



## REVIEW

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



Erik Boot<sup>1,2,3,\*</sup> , Sólveig Óskarsdóttir<sup>4,5,\*</sup>, Joanne C.Y. Loo<sup>2</sup>, Terrence Blaine Crowley<sup>6</sup>, Ani Orchanian-Cheff<sup>7</sup>, Danielle M. Andrade<sup>8</sup>, Jill M. Arganbright<sup>9</sup>, René M. Castelein<sup>10</sup>, Christine Cserti-Gazdewich<sup>11</sup>, Steven de Reuver<sup>10</sup>, Ania M. Fiksinski<sup>3,12</sup>, Gunilla Klingberg<sup>13</sup>, Anthony E. Lang<sup>14</sup>, Maria R. Mascarenhas<sup>15,16</sup>, Edward M. Moss<sup>17</sup>, Beata Anna Nowakowska<sup>18</sup>, Erwin Oechslin<sup>19</sup>, Lisa Palmer<sup>2</sup>, Gabriela M. Repetto<sup>20</sup>, Nikolai Gil D. Reyes<sup>14</sup>, Maude Schneider<sup>21</sup>, Candice Silversides<sup>22</sup>, Kathleen E. Sullivan<sup>16,23</sup>, Ann Swillen<sup>24</sup>, Therese A.M.J. van Amelsvoort<sup>3</sup>, Jason P. Van Batavia<sup>25,26</sup>, Claudia Vingerhoets<sup>1,3</sup>, Donna M. McDonald-McGinn<sup>6,16,27,\*</sup> , Anne S. Bassett<sup>2,28,29,30,\*</sup>

### ARTICLE INFO

#### Article history:

Received 3 May 2022

Received in revised form

15 November 2022

Accepted 15 November 2022

Available online 2 February 2023

#### Keywords:

Adults

Aging

Clinical practice guidelines

DiGeorge syndrome

Treatment

### ABSTRACT

This review aimed to update the clinical practice guidelines for managing adults with 22q11.2 deletion syndrome (22q11.2DS). The 22q11.2 Society recruited expert clinicians worldwide to revise the original clinical practice guidelines for adults in a stepwise process according to best practices: (1) a systematic literature search (1992–2021), (2) study selection and synthesis by clinical experts from 8 countries, covering 24 subspecialties, and (3) formulation of consensus recommendations based on the literature and further shaped by patient advocate survey results. Of 2441 22q11.2DS-relevant publications initially identified, 2344 received full-text review, with 2318 meeting inclusion criteria (clinical care relevance to 22q11.2DS) including 894 with potential relevance to adults. The evidence base remains limited. Thus multidisciplinary recommendations represent statements of current best practice for this evolving field, informed by the available literature. These recommendations provide guidance for the recognition, evaluation, surveillance, and management of the many emerging and chronic 22q11.2DS-associated multisystem morbidities relevant to adults. The recommendations also address key genetic counseling and psychosocial considerations for the increasing numbers of adults with this complex condition.

© 2023 The Authors. Published by Elsevier Inc. on behalf of American College of Medical Genetics and Genomics. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

\*Correspondence and requests for materials should be addressed to Erik Boot, Advism, 's Heeren Loo Zorggroep, Berkenweg 11, 3818 LA Amersfoort, The Netherlands. E-mail address: [erik.boot@sheerenloo.nl](mailto:erik.boot@sheerenloo.nl) OR Sólveig Óskarsdóttir, Department of Pediatric Rheumatology and Immunology, Queen Silvia Children's Hospital, SE-416 85, Gothenburg, Sweden. E-mail address: [solveig.oskarsdottir@vgregion.se](mailto:solveig.oskarsdottir@vgregion.se) OR Donna M. McDonald-McGinn, Division of Human Genetics, 22q and You Center, and Clinical Genetics Center, The Children's Hospital of Philadelphia and the Department of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania, 34th Street and Civic Center Boulevard, Philadelphia, Pennsylvania 19104. E-mail address: [mcginn@chop.edu](mailto:mcginn@chop.edu) OR Anne S. Bassett, The Dalglish Family 22q Clinic, Toronto General Hospital, University Health Network, 585 University Avenue, Toronto, Ontario M5G 2N2, Canada. E-mail address: [anne.bassett@utoronto.ca](mailto:anne.bassett@utoronto.ca)

Affiliations are at the end of the document.

doi: <https://doi.org/10.1016/j.gim.2022.11.012>

1098-3600/© 2023 The Authors. Published by Elsevier Inc. on behalf of American College of Medical Genetics and Genomics. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

## Introduction

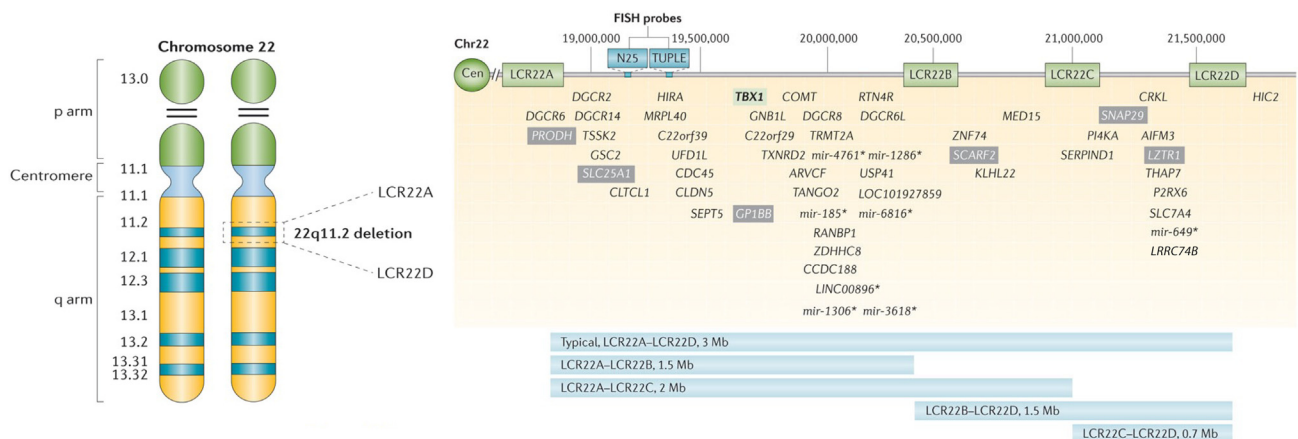
22q11.2 deletion syndrome (22q11.2DS) (OMIM #192430, #188400), [Figure 1](#), the most common microdeletion syndrome in humans,<sup>1</sup> is a multisystem disorder associated with congenital and later-onset health issues, with an estimated prevalence of 1 in 2148 live births (4.7 per 10,000) based on a recent population-based newborn screening study.<sup>2</sup> Despite the prevalence, substantial morbidity, and availability of clinical testing, 22q11.2DS, previously known as DiGeorge syndrome or velo-cardio-facial syndrome, remains largely unrecognized in adults by both health care providers and society at large.

The first clinical practice guidelines for managing adults with 22q11.2DS were published in 2015.<sup>3</sup> Subsequently, there has been considerable new research on associated conditions and functioning. With a growing adult population with 22q11.2DS, owing primarily to improved detection and clinical care of children, updated guidance is needed. Using a

systematic review of the literature published between 1992–2021, we have updated the 2015 clinical practice guidelines for adults with 22q11.2DS. Adults are defined in this study as age 18 years and older, thus spanning transition from pediatric care to the elderly age range.

## Materials and Methods

The 22q11.2 Society recruited expert clinicians worldwide to revise the original clinical practice guidelines for adults in 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](#)),<sup>4</sup> guided by a methodologist, (2) study selection and synthesis by these clinical experts from 8 countries, covering 24 subspecialties, and (3) creation of a multidisciplinary consensus document using the Grading of Recommendations Assessment, Development and



**Figure 1** Chromosome 22 ideogram and genes within the chromosome 22q11.2 LCR22A to LCR22D region. On the left is a 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 2 horizontal lines in the p arm. The recurrent 22q11.2 deletions occur 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) on 22q11.2 (LCR22A and LCR22D), which flank the typical 2.5 to 3 Mb deletion, are indicated. On the right is a schematic representation of the 2.5 to 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), approximate coordinates are from genome build GRCh37. Common 22q11.2 deletions are shown, with the typical 2.5 to 3 Mb deletion (LCR22A to LCR22D) on top and the nested deletions, with their respective deletion sizes, indicated below. Each of the deletions shown is flanked by a particular set of 2 LCR22s. Rare deletions not mediated by LCRs are not shown. Common commercial probes for FISH are indicated (N25 and TUPLE). The 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. Pathogenic 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 hyperprolinemia), 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  $\beta$ -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). Other genes associated with autosomal recessive conditions include cell division cycle protein 45 (*CDC45*; associated with CGS (craniosynostosis cleft lip/palate gastrointestinal and genitourinary) syndrome; and Meier–Gorlin syndrome), and transport and Golgi organization 2 homolog (*TANGO2*; associated with metabolic crisis with encephalopathy, rhabdomyolysis, cardiac arrhythmia, neurodegeneration, and sudden death). FISH, fluorescence in situ hybridization; Mb, megabase. (Figure adapted with permission from McDonald-McGinn et al.<sup>1</sup>)

Evaluation framework,<sup>5</sup> based on the literature, 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 22q11.2 deletion region (ie, overlapping the low-copy repeats (LCRs) LCR22A to LCR22B region and most commonly overlapping the LCR22A to LCR22D region; see Genetics section and [Figure 1](#)). Reports involving other conditions, such as distal 22q11.2 deletions or restricted to prenatal issues, were excluded. Given the limited number of systematic studies, eg, randomized controlled trials, in the 22q11.2DS literature, 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.<sup>5</sup> Draft recommendations per subspecialty/topic were formulated based on critical appraisal of the literature, consideration of being more beneficial than harmful, and best practice per the experts involved (each having seen tens to hundreds of adult patients with 22q11.2DS), while incorporating input from patient advocate survey results. The revised document was subsequently approved for submission by 2 external reviewers (a family member of an adult with 22q11.2DS and a genetics expert), neither of whom were part of the guidelines updating process. A list of subspecialty areas of the expert panel is provided in [Supplemental Table 1](#).

[Supplemental Methods](#) contain further details of methods used, including the full search strategy.

## Results

The systematic literature search (January 1, 1992 to April 14, 2021) initially identified 6018 citations putatively related to 22q11.2DS across the lifespan ([Supplemental Figure 1](#)); 3577 were excluded after screening (most were duplicates or involved other conditions) and 97 were not able to be retrieved. This resulted in 2344 reports included for full-text review, of which a final 2318 met inclusion criteria. Of these, 894 were deemed to have potential relevance to adults. See [Supplemental Table 2](#) for the list of the 2441 articles that were sought for retrieval.

The patient advocate survey results, completed by eight 22q11.2DS patient advocacy organizations, based in 7 countries on 3 continents and representing 7624 families, prioritized updated guidelines to improve awareness among 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. They ranked the top 5 most relevant subspecialty areas of care, regardless of age, as cardiology; brain and behavior (psychiatry, neurology, early intervention, education); genetics (testing, counseling, reproductive health); ear, nose, and throat (chronic infections, hearing, palate); and immunology, rheumatology, and hematology-oncology. Regarding knowledge transfer, the respondents conveyed a need for guidelines to be shareable, portable, and available on the internet/social media.

