crystalline nephropathies, such as CSH and crystalglobulin-induced nephropathy • In patients with a monoclonal gammopathy in whom kidney biopsy samples show C3 glomerulonephritis or unclassified proliferative glomerulonephritis in the context of negative findings by immunofluorescence on frozen tissue samples (including in patients with features of cryoglobulinaemic glomerulonephritis on light or electron microscopy) • In patients with fibrillary glomerulonephritis who have apparent light-chain restriction detected by immunofluorescence on frozen tissue	
Renal amyloid typing by liquid chromatography and mass spectrometry	Recommended in the following situations: • When frozen tissue for immunofluorescence is not available • Negative immunofluorescence staining for κ and λ light chains, with negative immunoperoxidase staining for SAA and LECT2 • Equal staining for κ and λ light chains by immunofluorescence • Bright staining for IgG and/or IgA by immunofluorescence • Equivocal Congo red staining • To enable distinction between AHL amyloidosis and congophilic fibrillary glomerulonephritis	
Flow cytometry or other immunotyping	• Neoplastic plasma cells frequently show aberrant loss of CD45 and CD19, as well as aberrant expression of CD56 and CD117; therefore, these markers (in addition to κ and λ light chains and CD38) are useful in identifying small plasma cell clones • Including CD5 and CD20 in the immunophenotyping of B cells can frequently separate small clones from polytypic cells • The most sensitive assay available at a given institution should be used. Although there is no established gold standard, many laboratories have the capability to determine minimal residual disease in MGRS at a sensitivity of 10^{-4} to 10^{-6} monoclonal cells. The sensitivity of flow cytometry immunophenotyping depends on the total number of collected cells, the number of antibodies used to find an aberrant phenotype, the phenotype of the abnormal clone and sample quality	
Immunohistochemistry	• Immunohistochemistry of bone marrow biopsy samples has a low sensitivity for detecting κ-expressing and λ-expressing plasma cells and could be useful only if there is a major plasma cell clone and a lack of polyclonal plasma cells • Immunohistochemistry might be useful in the evaluation of atypical lymphoid infiltrates, particularly if flow cytometry is not available or infiltrates are very focal • If an abnormal clone is detected, the light-chain isotype should be compared with that present in renal lesions and additional information should be obtained	
Mutational analysis	The MYD88 L265P mutation is found in over 90% of patients with lymphoplasmacytic lymphoma or Waldenström macroglobulinaemia but in only 40–60% of individuals with IgM MGUS	1
FISH	Cyclin D1 FISH with immunostaining for CD10, BCL2 and BCL6 to subclassify diffuse large cell lymphoma, and prognostic FISH panels for MM and CLL, can also be useful	1

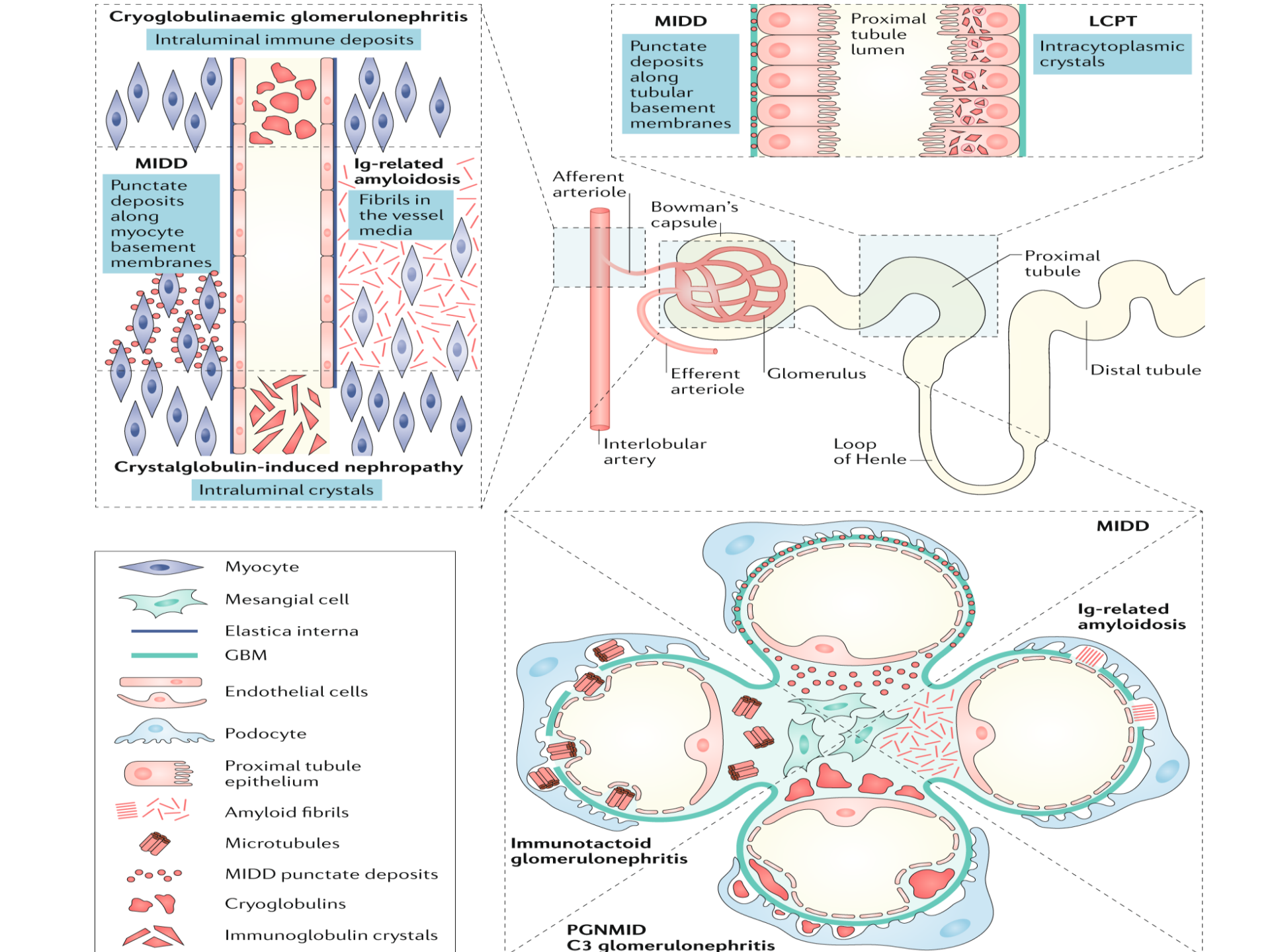
AHL, immunoglobulin A heavy-and-light chain; CLL, chronic lymphocytic leukaemia; CSH, crystal-storing histiocytosis; FISH, fluorescence in situ hybridization; LCPT, light-chain proximal tubulopathy; LECT2, leukocyte cell-derived chemotaxin 2; MGRS, monoclonal gammopathy of renal significance; MGUS, monoclona gammopathy of undetermined significance; MM, multiple myeloma; NA, not applicable; SAA, serum amyloid A protein.

