Registries & Natural History Studies

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Despite major advancements in research, 95% of all rare disorders still don’t have an FDA-approved therapy1

- With novel therapeutic approaches, including gene and cell therapies, there is increasing investment in drug development for rare disorders
- However, **FDA requires inclusion of observational data (like natural history)** to evaluate therapies for these conditions

1.Global Genes Rare Disease Facts. Accessed May 23, 2022. https://globalgenes.org/rare-disease-facts/

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- In order to generate a hypothesis, we need to actually **understand the disease.**
- In order to understand the disease, we need to **generate and access data** about the disease

What’s what?

Four key terms that are important to understand and distinguish:

Clinical Study	Patient Registry	Observational Study	Natural History Study

Observational vs. Clinical Studies

Observational studies observe people in normal settings. Researchers gather information, group volunteers according to broad characteristics, and compare changes over time.

- **No experimental therapy or intervention**
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Clinical trials are research studies performed in people that are aimed at evaluating a medical, surgical, or behavioral intervention. They are the primary way that researchers find out if a new treatment, like a new drug or diet or medical device (for example, a pacemaker) is safe and effective in people.

- **Focus on safety/efficacy of intervention**
- Critical step to approving a therapy
- Generally take place after disease is understood

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Observational data supports trial success

Pre-Clinical

- Support phenotype characterization across the lifespan
- Define study inclusion/exclusion criteria
- Support endpoint selection and characterization
- Inform clinical trial design

Phase 1 / 2 / 3

- Serve as external control arm
- Support or confirm evidence of efficacy
- Enable effective recruitment and site planning strategies

Postmarket

- Support or confirm evidence of efficacy
- Monitor for long-term outcomes and/or adverse effects
- Evaluate real world prescribing, use, and/or reimbursement

Challenges of observational studies

- Difficult to execute & expensive
- Takes years to collect enough data to understand a disease
- Fragmentation of care leads to incomplete data
- Participants have to travel to a clinic, resulting in selection bias
- Participants don’t have access to data collected

Registries and Natural History Studies

“A registry is an organized system that collects clinical and other data in a standardized format for a population defined by a particular disease, condition, or exposure” - FDA

- Clinician-reported outcomes
- **Patient- and observer-reported outcomes**
- Medical claims data
- Pharmacy records
- Electronic medical records

A natural history study collects information about the natural history of a disease in the absence of an intervention, from the disease's onset until either its resolution or the individual's death.

- **Clinician-reported outcomes**
- Patient- and observer-reported outcomes
- Medical claims data
- Pharmacy records
- Electronic medical records

Rare disease registries are powerful but present limitations for natural history data

- Registries have powerful applications:
    - Identify participants for a clinical trial
    - Clinical endpoint selection and characterization
    - Serve as an external (historical) control
- And importantly, create an opportunity to incorporate the patient perspective

Challenge

Since in-person observational studies to conduct natural history are expensive and burdensome, we often rely on patient-reported data as a “proxy” to collect clinical information. Often times, the use of this data in research or for regulatory purposes is limited due to data quality challenges as the data isn’t confirmed by a doctor or clinician.

Ciitizen: a novel approach to accelerating research

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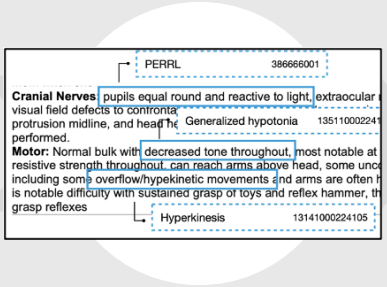
Ciitizen follows the patient and leverages HIPAA right of access to obtain medical records from all providers patient sees (average 6+ providers)

