Public Meeting on Patient-Focused Drug Development on Neurological Manifestations of Inborn Errors of Metabolism

June 10, 2014

Welcome

Sara Eggers, PhD
Office of Strategic Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

June 10, 2014

Agenda

- **Setting the context**
  - Opening Remarks
  - Overview of FDA's Patient-Focused Drug Development Initiative
  - Background on Inborn Errors of Metabolism and Therapeutic Options
  - Overview of Discussion Format

- **Discussion Topic 1**: Disease symptoms and daily impacts that matter most to patients

- **Discussion Topic 2**: Patients' perspectives on current approaches to treating inborn errors of metabolism

- **Open Public Comment**

- **Closing Remarks**

Opening Remarks

Donna Griebel, MD
Director, Division of Gastroenterology and Inborn Error Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

June 10, 2014

FDA's Patient-Focused Drug Development Initiative

Theresa Mullin, PhD
Director, Office of Strategic Program
Center for Drug Evaluation and Research
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June 10, 2014

Patient-Focused Drug Development under PDUFA V

- **FDA is developing a more systematic way of gathering patient perspective on their condition and available treatment options**
  - Patient perspective helps inform our understanding of the context for the assessment of benefit-risk and decision making for new drugs
  - Input can inform FDA's oversight both during drug development and during our review of a marketing application

- **Patient-Focused Drug Development is part of FDA commitments under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V)**
  - FDA will convene at least 20 meetings on specific disease areas over the next five years
  - Meetings will help develop a systematic approach to gathering input

Identifying Disease Areas for the Patient-Focused Meetings

- **In September 2012, FDA announced a preliminary set of diseases as potential meeting candidates**
  - Public input on these nominations was collected. FDA carefully considered these public comments and the perspectives of our drug review divisions at FDA

- **FDA selected a set of 16 diseases selected to be the focus of meetings for fiscal years 2013-2015**
  - Another public process will be initiated in 2015 to determine the set for fiscal years 2016-2017

Disease Areas to be the focus of meetings for FY 2013-2015

FY 2013

- Chronic fatigue syndrome
- HIV
- Lung cancer
- Narcolepsy

FY 2014

- Sickle cell disease
- Fibromyalgia
- Pulmonary arterial hypertension
- **Inborn errors of metabolism**

FY 2014 – 2015

- Alpha-1 antitrypsin deficiency
- Breast cancer
- Chronic Chagas disease
- Female sexual dysfunction
- Hemophilia A, Hemophilia B, von Willebrand disease, and other heritable bleeding disorders
- Idiopathic pulmonary fibrosis
- Irritable bowel syndrome, gastroparesis, and gastroesophageal reflux disease
- Parkinson's disease and Huntington's disease

Tailoring Each Patient-Focused Meeting

- **Each meeting focuses on a set of questions that aim to elicit patients' perspectives on their disease and on treatment approaches**
  - We start with a set of questions that could apply to any disease area; these questions are taken from FDA's benefit-risk framework and represent important considerations in our decision-making
  - We then further tailor the questions to the disease topic of the meeting (e.g., current state of drug development, specific interests of the FDA review division, and the needs of the patient population)
- **Focus on relevant current topics in drug development for the disease at each meeting**
  - E.g., focus on HIV patient perspectives on potential "cure research"
- **We've learned that active patient involvement and participation is key to the success of these meetings.**

"Voice of the Patient" Reports

- Following each meeting, FDA publishes a Voice of the Patient report that summarizes the patient testimony at the meeting, perspectives shared in written docket comments, as well as any unique views provided by those who joined the meeting webcast.
- These reports serve an important function in communicating to both FDA review staff and the regulated industry what improvements patients would most like to see in their daily life.
- FDA believes that the long run impact of this program will be a better, more informed understanding of how we might find ways to develop new treatments for these diseases.

Background on Inborn Errors of Metabolism and Therapeutic Options

Teresa Buracchio, MD
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June 10, 2014

Introduction

- Inborn errors of metabolism (IEM) are a group of rare disorders that leave the body unable to properly break down or synthesize certain substances in the body
  - Genetic defects cause deficiencies of specific enzymes that convert one substance to another (e.g., galactose to glucose)

- Metabolic dysfunction can cause progressive and permanent damage by:
  - Causing accumulation of a substance to toxic levels in the body
  - Depriving the body of essential substances needed to support specific functions
  - Alteration of other (unknown) pathways

Introduction

- There are over 200 known inborn errors of metabolism
- IEM disorders vary in their symptoms, severity, and disease progression
  - Many are fatal in childhood or early adulthood
  - Some progress slowly or may not show symptoms until adulthood (e.g., Wilson's disease, Alexander disease)
- Diagnosis can be difficult because symptoms may be non-specific and there may be a delay in the onset of symptoms
  - New screening technologies are increasing identification of IEM disorders before symptoms arise
  - Earlier identification may improve morbidity and mortality

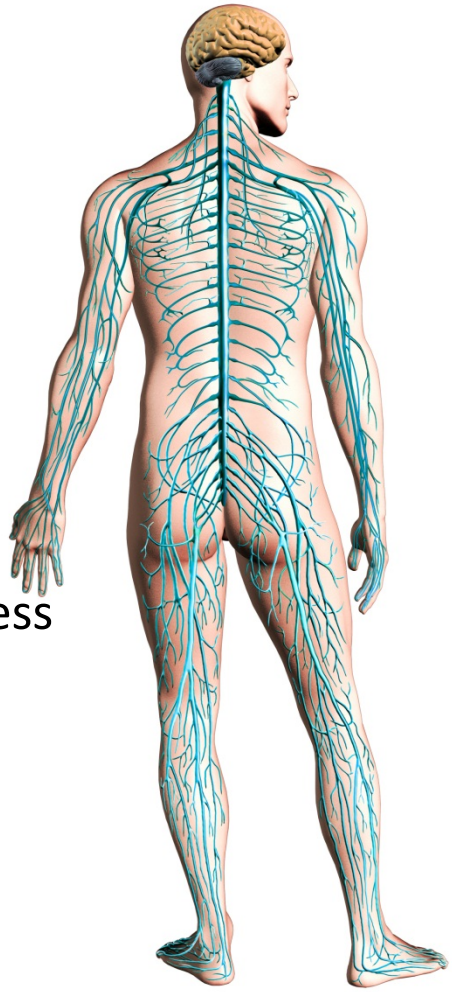
Signs and Symptoms

- The manifestations (effects) of IEM vary greatly depending on the specific underlying disorder.

