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DOWN SYNDROME

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INTRODUCTION

Incidence

The prevalence of Down syndrome is currently estimated at approximately 1 in 792 live births (de Graaf et al. 2015). Estimates of the prevalence of Down syndrome are highly dependent on the gestational timing at ascertainment and maternal age. Trisomy 21 accounts for about 1 in 150 first-trimester spontaneous abortions, and 35% of cases diagnosed between 15 and 28 weeks of gestation result in pregnancy loss with the actual loss rate varying inversely with gestation at ascertainment. Prevalence rises from 1/1445 live births at maternal age of 20 years to about 1/25–1/30 at the age of 45 years. Some data suggest prevalence does not continue to rise beyond the age of 45 years but remains stable at about 1/30. Prevalence of Down syndrome has been influenced by the increasing trend for termination of pregnancies with chromosome abnormalities owing to non-invasive prenatal screening (NIPS) using cell-free DNA. This screening has been commercially available since 2011, offering expectant women the option to determine (with near 99% sensitivity and specificity) whether their fetus might have Down syndrome. Prior to NIPS, this number was lower. In the US, the live birth prevalence for Down syndrome in the most recent years (2006–2010) was estimated at 12.6 per 10,000, with around 5300 births annually (de Graaf et al 2015). During this period, an estimated 3100 Down syndrome-related elective pregnancy terminations were performed annually. As of 2007, the estimated rate at which live births with Down syndrome were reduced as a consequence of these elective terminations was 30% for the US. Apart from advanced maternal age and selective terminations by prenatal testing, increase in birth control measures and decrease in family sizes also play a role in the prevalence rates in more recent times.

Life expectancy tables are estimated on the basis of cross-sectional survival rates to specific ages. If the birth prevalence of Down syndrome is constant, one can compare the prevalence of Down syndrome at age 50 years with that at birth in different decades and calculate and compare survival rates with that at age 50 years. Comparisons of survival rates for Down syndrome over time are complicated by changing birth prevalence and other factors such as improved neonatal ascertainment and uneven improvement in survival across different age groups. Increased maternal age also influences the data on survival curves, as the occurrence of Down syndrome is highly maternal age dependent. If more mothers over 35 years of age begin having children, and thus increase the birth prevalence, more children are available to survive, thus causing an "apparent" increased survival to age 50 years. Increased use of maternal serum screening and prenatal diagnosis would have the opposite effect. An improvement in early survival will again present more cases surviving at later ages, without necessarily signaling improved longevity for older individuals. Notwithstanding these caveats, several geographically disparate studies have concluded that

Cassidy and Allanson's Management of Genetic Syndromes, Fourth Edition.
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survival in individuals with Down syndrome has shown marked improvement, particularly over the past 25–30 years. Most of the improvement has resulted from the treatment of congenital heart disease and respiratory infections during the first decade. Reduced institutionalization with increased mobility and integration into society have also played a role. A recent data set from Western Australia on 772 children with Down syndrome showed survival rates of 57% at 60 years for those born between 1953 and 1959, and survival estimates improved for subsequent generations (Glasson et al. 2016).

Mortality during the first five years continues to be higher than in the general population. A retrospective cohort study of over 16,000 infants with Down syndrome in the US showed modest improvement in survival over the study period of 20 years, with neonatal survival remaining similar at about 98% (Kucik et al. 2013). Survival at 1 year and 20 years was estimated to be 93% and 88%, respectively. The infant mortality rate in Down syndrome has remained at about five times that of the general population. Factors associated with lowered survival include congenital heart defects, birth weight <1500 g, and race/ethnicity (with non-Hispanic children with an African origin having lower survival rates), highlighting the impact of socioeconomic status and access to medical care on survival. From ages 5 to 39 years, the survival curves are parallel but mortality somewhat exceeds the general population. There is an increase in the mortality rate that is greater than that of both the general population and other individuals with intellectual disabilities. Increased risk for comorbidities such as seizures, depressive symptoms, and dementia appear as factors that are potentially contributory for this reduced survival.

Diagnostic Criteria

The gold standard for the diagnosis of Down syndrome is karyotypic demonstration of an extra copy of the long arm of chromosome 21. However, Down syndrome may be clinically diagnosed based on the characteristic appearance (gestalt) and behavior of affected individuals. This may be more challenging in premature infants, in some older adults, in an unfamiliar racial/ethnic group, or in individuals whose features are modified by significant mosaicism or a structural chromosome change that results in only partial duplication of 21q22. As with any syndrome, the associated features are variable. Children born at home show a significant delay in diagnosis (10.2 versus 1.8 days).

Typical features in neonates with Down syndrome include characteristic hypotonia, hyper-extensibility, and poor behavioral responses. The skull is mildly microcephalic and brachycephalic with a flat occiput. The fontanels tend to be large, a third fontanel may be palpable, and they close late. The posterior hair whorl is more likely to be midline, and the hair is fine. The face is round in the neonate and infant (Figure 24.1), and becomes more oval with age (Figures 24.2 and 24.3).

Underdevelopment of the midface gives a flat appearance, and the upper facial depth and length of the maxillary

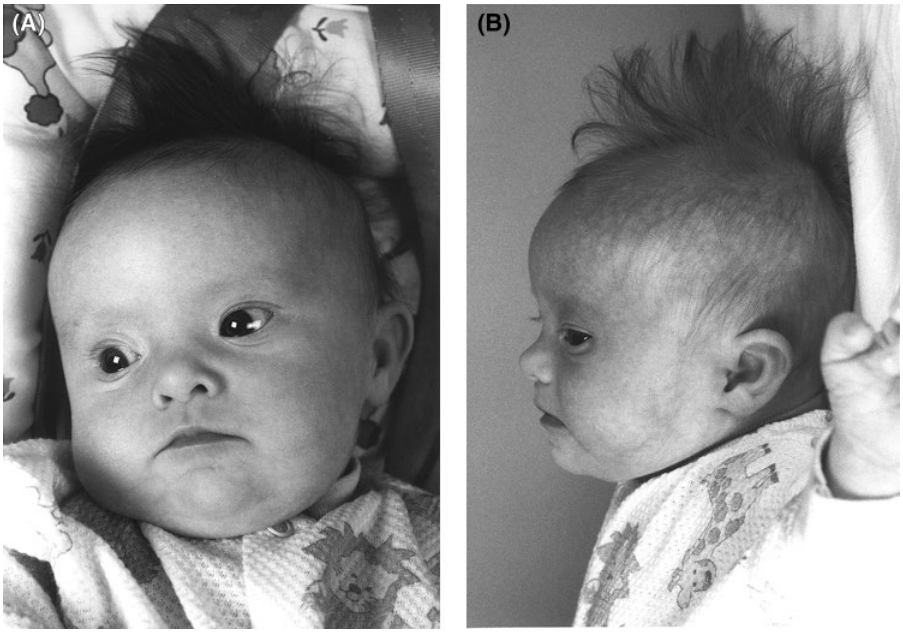

FIGURE 24.1 (A) A 6-week-old girl with Down syndrome illustrating round face with flat malar area, depressed nasal root, epicanthal folds, and upslanting palpebral fissures. Even at rest there is some pursing around the eyes. Her nose is short and the corners of her mouth downturned. (B) A lateral view of the same child shows mottling of the skin, malar flatness, and a small nose. The ear is slightly small with mild overfolding of the helix.

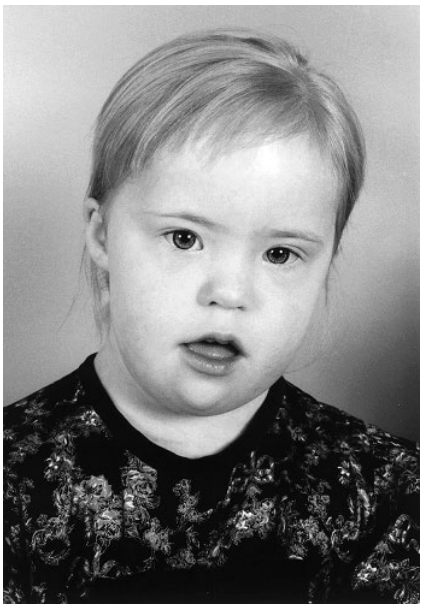

FIGURE 24.2 A 4-year-old girl with Down syndrome showing that the face has lengthened from that of the newborn but maintains the characteristic depressed nasal root, epicanthal folds, and upslanting palpebral fissures. Brushfield spots can be seen close to the iris margin. There is malar underdevelopment. The ear is small with a slight overfolding and crimping of the upper helix.

arch are disproportionately reduced. Epicanthal folds and upslanting palpebral fissures are typical, and the palpebrae "purse" on laughing or crying. Brushfield spots of the iris are common and are more peripherally placed than those seen in the general population. Ophthalmologic evaluation often reveals fine opacities of the lens. The optic disk is rosy colored, and has an increased number of retinal vessels. The nose is short with a depressed nasal bridge and, usually, small nares. The mouth is downturned, and a small oral cavity contributes to a tendency to protrude the tongue and to mouth breathe. Growth of the mandible tends to outpace that of the palate, leading to prognathism. The ears are small and may be cupped or show an overfolded upper helix contributing to a small, square shape. The neonate often has redundant nuchal skin, and, with age, the neck may appear wide when viewed from behind, perhaps partly because of the relative microbrachycephaly.

The chest may reveal signs of congenital heart disease. The hands are short with a high frequency of single palmar creases (not pathognomonic). The middle phalanx of the fifth finger is short and/or triangular, resulting in a single flexion crease or clinodactyly, respectively. Dermatoglyphic analysis is not performed often currently, but characteristic findings include a higher frequency of arches and ulnar loops on the thumb, ulnar loops on the index and middle fingers, and radial loops on the fourth and fifth fingers, a distal

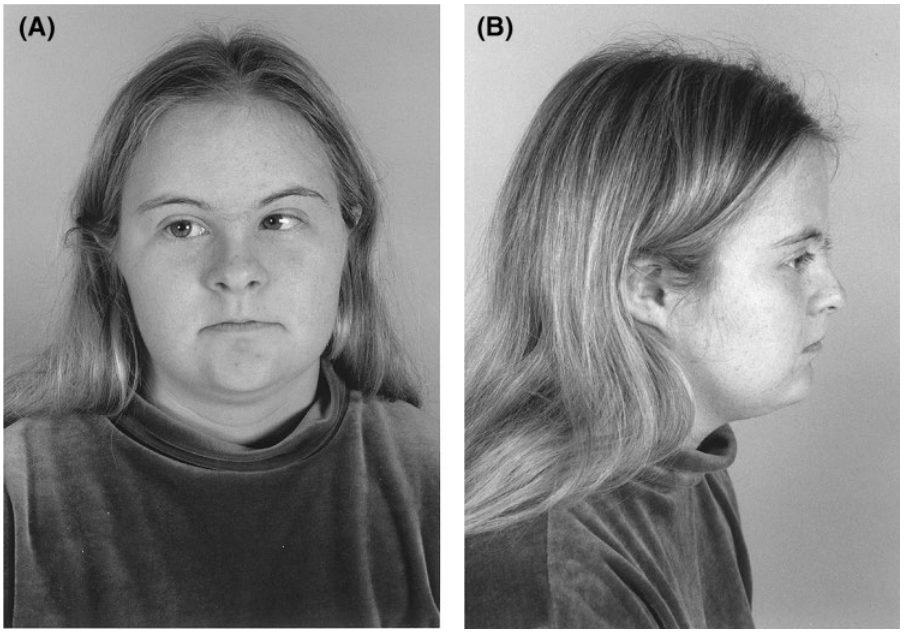

FIGURE 24.3 (A) An 18-year-old girl with Down syndrome demonstrating mild upslanting of the palpebral fissures, epicanthal folds, strabismus, and Brushfield spots. Although there has been growth of the nose, it remains small and short with a relatively depressed root and bridge. There continues to be a downturn to the corners of the mouth, and the lower jaw is small. (B) The lateral view demonstrates brachycephaly, a small ear with a slightly overfolded helix, and a small nose and jaw.

palmar triradius, and interdigital loops at I1 and I3. The space between the first and second toes is increased and accompanied by a vertical plantar crease with an origin at the space (sandal gap appearance). Cutis marmorata is common. The diagnosis may be aided by radiological evidence of an additional manubrial ossification center, a flat acetabular angle, and hypoplastic iliac wings that flare outward.

Despite the known myriad of clinical features, there are some limitations in the timely diagnosis of individuals with Down syndrome in many countries. Two main reasons are phenotypic variations in different ethnicities and the lack of antenatal screening facilities in developing countries. For a postnatal clinical diagnosis, many clinicians are trained using standard references which are specific to European or American resources. However, Kruszka and colleagues (2017) demonstrated that clinical features including brachycephaly, ear anomalies, clinodactyly, sandal gap, and nuchal skin differ across ethnicities. The most common features are upslanting palpebral fissures (61%) and flat facial profile (51%), but there is a large variation in facial findings even among individuals within the same ethnic groups. Further studies to improve our understanding of differences in the Down syndrome phenotype among individuals of different ancestries will be useful for clinicians around the world.

As Down syndrome and congenital malformations are both relatively common occurrences, a wide variety of birth defects may be expected to be seen in children with Down syndrome by chance alone. Comparison of the rates of specific malformations between children with and without Down syndrome is required to determine which malformations are causally related to Down syndrome. Torfs and Christianson (1998) have provided a review of the literature and a comparison of the rates of 61 anomalies between 2894 individuals with Down syndrome and a control population of 2.5 million from the same newborn surveillance registry. Forty-five of the malformations were reported significantly more frequently in Down syndrome, and every major system was represented. Risk ratios varied from nonsignificant to 1009 (atrioventricular canal defect). Risk ratios of over 100 were obtained for patent ductus arteriosus (152), overriding aorta (200), stenosis of the small intestine (142), duodenal atresia (265), Hirschsprung disease (102), annular pancreas (430), and hernia of Morgagni (246). Of equal interest are malformations that did not show an increased rate, including other types of diaphragmatic hernia, cleft lip with or without cleft palate, renal agenesis, neural tube defects, omphalocele, pyloric stenosis, and most cardiac malformations classified as conotruncal or looping defects. However, a recent study comparing the rates of congenital anomalies in 728 infants with Down syndrome from a registry of over 400,000 pregnancies (Stoll et al. 2015) found increased frequencies of duodenal atresia and anomalies of the urinary, musculoskeletal, and respiratory systems compared to both the general population and to the study by Torfs and Christianson (1998). The study also found decreased frequency of anal atresia, annular pancreas and limb reduction defects compared to prior studies. Discrepancies in the types and frequency of associated anomalies are likely related to methodological differences between studies.

Etiology, Pathogenesis, and Genetics

Down syndrome is caused by trisomy for chromosome 21. About 95% of cases result from nondisjunction and resultant standard trisomy 21. The remaining 5% are relatively evenly split between Robertsonian translocations, of which the 14;21 translocation is most common and about half are familial, and trisomy 21 mosaicism Down syndrome. Mosaicism may arise by postzygotic (mitotic) nondisjunction of a disomic zygote or the postzygotic loss of a chromosome 21 from a trisomic zygote. The lack of any maternal age association with mosaicism suggests that the former is more important. A small minority of affected individuals has other types of chromosome rearrangements, some of which result in partial duplications of chromosome 21.

The etiology of the characteristic appearance and specific associated features of Down syndrome is presumed to relate to dosage effects of genes on chromosome 21, but epigenetic effects may also contribute. The expression and dosage sensitivity of the genes on chromosome 21 is variable, and it has been hypothesized that the most dosage-sensitive genes are most likely to contribute to the Down syndrome phenotype. An alternative view is that the extra genetic material, as a whole, may disrupt multiple developmental pathways. Efforts are underway to study animal models of Down syndrome, individuals with partial 21q duplications, and effects of differential gene expression on the phenotype of Down syndrome. The creation of the Ts65Dn mouse that is trisomic for the equivalent of the critical region of human chromosome 21 has contributed significantly to the understanding of the developmental differences in Down syndrome (Bartesaghi et al. 2015; Gardiner 2015).

