Endpoint Considerations to Facilitate Drug Development for Niemann-Pick Type C (NPC)

January 24-25, 2022

FDA U.S. FOOD & DRUG ADMINISTRATION | Duke MARGOLIS CENTER for Health Policy

Welcome and Overview | Day 1

Mark McClellan

Director, Duke-Margolis Center for Health Policy

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Remote Participation Instructions

Mute & Slides

- **You have been placed on mute**; speakers can mute/unmute throughout
- We will advance the slide deck, please prompt us to advance

Questions

- Please feel free to type your questions and comments into the Q&A box and we will use your input to inform the open discussion portions of the event

Zoom Issues? Please Zoom message Luke Durocher or email luke.durocher@duke.edu

Meeting Agenda (Day 1)

12:05 pm Opening Remarks from FDA

12:15 pm Clinical Overview of NPC

12:25 pm Session 1: Challenges and Opportunities with the NPC Clinical Severity Scale (NPCCSS)

1:25 pm Session 2: Functional Measures for Swallowing

2:25 pm Break

2:40 pm Session 3: Functional Measures for Ambulation, Speech, and Fine Motor

3:35 pm Closing Remarks

3:40 pm Adjournment

Meeting Agenda (Day 2)

12:00 pm Welcome and Overview

12:05 pm Opening Remarks from FDA

12:15 pm Session 4: Exploring Digital Health Technology to Measure Functional Endpoints

1:15 pm Session 5: Future Biomarker Considerations in NPC

2:15 pm Break

2:30 pm Session 6: Closing Panel and Forward Looking

3:25 pm Closing Remarks

3:30 pm Adjournment

FDA Public Comment Docket

You may submit comments for this workshop to Docket FDA-2021-N-1297.

The Docket will be open until April 25, 2022.

Comments in the Docket will be reviewed after the Docket closes.

Opening Remarks from FDA

Patrizia Cavazzoni

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Clinical Overview of NPC

Forbes D. Porter

National Institute of Childhood Health and Human Development

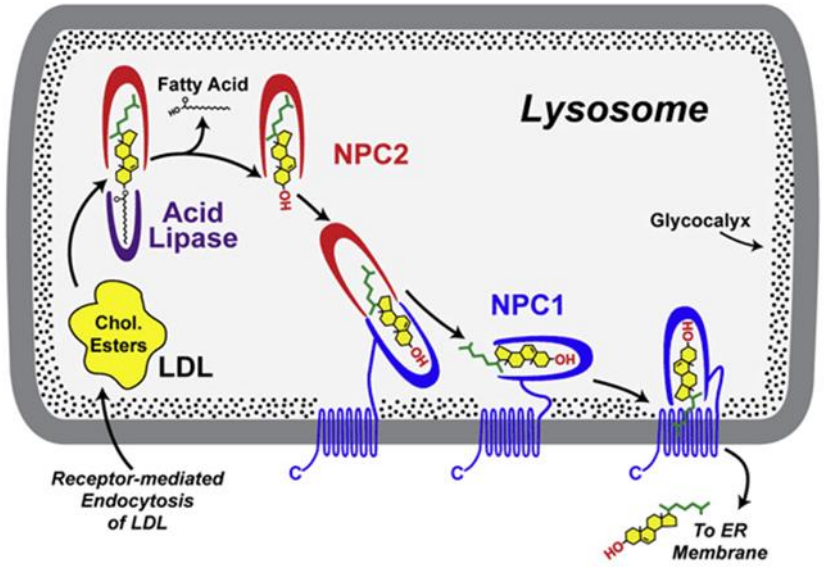
National Institutes of Health

Niemann-Pick Disease, type C

Forbes D. Porter, MD, PhD
Senior Investigator and Clinical Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health

Niemann-Pick disease, type C

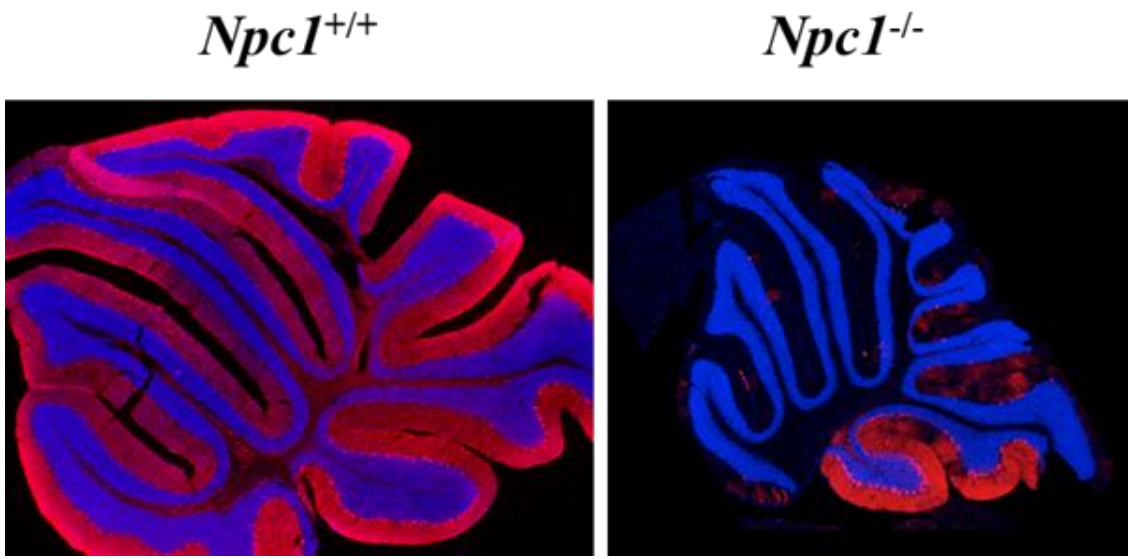
- Autosomal recessive, progressive, lethal, neurodegenerative disorder due to mutation of either *NPC1* or *NPC2*
- Endolysosomal storage of unesterified cholesterol and lipids
  - Lysosomal storage ("cellular stress")
  - Decreased cholesterol bioavailability
- Incidence: ~1/100,000
  - Late Onset 1/20,000-1/40,000



Kwon (2009) Cell 137: 1213

Niemann-Pick disease, type C

- Neuropathology
  - Intracellular accumulation of unesterified cholesterol and lipids
  - Neuroinflammation (microgliosis and astrogliosis)
  - Neuronal death



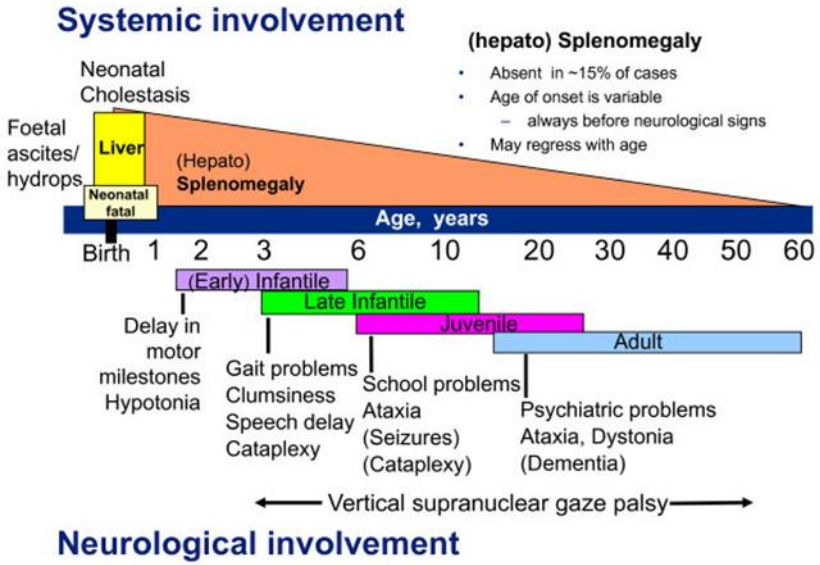
<u>Progressive neurological impairment</u>

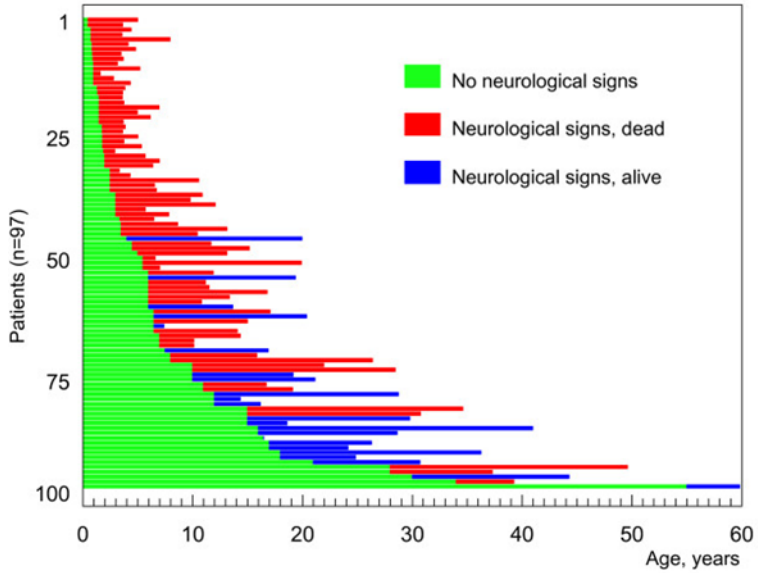
Cerebellar ataxia/dysfunction
- Ambulation
- Fine motor
- Speech
- Swallowing

Vertical supranuclear gaze palsy

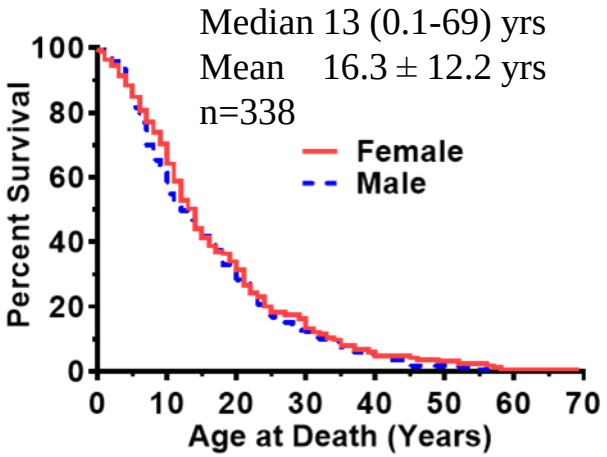
Cognitive impairment and dementia

Niemann-Pick disease, type C





Vanier (2010) Orphanet J. Rare Diseases 5:16

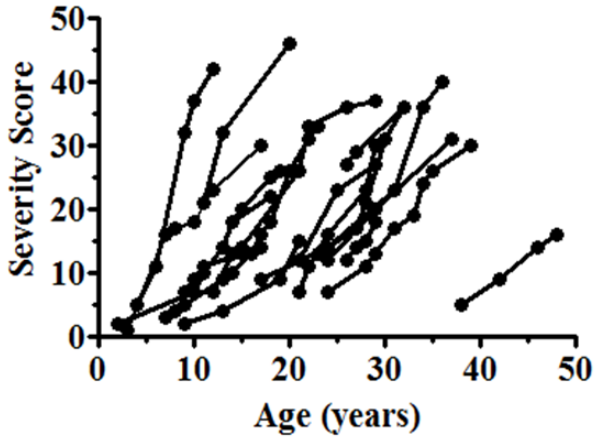


Bianconi et al. (2019) MGM 126: 466

Rare
Heterogeneous phenotype and age of onset
Progressive morbidity occurring over years
Lethal

Niemann-Pick disease, type C

- NPC-Neurological Severity Score



Yanjanin et al. (2010) Am J Med Genet Part B. 153B: 132-140

Major Domains	Minor Domains
Ambulation	ABR
Cognition	Behavior
Eye Movement	Gelastic Cataplexy
Fine Motor	Hyperreflexia
Hearing	Incontinence
Memory	Narcolepsy
Seizures	Psychiatric
Speech	Respiratory
Swallowing	

- Likert-like scale (0-61)
  - Nine major domains (0-5)
  - Eight minor domains (0-2)
- Retrospective and prospective

Niemann-Pick disease, type C

- Inter-rater reliability
  - Yanjanin et al. (2010) AJMG, 153B: 132-140.
  - Shin et al. (2011) PloS One 6:e23666
  - Mengel et al. (2020) Orphanet J Rare Dis, 15:328.
  - Farhat et al. (2021) Pediatric Neurology, 127: 32-38.

- Clinical Relevance
  - Cortina-Borja et al. (2018) Orphanet J Rare Dis, 13:143.
  - Evans et al. (2021) Orphanet J Rare Dis, 16:482.
  - Patterson et al. Orphanet J Rare Dis, 16:79.

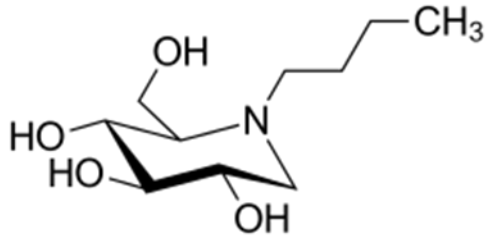
- Correlation with disease biomarkers
  - MRI Imaging
    - Lee et al. (2014) Pediatric Neurology, 51: 669-674
  - Cerebral Spinal Fluid Analytes
    - N-palmitoyl-O-phosphocholineserines (lyso-SM509)
      - Sidhu et al. MGM (2020) 129:292-302
    - Neurofilament light
      - in preparation

- Prognosis (ASIS)
  - Cortina-Borja et al. (2018) Orphanet J Rare Dis, 13:143.

