Arthritis & Rheumatology
Vol. 0, No. 0, Month 2022, pp 1–17
DOI 10.1002/art.42087

American College of Rheumatology
Empowering Rheumatology Professionals

The 2021 European Alliance of Associations for Rheumatology/American College of Rheumatology Points to Consider for Diagnosis and Management of Autoinflammatory Type I Interferonopathies: CANDLE/PRAAS, SAVI, and AGS

Kader Cetin Gedik,[1] Lovro Lamot,[2] Micol Romano,[3] Erkan Demirkaya,[3] David Piskin,[4] Sofia Torreggiani,[5] Laura A. Adang,[6] Thais Armangue,[7] Kathe Barchus,[8] Devon R. Cordova,[9] Yanick J. Crow,[10] Russell C. Dale,[11] Karen L. Durrant,[12] Despina Eleftheriou,[13] Elisa M. Fazzi,[14] Marco Gattorno,[15] Francesco Gavazzi,[16] Eric P. Hanson,[17] Min Ae Lee-Kirsch,[18] Gina A. Montealegre Sanchez,[1] Bénédicte Neven,[19] Simona Orcesi,[20] Seza Ozen,[21] M. Cecilia Poli,[22] Elliot Schumacher,[8] Davide Tonduti,[23] Katsiaryna Uss,[1] Daniel Aletaha,[24] Brian M. Feldman,[25] Adeline Vanderver,[26] Paul A. Brogan,[13] and Raphaela Goldbach-Mansky[1]

Objective. Autoinflammatory type I interferonopathies, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature/proteasome-associated autoinflammatory syndrome (CANDLE/PRAAS), stimulator of interferon genes (STING)–associated vasculopathy with onset in infancy (SAVI), and Aicardi-Goutières syndrome (AGS) are rare and clinically complex immunodysregulatory diseases. With emerging knowledge of genetic causes and targeted treatments, a Task Force was charged with the development of "points to consider" to improve diagnosis, treatment, and long-term monitoring of patients with these rare diseases.

Methods. Members of a Task Force consisting of rheumatologists, neurologists, an immunologist, geneticists, patient advocates, and an allied health care professional formulated research questions for a systematic literature review. Then, based on literature, Delphi questionnaires, and consensus methodology, "points to consider" to guide patient management were developed.

Results. The Task Force devised consensus and evidence-based guidance of 4 overarching principles and 17 points to consider regarding the diagnosis, treatment, and long-term monitoring of patients with the autoinflammatory interferonopathies, CANDLE/PRAAS, SAVI, and AGS.

Conclusion. These points to consider represent state-of-the-art knowledge to guide diagnostic evaluation, treatment, and management of patients with CANDLE/PRAAS, SAVI, and AGS and aim to standardize and improve care, quality of life, and disease outcomes.

This article is published simultaneously in *Annals of the Rheumatic Diseases*.

Supported by the European Alliance of Associations for Rheumatology/American College of Rheumatology, and supported in part by the intramural research program of the NIH (National Institute of Allergy and Infectious Diseases [Drs. Cetin Gedik and Goldbach-Mansky], National Human Genome Research Institute, and National Institute of Arthritis and Musculoskeletal and Skin Diseases), the Deutsche Forschungsgemeinschaft (grant CRC237 369799452/B21 to Dr. Lee-Kirsch), the Autoinflammatory Alliance, and the Systemic JIA Foundation.

[1]Kader Cetin Gedik, MD, Gina A. Montealegre Sanchez, MD, Katsiaryna Uss, Raphaela Goldbach-Mansky, MD: National Institute of Allergy and Infectious Diseases, NIH, Bethesda, Maryland; [2]Lovro Lamot, MD, PhD: University of Zagreb School of Medicine, Zagreb, Croatia; [3]Micol Romano, MD, Erkan Demirkaya, MD: University of Western Ontario, London, Ontario, Canada; [4]David Piskin, MD: University of Western Ontario, London Health Sciences Center, and Lawson Health Research Institute, London, Ontario, Canada; [5]Sofia Torreggiani: National Institute of Allergy and Infectious Diseases, NIH, Bethesda, Maryland, and UOC Pediatria a Media Intensità di Cura, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [6]Laura A. Adang, MD, PhD: Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; [7]Thais Armangue, MD, PhD: Sant Joan de Deu Children's Hospital and IDIBAPS–Hospital Clinic; University of Barcelona, Barcelona, Spain; [8]Kathe Barchus, Elliot Schumacher: Autoinflammatory Alliance, San Francisco, California; [9]Devon R. Cordova: Aicardi-Goutieres Syndrome Americas Association, Manhattan Beach, California; [10]Yanick J. Crow, PhD: University of Edinburgh, Edinburgh, UK, and Laboratory of Neurogenetics and Neuroinflammation, Institut Imagine, University of Paris, Paris, France; [11]Russell C. Dale, MD: University of Sydney, Sydney, New South Wales, Australia;

INTRODUCTION

Autoinflammatory type I interferonopathies are genetically defined (monogenic or digenic) immunodysregulatory disorders characterized by the presence of a type I interferon (IFN) signature in peripheral blood and variable systemic inflammation (1–3). In this expanding group of ultra-rare diseases, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature/proteasome-associated autoinflammatory syndrome (CANDLE/PRAAS), stimulator of interferon genes (STING)–associated vasculopathy with onset in infancy (SAVI), and Aicardi-Goutières syndrome (AGS) are the most common.

Patients with type I interferonopathies present early in life often within the first week of life; prenatal onset has been reported in patients with AGS. However, late-onset cases presenting at ages 14, 18, and 5.6 years with CANDLE/PRAAS, SAVI, and AGS, respectively, have been reported (4–11). Despite CANDLE/PRAAS, SAVI, and AGS having distinct clinical phenotypes of varying disease severity, the individual clinical manifestations of these diseases can overlap, and all are associated with high morbidity and mortality if untreated (4–12). Recent advances in the genetic description of these disorders permit better characterization of disease-specific clinical manifestations, and provide evidence supporting the pathogenic role of type I IFN signaling (1,2,12,13). These developments prompted the Task Force led by the steering committee (2 convenors [PAB, RG-M], a neurologist [AV], 2 methodologists [BMF, ED], and 3 pediatric rheumatologists/European Alliance of Associations for Rheumatology [EULAR] fellows [KCG, LL, MR] and a rheumatologist [ST]) to review the existing data and develop consensus statements, with the aim of formulating state-of-the-art guidance on the diagnosis, treatment, and long-term monitoring of patients with these rare diseases.

Thus, the objective of this project was to develop points to consider for the diagnosis, treatment, and long-term monitoring of patients with CANDLE/PRAAS, SAVI, and AGS.

The Task Force targets its guidance to pediatricians, internists, and subspecialists involved in the care of patients with autoinflammatory type I interferonopathies and to patients and caregivers. These points to consider were developed not only to provide a resource for physicians to facilitate management but also for policy makers governing who has a role in authorizing patients' access to various diagnostic tools and treatment options, all with the ultimate goal to harmonize the level of care and to improve quality of life and disease outcomes in this patient population.

METHODS

The EULAR (14) and the American College of Rheumatology (ACR) standardized operating procedures were followed during the project period (see Supplementary Methods, on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42027). With approval from the EULAR and ACR Executive Committees, an international Task Force consisting of worldwide recognized experts from North America, South America, Europe, and Australia convened to develop points to consider for the diagnosis, treatment, and long-term monitoring of 3 type I interferonopathies: CANDLE/PRAAS, SAVI, and AGS. The Task Force members were selected based on expertise in treatment and care of these patients.

A face-to-face meeting in August 2019 defined the goal of the project and the target population. Then, the Task Force developed research questions related to diagnosis, treatment, and long-term monitoring of these diseases using the Population, Intervention, Comparison, Outcome (PICO) format. Search terms were derived from PICO questions and a systematic literature review (SLR) was performed by 3 research fellows (KCG, MR, LL), with support from a librarian (Darren Hamilton, London Health Sciences Center, London, Ontario, Canada), an epidemiologist (DP), and a senior methodologist (ED) to identify relevant literature published before September 2020.