Maternal age is the single most important determinant of nondisjunction trisomy 21, and molecular techniques have shown that 85–90% of cases result from maternal and 5–10% from paternal meiotic errors, whereas up to 5% of cases may represent postzygotic mitotic nondisjunction. About 75% of maternal and 50% of paternal nondisjunction occurs in meiosis I, with the remainder occurring in meiosis II. The observation that the odds ratio increases with age for both maternal meiosis I and II errors suggests that there is an age-sensitive risk factor acting at the time of conception. A decreased rate, or more centromeric or distal location of crossover events appears to play a role in nondisjunction generally (Ghosh, Feingold & Dey, 2009).

Several studies have investigated whether other potential factors like environmental or genetic factors could increase

the chance for Down syndrome in pregnancy. Carothers and colleagues (2001) studied 3157 cases of Down syndrome and found no association with paternal age, birth order, ancestry, country of birth, maternal education, blood group, or pregnancy interval. Maternal smoking has been studied as a factor potentially contributing to proper segregation of chromosome 21 in the meiosis I phase of oogenesis, but studies have shown mixed results. The data concerning natural, medical, and accidental radiation exposure and the risk of trisomy are contradictory and unconvincing, but there is a need for further properly designed studies.

There has been a discussion of a possible role of hypomethylation in the etiology of Down syndrome. A recent meta-analysis examined the association between maternal polymorphisms in folate metabolism genes [RFC-1 A80G (located on chromosome 21)/MTR A2756G (located on chromosome 1)/CBS 844ins68 (located on chromosome 21)] and chance for Down syndrome in their offspring (Gu 2017). The A80G polymorphism of the Reduced Folate Carrier-1 (*RFC-1*) gene was associated with a chance for Down syndrome, but there was no evidence of an association between the MTR A2756G/CBS 844ins68 polymorphisms and Down syndrome. Further well-designed large studies are required to investigate gene-environment interactions, gene-maternal age interactions, and combinations of gene polymorphisms.

The potential role of genes related to Alzheimer disease in the mechanisms of Down syndrome has also been discussed. Presenilin-1 (*PSEN-1* gene on chromosome 14) and Apolipoprotein E (*APOE* gene on chromosome 19) genes are associated with early and late onset of Alzheimer disease, respectively. A case control study (Bhaumik et al. 2017) found that younger mothers (under age 35) of children with Down syndrome had a higher frequency of the *PSEN-1* T allele and TT genotype in the presence of the *APOE* epsilon4 allele compared to mothers of children with normal karyotypes. This association was found in mothers with meiosis II nondisjunction, but not among mothers with meiosis I nondisjunction. This study suggests that *PSEN-1* may be a prospective molecular candidate that relates Alzheimer disease and Down syndrome.

The recurrence chance estimates for parents of children with trisomy 21 Down syndrome vary with the age of the mother at the time of the birth of the child. Mothers who have had a child with Down syndrome and who were of older age maintain their current age-related chance, whereas those who were younger (<30 years) have an increased recurrence chance (up to six-fold) compared with same-aged peers. For a mother of a child with trisomy 21, the recurrence chance for trisomy 21 in a future pregnancy is estimated at approximately 1%, until the maternal age-related chance exceeds 1% (around age 40). The basis for this increased chance compared to the general population remains unknown, but could be due to a decreased likelihood of spontaneous abortion in pregnancies with trisomic fetuses, to an age-independent increased propensity to nondisjunction, or to gonadal mosaicism. There has been some evidence of increased prior fetal loss in young mothers of children with Down syndrome. No evidence for increased prevalence of Down syndrome has been found in second- and third-degree relatives of individuals with trisomy 21 (Berr et al. 1990). A common question is that of the chance for Down syndrome for a couple in which one member has a relative with Down syndrome of unknown karyotype. The known age-specific rates of trisomy versus translocation Down syndrome and the likelihood of male and female transmission of a translocation can be used to calculate the chances for specific relatives of the affected person. The highest chance is about 1 in 640, and it applies to the children of the sister of the person with Down syndrome. This is not greatly different from the population prevalence, and the chance declines rapidly with the degree of relationship and is lower when the connection is through a male. Parents of children with de novo translocations do not have a significantly increased chance for recurrence, whereas a man with a balanced Robertsonian translocation has a 3–5% chance, and a woman a 10–15% chance for recurrent Down syndrome. Note must be taken of the special circumstance of a parental 21;21 translocation, where the recurrence is 100%. For a child with Down syndrome due to any translocation, a referral for parents to a medical genetics clinic for counseling and parental testing is indicated.

Diagnostic Testing

Non-invasive prenatal screening (NIPS) or testing (NIPT) (also known as cell free fetal DNA testing – cffDNA) is considered a highly accurate screening test for Down syndrome compared with conventional combined first trimester screening (FTS). The test counts fragments of fetal DNA (called cell-free DNA), thought to be primarily derived from the placenta, circulating in the maternal blood. If there are extra fragments of chromosome 21, for example, three copies of chromosome 21 instead of the usual two, this indicates that the fetus may have Down syndrome. It can be done in the 10th week of pregnancy and the results usually take about 1–2 weeks. In October 2011, NIPS became commercially available in the USA and China, and was rapidly inculcated into standard prenatal care in many countries. While the majority of validation data on NIPS has been based on populations of women at higher risk for chromosome abnormalities in pregnancy, recent studies have investigated performance of NIPS for detecting aneuploidy in the general population. A recent prospective, blinded study of over 15,000 participants from an unselected population of women across 35 diagnostic centers found that when compared to standard screening, NIPS had higher sensitivity (100% for NIPS versus 78.9% for FTS), a lower false positive rate

(0.06% for NIPS versus 5.4% for FTS), and a higher positive predictive value (80.9% for NIPS versus 3.4% for FTS) (Norton and Wapner 2015).

The prenatal Down syndrome screening strategy that has conventionally been used in lower-risk groups (FTS) is based on predicting risks using non-invasive measures, including a combination of gestational age, maternal age and weight, maternal biochemical markers, ultrasound measurements, and more recently non-invasive prenatal screening. Ultrasounds in the first trimester are done at 11–14 weeks to detect nuchal translucency, nasal bone abnormalities and ductal venous flow measurements. These measurements, along with the mother's age and the gestational age, improve the odds ratio of detecting Down syndrome. When performed with a maternal blood test, its accuracy may be improved. Ultrasounds in the second trimester detect soft biomarkers that do not in themselves confirm a diagnosis but are seen more frequently in fetuses with an abnormality. Soft biomarkers include echogenic intracardiac focus, ventriculomegaly, nuchal fold thickness >6 mm, echogenic bowel, hypoplastic/absent nasal bone, shortened humerus, mild pyelectasis, shortened femur, and aberrant right subclavian artery (ARSA). Each biomarker is assigned positive, negative, and isolated likelihood ratios. The chance of Down syndrome is recalculated as baseline chance times likelihood ratio. The new likelihood ratio is calculated by multiplying all positive likelihood ratios (of markers present) and all negative likelihood ratios (of markers absent). If a single marker is present, then the isolated likelihood ratio is considered. The importance of clustering of markers forms the basis of a scoring index, such that individual markers are assigned point values based on their sensitivity and specificity in the detection of Down syndrome. The points acquired by each fetus are tabulated into a final score. Ultrasounds by themselves have low detection rates for Down syndrome. Ultrasonographic skills are highly variable, and their use in prenatal screening for Down syndrome requires a high level of training and a standardized approach.

Algorithms for combining ultrasound with maternal serum screening have been developed and evaluated. Some of these include graduated risk ratios dependent on the degree to which a specific sign or measurement is abnormal. A number of programs combine first-trimester nuchal translucency measurements and biochemical screening with second-trimester biochemical tests (integrated prenatal screening) to obtain detection rates in the range of 90% and low initial positive rates of about 2%. Urine markers have also been explored. Alldred and colleagues (2017) used meta-analytical methods involving 228,615 pregnancies (including 1067 with Down syndrome). Thirty-two different test combinations were evaluated from combinations of eight different tests and maternal age; first trimester nuchal translucency and the serum markers AFP (alpha fetoprotein), uE3 (unconjugated estriol), total hCG (human chorionic gonadotropin), free hCG, Inhibin A, PAPP-A (plasma protein A), and ADAM12 (a disintegrin and metalloprotease 12). They reviewed tests that combine the first and second trimester markers with or without ultrasound as complete tests, and examined stepwise and contingent strategies. Meta-analysis of the six most frequently evaluated test combinations showed that a test strategy involving maternal age, a combination of first trimester nuchal translucency and PAPP-A, and second trimester total hCG, uE3, AFP and Inhibin A significantly outperformed other test combinations that involved only one serum marker or nuchal translucency in the first trimester, detecting about 9 out of every 10 cases of fetal Down syndrome at a 5% false positive rate. The choice of screening tests is dependent on many factors including cost-effectiveness, willingness of parents for prenatal testing, prior obstetric history, family history, singleton/twin pregnancy, gestational age, availability of non-invasive versus invasive techniques, limitations of tests, psychological issues involving care of an affected child, availability of other options (termination or adoption), and ethics.

While non-invasive prenatal screening methods provide accurate detection of fetal Down syndrome, karyotyping using chromosome analysis is the gold standard test to confirm the diagnosis. Chromosome analyses may be completed prenatally using amniocentesis or chorionic villus sampling, or may be done postnatally on peripheral blood. Amniocentesis and chorionic villus sampling are relatively costly, have a risk for miscarriage, and have a relatively low yield, especially if applied to younger women. This has driven the search for population-based screening methods, which are more cost-effective and have a lower risk of miscarriage.

The diagnosis of Down syndrome can also be made on interphase nuclei using fluorescence in situ hybridization (FISH), microarrays, and quantitative fluorescent polymerase chain reaction (QF-PCR). The main limitation of chromosome analysis is the requirement of tissue culture and limited genomic resolution. It cannot detect submicroscopic deletions/duplications of clinical relevance; for example, 22q11.2 microdeletion associated with fetal cardiac abnormalities. Chromosomal microarray (using comparative genomic hybridization, CGH) shows excellent diagnostic performance with improved detection rates compared to karyotyping for prenatal diagnosis of clinically relevant fetal chromosomal abnormalities. However, chromosome analysis is necessary to distinguish between Down syndrome due to free trisomy 21 versus a Robertsonian translocation, which has important implications for recurrence estimates in future pregnancies (see section above).

All pregnant women should be offered prenatal genetic screening tests for Down syndrome. Women with a positive screening test for fetal genetic conditions should always be offered further counseling and prenatal diagnostic testing.

They should be educated about the possible false positive and false negative screening test results. Counseling should include family education and options pertaining to medical termination, psychological and genetic counseling, adoption, referral to tertiary care centers for better infrastructure to manage complicated neonates, and perinatal hospice care if a neonate's condition is incompatible with life. For persons suspected of having Down syndrome and in whom a normal chromosome result is reported, it may be appropriate to refer to a specialist in dysmorphology, who may look for mosaicism in more cells or another tissue.

Differential Diagnosis

Down syndrome is common and distinctive, and should not often be confused with other syndromes. However, there may be confusion when a typically developing neonate has one or more of the common signs or minor anomalies that physicians associate with Down syndrome (e.g., hypotonia, "large" tongue, and single palmar crease). Noting the absence of the other common signs and the facial gestalt of Down syndrome should avoid this error. Likewise, hypothyroidism and Beckwith–Wiedemann syndrome (see Chapter 9) can be distinguished by their own typical signs and the lack of other characteristics of Down syndrome.

A number of young children with Smith–Magenis syndrome (see Chapter 54) have been diagnosed fortuitously when the diagnostic deletion of 17p11.2 was detected on a karyotype requested for suspected Down syndrome. The overlapping features include brachycephaly, round face, upslanting palpebral fissures, midface hypoplasia, a small, wide nose, and Wölfflin–Krückmann iris spots that may be confused with Brushfield spots. Other signs of Down syndrome are absent; however, with time the more typical appearance and behavior of Smith–Magenis syndrome become apparent.

Zellweger syndrome, a peroxisomal disorder, shares a number of findings with Down syndrome including hypotonia, large fontanels, flat occiput and face, anteverted nares, epicanthal folds, Brushfield spots, cataracts, abnormal helices, single palmar crease, and cardiac septal defects. Distinguishing signs include severe early developmental delay, seizures, a high forehead, shallow orbits, hepatomegaly, joint contractures, stippled epiphyses, and brain migrational anomalies in Zellweger syndrome. The diagnosis can be confirmed by finding elevated very long-chain fatty acids in plasma.

MANIFESTATIONS AND MANAGEMENT

The American Academy of Pediatrics (AAP) has published guidelines for the healthcare management of children with Down syndrome (Bull 2011). Down syndrome specialty clinics have been created across the United States with the goal of supporting healthcare management and improving adherence to the AAP guidelines. Down syndrome specialty clinics can identify and address specific needs for children with Down syndrome beyond what is typically available in primary care settings (Skotko et al. 2013). Lists of specialty clinics are available through the websites for the National Down Syndrome Society (NDSS 2019) and the Global Down Syndrome Foundation (2017). The following sections below detail the manifestations and management for multiple specific systems in Down syndrome.

Growth and Feeding

Feeding difficulties due to hypotonia, large tongue, small oral cavity, dysphagia, constipation, and gastrointestinal regurgitation syndrome are common in individuals with Down syndrome. Decreased tone in perioral muscles, lips and muscles of mastication as well as decreased tongue movements may lead to sucking difficulties in infants with Down syndrome. They tend to breastfeed for a shorter time, have more respiratory infections, and develop non-nutritive oral sucking habits (like increased dependence on bottle feeding, finger sucking, and pacifier use). Improved guidance for parents to encourage healthier feeding habits, advocating techniques to reduce feeding problems (like smaller feeds, keeping the child upright for 30 minutes post feeds, head elevation during feeds), and promoting breastfeeding will alleviate some of these problems during infancy. The same oral and motor difficulties may cause a delay in the introduction of solid foods, and the primary care physician has an important role in ensuring that a balanced diet is being maintained throughout infancy. Through childhood, uncorrected feeding problems may lead to unbalanced dietary habits.

Standard growth charts may not provide accurate information about the development of children with Down syndrome. These children can have lower birth weights and slower growth rates which are appropriate for a child with Down syndrome; yet can be misinterpreted as poor growth if compared to typically developing children. WHO and CDC growth charts are being used worldwide to monitor growth, but Down syndrome-specific growth charts have been developed for children in the United States (Zemel et al. 2015), as well as for children in multiple other countries (e.g., Afifi et al. 2012; Bertapelli et al. 2017; Su et al. 2014; Tuysuz et al. 2012). The mean birth length in infants with Down syndrome has been estimated to be one standard deviation lower than in the general population, indicating that fetal growth may be slower. During the first three years of life, the linear growth rate is slower compared to the general population. The gap stays relatively constant during the age interval of 3–12 years. After the age of 12 years a further relative slower rate of growth decline is observed. This pattern is observed

to be the same in boys and girls with Down syndrome. Hence, the slowing in linear growth rate occurs in the three critical periods of growth, resulting in shorter adult stature.

Down syndrome is associated with increased risk for obesity. From late infancy, children with Down syndrome show a relative increase in mean weight for height and in weight/height^2, and excessive weight is a significant problem in adulthood. Individuals with Down syndrome appear to have higher leptin levels than their unaffected siblings even after correction for percent body fat. People with Down syndrome also have a lower metabolic rate than typically developing individuals. Collaboration between parents and health personnel is important to help improve nutrition and address issues related to being overweight.