Medical records & images scanned and uploaded to patient's account

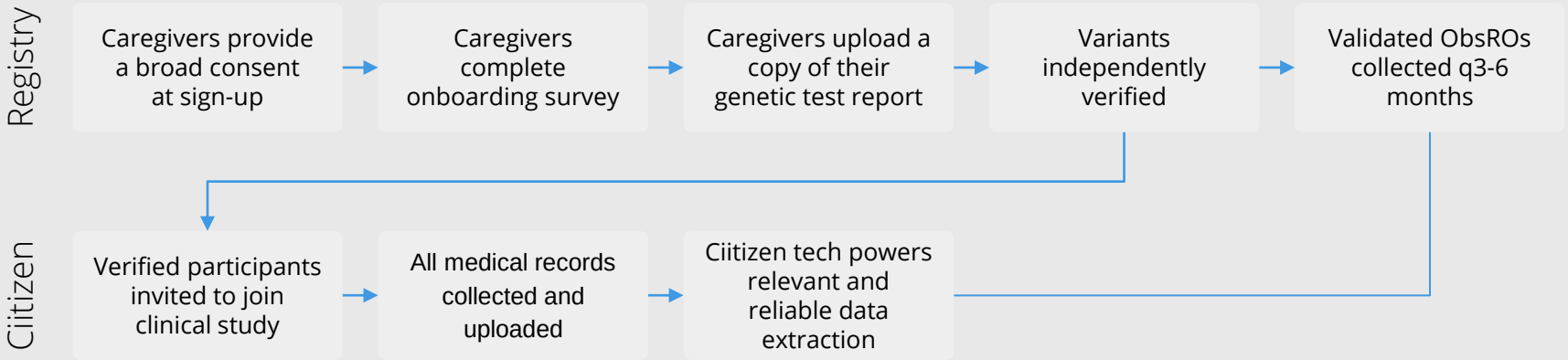


Raw records processed by machine-learning engine + human QA to extract, normalize and codify defined data elements

De-identified data output is structured and ready to share for research

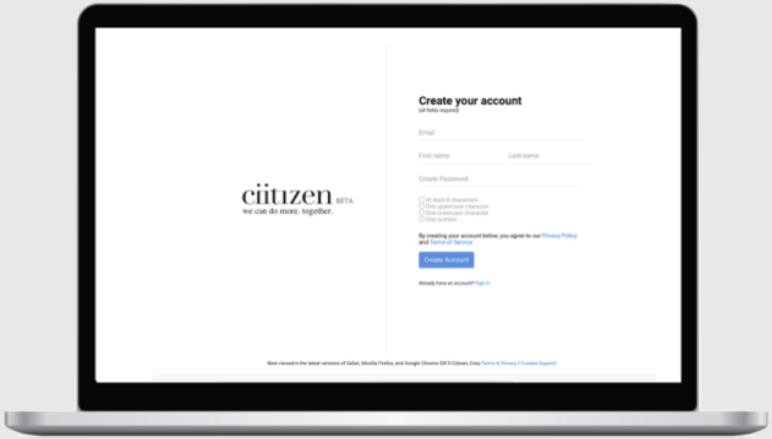
Registry aims and architecture

How can a patient advocacy organization accelerate collection of relevant clinical outcome assessments to de-risk pharma investment in rare disease?



