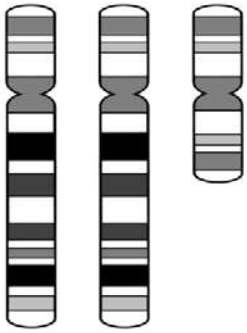
THE CHROMOSOME 18 REGISTRY & RESEARCH SOCIETY

UT Health San Antonio
The Chromosome 18 Clinical Research Center

Tetrasomy 18p
Treatment and Surveillance

ICD-10 =Q93.2

These recommendations are inclusive of the entire population of people with Tetrasomy 18p. It should be noted that there is a great deal of variation among individuals with Tetrasomy 18p. Not all complications or concerns will be listed in this document. However, the recommendations contained here should be used as a baseline for monitoring and the health of individuals with Tetrasomy 18p



Potential conditions in a neonate:

- Structural
  - Palatal anomalies – 81%
  - Heart abnormalities – 47% by Echo/ECG
  - Congenital orthopedic abnormalities – 45%
  - Hernias – 12%
  - Myelomeningocele – 7%
- Functional
  - Feeding problems – 83%
  - Respiratory distress – 31%
- Biochemical
  - Jaundice – 57%

Initial evaluations after diagnosis:

- Ophthalmology
  - Strabismus – 75%
  - Refractive errors – 71%
- Audiology/Otolaryngology
  - Hearing loss – 32%
  - Recurrent otitis media – 57%
- Genitourinary
  - Cryptorchidism – 63%
  - Hypospadias – 7%
  - Urinary tract anomalies – 28%

Immediate Referrals to:

- Appropriate subspecialist as indicated by initial evaluations
- Genetics follow-up if not previous to diagnosis
- Early intervention/developmental services
- The Chromosome 18 Registry & Research Society
- The Chromosome 18 Clinical Research Center

Closely monitor and manage:

- Failure to thrive/ growth failure
  - Underweight (<3rd percentile)
- Endocrinology
  - Short stature (<25th percentile)
  - Growth hormone deficiency
- Otorhinolaryngology
  - Recurrent otitis media
  - Hearing loss
- Gastroenterology
  - Constipation
  - GE reflux
  - Hernias
  - Eosinophilic esophagitis
- Immunology/Rheumatology
  - Atopic disorders
  - IgA deficiency
  - Eosinophilic esophagitis
- Orthopedics
  - Congenital hip dysplasia
  - Foot abnormalities
  - Decreased bone mineral density
- Development
  - Milestones
  - School performance
  - Psychometric data
- Dental
- Neurology
  - Seizures
  - Hypotonia
- Behavior/mood changes

Annual Screenings:

- Vision
- Hearing

Current Adult Status

Age and Cause of Death

Updated 2020

Potential conditions in a neonate:

- Structural
    - Palatal anomalies – 81%
        - High, arched or narrow
    - Cardiac abnormalities – 47% by Echo and ECG
        - Most common: PDA 17%, VSD 14%, PFO 7%, ASD 5%. None of these required surgery as most of these closed spontaneously
        - Other less occurred cardiac anomalies have included : hypoplastic transverse aortic arch; right ventricular hypertrophy; pulmonic stenosis; and valve abnormalities
    - Congenital orthopedic abnormalities – 45%
        - Club foot – 14%
        - Vertical talus – 5%
        - Metatarsus adductus – 5%
        - Rocker bottom foot – 5%
        - Hip dysplasia – 17%
    - Hernias (hiatal, inguinal, umbilical) – 12%
    - Myelomeningocele – 7%
- Functional
    - Feeding problems – 83%
        - Due to hypotonia, high arched palate or gastroesophageal reflux
    - Respiratory distress – 31%
- Biochemical
    - Jaundice – 57%

Initial evaluations after diagnosis:

- **Ophthalmology**
    - Strabismus – 75%
    - Esotropia – 17%
        - Accommodative – 30%
        - Infantile – 21%
        - Acquired non-accommodative – 8%
        - Intermittent – 8%
    - Esophoria – 4%
    - Intermittent exotropia – 4%
    - Refractive errors – 71%
        - Myopia – 17%
        - Hyperopia – 33%
        - Astigmatism – 25%
    - Anisometropia – 17%

- **Audiology / Otorhinolaryngology**
    - Hearing loss – 32%
        - Conductive, sensorineural, and mixed hearing loss have all been reported
    - Recurrent otitis media – 57%
    - Small or narrow ear canals – 42%
    - Laryngomalacia – 2%

- **Genitourinary**
    - Cryptorchidism – 63%
    - Hypospadias – 7%
    - Urinary tract anomalies – 28% (horseshoe kidney and bladder diverticuli, small kidney, renal cyst, hydronephrosis, vesicoureteral reflux varying degrees)
        - The actual incidence of kidney abnormalities may be higher than reported in the literature as abdominal ultrasounds have not performed on all individuals

Immediate Referrals to:

- **Genetics**
    - Referral to genetics is appropriate to review the condition, its management, and implications for other family members
    - A minority of parents of children with Tetrasomy 18p have a chromosome abnormality
    - There have been case reports of parents with mosaicism or with some type of chromosome rearrangement

