REVIEW ARTICLE

Allan H. Ropper, M.D., *Editor*

Down Syndrome

Marilyn J. Bull, M.D.

From the Division of Developmental Pediatrics, Riley Hospital for Children at Indiana University Health, Indianapolis. Address reprint requests to Dr. Bull at 1002 Wishard Blvd., Suite 3120, Indianapolis, IN 46202, or at mbull@iu.edu.

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Down syndrome, also called Down's syndrome (DS), is the most common chromosomal condition associated with intellectual disability and is characterized by a variety of additional clinical findings. It occurs in approximately 1 of 800 births worldwide. In the United States, DS accounts for approximately 500 live births annually, and more than 200,000 persons are living with the disorder.[1] The original description of the syndrome, in 1866, has been attributed to John Langdon Down, a physician from Cornwall, England.[2] More than 90 years later, the chromosomal cause was delineated[3,4] and the condition was named Down syndrome.[5]

The potential for the development and socialization of persons with DS has been increasingly realized, and early support for affected children and their families is widely implemented, although disparity in access to health care and other supportive resources still exists. There is considerable phenotypic variation among patients, and intellectual disability is most commonly moderate but ranges from mild to severe, whereas social function is often high relative to the cognitive impairment. There are also differences in the incidence and presentation of DS according to ethnic background and geographic region.

Genetic Features

A third copy of chromosome 21, trisomy 21, has long been recognized as the cause of DS. The 200 to 300 genes on chromosome 21, as well as epigenetic factors,[6] have been identified as contributors to clinical features of the syndrome. Multiple genes both on chromosome 21 and at other sites in the genome, such as polymorphisms of the Down syndrome cell-adhesion molecule (DSCAM) and of the amyloid precursor protein gene, contribute to the variation in clinical manifestations. Trisomy 21 occurs either by nondisjunction, with the presence of 47 chromosomes, or by translocation of an additional chromosome 21 to another chromosome (Table 1); the clinical features do not differ between the two causes of trisomy 21. Mosaicism of trisomy 21 and partial trisomy 21 are other genetic diagnoses and are usually associated with fewer clinical features of DS.

Prenatal Diagnosis

The development of cell-free prenatal screening and parallel sequencing of maternal plasma cell-free DNA (cfDNA) has resulted in changes in the approach to prenatal diagnosis of DS.[10] Use of this type of noninvasive prenatal screening has reduced the use of invasive testing (i.e., amniocentesis or chorionic villus sampling), though regional and cultural differences in the rates of noninvasive screening exist. The high specificity of cfDNA for the detection of DS (99.7%) is valuable for a parent who is a carrier of a translocation and for a woman at increased risk

Table 1. Chromosomal Basis of Down Syndrome.*

Chromosomal Feature	Description	Percent of Cases
Meiotic nondisjunction	Occurs in the egg in 95% of cases, and the risk increases with mother's age	96
Translocation	Usually occurs with one chromosome 21 attached to chromosome 14, 21, or 22 In 14/21 translocation, 1 of every 3 cases involves a parental carrier; in 90% of such cases, the carrier is the mother; risk of recurrence is 10–15% with a maternal carrier and 2–5% with a paternal carrier In 21/21 translocation, 1 of every 14 cases involves a parental carrier; in 50% of such cases, the carrier is the father	3–4
Mosaicism	The number of affected cells varies among persons; clinical findings vary widely; there are fewer medical complications and often less severe intellectual disability in cases characterized by mosaicism	1–2
Partial trisomy	Duplication of a delimited segment of chromosome 21 is present	<1

* Information is from Hook[7] regarding meiotic nondisjunction and translocation, Papavassiliou et al.[8] regarding mosaicism, and Pelleri et al.[9] regarding partial trisomy.

for having an affected fetus. Parents should be given information at the time of prenatal diagnosis of DS regarding possible evaluation of the fetus for potentially treatable cardiac and gastrointestinal defects. Parents are more likely to choose to proceed with diagnostic testing (cfDNA) if prenatal ultrasonography reveals congenital anomalies.

