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REVIEW

Updated clinical practice recommendations for managing children with 22q11.2 deletion syndrome

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ABSTRACT

This review aimed to update the clinical practice guidelines for managing children and adolescents with 22q11.2 deletion syndrome (22q11.2DS). The 22q11.2 Society, the international scientific organization studying chromosome 22q11.2 differences and related conditions, recruited expert clinicians worldwide to revise the original 2011 pediatric clinical practice guidelines in a stepwise process: (1) a systematic literature search (1992-2021), (2) study selection and data extraction by clinical experts from 9 different countries, covering 24 subspecialties, and (3) creation of a draft consensus document based on the literature and expert opinion, which was further shaped by survey results from family support organizations regarding perceived needs. Of 2441 22q11.2DS-relevant publications initially identified, 2344 received full-text reviews, including 1545 meeting criteria for potential relevance to clinical care of children and adolescents. Informed by the available literature, recommendations were formulated. Given evidence base limitations, multidisciplinary recommendations represent consensus statements of good practice for this evolving field. These recommendations provide contemporary guidance for evaluation, surveillance, and management of the many 22q11.2DS-associated physical, cognitive, behavioral, and psychiatric morbidities while addressing important genetic counseling and psychosocial issues.

Introduction

22q11.2 deletion syndrome (22q11.2DS) Figure 1 (OMIM 192430, OMIM 188400), a multisystem disorder including physical, cognitive, and behavioral issues of variable severity,[2] is the most common microdeletion syndrome in humans, with an estimated prevalence of 1 in 2148 live births and 1 in 992 pregnancies.[3,4] 22q11.2 deletion is the most frequent cause of DiGeorge syndrome and several other conditions previously described clinically (velocardiofacial syndrome, conotruncal anomaly face syndrome, Cayler cardiofacial) and a subset of patients with Opitz G/BBB syndrome.[5-10]

22q11.2DS is often suspected because of congenital abnormalities, primarily cardiac and speech/language deficits, learning/behavioral problems, recurrent infections, and subtle dysmorphic features. Occasional cases are identified via newborn screening for severe combined

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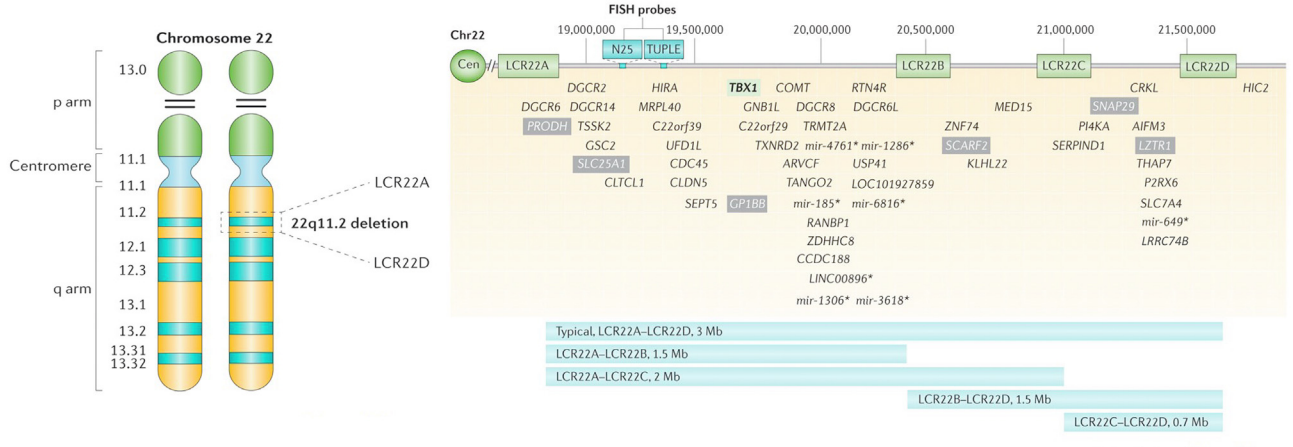

Figure 1 Chromosome 22 ideogram and genes within the chromosome 22q11.2 LCR22A-LCR22D region. Cytogenetic representation of chromosome 22 showing the short (p) and long (q) arms along with the centromere, which functions to separate both arms. Chromosome 22 is an acrocentric chromosome, as indicated by the two horizontal lines in the p arm. The 22q11.2 deletion occurs on the long arm of 1 of the 2 chromosomes, depicted by dashed lines in the 22q11.2 band. The position of the 2 low copy repeats (LCRs), LCR22A and LCR22D, which flank the typical 3 Mb deletion, on 22q11.2 are indicated. Schematic representation of the 3 Mb chromosome 22q11.2 region that is commonly deleted in 22q11.2 deletion syndrome, including the 4 LCRs (LCR22s) that span this region (LCR22A, LCR22B, LCR22C, and LCR22D) and genes within the region. Common commercial probes for fluorescence in situ hybridization (FISH) are indicated (N25 and TUPLE). Protein-coding and selected noncoding (*) genes are indicated with respect to their relative position along chromosome 22 (Chr22). T-box 1 (*TBX1*; green box) is highlighted as the most widely studied gene within the 22q11.2 region. Variants in this gene have resulted in conotruncal cardiac anomalies in animal models and humans. Several known human disease-causing genes that map to the region are indicated in gray boxes. These include proline dehydrogenase 1 (*PRODH*; associated with type I hyperprolinaemia), solute carrier family 25 member 1 (*SLC25A1*; encoding the tricarboxylate transport protein and is associated with combined D-2- and L-2-hydroxyglutaric aciduria), platelet glycoprotein Ib β-polypeptide (*GP1BB*; associated with Bernard–Soulier syndrome), scavenger receptor class F member 2 (*SCARF2*; associated with Van den Ende–Gupta syndrome), synaptosomal-associated protein 29 kDa (*SNAP29*; associated with cerebral dysgenesis, neuropathy, ichthyosis and palmoplantar keratoderma syndrome), and leucine-zipper-like transcription regulator 1 (*LZTR1*; associated with schwannomatosis 2 and autosomal recessive Noonan syndrome). Additional genes associated with autosomal recessive conditions include cell division cycle protein 45 (*CDC45*; associated with craniosynostosis, cleft lip/palate, gastrointestinal and genitourinary anomalies, skeletal differences and short stature; CGS syndrome, C—craniosynostosis, cleft lip/palate, G—gastrointestinal and genitourinary, S—skeletal and short stature; and Meier-Gorlin syndrome) and transport and Golgi organization 2 homolog (*TANGO2*; associated with metabolic crisis with rhabdomyolysis, seizures, hypoglycemia, thyroid disease, optic nerve atrophy, amblyopia, dysconjugate gaze, dysarthria, hypotonia, hypertonia, dystonia, hyperreflexia, clonus, positive Babinski, spastic Achilles tendons, multiple joint contractures, progressive microcephaly, cerebral atrophy, progressive intellectual disability, encephalopathy, cardiac arrhythmia, left ventricular hypertrophy, dilated cardiomyopathy, prominent trabeculations, decreased left ventricular function, long QT, torsades de pointes, and sudden death; *TANGO2*-related disorders). Common 22q11.2 deletions are shown, with the typical 3 Mb deletion flanked by LCR22A and LCR22D (LCR22A-LCR22D) on top and the nested deletions with their respective deletion sizes indicated below. Each of the deletions portrayed is flanked by a particular LCR22. Those rare deletions not mediated by LCRs are not shown. Additional genes in the region include *AIF3M*, apoptosis-inducing factor mitochondrion- associated 3; *ARVCF*, armadillo repeat gene; *CLDN5*, claudin 5; *CLTCL1*, clathrin heavy chain-like 1; *COMT*, catechol-*O*-methyltransferase; *CRKL*, v-crk avian sarcoma virus CT10 oncogene homologue-like; *DGCR*, DiGeorge syndrome critical region; *GNB1L*, guanine nucleotide-binding protein (G protein), β-polypeptide 1-like; *GSC2*, goosecoid homeobox 2; *HIC2*, hypermethylated in cancer 2; *HIRA*, histone cell cycle regulator; *KLHL22*, kelch-like family member 22; *LINC00896*, long intergenic non-protein-coding RNA 896; *LOC101927859*, serine/arginine repetitive matrix protein 2-like; *CCDC188*, coiled-coil domain-containing 188; *LRRC74B*, leucine-rich repeat-containing 74B; *MED15*, mediator complex subunit 15; *mir*, microRNA; *MRPL40*, mitochondrial ribosomal protein L40; *P2RX6*, purinergic receptor P2X ligand-gated ion channel 6; *PI4KA*, phosphatidylinositol 4-kinase catalytic-α; *RANBP1*, Ran-binding protein 1; *RTN4R*, reticulon 4 receptor; *SEPT5*, septin 5; *SERPIND1*, serpin peptidase inhibitor clade D (heparin co-factor) member 1; *THAP7*, THAP domain-containing 7; *TRMT2A*, tRNA methyltransferase 2 homologue A; *TSSK2*, testis-specific serine kinase 2; *TXNRD2*, thioredoxin reductase 2; *UFD1L*, ubiquitin fusion degradation 1-like; *USP41*, ubiquitin-specific peptidase 41; *ZDHHC8*, zinc-finger DHHC-type-containing 8; *ZNF74*, zinc-finger protein 74. (Figure adapted with permission from McDonald-McGinn et al.[1])

immunodeficiency.[1,11] Feeding difficulties, hypocalcemia, and numerous structural anomalies may also be early alerting features.[1] Although awareness of 22q11.2DS has increased, the diagnosis is often delayed or missed, especially in those without serious congenital heart disease (CHD).[12-14]

Clinical practice guidelines for managing patients with 22q11.2DS were first published in 2011.[14] Subsequent research has highlighted important novel associations. The aim in this study was to systematically review the literature and provide updated recommendations to facilitate optimal care for children and adolescents with 22q11.2DS.

Materials and Methods

The 22q11.2 Society recruited expert clinicians worldwide to revise the original clinical practice guidelines for children through a stepwise process: (1) a systematic literature search, according to best practices (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, 2020; Supplemental Figure 1),[15] guided by a methodologist, (2) study selection and synthesis by the clinical experts from 9 countries, covering 24 subspecialties, and (3) creation of a multidisciplinary consensus document using the Grading of Recommendations Assessment, Development and Evaluation framework (GRADE)[16] based on the literature and best practice and shaped by patient advocate survey results, with subsequent independent approval sought.

Inclusion criteria comprised any report with relevance to clinical care of individuals born with a 22q11.2 deletion involving the typical deletion region. Reports involving other conditions including distal 22q11.2 deletions or restricted to prenatal issues were excluded. Given the limited number of systematic studies in 22q11.2DS, a qualitative synthesis of the evidence was performed by a multidisciplinary panel of clinical experts, with review of all reports available from the systematic search.

Using the Grading of Recommendations Assessment, Development and Evaluation framework, high confidence evidence was deemed too limited to justify formal grading of individual recommendations with respect to the quality of available scientific literature or of fine gradations of strength.[16] Consensus recommendations were formulated based on the literature, consideration of being more beneficial than harmful, and best practice according to the experts involved (each having seen tens to hundreds of patients), and input from patient advocate survey results. The revised guidelines were subsequently approved for submission by 2 external reviewers (parent of a child with 22q11.2DS and a genetics expert), neither of whom were part of the guidelines updating process.

Supplemental Material, Study Selection and Data Extraction under Methods contains further details of methods used including full search strategy, protocol, and methodological checklist.

Results

The systematic literature search initially identified 6018 publications regarding 22q11.2DS across the lifespan (Supplemental Figure 1); 3577 were excluded after initial screening (most were duplicates, or involved other conditions) and 97 could not be retrieved, resulting in 2344 reports included for full-text review. Thereafter, 26 reports were excluded as they had no relevance to clinical care. Of the final 2318 that met the inclusion criteria (list included in Supplemental Material, Study Selection and Data Extraction under Methods), 1545 were deemed to have potential relevance to children and adolescents.

The patient advocate survey results, completed by eight 22q11.2DS patient advocacy organizations, based in 7 countries on 3 continents and representing 7624 families, supported updated guidelines to improve: awareness for health care providers and the public; access to 22q11.2DS specific clinics, knowledgeable providers, and comprehensive care; and access to genetic testing and genetic counseling. The respondents ranked the top 5 most relevant subspecialty areas of care, through a combination of free responses and checkboxes of predetermined options as (1) cardiology, (2) brain and behavior (psychiatry, neurology, early intervention, education), (3) genetics (testing, counseling, reproductive health), (4) ear, nose, and throat (ENT) (chronic infections, hearing, palate), and (5) immunology, rheumatology, hematology, and oncology. Regarding knowledge transfer, the respondents conveyed a need for guidelines to be shareable, portable, and available on the internet/social media.

The vast majority of scientific literature relevant to clinical management of children with 22q11.2DS involved study designs in low confidence categories,[16] with few randomized clinical trials, formal systematic reviews, or meta-analyses. Given the state of the scientific evidence available and the challenges inherent to 22q11.2DS that include multiple comorbidities and high inter-individual variability, recommendations in these updated guidelines were not formally graded on an individual basis.[16] The recommendations rather emphasize those with lowest harm and highest potential benefit for patients with this rare condition, informed by long term experience with patients and their families, that reflect current best practice.[16]

Review and Practice Guidelines

Brief overview

Pediatric care for patients with 22q11.2DS requires both generalists and specialists in multiple fields to appreciate the overall interrelated effects of associated medical and developmental features and their impact on well-being and quality of life. Basic knowledge about variable expressivity, severity of features, and changes over time, as well as an emphasis on family-centered care,[17] are essential.

Periodic assessments may identify new or anticipated features enabling early treatment. Preventive management of developmental issues can mitigate frustration and support achieving full potential. Coordination of care with multidisciplinary evaluations is required. Relatives, including parents, siblings, and often grandparents, benefit from information and support. Optimizing health, functioning, and quality of life is the overall goal of these recommendations.

We summarize main features and management recommendations by system in the following sections and in corresponding tables. Figure 2 presents the multisystem features, and Table 1 highlights recommended assessments and health monitoring at diagnosis and by age. In addition, important “Do’s” and “Do not’s” are provided in Table 2.

Genetics
Additional clinically relevant variant
Prenatal
Congenital heart disease (mostly conotruncal)
Thymic hypoplasia/aplasia
Dilated cavum septum pellucidum
Palatal anomalies
Renal anomalies, umbilical hernia
Skeletal (butterfly vertebrae, club foot, polydactyly)
Polyhydramnios
Congenital diaphragmatic hernia, spina bifida
Cardiology
Congenital heart disease (mostly conotruncal)
Aortic arch anomalies (right aortic arch, vascular ring)
Dilated aortic root
ENT /Palate/Speech
Palatal anomalies (velopharyngeal dysfunction, SMCP, bifid uvula, overt cleft palate, CL/P)
Speech disorders (especially hypernasality)
Otitis media (acute or chronic with effusion)
Hearing loss (conductive, sensorineural, mixed), cochlear abnormalities
Airway anomalies (subglottic stenosis, laryngeal web)
Obstructive sleep apnea
Microtia, anotia, choanal atresia
Ophthalmology
Refractive errors (hyperopia/astigmatism)
Strabismus, exotropia/phoria, ptosis
Sclerocornea
Tortuous retinal vessels, posterior embryotoxon
Odontology
Caries
Enamel defects
Decreased saliva secretion
Delayed tooth eruption/agenesis
Malocclusion
Endocrinology
Hypocalcaemia/hypoparathyroidism
Hypothyroidism, hyperthyroidism
Growth hormone deficiency
Growth
Growth restriction in infancy and childhood
Short stature
Obesity in adolescence
Gastroenterology and Nutrition
Feeding difficulty
Constipation
Gastrointestinal reflux disease, dysphagia
Aspiration, NG/G-tube feeds/Nissen fundoplication
Malformations (imperforate anus, Hirschsprung's, intestinal malrotation, esophageal/tracheal atresia, TEF)
Cyclical vomiting
Genitourinary
Renal anomalies (e.g. hydronephrosis, renal agenesis, multicystic/dysplastic kidney)
Dysfunctional voiding
Males: cryptorchidism, hypospadias, phimosis
Females: vaginal agenesis, absent uterus

Immunology
T cell lymphopenia
Recurrent infections
Low immunoglobulins, humoral deficits
Asthma and allergies
Autoimmune cytopenia (ITP, AHA)
Juvenile idiopathic arthritis, vitiligo
Hematology/Oncology
Low platelet numbers
Bleeding, bruising, epistaxis
Bernard-Souiler
Malignancy
Skeletal
Scoliosis
Cervical spine anomalies
Butterfly vertebrae, 13 pairs of ribs
Recurrent patellar dislocations
Clubfoot, polydactyly, syndactyly
Craniosynostosis
Neurology
Hypotonia
Seizures/epilepsy
Microcephaly
Polymicrogyria, heterotopias, spina bifida, tethered cord, dystonia, Parkinsonism/Early onset Parkinson disease
General Surgery
Hernia (all types)
Surgical complications (all types)
Congenital diaphragmatic hernia
Sleep
Sleep pattern disturbances, obstructive sleep apnea
Cognitive Functioning and Development
Delayed gross motor milestones
Fine motor difficulties
Delayed bladder control
Developmental coordination disorder
Speech-language delay/disorders
Learning difficulties, cognitive deficits, NVLD
Intellectual disabilities (mostly mild)
Visuo-spatial impairments
Psychiatry
Attention deficit disorder or ADHD
Autism spectrum disorder
Anxiety disorders
Subclinical psychotic symptoms
Schizophrenia spectrum disorders
Depression
Anorexia

Key
Common
Less common
Rare, but clinically relevant
Common, but not requiring clinical attention

Figure 2 Features and risks in children and adolescents with 22q11.2 deletion syndrome. Figure 2 presents the associated multisystem features observed in children and adolescents with 22q11.2 deletion syndrome. The relative prevalence of each feature is indicated as a gradient of blue, with the darkest shade indicating the most common, intermediate blue specifying less common, and pale blue signifying rare but clinically relevant. White boxes denote features that may be commonly associated but do not necessarily require clinical attention. ADHD, attention deficit hyperactivity disorder; CL/P, cleft lip/palate; AHA, autoimmune hemolytic anemia; ITP, immune thrombocytopenia; NG/G, nasogastric/gastric; NVLD, nonverbal learning disorder; SMCP, submucous cleft palate; TEF, tracheoesophageal fistula.