Two rounds of pre–consensus meeting questionnaires, using the Delphi technique (15), including questions pertaining to diagnosis, treatment, and long-term monitoring, were sent to all Task Force members to indicate their agreement with each question or statement with yes/no using the Delphi technique; the Delphi questionnaire was sent to 28 Task Force members, of whom 22 were voting members. The Task Force members were asked to indicate their agreement with each statement, and a free text option was provided to capture every member's comment for each statement. Draft statements and items in questions with 80% or higher agreement were retained for voting at the

[12]Karen L. Durrant, RN: Autoinflammatory Alliance and Kaiser San Francisco Hospital, San Francisco, California; [13]Despina Eleftheriou, PhD, Paul A. Brogan, PhD: University College London, London, UK; [14]Elisa M Fazzi, PhD: ASST Civil Hospital and University of Brescia, Brescia, Italy; [15]Marco Gattorno, MD: IRCCS Istituto Giannina Gaslini, Genoa, Italy; [16]Francesco Gavazzi, MD, PhD: Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, and University of Brescia, Brescia, Italy; [17]Eric P. Hanson, MD: Riley Hospital for Children and Indiana University School of Medicine, Indianapolis; [18]Min Ae Lee-Kirsch, PhD: Technische Universität Dresden, Dresden, Germany; [19]Bénédicte Neven, MD: Necker Children's Hospital, AP-HP, Institut Imagine Institut des Maladies Genetiques, University of Paris, Paris, France; [20]Simona Orcesi, MD: IRCCS Mondino Foundation and University of Pavia, Pavia, Italy; [21]Seza Ozen, MD: Hacettepe University, Ankara, Turkey; [22]M. Cecilia Poli, MD, PhD: Universidad del Desarrollo, Santiago, Chile; [23]Davide Tonduti, MD: V. Buzzi Children's Hospital, Milan, Italy; [24]Daniel Aletaha, MD: Medical University of Vienna, Vienna, Austria; [25]Brian M. Feldman, MD: Hospital for Sick Children and University of Toronto Institute of Health Policy Management and Evaluation, Toronto, Ontario, Canada; [26]Adeline Vanderver, MD: Children's Hospital of Philadelphia and University of Pennsylvania, Philadelphia.

Drs. Cetin Gedik, Lamot, and Romano contributed equally to this work.

Address correspondence to Raphaela Goldbach-Mansky, MD, Translational Autoinflammatory Diseases Section, Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, Maryland. Email: goldbacr@mail.nih.gov.

Submitted for publication November 7, 2021; accepted in revised form January 11, 2022.

consensus meetings. Statements and items in questions that did not reach a greater than 80% consensus were reviewed and reworded and sent out in a second round of the Delphi questionnaire. The original and the revised/modified draft statements with the previously achieved level of agreement and the participants' comments were included in the second survey. A free text option to capture comments and additional items was again included. Draft statements with 80% or higher agreement were retained for voting at the consensus meetings, and statements which did not achieve 80% agreement were marked for further discussion and refinement at the 2 consensus meetings. Responses were anonymous.

Based on the SLR findings and 2 pre–consensus meeting Delphi questionnaires, draft statements were refined by the steering group and were sent to the voting members prior to the consensus meetings. These draft statements were reviewed, discussed, revised, and voted on in 2 consensus meetings that were held online in October 2020 due to the COVID-19 pandemic, one for CANDLE/PRAAS and SAVI, and one for AGS.

Two conveners (RG-M, PAB), 3 methodologists (BMF, ED, DA), 3 fellows, an allied health professional, and 3 disease experts attended both consensus meetings and, otherwise, participation was based on disease-specific expertise. The voting panel included 19 experts, 1 allied health professional, and 1 patient representative for each disease. The joint statements addressing all 3 interferonopathies were voted on by the entire voting panel; CANDLE/SAVI-specific statements were voted on by 10 experts, 1 allied health professional, 1 SAVI, and 1 CANDLE/PRAAS patient presentative, and AGS-specific statements were voted on by 14 experts, 1 allied health professional, and 1 AGS patient representative. During the meetings, statements that achieved at least 80% agreement were accepted; statements with <80% were discussed a final time in a Nominal Groups round robin discussion (https://www.cdc.gov/healthyyouth/evaluation/pdf/brief7.pdf) and were only accepted if the revised statement reached an 80% agreement.

The Oxford Levels of Evidence (LoE) were applied to each point to consider (16). The strength of each statement ranged from A (directly based on level I evidence) to D (directly based on level IV evidence or extrapolated recommendations from level I, II, or III evidence) (16). Finally, the finalized statements were circulated in a post–consensus meeting Delphi questionnaire to determine level of agreement (LoA). Members of the Task Force were asked to provide their final LoA for each point to consider using a scale of 0 (completely disagree) to 10 (completely agree), which is reported in the tables below.

RESULTS

Systematic literature review

A summary of the literature search strategy and results is provided in the Supplementary Methods (https://onlinelibrary.wiley.com/doi/10.1002/art.42027). Based on SLR and consensus conferences, 4 overarching principles and 17 disease-specific points to consider pertaining to the genetically defined interferonopathies (Table 1) with their respective LoE, grade of recommendation, and LoA were generated (17).

Overarching principles guiding the management of patients with CANDLE/PRAAS, SAVI, and AGS

The systemic inflammatory multiorgan involvement in patients with CANDLE/PRAAS, SAVI, or AGS can ultimately result in progressive organ injury and early mortality (4). Damage accrues over time, often manifesting later in life, thus highlighting the importance of early diagnosis and treatment (1,12).

Autoinflammatory syndromes may present with phenotypic overlap early in life, which poses diagnostic challenges (12). In addition, mutations in individual genes may be associated with considerable phenotypic heterogeneity and variable disease severity (18,19). Genetic confirmation is thus essential for making a precise diagnosis which then facilitates targeted therapy and initiation of genetic counseling with the goal of achieving better clinical outcomes. Patients, their parents, and siblings should have access to formal genetic counseling. Genetic counseling can initiate the risk assessment process depending on the type of inheritance for specific disease-causing mutations and help patients understand their test results, including the medical implications for themselves, their reproductive health concerns, and impact on their relatives. Patients with clinical symptoms of CANDLE/PRAAS, SAVI, or AGS who do not harbor any of the disease-causing mutations described here should be referred to specialty/research centers that can guide further workup and treatment. There is no cure for type I interferonopathies. Current treatment options therefore aim to prevent development or progression of end organ damage by controlling systemic and organ inflammation (20,21), to improve quality of life, and to improve disease outcomes (1). Given the paucity of long-term outcome data on newly available treatments, monitoring of disease activity and development of organ-specific and treatment-related complications is essential (1,22,23). A multidisciplinary team is required to provide optimal care in the context of multiorgan system involvement (24,25).

Points to consider 1–8: diagnostic evaluation focuses on raising an early suspicion and on facilitating genetic testing, appropriate clinical and laboratory workup, and early treatment

Diagnostic evaluation. The presence of a chronically elevated peripheral blood IFN signature is a common finding in patients with the type I interferonopathies CANDLE/PRAAS, SAVI, and AGS. In contrast, traditional inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate are

Table 1. Points to consider for the diagnosis, treatment, and long-term monitoring of patients with type I interferonopathies, CANDLE/PRAAS, SAVI, and AGS*

