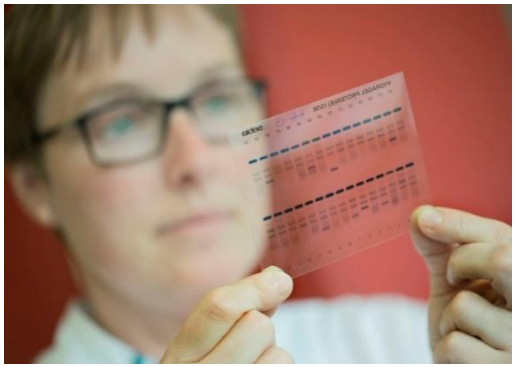
M proteine diagnostiek

SKML nabespreking, sectie HIM



18 november 2014

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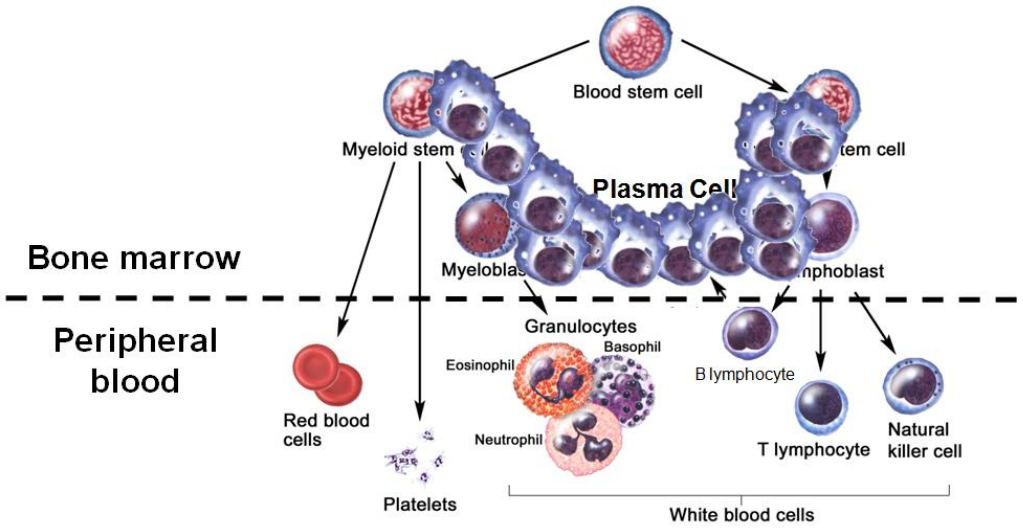
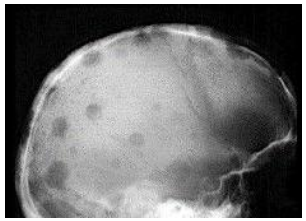
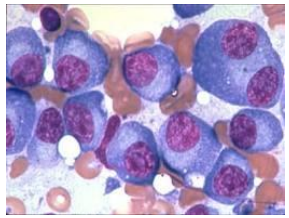
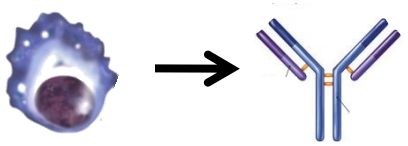
Monoclonal gammopathy; multiple myeloma

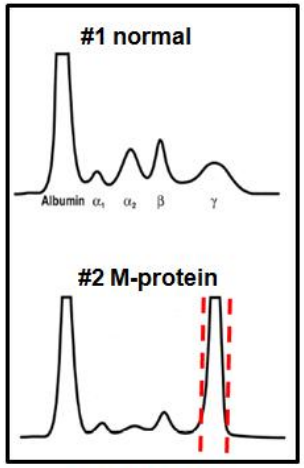




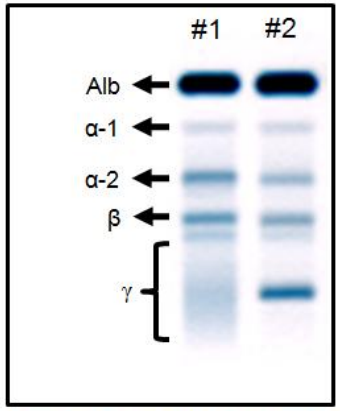




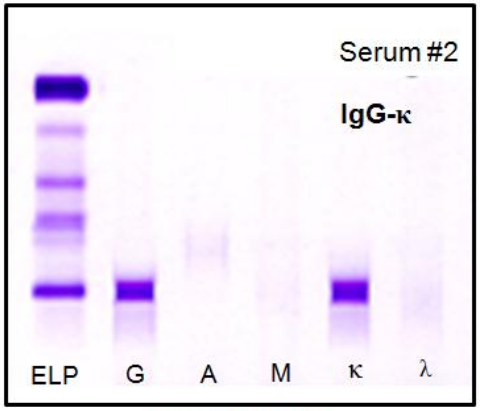
Gel electrophoresis



Densitometry

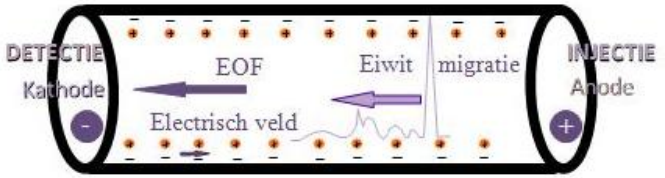


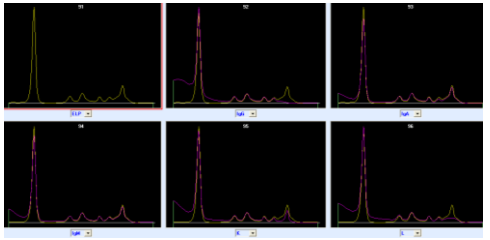
Serum protein electrophoresis



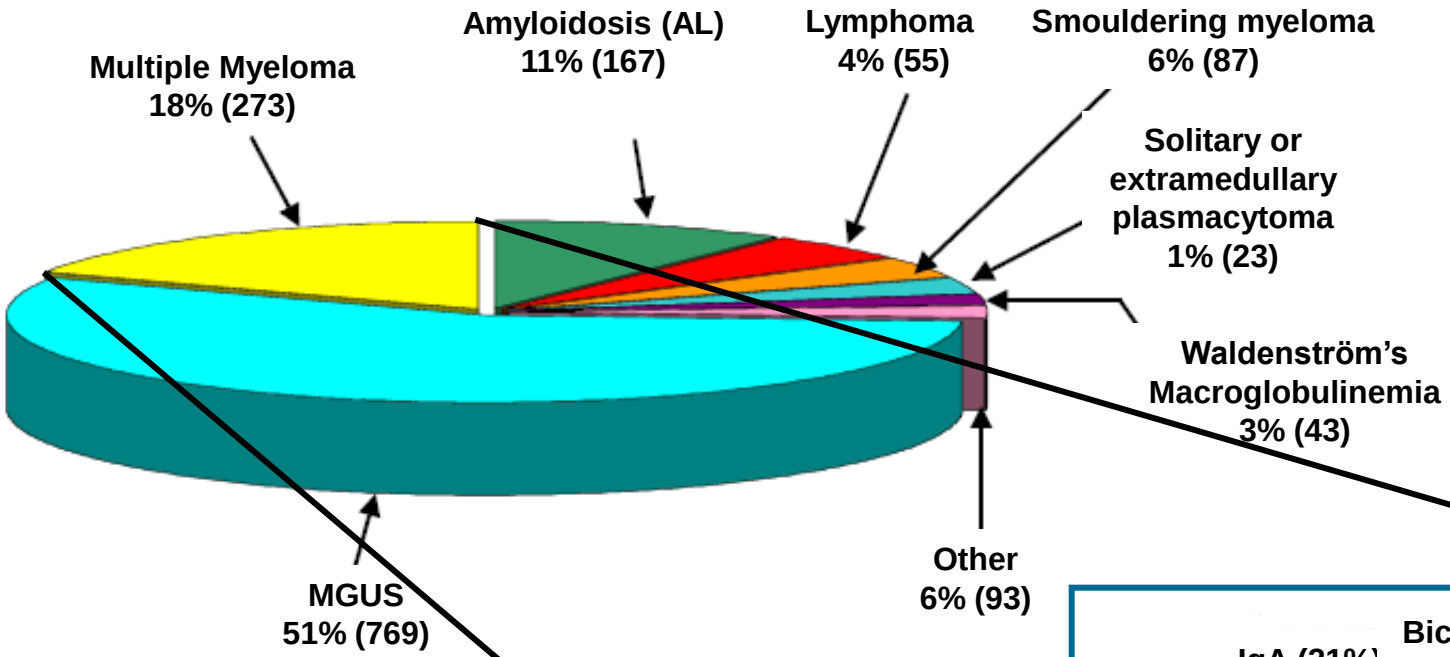
Immunofixation

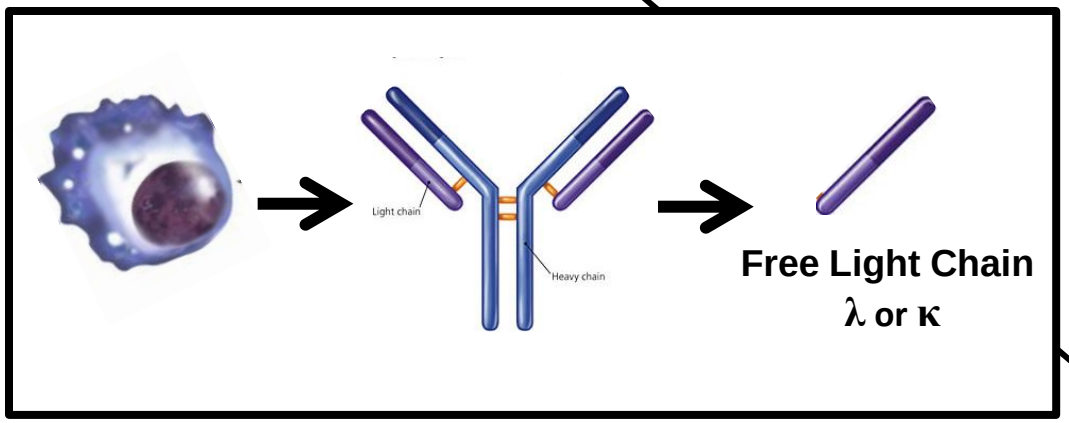
Capillary electrophoresis

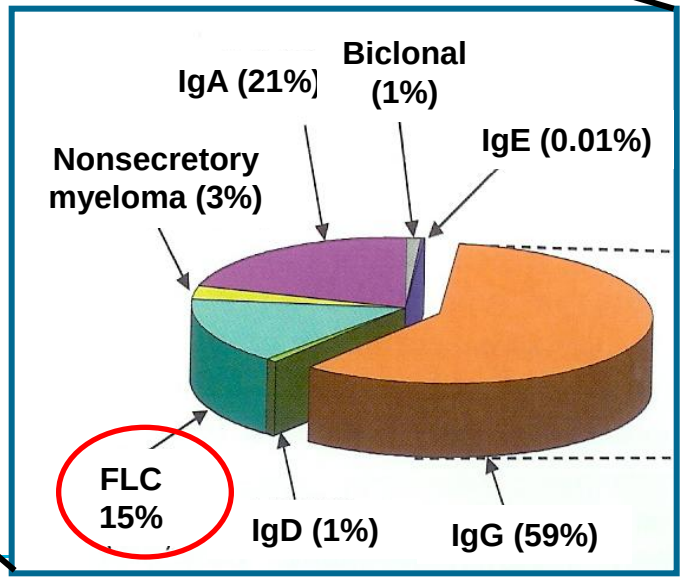




Monoclonal gammopathies





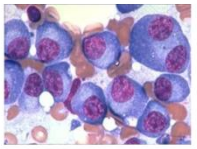


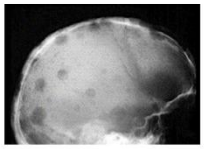
Diagnosed at Mayo Clinic 2002

Diagnosticeren van een multipel myeloom

Stats:

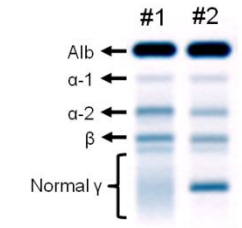
- Incidence approximately 5 per 100.000
- 60 000 new cases in Europe each year, 250 000 worldwide
- Median age 62 year, but 2% under 40 year

