Arginase 1 Deficiency (ARG1-D)

A Systematic Literature Review

Presentation Outline

- ARG1-D background
- Objectives of the systematic literature review (SLR)
- Methods
- Results
- Conclusions

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ARG1-D Background

ARG1-D Background

- ARG1-D Definition
  - ARG1-D is a debilitating, progressive, inherited, metabolic disease characterized by persistent elevation of arginine and its metabolites, which leads to significant morbidity and early mortality

- Manifestations of ARG1-D
  - ARG1-D is a distinct urea cycle disorder (UCD) which presents in childhood with manifestations that include spasticity, developmental delay, intellectual disability, and seizures
    - Hyperammonemia occurs but is usually less frequent and less severe than in other UCDs

- Burden of Disease
  - ARG1-D results in functional disability and impairment of activities of daily living, placing a significant burden on the patient and caregivers, as well as on healthcare systems

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ARG1-D Background

- Diagnosis
  - Diagnosis can be readily made with plasma arginine measurement or genetic analysis
    - Delays in diagnosis are common
    - Patients can also be misdiagnosed with conditions such as cerebral palsy or hereditary spastic paraplegia

- Current standard of care (SOC) for ARG1-D
  - Severe dietary protein restriction
  - Essential amino acid (EAA) supplementation
  - Ammonia scavengers (to address the risk of hyperammonemia)

- SOC is ineffective at reducing arginine levels to the goal, due to difficulty with adherence as well as its failure to address endogenous arginine production

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Objectives of the SLR

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- The objective of this review was to identify the published evidence and describe the natural history of ARG1-D, the impact of ARG1-D on patients and their caregivers, the effectiveness of available treatments, and unmet needs of patients

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Methods

Methods

Population, Intervention, Comparator, Outcomes, and Study Design (PICOS) Criteria

Criteria	Description	
Population	Pediatric and adult patients with Arginase 1 Deficiency (ARG1-D)	
Interventions	No restriction	
Comparators	No restriction	
Outcomes (& data collected)	• Patient demographics/characteristics • Method of diagnosis • Lab values • Developmental delays and age of onset • Cognitive impairment/intellectual disability • Motor Deficits/spasticity • Seizures • Other measures, signs, presentations (e.g., abnormal EEG, microcephaly, cerebral atrophy, hepatomegaly, vomiting, short stature, somatic growth, adaptive behavior issues, deficits in activities of daily living and/or self-care, comorbidities, disease severity) • Dietary, pharmacologic, and medical treatments • Improvement after using current standard of care (SOC) • Hospitalization and/or death • Quality of life among caregivers	
Study design	Inclusion criteria: Case reports, controlled and uncontrolled clinical trials, cross-sectional and case-control studies	Exclusion criteria: All studies that do not report the individual ARG1-D patients' data of interest, systematic and targeted literature reviews, comments, editorials
Language	English language only	

Databases

Search include the following databases:
• MEDLINE • EMBASE • Cochrane Central Register of Controlled Trials • Cochrane Database of Systematic Reviews • Health Technology Assessment • NHS Economic Evaluation Database • EconLit