	LoE and GoR, C/S/AGS†	LoA (0–10), mean ± SD
Overarching principles		
A. Patients with autoinflammatory interferonopathies CANDLE/PRAAS, SAVI, or AGS present with chronic systemic and organ-specific inflammation; when untreated, chronic inflammation results in progressive organ damage, early morbidity, and increased mortality.	4C/4C/4C	9.8 ± 0.7
B. A confirmed genetic diagnosis is required to make the diagnosis of CANDLE/PRAAS, SAVI, and AGS, which facilitates initiation of targeted treatments, genetic counseling, screening for complications, and informs prognosis.	5D/5D/4C	9.5 ± 1.0
C. The goal of treatment of type I interferonopathies is to reduce systemic and organ inflammation to prevent or limit the development of and/or the progression of organ injury and damage, and to improve quality of life.	2B/2B/2B	9.8 ± 0.5
D. In CANDLE/PRAAS, SAVI, or AGS, long-term monitoring of disease activity, organ-specific injury/damage and of treatment related complications is required and involves a multidisciplinary team.	5D/5D/4C	9.9 ± 0.3
Individual points to consider		
I. Points to consider for diagnostic evaluation		
1. Patients presenting with unexplained systemic inflammation (including elevations of CRP, ESR, and/or an IFN signature) and clinical features‡ that include rashes, lipodystrophy, musculoskeletal, neurologic, pulmonary, and metabolic findings should receive a prompt diagnostic workup for CANDLE/PRAAS, SAVI, and AGS comprising: • Genetic evaluation. • Clinical evaluation focusing on the extent of inflammatory organ involvement. • Screening for disease-related comorbidities.	4C/4C/4C	9.8 ± 0.7
2. Patients with clinical symptoms of CANDLE/PRAAS, SAVI, or AGS who do not carry any of the disease-causing mutations described here should be referred to specialty/research centers that can guide further workup and treatment.	5D/5D/5D	9.8 ± 0.5
Genetic evaluation		
3. Mutations in the following disease-causing genes should be included in the genetic analyses: • CANDLE/PRAAS: *PSMB8*, *PSMA3, PSMB4*, *PSMB9*, *PSMB10*, *POMP*, and *PSMG2*. • SAVI: *STING1* (previously *TMEM173*). • AGS: *TREX1*, *RNASEH2A, RNASEH2B*, *RNASEH2C*, *SAMHD1*, *ADAR1*, *IFIH1, LSM11*§, and *RNU7-1*§.	4C/4C/4C	9.8 ± 0.6
4. Genetic mimics of CANDLE/PRAAS, SAVI, and AGS are recognized and should be included in the diagnostic workup (a non-exhaustive list is below for reference): • For CANDLE-like conditions: splice variants in *IKBKG*, frameshift mutations in *SAMD9L*, and recessive mutations in *RNASEH2* (*A*, *B*, *C*). • For SAVI-like conditions: *TREX1*, *ADA2*, and *COPA*. • For AGS-like conditions: *RNASET2*.	4C/4C/4C	9.4 ± 0.9
Clinical evaluation (see also Tables 3 and 4)		
5. In patients with suspected CANDLE/PRAAS, SAVI, or AGS, assessment for disease- and treatment-related comorbidities should include screening for: • *Skin manifestations*: nodular rashes, violaceous annular rashes, panniculitis, lipodystrophy, or vasculopathic skin lesions. • *Neurologic manifestations*: intracerebral calcifications, leukoencephalopathy, progressive microcephaly, or cerebral atrophy. • *Pulmonary manifestations*: interstitial lung disease/pulmonary hypertension. • *Hepatic manifestations*: hepatic steatosis, hepatitis, hepatosplenomegaly. • *Metabolic manifestations*: hypertension, hyperlipidemia, glucose intolerance (=metabolic syndrome). • *Musculoskeletal manifestations*: arthritis, contractures, and myositis. • *Growth and development*: growth retardation, osteoporosis, bone development delay, pubertal delay. • *Hematologic manifestations*: cytopenias (e.g., more specifically lymphopenia, thrombocytopenia). • *Ophthalmologic manifestations*: episcleritis, keratitis, retinopathy, glaucoma. • *Cardiac manifestations*: cardiomyopathy.	4C/4C/4C	9.7 ± 0.6
6. Neuroimaging should be performed in individuals with suspected neurologic symptoms. • MRI best identifies white and grey matter changes. • CT is generally more sensitive for detecting cerebral calcification and can be considered when calcium-sensitive modalities on MRI are not available or do not detect calcifications.	4C/4C/4C	9.8 ± 0.4
7. In patients with presumed CANDLE/PRAAS, SAVI, or AGS, tissue sampling as appropriate (e.g., CSF if neurologic involvement is suspected, or lesional skin biopsies) may support the diagnosis.	4C/4C/4C	9.4 ± 1.1
8. All patients should undergo a basic immunodeficiency workup that includes a history of infections, lymphocyte subsets, and immunoglobulin levels, as a minimum.	4C/4C/4C	9.3 ± 1.5

(Continued)

Table 1. (*Cont'd*)

	LoE and GoR, C/S/AGS†	LoA (0–10), mean ± SD
II. Points to consider for treatment		
9. Treatment of patients with CANDLE/PRAAS, SAVI, and AGS should be aimed at achieving disease control or low disease activity to prevent progression of organ damage.	2B/2B/2B	9.4 ± 1.2
For patients with SAVI and CANDLE/PRAAS, disease control should be maintained with the lowest possible dose of glucocorticoids.	4C/4C/NA	
10. JAKIs are of benefit for improving symptoms¶ in CANDLE/PRAAS, SAVI, and AGS.	2B/2B/2B	9.3 ± 0.9
11. In patients with CANDLE/PRAAS, SAVI, or AGS on JAKI, screening for treatment-related comorbidities is important. We currently recommend monitoring for BK viral loads in urine and blood to prevent viral organ injury such as nephropathy.	4C/4C/5D	9.3 ± 1.6
12. Glucocorticoids are of benefit for improving symptoms¶ in CANDLE/PRAAS or SAVI. Chronic glucocorticoids do not improve the neurologic features of AGS although acute courses of glucocorticoids may be useful for the treatment of non-CNS inflammatory conditions.	4C/4C/5D	9.0 ± 1.3
III. Points to consider for long-term monitoring and management		
Disease related comorbidities and disease progression		
13. A multidisciplinary management team is required for optimal care of patients with CANDLE/PRAAS, SAVI, and AGS, that is customized based on patient's disease manifestations.	5D/5D/5D	9.9 ± 0.3
14. Disease activity and burden of disease should be monitored regularly depending on disease activity and severity (see Table 4).	5D/5D/5D	9.3 ± 1.8
• Symptom control can be monitored by assessing disease-specific symptoms¶ using validated patient reported outcome and quality of life assessments, and by recording missing school or workdays.	5D/5D/5D	
15. Disease and development of children should be monitored at each visit.	5D/5D/5D	9.8 ± 0.4
Risk of COVID-19		
16. At the time of writing, there is no evidence to suggest that risks to patients with CANDLE/PRAAS, SAVI, or AGS of COVID-19 are any different from the healthy population. Therefore, treatment for interferonopathy should not be stopped unless a specific contraindication to ongoing treatment arises.	5D/5D/5D	9.5 ± 0.8
Vaccinations		
17. Generally, for CANDLE/PRAAS and SAVI all routine vaccines (live and killed) are indicated when not receiving immunosuppressive treatments or glucocorticoids, although this should be considered on a case-by-case basis.	5D/5D/5D	9.4 ± 0.9

* CANDLE/PRAAS = chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature/proteasome-associated autoinflammatory syndrome; SAVI = STING-associated vasculopathy with onset in infancy; AGS = Aicardi-Goutières syndrome; LoA = level of agreement; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IFN = interferon; MRI = magnetic resonance imaging; CT = computed tomography; CSF = cerebrospinal fluid; NA = not applicable; JAKIs = Janus kinase inhibitors; CNS = central nervous system.
† Level of evidence (LoE) is classified as follows: 1a = systematic review of randomized controlled trials (RCTs); 1b = individual RCT; 2a = systematic review of cohort studies; 2b = individual cohort study (including low-quality RCT); 3a = systematic review of case–control studies; 3b = individual case–control study; 4 = case-series (and poor-quality cohort and case–control studies); 5 = expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles." Grade of recommendation (GoR) is classified as follows: A = based on consistent level 1 studies; B = based on consistent level 2 or 3 studies or extrapolations from level 1 studies; C = based on level 4 studies or extrapolations from level 2 or 3 studies; D = based on level 5 studies or on troublingly inconsistent or inconclusive studies of any level. LoE and GoR are reported separately for CANDLE/PRAAS (C), SAVI (S), and AGS (A).
‡ Disease-characteristic clinical features are listed in Table 3.
§ These 2 genes were published after the consensus meeting occurred.
¶ Clinical symptoms are listed in Table 3 and Table 4.

typically elevated in CANDLE/PRAAS and SAVI but rarely in patients with AGS (2,7,12,18,26–30). A peripheral blood IFN signature may be measured using different methodologies, including a 28-gene IFN scoring system using NanoString technology or by quantitative reverse transcriptase polymerase chain reaction methods. Gene subsets should be measured repeatedly to establish chronic elevation (13). Scores may be negative in the diagnostic phase in patients with milder disease, or in response to glucocorticoid treatment. In addition, patients with AGS with *RNASEH2B* mutations may have a negative IFN signature even with active disease (31). A practical barrier is the limited number of centers with the ability to check an IFN signature. Thus, a chronically elevated peripheral blood IFN signature is not required for diagnosis but can be very useful in raising the suspicion of an interferonopathy. For most IFN signatures, sensitivity and specificity data are not available. However, in a retrospective study, the IFN signature at a set cut-off score was helpful in differentiating patients with an interferonopathy from healthy controls and from patients with cryopyrin-associated periodic syndrome (an interleukin-1–mediated autoinflammatory disease). The IFN signature demonstrated an area under the receiver operator characteristic curve of 0.98, with sensitivity and specificity exceeding 0.8 (12). Currently, the IFN signature should be interpreted in the context of normal values of the laboratory that conducts the test, since no internationally standardized methodologies or reference ranges are currently available.

