NORD®
National Organization for Rare Disorders

FROM DIAGNOSIS TO DRIVING RESEARCH

From Diagnosis to Driving Research

P.J. Brooks, PhD

Program Director, Office of Rare Diseases Research

National Center for Advancing Translational Sciences (NCATS), NIH

Thousands of Rare Diseases, far fewer etiologies

- Two major types of monogenic diseases
  - Dominant
    - Gain of function
  - Recessive
    - Loss of function
- Limited number of mutation types
  - Nonsense mutations - premature stop codon
    -
  - Missense mutations → abnormal protein folding
    -
  - Abnormal RNA splicing

  - Dominant (gain of function) mutations

LABORATORY identifiers and contact information

GEN ***CRONYME HRF]***

ended name HRF)

Name of referring health care professional :
Date of receipt of the sample :

Subject: [*Family name, given name patient*]

Date of birth: --/--/----
Patient ID: [*internal ID*]
Type of sample: [*DNA/blood*]

Indication for testing:

Method: Method (sequencing, kit etc…) and extent of the screening (exons ---) of the [*HRF]* gene **(ref seq:** NM_XXXX.X). This allows identification of XX% of the known mutations.

Results: Two [type of the variants] were found
Mutations and genotype to be given using HGVS nomenclature

Mutations	DNA level	Protein level
1.	c.---	**p.---**
2.	c.---	**p.---**

Genotype:

p.[---];[---]	**if phased not allelic**
p.[---;---]	**if phased allelic**
p.[---(;)---]	**if not phased**

Interpretation:
XQ-Z syndrome

Recommendations: Genetic counseling is advised.

Date of report
Name of the molecular geneticist(s)

c.2047C > T r.2047c > u p.Arg683X

Nonsense mutation - premature stop codon

c.2612T > C r.2612u > c p.Leu871Pro

Missense mutation → abnormal protein folding?

c.2599–26A > G r.2598_2599ins2599-25_2599-1 = partial insertion of intron 13 p.Met867ThrfsX14

Abnormal RNA splicing

National Center for Advancing Translational Sciences

Thousands of Rare Diseases, far fewer etiologies

- Biochemical signaling pathway defects ("signalopathies")
  - mTOR
  - RAS
  - Tau
  - Ubiquitin
  - TRPV4
  - PIK3CA
  - Interferon
  - MHC-I
  - TGF-beta
  - Synuclein
  - SHANK3
  - TRAPPC11
  - Valosin-containing Protein

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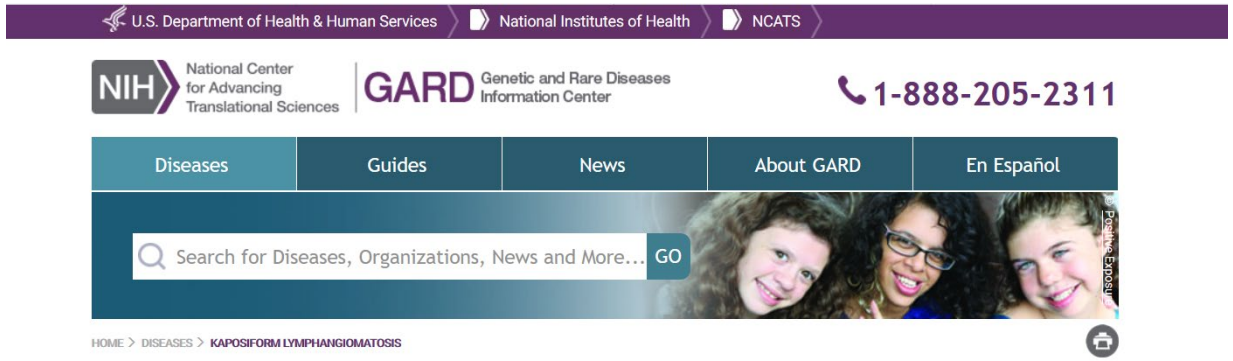

