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Review article

Epidemiology, methods of diagnosis, and clinical management of patients with arginase 1 deficiency (ARG1-D): A systematic review

Aseel Bin Sawad [a,*], John Jackimiec [a], Mark Bechter [a], Allison Trucillo [a], Kristina Lindsley [b], Anil Bhagat [b], Jennifer Uyei [b], George A. Diaz [c]

[a] Aeglea BioTherapeutics, Austin, TX, USA
[b] IQVIA, Inc, Durham, NC, USA
[c] Division of Medical Genetics and Genomics in the Department of Genetics and Genomic Sciences at the Icahn School of Medicine at Mount Sinai, New York, NY, USA

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ABSTRACT

Background: Arginase 1 Deficiency (ARG1-D) is a rare, progressive, metabolic disorder that is characterized by devastating manifestations driven by elevated plasma arginine levels. It typically presents in early childhood with spasticity (predominately affecting the lower limbs), mobility impairment, seizures, developmental delay, and intellectual disability. This systematic review aims to identify and describe the published evidence outlining the epidemiology, diagnosis methods, measures of disease progression, clinical management, and outcomes for ARG1-D patients.

Methods: A comprehensive literature search across multiple databases such as MEDLINE, Embase, and a review of clinical studies in ClinicalTrials.gov (with results reported) was carried out per PRISMA guidelines on 20 April 2020 with no date restriction. Pre-defined eligibility criteria were used to identify studies with data specific to patients with ARG1-D. Two independent reviewers screened records and extracted data from included studies. Quality was assessed using the modified Newcastle-Ottawa Scale for non-comparative studies.

Results: Overall, 55 records reporting 40 completed studies and 3 ongoing studies were included. Ten studies reported the prevalence of ARG1-D in the general population, with a median of 1 in 1,000,000. Frequently reported diagnostic methods included genetic testing, plasma arginine levels, and red blood cell arginase activity. However, routine newborn screening is not universally available, and lack of disease awareness may prevent early diagnosis or lead to misdiagnosis, as the disease has overlapping symptomology with other diseases, such as cerebral palsy. Common manifestations reported at time of diagnosis and assessed for disease progression included spasticity (predominately affecting the lower limbs), mobility impairment, developmental delay, intellectual disability, and seizures. Severe dietary protein restriction, essential amino acid supplementation, and nitrogen scavenger administration were the most commonly reported treatments among patients with ARG1-D. Only a few studies reported meaningful clinical outcomes of these interventions on intellectual disability, motor function and adaptive behavior assessment, hospitalization, or death. The overall quality of included studies was assessed as good according to the Newcastle-Ottawa Scale.

Conclusions: Although ARG1-D is a rare disease, published evidence demonstrates a high burden of disease for patients. The current standard of care is ineffective at preventing disease progression. There remains a clear need for new treatment options as well as improved access to diagnostics and disease awareness to detect and initiate treatment before the onset of clinical manifestations to potentially enable more normal development, improve symptomatology, or prevent disease progression.

Abbreviations: ARG1-D, Arginase 1 Deficiency; BRIEF, Behavior Rating Inventory of Executive Function; CSF, cerebrospinal fluid; EEG, electroencephalogram; Embase, Excerpta Medica database; IQ, intellectual quotient; MEDLINE, MedicalLiterature Analysis and Retrieval System Online; NBS, newborn screening; NHS EED, National Health Service Economic Evaluation Database; NOS, Newcastle-Ottawa Scale; PCR, polymerase chain reaction; PICOS, population, interventions, comparisons, outcomes, and study design; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QoL, quality of life; UCDs, urea cycle disorders; US, United States.

* Corresponding author at: Aeglea BioTherapeutics, Austin, TX, USA.
E-mail address: abinsawad@aeglea.com (A. Bin Sawad).

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1. Introduction

Arginase 1 Deficiency (ARG1-D) is a rare genetic metabolic disorder characterized by persistently elevated levels of arginine in plasma and cerebrospinal fluid (CSF) [1,2]. An autosomal recessive trait, ARG1-D occurs due to mutations in the *ARG1* gene that code for arginase 1, the final enzyme in the urea cycle pathway that converts arginine to ornithine and urea [2,3]. Lack of arginase activity leads to elevated arginine levels and its metabolites resulting from the normal production of nitrogen, primarily due to protein turnover in the body, with a small portion dependent on diet [4]. Hyperargininemia may lead to the manifestations associated with the disease such as spastic paraparesis, progressive neurological and motor deterioration affecting mobility, growth and developmental delays, cognitive delays, seizures, and the potential for early mortality are frequently seen in ARG1-D. Although less common in patients with ARG1-D than with other urea cycle disorders (UCDs), episodes of symptomatic and even severe hyperammonemia may occur, which may lead to death, have been reported [2,4,5].

While the clinical presentation of ARG1-D varies by individual, most patients appear to have normal development from birth to toddlerhood, with symptoms beginning sometime between ages 1–3 [3,5]. Manifestations include spasticity (predominately affecting the lower limbs), mobility impairment, developmental delays, intellectual disability, and seizures [3–6]. The rate of development and disease progression in ARG1-D patients varies, however the clinical picture is strikingly uniform over time, leading to loss of developmental milestones, reduced mobility, and neurocognitive delays and deterioration [6,7]. The highly progressive and devastating nature of the disease and the extent of care required after diagnosis can be stressful, burdensome, and substantially impact the quality of life (QoL) of both patients and their caregivers [6].

ARG1-D is the least common of all UCDs, with an estimated incidence of approximately ranging from 1 in 726,000 [8] to 1 in 950,000 [9]. Although there are multiple and straightforward means of diagnosis (e.g., plasma arginine levels, genetic testing or arginase enzyme activity in red blood cells) [10], delays in diagnosis or misdiagnosis still occurs. This is possibly due to the heterogeneous nature of the clinical presentation overlapping with other conditions, such as cerebral palsy and hereditary spastic paraplegia, and insufficient disease awareness among health care professionals [2,3,5,11,12]. Early diagnosis and treatment can be improved with increased availability of testing and disease education [11,13]. Treatment initiated immediately after birth has been shown to potentially delay the onset of symptoms [14]. Early reliable diagnosis through prenatal or newborn screening (NBS) is beneficial to patients and their families to provide counseling and support, as well as being critical for early intervention with the potential for improved prognosis. However, there are certain limitations with large-scale newborn screening programs as they are not universally available, there is no standard diagnostic threshold, and false negatives may result due to the maternal blood supply of arginase, masking the disease in the neonatal period [14–17].

