Maastricht UMC+

Harmonization of autoantibodies in idiopathic inflammatory myopathies

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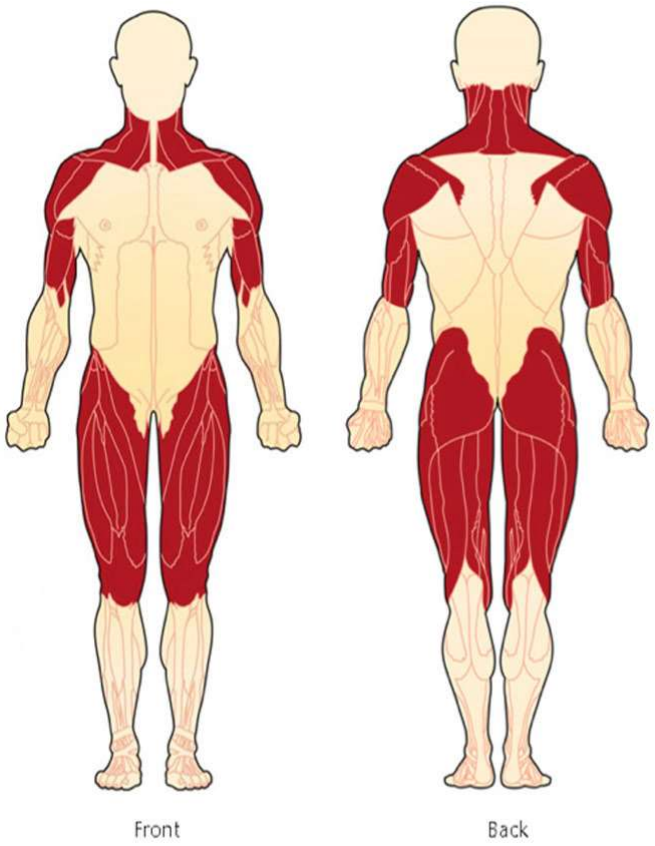
Disclosures

Consultancy:	ThermoFisher/Phadia, Werfen/Inova
Speakers fee:	Euroimmun, ThermoFisher/Phadia, Werfen/Inova, Menarini
Reagents:	ThermoFisher/Phadia, Werfen/Inova, Euroimmun
Scientific collaboration:	D-tek, Euroimmun, ThermoFisher/Phadia

Content

- Autoimmune serology in IIM
- Concept of harmonization
- 256th ENMC workshop
- Dutch EASI survey
- 274th ENMC workshop
- Ongoing initiatives