Genetic evaluation. As there can be significant overlap of clinical features across several autoinflammatory disorders, a confirmed genetic diagnosis is critical to facilitating a precision medicine approach and targeted therapy. Next-generation sequencing (e.g., targeted gene panel, whole exome or whole genome sequencing) to screen for pathogenic variants rather than single-gene Sanger sequencing is recommended. Sanger sequencing of individual genes may still be cost effective in patients with known familial disease, and may be the only available option if next-generation sequencing is not yet available to the patient. However, this increasingly outdated "gene by gene" approach ultimately may result in diagnostic delay and may not be cost-effective (32). In addition to the known disease-causing genes (1,2,5,7,12,18,31,33–39) (Table 1), screening should be considered for diseases that can mimic one of these disorders; their genetic causes (8,12,40–45) are listed in Table 2. Allelic, monogenic or digenic, double heterozygous mutations in genes encoding proteasome or immunoproteasome subunits are the cause for CANDLE/PRAAS, with biallelic pathogenic *PSMB8* variants being the most common cause. Digenic disease-causing mutations including *PSMB8*, *PSMA3*, *PSMB4*, and *PSMB9* (1,2,26), compound heterozygous mutations including *PSMB4*, *PSMB8i*, and *PSMG2* (2,12), and autosomal dominant loss-of-function mutations in *POMP* (2) also cause CANDLE/PRAAS but are rarer. However, novel disease-causing genes are being added as causes for CANDLE/PRAAS. All proteasome genes should be specifically assessed in a patient with a suggestive clinical phenotype. Both parents may need to be tested to confirm digenic inheritance. The inheritance of SAVI is mostly autosomal dominant, and most patients harbor a de novo heterozygous missense mutation in the *STING1* gene that confers a gain-of-function by increasing TANK-binding kinase 1–mediated IRF3 phosphorylation and *IFNB1* transcription (7,46). Liu et al also reported somatic mosaic mutations in one patient (OMIM-615934). So far only additive *STING1* gain-of-function mutations in p.R284W require homozygosity to confer disease (47). Furthermore, mostly loss-of-function mutations in genes encoding proteins that regulate nucleic acid metabolism or signaling cause AGS (34). These include biallelic null mutations in *TREX1* and *SAMHD1*; biallelic null mutations in the disease-causing genes, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, or *ADAR1* have not been reported. Disease-causing *IFIH1* variants are all heterozygous gain-of-function mutations that increase type I IFN signaling (34). Recently, biallelic mutations in *LSM11* and *RNU7-1*, which encode components of the replication-dependent histone pre-mRNA–processing complex, extend defects in nucleic acid metabolism to histone mRNAs (48). It is important to note that large deletions, such as deletions in AGS-related genes including *SAMHD1*, may be missed on exome sequencing and need to be reviewed using other testing modalities (31,49,50). If, following routine genetic workup, a molecular diagnosis is not established in a patient with suggestive phenotypic features, referral to a research center of excellence for further evaluation should be considered.

Table 2. List of genetically defined diseases and genes that should be considered in the differential diagnosis of CANDLE/PRAAS, SAVI, and AGS*

Genetically defined diseases	Genes
CANDLE/PRAAS mimics/overlaps	
Differential diagnoses:	
• NEMO deleted exon 5 autoinflammatory syndrome (NEMO-NDAS)	*IKBKG* (exon 5 deletion/splice variant)
• SAMD9L associated autoinflammatory disease (SAAD)	*SAMD9L* (frameshift mutations)
• Other	*RNASEH2B*
SAVI mimics/overlaps	
Differential diagnoses:	
• Deficiency of the enzyme adenosine deaminase 2 (DADA2)	*ADA2*
• Familial chilblain lupus (CHBL)	*TREX1*, *SAMHD1*
• COPA syndrome	*COPA*
AGS mimics/overlaps	
Differential diagnoses:	
• Other	*RNASET2*
Other disorders with partially overlapping phenotypes	
Differential diagnoses:	
• Spondyloenchondrodysplasia (SPENCD)	*ACP5*
• Singleton Merten syndromes	*IFIH1*, *DDX58*
• Retinal vasculopathy with cerebral leukodystrophy (RVCL)	*TREX1*
• Trichohepatoenteric syndrome (THES)	*TTC37*, *SKIV2L*
• Lipopolysaccharide responsive and beige-like anchor protein (LRBA) deficiency	*LRBA*
• Monogenic early onset lupus	e.g., *C1Q* (*A*, *B*, *C*), several others

* Based on current evidence, all type I interferonopathies, including but not limited to the genetically defined diseases listed in the table, should be considered in the differential diagnosis of chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature/proteasome-associated autoinflammatory syndrome (CANDLE/PRAAS), STING-associated vasculopathy with onset in infancy (SAVI), or Aicardi-Goutières syndrome (AGS) because of overlapping clinical and laboratory features.

Table 3. Clinical features suggestive of CANDLE/PRAAS, SAVI, and AGS*

Systemic inflammation	
CANDLE/PRAAS, SAVI, AGS	*Clinical features*: Recurrent fever, hepatosplenomegaly *Laboratory features*: Elevated CRP, ESR, and IFN signature
Skin manifestations	
CANDLE/PRAAS	Neutrophilic panniculitis, nodular rashes, violaceous annular rashes, lipodystrophy
SAVI	Vasculopathy (i.e., chilblain lesions, acral ischemia ranging from Raynaud's phenomenon to gangrene), loss of digits
AGS	Chilblain lesions, acral lesions (including Raynaud's phenomenon), panniculitis
Neurologic manifestations	
CANDLE/PRAAS	*Clinical features*: Headache, cognitive impairment *Lumbar puncture*: Sterile pleocytosis *Neuroimaging*: Basal ganglia calcifications
SAVI	*Neuroimaging*: Basal ganglia calcifications (rare)
AGS	*Clinical features*: Subacute or acute onset of neurologic symptoms including developmental delay, irritability, neurologic impairment or regression, dystonia and spasticity, focal motor findings, progressive microcephaly, seizures *Lumbar puncture*: Sterile pleocytosis, elevated CSF neopterin and tetrahydrobiopterin, elevated IFNα *Neuroimaging*: leukoencephalopathy, cerebral calcifications, early and rapid cerebral atrophy with or without calcification, Moyamoya disease†
Pulmonary manifestations	
CANDLE/PRAAS	Pulmonary hypertension without fibrosis
SAVI	Interstitial lung disease with or without secondary pulmonary hypertension
AGS	Pulmonary hypertension
Hepatic manifestations	
CANDLE/PRAAS	Elevated transaminases, hepatic steatosis
AGS	Elevated transaminases, autoimmune hepatitis
Metabolic and endocrine manifestations	
CANDLE/PRAAS	Hypertension, hyperlipidemia, glucose intolerance (=metabolic syndrome)
AGS	Hypothyroidism, diabetes insipidus, diabetes
Musculoskeletal manifestations	
CANDLE/PRAAS, SAVI, AGS	Myositis
CANDLE/PRAAS, SAVI, AGS	Arthritis, joint contractures
Growth and development	
CANDLE/PRAAS, SAVI, AGS	Growth retardation, osteoporosis, bone development delay, pubertal delay
Hematologic manifestations	
CANDLE/PRAAS, SAVI, AGS	Anemia, leukopenia, lymphopenia, and/or thrombocytopenia
Ophthalmologic manifestations	
CANDLE/PRAAS	Episcleritis and keratitis
SAVI, AGS	Retinopathy, glaucoma
Cardiac manifestations	
AGS	Cardiomyopathy, valve calcifications

* CANDLE/PRAAS = chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature/proteasome-associated autoinflammatory syndrome; SAVI = STING-associated vasculopathy with onset in infancy; AGS = Aicardi-Goutières syndrome; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IFN = interferon; CSF = cerebrospinal fluid.
† Vasculopathy characterized by progressive narrowing of the terminal intracranial portion of the internal carotid artery and circle of Willis.

Clinical evaluation. In patients with undifferentiated autoinflammatory diseases or otherwise unexplained systemic inflammation, certain clinical features are suggestive of CANDLE/PRAAS, SAVI, or AGS (Tables 1 and 3).

The following clinical features are relevant to the workup of patients with suspected interferonopathies:

Cutaneous manifestations. Inflammatory skin lesions are present in all 3 diseases; however, the nature of the rash differs. Nodular rashes or violaceous annular rashes should prompt a diagnostic workup for CANDLE/PRAAS. Another specific cutaneous finding for CANDLE/PRAAS is panniculitis (particularly neutrophilic panniculitis) and panniculitis-induced lipodystrophy, which are hallmarks of the disease (1,2,9,12, 18,36,37,51).