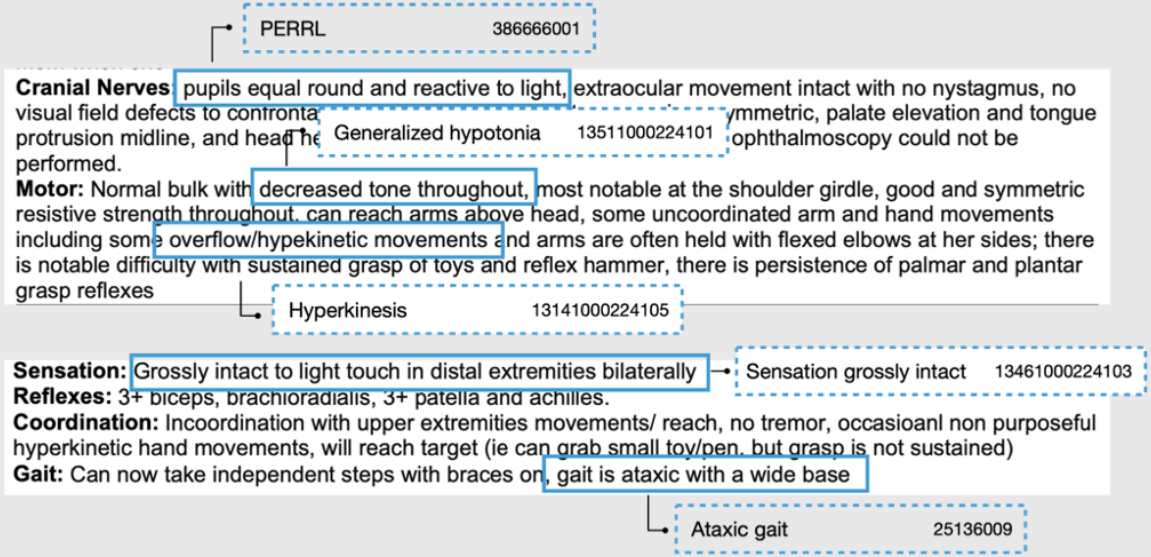
Data is collected for and owned by the patient

- Completely digital - no clinic visit required
- Collects participant's medical records from all the institutions visited
- Data from medical records is organized and summarized at no cost to the patient
- Extracts large amount of critical data in weeks (not years)
- Participants get full access to their medical records and can choose to share with researchers



It only takes 10 minutes for patients or caregivers to register - we do the heavy lifting!

Research-ready data is created from unstructured records



- Machine learning/NLP-assisted extraction engine that normalizes data
- Human assistance and review of pipeline generated data for QA/QC
- Terminologies such as SNOMED, RXNORM and LOINC used for normalization

Comprehensive entity extraction focused on defining history of disease and endpoints that can be measured

Demographic
Year of birth, Date and Age of Diagnosis, Ethnicity

Seizure History
Classification, Frequency, >5 min, Meds

Clinical Diagnosis (includes comorbidities)
Diagnosis, Date, Status

Genetic Diagnosis
Gene and Variant

Diagnostic Imaging
Modality, Date, Abnormal/Normal findings

Hospital Admissions
Admission/Discharge Date, Diagnosis, Significant Event

Growth
Height, weight

Diagnostic Procedures
Procedure, Date, Abnormal/Normal findings

Procedures
Surgical Procedure, EEG, NCV, Polysomnogram

Physical Exam Findings
Date, Cranial Nerves, Muscle Bulk/Tone & Strength, Gait, Sensation, Coordination, Reflexes

Development
Milestone, Age, Attainment, Standardized Assessments, Regression, Use of Devices

Medication
Name, Indication, Start/Stop Date, Dose, Frequency, Route of Admin, Treatment & Adverse Effect

Considerations for registry design

Thoughtful registry design broadens utility:

Relevance	Reliability	Curation
Ensure capture of key data elements across a representative patient population	Input processes to maximize data accuracy and comprehensiveness	Harmonize source data through use of terminologies

