# Pediatric Neurosurgeon's Role in Rare Disease Advancement


Ramin Eskandari, MS MD FAANS
Associate Professor of Neurosurgery
Chief, Division of Pediatric Neurosurgery
Medical University of South Carolina

musc Shawn Jenkins Children's Hospital
Medical University of South Carolina

MUSC Health
Medical University of South Carolina

# Disclosures

- Biorepository funding – Combined Brain
- Anuncia Medical Inc –consultant, CMO
- Synaptive Medical Inc –consultant

# CTNNB1 Genetic Mutation and Tethered Spinal Cord

**Increasing awareness**

- **CTNNB1 community of foundations**
- **Scientific community**
- **Eventually…medical community**

**Screening – Fast Spine MRI, Urology and Orthopedics**

**Major Foundation Websites**

CTNNB1
CONNECT AND CURE

## CTNNB1 and Cerebral Palsy

CTNNB1 Syndrome and Cerebral Palsy (CP) have several overlapping clinical similarities. In fact, this overlap of symptoms is so prominent that some individuals with a CTNNB1 gene mutation may not be aware because they received a diagnosis of Cerebral Palsy and were not offered genetic testing to check for any genetic causes.

### You can have *both* CP and CTNNB1!

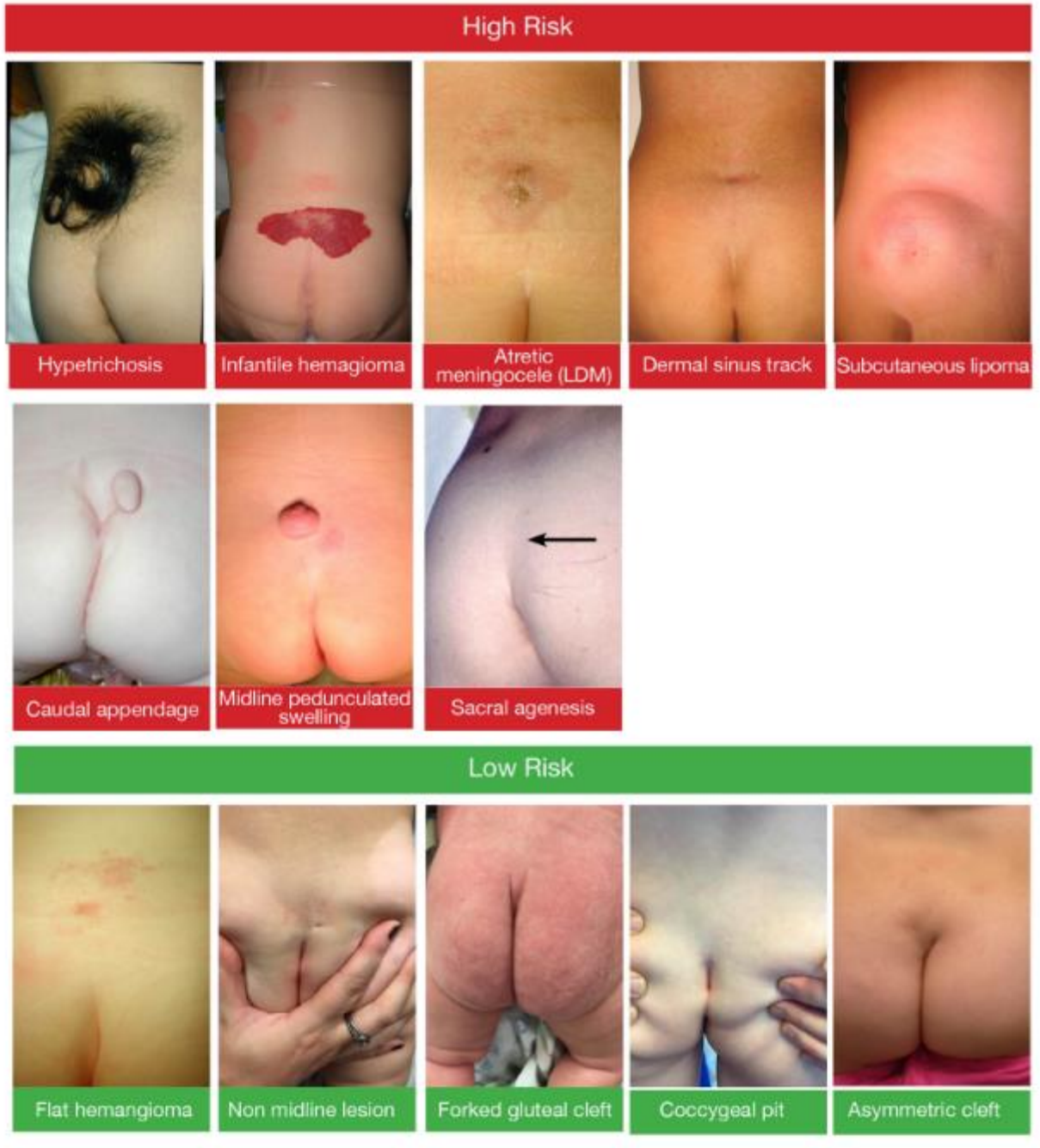
Cerebral Palsy is a clinical diagnosis that provides understanding, resources and therapies for associated motor challenges, while CTNNB1 Syndrome is a genetic diagnosis that allows for more support for other disease-related medical concerns.