Idiopathic inflammatory myopathies

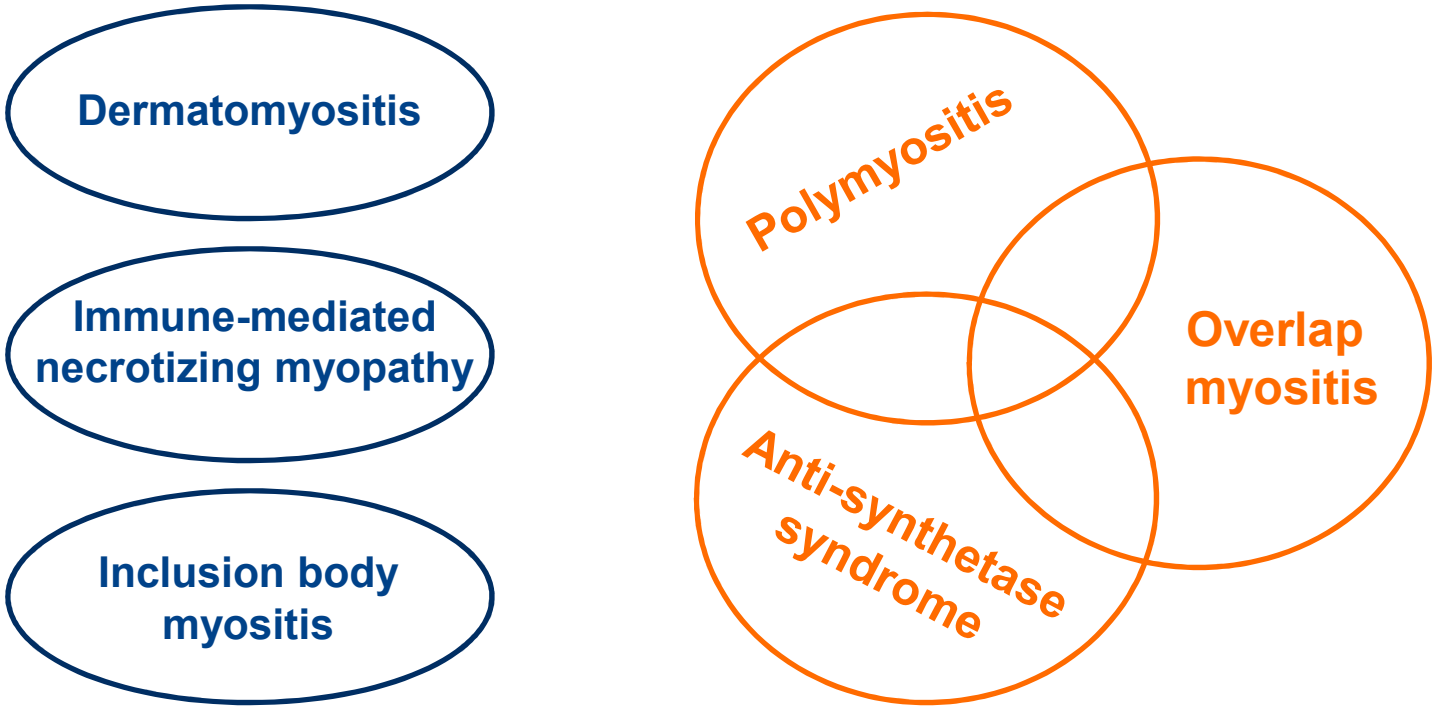


Besides (proximal) muscle weakness:

- Fever
- Arthritis
- Raynaud phenomenon
- Calcinosis
- Mechanic hands
- Heliotropic rash
- Gottron's papules
- Shawl sign rash
- Interstitial lung disease
- Myocarditis
- Dysphagia
- Malignancy

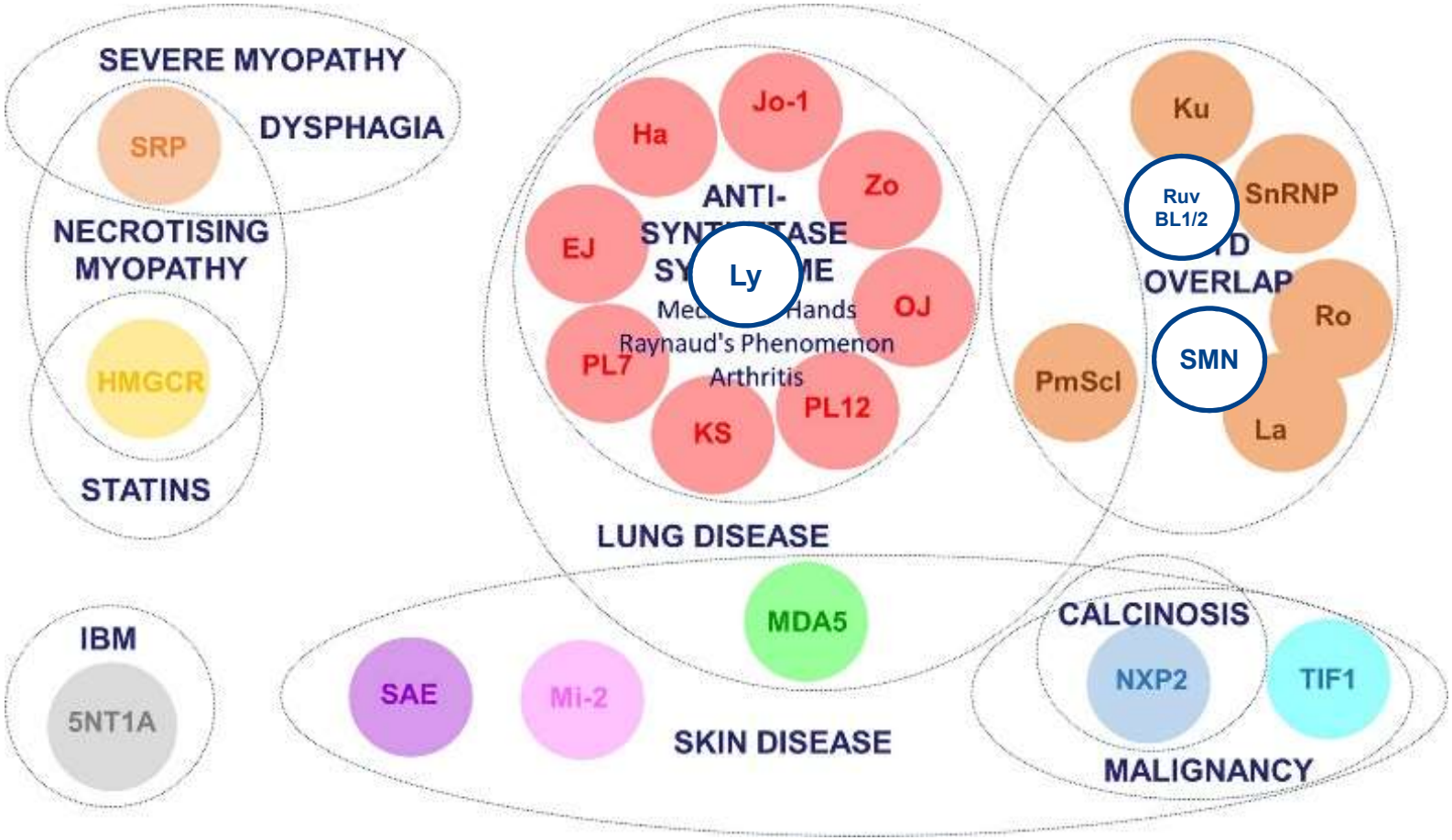
Lundberg et al, 2021
Nat Rev Dis Primers

