BMJ Best Practice

DiGeorge syndrome

Straight to the point of care

Last updated: Nov 03, 2020

Table of Contents

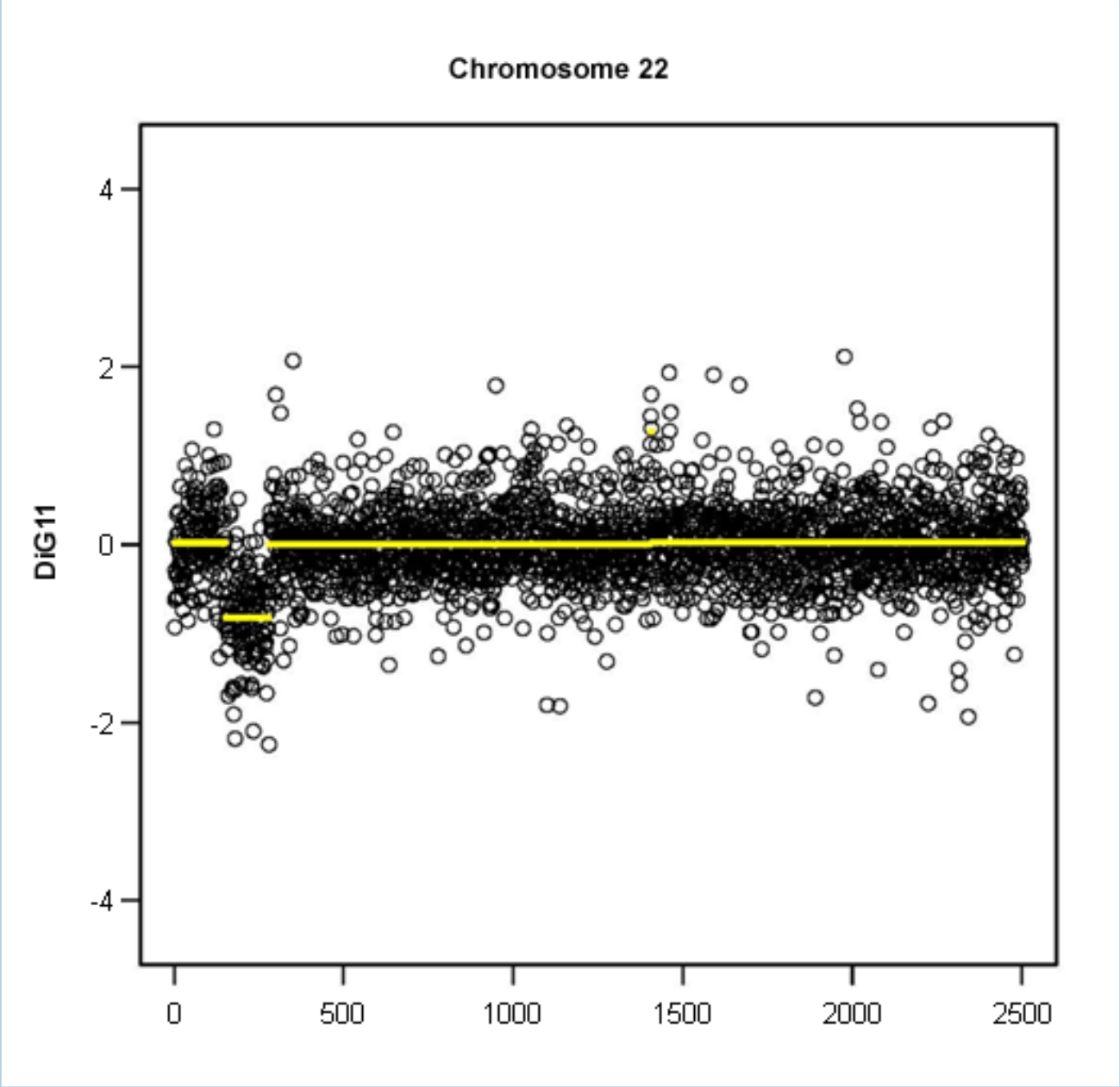
Summary

- Typically results from a deletion in chromosome 22, which disrupts the development of the pharyngeal arches and pouches, and may also cause neurological, immunological, endocrinological, or cognitive deficits.
- Classic presentation is a triad of cardiac anomalies, hypoplastic thymus, and hypocalcaemia, but clinical manifestations are highly variable, ranging from mild learning disabilities to the complete spectrum of congenital malformations. This phenotypic variability occurs despite a highly consistent genetic lesion.
- Presenting signs and symptoms depend on age at diagnosis and the organ system affected. Knowledge of the particular characteristics for a given age helps guide follow-up and management.
- Treatment modalities depend on clinical manifestations present in the individual patient. Management is symptomatic and generally follows typical practice for patients without the syndrome, for any given feature.

Definition

The classical presentation is a triad of cardiac anomalies, hypoplastic thymus, and hypocalcaemia (resulting from parathyroid hypoplasia). 22q deletion syndrome (22qDS), described as DiGeorge syndrome or velocardiofacial syndrome, is the set of characteristic morphological and neurological features that result from the deletion of 1 copy of 22q11.2. The deletion causes a reduction in TBX1, a key transcription factor for development of the pharyngeal arches. This developmental disruption may cause cardiac anomalies, immunological abnormalities, cleft lip and palate, hypoparathyroidism, learning disabilities, and schizophrenia. The disorder is notable for marked variation in the penetrance of the various features. The syndrome has been known by multiple other names, including CATCH22 and Shprintzen's syndromes. The complexity of the nomenclature is due to great variability in the clinical syndrome.

The phenotype of DiGeorge syndrome may be divided into 2 components. The first, pharyngeal component consists of congenital heart disease, hypoplasia of the parathyroid glands, thymic hypoplasia with T-cell immunodeficiency, cleft lip and palate, and mild dysmorphic facial features. The second, neurological phenotype consists of mild cognitive dysfunction, which typically presents as learning disabilities, speech impairment, and an increased incidence of schizophrenia.



Loss of 1 copy of 22q11.2, demonstrated by microarray copy number analysis

From the collections of Sean A. McGhee, MD and Maria Garcia Lloret, MD

Epidemiology

DiGeorge syndrome (22qDS) is the most common interstitial deletion syndrome, and only slightly less common than trisomy 21 (Down's syndrome). Evidence from the Western Götaland region of Sweden shows the mean annual incidence is approximately 14 per 100,000 live births (approximately 23 per 100,000 live births in Gothenburg, where a multidisciplinary specialist team is based), and the prevalence is approximately 13 per 100,000 children below 16 years of age (approximately 23 per 100,000 in Gothenburg).[8] The incidence of 22q deletions is 1/4000 to 1/6000 live births in the US.[9] Evidence from North and South America shows that the sexes are equally affected, and there is no demonstrated ethnic predisposition, although it may influence the specific manifestations of the disorder.[9] [10]

Most 22q deletions presenting with cardiac disease or hypocalcaemia are detected in infancy. Patients who do not have such overt manifestations may be easily overlooked, and the syndrome may be diagnosed later because of learning disabilities, palatal insufficiency, or psychiatric disease. The disorder was previously thought to be rare in adults, but with improved survival after cardiac surgery and more widespread use of fluorescence in situ hybridisation testing for the deletion, more adults are being identified. Complete DiGeorge syndrome requiring immune reconstitution through thymic transplant or adoptive transfer of mature T cells is rare, as is the atypical form of the syndrome (complete syndrome with proliferating autoreactive oligoclonal T-cell populations).[3] [11]

Aetiology

DiGeorge syndrome results from a deletion of 1 copy of the 22q11.2 chromosomal region.[12] The deletion results in hemizygosity for at least 30 genes, including TBX1, a key transcription factor for the development of the pharyngeal arches.[13] This particular deletion is much more common than other interstitial deletions due to the genomic structure of this region of chromosome 22.[14] Two areas of low copy number repeats occur at the breakpoints of the deletion. The deletion itself arises when these 2 recombine abnormally during meiosis.[15] The highly similar structure of the low copy number repeats results in mispairing and a deletion of the portion of the chromosome between the 2 repeats. The typical deletion is 3 megabases, although 10% to 15% of patients may have a smaller deletion of about 1.5 megabases.[16] This smaller deletion results from abnormal recombination with a third low copy number repeat. Although these deletions are the primary cause of the syndrome, 2% of patients have small atypical 22q deletions, and a few patients have no deletion.[17] [18] [19] [20] [21] [22] Some of these patients have been found to have point mutations in TBX1, while others have deletions at 10p or mutations in chromodomain-helicase DNA-binding protein.[18] [19] [20] Phenocopies of DiGeorge syndrome also exist, such as may be found in infants of diabetic mothers.[23] Genetic variation in TBX1, the principal gene responsible for the syndrome, does not account for the variability in the phenotype seen in the syndrome.[24] There are no known modifiable risk factors for the deletion. Most DiGeorge syndrome cases are sporadic, but known mutations are inherited in an autosomal dominant fashion.[9]

Pathophysiology

DiGeorge syndrome is the set of characteristic morphological and neurological features that result from the deletion of 1 copy of 22q11.2. The deletion causes a reduction in TBX1, a key transcription factor for development of the pharyngeal arches. This developmental disruption may cause cardiac anomalies, immunological abnormalities, cleft lip and palate, hypoparathyroidism, learning disabilities, and schizophrenia.

The deletion of 1 copy of TBX1 results in inadequate production of the TBX1 protein in the pharyngeal arches.[21] TBX1 interacts with multiple other signalling molecules, including fibroblast growth factors and vascular endothelial growth factors, to promote pharyngeal arch development.[25] Because TBX1 is insufficient, the pharyngeal arches and pouches are malformed, and the structures they produce are hypoplastic.[26] Haploinsufficiency of TBX1 in mice is sufficient to disrupt the fourth pharyngeal arch artery, replicating a major feature of DiGeorge syndrome.[26] Mice homozygous for TBX1 deletions show complete absence of the thymus and parathyroids, and mice hemizygous for the syntenic deletion show abnormal thymuses.[13] [27] TBX1 is also found in the secondary heart field and in the brain, where it may contribute to the development of the neurological phenotype.[28] Work in mice indicates that when TBX1 is deficient all embryos initially develop features of the disorder, but some seem to be able to correct the defect during

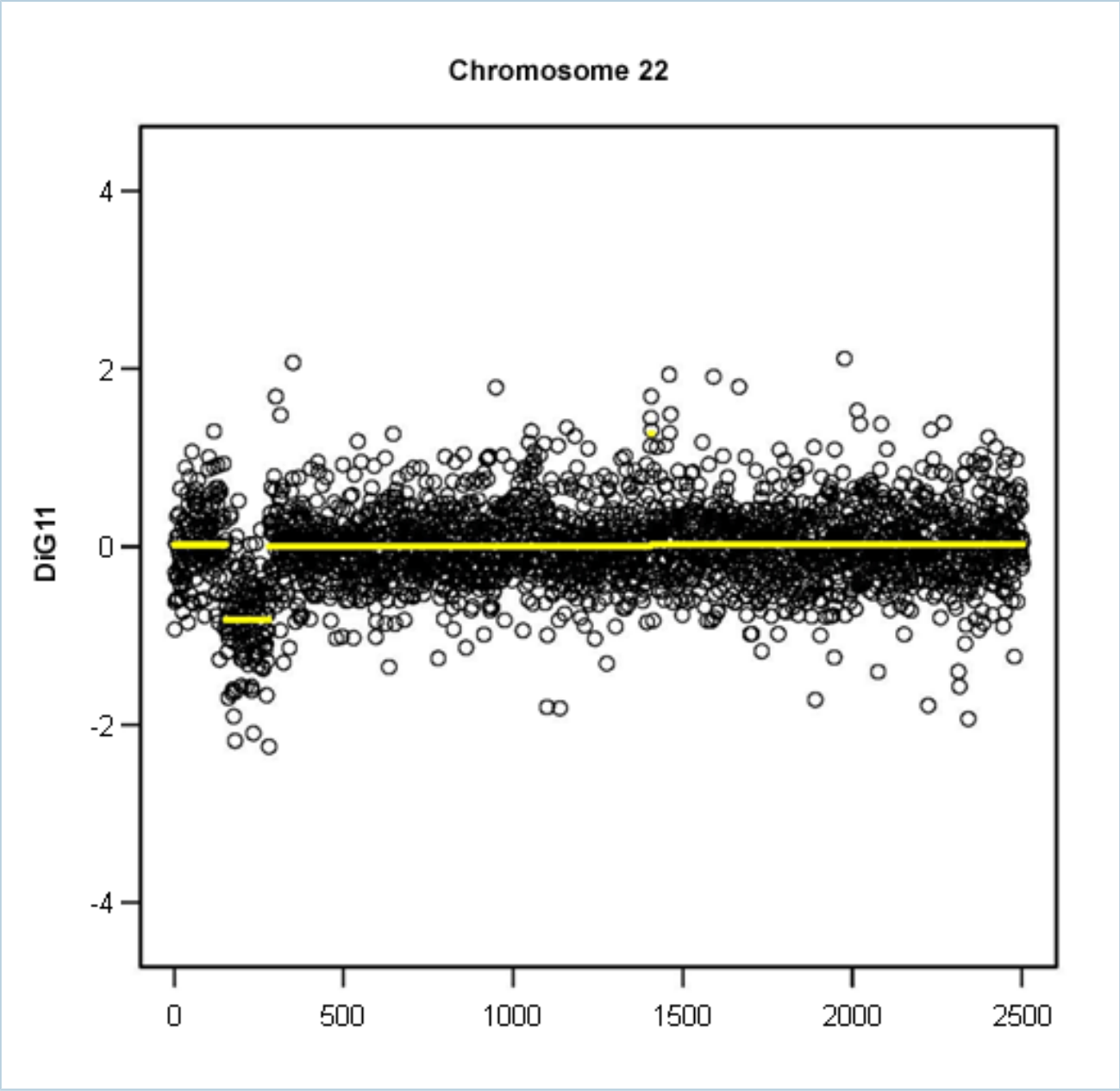
later stages of development.[27] This implies that other genes may have a role in modifying the disorder, and might also suggest that development of at least some disease features is preventable.