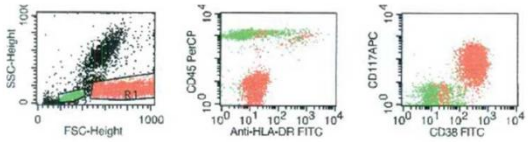




Symptoms

- Bleeding
- Bone and back pain
- Increased sensitivity to infections
- Symptoms of anemia (tiredness, respiratory problems)
- Unexplained fracture





MGUS (undetermined signific.)	Asymptomatisch Myeloom	Symptomatisch Myeloom
M-protein < 30 g/l	M-protein > 30 g/l	M-protein present
BM clonal plasma cells <10%	BM clonal plasma cells >10%	BM clonal plasma cells present
No myeloma associated impairment*	No myeloma associated impairment*	Any myeloma associated impairment*

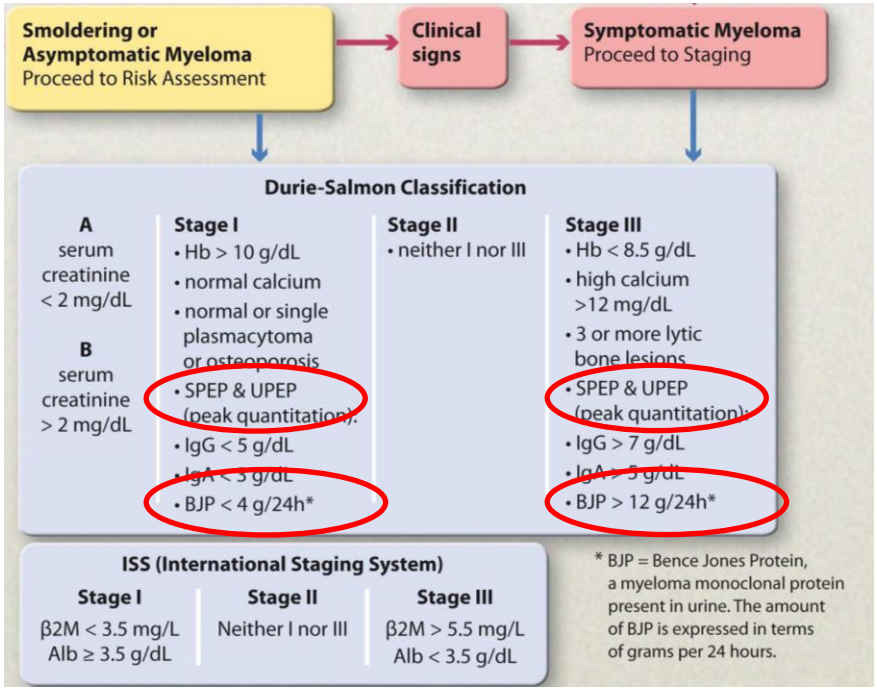
*CRAB-criteria:

Calcium increased (serum calcium > 115 mg/L; > 2.65 mmol/L)
Renal-insufficiency (serum creatinine > 20 mg/L; > 177 umol/L)
Anemia (hemoglobin < 100 g/L; < 12.5 mmol/L)
Bonedisease (lytic lesions, severe osteopenia, or pathologic fractures)

Kyle et al. Leukemia 2009

M-proteine diagnostiek voor stadiering en monitoring

Staging



Monitoring

Table 5 International Myeloma Working Group uniform response criteria

Response	*Response criteria*[a]
sCR	CR as defined below plus Normal FLC ratio and ~~Absence of clonal cells in~~ bone marrow[b] by immunohistochemistry or immunofluorescence[c]
CR	Negative immunofixation on the serum and urine and ~~Disappearance of any soft tissue plasmacytomas and~~ ≤5% plasma cells in bone marrow[b]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
PR	≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h If the serum and urine M-protein are unmeasurable,[d] a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
SD	Not meeting criteria for CR, VGPR, PR or progressive disease

Durie et al. Leukemia 2006
IMWG guideline: Kyle and Rajkumar. Leukemia 2009

Radboudumc

Improved treatment regimes require increased assay sensitivity

Parameters

Patient specific

Age	Consider ASCT in 'younger patients'
Neuropathy	Avoid bortezomib and thalidomide if feasible, if not, use weekly and subcutaneous bortezomib
Light chain-induced nephropathy	Use preferentially bortezomib combinations, adaptation of dose of lenalidomide according to GFR mandatory

Disease specific

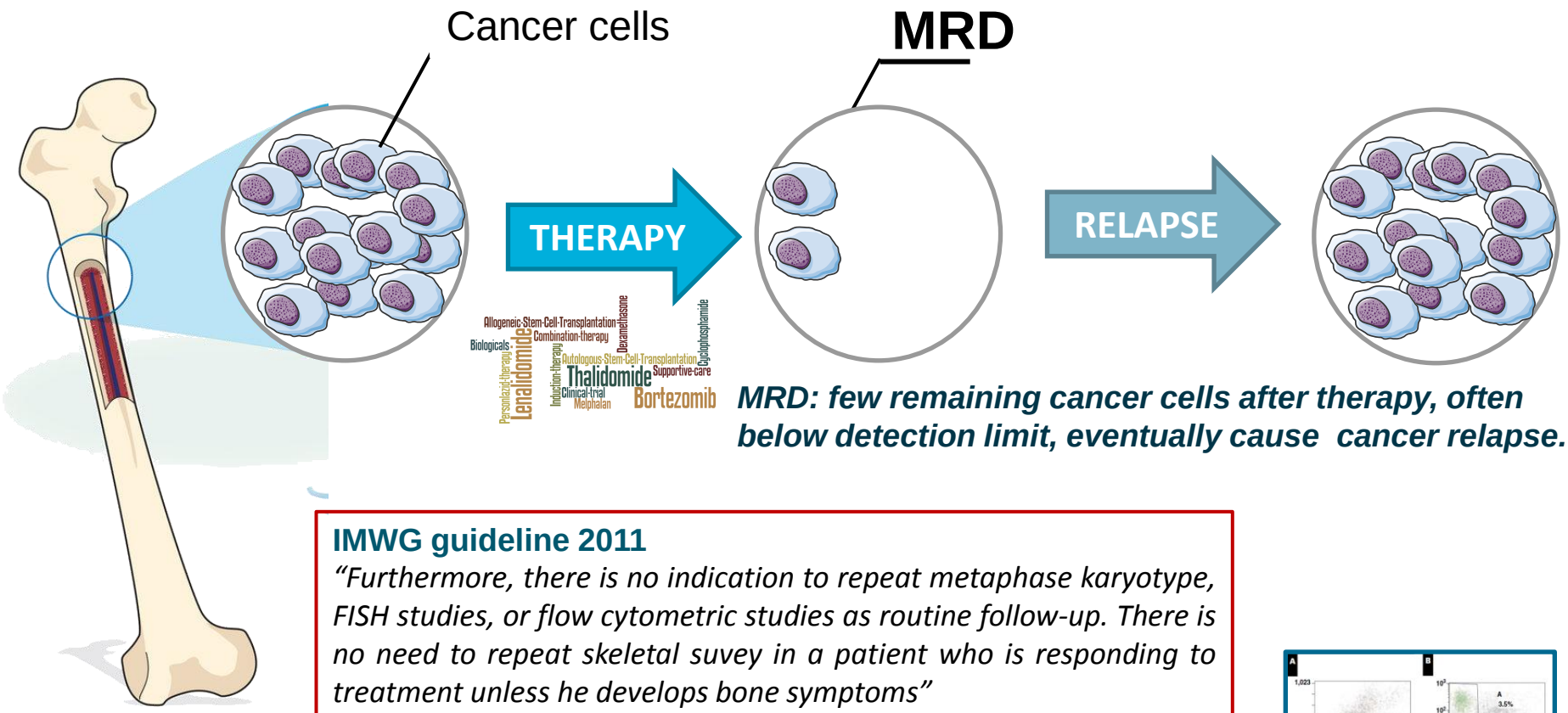
Good prognosis	Retreatment with effective and well tolerated first line regimen feasible
Symptomatic and rapidly progressive	Switch drug class, incorporate novel agents
High risk cytogenetics	Consider bortezomib combinations ± bendamustine

Treatment specific

Significant response to previous treatment, long PFS, well tolerated	Consider retreatment
Insufficient response to previous treatment	Switch drug class and change regimen
All common regimens exploited	Consider DCEP, DT-PACE, enrollment in clinical trials

IMWG guideline: Ludwig et al. Leukemia 2013

Minimal residual disease (MRD)



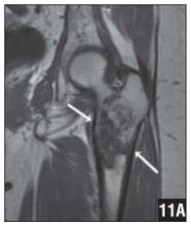
MRD: few remaining cancer cells after therapy, often below detection limit, eventually cause cancer relapse.

IMWG guideline 2011

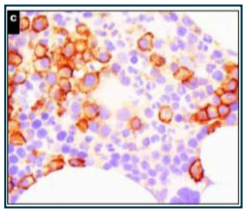
"Furthermore, there is no indication to repeat metaphase karyotype, FISH studies, or flow cytometric studies as routine follow-up. There is no need to repeat skeletal suvey in a patient who is responding to treatment unless he develops bone symptoms"

PET

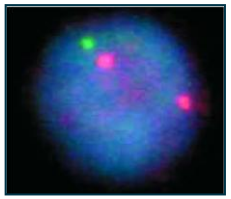
X ray



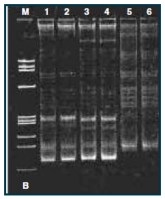
MRI



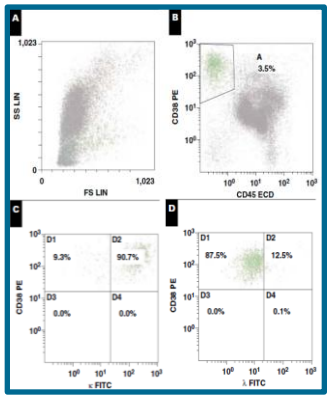
IHC



FISH



PCR



FCM

M-proteine rondzendingen

Periode 2012.4 t/m 2014.3

- 4 rondzendingen per jaar, 77 deelnemers
- Elke rondzending 3 monsters (A,B,C), soms met casus
- Invoer en rapportage via Qbase

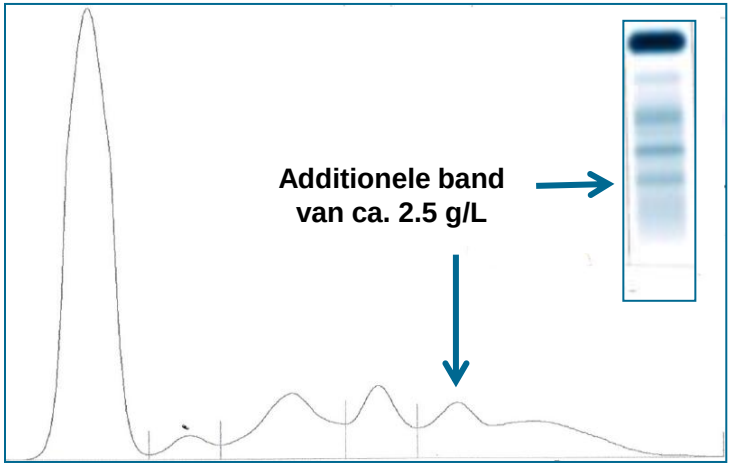
Inventarisatie:

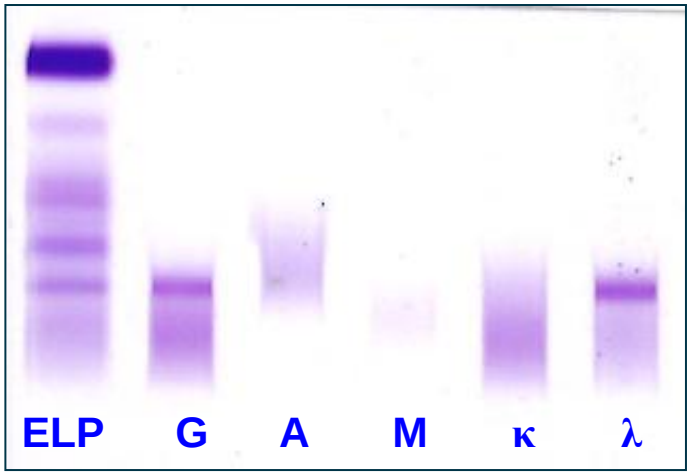
- Typering M proteine
- Kwantificering M proteine
- Kwantificering Vrije Lichte Ketens (VLK)
- Kwantificering totaal eiwit, Ig's
- Soms additionele vraag

Wat is er rondgestuurd in deze periode:

IgG-K	5x
IgG-L	3x
IgM-K	2x
IgM-L	1x
IgA-K	2x
IgA-L	2x
IgD-L	1x
VLK-L	2x
VLK-K	2x
Urine BJL	1x
Geen MPR	7x

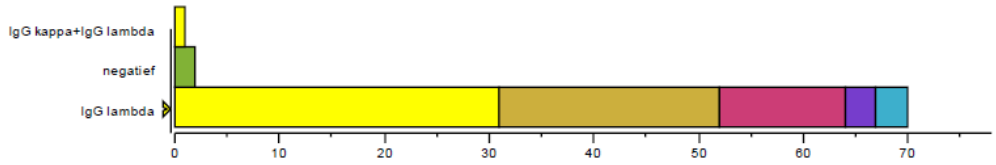
Casus 2013.3A. Weergave in MUSE.