Table 1 Recommendations for periodic assessments and management of children and adolescents with 22q11.2 deletion syndrome

Assessments and Management	At Diagnosis	Annual/ Biennial	0-1 y	1-5 y	6-12 y	13-18 y
Genetic						
Genetic testing (proband: MLPA or microarray; FISH if only available method) (parents: MLPA or FISH)[a]	✔					
Genetic counseling (etiology, natural history, recurrence risk, prenatal/ preconception screening/diagnostics)	✔	✔				✔
Remaining allele/exome sequencing (when appropriate)[b]	✔					
General						
Consultation with clinician(s) experienced with 22q11.2DS[c]	✔	✔	✔	✔	✔	✔
Comprehensive history-taking (including family history)	✔	✔	✔	✔	✔	✔
Physical examination	✔	✔	✔	✔	✔	✔
Nutritional assessment, feeding, swallowing, GERD, constipation, and growth	✔	✔	✔	✔	✔	✔
Neurologic and developmental assessment (neurologic exam, milestones, sacral dimple, neuroimaging as needed)	✔		✔	✔	✔	✔
Assessment of history of infections, allergy, asthma, autoimmunity, and malignancy	✔	✔	✔	✔	✔	✔
Assessment of access to specialized health care and community, developmental, and government resources	✔		✔	✔	✔	✔
Other clinical assessments						
Cardiac evaluation (using echocardiogram and EKG; determine arch sidedness)	✔					
Long term follow-up for all with CHD; transition to GUCH if CHD		✔	✔	✔	✔	✔
Periodic screening for arrythmias/EKG abnormalities and dilated aortic root[d]				✔	✔	✔
Periodic EKG screening in at-risk patients (antiepileptic/neuropsychiatric treatment, hypocalcemia, thyroid disease)		✔				
Referral to cleft-palate team to assess for overt cleft, SMCP, and VPD (nasoendoscopy/videofluoroscopy as needed)[e]	✔		✔	✔	✔	✔
Evaluation of speech and language by speech-language pathologist[f]	✔		✔	✔	✔	✔
Evaluation by otolaryngologist for recurrent otitis media and possible laryngo-tracheo-esophageal anomalies	✔		✔	✔	✔	✔
Evaluation of hearing using audiogram +/– tympanometry	✔	✔	✔	✔	✔	✔
Ophthalmic evaluation/vision (refractive errors, strabismus, exotropia, sclereocornea, coloboma, ptosis)	✔		✔	✔		
Dental evaluation (measure saliva secretion rate from 6 y)[g]				✔	✔	✔
Endocrinological assessment (PTH, calcium, magnesium, creatinine, TSH, and free T4; GH studies as needed)	✔	✔	✔	✔	✔	✔
Consider clinical (multidisciplinary) feeding and/or swallowing evaluation including assessment of airway[h]			✔	✔		
Renal and bladder ultrasound	✔					
Immunologic assessment: T- and B cell phenotyping[i]	✔		✔	✔		✔
Immunologic assessment: IgG, IgA, IgM, IgE levels (not before 6 mo)			✔	✔		✔
Immunologic assessment: vaccine responses[j]			✔	✔		
Complete blood count and differential	✔	✔	✔	✔	✔	✔
Routine scoliosis screening with scoliometer and with x-ray when clinically indicated					✔	✔
Radiography of the cervical spine at age ~4 y to exclude instability[k]				✔		
Sleep evaluation (consider polysomnography pre and post VPD repair), sleep hygiene recommendations[l]				✔	✔	
Cognitive development, academic functioning, and child psychiatry						
Assessment of cognitive/learning capacities including language domains with standardized measures	✔			✔	✔	✔

(continued)

Table 1 Continued

Assessments and Management	At Diagnosis	Annual/ Biennial	0-1 y	1-5 y	6-12 y	13-18 y
Assessment of adaptive functioning (eg, daily living skills)	✔			✔	✔	✔
Psychiatric assessment (ASD, ADHD/ADD, anxiety, and psychotic disorders)	✔			✔	✔	✔

Table 1 provides recommendations for periodic assessment and management of children and adolescents with 22q11.2 deletion syndrome at diagnosis, annually/biannually, and by age.

ADD, attention deficit disorder; *ADHD*, attention deficit hyperactivity disorder; *ASD*, autism spectrum disorders; *CHD*, congenital heart disease; *EKG*, electrocardiogram; *FISH*, fluorescence in situ hybridization; *GERD*, gastroesophageal reflux disease; *GH*, growth hormone; *GUCH*, grown-up congenital heart disease; *MLPA*, multiplex-ligation dependent probe amplification; *PTH*, parathyroid hormone; *SLP*, speech language pathologist; *SMCP*, submucosal cleft palate; *TSH*, thyroid stimulating hormone; *VPD*, velopharyngeal dysfunction.

[a]Proband and parents; strategy depending on test availability.

[b]When rare recessive condition associated with 22q11.2 region is suspected or atypical phenotypic features observed.

[c]Having seen many pediatric patients with 22q11.2DS both in consultation and in follow-up.

[d]Applies to children with and children without known CHD.

[e]Consider velopharyngeal port imaging (eg, nasopharyngoscopy or speech videofluoroscopy) with cleft team (SLP and surgeon) when adequate speech output and articulation skills are present to allow for valid diagnostic imaging.

[f]Should include assessment of speech (eg, articulation, resonance, voice), receptive and expressive language, and social/pragmatics skills.

[g]Dental assessment not relevant before age 2 years.

[h]Consider videofluoroscopic swallow study or fiberoptic endoscopic evaluation of swallowing if any signs or symptoms of aspiration.

[i]T cell phenotyping; CD3, CD4, CD8 cell counts (+ CD4/CD45RA). B cell count (CD19) and switched memory B cells (CD19 or CD20+, CD27+IgM-).

[j]Include antibodies against tetanus, diphtheria, and pneumococci.

[k]Especially important before VPD surgery to exclude instability; can be performed from age 4 years when sufficient bony ossification has occurred.

[l]Increased risk for obstructive sleep apnea after VPD surgery.

In this, international/local differences should be considered. Of note, these recommendations are most relevant to high-income countries and corresponding resources.

Genetics

22q11.2DS is a contiguous gene deletion syndrome. Affected individuals have a heterozygous loss of 1 copy of the chromosome 22q11.2 region. Most deletions occur as de novo events but approximately 10% are inherited from a parent.[12,69,70]

The typical 22q11.2 deletion originates from nonallelic homologous recombination between low copy repeats (LCRs),[71-74] most commonly LCR22A to LCR22D (85%-90%), resulting in an approximately 2.5 to 3 megabase (Mb) deletion involving approximately 50 protein-coding genes.[1] Smaller LCR22A to LCR22B (1.5 Mb) and LCR22A to LCR22C (2.0 Mb) deletions occur in 5% to 10% of the cases.[1,18] Rarer LCR22B to LCR22D and LCR22C to LCR22D deletions (~5%) occur with overlapping features as this region includes the important developmental gene *CRKL* associated with congenital heart disease and renal anomalies.[12,75] Distal deletions beyond LCR22D (involving other LCRs, LCR22E to LCR22H, OMIM 611867), comprising a distinct entity, should not be confused with 22q11.2DS and are not the subject of these recommendations.

Beginning in the 1990's, the 22q11.2 deletion was identified using fluorescence in situ hybridization (FISH) and probes located between LCR22A-LCR22B.[18] Later, multiplex-ligation dependent probe amplification became available, providing deletion sizing,[76,77] but both tests required an elevated index of suspicion. Chromosomal microarray analysis (CMA) identifies genome-wide copy number variants (CNVs), thus 22q11.2 deletions and their breakpoints and in a minority of patients any other relevant CNVs if present.[78,79] Even the common 2.5 Mb deletion is usually submicroscopic, ie, missed in karyotyping except for rare unbalanced translocations. Thus, CMA currently provides the most clinically useful information for diagnosis and genetic counseling, but we acknowledge that it may not be available or covered in many settings around the world.

Occasionally, the 22q11.2 deletion may uncover a pathogenic variant or small CNV involving a disease-producing gene in the remaining allele, unmasking an autosomal recessive condition. Examples include *PRODH* (hyperprolinemia),[80] *CDC45* (C—craniosynostosis, cleft lip/palate; G—gastrointestinal and genitourinary; S—skeletal and short stature [CGS syndrome]/Meier-Gorlin syndrome),[81] *GP1BB* (Bernard-Soulier),[82-85] *SCARF2* (van den Ende-Gupta syndrome),[86,87] *LZTR1* (autosomal recessive Noonan syndrome),[88] *SNAP29* (cerebral dysgenesis, neuropathy, ichthyosis, and keratoderma syndrome), and *TANGO2*-related disease.[18,89] If atypical features are noted, targeted or exome/genome sequencing should be considered to identify single nucleotide variants or small CNVs on the remaining intact allele.

Genetic counseling

Parental testing is always recommended to determine whether the 22q11.2 deletion is de novo or transmitted from a parent to provide care and genetic counseling for the affected parent.[14,90] This includes the opportunity to identify the rare parent with somatic mosaicism. Parents of a child with a de novo deletion have a small increased recurrence risk over the

Table 2 Do's and Do not's

Topic	Do's	Do not's
Genetics	Check genetic test report for details: deletion size and any clinically relevant variant/s (if applicable),[1,18] perform parental studies even if both parents have negative histories because parents may be mildly affected and somatic and germline mosaicism are possible,[19,20] provide genetic counseling across the lifespan[14]	Ignore clinical findings that are atypical for the 22q11.2 deletion,[18] skip parental testing, provide genetic counseling only at diagnosis, assume parents are unaffected and not test them[14]
Cardiology	Consider perioperative antifungal coverage in addition to antibiotics[21,22]	Transfuse with unirradiated blood products to infants with severely low T cells[21,23]
Palate	Be aware of risk of causing or worsening hypernasality after adenoidectomy,[24,25] and OSA after VPD repair[26]	Perform adenoidectomy without consulting a cleft-palate team,[25,27,28] consider nasal regurgitation normal,[1] ignore postoperative OSA[26]
Endocrinology	Recommend vitamin D to reduce the risk of hypocalcemia; routinely monitor calcium, growth, and thyroid[14,29,30]	Assume normal endocrinological functions in the absence of complaints,[12,29,31-33] overtreat hypocalcemia potentially leading to nephrocalcinosis[29,30]
Growth	Be aware of the risk of developing obesity in adolescence[34,35]	Forget to follow growth curves in older children and to encourage physical activity[34,35]
Gastroenterology	Investigate feeding and swallowing problems as soon as they present[36-38]	Assume feeding difficulty is related to congenital heart disease[36-38]
Surgical procedures	Monitor calcium and CBC perioperatively[39-42]	Ignore anatomical variants[1]
Vaccinations	Check immune status before vaccination with live vaccines and provide all vaccinations otherwise as usual, check antibodies to confirm immunity[23]	Vaccinate with live vaccines if T cells are very low (CD4 <400 or naive CD4 <100 cells/mm^3)[23]
Hematology	Be aware that many patients have mild thrombocytopenia of no clinical relevance[42]	Neglect a history of significant bleeding that is present in a substantial minority of patients[42]
Musculoskeletal	Routine scoliosis screening from age 6 years, with scoliometer and with x-ray when clinically indicated[43,44]	Assume leg pain is idiopathic without considering rheumatologic/neurologic (tethered cord) causes[14,45-47]
CNS	Check calcium in persons with seizures and refer to neurology if idiopathic[47,48]	Assume seizures are hypocalcemic without further investigations[47,48]
Sleep	Consider that poor sleep can affect overall functioning, behavior, and learning capacities[49]	Forget that sleep quality should be monitored with low threshold to obtain a sleep study[50]
Functioning	Consider discrepancies in functioning between cognitive, adaptive, and emotional domains;[51-53] check hearing and vision;[54-56] support total communication (eg, sign language) to avoid frustration[24]	Consider an intelligence test as a static constant or a complete picture of the child's abilities,[53,57] assume hearing and vision are normal,[54-56] assume sign language will delay emergence of verbal speech[24]
Psychiatry	Refer to a specialist when there are changes in thinking, emotions, behavior,[58-61] be aware that subclinical psychotic symptoms may be transient[62,63]	Rely solely on caregiver report (or solely on patient report) without assessing the child[64]
Transition to adulthood	Refer all patients for continued follow-up in adulthood regardless of whether they have health-related problems at the time of transition or not[14,65]	Forget to prepare the adolescent for transition to adulthood in a stepwise manner including health and social issues[66-68]
Multimorbidity	Designate 1 clinician to coordinate medical and health-related social needs, be familiar with the important common and rare associated features, recognize that symptoms change over time and family members/caregivers are essential members of the team[30,65]	Expect the adolescent with 22q11.2DS to present all their symptoms without prompts, overwhelm families with a list of nonactionable associated features, exclude family members from participating in care discussions[17]

Table 2 presents important management tips in the form of "Do's" and "Do not's" for 16 topic areas pertinent to clinicians caring for children and adolescents with 22q11.2 deletion syndrome.

CBC, complete blood count; *CNS*, central nervous system; *OSA*, obstructive sleep apnea; *VPD*, velopharyngeal dysfunction.

general population based on reports of germline mosaicism.[19,20] Reproductive counseling will include discussions regarding prenatal screening/definitive testing options. Affected individuals, both males and females, have a 50% chance of having a child with 22q11.2DS in each pregnancy. In addition to care recommendations, as for any newly diagnosed individual, risk of transmission and variable expressivity are key discussion points. Available reproductive options including prenatal screening and preconception options such as preimplantation genetic diagnostics using *in vitro* fertilization should also be reviewed.

Prenatal considerations

Prenatal features may be observed on fetal ultrasound/echocardiogram in the first trimester, but more commonly at $\geq$20 weeks' gestation. Cardiac anomalies are frequently associated but extracardiac abnormalities, affecting all systems, can be present in as many as 90%.[91,92] However, not all congenital features are appreciated prenatally (eg, laryngeal web). Ultrasound anomalies warrant referral to maternal-fetal medicine and genetic counseling. Prenatal diagnostic testing via chorionic villus sampling or amniocentesis is recommended to optimize delivery planning. CMA remains the most comprehensive test.[93-96] Noninvasive prenatal screening is bringing some affected pregnancies, and previously undiagnosed mothers, to attention but it requires confirmatory diagnostic testing.[97-102] Management of affected pregnancies warrants close monitoring,[91] eg, for CHD (monitoring cardiac function) and polyhydramnios (potential for preterm labor).[91] Fetuses with a 22q11.2 deletion may be considered high risk for pregnancy/delivery given elevated prevalence of late preterm births and intrauterine growth restriction.[103] Location/mode of delivery may be influenced by the diagnosis with or without structural anomalies.

Individual system, medical, and surgical issues

Cardiovascular

CHD is found in approximately two-thirds of children with 22q11.2DS.[12,13,104,105] The most common major CHD subtypes include conotruncal defects (CTD), eg, tetralogy of Fallot, interrupted aortic arch type B, and truncus arteriosus.[21,104,106] Additional severity may be conveyed by associated pulmonary atresia, major aortopulmonary collaterals, and/or discontinuity of pulmonary arteries. Other congenital anomalies, including crossed pulmonary arteries, aberrant subclavian artery, and aortic arch anomalies, may raise clinical suspicion both as isolated findings or as associated with CTD.[21,104,106,107] Vascular anomalies may cause a vascular ring that can compress the trachea/esophagus, manifesting as stridor/feeding and swallowing difficulties and may require studies beyond an echocardiogram, such as a chest MRI, for confirmation.[108,109] Ventricular septal defects, although considered minor CHD, are the most common CTDs.[12,13,21]

CTDs usually require intracardiac repair in infancy or early childhood, necessitating syndrome-specific perioperative and multidisciplinary management to minimize increased complication risk; eg, prolonged mechanical ventilation and length of hospital stay.[110] For all CHD, increased perioperative risk may be conveyed by greater anatomical cardiovascular complexity[111-113] and noncardiac comorbidities.[22,114-117]

Long term cardiac follow-up is required for those who undergo surgical intervention.[118] CTDs often require reintervention in childhood and/or adolescence.[118] Dilated aortic root and arrhythmias have been reported, even in children without CHD, therefore periodic surveillance is recommended for all.[21,119,120]

Ear, nose, and throat

Palate/speech and language

Palatal abnormalities are seen in about two-thirds of children and typically include velopharyngeal dysfunction (VPD) with or without a formal diagnosis of submucous cleft palate (SMCP), with overt cleft palate and cleft lip/palate occurring less frequently.[121] The inability of the soft palate and pharyngeal walls to close properly during speech may be complicated by anatomical and functional factors such as palatal clefting, altered velopharyngeal dimensions, cranial nerve abnormalities, and velopharyngeal muscle hypoplasia. This may result in severe VPD with hypernasality, compensatory articulation patterns, and poor intelligibility.[24,122-124]

Communication disorders are hallmark features of 22q11.2DS.[24] Children often present with a complex communication profile including structural, neurologic, developmental, and cognitive speech-language disorders and social/pragmatic deficits that vary with regards to time of presentation and clinical profile. Emergence of speech and language is typically delayed, with high prevalence of both receptive and expressive language delays/disorders including apraxia. More pronounced expressive deficits are often evident in preschool years.[125] Multiple factors affect speech development and resonance, including palate anomalies and VPD,[121] motor/developmental/neurologic deficits/compensatory speech disorders,[126] recurrent/chronic middle ear infections accompanied with hearing loss,[127] and cognitive function.[57,128]

At diagnosis, patients should undergo a palatal examination and speech/language assessment by cleft/craniofacial specialists.[14,25,27,28] Speech/language assessments are required beginning at 6-18 months and routinely thereafter.

