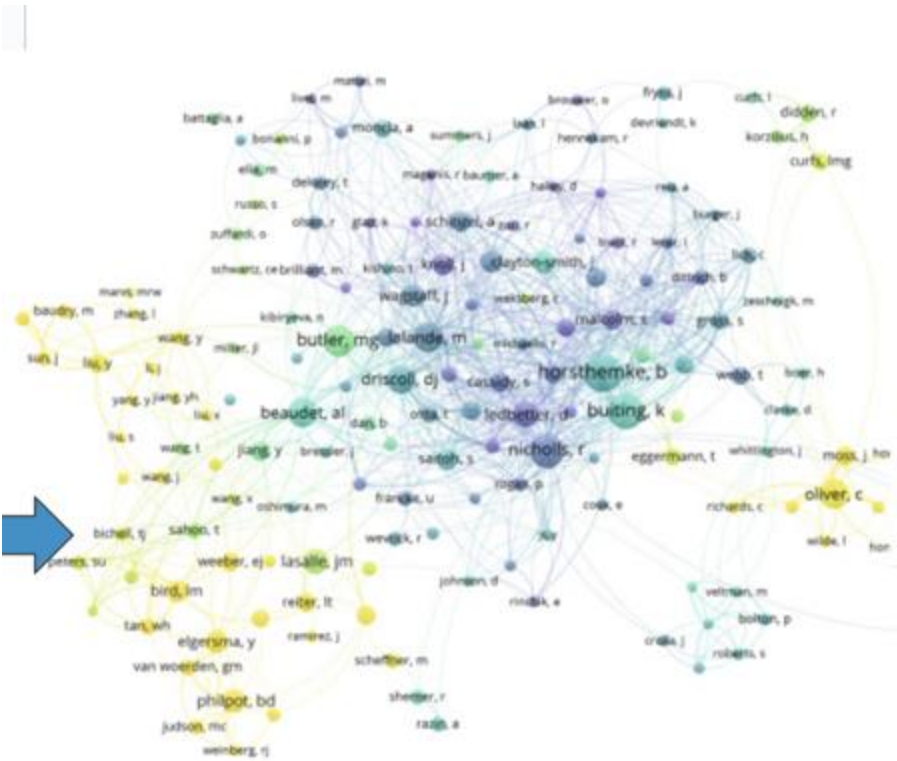# COMBINEDBrain

Terry Jo Bichell, MPH, PhD
CEO

My motivation - Lou has Angelman syndrome

