

18p-

Treatment and SurveillanceICD-10 = Q99.9 or Q93.89

These recommendations are inclusive of the entire population of people with 18p deletions. Even though about half of this group have deletions of the entire short arm of the chromosome and the other half have individually unique deletion of only a portion of the chromosome arm. Consequently, not everyone with 18p- has exactly the same genes that are hemizygous. The specific hemizygous genes for an individual patient will dictate the probability of particular phenotypes. However, the information in this document includes the global 18p- evaluation and management plan.

**18p-**

An interstitial or terminal deletion of any region of chromosome 18p between the end of the chromosome (at 1bp) and the centromere (at 15.6 Mb). 18p has 66 genes, only a few of which are thought to either lead to haploinsufficiency or are conditionally dosage sensitive. For more information on the genes see:

<https://wp.uthscsa.edu/chromosome-18/research>

Potential conditions in a neonate:

- Structural
 - Hernias (inguinal, umbilical)
 - Heart abnormalities
 - Cryptorchidism
 - Sacral agenesis / myelomeningocele
- Functional
 - Respiratory distress
 - Feeding problems
 - Hypotonia
- Biochemical
 - Jaundice
 - Hypoglycemia

Initial evaluations after diagnosis

- Cerebral MRI - abnormalities - >70%
- Ophthalmology exam –
 - ptosis – 47%
 - vision and optic problems - >38%
- Audiology evaluation - hearing deficits - >22%
- Thyroid evaluation -thyroid problems – 17%
- Cardiology exam - cardiac defects - 45%
- Orthopedic exam - orthopedic problems 47%
- Renal ultrasound- hydronephrosis or malformations – 14%

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**
 - Weight gain
 - Linear growth
- **Ear infections**
- **Immunology/Rheumatology:**
 - Atopic disorders
 - Arthritis
 - Other autoimmune conditions
- **Orthopedics**
 - Scoliosis or kyphosis
 - Sacral agenesis
- **Development:**
 - Milestones
 - Psychometric data
 - Current Adult Status
- **Neurology:**
 - Seizure disorder
 - Balance problems
 - Muscle weakness
 - Hypotonia

Annual screenings

- Thyroid
- Vision
- Hearing

Current Adult StatusAge and Cause of Death

Potential conditions in a neonate:

- Structural
 - Hernias (inguinal, umbilical) – 29%
 - Cardiac abnormalities – 56%
 - Cryptorchidism in 14%
 - Sacral agenesis - 6%
 - Myelomeningocele - 3%
- Functional
 - Respiratory distress and feeding difficulties – 42%
 - Feeding problems- 42%
 - Hypotonia – 71%
 - Mixed abnormal tone – 13%
- Biochemical
 - Jaundice – 29%
 - Hypoglycemia in 8% and 5% were diagnosed with panhypopituitarism.

Initial evaluations after diagnosis:

- **Cerebral MRI/ Neurology**
 - Holoprosencephaly or HPE microform – 13%
 - Other MRI abnormalities – 66%
 - Seizures – 13%
 - Myelomeningocele – 3%
- **Ophthalmology**
 - Ptosis – 47%
 - Strabismus – 38% . The exact gene responsible has not been identified but it is known to be within a small region between 1 and 1,192,031Mb. Only persons with a deletion including this region have this risk for this condition.
 - Myopia – 17%
 - Nystagmus – 9%
 - Congenital cataract – 6%
 - Optic nerve hypoplasia – 6%
- **Audiology and Otolaryngology**
 - Within the total population of people with 18p deletions:
 - Conductive hearing loss – 22%. The exact gene responsible has not been identified but it is known to be within a small region between 1 and 2,931,532 Mb. Only persons with a deletion including this region have this risk for this condition.
 - Sensorineural hearing loss – 8%. The exact gene responsible has not been identified but it is known to be within a small region between 1 and 1,192,031Mb. Only persons with a deletion including this region have this risk for this condition.
 - Narrow ear canals – 2%
 - Recurrent ear infections – 61%
- **Thyroid levels**
 - thyroid dysfunction – 17%
 - Secondary hypothyroidism is the most common
 - Antibody positive hypothyroidism is less common
 - Hyperthyroidism has been reported

- **Cardiology**
 - cardiac abnormality – 56% of those who had ECG
 - ASD or VSD – 40%
 - Tetralogy of Fallot – 15%
 - The exact gene responsible has not been identified but it is known to be within a region between 1 and 9,148,02Mb. Only persons with a deletion including this region have this risk for this condition.
 - The actual incidence of heart defects may be higher as ultrasound and ECG evaluations have not been consistently been performed on all affected individuals.
- **Orthopedic**
 - Orthopedics problems – 47%:
 - Scoliosis or kyphosis – 33%. The exact gene responsible has not been identified but it is known to be within a small region between 1 and 2,931,532 Mb. Only persons with a deletion including this region have this risk for this condition.
 - Pectus excavatum – 29%
 - Pes planus – 15%
 - Sacral agenesis - 3%
 - Hip dysplasia – 3%
- **Renal ultrasound**
 - Kidney abnormality - 14% - hydronephrosis or malformations
 - The actual incidence of kidney abnormalities may be different as abdominal ultrasound was not performed on all individuals.

Referrals to:

- **Genetics follow-up**
 - Genetics follow-up may be necessary if parental chromosomes have not been evaluated to rule out inherited rearrangement. ~12% of the participants in our study have a parent with a balanced rearrangement. Even if no other children are planned, if one parent has a balanced rearrangement then their other children or the siblings of that parent are a risk for having the same rearrangement and consequently have a very high risk of passing on an unbalanced chromosome compliment.
 - A genetics follow-up may also be indicated if the original diagnosis was performed using cytogenetic techniques or low resolution microarray technology. A high resolution SNP or CGH microarray can determine exactly which genes are involved in the deletion. This information will become increasingly important over time as gene-specific interventions are developed.

- **Early intervention/developmental services**

- Developmental delay – 100%. Prompt referral to a program that includes physical, occupational and speech therapy is important in order to maximize their development.
- Speech delay – 100%
 - Articulation problems – 49%
 - Delayed speech development – 30%
 - Apraxia – 12%
 - Non-verbal – 9%
- Motor delay – 96%
- Hypotonia / mixed tone abnormality – 84%

- **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**

- Weight gain
 - Due to their hypotonia, sucking or feeding may be more difficult for the child. Children <3 years who are failing to meet expected rates of weight gain should be evaluated for placement of a feeding tube.
 - 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 .

