ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

Postlude: International Registries and Cross-boarder Sample Sharing

Chairs: Alexander Carpinteiro and Stefano Perlini

Faculty: Ute Hegenbart, Giovanni Palladini, Per Westermark, Eloisa Riva

SESSION Postlude.
International registries and cross-border sample sharing

National registries: opportunities and pitfalls

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Universitätsklinikum Heidelberg

UK HD

Disclosures

- Honorarium for talks: Janssen, Pfizer, Alnylam, Prothena, Astra Zeneca
- Financial support of congress participation; Janssen, Prothena, Pfizer
- Advisory Boards: Pfizer, Prothena, Janssen, Alexion, Alnylam, Neurimmune
- Financial sponsoring of Amyloidosis Registry: Janssen, Alexion, Prothena
  - All fees have been transferred to my institution

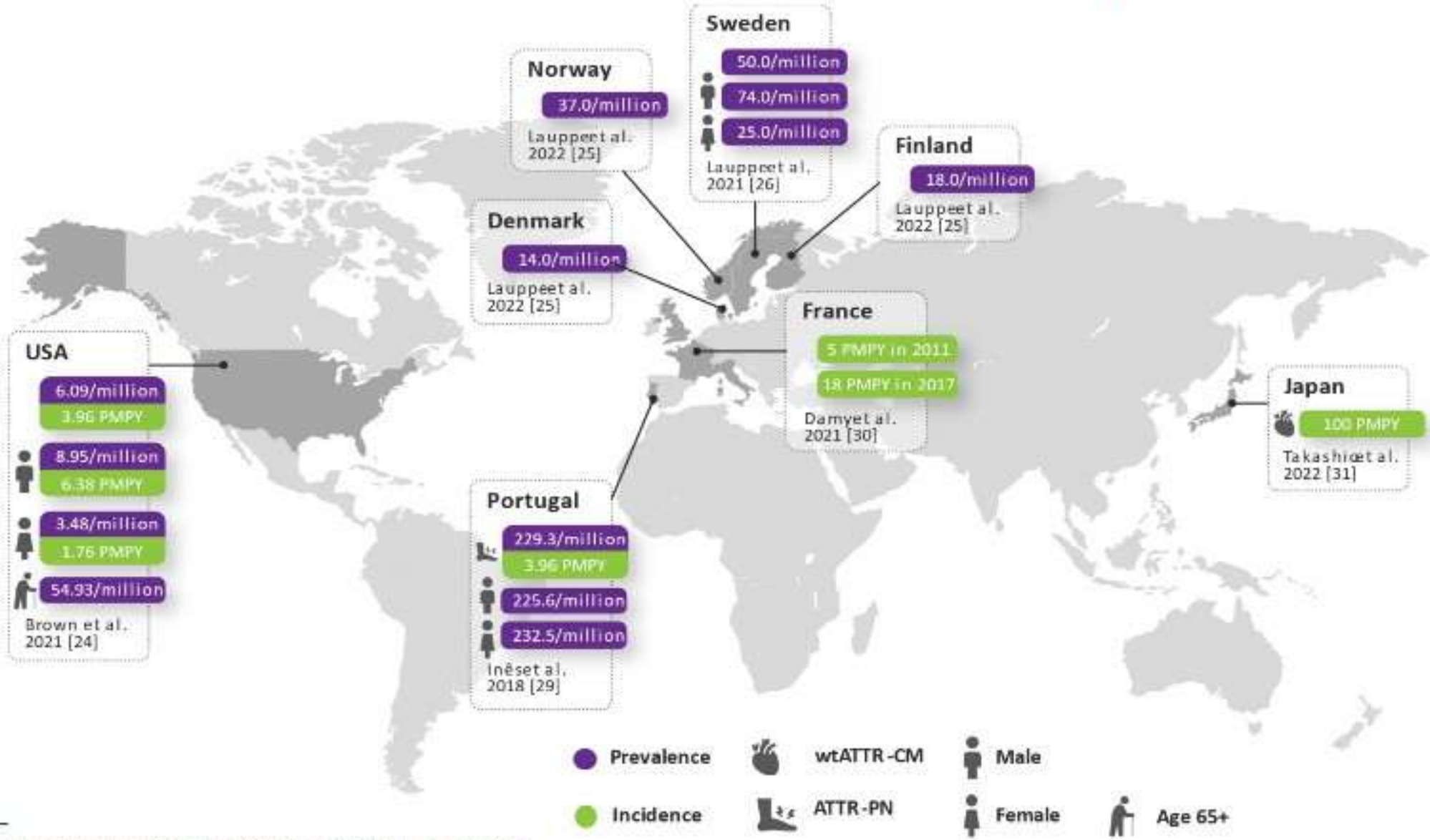
Sources of information

- Prospective Registry
  - National
  - International (e.g. THAOS for ATTR) or liver transplant registry (FAPWTR)
- Retrospective data collection, e.g.
  - electronic health records (ICD-10 coding)
  - TriNetX, a health research network
  - Healthcare Insurance Research databases

What do we know about the incidence of amyloidosis?

- **AL amyloidosis** (Kyle et al., 2019)
  - 1990-2015: 1.2 per 100,000 person-years,
  - Rates similar across the decades 1990-1999, 2000-2009, and 2010-2015 at 1.1, 0.9, and 1.6 per 100,000 person-years, no increasing rate during the 26 years
- Few published data for Europe
  - Sweden: “non-hereditary”: 8.29 per million person-years (Hemminki et al. 2012) and „from 2011 to 2019 incidence increased from 10.5 to 15.1 cases per million” (Mellqvist 2023)

Incidence and Prevalence of ATTR amyloidosis



Delgado et al. Orphanet J of RD 2025

German National Registry

- Germany has 83.6 million inhabitants
- Prospective registry, started in January 2018
  - A: registration by referral pathologists (with amyloid typing)
  - B: clinical registry (with signed IC, broad spectrum of disease characteristics + OS)

Increase of recruitment over the time

Registry 1

01/2018-03/2020: within 27 months 1159 patients

Registry 2

4/2020-01/2022: within 21 months 2615 patients

(A: Pathology and B: clinical reg. each 1500, including 385 pts. in both arms)

Summary prospective registries

- Opportunities:
  - Get data about incidence and prevalence of amyloidosis
  - Clinical characterisation of patients
  - Real-world data: treatment and overall survival
- Pitfalls
  - Correctness of the diagnosis depends on the registry type (amyloid typing available)?
  - Representativeness / how many patients will be missed?

Summary retrospective data collection

- Opportunities:
  - Big data

- Pitfalls
  - Correctness of the diagnosis depends on the registry type (amyloid typing available)?
  - Representativeness / how many patients will be missed?