The main goal of long-term management for ARG1-D patients is to lower levels of plasma arginine. The current standard of care is dietary restriction, aimed at limiting arginine and protein intake through a low-protein diet, often supplemented by essential amino acids [2,3]. Such rigorous dietary restrictions are often ineffective in preventing hyperargininemia and patients rarely achieve current treatment goal of <200 μm, as strict regimens are often unpalatable and challenging [5]. Although dietary modifications can produce modest reductions in plasma arginine, levels remain markedly elevated in most patients, as arginine flux is largely due to whole body protein turnover and minimally affected by dietary intake [18]. Nitrogen scavenger drugs such as sodium phenylacetate, sodium benzoate, and glycerol phenylbutyrate also may be used to reduce the risk of hyperammonemia by removing excess nitrogen through an alternative pathway [5] but have no effect on arginine levels.

There is limited and disparate published literature describing the treatment, outcomes, and recommended clinical practice guidelines for the management of ARG1-D. The objective of this literature review was to systematically identify the published evidence and describe the epidemiology, methods of diagnosis, impact of early diagnosis on disease management, measures of disease progression, medical management, and clinically meaningful outcomes among patients with ARG1-D.

2. Methods

2.1. Overview

This protocol-driven systematic review followed the approaches outlined in the Cochrane Handbook for Systematic Reviews of

Interventions [19], the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement [20], and the United States (US) Food and Drug Administration's meta-analysis draft guidance for industry [21]. The PRISMA checklist is provided in Supplement 1.

2.2. Eligiblity criteria

Study eligibility criteria were pre-defined in terms of population, interventions, comparisons, outcomes, and study design (PICOS). Studies reporting data specific to patients with ARG1-D were included, whereas studies discussing ARG1-D patients as part of broader patient populations (e.g., UCDs) without providing information specific to patients with ARG1-D were excluded. Any intervention or comparison (or lack of comparison) was eligible. Outcome domains included epidemiology, methods of diagnosis, measures of disease progression, treatments, and clinical outcomes. Clinical trials and observational studies were eligible for inclusion if published results were available. Case reports were excluded to focus on the population level data.

2.3. Study identification

The search was designed using a combination of key words, indexing terms, and Boolean operators to be both comprehensive and sensitive in identifying relevant studies associated with ARG1-D. Terms for UCDs also were added to the search strategy to capture studies not indexed under ARG1-D or hyperargininemia terms specifically. Databases searched included the Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (Embase), Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, the Health Technology Assessment Database, EconLit, and National Health Service Economic Evaluation Database (NHS EED). The searches were executed on April 20, 2020, with the language of publication restricted to English. Clinicaltrials.gov also was searched for recent and ongoing studies with published final or interim results and the reference lists of related reviews screened to identify additional citations. The complete search strategies and results are presented in Supplement 2.

2.4. Study selection

All unique publications identified through the systematic review were evaluated in a two-step process to assess their inclusivity for data extraction based on pre-defined eligibility criteria.

The first step involved two independent reviewers (ABS and MB) evaluating all unique titles and abstracts identified by the searches. Records assessed as irrelevant were excluded, while the potentially relevant were retained for full-text review. Subsequently, both reviewers independently evaluated each full-text publication to determine eligibility while documenting any reason for exclusion.

At any stage, in case of uncertainty related to eligibility criteria or a discrepancy between the two primary reviewers, a third reviewer adjudicated a decision to include or exclude. Additionally, two reviewers (KL and ABS) reviewed inclusion and exclusion decisions prior to beginning data extraction. The process of study identification and selection is summarized with a PRISMA flow diagram [20,22].

2.5. Data collection, quality assessment, and synthesis

A data extraction template was developed to capture study and patient characteristics, epidemiology, methods of diagnosis, author-reported impact of early diagnosis, measures of disease progression, interventions administered, and clinical outcomes for all included studies. Data extraction was conducted by two independent reviewers and verified against the source document by a third reviewer in case of any discrepancy. Extracted data were reported by the study authors; no data were imputed for the purposes of this review. Data were synthesized descriptively; no meta-analysis was planned or undertaken.

A quality assessment of individual papers was performed using a modified Newcastle-Ottawa Scale for non-comparative studies [23]. Two independent reviewers scored each of the quality domains, and a third reviewer adjudicated the final assessment in case of any discrepancy. Data were synthesized descriptively as proportions, means, and medians, as appropriate.

3. Results

3.1. Search and screening summary

The database search identified 1102 records (Fig. 1). Following deduplication and supplemental searching, 918 records underwent title and abstract screening, of which 278 were retained for full-text review. A total of 55 records met the eligibility criteria and were included in the review. The 55 included records reported 40 completed studies (from 52 records) and 2 ongoing studies with interim results (3 clinicaltrial.gov records). The full citation information for included reports is provided in Supplement 3.

Clinical practice guidelines specific to ARG1-D were identified from the extensive search. Recommendations for the diagnosis, management and treatment of ARG1-D were provided in the 2019 publication "Suggested guidelines for the diagnosis and management of Urea Cycle Disorders: First Revision" by Häberle et al. [3].

3.2. Study characteristics

A combination of 40 completed cohort characterizations and clinical studies identified, 21 cohort and 19 cross-sectional studies; with a median year of publication of 2013 (range 1977–2019). The studies were geographically distributed across Asia (9 studies), Europe (13 studies), North America (15 studies), and South America (1 study), while 2 studies were multicontinental. The various patient settings or specific cohorts included hospital-based (16 studies), NBS (8 studies), specialty centers (7 studies), and laboratories (5 studies); other data sources reported by one study each were a clinical trial, consortium, registry, and surveillance study. Most studies obtained data from medical or laboratory records (30 studies); 3 studies used questionnaires and 7 studies used other methods or a combination of methods (e.g., disease registry, surveillance). The study characteristics are compiled in Table 1.

3.3. Quality assessment of included studies

Quality assessment for the 40 primary records was carried out using a modified Newcastle-Ottawa Scale (NOS) based on the study design. >50% of cohort studies (11 out of 21) scored 5 or 6 points, and none scored <3 on the NOS, indicating good overall quality of the cohort studies (Fig. 2a). However, the quality for the cross-sectional studies was lower, with most of the studies (16 out of 19) scoring 3 or 4 points and no study scoring 5 or more (Fig. 2b). The complete assessments for the NOS for all 40 studies and each rating domain are provided in Supplement 4.