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NRAS-opathy

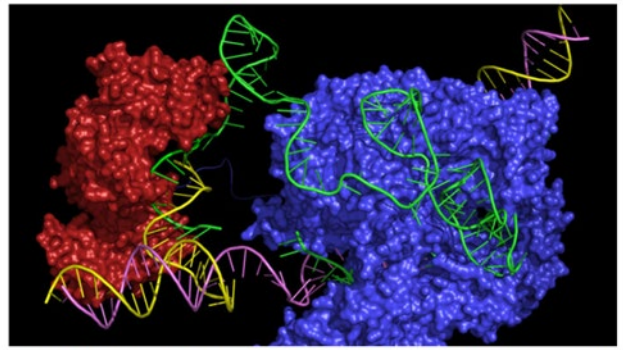
nature

Article | Published: 21 October 2019

Search-and-replace genome editing without double-strand breaks or donor DNA

Andrew V. Anzalone, Peyton B. Randolph, Jessie R. Davis, Alexander A. Sousa, Luke W. Koblan, Jonathan M. Levy, Peter J. Chen, Christopher Wilson, Gregory A. Newby, Aditya Raguram & David R. Liu

Nature **576**, 149–157(2019) | Cite this article



A new way to modify DNA, "prime editor" couples two enzymes, Cas9 (blue) and reverse transcriptase (red), to a guide RNA (green) that takes the complex to a specific place on DNA's double helix (yellow and purple) and also holds the code for an insertion of new DNA at that spot. PEYTON RANDOLPH

New 'prime' genome editor could surpass CRISPR

By Jon Cohen | Oct. 21, 2019 , 11:00 AM

doi:10.1126/science.aaz9297

"Prime editing substantially expands the scope and capabilities of genome editing, and in principle could correct up to 89% of known genetic variants associated with human diseases."

Key points

- Genetic diagnosis more than a disease
  - Mutations and other information matters
- Engage researchers, including disease experts and bench scientists, in considering pathways to clinical trials and therapeutic options

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National Center for Advancing Translational Sciences

A Pilot Natural History Study of Rare Disease: The Metachromatic Leukodystrophy Study

Martin Ho

Associate Director

Office of Biostatistics & Epidemiology

Center for Biologics Evaluation & Research, FDA

April 28, 2021

Disclaimer

This presentation is an informal communication and represents my own best judgment.

These comments do not bind or obligate the FDA.

Randomized Clinical Trial (RCT) vs. Natural History Study (NHS)

- A NHS follows a group of people over time who have, or are at risk of developing, a specific medical condition or disease to provide understanding on how the medical condition or disease develops and how to treat it.*
- Gaps between RCT and NHS
  a) Biases & confounders: randomized vs. observational
  b) Data quality: regulated vs. not regulated
  c) Study population: homogeneous vs. heterogeneous

* Source: The National Cancer Institute Dictionary of Cancer Terms (go.usa.gov/xvvXb)

The Natural History Of Metachromatic Leukodystrophy Study

NORD National Organization for Rare Disorders

FDA

rarediseases.org/mld-home-study

#leukodstrophy #mld

Let's Upgrade Traditional NHS

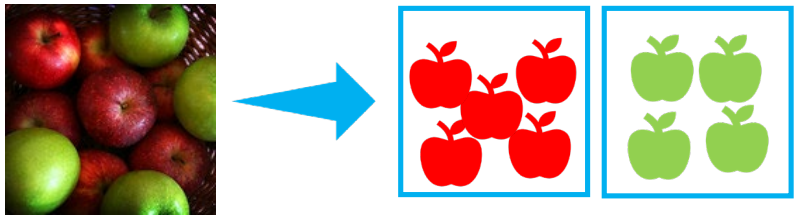
1. Prevent attrition & missing data

- Site-less: Reduce patients' burdens
- Mobile app: Timely data entry
- Tablets: Video outcome assessment



3. Mitigate biases & confounders

- Matching: Comparing "apple to apple"
- With sufficient data, a NHS can augment control groups of multiple RCTs in the future.