- Linear growth
 - Short (<2SD) - ~40%
 - Growth hormone deficient - ~30%
 - 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 typically done by a pediatric endocrinologist.
 - All treated individuals responded to GH replacement therapy (0.3 mg/kg/week) with rates of growth comparable to children with classical isolated GH deficiency

- **Ear infections**

- Recurrent otitis media – 63%

- **Immunology/Rheumatology:**

- Autoimmune disorders – 62%
- Atopic disorders /Hypersensitivity – 30%
- IgA, IgG or IgM deficiency – 13%
- Arthritis – 3%

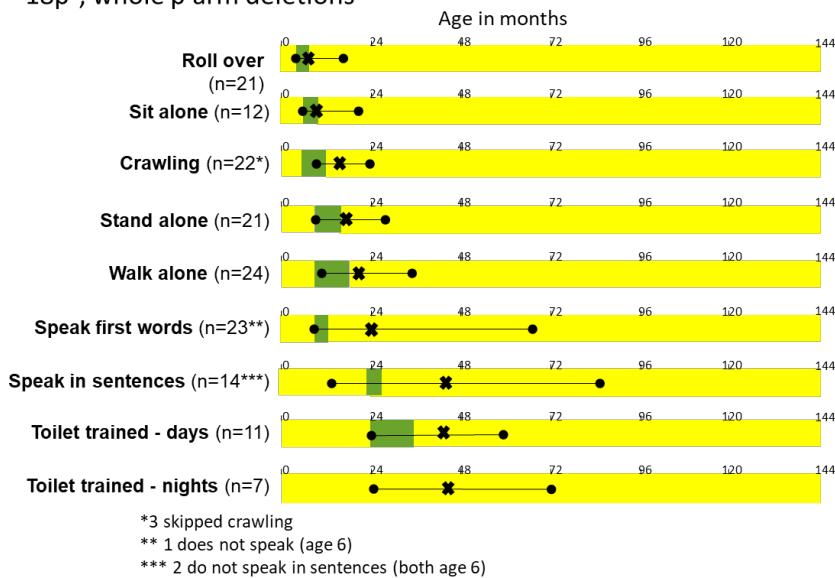
- **Orthopedics**

- Scoliosis or kyphosis – 33%
- Sacral agenesis – 6%

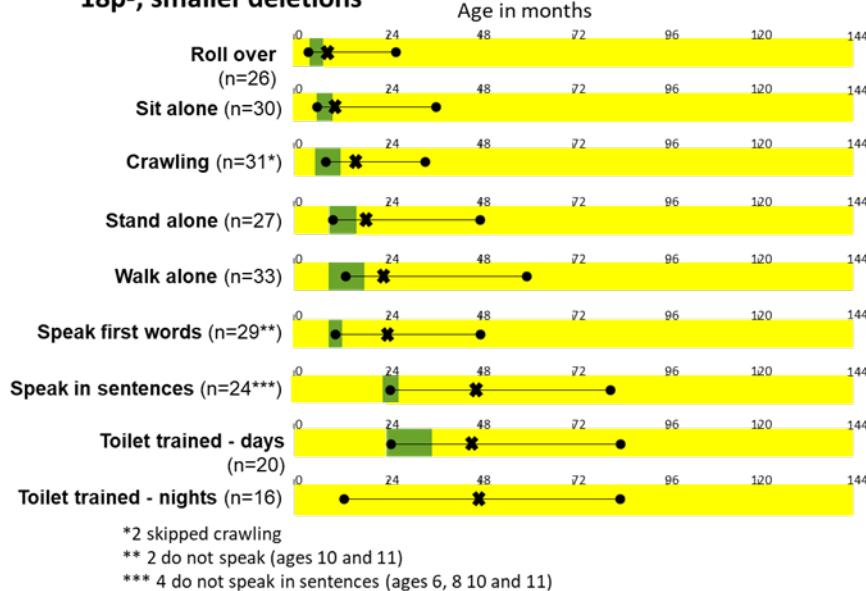
- **Development:**

- Milestones

18p-; whole p arm deletions



18p-; smaller deletions



- School performance— assure appropriate special educational services and support.
- Psychometric data
 - The following data are presented on a color coded bar graphs with the actual instrument's scale numbers indicated at the top of each.
 - The first set of data are from individuals with whole p arm deletions. These are followed by the same evaluations from people with smaller 18p deletions.

Within Normal Limits

At Risk

Clinically Significant

X = average score

● = the range of all the scores

N = the number of participants

Full Scale IQ
N=18

Verbal IQ
N=17

Nonverbal IQ
N=14

■ = normal IQ range

— = average IQ score

■ = mild ID range

■ = severe to profound

Autism (n=21)

Asperger's (n=19)

Adaptive Behavior (n=19)
Vineland-II

Adaptive Behavior (n=14)
ABAS-II

Externalizing Problems (n=21)

Internalizing Problems (n=21)

Adaptive Skills (n=21)

Executive Function (n=21)

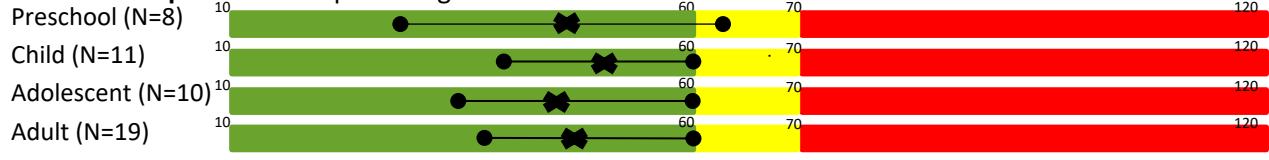
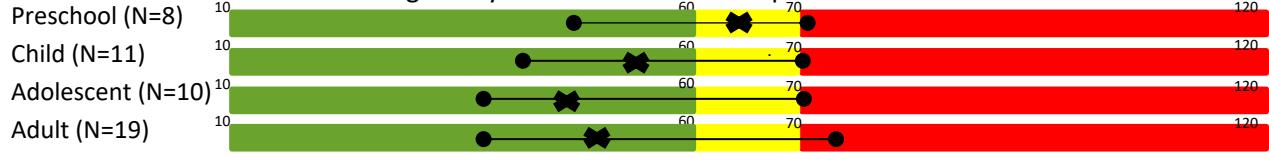
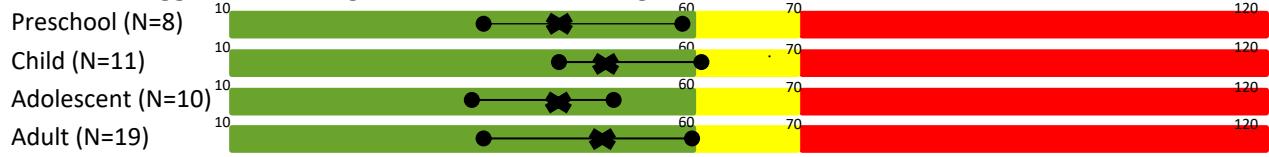
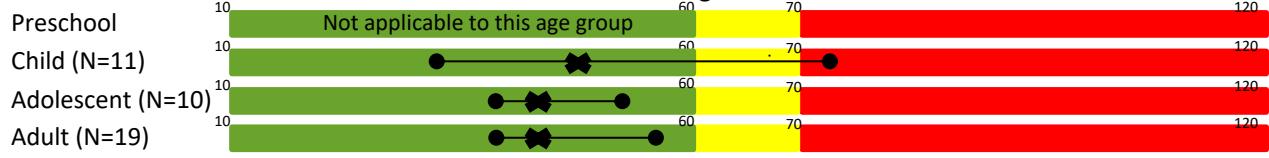
X = Average score