Overt palatal clefts are typically repaired around age 1 year. SMCP or VPD should be assessed jointly with speech-language pathologists, including evaluation with velopharyngeal imaging (nasendoscopy/videofluoroscopy) when VPD is clinically suspected and once adequate speech is present.[129] Surgical treatment can lead to significant improvements in intelligibility and quality of life.[121,130,131]

Many children require intensive speech-language therapy throughout childhood. Progress may be slow because of

cognitive/learning and behavioral differences.[24] Early implementation of augmentative communication (eg, sign language) can promote language use and help avoid frustration.[24] Periodic evaluations of speech-language profiles are important as they may change over time.[24]

Obstructive sleep apnea

Sleep-disordered breathing and obstructive sleep apnea (OSA) are reported in children with 22q11.2DS.[50,132-134] Risk factors include retrognathia and pharyngeal hypotonia. OSA may develop after VPD-related palatal surgeries,[26] thus should always be assessed both pre- and postoperatively. Risk may be mitigated through OSA treatment postoperatively.[134] Tonsillectomy may help treat OSA in childhood, but residual mild-moderate OSA remains an issue,[133,134] with increased risk for airway complications.[135]

Airway

Airway anomalies, including laryngomalacia, tracheomalacia, subglottic stenosis, glottic web, vocal fold paralysis, and laryngeal cleft, occur in approximately 20% of children.[136,137] Symptoms include stridor/noisy breathing, aspiration, and need for supplemental oxygen with a subset (often those with concomitant CHD) requiring tracheostomy. Screening should occur routinely with formal airway evaluation recommended as symptoms warrant.[138,139] Esophageal atresia, tracheoesophageal atresia, and trachea atresia have also been observed. Feeding and swallowing disorders,[136,140] that may be related to pharyngeal hypotonia,[141] require monitoring for symptoms of aspiration during routine otolaryngologic visits, with a low threshold to obtain a swallowing study.[50]

Ears/hearing

Many children have recurrent and/or chronic otitis media with and without effusion.[13,54,55,136] Narrow ear canals increase wax accumulation, which may affect hearing. Hearing loss is common and usually mild.[54,55,140,142] It is most often conductive because of eustachian tube dysfunction/chronic otitis media with effusion (COME),[143,127] but combined or sensorineural types are also observed.[144,145] Ossicular/middle- and inner ear anomalies may be present, including abnormal stapes, cochlea, vestibule, and lateral semicircular canal.[146,147] External ears are often small with minor anomalies.[136,148] Microtia/anotia, preauricular tags/pits have also been reported.[14,149]

Periodic ear exams and audiograms are recommended.[142] For patients with chronic otitis media with effusion, myringotomy with ear tube placement should be considered to optimize hearing. Occasionally hearing loss is severe, requiring hearing aids.[150]

Eyes/vision

Ocular findings are common including strabismus, refractive errors (hyperopia and astigmatism), and incidental features (retinal vascular tortuosity, posterior embryotoxon, eyelid hooding).[56,151-153] Refractive errors, strabismus, and amblyopia require early correction. About one-third need glasses.[56] Sclerocornea has been reported and requires urgent care.[154]

A comprehensive eye examination is recommended at diagnosis with follow-up as indicated by findings.[152]

Dental abnormalities

Common dental abnormalities, including caries, impaired saliva secretion, enamel defects, and malocclusions can affect general health and quality of life.[155-160] Diet, infections, fine motor skills, and cognitive/behavioral (eg, anxiety) issues can contribute to dental problems.

Children aged $\geq$ 2 years should be referred for dental assessment at diagnosis, with monitoring of enamel, tooth eruption, and occlusion.[156-160] Caries prevention includes oral hygiene, fluorides, and sealants. Some children need examination/treatment under anesthesia. For CHD-related endocarditis risk, consult national guidelines regarding preventive antibiotics.[161]

Endocrinology

Endocrinological issues most often involve hypoparathyroidism/hypocalcemia and/or thyroid disease.[31-33,162]

Hypocalcemia is reported in approximately 60% of children,[149,163,164] presenting at any age with relative or complete hypoparathyroidism.[29,165] Transient neonatal hypocalcemia may occur, and hypocalcemic seizures may be the first sign of 22q11.2DS. Hypocalcemia can recur during periods of biologic stress, eg, perioperative, with acute illness, puberty, in pregnancy, or decreased oral intake,[40] and may lead to fatigue, irritability, seizures, paresthesias, muscle cramps, tremors, and/or rigidity.[165]

Parents should be informed about these potential symptoms but informed that most commonly hypocalcemia is mild. Calcium-relevant parameters (including calcium or ionized calcium, parathyroid hormone, magnesium, and 25-hydroxy vitamin D [25-OH D]) should be measured regularly (at least annually) and during stressors.

Calcium and vitamin D supplements should be considered if dietary intake is insufficient and/or calcium levels are low. In more recalcitrant cases, active vitamin D metabolites, eg, calcitriol (1, 25-dihydroxy vitamin D) may be needed, usually requiring endocrinology consultation. Severe hypocalcemia or tetany should be treated with slow infusion of parenteral calcium. The calcium levels should be maintained in the low-normal range to minimize hypercalciuria and risk of nephrolithiasis. Patients on long term calcium and/or calcitriol should be monitored with annual urinary calcium and renal ultrasound every few years.[14,29,30]

Thyroid dysfunction occurs in approximately 10% to 20% of children, primarily hypothyroidism, but also hyperthyroidism due to Graves' disease.[166] Autoimmune thyroid disorders may be related to the overall increased risk of autoimmune disease in this condition.

Monitoring for thyroid abnormalities with thyroid stimulating hormone (TSH) and free T4 is recommended every 1 to 2 years.[30,166]

Growth

Growth restriction in infancy and childhood commonly shows a pattern of early deceleration of weight gain and stature, then weight gain recovery with less catch-up in stature; with mean height at age 19 years of −0.89 SD for females and −0.72 SD for males,[35] and short stature (<2.5th percentile) in a minority.[33] Feeding difficulties and failure to thrive may contribute to growth issues. Growth hormone deficiency is rare but when present, responds well to growth hormone therapy.[33,167]

Height and weight should be measured regularly,[33] considering parental height, when evaluating short stature. Growth hormone therapy is a consideration if testing indicates deficiency.

Gastroenterology and nutrition

Many children experience one or more gastrointestinal (GI) symptoms. Hernias (diaphragmatic, umbilical, inguinal) are common. Other congenital malformations (eg, esophageal atresia, tracheoesophageal fistula, malrotation/nonrotation, intestinal atresia, anal atresia/stenosis, imperforate anus, Hirschsprung disease) and autoimmune diseases (eg, celiac disease, inflammatory bowel disease, autoimmune enteritis) are rarer.[1,14,168,169] Common GI conditions include feeding and swallowing disorders, nasopharyngeal reflux, and dysmotility of the GI tract, eg, gastroesophageal reflux disease, vomiting, esophageal dysmotility, gastroparesis, and significant constipation. Contributing factors to consider include musculoskeletal (posture, oral motor, coordination, and tongue retraction), neurologic (hypotonia, polymicrogyria, cerebellar abnormalities), respiratory (congestion, increased work of breathing, vascular ring and/or laryngeal anomalies), and/or endocrinological disorders (hypocalcemia, abnormal thyroid function).[36-38]

Many early GI problems improve over time. Nasopharyngeal reflux is especially common in infants with SMCP and those at risk for VPD. These children will often present with poor breast feeding and some will present with failure to thrive in infancy. Some children will benefit from special feeding techniques and bottles used to feed children with overt cleft palate. Severely affected patients may require supplemental or postpyloric feeding tubes or Nissen fundoplication. Risk for obesity becomes an important consideration in adolescence, requiring active attention to diet and physical activity.[33-35]

Genitourinary

Genitourinary tract (GU) abnormalities affect approximately 15% of patients with 22q11.2DS,[170] including hydronephrosis, unilateral renal agenesis, multicystic dysplastic or hypoplastic kidney, and simple renal cysts. Bilateral renal agenesis has been reported. Ureteral and bladder anomalies, eg, vesicoureteral reflux and megaureter, are less prevalent. Some urinary tract findings may resolve spontaneously, eg, milder forms of hydronephrosis and vesicoureteral reflux. Genital anomalies are more prevalent in males (eg, cryptorchidism, hypospadias) than in females (eg, absent vagina and/or uterus).[170] Voiding dysfunction may be present, eg, related to developmental delay/constipation.[171]

All patients are recommended to have a complete physical examination at diagnosis including genital exam and screening renal and bladder ultrasound. Consultation with a urologist, general surgeon, gynecologist, and/or nephrologist may be warranted, and certain genitourinary abnormalities require surgical repair.[170]

General surgery

General surgery considerations are related to the overall higher likelihood of surgical complications in 22q11.2DS than in the general population because of risks of bleeding, seizures, and difficult intubation.

Recommendations include careful perioperative and postoperative monitoring, including monitoring calcium levels, platelets, oxygen saturation, and preanticipating the need for smaller intubation equipment.[39,41]

Immunology

Immunodeficiency associated with 22q11.2DS is highly variable and dynamic. Main features in early infancy relate to the hypoplastic thymus, with 80% of infants having diminished T cell numbers.[1,172] Over time, because of homeostatic expansion and accumulating T cells, T cell counts typically approach normal.[173] However, the character of T cells, altered through this process, may lead to functional deficits, increased apoptosis, and premature aging of T cells.[172,174-178] Another feature of 22q11.2DS immunodeficiency is a progressive loss of antibody function followed by diminished levels of immunoglobulins in a minority of children.[179] Recurrent and prolonged upper and lower respiratory tract infections are common.[13,173,176,180] In addition, secondary consequences related to the altered behavior of T cells include susceptibility to autoimmunity (up to 20%),[23,176,177,181-184] and to allergies (up to 40%).[23,176,182]

In early infancy, it is important to determine whether the T cell deficiency is so severe as to require a thymus transplant,[23,172,185] and/or if blood transfusions need to be irradiated.[23] T cell evaluations are also warranted to determine whether and when there are sufficient T cells to safely allow the administration of live viral vaccines (and Bacille Calmette-Guérin against tuberculosis when indicated).[186-189] Subsequent evaluations monitor for humoral deficiency with additional assessments in individual cases depending on immune-related problems.

Hematology and oncology

Mild to moderate thrombocytopenia that may progress with age and increased platelet volume are common in 22q11.2DS.[42] Bleeding, usually mild, including epistaxis and bruising, is reported,[42,190,191] with limited evidence of increased risk of procedural bleeding.[42,192] Platelet dysfunction may be related to heterozygosity of the *GPIBB* gene. A pathogenetic variant on the remaining allele may

lead to Bernard-Soulier syndrome, a very rare but severe bleeding disorder.[83] There is an increased risk for hematologic autoimmunity, most often immune thrombocytopenia but also autoimmune hemolytic anemia and autoimmune neutropenia.[179,180,193-195]

Yearly complete blood counts will facilitate monitoring platelets over time. Caution is required to differentiate a normal decrease from conditions requiring treatment to ensure unnecessary investigations and therapies are avoided.[42]

Pediatric malignancies have been reported, including Wilms tumor/hepatoblastoma, lymphoma and B cell malignancies, pineoblastoma, medullary thyroid carcinoma, melanoma, and primitive neuro-ectodermal tumors.[42,196,197] Further studies are needed to identify the mechanisms by which individuals with 22q11.2DS may have an increased risk of malignancy and to determine what the true incidence and prevalence is within this patient population. Currently, routine surveillance is not recommended for patients with 22q11.2DS but patients with concerning symptoms require prompt evaluation.

Musculoskeletal

Scoliosis, usually of adolescent idiopathic type, is common and may be clinically significant,[43,44,198,199] sometimes requiring bracing/spinal surgery.[198,200,201] Other skeletal issues sometimes requiring surgical intervention include patellar dislocation,[198,202,203] clubfoot,[13,45,203-205] polydactyly,[13,163,206] hammer toe and other foot anomalies.[163,206-208] Cervical/occipital anomalies found in almost all children are rarely consequential (although surgical intervention may be required),[209,210] likewise, for butterfly vertebrae and 13 pairs of ribs.[206] Several cases of juvenile idiopathic arthritis often polyarticular and associated with IgA deficiency have been reported.[45,46,205,211]

Underrepresented in the literature are frequent nonspecific lower leg/foot pains,[14] which may be associated with pes planovalgus and may benefit from orthotics. Cramping pain from hypocalcemia and other causes, including juvenile idiopathic arthritis, should be considered.

Routine scoliosis screening is recommended, with scoliometer and with x-ray when clinically indicated, with some sites screening from age 6 years with radiography at 2-year intervals until skeletal maturity.[44] A one-time screening for cervical spinal anomalies and instability, with radiography including atlas-dens measurements in flexion and extension is recommended around age 4 years.[43,209,212] In older children and adolescents, if patellar dislocation is suspected, radiographs are indicated.

Neurology and neurosurgery

Provoked (hypocalcemic) neonatal seizures and jitteriness, hypotonia, and motor/speech delays are the most common early neurologic features of 22q11.2DS.[213] Most patients have some degree of motor dysfunction and speech/language deficits,[213] including apraxia.[126] Dystonia has been reported and should prompt consideration of *TANGO2*-related disease.[214,215] Structural brain abnormalities including polymicrogyria, gray matter heterotopia, Chiari malformation, cervical spine instability requiring decompression, and myelomeningocele are rare, as is stroke occurring as a secondary insult, whereas tethered cord seems to be more common.[47,89,216] Unprovoked seizures and epilepsy occur in up to 15% of patients.[47,48] Provoked seizures may result from hypocalcemia, hypomagnesemia, fever/infection, and medications.[47] Any seizure requires investigation including bloodwork, with electroencephalogram (EEG) and magnetic resonance imaging (MRI) if unprovoked. Cyclical vomiting (sometimes referred to as abdominal migraines), have been observed in a small subset of patients.

Early interventions (eg, physical, occupational and speech therapies) can help maximize function. Neurologic evaluation at diagnosis is recommended. Focal neurologic findings, muscle weakness, abnormal deep tendon reflexes, and/or severe abnormalities in muscle tone may require additional interrogation, including brain MRI. In those with bowel and bladder dysfunction/lower limb upper motor neuron signs, lumbar spine MRI should be considered to rule out tethered cord, especially when a sacral dimple is present.[47]

Other

Sleep

Sleep disorders such as insomnias and restless sleep are common and associated with neuropsychiatric problems that can in turn negatively affect behavior, cognition, and anxiety, in addition to physical health issues.[49,50,217] A low threshold for a formal sleep study, ie, polysomnography, to assess for obstructive/central sleep apnea should be considered. Interventions including good sleep hygiene, consistent bedtime routine, and appropriate sleep environment are beneficial. As with children without 22q11.2DS, employing additional strategies such as use of melatonin/a weighted blanket, etc may be beneficial.

Fatigue

Fatigue is a major concern for parents of children/adolescents with 22q11.2DS, but to date has only been studied in adults.[218] Current understanding of causation is insufficient because fatigue can have many origins. Given the multisystem nature of the disorder, underlying somatic (eg, OSA, metabolic/mitochondrial/cardiac etiologies) and psychiatric causes (eg, anxiety disorders) of fatigue require investigation.

Mortality

Mortality rates in children range from 5% to 15%, with most deaths occurring during the first year of life.[12,105] Mortality is primarily related to complex CHD, often in combination with other comorbid conditions such as hypocalcemia, infection, and airway anomalies.[41] In addition, the rare occurrence of autosomal recessive conditions such as CEDNIK (cerebral dysgenesis, neuropathy, ichthyosis, and

keratoderma) syndrome and *TANGO2*-related disease[89,215] due to variants/CNVs involving the *SNAP29* or *TANGO2* genes, respectively, on the intact chromosome 22q11.2 allele, may also contribute to premature death.[79,105] The death rate in children with 22q11.2DS and CHD is greater than that of children with comparable CHD without 22q11.2DS.[105] Further studies are required to better understand mortality in the context of multimorbidity.

Cognitive functioning and development

During infancy and toddlerhood, gross/fine motor and coordination difficulties,[219,220] and speech and language delays/disorders predominate.[125,221] From preschool onward, the variable and often complex cognitive profile reveals itself, with borderline and mild intellectual disabilities being common. Average intellectual functioning (IQ 85-115) and moderate to severe ID are less common.[57,222] Verbal IQ often exceeds performance IQ by >10 points, rendering full scale IQ estimates less valid, which can have a significant effect on cognitive remediation.[128,222-226]

Learning difficulties, especially in mathematics and language comprehension, are ubiquitous regardless of IQ.[227,228] Cognitive deficits occur in most children, typically in sustained attention, executive function, memory, and visuo-spatial perception and processing.[229-231] A decline in IQ, especially verbal IQ, over time is common,[57,59,232] with concomitant decrease in mainstream school placement and increased need for assistance.[233-235] A subset attend postsecondary school, often with accommodations.