Work with the mouse model of 22q deletion has suggested that alterations in microRNA processing caused by deficiency of DGCR8, a gene found in the deleted region, may contribute to the neurological abnormalities and abnormal brain imaging seen in DiGeorge syndrome.[29] [30]

Polymorphisms in some genes have been identified that seem to increase the risk of specific complications.[31] [32] [33]

Polymorphisms in the catechol-O-methyltransferase gene in the deleted region may increase the risk of schizophrenia, although studies are conflicting. Vascular endothelial growth factor polymorphisms alter the incidence of heart disease in a murine model of the disorder. Similar mechanisms may be at work in humans. These polymorphisms are not yet available for clinical testing or predicting outcomes for patients.

Autoimmunity is also a feature of 22q11.2 deletion and is correlated with the severity of T-cell lymphopenia.[34]



Loss of 1 copy of 22q11.2, demonstrated by microarray copy number analysis

From the collections of Sean A. McGhee, MD and Maria Garcia Lloret, MD

Classification

Complete and partial DiGeorge syndrome (ESID/PAGID diagnostic criteria)[1]

DiGeorge syndrome has been historically divided into complete and partial DiGeorge syndrome, although a greater appreciation of the syndrome's variability has made this distinction less useful.

- Complete DiGeorge syndrome was used if patients had the full spectrum of typical manifestations, including severe immunodeficiency.

- Partial DiGeorge syndrome was used if patients had only some manifestations of the disorder, particularly those without evident immunodeficiency. Partial DiGeorge syndrome is far more common than complete.
- Measurement of naive T-cell numbers is key to distinguishing partial from complete DiGeorge syndrome.[2]

Typical and atypical DiGeorge syndrome[3]

Observations have identified a small subset of DiGeorge syndrome patients who have T-cell immunodeficiency but develop abnormal oligoclonal T cells, resulting in a graft-versus-host disease-like rash and requiring immunosuppression to avoid complications of lymphoproliferation.[3]

- Typical DiGeorge syndrome is used when patients have varying degrees of immunodeficiency but no oligoclonal T-cell populations.
- Atypical DiGeorge syndrome is used when patients have proliferating autoreactive oligoclonal T-cell populations.

Both of these distinctions (typical and atypical) apply only to patients with complete DiGeorge syndrome, which specifically refers to severe T-cell immunodeficiency (athymia).

DiGeorge syndrome can also be associated with significant B-cell abnormalities in a higher proportion of patients than previously thought.[4] [5]

Screening

The asymptomatic population is generally not screened for DiGeorge syndrome. However, there is a developing impetus for lymphopenia screening to detect severe combined immunodeficiency as part of the normal newborn screening panel, and this has the potential to detect some (although not most) patients with 22q deletion syndrome as well. There is a pilot effort to screen all newborns for 22q deletion syndrome in one state in the US. This may be useful, since at least 1 in 4 newborns with 22q deletion are missed clinically,[75] but the benefit of newborn screening for 22q deletion syndrome is unknown, and this screening will not detect DiGeorge syndrome resulting from causes other than 22q deletion.[76] [77] Testing only those with conotruncal abnormalities has only 70% sensitivity for identifying 22q11.2 deletion. Consideration should be given to screening any patient with an aortic arch abnormality.[78] There is probably little advantage to screening patients with schizophrenia who do not have other features of DiGeorge syndrome.[79] New strategies are needed for identifying those with other congenital heart diseases that would benefit from testing.[80]

Secondary prevention

Genetic counselling is important because of the high risk in the children of affected parents. Because of the sporadic nature of the disease, most healthy parents are not at risk of additional children with the disorder, but because the presentation may be mild, a careful assessment of apparently healthy parents is warranted before determining the recurrence risk. Complex congenital heart disease may be more likely in relatives of individuals with 22q11.2 deletion syndrome, regardless of whether they also have a deletion.[29]

Case history

Case history #1

A newborn girl presents with cyanosis after an unremarkable pregnancy and delivery. A hyperoxia test suggests congenital heart disease, and an echocardiogram confirms tetralogy of Fallot. The infant subsequently has a seizure, and serum calcium is 5.8 mg/dL. Intact PTH level is low. T-cell enumeration by flow cytometry reveals a CD3+ cell count of 780 cells/mm^3. At age 4, she begins schooling but has difficulty performing up to the level of her peers. She has hypernasal speech that is sometimes difficult to understand. Nevertheless, she completes her schooling and is able to work productively.

Other presentations

The variability of the syndrome leads to many different presentations other than the classic one described. A patient may have only 1 or 2 of the features, and if he or she does not have cardiac disease or symptomatic hypocalcaemia, the diagnosis may be missed. The diagnosis may only be discovered when the patient's child inherits the disorder and has a more severe presentation. The presentation may vary even within families and with identical deletions.[6] The syndrome may also occasionally present with rash and lymphadenopathy as in the case of atypical DiGeorge syndrome (complete syndrome with proliferating autoreactive oligoclonal T-cell populations).[3] A wide range of congenital anomalies other than the typical ones has been described in some patients with 22qDS. Additionally, some patients with Parkinson's disease have been found to have deletions in 22q11.[7]

Step-by-step diagnostic approach

Because there is a reliable diagnostic test, the primary issue in the diagnosis of DiGeorge syndrome is to determine which patients to test. Presenting signs and symptoms depend on the patient's age at diagnosis and on the organ system affected. In young infants, classic manifestations include congenital heart disease, hypocalcaemia, and GI reflux. Mild to moderate T-cell deficiencies are not uncommon, but opportunistic infections are rare. Speech delay and cognitive impairment may be presenting manifestations of DiGeorge syndrome in older children and schizophrenia in young adults. Knowledge of the particular characteristics for a given age helps to guide follow-up and management.

Determining which populations to test

Children should be tested if they have features suggesting DiGeorge syndrome.

In general, any patient with 2 or more common features of DiGeorge syndrome should be screened for the deletion. These features include any congenital heart defect, features of hypocalcaemia/hypoparathyroidism (which can manifest as seizures) in infancy, evidence of any velopharyngeal insufficiency, including cleft palate or hypernasal voice, characteristic facial appearance, and T-cell lymphopenia.[36] In addition, testing should be considered in those who have learning disorders or schizophrenia together with any other feature of the disorder. Patients may have frequent sinopulmonary or viral infections. Children may present with heart failure, cyanosis, and abnormal facial features in infancy. The characteristic facial appearance may provide an indication for further testing. Young patients tend to have prominent, cup-shaped ears and a relatively bulbous nose tip.

Children of parents with DiGeorge syndrome are at risk of inheriting the disorder because it is passed on in an autosomal dominant fashion.

- Neonates and infants frequently have trouble with feeding, attributed partly to cleft lip and palate. However, feeding difficulty also occurs without associated cleft palate. Consistent reductions in olfaction have also been demonstrated in children with 22q11.2 deletion.[37]
- Children frequently exhibit speech development delay and learning disorders.
- Syndrome-specific growth charts have now been developed for 22q11.2 syndrome.[38] [39] Growth failure is common in comparison with WHO standard growth charts.
- Certain cardiac lesions are characteristic. A type B interrupted aortic arch is the most suggestive, as around 50% of those with this lesion have 22q11.2DS.[36] Patients with tetralogy of Fallot or truncus arteriosus probably also warrant screening, although the yield is lower in these groups.[40] Those with more common cardiac lesions, such as ventricular septal defect, should probably be screened only if they have other features of the syndrome.
- Schizophrenia and other psychiatric disorders occur later in adulthood, although testing these patients without features of DiGeorge syndrome is not practical.
- Some patients with 22qDS phenocopies, such as retinoic acid embryopathy, or some infants of mothers with diabetes have a similar phenotype but do not have 22q deletions.

Cardiologists identify and refer most DiGeorge syndrome patients, and those who have been trained to recognise the syndrome identify more patients than those who do not have experience with the disorder.[8]

Patients with primary hypoparathyroidism and those with coloboma of the eye, heart defects, atresia of the nasal choanae, retardation of growth and/or development, genital and/or urinary abnormalities, and ear abnormalities and deafness (CHARGE syndrome) should also be screened.

Because of the great variability in the syndrome, if a patient shows any 1 sign of DiGeorge syndrome, it is important to carefully assess for other signs to determine whether screening is indicated.

Testing for the deletion

Once tested, evidence of a deletion of 1 copy of 22q11.2 is definitive. Fluorescence in situ hybridisation (FISH) with the TUPLE1 gene probe is the most common test used for identifying the deletion. A fluorescent probe hybridises to the TUPLE1 gene within the deleted region on a metaphase chromosome spread. Because human cells are diploid, 2 fluorescent spots should be seen. If only 1 is seen, the person is hemizygous at TUPLE1. This confirms the diagnosis of DiGeorge syndrome.

Occasionally, a patient is encountered who has a highly typical clinical presentation, but who has a normal FISH probe. Although this is a fairly unusual finding (5% to 10% of cases), some mechanisms have been proposed by which it might occur.[25] In patients with point mutations of TBX1, for instance, sequencing of this gene could clarify the diagnosis. Some DiGeorge-like patients without 22q11.2 deletions have deletions at 10p13-p14.[18] In addition, some infants of mothers with diabetes and CHARGE syndrome patients may have features similar to DiGeorge syndrome.[23] [41] [42] [43] [44] [45] [46] Karyotyping should also be performed along with chromodomain-helicase DNA-binding protein molecular testing to look for CHARGE syndrome or other copy number alterations. Microarray copy analyses can detect much smaller deletions than karyotyping, and can do so across the whole genome, unlike FISH, which can assess only 1 locus at a time. DiGeorge syndrome is not the only cause of athymia, and other causes of T-cell deficiency should be considered if this is the primary presenting feature.

Other tests

In patients with suspected or confirmed 22q11.2 syndrome, it is crucial to define the extent of the manifestations of the disorder. DiGeorge syndrome is a multisystem disorder, and serious anomalies could be overlooked if not specifically assessed. The initial diagnostic work-up should include echocardiography, serum calcium, and PTH level. Evaluating immune function is of prime importance and should include an FBC with differential and immunophenotyping, serum immunoglobulins (IgG, IgA, and IgM), and, in previously immunised children, levels of specific antibodies. Patients frequently have renal anomalies, including obstruction, dysplasia, and reflux. At the time of diagnosis, a renal ultrasound is indicated to screen for these.[47] Dental evaluation and chest x-ray should also be performed together with an evaluation for velopharyngeal insufficiency, cleft palate, or submucous cleft. Nasopharyngeal endoscopy may be required to adequately identify palatal abnormalities.[48] Audiometry and ophthalmological evaluations should be done. Early involvement of developmental specialists and early intervention are important, as the degree of cognitive difficulty is a major factor in the degree of disability 22qDS patients must contend with. Many other types of anomalies have occasionally been associated with DiGeorge syndrome, and the index of suspicion for other congenital malformations should remain high. Proliferation in response to mitogens and antigens may be used in equivocal cases to help decide if vaccines may be safely given. If proliferation is normal, vaccines are likely to be tolerated.[49]

Risk factors

Strong

parent with DiGeorge syndrome

- A child of a parent with DiGeorge syndrome is at high risk of the syndrome, as it will be inherited in an autosomal dominant fashion. Therefore, there is a 50% risk of the disorder in each pregnancy, when one parent is affected, and the disorder may be more severe in the child.
- Although this risk factor is thought to be uncommon, findings in parents may be extremely subtle, and careful examination and consideration of 22q11.2 deletion testing is recommended, as the risk to future children is high if the parents have the deletion.[35]
- Most DiGeorge syndrome cases are sporadic and no risk factors are known.[9]

History & examination factors

Key diagnostic factors

presence of risk factors (common)

- A strong risk factor is a parent with DiGeorge syndrome.

cyanosis (common)

- May be seen in tetralogy of Fallot and truncus arteriosus, 2 characteristic cardiac disorders.

signs of heart failure (common)

- Interrupted aortic arch and ventricular septal defect may present with signs of heart failure, such as hepatomegaly, oedema, poor feeding, or cardiogenic shock.

heart murmur (common)

- Many of the cardiac lesions have murmurs associated with them.

characteristic facial features (common)

- Present in most patients.[50] These include a bulbous nose tip and prominent ears.
- Facial features become less prominent as the child gets older.

cleft lip and palate (common)

- May range from velopharyngeal insufficiency to submucous clefts to overt cleft palate.[52]
- Hypernasal speech is common even in those without overt clefts.[53]

growth failure (common)

- Syndrome-specific growth charts have now been developed for 22q11.2 syndrome.[38] [39] Growth failure is common in comparison with WHO standard growth charts.

seizure or tetany (uncommon)

- Hypocalcaemia is common, although only a subset of patients actually present with seizure.[58]

Other diagnostic factors

presentation in infancy (common)

- Although patients may present at any age, the vast majority are still diagnosed in infancy.[50]

feeding difficulty (common)

- A non-specific finding but highly characteristic of the syndrome, not necessarily due to cleft palate.[51]
- Consistent reductions in olfaction have also been demonstrated in children with 22q11.2 deletion.[37]

speech delay (common)

- Occurs in most patients and is unrelated to the palatal insufficiency.[54]

non-verbal learning disorder (common)

- Mathematical ability is much more affected than language skills.[55]
- The learning disorder is primarily non-verbal, but this may not be appreciated early in life because of speech delay. Once speech is acquired; however, language ability is relatively preserved.

frequent infections (common)

- Sinopulmonary infection and viral infection incidences are increased [59] Occur regardless of presence of detectable immunodeficiency. Bacterial infections should be promptly managed with appropriate antibiotic therapy.

schizophrenia (uncommon)

- Occurs at the same age as typical schizophrenia and is indistinguishable from it.[56]
- Screening of people with schizophrenia who do not have other signs of DiGeorge syndrome is usually not useful.[57]
- Up to 20% of patients may develop schizophrenia.[56]

features of CHARGE syndrome (uncommon)

- Should be tested genetically.