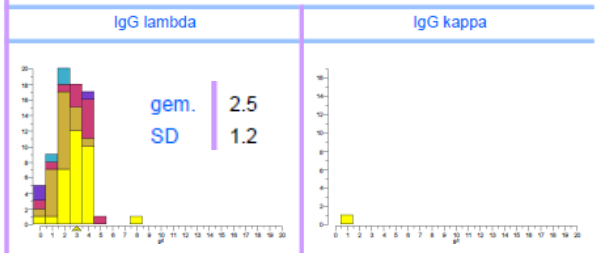




M-proteïne	Expert uitslag	Score	Uw uitslag	Score
	IgG lambda	2	IgG lambda Kwantitatief: 3 g/l	2
			Totaalscore :	2

Histogram

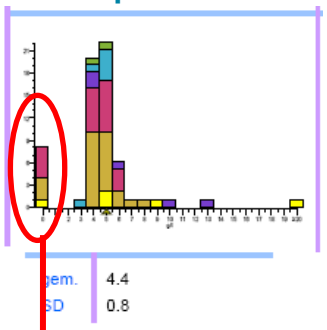




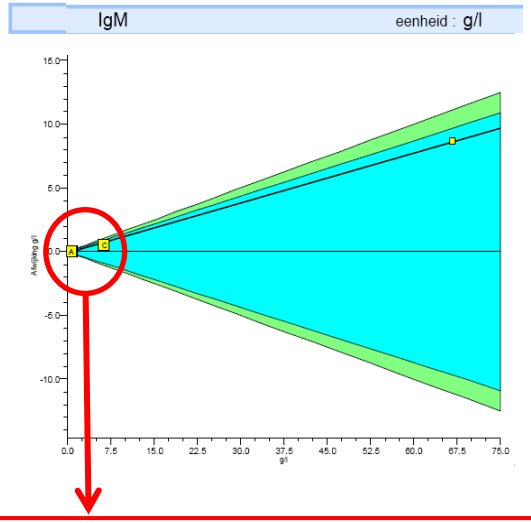
Weergave volgens MUSE is nog niet ‘af’

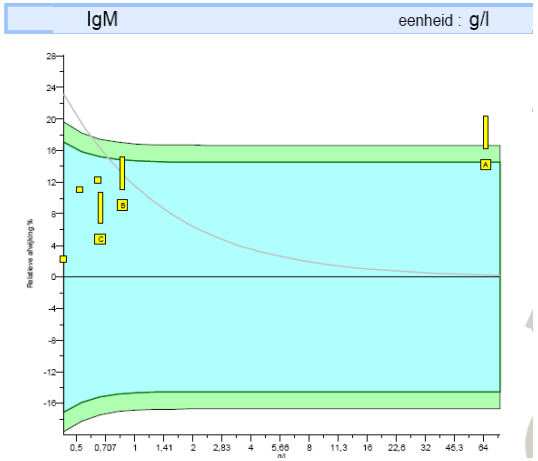
Meest recente aanpassingen

Kwantificering M-proteine



‘NTK’ en ‘NV’.
Weg uit histogram.





M-proteines (incl VLK) logaritmische schaal en relatieve afwijking

Er wordt niet meer gescoord op kwantificering van het M-proteine (niet mogelijk in nieuwe software)

Suggesties voor verbetering van invoer en weergave van uitslagen blijven welkom

Reproduceerbaarheid (tussen laboratoria)

Zelfde sample zonder M-proteine 3x rondgestuurd (serumpool patiënten met nierfalen)

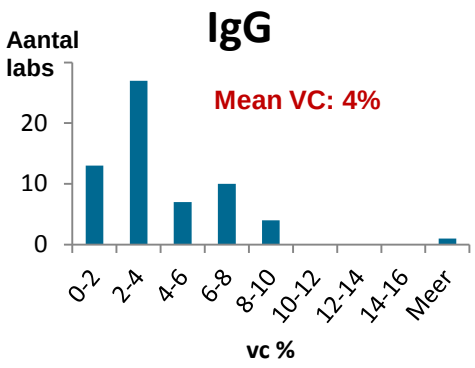
	2011.3A		2012.3A		2013.4B	
Bepaling	Mean	V.C. (%)	Mean	V.C. (%)	Mean	V.C. (%)
IgG (g/L)	9,41	5,9	9,34	7,2	9,61	5,7
IgA (g/L)	1,81	4,5	1,80	4,5	1,77	5,6
IgM (g/L)	0,73	7,9	0,71	6,7	0,73	8,3
Totaal eiwit (g/L)	63,8	3,2	63,9	3,3	64,4	3,1
sVLK kappa (mg/L)	79,3	15,6	91,3	15,6	96	12,5
sVLK lambda (mg/L)	77,8	19,5	76,7	13,4	83	8,4
FLC-ratio (kappa/lambda)	1,003	12,6	1,135	12,9	1,175	17,7

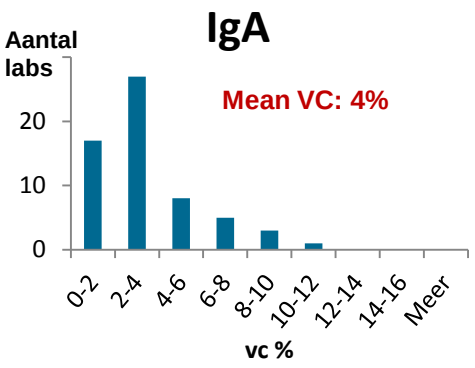
- Ig's stabiel en homogeen

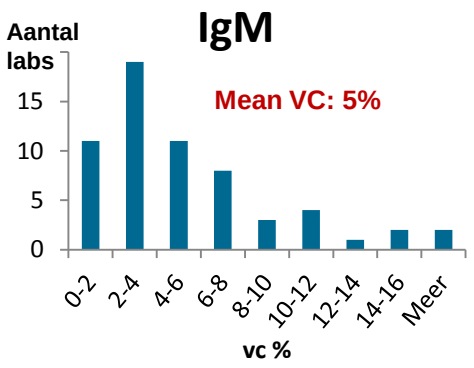
Pattenden et al. Ann Clin Biochem 2007
Jacobs et al. Clin Chem Lab Med 2014

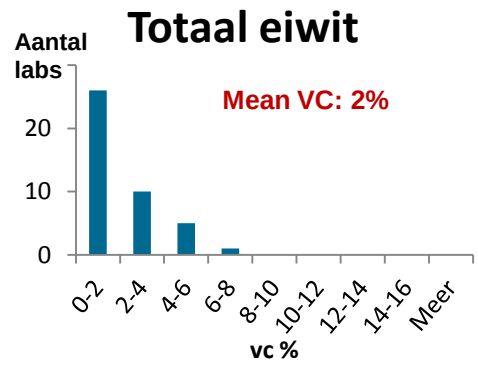
Reproduceerbaarheid (binnen laboratoria)

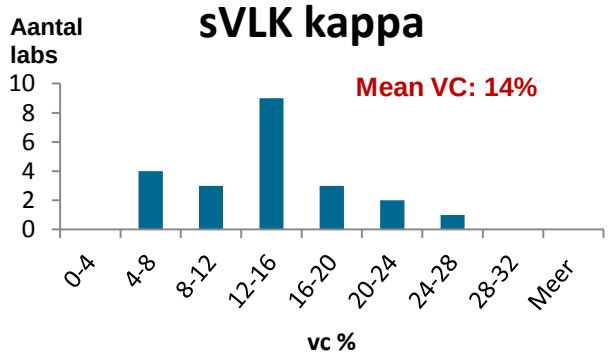
Alleen analyses gedaan indien lab alle drie de resultaten rapporteerde

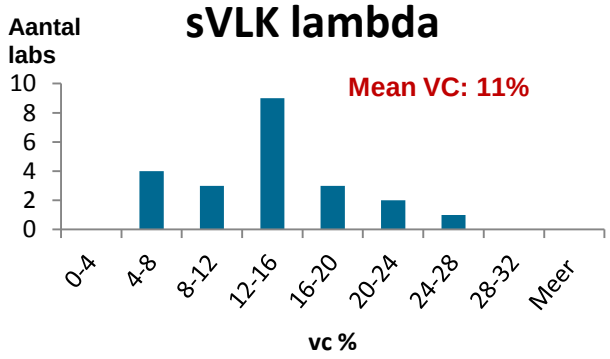


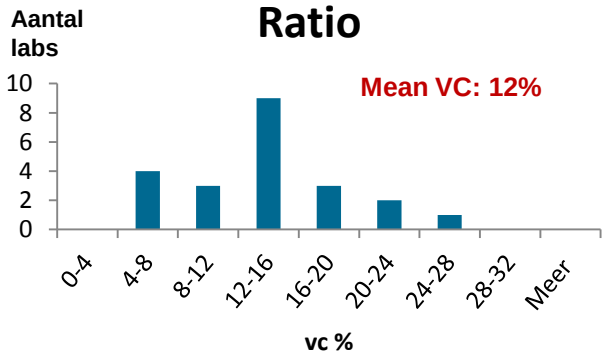






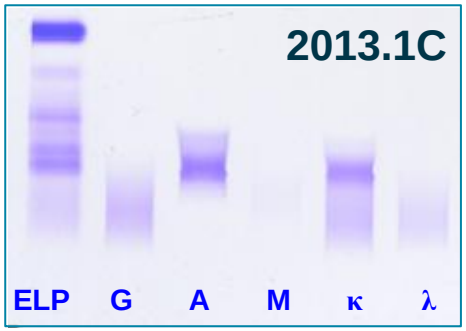


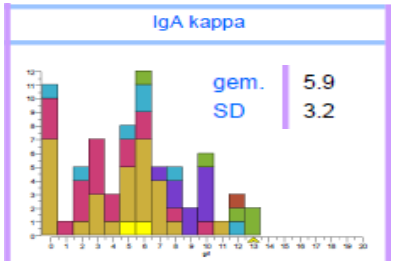




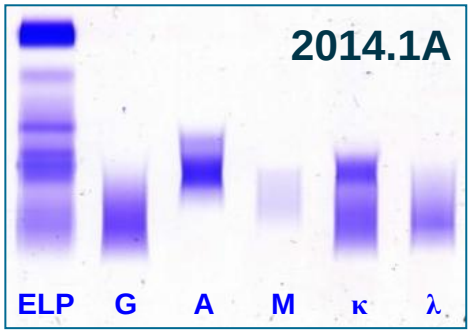
Tate et al. Clin Biochem Rev 2009

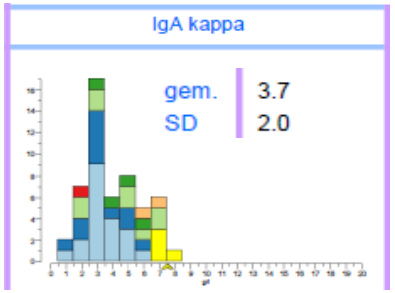
IgA kappa M-proteine in β-gebied



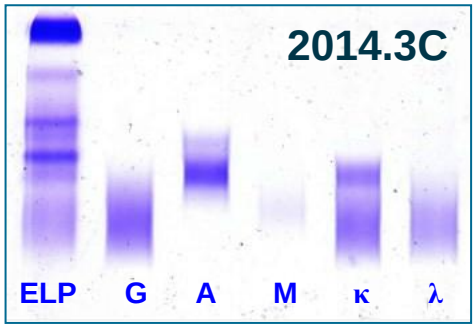


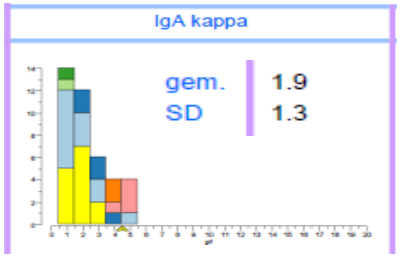
97 % typeert correct.
ALTM IgA = 11.5 g/L