—●— = the full range of scores

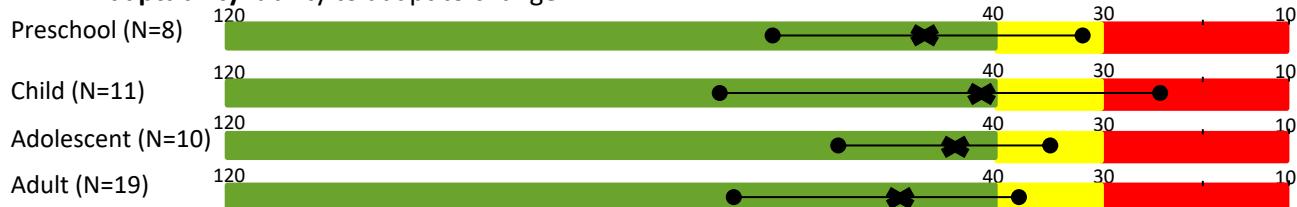
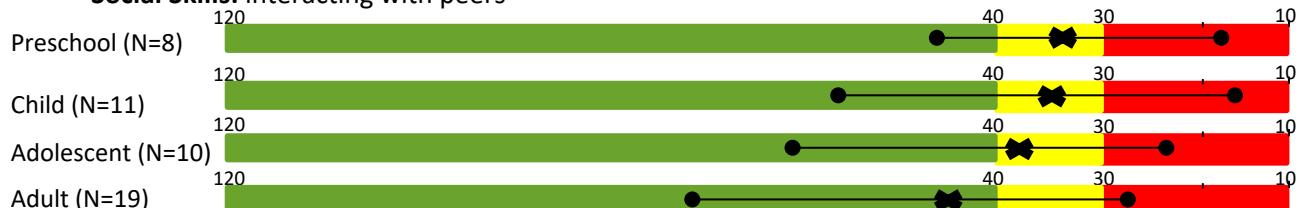
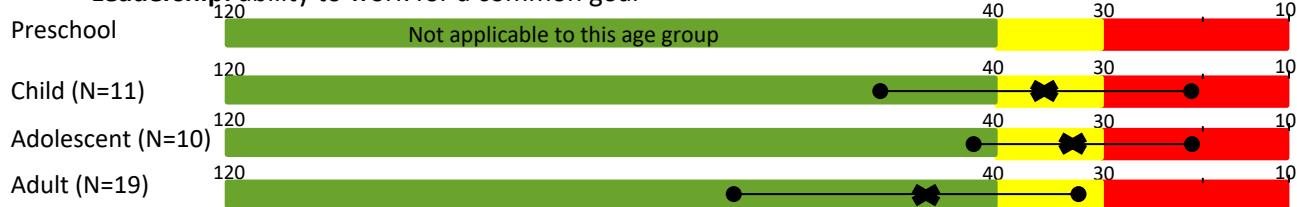
■ = normal range

■ = "at risk" range

■ = problem range

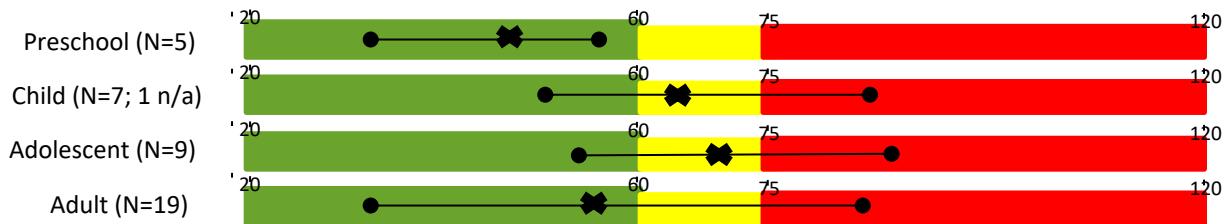
Data from the Behavior Assessment System for Children and Adults (BASC)**Internalizing Behaviors** (problems that manifest internally)**Anxiety:** nervous, fearful and worrisome tendencies**Depression:** incapacitating sadness or stress**Somatization:** behaving overly sensitive about minor problems**Externalizing 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

18p-; whole p arm deletions

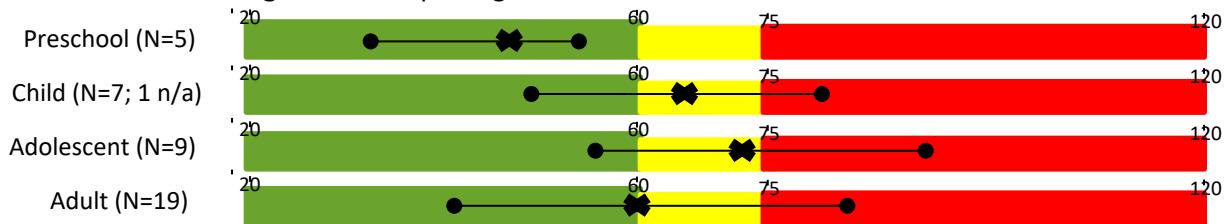
Data from the Behavior Assessment System for Children and Adults (BASC) - continued**Adaptive Skills:** skills learned and used in daily life**Adaptability:** ability to adapt to change**Social Skills:** interacting with peers**Leadership:** ability to work for a common goal**Functional Communication:** expressing ideas in a way understood by others**Activities of Daily Living:** performing basic tasks safely

