Diagnostic Challenges and Advances in Amyloidosis

Patrik Flodr[1], Martina Navrátilová[1], Pavla Flodrová[1], Jaroslav Michálek[1], Dušan Holub[2], Tomáš Pika[3], Petr Džubák[2]

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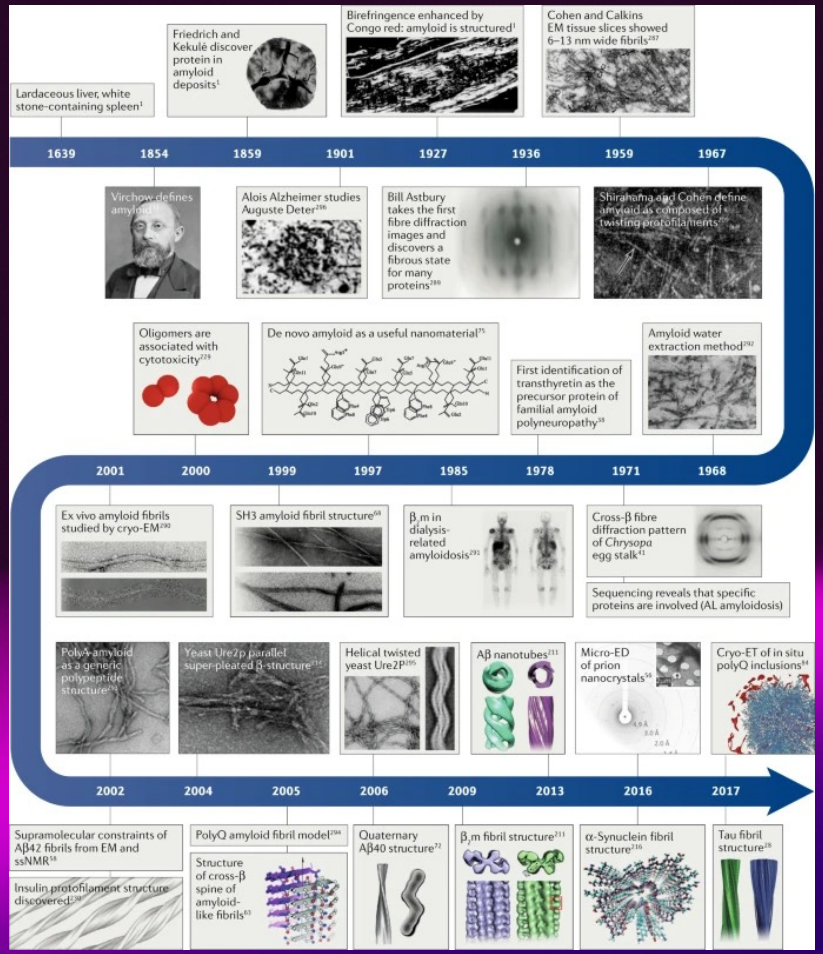
2) Department of Molecular and Translational Medicine, FMD Palacký University Olomouc, CZ
3) Department of Hemato-oncology, FH Olomouc, Olomouc, CZ



Iadanza, M.G., Jackson, M.P., Hewitt, E.W. *et al.* A new era for understanding amyloid structures and disease. *Nat Rev Mol Cell Biol* **19**, 755–773 (2018). https://doi.org/10.1038/s41580-018-0060-8

motto

Amyloidosis affects millions of people

The many forms of the disorder have one underlying principle - misfolded proteins

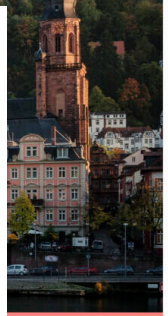
Prompt, correct diagnosis is essential, especially in the inherited forms of amyloidosis

Ikura, H.; Endo, J.; Kitakata, H.; Moriyama, H.; Sano, M.; Fukuda, K. Molecular Mechanism of Pathogenesis and Treatment Strategies for AL Amyloidosis. *Int. J. Mol. Sci.* **2022**, *23*, 6336. https://doi.org/10.3390/ijms23116336

XVIII. International Symposium on Amyloidosis 4th – 8th September 2022 | Heidelberg

ISA 2022

XVIII. International Symposium or



elberg

ISA 2022

Amyloid
The Journal of Protein Folding Disorders

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Amyloid nomenclature 2020: update and recommendations by the International Society of Amyloidosis (ISA) nomenclature committee

Merrill D. Benson , Joel N. Buxbaum , David S. Eisenberg , Giampaolo Merlini , Maria J. M. Saraiva , Yoshiki Sekijima , Jean D. Sipe & Per Westermark

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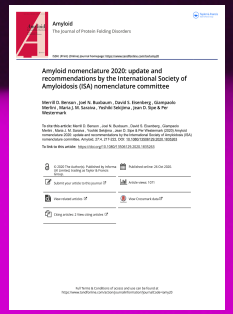
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Amyloidosis Current View

International Society of Amyloidosis (ISA) guidelines/classification 2022

42 subtypes of amyloidosis

14 proteins in systemic amyloidosis

24 proteins as a part of localised forms of amyloidosis

4 proteins in both forms

Amyloidosis Current View

Nomenclature

A + suffix + amyloidosis

AL, ATTRwt, ATTRv, ATTRV30M, AA, ALys… amyloidosis

Fibril protein 2020	Precursor protein	Systemic and/or localised	Acquired or hereditary	Target organs
AL	Immunoglobulin light chain	S, L	A, H	All organs, usually except CNS
AH	Immunoglobulin heavy chain	S, L	A	All organs except CNS
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Aβ2M	β2-microglobulin, wild type	S	A	Musculoskeletal system
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AApoAI	Apolipoprotein A I, variants	S	H	Heart, liver, kidney, PNS, testis, larynx (C terminal variants), skin (C terminal variants)
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[illegible]022				
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ATMEM106B	Transmembrane 106B (TMEM106B)	L	A	Frontotemporal lobar degeneration diseases
ASom	(Pro)somatostatin	L	A	Somatostatinomas
AGluc	Glucagon	L	A	Glucagonomas
APTH	Parathyroid hormone	L	A	Parathyroid tumours, Ageing parathyroid glands
AGLP1	Glucagon-like peptide 1 analog	L	I	Iatrogenic, local injection
AIL1RAP	Interleukin-1 receptor antagonist protein	L	I	Iatrogenic, local injection

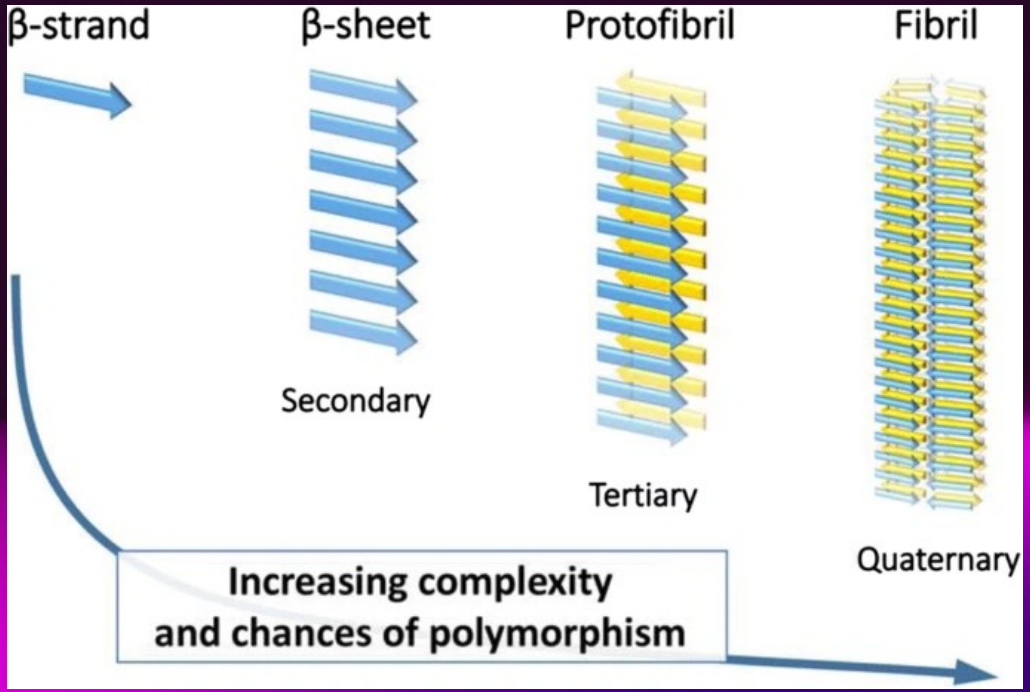
Amyloidosis Current View

Amyloid fibril

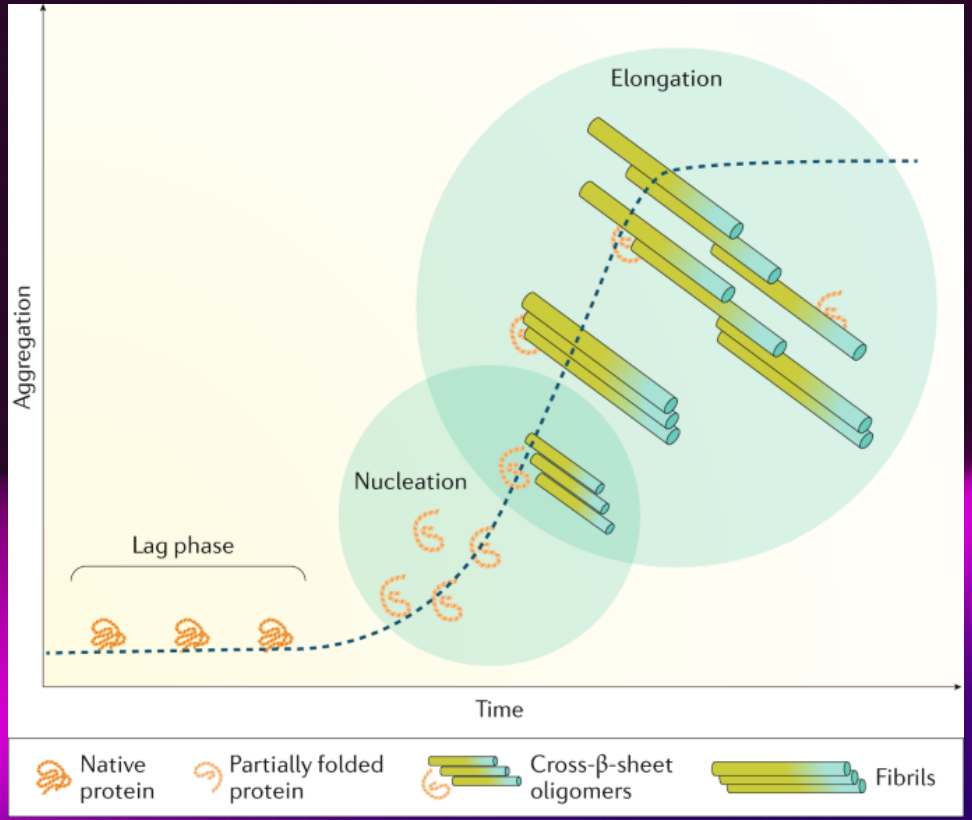
- twisted protofilaments (usualy 1-4) in β-sheets

Additional components

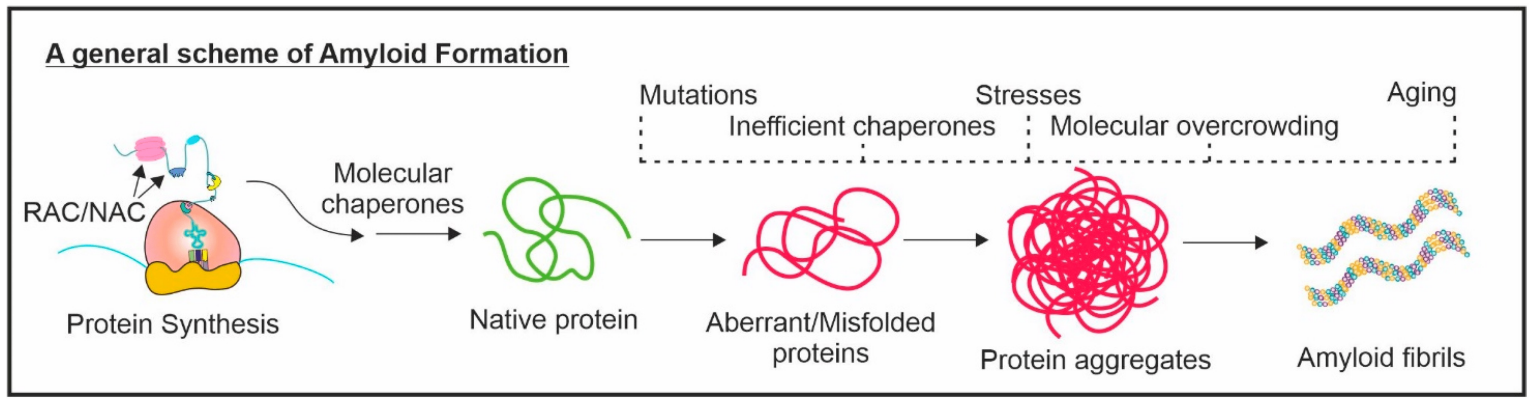
- signature proteins (HSPG, SAP, apoAI, apoAIV, apoE…) ubiquitous



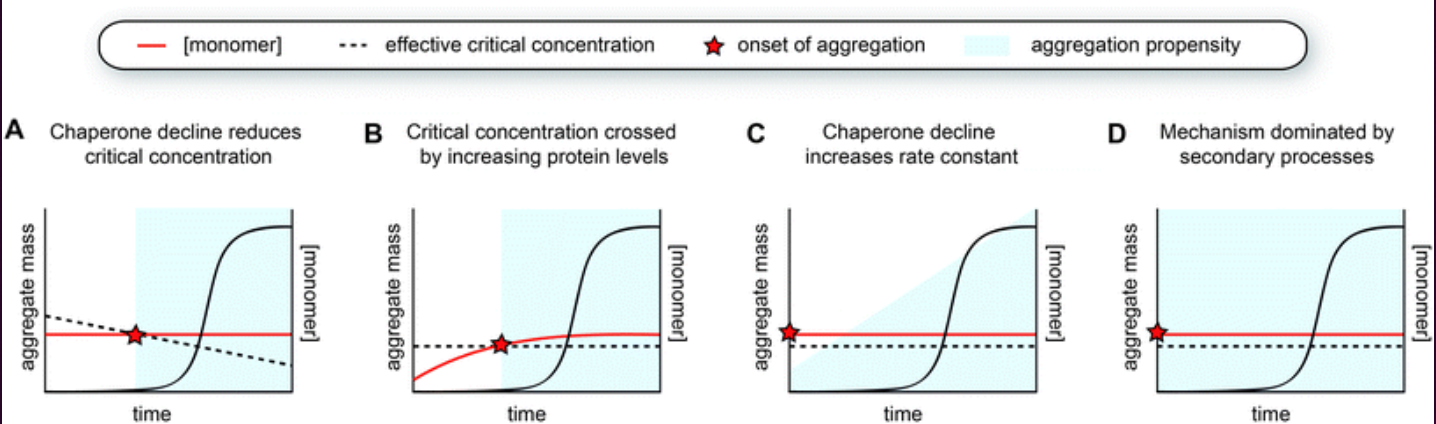
Martial, B., Lefèvre, T. & Auger, M. Understanding amyloid fibril formation using protein fragments: structural investigations via vibrational spectroscopy and solid-state NMR. Biophys Rev 10, 1133–1149 (2018). https://doi.org/10.1007/s12551-018-0427-2

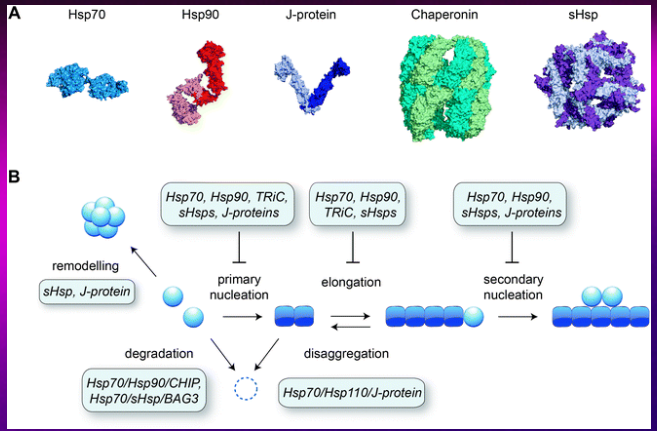


Merlini, G., Dispenzieri, A., Sanchorawala, V. *et al.* Systemic immunoglobulin light chain amyloidosis. *Nat Rev Dis Primers* **4**, 38 (2018). https://doi.org/10.1038/s41572-018-0034-3



Upadhyay, A. Vesicular Transport and Amyloids: The Growing Relationship. *Biologics* **2024**, *4*, 376-389. https://doi.org/10.3390/biologics4040023