The new Down syndrome-specific length/height growth charts for children in the United States (Zemel et al. 2015) have improved diagnosis of growth failure (short stature). Growth failure is a diminished linear growth velocity, crossing height growth centile markings on Down syndrome-specific growth charts, in the absence of malnutrition and of symptoms and signs pointing to another diagnosis. People with Down syndrome and growth failure have a specific reduction in insulin-like growth factor-1 (IGF-1). Failure to thrive is defined as undernutrition/malnutrition, associated or not associated with linear growth failure. The weight growth charts are more useful for the diagnosis of failure to thrive than for overweight and obesity. The high prevalence of overweight and obesity in Down syndrome make the diagnoses of these based on centile cutoffs inappropriate. Therefore, the 85th centile on the new CDC BMI growth charts is likely a better indicator of adiposity than the 85th centile on the new Down syndrome specific BMI growth charts. Further studies using techniques to measure lean body mass in a large population-based sample of people with Down syndrome would provide a better understanding of both assessment of nutritional state and of the effects of race and ethnicity on growth. There is no case series of children with Down syndrome who have failure to thrive to guide an evaluation, and a full discussion of this problem is beyond the scope of this review.

Evaluation

- Appropriate tests should be performed to diagnose common causes of growth failure, including hypothyroidism, growth hormone deficiency, and celiac disease.
- For severe failure to thrive, a hospitalization is often needed to determine etiology and to begin treatment. High output heart failure from congenital heart disease is probably the most common cause. Psychosocial failure to thrive (parental neglect or inadequate education) should always be considered as a diagnostic possibility in children with Down syndrome. A careful dietary history, a thorough review of symptoms, and a good physical examination are essential.
- Infants who have marked hypotonia and slow feeding, infants who choke with feeds, infants and children who have recurrent pneumonia or who have other recurrent or persistent respiratory symptoms, and infants and children who have unexplained failure to thrive should all have a videofluoroscopic swallow study and a barium swallow with small bowel follow through to rule out a tracheoesophageal fistula and gastroesophageal reflux, small bowel stenosis or duodenal stenosis associated with annular pancreas, and to rule out other gut malformations.
- All children with Down syndrome who have failure to thrive or growth failure should be evaluated for thyroid disease and celiac disease, whether or not they have gastrointestinal symptoms.
- For children with Down syndrome who have obesity, complete dietary and activity histories are essential. A careful history of diabetes, hypothyroidism, and sleep disordered breathing should be obtained.
- If obesity is severe and there is shortness of breath, an evaluation for pulmonary hypertension should be done, as individuals with Down syndrome are more susceptible to developing pulmonary hypertension than the general population.
- Those who are obese should be evaluated for insulin resistance by obtaining a random glucose concentration, insulin level and hemoglobin A1C level and for hypothyroidism with TSH and serum free T4 levels.

Management

- Disorders of growth and nutrition require referral to specialty clinics: to endocrinology for management of growth failure not due to celiac disease; to gastroenterology for diagnosis and management of feeding and swallowing problems, psychosocial failure to thrive and problems following surgery for gastrointestinal malformations; and to a healthy lifestyles (obesity) clinic for management of obesity. After a thorough evaluation with an endocrinologist, certain patients with growth failure can be given supplemental growth hormone. The treatment with growth hormone should be considered only if there is a documented deficiency, because inadvertent use of growth hormone can lead to adverse effects like insulin resistance, benign intracranial hypertension, edema, and gynecomastia. There are no long-term studies of growth hormone treatment in individuals with Down syndrome. If growth hormone is used, long-term follow-up of patients is warranted to monitor them at regular intervals.
- For infants with failure to thrive who have difficulty sucking, it is important that the child is well awake, that the child is properly supported with the chin steadied,

that the mouth and nose are clear of mucus (a syringe with a small amount of normal saline may help clear the nose), and that the child is burped regularly. These simple measures will usually overcome minor, self-limited problems. With breast-feeding it may be helpful to facilitate attachment to the breast by first expressing a small amount of milk and by feeding more often (every 2–3 hours) to stimulate milk production. In a minority of cases, the difficulties may be more marked and persistent and require referral to a feeding specialist.

- It is helpful to tell parents of an obese child with Down syndrome that their child's obesity may not be not their fault, but changes will need to be made in diet and activity for the long-term health of their child. The National Down Syndrome Society website provides a list of additional resources for caregivers to support healthy eating habits and weight management (NDSS 2019).

Development and Behavior

Down syndrome is the most common genetic cause of intellectual disability. The cognitive ability of individuals with Down syndrome, as measured by standardized intelligence tests, generally ranges from profound intellectual disability to borderline intellectual functioning. There is evidence that the intelligence quotient (IQ) of children with Down syndrome correlates approximately, as expected, with mean parental IQ. Still, overall IQ is a poor measure of an individual's spectrum of abilities that may be highly variable. Standardized measures of an individual's adaptive functioning, in conjunction with IQ scores, are required to establish the actual severity of the intellectual disability. Cognitive development in Down syndrome has been associated with individual differences in temperament, maternal education, severity of medical conditions and school experiences (Couzens et al. 2012).

Newborns with Down syndrome typically have hypotonia that affects gross motor development. Although tone will improve, developmental delays are universally present. Time to reach motor developmental milestones is generally about twice as long as in a typically developing child; 92% will walk by 36 months of age. Curves for the expected rates of motor acquisition for children with Down syndrome are available (Palisano et al. 2001). There is evidence that early intervention and physical therapy for children with Down syndrome increase their likelihood of performing more complex motor functions.

Although individuals with Down syndrome tend to achieve fine motor skills at a later age than observed in the general population, their fine motor skill development is varied and occurs over a broad age range. This range gets wider over time, as the skills become more challenging (Frank and Esbensen 2015). It is important that children with Down syndrome master foundational skills first (such as a raking grasp) before acquiring more refined skills (such as self-feeding finger foods) (Frank and Esbensen 2015).

At an early stage, language is acquired in a pattern similar to, but delayed, when compared with typically developing children with equivalent mental ages. Babbling is often delayed, has a different quality, and continues to occur over a more prolonged period. In several areas related to speech/language development, the level of impairment is greater than expected for overall mental age. Receptive language ability is generally stronger than expressive language skills. By school age, children with Down syndrome lack the typical correlation between the production and comprehension of language, and the relative level of vocalization and grammatical usage falls in those over the age of 10 years. Development and use of syntax are relatively more impaired, whereas the use of language in social context (pragmatics) is a strength. Another important issue is the poor articulation and associated intelligibility of speech in individuals with Down syndrome. Several other issues involving language development have been described (Abbeduto et al. 2007). Physical factors related to the oral cavity, particularly the high narrow contours of the anterior hard palate that may affect lingual-palate contact, and the hypotonia and tendency for persons with Down syndrome to drop consonants and last syllables may all play a role.

Children with Down syndrome show less attentional focus and inhibitory control, more restricted play, as well as stereotypic and repetitive behavior, which is less goal oriented and organized. Children with Down syndrome have the cognitive skills to detect, distinguish, and respond to novel target stimuli, and to maintain their attention. However, the attention "process" in target detection is neurophysiologically different, with more cognitive effort required to produce the same performance as typically developing peers.

Processing of social information may differ in individuals with Down syndrome compared to typically developing children. Eye contact with caregivers may be delayed, and once it is established it is maintained longer, which may inhibit development of other spheres of eye contact. There appears to be a specific defect in recognizing facial expressions of emotion and in identifying familiar faces. Early temperament is very similar to that of a typically developing child, but reactions tend to be muted. Social facial expressions and emotional vocalizations show the same pattern as children without Down syndrome but the evolution is delayed and they are produced with less frequency, duration, and intensity.

Down syndrome may be associated with specific behavioral challenges. Although studies have shown there is some truth to the stereotype of children with Down syndrome as happy, affectionate, and outgoing, the picture is more complex. Compared to siblings and typically developing children, parents of children with Down syndrome

report a higher rate of noncompliance, difficulty persisting with tasks, and stubbornness (Grieco et al. 2015). In addition, reports of externalizing behaviors in preschool and school-aged children with Down syndrome showed higher rates of hyperactivity, impulsivity, tantrums, agitation, argumentativeness, repetitive movements, and sensory dysregulation (Capone et al. 2006). Obsessive compulsive behaviors have also been reported among school aged children with Down syndrome (Siegel and Smith 2011). The development and retention of challenging behavior may be related to what is perceived by the child as a reward, either obtaining what is desired (e.g., attention) or avoiding what is not wanted, or is perceived as being overly difficult (e.g., intellectual challenge). Disruptive behavior may also be related to the child's limited expressive language communication skills or to discomfort related to medical issues (Skotko et al. 2013). Children with Down syndrome may use social distraction to avoid completing a requested task.

Individuals with Down syndrome frequently "self-talk" and have imaginary friends. These behaviors are not associated with behavioral, communication, or socialization problems, and should be considered adaptive and not pathological.

Supports are available to help adolescents with Down syndrome transition to adulthood. Although many individuals with Down syndrome continue to spend a longer period with their parents than the typically developing child, there is a trend to reside more within the community with differing levels of supervision depending on the degree of independence. Current goals are, therefore, to maximize self-help skills and foster independence. There is an increasing number of post-secondary programs for individuals with an intellectual disability on college campuses which may further aid integration. A major challenge now and in the future will be to find meaningful employment for individuals with Down syndrome. A recent survey of adults with Down syndrome found that only about 11% were in work placements, out of which 56% had a paid job (mainly in restaurant/food services, office/clerical, grocery stores, and cleaning/housekeeping departments), 26% had a volunteer position, and 3% were self-employed (Kumin and Schoenbrodt 2016).

There is a long history of claims of therapeutic value for supplements, hormones, vitamins, and related therapies to improve the motor and cognitive function of individuals with Down syndrome, which include growth and thyroid hormone, vitamins, 5-OH-tryptophan, glutamic acid, injection of fetal cells, and various "cocktail" mixtures. Growth hormone has been shown to have no benefit for the growth of head circumference or cognitive development. People with Down syndrome are not deficient in any of these substances, properly controlled trials have failed to show benefit, and studies claiming benefit are anecdotal or uncontrolled, and in general, any benefit can be ascribed to a placebo effect resulting from increased intervention and attention.

Comorbid Conditions Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are commonly found in individuals with Down syndrome, leading to increased advocacy for early detection and diagnosis. In the general population, the prevalence of ASD is about 1%; In children with Down syndrome, it has been estimated at 41%. ADHD has been found in 34% of children with Down syndrome, with 22% found to have both ADD and ADHD (Oxelgren et al. 2017). Therefore, there is a growing need for a screening test for ASD/ADHD in children with Down syndrome at the age of 3 years and before entering school.

Rates of neuroses, conduct disorders, and psychoses are considered to be lower in Down syndrome than in other individuals with disabilities. However, the prevalence rates of neurobehavioral and psychiatric illness in children with Down syndrome are estimated to be 18–38% (Capone et al. 2006). These neuropsychiatric conditions are considered to be treatable. Adolescents with Down syndrome exhibit more behavior difficulties than typically developing peers. The severity of these psychiatric problems is correlated with the severity of their intellectual disability. Behavior problems (disruptiveness, communication disturbance, anxiety, being self-absorbed, antisocial behavior) in young adults with Down syndrome may improve over time but depressive symptoms and social relating behavior problems may persist into adulthood. It is possible that those with persistent depressive symptoms are at a high risk for developing depressive illness in adulthood. Depression, with a mean age of onset of 29 years, has been reported in up to 10% of adults. There is a growing consensus that there is a significant risk of anxiety and depression in adults with Down syndrome, which in late adulthood may relate to the onset of dementia. It is important to separate learned behavior from true psychiatric symptoms. Guidelines to aid in doing so are available (Capone et al. 2006). It is also important to exclude organic causes of depression. Hence, always consider possible associated psychosocial stressors and medical factors, such as sleep disturbance, hypothyroidism, etc.

Down syndrome disintegrative disorder is a condition that is being increasingly recognized, characterized by a sudden deterioration in skills and new onset of autistic characteristics in children or young adults with Down syndrome. Worley and colleagues (2014) described 11 children with Down syndrome disintegrative disorder, characterized by autistic regression, cognitive decline (dementia-like), new onset insomnia, and thyroid autoimmunity. These clinical characteristics could not be explained by any other diagnosis. Furthermore, the autistic regression seen in these individuals with Down syndrome was seen at an older age (mean age of 11.4 years) compared to the autistic regression seen in children with disintegrative disorder who did not have Down syndrome. Larger studies, more awareness and better screening techniques to diagnose such clinical

outcomes will help with further characterization of Down syndrome disintegrative disorder. It should also be noted that while thyroid autoimmunity was described in all cases in the study by Worley et al. (2014), Down syndrome disintegrative disorder has also been recognized in individuals who do not have thyroid autoimmunity (personal experience). While increased thyroid auto-antibodies may be an epiphenomenon in Down syndrome disintegrative disorder, there may be a potential role of autoimmunity in the etiology of this condition. Immunotherapy was shown to significantly improve symptoms of catatonia, insomnia, autistic features, cognition, and psychosis in four children with Down syndrome disintegrative disorder (Cardinale et al. 2018).

Alzheimer Disease Individuals with Down syndrome have a third copy of the amyloid precursor protein (*APP)* gene on chromosome 21 that is linked to risk for Alzheimer disease. Autosomal dominant Alzheimer disease has been reported in families with an isolated duplication of the *APP* gene. Individuals with Down syndrome have been found to have elevated levels of amyloid β (Aβ) precursor protein, Aβ42, and s100β in plasma and cerebrospinal fluid compared with the general population, consistent with their putative role in the pathogenesis of Alzheimer disease. Recently it was shown that individuals with Down syndrome without dementia who have Aβ42 values in the upper tercile are at significantly greater risk of dementia in the ensuing 14–18 months than those in the lower terciles. Increased expression of the *DYRK1A* gene on chromosome 21 also leads to hyperphosphorylated τ (tau) protein, contributing to the pathogenesis of Alzheimer disease.

It is now well established that almost 100% of individuals with Down syndrome show the neuropathologic changes of Alzheimer disease by the age of 35–40 years (Head et al. 2012). The pathology of Alzheimer disease in individuals with Down syndrome consists of neurofibrillary tangles and senile plaques, which are similar in Alzheimer disease in the general population. However, the exact pathogenesis and neuroanatomical variations are not clearly understood among individuals with Down syndrome. Neuronal pathological findings occur decades earlier in Down syndrome (as early as first-second decades) compared to the sporadic form of Alzheimer disease in the general population (fourth-fifth decades). Individuals with Down syndrome may also have differences in neuronal pathology with more APP plaques and fewer βA4 peptide plaques than seen in sporadic Alzheimer disease (Egensperger et al. 1999).

Onset of clinical dementia lags significantly behind the appearance of the neuropathologic changes, but current evidence suggests that it is highly penetrant, with the average age of onset at 51–54 years (range 38–70 years) and an average survival from diagnosis of about five years. It is often difficult to recognize dementia when preexisting cognitive impairments of varying severities are already present. There are no "standardized" methods for clinical diagnosis. However, diagnosis may be facilitated by documenting substantial decline from previous status and relying on these findings to inform clinical judgment, and by making attempts to develop empirically validated methods. Novel approaches to develop various biomarkers to track the progression of the disease in its earliest stages, or even before dementia sets in, are underway.