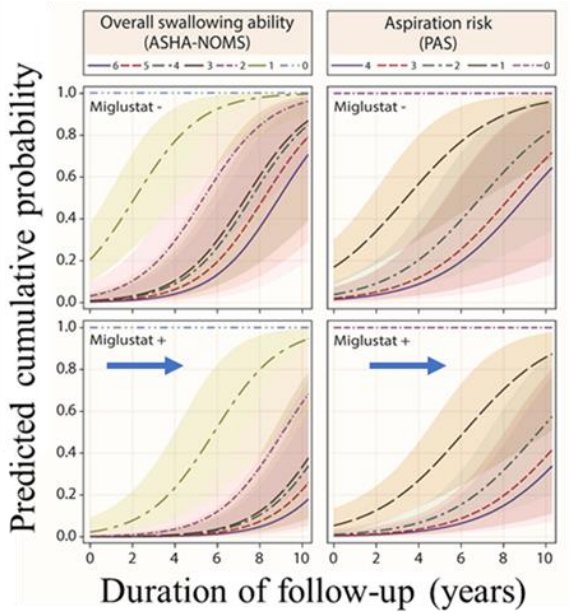
- Construct validity
  - Patterson et al. (2021) Orphanet J Rare Dis, 16:79.
  - RUMC/NIH data
    - in preparation

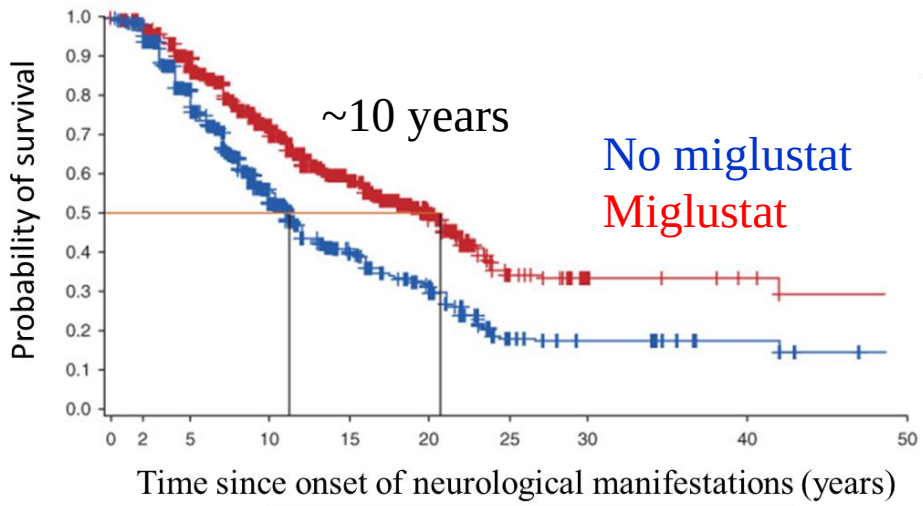
Niemann-Pick disease, type C

Treatment/Standard of Care



- Miglustat
  - Iminosugar which inhibits glycosphingolipid synthesis
  - Approved for NPC in most countries, Off-label use in US (Gaucher disease)
  - ~$30K/month





Real-life efficacy will take years to establish
Symptom/sign reversal is unlikely
Slowing/halting progression is the goal
Combination therapy will ultimately be required

Solomon et al. (2020) JAMA Neurology. 77: 1564-1568. Patterson et al. (2020) J Inherit Metab Dis. 43: 1060-1069.

Niemann-Pick disease, type C

- NPC is a rare genetic disorder of lysosomal function
- NPC is a lethal disease characterized by progressive and irreversible neurodegeneration
- The NPC phenotype is heterogeneous with respect to individual age of neurological onset and symptom complex
- The NPC Neurological Severity Score was developed to provide a tool to address the issue of phenotypic heterogeneity and describe disease progression
- There is accumulating evidence that the NPC-NSS can be reliably measured, has construct validity and is clinically relevant
- The inherent aspects of the disease need to guide and inform both outcome measures and therapeutic trial design

Session 1: Challenges and Opportunities with the NPC Clinical Severity Scale (NPCCSS)

12:25 pm – 1:25 pm EST

Naomi Knoble

Division of Clinical Outcome Assessment

Office of New Drugs

U.S. Food and Drug Administration

Challenges and Opportunities with the NPC Clinical Severity Scale (NPCCSS)

Naomi Knoble, PhD
Division of Clinical Outcome Assessment
Office of New Drugs
January 25, 2022

DISCLAIMER

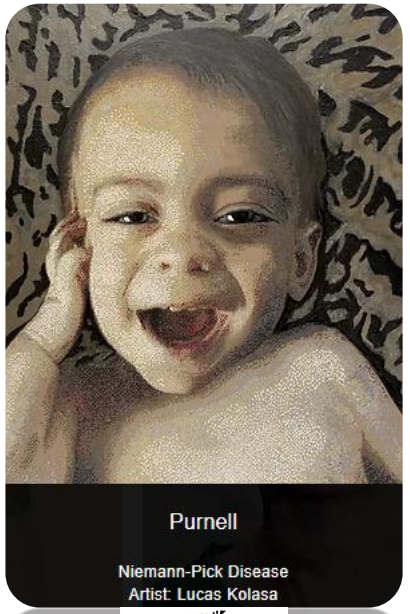
The views expressed in this presentation are mine and do not represent an official FDA position.

I have no financial interests to disclose.

I have no actual or potential conflicts of interest in relation to this activity.

Objectives

- High-level overview of selecting assessments for clinical trials
- Evidence gaps for the 5DNPCCSS
- Possible solutions



beyondthediagnosis.org/gallery

Selecting Clinical Outcome Assessments for Use in Clinical Trials

- Choosing **what** to measure in clinical trials includes:
  - knowledge of the disease natural history, symptoms, impacts
  - patient, caregiver, and clinical expert input
  - having an idea of what is likely to change in the time-period of the clinical trial
  - effects of the novel treatment
- Not everything that is important to measure *can* be measured within the constraints of a trial, the selected patient population, and given the expected effects of the novel treatment

Selecting Clinical Outcome Assessments for Use in Clinical Trials

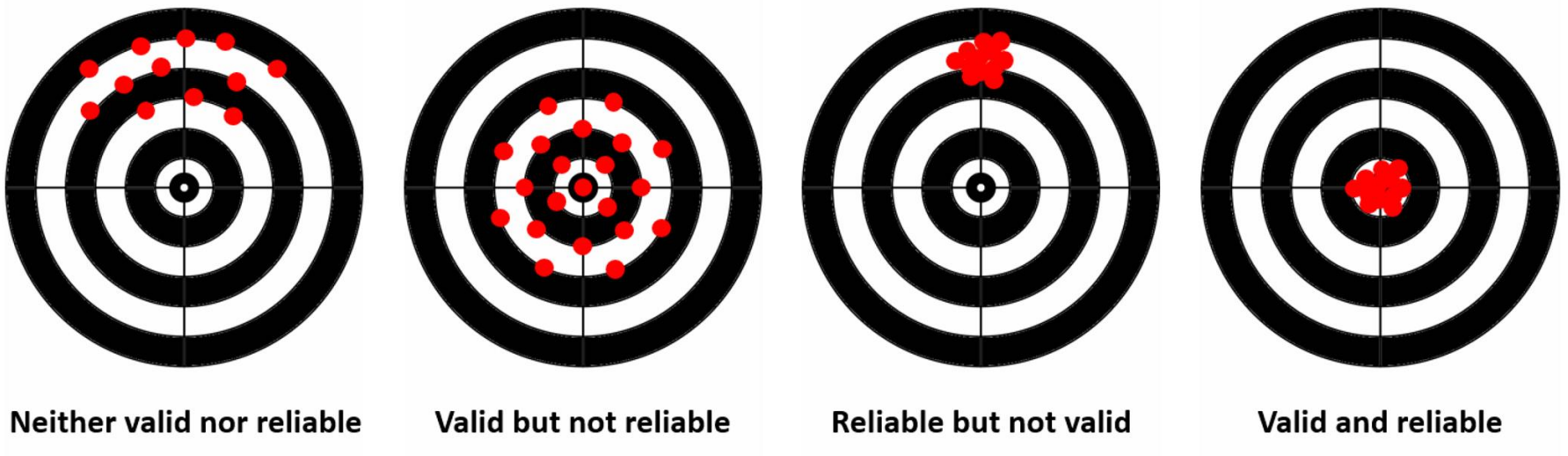
- One part of choosing **what** to measure in a clinical trial is identifying clinically meaningful concepts to patients, caregivers, and clinical experts
  - The qualitative concept elicitation and identification research conducted by and with the NPC patient and clinical expert community was well done and, hopefully, is an example for other rare disease communities.
- It is clear: the five areas of functioning identified (speech, ambulation, fine motor, swallowing, and cognition) are relevant concepts.
  - Choosing **how** to measure **which** of these areas in clinical trials can be done in many ways, which will be explored throughout the sessions in this workshop.

Federal Rules and Regulations

- FDA has to follow evidentiary standards under federal rule and regulations
  - Specifically that **endpoints**, the methods of assessment of patients' response, are well-defined and reliable, which is in the code of federal regulations (CFR §314.126)
  - Endpoints are derived from **assessments** that are fit for this purpose (fit-for-purpose)
- Some of the evidence comprising "well-defined and reliable" falls into two broad categories:
  - **validity** and
  - **reliability**
- Validity and reliability are essential to support score interpretation and know if there is improvement, deterioration, or stability, which is fundamental to understanding clinical trial results.

Validity Evidence for COAs

- Validity refers to evidence supporting the response options, scores, training, standardization, so that scores reflect what they are intended to measure
- Validity needs to be established first and cannot be assumed based on reliability evidence.
  - There could be a reliable assessment that does not measure what is intended



NPC Clinical Severity Scale

- The 17-domain NPCCSS has played a key role in the characterization of NPC's natural history and in the clinical management of NPC, including assessment of disease burden, response to therapy, and prognosis, as well as multiple clinical studies
- The 5-domain version, 5DNPCCSS, assesses ambulation, fine motor, speech, cognition, and swallowing

Evidence Needed for the 5DNPCCSS

- The 5DNPCCSS has gaps in the available validity evidence that can be addressed, specifically:
  - **Qualitative evidence:** that the response options are relevant for the full age spectrum, not overlapping, are clearly defined, consistently interpretated, and correctly ordered by severity
  - **Quantitative evidence:** that the COA and endpoints are measuring what it is intended to be measured when compared to other well-defined, reliable endpoints and assessments
  - **Standardized implementation:** ensuring that the same assessment happens the same way with every patient at every assessment by all clinicians across all sites
    - Standardized implementation, including documentation, makes explicit how information was gathered and what information clinicians use to arrive at rating scores.

Possible Paths Forward to Generate Additional Evidence for the 5DNPCCSS

- Validity evidence could include:
  - **Qualitative research:** cognitive interviews (cognitive debriefing) with clinical experts in NPC and the five functional areas (e.g., speech, swallowing) to evaluate whether response options and associated scores are clearly, consistently interpreted and gather suggested modifications
  - **Quantitative research:** Analyze existing data with NPC patients across the full range of disease severity within each concept to generate quantitative validity evidence evaluating the relationship of each of the 5DNPCCSS domains with other standardized assessments measuring similar concepts

Possible Paths Forward to Generate Additional Evidence for the 5DNPCCSS

- Administration and rating procedures could include:
  - Standardized clinical evaluation procedures that are conducted with each patient at each assessment at every clinical trial site to inform the scoring of each domain to which clinician report contributes;
  - Specification of how, for each domain, a response option is to be selected if a patient's level of impairment in that functional area varied over the duration of the assessment period.
  - Training materials used to help parents/caregivers evaluate the patient's level of impairment with respect to each 5DNPCCSS domain to which parent/caregiver report contributes via direct observation in everyday life; and
  - A daily diary or other measurement approaches for parents/caregivers to systematically record their observations (if these observations are used to inform clinician ratings)

Collaboration

- While rare diseases are -- by definition -- uncommon, there are common challenges across rare disease clinical trials regardless of the disease, such as measurement challenges within NPC clinical trials.
- Through global collaboration in the pre-competitive space, such as this Duke Margolis NPC meeting and efforts like C-Path's Rare Disease COA Consortium and the Rare Disease Cures Data and Analytics Platform, we stand the best chance of advancing regulatory science and creating solutions for these challenges for the benefit of all people living with rare diseases and their families who love them.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FDA COA Guidance Documents

- 2009 FDA PRO Guidance – *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims

- FDA Patient-Focused Drug Development Guidance Series
  - https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

Session 1: Challenges and Opportunities with the NPC Clinical Severity Scale (NPCCSS)

Panelists*:*

- Elizabeth Berry-Kravis, Rush University Medical Center
- Ebony Dashiell-Aje, BioMarin
- Lise Kjems, Cyclo Therapeutics
- Naomi Knoble, U.S. Food and Drug Administration
- Forbes D. Porter, National Institutes of Health
- Phil Marella, Patient Representative

Session 1 | Discussion Questions

1. What are key strengths and limitations of the five-domain NPCCSS in the context of clinical trials?
2. How do the measures included in the five-domain NPCCSS reflect the patient and caregiver experience of NPC?
3. As experience with the use of the abbreviated NPCCSS in clinical trials grows, are there specific modifications you would recommend for the NPCCSS to ensure it is sensitive to treatment effects in trials?
4. What are the barriers to standardizing administration of the NPCCSS? What recommendations would you make to ensure standardization of NPCCSS across clinical trial sites?
5. What are additional sources of evidence that could be used to bolster the validity of all or part of the NPCCSS?
6. What, if any, other modifications or considerations might help facilitate optimization of the NPCCSS for use in clinical trials?

Session 2: Functional Measures for Swallowing

1:25 pm – 2:25 pm EST

Beth Solomon

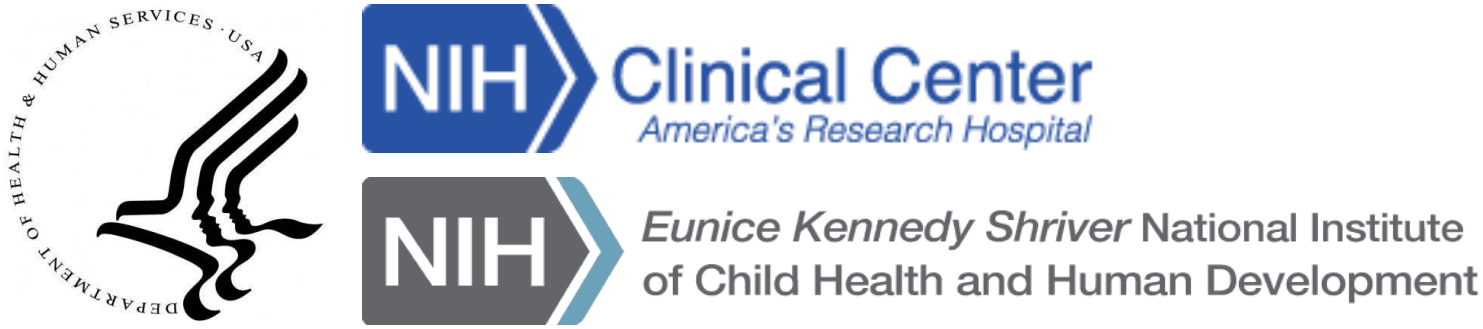
Lead Senior Speech Language Pathologist

Speech Pathology Section, Rehabilitation Medicine Department

National Institutes of Health

Swallowing Endpoints in NPC1 and Other Rare Disease Research

Beth Solomon, MS, CCC-SLP
Speech Pathology Section, Rehabilitation Medicine Department
National Institutes of Health
Bethesda, Maryland



Colleagues

Forbes Porter, M.H.S., M.S., M.D, Ph.D[1]
Nicole Farhat M.H.S., M.S.N.[1]
Andrew C. Smith B.A.[1]
Andrea M. Muñoz, B.S.[1]
Leonza Machielse, M.S.[1]
Ninet Sinaii, M.P.H., Ph.D.[2]
Michael Backman, M.S.[3]
Monique C. King, M.A., CCC-SLP [4]

[1]Eunice Kennedy Shriver National Institute of Child Health and Human Development
[2]Biostatistics and Clinical Epidemiology Service, NIH Clinical Center, National Institutes of Health, Bethesda, MD
[3]George Washington University Biostatistics Center, Milken Institute School of Public Health, Rockville, MD
[4]Speech-Language Pathology Section, Rehabilitation Medicine Department, Mark O. Hatfield Clinical Center

Thank you to the NPC1 participants and their families!