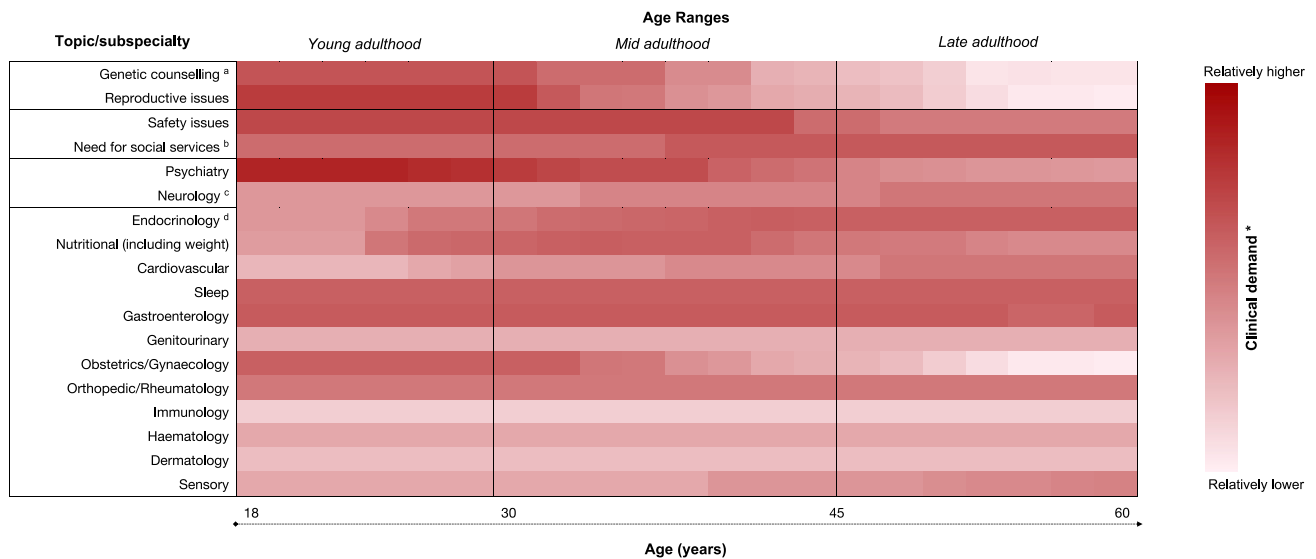
The vast majority of scientific literature relevant to clinical management of adults with 22q11.2DS involved study designs in low confidence categories,<sup>5</sup> with vanishingly few randomized clinical trials, formal systematic reviews, or meta-analyses. Given the state of the scientific evidence available and the challenges inherent to 22q11.2DS, which include multiple comorbidities and high interindividual variability, recommendations in these updated guidelines were not formally graded on an individual basis.<sup>5</sup> Globally, the recommendations should therefore be considered to be weak (ie, conditional or individualized), in all cases emphasizing those with lowest harm and highest potential benefit for patients with this rare condition, informed by long-term experience with patients with 22q11.2DS and their families, that reflect current best practice.<sup>5</sup>

## Clinical Practice Recommendations—General Aspects of Management

### Brief overview

Adults with 22q11.2DS require follow-up, regardless of age at diagnosis. There may be congenital/early-onset manifestations of 22q11.2DS with persisting ramifications, but in virtually all cases, later-onset conditions emerge that require clinical attention. Knowledge about the high variability in number and severity of manifestations and 22q11.2DS-related risks is essential. Periodic assessments may reveal (previously) undetected medical conditions, enabling early treatment, and should be tailored to different life stages. The multisystem nature and developmental complexity of 22q11.2DS demand broad consideration of signs and symptoms ([Figures 2](#) and [3](#)), with visits therefore often necessitating considerable time and effort. Having an interested/informed generalist involved for patient care/follow-up/coordination is advantageous.

Typically, for the associated conditions, standard management and treatment strategies apply, as for idiopathic forms of each condition, with similar efficacy expected. The main caveat is that 22q11.2DS-related comorbidity demands attention by all clinicians, regardless of their subspecialty, with balancing of risks/benefits for proposed treatments. Repetition and reinforcement of information, written summaries, and use of simple diagrams and visual aids to illustrate major points can be helpful.



**Figure 2** Estimated multidisciplinary demand over time for adults with 22q11.2 deletion syndrome. Lasagna plot displaying current estimates of both the proportion of individuals requiring attention on a specific topic/subspecialty and the severity of the manifestations over time. Lighter shades should not be interpreted as inconsequential but weighed relative to patient population prevalence and intensity of symptoms/conditions. <sup>a</sup>Caveats for genetic counseling and reproductive issues would be to consider providing information about new clinical expectations, and for men about reproductive risks, regardless of age. <sup>b</sup>Which services are needed will change over time for the individual. <sup>c</sup>Neurologic manifestations involve both seizures and movement disorders, including age-dependent parkinsonism. <sup>d</sup>Spectrum of endocrinological manifestations, including chronic diseases (eg, hypothyroidism and type 2 diabetes). \*Clinical demand estimates may be higher or lower for certain individuals than the estimates portrayed.

Involvement of families and/or caregivers, who often provide monitoring/oversight of treatment compliance and results, is usually essential.<sup>3</sup> Patients and relatives/caregivers require their own individual time with professionals. Personalized medical information cards may be useful.<sup>6</sup> Optimizing lifetime health and functioning is the overall goal and includes clear coordination between all involved.

Figure 3 presents the multisystem features and Table 1 an overview of recommendations for periodic assessments and health monitoring, in order of their clinical relevance to 22q11.2DS and the clinical attention typically required.<sup>3,7</sup> International/local differences should be considered. Of note, however, these recommendations are most relevant to high-income countries and with corresponding resources. We begin with general cross-cutting issues then address individual systems, ordering these in line with clinical relevance, as in Figure 3 and Table 1.

## Genetic testing and related issues

22q11.2DS is a contiguous gene deletion syndrome, ie, affected individuals have loss of 1 copy at the 22q11.2 locus. Most deletions occur as de novo (spontaneous) events, unrelated to maternal or paternal age.<sup>8</sup> Approximately 5% to 10% are inherited from a parent who may be unaware of their genetic diagnosis, with clinical features ranging from characteristic to relatively mild.<sup>9-12</sup> Males and females with

the 22q11.2 deletion have a 50% chance of transmitting the deletion at each pregnancy. Genetic testing should be offered to all parents of affected patients, regardless of age.<sup>3,9-12</sup> When neither parent has the deletion, reproductive counselling includes a small elevated recurrence risk due to the rare report of germline mosaicism.<sup>13,14</sup> Notably, features in an affected parent do not predict possible findings in affected offspring and vice versa. A genetic diagnosis and genetic counseling can be helpful at any age and regardless of reproduction-related issues.<sup>3,15</sup>

Recurrent 22q11.2 deletions originate from nonhomologous allelic recombination between LCRs.<sup>16-18</sup> The most common 22q11.2 deletion occurs between LCR22s A to D (85%-90%). This approximately 2.5 to 3-megabase (Mb) deletion involves more than 40 protein-coding genes.<sup>1</sup> Smaller nested proximal 1.5 Mb (LCR22A to LCR22B) and 2.0 Mb (LCR22A to LCR22C) deletions account for 5% to 10% of deletions.<sup>1,19</sup> Rarer LCR22B to LCR22D and LCR22C to LCR22D nested distal deletions appear to have an overlapping phenotype.<sup>20</sup> Distal deletions beyond LCR22D (involving other LCRs, LCR22E to LCR22H, OMIM #611867) should not be confused with 22q11.2DS<sup>21</sup> and are not the subject of these clinical practice recommendations.

Several laboratory techniques are available to confirm or exclude the presence of a 22q11.2 deletion, including chromosomal microarray analysis (CMA), which identifies genome-wide copy number variants (CNVs). CMA results provide information on 22q11.2 deletion size and the presence of additional clinically relevant genome-wide CNVs.<sup>1</sup>

Two other commonly available methods require an index of suspicion: fluorescence in situ hybridization and multiplex-ligation dependent probe amplification. Standard fluorescence in situ hybridization probes target the proximal LCR22A to LCR22B region and cannot determine deletion size nor identify deletions outside of the proximal LCR22A to LCR22B region, eg, LCR22B to LCR22D.<sup>1,19</sup> Multiplex-ligation dependent probe amplification interrogates the LCR22A to LCR22D region using several probes, providing information on deletion size but not about changes beyond this region.<sup>22,23</sup> Except for very rare translocations, karyotyping will not detect 22q11.2 deletions.

Patients with atypical features should prompt consideration of additional relevant variants. These may not be rare in 22q11.2DS<sup>24</sup> and include genome-wide CNVs and other pathogenic variants<sup>25</sup> and variants on the remaining chromosome 22 allele that unmask an autosomal recessive condition.<sup>19,26-36</sup> CMA reveals CNVs; exome or genome sequencing may reveal other types of variants.<sup>37</sup> Limitations of most genetic tests include high cost, limited availability, and lack of reimbursement or coverage by health systems.

## Genetic counseling

Genetic counseling is essential in the ongoing management of adults with 22q11.2DS and for their relatives at multiple time points.<sup>3,7</sup> Clinicians should provide updated information, adapted to the life stage and presentation of the individual and family. A stepwise approach discussing later-onset features and their management, while addressing possible stigma associated with psychiatric illness, is helpful.<sup>38,39</sup> Traditional genetic counseling approaches must be modified to take into account learning deficits and common neuropsychiatric/other medical issues, eg, for adults who may need extra help to appreciate the information.<sup>3,40,41</sup> Involving caregivers and/or partners is often essential.

Perceptions of the condition may differ for a parent with 22q11.2DS from those of parents of an offspring with a de novo 22q11.2 deletion.<sup>42</sup> Explaining to affected adults how their child may be “like them” (in having a 22q11.2 deletion) and yet not “like them” (in having a different clinical expression) can be challenging.<sup>3</sup> A diagram showing the contribution of a different intact chromosome 22 for a parent and offspring may be helpful. When a parent is identified as having 22q11.2DS only after the birth of an affected child, they require genetic counseling that focuses on their own diagnosis and associated features and risks, in addition to counseling provided in regard to the child that includes assessing the need for additional supports.<sup>3,15,42,43</sup> Available reproductive options, including prenatal testing and pre-conception options such as preimplantation genetic diagnostics using in vitro fertilization, should also be discussed to prepare for any potential future pregnancy.<sup>15</sup>

## Transition to adult care

Transition planning requires a timely and stepwise approach, starting from puberty, that attends to each of the multidimensional needs of the individual with 22q11.2DS.<sup>44,45</sup> Ongoing mental and physical health monitoring is essential, and coordinated multidisciplinary care should involve the family health care provider and interested adult specialists, with transfer of care organized by the pediatric providers.<sup>46</sup> Other fundamental transition components include education or vocational training, employment, and housing. Caregivers and/or relevant agencies may facilitate the acquisition and maintenance of employment and/or volunteer work opportunities, all of which can enhance schedule/routine, mental and physical health, and self-esteem. Optimal independent living situations support community integration and functional independence while maintaining safety. Other considerations include legal guardianship, ideally before age 18 years, and medical benefits when universal health care is unavailable.

## Aging and outcome

The lifetime burden of illness is substantial, with concurrence of medical conditions (multimorbidity)<sup>47</sup> comparable with that of the general population several decades older.<sup>48,49</sup> At relatively young ages, adults with 22q11.2DS have increased vulnerability to age-related diseases including obesity, type 2 diabetes, Parkinson disease (PD), and hearing loss.<sup>50-55</sup> Life expectancy for adults on average is less than that expected for unaffected relatives.<sup>56</sup> Probability of survival to age 45 years has been reported to be approximately 95% for those with no major congenital heart disease (CHD) and 72% for those with major CHD (eg, tetralogy of Fallot, truncus arteriosus); no significant effects of intellectual disability or treated major psychiatric illness were detected.<sup>56</sup> Deaths are most commonly due to cardiovascular causes, even when compared with other individuals with CHD, and with proportionately more sudden cardiac deaths in individuals with 22q11.2DS.<sup>56-60</sup>

Further studies at older ages are required to better define natural history. To date, most reports involve adults in their mid-30s on average.<sup>3</sup> Multimorbidity and related polypharmacy<sup>49</sup> urge the need for a holistic, proactive, multisystem approach versus one solely focused on demand-driven care or on one organ system. Medication reviews may optimize appropriate prescribing.<sup>61</sup> Monitoring and prompts for medication intake are often needed. At any age, selected patients and families could potentially benefit from palliative care support. Long-term planning, eg, as parents/primary caregivers age, may involve siblings, partners, and/or agencies and others in the circle of care.

