Defining Idiopathic Inflammatory Myopathies (IIMs) and Classification Criteria INTERNATIONAL ANNUAL PATIENT CONFERENCE September 7, 2024

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Disclosure

- Advisory board: Argenx, Bristol-Myers Squibb, EMD Serono Research & Development Institute, Janssen, Pfizer, Chugai, Novartis
- Unrestricted grant: Astra-Zeneca
- Stock shares: Novartis, Roche

Karolinska Institutet

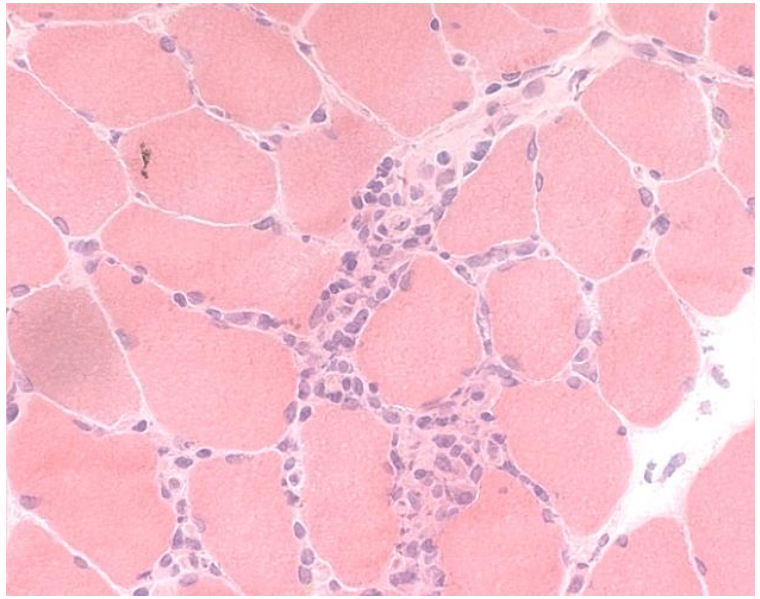
Outline of presentation

- Myositis traditional presentation
- Diagnosis of myositis
- New myositis subgroups
- Myositis autoantibodies
- Classification criteria for myositis

- Reveiw "Idiopathic inflammatory myopathies" https://rdcu.be/cCs4c

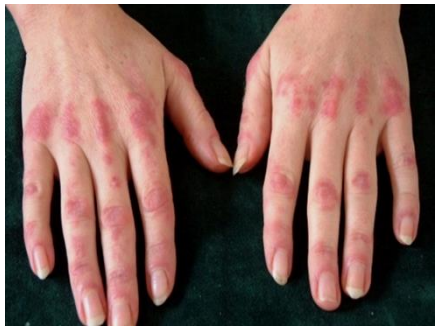
Idiopathic inflammatory myopathies (IIM) or myositis- traditional presentation

- Muscle weakness and low muscle endurance
- Cellular infiltrates in muscle tissue



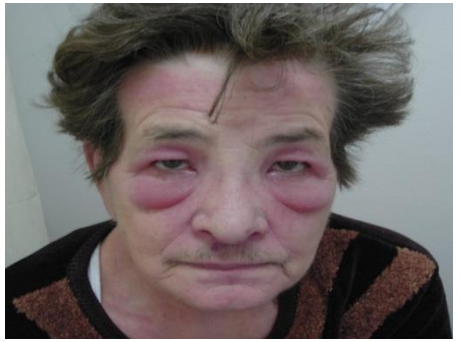
Diagnosis - myositis

- Muscle weakness- proximal, symmetrical
- Elevated serum levels of muscle enzymes CK, LD
- Electromyogram (EMG) -pathology
- Muscle biopsy – inflammation, regeneration, degeneration of muscle fibres
- Skin rash: Gottron´s, heliotrope rash
- Bohan &Peter 1975

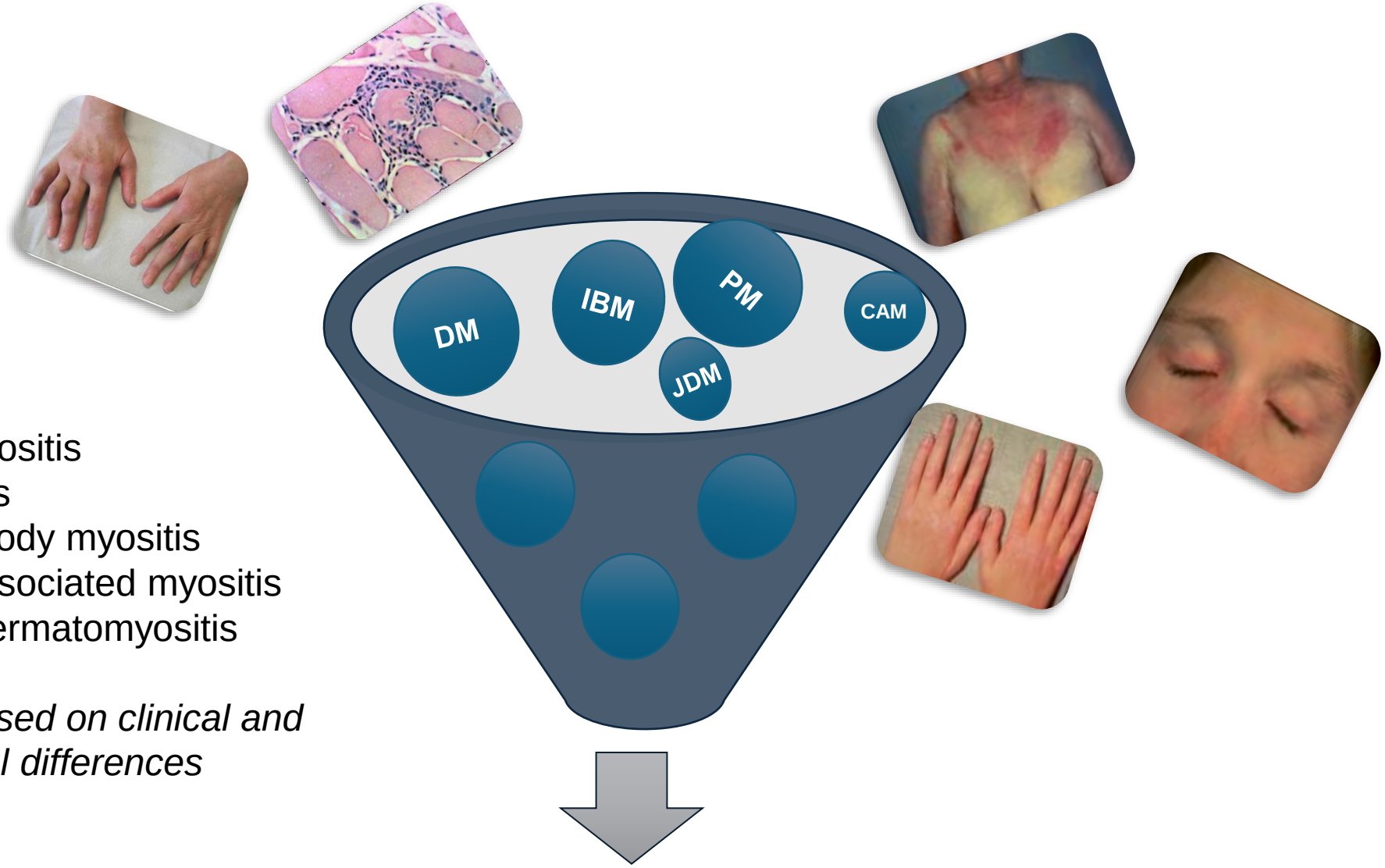


Today we also have:

- Magnetic resonance imaging (MRI) oedema of skeletal muscle to identify inflammation
- Autoantibodies