Social Responsiveness Scale (SRS)

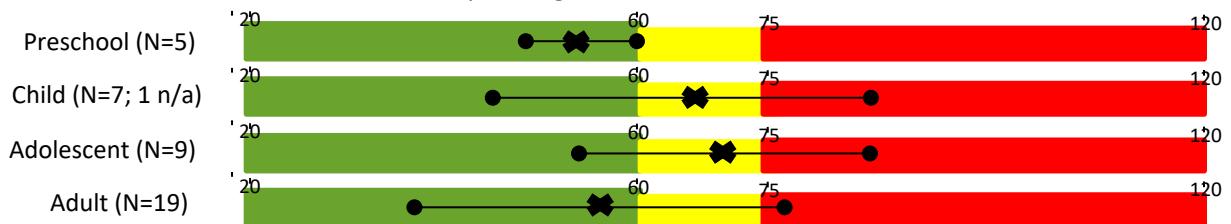
Social Awareness: ability to pick up on social cues



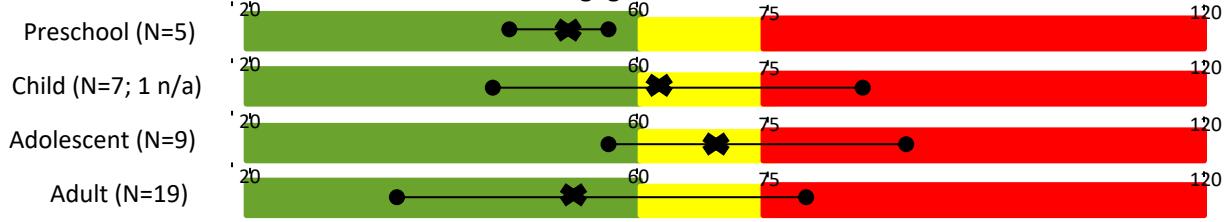
Social Cognition: interpreting social cues



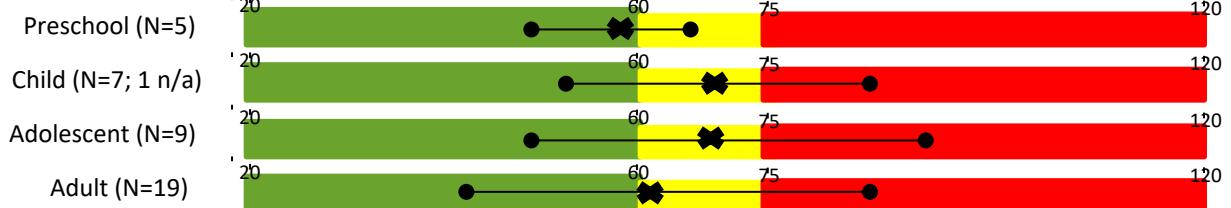
Social Communication: expressing social communication



Social Motivation: motivation to engage in social behavior



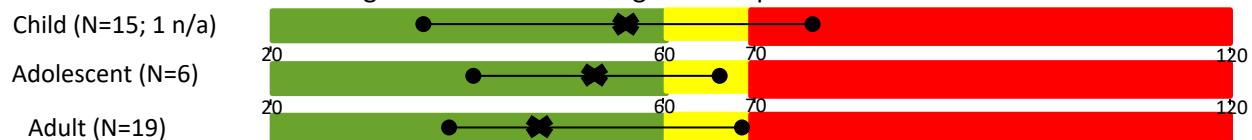
Restricted Interest and Repetitive Behavior: repeating behaviors/obsessing over routines



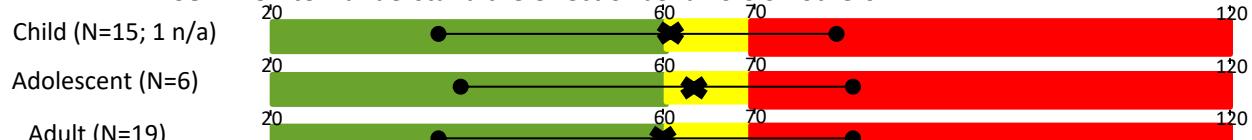
18p-; whole p arm deletions

Behavioral Regulation: ability to regulate and monitor behavior effectively

Inhibit: inhibiting behavior or not acting on an impulse

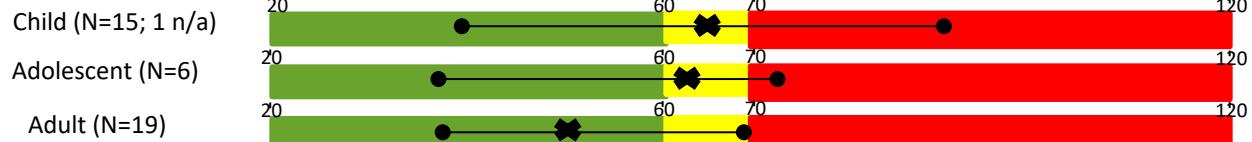


Self-Monitor: understand the effect of behaviors on others



Emotional Regulation: ability to regulate emotional responses

Shift: move from one situation to another

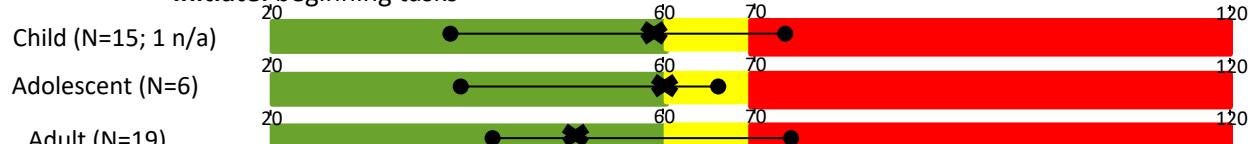


Emotional Control: modulating emotional response

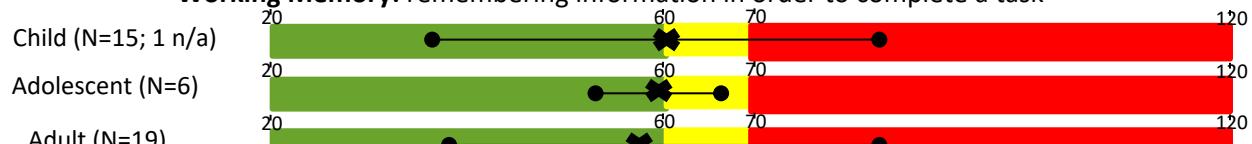


Cognitive Regulation: ability to control and manage cognitive processes and problem solve effectively

