LBSL Natural History Update

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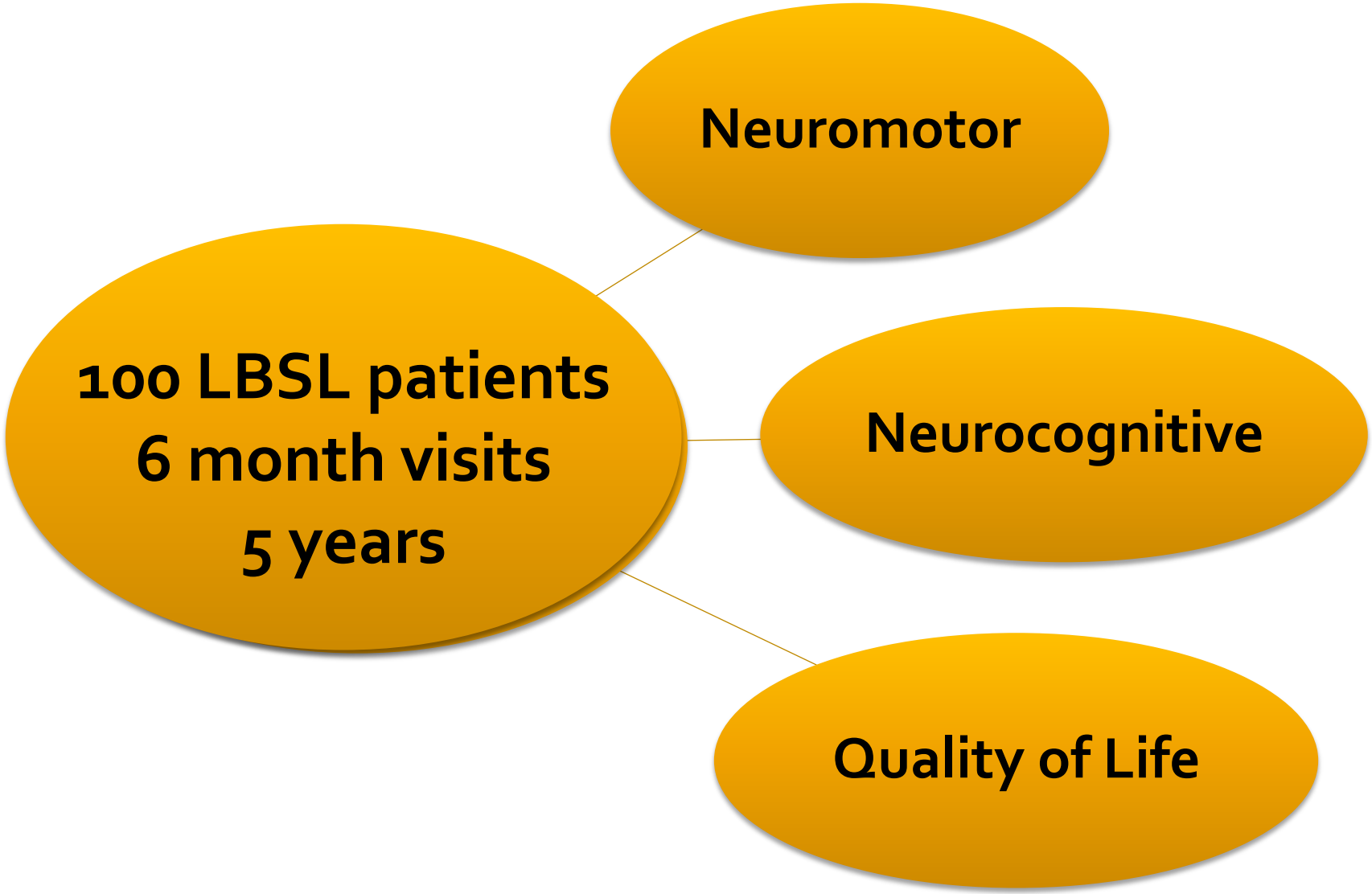
LBSL Summit at the Kennedy Krieger Institute
Baltimore, MD
April 19, 2018

Presenter Notes are in italics at the bottom right hand of the page

PART I

Role of the natural history study in rare genetic disease

What is a natural history study?



A natural history study involves the collection of health data repeatedly over time to understand symptoms of a disorder and how it progresses

This will provide a baseline understanding of disease symptoms and outcomes to compare results to when treatments are one day developed

Our LBSL natural history study aims to gather health data from 100 people with LBSL during virtual visits every 6 months over the next 5 years

Why start a natural history study of LBSL?

- We don't really know how LBSL progresses over time…
- We don't yet have a cure
- We don't yet have guidelines for care in LBSL

We have a limited understanding about how LBSL progresses over time for persons with onset in infancy, childhood and adulthood
We know enough to realize LBSL progression might look different for each group depending on age of symptom onset, which is the case for many other rare genetic disorders

No cure

We don't yet have clear guidelines about the type of care that children and adults with LBSL should receive in the meantime
Some important questions about management include
Are there non-medical therapies that can help slow disease progression or prevent complications?
Are there existing medical therapies that could slow disease progression?
Should we be monitoring persons with LBSL for subtle changes in cognition, attention or communication that could impact quality of life or experience in school?

Natural history study example

- **Friedreich's ataxia is a debilitating, life-shortening degenerative disorder**
  - Autosomal recessive inheritance
  - 1:100 are carriers and 1:50,000 affected in US
  - Onset of symptoms at 5 – 18 years of life, less common adult onset
  - The *FXN* gene decreases production of the mitochondrial protein frataxin
  - Eventual loss of the ability to walk and dependency for daily activities
- Younger age of onset → faster disease progression
- A simple clinical rating scale (SARA) accurately detects worsening ataxia
- They used a checklist of daily self-care activities to monitor changes in function
- They obtained calculations for the design of upcoming treatment trials

FARA Friedreich's Ataxia Research Alliance

Reetz et al 2016

Rare genetic disease research typically starts with a comprehensive natural history study and there many recent examples of success in rare genetic disorders

A disease that shares some similarities with the research goals we have in LBSL is Friedreich's ataxia.
Friedrich ataxia is…
A natural history study looking over 2 years found that…
Younger age at disease onset is a major predictor for faster disease progression
They found an accurate clinical rating scale to detect deterioration of ataxia symptoms
They found a simple, appropriate way to monitor changes in daily self-care activities (Scale for the assessment and rating of ataxia, the same as us)
They determined outcome measures and sample size calculations for the design of upcoming clinical trials

Frataxin discovered about 14 years ago

Clinic-based natural history studies

- Typically the studies are done in clinic or in a clinical research space
  - There are limitations in terms of recruitment, enrollment and retention
    - The National Institutes of Health (NIH) reports **40 to 60%** of medical studies fail to meet their target enrollment
    - A study at Tufts University found **11%** of trials fail to enroll even one patient and **37%** under-enroll

Dorsey 2015

Why are the participation rates so low?

