



A Proposed Staging System for CLN3 Disease (Juvenile Batten disease)

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Introduction

The Neuronal Ceroid Lipofuscinoses (NCLs) comprise more than 10 different rare, inherited, fatal lysosomal diseases of childhood. Juvenile Batten Disease, due to mutations in *CLN3*, is characterized by progressive vision loss, epilepsy, dementia, behavioral difficulties, and motor impairment.

The Unified Batten Disease Rating Scale (UBDRS) is a disease-specific rating scale that was developed to assess disease severity in 4 domains: physical, behavior, seizures, and functional capability.

Objectives

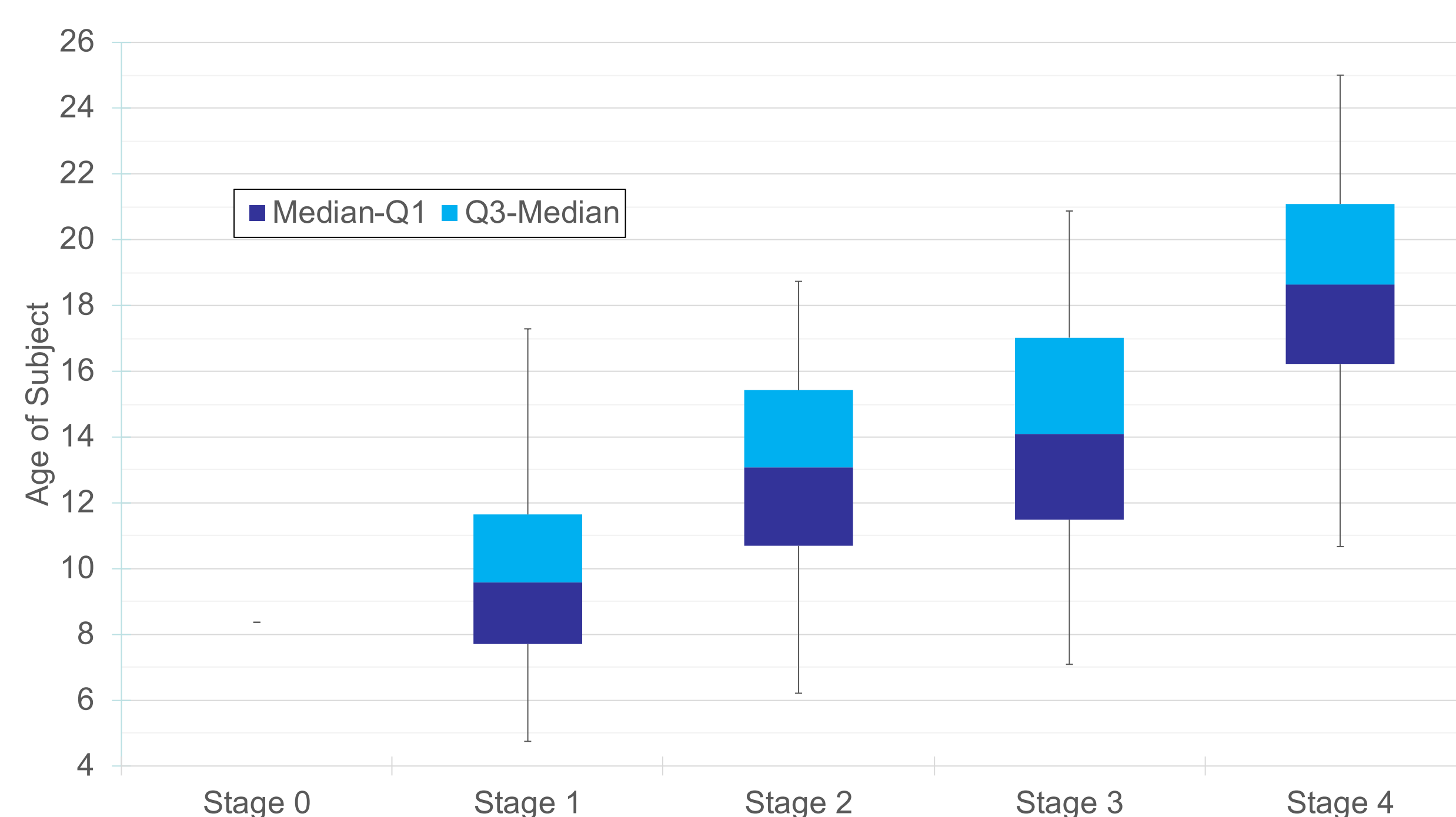
To develop a staging system for CLN3 disease based on clinically meaningful endpoints that can facilitate stratification by disease severity for use in future clinical trials.

Methods

- Data from individuals with genetically confirmed CLN3 disease were extracted from the University of Rochester natural history database.
- Data from 100 unique individual subjects consisting of a total of 290 evaluations were used for development and testing.
- The initial system tested (System 1) consisted of 5 stages. Stages were proposed based on discrete endpoints.