Initiate: beginning tasks



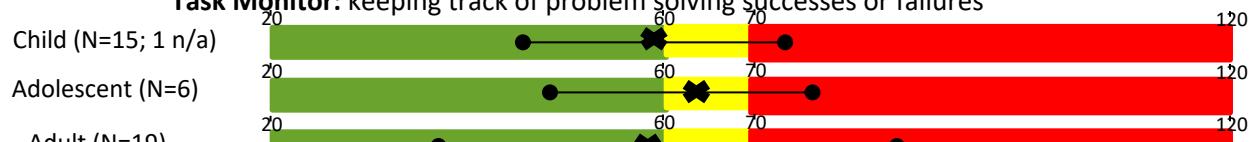
Working Memory: remembering information in order to complete a task



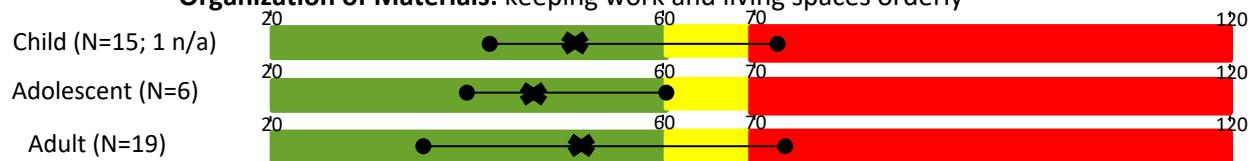
Plan / Organize: managing current and future orientated tasks



Task Monitor: keeping track of problem solving successes or failures



Organization of Materials: keeping work and living spaces orderly



Adaptive Behavior Assessment System (ABAS)

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

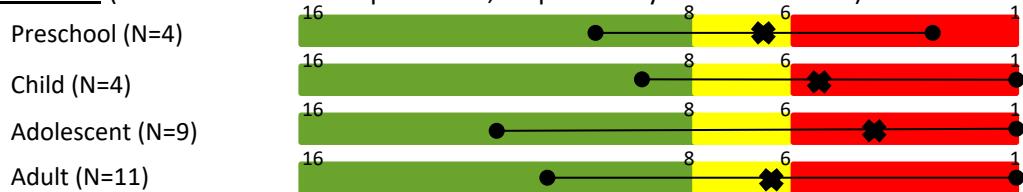
Communication (speech, language, and listening skills needed for communication with other people)



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

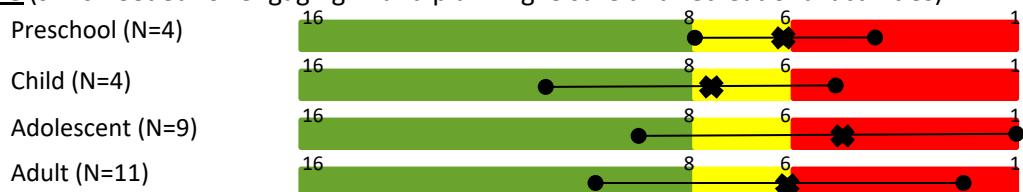


Self-Direction (skills needed for independence, responsibility and self-control)

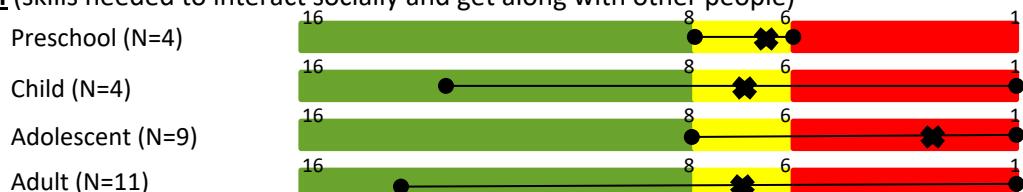


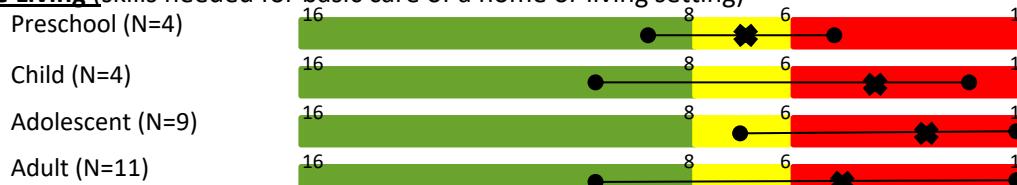
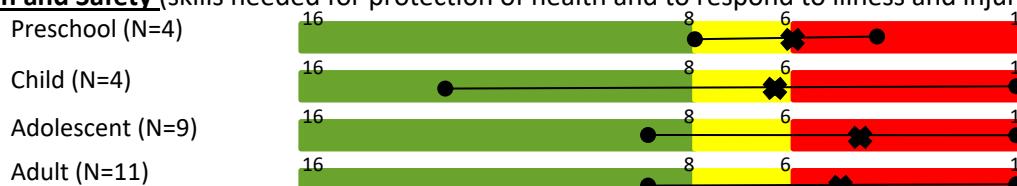
Social Composite (skills needed to interact with others)

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)

18p-; smaller deletions

Within Normal Limits

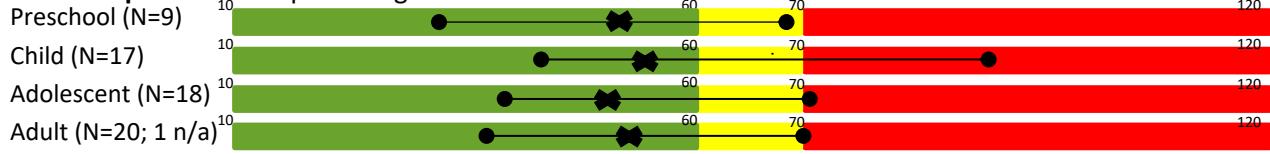
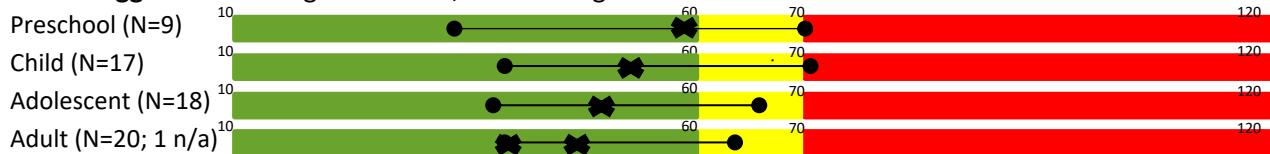
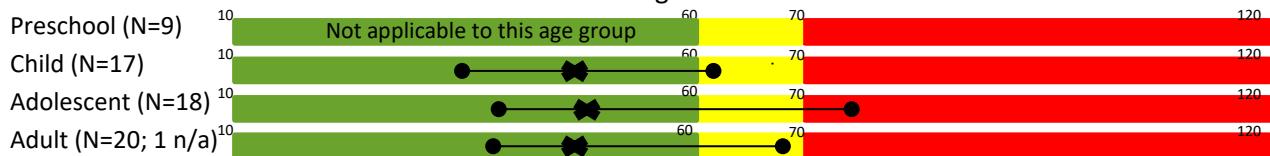
At Risk

