Down Syndrome: Medical and Neurodevelopmental Updates for Healthcare Clinicians

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No financial disclosures or conflicts

Relevant information:

I am a President of the Board of Directors for the Down Syndrome Medical Interest Group-USA

I am a Vice President of the Board of Directors for the National Down Syndrome Congress

I am a member of the Global Down Syndrome Foundation Medical and Scientific Advisory Board

My sister, Heather, has Down syndrome

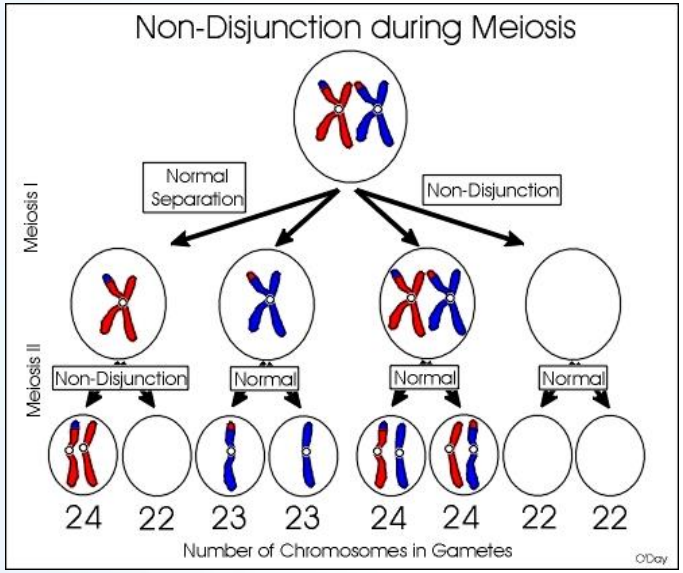
Baumer 2013

TOMORROW, 3/21!

Objectives

- Discuss the current healthcare guidelines for children with Down syndrome
- Describe screening, diagnosis, and interventions for common medical and developmental issues that are encountered in Down syndrome
- Review information about the Sie Center for Down syndrome and available resources to further knowledge in care of a child with Down syndrome

Genetic Causes of Down Syndrome



Down syndrome is a genetic disorder caused by the presence of all or part of a third copy of chromosome 21

- **Trisomy 21:** 92-95%
  - Most commonly uneven cell division during meiosis I produces egg with 24 instead of 23 chromosomes, when this fuses with sperm, a cell with 47 chromosomes (extra 21st chromosome) instead of 46 chromosomes results
- **Translocation** 21: 3-4%
  - Usually chr 21 attached to chr 14
- **Mosaic:** 2-4%
  - Only some cells have extra chr 21

Epidemiology

- Down syndrome occurs in about 1/ 700 live births
  ≈6000 births per year
  ≈400,000 in US
  > 6 million people with DS in the world

- Maternal age is the only known risk factor: Increased risk with increased age, BUT majority of births to women <35 years

- Life expectancy increased dramatically after 1970 (CHD repair, de-institutionalization), now ≅ 60 years