Genetic analysis of karyotype obtained by amniocentesis or chorionic villus sampling is 99% accurate and is required for a definitive diagnosis of DS, which could help inform parental decision making regarding pregnancy continuation or additional prenatal diagnostic studies. The American College of Obstetricians and Gynecologists recommends discussing the risks and benefits of various methods of prenatal screening and diagnostic testing, including the option of no testing, with all patients, regardless of age, who are pregnant or considering pregnancy.[11]

Clinicians should understand that information shared before birth or at the time of delivery about a suspected diagnosis of DS has a profound effect on parents. The information must be provided with empathy, as soon as possible, in a private setting, and with supportive family members or friends present. Parents appreciate first being congratulated on the birth of their baby. Not surprisingly, parents value information regarding the cause of DS, common associated medical conditions, and the potential future of the affected fetus or infant.[12] Parents should be given accurate and current information, including an overview of DS[13] and referral to a support group, which can be located through the National Down Syndrome Society (www.ndss.org/resources/local-support/) and the National Down Syndrome Congress (www.ndsccenter.org/programs-resources/affiliate-organizations/local-and-national-support-networks/) and at Parent to Parent (www.p2pusa.org/parents) and Family Voices (familyvoices.org/affiliates/). Survival and health for some mothers and infants can be improved by delivery at a center specializing in maternal and fetal care.[14]

POSTNATAL DIAGNOSIS

At delivery, nurses and physicians are usually aware of the possibility of DS on the basis of the appearance of the infant. Physical examination is the most accurate initial diagnostic assessment, and an experienced clinician will recognize the body habitus and physiognomic features, often accompanied by muscular hypotonia, that suggest the diagnosis of DS (Fig. 1).

When DS is suspected postnatally, the most appropriate genetic test is a karyotype (Table 2), since the results are essential for genetic counseling. If confirmation of the diagnosis is urgently needed for decisions regarding clinical management, the results of fluorescence in situ hybridization (FISH) of chromosome 21 can usually be obtained in a day. A diagnosis of trisomy 21 by means of FISH is followed by a

karyotype to determine whether the cause is a translocation or nondisjunction. For parents who have had a child with DS, the risk of having another child with the syndrome depends on maternal age, karyotype results, and the type of translocation, if any (Table 1).

ASSOCIATED MEDICAL CONDITIONS AND CLINICAL INTERVENTIONS

Many medical conditions are more common in persons with DS than in the general population and affect health, development, and function.