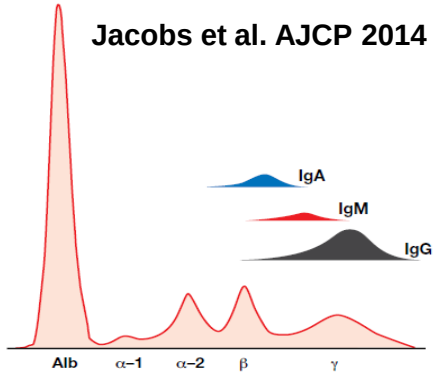
97 % typeert correct.
ALTM IgA = 9.0 g/L





93 % typeert correct.
ALTM IgA = 4.4 g/L

Jacobs et al. AJCP 2014



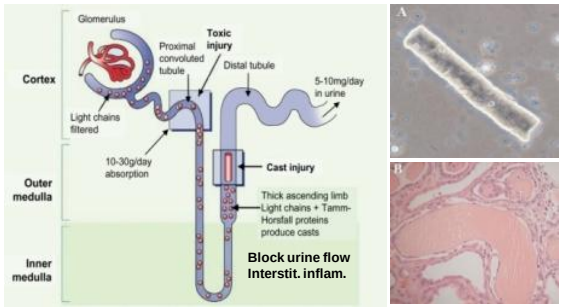
- M-proteine wordt gemist indien ESP niet kritisch bekeken
- Kwantificeren is lastig, spiken is niet mogelijk…
- ‘Second best’ is immunochemisch totaal IgA (cave polyclonaal IgA)

Richtlijn M-proteine diagostiek: Ruinemans-Koerts et al. NTvH 2011

Radboudumc

Multipel myeloom en nierschade

hyperCalcemia, Renal impairment, Anemia, Bone disease (CRAB diagnostic criteria MM)



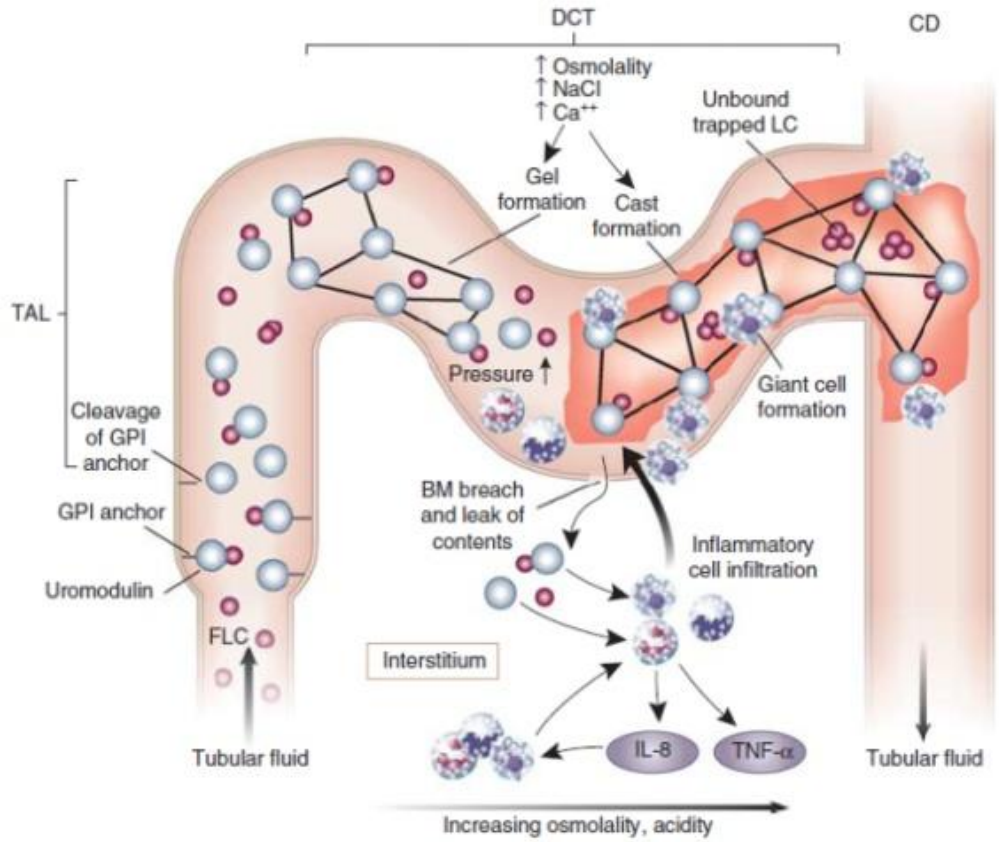
Multiple myeloma at initial presentation

- 18-50% renal impairment (serum creat ↑)
- 12-15% acute renal failure
- 8% become dialysis dependent

Pathology

- Cast nephropathy (myeloma kidney)
- Light chain (AL) amyloidosis
- Light chain deposition disease
- Hypercalcemia
- Nephrotoxic drugs
- Hyperviscosity syndrome
- Monoclonal Ig deposition disease

…



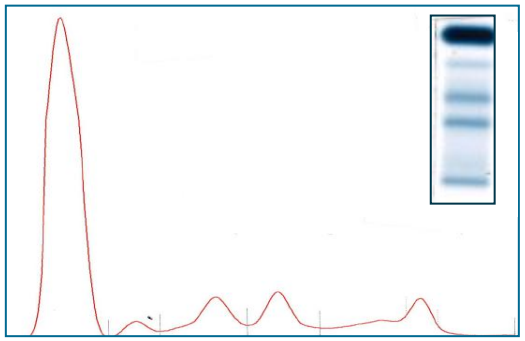
Dimopoulos et al. J Clin Oncol 2010
Basnayake et al. Kidney Int 2011

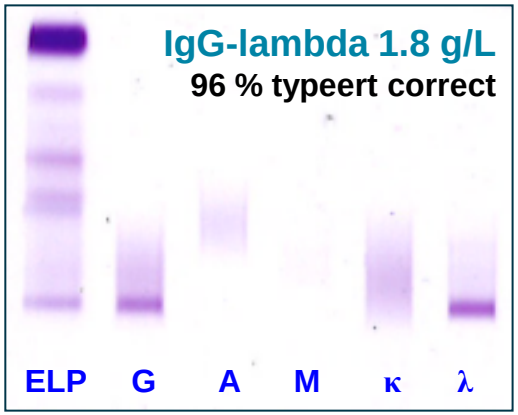
Radboudumc

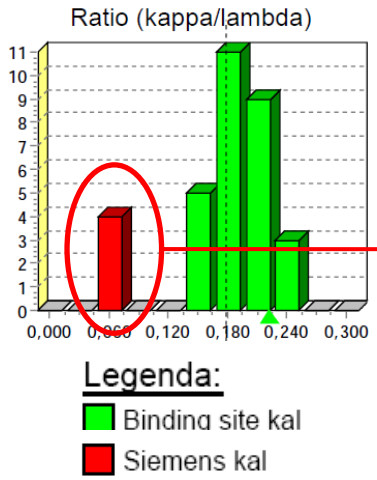
Casus 2012.4A.: MGUS, of toch minder onschuldig?

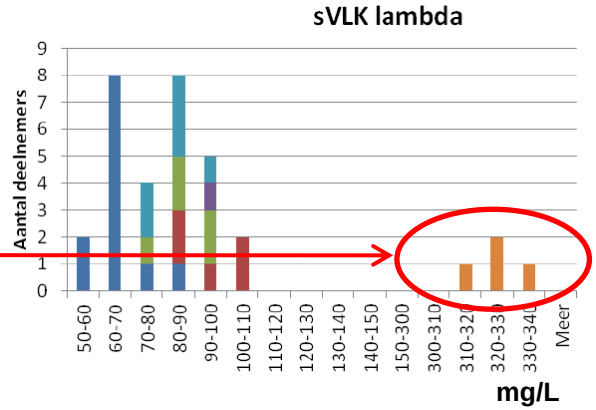
MGRS: Monoclonal Gammopathy of Renal Significance

- 60 jarige man onder behandeling bij nefroloog met voornamelijk oedeem klachten
- Membranoproliferatieve glomerulonefritis type 1 (PA-verslag: lambda restrictie)
  MPGN: infectieus, sytemische AI, complement stoornis









- Voldoet niet aan de criteria van MM
  (volgens criteria: MGUS…)

Te Velthuis et al. Clim Chem Lab Med 2011
Hoedemakers et al. Clim Chem Lab Med 2011.

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MGRS: Monoclonal Gammopathy of Renal Significance

Table 1. Pathologic classification of diseases with tissue deposition or precipitation of monoclonal Ig

Organized			Nonorganized (granular)	
Crystals	**Fibrillar**	**Microtubular**	**MIDD (Randall type)**	**Other**
Myeloma cast nephropathy	Light chain amyloidosis	Type I and type II cryoglobulinemic glomerulonephritis	LCDD	Proliferative GN with monoclonal Ig deposits
Light chain proximal tubulopathy (with or without Fanconi syndrome)	Nonamyloid	Immunotactoid GN	LHCDD	Waldenström
Crystal-storing histocytosis	Fibrillary GN*	GOMMID	HCDD	Macroglobulinemia

GN indicates glomerulonephritis; GOMMID, glomerulonephritis with organized microtubular monoclonal Ig deposits; LCDD, light-chain deposition disease; LHCDD, light- and heavy-chain deposition disease; and HCDD, heavy-chain deposition disease.

*Mostly associated with polyclonal IgG deposits.

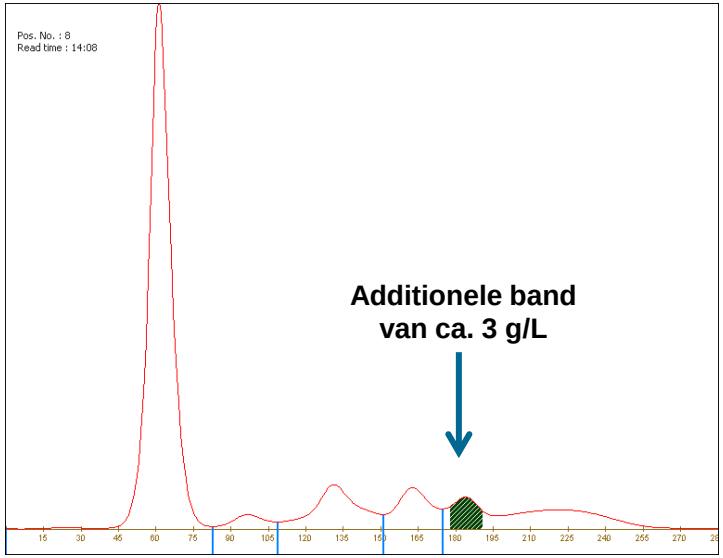
MGRS

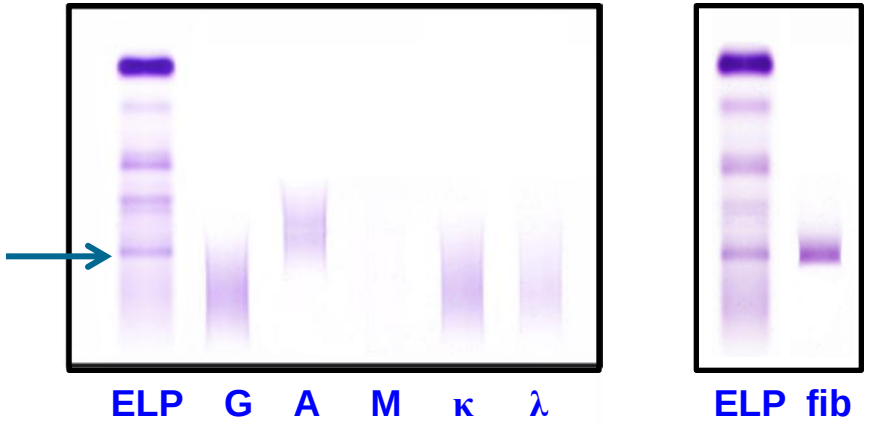
- **Hematologisch lijkend op MGUS**
- **Met daarbij causaal verband tussen M proteïne en nierschade**
- **Verschillende histopathologische beelden en lokalisaties in het nefron**
- **Behoud en herstel nierfunctie is mogelijk bij adequate behandeling clonale gammopathie**
- **Bereik van hematologische complete remissie voorkomt rejectie na niertransplantatie**
- **Behandeling gericht op verbeterde nierfunctie, niet op betere overleving**
- **Behandel-regime nu gebaseerd op ervaringen bij behandeling van MM**
- **Grote klinische trials voor behandeling MGRS worden nu gestart**

Leung et al. Blood 2012
Fermand et al. Blood 2013

Casus 2013.2B.