A major reason for the low rate of participation is the need for frequent in-person visits and the resulting time and travel costs to the patient

Accurate and reliable natural history data are essential for future research

So how do we circumvent the barriers to participation?

Virtual natural history studies – an alternative

Dorsey 2015
Jadhav 2016

- Virtual clinical research is a newer phenomenon in the medical field
  - Telephone, video, apps, texting
  - Wearable technology
  - ↑ Participation
  - ↓ Burden on the participants
  - ↓ Variability

So how do we circumvent the barriers to participation?

One approach gaining popularity is to conduct virtual or remote studies In fact, assessment of clinical outcomes in neurology (e.g. for stroke) are increasingly captured remotely

The data for such studies is collected by phone apps, texting or even wearable technology

Pros and cons of a virtual trial in LBSL

What are your thoughts?

We hope this will mean participants' performance will be more representative of their actual ability

Any other pros you can think of?
We can more easily include participants who don't live near Kennedy Krieger
We will eliminate the expense, time and energy required to travel to Baltimore every few months
Performance on testing can vary based on comfort level in the office or lab, distractions in that setting, or time of day, which influences participant's level of fatigue and engagement
We can control more of these factors with the flexibility of testing at home
Participants' performance may be more representative of their actual ability
The process is cooperative and even fun!

PART II

Key questions and goals for ongoing research in LBSL

What do we hope to learn and achieve? Let's start by reviewing what we already know from the literature and we'll integrate the new questions as we go along

Brief LBSL literature review

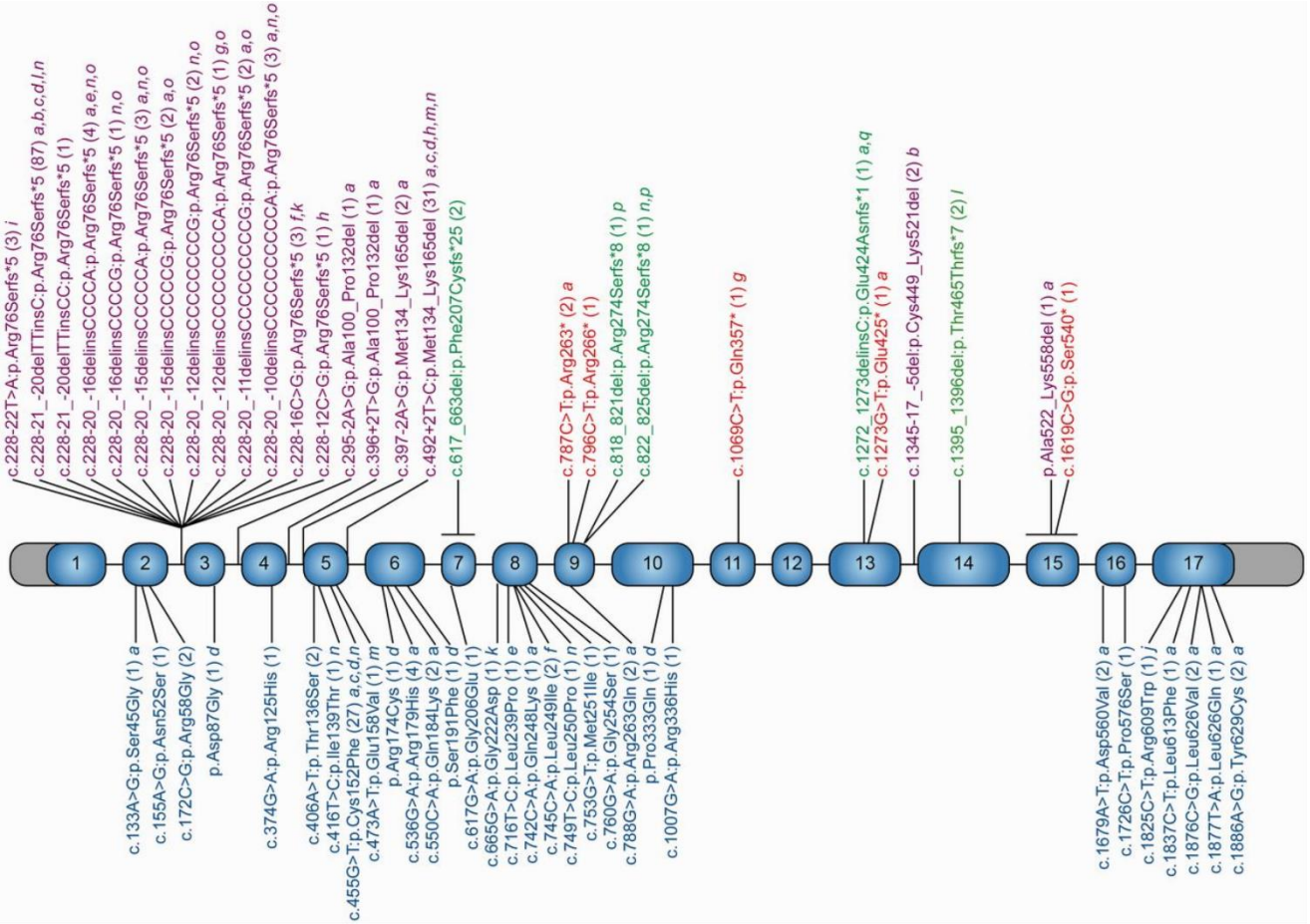
- There are 3 hallmarks of LBSL
  - *DARS2* mutations
  - MRI brain changes
  - Clinical characteristics

Per literature review there are 3 primary hallmarks of LBSL: DARS2 mutations, MRI brain features and clinical characteristics

We will go into each in more detail over the next few slides

What do the *DARS2* mutations look like?