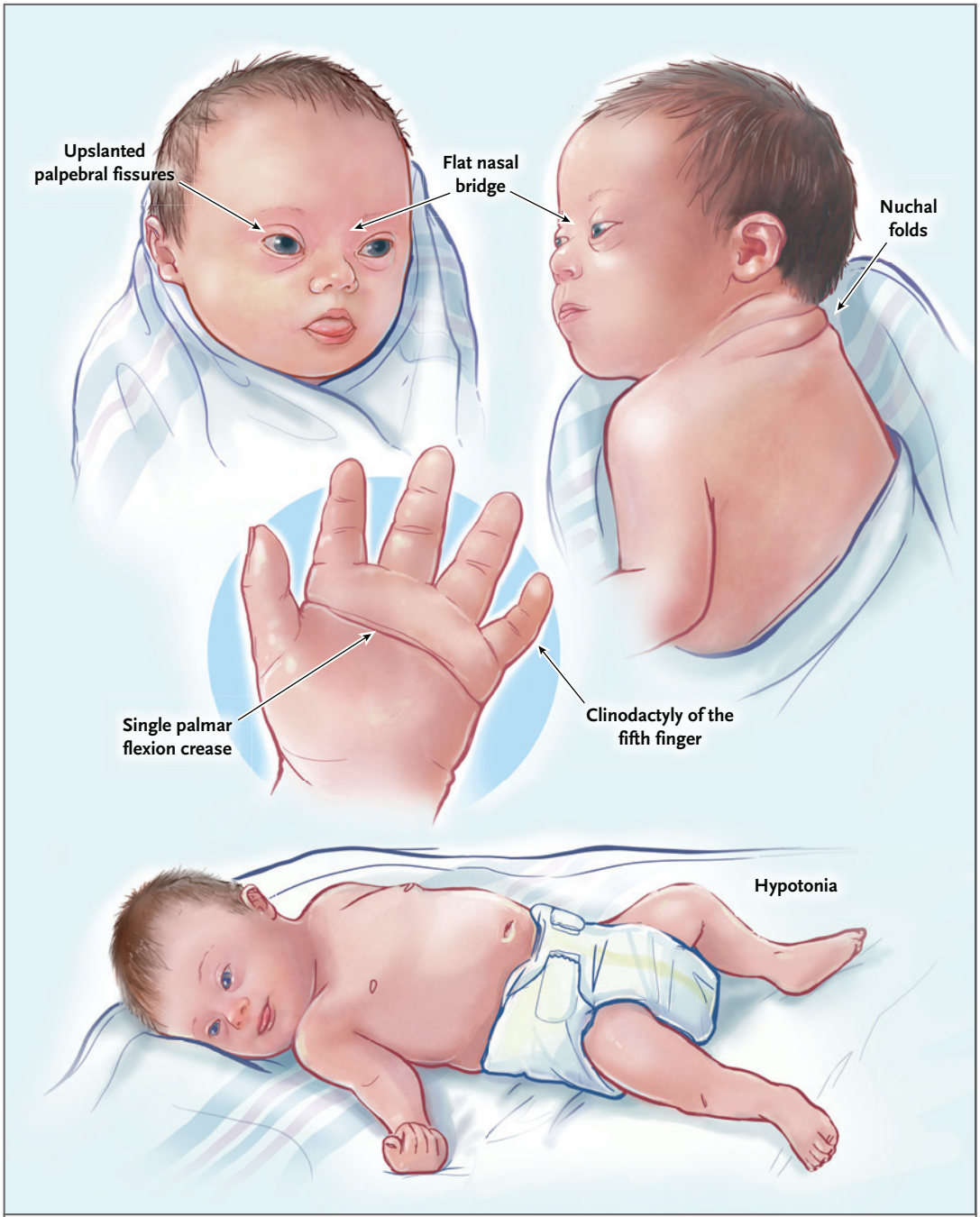

Figure 1. Features of an Infant with Down Syndrome.

Table 2. Perinatal Assessment of Infants with Down Syndrome.*

Karyotype or review of amniocentesis or chorionic villus sampling
Complete blood count with differential
Blood thyrotropin level (included in newborn screening in some U.S. states)
Echocardiogram, even if obtained prenatally
Identification of gastrointestinal anomalies

* Information is from the Committee on Practice Bulletins — Obstetrics, Committee on Genetics, and the Society for Maternal-Fetal Medicine[11] and Bull.[15]

Some of these conditions require immediate intervention at birth (Table 2), and others warrant lifelong surveillance (Table 3).

CARDIAC COMPLICATIONS

Improved management of congenital heart disease has contributed to an increase in life expectancy for patients with DS, from 30 years in 1973 to 60 years by 2002.[38] Pulmonary-artery hypertension, with or without congenital heart disease, occurs in 1.2 to 5.2% of persons with DS.[17] Infants who are initially unaffected by complications of pulmonary-artery hypertension may become symptomatic in childhood or later. Early repair of heart defects and surveillance for airway obstruction have been recommended to minimize the risks of heart failure and irreversible pulmonary vascular disease.[39] Surveillance for pulmonary-artery hypertension throughout childhood is indicated, since this disorder is associated with other conditions that are common in patients with DS, including obstructive airway disease (obstructive sleep apnea), gastroesophageal reflux, and obesity, which require assessment and intervention to prevent complications.[39,40]

AIRWAY, PULMONARY, AND HEARING DISORDERS

Airway management in patients with DS is a challenge because of airways that are small for the patient's age, micrognathia, relative macroglossia, tracheal stenosis caused by complete tracheal rings, hypotonia, and obstructive airway disease.[41] As a result, respiratory disorders are common causes of illness and death in affected children and adults.

Social integration and habilitation are important considerations in building on the intellectual abilities of a child with DS and assessing the level of independence that a child or adult is able to achieve. These outcomes depend on optimizing speech and communication. Hearing impairment, which may fluctuate over time, is common in DS (Table 3), and speech development depends on hearing well. Accurate assessment and treatment of hearing impairment are especially important for a child at risk for intellectual disability.[40] Normal or nearly normal hearing can be achieved with otolaryngologic and audiologic interventions.[42]

GROWTH

Weight gain and growth are indications of general health in patients with DS. Syndrome-specific charts for weight, height, and head circumference[43] can be used to monitor weight, height, and head-circumference trajectories. For children 10 years of age or older, the body-mass index chart of the National Center for Health Statistics is used as the best indicator of excess adiposity in this age group.[44] Obesity, occurring in 25% of children and at least 50% of adults with DS, complicates many problems in DS, including obstructive sleep apnea, diabetes, and cardiopulmonary conditions. Surveillance of trends in weight gain allows early detection and intervention to help promote healthy patterns of eating and activity.