Session 2: Functional Measures for Swallowing

Panelists:

- Kiera Berggren, Virginia Commonwealth University
- Diana Bohm, Northwestern Medicine
- Barbara Lazarus, Patient Representative
- Beth Solomon, National Institutes of Health
- Dina Zand, U.S. Food and Drug Administration

Session 2 | Discussion Questions

1. Are there aspects of swallowing that are more directly assessed by some instruments than others? What are the opportunities and challenges with using these different instruments?
2. Is there variability in tool administration or disease pathology that impacts interpretation across raters and over time? If so, what steps can be taken to mitigate these issues and determine interpretability of measurements on the individual level and of clinical trials?
3. What are the overall strengths and limitations of each assessment tool? What are the strengths and limitations of each assessment tool for use in NPC clinical trials specifically?
4. What challenges and opportunities exist with these different tools in relation to the patient and caregiver experience in clinical trials?

Break

We will be back momentarily.

The next panel will begin at 2:40 p.m. (U.S. Eastern Time)

Session 3: Functional Measures for Ambulation, Speech, and Fine Motor

2:40 pm – 3:35 pm EST

Dawn Phillips

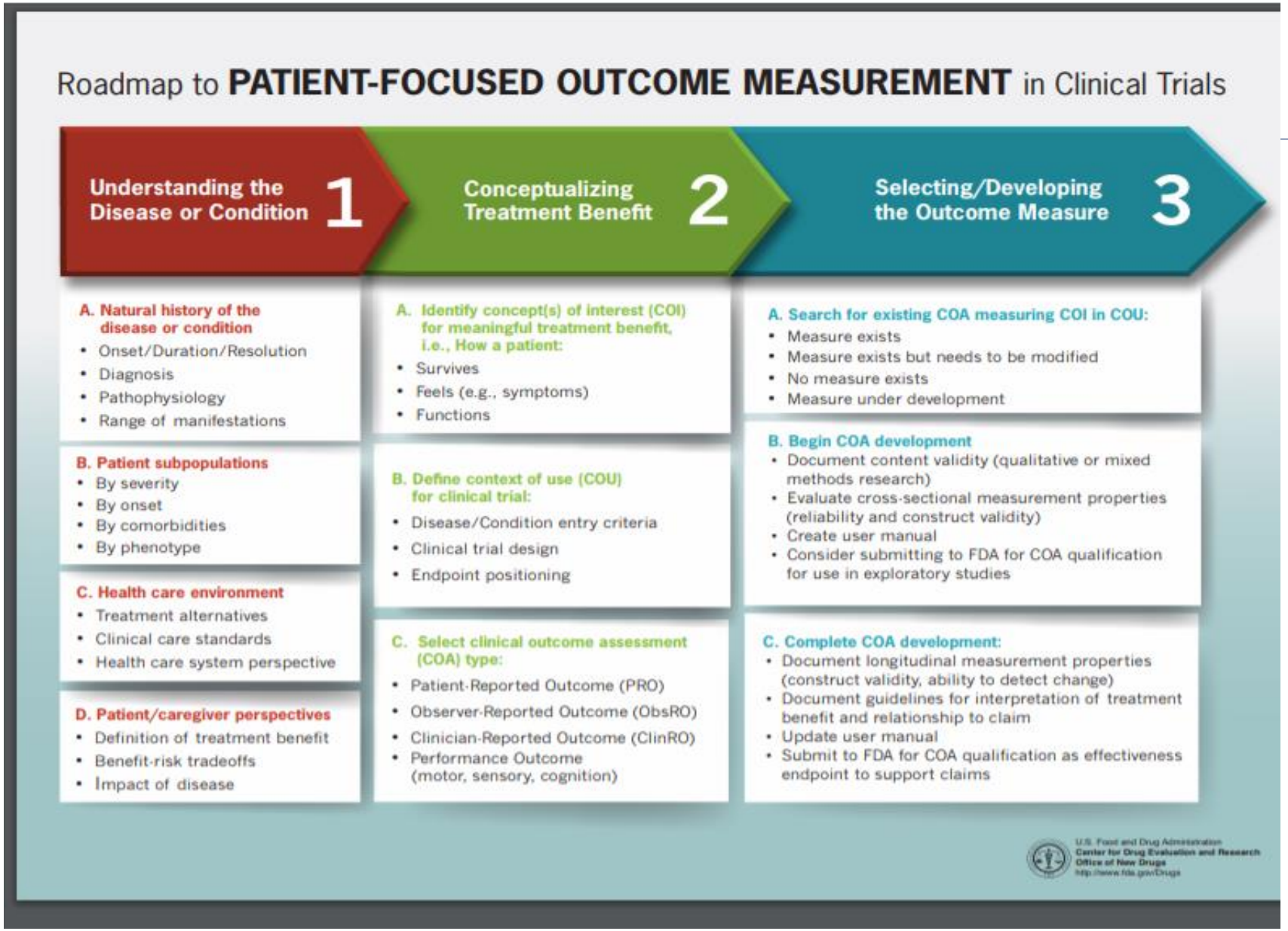
Director, Clinical Outcomes Research

REGENXBIO

Clinical Outcome Assessments(COAs) in Niemann-Pick C

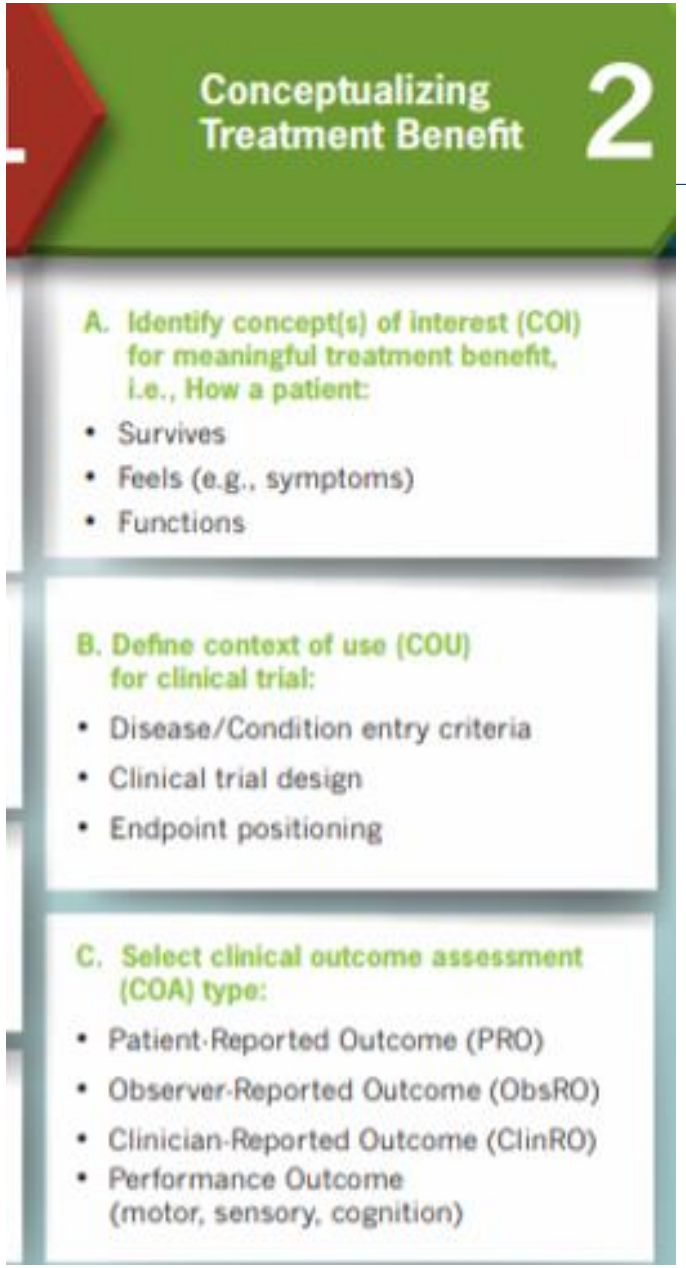
Dawn Phillips PT, MS, PhD
Director Clinical Outcomes Research
REGENXBIO Inc.

Disclaimer: The views and opinions expressed are those of the author and do not necessarily represent the views and opinions of REGENXBIO Inc.



- What are the unique considerations for developing an endpoint model and selecting or modifying COAs related to NPC and the anticipated treatment effect?

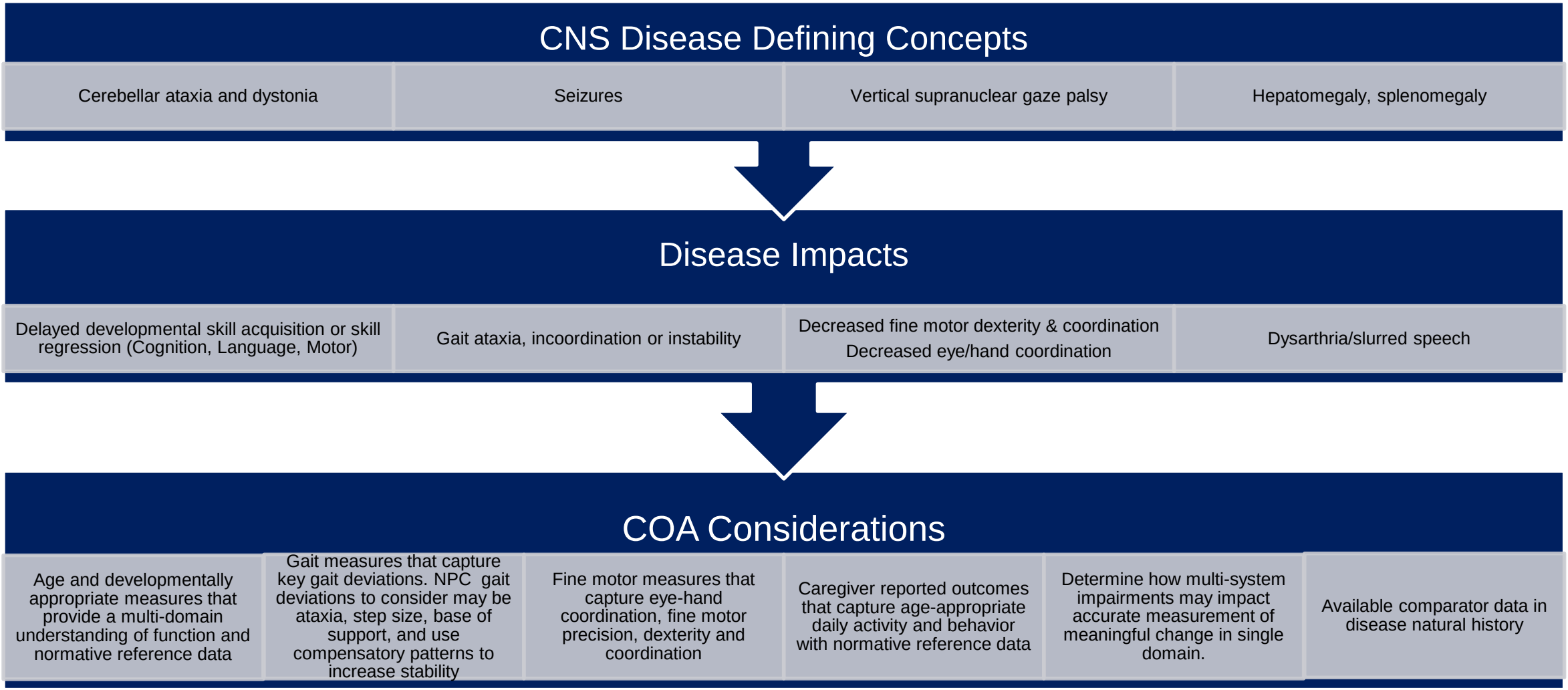
- Characterize disease by age, phenotype and functional level using literature, natural history data, KOLs, patient and caregiver perspectives
  - Clearly understand how infantile and juvenile/attenuated onset patients differ in disease presentation
  - How does COA use differ by age, phenotype, functional level, or stage of disease progression?
- Develop a patient centered disease conceptual model
  - Use content to define concepts of interest (COI) that links mechanism and primary body system of treatment to function
  - Map disease concepts of interest to clinical outcome assessments

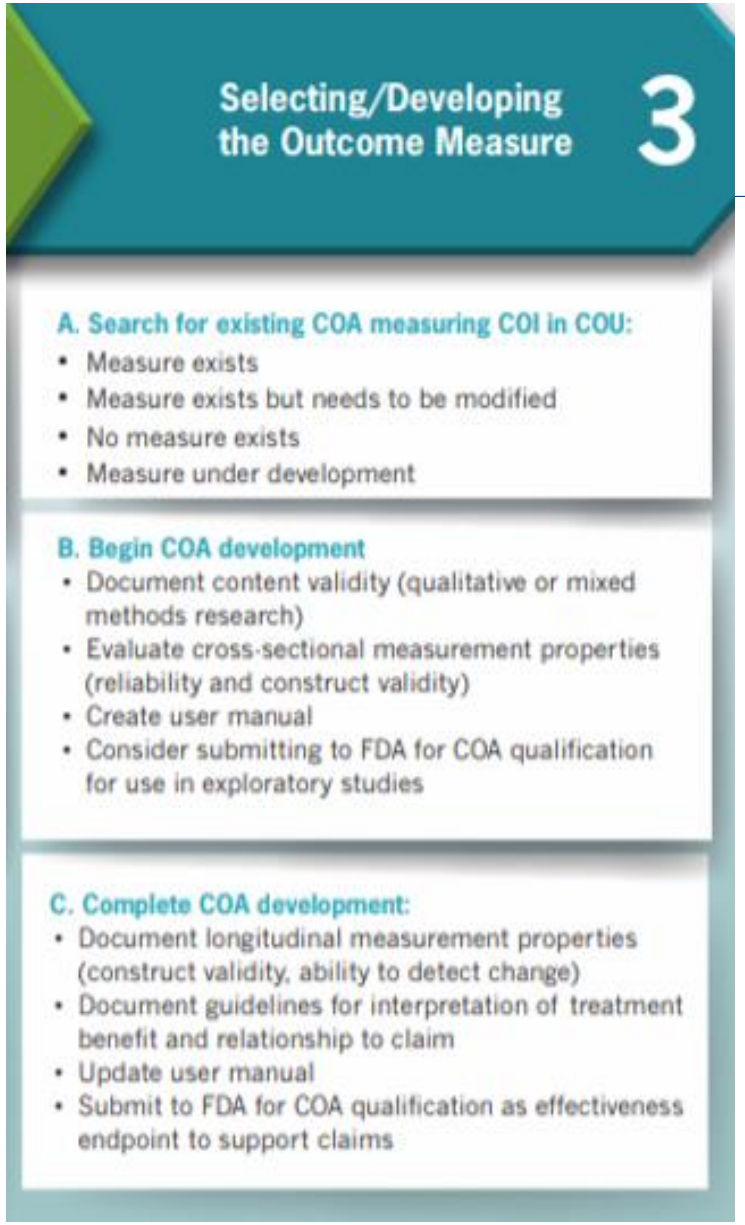


B. Concept of Use (COU)

- What COIs are unique to your treatment and a well-defined sub-population of the disease?
  - What is the desired range of function that you need to capture within a COA?
  - How do the COA psychometric properties inform your endpoint model? If the measure has a ceiling or floor effect how do you control for sample with eligibility criteria?

