

An update from the new Rett digital natural history study

*How our children's medical records created
a decades-long study in months*

Agenda

- Introductions
- Overview of utilizing untapped resources support research
- What is a digital natural history study?
- Why is a digital natural history study important?
- Data review from the ongoing Rett study
- Q and A



Invited Speakers



Monica Coenraads, MBA

*Digital Natural History Study Parent
CEO, RSRT*



Cary Fu, MD

*Clinical Lead
Rett Syndrome Global Registry &
Digital Natural History Study
Vanderbilt University Medical Center*



Bernhard Suter, MD

*Clinical Lead
Rett Syndrome Global Registry &
Digital Natural History Study
Texas Children's Hospital*



Kristina Hone, MBA

*Lead Data Scientist
CEO, CASK gene Foundation*

Combine Untapped Resources to Expand Rett Therapeutics

Comprehensive medical records are not utilized

Parents have valuable knowledge that is not captured

How do we access this?

How do we support care, research, and development?

Can we give support tools back to parents?



Part 1

Clinical Component
via Medical Record Summaries

- Consolidate all medical care received into a research-ready, coded dataset

Part 2

Parent-Reported Component
to Support Day-to-Day Care

- Rett history, symptom burden, care strategies, family life, clinical trial perspectives
- Individualized symptom/episode tracking & graphing





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What is the new Rett syndrome digital natural history study?

Monica Coenraads, MBA

Rett Digital Natural History Study Parent

CEO, RSRT

What is a Natural History Study (NHS)?

Natural History Study

- collects health information from a group of people to learn how the condition develops over time

Rett Syndrome Natural History Study

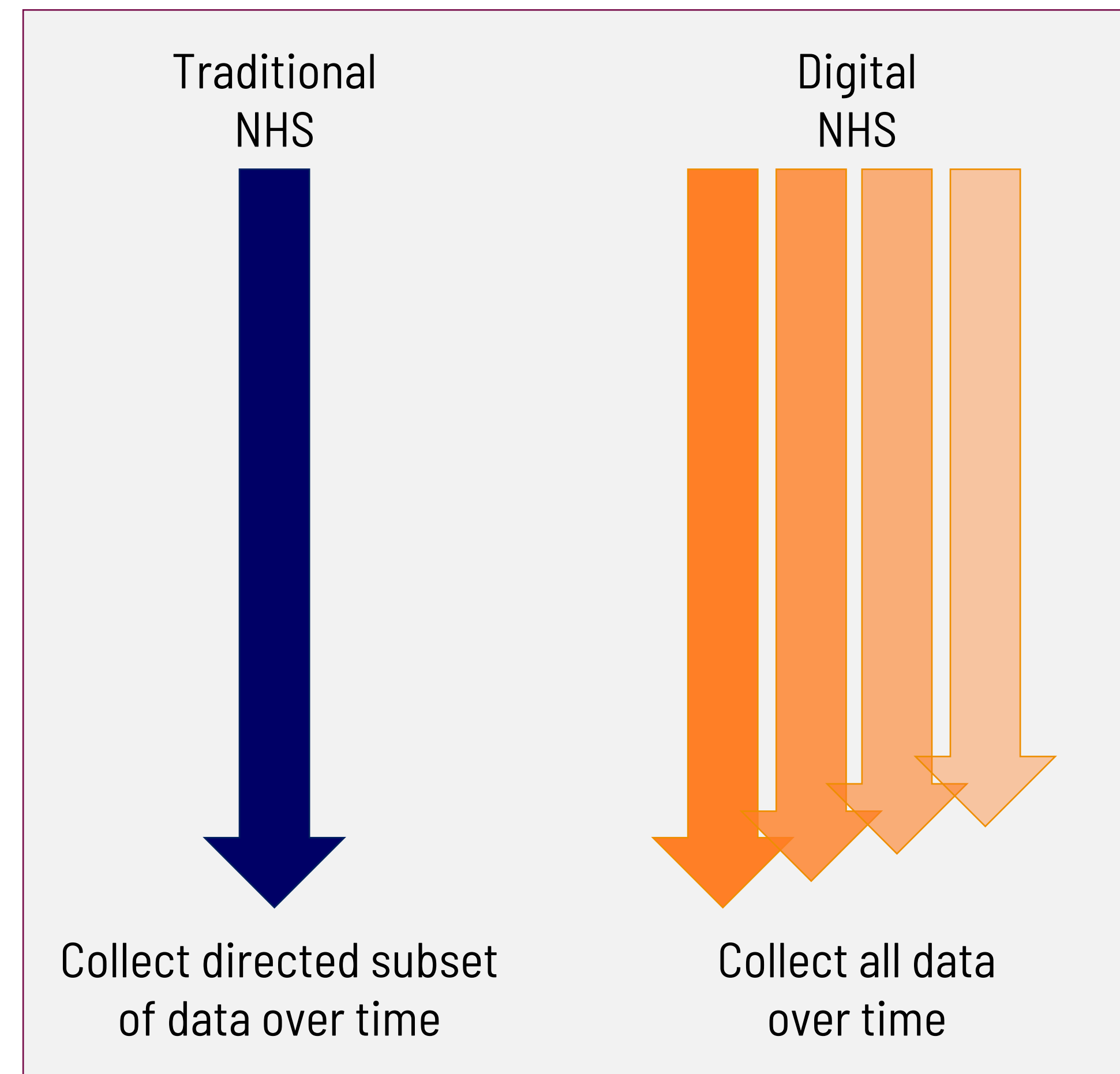
- Focused on Rett syndrome and related disorders
- US based
- 15 years of in-person clinical data
- 1000+ individuals enrolled
- Generated dozens of publications

What is a digital NHS?



Key Features of a dNHS

- No clinic visits required
- Captures all information from medical records
- Unbiased approach without pre-defined data collection
- Not dependent on parents' memories
- Collects years of data in one fell swoop
- Traditional NHS and dNHS each have pros and cons
- dNHS adds data from untapped resources to enhance the knowledge base. Does not replace NHS but rather expands on it.



Who is citizen / Invitae?



citizen is a technology company that puts patients in control of their medical records and gives them the ability to share their records with whom they choose

- Founded by Anil Sethi in honor of his sister Tania who died from metastatic breast cancer
- She saw 17 oncologists and other physicians at 23 institutions
- Doctors made life-and-death decisions from limited information because her health history was fragmented
- Anil set out to change this
- Invitae, a medical genetics company, acquired citizen in 2021



Parent Portal: Dashboard

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Search

Home

My Records

Manage

CC

Hello, Chelsea

Your Health Records



Your Documents

As of : 9/19/2022



Disease Summary Report

As of : 4/4/2023

Add new records



Help us find your records by letting us know all the places you've been seen for your condition.

[Request Records >](#)

Parent Portal: My Records View

Health Records

Multiple documents



136893.pdf
Sep 19, 2022



Chelsea Coenraads Y...
Jul 25, 2022



102420.pdf
Dec 21, 2021



Records.pdf
Sep 16, 2021



100425.pdf
Sep 10, 2021



110207.pdf
Sep 7, 2021



Chelsea Coenraads Y...
Oct 7, 2020



1174903-MMC-021...
Sep 25, 2020




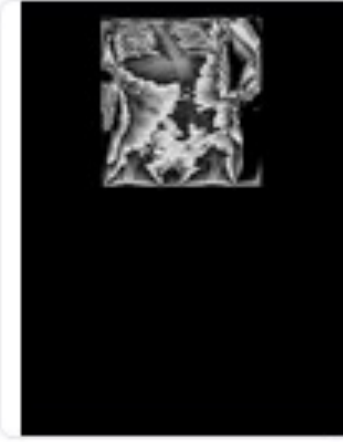



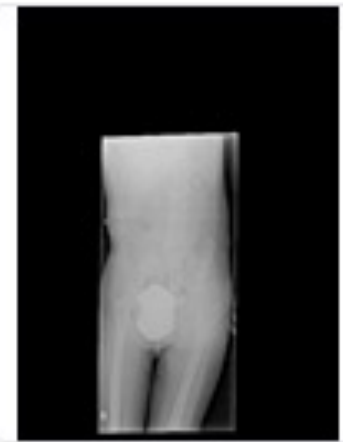





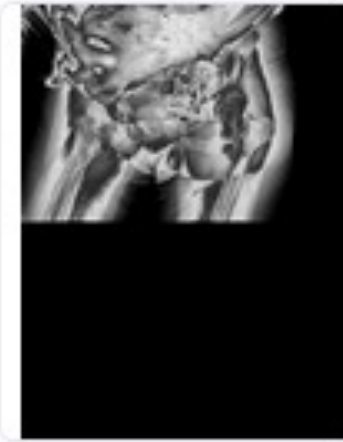

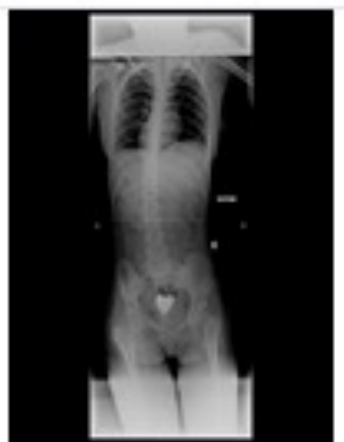






000014_001.pdf
Sep 24, 2020



000012_001.pdf
Sep 24, 2020

Parent Portal: Imaging View

 <p>diagnostic.png Sep 11, 2020</p>	 <p>diagnostic.png Sep 11, 2020</p>	 <p>diagnostic.png Sep 11, 2020</p>	 <p>diagnostic.png Sep 11, 2020</p>	 <p>thumbnail.jpeg Sep 11, 2020</p>	 <p>diagnostic.png Sep 11, 2020</p>	 <p>thumbnail.jpeg Sep 11, 2020</p>	 <p>thumbnail.jpeg Sep 11, 2020</p>	 <p>diagnostic.png Sep 11, 2020</p>	 <p>diagnostic.png Sep 11, 2020</p>
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As of : 9/19/2022



Disease Summary Report

As of : 4/4/2023

Add new records




Help us find your records by letting us know all the places you've been seen for your condition.

[Request Records >](#)

Parent Portal: Disease Summary Report

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Disease Summary Report

 **About the Disease Summary** ▾

Filters ▾ Sort by: Oldest Latest

Primary Diagnosis

Rett Syndrome
Primary Diagnosis
[View Related History](#)

Related conditions	
Fine motor developmental regression Medical Condition 	
Ability to use pincer grasp: Able Fine Motor Development 	11/22/99
Ability to use at least one word: Able Language Development 	06/10/97
Language developmental regression Medical Condition 	10/10/97
Language developmental regression Medical Condition 	10/31/97



Parent Portal: Symptom Overview

Chronic cough
Medical Condition


 | [View Related History](#)


Chronic cough


Medical Condition 01/31/22

Medical Condition

Provenance related to this condition

	Code 68154008 SNOMEDCT_US
	Report Type progress_note
	Original Text Positive for cough

	Code 68154008 SNOMEDCT_US
	Report Type progress_note
	Original Text Two weeks ago, she started having increasing coughing episodes, sometimes productive, sometimes dry, and have been tending to occur in the middle of the night sometimes up to 1-2 hours.

	Code 68154008 SNOMEDCT_US
	Report Type progress_note
	Original Text She coughs every day, but doesn't have coughing attacks every day.