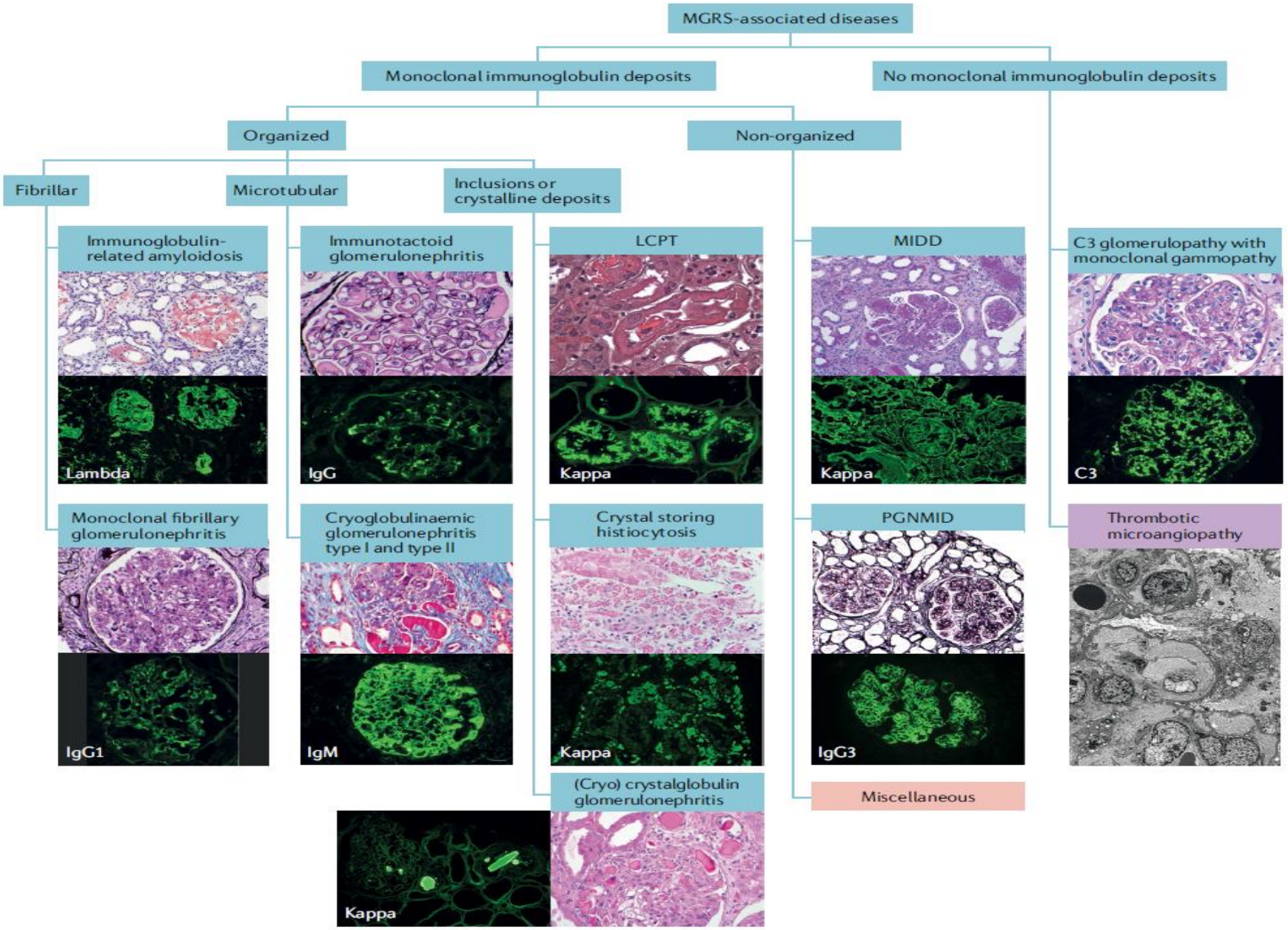

Possible MGRS (or known MGUS)
Laboratory evaluation of kidney disease
• Kidney function testing: creatinine-based eGFR
• Urinalysis: diptest, albumin:creatinine ratio and protein:creatinine ratio
• Metabolic testing: serum bicarbonate, chloride, phosphate and uric acid levels; serum and urine glucose levels for Fanconi syndrome assessment
Creatinine
eGFR
Urinalysis
Metabolic
Biopsy advised (if one or more of)
• AKI stage 3
• eGFR <60 ml/min/1.73m² and >2 ml/min/1.73m² per year decline
• Proteinuria and haematuria
• Albumin:creatinine ratio >30 mg/mmol
• Fanconi syndrome (hypouricaemia)
Biopsy consider (if one or more of)
• AKI stage 1 or 2
• eGFR <60 ml/min/1.73m² and <2 ml/min/1.73m² per year decline
• Albumin:creatinine ratio 3–30 mg/mmol and eGFR >60 ml/min/1.73m²
• Haematuria and eGFR <60 ml/min/1.73m²
• Evidence of light-chain proteinuria
Biopsy defer
• Stable eGFR
• Bland urinalysis
• No evidence of light-chain proteinuria
Kidney biopsy


Kidney biopsy
Light microscopy
TMA
Immunofluorescence findings
Light chains only
Light and heavy chains
Heavy chains only
C3 dominant
Amyloidosis or MIDD detected by light or electron microscopy with negative or inconclusive immunofluorescence findings
+ serum or urine monoclonal immunoglobulin
IgG subclasses when heavy chains are IgG
+ serum or urine monoclonal immunoglobulin
Liquid chromatography and mass spectrometry or immunogold electron microscopy
Light-chain restriction
Heavy-chain restriction
Diagnosis of MGRS lesions

Spectrum of Monoclonal Gammopathy of Renal Significance (MGRS)				
MGRS Lesion	**Underlying Clone Type**	**Type and Location of Renal Deposit**	**Renal Manifestations**	**Extrarenal Manifestations**
Ig light chain, heavy chain, and heavy and light chain amyloidosis	PC, CLL, NHL	Fibril, glomerulus (tubulointerstitual and perivascular involvement common)	Proteinuria, NS, CKD	Common: heart, peripheral and autonomic nerves, soft tissue, liver
Immunotactoid GN/GOMMID	NHL, CLL, PC	Microtubules, glomerulus	Proteinuria, NS, CKD	Uncommon
Type 1 cryoglobulinemic GN	PC, LPL	Microtubules, glomerulus	Proteinuria, NS, CKD, microhematuria, hypertension, nephritic syndrome	Common– skin, peripheral nerves, joints
Light chain proximal tubulopathy	PC	Crystals, tubules	Fanconi syndrome, tubular proteinuria, slowly progressive CKD	None
Crystal–storing histiocytosis	PC, LPL	Intracytoplasmic eosinophilic crystalline inclusions within interstitial histiocytes, proximal tubular cells and podocytes	CKD	Common–bone marrow, liver, spleen, LN, skin, cornea, lung
Monoclonal immunoglobulin deposition disease	PC, LPL	Granular deposits/inclusions, glomerulus	Proteinuria, NS, CKD, microhematuria, hypertension	Heart, lung, liver
Proliferative GN with monoclonal immunoglobulin deposits	PC, NHL	Granular deposits/inclusions, glomerulus	Proteinuria, NS, CKD, microhematuria, hypertension	None
C3 glomerulopathy with monoclonal gammopathy	PC	Granular deposits/inclusions, glomerulus	Proteinuria, NS, CKD, microhematuria, hypertension	None


MGRS-associated renal lesions
Organized deposits or inclusions
Non-organized deposits/inclusions
Fibrils
Microtubules
Crystals or inclusions
Ig-related amyloidosis (AL, AHL, AH)
Fibrillary GN
Immunotactoid GN/GOMMID
Type 1 cryoglobulinemic GN
LIght chain proximal tubulopathy (with or without Fanconi syndrome)
Crystal-storing histiocytosis
Monoclonal immunoglobulin deposition disease (LCDD, LHCDD, HCDD)
Proliferative GN with mono-clonal Ig deposits (PGNMID)
C3 glomerulopathy associated with monoclonal gammopathy