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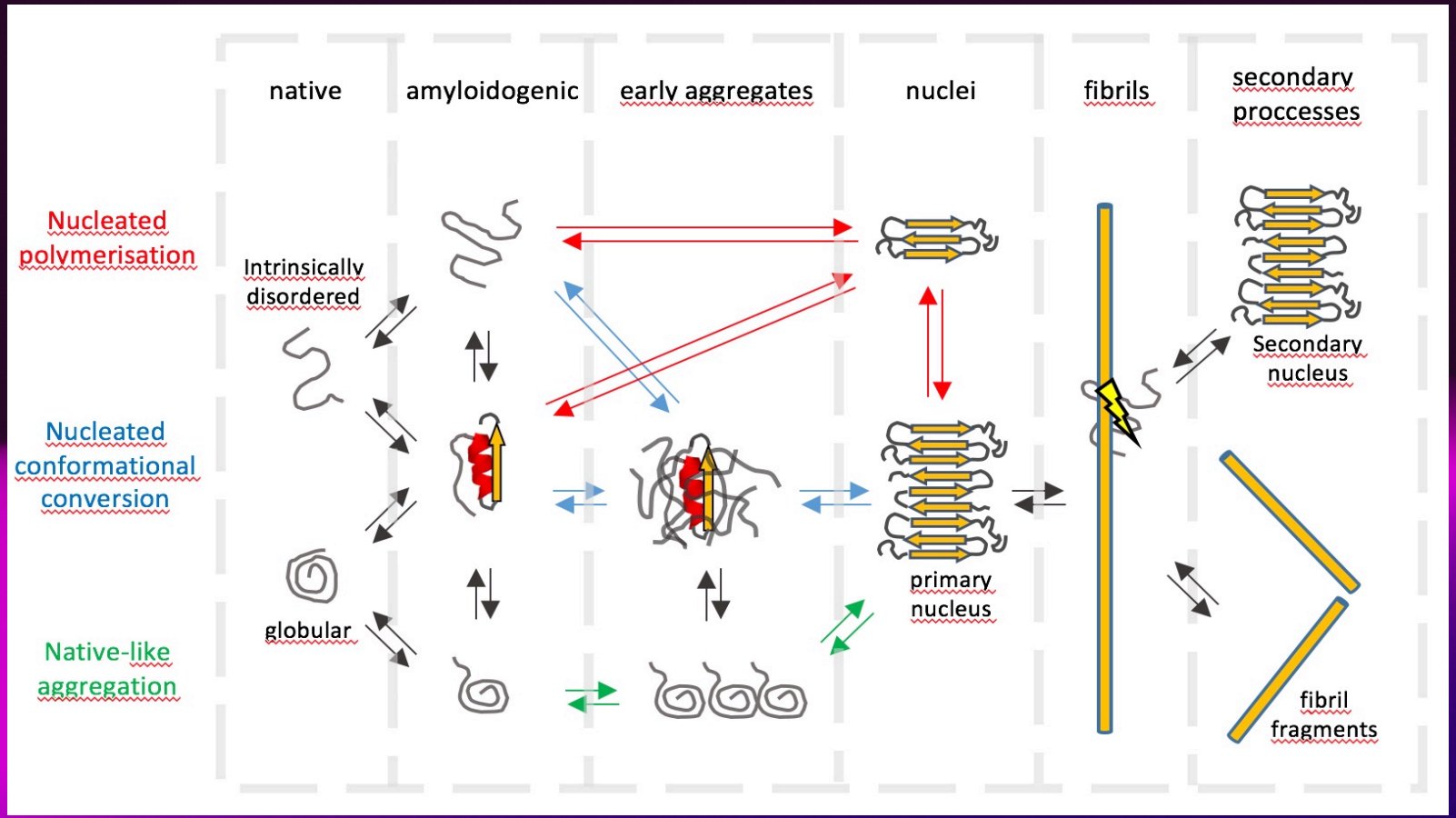

native
amyloidogenic
early aggregates
nuclei
fibrils
secondary proccesses
Nucleated polymerisation
Intrinsically disordered
Secondary nucleus
Nucleated conformational conversion
primary nucleus
globular
Native-like aggregation
fibril fragments

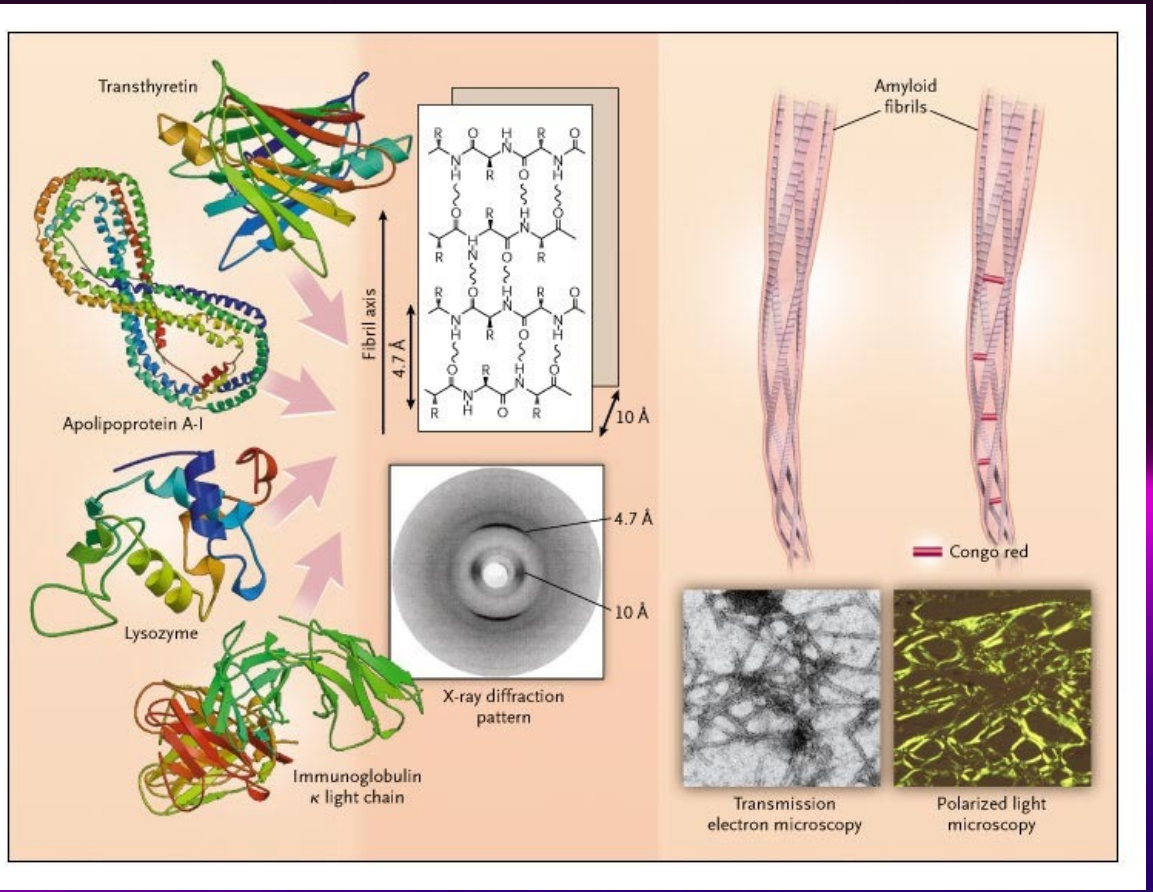
Amyloidosis Current View

Cytotoxicity

Oligomers – small non-fibrillar amyloid protein aggregates

Protofibrils – delineation towards oligomers is not absolutely clear

Both produce tissue damage


Transthyretin
Apolipoprotein A-I
Lysozyme
Immunoglobulin
κ light chain
Fibril axis
4.7 Å
10 Å
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X-ray diffraction
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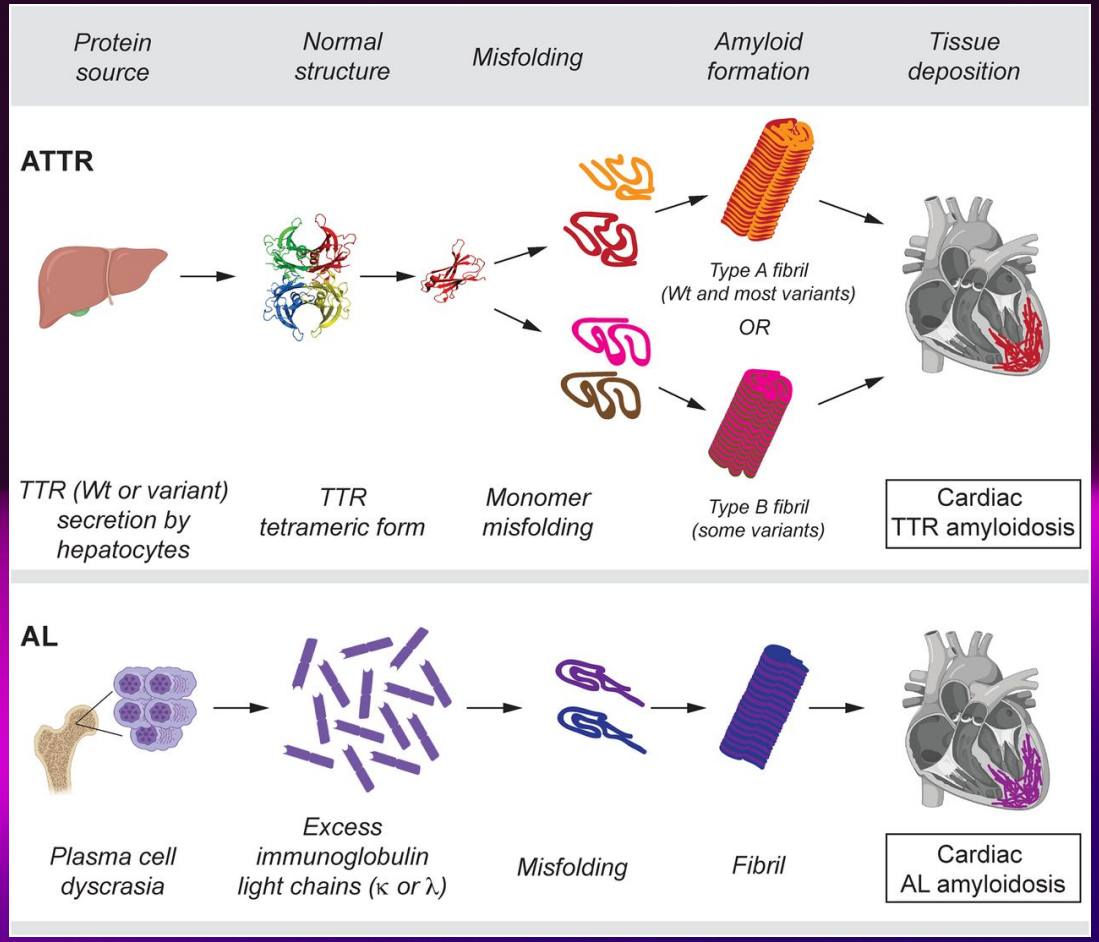
Protein source
Normal structure
Misfolding
Amyloid formation
Tissue deposition
ATTR
Type A fibril
(Wt and most variants)
OR
Type B fibril
(some variants)
TTR (Wt or variant) secretion by hepatocytes
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AL
Plasma cell dyscrasia
Excess immunoglobulin light chains (κ or λ)
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Fibril
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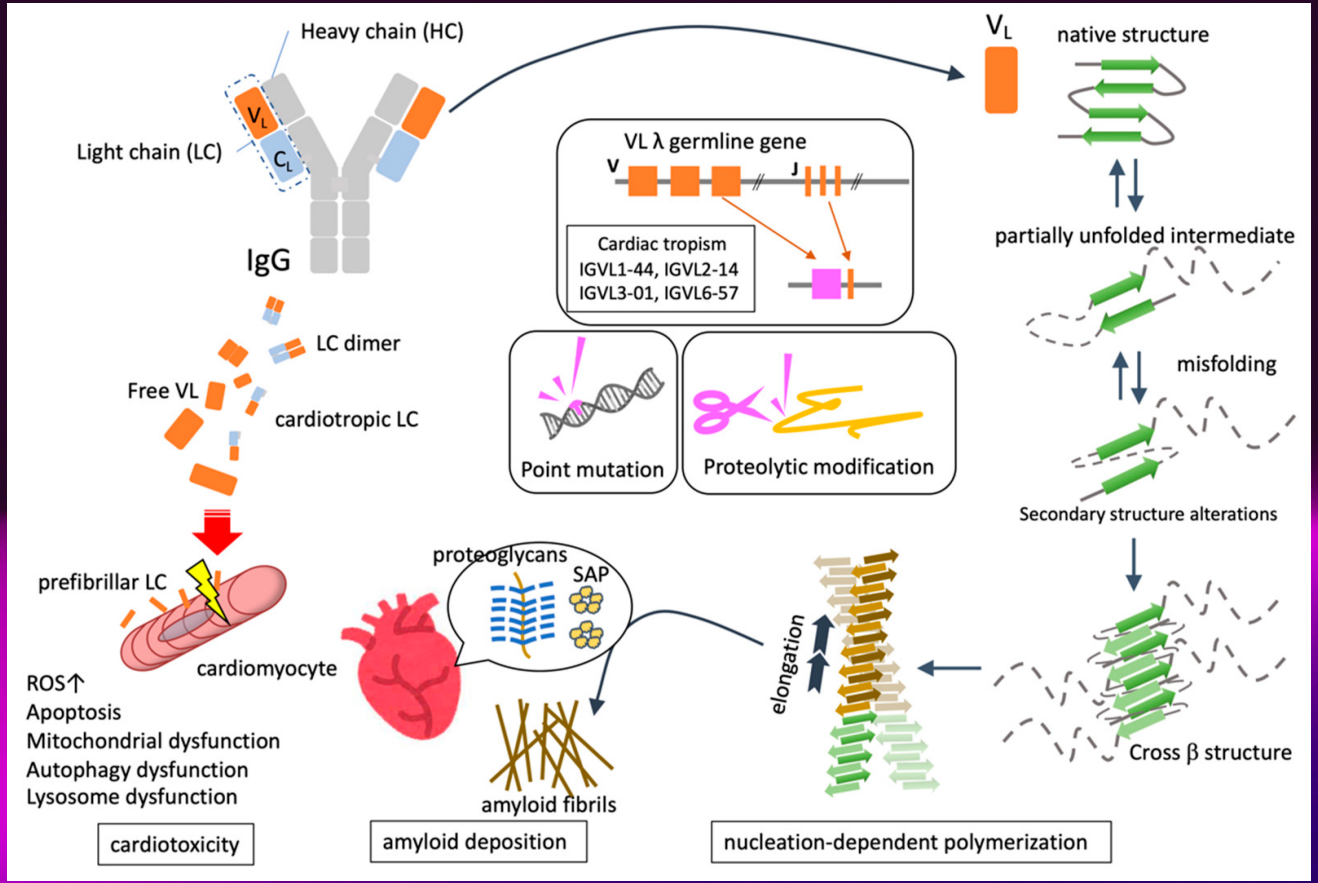

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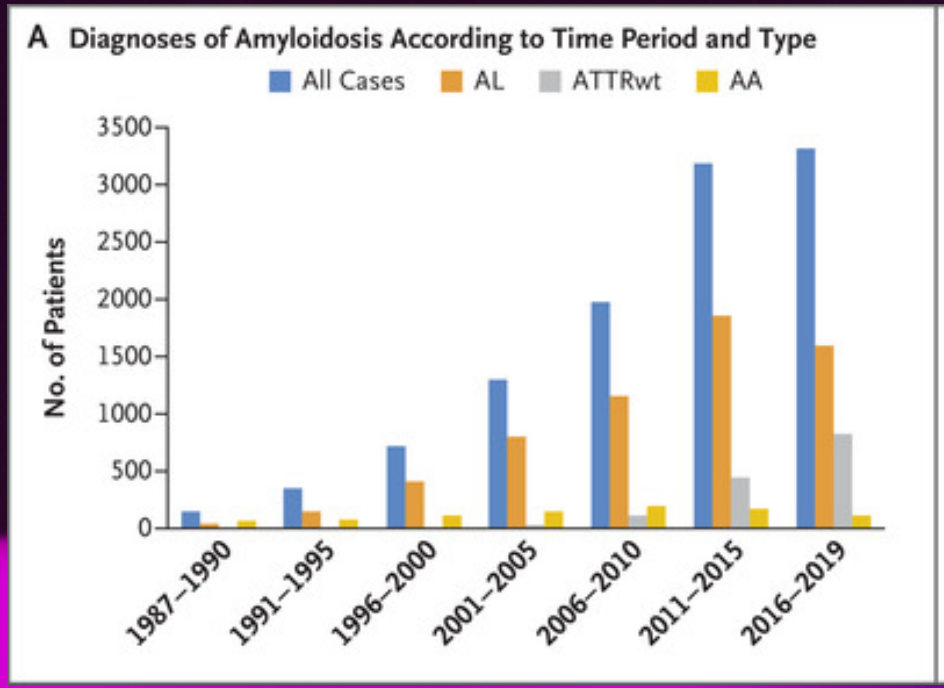
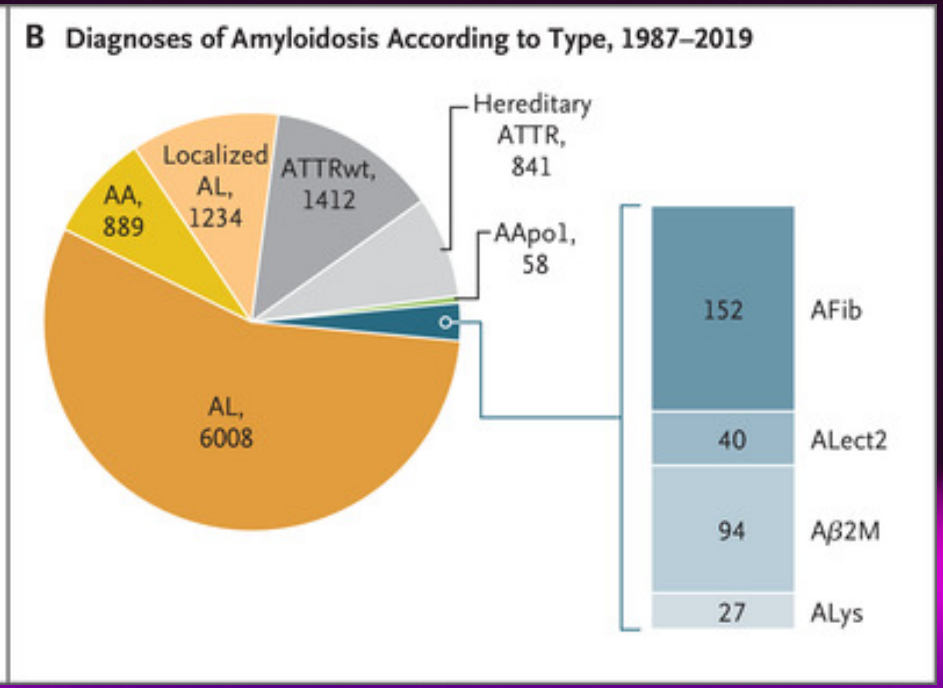




