



The new classification criteria for MAS in systemic JIA

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Why classification (diagnostic) criteria for MAS are important?

- MAS is a serious, life-threatening complication
- Early recognition and treatment are critical

- **However, early diagnosis can be difficult**

- **<u>Differential diagnoses</u>**: disease flares, infections, medication side effects

Is MAS underdiagnosed?

- Retrospective review of 15 patients with syst JIA who underwent BM aspiration within initial diagnostic workup
- Eight of 15 (53%) patients had BM aspirate suggestive of MAS
- Two patients were diagnosed clinically with MAS
- Three patients had frank hemophagocytosis, only 1 of whom was diagnosed with MAS clinically
- **Suggestion**: MAS may be an integral part of the spectrum of syst JIA, ranging from its most severe, life-threatening form to its mild, occult form manifest only by biochemical abnormalities and BM hemophagocytosis

Berhens EM et al. J Rheumatol 2007;34:1133-8

Aims of classification criteria

- To help standardize classification of the syndrome for research purposes and use in publication
- To assist in the evaluation of different therapeutic approaches
- To foster interaction between specialists in different fields
- To facilitate early diagnosis

Preliminary diagnostic guidelines for MAS complicating systemic JIA

Laboratory criteria

- Decreased PLT (≤ 262 x $10^{9)}$
- Elevated GOT/AST (> 59 mU/L)
- Hypofibrinogenemia (≤ 2.5 g/L)
- Decreased WBC (≤ 4.0 x 10^9/L)

Clinical criteria

- Hemorrhages (purpura, easy bruising, mucosal bleeding)
- CNS dysfunction (irritability, disorientation, lethargy, headache, seizures, coma)
- Hepatomegaly (≥ 3 cm below the costal arch)

Histopathologic criterion

Hemophagocytosis in the bone marrow

Diagnostic rule: the diagnosis of MAS requires the presence of any 2 of the 4 laboratory criteria. A BM aspirate for the demonstration of macrophage hemophagocytosis may be required only in doubtful cases

Ravelli A et al. J Pediatr 2005;146:598-604

Limitations of preliminary diagnostic guidelines

- Retrospective/literature data for most patients
- Lack of several laboratory measurements in a number of patients
- Insufficient data for some laboratory parameters
- Lack of validation

HLH-2004 diagnostic guidelines

1. Fever
2. Splenomegaly
3. Cytopenia (at least 2 of the 3):
   - HB < 90 g/l
   - PLT <100 x 10 9 /l
   - Neutrophils <1,0 x 10 9 /l
4. Hypertriglyceridmia and/or hypofibrinogenemia:
   - TG ≥ 265 mg/dl
   - Fibrinogen ≤ 1.5 g/l
5. Hemophagocytosis in BM, spleen or LN (no evidence of malignancy)
6. Low or absent NK cell activity
7. Ferritin ≥ 500 ng/ml
8. Soluble CD 25 ≥ 2 400 U/ml

Diagnostic rule: HLH is diagnosed when at least 5 criteria are met

Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al.
HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis.
Pediatr Blood Cancer 2007;48:124-31

Sensitivity, specificity and k value of HLH-2004 guidelines and preliminary MAS guidelines

Diagnostic guidelines	Sensitivity	Specificity	Kappa
HLH-2004 guidelines (4/5 criteria)	35	100	0.36
HLH-2004 guidelines (3/5 criteria)	79	75	0.53
Prel. MAS guidelines	86	86	0.71
Prel. MAS guidelines + ferritin ≥ 500 μg/ml	86	50	0.41
Prel. MAS guidelines + ferritin ≥ 1,000 μg/ml	84	63	0.48
Prel. MAS guidelines + ferritin ≥ 2,000 μg/ml	69	78	0.46

Davì S et al. A&R 2014

Aims of the project

1. To develop new classification criteria for MAS complicating systemic JIA

2. To identify the laboratory tests whose change over time is most valuable for the timely diagnosis of MAS in the clinical setting

Flow chart of the project



Flow chart of the project



An International Consensus Survey of Diagnostic Criteria for Macrophage Activation Syndrome in Systemic Juvenile Idiopathic Arthritis

SERGIO DAVÌ, ALESSANDRO CONSOLARO, DINARA GUSEINOVA, ANGELA PISTORIO, NICOLINO RUPERTO, ALBERTO MARTINI, RANDY Q. CRON, and ANGELO RAVELLI

ABSTRACT. ***Objective.*** To identify candidate diagnostic criteria for macrophage activation syndrome (MAS) complicating systemic juvenile idiopathic arthritis (sJIA) using international consensus formation through a Delphi questionnaire survey.

Methods. A questionnaire listing 28 clinical, laboratory, and histopathologic features of MAS elicited by literature review was sent to 505 pediatric rheumatologists worldwide. Respondents were asked to select the 10 features that they felt were most important and useful in the diagnosis of MAS, and to order the 10 selected features by assigning the number 10 to the most important, and ending with 1 as the least important.

Results. The response rate was 46% (232 physicians from 47 countries). The items selected by more than 50% of respondents were, in order of frequency, falling platelet count, hyperferritinemia, evidence of macrophage hemophagocytosis in the bone marrow, increased liver enzymes, falling leukocyte count, persistent continuous fever ≥ 38°C, falling erythrocyte sedimentation rate, hypofibrinogenemia, and hypertriglyceridemia.

