AL Amyloidosis

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  - Janssen
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  - Alexion
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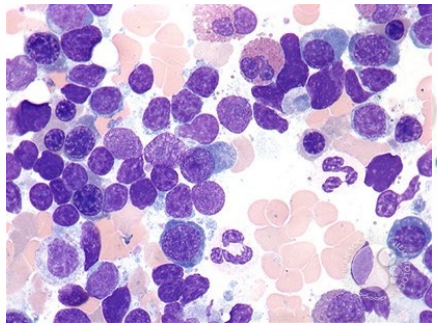
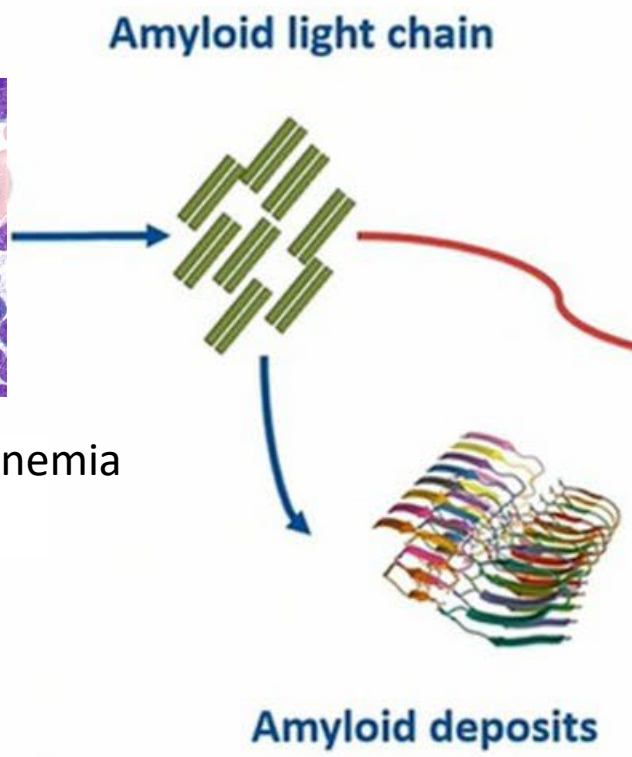
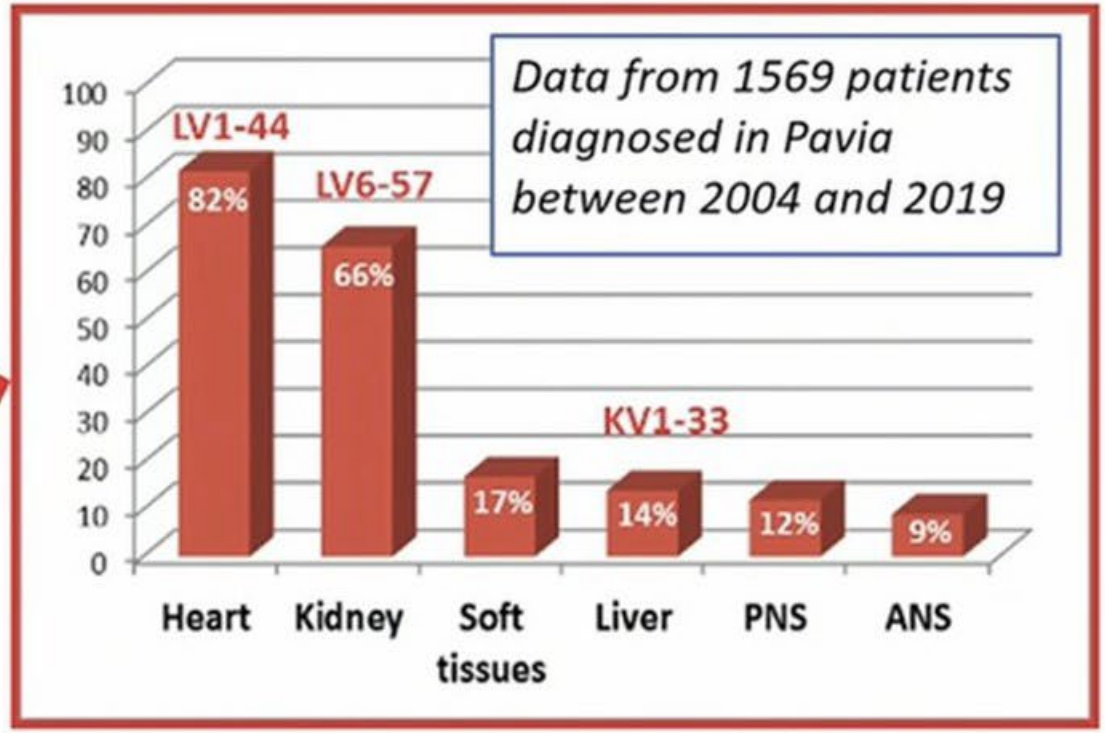
  - Caelum
  - Janssen
  - Sanofi

Light-chain Amyloidosis (AL)



Waldenstrom macroglobulinemia





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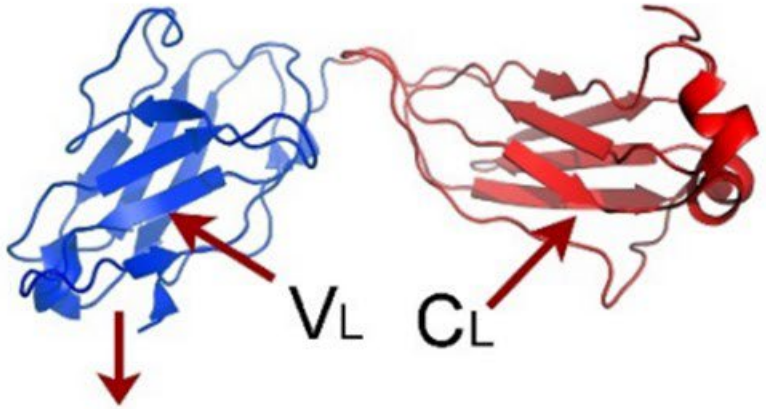
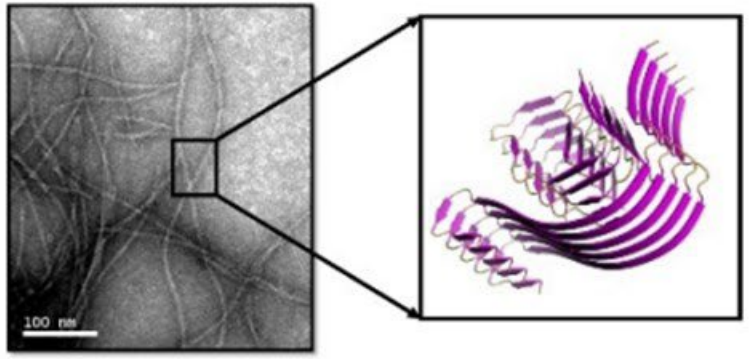
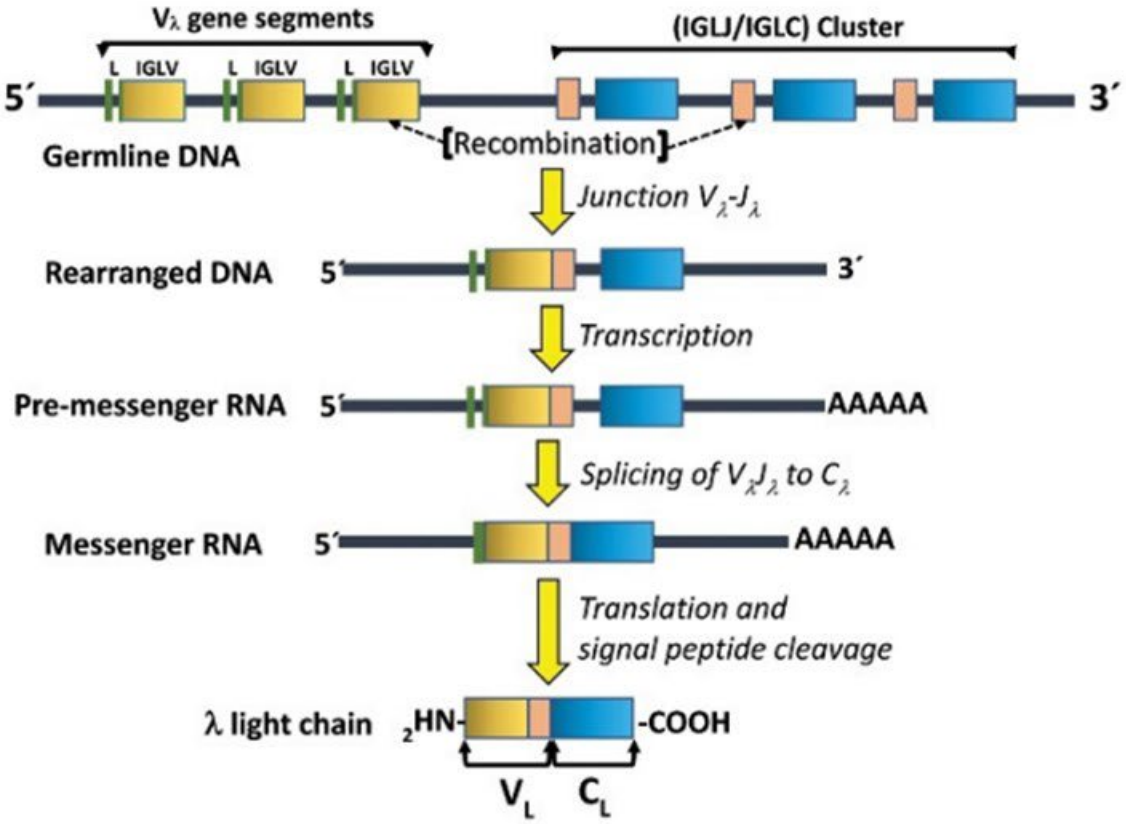
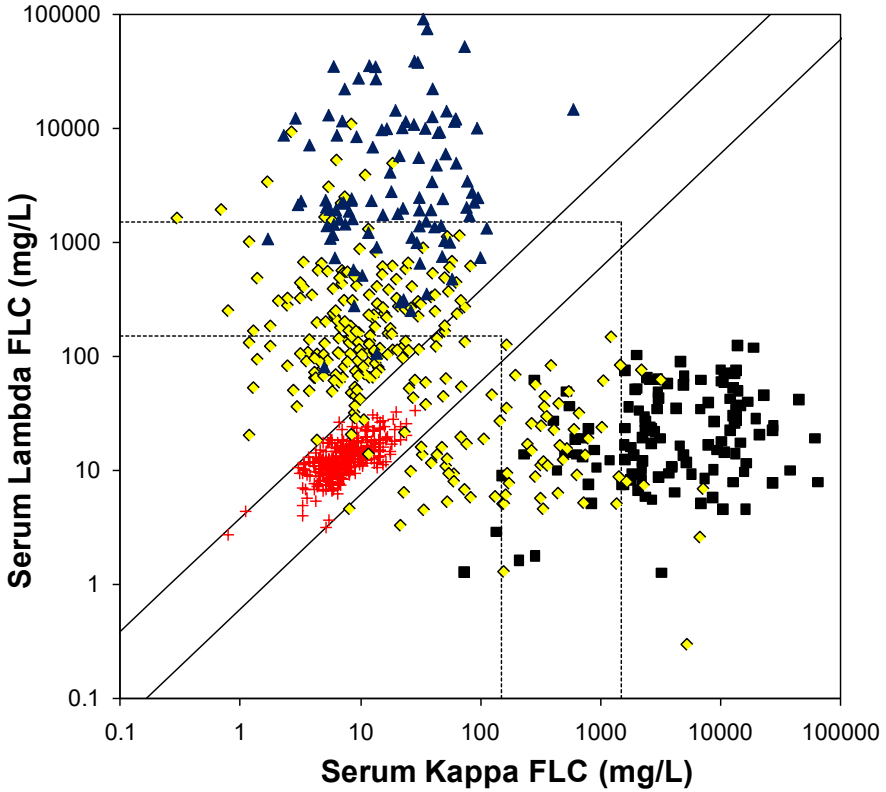