N Engl J Med 2020; 382:1567-1568, DOI: 10.1056/NEJMc1917321

Monoclonal gammopathy of unknown significance/MGUS

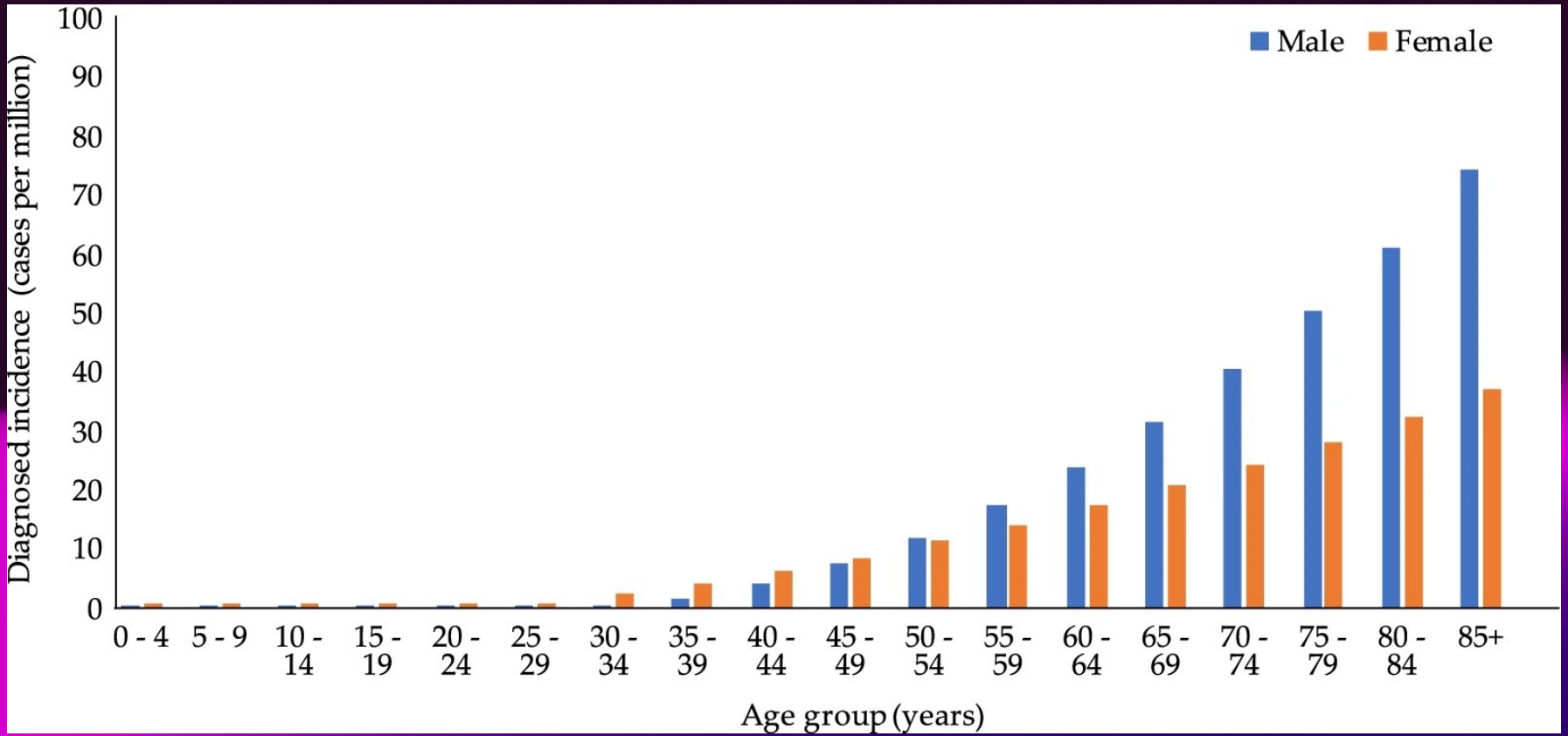
- the relative risk is 8.8
- 1% incidence of AL amyloidosis observed in a study involving 1384 patients with MGUS

Multiple myeloma

- AL amyloidosis is diagnosed in 10 to 15% of MM patients

Sanchorawala V. Systemic Light Chain Amyloidosis. N Engl J Med. 2024 Jun 27;390(24):2295-2307. doi: 10.1056/NEJMra2304088. PMID: 38924733.

Age-specific incidence of AL amyloidosis, by sex



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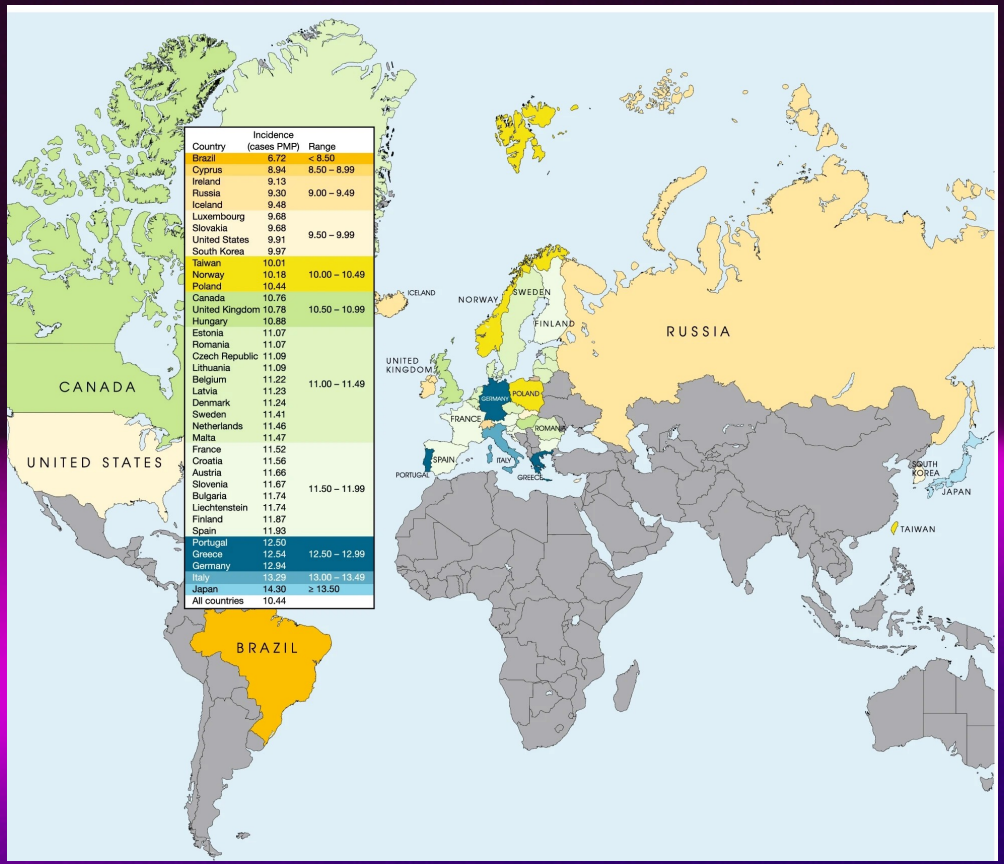
Calculated crude incidence in 2018, by country



Country	Incidence (cases PMP)	Range
Brazil	6.72	< 8.50
Cyprus	8.94	8.50 – 8.99
Ireland	9.13	
Russia	9.30	9.00 – 9.49
Iceland	9.48	
Luxembourg	9.68	
Slovakia	9.68	9.50 – 9.99
United States	9.91	
South Korea	9.97	
Taiwan	10.01	
Norway	10.18	10.00 – 10.49
Poland	10.44	
Canada	10.76	
United Kingdom	10.78	10.50 – 10.99
Hungary	10.88	
Estonia	11.07	
Romania	11.07	
Czech Republic	11.09	
Lithuania	11.09	
Belgium	11.22	11.00 – 11.49
Latvia	11.23	
Denmark	11.24	
Sweden	11.41	
Netherlands	11.46	
Malta	11.47	
France	11.52	
Croatia	11.56	
Austria	11.66	
Slovenia	11.67	11.50 – 11.99
Bulgaria	11.74	
Liechtenstein	11.74	
Finland	11.87	
Spain	11.93	
Portugal	12.50	
Greece	12.54	12.50 – 12.99
Germany	12.94	
Italy	13.29	13.00 – 13.49
Japan	14.30	≥ 13.50
All countries	10.44	

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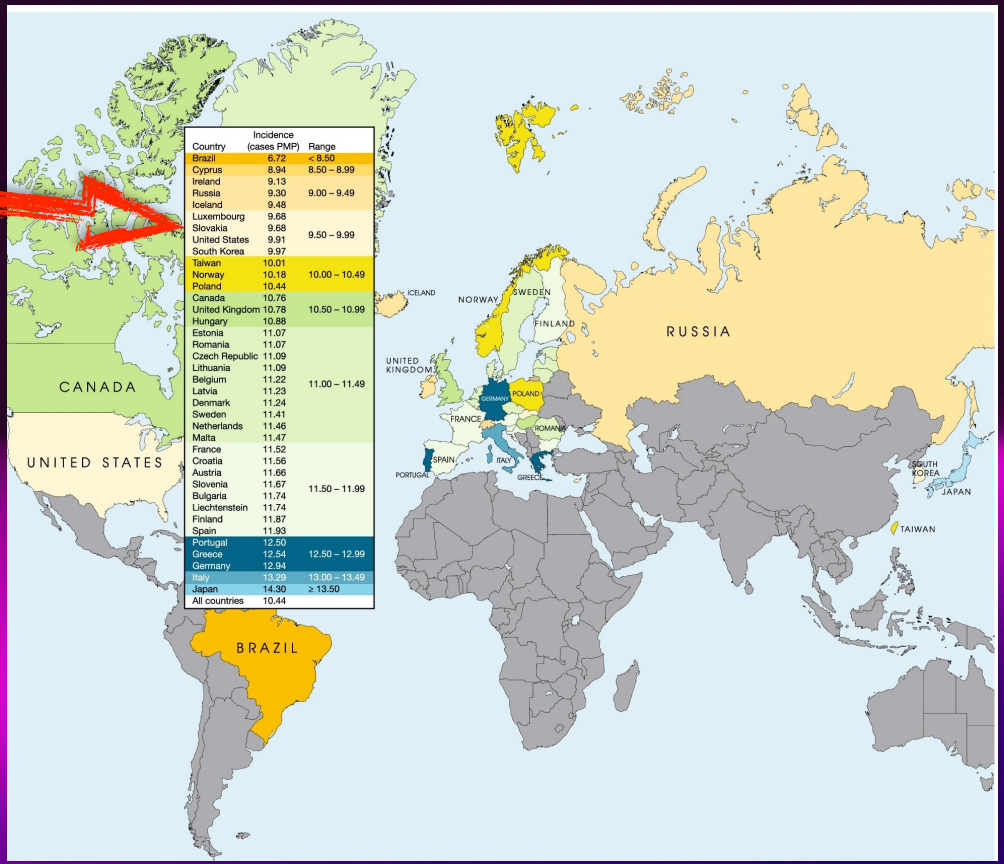

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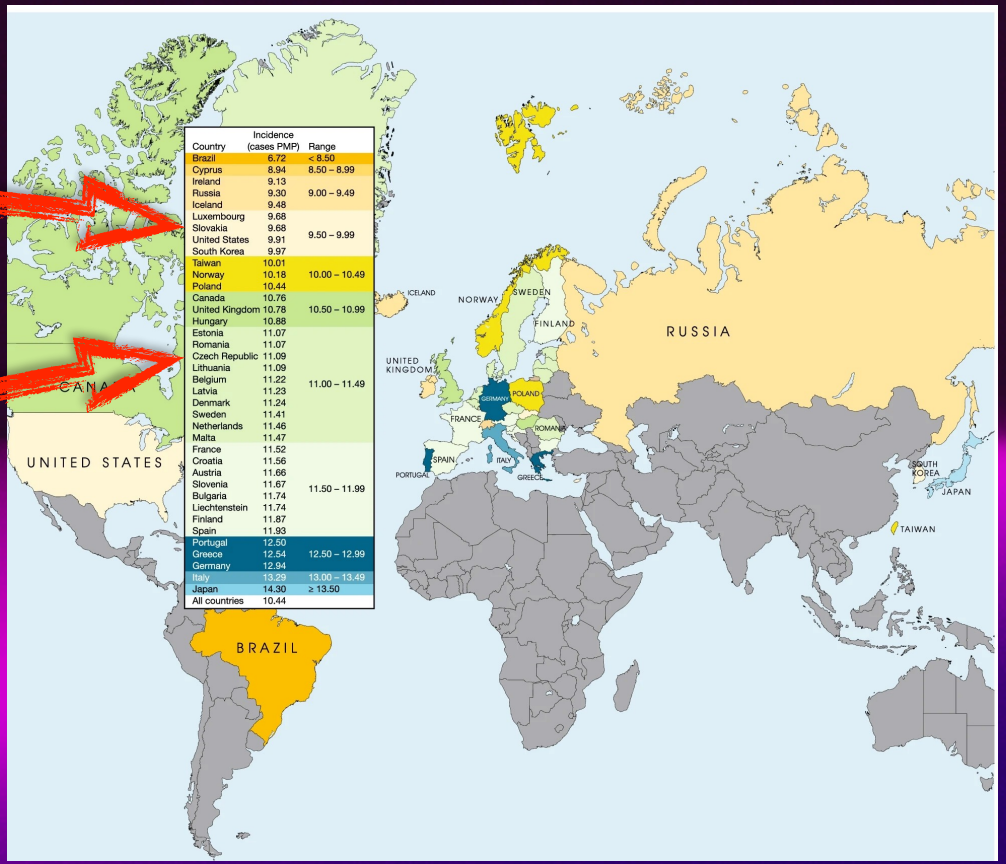

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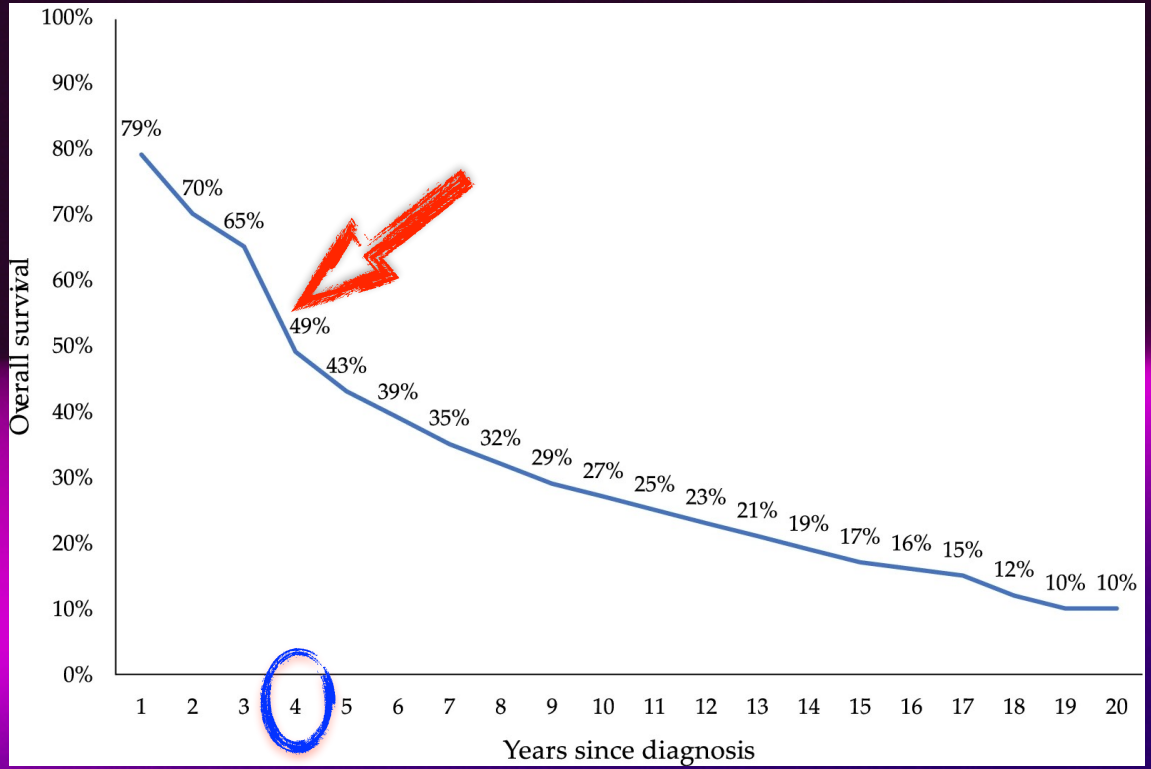
Relative survival of AL amyloidosis, by year since diagnosis



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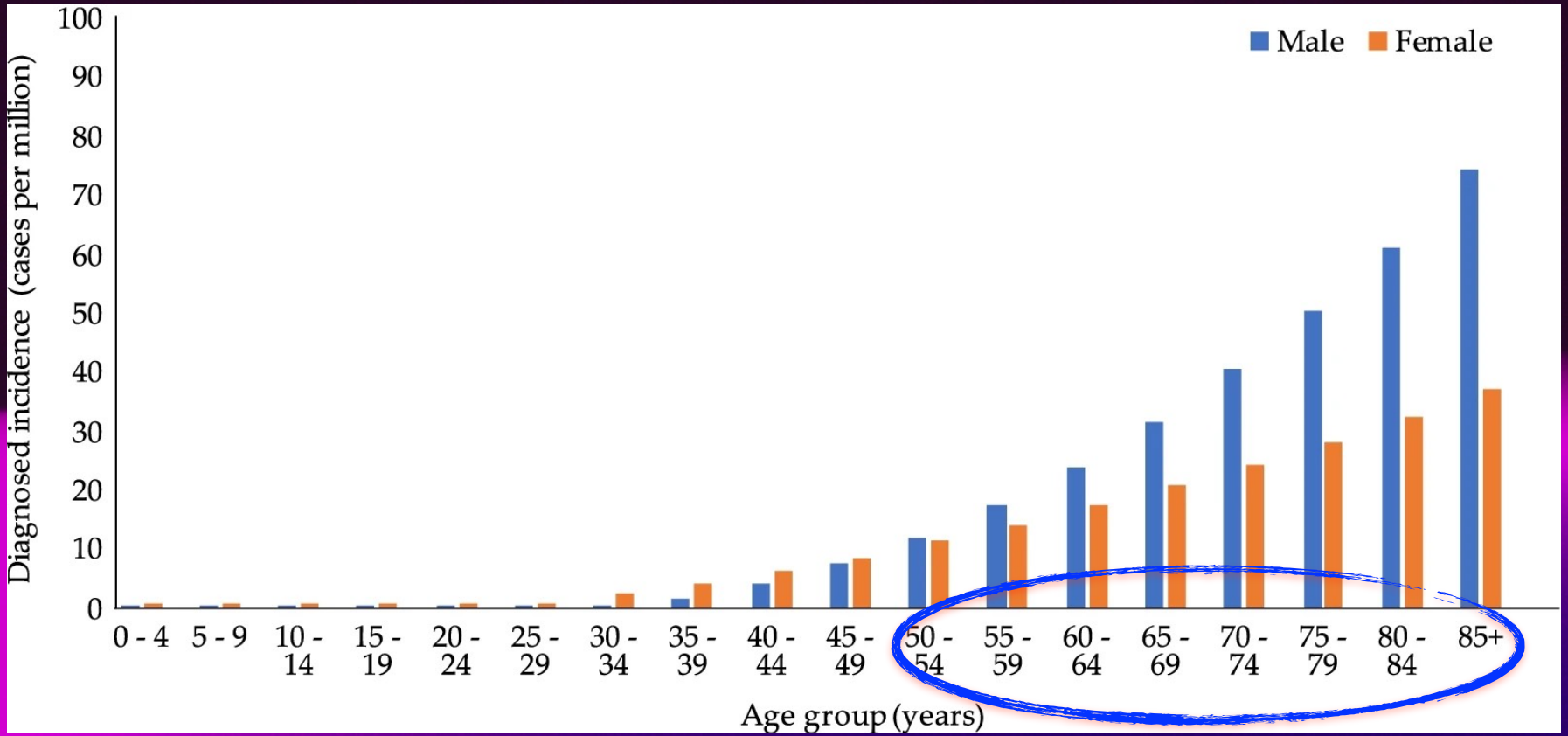

