Congenital DM1:
what to expect and management tips

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Schulich
MEDICINE & DENTISTRY

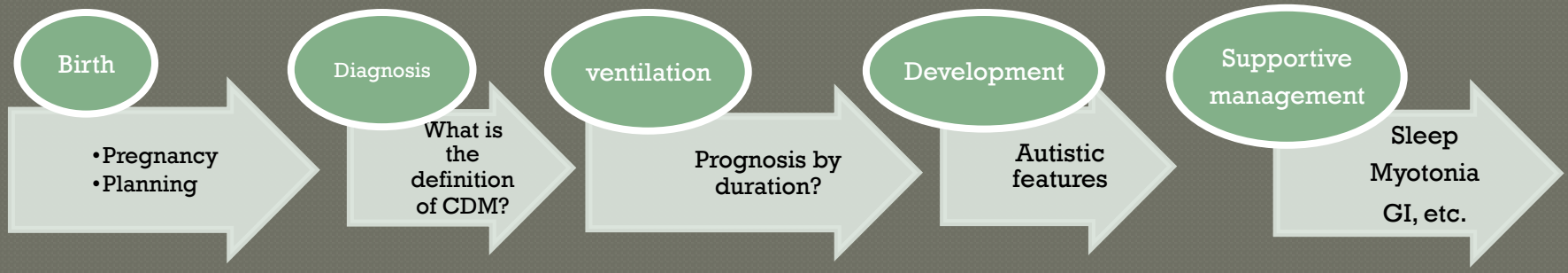
Objectives

- Disclosure statement
  - Involved in clinical trial activity with Biogen and Isis for SMA
  - Have consultation agreements in the past with GSK, Acceleron and Shire
  - Sit on PTC Therapeutics Advisory Board (volunteer)

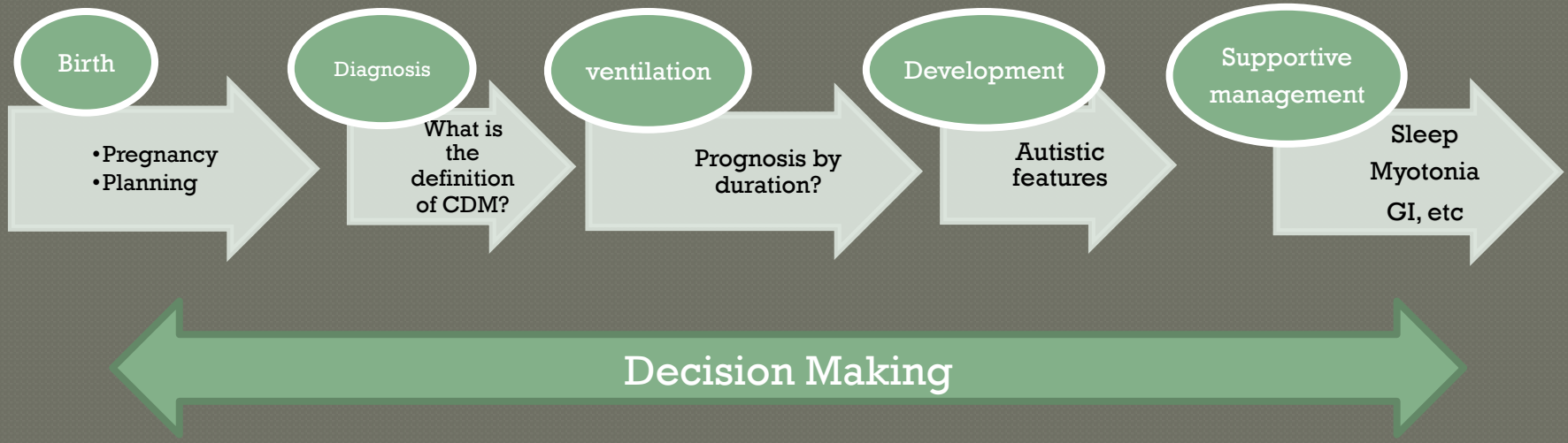
Objectives

- Walk through the life of a child with congenital DM1 and pick out some of the more significant issues
- Learning from each other
- Data from studies we have conducted with Dr. Johnson, Utah

Childhood DM1 profile



Childhood DM1 profile



- Are we giving the best advice and opportunity to discuss family planning?
- Approximately half the time the child is the index ‘case’ for the family

- Maternal age 22-37 years
- 59% the neonate was the index case for the family

- 79% offered genetic counseling after the birth of their CDM child
- 79% said they had enough knowledge of CDM to make educated decisions about future pregnancies
- No one in the study actually had prenatal testing for the reported cases

Mothers who knew they had DM1

- 15-35 years old at diagnosis
- 50% had counseling to explain risk of CDM
- 50% had prenatal testing offered
- No one chose to have prenatal testing
- 50% said now that they had a child with DM1 they would decide not to have another child
- 25% would have more children, and 25% undecided

Mothers who did not know they had DM1

- 60% said they would have another child
- 30% no more children
- 10% undecided
- For the mothers who would have another child all said they would have prenatal testing for future pregnancies

Diagnosis

What is the definition of CDM?

- There is no uniform definition of congenital DM1
  - Hypotonia only vs. severe
  - Family history
  - Cut off birth, 1 year?
- Childhood/juvenile/early onset definition also problematic
  - Why cut off at 10yo?

Diagnosis

What is the definition of CDM?