- Features include coloboma of the eye, heart defects, atresia of the nasal choanae, retardation of growth and/or development, genital and/or urinary abnormalities, and ear abnormalities and deafness (CHARGE syndrome).

Diagnostic tests

1st test to order

Test	Result
serum calcium • Hypocalcaemia may occur due to hypoparathyroidism.	**low**
serum intact PTH • Hypoparathyroidism may be seen due to failure of embryological development of the parathyroid glands. It is associated with a higher likelihood of significant immune dysfunction and may also be associated with the presence of hypothyroidism.	**low**
T-cell count • T-cell lymphopenia is seen often, although not uniformly. Although not a diagnostic test, detection of T-cell lymphopenia supports the diagnosis of DiGeorge syndrome. • T- (CD3, CD4, CD8) and B- (CD20) cell subsets are routinely enumerated by flow cytometry in most clinical laboratories. • Most patients have some degree of T-cell lymphopenia, usually not severe enough to cause clinical symptoms.[60]Profound T-cell dysfunction is rare, but when present requires immune reconstitution through thymic transplantation or adoptive transfer of mature T cells. • One study proposes using the thymic to thoracic ratio as a screening parameter to identify newborns who require evaluation for 22q deletion.[61]	**low**
fluorescence in situ hybridisation • Should be ordered in any patient with 2 or more features of DiGeorge syndrome, or in all infants with typical cardiac anatomy (i.e., interrupted aortic arch or tetralogy of Fallot). • Because the deletion is a meiotic event, mosaicism is generally not found.[62]	**1 copy of probe per cell confirms 22q11.2 deletion**
immune-specific titres (if previously immunised) • Patients who have been immunised should have positive titres. Absence of positive titres to immunisations suggests T-cell-mediated immunodeficiency.	**may be absent**
FBC • Lymphopenia may be present.	**abnormal**
TSH • Should be checked initially and at least yearly, as there is a risk of development of thyroid dysfunction.	**may be high**
chest x-ray • DiGeorge syndrome is characterised by failure of development of a thymus gland.	**absent thymus**
ECG • The QT interval may be prolonged if hypocalcaemia is present.	**may show prolonged QT interval**
serum immunoglobulins • In addition to T-cell lymphopenia, may have immunoglobulin deficiency.	**may be low**

Other tests to consider

Test	Result
lymphocyte mitogen and antigen proliferation • Proliferation in response to mitogens and antigens may be used in equivocal cases to help decide if vaccines may be safely given. If proliferation is normal, vaccines are likely to be tolerated.[49]	**may be low**
karyotype • Generally done at the same time as fluorescence in situ hybridisation but does not usually detect 22q11.2 deletion.	**may detect other genetic abnormalities**
echocardiogram • Some heart defects are associated with DiGeorge syndrome, including tetralogy of Fallot and truncus arteriosus defect. Should be done in any patient with congenital murmurs or cyanosis.	**abnormal structural heart disease**
renal ultrasound • Urinary tract disorders may be seen, which may require consultation from a specialist. • Patients frequently have renal anomalies, including obstruction, dysplasia, and reflux.	**renal agenesis or obstruction**
audiometry • Hearing disorders may be seen, which may contribute to delayed speech development and learning disability.	**abnormal**
dental and palatal evaluations • Evaluation for velopharyngeal insufficiency, cleft palate, or submucous cleft. • Nasopharyngeal endoscopy may be required to adequately identify palatal abnormalities.[48]	**may show typical abnormalities**
ophthalmology evaluation • Coloboma of the eye may be seen in some patients.	**may show coloboma of the eye**

Emerging tests

Test	Result
microarray copy number analysis • When positive, a loss of 1 copy is seen at the 22q11.2 locus. Microarrays are emerging as tools for fine resolution determination of copy number variations such as are found in DiGeorge syndrome.[63] • Can detect much smaller deletions than karyotyping and can do so across the whole genome, unlike fluorescence in situ hybridisation, which can assess only 1 locus at a time.	**positive**
mean platelet volume • Has been reported to be useful in screening congenital heart disease patients for DiGeorge syndrome, but has only been studied in a limited number of patients.[64]	**<10 femtolitres**

Differential diagnosis

Condition	Differentiating signs / symptoms	Differentiating tests
Non-syndromic anomalies	• The variable penetrance of DiGeorge may produce features that overlap with other syndromes.	• Assessment for 22q deletions distinguishes most patients with DiGeorge syndrome from the non-syndromic variants of the specific anomalies. • Routine screening of otherwise asymptomatic people with schizophrenia is generally not helpful.
Isotretinoin exposure	• Fetal exposure to isotretinoins, such as those used for acne, causes the syndrome known as retinoic acid embryopathy, which can result in similar features to DiGeorge syndrome.[65] [66] [67] [68] A history of isotretinoin exposure is useful in differentiating this syndrome. More common in this syndrome than in 22qDS are microtia or anotia, micrognathia, and spontaneous abortion.[65]	• Generally, these patients are missing the 22q deletion syndrome.
CHARGE syndrome	• Infants with coloboma of the eye, heart defects, atresia of the nasal choanae, retardation of growth and/or development, genital and/or urinary abnormalities, and ear abnormalities and deafness (CHARGE syndrome) have features that may overlap with DiGeorge syndrome, and some patients described as having CHARGE syndrome have been found to have 22q deletions.[69] [70] [71] [72] [73] [74]	• Some patients with CHARGE syndrome may have 22q deletions, while others will have CHD7 mutations.[72] Infants with CHARGE syndrome should have a T-cell count to exclude immunodeficiency.

DIAGNOSIS

Diagnostic criteria

European Society for Immunodeficiencies diagnostic criteria[1]

Definitive

Patient with reduced numbers of CD3+ T cells (less than 500/mm3) and two of the three following characteristics:

- Conotruncal cardiac defect (truncus arteriosus, tetralogy of Fallot, interrupted aortic arch, or aberrant right subclavian)
- Hypocalcemia of greater than 3 weeks duration that requires therapy
- Deletion of chromosome 22q11.2.

Probable

Patient with reduced numbers of CD3+ T cells (less than 1500/mm^3) and a deletion of chromosome 22q11.2.

Possible

Patient with reduced numbers of CD3+ T cells (less than 1500/mm^3) and at least one of the following:

- Cardiac defect
- Hypocalcemia of greater than 3 weeks duration that requires therapy
- Dysmorphic facies or palatal abnormalities.

Recommendations

The treatment approach involves managing complications of the disorder. Because complications occur at predictable ages in a patient's life, management should be tailored to the age of the patient.[59]

Birth to 4 months

General care and stabilisation

- Parents should be evaluated for signs of DiGeorge syndrome, with further diagnostic testing if there are signs of the syndrome, such as developmental delay or a history of hypocalcaemia.
- Determining the extent of the disorder is required. This consists of determining lymphocyte counts, immunoglobulin levels, intact PTH level, and serum calcium level. Chest x-ray helps to evaluate thymic size and cardiac anatomy. Examination for cleft palate should be performed and ophthalmological examination arranged. Renal ultrasound should be performed to identify renal hypoplasia or obstruction. Hearing screening should be performed as well.
- Treatment of infants is characterised by stabilising life-threatening abnormalities and characterising the extent of disease. Stabilisation usually consists of treatment of hypocalcaemic seizures with intravenous calcium replacement. Cardiac anomalies must be managed as appropriate, and echocardiography performed to define the cardiac anatomy and plan surgical repair. Infants with cardiac disease are managed as other infants with the same cardiac anatomy.

With hypocalcaemia

- Hypocalcaemia is treated with intravenous calcium replacement when symptomatic seizures, tetany, or rhythm disturbances occur. Otherwise, it may be managed with oral calcium and vitamin D with or without hydrochlorothiazide.

With cleft palate

- Cleft palate should be managed by adaptive feeding regimens in consultation with nutritionists, occupational therapists, feeding specialists, and orthodontists. Options include specialised nipples, prosthetics, and frequent burping. Otitis media and airway obstruction occur commonly with clefts and should be evaluated. Surgery is an option if other measures are not successful.
- Growth parameters should be carefully monitored, particularly to allow for early detection of feeding difficulties.

With feeding difficulty

- Some children may have feeding difficulty, not necessarily due to cleft palate. Modified feeding regimens may be implemented for them, and some may require a percutaneous gastrostomy tube.

With thyroid dysfunction

- Thyroid function should be assessed regularly by TSH screening, with replacement therapy started accordingly. Most US patients undergo thyroid screening at birth, but continued monitoring (at least yearly) is necessary because of the possibility of developing autoimmune or acquired thyroid disease.

Other major congenital anomalies

- These should be managed as appropriate. A wide variety of possible anomalies have been described in 22qDS patients, and a healthy respect for the range of possible findings should be maintained.

Infants and toddlers (4 months to 5 years)

Many in this age range still require further repair of their cardiac defects. Infants with hypocalcaemia should continue to receive calcium and calcitriol supplementation.

Children in this age group routinely have feeding difficulties that may or may not be associated with cleft palate. The first-line therapy is a modified feeding procedure to ease feeding, including changing nipples, using bottle feeding if breastfeeding is inadequate, thickening feeds, or changing formulas. Second-line therapy may be required and usually involves placing a gastric tube. This should be considered if the child does not gain weight despite other feeding interventions. Feeding difficulties can easily persist for months to years, and percutaneous gastrostomy tubes should be considered if oral intake is inadequate.

In older toddlers, delayed acquisition of speech will become a problem. This is not due solely to palate defects, which may need continued management, but occurs in most children. This should be treated with speech therapy early and use of bridging sign language. Specific recommendations are available for the management of speech therapy in DiGeorge syndrome.[81] For those with velopharyngeal insufficiency, surgical repair may be indicated to improve speech outcomes.[82] Therapy is continued as needed for hypothyroidism or hypoparathyroidism.

With immunodeficiency

- Patients with demonstrated immune dysfunction should be referred to an immunologist. Those with mild to moderate immunodeficiency should be monitored for the presence of infection. Those with significant T-cell deficiency (marked T-cell lymphopenia and absent proliferative responses) should be given trimethoprim–sulfamethoxazole prophylaxis and intravenous immunoglobulin, prepared for thymic transplant, or have adoptive transfer of mature T cells arranged.[11] [83] Infants should be monitored for the development of oligoclonal T-cell populations with frequent flow cytometric T-cell counts. Infants with significant T-cell immunodeficiency (<600 T cells/mm^3) should receive no live virus vaccines and should receive only irradiated, filtered (leukodepleted) blood products.[84] [85] [86] [87] [88] [89] [90]

School age (5 years to 18 years)

By school age, most feeding issues have improved. The primary issues in this age range are learning disorders and behavioural problems. DiGeorge syndrome children may be shy, withdrawn, or anxious. Rates of attention-deficit/ hyperactivity disorder, oppositional defiant disorder, and autistic spectrum disorders are higher than in the general population.[91] The initial approach should involve standard behavioural modification techniques. Management of these symptoms may require consultation with developmental paediatricians and psychiatrists.

Although children with 22qDS have speech delay, their language abilities are relatively preserved later in life when non-verbal learning disorders become predominant. Maths skills may be weak. These aspects should be approached with an individualised education plan.

Monitoring and treatment of sinopulmonary infections are important. Therapy is continued as needed for hypothyroidism or hypoparathyroidism. Patients with congenital heart disease and cleft palate may need continued follow-up.

Adult

The learning disability and behavioural issues may affect employment of DiGeorge syndrome patients, although these issues are generally mild enough that independent living and full employment are possible.

Psychiatric disorders may become more problematic in this age group. Psychiatrists should manage patients with psychosis or schizophrenia with appropriate antipsychotic therapy. Depression and bipolar disorder also occur and are managed typically.

Therapy of schizophrenia is generally typical, but there may be more resistance to antipsychotic therapy. There are few published data on therapeutic recommendations for 22q11.2DS patients, but one case report has successfully used aripiprazole for treatment of resistant psychosis, while another successfully used quetiapine. If hypocalcaemia is present it should be corrected, as hypocalcaemia alone may provoke psychosis.[92]

Increased risk for sinopulmonary infections persists, and infections should be treated aggressively with appropriate antibiotic therapy. Therapy is continued as needed for hypothyroidism or hypoparathyroidism. Patients with congenital heart disease may continue to need follow-up into adulthood.

