JAMA Network Open

Consensus Statement | Pediatrics

Evaluation and Management of Deficiency of Adenosine Deaminase 2
An International Consensus Statement

Pui Y. Lee, MD, PhD; Brad A. Davidson, BS; Roshini S. Abraham, PhD; Blanche Alter, MD, MPH; Juan I. Arostegui, MD, PhD; Katherine Bell, MFA; Alexandre Belot, MD, PhD; Jenna R. E. Bergerson, MD, MPH; Timothy J. Bernard, MD, MSCS; Paul A. Brogan, BSc, MBChB, MSc, PhD; Yackov Berkun, MD; Natalie T. Deuitch, MS, CGC; Dimana Dimitrova, MD; Sophie A. Georgin-Lavialle, MD, PhD; Marco Gattorno, MD; Bodo Grimbacher, MD; Hasan Hashem, MD; Michael S. Hershfield, MD; Rebecca N. Ichord, MD; Kazushi Izawa, MD, PhD; Jennifer A. Kanakry, MD; Raju P. Khubchandani, MD; Femke C.C. Klouwer, MD, PhD; Evan A. Luton, MAT; Ada W. Man, MD; Isabelle Meyts, MD, PhD; Joris M. Van Montfrans, MD, PhD; Seza Ozen, MD; Janna Saarela, MD, PhD; Gustavo C. Santo, MD; Aman Sharma, MD; Ariane Soldatos, MD, MPH; Rachel Sparks, MD; Troy R. Torgerson, MD, PhD; Ignacio Leandro Uriarte, MD; Taryn A. B. Youngstein, MB, BS, MD; Qing Zhou, PhD; Ivona Aksentijevich, MD; Daniel L. Kastner, MD, PhD; Eugene P. Chambers, MD; Amanda K. Ombrello, MD; for the DADA2 Foundation

Abstract

IMPORTANCE Deficiency of adenosine deaminase 2 (DADA2) is a recessively inherited disease characterized by systemic vasculitis, early-onset stroke, bone marrow failure, and/or immunodeficiency affecting both children and adults. DADA2 is among the more common monogenic autoinflammatory diseases, with an estimate of more than 35 000 cases worldwide, but currently, there are no guidelines for diagnostic evaluation or management.

OBJECTIVE To review the available evidence and develop multidisciplinary consensus statements for the evaluation and management of DADA2.

EVIDENCE REVIEW The DADA2 Consensus Committee developed research questions based on data collected from the International Meetings on DADA2 organized by the DADA2 Foundation in 2016, 2018, and 2020. A comprehensive literature review was performed for articles published prior to 2022. Thirty-two consensus statements were generated using a modified Delphi process, and evidence was graded using the Oxford Center for Evidence-Based Medicine Levels of Evidence.

FINDINGS The DADA2 Consensus Committee, comprising 3 patient representatives and 35 international experts from 18 countries, developed consensus statements for (1) diagnostic testing, (2) screening, (3) clinical and laboratory evaluation, and (4) management of DADA2 based on disease phenotype. Additional consensus statements related to the evaluation and treatment of individuals with DADA2 who are presymptomatic and carriers were generated. Areas with insufficient evidence were identified, and questions for future research were outlined.

CONCLUSIONS AND RELEVANCE DADA2 is a potentially fatal disease that requires early diagnosis and treatment. By summarizing key evidence and expert opinions, these consensus statements provide a framework to facilitate diagnostic evaluation and management of DADA2.

JAMA Network Open. 2023;6(5):e2315894. doi:10.1001/jamanetworkopen.2023.15894

Key Points

Question What are the optimal approaches to diagnose and treat patients with deficiency of adenosine deaminase 2 (DADA2)?

Findings This consensus statement addresses key questions about diagnostic testing, screening, clinical evaluation, and management of DADA2 based on a comprehensive literature review and expert opinions by the DADA2 Consensus Committee comprised of patient representatives and global experts representing adult and pediatric subspecialties.

Meaning The consensus statement provides a framework to facilitate the diagnostic evaluation and management of DADA2.

+ Invited Commentary

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Introduction

Deficiency of adenosine deaminase 2 (DADA2) is a monogenic autoinflammatory disease characterized by systemic vasculitis, early-onset stroke, bone marrow failure, and/or immunodeficiency.[1,2] DADA2 is caused by biallelic pathogenic variants in the *ADA2* gene (formerly known as *CECR1*) on chromosome 22q11.[3] This condition was first described in 2014 and more than 400 cases have been published to date.[4,5] While affected individuals were mostly young children in

the early case series, adult-onset cases of DADA2 are increasingly recognized.[6,7] Based on population genetics, the aggregate carrier frequency of deleterious *ADA2* variants is approximately 1 in 236 individuals, which translates into an estimated disease prevalence of 1 case per 222 000 individuals.[8] This estimate makes DADA2 a rare disease according to the US Food and Drug Administration.[9] However, such prevalence also establishes DADA2 as a more common monogenic autoinflammatory diseases with an estimated 35 000 affected individuals worldwide.[8]

The clinical spectrum of the disease is remarkably broad. Early studies described DADA2 as a familial form of vasculitis that mimics polyarteritis nodosa.[4,5,10-12] Subsequent reports found that DADA2 can cause a wide range of hematologic abnormalities, including pure red cell aplasia and bone marrow failure.[13-15] While mild hypogammaglobulinemia is frequently seen, common variable immunodeficiency and recurrent infections can also be presenting features of DADA2.[16,17]

Early diagnosis and management are essential to minimize organ damage and long-term morbidities. The mortality of DADA2 is estimated to be approximately 8% before the age of 30 years, but the actual number may be considerably higher due to misdiagnosis and underdiagnosis.[18] Barriers to a timely diagnosis include limited physician awareness, the lack of screening and diagnostic criteria, and limited availability of diagnostic studies. To improve the care of patients with DADA2, the DADA2 Foundation assembled a committee consisting of 3 patient representatives and 35 experts from 18 countries. This DADA2 Consensus Committee was tasked to review the available evidence, synthesize key questions, and develop consensus statements to address these questions. Through several iterations of virtual meetings, statement editing, and voting using a modified Delphi process, the Committee drafted the first international consensus statement for the evaluation and management of DADA2.

Methods

This article was drafted after all consensus statements were finalized and formatted based on Revised Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0) reporting guideline.[27] The consensus study was conducted through literature review of publicly available studies. The study did not involve specific human participants or any identifiable data, and therefore, institutional review board approval and informed consent were not required.

Consensus Committee, Workstreams, and Voting Members

The DADA2 Foundation is a nonprofit organization founded in 2016, with the mission to accelerate the search for a cure for the disease, increase awareness and diagnosis, and ensure that patients around the world and their medical teams have access to the most up-to-date treatments. The DADA2 Foundation selected 3 patient representatives (parents of DADA2 patients) and 25 international experts to form the DADA2 Consensus Committee based on their clinical and/or scientific expertise, experience with DADA2, and participation in previous international meetings. P.Y.L. and A.K.O. were appointed to lead the Committee and the other members were assigned to 1 of 5 workstreams (genetics, hematology/transplantation, immunology, neurology, and rheumatology) based on their expertise. After drafting the preliminary statements, 10 additional experts were invited to review the statements and participate in the voting process. Details of all participants, including their institutional affiliations and clinical specialties, are provided in eTable 1 in Supplement 1.