3.4. Patient characteristics

A total of 291 patients with ARG1-D were included. Many of the studies enrolled broader populations, such as patients with any type of UCD or other metabolic disorder. Thus, data specific to patients with ARG1-D were inconsistently and infrequently reported across studies. In some cases, the ARG1-D population made up less than half of the patients for any given patient-level characteristic.

Overall, included studies represented an equal number of patients from both sexes (49% female) and broad age range (3–27 years); of the studies that included age of diagnosis, all indicated that the

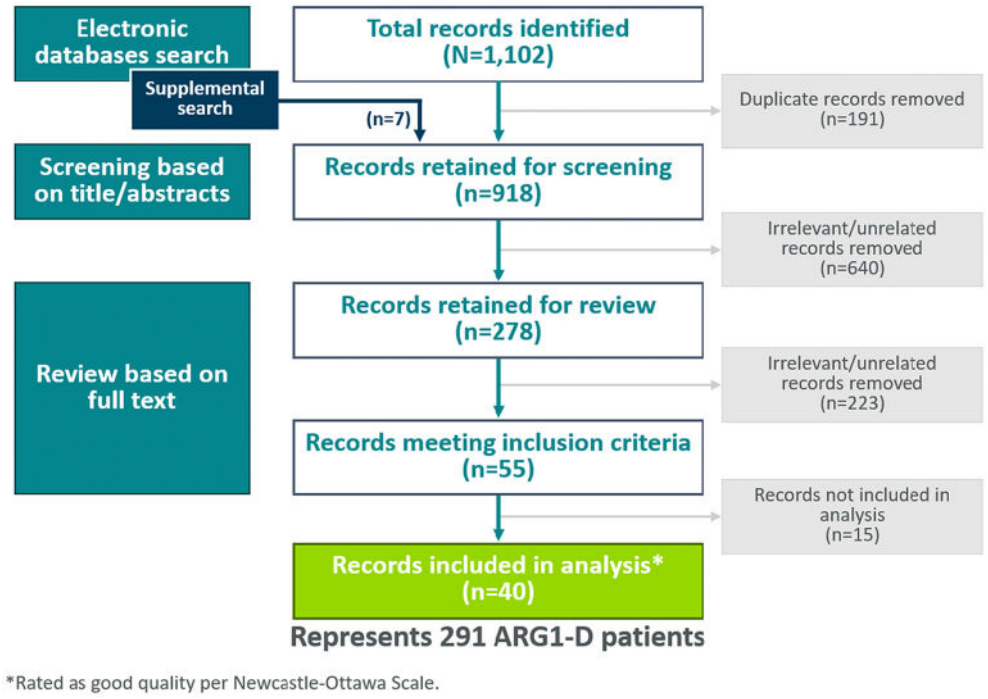

Fig. 1. PRISMA flow diagram.

Table 1
Study characteristics.

Geographic distribution of studies (40 included studies)		
Continent and corresponding publications, n (%)	Country	Studies included per country, n (%)
Asia, 9 (22.5)	China	3 (7.5)
	India	2 (5.0)
	Japan	2 (5.0)
	Lebanon	1 (2.5)
	Singapore	1 (2.5)
Europe, 13 (32.5)	Belgium	2 (5.0)
	Czech Republic	2 (5.0)
	Finland	1 (2.5)
	France	1 (2.5)
	Germany	1 (2.5)
	Switzerland	1 (2.5)
	Multiple European countries	5 (12.5)
North America, 15 (37.5)	Canada	1 (2.5)
	Mexico	1 (2.5)
	US	12 (30.0)
	US and Canada	1 (2.5)
South America, 1 (2.5)	Brazil	1 (2.5)
Multicontinental, 2 (5.0)	US, Canada, Europe	2 (5.0)
Other study characteristics		
Study design, n (%)		
Cohort study		21 (52.5)
Cross-sectional study		19 (47.5)
Patient setting or clinical site category, n (%)		
Hospital-based		16 (40.0)
Newborn screening		8 (20.0)
Specialty centers		7 (17.5)
Laboratories		5 (12.5)
Others (clinical trial, consortium, registry, and surveillance)		4 (10.0)
Source of data, n (%)		
Medical records		30 (75.0)
Questionnaires		3 (7.5)
Others (e.g., disease registry, surveillance program)		7 (17.5)

US - Unites States.

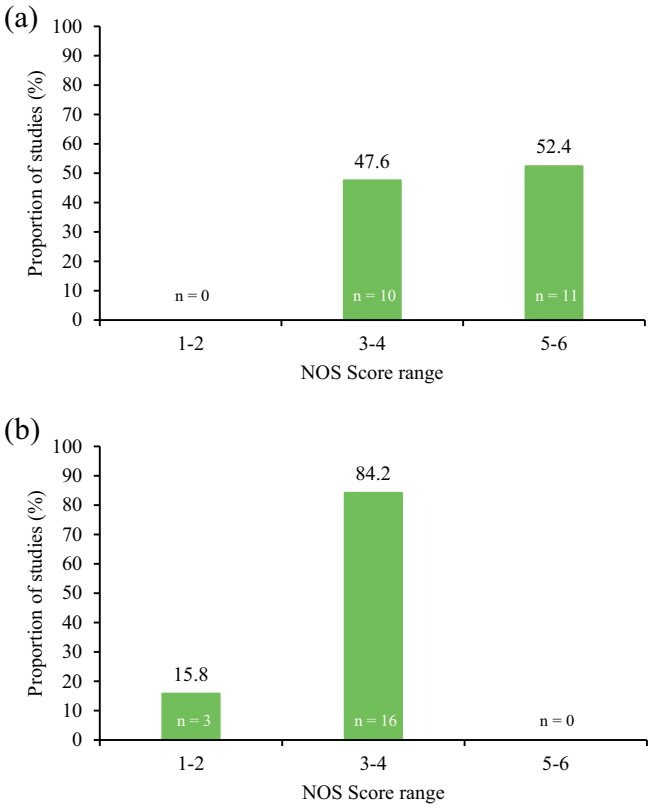

Fig. 2. (a) NOS scoring system-based quality assessment of cohort studies (21 studies). (b) NOS scoring system-based quality assessment of cross-sectional studies (19 studies). NOS - Newcastle-Ottawa Scale.

diagnosis of ARG1-D was made during childhood (ages 0–9 years). Twelve studies reported the mean age of ARG1-D patients at the time of the report (24%, 70 patients), with the ages ranging from: 3–4 years (2 studies), 6–9 years (3 studies), 11–12 years (2 studies), 19–21 years (3 studies), and 23–27 years (2 studies). Thirteen studies (37%, 107 patients) reported the mean age at diagnosis with the mean range found to be 0–9 years. For the 5 studies with available data, 46% (21 out of 46 patients) had consanguineous parents. Patient demographics are summarized in Table 2.