Chronic cough

 [About the Disease Summary](#) ▾

Disease Summary Report
↳ [Chronic cough](#)

Filters ▾

Sort by: Oldest Latest

albuterol

Medication



ipratropium

Medication



Parent Portal: Manage Data

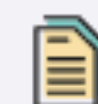
Manage Data



Share Records



Request Records



Upload document

People you are sharing to

Institutions with access to your data

Your record requests

Documents You have uploaded

Who Can See Your Data

People you're sharing to

The following people can access your data because you've previously shared it with them.

SL

Shared Link



Full Profile

08/29/2021



pue.farooque@yale.edu



Full Profile



Share Records

Benefits for dNHS Families

- Availability of medical records varies across institutions as the transition to digital files occurs
- Access records in one place
- View information by symptoms
- Easily share with new providers
- Contribute to research with minimal effort



Benefits for dNHS Families

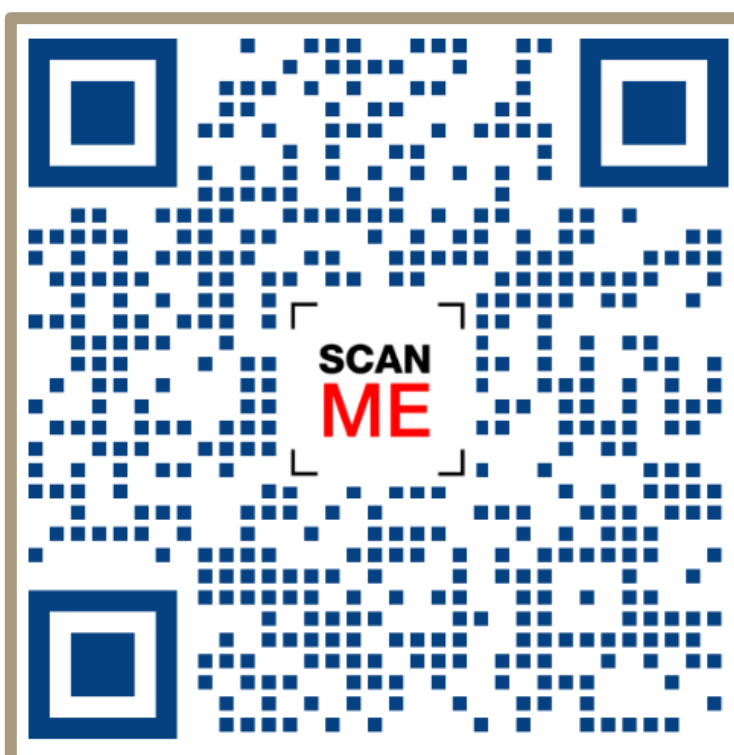
Help move the needle for all

- Don't let valuable information languish. Put that valuable information to work.
- Share results with the community and improve care
- Inform disease progression over time
- Improve clinical trial design and execution
- Speed up time getting new treatments to patients
- A goal – use dNHS in lieu of placebo groups



Join Today!

<https://www.ciitizen.com/rett/RSRT>



You will need

- Drivers License or other form of ID
- Child's birth certificate
- Child's legal guardianship papers if they're over 18
- US only for now

The screenshot shows the top navigation bar of the Ciitizen website. It includes the INVITAE logo, the Ciitizen logo, and links for ABOUT, JOIN US, OUR PARTNERS, PRESS, PRIVACY, JOBS, and a LOG IN button. There is also a link to Visit Invitae.com and the Rett Syndrome Research Trust logo.

The main content area features a large image of a young girl with blonde hair, wearing a pink polka-dot top, sitting in a wheelchair. Overlaid on the image is the text: "Ciitizen is conducting a next generation, digital Natural History Study to learn more about Rett syndrome and to accelerate the drug development efforts". Below this text is a blue "Join Today" button.

At the bottom of the main content area, there is a small text box that reads: "This study is only open to US residents with a diagnosis of Rett Syndrome and a confirmed alteration in MECP2."



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How have we analyzed the data extracted from medical records?

Kristina Hone, MBA, TRS

Lead Data Scientist

CEO, CASK gene Foundation

Extracting and Coding Information

• PERRL 386666001

Cranial Nerves: pupils equal round and reactive to light, extraocular movement intact with no nystagmus, no visual field defects to confrontation, symmetric, palate elevation and tongue protrusion midline, and head tilt. Generalized hypotonia 13511000224101 ophthalmoscopy could not be performed.

Motor: Normal bulk with decreased tone throughout, most notable at the shoulder girdle, good and symmetric resistive strength throughout. can reach arms above head, some uncoordinated arm and hand movements including some overflow/hyperkinetic movements and arms are often held with flexed elbows at her sides; there is notable difficulty with sustained grasp of toys and reflex hammer, there is persistence of palmar and plantar grasp reflexes

• Hyperkinesia 13141000224105

Sensation: Grossly intact to light touch in distal extremities bilaterally → Sensation grossly intact 13461000224103

Reflexes: 3+ biceps, brachioradialis, 3+ patella and achilles.

Coordination: Incoordination with upper extremities movements/ reach, no tremor, occasional non purposeful hyperkinetic hand movements, will reach target (ie can grab small toy/pen, but grasp is not sustained)

Gait: Can now take independent steps with braces on, gait is ataxic with a wide base

• Ataxic gait 25136009



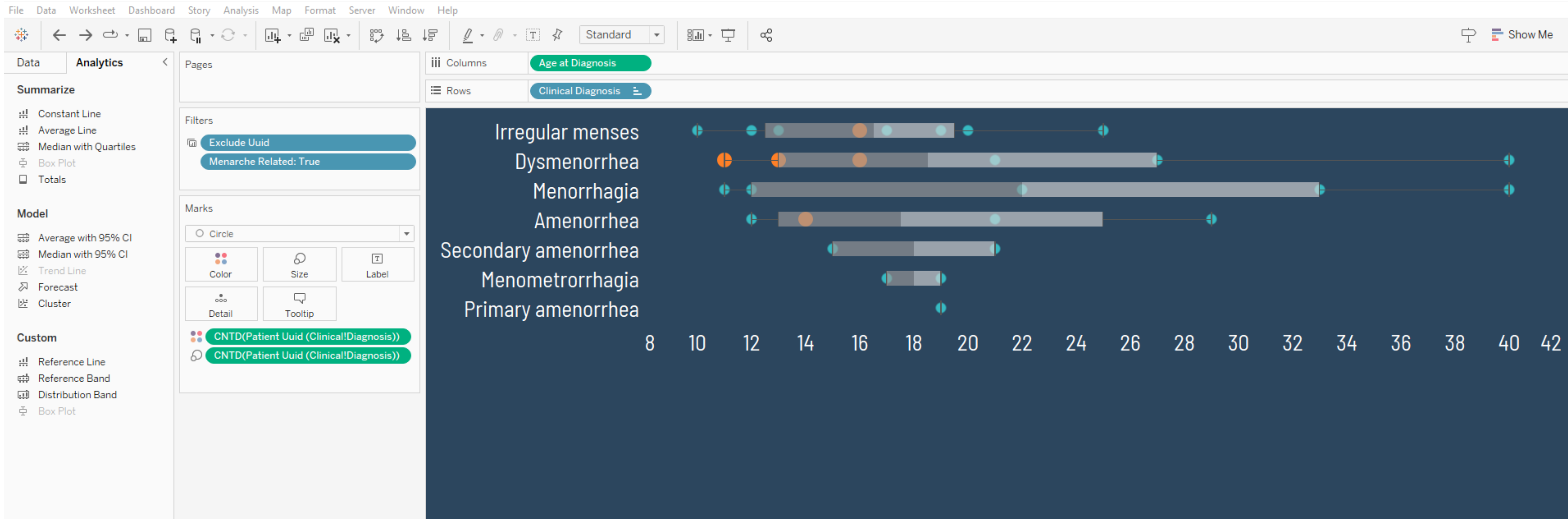
Receiving and Relating Data

Patient ID	Sex	Age	Primary Diagnosis	Age at Diagnosis	Patient ID	Clinical Diagnosis	Age at Diagnosis
6fc8c6c6-12e6-4154-bd04-8e5456cfd492	Female	39	Rett Syndrome	12	6fc8c6c6-12e6-4154-bd04-8e5456cfd492	Abnormal gait	13
					6fc8c6c6-12e6-4154-bd04-8e5456cfd492	Abnormal weight loss	21
					6fc8c6c6-12e6-4154-bd04-8e5456cfd492	Aggressive behavior	19
					6fc8c6c6-12e6-4154-bd04-8e5456cfd492	Anxiety	20
					6fc8c6c6-12e6-4154-bd04-8e5456cfd492	Apraxia	34
					6fc8c6c6-12e6-4154-bd04-8e5456cfd492	Breathholding spell	16
					6fc8c6c6-12e6-4154-bd04-8e5456cfd492	Bruxism	19
					6fc8c6c6-12e6-4154-bd04-8e5456cfd492	Chorea	30
					6fc8c6c6-12e6-4154-bd04-8e5456cfd492	Constipation	23

Patient ID	Sex	Age	Patient ID	Seizure Type	Age at Record	# of Seizures	Frequency
6fc8c6c6-12e6-4154-bd04-8e5456cfd492	Female	39	6fc8c6c6-12e6-4154-bd04-8e5456cfd492	Seizure	23	>=7	Per Day
			6fc8c6c6-12e6-4154-bd04-8e5456cfd492	Seizure	23	>=1	Per Day
			6fc8c6c6-12e6-4154-bd04-8e5456cfd492	Seizure	13	9	Per Hour
			6fc8c6c6-12e6-4154-bd04-8e5456cfd492	Clonic seizure	23	>1	Per Month
			6fc8c6c6-12e6-4154-bd04-8e5456cfd492	Clonic seizure	23	0	Per Month
			6fc8c6c6-12e6-4154-bd04-8e5456cfd492	Generalized tonic-clonic seizure	14	10	Per Month
			6fc8c6c6-12e6-4154-bd04-8e5456cfd492	Subclinical seizure	14	2	Per Week
			6fc8c6c6-12e6-4154-bd04-8e5456cfd492	Tonic seizure	19	0	Per Week
			6fc8c6c6-12e6-4154-bd04-8e5456cfd492	Tonic seizure	20	2	Per Week