Stages	System 1	System 2
Stage 0	Genetic Diagnosis (Asymptomatic)	Genetic Diagnosis (Asymptomatic)
Stage 1	Loss of vision	Loss of vision
Stage 2	First seizure	First seizure
Stage 3	Loss of independence in ADLs	Loss of independent gait
Stage 4	Loss of independent gait	

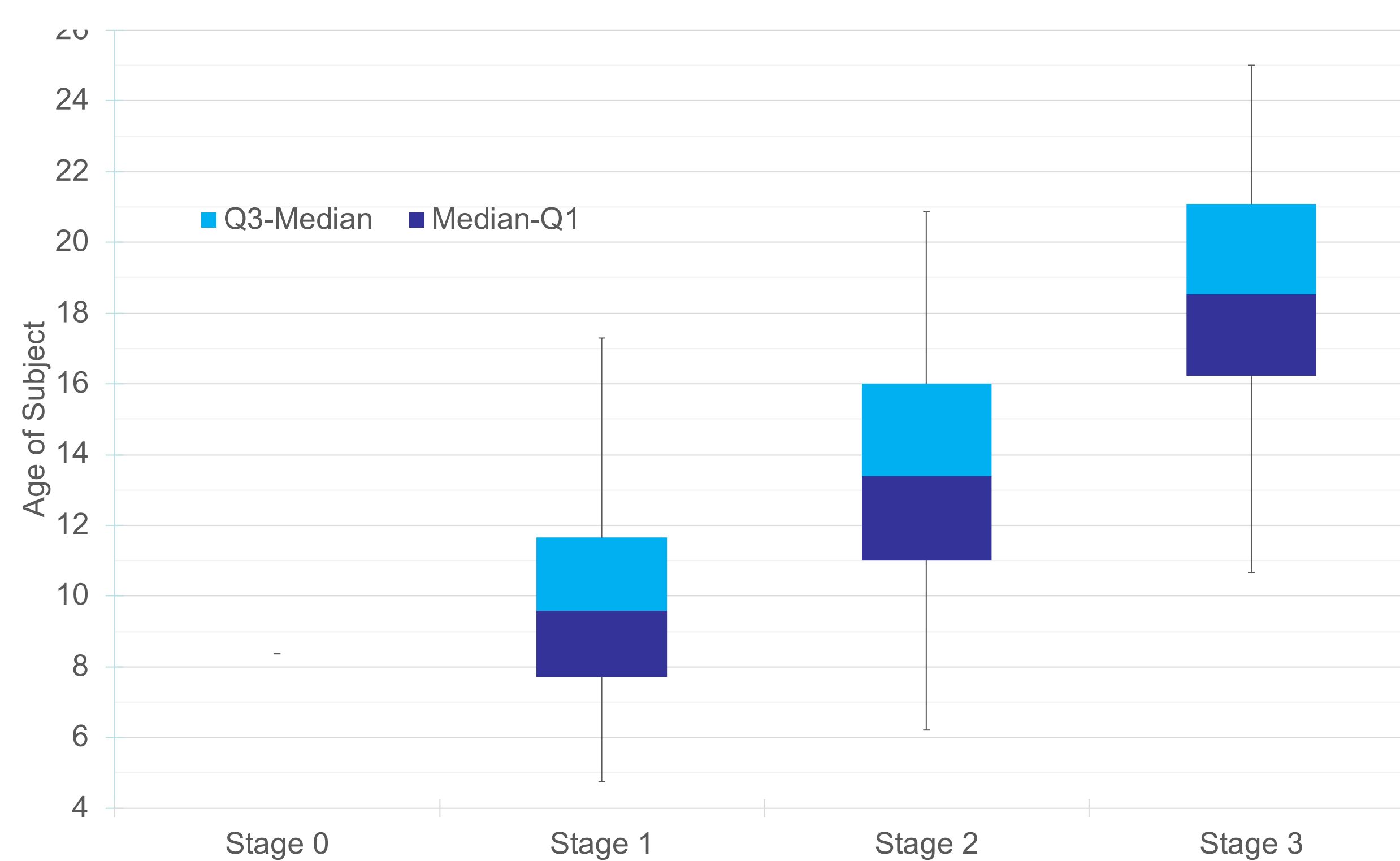
STAGING SYSTEM 1



Stages	Median Age Difference	95% Confidence Interval	P Value
Stage 1 vs. Stage 2	3.2	1.5 - 4.9	< 0.0001
Stage 2 vs. Stage 3	1.3	0.2 - 2.7	0.15
Stage 2 vs. Stage 4	5.6	4.3 - 6.9	< 0.0001
Stage 3 vs. Stage 4	4.3	2.8 - 5.8	< 0.0001