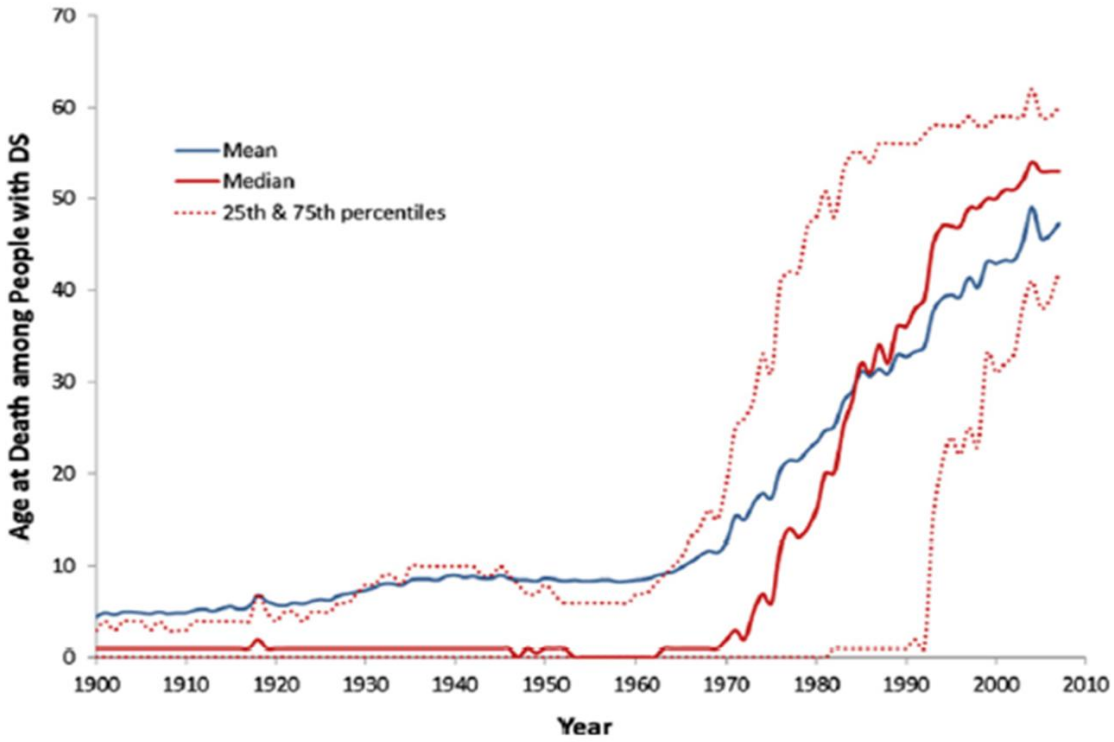
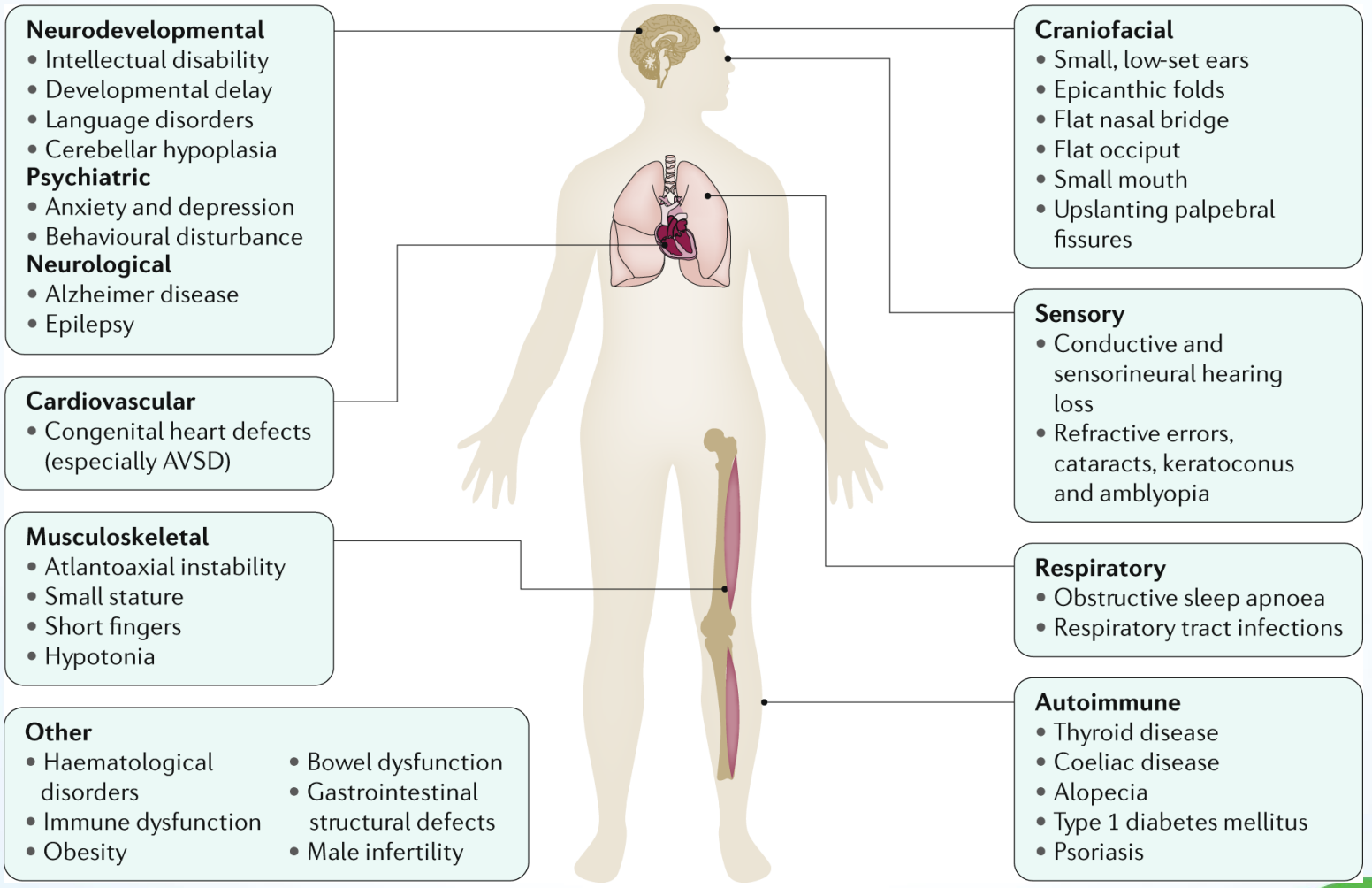


