Down Syndrome: Birth and Beyond

Dannah Raz, MD, MPH
Director, Pediatric Down Syndrome Clinic
Section Chief, Developmental and Behavioral Pediatrics

Learning Objective

Participants will be able to	Understand updated healthcare guidelines for children with Down syndrome within their practice
	Effectively and compassionately communicate a diagnosis of Down syndrome
	Consider differential for regression in Down syndrome

Disclosure

- Served on expert panel for Illumina Genetics

BARROW Neurological Institute | PHOENIX CHILDREN'S

Down syndrome (Ds)

- The most common chromosomal condition diagnosed in the US
  - 1 in 800-1,000 live births
  - Approximately 400,000 with Down syndrome are living in the US
- Associated with increasing maternal age (35+)
  - Majority of babies with Down syndrome are born to those <35 years of age

cdc.gov

Inclusion and Quality of Life

Individuals with Down syndrome:

- Attend school, work
- Participate in decision making
- Meaningful relationships
- Vote
- Contribute to society

Preferred Language

Down vs. Down's – Down syndrome (no apostrophe)

People first – a child with Down syndrome, NOT a Down syndrome child

Avoid using "Down's child," "He has Down's"

People "have" Down syndrome

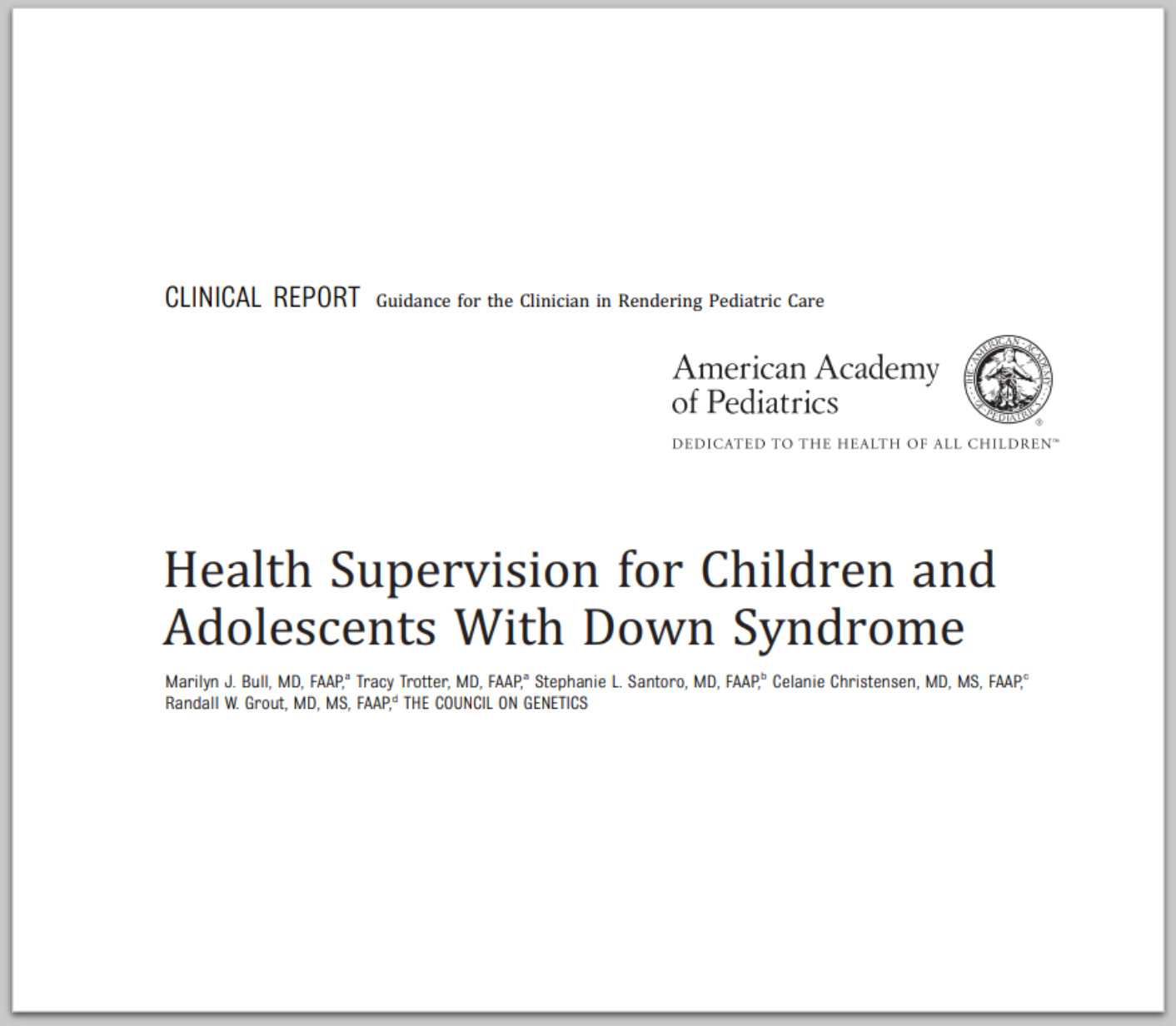
Intellectual Disability or Cognitive Disability NOT mental retardation