Formulation of Research Questions and Systematic Literature Review

Research questions for the development of consensus statements were formulated based on questions submitted by patients, families, clinicians, and researchers during the international DADA2 conferences in 2016, 2018, and 2020. Questions were compiled, categorized, and whenever possible, organized using patient or population, intervention, comparison, and outcomes (PICO) question format.[19] eTable 2 in Supplement 1 lists the research questions that form the framework for consensus statement development.

Details of the literature review are described in eAppendix in Supplement 1. The National Center for Biotechnology Information PubMed MEDLINE database was used for literature review. The literature search included publications between January 1, 2014, to December 31, 2021, using the following term: *DADA2* OR *deficiency of adenosine deaminase 2* OR *ADA2 [Title/Abstract]* OR *DADA2 [Title/Abstract]*. Among 540 abstracts reviewed, 40 full-text articles were included for the development of consensus statements (eTable 3 in Supplement 1).

Definition of Disease Phenotypes

Given the broad clinical spectrum of DADA2, we designated 4 disease phenotypes to facilitate discussion of statements that are phenotype-specific (**Table 1**). Except for the presymptomatic group, these disease phenotypes are not mutually exclusive. While the majority of patients show a predominant phenotype, some patients possess overlapping manifestations of vasculitis or inflammation, hematologic abnormalities, and/or immunodeficiency. Uncommon presentations of DADA2, such as lymphoproliferative disease, Castleman disease, and antiphospholipid syndrome, were not discussed in detail.[20-22]

Development of Consensus Statements

Details of the consensus building process are described in the eAppendix in Supplement 1. A modified Delphi method was used to develop the consensus statements.[23] Statements were graded using the Oxford Center for Evidence-Based Medicine Levels of Evidence and grades of recommendation.[24] Voting was conducted using a 9-point Likert scale according to the RAND/UCLA Appropriateness Method.[25] Voters were asked to score each item along a bar with the anchors: 1, completely disagree; 5, moderately agree; 9, completely agree. The median and interpercentile range (IPR) were calculated of the data collected from all 38 voting members. Agreement was calculated using the Interpercentile Range Adjusted for Symmetry (IPRAS) index between the 10th and 90th percentile.[25] Agreement was established with IPRAS disagreement index (IPRAS-DI) less than 1.[25,26] Finalized statements were reviewed and approved by all voting members.

Results

The DADA2 Consensus Committee consisted of patient representatives and global experts representing multiple adult and pediatric subspecialities and developed consensus statements for diagnostic testing, screening, clinical evaluation, and management of DADA2. Shared decision-making between patients and clinicians should be considered whenever possible to help patients consider available options and make informed choices based on available evidence.

Table 1. Definition of DADA2 Disease Phenotypes[a]

Phenotype	Clinical manifestations
Inflammatory and/or vasculitic	Patients with recurrent fever episodes, elevated inflammatory markers and/or manifestations of vasculitis, including cutaneous vasculitis (livedo racemosa, cutaneous ulcers, skin necrosis), ischemic stroke, intracranial hemorrhage, neuropathy, visceral organ vasculitis, vascular aneurysm, ischemia, and infarction. Patients with this phenotype are often diagnosed with classic PAN, cutaneous PAN, or Sneddon syndrome.
Hematologic	Patients may have variable anemia, neutropenia, thrombocytopenia, or pancytopenia. Anemia could be either (pure) red cell aplasia or autoimmune hemolytic anemia. Cytopenias may occur in the context of bone marrow failure or immune-mediated destruction. Patients may present with lymphoproliferation resembling autoimmune lymphoproliferative disease, large granular lymphocytosis, or less commonly lymphoma. Patients with this phenotype may be diagnosed with Diamond-Blackfan anemia, Evans Syndrome, or idiopathic thrombocytopenic purpura.
Immunodeficient	Patients with hypogammaglobulinemia, lymphopenia, and/or evidence of recurrent infection and/or opportunistic infection. Patients with this phenotype may be diagnosed with common variable immunodeficiency.
Presymptomatic	Patients with DADA2 but no symptoms or features of the above phenotypes. These individuals are usually detected by family screening following identification of the proband.

Abbreviations: DADA2, deficiency of adenosine deaminase 2; PAN, polyarteritis nodosa.

[a] Patients with DADA2 typically have a predominant disease phenotype, although some patients have overlapping phenotypes.

Diagnostic Testing for DADA2

Consensus statements focused on the diagnostic testing for DADA2 are listed in **Table 2**. A diagnosis of DADA2 can be determined by measurement of plasma or serum ADA2 enzymatic activity or by sequencing of the *ADA2* gene. Both methods should be used if available because each has its own advantages and disadvantages.

ADA2 activity testing can rule-in or rule-out DADA2 with a rapid turnaround time, although availability is currently limited to a few laboratories around the world. Where available, diagnostic testing should be performed by a laboratory that has been certified to measure ADA2 activity by a validated assay. ADA2 activity in the plasma or serum is typically quantified using spectrometric assays that couple the deamination of adenosine to the release of ammonia.[5,15,28] The use of high performance liquid chromatography is also described.[10] The normal range is typically established by data from healthy controls. Near-absent ADA2 levels are considered diagnostic for DADA2 whereas normal ADA2 levels are sufficient to rule out DADA2. However, the units of measurement and the normal range may vary between laboratories.

As a recessive condition, DADA2 is diagnosed genetically by biallelic pathogenic or likely pathogenic *ADA2* variants as determined by guidelines established by the American College of Medical Genetics and Genomics.[29] Targeted sequencing of *ADA2* is available commercially, and *ADA2* is also included in most commercial sequencing panels designed to evaluate inborn errors of immunity and/or autoinflammatory syndromes. All exons of *ADA2* should be sequenced as pathogenic or likely pathogenic variants have been described in each exon. Individuals with monoallelic pathogenic or likely pathogenic *ADA2* variants are considered carriers. In individuals with monoallelic or biallelic *ADA2* variants of unknown significance (VUS), measurement of ADA2 enzyme activity should be strongly considered to further evaluate the possibility of DADA2. There are rare instances in which standard sequencing techniques are unsuccessful in identifying intronic variants, splicing variants, and gene structural variants (ie, deletions, duplications, inversions).[30,31] If clinical suspicion for DADA2 remains in patients without supportive genetic findings, ADA2 enzyme activity and additional genetic evaluation of noncoding sequences and/or copy number variation should be considered.