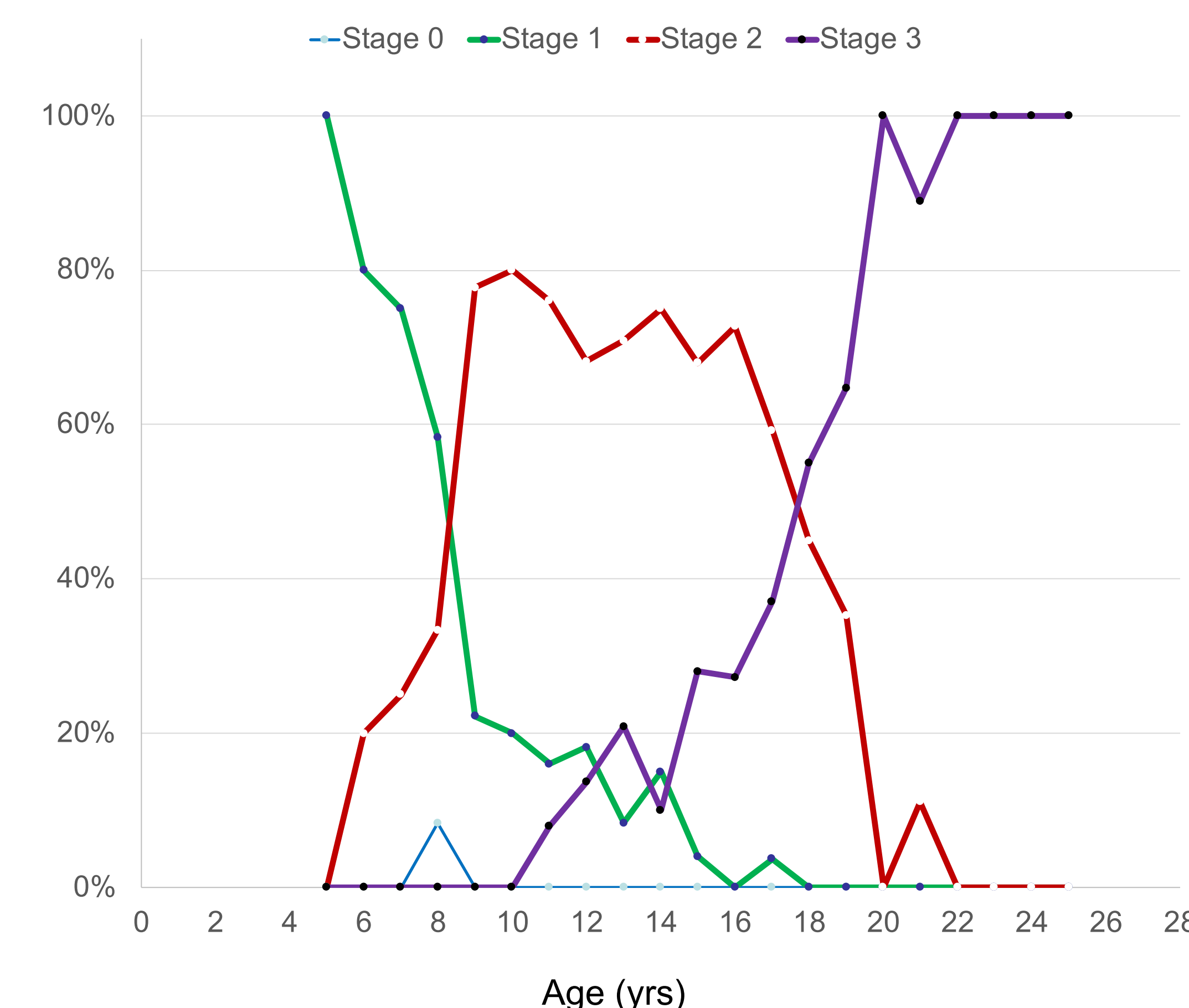
Stage 2 (First Seizure) and Stage 3 (Loss of Independence in ADLs) overlapped substantially. We eliminated Stage 3 because the First Seizure was a more discrete end-point.

STAGING SYSTEM 2



Stages	Median Age Difference	95% Confidence Interval	P Value
Stage 1 vs. Stage 2	3.7	2.2 - 5.2	< 0.0001
Stage 2 vs. Stage 3	5.1	4.0 - 6.2	< 0.0001

Sharp transitions between stages with slight overlap. No individual skipped a stage. Progression between stages was unidirectional.



Discussion

- The proposed staging system is based on clinically meaningful end-points and has excellent construct validity
- In this proposed staging system, individuals with CLN3 disease progress through each stage of the disease as a function of age.
- Elimination of the "Loss of Independence in ADLs" stage from System 1 resulted in more discrete stages with little overlap.
- A valid staging system has high potential for use in stratification for clinical trials and for development of stage-specific outcome measures.

Acknowledgements

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