Treatment details overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing (summary)

birth to 4 months		
	1st	monitoring and stabilisation
with congenital heart disease	plus	surgical repair after stabilisation
with cleft palate or lip	plus	supportive specialty care
	adjunct	surgery
with feeding difficulty	plus	feeding therapy
with hypocalcaemia	plus	calcium + calcitriol
	adjunct	hydrochlorothiazide
	adjunct	intravenous calcium for any episode of tetany, seizure, or prolonged QT interval
with hypothyroidism	plus	levothyroxine
with renal obstruction or hypoplasia	plus	specialist consultation
infants and toddlers		
	1st	continued monitoring
with congenital heart disease	plus	monitoring and possible surgery
with marked immunodeficiency	plus	trimethoprim/sulfamethoxazole + intravenous immunoglobulin
	plus	immune reconstitution
with hypocalcaemia	plus	calcium + calcitriol
	adjunct	hydrochlorothiazide
	adjunct	intravenous calcium for any episode of tetany, seizure, or prolonged QT interval
with sinopulmonary infections	plus	targeted antibiotic therapy
with hypothyroidism	plus	levothyroxine
with feeding difficulty	plus	feeding therapy
with delayed speech acquisition	plus	speech therapy and early bridging sign language +/- surgery
school-aged children		
	1st	continued monitoring
with hypocalcaemia	plus	calcium + calcitriol
	adjunct	hydrochlorothiazide

Ongoing (summary)			
		adjunct	intravenous calcium for any episode of tetany, seizure, or prolonged QT interval
	with sinopulmonary infections	plus	targeted antibiotic therapy
	with hypothyroidism	plus	levothyroxine
	with learning disorders and behavioural problems	plus	behavioural modification techniques
adults			
		1st	continued monitoring
	with hypocalcaemia	plus	calcium + calcitriol
		adjunct	hydrochlorothiazide
		adjunct	intravenous calcium for any episode of tetany, seizure, or prolonged QT interval
	with sinopulmonary infections	plus	targeted antibiotic therapy
	with hypothyroidism	plus	levothyroxine
	with psychiatric disorders	plus	psychiatric consultation and management

Treatment options

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing

birth to 4 months

birth to 4 months — **1st** — **monitoring and stabilisation**

» Treatment involves managing complications. Because complications occur at predictable ages in a patient's life, management should be tailored to the age of the child. Newborns should be assessed for specific conditions common at this age, and treatment should be targeted accordingly.

» Evaluation includes assessing parents and determining the extent of the disorder (lymphocyte counts, immunoglobulin levels, intact PTH and serum calcium levels, TSH, chest x-ray examination for cleft palate, ophthalmological and hearing tests, renal ultrasound, and echocardiogram).

» Acute stabilisation issues generally are treatment for hypocalcaemic seizures or cardiac anomalies, in addition to ongoing therapies.

with congenital heart disease — **plus** — **surgical repair after stabilisation**

Treatment recommended for ALL patients in selected patient group

» Acute cardiac anomalies must be managed as appropriate, and echocardiography performed to define the cardiac anatomy and plan surgical repair.

» Infants with cardiac disease are managed as other infants with the same cardiac anatomy.

with cleft palate or lip — **plus** — **supportive specialty care**

Treatment recommended for ALL patients in selected patient group

» Managed by adaptive feeding regimens in consultation with nutritionists, occupational therapists, feeding consultants, and orthodontists. Options include specialised nipples, prosthetics, and frequent burping. Additional options include prosthetic devices that may improve palatal function without surgical intervention. Some feeding support may be required up to the point that the palate defect is repaired.

adjunct — **surgery**

Treatment recommended for SOME patients in selected patient group

» Surgical repair is required for frank clefts and submucous clefts. Patients who have only palatal insufficiency may not need surgical

Ongoing

correction, although if speech therapy fails to adequately improve diction and intelligibility, there are surgical options to improve this. Speech outcomes are improved by surgical intervention to improve oronasal closure.[82] There are multiple possible procedures to accomplish this. One report has found repair with pharyngeal flaps to be superior to sphincter pharyngoplasty.[93] Another systematic review found modest evidence that obstructive pharyngoplasties were superior to the less obstructive fat injection or palatoplasty. Obstructive sleep apnoea is a complication of any of these procedures and should be monitored for following surgery.[94]

with feeding difficulty **plus** **feeding therapy**

Treatment recommended for ALL patients in selected patient group

» Children in this age group routinely have feeding difficulties, which may not be associated with cleft palate. First-line therapy is a modified feeding procedure to ease feeding, including changing nipples, using bottle feeding if breastfeeding is inadequate, thickening feeds, or changing formulas. Second-line therapy may be required and usually involves placing a percutaneous gastrostomy tube. This should be considered if a child does not gain weight despite other feeding interventions. Feeding difficulties may persist for months to years, but generally have resolved before school age.

with hypocalcaemia **plus** **calcium + calcitriol**

Treatment recommended for ALL patients in selected patient group

Primary options

» calcium gluconate: 200-1000 mg/kg/day orally given in 4 divided doses
-and-
» calcitriol: 0.25 micrograms orally once daily

» Present in up to 60% of patients. All patients should be screened with serum calcium and intact PTH levels. Often becomes less problematic as the child matures.[50]

» Managed by calcium and vitamin D with supplementation as necessary. Calcium levels should be corrected for albumin, or ionised calcium measurements used.

» Both calcium and calcitriol should be given, and doses titrated to reach low-normal calcium levels.

Ongoing

» Calcium levels may be corrected orally in most cases, but if there are significant symptoms, such as tetany, seizure, or prolonged QT interval, intravenous correction is indicated.

» If long-term correction is required, urine should be checked to maintain 24-hour urine calcium <300 mg.

adjunct **hydrochlorothiazide**

Treatment recommended for SOME patients in selected patient group

Primary options

» hydrochlorothiazide: 2 mg/kg/day orally given in 2 divided doses

» Hypercalciuria is the major complication of treatment for hypocalcaemia. If urinary calcium is >300 mg in 24 hours, dose of calcium and vitamin D must be reduced or hydrochlorothiazide may be added to reduce urine calcium excretion if required.

adjunct **intravenous calcium for any episode of tetany, seizure, or prolonged QT interval**

Treatment recommended for SOME patients in selected patient group

Primary options

» calcium gluconate: 100-200 mg/kg intravenously as a single dose, may repeat every 6 hours

» Calcium levels may be corrected orally in most cases, but if there are significant symptoms, such as tetany, seizure, or prolonged QT interval, intravenous correction is indicated.

» Up to 60% of patients have hypocalcaemia, and hypocalcaemic seizures are common in neonates.[50] Patients should be screened with serum calcium and intact PTH levels. Hypocalcaemia often becomes less problematic as the child matures.[50]

» Calcium levels should be corrected for albumin, or ionised calcium measurements used. Infusion should be adjusted to maintain serum calcium of about 8.0 mg/dL.

» Intravenous calcium is highly irritating if extravasation occurs, and infusion that is too rapid can cause cardiac arrest. A central line should be used if possible, and bicarbonate and phosphate are incompatible and must be infused

Ongoing

in another line. Cardiac monitoring is strongly recommended when giving intravenous calcium.

with hypothyroidism — **plus** — **levothyroxine**

Treatment recommended for ALL patients in selected patient group

Primary options

» levothyroxine: 10-15 micrograms/kg/day orally

» Thyroid function should be assessed regularly by TSH screening, and replacement therapy started accordingly. Most US patients undergo thyroid screening at birth, but continued monitoring (at least yearly) is necessary because of the possibility of developing autoimmune or acquired thyroid disease. Dose is adjusted at 4- to 6-week intervals according to serum TSH.

with renal obstruction or hypoplasia — **plus** — **specialist consultation**

Treatment recommended for ALL patients in selected patient group

» Ultrasound should be performed to identify renal hypoplasia or obstruction. Specialty consultation is needed for management.

infants and toddlers

infants and toddlers — **1st** — **continued monitoring**

» Treatment involves managing complications. Because complications occur at predictable ages in a patient's life, management should be tailored to the age of the child. Infants and toddlers should be assessed for specific conditions common at this age, and treatment should be targeted accordingly. Those with a history of cleft lip or palate may require continued management.

with congenital heart disease — **plus** — **monitoring and possible surgery**

Treatment recommended for ALL patients in selected patient group

» Cardiac anomalies must be managed as appropriate, and echocardiography performed to define the cardiac anatomy and plan surgical repair. Neonates may need additional surgery later as infants or toddlers to complete repairs.

» Children with 22q11.2 deletion are more likely to experience complications post cardiac surgery, but do not have greater mortality or longer hospital stays.[95]

with marked immunodeficiency — **plus** — **trimethoprim/sulfamethoxazole + intravenous immunoglobulin**

Ongoing

Treatment recommended for ALL patients in selected patient group

Primary options

» trimethoprim/sulfamethoxazole: children >2 months of age: 150 mg/square metre of body surface area orally twice daily on three days each week
Dose refers to trimethoprim component.
-and-
» normal immunoglobulin human: 400 mg/kg intravenously once monthly

» Patients with demonstrated immune dysfunction should be referred to an immunologist. Those with mild to moderate immunodeficiency should be monitored for infection. Those with significant T-cell deficiency should be given trimethoprim/sulfamethoxazole prophylaxis and intravenous immunoglobulin, and should undergo thymic transplant or adoptive transfer of mature T cells. Infants with significant T-cell immunodeficiency (<600 T cells/mm^3) should receive no live virus vaccines and should receive only irradiated, filtered (leukodepleted) blood products.[84] [85] [86] [87] [88] [89] [90]

plus **immune reconstitution**

Treatment recommended for ALL patients in selected patient group

» For patients with severe immunodeficiency, transplantation of thymus restores T-cell numbers and improves survival. Thymus is harvested from thymectomy at the time of cardiac surgery and cultured to remove T cells. The remaining thymic epithelium is transplanted into the quadriceps muscle of the recipient. As the immunodeficit in DiGeorge syndrome is due to lack of an appropriate developmental environment (T cells are produced normally by the bone marrow, but have no thymus in which to develop), replacing the thymus corrects the defect. However, the procedure is technically demanding and available in only two centres worldwide.[96]

» As an alternative method for immune reconstitution, mature T cells may be transferred from a matched donor by peripheral blood mononuclear cell transfusion or unconditioned bone marrow transplantation. Mature T cells can proliferate without the need for a thymus, and reported outcomes have been similar to those of thymic transplant. Adoptive transfer of T cells has the advantage of being much easier

Ongoing

to perform, but repopulating the T-cell pool does not include as many naive T cells as thymic transplant.[11]

with hypocalcaemia **plus** **calcium + calcitriol**

Treatment recommended for ALL patients in selected patient group

Primary options

» calcium gluconate: 200-1000 mg/kg/day orally given in 4 divided doses
-and-
» calcitriol: 0.25 micrograms orally once daily

» Up to 60% of patients have hypocalcaemia. All patients should be screened with serum calcium and intact PTH levels. Often becomes less problematic as the child matures.[50]

» Managed by calcium and vitamin D supplementation as necessary. Calcium levels should be corrected for albumin, or ionised calcium measurements used.

» Both calcium and calcitriol should be given and doses titrated to reach low-normal calcium levels.

» Calcium levels may be corrected orally in most cases, but if there are significant symptoms, such as tetany, seizure, or prolonged QT interval, intravenous correction is indicated.

» If long-term correction is required, urine should be checked to maintain 24-hour urine calcium <300 mg.

adjunct **hydrochlorothiazide**

Treatment recommended for SOME patients in selected patient group

Primary options

» hydrochlorothiazide: 2 mg/kg/day orally given in 2 divided doses

» Hypercalciuria is the major complication of treatment for hypocalcaemia. If urinary calcium is >300 mg in 24 hours, dose of calcium and vitamin D must be reduced or hydrochlorothiazide may be added to reduce urine calcium excretion if required.

adjunct **intravenous calcium for any episode of tetany, seizure, or prolonged QT interval**

Treatment recommended for SOME patients in selected patient group

Ongoing

Primary options

» calcium gluconate: 100-200 mg/kg intravenously as a single dose, may repeat every 6 hours

» Calcium levels may be corrected orally in most cases, but if there are significant symptoms, such as tetany, seizure, or prolonged QT interval, intravenous correction is indicated.

» Up to 60% of patients have hypocalcaemia, and hypocalcaemic seizures are more common in neonates.[50] Patients should be screened with serum calcium and intact PTH levels. Often becomes less problematic as the child matures.[50]

» Calcium levels should be corrected for albumin, or ionised calcium measurements used. Infusion should be adjusted to maintain serum calcium of about 8.0 mg/dL. Intravenous calcium is highly irritating if extravasation occurs, and infusion that is too rapid can cause cardiac arrest. A central line should be used if possible, and bicarbonate and phosphate are incompatible and must be infused in another line.