Screening for DADA2

Consensus statements focused on screening for DADA2 are displayed in **Table 3**. For families with a confirmed case of DADA2 (proband), screening of the proband's full sibling(s) by either ADA2 activity or gene sequencing should be strongly considered because each sibling is independently at risk for

Table 2. Statements for Diagnostic Testing of DADA2

Consensus statement	LOE (grade)	LOA (SD)	IPRAS-DI
2.1 The diagnosis of DADA2 is established by (1) near-absent ADA2 enzymatic activity in the blood (plasma or serum), and/or (2) genetic testing confirming the presence of a confirmatory genotype in *ADA2*.	2 (B)	8.6 (0.7)	0.19
2.2 The order of testing (ADA2 activity vs genetic testing) depends on availability to the provider. If available, confirmation by both methods should be considered.	5 (D)	8.7 (0.6)	0.13
2.3 Near-absent ADA2 enzymatic activity in the blood is diagnostic of DADA2. Normal ADA2 enzymatic activity excludes the diagnosis of DADA2.	2 (B)	7.9 (1.4)	0.75
2.4 The presence of biallelic pathogenic or likely pathogenic variants in *ADA2* defines a confirmatory genotype and is diagnostic of DADA2.	2 (B)	8.3 (0.7)	0.29
2.5 Individuals with monoallelic pathogenic or likely pathogenic *ADA2* variants are considered carriers.	2 (B)	8.4 (1.1)	0.29
2.6 Individuals with clinical features of DADA2 and nonconfirmatory genotypes (monoallelic or biallelic variants of unknown significance in *ADA2*) should undergo further evaluation with ADA2 enzyme activity and/or additional genetic tests.	4 (C)	8.7 (0.5)	0.13
2.7 The absence of detectable *ADA2* variants by targeted Sanger sequencing, next generation sequencing, or exome sequencing methods does not necessarily exclude the diagnosis of DADA2.[a] Further evaluation by enzymatic assay and/or additional genetic tests should be considered if clinical suspicion remains.	4 (C)	8.1 (1.6)	0.49

Abbreviations: ADA2, adenosine deaminase 2; DADA2, deficiency of adenosine deaminase 2; IPRAS-DI, interpercentile range adjusted for symmetry disagreement index; LOA, level of agreement; LOE, level of evidence.

[a] Standard sequencing technology may not be able to detect *ADA2* variants in regulatory regions, intronic regions, and copy number variations.

DADA2. If routine screening for siblings is not possible, careful follow up with frequent clinical examinations and laboratory tests for acute phase reactants should be considered. Parents of the proband are expected to be carriers and screening can confirm carrier status. Screening should be considered for other family members with signs and symptoms concerning for DADA2. Screening should also be considered for potential donors for allogeneic hematopoietic stem cell transplantation (HSCT) for patients with DADA2. Genetic counseling should be considered for questions related to screening of at-risk family members, reproductive decision-making, and prenatal testing.

Clinical manifestations that warrant consideration for DADA2 screening are described in Statements 3.4 to 3.7 (Table 3). While these clinical manifestations have been described in patients with DADA2, the relative sensitivity and specificity of these features have not been established. Screening considerations for each individual should take into account other factors, including the age of onset, severity of symptoms, combination of clinical features, and inheritance pattern. Clinicians are encouraged to discuss specific cases with DADA2 experts.

Clinical Evaluation of DADA2

Table 4 provides consensus statements on the evaluation of a patient suspected to have DADA2 or confirmed to have DADA2. The goal of initial evaluation is to obtain a thorough history, provide a comprehensive assessment of the clinical manifestations, and determine the extent and severity of organ involvement. These general suggestions for physical examination, laboratory studies, and imaging studies (Statement 4.1-4.4) should be considered for DADA2 patients with any disease phenotype, including presymptomatic individuals (Table 4). Blood pressure measurement and ophthalmology examination are included as part of the comprehensive physical examination to address the common findings of early onset hypertension and ocular involvement in patients with DADA2.[5,32,33] Abdominal ultrasonography with Doppler is included to assess the liver and spleen as patients can present with noncirrhotic portal hypertension and vascular or inflammatory findings, such as focal nodular hyperplasia and nodular regenerative hyperplasia.[29]

A second-tier diagnostic evaluation should be considered based on organ-specific manifestations and/or clinical suspicion (Statement 4.5) (Table 4). Availability of these tests and modalities likely vary among different institutions. Consultation with clinicians experienced with DADA2 should be considered to determine the necessity and order of performing these tests.

Table 3. Statements for Screening of DADA2

Consensus statement	LOE (grade)	LOA (SD)	IPRAS-DI
3.1 Screening for DADA2 should be considered for all full siblings of a proband with confirmed DADA2, even in the absence of symptoms. Siblings are independently at risk for DADA2 while parents are expected to be carriers.	5 (D)	8.2 (1.2)	0.37
3.2 Screening should be considered for other family members with symptoms concerning for DADA2, and for individuals being considered as a donor for allogenic HSCT for a proband within the family.	5 (D)	8.8 (0.5)	0.13
3.3 Genetic counseling should be considered for identification of at-risk family members, reproductive decision making, prenatal testing, and psychosocial support.	5 (D)	8.4 (1.1)	0.29
3.4 Screening should be considered for individuals with pediatric- or adult-onset or familial forms of polyarteritis nodosa, Sneddon syndrome, livedo racemosa associated with inflammation, or unexplained autoinflammatory syndrome with features of DADA2.	5 (D)	8.6 (0.8)	0.13
3.5 Screening should be considered for individuals with cryptogenic ischemic stroke during childhood or early adulthood; and for individuals with unexplained brain hemorrhage (including aneurysm), or spinal cord stroke during childhood or early adulthood.	5 (D)	8.4 (1.4)	0.19
3.6 Screening should be considered for individuals with unexplained and/or refractory bone marrow failure, aplastic anemia, pure red cell aplasia, neutropenia, thrombocytopenia, and combinations thereof; individuals with unexplained immune cytopenia and lymphoproliferation; individuals previously diagnosed with autoimmune lymphoproliferative syndrome or Diamond-Blackfan anemia but negative genetic evaluations for these disorders.	5 (D)	8.5 (0.9)	0.29
3.7 Screening should be considered for individuals with common variable immunodeficiency who lack a molecular diagnosis, particularly those with low IgM and/or low class-switched memory B cells.	5 (D)	7.8 (1.3)	0.49

Abbreviations: DADA2, deficiency of adenosine deaminase 2; HSCT, hematopoietic stem cell transplantation; IPRAS-DI, interpercentile range adjusted for symmetry disagreement index; LOA, level of agreement; LOE, level of evidence.

Long-term management of DADA2 requires a multidisciplinary team tailored to the patient's clinical manifestations. For outpatient management, patients should be followed up at least every 3 to 6 months and evaluation at each visit should include physical examination and routine laboratory studies. Follow up of other laboratory and imaging studies should be guided by disease manifestations and baseline abnormalities.

