Diagnostic criteria for cryopyrin-associated periodic syndrome (CAPS)

Title

Diagnosing cryopyrin-associated periodic syndromes (CAPS)

Authors

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Acknowlegements:

Travel and accommodation for the Istanbul consensus conference was kindly supported by ABVIE. The 1000minds decision analysis software was kindly provided to the team by the company at no costs. The study team would like to acknowledge the significant administrative contribution of Dr. Iris Haug, University Children's Hospital Tuebingen and the support of Brendon (Pascal to add last name) with the 1000minds decision analysis. We would like to thank Ken Abrahams for kindly allowing the team to include the CAPS β-confident registry for item generation and validation.

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Keywords: Cryopyrin-Associated Periodic Syndromes, autoinflammation, diagnosis, criteria, rare diseases, Interleukin-1

Abstract

Background: Cryopyrin-Associated Periodic Syndromes (CAPS) are a rare, heterogeneous group of devastating inflammatory illnesses associated with gain-of function mutations in the *NLRP3* gene resulting in unceasingly raised IL-1 secretion. Early recognition is crucial, rapid start of IL1 inhibition prevents organ damage in children and adults with CAPS. The aim of the study was to develop and validate diagnostic criteria for CAPS.

Methods

An innovative, rigorous process was followed including a) interdisciplinary team building of pediatric and adult subspecialists and rare diseases methods experts, b) item generation: systematic literature review, review of CAPS registry items, expert survey and consensus conference for item refinement, c) item reduction and weighting using 1000minds decision software. Resulting CAPS criteria were tested in a large cohort of CAPS cases and true controls using correspondence analysis. Diagnostic models were explored using sensitivity analyses. Subanalyses were performed for CAPS subtypes.

Findings

The international team included 16 experts. Systematic literature and registry review identified 32 unique CAPS-typical items; the consensus conference reduced and refined these to 12. 1000minds exercises ranked variables based on importance for the diagnosis CAPS. Validation: Correspondence analysis determined variables consistently associated with the diagnosis of CAPS using 284 cases and 873 controls. Seven variables were significantly associated with CAPS ($p<0.001$ for all). The best diagnosis model included: “Raised inflammatory markers (CRP/SAA) plus ≥ two of six CAPS typical symptoms: urticaria-like rash, cold triggered episodes, sensorineural hearing loss, musculoskeletal symptoms, chronic aseptic meningitis, skeletal abnormalities. Sensitivity was 81%, specificity 94%. It performed superbly well for all subtypes and in subgroups with and without evidence of *NLRP3* mutations.

Interpretation

The novel approach integrated traditional methods of evidence synthesis with expert consensus, web-based decision tools and innovative statistical methods and may serve as a model for other rare diseases. The model will enable a rapid diagnosis for children and adults with CAPS.

Funding

None.

Introduction

Cryopyrin associated period syndromes (CAPS) encompasses a spectrum of clinical phenotypes associated with mutations in the NLRP3 gene encoding cryopyrin, a key regulatory protein of cellular IL-1 production [1,2]. While previously considered three distinct clinical diseases including familial cold-associated periodic syndrome (FCAS), Muckle Wells-syndrome (MWS) and Chronic infantile neurological, cutaneous(CINCA) and Neonatal-onset Multisystem Inflammatory Disorders (NOMID), the discovery of the causative gene defect lead to an amalgamation into the entity CAPS [3]. NLRP3 gain of function mutations were shown to result in characteristic, yet diverse clinical symptoms of systemic and organ specific inflammation and raise of inflammatory markers, most importantly C-reactive protein (CRP), serum amyloid A (SAA) and the neutrophil protein S100A12 [4,5].

CAPS are rare, affecting 1-3/1Mio children and adults worldwide; no gender or ethnic predilection has been identified [6]. In clinical practice, establishing the diagnosis of a rare disease such as CAPS is challenging and often delayed [7]. This delay or even complete lack of recognition can be attributed to different factors including limited awareness of health care providers overall for each single rare disease and the diversity of practitioners heading the care of patients with rare diseases. Commonly, the latter is primarily determined by the leading affected organ manifestations such as hearing loss, urticaria-like skin rash or nephritis in patients with CAPS.

Diagnostic criteria are limited in rare diseases overall. Their development heavily relies on international collaborative efforts of small numbers of medical experts. Currently, there are no diagnostic criteria available for CAPS, resulting in a high risk of missing a window of opportunity for reversal of IL-1 mediated inflammation and prevention of organ damage. Therefore the aims of the study were to develop and validate diagnostic criteria for children and adults with CAPS to enable an early diagnosis of CAPS and prevent irreversible organ damage secondary to inflammation.

Methods

A rigorous and innovative process was followed including: a) interdisciplinary, international expert team building of different pediatric and adult CAPS subspecialty experts plus rare diseases methods experts, b) item generation and refinement: systematic literature review, review of CAPS items in registries, CAPS expert survey and consensus conference, c) item reduction and weighting, d) diagnostic model building using correspondence analysis and e) model validation.

- **Expert team building**

The multidisciplinary team had to include experts in the care of children and adults with CAPS including rheumatologists and other subspecialists and experts in rare diseases research and methodology from both Europe and North America. Participants were invited based on their clinical and scientific expertise and geographic representation. They remained connected throughout the process including multiple surveys, decision analysis exercises and iterative face-to-face meetings.