Kumar N, Zhang NJ, Cherepanov D, Romanus D, Hughes M, Faller DV. Global epidemiology of amyloid light-chain amyloidosis. Orphanet J Rare Dis 2022; 17: 27

The 20-year prevalence

- for all countries was estimated at **51.27 PMP**
- ranging from 32.22 PMP in Brazil to 71.08 PMP in Japan

An **increase in AL amyloidosis prevalence**

- observed over time in all the countries under the study

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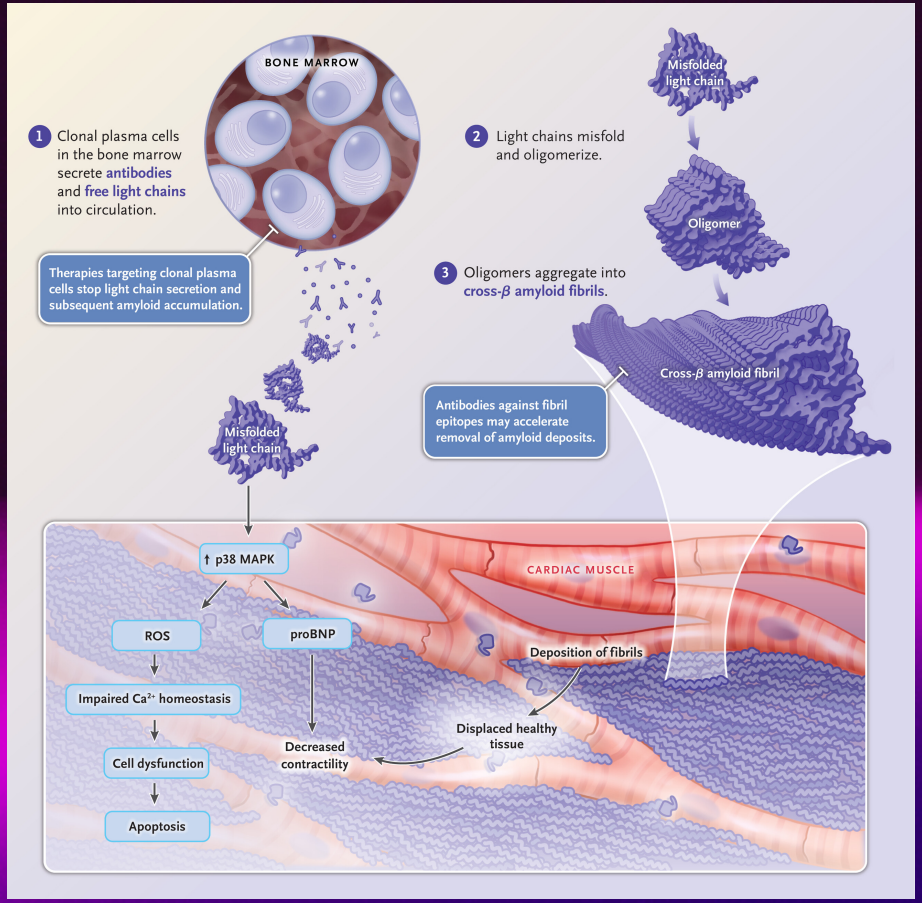

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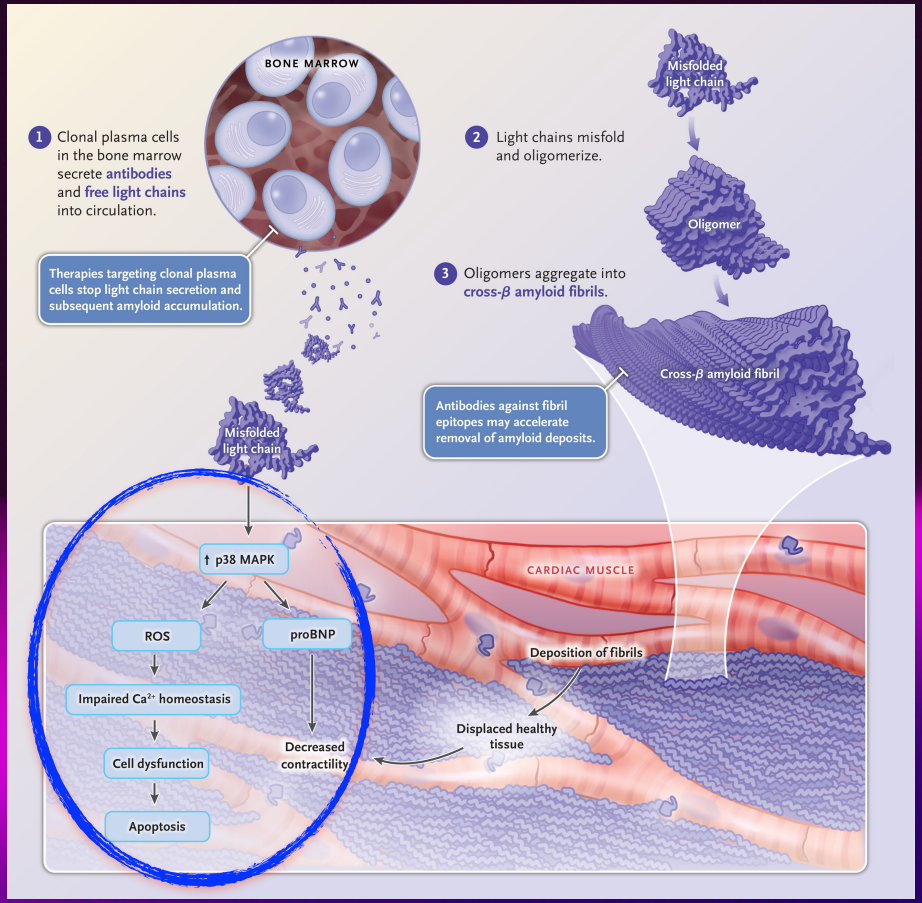

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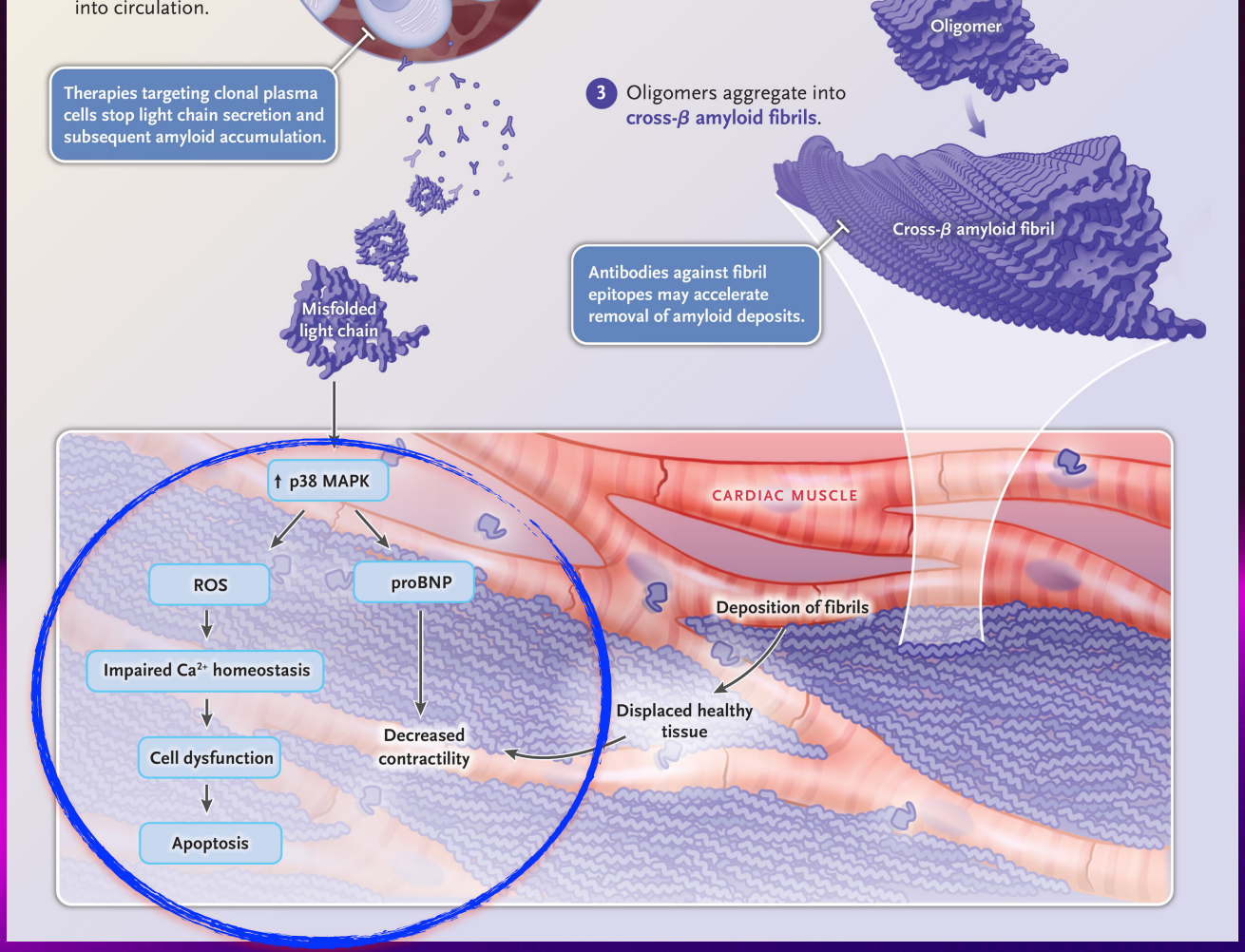

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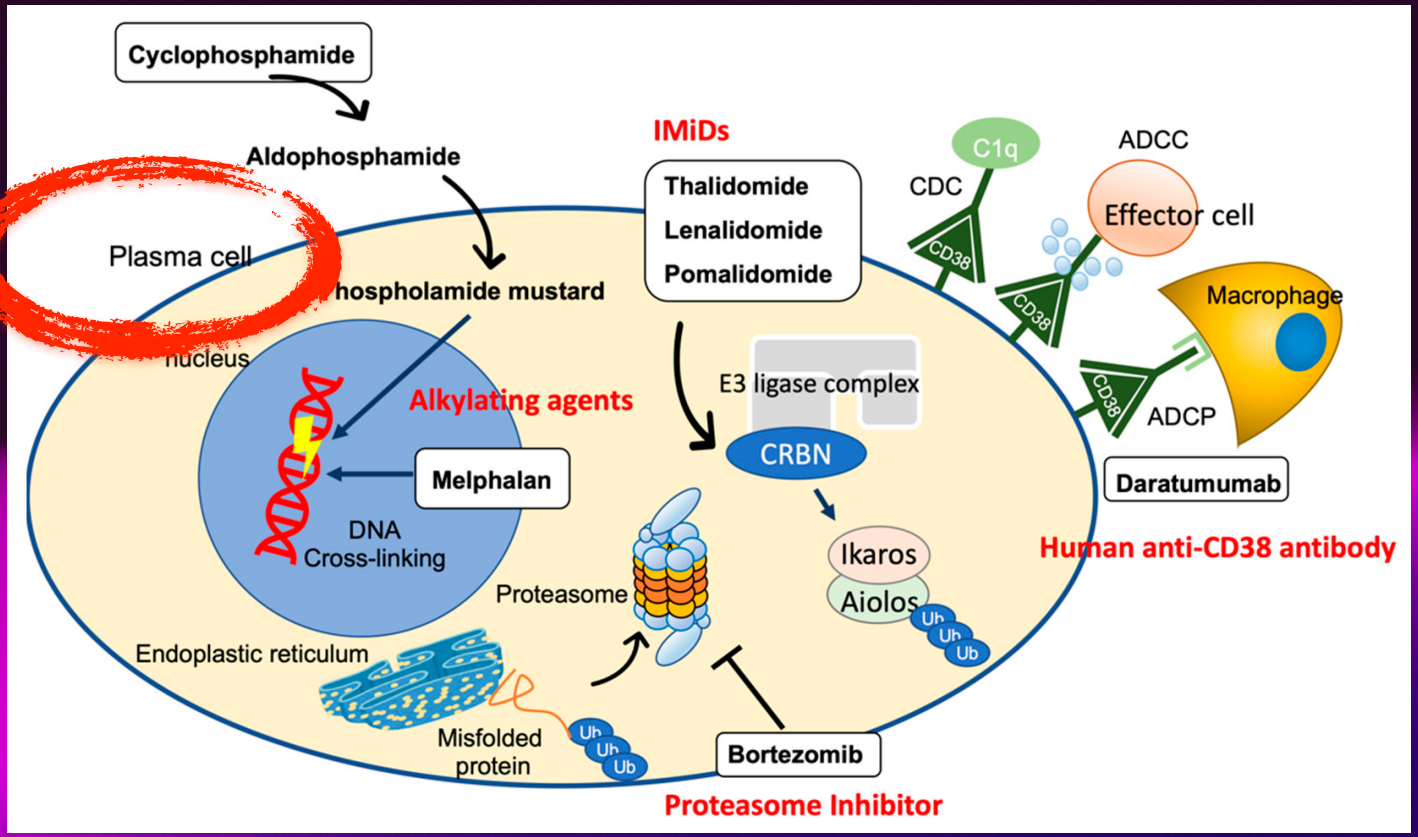
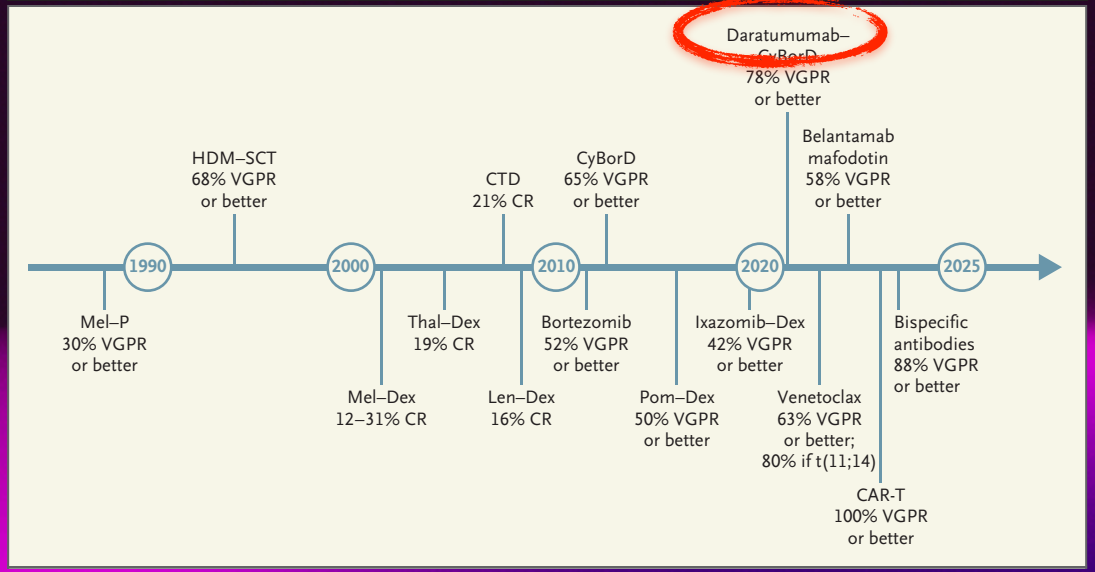
Therapeutic Landscape of AL Amyloidosis



Ikura, H.; Endo, J.; Kitakata, H.; Moriyama, H.; Sano, M.; Fukuda, K. Molecular Mechanism of Pathogenesis and Treatment Strategies for AL Amyloidosis. *Int. J. Mol. Sci.* **2022**, *23*, 6336. https://doi.org/10.3390/ijms23116336