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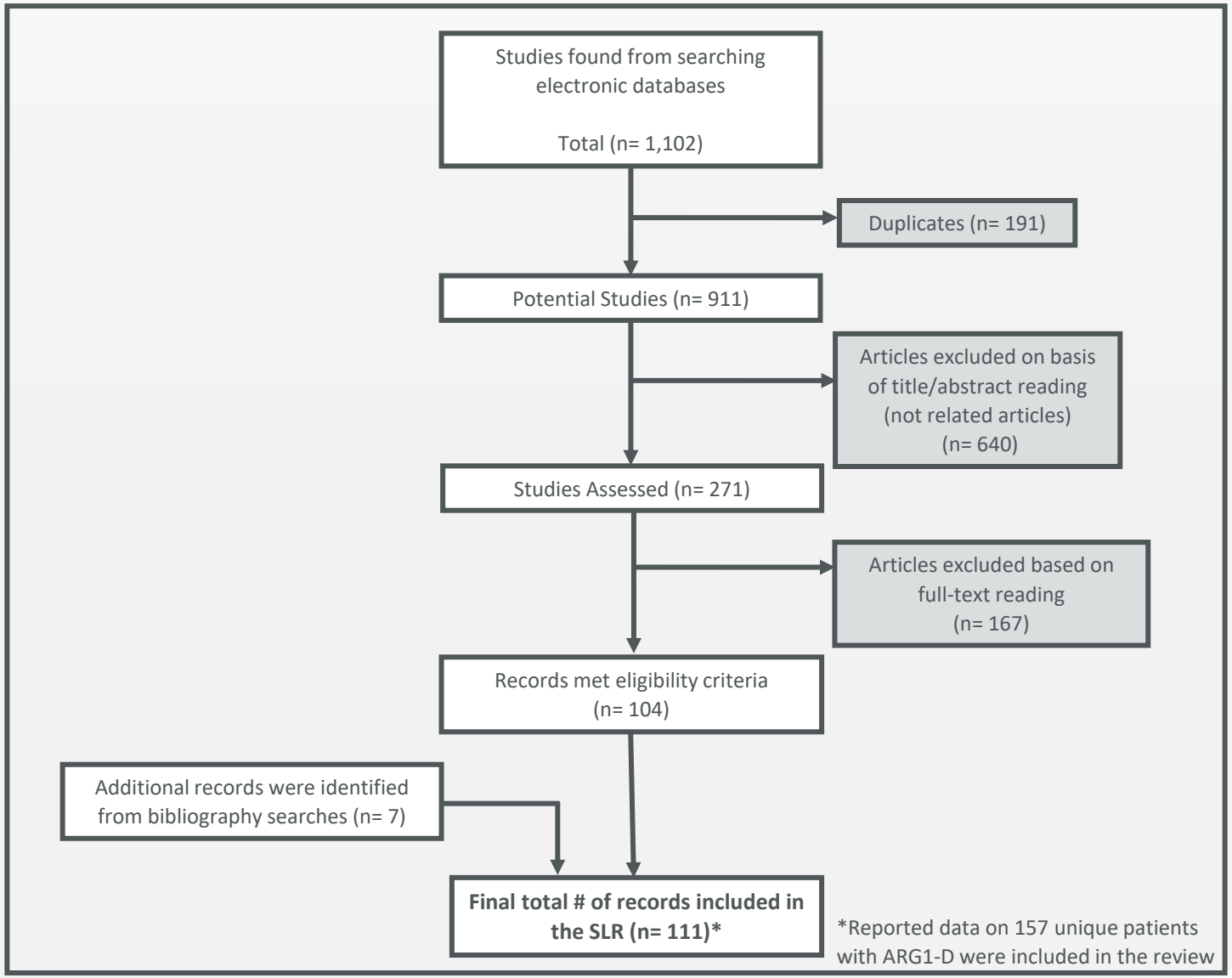
Results

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)



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SLR Results (Demographics)

