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AHA SCIENTIFIC STATEMENT

Trisomy 21 and Congenital Heart Disease: Impact on Health and Functional Outcomes From Birth Through Adolescence: A Scientific Statement From the American Heart Association

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ABSTRACT: Due to improvements in recognition and management of their multisystem disease, the long-term survival of infants, children, and adolescents with trisomy 21 and congenital heart disease now matches children with congenital heart disease and no genetic condition in many scenarios. Although this improved survival is a triumph, individuals with trisomy 21 and congenital heart disease have unique and complex care needs in the domains of physical, developmental, and psychosocial health, which affect functional status and quality of life. Pulmonary hypertension and single ventricle heart disease are 2 known cardiovascular conditions that reduce life expectancy in individuals with trisomy 21. Multisystem involvement with respiratory, endocrine, gastrointestinal, hematological, neurological, and sensory systems can interact with cardiovascular health concerns to amplify adverse effects. Neurodevelopmental, psychological, and functional challenges can also affect quality of life. A highly coordinated interdisciplinary care team model, or medical home, can help address these complex and interactive conditions from infancy through the transition to adult care settings. The purpose of this Scientific Statement is to identify ongoing cardiovascular and multisystem, developmental, and psychosocial health concerns for children with trisomy 21 and congenital heart disease from birth through adolescence and to provide a framework for monitoring and management to optimize quality of life and functional status.

Key Words: AHA Scientific Statements ■ autism spectrum disorder ■ cognition ■ Down syndrome ■ heart defects, congenital ■ mental health ■ quality of life

Down syndrome or trisomy 21 (T21) is the most commonly occurring aneuploidy, affecting approximately 1 in 800 live births, and ≈35% to 50% of children with T21 are also affected by congenital heart disease (congenital HD).[1] T21 is associated with significant physical, neurodevelopmental, psychological, and functional conditions that co-occur and interact with congenital HD to impact overall health, functional status, and quality of life (QOL) across the lifespan.[1–3] Improvements in cardiac interventions and perioperative management have resulted in greatly improved survival over the past several decades for all infants and children with congenital HD, including those with T21.[4–6] Social determinants of health also influence outcomes in infants and children with T21 and congenital HD; their intellectual disabilities and chronic health conditions contribute to discrimination, bias, and inequity in addition to the effects of race

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and ethnicity, education, or socioeconomic status.[7] Children with T21 and congenital HD are now regularly living to adulthood with improved functional outcomes; therefore, it is important to provide comprehensive, evidence-based management strategies to maximize their functional status and health outcomes. The purpose of this Scientific Statement is to identify ongoing physical, developmental, psychosocial, and functional health concerns in infants, children, and adolescents with T21 and congenital HD, and to provide strategies for monitoring and management to optimize equitable health and QOL.

CARDIOVASCULAR HEALTH

Congenital HD

The most common forms of congenital HD in children with T21 are partial, transitional, or complete atrioventricular septal defects, ventricular septal defects, and atrial septal defects which, in aggregate, constitute ≈70% of cases of T21 with congenital HD.[8] The most common anatomical subtype of single ventricle heart disease in children with T21 is usually a form of unbalanced atrioventricular septal defects.[9] Children with T21 and single ventricle heart disease have much higher risk of short- and long-term mortality compared with children with similar congenital HD and who were euploidic.[9–12] Other lesions frequently seen include tetralogy of Fallot, coarctation of the aorta, and patent ductus arteriosus. With increasing surveillance for T21 and congenital HD during pregnancy, the epidemiology may be shifting, reducing the frequency of more complex forms of congenital HD among live-born infants with T21.[13] This change could also be reflective of improved detection of less complex congenital HD due to advances in prenatal imaging.[14] Advanced maternal age (≥35 years) is associated with higher incidence of T21, but most infants with T21 are born to women <35 years of age due to their increased birth rate.[15]

Overall management of congenital HD in the context of T21 is similar to approaches for affected individuals without T21, with a few notable differences.[8] First, routine echocardiographic imaging is recommended for all fetuses and infants diagnosed with T21. Because some forms of congenital HD, including ones prevalent in T21 such as atrial septal defect or tetralogy of Fallot, may be difficult to discern prenatally,[16] postnatal screening with echocardiography is generally performed even if fetal imaging was normal. Second, the timing and type of procedure (corrective versus palliative) can depend on comorbidities associated with T21. Concerns about pulmonary hypertension, in particular, dictate earlier intervention for infants with posttricuspid shunt lesions. The major surgical risks are due to the adverse effects of earlier onset of elevated pulmonary vascular resistance, which may result from persistent neonatal pulmonary hypertension, earlier onset due to congenital HD, or exacerbated by pulmonary vascular hypoplasia in patients with T21.[8,11,17,18] Respiratory diseases, such as obstructive sleep apnea or aspiration, are also risk factors for development or exacerbation of pulmonary hypertension in children with T21.[19] For patients with single ventricle heart disease and T21, the in-hospital mortality rate for stage I palliative procedures is high ranging from 24% to 57%[9,20] as well as for the Fontan procedure ranging from 12% to 24% but appears to be improving in more recent eras.[21] In comparison, other studies have reported in-hospital mortality rate for stage I palliative procedures ranging from 6.4% for aortopulmonary shunt to 15.6% for the Norwood procedure,[22] and 1.4% to 8.3% for different types of Fontan palliation.[10,22,23] Data support the conclusion that stopping the single ventricle palliation at the bidirectional cavopulmonary anastomosis stage confers a similar mortality outcome as after having a Fontan procedure.[9] This approach must balance risks and benefits, including risks of continued heart failure due to single ventricle volume loading and the potential development of pulmonary arteriovenous malformations. Many children with T21 undergo fenestrated Fontan palliation, which results in some degree of intracardiac mixing and may result in similar risks specific to long-term cyanosis.[24] Long-term survival in children with T21 and single ventricle heart disease was reported as 67% at 10 years, compared with 92% in comparators without heterotaxy but who were euploidic.[9]

Although several studies report that T21 is not associated with increased in-hospital or short-term mortality following surgical intervention for many types of congenital HD,[18,25–28] longer length of stay and respiratory complications are more prevalent in children with T21.[18] In children with complete atrioventricular septal defects, in-hospital mortality for children with T21 is lower than children without T21.[18] Children with T21 who undergo congenital heart surgery, especially ventricular septal defect closure, are more likely to require a permanent pacemaker than children without T21, which confers the need for additional lifelong care and interventions.[29] A recent study found T21 was not a risk factor for long-term, congenital HD–related mortality with biventricular physiology but was a risk factor for all-cause-related long-term mortality.[4] This supports the premise that co-occurring conditions play an important role in long-term survival of children with T21 following cardiac surgery.