3.5. Epidemiology findings

Ten studies (7 NBS) reported the prevalence of ARG1-D in the general population (Table 3). The median reported prevalence was 1 in 1,000,000 but ranges were broad. Studies from Asia reported both the highest and lowest prevalence: an NBS study from China reported the highest prevalence of 2 out of 100,077 children screened [24], while the lowest prevalence was reported in a Japanese retrospective cohort estimating a prevalence of 1 in 2,200,000 [13] and an NBS study from Singapore that did not identify any patients out of the 177,267 children screened [25].

Twenty geographically dispersed studies (2 NBS) reported the prevalence of ARG1-D within the UCD population. The range within the UCD population for ARG1-D was 0–27.1% with a median of 3.8%. The highest prevalence rates among the UCD population were 27.1% and 18.9%, and were reported in a US study and Mexican study, respectively [26,27]. The lowest prevalence rate of ≤2% was documented in 4 studies from Europe and 1 study from Japan [28–32]. The prevalence ranged from 6.0% to 27.1% for 3 US studies [26,33,34], and the median prevalence for 9 European studies was 2.6% [29–32,35–39].

3.6. Investigations and methods of diagnosis

Diagnostic methods for ARG1-D were mentioned in 37 studies (Table 4). Genetic testing was the mostly frequently reported (12 studies), generally using polymerase chain reaction (PCR) to detect mutations in the *ARG1* gene. The most common diagnostic laboratory assessments used were plasma arginine levels (22 studies; usually via mass spectrometry) and red blood cell arginase activity (16 studies) using both fresh and dried blood samples [24,40–43]. Arginine levels also were tested in other types of specimens, such as in CSF (2 studies), urine (2 studies), and leukocytes (1 study). Six studies evaluated levels of additional amino acids such as ornithine (5 studies), glutamine (2 studies), phenylalanine (2 studies) and aspartic acid, lysine, threonine (1 study each) in plasma and erythrocytes, although these were corroborating and not diagnostic. Metabolites were evaluated in plasma, serum, or erythrocytes for 10 studies (4 for orotic acid, 2 for guanidino compounds, 1 each for glutathione, prealbumin, and pyrimidine; 1 study did not specify the metabolite).

Although not sufficient as a lone method of diagnosis, 13 studies reported the use of blood ammonia levels as part of the diagnostic work-up in two ways. The most common approach included evaluating blood ammonia levels in combination with one of the following methods: NBS, absence of arginase activity in red blood cells, and/or elevated plasma arginine (11 studies). The second methodology used elevated blood ammonia levels as triage, followed by confirmation with genetic or lab testing of arginine levels (2 studies).

Out of the 15 studies identifying patients through NBS, nearly all tested blood samples. Other reported investigations were abnormal electroencephalogram (EEG, 2 studies), abnormal brain imaging (1 study), and clinical presentation and family history (3 studies). Thirteen studies discussed the potential positive impact of early diagnosis (most recommended NBS), to afford better management of the disease, opportunity to provide early counseling for patients and caregivers, initiation of treatment before onset of symptoms to prevent, delay, and/or minimize clinical manifestations of the disease, and improvement of the QoL of patients and caregivers.

Table 2
Patient demographics.

Patient demographics (291 included patients)	
Gender, n (%)	
Patients with data reported (15 studies)	88 (30.2)
Male	45 (51.1)
Female	43 (48.9)
Parental consanguinity, n (%)	
Patients with data reported (5 studies)	46 (15.8)
Yes	21 (45.7)
No	25 (54.3)
Age distribution across studies, n (%)	
Range of mean age at time of report (12 studies; 70 patients)	
3–4 years	2 studies (16.7%)
6–9 years	3 studies (25.0%)
11–12 years	2 studies (16.7%)
19–21 years	3 studies (25.0%)
23–27 years	2 studies (16.7%)
Mean age at diagnosis (13 studies: 107 patients)	107 (36.8%)
<1 year (8 studies of newborn screening)	9 studies (69.2%)
>1 year	4 studies (30.8%)

Table 3
Epidemiology of ARG1-D.

Region	Proportion, %	Author-reported incidence/prevalence
General population (10 reported studies; 7 NBS)		
Multicontinental		
Europe/North America	NR	<1/1,000,000
US/Europe	NR	1:950,000
North America		
US	0.002%	5 (estimated per 1,000,000)
US	0.0001%	1:1,119,500
Canada	0.0002%	1.62 (estimated per 1,000,000)
Europe		
Czech Republic	0.0%	1:1,000,000
Finland	NR	1:1,616,000 (imputed)
Asia		
China	0.002%	NR
Japan	NR	1:2,200,000
Singapore	0.0%	0
UCD population (20 reported studies; 2 NBS) (Range 27.1, Median 3.8)		
Multicontinental		
US and Europe	2.7	
US, Canada, Europe	3.8	
North America		
US	27.1	
US	6.0	
US	9.1	
Canada	7.1	
US, Canada	2.3	
Mexico	18.9	
Europe (Range 0–8.7, Median 2.6)		
European countries	5.0	
European countries	0.0	
European countries	2.6	
European countries	2.0	
European countries	3.8	
Switzerland	8.7	
Germany	6.7	
France	1.6	
Finland	1.8	
Asia		
Japan (1 study)	0.6	
Japan (1 study)	3.2	
India (1 study)	7.3	

NBS - Newborn Screening; NR - Not reported; UCD - Urea Cycle Disorder; US - Unites States.

Table 4
Investigations and methods of diagnosis.