Considerations for registry design

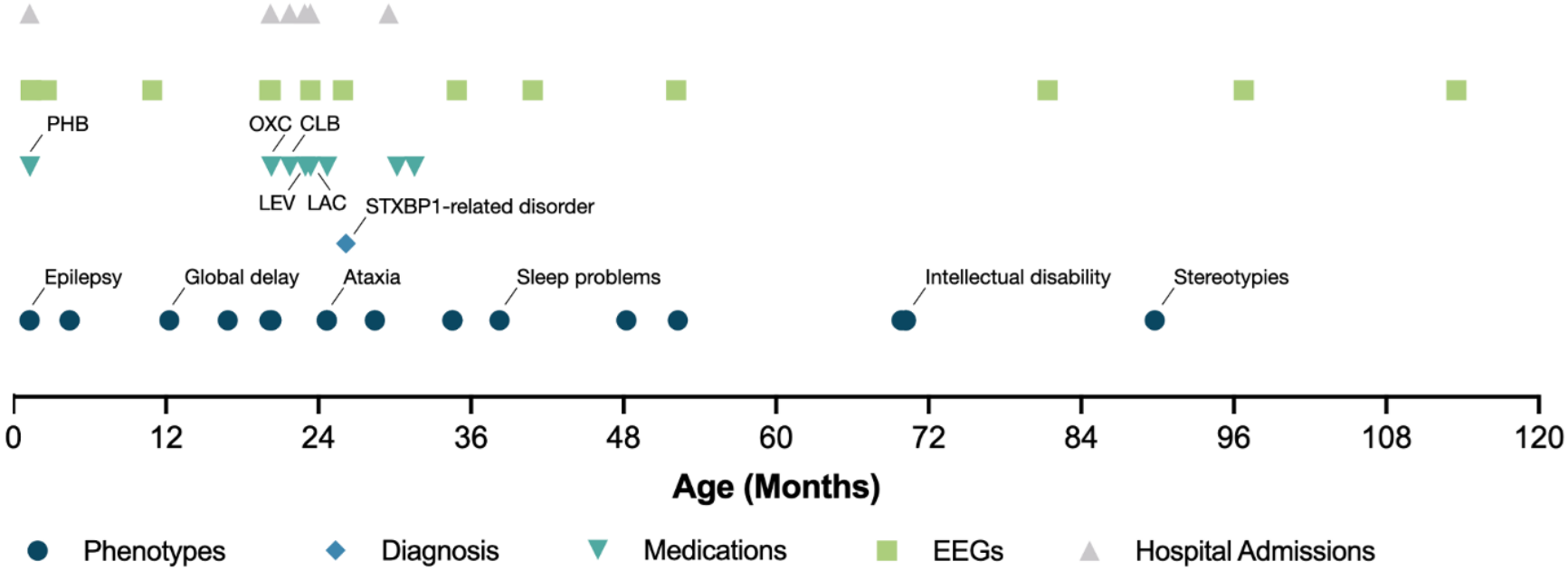
Patient privacy and security are paramount:

Privacy	Data Access	Term of Use
Remove common identifiers, assign unique identifiers, store data securely	Control who has (and who is given) access to patient-level data	Specify conditions and restrictions for users of the data to protect patient privacy