Courtesy J Vencovsky



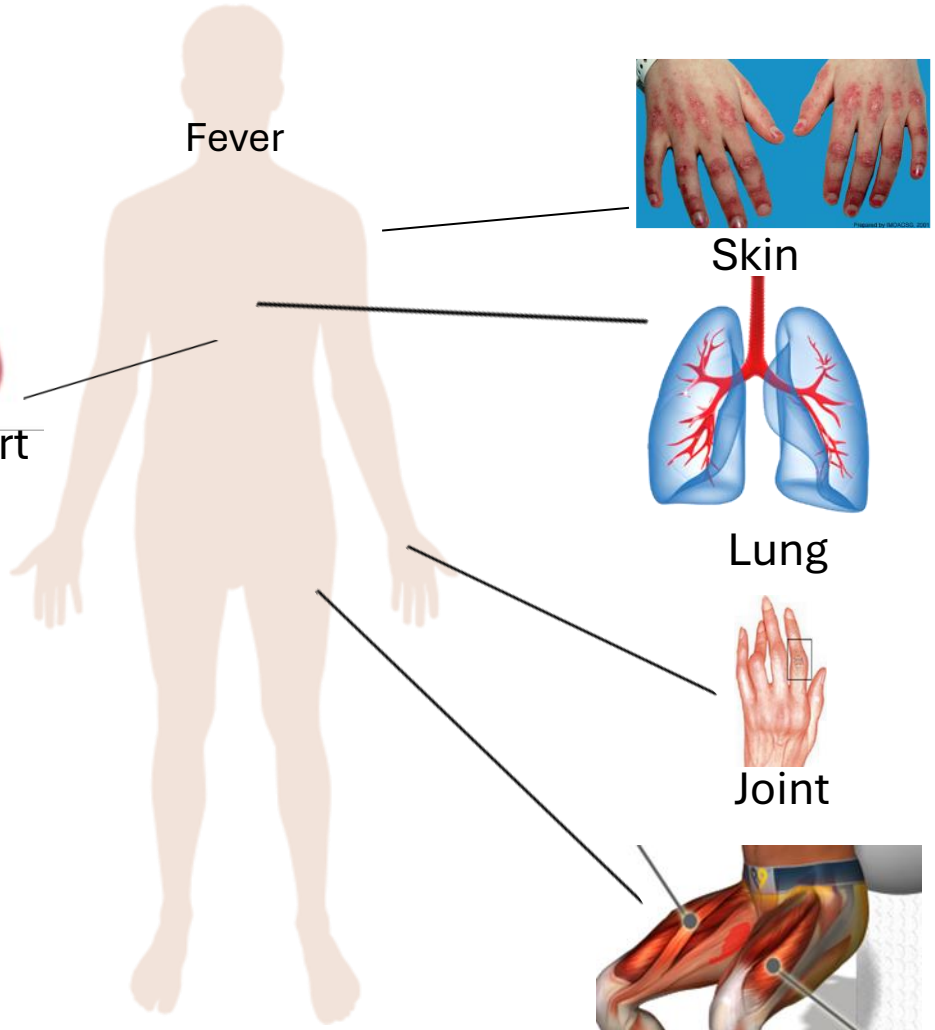
DM, dermatomyositis
PM, polymyositis
IBM, inclusion body myositis
CAM, cancer associated myositis
JDM, juvenile dermatomyositis

Subgrouping based on clinical and histopathological differences

Idiopathic inflammatory myopathy, myositis

Courtesy Dr Antonella Notarnicola

Myositis: often a systemic disease



Rash
Nailfold capillary changes
Raynaud's phenomenon
Cuticular overgrowth
Mechanic's Hands

Interstitial lung disease

Arthritis

Muscle weakness

The Muscular and Extramuscular Features of IIM

Courtesy L. Christopher Stine

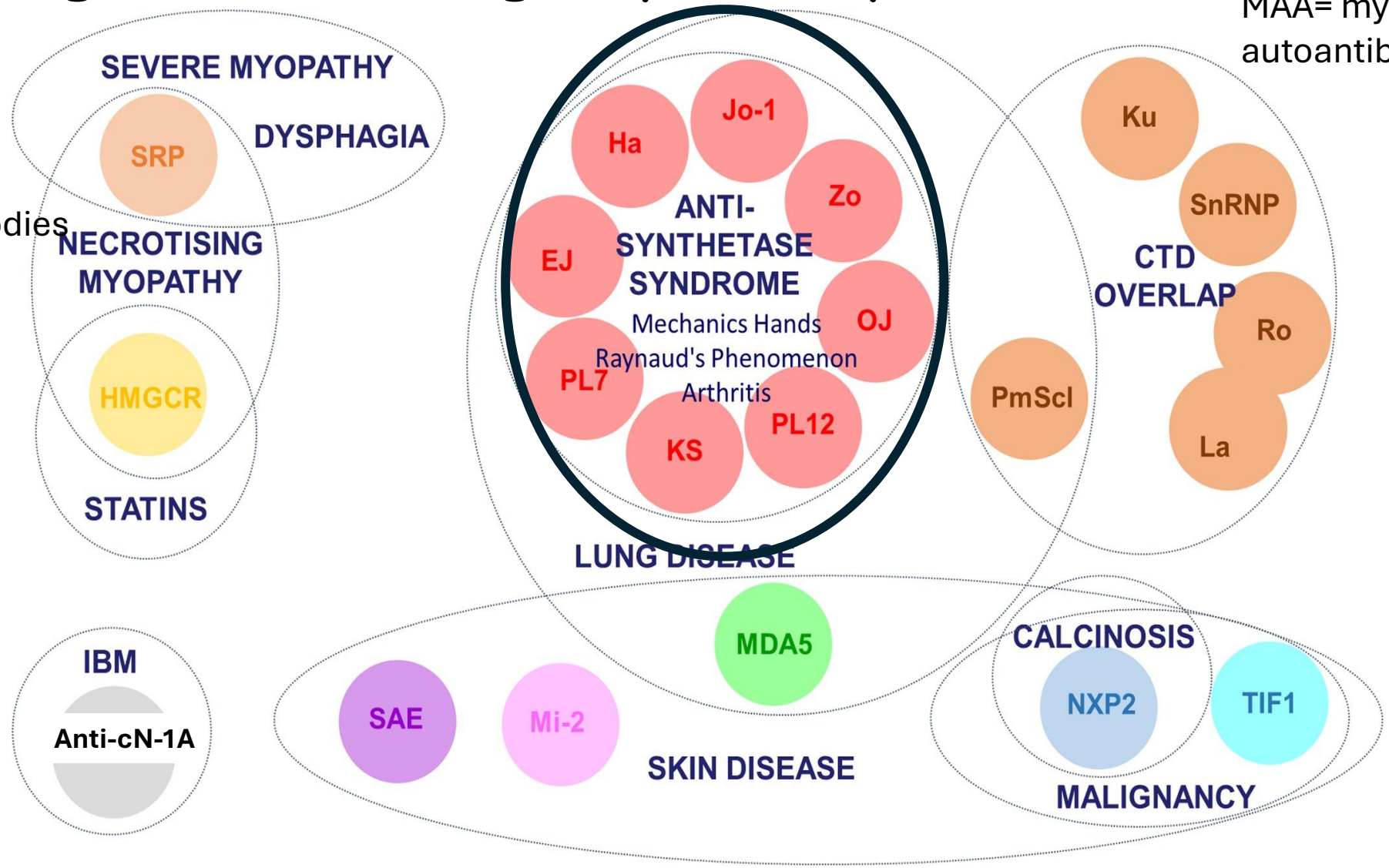
New subtypes of myositis

Myositis disease spectrum

Myositis-specific autoantibodies: an important tool to support diagnosis and subgroups of myositis

MAA= myositis associated autoantibodies

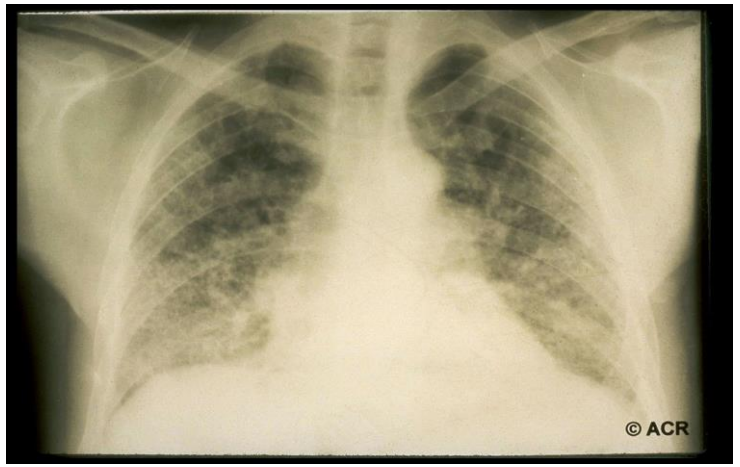
MSA= myositis Specific autoantibodies

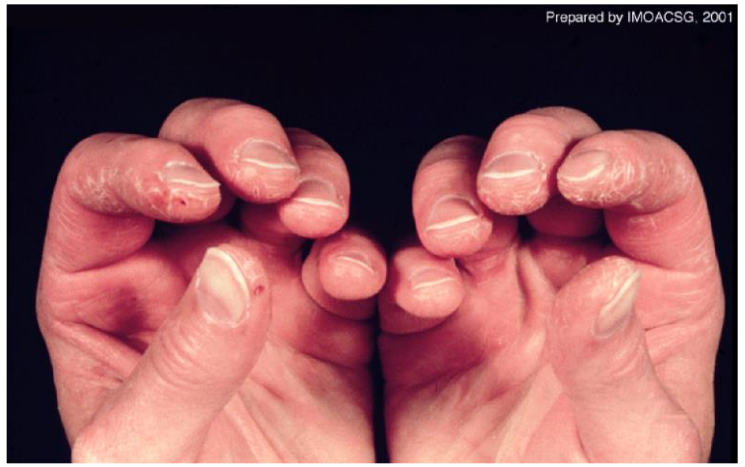


Betteridge Z et al J Int Med. 2015. 280:8-23

Anti-synthetase syndrome
(Anti-tRNA synthetase autoantibodies, eg anti-Jo1)