2. Relevant design, high-quality study

- Multi-stakeholder approach throughout the entire study life cycle
- Patients & caregivers, patient groups, physicians, industry, regulators

Picture source: NORD

Questions and/or comments?

martin.ho@fda.hhs.gov

A Non-Profit's Role in Rare Disease Research

KrabbeConnect
CONNECTING PATIENTS & RESEARCH

My Disclosures

Board Director of The Legacy of Angels Foundation

Krabbe disease

- Also known as Globoid Cell Leukodystrophy.
- Krabbe disease is described as a severe neurological condition that results from the loss of the protective covering (myelin sheath) surrounding nerve cells.
- This protective myelin sheath is essential to insulate the nerves and ensure the rapid transmission of nerve signals throughout the body.
- Individuals affected by Krabbe disease do not make enough of a specific lysosomal enzyme called galactocerebrosidase (GALC).
- Patients affected often live a shortened life.

Our Role….

- Work to ensure the needs of Krabbe patients are being voiced
- Help to improve science and institutes data sharing
- Provide educational videos and continuing education courses
- Fill gaps in research
- Be a resource for clinical trial opportunities

Two KrabbeConnect Initiatives

Assess the Burden of Krabbe Disease → Patient-Focused Drug Development Meeting with the FDA

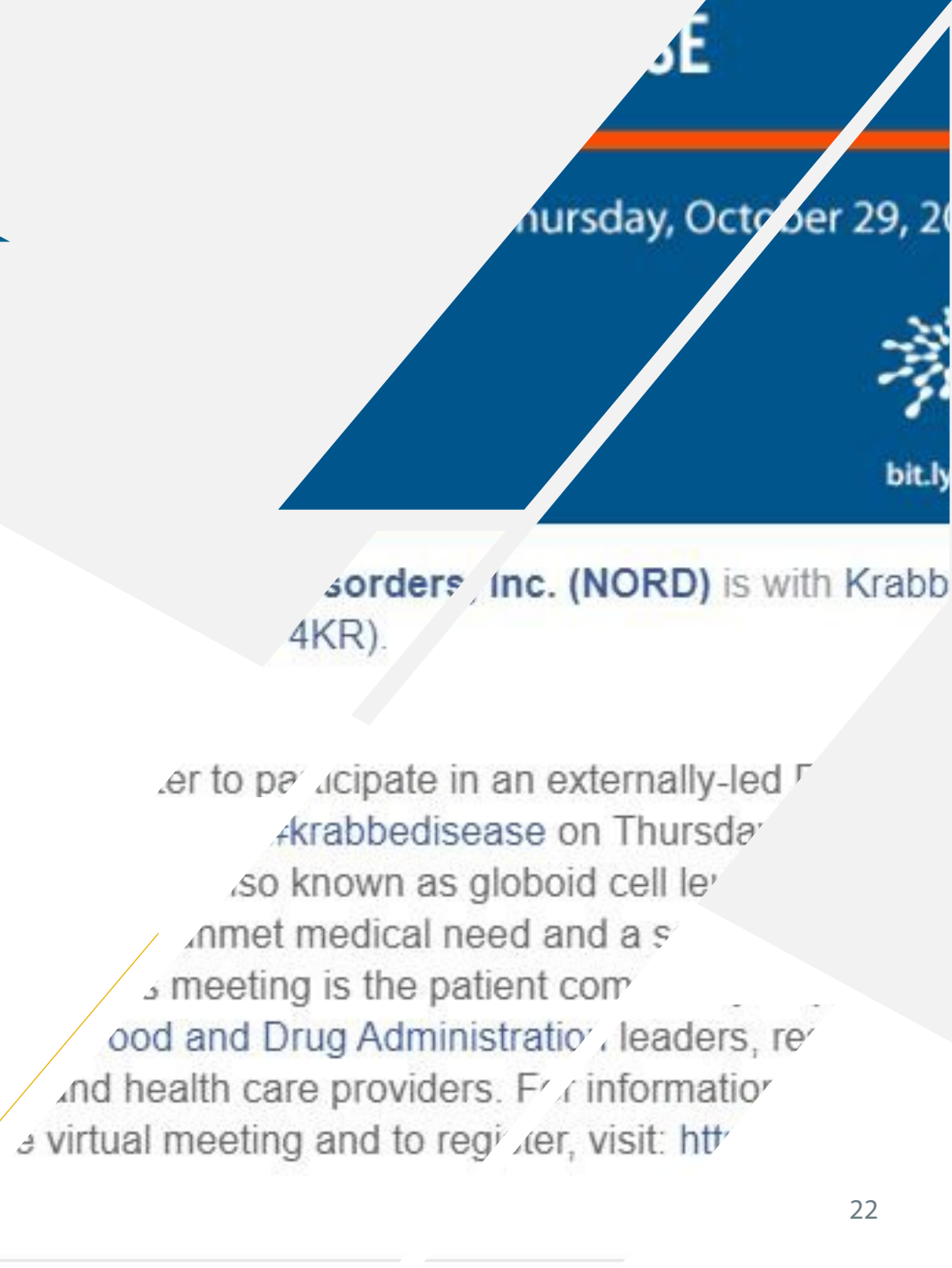
New Insights and Info to Researchers and Pharma → KrabbeCURES