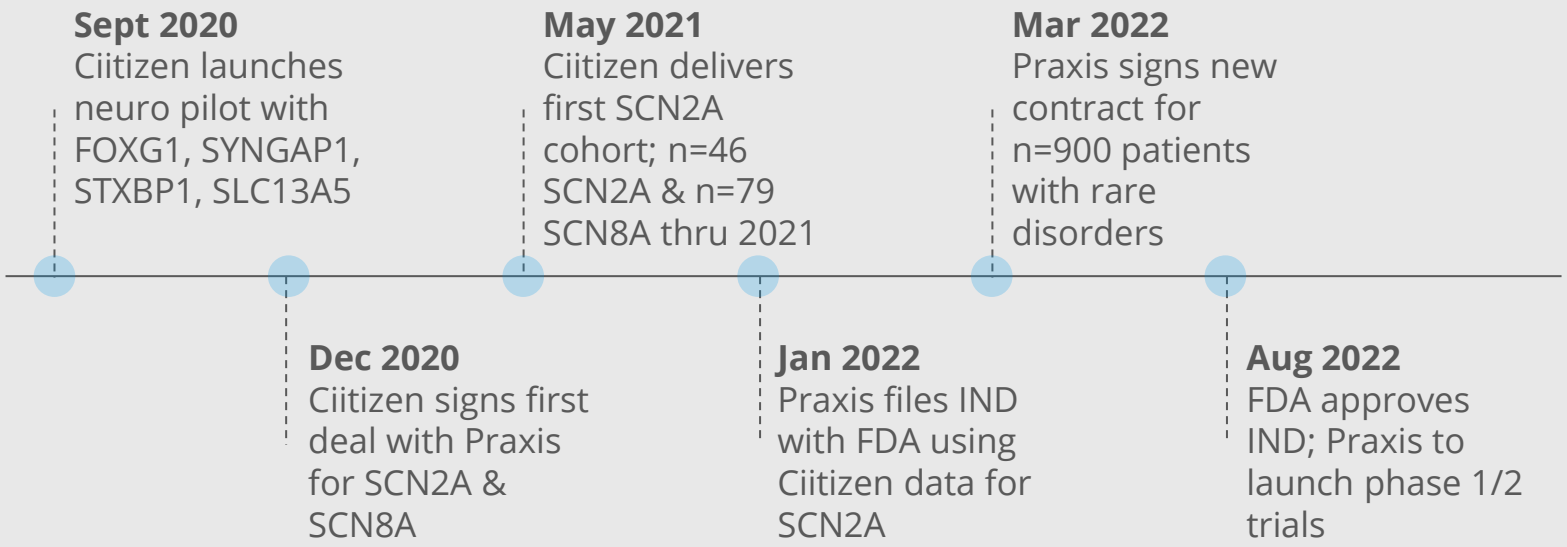
Data access and control

Row-Level + Identifiers	Row-Level - Identifiers	Aggregate - Identifiers
● Key foundation staff ● Key registry staff ● Key partner or vendor staff	● Approved research uses from legitimate partners (i.e. academia, pharma, biotech + IRB-approved protocol)	● Members of the advocacy group ● Members of the rare disease community ● Use in fundraising and social media