Figure 1. Gender Distribution

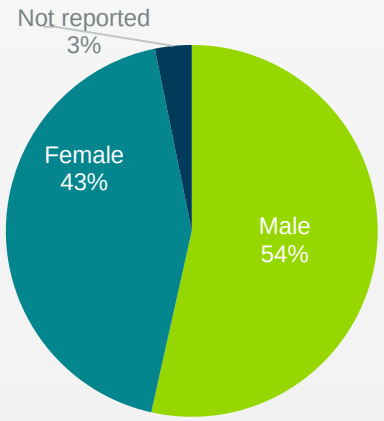


Figure 2. Parental Consanguinity

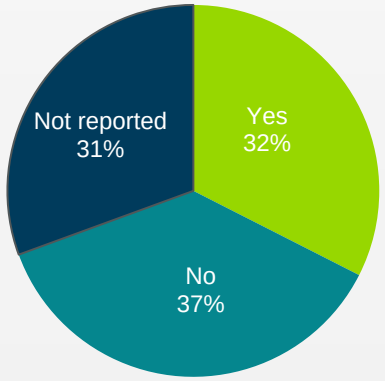


Figure 3. Ethnicity/Race of Patient

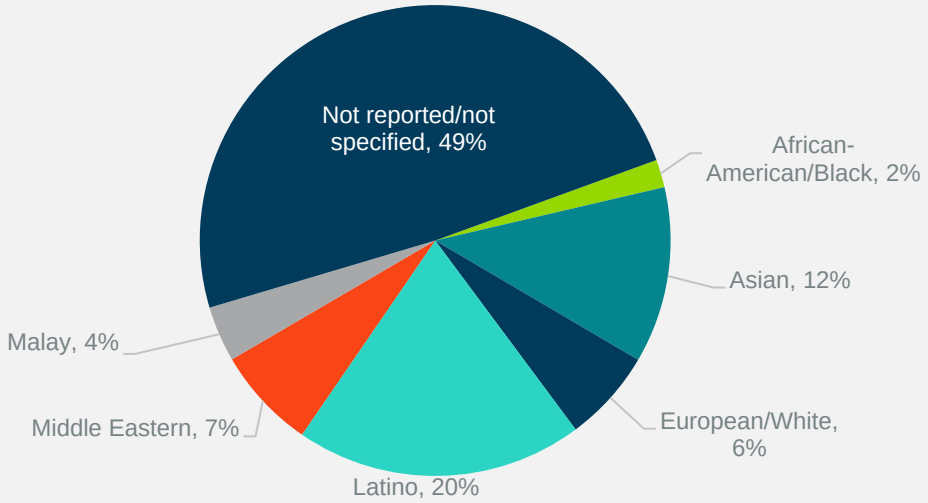
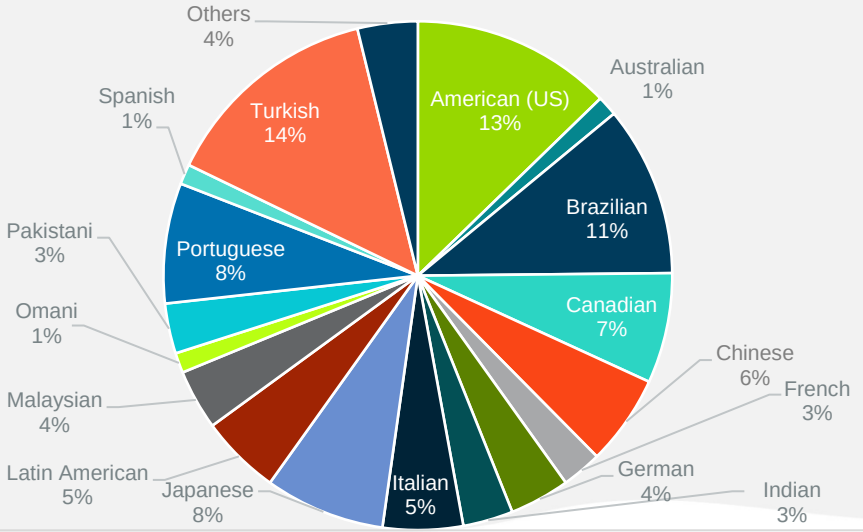