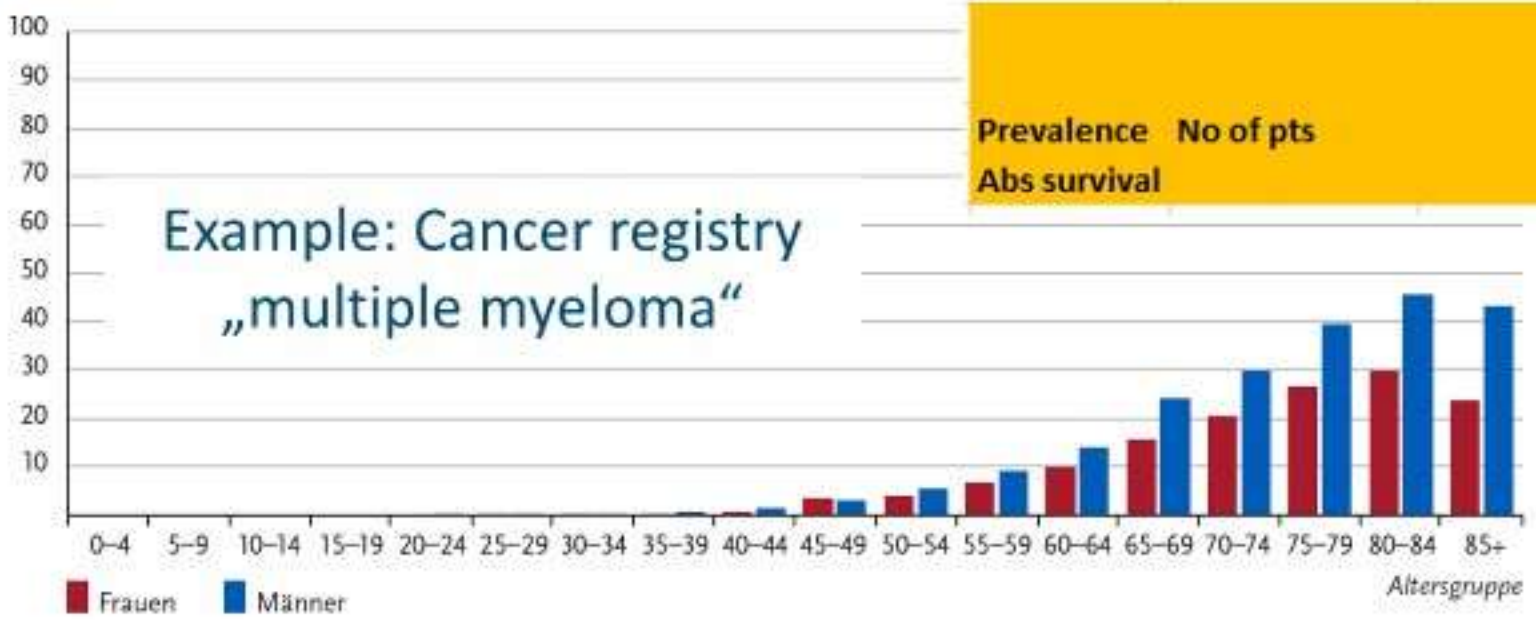
Outreach

- Could we start an initiative to make „amyloidosis“ a „reportable disease“?

		2017		2018	
		Women	Men	Women	Men
Incidence	No of newly dx	3.340	3.820	2.810	3.540
Mortality	No of deaths	1.851	2.287	1.881	2.299

		5 years		10 years	
		Women	Men	Women	Men
Prevalence	No of pts	9.500	11.500	14.200	16.800
Abs survival		47%	47%	28%	26%

Abbildung 3.30.2
Altersspezifische Neuerkrankungsraten nach Geschlecht, ICD-10 C90, Deutschland
je 100.000



Example: Cancer registry „multiple myeloma“

ref

Thanks to: my colleagues and partners of the Amyloidosis Center sponsors and patients

Stefan Schönland

<u>Registry:</u>
Angelika Bari
Rita Ziehl
Laura Huber
Niklas Fuhr
Sena Gölgeci
Selin Özgoz

<u>Sponsors:</u>
Prothena, **Janssen**
Alexion

AMYLOIDOSE ZENTRUM
Universitätsklinikum Heidelberg

ZENTRUM FÜR SELTENE ERKRANKUNGEN
Universitätsmedizin Heidelberg

EuroBloodNet
European Reference Network for Rare Hematological Diseases

BEFÖRDERT VOM

Bundesministerium für Bildung und Forschung

DGAK Deutsche Gesellschaft für Amyloid-Krankheiten

DGHO
Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie

ÖGHO

SSMO SGMO

SGKSSH

DFG Deutsche Forschungsgemeinschaft

EBMT

Geramy
Nationales Netzwerk für Amyloidose Erkrankungen

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The EUREKA project and beyond

Giovanni Palladini

Amyloidosis Research and Treatment Center
Foundation «IRCCS Policlinico San Matteo»
Department of Molecular Medicine
University of Pavia
Pavia, Italy

Disclosures

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- Alexion (Advisory Board)
- Abbvie (Advisory Board)
- Bayer (Advisory Board)
- GSK (Advisory Board)
- Janssen (Honoraria)
- Life Molecular Science (Advisory Board)
- Neuroimmune (Advisory Board)
- Protego (Advisory Board)
- Pfizer (Advisory Board)
- Prothena (Advisory board)
- Regeneron (Advisory Board)

International prospective patient registries in systemic amyloidosis

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- Major advances have been made based on retrospective or prospectively-maintained databases at referral centers (e.g., ALchemy).
- In 2018 the ISA Board and ISA members highlighted the need for a prospective academic patient registry, but funding was lacking.
- In 2019 an international consortium (Pavia, Barcelona, Groningen, Heidelberg, Jerusalem, Limoges, Warsaw) proposed a registry project to apply to the EJP-RD call, but the project was not funded.
- Database standardization and improvement of list of variables continued and were incorporated in an embryonic Italian registry (ReAL, NCT04839003, 2020).
- In 2022 the Italian Transthyretin Amyloidosis Web-Network (ITA-WebNet, NCT05444920) was funded by Global Bridges.

EUREKA and PRODIGALITY studies

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Inserm

Ministero della Salute

EUREKA

A EUropean REgistry and sample sharing networK to promote the diagnosis and management of light chain Amyloidosis

- Pavia - Italy
  Amyloidosis Research Center
- Pamplona – Spain
  IdiSNA Center
- Utrecht – The Netherlands
  Amyloidis Expertise Center
- Heidelberg - Germany
  Amyloidosis Center
- Muttenz – Switzerland
  Institute of Medical Engineering and Medical Informatics

PRODIGALITY

Promoting Diagnosis and management of AL in Italy

- PV – Pavia – Coordinator
  Amyloidosis Research Center
  IRCCS Policlinico San Matteo
- BA – Bari
  AOU Consorziale Policlinico
  San Giovanni XVIII
- CT – Catania
  A.O.U. Policlinico G. Rodolico
  San Marco
- TO – Torino
  A.O.U. Citta della Salute e della Scienza di Torino

Aims:

- Study the biology of the plasma cell clone
- Refine staging system and response criteria
- Study the role of MRD (incl. new techniques)

Aims:

- Implement biomarker-based screening of MGUS/SMM
- Promote early diagnosis and management of pts
- Intercept pts not directly evaluated in Pavia (real-world)

Aims of the project

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- Describe the natural history of AL amyloidosis in a real-world setting and in the contemporary era of novel drugs
- Define and validate prognostic and predictive models, response and relapse criteria
- Assess the role of Minimal Residual Disease (MRD) assessment

Consortium

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Name	Institution - Country	Expertise
Giovanni Palladini	Foundation IRCCS Policlinico San Matteo, Pavia – ITALY	Light chain sequencing, mass spectrometry, clinical studies
Stefan Schönland	University Hospital Heidelberg – GERMANY	Molecular cytogenetics, clinical studies
Bruno Paiva	Instituto de Investigación Sanitaria de Navarra, Pamplona – SPAIN	Flow cytometry, RNA-sequencing, clinical studies
Monique Minnema	UMC Utrecht – THE NEDERLANDS	Heart-on-a-chip, clinical studies
Enkelejda Miho	University of Applied Sciences and Arts Northwestern Switzerland, Muttenz – SWITZERLAND	Big data analysis, artificial intelligence, antibody repertoire analysis

PAO	Role
Amyloidosis Alliance (international federation of amyloidosis pts associations)	Consulted for the preparation of informed consents for pts Advertise the existence of the study among pts to increase pts referral to participating centers and pts recruitment Dissemination activities

Project overview – Registry & Biobank patients

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ENROLLMENT

of **400(+) pts** with AL at diagnosis
with complete dataset (Registry & Biobank)

Recording of clinical data

on a secure web-based registry at
first visit and follow up evaluations

This part of the project is also open to other Centers wishing to contribute to the registry

No sample shipment / sharing is needed

Only prospective clinical data are collected

Data analysis

with classical statistical approaches,
big data analysis and artificial intelligence

Data transfer agreement

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- Submitting Centers retain ownership and control of their data
- Data can be accessed and used for specific studies only upon approval of submitting centers
- New studies can be proposed by members of the EUREKA Consortium or external parties
- Each Center can opt whether to participate or not in a given study and contribute their data to it
- Authorship will be agreed upon by on the basis of the conceptualization and execution of the specific experimental and analytical work, as well as the number of patients contributed by each clinical center

Interested Centers – what are the next steps

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- Contact the current PI (giovanni.palladini@unipv.it)
- Get approval by the local IRB
- Sign the Consortium Agreement
- Start patient enrollment
- Data entry in the REDCap registry through a dedicated account