Formal neuropsychological testing is strongly recommended for all children.[232,236-238] Early assessment of deficits and implementation of interventions are critical. For infants/toddlers, early remediation often includes physio/occupational/sensory integration therapies.[237] Assessment of language and communication should include language comprehension. If overlooked, this can lead to overestimation of capacities.[239]

For school-aged children, reassessment of IQ and adaptive functioning, particularly at transition periods (eg, primary to secondary school, secondary to postsecondary), is recommended.[57,240] The type of schooling that best supports the individual child depends on overall cognitive capacities, the learning profile, and other individual and environmental factors. For some, additional supports from an Individualized Education Program will suffice. Others require more intensive interventions.

At all stages, there needs to be monitoring of changing and increasing environmental demands with age and flexibility to avert undue stress. A multidisciplinary approach, integrating findings from all involved is crucial.[51,62,64,171,237,241]

Considerations include the complex and changing developmental profile[52,57,225] that may be affected by medical comorbidities, early hospitalizations, and/or psychiatric manifestations,[59,238] in addition to sleep disturbances[50] and reduced physical/emotional stamina. Close monitoring of these inter-relationships is recommended,[53,237] as is acknowledgment of the burdens imposed by 22q11.2DS, with provision of supports and interventions for the family often beneficial.[242,243]

Psychiatry

Early neuropsychiatric expression in 22q11.2DS involves neurodevelopmental disorders, including attention deficit hyperactivity disorder (up to ~40%), most commonly the inattentive type and autism spectrum disorder (ASD; up to ~30%),[63] with or without intellectual disability and/or language disorder supporting the need for periodic (~every 3 years) formal neuropsychological assessments.[244,245] Approximately 35% of children are diagnosed with an anxiety disorder, most commonly specific phobia, social phobia, and generalized anxiety disorder.[63] Subclinical psychotic symptoms emerge in childhood and adolescence[246] but are not necessarily associated with an increasing prevalence of a diagnosable psychotic disorder that may affect about 10% by late adolescence.[63]

Across categorical diagnoses, pediatric symptom domains converge on attention deficits, social-communicative impairments, repetitive behaviors, and anxiety apparently unrelated to cognitive ability.[225,236,247-250] Low (especially verbal) IQ, and/or IQ decline, is correlated with a somewhat increased risk of a psychotic disorder.[251] Language decline in school-age years, similarly, has been related to risk of psychotic illness in some patients.[252] ASD is not associated with increased risk for psychotic illness,[58,253] but some sites report association with childhood attention deficit hyperactivity disorder inattentive type and/or anxiety.[60,254] As for schizophrenia in general, cognitive, attentional, and mood changes are known aspects of the evolving neurodevelopmental disorder itself.[62,70,128]

Optimal assessment of psychopathology in children with 22q11.2DS occurs in the context of language/cognitive/psycho-educational assessment, overall functioning, and physical conditions, including thyroid dysfunction and hypocalcemia.[1] Certain psychotherapeutic/cognitive-behavioral modalities may not be effective in those with weak verbal/cognitive skills.[70] Also, discrepancy between abilities and expectations may contribute to symptoms.[70] Standard management of treatable psychiatric conditions, including attention deficit hyperactivity disorder, ASD, anxiety, and psychotic disorders, is recommended but may not be available or provided for affected children.[61,255,256] There are no known preventions for any psychiatric illness. However, decreasing stress and avoidance of alcohol and drugs, especially of early and chronic use of marijuana, is recommended to lower risk especially for mood- and psychotic illness.[257]

Transition to adult care and internet safety

Adolescence is a vulnerable time for those with developmental disabilities, who are at increased risk for adverse medical and social outcomes.[66,258,259] Youth with 22q11.2DS generally have greater immaturity than their peers. Thus, despite being arbitrarily considered adults at age 18 years, individuals with 22q11.2DS often require significant parental/caregiver support at transition, including for health care, education, and other life decisions (eg, guardianship plan, contraception).[67] Individuals with 22q11.2DS are especially vulnerable to bullying, including cyberbullying.[260] Sexual vulnerability through social media or other social interactions may also be an issue. In addition, there may be social limitations, and although desirous of friendship, impulsivity and deficits in critical judgment may adversely affect relationship-building.[261]

Limiting screen time early on, monitoring social media contacts, while avoiding screen-time conflict and encouraging alternative activities (eg, sport, music, art), can potentially reduce risk for adverse outcomes.[262]

Transitioning from pediatric to adult care is a stepwise approach to health care needs.[68] It is essential for pediatric clinicians to identify, and ideally communicate directly with, appropriate adult practitioners, including one provider who has overall responsibility for assessment and follow-up, in addition to subspecialists depending on needs.[65] Timely record transfer/creating portable health care summaries prevents gaps in care.[263] Legal guardianship must be considered before age 18 years. Formal neuropsychological assessment can help optimize both health care and educational/vocational attainment and is essential for support programs.[128,237]

Conclusion

In these updated clinical practice guidelines, we provide recommendations for evaluation, management, and follow-up of children with 22q11.2DS from birth to 18 years of age. We outline associated features and the changing phenotype over the pediatric lifespan (Figure 3). The recommendations are based on the current state of knowledge and consensus by

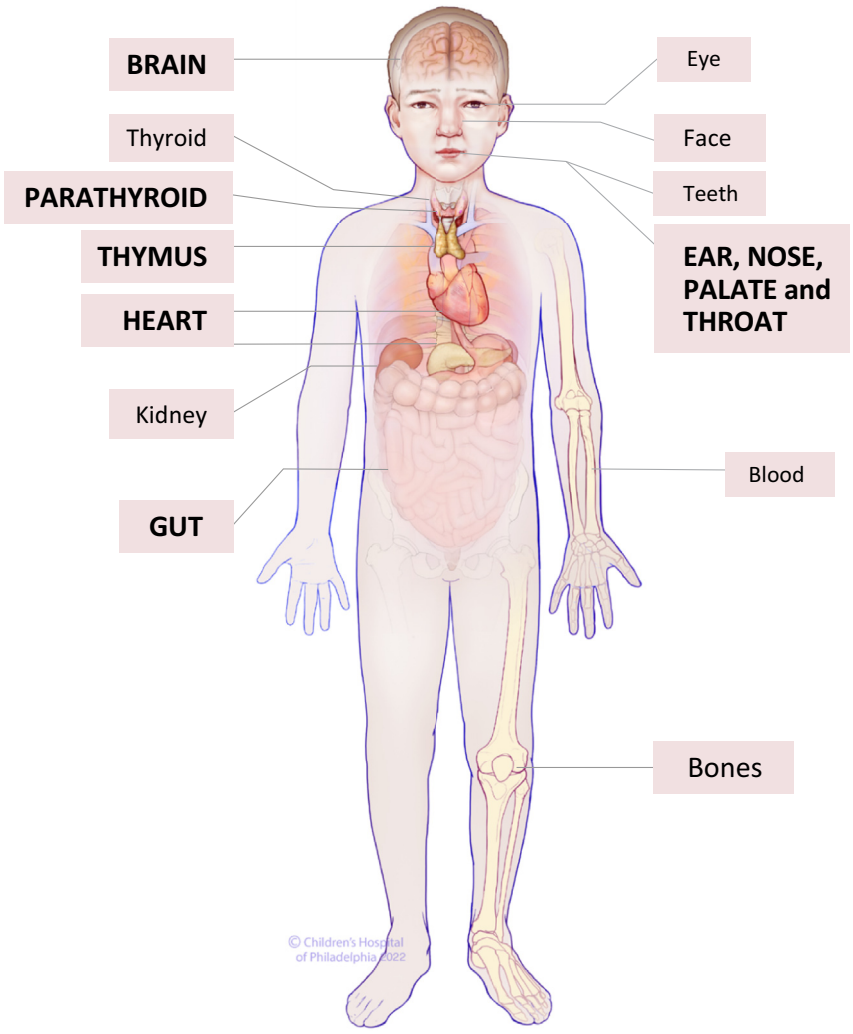

Figure 3 Schematic of organ and system involvement associated with the chromosome 22q11.2 deletion syndrome in children and the multidisciplinary demand over time. Chromosome 22q11.2 deletion syndrome leads to significant morbidity and some premature (Continued)

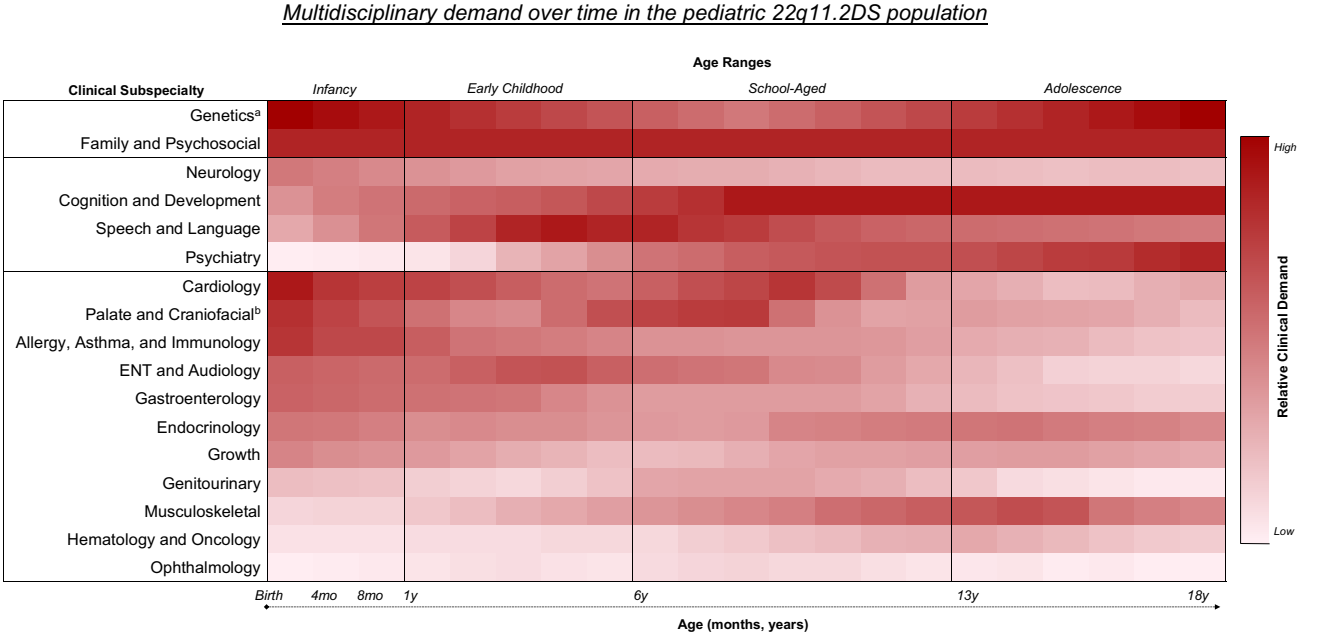

Figure 3 (Continued). mortality, with frequent multiorgan system involvement. Structural abnormalities, such as cardiac and overt palatal abnormalities are primarily noted in infancy. Associated functional differences may occur at any time across the lifespan including in infancy, eg, immunodeficiency, endocrine and gastrointestinal problems, velopharyngeal incompetence, and genitourinary anomalies. Developmental delay, variable cognitive deficits, and behavioral differences are generally recognizable in early to late childhood but become particularly evident in adolescence as individuals face increasing environmental demands both educationally and socially. Less frequent manifestations, when present, contribute to substantial morbidity, such as idiopathic seizures, polymicrogyria, cerebral dysgenesis, neuropathy, dystonia, neural tube defects, tethered cord, sclerocornea, coloboma, deafness, choanal atresia, laryngeal cleft or web, tracheoesophageal fistula, autoimmune disease including hypo- or hyperthyroidism, juvenile idiopathic arthritis, immune thrombocytopenia, celiac disease, inflammatory bowel disease, vitiligo, and autoimmune hemolytic anemia, growth hormone deficiency, craniosynostosis, scoliosis, patellar dislocation, club foot, intestinal malrotation/nonrotation, Hirschsprung disease, imperforate anus, acne vulgaris, ichthyosis, palmoplantar keratoderma, and malignancy. Minor malformations generally confer little indisposition but may enhance ascertainment. These generally include mild dysmorphic craniofacial features, such as malar flatness, upslanting palpebral fissures, hooded eyelids, allergic shiners, auricular anomalies including overfolded helices, microtia, anotia, protuberant ears, preauricular tags or pits, nasal differences involving a prominent nasal root, bulbous nasal tip with or without a nasal dimple/crease/hemangioma, hypoplastic alae nasi, atopic dimples lateral to the nares, and asymmetric crying facies; posterior embryotoxon and tortuous retinal vessels; cervical and thoracic vertebral anomalies including a cervical "Nike swoosh," butterfly vertebrae, supernumerary ribs, arachnodactyly, camptodactyly, 2 to 3 syndactyly, polydactyly (preaxial and postaxial of the hands and postaxial of the feet); and prenatal indicators besides congenital heart disease and palatal anomalies such as absent thymus, cavum septum pellucidum, diaphragmatic hernia, and polyhydramnios. **The lasagna plot** visually demonstrates the proportion of individuals requiring attention across health care subspecialties and the relative demands over time from birth through 18 years, concurrently considering both frequency and severity of features. Lighter shades should not be interpreted as inconsequential but weighed relative to patient population prevalence and intensity of symptoms/conditions. ENT, ear, nose, and throat. [a]Genetics includes genetics and genetic counseling. [b]Palate and craniofacial includes dental.

experts in the field from many countries. Although some recommendations are relevant for all, management must be targeted to suit the individual and the individual condition(s). In addition, local differences in health care, educational, social, and other systems need consideration. Coordination of care, involving generalists and specialists from a wide range of needed services, is important to help diminish the burden on patients and their families.

Since the publication of the first practical guidelines for managing patients with 22q11.2DS in 2011,[14] our knowledge and understanding of many associated features has increased, and recently, subspecialty guidelines have been developed for speech-language disorders and prenatal considerations.[24,264] Primarily observational research has included new data on physical features, such as the risk of developing scoliosis, and the developmental, cognitive, and psychiatric phenotypes that are of major concern to parents throughout the pediatric years and beyond. Research examining the evolving expression of 22q11.2DS across developmental ages and stages and interrelated effects of physical, neuropsychiatric, and developmental features reinforce the need for multidisciplinary care with a holistic view.

There remain many gaps however in our knowledge and understanding of this multisystem disorder. The lack of high-quality evidence limits the strength of the

recommendations. Particularly, there is a need for well-designed studies to evaluate recommendations contained in these guidelines, determine possible differences for individuals with atypical nested 22q11.2 deletions, further contribute to the problematic area of predicting outcome, and assess current and novel treatment modalities. Such studies will strengthen our future recommendations so that we may move closer to our primary goal to optimize health, functioning, and quality of life for children with 22q11.2DS. The lack of systematic studies and high-quality evidence in 22q11.2DS made many steps and processes that would be typically undertaken in a rigorous systematic review not available. Thus, these multidisciplinary pediatric recommendations, along with the companion adult recommendations,[265] represent consensus statements of good practice for this evolving field, including contemporary guidance for evaluation, surveillance, and management of the many 22q11.2DS-associated physical, cognitive, behavioral, and psychiatric morbidities, while addressing important genetic counseling and psychosocial issues. As for our initial publication, these recommendations will continue to require updating, proposed for 5 years hence, as new information becomes available.

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Ethics Declaration

No ethical approval was obtained because the data retrieved and analyzed originated from previous published studies in which informed consent was obtained by primary investigators.

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Conflict of Interest

The authors declare no conflicts of interest.