The presence of vasculopathic skin lesions such as pernio ("chilblain lesions") or acral ischemia presenting as Raynaud's phenomenon, and/or "purple toes" is suggestive of SAVI (7,44,47) and AGS (33,52–55); the development of gangrene with prolonged ischemic attacks is a feature of SAVI (1,7,44) (Table 3). Skin involvement is the most common symptom in patients with SAVI at presentation (1,7,56–59) but some patients can present with severe lung disease and only minimal skin involvement (8,46,60,61).

In addition to chilblain-like lesions and acrocyanosis, other skin manifestations, such as periungual erythema, or necrotic lesions of the toes, fingers, and outer helix, can be seen in patients with AGS (33,52–55). Moreover, some patients with AGS can have panniculitis as well (34). Finally, some patients with AGS have recurrent oral ulcers (50,62).

Table 4. Evaluation of inflammatory disease manifestations and organ involvement with proposed interval monitoring*

		Follow-up frequency
A. Monitoring of systemic inflammation and development		
	ESR, CRP, CBC with differential (cytopenias), IFN signature when available	At each visit†
	Urinalysis (proteinuria, renal disease)	At each visit†
	Renal ultrasound	To consider at baseline
	Hepatosplenomegaly and lymphadenopathy	At each visit†
	Height and weight	At each visit†
	DEXA scan‡ (BMD)	As clinically indicated
	Sexual development	As clinically indicated
B. Monitoring of clinical disease signs and symptoms		
CANDLE/PRAAS		
	Fever, rash, progressive lipodystrophy, headache, musculoskeletal symptoms (joint pain, contractures, weakness), shortness of breath, weight changes, developmental assessment, fatigue	At each visit†
SAVI		
	Fever, rash, peripheral acral vasculitis and dystrophic changes, respiratory symptoms (shortness of breath, tachypnea, digital clubbing), fatigue	At each visit†
AGS		
	Developmental assessment, changes in neurologic tone affecting joint integrity, skin findings, musculoskeletal findings, clinical evidence of cytopenias, endocrine disturbance, ocular abnormalities, or cardiomyopathy	At each visit†
C. Monitoring of organ manifestations		
CANDLE/PRAAS		
Skin disease	Skin exam, assessment of lipodystrophy	Every 3–6 months till stable then every 6–12 months
	Lesional skin biopsy (neutrophilic panniculitis)	Baseline only
Musculoskeletal disease	Arthritis, contractures, weakness	Every 6-12 months
	CK, aldolase, LDH for myositis	
Endocrine, metabolic disease‡	Metabolic syndrome	Every 12–36 months depending on symptoms
	Lipid profile (dyslipidemia), fasting glucose, hemoglobin A1C, serum insulin (insulin resistance)	At each visit†
	BP measurement (systemic hypertension)	At each visit†
Hepatic disease‡	ALT, AST, GGT, liver elastography, or screening for hepatic steatosis with the best available method	Every 6–12 months
Pulmonary arterial hypertension‡	Echocardiography, cardiology and/or pulmonology referral if signs of PAH	Every 6–12 months, if PAH then as clinically indicated
CNS disease‡	Lumbar puncture (if headaches), brain MRI	Every 12–36 months depending on symptoms
Eye disease‡	Scleritis, episcleritis, keratitis	Yearly or based on clinical need
Dental disease	Tooth abnormalities (tooth agenesis, hypodontia), delayed tooth eruption	Yearly or based on clinical need
SAVI		
Skin disease	Wound care (including wound culture as necessary)	As needed
Pulmonary disease‡	Low radiation chest CT	At baseline and then as needed
	PFTs	Every 3–6 months
	Pulmonology referral	If signs of ILD: as needed
AGS		
Neurologic damage/ progression‡	Brain MRI (cerebral white and grey matter changes)	At baseline and then as needed
	MRI/MRA in patients with *SAMHD1*-associated AGS (intracerebral vasculitis)	At baseline and then as needed
	Electroencephalogram (epilepsy)	Yearly
	Muscle MRI or ultrasound (myositis)	As needed
Hepatic disease‡	ALT, AST, GGT, bilirubin total and direct, albumin, and INR (autoimmune hepatitis)	Every 6–12 months

(Continued)

Table 4. (*Cont'd*)

		Follow-up frequency
Endocrinopathies	TSH (hypothyroidism) GH testing and glucose tolerance test	Yearly As needed based on symptoms
Renal disease	Urinalysis	Every 6–12 months
Eye disease‡	Ophthalmologic evaluation (glaucoma)	Yearly
Cardiorespiratory	Echocardiogram (cardiomyopathy and PAH)	Every 1–2 years
Scoliosis, hip dislocation‡	Hip x-rays and spine screening in non-ambulatory patients (hip dislocation)	Every 6–12 months
D. Monitoring of autoimmunity, cytopenias, immunodeficiency, and JAKI-related complications		
Autoimmunity and cytopenias and immunodeficiency	Screening for autoimmunity (autoantibodies as indicated), CBC with differential (screening for anemia, thrombocytopenia, leukopenias) History of infections, lymphocyte subsets, immunoglobulin levels Consider immunology or hematology referral	Every 6–12 months and when indicated At baseline and then every 3–6 months
Infections	Clinical history, viral reactivation (on JAKIs), opportunistic infections	At each visit
JAKI monitoring	CBC with differential, LFTs, urinalysis, renal function, creatinine clearance, BK viral loads in urine and blood, urine β_2-microglobulin	At each visit

* ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; CBC = complete blood count; IFN = interferon; DEXA = dual-energy x-ray absorptiometry; BMD = bone mineral density; CANDLE/PRAAS = chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature/proteasome-associated autoinflammatory syndrome; SAVI = STING-associated vasculopathy with onset in infancy; AGS = Aicardi-Goutières syndrome; CK = creatinine kinase; LDH = lactate dehydrogenase; BP = blood pressure; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyl transferase; PAH = pulmonary arterial hypertension; MRI = magnetic resonance imaging; CT = computed tomography; PFTs = pulmonary function tests; ILD = interstitial lung disease; MRA = magnetic resonance angiography; INR = international normalized ratio; TSH = thyroid-stimulating hormone; GH = growth hormone; JAKI = Janus kinase inhibitor; LFTs = liver function tests.
† The visit frequency is set according to clinical need and the patient's disease activity. If there is no active disease, then patients should be followed every 3 months to assess disease activity and monitor drug toxicity.
‡ Requires subspecialty evaluation.

Lesional skin biopsies in areas that can safely be biopsied can be beneficial in revealing the neutrophilic dermatosis, small vessel vasculitis (from necrotic area), fasciitis (57), and granulomatous nodular dermatitis (59), thus supporting the diagnosis of SAVI while in AGS specifically, a lesional biopsy can demonstrate deposition of immunoglobulin and complement in the walls of small vessels (63).

Neurologic manifestations. Although CANDLE/PRAAS-affected patients present with headaches and may develop aseptic meningitis (24), neurologic findings are most common and severe in AGS and include subacute or acute neurologic decline, unexplained developmental delay, progressive microcephaly, dystonia, spasticity, encephalopathy, irritability, and focal motor findings. A lumbar puncture typically shows sterile cerebrospinal fluid (CSF) pleocytosis (11,64,65).

Neuroimaging should be performed in individuals with a suspected diagnosis of an interferonopathy in the presence of neurologic symptoms. The initial workup may include magnetic resonance imaging (MRI) of the brain which identifies best white and grey matter changes (41). Head computed tomography (CT) should be considered when calcium-sensitive modalities on MRI are not available or not able to detect calcifications, since it is more sensitive for the detection of cerebral calcification (66). Risks and benefits of sedating a child for brain MRI should be considered (67). It is useful to have a baseline brain MRI to assess the severity and to monitor disease-associated complications; however, this is not a diagnostic prerequisite, especially for SAVI and CANDLE/PRAAS. Neuroimaging may be particularly helpful in patients with suspected AGS due to the dominant neurologic phenotype which should be differentiated from mimickers of interferonopathies.

Basal ganglia or other intracerebral calcifications are overlapping neuroimaging findings for all 3 diseases (68); they are more common, more severe, and typically start earlier in life in patients with AGS compared with CANDLE/PRAAS, while calcifications are rare in SAVI (8,41,68,69). In addition, the presence of leukoencephalopathy is suggestive of AGS and typically starts early in life in AGS patients with severe disease; it is unusual in CANDLE/PRAAS or SAVI (11,70,71). Other supportive neuroimaging characteristics for AGS are early and rapid cerebral atrophy with or without calcifications, cerebral white and grey matter changes, and Moyamoya disease (12,41,69,70,72–74). Intracerebral large vessel vasculitis or Moyamoya can be seen and is associated with *SAMHD1* mutations (49,74–77).