Fibrinogeen: wel een extra band, geen M-proteine





Fibrinogeen:

- plasma
- serum niet voldoende gestold
- ligging in het spectrum zeer karakteristiek

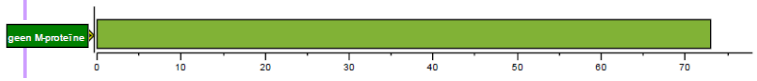
Rapportage bij sera zonder M-proteine

➢ **95 % van de deelnemers rapporteert terecht geen M-proteine**

2013.3B

M-proteïne	Expert uitslag	Score	Uw uitslag	Score
	Geen M-proteïne	2	Geen M-proteïne Kwantitatief: g/l	2
			Totaalscore :	2

Histogram

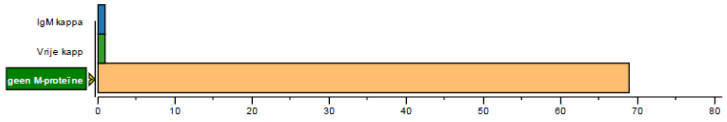


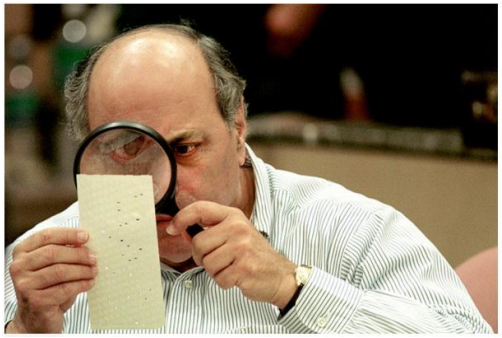
Indien er een M-proteine wordt gerapporteerd dan (doorgaans) ‘NTK’

2013.4C

M-proteïne	Expert uitslag	Score	Uw uitslag	
	Geen M-proteïne	2	Geen M-proteïne	✓
			Totaalscore :	2

Histogram





Hoe duidelijk moet een bandje zijn voordat je rapporteert?

Relevantie van kleine bandjes…?

Laboratory Persistence and Clinical Progression of Small Monoclonal Abnormalities AJCP, 138:609, 2012

David L. Murray, MD, PhD,[1] Justin L. Seningen, MD,[1] Angela Dispenzieri, MD,[1,2] Melissa R. Snyder, PhD,[1] Robert A. Kyle, MD,[1,2] S. Vincent Rajkumar, MD,[2] and Jerry A. Katzmann, PhD[1,2]

- Dysproteinemia Database
- Termed IFE M-proteins
- 439 patients at least one Follow-up
- Median follow-up 3.9 yrs (0.2-13 yrs)
- 3.2% progressed
- About 1% per year

Murray et al AJCP, 138:609, 2012

Type of Clinical Progression in Patients With IFE MGUS

Disease	Sex	Ig Class	Time to Progression, y
Multiple myeloma	M	IgA	1.0
	F	IgG	2.8
	M	IgA	9.9
	M	IgA	2.1
	M	IgG	3.5
	F	IgG	1.7
	F	IgA	1.3
	F	IgA	2.5
Smoldering myeloma	M	IgA	5.1
	M	IgA	4.5
Primary amyloidosis	M	IgG	4.5
Light chain deposition disease	F	IgG	8.9
Extramedullary myeloma	F	IgG	0.4
Lymphoplasmacytic lymphoma	F	IgA	5.6

IFE immunofixation electrophoresis; Ig, immunoglobulin; MGUS, monoclonal gammopathy of undetermined significance.

Samenvatting van dubieuze banden (NTK):

- **84% van patienten persisteerd het M-proteine tijdens follow-up**
- **1% per jaar van de patienten vertoont klinische progressie**
- **8 ‘progressors’ zijn IgA**
- **6 ‘progressors’ zijn IgG**

Murray et al. American J Clin Pathol 2012

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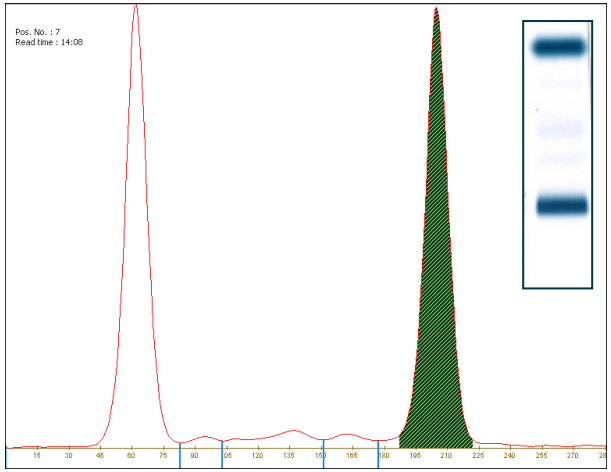
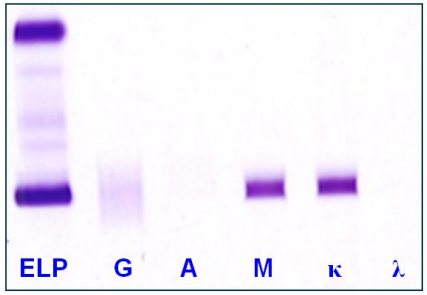
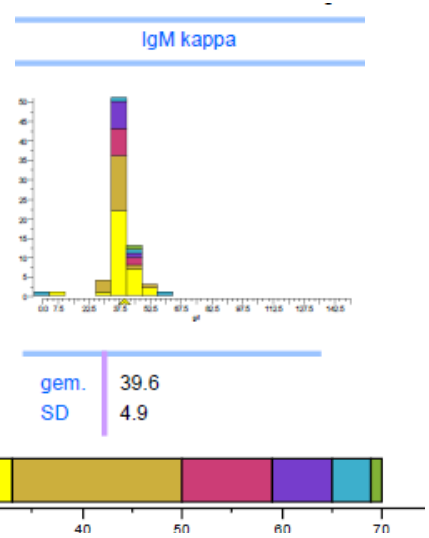
Casus 2013.2A.

IgM kappa M-proteine

- 65 jarige man meldt zich bij huisarts
- Vermoeidheid, verminderde visus, krachtsverlies en tintelingen in handen en voeten
- Lichamelijk onderzoek: vergrootte milt + div. lymfeklieren → Hematoloog



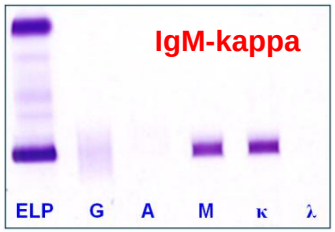


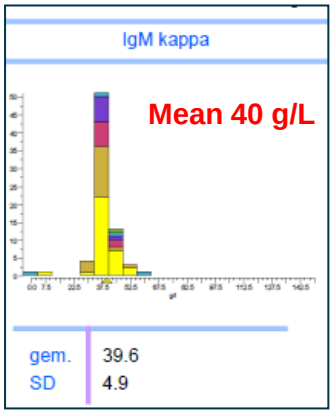


- Diagnose macroglobulinemie (ziekte van Waldenström)
- Klachten doorgaans op basis van:
  - onderdrukt beenmerg (infecties en bloedingen)
  - hyperviscositeit van bloed (verminderde visus, krachtsverlies, perifere neuropathie)
- Behandeling: chemotherapie / rituximab / autologe SCT / plasmaferese

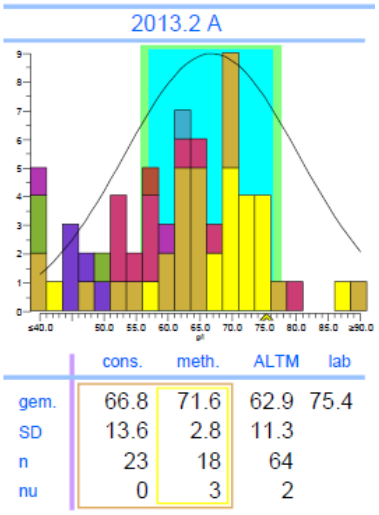
Casus 2013.2A.

Analytische problemen bij hoge concentratie M-proteine



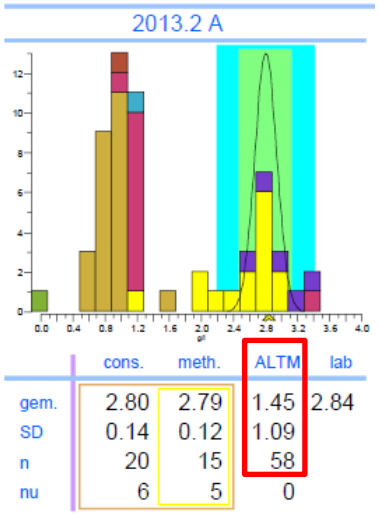


Totaal IgM



Mean 63 g/L

Totaal IgG



- **Vaak slechte correlatie M-proteine concentratie: Immunochemisch vs Electrophorese**
- **Hoge concentratie M-proteine kan interfereren met andere analyses:**
  - **Ig-bepalingen, electrolyten, Vrije Lichte Ketens…**

Jelinek and Bachmann. Clin Chemistry 2014
Jacobs et al. Clin Chim Acta 2012
Ruinemans et al. NTVH 2009

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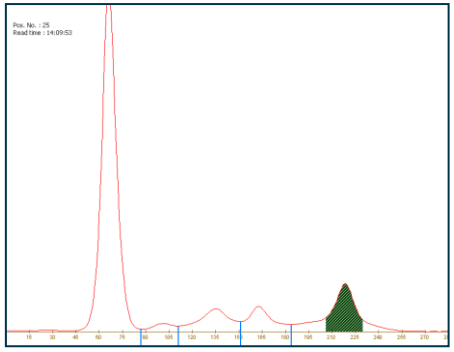
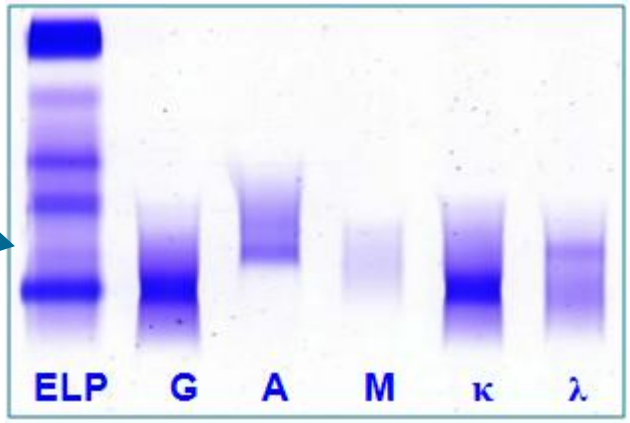
2014.1C.