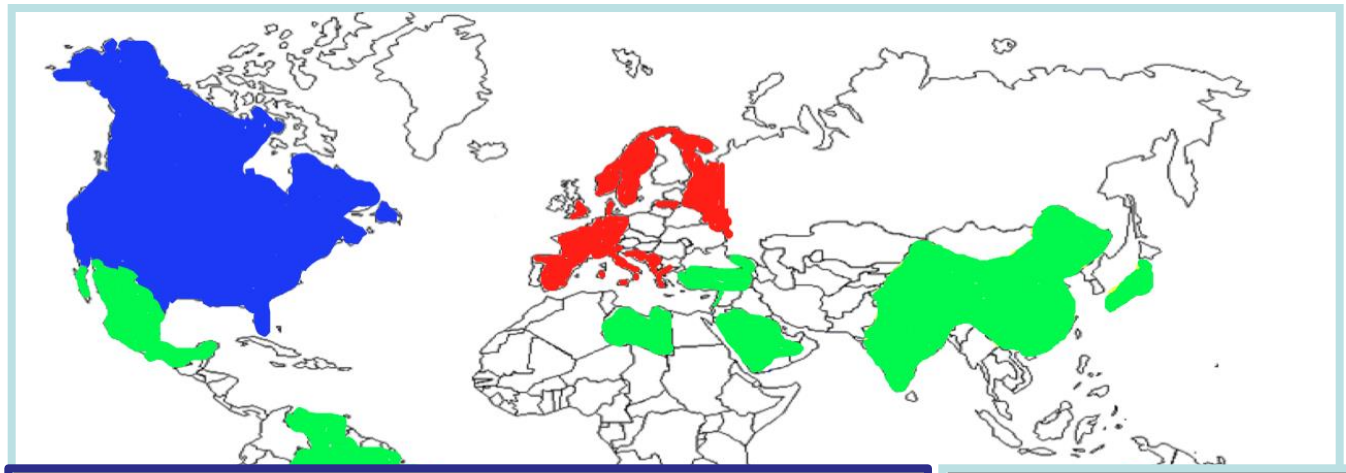
Conclusion. Our process led to identification of features that were felt to be most important as candidate diagnostic criteria for MAS by a large sample of international pediatric rheumatologists.
(First Release Feb 1 2011; J Rheumatol 2011;38:764–8; doi:10.3899/jrheum.100996)

J Rheumatol 2011;38:764-8

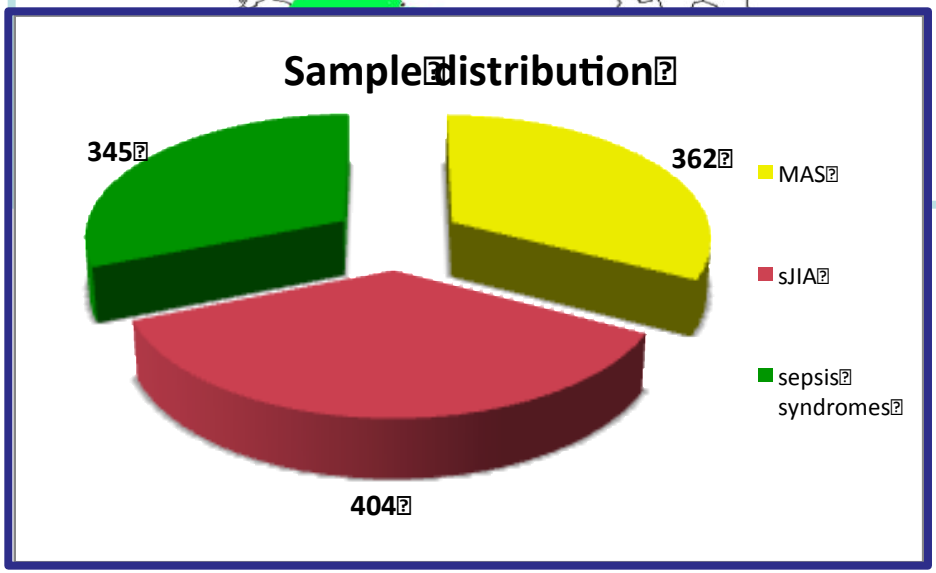
Flow chart of the project

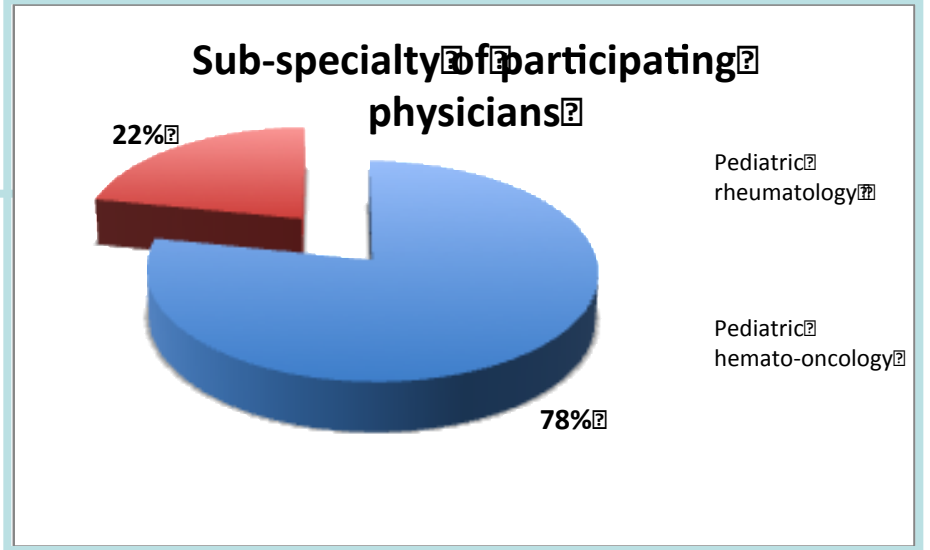


Data collection phase



- Retrospective cohort of **1111 patients**
- **95** investigators from **33** countries
- Web-based