Cryoglobulinaemic glomerulonephritis
Intraluminal immune deposits
MIDD
Punctate deposits along myocyte basement membranes
Ig-related amyloidosis
Fibrils in the vessel media
Crystalglobulin-induced nephropathy
Intraluminal crystals
MIDD
Punctate deposits along tubular basement membranes
Proximal tubule lumen
LCPT
Intracytoplasmic crystals
Afferent arteriole
Bowman's capsule
Proximal tubule
Efferent arteriole
Glomerulus
Distal tubule
Interlobular artery
Loop of Henle
Myocyte
Mesangial cell
Elastica interna
GBM
Endothelial cells
Podocyte
Proximal tubule epithelium
Amyloid fibrils
Microtubules
MIDD punctate deposits
Cryoglobulins
Immunoglobulin crystals
MIDD
Ig-related amyloidosis
Immunotactoid glomerulonephritis
PGNMID
C3 glomerulonephritis


MGRS-associated diseases
Monoclonal immunoglobulin deposits
No monoclonal immunoglobulin deposits
Organized
Non-organized
Fibrillar
Microtubular
Inclusions or crystalline deposits
Immunoglobulin-related amyloidosis
Lambda
Immunotactoid glomerulonephritis
IgG
LCPT
Kappa
MIDD
Kappa
C3 glomerulopathy with monoclonal gammopathy
C3
Monoclonal fibrillary glomerulonephritis
IgG1
Cryoglobulinaemic glomerulonephritis type I and type II
IgM
Crystal storing histiocytosis
Kappa
PGNMID
IgG3
Thrombotic microangiopathy
(Cryo) crystalglobulin glomerulonephritis
Kappa
Miscellaneous