- **Early intervention/developmental services**
    - All children with chromosome 18 abnormalities have a significant risk for developmental delay and intellectual disabilities. Prompt referral to a program the includes physical, occupational and speech therapy is important in order maximize their development
    - 100% with Tetrasomy 18p have developmental delay
    - 100% have muscle tone abnormalities that may benefit from physical therapy
    - 100% have intellectual disability, though the degree of severity varies

- **Referral to Chromosome 18 Registry & Research Society**
    - The Chromosome 18 Registry is a parent support organization that provides family members with the opportunity to meet and learn from those who have gone before them. These are complex conditions to manage even in the least affected children, making the establishment of a network of support a crucial component for maximizing the affected child's potential. The Registry has annual national and international conferences, regional get-togethers and social media outlets, all with programs for parents, siblings and affected adults. The Registry works closely with and financially supports the Chromosome 18 Clinical Research Center. (www.chromosome18.org)

- **Referral to the Chromosome 18 Clinical Research Center**
    - The goal of the Chromosome 18 Clinical Research Center is to make the chromosome 18 abnormalities the first treatable chromosome abnormalities. Anyone with any chromosome 18 abnormality is eligible to enroll and encouraged to enroll. Once enrolled, participants have the opportunity to be involved in longitudinal studies of developmental progress, and when available, other studies that could include surveys or treatment trials. Families enrolled in the Research Center will also be the first to know new information about the conditions when it becomes available. Enrollment is a key part of proactive clinical management (www.pediatrics.uthscsa.edu/centers/chromosome18)

Closely monitor and manage:

- **Failure to thrive/ growth failure**
    - Underweight (<3rd%) – 19%
    - Weight gain

      Due to their hypotonia, feeding may be more difficult for an infant with Tetrasomy 18p. In addition, many affected children have gastroesophageal reflux, which increases not only their risk for aspiration, but also for pain, discomfort or emesis after feeding. Children <3 years who are failing to meet expected rates of weight gain should be evaluated for reflux and potentially for placement of a feeding tube. In addition, there have been a few individuals with Tetrasomy 18p that have been diagnosed with eosinophilic esophagitis

- **Endocrinology**
    - Short stature (<25%) – 52%
    - Failed two growth hormone provocative tests – 19%
    - IGF1 and IGFBP3 are not definitive tests for GH deficiency in these children
    - Children that are failing to grow linearly (length or height) at expected rates for age and sex should be tested using growth hormone stimulation (provocative) testing. This testing is typical performed by a pediatric endocrinologist
    - Thyroid and gonadotropin testing was normal in all participants but one individual (12 years old) is on thyroid medication because of hypothyroidism
    - Type 2 Diabetes – 1%

- **Otorhinolaryngology**
    - Recurrent otitis media – 57%
        - It is important to monitor hearing and treat ear infections quickly to avoid hearing loss and delayed speech development
    - Hearing loss – 32%
        - Conductive – 29%
        - Sensorineural – 12 %
        - Mixed hearing loss – 7%
        - Unspecified – 8%

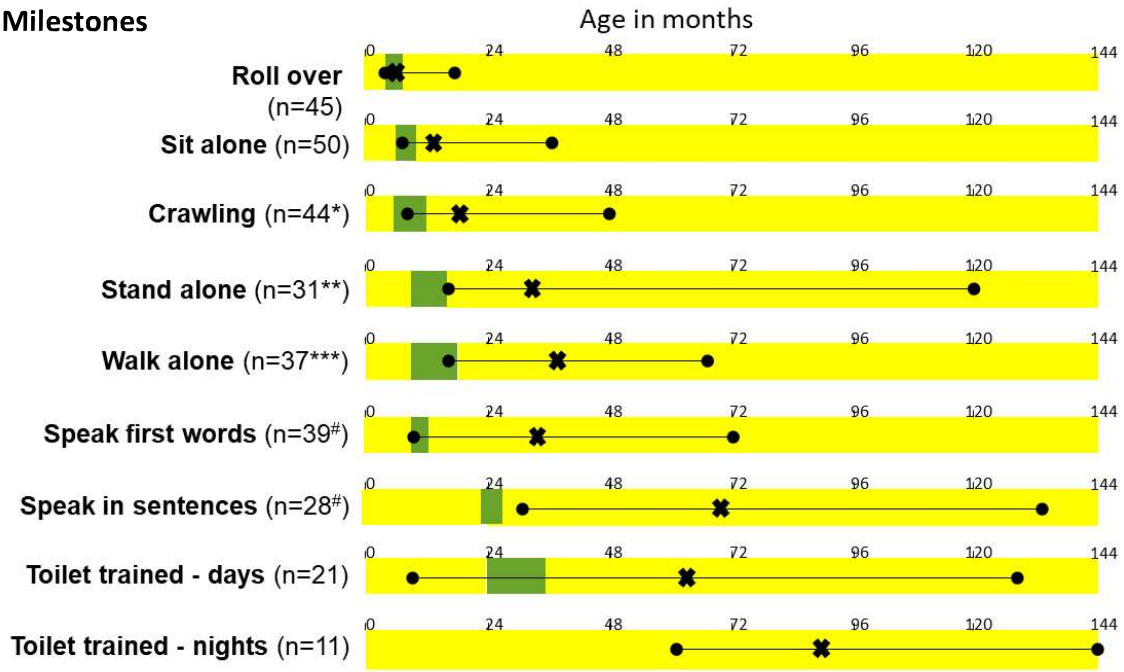
- **Gastroenterology**
    - Chronic constipation – 76%
        - This is a chronic issue and failure to successfully manage bowel issues has resulted in failure to ever achieve bowel continence and has even resulted in the need for ileostomy. There are no data indicating neuogenic bowel disease but the serious and chronic nature of the constipation resembles such a condition
    - GE reflux – 36%
    - Hernias (hiatal, inguinal, umbilical) – 12%
    - Pyloric stenosis – 5%
    - Eosinophilic esophagitis – only a few individuals have been definitively diagnosed by endoscopy, however a significant proportion have some symptomology