Identifying the Need for a PFDD

- Ensure researchers, drug developers and the Food and Drug Administration (FDA) have a robust understanding of patients' and caregivers' experiences with the disease.
- Provided an avenue for individuals with Krabbe disease and/or their caregivers to voice their view on quality of life (with transplant and without).
- Keep all attuned to what aspects of the disease are most problematic for patients, and what actions patients and caregivers utilize to treat and cope with this disease (burden of the disease).

Stronger Together

- Spent three months researching our options for executing a PFDD
- A large expense ranging from $50,000 -$100,000 to organize and complete
- Board voted to utilize **NORD** for three reasons-
  - They have a strong relationship with the FDA
  - They're a neutral party. A few organizations in Krabbe disease and we wanted all to come together.
  - They truly care about assisting the goals of the rare disease community.



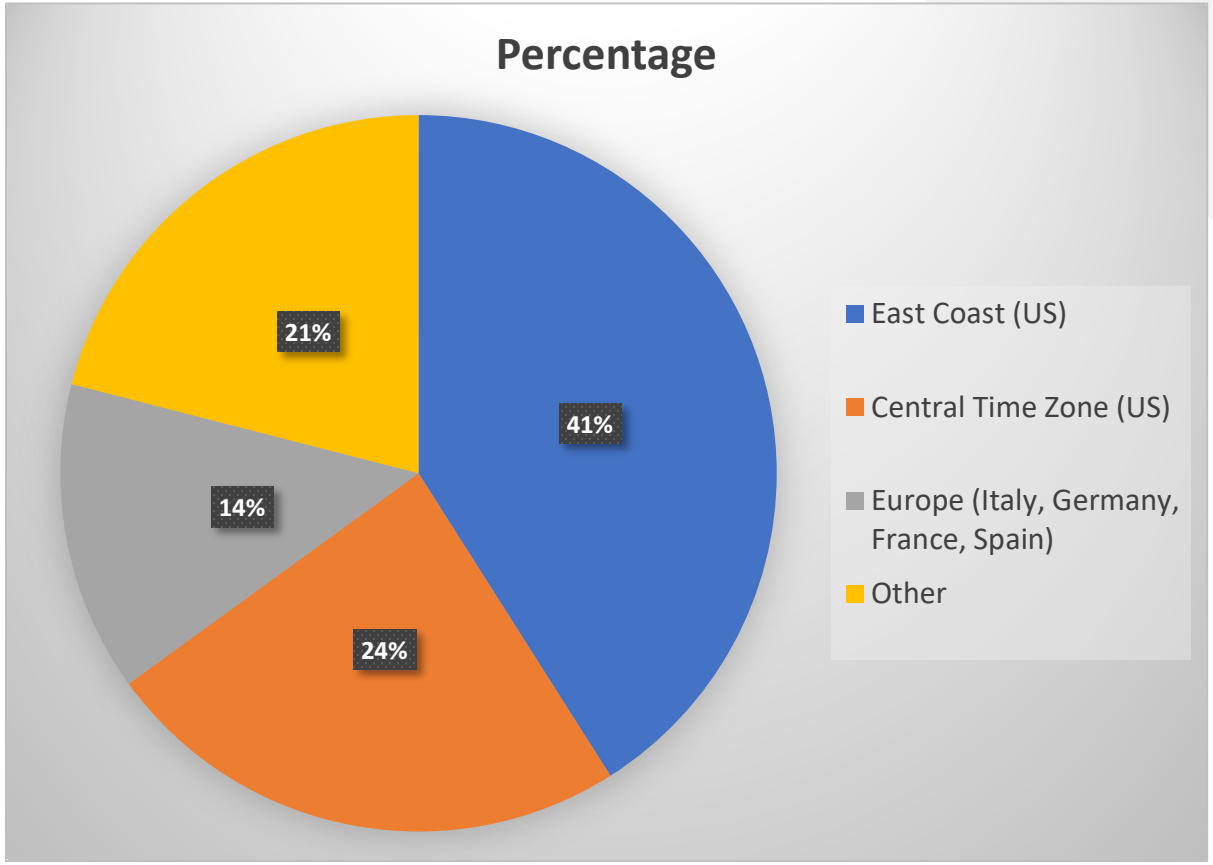
Overview-a year of work!