Subtypes of IIM



Lundberg et al, 2021
Nat Rev Dis Primers

IIM-specific autoantibodies

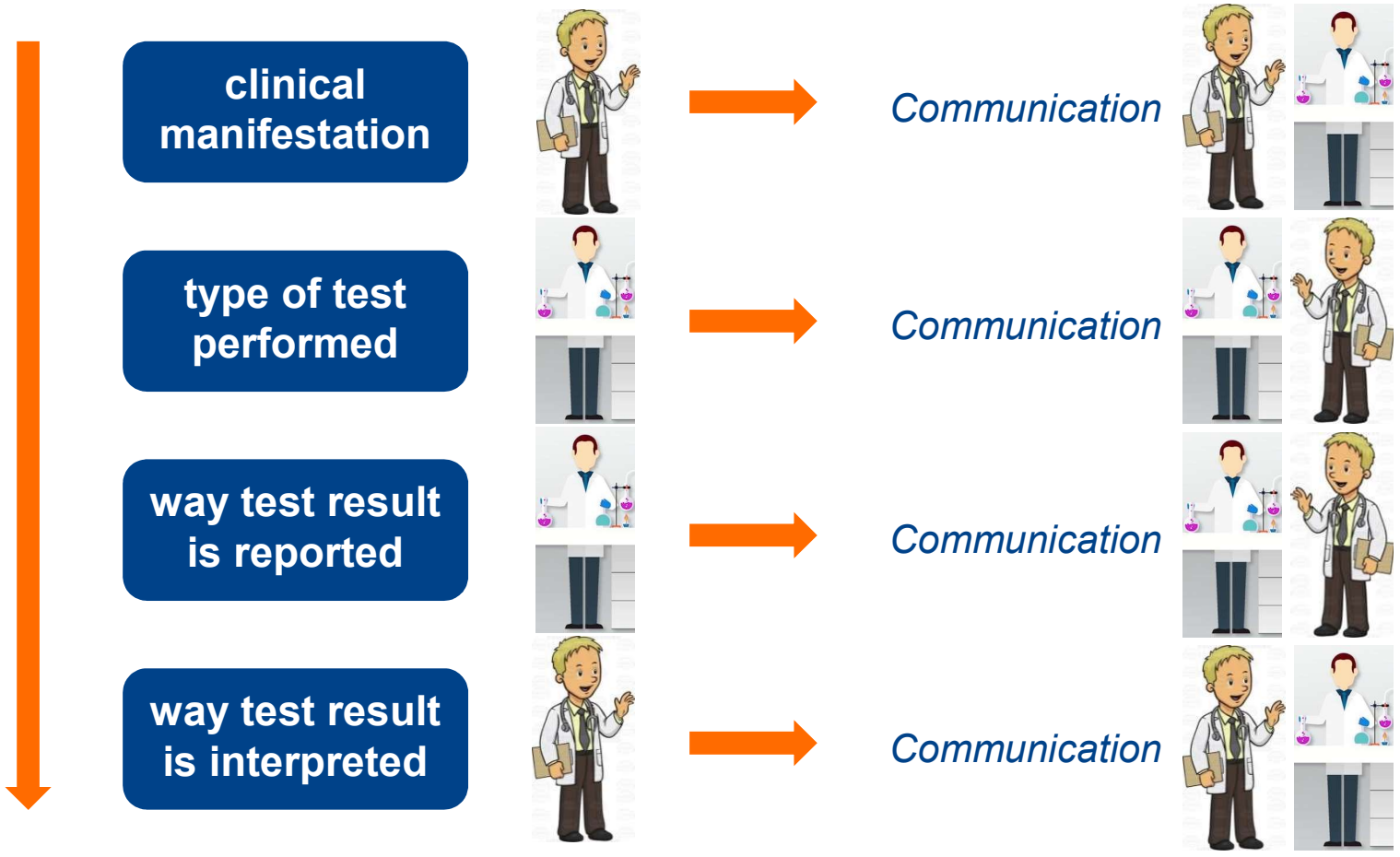


Betteridge et al
J Intern Med (2016)

Harmonisation

- Adjustment of differences and/or inconsistencies among different measurements, methods, and procedures to make them uniform or mutually compatible, typically achieved by agreement (recommendations and/or guidelines).