Several studies have investigated potential factors that may be predictive of the onset of Alzheimer disease in individuals with Down syndrome, including total cholesterol levels, the presence of an apolipoprotein E ε4 allele and presence of apolipoprotein E ε2 allele (as a protective factor). However, it is unclear whether screening for apolipoprotein E genotype would have benefit in predicting the onset of Alzheimer disease in the Down syndrome population. Other factors include hyperphosphorylation of tau protein, oxidative stress, reduction in estrogen during menopause, brain developmental abnormalities, and cognitive reserve. Presenilin polymorphisms do not play an important role. There is a higher frequency of associated seizures (15–20%), but Parkinsonian signs, and maladaptive and aggressive behaviors may be less common in Alzheimer disease in individuals with Down syndrome. There is evidence suggesting that young mothers (~35 years) who have a child with Down syndrome may be at increased risk for Alzheimer disease, and this risk does not apply to other trisomies. If confirmed, this raises the possibility of a common factor in the etiology of both Down syndrome and Alzheimer disease.

Currently there is no curative treatment for Alzheimer disease, and although some therapies show promise in slowing the process or alleviating the symptoms, it cannot be assumed that their effect will be comparable in individuals with Down syndrome. Short-term benefit as well as significant reversible adverse reactions have been reported with donepezil, a cholinesterase inhibitor. While donepezil is approved for treatment of Alzheimer disease in the general population, the evidence to date has not demonstrated efficacy for treating cognitive decline in individuals with Down syndrome (Hart et al. 2017; Livingstone et al. 2015). The paradigm shift of conducting clinical trials for the treatment of Alzheimer disease alone to clinical trials for improving cognitive and adaptive behaviors has broadened the scope for future research on multifaceted interventions for the development of individuals of Down syndrome. Hart and colleagues (2017) provide a review of the history of clinical trials for cognition and adaptive behavior, and describe strategies for the pharmaceutical industry to advance the field in drug discovery for Down syndrome. A major challenge in the field is determining appropriate endpoints to document clinical benefit.

Evaluation

- Per AAP guidelines (Bull 2011), discuss the child's behavioral and social progress, and intrafamilial relationships with caregivers at every visit. Evaluate the developmental needs and the support system involved.
- Ensure that the child has been connected with the local agency providing early intervention services. Research has shown that children with disabilities benefit significantly from early intervention (Dreyer 2011). This may include services from a multidisciplinary team of providers, including physical therapy, occupational therapy, speech and language therapy, behavior therapy, and special education. Other team members may include a behavior therapist, psychologist, and/or developmental-behavioral pediatrician depending on the child's needs. Early intervention services may be initially provided in the child's home, and later in a clinic and/or school setting.
- Discuss the child's transition from early intervention services to the public school system at 3 years of age (Bull 2011). A team consisting of family members and school personnel would develop an Individualized Education Program (IEP) at that time, based on the child's strengths and needs. The IEP will detail academic and functional goals, classroom accommodations, modification to the child's curriculum, the amount of small group or individualized instruction per week, and the therapy services provided to meet the child's educational needs. The IEP should be revised on a yearly basis or sooner, if necessary. As the child transitions to middle school and high school, the IEP team should also develop goals targeting work skills and vocational training.
- Routine screening for autism spectrum disorder, attention-deficit/hyperactivity disorder and/or other psychiatric illnesses or behavioral problems should be done when age appropriate.
- Medical problems including thyroid abnormalities, celiac disease, sleep apnea, gastroesophageal reflux, and constipation are associated with behavior changes. Evaluate for these problems in individuals with Down syndrome.
- Encourage parents to create a long-term financial plan for their child, which may include federal and state funding (such as Social Security Benefits) as well as private funding sources. It is often necessary to designate a legal guardian for their child at 18 years of age. Potential adult morbidities including premature aging and Alzheimer disease may also be discussed. Discuss group homes and independent living opportunities, workshop settings, and other community-supported employment. Facilitate transition to adult medical care (Bull 2011).
- Early signs of Alzheimer disease in high-functioning individuals include a decline in memory and verbal capability, whereas others may show a decrease in social interaction and attention and increasing apathy. It is important to rule out hypothyroidism and depression in such cases. Cholesterol values should be assessed.

Management

- Those working with the child and family should have a positive and optimistic approach. The best providers are likely to be those that recognize that children with Down syndrome are not simply delayed but may have specific deficits that require imaginative approaches to teaching. Innovative methods may be particularly important in the area of communication.
- Early behavioral intervention may be an important preventive measure for some children.
- While multiple clinical trials have been conducted over the past several decades investigating the efficacy of pharmaceutical interventions to improve cognition in Down syndrome, results have shown limited success to date (Hart et al. 2017). At this time there is insufficient evidence to support the clinical use of pharmaceutical interventions to improve cognition in individuals with Down syndrome.
- Caution is needed in using psychotropic medications in children and adults with Down syndrome; little or nothing is known about drug metabolism and kinetics for most psychotropic medications in Down syndrome. A good rule of thumb pertaining to dosing these drugs is to "start low and go slow", following the patient carefully for medication effects and side effects (personal experience). Those with congenital heart disease should be seen and "cleared" by a cardiologist before starting a stimulant medication for ADHD or a neuroleptic for more serious behavior problems. Weight gain is often a serious complication of psychotropic drugs in people with Down syndrome. Close follow up is necessary if any psychotropic medication is prescribed. If this is not possible, then the individual should be referred to a psychiatrist.
- For medical problems that are associated with behavior changes, intervention strategies depend on various factors such as the individual's age range, severity of the medical problem, and the specific settings in which a problem occurs. Referrals may be required to community programs, psychosocial services for consultative care, or behavioral specialists who are experienced in working with children with special needs. Since children with Down syndrome may be more sensitive to certain medications that are used to address behavior issues, there should be discussions between the child's primary care physician and their specialists to use these medications. Children with Down syndrome may differ in their responses to these medications compared to their peers (Bull 2011).
- Institution of any treatments such as cholinesterase inhibitors should be as part of properly designed scientific studies. Lowering elevated cholesterol, as part of standard care, has been suggested to have some benefit with respect to onset of dementia.

Family Adjustment

A number of studies have suggested that families of children with Down syndrome cope better and experience less stress than families of children with other types of disabilities. Some studies have concluded that this "Down syndrome advantage" is due to the child-based characteristics, such as their prolonged eye contact, the tendency to use charm to avoid tasks (see Development and Behavior), and the generally low levels of childhood psychopathology. Other explanations include societal awareness of Down syndrome and available support networks. Studies show that mothers of children with Down syndrome do better on some (generally not all) aspects of coping/adaptation than mothers of children with other types of intellectual disability or autism, but this advantage is not seen when comparing them with mothers of typically developing children.

Other socio-cultural populations may differ in their adjustment to having a child with Down syndrome, especially in families influenced by the Confucian beliefs (where the mother and the eldest sibling are solely responsible for household chores and caregiving). In their integrated review, Choi and Van Riper (2017) found that families with children with Down syndrome in the East Asian populations experience both positive and negative consequences. They emphasize the importance of developing revised healthcare policies taking into account factors such as ethnicity, religion, and worldviews. Across populations, the factors that contribute to the fathers' stress are said to be different from those of the mothers. Fathers focus more on financial burden, the potential impact on the broader family, and the public perception and attitude of society for accepting their children.

Recent studies also focus on siblings of children with disabilities. In general, there may be some increased anxiety and depression in these siblings during childhood, but there is no evidence of greater behavioral problems. There may be positive aspects in greater empathy and understanding of others with a disability and improved social interactions. In adulthood, the impact seems to be minor and is influenced by whether or not the sibling with disabilities has behavioral problems. Again, there is some evidence of a Down syndrome advantage when comparing with other conditions such as autism. Interventions such as SibworkS, a six-week manual-based, cognitive-behavioral group support program focused on strengthening siblings' social support, self-esteem, problem-solving skills, adaptive coping behaviors, and positive sibling relationships can be helpful for siblings of children with Down syndrome and the family as a whole (Strohm and Nesa 2010)

Divorce is far less common among families of children with disabilities than is generally thought. One study suggested that families of children with Down syndrome may be less likely to divorce than those whose children do not have identified disabilities (Urbano and Hodapp 2007). However, when divorce occurs, it is significantly more likely to occur during the first two years after the child's birth and is associated with demographic variables such as younger parental age and lower education levels, and living in a rural area.

Health care providers are a vital link in helping families cope with stressors. A multi-disciplinary team of experienced professionals should be available from the delivery of the news of a diagnosis of Down syndrome and throughout childhood and adulthood. Some studies suggest that healthcare professionals lack the training for informing families about such conditions in an empathetic way, using appropriate language during clinical visits and sharing knowledge about the psychosocial influences surrounding the condition. Skotko and colleagues (2009) provide guidelines for delivery of the news after a prenatal and postnatal diagnosis. These resources provide useful guidance for both healthcare management and facilitation of family adaptation following a diagnosis of Down syndrome.

Evaluation

- Explore what the parents know and have been told, their experience, if any, with individuals with Down syndrome, and the questions they have.
- Clarify the potential social/support network available, who has been told, and what they have been told, as well as any issues that have arisen in that regard.
- Explore the parents' feelings about having a baby with Down syndrome, and how they feel they will cope, with the potential maternal/paternal differences kept in mind.
- Personal and local social resources should be identified.

Management

- Pediatricians and obstetricians should be the first to deliver the news to the parents present together (exceptions to this would include when the father is not available, the mother does not wish for the father's presence or if the mother is seriously ill after childbirth). A follow-up meeting with a certified genetic counselor, a clinical geneticist, or a developmental-behavioral pediatrician can help in providing the family with appropriate information to meet their needs.
- Parents need to be given accurate information in understandable terms. The focus should be on explaining Down syndrome, what causes it, and what their child may need to maximize his/her potential.
- A **balanced perspective** should be provided regarding Down syndrome by an experienced and trained individual, including information about positive aspects of having a child with Down syndrome as well as the challenges commonly encountered (Sheets et al. 2011).

- It is helpful to mention that caring for a child with Down syndrome is generally not greatly different from the care of other children. However, some children with Down syndrome may have health complications that need to be addressed.
- When possible, the provider should refer the family to a local Down syndrome clinic where they can be followed by a team of professionals.
- The parents' misconceptions and misinformation should be corrected.
- Parents should be informed that children with Down syndrome generally attain developmental milestones at later and more variable ages than typically developing children, but can be expected to show continued developmental progress.
- It is important that siblings, extended relatives and family friends be made aware of the infant's diagnosis and their questions addressed. Parents may need assistance in this process. The burden and concerns regarding medical issues should be shifted, as much as possible, to health care providers, and an effort made to assure the availability of support services and resources that may be required.

For a prenatal diagnosis:

- Discuss the findings from screening and diagnostic tests, potential chances for recurrence in future pregnancies, prognosis and phenotypic manifestations – the wide-variability, information about additional studies to refine the estimation of the prognosis, consultation with appropriate medical subspecialists like pediatric cardiologists or pediatric surgeons, current available treatment options and interventions, and options such as medical termination, raising the child in a well-informed family with resources, foster care placements, and adoptions. If the pregnancy is continued, discuss a plan for delivery and neonatal care, parent-to-parent contacts through local and national support organizations, future reproductive options and evaluation of the chance to have a child with Down syndrome for other family members.

For a postnatal diagnosis:

- Pediatricians and obstetricians should coordinate their messages and deliver the news to both parents, as a couple, preferably with the baby next to them.
- Physicians should inform parents of their suspicion for Down syndrome immediately, even if the diagnosis has not been confirmed with karyotyping. This way parents are prepared psychologically in a stepwise manner.
- Physicians should deliver the news in a private hospital room without any visitors or other health personnel present and without any interruptions.
- Physicians should begin their conversation with positive words to congratulate the parents on the birth of their child. They should refrain from using words like 'so sorry to tell you' or 'I know this is going to be tough on you'. Some studies have shown that during communication of the diagnosis, the first words and their tone have a significant impact on families (Skotko et al. 2009).
- Physicians should consider limiting their first conversation on possible medical conditions seen during infancy (Skotko et al. 2009). Overloading the parents with long-term complications seems to have a negative impact on parents.
- Follow-up appointments should be arranged with medical experts and a team prior to discharge from the hospital. This will help minimize the stress on the parents. Discuss the various social networking strategies to cope with the news, such as support programs, online groups, and resources.

Cardiovascular

Congenital heart disease occurs in 40–50% of individuals with Down syndrome and is an important determinant of survival. The actual rate and relative frequency of specific anomalies vary with ascertainment. The most common cardiac malformation in Down syndrome is atrioventricular septal defect (endocardial cushion defect), followed by atrial septal defect, ventricular septal defect, patent ductus arteriosus, co-arctation of aorta, and tetralogy of Fallot (Stoll et al. 2015). Females with Down syndrome may be at higher risk of developing an atrioventricular septal defect than males (Diogenes et al. 2017). Atrioventricular septal defect is more common in populations of African origin than in Caucasian children and is relatively underrepresented in Asian children with Down syndrome. Muscular ventricular septal defect is relatively underrepresented overall. Hypertrophic cardiomyopathy is not common in Down syndrome, but when it occurs in adults it tends to be of the apical left ventricular type.

Individuals with Down syndrome also have a higher propensity for risk factors such as obesity and metabolic disturbances for developing coronary artery disease, particularly atherosclerosis. Despite this, they have a lower incidence rate of coronary artery disease. Recent studies are evaluating the causes for this low incidence of coronary artery disease among individuals with Down syndrome, including lower intimal thickening of arteries, lower blood pressures, different autonomic nervous system responses, or protective genetic mechanisms.

Several recent studies have identified regions of chromosome 21 containing genes that influence the occurrence of congenital heart disease, and heterotrisomy (inheritance of an allele from three different grandparents) has been associated with the presence of a ventricular septal defect. The *RCAN1* gene significantly contributes to congenital heart disease in Down syndrome, and a novel variant of g.482G>T in the *RCAN1* gene causes the overexpression of *RCAN1.4* (which is highly expressed in the heart muscle). Missense variants in *CRELD1*, located on chromosome 3p25, have been found to be associated with about 3% of endocardial cushion defects in the general population and, based on one report, with about 5% of those in individuals with Down syndrome. Maternal smoking, lack of folic acid/multivitamin supplementation, and parental consanguinity have also been identified as potential contributing factors for congenital heart disease in children with Down syndrome.

Mortality rates for five major biventricular repair procedures (ventricular septal defect repair, atrioventricular septal defect repair, patent ductus arteriosus closure, atrial septal defect repair, and tetralogy of Fallot repair) and bidirectional Glenn have been found to be similarly low in patients with Down syndrome compared with patients without Down syndrome. On the other hand, mortality after Fontan operation in patients with Down syndrome was significantly higher than in patients without Down syndrome, implying that indications for the Fontan operation should be carefully considered. It is known that uncorrected septal defects lead to shunting of systemic blood to the pulmonary circulation, increased blood flow and pulmonary arterial hypertension, which may persist even after a surgical correction. Sullivan et al. (2017) demonstrated that children with Down syndrome who underwent surgical repair for tetralogy of Fallot had an increased degree of pulmonary regurgitation. These individuals required earlier assessment by cardiac magnetic resonance imaging to determine timing of pulmonary valve replacement to manage preventable causes of pulmonary hypertension. There is a common understanding that, with the advent of new catheter-based interventions, surgeries benefit individuals with Down syndrome and are associated with prolonged survival rates. Cardiac catheterization provides important information like pulmonary arterial resistance, which is paramount in assessing the severity and response to vasodilating agents, preventing postoperative pulmonary hypertension crisis and prolonged pulmonary hypertension, and in assessing the possibility of intracardiac repair. It is important to systematically evaluate perioperative complications among individuals with Down syndrome undergoing surgical procedures.