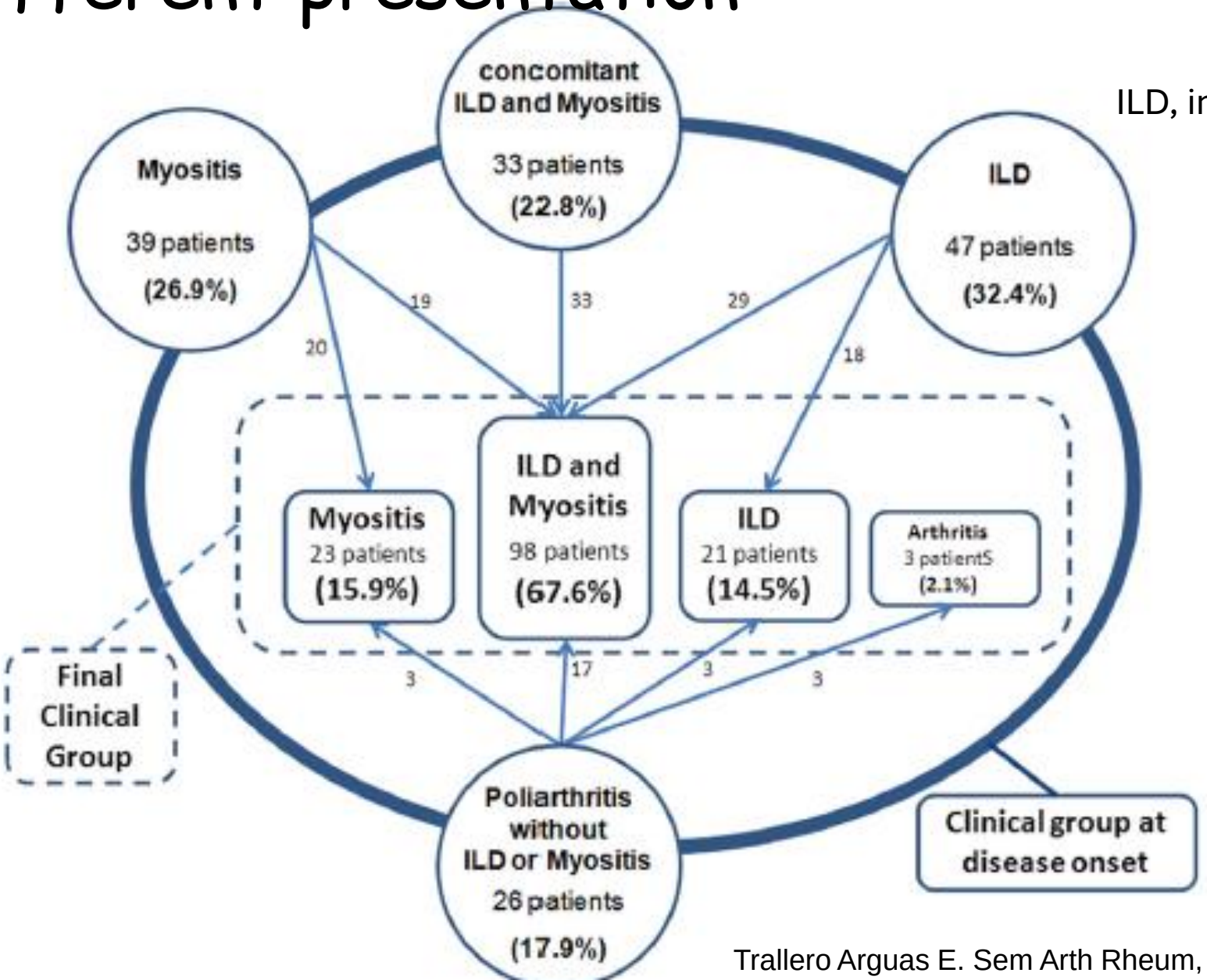
- Myositis
- Interstitial lung disease (ILD)
- Arthritis
- Fever
- Raynaud
- Mechanic´s hands
- **HLA-DRB1*0301 association**





Love et al 1991 Arnett et al 1996

Anti-Jo-1 positive patients with different presentation



ILD, interstitial lung disease

(n=148)

Trallero Arguas E. Sem Arth Rheum, 2016

Anti-synthetase autoantibodies

ILD = interstitial lung disease

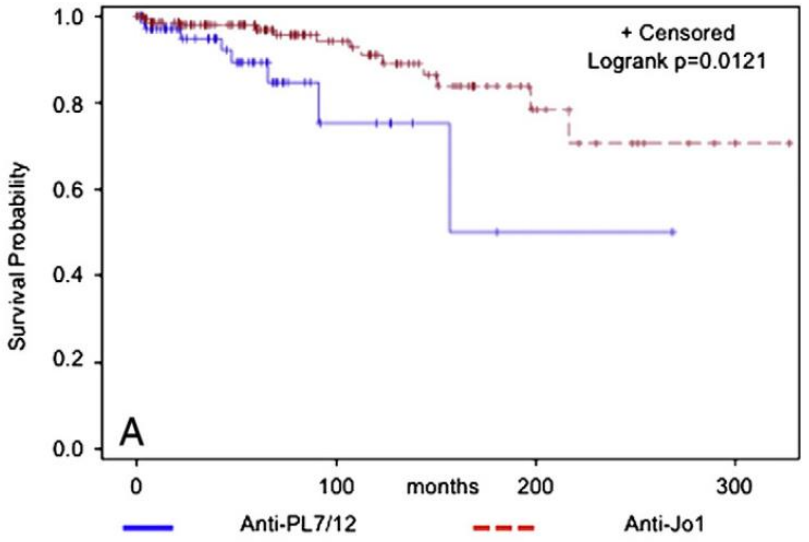
- *anti-Jo-1 (anti-histidyl tRNA synthetase)*
- *anti-PL-7 (anti- threonyl synthetase)* - **ILD**
- *anti-PL-12 (anti-alanyl synthetase)* - **ILD**
- *anti-EJ (anti-glycyl-synthetase)*
- *anti-OJ (anti-isoleucyl-tRNA synthetase)* - **ILD**
- anti-KS (asparaginyl-synthetase) - **ILD**
- anti-Ha (tyrosyl-synthetase)
- anti- Zo (anti-phenylalanyl synthetase) - **ILD**

Betteridge Z et al, Rheumatol, 2007

Antisynthetase syndrome anti-Jo1 vs anti-PL7/anti-PL12

Antisynthetase ab	Anti-Jo1 (n=160)	Anti-PL7 (n=25)	Anti-PL12(n=48)
Interstital lung disease (ILD)	67%*	80%*	88%
FVC	75±21*	66±18 (PL7/PL12)	
Muscle weakness	74%*	47%	44%

- **Anti-PL7/PL12 vs anti-Jo1**
- More frequent and more severe ILD
- Less myositis
- Worse survival