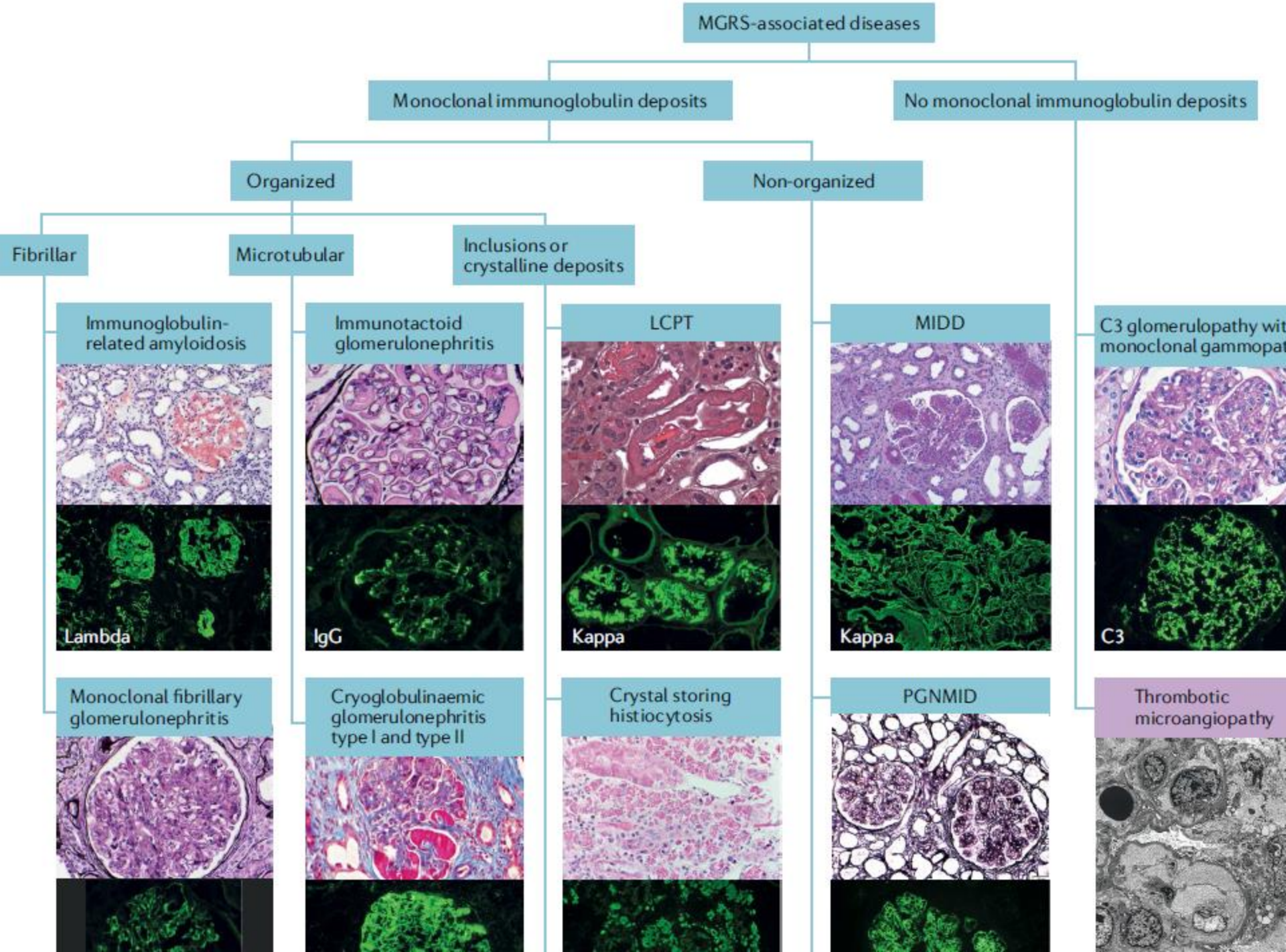

MGRS-associated diseases
Monoclonal immunoglobulin deposits
No monoclonal immunoglobulin deposits
Organized
Non-organized
Fibrillar
Microtubular
Inclusions or crystalline deposits
Immunoglobulin-related amyloidosis
Immunotactoid glomerulonephritis
LCPT
MIDD
C3 glomerulopathy wit monoclonal gammopat
Lambda
IgG
Kappa
Kappa
C3
Monoclonal fibrillary glomerulonephritis
Cryoglobulinaemic glomerulonephritis type I and type II
Crystal storing histiocytosis
PGNMID
Thrombotic microangiopathy

Table 3 | **Renal lesions associated with monoclonal gammopathy**

Lesion	Proportion of lesions (%)					
	Monoclonal immuno-globulin deposits	Detectable monoclonal immuno-globulin	MM	MGRS	Other[a]	Refs
Light-chain cast nephropathy	100	100	99	0	~1	2,4,11,13
Immunoglobulin-related amyloid amyloidosis	96	99	16	80	1–4	43,113,128,129
MIDD	100	100	0–20	78–100	1–2	29,31,68,130,131
Light-chain proximal tubulopathy	100	97[b]	12–33	61–80	3–8	32,56,58,132
Cryoglobulinaemic (type I) glomerulonephritis	100	90–100	6–8	47–52	24–56	133–136
Cryoglobulinaemic (type II) glomerulonephritis	100	49	0	20	7	133–136
PGNMID	100	30–32	4	96	~1	24,72
Crystal-storing histiocytosis	83	90	33	8	50	137
Cryocrystalglobulin or crystalglobulin nephropathy	91	82	61	18	4	138
Immunotactoid glomerulonephritis	69–93	63–71	0–13	25–50	25–50	23,51
C3 glomerulopathy with monoclonal gammopathy[c]	0	28–83[d]	0–40[d]	40–90	6–10	25,74,75,104
Monoclonal fibrillary glomerulonephritis[e]	100	7–17	0–54	55–98	2–10	44,47,139