- **Item generation**

Systematic literature review: Published studies were identified through searches of MEDLINE, COCHRANE and EMBASE (**Excerpta Medica**) databases for the period from 1970 to 2013 following the EULAR rules for developing best practices [8]. Keyword, title and abstract information were used. All synonyms of CAPS, CINCA/NOMID, MWS and FCAS were searched. In addition, a search for 'autoinflammatory diseases' and synonyms was performed; references and reviews were screened for additional articles. The review was performed as previously described [9].

CAPS registry item review: All actively recruiting North American and European autoinflammatory registries were reviewed for CAPS diagnosis items including Eurofever, Canakinumab Registry (β-confident, Novartis), ARDIS (Arthritis and Rheumatology Documentation and Information System) and AID-NET (AutoInflammatory Disease-NET). A total of 32 CAPS items were identified from the review of the literature and CAPS registries.

- **Item refinement, reduction and weighing**

CAPS expert survey: Using web-based survey methodology, experts were asked to review all items, add additional items, if applicable, and evaluate each item for its relevance in making the diagnosis of CAPS and/or CAPS subtypes including FCAS, FCAS/MWS, MWS, MWS/CINCA/NOMID, CINCA/NOMID. The survey had to be completed and returned by > 80% of participants. Items were considered relevant, if there was ≥80 % agreement amongst experts. Experts were asked to provide additional CAPS items, if applicable.

CAPS consensus conference Istanbul: Survey results were shared. All items were discussed and refined using nominal group technique [10]. Refined items were voted on for their relevance for diagnosing CAPS and/or CAPS subtypes. Items were considered relevant, if there was ≥80 % agreement amongst experts.

CAPS consensus meeting Boston: Putative CAPS diagnosis items were shared and refined further using nominal group technique. Fourteen final putative CAPS diagnosis items were ranked for their relevance using 1000minds decision analysis software [11]. Experts were presented pairs of CAPS items and asked to identify the item of higher relevance for diagnosing CAPS (e.g., sensorineural hearing loss present and amyloidosis absent *or* sensorineural hearing loss absent and amyloidosis present, all other manifestations being considered equal). A resulting ranking of CAPS items was computed; correlations between expert decisions were calculated.

- **Diagnostic model development**

Multiple correspondence analyses were used to assess the multi-dimensional relationship between putative CAPS diagnosis items and patient diagnoses. Item with close relationship to the diagnosis CAPS were then tested in multivariable logistic regression models resulting in a proposed diagnostic model. All analyses were performed using SAS software, V.9.4 (SAS Institute, Cary, North Carolina, USA).

- **Diagnostic model validation**

The proposed diagnostic model was validated in a large, multicenter cohort of 284 children and adult with CAPS including 30 patients with FCAS, 164 with MWS and 90 with NOMID. The controls included 873 children and adults with the following conditions: systemic JIA

(100), Schnitzler syndrome (13), Familial Mediterranean Fever (FMF) (178), unclassified fever syndromes (93), typical Kawasaki disease (KD) (280) and incomplete KD (173). Subanalyses were performed for all CAPS subtypes and evidence of NLRP3 mutation. Sensitivity analyses were performed.

Results

The multidisciplinary CAPS team included a total of 16 pediatric (JKD, SO, IKP, HH, EWR, BH, TK, MG, FD, LC) and adult (RGM, HL, NB, AG) subspecialists and methodology experts in rare diseases research (PT, SB) and was supported by two fellows (NTH, MO). The team members were selected based on their exceptional expertise in care and research in autoinflammatory diseases and the clinical severity spectrum of CAPS.

- **Item generation**

Systematic literature review: A total of 1698 unique papers were identified; 47 were selected for full-text screening, of which 33 were relevant and underwent validity assessment. After excluding four articles with poor validity, data from 29 publications were utilized for identification for CAPS relevant items (Figure 1). A total of 29 studies were identified including a total of 794 CAPS patients and generating 33 CAPS typical items. Review of CAPS registries: The review of the CAPS registries did not yield any additional diagnosis items beyond those identified in the systematic literature review.

- **Item refinement, reduction and weighing**

CAPS expert survey: The survey was completed and returned by 100% of participants. A total of 33 items were included in the expert survey and item response was 31/33 items; 25 items were considered to be relevant. Additional 7 items were suggested by CAPS experts in their responses.

CAPS consensus conference Istanbul: A total of 40 items were discussed, refined and grouped into 1) patient-related items including positive family history of CAPS and evidence of NLRP3 mutation, 2) disease course-related items: symptom-onset in infancy, persistent inflammation with/without episodic attacks with worsening symptoms and induction of characteristic symptoms after generalized cold exposure, clinical signs and symptoms of CAPS coupled with laboratory findings of acute phase response 3) CAPS typical symptoms: recurrent episodes of systemic symptoms of fever and/or chills/rigors and/or fatigue, diffuse urticaria-like rash, recurrent eye inflammation including conjunctivitis with/without other inflammatory ocular findings, sensorineural hearing loss, clinical, laboratory and/or imaging evidence of chronic aseptic meningitis, musculoskeletal signs and symptoms of arthralgia,

myalgia, arthritis and/or periarticular swelling, skeletal abnormalities including clubbing and/or frontal bossing and/or epiphyseal bony overgrowth, amyloidosis. A total of 14 CAPS items reached ≥80 % agreement amongst experts (Table 1).