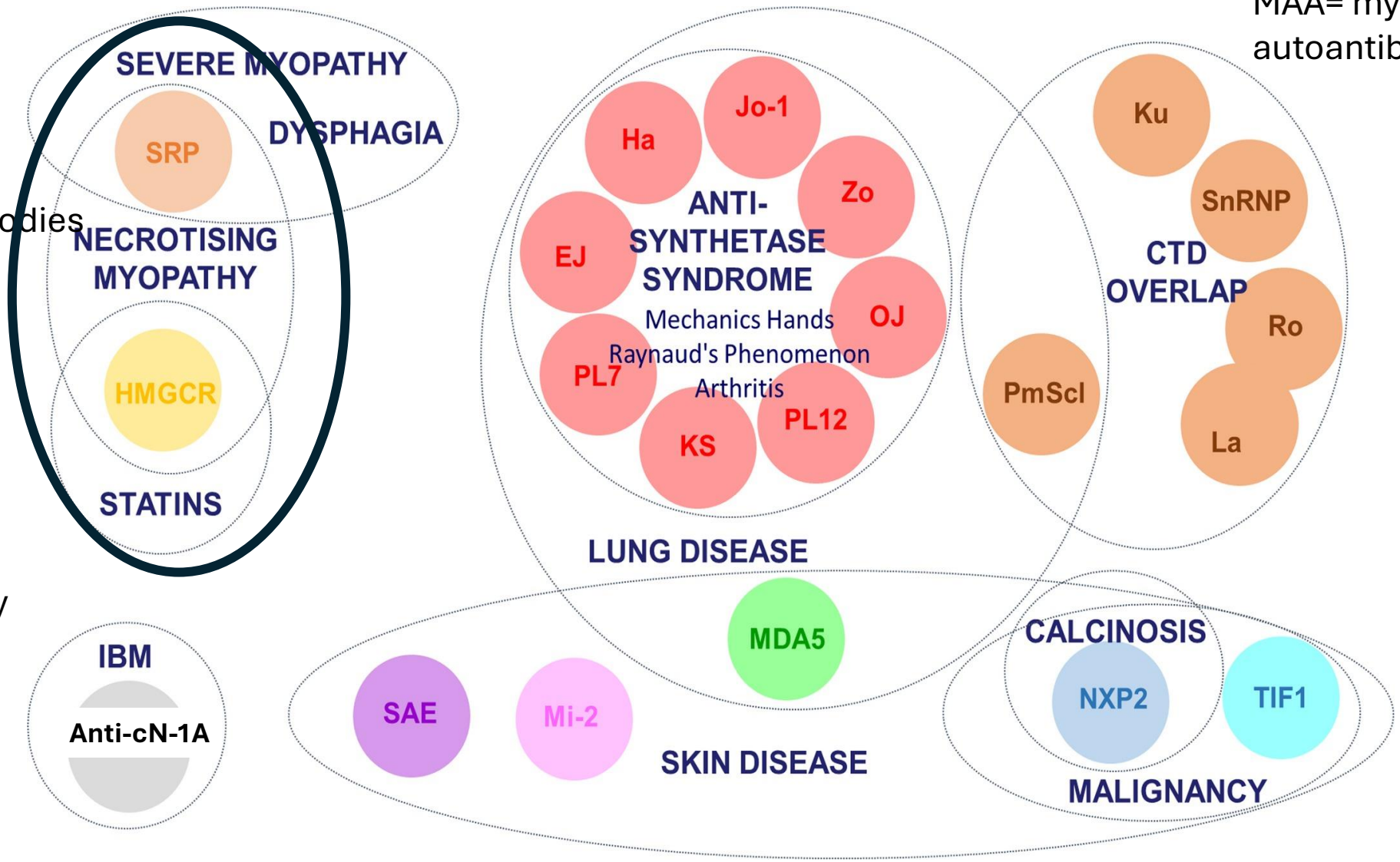


Hervier B et al Autoimmun Rev 2012;12:2010-17; Pinal-Fernandez I et al Rheumatology. 2017;56:999–1007; Aggarwal R et al Ann Rheum Dis, 2014;73:227-32

Myositis-specific autoantibodies: an important tool to support diagnosis and subgroups of myositis

MAA= myositis associated autoantibodies

MSA= myositis Specific autoantibodies

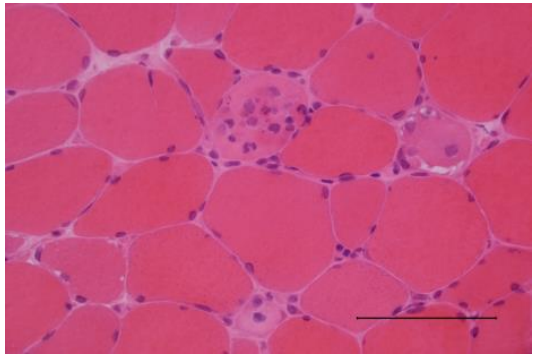


Betteridge Z et al J Int Med. 2015. 280:8-23

Immune mediated necrotising myopathy (IMNM)

- **Anti-SRP** autoantibodies Love L et al Medicine (Baltimore),70:360, 1991
- **Anti-HMGCR** autoantibodies, associated with statins, but can also be seen without statin treatment Christopher-Stine L et al Arthritis Rheum, 62:2757-66, 2010
- **Seronegative** cancer associated

- Pronounced proximal muscle weakness
- High serum levels of CK
- Lung involvement is rare
- **Microscopy: muscle fiber necrosis, regeneration** limited inflammation
  - Hengstman GJD Ann Rheum Dis 65:1635, 2006



Courtesy Antonella Notarnicola

Myositis-specific autoantibodies: an important tool to support diagnosis and subgroups of myositis

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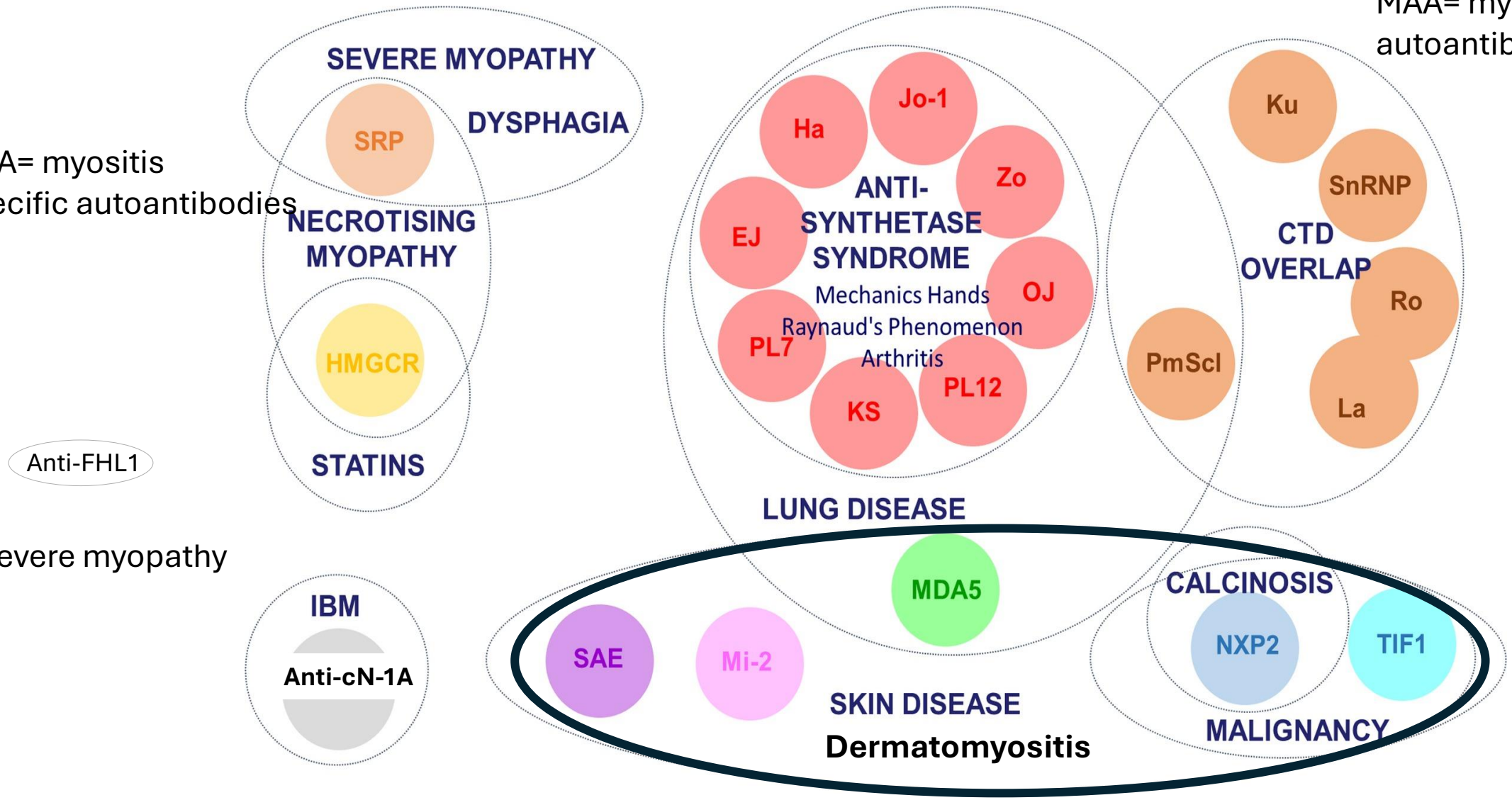
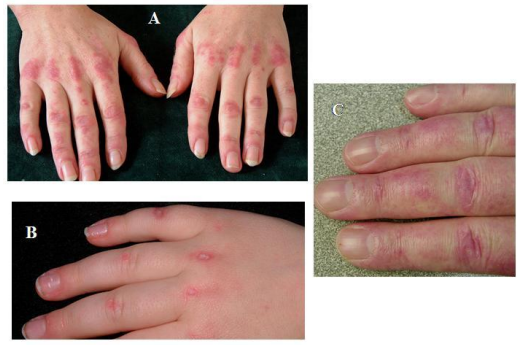


Betteridge Z et al J Int Med. 2015. 280:8-23

Anti-TIF1 gamma autoantibodies

- Positive in 20-30 % of adult patients with dermatomyositis
- Positive in 25% of children with dermatomyositis
- Increased risk for cancer **in adult** patients with anti-TIF1 gamma but not in children
- But only 50% of patients with dermatomyositis and anti-TIF1 gamma develop cancer
- May be explained by protective antibodies: Anti-CCAR1-antibodies

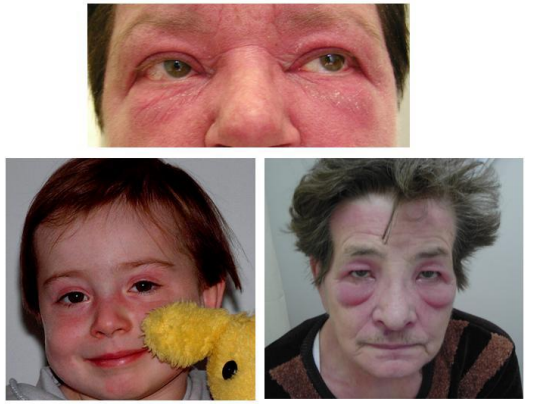


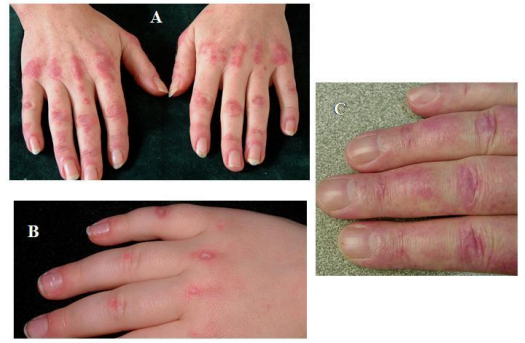
Fiorentino D et al J Clin Invest. 2022;132(2):e150201