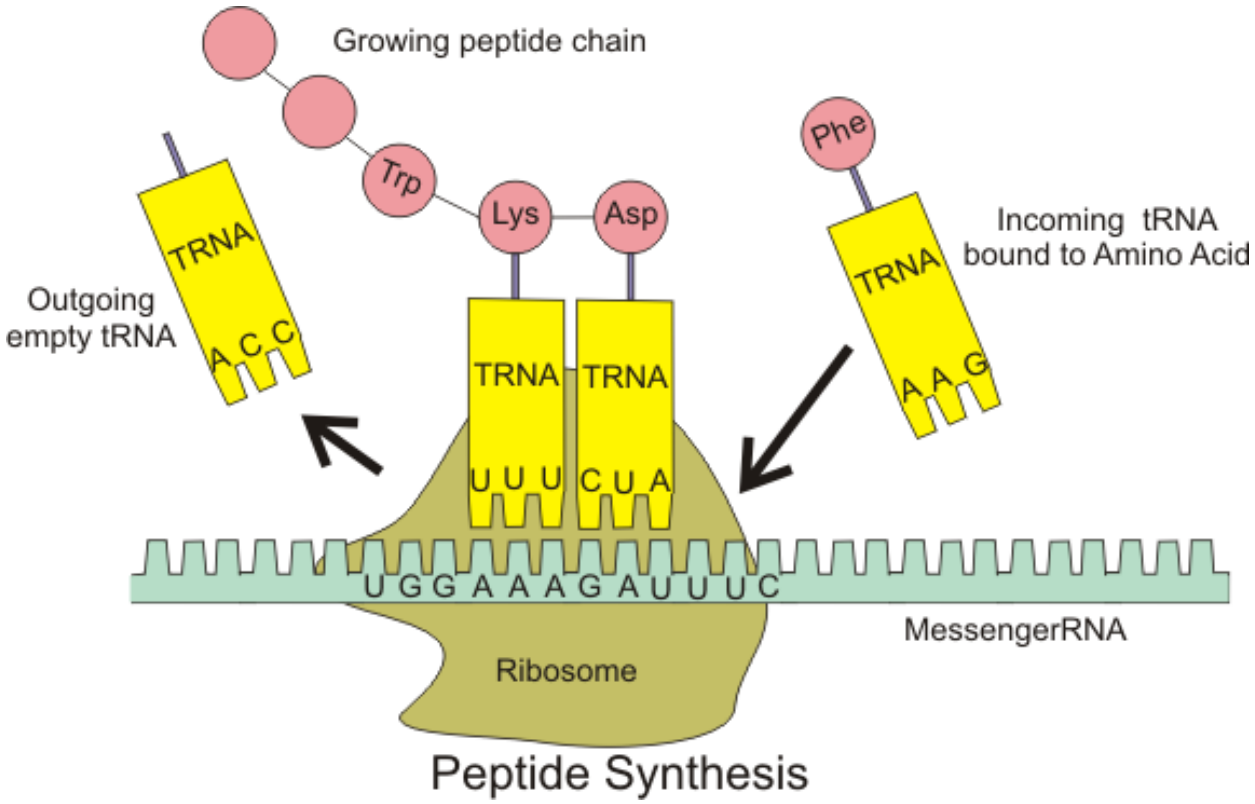
- Inheritance pattern is autosomal recessive van der Knaap et al 2010
- 60+ mutations van Berge et al 2014



What do the DARS2 mutations look like?
The inheritance pattern is autosomal recessive (MS van der Knaap 2010)
There are over 60 mutation!
This schematic is from a review of case reports as of 2014:
There are many kinds of mutations –
Splice site mutations are indicated in purple, missense mutations in blue, deletions in green, and nonsense mutations in red

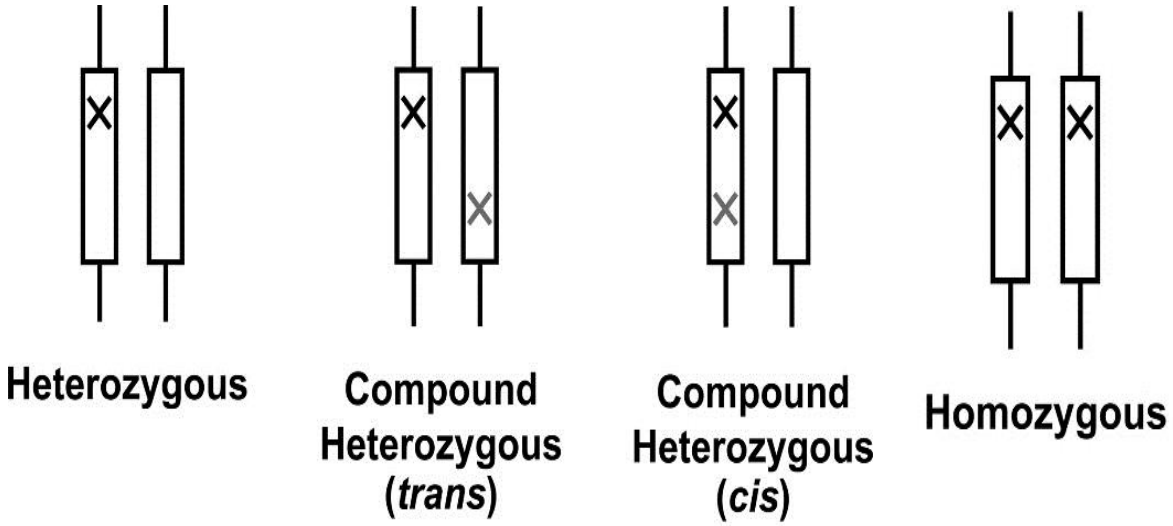
What do the *DARS2* mutations look like?

- *DARS2* encodes mitochondrial **aspartyl-tRNA synthetase**, the enzyme that attaches aspartate to the correct mitochondrial transfer RNA
  - Aspartyl-tRNA is necessary in the translation of mitochondrial messenger RNA into protein

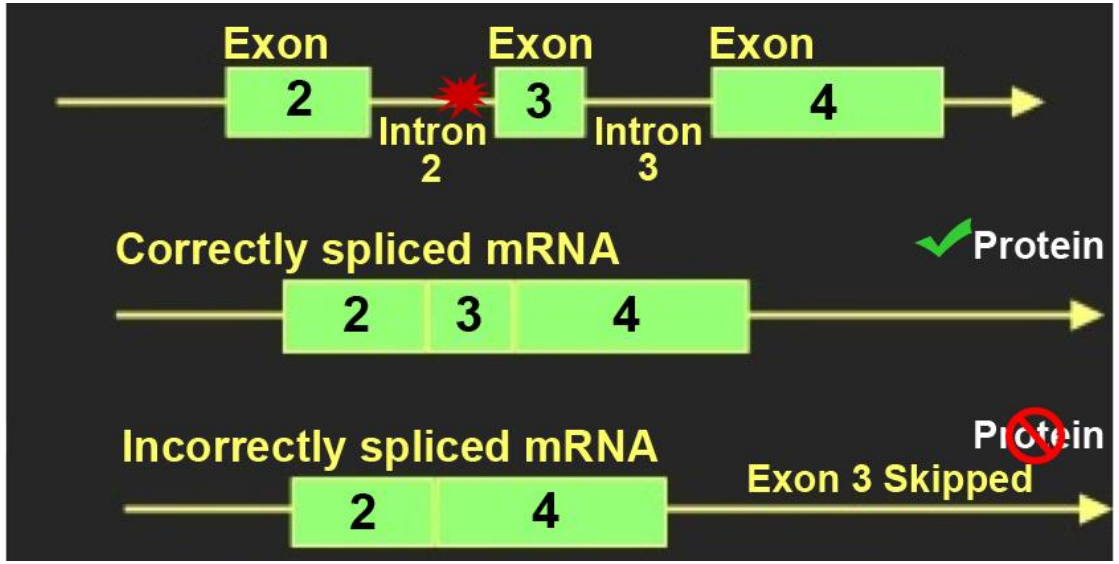


The amino acid aspartate

What do the *DARS2* mutations look like?



