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Natural History, Clinical Outcomes, and Unmet Needs of Patients with Arginase 1 Deficiency (ARG1-D): A Systematic Review of Case Reports

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Background
ARG1-D overview

Progressive, life-threatening inherited metabolic disease characterized by persistent high levels of arginine and arginine metabolites[1,2]

Key manifestations (**spasticity, developmental delay, intellectual disability, seizures**) typically begin in **early childhood**[2-4]

Diagnosis may be delayed, leading to disease progression and worse clinical outcomes[5]

High patient and caregiver burden with severely impaired quality of life; most patients lose ability to walk independently[2]

Managed with severe dietary protein restriction, which can have detrimental health effects and rarely reduces arginine levels to target[2,3,6]

New, effective therapies are needed

1. Carvalho DR, et al. *Gene.* 2012;509:124–130; 2. Carvalho DR, et al. *Pediatr Neurol.* 2012;46:369–374; 3. Amayreh W, et al. *Dev Med Child Neurol*. 2014;56:1021–1024; 4. Bakhiet M, et al. *Medicine (Baltimore).* 2018;97:e10780; 5. Huemer M, et al. *J Inherit Metab Dis.* 2016;39:331–340; 6. Haberle J, et al. *Orphanet J Rare Dis.* 2012;7:32.

Background

ARG1-D pathophysiology and diagnosis

- Distinct urea cycle disorder
  - Defective/deficient arginase activity → high levels of arginine and arginine metabolites[1-3]
    - Elevated arginine → clinical manifestations of ARG1-D[1-3]
  - In most patients, average arginine levels 3.5- to 10-fold higher than normal levels (normal reference range, 41–114 µmol/L)[4]

- Diagnosis readily made by:

Amino acid analysis
High plasma arginine

Genetic analysis
Pathologic *ARG1* variant

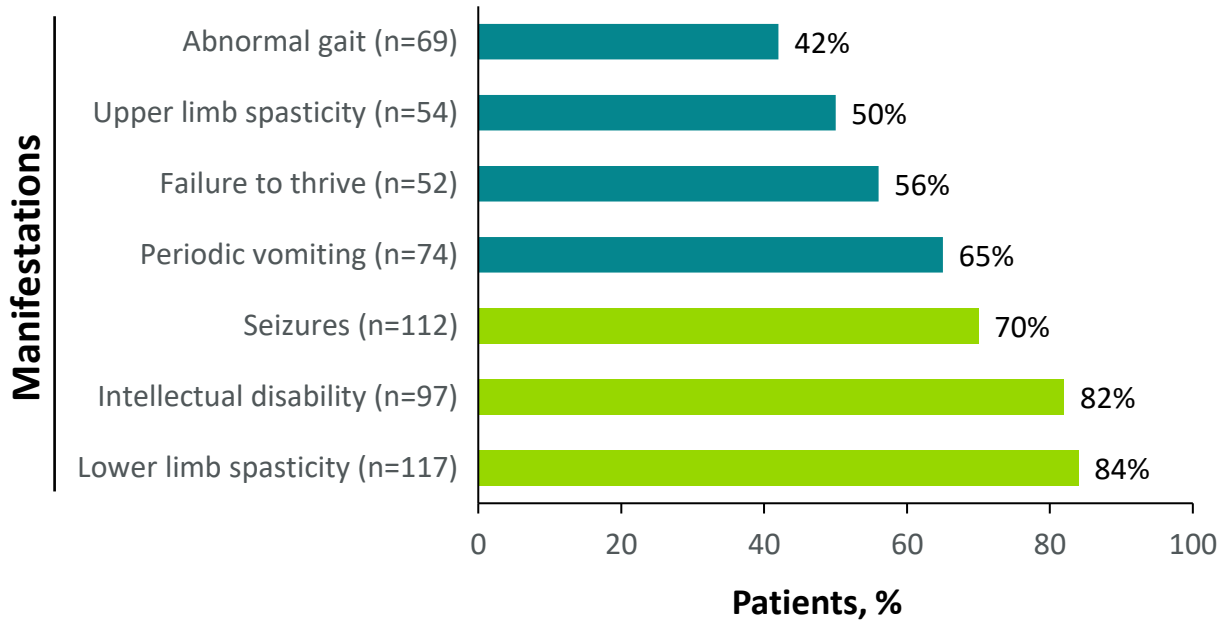
- Delays in diagnosis can occur if:
  - Not identified at birth (eg, limitations of/access to newborn screening)
  - Misdiagnosed with a condition with similar neurologic manifestations (eg, cerebral palsy, hereditary spastic paraplegia)

1. Carvalho DR, et al. *Gene.* 2012;509:124–130; 2. Carvalho DR, et al. *Pediatr Neurol.* 2012;46:369–374; 3. Sun A et al. GeneReviews [May 2020]; available at https://www.ncbi.nlm.nih.gov/books/NBK1159;
4. Luneburg et al. J Nutr. 2011;141(2186-2190).