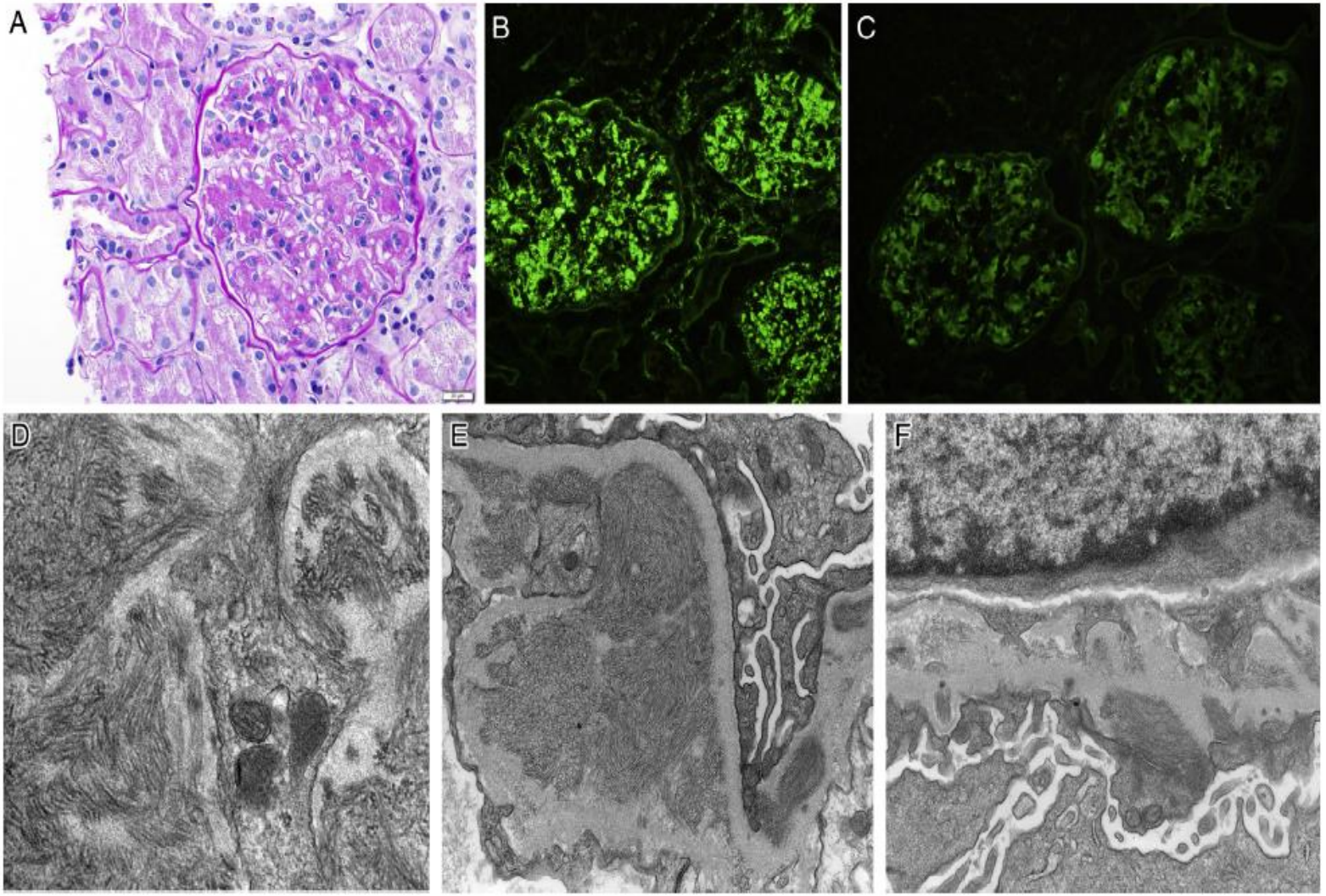


Figure 4. Kidney biopsy specimen from a patient with immunotactoid glomerulopathy. (A) Glomerulus shows mesangioproliferative pattern of injury with mildly thickened capillary walls (periodic acid–Schiff; original magnification, ×20). Glomeruli demonstrate coarse staining of mesangium and peripheral capillary walls with (B) immunoglobulin G (IgG; 3+) and (C) κ light chain (1+). There is no staining of glomeruli with λ light chain. Ultrastructural studies demonstrate organized microtubular deposits in (D) the mesangium and (E, F) subendothelial and subepithelial aspects.