New partners – EUREKA registry

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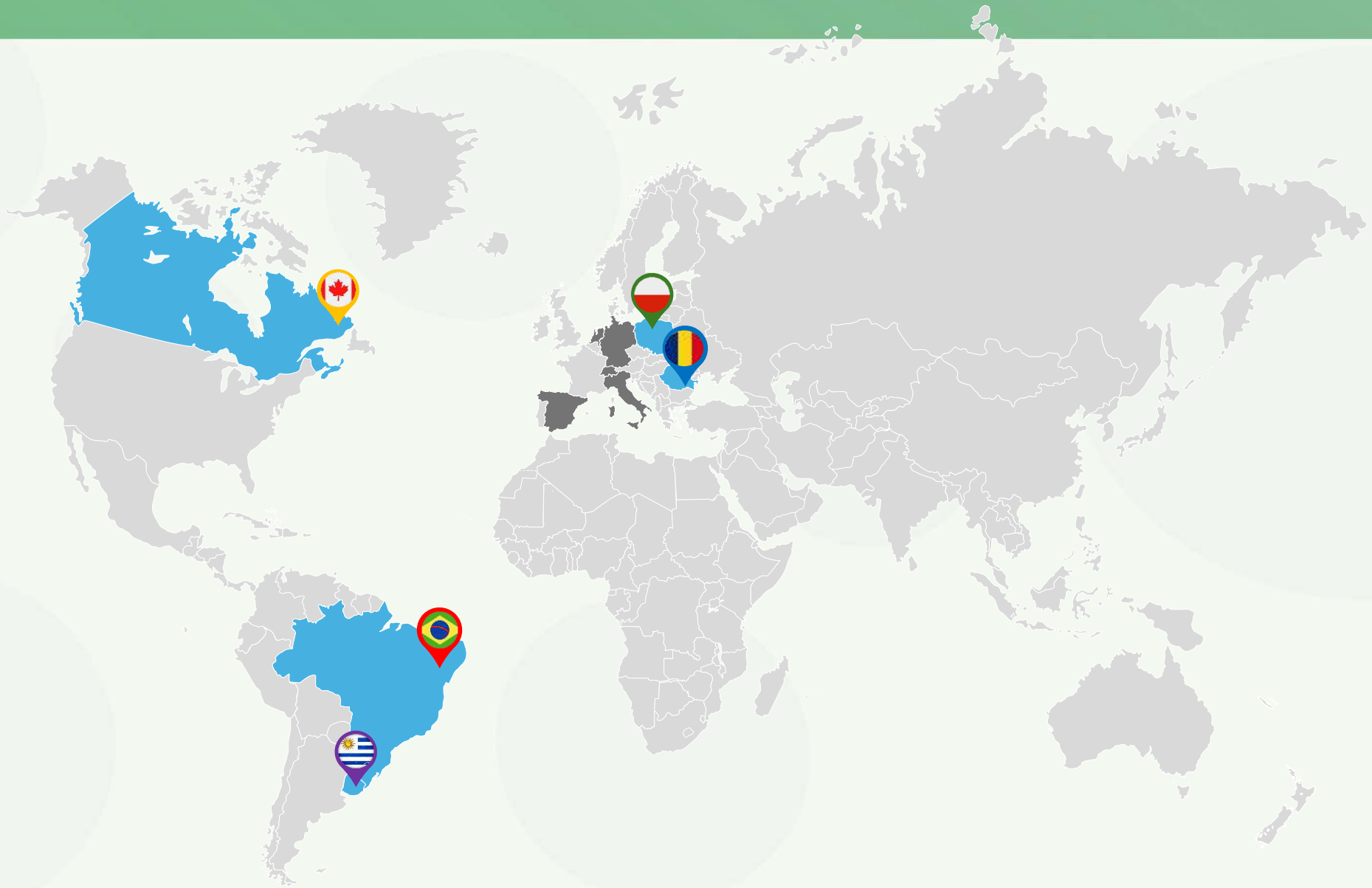
- Brasil
- Canada
- Poland
- Romania
- Uruguay



International Standards for Tissue Typing

Per Westermark

Uppsala University

Idea: Sharing the same tissue for independent typing by MS

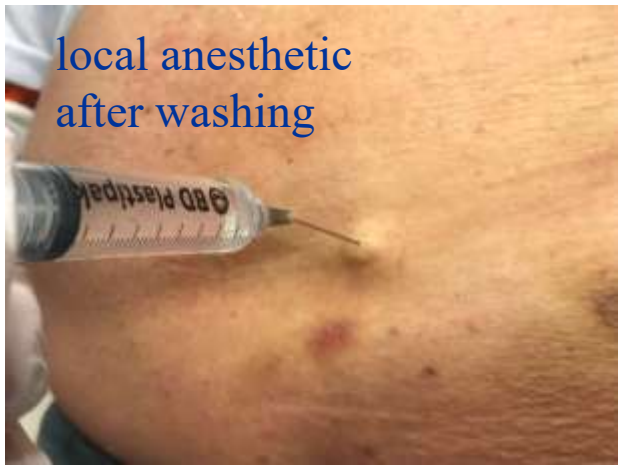
The subject includes three different parts:

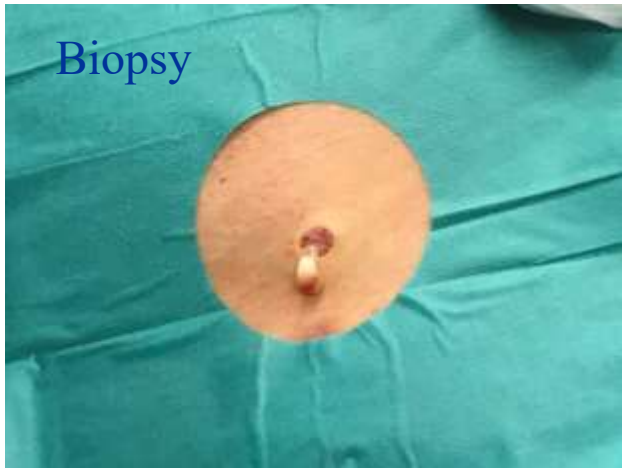
- Biopsy material
- Amyloid detection in tissue
- Amyloid typing

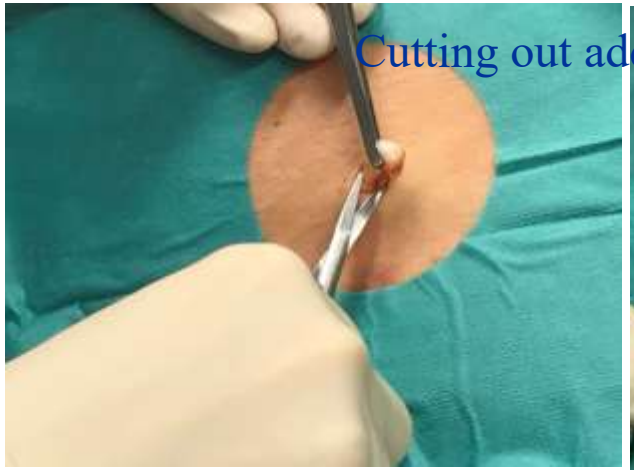
The materials vary

- Formalin-fixed, paraffin-embedded tissue for sectioning (often most)
- Specially fixated tissue for immuno-fluoresence and cryo sectioning (e.g. renal biopsies)
- Fresh tissue, e.g. subcutaneous adipose tissue