Therapeutic Landscape of AL Amyloidosis

targeting the underlying plasma cell clone



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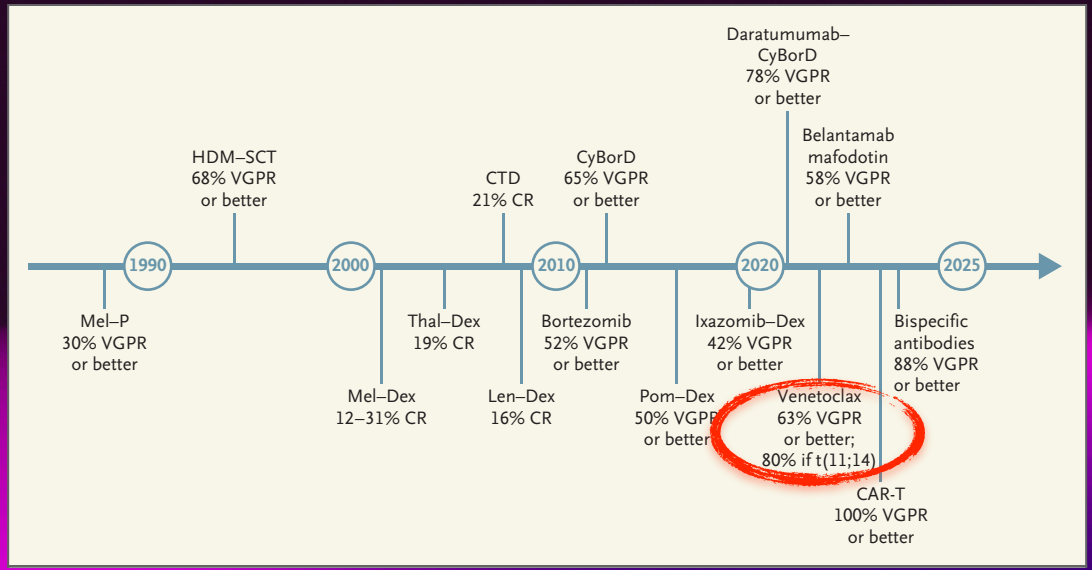

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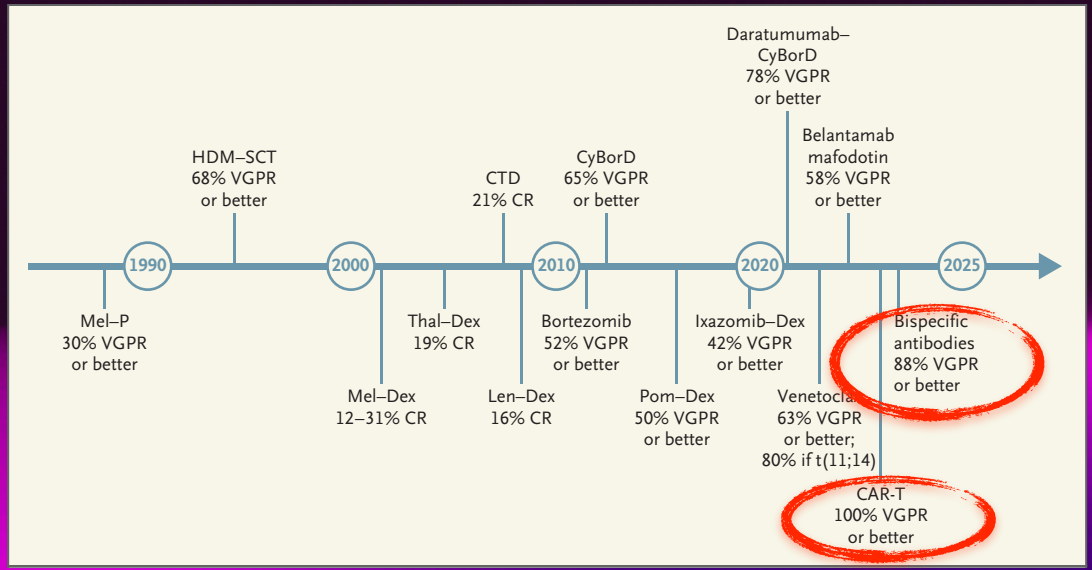

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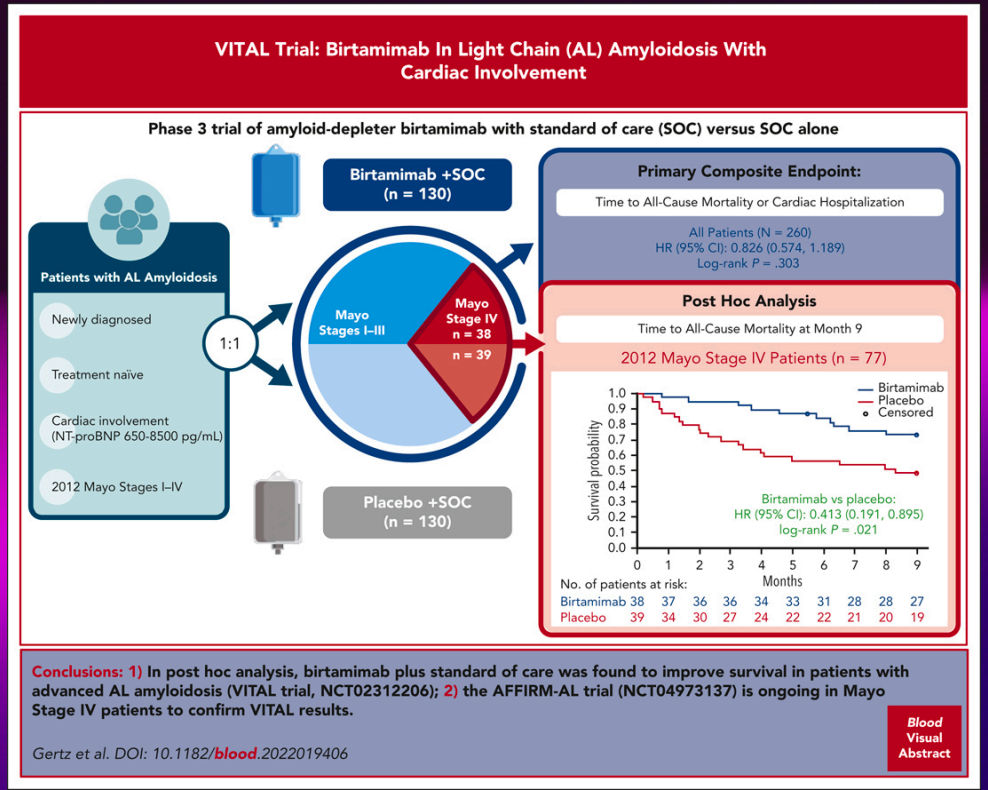
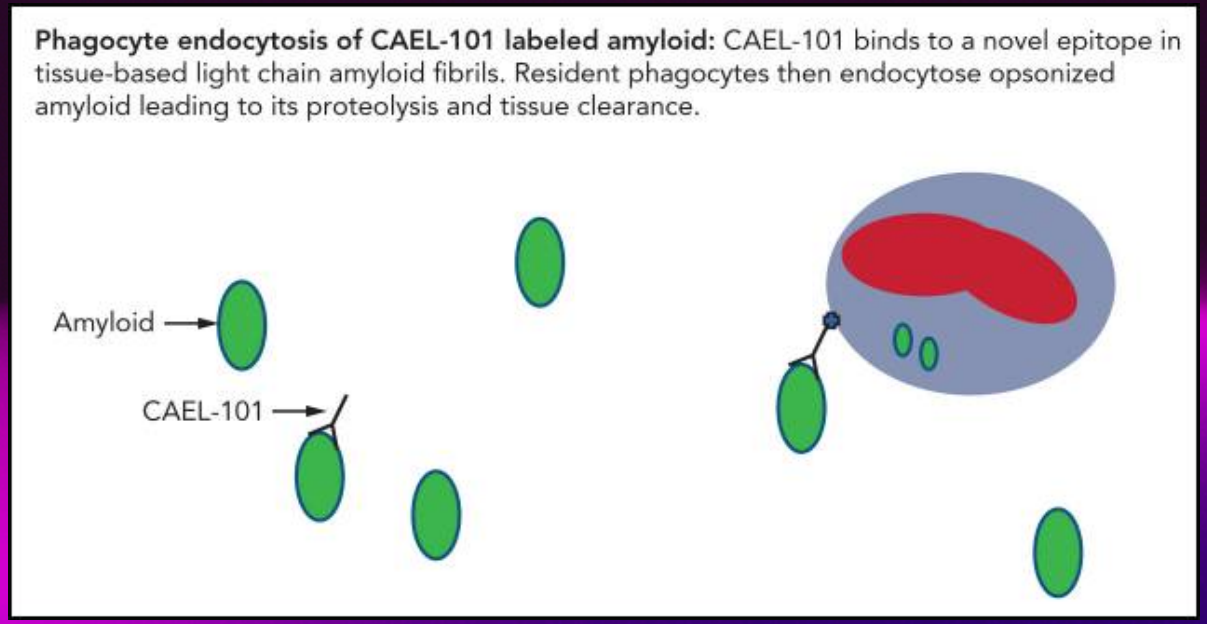
Birtamimab/NEOD0001

Fully humanized monoclonal antibody targeting a cryptic epitope on serum amyloid A protein and crossreacts with immunoglobulin light chain amyloid fibrils



Anselamimab/CAEL-101

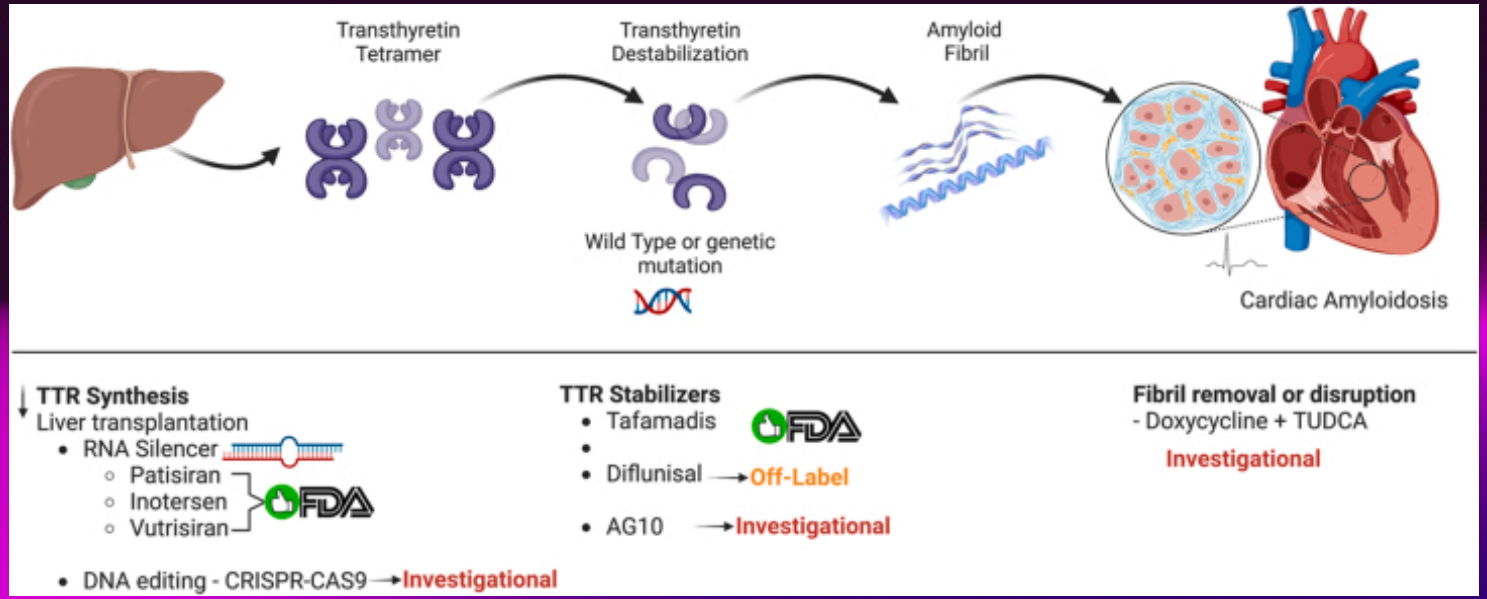
Chimeric monoclonal antibody targeting a cryptic epitope on immunoglobulin light chains



Edwards CV, Rao N, Bhutani D, Mapara M, Radhakrishnan J, Shames S, Maurer MS, Leng S, Solomon A, Lentzsch S, Eisenberger A. Phase 1a/b study of monoclonal antibody CAEL-101 (11-1F4) in patients with AL amyloidosis. Blood. 2021 Dec 23;138(25):2632-2641. doi: 10.1182/blood.2020009039. PMID: 34521113; PMCID: PMC8703360.