- **Immunology/Rheumatology**
  - Atopic disorders
    - Food allergies – 33%
    - Asthma – 9%
    - Hay fever – 45%
    - Eczema – 21%
  - IgA deficiency – 18%
  - Arthritis – 5%
  - Celiac disease in one individual
  - Eosinophilic esophagitis – only 3 individuals have been definitively diagnosed by endoscopy

- **Orthopedics**
  - Orthopedic abnormalities – 69%
    - Scoliosis or kyphosis – 53%
    - Pes planus – 49%
    - Hip dysplasia –17%
    - Club foot – 14%
    - Metatarsus adductus 5%, Rocker bottom feet 5%, Vertical talus 5%
  - Low BMD (so far 100% of those assessed have low bone mineral density)

- **Development**
  - The average full scale IQ score is 48
  - Cognitive abilities vary significantly;
    - 37% in the mild range
    - 37% moderate
    - 26% in the severe to profound range

- **Milestones**



*2 skipped crawling
** 2 can not stand alone (ages 2 and 6)
*** 4 can not walk alone (ages 2,2, 6 and 13)
# 7 do not speak (ages 2, 2, 5, 6, 11, 13, 15)

Updated 2020

Tetrasomy 18p

June 2020

Within Normal Limits | At Risk | Clinically Significant

✖ = average score
●—● = the range of all the scores
N= the number of participants

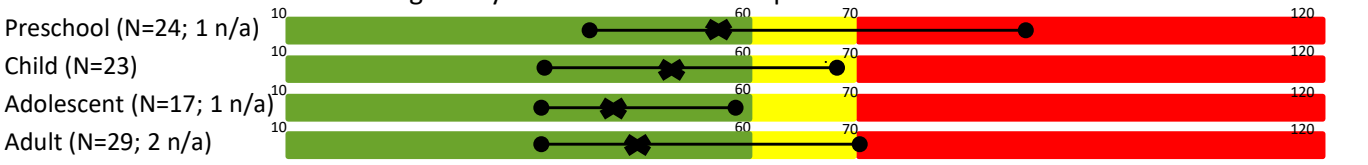
Data from the Behavior Assessment System for Children and Adults (BASC)

Internalizing Behaviors (problems that manifest internally

Anxiety: nervous, fearful and worrisome tendencies

Depression: incapacitating sadness or stress

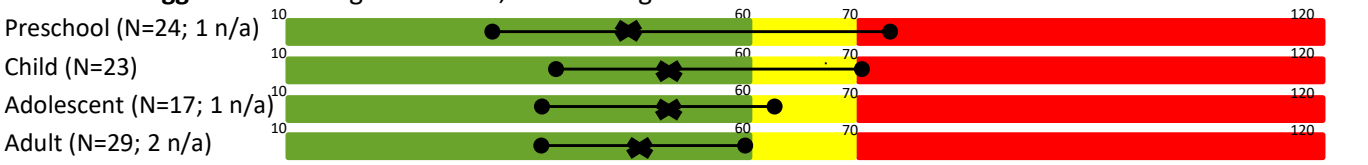
Somatization: behaving overly sensitive about minor problems



Externalizing Behaviors (problems that manifest externally)