How to perform a fat pad biopsy

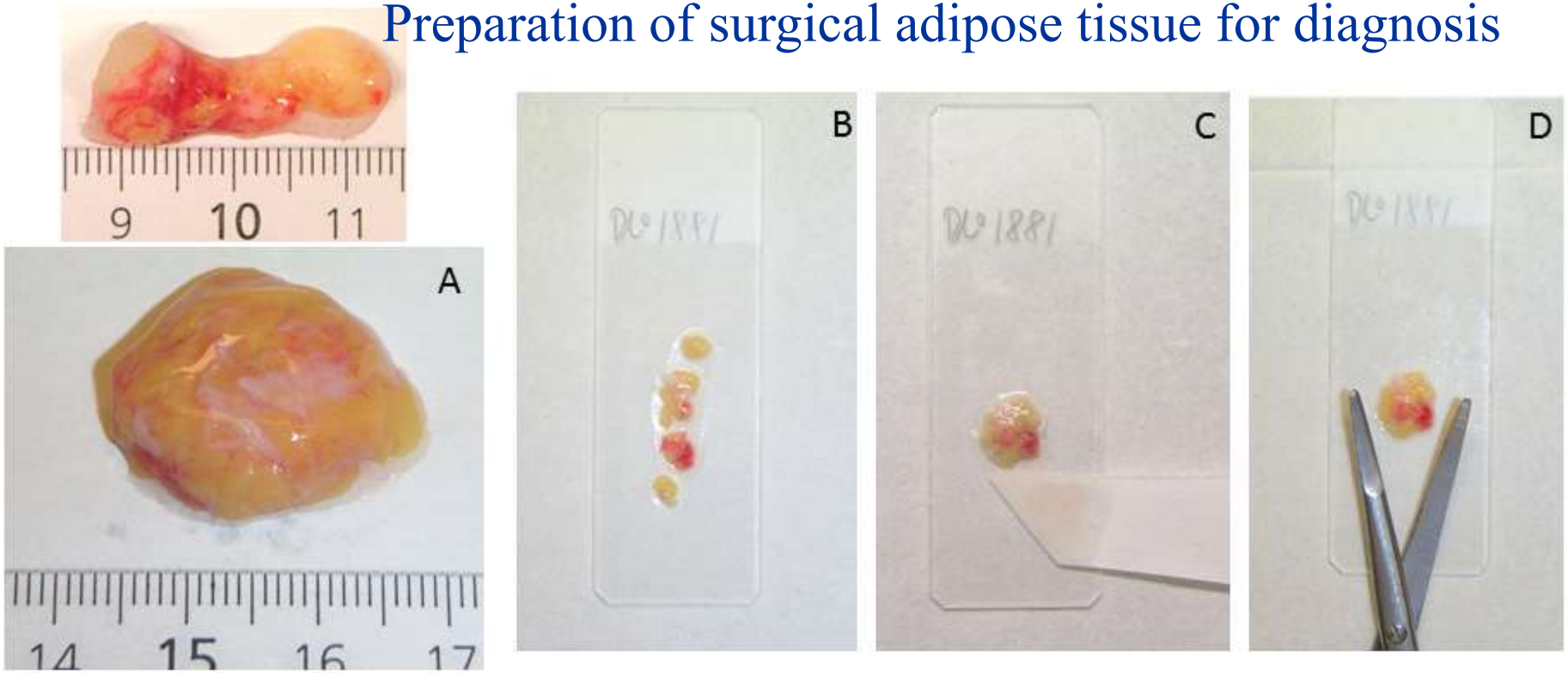






Paulsson Rokke H et al.
Orphanet J Rare Dis. 2020;15(1):278

Preparation of surgical adipose tissue for diagnosis



Westermark
In: Amyloid proteins
Springer protocols 2012

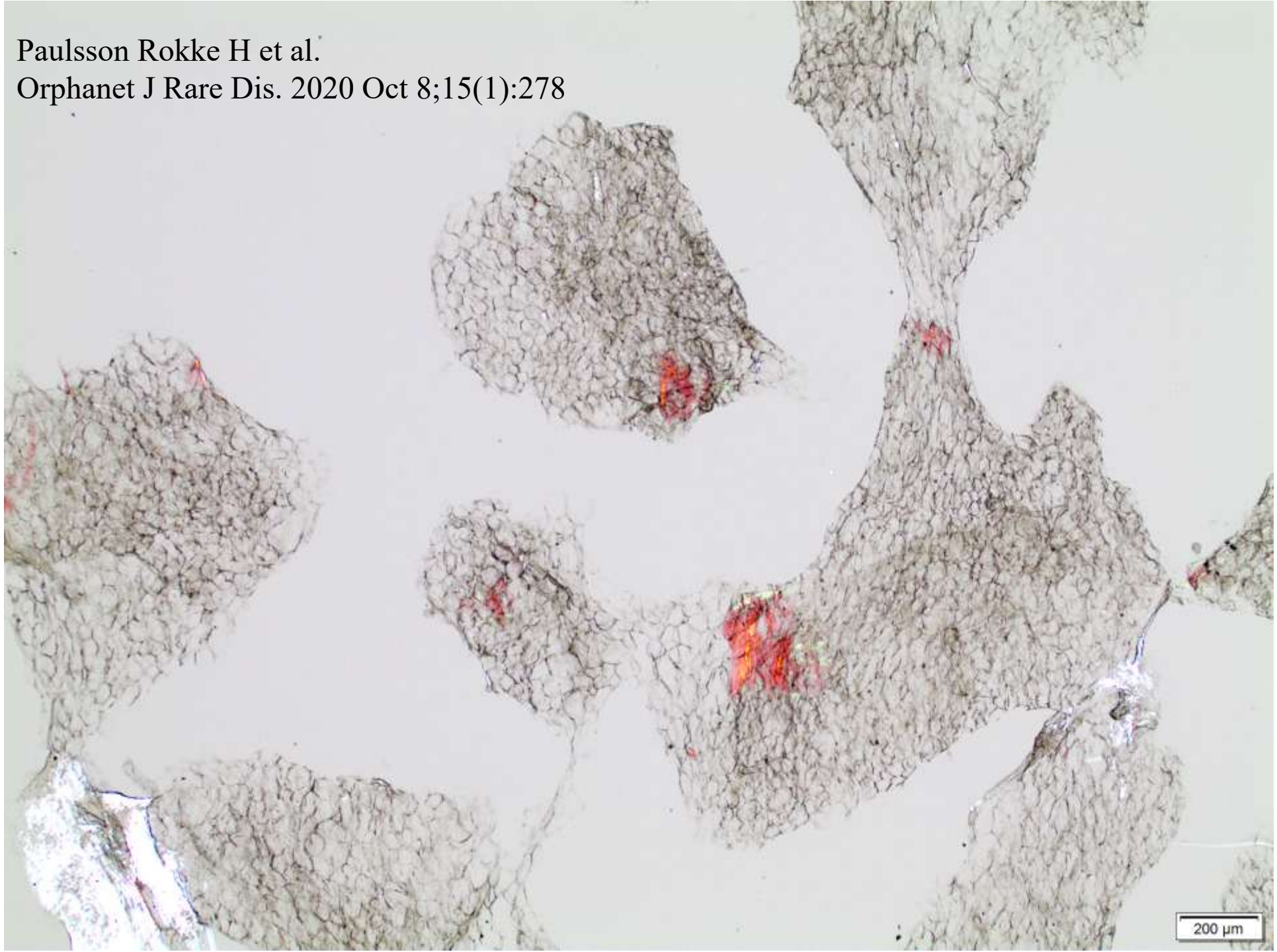
Congo red is a tricky dye

If not controlled, it can stain almost everything

But is in the same time a wonderful molecule

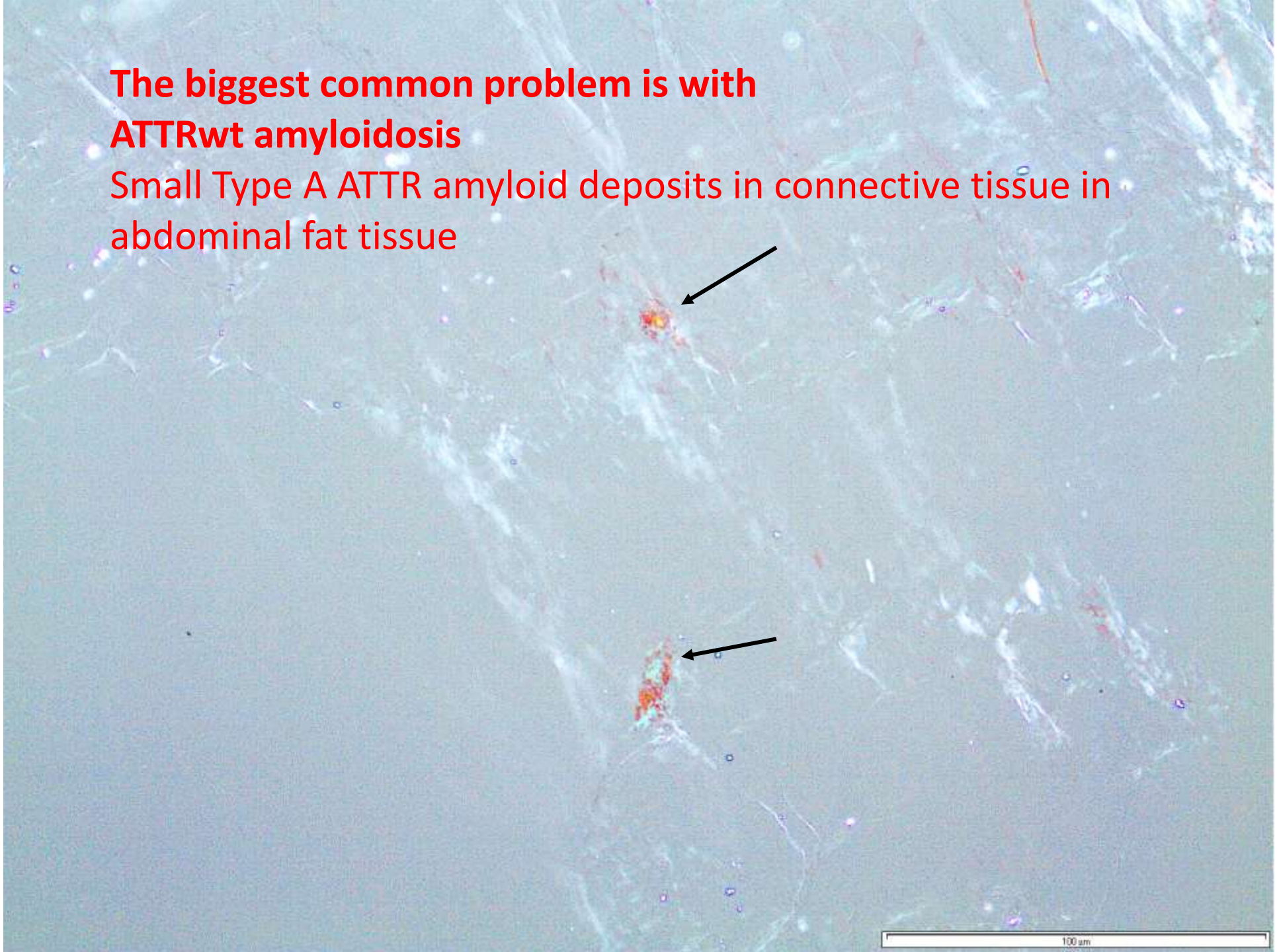
We use Puchtler’s method from 1962, but **diluted** (1:10-1:40)