Figure 4. Nationality of Patient



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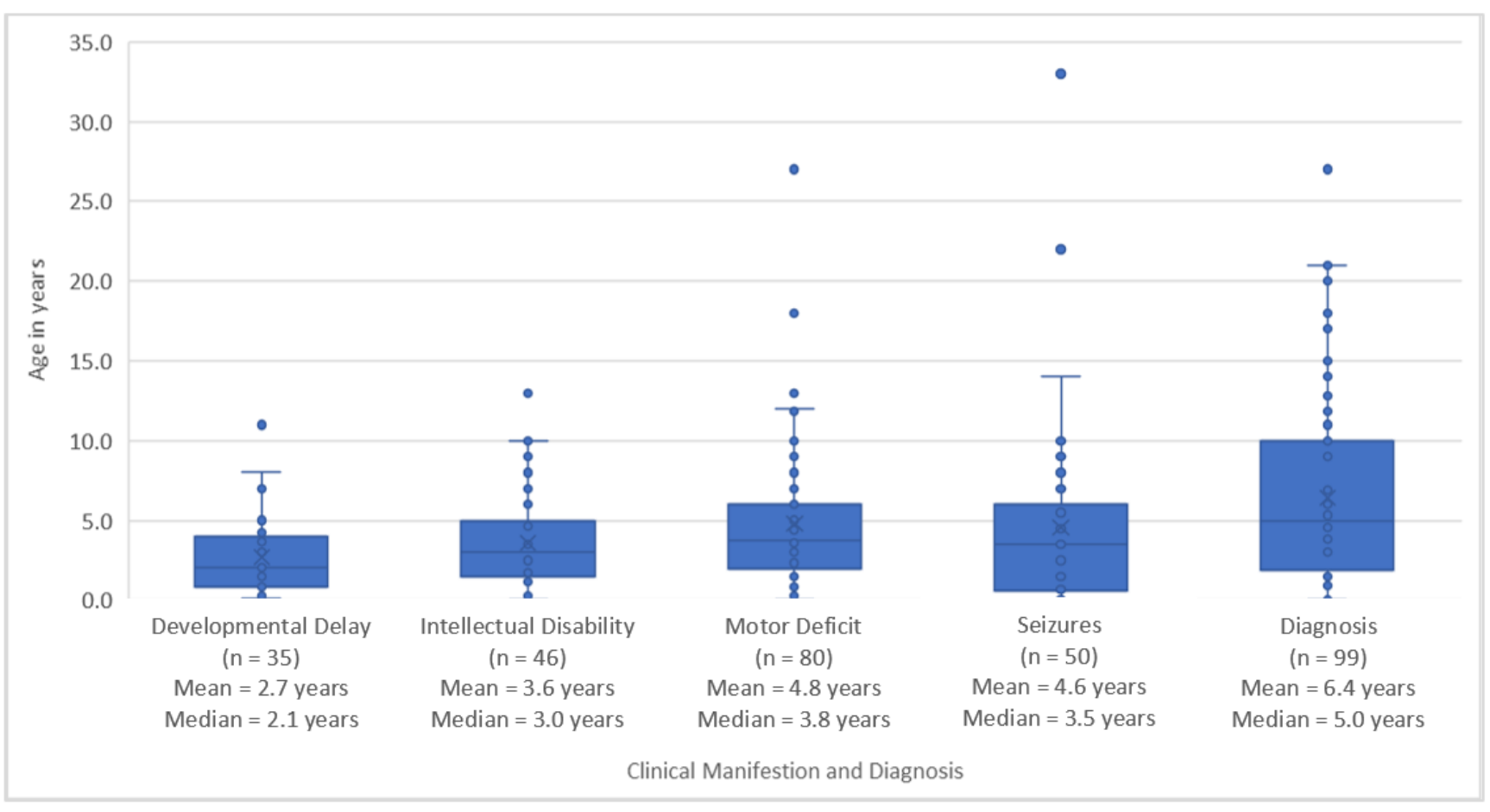
Natural History of ARG1-D: Age of Onset of Clinical Manifestations and Diagnosis



Note:

Early ARG1-D detection has been shown to have a