

amyloidose

laboratoriumgeneeskunde: van lab naar kliniek en terug

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amyloïdose: stappenplan bij verdenking, diagnose en behandeling

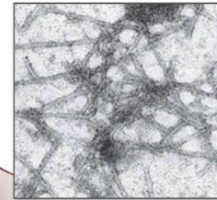
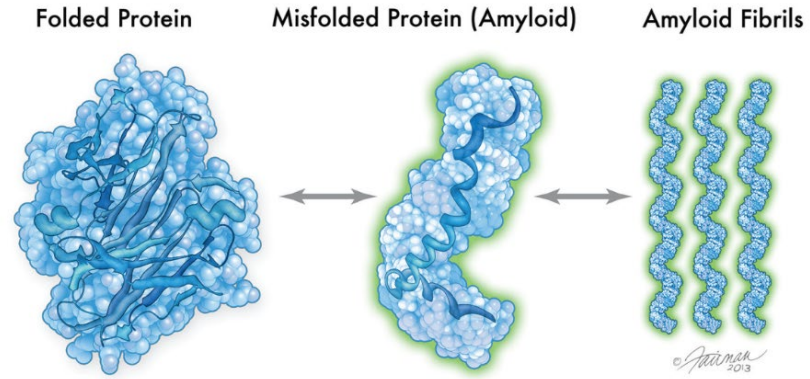
- 1) aanwezigheid van amyloïd
- 2) orgaanbetrokkenheid (amyloïd depositie)
- 3) typeren van het amyloïd
- 4) evaluatie van het “precursor” eiwit
- 5) klinische evaluatie van de ziekte en prognose
- 6) behandeling / ondersteunende behandeling
- 7) vervolgen van de effectiviteit van de behandeling

Wat is amyloïd(ose)

Hoe meet je amyloïd

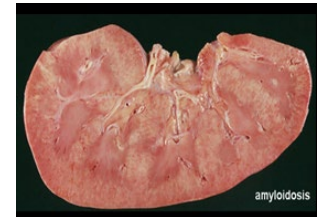
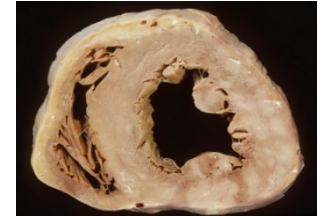
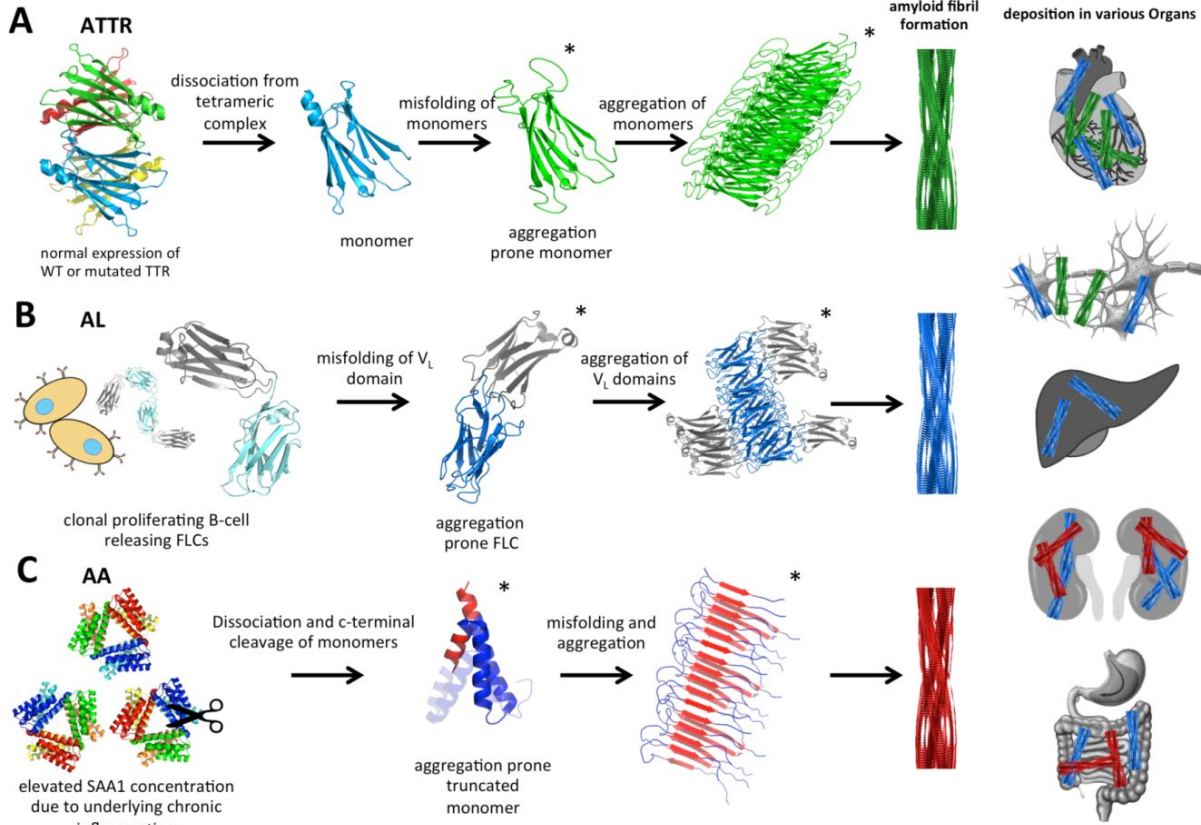
(Hoe meet je progressie van ziekte / effectiviteit van behandeling)

what is amyloid

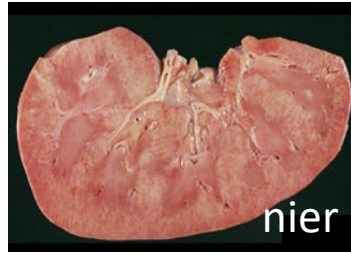
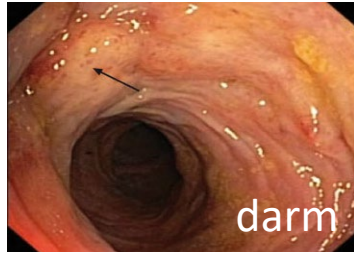


Scanning electron
microscopic view
of amyloid fibrils

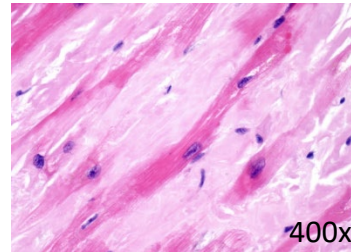
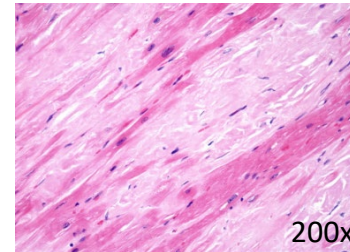
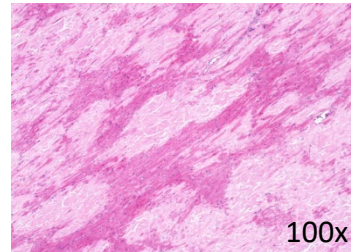
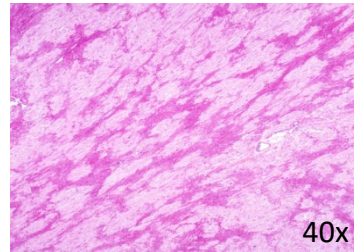
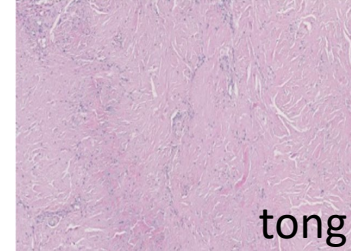
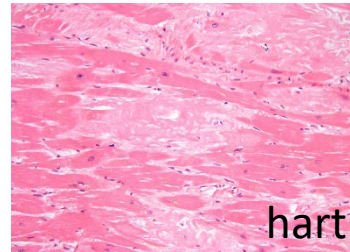
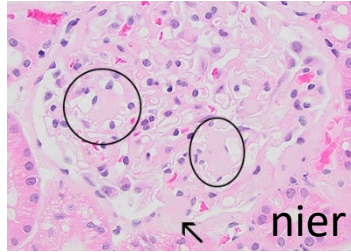
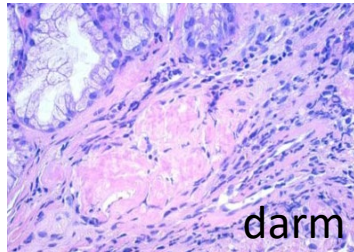
amyloid ontstaat uit misvouwing en aggregatie van een normaal eiwit