Overview of Milestones	Date Completed
Research and Negotiation of Vendor	8/2019-11/19/2019
Invitation to collaborate/Request for Letters of Support	Dec 9th, 2019
KrabbeConnect/NORD Press Release on PFDD Initiative	Dec 17th, 2019
Letter of Intent to FDA	January 6th, 2020
Confirmation of Meeting with FDA	March 1st, 2020
Develop Sponsor Plan	March 1, 2020
Develop Social Media Plan	March-August 2020
Develop Website Content to Inform of PFDD	March
Execute Speaker Recruitment	March-August 2020
Conduct Webinar on PFDD-Educate Community Further	June 16th, 2020
Conduct Speaker Workshop	August/September 2020
PFDD Meeting goes LIVE	October 29th, 2020
PFDD Quality Survey	November 1, 2020

Meeting Participants

The Demographics

- Total of 173 participants
- More than half were patients and caregivers impacted by Krabbe disease
- Other category-from other parts of the US, Mexico, or other regions



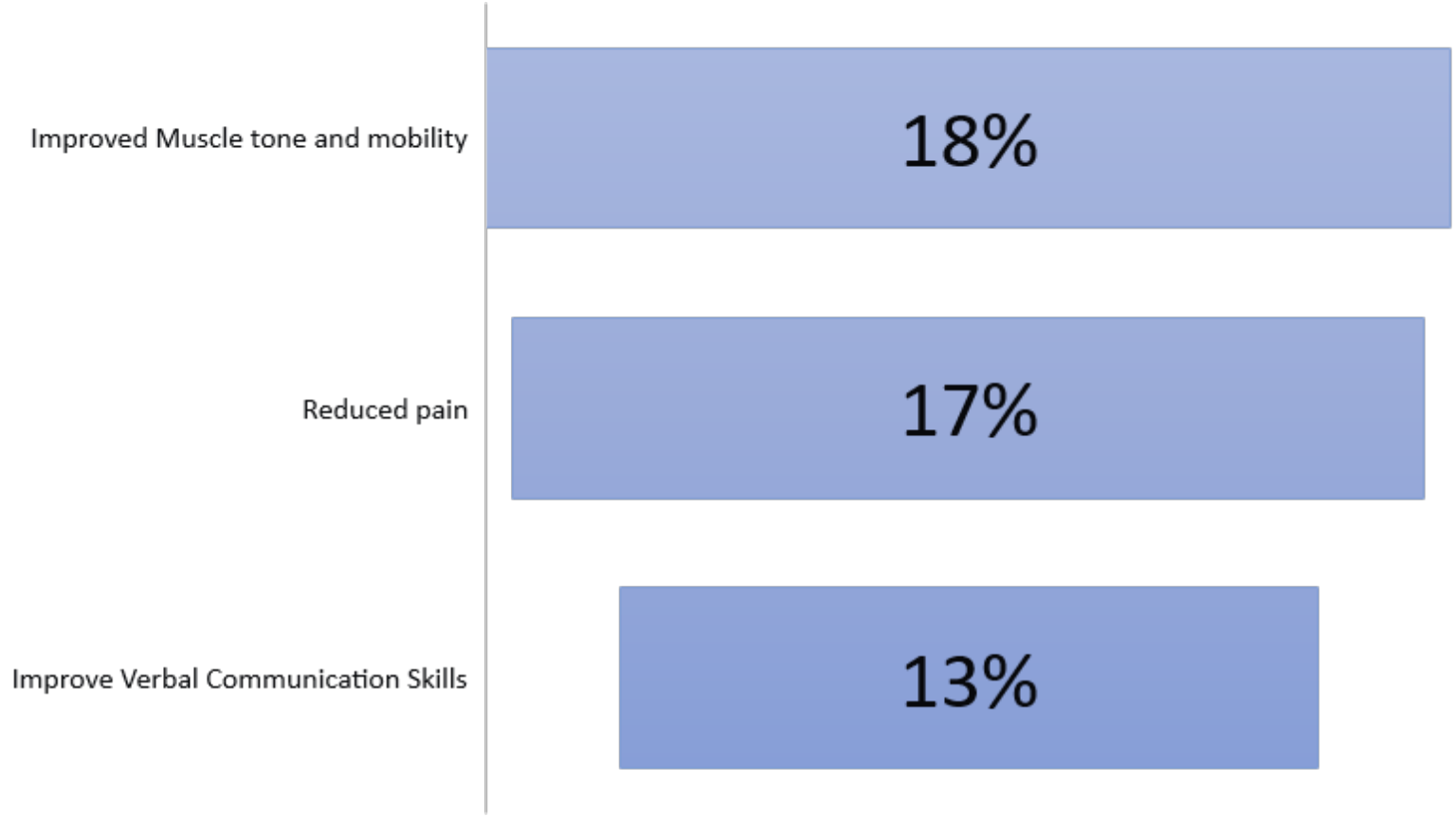
PFDD Topic 1: Living with Krabbe disease- Burden and Symptoms

The top difficulties with the disease:

A. Gastrointestinal issues- **12%**
B. Neurological difficulties- **12%**
C. Body Temperature Regulation and/or fever-**11%**
D. Respiratory Infection-**10%**
E. Peripheral Nerve Disease- **9%**
F. Apnea- **9%**

PFDD Topic 2:
Current & Future Therapies

Short of a cure, what specific things would you look for in an ideal treatment. The top 3 are as follows:



PFDD Topic 2:
Current & Future Therapies

Without considering side effects, which one of the following would be most important to you in a future Krabbe disease therapy?

73%-a drug that <u>does not</u> extend life, but will reduce the severity of symptoms

PFDD Data Collection Mechanisms

I. **The Speakers:**
   a. Collected interest through phone calls, emails and social media
   b. All candidates screened by way of the PFDD committee.
   c. Lots of interest, not easy narrowing the selection of candidates down

II. **Polling Questions:**
   a. Patient stories and experiences organically formed many of the questions
   b. PFDD committee, and medical experts reviewed and refined questions
   c. NORD reviewed to ensure they worked in the poll software technology such a question length and number of answers for options.

II. **PFDD Comments:**
   a. Meeting was set up to have an open question submission
   b. All submissions integrated into the report

IV. **Live Q&A**
   a. NORD selected the most appropriate questions with the assistance of Krabbe disease leaders across the nonprofit organizations

The Report

Now Available-MARCH 2021

VOICE OF THE PATIENT REPORT: KRABBE DISEASE

Externally-Led Patient-Focused Drug Development Meeting

Meeting Date: October 29, 2020
Report Date: TBD

KrabbeCURES

KrabbeCURES

Fill Gaps in Research to #curekrabbe

JOIN THE KRABBE COMMUNITY UNITED RESEARCH ENGAGEMENT STUDY TODAY!