Success is a decision. Failure is not an option.
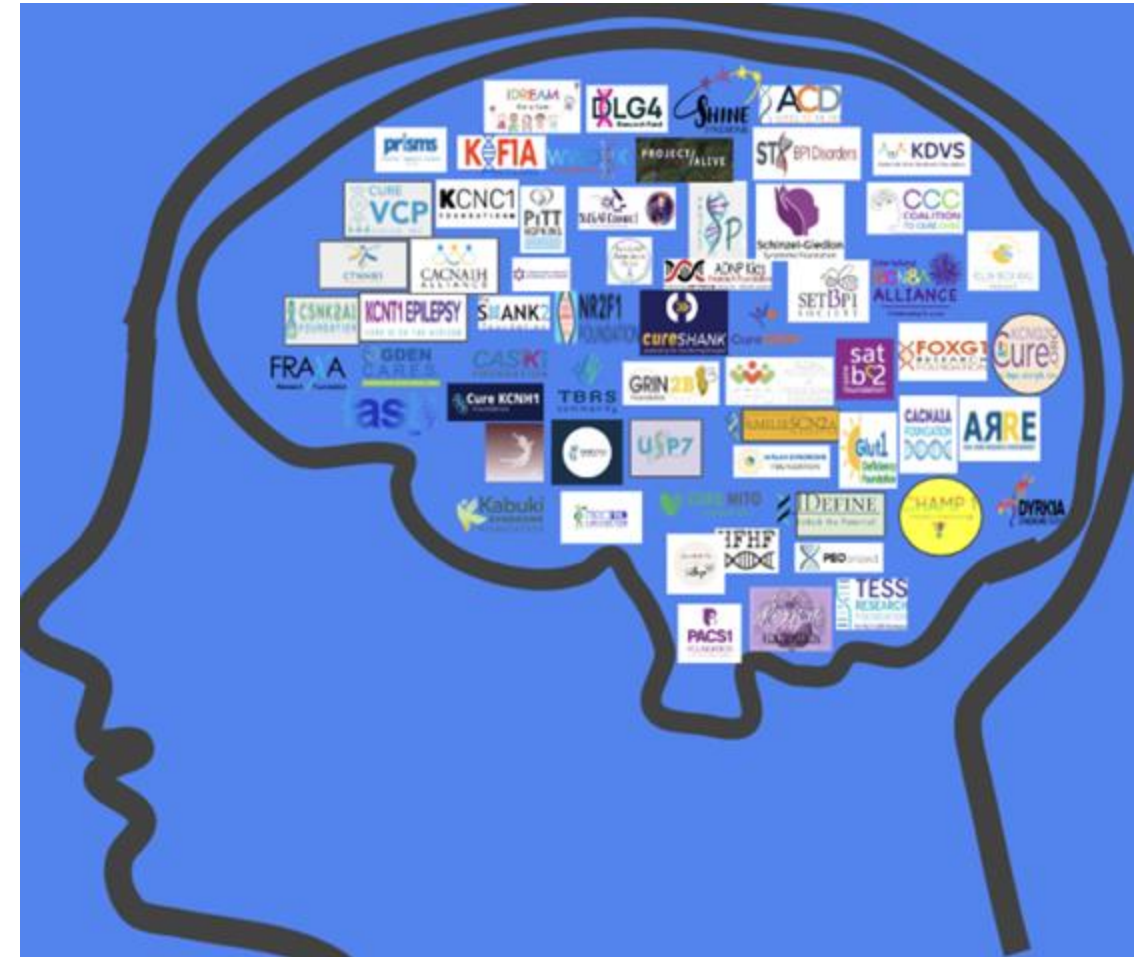
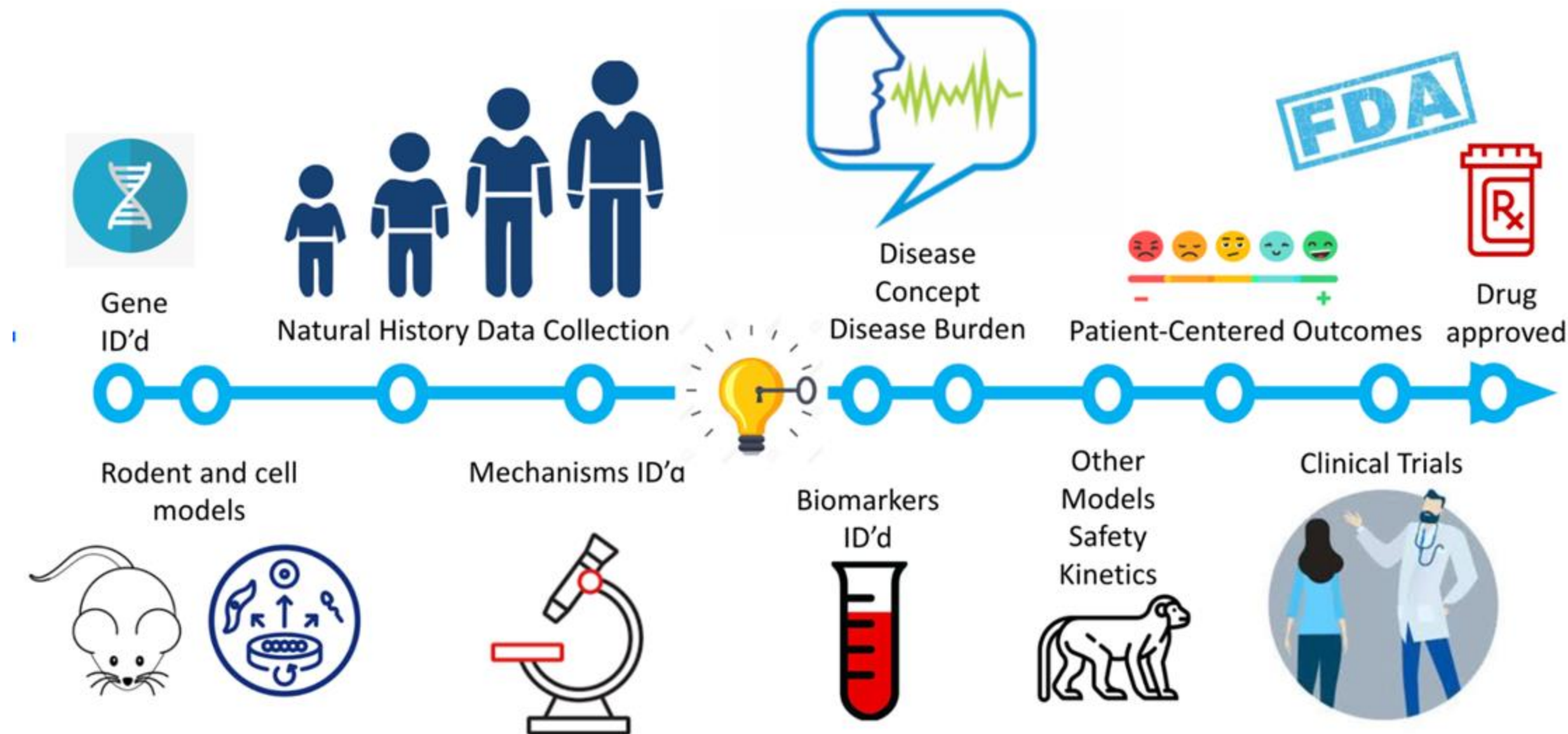Zampeta 2022