Serious conditions that may be missed without a genetic diagnosis of CTNNB1:

| CONDITION | RISK IF NOT FOUND AND TREATED |
|---|---|
| Tethered Spinal Cord | Permanent nerve damage |
| Exudative Vitreoretinopathy | Blindness |

# Tethered Spinal Cord

- Depending on age – presentation can vary
- Early suspicion can lead to early diagnosis
- Imaging evaluation
  - Ultrasound – technically depenedent and usually poor quality
  - Goal is to prevent radiation (CT/Xray) and sedation (traditional MRI)
  - Fast Spine MRI – obviates the need for radiation *and* sedation




REVIEW ARTICLE 2017

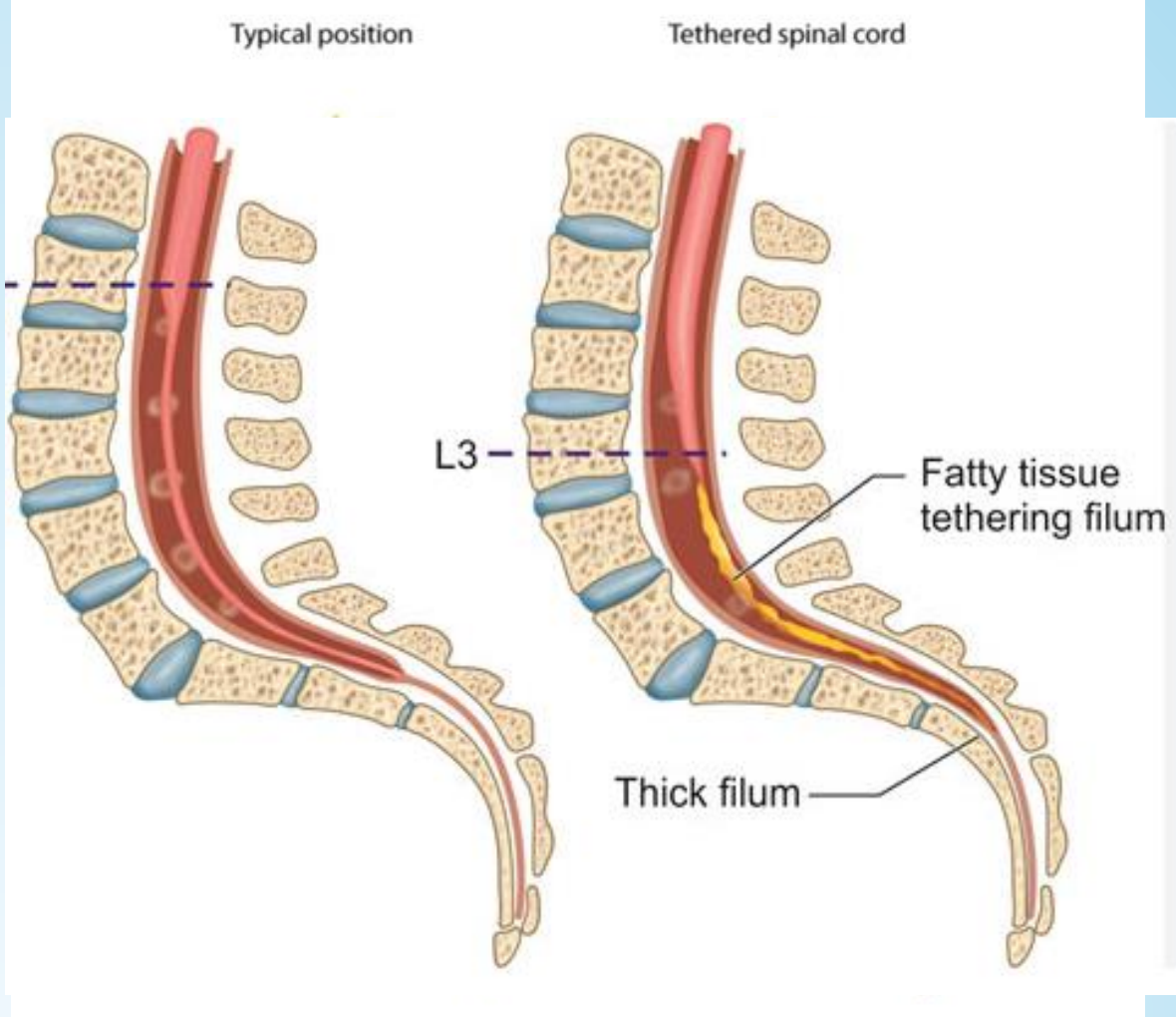
WILEY Neurourology Urodynamics ICS SUFU

**Evaluation and management of tethered cord syndrome in occult spinal dysraphism: Recommendations from the international children's continence society**

Gerald F. Tuite[1] | Dominic N.P. Thompson[2] | Paul F. Austin[3] | Stuart B. Bauer[4]

# Tethered Spinal Cord

- **Skin changes:** Dimples, birthmarks, or patches of hair on the lower back.
- **Foot and spinal deformities:** High arches, curled toes, clubbed or turned feet or scoliosis (curvature of the spine).