Background
Manifestations and morbidity

- Progressive and debilitating
- Persistently high arginine and arginine metabolites are likely cause of neuropathology[2]
  - Progressive, variable neuromotor decline[3,4]
  - If untreated, can progress to severe spasticity and intellectual disability[5]
- Impairment/disability place significant burden on patients, caregivers, and healthcare systems
- Life expectancy is reduced[1,4,6,7]

Commonly reported manifestations[1]



Adapted from Diaz et al, EPNS 2019:P06-34

1. Diaz GA, et al. EPNS Congress; September 17-21, 2019; Athens, Greece [P06-34]; 2. Diez-Fernandez C, et al. Hum Mutat. 2018;39:1029–1050; 3. Carvalho DR, et al. Pediatr Neurol. 2012;46:369–374; 4. Crombez EA, Cederbaum SD. Mol Genet Metab. 2005;84:243–251; 5. Wong D, et al. eds. GeneReviews®. 2014; 6. Schlune A, et al. Amino Acids. 2015;47:1751–1762; 7. Huemer M, et al. J Inherit Metab Dis. 2016;39:331–340.

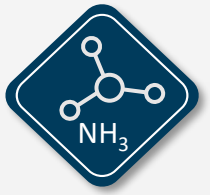
Background

Management and unmet need

- Current standard of care (SOC) relies on individualized disease management with:

Severe dietary protein restriction

Essential amino acid supplementation



Nitrogen (ammonia) scavengers

- Novel therapies are needed
  - SOC does not address endogenous arginine
  - SOC is difficult to adhere to
  - Patients continue to progress

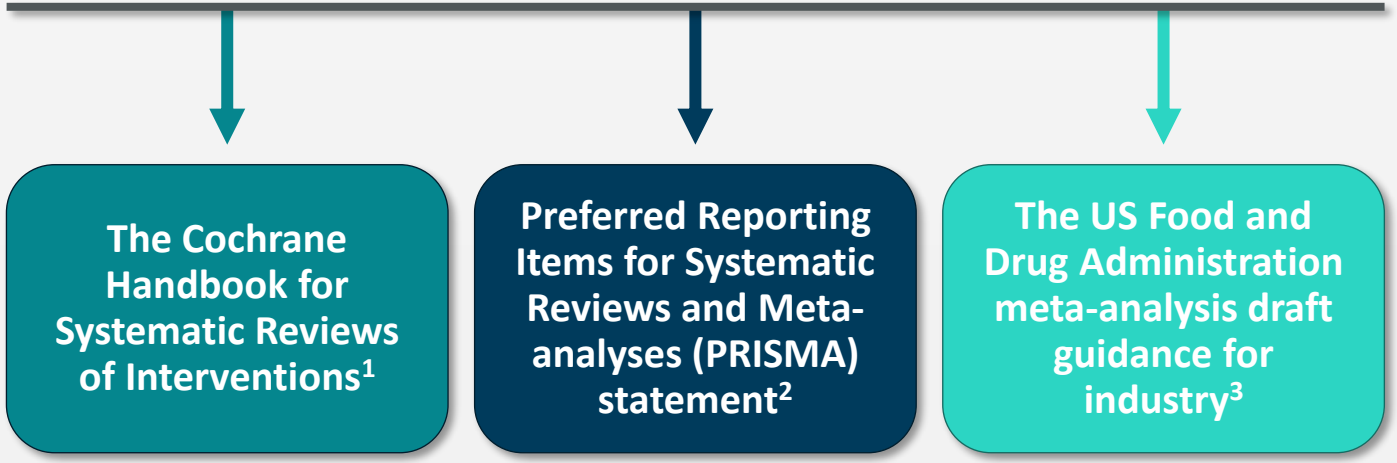
SOC is not sufficiently effective in reducing arginine levels to goal

Objectives

1. To describe the natural history and patient impact of ARG1-D
2. To examine published evidence on ARG1-D management
3. To identify unmet needs of ARG1-D patients

Methods

This systematic literature review was conducted according to:



Databases searched

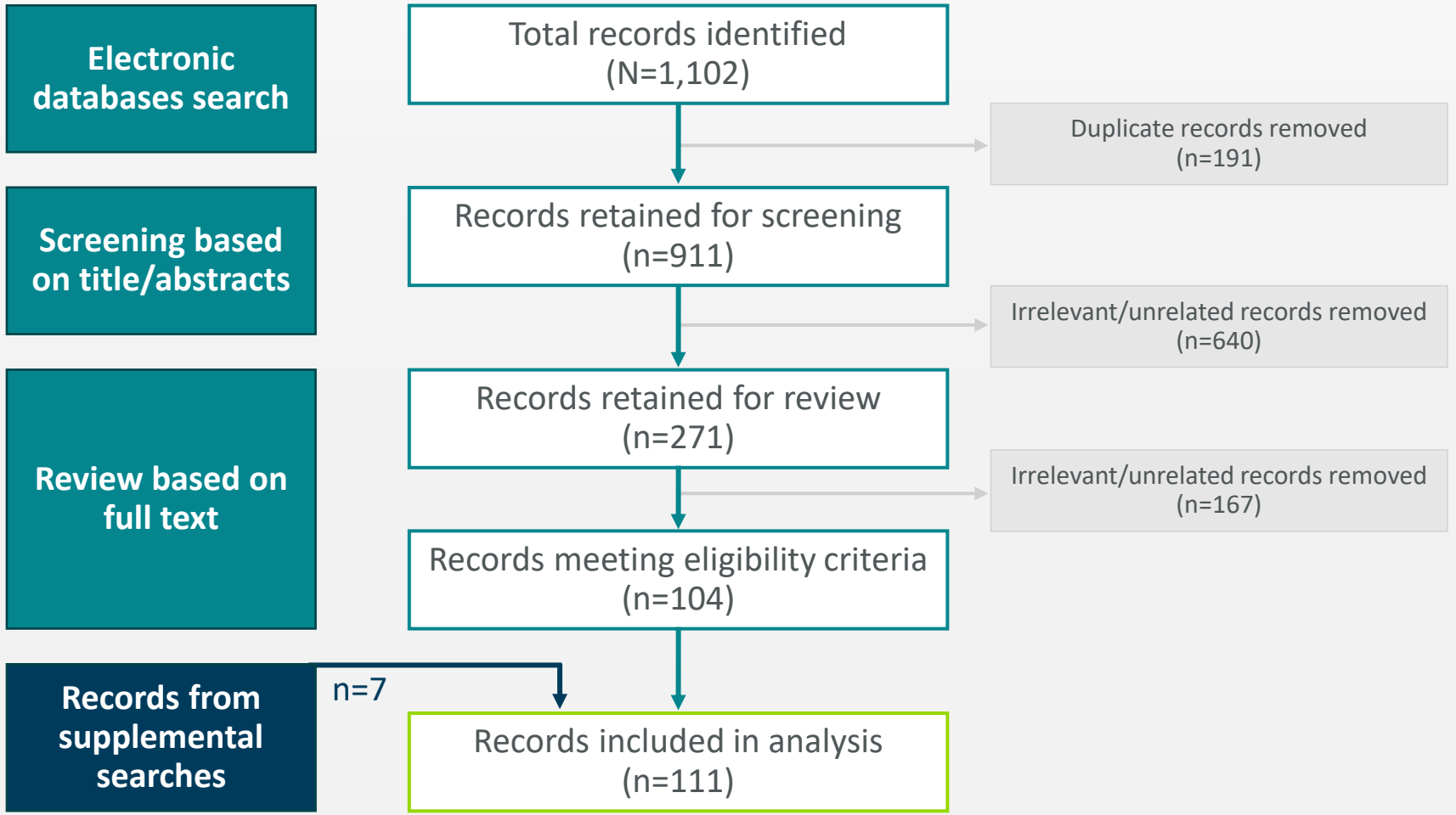
- EMBASE
- MEDLINE
- Cochrane Database of Systematic Reviews
- Cochrane Central Register of Controlled Trials
- Health Technology Assessment Database
- NHS Economic Evaluation Database
- EconLit

- A detailed, prospectively registered protocol is available in PROSPERO (registration ID CRD42020212142)

1. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Available from www.training.cochrane.org/handbook. Published 2020. 2. J Clin Epidemiol. 2009;62(10):1006-1012. 3. Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products Guidance for Industry [DRAFT GUIDANCE], 2018. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/meta-analyses-randomized-controlled-clinical-trials-evaluate-safety-human-drugs-or-biological.