AL fibril (EM)

AL fibril (cryo-EM)

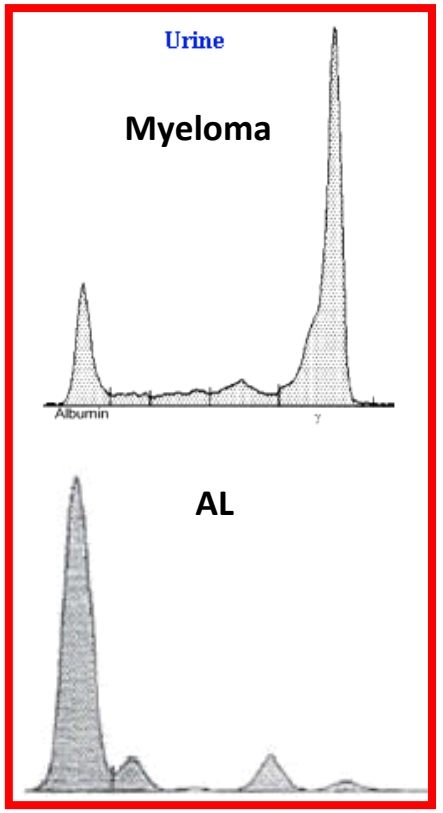




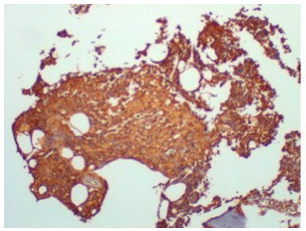
- Normal Sera
- Kappa LCMM
- AL Amyloid
- Lambda LCMM

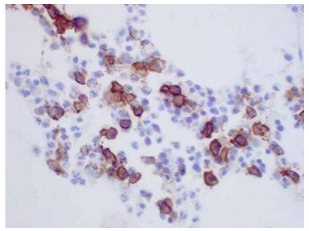
Involved Free Light Chain (***iFLC***)

iFLC minus uninvolved FLC (***dFLC***)

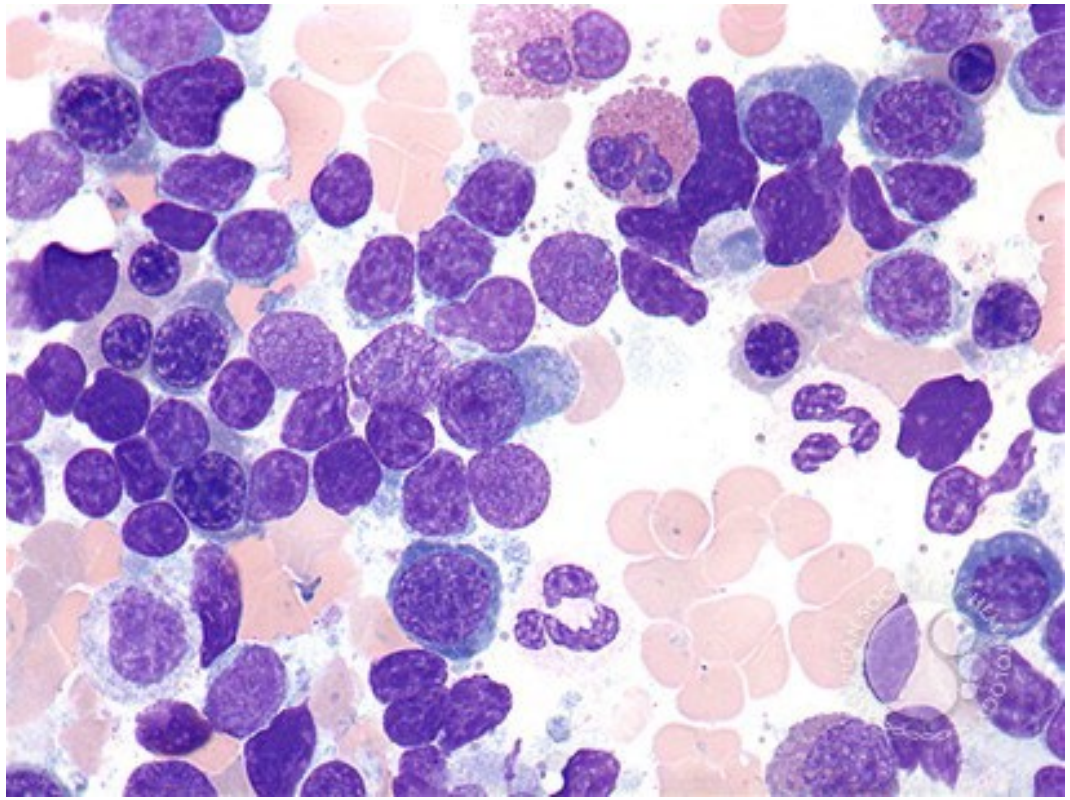


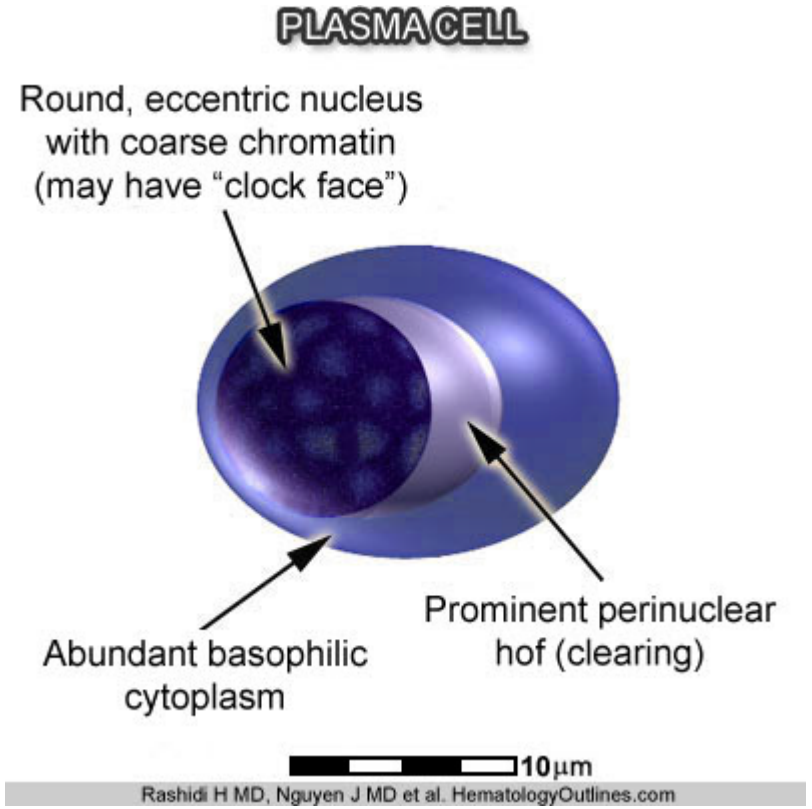
	MM (%)	AL (%)
t(11;14)	21	59
gain 1q	10	23
t(4:14)	14	3
del 13q	48	30
del 17p	11	2