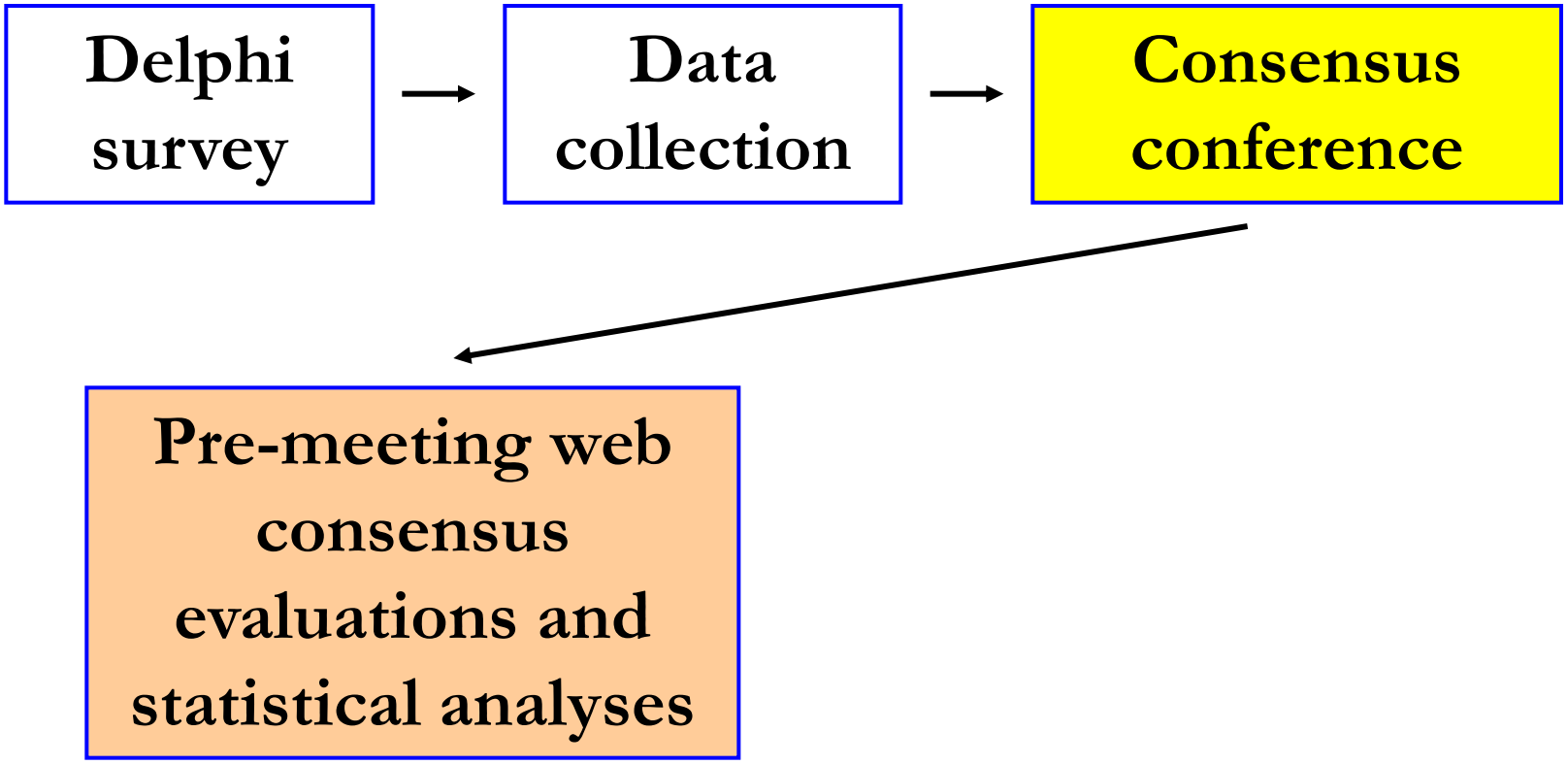




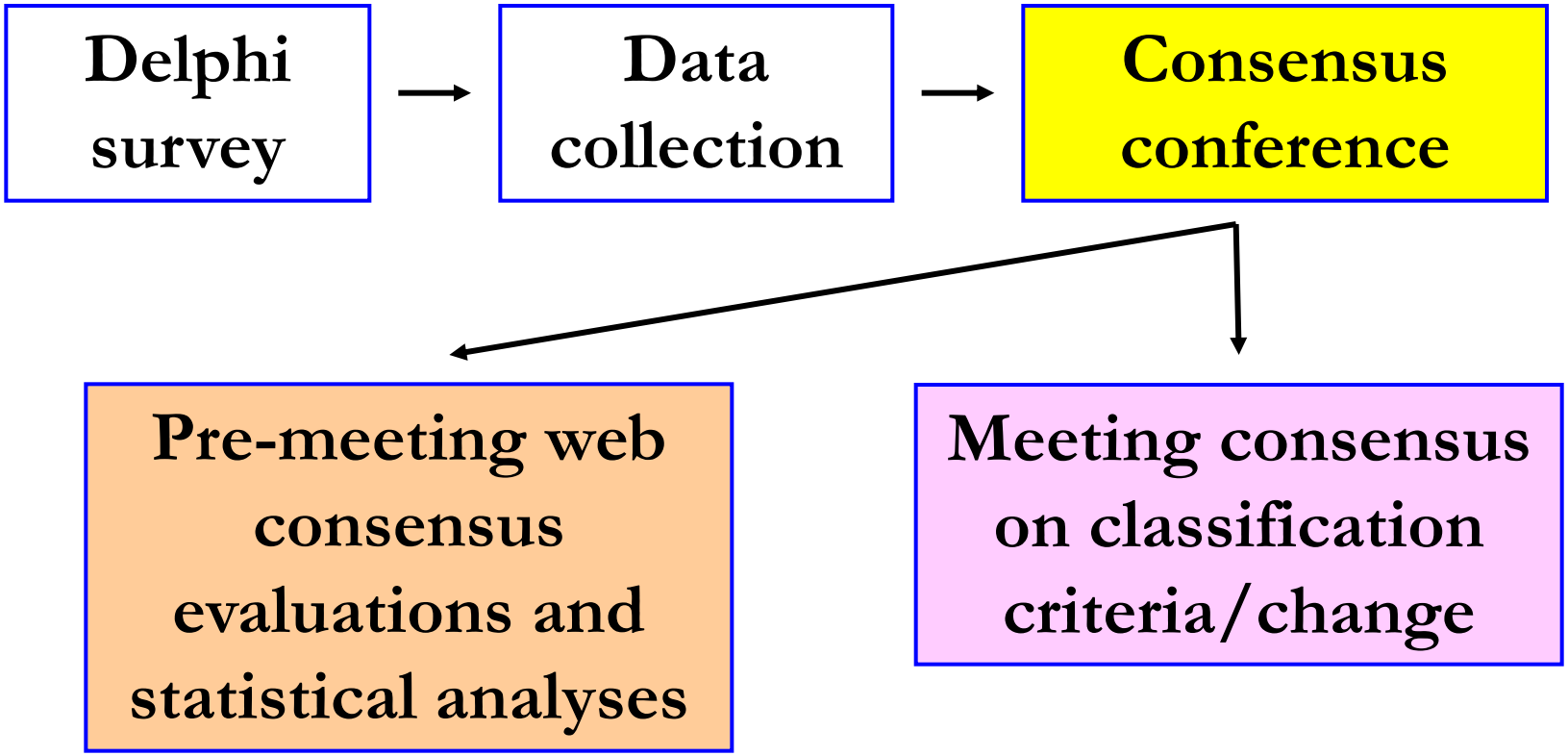
Flow chart of the project



Flow chart of the project



Flow chart of the project



Web-consensus expert panel (n = 27)

- 19 pediatric rheumatologists
- 8 pediatric hemato-oncologists