COMBINEDBrain

Mission:
The Consortium for Outcome Measures and Biomarkers for Neurological Disorders is devoted to speeding the path to clinical treatments for people with severe rare genetic neurological disorders by pooling efforts, studies and data.

Structure:
Non-profit consortium led by patient advocacy foundations, working with the clinicians, researchers and pharmaceutical firms that are developing treatments for the disorders they represent.

What is COMBINEDBrain?

Gene ID'd

Natural History Data Collection

Disease Concept Disease Burden

Patient-Centered Outcomes

Drug approved

Rodent and cell models

Mechanisms ID'a

Biomarkers ID'd

Other Models Safety Kinetics

Clinical Trials

What is COMBINEDBrain?

Disorder Identification — **Drug Discovery** — **Drug Development** — **Drug Approval**

Diagnosis - Modeling - Phenotyping - Treatment Strategy - Collaboration - Natural History - BOMs - Agency - Trials

DIAGNOSTICS
BeginNGS partnership
Project FIND-OUT
Genomenon partner

DISEASE MODELS
Mouse model grants
Model technical assistance
Assay development
Biomarker projects

PATIENT-LED BIOREPOSITORY
Biosample collection
Sample storage and shipping
Fibroblast expansion
Plasma processing

REPURPOSING PATHWAY
Screen design
IND Preparations
Investigator Initiated Trials

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ORTAS Toileting Survey
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CLINICAL TRIAL DESIGN
Endpoint selection