| Genetics                                    |                                                                  |
|---------------------------------------------|------------------------------------------------------------------|
|                                             | Additional clinically relevant variant                           |
| Cognitive and adaptive functioning          |                                                                  |
|                                             | Intellectual disabilities                                        |
|                                             | Intellectual decline                                             |
|                                             | Deficits in adaptive functioning                                 |
|                                             | Impairments in executive functions                               |
| Psychiatry                                  |                                                                  |
|                                             | Anxiety disorders                                                |
|                                             | Psychotic disorders, schizophrenia                               |
|                                             | Autism spectrum disorders                                        |
|                                             | Persisting attention deficit disorders                           |
|                                             | Substance-use disorders                                          |
|                                             | Catatonia                                                        |
| Neurology                                   |                                                                  |
|                                             | Seizures, often secondary, recurrent                             |
|                                             | Epilepsy                                                         |
|                                             | Parkinsonism, early-onset Parkinson's disease                    |
|                                             | Other motor disorders (e.g., dystonia, myoclonus)                |
|                                             | Asymmetric facies / hemifacial paresis                           |
|                                             | White matter hyperintensity signals on MRI                       |
| Endocrinology and metabolism                |                                                                  |
|                                             | Hypocalcaemia / hypoparathyroidism                               |
|                                             | Hypomagnesaemia                                                  |
|                                             | Thyroid disease, usually hypothyroidism                          |
|                                             | Obesity                                                          |
|                                             | Type 2 diabetes                                                  |
| Cardiology / cardiovascular and respiratory |                                                                  |
|                                             | Congenital heart disease requiring follow-up                     |
|                                             | Hypertension, arrhythmia / heart failure, aortic root dilatation |
|                                             | Lymphedema                                                       |
|                                             | Asthma                                                           |
| Sleep                                       |                                                                  |
|                                             | Sleep pattern disruptions                                        |
|                                             | Obstructive sleep apnea                                          |
| Gastroenterology                            |                                                                  |
|                                             | General GI symptoms (e.g., constipation, dysphagia)              |
|                                             | Gastro-esophageal reflux disease                                 |
|                                             | Cholelithiasis                                                   |
|                                             | Fatty liver                                                      |
| Genitourinary, gynecology                   |                                                                  |
|                                             | Congenital anomalies, renal cysts, renal failure                 |
|                                             | Menstrual disorders (e.g., dysmenorrhea)                         |
| Sexual and reproductive health / obstetrics |                                                                  |
|                                             | Sexual / reproductive knowledge deficits                         |
|                                             | High-risk sexual behaviours / STIs                               |
|                                             | Pregnancy and delivery complications                             |
| General surgery                             |                                                                  |
|                                             | Surgical complications (all types)                               |
|                                             | Hernias, all types                                               |
|                                             | Pilonidal sinus, varicose veins                                  |
| Skeletal                                    |                                                                  |
|                                             | Scoliosis of varying degrees                                     |
|                                             | Patellar dislocation                                             |
|                                             | Clubfoot                                                         |
|                                             | Arthritis, rheumatoid and others                                 |
|                                             | Minor vertebral / rib anomalies                                  |
| Immunology and related                      |                                                                  |
|                                             | Autoimmune disease and atopy                                     |
|                                             | Poor vaccine responses                                           |
|                                             | Recurrent infections                                             |
| Haematology and oncology                    |                                                                  |
|                                             | Mild-moderate thrombocytopenia / mild cytopenias                 |
|                                             | Immune thrombocytopenia (ITP) / hemolytic anemia                 |
|                                             | Impaired hemostasis (e.g. epistaxis, menorrhagia)                |
|                                             | Anemia of chronic disease                                        |
|                                             | Possible increased risk of cancer                                |
| Sensory deficits                            |                                                                  |
|                                             | Refractive errors requiring glasses                              |
|                                             | Hearing loss (especially high-frequency loss)                    |
|                                             | Severe olfactory deficits                                        |
|                                             | Tortuosity of retinal vessels                                    |
| Dental                                      |                                                                  |
|                                             | Dental caries                                                    |
|                                             | Enamel hypoplasia, low saliva secretion                          |
|                                             | Malocclusion                                                     |
| Aging and outcome                           |                                                                  |
|                                             | Multimorbidity and polypharmacy                                  |
|                                             | Elevated premature mortality risk                                |

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

**Figure 3 Features and risks in adults with 22q11.2 deletion syndrome.** This figure presents the multisystem features and relative risks of these features associated with 22q11.2 deletion syndrome in adults with this genetic condition. The relative prevalence of each feature is indicated by a box to the left of the named feature; thus, features that are most common have a dark blue box, less common an intermediate blue box, and rare but clinically relevant a pale blue box. A white box indicates features that may be commonly associated but do not require clinical attention. *GI*, gastrointestinal; *MRI*, magnetic resonance imaging; *STI*, sexually transmitted infection.

## Cognitive and adaptive functioning

There is substantial variability in intellect in adults with 22q11.2DS. The most prevalent full scale IQ is in the borderline range (70 to 85).<sup>40,62</sup> 22q11.2DS imparts on average a 30 IQ point deficit relative to parental IQ,<sup>63</sup> with

expectations lower for those with an inherited deletion<sup>64</sup> and somewhat higher for those with a nested LCR22A to LCR22B deletion.<sup>65</sup>

Regardless of intellect, specific learning disabilities/impairments in cognitive functioning may be present. Although there are often no significant differences between

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

| Assessments and Management                                                                                                                                                         | At Diagnosis/Initial Assessment | At Follow-up (Every 1-2 y) |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|----------------------------|
| <b>Genetic</b>                                                                                                                                                                     |                                 |                            |
| Parental genetic testing (FISH, MLPA, or microarray) <sup>a</sup>                                                                                                                  | ✓                               |                            |
| Genetic counseling (including recurrence risk, update on natural history, management)                                                                                              | ✓                               | ✓                          |
| Family planning, reproductive and prenatal counseling                                                                                                                              | ✓                               | ✓                          |
| Additional genetic testing <sup>b</sup>                                                                                                                                            | If applicable                   |                            |
| <b>General</b>                                                                                                                                                                     |                                 |                            |
| Consultation with clinician(s) experienced with 22q11.2DS <sup>c</sup>                                                                                                             | ✓                               | ✓                          |
| Comprehensive history-taking (including family history), systems review, and medication review                                                                                     | ✓                               | ✓                          |
| Assessment of need for/coordination with specialist(s) providing care                                                                                                              | ✓                               | ✓                          |
| Nutritional assessment; diet and exercise counseling                                                                                                                               | ✓                               | ✓                          |
| Sleep evaluation (consider polysomnography), sleep hygiene recommendations                                                                                                         | ✓                               | ✓                          |
| Vaccination counseling, other standard preventive health care measures                                                                                                             | ✓                               | ✓                          |
| Assessment of functioning (including hygiene), care/supports (family/community/government), safety issues (eg, financial, internet)                                                | ✓                               | ✓                          |
| <b>Physical examination and additional diagnostic tests</b>                                                                                                                        |                                 |                            |
| BMI, resting heart rate, blood pressure                                                                                                                                            | ✓                               | ✓                          |
| 22q11.2DS-relevant laboratory tests <sup>d</sup>                                                                                                                                   | ✓                               | ✓                          |
| Echocardiogram                                                                                                                                                                     | ✓^                              |                            |
| Abdominal ultrasound                                                                                                                                                               | ✓^                              |                            |
| Routine care/hearing, vision, dental assessment <sup>e</sup>                                                                                                                       | ✓                               | ✓                          |
| <b>Targeted clinical assessments<sup>f</sup></b>                                                                                                                                   |                                 |                            |
| CNS—psychiatric, neurologic, neurocognitive assessments (including for anxiety, psychosis, seizures, movement disorders, formal testing of cognitive and adaptive functioning/ADL) | ✓                               | ✓                          |
| Congenital cardiac (ACHD) and cardiovascular risk assessment                                                                                                                       | ✓                               | ✓                          |
| Endocrinology                                                                                                                                                                      | ✓                               | ✓                          |
| Genitourinary, obstetrics/gynecology assessment (including contraception, pregnancy risks, and safe sex counseling)                                                                | ✓                               | ✓                          |
| Hematology, gastroenterology, orthopedic/rheumatology, respiratory, immunology, otolaryngology, ophthalmology, dermatology                                                         | ✓                               | ✓                          |

“✓^” indicates if not previously performed as an adult or in recent years, and with a low threshold for late-onset manifestations of 22q11.2DS, including aortic root dilation, gallstones, fatty liver, and nephrocalcinosis.

22q11.2DS, 22q11.2 deletion syndrome; ACHD, adult congenital heart disease; ADL, activities of daily living; BMI, body mass index; CBC, complete blood count; CNS, central nervous system; FISH, fluorescence in situ hybridization; MLPA, multiplex-ligation dependent probe amplification.

Adapted from Fung et al.<sup>3</sup> and Bassett et al.<sup>7</sup>

<sup>a</sup>Strategy depending on test availability.

<sup>b</sup>When rare recessive condition associated with a gene in the 22q11.2 deletion region is suspected or atypical phenotypic features are observed.

<sup>c</sup>Having seen several adult patients with 22q11.2DS both in consultation and follow-up (if possible).

<sup>d</sup>CBC and differential, thyroid-stimulating hormone, (pH-corrected ionized) calcium, magnesium, creatinine, lipid profile, glucose, and HbA1c; other examples are parathyroid hormone, electrolytes, and liver function tests (especially alanine aminotransferase); checking CBC and calcium preoperatively and postoperatively, as well as regularly during pregnancy, also recommended.

<sup>e</sup>Follow-up intervals may be longer.

<sup>f</sup>Consideration of referral to and collaboration with (medical) specialists in individual cases; especially in cases with complex diagnosis and/or complex management, taking into account the variability in natural history between patients and increased risk of many health issues.

verbal and performance IQ in adults with 22q11.2DS,<sup>62,66</sup> many have relative strength in verbal abilities, thus may have a “hidden disability.” Executive functions, such as problem solving, flexibility, working memory, concentration, and impulse inhibition, may be differentially affected.<sup>67</sup> Thinking is often literal or concrete, arithmetic particularly challenging, and social cognition is frequently affected, with difficulty recognizing emotions or sarcasm and interpreting others’ intentions and behavior (theory of mind).<sup>40,66-69</sup> Collectively, cognitive deficits may contribute to poor social judgment and decision-making. Some individuals may be impulsive, emotionally immature, and/or lack critical judgment yet be desirous of friendship. These factors increase the risk of experiencing traumatic events such as financial and/or sexual exploitation, bullying/abuse, and safety issues, including those related to the internet.<sup>70,71</sup> Challenges may be compounded by reluctance and/or inability to admit to or recognize deficits and/or to ask for assistance.

Levels of adaptive functioning also vary widely.<sup>66,67,72</sup> Higher IQ, better executive functioning, and absence of psychotic illness predict better overall adaptive functioning, on average.<sup>66,67</sup> Stress,<sup>73</sup> sleep disturbances,<sup>74</sup> and fatigue<sup>75</sup> may negatively affect functioning. Relative strengths include daily living skills such as household chores and employment suited to the individual;<sup>66,67</sup> more than 60% of adults are employed in the open market or assisted employment.<sup>66,76</sup> Most require assistance with completing forms, managing money, and making complex life and work decisions. Some require more basic help, eg, assistance with or reminders for personal hygiene. Although many meet criteria for intellectual disability, severe disabilities are relatively rare.<sup>77</sup>

Individuals with 22q11.2DS may perceive more stress and/or have less resilience in coping with day-to-day stress, including change, than others.<sup>73,78-81</sup> However, response to stressors may not be predictable,<sup>73,78-81</sup> eg, many adults with 22q11.2DS cope better than expected with major events such as bereavement, especially when regular routines and supports remain in place.

Assessment of cognitive and adaptive strengths and weaknesses, especially at transition to adulthood, is recommended, with more detailed neurocognitive assessments needed in individual cases. This is often essential to provide evidence of need for supports and services and can help prevent overestimation of abilities. Counseling caregivers and others about realistic expectations given the individual’s capabilities and hidden disabilities can reduce stress and thus improve outcomes.<sup>66,67</sup> Repeated assessments of cognition and adaptive functioning are recommended when changes are noted and/or new neuropsychiatric illnesses (eg, schizophrenia, PD) arise.<sup>77,82,83</sup>

Generally, structure and daily routine, in addition to adequate treatment of comorbid illnesses, facilitate optimal overall functioning. Relative strengths in visual over verbal memory and in domains of daily life functioning can be used to optimize and/or sustain independence. Remediating and compensating measures for problem areas should be

taken as possible. Family members, other caregivers, and professionals involved in care should be cognizant of potential problems to provide support accordingly.<sup>3</sup> To facilitate understanding, it may help to ask the patient to explain things back and/or write/text them. Part-time employment may be preferred and accommodations in the workplace may be needed, eg, more breaks, shorter working hours, and/or repeated instruction. Because patients may not complain, even when symptoms are significant, extra effort may be required in clinical assessments.

## Clinical Practice Recommendations—By System, Emphasizing Treatable Associated Conditions

Table 1 and Figure 3 provide details pertinent to both the section above on general aspects of management, and to the following recommendations that emphasize treatable associated conditions that are presented by system.

### Psychiatry

Psychiatric illnesses comprise the most common group of later-onset conditions in 22q11.2DS<sup>48,84,85</sup> and are typically of greatest concern to patients and their families because of perceived burden, stigma, and effects on quality of life/daily functioning.<sup>66,81,86,87</sup> Reassuringly, these are treatable conditions although may constitute management challenges and comorbidity is common.<sup>3,84,88-90</sup>

Most common in 22q11.2DS are anxiety disorders, with about 2 to 3 times the expected population prevalence.<sup>84,91</sup> Also important are psychotic disorders such as schizophrenia given the 20-fold increased risk over general population expectations; about 1 in every 4 to 5 adults with 22q11.2DS will develop schizophrenia.<sup>48,84,85,92,93</sup> Autism spectrum disorders and some cases of attention deficit disorders diagnosed in childhood persist in adulthood and may co-occur with other psychiatric disorders.<sup>84,91,94,95</sup> Major depression and bipolar disorder appear to have similar prevalence as in the general population.<sup>48,84,85</sup> Substance use disorders may be less common<sup>78,96</sup> yet remain important for individual management (cannabis, eg, conveys risk for psychotic, mood and hyperemesis disorders, and poor functioning).<sup>97</sup> There is some evidence for increased risk of catatonia, usually with psychotic illness.<sup>88</sup>

Appreciation of learning/intellectual disabilities and issues such as suggestibility is important as well as appreciation of comorbid physical conditions, symptoms, and treatments. Also noteworthy is worsening of emotional/temper outbursts that are common in 22q11.2DS.<sup>3</sup> These are often a harbinger of untreated or undertreated anxiety or psychotic illness. Other illnesses (eg, epilepsy, obstructive sleep apnea, asthma, hypocalcemia), and factors such as caffeine<sup>3</sup> and emotional immaturity may contribute but are rarely wholly causal.<sup>98</sup>

The individual with 22q11.2DS may need extra time and a comfort level difficult to achieve in a brief encounter compared with other patients and may still have difficulty articulating symptoms and changes in functioning. Collateral information and obtaining an appreciation of the environment and its challenges are valuable as well as weighing expectations and individual capabilities.<sup>3,66,67</sup> Challenges with respect to diagnosis of psychiatric disorders in the context of intellectual disabilities can be overcome in most cases with extra care in history-taking and collateral information from those who know the patient best.<sup>77,99</sup>

Early detection, diagnosis, and prompt institution of treatment are important for effective management. Awareness of the patient's long-term baseline state and monitoring for changes in emotions, thinking, sleep, fatigue and other physical states, behavior, and overall functioning is crucial. This will facilitate diagnosis and ongoing management and provides goals for determining efficacy of treatment.<sup>3,75,77,88</sup> Attention to other 22q11.2DS-associated conditions should include caution about endless searches for physical causes of treatable psychiatric illness.