Investigations/methods of diagnosis (37 reported studies)	Author-reported assessment
	Studies reporting method, n (%)
Methods of diagnosis	
Elevated arginine level	
Plasma	22 (59.5)
CSF	2 (5.4)
Urine	2 (5.4)
Leukocytes	1 (2.7)
RBC arginase absence	16 (43.2)
Genetic testing	12 (32.4)
Other investigations	
NBS	15 (40.5)
Elevated blood ammonia	13 (35.1)
Abnormal EEG	2 (5.4)
Abnormal brain imaging	1 (2.7)
Other amino acid levels	
Ornithine	5 (13.5)
Glutamine	2 (5.4)
Phenylalanine	2 (5.4)
Aspartic acid	1 (2.7)
Lysine	1 (2.7)
Threonine	1 (2.7)
Metabolite levels (plasma, serum, erythrocytes)	
Orotic acid	4 (10.8)
Guanidino compounds	2 (5.4)
Glutathione	1 (2.7)
Prealbumin	1 (2.7)
Pyrimidine	1 (2.7)
Not specified	1 (2.7)
Clinical presentation or family history	3 (8.1)

CSF - Cerebrospinal fluid; EEG – Electroencephalogram; NBS - Newborn Screening; RBC - Red blood cell;
Patient proportions not disclosed in reported studies.

3.7. Measures of disease progression

Measures of disease progression were reported in 23 studies, with 18 reporting clinical manifestations and 14 reporting lab measures (Table 5).

Overall, progression was primarily characterized using subjective clinical assessments. Investigators noted frequent reductions in motor function/mobility, worsening of intellectual disability, developmental delays, or development of seizures. Among studies reporting progression, motor function/mobility was the most frequent measure of worsening of disease (14 studies), wherein 71% (70 out of 99) patients had reduction in motor dysfunction/disability (13 studies) and 81% (52 out of 64) patients had increased spasticity (8 studies). Most subjects, 85% (84 out of 99), were assessed as having some form of intellectual disability (9 studies) as the second most frequently reported method of identification of disease progression (12 studies). Other measures used included worsening of developmental delay (8 studies; 49% [33 out of 67] patients), new onset of seizures (9 studies; 60% [44 out of 73] patients), and regression in adaptive behaviors (7 studies; 13% [7 out of 53] patients). Less frequently reported assessments of progression included delays in physical growth (2 studies; 90% [28 out of 31] patients), development of vomiting (3 studies; 16% [4 out of 25] patients), new laboratory detection of liver dysfunction (4 studies; 14% [3 out of 22] patients), development of ataxia (2 studies; 7% [2 out of 31] patients) and imaging noting cerebral atrophy (1 study; 20% [3 out of 15] patients) (Fig. 3).

Laboratory assessments have also been used to document disease progression including changes in plasma amino acids (6 studies) and increases in blood ammonia (11 studies). Other measures (2 studies) were changes in total blood protein, blood albumin, blood vitamins and minerals, plasma metabolites, urinary orotic acid, and urinary pyrimidines.

Table 5
Measures of disease progression.

Measures of disease progression (23 reported studies)	Studies reporting data, n	Studies reporting quantitative data, n	Total patients with data reported, n	Proportion of patients displaying manifestations
Manifestations[a] (18 reported studies)				
Motor deficits	14	13	99	70/99 (70.7%)
Intellectual disability	12	9	99	84/99 (84.8%)
Developmental delay	8	8	67	33/67 (49.3%)
Seizures	9	9	73	44/73 (60.3%)
Adaptive behavior issues	7	5	53	7/53 (13.2%)
Spasticity	8	8	64	52/64 (81.3%)
Impaired balance or ataxia	3	2	31	2/31 (6.5%)
Vomiting	6	3	25	4/25 (16.0%)
Physical growth	5	2	31	28/31 (90.3%)
Liver function	6	4	22	3/22 (13.6%)
Cerebral atrophy	1	1	15	3/15 (20.0%)
Lab measures[b] (14 reported studies)				
Plasma amino acids levels	6	2	21	21/21 (100%)
Blood ammonia levels	11	1	15	13/15 (86.7%)

Cognitive/behavioral/motor assessments reported (no quantitative data) – IQ test (3 studies), child behavior check (1 study), BRIEF (1 study), Bayley Scaled of Infant Development (1 study) and grooved pegboard test (1 study).
[a] Additional manifestations reported in 1–2 studies - encephalopathy, failure to thrive, feeding problems, impaired consciousness, malnutrition, odor, other organ manifestations, sepsis-like appearance, sphincter or urinary control, structural issues.
[b] Additional lab measures reported in 1–2 studies (no quantitative data reported) - Total blood protein, blood albumin, abnormal blood tests, blood vitamins and minerals, clinical tests, plasma metabolites, urinary orotic acid and urinary pyrimidines.

No routine clinical outcome tools were reported across studies; however, a few studies reported use of standard cognitive, behavioral, or motor assessments, including the intellectual quotient (IQ) test (3 studies), Child Behavior Checklist (1 study), Behavior Rating Inventory of Executive Function (BRIEF, 1 study), Bayley Scales of Infant Development (1 study), and the grooved pegboard test (1 study).

3.8. Treatments and clinical outcomes

Fifteen studies included information about management of ARG1-D patients, including dietary protein restriction (10 studies), nitrogen scavengers (12 studies), essential amino acid supplementation (6 studies), dialysis (2 studies), blood transfusion and liver transplantation (2 studies). Not all studies reported quantitative data. The treatments are summarized in Table 6.

The most widely reported intervention was dietary protein restriction (7 studies; 95% [72 out of 76] patients), followed by prescribing nitrogen scavengers to reduce the risk or treat hyperammonemia (10 studies; 62% [70 out of 113] patients) and supplementation with essential amino acids (5 studies; 45% [37 out of 82] patients) (Fig. 4).

Standard treatments for ARG1-D were reported as generally ineffective to reduce arginine levels to recommended levels to prevent symptoms or slow progression of disease. Burrage et al. [26] reported that even after following dietary protein restrictions, plasma arginine levels far exceeded the upper limit of the treatment guidelines of <200 μm. Another study by Carvalho et al. [44] noted that adherence to strict dietary restrictions was challenging due to established feeding habits in patients prior to diagnosis and the socioeconomic limitations of families to obtain additional nutritional therapies. Interpatient and intrapatient studies indicated that protein restriction alone is not an adequate solution to treat hyperargininemia as the bulk of arginine comes from endogenous protein turnover [45].