TTR Amyloidosis

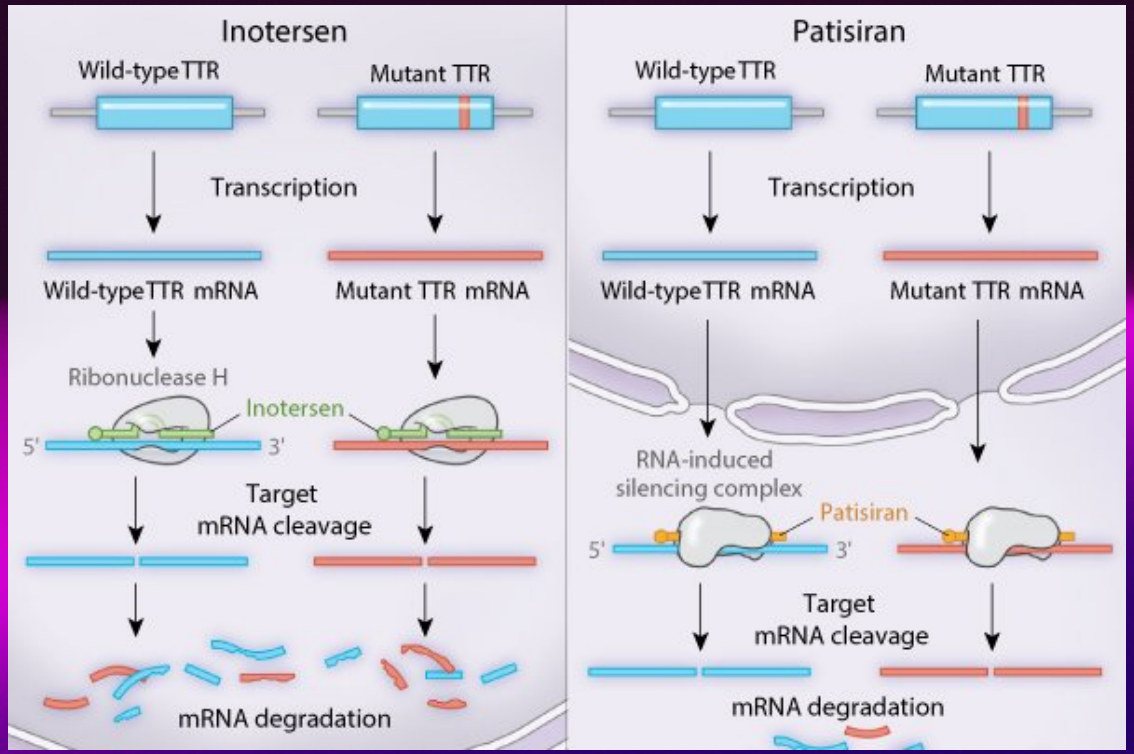
Current State

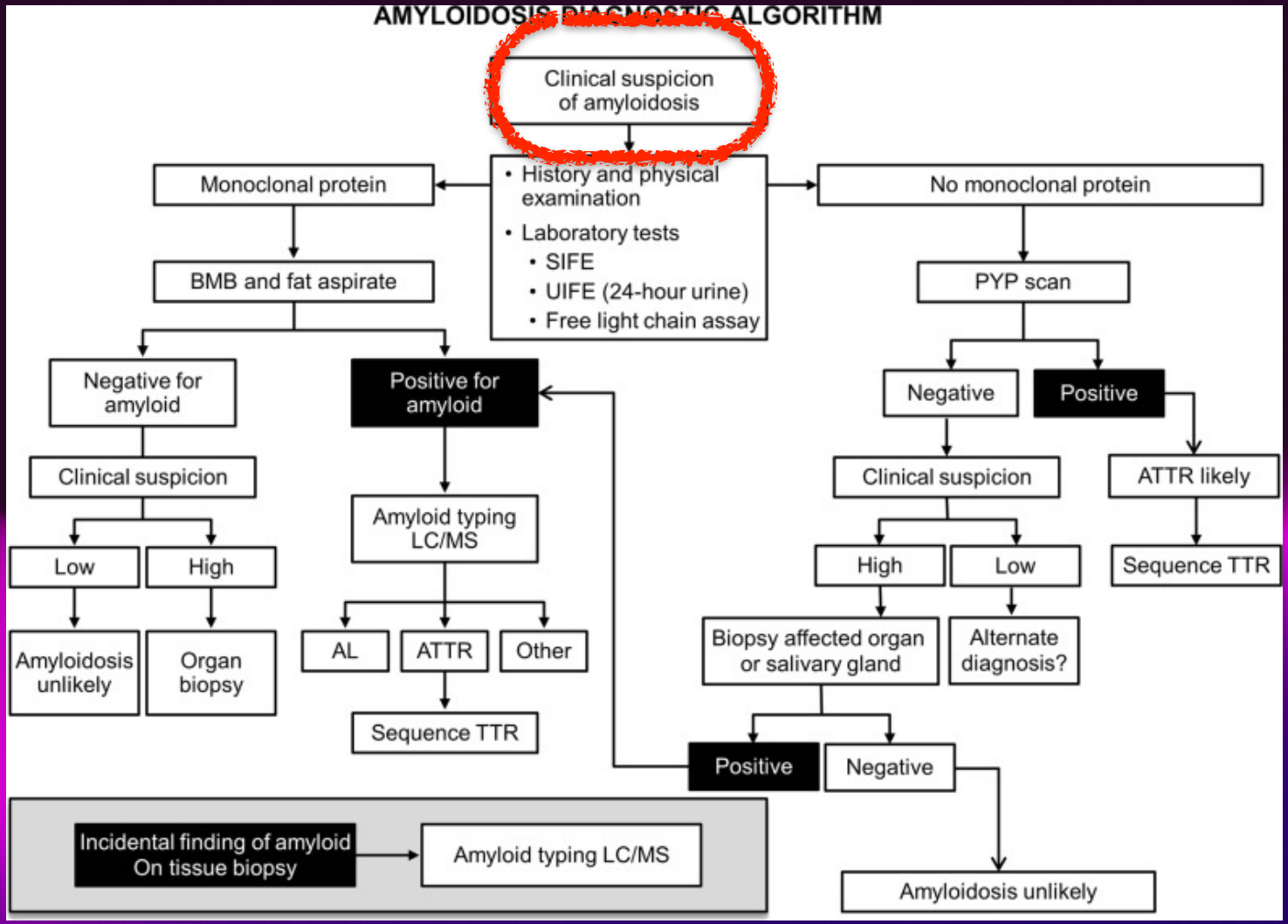


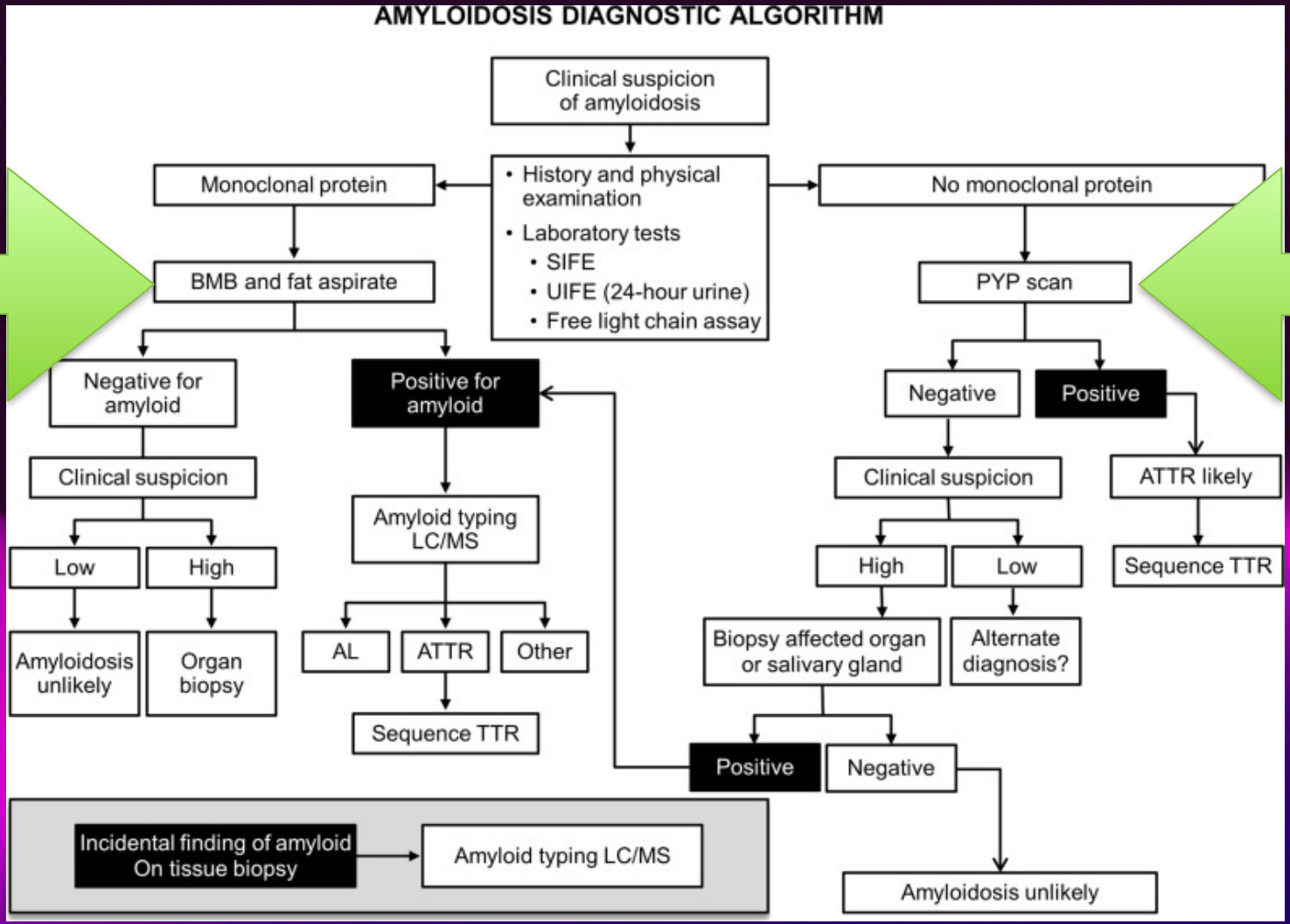
Brailovsky Y, Rajapreyar I, Alvarez R. TTR Amyloidosis: Current State of Affairs and Promise for the Future. JACC Case Rep. 2023 Mar 15;10:101759. doi: 10.1016/j.jaccas.2023.101759. PMID: 36974058; PMCID: PMC10039388.

Patisiran and inotersen

Recently approved by the FDA and the European Medicines Agency for the treatment of hereditary ATTR amyloidosis and ATTRwt amyloidosis




AMYLOIDOSIS DIAGNOSTIC ALGORITHM
Clinical suspicion of amyloidosis
• History and physical examination
• Laboratory tests
• SIFE
• UIFE (24-hour urine)
• Free light chain assay
Monoclonal protein
BMB and fat aspirate
Negative for amyloid
Clinical suspicion
Low
High
Amyloidosis unlikely
Organ biopsy
Positive for amyloid
Amyloid typing LC/MS
AL
ATTR
Other
Sequence TTR
No monoclonal protein
PYP scan
Negative
Positive
Clinical suspicion
ATTR likely
High
Low
Sequence TTR
Biopsy affected organ or salivary gland
Alternate diagnosis?
Positive
Negative
Amyloidosis unlikely
Incidental finding of amyloid On tissue biopsy
Amyloid typing LC/MS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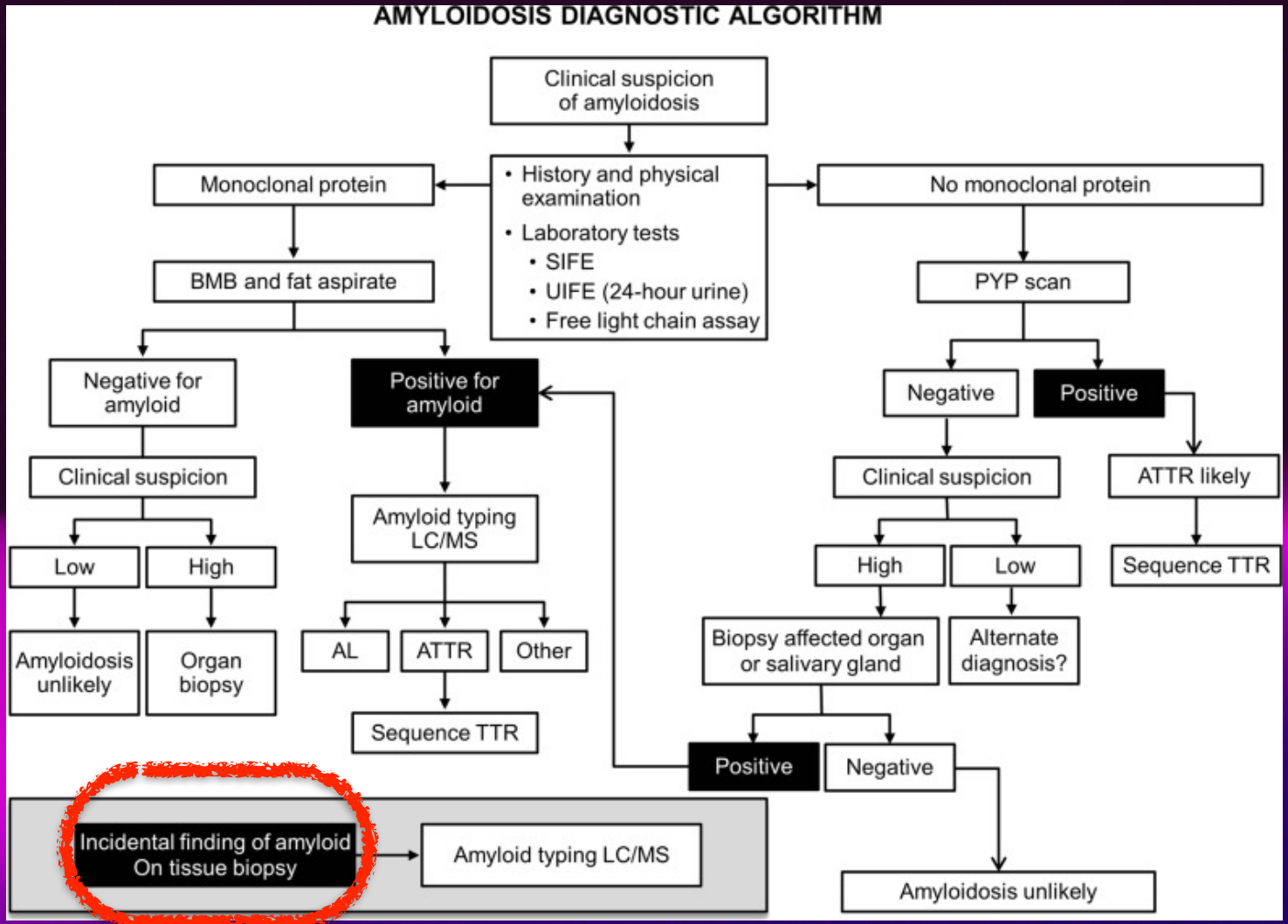
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Amyloidosis Current Analysis

Detection steps

Affinity for Congo red and their yellow-green birefringence/dichroism under polarized light, Saturn red, Thioflavin T

Typing steps

IHC/IF analysis (kappa, lambda, IgH, TTR, AA, lysozyme, fibrinogen…)

LCM-LC/MS - thousands of proteins in one run

Fat pad – direct CR with LC/MS without IHC/IF and LCM

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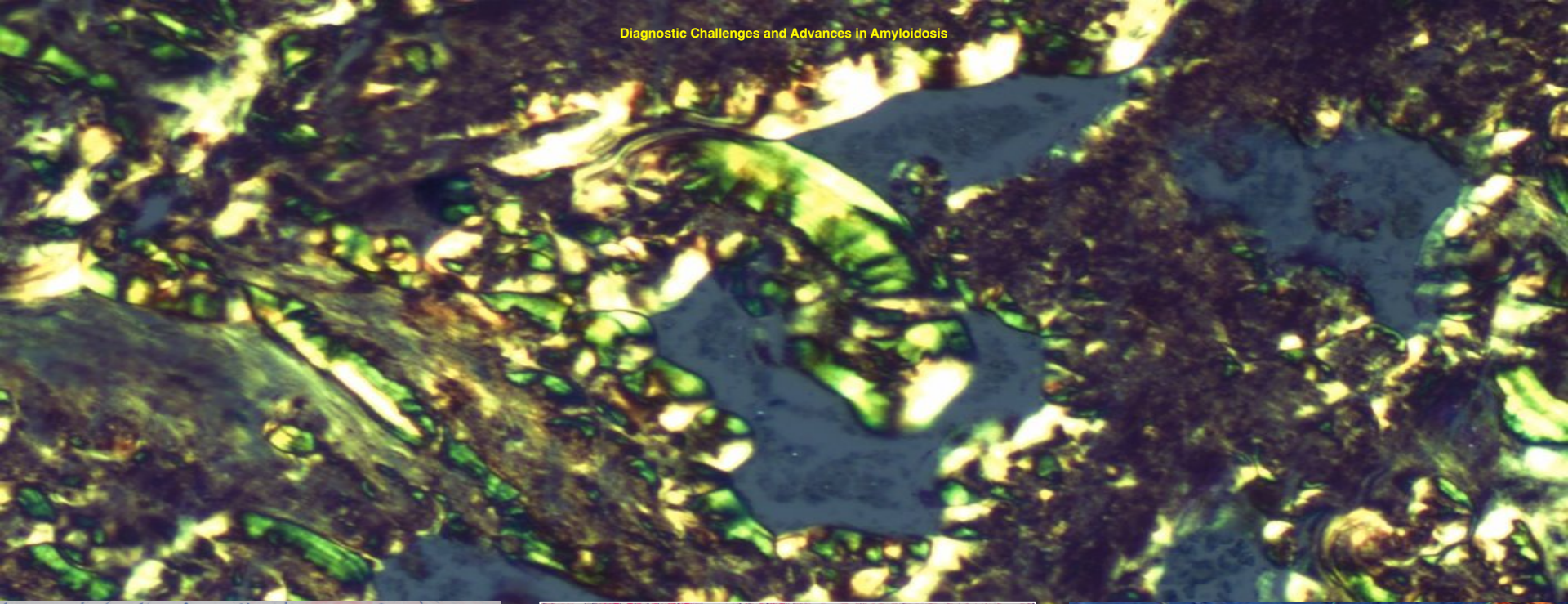
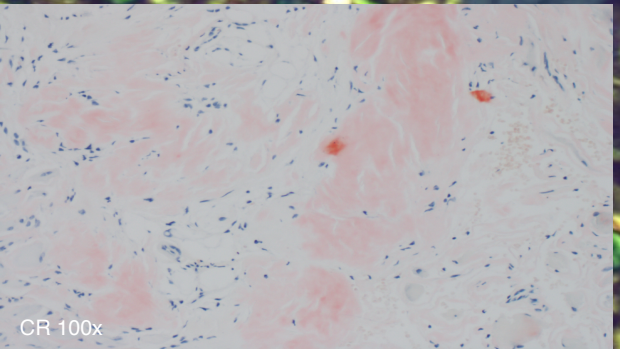
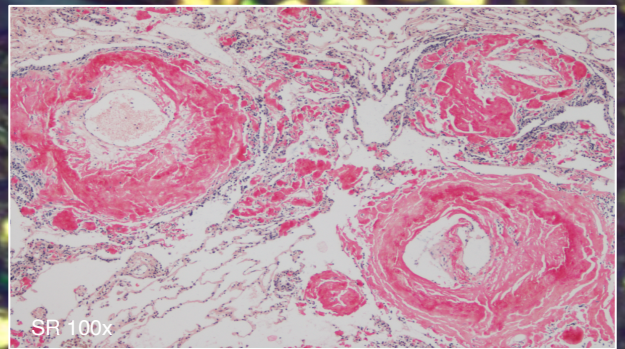
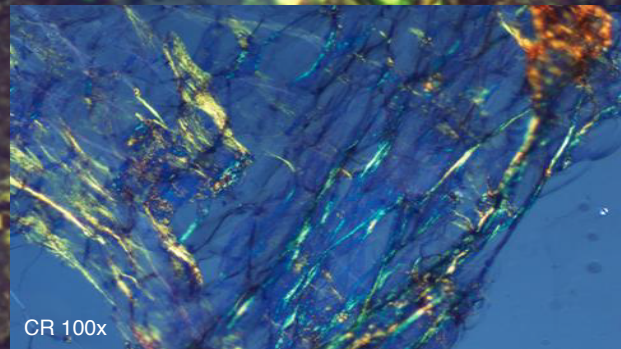
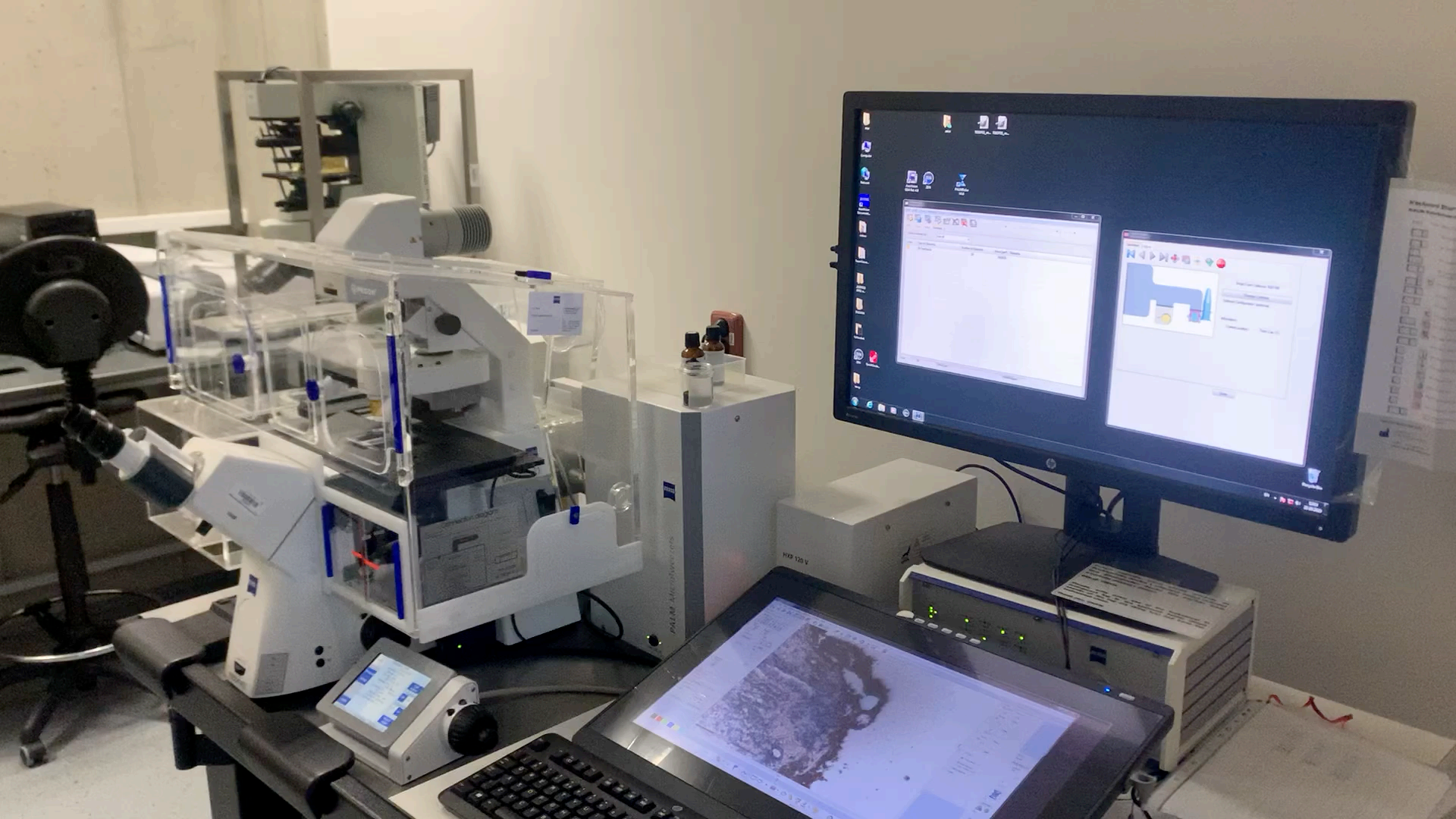
Diagnostic Challenges and Advances in Amyloidosis