Scheper *et al*, 2007
Adapted from Van Berge *et al*, 2012



Strikingly, almost all patients are compound heterozygous for two DARS2 mutations, which means…
There are actually 2 different "hits" that have the combined effect of causing disease
One "hit" can be on the maternal and a different "hit on the paternal allele (trans) OR, both "hits" can be on the same allele
Homozygous means the same "hit" is on both the maternal and paternal allele
Heterozygous means there is only 1 "hit" on either allele –
to our knowledge these persons are completely unaffected by LBSL symptoms

One of the 2 mutations is almost invariably a splice site mutation in intron 2, upstream of exon 3
As a consequence of such a mutation, exon 3 is not included in the messenger RNA
This leads to a frameshift, premature stop and absence of functional protein
These splice site mutations are, however, 'leaky'
This means that for part of the mutated messenger RNAs, exon 3 is included, from which normal full-length protein is formed

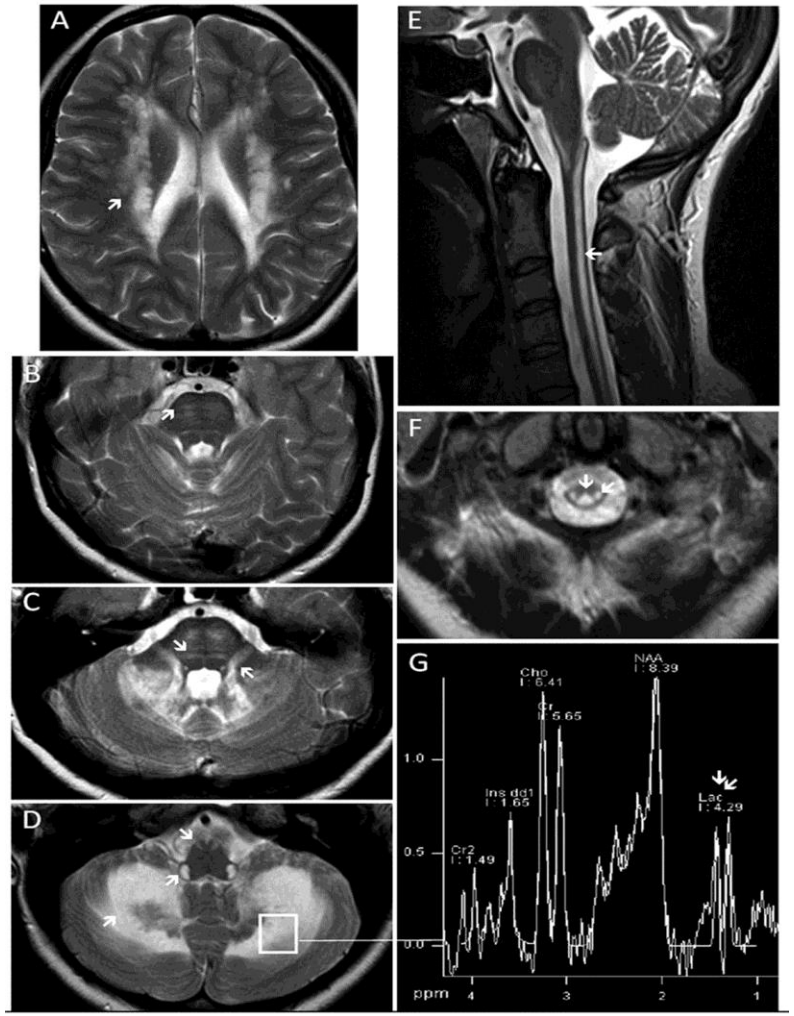
What do the *DARS2* mutations look like?

- A few patients have **homozygous** *DARS2* mutations
  - Are the clinical symptoms different for those with heterozygous vs. homozygous mutations?
  - Are the long-term outcomes different for these two groups?
- Do *DARS2* mutation carriers have subtle clinical symptoms?
  - Can start to answer via detailed family tree (pedigree) analysis

Although most LBSL cases are due to compound heterozygous DARS2 mutations,
at least 7 patients with homozygous DARS2 mutations have been reported
So, homozygous mutations do not necessary cause fetal demise
It will be important for us to know:
Are the clinical symptoms different for these two groups?
Are the long-term outcomes different for these two groups?

Also it is unclear of any of the individuals carrying only a single DARS2 mutation have subtle clinical symptoms
We can start to answer via detailed family tree (pedigree) analysis

What does the MRI brain and spinal cord look like?



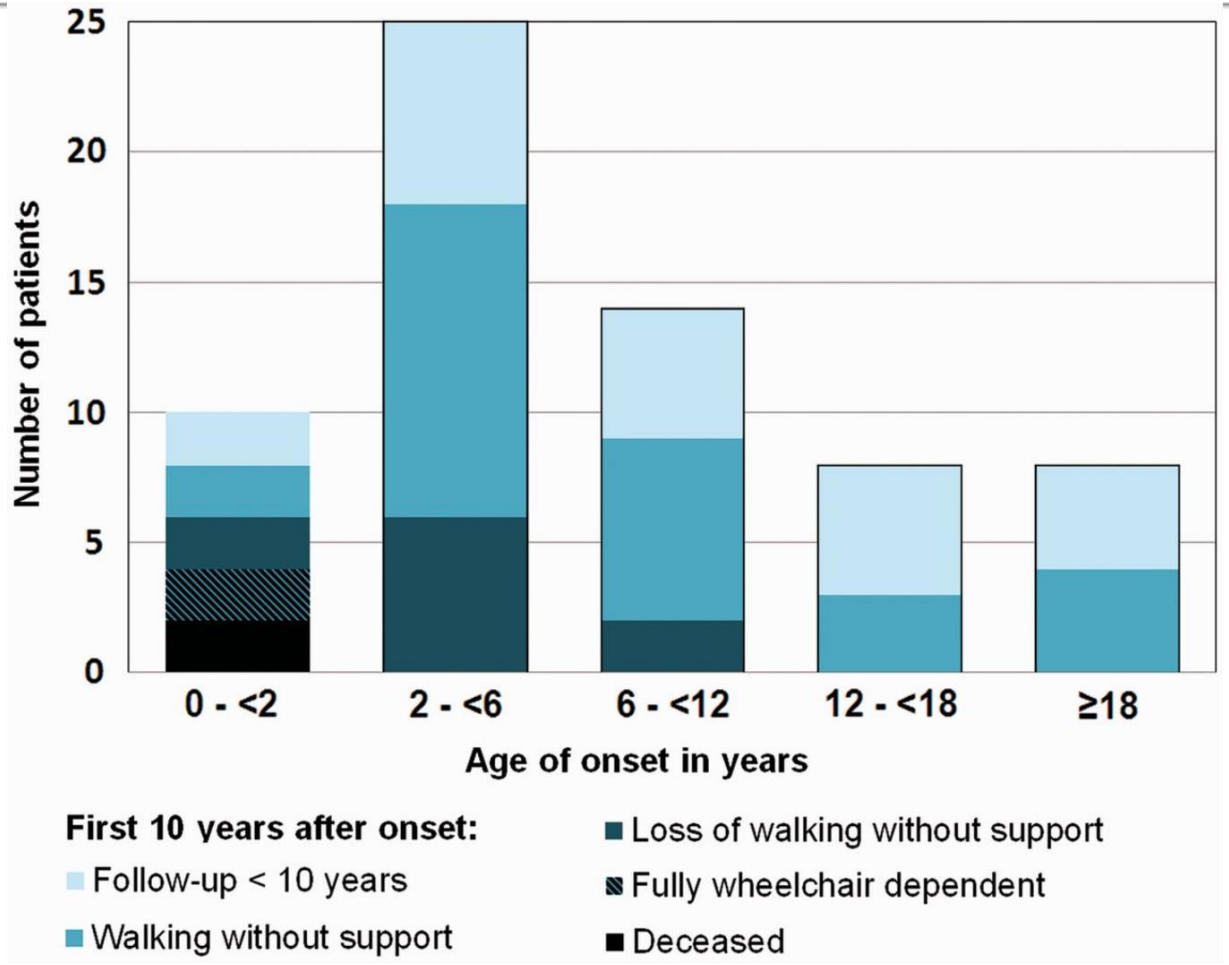
Julia Schicks et al. Neurology 2013;80:e176-e177

