# Development of New Classification Criteria for Idiopathic Inflammatory Myopathies

International Myositis Classification Criteria Project (IMCCP)
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# Disclosure

Nothing to disclose

# Aim

- Develop classification criteria for use by basic and clinical scientists that distinguish idiopathic inflammatory myopathies (IIMs) from other major mimicking conditions with high sensitivity and specificity; and

- Develop classification criteria for use by basic and clinical scientists that separate the major subgroups of the IIM from each other with high sensitivity and specificity.

- Test reliability of new classification criteria

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

# Process

- Identification and definition of potential criterion
- Data collection
- Analysis
- Validation
- Subgroup criteria

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# IMCCP Variables

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

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# Inclusion Criteria

**Idiopathic Inflammatory Myopathy**

i. The physician is certain of the diagnosis – only cases with known idiopathic inflammatory myopathy (IIM)
ii. The subject has been diagnosed for at least 6 months
iii. The subjects in whom most complete data are available
iv. The most recent subjects are chosen first – these would likely result in more consistent evaluations and therapy

**Comparator cases**

- Dystrophies
- Drug/toxin associated myopathies
- Metabolic myopathies
- Mitochondrial myopathies
- Endocrine myopathies
- Systemic inflammatory diseases
- Dermatologic conditions
- Infectious myopathies
- Motor neuron diseases
- Systemic vasculitis
- Neuromuscular diseases
- Immune-mediated skin conditions

# 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 | 0.75 |
| Immune-mediated necrotizing myopathy | 11 | 0.69 |
| Juvenile polymyositis | 5 | 0.31 |
| Non-inflammatory myopathy | 624 | 39.0 |

**Participating clinics** (n=47)

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

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# Analysis

- Crude pair-wise associations among all variables measured and between each variable and clinician's diagnosis
- Assessment of number of observations per variable
- Three approaches for derivation of classification criteria were explored:

1. **Traditional**: case defined by specified number of items from a set
2. **Probability model**: patient assigned a probability score by summing score-points associated with the variables
3. **Classification tree**: case defined by a decision tree

# Variables in the new Classification Criteria

| "When no better explanation for the symptoms exists this classification criteria can be used" | | |
|---|---|---|
| **ITEM** | **Score** | |
| | **Without muscle biopsy data** | **With muscle biopsy data** |
| 18 ≤ Age of onset of first symptom assumed to be related to the disease < 40 | 1.3 | 1.5 |
| Age of onset of first symptom assumed to be related to the disease ≥ 40 | 2.1 | 2.2 |
| **Muscle weakness** | | |
| Objective symmetric weakness, usually progressive, of the proximal muscles of upper extremities | 0.7 | 0.7 |
| Objective symmetric weakness, usually progressive, of the proximal muscles of 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 manifestations** | | |
| Heliotrope rash | 3.1 | 3.2 |
| Gottron´s papules | 2.1 | 2.7 |
| Gottron's sign | 3.3 | 3.7 |
| **Other clinical manifestations** | | |
| Dysphagia or esophageal dysmotility | 0.7 | 0.6 |

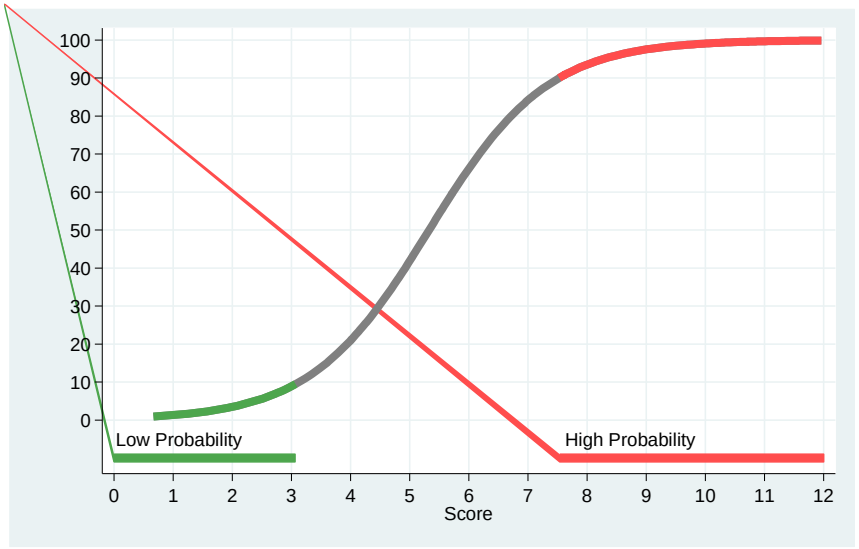
# New Classification Criteria

| ITEM | Score | |
|---|---|---|
| | Without muscle biopsy data | With muscle biopsy data |
| **Laboratory measurements** | | |
| Anti-Jo-1 antibody positivity | 3.9 | 3.8 |
| Serum creatine kinase activity (CK) activity or<br>Serum lactate dehydrogenase (LDH) activity or<br>Serum aspartate aminotransferase (ASAT/AST/SGOT) activity or<br>Serum alanine aminotransferase (ALAT/ALT/SGPT) activity | 1.3 | 1.4 |
| **Muscle biopsy features** | | |
| 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 |