Health Supervision

- **New!! 2022 AAP Healthcare Guidelines for Children and Adolescents with Down Syndrome**
- Age based recommendations
- Medical/Community recommendations

Update healthcare guidelines

- *Pediatrics* May 2022
- Last previous update 2011



CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

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

BARROW Neurological Institute | PHOENIX CHILDREN'S

Updated guidelines

What is the same:

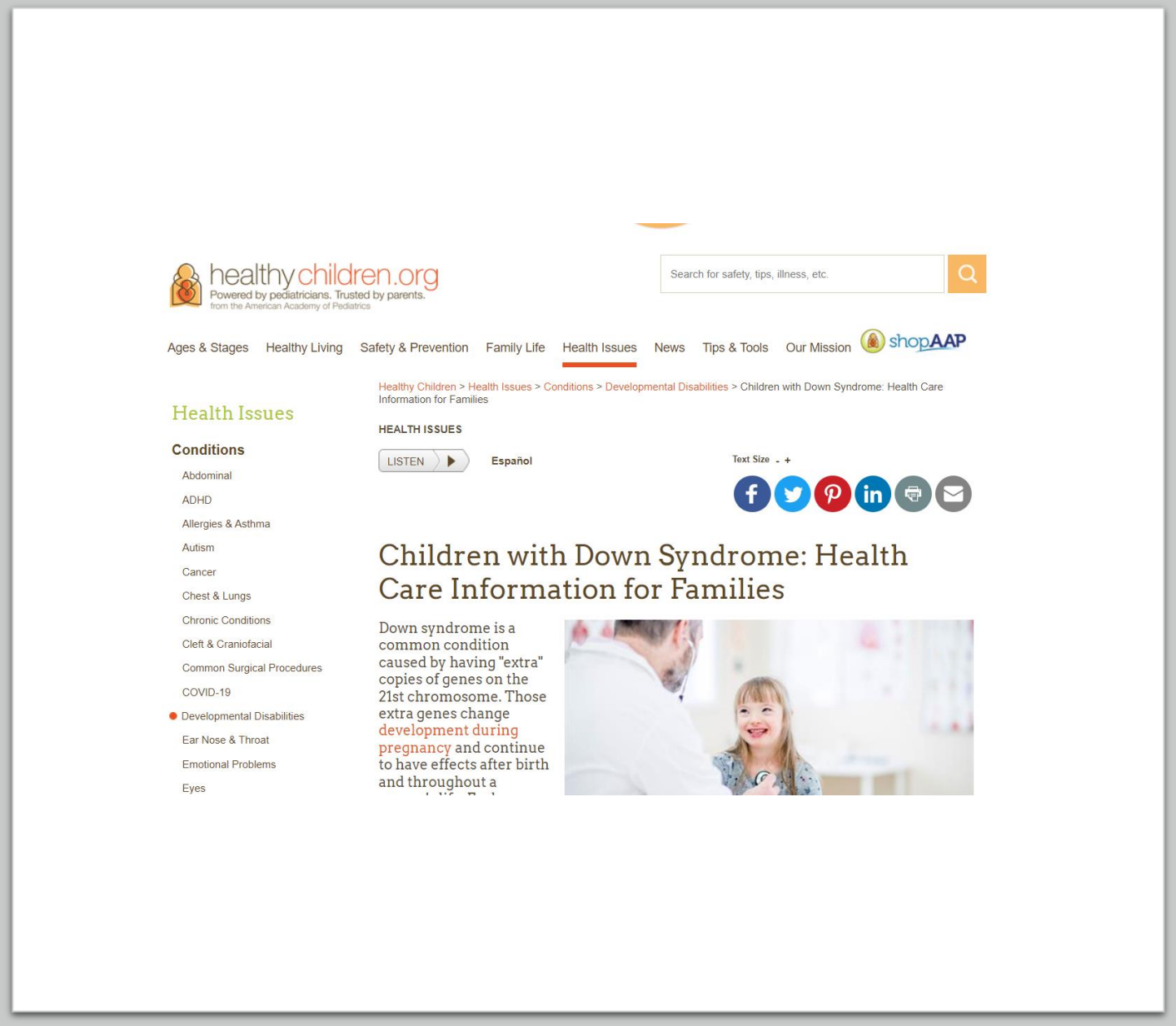
- Hearing screen frequency
- Atlanto-axial instability recommendations
- Thyroid screening
- Celiac screening