- Hard to prognosticate and inform parents without a clear definition
- Difficult for science and study
- Not physiologically important

Diagnosis

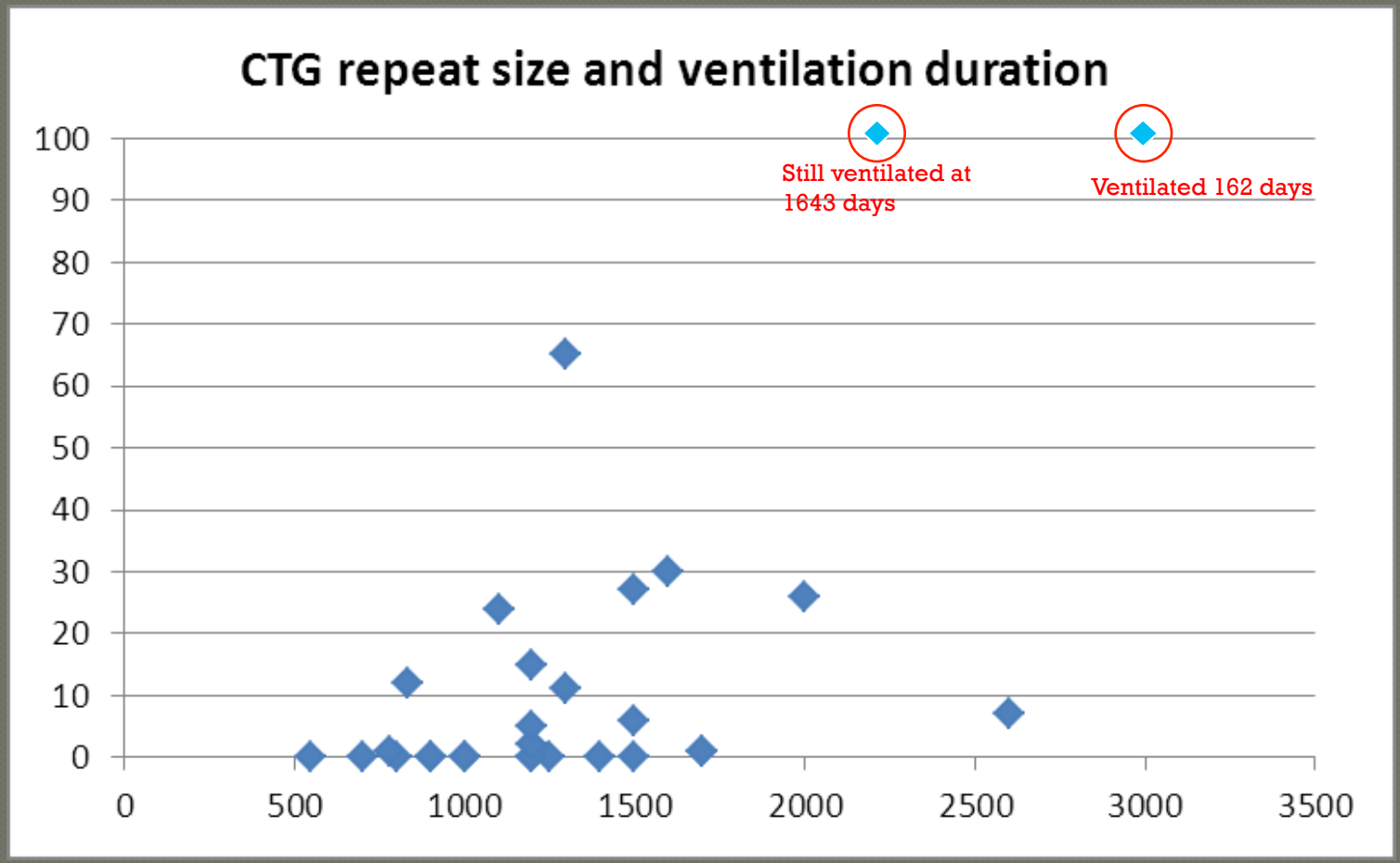
What is the definition of CDM?

- Any newly diagnosed child up to age 3 years meeting the following criteria:
1. Has symptoms in the neonatal period causing death or admission to hospital for greater than 72 hours related to DM1
2. Has a genetically confirmed diagnosis of DM1 in child (or mother)
3. Repeat size >200