Data Analysis





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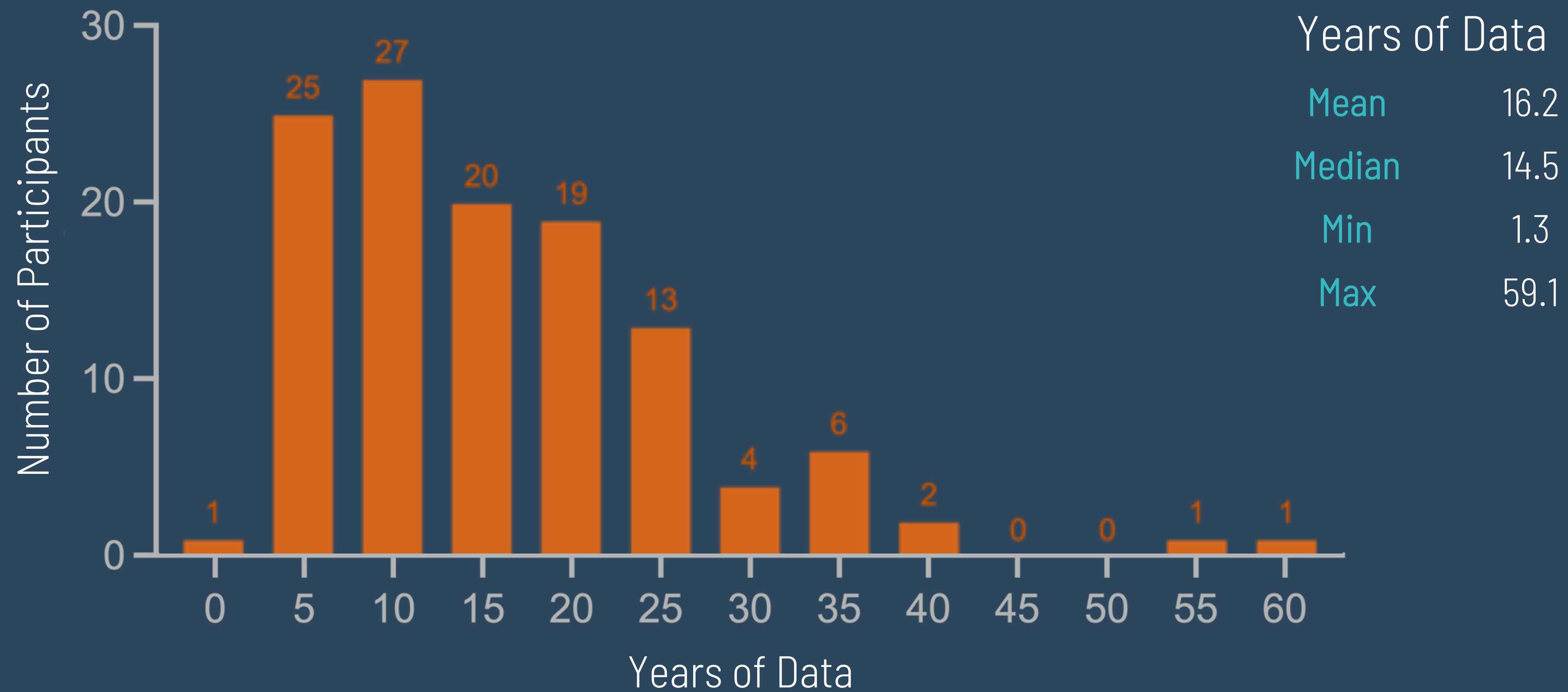
What have we learned so far from the next-generation digital NHS?

Cary Fu, MD

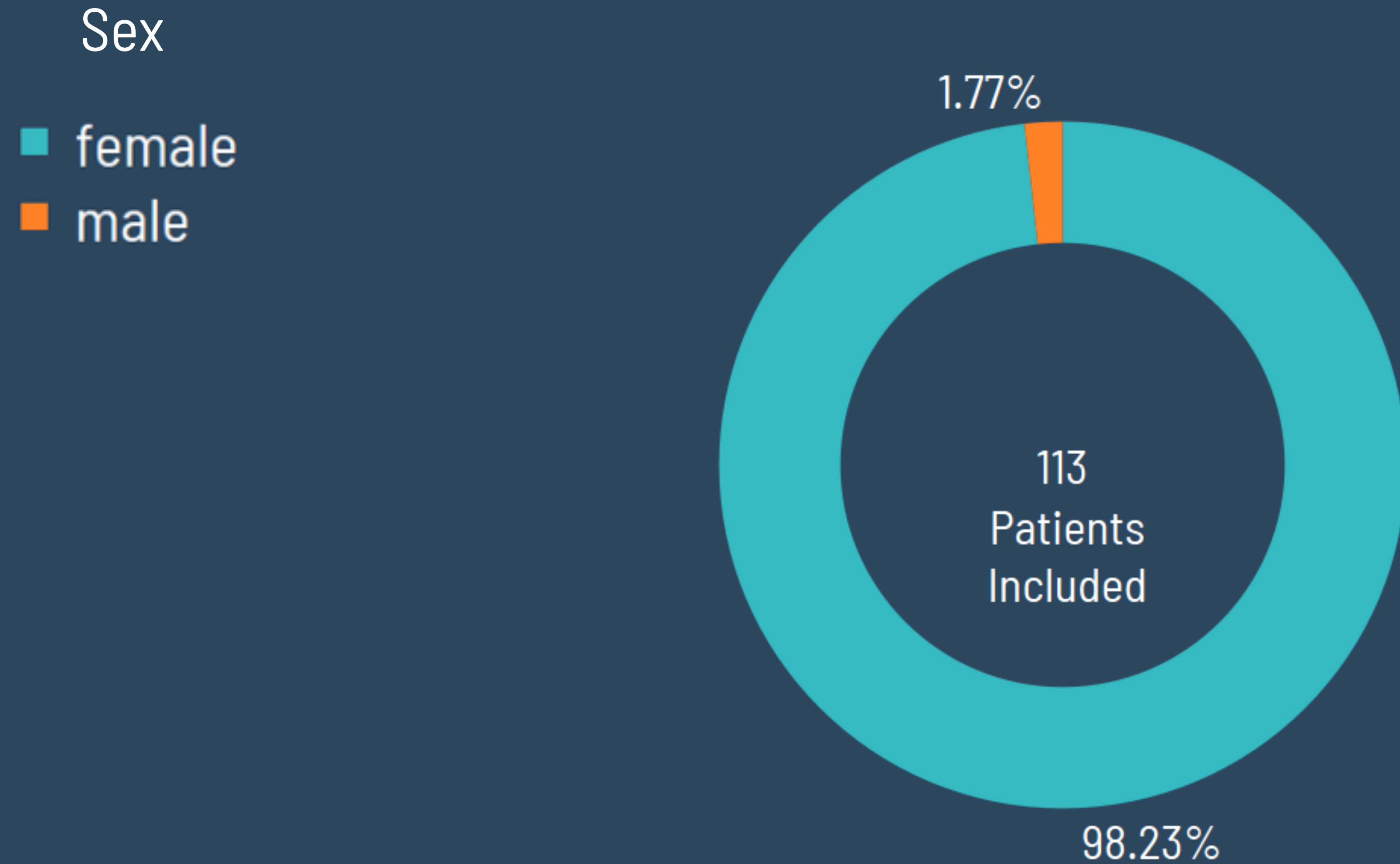
Clinical Lead , Rett Syndrome Global Registry & Digital Natural History Study