Example of Possible Content for a Conceptual Model Focused on the Central Nervous System (CNS)





A. Search for existing COA that measures COI in COU

- Biggest mistake is starting here without understanding unique considerations of disease and your specific COU
- Mapping: compare disease specific COI to item content on COAs
- Considerations for generic versus disease specific COAs
  - Developing a disease specific measure may be desirable for a rare disease but it takes considerable time and cost and requires many layers of validation
  - Rare disease small sample sizes may be insufficient to divide by group level differences for age and function
  - Cognition, language and motor skills vary by age and it may be difficult to distinguish developmental maturation from treatment effect
  - Existing standardized developmental assessments can provide a range of values to characterize disease presentation and to measure treatment benefits
    - Normative data can be used to classify function relative to a normative age reference

Domains	Examples of Possible COAs

Age-appropriate developmental measures	• Bayley Scales of Infant Development (BSID) third or fourth edition
	  • Cognition, Expressive and Receptive Language, Fine and Gross Motor
	• Mullen Scales of Early Learning (MSEL)
	  • Visual Reception, Expressive and Receptive Language, Fine and Gross Motor
	• Peabody Developmental Motor Scales second edition (PDMS-2)
	  • Fine and Gross Motor
	• Bruininks - Oseretsky Test of Motor Proficiency second edition (BOT-2)
	  • Fine and Gross Motor

Cognitive Measures	• BSID III or IV • MSEL • Kaufman Assessment Battery for Children (KABC) • Wechsler Preschool and Primary Scale of Intelligence-fourth edition (WPPS-IV) • Wechsler Abbreviated Scale Intelligence-second edition (WASI-II)
Fine Motor	• PDMS-2: visual motor and grasping subtest • BOT-2: fine motor precision, manual dexterity and bilateral coordination subtests • NIH Toolbox-9 Hole Pegboard

Domains	Examples of Possible COAs
Gross Motor/ Gait	• PDMS-II: locomotion subtest • BOT-2: bilateral coordination, running speed and agility and strength subtests • Gross Motor Function Measure 88 • GAITRite or Zeno walkway • Accelerometers (Fitbit) • Video analysis of gait: Modified POMA-G
Ataxia	• Scale and modified scale for the rating of ataxia-(SARA) • Gait stance, sitting, speech disturbance, finger chase, nose- finger test, fast alternating hand movements, heel shin slide • NIH Toolbox 9 Hole Peg Test • BOT-2 Items
Language	• BSID-III/IV • MSEL • Preschool Language Scales –Fifth edition (PLS-5)

Daily Activity	• Caregiver or patient reported outcomes
	  • PEDI or PEDICAT
	  • PedsQL: Generic Core Scales, Family Impact Module
	  • Vineland Adaptive Behavior Scales II or III (VABS)
	  • PROMIS measures: Mobility, Physical Function (evaluate item relevance)
	  • Video data collection in home apps
	  • Developmental measures

Seizures	• Seizure apps for real time documentation (Seizure Tracker)

Use of Generic Measures with Normative Data

- **Normative Data**
  - Developmental function varies greatly by age, especially in children <5 years
  - Normative data quantifies function/development compared to mean and standard deviation (SD) of a sample of typically developing children of the same age
  - May be labelled as composite, standard or scale score or percentile rank
  - Works well to define distribution of population, to compare to rate of decline in natural history or as a component in eligibility criteria
  - Rate of skill acquisition in response to a treatment may be slower than in the normative sample and improvement may be not be reflected in normative data
  - Can be insensitive to change in low-functioning children because either the children fall below the test floor or the rate of change is slower than in typically developing children in the normative sample, and standard scores either plateau or decline
- **Age Equivalents (AE)**
  - Represents the mean age of the raw score in the normative sample
  - Treatment effect may be indicated by an increase in AE score
  - In a progressive condition in which treatment is focused on arresting deterioration, a treatment response may be indicated only by stable AE values

Session 3: Functional Measure for Speech, Ambulation, and Fine Motor Skills

Panelists:

- Emily Freilich, U.S. Food and Drug Administration
- Eric Marsh, Children's Hospital of Philadelphia
- Sara McGlocklin, Patient Representative
- Marc Patterson, Mayo Clinic
- Dawn Phillips, REGENXBIO
- Kevin Weinfurt, Duke University

Session 3 | Discussion Questions

1. In considering potential functional assessment tools, are there aspects for ambulation, speech, and fine motor that are more directly assessed by some instruments than others? What are the opportunities and challenges with using these different instruments?
2. Is there variability in tool administration or disease pathology that impacts interpretation across raters? If so, what steps can be taken to mitigate these issues and determine interpretability of measurements on the individual level and of clinical trials?
3. What are the overall strengths and limitations of each assessment tool? What are the strengths and limitations of each assessment tool for use in NPC clinical trials specifically?
4. What challenges and opportunities exist with these different tools in relation to the patient and caregiver experience in clinical trials?

Closing Remarks | Day 1

Mark McClellan

Director, Duke-Margolis Center for Health Policy

Thank You!

Contact Us

healthpolicy.duke.edu

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1201 Pennsylvania Avenue, NW, Suite 500
Washington, DC 20004

DC office: 202-621-2800
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Endpoint Considerations to Facilitate Drug Development for Niemann-Pick Type C (NPC)

Duke-Margolis Center for Health Policy | Virtual Meeting

January 24-25, 2022

Welcome and Overview | Day 2

Mark McClellan

Director, Duke-Margolis Center for Health Policy

Statement of Independence

The Robert J. Margolis, MD, Center for Health Policy is part of Duke University, and as such it honors the tradition of academic independence on the part of its faculty and scholars. Neither Duke nor the Margolis Center take partisan positions, but the individual members are free to speak their minds and express their opinions regarding important issues.

For more details on relevant institutional policies, please refer to the Duke Faculty Handbook, including the Code of Conduct and other policies and procedures. In addition, regarding positions on legislation and advocacy, Duke University policies are available at http://publicaffairs.duke.edu/government.

Disclaimer

Funding for this workshop was made possible in part by a cooperative agreement from the U.S. Food and Drug Administration. The views expressed in written workshop materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services nor does mention of trade names, commercial practices, or organizations imply endorsements by the U.S. Government.

Remote Participation Instructions

Mute & Slides

- **You have been placed on mute**; panelists can mute/unmute throughout
- We will advance the slide deck, please prompt us to advance

- Questions
- Please feel free to type your questions and comments into the Q&A box and we will use your input to inform the open discussion portions of the event

Zoom Issues? Please Zoom message Luke Durocher or email luke.durocher@duke.edu

Meeting Agenda (Day 2)

12:00 pm Welcome and Overview

12:05 pm Opening Remarks from FDA

12:15 pm Session 4: Exploring Digital Health Technology to Measure Functional Endpoints

1:15 pm Session 5: Future Biomarker Considerations in NPC

2:15 pm Break

2:30 pm Session 6: Closing Panel and Forward Looking

3:25 pm Closing Remarks

3:30 pm Adjournment

All times listed in EST

FDA Public Comment Docket

You may submit comments for this workshop to Docket FDA-2021-N-1297.

The Docket will be open until April 25, 2022.

Comments in the Docket will be reviewed after the Docket closes.

Opening Remarks from FDA

Peter Stein

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Session 4: Exploring Digital Health Technology to Measure Functional Endpoints

12:15 pm – 1:15 pm EST

Ray Dorsey

Director

Center for Health + Technology

University of Rochester Medical Center

UNIVERSITY of ROCHESTER

CHeT
CENTER FOR HEALTH + TECHNOLOGY

NEW APPROACH TO CLINICAL TRIALS

Prepared for

Duke-Margolis Center for Health Policy

Date

January 25, 2022

Outline

1. Ideal outcome measures
2. Clinical trials of the future
3. A path forward

Outline

1. Ideal outcome measures
2. Clinical trials of the future
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Disease measures should be objective, sensitive and continuous. Rating scales are not.

3.10 GAIT

Instructions to examiner: Testing gait is best performed by having the patient walking away from and towards the examiner so that both right and left sides of the body can be easily observed simultaneously. The patient should walk at least 10 meters (30 feet), then turn around and return to the examiner. This item measures multiple behaviors: stride amplitude, stride speed, height of foot lift, heel strike during walking, turning, and arm swing, but not freezing. Assess also for "freezing of gait" (next item 3.11) while patient is walking. Observe posture for item 3.13.

0: Normal:	No problems.
1: Slight:	Independent walking with minor gait impairment.
2: Mild:	Independent walking but with substantial gait impairment.
3: Moderate:	Requires an assistance device for safe walking (walking stick, walker) but not a person.
4: Severe:	Cannot walk at all or only with another person's assistance.

Parkinson's: MDS-UPDRS (gait)

CLINICAL DEMENTIA RATING (CDR™):	0	0.5	1	2	3

	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

Alzheimer's: Clinical Dementia Rating (cognition)

Sources: *Movement disorders: official journal of the Movement Disorder Society* 2008;23:2129-2170, *Movement disorders clinical practice* 2018;5:111-117

Subjective, categorical measures lead to false negatives

Table 1 5-domain NPCCSS

Domain	Scoring	Minimum–Maximum Score
Ambulation	0 = Normal 1 = Clumsy 2 = Ataxic unassisted gait or not walking by 18 months 4 = Assisted ambulation or not walking by 24 months 5 = Wheelchair dependent	0–5
Fine Motor Skills	0 = Normal 1 = Slight dysmetria/dystonia (independent manipulation) 2 = Mild dysmetria/Dystonia (requires little to no assistance, able to feed self without difficulty) 4 = Moderate dysmetria/dystonia (limited fine motor skills, difficulty feeding self) 5 = Severe dysmetria/Dystonia (gross motor limitation, requires assistance for selfcare activities)	0–5
Swallow	0 = Normal, no dysphagia 1 = Cough while eating Intermittent dysphagia* +1 = w/Liquids +1 = w/Solids Dysphagia* +2 = w/Liquids +2 = w/Solids 4 = Nasogastric tube or gastric tube for supplemental feeding 5 = Nasogastric tube or gastric tube feeding only	0–5
Cognition	0 = Normal 1 = Mild learning delay, grade appropriate for age 3 = Moderate learning delay, individualized curriculum or modified work setting 4 = Severe delay/plateau, no longer in school or no longer able to work, some loss of cognitive function^ 5 = Minimal cognitive function	0–5
Speech	0 = Normal 1 = Mild dysarthria (easily Understood 2 = Severe dysarthria (difficult to understand) 3 = Non-verbal/functional communication skills for needs 5 = Minimal communication	0–5
5-domain NPCCSS score	Sum of all scores from the 5 domains above	0–25 (higher score = more severe clinical impairment)

* Score is additive (to the "cough while eating"-score of 1) within the two subsections of intermittent dysphagia and dysphagia (example: for intermittent dysphagia with solids and dysphagia with liquids a score of 4 applies (1 + 1 + 2))

Sources: J Rare Dis (2021) 16:79; Am J Med Genet Part B (2010) 153B:132–140.

Outline

1. Ideal outcome measures
2. Clinical trials of the future
3. A path forward

Wearable devices can track activity levels and steps taken

Fitbit Charge HR

Effects of a before-school program on student physical activity levels

Angie L. Cradock [a], Jessica L. Barrett [a], Elsie M. Taveras [b, c], Stephanie Peabody [d], Chasmine N. Flax [a], Catherine M. Giles [a], Steven L. Gortmaker [a]

Table 3
Within-person comparison of total daily physical activity outcomes on BOKS before school program days vs. other days in Massachusetts and Rhode Island, Fall 2016[a].

Outcome	Unadjusted mean (SD)	Adjusted mean (SE)[b]	Adjusted mean difference (95% CI)	*P* value[c]
Steps				
BOKS day	11,571 (4017)	11,291 (238)	1153 (841, 1464)	< **0.001**
Not BOKS day	9815 (4413)	10,138 (236)		
MVPA minutes				
BOKS day	43.7 (48.8)	38.9 (1.4)	8.8 (5.3, 12.2)	< **0.001**
Not BOKS day	25.5 (34.8)	30.2 (1.4)		
VPA minutes				
BOKS day	12.6 (19.4)	10.8 (0.6)	3.0 (1.6, 4.5)	< **0.001**
Not BOKS day	6.1 (12.7)	7.8 (0.5)		
Total PA minutes[d]				
BOKS day	420.3 (117.0)	406.9 (5.1)	20.8 (13.6, 28.1)	< **0.001**
Not BOKS day	371.5 (124.4)	386.1 (5.0)		

Abbreviations: BOKS, Build Our Kids' Success; SE, standard error; CI, confidence interval, MVPA, moderate-to-vigorous physical activity; VPA, vigorous physical activity; PA, physical activity.