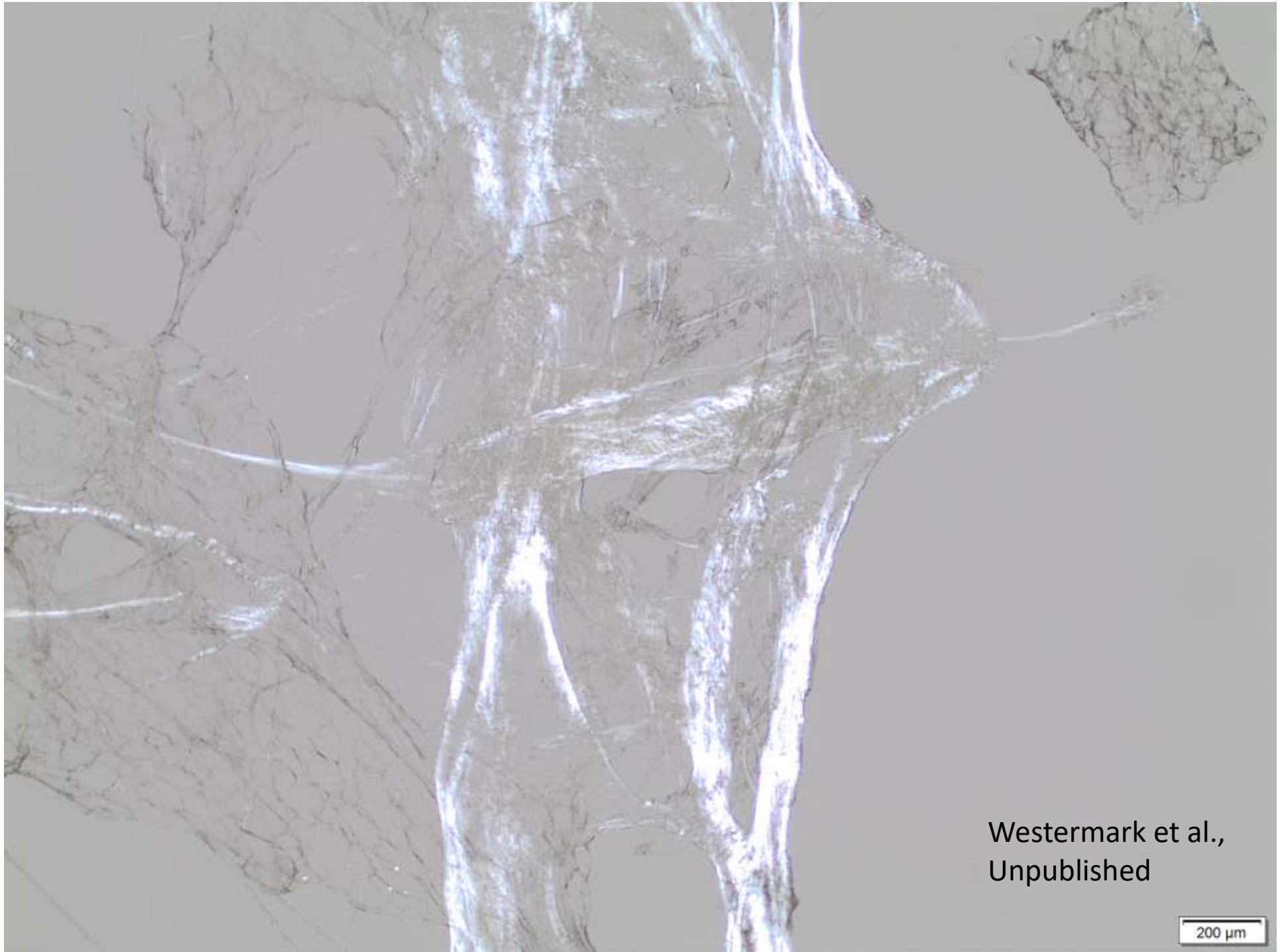
Paulsson Rokke H et al.
Orphanet J Rare Dis. 2020 Oct 8;15(1):278



The biggest common problem is with ATTRwt amyloidosis

Small Type A ATTR amyloid deposits in connective tissue in abdominal fat tissue




Westermark et al.,
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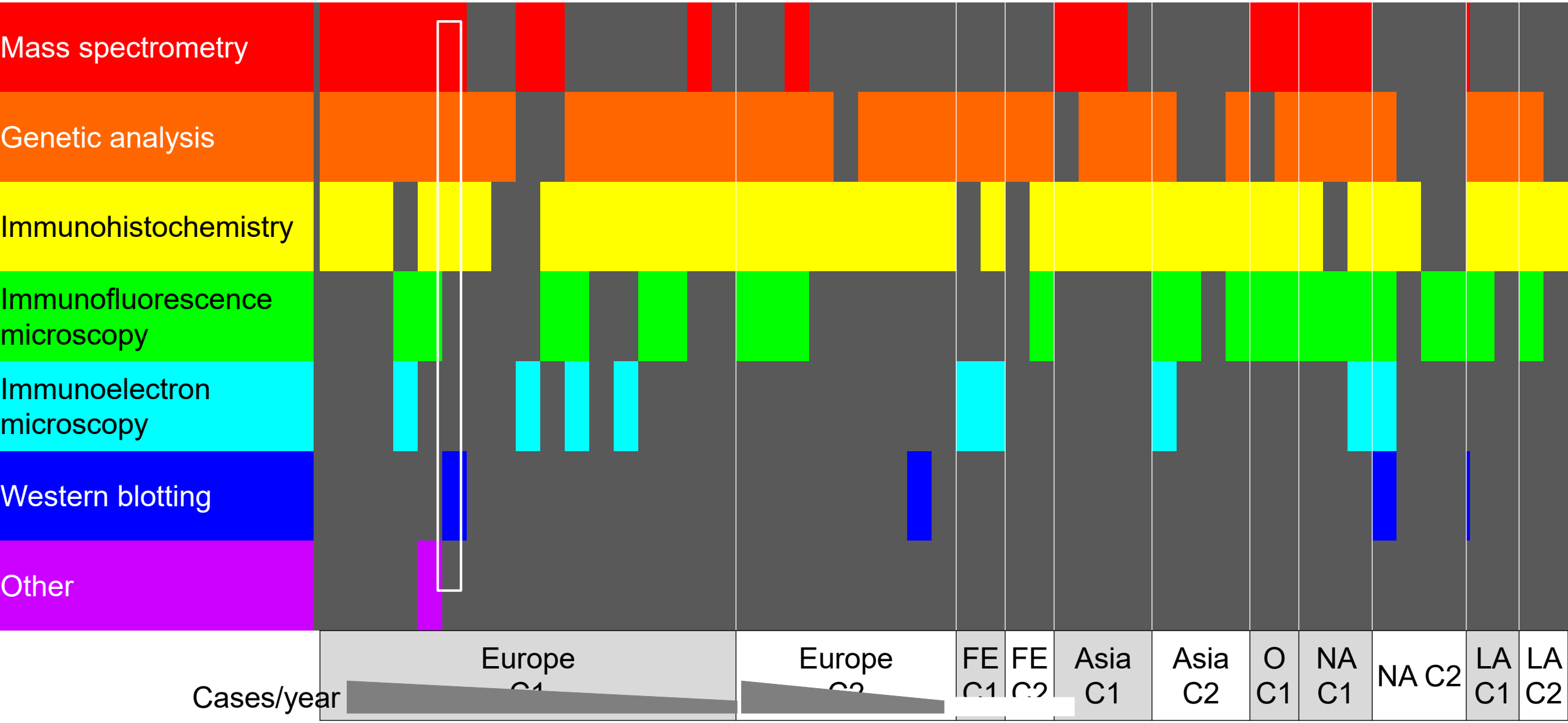