Management of DADA2

Consensus statements for the management of DADA2 are displayed in **Table 5**. Due to the lack of randomized clinical trials for DADA2, these statements are based on case series and expert opinions. For patients with the inflammatory or vasculitic phenotype, retrospective studies consistently demonstrate a clear beneficial role of tumor necrosis factor inhibitors (TNFi). Treatment with TNFi significantly lowers the risk for ischemic and hemorrhagic strokes and other vasculitic organ injury.[29,31] Treatment also reduces the overall inflammatory burden of disease.[32,34,35] Soluble TNF receptor (etanercept) and monoclonal antibodies against TNF (adalimumab, infliximab, and golimumab) all appear to be effective. The use of glucocorticoids, disease-modifying antirheumatic drugs (DMARDs), and biologics targeting interleukin (IL)-1 and IL-6 have been described in patients with DADA2 but long-term efficacy of these approaches appears to be limited based on descriptions of refractory and relapsing disease.[7,11] In patients with the inflammatory or vasculitic phenotype combined with bone marrow failure and/or immunodeficiency, the added risk for infection from chronic immunosuppression should be considered.[14,16]

Treatment with TNFi is expected to be lifelong for patients with the inflammatory or vasculitic phenotype until another effective treatment option becomes available. Disease flares associated with suboptimal dosing of TNFi and treatment discontinuation have been described.[7] Antidrug antibodies to infliximab, adalimumab, and golimumab can also impair the therapeutic efficacy of these biologic agents. The risk of developing these neutralizing antibodies in patients with DADA2 is currently unknown. Screening for antidrug antibodies and/or concurrent use of DMARDs, such as

Table 4. Statements for Clinical Evaluation of DADA2

Consensus statement	LOE (grade)	LOA (SD)	IPRAS-DI
4.1 Initial evaluation of a patient suspected to have DADA2 or confirmed to have DADA2 should include a familial history with pedigree, complete physical exam, laboratory studies and imaging studies.	5 (D)	8.9 (0.4)	0
4.2 Physical examination should include blood pressure and ophthalmology examination.	5 (D)	8.1 (1.3)	0.49
4.3 Recommended laboratory studies include complete blood count with differentials, reticulocyte count, erythrocyte sedimentation rate, C-reactive protein, liver function, renal function, urinalysis, serum immunoglobulin levels (IgA, IgM, IgG), lymphocyte subset (T/B/NK) quantitation and plasma ADA2 enzyme activity.	5 (D)	8.6 (0.7)	0.13
4.4 Recommended diagnostic modalities include MRI/MRA brain, abdominal ultrasound with Doppler, and electrocardiogram. Catheter arteriography may also be indicated to stage the extent of arterial involvement.	5 (D)	8.0 (1.3)	0.61
4.5 Additional testing should be considered based on organ-specific manifestations and/or clinical suspicion. These tests may include, but not limited to, skin biopsy, nerve biopsy, bone marrow aspirate and trephine biopsy with histopathology and flow cytometry, liver biopsy, transient elastography/ fibroscan, MRI/MRA abdomen, MRA of lower and/or upper extremities, catheter arteriogram, audiogram, echocardiogram, autoantibody profiling, antibody response to immunization, and neuropsychiatric/neuropsychological testing.	5 (D)	8.5 (0.9)	0.29
4.6 Patients with DADA2 require a multidisciplinary team of health care clinicians. Depending on disease phenotype, disease activity and complications, these subspecialties may include (but are not limited to) rheumatology, immunology, hematology, dermatology, hepatology, gastroenterology, neurology, neurosurgery, cardiology, nephrology, ophthalmology, genetic counseling, rehabilitation medicine, and obstetrics.	5 (D)	8.6 (0.8)	0.19
4.7 Patients with controlled disease should be followed by experienced clinicians at least every 3 to 6 mos. Evaluation at each visit should include physical examination and routine laboratory studies (CBC with differential, ESR, CRP, liver function and kidney function). Follow-up of other laboratory and imaging studies should be guided by the patient's disease manifestations and baseline findings.	5 (D)	8.5 (1.0)	0.29

Abbreviations: ADA2, adenosine deaminase 2; CBC, complete blood cell; CRP, C-reactive protein; DADA2, deficiency of adenosine deaminase 2; ESR, erythrocyte sedimentation rate; IPRAS-DI, interpercentile range adjusted for symmetry disagreement index; LOA, level of agreement; LOE, level of evidence; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging.

methotrexate, to minimize the development of these antibodies should be considered, particularly for patients treated with monoclonal antibodies against TNF.

In the event of an acute stroke in a patient with DADA2, neuroprotective strategies should be applied and antiinflammatory treatment with glucocorticoids and/or TNFi should be initiated. Data comparing the efficacy of glucocorticoids and TNFi for this purpose are lacking but only TNFi has been shown to prevent additional strokes.[34,35] The use of antiaggregants, anticoagulants, and/or antithrombotic therapy in patients with DADA2 is controversial given the unclear benefit and the potential risk for brain hemorrhage. As secondary hemorrhagic stroke conversion has been documented, the use of these agents is not routinely suggested at this time.[29]

Except for mild anemia secondary to chronic inflammation, the hematologic features of DADA2 are largely refractory to TNFi and glucocorticoids.[14,15,34] Allogeneic HSCT is a curative option for patients with pure red cell aplasia, bone marrow failure, or refractory immune cytopenias.[36,37] Allogeneic HSCT is also effective for severe immunodeficiency or vascular involvement refractory to immunomodulators.[38] Considerations for allogeneic HSCT should include disease burden, donor human leukocyte antigen (HLA)-match and availability, and potential transplant related complications. While a full 10 of 10 HLA-matched donor is preferred, there are insufficient data to comment on the effects of mismatched donor status on transplant outcome or risk of developing graft-vs-host disease. Measurement of plasma or serum ADA2 activity may be helpful in confirming