Pulmonary Hypertension

The prevalence of pulmonary hypertension is as high as 25% in children with T21 and increases up to 45% in those with congenital HD.[19,30,31] The prevalence of

pulmonary hypertension appears to rise with age, increasing from 6% at 1 year of age up to 15% at 10 years of age.[32] A registry study reported 3- and 5-year survival for children with T21 and pulmonary hypertension as 90% (95% CI, 82%–98%) and 88% (95% CI, 80%–97%), respectively.[31]

The development of pulmonary hypertension in T21 is multifactorial with intrinsic and extrinsic risk factors. Intrinsic factors include abnormal lung development with decreased alveolarization and pulmonary hypoplasia as well as pulmonary vascular dysfunction. Extrinsic factors include congenital HD, upper airway obstruction, chronic aspiration, and recurrent pneumonia.[17,33] In patients with T21, pulmonary hypertension is most prevalent in the first year of life, with persistent pulmonary hypertension of the newborn (a disorder of delayed vascular transition at birth) and congenital HD being the primary drivers of disease.[32] In patients with resolution of pulmonary hypertension, there is a 12% to 16% risk of recurrence later in life, often related to airway and respiratory co-occurring conditions.[19]

Interventions to treat pulmonary hypertension in children, with some consideration specific to children with T21, have been published previously; in children with congenital HD, the impact of unrepaired or residual congenital HD as an important driver of new or recurrent pulmonary hypertension should be considered.[33,34] It is crucial to address other modifiable contributors to pulmonary hypertension in children with T21, such as obstructive sleep apnea, aspiration, and other pulmonary diseases on an ongoing basis; such treatment may resolve pulmonary hypertension, prevent deterioration, or negate the need for pharmacologic therapies. Pharmacologic treatments for pulmonary hypertension in children with T21 lack strong evidence due to a small population and challenges in participating in clinical trials such as the ability to recognize and report adverse events, or concerns about cognitive ability to provide assent (in children) or informed consent (in adults).[31,34] In a registry study of children with T21 and pulmonary hypertension, pharmacotherapy did not differ between children with and without T21.[31] Currently, there are no national pulmonary hypertension screening recommendations specific to children with T21.

Residual Cardiac Lesions

With the high preponderance of patients with T21 and atrioventricular septal defects, the presence of significant residual lesions, most commonly atrioventricular valve regurgitation and less commonly residual ventricular septal defect, confers a potential need for additional reinterventions.[35] Left-to-right shunting and increased pulmonary blood flow due to residual septal defects can also contribute to or accelerate the development of pulmonary vascular disease. Overall, significant residual lesions in the congenital HD population, including those with T21, confer risk for increased mortality and length of stay.[36] Patients with T21 and tetralogy of Fallot develop more significant and earlier pulmonary valve regurgitation following definitive surgical repair and require earlier pulmonary valve replacement.[37,38]

Heart Transplant

Although children with congenital HD and T21 are routinely offered necessary cardiac care, heart transplantation has only recently been offered at some centers, and this practice continues to stir some ethical discussions.[39] Children with T21 are at increased risk of end-stage cardiac disease, attributable to their high incidence of congenital HD as well as an increased prevalence of acquired heart disease, most notably anthracycline-associated cardiomyopathy related to the T21-associated risk for leukemia. Despite this, referrals of patients with T21 for consideration for heart transplantation appear to be disproportionately reduced.[40] Of US centers performing solid organ transplantation, 76% consider T21 as a contraindication due to intellectual delays and disabilities.[41] Ethicists note that intellectual delays and disabilities alone should not exclude patients for consideration of solid organ transplantation.[42] Additional medical concerns raised for patients with T21 in need of heart transplantation include pulmonary hypertension, immunodeficiency, and malignancy risk. Outcome data for heart transplant recipients with T21 are sparse. A recent retrospective review of 26 cases of patients with T21 listed for heart transplantation revealed no differences in waitlist or posttransplant outcomes compared with matched patients without T21.[39] Typical immunosuppressive regimens were used, and rejection, posttransplantation lymphoproliferative disease, and infection were not increased in the T21 cohort.

CO-OCCURRING PHYSICAL CONDITIONS THAT IMPACT CONGENITAL HD

Children with T21 and congenital HD often have complex co-occurring physical conditions that interact with their congenital HD to produce unique health-related considerations. Table 1 describes these co-occurring physical conditions and resulting interactions and implications with congenital HD. Considerations for comprehensive management related to cardiovascular health and co-occurring physical conditions are outlined in Table 2.

Table 1. Co-Occurring Physical Conditions and Interaction With Congenital HD

System	Diagnosis	Signs/symptoms	Interactions/implications with congenital HD
Gastrointestinal	Feeding and swallowing difficulties[43,44]	Fatigue, congestion, slow feeding, choking, desaturation Poor weight gain Failure to thrive Aspiration	Tachypnea due to intracardiac shunt causes uncoordinated suck/swallow/breathe Aspiration may exacerbate pulmonary hypertension Failure to thrive and malnutrition may add risk to cardiac intervention
	Structural gastrointestinal tract anomalies[45] Hirschsprung Duodenal obstruction Imperforate anus TEF	Abdominal distention Vomiting Failure to pass meconium in 48 h TEF: coughing or choking with feeds, vomiting	Possible increased anesthetic risk due to pulmonary hypertension, shunt physiology, or heart failure Aspiration may exacerbate pulmonary hypertension
	Functional anomalies[45,46] GERD Celiac disease Constipation	GERD: vomiting, fussiness, arching Celiac disease: vomiting, diarrhea or constipation, bloating, abdominal pain Constipation: straining with stooling	Nutritional deficiencies and malnutrition may complicate cardiovascular management
Respiratory	Structural abnormalities[45,47] Macroglossia Laryngomalacia Tracheomalacia Tonsillar and adenoidal hypertrophy Tracheal ring	Noisy breathing Unusual sleeping position Snoring Respiratory distress	Respiratory depression from sedation or general anesthesia may complicate periprocedural course Respiratory depression may exacerbate pulmonary hypertension Potential for challenging intubations
	Recurrent upper and lower infections[45,47]	Congestion Coughing Wheezing Respiratory distress	Increased risk for severe illness with significant congenital HD
	Sleep-disordered breathing or OSA[47]	Snoring Breathing pauses Restlessness Unusual sleeping position Excessive sleepinessand daytime fatigue	Congenital HD + OSA increases and exacerbates pulmonary hypertension[46]
Endocrine	Thyroid dysfunction[48–51]	Weight changes High or low cortisol levels Tachycardia or bradycardia Fatigue or insomnia	May require stress dose steroids May require prolonged mechanical ventilation or higher vasoactive support[52]
	Diabetes[53,54]	Symptoms of hypo- or hyperglycemia	Anticipate cardiopulmonary bypass effect on glucose levels TGC not demonstrated to improve congenital heart surgery outcomes[55] TGC studies excluded patients with diabetes
Hematologic/oncologic	Hematologic[56] Polycythemia Macrocytosis Thrombocytopenia Thrombocytosis Leukopenia Leukemoid reaction Oncologic[57,58] Transient myeloproliferative disorder Acute leukemia Germ cell tumors	Frequent or recurrent infections Unexplained fatigue or lethargy	May complicate recovery from cardiac procedures Hematologic malignancies may complicate organ transplant outcomes
Neurologic	Hypotonia[2]	Generalized reduced muscle strength	May adversely impact feeding ability as well as gross/fine motor milestone development
	Seizures[45]	Infantile spasms: brief jerking movements lasting seconds Other types of seizures: tonic-clonic or partial	May add to developmental delay associated with congenital HD

(*Continued*)

Table 1. Continued

System	Diagnosis	Signs/symptoms	Interactions/implications with congenital HD
Sensory	Reduced visual acuity[59]	Squinting Clumsiness Need to sit close to screen Cloudy lens Abnormal red reflex Abnormal object tracking	May also be related to neurologic complications of congenital HD May complicate neurodevelopmental assessment and trajectory
	Hearing impairment[60]	Lack of response to sound Recurrent otitis media Speech delay	Consider potential ototoxic effect of medications, neurologic complications of congenital HD May complicate neurodevelopmental assessment or trajectory

GERD indicates gastroesophageal reflux disease; HD, heart disease; OSA, obstructive sleep apnea; TEF, tracheoesophageal fistula; and TGC, tight glycemic control.