Medical Director, Rett Syndrome Clinic at Vanderbilt University Medical Center

Years of Data per Participant



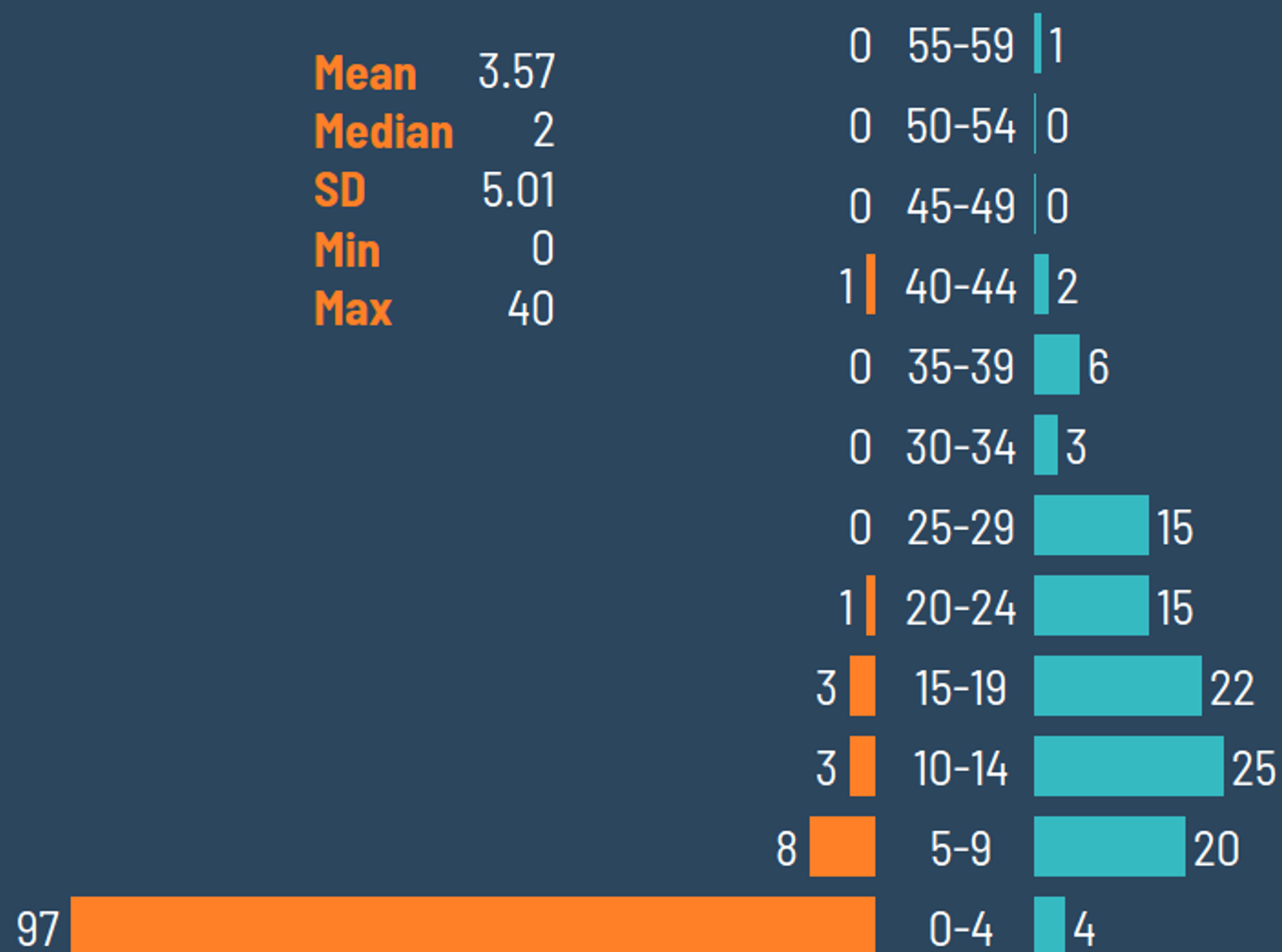
Participant population



Participant Ages

Age at Diagnosis

Mean 3.57
Median 2
SD 5.01
Min 0
Max 40

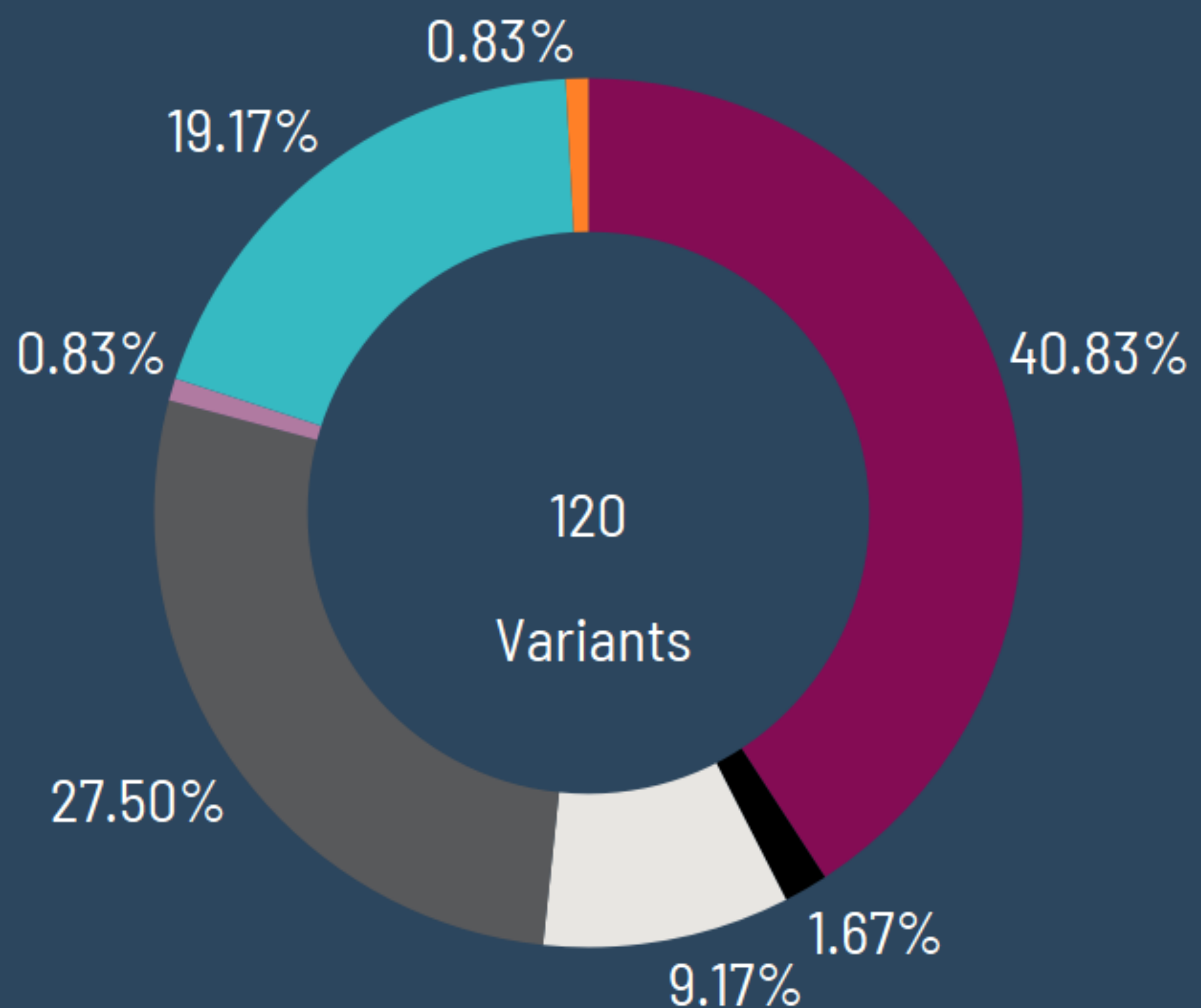


Current Age

Mean 17.93
Median 17
SD 10.17
Min 2
Max 59

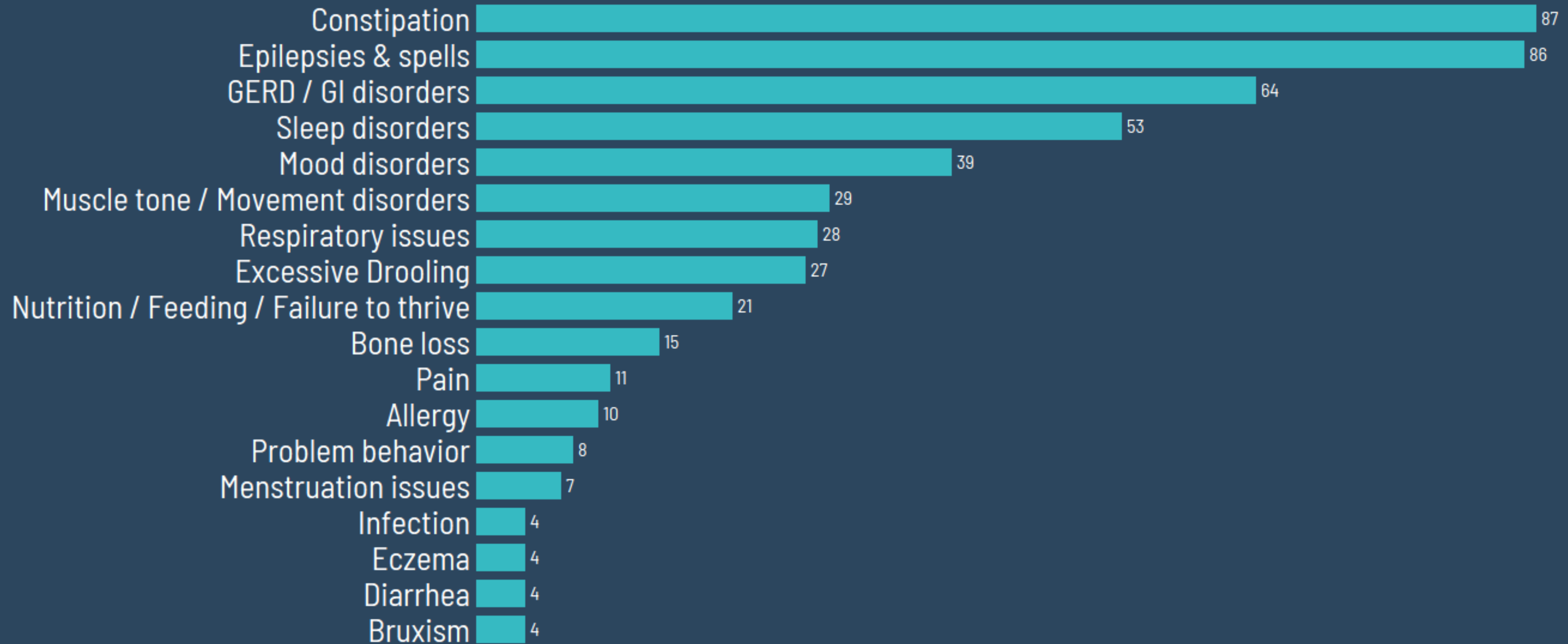
MECP2 Mutations

Variant Type	Example
missense	T158M; R306C
splicing	IVS2-2A>G
deletion	del exons 3-4
nonsense	R168X; R270X
silent	S411S
frameshift	G269Afs*20
insertion	gain - exon 3



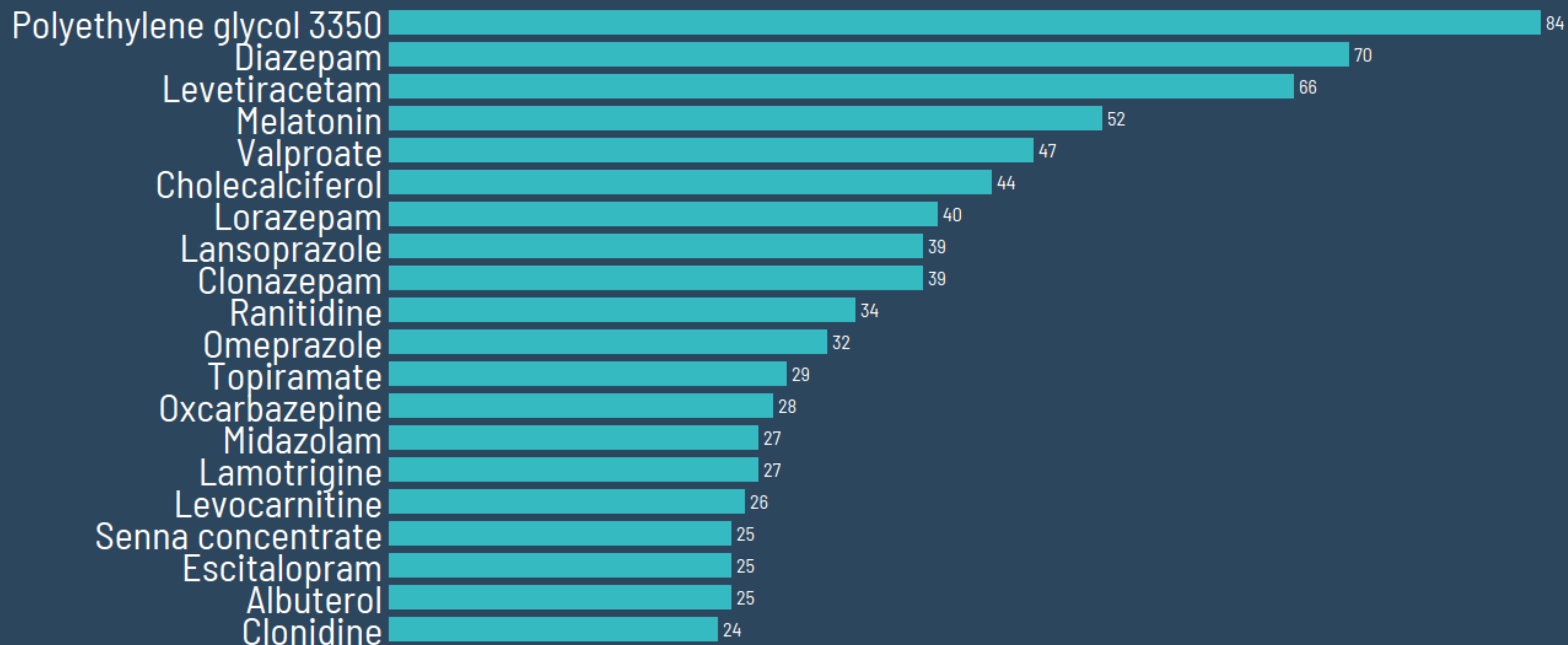
Medications by Indication

Common Indications for Medications (by N of distinct patients treated)