ITG

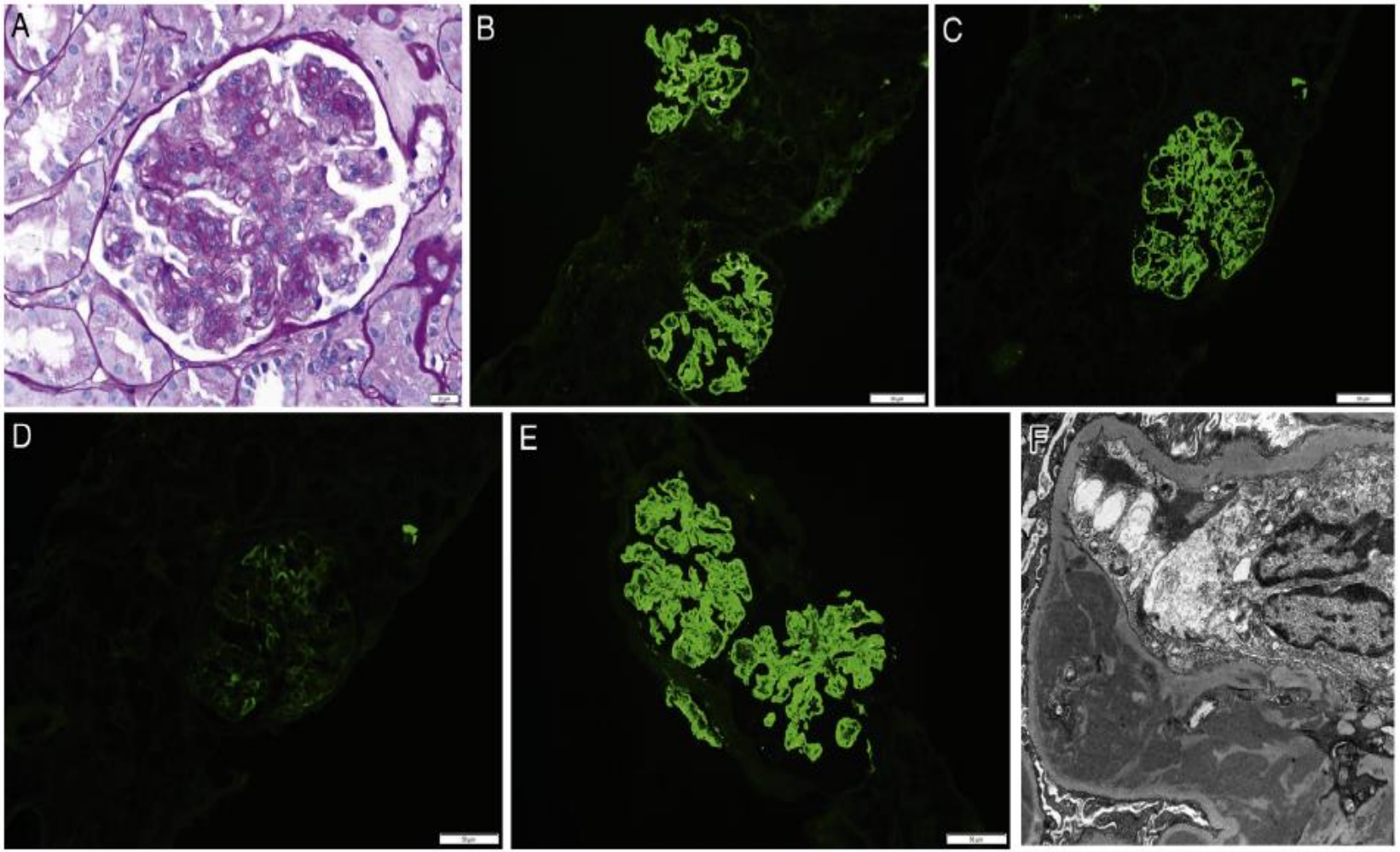


Figure 3. Kidney biopsy specimen from a patient with proliferative glomerulonephritis with monoclonal immunoglobulin G3 (IgG3) κ deposits. (A) Membranoproliferative pattern of glomerular injury is appreciated on periodic acid–Schiff–stained section. Granular mesangial and peripheral capillary wall deposits are noted that stain brightly with (B) immunoglobulin G (IgG) and (C) κ but (D) not λ. (E) Deposits show IgG3-restricted staining. (F) Ultrastructural studies show granular electron-dense deposits in the mesangium and peripheral capillary walls. The deposits do not have substructure.