- All others are childhood or pediatric DM1

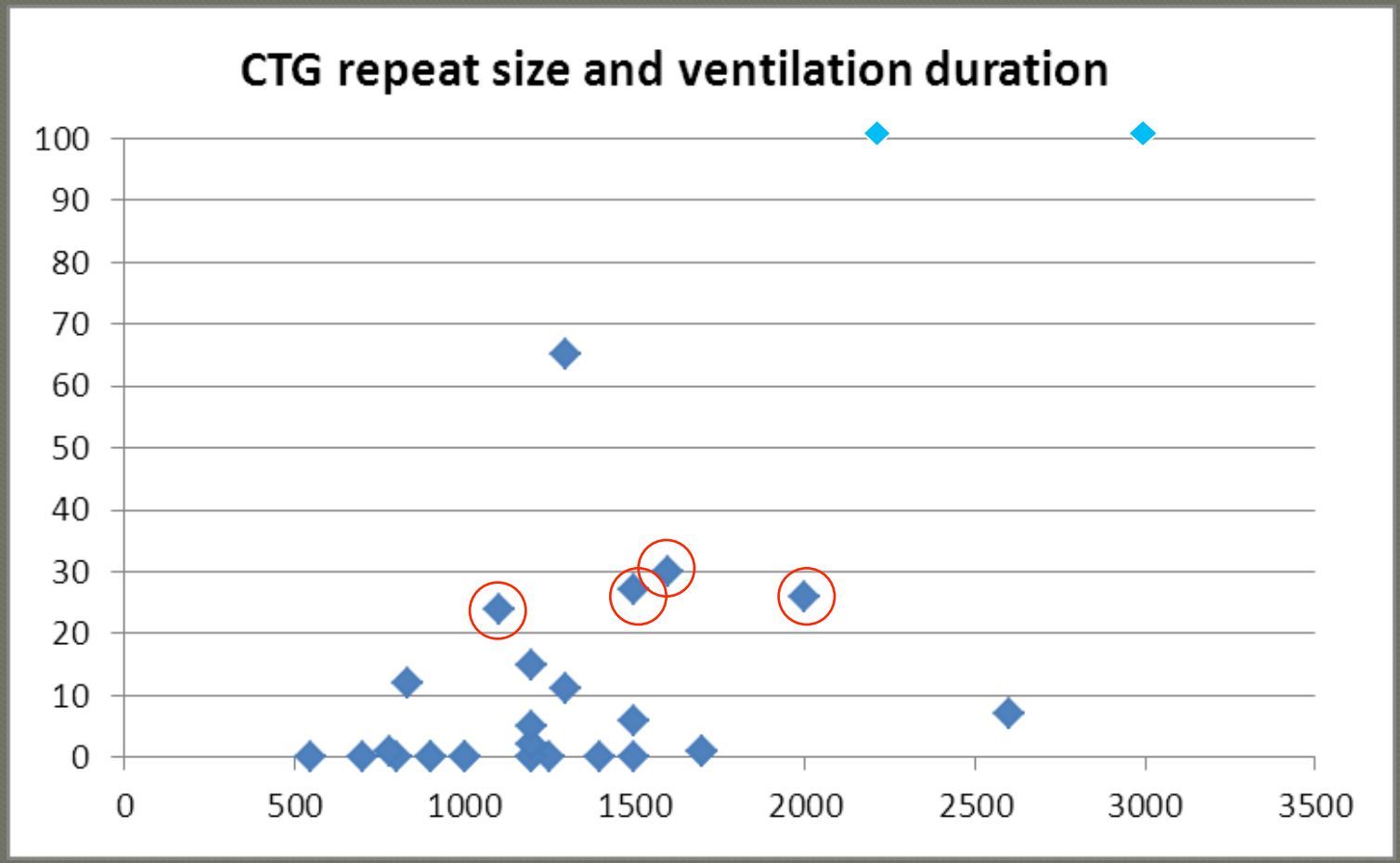
Ventilation

Duration and Prognosis



Ventilation

Duration and Prognosis



Ventilation

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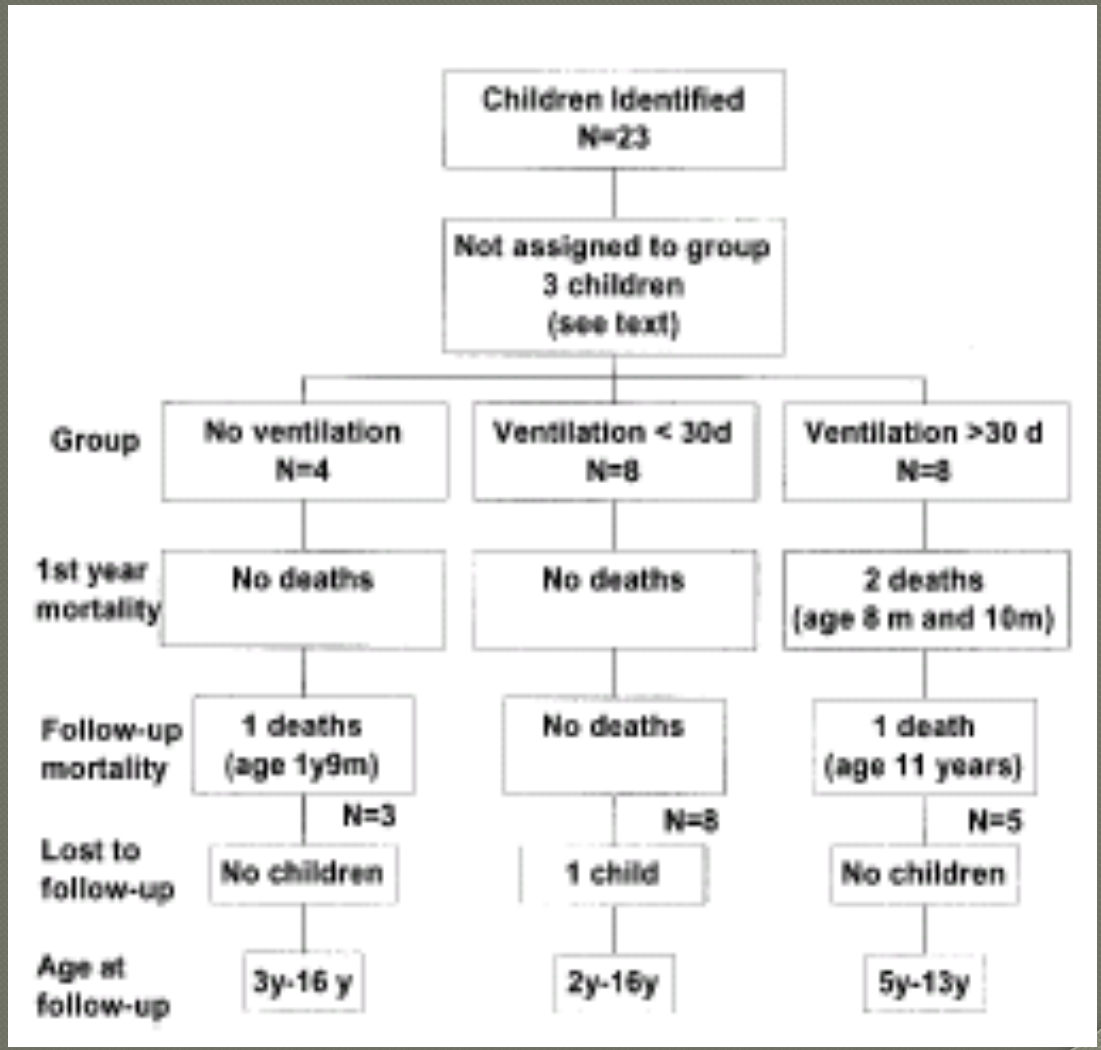