	Overall (n=426)	Intervention (n=241)	Control (n=185)
Male	226 (53)	132 (55)	94 (51)
Female	200 (47)	109 (45)	91 (49)
Average age, years (SD)	8.6 (1.8)	8.4 (1.8)	8.8 (1.7)
Days monitored, mean (SD)	3.2 (0.7)	3.3 (0.7)	3.1 (0.8)
Average wear hours/day (SD)			
Before school	8.8 (0.5)	8.8 (0.5)	8.8 (0.6)
During school	5.7 (0.7)	5.7 (0.7)	5.7 (0.8)
Total day	21.7 (3.9)	21.6 (3.9)	21.7 (3.9)

Sources: *Preventive Medicine Reports 15 (2019) 1009407*

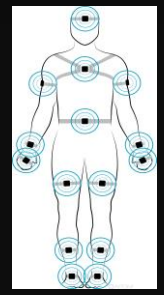
WATCH-PD is evaluating a smartwatch to develop novel measures for early, untreated Parkinson's disease

HOME ASSESMENTS

6 activity periods of 7 days with Apple Watch and iPhone

Bi-weekly smartphone exercise to evaluate motor and cognitive abilities

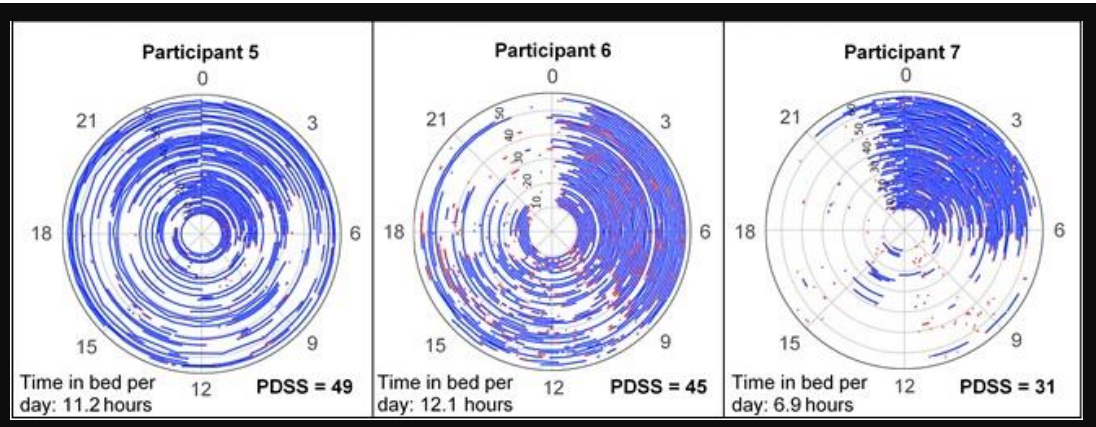
CLINIC ASSESMENTS



5 clinic visits for MDS-UPDRS assessment and custom APDM Sensor

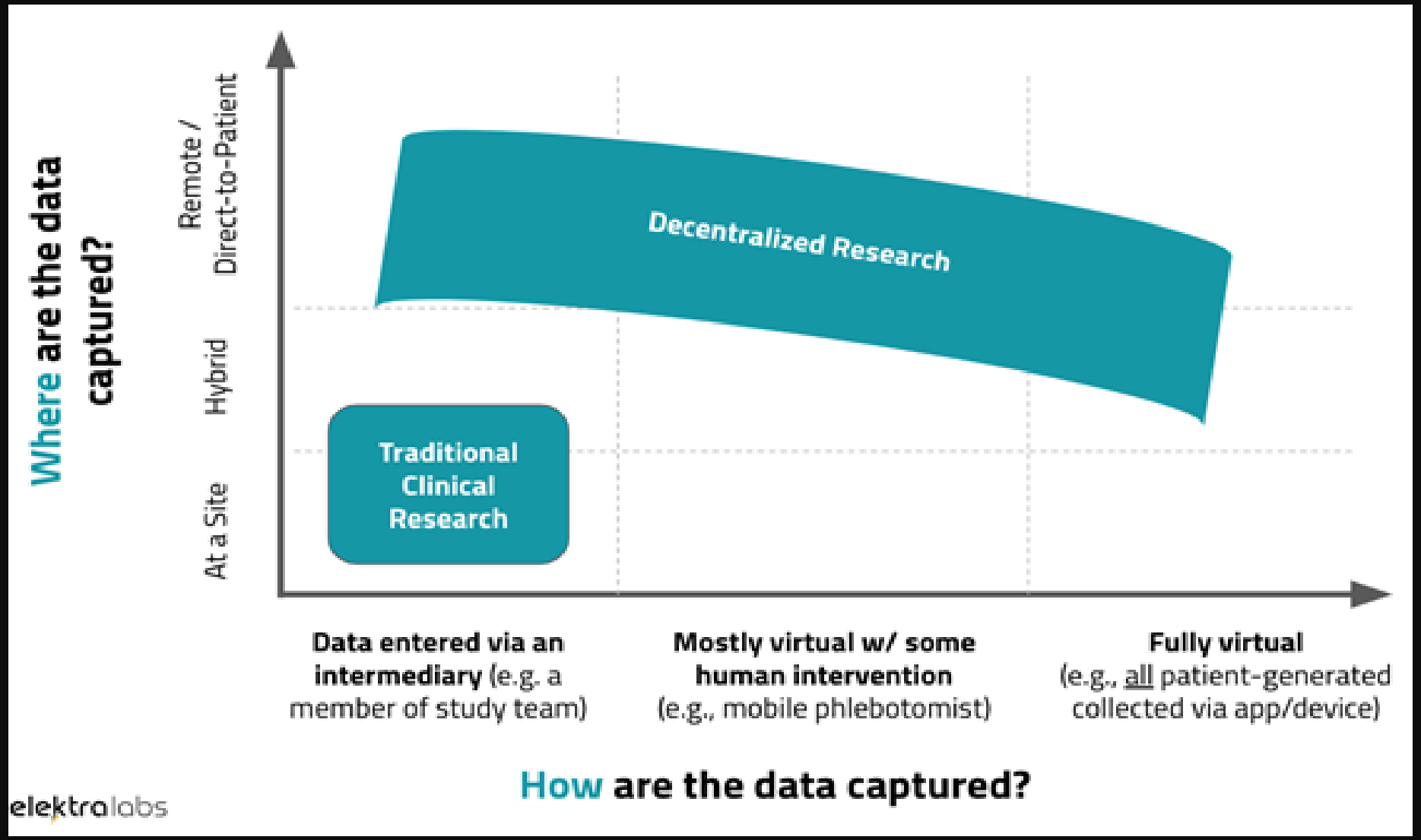
Sources: *WATCH-PD Study*

Objective, continuous, sensitive measures are also available in the home



Source: *Digital Biomarkers* 2019;3:22-30

Digital measures are part of a move toward decentralized trials



Source: Andrea Coravos, Elektra Labs

We have recruited, characterized, and are following a national cohort of individuals at genetic risk for Parkinson's disease remotely

LRRK 2
Carriers

Annual Virtual Visits

Questionnaires
Cognitive testing
Remote examination

Participants want to be a part of virtual trials

Percent willing to participate in future research with virtual research visits

84%

Interventional trial evaluating treatment for symptoms

93%

Interventional trial evaluating treatment to prevent development

99%

Observational study

Source: Valor-PD study, preliminary and unpublished data

Outline

1. Ideal outcome measures
2. Clinical trials of the future
3. A path forward

Nearly everyone with NPC can participate in a decentralized, observational research study

Individuals with Niemann-Pick Type C nationally or globally

		Baseline	Month 6	Month 12	Month 18 …
Demographics		X			
Clinical	Vitals	X	X	X	X
	NPCCSS scale	X		X	
	Patient/parent-reported outcomes	X	X	X	X
	Other clinical measures	X	X	X	X
Biological	Home blood draw	X		X	
Digital	Step counter/activity monitor	X	X	X	X

Pool of well-characterized participants for future clinical trials

Session 4: Exploring Digital Health Technology to Measure Functional Endpoints

Panelists:

- Michelle Campbell, U.S. Food and Drug Administration
- Ray Dorsey, University of Rochester Medical Center
- Alec Koujaian, Patient Representative
- Harry Koujaian, Patient Representative
- Greg Licholai, Yale University
- David Lynch, Children's Hospital of Philadelphia
- Anindita Saha, U.S. Food and Drug Administration

Session 4 | Discussion Questions

1. What functional aspects of NPC (e.g., ataxia) could be meaningfully and accurately measured by digital health technologies?
2. How would potential use of digital health technologies enhance your ability to participate in a clinical trial or run a clinical trial?
3. What are the opportunities and challenges with digital health technologies in patients with neurodegenerative disorders, in particular in progressive and heterogeneous diseases, such as NPC?
4. What considerations are important for ensuring that an endpoint measured using digital health technologies is clinically relevant to patients?

Session 5: Future Biomarker Considerations in NPC

1:15 pm – 2:15 pm EST

Jeffrey Siegel

Director

Office of Drug Evaluation Sciences

U.S. Food and Drug Administration

Biomarkers to facilitate Drug Development

CDER & Duke Margolis NPC Endpoints Workshop

Jeffrey Siegel, MD
Director
Office of Drug Evaluation Sciences
Center for Drug Evaluation and Research / FDA
January 25, 2022

Disclaimers

- Views expressed in this presentation are those of the speaker and do not necessarily represent an official FDA position

Agenda

- Different types of biomarkers
- Analytic and clinical validation of biomarkers
- Regulatory process for incorporating biomarkers in clinical development programs

How biomarkers can aid drug development

- Can improve efficiency of clinical trials
- Addressing unmet medical need: rare diseases
- Precision medicine

BIOMARKER TERMINOLOGY

A Biomarker is:

- A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.
- Molecular, histologic, radiographic, or physiologic characteristics are types of **biomarkers**.
- A **biomarker** is not an assessment of how an individual feels, functions, or survives, these are Clinical Outcomes Assessments (COA)

BEST: BIOMARKERS, ENDPOINTS, AND OTHER TOOLS RESOURCE

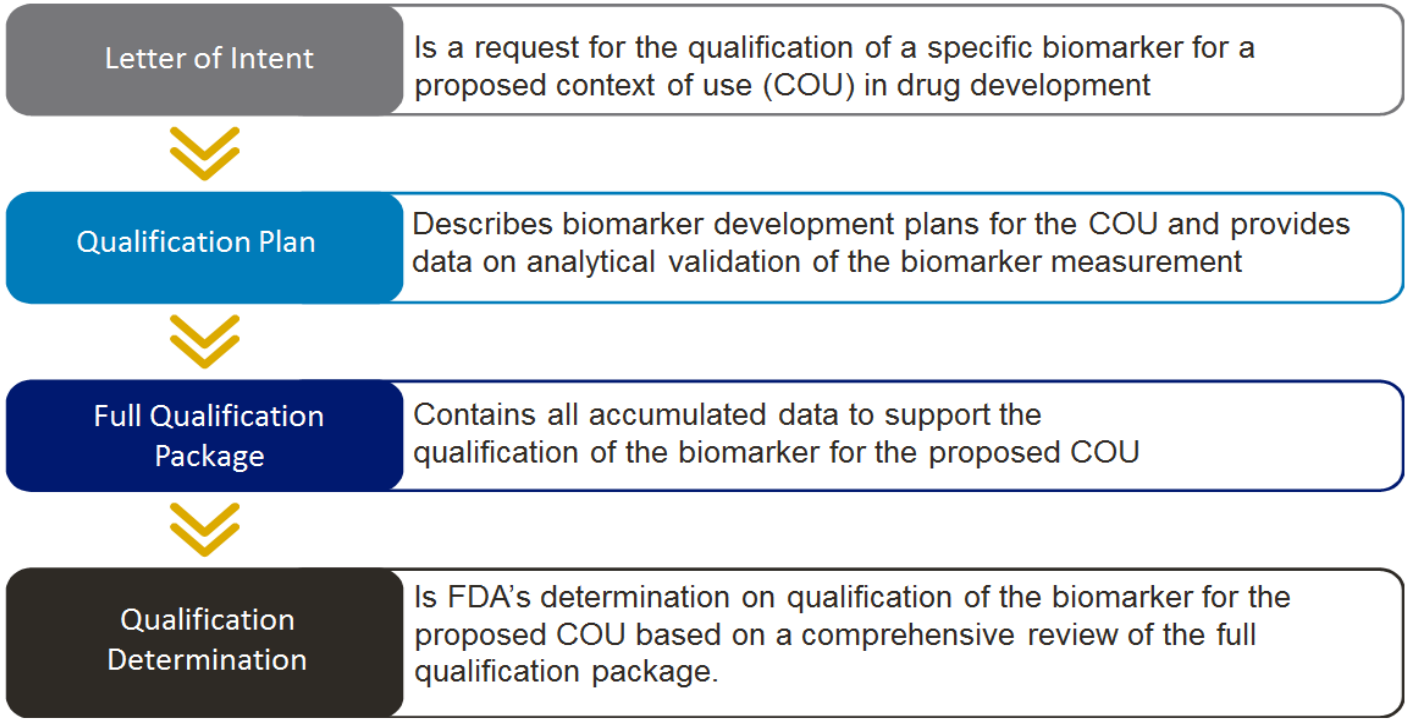
- A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care
- Created by the NIH-FDA Biomarker Working Group
- Publicly available at http://www.ncbi.nlm.nih.gov/books/NBK326791/