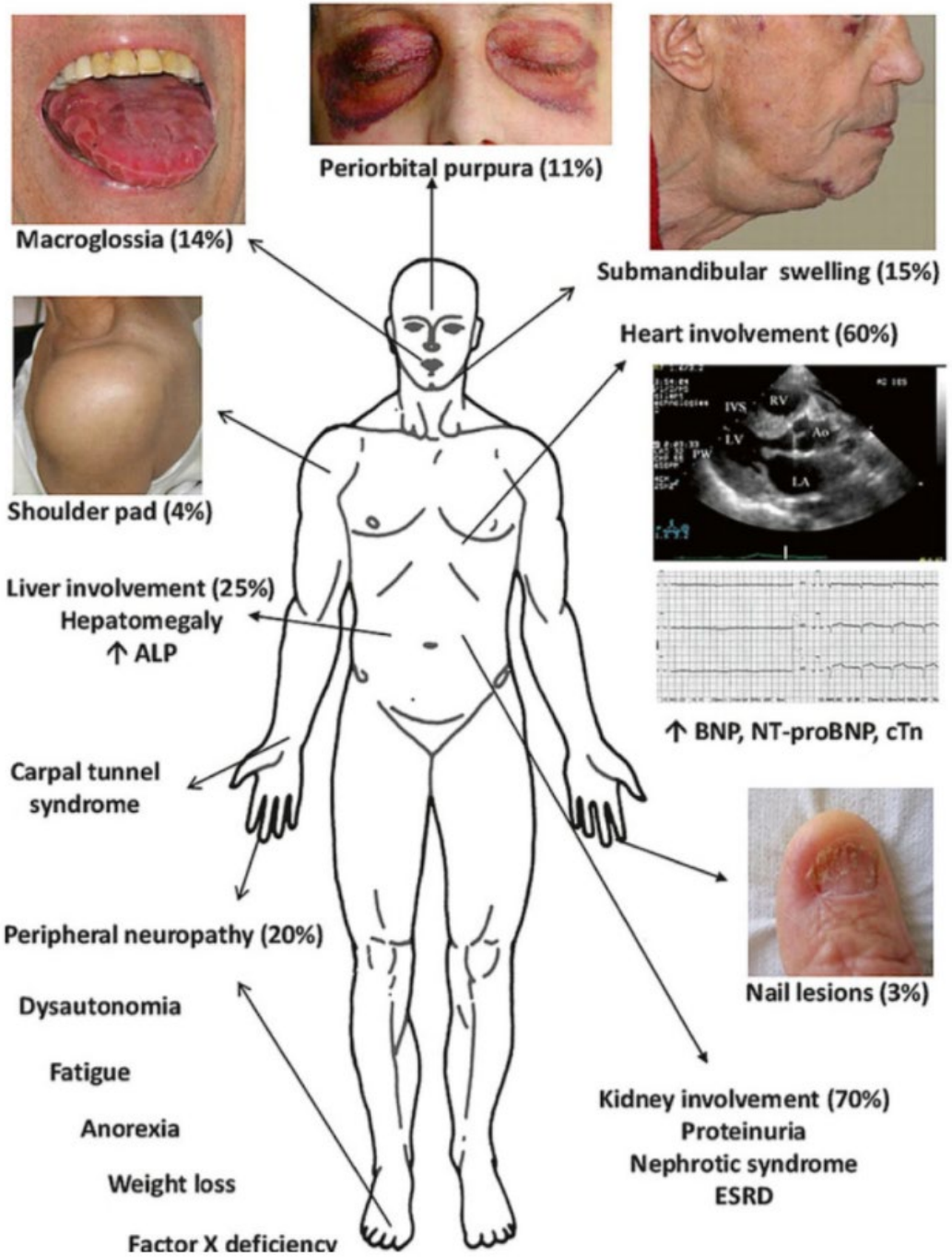


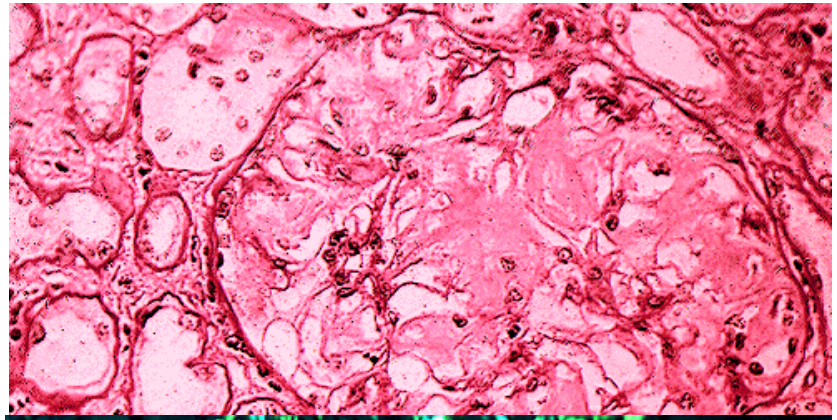


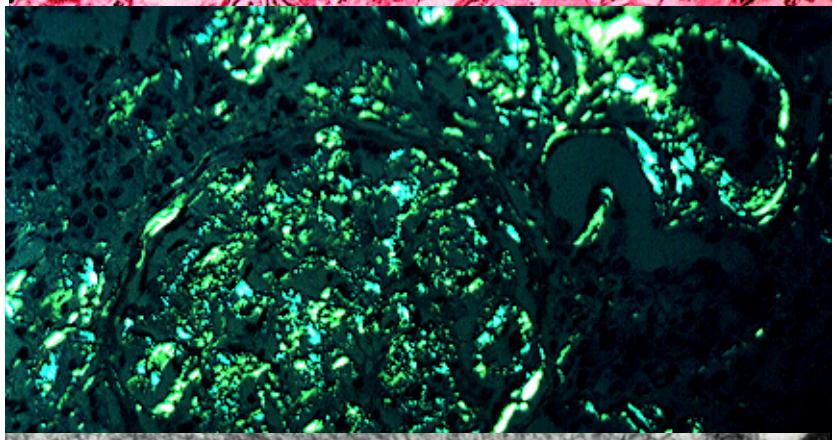
Br J Haematol 2003;122 :78
Blood 2007;109:3489
Blood 2008;111:4700
Amyloid 2014; 21: 9