Gastrointestinal and Feeding Difficulties

Over 75% of neonates with T21 experience feeding and swallowing difficulties due to dysphagia, gastroesophageal reflux, hypotonia impacting neuromotor coordination, and anatomic factors including small jaw, macroglossia, and high palatal arch that adversely impact the acquisition of oro-motor feeding skills.[43] Sequelae include poor weight gain, failure to thrive, and aspiration with associated respiratory complications.[44] Tachypnea and increased work of breathing due to congenital HD–related pulmonary overcirculation compromises coordination of the suck-swallow-breathe sequence and increases metabolic demands, resulting in fatigue and reduced oral intake. Nutritional supplementation is often needed in the form of increased caloric density of enteral feeds or placement of a durable feeding tube (nasogastric or gastrostomy). Breastfeeding an infant with T21 and congenital HD can be challenging due to hypotonia and tachypnea related to heart failure; 1 study reported the median breastfeeding duration in infants with T21 and congenital HD was 30 days, and only 38.7% received breast milk for at least 6 months.[63] Nonpharmacological interventions and therapies for feeding issues and other limitations in children with T21 and congenital HD are described in Table 3.

T21-associated congenital anomalies of the gastrointestinal tract necessitating surgical intervention in infancy include Hirschsprung disease (2%–15%), duodenal obstruction (5%), imperforate anus (3%), and tracheoesophageal fistula (1%).[45] Pathophysiologic disturbances in the gastrointestinal tract in individuals with T21 are felt to be related to abnormal development of the enteric nervous system, similar to the influence that T21 genetic variation has on the central nervous system development.[80] The most prevalent functional disorder in individuals with T21 is chronic constipation due to Hirschsprung disease, celiac disease, or hypothyroidism in addition to behavioral causes.[45] Hypotonia affects the smooth muscles of the gastrointestinal tract and contributes to both constipation and gastroesophageal reflux disease. The prevalence of celiac disease in individuals with T21 is 6 times greater than in the general population.[46,81] Untreated celiac disease can result in nutritional deficiencies, anemia, and malnutrition. Children with T21 may have a lower risk of dental caries than children without T21[82] but have a much higher incidence of periodontal disease,[83] which may be an avenue for the development of infective endocarditis in a population already at risk due to congenital HD.[84]

Respiratory

Over 50% of children with T21 will develop sleep-disordered breathing or obstructive sleep apnea compared with <5% of the general pediatric population.[47] Respiratory symptoms and illness may be exacerbated by silent or recurrent aspiration.[2,45,47] Co-occurring respiratory conditions also commonly cause or exacerbate pulmonary hypertension in children with T21.[2,45] Airway structural abnormalities may complicate care related to endotracheal intubation, in the context of additional risks due to pulmonary hypertension and other co-occurring conditions.[85] A large study of anesthetic complications in children with T21 reported a higher incidence of perioperative respiratory adverse events, most significantly obstructed ventilation, compared with propensity-matched controls.[86] Structural anomalies predispose children with T21 to both upper and lower respiratory illness, such as respiratory syncytial virus, bronchiolitis, COVID-19, and pneumonia, and are often more severe than in typically developing children, especially for those with concomitant immune system abnormalities.[45,47,87]

Endocrine

Children with T21 have a higher incidence of endocrine disorders, including thyroid dysfunction as well as type 1

Table 2. Considerations for Management of Cardiovascular and Co-Occurring Physical Conditions

Focus	Specific considerations
Congenital HD and surgical considerations	Need for earlier intervention due to pulmonary hypertension
	Consider impact of co-occurring conditions on physiologic state and potential complications
	Minimize residual defects early in the perioperative course[36]
	Consider earlier cardiac magnetic resonance imaging to quantify need for pulmonary valve replacement[37]
Pulmonary hypertension	Consider cardiac catheterization to document baseline pulmonary hypertension and effect of therapy
	Close monitoring for treatable causes of pulmonary hypertension before and after congenital HD intervention[17,19]
	Long-term follow-up for recurring pulmonary hypertension is necessary[19]
Single ventricle heart disease	High risk for in-hospital and late mortality
	Incomplete palliation may be considered in children with elevated pulmonary vascular resistance; risk/benefit analysis crucial
Gastrointestinal and feeding difficulties	Screen clinically for feeding or swallowing problems
	If feeding/swallowing concerns, consider speech/feeding therapy consult, video swallow study, or flexible laryngoscopy to determine if feeding modifications are indicated
	Dietician consult to optimize nutrition
	Partner with cardiac anesthesia during noncardiac procedures
Respiratory	Routinely evaluate snoring, breathing pauses, restlessness, unusual sleeping position, excessive sleepiness, and fatigue[2]
	If concerned about OSA or pulmonary hypertension, refer to an otorhinolaryngologist or pulmonologist for further evaluation, including a sleep study[2]
	RSV prophylaxis (palivizumab or nirsevimab-alip) should be considered[2,47]
	Encourage adherence to AAP vaccination schedule[61]
	Anticipate need for additional respiratory support during recovery from sedation and anesthesia
Endocrine	Thyroid function tests as per AAP guidelines
	Monitor BMI and consider the impact of co-occurring conditions and physical activity on the development of overweight/obesity[62]
	Use T21-specific growth charts; growth charts for typically developing children underestimate weight for age *Z* score
	Preoperative optimization of noncardiac conditions is recommended[8]
Hematologic/oncologic	Hematology referral for concerning CBC values
	Consider potential for hematologic complications when considering heart transplant
Neurologic	Consider neurologic consultation/referral for any concerning neurologic findings before elective cardiac intervention
	Prioritize timely electroencephalogram in the event of abnormal movements to rule out seizures or hypsarrhythmia
Sensory	Ensure that audiology referrals for failed newborn hearing screen are completed
	Coordination and communication for assessment of vision and hearing, along with referrals for treatment

AAP indicates American Academy of Pediatrics; BMI, body mass index; CBC, complete blood count; HD, heart disease; OSA, obstructive sleep apnea; RSV, respiratory syncytial virus; and T21, trisomy 21.

and type 2 diabetes, than children without T21. Thyroid dysfunction has a prevalence between 8% and 49%[48] and presents in several forms, including subclinical hypothyroidism (12%–33%), congenital hypothyroidism (1%–4%), acquired hypothyroidism (0.3%–3.2%), and hyperthyroidism (0.3%–1.4%).[49] Overall risk of developing thyroid dysfunction increases 10% yearly and is up to 50% in adulthood.[48] Transient thyroid dysfunction has been described following cardiopulmonary bypass,[50,51] and lower serum thyroid concentration has been associated with prolonged mechanical ventilation and higher vasoactive support.[50,52]