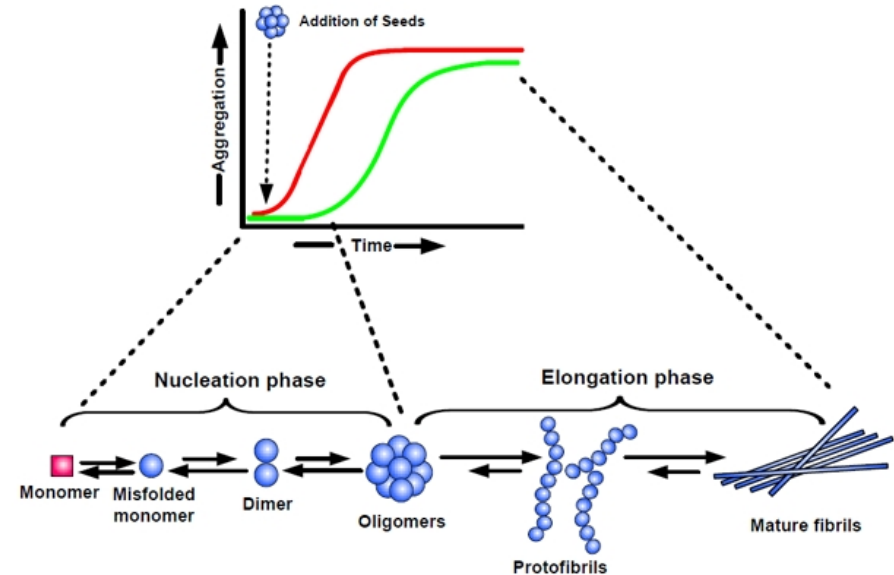
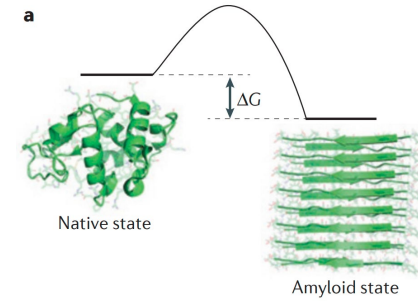
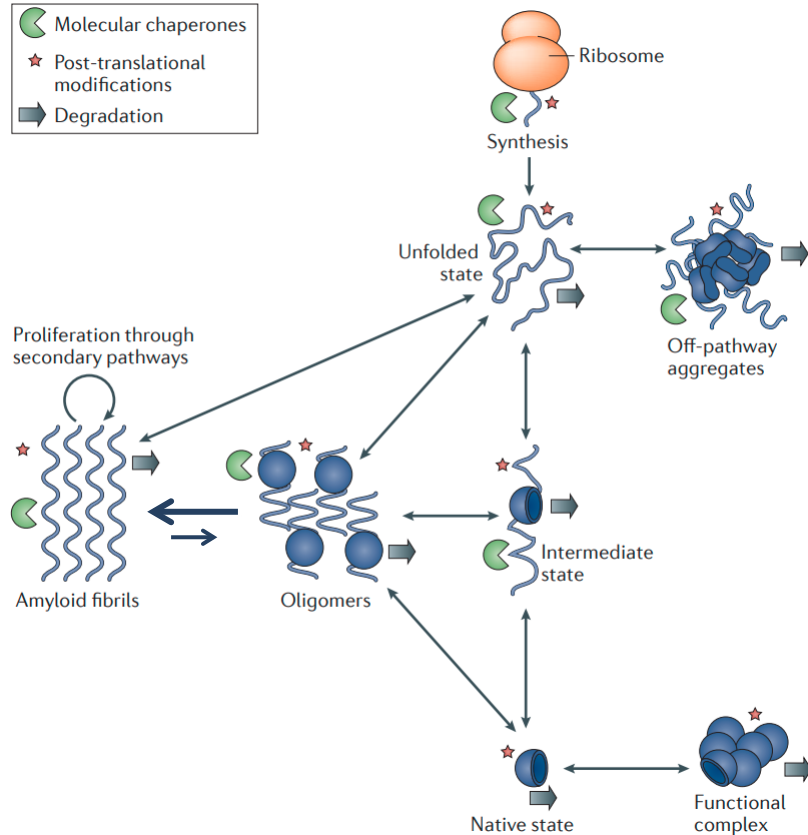
amyloïdose: macroscopische uitingsvormen = kliniek

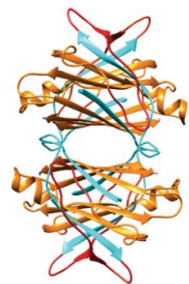


amyloïdose: microscopisch-histologische H&E kleuring

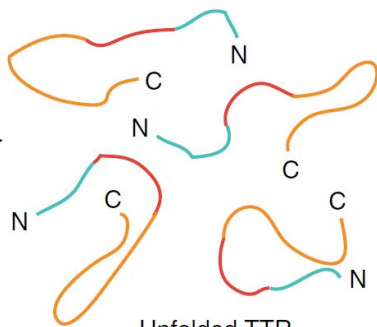


eiwit (mis)vouwing en amyloïdogenese

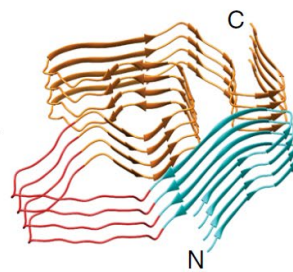




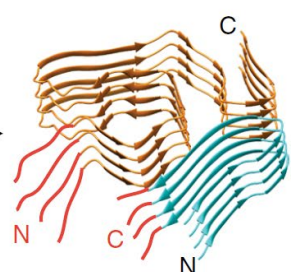
Native TTR



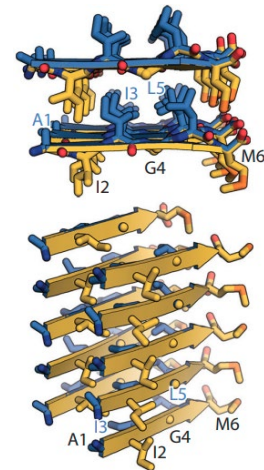
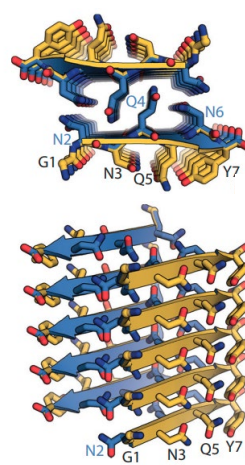
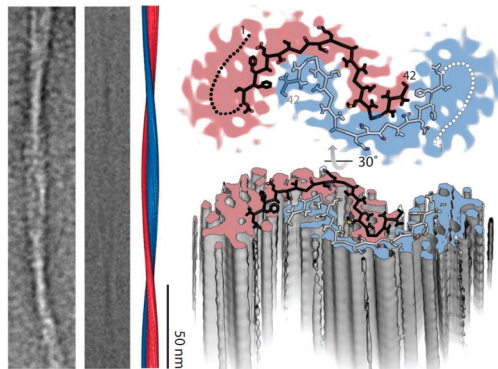
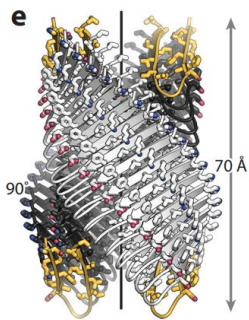
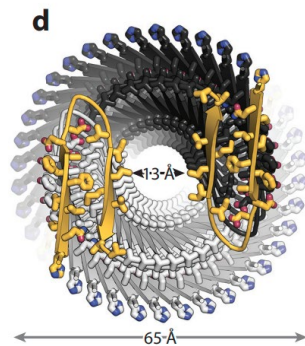
Unfolded TTR