Figure 1

Naiki et al., Amyloid 2025

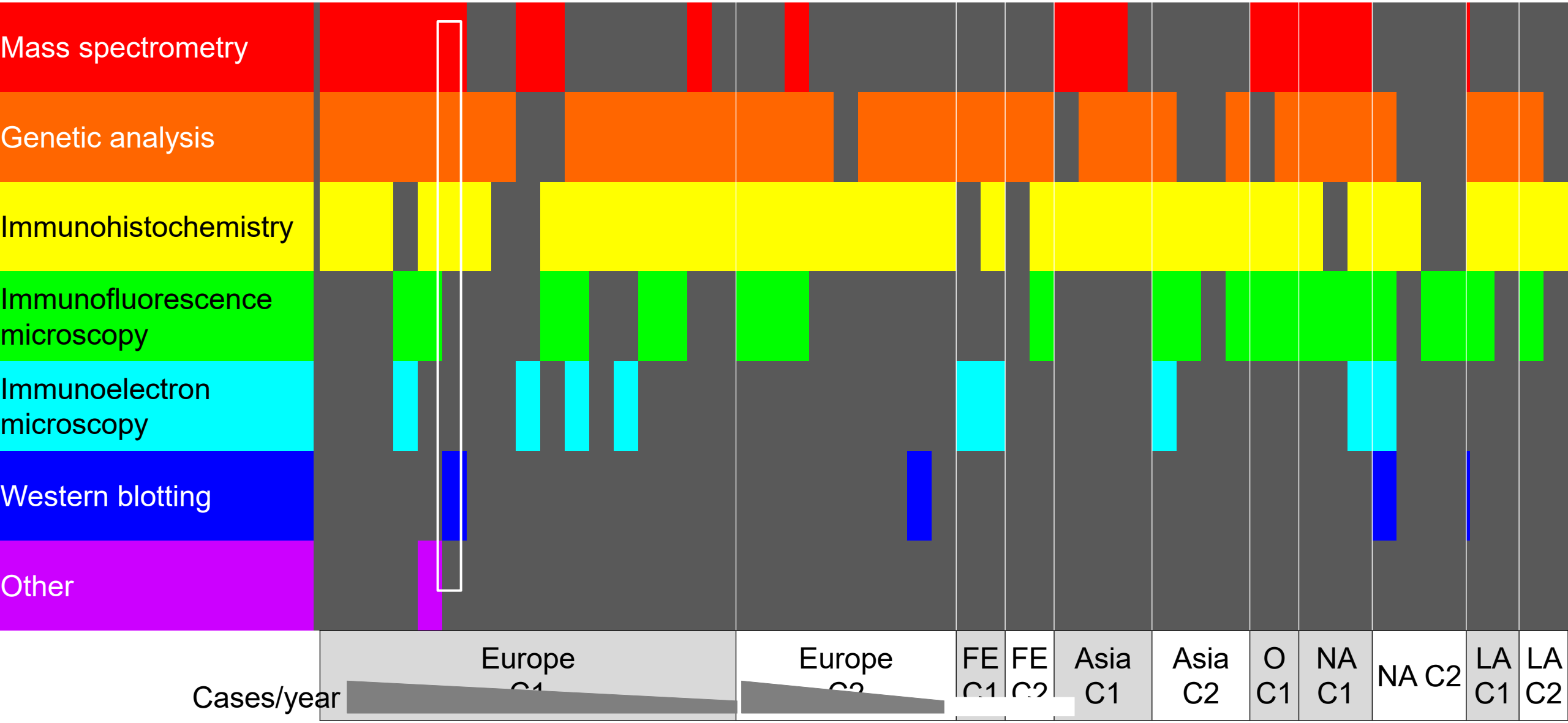
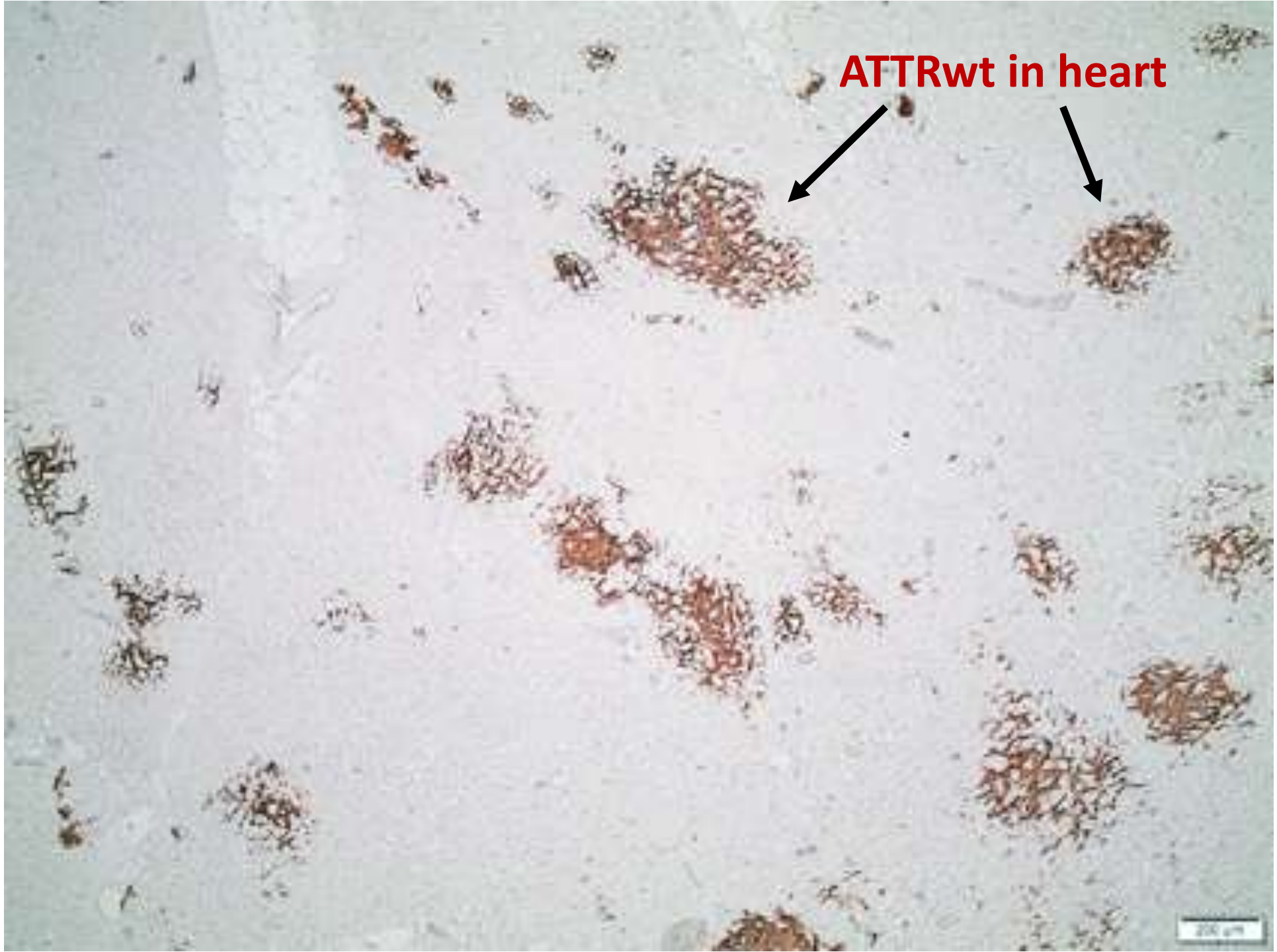