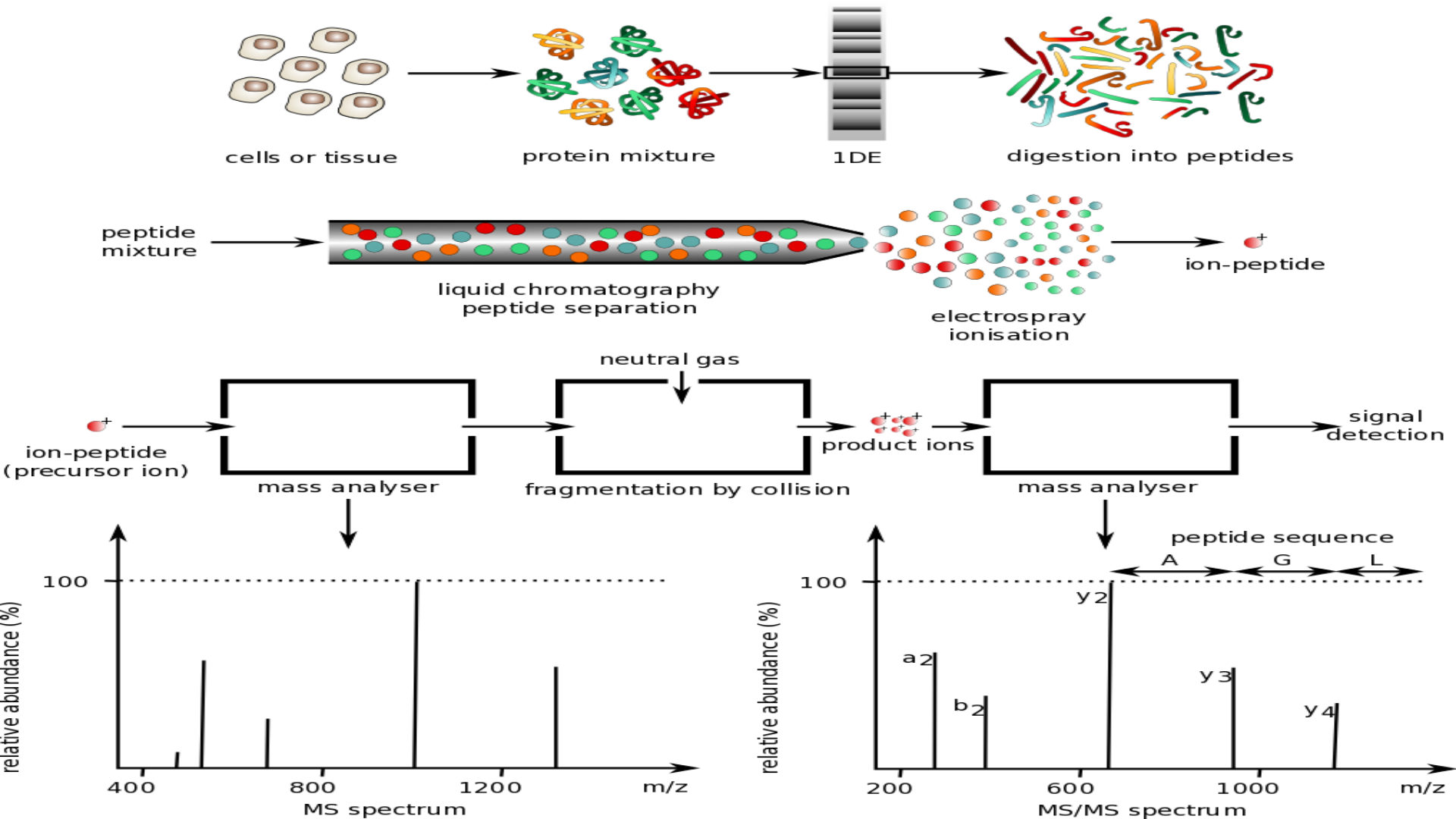











cells or tissue
protein mixture
1DE
digestion into peptides
peptide mixture
liquid chromatography peptide separation
electrospray ionisation
ion-peptide
neutral gas
ion-peptide (precursor ion)
mass analyser
fragmentation by collision
product ions
mass analyser
signal detection
peptide sequence
A
G
L
100
relative abundance (%)
400
800
1200
m/z
MS spectrum
100
relative abundance (%)
a2
b2
y2
y3
y4
200
600
1000
m/z
MS/MS spectrum

Amyloid (CR, SR, 789 specimens analysed)	
Positive	379
Negative	410

Amyloid	AL Σ	AL lambda	AL kappa	AL/ATTR comb./hybrid	AL/AApoAIV comb./hybrid	AL/AH comb./hybrid	ATTR	AA	AH	AApoAI	AIAPP	ASem1	ACal	ALac
	100	69	31	1	2	5 4 l/IgG1 1 l/k/IgG1	103	11	5	1	1	5	6	2

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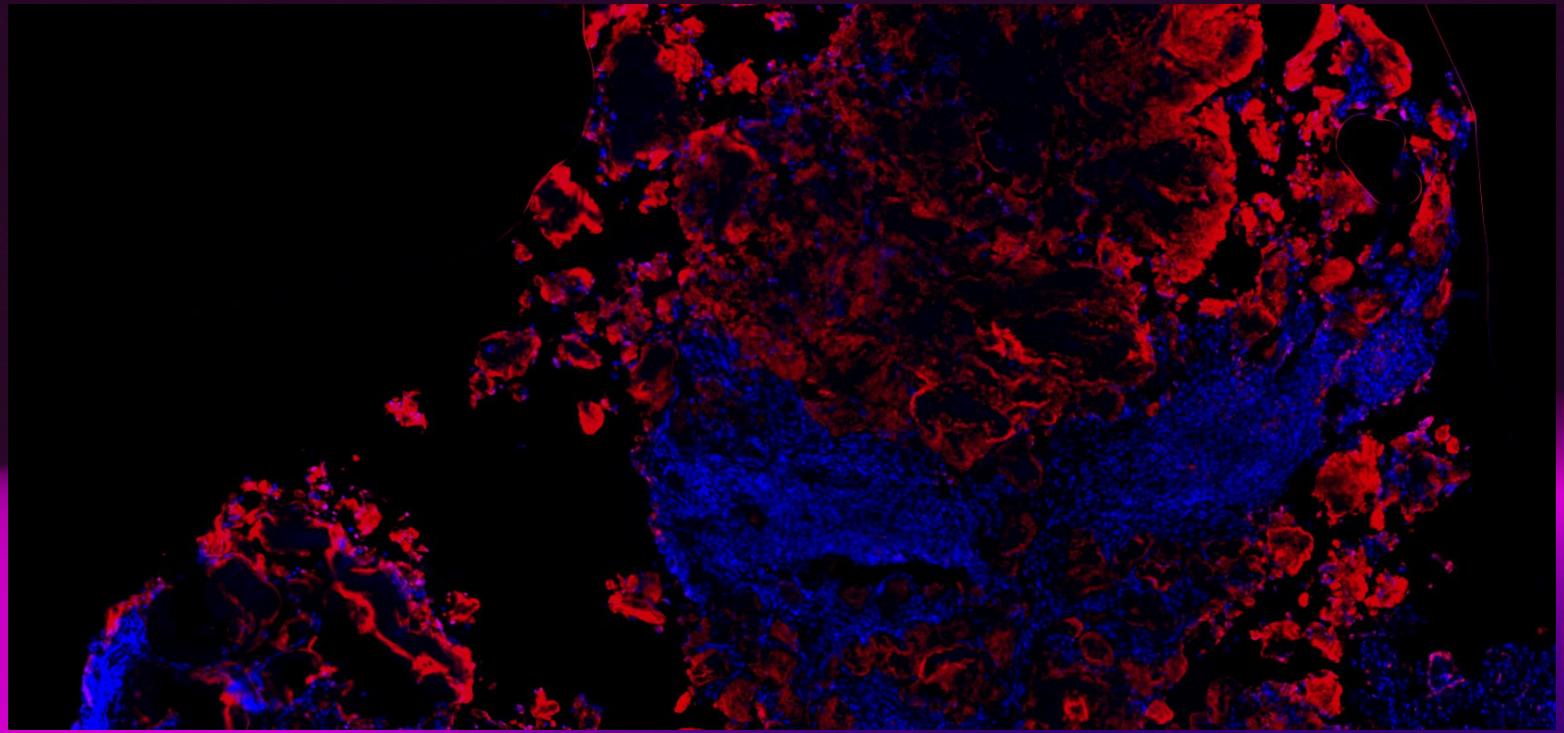
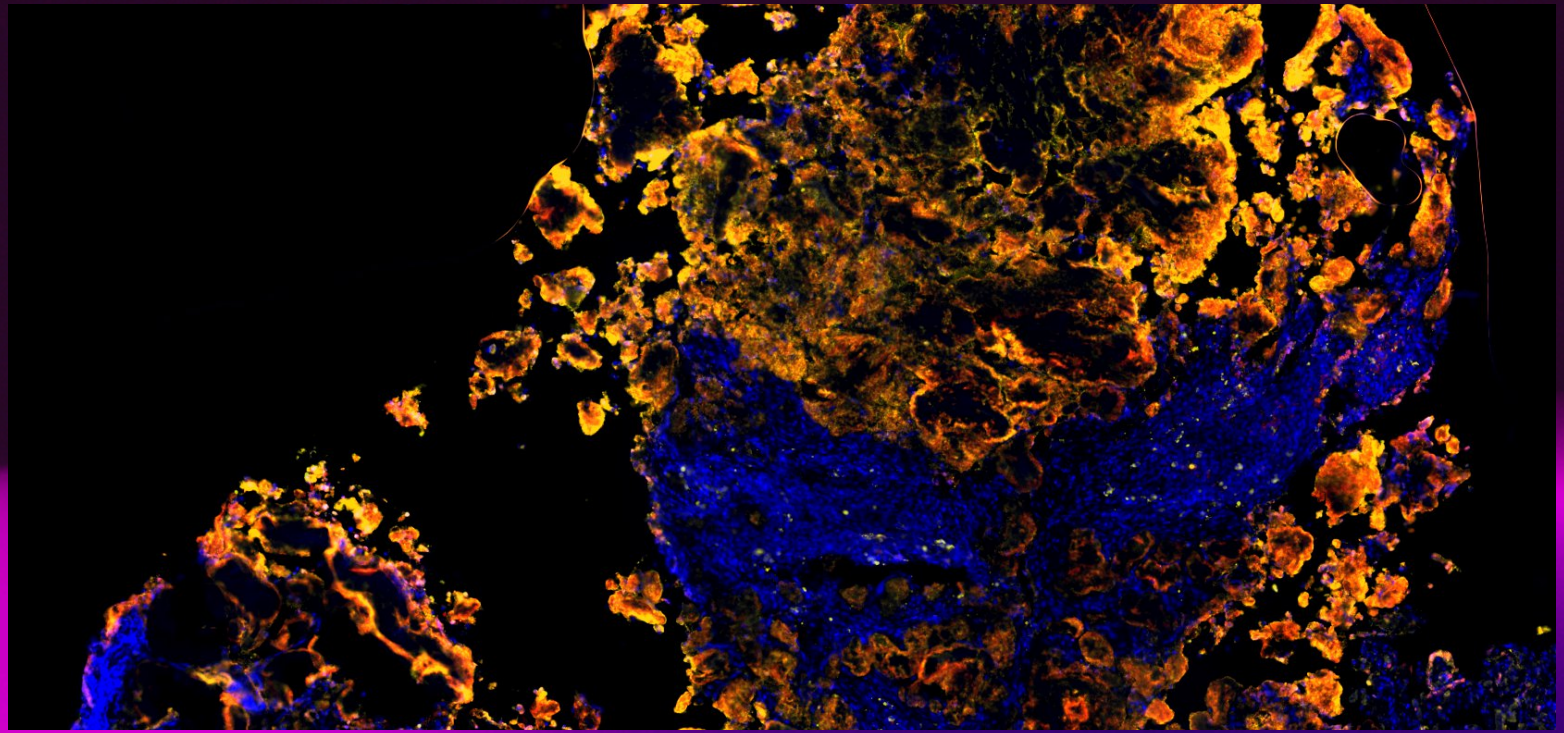
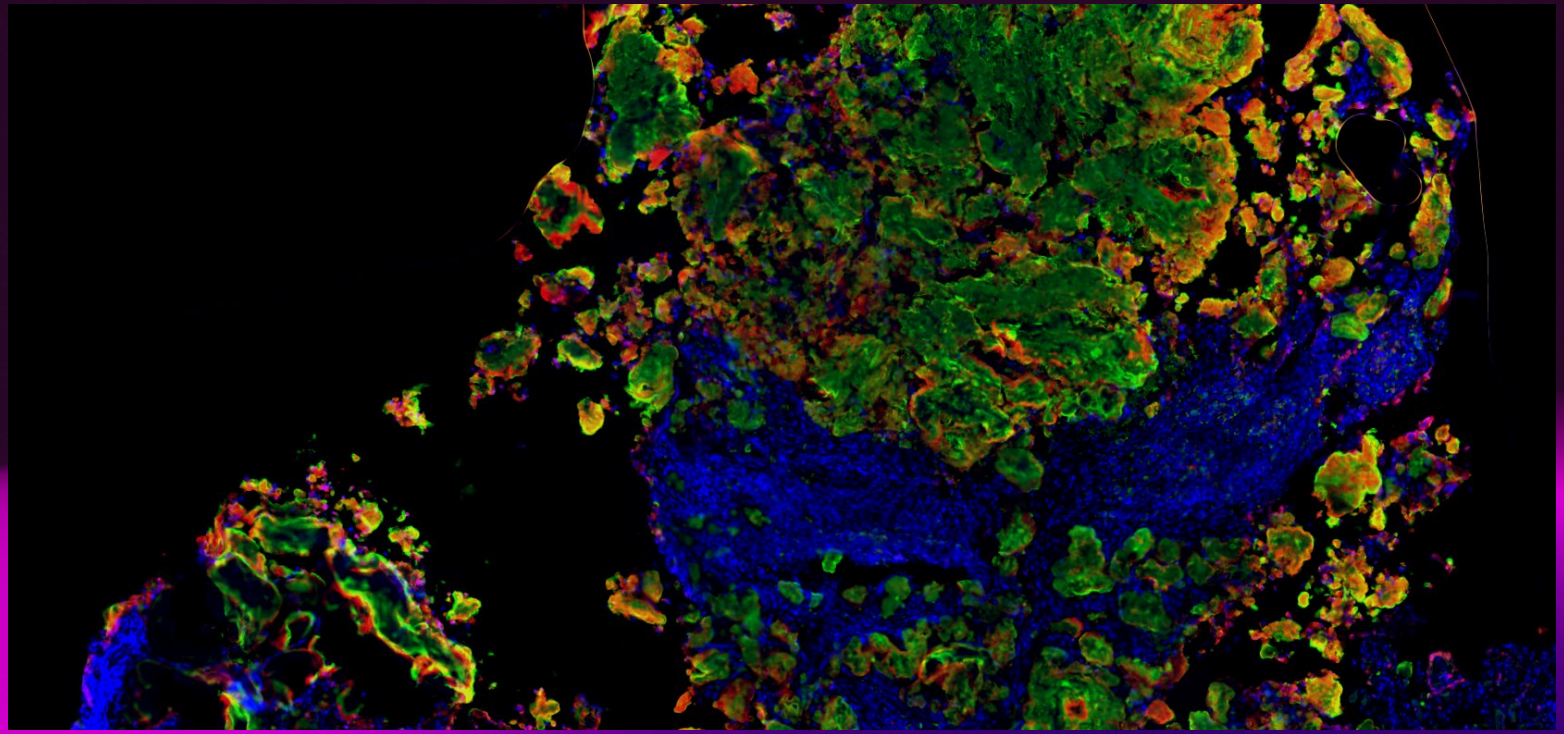
Amyloid	AL Σ	AL lambda	AL kappa	AL/ATTR comb./hybrid	AL/AApoAIV comb./hybrid	AL/AH comb./hybrid	ATTR	AA	AH	AApoAI	AIAPP	ASem1	ACal	ALac
	100	69	31	1	2	5 4 l/IgG1 1 l/k/IgG1	103	11	5	1	1	5	6	2