Proliferative GN

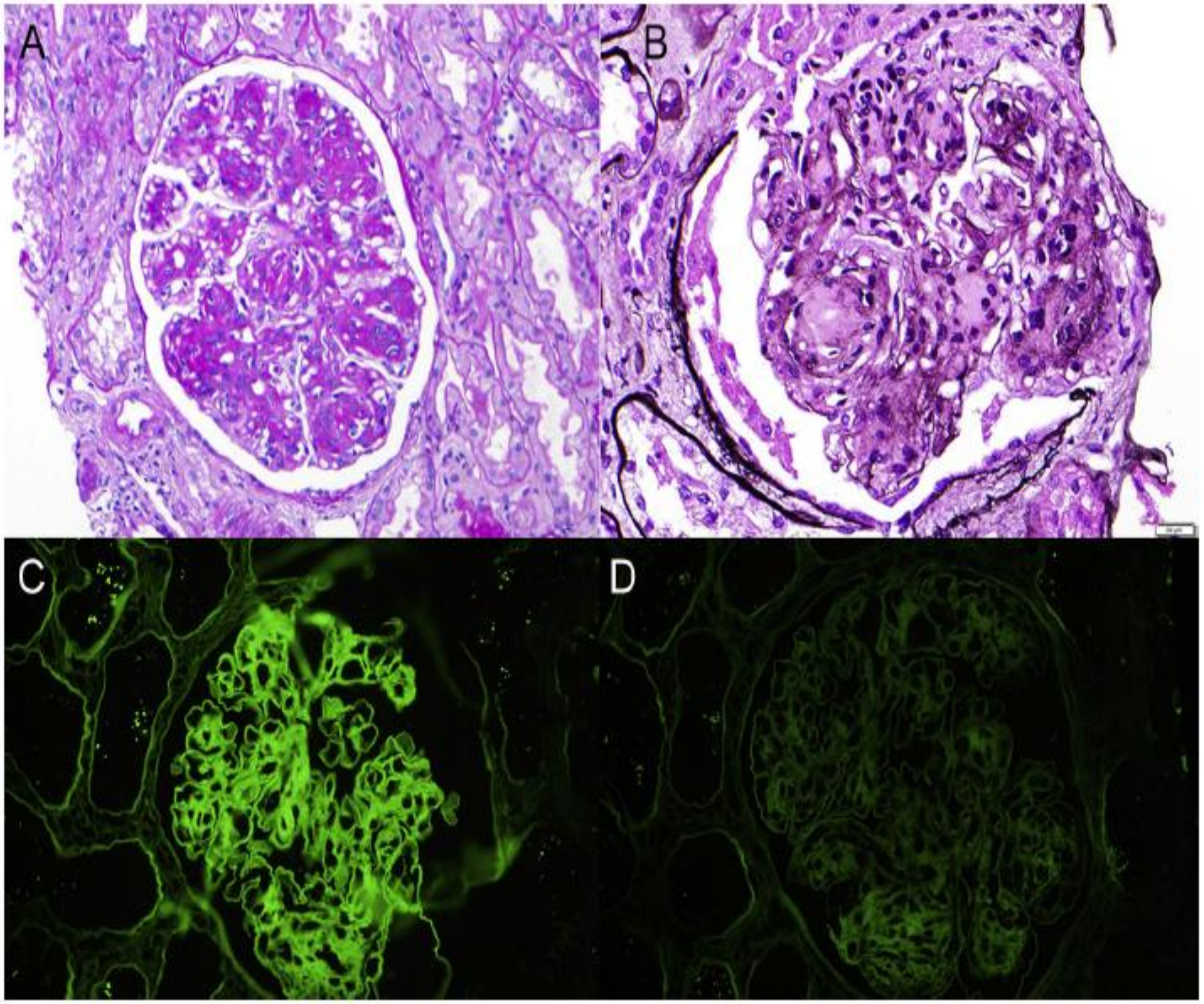
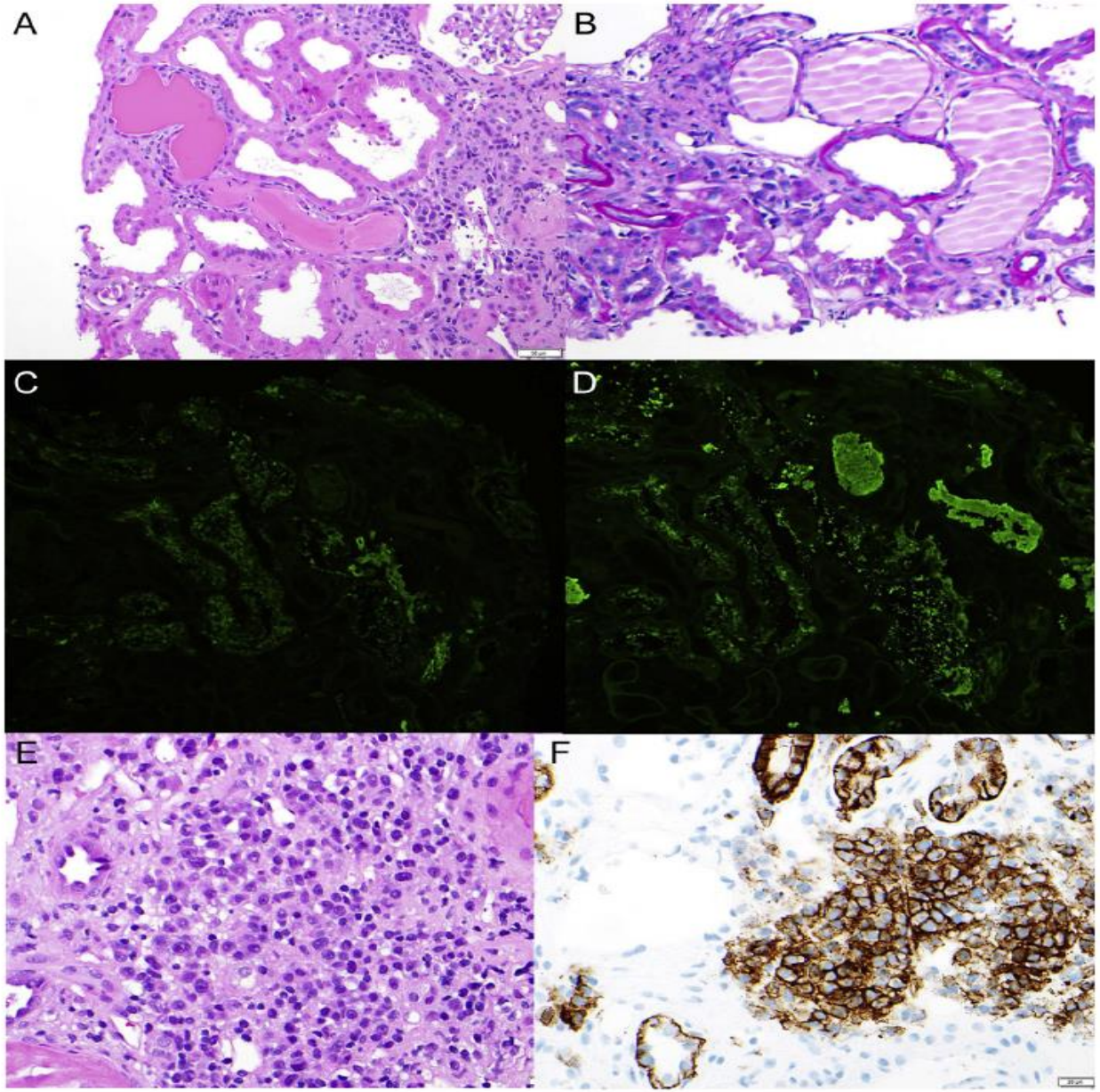


Figure 2. Kidney biopsy specimen from a patient with κ light chain monoclonal immunoglobulin deposition disease. Nodular glomerulosclerosis with (A) periodic acid–Schiff–positive but (B) silver-negative mesangial matrix expansion. (C) Glomeruli and tubular basement membranes stain brightly with κ light chain and (D) without staining for λ light chain.

MIDD(LC)



LC cast nephropathy

Treatment of MGRS

1-Proteasome inhibitors

2-Monoclonal antibodies

3-Cytotoxic chemotherapy

4-Immunomodulatory agents

5-Stem cell transplant

6-??????????????