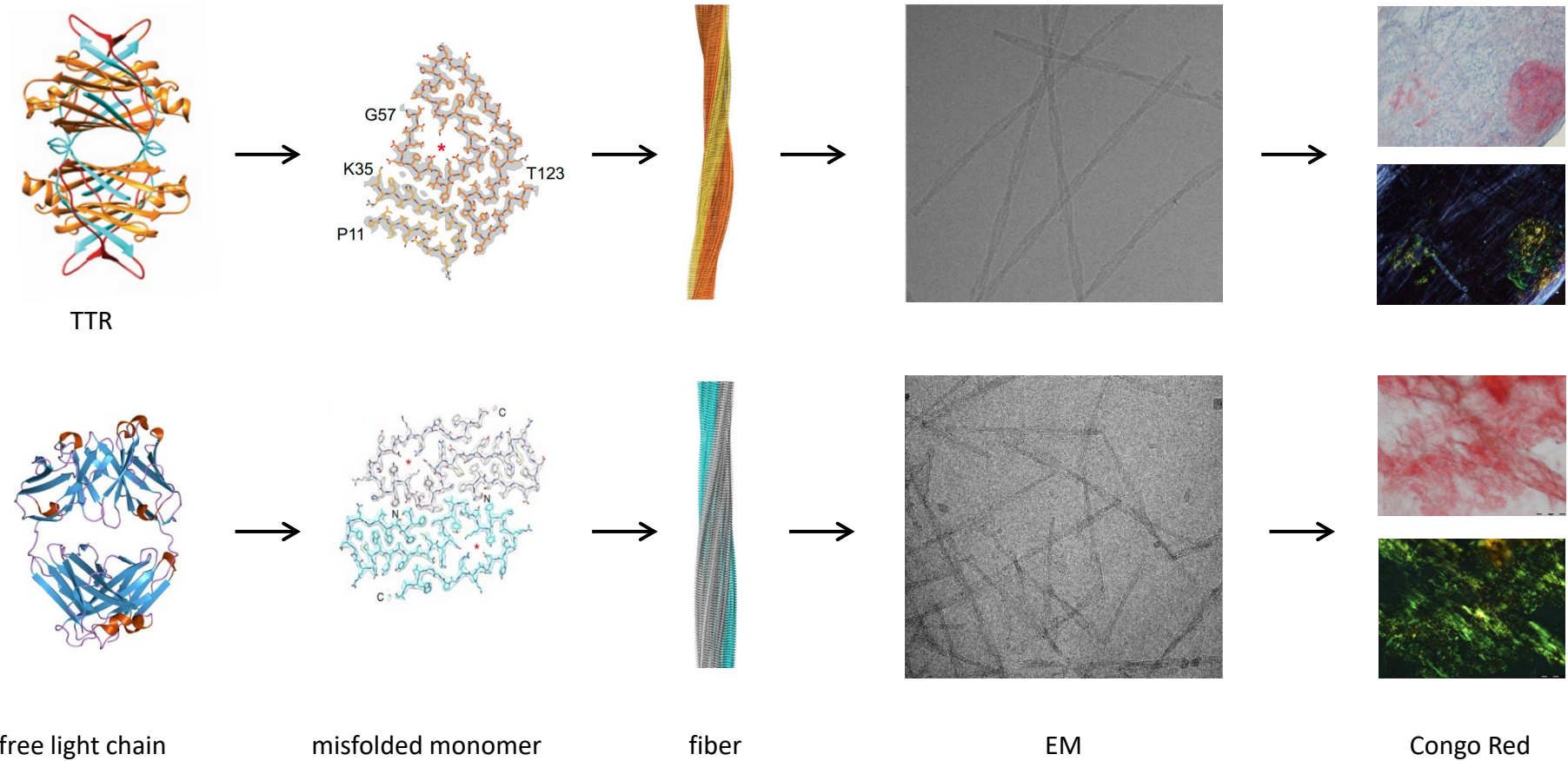
Early fibril state



Mature ATTR amyloid fibril

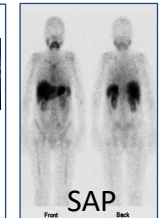
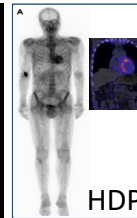
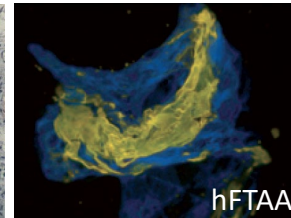
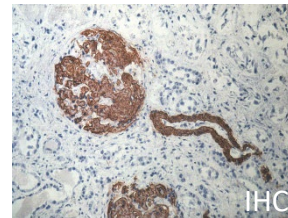
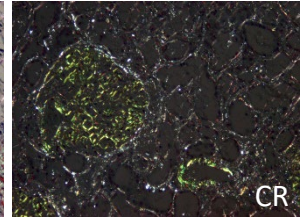
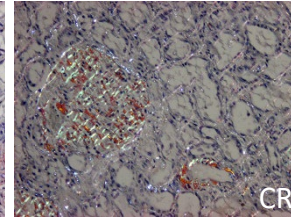
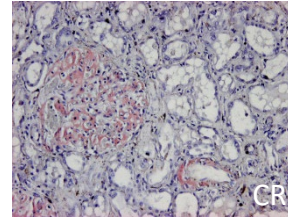
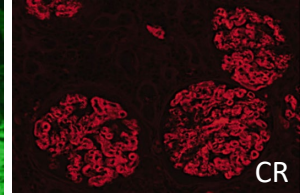
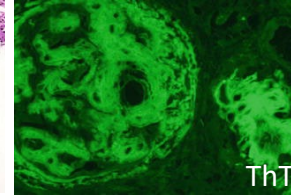
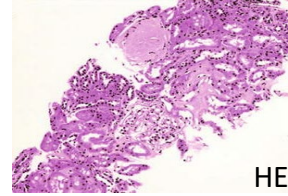
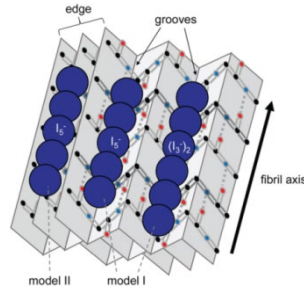
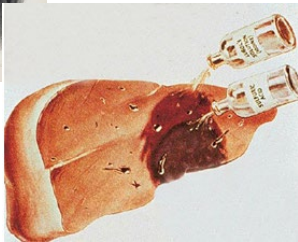
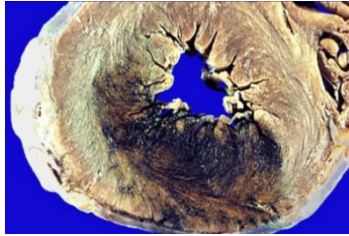


amyloid: subtiel verschillend

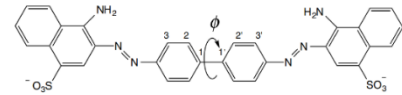


aantonen van amyloid

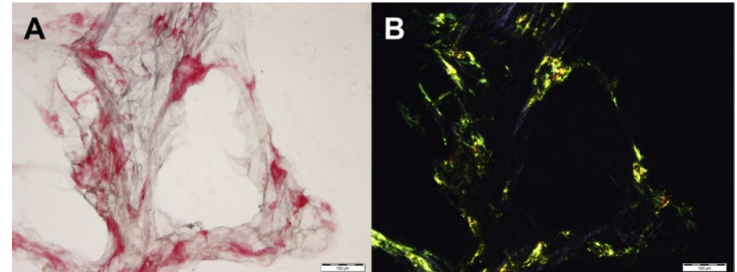
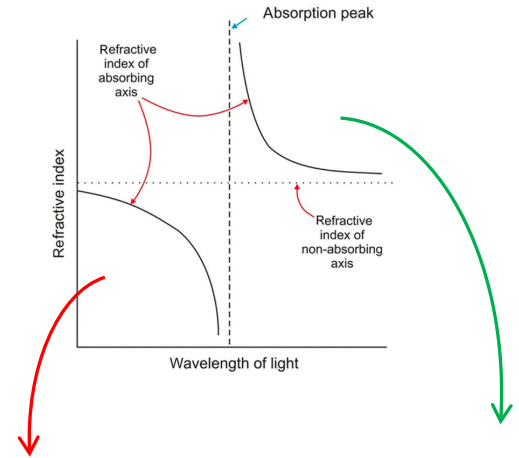
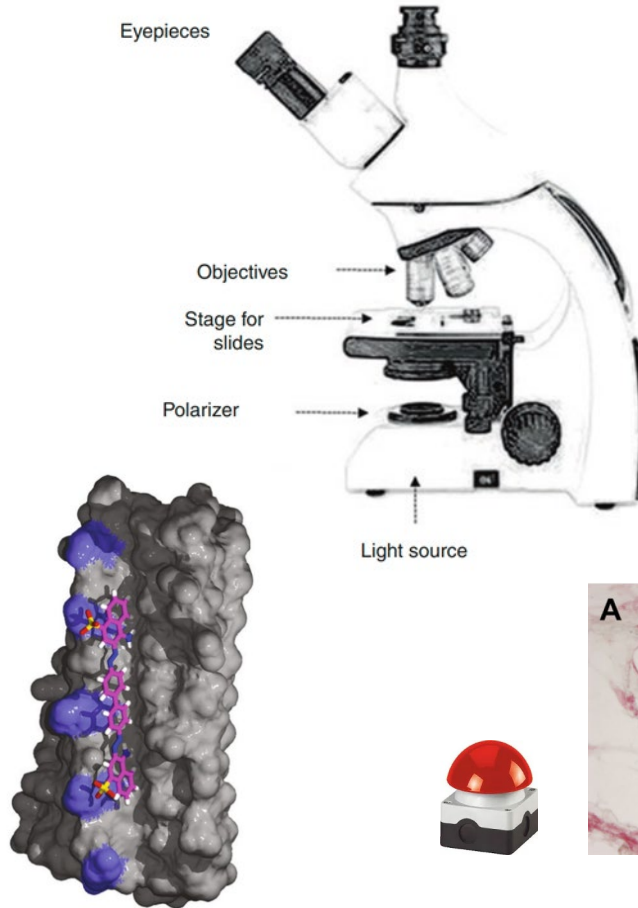
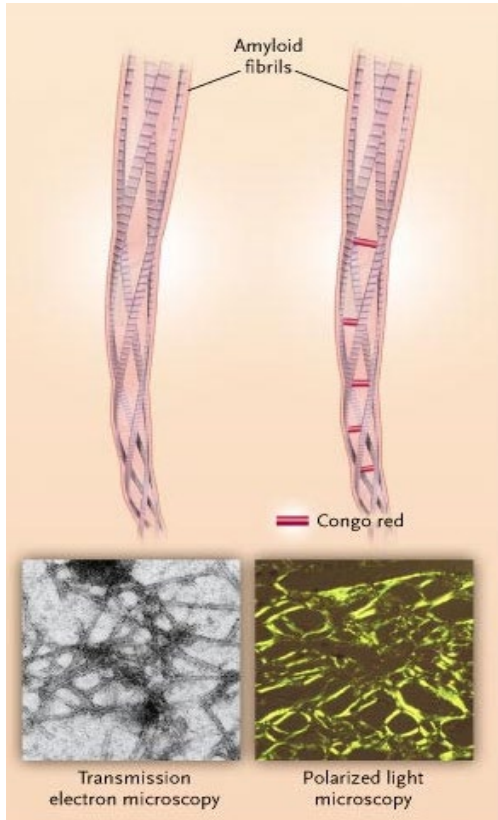
historie (1854) —————> heden