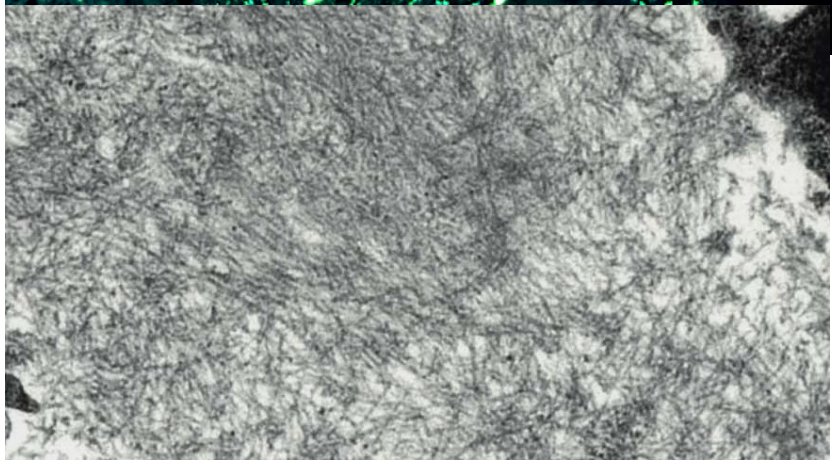


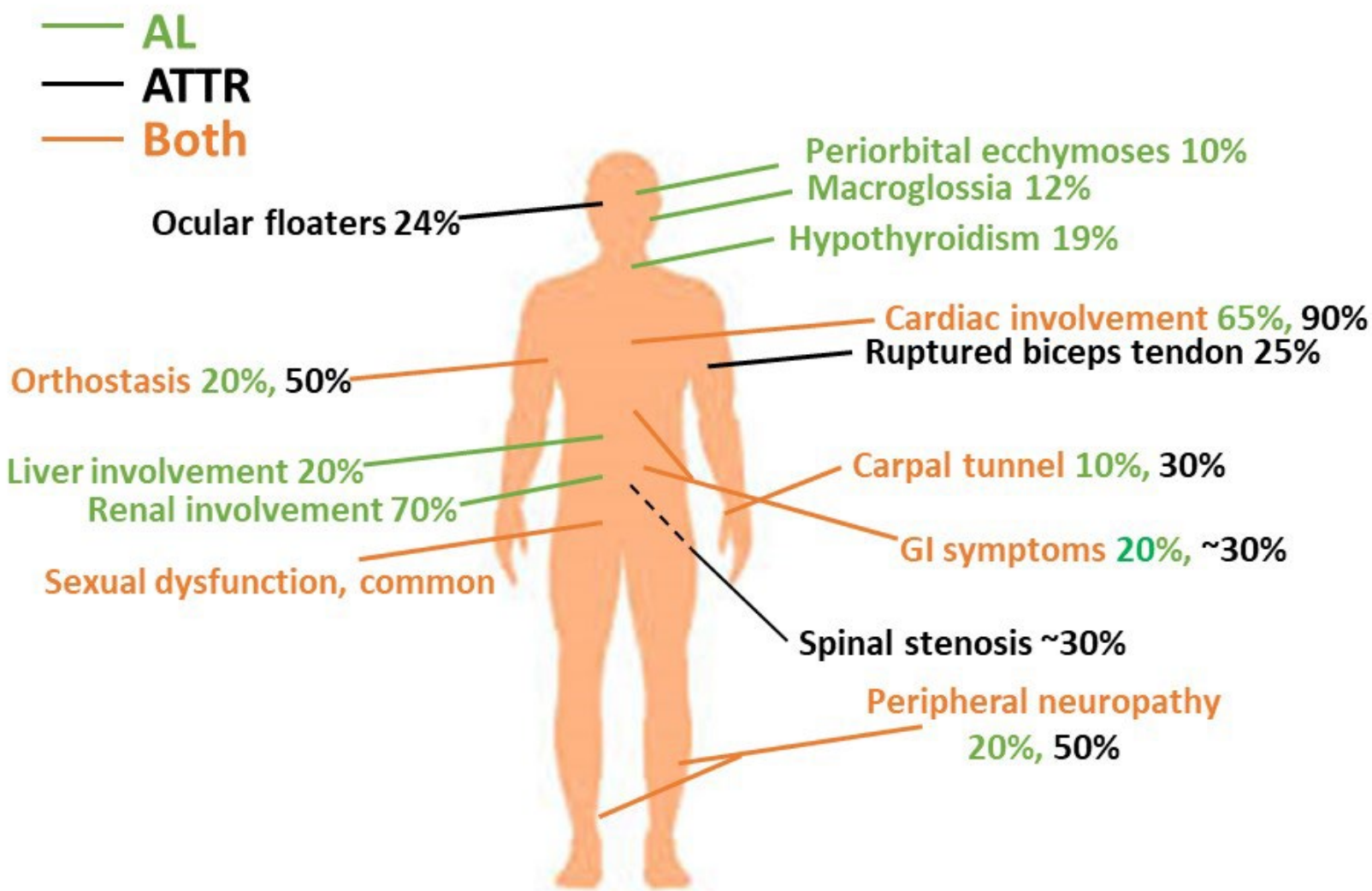

PLASMA CELL
Round, eccentric nucleus with coarse chromatin (may have "clock face")
Abundant basophilic cytoplasm
Prominent perinuclear hof (clearing)
10µm
Rashidi H MD, Nguyen J MD et al. HematologyOutlines.com

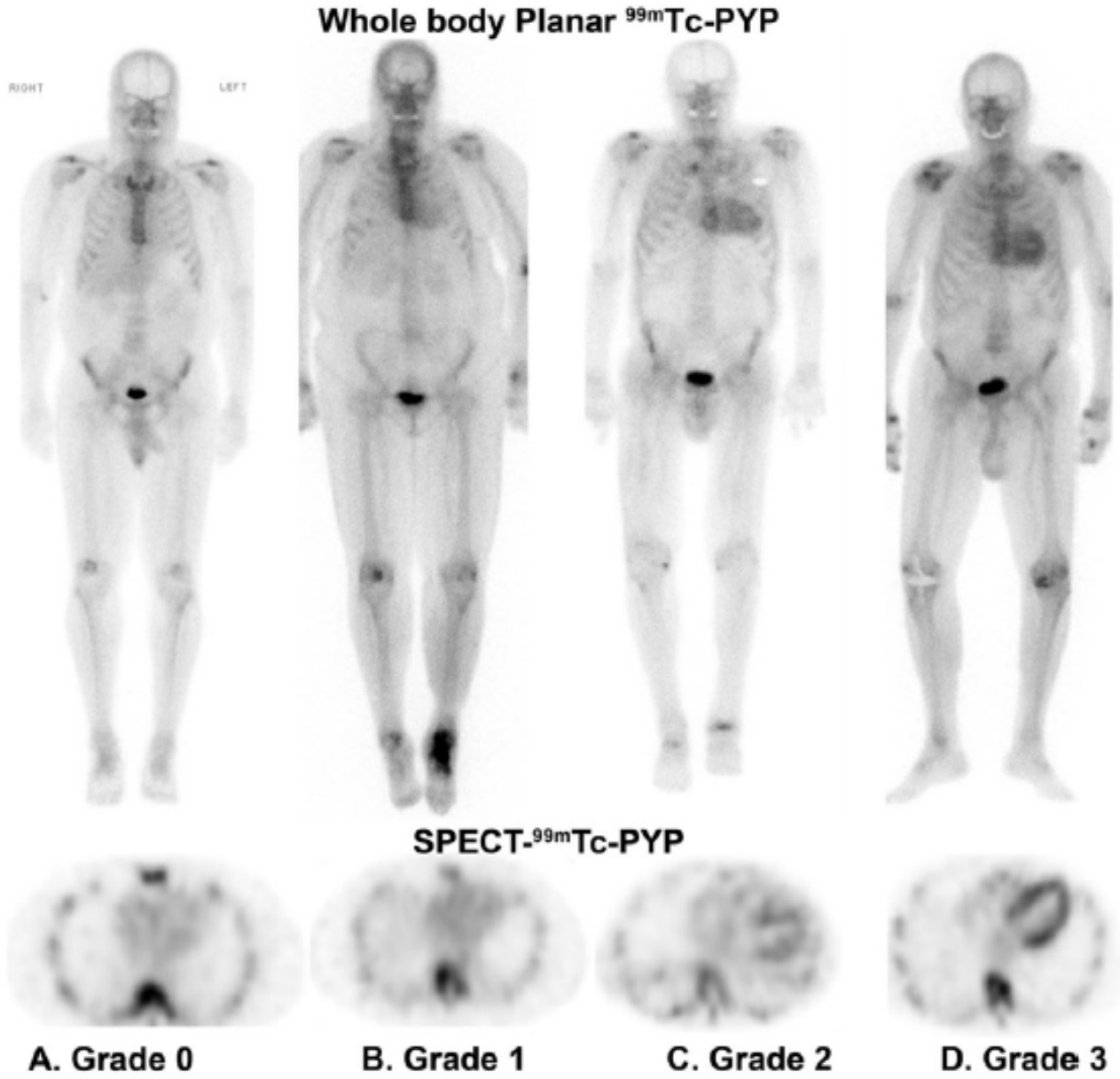

Periorbital purpura (11%)
Macroglossia (14%)
Submandibular swelling (15%)
Heart involvement (60%)
Shoulder pad (4%)
IVS
RV
LV
Ao
PW
LA
Liver involvement (25%)
Hepatomegaly
↑ ALP
↑ BNP, NT-proBNP, cTn
Carpal tunnel syndrome
Peripheral neuropathy (20%)
Nail lesions (3%)
Dysautonomia
Fatigue
Anorexia
Weight loss
Factor X deficiency
Kidney involvement (70%)
Proteinuria
Nephrotic syndrome
ESRD







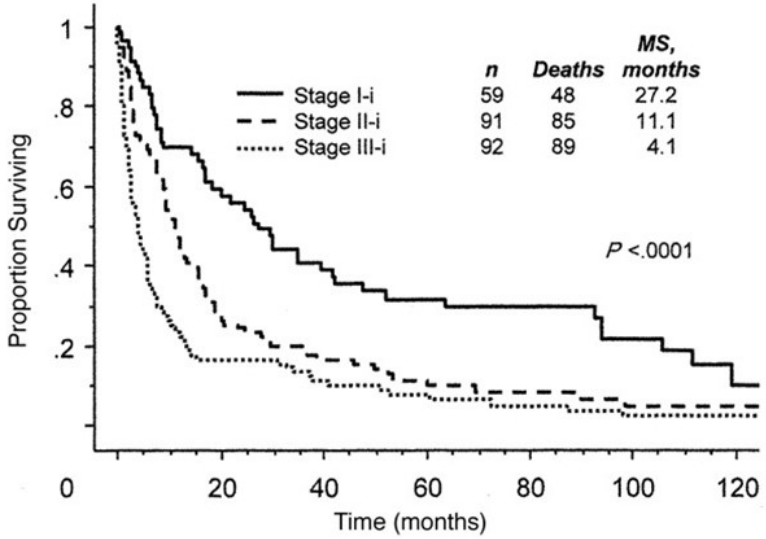

AL
ATTR
Both
Periorbital ecchymoses 10%
Macroglossia 12%
Ocular floaters 24%
Hypothyroidism 19%
Cardiac involvement 65%, 90%
Ruptured biceps tendon 25%
Orthostasis 20%, 50%
Liver involvement 20%
Carpal tunnel 10%, 30%
Renal involvement 70%
GI symptoms 20%, ~30%
Sexual dysfunction, common
Spinal stenosis ~30%
Peripheral neuropathy
20%, 50%