Figure 2.
Mean, median, and 25th and 75th percentiles for age at death in persons with Down syndrome, 1900–2007. The mean and median age at death for persons with Down syndrome have increased significantly over the past 40 years. In 2007, the mean and median ages at death were 47.3 and 53 years, respectively, reflecting a 3.75–fold increase in average life expectancy since 1970.

Presson, Angela P., Ginger Partyka, Kristin M. Jensen, Owen J. Devine, Sonja A. Rasmussen, Linda L. McCabe, and Edward RB McCabe. "Current estimate of Down syndrome population prevalence in the United States." *The Journal of pediatrics* 163, no. 4 (2013): 1163-1168.

Down syndrome:
May impact nearly all body systems



Nature Reviews Primers, Down syndrome 2020

Characteristics of Down Syndrome

desire to learn

beautiful eyes

smile that lights up a room

ears to hear words of encouragement

feelings and emotions

heart full of love

arms for hugging

need to belong

many unique qualities like everyone else

legs for running and jumping

feet to take him as far in life as others will support him to go

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OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Key point

CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

2022 Update!

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Health Supervision for Children and Adolescents With Down Syndrome

Marilyn J. Bull, MD, FAAP,[a] Tracy Trotter, MD, FAAP,[a] Stephanie L. Santoro, MD, FAAP,[b] Celanie Christensen, MD, MS, FAAP,[c] Randall W. Grout, MD, MS, FAAP,[d] THE COUNCIL ON GENETICS

- Health Care guidelines exist to screen for conditions that are more common in individuals with Down syndrome
- Resources for families: Age-based checklists https://www.healthychildren.org

Associated Medical Conditions

More research between 2011-2022 allowed for expanded list of associated medical conditions

- 11 associated medical conditions in 2011
- 36 associated medical conditions in 2022

General prevalence estimates for most conditions remained the same, however, some notable differences

TABLE 1 Medical Problems Common in Down Syndrome

Condition	%
Hearing problems	75
Vision problems	60
Cataracts	15
Refractive errors	50
Obstructive sleep apnea	50–75
Otitis media	50–70
Congenital heart disease	40–50
Hypodontia and delayed dental eruption	23
Gastrointestinal atresias	12
Thyroid disease	4–18
Seizures	1–13
Hematologic problems	
Anemia	3
Iron deficiency	10
Transient myeloproliferative disorder	10
Leukemia	1
Celiac disease	5
Atlantoaxial instability	1–2
Autism	1
Hirschsprung disease	<1

TABLE 1 Medical Problems Common in Down Syndrome

Condition	%
Hearing problems	75
Vision problems	60–80
Nystagmus	3–33
Glaucoma	<1–7
Nasolacrimal duct occlusion	3–36
Cataracts	3
Strabismus	36
Refractive errors	36–80
Keratoconus	1–13
Obstructive sleep apnea	50–79
Otitis media with effusion	50–70
Congenital heart disease	40–50
Feeding difficulty	31–80
Respiratory infection	20–36
Dermatologic problems	56
Hypodontia and delayed dental eruption	23
Congenital hypothyroidism	2–7
Antithyroid antibody positive (Hashimoto thyroiditis; incidence dependent on age)	13–39
Hyperthyroidism	0.65–3
Thyroid disease by adulthood	50
Gastrointestinal atresias	12
Seizures	1–13
Hematologic problems	
Anemia	1.2
Iron deficiency	6.7
Transient abnormal myelopoiesis	10
Leukemia	1
Autoimmune conditions	
Hashimoto thyroiditis	13–39
Graves' disease	1
Celiac disease	1–5
Type 1 diabetes	1
Juvenile idiopathic arthritis	<1
Alopecia	5
Symptomatic atlantoaxial instability	1–2
Autism	7–19
Hirschsprung disease	<1
Moyamoya disease	Down syndrome 26 times greater in patients with Moyamoya than Down syndrome in live births