Additional Information

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References

1. McDonald-McGinn DM, Sullivan KE, Marino B, et al. 22q11.2 deletion syndrome. *Nat Rev Dis Primers*. 2015;1:15071. http://doi.org/10.1038/nrdp.2015.71
2. McDonald-McGinn DM. 22q11.2 deletion – a tiny piece leading to a big picture. *Nat Rev Dis Primers*. 2020;6(1):33. http://doi.org/10.1038/s41572-020-0169-x
3. Blagojevic C, Heung T, Theriault M, et al. Estimate of the contemporary live-birth prevalence of recurrent 22q11.2 deletions: a cross-sectional analysis from population-based newborn screening. *CMAJ Open*. 2021;9(3):E802-E809. http://doi.org/10.9778/cmajo.20200294
4. Grati FR, Molina Gomes D, Ferreira JC, et al. Prevalence of recurrent pathogenic microdeletions and microduplications in over 9500 pregnancies. *Prenat Diagn*. 2015;35(8):801-809. http://doi.org/10.1002/pd.4613
5. McDonald-McGinn DM, Hoffman E, Lairson A, McGinn DE, Zackai EH. Chapter 1 - 22q11.2 deletion syndrome: setting the stage. In: McDonald-McGinn DM, ed. *The Chromosome 22q11.2 Deletion Syndrome*. Academic Press; 2022:2-32.
6. Driscoll DA, Salvin J, Sellinger B, et al. Prevalence of 22q11 microdeletions in DiGeorge and velocardiofacial syndromes:

implications for genetic counselling and prenatal diagnosis. *J Med Genet*. 1993;30(10):813-817. http://doi.org/10.1136/jmg.30.10.813
7. Burn J, Takao A, Wilson D, et al. Conotruncal anomaly face syndrome is associated with a deletion within chromosome 22q11. *J Med Genet*. 1993;30(10):822-824. http://doi.org/10.1136/jmg.30.10.822
8. Giannotti A, Digilio MC, Marino B, Mingarelli R, Dallapiccola B. Cayler cardiofacial syndrome and del 22q11: part of the CATCH22 phenotype. *Am J Med Genet*. 1994;53(3):303-304. http://doi.org/10.1002/ajmg.1320530320
9. McDonald-McGinn DM, Driscoll DA, Bason L, et al. Autosomal dominant "Opitz" GBBB syndrome due to a 22q11.2 deletion. *Am J Med Genet*. 1995;59(1):103-113. http://doi.org/10.1002/ajmg.1320590122
10. McDonald-McGinn DM, LaRossa D, Goldmuntz E, et al. The 22q11.2 deletion: screening, diagnostic workup, and outcome of results; report on 181 patients. *Genet Test*. 1997;1(2):99-108. http://doi.org/10.1089/gte.1997.1.99
11. Barry JC, Crowley TB, Jyonouchi S, et al. Identification of 22q11.2 deletion syndrome via newborn screening for severe combined immunodeficiency. *J Clin Immunol*. 2017;37(5):476-485. http://doi.org/10.1007/s10875-017-0403-9
12. Campbell IM, Sheppard SE, Crowley TB, et al. What is new with 22q? An update from the 22q and You Center at the Children's Hospital of Philadelphia. *Am J Med Genet A*. 2018;176(10):2058-2069. http://doi.org/10.1002/ajmg.a.40637
13. Oskarsdóttir S, Persson C, Eriksson BO, Fasth A. Presenting phenotype in 100 children with the 22q11 deletion syndrome. *Eur J Pediatr*. 2005;164(3):146-153. http://doi.org/10.1007/s00431-004-1577-8
14. Bassett AS, McDonald-Mcginn DM, Devriendt K, et al. Practical guidelines for managing patients with 22q11.2 deletion syndrome. *J Pediatr*. 2011;159(2):332-339.e1. http://doi.org/10.1016/j.jpeds.2011.02.039
15. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. http://doi.org/10.1136/bmj.n71
16. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. http://doi.org/10.1136/bmj.39489.470347.AD
17. Berens J, Wozow C, Peacock C. Transition to adult care. *Phys Med Rehabil Clin N Am*. 2020;31(1):159-170. http://doi.org/10.1016/j.pmr.2019.09.004
18. Morrow BE, McDonald-McGinn DM, Emanuel BS, Vermeesch JR, Scambler PJ. Molecular genetics of 22q11.2 deletion syndrome. *Am J Med Genet A*. 2018;176(10):2070-2081. http://doi.org/10.1002/ajmg.a.40504
19. Kasprzak L, Der Kaloustian VM, Elliott AM, Shevell M, Lejtenyi C, Eydoux P. Deletion of 22q11 in two brothers with different phenotype. *Am J Med Genet*. 1998;75(3):288-291.
20. Chen W, Li X, Sun L, Sheng W, Huang G. A rare mosaic 22q11.2 microdeletion identified in a Chinese family with recurrent fetal conotruncal defects. *Mol Genet Genomic Med*. 2019;7(8):e847. http://doi.org/10.1002/mgg3.847
21. Unolt M, Versacci P, Anaclerio S, et al. Congenital heart diseases and cardiovascular abnormalities in 22q11.2 deletion syndrome: from well-established knowledge to new frontiers. *Am J Med Genet A*. 2018;176(10):2087-2098. http://doi.org/10.1002/ajmg.a.38662
22. McDonald R, Dodgen A, Goyal S, et al. Impact of 22q11.2 deletion on the postoperative course of children after cardiac surgery. *Pediatr Cardiol*. 2013;34(2):341-347. http://doi.org/10.1007/s00246-012-0454-x
23. Morsheimer M, Brown Whitehorn TF, Heimall J, Sullivan KE. The immune deficiency of chromosome 22q11.2 deletion syndrome. *Am J Med Genet A*. 2017;173(9):2366-2372. http://doi.org/10.1002/ajmg.a.38319
24. Solot CB, Sell D, Mayne A, et al. Speech-language disorders in 22q11.2 deletion syndrome: best practices for diagnosis and management. *Am J Speech Lang Pathol*. 2019;28(3):984-999. http://doi.org/10.1044/2019_AJSLP-16-0147
25. Cable BB, Mair EA. Avoiding perils and pitfalls in velocardiofacial syndrome: an otolaryngologist's perspective. *Ear Nose Throat J*. 2003;82(1):56-60.
26. Crockett DJ, Goudy SL, Chinnadurai S, Wootten CT. Obstructive sleep apnea syndrome in children with 22q11.2 deletion syndrome after operative intervention for velopharyngeal insufficiency. *Front Pediatr*. 2014;2:84. http://doi.org/10.3389/fped.2014.00084
27. Perkins JA, Sie K, Gray S. Presence of 22q11 deletion in post-adenoidectomy velopharyngeal insufficiency. *Arch Otolaryngol Head Neck Surg*. 2000;126(5):645-648. http://doi.org/10.1001/archotol.126.5.645
28. Havkin N, Tatum SA, Shprintzen RJ. Velopharyngeal insufficiency and articulation impairment in velo-cardio- facial syndrome: the influence of adenoids on phonemic development. *Int J Pediatr Otorhinolaryngol*. 2000;54(2-3):103-110. http://doi.org/10.1016/s0165-5876(00)00350-5
29. Cheung ENM, George SR, Costain GA, et al. Prevalence of hypocalcaemia and its associated features in 22q11.2 deletion syndrome. *Clin Endocrinol (Oxf)*. 2014;81(2):190-196. http://doi.org/10.1111/cen.12466
30. Habel A, Herriot R, Kumararatne D, et al. Towards a safety net for management of 22q11.2 deletion syndrome: guidelines for our times. *Eur J Pediatr*. 2014;173(6):757-765. http://doi.org/10.1007/s00431-013-2240-z
31. Levy-Shraga Y, Gothelf D, Goichberg Z, et al. Growth characteristics and endocrine abnormalities in 22q11.2 deletion syndrome. *Am J Med Genet A*. 2017;173(5):1301-1308. http://doi.org/10.1002/ajmg.a.38175
32. Kawame H, Adachi M, Tachibana K, et al. Graves' disease in patients with 22q11.2 deletion. *J Pediatr*. 2001;139(6):892-895. http://doi.org/10.1067/mpd.2001.119448
33. Weinzimer SA. Endocrine aspects of the 22q11.2 deletion syndrome. *Genet Med*. 2001;3(1):19-22. http://doi.org/10.1097/00125817-200101000-00005
34. Tarquinio DC, Jones MC, Jones KL, Bird LM. Growth charts for 22q11 deletion syndrome. *Am J Med Genet A*. 2012;158A(11):2672-2681. http://doi.org/10.1002/ajmg.a.35485
35. Habel A, McGinn MJ 2nd, Zackai EH, Unanue N, McDonald-McGinn DM. Syndrome-specific growth charts for 22q11.2 deletion syndrome in Caucasian children. *Am J Med Genet A*. 2012;158A(11):2665-2671. http://doi.org/10.1002/ajmg.a.35426
36. Eicher PS, McDonald-Mcginn DM, Fox CA, Driscoll DA, Emanuel BS, Zackai EH. Dysphagia in children with a 22q11.2 deletion: unusual pattern found on modified barium swallow. *J Pediatr*. 2000;137(2):158-164. http://doi.org/10.1067/mpd.2000.105356
37. Ebert B, Morrell N, Zavala H, Chinnadurai S, Tibesar R, Roby BB. Percutaneous enteral feeding in patients with 22q11.2 deletion syndrome. *Cleft Palate Craniofac J*. 2022;59(1):121-125. http://doi.org/10.1177/1055665621996117
38. Wong NS, Feng Z, Rappazzo C, Turk C, Randall C, Ongkasuwan J. Patterns of dysphagia and airway protection in infants with 22q11.2-deletion syndrome. *Laryngoscope*. 2020;130(11):2532-2536. http://doi.org/10.1002/lary.28317
39. Shen L, Gu H, Wang D, et al. Influence of chromosome 22q11.2 microdeletion on postoperative calcium level after cardiac-correction surgery. *Pediatr Cardiol*. 2011;32(7):904-909. http://doi.org/10.1007/s00246-011-0012-y
40. Kapadia CR, Kim YE, McDonald-McGinn DM, Zackai EH, Katz LEL. Parathyroid hormone reserve in 22q11.2 deletion syndrome. *Genet Med*. 2008;10(3):224-228. http://doi.org/10.1097/GIM.0b013e3181634edf
41. Yang C, Ge J, Zhang R, Chen C, Yi L, Shen L. The correlation between severity of postoperative hypocalcemia and perioperative mortality in chromosome 22q11.2 microdeletion (22q11DS) patient

after cardiac-correction surgery: a retrospective analysis. *Heart Surg Forum*. 2020;23(5):E549-E554. http://doi.org/10.1532/hsf.2957

42. Lambert MP, Arulselvan A, Schott A, et al. The 22q11.2 deletion syndrome: cancer predisposition, platelet abnormalities and cytopenias. *Am J Med Genet A*. 2018;176(10):2121-2127. http://doi.org/10.1002/ajmg.a.38474
43. Homans JF, Tromp IN, Colo D, et al. Orthopaedic manifestations within the 22q11.2 Deletion syndrome: a systematic review. *Am J Med Genet A*. 2018;176(10):2104-2120. http://doi.org/10.1002/ajmg.a.38545
44. Homans JF, Baldew VGM, Brink RC, et al. Scoliosis in association with the 22q11.2 deletion syndrome: an observational study. *Arch Dis Child*. 2019;104(1):19-24. http://doi.org/10.1136/archdischild-2018-314779
45. Davies K, Stiehm ER, Woo P, Murray KJ. Juvenile idiopathic polyarticular arthritis and IgA deficiency in the 22q11 deletion syndrome. *J Rheumatol*. 2001;28(10):2326-2334.
46. Sato S, Kawashima H, Suzuki K, Nagao R, Tsuyuki K, Hoshika A. A case of juvenile idiopathic polyarticular arthritis complicated by IgA deficiency in 22q11 deletion syndrome. *Rheumatol Int*. 2011;31(8):1089-1092. http://doi.org/10.1007/s00296-009-1245-4
47. Hopkins SE, Chadehumbe M, Blaine Crowley T, Zackai EH, Bilaniuk LT, McDonald-McGinn DM. Neurologic challenges in 22q11.2 deletion syndrome. *Am J Med Genet A*. 2018;176(10):2140-2145. http://doi.org/10.1002/ajmg.a.38614
48. Eaton CB, Thomas RH, Hamandi K, et al. Epilepsy and seizures in young people with 22q11.2 deletion syndrome: prevalence and links with other neurodevelopmental disorders. *Epilepsia*. 2019;60(5):818-829. http://doi.org/10.1111/epi.14722
49. Moulding HA, Bartsch U, Hall J, et al. Sleep problems and associations with psychopathology and cognition in young people with 22q11.2 deletion syndrome (22q11.2DS). *Psychol Med*. 2020;50(7):1191-1202. http://doi.org/10.1017/S0033291719001119
50. Arganbright JM, Tracy M, Hughes SS, Ingram DG. Sleep patterns and problems among children with 22q11 deletion syndrome. *Mol Genet Genomic Med*. 2020;8(6):e1153. http://doi.org/10.1002/mgg3.1153
51. Campbell LE, McCabe KL, Melville JL, Strutt PA, Schall U. Social cognition dysfunction in adolescents with 22q11.2 deletion syndrome (velo-cardio-facial syndrome): relationship with executive functioning and social competence/functioning. *J Intellect Disabil Res*. 2015;59(9):845-859. http://doi.org/10.1111/jir.12183
52. Baker KD, Skuse DH. Adolescents and young adults with 22q11 deletion syndrome: psychopathology in an at-risk group. *Br J Psychiatry*. 2005;186:115-120. http://doi.org/10.1192/bjp.186.2.115
53. Fiksinski AM, Schneider M, Zinkstok J, Baribeau D, Chawner SJRA, Vorstman JAS. Neurodevelopmental trajectories and psychiatric morbidity: lessons learned from the 22q11.2 deletion syndrome. *Curr Psychiatry Rep*. 2021;23(3):13. http://doi.org/10.1007/s11920-021-01225-z
54. Suzuki N, Kanzaki S, Suzuki T, Ogawa K, Yamagishi H. Clinical features of 22q11.2 deletion syndrome related to hearing and communication. *Acta Otolaryngol*. 2020;140(9):736-740. http://doi.org/10.1080/00016489.2020.1769862
55. Ford LC, Sulprizio SL, Rasgon BM. Otolaryngological manifestations of velocardiofacial syndrome: a retrospective review of 35 patients. *Laryngoscope*. 2000;110(3 Pt 1):362-367. http://doi.org/10.1097/00005537-200003000-00006
56. von Scheibler ENMM, van der Valk Bouman ES, Nuijts MA, et al. Ocular findings in 22q11.2 deletion syndrome: a systematic literature review and results of a Dutch multicenter study. *Am J Med Genet A*. 2022;188(2):569-578. http://doi.org/10.1002/ajmg.a.62556
57. Fiksinski AM, Bearden CE, Bassett AS, et al. A normative chart for cognitive development in a genetically selected population. *Neuropsychopharmacology*. 2022;47(7):1379-1386. http://doi.org/10.1038/s41386-021-00988-6
58. Fiksinski AM, Breetvelt EJ, Duijff SN, Bassett AS, Kahn RS, Vorstman JAS. Autism spectrum and psychosis risk in the 22q11.2 deletion syndrome. Findings from a prospective longitudinal study. *Schizophr Res*. 2017;188:59-62. http://doi.org/10.1016/j.schres.2017.01.032
59. Vorstman JA, Breetvelt EJ, Duijff SN, et al. Cognitive decline preceding the onset of psychosis in patients with 22q11.2 deletion syndrome. *JAMA Psychiatry*. 2015;72(4):377-385. http://doi.org/10.1001/jamapsychiatry.2014.2671
60. Gothelf D, Schneider M, Green T, et al. Risk factors and the evolution of psychosis in 22q11.2 deletion syndrome: a longitudinal 2-site study. *J Am Acad Child Adolesc Psychiatry*. 2013;52(11):1192-1203.e3. http://doi.org/10.1016/j.jaac.2013.08.008
61. Kates WR, Mariano MA, Antshel KM, et al. Trajectories of psychiatric diagnoses and medication usage in youth with 22q11.2 deletion syndrome: a 9-year longitudinal study. *Psychol Med*. 2019;49(11):1914-1922. http://doi.org/10.1017/S0033291718002696
62. Fiksinski AM, Schneider M, Murphy CM, et al. Understanding the pediatric psychiatric phenotype of 22q11.2 deletion syndrome. *Am J Med Genet A*. 2018;176(10):2182-2191. http://doi.org/10.1002/ajmg.a.40387
63. Schneider M, Debbané M, Bassett AS, et al. Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. *Am J Psychiatry*. 2014;171(6):627-639. http://doi.org/10.1176/appi.ajp.2013.13070864
64. Fonseca-Pedrero E, Debbané M, Schneider M, Badoud D, Eliez S. Schizotypal traits in adolescents with 22q11.2 deletion syndrome: validity, reliability and risk for psychosis. *Psychol Med*. 2016;46(5):1005-1013. http://doi.org/10.1017/S0033291715002500
65. Fung WL, Butcher NJ, Costain G, et al. Practical guidelines for managing adults with 22q11.2 deletion syndrome. *Genet Med*. 2015;17(8):599-609. http://doi.org/10.1038/gim.2014.175
66. Islam Z, Ford T, Kramer T, et al. Mind how you cross the gap! Outcomes for young people who failed to make the transition from child to adult services: the TRACK study. *BJPsych Bull*. 2016;40(3):142-148. http://doi.org/10.1192/pb.bp.115.050690
67. Kerin L, Lynch D, McNicholas F. Participatory development of a patient-clinician communication tool to enhance healthcare transitions for young people with 22q11.2. *Ir J Med Sci*. 2020;189(3):761-769. http://doi.org/10.1007/s11845-019-02104-6
68. Lose EJ, Robin NH. Caring for adults with pediatric genetic diseases: a growing need. *Curr Opin Pediatr*. 2007;19(6):611-612. http://doi.org/10.1097/MOP.0b013e3282f18a01
69. Lu JH, Chung MY, Hwang B, Chien HP. Prevalence and parental origin in tetralogy of Fallot associated with chromosome 22q11 microdeletion. *Pediatrics*. 1999;104(1 Pt 1):87-90. http://doi.org/10.1542/peds.104.1.87
70. Green T, Gothelf D, Glaser B, et al. Psychiatric disorders and intellectual functioning throughout development in velocardiofacial (22q11.2 deletion) syndrome. *J Am Acad Child Adolesc Psychiatry*. 2009;48(11):1060-1068. http://doi.org/10.1097/CHI.0b013e3181b76683
71. Edelmann L, Pandita RK, Spiteri E, et al. A common molecular basis for rearrangement disorders on chromosome 22q11. *Hum Mol Genet*. 1999;8(7):1157-1167. http://doi.org/10.1093/hmg/8.7.1157
72. Guo T, Diacou A, Nomaru H, et al. Deletion size analysis of 1680 22q11.2DS subjects identifies a new recombination hotspot on chromosome 22q11.2. *Hum Mol Genet*. 2018;27(7):1150-1163. http://doi.org/10.1093/hmg/ddy028
73. Edelmann L, Pandita RK, Morrow BE. Low-copy repeats mediate the common 3-Mb deletion in patients with velo-cardio-facial syndrome. *Am J Hum Genet*. 1999;64(4):1076-1086. http://doi.org/10.1086/302343
74. Shaikh TH, Kurahashi H, Saitta SC, et al. Chromosome 22-specific low copy repeats and the 22q11.2 deletion syndrome: genomic organization and deletion endpoint analysis. *Hum Mol Genet*. 2000;9(4):489-501. http://doi.org/10.1093/hmg/9.4.489
75. Rozas MF, Benavides F, León L, Repetto GM. Association between phenotype and deletion size in 22q11.2 microdeletion syndrome:

systematic review and meta-analysis. *Orphanet J Rare Dis*. 2019;14(1):195. http://doi.org/10.1186/s13023-019-1170-x
76. Fernández L, Lapunzina P, Arjona D, et al. Comparative study of three diagnostic approaches (FISH, STRs and MLPA) in 30 patients with 22q11.2 deletion syndrome. *Clin Genet*. 2005;68(4):373-378. http://doi.org/10.1111/j.1399-0004.2005.00493.x
77. Vorstman JAS, Jalali GR, Rappaport EF, Hacker AM, Scott C, Emanuel BS. MLPA: a rapid, reliable, and sensitive method for detection and analysis of abnormalities of 22q. *Hum Mutat*. 2006;27(8):814-821. http://doi.org/10.1002/humu.20330
78. Busse T, Graham JM Jr, Feldman G, et al. High-resolution genomic arrays identify CNVs that phenocopy the chromosome 22q11.2 deletion syndrome. *Hum Mutat*. 2011;32(1):91-97. http://doi.org/10.1002/humu.21395
79. Cohen JL, Crowley TB, McGinn DE, et al. 22q and two: 22q11.2 deletion syndrome and coexisting conditions. *Am J Med Genet A*. 2018;176(10):2203-2214. http://doi.org/10.1002/ajmg.a.40494
80. Afenjar A, Moutard ML, Doummar D, et al. Early neurological phenotype in 4 children with biallelic PRODH mutations. *Brain Dev*. 2007;29(9):547-552. http://doi.org/10.1016/j.braindev.2007.01.008
81. Unolt M, Kammoun M, Nowakowska B, et al. Pathogenic variants in CDC45 on the remaining allele in patients with a chromosome 22q11.2 deletion result in a novel autosomal recessive condition. *Genet Med*. 2020;22(2):326-335. http://doi.org/10.1038/s41436-019-0645-4
82. Nakagawa M, Okuno M, Okamoto N, Fujino H, Kato H. Bernard-Soulier syndrome associated with 22q11.2 microdeletion. *Am J Med Genet*. 2001;99(4):286-288. http://doi.org/10.1002/1096-8628(2001)9999:9999<::aid-ajmg1176>3.0.co;2-t
83. Budarf ML, Konkle BA, Ludlow LB, et al. Identification of a patient with Bernard-Soulier syndrome and a deletion in the DiGeorge/velocardio-facial chromosomal region in 22q11.2. *Hum Mol Genet*. 1995;4(4):763-766. http://doi.org/10.1093/hmg/4.4.763
84. Souto Filho JTD, Ribeiro HAA, Fassbender IPB, Ribeiro JMMC, Ferreira Júnior WDS, Figueiredo LCS. Bernard-Soulier syndrome associated with 22q11.2 deletion and clinical features of DiGeorge/velocardiofacial syndrome. *Blood Coagul Fibrinolysis*. 2019;30(8):423-425. http://doi.org/10.1097/MBC.0000000000000849
85. Kunishima S, Imai T, Kobayashi R, Kato M, Ogawa S, Saito H. Bernard-Soulier syndrome caused by a hemizygous GPIbbeta mutation and 22q11.2 deletion. *Pediatr Int*. 2013;55(4):434-437. http://doi.org/10.1111/ped.12105
86. Bedeschi MF, Colombo L, Mari F, et al. Unmasking of a recessive SCARF2 mutation by a 22q11.12 de novo deletion in a patient with van den Ende-Gupta syndrome. *Mol Syndromol*. 2010;1(5):239-245. http://doi.org/10.1159/000328135
87. Anastasio N, Ben-Omran T, Teebi A, et al. Mutations in SCARF2 are responsible for Van Den Ende-Gupta syndrome. *Am J Hum Genet*. 2010;87(4):553-559. http://doi.org/10.1016/j.ajhg.2010.09.005
88. Johnston JJ, van der Smagt JJ, Rosenfeld JA, et al. Autosomal recessive Noonan syndrome associated with biallelic *LZTR1* variants. *Genet Med*. 2018;20(10):1175-1185. http://doi.org/10.1038/gim.2017.249
89. McDonald-McGinn DM, Fahiminiya S, Revil T, et al. Hemizygous mutations in SNAP29 unmask autosomal recessive conditions and contribute to atypical findings in patients with 22q11.2DS. *J Med Genet*. 2013;50(2):80-90. http://doi.org/10.1136/jmedgenet-2012-101320
90. McDonald-McGinn DM, Tonnesen MK, Laufer-Cahana A, et al. Phenotype of the 22q11.2 deletion in individuals identified through an affected relative: cast a wide FISHing net. *Genet Med*. 2001;3(1):23-29. http://doi.org/10.1097/00125817-200101000-00006
91. Schindewolf E, Khalek N, Johnson MP, et al. Expanding the fetal phenotype: prenatal sonographic findings and perinatal outcomes in a cohort of patients with a confirmed 22q11.2 deletion syndrome. *Am J Med Genet A*. 2018;176(8):1735-1741. http://doi.org/10.1002/ajmg.a.38665
92. Cohen V, Powell E, Lake C. Failure of neuraxial anaesthesia in a patient with velocardiofacial syndrome. *Int J Obstet Anesth*. 2011;20(3):256-259. http://doi.org/10.1016/j.ijoa.2010.12.007
93. Luo S, Meng D, Li Q, et al. Genetic testing and pregnancy outcome analysis of 362 fetuses with congenital heart disease identified by prenatal ultrasound. *Arq Bras Cardiol*. 2018;111(4):571-577. http://doi.org/10.5935/abc.20180144
94. Vialard F, Simoni G, Gomes DM, et al. Prenatal BACs-on-beads™: the prospective experience of five prenatal diagnosis laboratories. *Prenat Diagn*. 2012;32(4):329-335. http://doi.org/10.1002/pd.2934
95. Moore JW, Binder GA, Berry R. Prenatal diagnosis of aneuploidy and deletion 22q11.2 in fetuses with ultrasound detection of cardiac defects. *Am J Obstet Gynecol*. 2004;191(6):2068-2073. http://doi.org/10.1016/j.ajog.2004.05.022
96. Li S, Jin Y, Yang J, et al. Prenatal diagnosis of rearrangements in the fetal 22q11.2 region. *Mol Cytogenet*. 2020;13:28. http://doi.org/10.1186/s13039-020-00498-y
97. Wang JC, Radcliff J, Coe SJ, Mahon LW. Effects of platforms, size filter cutoffs, and targeted regions of cytogenomic microarray on detection of copy number variants and uniparental disomy in prenatal diagnosis: results from 5026 pregnancies. *Prenat Diagn*. 2019;39(3):137-156. http://doi.org/10.1002/pd.5375
98. Martin K, Iyengar S, Kalyan A, et al. Clinical experience with a single-nucleotide polymorphism-based non-invasive prenatal test for five clinically significant microdeletions. *Clin Genet*. 2018;93(2):293-300. http://doi.org/10.1111/cge.13098
99. Zhao C, Tynan J, Ehrich M, et al. Detection of fetal subchromosomal abnormalities by sequencing circulating cell-free DNA from maternal plasma. *Clin Chem*. 2015;61(4):608-616. http://doi.org/10.1373/clinchem.2014.233312
100. Wapner RJ, Babiarz JE, Levy B, et al. Expanding the scope of noninvasive prenatal testing: detection of fetal microdeletion syndromes. *Am J Obstet Gynecol*. 2015;212(3):332.e1-e9. http://doi.org/10.1016/j.ajog.2014.11.041
101. Jensen TJ, Dzakula Z, Deciu C, van den Boom D, Ehrich M. Detection of microdeletion 22q11.2 in a fetus by next-generation sequencing of maternal plasma. *Clin Chem*. 2012;58(7):1148-1151. http://doi.org/10.1373/clinchem.2011.180794
102. Xie X, Wang M, Goh ES, et al. Noninvasive prenatal testing for trisomies 21, 18, and 13, sex chromosome aneuploidies, and microdeletions in average-risk pregnancies: a cost-effectiveness analysis. *J Obstet Gynaecol Can*. 2020;42(6):740-749.e712. http://doi.org/10.1016/j.jogc.2019.12.007
103. Van L, Butcher NJ, Costain G, Ogura L, Chow EW, Bassett AS. Fetal growth and gestational factors as predictors of schizophrenia in 22q11.2 deletion syndrome. *Genet Med*. 2016;18(4):350-355. http://doi.org/10.1038/gim.2015.84
104. Marino B, Digilio MC, Toscano A, et al. Anatomic patterns of conotruncal defects associated with deletion 22q11. *Genet Med*. 2001;3(1):45-48. http://doi.org/10.1097/00125817-200101000-00010
105. Repetto GM, Guzmán ML, Delgado I, et al. Case fatality rate and associated factors in patients with 22q11 microdeletion syndrome: a retrospective cohort study. *BMJ Open*. 2014;4(11):e005041. http://doi.org/10.1136/bmjopen-2014-005041
106. Park IS, Ko JK, Kim YH, et al. Cardiovascular anomalies in patients with chromosome 22q11.2 deletion: a Korean multicenter study. *Int J Cardiol*. 2007;114(2):230-235. http://doi.org/10.1016/j.ijcard.2005.12.029
107. Babaoğlu K, Altun G, Binnetoğlu K, Dönmez M, Ö Kayabey, Anık Y. Crossed pulmonary arteries: a report on 20 cases with an emphasis on the clinical features and the genetic and cardiac abnormalities. *Pediatr Cardiol*. 2013;34(8):1785-1790. http://doi.org/10.1007/s00246-013-0714-4
108. McElhinney DB, Clark BJ 3rd, Weinberg PM, et al. Association of chromosome 22q11 deletion with isolated anomalies of aortic arch laterality and branching. *J Am Coll Cardiol*. 2001;37(8):2114-2119. http://doi.org/10.1016/s0735-1097(01)01286-4

109. McElhinney DB, McDonald-McGinn D, Zackai EH, Goldmuntz E. Cardiovascular anomalies in patients diagnosed with a chromosome 22q11 deletion beyond 6 months of age. *Pediatrics*. 2001;108(6):E104. http://doi.org/10.1542/peds.108.6.e104
110. Yeoh TY, Scavonetto F, Hamlin RJ, Burkhart HM, Sprung J, Weingarten TN. Perioperative management of patients with DiGeorge syndrome undergoing cardiac surgery. *J Cardiothorac Vasc Anesth*. 2014;28(4):983-989. http://doi.org/10.1053/j.jvca.2013.10.025
111. Anaclerio S, Di Ciommo V, Michielon G, et al. Conotruncal heart defects: impact of genetic syndromes on immediate operative mortality. *Ital Heart J*. 2004;5(8):624-628.
112. Michielon G, Marino B, Oricchio G, et al. Impact of DEL22q11, trisomy 21, and other genetic syndromes on surgical outcome of conotruncal heart defects. *J Thorac Cardiovasc Surg*. 2009;138(3):565-570.e2. http://doi.org/10.1016/j.jtcvs.2009.03.009
113. Hamzah M, Othman HF, Daphtary K, Komarlu R, Aly H. Outcomes of truncus arteriosus repair and predictors of mortality. *J Card Surg*. 2020;35(8):1856-1864. http://doi.org/10.1111/jocs.14730
114. O'Byrne ML, Yang W, Mercer-Rosa L, et al. 22q11.2 Deletion syndrome is associated with increased perioperative events and more complicated postoperative course in infants undergoing infant operative correction of truncus arteriosus communis or interrupted aortic arch. *J Thorac Cardiovasc Surg*. 2014;148(4):1597-1605. http://doi.org/10.1016/j.jtcvs.2014.02.011
115. Koth A, Sidell D, Bauser-Heaton H, et al. Deletion of 22q11 chromosome is associated with postoperative morbidity after unifocalisation surgery. *Cardiol Young*. 2019;29(1):19-22. Published correction appears in *Cardiol Young*. 2019;29(1):23. http://doi.org/10.1017/S1047951118001427
116. Ackerman MJ, Wylam ME, Feldt RH, et al. Pulmonary atresia with ventricular septal defect and persistent airway hyperresponsiveness. *J Thorac Cardiovasc Surg*. 2001;122(1):169-177. http://doi.org/10.1067/mtc.2001.114942
117. Wise-Faberowski L, Irvin M, Sidell DR, et al. Assessment of airway abnormalities in patients with tetralogy of Fallot, pulmonary atresia, and major aortopulmonary collaterals. *Cardiol Young*. 2019;29(5):610-614. http://doi.org/10.1017/S1047951119000301
118. Guidelines for the management of congenital heart diseases in childhood and adolescence. *Cardiol Young*. 2017;27(S3):S1-S105. http://doi.org/10.1017/S1047951116001955
119. John AS, McDonald-McGinn DM, Zackai EH, Goldmuntz E. Aortic root dilation in patients with 22q11.2 deletion syndrome. *Am J Med Genet A*. 2009;149A(5):939-942. http://doi.org/10.1002/ajmg.a.32770
120. de Rinaldis CP, Butensky A, Patel S, et al. Aortic root dilation in patients with 22q11.2 deletion syndrome without intracardiac anomalies. *Pediatr Cardiol*. 2021;42(7):1594-1600. http://doi.org/10.1007/s00246-021-02645-7
121. Jackson O, Crowley TB, Sharkus R, et al. Palatal evaluation and treatment in 22q11.2 deletion syndrome. *Am J Med Genet A*. 2019;179(7):1184-1195. http://doi.org/10.1002/ajmg.a.61152
122. Kirschner RE, Baylis AL. Surgical considerations in 22Q11.2 deletion syndrome. *Clin Plast Surg*. 2014;41(2):271-282. http://doi.org/10.1016/j.cps.2013.12.002
123. Ruotolo RA, Veitia NA, Corbin A, et al. Velopharyngeal anatomy in 22q11.2 deletion syndrome: a three-dimensional cephalometric analysis. *Cleft Palate Craniofac J*. 2006;43(4):446-456. http://doi.org/10.1597/04-193.1
124. Persson C, Lohmander A, Jönsson R, Oskarsdóttir S, Söderpalm E. A prospective cross-sectional study of speech in patients with the 22q11 deletion syndrome. *J Commun Disord*. 2003;36(1):13-47. http://doi.org/10.1016/s0021-9924(02)00133-8
125. Solot CB, Gerdes M, Kirschner RE, et al. Communication issues in 22q11.2 deletion syndrome: children at risk. *Genet Med*. 2001;3(1):67-71. http://doi.org/10.1097/00125817-200101000-00015
126. Baylis AL, Shriberg LD. Estimates of the prevalence of speech and motor speech disorders in youth with 22q11.2 deletion syndrome. *Am J Speech Lang Pathol*. 2019;28(1):53-82. http://doi.org/10.1044/2018_AJSLP-18-0037
127. Verheij E, Kist AL, Mink van der Molen AB, et al. Otologic and audiologic findings in 22q11.2 deletion syndrome. *Eur Arch Otorhinolaryngol*. 2017;274(2):765-771. http://doi.org/10.1007/s00405-016-4365-y
128. Swillen A, McDonald-McGinn D. Developmental trajectories in 22q11.2 deletion. *Am J Med Genet C Semin Med Genet*. 2015;169(2):172-181. http://doi.org/10.1002/ajmg.c.31435
129. Jackson OA, Paine K, Magee L, et al. Management of velopharyngeal dysfunction in patients with 22q11.2 deletion syndrome: a survey of practice patterns. *Int J Pediatr Otorhinolaryngol*. 2019;116:43-48. http://doi.org/10.1016/j.ijporl.2018.10.016
130. Rouillon I, Leboulanger N, Roger G, et al. Velopharyngoplasty for noncleft velopharyngeal insufficiency: results in relation to 22q11 microdeletion. *Arch Otolaryngol Head Neck Surg*. 2009;135(7):652-656. http://doi.org/10.1001/archoto.2009.64
131. Swanson EW, Sullivan SR, Ridgway EB, Marrinan EM, Mulliken JB. Speech outcomes following pharyngeal flap in patients with velocardiofacial syndrome. *Plast Reconstr Surg*. 2011;127(5):2045-2053. http://doi.org/10.1097/PRS.0b013e31820e91e6
132. Moraleda-Cibrián M, Edwards SP, Kasten SJ, Berger M, Buchman SR, O'Brien LM. Symptoms of sleep disordered breathing in children with craniofacial malformations. *J Clin Sleep Med*. 2014;10(3):307-312. http://doi.org/10.5664/jcsm.3536
133. Kennedy WP, Mudd PA, Maguire MA, et al. 22q11.2 Deletion syndrome and obstructive sleep apnea. *Int J Pediatr Otorhinolaryngol*. 2014;78(8):1360-1364. http://doi.org/10.1016/j.ijporl.2014.05.031
134. Lee A, Chang BL, Solot C, et al. Defining risk of postoperative obstructive sleep apnea in patients with 22q11.2DS undergoing pharyngeal flap surgery for velopharyngeal dysfunction using polysomnographic evaluation. *Cleft Palate Craniofac J*. 2020;57(7):808-818. http://doi.org/10.1177/1055665619900871
135. Blenke EJSM, Anderson AR, Raja H, Bew S, Knight LC. Obstructive sleep apnoea adenotonsillectomy in children: when to refer to a centre with a paediatric intensive care unit? *J Laryngol Otol*. 2008;122(1):42-45. http://doi.org/10.1017/S0022215107007566
136. Dyce O, McDonald-McGinn D, Kirschner RE, Zackai E, Young K, Jacobs IN. Otolaryngologic manifestations of the 22q11.2 deletion syndrome. *Arch Otolaryngol Head Neck Surg*. 2002;128(12):1408-1412. http://doi.org/10.1001/archotol.128.12.1408
137. Ebert B, Sidman J, Morrell N, Roby BB. Congenital and iatrogenic laryngeal and vocal abnormalities in patients with 22q11.2 deletion. *Int J Pediatr Otorhinolaryngol*. 2018;109:17-20. http://doi.org/10.1016/j.ijporl.2018.03.006
138. Jones JW, Tracy M, Perryman M, Arganbright JM. Airway anomalies in patients with 22q11.2 deletion syndrome: a 5-year review. *Ann Otol Rhinol Laryngol*. 2018;127(6):384-389. http://doi.org/10.1177/0003489418771711
139. Sacca R, Zur KB, Crowley TB, Zackai EH, Valverde KD, McDonald-McGinn DM. Association of airway abnormalities with 22q11.2 deletion syndrome. *Int J Pediatr Otorhinolaryngol*. 2017;96:11-14. http://doi.org/10.1016/j.ijporl.2017.02.012
140. Grasso F, Cirillo E, Quaremba G, et al. Otolaryngological features in a cohort of patients affected with 22q11.2 deletion syndrome: a monocentric survey. *Am J Med Genet A*. 2018;176(10):2128-2134. http://doi.org/10.1002/ajmg.a.40518
141. Zim S, Schelper R, Kellman R, Tatum S, Ploutz-Snyder R, Shprintzen R. Thickness and histologic and histochemical properties of the superior pharyngeal constrictor muscle in velocardiofacial syndrome. *Arch Facial Plast Surg*. 2003;5(6):503-510. http://doi.org/10.1001/archfaci.5.6.503
142. Verheij E, Derks LSM, Stegeman I, Thomeer HGXM. Prevalence of hearing loss and clinical otologic manifestations in patients with 22q11.2 deletion syndrome: a literature review. *Clin Otolaryngol*. 2017;42(6):1319-1328. http://doi.org/10.1111/coa.12874
143. Reyes MR, LeBlanc EM, Bassila MK. Hearing loss and otitis media in velo-cardio-facial syndrome. *Int J Pediatr Otorhinolaryngol*. 1999;47(3):227-233. http://doi.org/10.1016/s0165-5876(98)00180-3
144. Weir FW, Wallace SA, White DR, Hatch JL, Nguyen SA, Meyer TA. Otologic and audiologic outcomes in pediatric patients with Velo-