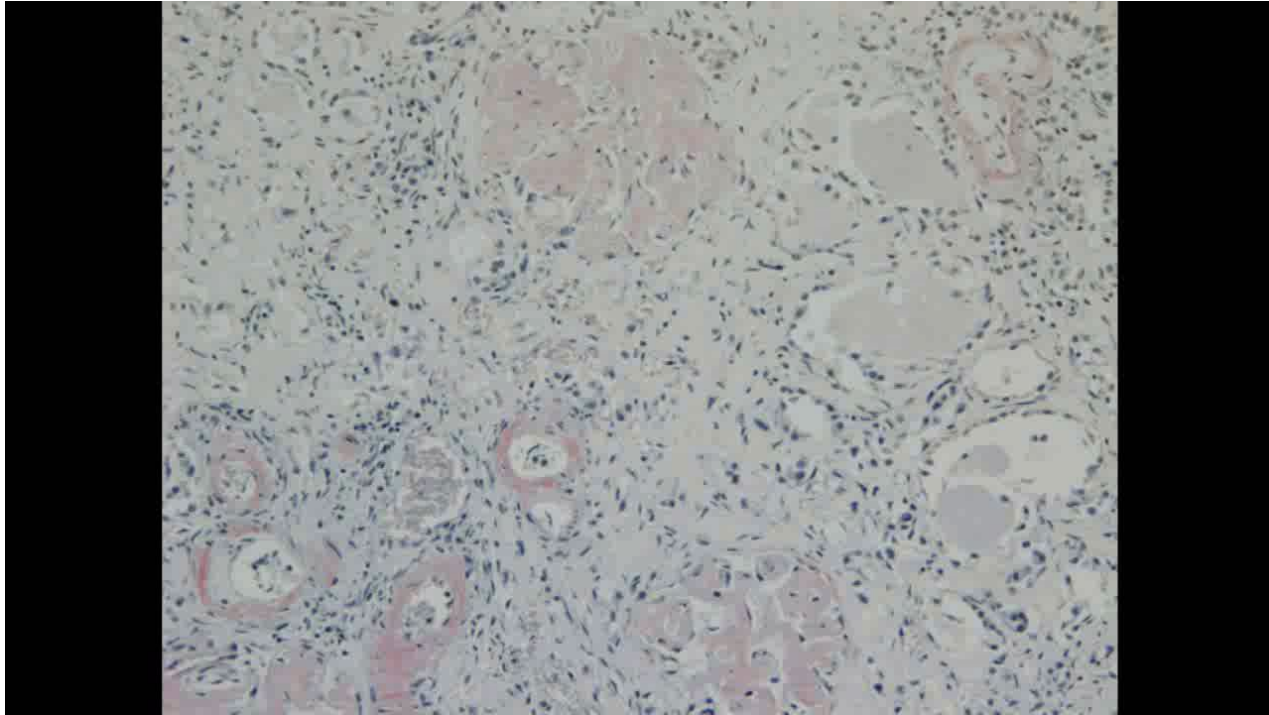
aantonen van amyloid: Congo rood

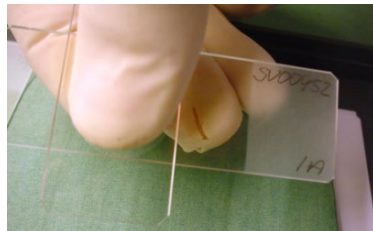


Congo rood

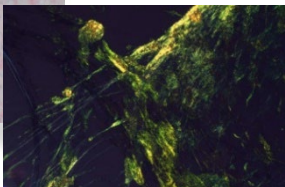
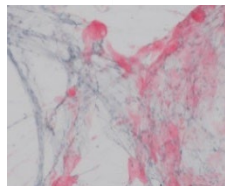


Zie voor het filmpje de website
<https://www.amyloid.nl/diagnose/#biopt>

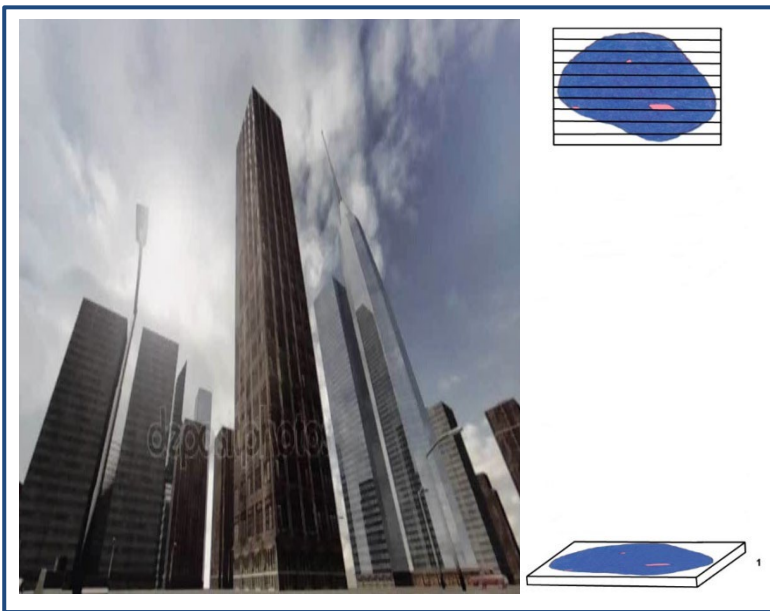
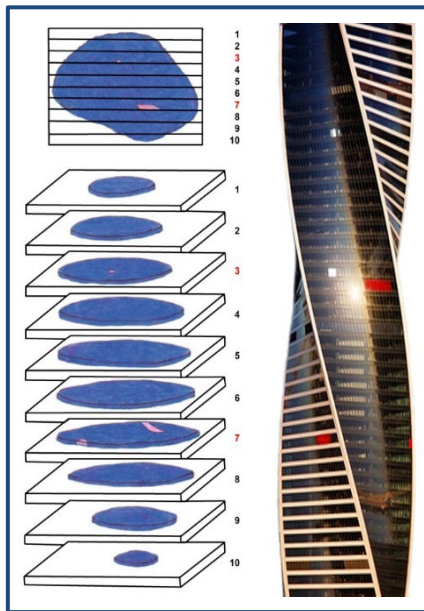




Fat pad aspirate



Congo rood kleuring



beoordelen van de Congo Rood kleuring

- twee beoordelaars!
- semi-kwantitatieve score (0 - 4+)

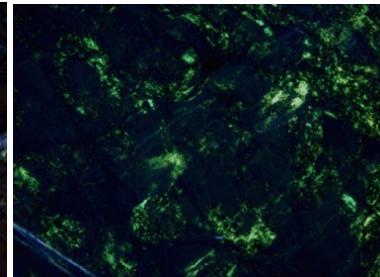
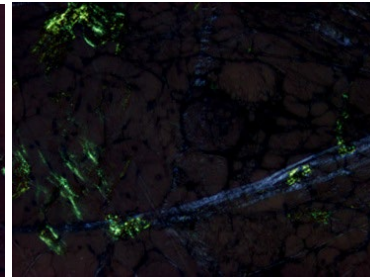
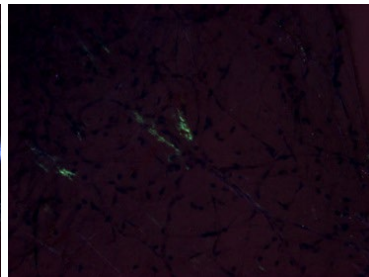
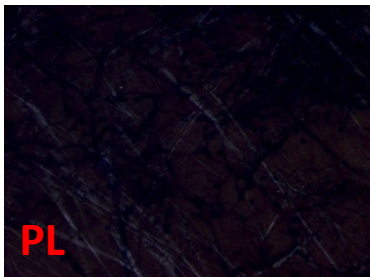
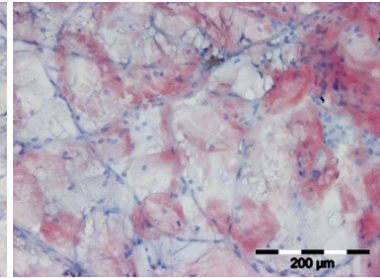
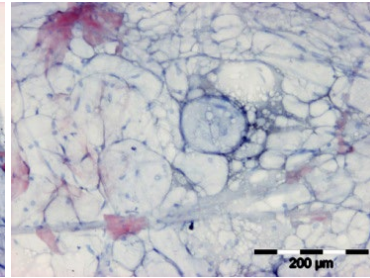
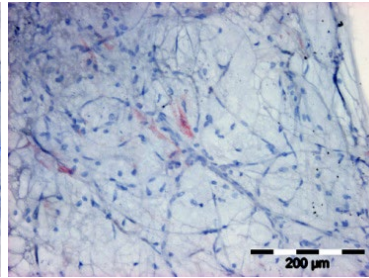
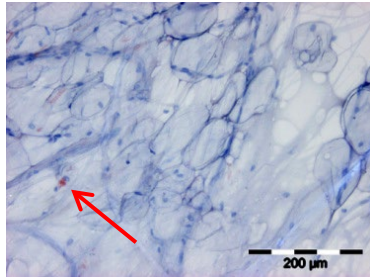
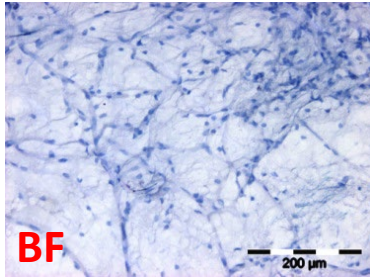
negatief

1+ ($< 1\%$ opp)

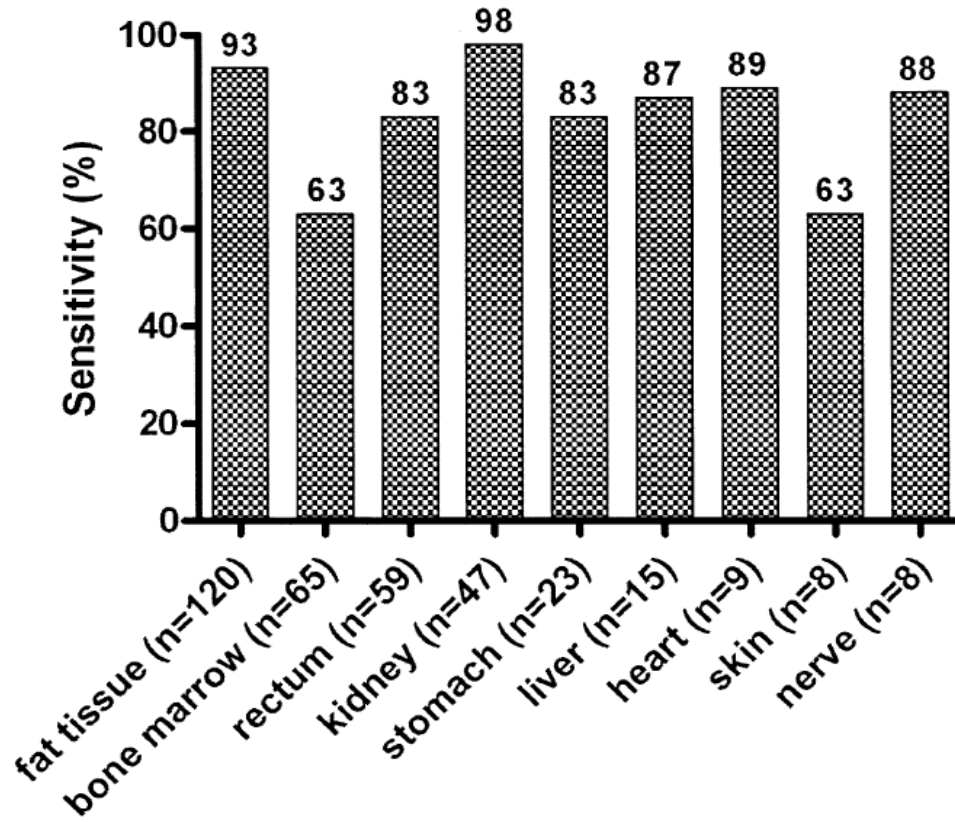
2+ ($1\% < \text{opp} < 10\%$)