Courtesy Antonella Notarnicola

Clinically amyopathic dermatomyositis (CADM)

- Skin rash typical of DM
- Skin biopsy consistent with dermatomyositis
- Absence of clinical or laboratory evidence of myositis
- **Interstitial Lung Disease (Rapidly progressive ILD)**
- **Anti-MDA-5 antibodies**



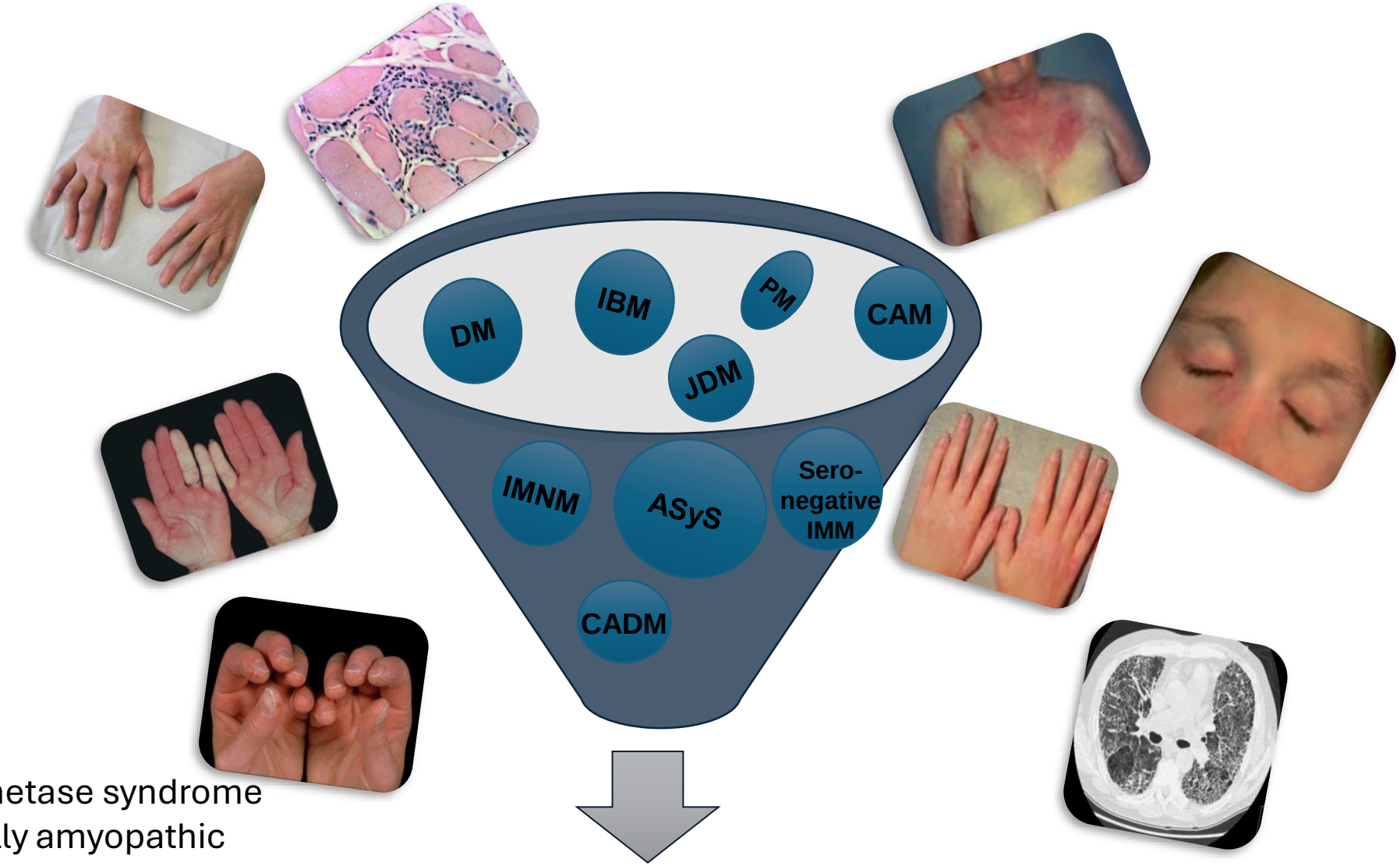


Courtesy J. Vencovsky

Gerami P et al J Am Acad Dermatol. 54:597 2006

Sontheimer R J Am Acad Derm 2006

Sato s et al Arthritis Rheum 2009;60:2193-200



ASyS=antisynthetase syndrome
CADM= clinically amyopathic dermatomyositis
IMNM=immune mediated necrotizing myopathy

Myositis disease spectrum

Courtesy Dr Antonella Notarnicola

Karolinska Institutet

Diagnosis as help in the clinic

- **For making decisions on treatment**
- **For prediction of prognosis**

How can we improve treatment and life for patients with myositis?

Hypothesis: Different subsets may benefit from different interventions

- We need to know more about the molecular pathophysiology in myositis and its subsets to develop new therapies
- Can be acheived by detailed clinical and molecular characterization of patients
- Can be tested by using Targeted therapies
- For research and clinical trials we need classification criteria

Classification criteria vs diagnostic criteria

- A lack of a single gold standard diagnostic test for myositis
- We need criteria for diagnosis
- We need classification criteria for research and clinical trials
- Different methodology for development of diagnostic and classification criteria

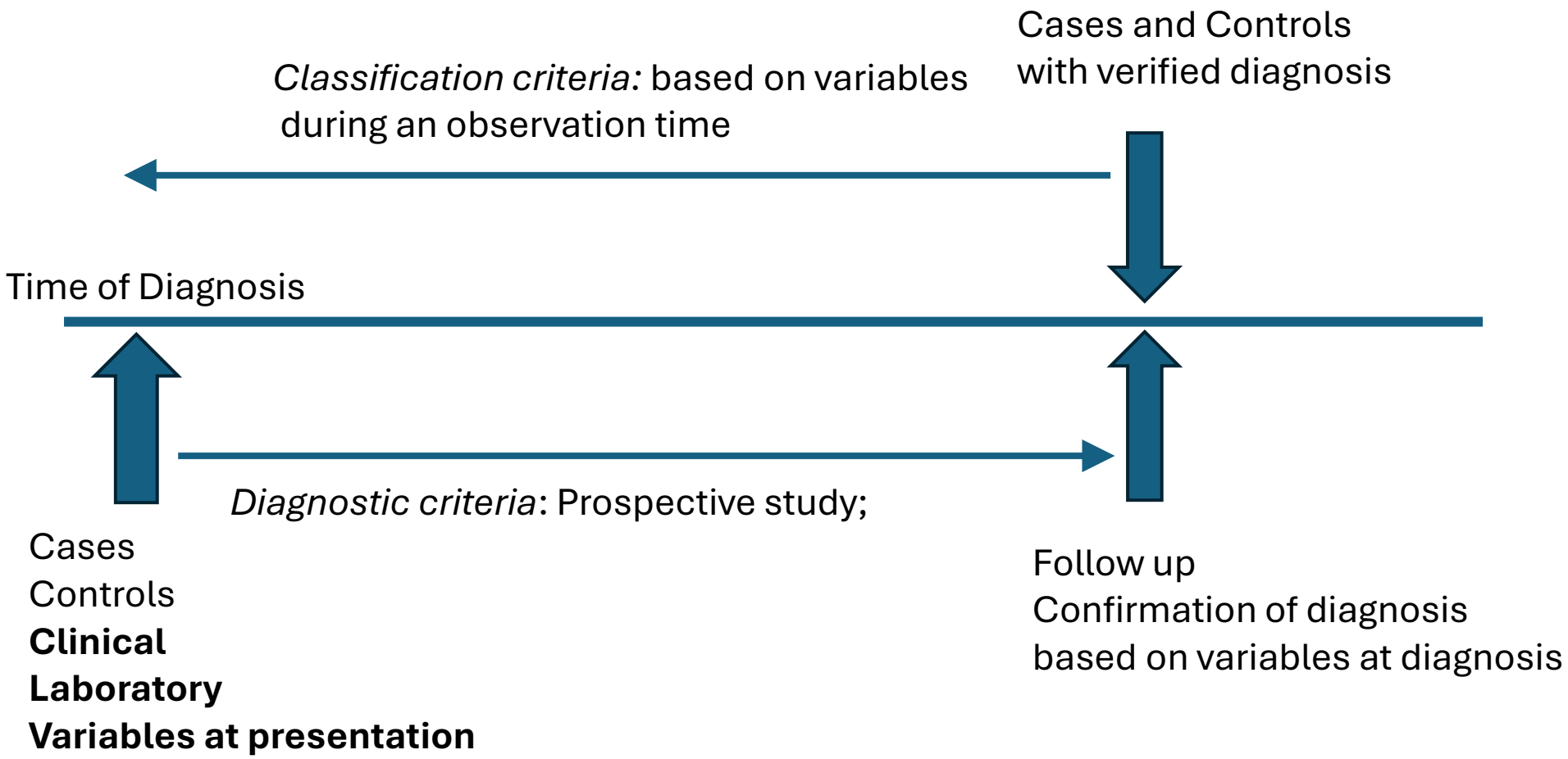
Johnson SR et al A&R (Arthritis Care & Research), 2007;57:1119 –1133