Additional workup for neurodegenerative diseases in patients with suspected AGS may also be considered. Lumbar punctures are not required to make the diagnosis of AGS but may support the diagnosis (72) and characterize the immunologic features of the central nervous system (CNS) inflammation, including the presence of lymphocytosis and raised levels of IFNα, CXCL10, and CCL2 in the CSF (31,54,69). The CSF studies are most beneficial if a molecular diagnosis of AGS is not confirmed by genetic testing and provide support for additional molecular testing (72).

Pulmonary manifestations. The presence of early onset interstitial lung disease (ILD) raises suspicion for SAVI, in particular in the context of unexplained systemic inflammation (1,7,46,56,61). Many patients with SAVI are reported to have lung involvement, mostly manifested as ILD, ranging from mild ILD with no respiratory symptoms to lung fibrosis. Also, alveolar hemorrhage is reported as the presenting feature in a few cases with SAVI (47,60). Although ILD is a major concern for patients with SAVI, it is rarely present in patients with CANDLE/PRAAS (1,18,51) and not reported in AGS. Low radiation chest CT and pulmonary function tests are recommended modalities to screen for ILD (8). Lung biopsies may distinguish infectious from inflammatory disease but are not required to make the diagnosis of SAVI (7,46,60,61).

Another significant pulmonary manifestation is pulmonary hypertension, which is a potentially life threatening and possibly underdiagnosed complication of CANDLE/PRAAS and AGS (1,12,78). While CANDLE/PRAAS and AGS are known to affect the vascular system, the full impact of systemic vasculopathy is currently undercharacterized. All patients with suspected CANDLE/PRAAS and AGS should undergo regular evaluation for pulmonary hypertension; echocardiography is recommended as a screening and monitoring tool.

Hepatic manifestations. Forty to eighty percent of patients with CANDLE/PRAAS develop metabolic syndrome and hepatic steatosis, often in the first decade of life (1). In addition, patients may develop hepatosplenomegaly which could be due to extensive metabolic disturbance in fat processing (2,5,9,36,37,39,51). In an open-label trial in CANDLE/PRAAS, it is reported that baricitinib did not significantly improve hepatic steatosis in 2 patients with hepatic steatosis prior to baricitinib treatment nor prevent it in 3 patients with hyperlipidemia at baseline, pointing to the role of proteasome dysfunction in the etiology of hepatic steatosis (1).

In AGS, hepatosplenomegaly and/or transaminitis can be an initial presentation in the neonatal period when it resembles congenital viral infection (31,33,72,79). Patients can develop autoimmune hepatitis; the presence of liver-specific antibodies has been described (34,62,80).

Transaminases should be evaluated at presentation and may be monitored as a marker for hepatic disease activity in patients with type I interferonopathies, although it should be noted they can also be elevated in CANDLE/PRAAS and AGS due to myositis (12).

Information about the clinical features of hepatic involvement in patients with SAVI is limited. However, case reports of patients with SAVI presenting with hepatic disease, such as necrotizing granulomatous hepatitis, cholestatic hepatitis, and cholangitis and multiple biliary cysts, are presented (58,81).

Metabolic manifestations. Metabolic abnormalities are significant concerns in patients with CANDLE/PRAAS and patients can develop metabolic syndrome defined by Ford et al (presence of at least 3 of the following 5 criteria: hypertriglyceridemia ≥110 mg/dl, low high-density lipoprotein cholesterol ≤40 mg/dl, abdominal obesity with waist circumference ≥90th percentile [sex specific], hyperglycemia ≥110 mg/dl, systolic or diastolic blood pressure ≥90th percentile [age, height, sex specific]) (82). In addition, these patients can have increased abdominal girth secondary to intra-abdominal fat deposition (1,51). The workup in CANDLE/PRAAS should include screening for metabolic abnormalities.

Patients with AGS may have hypothyroidism, often requiring replacement therapy, and insulin-dependent diabetes mellitus is reported (34,49,53,54,77,83–85). Other endocrine manifestations include central diabetes insipidus, growth hormone deficiency, and adrenal insufficiency (34,83).

Musculoskeletal manifestations. Myositis is a common feature of patients with CANDLE/PRAAS. It is usually patchy in distribution and can be demonstrated by muscle MRI (1,39,51). In addition, most patients with CANDLE/PRAAS will develop variable degrees of joint contractures in the hands and feet; these can be severely disabling (1,2,9,37,51). Myopathy is described in individual case reports in AGS (86). In AGS-affected patients, joint involvement can include a lupus-like arthritis, or progressive arthropathy with joint contractures (50,87,88). Articular involvement in SAVI is seen in one-third of the patients (8). Rheumatoid factor (RF) positivity was reported in a majority of cases (57%) (8) while anti–cyclic citrullinated peptide (anti-CCP) was not common in patients with SAVI but systematic testing has not been performed. Interestingly, the course of the arthritis in SAVI can be destructive, especially in childhood, when associated with RF and anti-CCP antibodies (7,43).

Growth and development. Many children with chronic inflammation, including patients with type I interferonopathies, have lengths/heights and bone mineral density (BMD) that are below that of age-matched controls. Height and BMD are further decreased in the context of treatment with glucocorticoids. Weight percentiles can increase sharply with high doses of glucocorticoids, and this should be taken into consideration when evaluating weight (1).

In addition to abnormalities in stature, patients with AGS can have significant developmental delay; after a subacute onset most individuals develop profound neurologic regression and present with severe impairment in psychomotor development (22,23,34). Patients with AGS and CANDLE/PRAAS may also present with mild developmental delay (5,22,51); these delays are not reported in patients with SAVI (8).

Hematologic manifestations. Cytopenias can occur in all 3 diseases due to temporary bone marrow suppression or homing changes and may correlate with disease activity (1,12). Cytopenias including autoimmune cytopenias occur more frequently in patients with CANDLE/PRAAS and AGS but are also seen in patients with SAVI (1,8,18,33,50,52,54,60,79,83,89). Thrombocytopenia in patients with AGS can be present during the neonatal period mimicking congenital infection, but also later during the course of the disease associated with other hematologic abnormalities such as anemia and leukopenia (19,79). Complete blood count with differential should be evaluated at presentation and may be monitored as a marker for disease activity in patients with type I interferonopathies.

Ophthalmologic manifestations. Patients with type I interferonopathies can develop different types of ophthalmologic manifestations. While patients with CANDLE/PRAAS can present with keratitis and/or episcleritis (2,18,51), patients with SAVI and AGS can develop glaucoma (8,54,76). Glaucoma has been reported in 6.3% of patients with AGS (up to 20.8% of patients with *SAMHD1* mutations), with most cases presenting in the first 6 months of life, in patients who were not receiving glucocorticoids (34,76). Retinopathy has been described in AGS and SAVI but it remains unclear whether this occurs in the context of secondary mutations (90).

Cardiac manifestations. Patients with AGS, especially those with mutations in *TREX1*, are prone to develop infantile-onset hypertrophic cardiomyopathy (31,34). There is an important risk of cardiac valve calcification in disease related to mutations in *IFIH1* and *ADAR* (91).

Other considerations

Immunodeficiency workup. Patients with known type I interferonopathies may have some degree of immunodeficiency, either due to chronic disease and cytopenias or due to treatment with immunosuppressants (92). Early manifestations may overlap with non–type I interferonopathy immunodeficiencies. Therefore, a basic immunologic workup should be considered even in the context of a confirmed diagnosis. The workup should include a history of infections and assessment of lymphocyte subsets and immunoglobulin levels, as a minimum (1,12,93).

Infections in patients with CANDLE/PRAAS can be associated with the development of macrophage activation syndrome. Opportunistic infections in patients with other CANDLE/PRAAS mutations or SAVI and AGS are rare, although pneumocystis infection has been reported in a patient with SAVI who was not on any immunosuppressive treatment (89). Furthermore, defects in maturation of CD8+ cells are identified in patients with CANDLE/PRAAS (2,94), and in some patients with SAVI (8,57,89). Severe infections are reported in 2 patients with *POMP* mutations (94), which may be modified by additional genetic variants.

Points to consider 9–12: treatment focus on optimizing inflammatory disease control

The goal of treatment is the control of the systemic and organ-specific disease manifestations and to manage complications of existing organ damage that are consequences of untreated disease.