Type 1 diabetes tends to develop earlier in children with T21.[53,54] The impact of diabetes or insulin resistance in children with T21 and congenital HD has not been reported, other than an association of type 2 diabetes and obesity. The use of cardiopulmonary bypass and glucocorticoids is associated with hyperglycemia in children with congenital HD; careful observation and intervention for hyperglycemia is warranted in some scenarios, but tight glycemic control outside of patients with diabetes has not been demonstrated to be beneficial following congenital heart surgery.[55] Children with T21 are also

Table 3. Nonpharmacological Interventions and Therapies for Children With T21

Specific therapy	Exemplar areas of focus
PT, OT[64]	PT: Improve gross motor development, balance, and coordination
	PT: Improve specific neuromuscular weakness or deficit
	OT: Increase independence and participation in daily activities and skills; feeding in infancy, play and school activities in childhood, independent living in young adulthood
	OT: Improve sensory integration and socialization skills, dealing with anxiety in social/medical situations
Feeding (speech/OT)[64]	Identify infants at risk for feeding dysfunction
	Perform feeding assessments and interventions
	Develop oro-motor oral feeding skills
	Dietician to promote optimal nutrition
	Lactation support to promote breastfeeding and use of human milk[65,66]
	Assess feeding and drinking skills in childhood
Speech[64]	Identify speech delay early to implement intervention
	Use of alternative communication if needed (eg, sign language)
	Identify sensory deficits early and facilitate evaluation
	Interventions to improve speech clarity, vocabulary, and comprehension
Music therapy[67]	Improve communication skills, emotional expression, motor skills and coordination, and social interactions[67]
Behavioral and psychological therapies[68–74] (limited evidence in children with T21)	Anxiety, depression, behavioral difficulties: tailored, developmentally responsive psychological therapies, including cognitive-behavioral therapy
	Individually tailored behavioral therapies enhance communication and social skills, as well as participation in daily living activities
	Applied behavioral analysis or other therapies for children with autism spectrum disorder may enhance communication, reduce maladaptive behavior, improve social skills
	Psychological and peer support programs for parents, caregivers, and other family members (eg, siblings), as well as parenting interventions to assist in understanding and supporting the child's needs and development
Exercise and physical activity	Exercise prescription to improve cardiovascular health and reduce overweight/obesity[75,76]
Neurodevelopmental team[77,78]	Neurodevelopmental follow-up throughout infancy, childhood, and adolescence is crucial
	Incorporate family-centered, developmentally supportive, and trauma-informed care
	Periprocedural and inpatient care should include consultation with the cardiac neurodevelopmental care team, including child life specialists and psychologists
	Risk assessment, screening and referral guidelines for neurodevelopmental follow-up are available for children with congenital HD and children with T21[2,3]
Education support[74,79]	Individualized education plans and inclusion in mainstream classrooms
	Educational support may continue to 21 years of age

Interventions and therapies, including physical, speech-language, occupational, behavioral, and psychological therapies, should be offered to children with T21 and their families as early as possible and based on the child's individual strengths, weaknesses, needs, and preferences.

HD indicates heart disease; OT, occupational therapy; PT, physical therapy; and T21, trisomy 21.

at higher risk of autoimmune disorders, lower bone mineral density, hypergonadotrophic hypogonadism, growth retardation, and obesity.[88,89] Individuals with T21 are at higher risk than the general population of being overweight or obese during adolescence and adulthood. Contributing factors include low resting metabolic rate, inactivity, thyroid dysfunction, and unhealthy dietary behaviors that may result in development of pulmonary hypertension, obstructive sleep apnea, dyslipidemia, and type 2 diabetes.[90]

Hematological

T21 affects hematopoiesis, and many children with T21 either have quantitative or qualitative disorders within the myeloid compartment, even if clinically insignificant or resolved in early infancy.[57] Oncological issues, such as transient myeloproliferative disorder, acute leukemia, and occurrence of germ cell tumors, can also be seen.[57] Although transient myeloproliferative disorder typically resolves without intervention, it is sometimes associated with life-threatening symptoms such as hyperviscosity, hepatosplenomegaly causing respiratory compromise, or other organ dysfunction; infants with hepatic involvement or life-threatening symptoms were more likely to develop acute myeloid leukemia and had reduced long-term survival.[58] Patients with T21 and congenital HD were also more likely to die from leukemia and other cancers than those without T21 and similar congenital HD (8.9% versus 2.4%).[4]

Neurologic

Hypotonia, present in all individuals with T21, may impair oral feeding ability as well as delay gross and fine motor milestone achievement.[2] Infantile spasms occur more commonly in infants with T21 than in infants without T21; early treatment may improve outcomes, but relapse is also more common in children with T21.[45] Other forms of epilepsy are also more common in children with T21 than children without chromosomal abnormality; causes can include neurological complications of congenital HD and its treatment.[45]

Sensory Deficits

Sensory deficits are important to overall functional status and negatively affect the development of language and communication, cognition, and social behavior. Children with T21 commonly have reduced visual acuity due to multifactorial causes including refractive errors, strabismus and amblyopia, nystagmus, hypo-accommodation, optic nerve abnormalities, and congenital or early-onset cataracts.[59] Children with T21 and congenital HD may also be at risk for visual problems related to neurological complications of their congenital HD and its treatment. Hearing loss is common in children with T21; a large audiogram database study reported 921 of 1088 (85%) children with T21 (including 515 with congenital HD) had hearing loss, with 19% of these characterized as having moderate-to-profound hearing loss.[60] Language development is often delayed in children with T21, including acquisition of vocabulary as well as speech intelligibility, and hearing loss contributes to these difficulties.[91] The presence of congenital HD adds to risk for hearing loss due to complications such as perioperative neurological injury or the use of ototoxic medications. Nonpharmacological therapies for children with T21 and congenital HD and sensory deficits are described in Table 3.

NEURODEVELOPMENTAL, BEHAVIORAL, AND PSYCHOLOGICAL HEALTH

Among infants and children with T21, between one-quarter and one-third experience behavioral difficulties, and the reported prevalence of psychiatric disorders, including autism spectrum disorder, depression, and attention-deficit hyperactivity disorder, varies widely, from 6% to >50%.[92,93] Both T21 and congenital HD have been separately shown to increase the risk of neurodevelopmental conditions and mental health conditions in affected children. To date, no published studies of psychological outcomes have focused on individuals with both T21 and congenital HD.[68] Management considerations related to neurodevelopmental, behavioral, and psychological outcomes are shown in Table 4.