HEMATOLOGIC AND ONCOLOGIC DISORDERS

Hematologic abnormalities are common in patients with DS, manifested as transient abnormal myelopoiesis (formerly called transient myeloproliferative disorder) in infancy, iron deficiency in childhood, and an increased incidence of leukemia. Transient abnormal myelopoiesis, a form of myeloid preleukemia, occurs in up to 10% of neonates with DS and is due to mutations in *GATA1*. The disorder, which occurs predominantly in newborns and almost always before the age of 5 years, usually resolves spontaneously, but early detection and monitoring by pediatric hematologic specialists are recommended, since the risk of leukemia among patients with transient abnormal myelopoiesis is 20 to 30%. Leukemia independent of transient abnormal myelopoiesis develops in 2 to 3% of all patients with DS, particularly acute myeloid leukemia, which responds to current therapies, and acute lympho-

Table 3. Incidence of Coexisting Medical Conditions in Patients with Down Syndrome (DS).*

Condition	Incidence	Study
	%	
Congenital heart disease	44 (Including stillbirths)	Freeman et al.[16]
Atrioventricular septal defect†	45	
Ventricular septal defect	35	
Secundum atrial septal defect	8	
Tetralogy of Fallot	4	
Patent ductus arteriosus	7	
Pulmonary hypertension	1.2–5.2	Weijerman et al.[17]
Infections, especially respiratory, due in part to immunodeficiencies	Deaths due to infection, 34–40	O'Leary et al.[18]
Hearing deficits		Kreicher et al.,[19] Park et al.[20]
Conductive	84	
Sensory	2.7	
Mixed	7.8	
Hematologic and oncologic disorders		
Transient abnormal myelopoiesis	≤10 (Resolves spontaneously but is associated with a 20–30% risk of AML)	Taub et al.[21]
Leukemia and tumors	2–3 (Patients with DS are protected against most solid tumors; only testicular cancer is more frequent in such patients than in the general population)	Hasle et al.[22]
Anemia or iron deficiency	Anemia, 2.6; iron deficiency, 10.5 (masked by macrocytosis and elevated MCH)	Dixon et al.[23]
Sleep disorders	65	Hoffmire et al.[24]
Thyroid abnormalities		Pierce et al.[25]
Congenital hypothyroidism	1–2	
Hypothyroidism and Hashimoto's disease in adults	50	
Dysphagia	55	Jackson et al.[26]
Neurodevelopmental disorders		Stafstrom et al.[27]
Seizures	5–8	
Partial seizures	2–13	
Infantile spasms	2 to 5	
Disintegrative disorder‡		Worley et al.[28]
Moyamoya disease§		Kainth et al.[29]
Dementia	At <40 yr of age, <5; by 65 yr of age, 68–80	Wiseman et al.[30]
Autism	7–16	DiGuiseppi et al.[31]
Celiac disease	5.4	Szaflarska-Popławska et al.[32]
Gastrointestinal anomalies	6	Stoll et al.[33]
Juvenile idiopathic arthritis	<1	Juj et al.[34]
Orthopedic problems	2.8	Brockmeyer,[35] Caird et al.[36]
Visual problems	56.8	Roizen et al.[37]

* The incidence percentages are approximate and are from the cited studies, most of which involved large case series. The percentages for subcategories represent the incidence among infants with that particular condition. For example, among patients with congenital heart disease, the incidence of atrioventricular septal defect is 45%. AML denotes acute myeloid leukemia, and MCH mean corpuscular hemoglobin.
† Atrioventricular septal defect is also known as endocardial cushion defect.
‡ The definition of the criteria associated with disintegrative disorder is under development.
§ The prevalence of DS among patients with moyamoya disease is 26 times as high as the prevalence of DS in the general population.[29]

blastic leukemia, which tends to have a poorer outcome in children who have DS than in those who do not.[21]

Epidemiologic studies suggest that DS may provide overall protection against the development of solid tumors. However, testicular cancer occurs more frequently in persons with DS than in age-matched populations.[22]

Iron deficiency is as common in persons with DS as in the general population, but the associated microcytosis may be masked by macrocytosis and an elevated mean corpuscular volume, findings reported in 45 to 66% of children with DS.[23] Testing for ferritin and C-reactive protein or transferrin saturation to assess the need to treat iron deficiency and minimize its potential effects on cognitive and motor development and on sleep is recommended in children with DS.[24]