Results

Patients and publications included: PRISMA flow diagram

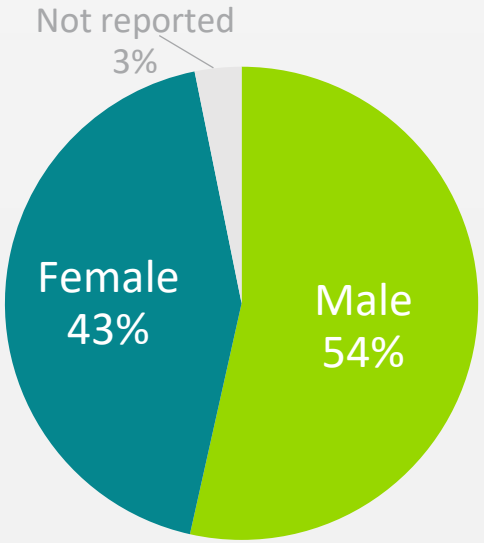


157 unique patients identified from 111 publications included in analysis

Results

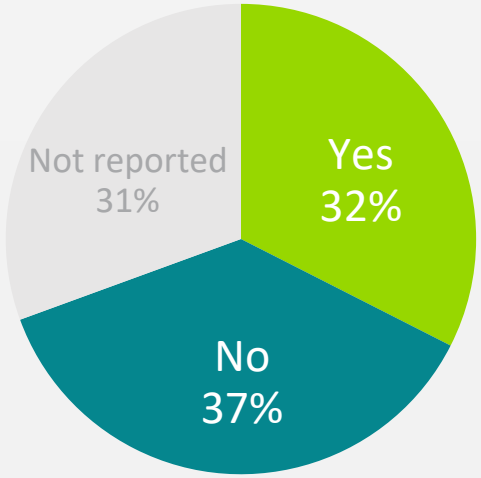
Patient characteristics described in the SLR are reflective of a typical ARG1-D cohort