3+ ($10\% < \text{opp} < 60\%$)

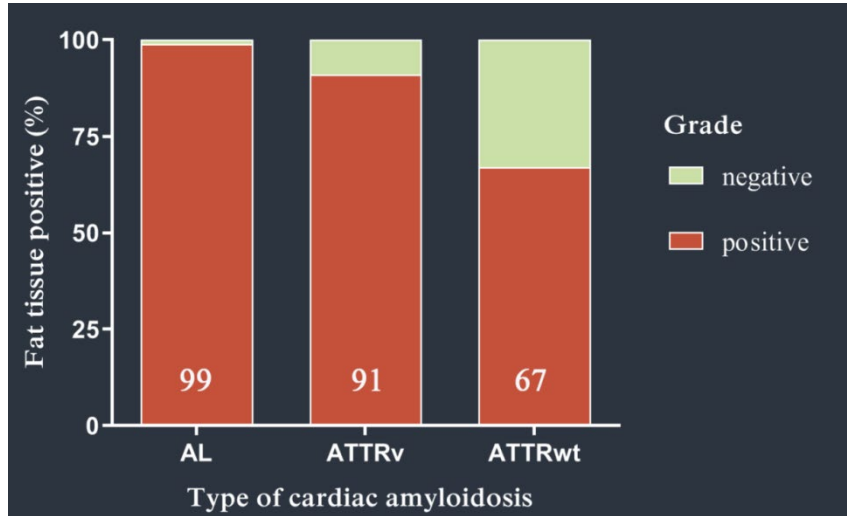
4+ ($\text{opp} > 60\%$)



gevoeligheid van het vetbiopt



gevoeligheid van het vetbiopt

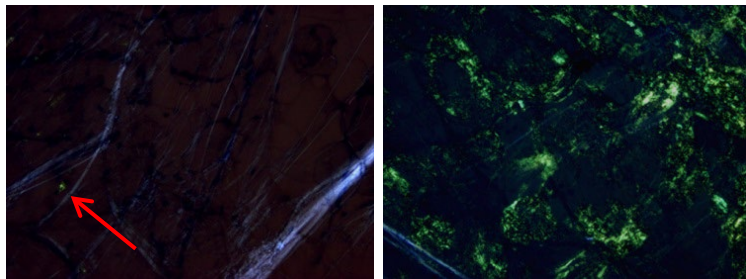
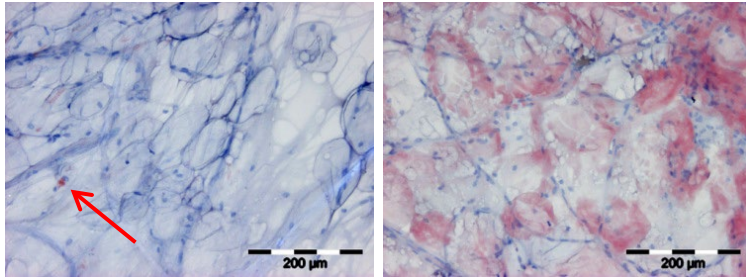


wildtype ATTR vs variant ATTR

	Total	Control	AL	ATTRv	ATTRwt
<i>n</i>	248		100	82	66
Age, years (SD)	66 (11)		66 (9)	60 (12)	73 (6)
Sex, <i>n</i> (%)	181 (73)		61 (61)	58 (71)	62 (94)
Semi-quantitative score, <i>n</i> (%)					
0	30 (12)		1 (1)	7 (9)	22 (33)
1+	49 (20)		7 (7)	13 (16)	29 (44)
2+	30 (12)		13 (13)	12 (15)	5 (7)
3+	62 (25)		28 (28)	25 (30)	9 (14)
4+	77 (31)		51 (51)	25 (30)	1 (2)
Positive biopsy, <i>n</i> (%)	218 (89)		99 (99)	75 (91)	44 (67)

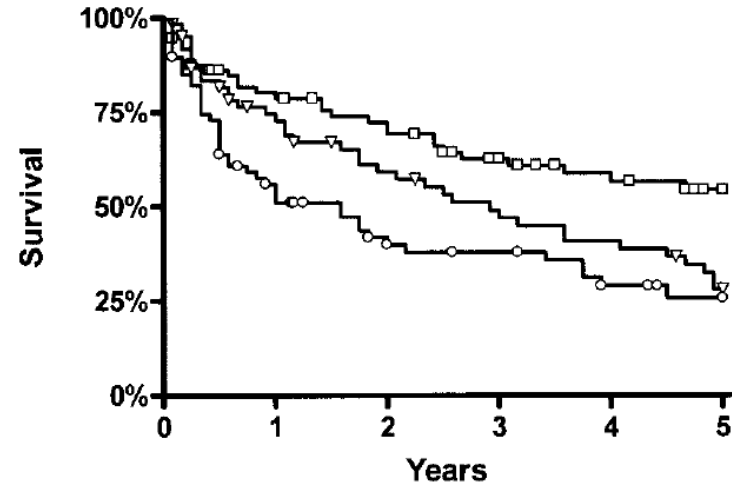
- myocardbiopt: hoogste sensitiviteit; klein risico op (ernstige) complicaties
- buikvet biopt: interpretatie icm klinische verdenking (echo, MRI, biomarkers)
- typering: ELISA; IHC; massaspectrometrie; immuno-EM
- negatief biopt maar blijvende verdenking cardiale amyloïdose → revisie!

klinische betekenis van vetbiopt Congo rood score



1+

4+



No. at Risk

Grade 0-2+	77	54	47	37	29	23	—□—
Grade 3+	71	41	31	25	22	15	—▽—
Grade 4+	72	36	24	19	14	9	—○—

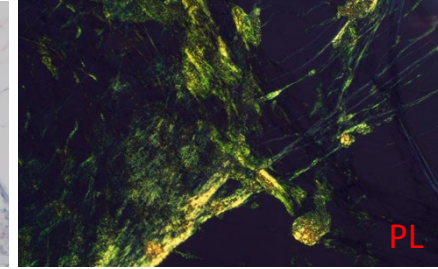
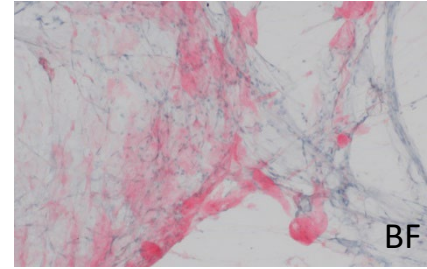
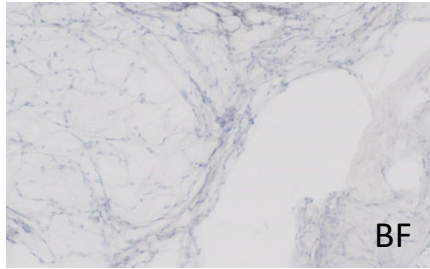
juiste interpretatie van de Congo rood kleuring: expertise vereist

handmatig vs machinaal

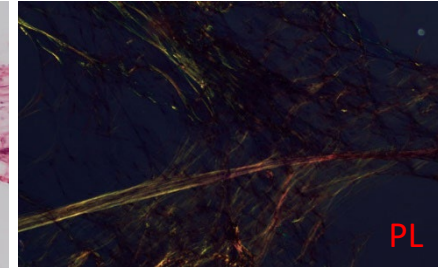
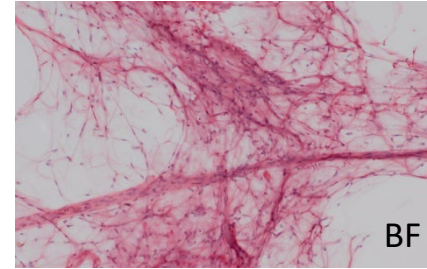
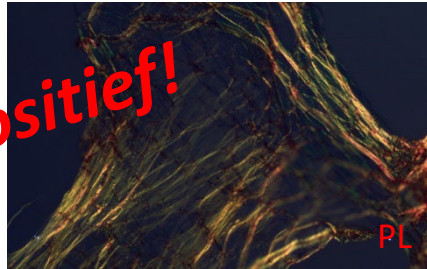
negatief vetbiopt

positief vetbiopt

Puchtler methode (handmatig)

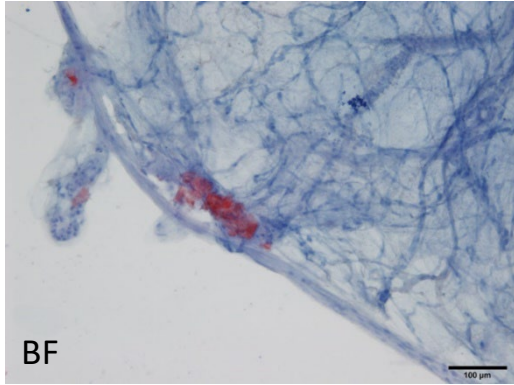


Ventana methode (machinaal)



juiste interpretatie van amyloïd aankleuring: expertise vereist
CR kleuring: polarisatie vs fluorescentie microscopie

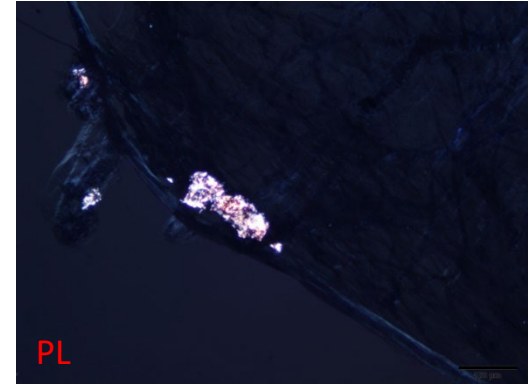
amyloïd?



positief?



negatief!