AUTOIMMUNE DISORDERS

Autoimmune conditions, including Hashimoto's disease, type 1 diabetes, alopecia, celiac disease, juvenile idiopathic arthritis, and vitiligo, occur in disproportionate numbers among persons with DS as compared with age-matched cohorts. Early recognition and treatment of such conditions may minimize complications across the life span. In states where newborn thyroid screening includes only the blood thyroxine level, babies with DS should also have the thyrotropin level measured to detect hypothyroidism. Persons with DS should be tested for thyroid disorders at birth, in early infancy, annually throughout life, and whenever any suggestive symptoms, such as dry skin, constipation, change in growth trajectory, and unexplained weight gain, occur.[15] The incidence of thyroid abnormalities, including persistent hypothyroidism and Hashimoto's disease, among persons with DS is approximately 50% by 45 years of age.[25] Celiac disease also occurs at higher rates among persons with DS than in the general population. A variety of gastrointestinal symptoms and behavioral changes have been attributed to celiac disease in persons with DS, but treatment may not be indicated for those who are asymptomatic.[33,45] Juvenile idiopathic arthritis is another autoimmune disorder that occurs in persons with DS at a higher frequency than in age-matched populations, and early recognition and treatment can prevent complications.[34]

MUSCULOSKELETAL DISORDERS

Skeletal syndromes are common in persons with DS and include dislocation of the hip, patellar dislocation, and planovalgus feet. Atlantoaxial instability is a particularly dangerous complication of DS, since it may lead to cervical cord–medullary compression. Screening for this disorder has not been reliable, and imaging studies do not correlate well with the risk of myelopathy.[46] Early detection depends on neurologic examination and caregiver recognition of changes in gait, new difficulty in the use of hands, bladder and bowel dysfunction, and reduction in overall activity.[15] Evaluation and surgical intervention by a neurosurgeon or orthopedic surgeon who is skilled in the treatment of atlantoaxial instability have been advised.[35] Degenerative diseases of the cervical spine, including spondylosis and cervical spondylotic myelopathy, can develop; if so, they typically occur earlier in adults with DS than in adults without DS.

NEURODEVELOPMENTAL DISORDERS

Intellectual disability and related issues in persons with DS require intervention to ensure a meaningful and happy life. Family involvement and collaboration with caregivers contribute greatly to the outcome. Early intervention by therapists skilled in building on the strengths of infants and toddlers and enrollment of school-age children in an individualized education program in the least restrictive environment have been found to be helpful. Managing the transition from these programs to adulthood is considered to be essential for a satisfying life with DS.

Neurodevelopmental problems, including limited social awareness, decreased motor coordination, an increased incidence of autism spectrum disorder, psychiatric problems, and later in life, dementia, have been recognized.[47] The incidence of these conditions is difficult to determine accurately in the DS population. On an individual basis, assessment for alternative causes of intellectual deterioration should include thyroid dysfunction, disordered breathing during sleep, celiac disease, depression, psychosis, and aggression.[47] The frequency of autism among persons with DS ranges from 7 to 16%[31] in various studies, and the criteria for diagnosis have varied.

Therapy for children with DS who have symp-

toms of autism such as delayed eye contact and lack of joint attention (the ability to share attention with other people, such as following their gaze or their finger pointing) is often delayed. In many cases, the reason for the delay is that the features of autism are confused with common features of DS, a phenomenon referred to as overshadowing.[47]

Most persons with DS have histopathological features of Alzheimer's disease after the age of 40 years. However, such persons usually remain asymptomatic, with cognitive decline developing decades later.[30]

Among persons with trisomy 21 who are older than 45 years of age, dementia is more likely to develop in those who have seizures than in those without seizures. Drugs for the treatment of cognitive decline, including memantine and donepezil, that have been approved for patients with Alzheimer's disease have not had a significant effect in patients with DS.[48]

Children with DS benefit from applied behavior analysis, a method for developing appropriate behavior, but schools and insurance plans often require a diagnosis of autism to access this intervention.[49] Medications for attention deficit–hyperactivity disorder, behavior management, and psychiatric disorders can be effective in children with DS when the diagnostic criteria for these disorders are clearly documented. However, such children are often sensitive to the side effects of these medications and have a response to lower doses than those conventionally prescribed; doses should be increased slowly as needed.[50]

An unusual neurodevelopmental disorder in persons with DS has been termed "disintegrative disorder." It is manifested as autistic-like regression and dementia occurring at an older age than usual for autism (mean age at onset, 11 to 14 years). Patients present with catatonia, depression, delusions, stereotypies, decreased self-care functioning, whispering, and reduced academic skills.[28] Treatment includes supportive care, medication with benzodiazepines, electroshock therapy when indicated, and perhaps immunotherapy.