BIOMARKER CATEGORIES: BEST DEFINITIONS

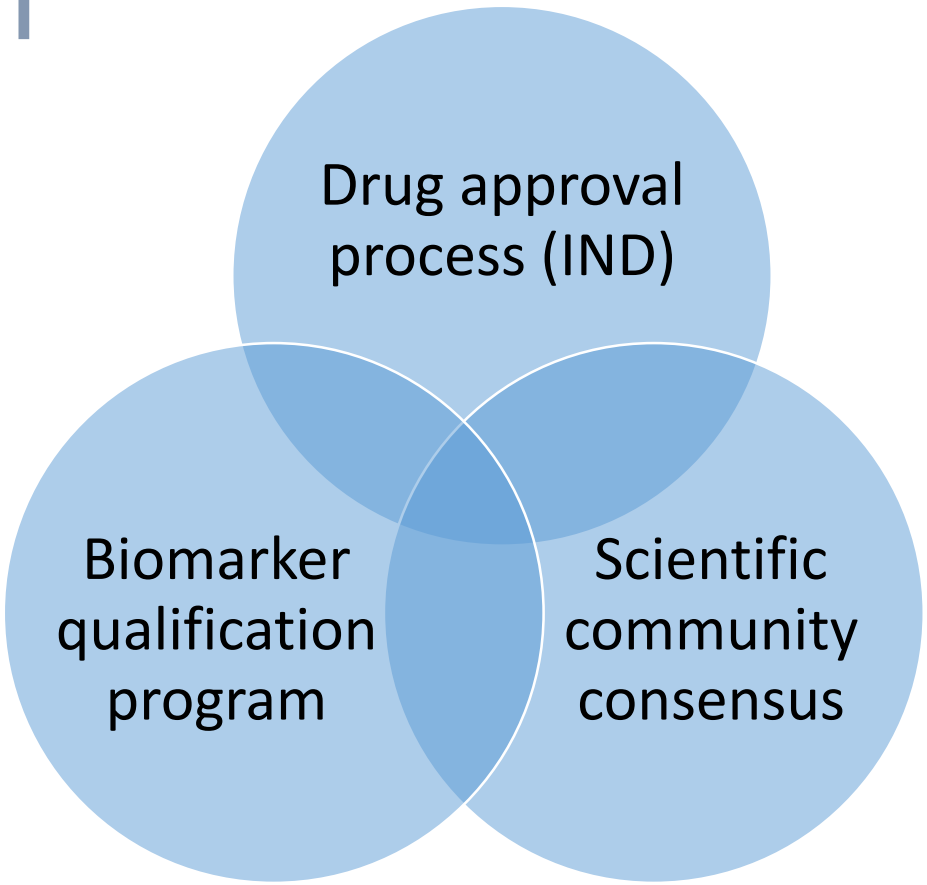
- **Susceptibility/Risk:** Indicates potential for developing disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition
- **Diagnostic:** Detects or confirms the presence of a disease or condition of interest or to identify individuals with a subset of the disease
- **Monitoring:** Assesses status, through serial measurement, of a disease or medical condition including degree or extent of disease
- **Prognostic:** Identifies likelihood of a clinical event, disease recurrence or progression, in patients who have the disease or medical condition of interest in the absence of a therapeutic intervention
- **Predictive:** Identifies patients who are more likely to experience a favorable or unfavorable effect from a specific treatment
- **Pharmacodynamic/Response:** Indicates that a biological response has occurred in a patient who has received a therapeutic intervention. May become clinical trial endpoints and for a very small subset, surrogate endpoints.
- **Safety:** Indicates the likelihood, presence, or extent of toxicity to a therapeutic intervention when measured before or after that intervention

BIOMARKER QUALIFICATION AND 21ST CENTURY CURES DDT LEGISLATION

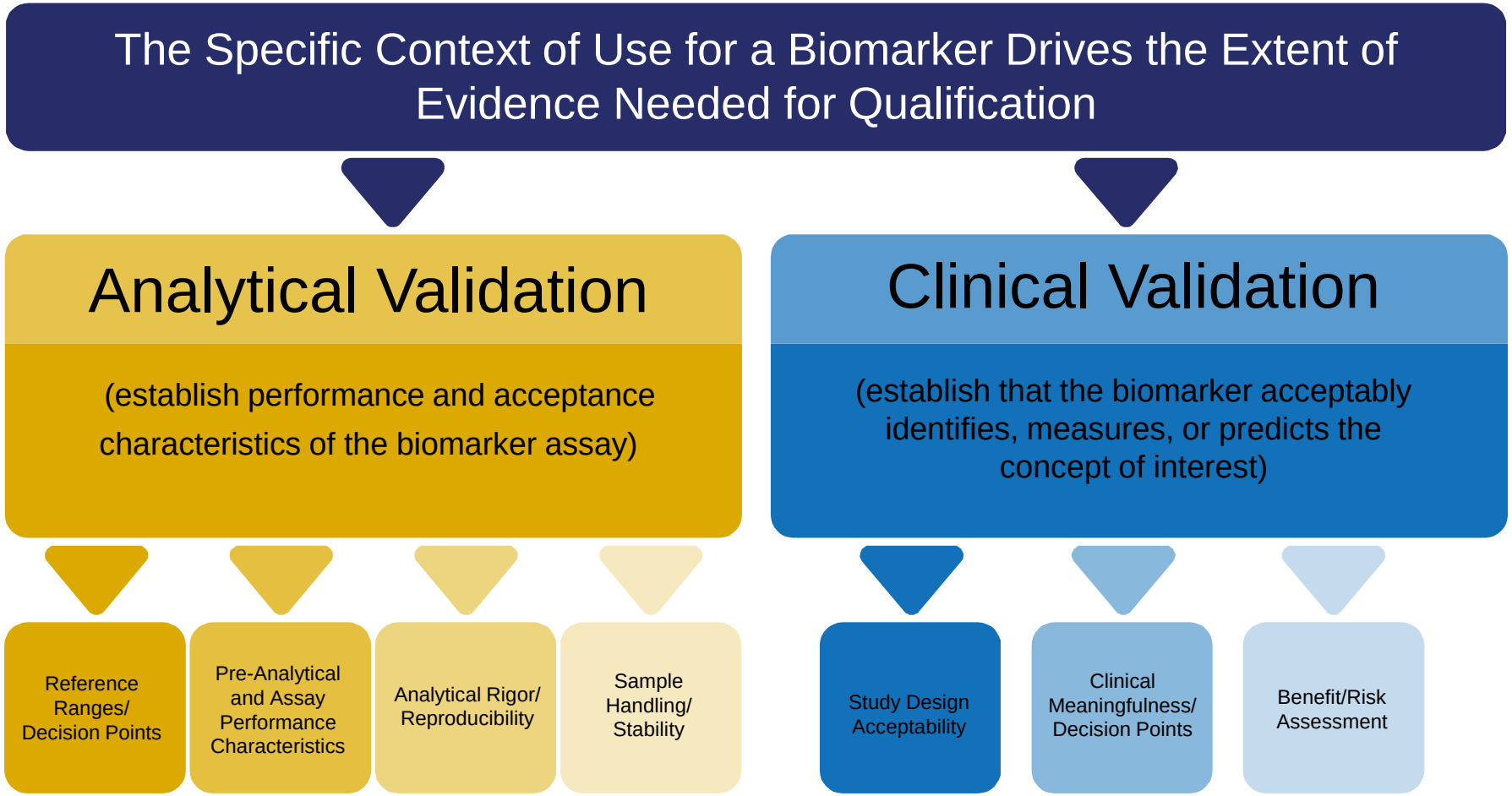
Biomarker Qualification Process



BIOMARKER INTEGRATION INTO DRUG DEVELOPMENT



ANALYTICAL ASSAY AND CLINICAL VALIDATION CONSIDERATIONS IN BIOMARKER QUALIFICATION



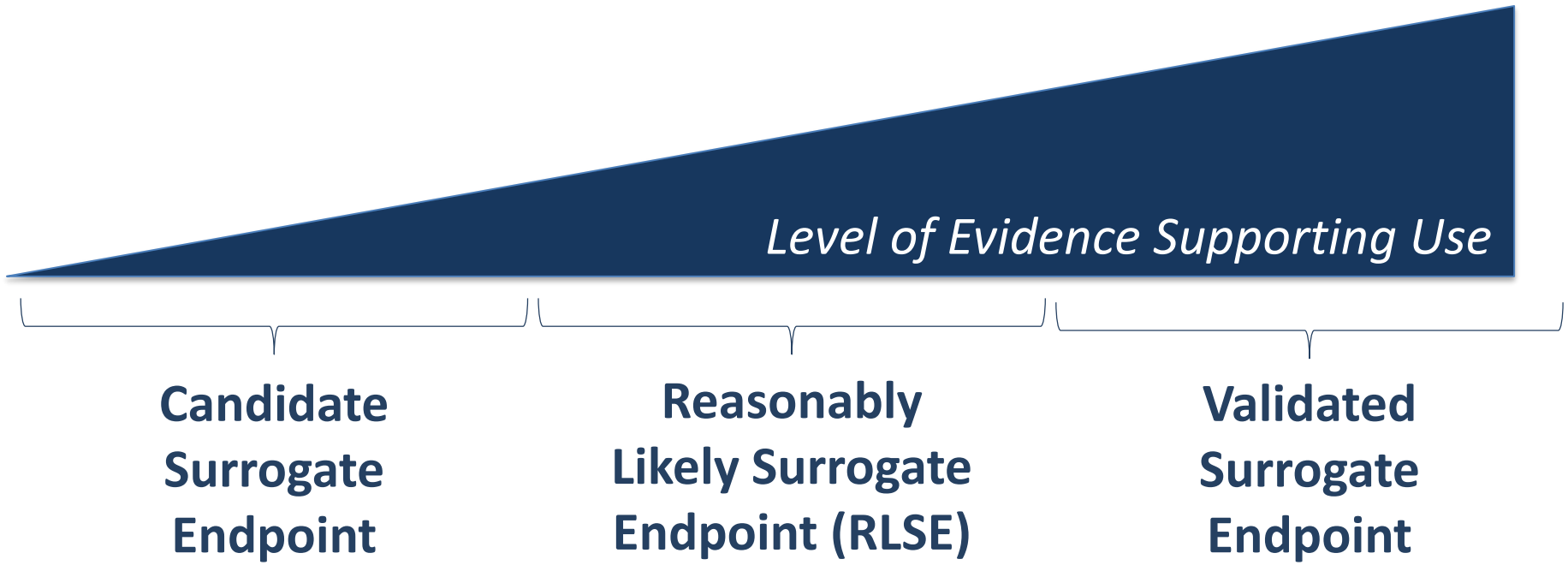
Surrogate endpoints

To support approval, FDA expects substantial evidence of effectiveness – that shows that a drug improves meaningful clinical outcomes: how a patient ***feels, functions, or survives***

- A **validated surrogate endpoint**: accepted by FDA that the effect on the biomarker *predicts* a specific clinical outcome. Validated endpoints have strong and diverse evidence supporting the relationship of the BM and the outcome. Used to support traditional approval.

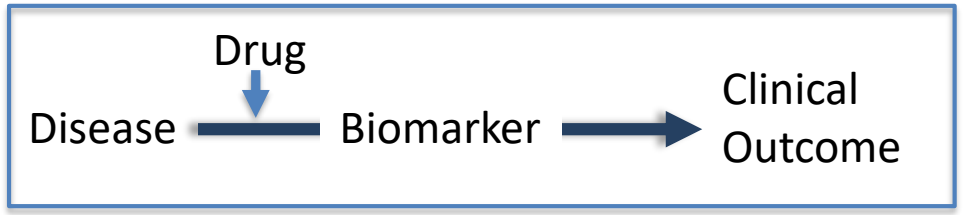
- A **"reasonably likely" surrogate endpoint**: an endpoint supported by strong mechanistic and/or epidemiologic rationale such that an effect on the surrogate endpoint is *expected* to be correlated with a clinical benefit, but not yet reaching the standard for validation. Used for accelerated approval for product intended to treat a serious or life-threatening disease or condition.

Types of Surrogate Endpoints

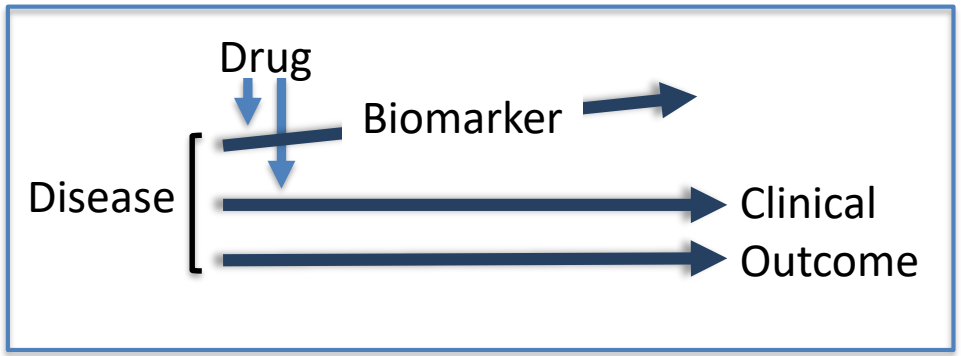


The limitations of surrogate endpoints

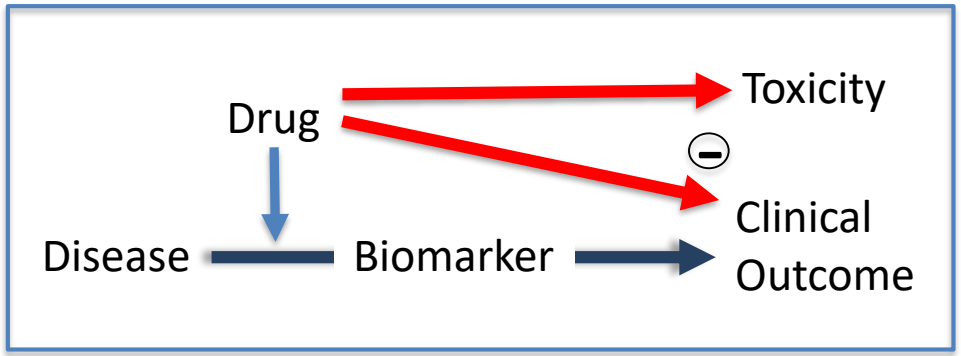
Surrogate on **causal pathway** modulated by drug



Surrogate ***not*** **on causal pathway** by which drug leads to benefit, or **multiple pathways of leading to clinical outcome,** BM *may or may* not reflect key pathways



Drug may induce **adverse effects on desired clinical outcome** through a pathway *not reflected* by BM, or may lead to other toxicities = BM does not reflect benefit (or risk)



After Fleming Statistics in Medicine 2012

Supporting evidence for SE: Relationship to clinical outcome

- Rationale for use as primary endpoint
- Relationship to causal pathway
- Threshold for change required to show clinical relevance
- Consistency across different conditions
- Availability of tools to assess clinical outcome

Role of mechanistic data in acceptance of SE's

- In some cases, mechanistic data tying biomarker to pathophysiology of disease may be strong enough along with epidemiologic data to support surrogacy:
  - Single causal pathway to disease with biomarker reflecting that pathway
  - Examples: PTH levels in secondary hyperparathyroidism, substrate levels in certain rare genetic enzyme deficiency disorders*, urinary oxalate levels for hyperoxaluria