Sex distribution



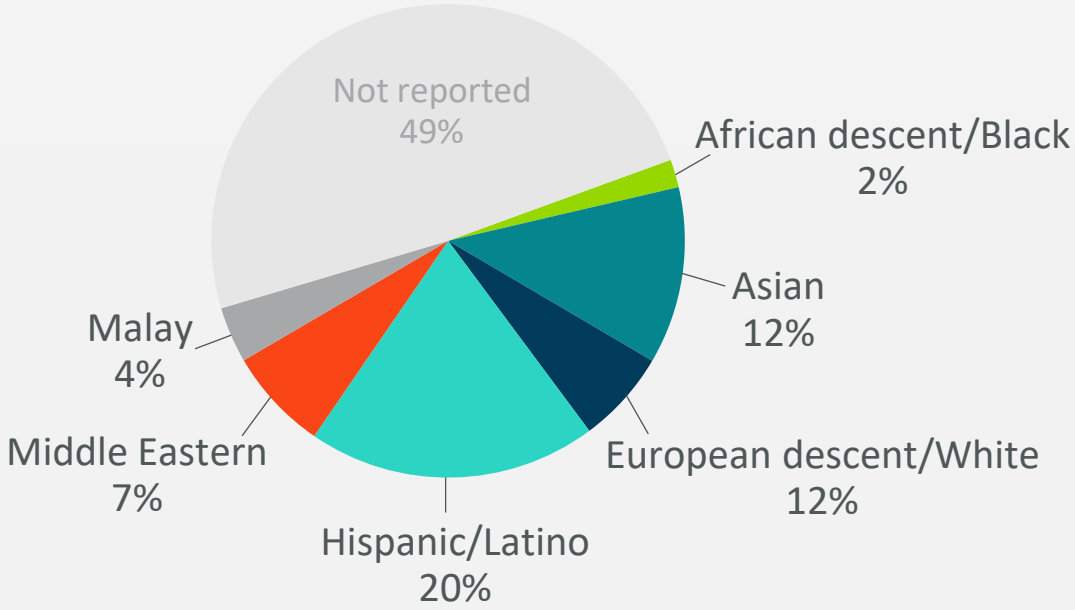
Roughly equal male:female

Consanguinity



Reported in ≈1/3 of parents

Range of ethnicities

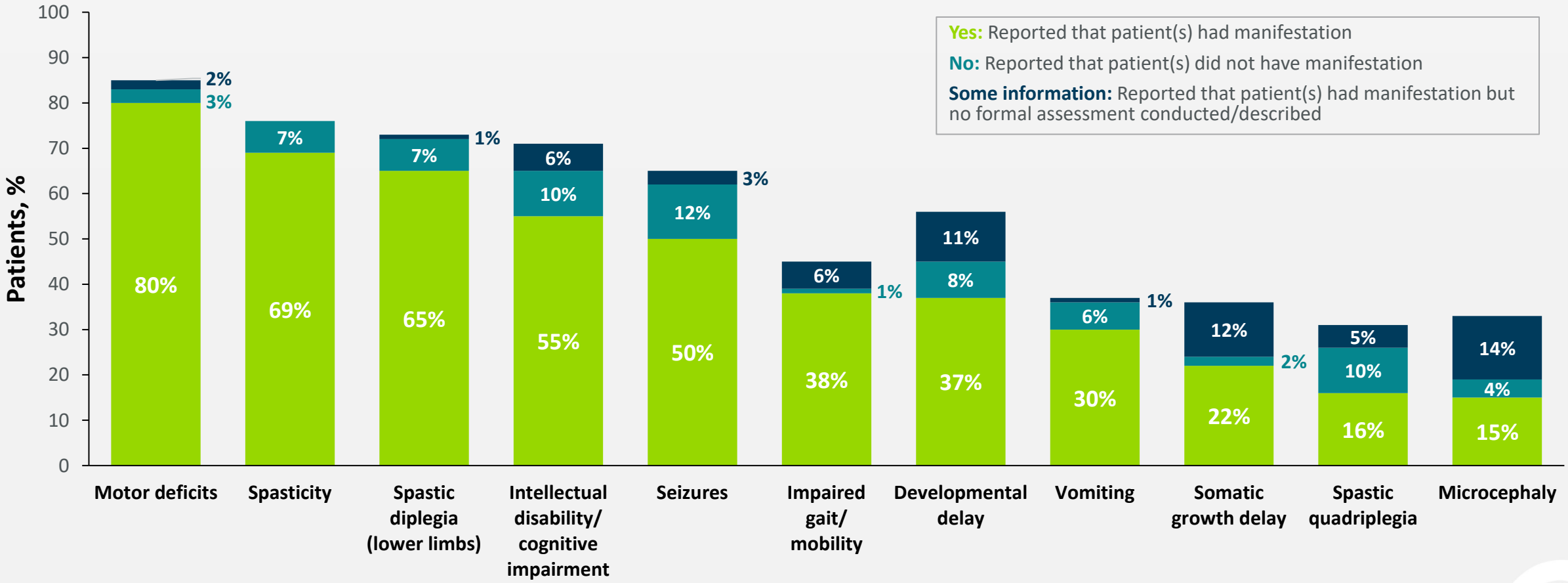


1/5 Hispanic or Latino

Results

Motor deficits, spasticity, developmental delay, and intellectual disability are the most frequently reported manifestations

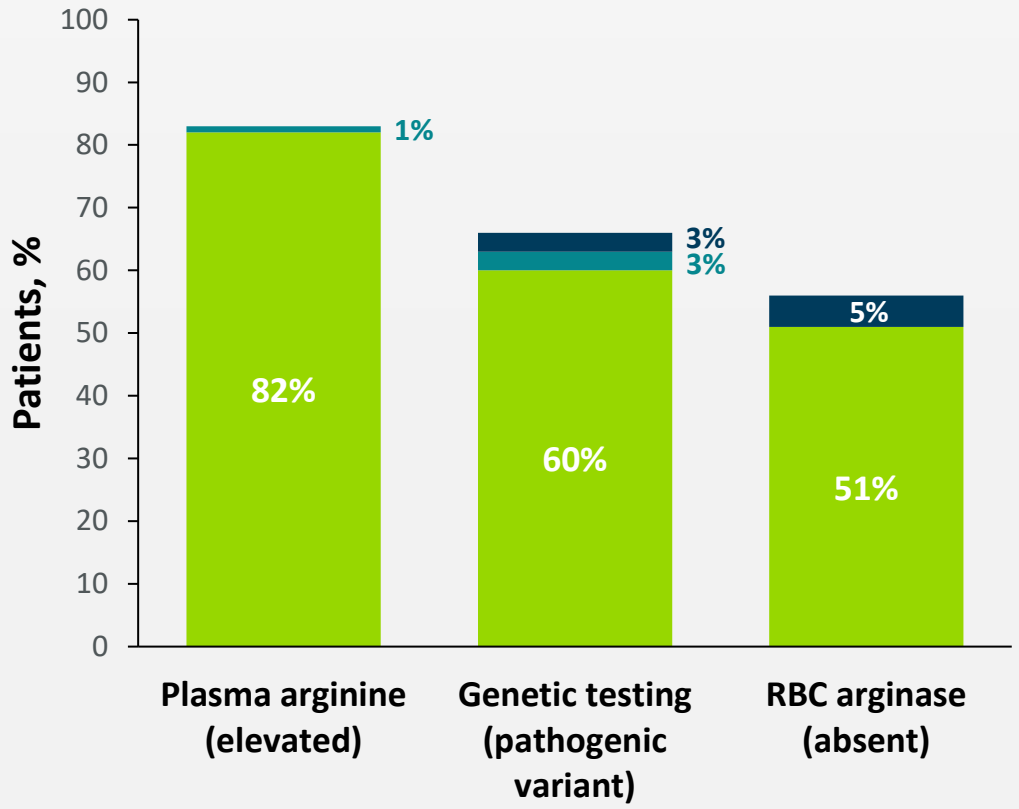
Motor deficits were present in 80% of patients