Blood Rev. 2021 Jan;45:100720. doi: 10.1016/j.blre.2020.100720. Epub 2020 Jun 23

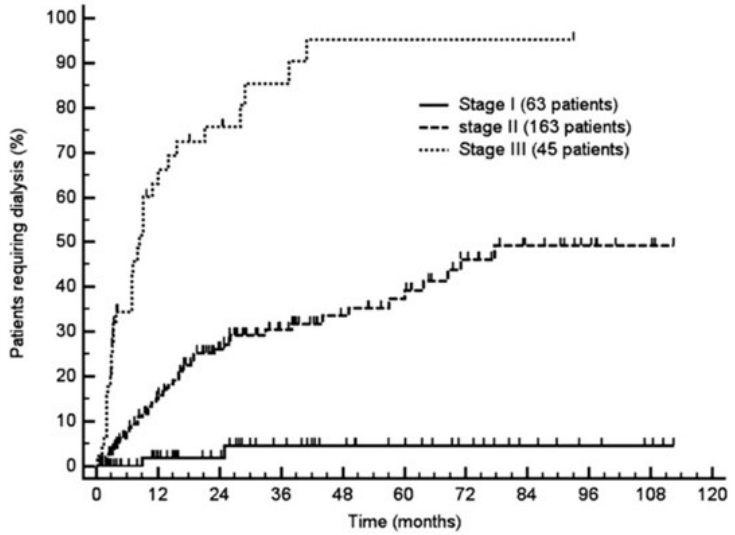
Systemic AL: Staging

Cardiac



JCO 2004;22:3751

Renal



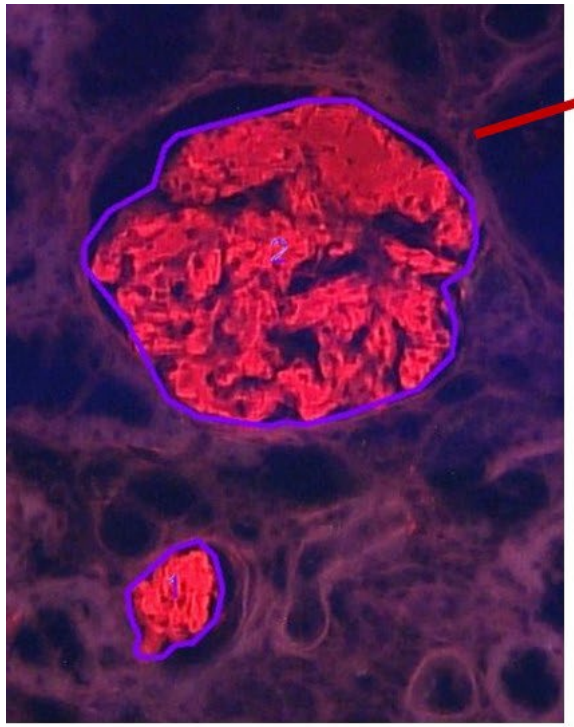
Blood 2014;124:2325

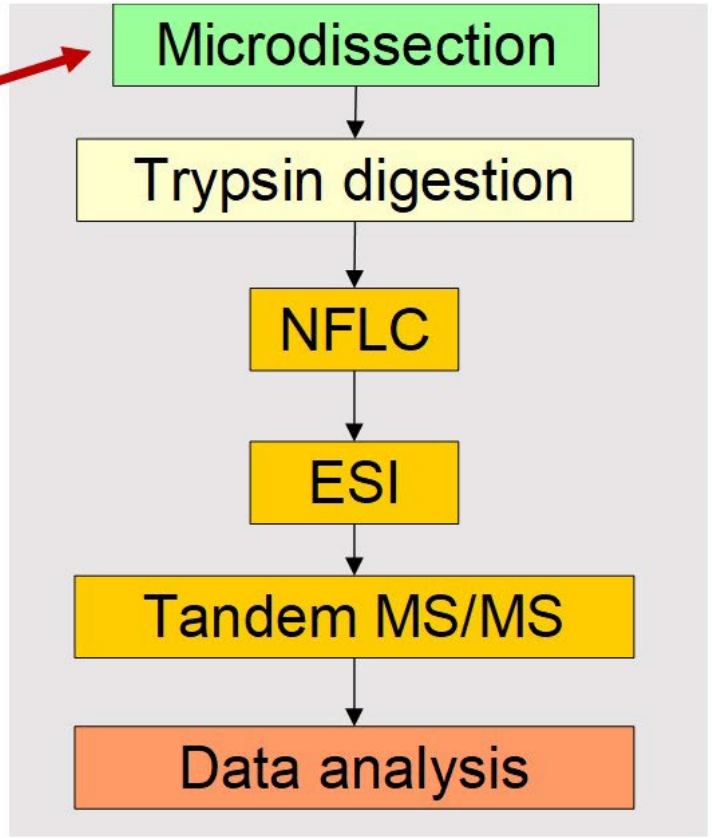
One point for each if
FLC-diff > 180 mg/L
cTnT ≥ 0.025 ng/mL
NT-proBNP ≥ 1,800 pg/mL,

Score	Stage	% (N)	Overall survival (months)
0	I	25 (189)	94.1
1	II	27 (206)	40.3
2	III	25 (186)	14
3	IV	23 (177)	5.8