» Cardiac monitoring is strongly recommended when giving intravenous calcium.

with sinopulmonary infections **plus** **targeted antibiotic therapy**

Treatment recommended for ALL patients in selected patient group

» Recurrent infections with pneumonia, mastoiditis, and evidence of bronchiectasis may be seen. Antibiotics are adjusted according to syndrome and culture results. Patients with hypogammaglobulinaemia are particularly susceptible to encapsulated organisms, including *Streptococcus pneumoniae* and *Haemophilus influenzae* type B, enteroviral infections, and *Giardia lamblia* .[97]

» Therapy for infections is performed according to typical sinusitis management, but if hypocalcaemia is present, it should be corrected to avoid potential complications with macrolide antibiotics.

with hypothyroidism **plus** **levothyroxine**

Treatment recommended for ALL patients in selected patient group

Primary options

TREATMENT

Ongoing

» levothyroxine: children 0-3 months of age: 10-15 micrograms/kg orally once daily; children >3-6 months: 8-10 micrograms/kg orally once daily; children >6-12 months of age: 6-8 micrograms/kg orally once daily; children >1-5 years of age: 5-6 micrograms/kg orally once daily

» Thyroid function should be assessed regularly by TSH screening, and replacement therapy started accordingly. Most US patients undergo thyroid screening at birth, but continued monitoring (at least yearly) is necessary because of the possibility of developing autoimmune or acquired thyroid disease. Dose is adjusted at 4- to 6-week intervals according to serum TSH.

with feeding difficulty — **plus** — **feeding therapy**

Treatment recommended for ALL patients in selected patient group

» Children in this age group routinely have feeding difficulties that may not be associated with cleft palate. First-line therapy is a modified feeding procedure to ease feeding, including changing nipples, using bottle feeding if breastfeeding is inadequate, thickening feeds, or changing formulas. Second-line therapy may be required and usually involves placing a percutaneous gastrostomy tube. This should be considered if a child does not gain weight despite other feeding interventions.

with delayed speech acquisition — **plus** — **speech therapy and early bridging sign language +/- surgery**

Treatment recommended for ALL patients in selected patient group

» In older toddlers, delayed acquisition of speech will become a problem. This is not due solely to palate defects, but occurs in most children. Should be treated with speech therapy early and use of bridging sign language. Specific recommendations are available for the management of speech therapy in DiGeorge syndrome.[81]

» For those with velopharyngeal insufficiency, surgical repair may be indicated to improve speech outcomes.[82]

school-aged children

school-aged children — **1st** — **continued monitoring**

» By school age, most feeding issues have improved. The primary issues in this age range are learning disorders and behavioural problems. Those with a history of cleft lip and

Ongoing

palate or congenital heart disease may require continued follow-up.

with hypocalcaemia **plus** **calcium + calcitriol**

Treatment recommended for ALL patients in selected patient group

Primary options

» calcium gluconate: 200-1000 mg/kg/day orally given in 4 divided doses
-and-
» calcitriol: 0.25 micrograms orally once daily

» Managed by calcium and vitamin D supplementation as necessary. Calcium levels should be corrected for albumin, or ionised calcium measurements used.

» Both calcium and calcitriol should be given and doses titrated to reach low-normal calcium levels.

» Calcium levels may be corrected orally in most cases, but if there are significant symptoms, such as tetany, seizure, or prolonged QT interval, intravenous correction is indicated.

» If long-term correction is required, urine should be checked to maintain 24-hour urine calcium <300 mg.

adjunct **hydrochlorothiazide**

Treatment recommended for SOME patients in selected patient group

Primary options

» hydrochlorothiazide: 2 mg/kg/day orally given in 2 divided doses

» Hypercalciuria is the major complication of treatment for hypocalcaemia. If urinary calcium is >300 mg in 24 hours, dose of calcium and vitamin D must be reduced or hydrochlorothiazide may be added to reduce urine calcium excretion if required.

adjunct **intravenous calcium for any episode of tetany, seizure, or prolonged QT interval**

Treatment recommended for SOME patients in selected patient group

Primary options

» calcium gluconate: 100-200 mg/kg intravenously as a single dose, may repeat every 6 hours

Ongoing

» Calcium levels may be corrected orally in most cases, but if there are significant symptoms, such as tetany, seizure, or prolonged QT interval, intravenous correction is indicated.

» Up to 60% of patients have hypocalcaemia, and hypocalcaemic seizures are more common in neonates.[50] Patients should be screened with serum calcium and intact PTH levels. Often becomes less problematic as the child matures.[50]

» Calcium levels should be corrected for albumin, or ionised calcium measurements used. Infusion should be adjusted to maintain serum calcium of about 8.0 mg/dL. Intravenous calcium is highly irritating if extravasation occurs, and infusion that is too rapid can cause cardiac arrest. A central line should be used if possible, and bicarbonate and phosphate are incompatible and must be infused in another line. Cardiac monitoring is strongly recommended when giving intravenous calcium.

with sinopulmonary infections **plus** **targeted antibiotic therapy**

Treatment recommended for ALL patients in selected patient group

» Recurrent infections with pneumonia, mastoiditis, and evidence of bronchiectasis may be seen. Antibiotics are adjusted according to syndrome and culture results. Patients with hypogammaglobulinaemia are particularly susceptible to encapsulated organisms, including *Streptococcus pneumoniae* and *Haemophilus influenzae* type B, enteroviral infections, and *Giardia lamblia* .[97]

» Therapy for infections is performed according to typical sinusitis management, but if hypocalcaemia is present, it should be corrected to avoid potential complications with macrolide antibiotics.

with hypothyroidism **plus** **levothyroxine**

Treatment recommended for ALL patients in selected patient group

Primary options

» levothyroxine: children 1-5 years of age: 5-6 micrograms/kg orally once daily; children 6-12 years of age: 4-5 micrograms/kg orally once daily; children >12 years of age: 2-3 micrograms/kg orally once daily; children post puberty: 1.7 micrograms/kg orally once daily

Ongoing

		» Thyroid function should be assessed regularly by TSH screening, and replacement therapy started accordingly. Most US patients undergo thyroid screening at birth, but continued monitoring (at least yearly) is necessary because of the possibility of developing autoimmune or acquired thyroid disease. Dose is adjusted at 4- to 6-week intervals according to serum TSH.
with learning disorders and behavioural problems	**plus**	**behavioural modification techniques** Treatment recommended for ALL patients in selected patient group » Children may be shy, withdrawn, or anxious. Rates of attention-deficit/hyperactivity disorder, oppositional defiant disorder, and autistic spectrum disorders are higher than in the general population.[91] Initial approach should involve standard behavioural modification techniques. Managing these symptoms may require consultation with developmental paediatricians and psychiatrists. » Although children with 22q deletion syndrome have speech delay, their language abilities are relatively preserved later in life when non-verbal learning disorders become predominant. Maths skills may be weak. These aspects should be approached with an individualised education plan.
adults		
adults	**1st**	**continued monitoring** » Learning disability and behavioural issues may affect employment, although these issues are generally mild enough that independent living and full employment are possible. » Psychiatric disorders may become more problematic in this age group. Psychiatrists should manage patients with psychosis or schizophrenia with appropriate antipsychotic therapy. Depression and bipolar disorder also occur and are managed typically. » Increased risk for sinopulmonary infections persists, and infections should be treated aggressively with appropriate antibiotic therapy. » Those with a history of cleft lip and palate or congenital heart disease may require continued follow-up.
with hypocalcaemia	**plus**	**calcium + calcitriol** Treatment recommended for ALL patients in selected patient group

Ongoing

Primary options

» calcium gluconate: 500-2000 mg orally two to four times daily
-and-
» calcitriol: 0.25 micrograms orally once daily

» Managed by calcium and vitamin D supplementation as necessary. Calcium levels should be corrected for albumin, or ionised calcium measurements used.

» Both calcium and calcitriol should be given and doses titrated to reach low-normal calcium levels.

» Calcium levels may be corrected orally in most cases, but if there are significant symptoms, such as tetany, seizure, or prolonged QT interval, intravenous correction is indicated.

» If long-term correction is required, urine should be checked to maintain 24-hour urine calcium <300 mg.

adjunct **hydrochlorothiazide**

Treatment recommended for SOME patients in selected patient group

Primary options

» hydrochlorothiazide: 25-200 mg/day orally given in 2 divided doses

» Hypercalciuria is the major complication of treatment for hypocalcaemia. If urinary calcium is >300 mg in 24 hours, dose of calcium and vitamin D must be reduced or hydrochlorothiazide may be added to reduce urine calcium excretion if required.

adjunct **intravenous calcium for any episode of tetany, seizure, or prolonged QT interval**

Treatment recommended for SOME patients in selected patient group

Primary options

» calcium gluconate: 1000-3000 mg intravenously as a single dose, may repeat every 6 hours

» Calcium levels may be corrected orally in most cases, but if there are significant symptoms, such as tetany, seizure, or prolonged QT interval, intravenous correction is indicated.

Ongoing

» Up to 60% of patients have hypocalcaemia.[50] Patients should be screened with serum calcium and intact PTH levels.[50]

» Calcium levels should be corrected for albumin, or ionised calcium measurements used. Infusion should be adjusted to maintain serum calcium of about 8.0 mg/dL. Intravenous calcium is highly irritating if extravasation occurs, and infusion that is too rapid can cause cardiac arrest. A central line should be used if possible, and bicarbonate and phosphate are incompatible and must be infused in another line. Cardiac monitoring is strongly recommended when giving intravenous calcium.

with sinopulmonary infections **plus** **targeted antibiotic therapy**

Treatment recommended for ALL patients in selected patient group

» Increased risk for sinopulmonary infections persists, and infections should be treated aggressively with appropriate antibiotic therapy.

» Recurrent infections with pneumonia, mastoiditis, and evidence of bronchiectasis may be seen. Antibiotics are adjusted according to syndrome and culture results. Patients with hypogammaglobulinaemia are particularly susceptible to encapsulated organisms, including *Streptococcus pneumoniae* and *Haemophilus influenzae* type B, enteroviral infections, and *Giardia lamblia* .[97]

» Therapy for infections is performed according to typical sinusitis management, but if hypocalcaemia is present, it should be corrected to avoid potential complications with macrolide antibiotics.

with hypothyroidism **plus** **levothyroxine**

Treatment recommended for ALL patients in selected patient group

Primary options

» levothyroxine: 1.7 micrograms/kg orally once daily

» Thyroid function should be assessed regularly by TSH screening, and replacement therapy started accordingly. Most US patients undergo thyroid screening at birth, but continued monitoring (at least yearly) is necessary because of the possibility of developing autoimmune or acquired thyroid disease. Dose is adjusted at 4- to 6-week intervals according to serum TSH.

with psychiatric disorders **plus** **psychiatric consultation and management**

Ongoing

Treatment recommended for ALL patients in selected patient group

» Psychiatric disorders may become more problematic in this age group. Psychiatrists should manage patients with psychosis or schizophrenia with appropriate antipsychotic therapy. Depression and bipolar disorder also occur and are managed typically.

» Therapy of schizophrenia is generally typical, but there may be more resistance to antipsychotic therapy. There are few published data on therapeutic recommendations for 22q11.2DS patients, but one case report has successfully used aripiprazole for treatment of resistant psychosis, while another successfully used quetiapine. If hypocalcaemia is present it should be corrected, as hypocalcaemia alone may provoke psychosis.[92]

Emerging

Teriparatide

One study has investigated the use of recombinant parathyroid hormone (teriparatide) in children with syndromic hypoparathyroidism, including two patients with DiGeorge syndrome. The drug was effective in reducing the requirement for calcium and vitamin D supplementation, but such use is off-label and long-term safety in children is not known.[98]

Parathyroid transplant

Parathyroids have been transplanted in a few patients with DiGeorge syndrome, primarily in association with thymic transplants for immunodeficiency. At least 2 patients have produced PTH after transplant, although not all have maintained PTH production.[99]

Recommendations

Monitoring

22qDS is best managed in a multispecialty framework. Because different features of the disorder are important at different life stages, long-term follow-up by a single centre or provider is also beneficial. The frequency with which a patient will need to be seen will vary depending on the severity of the manifestations, but at least yearly visits are probably required to identify emerging problems. The specific testing and intervention required at a given visit also depend on the specific manifestations of the disorder in a specific patient. Awareness of the common complications will help the provider to anticipate potential problems and identify them early.

Patient instructions

Patients with significant immunodeficiency (defined as <600 CD3+ cells/mm^3) should avoid unnecessary exposure to infectious people and should avoid live virus vaccines.[90] However, most patients who have T-cell counts >600 cells/mm^3 can safely receive these vaccines.[84] [85] [86] [87] [88] [89] [106] Patients with significant immunodeficiency should also be aware of the need to present early to the physician with any fever or other signs of illness. Awareness of the potential for specific learning disorders can help parents to intervene early with requests for individualised education plans for their children. Patients should also be aware of the recurrence risk in their children. Half of their offspring would be expected to have the disorder, and the severity may be worse in their children.