New Associated Conditions:

Feeding

Respiratory

Dermatologic

Autoimmune Conditions

Moyamoya

Updated Prevalence:

Vision Problems: now includes additional conditions (e.g. keratoconus)

Autism: dramatic increase

Communicating with Families

- First, congratulate the family
- Have infant present; refer to infant by name
- Use a respectful bedside manner
- Time discussion after labor is complete and as soon as diagnosis is suspected (not necessarily confirmed)
- Have a support person present for mother, father, and family members as appropriate
- Use a cohesive, physician-led team approach

Helpful discussion will include:

- Up-to-date, accurate information
- A balanced approach rather than relying on personal opinions an experience
- Person-first language (ie, child with Down syndrome)
- Connection to other parents and resource groups
- Discussion of life potentials for people with Down syndrome

Bull, et al. PEDIATRICS Volume 149, number 5, May 2022:e2022057010

AAP Guidelines

- The Prenatal Visit
- Age-Based Visit Recommendations:
    - Newborn Infants: Birth to 1 month
    - Infancy: 1 month – 1 year
    - Early Childhood: 1 to 5 years
    - Late Childhood: 5 to 12 years
    - Adolescence to Early Adulthood: 12 to 21 years
  - Health Supervision
    - Physical Examination / Laboratory Studies / Diagnostic Tests
    - Issues to Discuss and Review
    - What to Evaluate For
  - Anticipatory Guidance
  - Resources for Families

Newborns: Making the Diagnosis: Physical Exam Characteristics most sensitive

Facial features:

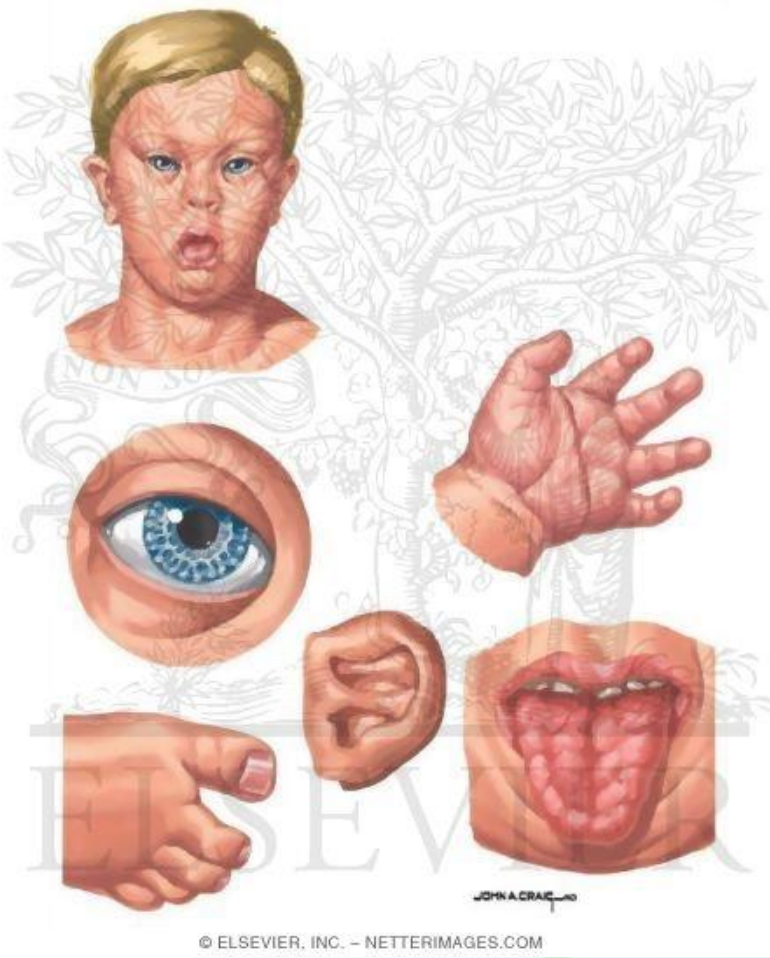
- Flat nasal bridge
- **Slanted palpebral fissures (98%)**
- Epicanthal folds
- Small round ears
- Brushfield spots
- Big wrinkled tongue