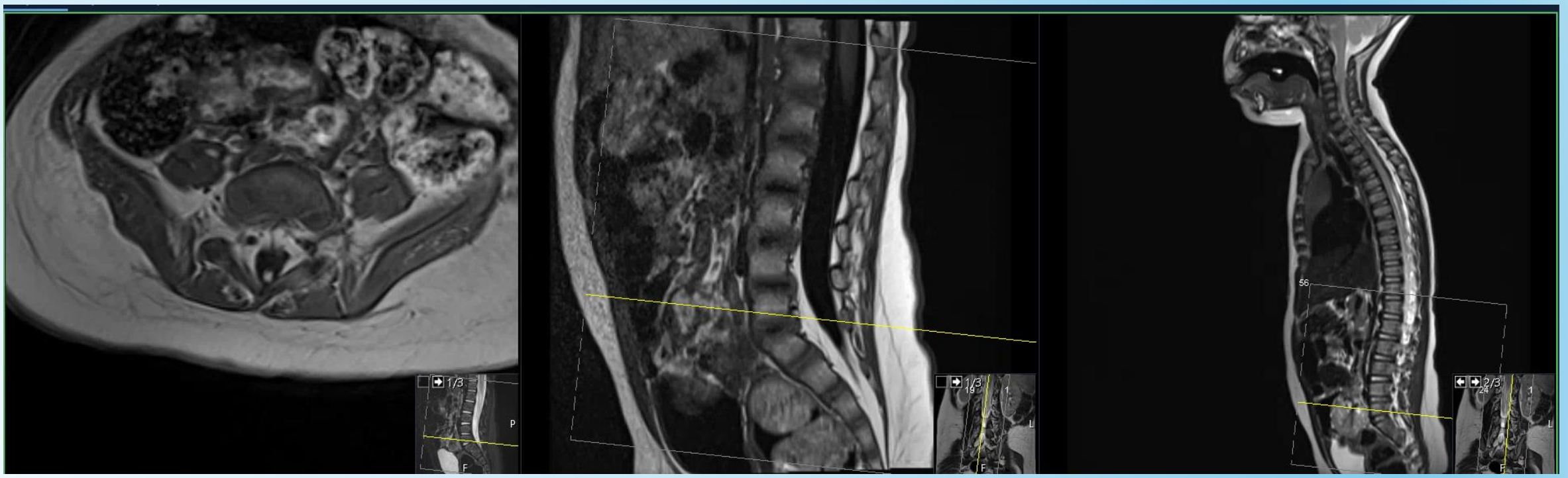

***Most common signs & symptoms***

- **Sensory**
  - Back and leg pain: This can be a dull ache or a sharp, shooting pain that may radiate down the legs.
  - Numbness: can present as inability sense things that others can sense – extreme heat or cold *tolerance*
- **Motor**
  - Weakness: usually in legs, difficulty walking, or changes in gait (how someone walks).
  - Balance: coordination issues and frequent falls
- **Bowel and bladder**
  - Urinary: Retention >>> Incontinence. Frequent urinary tract infections (UTI), feeling like you have to go but cannot. Can cause kidney damage if untreated
  - Bowel: SEVERE Constipation, intestinal mobility is lowered

Case Presentation: 10 mo old female with CTNNB1 genetic mutation with a sacral dimple. Spine Ultrasound at ~3-4mo old demonstrated nothing abnormal. However due to high prevalence of spasticity in this population, her geneticist recommended outside evaluation for possible tethered cord. Her OT/PT have noticed increased tone in her lower extremities. She cannot sit independently yet and slides across the floor on her belly without crawling. She can bear weight on her legs, and there is no foot/leg deformity or spinal deformity of the curve

Recommendation: MRI of the L-spine – which at the time of evaluation also gets the entire spine/bottom of the brain/skull base as well as the pelvis and bladder all in one shot

MRI scan done – demonstrates long segment Fibrolipoma (benign fatty tumor infiltration) of the Filum Terminale (connective tissue band that connects the bottom of the spinal cord to the lowest part of the inner spinal canal)



Follow up with pediatric neurosurgeon and discussion of imaging and possible future plans

The longer the segment of fatty infiltration, the less chance that growth of the child will be symptom free – Fat does not stretch well and typically the filum is abnormal, causing worsening tethering as the child grows.

Balance of surgical timing for tethered cord and safety.

- Anesthesia risks – the older the better
- Surgical Risks – more tissue, better closure, more space
- Neuromonitoring risks – nerves are significantly better to monitor with more accurate finding and more reliable
- Recovery – the younger the better and less stress and less memory of the situation
- Wound Healing – the younger the better (to a point), and the potential for wound infection with being better toilet trained
- Bone Removal/Healing – old enough to have bone to replace and not need to resect the bone to get to the filum
- Activity restriction – younger is easier but will need medication to keep them flat after surgery; older is easier if they are able to listen to instruction; older is harder to recover at home because of activity restriction

Follow up with this patient was to see her back in a few months and see how she was doing.

Over time, she underwent urological evaluation which was normal and at ~13 and 16 months old was seen again for follow up.  She had started to develop some internal rotation of the legs/feet and was starting to buckle a little more under her own body weight. This can be seen in the syndrome with hypotonia but was also concerning in the face of the known long-segment fibrolipoma of the spinal cord filum terminale.