JCO 2012;30:989-995

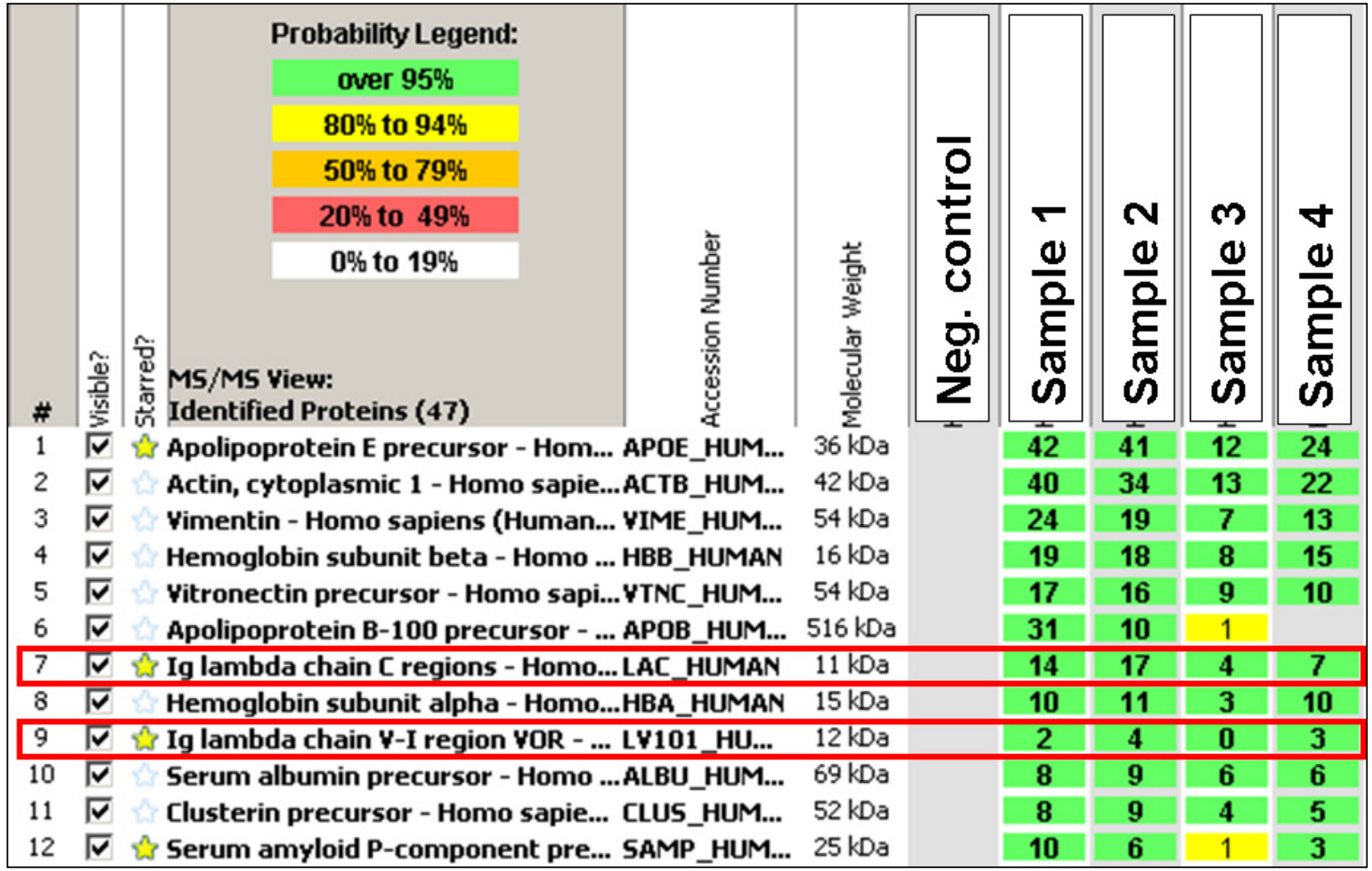
Laser Microdissection and Mass Spec





NFLC=nano flow liquid chromatography
ESI=electrospray ionization

Courtesy of Ahmet Dogan, MD



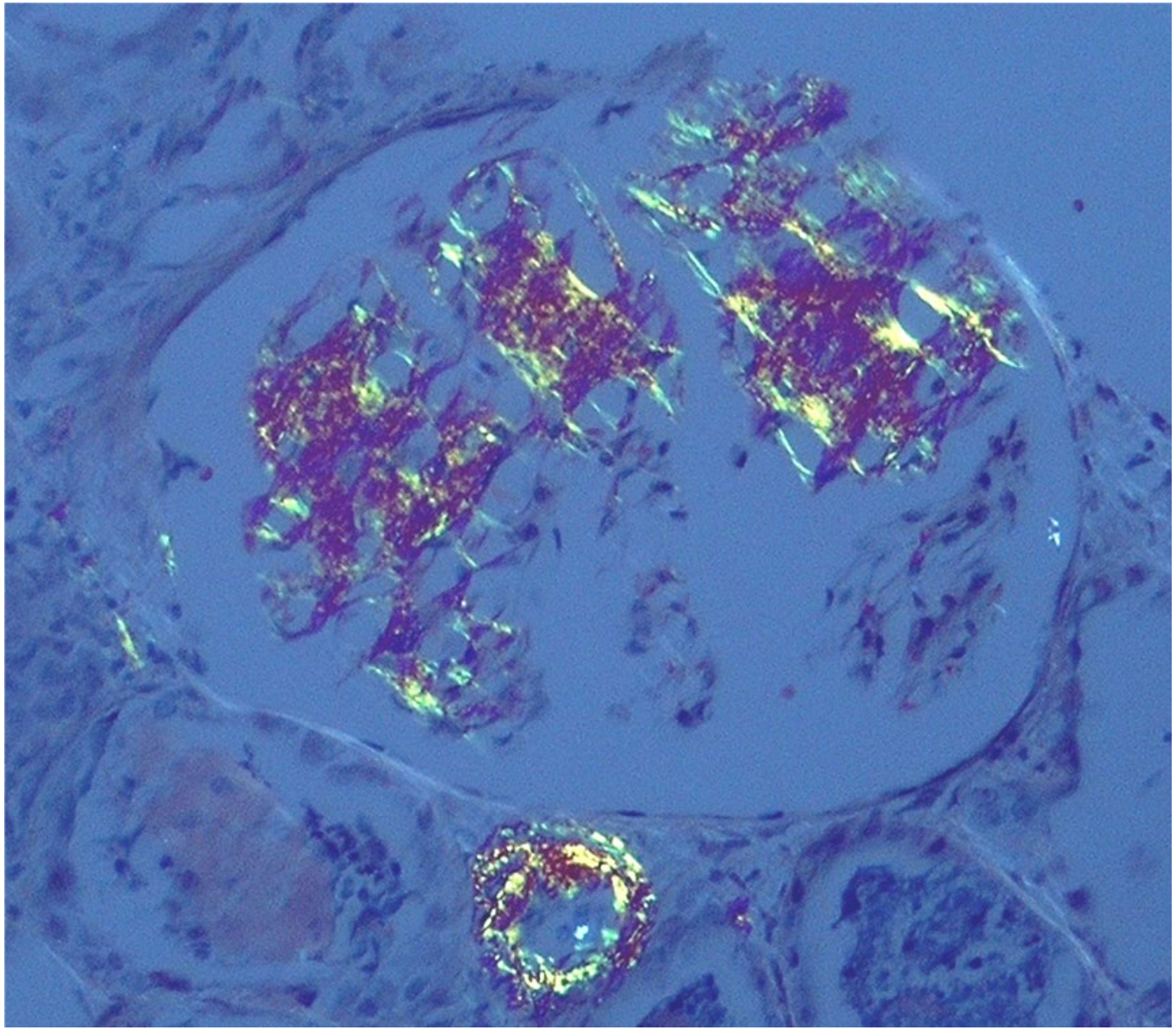
Probability Legend:

- over 95%
- 80% to 94%
- 50% to 79%
- 20% to 49%
- 0% to 19%

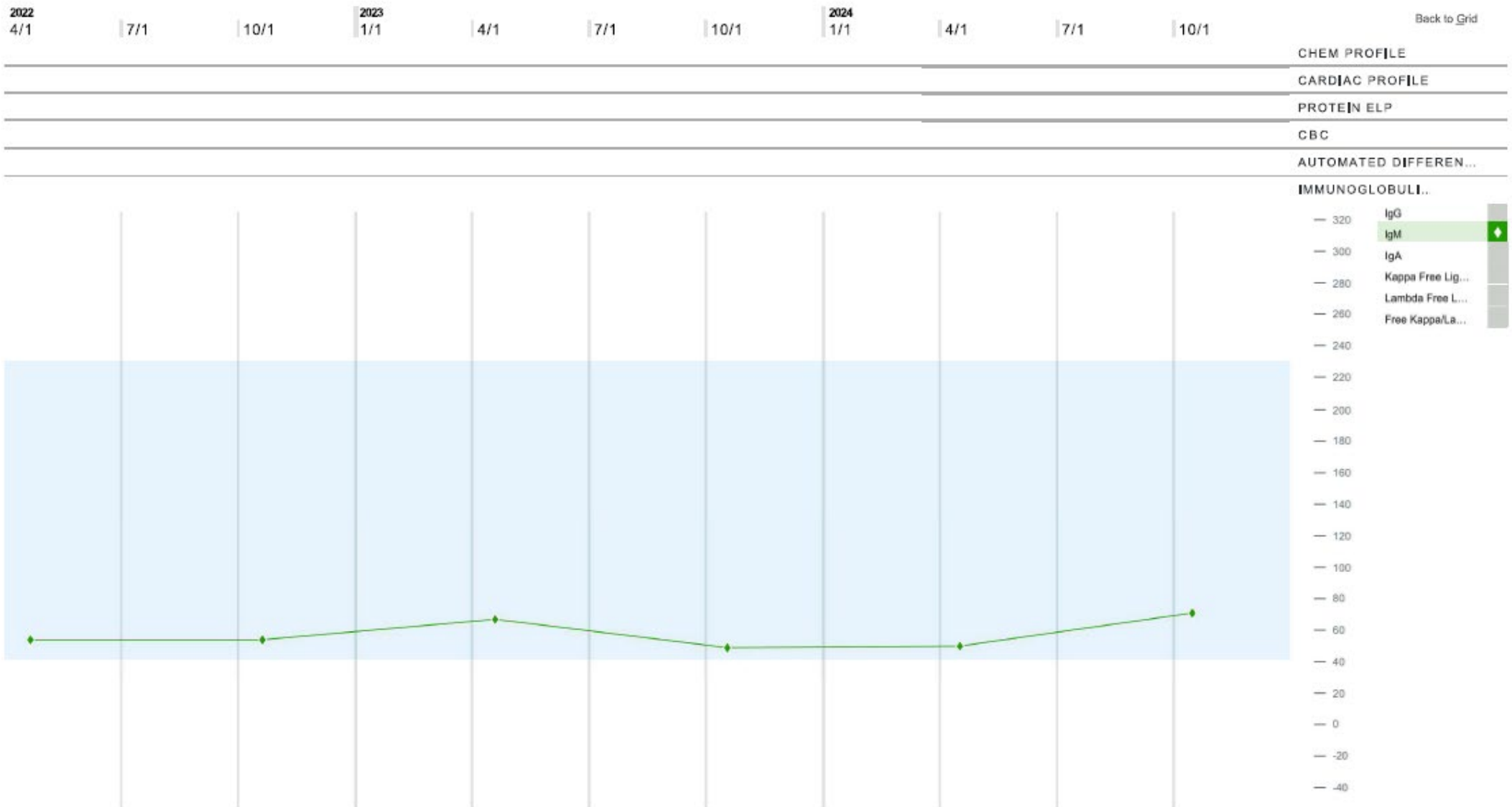
#	Visible?	Starred?	MS/MS View: Identified Proteins (47)	Accession Number	Molecular Weight	Neg. control	Sample 1	Sample 2	Sample 3	Sample 4
1	☑	★	Apolipoprotein E precursor - Hom...	APOE_HUM...	36 kDa		42	41	12	24
2	☑	☆	Actin, cytoplasmic 1 - Homo sapie...	ACTB_HUM...	42 kDa		40	34	13	22
3	☑	☆	Vimentin - Homo sapiens (Human...	VIME_HUM...	54 kDa		24	19	7	13
4	☑	☆	Hemoglobin subunit beta - Homo ...	HBB_HUMAN	16 kDa		19	18	8	15
5	☑	☆	Vitronectin precursor - Homo sapi...	VTNC_HUM...	54 kDa		17	16	9	10
6	☑	☆	Apolipoprotein B-100 precursor - ...	APOB_HUM...	516 kDa		31	10	1	
7	☑	★	Ig lambda chain C regions - Homo...	LAC_HUMAN	11 kDa		14	17	4	7
8	☑	☆	Hemoglobin subunit alpha - Homo...	HBA_HUMAN	15 kDa		10	11	3	10
9	☑	★	Ig lambda chain V-I region VOR - ...	LV101_HU...	12 kDa		2	4	0	3
10	☑	☆	Serum albumin precursor - Homo ...	ALBU_HUM...	69 kDa		8	9	6	6
11	☑	☆	Clusterin precursor - Homo sapie...	CLUS_HUM...	52 kDa		8	9	4	5
12	☑	★	Serum amyloid P-component pre...	SAMP_HUM...	25 kDa		10	6	1	3