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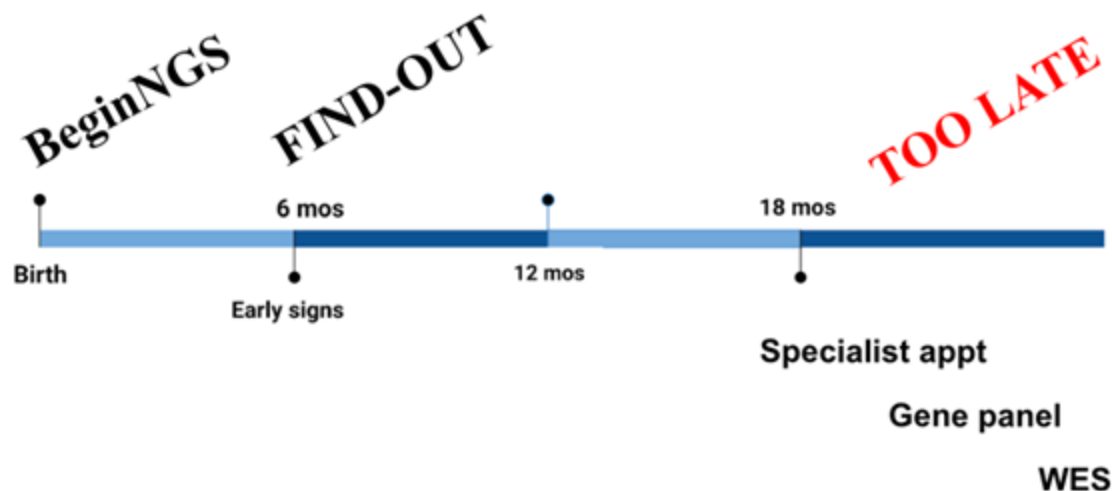**CLINICAL TRIAL DESIGN**
Endpoint selection

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Project FIND-OUT - www.projectfindout.org

Fast Infant Neurogenetic Diagnosis via Outpatient Testing

- Educate primary care practitioners on risk signs
- Refer for whole genome sequencing
- Genetic counselor before and after
- Referral to pediatric neurology
- Estimate 20% positive diagnoses
- Refine protocol after pilot

https://projectfindout.org/

Contact ElizabethRountree@combinedbrain.org

F	Feeding difficulties
I	Issues with movement
N	NICU admission
D	Developmental delay
O	Other malformations
U	Unprovoked seizures
T	Tone

Project FIND-OUT

Pathogenic/Likely Pathogenic Results (n=18)	Pathogenic Incidental and Secondary Findings
1. 9P deletion syndrome 2. Noonan syndrome 3. AHDC1-related intellectual disability, obstructive sleep apnea, mild dysmorphism 4. GABRA1 mutation 5. KLHL20-related neurodevelopmental disorder 6. IQSEC2 7. GATAD2B 8. Ciliopathy (CC2D2A) 9. 16p11.2 microdeletion syndrome 10. Pitt Hopkins 11. X-linked hypophosphatemia 12. RAC1 Syndromic intellectual disability 13. ATP6V0A1 Developmental and Epileptic Encephalopathy 14. NR2F1 - Bosch-Boonstra-Schaaf optic atrophy syndrome 15. FBN1 - Marfan Syndrome 16. 17p12(141917 95-15442917)C NV Pathogenic Duplication - Charcot-Marie-Tooth 17. Rett Syndrome (n = 2)	**Pathogenic Incidental (n=8):** 1. G6PD deficiency (n=4) 2. UROD-related inherited porphyria 3. SPINK1 chronic pancreatitis 4. UGT1A1-associated hyperbilirubinemia 5. Glomuvenous malformations (GLMN) **Secondary Findings (n=5)** 1. Hypertrophic cardiomyopathy (n=2) 2. Hereditary TTR Amyloidosis 3. Catecholaminergic polymorphic ventricular tachycardia 4. MUTYH-associated polyposis Note that some patients received multiple diagnoses (e.g., a pathogenic finding plus an incidental finding or a secondary finding)