Clinically Significant

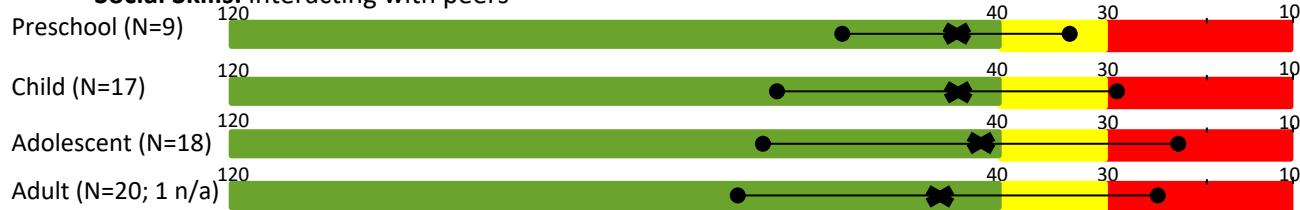
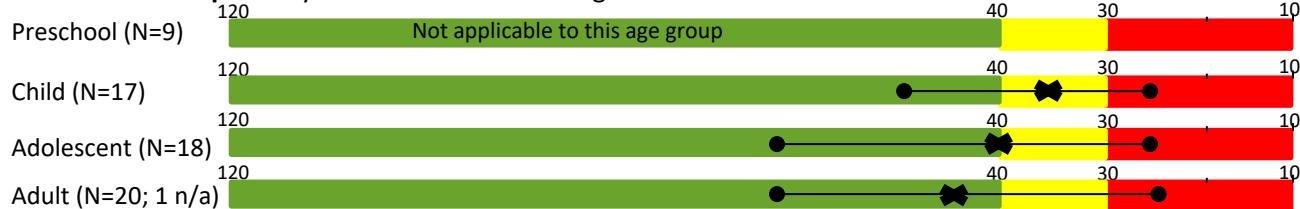
= average score

● = the range of all the scores

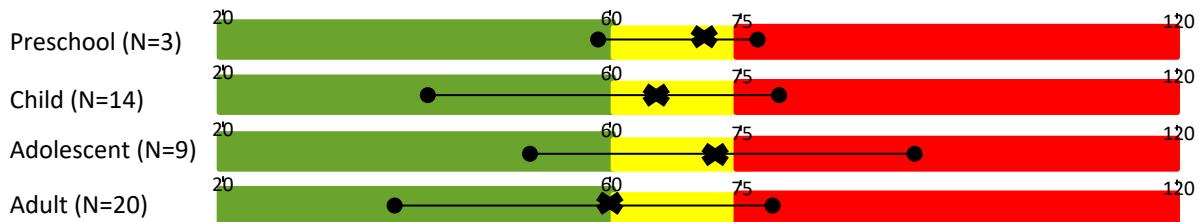
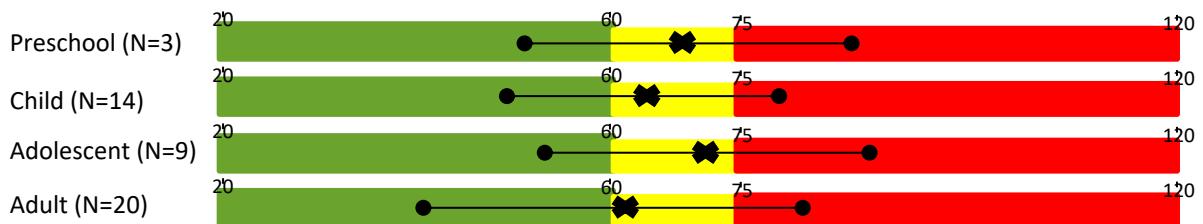
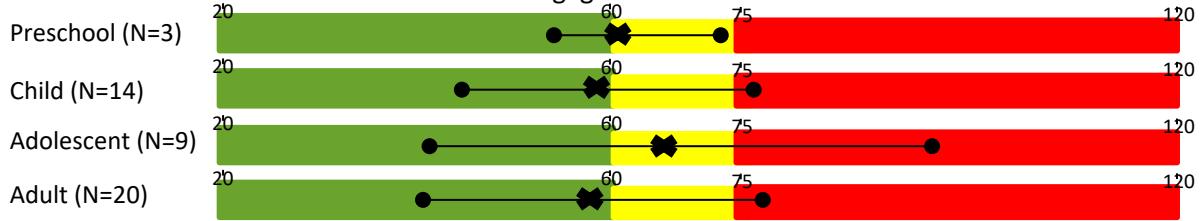
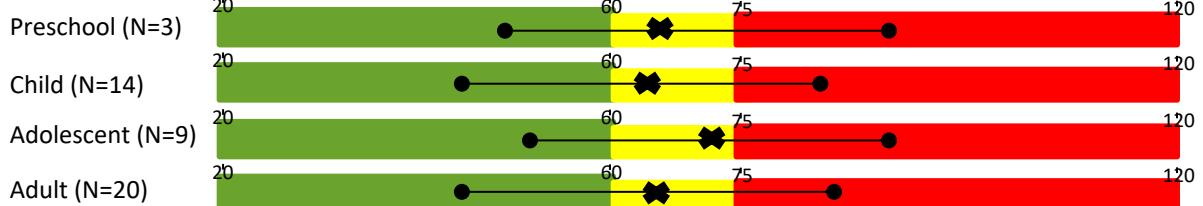
N= the number of participants