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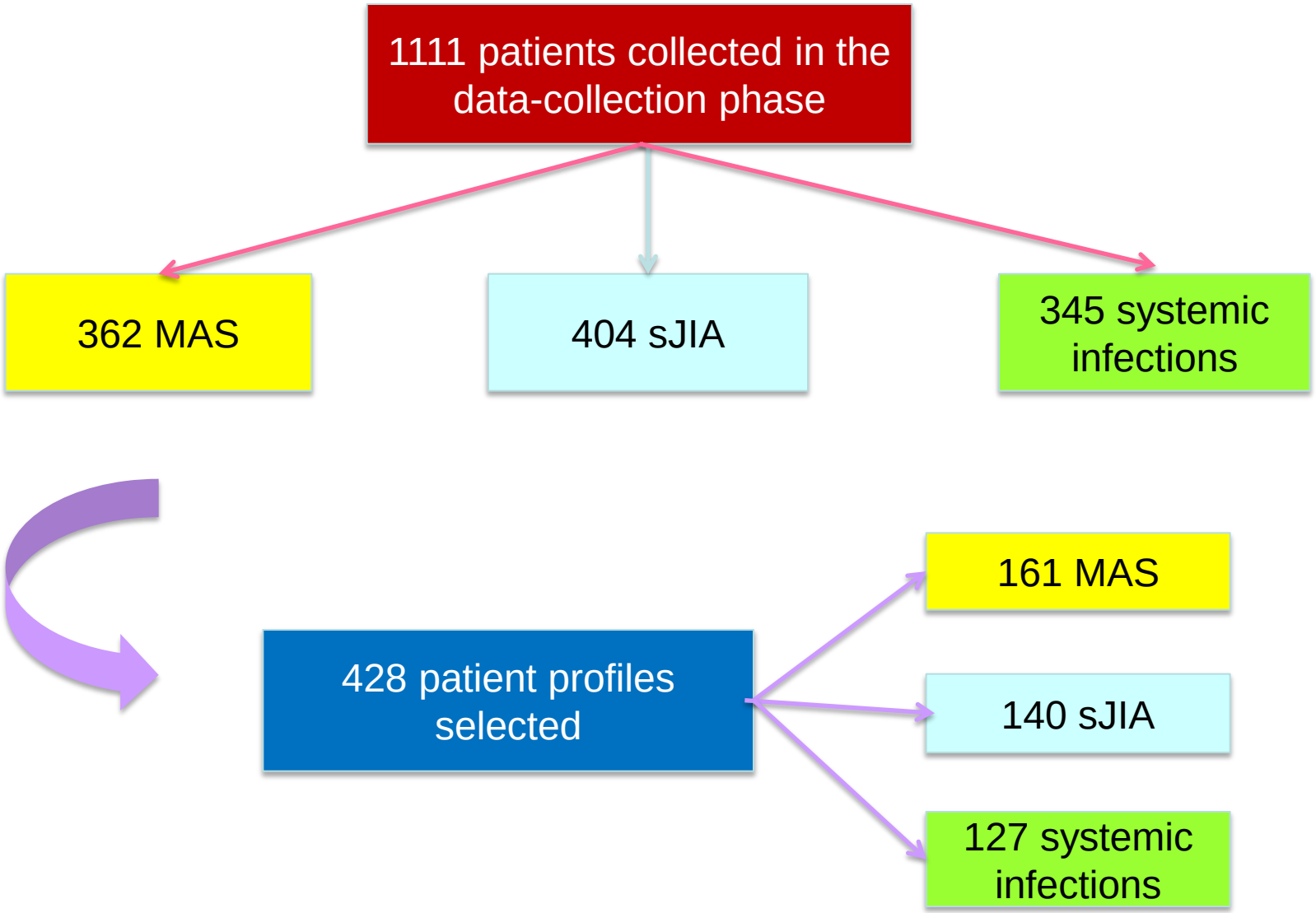
Goals of pre-meeting web-consensus evaluations

1. To classify «real patients» by consensus among experts (≥ 22/27; 80%) as:
   - Positive for MAS
   - Negative for MAS
   - Not classified (consensus <80%)

based on:

Clinical and laboratory data at disease onset

Patient sample



Scoring patient profiles…













Example of a patient profile

Clinical features AT ONSET	yes	no
Fever		
Lymphoadenopathy		
Hepatomegaly		
Splenomegaly		
Hemorrhagic manifestations		
CNS involvement		
Arthritis		
Jaundice		
Heart involvement		
Lung involvement		
Kidney involvement		

Example of a patient profile

Clinical features AT ONSET	yes	no
Fever	X	
Lymphoadenopathy	X	
Hepatomegaly	X	
Splenomegaly		X
Hemorrhagic manifestations		X
CNS involvement		X
Arthritis	X	
Jaundice		X
Heart involvement		X
Lung involvement		X
Kidney involvement		X

Example of a patient profile

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CNS involvement		X
Arthritis	X	
Jaundice		X
Heart involvement		X
Lung involvement		X
Kidney involvement		X

Laboratory features AT ONSET	Normal range	MAS onset
Hb, g/l		
WBC, $x10^9$/l		
Neutrophils, $x10^9$/l		
PLT, $x10^9$/l		
ESR, mm/h		
CRP, mg/dl		
AST, U/l		
Triglycerides, mg/dl		
LDH, U/l		
Fibrinogen, mg/dl		
Ferritin, ng/ml		
D-dimer, mg/dl		

Example of a patient profile

Clinical features AT ONSET	yes	no
Fever	X	
Lymphoadenopathy	X	
Hepatomegaly	X	
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CNS involvement		X
Arthritis	X	
Jaundice		X
Heart involvement		X
Lung involvement		X
Kidney involvement		X

Laboratory features AT ONSET	normal range	MAS onset
Hb, g/l	12.5 – 14.8	9.4
WBC, $x10^9$/l	4.5 – 13.5	2.9
Neutrophils, $x10^9$/l	1.8 – 10.0	1.0
PLT, $x10^9$/l	150 – 400	177
ESR, mm/h	0 – 20	57
CRP, mg/dl	< 0.46	4
AST, U/l	0 – 35	283
Triglycerides, mg/dl	30 – 160	523
LDH, U/l		
Fibrinogen, mg/dl	170 – 400	122
Ferritin, ng/ml	20 -200	10,043
D-dimer, mg/dl		

Example of a patient profile

Clinical features AT ONSET	yes	no
Fever	X	
Lymphoadenopathy	X	
Hepatomegaly	X	
Splenomegaly		X
Hemorrhagic manifestations		X
CNS involvement		X
Arthritis	X	
Jaundice		X
Heart involvement		X
Lung involvement		X
Kidney involvement		X

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D-dimer, mg/dl		

Does this patient have MAS ? **YES** □

NO □

Example of a patient profile

Clinical features AT ONSET	yes	no
Fever	X	
Lymphoadenopathy	X	
Hepatomegaly	X	
Splenomegaly		X
Hemorrhagic manifestations		X
CNS involvement		X
Arthritis	X	
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Heart involvement		X
Lung involvement		X
Kidney involvement		X

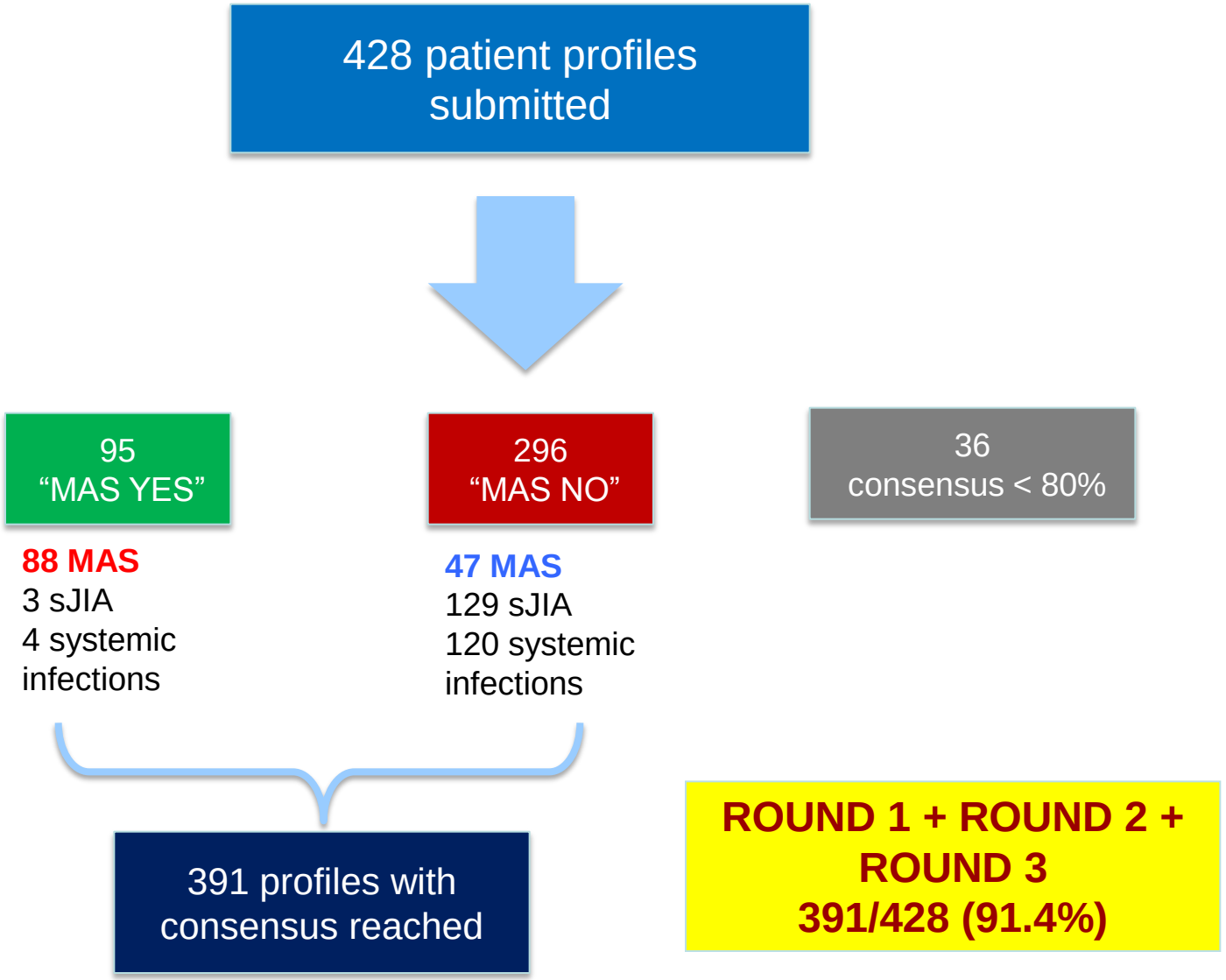
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Ferritin, ng/ml	20 -200	10,043
D-dimer, mg/dl		