What is new:

- Discussion with family
- CBC with diff by day of life 3
- Check iron stores annually
- Growth charts
- Vision – photoscreening
- Sleep study – time frame
- Dermatologic addition
- Gynecologic care
- Safety

For parents

- Updated guidelines for parents in progress
  - Healthy Children (healthychildren.org)



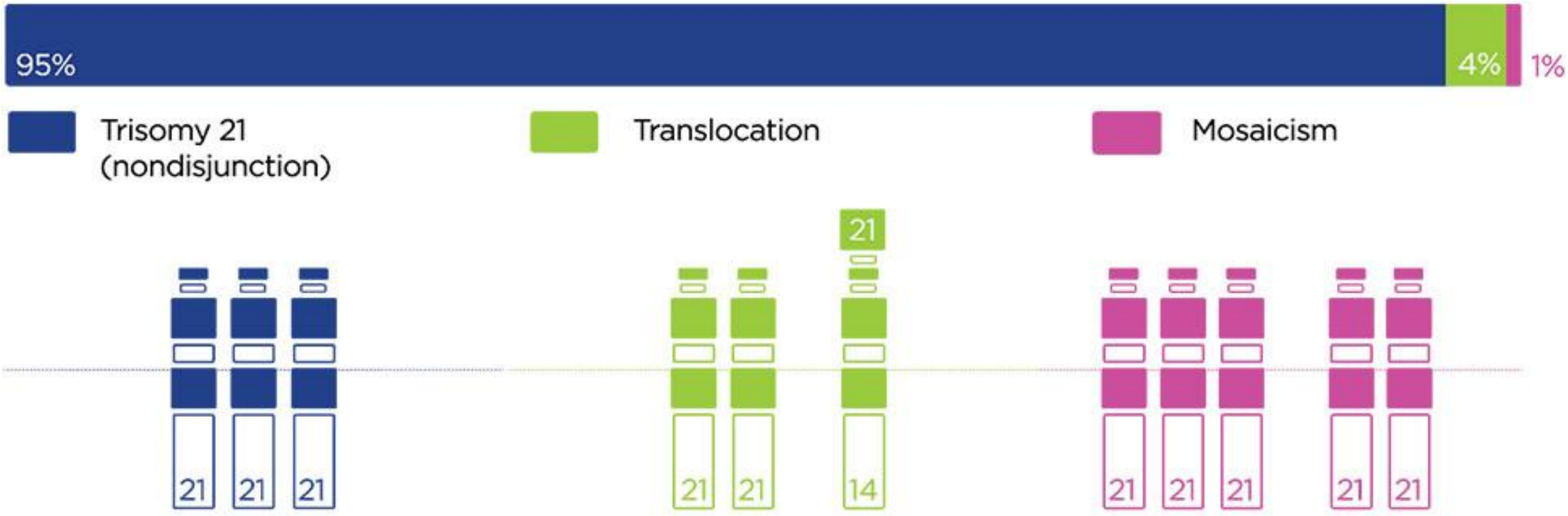
BARROW Neurological Institute | PHOENIX CHILDREN'S

Common Medical Problems

- Hearing problems (75%)
- Vision problems (60-80%)
  - Nystagmus, Glaucoma, Nasolacrimal duct obstruction, cataracts
- Obstructive sleep apnea (50-79%)
- Otitis media with effusion (50-70%)
- Congenital heart disease (40-50%)
- Feeding difficulty (40-50%)
- Respiratory infection (31-80%)
- Dermatologic problems (56%)
- Hypodontia and delayed tooth eruption (23%)

Common medical problems cont…

- Thyroid disease (2-50%)
- Seizures (1-13%)
- Gastrointestinal atresia (12%)
- Hematologic problems (% variable by problem)
  - Anemia, iron deficiency, transient abnormal myelopoiesis, leukemia
- Autoimmune conditions
- Symptomatic atlantoaxial instability (1-2%)
- Autism (7-19%)
- Hirschsprung disease (<1%)



Baby is born with an extra copy of chromosome 21, meaning there are three copies of chromosome 21 instead of the usual two.