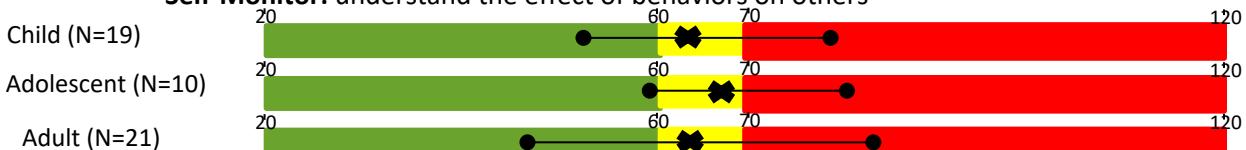
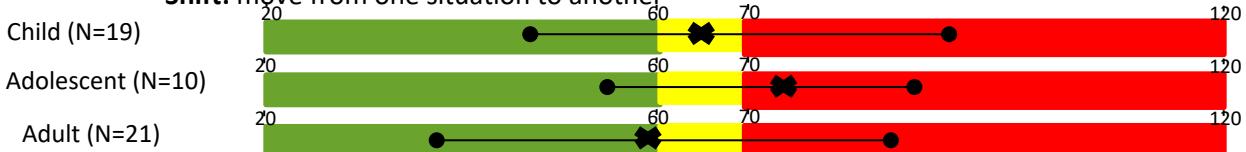
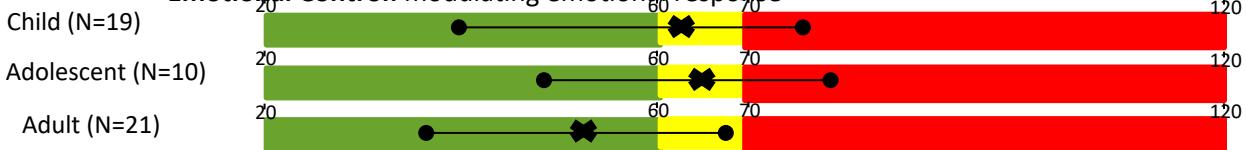
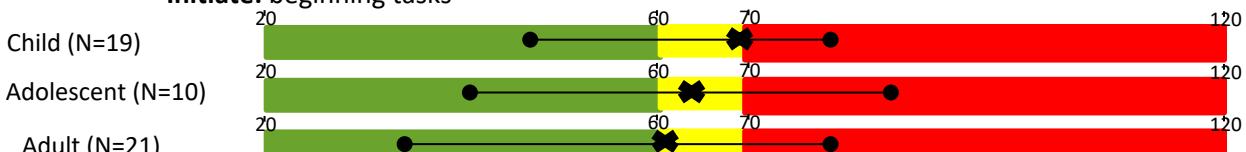
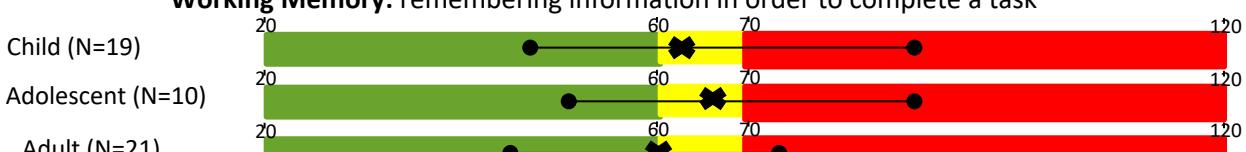
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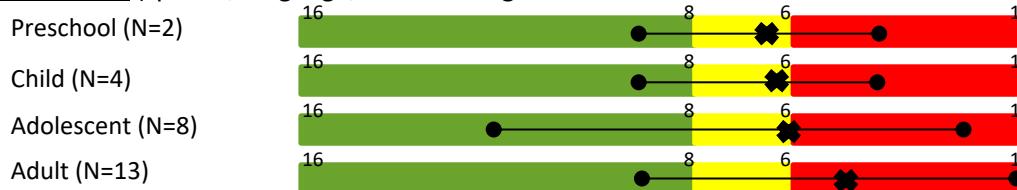
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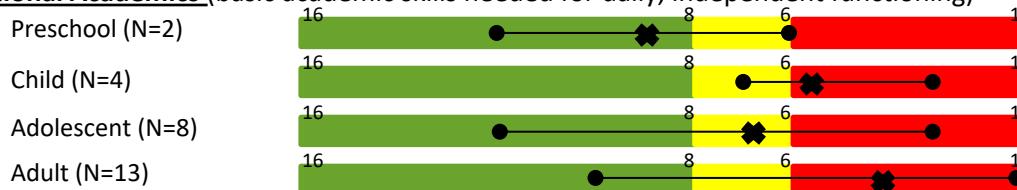
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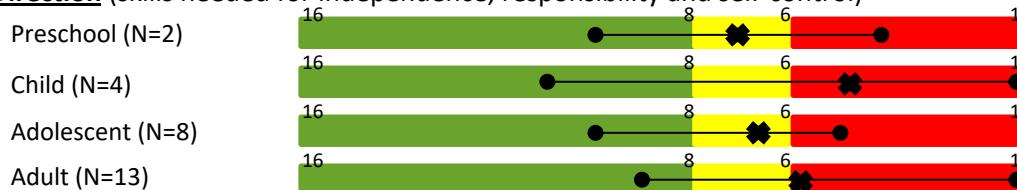
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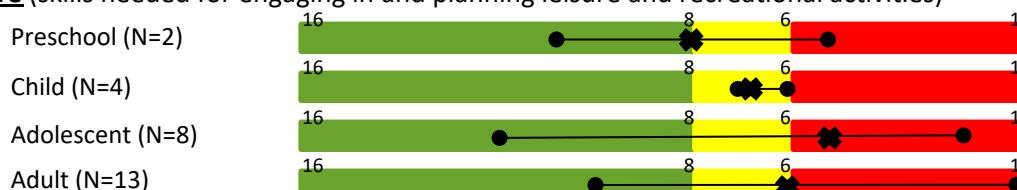