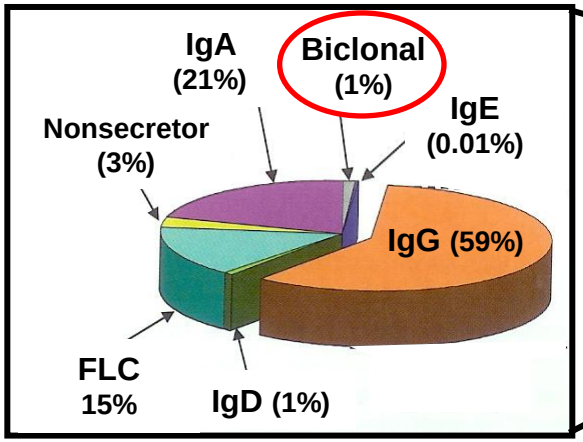
2 banden: IgG-kappa en IgA-lambda

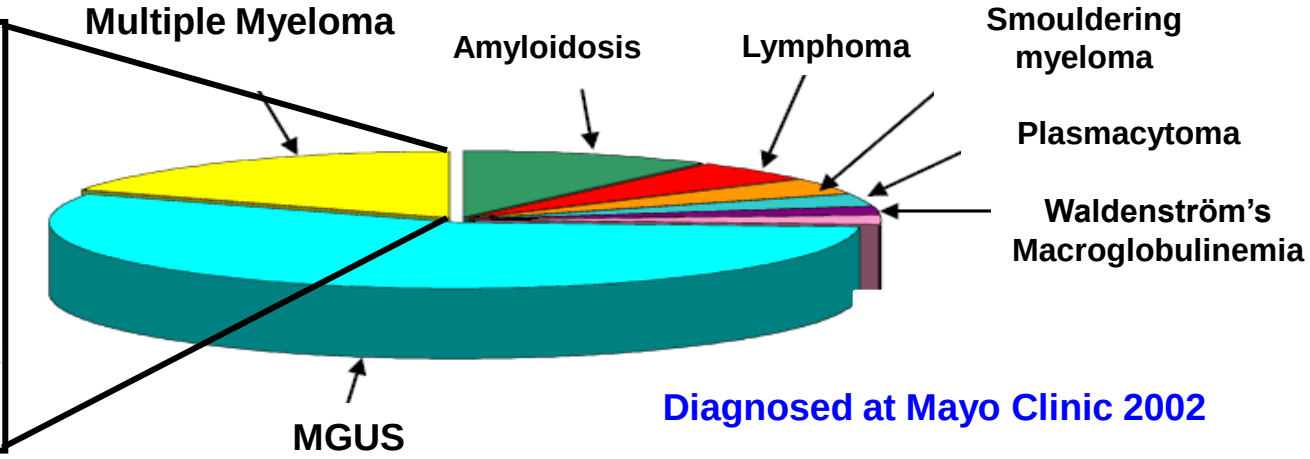


IgA-lambda < 2 g/L

IgG-kappa 7 g/L





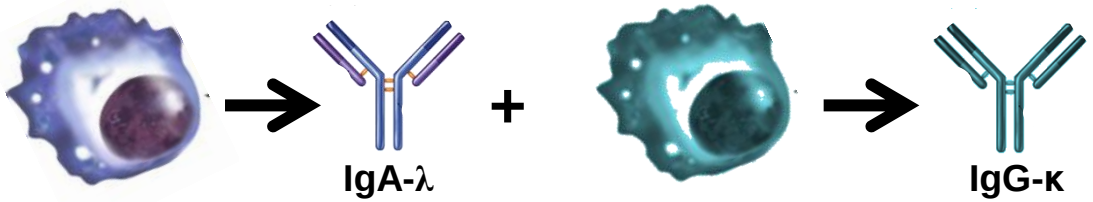


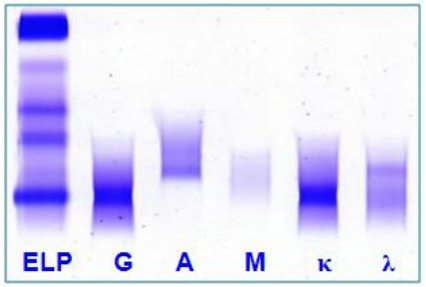
Diagnosed at Mayo Clinic 2002

Kyle et al. Am J of Med 1981

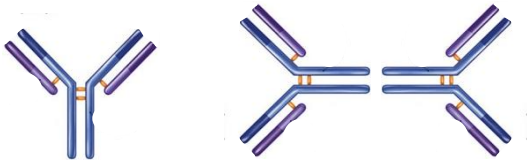
2 banden in het eiwitspectrum: biclonaal of monoclonaal?

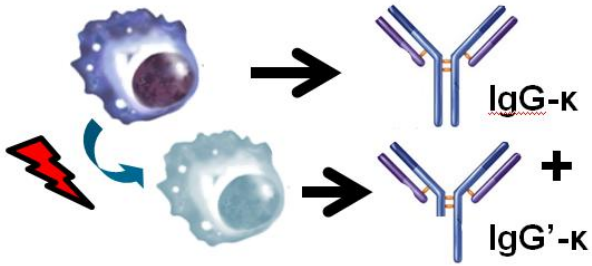
Altijd biclonaal indien verschillende lichte ketens

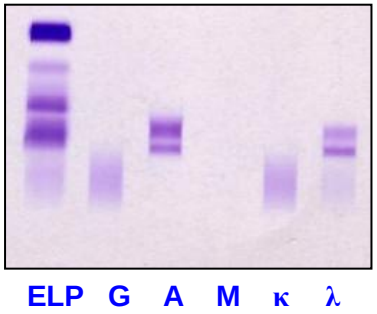


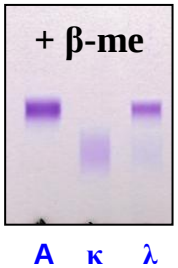


Monoclonaal ?





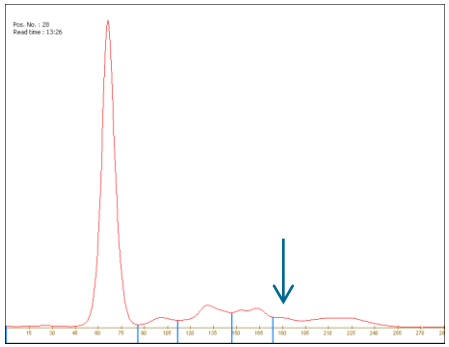


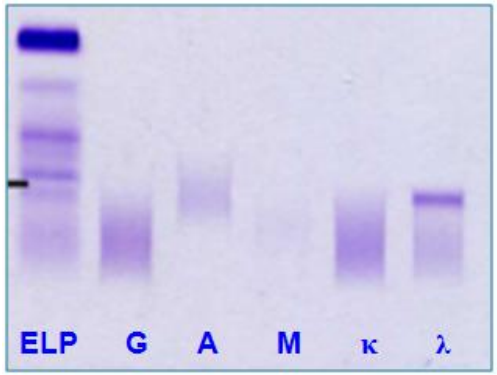


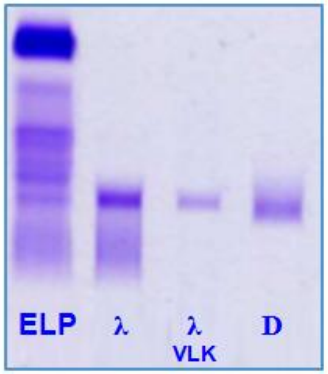
Casus 2013.1A.

Cardiomyopathie

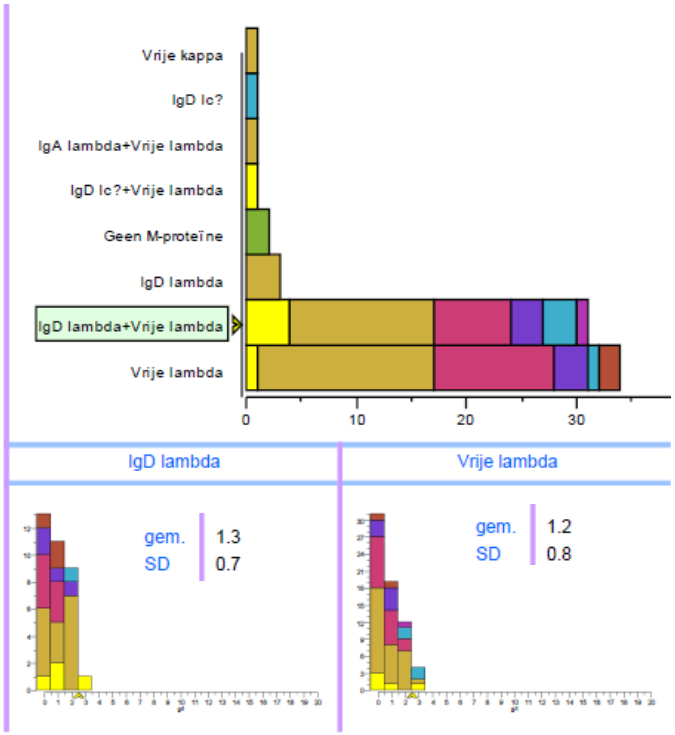
- 58 jarige man met blanco voorgeschiedenis meldt zich bij huisarts.
- Extreme moeheid, tintelende vingers en progressieve kortademigheid.
- Patiënt heeft geen koorts, beetje oedeem rond enkels.
- Verwezen naar cardioloog i.v.m. eiwit in urine + afwijkend ECG.
- Cardioloog constateert een snel progressief hartfalen.







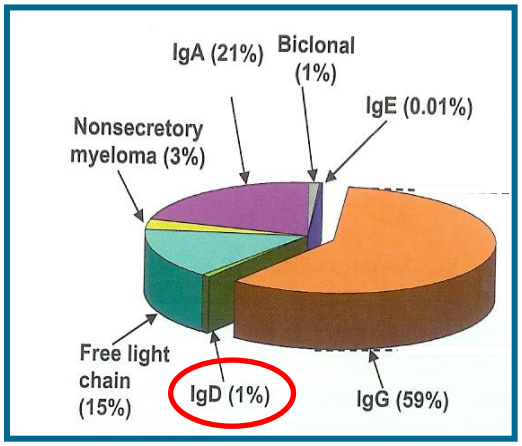
Histogram



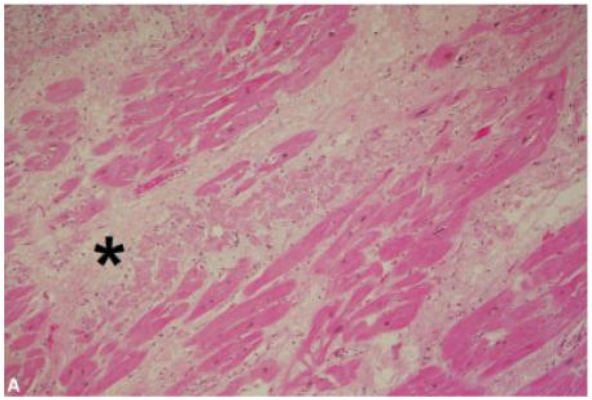
Casus 2013.1A.

IgD multipel myeloom + amyloidose

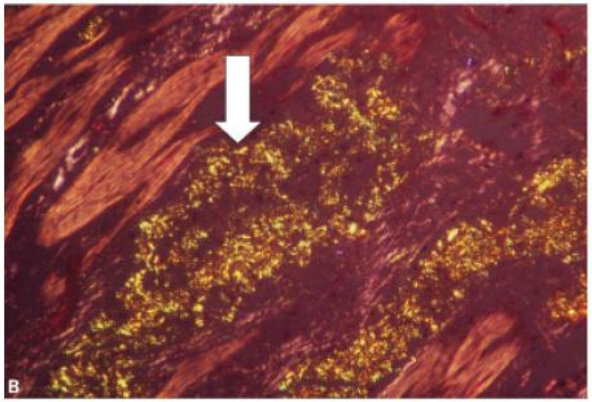
- Zeldzaam (circa 1% van de MM patiënten)
- Relatief slechte prognose
- Vaak al klinische symptomen bij lage [M-prot.]
- Vaak samen met monoclonale VLK (AL-amyloidose)
- Diagnose bevestigd met PA
- Klachten afhankelijk van localisatie amyloid
- Nefrotisch syndroom, cardiomyopathie, perifere neuropathie



Diagnosed at Mayo clinic 2002



HE-kleuring

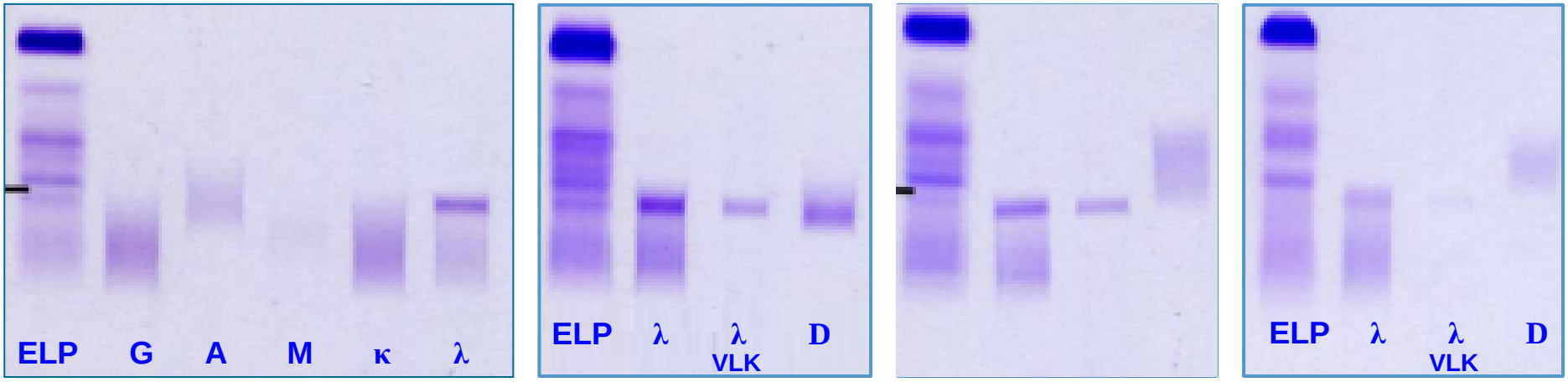


Congo-rood-kleuring

Bahat et al. Amyloid 2007

Casus 2013.1A.