*FDA guidance: Slowly Progressive, Low-Prevalence Rare Diseases With Substrate Deposition That Result From Single Enzyme Defects

Summary

- Different types of biomarkers require different levels of evidence
- Surrogate endpoints require the highest level of evidence
- Evidence linking the biomarker to the causal pathway of disease and multiple lines of evidence linking the biomarker to clinical outcomes increase confidence a biomarker can serve as a SE
- Consult clinical review division early

Daniel Ory

Chief Medical Officer

Casma Therapeutics

CASMA THERAPEUTICS

Endpoint Considerations to Facilitate Drug Development for Niemann-Pick Type C (NPC) Virtual Public Workshop

Session 5: Future Biomarker Considerations in NPC

Daniel Ory MD | January 25, 2022

Chief Medical Officer, Casma Therapeutics

Disclosures

Dr. Ory is an employee of Casma Therapeutics and holds patents related to NPC1 biomarkers

Biomarker Categories

- Susceptibility risk
- Diagnostic
- Monitoring
- Prognostic
- Predictive
- Pharmacodynamic/Response
- Safety

Biomarker Categories

- Susceptibility risk
- Diagnostic
- Monitoring
- Prognostic
- Predictive
- Pharmacodynamic/Response
- Safety

NPC1 Diagnostic Biomarkers

Oxysterols

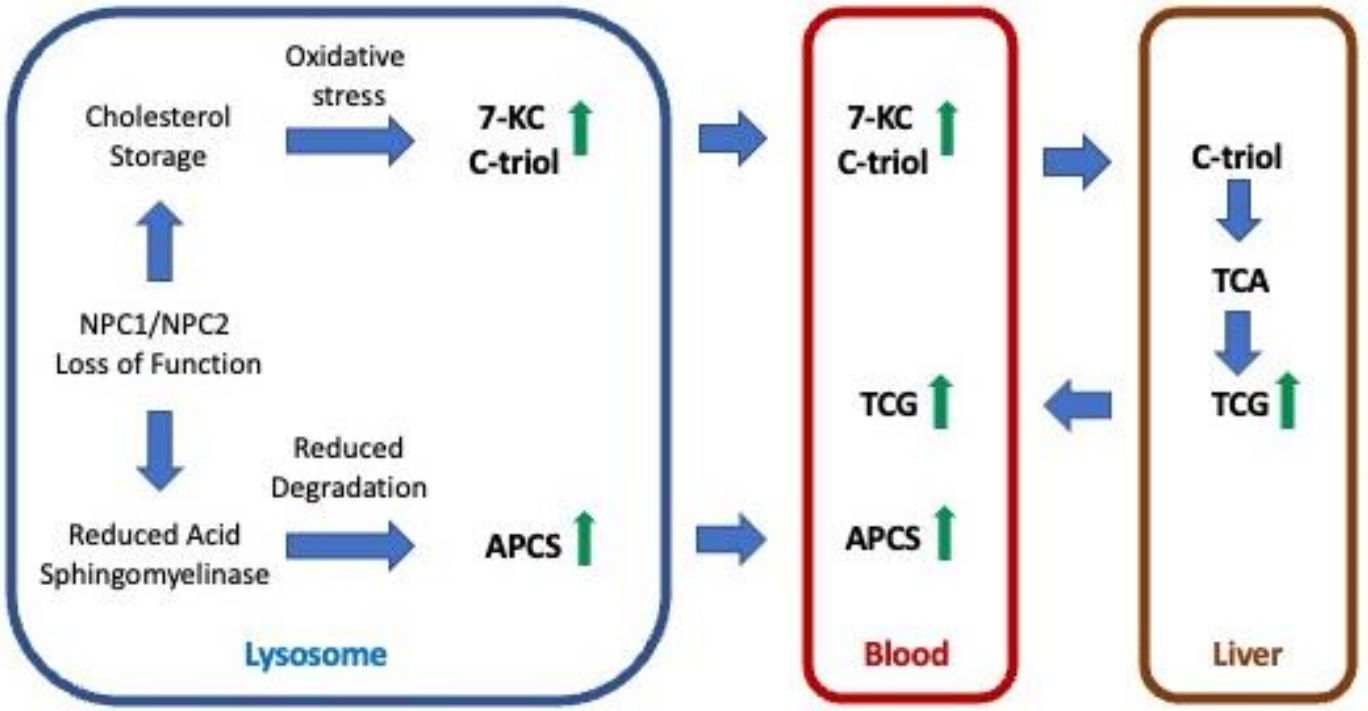
- 3β,5α,6β-cholestantriol (C-triol)
- 7-ketocholesterol

Bile acids

- Trihydroxycholanic glycinate (TCG)

APCS

- *N-palmitoyl*-O-phosphocholineserine (lysoSM-509)

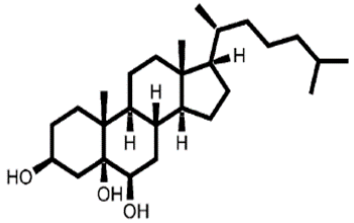


Jiang et al., Expl Neuro Ther 2021

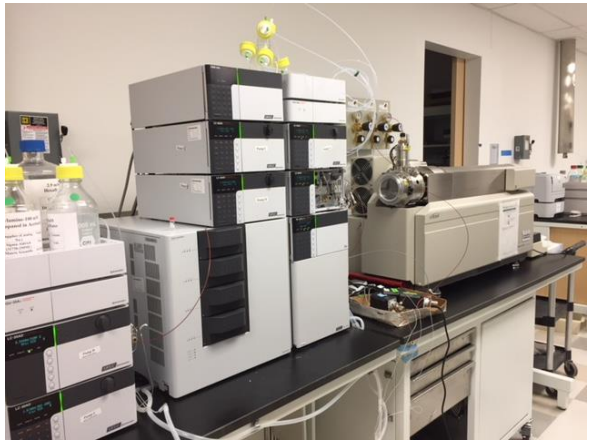
NPC1 Diagnostic Biomarkers: Oxysterols

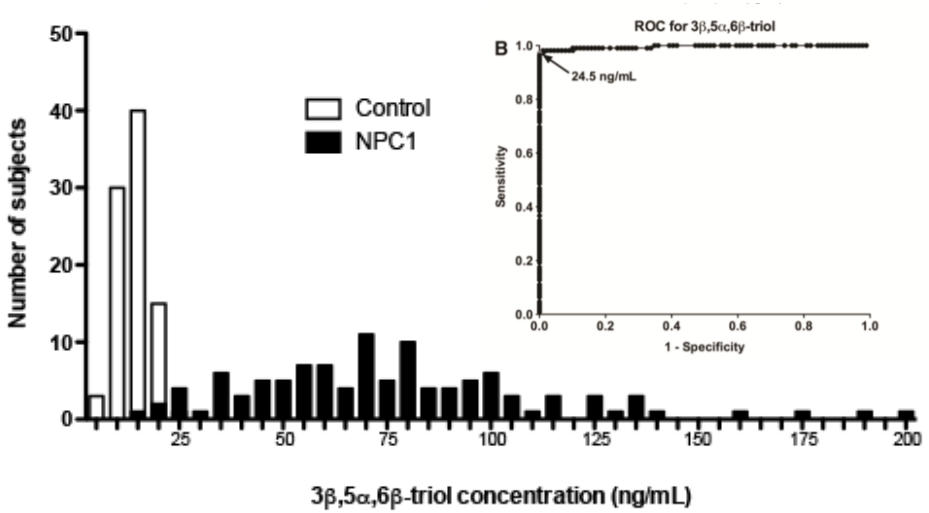
Tandem MS

Oxysterol Assay

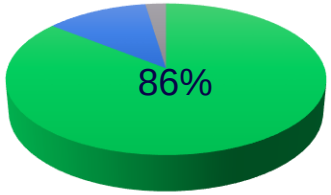


C-triol

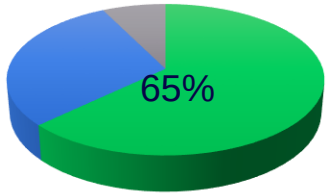




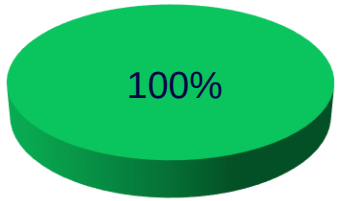
DNA Sequencing *NPC1/2* genes



Filipin Staining



Oxysterols



NPC diagnosed

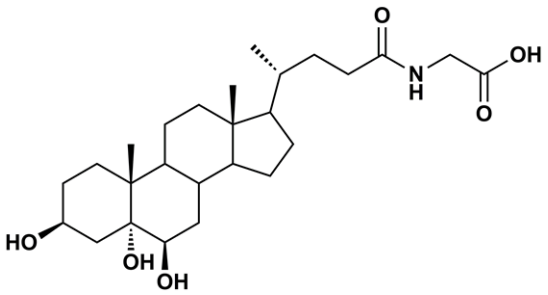
NPC probable

NPC possible

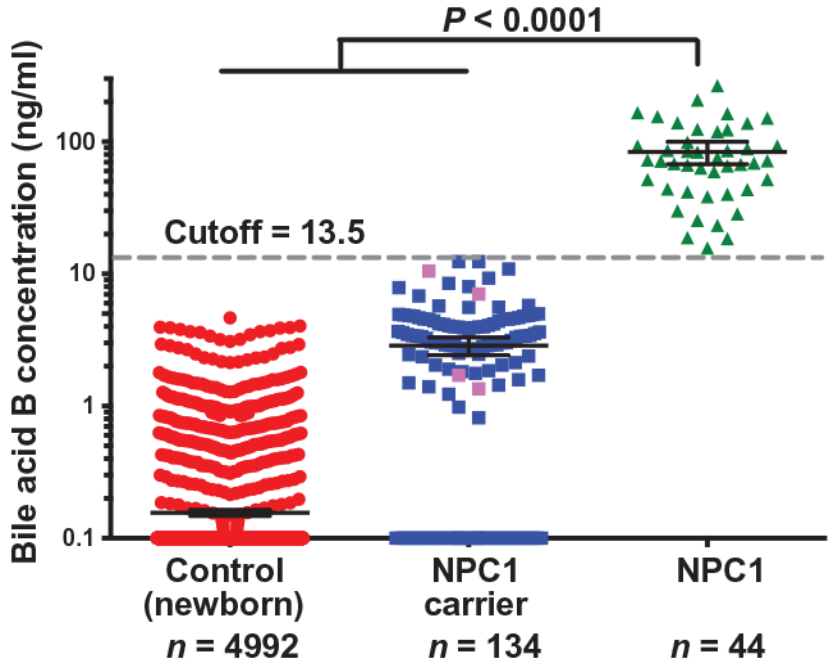
CASMA

Jiang et al., J Lipid Res 2011
Stampfer et al., OJRD 2013

NPC1 Diagnostic Biomarkers: Bile Acids



Trihydroxycholanic acid (TCG)



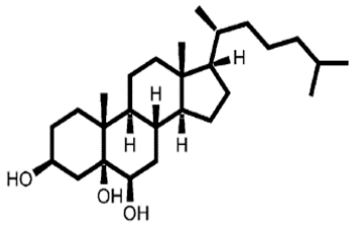
TCG biomarker being prospectively validated in ScreenPlus NBS pilot in NY

CASMA

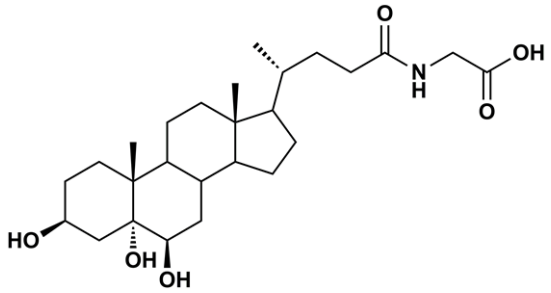
Jiang et al., Sci Trans Med 2016
Jiang et al, Mol Genet Metab 2018

NPC1 Diagnostic Biomarkers: Assay Comparison

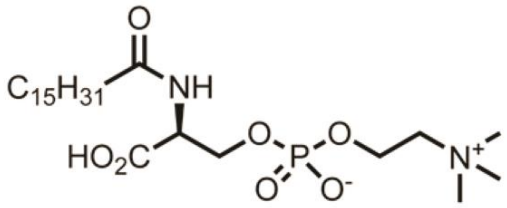
C-triol



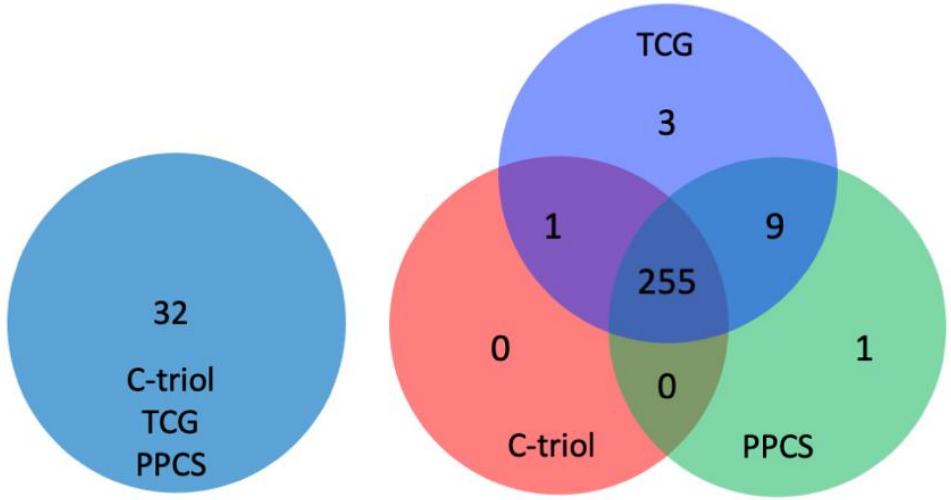
TCG



PPCS



Comparison of C-triol, TCG and PPCS Plasma Assays



NPC1 true positives

NPC1 false positives

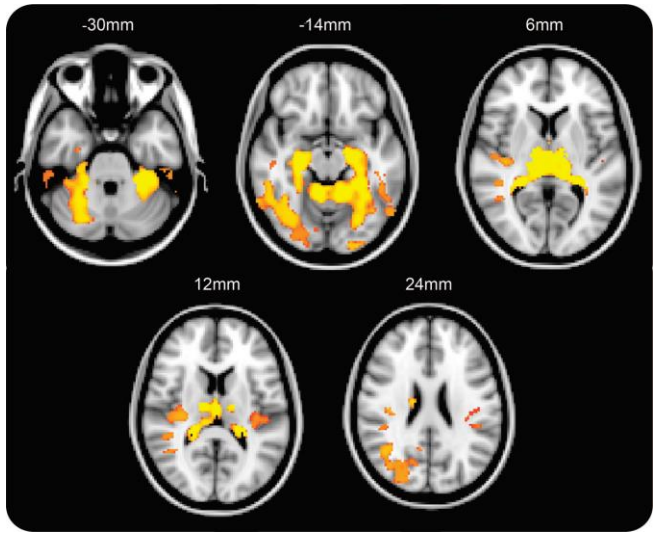
TCG biomarker has highest ROC performance and is diagnostic assay of choice