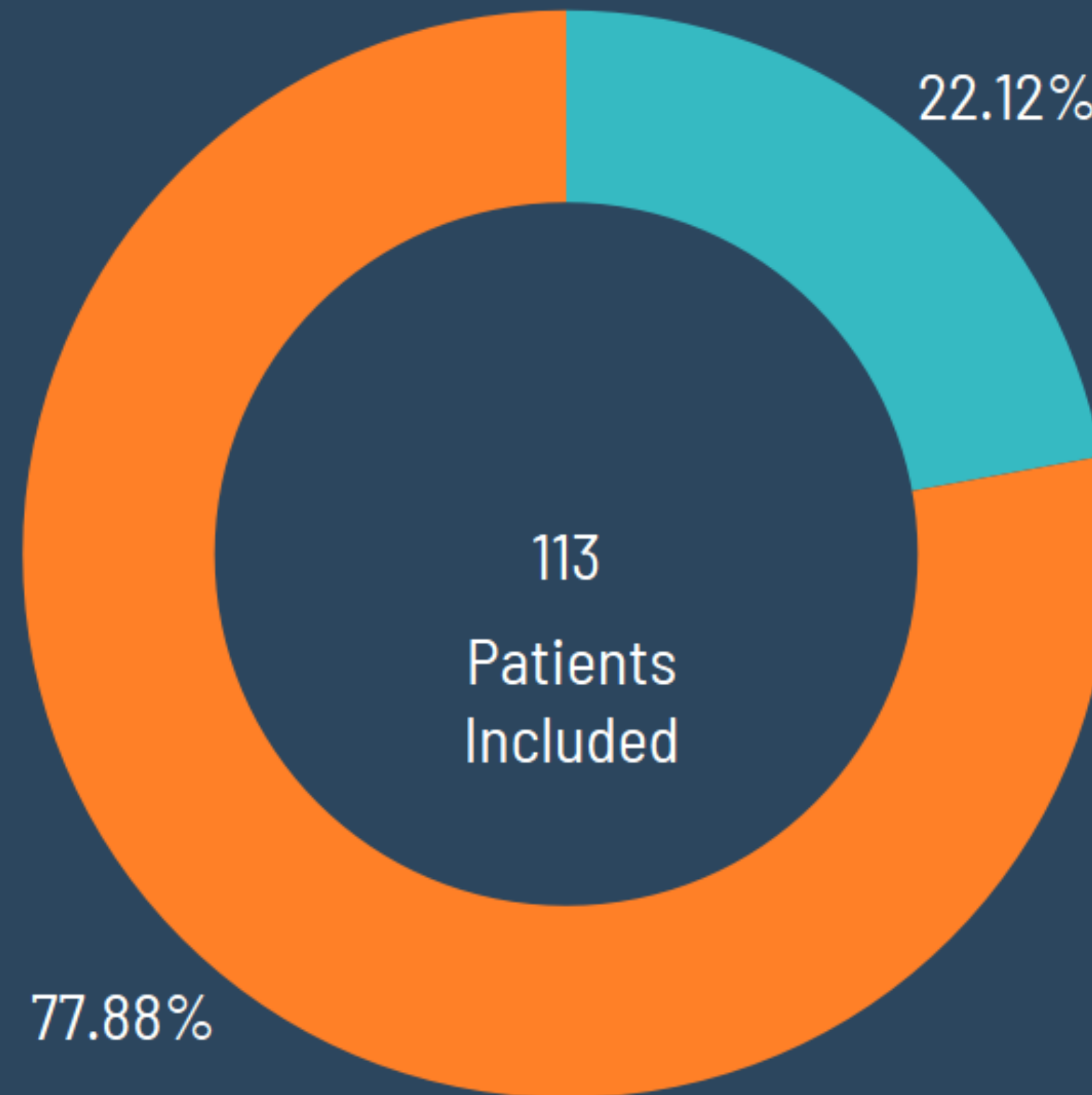
Most Common Medications

Top 20 Prescribed Medications (by N of patients who have used each)



Percent of Participants with Epilepsy

- Without Epilepsy
- With Epilepsy



Without Epilepsy

- No clinical diagnosis of epilepsy
- No record of seizure events
- No AED prescribed

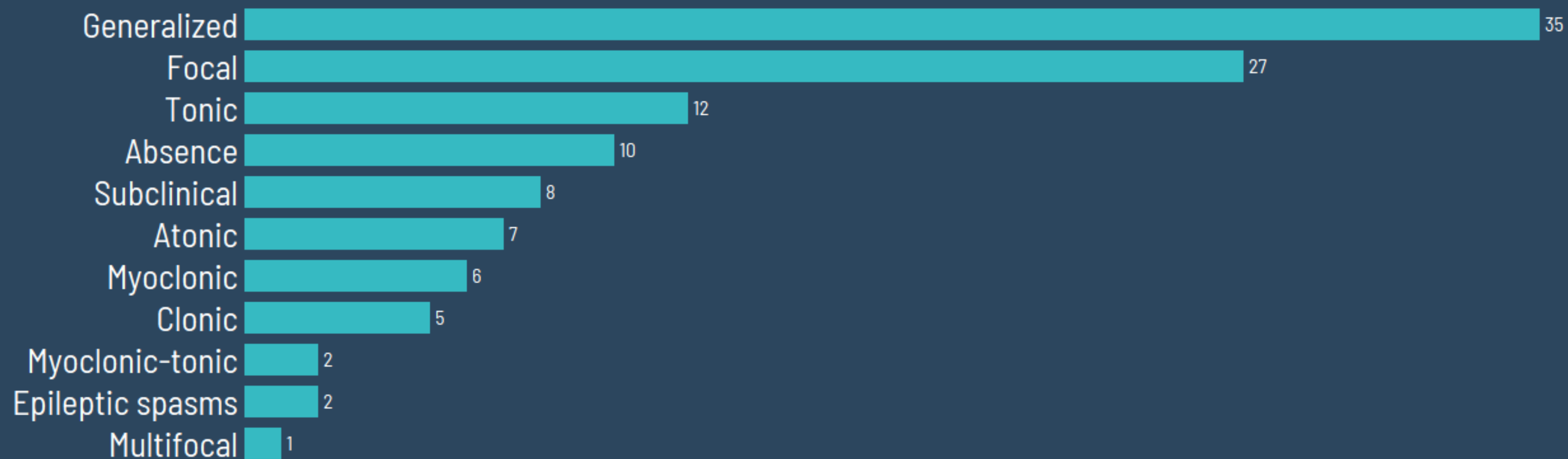
With Epilepsy

- Clinical diagnosis of epilepsy
- Record of seizure events
- Prescribed AED for epilepsy



Epileptic Seizure Types

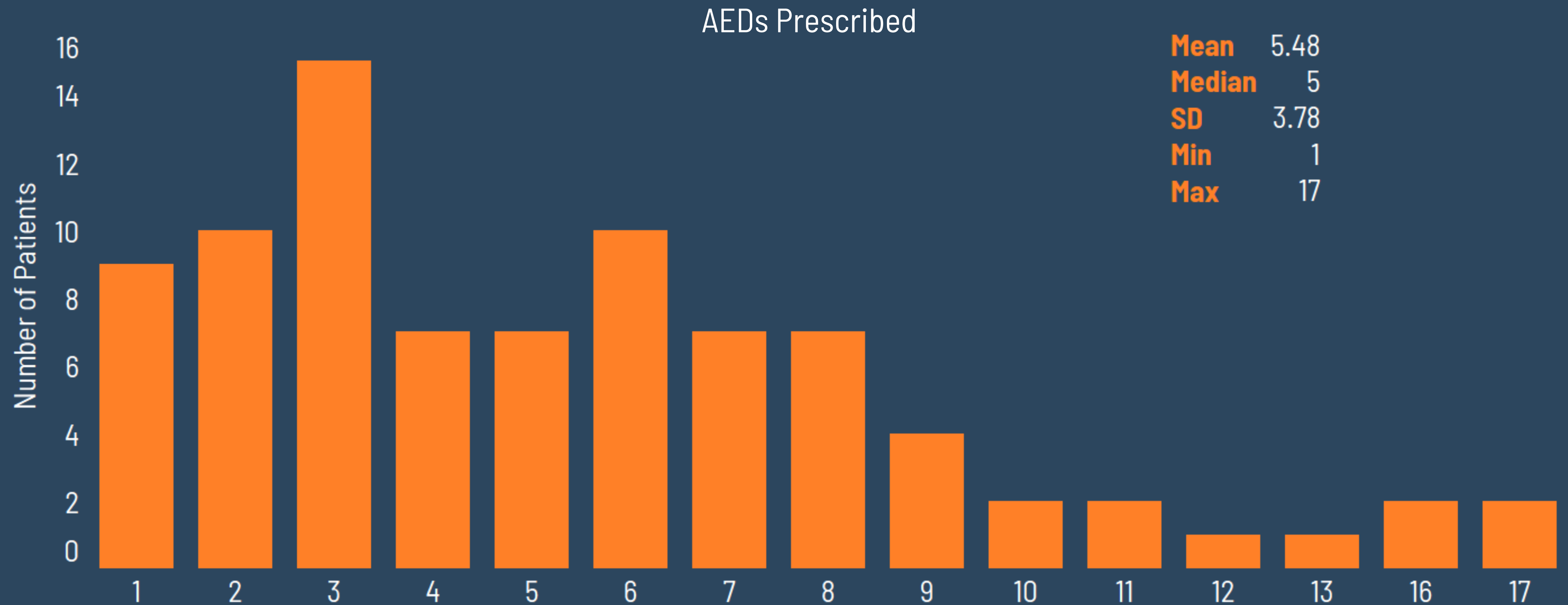
Seizure Types (by N of Patients who were reported to experience each)



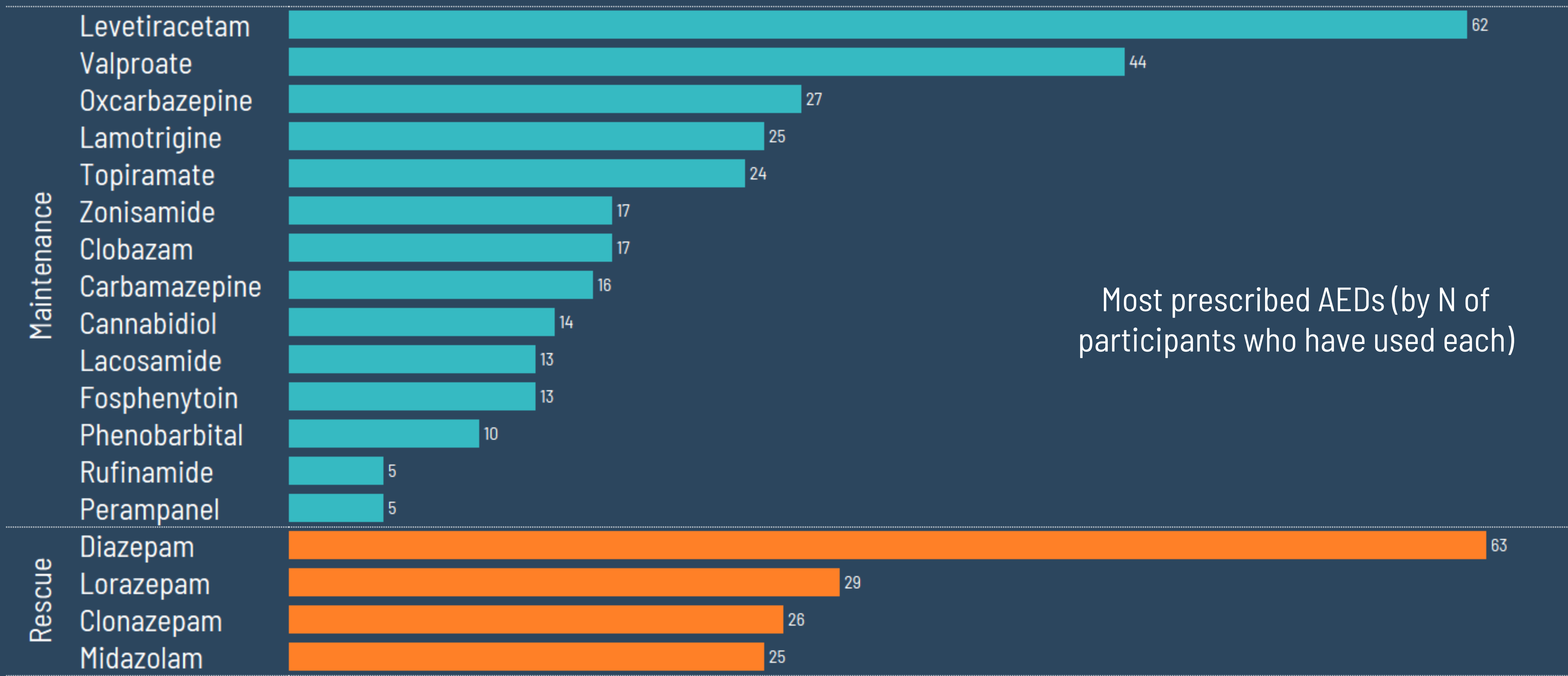
Prolonged Seizures



Number of Anti-Epileptic Drugs Prescribed Over Time



Most Common AEDs Prescribed for Seizures



Most prescribed AEDs (by N of participants who have used each)