positive impact later in life, possibly due to early treatment intervention[1,2,3]

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

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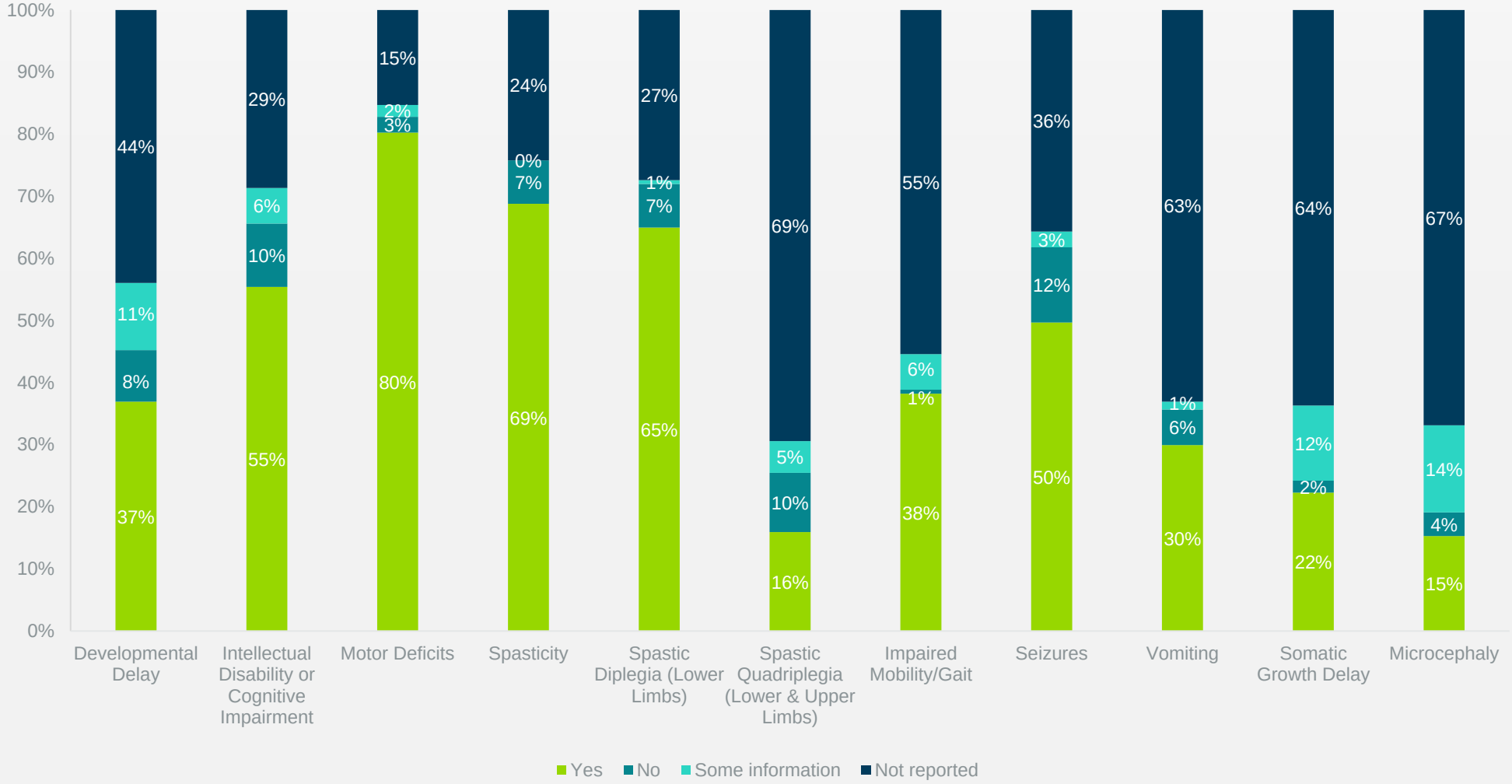
SLR Results (Clinical Manifestations)