As for virtually all 22q11.2DS-associated conditions, standard management according to general clinical practice guidelines for the psychiatric illness is recommended. This includes pharmacologic treatments, eg, antipsychotic and antianxiety/antidepressant medications, with proven efficacy.<sup>100-103</sup> The main caveat is attention to both existing comorbidities and risks in 22q11.2DS. Thus, careful monitoring and management strategies for anticipated side effects are needed.<sup>54,55,104-106</sup> Patients may benefit from a "start low, go slow" approach to medication dosing. One example is the effective treatment with clozapine for schizophrenia, in which the lowered seizure threshold of 22q11.2DS may be managed by this strategy and consideration of prophylactic use of anticonvulsant medication.<sup>106</sup> Standard non-pharmacologic treatments are also often helpful but may need to be adapted to specific needs of the affected individuals.<sup>107</sup> Fear of, and associated stigma related to, standard treatments for psychiatric illness should not prevent the adult with 22q11.2DS from receiving effective recommended management.

## Neurology

The main neurologic manifestations involve seizures and movement disorders, with a lower threshold for both in 22q11.2DS related to primary cerebral dysfunction and secondary to other 22q11.2DS-associated conditions and/or their treatments.

Single and recurrent seizures are common and can be of various types, including generalized tonic-clonic, typical or atypical absences, myoclonic, or focal with preserved or impaired awareness. Atonic, clonic, and tonic seizures are rare.<sup>108-111</sup> Adults with 22q11.2DS have a 4-fold increased risk of epilepsy.<sup>112</sup> Seizures deemed acute symptomatic or

provoked may be secondary to hypocalcemia, hypomagnesemia, fever, medications, etc.<sup>108,110-113</sup> In some patients, seizures/epilepsy may be associated with stroke or malformations of cortical development (eg, polymicrogyria, focal cortical dysplasia, periventricular nodular heterotopia, and/or hippocampal malrotation).<sup>110-112,114,115</sup> Increased white matter hyperintensity signals are common but have no clear clinical relevance.<sup>116</sup>

Adults also have an increased risk of developing PD, particularly early-onset PD.<sup>50,51</sup> Clinical and neuropathological findings and treatment response are largely indistinguishable from idiopathic PD.<sup>50,53</sup> Parkinsonism not meeting criteria for PD, dystonia, and functional neurologic disorders, may also be more common in adults with 22q11.2DS than in the general population.<sup>105,117,118</sup> Myoclonus, motor tics, restless legs, postural and action tremors, and drug-induced movement disorders are also reported.<sup>105,118-120</sup> Hypocalcemia may induce or worsen movement disorders.<sup>121,122</sup>

To ensure prompt diagnosis and treatment, periodic neurologic enquiry/assessments should be considered for seizures/seizure-like episodes and cardinal motor features of PD or other movement disorders, supplemented by standardized rating scales and ancillary procedures.<sup>82,88</sup> When diagnostic uncertainty exists, dopaminergic imaging (when available) may assist in differentiating drug-induced from neurodegenerative parkinsonism.<sup>53,123</sup> Treatment of seizures is tailored to seizure type and contributing conditions, as for idiopathic epilepsy. For patients with suggestive features, collaboration with a 22q11.2DS specialist, epileptologist, and/or movement disorders neurologist is recommended.<sup>82,88</sup>

## Other individual systems, medical and surgical issues

### Endocrinology and metabolism

Endocrinopathies that require ongoing attention comprise a major part of the multimorbidity observed in adults with 22q11.2DS.<sup>49</sup>

Hypocalcemia associated with relative or absolute hypoparathyroidism is an issue for most patients and may arise or recur at any age and despite apparent resolution in childhood.<sup>113,124</sup> There is an increased risk with any biological stress, including surgery, fracture, injury, childbirth, or infection. In some cases, hypothyroidism and hypomagnesemia may be associated and/or contributory conditions.<sup>113</sup> Hypocalcemia may be asymptomatic, associated with fatigue, irritability, and abnormal involuntary movements of any sort, or prolongation of the QT interval on electrocardiogram. Undetected/untreated hypocalcemia can have serious consequences, including seizures, cardiac arrhythmias, and rarely, cardiomyopathy.<sup>112,125</sup> Longer term issues may include lower bone mineral density,<sup>126</sup> with risk for osteopenia/osteoporosis. Hypocalcemia may be worsened by alcohol or soda drinks, especially colas.<sup>127</sup>

Regular investigations include calcium, parathyroid hormone, magnesium, thyroid-stimulating hormone, and creatinine concentrations. Targeted calcium monitoring should be considered at vulnerable times, including peri-operatively, perinatally, in pregnancy, and during acute illness. Daily vitamin D supplementation is recommended for all adults, sometimes with calcium supplementation. Management using hormonally active vitamin D metabolites, eg, calcitriol, is reserved for more severe/refractory cases usually with endocrinologist consultation. Caution is advised with respect to overcorrection, which can result in iatrogenic hypercalcemia, renal calculi, and renal failure. This can be inadvertent, eg, with dehydration or treatment compliance changes, but needs to be identified and reversed.

Thyroid disease is common in adults. Nearly 1 in 4 require treatment for primary hypothyroidism, with onset on average decades earlier and with less female predominance, compared with general population expectations.<sup>49,113</sup> Another 1 in 20 has hyperthyroidism, often requiring management of secondary hypothyroidism after treatment. Symptoms of thyroid disease may be confused with those of neuropsychiatric and other conditions.<sup>113</sup> Thyroid function should be assessed annually. Standard treatments are effective.

Predisposition to obesity appears to be part of 22q11.2DS, with onset often in adolescence or young adulthood.<sup>54</sup> Also, even after accounting for known risk factors (eg, family history, ethnicity, medications, obesity), the 22q11.2 deletion conveys increased risk of type 2 diabetes with on average younger (by 18 years) onset than population expectations.<sup>55</sup> Thus, implementing dietary and exercise preventive/management measures as early as possible is recommended and other standard treatments, eg, hypoglycemics, statins, as indicated. As yet, less is known about metabolic syndrome, nonalcoholic fatty liver, and other cardiometabolic conditions including hyperlipidemias in 22q11.2DS.<sup>128</sup>

### Cardiovascular and respiratory

CHD represents a chronic disease requiring regular follow-up at an adult CHD center.<sup>129,130</sup> Prevalence in adults appears lower than that reported in children with 22q11.2DS, likely related to broader ascertainment strategies, but elevated mortality risk, including premature sudden death, may also be a factor.<sup>48,56,59,60,131,132</sup>

Assessment for the necessity of and/or timing of catheter-based and/or surgical reinterventions (eg, valve/conduit replacement), and management of heart failure and arrhythmia, by a multidisciplinary team of experts proceeds as recommended for the individual CHD.<sup>129,130</sup> Even in the absence of CHD history, adults require periodic cardiovascular assessment for aortic root dilation,<sup>132-134</sup> cardiovascular risk factors (obesity, diabetes mellitus, hyperlipidemia),<sup>54,55,128</sup> and systemic arterial hypertension. Consideration of edema includes 22q11.2DS-related predisposition to varicose veins and lymphedema.<sup>3,135</sup>

Asthma can persist or arise as a management issue for adults with 22q11.2DS and can be a treatable cause of

abnormal pulmonary function in CHD.<sup>136</sup> Consideration of obstructive sleep apnea (OSA) is also important.<sup>137</sup>

### Sleep

Insomnia and disrupted sleep patterns are a burden to many adults and may be attributable to improper sleep behavior, untreated/undertreated psychiatric illness, OSA, restless legs, stress, and/or caffeine.<sup>88,91,119,137-139</sup> Poor sleep quality may affect daily life through fatigue, cognitive impairment, and/or negative mood.<sup>74,75,137,138</sup>

Routine evaluation should include information about sleep behaviors, duration, and quality, with formal sleep study, ie, polysomnography, considered for those with histories suggestive of OSA and/or related risk factors (eg, palatal anomalies, obesity). Management involves standard sleep hygiene recommendations; hypnotics are seldom needed.<sup>140</sup> Treatment of underlying conditions improves sleep and often also physical and mental health. Continuous positive airway pressure therapy for OSA may require attention to optimal mask-fitting, managing claustrophobia, and encouraging use.

### Gastroenterology

Common gastrointestinal (GI) issues include constipation, dysphagia, easy gagging/vomiting, and gastro-esophageal reflux disease, with cholelithiasis and fatty liver in a substantial minority.<sup>48</sup> Diet, supplements, medications, and comorbid non-GI conditions, including anxiety, thyroid disease, and PD, may contribute to or account for GI symptoms.<sup>3,48</sup>

History-taking includes the above considerations and ongoing vigilance for constipation. Dietary interventions are a mainstay, with prophylactic laxatives suggested for patients taking clozapine.<sup>141</sup> Consulting a pharmacist may suggest alternatives for those having difficulties swallowing pills. Gallstones and fatty liver may be detected through abdominal ultrasound scanning.

### Genitourinary, obstetrics and gynecology, and sexual health

Although genitourinary manifestations may involve congenital anomalies (eg, hydronephrosis, renal cysts, renal agenesis, phimosis, hypospadias, absent uterus),<sup>142-144</sup> detection and/or secondary problems may be delayed until adulthood. Those treated with calcium supplements and/or calcitriol have increased risk for iatrogenic nephrocalcinosis and/or decreased glomerular filtration. Data are limited but other renal diseases appear to be rare; diabetes could increase risk. Gynecologic issues include dysmenorrhea and ovarian cysts. Obstetrical risks are elevated given frequent comorbidities including learning disabilities; affected fetuses further signal a high-risk pregnancy.<sup>3,145</sup>

Intimate partnerships, sexual activity, and considerations about pregnancy are important for many individuals with 22q11.2DS.<sup>3,71</sup> Although there is little evidence of infertility,<sup>1</sup> reproductive fitness is somewhat reduced for men,

those with severe CHD, and more so for those with severe intellectual disability or psychotic illness.<sup>146,147</sup> Pregnancy loss is an important health issue.<sup>147</sup> There may be limited knowledge about this, or regarding sexual health in general and genetic risk to offspring.<sup>71,147</sup> Unplanned pregnancies or sexually transmitted infections, which may be related to exploitation, have the potential to worsen pre-existing medical and social conditions.<sup>71,145</sup> For some affected parents, there is an elevated likelihood of involvement with child protective services.<sup>71,145</sup>

Careful history-taking will reveal changes, including in urinary functioning and menstrual periods. Physical examination and screening abdominal-pelvic ultrasound may reveal ameliorable issues.

Routine assessments to identify the wants, needs, and concerns of individuals related to sexual and reproductive health are recommended.<sup>71</sup> This may involve views and concerns of partners and/or caregivers. Developmentally and culturally appropriate counseling, education, and management, including for sexually transmitted infections, cervical cancer screening, and other preventive initiatives (eg, human papillomavirus vaccines for both sexes), should be provided.<sup>71</sup> Contraceptive options should be discussed with all patients. Preconception folate supplements and as above, genetic counseling, are standard for those considering reproduction.<sup>71</sup>

Preconception, pregnancy, delivery, and postpartum monitoring of 22q11.2DS-associated conditions will help elucidate risks and can prevent potential complications;<sup>3,7,15,145</sup> CHD requires special considerations.<sup>129,130,148,149</sup> For fetuses with 22q11.2DS, there is an elevated risk for prenatal growth abnormalities (small for gestational age at birth) and other conditions, eg, polyhydramnios, regardless of the affected status of parents;<sup>2,145,150</sup> specialist care and delivery at a tertiary care facility are recommended.<sup>15</sup>

## General surgery

Hernias, cysts of all types, pilonidal sinus, and varicose veins are surgical issues in adults.<sup>3,48</sup> There is an overall somewhat increased risk of surgical complications in 22q11.2DS, including bleeding, infections, seizures, atelectasis, and difficult intubation.<sup>3,7,151,152</sup>

Careful management with attention to comorbid conditions and anatomical variants<sup>153,154</sup> will mitigate increased risks and decrease fears. Recommendations include careful perioperative monitoring of complete blood count with differential and of calcium levels.<sup>3,113</sup> Intubation may require smaller sized equipment and, rarely, attention to cervical spine anomalies.