multiplex IF IgG



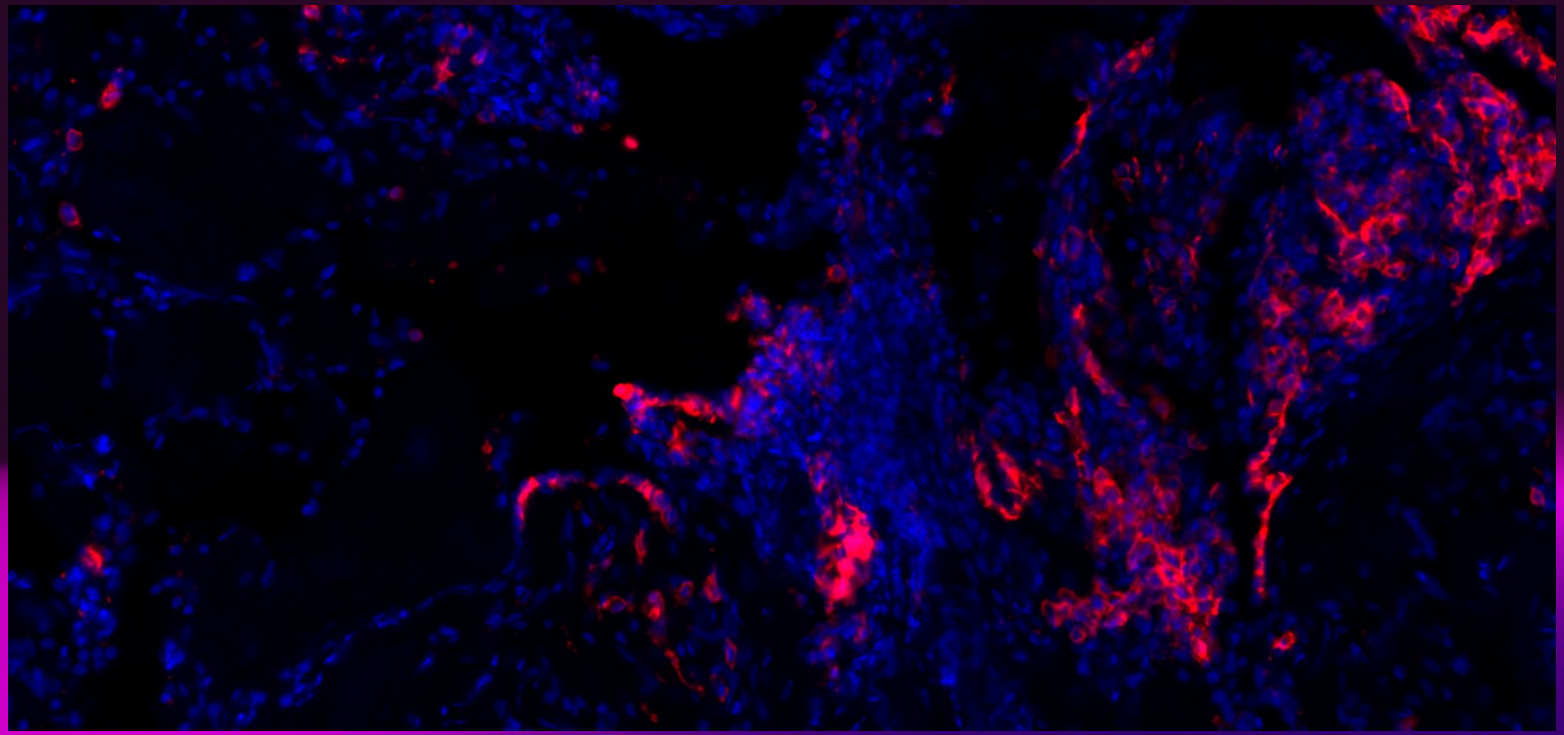
multiplex IF IgG - kappa



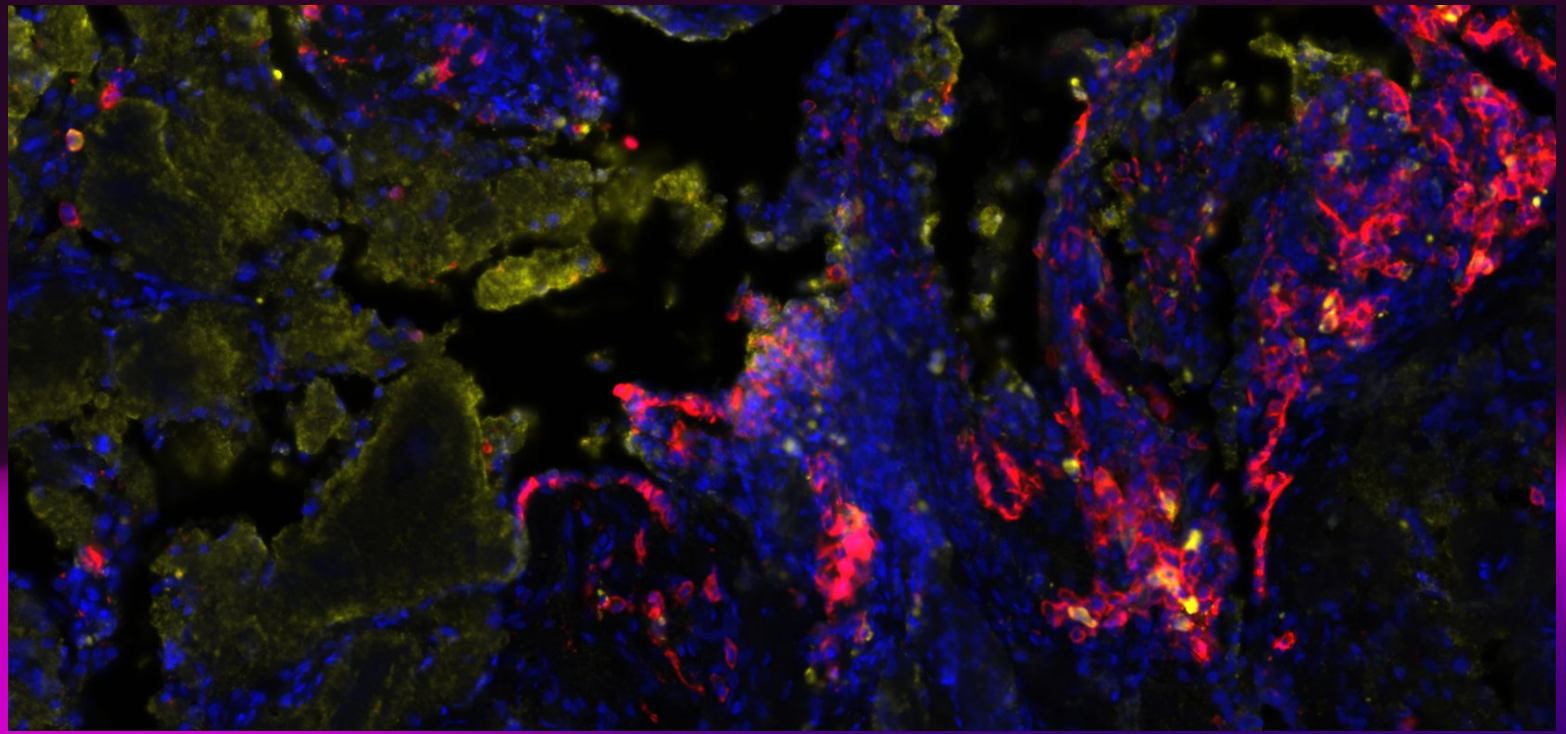
multiplex IF IgG - kappa - lambda

Suggestions

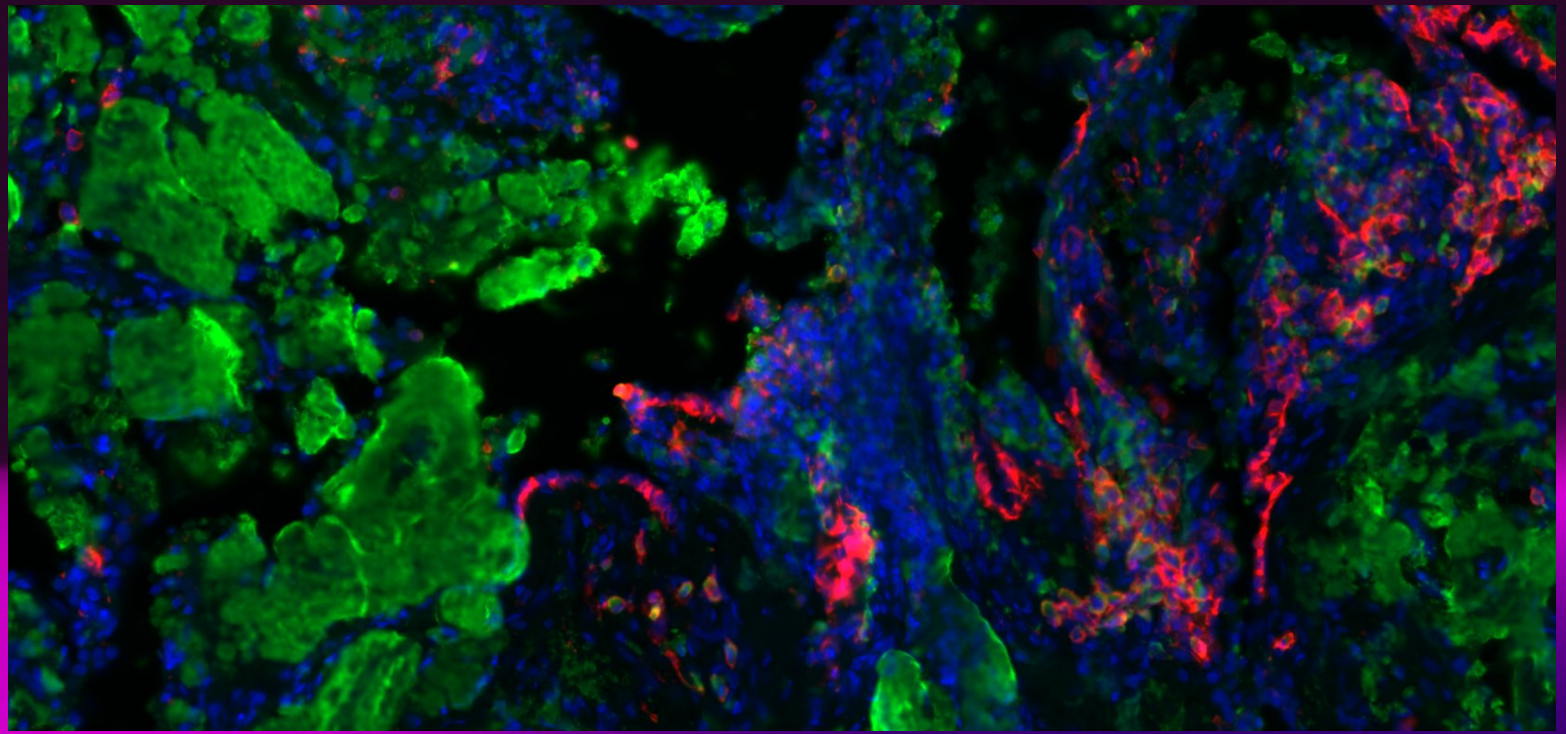
- Combined/hybrid amyloidosis
  - Simple coincidence of variable subtypes of amyloidosis
  - True hybrid amyloidosis
  - Combined seeding and fibrilogenesis



multiplex IF DAPI - CD138



multiplex IF DAPI - CD138 - kappa



multiplex IF DAPI - CD138 - lambda

Amyloidosis Associated with Localised B-cell Neoplasia of Undetermined Significance

Deposition site	Light chains ratio	Proteomic analysis (LC/MS/MS)	Clonal rearrangement IgVH/IgL	Amyloid typing
Conjunctiva	lambda/kappa 6-10:1	Ig lambda-like polypeptide 5	NA (limited volume)	AL lambda
Lung	lambda/kappa 3-4:1	IgG1 chain C region, Ig lambda constant 2	IgVH, IgL lambda	AL/AH lambda/IgG
Skin	lambda/kappa 35-50:1	IgG1 chain C region, Ig lambda-like polypeptide 5	IgVH, IgL lambda	AL/AH lambda/IgG
Soft tissue	kappa/lambda 45-140:1	Ig kappa chain C region	IgVH, IgL kappa	AL kappa
Lung	lambda/kappa 3-4:1	IgG1 chain C region, Ig lambda-like polypeptide 5, Ig kappa chain C region	IgVH oligoclonal, IgL kappa	AL/AH lambda/kappa/ IgG
Large bowel	lambda/kappa 4-5:1	NA (limited volume, only IHC lambda+)	NA (limited volume)	AL lambda
Striated muscle	kappa/lambda 5-20:1	Ig kappa chain C region	IgVH, IgL kappa	AL kappa

Flodr et al., 2025

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Skin	lambda/kappa 35-50:1	IgG1 chain C region, Ig lambda-like polypeptide 5	IgVH, IgL lambda	AL/AH lambda/IgG
Soft tissue	kappa/lambda 45-140:1	Ig kappa chain C region	IgVH, IgL kappa	AL kappa
Lung	lambda/kappa 3-4:1	IgG1 chain C region, Ig lambda-like polypeptide 5, Ig kappa chain C region	IgVH oligoclonal, IgL kappa	AL/AH lambda/kappa/ IgG
Large bowel	lambda/kappa 4-5:1	NA (limited volume, only IHC lambda+)	NA (limited volume)	AL lambda
Striated muscle	kappa/lambda 5-20:1	Ig kappa chain C region	IgVH, IgL kappa	AL kappa

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Flodr et al., 2025

Amyloidosis Associated with Localised B-cell Neoplasia of Undetermined Significance

LBCNUS/Amyloid	AL kappa	AL lambda	Double hybrid AL lambda/AH	Triple hybrid AL lambda/ kappa/AH	NA/ND	Σ
Clonal IgVH and IgL lambda	0	0	2	0	0	**2**
Clonal IgVH and IgL kappa	2	0	0	0	0	**2**
Oligoclonal IgVH and clonal kappa	0	0	0	1	0	**1**
NA/ND	0	2	0	0	0	**2**

Flodr et al., 2025

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Take home messages

Do not consider amyloidosis as an orphan disease

- formally YES - orphan status <5 person per 10,000 in EU countries

Diagnosis and therapeutic options improved

Precise amyloid typing without LCM and LC/MS is nearly impossible

IHC/IF is still prompt method with limited accuracy

Multiplex IF helps to colocalize hybrid amyloidosis

Microdissection with LC/MC of different microanatomical deposits

reveal variants of hybrid amyloidosis

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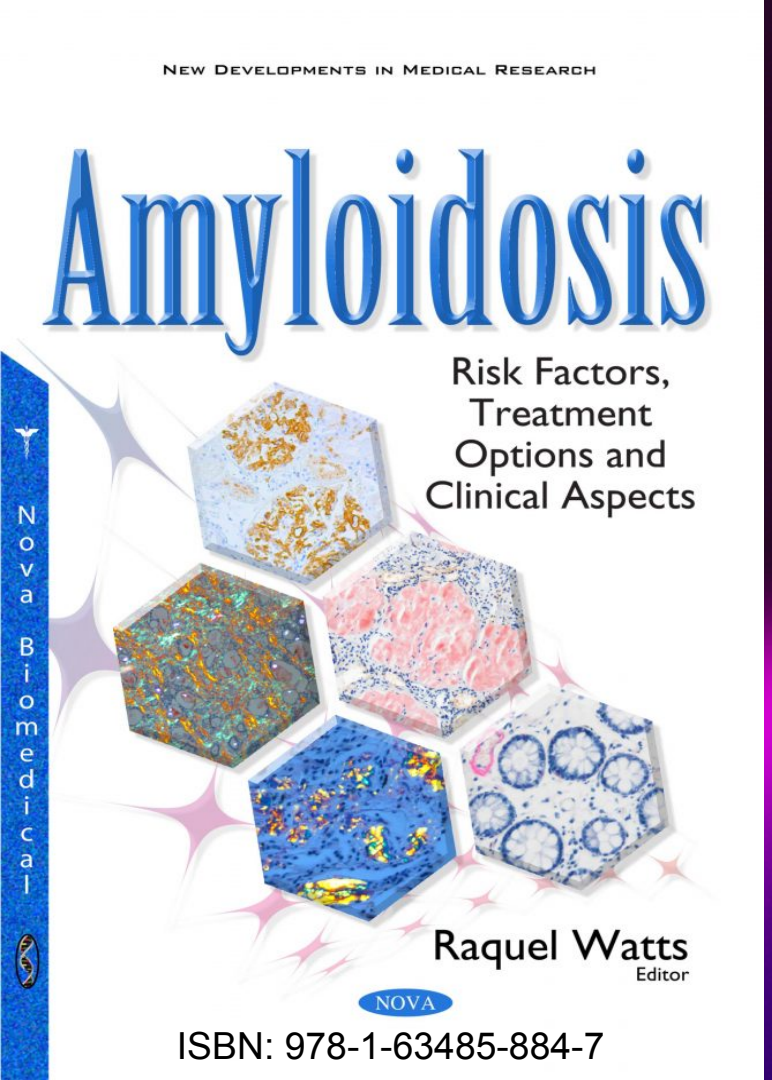
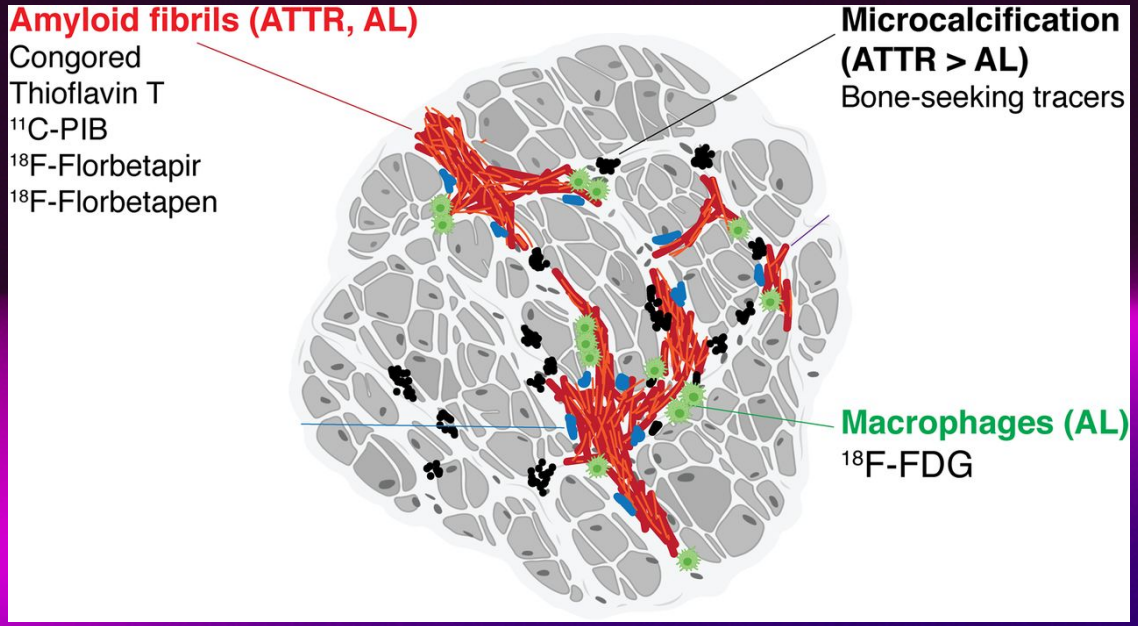


ISBN: 978-1-63485-884-7

Amyloid-specific radiotracers for PET



Novel Tracers for the Imaging of Cardiac Amyloidosis. Mrinali Shetty, Saurabh Malhotra. Journal of Nuclear Medicine Technology Jun 2023, 51 (2) 120-124; DOI: 10.2967/jnmt.123.265568


TIME
To Start
A New
CHAPTER
Happy
Farewell

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The European Proteomics Amyloid Network (EPAN) is a multicentre collaboration, involving scientists and clinicians who share the common interest in standardizing proteomics methods for amyloidosis diagnosis and improve knowledge on disease mechanisms.