A more than 10-fold increased incidence of persistent pulmonary hypertension of the newborn, which cannot be accounted for by demographic variables including gestational age at birth and the presence of congenital heart disease, has been reported in Down syndrome. Pulmonary hypertension occurs more often and earlier in children with congenital heart disease and Down syndrome, especially in the presence of large right to left shunts. Infants and children with Down syndrome are at increased risk of pulmonary hypertension, even in the absence of intracardiac structural defects. Obstructive sleep apnea is a major contributing factor towards development of pulmonary hypertension among individuals with Down syndrome (See Sleep Disorders section for details). Nir et al. (2017) found that the prevalence of pulmonary hypertension among adults with congenital heart disease and Down syndrome was 53%, compared to 6% for all adults with congenital heart disease. Morbidity included cerebral vascular accident or transient ischemic attack in 22% (mostly in people with right-to-left shunt) and arrhythmia in 37% of the patients.

A rare cause of pulmonary hypertension, pulmonary veno-occulsive disease, was recently reported in an infant with Down syndrome (Muneuchi et al. 2017). This condition has a worse prognosis and higher risks of developing severe pulmonary edema with specific vasodilator therapy, leading to rapid deterioration. It can be misdiagnosed because it is clinically similar to idiopathic pulmonary arterial hypertension, despite the histopathological differences. The actual incidence of pulmonary veno-occlusive disease is probably underestimated, because many cases may be classified as idiopathic pulmonary arterial hypertension. This study emphasizes the importance of high-resolution computed tomography, lung biopsy, and diagnosing a rare entity during the management of pulmonary hypertension in individuals with Down syndrome.

Evaluation

- As per the AAP guidelines (Bull 2011), a thorough clinical examination and a mandatory echocardiography should be a part of routine newborn screening of babies with Down syndrome. Infants with an abnormal echocardiogram should be referred to a pediatric cardiologist for further evaluation. Structural heart defects with ‘silent’ murmurs that do not present themselves as typical murmurs could be missed if one relies on clinical examination alone. Monitor all heart defects for complications, and educate parents to recognize signs of heart failure such as tachypnea, feeding difficulties, and poor weight gain. In older children and adults with Down syndrome, annual cardiac examinations may help in early diagnosis of acquired valvular diseases. Individuals with Down syndrome should be educated to recognize common symptoms like fatigue, shortness of breath, or dyspnea on exertion, which may warrant further cardiac testing.
- Echocardiography and competent clinical evaluation, electrocardiogram, and early follow-up should detect most congenital heart disease that will require treatment.

Management

- Although there has been controversy regarding the merits of medical versus surgical management of significant congenital heart malformations in individuals with Down syndrome, and over the timing of surgery, there is now a consensus favoring early surgical intervention. Medical treatment of atrioventricular septal defect has less than a 5% five-year survival rate compared with almost 70% for surgically treated defects, which compares favorably with children who have the equivalent lesion but do not have Down syndrome.
- Babies with Down syndrome who have large ventricular septal defects without obstruction to pulmonary blood flow require surgical repair before 4 months of age to avoid further complications (Bull 2011).
- Medical management (along with education on proper nutrition) should be offered to those who are not fit for surgery.
- Individuals with Down syndrome have an increased rate and more prolonged course of postoperative thrombocytopenia than the general population, and may have an increased risk of post-discharge syncope because of complete atrioventricular block. Close monitoring and early follow up after surgery with complete blood counts are needed.

Endocrinologic

Thyroid Disease Thyroid disease commonly occurs with Down syndrome, with hypothyroidism being the most prevalent endocrine condition. Children with thyroid disease and Down syndrome require appropriate and timely treatment to avoid stunted growth velocities and significant intellectual disabilities. Therefore, there is a need for additional screening, in addition to newborn screening, especially in the first year of life. Thyroid screening using TSH and serum free T4 is recommended to be continued throughout the lifespan of individuals with Down syndrome. With continued early ascertainment through routine surveillance, and detection and treatment of hypothyroidism, the effect of hypothyroidism on development should be minimized.

When borderline abnormal thyroid function screening tests are found, it is customary to repeat the tests in six weeks to be sure they are abnormal. If they are still abnormal, a referral to a pediatric endocrinologist is indicated. Many infants have a mildly elevated serum free T4 level with a normal TSH level. If the infant is asymptomatic, this is not necessarily a pathologic state. The tests should be repeated in a few months. It has been noted that thyroid disease in individuals with Down syndrome is unrelated to sex, obesity, or other comorbidities.

In a study of 508 individuals with Down syndrome, 24% had a documented history of a thyroid-related diagnosis with the following prevalence: 2% congenital hypothyroidism, 10% subclinical hypothyroidism, 1% overt hypothyroidism, 4.5% isolated hyperthyrotropinemia, 4.3% unknown hypothyroidism, and 1.6% hyperthyroidism (Pierce et al. 2017). The median age at diagnosis with any thyroid disease was 4 years and 10 months, whereas for hyperthyroidism, it was just under 9 years. The odds of developing thyroid disease increased by 10% per year with increasing age. For the development of thyroid disease, it was estimated that 25% of those with Down syndrome will have thyroid dysfunction by age 7.5 years and up to 50% by the time they reach adulthood. When tested, approximately 50% of individuals with subclinical hypothyroidism had positive antithyroid antibodies, and this rate was 100% in overt hypothyroidism (Pierce et al. 2017). The study highlights the need for additional screening of TSH along with free T4, between the newborn screening and the currently recommended sixth month screening, as a significant number of children with Down syndrome were diagnosed with thyroid disorders before the age of 6 months.

Sexual Maturation Much of the literature regarding sexual development and function in individuals with Down syndrome is based on older reports of persons living in institutions, and detailed hormonal data are sparse. Such studies suggested that men with Down syndrome had relatively small genitalia, higher incidence of testicular failure with elevated follicle stimulating hormone (FSH) and luteinizing hormone (LH), decreased Leydig cell function, and germinal cell hypoplasia. Newer data suggest that men with Down syndrome have normal onset and chronology of puberty and may have fewer differences in hormonal levels than previously thought. A study of young adult males with Down syndrome (mean age 26.5 years) confirmed normal levels of FSH, testosterone, and dehydroepiandrosterone (DHEA-S) but showed elevated levels of LH and 17-OH progesterone compared with controls (Sakadamis et al. 2002). These individuals also showed significantly decreased bone mineral density that might be in part related to mild chronic hypogonadism. Men with Down syndrome have an increased risk of cryptorchidism (uni- or bilateral), but the mechanisms causing its onset are not clear. Spermatogenesis is known to be insufficient in males, but the definitive cause remains to be discovered.

Female pubertal development appears to be normal. The mean age at menarche of 12.6 years does not differ from that of typically developing siblings, and there does not appear to be any excess of menstrual problems or irregularities. In some women, menarche may be somewhat earlier and this may relate to obesity. FSH and LH rise normally with maturation. There is some evidence that young women with Down syndrome may have relatively increased levels of prolactin, LH, testosterone, and 17-OH progesterone, possibly raising the issue of subtle differences in the pituitary-gonadal and/or adrenal axis (Angelopoulou et al. 1999). Although earlier studies reported high rates of ovarian abnormalities and anovulatory cycles, recent ultrasound studies have found

normal ovaries with follicles at various stages of maturation, and normal uteri and uterine wall thickness. Age at which menopause occurs varies widely, but typically occurs before the age of 40 years.

Despite evidence of normal sexual development, there remain fewer than 50 cases of documented fertility in women with Down syndrome and four reported cases in non-mosaic males, one of whom achieved a pregnancy following preimplantation genetic screening (Aghajanova et al. 2015). Potential contributors to infertility may be hormonal abnormalities, gonadal malformations, and psychological and social factors. Many individuals with Down syndrome show age-appropriate interest in the opposite sex, and need to be educated about their bodies, contraception and fertility (Bull 2011). There may be a trend towards a decline in sex education for adolescents with Down syndrome, which highlights the need to train adolescents with developmental disabilities through better sex education programs.

Evaluation

- Screening for neonatal hypothyroidism is important for children with Down syndrome. This occurs through mandatory newborn screening in most jurisdictions. Measure the TSH and free T4 routinely throughout the lifespan. Check for antibodies, based on clinical judgement. Secondary and tertiary causes of thyroid disorder should be kept in mind while making a diagnosis. Perform routine screening, along with newborn screening and annual examinations, throughout life for individuals with thyroid disease and Down syndrome.
- There is compelling evidence that clinical examination is inadequate to detect thyroid disease in individuals with Down syndrome, at least in part because of the overlap of signs, sensitivity and specificity are poor. Growth velocity may decline or other symptoms may develop at least a year before the clinical recognition of hypothyroidism in children, and it may masquerade as depression or even Alzheimer disease in adults.
- Any variation from normal physiological sexual maturation is unexpected and requires a standard evaluation for cause.
- Women require standard gynecological care. This may be facilitated if carried out by a familiar health care provider and by taking special care to educate the woman in advance about any examinations or procedures.

Management

- Treatment of hypothyroidism is standard replacement with L-thyroxine and continued monitoring of blood levels. Some centers treat with low-dose thyroxine in the face of significantly elevated TSH and normal T_4 levels.
- With integration of individuals with Down syndrome into society, adolescents and young adults with Down syndrome need properly tailored education, advice, and counseling concerning interpersonal relationships, appropriate social behavior, sexual activity, and situations that may place them at increased risk for sexual abuse. Success will generally require the understanding and participation of parents. Encourage independence with personal hygiene and self-care.
- As per the AAP guidelines (Bull, 2011), parents should be made aware of the physical and psychological changes during childhood and adolescence, issues of fertility and contraception, and the need for more preparation during these changes. Discuss the need for gynecologic care and menstrual hygiene for women.
- Despite high rates of infertility, it is important to talk about the chance of Down syndrome, if a pregnancy were to occur. This is true for both genders. Birth control and prevention of sexually transmitted diseases should be discussed with individuals with Down syndrome and their families.

Audiologic

Over 90% of ear lengths in individuals with Down syndrome fall below the third centile for the general population; the helix is often angulated and overfolded, and the lobes are small to absent. The osteocartilaginous junction is narrow to stenotic and may compromise visualization of the tympanic membrane and increase the susceptibility to obstruction by wax. A small minority has been found to have congenitally malformed stapes, and other ossicular anomalies may be acquired.

Malformations of the inner ear may also be common. Inner ear structures have been found to be hypoplastic in many studies. Inner ear anomalies have been observed in a large proportion of individuals with Down syndrome, including malformed bone islands of lateral semicircular canal, narrow internal auditory canals, cochlear nerve canal stenoses, semicircular canal dehiscence, and enlarged vestibular aqueducts. Internal auditory canal stenosis has the highest odds ratio for sensorineural hearing loss (Intrapiromkul et al. 2012). Further studies are needed to properly understand such variations in inner ear anatomy and their role in hearing loss.

Individuals with Down syndrome are at high risk for conductive hearing loss, although mixed and pure sensorineural hearing loss may also occur. Some degree of hearing loss occurs in over 60% of those with Down syndrome, with conductive hearing loss accounting for the majority. One reason is the high incidence of inflammatory processes such as otitis media. Dysfunction of the eustachian tube, due to its abnormal anatomy and muscular hypotonia of surrounding structures like the tensor veli palatine, plays an important role in the etiology of otitis media with effusion among persons with Down syndrome. A study of 107 children with Down syndrome (ages 6 months to 12 years) found a high

prevalence of otitis media with effusion at the age of 1 year (67%), with a second peak prevalence of 60% at 6–7 years (Maris et al. 2014). A declining trend was observed in children ≥8 years. Overall, 52% of children had either otitis media with effusion or ventilation tubes at the time of evaluation. Parental report suggested that otitis media with effusion had more impact on speech, language and communication than on hearing. Recurrent ear infections and middle ear effusions are to be anticipated, but with a team approach to hearing care, most children with Down syndrome can maintain adequate hearing to prevent interference with their speech development and educational efforts.

Evaluation

- Based on the AAP guidelines (Bull 2011), newborns should be assessed for congenital hearing loss with objective testing such as brainstem auditory evoked response (BAER) or optoacoustic emission, according to the universal newborn hearing screening guidelines. Newborns should have a follow-up at 3 months thereafter. In younger children, review the risks associated with serous otitis media. Follow-up annually or every 6 months.
- Refer to an otolaryngologist for conducting ear examinations of children with stenotic ear canals.
- For older, school-aged children, make sure to conduct annual audiologic evaluations.

Management

- Treatment of acute and chronic complications, which may compromise hearing and thereby interfere with speech and education, should be aggressive. Treatment methods are standard.
- A significant proportion of individuals with Down syndrome may benefit from classroom accommodations for hearing loss by some means of amplification. Children with Down syndrome who have impaired hearing may benefit from early interventions by an experienced speech-language pathologist.

Ophthalmologic

Ophthalmologic abnormalities are found more frequently in children with Down syndrome than in the general population. Overall, hyperopia, strabismus, astigmatism, and blepharitis have the highest prevalence rates among many studies. Table 24.1 indicates the prevalence ranges for specific ophthalmologic findings (adapted from Creavin and Brown 2009).

TABLE 24.1 Summary of ophthalmologic findings in Down syndrome (adapted from Creavin and Brown 2009)

Condition	Frequency	Comment
Hyperopia	4–59%	
Myopia	8–41%	
Strabismus	<20–60%	Majority reported prevalence of 20–40%. Esotropia more common than exotropia
Nasolacrimal duct obstruction	<10–36%	Majority reported prevalence of 17–36%
Epiphora	15–32%	
Astigmatism	6–60%	Majority reported prevalence of 20–30%
Weak/absent pupillary reflex	17–26%	
Nystagmus	10–20%	
Amblyopia	3–20%	
Cataract	<5–37%	Majority reported prevalence of <15%
Anisometropia	1–13%	
Blepharitis	<10–50%	Majority reported prevalence of <10%
Retinal anomalies	<10–40%	Majority reported prevalence of <10%. Most common finding extra retinal vessels
Ptosis	3–7%	
Corneal opacity	1–6%	
Optic nerve abnormalities	1–5%	Includes optic nerve elevation or optic disk pallor
Sty	3%	
Chalazion	1–3%	
Entropion	2%	
Congenital dacryocutaneous fistulae	1%	
Lateral eyelash diversion	1%	
Glaucoma	<1–7%	Majority reported prevalence <1%
Keratoconus	1–12%	Majority of studies found it in none of the study participants

Careful examination in childhood may reveal early opacities. Cataracts develop in over half of those individuals. Hypoplastic peripheral irides and Brushfield spots are common. Some studies show that esotropia is more common at a younger age and exotropia is more common among older adults with Down syndrome. Keratoconus also has a higher rate of incidence in Down syndrome, presenting at a younger age compared to typically developing children. Individuals with advanced keratoconus are more subject to development of acute hydrops (stromal edema) with its accompanying severe visual impairment.

There is some concern for vision later in life, as infranasal limbus and degenerative retinal changes may be seen in adults. However, ophthalmic studies on adults with Down syndrome are limited. While astigmatism and refractive errors are more prevalent in younger individuals, cataracts and blepharitis are more common in older individuals with Down syndrome. Senile cataracts occur earlier compared to the general population.

It is increasingly apparent that visual problems may adversely affect potential for learning in children with Down syndrome. Strabismus and ocular pathology has been associated with lower IQ in children with disabilities (Salt and Sargent 2014). However, with routine ophthalmologic assessments and appropriate care, the prognosis for vision in childhood and young adulthood is good.