Table 5. Statements for Management of DADA2

Consensus statement	LOE (grade)	LOA (SD)	IPRAS-DI
5.1 TNFi is the treatment of choice for DADA2 patients with vasculitis, stroke, and/or evidence of persistent systemic inflammation.	4 (C)	8.7 (0.9)	0.13
5.2 Treatment with TNFi is lifelong in symptomatic patients with the inflammatory / vasculitic phenotype. Screening for tuberculosis is required before treatment initiation. TNFi drug level and antidrug antibody monitoring (eg, every 6-12 mos) and antidrug antibody prophylaxis (eg, with methotrexate or other nonbiological DMARD) should be considered.	5 (D)	8.6 (0.6)	0.13
5.3 TNFi should be considered in patients with overlapping features of vasculitis, immunodeficiency, and/or bone marrow failure, balancing potential benefits with access to therapy, risk of infection, and long-term effects.	5 (D)	8.4 (1.1)	0.29
5.4 Acute management of stroke in a patient with confirmed (or suspected) DADA2 should include neuroprotective measures to optimize the cerebral blood flow and oxygenation, treatment of inflammation with glucocorticoids and/or TNF inhibitors, and vasodilators for acute peripheral ischemia in select cases. TNF inhibitors should be considered for prevention of further strokes.	5 (D)	7.7 (1.8)	0.75
5.5 Antiaggregants, anticoagulants, and/or antithrombotic therapy in patients with DADA2 should be avoided to prevent hemorrhagic stroke.	5 (D)	8.3 (1.3)	0.29
5.6 Allogeneic HSCT is the most effective treatment for patients with bone marrow failure or refractory immune cytopenias. Glucocorticoids, cyclosporine, or other immunosuppressive agents may offer transient control of immune-mediated cytopenias, but allogeneic HSCT is likely to be required for patients with severe immunodeficiency or vascular involvement refractory to immunomodulators.	4 (C)	8.4 (0.9)	0.22
5.7 Immunoglobulin replacement and/or prophylactic antimicrobials should be considered for patients with hypogammaglobulinemia and recurrent infections. Prophylactic antibiotics should be considered for those who are profoundly neutropenic (neutrophil <500/mm^3) or lymphopenic (CD4+ T cell <200/mm^3). Systemic antiviral therapy should be considered for patients with immunodeficiency and recurrent episodes of herpetic infection.	4 (C)	7.8 (1.3)	0.41
5.8 Routine inactivated (nonlive) vaccines and boosters are recommended for DADA2 patients who are not on IgG replacement therapy. In addition, nonlive annual influenza and SARS-CoV-2 vaccines should be strongly considered for all patients in accordance with local regulations.	5 (D)	8.3 (1.4)	0.66
5.9 Live vaccines are generally contraindicated for patients taking immunosuppressive medications. DADA2 patients currently taking immunosuppressive medications and patients with a history of recurrent infection and/or immune deficiency should consult with a specialist for recommendations on immunization.	5 (D)	8.2 (1.7)	0.74
5.10 TNFi should be considered for presymptomatic individuals with DADA2 due to unpredictable disease onset and the potential risk for stroke and other severe consequences of vascular inflammation.	5 (D)	8.8 (0.8)	0.29
5.11 Most carriers of monoallelic *ADA2* variants are asymptomatic and require no specific management. Whether features of DADA2 may develop in a subset of these individuals is a topic of active research.	5 (D)	8.2 (1.2)	0.37

Abbreviations: *ADA2*, adenosine deaminase 2; DADA2, deficiency of adenosine deaminase 2; DMARD, disease-modifying antirheumatic drug; HSCT, hematopoietic stem cell transplantation; IPRAS-DI, interpercentile range adjusted for symmetry disagreement index; LOA, level of agreement; LOE, level of evidence; TNFi, tumor necrosis factor inhibitor.

the effectiveness of HSCT.[36,39] Clinicians are encouraged to consult with experts with experience in HSCTs for patients with DADA2 regarding additional questions related to transplantation.

The immunodeficiency phenotype of DADA2 encompasses abnormalities in B cell, T cell, and NK cell compartments.[40] In patients with recurrent infections, the use of prophylactic antimicrobials should be considered. Intravenous immunoglobulins (IVIG) should be considered for patients with humoral immunodeficiency and recurrent infections. While some IVIG preparations may contain ADA2,[41] there is no evidence that IVIG is beneficial for disease manifestations other than immunodeficiency or recurrent infections.

Immunizations are imperative for patients with DADA2 given the prevalence of underlying immunodeficiency and the use of immunosuppressive medications. For patients not receiving IVIG, routine inactivated (nonlive) vaccines and boosters are recommended. Nonlive annual influenza and SARS-CoV-2 immunizations should be strongly considered for all patients in accordance with local regulations. To our knowledge, there have not been any documented cases of infection linked to live attenuated vaccines in patients with DADA2. Nevertheless, live vaccines may be contraindicated in the setting of immunosuppressive therapy. Patients currently taking immunosuppressive medications and patients with a history of recurrent infections and/or severe immunodeficiency should consider consulting with a specialist regarding immunization recommendations.

Treatment of presymptomatic individuals with DADA2 is a subject of debate. Given the unpredictable nature of the disease, lack of reliable biomarkers to estimate disease onset, and the possibility of a life-threatening stroke or other emergencies as the first presenting feature, TNFi therapy should be considered for these individuals. The potential benefit of disease prevention should be balanced with the risk of long-term immunosuppression in guiding treatment decisions.

Some carriers may experience features of DADA2. Mild subclinical immunologic abnormalities associated with DADA2 have been described in carriers.[40] However, in the collective clinical experience of the Consensus Committee, most carriers (ie, parents and siblings of patients with DADA2) are healthy and asymptomatic. Natural history studies and immunophenotyping analyses are needed to better understand the clinical significance of carrier status. Therefore, there is insufficient evidence to guide the evaluation and management of carriers.

Areas of Future Research

Acknowledging that much more work is needed to understand the biology of DADA2 and improve the care of patients, each voting member of the Consensus Committee was asked to identify questions that have not been adequately addressed (eTable 4 in Supplement 1). Among the most common questions were inquiries regarding (1) stability of clinical phenotypes; (2) the need for TNFi in all patients regardless of phenotype; (3) evaluation and management of symptomatic carriers; and (4) progress on developing additional therapeutic options including gene replacement, gene editing, and enzyme replacement therapy. These topics will guide the design of research studies and development of updated consensus statements in the future.

Discussion

DADA2 is an intriguing monogenic disease with a broad spectrum of clinical manifestations that span many subspecialties. Population genetics estimates that DADA2 may be 1 of the most common monogenic autoinflammatory diseases in the world. While the pathophysiology of DADA2 remains to be clarified, tremendous progress has been made in understanding and managing the various disease phenotypes. Unfortunately, delayed diagnosis and misdiagnosis are still common for patients with DADA2 due to a lack of awareness or expertise among clinicians and limited availability of diagnostic tests. Establishing a consensus approach is important for DADA2 as timely diagnosis and treatment are essential to minimize morbidity and mortality.

With the mission to ensure that patients around the world and their medical teams have access to the latest information, the DADA2 Foundation partnered with patient representatives and an

international team of experts to develop these consensus statements. We recognize that clinical practice is constrained by the availability of resources. Some of the approaches discussed in the consensus statements, including diagnostic tests for DADA2 and treatment options, are not uniformly available. For additional information and questions beyond these statements, clinicians are encouraged to contact the DADA2 Foundation and/or consult with clinicians with expertise on DADA2.

Limitations

This study had limitations. A major limitation of this work is the paucity of evidence behind many consensus statements. In the absence of clinical trials or natural history studies on DADA2, the consensus statements rely heavily on published case series and expert experience or opinions, resulting in relatively low evidence grading. This is a challenge for the development of guidelines for rare diseases in general, as illustrated by recent efforts in creating consensus statements for IL-1-mediated autoinflammatory diseases and type I interferonopathies.[42-44] Given the limited evidence, we favor the use of statements instead of guidelines or recommendations. However, as a starting point, these statements are intended to address many questions raised by the DADA2 community on the topics of diagnostic evaluation, screening, and treatment with the most up-to-date information. We envision that these statements will help establish more uniform approaches in the field as a necessary step to develop future evidence-based guidelines.

Conclusions

An international team of expert clinicians, researchers, and patient family representatives developed the first consensus statement for the diagnostic evaluation and management of DADA2. These statements summarize the best-available evidence and provide a framework to standardize the care of patients with DADA2.

