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.
the early case series, adult-onset cases of DADA2 are increasingly recognized. 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. This estimate makes DADA2 a rare disease according to the US Food and Drug Administration. However, such prevalence also establishes DADA2 as a more common monogenic autoimmune inflammatory diseases with an estimated 35,000 affected individuals worldwide.

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

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. 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. 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 subspecialties 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**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Clinical manifestations</th>
<th>Abbreviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory and/or</td>
<td>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.</td>
<td></td>
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<tr>
<td>vasculitic</td>
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<tr>
<td>Hematologic</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Immunodeficient</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Presymptomatic</td>
<td>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.</td>
<td></td>
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</tbody>
</table>

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

* 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. The use of high performance liquid chromatography is also described. 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. 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). 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 DADA2.

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**Table 2. Statements for Diagnostic Testing of DADA2**

<table>
<thead>
<tr>
<th>Consensus statement</th>
<th>LOE (grade)</th>
<th>LOA (SD)</th>
<th>IPRAS-DI</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>2 (B)</td>
<td>8.6 (0.7)</td>
<td>0.19</td>
</tr>
<tr>
<td>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.</td>
<td>5 (D)</td>
<td>8.7 (0.6)</td>
<td>0.13</td>
</tr>
<tr>
<td>2.3 Near-absent ADA2 enzymatic activity in the blood is diagnostic of DADA2. Normal ADA2 enzymatic activity excludes the diagnosis of DADA2.</td>
<td>2 (B)</td>
<td>7.9 (1.4)</td>
<td>0.75</td>
</tr>
<tr>
<td>2.4 The presence of biallelic pathogenic or likely pathogenic variants in ADA2 defines a confirmatory genotype and is diagnostic of DADA2.</td>
<td>2 (B)</td>
<td>8.3 (0.7)</td>
<td>0.29</td>
</tr>
<tr>
<td>2.5 Individuals with monoallelic pathogenic or likely pathogenic ADA2 variants are considered carriers.</td>
<td>2 (B)</td>
<td>8.4 (1.1)</td>
<td>0.29</td>
</tr>
<tr>
<td>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.</td>
<td>4 (C)</td>
<td>8.7 (0.5)</td>
<td>0.13</td>
</tr>
<tr>
<td>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.* Further evaluation by enzymatic assay and/or additional genetic tests should be considered if clinical suspicion remains.</td>
<td>4 (C)</td>
<td>8.1 (1.6)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

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.

* 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. 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.

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

<table>
<thead>
<tr>
<th>Consensus statement</th>
<th>LOE (grade)</th>
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</thead>
<tbody>
<tr>
<td>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.</td>
<td>5 (D)</td>
<td>8.2 (1.2)</td>
<td>0.37</td>
</tr>
<tr>
<td>3.2 Screening should be considered for other family members with symptoms concerning for DADA2, and for individuals being considered as a donor for allogeneic HSCT for a proband within the family.</td>
<td>5 (D)</td>
<td>8.8 (0.5)</td>
<td>0.13</td>
</tr>
<tr>
<td>3.3 Genetic counseling should be considered for identification of at-risk family members, reproductive decision making, prenatal testing, and psychosocial support.</td>
<td>5 (D)</td>
<td>8.4 (1.1)</td>
<td>0.29</td>
</tr>
<tr>
<td>3.4 Screening should be considered for individuals with pediatric- or adult-onset or familial forms of polyarteritis nodosa, Shéeldon syndrome, livedo racemosa associated with inflammation, or unexplained autoimmune/inflammatory syndrome with features of DADA2.</td>
<td>5 (D)</td>
<td>8.6 (0.8)</td>
<td>0.13</td>
</tr>
<tr>
<td>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.</td>
<td>5 (D)</td>
<td>8.4 (1.4)</td>
<td>0.19</td>
</tr>
<tr>
<td>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.</td>
<td>5 (D)</td>
<td>8.5 (0.9)</td>
<td>0.29</td>
</tr>
<tr>
<td>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.</td>
<td>5 (D)</td>
<td>7.8 (1.3)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

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. Treatment also reduces the overall inflammatory burden of disease. 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. 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.

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. 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

<table>
<thead>
<tr>
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<th>IPRAS-DI</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>5 (D)</td>
<td>8.9 (0.4)</td>
<td>0</td>
</tr>
<tr>
<td>4.2 Physical examination should include blood pressure and ophthalmology examination.</td>
<td>5 (D)</td>
<td>8.1 (1.3)</td>
<td>0.49</td>
</tr>
<tr>
<td>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.</td>
<td>5 (D)</td>
<td>8.6 (0.7)</td>
<td>0.13</td>
</tr>
<tr>
<td>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.</td>
<td>5 (D)</td>
<td>8.0 (1.3)</td>
<td>0.61</td>
</tr>
<tr>
<td>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.</td>
<td>5 (D)</td>
<td>8.5 (0.9)</td>
<td>0.29</td>
</tr>
<tr>
<td>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.</td>
<td>5 (D)</td>
<td>8.6 (0.8)</td>
<td>0.19</td>
</tr>
<tr>
<td>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.</td>
<td>5 (D)</td>
<td>8.5 (1.0)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

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.34,35,34 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>
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<th>LOA (SD)</th>
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</thead>
<tbody>
<tr>
<td>5.1 TNFi is the treatment of choice for DADA2 patients with vasculitis, stroke, and/or evidence of persistent systemic inflammation.</td>
<td>5 (D)</td>
<td>8.3 (1.1)</td>
<td>0.29</td>
</tr>
<tr>
<td>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.</td>
<td>5 (D)</td>
<td>8.6 (0.6)</td>
<td>0.13</td>
</tr>
<tr>
<td>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.</td>
<td>5 (D)</td>
<td>8.4 (1.1)</td>
<td>0.29</td>
</tr>
<tr>
<td>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 TNFi inhibitors, and vasodilators for acute peripheral ischemia in select cases. TNFi inhibitors should be considered for prevention of further strokes.</td>
<td>5 (D)</td>
<td>7.7 (1.8)</td>
<td>0.75</td>
</tr>
<tr>
<td>5.5 Antiaggregants, anticoagulants, and/or antithrombotic therapy in patients with DADA2 should be avoided to prevent hemorrhagic stroke.</td>
<td>5 (D)</td>
<td>8.3 (1.3)</td>
<td>0.29</td>
</tr>
<tr>
<td>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.</td>
<td>4 (C)</td>
<td>8.4 (0.9)</td>
<td>0.22</td>
</tr>
<tr>
<td>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 &lt;500/mm3) or lymphopenic (CD4+ T cell &lt;200/mm3). Systemic antiviral therapy should be considered for patients with immunodeficiency and recurrent episodes of herpetic infection.</td>
<td>4 (C)</td>
<td>7.8 (1.3)</td>
<td>0.41</td>
</tr>
<tr>
<td>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.</td>
<td>5 (D)</td>
<td>8.3 (1.4)</td>
<td>0.66</td>
</tr>
<tr>
<td>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.</td>
<td>5 (D)</td>
<td>8.2 (1.7)</td>
<td>0.74</td>
</tr>
<tr>
<td>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.</td>
<td>5 (D)</td>
<td>8.8 (0.8)</td>
<td>0.29</td>
</tr>
<tr>
<td>5.11 Most carriers of monosialic 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.</td>
<td>5 (D)</td>
<td>8.2 (1.2)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

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. 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. 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, 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. 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.
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REFERENCES


**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