Extremities:

- Short, broad hands
- Single palmar crease (45%)
- **Gap between big toe and 2nd toe (96%)**
- Hypoplasia of small finger, middle finger
- 5th finger clinodactyly

Hypotonia (most)

Loose skin on back of neck (87%)



Newborns

- Karyotype
- Congenital Heart Disease (50%), 50% need surgical repair (CAVSD most common)
  - May not have a murmur, may be masked by pulmonary hypertension which can be persistent
  - **Echocardiogram for all, even if fetal echo!**
- Congenital Hypothyroidism (2-7%)
  - **TSH for all.** Verify results of newborn thyroid function screening which should include TSH (some only do free T4)
- Polycythemia, Transient abnormal myelopoiesis (TAM, previously TMD)
  - **CBC for all by 3 days of age, monitor, refer to heme if persistently abnormal**
- Conductive and sensorineural hearing loss
  - **Hearing screen with objective testing (Brain-stem auditory evoked response or otoacoustic emission). Repeat by 3 months if not passed**
- Cataracts, nystagmus, nasolacrimal duct stenosis
  - **Check for red reflex, Ophtho evaluation for all within 6 months**
- Congenital gastrointestinal malformations: Duodenal atresia, stenosis, web; annular pancreas, tracheoesophageal fistula, pyloric stenosis, imperforate anus, Hirschsprung disease
  - **Assess with history / physical examination**

EI Referral for all, Discuss resources**

Infants

- Monitor weight for length, DS-specific growth charts
- Hearing evaluation at 6 months
  - Otitis media with effusion 50-75%
  - If canals are stenotic – refer to ENT
- Ophthalmology evaluation at 6 months
- TSH at 6 months & 12 months
- CBC / iron studies
- GI: Monitor for feeding problems, GE reflux, constipation
- Routine immunizations, +RSV if qualifying conditions
- Counsel about risk for Infantile / Epileptic Spasms (1-5%)
  - Most common epilepsy syndrome, can be subtle, and delayed diagnosis from onset of symptoms common in DS and may impact outcomes
  - Onset on average between 6-8 months of age, but can be as late as 18 months
  - Presenting symptom may be developmental plateau / regression

Infantile Spasms

West Syndrome: TRIAD of symptoms:

1. Infantile Spasms
2. Hypsarrhythmia on EEG
3. Developmental regression or arrest

- High level of suspicion needed
- Urgent evaluation needed, key is to diagnose and treat early!
- Seizure and ND outcomes highly variable

Childhood / Adolescence:

- Hearing: Behavioral audiogram and tympanometry should be performed every 6 months until normal hearing levels are established bilaterally by ear-specific testing, then annually
  - If you can't establish normal hearing with behavioral testing, objective testing (with sedation if necessary) needed
- Vision: Annually from 1-5 years of age, then at least every two years from 5-13 years, and every three years from 13 years+
  - Photoscreening: helpful when child cannot do vision chart testing
- Check TSH annually: Risk of thyroid abnormalities 50% by late childhood
  - Many have elevated TSH and normal free T4 (subclinical hypothyroidism) – can check antibodies and monitor every 6 months
- Annual anemia / new recommendations to check specifically for iron deficiency / insufficiency, which is not more likely in DS, but harder to detect.
  - MCV is not reliable because macrocytosis (large RBC) common

1) Annual CBC with differential AND

2) Ferritin and C-reactive Protein (CRP) (markers of inflammation)

OR Serum iron and Total iron binding capacity (TIBC)

- Sleep study between 3-4 years of age. Obstructive Sleep Apnea very common, and poor correlation between parent report of symptoms and PSG results

Childhood / Adolescence:

- Obesity: Monitor on DS-specific growth charts, BMI on CDC charts after 10 years of age. Obesity risk factor for obstructive sleep apnea
- Keratoconus – risk 1-13%, typically diagnosed after puberty; can cause blurred vision, corneal haze
- Skin problems: monitor, increased autoimmune etiology, new clinical trials coming
- Cancer: Increased but low leukemia risk; decreased overall risk for solid tumors. Testicular cancer the only solid tumor more common in DS → Testicular exams with all health supervision visits
- Atlantoaxial instability: No asymptomatic radiograph screening; discuss safe positioning during procedures, avoid high risk activities, monitor for myelopathic signs and symptoms at every visit
- Celiac disease: AAP does not recommend routine asymptomatic lab screening, screen for symptoms – checked every few years in the Sie Center

Childhood / Adolescence: Top 5 Annual Evaluations

1. Hearing – Audiogram annually
2. Vision – Age-specific cadence
3. Thyroid – TSH annually
4. Anemia AND Iron Deficiency annually
5. Sleep study between 3-4 years, screen for symptoms annually

Development and Behavior

- Most children with Down syndrome have delays in their development, and reach early milestones about 1.5-2 times later than other children
- Early Intervention services – speech, physical, occupational therapy are very important to help optimize development (birth to age 3 years)
- Special education services in school through Individualized Education Program (IEP):
  - Meaningful inclusion with peers
  - Specialized instruction
  - Learning goals tailored to child's needs

Clinical Goals: identify strengths / challenges, assess for meaningful progress, ensure services / supports meet developmental profile / needs

Developmental Skills / Milestones in Down Syndrome

- Recent study, Boston Children's Hospital

Developmental Milestones for Children with Down Syndrome, Baumer et.al PEDIATRICS Volume 154, number 4, October 2024:e2023065402

Goal: move field toward more tailored, evidence based developmental guidance for children with Down syndrome that recognizes unique and varied trajectories

Note: development of "milestones" is not meant to impose rigid expectations but to offer clinicians tools to understand the range of developmental patterns

- Used longitudinal primarily parent-reported data from specialized DSP to estimate ranges at which children with Down syndrome reached different milestones.
- Children with Down syndrome have well known developmental delays, and understanding skills relative to others with DS enables early identification of age-expected or delayed development allowing for appropriate targeted intervention
- Limitations – overrepresentation of those with more significant medical and developmental complexity, limitations to analytic methods
- Key findings:

→ There is wide variability in achievement of different milestones children with Down syndrome; and ongoing acquisition of skills at older ages

Gross Motor Development in Down Syndrome

- References for gross motor skill achievement for children with DS, along with the 5th, 25th, 75th and 95th percentiles, are provided for 44 birth to walking skills and post walking skills

Winders, P., K. Wolter-Warmerdam, and F. Hickey. "A schedule of gross motor development for children with Down syndrome." Journal of Intellectual Disability Research 63.4 (2019): 346-356.

Neurodevelopmental Profile

Strengths	Challenges
Receptive Language	Expressive language
Visual-spatial processing and visual short-term memory	Verbal/Auditory processing and short-term auditory memory
Social interest & engagement	Motivation and engagement with non-preferred topics/tasks
Recognizing emotions	Noncompliant behavior and difficulty with task persistence
Procedural learning of routines and daily living skills	Fact-based learning, executive function and organization