Hyperactivity: overly active, acting without thinking

Aggression: acting in a hostile, threatening manner

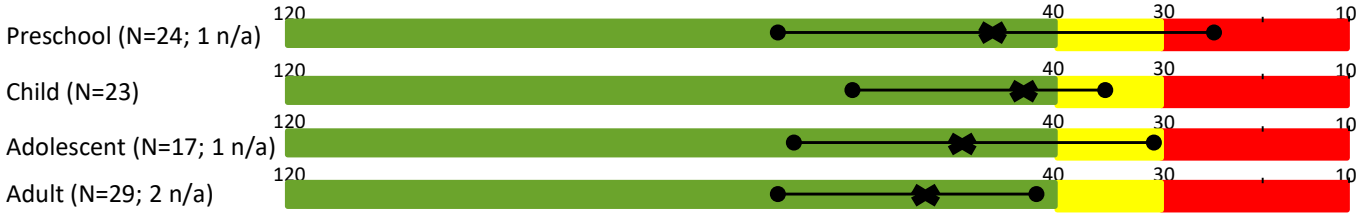


Conduct Problems: anti-social and rule-breaking behaviors

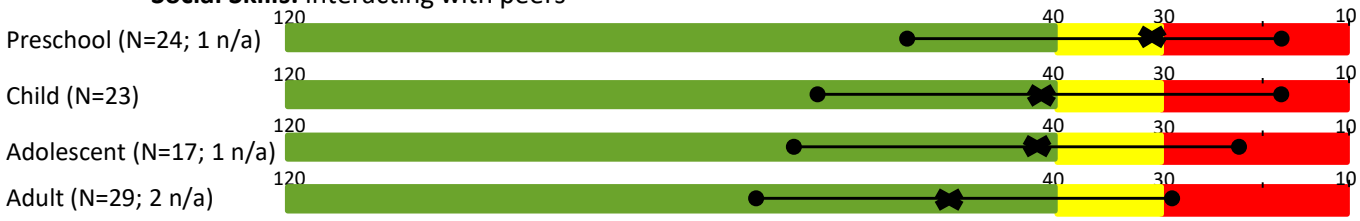
Data from the Behavior Assessment System for Children and Adults (BASC) - continued

Adaptive Skills: skills learned and used in daily life

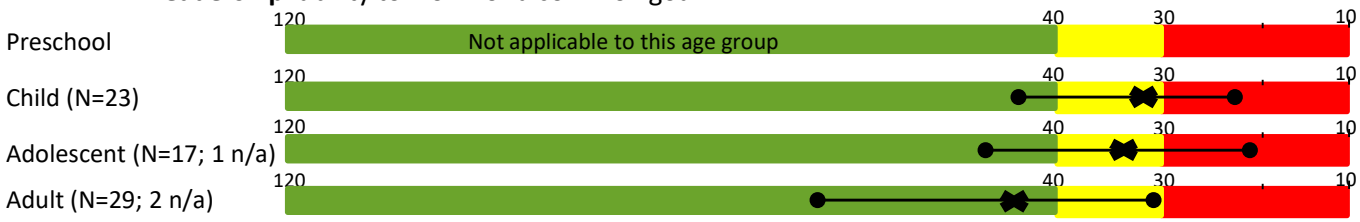
Adaptability: ability to adapt to change



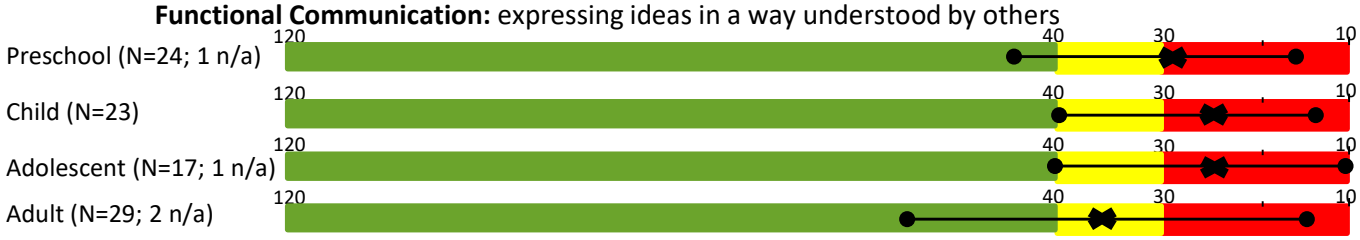
Social Skills: interacting with peers



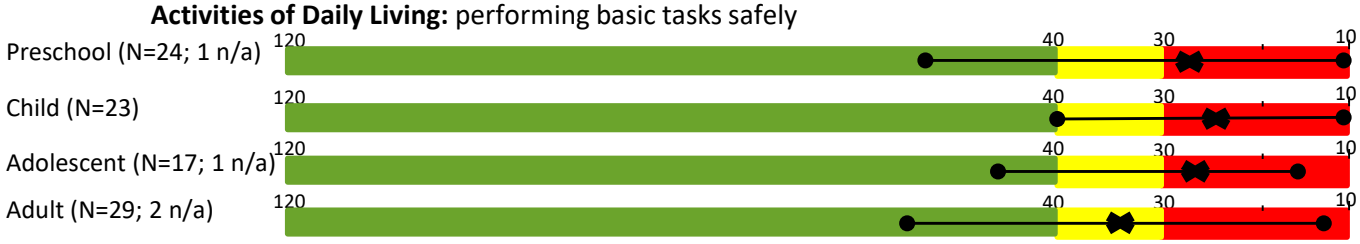
Leadership: ability to work for a common goal