Dougados et al A&R (Arthritis Care & Research) 2007;57:1112–1115

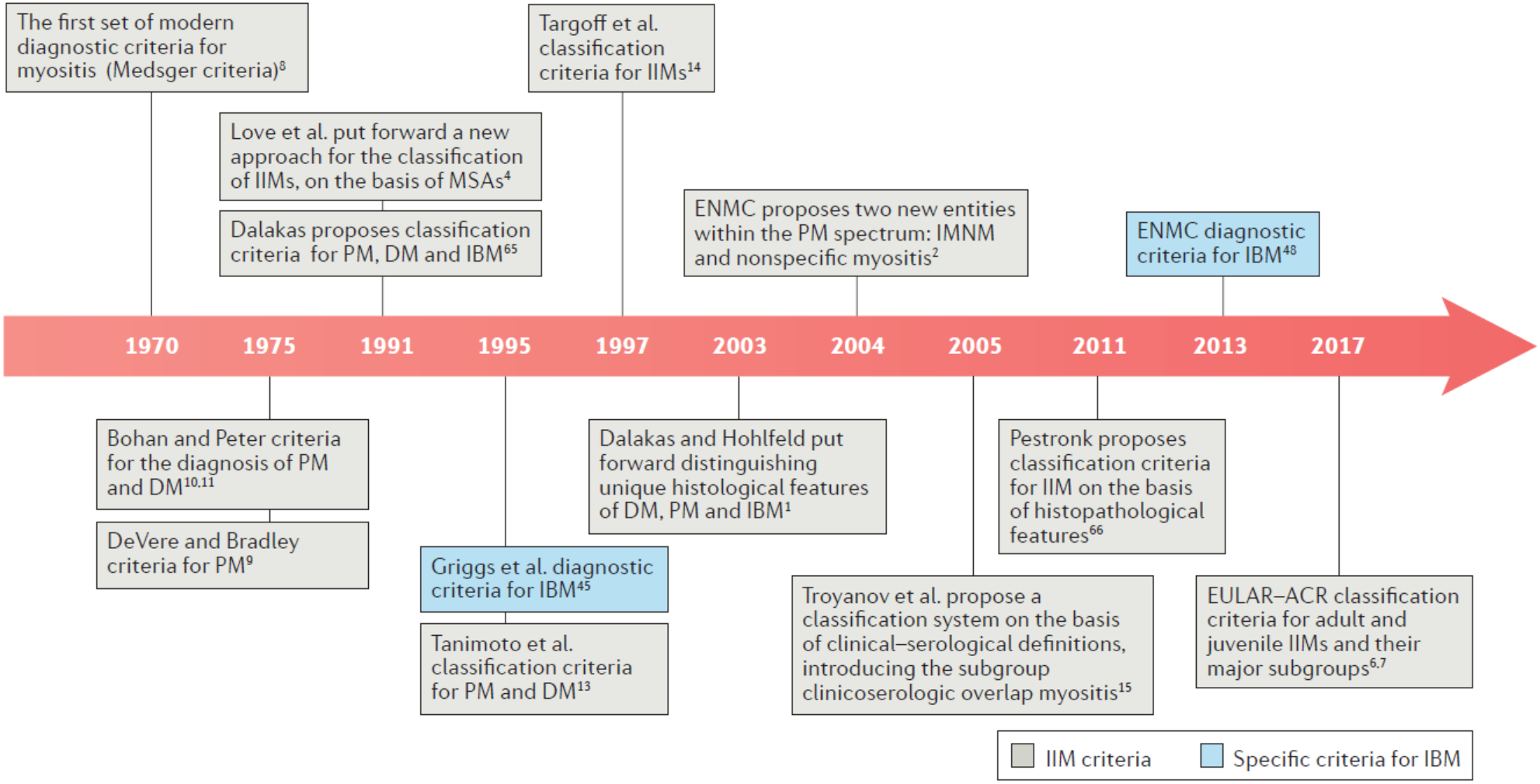
Diagnostic criteria

- To be used to support diagnosis (of myositis)

Development of Diagnostic vs Classification criteria



Classification criteria for myositis



Lundberg IE at al Nat Rev Rheum 2018:14:269:

First, published on October 27, 2017 as 10.1136/annrheumdis-2017-211468

2017 European League Against Rheumatism/ American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups

Ingrid E Lundberg,[1] Anna Tjärnlund,[1] Matteo Bottai,[2] Victoria P Werth,[3] Clarissa Pilkington,[4] Marianne de Visser,[5] Lars Alfredsson,[2] Anthony A Amato,[6] Richard J Barohn,[7] Matthew H Liang,[8] Jasvinder A Singh,[9,10] Rohit Aggarwal,[11] Snjolaug Arnardottir,[12] Hector Chinoy,[13] Robert G Cooper,[14] Katalin Dankó,[15] Mazen M Dimachkie,[7] Brian M Feldman,[16] Ignacio Garcia-De La Torre,[17] Patrick Gordon,[18] Taichi Hayashi,[19] James D Katz,[20] Hitoshi Kohsaka,[21] Peter A Lachenbruch,[22] Bianca A Lang,[23] Yuhui Li,[24] Chester V Oddis,[11] Marzena Olesinska,[25] Ann M Reed,[26] Lidia Rutkowska-Sak,[27] Helga Sanner,[28] Albert Selva-O'Callaghan,[29] Yeong-Wook Song,[30] Jiri Vencovsky,[31] Steven R Ytterberg,[32] Frederick W Miller,[33] Lisa G Rider,[33] The International Myositis Classification Criteria Project consortium, The Euromyositis register and The Juvenile Dermatomyositis Cohort Biomarker Study and Repository (JDRG) (UK and Ireland)

Ann Rheum Dis. 2017 Dec;76:1955-1964

Aims of the classification criteria project

- To develop classification criteria for use by basic and clinical researchers that **distinguish IIM from other major mimicking conditions** with high sensitivity and specificity; and

- To develop classification criteria that **separate the major subgroups** of the IIM from each other with high sensitivity and specificity.

- Data driven
- Combined effort to address both adult-onset and childhood-onset myositis, international, multidisciplinary

IMCCP variables
in total 93 variables

- **Demographic data**
  - Gender
  - Age
  - Ethnicity
- **Clinical muscle variables**
  - Pattern of weakness
- **Skin manifestations**
- **Other clinical variables**
  - ILD
  - Dysphagia
  - Response to treatment
- **Laboratory data**
  - Muscle enzymes
  - Autoantibodies
- **Muscle biopsy**
  - Histopathology
  - Immunohistochemistry
  - Electron microscopy
- **Electromyogram** (EMG)
- **Magnetic resonance imaging** (MRI)

Data collection

1600 IIM and comparators

IIM	976 (74% adults; 26% children)
Comparators	624 (81% adults; 19% children)

SUBGROUPS IIM	n	%
Juvenile dermatomyositis	251	15.7
Polymyositis	241	15.1
Dermatomyositis	236	14.8
Inclusion body myositis	176	11.0
Amyopathic dermatomyositis	44	2.8
Hypomyopathic dermatomyositis	12	0.8
Immune-mediated necrotizing myopathy	11	0.7
Juvenile polymyositis	5	0.3
Non-inflammatory myopathy	624	39.0

Participating clinics (n=47)

North America:	17
South America:	1
Europe:	23
Asia:	6

2017 EULAR/ACR Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies and their Major Subgroups

VARIABLE	SCORE POINTS	
	Without muscle biopsy data	With muscle biopsy data
18 ≤ Age of onset of first symptom < 40	1.3	1.5
Age of onset of first symptom ≥ 40	2.1	2.2
Clinical Muscle Variables		
Objective symmetric weakness, usually progressive, of the proximal upper extremities	0.7	0.7
Objective symmetric weakness, usually progressive, of the proximal lower extremities	0.8	0.5
Neck flexors are relatively weaker than neck extensors	1.9	1.6
In the legs proximal muscles are relatively weaker than distal muscles	0.9	1.2
Skin variables		
Heliotrope rash	3.1	3.2
Gottron´s papules	2.1	2.7
Gottron's sign	3.3	3.7
Other Clinical Variables		
Dysphagia or esophageal dysmotility	0.7	0.6
Laboratory Variables		
Elevated serum levels of creatine kinase (CK) *or*, Serum lactate dehydrogenase (LDH) *or*, Serum aspartate aminotransferase (ASAT) *or*, Serum alanine aminotransferase (ALAT)	1.3	1.4
Anti-Jo-1 (anti-Histidyl-tRNA synthetase) autoantibody positivity	3.9	3.8
Muscle Biopsy Variables		
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers		1.7
Perimysial and/or perivascular infiltration of mononuclear cells		1.2
Perifascicular atrophy		1.9
Rimmed vacuoles		3.1