## Skeletal

Clinically relevant manifestations include scoliosis,<sup>48,155,156</sup> recurrent patellar dislocation,<sup>48</sup> musculoskeletal pain, persisting juvenile idiopathic and later-onset forms of arthritis (eg, psoriatic, osteoarthritis),<sup>157,158</sup> clubfoot,<sup>159,160</sup> hammetoes and other foot abnormalities. Recurrent limb pains

may relate to flat feet, vitamin D deficiency, or possibly mitochondrial dysfunction.<sup>161</sup> There are also reports of exercise intolerance and reduction in bone mass.<sup>126</sup>

Routine history and physical examination, eg, for scoliosis (early adulthood) and joint abnormalities, are recommended with radiographic screening weighed against radiation exposure. Standard management for individual conditions is recommended. Severe scoliosis or recurrent patellar dislocation may require bracing or surgical management.<sup>48,162,163</sup> Employment restrictions and accommodations may be warranted.

## Immunology and related issues

Autoimmune diseases and atopy are important ongoing and emerging conditions in adults.<sup>3</sup> These may affect infection frequency, but recurrent infections are generally less problematic in adults with 22q11.2DS than in children with 22q11.2DS.<sup>164</sup> In a minority, immune compromise persists into adulthood, often associated with some type of antibody dysfunction and/or deficiency.<sup>164,165</sup> Delineating the full range of autoimmune disease and infection risk in aging adults with 22q11.2DS awaits formal study.

Vigilance for and management of autoimmune diseases is warranted, including routine screening for thyroid disease.<sup>3,113</sup> Immunologic evaluation is recommended only for those with recurrent (IgG, IgA, or IgM-related) or opportunistic (T cell-related) infections and/or severe atopy to identify risks that require active mitigation. A minority of patients require immunoglobulin replacement therapy.<sup>164</sup> All benefit from standard vaccinations, including COVID-19 and influenza, although some may have reduced response.<sup>166</sup> Table 2 presents some further management tips.

## Hematology and oncology

On average, platelet counts are lower in 22q11.2DS.<sup>167-171</sup> Thrombocytopenia, large platelets and reduced platelet quality, as well as anemia and leukopenia, are common but usually mild. Immune thrombocytopenia,<sup>164</sup> Bernard-Soulier syndrome, and autoimmune hemolytic anemia are rare but can be severe.<sup>172</sup> Increased bleeding may be an issue for some.<sup>169-172</sup> Some reports suggest a somewhat increased risk of cancer.<sup>173-176</sup>

Platelet function studies may be considered for significant bleeding histories. Specialized immunology testing for recurrent and/or severe immune cytopenia, eg, immune thrombocytopenia, and immune suppressive strategies to treat these, may be required.<sup>172,177</sup> Clinicians should be vigilant regarding malignancy and ensure routine preventive measures are applied.

## Dermatology

Skin diseases are often seen in adults with 22q11.2DS that may relate to autoimmune disease (eg, psoriasis, vitiligo), acne, and seborrhea/dermatitis.<sup>48</sup> Standard treatments are required.

**Table 2** Do's and Do not's

| Topic                    | Do's                                                                                                                                                    | Do not's                                                                                                                               |
|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Genetics                 | Check the genetic test report for details: specific region, size, <sup>1</sup> and any other clinically relevant variants (if applicable) <sup>24</sup> | Ignore clinical findings that are atypical for the 22q11.2 deletion (eg, profound intellectual disability) <sup>1,24</sup>             |
| Communication            | Use concrete nonjudgmental language and written summaries in a positive tone <sup>3,7,41,71</sup>                                                       | Ignore collateral information <sup>3</sup>                                                                                             |
| Multimorbidity           | Designate 1 clinician to coordinate medical and health-related needs and concerns <sup>45</sup>                                                         | Expect the adult with 22q11.2DS to present all symptoms without prompts or additional information from collateral sources <sup>3</sup> |
| Pregnancy and postpartum | Consider potential worsening of pre-existing medical and social conditions <sup>71,113</sup>                                                            | Forget to refer to specialized health care and family and community-based supports, as available <sup>15,71</sup>                      |
| Surgical procedures      | Monitor calcium and CBC perioperatively <sup>3,113</sup>                                                                                                | Ignore anatomical variants <sup>153,154</sup>                                                                                          |
| Functioning              | Consider discrepancies in functioning between cognitive, adaptive, and emotional domains <sup>66,67</sup>                                               | Consider an intelligence test as a static constant or complete picture of the person's abilities <sup>66,77,83</sup>                   |
| Sleep                    | Consider formal sleep study (ie, polysomnography for obstructive sleep apnea) <sup>137</sup>                                                            | Assume a normal sleeping pattern in the absence of complaints <sup>3,137</sup>                                                         |
| Neurology                | Consider using standardized clinical rating scales (eg, MDS-UPDRS), video recordings, and/or EEG <sup>3,53,112</sup>                                    | Attribute parkinsonism to antipsychotic medication without monitoring for progression over time <sup>50,53</sup>                       |
| Antipsychotic use        | Consider a concomitant anticonvulsant to mitigate the increased seizure risk when prescribing clozapine <sup>106</sup>                                  | Ignore risks and management strategies for metabolic and motor side effects <sup>50,53-55</sup>                                        |
| Endocrinology            | Strongly recommend/prescribe vitamin D to reduce the risk of hypocalcemia/seizures <sup>3,112,113</sup>                                                 | Assume normal endocrinological functions in the absence of complaints <sup>3</sup>                                                     |
| Hematology               | Be aware that many patients have mild thrombocytopenia of no clinical relevance <sup>3,167,168</sup>                                                    | Neglect a history of chronic bleeding that patients may minimize, eg, hemorrhoids, lesions <sup>3</sup>                                |
| Immunology               | Refer patients with recurrent/opportunistic infections to specialists in immunology <sup>164,165</sup>                                                  | Order redundant tests for patients without symptoms <sup>164</sup>                                                                     |
| Vaccinations             | Counsel on the importance of vaccines and facilitate convenience of their provision <sup>166</sup>                                                      | Apply recommendations to adults that are pertinent only to infants <sup>166</sup>                                                      |

This table presents some management tips in the form of “Do’s” and “Do not’s” for 13 topic areas pertinent to clinicians caring for adults with 22q11.2 deletion syndrome.

CBC, complete blood count; EEG, electroencephalogram; MDS-UPDRS, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale.

## Sensory deficits

Hearing loss is common,<sup>48,178</sup> particularly high-frequency loss, and can be conductive and/or sensorineural. The most clinically relevant ocular findings involve persisting strabismus and/or refractive errors, especially hyperopia (farsightedness) and astigmatism; other findings (eg, tortuous retinal vessels, posterior embryotoxon) have no clinical consequences.<sup>48,179,180</sup> Olfactory deficits may hinder detection of toxic fumes, smoke, and spoiled food and affect enjoyment of food.<sup>119,123</sup> Although sensory deficits increase with age in the general population, systematic data in later adulthood are lacking in 22q11.2DS.

A low threshold for formal testing of sensory functions must be considered, especially with regard to hearing and vision, given their importance for social interactions and communication. Information regarding impact of sensory deficits should be provided to patients and their families/

caregivers. Many adults need regular ear wax removal, and hearing aids can help those with hearing loss. Glasses are prescribed for the majority.<sup>179</sup>

## Dental

Enamel defects and impaired saliva secretion are frequent<sup>181-185</sup> and together with poor oral hygiene, unhealthy diet and impaired fine motor skills, may contribute to dental caries. Dental anxiety is common. Poor oral health negatively impacts quality of life and conveys risk of infective endocarditis in those with major CHD.<sup>186,187</sup>

Regular dental care is recommended, as is standard management of malocclusion. Periodic evaluation of saliva secretion may be helpful. Caries prevention, including help with oral hygiene and use of fluorides, is important.<sup>181-183</sup> Standard antibiotic prophylaxis guidelines for prevention of infective endocarditis apply.<sup>186,187</sup>

## Conclusion

Since the publication of the initial clinical practice guidelines for managing adults with 22q11.2DS,<sup>3</sup> research has served to emphasize the evolving expression and complex care required at all life stages in 22q11.2DS (Tables 1 and 2 and Figures 2 and 3). In addition to previously associated conditions, recent studies have revealed and/or confirmed associations with endocrinopathies and neurologic disorders that require proactive attention and need to be taken into account when following up those with 22q11.2DS.

Limitations imposed by the very nature of this complex condition and the lack of studies meeting formal criteria for high-quality evidence, ie, randomized controlled trials vs observational studies, constrained the ability of the panel to meet all of the requirements of a systematic review of the 2318 articles, including the 894 related to adults. The inherent variability and multisystem complexity of 22q11.2DS increase risk of bias (eg, sample selection) for all study types.<sup>5</sup> The recommendations are most relevant to higher-income countries. Collectively, these issues limit the overall strength of the recommendations. Mitigating this were the expert panel's conservative approach to the recommendations, focus on optimizing potential benefit and minimizing harm, and avoidance of an overprescriptive approach at this relatively early stage of the field. The emphasis is on clinical judgment tailored to the individual patient and situation in the context of appreciating the multisystem and evolving features of 22q11.2DS.

Most importantly, the adult 22q11.2DS population remains understudied. There is an urgent need for data on the natural history of 22q11.2DS, especially studies of older patients and prospective outcome research. Such research and accounting for multisystem complexity and ascertainment would facilitate systematic treatment trials, both pharmacologic and nonpharmacologic, including early interventions as well as studies of illness burden and long-term planning. This information is also key for future global 22q11.2DS clinical practice guidelines review/updates, proposed for 5 years hence in addition to subspecialty-specific guidelines planned for the near future.<sup>15,188</sup> All will benefit from involving both patients and their families and caregivers. Increasing our knowledge may empower the expertise of health care providers, whether or not they are associated with 22q11.2DS-specific clinics, and increase awareness about 22q11.2DS, thereby improving comprehensive care for all patients.

## Acknowledgments

The authors acknowledge the support and endorsement provided by The 22q11.2 Society (<http://www.22qsociety.org>) for this work, and inspiration from patients with 22q11.2DS, and their caregivers and clinicians.

A.S.B. holds the Dalglish Chair in 22q11.2 Deletion Syndrome at the University Health Network and University of Toronto.

## Funding

No funding was received for this work.

## Author Information

Conceptualization: E.B., A.S.B., D.M.M.-M., S.Ó.; Data Curation: E.B., D.M.A., J.M.A., R.M.C., T.B.C., C.C.-G., S.d.R., A.M.F., G.K., A.E.L., J.C.Y.L., M.R.M., E.M.M., B.A.N., E.O., A.O.-C., S.Ó., L.P., G.M.R., N.G.D.R., M.S., C.S., K.E.S., A.S., T.A.M.J.v.A., J.P.V.B., C.V., D.M.M.-M., A.S.B.; Formal Analysis: E.B., S.Ó., D.M.M.-M., A.S.B.; Investigation: E.B., S.Ó., D.M.M.-M., A.S.B.; Methodology: E.B., S.Ó., D.M.M.-M., A.S.B.; Project Administration: E.B., S.Ó., D.M.M.-M., A.S.B.; Resources: E.B., A.S.B., D.M.M.-M., S.Ó., J.C.Y.L., T.B.C., A.O.-C.; Supervision: E.B., S.Ó., D.M.M.-M., A.S.B.; Validation: E.B., A.S.B., D.M.M.-M., S.Ó.; Visualization: E.B., S.Ó., T.B.C., D.M.M.-M., A.S.B.; Writing-original draft: E.B., A.S.B., D.M.M.-M., S.Ó., D.M.A., J.M.A., R.M.C., C.C.-G., S.d.R., A.M.F., G.K., A.E.L., M.R.M., E.M.M., B.A.N., E.O., A.O.-C., L.P., G.M.R., N.G.D.R., M.S., C.S., K.E.S., A.S., T.A.M.J.v.A., J.P.V.B., C.V.; Writing-review and editing: E.B., A.S.B., D.M.M.-M., S.Ó., T.B.C., D.M.A., J.M.A., R.M.C., C.C.-G., S.d.R., A.M.F., G.K., A.E.L., J.C.Y.L., M.R.M., E.M.M., B.A.N., E.O., A.O.-C., L.P., G.M.R., N.G.D.R., M.S., C.S., K.E.S., A.S., T.A.M.J.v.A., J.P.V.B., C.V.

## Conflict of Interest

The authors declare no conflicts of interest.

## Additional Information

The online version of this article <https://doi.org/10.1016/j.gim.2022.11.012> contains supplementary material, which is available to authorized users.