Ventilation

Duration and Prognosis

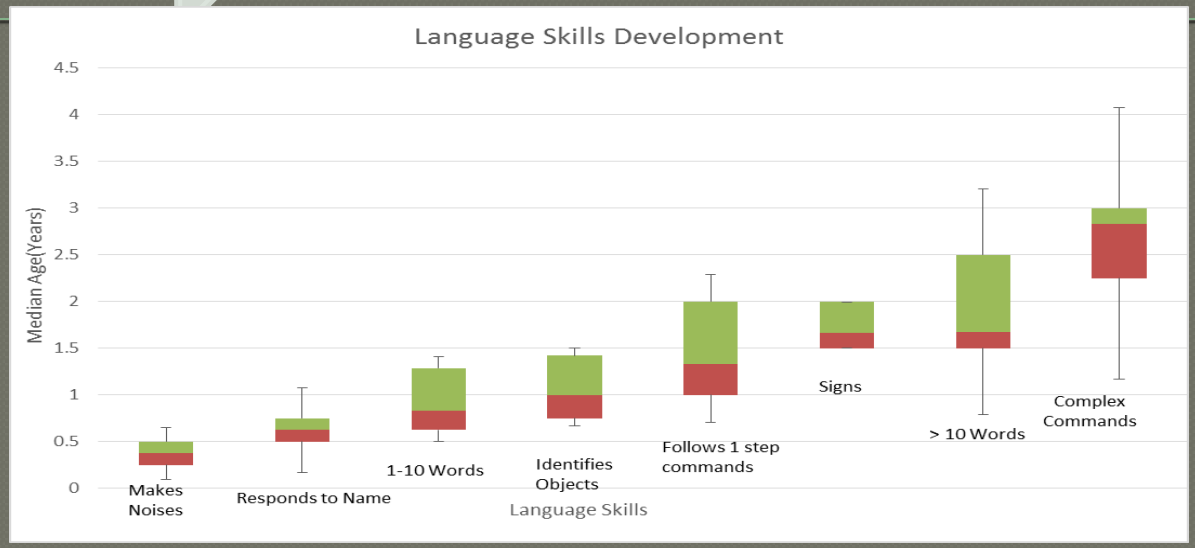
- CDM1 is a disorder of muscle immaturity
- There is still a prevailing sense that ventilation beyond 30 days is futile
- There are many complications that can occur in the neonatal period that impact breathing and feeding
- Long term ventilation is a care challenge
- Families should be given the proper information