Results

Plasma arginine assessment is the most frequently reported method of diagnosis

>80% of reported diagnoses made by amino acid testing (elevated plasma arginine)



Yes: Reported that diagnostic method was used

No: Reported that diagnostic method was not used

Some information: Reported that diagnostic method was used but no formal assessment conducted/described

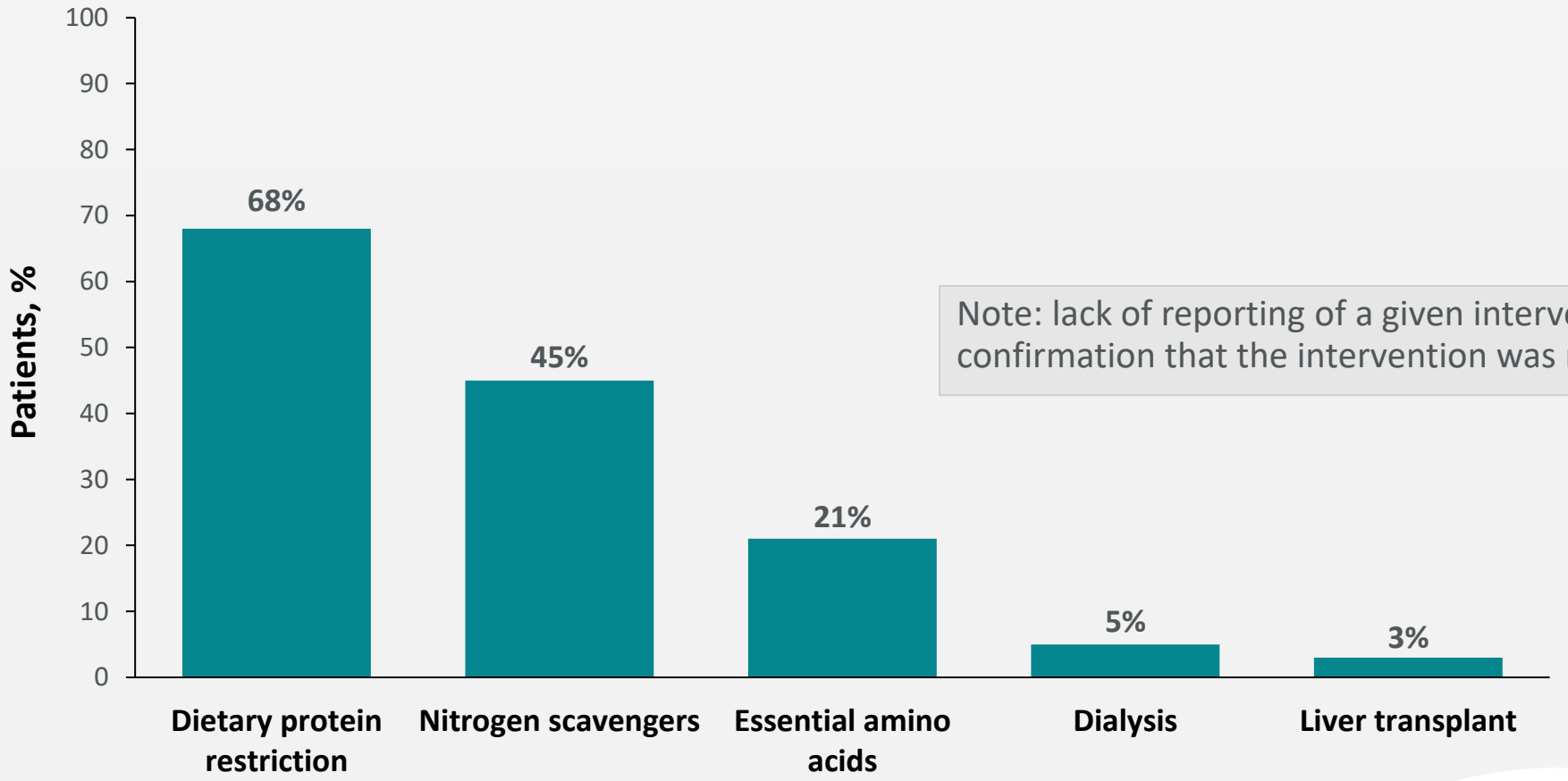
- Elevated blood ammonia was reported as prompting further workup/diagnosis for 51% of patients
- Other clinical observations leading to a diagnosis of ARG1-D being made included:
  - Abnormal electroencephalogram (EEG; 27%)
  - Abnormal brain imaging (28%)
  - Cerebral atrophy (20%)