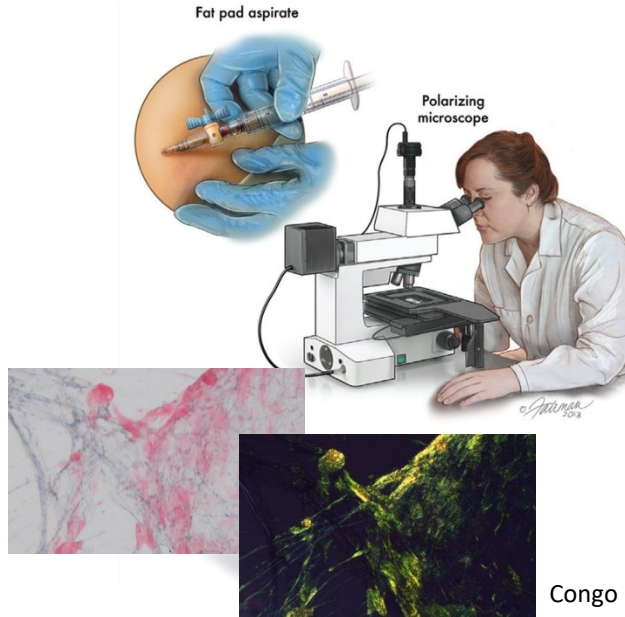


- Ventana, fluorescentie en thioflavine: (incidenteel) vals positief
- hFTAA: mogelijk iets gevoeliger dan Congo rood, maar lastig te interpreteren
- Congorood kleuring (Puchtler methode) met polarisatie microscopie: gouden standaard!

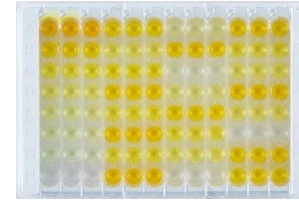
laboratorium-bepalingen tbv het diagnosticeren van amyloïdose

1) vaststellen van aanwezigheid van amyloïd

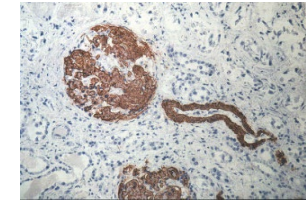
2) typeren van amyloïd



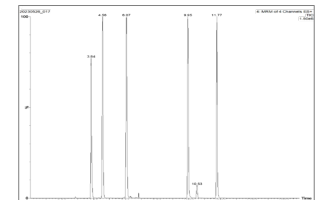
ELISA



IHC



MS



ELISA-4-amyloid: diagnostic accuracy of an ELISA panel for typing the four main types of systemic amyloidosis in subcutaneous abdominal fat tissue samples

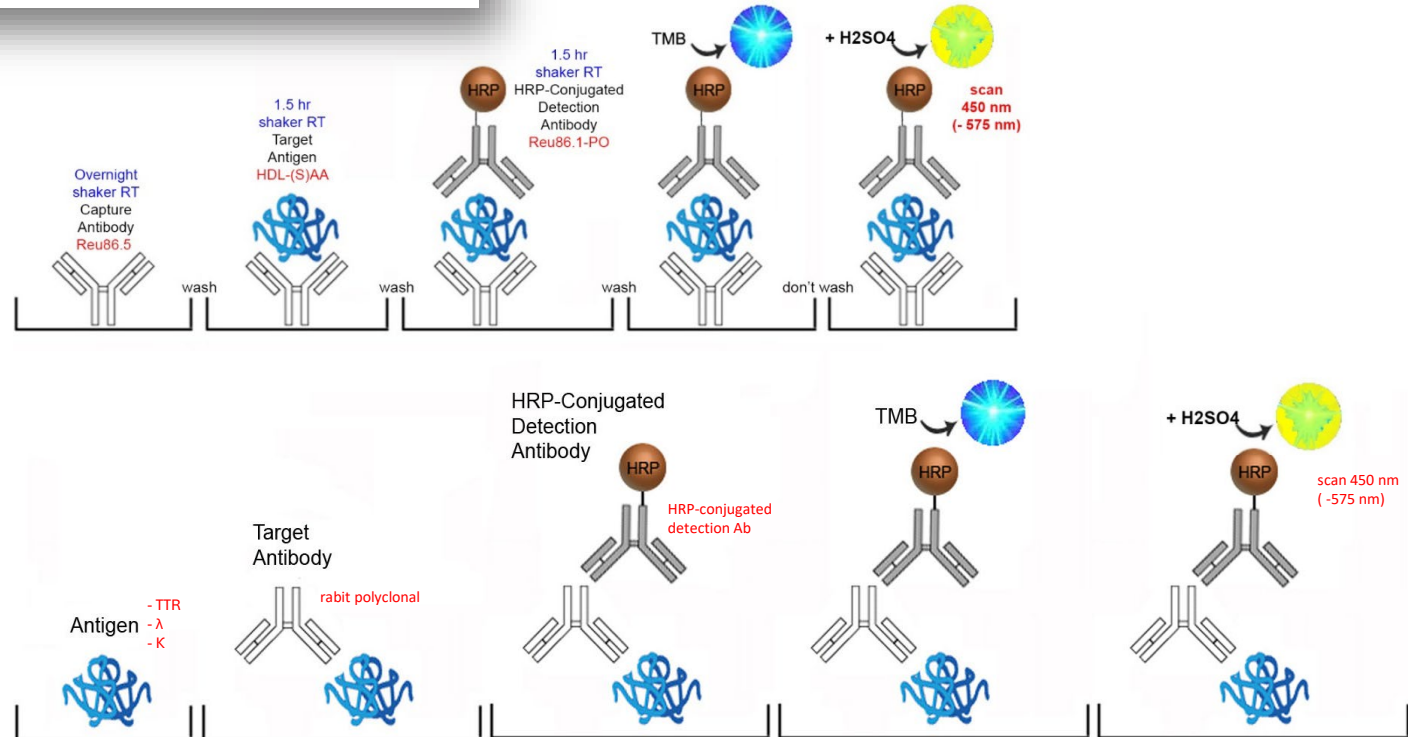
Johan Bijzet^a, Hans L. A. Nienhuis^b, Bart-Jan Kroesen^a, Arjan Diepstra^c and Bouke P. C. Hazenberg^d

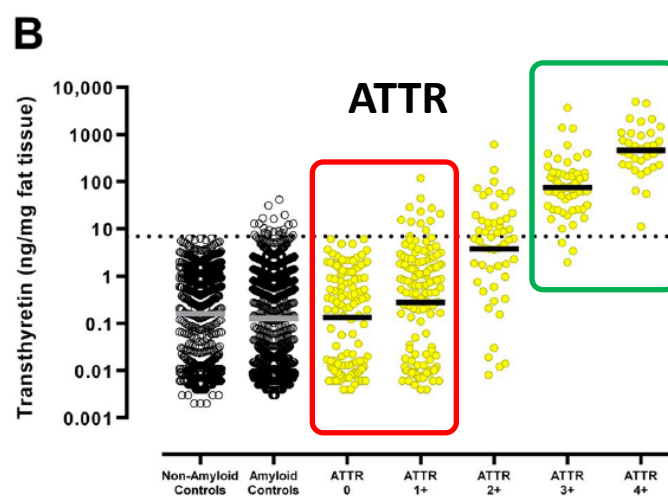
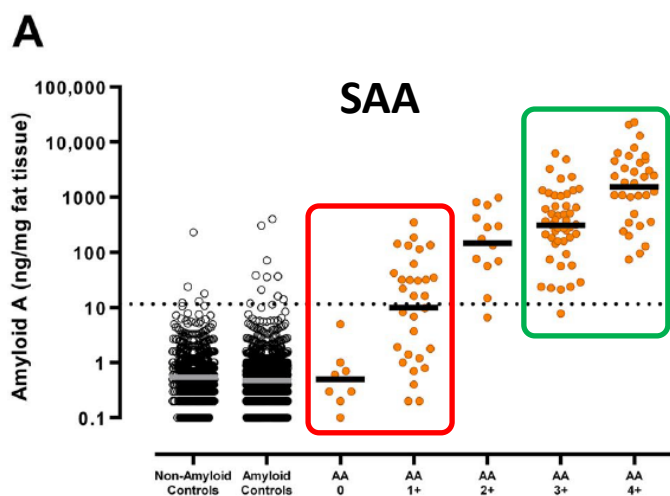
ELISA-4-amyloid: design