Evaluation

- Early eye assessment with appropriate therapy and follow-up is important to prevent loss of binocular vision and/or amblyopia, and to maximize visual acuity. Strabismus must be distinguished from pseudostrabismus caused by epicanthal folds.
- As per the AAP guidelines (Bull 2011), children with Down syndrome should be evaluated by a pediatric ophthalmologist within the first six months of life. Children should be evaluated for congenital cataracts, strabismus, nystagmus, and other specific conditions at regular intervals. Based on different ages, clinical condition and clinical judgements, annual or two-yearly eye examinations should be conducted to eliminate the risks of developing refractive errors, amblyopia, keratoconus, cataracts, etc.
- Causes of eye irritation or behavior that may increase the risk of self-induced ocular trauma should be sought and treated.
- Ophthalmologists should be aware of the possibility of pseudotumor cerebri in people with Down syndrome with an elevated optic disk. Untreated, this may result in optic atrophy.

Management

- Refractive errors are the most common and important visual problems and require early refraction studies and prescription for glasses. Bifocal or progressive glasses may benefit some if they are tolerated.
- Strabismus may respond to eye patching or may require surgery and is treated in a standard fashion.
- Blepharitis usually will respond to lid cleansing and topical antibiotics.
- Cataract may require removal of the lens and a prosthetic implant, and significant keratoconus may be treated with penetrating keratoplasty and a corneal transplant.
- Pseudotumor cerebri may respond to weight loss and acetozolamide therapy.

Musculoskeletal

Children with Down syndrome have an increased prevalence of numerous musculoskeletal complications in varying degrees, the most common ones being hypotonia, and ligament laxity that leads to excessive joint flexibility. There is a delayed achievement of motor milestones (see Behavior and Development section). Other orthopedic problems include scoliosis, neck instabilities, hip anomalies (subluxation, Legg–Calve–Perthes disease, slipped capital femoral epiphysis), patellofemoral joint instability, genu valgum, hallux valgus, foot deformities (pes planus, metatarsus primus varus), trigger finger, and trigger thumb. There is also increased risk of developing arthritis/arthropathy precociously. Individuals with Down syndrome have a higher prevalence of gait abnormalities, despite having an independent gait. Orthotic supports seem to be very beneficial in children with Down syndrome who have an established walking pattern. Custom made foot insoles provide the additional physical support and could help prevent future surgical corrections when used as an early intervention to correct gait abnormalities. There is evidence that some of the gait difficulties can be ameliorated by specific exercises in early intervention, which have been found to provide long-term benefits on the development of basic gait parameters.

A high percentage of adults with Down syndrome have reduced bone density. There is a growing concern regarding the high risk of fractures with age and early detection. Factors found to be associated with decreased bone density have included male sex, low levels of exercise, low antioxidant capacity due to high oxidative stress, hypothyroidism, certain drugs that are used to treat comorbidities, and lack of exposure to sunlight. Individuals with Down syndrome have a higher prevalence of hypovitaminosis D. Individuals with Down syndrome who are obese and those who have autoimmune diseases may require a higher supplementation of vitamin D to maintain normal levels (Stagi et al. 2015).

The incidence of occipitoatlantoaxial instability among persons with Down syndrome is about 10–30%, with neurological symptoms occurring in approximately 1% of individuals. The occiput, the atlas (C1), and the axis (C2)

form the occipitoatlantoaxial joint, and the surrounding ligaments keep these bony structures in place and enable flexibility. The occipitoatlantal joint provides principally flexion, with a small amount of lateral bend and rotation, whereas the atlantoaxial joint is most responsible for rotation but does provide significant flexion/extension and a small amount of lateral bend. In flexion, an anterior translation of C1 on C2 exists, which normally does not exceed 3 mm in adults. In children younger than 8 years, this translation can be as wide as 5 mm. In pathologic conditions (e.g., abnormalities of the odontoid bone or in the ligament laxity), this displacement increases and bone structures can pressure the spinal cord, producing clinical symptoms.

The occipitoatlantoaxial instability among individuals with Down syndrome was recognized in the 1960s, and gained notoriety in the early 1980s when there were several reports of individuals with significant signs of cervical cord damage. The instability is primarily anterior and is because of ligamentous laxity, exacerbated by anatomic osseous variants, such as loss of the normal concavity of the superior surface of C1, that result in a less stable joint structure. Rotatory instability is also relatively common in Down syndrome. By 1984, over 500,000 individuals with Down syndrome had participated in the Special Olympics without a single known occurrence of serious neck injury. A review by the AAP of 41 reports of individuals with symptomatic atlantoaxial instability showed that the majority of those cases recovered, and there was no evidence that radiographs could predict those who would become symptomatic. Our current understanding is that about 10–30% individuals with Down syndrome may have radiological evidence of occipitoatlantoaxial instability, but only a small minority of individuals will develop neurological complications, and an even smaller number will suffer a catastrophic event in the absence of some earlier neurological signs. These events can be minimized by encouraging lower risk sports and neurological monitoring. Evidence to date is that pure atlantoaxial instability is unlikely to undergo significant change in the absence of bony abnormalities. With time, some persons may develop an os odontoideum, which is considered an avulsion fracture of the odontoid and is therefore evidence of chronic instability and secondary bony changes.

Intervention in the presence of neurological signs attributable to the cervical spine should not be delayed, as chronic changes are unlikely to be reversible, and complications appear higher in late-treated cases. For individuals with Down syndrome, careful anesthetic procedures and airway management is required because of the high risk of the cervical spine instability. Signs such as newly decreased motor skills, gait abnormalities, torticollis, progressive paralysis, neurological signs of nerve compression at the cervical level, or vertebrobasilar insufficiency should raise suspicion for cervical spine instability. At present, there is no real consensus of which radiographic techniques can be used with maximum efficacy to identify impending problems. The commonly used radiological parameters are atlantodens interval and the space available for the spinal cord (SAC). Some argue that these are associated with poor inter- and intra-observer reliability and could cause a neuropathy as they require radiographs to be performed with the cervical spine in flexion. Nakamura and colleagues (2016) assessed the reliability of two new radiological parameters that can be measured with the cervical spine in the neutral position (the C1/4 SAC ratio and the C1 inclination angle), and they investigated cut-off values to identify an indication for surgery. The normal values for the C1/4 SAC ratio and inclination angle were found to be about 1.2º and 15º, respectively. Children with a C1/4 SAC ratio of <0.8 have a high risk of developing neurological symptoms or signs and referral to a pediatric spinal surgeon is recommended. They also recommend that all pediatricians who are not specialized in the cervical spine to use these new parameters.

Evaluation

The AAP guidelines recommend the following (Bull 2011). *Newborns*: Evaluate hypotonia.

Infancy–adulthood: Once every 2 years, parents should be educated about the signs and symptoms of myelopathy and about the precautions of to avoid excess extension and flwxion during anesthesia, and surgical or radiological processes. At every visit, a thorough a meticulous history and physical examination should be performed to evaluate for signs of myelopathy.

For asymptomatic atlantoaxial instability: Since radiographs are not predictive of instability, radiologic evaluation or screening of the cervical spine in asymptomatic children is not recommended. Parents should be advised that participation in some sports, including contact sports such as football, soccer and gymnastics, places children at increased risk of spinal cord injury. Trampoline use should be avoided by children younger than 6 years, and by older children unless under direct professional supervision. Special Olympics has specific screening requirements for participation in some sports. Parents should be educated that participation in sports such as football, soccer, and gymnastics may place the child at an increased risk of spinal cord injury. Use of trampolines should be avoided in children less than 6 years, and older children require direct professional supervision. Educate the family that there are specific screening requirements for participation in some sports at the Special Olympics.

For symptomatic atlantoaxial instability: If a child has signs/symptoms of myelopathy, plain cervical spine radiography should be done in the neutral position of the cervical spine. If significant abnormalities are seen in the radiography, the child should be immediately referred to pediatric

neurosurgery/pediatric orthopedic surgery to further manage the atlantoaxial instability. If there are no significant abnormalities, flexion/extension radiographs may be obtained before the child is referred to the specialists.

- If standard radiographs raise concern, magnetic resonance imaging could be considered. Computed tomography is not likely to add useful information.
- A medical history and physical examination for joint complaints should be part of routine clinical care.
- A routine clinical assessment for scoliosis should continue into adulthood.

Management

- Participation in high-risk activities should be discouraged if there is evidence of chronic instability, such as an os odontoideum or 7 mm or more of instability.
- A small minority of children with Down syndrome will require stabilizing surgery with a C1–C2 and/or atlantooccipital fusion. A Gallie C1–C2 fusion appears to be a satisfactory approach for symptomatic anterior atlantoaxial subluxation, and some authors suggest a period of prior traction as well as a postoperative halo to assure stability and fusion. Recent neurological series have reported greater success in achieving fusion, and lower rates of significant complications.
- Complication rates for cervical surgery to repair atlantoaxial instability were up to 100% in some historical studies. A recent retrospective review found that postoperative complications continue to challenge most patients (82%) (Siemionow et al. 2017). Although 94% of patients demonstrated stabilization or improvement in neurologic status, several postoperative complications were observed, with postoperative pneumonia being the most common complication. Also, the anterior approach resulted in a higher risk of complications than posterior.
- There is no doubt that early interventions are better than late surgery with complications. The decision regarding cervical surgery for occipitoatlantoaxial instability requires the involvement of experienced and expert surgeons, a careful weighing of the evidence of present or impending neurological damage, and consideration of the benefits and risks of the surgical approach. Anesthesia may increase instability.
- Most joint findings related to laxity do not require treatment or can be managed with advice from experts such as a physical therapist. Significant scoliosis should be managed as for standard practice.
- Neuromuscular training could be beneficial to optimize general and maximal muscular strength development in children and young adults with Down syndrome (Sugimoto et al. 2016).

Gastrointestinal

Functional or structural gastrointestinal anomalies are found in over 2/3 of individuals with Down syndrome. Individuals with Down syndrome are more susceptible to hypotonia, large tongue, small oral cavity, tracheoesophageal fistula, dysphagia, constipation, gastrointestinal regurgitation syndrome, duodenal atresia, annular pancreas, celiac disease, Hirschsprung disease, pyloric stenosis, and anal atresia/stenosis. There is also evidence to suggest that a paucity of bile ducts is common. Some features such as duodenal/anal atresia or tracheoesophageal fistula may be suspected on prenatal ultrasound or will be present at birth. However, a number of these features may not lead to symptoms until several months after birth, including Hirschsprung disease, duplication cysts, and duodenal or anal stenosis. Hypotonia and relative inactivity may account for a higher rate of constipation in the euthyroid and otherwise healthy child with Down syndrome, and chronic unexplained diarrhea may affect up to 20% of adults. *Helicobacter pylori* infection has been noted to be common in adults. Non-immunity to Hepatitis A and B is high and immunization against these is important (See Immunologic section).

Celiac disease has a high prevalence rate among children with Down syndrome (up to 18.6%), depending on the age of the child, geographical location, and diet (Pavlovic et al. 2017). The symptomatic form of celiac disease is more frequent in children with Down syndrome than the asymptomatic form, but about one-third of children with Down syndrome and celiac disease have no gastrointestinal symptoms. Symptoms of celiac disease include diarrhea or protracted constipation, slow growth, unexplained failure to thrive (in infancy), anemia, abdominal pain or bloating, refractory developmental or behavioral problems, and irritability. A known complication of celiac disease among affected individuals who do not follow a gluten-free diet or those who do not seek appropriate evaluations is the risk of developing intestinal lymphoma. Due to a high prevalence rate, presence of asymptomatic cases, and complications of celiac disease, routine screening for celiac disease among children with Down syndrome should be performed.

Evaluation

- Digestive difficulties should be evaluated aggressively, given the high rate of gastrointestinal malformations.
- Based on the AAP guidelines (Bull 2011), infants with marked hypotonia and feeding difficulties, recurrent pneumonia, respiratory problems, and failure to thrive

require radiographic swallow studies for further evaluation to diagnose various neuroanatomical defects. Evaluate duodenal atresia or anorectal atresia/stenosis or tracheoesophageal fistula by performing a history and clinical examination. Evaluate for reduced fluid intake, hypothyroidism, gastrointestinal tract malformations or hypotonia, if constipation is present.

- Checking for stool in the rectum by rectal examination should be done as part of a work up for Hirschsprung disease. An abdominal X-ray should be obtained to determine if the child is constipated and if so, the child should have a barium enema without doing a preparatory bowel clean out first, looking for short or long segment Hirschsprung disease. For severe chronic cases of constipation, a rectal biopsy is indicated for possible Hirschsprung disease.
- For celiac disease, there is no universal consensus about routine screening among all children with Down syndrome. Based on the AAP guidelines (Bull et al. 2011), after the age of one year, those on a gluten diet should be evaluated for symptoms of celiac disease at each wellness visit. Symptomatic children need an assessment of tissue transglutaminase immunoglobulin A (IgA) level and quantitative IgA. It is recommended that those with abnormal laboratory values be referred for specialty assessment. Small intestinal biopsy is typically used to confirm the diagnosis. Screening is recommended to be done at least every third year, and more frequently in those with a family medical history of celiac disease or those with possible symptoms from the condition.

Management

- Malformations and functional gastrointestinal problems should be treated as in the general population.
- Adequate response to chronic constipation is generally obtained with a standard pediatric approach when not caused by a malformation or Hirschsprung disease or hypothyroidism.
- Treatment for celiac disease is as for the general population, with a gluten-free diet.

Sleep Disorders

Sleep problems in individuals with Down syndrome have been associated with differences in facial morphology, hypotonia, obesity, irregular sleep habits and sleep resistance, family stresses, obstructive sleep apnea, medications being used for other conditions, and various infections causing general discomfort (Nakamura et al. 2016). Poor sleep may be associated with daytime drowsiness or a decline in behavior. Fernandez and colleagues (2017) found that general sleep quality was poor and efficiency scores were lower in infants and toddlers with Down syndrome than in typically developing children. Infants with Down syndrome exhibited the worst sleep fragmentation; however, sleep efficiency and consolidation increased across age. With advances in technology and sleep studies, further research with more precision and age-wise distribution of sleep patterns are needed to clearly understand various aspects of sleep problems among children with Down syndrome.

As many as 50% of children with Down syndrome may have sleep apnea, with a higher prevalence among adults. The relative underdevelopment of the midface, sometimes associated with a narrow nasopharynx, and the high rate of hypotonia appear to place children with Down syndrome at an increased risk for obstructive sleep apnea, even with nearly normal-sized tonsils and adenoids. It is important to note that obstructive sleep apnea may increase the risk for pulmonary hypertension in susceptible individuals. Obstructive sleep apnea may also be a common comorbidity among adolescents and young adults with Down syndrome who have depression, suggesting that it could be a potential contributor to new-onset mood disorder or decline in adaptive skills (Capone et al. 2013).

One retrospective study of children with Down syndrome and obstructive sleep apnea found that only one-third of those who had standard tonsillectomy and adenoidectomy had a normal postoperative polysomnogram and that adding lateral pharyngoplasty was of no added benefit (Merrell and Shott 2007). Ingram et al. (2017) found that tonsillectomy with concurrent or prior adenoidectomy resulted in significant improvements in respiratory parameters, including obstructive apnea-hypopnea index, percent sleep time with oxygen saturations <90% and percent sleep time with end-tidal carbon dioxide above 50 mmHg. They experienced improvements in both respiratory event frequency and gas exchange but approximately half still had moderate to severe residual obstructive sleep apnea. Future studies are needed to quantify the effects of tonsillectomy and adenoidectomy as a treatment for obstructive sleep apnea in Down syndrome.

Evaluation

- As per the AAP guidelines (Bull 2011), at least once during the first six months of life, discuss with parents symptoms of obstructive sleep apnea, including heavy breathing, snoring, uncommon sleep positions, frequent night awakening, daytime sleepiness, apneic pauses, and behavior problems that could be associated with poor sleep. A referral to a sleep specialist for further evaluation of a possible sleep disorder should be made if necessary. It has been recommended that all children with Down syndrome should have a sleep study by the age of 4 years old. This issue requires further study as obtaining a sleep study for all individuals with Down syndrome is a challenge, and pediatric

sleep labs are not available in many parts of the country. Parents should be made aware that obesity is a risk factor for sleep apnea.