CASMA

Sidhu et al., Mol Genet Metab 2021
Jiang et al., Expl Neuro Ther 2020

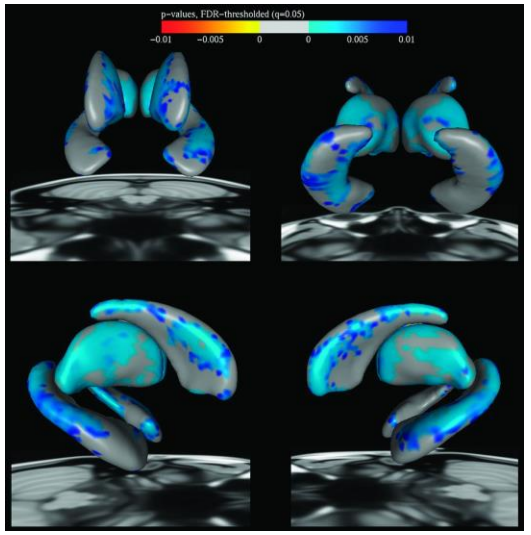
NPC1 Monitoring Biomarker: Diffusion Tensor Imaging

Comparison Grey Matter Volumes



Yellow indicates loss in NPC1

Comparison Subcortical Volumes



Blue indicates loss in NPC1

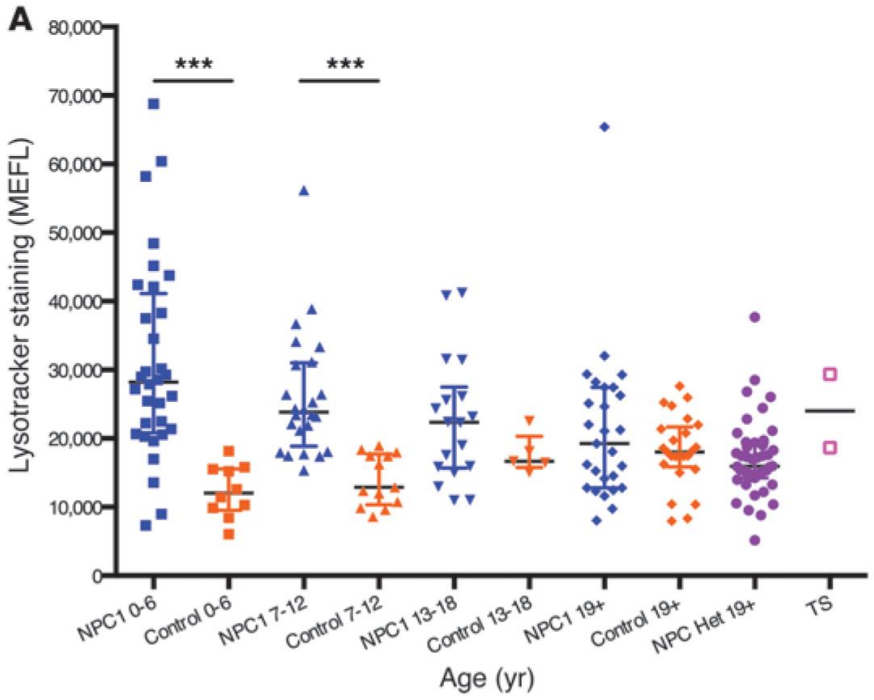
Performance of DTI in non-cross-sectional, longitudinal studies has not been determined

CASMA

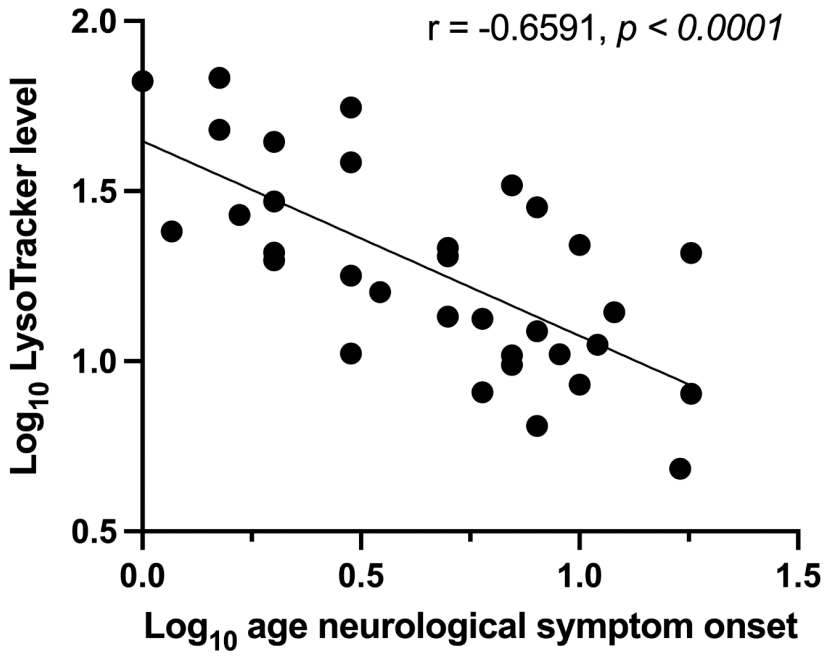
Walterfang et al., Neurology 2010
Walterfang et al., AJNR 2013

NPC1 Prognostic Biomarkers: Lysotracker Staining

B Cell Lysotracker Staining



Fibroblast Lysotracker Staining

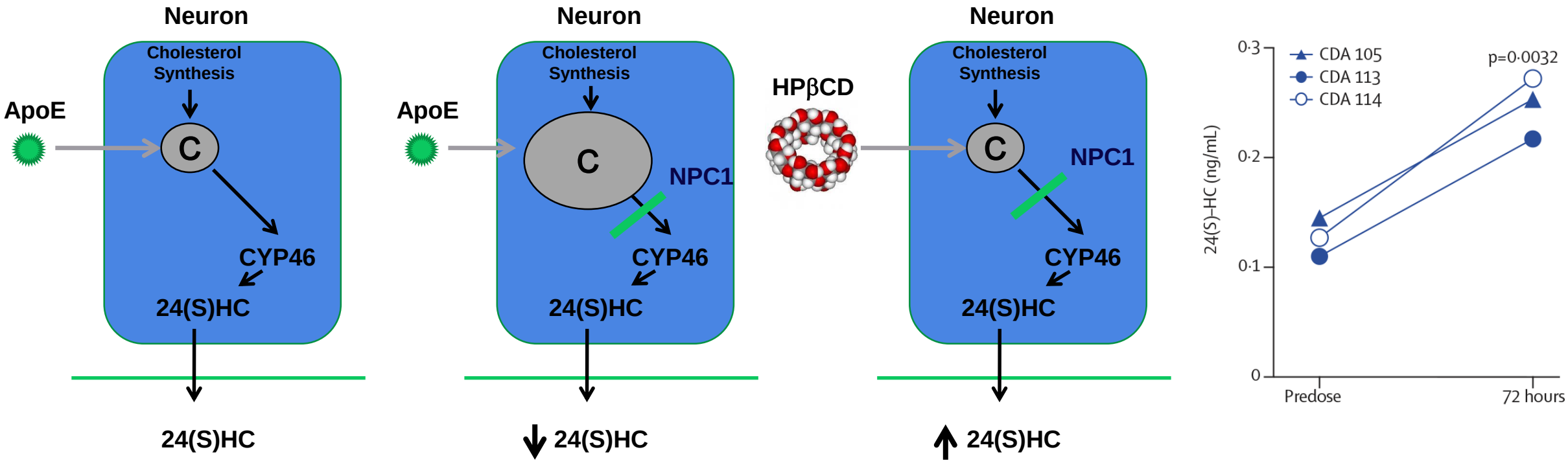


Lysotracker phenotyping has potential to predict disease progression

CASMA

teVruchte et al., JCI 2014
Baxter et al., In press 2022

NPC1 Pharmacodynamic Biomarker: 24-HC



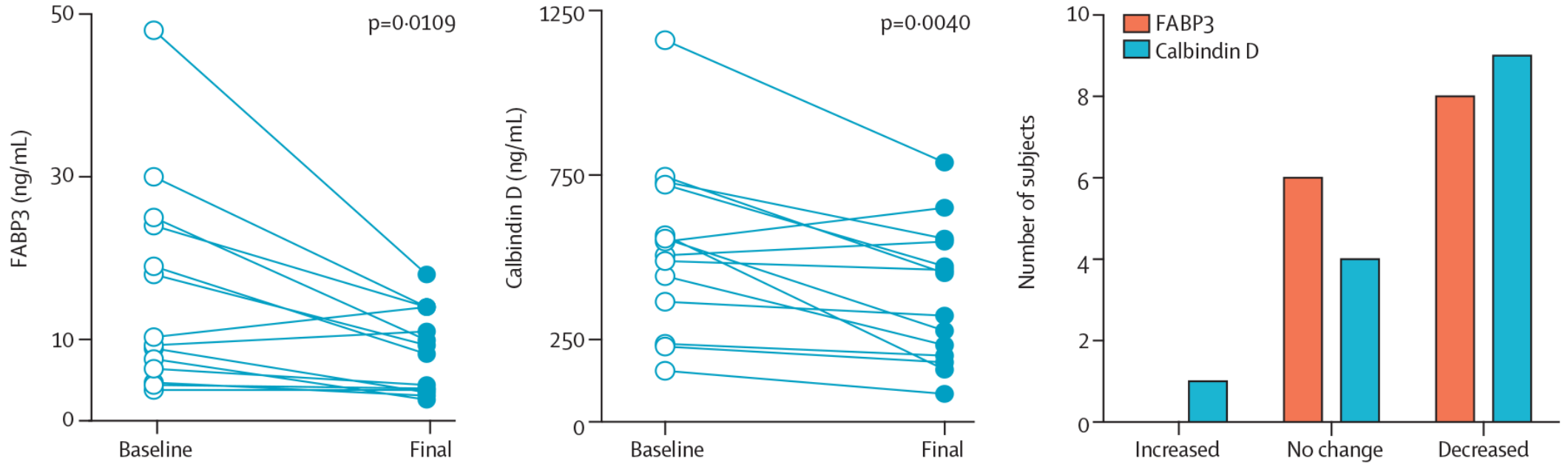
CNS 24-HC synthesis serves as target engagement for intrathecal HPβCD treatment

Porter et al., Sci Trans Med 2010
Tortelli et al., Hum Mol Genet 2014
Ory et al., Lancet 2017

CASMA

NPC1 Response Biomarkers: CSF FABP3 and Calbindin D

Ph 1/2 trial of Intrathecal HPβCD



CSF proteins have potential as response biomarkers

CASMA

Ory et al., Lancet 2017

NPC1 Biomarkers: Summary

- Plasma biomarkers have facilitated NPC1 diagnosis and may enable newborn screening
  - Largely produced by peripheral tissues
  - Limited utility as CNS response biomarkers
- Fibroblast lysotracker staining may have potential as prognostic biomarker
- Potential for target engagement biomarkers developed for cyclodextrin to be extended to other therapeutics
- CSF protein biomarkers provide insight into CNS pathology and could serve as pharmacodynamic response biomarkers

NPC1 Biomarkers: Next Steps

- Biospecimens from intrathecal cyclodextrin clinical trials and expanded access protocols provide rich resource for discovery and validation of CNS response biomarkers
- Global proteomics and targeted/untargeted metabolomic platforms sufficiently mature to support biomarker discovery
- Candidate biomarkers validated in other neurodegenerative disorders (e.g. Neurofilament light chain) are being examined in existing biospecimen collections

Session 5: Future Biomarker Considerations in NPC

Panelists:

- Patti Dickson, Washington University School of Medicine in St. Louis
- Carole Ho, Denali Therapeutics
- Daniel Ory, Casma Therapeutics
- Jack Wang, U.S. Food and Drug Administration

Session 5 | Discussion Questions

1. What are the strengths and weaknesses of the various biomarkers being explored for NPC?
2. What is the role of blood biomarkers vs CNS biomarkers in assessing the severity of neurologic disease?
3. In the development of biomarkers for NPC, what are the advantages and disadvantages of animal models for biomarker discovery and development?
4. What are important considerations for the future of biomarker development in NPC?
5. Are there considerations related to biomarker development in other diseases that are relevant to biomarker considerations in NPC?
6. What are the challenges associated with validating biomarkers for NPC, and what approaches may support efficient biomarker validation?

Break

We will be back momentarily.

The next panel will begin at 2:30 p.m. (U.S. Eastern Time)

Session 6: Closing Panel and Forward Looking

2:30 pm – 3:25 pm EST

Session 6: Closing Panel and Forward Looking

Panelists:

- Debbie Kaflowitz, Patient Representative
- Janet Maynard, U.S. Food and Drug Administration
- Jennifer Pippins, U.S. Food and Drug Administration
- Forbes D. Porter, National Institutes of Health
- Sean Recke, Patient Representative
- Steve Romano, Mallinckrodt
- Segundo Mariz, European Medicines Agency

Session 6 | Discussion Questions

1. Reflecting on the day, what are key strategies optimizing endpoints in NPC clinical trials?
2. What steps can be taken to make therapeutic development for NPC more efficient while ensuring the collection of robust clinical data to support regulatory and clinical decision making?
3. How can clinical trials be designed to best support patient access and ease burdens associated with trial participation?
4. Beyond endpoint selection, what are the other key considerations for supporting the approval of safe and effective treatments for NPC?
5. What are key strategies for facilitating collaboration between stakeholders, including patients and caregivers, with the overall goal of developing safe and effective treatments for NPC?

Closing Remarks | Day 2

Mark McClellan

Director, Duke-Margolis Center for Health Policy

Thank You!

Contact Us

healthpolicy.duke.edu

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dukemargolis@duke.edu

1201 Pennsylvania Avenue, NW, Suite 500
Washington, DC 20004

DC office: 202-621-2800
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