CAPS consensus conference Boston: Items were reviewed and refined further resulting in a final list of 12 items. All experts participated in the iterative 1000minds exercise process ranking the items based on their importance for the diagnosis CAPS. Items were revised and refined. Results demonstrated excellent correlations with disease subtypes and between experts.

- **Diagnostic model development**

Correspondence analysis revealed three distinct entities: CAPS, non-CAPS autoinflammatory diseases and monophasic inflammatory diseases (Figure 2). Key variables consistently associated with the diagnosis of CAPS included urticaria-like rash, triggered episodes, sensorineural hearing loss, amyloidosis, musculoskeletal symptoms of arthralgia/arthritis/myalgia, chronic aseptic meningitis, skeletal abnormalities of epiphyseal overgrowth/frontal bossing. Raised inflammatory markers (CRP/SAA) and systemic symptoms were associated with all three entities. In contrast, conjunctivitis was closely associated with monophasic inflammatory diseases, while continuous/persistent symptoms and episodic nature of disease had a closer relationship with non-CAPS autoinflammatory diseases. NLRP3 mutation was removed as pre-defined, and amyloidosis due to its rarity.

- **Diagnostic model validation**

Different combinations of variables significantly associated with CAPS were tested for their association. Different models were explored. The best CAPS diagnosis criteria model included: raised inflammatory markers (CRP/SAA) plus ≥ two of six CAPS-typical signs/symptoms including 1) urticara-like rash, 2) cold/stress triggered episodes, 3) sensorineural hearing loss, 4) musculoskeletal symptoms of arthralgia/arthritis/myalgia, 5) chronic aseptic meningitis, and 6) skeletal abnormalities of epiphyseal overgrowth/frontal bossing ($p<0.001$) (Figure 3). The final CAPS diagnosis criteria model had a specificity of 94%, the sensitivity was 81%. It performed equally well for all CAPS subtypes and in subgroups

with and without evidence of NLRP3 mutation ($p<0.001$).

Discussion

Diagnostic criteria for CAPS, rare and clinically heterogeneous inflammatory illnesses, were developed and validated by an international team of experts using an innovative approach that integrated published evidence, registry expertise and expert opinion. It resulted in a comprehensive, well-defined list of putative CAPS diagnosis items capturing the heterogeneous phenotype and the disease severity spectrum in children and adults. The iterative review and refinement strategy using nominal group technique coupled with the 1000minds decision analysis tool allowed for the development of a CAPS diagnosis model, which contained clinical and laboratory variables only, resulting in excellent generalizability. Most importantly, it does not mandate evidence of a disease-causing NLRP3 mutation. It performed superbly well in a large validation cohort of more than 1000 patients with CAPS and controls ($p<0.001$) achieving a high sensitivity and specificity.

The CAPS diagnosis criteria development followed an innovative, comprehensive process, which integrated diverse clinical expertise with rare diseases research methodology. The process was iterative, items were refined and followed strict rules of communication and knowledge gain (nominal group technique). It utilized an easy-to-use web-based decision tool, the 1000minds instrument, which was given to the group free-of charge by the developers. This item generation and refinement strategy had been successfully used previously for the development of classification criteria for adult scleroderma [12]. Both, the European and North American rheumatology societies promote it's application.
The unique next step in this study was the exploration of the relevance of putative diagnosis items using correspondence analyses. This analysis highlighted the principles of the differential diagnostic challenges when diagnosing CAPS and its subtypes including other autoinflammatory disease and monophasic inflammation. It depicted both disease specific variables and those representing the overlap between illnesses. It then permitted the development of a highly specific, sensitive and most importantly clinically relevant diagnostic model for CAPS. This approach may serve as a model for other rare diseases.

The proposed criteria are diagnostic criteria for CAPS and its subtypes. The study suggests that the presence of raised inflammatory markers (CRP/SAA) plus ≥ two of six CAPS typical signs/symptoms including 1) urticara-like rash, 2) cold/stress triggered episodes, 3)

sensorineural hearing loss, 4) musculoskeletal symptoms of arthralgia/arthritis/myalgia, 5) chronic aseptic meningitis, and 6) skeletal abnormalities of epiphyseal overgrowth/frontal bossing is highly likely to confirm the diagnosis of CAPS, even in the absence of information about a disease-causing NLRP3 mutation. There are very few diagnostic criteria in inflammatory diseases. The most commonly cited and used criteria are the Jones criteria for rheumatic fever [13] and the Kawasaki criteria [14]. Both are derived from clinical expert observation. The Kawasaki criteria were refined by the American Heart Association in order to capture the entire disease spectrum even including children with incomplete features utilizing laboratory markers to confirm the diagnosis [15]. The vast majority of criteria for inflammatory diseases are classification criteria, developed within a group of overlapping conditions and aiming to establish well-characterized cohorts for research [16,17]. Recently proposed classification criteria include the pediatric EULAR/PRINTO/PRES criteria for childhood vasculitis [18], the EUROFEVER classification criteria for autoinflammatory disease [17], the FMF Criteria [19] and the Pediatric Behcet criteria (**Kone-Paut et al 2015 submitted**).
In daily practice, criteria that enable a rapid diagnosis are urgently needed, in particular in autoinflammatory disease resulting in organ damage. To our knowledge the only other initiative aiming to develop and validate diagnostic criteria for inflammatory diseases is the Diagnosis and Classification Criteria for Vasculitis Study (DCVAS) that has recruited over 5000 patients – adult vasculitis cases and vasculitis mimic controls – from 129 sites worldwide [20]. In both disease entities, vasculitis and CAPS, a rapid diagnosis and initiation of target therapy is essential to prevent organ damage from inflammation.