Figure 6. Clinical Manifestations



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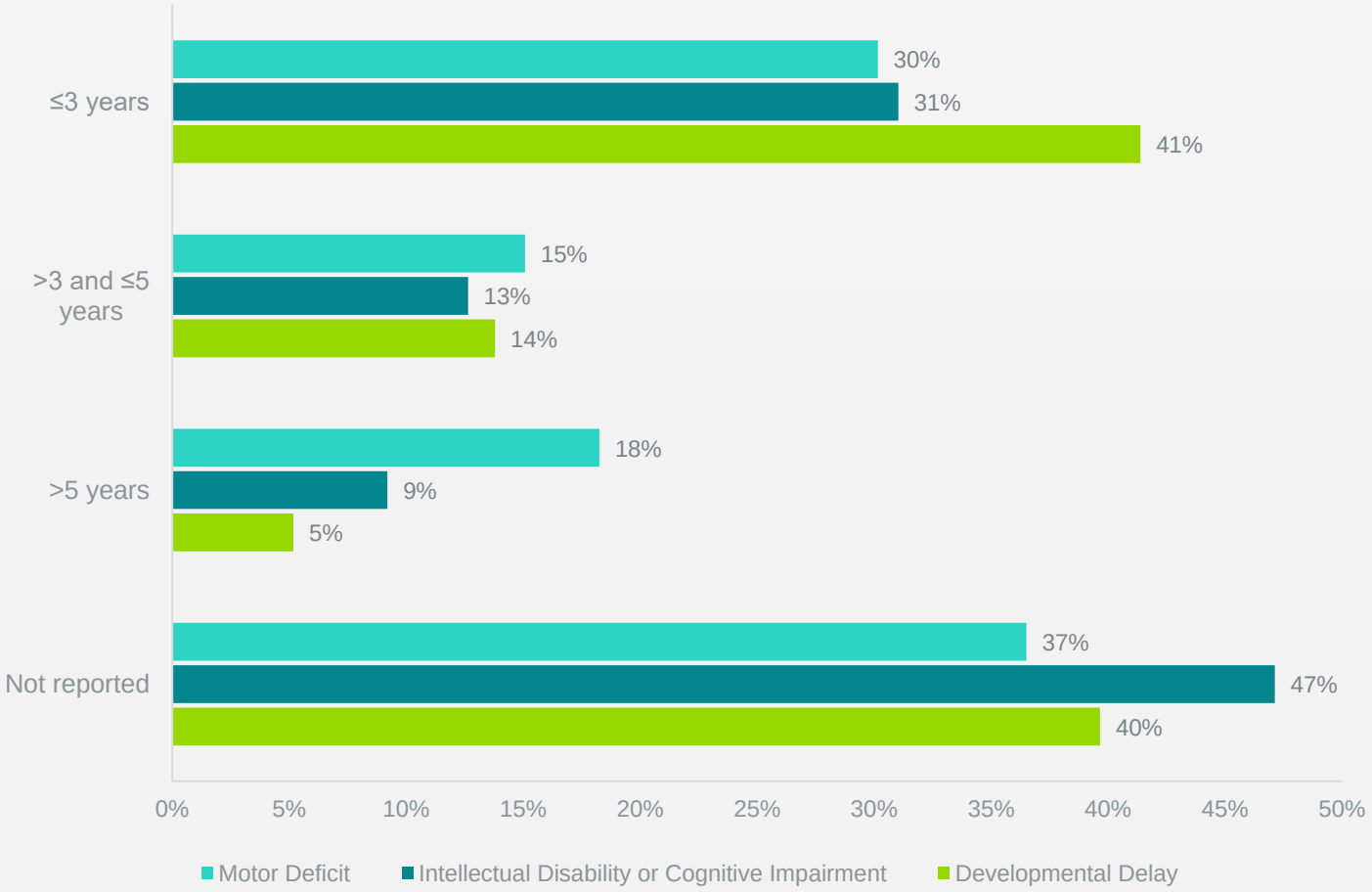
SLR Results (Age of Manifestation Onset)