# Score vs Probability

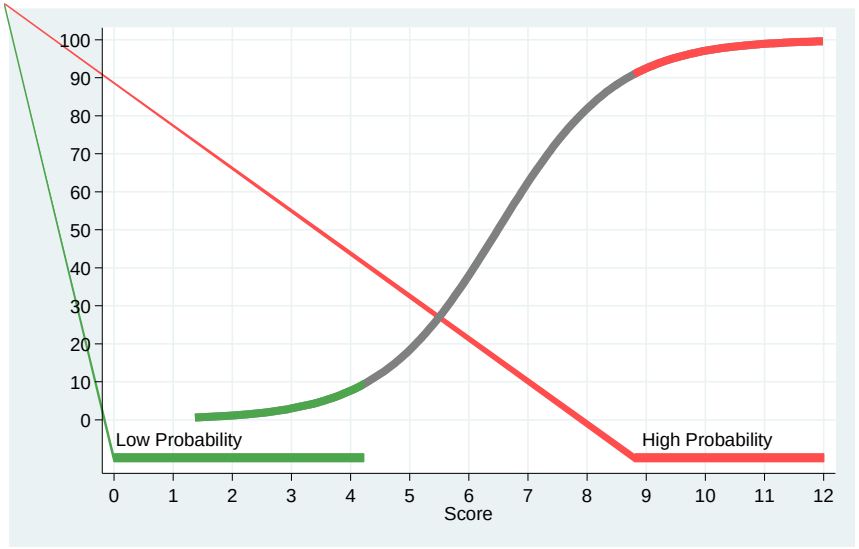
**Without muscle biopsies**

Best balance sensitivity/specificity:
55-60% probability




**With muscle biopsies**

Best balance sensitivity/specificity:
55-75% probability



# Performance

| PERFORMANCE OF NEW AND EXISITING CLASSIFICATION / DIAGNOSTIC CRITERIA FOR IIM | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Performance (%)** | **New classification criteria[a]** | | **Bohan & Peter[b]** | **Tanimoto *et al*.** | **Targoff *et al*.[b]** | **Dalakas & Hohlfeld[b]** | **Hoogendijk *et al*.[b]** |
| | Without muscle biopsy data | With muscle biopsy data | | | | | |
| Sensitivity | 86 | 90 | 98 | 96 | 93 | 6 | 52 |
| Specificity | 84 | 90 | 55 | 31 | 89 | 99 | 97 |
| Correctly classified | 85 | 90 | 86 | 79 | 91 | 45 | 70 |

[a] Cut point for probability: 55%

[b] Definite and probable polymyositis and dermatomyositis

# Performance

| Current subgroups (%) | New classification criteria | | Bohan & Peter | Tanimoto *et al*. | Targoff *et al*. | Dalakas & Hohlfeld | Hoogendijk *et al*. |
|---|---|---|---|---|---|---|---|
| | Without muscle biopsy data | With muscle biopsy data | | | | | |
| **Amyopathic DM** | 100 | 100 | 25 | 14 | 0 | 0 | 0 |
| **DM** | 99 | 100 | 100 | 96 | 99 | 7 | 83 |
| **Hypomyopathic DM** | 100 | 100 | 80 | 40 | 67 | 0 | 20 |
| **IMNM** | 100 | 100 | 100 | 100 | 100 | 0 | 10 |
| **IBM** | 68 | 94 | 97 | 97 | 91 | 1 | 1 |
| **JDM** | 98 | 96 | 100 | 96 | 98 | 5 | 86 |
| **PM** | 83 | 90 | 95 | 100 | 85 | 11 | 9 |
| **Non IIM** | 9 | 11 | 45 | 69 | 11 | 1 | 3 |