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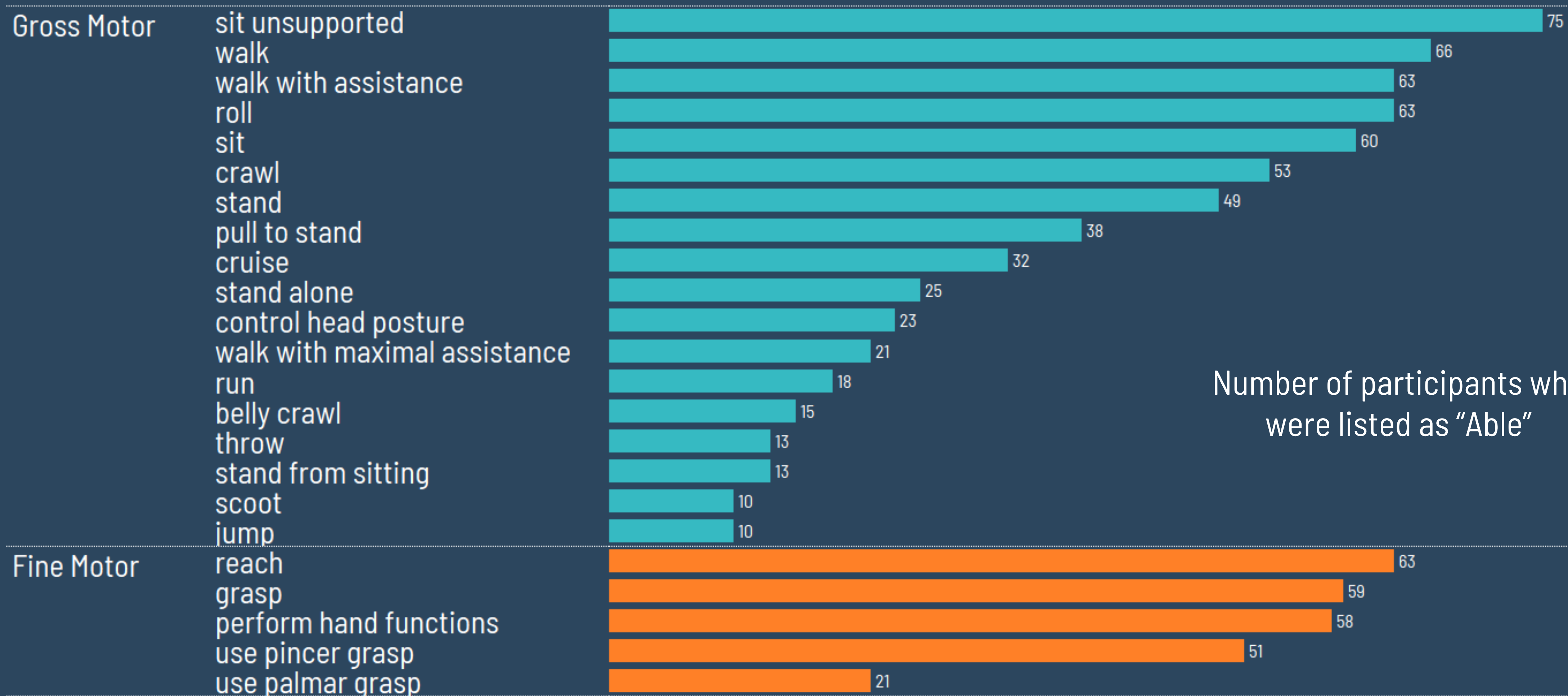
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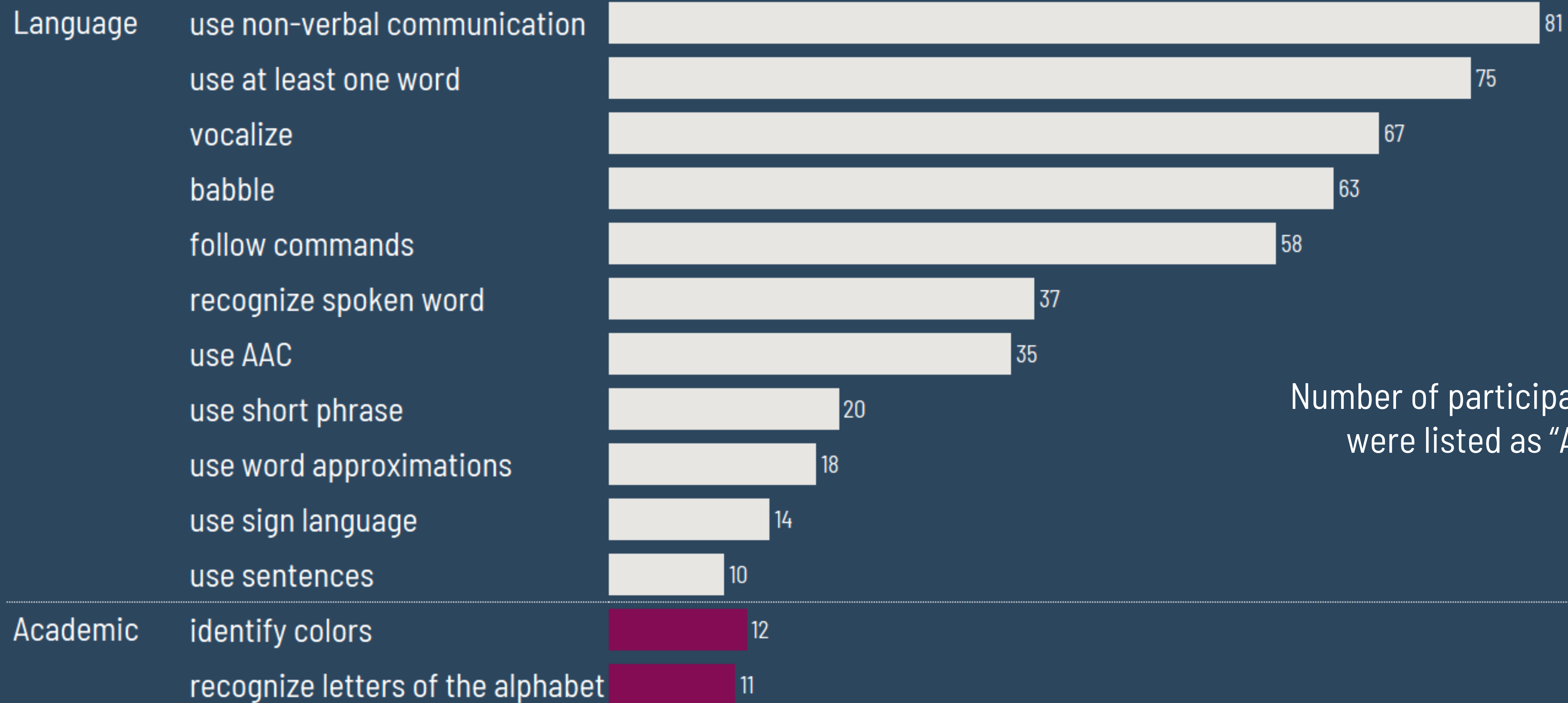
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Gross and Fine Motor Development