- Modified Loes severity score for LBSL
- Does the score predict impairment in LBSL based on:
  - The brain regions involved?
  - The degree of white matter change in those regions?

An MRI severity score has been developed for the LBSL study
We modified the Loes severity score, a standard leukodystrophy MRI scoring system
The Loes score is routinely used in the clinic by radiologists
Dr. Ali Fatemi trained under Dr. Daniel Loes and has published on this scoring method

We are seeking to know if the modified Loes score can predict impairment in LBSL based on:
The brain regions involved?
The degree of white matter change in those regions?

What do the clinical symptoms look like over time?



From: Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation: clinical and genetic characterization and target for therapy
Brain. 2014;137(4):1019-1029. doi:10.1093/brain/awu026

This figure shows LBSL disease progression by age of onset over the first 10 years, when the data is available

Deterioration of motor skills usually starts in childhood or adolescence, occasionally not until adulthood
Neonatal or early-infantile onset cases have a severe disease course and may die
Late-infantile and early childhood onset cases are associated with early wheelchair dependency

On the Y axis is the number of patients with LBSL PER the age category of disease onset on the X axis
Patients who were followed for < 10 years are represented in LIGHTEST blue
At a glance, you can see most patients are in the 2-6 or 6-12 year onset category
At a glance, you can also see there is more disability reported for infants from 0 – 2 years of age, including wheelchair dependency or even death
Loss of walking without support APPEARS to be more frequently reported in the young and older school age groups, but a higher proportion of adolescent and adult patients were followed < 10 years, which is a confounder

What do the clinical symptoms look like over time?

van der Knaap et al 2010

Pinto et al 2014

- The lower limbs appear to be primarily affected in LBSL
  - Spasticity, ataxia, weakness, leg cramps, wasting of leg muscles
- New, non-classic symptoms have also been reported
  - Eye-movement problems, speech difficulty, upper extremity dysfunction
- Our study will look broadly for such atypical symptoms

Regardless of age of onset, across the board, the lower limbs appear to be primarily affected in LBSL

Case reports of at least 17 LBSL patients found leg muscle cramps, polyneuropathy, ataxia, spasticity, weakness and wasting of leg muscles [Pinto et al 2014]

One question is, are the lower limbs exclusively or only predominantly affected in LBSL?
New, non-classic symptoms have also been reported - Exercise-induced ataxia, optic atrophy, fever after minor head trauma, hypoacusis, ptosis, diplopia, anemia and nephrolithiasis[Pinto]

Our study will look closely at arm and hand function, speech and eye movements (with SARA, speech, Archimedes spiral, MACS, eye movement analysis)

What does cognition look like in LBSL?

- Detailed data on neurocognitive symptoms and functioning in patients with LBSL is scarce
- The few case studies report unclear findings
  - Cognition is reported as normal in some studies
  - Other studies report that 25% to 50% of patients have learning problems or cognitive dysfunction without further specification

Cheng et al 2013
Martikainen et al 2013
van Berge et al 2014

…or findings that vary between ages of onset

Therefore, casual assessment or reliance on self-reported symptoms may result in underestimation of cognitive impairment
A formal neuropsychological investigation will result in a more detailed and accurate data on cognitive function

There has been one longitudinal study of 3 LBSL patients who had neuropsychological testing at age 17–30 years revealed abnormalities in all patients:
In fact, the cognitive profile was similar to that reported in patients with MS, namely impairment of information-processing speed and working memory

LBSL patients should be evaluated with formal neuropsychological testing even if initial clinical assessment or patient self-report does not reveal definite cognitive decline

We are seeking to know:
How often and with what tools should we be screening for cognitive changes? This has important Implications for referrals for therapy or special instruction

Summary

- The clinical signs and symptoms in LBSL appear to be broader than first realized 15 years ago…
- A large, comprehensive study can help us start to understand which mutations are responsible for a classical vs. non-classical clinical picture in LBSL
  - Can intervention with physical therapy, occupational therapy or speech therapy slow the progression of motor function deterioration?
  - Can any treatments currently being tried in some clinics be effective in LBSL?

This is also an opportunity to learn if early intervention with PT, OT or SLP can slow the progression of motor function deterioration
Or prevent secondary complications

Until treatments specific to LBSL are developed, we hope to closely look at what treatments are being tried currently and if they are of benefit in LBSL, such as:
Steroids
Mitochondrial cocktail
Carbonic Anhydrase inhibitors

Steroids[JNS 2017]
Diplopia improved with steroids in one case of an adult-onset patient with a CH mutation[Cheng 2013]
Acetazolamide and other carbonic anhydrase partial inhibitors[Synofzik et al 2011]
A DARS2 homozygous mutation carrier with an atypical phenotype of exercise-induced paroxysmal gait ataxia and areflexia showed a dose-dependent sustained treatment response to a carbonic anhydrase inhibitor
Cantharidin
A direct antisense oligonucleotide
An important splicing modulator
Affects the intron 2/exon 3 event splicing, the most commonly affected in LBSL[van Berge et al 2014]
No studies in people