Part of chromosome 21 breaks off during cell division and attaches to another chromosome.

There is a mixture of two types of cells - some containing the usual 46 chromosomes and others containing 47.

Photo from: wecapable.com

BARROW Neurological Institute | PHOENIX CHILDREN'S

Bull, et al. and Committee on Genetics

Prenatal Screening

First trimester screen

- Maternal age
- Nuchal translucency ultrasound
- Measurement of beta-HCG, chorionic gonadotropin, pregnancy-associated plasma protein A

Second Trimester Screen (quad screen)

- Maternal age risk
- Maternal beta HCG
- Unconjugated estradiol
- Alpha feto-protein
- Inhibin levels

Cell Free DNA

Confirm prenatal Diagnosis

- Chorionic Villus Sampling
- Amniocentesis

Other things to consider…

- **Extra testing**
  - Fetal Echocardiogram
  - Ultrasound evaluation of GI tract

- **Offer prenatal counseling**
  - Geneticist, Developmental Behavioral Pediatrician

Confirming the diagnosis - Postnatal

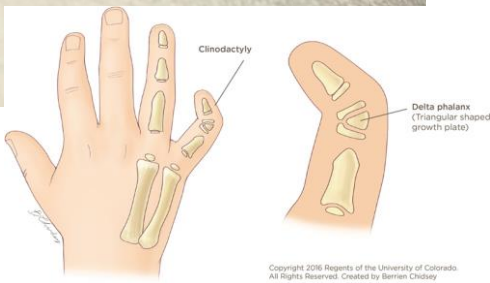
Physical examination to identify concern for Trisomy 21

Chromosomal evaluation

- Fluorescent In Situ Hybridization (FISH) – fast resulting time
- Karyotype to evaluate for translocation or mosaicism

Phenotype

- Hypotonia
- Brachycephalic head
- Epicanthal folds
- Flat nasal bridge
- Upward slanting palpebral fissures
- Brushfield spots
- Small mouth
- Small ears
- Excessive skin at the nape of neck
- Single transverse palmer crease
- Short fifth finger with clinodactyly and wide spacing
- Deep plantar groove between 1st and second toes
- Large tongue



BARROW Neurological Institute | PHOENIX CHILDREN'S

Giving the diagnosis (Skotko et al 2009)

- Congratulate the parents on the birth of their child
- Refer to the baby by name
- Tell the parents as soon as possible
- Both parents together or have support person available
- Use family's preferred language –medical interpreter
- Private setting
- In person, by healthcare professional

Giving the diagnosis

Provide balanced and accurate and up to date information

Discuss positive aspects and potential challenges related to Down syndrome

Use Neutral language – avoid “I’m sorry” or “I have bad news”

Use sensitive language and avoid outdated terminology

Allow for silence and tears. Offer family time alone

Validate feelings, use active listening and empathetic responses to support

Informational resources should be provided

Postnatal care

- Echocardiogram
- Monitor feeding
  - Look for signs of possible aspiration
- Red reflex examination - cataracts
- Hearing test
- Car seat evaluation
- Monitor stooling
- Monitor breathing
- Complete blood count (CBC) with differential
- Newborn screening
  - May need to add Thyroid Stimulating Hormone (TSH) (AZ screens have TSH)

Transient Abnormal Myelopoiesis

- Formerly called Transient Myeloproliferative Disorder
- Clonal myeloproliferation
- Variable presentation
- Spontaneous regression in most cases, not all
- May require chemotherapy
- Increased risk of death in first 6 months
- Increased risk of developing Acute Myeloid Leukemia (AML) by 4 years of age
- Consultation with Heme/Onc