Figure 1

Naiki et al., Amyloid 2025

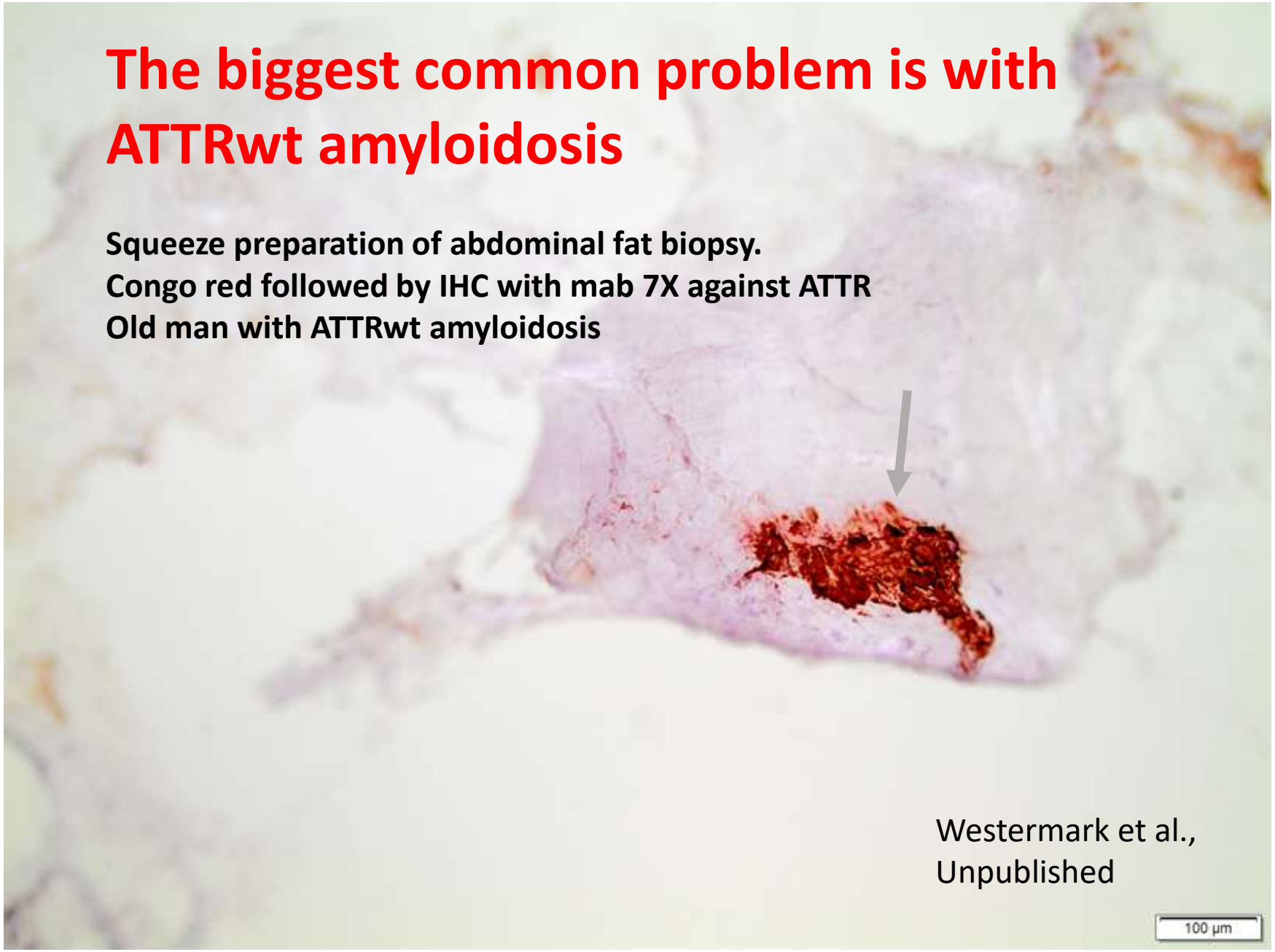
In a Japanese study, 92.3 % of 4420 cases with amyloid deposits were safely typed by immunohistochemistry

Naiki et al, Amyloid 2023


ATTRwt in heart

The biggest common problem is with ATTRwt amyloidosis

Squeeze preparation of abdominal fat biopsy.
Congo red followed by IHC with mab 7X against ATTR
Old man with ATTRwt amyloidosis



Westermark et al.,
Unpublished

Comparison of methods

- **Immunohistochemistry**

Generally available

Technically not complicated

Cheap

Different information: e.g. Depositions structure, distribution in tissues, double amyloids etc.

- **Mass spectrometry**

Only in few laboratories

Complicated

Expensive

Different information: e.g. variants

So, for a new laboratory the logical suggestion would be to start with validated antibodies, shared between different laboratories and use mass spectrometry for special cases (or for specific purposes)

Legal Problems: For EU the In Vitro Diagnostic Regulation

▼B

REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

(Text with EEA relevance)

CHAPTER I

INTRODUCTORY PROVISIONS

Section 1

Scope and definitions

Article 1

Subject matter and scope

1. This Regulation lays down rules concerning the placing on the market, making available on the market or putting into service of *in vitro* diagnostic medical devices for human use and accessories for such devices in the Union. This Regulation also applies to performance studies concerning such *in vitro* diagnostic medical devices and accessories conducted in the Union.
2. For the purposes of this Regulation, *in vitro* diagnostic medical devices and accessories for *in vitro* diagnostic medical devices shall

In Vitro Diagnostic Regulation

The **In Vitro Diagnostic Regulation (IVDR)** (EU 2017/746) governs the regulation of in vitro diagnostic medical devices in the European Union. It ensures **safety, performance, and harmonized standards** across member states, covering everything from development to market surveillance and application. The IVDR sets out the requirements that in vitro diagnostics must meet to be marketed and operated within the EU. It is essential for manufacturers, importers, and national authorities to comply with these regulations to ensure the quality and reliability of diagnostic devices. EUR-Lex +4

EUR-Lex

2017/746 - EN - Medical Device Regulation - EUR-Lex

Wikipedia

Verordnung (EU) 2017/746 über In-vitro-Diagnostika – Wikipedia

www.wko.at

IVDR - aktuelle Informationen - W

IVDR Training : In Vitro Diagnostic Medical Devices Regulation 2017/746

★★★★★ (55 reviews)

’In the best of all possible worlds’

(Wilhelm Leibniz, Voltaire)

Antibodies for IHC and other antibody-based techniques

Immunohistochemistry with optimized antibodies shared between laboratories around the world

Mass spectrometry with shared libraries

Auxiliary methods

DPD-Scintigraphy

Suggestions for new laboratories

- **Get association with an already established, well working center**
- Start with optmisation of amyloid detection with Congo red
- Immunohistochemistry with well characterized antibodies. Protein AA is usually the most easy amyloid fibril type to distingish

- Mass spectrometry for selected cases. To be performed by highly specialized laboratories.

- Auxiliary methods, e.g. cardiac scintigraphy

Suggestions for new laboratories

- **Get association with an already established, well working center**
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- Mass spectrometry for selected cases. To be performed by highly specialized laboratories.

- Auxiliary methods, e.g. cardiac scintigraphy

Unmet needs in the diagnosis and treatment of amyloidosis in South America

Dr Eloísa Riva, MD, MEd.

Hospital de Clínicas / Hospital Británico

Montevideo, Uruguay

Amyloidosis represent a challenge

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- Low disease awareness
- Limited access to specialized care: typing
- Few reference centers and lack of multidisciplinary teams
- Suboptimal treatment options and outcomes
- Scarcity of local data and registries
- Economic and regulatory barriers delaying drug approvals and reimbursement

1. Low awareness = delayed diagnosis

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- Single, University Brazilian center
- **>3 specialists were seen before the diagnosis was done**
  - GP (57%)
  - Nephrologists (45%)
  - Cardiologists (38%).
- Organ involvement: renal (54%) and cardiac (41%); cachexia (36%).
- In 72% of the cases, ≥ 2 biopsies were required until the final diagnosis.
- Median time to diagnosis 10.9 months, and most patients (75%) had ≥ 2 organs involved.
- Subtypes: AL (68%), ATTR (13%), AA (8%), AFib (4%), and inconclusive (7%). Mass spectrometry not routinely available.
- Median OS was 74.3 months in the non-AL subgroup and 18.5 months in AL.