Functional Communication: expressing ideas in a way understood by others



Activities of Daily Living: performing basic tasks safely

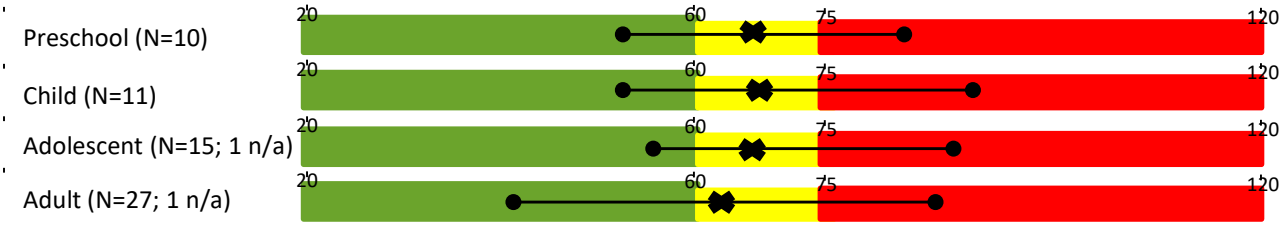


Tetrasomy 18p

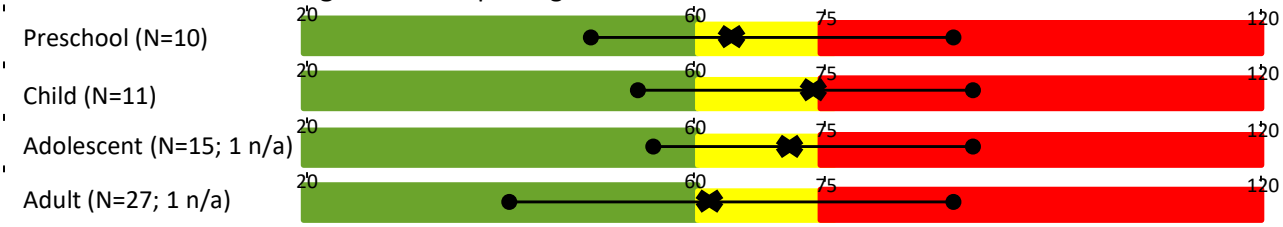
June 2020

Social Responsiveness Scale (SRS)

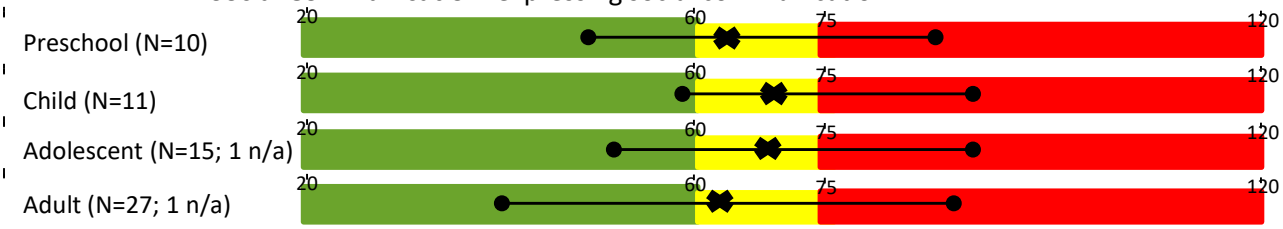
Social Awareness: ability to pick up on social cues



Social Cognition: interpreting social cues

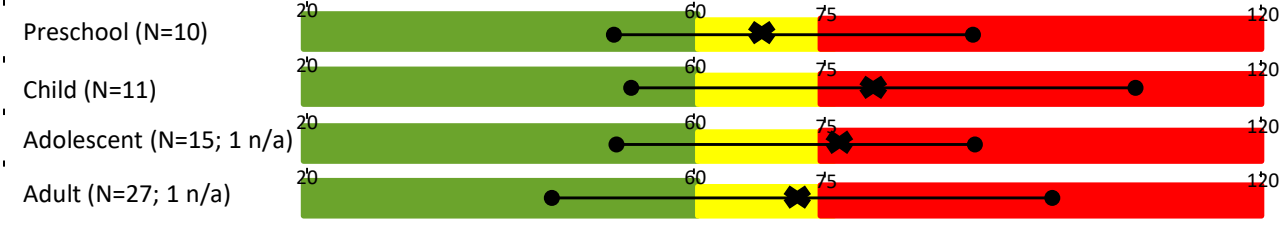


Social Communication: expressing social communication



Social Motivation: motivation to engage in social behavior

Restricted Interest and Repetitive Behavior: repeating behaviors/obsessing over routines



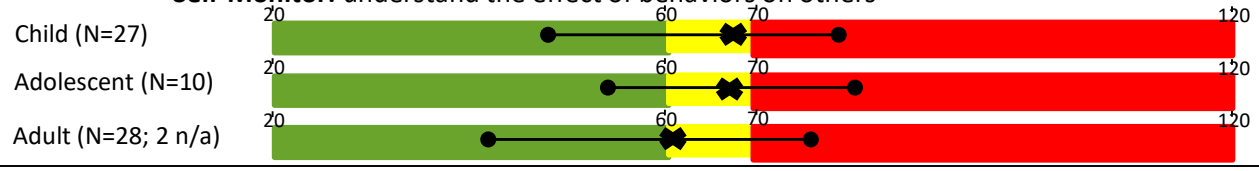
Tetrasomy 18p

Behavior Rating Inventory of Executive Function (BRIEF)

Behavioral Regulation: ability to regulate and monitor behavior effectively

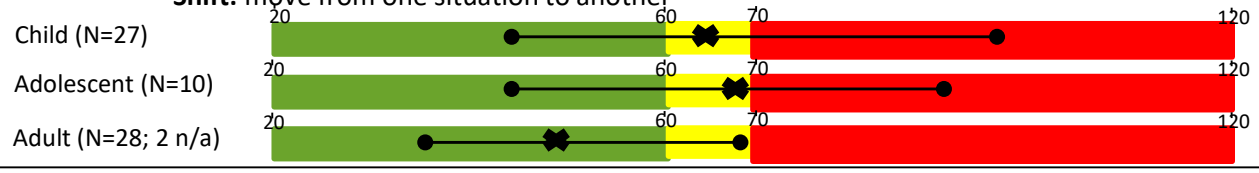
Inhibit: inhibiting behavior or not acting on an impulse