Four levels of harmonization



256th ENMC Workshop *(8-10 October 2021)*
Myositis-specific antibodies

EUROPEAN NEURO MUSCULAR CENTRE

- 20 participants from 10 countries (Belgium, China, Czech Republic, France, Germany, Netherlands, Spain, Sweden, UK, and USA)
- Clinicians from different disciplines, laboratory specialists, researchers and patient representatives
- Due to the Covid-19 pandemic it was a hybrid meeting with half of the participants gathered in Amsterdam and the other half was on-line
- Participants presented about their area of expertise and the shared information was used in the discussion to achieve consensus

Goals of the 256th ENMC Workshop

EUROPEAN NEURO MUSCULAR CENTRE

- Consensus regarding the clinical indications that ask for detection of myositis-specific autoantibodies (MSA)
- Consensus regarding the optimal testing strategy for patients suspected of IIM
- Consensus on the format for reporting results to the clinician in order to enable optimal interpretation
- Proposition of the research agenda to obtain reliable data on the test-characteristics of the immuno-assays for MSA

Clinical indications (1)

Myositis syndrome features that ask for detection of MSA:

- The triad of myositis, ILD, and arthritis, possibly accompanied by Raynaud's phenomenon, mechanic's hand, and fever.
- Characteristic skin rash, including Gottron's papules, shawl sign, and heliotrope rash, often in combination with symmetrical proximal muscle weakness.
- Severe proximal muscle weakness with a sub-acute onset and without clinical extra-muscular manifestations.
- Slowly progressive muscle weakness with an asymmetrical distribution involving both proximal and distal muscles, typically presenting after the age of 40 (only anti-cN1A*).

Damoiseaux et al 2022
Neuromuscular Disorders

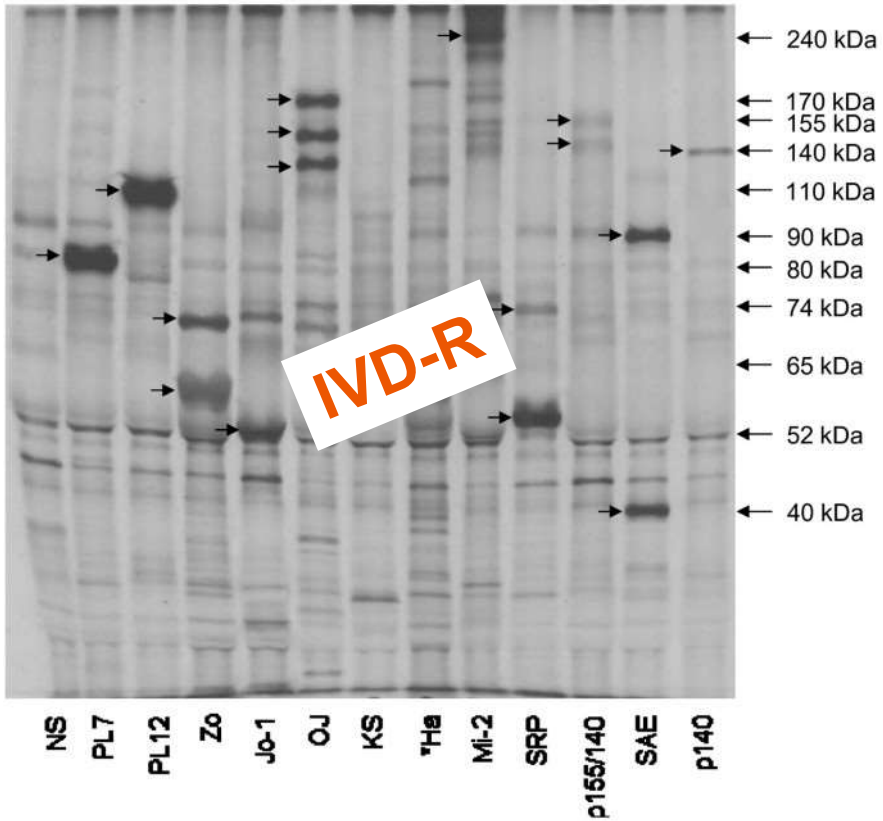
Clinical indications (2)

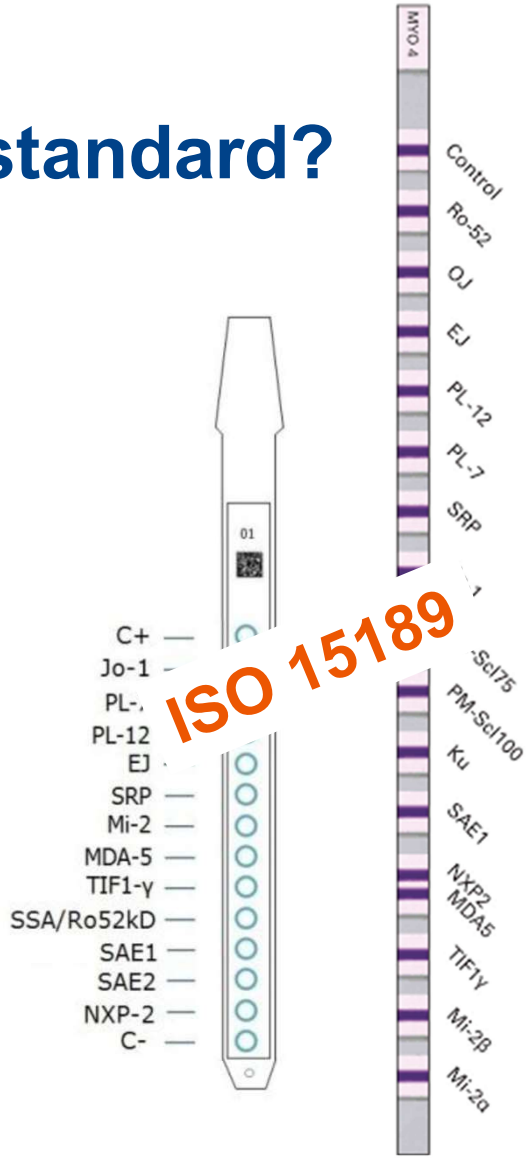
Myositis syndrome features for which detection of myositis specific autoantibodies should be considered after excluding other, more common, diagnoses:

- Isolated seronegative and non-erosive polyarthritis (anti-synthetases).
- ILD of unknown cause.
- Isolated high CK level on repeated samples.
- LGMD-like disease with no known molecular diagnosis nor familial history (anti-SRP and -HMGCR).

Damoiseaux et al 2022
Neuromuscular Disorders

Immunoprecipitation as gold-standard?



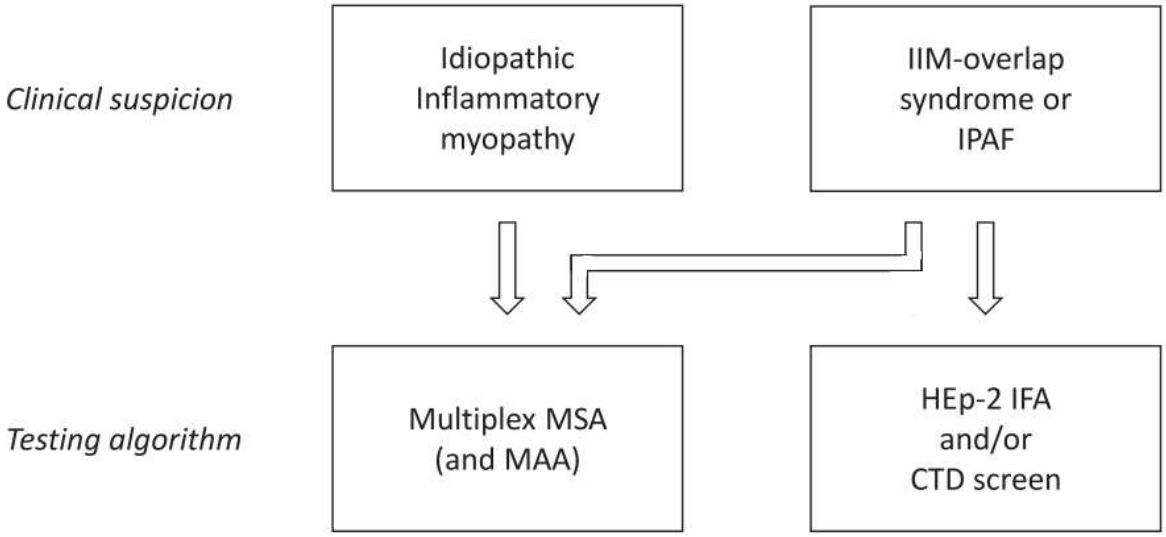


HEp-2 patterns for MSA

Idiopathic inflammatory myopathies		*Nuclear*	*Cytoplasmic*
Jo1[a]	Antisynthetase syndrome	None	Fine speckled can be missed
PL7, PL12, OJ, EJ, KS, Ha or Zo	Antisynthetase syndrome	None	(Dense) fine speckled can be missed
Mi2	Dermatomyositis	Fine speckled	None
MDA5	Dermatomyositis	None	Fine speckled in a subset of cells; can be missed
TIF1γ	Dermatomyositis	Fine speckled can be missed	None
NXP2	Dermatomyositis	Multiple nuclear dots can be missed	None
SAE	Dermatomyositis	Fine speckled	None
SRP	Necrotizing myositis	None	Fine speckled can be missed
HMGCR	Necrotizing myositis	None	Staining (fine speckled) in only a few cells can be missed