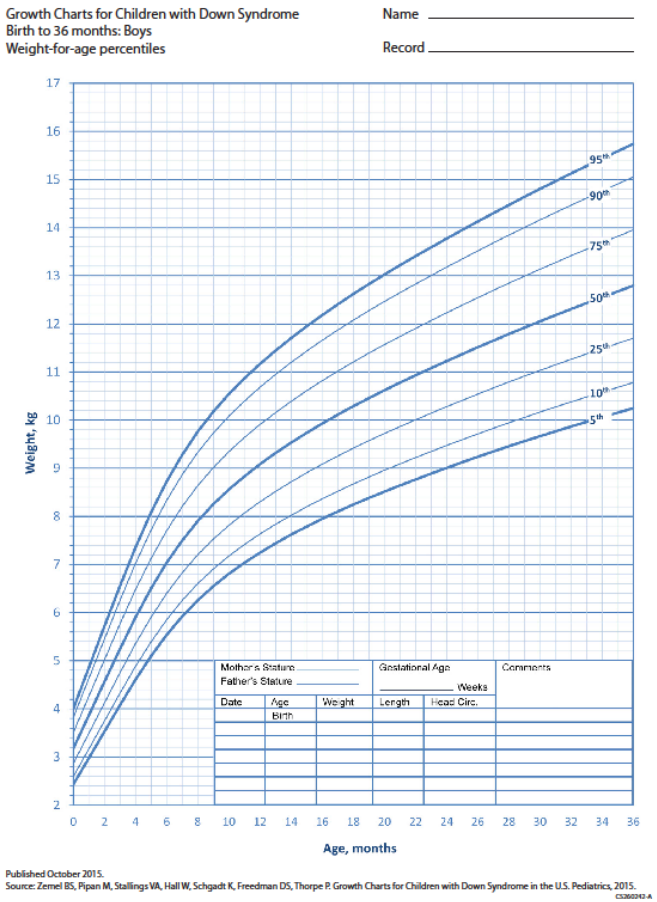
Prior to Discharge

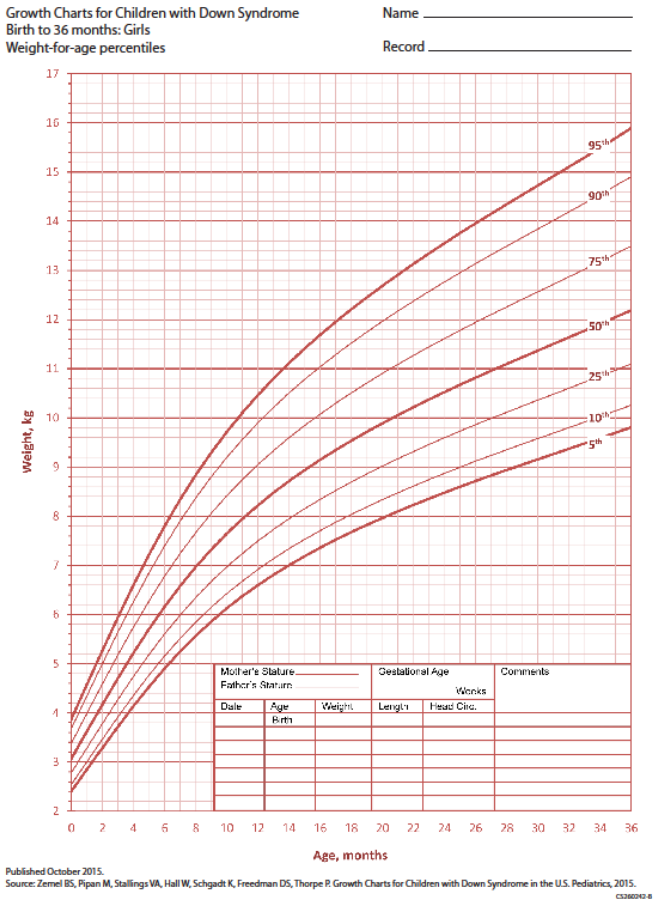
- Referral to early intervention services
- Provide families community resources and information regarding support groups
  - Gigi's Playhouse
  - Local Down Syndrome Groups
  - Global Down Syndrome (National)
- Discuss family/community supports
- Discuss avoiding excessive extension or flexion of neck
- Increase risk of respiratory tract infections
  - Synagis qualifications for some
- Discuss complimentary treatments risks/benefits

To discuss at each appointment

- Support for family
- Age specific Down syndrome related medical and developmental conditions
- Financial and medical support programs
- Injury and abuse prevention
- Nutrition and activity

Growth

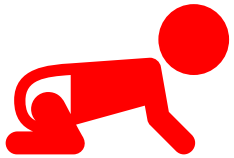




Zemel et.al (2015)

BARROW Neurological Institute | PHOENIX CHILDREN'S

Development and Cognition



Global Developmental Delay
- Motor Skills (fine and gross motor)
- Speech/Language
- Adaptive Skills

Intellectual Disability (ID) (5-6y+)
- Most common chromosomal cause of ID
- Range from mild to severe

Social Skills
- Typically a strength
- Autism spectrum disorder (ASD)

Autism and Down syndrome (Hamner et al 2019)

- Developmental/cognitive profile consideration
- Ds and ASD lowest cognitive abilities than Ds or ASD alone
- Overall less severe ASD symptoms than ASD alone
  - Social affect AND repetitive behaviors
- Social affect was more impaired than Ds alone
- Presentation of repetitive behavior similar to Ds alone
- Further research needed