Less commonly described interventions included liver transplantation, dialysis, and blood transfusions. Liver transplantation has been proposed as an effective means to overcome enzymatic deficiency in the liver, eliminating the need for strict dietary restrictions and nitrogen

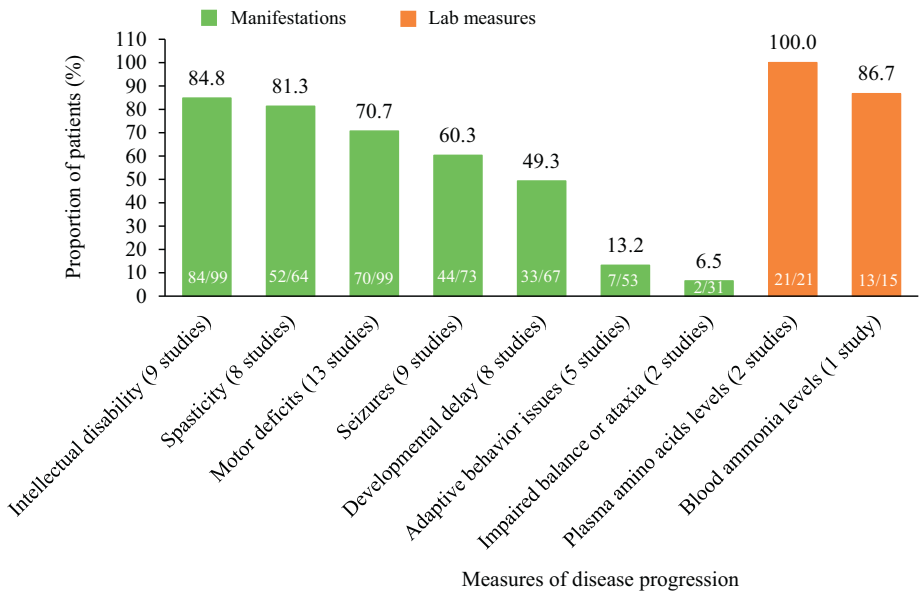

Fig. 3. Proportion of patients displaying various measures of disease progression.

scavenger treatment to prevent hyperammonemia [46]. Studies suggest that it helps normalize arginine and ammonia levels and prevents further neurological impairment [47,48]; however, liver transplantation is resources intensive and considered high-risk for cases of acute liver failure or encephalopathy [3]. Dialysis and blood transfusion have been used to acutely reduce levels of plasma arginine and ammonia; however, the treatment is short-term, with clinical effects lasting only for a few months [27,49]. Given the challenges and feasibility of these treatments, these options are rarely pursued [50,51], and were infrequently reported in the literature.

Few studies reported quantitative assessment of the effect of treatment on clinical outcomes; of those that did, most reported continued progression from baseline or worsening of disease manifestations despite initiation of therapy. Four studies reported the number of patients with intellectual disability (93%, [27 out of 29 patients]); 5 studies assessed impaired motor function, including 1 study providing the number of patients with spasticity (38% [3 out of 8] patients); and 3 studies incorporated an adaptive behavior assessment, with 1 study reporting results (13% [1 out 8] patients with behavior issues). Hospitalization as an outcome was assessed in 3 studies (25% [1 out of 4] patients reported from 1 study), while death was reported in 10 studies (20% [6 out of 30] patients reported from 7 studies) (Table 6; Fig. 5).

3.9. Update of search

An updated search was conducted to determine whether additional studies published since the date of the last search (April 20, 2020) to

Table 6
Treatments and outcomes reported by included studies.

Treatments (15 reported studies)	Studies reporting data, n	Studies reporting quantitative data, n	Total patients with data reported, n	Proportion of patients displaying manifestations
Dietary protein restriction, n (%)	10	7	76	72/76 (94.7%)
Nitrogen scavengers, n (%)	12	10	113	70/113 (61.9%)
Essential amino acid, n (%)	6	5	82	37/82 (45.1%)
Dialysis, n (%)	2	2	33	4/33 (12.1%)
Liver transplantation, n (%)	2	2	17	1/17 (5.9%)
Others				
Antibiotics	1	1	12	0/12 (0.0%)
Antiepileptic drugs	1	1	16	14/16 (87.5%)
BCAA supplements	1	1	9	1/9 (11.1%)
Energy supplements	1	1	9	8/23 (34.8%)
Fluid electrolyte therapy	1	1	26	23/26 (88.5%)
Insulin	1	1	26	0/26 (0.0%)
Lipids	1	1	26	15/26 (57.7%)
Tube feeding	1	1	12	3/12 (25%)
Clinical outcomes – 15 reported studies				
Intellectual disability	7	4	29	27/29 (93.1%)
Mobility/motor function	5	1	8	3/8 (37.5%)
Spasticity	1	1	8	3/8 (37.5%)
Adaptive behavior assessment	3	1	8	1/8 (12.5%)
Hospitalization	3	1	4	1/4 (25%)
Death	10	7	30	6/30 (20%)

BCAA - Branched chain amino acids.
Three ongoing pegzilarginase treatment studies reported.
Additional clinical outcomes reported (no quantitative data) - plasma essential amino acids (3 studies), adverse events (1 study), blood ammonia (3 studies) and organ trasplantation (1 study).

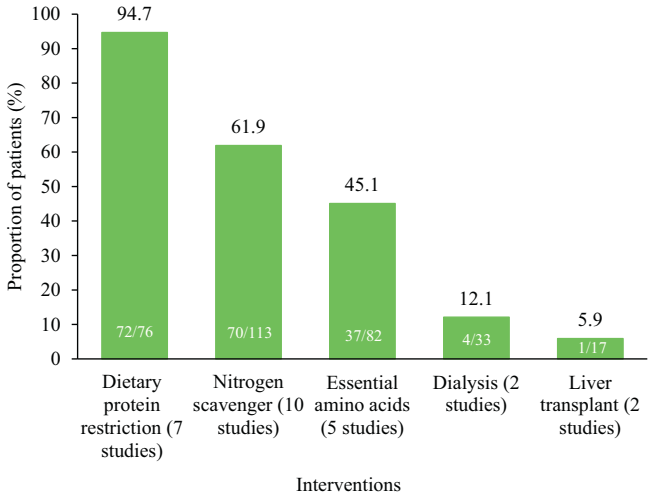

Fig. 4. Proportion of patients receiving various treatment interventions.