FOLLOW UP

Complications

Complications	Timeframe	Likelihood
hypoparathyroidism	**short term**	**high**
Up to 60% of patients have hypocalcaemia, and hypocalcaemic seizures are common.[50] All patients should be screened with serum calcium and intact PTH levels. The hypocalcaemia often becomes less problematic as the child matures.[50]		
congenital heart disease	**long term**	**high**
About 80% of patients have congenital heart disease.[40] Conotruncal anomalies such as interrupted aortic arch type B and truncus arteriosus are the most characteristic, but tetralogy of Fallot, ventricular septal defect, and others are also common.[101] [102]		
palatal insufficiency and cleft palate	**long term**	**high**
The most common manifestation of palatal disease is velopharyngeal insufficiency, resulting in hypernasal speech and poor intelligibility.[52] [53] Speech therapy may help, but some patients require surgical treatment. In general, the response to surgical treatment is not as good for 22qDS patients as for others. Cleft palate and submucous clefts occur in up to 20% of children and are managed surgically in the usual fashion.		
dental anomalies	**long term**	**high**
Three-quarters of patients have at least some tooth abnormality, mostly hypoplastic dentition of the mandibular first premolar or enamel opacities.[109] Those with cleft palate may have additional dental issues related to the cleft palate. Tooth agenesis and supernumerary teeth are not associated with 22qDS.		
schizophrenia	**long term**	**medium**
Patients are at risk of schizophrenia, bipolar disorder, and depression.[56] The risk of schizophrenia may be as high as 20% of the 22qDS population.		
hearing loss	**long term**	**medium**
A study of hearing loss in 22qDS demonstrated that high-tone sensorineural or mixed hearing loss was common. Children with the COMT Met allele were less severely affected, suggesting a protective effect for this modifier gene.[113]		
hypothyroidism	**long term**	**low**
Up to 20% of patients have thyroid disease of some type, as in many other disorders resulting from chromosomal alterations.[103] Hashimoto's thyroiditis and Graves' disease have also been observed.[104] More subtle abnormalities of the thyroid are evident in up to 46% of patients.[105]		
infections	**variable**	**high**
Incidence of sinopulmonary and viral infections is increased.[59] They occur regardless of the presence of detectable immunodeficiency. Bacterial infections should be promptly managed with appropriate antibiotic therapy.		
gastro-oesophageal reflux	**variable**	**high**

Complications	Timeframe	Likelihood
Significant reflux is common and may contribute to feeding difficulties.[108] Reflux may be diagnosed by pH probe. Patients are managed in the usual fashion but may require more significant intervention to control symptoms, including fundoplication.		
atopy and allergy	**variable**	**medium**
Allergies are common with 22q11.2 deletions. This may be due to dysregulated T and B cell function as a result of the low thymic output that may force homeostatic proliferation of T cells. These T cells are more likely to be of TH2 phenotype and thus favour the development of allergy.[110]		
ophthalmological complications	**variable**	**medium**
Up to 70% of patients have posterior embryotoxon and abnormal retinal vessels, although they do not usually impair vision.[112]		
T-cell immunodeficiency	**variable**	**low**
Significant T-cell deficiency is uncommon, although most infants have some T-cell lymphopenia.[60] All patients should have T-cell enumeration by flow cytometry to identify any need for immune reconstitution. Trimethoprim/sulfamethoxazole prophylaxis and avoiding live virus vaccines are generally not required unless there is T-cell dysfunction (T-cell counts <600 cells/mm^3) and/or immune reconstitution is planned.[84] [85] [86] [87] [88] [89] [106] Although there are no studies in large numbers of patients, data suggest that those with T-cell counts >600 cells/mm^3 may safely receive live vaccines. Measuring lymphocyte proliferative responses may also help distinguish those who need immune reconstitution.		
autoimmune disease	**variable**	**low**
About 10% of patients develop autoimmune disease. Juvenile rheumatoid arthritis is the most common, but blood cytopenias, diabetes, and thyroid disease also occur.[107] These complications are not predictable and are managed in the usual fashion when they occur.		
thrombocytopenia	**variable**	**low**
Platelet counts are lower on average than in healthy controls, but this finding does not seem to have clinical significance, and the platelet counts are not in a clinically significant deficit.[111] No special precautions are required to manage thrombocytopenia.		

Prognosis

The disorder is highly variable, and outcome is determined by the severity of complications. The disorder may be fatal if cardiac disease cannot be adequately treated or other severe anomalies are present. Alternatively, the patient may have only mild learning disabilities and go without a diagnosis. The outcome of the patient may generally be predicted by the usual natural history of each complication. Intelligence and schizophrenia predict functional outcomes as an adult, but mood or congenital heart disease do not.[100]

Diagnostic guidelines

Europe

Thyroid function disorders (http://www.njmonline.nl/issue.php?i=100)

Published by: Netherlands Association of Internal Medicine **Last published:** 2008

UK guidelines for the use of thyroid function tests (http://www.british-thyroid-association.org/current-bta-guidelines-)

Published by: British Thyroid Association **Last published:** 2006

International

ESID registry - working definitions for clinical diagnosis of PID (https://esid.org/Working-Parties/Registry-Working-Party/Diagnosis-criteria)

Published by: European Society for Immunodefiencies **Last published:** 2019

Treatment guidelines

Europe

Thyroid function disorders (http://www.njmonline.nl/issue.php?i=100)

Published by: Netherlands Association of Internal Medicine **Last published:** 2008

International

Practical guidelines for managing adults with 22q11.2 deletion syndrome (http://www.nature.com/gim/journal/vaop/ncurrent/full/gim2014175a.html)

Published by: International panel of multidisciplinary experts **Last published:** 2015

North America

22q11.2 deletion syndrome (http://www.ncbi.nlm.nih.gov/books/NBK1523/)

Published by: Children's Hospital of Philadelphia **Last published:** 2013

Consensus guidelines on the management of community-acquired pneumonia in adults (https://www.thoracic.org/statements/tuberculosis-pneumonia.php)

Published by: Infectious Diseases Society of America; American Thoracic Society **Last published:** 2007

Key articles

- European Society for Immunodeficiencies. Clinical Working Party diagnostic criteria for PID: DiGeorge syndrome diagnostic criteria [internet publication]. Full text (https://esid.org/Working-Parties/Clinical-Working-Party/Resources/Diagnostic-criteria-for-PID2#Q5)
- Botto LD, May K, Fernhoff PM, et al. A population-based study of the 22q11.2 deletion: phenotype, incidence, and contribution to major birth defects in the population. Pediatrics. 2003;112:101-107. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12837874?tool=bestpractice.bmj.com)
- Land MH, Garcia-Lloret MI, Borzy MS, et al. Long-term results of bone marrow transplantation in complete DiGeorge syndrome. J Allergy Clin Immunol. 2007;120:908-915. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17931564?tool=bestpractice.bmj.com)
- Baumer A, Riegel M, Schinzel A. Non-random asynchronous replication at 22q11.2 favours unequal meiotic crossovers leading to the human 22q11.2 deletion. J Med Genet. 2004;41:413-420. Full text (http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1735820&blobtype=pdf) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15173225?tool=bestpractice.bmj.com)
- Taddei I, Morishima M, Huynh T, et al. Genetic factors are major determinants of phenotypic variability in a mouse model of the DiGeorge/del22q11 syndromes. Proc Natl Acad Sci U S A. 2001;98:11428-11431. Full text (http://www.pnas.org/content/98/20/11428.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11562466?tool=bestpractice.bmj.com)
- 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;34:798-804. Full text (http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1051084&blobtype=pdf) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9350810?tool=bestpractice.bmj.com)
- Piliero LM, Sanford AN, McDonald-McGinn DM, et al. T-cell homeostasis in humans with thymic hypoplasia due to chromosome 22q11.2 deletion syndrome. Blood. 2004;103:1020-1025. Full text (http://www.bloodjournal.org/content/103/3/1020.long?sso-checked=true) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/14525774?tool=bestpractice.bmj.com)
- Markert ML, Boeck A, Hale LP, et al. Transplantation of thymus tissue in complete DiGeorge syndrome. N Engl J Med. 1999;341:1180-1189. Full text (http://www.nejm.org/doi/full/10.1056/NEJM199910143411603#t=article) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10523153?tool=bestpractice.bmj.com)

References

1. European Society for Immunodeficiencies. Clinical Working Party diagnostic criteria for PID: DiGeorge syndrome diagnostic criteria [internet publication]. Full text (https://esid.org/Working-Parties/Clinical-Working-Party/Resources/Diagnostic-criteria-for-PID2#Q5)

REFERENCES

2. Knutsen AP, Baker MW, Markert ML. Interpreting low T-cell receptor excision circles in newborns with DiGeorge anomaly: importance of assessing naive T-cell markers. J Allergy Clin Immunol. 2011;128:1375-1376. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22018899?tool=bestpractice.bmj.com)

3. Markert ML, Alexieff MJ, Li J, et al. Complete DiGeorge syndrome: development of rash, lymphadenopathy, and oligoclonal T cells in 5 cases. J Allergy Clin Immunol. 2004;113:734-741. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15100681?tool=bestpractice.bmj.com)

4. Björk AH, Oskarsdóttir S, Andersson BA, et al. Antibody deficiency in adults with 22q11.2 deletion syndrome. Am J Med Genet A. 2012;158A:1934-1940. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22786729?tool=bestpractice.bmj.com)

5. Patel K, Akhter J, Kobrynski L, et al. Immunoglobulin deficiencies: the B-lymphocyte side of DiGeorge syndrome. J Pediatr. 2012;161:950-953. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22809661?tool=bestpractice.bmj.com)

6. Leana-Cox J, Pangkanon S, Eanet KR, et al. Familial DiGeorge/velocardiofacial syndrome with deletions of chromosome area 22q11.2: report of five families with a review of the literature. Am J Med Genet. 1996;65:309-316. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8923941?tool=bestpractice.bmj.com)

7. 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;15:585-596. Full text (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4828586/) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27017469?tool=bestpractice.bmj.com)

8. Oskarsdottir S, Vujic M, Fasth A. Incidence and prevalence of the 22q11 deletion syndrome: a population-based study in Western Sweden. Arch Dis Child. 2004;89:148-151. Full text (http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1719787&blobtype=pdf) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/14736631?tool=bestpractice.bmj.com)

9. Botto LD, May K, Fernhoff PM, et al. A population-based study of the 22q11.2 deletion: phenotype, incidence, and contribution to major birth defects in the population. Pediatrics. 2003;112:101-107. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12837874?tool=bestpractice.bmj.com)

10. Munoz S, Garay F, Flores I, et al. Clinical heterogeneity of the chromosome 22q11 microdeletion syndrome. Rev Med Chil. 2001;129:515-521. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11464533?tool=bestpractice.bmj.com)

11. Land MH, Garcia-Lloret MI, Borzy MS, et al. Long-term results of bone marrow transplantation in complete DiGeorge syndrome. J Allergy Clin Immunol. 2007;120:908-915. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17931564?tool=bestpractice.bmj.com)

12. Wilson DI, Cross IE, Goodship JA, et al. A prospective cytogenetic study of 36 cases of DiGeorge syndrome. Am J Hum Genet. 1992;51:957-963. Full text (http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1682842&blobtype=pdf) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/1415264?tool=bestpractice.bmj.com)

13. Jerome LA, Papaioannou VE. DiGeorge syndrome phenotype in mice mutant for the T-box gene, Tbx1. Nat Genet. 2001;27:286-291. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11242110?tool=bestpractice.bmj.com)

14. 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;9:489-501. Full text (http://hmg.oxfordjournals.org/cgi/content/full/9/4/489) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10699172?tool=bestpractice.bmj.com)

15. Baumer A, Riegel M, Schinzel A. Non-random asynchronous replication at 22q11.2 favours unequal meiotic crossovers leading to the human 22q11.2 deletion. J Med Genet. 2004;41:413-420. Full text (http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1735820&blobtype=pdf) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15173225?tool=bestpractice.bmj.com)

16. Carlson C, Sirotkin H, Pandita R, et al. Molecular definition of 22q11 deletions in 151 velo-cardio-facial syndrome patients. Am J Hum Genet. 1997;61:620-629. Full text (http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1715959&blobtype=pdf) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9326327?tool=bestpractice.bmj.com)

17. Edelmann L, Pandita RK, Spiteri E, et al. A common molecular basis for rearrangement disorders on chromosome 22q11. Hum Mol Genet. 1999;8:1157-1167. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10369860?tool=bestpractice.bmj.com)

18. Yagi H, Furutani Y, Hamada H, et al. Role of TBX1 in human del22q11.2 syndrome. Lancet. 2003;362:1366-1373. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/14585638?tool=bestpractice.bmj.com)

19. Daw SCM, Taylor C, Kraman M, et al. A common region of 10p deleted in DiGeorge and velocardiofacial syndromes. Nat Genet. 1996;13:458-460. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8696341?tool=bestpractice.bmj.com)

20. Sanka M, Tangsinmankong N, Loscalzo M, et al. Complete DiGeorge syndrome associated with CHD7 mutation. J Allergy Clin Immunol. 2007;120:952-954. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17931565?tool=bestpractice.bmj.com)

21. Vitelli F, Taddei I, Morishima M, et al. A genetic link between Tbx1 and fibroblast growth factor signaling. Development. 2002;129:4605-4611. Full text (http://dev.biologists.org/cgi/content/full/129/19/4605) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12223416?tool=bestpractice.bmj.com)

22. Lindstrand A, Malmgren H, Verri A, et al. Molecular and clinical characterization of patients with overlapping 10p deletions. Am J Med Genet A. 2010;152A:1233-1243. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20425828?tool=bestpractice.bmj.com)

23. Rope AF, Cragun DL, Saal HM, et al. DiGeorge anomaly in the absence of chromosome 22q11.2 deletion. J Pediatr. 2009;155:560-565. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19595366?tool=bestpractice.bmj.com)

REFERENCES

24. Guo T, McDonald-McGinn D, Blonska A, et al. Genotype and cardiovascular phenotype correlations with TBX1 in 1,022 velo-cardio-facial/DiGeorge/22q11.2 deletion syndrome patients. Hum Mutat. 2011;32:1278-1289. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/3196824?tool=bestpractice.bmj.com)

25. Piotrowski T, Ahn D, Schilling TF, et al. The zebrafish van gogh mutation disrupts tbx1, which is involved in the DiGeorge deletion syndrome in humans. Development. 2003;130:5043-5052. Full text (http://dev.biologists.org/cgi/content/full/130/20/5043) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12952905?tool=bestpractice.bmj.com)

26. Lindsay EA, Vitelli F, Su H, et al. Tbx1 haploinsufficiency in the DiGeorge syndrome region causes aortic arch defects in mice. Nature. 2001;410:97-101. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11242049?tool=bestpractice.bmj.com)