cardio-facial (22q11 deletion) syndrome. *Otol Neurotol*. 2017;38(1):73-78. http://doi.org/10.1097/MAO.0000000000001226
145. Digilio MC, Pacifico C, Tieri L, Marino B, Giannotti A, Dallapiccola B. Audiological findings in patients with microdeletion 22q11 (di George/velocardiofacial syndrome). *Br J Audiol*. 1999;33(5):329-333. http://doi.org/10.3109/03005369909090116
146. Loos E, Verhaert N, Willaert A, et al. Malformations of the middle and inner ear on CT imaging in 22q11 deletion syndrome. *Am J Med Genet A*. 2016;170(11):2975-2983. http://doi.org/10.1002/ajmg.a.37872
147. Verheij E, Elden L, Crowley TB, et al. Anatomic malformations of the middle and inner ear in 22q11.2 deletion syndrome: case series and literature review. *AJNR Am J Neuroradiol*. 2018;39(5):928-934. http://doi.org/10.3174/ajnr.A5588
148. Oskarsdóttir S, Holmberg E, Fasth A, Strömland K. Facial features in children with the 22q11 deletion syndrome. *Acta Paediatr*. 2008;97(8):1113-1117. http://doi.org/10.1111/j.1651-2227.2008.00858.x
149. McDonald-McGinn DM, Kirschner R, Goldmuntz E, et al. The Philadelphia story: the 22q11.2 deletion: report on 250 patients. *Genet Couns*. 1999;10(1):11-24.
150. Jiramongkolchai P, Kumar MS, Chinnadurai S, Wootten CT, Goudy SL. Prevalence of hearing loss in children with 22q11.2 deletion syndrome. *Int J Pediatr Otorhinolaryngol*. 2016;87:130-133. http://doi.org/10.1016/j.ijporl.2016.06.005
151. Gokturk B, Topcu-Yilmaz P, Bozkurt B, et al. Ocular findings in children with 22q11.2 deletion syndrome. *J Pediatr Ophthalmol Strabismus*. 2016;53(4):218-222. http://doi.org/10.3928/01913913-20160427-01
152. Forbes BJ, Binenbaum G, Edmond JC, DeLarato N, McDonald-McGinn DM, Zackai EH. Ocular findings in the chromosome 22q11.2 deletion syndrome. *J AAPOS*. 2007;11(2):179-182. http://doi.org/10.1016/j.jaapos.2006.08.006
153. Casteels I, Casaer P, Gewillig M, Swillen A, Devriendt K. Ocular findings in children with a microdeletion in chromosome 22q11.2. *Eur J Pediatr*. 2008;167(7):751-755. http://doi.org/10.1007/s00431-007-0582-0
154. Binenbaum G, McDonald-McGinn DM, Zackai EH, et al. Sclerocornea associated with the chromosome 22q11.2 deletion syndrome. *Am J Med Genet A*. 2008;146A(7):904-909. http://doi.org/10.1002/ajmg.a.32156
155. Oberoi S, Huynh L, Vargervik K. Velopharyngeal, speech and dental characteristics as diagnostic aids in 22q11.2 deletion syndrome. *J Calif Dent Assoc*. 2011;39(5):327-332.
156. Nordgarden H, Lima K, Skogedal N, Følling I, Storhaug K, Abrahamsen TG. Dental developmental disturbances in 50 individuals with the 22q11.2 deletion syndrome; relation to medical conditions? *Acta Odontol Scand*. 2012;70(3):194-201. http://doi.org/10.3109/00016357.2011.629624
157. Klingberg G, Lingström P, Oskarsdóttir S, Friman V, Bohman E, Carlén A. Caries-related saliva properties in individuals with 22q11 deletion syndrome. *Oral Surg Oral Med Oral Pathol Oral Rad Endod*. 2007;103(4):497-504. http://doi.org/10.1016/j.tripleo.2006.09.018
158. Klingberg G, Oskarsdóttir S, Johannesson EL, Norén JG. Oral manifestations in 22q11 deletion syndrome. *Int J Paediatr Dent*. 2002;12(1):14-23.
159. da Silva Dalben G, Richieri-Costa A, de Assis Taveira LA. Tooth abnormalities and soft tissue changes in patients with velocardiofacial syndrome. *Oral Surg Oral Med Oral Pathol Oral Rad Endod*. 2008;106(2):e46-e51. http://doi.org/10.1016/j.tripleo.2008.04.019
160. Wong DH, Rajan S, Hallett KB, Manton DJ. Medical and dental characteristics of children with chromosome 22q11.2 deletion syndrome at the Royal Children's Hospital, Melbourne. *Int J Paediatr Dent*. 2021;31(6):682-690. http://doi.org/10.1111/ipd.12755
161. Wilson WR, Gewitz M, Lockhart PB, et al. Prevention of viridans group streptococcal infective endocarditis: a scientific statement from the American Heart Association. *Circulation*. 2021;143(20):e963-e978. Published correction appears in *Circulation*. 2021;144(9):e192. Published correction appears in *Circulation*. 2022;145(17):e868. http://doi.org/10.1161/CIR.0000000000000969.
162. Choi JH, Shin YL, Kim GH, et al. Endocrine manifestations of chromosome 22q11.2 microdeletion syndrome. *Horm Res*. 2005;63(6):294-299. http://doi.org/10.1159/000086745
163. Ryan AK, Goodship JA, Wilson DI, et al. Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study. *J Med Genet*. 1997;34(10):798-804. http://doi.org/10.1136/jmg.34.10.798
164. Rayannavar A, Levitt Katz LE, Crowley TB, et al. Association of hypocalcemia with congenital heart disease in 22q11.2 deletion syndrome. *Am J Med Genet A*. 2018;176(10):2099-2103. http://doi.org/10.1002/ajmg.a.40495
165. Fujii S, Nakanishi T. Clinical manifestations and frequency of hypocalcemia in 22q11.2 deletion syndrome. *Pediatr Int*. 2015;57(6):1086-1089. http://doi.org/10.1111/ped.12665
166. Shugar AL, Shapiro JM, Cytrynbaum C, Hedges S, Weksberg R, Fishman L. An increased prevalence of thyroid disease in children with 22q11.2 deletion syndrome. *Am J Med Genet A*. 2015;167(7):1560-1564. http://doi.org/10.1002/ajmg.a.37064
167. Weinzimer SA, McDonald-McGinn DM, Driscoll DA, Emanuel BS, Zackai EH, Moshang T Jr. Growth hormone deficiency in patients with a 22q11.2 deletion: expanding the phenotype. *Pediatrics*. 1998;101(5):929-932. http://doi.org/10.1542/peds.101.5.929
168. Uy R, Jacobs N, Mziray-Andrew C. Inflammatory bowel disease and diverticulosis in an adolescent with DiGeorge syndrome. *J Pediatr Gastroenterol Nutr*. 2016;62(5):e43-e45. http://doi.org/10.1097/MPG.0000000000000497
169. Digilio MC, Giannotti A, Castro M, et al. Screening for celiac disease in patients with deletion 22q11.2 (DiGeorge/velo-cardio-facial syndrome). *Am J Med Genet A*. 2003;121A(3):286-288. http://doi.org/10.1002/ajmg.a.20254
170. Van Batavia JP, Crowley TB, Burrows E, et al. Anomalies of the genitourinary tract in children with 22q11.2 deletion syndrome. *Am J Med Genet A*. 2019;179(3):381-385. http://doi.org/10.1002/ajmg.a.61020
171. Óskarsdóttir S, Belfrage M, Sandstedt E, Viggedal G, Uvebrant P. Disabilities and cognition in children and adolescents with 22q11 deletion syndrome. *Dev Med Child Neurol*. 2005;47(3):177-184. http://doi.org/10.1017/s0012162205000320
172. Urschel D, Hernandez-Trujillo VP. Spectrum of genetic T-cell disorders from 22q11.2DS to CHARGE. *Clin Rev Allergy Immunol*. 2022;63(1):99-105. http://doi.org/10.1007/s12016-022-08927-z
173. Sullivan KE. Chromosome 22q11.2 deletion syndrome and DiGeorge syndrome. *Immunol Rev*. 2019;287(1):186-201. http://doi.org/10.1111/imr.12701
174. McDonald-McGinn DM, Sullivan KE. Chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). *Medicine (Baltimore)*. 2011;90(1):1-18. http://doi.org/10.1097/MD.0b013e3182060469
175. Cancrini C, Romiti ML, Finocchi A, et al. Post-natal ontogenesis of the T-cell receptor CD4 and CD8 Vbeta repertoire and immune function in children with DiGeorge syndrome. *J Clin Immunol*. 2005;25(3):265-274. http://doi.org/10.1007/s10875-005-4085-3
176. Giardino G, Radwan N, Koletsi P, et al. Clinical and immunological features in a cohort of patients with partial DiGeorge syndrome followed at a single center. *Blood*. 2019;133(24):2586-2596. http://doi.org/10.1182/blood.2018885244
177. Framme JL, Lundqvist C, Lundell AC, et al. Long-term follow-up of newborns with 22q11 deletion syndrome and low TRECs. *J Clin Immunol*. 2022;42(3):618-633. http://doi.org/10.1007/s10875-021-01201-5
178. Smetanova J, Milota T, Rataj M, Bloomfield M, Sediva A, Klocperk A. Accelerated maturation, exhaustion, and senescence of T cells in 22q11.2 deletion syndrome. *J Clin Immunol*. 2022;42(2):274-285. http://doi.org/10.1007/s10875-021-01154-9

179. Björk AH, Óskarsdóttir S, Andersson BA, Friman V. Antibody deficiency in adults with 22q11.2 deletion syndrome. *Am J Med Genet A*. 2012;158A(8):1934-1940. http://doi.org/10.1002/ajmg.a.35484
180. Maggadottir SM, Sullivan KE. The diverse clinical features of chromosome 22q11.2 deletion syndrome (DiGeorge syndrome). *J Allergy Clin Immunol Pract*. 2013;1(6):589-594. http://doi.org/10.1016/j.jaip.2013.08.003
181. Cancrini C, Puliafito P, Digilio MC, et al. Clinical features and follow-up in patients with 22q11.2 deletion syndrome. *J Pediatr*. 2014;164(6):1475-1480.e2. http://doi.org/10.1016/j.jpeds.2014.01.056
182. Deshpande DR, Demirdag YY, Marsh RA, Sullivan KE, Orange JS, USIDNET Consortium. Relationship between severity of T cell lymphopenia and immune dysregulation in patients with DiGeorge syndrome (22q11.2 deletions and/or related TBX1 mutations): a USIDNET Study. *J Clin Immunol*. 2021;41(1):29-37. http://doi.org/10.1007/s10875-020-00854-y
183. Gennery AR, Barge D, O'Sullivan JJ, Flood TJ, Abinun M, Cant AJ. Antibody deficiency and autoimmunity in 22q11.2 deletion syndrome. *Arch Dis Child*. 2002;86(6):422-425. http://doi.org/10.1136/adc.86.6.422
184. Di Cesare S, Puliafito P, Ariganello P, et al. Autoimmunity and regulatory T cells in 22q11.2 deletion syndrome patients. *Pediatr Allergy Immunol*. 2015;26(6):591-594. http://doi.org/10.1111/pai.12420
185. Markert ML, Gupton SE, McCarthy EA. Experience with cultured thymus tissue in 105 children. *J Allergy Clin Immunol*. 2022;149(2):747-757. http://doi.org/10.1016/j.jaci.2021.06.028
186. Perez EE, Bokszczanin A, McDonald-McGinn D, Zackai EH, Sullivan KE. Safety of live viral vaccines in patients with chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). *Pediatrics*. 2003;112(4):e325. http://doi.org/10.1542/peds.112.4.e325
187. Iroh Tam PY, Hanisch BR, Klammer K, DeVries AS. Measles vaccine strain from the skin rash of a DiGeorge patient receiving tumor necrosis factor inhibitor. *Pediatr Infect Dis J*. 2014;33(1):117. http://doi.org/10.1097/INF.0000000000000073
188. Hofstetter AM, Jakob K, Klein NP, et al. Live vaccine use and safety in DiGeorge syndrome. *Pediatrics*. 2014;133(4):e946-e954. http://doi.org/10.1542/peds.2013-0831
189. Moylett EH, Wasan AN, Noroski LM, Shearer WT. Live viral vaccines in patients with partial DiGeorge syndrome: clinical experience and cellular immunity. *Clin Immunol*. 2004;112(1):106-112. http://doi.org/10.1016/j.clim.2004.02.008
190. Patel PO, Baylis AL, Hickey SE, et al. Bleeding severity and phenotype in 22q11.2 deletion syndrome – a cross-sectional investigation. *J Pediatr*. 2021;235:220-225. http://doi.org/10.1016/j.jpeds.2021.03.071
191. Zwifelhofer NMJ, Bercovitz RS, Weik LA, et al. Hemizygosity for the gene encoding glycoprotein Ibβ is not responsible for macrothrombocytopenia and bleeding in patients with 22q11 deletion syndrome. *J Thromb Haemost*. 2019;17(2):295-305. http://doi.org/10.1111/jth.14357
192. Brenner MK, Clarke S, Mahnke DK, et al. Effect of 22q11.2 deletion on bleeding and transfusion utilization in children with congenital heart disease undergoing cardiac surgery. *Pediatr Res*. 2016;79(2):318-324. http://doi.org/10.1038/pr.2015.216
193. Kratz CP, Niehues T, Lyding S, Heusch A, Janssen G, Göbel U. Evans syndrome in a patient with chromosome 22q11.2 deletion syndrome: a case report. *Pediatr Hematol Oncol*. 2003;20(2):167-172. http://doi.org/10.1080/0880010390158685
194. Akar NA, Adekile AD. Chromosome 22q11.2 deletion presenting with immune-mediated cytopenias, macrothrombocytopenia and platelet dysfunction. *Med Princ Pract*. 2007;16(4):318-320. http://doi.org/10.1159/000102157
195. Davies JK, Telfer P, Cavenagh JD, Foot N, Neat M. Autoimmune cytopenias in the 22q11.2 deletion syndrome. *Clin Lab Haematol*. 2003;25(3):195-197. http://doi.org/10.1046/j.1365-2257.2003.00508.x
196. Stevens T, van der Werff Ten Bosch J, De Rademaeker M, Van Den Bogaert A, van den Akker M. Risk of malignancy in 22q11.2 deletion syndrome. *Clin Case Rep*. 2017;5(4):486-490. http://doi.org/10.1002/ccr3.880
197. McDonald-McGinn DM, Reilly A, Wallgren-Pettersson C, et al. Malignancy in chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome) 5. *Am J Med Genet A*. 2006;140A(8):906-909. http://doi.org/10.1002/ajmg.a.31199
198. Bassett AS, Chow EW, Husted J, et al. Clinical features of 78 adults with 22q11 deletion syndrome. *Am J Med Genet A*. 2005;138(4):307-313. http://doi.org/10.1002/ajmg.a.30984
199. de Reuver S, Homans JF, Schlösser TPC, et al. 22q11.2 deletion syndrome as a human model for idiopathic scoliosis. *J Clin Med*. 2021;10(21):4823. http://doi.org/10.3390/jcm10214823
200. Morava E, Lacassie Y, King A, Illes T, Marble M. Scoliosis in velocardio-facial syndrome. *J Pediatr Orthop*. 2002;22(6):780-783.
201. Cheng JC, Castelein RM, Chu WC, et al. Adolescent idiopathic scoliosis. *Nat Rev Dis Primers*. 2015;1:15030. http://doi.org/10.1038/nrdp.2015.30
202. Boot E, Butcher NJ, van Amelsvoort TA, et al. Movement disorders and other motor abnormalities in adults with 22q11.2 deletion syndrome. *Am J Med Genet A*. 2015;167A(3):639-645. http://doi.org/10.1002/ajmg.a.36928
203. Friedman N, Rienstein S, Yeshayahu Y, Gothelf D, Somech R. Post-childhood presentation and diagnosis of DiGeorge syndrome. *Clin Pediatr (Phila)*. 2016;55(4):368-373. http://doi.org/10.1177/0009922815591090
204. Poirsier C, Besseau-Ayasse J, Schluth-Bolard C, et al. A French multicenter study of over 700 patients with 22q11 deletions diagnosed using FISH or aCGH. *Eur J Hum Genet*. 2016;24(6):844-851. http://doi.org/10.1038/ejhg.2015.219
205. Sullivan KE, McDonald-McGinn DM, Driscoll DA, et al. Juvenile rheumatoid arthritis-like polyarthritis in chromosome 22q11.2 deletion syndrome (DiGeorge anomalad/velocardiofacial syndrome/conotruncal anomaly face syndrome). *Arthritis Rheum*. 1997;40(3):430-436. http://doi.org/10.1002/art.1780400307
206. Ming JE, McDonald-McGinn DM, Megerian TE, et al. Skeletal anomalies and deformities in patients with deletions of 22q11. *Am J Med Genet*. 1997;72(2):210-215. http://doi.org/10.1002/(sici)1096-8628(19971017)72:2<210::aid-ajmg16>3.0.co;2-q
207. Derbent M, Yilmaz Z, Baltaci V, Saygili A, Varan B, Tokel K. Chromosome 22q11.2 deletion and phenotypic features in 30 patients with conotruncal heart defects. *Am J Med Genet A*. 2003;116A(2):129-135. http://doi.org/10.1002/ajmg.a.10832
208. Vantrappen G, Devriendt K, Swillen A, et al. Presenting symptoms and clinical features in 130 patients with the velo-cardio-facial syndrome. The Leuven experience. *Genet Couns*. 1999;10(1):3-9.
209. Ricchetti ET, States L, Hosalkar HS, et al. Radiographic study of the upper cervical spine in the 22q11.2 deletion syndrome. *J Bone Joint Surg Am*. 2004;86(8):1751-1760. http://doi.org/10.2106/00004623-200408000-00020
210. Veerapandiyan A, Blalock D, Ghosh S, Ip E, Barnes C, Shashi V. The role of cephalometry in assessing velopharyngeal dysfunction in velocardiofacial syndrome. *Laryngoscope*. 2011;121(4):732-737. http://doi.org/10.1002/lary.21449
211. Pelkonen P, Lahdenne P, Lantto R, Honkanen V. Chronic arthritis associated with chromosome deletion 22q11.2 syndrome. *J Rheumatol*. 2002;29(12):2648-2650.
212. Torg JS, Ramsey-Emrhein JA. Management guidelines for participation in collision activities with congenital, developmental, or postinjury lesions involving the cervical spine. *Clin Sports Med*. 1997;16(3):501-530. http://doi.org/10.1016/s0278-5919(05)70037-5
213. Roizen NJ, Higgins AM, Antshel KM, Fremont W, Shprintzen R, Kates WR. 22q11.2 deletion syndrome: are motor deficits more than expected for IQ level? *J Pediatr*. 2010;157(4):658-661. http://doi.org/10.1016/j.jpeds.2010.04.073
214. Cunningham AC, Fung W, Massey TH, et al. Movement disorder phenotypes in children with 22q11.2 deletion syndrome. *Mov Disord*. 2020;35(7):1272-1274. http://doi.org/10.1002/mds.28078