Create detailed patient journeys

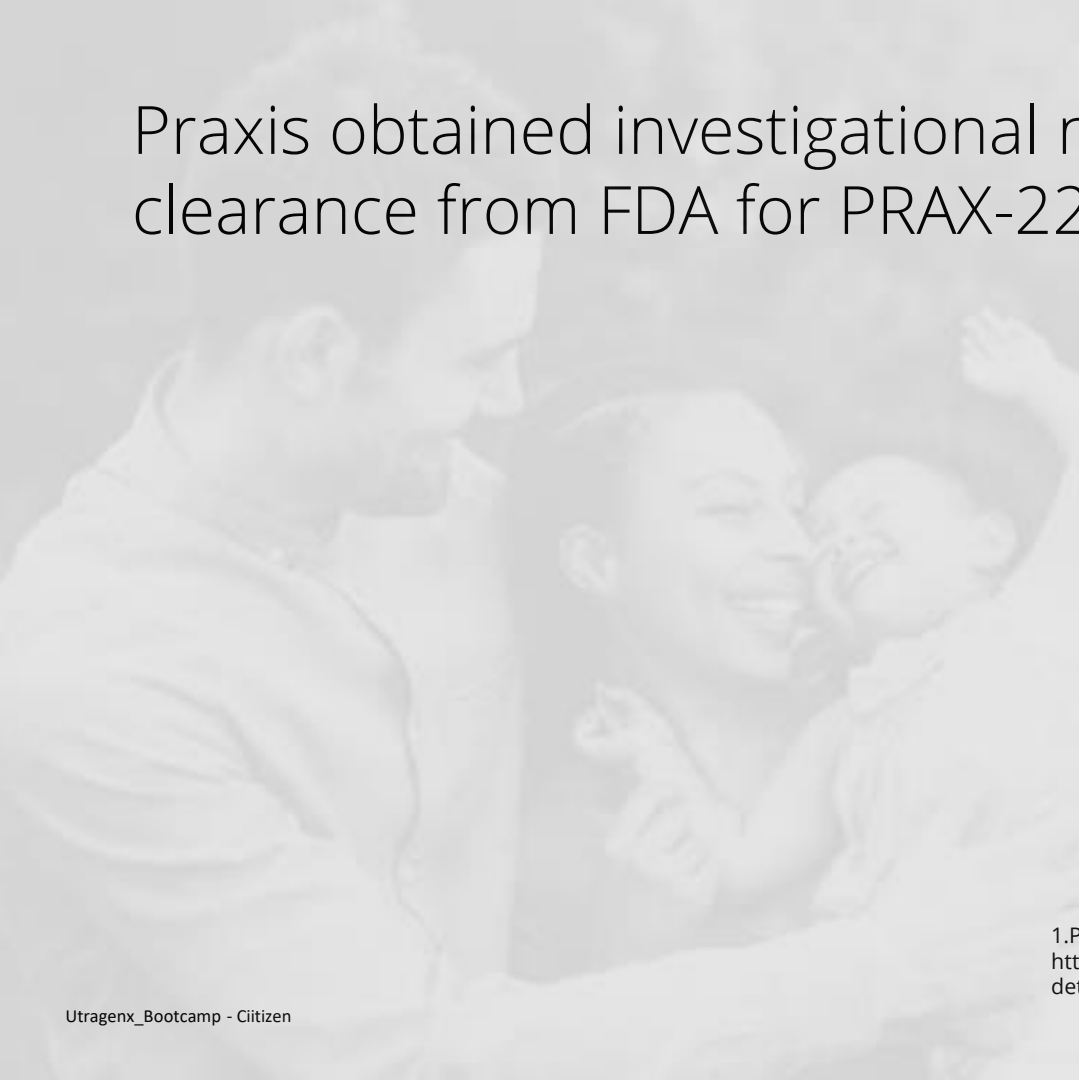


Ciitizen and Praxis, a proof-of-concept



Through exclusive use of Ciitizen for clinical data, Praxis to launch trials years earlier.

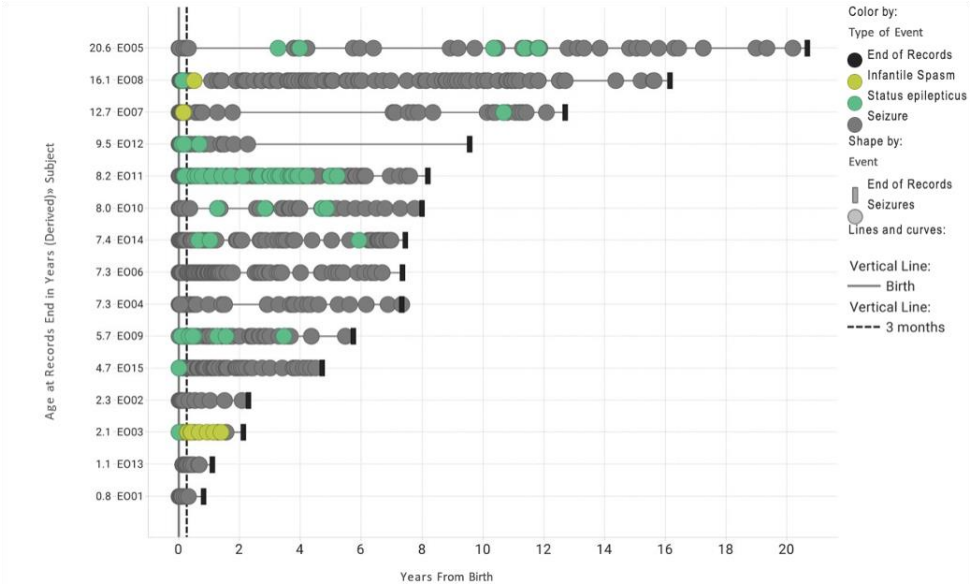
Praxis obtained investigational new drug (IND) clearance from FDA for PRAX-2221



- PRAX-222 - ASO therapy for SCN2A-DEE
- Invitae's Ciitizen RWD used to synthesize lived experience of SCN2A-DEE patients
- Invitae's Ciitizen data was the only natural history data used in FDA submission package
- Using Ciitizen data led to ~5 years in time savings

1.Praxis Precision Medicines Press Release. Issued September 7, 2022. https://investors.praxismedicines.com/news-releases/news-release-details/praxis-precision-medicines-provides-updates-clinical-stage

Praxis use of Ciitizen data: Seizure frequency as primary endpoint for SCN2A-DEE throughout life