- Suspicion should be raised if parents or care providers note an unusual sleeping position, such as with the head hyperextended or on the stomach with the knees drawn up, or if other signs of sleep disturbances are noted.
- A careful assessment of the cause of sleep apnea should be sought before treatment, especially surgery, is suggested.

Management

- Many symptomatic individuals with obstructive sleep apnea will respond adequately to tonsillectomy and adenoidectomy.
- Continuous positive airway pressure may be the appropriate intervention for some.
- Very occasionally, more involved surgery, such as enlargement of the midface, may be required.

Dental

Dental anomalies are common in individuals with Down syndrome, and include delayed and asynchronous primary dentition (completed by 4–5 years) and secondary dentition. Primary dentition tends to be larger than in typically developing children, with a degree of microdontia and thinner than normal dentin and enamel in the permanent dentition. Primary teeth may be retained, and there is a greater rate of supernumerary teeth, taurodontism (reported in 50% of one group aged 3–35 years), tooth hypoplasia, hypocalcification, and crown variants, especially on the labial surfaces. Crowns are more likely to be conical, small, and short. The roots are complete but short, and this may contribute to instability and susceptibility to tooth loss associated with periodontal disease. Partial anodontia affects over half as compared with 2% of the general population, and the agenesis occurs in a pattern different from that seen in the general population. Involvement is usually mild with approximately two teeth missing about 60% of the time and three to five absent in about one-third of those affected. The third molars are absent about 75% of the time, and impaction of the maxillary canines and maxillary canine-first premolar transposition are not uncommon. Occlusal problems, most often of the central and lateral incisors and canines, are common and result from mouth breathing, impaired chewing, tooth agenesis, shortness and asymmetry of the maxillary arch, and temporomandibular problems. There is also a high incidence of aphthous ulcers, oral candidiasis, and acute ulcerative gingivitis. Dental wear is twice as common in children with Down syndrome and is much more likely to be severe. The cause is unclear but there is a high rate of bruxism that may have some association with gastric reflux. Rates of bruxism could also be influenced by anxiety, craniofacial abnormalities, temporomandibular joint dysfunction, and orofacial hypotonia.

Children with Down syndrome have rates of periodontal disease that are equivalent to those of other children with intellectual disabilities and are higher than in the general population. The high incidence of periodontal disease may be due to hypotonia, dentoalveolar joint laxity, poor dental hygiene, and impairments of the immune system. Prevalence of periodontal diseases in young adults with Down syndrome is about 35% with increasing prevalence in the third and fourth decades. Decreased salivary flow and an increase in pH and bicarbonate buffer may result in mucosal thinning and xerostomia, while offering some protection against dental caries. There is no evidence of qualitative or quantitative differences in the carriage of putative oral pathogens in individuals with Down syndrome.

Evaluation

- Early referral for regular semiannual dental care is important both for repeated instruction in dental hygiene for the prevention of gum disease and the longer term planning of possible orthodontics.
- Parents may have particular difficulty finding access to dental expertise (personal experience). Pediatric dentists and pediatric dental hygienists are recommended for children with Down syndrome.

Management

- Educate the parents of young children with Down syndrome about the possible dental anomalies in primary and secondary dentition, including delayed or irregular dental eruption and hypodontia.
- Instruction in dental hygiene, one-on-one help, and brushing and flossing must begin at an early age for all children with Down syndrome, and dental hygiene must become a lifelong habit. In the absence of a successful program of gum care, early tooth loss can be anticipated. Awareness of periodontitis is important. An aggressive preventive dental program may be recommended. Specific dental anomalies will vary widely from individual to individual and will require a tailored approach. More frequent visits to a dentist (three to four per year) may be helpful. Many dentists believe that regular use of a fluoride-free chlorhexidine mouthwash can help reduce periodontal disease.
- Dietary counseling with avoidance of certain foods that affect the pH in the oral cavity should be encouraged, while maintaining a proper nutritious, balanced diet.
- Topical fluoride application will help in the prevention of dental caries and improve gum and enamel health.

- Antibiotic prophylaxis against subacute bacterial endocarditis is required at the time of dental care for many individuals with Down syndrome and congenital heart disease.
- Significant malocclusion can be treated in a standard fashion, although braces may complicate gum care.
- Psychological treatment may be beneficial for some children with bruxism.

Dermatologic

Dermatologic conditions are among the more common issues in individuals with Down syndrome. The skin in infancy is generally soft and velvety, and cutis marmorata occurs in about 8–13% of children. Premature wrinkling, graying, and loss of hair suggest an accelerated ectodermal aging. The hair is often fine and hypopigmented. A wide variety of skin disorders are reported in Down syndrome, and many are age related. These are summarized in Table 24.2 (data adapted from Barankin and Guenther (2001) and Daneshpazhooh et al. (2007)).

Seborrheic dermatitis may occur in up to 30% of persons with Down syndrome (general population 2–5%), with red cheeks being common. With time, the skin has a tendency to become dry and rough and may show local thick and scaly hyperkeratotic patches on the limbs. Fewer than five cases of multiple dermatofibromas have been described in the literature among individuals with Down syndrome, and all had some underlying condition such as autoimmune diseases, leukemia, or immunodeficiency. Cases of psoriasis have also been observed. Alopecia areata, an autoimmune condition, is also more common in Down syndrome than in the general population with prevalence estimates ranging from 1.3 to 11%. In Down syndrome, alopecia areata tends to occur most frequently on the scalp and has a variable period of duration, but can be permanent.

Evaluation

- A careful skin examination should be part of routine anticipatory care. Discuss skin, hair and scalp care at every visit.

Management

- Any problem identified should be treated as in the general population.
- Individuals with alopecia areata should be referred to a dermatologist.

TABLE 24.2 Summary of dermatologic findings in Down syndrome

Condition	Frequency	Comment
Fissured tongue	Reported in 20–95%	2–5% general population, most asymptomatic
Xerosis	<10–85%	Highly age dependent, high rates in adults
Lichen simplex (lichenification)	Up to 80%	Rate increases with age
Palmoplantar hyperkeratosis	10 to >75%	High rates seen over age 5 years
Atopic dermatitis	Up to 50%	Recent studies point to a low prevalence
Onychomycosis	>50%, general population ~20%	
Eruptive syringomas	18–39%; more females	Benign dermal papules, eccrine, often periorbital
Hidradenitis suppurativa (Sehgal, Sehgal & Sehgal, 2017)	38%	Solitary or multiple isolated abscesses without scarring or sinus tracts, recurrent abscesses, in inner thighs, groin, and buttocks
Furunculosis	Scarring in up to 26%	Perigenital, thigh, buttock common sites
Acanthosis nigricans	50% of those with atopic dermatitis	10-fold increase
Follicular papular dermatosis	45% of males	Same as Malassezia type folliculitis
Cheilitis	6–13%; more males	Age dependent, vertical fissures, enlargement
Alopecia areata	6–11%; more females	More severe than usual; associated with vitiligo
Geographic tongue	4–11, 40% also have fissured tongue	Inflammatory; loss/regrowth filiform papillae
Alopecia areata	1.3–11%	
Hypertrophic tongue papilla	22%	Physical variant
Premature graying	14%	
Folliculitis (pityrosporum)	10%	Upper back, chest, shoulders most common
Syringoma	6%	
Trichotillomania	4%	
Vitiligo	3%	
Anectoderma	Not common	Flaccid skin; lacks elastic tissue; fat herniation
Elastosis perforans	Not common, more males	Onset second decade, more severe than usual
Propensity to crusted scabies	More common in DS	Asymptomatic crusting of hands and feet

Immunologic

Children with Down syndrome are known to have more frequent infection rates, impaired immunity, suboptimal immunologic response to vaccinations, and higher rates of autoimmune diseases. As the survival of individuals with Down syndrome increases, there is a growing need to strategize our application of preventive medicine against common ailments affecting this high risk group. Vaccinations play an important role.

Abnormalities have been reported in virtually all aspects of the immune system. There is a mild-to-moderate reduction in T-cell and B-cell counts, absence of normal lymphocyte expansion in infancy, variable thymus size, mild-to-moderate reduction in naive T-cell percentages with corresponding reduction of T-cell excision circles, suboptimal antibody responses to immunizations, decreased total and specific immunoglobulin A in saliva, and decreased neutrophil chemotaxis (Colvin and Yeager 2017). Individuals with Down syndrome also have higher percentages of natural killer cells with reduced functionality and higher percentages of apoptotic lymphocytes. There is also evidence of secondary causes for immunodeficiency, like nutritional deficiency of zinc. Decreased cilial beat frequency could also be a contributing factor, which is considered secondary to chronic hyperproduction of mucous. Many aspects of immunological influences and effective corrective measures are yet to be discovered.

Multiple aspects of humoral immunity have been found to be different in Down syndrome compared to typically developing individuals. Carsetti and colleagues (2015) found that transitional and mature-naïve B-cell numbers were reduced by 50%, whereas switched memory B-cells represented only 10–15% of the numbers in age-matched controls. Following the primary influenza vaccination, children with Down syndrome had significantly fewer vaccine-induced immunoglobulin G-producing B-cells than controls. After these same children received a pneumococcal booster vaccination, the number of vaccine-induced IgG-producing B-cells showed a significant increase. Both groups reached similar vaccine efficacy after the booster dose for children with Down syndrome. Eijsvoogel and colleagues (2017) found that after primary vaccination of Hepatitis B, only 48% of children aged 7–10 years and 32% aged over 10 years had protective immunity against Hepatitis B. The evidence taken together suggests that children with Down syndrome may require repeated antigen-stimulation by recurrent natural infection or booster vaccination to reach an adequate level of immune protection.

The fetal thymus in Down syndrome may be hypotrophic and shows differences in function including abnormalities of specific antigen responses and receptor formation. Although the percentage of T-cells is maintained, the total number of circulating lymphocytes and of T-cells is reduced, with alterations in specific subsets of cells and an impaired T-cell-mediated response. Some authors have suggested that there is an upregulation of inhibitory receptors which causes a phenomenon called T-cell exhaustion, contributing to frequent infection episodes among individuals with Down syndrome.

Children with Down syndrome are more susceptible to infections compared to the general population, due to abnormal structural morphologies, comorbidities, developmental delays, and immunologic deficits. Improvements in medical care, early diagnosis, preventive measures, and outpatient services may contribute to findings of reduced hospitalization rates for older individuals. Despite advances in treatment, children and adults with Down syndrome continue to show relatively high morbidity and mortality from infectious disease. A study in a population-based cohort showed that on an average, each child with Down syndrome was admitted to a hospital nearly ten times in their lifetime, with the most common primary admission diagnoses being otitis media, lower respiratory tract infection, upper respiratory tract infection, cardiac septum defects, and adenoid/tonsillitis (Fitzgerald et al. 2013). Infections occurred in 80% of children and the median age of first hospital admission was 1.2 years. Infections accounted for 33% of all hospital admissions.

Respiratory tract infections are the leading causes of morbidity and mortality among children with Down syndrome. The factors associated with high mortality among this group are history of congenital heart disease, chronic upper airway obstruction and mechanical ventilation, and the occurrences of sepsis, pulmonary arterial hypertension, acute respiratory distress syndrome, and infections acquired during a hospital stay (Joffre et al. 2016). Some studies have shown that children with Down syndrome who are hospitalized for respiratory syncytial virus infection tend to be older and have more severe illness than children without Down syndrome. Pidotimod, an immunostimulant, and palivizumab, a human monoclonal antibody, may have roles in preventing respiratory tract infections in children with Down syndrome, with palivizumab being particularly effective in young children (under 2 years of age) against respiratory syncytial virus-related hospitalizations (Manikam et al. 2016). Increased expression of the *Ksp37* gene may be associated with increased susceptibility to Epstein–Barr virus infections and autoimmune problems (Salemi et al. 2016).

Down syndrome has an increased prevalence of autoimmune diseases affecting both endocrine and non-endocrine systems. These include Addison's disease, allergic dermatitis, alopecia, celiac disease, chronic autoimmune hepatitis, diabetes mellitus (type I more common than II), hypo- and hyperthyroidism, autoimmune hemolytic anemia, dermatomyositis, multiple sclerosis, pernicious anemia, polyarteritis nodosa, primary sclerosing cholangitis, rheumatoid arthritis, scleroderma, Sjogren's syndrome, and systemic lupus erythematosus. An unbalanced relation between anti- and

proinflammatory immune responses may favor the development of autoimmunity in Down syndrome (Schoch et al. 2017). Although auto-antibodies may be present, in general there is poor correlation with the presence of actual disease. Thus, caution is needed in interpreting any such results. Finally, Down syndrome disintegrative disorder, characterized by sudden decline in skills and autistic regression (see section on Development and Behavior), has also been associated with elevated antithyroperoxidase antibodies and other autoimmune conditions. Current research is ongoing to better elucidate the potential role of autoimmunity in this condition.

Evaluation

- Although children with Down syndrome show greater susceptibility to infectious disease, and several anomalies of immune responsiveness may be found, there does not appear to be justification for routine immunologic evaluation. Such studies should be reserved for those individuals with unusually severe problems and/or evidence of frank immunodeficiency or autoimmune disease.
- Per AAP guidelines (Bull 2011), evaluate respiratory and cardiac comorbidities during newborn examinations and routinely thereafter during wellness visits. Consult specialists and enable prompt treatment of infections and other factors that lead to increased prevalence of infections in individuals with Down syndrome.

Management

- Although response to vaccinations may not be as effective in people with Down syndrome, it is recommended that they follow a normal vaccination schedule, including hepatitis B, for which they are at significant risk to become chronic carriers. Children with confirmed comorbidities should have respiratory syncytial virus prophylaxis. Influenza vaccine should be given annually. Children with chronic cardiac or respiratory diseases should be given the 23-valent pneumococcal polysaccharide vaccine (PPS23) at 2 years or older (Bull 2011).
- The possible role of vitamin A and zinc in normalizing some aspects of the immunodeficiency in Down syndrome remains controversial. Based on clinical judgement, these may be replaced if low.

Neurologic

An array of neurological manifestations has been described among individuals with Down syndrome. Neuromuscular hypotonia, epilepsy, intellectual disability (see Behavior and Development section), neuropsychiatric problems (see Behavior and Development section), cervical cord compression (see Musculoskeletal section), gait abnormalities (see Musculoskeletal section), cerebrovascular events leading to early strokes, sleep disorder (see Sleep Disorders section), and defects in vision and hearing (see Ophthalmologic and Audiologic sections) have been widely observed. A thorough neurological evaluation for newborns, and then at every wellness visit is essential to manage these problems.

Seizures occur more often in children with Down syndrome than in the general population but are less frequent than among those with other forms of intellectual disabilities. Goldberg-Stern and colleagues (2001) reported seizures in 8% of 350 children and adolescents with Down syndrome, and found that 47% were partial, 32% infantile spasms, and 21% generalized tonic clonic. Seizure onset occurs most commonly during infancy or before age 12 years. Infantile spasms are 8–10 times more common than in the general population. The higher incidence of seizures in children with Down syndrome may be explained partly because of the greater frequency of potential causative factors such as cardiac hypoxia, cerebral artery occlusion, perinatal complications, infections and fevers, neurotransmitter imbalances, and chemotherapy. Sex distribution for epilepsy in children with Down syndrome has not been uniformly reported, but infantile spasms tend to occur more frequently in males.