The study has several limitations. The number of CAPS cases and controls for validation was limited. Not all possible differential diagnoses may have been included potentially leading to an overestimation of the specificity of the proposed model. However, the group dedicated long, thorough discussions to the identification of clinically relevant control populations and the team collected the largest number of CAPS cases and controls studied today. Not all subspecialists involved in the care of children and adults with CAPS were part of the team. The group did not identify any Ear-Nose-Throat or ophthalmology CAPS experts, which may have caused an underrepresentation of clinical CAPS items generated from these subspecialists. However, all team members provide care in an interdisciplinary team and felt that all specific organ-related items were integrated.

Conclusion

The CAPS diagnosis model is the result of a unique collaborative team approach. It captures all diseases in the spectrum of CAPS and therefore enables a rapid diagnosis and initiation of treatment for children and adults with CAPS, a rare, heterogeneous inflammatory disease. The novel approach integrated traditional methods of evidence synthesis with expert consensus, web-based decision tools and innovative statistical methods and may serve as a model for the diagnosis of other rare diseases.

References

1. Stojanov S, Kastner DL. Familial autoinflammatory diseases: genetics, pathogenesis and treatment. *Curr Opin Rheumatol* 2005; **17**(5): 586-99.
2. Shinkai K, McCalmont TH, Leslie KS. Cryopyrin-associated periodic syndromes and autoinflammation. *Clin Exp Dermatol* 2008; **33**(1): 1-9.
3. Hoffman HM, Mueller JL, Broide DH, Wanderer AA, Kolodner RD. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. *Nat Genet* 2001; **29**(3): 301-5.
4. Lachmann HJ, Goodman HJ, Gilbertson JA, et al. Natural history and outcome in systemic AA amyloidosis. *N Engl J Med* 2007; **356**(23): 2361-71.
5. Wittkowski H, Kuemmerle-Deschner JB, Austermann J, et al. MRP8 and MRP14, phagocyte-specific danger signals, are sensitive biomarkers of disease activity in cryopyrin-associated periodic syndromes. *Annals of the rheumatic diseases* 2011; **70**(12): 2075-81.
6. Cuisset L, Jeru I, Dumont B, et al. Mutations in the autoinflammatory cryopyrin-associated periodic syndrome gene: epidemiological study and lessons from eight years of genetic analysis in France. *Ann Rheum Dis* 2011; **70**(3): 495-9.
7. Toplak N, Frenkel J, Ozen S, et al. An international registry on autoinflammatory diseases: the Eurofever experience. *Ann Rheum Dis* 2012; **71**(7): 1177-82.
8. Dougados M, Betteridge N, Burmester GR, et al. EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees. *Ann Rheum Dis* 2004; **63**(9): 1172-6.
9. Ter Haar NM, Oswald M, Jeyaratnam J, et al. Recommendations for the management of autoinflammatory diseases. *Ann Rheum Dis* 2015; **74**(9): 1636-44.
10. Harvey N, Holmes CA. Nominal group technique: an effective method for obtaining group consensus. *Int J Nurs Pract* 2012; **18**(2): 188-94.
11. Hansen P, Ombler F. A new method for scoring multi-attribute value models using pairwise ranking of alternatives. *J Multi-Crit Decis Anal* 2009; **15**: 87-107.
12. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum* 2013; **65**(11): 2737-47.
13. Dajani AS, Ayoub E, Bierman FZ, et al. Guidelines for the Diagnosis of Rheumatic Fever
Jones Criteria, 1992 Update. *JAMA* 1992; **268**(15): 2069-73.

14. AHA Scientific Statement. Diagnostic Guidelines for Kawasaki Disease. *Circulation* 2001; **103**: 335-6.
15. Yellen ES, Gauvreau K, Takahashi M, et al. Performance of 2004 American Heart Association recommendations for treatment of Kawasaki disease. *Pediatrics* 2010; **125**(2): e234-41.
16. Basu N, Watts R, Bajema I, et al. EULAR points to consider in the development of classification and diagnostic criteria in systemic vasculitis. *Ann Rheum Dis* 2010; **69**(10): 1744-50.
17. Federici S, Sormani MP, Ozen S, et al. Evidence-based provisional clinical classification criteria for autoinflammatory periodic fevers. *Ann Rheum Dis* 2015; **74**(5): 799-805.
18. Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. *Ann Rheum Dis* 2010; **69**(5): 798-806.
19. Giancane G, Ter Haar NM, Wulffraat N, et al. Evidence-based recommendations for genetic diagnosis of familial Mediterranean fever. *Ann Rheum Dis* 2015; **74**(4): 635-41.
20. Craven A, Robson J, Ponte C, et al. ACR/EULAR-endorsed study to develop Diagnostic and Classification Criteria for Vasculitis (DCVAS). *Clin Exp Nephrol* 2013; **17**(5): 619-21.