Autism Spectrum Disorder

Autism spectrum disorder is a neurodevelopmental condition characterized by social interaction and communication difficulties, and restricted or repetitive behaviors, interests, or activities. Typically diagnosed in early childhood, autism spectrum disorder is a lifelong condition and is highly heterogeneous in cause and phenotype. A small percentage (<10%) of children diagnosed with autism spectrum disorder, usually those with higher cognitive abilities and who have received early intervention, may no longer meet diagnostic criteria for autism spectrum disorder in young adulthood, but this has not been reported in children with T21.[102] Among children with T21, the prevalence of autism spectrum disorder is substantially higher (18.2% overall and ranging from 5% to 42%) than in the general population (≈2%).[103] Although chromosomal regions other than chromosome 21, as well as specific genes, have been implicated in modifying the likelihood of developing autism spectrum disorder in this population, the exact genetic mechanisms underlying this association with T21 are still under investigation. Autism spectrum disorder and congenital HD are strongly linked[104–106]; a recent meta-analysis indicated that having congenital HD almost doubled the odds of autism spectrum disorder compared with unaffected children.[94] Genetic, perinatal, and early cognitive and developmental delays are thought to contribute to the risk of autism spectrum disorder among patients with congenital HD.[94]

It can be difficult to diagnose autism spectrum disorder in children with T21 due to overlapping features and communication difficulties associated with both conditions. Historically, diagnostic criteria for autism spectrum disorder did not fully capture the specific presentation in this population. Diagnostic evaluation involves medical and neurological examination, performance-based assessment of the child's neurodevelopmental abilities, observation of the child's behavior, in-depth interview with caregivers about the child's behavior and development including administration of age-appropriate measures, and assessment of developmentally appropriate skills. Screening measures for autism spectrum disorder in children with T21 are imperfect, with lower specificity in children with T21, especially among those with lower receptive language skills, highlighting the importance of specialist evaluation.[107–109] Overall, research suggests children with T21 who meet screening criteria for autism spectrum disorder show similar profiles of communication and repetitive behaviors, but tend to have milder social difficulties than children without T21.[95,110]

Table 4. Considerations for Management: Psychosocial and Psychological Aspects of Care

Focus	Specific considerations
Neurodevelopmental, behavioral, and psychological health	
Autism spectrum disorder[94,95]	Awareness of differences in autism spectrum disorder in children with or without T21 is important to ensure correct diagnosis and early access to specialist intervention and education services.
Other mental health conditions[96]	Evaluate for nonpsychiatric causes in addition to comprehensive mental health evaluation.
	Refer for specialty diagnosis and interventions.
Neurodevelopment and intellectual disability[77,97]	A lifespan approach is essential to understanding neurodevelopmental outcomes and intellectual disabilities of individuals with T21 and congenital HD.
	It is unknown if a cardiac neurodevelopmental follow-up clinic is preferable to a T21-specific clinic, and many resource-limited settings may not have both options.
Functional outcomes and quality of life	
Functional outcomes	Assistive devices and technology to enhance learning or make tasks easier should be considered at all ages.
	Consider transition education programs to foster independence.
	Therapeutic interventions, such as physical therapy, should be cognizant of potentially reduced exercise tolerance due to heart failure or cyanosis, as well as sternal or prone positioning precautions in the early recovery from congenital HD surgery.
Quality of life	Family-centered and individualized psychological and educational interventions should be offered as early as possible and throughout the continuum of care to support psychological well-being as well as realistic functional outcome expectations.
Caregiver stress	Assist families to identify resources and services for support and respite if identified as a need.
Family-centered care and the medical home	
Care coordination and access to services	Dedicated care coordinators are vital to provide coordinated care within and between members of the medical home and children and their caregivers.
	Standards for care coordination should be used to develop high-quality care services and to measure outcomes.
	Palliative care consultation as appropriate.[98]
Transition to adult primary and specialty care	Preparation for transition should start early in adolescence and continue beyond the conclusion of pediatric care, until the individual with T21 feels well-established in adult care.
	Web-based congenital HD-specific transition tools may be helpful. Transition practices must consider the adolescent's cognitive capacity, effective learning methods, and decision-making capacity.
Adult cardiovascular risk	Ongoing evaluation for pulmonary hypertension is necessary.
	Cardiovascular risk profile may be different from adults with congenital HD and without T21.
	Screening for early-onset dementia and Alzheimer disease is appropriate.
Planning for the future	A decision-making capacity assessment should be completed for all individuals with T21 as they near the age of consent.
	Consider options to provide needed decision-making support.

Examples of web-based transition tools include: (1) Pediatric to Adult Care Transitions Initiative[99] (available at: https://www.acponline.org/clinical-information/high-value-care/resources-for-clinicians/pediatric-to-adult-care-transitions-initiative), (2) I Heart Change[100] (available at: https://iheartchange.org/), and (3) Got Transition[101] (available at: https://www.gottransition.org).

HD indicates heart disease; and T21, trisomy 21.

Interventions and educational therapies, including a range of specialized services for children with T21 should be offered as early as possible to maximize functional independence and reduce problem behaviors (see Table 3).[102] Early intervention programs that address language and social communication skills[111] have shown promise in improving outcomes for children with T21 and autism spectrum disorder.

Attention Deficit/Hyperactivity Disorder and Psychiatric Conditions

Children with congenital HD have been reported to have a nearly 3-fold increase in attention deficit/hyperactivity disorder (ADHD), compared with children without congenital HD.[112] ADHD can be difficult to diagnose in children with T21, and reports of the prevalence of ADHD in this population vary. One small study diagnosed ADHD in 44% of children with T21,[113] whereas another large database study of children and adults with T21 (n=6078) reported a lower prevalence of ADHD among individuals with T21 compared with age- and sex-matched individuals without T21.[114] In this study, other mental health conditions, such as mood disorders (including depression), anxiety disorders (including obsessive compulsive disorder), schizophrenia, and psychosis were more prevalent among individuals with T21 compared with controls, but specific prevalence in children and adolescents with T21 has not been well studied.[96,111] An important consideration is that many

other conditions commonly present in children with T21 can mimic signs of psychiatric disorders, such as sensory deficits, celiac disease, thyroid dysfunction, and sleep disorders, highlighting the importance of careful and comprehensive evaluation.[115] Children with congenital HD are also at increased risk of mental health disorders such as anxiety and depression, compared with children without congenital HD; however, the presence or absence of T21 in this study's participants was not reported.[116]

Intellectual Disability and Neurodevelopment

Individuals with T21 experience developmental delay, intellectual disability, and early onset of neurodegeneration and dementia, including Alzheimer disease.[117] Most children present with mild-to-moderate intellectual disability, with a mean IQ of ≈50 (range, 35–70), with fewer having severe intellectual disability.[118] However, children with mosaic T21 can have a mean IQ of ≈70,[119] which emphasizes the genetic variability in intellectual disability.

The cognitive phenotype in children with T21 can differ, with prominent deficits in attention, executive function, expressive language, verbal processing, and memory.[97] Although these deficits occur in the presence of multiple co-occurring medical conditions, the extent to which specific conditions influence cognitive ability is unclear.[97] Few reports in children with T21 identify congenital HD,[120] obstructive sleep apnea,[121] epilepsy,[122] and autism spectrum disorder[123] as having the greatest impact on cognitive outcomes. Children with co-occurring genetic conditions and congenital HD have the highest prevalence of developmental delays compared with other children with congenital HD and are identified as a high-risk group for ongoing neurodevelopmental evaluation.[3] However, toddlers with T21 and congenital HD were less likely to attend cardiac neurodevelopmental follow-up than other toddlers with congenital HD, although it is possible that toddlers with T21 and congenital HD underwent neurodevelopmental evaluation at T21-focused follow-up clinics.[89] Cardiac neurodevelopmental follow-up clinics have a unique focus on the effects of congenital HD on neurodevelopment, whereas T21-focused clinics may have less expertise in the cardiac aspects of care. Regardless of where neurodevelopmental follow-up occurs, it is important to ensure that it takes place. To date, there are no published recommendations for neurodevelopmental risk assessment, screening, and referral specific to children with both congenital HD and T21; absent these recommendations, clinicians should consider using guidelines available for children with congenital HD and for children with T21, based on assessment of the greatest need.[2,3]

FUNCTIONAL OUTCOMES AND QUALITY OF LIFE

The focus of clinical care and research involving children with T21 and co-occurring conditions, such as congenital HD, has shifted from survival to improving functional outcomes and QOL. Considerations for management related to functional outcomes and QOL are described in Table 4.