Adults with Down syndrome and Alzheimer disease appear to have a higher frequency of seizures than those with Alzheimer disease in the general population. In a study of 68 adults with Down syndrome, Puri et al. (2001) found that 26.5% had a history of seizures and that there was a bimodal age of onset in the first and second decades and the fifth and sixth decades. Seizures starting over the age of 45 years were more common in females and were strongly associated with the occurrence of Alzheimer disease, whereas seizures with onset at younger ages showed no such association. There have also been reports of senile seizures (after 50 years of age) called senile myoclonic epilepsy of Genton or late-onset myoclonic epilepsy in Down syndrome, which shows generalized fast spike waves, polyspikes, or polyspike waves.

Focal weakness may affect about 1% of individuals with Down syndrome and has a wide gamut of causes (Worley et al. 2004). Worley and colleagues studied 10 children with Down syndrome (median age of 4 years) with new-onset focal weakness. They found the causes of the new onset focal weakness were: stroke from Moyamoya disease (two patients); stroke from vaso-occlusive disease (one patient); stroke from venus sinus thrombosis (one patient); traumatic subdural hematoma (one patient); brain abscess (one patient); spinal cord injury from cervical spinal stenosis (two patients); spinal cord injury from atlantoaxial instability (one patient); and brachial plexus injury (one patient).

Stereotypic movements are common among individuals with Down syndrome. A study of 145 participants (mean age of 40 years) found that at least 90% had dyskinesias, almost all with orofacial and about 20% with limb or trunk signs (Haw et al. 1996). Tongue thrust (68%), an impassive face (57%), and decreased arm swing occurred in 50% or more of these individuals. Bradykinesias (33%) and global Parkinsonism (4%) were only seen in those with dementia, and this has been confirmed in other studies. Brief random movements, grimacing, abnormal facial movements, and postural and gait abnormalities were commonly observed. About 40% of affected individuals showed stereotypic movements including trunk rocking, rubbing a hand on the chest, or waving the hands in front of the eyes. There appears to be a positive correlation between the occurrence of dyskinesia and the severity of intellectual disability and lack of academic and practical skills.

Evaluation

- Evaluation of seizures does not differ from that in the general population; an electroencephalogram is indicated if there is a suspicious history.
- Monitor for signs of neurologic dysfunction including seizures. New focal weakness should be fully investigated, as the cause may be treatable.

Management

- Treatment of seizures does not differ from that in the general population.
- Abnormal movements do not usually require treatment, although medication or other toxicity should be ruled out.

Neoplasia

The pattern of malignancies observed in individuals with Down syndrome is significantly different from that observed in the general population (Hasle et al. 2016). At younger ages, the overall risk is relatively higher because of the increased risk of leukemias. In the adult population, the risk is much lower because of the significantly decreased occurrence of solid tumors in older persons with Down syndrome. The increased risk for leukemia in individuals with Down syndrome is present from the age of 1–10 years. The incidence risk of leukemia in Down syndrome is about 20 times that in the general population. Acute lymphoblastic leukemia (DS-ALL) and acute non-lymphocytic leukemia (ANLL) like acute megakaryocytic leukemia (AML-M7/AMKL) are the most common leukemias noted in childhood in individuals with Down syndrome. Chronic myeloid and chronic lymphocytic leukemia are less common than expected.

About half the cases of ANLL are acute megakaryocytic leukemia (AML-M7/AMKL), a rate about 500 times higher than in the general population. AMKL occurs in about 1–2% of children with Down syndrome, especially in early childhood (1–5 years). Up to 10% of neonates with Down syndrome may show a transient leukemoid reaction, also referred to in the literature as transient leukemia, transient megaloblastic leukemia, transient abnormal myelopoiesis, and transient myeloproliferative disorder (TMD). TMD appears to be virtually limited to persons with a trisomy 21 cell line. Several individuals have been diagnosed on fetal blood samples obtained during prenatal diagnostic testing. In most cases, TMD regresses spontaneously in three months, about 20% develop an early life threatening illness (e.g., hepatic fibrosis, liver failure, pulmonary edema, pericardial effusion), and about 20–30% go on to develop acute megakaryocytic leukemia (AMKL, AML-M7) within a mean interval of 1.2–1.5 years (Gamis and Smith, 2012). Individuals whose AMKL is preceded by TMD respond better to treatment than those where it is not. The transformation to leukemia from TMD may be preceded by myelodysplastic syndrome (MDS), in which there are fewer than 20% blasts in the bone marrow. The blasts of TMD and myeloid proliferations in Down syndrome contain acquired *GATA1* variants, which are considered pathognomonic of these disorders. AMKL and MDS occurring in young children with Down syndrome with *GATA1* somatic variants are collectively termed myeloid leukemia of Down syndrome (ML-DS). At this time, there have been very few reported cases of non-Down syndrome-AMKL with *GATA1* variants and acquired trisomy 21, who were all phenotypically and cytogenetically not Down syndrome.

GATA1 variants are found in almost one third of neonates with Down syndrome but are frequently hematologically "silent". Recent studies have shown that although *GATA1* variants have been thought of as causative factors for AMKL/TMD in Down syndrome, fetal studies have shown that *GATA1* variants occur much later in the fetal development, and that trisomy 21 itself alters human fetal hematopoietic stem/progenitor cell biology causing complex abnormalities in myelopoiesis and B-lymphopoiesis. This seems to be a complex process involving specific tissues and cell lineages among children with Down syndrome. AMKL preceded by TMD also has TMD cloning through additional acquired variants. Multiple other genetic factors have been linked to susceptibility to myeloid leukemia, including trisomy 8 (occurring in approximately in 13–36% of cases) and losses of chromosomes 5 and 7. Telomere shortening and stem/progenitor cells deficiency have been documented in fetal life in individuals with Down syndrome and might play some role in the susceptibility to leukemia.

Children with Down syndrome account for about 2% of all patients with acute lymphoblastic leukemia (ALL). After age 10, ALL is more predominant than other leukemias in children with Down syndrome. DS-ALL is characterized by lower levels of both favorable and unfavorable cytogenetic

findings such as hyperdiploidy and of a number of common translocations including the transient encephalopathy leukemia/acute megakaryocytic leukemia 1 phenotype t(12;21), t(9;22) and *MLL* gene rearrangements. DS-ALL is a high-risk B-cell precursor leukemia in most cases, with very rare cases of mature B cell ALL (Burkitt leukemia) and T-cell ALL. Several different mechanisms are currently being studied for therapeutic purposes to design new drugs and to understand their correlations with relapses or remissions, including activating variants in the JAK-STAT pathway and targeting the *HMGN1* and *PRC2* genes.

Children with Down syndrome and certain leukemias who are treated on trial chemotherapeutic protocols generally have better outcomes. Persons with Down syndrome are showing greater participation rates in clinical trials and improved survival. AMKL has higher cure rates with 80–100% event-free survivals; however, ALL is associated with a worse prognosis in children with Down syndrome compared to those without Down syndrome. The outcome for children who present at less than 2 years of age is significantly better than for those who present later. Although Down syndrome has been shown to be a negative prognostic factor in ALL treated by conventional therapy, event-free survival and overall survival are very close to those in the general population when both are treated with an intensive regime. Historic treatment failures were largely the result of undertreatment and late diagnosis. Children with Down syndrome and AMKL should not be undertreated because they have very high cure rates. If certain treatment protocols are contraindicated (due to severe cardiac disease, unstable patients, or drug toxicities), very low-dose araC regimens could be tried.

There is less evidence to support efficacy of bone marrow transplant in treatment of AML as compared to chemotherapy in Down syndrome. Hitzler and colleagues (2013) compared results of bone marrow transplantation for children with and without Down syndrome in one of the largest studies. They found that the three-year probability of overall survival was only 21% among children with Down syndrome (compared to 52% in children without Down syndrome), owing to risks of relapse and transplant-related mortality. A study by Muramatsu and colleagues (2014) in a Japanese population investigated the use of a lower-intensity conditioning regimens preceding bone marrow transplant for children with Down syndrome and AML. The three-year event-free survival rates were approximately 80%, which were significantly better than in the group that received a more standard conditioning regimen (event-free survival rate of approximately 10%). Here, the common cause of treatment failure after transplant was relapse, as opposed to treatment-related mortality. Further studies with larger number of patients are required to confirm these findings.

In contrast to leukemia, individuals with Down syndrome are largely protected from solid tumors, with a significantly lower risk of lung cancer, breast cancer, and cervical cancer (Hasle et al. 2016). Testicular cancer is the only solid tumor with an increased standardized incidence rate, out of all the solid tumors. Cryptorchidism alone cannot explain the increased risk, since only less than a quarter of males with Down syndrome have cryptorchidism along with testicular tumors. The risk of developing ovarian cancer is comparable to that of the general population. Cancers pertaining to embryogenic tissues are negligible.

Evaluation

- The AAP guidelines have the following recommendations (Bull 2011). *For newborns*: Obtain a complete blood cell count. *Infants* with transient myeloproliferative disorder or polycythemia should be referred to a pediatric hematologist/oncologist for consultation and should be followed according to consultation recommendations. Parents of *younger children* with transient myeloproliferative disorder should be counseled regarding the risk of leukemia and be made aware of the suggestive clinical signs, including easy bruising, petechiae, onset of lethargy, or change in feeding patterns. The signs and symptoms of individuals with Down syndrome and leukemia do not differ significantly from those in the general population. Individuals with Down syndrome are slightly older at the time of diagnosis and have slightly higher initial hemoglobin values.
- No routine screening is indicated by current AAP guidelines.
- The testes should be examined periodically because of the higher rate of testicular germ cell tumors.

Management

- If possible, treatment should be carried out in experienced tertiary care centers that participate in standard and research protocols and where there is experience in treating children with Down syndrome.
- Children with Down syndrome and leukemia who are treated have not been found to have greater risk of relapses or mortality when compared with typically developing children with leukemias. They may have more side effects due to chemotherapy because they are more sensitive to toxicity from chemotherapy, particularly from methotrexate, because of slower clearance.
- Bone marrow transplants for treatment of AML are known to be less effective compared to standard chemotherapy regimens and are generally not used as the first line of management. If there are regimens tailored to reduce the leukemic burden prior to bone marrow transplants, it may be possible that bone marrow transplants work better than standard chemotherapy.
- In July 2017, the FDA approved a new innovative single-dose gene therapy called CAR-T cell therapy/

Kymriah for the treatment of B cell-ALL in young adults, for whom other treatment modalities have failed. Further studies on patients with Down syndrome may shed some light on how this treatment may modify the prognosis of the disease among this high-risk group.

Craniofacial

Craniofacial morphologies vary widely among ethnic and geographical groups across the world. Several studies have implied that the craniofacial morphological differences change or become more prominent with increasing age. Individuals with Down syndrome tend to breathe through the mouth, exhibiting open bite and opened lips, with orofacial hypotonia and normal mandible (pseudo-progeny). This exaggerates the mid face hypoplasia, along with malformations of bony skull structures. Relative macroglossia and hypotonicity of the tongue and muscles of the oropharynx contribute to difficulties in feeding, breathing, swallowing, and speaking. Hypotonia of the facial muscles can result in chronic drooling, chapping, and cheilitis, which may play a role in the increased rate of upper-respiratory infections and peridontitis.

There have been some cases of facial plastic surgery among individuals with Down syndrome, but there are ethical concerns with such procedures. Surgical options such as partial glossectomy, internally rotating the lower lip, neck and cheek liposuctions, augmenting the nasal bridge or midfacial area, and repositioning epicanthal folds are available. There are claims that these procedures improve speech, mouth breathing and/or aesthetics, and reduce oral inflammation, chieliosis, and halitosis and dental problems. While there are cases where such procedures have been reported to boost self-confidence and increase the emotional quotients of individuals with Down syndrome, the expected outcomes and improvement in quality of life varies widely, and not all procedures have benefits. Parents and adults with Down syndrome need to be well informed about all potential complications and the uncertainties of the outcomes, and they should consider speaking with other parents who have gone through such procedures with their children.

Evaluation

- Discuss with parents about hypotonia and facial appearance, acknowledging the presence of familial characteristics, at the time of birth.
- Medical history and physical examination should be obtained to identify any potentially deleterious effects of a prominent tongue.
- Since Down syndrome is characterized by wide variability in morphological features, a multidisciplinary team of pulmonologists, speech language pathologists, dentists, school teachers, psychologists, and parents is essential for supporting social acceptability and capabilities for speech and feeding.

Management

- Due to controversy surrounding plastic surgeries, it is important to discuss the risk versus benefit ratio with parents, based on each individual, case by case.

Urologic

The urinary tract in individuals with Down syndrome has received relatively little attention. However, there are urogenital anomalies that in some cases may cause significant morbidity and even mortality. Their incidence cannot yet be determined, as most surveys are small and come from individuals specifically referred for renal evaluation. Anomalies reported include bladder extrophy, hypospadias, posterior urethral valves, micropenis (microphallus), reflux, renal hypoplasia, elevated urinary and/or blood uric acid, dysfunctional voiding as a result of both neurogenic and non-neurogenic bladder, and chronic renal failure. A wide spectrum of congenital and acquired renal anomalies has been reported among individuals with Down syndrome, including acute kidney failure, urinary symptoms (dysuria, increased frequency, hesitancy, dribbling urine, and incontinence), decreased clearance of uric acid, hypercalciuria, and end-stage renal disease. At present, screening for urological anomalies among individuals with Down syndrome is not standard care during newborn evaluations.

Undescended testes (cryptorchidism) occur with increased frequency. If uncorrected, cryptorchidism can lead to infertility, testicular cancer, hernias and testicular torsion. Testicular cancer is the only solid tumor which is more common in Down syndrome (see Neoplasia section). Many individuals with Down syndrome may be unaware of the lump in the testes, and are diagnosed with testicular cancer incidentally following a thorough physical examination. A high cure rate is expected for this cancer, and so it is imperative to palpate the testes yearly for detection of a mass.

Evaluation

- Early and continued confirmation of a normal urinary stream and bladder voiding pattern is important.
- As renal and urinary tract anomalies have been reported to occur at an increased frequency among persons with Down syndrome, standardized screening for these anomalies with renal ultrasound has been suggested (Kupferman et al. 2009). Currently, more studies are needed to document that screening improves outcomes.
- Physical examination of males for cryptorchidism should occur at diagnosis, with follow-up examination in a standard manner if they cannot be palpated.

- The testes should be palpated yearly. Parents should be taught how to do an examination of the testes for detection of a mass.

Management

- If anomalies are detected during screening, an evaluation by a nephrologist or urologist is indicated.
- Treatment for anomalies, including undescended testes, is as for the general population.

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WEBSITES

US National Down Syndrome Society
www.ndss.org

National Down Syndrome Congress (US)
www.ndsccenter.org

Lettercase (print or digital resources about genetic conditions)
lettercase.org

Canadian Down Syndrome Society
www.cdss.ca

United Kingdom Down Syndrome Association
http://www.downs-syndrome.org.uk/

European Down Syndrome Association
http://www.edsa.eu/

New Zealand Down Syndrome Association
www.nzdsa.org.nz (each Australian state has its own Association)

International listing associations and resources
www.kumc.edu/gec/support/down_syn.html
https://www.ds-int.org/

Dr Len Leshin's Health Page
www.ds-health.com

Phone Contacts

US National Down Syndrome Society
666 Broadway, New York, NY, 10012-2317, USA
Phone: 1-800-221-4602 (US), 212-460-9330
Email: *info@ndss.org*
Website: *www.ndss.org*

US National Down Syndrome Congress
30 Mansell Court, Suite 108, Roswell, GA, 30076, USA
Phone: 800-232-NDSC(6372), 770-604-9500
Email: *info@ndsccenter.org*
Website: *www.ndsccenter.org*

Canadian Down Syndrome Society
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