Guidelines

- Age categorization
  - 1 month to 1 year
  - 1 year to 5 years
  - 5 year to 12 years
  - 12 years to 21 years or older

1 month to 1 year

- Review genetic testing/order if not already completed
- Monitor weight and follow growth trends
- Otitis media and hearing
- Vision
  - Referral to pediatric ophthalmologist – 6 months
  - Lacrimal duct obstruction common, refer for evaluation if not resolved by 9-12 months
- Sleep
  - Review s/s of obstructive sleep apnea
- Monitor feeding
  - Obtain MBS if needed

1 month to 1 year

- Discussion regarding cervical spine positioning
- Thyroid
  - Review newborn screening results
  - Repeat TSH at 6 months and 12 months
- CBC at 1 year with either:
  - Ferritin and CRP
  - Iron and TIBC
- Monitor infants with cardiac defects for cardiac failure
  - Tachypnea, feeding difficulties, poor weight gain

Common skin findings

- Xerosis
  - Thyroid
- Cutis marmorata
- Alopecia Areata
- Vitiligo
- Folliculitis
- Keratosis pilaris

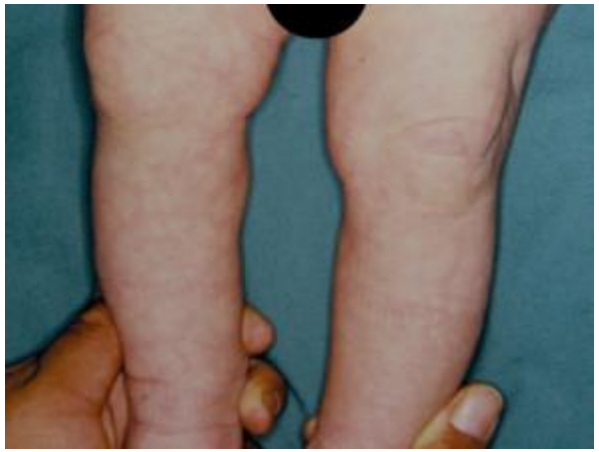


Photo credit: Dermnet

Anticipatory Guidance

- Resources
- Emotional status and supports
- Early intervention
- Review understanding of recurrence and offer genetic counseling if appropriate/desired

1 year to 5 years

- CBC and Iron studies annually
- Audiology every 6 months until bilateral ear specific testing normal
- Vision screens use photoscreening
- TSH at 1 year of age and annually
- Monitor for signs/symptoms of atlantoaxial instability
- Celiac screening
- Monitor sleep
  - Routine sleep study recommended at 3 to 4 years of age
- Appropriate Cardiology follow up
- Testicular examination (Hasle et al 2016)

Atlanto-Axial Instability (AAI) (Ali et al 2006)

- Increased mobility of C2 related to C1
- Symptomatic in 1-2%
- Sign/Symptoms
  - Neck pain
  - Torticollis
  - Weakness
  - Spasticity or change in muscle tone
  - Gait difficulties
  - Hyperreflexia
  - Change in bowel or bladder function
  - Other signs of myelopathy

AAI

- 3 years of age or older for accurate radiograph assessment
- Contact sports (football, gymnastic, etc.) – higher risk of injury
- Avoid trampoline
- Precautions on excessive extension or flexion with surgeries, procedures, radiographs
- Asymptomatic patient
  - Routine radiographs are no longer recommended
- Symptomatic patient
  - Cervical spine radiography in neutral position
    - If instability noted in neutral position, refer to Pediatric Neurosurgery
  - If no abnormalities in neutral position, radiography in extension and flexion

1 year to 5 years

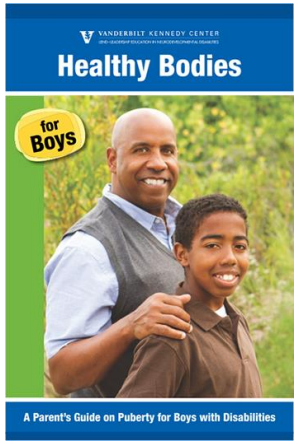
- Monitor development
  - Equipment needed (communication device, gait trainer)
- Evaluate for autism spectrum disorder, ADHD, behavior concerns
- Ensure patient is receiving appropriate therapies in community
- Transition from early intervention to preschool at 3 years of age
  - Individualized Education Plan (IEP)
- Model accurate terms for body parts
- Discuss with family increased risk of exploitation