Classification Criteria for Idiopathic Inflammatory Myopathies

Probability (min - max): 0 - 100%

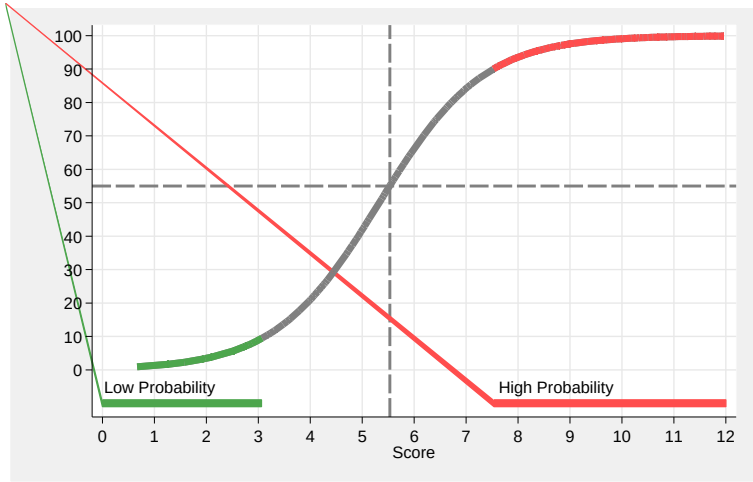
Age of onset of first symptom ☐ 0-17 ☐ 18-39 ☐ 40+

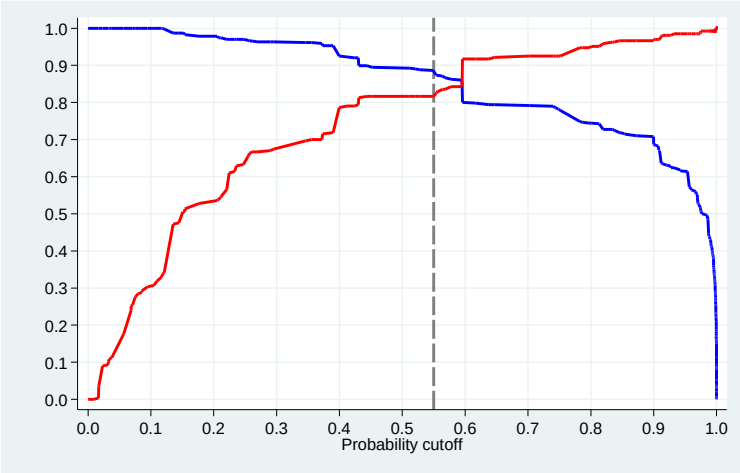
	Yes	No
Objective symmetric weakness, usually progressive, of the proximal upper extremities	☐	☐
Objective symmetric weakness, usually progressive, of the proximal lower extremities	☐	☐
Neck flexors are relatively weaker than neck extensors	☐	☐
In the legs proximal muscles are relatively weaker than distal muscles	☐	☐
Heliotrope rash	☐	☐
Gottron´s papules	☐	☐
Gottron's sign	☐	☐
Dysphagia or esophageal dysmotility	☐	☐
Anti-Jo-1 (anti-His)	☐	☐
Serum creatine kinase activity (CK) activity or Serum lactate dehydrogenase (LDH) activity or Serum aspartate aminotransferase (ASAT/AST/SGOT) activity or Serum alanine aminotransferase (ALAT/ALT/SGPT) activity	☐	☐
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers	☐	☐
Perimysial and/or perivascular infiltration of mononuclear cells	☐	☐
Perifascicular atrophy	☐	☐
Rimmed vacuoles	☐	☐