ARTICLE INFORMATION

Accepted for Publication: March 24, 2023.

Published: May 31, 2023. doi:10.1001/jamanetworkopen.2023.15894

Corresponding Authors: Pui Y. Lee, MD, PhD, Division of Immunology, Boston Children's Hospital, Harvard Medical School, 300 Longwood Ave, Boston, MA 02115 (pui.lee@childrens.harvard.edu); Amanda K. Ombrello, MD, Inflammatory Disease Section, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD (amanda.ombrello@nih.gov).

Author Affiliations: Division of Immunology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts (Lee); Vanderbilt University, Nashville, Tennessee (Davidson, Chambers); Department of Pathology and Laboratory Medicine, Nationwide Children's Hospital, Columbus, Ohio (Abraham); Center for Immuno-Oncology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland (Alter, Dimitrova, Kanakry); Hospital Clinic, Barcelona, Spain (Arostegui); Institut d'Investigacions Biomediques August Pi I Sunyer, Barcelona, Spain (Arostegui); DADA2 Foundation, Nashville, Tennessee (Bell, Luton, Chambers); National Reference Centre for Rare Rheumatic and Autoimmune Diseases in Children RAISE, Hospices Civils de Lyon, Lyon, France (Belot); National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland (Bergerson, Sparks); Section of Child Neurology, Department of Pediatrics and Hemophilia and Thrombosis Center, University of Colorado School of Medicine, Aurora (Bernard); University College London, Great Ormond Street Institute of Child Health, London, UK (Brogan); Department of Pediatrics, Hadassah-Hebrew University Medical Center, Mount Scopus, and Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel (Berkun); National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland (Deuitch, Aksentijevich, Kastner, Ombrello); Internal Medicine Department, Sorbonne University, Tenon Hospital, Paris, France (Georgin-Lavialle); Unit of Rheumatology and Autoinflammatory diseases, IRCCS Istituto G. Gaslini, Genova, Italy (Gattorno); Institute for Immunodeficiency, Center for Chronic Immunodeficiency (CCI), Medical Center, Faculty of Medicine,

Albert-Ludwigs University of Freiburg, Germany (Grimbacher); Division of Pediatric Hematology Oncology and BMT, King Hussein Cancer Center, Amman, Jordan (Hashem); Department of Medicine and Biochemistry, Duke University School of Medicine, Durham, North Carolina (Hershfield); Department of Neurology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (Ichord); Department of Pediatrics, Kyoto University Graduate School of Medicine, Kyoto, Japan (Izawa); SRCC Children's Hospital, Mumbai, India (Khubchandani); Department of Neurology and Pediatric Neurology, Amsterdam University Medical Centers, Amsterdam, the Netherlands. (Klouwer); Section of Rheumatology, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada (Man); Department of Pediatrics, University Hospitals Leuven, Laboratory for Inborn Errors of Immunity, Department of Microbiology, Immunology and Transplantation, KU Leuven, Leuven, Belgium (Meyts); Wilhelmina Children's Hospital, UMC Utrecht, Utrecht, the Netherlands (Van Montfrans); Department of Pediatric Rheumatology, Hacettepe University, Ankara, Turkey (Ozen); Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland (Saarela); Centre for Molecular Medicine Norway, University of Oslo, Oslo, Norway (Saarela); Department of Neurology, Centro Hospitalar e Universitário de Coimbra, CNC-CIBB, Coimbra, Portugal (Santo); Clinical Immunology and Rheumatology Wing, Department of Internal Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India (Sharma); National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland (Soldatos); Allen Institute for Immunology and University of Washington, Seattle (Torgerson); Immunology Unit, Hospital Materno Infantil V. Tetamanti—Escuela Superior de Medicina, Universidad Nacional de Mar del Plata, Bs As, Argentina (Uriarte); National Heart and Lung Institute, Imperial College London and Department of Rheumatology, Hammersmith Hospital, Imperial College NHS Healthcare Trust, London, United Kingdom (Youngstein); Life Sciences Institute, Zhejiang University, Zhejiang, China (Zhou).

Author Contributions: Drs Lee and Ombrello had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Lee, Davidson, Alter, Belot, Bergerson, Bernard, Brogan, Hashem, Khubchandani, Luton, van Montfrans, Soldatos, Youngstein, Aksentijevich, Kastner, Chambers, Ombrello.

Acquisition, analysis, or interpretation of data: Lee, Abraham, Arostegui, Bell, Bergerson, Brogan, Berkun, Deuitch, Dimitrova, Georgin-Lavialle, Gattorno, Grimbacher, Hashem, Hershfield, Ichord, Izawa, Kanakry, Klouwer, Man, Meyts, Ozen, Saarela, Santo, Sharma, Soldatos, Sparks, Torgerson, Uriarte, Zhou, Kastner, Ombrello.

Drafting of the manuscript: Lee, Bergerson, Bernard, Brogan, Berkun, Dimitrova, Hashem, Hershfield, Klouwer, Meyts, van Montfrans, Soldatos, Youngstein, Zhou, Kastner, Ombrello.

Critical revision of the manuscript for important intellectual content: Lee, Davidson, Abraham, Alter, Arostegui, Bell, Belot, Bergerson, Bernard, Brogan, Deuitch, Dimitrova, Georgin-Lavialle, Gattorno, Grimbacher, Hashem, Ichord, Izawa, Kanakry, Khubchandani, Klouwer, Luton, Man, Meyts, van Montfrans, Ozen, Saarela, Santo, Sharma, Soldatos, Sparks, Torgerson, Uriarte, Youngstein, Zhou, Aksentijevich, Kastner, Chambers, Ombrello.

Statistical analysis: Lee, Kanakry, Zhou.

Obtained funding: Meyts, Kastner.

Administrative, technical, or material support: Davidson, Belot, Bergerson, Brogan, Hashem, Man, Ozen, Saarela, Youngstein, Zhou, Kastner, Chambers, Ombrello.

Supervision: Alter, Bergerson, Berkun, Gattorno, Hashem, Sharma, Uriarte, Youngstein, Aksentijevich, Ombrello.