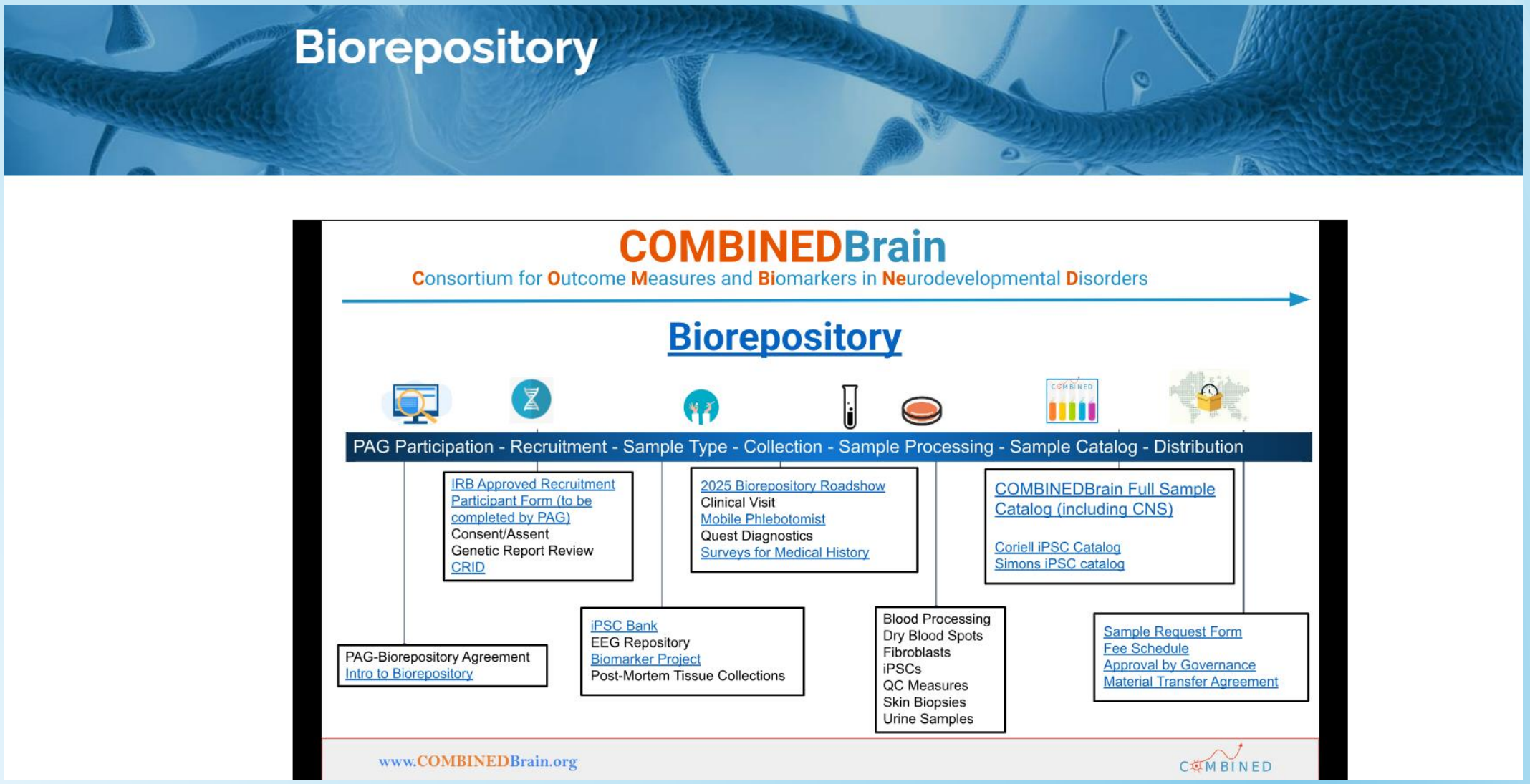
Underwent surgical detethering operation at ~16mo old with neuromonitoring of the bladder, lower extremities and anal sphincter with great results.