Webcalculator: www.imm.ki.se/biostatistics/calculators/iim

Probability of IIM vs. score

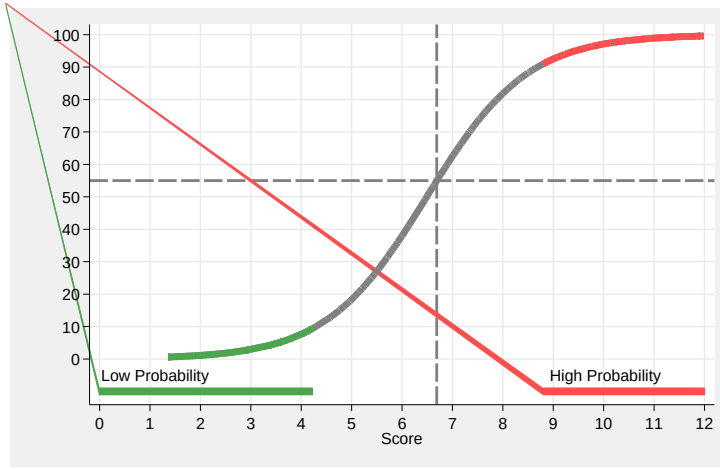
Without muscle biopsy, 55-60%

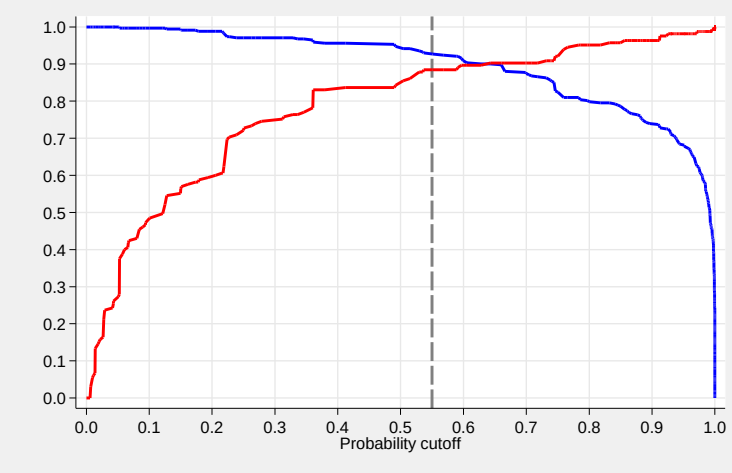




Sensitivity and specificity, cut off 55% for IIM

With muscle biopsy, 55-75%



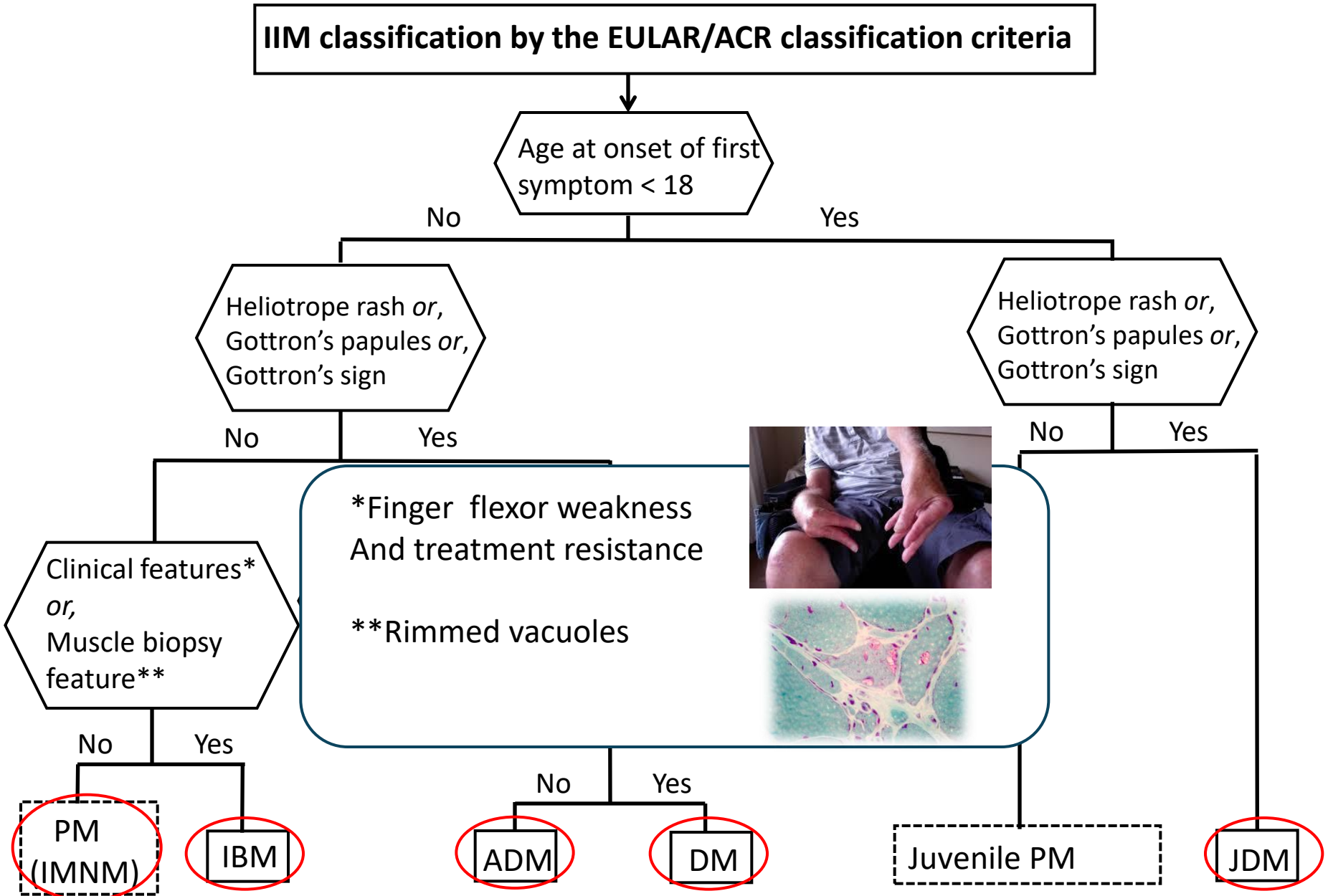


The best balance between sensitivity and specificity can be found for a probability of 55-60% (**total aggregated score of ≥5.5 and ≤ 5.7**) for the criteria without muscle biopsy data, 55-75% (**total aggregated score ≥6.7 and ≤ 7.6**) with muscle biopsy data, cutoff for IIM is 55%

Definitions

- A probability of ≥90%, or a total aggregate score of ≥7.5 without muscle biopsy and ≥8.7 with muscle biopsy, corresponds to “definite IIM”
- Patients with a probability of ≥55% to <90% are designated “probable IIM”.
- Probability ≥50% to <55% is termed “possible IIM”

Subgroup classification criteria



2023 start of
REVISION OF THE MYOSITIS CLASSIFICATION CRITERIA PROJECT

Limitations of the EULAR/ACR classification criteria

- Missing variables: interstitial lung disease (ILD), myositis specific autoantibodies other than anti-Jo1, muscle MRI, certain skin rash

- Missing new relevant myositis subgroups

AIM: To revise the 2017 EULAR/ACR classification criteria for juvenile and adult-onset idiopathic inflammatory myopathies and their major subgroups and validate the revised criteria

Organizational Structure

Executive Committee:

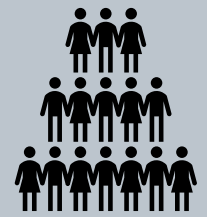
Project leaders (2), project coordinators (3) and biostatistician (1)

- Prepare background materials and evidence
- Analyse dataset

Steering Committee:

International experts (23), patient research partners (3)

- Data collection
- Sharing opinion
- Consensus discussions
- Decisions to be made



Working Committee:

Additional experts (25-40) identified through IMACS

- Data collection
- Sharing opinion

Updates on the Project

- Scoping review to systematically assess the performance of the 2017 Myositis Classification Criteria and inform the item selection process of the project was published in the Myositis supplement of CER

- Proposal to ACR and EULAR submitted in April 2024, and we got invited to submit full proposal by September 2024

- Circulated e-survey to the Steering Committee and Working Group Members to finalize the items that will be tested in the Revised Criteria

Results of the IMACS Feasibility Questionnaire General Feedback

Positive Feedback (descending order):

- Useful for clinical practice

- Useful for clinical trials

- The web calculator is particularly useful

- Not including EMG as it is not too sensitive/specific

- No need for muscle biopsy

- Useful for difficult cases

Results of the IMACS Feasibility Questionnaire
General Feedback

Negative Feedback (descending order):

- Lack of inclusion of additional autoantibodies
- Lack of inclusion of ILD
- Lack of Muscle MRI
- Lack of other skin criteria
- No distinction of IMNM
- Concerns regarding the use of the term polymyositis
- No distinction of ASyS
- Lack of EMG
- Lack of new histopathological parameters
- No distinction of Overlap-Myositis/ mixed-connective tissue diseases
- Poor ability in differentiating juvenile IIM subtypes
- Not useful for miscellaneous myositis, incl. granulomatous myositis, focal myositis
- Low representation of patients from different regions and ethnicities

Coming steps

Phase 1: Item generation

Phase 2: Data collection

Phase 3: Data analysis - Revision of the Criteria

Phase 4: Data analysis - Validation of the Criteria

Phase 5: Publication & Dissemination of the Results

Suggestions for additional variables by the working group - Imaging

2017 EULAR/ACR classification variables	What was previously collected as part of data collection?	Additional variable or changes proposed
-	Muscle edema on STIR or T2-weighted magnetic resonance imaging (MRI) Muscle atrophy and/or increased muscle fat content on T1-weighted MRI scanning consistent with myositis	MRI findings consistent with myositis (local MD interpretation)

Suggestions for inclusion of other myositis subtypes by the working group

IMNM

Overlap myositis/MCTD

ASyS (meets the classification criteria of ASyS)

DM sine dermatitis

Juvenile myositis

Revision of the myositis classification criteria

- We are in the starting phase
- We aim for information on 1000 patients with myositis, representing different subgroups and 1000 patients with mimicking conditions

- Timeline: data collection in 2025

- Analyses and summary in 2026

Acknowledgements

- **IMCCP management team**

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- Euromyositis register
- Juvenile Dermatomyositis Cohort Biomarker Study and Repository (UK and Ireland)

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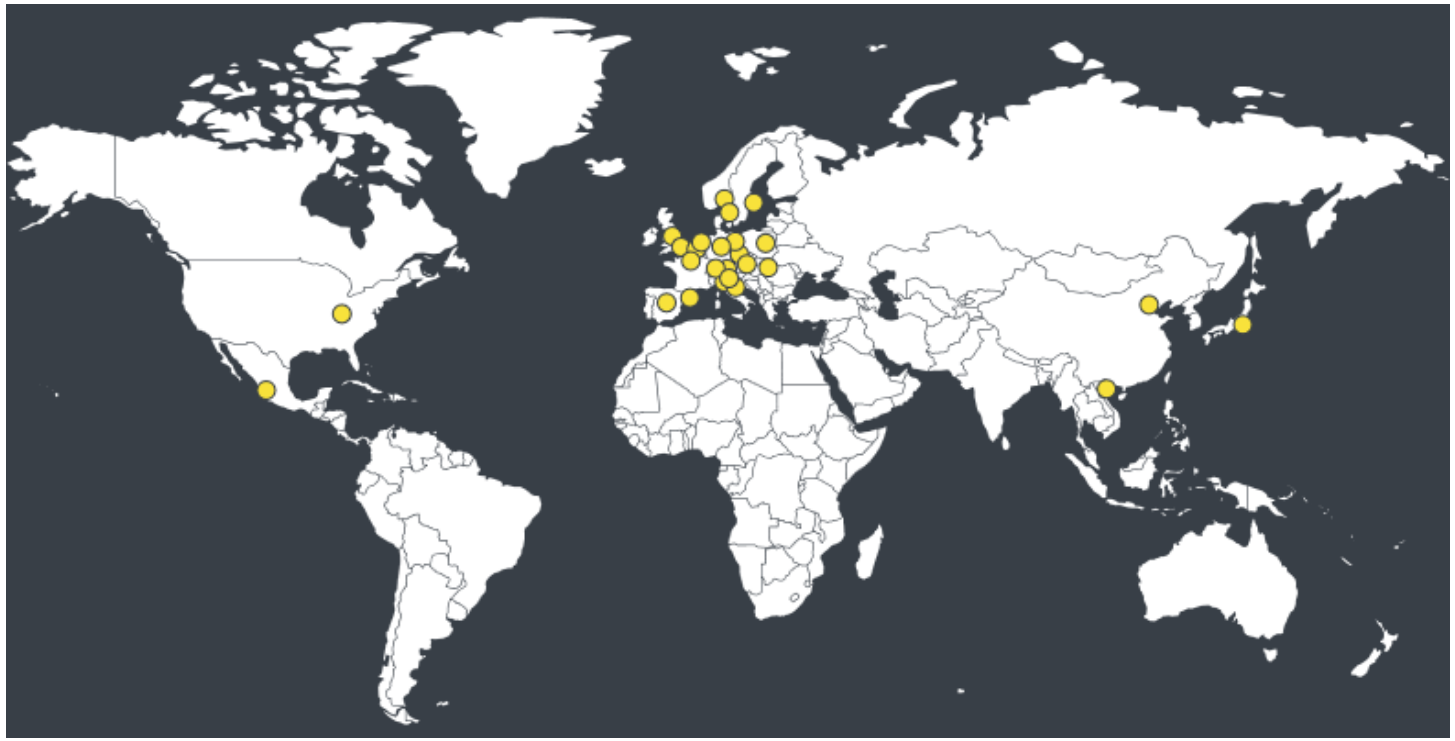
The Myositis Association

PRINTO

MyoNet (Euromyositis) Register

To be used in research and in clinical practice
We welcome new collaborators!



2024 more than **6 500** patients from 30 centers world wide
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Welcome to join the Euromyositis registry, find more information on **www.euromyositis.eu**
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