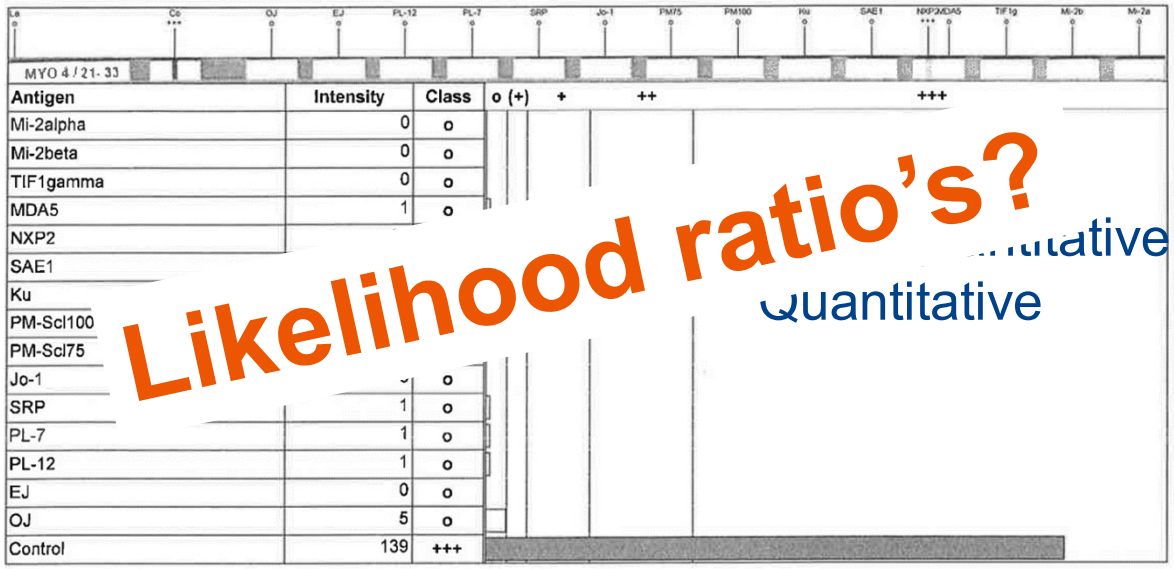
Bossuyt et al.
Nat Rev Rheumatol (2020)

Consensus on MSA-detection

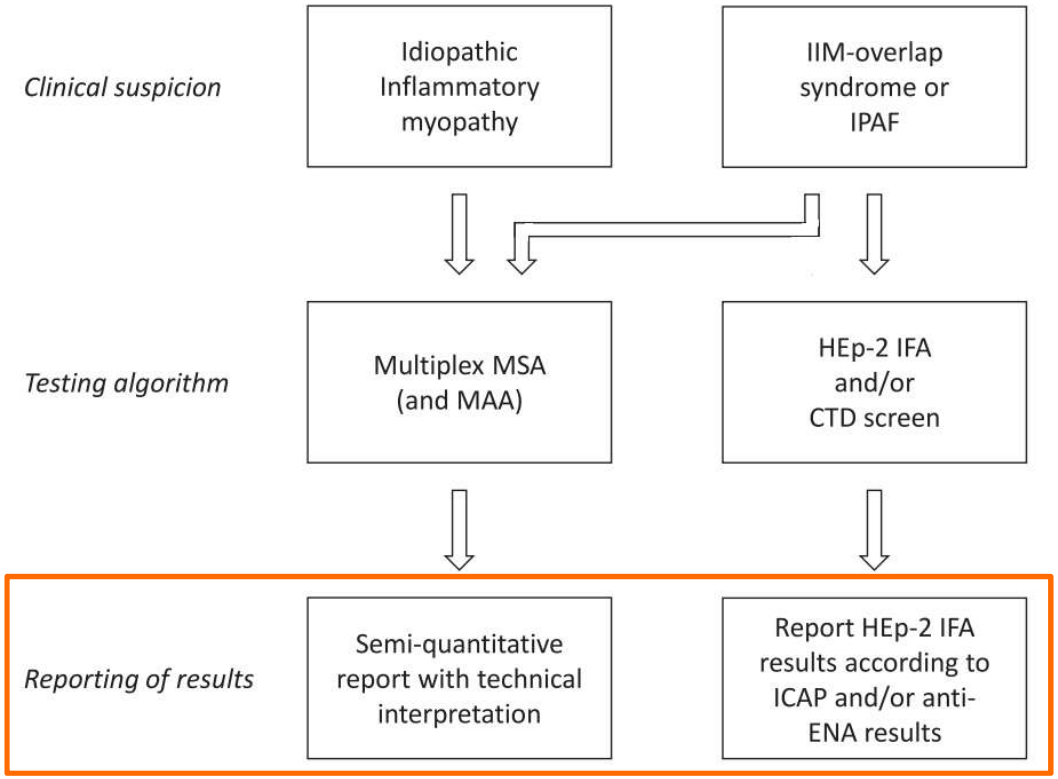


Damoiseaux et al 2022
Neuromuscular Disorders

Reporting of results



Consensus on MSA-reporting



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Damoiseaux et al 2022 Neuromuscular Disorders

Harmonization in the Netherlands

Myositis Netwerk Nederland

- Survey (23 questions)
- Distributed to 12 laboratories known to offer myositis serology
- Response by all 12 laboratories
- Formulation of 6 consensus statements (in line with ENMC consensus)
- Delphi-scoring of consensus statements (11 participants)
- Discussion round for fine-tuning

Damoiseaux et al 2023
NTvAKI 23:69-75

Dutch questionnaire (assay & analysis)

Myositis Netwerk Nederland

All laboratories use Euroimmun 16Ag (w/wo cN1A and HMGCR)

Which analyser is used:

4x No analyser → readout by scanner-software

5x EUROBlotOne → readout by photographic-software

1x EUROBlotMaster → readout by scanner-software

2x Other (AutoLIA & Dynablot Heat) → readout by scanner-software

Range result				
	Scanner	EUROBlotOne	Classification	Interpretation
	< 5	<7	-	Negative
	5 – 10	8 – 14	+/-	Negative
	11 – 25	15 – 35	+	Weak positive
	26 – 50	36 – 70	++	Positive
	>50	>70	+++	Strong positive

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NTvAKI 23:69-75

Dutch consensus (1)

Myositis Netwerk Nederland

Myositis serology should be restricted to 2nd and 3rd line health care (not general practionners)

Myositis serology should at least include Mi2, MDA5, TIF1γ, SAE, NXP2, SRP, Jo1, PL7, PL12, EJ, PM-Scl and Ku; simultaneous detection of anti-HMGCR is advised.