Does this patient have MAS ?

YES **X**

NO □

Final results after 3 rounds



Classification criteria tested

- Derived from the literature
  - Preliminary diagnostic guidelines for MAS in sJIA
  - Modified preliminary diagnostic guidelines for MAS in sJIA
  - HLH-2004 diagnostic criteria (modified)

- Derived from statistical analyses (generated from study data)
  - Combination of criteria approach (number of positive clinical/laboratory parameters selected from univariate analysis)
  - By assigning a weight to clinical and laboratory variables, on the basis of their association with the diagnosis of MAS made by the experts, through multivariable logistic regression analyses (MAS score: 0-100)

Selection of top definitions (45/982; 4.6%)

- Kappa level of agreement (≥0.85)
- Sensitivity (≥0.8)
- Specificity (≥0.93)
- Positive predictive value (PPV) (≥83%)
- Negative predictive value (NPV) (≥93%)
- Area under the curve (AUC) (≥0.9)

- Historical definitions (sJIA 2005 and HLH 2004) (K 0.53-0.76)

International consensus conference on MAS classification criteria

Villa Quartara della Castagna, Genoa, Italy, 21-22 March 2014





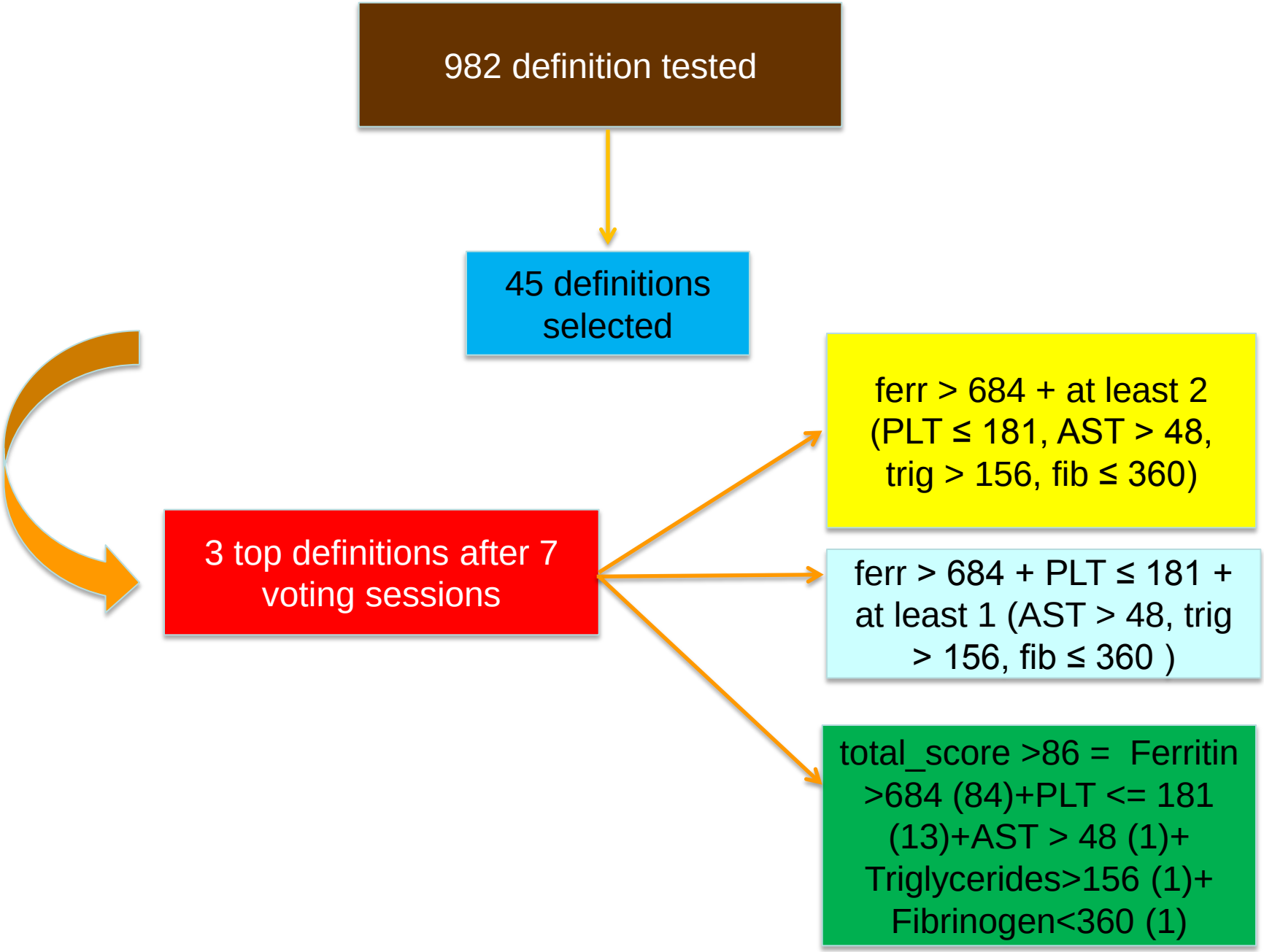
Day 1 - Nominal Group Technique

- 2 Tables
- Laptop connections
- Electronic vote

- **Goal: to select and rank all definitions (n = 45) from 1 to 5**


CONSENSUS CONFERENCE ON MAS CLASSIFIC
21-22 MARCH 2014 - GENOA, IT
Session 2 Table 7


TABLE 2


982 definition tested
45 definitions selected
3 top definitions after 7 voting sessions
ferr > 684 + at least 2 (PLT ≤ 181, AST > 48, trig > 156, fib ≤ 360)
ferr > 684 + PLT ≤ 181 + at least 1 (AST > 48, trig > 156, fib ≤ 360)
total_score >86 = Ferritin >684 (84)+PLT <= 181 (13)+AST > 48 (1)+ Triglycerides>156 (1)+ Fibrinogen<360 (1)

Final definition (>80% consensus)

A febrile patient with known or suspected systemic JIA is classified as having MAS if the patient has:

Ferritin > 684 ng/L

AND

at least 2 of the following 4 laboratory abnormalities:

- Platelets ≤ 181 x 10^9 /mL
- AST > 48 U/L
- Triglycerides > 156 mg/dL
- Fibrinogen ≤ 360 mg/mL

Aims of the project

1. To develop new classification criteria for MAS complicating systemic JIA

2. To identify the laboratory tests whose change over time is most valuable for the timely diagnosis of MAS in the clinical setting

Goals of pre-meeting web-consensus evaluations

1. To classify «real patients» by consensus among experts (≥ 22/27; 80%) as:
   - Positive for MAS
   - Negative for MAS
   - Not classified (consensus <80%)

based on:

<u>Change in laboratory tests over the course of MAS</u>

Goals of pre-meeting web-consensus evaluations