KC

Aims of KrabbeCURES

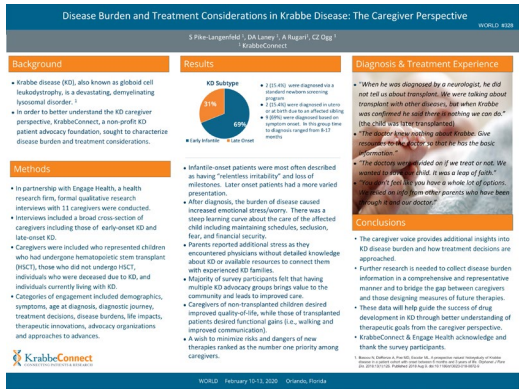
- Understand the burden of Krabbe disease
- Provide a convenient online platform for participants (or caregivers) to self-report cases of globoid cell leukodystrophy (Krabbe disease).
- Characterize and describe the globoid cell leukodystrophy population as a whole, enhancing the understanding of disease prevalence and phenotype as well as the rate of progression of disease characteristics.
- Develop a communications study within KrabbeCURES (e.g., to notify patients of research studies and clinical trials).
- Assist the globoid cell leukodystrophy community with the development of recommendations and standards of care.
- Be a case-finding resource to be used for researchers who seek to study the pathophysiology of Krabbe disease, retrospectively collate intervention outcomes, and design prospective trials of novel treatments.

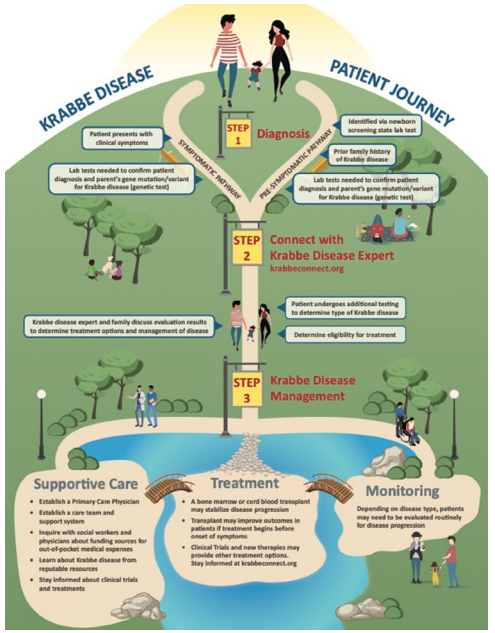
27 total participants since inception (8.1.2020)
24 of 27 consented to utilizing their data for research
Eight still need to completed surveys
16 fully completed surveys out of the 27 registered.

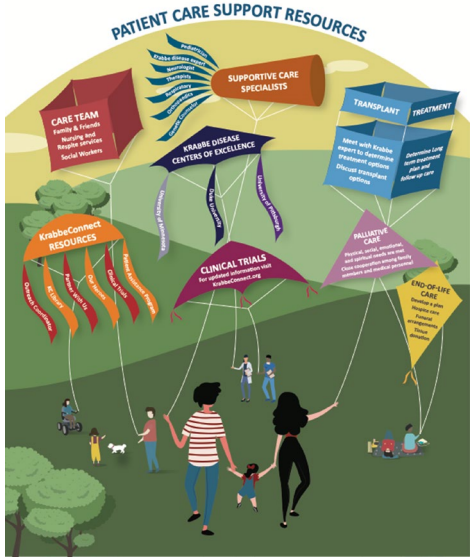
Other Projects

Completed through KrabbeConnect

- Disease Burden and Treatment Considerations in Krabbe Disease: The Caregiver Perspective
- Developed two maps to help families navigate Krabbe disease: (1) Krabbe disease patient journey and (2) Krabbe disease resources







Takeaways!

- Know the research happening in your disease space
- Form a working relationship with other nonprofits—working together will make you stronger
- Do what you can to help bring additional answers/insights to your disease space

Visit KrabbeConnect.org today!