Table 1

Criteria and definition for the classification of cryopyrin-associated periodic syndrome (CAPS)

Patient-related symptoms	
Family history of CAPS	Phenotype and or genetic confirmation of CAPS in other family members
Confirmed NLRP3 mutation	Genetic confirmation of NLRP3 mutation
CAPS disease course related variables	
Early disease onset	Age at onset of CAPS typical symptoms in infancy or early childhood
Episodic disease course characterized by CAPS typical symptoms with or without persistent inflammation	Disease course with episodes of clinically active CAPS disease
Triggered inflammatory attacks	Triggers: cold or other stressors
Evidence of raised inflammatory marker associated with CAPS clinical signs	Evidence of CAPS clinical signs coupled with systemic inflammation, e.g. CRP
CAPS typical symptoms	
Amyloidosis	Evidence of organ amyloid deposits, e.g. kidney
Recurrent episodes of systemic symptoms	Evidence of systemic features like fever and/or chills and/or fatigue and/or rigors
Urticaria-like rash	Histologically characterized

	by neutrophilic dermatitis
Chronic aseptic meningitis	Evidence of clinical, laboratory and/or imaging evidence of non infectious inflammatation of the meninges
Recurrent eye inflammation,	Recurrent non-allergic, non-infectious conjunctivitis with/without other inflammatory ocular manifestations
Sensorineural hearing loss	Evidence of increased hearing thresholds on audiogram
Musculoskeletal sign and symptoms	Evidence of arthralgia, myalgia, arthritis and/or periarticular swelling
Skeletal abnormalities	Evidence of epiphyseal overgrowth, frontal bossing, clubbing and/or growth failure

Table 2

Systematic literature review search items

CAPS Pubmed	"cryopyrin associated periodic syndromes"[MeSH Terms] OR "Cryopyrin Associated Periodic Syndromes"[tiab] OR "Cryopyrin Associated Periodic Syndrome"[tiab] OR "Cryopyrin Associated Periodic Fever Syndromes"[tiab] OR "Cryopyrin Associated Periodic Fever Syndrome"[tiab OR cryopyrinopath*[tiab] OR FCAS[tiab] OR "Familial Cold Autoinflammatory Syndrome"[tiab] OR "Familial Cold Urticaria"[tiab] OR MWS[tiab] OR "Muckle Wells Syndrome"[tiab] OR CINCA[tiab] OR (Chronic[tiab] AND Infantile[tiab] AND Neurological[tiab] AND Cutaneous[tiab] AND Articular[tiab]) OR NOMID[tiab] OR "Neonatal Onset Multisystem Inflammatory Disease"[tiab] OR "Infantile Onset Multisystem Inflammatory Disease"[tiab]	1056
CAPS Embase	'cinca syndrome'/exp OR 'muckle wells syndrome'/exp OR 'familial cold autoinflammatory syndrome'/exp OR 'cryopyrin associated periodic syndromes':ab,ti OR 'cryopyrin associated periodic syndrome':ab,ti OR 'cryopyrin associated periodic fever syndromes':ab,ti OR 'cryopyrin associated periodic fever syndrome':ab,ti OR cryopyrinopath*:ab,ti OR fcas:ab,ti OR 'familial cold autoinflammatory syndrome':ab,ti OR 'familial cold urticaria':ab,ti OR mws:ab,ti OR 'muckle wells syndrome':ab,ti OR cinca:ab,ti OR (chronic:ab,ti AND infantile:ab,ti AND neurological:ab,ti AND cutaneous:ab,ti AND articular:ab,ti) OR nomid:ab,ti OR 'neonatal onset multisystem inflammatory disease':ab,ti OR 'infantile onset multisystem inflammatory disease':ab,ti	1512
CAPS	MeSH descriptor: [Cryopyrin-Associated Periodic Syndromes] explode all trees OR "Cryopyrin Associated Periodic Syndromes" or "Cryopyrin Associated	29

	Periodic Syndrome" or "Cryopyrin Associated Periodic Fever Syndromes" or "Cryopyrin Associated Periodic Fever Syndrome" or cryopyrinopath* or FCAS or "Familial Cold Autoinflammatory Syndrome" or "Familial Cold Urticaria" or MWS or "Muckle Wells Syndrome" or CINCA or (Chronic and Infantile and Neurological and Cutaneous and Articular) or NOMID or "Neonatal Onset Multisystem Inflammatory Disease" or "Infantile Onset Multisystem Inflammatory Disease"(title/abstract)	
AID Pubmed	"Hereditary Autoinflammatory Diseases"[Mesh:NoExp] OR "autoinflammatory diseases"[tiab] OR "autoinflammatory syndromes"[tiab] OR "periodic fever syndromes"[tiab] OR "autoinflammatory disease"[tiab] OR "autoinflammatory syndrome"[tiab] OR "periodic fever syndrome"[tiab]	781 (all) 253[NtH1] (new)
AID Embase	'autoinflammatory disease'/de OR 'hereditary periodic fever'/de OR 'autoinflammatory diseases':ab,ti OR 'autoinflammatory syndromes':ab,ti OR 'periodic fever syndromes':ab,ti OR 'autoinflammatory disease':ab,ti OR 'autoinflammatory syndrome':ab,ti OR 'periodic fever syndrome':ab,ti	1388 all 508 new[NtH2]
AID Cochrane	MeSH descriptor: [Hereditary Autoinflammatory Diseases] this term only OR "autoinflammatory diseases" or "autoinflammatory syndromes" or "periodic fever syndromes" or "autoinflammatory disease" or "autoinflammatory syndrome" or "periodic fever syndrome"(title/abstract)	33