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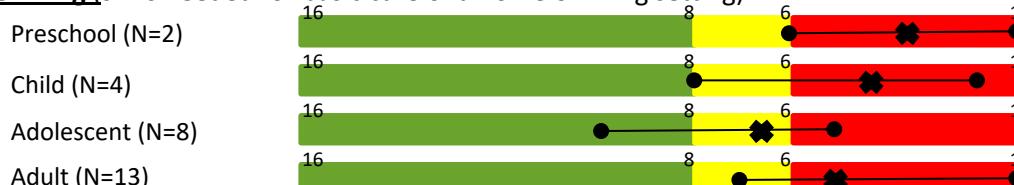
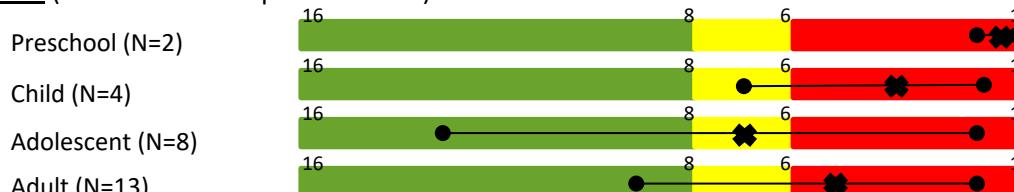
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Adult Status

(>18 years of age)

18p- whole p arm deletions	
Total N=33	
Received Responses: N=22	
No Contact or No Response: N=9	
Deceased: N=2	
LIVING ARRANGEMENTS	
Lives with parents/guardians	16
Lives with parents (independent part of home)	1
Lives away from parents (alone or with roommate) and receives assistance from support staff	3
Lives in group, foster or respite home	1
Lives with extended family	1
HIGHEST EDUCATION LEVEL	
Did not complete high school	1
Currently a high school student	4
Completed high school (certificate)	5
High School Graduate (received diploma)	5
Currently attends college/university	2
Completed some college, but no longer attends (no degree)	1
Completed transitional program post high school	1
Received continuing education/correspondence course certificate	1
Associates Degree	2
MARITAL STATUS	
Married (Yes)	0
Married (Never)	22
CHILDREN	
Children (Yes)	0
Children (No)	22
WORK POSITIONS	
Part Time PAID	5
Part Time PAID and through school (work study, etc...)	1
Part Time PAID and Volunteer	1
Part Time PAID and Day Habilitation Program	2
Volunteer	5
Through school (work study, etc...)	2
Attends day habilitation program	2
Does not work	4

Adult Status (>18 years of age)

18p- smaller deletions

Total N=39

Received Responses: N=33

No Contact or No Response: N=5

Deceased: N=1

LIVING ARRANGEMENTS

Lives with parents/guardians	26
Lives with parents (independent part of home)	2
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	3
Lives in a dormitory	1

HIGHEST EDUCATION LEVEL

Did not complete high school	1
Currently a high school student	1
Completed high school (certificate)	2
High School Graduate (received diploma)	11
Currently attends college/university	4
Completed some transitional program work, post high school but did not finish	2
Completed some college, but no longer attends (no degree)	2
Completed transitional program post high school	4
Vocational School Certificate/Degree	3
Associates Degree	3

MARITAL STATUS

Married (Yes)	0
Married (Never)	32
Divorced	1

CHILDREN

Children (Yes)	0
Children (No)	33

WORK POSITIONS

Full-Time PAID	1
Part Time PAID	7
Full-Time and Part-Time PAID	1
Part Time PAID and Volunteer	5
Part Time PAID and through school (work study, etc...)	1
Volunteer and day habilitation program	1
Volunteer	4
Attends day habilitation program	4
Does not work	9

- **Neurology:**

- Structural

- Cerebral MRI findings – >70%
 - White matter abnormalities – ~50% (delayed myelination; subtle thinning of white matter; white matter signal abnormalities; white matter changes due to ischemic insult; T2 hyperintensities and dysmyelination).
 - Pituitary abnormalities – 13% and hypothyroidism -7% (secondary or panhypopituitarism)
 - One individual had lobar holoprosencephaly and one had septo-optic dysplasia.
- Sacral agenesis – 6%
- Myelomeningocele – 3%

- Functional

- Hypotonia – 74%
- Speech disturbance/dysarthria – 68%
- Facial weakness – 13%
- Seizure disorder – 13%. The average age at onset is 6 years old. Age at onset between ~1 year old to 15 years old.
- Scapular winging – 8%
- Movement disorder – 6% (dystonia, tics, or myoclonic events)

Annual screenings

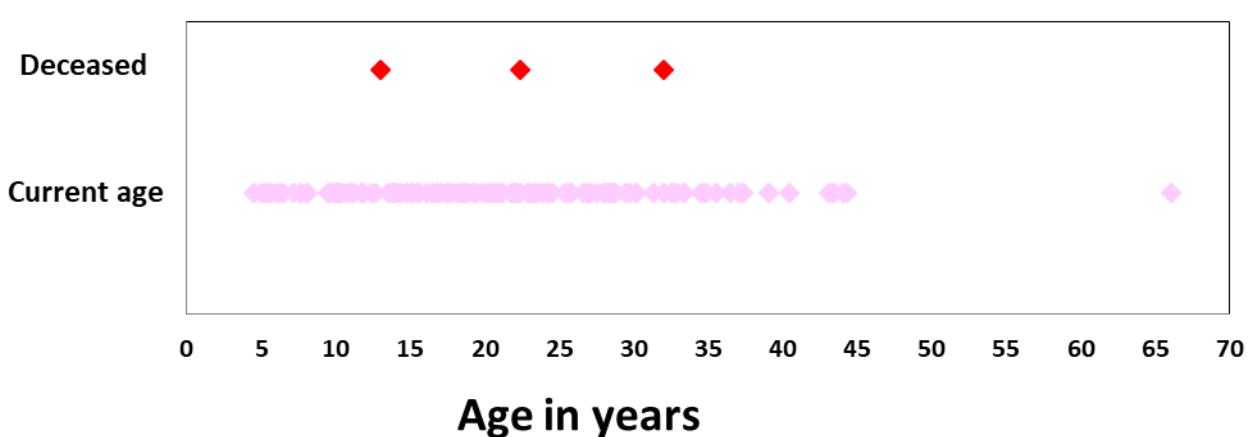
- Thyroid hormone and TSH
- Vision
- Hearing
 - Hearing loss – ~34%- conductive, sensorineural or mixed

Surgical/ Anesthesia

- 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.

Age and Cause of Death

18p- Current age & age at death



Age deceased	Gender	18p- Cause of death	Past medical history
13 years	F	Brain bleed post cardiac surgery.	Goldenhar syndrome; severe GE reflux; complex congenital heart disease.
22 years 4 months	F	Pneumonia complicated by lupus	Lupus nephritis; hypothyroid; adrenocorticotropic hormone deficiency
32 years 1 month	F	She choked on her lunch break at work (per parent answer)	Records available up to 26 years old: IUGR; heart abnormality; blepharophimosis and ptosis, inguinal hernia; depression; scoliosis

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