Conflict of Interest Disclosures: Dr Abraham reported receiving personal fees from Enzyvant Therapeutics Advisory Board, Horizon Pharma Advisory Board, Beckman Coulter, Springer Publishers, ClinGen, and National Institutes of Health Board of Scientific Counselors outside the submitted work. Dr Arostegui reported receiving personal fees from Novartis outside the submitted work. Dr Brogan reported receiving personal fees from Novartis, Sobi, and Roche outside the submitted work. Dr Gattorno reported receiving grants and personal fees from Novartis and personal fees from Sobi outside the submitted work. Dr Grimbacher reported receiving personal fees from Pharming Group NV, Epimune GmbH, Open Health Group, Page and Page, Bristol-Myers Squibb, and Roche Pharma AG outside the submitted work. Dr Hershfield reported performing functional testing for diagnosis of deficiency of adenosine deaminase 2. Dr Izawa reported receiving personal fees from Novartis and SOBI outside the submitted work. Dr Lee reported receiving royalties from UpToDate and personal fees from Exo Therapeutics and Fresh Track Therapeutics outside the submitted work. Dr Man reported receiving personal fees from Pfizer and Abbvie outside the submitted work. Dr Meyts reported receiving grants from CSL Behring and personal fees from Boehringer-Ingelheim during the conduct of the study. Dr Ozen reported receiving personal fees from Novartis and SOBI outside the submitted work. Dr Saarela reported receiving grants from Sanofi-Genzyme Research, European Union Research, South-Eastern Norway Regional Health Authority Research NordForsk Research, and Novo Nordisk Fonden Research, personal fees from Sanofi-Genzyme, and being the founder of VEIL.AI outside the submitted work. Dr Torgerson reported receiving personal fees from Takeda, X4 Pharma, Horizon, CSL Behring, Grifols, and GentiBio outside the submitted work. No other disclosures were reported.

Funding/Support: Dr Grimbacher was supported by grants GR1617/14-1/iPAD and SFB1160/IMPATH from Deutsche Forschungsgemeinschaf, COFUND from the European Commission, GAIN 01GM1910A from the German Federal Ministry of Education and Research, EXC-2189 from the Centre for Biological Signaling Studies, and RESIST EXC 2155 from Medizinische Hochschule Hannover. Dr Meyts was supported by grant G0B5120N from Research Foundation Flanders, the Jeffrey Modell Foundation, and grant 948959 from the European Research Council under the European Union's Horizon 2020 research and innovation program. Dr Lee was supported by the K Supplement award from the Rheumatology Research Foundation, the Child Health Research Award from the Charles H. Hood Foundation, and the All Arthritis Grant from the Arthritis National Research Foundation. The DADA2 Foundation was supported by the Rare-As-One grant from the Chan-Zuckerberg Initiative.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: Members of the DADA2 Foundation appear in Supplement 2.

Additional Contributions: We thank all patients, families, clinicians, and researchers in the DADA2 network for their participation in the 2016, 2018, and 2020 International Meetings on DADA2. We thank Reem Mustafa, MD, MPH, PhD (University of Kansas Medical Center, Kansas City), for helpful discussions during the planning phase of the study.

Additional Information: Data from the consensus building process will be shared upon request.

REFERENCES

1. Meyts I, Aksentijevich I. Deficiency of adenosine deaminase 2 (DADA2): updates on the phenotype, genetics, pathogenesis, and treatment. *J Clin Immunol*. 2018;38(5):569-578. doi:10.1007/s10875-018-0525-8

2. Lee PY, Aksentijevich I, Zhou Q. Mechanisms of vascular inflammation in deficiency of adenosine deaminase 2 (DADA2). *Semin Immunopathol*. 2022;44(3):269-280. doi:10.1007/s00281-022-00918-8

3. Aksentijevich I, Sampaio Moura N, Barron K. Adenosine Deaminase 2 Deficiency. In: Everman DB, Mirzaa GM, Pagon RA, et al, eds. *GeneReviews*. 2019.

4. Navon Elkan P, Pierce SB, Segel R, et al. Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. *N Engl J Med*. 2014;370(10):921-931. doi:10.1056/NEJMoa1307362

5. Zhou Q, Yang D, Ombrello AK, et al. Early-onset stroke and vasculopathy associated with mutations in ADA2. *N Engl J Med*. 2014;370(10):911-920. doi:10.1056/NEJMoa1307361

6. Fayand A, Chasset F, Boutboul D, et al. DADA2 diagnosed in adulthood versus childhood: a comparative study on 306 patients including a systematic literature review and 12 French cases. *Semin Arthritis Rheum*. 2021;51(6):1170-1179. doi:10.1016/j.semarthrit.2021.09.001

7. Sharma A, Naidu G, Sharma V, et al. Deficiency of adenosine deaminase 2 (DADA2) in adults and children: experience from India. *Arthritis Rheumatol*. 2020;73(2):276-285 doi:10.1002/art.41500

8. Jee H, Huang Z, Baxter S, et al. Comprehensive analysis of ADA2 genetic variants and estimation of carrier frequency driven by a function-based approach. *J Allergy Clin Immunol*. 2022;149(1):379-387. doi:10.1016/j.jaci.2021.04.034

9. Administration USFaD. Rare diseases at FDA. US Food and Drug Administration. Accessed December 1, 2022. https://www.fda.gov/patients/rare-diseases-fda

10. Caorsi R, Penco F, Grossi A, et al. ADA2 deficiency (DADA2) as an unrecognised cause of early onset polyarteritis nodosa and stroke: a multicentre national study. *Ann Rheum Dis*. 2017;76(10):1648-1656. doi:10.1136/annrheumdis-2016-210802

11. Nanthapisal S, Murphy C, Omoyinmi E, et al. Deficiency of adenosine deaminase type 2: a description of phenotype and genotype in fifteen cases. *Arthritis Rheumatol*. 2016;68(9):2314-2322. doi:10.1002/art.39699

12. Kasap Cuceoglu M, Sener S, Batu ED, et al. Systematic review of childhood-onset polyarteritis nodosa and DADA2. *Semin Arthritis Rheum*. 2021;51(3):559-564. doi:10.1016/j.semarthrit.2021.04.009

13. Hashem H, Egler R, Dalal J. Refractory pure red cell aplasia manifesting as deficiency of adenosine deaminase 2. *J Pediatr Hematol Oncol*. 2017;39(5):e293-e296. doi:10.1097/MPH.0000000000000805

14. Lee PY, Kellner ES, Huang Y, et al. Genotype and functional correlates of disease phenotype in deficiency of adenosine deaminase 2 (DADA2). *J Allergy Clin Immunol*. 2020;145(6):1664-1672.e10. doi:10.1016/j.jaci.2019.12.908

15. Özen S, Batu ED, Taşkıran EZ, et al. A monogenic disease with a variety of phenotypes: deficiency of adenosine deaminase 2. *J Rheumatol*. 2020;47(1):117-125. doi:10.3899/jrheum.181384

16. Schepp J, Proietti M, Frede N, et al. Screening of 181 patients with antibody deficiency for deficiency of adenosine deaminase 2 sheds new light on the disease in adulthood. *Arthritis Rheumatol*. 2017;69(8):1689-1700. doi:10.1002/art.40147

17. Schepp J, Bulashevska A, Mannhardt-Laakmann W, et al. Deficiency of adenosine deaminase 2 causes antibody deficiency. *J Clin Immunol*. 2016;36(3):179-186. doi:10.1007/s10875-016-0245-x

18. Sahin S, Adrovic A, Kasapcopur O. A monogenic autoinflammatory disease with fatal vasculitis: deficiency of adenosine deaminase 2. *Curr Opin Rheumatol*. 2019;32(1):3-14. doi:10.1097/BOR.0000000000000669

19. Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med Inform Decis Mak*. 2007;7:16. doi:10.1186/1472-6947-7-16