Figure 1: Systematic literature review – search results

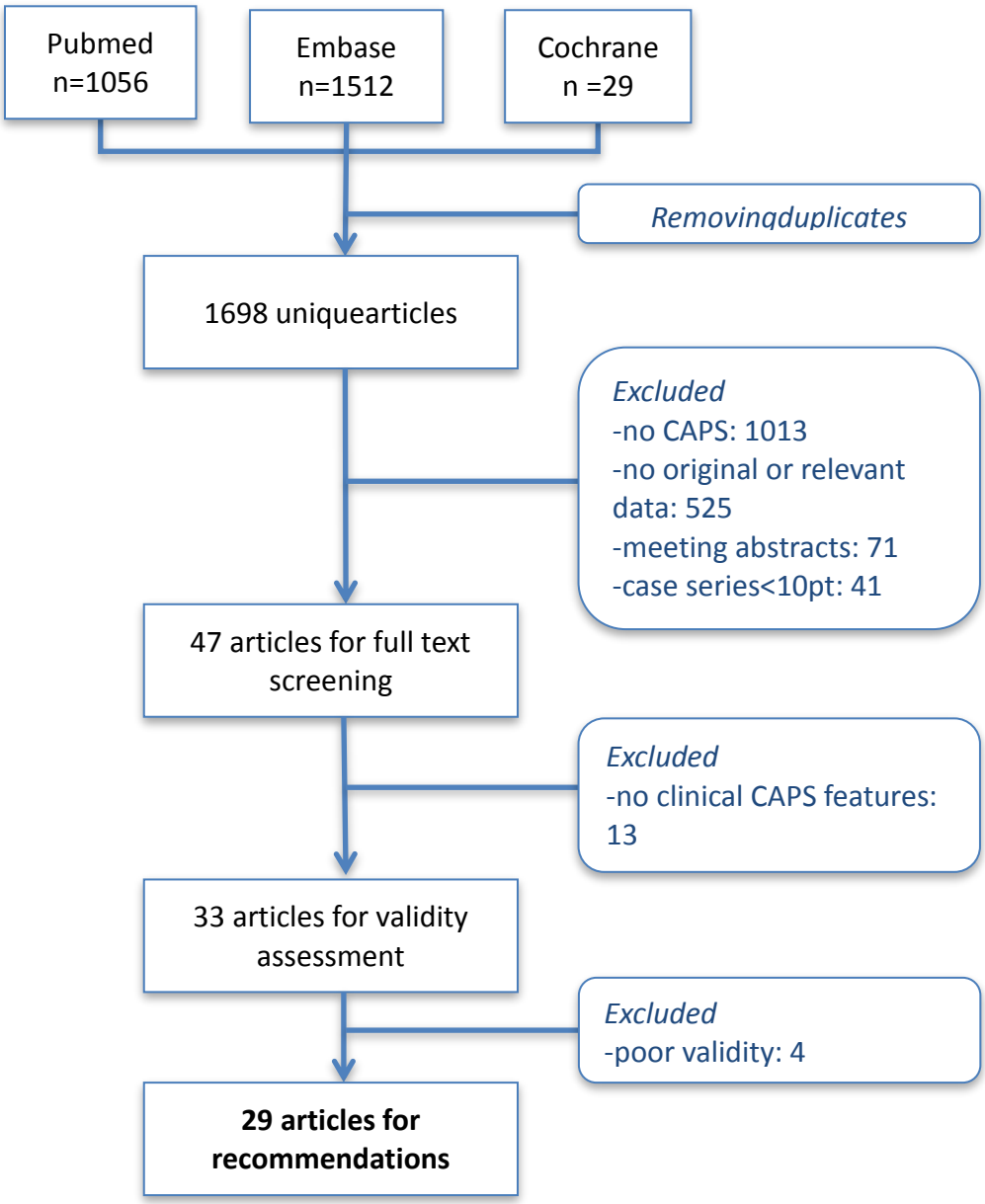
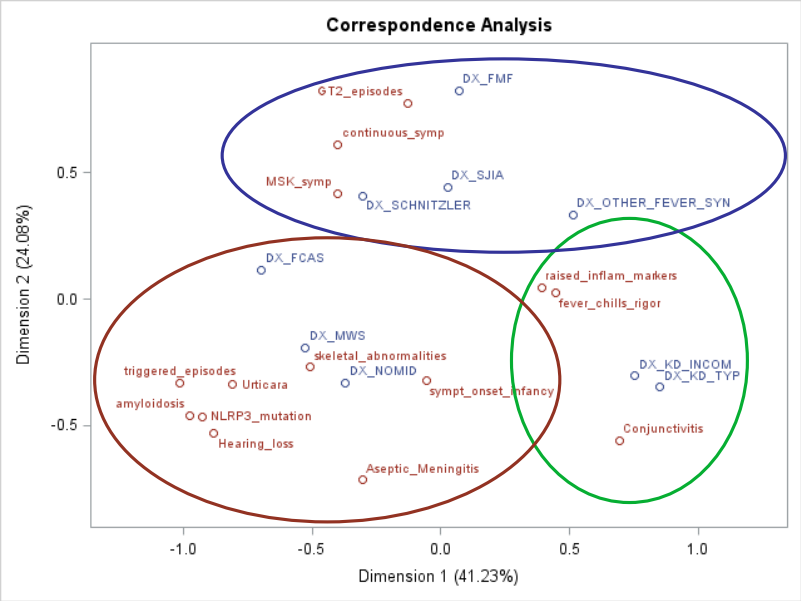