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# Validation

- **Internal validation**

  - Bootstrap methods

- **External validation**

  1. Euromyositis register (592 IIM cases)

  - No misclassification

  - Without muscle biopsy data: 83% classified, 17% not classified

  - With muscle biopsy data: 35% classified, 65% not classified

  2. Juvenile dermatomyositis cohort biomarker study and repository (UK and Ireland) (332 juvenile IIM cases)

  - No misclassification

  - No muscle biopsy data in register

  - 92% classified, 8% not classified

*IIM: min probability ≥ 50%; not IIM: max probability > 50%*

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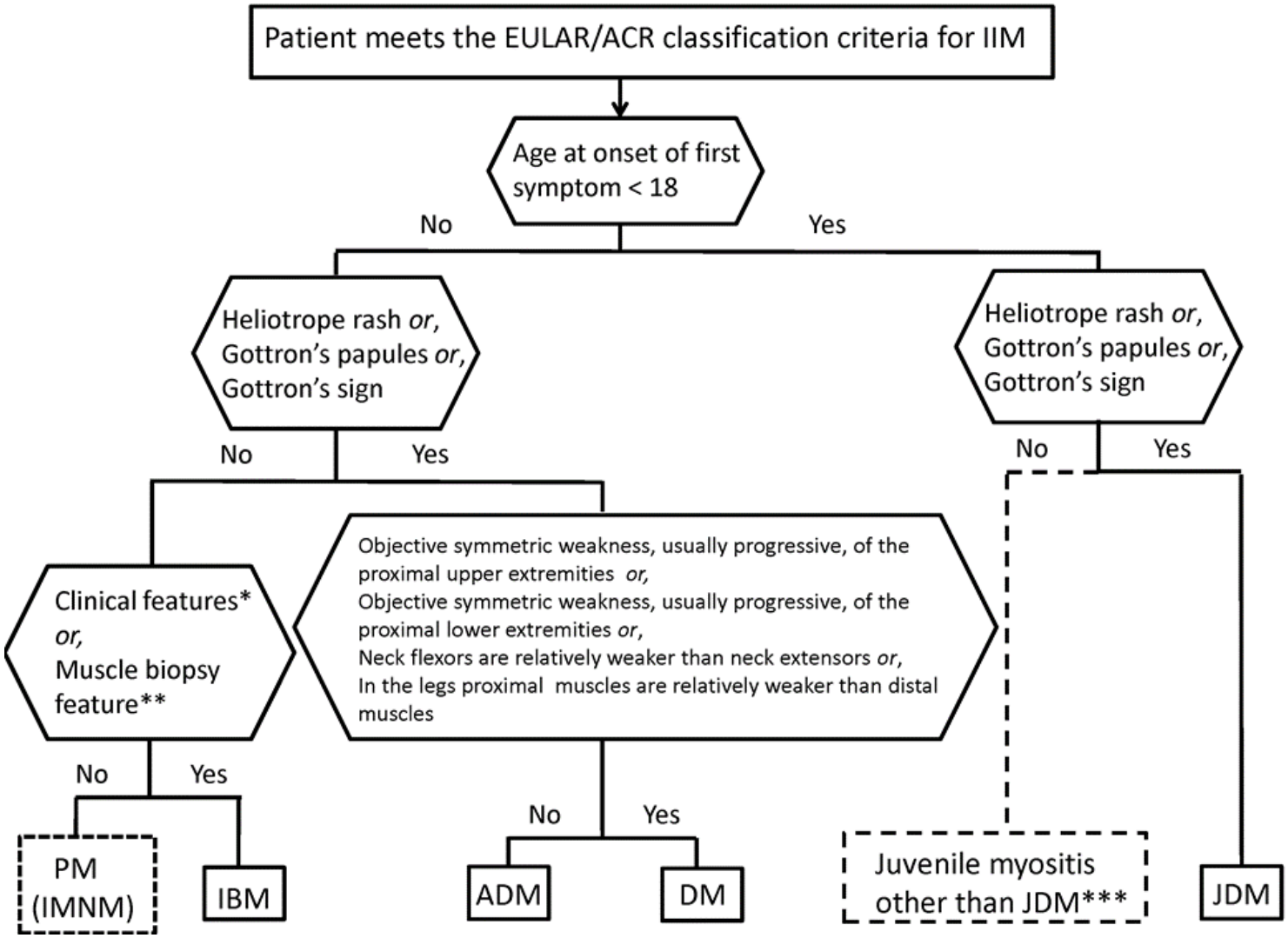
# IIM Sub-classification Criteria Tree




*finger flexor weakness and response to treatment: not improved, or

**muscle biopsy: rimmed vacuoles, is required for classification.

***Juvenile myositis other than JDM was developed based on expert opinion.

# Subgroup classification criteria

- New subgroups of IIM based on subgroup classification criteria

| **Current subgroups** | **New subgroups*** | | | | | | |
|---|---|---|---|---|---|---|---|
| | JDM | JM | DM | ADM | IBM | PM | **Total** |
| JDM | 233 | 0 | 0 | 0 | 0 | 0 | 233 |
| JM | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| DM | 0 | 0 | 190 | 5 | 0 | 8 | 203 |
| ADM | 1 | 0 | 1 | 29 | 0 | 0 | 31 |
| IBM | 0 | 1 | 0 | 0 | 59 | 5 | 65 |
| PM | 0 | 0 | 7 | 0 | 1 | 98 | 106 |
| **Total** | 234 | 1 | 198 | 34 | 60 | 111 | 638 |

**Initial classification as IIM using the new classification criteria with min probability >60% as cutoff for classification as IIM, and max probability <40% for classification as not IIM*

# 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<br>Serum lactate dehydrogenase (LDH) activity or<br>Serum aspartate aminotransferase (ASAT/AST/SGOT) activity or<br>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 | ☐ | ☐ |

# Acknowledgements

## To all participants in the IMCCP - working groups

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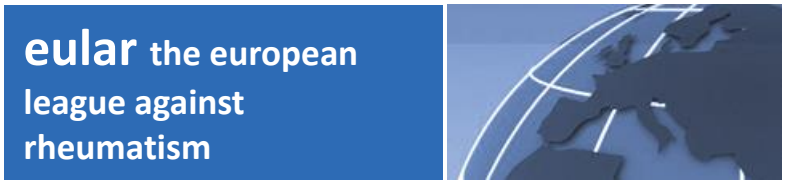


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The Myositis Association


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