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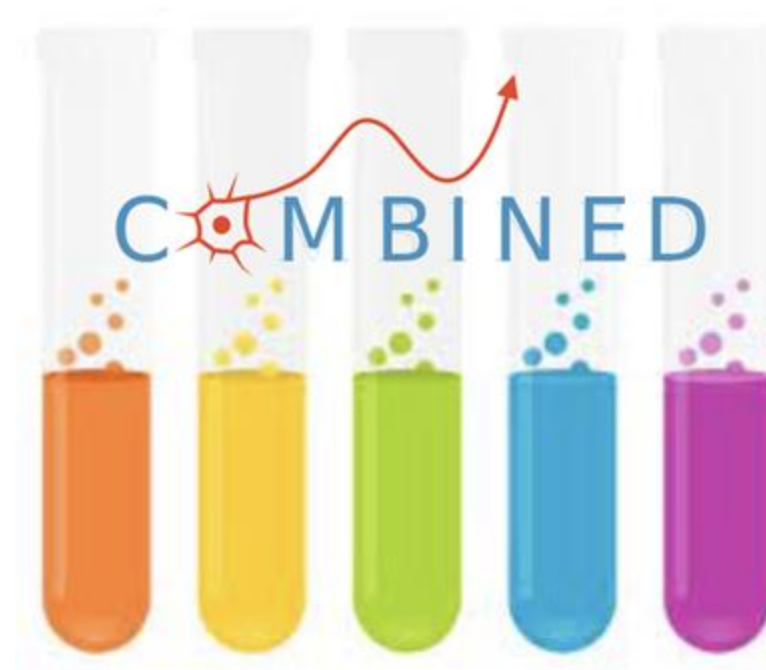Real World Evidence

CLINICAL TRIAL DESIGN
Endpoint selection

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COMBINEDBrain Biorepository

Cross Disorder Biorepository
- Launched Sept 2021
- ~2000 individuals/~23,000 samples
- Patients and controls
- Central IRB, online consent
- Mobile phlebotomy or Quest lab collection
- Governance via consortium and foundation
- Large portion of fees paid by requesters goes back to PAG
- Coordinate with U of MD Brain Bank for large tissue collection
- Blood, Urine, IPSC's, fibroblasts, dried blood spot, Stool samples, buccal swabs
- CSF and brain tissue bank launched Oct 2024
- Accepting transfers of additional CSF

biorepository@combinedbrain.ort
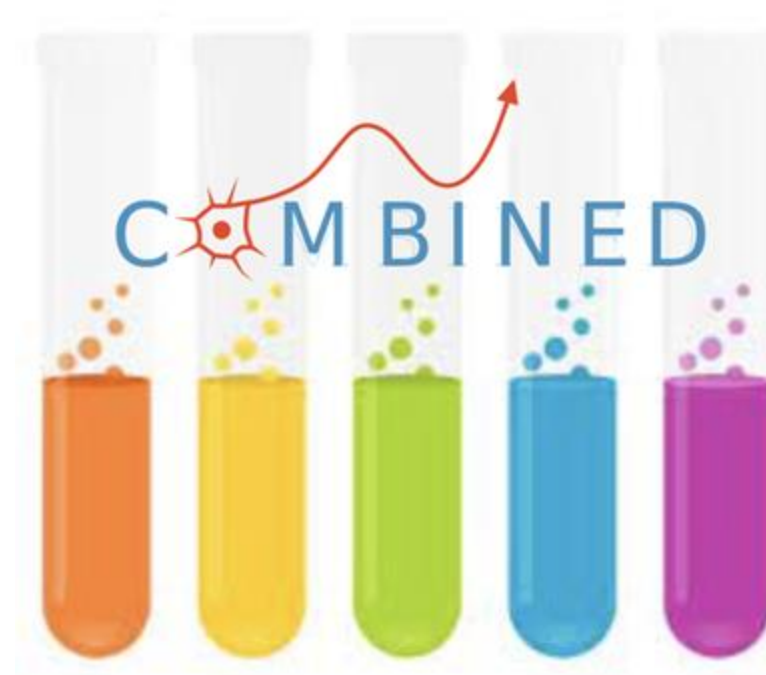
COMBINEDBrain Biorepository - iPSC Bank

Patient-centered biobank of patient-derived induced pluripotent stem cells available to researchers and industry at low cost.