Functional Outcomes

To date, there are no published studies that address functional outcomes in children with both T21 and congenital HD. Although children with T21 qualify for many types of early intervention and special education services, inclusion in mainstream schools with appropriate educational support is the norm.[124] Inclusive education strategies result in improved language and academic skills.[79] Early speech interventions can assist in improving communication and autonomy.[125] Physical and occupational therapy may improve gross and fine motor skills, increase independence in activities of daily living, and improve social skills and sensory integration in children with congenital HD as well as children with T21.[3,64]

Small studies have found teacher-reported executive functioning and behavioral difficulties, such as aggression and attentional problems, are associated with lower school functioning in children with T21.[124,126] With the help of specialized educational programs and support services, many children with T21 graduate from high school and take college courses, and more than half of adults hold jobs.[125,127] The most common types of jobs identified were in a restaurant or food service, office settings, cleaning, and grocery stores.[127] Children with T21 and congenital HD will likely have an individualized education plan in place, which in many states can also include public school services until 21 or 22 years of age, which may help further develop adaptive or occupational skills.

Individuals with T21 vary in the number and type of daily living activities they can complete, often due to variation in physical and mental health, cognitive abilities, and social skills. Fewer adults with T21 cook independently, whereas some are able to bathe and shower, most can brush their teeth, toilet, and eat independently.[127] Some individuals with T21 can live independently, whereas others require supervised housing.[127]

Quality of Life

A recent study showed children with T21 and congenital HD have similar parent-proxy–reported health-related QOL to children with T21 without congenital HD.[128] Others have found lower parent-reported

health-related QOL for children with congenital HD and a chromosomal abnormality compared with children with congenital HD and no chromosomal abnormality, especially in terms of physical and school functioning.[129] When medical treatment for a minor child would result in both benefits and burdens to the child, the parents' subjective views about the child's QOL are usually prioritized given their role as primary caregivers. The child's assent should also be sought when appropriate.[130] In a recent systematic review, many adults with T21 reported a wish to become more independent and self-determined, have friendships and intimate relationships, be included in the community, and use their human rights.[131] In addition, self-reported QOL among adults with T21 was higher than caregiver proxy reports.[131]

Congenital HD accompanied by a genetic condition has been identified as a potential trigger for specialty palliative care consultation.[98] Symptom management, advanced care planning, decision-making support, and end-of-life considerations (if appropriate) are foci for palliative care interventions to improve QOL.

Caregiver and Family Stress

Few studies of caregiver and family stress have been published in the setting of both T21 and congenital HD; expert opinion as well as evidence in populations of children with T21 or congenital HD provide support for this section. Caring for a child with T21 and congenital HD can bring tremendous joy and love but can also place emotional and practical demands on caregivers and family.[132,133] At the time of diagnosis, parents and family members often describe a range of emotions, including shock, worry, grief, and uncertainty about the future.[134,135] Parents of children with critical congenital HD report high levels of posttraumatic stress symptoms, depression, anxiety, and psychological distress.[136] Coming to terms with 2 diagnoses requires time and support. Managing the medical needs of a child with T21 and congenital HD can feel overwhelming; navigating frequent medical appointments, procedures, hospital stays, and specialized care within complex health care systems, often with multiple health care professionals, compounds logistical, financial, and psychological stress. Meeting the child's educational, therapeutic, and social needs also requires additional time, resources, and advocacy.

Balancing work, caregiving, and self-care may be especially challenging for parents and families. Few studies have examined family psychosocial outcomes associated with caring for a child with T21 and congenital HD.[132] One study reported relatively low levels of marital distress in parents of children with T21, and found that stress mediated the relationship between respite care and marital quality.[137] One caveat of respite care in children with T21 and congenital HD is that respite caregivers may need to have some additional competency such as medication administration. Connecting with other caregivers of children with T21 and congenital HD, through either support groups or online communities, can reduce feelings of isolation and foster emotional wellbeing, information sharing, and a sense of belonging. Siblings of a child with T21 and congenital HD may also experience a range of emotions, including jealousy, resentment, or concern for their brother or sister. Providing support and addressing the needs of siblings is an essential component of family-centered care.[78,138]

FAMILY-CENTERED CARE AND THE MEDICAL HOME

The foundations of family-centered, developmentally supportive care include care coordination and communication, a medical home, equity and inclusivity, and transition planning. Figure 1 depicts a comprehensive, family-centered, developmentally supportive care model for children with T21 and congenital HD and their families. Management considerations specific to family-centered care and the medical home are outlined in Table 4.

Care Coordination and Access to Services

Coordination between primary and specialty care providers across all care settings plays an important role in the management of individuals with T21. The medical home serves as a central hub for managing and coordinating the care needs of individuals with complex medical conditions by coordinating with specialist providers and promoting continuity of care, family-centered care, health promotion, and advocacy.[139–141] Effective care coordination through a medical home improves health care access; reduces delays in care, hospitalizations, and health care costs; enhances care satisfaction; and improves overall health outcomes in individuals with T21.[139–142] Figure 2 describes online services that may be helpful for families and children with T21 and congenital HD.

Standards for care coordination for children and youth with special health care needs are in place and are also applicable to a subset of children and youth with special health care needs identified as having medical complexity, which would include children with T21 and congenital HD.[145] The standards were developed through a lens of health equity, family-centered care, cultural competence, and