215. Dines JN, Golden-Grant K, LaCroix A, et al. TANGO2: expanding the clinical phenotype and spectrum of pathogenic variants. *Genet Med*. 2019;21(3):601-607. Published correction appears in *Genet Med*. 2019;21(8):1899. http://doi.org/10.1038/s41436-018-0137-y.
216. Leoni C, Stevenson DA, Geiersbach KB, et al. Neural tube defects and atypical deletion on 22q11.2. *Am J Med Genet A*. 2014;164A(11):2701-2706. http://doi.org/10.1002/ajmg.a.36701
217. Hyde J, Eidels A, van Amelsvoort T, Myin-Germeys I, Campbell L. Gene deletion and sleep depletion: exploring the relationship between sleep and affect in 22q11.2 deletion syndrome. *J Genet Psychol*. 2021;182(5):304-316. http://doi.org/10.1080/00221325.2021.1930995
218. Vergaelen E, Claes S, Kempke S, Swillen A. High prevalence of fatigue in adults with a 22q11.2 deletion syndrome. *Am J Med Genet A*. 2017;173(4):858-867. http://doi.org/10.1002/ajmg.a.38094
219. Roizen NJ, Antshel KM, Fremont W, et al. 22q11.2DS deletion syndrome: developmental milestones in infants and toddlers. *J Dev Behav Pediatr*. 2007;28(2):119-124. http://doi.org/10.1097/01.DBP.0000267554.96081.12
220. Cunningham AC, Delport S, Cumines W, et al. Developmental coordination disorder, psychopathology and IQ in 22q11.2 deletion syndrome. *Br J Psychiatry*. 2018;212(1):27-33. http://doi.org/10.1192/bjp.2017.6
221. Van Den Heuvel E, Manders E, Swillen A, Zink I. Atypical language characteristics and trajectories in children with 22q11.2 deletion syndrome. *J Commun Disord*. 2018;75:37-56. http://doi.org/10.1016/j.jcomdis.2018.06.001
222. Moss EM, Batshaw ML, Solot CB, et al. Psychoeducational profile of the 22q11.2 microdeletion: a complex pattern. *J Pediatr*. 1999;134(2):193-198. http://doi.org/10.1016/s0022-3476(99)70415-4
223. Woodin M, Wang PP, Aleman D, McDonald-McGinn D, Zackai E, Moss E. Neuropsychological profile of children and adolescents with the 22q11.2 microdeletion. *Genet Med*. 2001;3(1):34-39. http://doi.org/10.1097/00125817-200101000-00008
224. Moberg PJ, Richman MJ, Roalf DR, et al. Neurocognitive functioning in patients with 22q11.2 deletion syndrome: a meta-analytic review. *Behav Genet*. 2018;48(4):259-270. http://doi.org/10.1007/s10519-018-9903-5
225. De Smedt B, Devriendt K, Fryns JP, Vogels A, Gewillig M, Swillen A. Intellectual abilities in a large sample of children with Velo-cardio-facial syndrome: an update. *J Intellect Disabil Res*. 2007;51(Pt 9):666-670. http://doi.org/10.1111/j.1365-2788.2007.00955.x
226. Wang PP, Woodin MF, Kreps-Falk R, Moss EM. Research on behavioral phenotypes: velocardiofacial syndrome (deletion 22q11.2). *Dev Med Child Neurol*. 2000;42(6):422-427. http://doi.org/10.1017/s0012162200000785
227. De Smedt B, Swillen A, Verschaffel L, Ghesquière P. Mathematical learning disabilities in children with 22q11.2 deletion syndrome: a review. *Dev Disabil Res Rev*. 2009;15(1):4-10. http://doi.org/10.1002/ddrr.44
228. Tobia V, Brigstocke S, Hulme C, Snowling MJ. Developmental changes in the cognitive and educational profiles of children and adolescents with 22q11.2 deletion syndrome. *J Appl Res Intellect Disabil*. 2018;31(1):e177-e181. http://doi.org/10.1111/jar.12344
229. Quintero AI, Beaton EA, Harvey DJ, Ross JL, Simon TJ. Common and specific impairments in attention functioning in girls with chromosome 22q11.2 deletion, fragile X or Turner syndromes. *J Neurodev Disord*. 2014;6(1):5. http://doi.org/10.1186/1866-1955-6-5
230. Antshel KM, Fremont W, Ramanathan S, Kates WR. Predicting cognition and psychosis in young adults with 22q11.2 deletion syndrome. *Schizophr Bull*. 2017;43(4):833-842. http://doi.org/10.1093/schbul/sbw135
231. de Sonneville LMJ, Hidding E, van Engeland H, Vorstman JAS, Sijmens-Morcus MEJ, Swaab H. Executive functioning and its relation to ASD and ADHD symptomatology in 22q11.2 deletion syndrome. *Child Neuropsychol*. 2018;24(1):1-19. http://doi.org/10.1080/09297049.2016.1221064
232. Duijff SN, Klaassen PWJ, de Veye HFNS, Beemer FA, Sinnema G, Vorstman JA. Cognitive development in children with 22q11.2 deletion syndrome. *Br J Psychiatry*. 2012;200(6):462-468. http://doi.org/10.1192/bjp.bp.111.097139
233. Reilly C, Senior J, Murtagh L. A comparative study of educational provision for children with neurogenetic syndromes: parent and teacher survey. *J Intellect Disabil Res*. 2015;59(12):1094-1107. http://doi.org/10.1111/jir.12210
234. Mosheva M, Pouillard V, Fishman Y, et al. Education and employment trajectories from childhood to adulthood in individuals with 22q11.2 deletion syndrome. *Eur Child Adolesc Psychiatry*. 2019;28(1):31-42. http://doi.org/10.1007/s00787-018-1184-2
235. Antshel K, Hier B, Fremont W, Faraone SV, Kates W. Predicting reading comprehension academic achievement in late adolescents with velo-cardio-facial (22q11.2 deletion) syndrome (VCFS): a longitudinal study. *J Intellect Disabil Res*. 2014;58(10):926-939. http://doi.org/10.1111/jir.12134
236. Niklasson L, Gillberg C. The neuropsychology of 22q11 deletion syndrome. A neuropsychiatric study of 100 individuals. *Res Dev Disabil*. 2010;31(1):185-194. http://doi.org/10.1016/j.ridd.2009.09.001
237. Swillen A, Moss E, Duijff S. Neurodevelopmental outcome in 22q11.2 deletion syndrome and management. *Am J Med Genet A*. 2018;176(10):2160-2166. http://doi.org/10.1002/ajmg.a.38709
238. Morrison S, Chawner SJRA, van Amelsvoort TAMJ, et al. Cognitive deficits in childhood, adolescence and adulthood in 22q11.2 deletion syndrome and association with psychopathology. *Transl Psychiatry*. 2020;10(1):53. http://doi.org/10.1038/s41398-020-0736-7
239. Selten I, Boerma T, Everaert E, Vansteensel MJ, Vorstman J, Wijnen F. Narrative comprehension and production abilities of children with 22q11.2 deletion syndrome. *Res Dev Disabil*. 2021;119, 104109. http://doi.org/10.1016/j.ridd.2021.104109
240. Chawner SJRA, Doherty JL, Moss H, et al. Childhood cognitive development in 22q11.2 deletion syndrome: case-control study. *Br J Psychiatry*. 2017;211(4):223-230. http://doi.org/10.1192/bjp.bp.116.195651
241. Reilly C. Behavioural phenotypes and special educational needs: is aetiology important in the classroom? *J Intellect Disabil Res*. 2012;56(10):929-946. http://doi.org/10.1111/j.1365-2788.2012.01542.x
242. Sandini C, Schneider M, Eliez S, Armando M. Association between parental anxiety and depression level and psychopathological symptoms in offspring with 22q11.2 deletion syndrome. *Front Psychiatry*. 2020;11:646. http://doi.org/10.3389/fpsyt.2020.00646
243. Briegel W, Andritschky C. Psychological adjustment of children and adolescents with 22q11.2 deletion syndrome and their mothers' stress and coping-A longitudinal study. *Int J Environ Res Public Health*. 2021;18(5):2707. http://doi.org/10.3390/ijerph18052707
244. Swillen A, Vandeputte L, Cracco J, et al. Neuropsychological, learning and psychosocial profile of primary school aged children with the velo-cardio-facial syndrome (22q11 deletion): evidence for a nonverbal learning disability? *Child Neuropsychol*. 1999;5(4):230-241. http://doi.org/10.1076/0929-7049(199912)05:04;1-R;FT230
245. Niarchou M, Zammit S, van Goozen SHM, et al. Psychopathology and cognition in children with 22q11.2 deletion syndrome. *Br J Psychiatry*. 2014;204(1):46-54. http://doi.org/10.1192/bjp.bp.113.132324
246. Weisman O, Guri Y, Gur RE, et al. Subthreshold psychosis in 22q11.2 deletion syndrome: multisite naturalistic study. *Schizophr Bull*. 2017;43(5):1079-1089. http://doi.org/10.1093/schbul/sbx005
247. Yi JJ, Tang SX, McDonald-McGinn DM, et al. Contribution of congenital heart disease to neuropsychiatric outcome in school-age children with 22q11.2 deletion syndrome. *Am J Med Genet B Neuropsychiatr Genet*. 2014;165B(2):137-147. http://doi.org/10.1002/ajmg.b.32215
248. Serur Y, Sofrin Frumer D, Daon K, et al. Psychiatric disorders and autism in young children with 22q11.2 deletion syndrome compared to children with idiopathic autism. *Eur Psychiatry*. 2019;55:116-121. http://doi.org/10.1016/j.eurpsy.2018.10.007

249. Wagner KE, Kates WR, Fremont W, Antshel KM. Childhood predictors of young adult social functioning in 22q11.2 deletion syndrome. *J Autism Dev Disord*. 2017;47(8):2480-2501. http://doi.org/10.1007/s10803-017-3165-6
250. Hooper SR, Curtiss K, Schoch K, Keshavan MS, Allen A, Shashi V. A longitudinal examination of the psychoeducational, neurocognitive, and psychiatric functioning in children with 22q11.2 deletion syndrome. *Res Dev Disabil*. 2013;34(5):1758-1769. http://doi.org/10.1016/j.ridd.2012.12.003
251. Debbané M, Glaser B, David MK, Feinstein C, Eliez S. Psychotic symptoms in children and adolescents with 22q11.2 deletion syndrome: neuropsychological and behavioral implications. *Schizophr Res*. 2006;84(2-3):187-193. http://doi.org/10.1016/j.schres.2006.01.019
252. Solot CB, Moore TM, Crowley TB, et al. Early language measures associated with later psychosis features in 22q11.2 deletion syndrome. *Am J Med Genet B Neuropsychiatr Genet*. 2020;183(6):392-400. http://doi.org/10.1002/ajmg.b.32812
253. Vorstman JA, Breetvelt EJ, Thode KI, Chow EW, Bassett AS. Expression of autism spectrum and schizophrenia in patients with a 22q11.2 deletion. *Schizophr Res*. 2013;143(1):55-59. http://doi.org/10.1016/j.schres.2012.10.010
254. Niarchou M, Chawner SJRA, Fiksinski A, et al. Attention deficit hyperactivity disorder symptoms as antecedents of later psychotic outcomes in 22q11.2 deletion syndrome. *Schizophr Res*. 2019;204:320-325. http://doi.org/10.1016/j.schres.2018.07.044
255. Armando M, Lin A, Pontillo M, Vicari S. Prevalence and treatment of psychiatric disorders other than psychosis in children and adolescents with 22q11DS: examining associations with social and role functioning. *Psychiatry Res*. 2017;254:238-243. http://doi.org/10.1016/j.psychres.2017.04.019
256. Young AS, Shashi V, Schoch K, Kwapil T, Hooper SR. Discordance in diagnoses and treatment of psychiatric disorders in children and adolescents with 22q11.2 deletion syndrome. *Asian J Psychiatry*. 2011;4(2):119-124. http://doi.org/10.1016/j.ajp.2011.03.002
257. Khokhar JY, Dwiel LL, Henricks AM, Doucette WT, Green AI. The link between schizophrenia and substance use disorder: a unifying hypothesis. *Schizophr Res*. 2018;194:78-85. http://doi.org/10.1016/j.schres.2017.04.016
258. Fair C, Cuttance J, Sharma N, et al. International and interdisciplinary identification of health care transition outcomes. *JAMA Pediatr*. 2016;170(3):205-211. http://doi.org/10.1001/jamapediatrics.2015.3168
259. Stam H, Hartman EE, Deurloo JA, Groothoff J, Grootenhuis MA. Young adult patients with a history of pediatric disease: impact on course of life and transition into adulthood. *J Adolesc Health*. 2006;39(1):4-13. http://doi.org/10.1016/j.jadohealth.2005.03.011
260. Mayo D, Bolden KA, Simon TJ, Niendam TA. Bullying and psychosis: the impact of chronic traumatic stress on psychosis risk in 22q11.2 deletion syndrome – a uniquely vulnerable population. *J Psychiatr Res*. 2019;114:99-104. http://doi.org/10.1016/j.jpsychires.2019.04.011
261. Goodwin J, Swaab L, Campbell LE. 'She'll be able to live independently … as long as I'm around': the "lived" experience of parenting a child with 22q11.2 deletion syndrome in the transition to adulthood. *J Appl Res Intellect Disabil*. 2020;33(3):565-573. http://doi.org/10.1111/jar.12700
262. Buijs PCM, Boot E, Shugar A, Fung WLA, Bassett AS. Internet safety issues for adolescents and adults with intellectual disabilities. *J Appl Res Intellect Disabil*. 2017;30(2):416-418. http://doi.org/10.1111/jar.12250
263. Loo JCY, Boot E, Corral M, Bassett AS. Personalized medical information card for adults with 22q11.2 deletion syndrome: an initiative to improve communication between patients and healthcare providers. *J Appl Res Intellect Disabil*. 2020;33(6):1534-1540. http://doi.org/10.1111/jar.12747
264. Blagowidow N, Nowakowska B, Schindewolf E, et al. Prenatal Screening and Diagnostic Considerations for 22q11.2 Microdeletions. *Genes*. 2023;14(1):160. http://doi.org/10.3390/genes14010160
265. Boot E, Óskarsdóttir S, Loo JCY, et al. Updated clinical practice recommendations for managing adults with 22q11.2 deletion syndrome. *Genet Med*. 2023;25:100344. http://doi.org/10.1016/j.gim.2022.11.012