- IEM can affect each major organ system in the body
  - Changes in physical appearance
  - Respiratory
  - Cardiovascular
  - Joint or muscle
  - Liver
  - Neurological, cognitive, psychological or behavioral

Neurologic signs and symptoms

- Weakness
- Swallowing problems
- Spasticity/Stiffness
- Abnormal movements
- Coordination/Clumsiness
- Numbness/tingling
- Pain



- Seizures
- Vision/hearing loss
- Cognition/learning problems
- Poor attention/concentration
- Language delay
- Behavior problems
- Sleep problems

- Bowel or bladder problems
- Walking difficulties
- Balance problems

Treatment Options

- The goal for treatment for IEM disorders is to reduce symptoms and signs, improve quality of life, and/or slow/halt disease progression

- Current therapies include:
  - Dietary restrictions, dietary supplementation or medical foods
  - Enzyme Replacement Therapies, such as Elaprase or Naglazyme
  - Bone marrow or organ transplantation
  - Other supportive treatments, such as anticonvulsants, dialysis, gastrostomy tubes
  - Behavioral, physical or occupational therapy

Challenges in Drug Development for IEM Disorders

- Very small number of patients with the disease
- Diverse phenotypes (disease characteristics)
- Children and adults
  - Special ethical considerations for pediatric clinical trials
- Poorly described natural histories
  - What signs and symptoms should be measured, and how?
  - Do the disease symptoms progress in time course that can be captured in a clinical trial?
  - Is the measurement tool applicable to both children and adults?
  - Do biomarkers exist and do they have relevance as an endpoint?

Patient-Reported Outcomes

- For conditions like IEM, which are not fully understood, input from patients is especially important
- Patient-reported outcomes (PROs) can represent direct measures of treatment benefit – how a patient feels or functions
- All measurements need to be evaluated in adequate and well-controlled randomized trials
- Patient and caregiver input is essential to capture important and clinically-relevant disease symptoms in the PROs

U.S. Food and Drug Administration
Protecting and Promoting Public Health
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Overview of Discussion Format

Sara Eggers, PhD
Office of Strategic Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Discussion Overview

Topic 1: The neurological manifestations of IEM

- Which symptoms have the most significant impact on your/your child's daily life?
- How do these symptoms affect your/your child's ability to do specific activities?
- How do these symptoms change over time?

Topic 2: Current approaches to treating IEM

- What are you doing to treat or manage your/your child's IEM?
- How well do your treatments address the neurological effects?
- What are their biggest downsides?
- What would you look for in an "ideal" treatment?
- What is important to consider with respect to clinical trial participation and informed consent?

Discussion Format

- **We will first hear from a panel of patients**
  - The purpose is to set a good foundation for our discussion
  - They reflect a range of experiences with IEM

- **We will then broaden the dialogue to include patients and patient representatives in the audience**
  - The purpose is to build on the experiences shared by the panel
  - We will ask questions and invite you to raise your hand to respond
  - Please state your name before answering

Discussion Format, continued

- **You'll have a chance to answer "polling" questions**
  - Their purpose is to aid our discussion
  - In-person participants, use the "clickers" to respond
  - Web participants: answer the questions through the webcast
  - Patients and patient representatives only, please

- **Web participants can add comments through the webcast**
  - Although they may not all be read or summarized today, your comments will incorporated into our summary report
  - We'll occasionally go to the phones to give you another opportunity to contribute

Send us your comments!

- **You can send us comments through the "public docket".**
  - The docket will be open until August 11, 2014
  - Share your experience, or expand upon something discussed today
  - Comments will be incorporated into our summary report
  - Anyone is welcome to comment

Visit:
http://www.regulations.gov/#!documentDetail;D=FDA-2014-N-0396-0001

Click Comment Now!

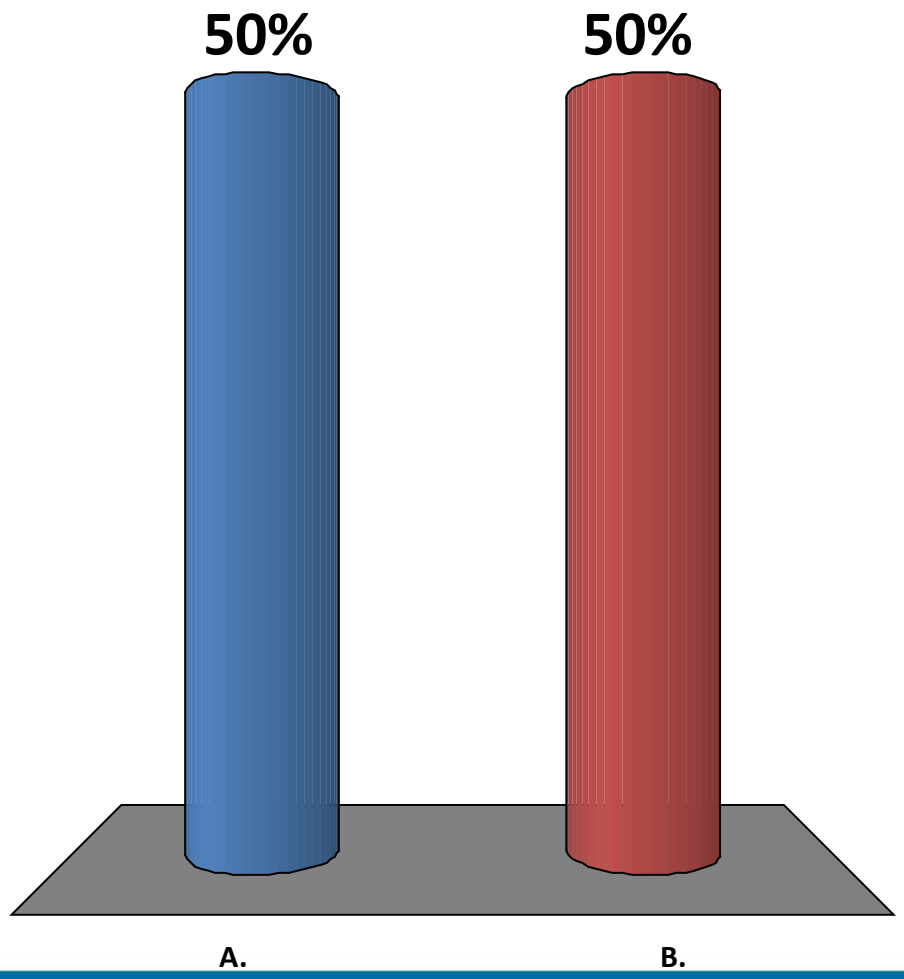
Discussion Ground Rules

- We encourage patients, caregivers and advocates to contribute to the dialogue
- FDA is here to listen
- Discussion will focus on symptoms and treatments
  - Open Public Comment Period is available to comment on other topics
- The views expressed today are personal opinions
- Respect for one another is paramount
- Let us know how the meeting went today; evaluations at registration desk

Where do you live?