## Affiliations

<sup>1</sup>Advism, 's Heeren Loo Zorggroep, Amersfoort, The Netherlands; <sup>2</sup>The Dalglish Family 22q Clinic, Toronto General Hospital, University Health Network, Toronto, Ontario, Canada; <sup>3</sup>Department of Psychiatry and Neuropsychology, Maastricht University, Maastricht, The Netherlands; <sup>4</sup>Department of Pediatric Rheumatology and

Immunology, Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden; <sup>5</sup>Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; <sup>6</sup>22q and You Center, Clinical Genetics Center, and Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, PA; <sup>7</sup>Library and Information Services, and The Institute of Education Research (TIER), University Health Network, Toronto, Ontario, Canada; <sup>8</sup>Adult Genetic Epilepsy Program, Toronto Western Hospital and University of Toronto, Toronto, Ontario, Canada; <sup>9</sup>Division of Otolaryngology, Children's Mercy Hospital and University of Missouri Kansas City School of Medicine, Kansas City, MO; <sup>10</sup>Department of Orthopedic Surgery, University Medical Center Utrecht, Utrecht, The Netherlands; <sup>11</sup>Hematology and Transfusion Medicine, University Health Network, Toronto, Ontario, Canada; <sup>12</sup>Department of Pediatric Psychology, University Medical Centre, Wilhelmina Children's Hospital, Utrecht, The Netherlands; <sup>13</sup>Faculty of Odontology, Malmö University, Malmö, Sweden; <sup>14</sup>The Edmond J. Safra Program in Parkinson's Disease and the Morton and Gloria Shulman Movement Disorders, Toronto Western Hospital, University Health Network, Toronto, Ontario, Canada; <sup>15</sup>Division of Gastroenterology and 22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA; <sup>16</sup>Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA; <sup>17</sup>Bryn Mawr, PA; <sup>18</sup>Department of Medical Genetics, Institute of Mother and Child, Warsaw, Poland; <sup>19</sup>Toronto Adult Congenital Heart Disease Program, Peter Munk Cardiac Centre, University Health Network and University of Toronto, Toronto, Ontario, Canada; <sup>20</sup>Rare Diseases Program, Institute for Sciences and Innovation in Medicine, Facultad de Medicina Clinica Alemana Universidad del Desarrollo, Santiago, Chile; <sup>21</sup>Clinical Psychology Unit for Intellectual and Developmental Disabilities, Faculty of Psychology and Educational Sciences, University of Geneva, Geneva, Switzerland; <sup>22</sup>Toronto ACHD Program, Mount Sinai and Toronto General Hospitals, University of Toronto, Toronto, Ontario, Canada; <sup>23</sup>Division of Allergy and Immunology and 22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA; <sup>24</sup>Center for Human Genetics, University Hospital UZ Leuven, Department of Human Genetics, KU Leuven, Leuven, Belgium; <sup>25</sup>Department of Surgery, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA; <sup>26</sup>Division of Urology and 22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA; <sup>27</sup>Department of Human Biology and Medical Genetics, Sapienza University, Rome, Italy; <sup>28</sup>Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada; <sup>29</sup>Clinical Genetics Research Program and Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada; <sup>30</sup>Department of Mental Health and Division of Cardiology, Department of Medicine, and Toronto General Hospital

Research Institute, University Health Network, Toronto, Ontario, Canada

## References

- 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>
- 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>
- Fung WLA, 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>
- 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>
- 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>
- 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>
- 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>
- Delio M, Guo T, McDonald-McGinn DM, et al. Enhanced maternal origin of the 22q11.2 deletion in velocardiofacial and DiGeorge syndromes. *Am J Hum Genet*. 2013;92(3):439-447. Published correction appears in *Am J Hum Genet*. 2013;92(4):637. <https://doi.org/10.1016/j.ajhg.2013.01.018>
- 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>
- Vogels A, Schevenels S, Cayenberghs R, et al. Presenting symptoms in adults with the 22q11 deletion syndrome. *Eur J Med Genet*. 2014;57(4):157-162. <http://doi.org/10.1016/j.ejmg.2014.02.008>
- 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. <http://europepmc.org/article/med/10191424>
- Digilio MC, Angioni A, De Santis M, et al. Spectrum of clinical variability in familial deletion 22q11.2: from full manifestation to extremely mild clinical anomalies. *Clin Genet*. 2003;63(4):308-313. <http://doi.org/10.1034/j.1399-0004.2003.00049.x>
- 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. [http://doi.org/10.1002/\(SICI\)1096-8628\(19980123\)75:3<288::AID-AJMG12>3.0.CO;2-L](http://doi.org/10.1002/(SICI)1096-8628(19980123)75:3<288::AID-AJMG12>3.0.CO;2-L)
- 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>
- Blagowidow N, Nowakowska B, Schindewolf E, et al. Prenatal screening and diagnostic considerations for 22q11.2 microdeletions. *Genes*. 2023;14:160. <https://doi.org/10.3390/genes14010160>
- 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>

17. 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>
18. 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>
19. 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>
20. Burnside RD. 22q11.2 deletion syndromes: a review of proximal, central, and distal deletions and their associated features. *Cytogenet Genome Res.* 2015;146(2):89-99. <http://doi.org/10.1159/000438708>
21. 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>
22. 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>
23. 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>
24. 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>
25. Bassett AS, Lowther C, Merico D, et al. Rare genome-wide copy number variation and expression of schizophrenia in 22q11.2 deletion syndrome. *Am J Psychiatry.* 2017;174(11):1054-1063. <http://doi.org/10.1176/appi.ajp.2017.16121417>
26. 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>
27. 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>
28. 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>
29. Souto Filho JTD, Ribeiro HAdA, 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>
30. Kunishima S, Imai T, Kobayashi R, Kato M, Ogawa S, Saito H. Bernard-Soulier syndrome caused by a hemizygous GPIIb mutation and 22q11.2 deletion. *Pediatr Int.* 2013;55(4):434-437. <http://doi.org/10.1111/ped.12105>
31. 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](http://doi.org/10.1002/1096-8628(2001)9999:9999::aid-ajmg1176>3.0.co;2-t)
32. Bedeschi MF, Colombo L, Mari F, et al. Unmasking of a recessive *SCARF2* mutation by a 22q11.2 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>
33. 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>
34. 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>
35. 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. <https://doi.org/10.1038/s41436-018-0137-y>
36. 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>
37. Durmaz AA, Karaca E, Demkow U, Toruner G, Schoumans J, Cogulu O. Evolution of genetic techniques: past, present, and beyond. *Biomed Res Int.* 2015;2015:461524. <http://doi.org/10.1155/2015/461524>
38. Martin N, Mikhaelian M, Cytrynbaum C, et al. 22q11.2 deletion syndrome: attitudes towards disclosing the risk of psychiatric illness. *J Genet Couns.* 2012;21(6):825-834. <http://doi.org/10.1007/s10897-012-9517-7>
39. Hart SJ, Schoch K, Shashi V, Callanan N. Communication of psychiatric risk in 22q11.2 deletion syndrome: a pilot project. *J Genet Couns.* 2016;25(1):6-17. <http://doi.org/10.1007/s10897-015-9910-0>
40. Chow EWC, Watson M, Young DA, Bassett AS. Neurocognitive profile in 22q11 deletion syndrome and schizophrenia. *Schizophr Res.* 2006;87(1-3):270-278. <http://doi.org/10.1016/j.schres.2006.04.007>
41. Finucane B. Genetic counseling for women with intellectual disabilities. In: Leroy BS, Veach PM, Bartels DM, eds. *Genetic Counseling Practice: Advanced Concepts and Skills.* Wiley-Blackwell; 2010:281-303.
42. Bretelle F, Beyer L, Pellissier MC, et al. Prenatal and postnatal diagnosis of 22q11.2 deletion syndrome. *Eur J Med Genet.* 2010;53(6):367-370. <http://doi.org/10.1016/j.ejmg.2010.07.008>
43. McDonald-McGinn DM, Zackai EH. Genetic counseling for the 22q11.2 deletion. *Dev Disabil Res Rev.* 2008;14(1):69-74. <http://doi.org/10.1002/ddrr.10>
44. 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.0b013e3282f28a01>
45. 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>
46. 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>
47. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet.* 2012;380(9836):37-43. [http://doi.org/10.1016/S0140-6736\(12\)60240-2](http://doi.org/10.1016/S0140-6736(12)60240-2)
48. Bassett AS, Chow EWC, 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>
49. Malecki SL, Van Mil S, Graffi J, et al. A genetic model for multimorbidity in young adults. *Genet Med.* 2020;22(1):132-141. <http://doi.org/10.1038/s41436-019-0603-1>
50. Butcher NJ, Kiehl TR, Hazrati LN, et al. Association between early-onset Parkinson disease and 22q11.2 deletion syndrome: identification of a novel genetic form of Parkinson disease and its clinical implications. *JAMA Neurol.* 2013;70(11):1359-1366. <http://doi.org/10.1001/jamaneurol.2013.3646>
51. Mok KY, Sheerin U, Simón-Sánchez J, et al. Deletions at 22q11.2 in idiopathic Parkinson's disease: a combined analysis of genome-wide association data. *Lancet Neurol.* 2016;15(6):585-596. [http://doi.org/10.1016/S1474-4422\(16\)00071-5](http://doi.org/10.1016/S1474-4422(16)00071-5)
52. 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>
53. Boot E, Butcher NJ, Udow S, et al. Typical features of Parkinson disease and diagnostic challenges with microdeletion 22q11.2. *Neurology.* 2018;90(23):e2059-e2067. <http://doi.org/10.1212/WNL.0000000000005660>