Figure 2: Correspondence analysis

Results correspondence analysis



Correspondence analysis revealed three distinct entities: CAPS (red circle), non-CAPS autoinflammatory diseases (blue circle) and monophasic inflammatory diseases (green circle)

Figure 3: Proposed CAPS diagnosis criteria model

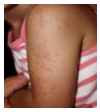
Step 6: Development of a diagnostic model

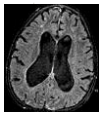
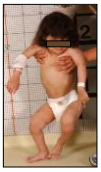
Raised inflammatory markers (CRP/SAA)
(Mandatory criteria)

plus

≥ 2 of 6 **CAPS typical signs/symptoms**:

- urticaria-like rash
- cold/stress triggered episodes
- sensorineural hearing loss
- musculoskeletal symptoms(arthralgia/arthritis/myalgia)
- chronic aseptic meningitis
- skeletal abnormalities
  (epiphyseal overgrowth/frontal bossing



Legend .

Specifity was 94% and sensitivity was 81% for the CAPS diagnosis criteria model. It performed equally well for all CAPS subtypes and in subgroups with or without evidence of NLRP3 mutation ($p<0.001$).

Figure 4 CAPS expert survey (supplemental material)

Q1 Family History

1. A positive family history of a genetically confirmed diagnosis of Cryopyrin-Associated Periodic Syndrome (CAPS) in a family member

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	○	⊗

This ranking applies to

⊗**all** diseases in the CAPS spectrum ***OR***

○**only some** diseases in the CAPS spectrum, *please check all applicable*

☐ FCAS ☐ FCAS/MWS ☐ MWS ☐ MWS/CINCA/NOMID ☐ CINCA/NOMID

2. A positive family history of clinical signs and symptoms associated with CAPS

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	⊗	○

This ranking applies to

⊗**all** diseases in the CAPS spectrum ***OR***

○**only some** diseases in the CAPS spectrum, *please check all applicable*

☐ FCAS ☐ FCAS/MWS ☐ MWS ☐ MWS/CINCA/NOMID ☐ CINCA/NOMID

Q2 Characteristic of active disease

1. Age at disease onset

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	⊗	○

This ranking applies to

○**all** diseases in the CAPS spectrum ***OR***

⊗**only some** diseases in the CAPS spectrum, *please check all applicable*

☐ FCAS ☐ FCAS/MWS ☐ MWS ☒ MWS/CINCA/NOMID ☒ CINCA/NOMID

2. Episodic nature of symptoms

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	⊗	○	○

This ranking applies to

○ all diseases in the CAPS spectrum***or***

○**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☒ FCAS/MWS overlap ☒ MWS ☒ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID

3. Duration of episodes

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	⊗	○	○	○

This score applies to

⊗ all diseases in the CAPS spectrum***or***

○**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☐ FCAS/MWS overlap ☐ MWS ☐ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID

4. External triggers resulting in disease flares

a) Cold-induced flares

I consider this variable	**not**	often**not**	undecided	**often**	**very**

relevant	relevant		relevant	relevant
○	○	○	⊗	○

This score applies to

○ all diseases in the CAPS spectrum***or***

⊗**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☒ FCAS ☒ FCAS/MWS overlap ☒ MWS ☒ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID

b) Stress-induced flares

I consider this variable	**not**	often**not**	undecided	**often**	**very**
	relevant	relevant		relevant	relevant
	○	○	○	⊗	○

This score applies to

○ all diseases in the CAPS spectrum***or***

⊗**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☒ FCAS/MWS overlap ☒ MWS ☐ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID

c) Infection-induced flares

I consider this variable	**not**	often**not**	undecided	**often**	**very**
	relevant	relevant		relevant	relevant
	○	○	○	⊗	○

This score applies to

○ all diseases in the CAPS spectrum***or***

⊗**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☒ FCAS/MWS overlap ☒ MWS ☐ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID

Q3 Systemic clinical symptoms of active disease

1. Fever

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	⊗	○

This score applies to

⊗ all diseases in the CAPS spectrum***or***

○**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☐ FCAS/MWS overlap ☐ MWS ☐ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID

2. Fatigue

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	○	⊗

This score applies to

⊗ all diseases in the CAPS spectrum***or***

○**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☐ FCAS/MWS overlap ☐ MWS ☐ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID

3. Headaches

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	⊗	○

This score applies to

○ all diseases in the CAPS spectrum***or***

⊗**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☐ FCAS/MWS overlap ☒ MWS ☒ MWS/CINCA/NOMID overlap ☒ CINCA/NOMID

4. Irritability

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	⊗	○

This score applies to

○ all diseases in the CAPS spectrum***or***

⊗**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☐ FCAS/MWS overlap ☒ MWS ☒ MWS/CINCA/NOMID overlap ☒ CINCA/NOMID

Q4 Organ-specific clinical symptoms of active disease

1. Eye manifestations

a) Conjunctivitis

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	○	⊗

This score applies to

○ all diseases in the CAPS spectrum***or***

⊗**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☒ FCAS/MWS overlap ☒ MWS ☒ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID

b) Keratitis

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	⊗	○

This score applies to

○ all diseases in the CAPS spectrum***or***

⊗**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☒ FCAS/MWS overlap ☒ MWS ☒ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID

c) Uveitis

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	⊗	○

This score applies to

○ all diseases in the CAPS spectrum***or***

⊗**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☒ FCAS/MWS overlap ☒ MWS ☒ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID

d) Papilledema and/or secondary optic nerve damage (atrophy, vision loss)