A. Within the Washington, D.C. metropolitan area (including the VA and MD suburbs)

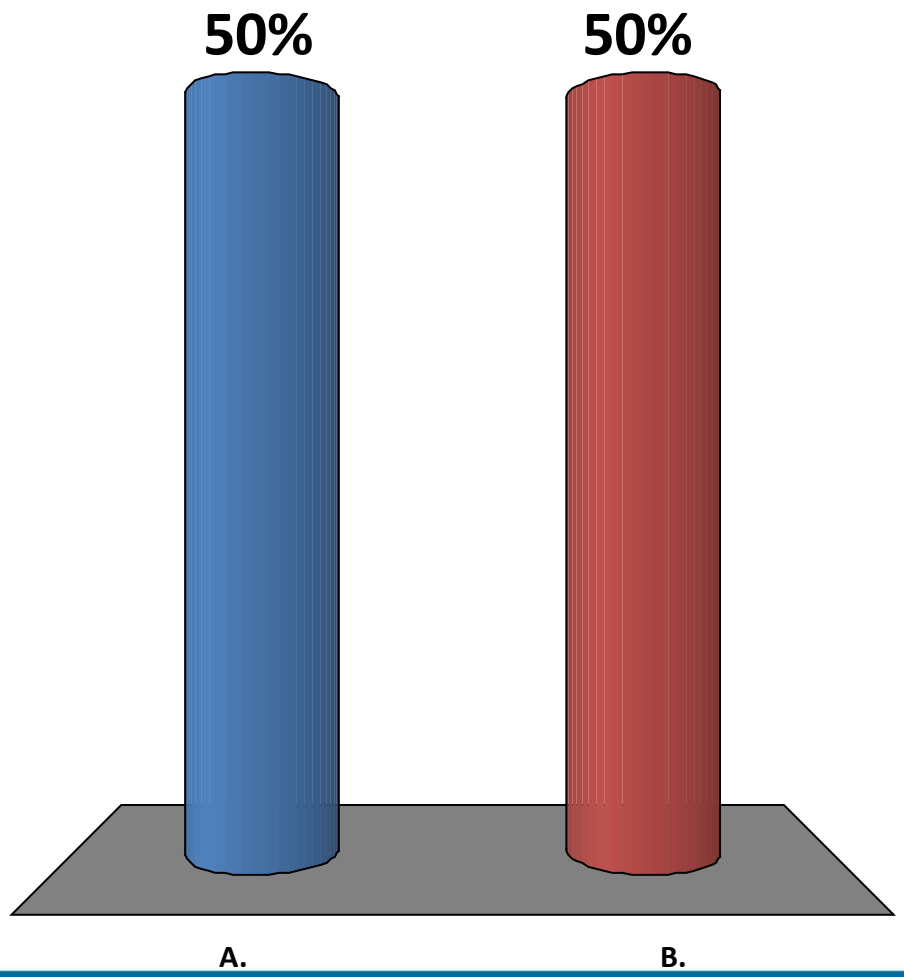
B. Outside of the Washington, D.C. metropolitan area



Have you/your loved one ever been diagnosed as having an inborn error of metabolism (IEM)?

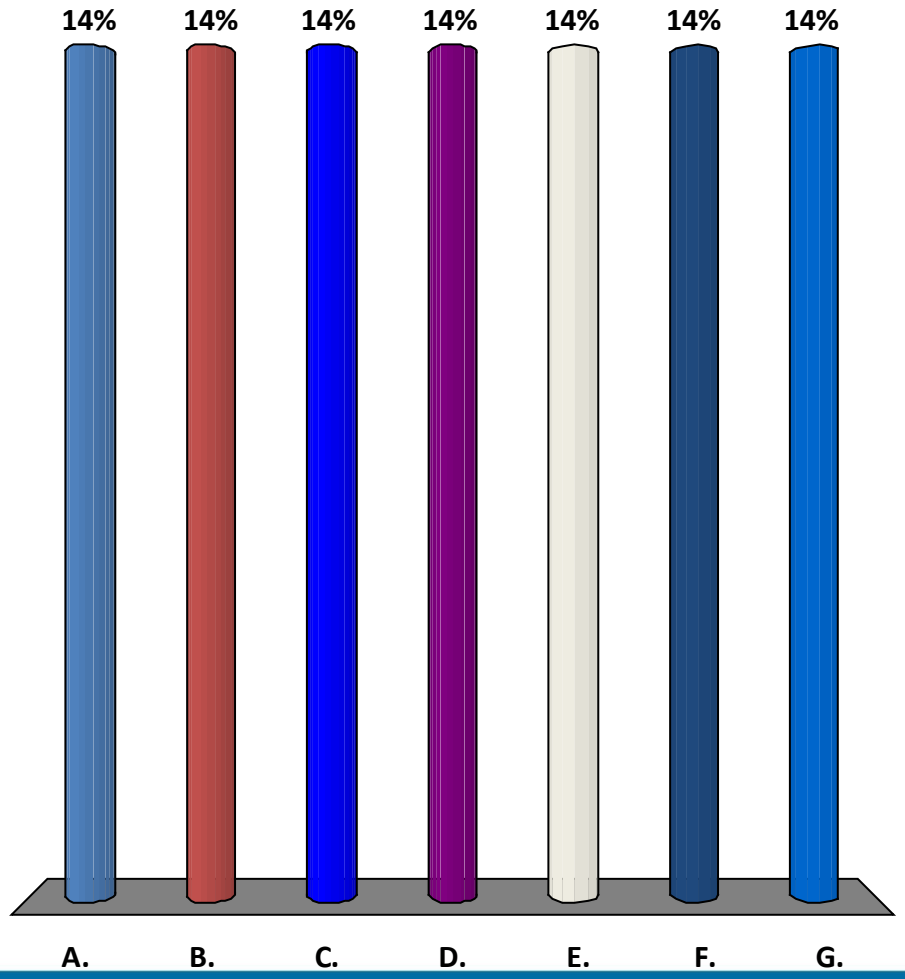
A. Yes

B. No



What is your/your loved ones age?