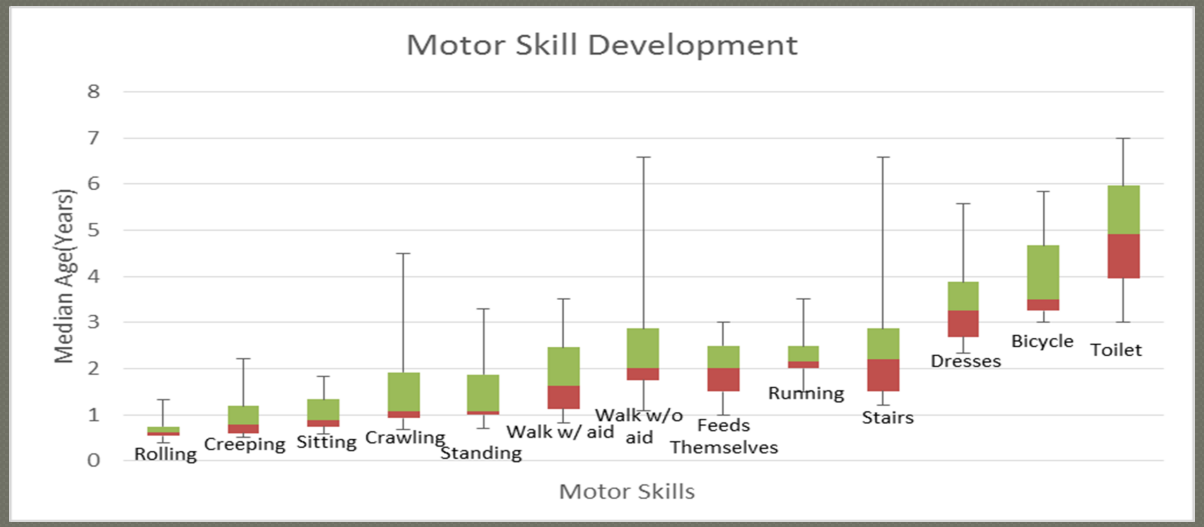
Development

Language

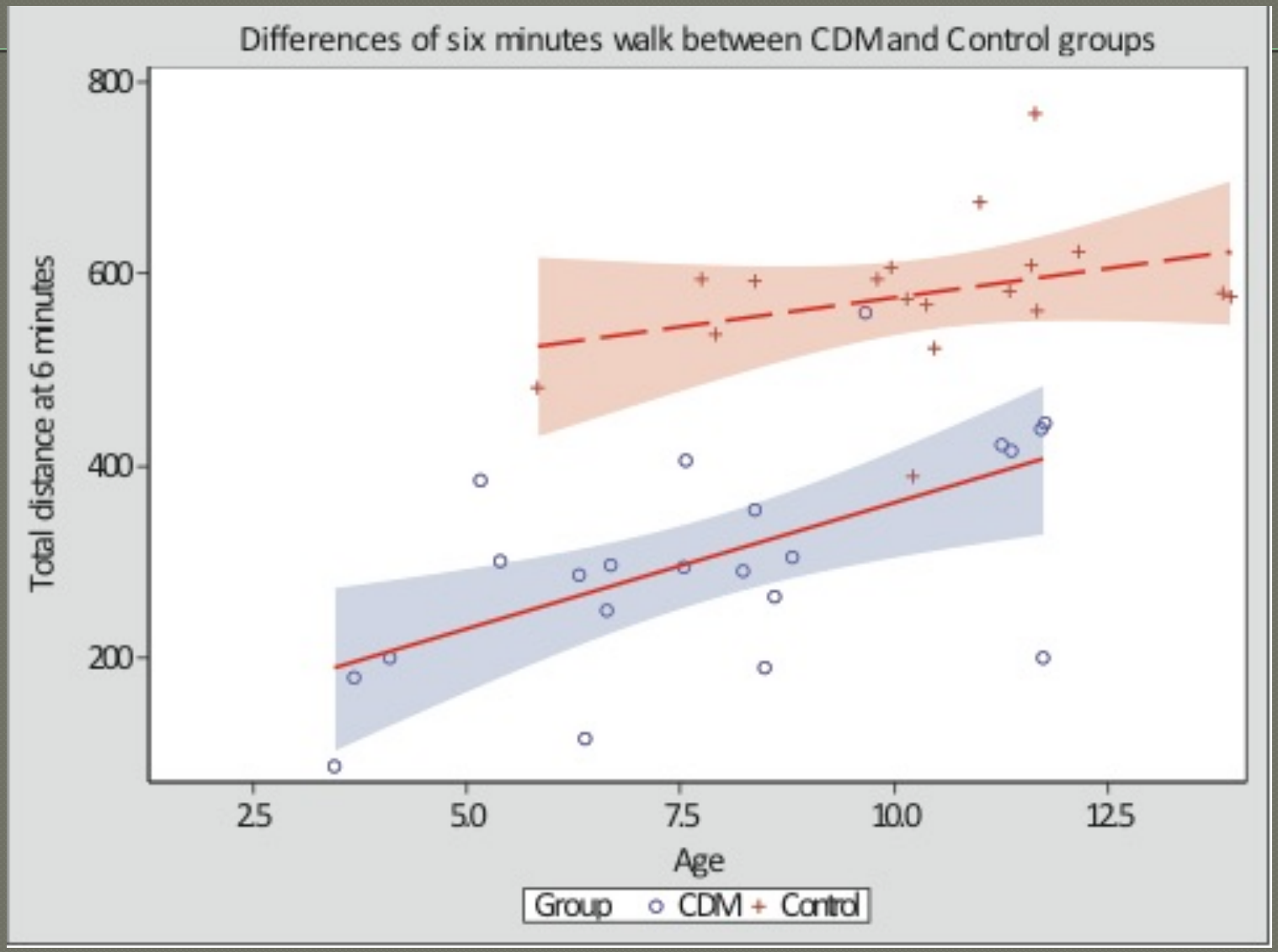
Motor

Autism



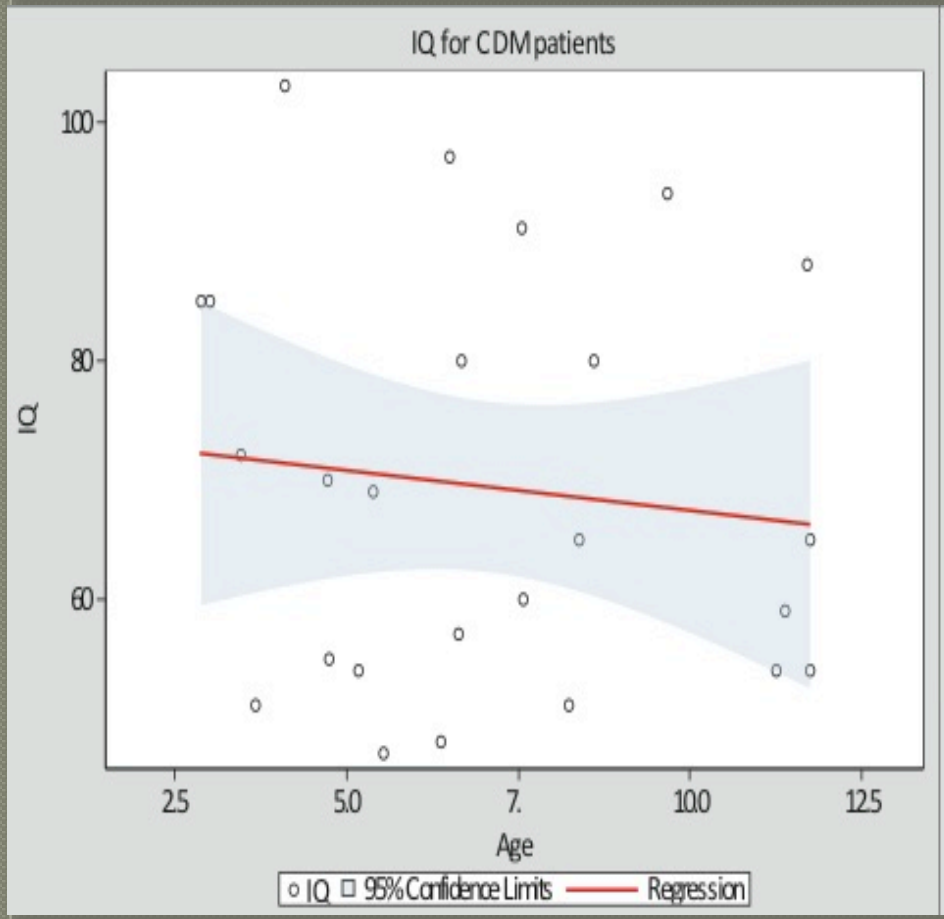


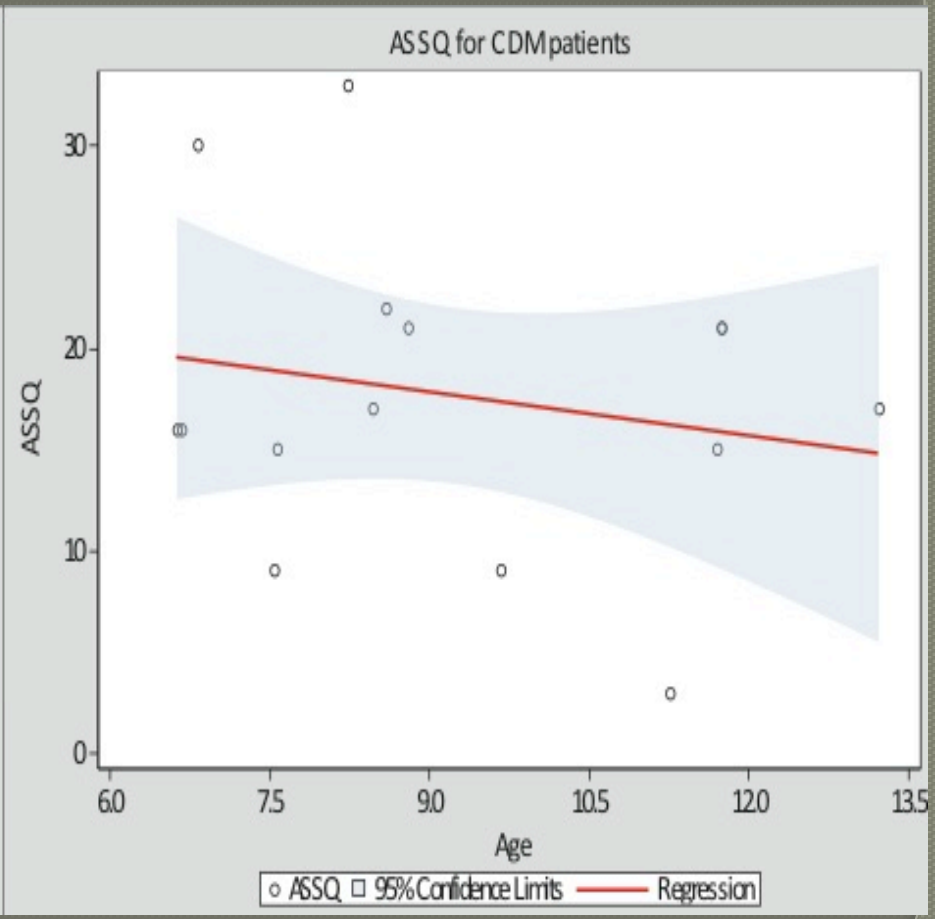
6 minute walk time by age



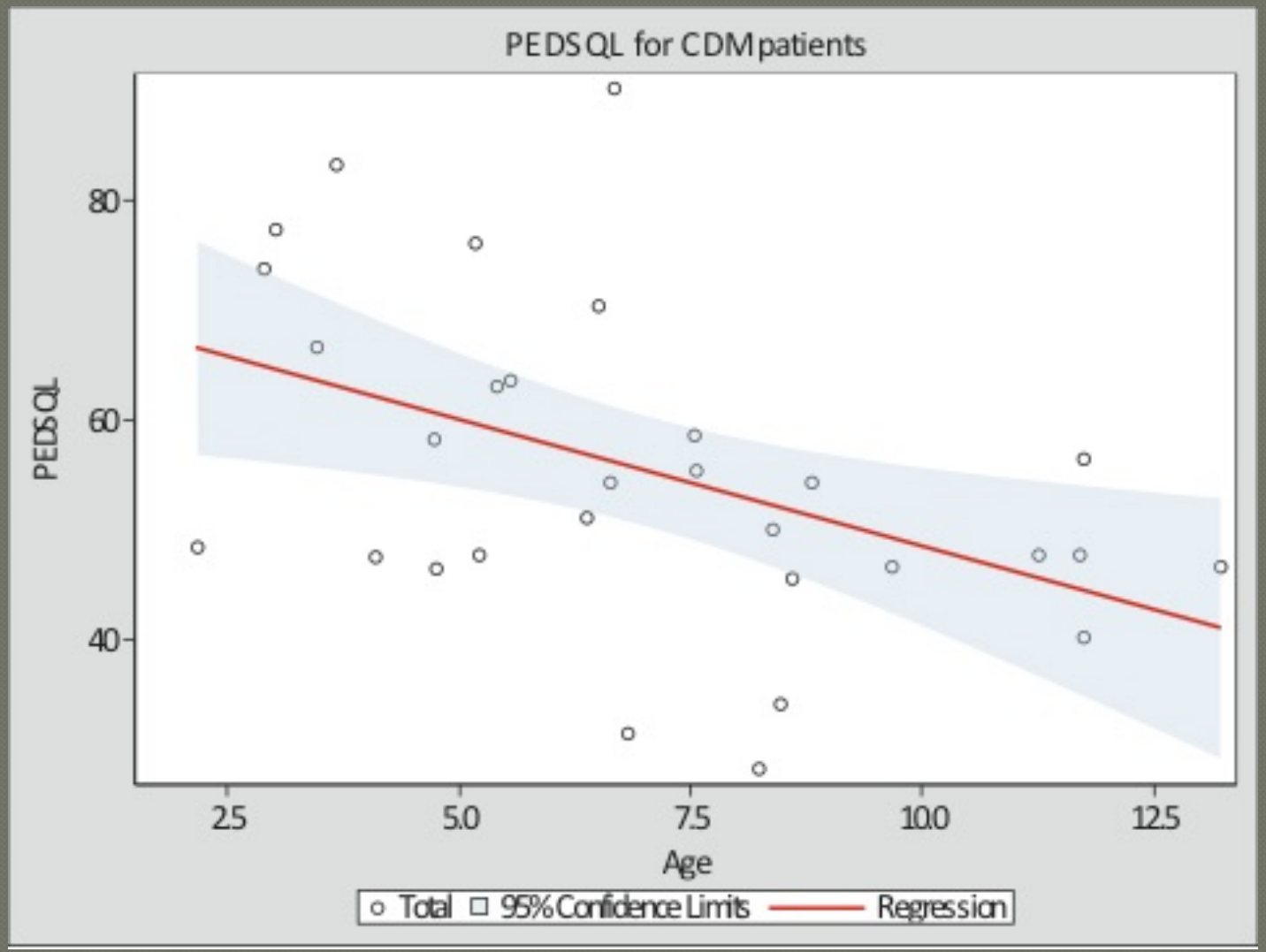
- Autism issue
  - Facial movement reduced
  - Recognition of facial expression impaired
  - Anxiety
  - Cognitive and language disability
  - Typically patients score clinically significant scores on traditional autism scales
- Do patients have autism or are there unique features of childhood DM1 that makes it appear so?