Positioning of Hep-2 analysis is in line with the ENMC recommendation

Damoiseaux et al 2023 NTvAKI 23:69-75

Dutch consensus (2)

Myositis Netwerk Nederland

Results of myositis serology should be reported semi-quantitative in the categories negative – weak positive/inconclusive – positive – strong positive preferentially according to the cut-off values provided by the manufacturer

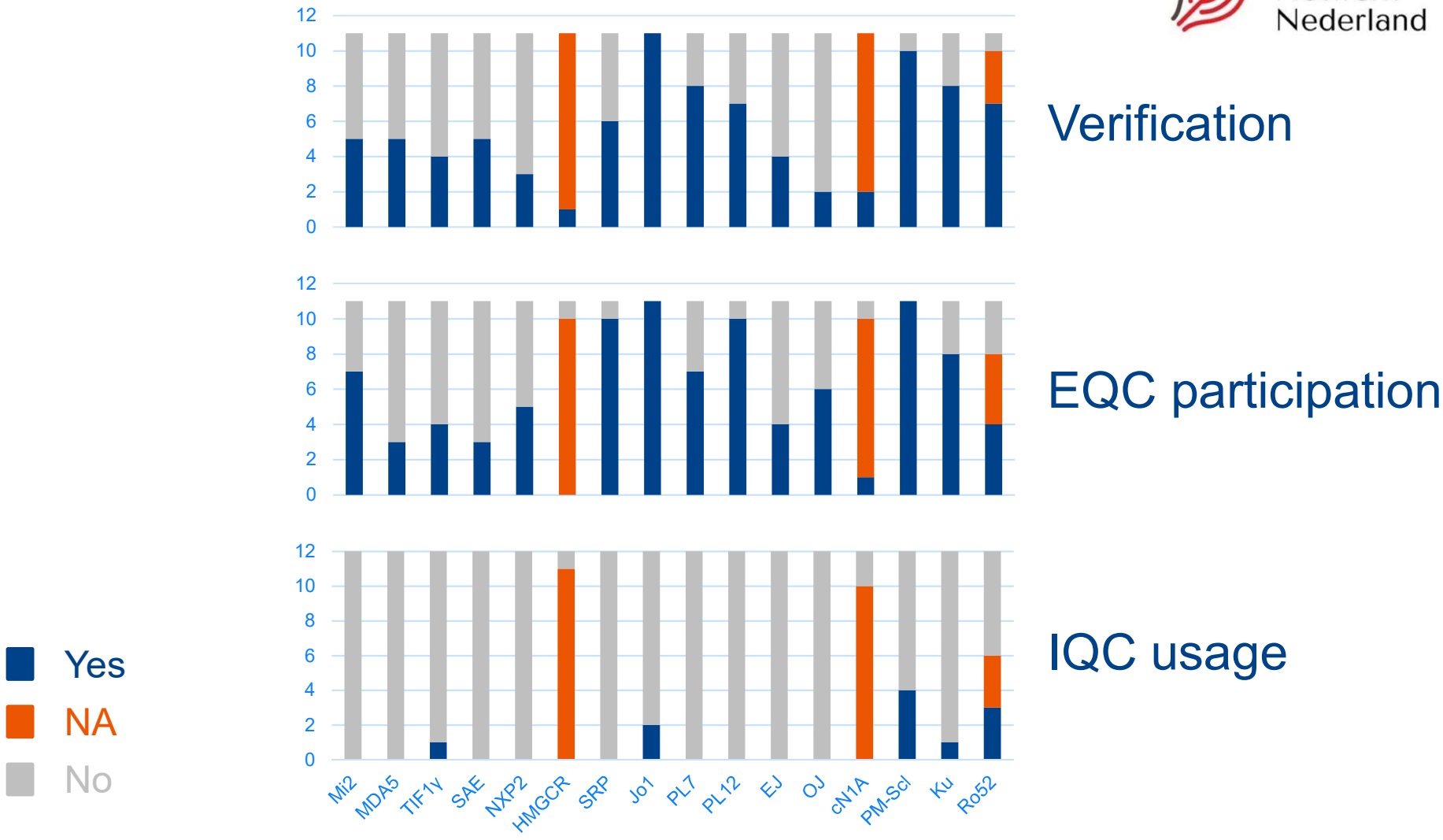
Results of MSA/MAA reactive with antigenic subunits (Mi2, PM-Scl, SAE, …) are to be reported separately. Interpretative comments are advised.