Patients and controls collected with natural history.

~80 lines from 35 disorders currently in biorepository
~10 additional lines in reprogramming process now

Large portion of fees paid by requesters goes back to PAG

COMBINEDBrain Biorepository - Roadshow

The COMBINEDBrain Biorepository team available at member conferences to collect samples, when requested by the PAG.

Any person with a COMBINEDBrain disorder and their controls may participate, with permission from their advocacy group. Cost $17,000 per conference for 100 samples

Samples collected:
- Blood
- Plasma
- Blood spots
- Urine
- Nasal brushings
- Additional samples as requested by PAG
- Fecal specimens

Pre-Competitive Biomarker Projects

Industry Partners	Plasma Proteomics	CSF Control Study
Shared design Shared costs Shared data Anonymous indications Cross-disorder comparisons Data shared with PAGs Other PAGs participate at cost	Pilot study completed ~800 samples ~150 controls Cross-disorder manuscript drafted Individual analysis by PAG and Industry Partners Longitudinal study launching	Pilot study underway ~25 controls Proteomics Age-wise progression

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Matrix Data Collection Platform

Available in COMBINEDBrain's Matrix portal:

- ClinGen head-to-toe surveys
- Vineland Adaptive Behavior Scales 3
- PELHS Seizure Survey
- Basic Ketogenic Diet survey
- CDC Developmental Milestone Survey
- Aberrant Behavior Checklist - Community
- QoL Inventory-Disability (QI-Disability)
- Vanderbilt ADHD Diagnostic Parent Rating Scale
- Nisonger Child Behavior Rating Form
- CHSQ - Children's Sleep Habits Questionnaire
- Soon - Cross disorder CGI

- Electronic Health Records
- EEG uploads

Patients & Caregivers   Researchers
Clinicians   Foundations

CO-CREATE & CO-DELIVER CARE

Patients/Caregivers	Clinicians	Foundations	Researchers
Manage your own health and/or the health of others.	Interact more closely with patients, and expand your insights.	Empower your community, and deliver beneficial collaboration.	Integrate into the community, and easily facilitate new trials/studies.

Choosing Meaningful Endpoints

- To succeed, a new drug must:
    - Treat what matters to patients
    - Affect how a patient feels, functions or survives
    - Make a meaningful change

- **A good drug can fail if the endpoint is wrong**

- Clinical trials cost more without appropriate endpoints
- A good drug can take too long to pass without surrogate endpoints

Disease Concept Models

2023	2024	2025	2026
STXBP1 Katie Rose Sullivan Univ. of Pennsylvania	**CACNA1A** Kara Skorge Univ. of Pennsylvania	**SynGAP1** Sydni Stewart Rutgers University	**Tatton-Brown** Mylie Siegel Rutgers University	**NR2F1** Vera Zanker Wake Forest Univ	**CASK** Elise Abney Vanderbilt Univ.

2023
- STXBP1 — Katie Rose Sullivan — Univ. of Pennsylvania
- SETBP1-HD — Anna Fangmeier — Vanderbilt Univ.
- PWS — Partnership with TREND
- SLC6A1 — Bichell/Goodspeed — CB/UTSW
- Waiting list on next page

2024
- CACNA1A — Kara Skorge — Univ. of Pennsylvania
- Malan — Amy Mook — Univ. of Michigan
- Schinzel-Giedion — Joan Kornkven — Vanderbilt Univ.
- Chr 8p — Sevil Mahfoozi — Stanford University
- FOXG1 — Kopika Kuhathaas — Harvard Univ
- SynGAP1 — Sydni Stewart — Rutgers University
- Kleefstra — Kristin Connors — Boston University
- KCNT1 — Jasmine Lafferty — Rutgers University