Note: lack of reporting of a given diagnostic test is not confirmation that the test was not performed

Results

Dietary protein restriction and nitrogen scavengers are the most frequently described interventions

- Standard care approaches far outweigh other interventions
  - Dietary protein restriction (physician-prescribed or self-selected) is most common intervention
  - Nitrogen scavengers used in nearly half of patients

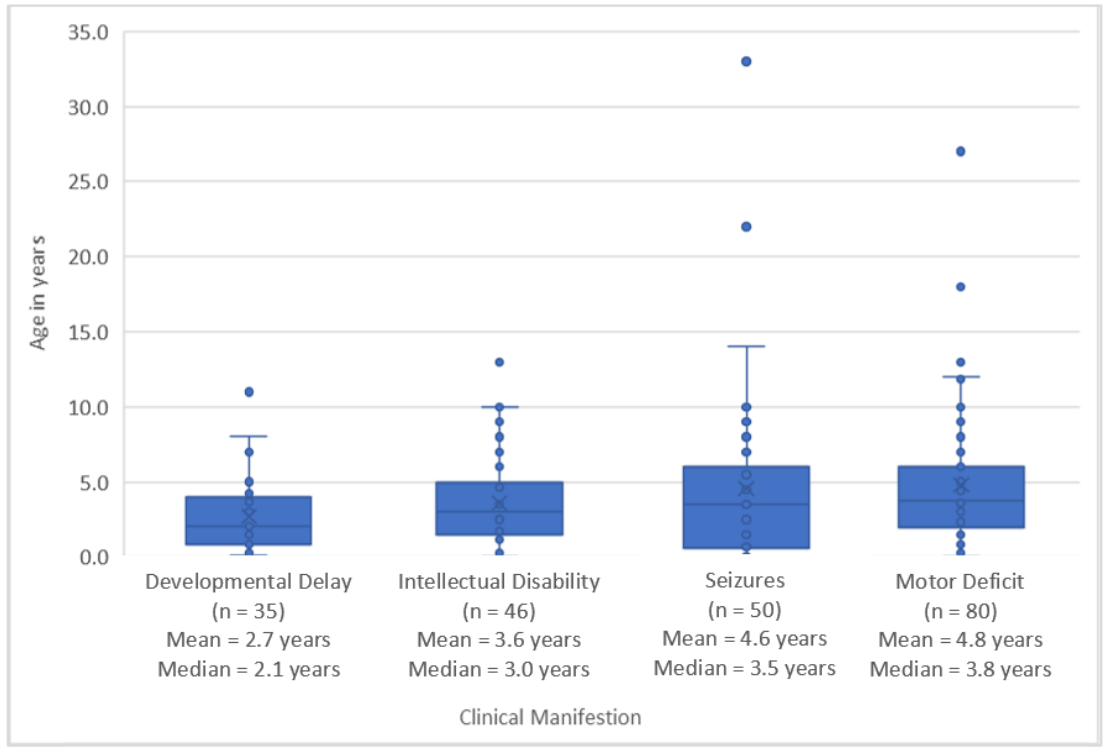


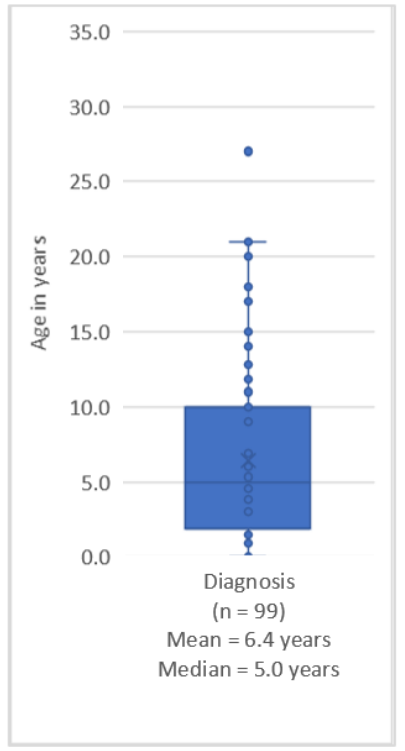
Note: lack of reporting of a given intervention is not confirmation that the intervention was not employed