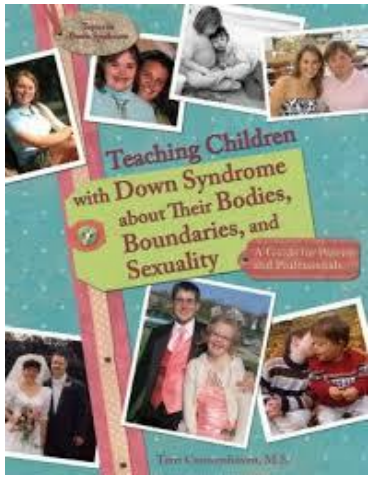
5 to 12 years of age

- Physical examination and growth
  - Down syndrome specific BMI chart up to age 10 years
  - CDC BMI chart over 10 years
- CBC and iron studies annually
- Annual ear specific audiology evaluation
- Photoscreening every visit
- Thyroid studies annually
- Monitor for signs/symptoms of atlantoaxial instability
- Celiac screening as needed
- Monitor sleep

5 to 12 years of age

- Monitor development
- Discuss self help skills
- Evaluate for autism spectrum disorder, ADHD, behavior concerns
- Ensure patient is receiving appropriate therapies in community
- Discuss transition from elementary to middle school
- Puberty
  - Gynecologic care for females
- Safety





BARROW Neurological Institute | PHOENIX CHILDREN'S

12 to 21 years of age

- Guidelines similar to younger ages
- Evaluate for mitral valve disease
  - Increasing fatigue, SOB, exertional dyspnea

12 to 21 years of age

- Discuss transition planning
  - Community resources
    - Guardianship, Power of Attorney, Medical decision making
    - Living arrangements
    - Work opportunities
    - Education
  - School support (mandated by IDEA 2004) https://sites.ed.gov/idea/about-idea/
  - Medical transition
- Safety
- Sexual Health
- Hygiene

Down Syndrome Regression Disorder
(Santoro, et.al. 2022)

- Previously referred to as
  - Down syndrome disintegrative disorder
  - Unexplained regression in Down syndrome
- Adolescents to young adults
- F>M

Manifestations

- Sub acute phase followed by a chronic phase
- Clinical diagnosis
- Symptoms can be heterogenous

Symptoms (Santoro et. al. 2022, Rosso et al 2019)

Altered Mental Status	Cognitive Decline	Developmental regression	New neurological deficits	Development of autism-like features that were not previously present
Movement Disorder *	Seizures	Insomnia	Psychiatric Symptoms	Language deficits

** Must be included in symptom clusters*

Recommendations for diagnosis

1. New onset of symptoms <12 weeks
    a. > 3 symptom clusters present = Possible DSRD
    b. >6 symptom clusters present = Probable DSRD

Differential

- Common medical conditions
  - OSA
  - Hypothyroidism
  - AAI
  - Celiac Disease
  - Nutritional deficiency
  - Sensorineural hearing loss
  - Vision issues
- Psychiatric
  - Depression
  - Anxiety
  - Stress or change to home environment
- Neurologic
  - Stroke
  - Moyamoya
  - TIA
  - Seizure
  - Autism spectrum
- Infectious
  - HIV
  - Syphillis
- Genetic
  - Fragile X
  - Rett
  - Comorbid neurometabolic disease

Work up (Santoro et. al., 2022_

- For all patients
  - Brin MRI with and without contrast on a 3T scanner
  - Blood tests
    - Ammonia, CBC, CMP, ESR, CRP, Lipid Panel, Hemoglobin A1C, B12 level, Vitamin D, TSH with T4, TPO Antibodies, anti-thyroglobulin antibodies, anti-thyroid stimulating hormone receptor, Celiac serology
  - Lumbar Puncture
  - Routine EEG

- Other work up as clinically indicated

Lucy's story

Shared with permission from Lucy's family

BARROW Neurological Institute | PHOENIX CHILDREN'S

Questions?

Each person with Down syndrome has different talents and the ability to thrive.