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	○	⊗

This score applies to

○ all diseases in the CAPS spectrum***or***

⊗**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☐ FCAS/MWS overlap ☐ MWS ☒ MWS/CINCA/NOMID overlap ☒ CINCA/NOMID

2. Oral /ear-nose-throat (ENT) manifestations

a) Oral ulcers or aphtous stomatitis

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	⊗	○

This score applies to

○ all diseases in the CAPS spectrum***or***

⊗**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☒ FCAS/MWS overlap ☒ MWS ☒ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID

b) Exudative pharyngitis

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	⊗	○

This score applies to

○ all diseases in the CAPS spectrum***or***

⊗**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☒ FCAS/MWS overlap ☒ MWS ☒ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID

c) Cervical lymphadenopathy

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	⊗	○

This score applies to

○ all diseases in the CAPS spectrum***or***

⊗**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☒ FCAS/MWS overlap ☒ MWS ☒ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID

d) Sensorineural hearing loss

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	○	⊗

This score applies to

○ all diseases in the CAPS spectrum***or***

⊗**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☒ FCAS/MWS overlap ☒ MWS ☒ MWS/CINCA/NOMID overlap ☒ CINCA/NOMID

3. Chest manifestations

a) Pleuritis / pericarditis / chest pain

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	⊗	○

This score applies to

○ all diseases in the CAPS spectrum***or***

⊗**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☒ FCAS/MWS overlap ☒ MWS ☒ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID

4. Abdominal manifestations

a) Abdominal pain

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	⊗	○

This score applies to

○ all diseases in the CAPS spectrum***or***

⊗**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☒ FCAS/MWS overlap ☒ MWS ☒ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID

b) Splenomegaly

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	⊗	○

This score applies to

○ all diseases in the CAPS spectrum***or***

⊗**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☒ FCAS/MWS overlap ☒ MWS ☒ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID

c) Renal manifestations: proteinuria

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	○	⊗

This score applies to

○ all diseases in the CAPS spectrum***or***

⊗**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☒ FCAS/MWS overlap ☒ MWS ☒ MWS/CINCA/NOMID overlap ☒ CINCA/NOMID

d) Renal manifestations: amyloidosis

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	○	⊗

This score applies to

○ all diseases in the CAPS spectrum***or***

⊗**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☒ FCAS/MWS overlap ☒ MWS ☒ MWS/CINCA/NOMID overlap ☒ CINCA/NOMID

5. Skin manifestations

a) Urticaria-like rash

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	○	⊗

This score applies to

○ all diseases in the CAPS spectrum***or***

⊗**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☒ FCAS ☒ FCAS/MWS overlap ☒ MWS ☒ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID

b) Maculo-papular rash

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	⊗	○

This score applies to

○ all diseases in the CAPS spectrum***or***

⊗**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☒ FCAS/MWS overlap ☒ MWS ☒ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID

6. Musculoskeletal manifestations

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	⊗	○

This score applies to

○ all diseases in the CAPS spectrum***or***

⊗**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☒ FCAS/MWS overlap ☒ MWS ☒ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID

b) Bone deformities (patella overgrowth, clubbing, frontal bossing)

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	○	⊗

This score applies to

○ all diseases in the CAPS spectrum***or***

⊗**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☐ FCAS/MWS overlap ☐ MWS ☒ MWS/CINCA/NOMID overlap ☒ CINCA/NOMID

b) Growth retardation

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	⊗	○

This score applies to

○ all diseases in the CAPS spectrum***or***

○**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☐ FCAS/MWS overlap ☐ MWS ☒ MWS/CINCA/NOMID overlap ☒ CINCA/NOMID

7. CNS manifestations

a) Meningitis headaches / aseptic meningitis

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	⊗	○

This score applies to

○ all diseases in the CAPS spectrum***or***

○**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☐ FCAS/MWS overlap ☐ MWS ☒ MWS/CINCA/NOMID overlap ☒ CINCA/NOMID

8. other manifestations, please specify

a) _____

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	○	○

This score applies to

○ all diseases in the CAPS spectrum***or***

○**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☐ FCAS/MWS overlap ☐ MWS ☐ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID

b) _____

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	○	○

This score applies to

○ all diseases in the CAPS spectrum***or***

○**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☐ FCAS/MWS overlap ☐ MWS ☐ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID

Q5 Inflammatory markers

a) Elevated CRP or SAA with clinical disease activity

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	○	○

This score applies to

○ all diseases in the CAPS spectrum***or***

○**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☐ FCAS/MWS overlap ☐ MWS ☐ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID

b) Elevated CRP or SAA without clinical disease activity in symptom free interval

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	○	○

This score applies to

○ all diseases in the CAPS spectrum***or***

○**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☐ FCAS/MWS overlap ☐ MWS ☐ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID

c) other: _____

I consider this variable	**not** relevant	often**not** relevant	undecided	**often** relevant	**very** relevant
	○	○	○	○	○

This score applies to

○ all diseases in the CAPS spectrum***or***

○**only some** diseases in the CAPS spectrum, *pleasecheck **all** applicable*

☐ FCAS ☐ FCAS/MWS overlap ☐ MWS ☐ MWS/CINCA/NOMID overlap ☐ CINCA/NOMID