Self-Monitor: understand the effect of behaviors on others

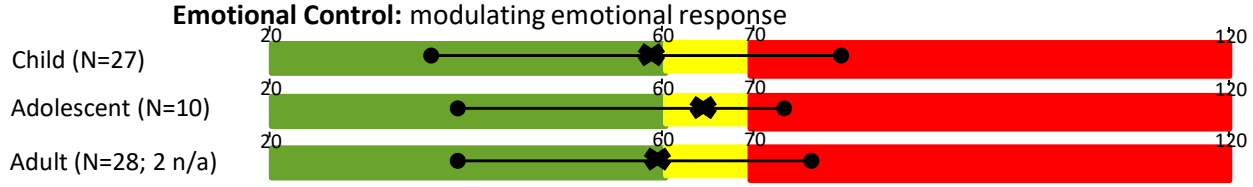


Emotional Regulation: ability to regulate emotional responses

Shift: move from one situation to another



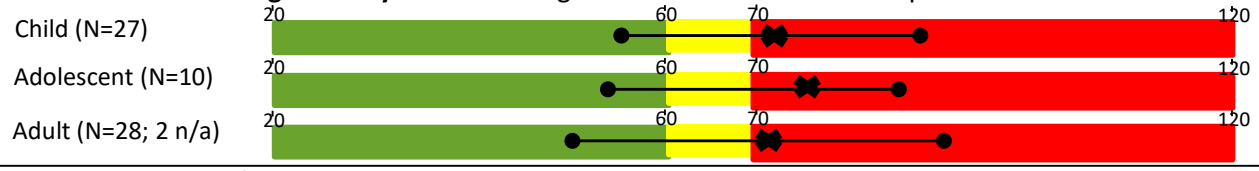
Emotional Control: modulating emotional response



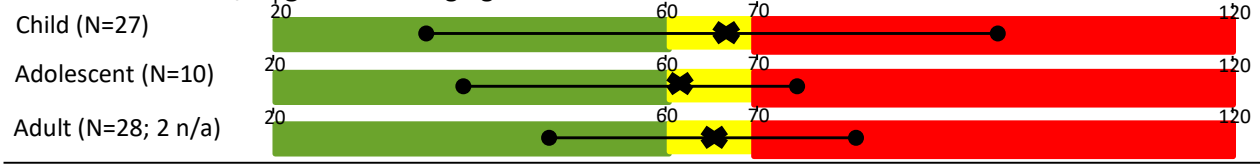
Cognitive Regulation: ability to control and manage cognitive processes and problem solve effectively

Initiate: beginning tasks

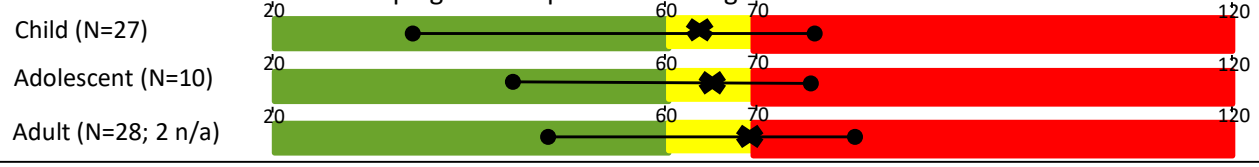
Working Memory: remembering information in order to complete a task



Plan / Organize: managing current and future orientated tasks



Task Monitor: keeping track of problem solving successes or failures



Organization of Materials: keeping work and living spaces orderly

June 2020

Adaptive Behavior Assessment System (ABAS)

Conceptual Composite (ideas that occur in the mind, speech or in thought)

Communication (speech, language, and listening skills needed for communication with other people)

Functional Academics (basic academic skills needed for daily, independent functioning)

Self-Direction (skills needed for independence, responsibility and self-control)

Social Composite (skills needed to interact with others)

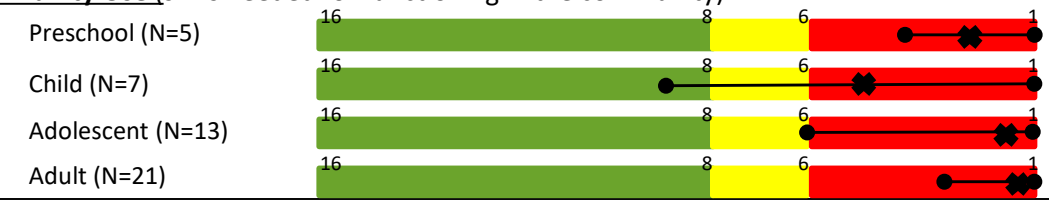
Leisure (skills needed for engaging in and planning leisure and recreational activities)

Social (skills needed to interact socially and get along with other people)

Adaptive Behavior Assessment System (ABAS - continued)