BARROW Neurological Institute | PHOENIX CHILDREN'S

- Ali, F. E., Al-Bustan, M. A., Al-Busairi, W. A., Al-Mulla, F. A., & Esbaita, E. Y. (2006). Cervical spine abnormalities associated with Down syndrome. International orthopaedics, 30(4), 284–289. https://doi.org/10.1007/s00264-005-0070-y
- Zemel, B. S., Pipan, M., Stallings, V. A., Hall, W., Schadt, K., Freedman, D. S., & Thorpe, P. (2015). Growth Charts for Children With Down Syndrome in the United States. Pediatrics, 136(5), e1204–e1211. https://doi.org/10.1542/peds.2015-1652
- Brian G. Skotko, George T. Capone, Priya S. Kishnani. Postnatal Diagnosis of Down Syndrome: Synthesis of the Evidence on How Best to Deliver the News. Pediatrics Oct 2009, 124 (4) e751-e758; DOI: 10.1542/peds.2009-0480
- Down Syndrome. Genetics Home Reference – NIH U.S. National Library of Medicine. https://ghr.nlm.nih.gov/condition/down-syndrome#inheritance
- Facts about Down Syndrome. Center for Disease Control and Prevention. https://www.cdc.gov/ncbddd/birthdefects/downsyndrome.html
- Gamis, A. S., Alonzo, T. A., Gerbing, R. B., Hilden, J. M., Sorrell, A. D., Sharma, M., Loew, T. W., Arceci, R. J., Barnard, D., Doyle, J., Massey, G., Perentesis, J., Ravindranath, Y., Taub, J., & Smith, F. O. (2011). Natural history of transient myeloproliferative disorder clinically diagnosed in Down syndrome neonates: a report from the Children's Oncology Group Study A2971. Blood, 118(26), 6752–6996. https://doi.org/10.1182/blood-2011-04-350017
- Healthy Bodies Toolkit. Vanderbilt Kennedy Center. https://vkc.mc.vanderbilt.edu/HealthyBodies/
- Mai CT, Isenburg JL, Canfield MA, Meyer RE, Correa A, Alverson CJ, Lupo PJ, Riehle-Colarusso T, Cho SJ, Aggarwal D, Kirby RS. National population-based estimates for major birth defects, 2010–2014. Birth Defects Research. 2019; 111(18): 1420-1435
- Norton, M. E., Brar, H., Weiss, J., Karimi, A., Laurent, L. C., Caughey, A. B., Rodriguez, M. H., Williams, J., 3rd, Mitchell, M. E., Adair, C. D., Lee, H., Jacobsson, B., Tomlinson, M. W., Oepkes, D., Hollemon, D., Sparks, A. B., Oliphant, A., & Song, K. (2012). Non-Invasive Chromosomal Evaluation (NICE) Study: results of a multicenter prospective cohort study for detection of fetal trisomy 21 and trisomy 18. American journal of obstetrics and gynecology, 207(2), 137.e1–137.e1378. https://doi.org/10.1016/j.ajog.2012.05.021
- Translocation Down Syndrome: What You Need to Know. MassGeneral for Children. https://www.massgeneral.org/children/down-syndrome/translocation-down-syndrome
- Hamner, Taralee MS[*,†]; Hepburn, Susan PhD[‡]; Zhang, Fengqing PhD[*]; Fidler, Deborah PhD[‡]; Robinson Rosenberg, Cordelia PhD[§]; Robins, Diana L. PhD[*,†]; Lee, Nancy R. PhD[*] Cognitive Profiles and Autism Symptoms in Comorbid Down Syndrome and Autism Spectrum Disorder, Journal of Developmental & Behavioral Pediatrics: April 2020 - Volume 41 - Issue 3 - p 172-179 doi: 10.1097/DBP.0000000000000745
- Bull MJ, Trotter T, Santoro SL, et al; AAP Council on Genetics. Health Supervision for Children and Adolescents With Down Syndrome. Pediatrics. 2022;149(5):e2022057010
- Hamner T, Hepburn S, Zhang F, Fidler D, Robinson Rosenberg C, Robins DL, Lee NR. Cognitive Profiles and Autism Symptoms in Comorbid Down Syndrome and Autism Spectrum Disorder. J Dev Behav Pediatr. 2020 Apr;41(3):172-179. doi: 10.1097/DBP.0000000000000745. PMID: 31599791.
- Hasle, H., Friedman, J., Olsen, J. *et al.* Low risk of solid tumors in persons with Down syndrome. *Genet Med* **18,** 1151–1157 (2016). https://doi.org/10.1038/gim.2016.23
- Santoro JD, Patel L, Kammeyer R, Filipink RA, Gombolay GY, Cardinale KM, Real de Asua D, Zaman S, Santoro SL, Marzouk SM, Khoshnood M, Vogel BN, Tanna R, Pagarkar D, Dhanani S, Ortega MDC, Partridge R, Stanley MA, Sanders JS, Christy A, Sannar EM, Brown R, McCormick AA, Van Mater H, Franklin C, Worley G, Quinn EA, Capone GT, Chicoine B, Skotko BG, Rafii MS. Assessment and Diagnosis of Down Syndrome Regression Disorder: International Expert Consensus. Front Neurol. 2022 Jul 15;13:940175. doi: 10.3389/fneur.2022.940175.