2025
- ALD — Felicity Emerson — Rutgers University
- CHAMP1 — Lauren Hoovener — Rutgers University
- Tatton-Brown — Mylie Siegel — Rutgers University
- USP7 — Elora Marvasi — Rutgers University
- DYRK1A — Olivia Solverson — Vanderbilt Univ
- MED13L — Kayla Clevenger — Rutgers University
- GRIN2B — Liana Cole — Univ of MN

2026
- NR2F1 — Vera Zanker — Wake Forest Univ
- KDVS — Madicyn Holmgren — Medical College of Wisconsin
- GABAB3 — Jenna Tangires — Rutgers University
- Myhre — Katie Rosen — Mass General
- CASK — Elise Abney — Vanderbilt Univ.
- CSNK2A1 — Grace Branger — Vanderbilt Univ
- Project Alive — Resh Meck — UAB
- CTNNB1 — Sophie Marek — Rutgers University

What is it? Click here

Rare Bootcamp™

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Repurposing Drug Pathway

UNRAVEL BIOSCIENCES

curetopia

Therapeutics for complex disorders

Because patients can't wait

Basket Trials

Condition #1

Condition #2

Condition #3

Condition #4

Condition #5
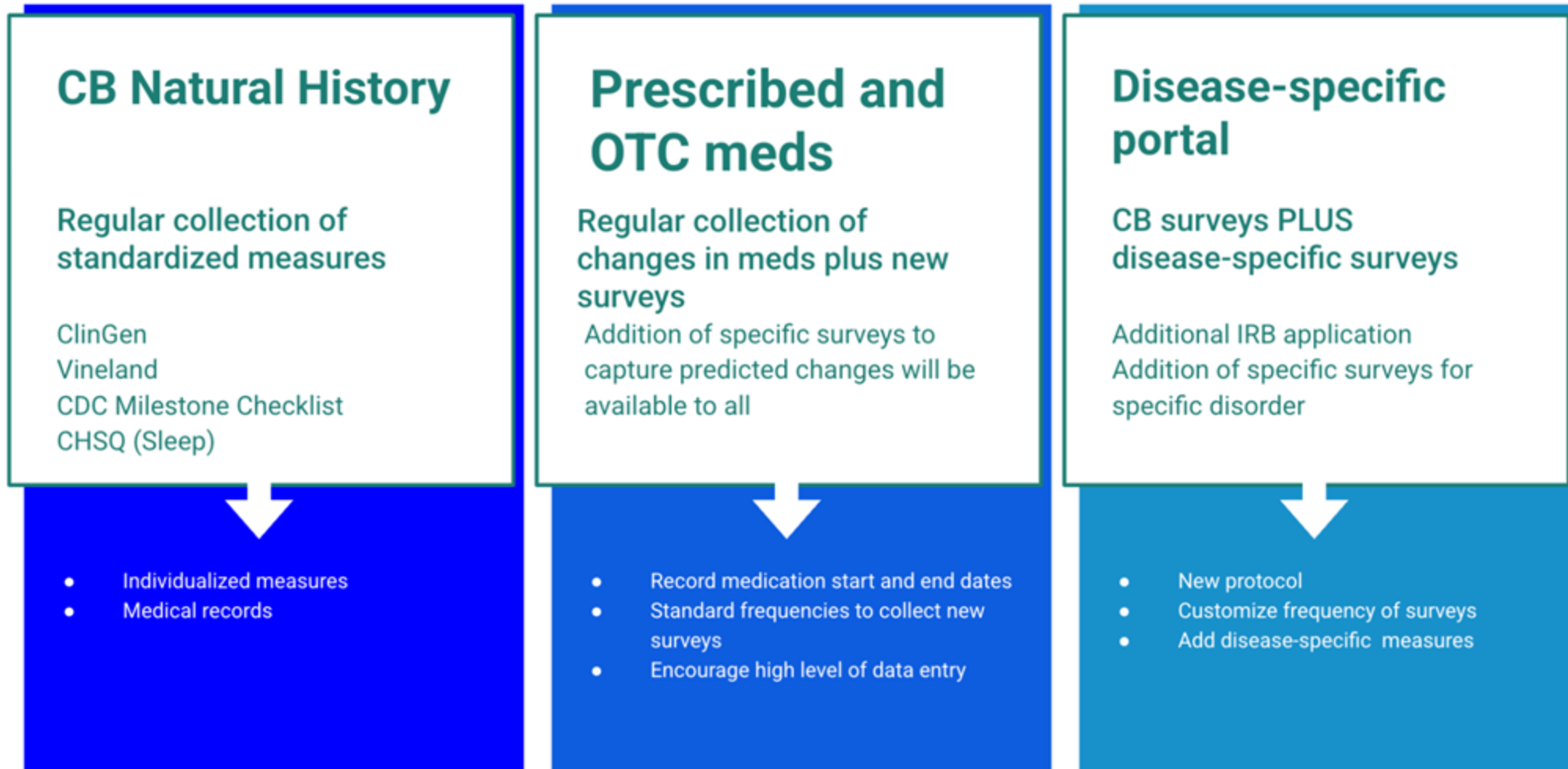
Matrix - Main or PAG Portal - Observational studies