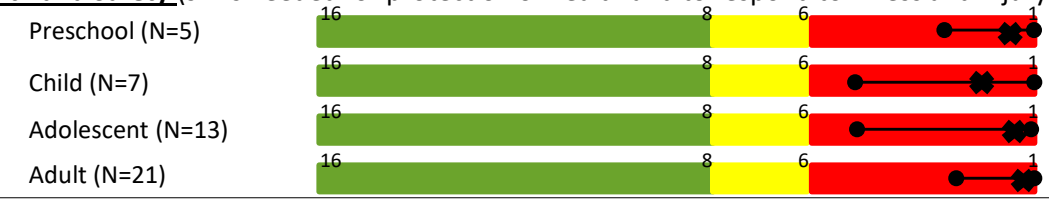
Practical Composite (skills needed for independent living)

Community Use (skills needed for functioning in the community)



Home Living (skills needed for basic care of a home or living setting)

Health and Safety (skills needed for protection of health and to respond to illness and injury)



Self-Care (skills needed for personal care)

Work (skills needed for successful functioning and holding a part/full time job)

Not in a composite

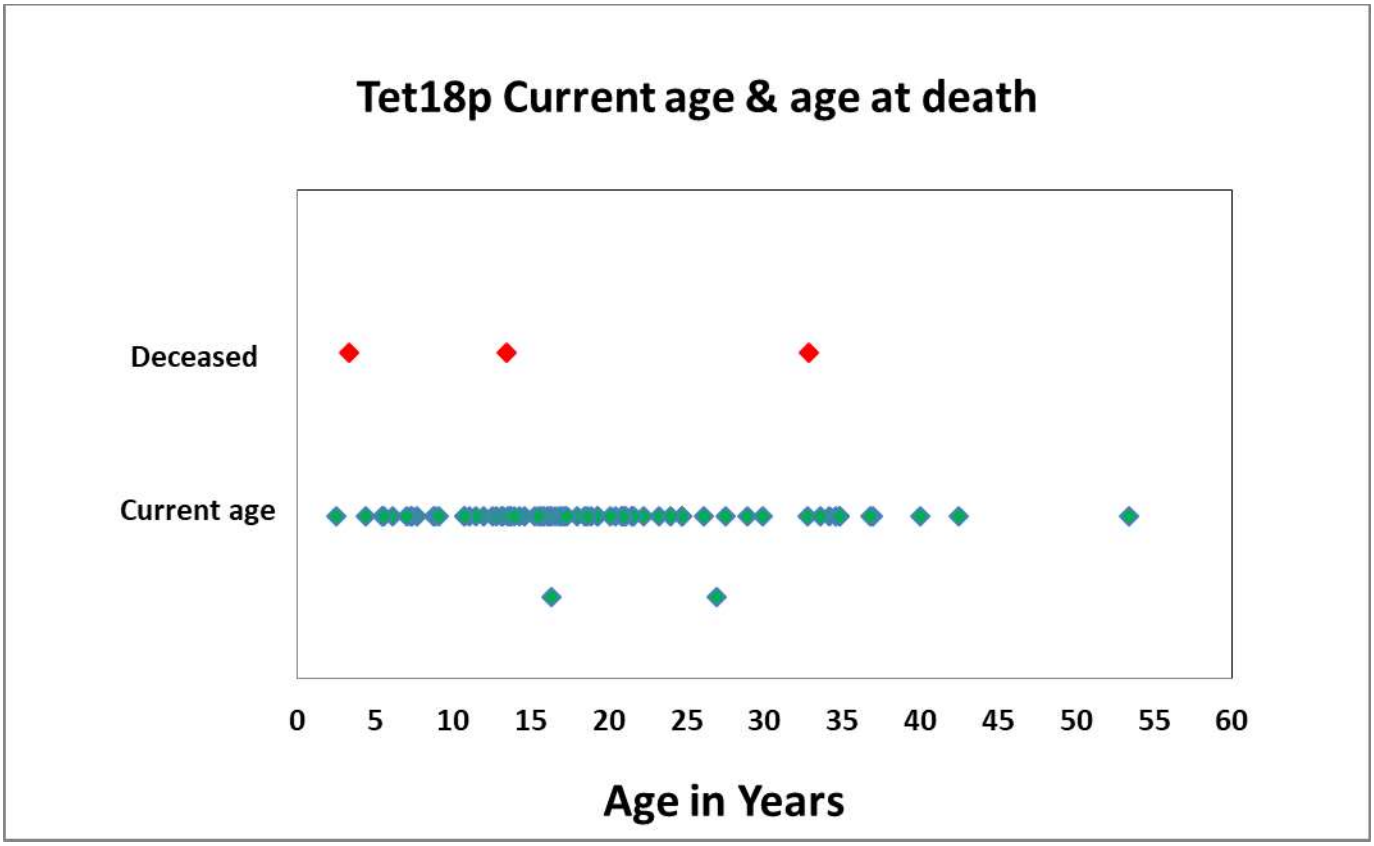
Motor (skills needed to perform fine and gross motor activities)