July 06, 2021, may impact the findings of this review. In addition to the pegzilarginase study described above, 3 other publications of patients with ARG1-D were identified [52–54]. All the articles were consistent with the review findings, providing further support.

There were 2 publications [52,53] that reported updated data from an already included study of UCD patients in Japan [33]. Of 229 UCD patients in the cohort, 8 had ARG1-D (4 males and 4 females, median age 21 years and 8 months). Compared with all UCD patients, patients with ARG1-D had the highest percentage of short stature (75% compared with 33% overall), poor weight gain (50% versus 23%), and spasticity (38% versus 8%). Median plasma arginine at time of onset or diagnosis was 527.8 umol/L (IQR 499.5–635.6). Most patients were diagnosed by RBC analysis (75%) or genetic mutation (63%); 2 patients were diagnosed in the neonatal period and 6 at 28 days or more after birth. Most patients were put on a low-protein diet (6/8) or special formula (7/8); 2 patients also received sodium benzoate and 4 received sodium phenylbutyrate. Among 7 ARG1-D patients with follow-up data, 3 patients with hyperargininemia exceeding 272 μmol/L developed cognitive impairment and 1 patient underwent liver transplantation.

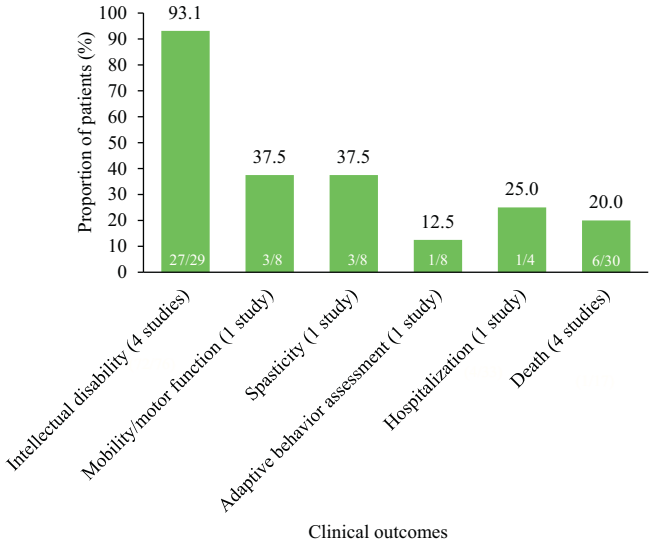

Fig. 5. Proportion of patients displaying clinical outcomes.

A study in the US examined the ratio of arginine to ornithine as diagnostic marker following a positive newborn screening result [54]. The rationale for the study was that plasma arginine may not always be elevated in newborns due to lingering effects of maternal arginase and therefore diagnosis based on plasma arginine levels alone may potentially miss making a timely diagnosis. Two patients in the study had normal plasma arginine levels at screening leading to delayed diagnosis which was associated with an adverse outcome (developmental delay, cognitive impairment, and spasticity) for 1 of the patients. From a database with over 6500 samples, the study found that an arginine to ornithine ratio > 1.4 could have identified all 14 patients with ARG-1 in the database. Further study of this methodology is warranted.

4. Discussion

To our knowledge, this is the first systematic review of published data that summarizes the epidemiology, methods of diagnosis, characterization of disease manifestations and measures of disease progression, as well as clinical management and assessment of treatment effectiveness for patients with ARG1-D. Nearly 300 patients were identified in the published literature during the period from 1977 to 2019. However, some patients/groups with ARG1-D may be included in more than one study, given the rarity of ARG1-D, and there was no further information to investigate this topic. Based on this systematic review, the median prevalence of this rare disease was found to be 1:1,000,000, with a higher number of patients in areas where consanguinuity is more common. Of the studies included in this review, the highest prevalence of ARG1-D was found in North America (US and Mexico), followed by Asia and Europe. Compared to the results of this systematic review, Catsburg et al. (2022) recently estimated a lower prevalence of ARG1-D (1 in 726,000) [8]. However, both studies used different research methods. Catsburg et al. used genetic databases as a tool to establish global prevalence [8] while our study systematically reviewed previously published literature.

Consistent with known current practice, three standard diagnostic approaches were reported in the literature for confirming diagnosis of ARG1-D in patients, including hyperarginemia, genetic detection of an abnormal *ARG1*, or reduced arginase activity in red blood cells. Blood ammonia levels were not used for diagnostic purposes, but were monitored as hyperammonemia may occur periodically in patients with ARG1-D, with catastrophic consequences in some [5]. Although uncommon, hospitalization and fatalities related to severe hyperammonemia have been documented [55,56].

The goal of early diagnosis and intervention is to prevent development or lessen the severity of the disease with initiation of treatment quickly after disease confirmation, leading to improved prognosis. Due to variation in the time to onset and high heterogeneity of the clinical manifestations of ARG1-D among patients, combined with the ultra rare nature of the disorder, there may be a delay in diagnosing ARG1-D at early stages [57]. Evidence of dietary protein aversion by the patient and the lack of risk factors for more common conditions may provide a signal to test for ARG1-D [58]. NBS by tandem mass spectrometry [59,60] may be used to quantify arginine within a few hours or days of birth. Unfortunately NBS is limited by false negatives due to the presence of the mother's arginase in neonatals, lack of standardization, and paucity of universal availability. Next-generation sequencing technologies may be useful in diagnosing patients with ARG1-D; however, there are considerable limitations due to high cost and novel mutations that occur among patients [61].

Many of the included studies reported various measures of disease progression; however, there was no consistency as to which measures were utilized nor was there standardization as to how they were reported (e.g., different criteria were used to determine developmental delays). A wide range of approaches have been used to monitor progression (caused by consistent elevated plasma arginine), such as worsening of motor deficits, in particular severity of spasticity of the lower

limbs. Many children displayed severe spasticity of the lower extremities, loss of ambulation, regression or delays in development, and seizures. Although congnitive development can progress normally during infancy, between 1 and 3 years [5], there is slowing or regression. If left untreated, severe intellectual disabilities, and neurological impairments occur. Protein aversion was reported as well, leading to inadequate nutrition and a requirement for a specific diet with supplemental feeding regimens. Patients with ARG1-D will need lifetime monitoring and supportive care to manage ARG1-D and treat comorbidities (e.g., spasticity and developmental delays) that develop over time. Thus, standardization of methods for evaluating and measuring disease progression over different stages of life is warranted [10].