Stabiliteit IgD M-proteine



Binnen 1 week na ontvangst monster (4ºC) — 3 wkn (4ºC) — 4 mnd (4ºC)

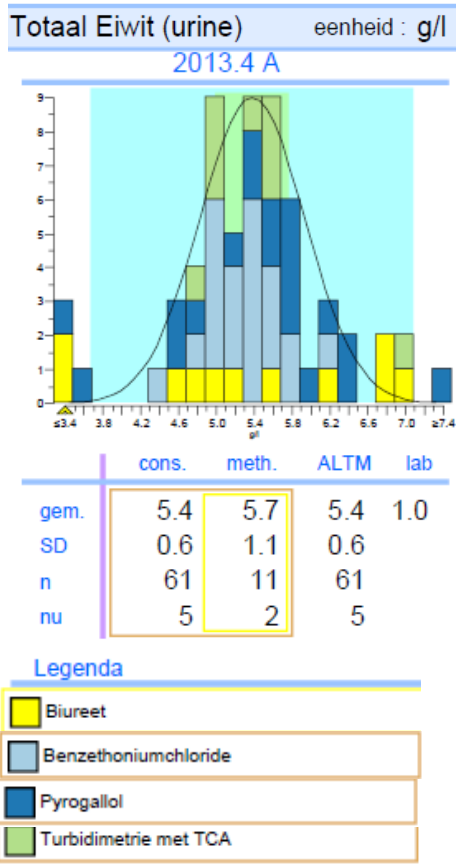
- IgD M-proteines zijn minder stabiel dan andere M-proteines
- IgD M-proteines kunnen al na enkele weken bij 4ºC spontaan degraderen

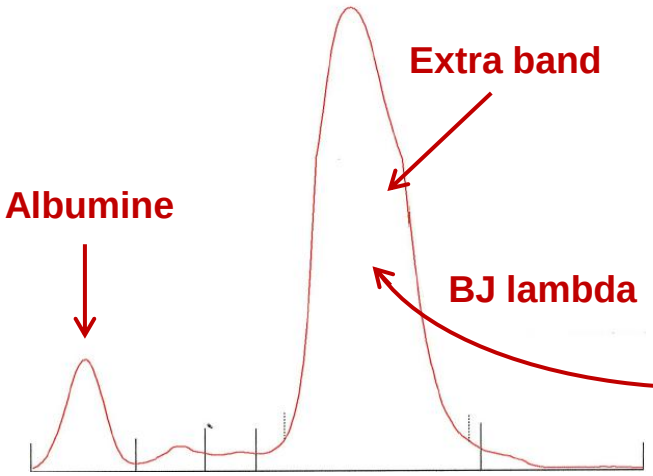
Griffiths et al. J Biol Chem 1972: spontaneous proteolytic degradation of IgD
Spiegelberg et al. Biochem 1970: structural studies of IgD M protein

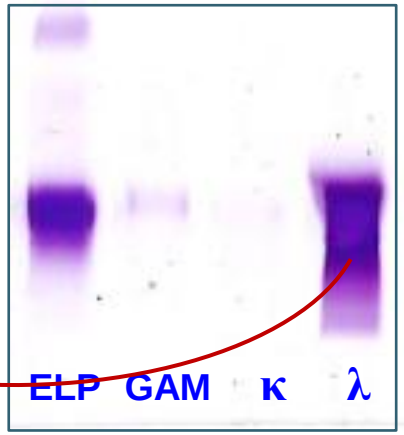
Casus 2013.4A.

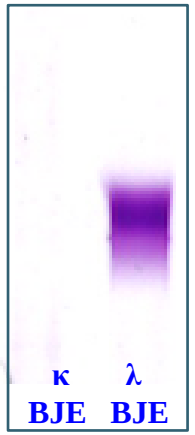
Bence Jones eiwitten

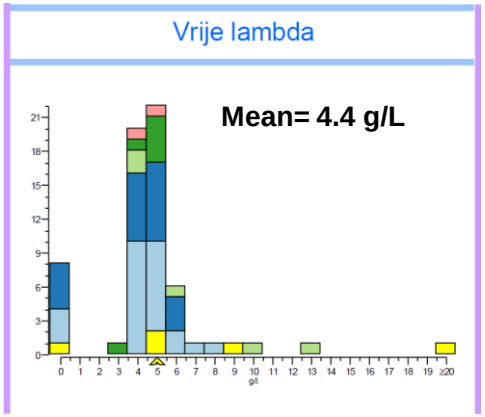
- Kwantificeren middels totaal eiwit in urine en spike in electrophorese











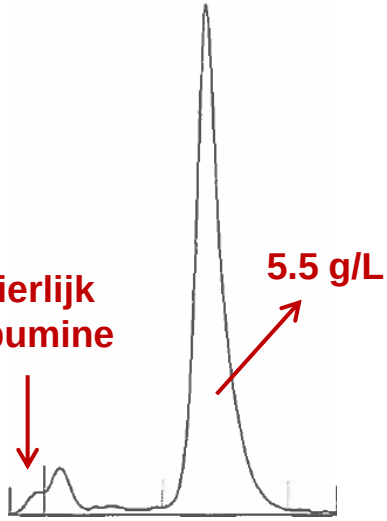
- Totaal eiwit meting in urine is vaak onnauwkeurig in aanwezigheid van BJE
- Alle beschreven methodes hebben moeite met de detectie van micro-eiwitten

Maisner et al. Clin. Biochem. 2011
Van Beek et al. NTKC 2012

Casus 2013.4A.

Kwantitatief BJE d.m.v. gelelectrophorse met interne standaard

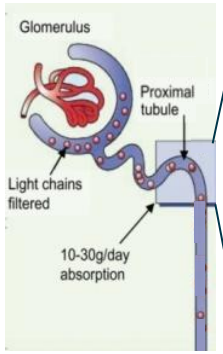
Bekende conc. dierlijk albumine
Toegevoegd aan vast volume urine



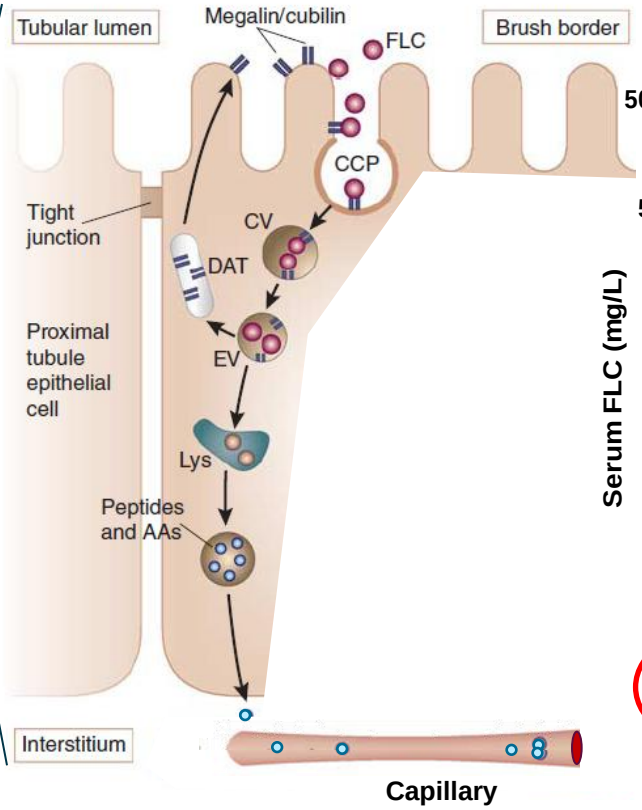
- Concentratie dierlijk albumine is bekend
- Alle fracties worden afgezet tegen deze standaard
- Methode is onafhankelijk van totaal eiwit bepaling

Van Beek et al. NTKC 2012

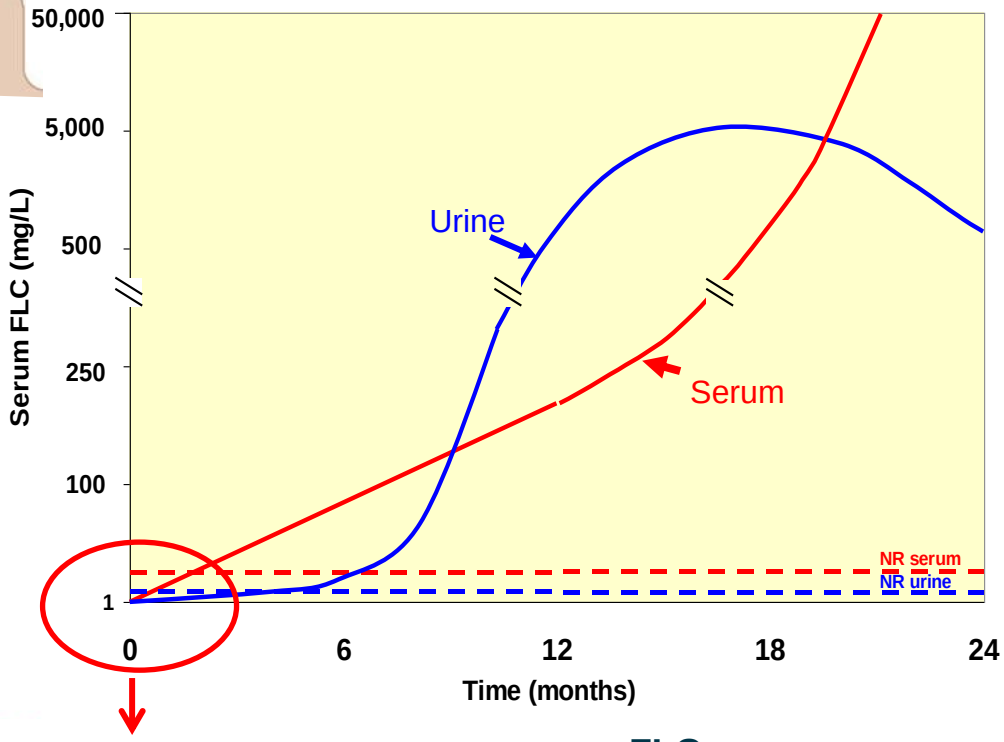
Can sFLC replace urine BJP analysis?



Max capacity 10-30 g/day



Effect of renal tubular reabsorption on urine FLC



Median sFLC required to produce overflow proteinuria	
sFLC kappa	113 mg/L (wide range)
sFLC lambda	278 mg/L (wide range)

uBJP \ sFLC	-	+
-	164	118
+	9	87

N=378 samples (from 82 MMpts)

Basnayake et al. Kidney Int 2011
Bradwell. sFLC analysis 6th edition
Nowrousian et al. Clin Cancer Res 2005

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Urine immunofixation electrophoresis complementary to sFLC

Table 3 Four hundred and twenty-eight patients with urinary monoclonal protein detected by immunofixation electrophoresis[20]

Laboratory test	*% abnormal*
Serum immunofixation electrophoresis	93.5
Serum protein electrophoresis	80.8
Serum FLC κ/λ ratio	85.7
Serum immunofixation electrophoresis or FLC ratio	99.5

Table 4. Results in 5 patients in whom the combination of serum immunofixation and κ/λ ratio failed to identify the amyloidogenic light chain.

ID	Sex	Serum IFE	Urine IFE	κ FLC, mg/L	λ FLC, mg/L	FLC κ/λ ratio[a]	IEH typing	Creatinine, μmol/L[b]	Organs involved	Cardiac stage[c]
2	F	Not detected	Free λ	29.0	60.3	0.48 (Normal)	λ	71	Kidney	I
5	M	Not detected	Free λ	11.2	11.7	0.96 (Normal)	λ	156	Kidney	I
39	F	Not detected	Free λ	22.3	37.8	0.59 (Normal)	λ	97	Heart	II
61	M	Not detected	Free λ	9.7	24.7	0.39 (Normal)	λ	94	GI[d]	I
91	F	Not detected	Free λ	53.5	71.3	0.75 (Normal)	λ	126	Kidney, heart, GI, PNS	III

[a] Also applying the recently published (8) new reference range for FLC ratio (0.37–3.1) for patients with abnormal renal function, the results do not change.
[b] Upper reference limit: males 115 μmol/L, females 97 μmol/L.
[c] Stages of cardiac involvement according to Dispenzieri et al. (7).
[d] GI, gastrointestinal system; PNS, peripheral nervous system.

Katzmann et al. Mayo Clin Proc 2006
Palladini et al. Clin Chem 2009 (AL amyloidosis)
Levinson (several casuistic literature)

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Bence Jones Protein analysis in guidelines

"Both serum and urine should be assessed for monoclonal protein. Agarose gel electrophoresis or capillary zone electrophoresis of serum and urine is preferred to screen for the presence of monoclonal protein."