Results

ARG1-D may not be diagnosed for years after first clinical manifestations

- Chronologic sequence of manifestations by age at first onset demonstrates progression of disease
- Diagnosis is frequently delayed compared with onset of manifestations





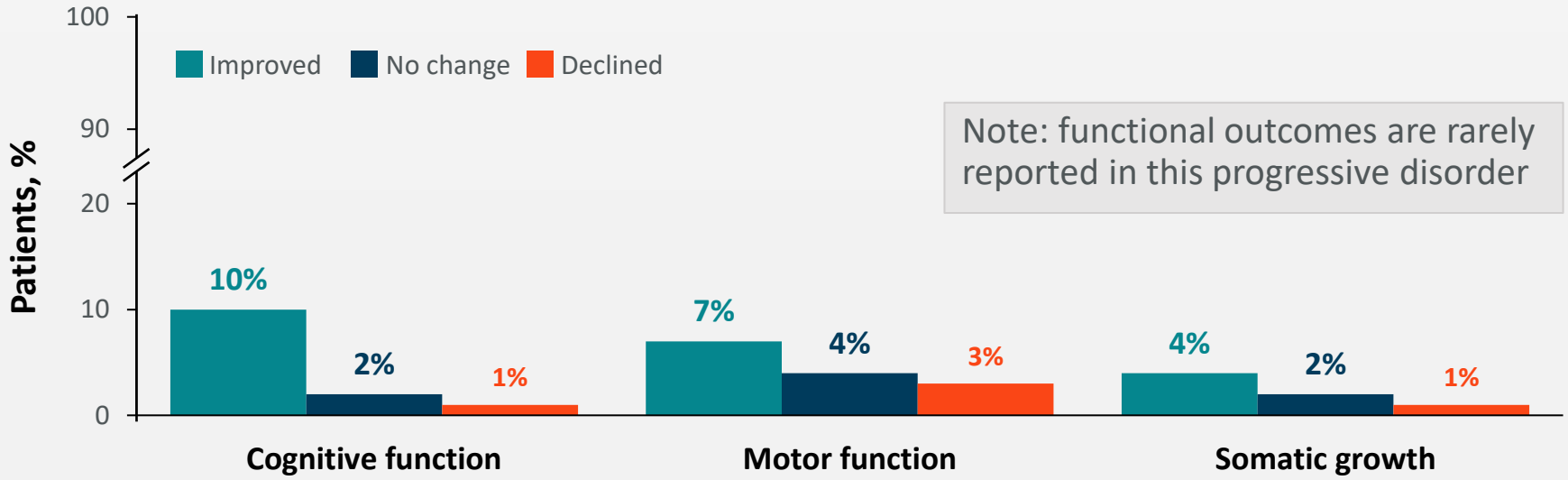
Early ARG1-D detection provides opportunity for earlier intervention and positive impact later in life[1-3]

1. Huemer M, et al. *J Inherit Metab Dis.* 2016;39:331–340; 2. Diez-Fernandez C, et al. *Hum Mutat.* 2018;39:1029–1050; 3. Edwards RL, et al. *J Inherit Metab Dis.* 2009;32:S197–200

Results

Insufficient effectiveness of current interventions creates large unmet medical need in ARG1-D

- Functional improvement is reported for only ≤10% of patients with current management approaches
- Continued decline in some patients is also reported
- A substantial proportion of existing reports (>74%) do not describe patient outcome data



Note: functional outcomes are rarely reported in this progressive disorder

- Standard care with a combination of dietary protein restriction, nitrogen scavengers, and supportive therapy with essential amino acid supplementation has been reported to improve manifestations, however:

Existing interventions do not achieve goals for reducing plasma arginine and therefore do not prevent disease progression[1,2]

1. Carvalho LC, et al. *Hum Mol Genet.* 2015;24:6417-6427; 2. Diaz GA, et al. EPNS Congress; September 17-21, 2019; Athens, Greece [P06-34].

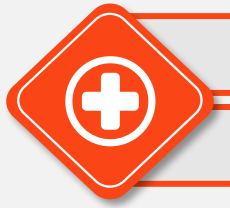
Conclusions

- This systematic literature review corroborates previous publications and highlights the high burden of disease and large unmet medical need in ARG1-D

Progressive and debilitating cognitive and neuromotor manifestations occur in most patients

Evidence supporting clinical effectiveness of existing management approaches is limited

Evidence suggests that diagnosis can lag behind clinical onset by several years



Evidence suggests that very few patients improve with existing management approaches

Current interventions do not lower arginine to target and do not prevent disease progression

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