ASSQ and IQ with age





Quality of life in older cohort



Supportive Management

Medical Treatment

- Sleep
- Myotonia
- Cardiac
- Gastrointestinal
- Ophthalmology
- Orthopedic

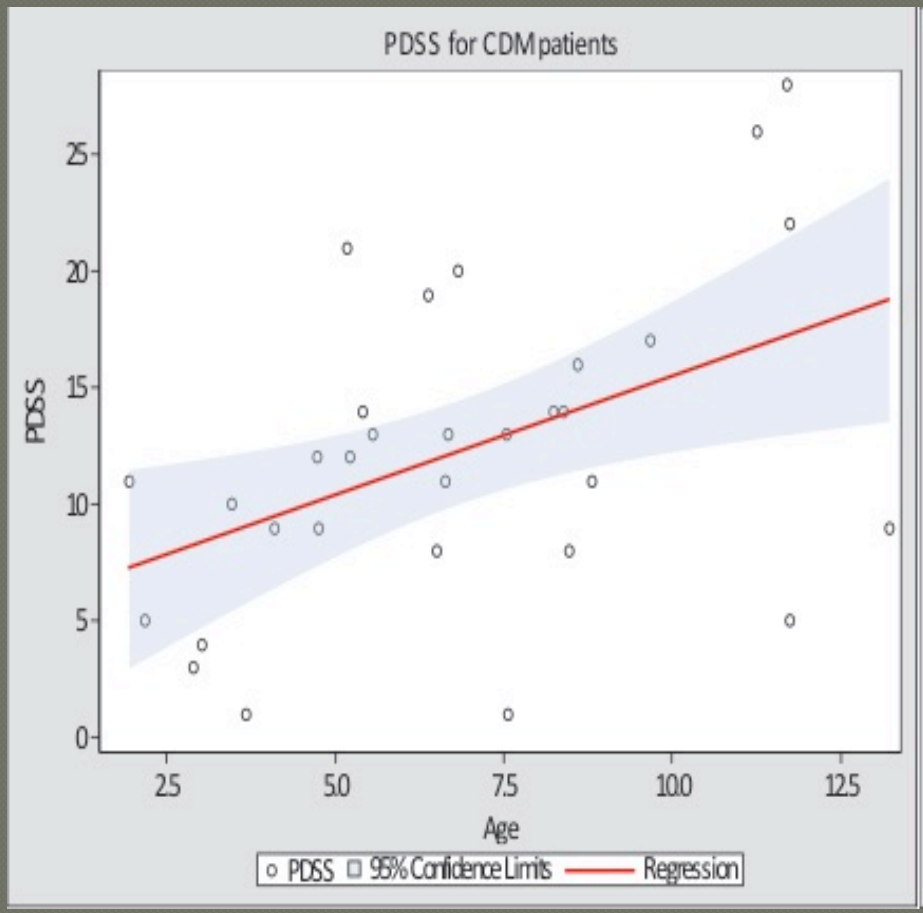
Medical Management and Monitoring

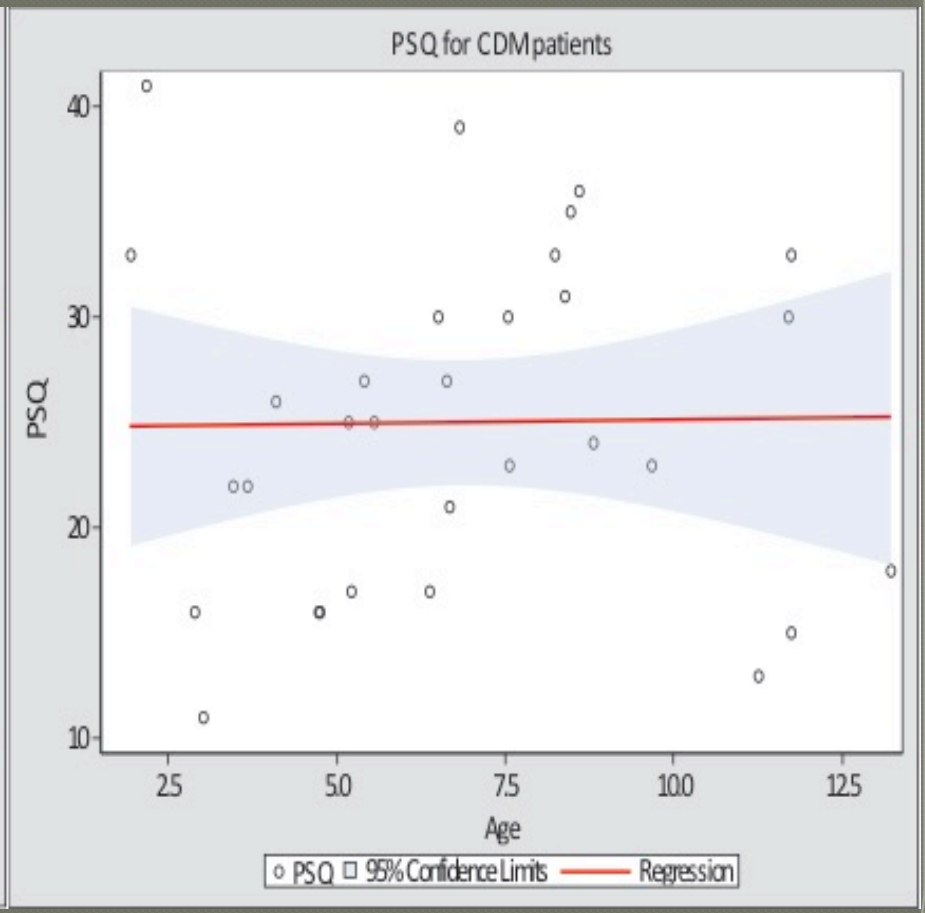
- Sleep
  - Excessive sleep often stated as a problem in clinic
  - RCT's of modafinil to treat hypersomnolence showed mixed results: improvement on sleep scale but not necessarily on activity level (adults)
  - No randomized trial of methylphenidate

Medical Management and Monitoring

US Registry	Never	Slight chance	Moderate chance	High chance	Total
Sitting and reading	8	1	1	1	11
Watching tv	6	2	2	1	11
Sitting inactive in a public place	7	2	1	1	11
As a passenger in car for an hour without break	3	3	4	1	11
Lying down in the afternoon for a nap	4	3	3	1	11
Sitting and talking to someone	9	1	1	1	11
Sitting quietly after lunch without alcohol	7	1	2	1	11
In a car while stopped a few minutes in traffic	7	2	1	1	11