- Literature suggests early onset seizures remit
- Ciitizen data found seizure frequency persists through life
- Data helped confirm primary endpoint and age criteria

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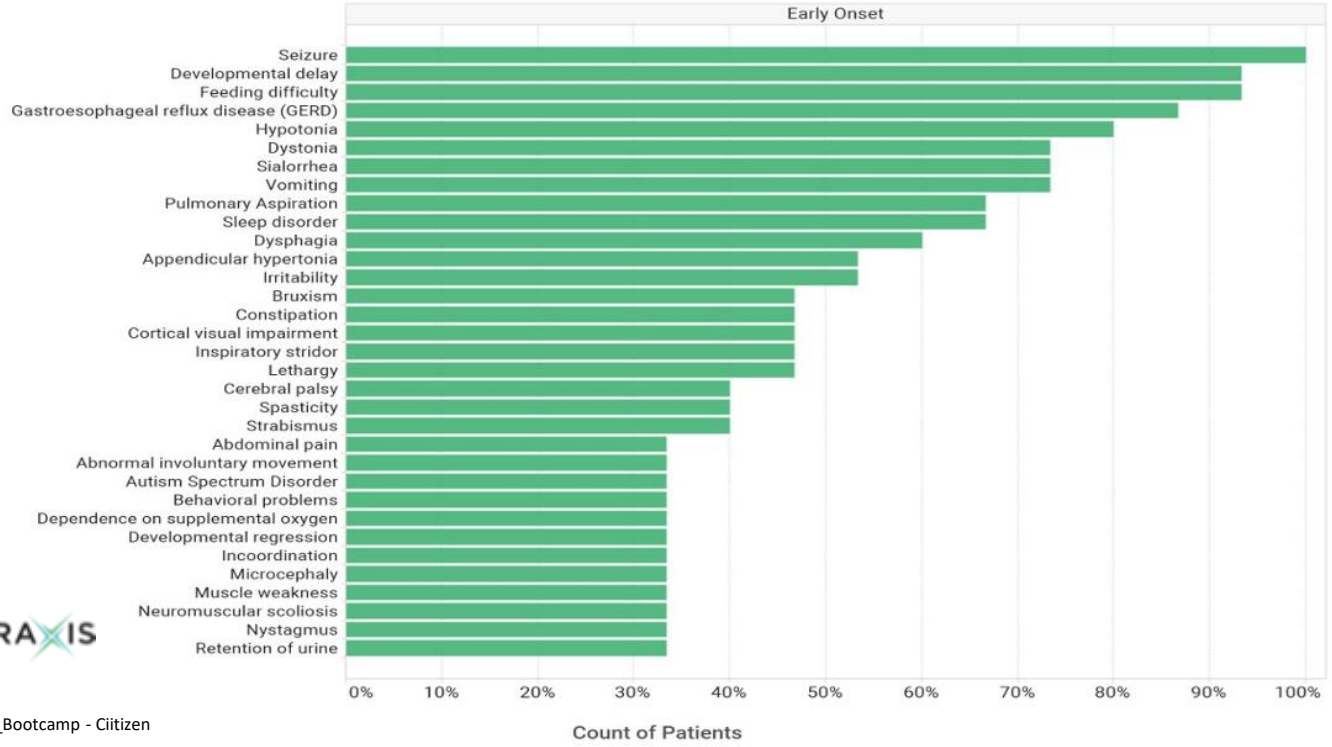
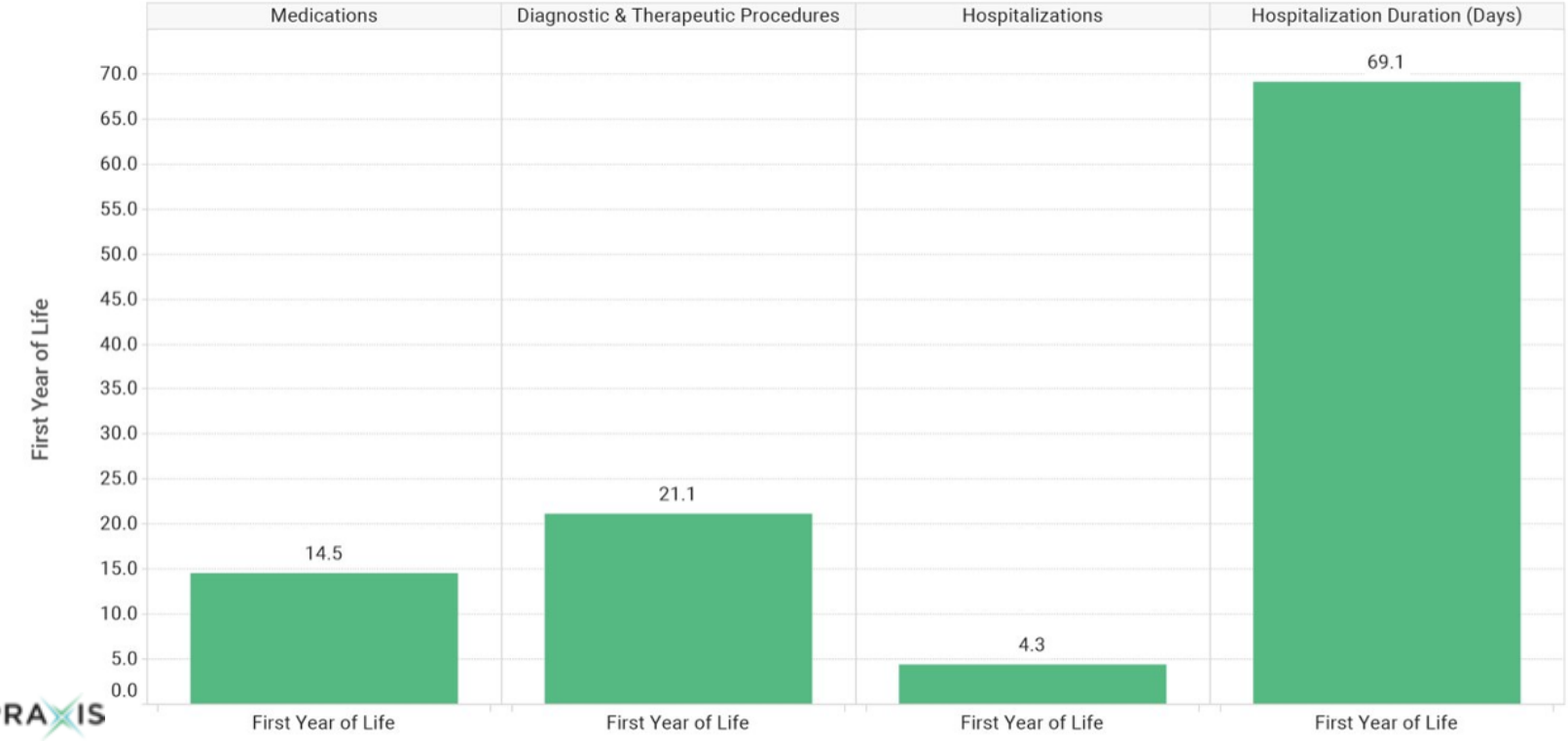
Praxis use of Ciitizen data: Exploratory endpoints and clinical design



Praxis use of Ciitizen data: Burden of Disease



Success Factors

- Ensure the data being generated in a registry OR traditional natural history study is accessible and can be democratized based on patient consent
- Data must be available to the individual patient so it can help in their course of care
- Focus on quality even if it is at smaller scale to identify the right signal for researchers
- Make data accessible to KOLs, academics and pharma to generate further interest

Where we are headed

- We go beyond the medical records to all different modalities such as wearables
- Generate this level of data seamlessly at all times so we understand cross-indication implications, long-term outcomes and have a continuous feedback loop
- Leverage data as a placebo arm to ensure interventions are available to more patients and accelerate path to treatment
- **…change the course of drug development for rare disease to shorten the cycle by at least 50%**

Thank you