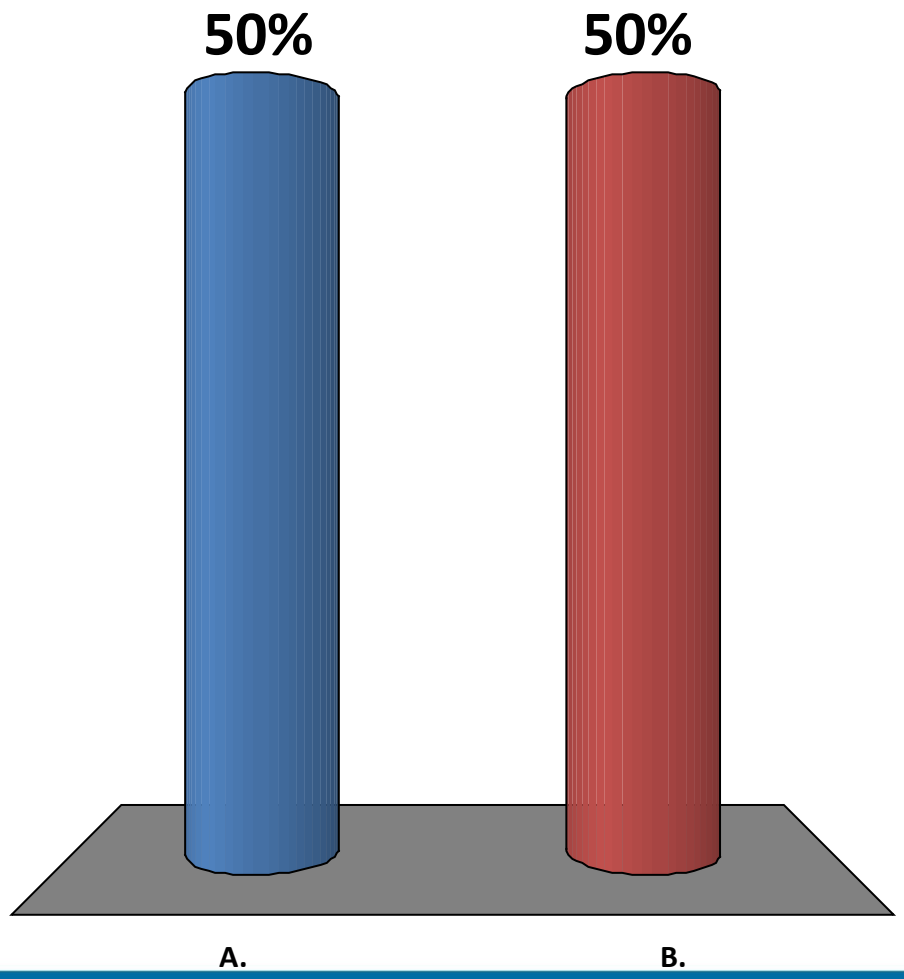
A. 0 – 2
B. 3 – 9
C. 10 – 17
D. 18 – 35
E. 34 – 49
F. 50 or greater
G. My loved one is deceased.



Are you/ Is your loved one:

A. Male

B. Female



Discussion Topic 1

Disease symptoms and daily impacts that matter most to patients

Sara Eggers
Facilitator

Topic 1 Panel Participants

- Whitnie Strauss
  - Child with creatine transport deficiency (CTD)
- Christine Brown
  - 2 children with phenylketonuria (PKU)
- Steve Holland
  - 3 children with mucopolysaccharidosis (MPS I)
- Melissa Bellini
  - Child with Gaucher Disease
- Tracy VanHoutan
  - 2 children with Batten Disease

Reid, age 4

CTD

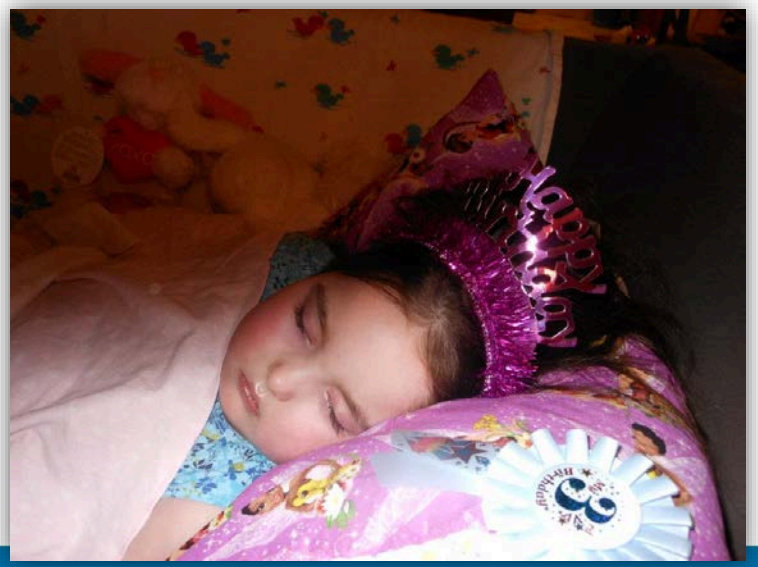
Connor, age 8
Kellen, age 6

PKU

Laynie, Spencer, and Maddie

MPS I

Olivia Bellini- Gauchers Disease 2/3
March 2 2009- March 4 2012



Noah, age 10
Laine, age 8

Batten

Topic 1 Discussion: Disease symptoms and daily impacts that matter most to patients