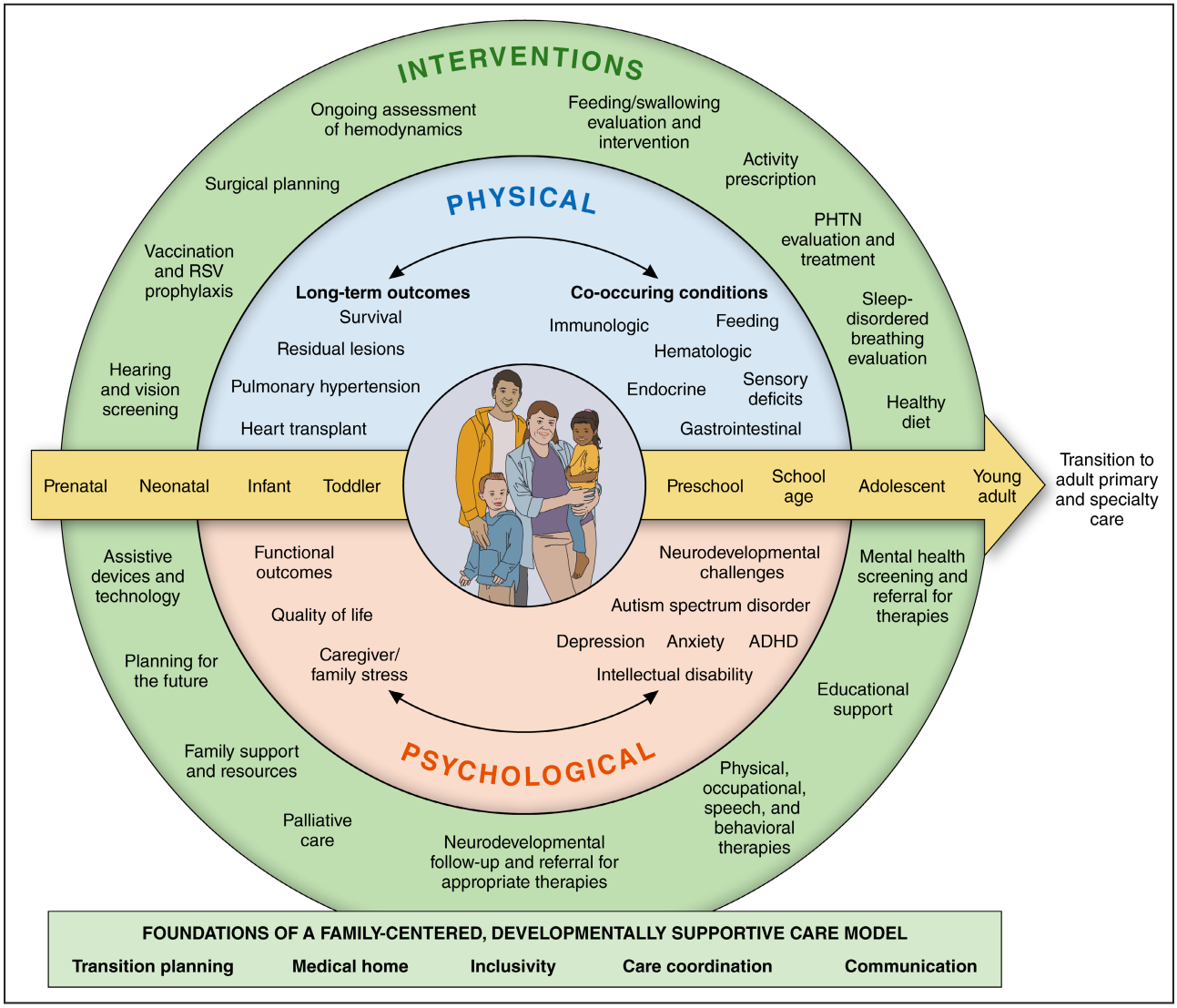

Figure 1. A family-centered, developmentally supportive care model for children with trisomy 21 and congenital heart disease from birth through adolescence.
ADHD indicates attention deficit/hyperactivity disorder; PHTN, pulmonary hypertension; and RSV, respiratory syncytial virus.

evidence-based practices. The 6 standard domains include (1) screening, identification, and assessment of a child's needs; (2) shared plan of care; (3) team-based communication; (4) child and family empowerment and skills development; (5) care coordination workforce, and (6) care transitions.[145]

Care coordination for children with T21 and congenital HD must encompass not only health care settings and providers, but also community and school settings and educators. One highly successful program for children with congenital HD leverages educator expertise to become the information hub between families, schools, health care settings, and the community to help implement educational, behavioral, and health supports in the child's school.[146] Funding such programs remains challenging.

Disparities in health care access and outcomes, and health inequities, are important drivers of outcomes for all children with congenital HD.[7] Children with T21 and congenital HD face additional sources of bias and discrimination. The Americans With Disabilities Act of 1990 broadly prohibits discrimination based on the presence of an individual's disability,[147] although there are significant opportunities for improvement. Implicit bias and stereotyping based on T21 phenotypical facial features has been identified in implicit association testing.[148] Special Olympics International recently initiated a campaign called The Revolution Is Inclusion to promote equity, belonging, and inclusion for people with intellectual disabilities, including children with T21.[149] In addition, the National Institutes of Health has designated people

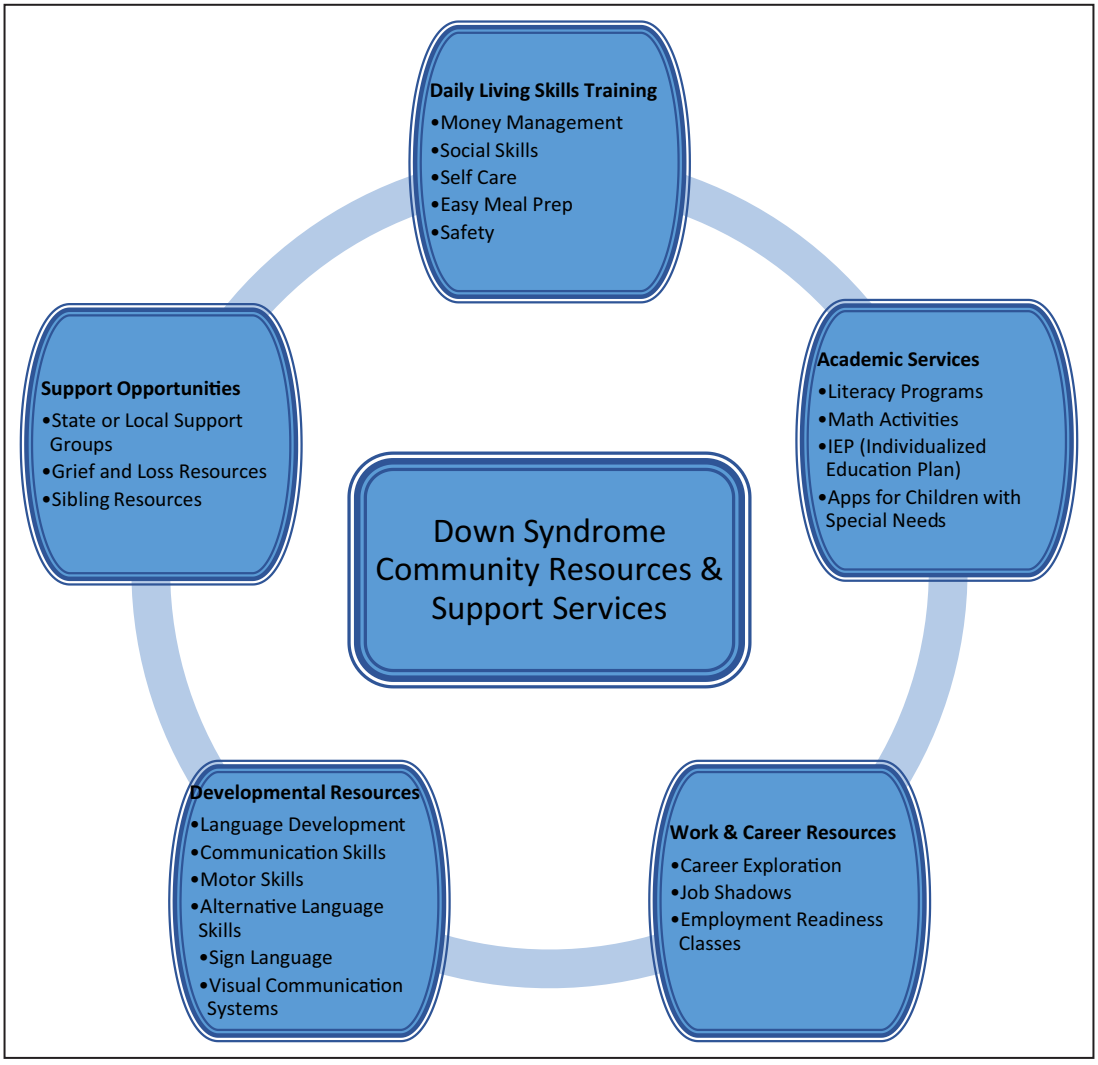

Figure 2. Online support and resources for children with trisomy 21 and congenital heart disease and their families.
Content courtesy of: National Down Syndrome Society Resources[143] and Support and the National Association for Down Syndrome Resources.[144]