~6 months post-op she was walking with her walker and no progression of her leg deformities
Followed by our pediatric rehabilitation team for equipment needs, toe-walking help and any future spasticity needs


Now a bigger mountain to get over…
Advancing treatments in rare diseases is *really* hard….but why?

# Pediatric Neurosurgical Biorepository

*When patient advocacy and medical curiosity merge in perfect harmony!*



# Pediatric Neurosurgical Biorepository

*How it started…*

4 year IRB battle by pediatric neurosurgeon for keeping tissue/blood/fluid which would otherwise be discarded

Life-long battle by patient's mother advocating for her daughter's condition and pushing scientific progress

**What happens when these two people meet?**

The first pediatric neurosurgical biorepository of **any/all tissues and fluids** which can be stored, cataloged and used to push the world of therapeutics forward at a much faster pace!

- Higher precision with stronger control samples to develop better and safer therapies for ALL kinds of diseases – especially RARE CHILDHOOD DISORDERS!

Anna Pfalzer, PhD
Chief Scientific Officer
Combined Brain

Emily Amerson, MS
President
CTNNB1 Connect and Cure

# Pediatric Neurosurgical Biorepository – Updated by the numbers…

## 3 Pediatric Neurosurgeons Now Collecting!!!

Consent done by →Pediatric Neurosurgery APP (PA or NP) usually

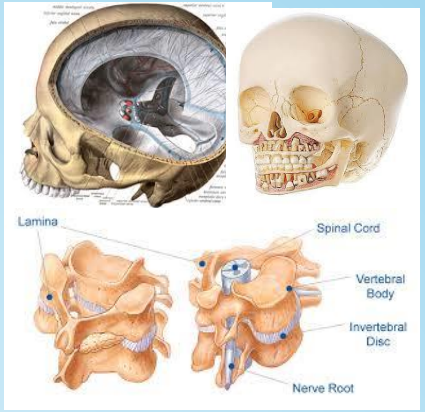
*I typically will tell the patients about this initiative and they are always very excited!*

- 79 unique patients have banked tissue/fluid
- First collection of CSF and brain tissue on 11/14/23
- Currently Collecting CSF, Non-Brain Tissues, Brain Tissue and Plasma
- Future is to expand to Adult Neurosurgery….then to General Surgery, Orthopedic and beyond!

Cameron Leyers - Pediatric Biorepository Coordinator

# Pediatric Neurosurgical Biorepository – Updated by the numbers…

- **CSF Collection**
  - 66 unique samples
  - 1820 aliquots




- **Tissue Collection (non-brain)**
  - 33 Unique samples
  - 333 aliquots
  - Includes arachnoid tissue, cartilage, cervical ligament, cervical occipital ligament, CNS tissue, epidural fat, excess myelomeningocele skin, fat/adipose tissue, free lamina, ligament, lipoma fat, muscle, nerve, nerve cord, periosteum tissue, scar tissue, skin, subdural scar tissue, wound eschar

- **Brain Collection**
  - 23 unique samples
  - 327 aliquots
  - Includes brain mantle core, corpus callosum, white matter, full mantle thicknesses cortex, gliotic scar, hippocampus, mixed brain tissue, front temporal lobe, right parietal lobe, temporal lobe, dura

- **Plasma Collection** – typically done at time of IV/Arterial line placement as patients are going to sleep for surgery
  - 30 unique samples
  - 239 (250ul) aliquots

# Conclusions…

- Neurosurgeons do have a role in advancing Rare Neurological Diseases
- Rare disease foundations, families and researchers can influence surgeons to get involved
- CNS Biorepository for *NORMAL* tissue and fluid is critical for large number of control samples
- Having large number of control samples increases accuracy and safety of new therapeutic development for neurological diseases


Thank you
Questions?
eskandar@musc.edu