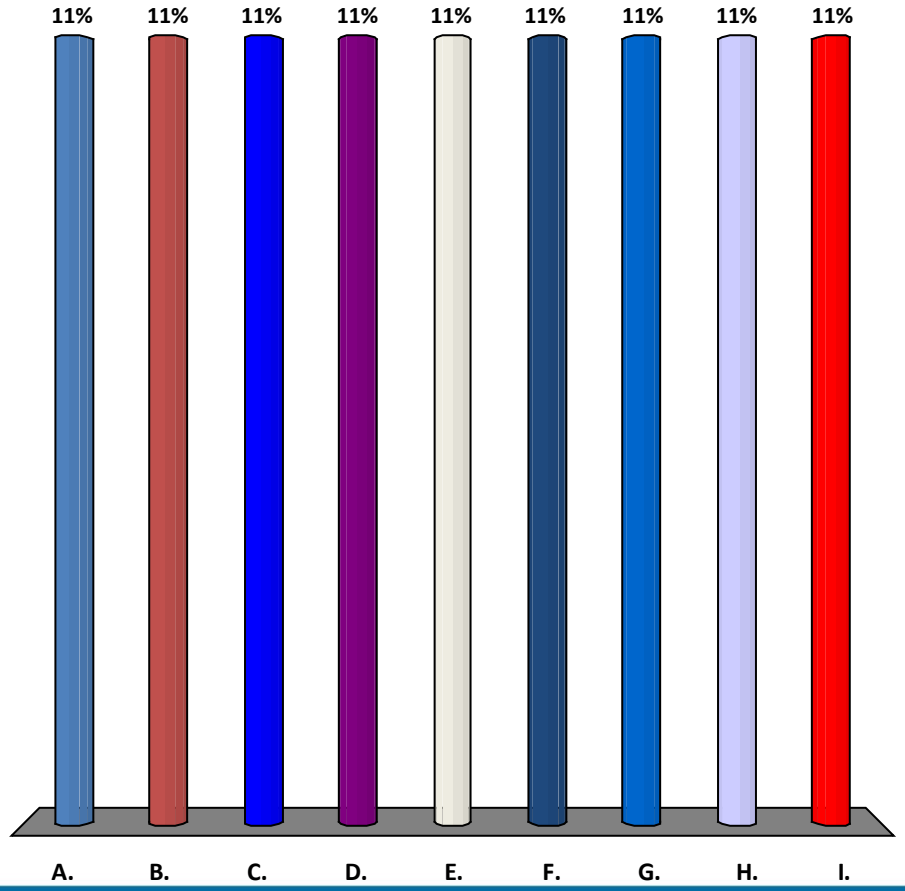
- Of all the symptoms that you/your child experiences because of your condition, which 1-3 neurologic signs and/or symptoms have the most significant impact on your/your child's life?

- Are there specific activities that are important to you/your child but that you/your child cannot do because of these neurologic signs or symptoms?

- How have your/your child's neurologic signs or symptoms changed over time?

Which of the following symptoms currently have a significant impact on you/your loved ones life? Choose all that apply.

A. Motor deficits (such as weakness, spasticity, walking problems)
B. Balance or coordination problems
C. Seizures
D. Sensory impairment (such as vision or hearing loss)
E. Impaired cognition or developmental delay
F. Behavioral problems (such as hyperactivity, hypersensitivity or aggression)
G. Bowel or bladder problems
H. Pain, such as headaches, nerve pain, or abdominal pain
I. Others, not mentioned



Topic 1 Discussion: Disease symptoms and daily impacts that matter most to patients

- Of all the symptoms that you/your child experiences because of your condition, which 1-3 neurologic signs and/or symptoms have the most significant impact on your/your child's life?

- Are there specific activities that are important to you/your child but that you/your child cannot do because of these neurologic signs or symptoms?

- How have your/your child's neurologic signs or symptoms changed over time?

BREAK

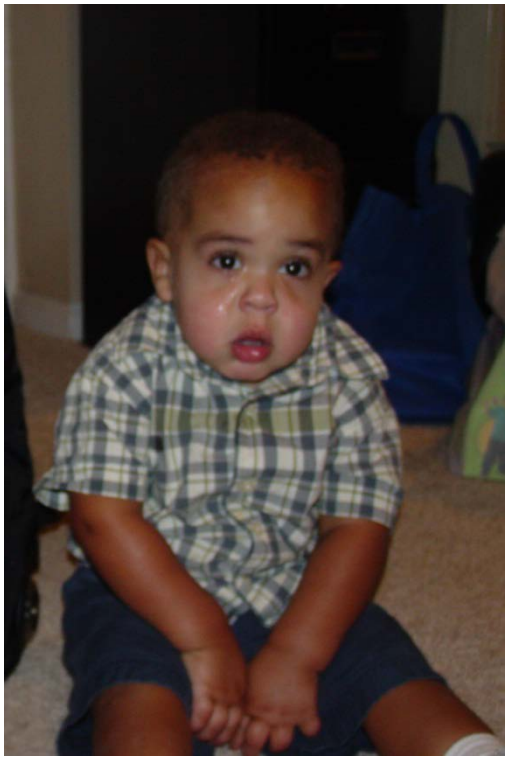
Discussion Topic 2

Patients' perspectives on current approaches to treating inborn errors of metabolism

Sara Eggers
Facilitator

Topic 2 Panel Participants

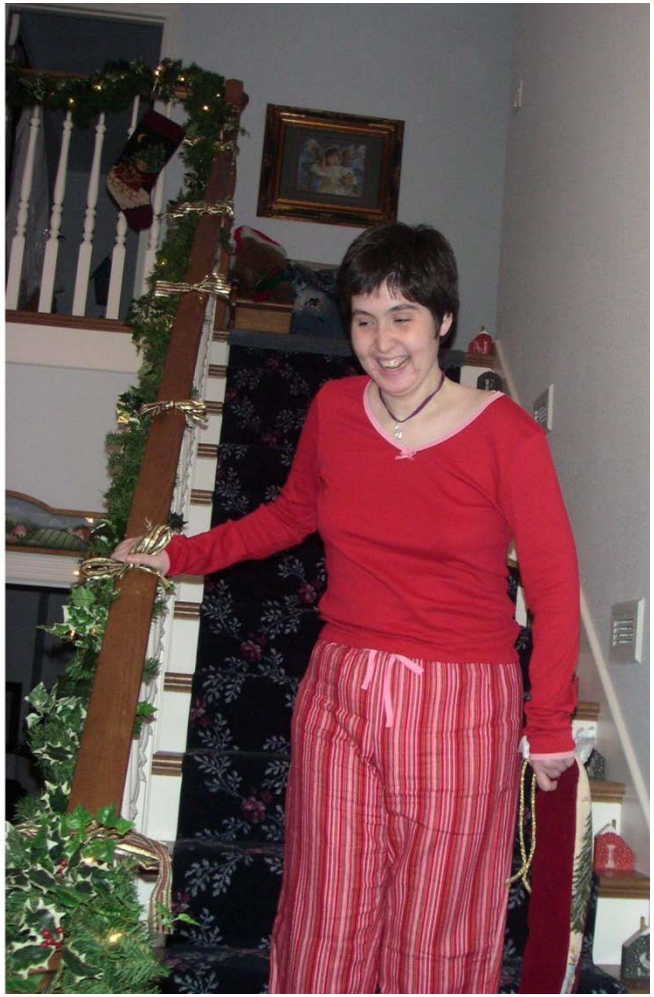
- Melissa Hogan
  - Child with Mucopolysaccharidosis (MPS II)
- Dean Suhr
  - 2 children with Metachromatic Leukodystrophy (MLD)
- Jennifer Payne
  - Phenylketonuria (PKU)
- Roy Zeighama
  - Child with Mucopolysaccharidosis (MPS IIIa)
- Andrea Smith
  - Child with Mitochondrial IEM