Pharmacologic treatment with Janus kinase inhibitors (JAKI), particularly baricitinib, is widely used to treat patients with type I interferonopathies (1,95–98). The JAKIs are reported to be beneficial in controlling inflammatory symptoms and in preventing progression of end organ damage. Specifically, treatment with baricitinib resulted in a significantly lower daily diary score as well as significant reduction in glucocorticoid use in patients with type I interferonopathies in different open-label trials (1,95). In the study by Sanchez et al, none of the patients had achieved remission before initiating baricitinib treatment, and 50% of patients with CANDLE/PRAAS achieved lasting remission with no clinical symptoms and normalization of inflammatory markers on baricitinib; all discontinued glucocorticoids. In addition, patients with CANDLE/PRAAS had improvement in myositis and cytopenias (hemoglobin, lymphocytes, and platelets). Moreover, significant clinical improvement, including fewer vasculitis flares, prevention of skin involvement/progression of spontaneous amputations/the development of gangrene, and stabilization of ILD by preserving pulmonary function, was achieved in patients with SAVI (1). However, to date, no patient with SAVI treated with JAKI achieved complete remission. Furthermore, JAKIs reduce IFNα-mediated STAT-1 phosphorylation in a dose-dependent manner in patients with interferonopathy (26,56), thus demonstrating an in vivo effect of the JAKIs on type I IFN signaling. The JAKIs ruxolitinib and tofacitinib are also reported as potential treatment options (44,56,59,98). Population pharmacokinetics and pharmacodynamic analyses in children treated with baricitinib showed a substantially shorter half-life in pediatric than in adult populations requiring more frequent dosing, and led to a proposed weight-based and estimated glomerular filtration rate–based dosing regimen to guide dose adjustments in the growing child (26). Doses of JAKI used to treat these conditions that were published are summarized in Supplementary Table 4, on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42027. A beneficial effect of JAKI on inflammatory disease manifestations is also observed in patients with AGS, including in an open-label trial. The treatment led to a decrease in interferon signaling gene expression scores and improvement of AGS-related symptoms, including neurologic disability, crying, sleep disturbances, irritability, seizures, fever, and skin inflammation of the trunk, arms, and legs (95–97). In all instances, preexisting organ damage is irreparable (e.g., the neurologic manifestations), stressing the need for early treatment. In patients with AGS, treatment with HIV-1 reverse-transcriptase inhibitors reduced IFN scores; however, clinical benefit was not demonstrated (99) and thus it is unclear if these drugs can be recommended.

Viral reactivation including BK viral reactivation has been reported in type I interferonopathy patients treated with JAKI (1,59). BK polyomavirus reactivation caused by therapeutic immunosuppression is a commonly reported complication in renal transplant patients that can result in nephropathy and renal allograft loss. There is no proven treatment for BK nephropathy and management is limited to early detection and to controlling BK viral load by reducing the dose of immunosuppressive medications (100,101). Monitoring for BK viral load in blood and urine and renal function prior to initiation of JAKI, at baseline, and then routinely at each visit is recommended.

Other viral reactivations, such as herpes, are reported in CANDLE/PRAAS and SAVI (1); however, there are insufficient data to routinely recommend anti-viral drug prophylaxis for patients with CANDLE/PRAAS and SAVI treated with JAKI. Similarly, in AGS, viral prophylaxis for patients on JAKI is not currently recommended.

Finally, the data from an open-label trial indicated that patients with AGS who are receiving baricitinib should be monitored closely for thrombocytosis, leukopenia, and infection, especially those with underlying thrombotic risk factors or those who are receiving systemic glucocorticoids or immunosuppressive regimens (95), while no such events were reported in 2 other reports (96,97).

Glucocorticoids are generally considered useful in CANDLE/PRAAS and SAVI patients with systemic inflammation, although their use is limited by toxicity (1). When used for a prolonged time, glucocorticoids cause serious side effects including growth arrest, truncal obesity, hypertension, glucose intolerance, and osteopenia (102). Therefore, the lowest possible dose of glucocorticoids should be targeted for disease control.

There is generally no role for chronic glucocorticoids in AGS, as glucocorticoids do not improve the long-term neurologic features nor outcome of AGS. However, short courses of glucocorticoids to treat acute CNS and non-CNS inflammatory manifestations, such as cytopenias and hepatitis, may be beneficial.

Points to consider 13–17: long-term monitoring and management focus on assessing inflammatory organ manifestations, minimizing treatment-related toxicities, and encouraging general health measures, including vaccines, and fostering of self-management skills and medical decision-making

A multidisciplinary team approach to regular clinical follow-up is recommended and may include access to medical subspecialists, including a rheumatologist, geneticist, neurologist, ophthalmologist, pulmonologist, cardiologist, hepatologist, gastroenterologist, hematologist, immunologist, dermatologist, endocrinologist, nephrologist, and access to supportive services including a physiatrist, wound care specialist, psychologist, bone health specialist, physical therapist, dental/oral surgeon, dietitian, psychiatrist, rehabilitation care, orthopedic care, and social support services. With current treatment strategies the ultimate treatment goal in inflammatory diseases, namely inflammatory remission, can only be achieved in a subset of patients. Remission is mainly described in patients with CANDLE/PRAAS (1). The current treatment goal is therefore to reduce systemic and organ inflammation and to prevent or limit the development or progression of organ injury/damage. This requires treatment adjustments and close monitoring of disease progression. Table 4 provides general and disease-specific guidance for the monitoring of disease activity and assessment of organ damage. The monitoring should include 1) assessment of the level of systemic inflammation, and of growth and sexual development, 2) the assessment of general and disease-specific clinical signs and symptoms including the use of validated instruments when available (1,22,23), 3) monitoring of disease-specific organ manifestations, and 4) monitoring of the development of autoimmune features (see Supplementary Table 5 [https://onlinelibrary.wiley.com/doi/10.1002/art.42027] for autoantibody associations with organ-specific autoimmune manifestations in CANDLE/PRAAS, SAVI, and AGS), cytopenias, treatment-related complications, and infections (immunodeficiencies). Preliminary guidance regarding the monitoring of JAKI treatment (Table 4) is provided but may need to be adjusted as experience with treatment of interferonopathies grows.

All patients should be evaluated at each visit for the presence of disease-specific symptoms and presence of systemic inflammation (Table 4).

Chronic inflammation and chronic glucocorticoid treatment negatively affect bone health (e.g., osteoporosis), growth (stunting), and development (1). These parameters should be monitored regularly, as well as cardiac (e.g., hypertension) and ophthalmologic complications of chronic glucocorticoid use.

Patients with CANDLE/PRAAS should also be monitored for headaches, skin and musculoskeletal disease, development of metabolic syndrome (hypertension, hyperglycemic and hepatic steatosis), and for development of primary pulmonary hypertension. Pulmonary hypertension can be insidious in onset. Although ILD is rare, it should be screened for at baseline and monitored as indicated by pulmonary function tests and low radiation chest CT. Ophthalmologic and dental assessment may be required in patients with eye inflammation and hypodontia and tooth eruption problems (1,2,5,9,18,36,37,39,51).

Patients with SAVI may require wound care (including wound culture as necessary) and close assessment of ILD and the development of secondary pulmonary hypertension. Patients should be screened for systemic hypertension, otolaryngology, ophthalmology, and dental disease at baseline and be followed as indicated. Patients should be instructed in self-care, including keeping peripheries warm, and in emergency management of acute ischemic digits (e.g., with, but not limited to, intravenous fluids, pentoxyphylline, or intravenous vasodilators), prompt use of antibiotics if infection is suspected, and meticulous wound care (1,8,103).

Patients with AGS are monitored for progression of neurologic disease including gross and fine motor function and cognitive function using validated scales when available (22,23). Patients with *SAMHD1* mutations require yearly MRI and MR angiography studies to screen for intracerebral artery disease (e.g., Moyamoya) (49,74,77). Patients should be monitored for the development of systemic hypertension, pulmonary hypertension, and cardiomyopathy (78). Other complications include autoimmune hepatitis

(25,83) and autoimmune endocrinopathies, most frequently hypothyroidism (34). Other manifestations that can develop insidiously include glaucoma and epilepsy, and should be monitored as clinically indicated (76,104). Neurologic tone abnormalities in nonambulatory patients can lead to joint dislocation and scoliosis and should be monitored. Families should be instructed in prevention of skin complications, physical therapy, management of disturbed sleep–wake patterns, and irritability commonly seen in AGS. Families can also participate in home stretching programs, and appropriate positioning of children with tone abnormalities.