55 year-old man with proteinuria

- 2011: Edema, fatigue, proteinuria, anemia
- 24-hour total urine protein 12,565mg, serum albumin 1.7g/dl, eGFR 111
- Renal biopsy in 11/2011: AL amyloidosis, lambda-type
- Marrow biopsy in 12/2011 showed **lymphoplasmacytic lymphoma**
- **IgM 1565mg/dl,** FLC lambda 44.4mg/L with kappa < 3.3
- Rituximab, cyclophosphamide, dexamethasone every 3 weeks x 8 cycles
- Lambda free light chains normalized after cycle 4 and IgM was reduced by 50%
- Plasma exchange to increase serum albumin to 3.0g/dL
- Stem cell mobilization with cyclophosphamide, rituxan and G-CSF
- BEAM autologous SCT (day 0 8/29/12)
- Post-SCT he completed 20/24 months of rituximab maintenance every 3 months. Diarrhea.
- He has achieved and maintained a hematologic complete response
- He has also achieved a renal response. eGFR > 90, protein:creatinine ratio < 100



Blood 2009;114:3147


2022
4/1
7/1
10/1
2023
1/1
4/1
7/1
10/1
2024
1/1
4/1
7/1
10/1
Back to Grid
CHEM PROFILE
CARDIAC PROFILE
PROTEIN ELP
CBC
AUTOMATED DIFFEREN...
IMMUNOGLOBULI..
IgG
IgM
IgA
Kappa Free Lig...
Lambda Free L...
Free Kappa/La...
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40

99 patients with WM

- Male/female ratio was 1.5
- Median age at diagnosis was 63 years (range, 37–90)
- Forty-one percent required therapy
- Median serum B2M was 2.3 mg/L, median hemoglobin 10 gm/dL, median serum viscosity 1.9 cp, and median platelet count 240 ×109/L
- Mean sFLC was 131.2 mg/L (95% CI 72–189)
- sFLC correlated with the serum IgM level (r=0.27; p=0.008).

Blood (2006) 108 (11): 2420.

49 patients with WM+AL

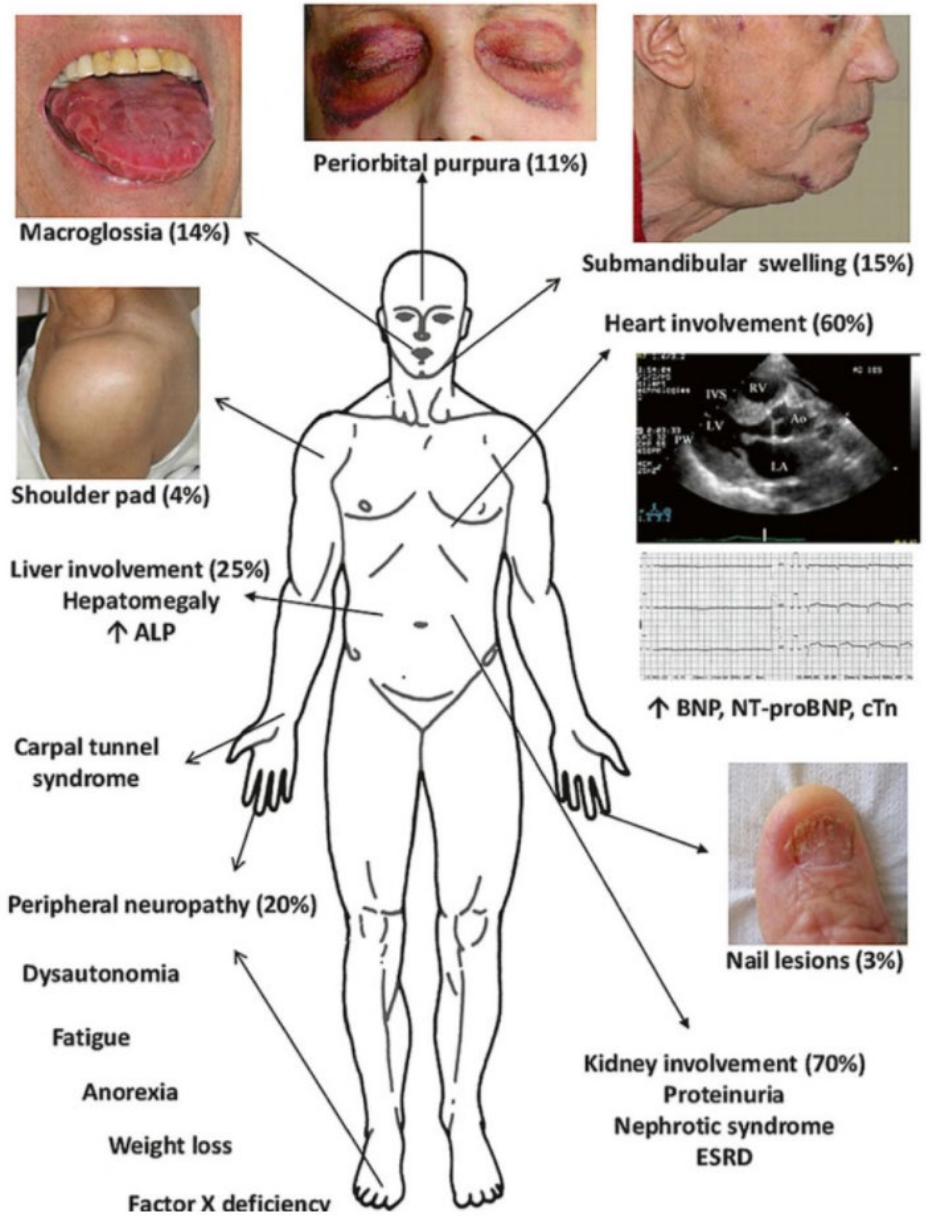
20% had WM+AL at diagnosis

80% had AL diagnosed a median of 3 months after WM (0-201)

24% had AL diagnosed > 5 years after WM

Patients' characteristics	All patients (N=49)
Age, years	
Median (range)	68 (56-86)
>65 years, N (%)	30/49 (61)
Sex, N (%)	
Male	27/49 (55)
Female	21/49 (45)
Light chain isotype, N (%)	
Kappa	19/49 (39)
Lambda	30/49 (61)
Hemoglobin level, g/dL	
Median (range)	12.4 (9.2-18.1)
≤11.5 g/dL, N (%)	13/48 (27)
Platelet count, $x10^9$/L	
Median (range)	263 (126-652)
≤100 $x10^9$/L, N (%)	0/48 (0)
β_2-microglobulin, mg/L	
Median (range)	3.2 (1.6-22.2)
>3 mg/L, N (%)	26/48 (54)
Serum IgM level, mg/dL	
Median (range)	1418 (284-5,498)
>4,000 mg/dL, N (%)	6/49 (12)
dFLC, mg/L	
Median (range)	73.7 (5.1-1,333.5)
>180 mg/L, N (%)	10/49 (20)
BM involvement by LPL, %	
Median (range)	20 (10-60)
>10%, N (%)	41/48 (85)
Tumor genotype, N (%)	
MYD88 mutation	17/21 (81)
CXCR4 mutation	3/9 (33)
t(11;14)	0/27 (0)

Haematologica 2023;108:1680



Patients' characteristics	All patients (N=49)
Urine protein excretion, mg/24 h	
Median (range)	655 (0-14,064)
>5,000 mg/24 h, N (%)	13/48 (27)
Alkaline phosphatase, IU/L	
Median (range)	91 (36-924)
>150 IU/L, N (%)	8/47 (17)
Brain natriuretic peptide, pg/mL	
Median (range)	77 (3-2,163)
>81 pg/mL, N (%)	23/48 (48)
NT-pro-BNP, pg/mL	
Median (range)	554 (62-5,732)
>332 pg/mL, N (%)	13/22 (59)
Troponin I, ng/mL	
Median (range)	0.012 (0.006-0.599)
>0.1 ng/mL, N (%)	4/48 (8)
BU cardiac stage, N (%)	
I	25/48 (52)
II	19/48 (40)
III	4/48 (8)
IPSSWM stage, N (%)	
Low	12/48 (25)
Intermediate	31/48 (65)
High	5/48 (10)
Organ involvement, N (%)	
Renal	25/49 (51)
Cardiac	17/49 (35)
Peripheral nervous system	16/49 (33)
Autonomic nervous system	10/49 (20)
Gastrointestinal	8/49 (16)
Lymph node	8/49 (16)
Pulmonary	7/49 (14)
Skin/soft tissue	7/49 (14)
Hepatic	3/49 (6)