- **Dental**
    - Dental crowding – 19%
- **Neurology**
    - Brain MRI variants – 58%
        - White matter changes (hyperintense /hypointense signal areas; low volume of white matter; hypomyelination) ~30%
        - Corpus callosum abnormalities (thin/hypoplastic)– 28%
        - Ventricular system enlargement – 23%
        - Choroid plexus cyst – 9%
        - Chiari malformation – 7%
        - Periventricular Leukomalacia – 7%
        - Iron deposition – 2%
        - Mastoiditis – 2%
        - There are other MRI changes in single individuals like: lipoma; extra fluid surrounding the brain; small pineal cyst
    - Seizures – 54% (most of the seizures were caused by fever/illness 33%, whereas 23% had no apparent trigger)
    - Microcephaly – 74%
    - Ptosis – 13%
    - Myelomeningocele – 7%
    - Abnormal muscle tone – 98%
        - Hypotonia – 50%
        - Hypertonia – 19%
        - Mixed tone – 28%
- **Behavior/mood changes:**
    - Children - Problems with functional communication (97%), activities of daily living (91%), attention problems (61%), hyperactivity (54%)
    - Adults – Problems with functional communication (62%), activities of daily living (62%), hyperactivity (54%)
- **Executive Function**:
    - Children – Problems with working memory (95%), task monitoring (90%), inhibiting (85%), initiating (70%), planning/organizing (70%), shifting (60%), emotional control (50%)
    - Adults – Problems with working memory (93%), initiating (71%), inhibiting (64%), shifting (64%), planning/organizing (64%), task monitoring (50%)
- **Social Impairment:**
    - Children and Adults – Problems with social cognition (91%), restricted interests and repetitive behaviors (91%), social awareness (82%), social communication (73%), social motivation (55%)

- There is no reason to think that they are at increased risk for surgical or anesthesia complications although they may need increased monitoring due to hypotonia.

Adult Status
(>18 years of age)

Tetrasomy 18p	
Total N=39	
Received Responses: N=32	
No Contact or No Response: N=5	
Deceased: N=2	
LIVING ARRANGEMENTS	
Lives with parents/guardians	24
Lives away from parents in a residence as part of a supervised independent living program	1
Lives away from parents (alone or with roommate) and receives assistance from support staff	1
Lives in group, foster or respite home	5
Lives with host family	1
HIGHEST EDUCATION LEVEL	
Did not complete high school	4
Completed high school (certificate)	11
High School Graduate (received diploma)	7
Currently attends centers based/transitional progam post high school	4
Completed transitional program post high school	4
Vocational School Certificate/Degree	2
MARITAL STATUS	
Married (Yes)	0
Married (Never)	32
CHILDREN	
Children (Yes)	0
Children (No)	32
WORK POSITIONS	
Part Time PAID	1
Part Time PAID and Volunteer	4
Volunteer and Day Habilitation Program	2
Volunteer	3
Through school (work study, etc…)	6
Attends day habilitation program	7
Does not work	9



Age deceased	Gender	Tet18p Cause of death	Past medical history
3 years 5 months	F	n/a	IUGR; static encephalopathy; severe GERD; G-tube; horseshoe kidney; scoliosis; medical records available only as a an infant.
13 years 5 months	F	Sudden heart arrest. One day of history of nausea, vomiting and lethargy. Autopsy: significant dilatation of her colon.	Significant constipation; question of seizures; a small VSD that closed on its own; broken bones (prone to accidents); left peroneal nerve palsy; osteoporotic ?;postleft tendo-Achilles lengthening.
32 years 11 months	M	n/a	Seizures; history of constipation (infant) dystonia; ataxia, tremors; sleep apnea;kidney disease;bilateral hydronephrosis ; cryporchidism; type 2 diabetes after kidney transplant (at 32 yrs old); deep vein thrombosis; low platelet count; IgA deficiency; cholecystectomy;

Updated 2020

References

Abeliovich D, Dagan J, Levy A, Steinberg A, Zlogogora J (1993). Isochromosome 18p in a mother and her child. Am J Med Genet 46: 391-393.

Boyle J, Sangha K, Dill F, Robinson WP, Young SL (2001). Grandmaternal origin of an isochromosome 18p present in two maternal half-sisters. Am J Med Genet 101:65-69.

O'Donnell L, Soileau BT, Sebold C, Gelfond J, Hale DE, Cody JD (2015). Tetrasomy 18p: Report of cognitive and behavioral characteristics. Am J Med Genet Part A 167A: 1474-1482.

Sebold C, Roeder E, Zimmerman M, Soileau B, Heard P, Carter E, Schatz M, White WA, Perry B, Reinker K, O'Donnell L, Lancaster J, Li J, Hasi M, Hill A, Pankratz L, Hale, DE, Cody JD (2010). Tetrasomy 18p: Report of the Molecular and Clinical Findings of 43 Individuals. Am J Med Genet Part A 152A: 2164-2172.

Soileau B, Hasi M, Sebold C, Hill A, O'Donnell L, Hale DE, Cody JD. Adults with Chromosome 18 Abnormalities. J Genet Couns. 2015 Aug;24(4):663-74

Takeda K, Okamura T, Hasegawa T (1989). Sibs with tetrasomy 18p born to a mother with trisomy 18p. J Med Genet 26: 195-197.