Table 2. Laboratory tests for multiple myeloma

History and physical examination
Complete blood count and differential; peripheral blood smear
Chemistry screen, including calcium and creatinine
Serum protein electrophoresis, immunofixation
Nephelometric quantification of serum immunoglobulins
Routine urinalysis, 24-hour urine collection for electrophoresis and immunofixation
Bone marrow aspirate and/or biopsy
Cytogenetics (metaphase karyotype and FISH)
Radiologic skeletal bone survey, including spine, pelvis, skull, humeri, and femurs; magnetic resonance imaging in certain circumstances
Serum β_2-microglobulin and lactate dehydrogenase
Measurement of serum-free light chains

IMWG guideline 2011

Diagnosis

Routine urinalysis is important in suspected myeloma. For screening, a random urine protein electrophoresis and urine immunofixation may be performed. Once a diagnosis of myeloma is suspected or established, all patients should undergo 24-hour urine collection to calculate the amount of proteinuria. An aliquot from an adequately concentrated 24-hour specimen should be sent for electrophoresis. A monoclonal protein appears as a homogeneous peak in the densitometer tracing. Its concentration can be calculated on the basis of the size of the peak and the amount of total protein in the 24-hour urine specimen. Immunofixation of an aliquot from a concentrated 24-hour urine collection is required to confirm the presence and type of heavy and light chain.[4] Immunofixation should be performed even if there is no measurable protein and even if there is no peak on urine electrophoresis. A 24-hour urine collection cannot be replaced by a morning urine sample. The use of random urine samples with analytes corrected relative to creatinine concentration requires further evaluation but cannot be recommended at this point. Measurement of urine-free light chain levels or urine total κ and total λ levels is not recommended.

myeloma.[11] Serum-free light chain estimation does not obviate the need for 24-hour urine studies. Serum-free light chains may be

Follow-up

follow-up of his disease. For patients with light chain myeloma, 24-hour urine collection with total protein and urine electrophoresis to quantify Bence Jones proteinuria is recommended. For patients with nonsecretory or oligosecretory myeloma, the free light chains should be serially assessed. For most patients, there is no necessity for bone marrow examination to assess response, provided that the myeloma can be monitored with serum and urine studies and there is no indication to change the patient's treatment.

Dimopoulos et al. Blood 2011

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Added value of different screenings panels

Table 2. Sensitivity of monoclonal gammopathy screening panels.

	n	All 5 tests	Serum PEL and IFE; urine IFE	Serum PEL, IFE, and FLC	Serum PEL and FLC	Serum IFE	Serum PEL	Serum FLC
Diagnosis, n								
All	1877	1851	1821	1828	1770	1632	1482	1395
MM	467	467	461	467	467	441	409	452
Macroglobulinemia	26	26	26	26	26	26	26	19
SMM	191	191	191	191	190	188	180	155
MGUS	524	524	524	509	465	486	429	222
Plasmacytoma	29	26	26	26	25	21	21	16
POEMS	31	30	30	30	23	30	23	3
Extramedullary plasmacytoma	10	2	2	1	1	1	1	1
Primary AL	581	570	547	564	559	429	383	513
LCDD	18	15	14	14	14	10	10	14
Diagnosis, %								
All		98.6	97.0	97.4	94.3	87.0	79.0	74.3
MM		100.0	98.7	100.0	100.0	94.4	87.6	96.8
Macroglobulinemia		100.0	100.0	100.0	100.0	100.0	100.0	73.1
SMM		100.0	100.0	100.0	99.5	98.4	94.2	81.2
MGUS		100.0	100.0	97.1	88.7	92.8	81.9	42.4
Plasmacytoma		89.7	89.7	89.7	86.2	72.4	72.4	55.2
POEMS		96.8	96.8	96.8	74.2	96.8	74.2	9.7
Extramedullary plasmacytoma		20.0	20.0	10.0	10.0	10.0	10.0	10.0
Primary AL		98.1	94.2	97.1	96.2	73.8	65.9	88.3
LCDD		83.3	77.8	77.8	77.8	55.6	55.6	77.8

Table 3. Screening panels for different plasma cell disorders.

	Serum PEL	Serum FLC	Serum IFE	Urine PEL/IFE
MM	Yes	Yes		
WM	Yes	Yes		
SMM	Yes	Yes		
MGUS	Yes	Yes		
Plasmacytoma	Yes	Yes	Yes	
POEMS	Yes	Yes	Yes	
AL	Yes	Yes	Yes	Yes
LCDD	Yes	Yes	Yes	Yes

Katzmann et al. Screening panels. Clin Chem. 2011

National guidelines can deviate from IMWG guidelines

IMWG guideline 2011

Routine urinalysis is important in suspected myeloma. For screening, a random urine protein electrophoresis and urine immunofixation may be performed. Once a diagnosis of myeloma is suspected or established, all patients should undergo 24-hour urine collection to calculate the amount of proteinuria. An aliquot from an adequately concentrated 24-hour specimen should be sent for electrophoresis. A monoclonal protein appears as a homogeneous peak in the densitometer tracing. Its concentration can be calculated on the basis of the size of the peak and the amount of total protein in the 24-hour urine specimen. Immunofixation of an aliquot from a concentrated 24-hour urine collection is required to confirm the presence and type of heavy and light chain.[4] Immunofixation should be performed even if there is no measurable protein and even if there is no peak on urine electrophoresis. A 24-hour urine collection cannot be replaced by a morning urine sample. The use of random urine samples with analytes corrected relative to creatinine concentration requires further evaluation but cannot be recommended at this point. Measurement of urine-free light chain levels or urine total κ and total λ levels is not recommended.

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Diagnosis

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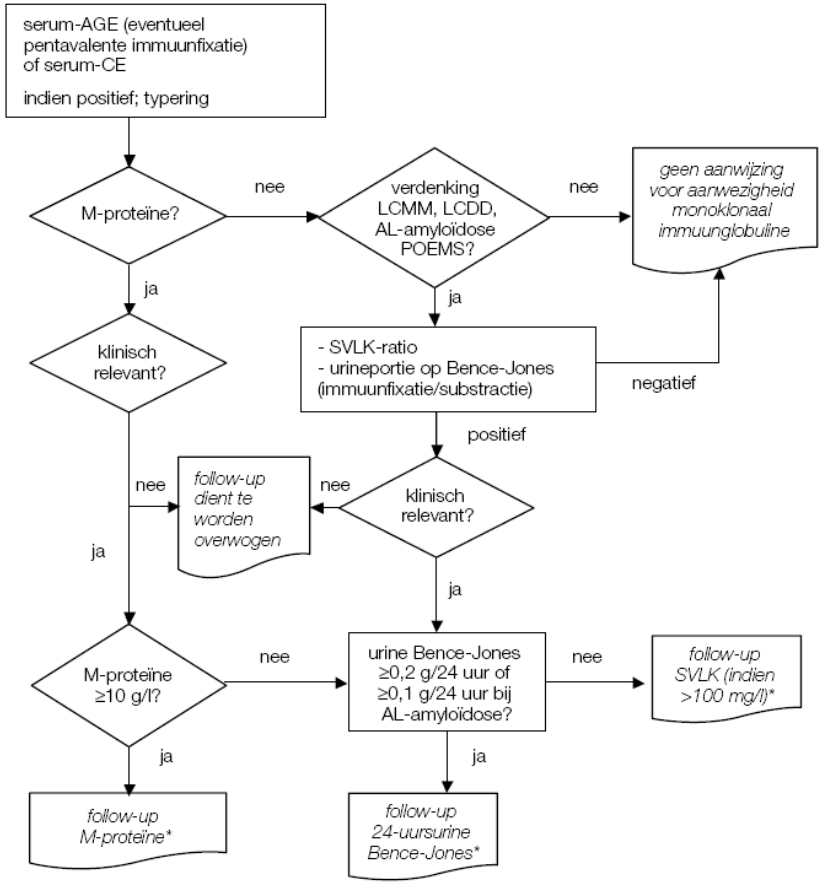
Follow-up



NVKC/CMI/HOVON richtlijn: Ruinemans-Koerts et al. NTvH 2011
IMWG guideline: Dimopoulos et al. Blood 2011

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Jaarraport

Jaarrapport 2013

Bepaling	Jaarscore	Ronde scores
IgG	1	
IgA	1	
IgM	1	
Totaal eiwit	1*	
sVLK kappa	8 / 8	
sVLK lambda	7 / 8	
Ratio (kappa/lambda)	8 / 8	

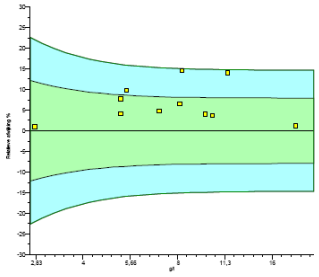
* = Voor SA 2 punten

M-proteïne	26 / 26	
IgA kappa		
IgD lambda		
IgG kappa		
IgG lambda		
IgM kappa		
IgM lambda		
Vrije lambda		
Geen M-proteïne		

Legenda: = Binnen TE = Binnen SA = Buiten TE/SA ▪ = expertwaarde = geen waarde = juist = onjuist

IgG

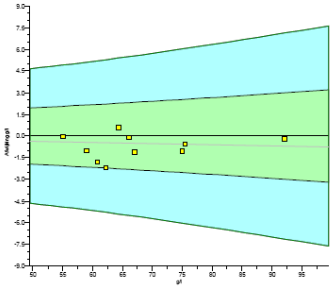
eenheid : g/l



Juistheid	+6.5%
Precisie	4.8%
Aantal	11
Uitbijters	0
Sigma-TE	1.5
Sigma-SA	4.3 1
Score pictogram	
Regressielijn	0.00 + 1.030.x
Consensusgroep	Beckman
Methode	Beckman (nefel)

Totaal eiwit

eenheid : g/l



Juistheid	-0.76%
Precisie	1.2%
Aantal	11
Uitbijters	0
Sigma-TE	2.6
Sigma-SA	6.0 2
Score pictogram	
Regressielijn	0.0 + 0.993.x
Consensusgroep	Overall
Methode	Biureet, automatisch

Meeste ontwikkelingen binnen M-proteine diagnostiek

- **Nieuwe therapieën**

Daratuzumab (anti-CD38)

- **Implementatie van sFLC in richtlijnen**

Table 1. Summary of the main applications of the free light chain assay in plasma cell dyscrasias.

Setting	Recommendations	Notes
Screening	Serum tests s-PE, s-IFE and rFLC, are indicated and sufficient to screen for PCDs other than AL amyloidosis which requires all the serum tests and u-IFE	Once a diagnosis of PCD is made urine studies are necessary in all conditions
Risk stratification	FLC needed for risk stratification in MGUS, SMM, AL amyloidosis and solitary plasmacytoma in association with other parameters depending on the condition	The 2011 IMWG specific guidelines on risk stratification in MM state that although the rFLC for prognostication in MM patients may be useful under some circumstances, the general applicability is unknown
Monitoring	Indicated in AL amyloidosis, oligosecretory MM and MM in advanced stage	FLC is essential in the management of AL amyloidosis. The IMWG experts recommend the use of the FLC assay (as alternative to u-IFE) in MM patients with advanced stage of the disease to screen for 'light chain escape'
Response assessment	FLC necessary for the definition of sCR in MM. Required in AL amyloidosis and oligosecretory MM	In AL amyloidosis the hematologic response is assessed solely on the basis of the FLC concentration

- **Hoe verhouden beiden sFLC assays zich tot elkaar (Freelite en N Latex)?**

IMWG guideline: Ludwig et al. Leukemia 2013
Graziani and Merlini. Expert Rev Mol Diagn 2014

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Tevens een interessant sample geschikt voor de M-proteine rondzending?

Zeer welkom!

- **100 ml serum nodig per monster (!)**
- **Echter, samples kunnen ook gespiked worden in normaal serum. In dat geval minder serum nodig.**
- **Graag contact:**

H.Jacobs@Radboudumc.nl

Literature

- **Dutch Guideline M protein diagnostics.**
  Ruinemans-Koets J. et al. NTvH 2011.
- **Guidelines for the diagnosis and management of multiple myeloma.**
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  Katzmann et al. Clin. Chem. 2009.
- **IMWG guidelines for serum-free light chain analysis in multiple myeloma and related disorders.**
  Dispenzieri A, Kyle R, Leukemia. 2009.
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- **IMWG recommendations for global myeloma care.**
  Ludwig H. et al., Leukemia 2013.
- **Review on sFLC analysis and management of monoclonal gammopathies.**
  Graziana and Merlini*. Expert Rev Mol Diagn 2014.*

Met dank aan:

Corrie de Kat Angelino
Gertrude van der Wiel
Renate van der Molen

Ondersteuning SKML