Part III

Design of the LBSL natural history study

LBSL Natural History Study Aims

- Describe neuromotor impairment
  - Functional and quantitative measures of gait, balance, mobility and manual dexterity through wearable technology and video-based testing
- Describe neurocognitive impairment
  - Domains of executive function, social communication, adaptive function and behavioral problems through electronically sent surveys
- Describe quality of life
  - Surveys that address physical, emotional, social and school functioning

Recruitment and Consent

- The study will consist of virtual visits every 6 months over the course of 5 years
- The study enrollment is up to 100 people
- A written consent form will be mailed and a phone appointment will be scheduled for review and questions

The study will consist of virtual visits every 6 months over the course of 5 years
The study enrollment is up to 100 affected individuals
Interested participants will be provided an overview of the study
If they wish to participate, a written consent form will be mailed and a phone appointment will be scheduled to review the consent form and answer any questions

Recruitment and Consent

- Participants will be recruited from three sources:
  - The leukodystrophy clinic at Kennedy Krieger Institute
  - The website and social media pages of leukodystrophy foundations, namely a Cure for Ellie and the United Leukodystrophy Foundation
  - A posting about the study on www.clinicaltrials.gov

Hugo W. Moser Research Institute
at Kennedy Krieger

A Cure for Ellie.org

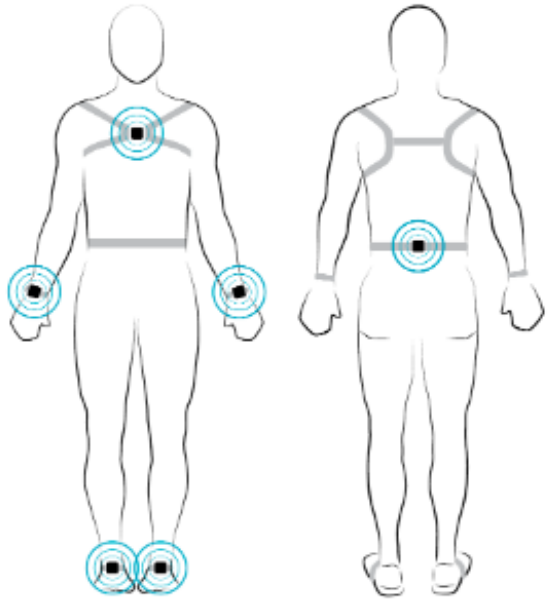
united LEUKODYSTROPHY FOUNDATION

Eligibility and Medical History

- After consent, participants will mail us their medical records in order for us to determine eligibility
- Once eligibility is determined by review of *DARS2* mutation analysis and neuroimaging, participants will be notified by phone to schedule an interview
- Participants will also be asked to provide all relevant neurological, developmental and genetics medical records

Neuromotor Aims

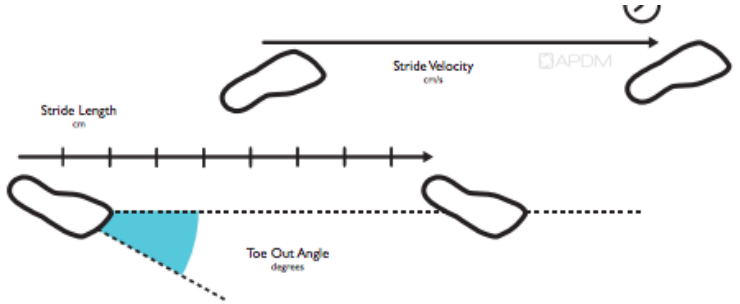
- During the scheduled video based assessment we will quantitatively measure gait, balance and mobility with wearable sensor technology
  - The wearable OPALS system consists of 3 watch sized battery-based accelerometers that submit synchronized signal to a central sensor through ultra low power radio frequency waves
  - These accelerometers will be placed on the participant's feet and waist during a series of 6 brief tests



obility Lab system comes with all or some of the sensors shown.

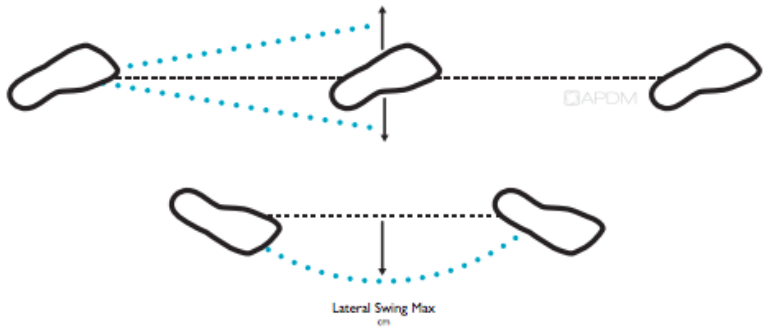
Neuromotor Aims

SPATIAL ANALYSIS

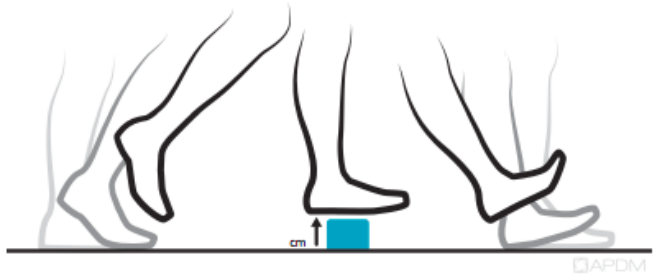


LATERAL STEP VARIABILITY

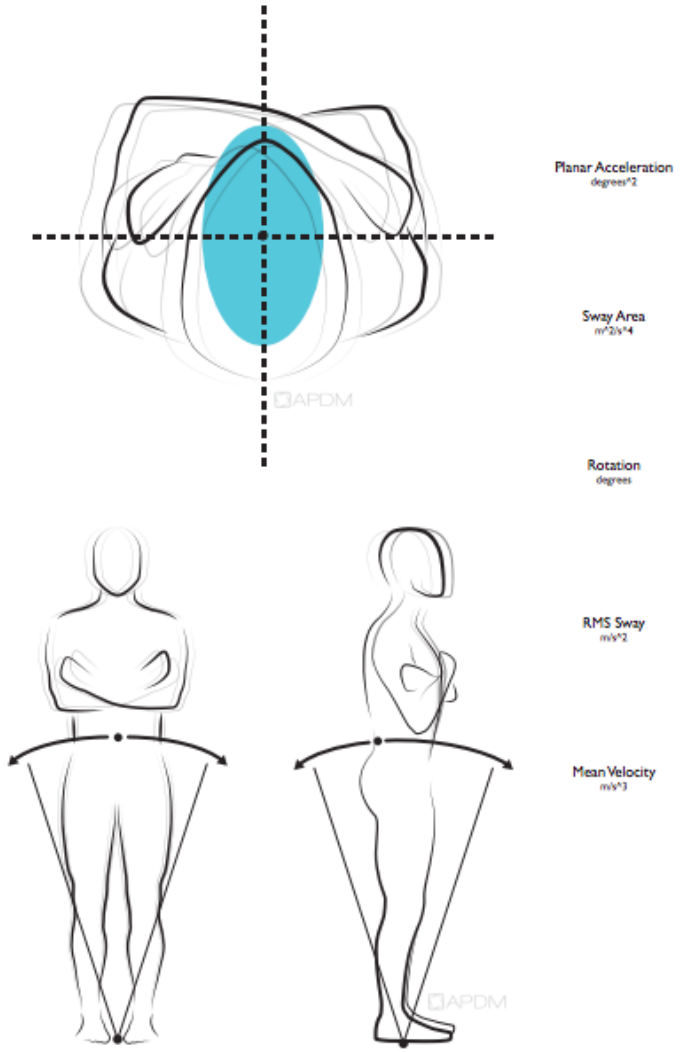
CIRCUMDUCTION



ELEVATION AT MIDSWING



POSTURAL SWAY



OPALS Testing

- What have we learned from the OPALS system in neurology and pediatrics?