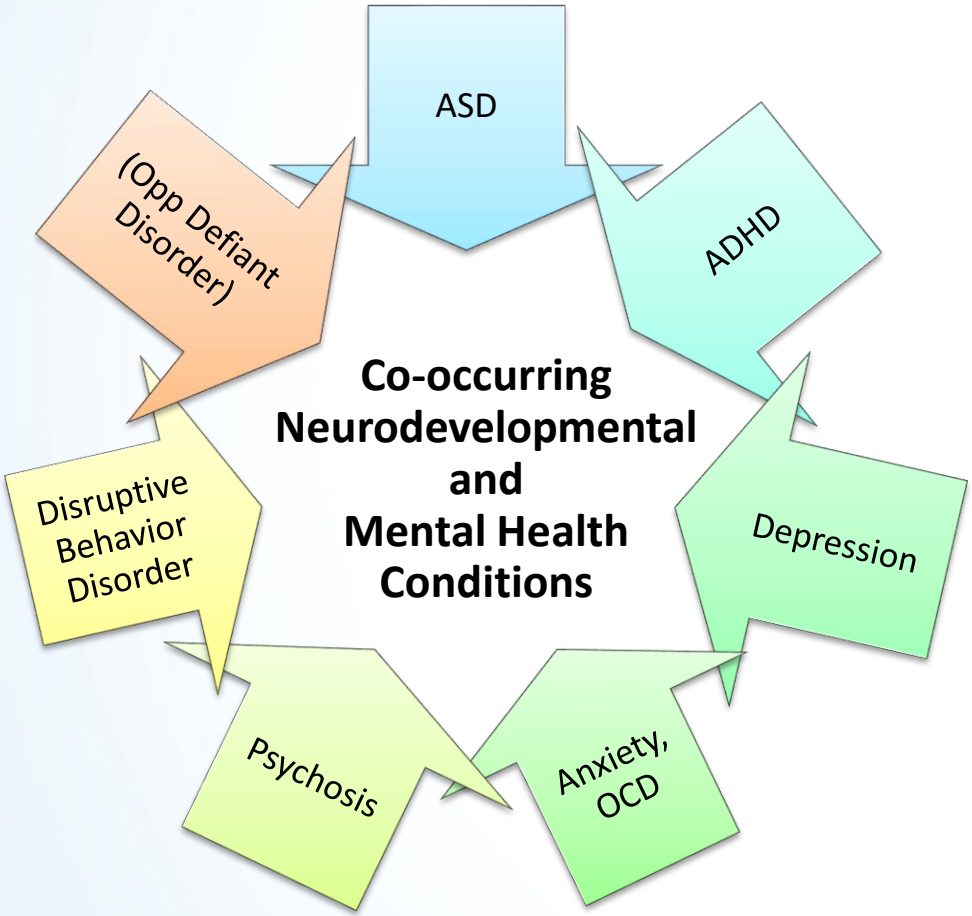
Common Behavioral Challenges

Oppositionality	Defiance	Aggression	Non-compliance
Irritability, Agitation	Restlessness	Anger, Mood swings	Hyperactivity
Disruptive	Impulsive	Inattentive	Destructive
Tantrums	Flopping	Eloping/Bolting	

Comprehensive Evaluation of Behavior

- Medical / Clinical Evaluation
- Detailed history, medications, family history
- Physical Exam, Labs, Diagnostic tests as needed
  - Celiac, sleep study, updated hearing / vision assessments)
- Psychosocial evaluation
  - Student-teacher fit, stressors, environmental change, loss, transition
  - Collateral information from school
- Assessment of skills / gaps
- Psychological assessment when possible
- Consider co-occurring neurodevelopmental, behavioral, mental health conditions
- Management: Positive behavioral support strategies, specialized supports / services, therapies, medications

Co-occurring neurodevelopmental, behavioral, mental health conditions



- Children and adolescents with Down syndrome should receive the same specialized diagnosis, intervention and care as children with these conditions who do not have Down syndrome

Indications / When to be concerned about a co-occurring diagnosis:

- Significant impairment in learning, socialization
- Dangerous behaviors associated with aggression, injury, destructiveness
- Behaviors occur across multiple environments

Specific treatment strategies depend on:

- Severity, Frequency
- Chronologic age AND developmental level of the child
- Developmental / diagnostic profile

Anna and John J. Sie Center for Down Syndrome

The Sie Center at Children's Hospital Colorado is one of the leading Down syndrome clinics in the United States. Our multidisciplinary team provides medical, educational and therapeutic care that helps children and adolescents with Down syndrome thrive.

Sie Center for Down Syndrome

- Total Sie Center for Down Syndrome (SCDS) patients **(n=2,393)**
  - Unique multidisciplinary model of care
  - Our clinic is one of the few, but the most comprehensive Down syndrome (DS) clinics in the Western U.S.
  - Serve approximately 88% of children with Down syndrome in the State of Colorado
    - Not only families in Colorado but from 28 states and 9 countries
- Prenatal Consultations
- Pediatric Evaluation and Treatment
  - Expertise in behavior, neurodevelopmental and mental health care, feeding, sleep
- Adolescent to Adult Transition Services