CB Natural History

Regular collection of standardized measures

ClinGen
Vineland
CDC Milestone Checklist
CHSQ (Sleep)

- Individualized measures
- Medical records

Prescribed and OTC meds

Regular collection of changes in meds plus new surveys

Addition of specific surveys to capture predicted changes will be available to all

- Record medication start and end dates
- Standard frequencies to collect new surveys
- Encourage high level of data entry

Disease-specific portal

CB surveys PLUS disease-specific surveys

Additional IRB application
Addition of specific surveys for specific disorder

- New protocol
- Customize frequency of surveys
- Add disease-specific measures

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COMBINEDBrain EEG Bank

Phase 1
- Collect previously recorded EEGs on Matrix
- De-Identify
- Store in accessible platform
- Convert to be analyzable across software systems
- Link to natural history data
- Link to biosamples
- Portion of fees returned to PAGs

Phase 2
- Collect prospective EEGs at-home
- Standard protocol
- Novel technologies alongside standard rig

Laan & Vein (2005)

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Patient-Reported Outcome Measures

ORCA
Observer-Reported Communication Ability Measure

- FDA Grant
- Duke University Team
- Angelman -> 12 Disorders
- Detect increases in abilities
- Meaningful changes for families
- Caregiver-entered

ORTAS
Restrooms

Observer-Reported Toileting Abilities Survey

- Internal funding for Development
- Pilot launch late 2023
- Hunter Syndrome -> CB Disorders
- Detect increases in abilities
- Meaningful changes for families
- Caregiver-entered

Rare Bootcamp™

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Rent-a-Brain Program

- Draft documents
  - edit and submit research manuscripts for publication
  - IRB proposal and consent forms
  - grant applications

- Scientific rationale
  - Support of off-label treatment
  - Clinical trial support
  - Pitch to industry for new disorder
  - Recommendations for novel assays
  - Literature review of specific mechanism
  - Review specific treatment strategy

- Large projects
  - Organize and conduct entire standard of care and/or clinical guidelines project
  - Development of entire Strategic Research Plan
  - Creation of grant review and application process
  - Review of endpoints for clinical trial design

- Government interactions
  - Letter of intent for FDA listening sessions
  - Preparation of presentations to FDA
  - Draft applications for ICD-10

- …Suggestions…What do you need?

Staff

Thank You!
Putting the pieces together...together!