Sleep concerns by age





Sleep and daytime sleepiness

Treatment options

1. Proper sleep hygiene, ENT and dental referral, medication review
2. Non-invasive ventilation
   - CPAP for obstructive sleep apnea
   - BiPAP for central apnea or hypoventilation
3. Medical management
   - Modafinil: mixed results (Cochrane Review 2006)
   - Stimulants : methylphenidate (vandermeche 1996, Puymirat 2012)

Medical Management and Monitoring

- Motor Strength and Myotonia
  - Myotonia rarely an issue in childhood
  - Muscle weakness initially improves over first years of life in CDM
  - Almost all children walk
  - More typical pattern of muscle weakness in those with childhood DM1
  - Hand and facial strength an issue for leisure, activities of daily living and eating

Medical Management and Monitoring
Motor Strength and Myotonia

Myotonia:

- Rarely a problem early – ie. before teen years, but after that can be an issue
- Mexiletine is used most often
- No quality study of drugs used in this situation (Cochrane review 2006)
- Phenytoin, carbamazepine, mexiletine have risk of cardiac arrhythmia- ECG pre/post
- Tricyclic antidepressants can be useful

Medical Management and Monitoring

- Cardiac
  - 80% of children with DM1 will have some ECG abnormality
  - Rare before age 10
  - Symptoms of fainting or palpitations common sign of heart problems
  - Can be asymptomatic or the first sign of DM1
  - An abnormal ECG is associated with cardiac death in adults (Groh 2008)
  - Treatment: pacemakers

Medical Management and Monitoring

- Gastro-Intestinal
  - Chewing and swallow difficulties
    - Change in feeding techniques, g-tube
  - Pseudo-obstruction
    - Symptomatic treatment
  - Gastro-esophageal reflux
    - Antacid
  - Diarrhea
  - Constipation in 34%
    - Motility agent
    - PEG 3350

Medical Management and Monitoring

- Ophthalmology
  - Strabismus (cross-eyed) in 25-50% of children
  - Amblyopia (22%)
  - Cataracts very uncommon in pediatric practice
  - Need for corrective lenses (86%)

Medical Management and Monitoring

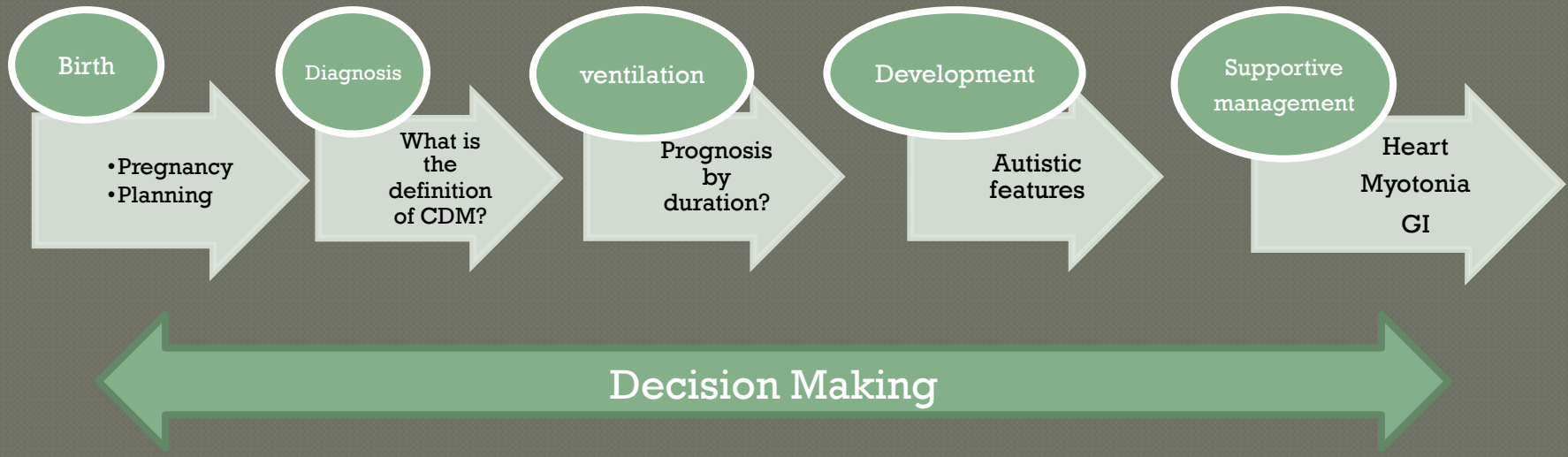
- Orthopedic
  - Scoliosis in 10%
    - Bracing and surgery
  - Contractures
    - Night splints, Ankle Foot Orthoses
  - Fragility fractures
    - Very uncommon, symptomatic management
  - Joint subluxation/dislocations

Medical Management and Monitoring
Motor Strength and Myotonia

- Other medical complications:
  - Diabetes: not reported until adulthood
  - Hypothyroidism: not reported until adulthood
  - Bladder dysfunction
  - Oral Health: more cavities and gingivitis than other children

- Potential treatment for DM1 with AON
  - Similar drug being used in babies with SMA
  - Data on safety in adult DM1 due soon
- What risk would one take for congenital DM1 child on a ventilator?
- Is that different for a child on feeding tube?
- What about the older child?
- Do you feel people with DM1 are more or less likely to take risks about treatment?

Childhood DM1 profile



Are you satisfied with the decision making process?
Are your preferences taken into account during decision making?
Are you satisfied with your decisions?
Are you compliant with your decisions?

Summary

- Congenital DM1 is not well defined and so it is difficult to paint a uniform picture for parents
- Disorder of muscle immaturity
- Developmental and intellectual issues are key to advocate for the children
- Many other medical issues need to be monitored and discussed
- Are we supporting decisions properly?
- Need to plan for clinical trials in pediatric patients

Thank you

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