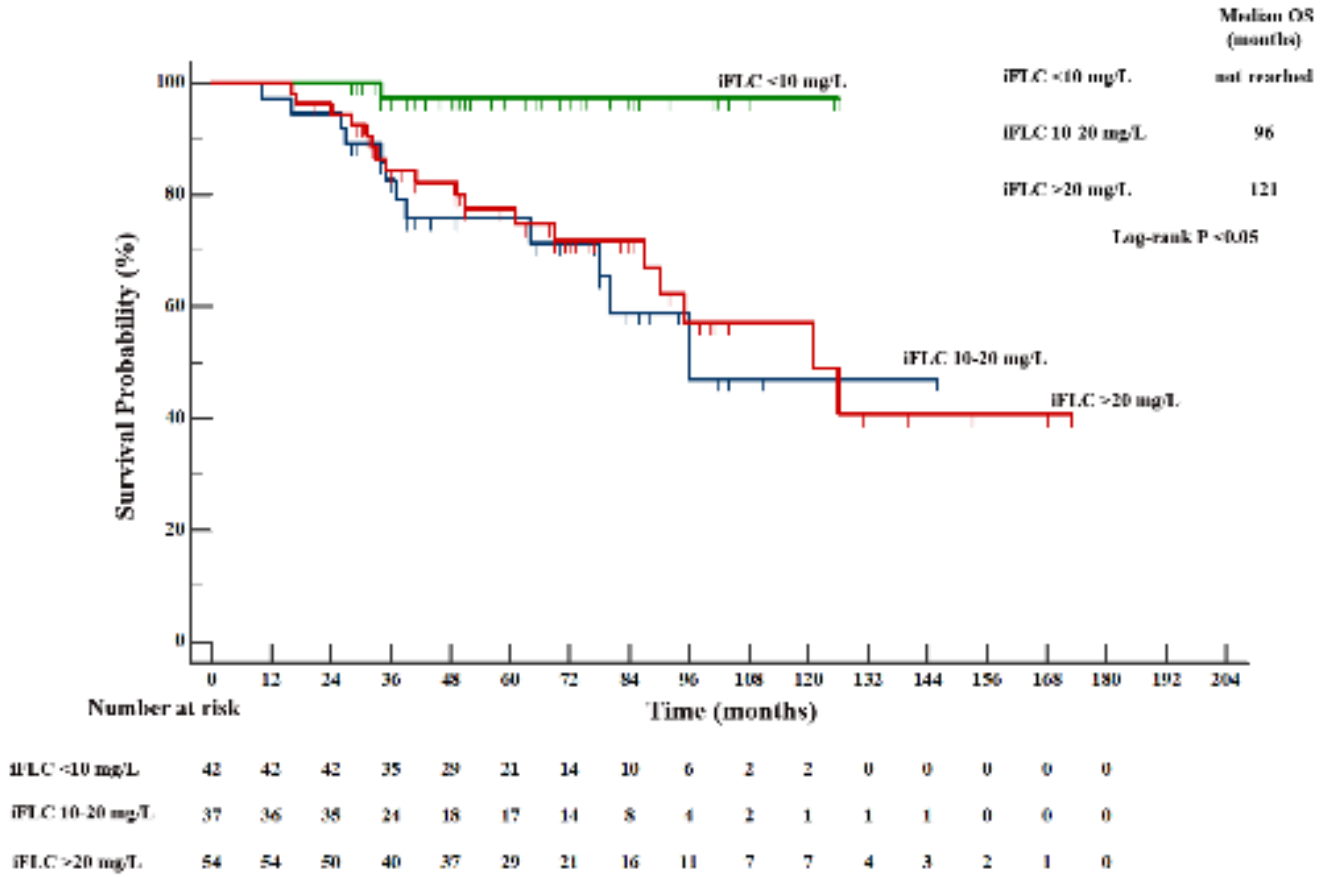
At Diagnosis

- Cardiac symptoms
  - NT-proBNP, hs Troponin T
  - Echo, EKG
- Proteinuria or unexplained worsening of renal function
- Unexplained enlargement of the liver
- Dizziness on standing & orthostatic vital signs
- Unexplained peripheral neuropathy
- Free light chains
- Fat pad aspirate, bone marrow biopsy, stained with Congo red

In Follow Up – Every 6 to 12 months

- Symptom changes
- Changes in functional status
- Weight loss
- Not just the IgM - Free light chains & trend them
- Fat pad aspirate, bone marrow biopsy, stained with Congo red
- Involved organ biopsy
- Previous bowel biopsies

OS with iFLC Response < 10mg/L



SCT
Bortezomib
Daratumumab

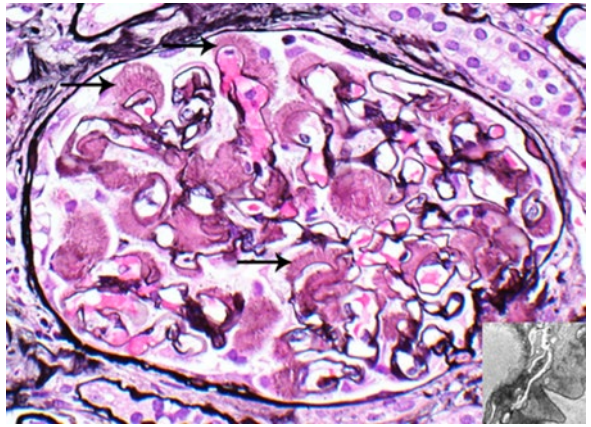
Goals remain:

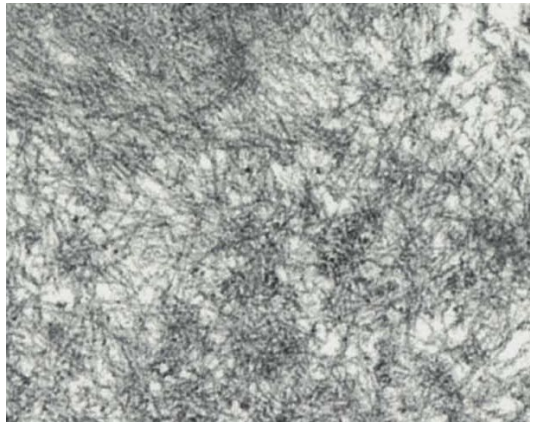
- Preserve organ function
- Maintain QOL
- Achieve MRD
- Long-term survival

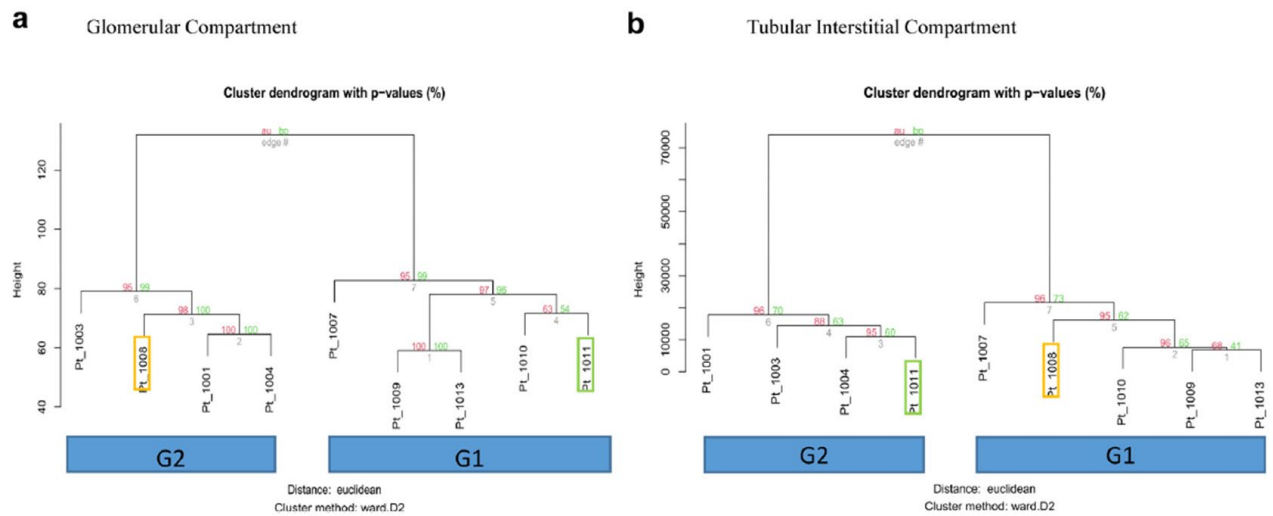
Am J Hematol 2021;96:E20; DOI: (10.1002/ajh.26025)

Many Known Unknowns

- Pathology
- Gene Expression Profiles
- Light-chain Tropism
- Reversal of Proteinuria
- Irreversible Renal Damage
- Dual Organ Connections
  - Heart & Kidney
  - Liver & Kidney
- Post-renal transplant hematologic maintenance







- Unsupervised hierarchical clusters

Clin J Am Soc Nephrol 2013;8: 1515
Br J Haematol 1999;106:744
Blood 2021;138 (S 1): 2715
Kidney Int Rep DOI:10.1016/j.ekir.2024.07.002

Advances in Therapy and Better Outcomes
Survivorship comes at a price

- **SCT**
  - **MEL 200**
  - **MEL 140 for ESRD Patients on HD**
  - **SCT post-solid organ transplant**
- **Bortezomib**
  - **VCD (CyBorD)**
- **Burden of Survivorship: MRD and PET/CT every 1 to 2 years**
- **Immunotherapies being studied**
- **BITEs**
  - **Teclistamab**
  - **Elranatamab**
  - **Talquetamab**
- **CAR-T cells**
  - **Nexcella**
  - **Cilta-cel**
  - **Ide-cel**

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