20. Sharma A, Naidu GSRSNK, Chattopadhyay A, Acharya N, Jha S, Jain S. Novel CECR1 gene mutations causing deficiency of adenosine deaminase 2, mimicking antiphospholipid syndrome. *Rheumatology (Oxford)*. 2019;58(1):181-182. doi:10.1093/rheumatology/key258

21. Trotta L, Martelius T, Siitonen T, et al. ADA2 deficiency: clonal lymphoproliferation in a subset of patients. *J Allergy Clin Immunol*. 2018;141(4):1534-1537.e8. doi:10.1016/j.jaci.2018.01.012

22. Van Nieuwenhove E, Humblet-Baron S, Van Eyck L, et al. ADA2 deficiency mimicking idiopathic multicentric castleman disease. *Pediatrics*. 2018;142(3):e20172266. doi:10.1542/peds.2017-2266

23. Jones J, Hunter D. Consensus methods for medical and health services research. *BMJ*. 1995;311(7001):376-380. doi:10.1136/bmj.311.7001.376

24. Group OLoEW. The Oxford Levels of Evidence 2. Centre for Evidence-Based Medicine. Accessed December 1, 2022. https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence

25. Fitch K, Bernstein SJ, Aguilar MD, et al. The RAND/UCLA Appropriateness Method User's Manual. RAND. 2001. Accessed May 11, 2023. https://www.rand.org/pubs/monograph_reports/MR1269.html

26. Maverakis E, Patel F, Kronenberg DG, et al. International consensus criteria for the diagnosis of Raynaud's phenomenon. *J Autoimmun*. 2014;48-49:60-65. doi:10.1016/j.jaut.2014.01.020

27. Ogrinc G, Davies L, Goodman D, Batalden P, Davidoff F, Stevens D. SQUIRE 2.0 (Standards for QUality Improvement Reporting Excellence): revised publication guidelines from a detailed consensus process. *BMJ Qual Saf*. 2016;25(12):986-992. doi:10.1136/bmjqs-2015-004411

28. Lee PY, Schulert GS, Canna SW, et al. Adenosine deaminase 2 as a biomarker of macrophage activation syndrome in systemic juvenile idiopathic arthritis. *Ann Rheum Dis*. 2020;79(2):225-231. doi:10.1136/annrheumdis-2019-216030

29. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405-424. doi:10.1038/gim.2015.30

30. Grossi A, Cusano R, Rusmini M, et al. ADA2 deficiency due to a novel structural variation in 22q11.1. *Clin Genet*. 2019;95(6):732-733. doi:10.1111/cge.13518

31. Schnappauf O, Zhou Q, Moura NS, et al. Deficiency of adenosine deaminase 2 (DADA2): hidden variants, reduced penetrance, and unusual inheritance. *J Clin Immunol*. 2020;40(6):917-926. doi:10.1007/s10875-020-00817-3

32. Barron KS, Aksentijevich I, Deuitch NT, et al. The spectrum of the deficiency of adenosine deaminase 2: an observational analysis of a 60 patient cohort. *Front Immunol*. 2022;12:811473. doi:10.3389/fimmu.2021.811473

33. Kurumoğlu İncekalan T, Kışla Ekinci RM, Naz Şimdivar GH, Doğan NC, Çiloğlu E. Evaluation of subclinical ocular involvement in patients with deficiency of adenosine deaminase 2 (DADA2). *Clin Rheumatol*. 2022;41(8):2533-2540. doi:10.1007/s10067-022-06194-z

34. Cooray S, Omyinmi E, Hong Y, et al. Anti-tumour necrosis factor treatment for the prevention of ischaemic events in patients with deficiency of adenosine deaminase 2 (DADA2). *Rheumatology (Oxford)*. 2021;60(9):4373-4378. doi:10.1093/rheumatology/keaa837

35. Ombrello AK, Qin J, Hoffmann PM, et al. Treatment strategies for deficiency of adenosine deaminase 2. *N Engl J Med*. 2019;380(16):1582-1584. doi:10.1056/NEJMc1801927

36. Hashem H, Bucciol G, Ozen S, et al. Hematopoietic Cell transplantation cures adenosine deaminase 2 deficiency: report on 30 patients. *J Clin Immunol*. 2021;41(7):1633-1647. doi:10.1007/s10875-021-01098-0

37. Hashem H, Kumar AR, Müller I, et al; Deficiency of Adenosine Deaminase Type 2 Foundation. Hematopoietic stem cell transplantation rescues the hematological, immunological, and vascular phenotype in DADA2. *Blood*. 2017;130(24):2682-2688. doi:10.1182/blood-2017-07-798660

38. Van Eyck L Jr, Hershfield MS, Pombal D, et al. Hematopoietic stem cell transplantation rescues the immunologic phenotype and prevents vasculopathy in patients with adenosine deaminase 2 deficiency. *J Allergy Clin Immunol*. 2015;135(1):283-7.e5. doi:10.1016/j.jaci.2014.10.010

39. Bucciol G, Delafontaine S, Segers H, et al. Hematopoietic stem cell transplantation in ADA2 deficiency: early restoration of ADA2 enzyme activity and disease relapse upon drop of donor chimerism. *J Clin Immunol*. 2017;37(8):746-750. doi:10.1007/s10875-017-0449-8

40. Yap JY, Moens L, Lin MW, et al. Intrinsic defects in B cell development and differentiation, T cell exhaustion and altered unconventional T cell generation characterize human adenosine deaminase type 2 deficiency. *J Clin Immunol*. 2021;41(8):1915-1935. doi:10.1007/s10875-021-01141-0

41. Zavialov AV, Engström A. Human ADA2 belongs to a new family of growth factors with adenosine deaminase activity. *Biochem J*. 2005;391(Pt 1):51-57. doi:10.1042/BJ20050683

42. Piskin D, Romano M, Aletaha D, et al. Developing guidelines for ultrarare rheumatic disorders: a bumpy ride. *Ann Rheum Dis*. 2022;81(9). doi:10.1136/ard-2022-222538

43. Romano M, Arici ZS, Piskin D, et al. The 2021 EULAR/American College of Rheumatology points to consider for diagnosis, management and monitoring of the interleukin-1 mediated autoinflammatory diseases: cryopyrin-associated periodic syndromes, tumour necrosis factor receptor-associated periodic syndrome, mevalonate kinase deficiency, and deficiency of the interleukin-1 receptor antagonist. *Ann Rheum Dis*. 2022;81(7):907-921. doi:10.1136/annrheumdis-2021-221801

44. Cetin Gedik K, Lamot L, Romano M, et al. 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. *Arthritis Rheumatol*. 2022;74(5):735-751. doi:10.1002/art.42087

SUPPLEMENT 1.

eAppendix. Literature Review and Development of Consensus Statements
eTable 1. Members of the DADA2 Consensus Committee
eTable 2. Questions from International DADA2 Conferences
eTable 3. Reference Studies for the Development of Consensus Statements
eTable 4. Questions for Future Research

SUPPLEMENT 2.

Group Information