ELISA
specificiteit

↑ - AA

↓ - TTR
- λ
- K





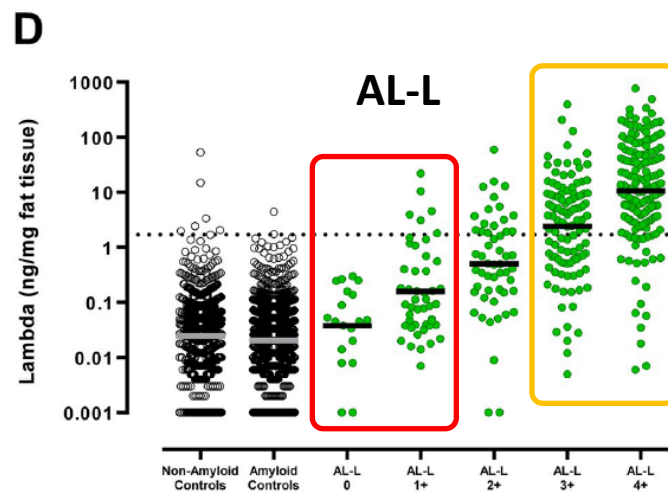
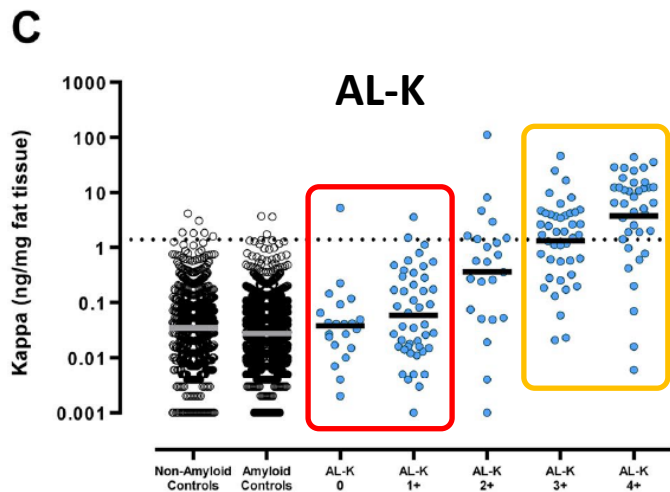
ELISA-4-amyloid

sensitivity

23,3

97,8

71,3



Typing of amyloid in 2207 fattissue samples

**ELISA-4
Amyloid
panel**

**AA > 11.6
ng/mg fat**

**TTR > 7.00
ng/mg fat**

**κ > 1.41
ng/mg fat**

**λ > 1.71
ng/mg fat**

Correctly typed

**Congo red
grading**

Percentage

**CR
1-2+**

62.8

**CR
3-4+**

98.8

**CR
1-2+**

18.1

**CR
3-4+**

96.8

**CR
1-2+**

13.2

**CR
3-4+**

66.7

**CR
1-2+**

23.0

**CR
3-4+**

75.9

Incorrectly typed

**Non-amyloid
Controls (%)**

0.6

0.0

0.7

0.7

**Amyloid
Controls (%)**

0.8

2.4

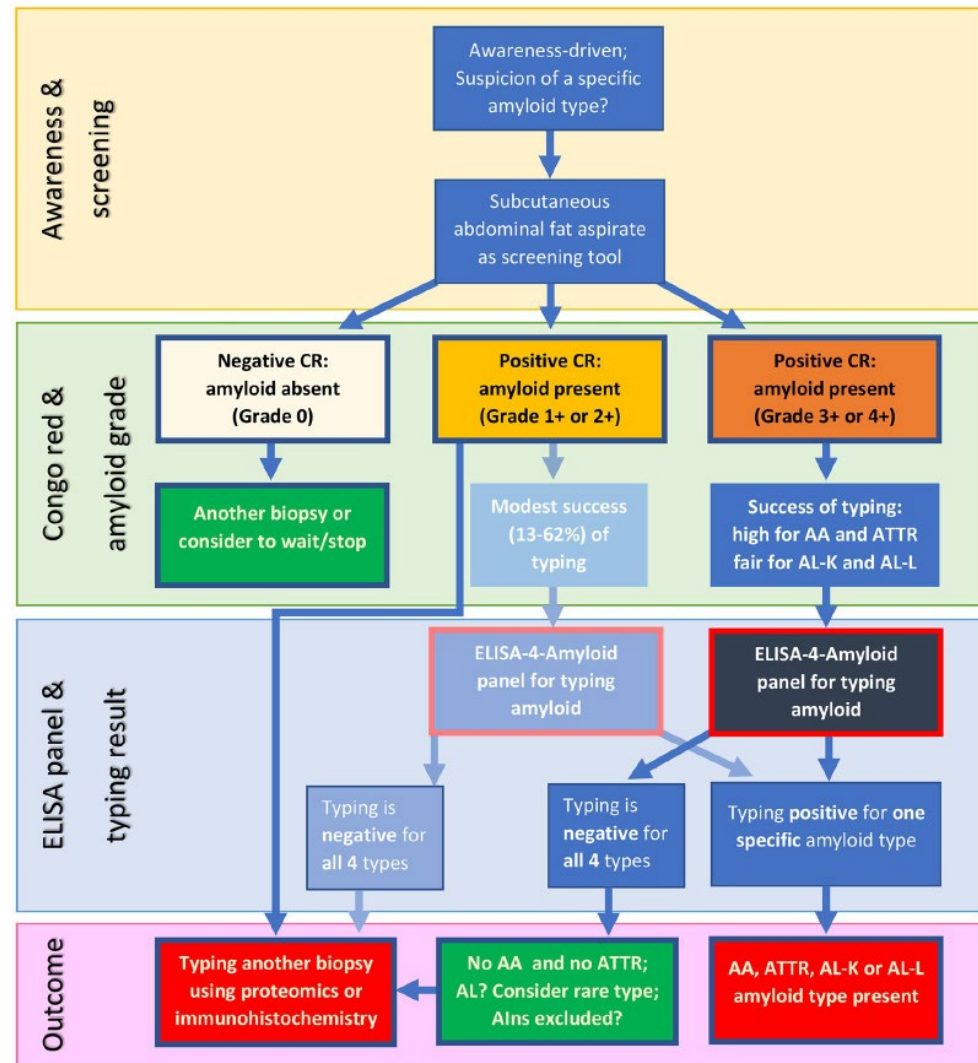
0.3

0.2

concluderend

screenen: - vetbiopt
- Congo rood

typeren: - ELISA (en genetisch onderzoek)
- sens. = precursor afhankelijk
- spec. = uitstekend (98%)



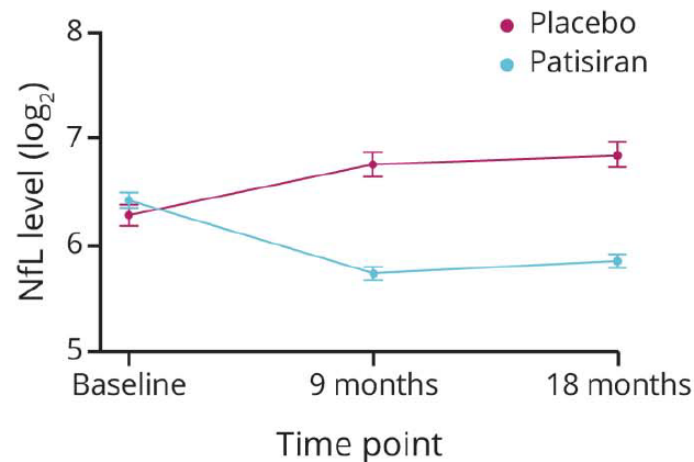
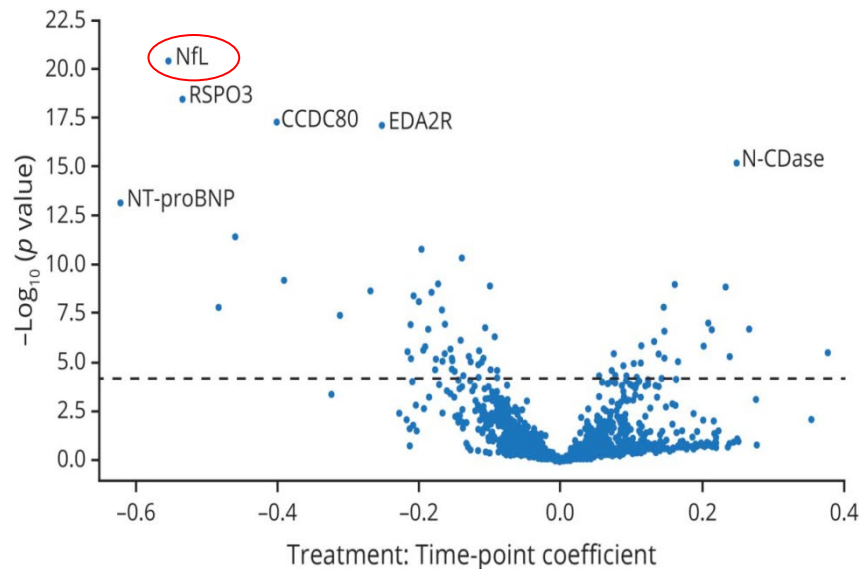
Neurofilament Light Chain as a Biomarker of Hereditary Transthyretin-Mediated Amyloidosis

Simina Ticau, PhD,* Gautham V. Sridharan, PhD,* Shira Tsour, MS, William L. Cantley, PhD, Amy Chan, PhD, Jason A. Gilbert, MS, David Erbe, PhD, Emre Aldinc, MD, Mary M. Reilly, MD, David Adams, MD, Michael Polydefkis, MD, Kevin Fitzgerald, PhD, Akshay Vaishnav, MD, and Paul Nioi, PhD