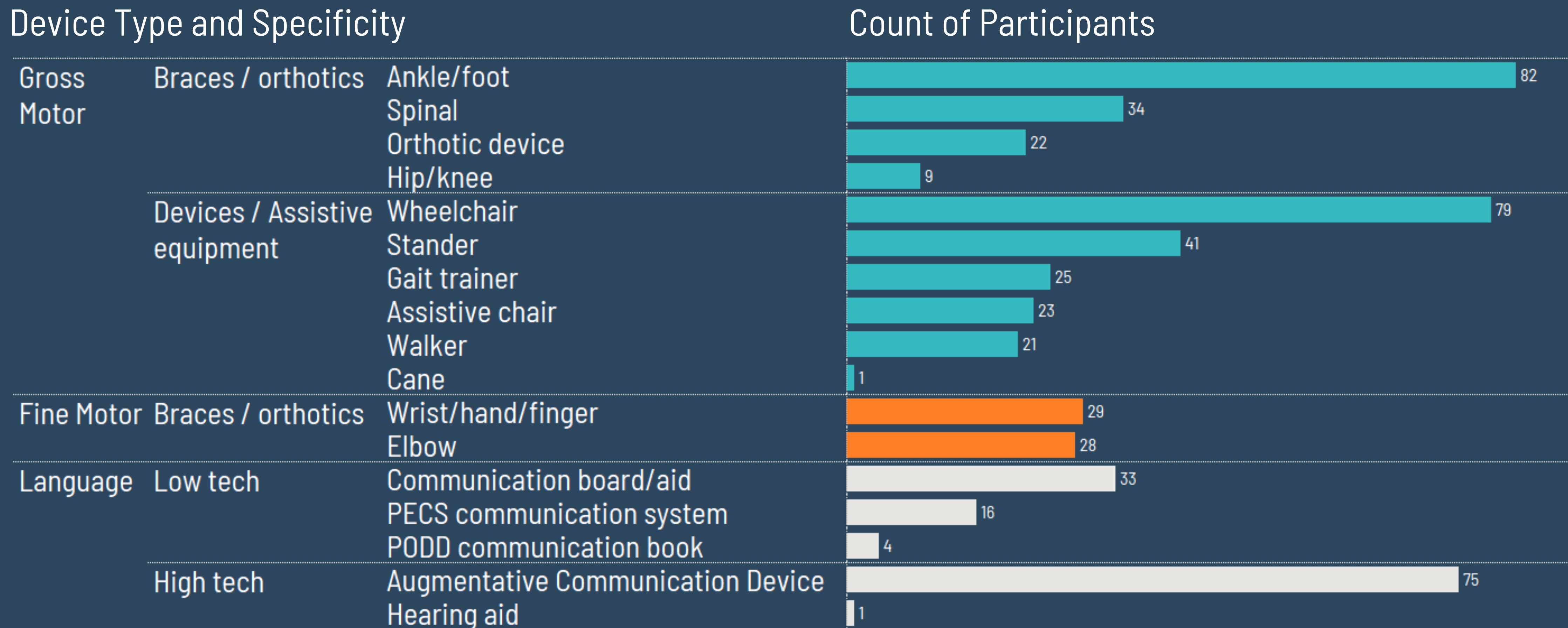


Language and Academic Development



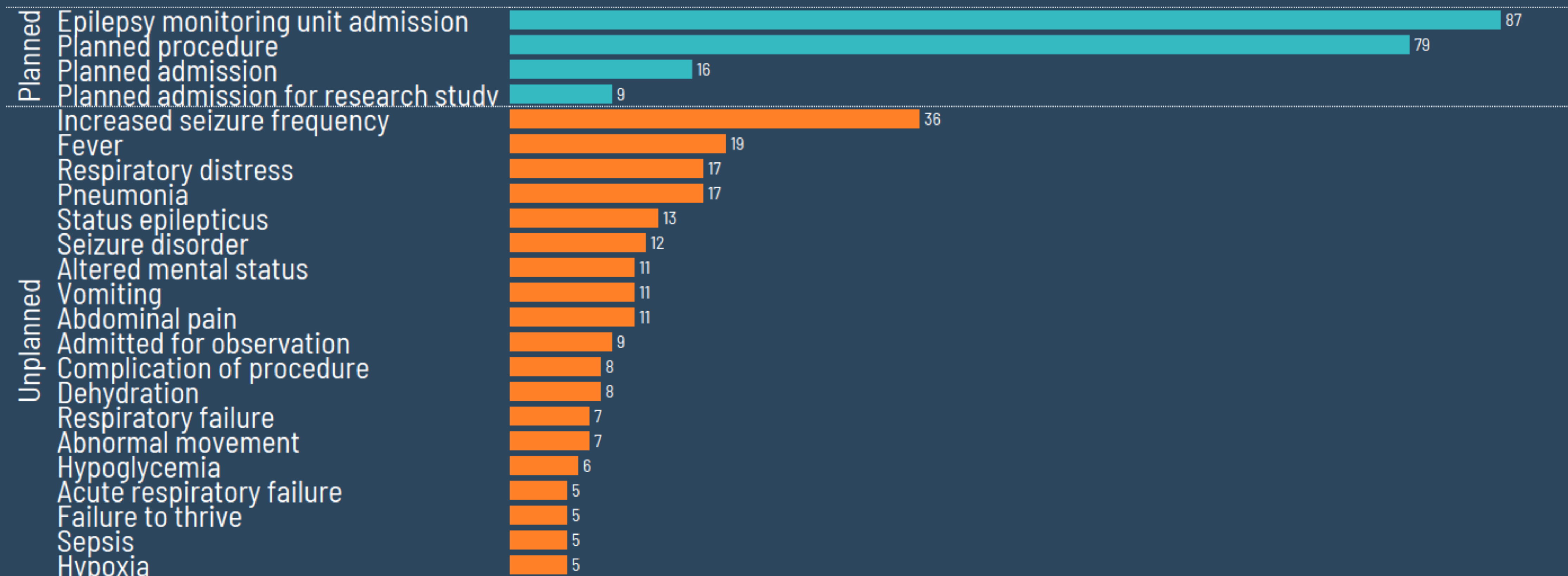
Number of participants who were listed as "Able"

Use of Orthotics and Assistive Devices



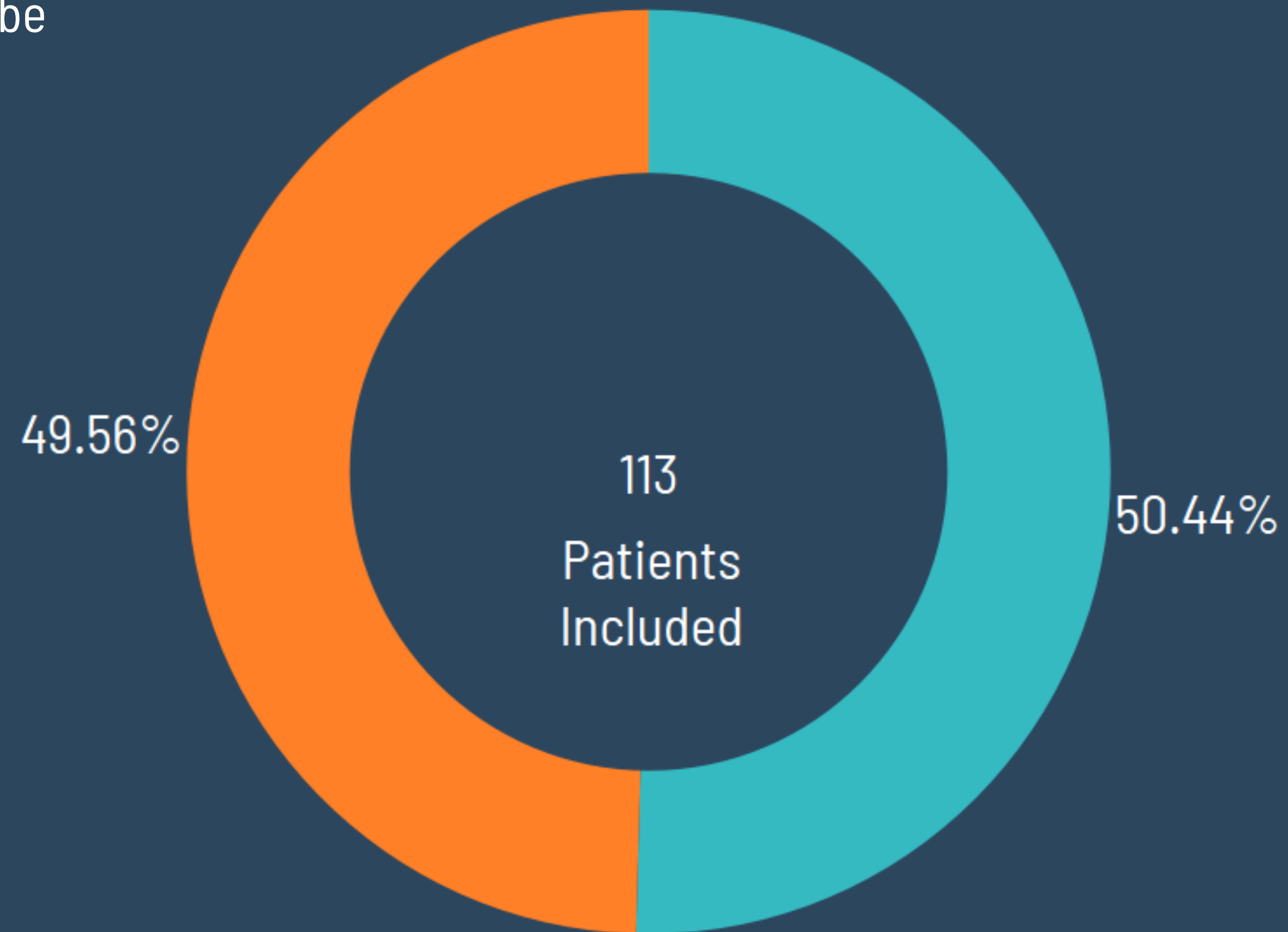
Reasons for Hospital Admissions

Common Admission Diagnoses



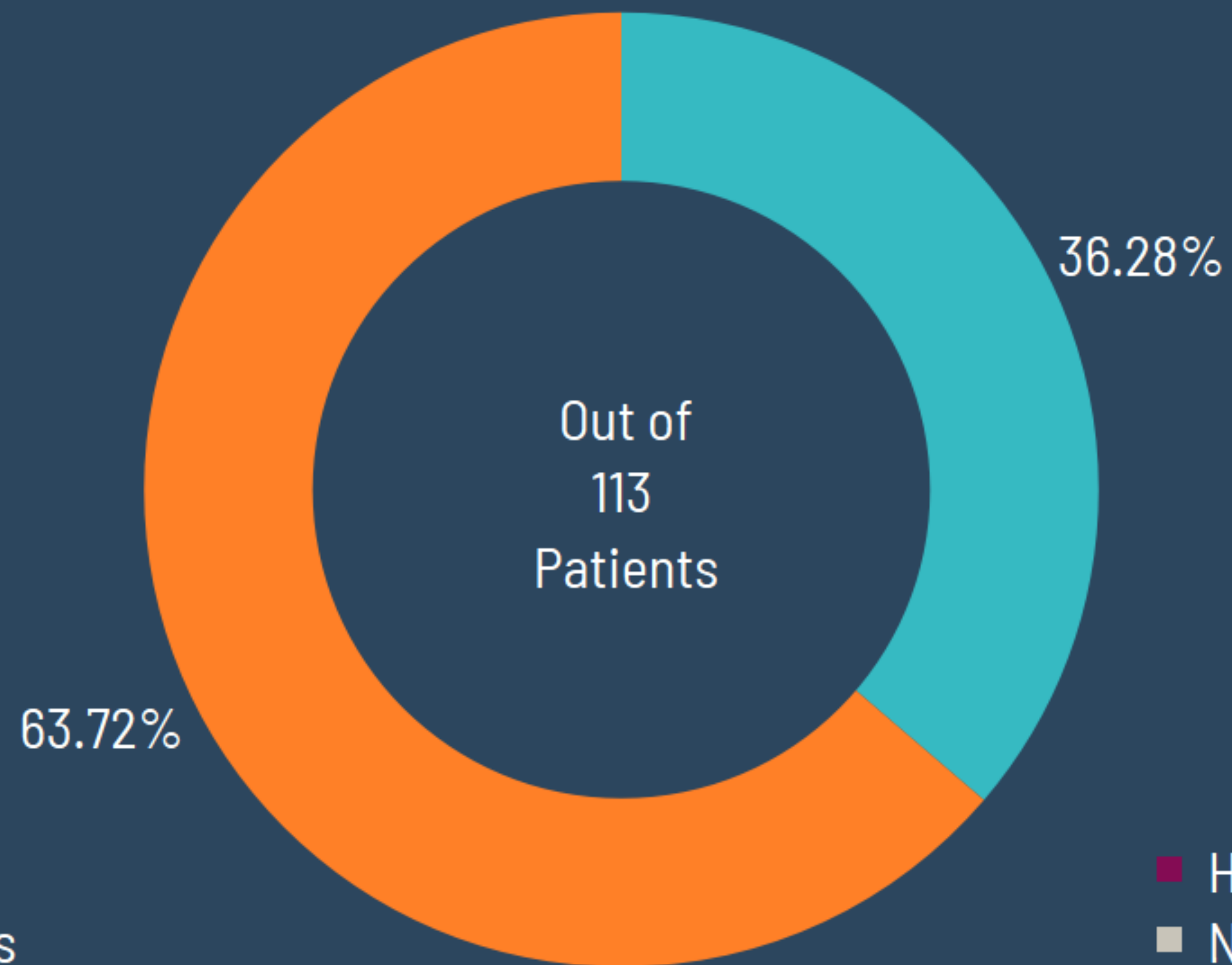
Percent of Participants with a Feeding Tube