The heightened type I interferon–mediated autoimmune response contributes to the development of autoantibodies and autoimmune diseases (105) (see Supplementary Table 5, https://onlinelibrary.wiley.com/doi/10.1002/art.42027). Antinuclear antibodies are seen in up to 62.5% of patients with SAVI (8), in up to 42% of patients with CANDLE/PRAAS (1,2,5,9,18,39,51,93), and 23% of patients with AGS (62). Moreover, antiphospholipid antibodies are present in patients with CANDLE/PRAAS, SAVI, and AGS (1,7,62). Antineutrophil cytoplasmic antibodies are, intermittently, elevated in up to 71% of patients with SAVI and 18% of patients with AGS (8,62), and RF positivity is reported in patients with SAVI (see above). Urinalysis for kidney dysfunction and screening for autoimmunity based on the disease symptoms are recommended as kidney disease is reported mostly in patients with AGS (50,62,79) and SAVI (8,106,107). Antibodies associated with specific autoimmune diseases including autoimmune arthritis, pauci-immune glomerulonephritis, autoimmune cytopenias, thyroiditis, and/or hepatitis have been described in CANDLE/PRAAS, SAVI, or AGS with variable frequencies (Supplementary Table 5). As it remains difficult to diagnose these diseases based on clinical symptoms, regular screening for autoantibodies as outlined in Table 4 is currently recommended. Renal pathology prior to treatment with JAKI should be assessed by a baseline renal ultrasound and urine protein/creatinine ratio (or albumin/creatinine ratio).

All patients and families should have access to formal genetic counseling and may require social and other support. Supportive care, including adaptive equipment (e.g., orthoses, walkers, wheelchairs, seating equipment), may be required.

Treatment during infections including COVID-19. Disease flares and progression can occur if immunosuppressive treatment is held (108) and disease can flare in the context of an infection. Thus, any patient who develops an acute infection (or other complications) may require adjustment of immunosuppressive treatment (and/or institution of other supportive treatment), which should be conducted only under expert supervision. In line with these suggestions, recently published ACR guidance recommends continuing or initiating immunosuppressants when indicated in patients with pediatric rheumatic diseases in the context of exposure to SARS–CoV-2 or if experiencing asymptomatic SARS–CoV-2 infection. Immunosuppressants may be temporarily delayed or withheld if a patient has symptomatic COVID-19 (109).

Box 1: Research agenda

To define autoinflammatory disease outcomes, including:
- Develop validated remission criteria for each disease including patient reported outcome measures.
- Develop minimal disease activity criteria.
- Identify sensitive biomarkers of progression of organ disease (including central nervous system).

To further assess efficacy of Janus kinase inhibitors (JAKI) and other type I IFN targeted therapies.

To assess long-term safety with treatment of JAKI.
- Assess long-term effect of chronic BK viral reactivation.
- Recommend monitoring guidance including frequency of BK viral load measurements and management of BK viremia.

To assess requirement of viral prophylaxis on JAKI.

To identify novel therapeutic targets and better treatments.

To validate an interferon signature to diagnose and monitor patients (e.g., number of interferon response genes to include, sensitivity and specificity of score).

To evaluate the effect of vaccination in triggering or exacerbating disease activity in patients with type I interferonopathies while on or off treatments with immunosuppressive medications and/or glucocorticoids.

To identify new genetic causes for interferonopathies.

Vaccination. Whether vaccination may trigger disease flares in interferonopathies is an important and currently unanswered question. There are no data suggesting that patients with CANDLE/PRAAS and SAVI develop disease flares with routine childhood vaccinations and the Task Force therefore recommended compliance with local regulations when patients are not treated with immunosuppressive treatments or glucocorticoids. No such consensus was achieved for AGS: the safety of vaccines in this population is not fully evaluated, and anecdotal reports of vaccine-induced neurologic regression were concerns debated by the Task Force. No specific recommendation on vaccination for AGS was therefore possible. In line with the general EULAR guidance, the Task Force recommends avoiding live vaccines in patients with CANDLE/PRAAS, SAVI, and AGS while on treatment with JAKI or other immunosuppressive medications (110). Treatment discontinuation can result in withdrawal flares. In general, we suggest following recommendations for other autoimmune and inflammatory rheumatic diseases (110,111); we however currently do not advise treatment adjustments for treatments recommended for the type I interferonopathies including JAKI.

RNA-based SARS–CoV-2 vaccines are not live vaccines, suggesting that they may be safe for immunosuppressed patients. Whether vaccines against COVID-19 have the potential to provoke

a disease flare is unknown; theoretical concerns about disease flare in type I interferonopathies caused by RNA vaccines exist. There are currently no data to back specific recommendations.

CONCLUSION

The aim of these points to consider is to address the unmet need to provide guidance for health care professionals involved in the care of patients with the recently characterized type I interferonopathies, CANDLE/PRAAS, SAVI, and AGS. A lack of high-level evidence is a limitation to these points to consider and reflects the challenges of studying novel, ultra-rare diseases. To address these challenges, the Task Force generated guidance statements based on results from a thorough SLR and on specialists'/experts' opinions where evidence was lacking or was insufficient. The Task Force included various specialists with broad expertise in relevant clinical areas and representing different regions, disease interests, and practice environments.

Important areas of future research are outlined in Box 1. The cost and availability of genetic testing, interferon signature assays, and JAKI treatment are substantial barriers that currently prevent optimized care for patients with interferonopathies. Furthermore, patients with the autoinflammatory interferonopathies CANDLE/PRAAS, SAVI, and AGS live in many different countries and are managed in different health care systems. These points to consider address the multiple challenges of managing patients with these ultra-rare diseases, by providing guidance on improving clinical recognition, support for decision-making on genetic testing, as well as treatment and long-term management. These points to consider were developed to increase awareness of these diseases, and to standardize the level of care by characterizing the diagnostic and therapeutic tools that can improve care.

ACKNOWLEDGMENTS

The Task Force gratefully thanks the librarian Darren Hamilton (London Health Sciences Center, London, Ontario, Canada) for his contribution to the systematic literature search, Hayyah Clairman and Natasha Naraidoo for their support in conducting the Delphi questionnaires using the REDCap platform, and the European Alliance of Associations for Rheumatology and the American College of Rheumatology for financial and logistical support. This project is part of a series of "points to consider" consensus efforts to standardize the diagnosis, treatment, and long-term monitoring of patients with the 3 major groups of known autoinflammatory diseases including 1) the interleukin-1–mediated diseases cryopyrin-associated periodic syndrome, tumor necrosis factor receptor–associated periodic syndrome, mevalonate kinase deficiency, and deficiency of the interleukin-1 receptor antagonist, 2) the autoinflammatory interferonopathies CANDLE/PRAAS, SAVI, and AGS, and 3) the early diagnosis, treatment, and long-term monitoring of inflammatory conditions with potential progression to hemophagocytic lymphohistiocytosis/macrophage activation syndrome. We would like to acknowledge and are grateful for the generous and invaluable financial and organizational support from the Autoinflammatory Alliance and the Systemic JIA Foundation. The Autoinflammatory Alliance substantially contributed to an international meeting and workgroup organization in August 2019 that developed the outline of the points to consider project. The funds for this preceding international meeting were largely due to patient fundraisers, online fundraising, and the work of countless volunteers who made this project possible.

AUTHOR CONTRIBUTIONS

All authors contributed to the formulation of the points to consider. In details, the steering committee of the Task Force (Drs. Goldbach-Mansky, Brogan, Vanderver, Feldman, and Demirkaya) defined the research questions for the SLR. A systematic literature review was conducted by Drs. Cetin Gedik, Romano, and Lamot with support from a librarian (nonauthor Darren Hamilton) and epidemiologist (Dr. Piskin) under supervision of a senior methodologist (Dr. Demirkaya). Drs. Cetin Gedik, Lamot, and Romano extracted the data. Drs. Goldbach-Mansky, Brogan, and Vanderver synthesized the results from SLR and Delphi questionnaires and generated draft statements. The manuscript was drafted by Drs. Cetin Gedik, Lamot, and Romano and revised by Drs. Goldbach-Mansky, Brogan, and Vanderver, Demirkaya, and Feldman. Dr. Aletaha oversaw the proceedings and provided advice on the points to consider project as EULAR methodologist. All other authors participated in the Task Force meetings, in 2 pre-meeting Delphi questionnaires, suggested and agreed upon the research questions, read the final statements prior to the manuscript, discussed results, and made contributions to the text. All authors approved the final version of the manuscript.

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