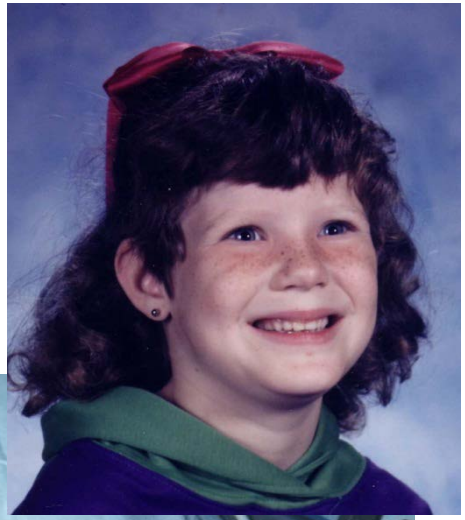
Case, age 7

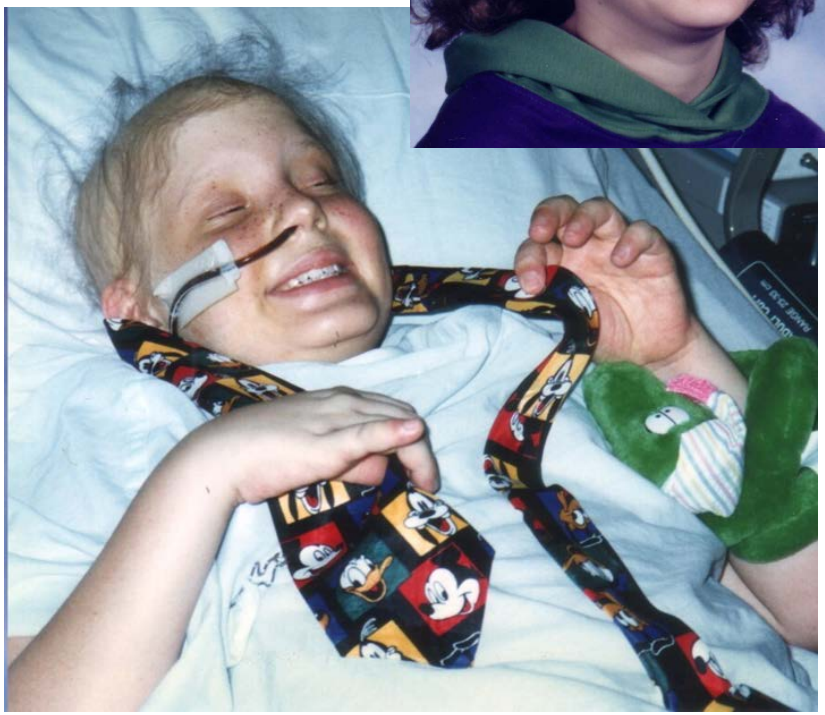
MPS II

Lindy
MLD



Darcee
MLD





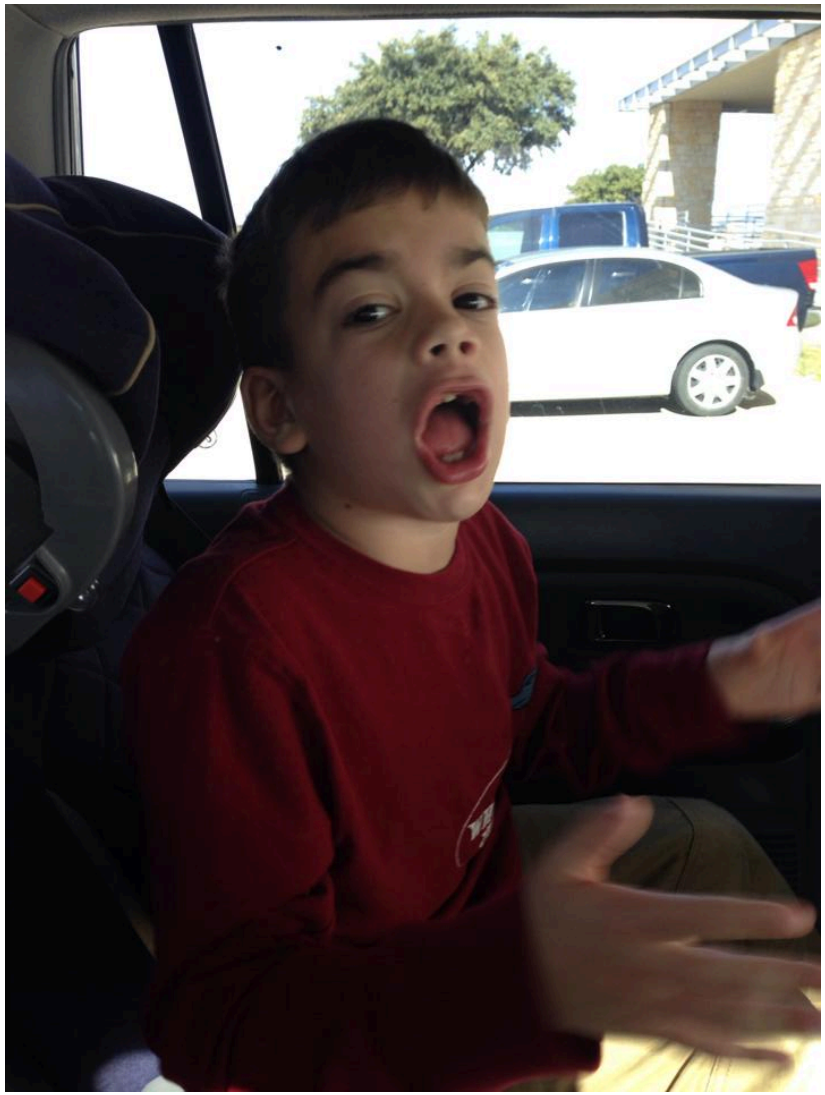
Jennifer

PKU

PKU, if untreated

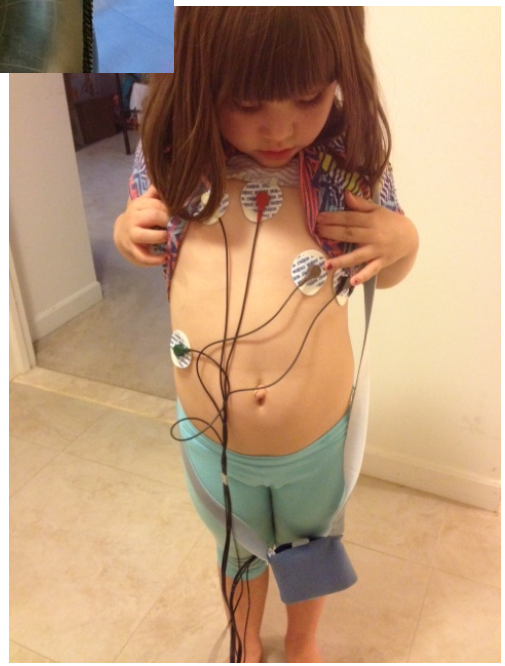
PKU, if treated

My Oldest Child, DOB 2004



Reed, age 6

MPS IIIA



Katie, age 6

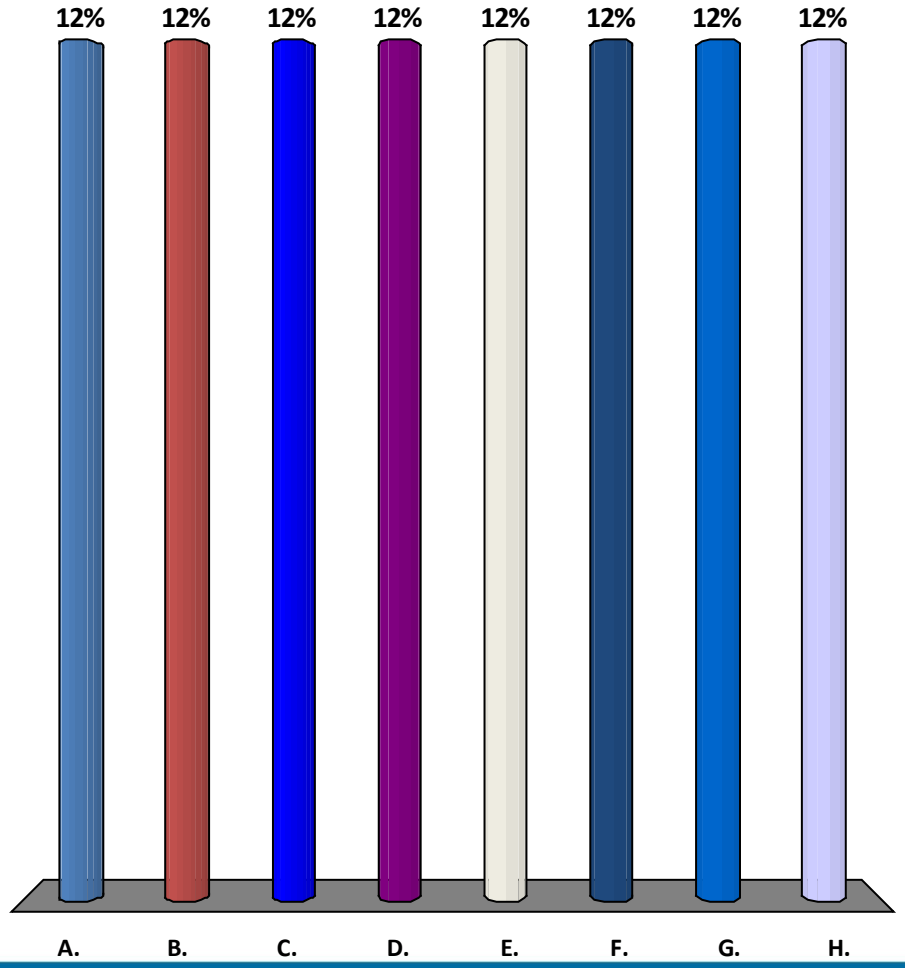
ATP/Mitochrondia

Topic 2 Discussion: Patients' perspectives on current approaches to treating inborn errors of metabolism

- What are you/your child currently doing to help treat the condition or its signs/symptoms?
- How well does this current treatment regimen treat the neurological symptoms of your/your child's disease?
- What specific things would you look for in an ideal treatment for the condition?
- In the informed consent process, what are important considerations to take into account when the potential participant is a child?

What therapies have you used to manage your/your loved one's condition? Check all that apply.

A. Dietary restrictions, dietary supplementation or medical foods
B. Enzyme Replacement Therapies, such as Elaprase or Naglazyme
C. Bone marrow or organ transplantation
D. Other prescription medications, such as anticonvulsants or psychiatric medications
E. Non-drug treatments, such as dialysis, gastrostomy tubes or splinting/bracing
F. Use of assistive technology, such as wheelchairs, walkers or readers
G. Other therapies, such as behavioral, physical or occupational therapy
H. None of the above.