OPAL

Quantitative assessment of developmental levels in overarm throwing using wearable inertial sensing technology Grimpampi et al. 2016	***Multilevel upper body movement control during gait in children with Cerebral Palsy*** Summa et al. 2016
Immediate effect of positioning devices on infant leg movement characteristics Jiang et al. 2016	***Complexity of human gait pattern at different ages assessed using multiscale entropy- from development to decline*** Bisi, Stagni 2016
Daily quantity of infant leg movement: wearable sensor algorithm and relationship to walking onset Smith et al. 2015	***Evaluation of toddler different strategies during the first six-months of independent walking: A longitudinal study*** Bisi, Stagni 2015

The OPALS has been used widely used in adult movement disorders, but has also been used in a number of pediatric populations…

However, it has never been used completely remotely, meaning the sensors are recording from the participant's home and no research staff is physically present in the home to assist

Our study will be the first

OPALS System Equipment and Setup

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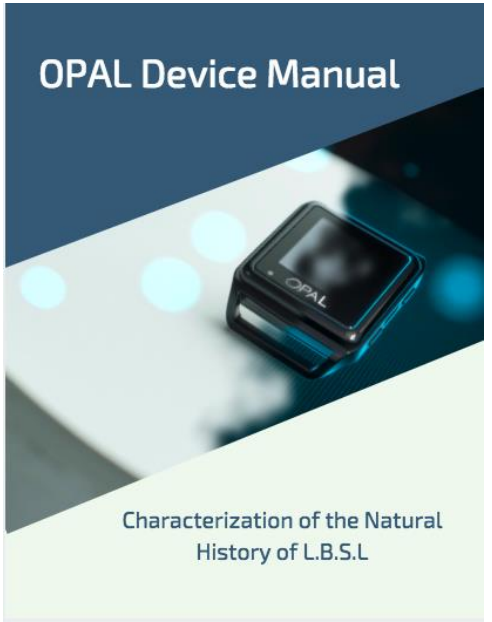
2.

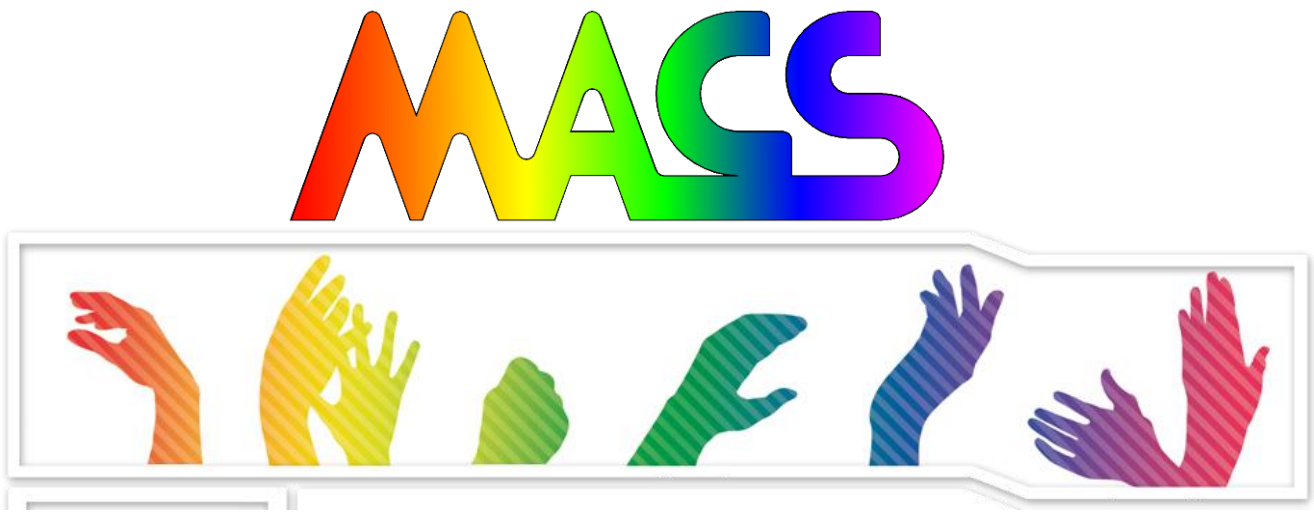
3.

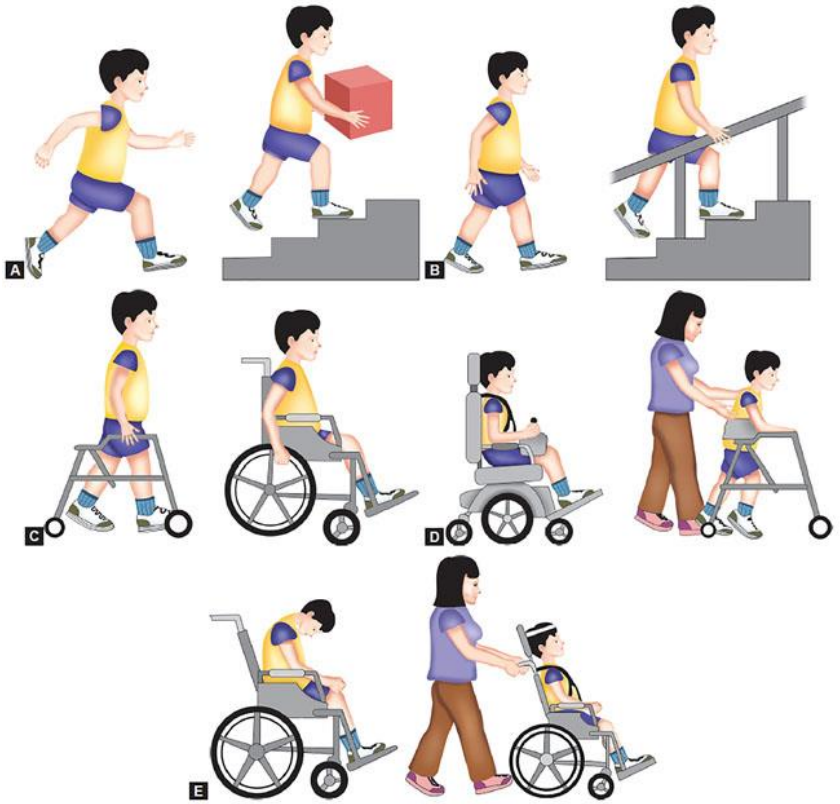
4.