A retrospective analysis of claims data in the US found that health care resource utilization was twice as high for individuals with ARG1-D than those without in terms of emergency room visits, 1.5 times higher for performing laboratory tests, and required hospitalization three times more often [62].

Current treatments have not been shown to be effective in preventing spasticity. Common treatment regimens are designed to reduce plasma arginine to guidance levels <200 μm primarily through dietary protein restrictions. Supplementation with arginine-free essential amino acids is often required to support growth and development to meet nutritional needs as best as possible. Nitrogen scavengers are frequently used to reduce the risk of hyperammonemia or treated episodic elevations of ammonia. Unfortunately, among the included studies, none of these options effectively treated hyperargininemia or minimized the patient burden of disease management [13]. Other rarely utilized treatment options included liver transplantation, dialysis, and red blood cell transfusion [27,49]. Due to the cost, limited availability and comorbidities associated with transplant, this option is not commonly used [3]. Dialysis is an extreme measure to reduce arginine levels, but is only temporizing, time consuming and costly. In addition, transfusion has been used with short term success but is limited by the risk of iron overload, blood borne illness, and the transient nature of its benefit [50,51].

A potential therapeutic option currently in development, is pegzilarginase, a novel recombinant human arginase 1 enzyme that was engineered to break down the amino acid arginine. Since the search in this review was initiated, the Phase 1/2 trial results and the data from the first 12 weeks of the open-label extension study have been published. Initial results showed that pegzilarginase was well tolerated and effective in rapidly and sustainably reducing plasma arginine to guidance levels in patients with ARG1-D and improving motor impairment (NCT03378531) [63]. The trial enrolled 16 patients from four countries who were at least 2 years of age with plasma arginine >200 uM at baseline, on standard disease management, were diagnosed with ARG1-D based on genetic testing or deficient red blood cell enzyme activity, and without severe uncontrolled hyperammonemia. All patients demonstrated reduced plasma arginine following treatment with pegzilarginase and 79% responded with clinically meaningful improvements using objective mobility assessments. The recent results of the pivotal Phase 3 PEACE clinical trial (Pegzilarginase Effect on Arginase 1 Deficiency Clinical Endpoints) showed that pegzilarginase was well tolerated, with a safety profile consistent with the previous Phase 1/2 study and no treatment discontinuations owing to tolerability [64]. A total of 32 patients were enrolled (pegzilarginase, $n = 21$; placebo, $n = 11$) in an ongoing randomized, double-blind, placebo-controlled trial with an open-label extension. The results showed that pegzilarginase significantly reduced mean plasma arginine from 365.4 μmol/L at baseline to 105.5 μmol at week 24, representing a reduction of 76.7% relative to placebo ($p < 0.0001$) [64]. Pegzilarginase has also shown a trend in clinical trials to improve mobility in patients. Further evaluation is underway to assess potential effects of longer-term use as relates to efficacy and safety, with assessment of anti-drug antibodies with continued exposure, although initial evidence suggests these to be transient and generally low-titer.

Other studies have suggested that guanidino compounds may play a role in the development of neurological abnormalities in patients with ARG1-D [65–69]. Recommendations to monitor the level of guanidinoacetate in the blood and cerebrospinal fluid have been proposed to prevent seizures and other neurological manifestations [70]. Another study suggested that hepatic arginase deficiency fosters dysmyelination during postnatal central nervous system development, and hence contribute to manifestations [71].

Although rigorous systematic review methods were employed, there are some limitations to this study. In developing a comprehensive literature search to identify studies on the the rare ARG1-D population, many focused on broader disease populations, such as UCDs. As such the published data specific to ARG1-D patients was sparse without standardard approaches to assessement or measurement of progressive diease. Secondly, most studies examined diagnosis methods, and/or the patient journey up to, during, and/or immediately following diagnosis but few reported on any intervention and long term follow-up therafter, precluding a clear depiction of patients' ongoing care, complications, rates of progression, burden of diease, and management in the literature. Finally, since no date restriction was employed while conducting searches and screening the literature, studies included in this review spanned five decades (1977–2020), with an evoloving knowledge of the disease and its managemt. Changes in clinical practice and advances in the understanding of ARG1-D influenced the treatment and management of patients in terms of overall improved outcomes of more recent cases. Unfortunately, regardless of date of publication, there is a lack of clinical effectiveness of current treatment modalities to effectively reduce arginine, prevent symptom development, or halt progressive disease resulting in a continued and significant unmet medical need for patients with ARG1-D.

5. Conclusions

This comprehensive review of available literature highlights the clear unmet need for an increased focus on ARG1-D patients. Studies included in this review indicate a lack of standardization of diagnosis and access to screening, diverse assessments used to measure baseline and progressive disease symtpomatology, challenges of maintaining therapeutic dietary interventions, the failure of a large number of patients to experience clinical benefit with currently available treatments, and the high burden of disease and its management among patients. Increases in disease awareness and improvements in access and in standardizing the availability of diagnostic pathways are needed to accurately identify patients in a timely manner. Ready access to diagnosis is critical in order begin management of the disease before the onset of clinical manifestations. Uniform methodologies should be developed to characterize symptoms and measure progression. Additional studies are needed to apply a standard apprach for capture and assess long term management. New treatment options are needed as the current standard of care is inadequate to bring arginine levels down sufficiently to positively impact the disease outcomes. In addition, clinical trials to evaluate clinically effective treatment options for patients with ARG1-D will be required. The aim of new therapies should address the underlying cause of disease (absence of arginase 1) while assessing the impact on clinically meaningful outcomes. The ultimate objective for the medical community in ARG1-D patients should be to reduce plasma arginine levels to treatment guidelines or to normal levels, and improve or halt progression of symptoms, with the goal of eventually delaying or preventing the onset of clinical manifestations.

Declaration of Competing Interest

This study was sponsored by Aeglea BioTherapeutics. Aseel Bin Sawad, John Jackimiec, Mark Bechter, and Allison Trucillo are employees

of Aeglea BioTherapeutics. Kristina Lindsley, Anil Bhagat, and Jennifer Uyei are employees of IQVIA. George A. Diaz is employed at the Division of Medical Genetics and Genomics in the Department of Genetics and Genomic Sciences at the Icahn School of Medicine at Mount Sinai and has served as an advisor/consultant and clinical trial investigator for Aeglea BioTherapeutics.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2022.08.005.

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