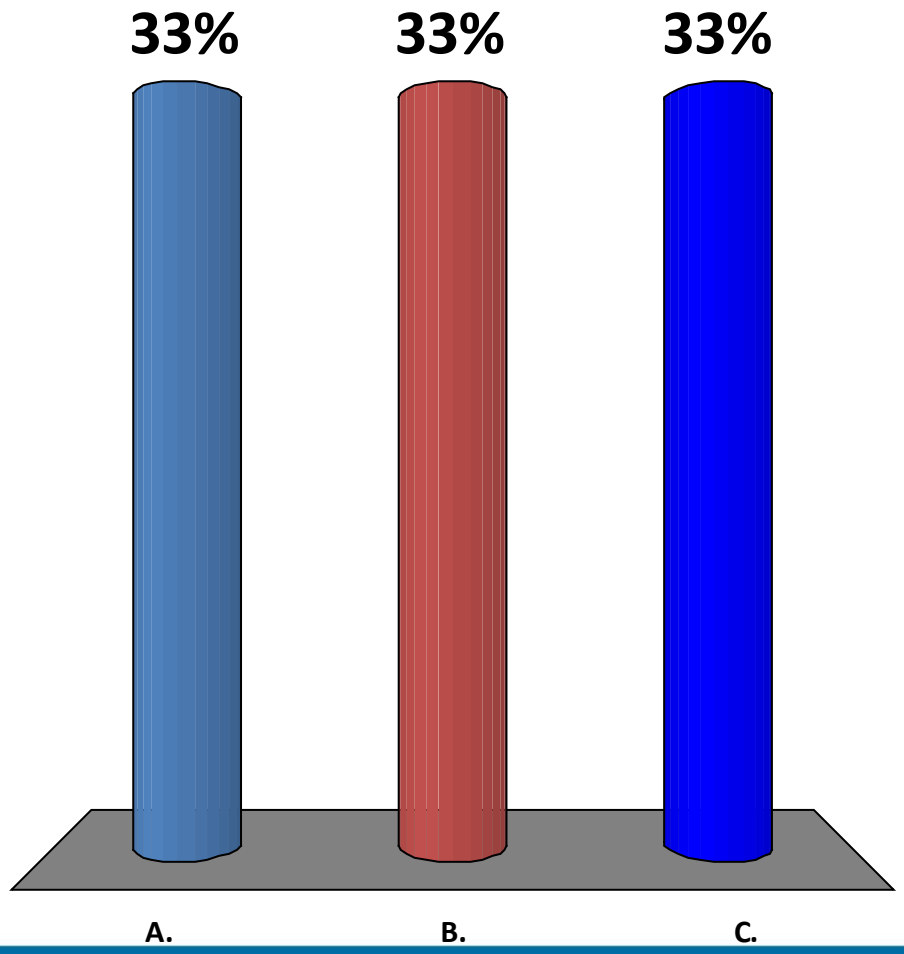


Topic 2 Discussion: Patients' perspectives on current approaches to treating inborn errors of metabolism

- What are you/your child currently doing to help treat the condition or its signs/symptoms?
- How well does this current treatment regimen treat the neurological symptoms of your/your child's disease?
- What specific things would you look for in an ideal treatment for the condition?
- In the informed consent process, what are important considerations to take into account when the potential participant is a child?

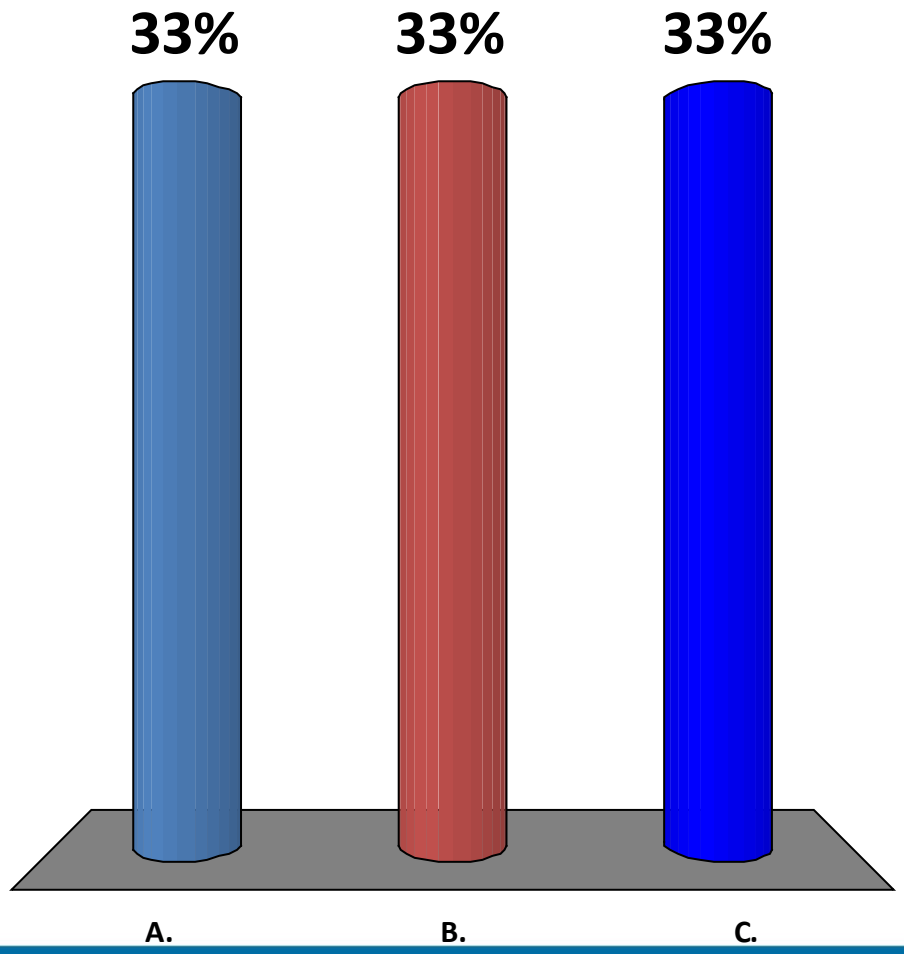
Have you /your loved one ever participated in any type of clinical trial studying experimental treatments for IEM?

A. Yes
B. No
C. I'm not sure



If you / your loved one (if you are the guardian) had the opportunity to participate in a clinical trial to study an experimental treatment, which of the following best describes your thoughts?

A. **Yes:** It would depend on many factors, but I am generally willing to consider participating
B. **No:** I would probably not consider participating
C. **Maybe:** I am not sure whether I would be generally willing to consider participating or not



Scenario for Discussion

- Imagine that you/your child had the opportunity to consider participating in a clinical trial for an experimental enzyme replacement therapy.

- This clinical trial is a Phase I first-in-human study involving approximately 10 patients.

- For this trial, there is less animal data available to evaluate safety than is typical for a first-in-human study of this type. The benefits and risks of this experimental treatment are highly uncertain.

What thoughts come to mind?

What questions would you have?

Open Public Comment Period

Closing Remarks

Teresa Buracchio, MD
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