- No Feeding Tube
- Feeding Tube

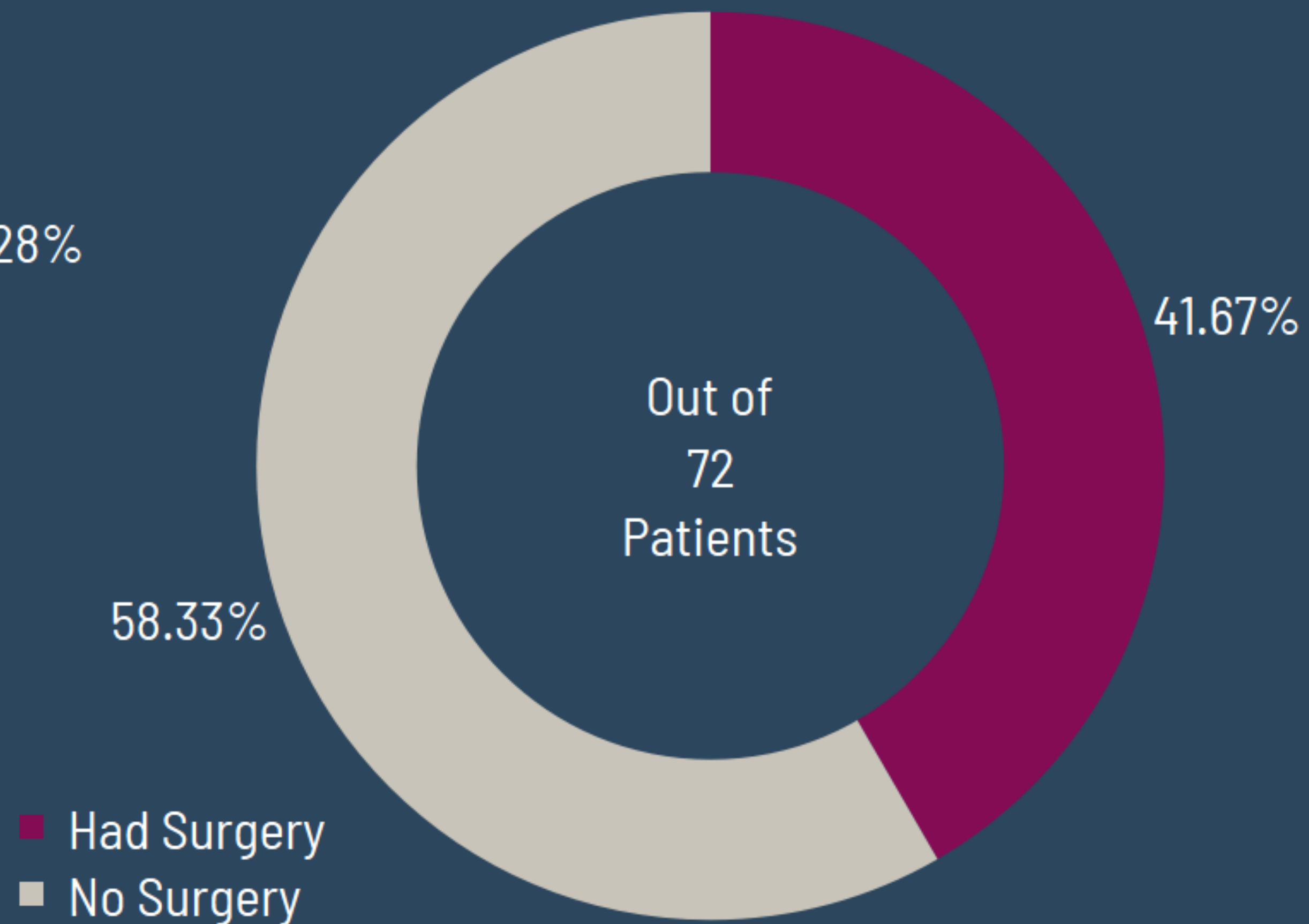


Percent of Participants with Scoliosis and Surgery

Percent of Population with Scoliosis

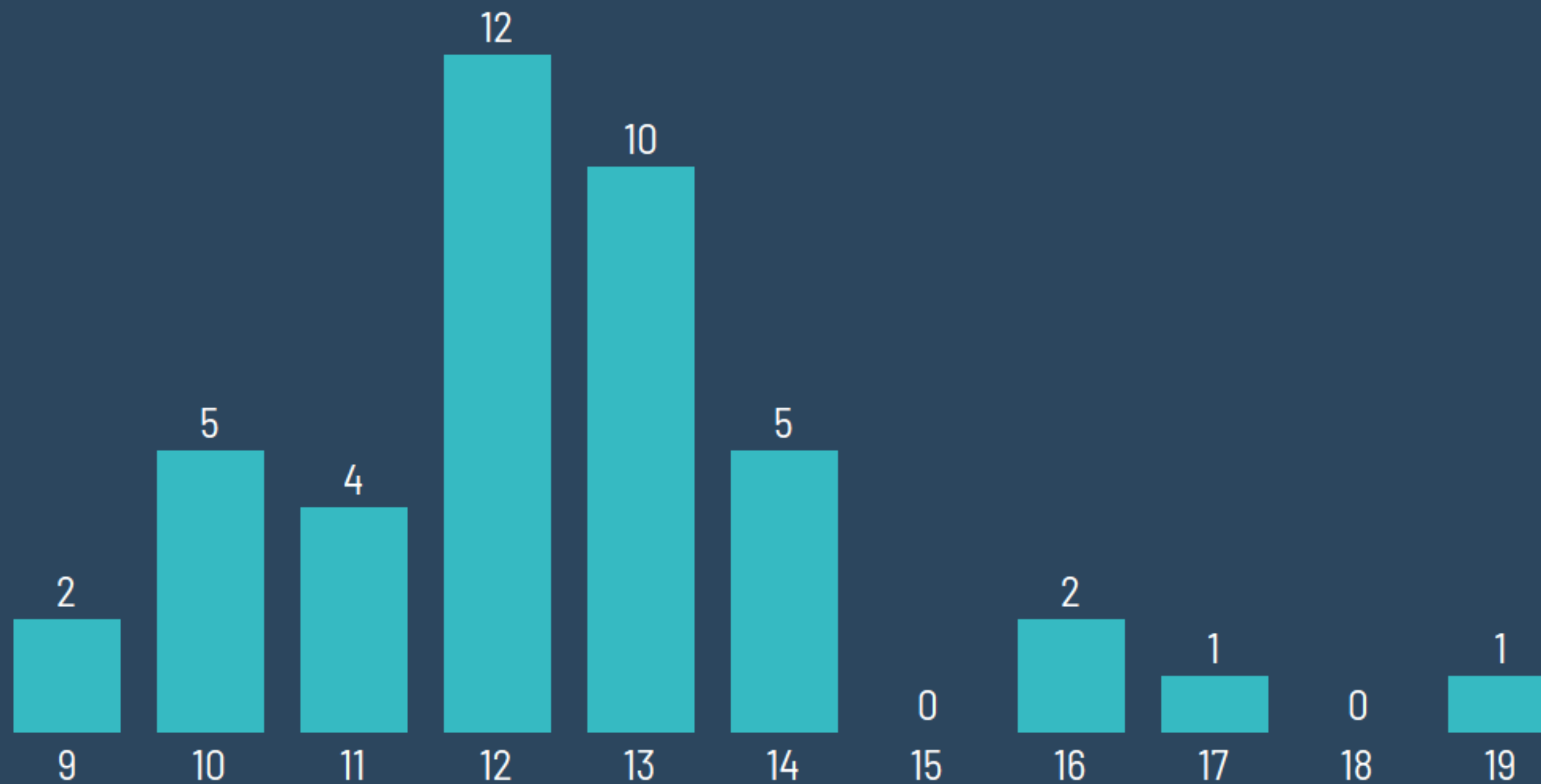


Percent of Those who had Surgery



Female development

Age at First Period (Menarche)



Mean	12.5
Median	12
SD	2.1
Min	9
Max	19

Thank you to the 119 parents who contributed so far!

Conclusions

- MECP2 mutation frequencies, seizure frequencies, and delayed menses mirror findings from the traditional NHS demonstrating dNHS data are valuable
- Most common non-seizure meds: polyethylene glycol (or OTC MiraLax) for constipation, melatonin for sleep
- Most prescribed AEDs: leviteracetam (Keppra), valproate (Depakote) and diazepam (Diastat) as rescue med
- Hospitalizations: about half are planned; unplanned stays mostly due to seizures/respiratory issues
- Surgeries: 50% for feeding tube; 40% for scoliosis
- Periods start around 12.5 years old

Limitations

- Data summaries are only as good as the detail recorded
- Inconsistent data recording leads to spotty data
- Medical records are sometimes inaccurate

Solutions

- Increase cohort size
- Participate in multiple studies



Combine Untapped Resources to Expand Rett Therapeutics

Comprehensive medical records are not utilized



Part 1

Clinical Component
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- Consolidate all medical care received into a research-ready, coded dataset

Parents have valuable knowledge that is not captured



Part 2

Parent-Reported Component
to Support Day-to-Day Care

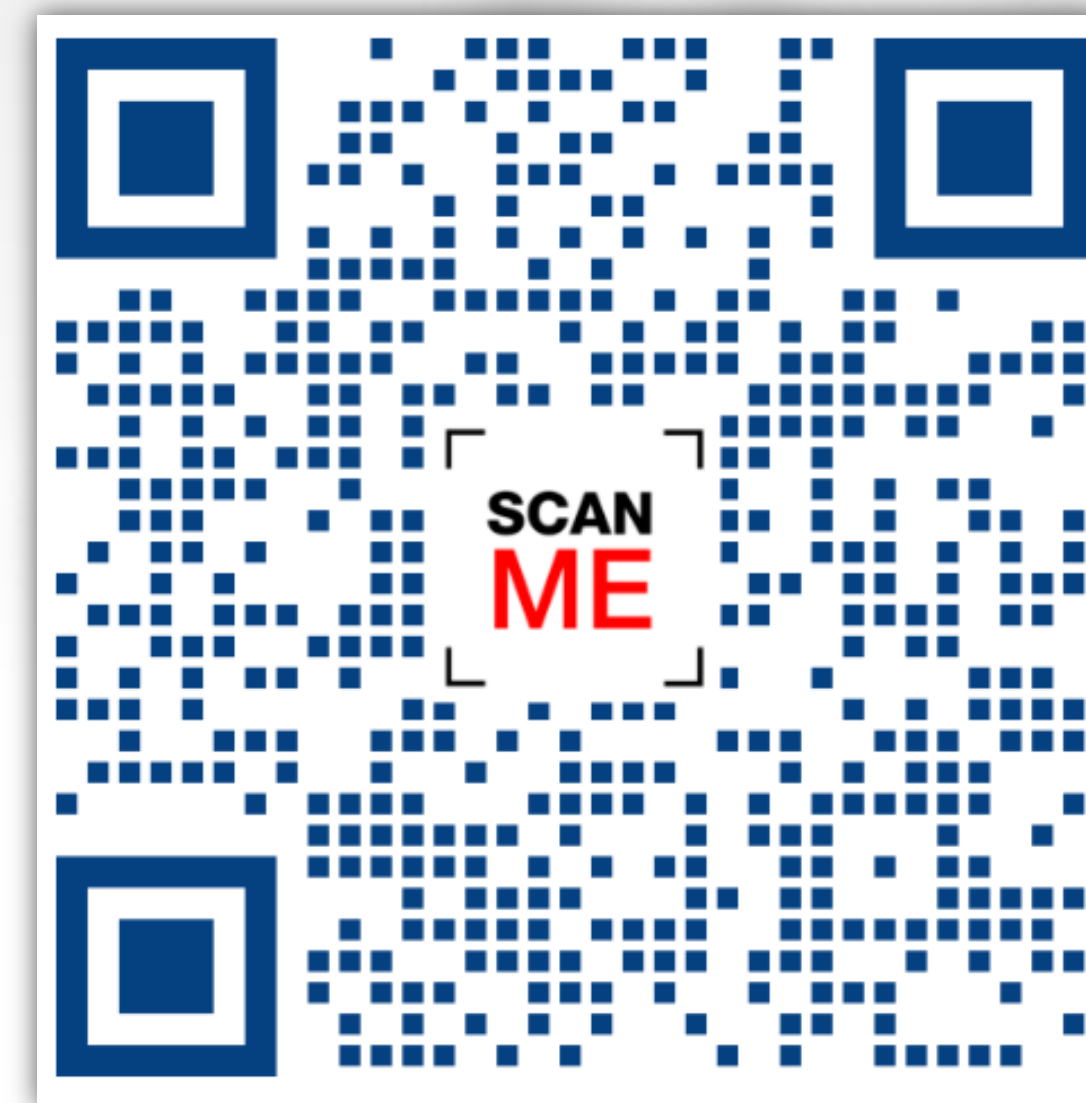
- Rett history, symptom burden, care strategies, family life, clinical trial perspectives
- Individualized symptom/episode tracking & graphing

Question and Answer Session

<https://www.ciitizen.com/rett/RSRT>

You will need

- Drivers License or other form of ID
- Child's birth certificate
- Child's legal guardianship papers if they're over 18
- US only for now



Thank you!