27. Taddei I, Morishima M, Huynh T, et al. Genetic factors are major determinants of phenotypic variability in a mouse model of the DiGeorge/del22q11 syndromes. Proc Natl Acad Sci U S A. 2001;98:11428-11431. Full text (http://www.pnas.org/content/98/20/11428.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11562466?tool=bestpractice.bmj.com)

28. Nowotschin S, Liao J, Gage PJ, et al. Tbx1 affects asymmetric cardiac morphogenesis by regulating Pitx2 in the secondary heart field. Development. 2006;133:1565-1573. Full text (http://dev.biologists.org/cgi/content/full/133/8/1565) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16556915?tool=bestpractice.bmj.com)

29. Swaby JA, Silversides CK, Bekeschus SC, et al. Complex congenital heart disease in unaffected relatives of adults with 22q11.2 deletion syndrome. Am J Cardiol. 2011;107:466-471. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21257016?tool=bestpractice.bmj.com)

30. Fénelon K, Mukai J, Xu B, et al. Deficiency of Dgcr8, a gene disrupted by the 22q11.2 microdeletion, results in altered short-term plasticity in the prefrontal cortex. Proc Natl Acad Sci U S A. 2011;108:4447-4452. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21368174?tool=bestpractice.bmj.com)

31. Stalmans I, Lambrechts D, De Smet F, et al. VEGF: a modifier of the del22q11 (DiGeorge) syndrome? Nat Med. 2003;9:173-182. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12539040?tool=bestpractice.bmj.com)

32. Gothelf D, Eliez S, Thompson T, et al. COMT genotype predicts longitudinal cognitive decline and psychosis in 22q11.2 deletion syndrome. Nat Neurosci. 2005;8:1500-1502. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16234808?tool=bestpractice.bmj.com)

33. Glaser B, Debbane M, Hinard C, et al. No evidence for an effect of COMT Val158Met genotype on executive function in patients with 22q11 deletion syndrome. Am J Psychiatry. 2006;163:537-539. Full text (http://ajp.psychiatryonline.org/article.aspx?articleid=178107) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16513880?tool=bestpractice.bmj.com)

34. Tison BE, Nicholas SK, Abramson SL, et al. Autoimmunity in a cohort of 130 pediatric patients with partial DiGeorge syndrome. J Allergy Clin Immunol. 2011;128:1115-1117. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21835443?tool=bestpractice.bmj.com)

35. 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;63:308-313. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12702165?tool=bestpractice.bmj.com)

36. 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 Oct;176(10):2087-2098. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6497171/) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29663641?tool=bestpractice.bmj.com)

37. Schecklmann M, Schwenck C, Taurines R, et al. A systematic review on olfaction in child and adolescent psychiatric disorders. J Neural Transm. 2013;120:121-130. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22806003?tool=bestpractice.bmj.com)

38. Tarquinio DC, Jones MC, Jones KL, et al. Growth charts for 22q11 deletion syndrome. Am J Med Genet A. 2012;158A:2672-2681. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22887711?tool=bestpractice.bmj.com)

39. Habel A, McGinn MJ 2nd, Zackai EH, et al. Syndrome-specific growth charts for 22q11.2 deletion syndrome in Caucasian children. Am J Med Genet A. 2012;158A:2665-2671. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22711268?tool=bestpractice.bmj.com)

40. Marino B, Digilio MC, Toscano A, et al. Anatomic patterns of conotruncal defects associated with deletion 22q11. Genet Med. 2001;3:45-48. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11339377?tool=bestpractice.bmj.com)

41. Wilson TA, Blethen SL, Vallone A, et al. DiGeorge anomaly with renal agenesis in infants of mothers with diabetes. Am J Med Genet. 1993;47:1078-1082. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8291527?tool=bestpractice.bmj.com)

42. Wang R, Martinez-Frias M, Graham JM Jr. Infants of diabetic mothers are at increased risk for the oculo-auriculo-vertebral sequence: a case-based and case-control approach. J Pediatr. 2002;141:611-617. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12410187?tool=bestpractice.bmj.com)

43. Gosseye S, Golaire MC, Verellen G, et al. Association of bilateral renal agenesis and Di George syndrome in an infant of a diabetic mother. Helv Paediatr Acta. 1982;37:471-474. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/6891697?tool=bestpractice.bmj.com)

44. Novak RW, Robinson HB. Coincident DiGeorge anomaly and renal agenesis and its relation to maternal diabetes. Am J Med Genet. 1994;50:311-312. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8209907?tool=bestpractice.bmj.com)

REFERENCES

45. Lupski JR, Langston C, Friedman R, et al. Di George anomaly associated with a de novo Y;22 translocation resulting in monosomy del(22)(q11.2). Am J Med Genet. 1991;40:196-198. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/1897574?tool=bestpractice.bmj.com)

46. DeBerardinis RJ, Medne L, Spinner NB, et al. DiGeorge anomaly in a patient with isochromosome 18p born to a diabetic mother. Am J Med Genet A. 2005;138A:155-159. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16114050?tool=bestpractice.bmj.com)

47. Stewart TL, Irons MB, Cowan JM, et al. Increased incidence of renal anomalies in patients with chromosome 22q11 microdeletion. Teratology. 1999;59:20-22. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9988879?tool=bestpractice.bmj.com)

48. Lay-Son G, Palomares M, Guzman ML, et al. Palate abnormalities in Chilean patients with chromosome 22q11 microdeletion syndrome. Int J Pediatr Otorhinolaryngol. 2012;76:1726-1728. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22939891?tool=bestpractice.bmj.com)

49. Habel A, Herriot R, Kumararatne D, et al. Towards a safety net for management of 22q11.2 deletion syndrome: guidelines for our times. Eur J Pediatr. 2014;173:757-765. Full text (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4032642/) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24384789?tool=bestpractice.bmj.com)

50. 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;34:798-804. Full text (http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1051084&blobtype=pdf) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9350810?tool=bestpractice.bmj.com)

51. Oskarsdottir S, Persson C, Eriksson BO, et al. Presenting phenotype in 100 children with the 22q11 deletion syndrome. Eur J Pediatr. 2005;164:146-153. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15565286?tool=bestpractice.bmj.com)

52. Goldberg R, Motzkin B, Marion R, et al. Velo-cardio-facial syndrome: a review of 120 patients. Am J Med Genet. 1993;45:313-319. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8434617?tool=bestpractice.bmj.com)

53. Zori RT, Boyar FZ, Williams NW, et al. Prevalence of 22q11 region deletions in patients with velopharyngeal insufficiency. Am J Med Genet. 1998;77:8-11. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9557885?tool=bestpractice.bmj.com)

54. D'Antonio LL, Scherer NJ, Miller LL, et al. Analysis of speech characteristics in children with velocardiofacial syndrome (VCFS) and children with phenotypic overlap without VCFS. Cleft Palate Craniofac J. 2001;38:455-467. Full text (http://cpcjournal.org/doi/full/10.1597/1545-1569%282001%29038%3C0455%3AAOSCIC%3E2.0.CO%3B2) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11522167?tool=bestpractice.bmj.com)

55. Wang PP, Woodin MF, Kreps-Falk R, et al. Research on behavioral phenotypes: velocardiofacial syndrome (deletion 22q11.2). Dev Med Child Neurol. 2000;42:422-427. Full text (http://onlinelibrary.wiley.com/doi/10.1111/j.1469-8749.2000.tb00125.x/pdf) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10875531?tool=bestpractice.bmj.com)

56. Bassett AS, Chow EW. 22q11 deletion syndrome: a genetic subtype of schizophrenia. Biol Psychiatry. 1999;46:882-891. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10509171?tool=bestpractice.bmj.com)

57. Arinami T, Ohtsuki T, Takase K, et al. Screening for 22q11 deletions in a schizophrenia population. Schizophr Res. 2001;52:167-170. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11705710?tool=bestpractice.bmj.com)

58. Barrett DJ, Ammann AJ, Wara DW, et al. Clinical and immunologic spectrum of the DiGeorge syndrome. J Clin Lab Immunol. 1981;6:1-6. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/6973633?tool=bestpractice.bmj.com)

59. Kobrynski LJ, Sullivan KE. Velocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11.2 deletion syndromes. Lancet. 2007;370:1443-1452. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17950858?tool=bestpractice.bmj.com)

60. Piliero LM, Sanford AN, McDonald-McGinn DM, et al. T-cell homeostasis in humans with thymic hypoplasia due to chromosome 22q11.2 deletion syndrome. Blood. 2004;103:1020-1025. Full text (http://www.bloodjournal.org/content/103/3/1020.long?sso-checked=true) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/14525774?tool=bestpractice.bmj.com)

61. Chaoui R, Heling KS, Lopez AS, et al. The thymic-thoracic ratio in fetal heart defects: a simple way to identify fetuses at high risk for microdeletion 22q11. Ultrasound Obstet Gynecol. 2011;37:397-403. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21308838?tool=bestpractice.bmj.com)

62. Saitta SC, Harris SE, McDonald-McGinn DM, et al. Independent de novo 22q11.2 deletions in first cousins with DiGeorge/velocardiofacial syndrome. Am J Med Genet A. 2004;124A:313-317. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/14708107?tool=bestpractice.bmj.com)

63. Stanczak CM, Chen Z, Nelson SF, et al. Representational oligonucleotide microarray analysis (ROMA) and comparison of binning and change-point methods of analysis: application to detection of del22q11.2 (DiGeorge) syndrome. Hum Mutat. 2008;29:176-181. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17694540?tool=bestpractice.bmj.com)

64. Naqvi N, Davidson SJ, Wong D, et al. Predicting 22q11.2 deletion syndrome: a novel method using the routine full blood count. Int J Cardiol. 2011;150:50-53. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20363518?tool=bestpractice.bmj.com)

65. Lammer EJ, Chen DT, Hoar RM, et al. Retinoic acid embryopathy. N Engl J Med. 1985 Oct 3;313(14):837-41. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/3162101?tool=bestpractice.bmj.com)

66. Zhang L, Zhong T, Wang Y, et al. TBX1, a DiGeorge syndrome candidate gene, is inhibited by retinoic acid. Int J Dev Biol. 2006;50(1):55-61. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16323078?tool=bestpractice.bmj.com)

67. Vermot J, Niederreither K, Garnier JM, et al. Decreased embryonic retinoic acid synthesis results in a DiGeorge syndrome phenotype in newborn mice. Proc Natl Acad Sci U S A. 2003 Feb 18;100(4):1763-8. Full text (http://www.pubmedcentral.nih.gov/articlerender.fcgi?

tool=pubmed&pubmedid=12563036) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12563036?tool=bestpractice.bmj.com)

68. Roberts C, Ivins SM, James CT, et al. Retinoic acid down-regulates Tbx1 expression in vivo and in vitro. Dev Dyn. 2005 Apr;232(4):928-38. Full text (http://onlinelibrary.wiley.com/doi/10.1002/dvdy.20268/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15736167?tool=bestpractice.bmj.com)

69. de Lonlay-Debeney P, Cormier-Daire V, Amiel J, et al. Features of DiGeorge syndrome and CHARGE association in five patients. J Med Genet. 1997 Dec;34(12):986-9. Full text (http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1051148&blobtype=pdf) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9429139?tool=bestpractice.bmj.com)

70. Markert ML, Devlin BH, Alexieff MJ, et al. Review of 54 patients with complete DiGeorge anomaly enrolled in protocols for thymus transplantation: outcome of 44 consecutive transplants. 2007 May 15;109(10):4539-47. Full text (http://www.bloodjournal.org/content/109/10/4539.long?sso-checked=true) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17284531?tool=bestpractice.bmj.com)

71. Janda A, Sedlacek P, Mejstrikova E, et al. Unrelated partially matched lymphocyte infusions in a patient with complete DiGeorge/CHARGE syndrome. Pediatr Transplant. 2007 Jun;11(4):441-7. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17493228?tool=bestpractice.bmj.com)

72. Gennery AR, Slatter MA, Rice J, et al. Mutations in CHD7 in patients with CHARGE syndrome cause T-B + natural killer cell + severe combined immune deficiency and may cause Omenn-like syndrome. Clin Exp Immunol. 2008 Jul;153(1):75-80. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18505430?tool=bestpractice.bmj.com)

73. Theodoropoulos DS. Immune deficiency in CHARGE association. Clin Med Res. 2003 Jan;1(1):43-8. Full text (http://www.clinmedres.org/cgi/content/full/1/1/43) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15931284?tool=bestpractice.bmj.com)

74. Lee KD, Okazaki T, Kato Y, et al. Esophageal atresia and tracheo-esophageal fistula associated with coarctation of the aorta, CHARGE association, and DiGeorge syndrome: a case report and literature review. Pediatr Surg Int. 2008 Oct;24(10):1153-6. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18696080?tool=bestpractice.bmj.com)

75. Agergaard P, Hebert A, Sørensen KM, et al. Can clinical assessment detect 22q11.2 deletions in patients with cardiac malformations? A review. Eur J Med Genet. 2011;54:3-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20965293?tool=bestpractice.bmj.com)

76. Tomita-Mitchell A, Mahnke DK, Larson JM, et al. Multiplexed quantitative real-time PCR to detect 22q11.2 deletion in patients with congenital heart disease. Physiol Genomics. 2010;42A:52-60. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20551144?tool=bestpractice.bmj.com)

77. Bales AM, Zaleski CA, McPherson EW. Patient and family experiences and opinions on adding 22q11 deletion syndrome to the newborn screen. J Genet Couns. 2010;19:526-534. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20496046?tool=bestpractice.bmj.com)