Behavioral management is often a challenge for the parents or caregivers of children with DS. Toddlers with better receptive than expressive communication skills have a predisposition to tantrums because of frustration. Noncompliance, disobedience, and wandering are other common issues throughout childhood. Counseling and behavioral support have been shown to be useful for families addressing these issues.[47]

Other neurodevelopmental issues include seizures, shuddering (benign, nonepileptic movement of the head and trunk), and moyamoya disease. Seizures occur more frequently in persons with DS (incidence, 8%) than in the age-matched general population.[27] In early infancy, infantile spasms account for the preponderance of seizures, with an incidence of 2 to 5%. The age at which infantile spasms first occur, the time to initiation of treatment, and the time to a treatment response are similar for children who have DS and those who do not, but children with DS are less likely to have subsequent epilepsy.[27] Seizures recur in some patients, and follow-up evaluations are recommended to determine whether movement or behavioral changes are due to seizures. Partial simplex, partial complex, and tonic–clonic seizures occur more frequently in older persons with DS than in older persons in the general population. The cause of the increased frequency of seizures among persons with DS is not understood.

Moyamoya disease is an uncommon vascular abnormality with an increased incidence among patients with DS.[29] It is due to stenosis of the supraclinoid portions of the internal carotid arteries. Children present with alternating hemiplegia or a fixed, unilateral, strokelike deficit, whereas adults more often have cerebral hemorrhage. Cerebral revascularization surgery has been performed in specialized centers.

COMPLEMENTARY AND INTEGRATIVE INTERVENTIONS

The use of integrative medicine is common in families with children who have DS, with an incidence, as reported by caregivers, of up to 38%. Providers are advised to ask families specifically about use of nonprescription medications and supplements. Megavitamins, sicca-cell injections, antioxidant therapies, and green tea extracts have been unadvisedly proposed to treat DS, all with no benefit and with potential harm.[51] Medications, including piracetam and fluoxetine, have been promoted to treat cogni-

tive aspects of DS, but no effect has been shown. Fluoxetine, however, may be an effective intervention for approved behavioral diagnoses in some children.[47]

TRANSITION TO ADULTHOOD

Involvement in community life has become increasingly important as persons with DS survive longer and achieve greater degrees of independence. Education involving inclusion in the classroom alongside typical students of the same age and teaching focused on the strengths of the child or adolescent enhance the progression to adulthood and provide persons with DS the chance to reach their full potential. Many transitions occur across the life span, and guidance in how they can be managed is available.

An emphasis on transitions such as employment, source of health care, and community involvement, as well as on legal issues (e.g., guardianship) and financial support (e.g., social security and trusts), has been found to be essential for the long-term well-being of persons with DS and their families.[52] As life expectancy and quality of life for persons with DS increase, clinical research and development of evidence-based care guidelines for adults are needed.

The most common cause of death in childhood and adulthood remains respiratory infection, in part related to immunodeficiencies. Congenital heart defects cause most deaths in early childhood, and although coronary artery disease occurs in adults, it is less common than in the general population. Dementia contributes to mortality in some studies.[18] Health supervision guidelines published and reviewed regularly by the American Academy of Pediatrics help clinicians and families ensure good care for children with DS, and work is under way to develop similar guidelines across the life span.[15,53]

RESEARCH

To advance research in community involvement, the National Institutes of Health (NIH) has established the Down Syndrome Consortium, a DS registry (DS-Connect),[54] and a research review group. Congress has funded the NIH to encourage research through the INCLUDE (Investigation of Co-occurring Conditions across the Lifespan to Understand Down Syndrome) project.[55] Independent foundations such as the LuMind IDSC Foundation, the Global Down Syndrome Foundation, International Mosaic Down Syndrome Association, and PCORI (Patient-Centered Outcomes Research Institute) are also targeting research efforts in this field.

CONCLUSIONS

The health issues and life trajectory of persons with DS are complex, and the condition is associated with many disparate medical, psychological, and social issues from infancy through adulthood. Persons with DS and their families generally have a positive attitude and express a desire for a high quality of life that builds on the strengths and skills of the affected child or adult. Published guidelines[15,53] provide recommendations and standards to allow persons with DS to reach their full potential.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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