1. To classify «real patients» by consensus among experts (≥ 22/27; 80%) as:
   - Positive for MAS
   - Negative for MAS
   - Unclassified (consensus <80%)

   based on:

   a) Clinical and laboratory data at disease onset
   b) Change in laboratory parameters over the course of MAS

2. To rank order the laboratory tests in order of importance based on their change over the course of MAS

Patient classification - Change

362 patients with MAS collected

115 patient profiles selected

Selection criterion:

At least 5 laboratory parameters with change available

Aim of the excercise:

To identify the laboratory parameters whose change over time is most relevant for making a timely diagnosis of MAS

Example of a patient profile

Laboratory tests	Normal range	Pre MAS visit	MAS onset	Absolute change	% change
Hb, g/l	11,5 – 14,5	10.0			
WBC, $x10^9$/l	5.5 – 13.0	18.0			
Neutrophils, $x10^9$/l	1.5 – 8.5	15.2			
PLT, $x10^9$/l	150 – 400	421			
ESR, mm/h	< 20	75			
AST, U/l	10 – 40	59			
Triglycerides, mg/dl	20-150	146			
LDH, U/l	470 – 920	623			
Fibrinogen, mg/dl	155-400	527			
Ferritin, ng/ml	15 – 150	252			
D-dimer, mg/dl	50 – 350	374			

Example of a patient profile

Laboratory tests	Normal range	Pre MAS visit	MAS onset	Absolute change	% change
Hb, g/l	11,5 – 14,5	10.0	9.7		
WBC, $x10^9$/l	5.5 – 13.0	18.0	14.1		
Neutrophils, $x10^9$/l	1.5 – 8.5	15.2	9.9		
PLT, $x10^9$/l	150 – 400	421	210		
ESR, mm/h	< 20	75	65		
AST, U/l	10 – 40	59	507		
Triglycerides, mg/dl	20-150	146	248		
LDH, U/l	470 – 920	623	18013		
Fibrinogen, mg/dl	155-400	527	256		
Ferritin, ng/ml	15 – 150	252	44.557		
D-dimer, mg/dl	50 – 350	374	6187		

Example of a patient profile

Laboratory tests	Normal range	Pre MAS visit	MAS onset	Absolute change	% change
Hb, g/l	11,5 – 14,5	10.0	9.7	-0.3	-3
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Neutrophils, $x10^9$/l	1.5 – 8.5	15.2	9.9	-5.3	-35
PLT, $x10^9$/l	150 – 400	421	210	-211	-50
ESR, mm/h	< 20	75	65	-10	-13
AST, U/l	10 – 40	59	507	448	759
Triglycerides, mg/dl	20-150	146	248	102	70
LDH, U/l	470 – 920	623	18013	17390	2791
Fibrinogen, mg/dl	155-400	527	256	-271	-51
Ferritin, ng/ml	15 – 150	252	44.557	44.304	17.553
D-dimer, mg/dl	50 – 350	374	6187	5813	1.552

Do you confirm the diagnosis of MAS ? **YES** □ **NO** □

Example of a patient profile

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Do you confirm the diagnosis of MAS ? **YES** **X**

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Example of a patient profile

Please rank the **5 most important** laboratory parameters, giving 5 to the most important and 1 to the least important