Figure 7. Age of Manifestation Onset



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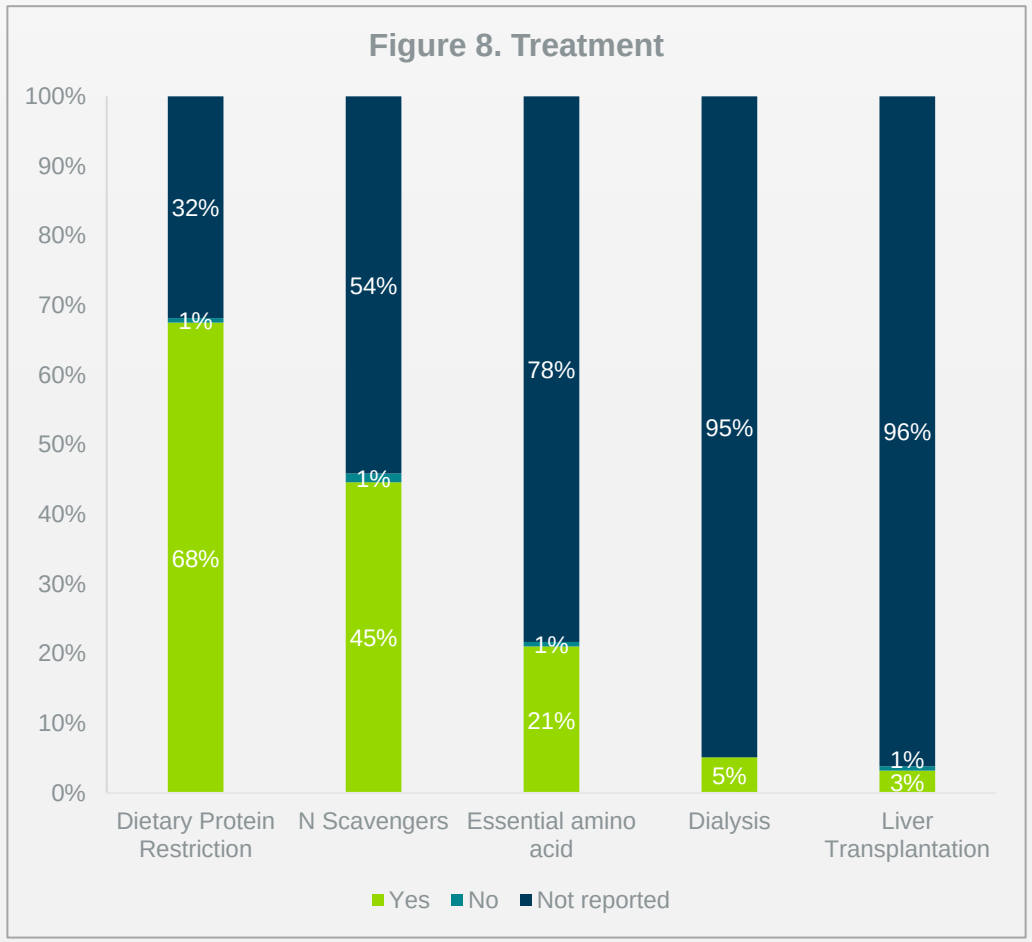
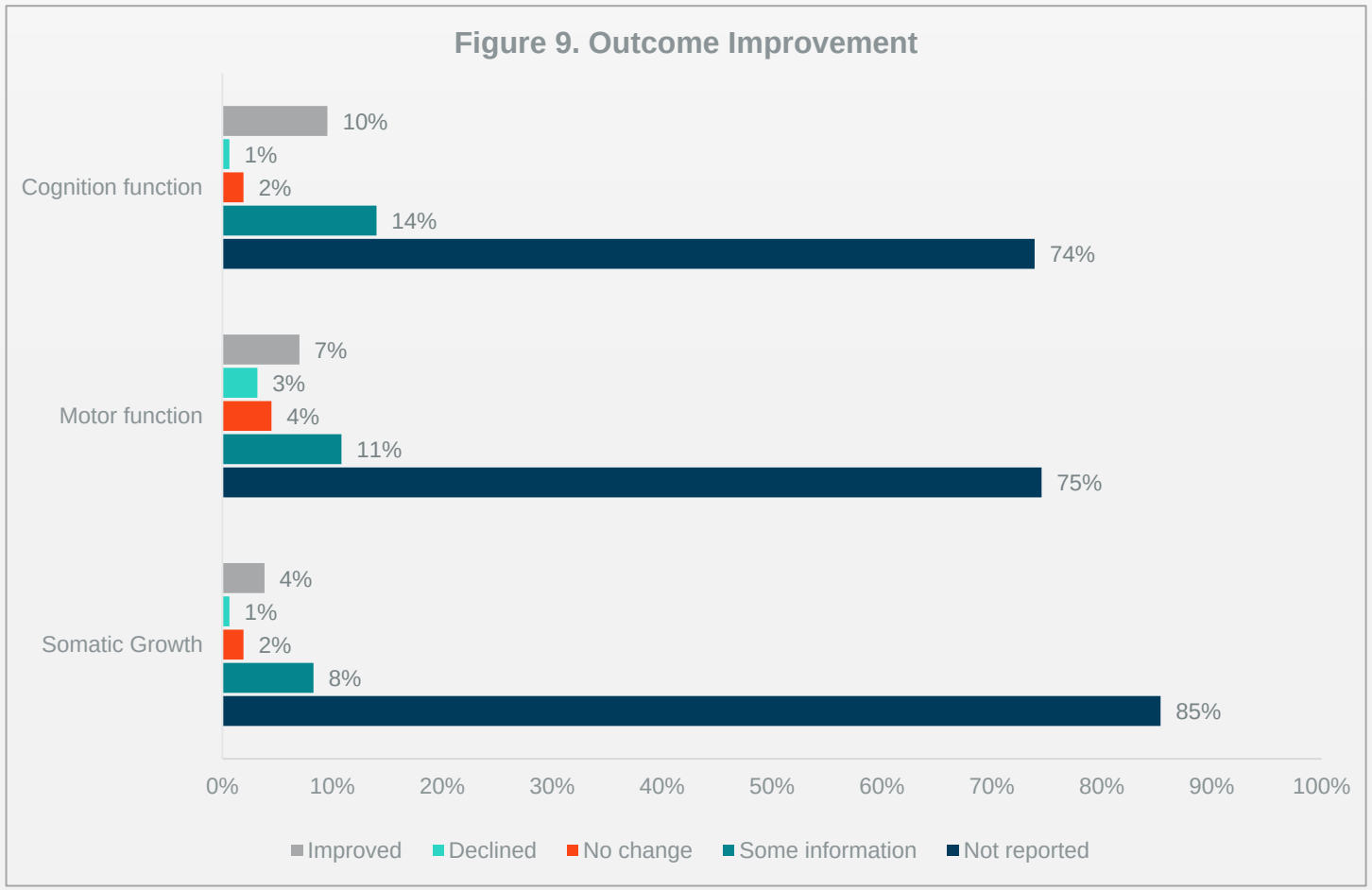
SLR Results (Treatment and Outcomes)





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SLR Results (Hospitalization and Death)