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(612) 387-3424

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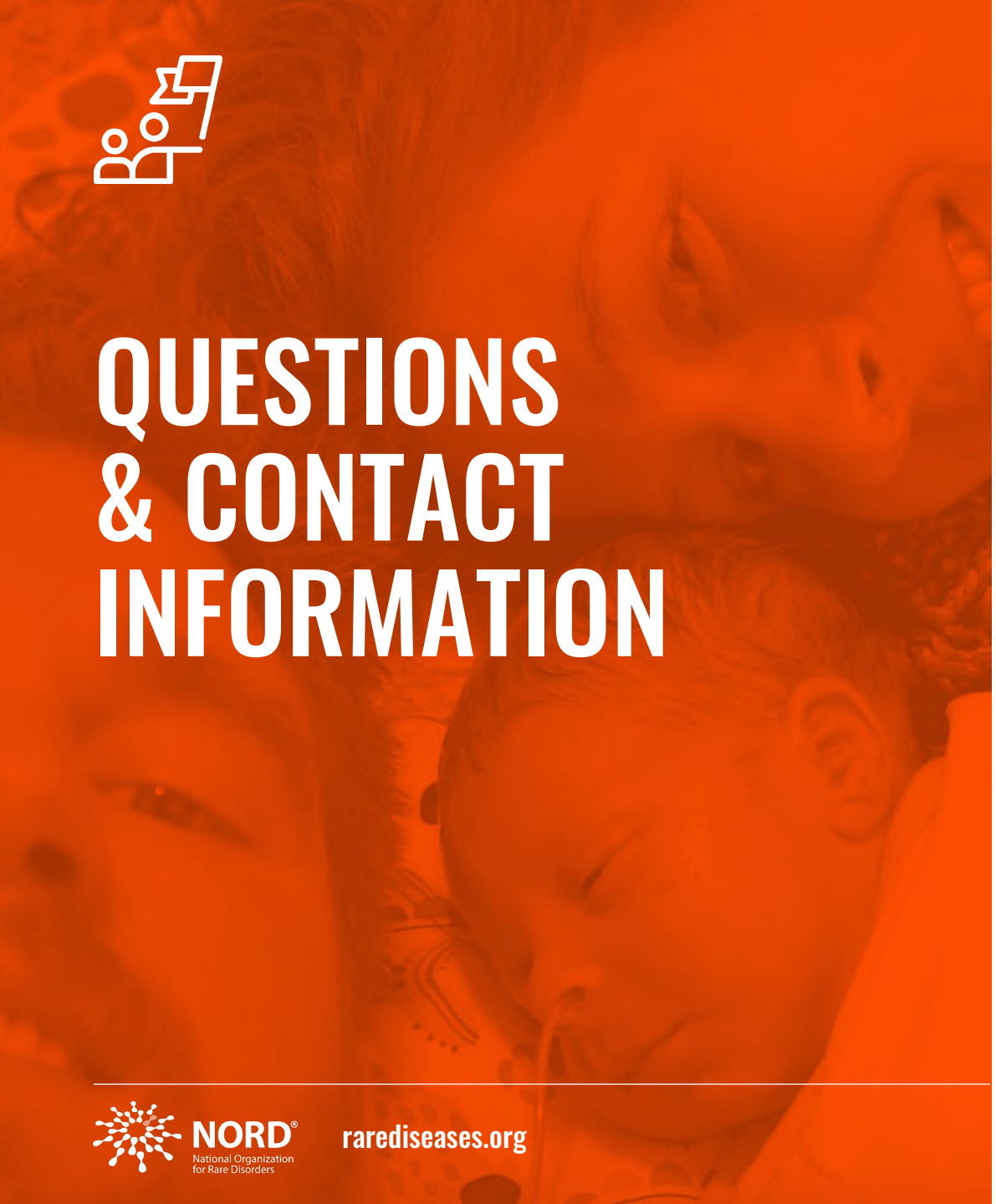

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Thank you.