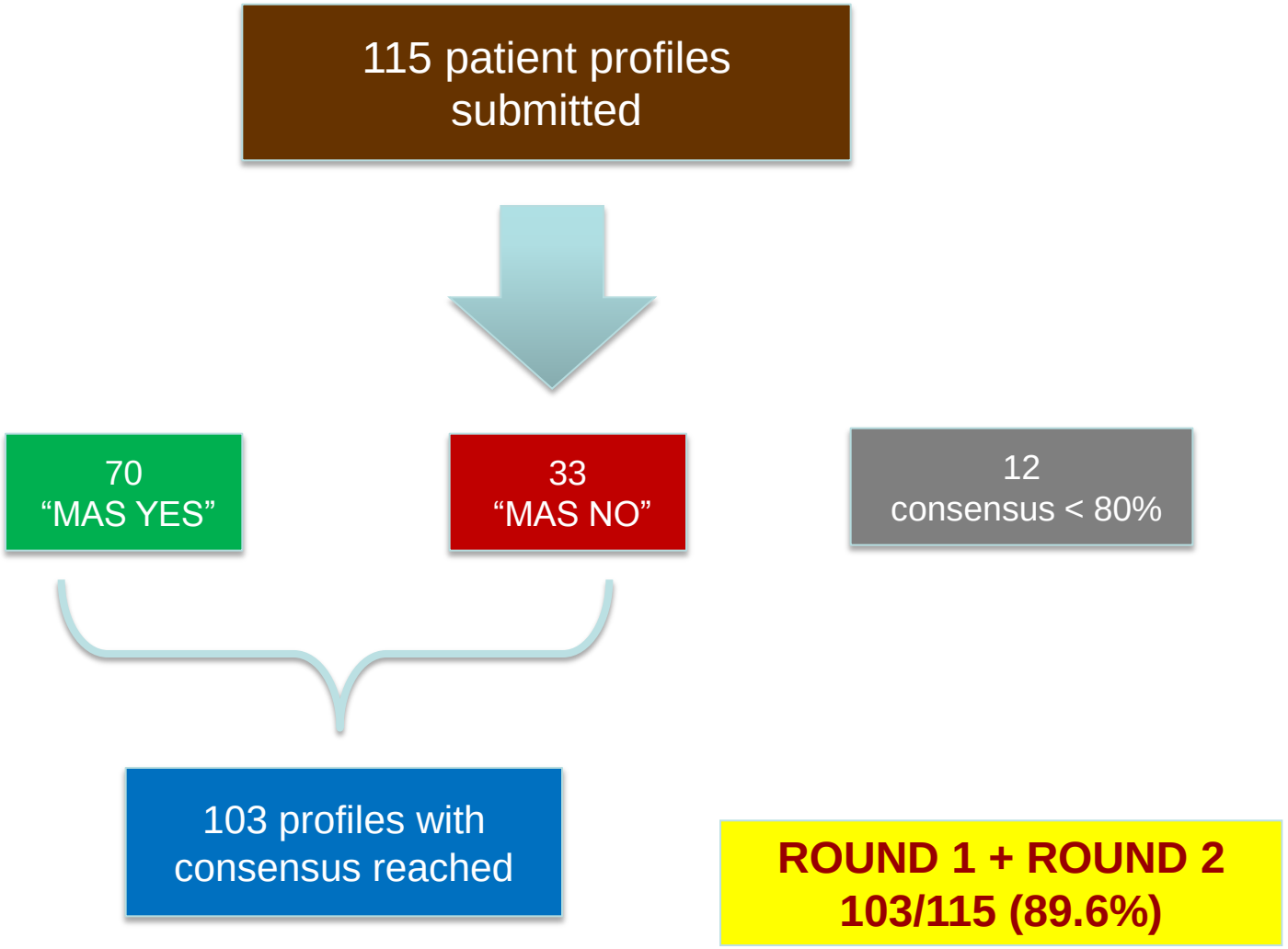
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WBC, $x10^9$/l	5.5 – 13.0	18.0	14.1	-3.9	-22	1
Neutrophils, $x10^9$/l	1.5 – 8.5	15.2	9.9	-5.3	-35	
PLT, $x10^9$/l	150 – 400	421	210	-211	-50	4
ESR, mm/h	< 20	75	65	-10	-13	
AST, U/l	10 – 40	59	507	448	759	3
Triglycerides, mg/dl	20-150	146	248	102	70	
LDH, U/l	470 – 920	623	18013	17390	2791	
Fibrinogen, mg/dl	155-400	527	256	-271	-51	2
Ferritin, ng/ml	15 – 150	252	44.557	44.304	17.553	5
D-dimer, mg/dl	50 – 350	374	6187	5813	1.552	

Final results after 2 rounds



Ranking analysis: results

	Sum of scores	Score 1 (lowest)	Score 2	Score 3	Score 4	Score 5 (highest)	Frequency of selection n (%)
PLT	**6732**	31	78	238	**609**	679	**1635/1821 (90)**
Ferritin	**5754**	59	93	153	240	**818**	**1363/1580 (86)**
AST	**2842**	**300**	**477**	**322**	118	30	**1247/1767 (71)**
WBC	**2176**	168	128	207	199	67	769/1847 (42)
Neutrophils	**2134**	112	132	168	221	74	707/1502 (47)
Fibrinogen	1748	166	184	169	143	27	**689/1164 (59)**
ESR	1290	165	149	150	78	13	555/1632 (34)
LDH	1045	209	171	104	43	2	529/1212 (44)
Hemoglobin	837	156	95	101	42	4	398/1847 (22)
Triglycerides	677	243	130	50	6	0	429/1110 (39)
D-dimer	490	106	78	53	16	1	254/606 (42)
	Median 1748						

Day 2 - Final ranking of change

	NGT score	Sum of scores	Final score
Platelet change	105	6732	706860
Ferritin change	109	5754	627186
AST change	58	2842	164836
Fibrinogen change	32	1748	55936
Neutrophil change	20	2134	42680
WBC change	13	2176	28288
LDH change	15	1045	15675
ESR change	5	1290	6450
D-dimer change	3	490	1470

Endorsement









Financial support



AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH









The harbor of Genoa

Gracias

angeloravelli@gaslini.org