We strive to meet complex Medical / Developmental / Psychosocial Needs

Supplies, Medical Equipment

Recreation / Community Activities

Education, Developmental Assessments, Therapies and Services

Legal and Financial

Family Support groups and advisories

Care Coordination: Subspecialty medical visits

Quality improvement, observational research, clinical database, clinical trials

Sie Center for Down Syndrome

Children's Hospital Colorado
Anna and John J. Sie Center for Down Syndrome

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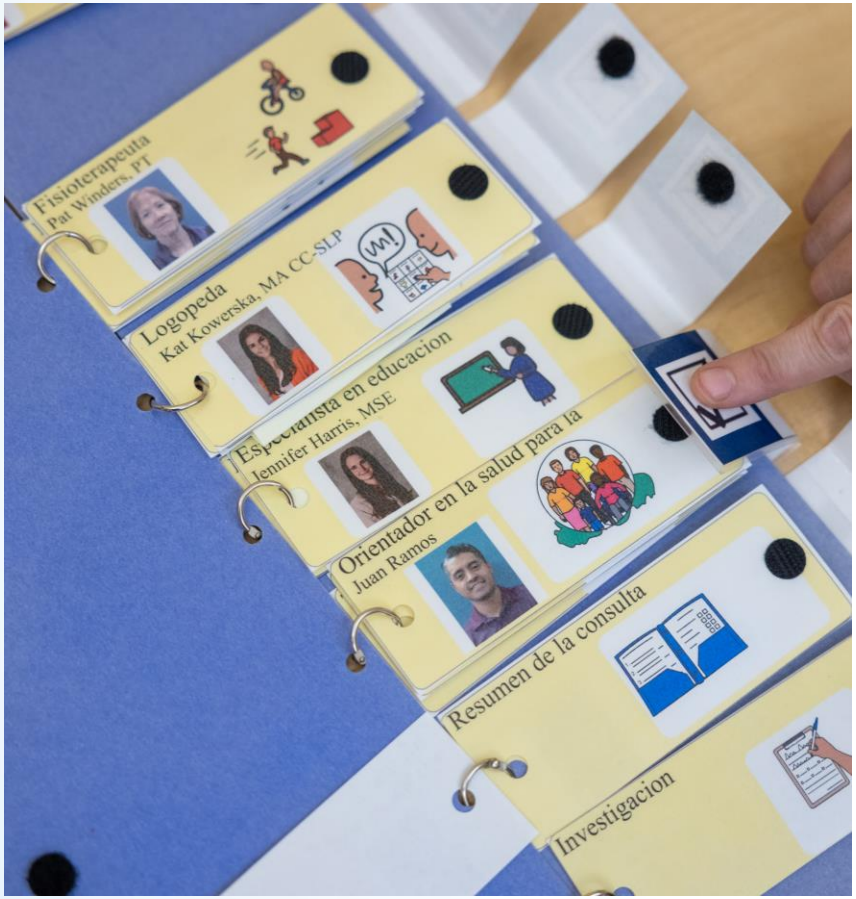
Services in Sie Center



- One dedicated team to meet each child's unique needs:
  - Medical provider (Pediatrician, neurologist, nurse practitioner)
  - Pediatric physical therapist
  - Pediatric speech-language pathologist
  - Augmentative and alternative communication speech therapist
  - Feeding specialists
  - Psychologist
  - Social worker
  - Pediatric occupational therapist
  - Education specialist
  - Psychiatrist
  - Registered nurse
  - Other subspecialists

Sie Center Research: Highlights

- Clinical Database: Sie Center studies have created national/international references for complete blood counts
- Best Practices for Medical Testing and Procedures:
  - Testing for lung function – oscillometry vs spirometry
  - Testing for airway obstruction and inflammation on bronchoscopy
  - Exploring need for standardized celiac disease screening in AAP DS Guidelines
  - Create an age-related guide for audiological testing
- ID and Treatment of Co-occurring Conditions
  - Pulmonary Hypertension
  - Infantile Spasms
  - RSV
  - Hearing Loss
  - Dysphagia

NIH INCLUDE: Early Development in Down Syndrome

Project CAPE-abilities

Communication And Play Early abilities in Down Syndrome

Colorado State University
Sie Center
Crnic Institute
Univ of San Francisco
Boston Children's Hospital

First large-scale, comprehensive, longitudinal study of early foundations of communication and play, their relation to other biomedical conditions, and the interplay between early learning and blood-based biomarkers in babies with DS

Take Home Points: Conditions / Guidelines

DS is characterized by a specific developmental, cognitive, and learning profile, as well as common associated conditions that require additional screening and monitoring

Health Care Guidelines exist, including family-friendly checklists to help pediatricians and families work together to ensure the best health care

Top 5 things to think about / order at every WCC: hearing/ vision, thyroid, anemia/iron, sleep, development

Reach out to us! We are happy to help and collaborate!