54. Voll SL, Boot E, Butcher NJ, et al. Obesity in adults with 22q11.2 deletion syndrome. *Genet Med*. 2017;19(2):204-208. <http://doi.org/10.1038/gim.2016.98>
55. Van L, Heung T, Malecki SL, et al. 22q11.2 microdeletion and increased risk for type 2 diabetes. *Eclinicalmedicine*. 2020;26:100528. <http://doi.org/10.1016/j.eclim.2020.100528>
56. Van L, Heung T, Graffi J, et al. All-cause mortality and survival in adults with 22q11.2 deletion syndrome. *Genet Med*. 2019;21(10):2328-2335. <http://doi.org/10.1038/s41436-019-0509-y>
57. 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>
58. 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>
59. Kauw D, Woudstra OI, van Engelen K, et al. 22q11.2 deletion syndrome is associated with increased mortality in adults with tetralogy of Fallot and pulmonary atresia with ventricular septal defect. *Int J Cardiol*. 2020;306:56-60. <http://doi.org/10.1016/j.ijcard.2020.02.064>
60. van Mil S, Heung T, Malecki S, et al. Impact of a 22q11.2 microdeletion on adult all-cause mortality in tetralogy of Fallot patients. *Can J Cardiol*. 2020;36(7):1091-1097. <http://doi.org/10.1016/j.cjca.2020.04.019>
61. Cooper JA, Cadogan CA, Patterson SM, et al. Interventions to improve the appropriate use of polypharmacy in older people: a Cochrane systematic review. *BMJ Open*. 2015;5(12):e009235. <http://doi.org/10.1136/bmjopen-2015-009235>
62. van Amelsvoort T, Henry J, Morris R, et al. Cognitive deficits associated with schizophrenia in velo-cardio-facial syndrome. *Schizophr Res*. 2004;70(2-3):223-232. <http://doi.org/10.1016/j.schres.2003.10.004>
63. Fiksinski AM, Heung T, Corral M, et al. Within-family influences on dimensional neurobehavioral traits in a high-risk genetic model. *Psychol Med*. 2022;52:3184-3192. <http://doi.org/10.1017/S0033291720005279>
64. Gothelf D, Aviram-Goldring A, Burg M, et al. Cognition, psychosocial adjustment and coping in familial cases of velocardiofacial syndrome. *J Neural Transm (Vienna)*. 2007;114(11):1495-1501. <http://doi.org/10.1007/s00702-007-0766-9>
65. Zhao Y, Guo T, Fiksinski A, et al. Variance of IQ is partially dependent on deletion type among 1,427 22q11.2 deletion syndrome subjects. *Am J Med Genet A*. 2018;176(10):2172-2181. <http://doi.org/10.1002/ajmg.a.40359>
66. Butcher NJ, Chow EWC, Costain G, Karas D, Ho A, Bassett AS. Functional outcomes of adults with 22q11.2 deletion syndrome. *Genet Med*. 2012;14(10):836-843. <http://doi.org/10.1038/gim.2012.66>
67. Fiksinski AM, Breetvelt EJ, Lee YJ, et al. Neurocognition and adaptive functioning in a genetic high risk model of schizophrenia. *Psychol Med*. 2019;49(6):1047-1054. <http://doi.org/10.1017/S0033291718001824>
68. Frascarelli M, Padovani G, Buzzanca A, et al. Social cognition deficit and genetic vulnerability to schizophrenia in 22q11 deletion syndrome. *Annali Dell'Istituto Superiore di Sanita*. 2020;56(1):107-113. [http://doi.org/10.4415/ANN\\_20\\_01\\_15](http://doi.org/10.4415/ANN_20_01_15)
69. Accinni T, Buzzanca A, Frascarelli M, et al. Social cognition impairments in 22q11.2DS individuals with and without psychosis: A comparison study with a large population of patients with schizophrenia. *Schizophrenia Bulletin Open*. 2021;3(1):1-10. <http://doi.org/10.1093/schizbullopen/sgab049>
70. 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>
71. Palmer LD, Heung T, Corral M, Boot E, Brooks SG, Bassett AS. Sexual knowledge and behaviour in 22q11.2 deletion syndrome, a complex care condition. *J Appl Res Intellect Disabil*. 2022;35(4):966-975. <http://doi.org/10.1111/jar.12927>
72. Dewulf D, Noens I, Swillen A. Adaptive skills, cognitive functioning and behavioural problems in adolescents with 22q11.2 deletion syndrome. Article in Dutch. *Tijdschr Psychiatr*. 2013;55(5):369-374. [https://www.tijdschriftvoorpsychiatrie.nl/en/artikelen/article/50-9754\\_Adaptieve-vaardigheden-cognitief-functioneren-en-gedragsproblemen-bij-adolescenten-met-het-22q11-2-deletiesyndroom](https://www.tijdschriftvoorpsychiatrie.nl/en/artikelen/article/50-9754_Adaptieve-vaardigheden-cognitief-functioneren-en-gedragsproblemen-bij-adolescenten-met-het-22q11-2-deletiesyndroom)
73. Armando M, Sandini C, Chambaz M, Schaer M, Schneider M, Eliez S. Coping strategies mediate the effect of stressful life events on schizotypal traits and psychotic symptoms in 22q11.2 deletion syndrome. *Schizophr Bull*. 2018;44(suppl\_2):S525-S535. <http://doi.org/10.1093/schbul/sby025>
74. Yirmiya ET, Mekori-Domachevsky E, Weinberger R, Taler M, Carmel M, Gothelf D. Exploring the potential association among sleep disturbances, cognitive impairments, and immune activation in 22q11.2 deletion syndrome. *Am J Med Genet A*. 2020;182(3):461-468. <http://doi.org/10.1002/ajmg.a.61424>
75. Vergaen 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>
76. 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>
77. Evers LJM, van Amelsvoort TAMJ, Candel MJJM, Boer H, Engelen JJM, Curfs LMG. Psychopathology in adults with 22q11 deletion syndrome and moderate and severe intellectual disability. *J Intellect Disabil Res*. 2014;58(10):915-925. <http://doi.org/10.1111/jir.12117>
78. Tang SX, Moore TM, Calkins ME, et al. The psychosis spectrum in 22q11.2 deletion syndrome Is comparable to that of nondeleted youths. *Biol Psychiatry*. 2017;82(1):17-25. <http://doi.org/10.1016/j.biopsych.2016.08.034>
79. Schneider M, Vaessen T, van Duin EDA, et al. Affective and psychotic reactivity to daily-life stress in adults with 22q11DS: a study using the experience sampling method. *J Neurodev Disord*. 2020;12(1):30. <http://doi.org/10.1186/s11689-020-09333-2>
80. van Duin EDA, Vaessen T, Kasanova Z, et al. Lower cortisol levels and attenuated cortisol reactivity to daily-life stressors in adults with 22q11.2 deletion syndrome. *Psychoneuroendocrinology*. 2019;106:85-94. <http://doi.org/10.1016/j.psyneuen.2019.03.023>
81. Van de Woestyne K, Vandensande A, Vansteelandt K, Maes B, Vergaen E, Swillen A. Resilience and quality of life in young adults with a 22q11.2 deletion syndrome: a patient's perspective. *Eur Child Adolesc Psychiatry*. 2022;31(12):1885-1894. <http://doi.org/10.1007/s00787-021-01822-6>
82. Boot E, Bassett AS, Marras C. 22q11.2 deletion syndrome-associated Parkinson's disease. *Mov Disord Clin Pract*. 2018;6(1):11-16. <http://doi.org/10.1002/mdc3.12687>
83. Vorstman JAS, 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>
84. 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>
85. Murphy KC, Jones LA, Owen MJ. High rates of schizophrenia in adults with velo-cardio-facial syndrome. *Arch Gen Psychiatry*. 1999;56(10):940-945. <http://doi.org/10.1001/archpsyc.56.10.940>
86. Karas DJ, Costain G, Chow EWC, Bassett AS. Perceived burden and neuropsychiatric morbidities in adults with 22q11.2 deletion syndrome. *J Intellect Disabil Res*. 2014;58(2):198-210. <http://doi.org/10.1111/j.1365-2788.2012.01639.x>
87. Hercher L, Bruenner G. Living with a child at risk for psychotic illness: the experience of parents coping with 22q11 deletion syndrome: an exploratory study. *Am J Med Genet A*. 2008;146A(18):2355-2360. <http://doi.org/10.1002/ajmg.a.32466>
88. Butcher NJ, Boot E, Lang AE, et al. Neuropsychiatric expression and catatonia in 22q11.2 deletion syndrome: an overview and case series.

- Am J Med Genet A*. 2018;176(10):2146-2159. <http://doi.org/10.1002/ajmg.a.38708>
89. Tang SX, Yi JJ, Calkins ME, et al. Psychiatric disorders in 22q11.2 deletion syndrome are prevalent but undertreated. *Psychol Med*. 2014;44(6):1267-1277. <http://doi.org/10.1017/S0033291713001669>
  90. Yi JJ, Calkins ME, Tang SX, et al. Impact of psychiatric comorbidity and cognitive deficit on function in 22q11.2 deletion syndrome. *J Clin Psychiatry*. 2015;76(10):e1262-e1270. <http://doi.org/10.4088/JCP.14m09197>
  91. Fung WLA, McEvilly R, Fong J, Silversides C, Chow E, Bassett A. Elevated prevalence of generalized anxiety disorder in adults with 22q11.2 deletion syndrome. *Am J Psychiatry*. 2010;167(8):998. <http://doi.org/10.1176/appi.ajp.2010.09101463>
  92. Bassett AS, Chow EWC, AbdelMalik P, Gheorghiu M, Husted J, Weksberg R. The schizophrenia phenotype in 22q11 deletion syndrome. *Am J Psychiatry*. 2003;160(9):1580-1586. <http://doi.org/10.1176/appi.ajp.160.9.1580>
  93. Vangkilde A, Olsen L, Hoeffding LK, et al. Schizophrenia spectrum disorders in a Danish 22q11.2 deletion syndrome cohort compared to the total Danish population—A nationwide register study. *Schizophr Bull*. 2016;42(3):824-831. <http://doi.org/10.1093/schbul/sbv195>
  94. 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>
  95. 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>
  96. Vingerhoets C, van Oudenaren MJF, Bloemen OJN, et al. Low prevalence of substance use in people with 22q11.2 deletion syndrome. *Br J Psychiatry*. 2019;215(5):661-667. <http://doi.org/10.1192/bjp.2018.258>
  97. Sorkhou M, Bedder RH, George TP. The behavioral sequelae of cannabis use in healthy people: a systematic review. *Front Psychiatry*. 2021;12:630247. <http://doi.org/10.3389/fpsy.2021.630247>
  98. Sappok T, Budczies J, Bölte S, Dziobek I, Dosen A, Diefenbacher A. Emotional development in adults with autism and intellectual disabilities: a retrospective, clinical analysis. *PLoS One*. 2013;8(9):e74036. <http://doi.org/10.1371/journal.pone.0074036>
  99. Ferrell RB, Wolinsky EJ, Kauffman CI, Flashman LA, McAllister TW. Neuropsychiatric syndromes in adults with intellectual disability: issues in assessment and treatment. *Curr Psychiatry Rep*. 2004;6(5):380-390. <http://doi.org/10.1007/s11920-004-0025-9>
  100. Dori N, Green T, Weizman A, Gothelf D. The effectiveness and safety of antipsychotic and antidepressant medications in individuals with 22q11.2 deletion syndrome. *J Child Adolesc Psychopharmacol*. 2017;27(1):83-90. <http://doi.org/10.1089/cap.2014.0075>
  101. Mosheva M, Korotkin L, Gur RE, Weizman A, Gothelf D. Effectiveness and side effects of psychopharmacotherapy in individuals with 22q11.2 deletion syndrome with comorbid psychiatric disorders: a systematic review. *Eur Child Adolesc Psychiatry*. 2020;29(8):1035-1048. <http://doi.org/10.1007/s00787-019-01326-4>
  102. Maeder J, Mancini V, Sandini C, et al. Selective effects of methylphenidate on attention and inhibition in 22q11.2 deletion syndrome: results from a clinical trial. *Int J Neuropsychopharmacol*. 2022;25(3):215-225. <http://doi.org/10.1093/ijnp/pyab057>
  103. Basel D, Mosheva M, Maeder J, et al. Stimulant treatment effectiveness, safety and risk for psychosis in individuals with 22q11.2 deletion syndrome. *Eur Child Adolesc Psychiatry*. 2022;31(9):1367-1375. <http://doi.org/10.1007/s00787-021-01780-z>
  104. de Boer J, Boot E, van Gils L, van Amelsvoort T, Zinkstok J. Adverse effects of antipsychotic medication in patients with 22q11.2 deletion syndrome: a systematic review. *Am J Med Genet A*. 2019;179(11):2292-2306. <http://doi.org/10.1002/ajmg.a.61324>
  105. Boot E, Butcher NJ, van Amelsvoort TAMJ, 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>
  106. Butcher NJ, Fung WLA, Fitzpatrick L, et al. Response to clozapine in a clinically identifiable subtype of schizophrenia. *Br J Psychiatry*. 2015;206(6):484-491. <http://doi.org/10.1192/bjp.bp.114.151837>
  107. Buijs PC, Bassett AS, Gold DA, Boot E. Cognitive behavioral therapy in 22q11.2 deletion syndrome: a case study of two young adults with an anxiety disorder. *J Intellect Disabil*. 2021;25(4):695-704. <http://doi.org/10.1177/1744629520942374>
  108. 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>
  109. de Kovel CGF, Trucks H, Helbig I, et al. Recurrent microdeletions at 15q11.2 and 16p13.11 predispose to idiopathic generalized epilepsies. *Brain*. 2010;133(1):23-32. <http://doi.org/10.1093/brain/awp262>
  110. Kao A, Mariani J, McDonald-McGinn DM, et al. Increased prevalence of unprovoked seizures in patients with a 22q11.2 deletion. *Am J Med Genet A*. 2004;129A(1):29-34. <http://doi.org/10.1002/ajmg.a.30133>
  111. Kim EH, Yum MS, Lee BH, et al. Epilepsy and other neuropsychiatric manifestations in children and adolescents with 22q11.2 deletion syndrome. *J Clin Neurol*. 2016;12(1):85-92. Published correction appears in *J Clin Neurol*. 2016;12(2):251. <https://doi.org/10.3988/jcn.2016.12.1.85>
  112. Wither RG, Borlot F, MacDonald A, et al. 22q11.2 deletion syndrome lowers seizure threshold in adult patients without epilepsy. *Epilepsia*. 2017;58(6):1095-1101. <http://doi.org/10.1111/epi.13748>
  113. 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>
  114. Rezazadeh A, Bercovici E, Kiehl TR, et al. Periventricular nodular heterotopia in 22q11.2 deletion and frontal lobe migration. *Ann Clin Transl Neurol*. 2018;5(11):1314-1322. <http://doi.org/10.1002/acn3.641>
  115. Andrade DM, Krings T, Chow EWC, Kiehl TR, Bassett AS. Hippocampal malrotation is associated with chromosome 22q11.2 microdeletion. *Can J Neurol Sci*. 2013;40(5):652-656. <http://doi.org/10.1017/s0317167100014876>
  116. Campbell LE, Daly E, Toal F, et al. Brain and behaviour in children with 22q11.2 deletion syndrome: a volumetric and voxel-based morphometry MRI study. *Brain*. 2006;129(5):1218-1228. <http://doi.org/10.1093/brain/awl066>
  117. Boot E, Mentzel TQ, Palmer LD, et al. Age-related parkinsonian signs in microdeletion 22q11.2. *Mov Disord*. 2020;35(7):1239-1245. <http://doi.org/10.1002/mds.28080>
  118. Kontoangelos K, Maillis A, Maltezos M, Tsiros S, Papageorgiou CC. Acute dystonia in a patient with 22q11.2 deletion syndrome. *Ment Illn*. 2015;7(2):5902. <http://doi.org/10.4081/mi.2015.5902>
  119. Buckley E, Siddique A, McNeill A. Hyposmia, symptoms of rapid eye movement sleep behavior disorder, and parkinsonian motor signs suggest prodromal neurodegeneration in 22q11 deletion syndrome. *NeuroReport*. 2017;28(11):677-681. <http://doi.org/10.1097/WNR.0000000000000815>
  120. Van Iseghem V, McGovern E, Apartis E, et al. Subcortical myoclonus and associated dystonia in 22q11.2 deletion syndrome. *Tremor Other Hyperkinet Mov (N Y)*. 2020;10. <http://doi.org/10.7916/tohm.v0.729>
  121. Hu ZX, Lu XD, Lou DN, et al. A case report of a Chinese patient with 22q11.2 deletion accompanied with EOPD, severe dystonia and hypocalcemia. *Clin Park Relat Disord*. 2019;1:72-73. <http://doi.org/10.1016/j.prdoa.2019.07.002>
  122. Moreira F, Brás A, Lopes JR, Januário C. Parkinson's disease with hypocalcaemia: adult presentation of 22q11.2 deletion syndrome. *BMJ Case Rep*. 2018;2018, bcr2017223751. <http://doi.org/10.1136/bcr-2017-223751>
  123. Butcher NJ, Marras C, Pondal M, et al. Neuroimaging and clinical features in adults with a 22q11.2 deletion at risk of Parkinson's disease. *Brain*. 2017;140(5):1371-1383. <http://doi.org/10.1093/brain/awx053>
  124. Lima K, Abrahamsen TG, Wolff AB, et al. Hypoparathyroidism and autoimmunity in the 22q11.2 deletion syndrome. *Eur J Endocrinol*. 2011;165(2):345-352. <http://doi.org/10.1530/EJE-10-1206>