with disabilities as a health disparity population, calling for research to understand the multiple levels of disparities experienced and to design interventions to address these inequities.[150]

Transition to Adult Congenital Cardiac and Primary Care

The importance of successful transition of care from pediatric to adult congenital HD care has been well documented.[151,152] Transition can be more challenging for adolescents with congenital HD and T21 due to their multiple comorbidities, intellectual disability, and multifaceted care needs. Increased medical complexity and neurodevelopmental disorders have been associated with the provision of fewer transition services, poor experiences, loss to follow-up, and worse health outcomes for adolescents with T21.[153]

Unique challenges in this population include identifying appropriate models of autonomy, self-management, and education training. A decision-specific capacity assessment by experienced individuals should be provided for all individuals with T21 as they near 18 years of age, along with decision supports to ensure appropriate informed consent.[8] Based on this assessment, guardianship or power of attorney may be required for some individuals with T21, but other options may be appropriate to consider including supported decision-making strategies, advanced directives, and a special-needs trust.[154,155] Legal considerations of these supports vary from state to state. To be effective, transition practices need to be patient-centered, developmentally and

cognitively appropriate, flexible, and well coordinated, with input from the adolescent, parents or guardians, and both the primary and specialty medical providers.[156] Recommendations for successful transition include maintaining insurance coverage, using a transition readiness assessment, developing a portable medical summary, establishing a formal transition program, and using a transition coordinator.[155,157]

Cardiovascular Risk in Adults

The primary cardiovascular risks for adults with T21 arise from sequelae of congenital HD, as well as pulmonary hypertension.[8] Cardiac and noncardiac comorbidities are typical for those encountered for adult congenital HD survivors generally. Due to the increased rates of childhood leukemias that are treated with anthracyclines, survivors are at risk for cardiomyopathy.[158] The cerebrovascular trait moyamoya arises more frequently among individuals with T21, with approximately half of cases presenting in adulthood.[159,160] These concerns lend support to the need for successful transition to adult congenital cardiac care for individuals with T21 and congenital HD.

With improving survival of individuals with T21, studies have examined the risks for acquired cardiovascular disease common in the general population. Adults with T21 appear to be at reduced risk for hypertension, hypercholesterolemia, coronary artery disease, and diabetes.[159,161,162] This is notable, because adults with T21 are at substantially increased risk for obesity. The reasons for this altered cardiovascular disease risk profile have not been elucidated, and neither is it clear whether routine cardiovascular care guidelines apply given the reduced risks.

Planning for the Future

A person-centered, shared decision-making model that considers family demands, perceptions, resources, communication, and coping resulting from a child having T21 and congenital HD should be used when planning care.[163]

People with T21 who express a wish to explore family planning should understand that infertility, especially among men, is common.[164] Reproductive decision making may involve decisions about the use of assisted reproductive technology, considerations about the risk of offspring inheriting T21, and the ability of the individual with T21 to parent, based on potential physical or cognitive challenges.[164] Genetic counselors can help assess the risk of T21 and congenital HD to offspring, which is higher in offspring of women with T21 than men.[90] Sterilization

Table 5. Clinical and Research Priorities for Children With T21 and Congenital HD

Area	Clinical directions	Research priorities
Cardiovascular health	Effective pharmacologic and nonpharmacologic treatments for pulmonary hypertension Heart transplant outcomes	Genetic mechanisms that mediate pulmonary hypertension Biomarkers for pulmonary hypertension Heart transplant vs Fontan palliation outcomes Contemporary long-term survival
Co-occurring conditions	Evaluation for OSA before elective congenital HD surgery Effect of OSA treatment on respiratory complications	Infant feeding strategies that promote breastfeeding and use of human milk Genetic mediators of hematologic abnormalities including pathogenesis of acute myeloid leukemia
Neurodevelopmental, behavioral, intellectual disability	Effective interventions to support child and family functioning in children with mental health conditions, T21, and congenital HD Individualized, family-centered developmental care Mechanisms to support neurodevelopmental follow-up programs and family participation	Screening tools to accurately identify children with T21 at risk for autism spectrum disorder and other mental health conditions Clinical trials of tailored, developmentally responsive psychological therapies and behavioral interventions to optimize mental health, well-being, and quality of life among individuals with T21 Genetic mediators of autism spectrum disorder and phenotypical variation of intellectual disability in children with T21 and congenital HD Biomarkers to detect early onset dementia in T21 with and without congenital HD Effect of individualized, family-centered developmental care on neurodevelopmental outcomes Effect of exposure to hospital environment and cardiopulmonary support techniques on neurodevelopmental outcomes
Functional outcomes, quality of life	Inclusive care Equity and belonging	Quality of life measures appropriate for children with T21 at varying levels of communication ability Effect of digital assistive technologies Do improvements in care result in improved functional outcome? Interventions to improve adaptive and cognitive function with aging
Family-centered care, medical home	Effective care coordination models and impact on outcomes Strategies to promote independence in daily living	Cardiovascular risk modeling and care guidelines applicable to adults with T21 and congenital HD Effective transition models in adolescents with T21 and congenital HD

HD indicates heart disease; OSA, obstructive sleep apnea; and T21, trisomy 21.

of people with T21 is considered ethically unjustifiable in most cases, but may be requested by the person with T21 (who can consent), or by parents or guardians if legally permissible, as a form of birth control.[164,165]

CONCLUSIONS AND RESEARCH PRIORITIES

Improved survival outcomes for infants, children, and adolescents with congenital HD with T21 parallels similar improvements in infants, children, and adolescents with congenital HD but without T21. This improved survival now mandates a shift in clinical and research focus to reducing the burdens of disease as well as improving functional outcomes and QOL. Table 5 outlines the clinical directions and research priorities to address.

Infants and children with T21 and congenital HD present unique management challenges due to the interaction of congenital HD with the co-occurring physical, neurodevelopmental, and psychological conditions. These conditions can adversely influence long-term survival, individual and family functioning, and QOL. Providing comprehensive quality care to infants and children with T21 and congenital HD requires a well-functioning interdisciplinary team approach that also includes children and families as team members. This scientific statement identifies these important aspects of caring for this unique population and provides strategies to maximize health and functional outcomes, as well as guidance for the future.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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