Figure 10. Hospitalization

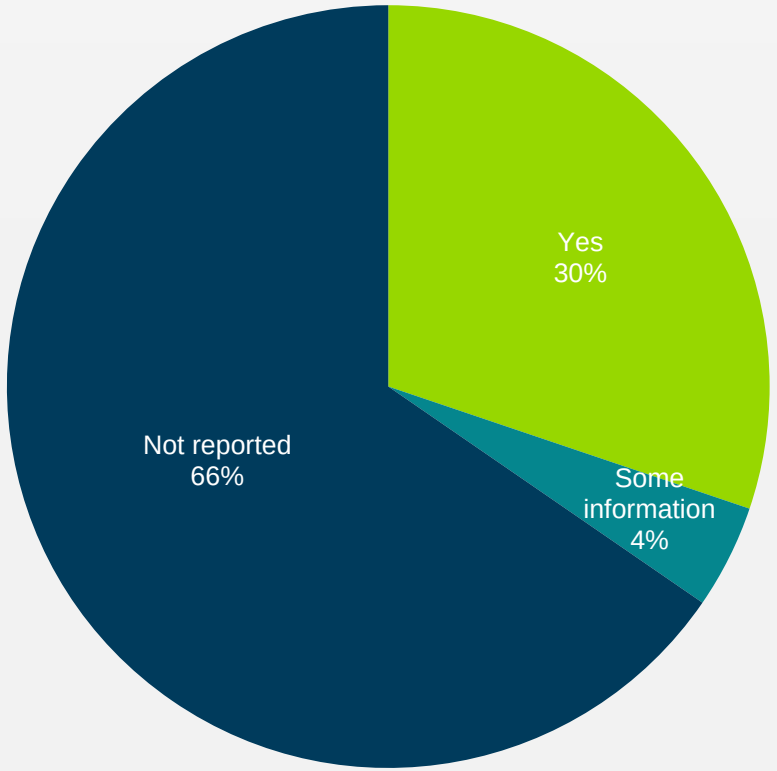
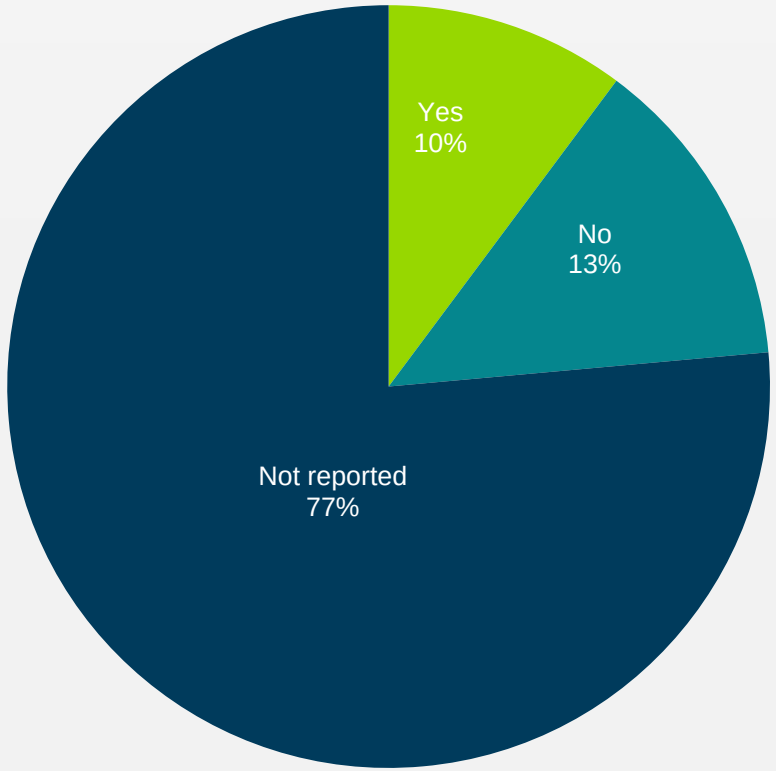


Figure 11. Death



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Conclusions

Conclusions

- In a large cohort of patients, the natural history of ARG1-D was reflected in a multitude of clinical manifestations, including developmental delays, intellectual disability, motor deficits (including spasticity and impaired mobility), and seizures
- On average, developmental delay was reported between 1-3 years of age, followed by intellectual disability, motor deficits, and seizures by 5 years of age
- This review highlights a clear unmet need for clinically effective treatment options for patients with ARG1-D and the importance of early and accurate diagnosis to allow for disease management before the onset of clinical manifestations

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805 Las Cimas Parkway Suite 100 Austin, TX 78746 aeglea.com