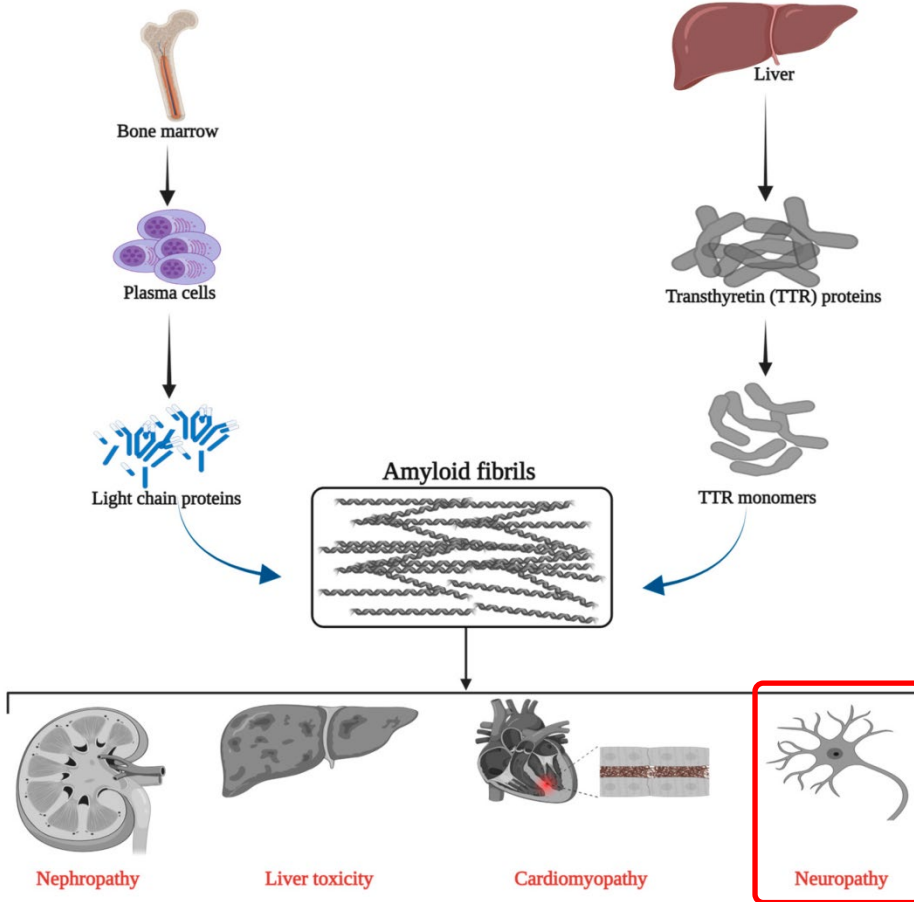
Correspondence

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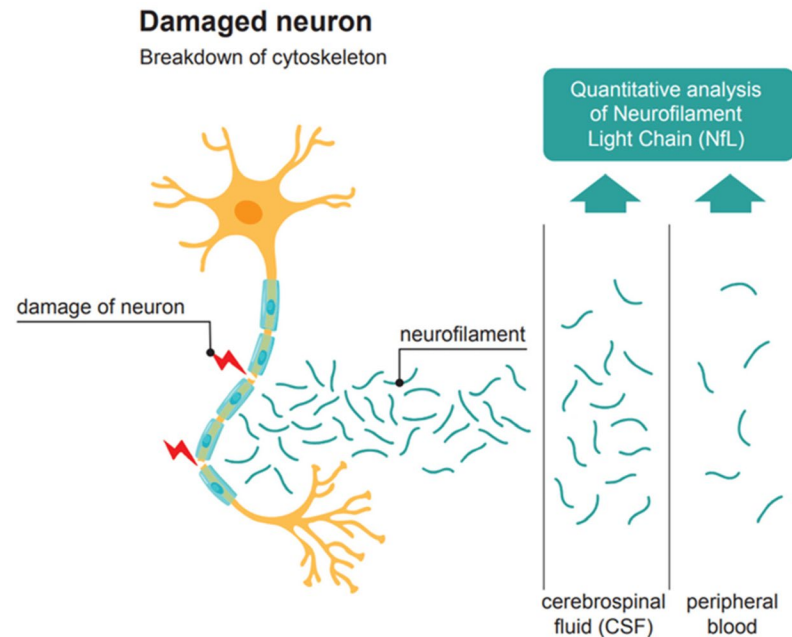
Neurology® 2021;96:e412-e422. doi:10.1212/WNL.0000000000011090



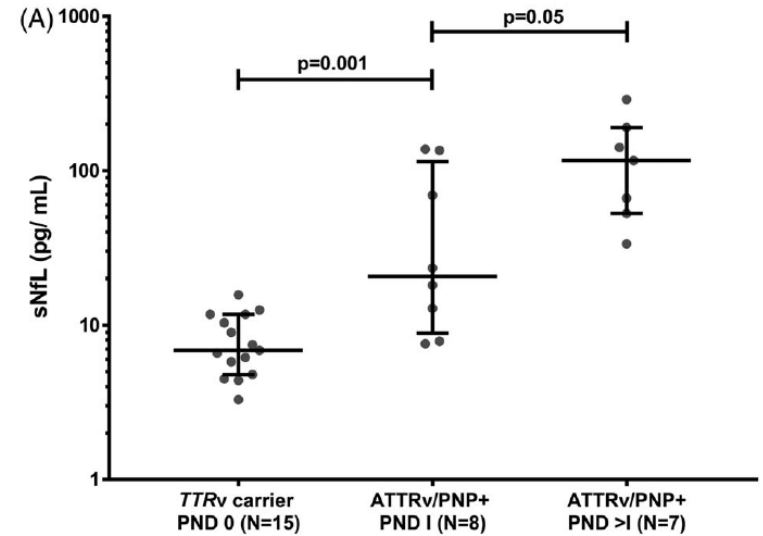
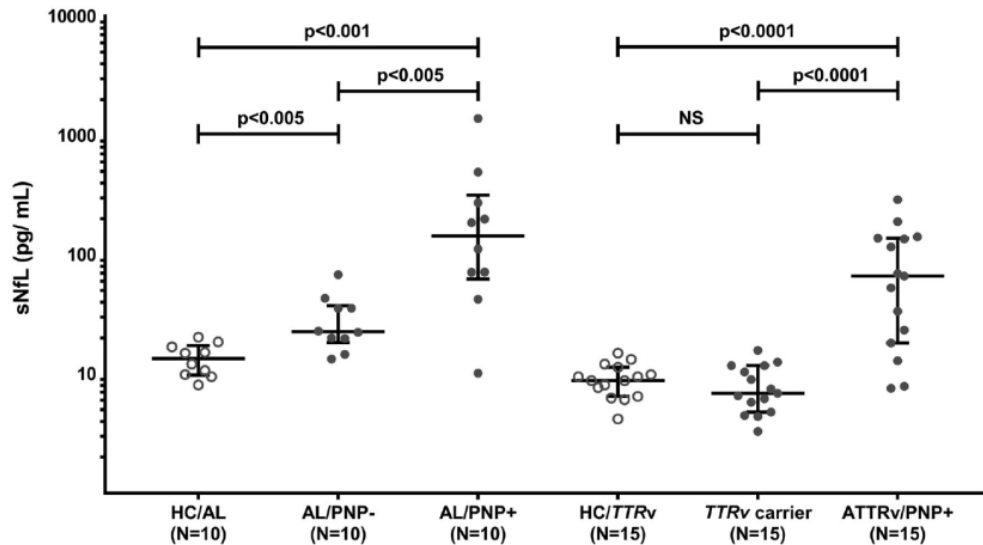
Light chain (AL) amyloidosis



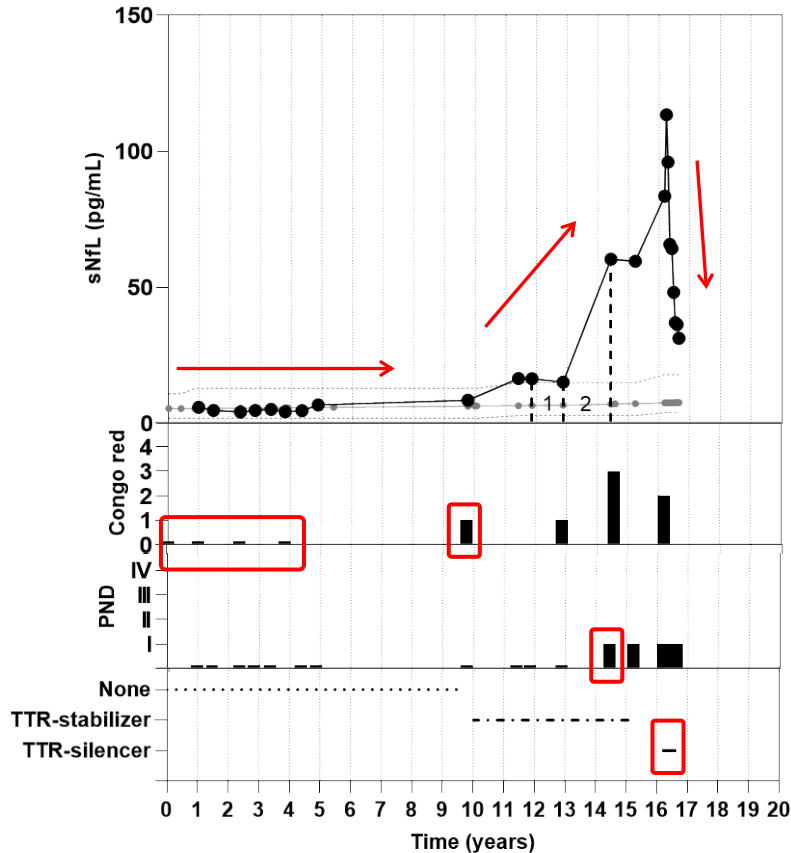
sNfL:
biomarker voor amyloïdose
geassocieerde neuronale schade



sNfL: biomarker voor amyloïdose geassocieerde neuronale schade



follow up of TTRv carrier → ATTR → treatment



sNfL:

- 1) sensitieve biomarker voor amyloïdose geassocieerde neuronale schade
- 2) biomarker voor ziekte progressie
- 3) biomarker voor behandeling (?)



www.amyloid.nl

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