Multireactivity is to be reported as it is. Interpretative comments are advised.

Damoiseaux et al 2023
NTvAKI 23:69-75

Dutch questionnaire (ISO 15189)

Myositis Netwerk Nederland



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Damoiseaux et al 2023
NTvAKI 23:69-75

Cut-off discussions

- Low positive is ill-defined
- Low positive is poorly associated with IIM (Platteel et al, JTA 2019)
- Low positive does not exclude IIM (Loarce-Martos et al, Rheum Int 2023)
- Cut-offs may have to be individually adapted (Bories et al, Sem Arthr Rheum 2022)
- Taking into account intensity of control band (Chang et al, Rheum Int 2023)

274th ENMC: anti-synthetase syndrome

Definition of a high confidence positive antisynthetase antibody result
Any antisynthetase antibody positive result detected by immunoprecipitation
Antisynthetase antibody positive results obtained in screen ELISA
Positive results for anti-Jo1, anti-PL7, or anti-PL12 obtained by DIA/LIA if at least two times above the cut-off for positive as defined by the manufacturer
Positive results for antisynthetase antibodies obtained by DIA/LIA that do not fulfil the aforementioned criterion but are confirmed in an alternative assay

Definition of a medium confidence positive antisynthetase antibody result
Positive results for any other antisynthetase antibody obtained by DIA/LIA if at least two times the cut-off for positive as defined by the manufacturer
Caution in case of co-occurence of another myositis specific autoantibody (MSA) or myositis associated autoantibody (MAA) as determined by IP or DIA/LIA

Stenzel et al 2024
NMD In Preparation

Ongoing initiatives

- International EASI Survey on myositis serology (Carolien Bonroy and Marie-Agnès Durey)
- Harmonization antisynthetase antibody nomenclature (Anushka Aggarwal)
- *Implementation novel autoantibodies*
- *Implementation IP-MS technology*

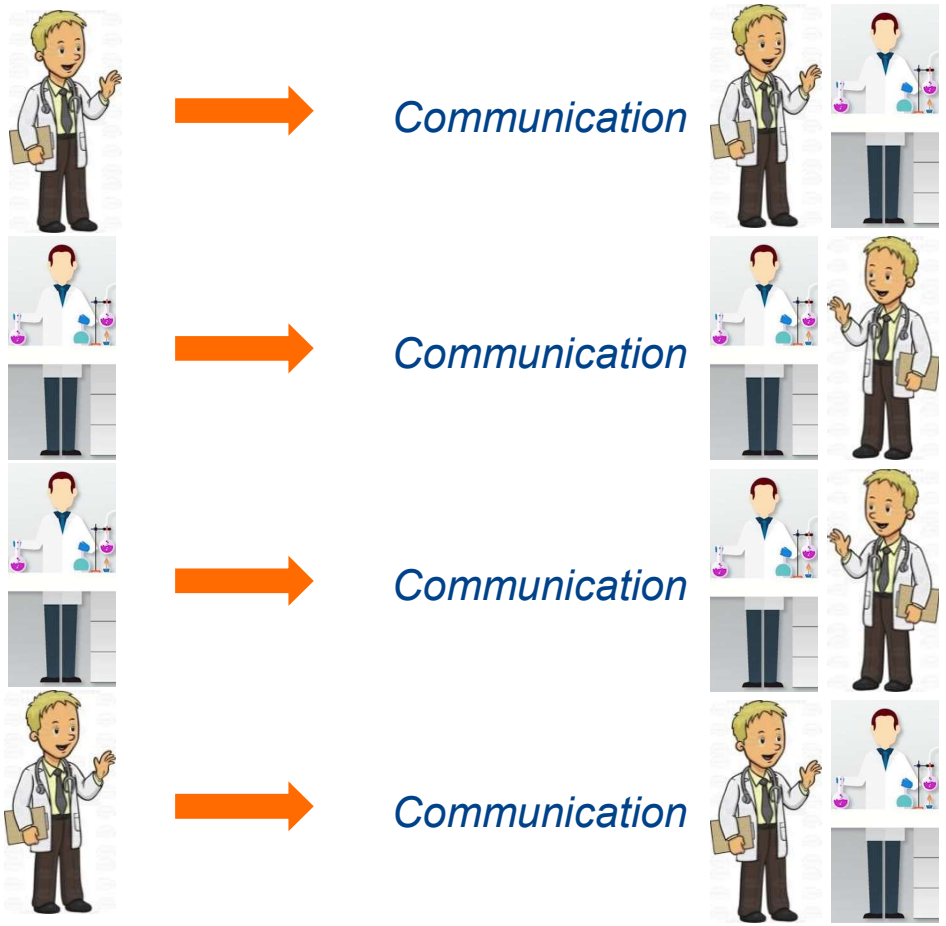
Conclusions

clinical manifestation

type of test performed

way test result is reported

way test result is interpreted



Thank you for your attent

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