Functional Measures

- **GMFCS and MACS**
  - Gross Motor Function Classification Scale
  - Manual ability classification scale
  - Across the lifespan
  - Gives functional motor disability estimate





Gives functional motor disability estimate for comparison over time and/or after treatment

Neurocognitive Surveys

- **CBCL** (Child or Adult Behavior checklist)
  - Attention, thought, mood, social relationships and somatic complaints
- **SCQ** (Social Communication Questionnaire)
  - Problems with social relationships and communication
  - It has been used as an autism spectrum disorder screen
- **BRIEF** (Behavior Rating Inventory of Executive Function)
  - Measures capacity for emotional control, working memory, planning and organization
- **ABAS-3** (Adaptive Behavior Assessment System)
  - Assesses conceptual, social and practical skills
  - Identifies developmental, learning, and behavioral disabilities

A series of web-based neurocognitive surveys will be sent electronically
Which will help us identify changes in some aspects of behavior, adaptive skills and communication

We will determine if these findings are correlated with DARS2 genotype or brain imaging

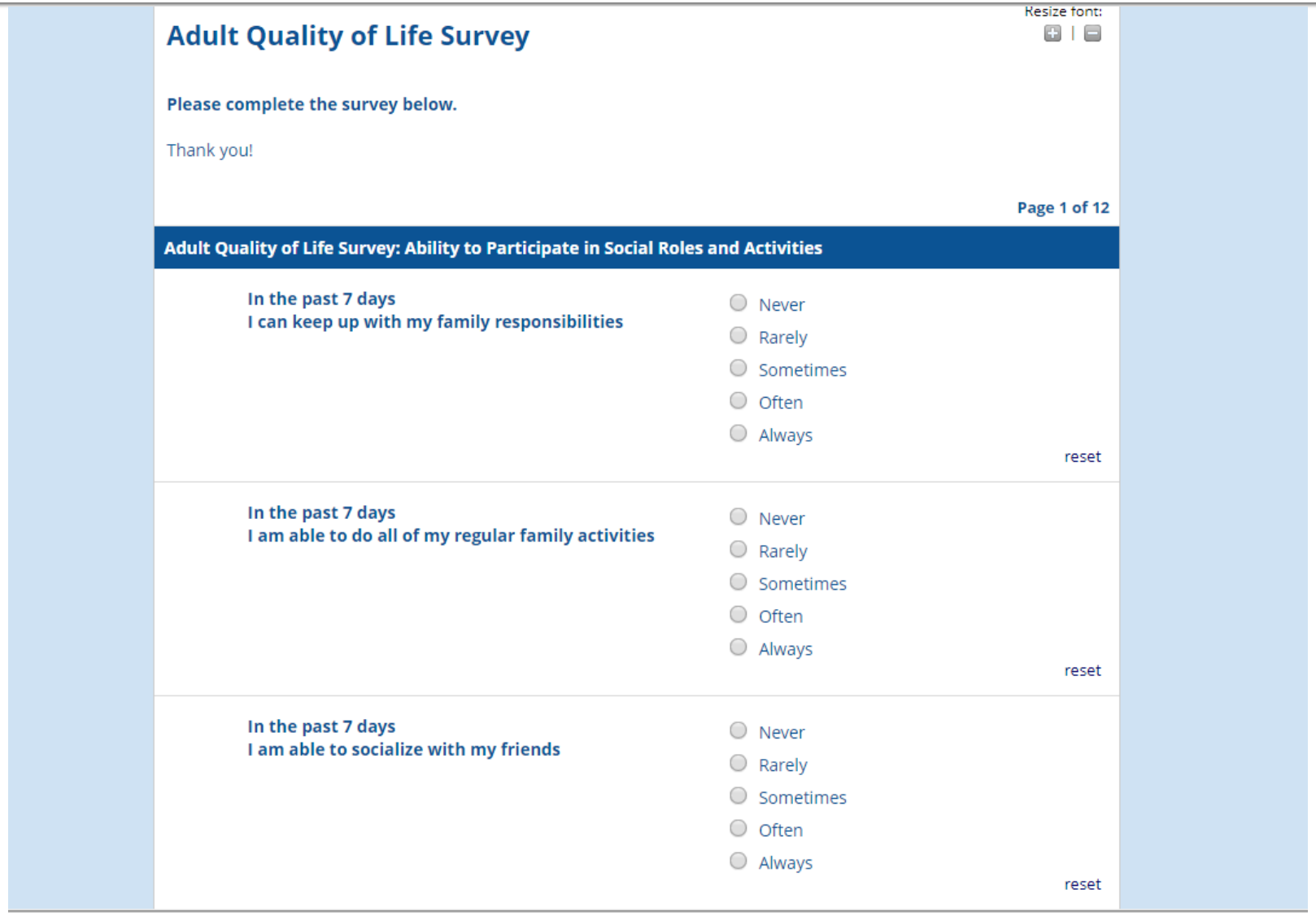
This will help us build guidelines for screening of patients in the future to make sure these needs are being addressed in the clinic

We will next adapt more detailed online neurocognitive assessments that would be closer to pen/paper neuropsychology testing in the psychologists' office

Quality of Life Assessments

- Information on quality of life in LBSL will be collected using scales addressing:
  - Physical
  - Emotional
  - Social
  - School or work functioning
- These scales have been used to assess quality of life for persons with spasticity, ataxia and chronic medical conditions

Quality of Life Assessments



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Adult Quality of Life Survey

Please complete the survey below.

Thank you!

Page 1 of 12

Adult Quality of Life Survey: Ability to Participate in Social Roles and Activities

In the past 7 days
I can keep up with my family responsibilities

- Never
- Rarely
- Sometimes
- Often
- Always

reset

In the past 7 days
I am able to do all of my regular family activities

- Never
- Rarely
- Sometimes
- Often
- Always

reset

In the past 7 days
I am able to socialize with my friends

- Never
- Rarely
- Sometimes
- Often
- Always

reset

Quality of Life Assessments

Resize font:

Pediatric Quality of Life Surveys

Please complete the survey below.

Thank you!

Page 1 of 9

Neuro Quality of Life Survey: Anger

In the past 7 days
Being angry made it hard for me to be with my friends

- Never
- Almost never
- Sometimes
- Often
- Almost Always

reset

In the past 7 days
It was hard to do schoolwork because I was angry

- Never
- Almost Never
- Sometimes
- Often

Timeline of LBSL Natural History Study