125. Jamieson A, Smith CJ. Dilated cardiomyopathy: a preventable presentation of DiGeorge syndrome. *J R Coll Physicians Edinb.* 2015;45(4):273-275. <http://doi.org/10.4997/JRCPE.2015.404>
126. Stagi S, Lapi E, Gambineri E, et al. Bone density and metabolism in subjects with microdeletion of chromosome 22q11 (del22q11). *Eur J Endocrinol.* 2010;163(2):329-337. <http://doi.org/10.1530/EJE-10-0167>
127. Guarnotta V, Riela S, Massaro M, et al. The daily consumption of cola can determine hypocalcemia: a case report of postsurgical hypoparathyroidism-related hypocalcemia refractory to supplemental therapy with high doses of oral calcium. *Front Endocrinol, Lausanne.* 2017;8:7. <http://doi.org/10.3389/fendo.2017.00007>
128. Blagojevic C, Heung T, Malecki S, et al. Hypertriglyceridemia in young adults with a 22q11.2 microdeletion. *Eur J Endocrinol.* 2022;187(1):91-99. <http://doi.org/10.1530/EJE-21-1104>
129. Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation.* 2019;139(14):e698-e800. Published correction appears in *Circulation.* 2019;139(14):e833-e834. <https://doi.org/10.1161/CIR.0000000000000603>
130. Baumgartner H, De Backer J, Babu-Narayan SV, et al. 2020 ESC guidelines for the management of adult congenital heart disease. *Eur Heart J.* 2021;42(6):563-645. <http://doi.org/10.1093/eurheartj/ehaa554>
131. Bassett AS, Chow EWC, Husted J, et al. Premature death in adults with 22q11.2 deletion syndrome. *J Med Genet.* 2009;46(5):324-330. <http://doi.org/10.1136/jmg.2008.063800>
132. 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>
133. 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>
134. 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>
135. Unolt M, Barry J, Digilio MC, et al. Primary lymphedema and other lymphatic anomalies are associated with 22q11.2 deletion syndrome. *Eur J Med Genet.* 2018;61(7):411-415. <http://doi.org/10.1016/j.ejmg.2018.02.006>
136. Blagojevic C, Heung T, van Mil S, et al. Abnormal spirometry in adults with 22q11.2 microdeletion and congenital heart disease. *Int J Cardiol Congenit Heart Dis.* 2021;3:100085. <http://doi.org/10.1016/j.ijcchd.2021.100085>
137. Mauro J, Diaz M, Córdova T, et al. Analysis of REM sleep without atonia in 22q11.2 deletion syndrome determined by domiciliary polysomnography: a cross sectional study. *Sleep.* 2022;45(2):zsab300. <https://doi.org/10.1093/sleep/zsab300>
138. 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>
139. Dufournet B, Nguyen K, Charles P, et al. Parkinson's disease associated with 22q11.2 deletion: clinical characteristics and response to treatment. *Rev Neurol (Paris).* 2017;173(6):406-410. <http://doi.org/10.1016/j.neurol.2017.03.021>
140. Buysse DJ. Insomnia. *JAMA.* 2013;309(7):706-716. <http://doi.org/10.1001/jama.2013.193>
141. Every-Palmer S, Inns SJ, Ellis PM. Constipation screening in people taking clozapine: a diagnostic accuracy study. *Schizophr Res.* 2020;220:179-186. <http://doi.org/10.1016/j.schres.2020.03.032>
142. 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>
143. Lopez-Rivera E, Liu YP, Verbitsky M, et al. Genetic drivers of kidney defects in the DiGeorge syndrome. *N Engl J Med.* 2017;376(8):742-754. <http://doi.org/10.1056/NEJMoa1609009>
144. Sundaram UT, McDonald-McGinn DM, Huff D, et al. Primary amenorrhea and absent uterus in the 22q11.2 deletion syndrome. *Am J Med Genet A.* 2007;143A(17):2016-2018. <http://doi.org/10.1002/ajmg.a.31736>
145. Chan C, Costain G, Ogura L, Silversides CK, Chow EWC, Bassett AS. Reproductive health issues for adults with a common genomic disorder: 22q11.2 deletion syndrome. *J Genet Couns.* 2015;24(5):810-821. <http://doi.org/10.1007/s10897-014-9811-7>
146. Costain G, Chow EWC, Silversides CK, Bassett AS. Sex differences in reproductive fitness contribute to preferential maternal transmission of 22q11.2 deletions. *J Med Genet.* 2011;48(12):819-824. <http://doi.org/10.1136/jmedgenet-2011-100440>
147. Palmer LD, McManus Z, Heung T, et al. Reproductive outcomes in adults with 22q11.2 deletion syndrome. *Genes (Basel).* 2022;13(11):2126. <http://doi.org/10.3390/genes13112126>
148. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J.* 2018;39(34):3165-3241. <http://doi.org/10.1093/eurheartj/ehy340>
149. Windram J, Grewal J, Bottega N, et al. Canadian Cardiovascular Society: clinical practice update on cardiovascular management of the pregnant patient. *Can J Cardiol.* 2021;37(12):1886-1901. <http://doi.org/10.1016/j.cjca.2021.06.021>
150. Van L, Butcher NJ, Costain G, Ogura L, Chow EWC, 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>
151. Nissen TE, Zaniletti I, Collins RT II, et al. Comparison of post-operative, in-hospital outcomes after complete repair of tetralogy of Fallot between 22q11.2 deletion syndrome and trisomy 21. *Pediatr Cardiol.* 2022;43(2):290-300. <http://doi.org/10.1007/s00246-021-02683-1>
152. McGovern PE, Crowley TB, Zackai EH, Burrows E, McDonald-McGinn DM, Nance ML. Surgical insights and management in patients with the 22q11.2 deletion syndrome. *Pediatr Surg Int.* 2022;38(6):899-905. <http://doi.org/10.1007/s00383-022-05>
153. 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>
154. Stransky C, Basta M, McDonald-McGinn DM, et al. Perioperative risk factors in patients with 22q11.2 deletion syndrome requiring surgery for velopharyngeal dysfunction. *Cleft Palate Craniofac J.* 2015;52(2):183-191. <http://doi.org/10.1597/13-206>
155. 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>
156. 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>
157. 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. <https://www.jrheum-org.mu.idm.oclc.org/content/28/10/2326.long>
158. 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>
159. 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>
160. Poirsirc 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>

161. Napoli E, Tassone F, Wong S, et al. Mitochondrial citrate transporter-dependent metabolic signature in the 22q11.2 deletion syndrome. *J Biol Chem*. 2015;290(38):23240-23253. <http://doi.org/10.1074/jbc.M115.672360>
162. 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>
163. Morava E, Lacassie Y, King A, Illes T, Marble M. Scoliosis in velocardio-facial syndrome. *J Pediatr Orthop*. 2002;22(6):780-783. [https://www.researchgate.net/publication/11054752\\_Scoliosis\\_in\\_Velocardio-Facial\\_Syndrome](https://www.researchgate.net/publication/11054752_Scoliosis_in_Velocardio-Facial_Syndrome)
164. 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>
165. 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>
166. Jawad AF, Prak EL, Boyer J, et al. A prospective study of influenza vaccination and a comparison of immunologic parameters in children and adults with chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). *J Clin Immunol*. 2011;31(6):927-935. <http://doi.org/10.1007/s10875-011-9569-8>
167. Lazier K, Chow EW, AbdelMalik P, Scutt LE, Weksberg R, Bassett AS. Low platelet count in a 22q11 deletion syndrome subtype of schizophrenia. *Schizophr Res*. 2001;50(3):177-180. [http://doi.org/10.1016/S0920-9964\(00\)00159-6](http://doi.org/10.1016/S0920-9964(00)00159-6)
168. Kato T, Kosaka K, Kimura M, et al. Thrombocytopenia in patients with 22q11.2 deletion syndrome and its association with glycoprotein Ib-beta. *Genet Med*. 2003;5(2):113-119. <http://doi.org/10.1097/01.GIM.0000056828.03164.30>
169. Pachtman SL, Deng K, Nanda D. Thrombocytopenia and postpartum hemorrhage in a woman with chromosome 22q11.2 deletion syndrome. *Case Rep Obstet Gynecol*. 2016;2016:2920375. <http://doi.org/10.1155/2016/2920375>
170. Gokturk B, Guner SN, Kara R, et al. Would mean platelet volume/platelet count ratio be used as a novel formula to predict 22q11.2 deletion syndrome? *Asian Pac J Allergy Immunol*. 2016;34(2):166-173. <http://doi.org/10.12932/AP0604.34.2.2016>
171. Liang HPH, Morel-Kopp MC, Curtin J, et al. Heterozygous loss of platelet glycoprotein (GP) Ib-V-IX variably affects platelet function in velocardiofacial syndrome (VCFS) patients. *Thromb Haemost*. 2007;98(6):1298-1308. <https://www.thieme-connect.com/products/ejournals/abstract/10.1160/TH07-05-0350>
172. Damlaj M, Séguin C. Refractory autoimmune hemolytic anemia in a patient with DiGeorge syndrome treated successfully with plasma exchange: a case report and review of the literature. *Int J Hematol*. 2014;100(5):494-497. <http://doi.org/10.1007/s12185-014-1648-1>
173. Soares DC, Dantas AG, Matta MC, et al. Lymphoproliferative disorder with polyautoimmunity and hypogammaglobulinemia: an unusual presentation of 22q11.2 deletion syndrome. *Clin Immunol*. 2020;220:108590. <http://doi.org/10.1016/j.clim.2020.108590>
174. Itoh S, Ohno T, Kakizaki S, Ichinohasama R. Epstein-Barr virus-positive T-cell lymphoma cells having chromosome 22q11.2 deletion: an autopsy report of DiGeorge syndrome. *Hum Pathol*. 2011;42(12):2037-2041. <http://doi.org/10.1016/j.humpath.2010.03.014>
175. Veerapandiyan A, Chinn IK, Schoch K, Maloney KA, Shashi V. Reactive lymphoid hyperplasia in association with 22q11.2 deletion syndrome and a BRCA2 mutation. *Eur J Med Genet*. 2011;54(1):63-66. <http://doi.org/10.1016/j.ejmg.2010.09.004>
176. McDonald-McGinn DM, Reilly A, Wallgren-Pettersson C, et al. Malignancy in chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). *Am J Med Genet A*. 2006;140(8):906-909. <http://doi.org/10.1002/ajmg.a.31199>
177. Vautier M, Georgin-Lavialle S, Hermine O, et al. Efficiency and good tolerance of rituximab for idiopathic thrombocytopenic purpura revealing a 22q11 deletion syndrome. Article in French. *Rev Med Interne*. 2016;37(11):766-770. <http://doi.org/10.1016/j.revmed.2016.01.008>
178. Persson C, Friman V, Óskarsdóttir S, Jónsson R. Speech and hearing in adults with 22q11.2 deletion syndrome. *Am J Med Genet A*. 2012;158A(12):3071-3079. <http://doi.org/10.1002/ajmg.a.35589>
179. 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>
180. 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>
181. Klingberg G, Lingström P, Óskarsdóttir 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>
182. Klingberg G, Óskarsdóttir S, Johannesson EL, Norén JG. Oral manifestations in 22q11 deletion syndrome. *Int J Paediatr Dent*. 2002;12(1):14-23. <https://onlinelibrary.wiley.com/doi/abs/10.1046/j.0960-7439.2001.00317.x>
183. 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>
184. 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>
185. 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 Radiol Endod*. 2008;106(2):e46-e51. <http://doi.org/10.1016/j.tripleo.2008.04.019>
186. 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. <https://doi.org/10.1161/CIR.0000000000000969>
187. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC guidelines for the management of infective endocarditis: the task force for the management of infective endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European association of nuclear medicine (EANM). *Eur Heart J*. 2015;36(44):3075-3128. <http://doi.org/10.1093/eurheartj/ehv319>
188. Óskarsdóttir S, Boot E, Crowley TB, et al. Updated clinical practice recommendations for managing children with 22q11.2 deletion syndrome. *Genetic Med*. 2023;25:100338. <https://doi.org/10.1016/j.gim.2022.11.006>