- Single, University Argentinian center
- **>3 specialists were seen before diagnosis**
  - GP 86%
  - Cardiology 50%
  - Nephrology 36%
- Median time to diagnosis 16 months
- 14% hospitalized at least 3 times before diagnosis
- 57% cardiac involvement
- Median OS 21 months, significantly higher for those diagnosed <12 months from the onset of symptoms

3+ specialists before dx
Median time to dx 1 year
OS related with time to dx

Szor, R.S., Fernandes, F., Lino, A.M.M. et al. Systemic amyloidosis journey from diagnosis to outcomes: a twelve-year real-world experience of a single center in a middle-income country. Orphanet J Rare Dis 17, 425 (2022). https://doi.org/10.1186/s13023-022-02584-3

Oses, L., Carretero, M., Posadas, M., Brulc, E., Nucifora, E., & Schutz, N. (2023). The Journey to Diagnosis of Light Chain Amyloidosis: A Real-World Experience from a Single Center in Latin America. Blood.

1. Low awareness

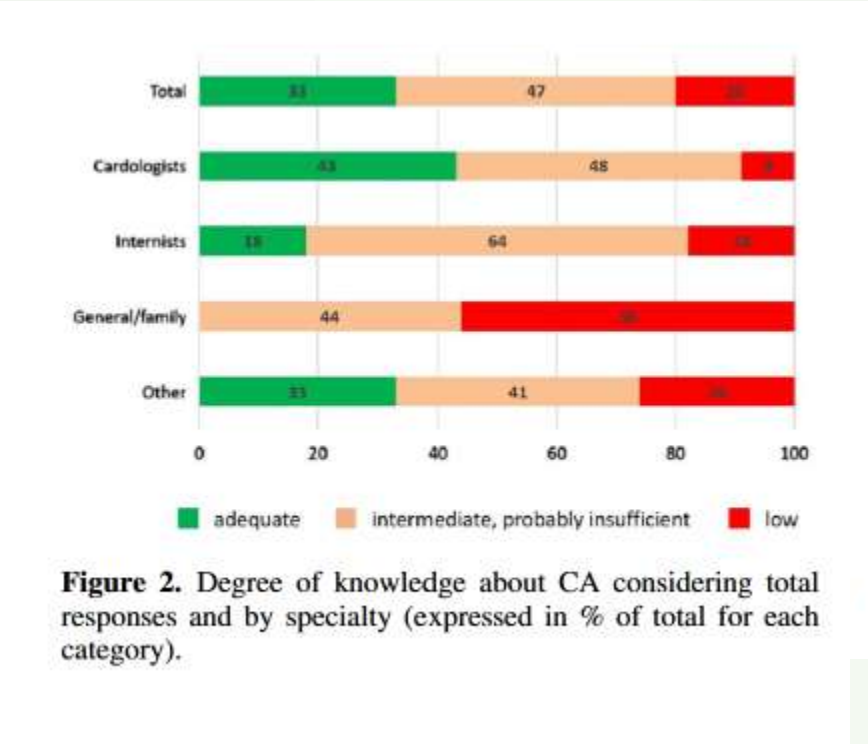

Figure 2. Degree of knowledge about CA considering total responses and by specialty (expressed in % of total for each category).

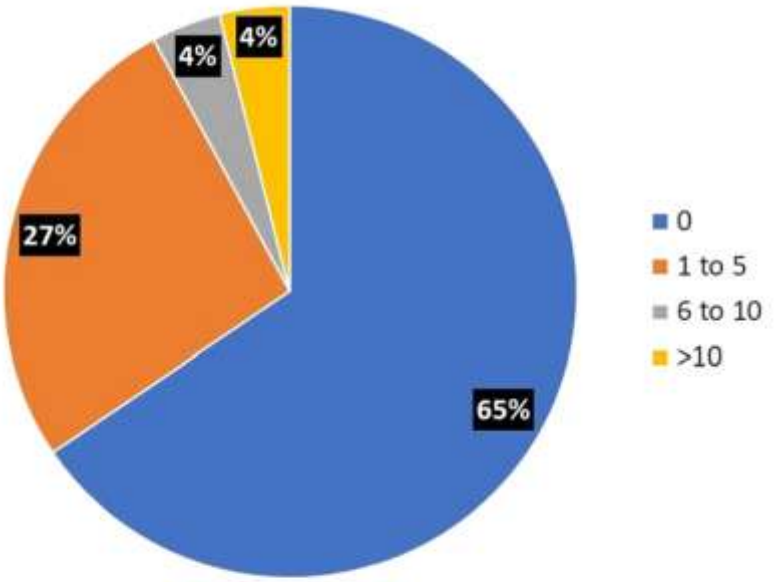

Figure 4. NM scans requested during the previous year, expressed as percentage of total responding physicians across all categories.

Mut F, Carvajal I, Camilletti J, Erriest J, Alexanderson E, Grossman GB. Cardiac amyloidosis in Latin America: Gaps and opportunities to increase awareness of the disease. Findings from the AMILO-LATAM research group. J Nucl Cardiol. 2023 Aug;30(4):1592-1601. doi: 10.1007/s12350-022-03005-5. Epub 2022 May 31. PMID: 35641695; PMCID: PMC9154028.

2. Limited access to diagnostic

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- Congo red staining not widely available or poorly standardized.
- Few centers can perform accurate amyloid typing (immunohistochemistry or mass spectrometry).
- Cardiac imaging (Tc-PYP/DPD scans, cardiac MRI) available in most countries, although limited to large cities.
- Protein electrophoresis, immunofixation and sFLC not available in 20%, and not reimbursed in more than 40%.
- Genetic tests available, not reimbursed.

Riva E, Schütz N, Peña C, Ruiz-Argüelles G, Hopkins CR, Bove V, Villano F, Andino L, Suárez L, Martínez H, Navarro J, López-Vidal H, Da Costa O, Pineda MR, Rubio Y, Ramirez J, Choque J, Fantl D. Significant differences in access to tests and treatments for multiple myeloma between public and private systems in Latin America. Results of a Latin American survey. GELAMM (Grupo de Estudio Latino Americano de Mieloma Múltiple). Ann Hematol. 2020 May;99(5):1025-1030. doi: 10.1007/s00277-020-03983-x. Epub 2020 Mar 10. PMID: 32157420.

3. Mass spectrometry

- Retrospective, observational, single-center study
- Consistency: clinical-lab model, IHC, MS.
- MS on tissue biopsies from patients with systemic amyloidosis

- N=78
- MS identified 5 subtypes: AL (56%), ATTR (25%), AA (6%), AFib (3%), AH (1%).

- IHC correctly subtyped amyloid in 28% of cases but failed in 66%.
- CLM correctly identified subtype in 80% but failed 20%.
- MS could not identify subtype in 9%

Szor, R.S., Castelli, J.B., Schuch, R.A. *et al.* Assessing the consistency of mass spectrometry, a clinical-laboratory model, and immunohistochemistry in amyloid subtyping: a Brazilian experience. *Clin Proteom* **22**, 35 (2025). https://doi.org/10.1186/s12014-025-09546-4

4. Limited reference centers

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

FUNDING

AWARENESS

COLLABORATION

5. Inequalities in access to novel therapies

- Unequal access to proteasome inhibitors and monoclonal antibodies for AL amyloidosis.
  - Significant differences between public and private settings

- Limited use of tafamidis or gene-silencing therapies for ATTR amyloidosis due to cost and regulatory delays.
  - Brazil, Argentina, Chile. Uruguay and Colombian (soon),
  - Approval does not mean reimbursement
- Delays in treatment initiation after diagnosis (>3 months).

- ASCT is available and reimbursed in most countries. Low MRT in centers of expertise (2-3%)

6. Systemic barriers

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- Lack of national referral networks.
- No diagnostic algorithms adapted to resource levels.
- Limited reimbursement.
- Insufficient training among general practitioners and non-specialist cardiologists/hematologists.
- Long and heterogeneous regulatory processes

Changes in the last decade

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- Regional groups
- More data is available
- Training and case discussion
- Multidisciplinary groups are showing positive results (Uruguay, Argentina, Chile, Brazil)

FIGURE 2 Timeline of research on amyloidosis in Latin America

AMILO-LATAM

GRUPO DE ESTUDIO LATINOAMERICANO DE MIELOMA MULTIPLE
GELAMM

Summary

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- Latin America faces structural and access challenges that delay care.
- Coordinated regional and global actions can close these gaps.
- Education, access, and collaboration are the pillars for change.

Summary

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

- Latin America faces structural and access challenges that delay care.
- Coordinated regional and global actions can close these gaps.
- Education, access, and collaboration are the pillars for change.