78. Peyvandi S, Lupo PJ, Garbarini J, et al. 22q11.2 deletions in patients with conotruncal defects: data from 1,610 consecutive cases. Pediatr Cardiol. 2013;34:1687-1694. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23604262?tool=bestpractice.bmj.com)

79. Monteiro FP, Vieira TP, Sgardioli IC, et al. Defining new guidelines for screening the 22q11.2 deletion based on a clinical and dysmorphologic evaluation of 194 individuals and review of the literature. 2013;172:927-945. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23440478?tool=bestpractice.bmj.com)

80. Agergaard P, Olesen C, Østergaard JR, et al. The prevalence of chromosome 22q11.2 deletions in 2,478 children with cardiovascular malformations: a population-based study. Am J Med Genet A. 2012;158A:498-508. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22190294?tool=bestpractice.bmj.com)

81. Solot CB, Sell D, Mayne A, et al. Speech-language disorders in 22q11.2 deletion syndrome: best practices for diagnosis and management. Am J Speech Lang Pathol. 2019 Aug 9;28(3):984-999. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6802924/) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31330115?tool=bestpractice.bmj.com)

82. Filip C, Matzen M, Aukner R, et al. Superiorly based pharyngeal flap for treatment of velopharyngeal insufficiency in patients with 22q11.2 deletion syndrome. J Craniofac Surg. 2013;24:501-504. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23524725?tool=bestpractice.bmj.com)

83. Markert ML, Boeck A, Hale LP, et al. Transplantation of thymus tissue in complete DiGeorge syndrome. N Engl J Med. 1999;341:1180-1189. Full text (http://www.nejm.org/doi/full/10.1056/NEJM199910143411603#t=article) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10523153?tool=bestpractice.bmj.com)

84. Moylett EH, Wasan AN, Noroski LM, et al. Live viral vaccines in patients with partial DiGeorge syndrome: clinical experience and cellular immunity. Clin Immunol. 2004;112:106-112. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15207787?tool=bestpractice.bmj.com)

85. Perez EE, Bokszczanin A, McDonald-McGinn D, et al. Safety of live viral vaccines in patients with chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). Pediatrics. 2003;112:e325. Full text (http://pediatrics.aappublications.org/cgi/content/full/112/4/e325) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/14523220?tool=bestpractice.bmj.com)

86. Chinen J, Rosenblatt HM, Smith EO, et al. Long-term assessment of T-cell populations in DiGeorge syndrome. J Allergy Clin Immunol. 2003;111:573-579. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12642839?tool=bestpractice.bmj.com)

87. Davis CM, Kancherla VS, Reddy A, et al. Development of specific T-cell responses to Candida and tetanus antigens in partial DiGeorge syndrome. J Allergy Clin Immunol. 2008;122:1194-1199. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18789819?tool=bestpractice.bmj.com)

88. Azzari C, Gamineri E, Resti M, et al. Safety and immunogenicity of measles-mumps-rubella vaccine in children with congenital immunodeficiency (DiGeorge syndrome). Vaccine. 2005;23:1668-1671. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15705470?tool=bestpractice.bmj.com)

89. Sullivan KE. Live viral vaccines in patients with DiGeorge syndrome. Clin Immunol. 2004;113:3. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15380522?tool=bestpractice.bmj.com)

90. Waters V, Peterson KS, LaRussa P. Live viral vaccines in a DiGeorge syndrome patient. Arch Dis Child. 2007;92:519-520. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16798784?tool=bestpractice.bmj.com)

91. Antshel KM, Fremont W, Roizen NJ, et al. ADHD, major depressive disorder, and simple phobias are prevalent psychiatric conditions in youth with velocardiofacial syndrome. J Am Acad Child Adolesc Psychiatry. 2006;45:596-603. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16670654?tool=bestpractice.bmj.com)

92. Lin CE, Hwang KS, Hsieh PH, et al. Treatment of schizophreniform disorder by aripiprazole in a female adolescent with 22q11.2 deletion syndrome. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34:1141-1143. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20493229?tool=bestpractice.bmj.com)

93. Ysunza A, Pamplona MC, Molina F, et al. Surgical planning for restoring velopharyngeal function in velocardiofacial syndrome. Int J Pediatr Otorhinolaryngol. 2009;73:1572-1575. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19720406?tool=bestpractice.bmj.com)

94. Spruijt NE, Reijmanhinze J, Hens G, et al. In search of the optimal surgical treatment for velopharyngeal dysfunction in 22q11.2 deletion syndrome: a systematic review. PLoS ONE. 2012;7:e34332. Full text (http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0034332) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22470558?tool=bestpractice.bmj.com)

95. McDonald R, Dodgen A, Goyal S, et al. Impact of 22q11.2 deletion on the postoperative course of children after cardiac surgery. Pediatr Cardiol. 2013;34:341-347. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22864648?tool=bestpractice.bmj.com)

96. Davies EG, Cheung M, Gilmour K, et al. Thymus transplantation for complete DiGeorge syndrome: European experience. J Allergy Clin Immunol. 2017 Dec;140(6):1660-1670.e16. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5716670/) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28400115?tool=bestpractice.bmj.com)

97. Braskett M, Roberts R. Evaluation and treatment of children with primary immune deficiency in the emergency department. Clin Pediatr Emerg Med. 2007;8:96-103.

98. Matarazzo P, Tuli G, Fiore L, et al. Teriparatide (rhPTH) treatment in children with syndromic hypoparathyroidism. J Pediatr Endocrinol Metab. 2014;27:53-59. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23945122?tool=bestpractice.bmj.com)

99. Chinn I, Olsen J, Skinner M, et al. Parathyroid and thymus transplantation in DiGeorge syndrome. Clin Immunol. 2006;119:S141.

100. Butcher NJ, Chow EW, Costain G, et al. Functional outcomes of adults with 22q11.2 deletion syndrome. Genet Med. 2012;14:836-843. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22744446?tool=bestpractice.bmj.com)

101. Goldmuntz E, Clark BJ, Mitchell LE, et al. Frequency of 22q11 deletions in patients with conotruncal defects. J Am Coll Cardiol. 1998:32;492-498. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9708481?tool=bestpractice.bmj.com)

102. Van Mierop LH, Kutsche LM. Cardiovascular anomalies in DiGeorge syndrome and importance of neural crest as a possible pathogenetic factor. Am J Cardiol. 1986;58:133-137. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/3728313?tool=bestpractice.bmj.com)

103. Bassett AS, Chow EW, Husted J, et al. Clinical features of 78 adults with 22q11 deletion syndrome. Am J Med Genet A. 2005;138A:307-313. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16208694?tool=bestpractice.bmj.com)

104. Choi JH, Shin YL, Kim GH, et al. Endocrine manifestations of chromosome 22q11.2 microdeletion syndrome. Horm Res. 2005;63:294-299. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15995343?tool=bestpractice.bmj.com)

105. Stagi S, Lapi E, Gambineri E, et al. Thyroid function and morphology in subjects with microdeletion of chromosome 22q11 (del(22)(q11)). Clin Endocrinol (Oxf). 2010;72:839-844. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19863572?tool=bestpractice.bmj.com)

106. Al-Sukaiti N, Reid B, Lavi S, et al. Safety and efficacy of measles, mumps, and rubella vaccine in patients with DiGeorge syndrome. J Allergy Clin Immunol. 2010;126:868-869. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20810153?tool=bestpractice.bmj.com)

107. 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;40:430-436. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9082929?tool=bestpractice.bmj.com)

108. Rommel N, Vantrappen G, Swillen A, et al. Retrospective analysis of feeding and speech disorders in 50 patients with velo-cardio-facial syndrome. Genet Couns. 1999;10:71-78. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10191432?tool=bestpractice.bmj.com)

109. 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:e46-e51. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18554940?tool=bestpractice.bmj.com)

110. Zemble R, Luning Prak E, McDonald K, et al. Secondary immunologic consequences in chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). Clin Immunol. 2010;136:409-418. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20472505?tool=bestpractice.bmj.com)

REFERENCES

111. Lawrence S, McDonald-McGinn DM, Zackai E, et al. Thrombocytopenia in patients with chromosome 22q11.2 deletion syndrome. 2003;143:277-278. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12970648?tool=bestpractice.bmj.com)

112. Mansour AM, Goldberg RB, Wang FM, et al. Ocular findings in the velo-cardio-facial syndrome. J Pediatr Ophthalmol Strabismus. 1987;24:263-266. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/3681616?tool=bestpractice.bmj.com)

113. Zarchi O, Attias J, Raveh E, et al. A comparative study of hearing loss in two microdeletion syndromes: velocardiofacial (22q11.2 deletion) and Williams (7q11.23 deletion) syndromes. J Pediatr. 2011;158:301-306. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20846670?tool=bestpractice.bmj.com)

Images

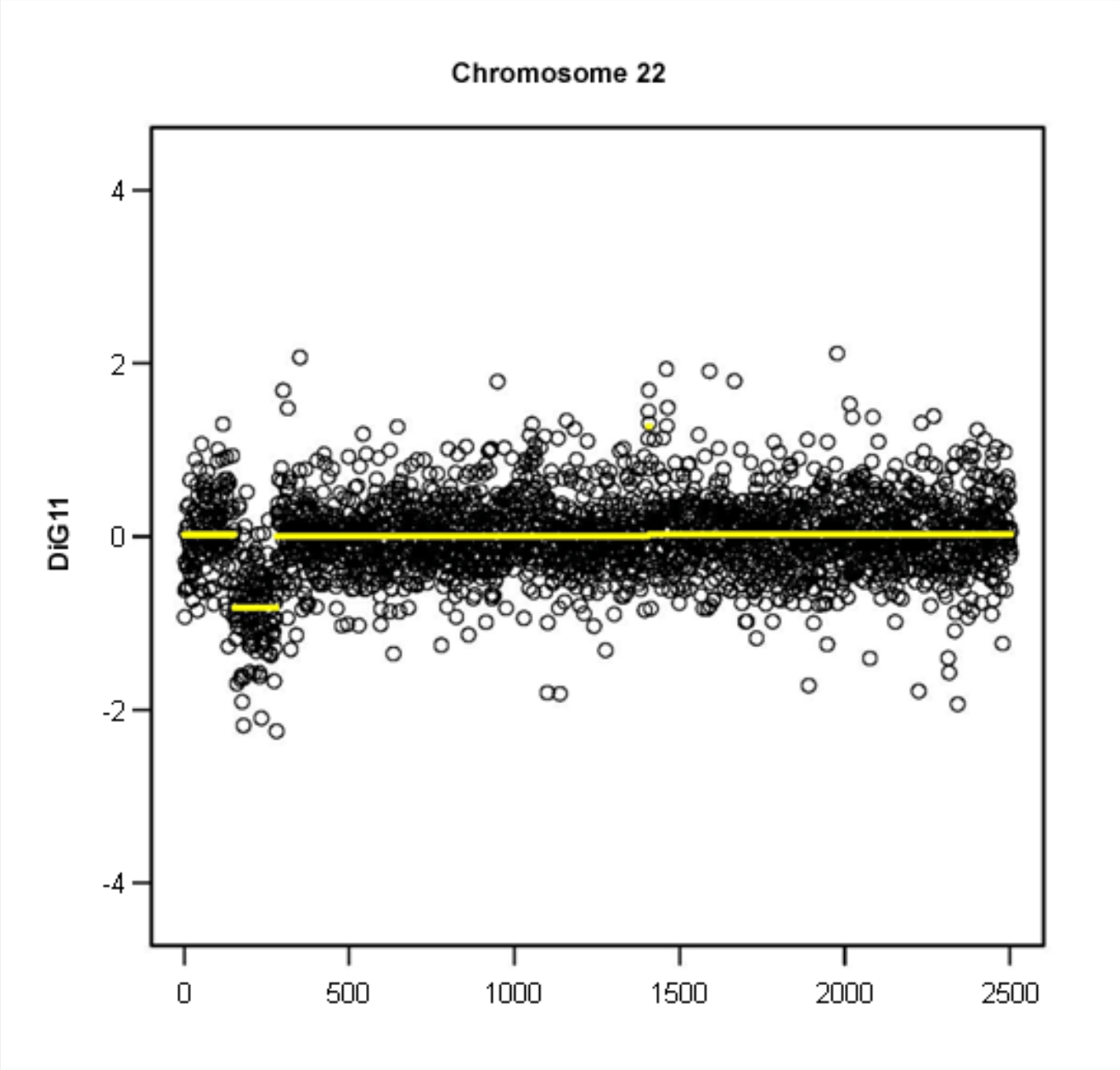


Figure 1: Loss of 1 copy of 22q11.2, demonstrated by microarray copy number analysis

From the collections of Sean A. McGhee, MD and Maria Garcia Lloret, MD

Disclaimer

BMJ Best Practice is intended for licensed medical professionals. BMJ Publishing Group Ltd (BMJ) does not advocate or endorse the use of any drug or therapy contained within this publication nor does it diagnose patients. As a medical professional you retain full responsibility for the care and treatment of your patients and you should use your own clinical judgement and expertise when using this product.

This content is not intended to cover all possible diagnosis methods, treatments, follow up, drugs and any contraindications or side effects. In addition, since such standards and practices in medicine change as new data become available, you should consult a variety of sources. We strongly recommend that you independently verify specified diagnosis, treatments and follow-up and ensure it is appropriate for your patient within your region. In addition, with respect to prescription medication, you are advised to check the product information sheet accompanying each drug to verify conditions of use and identify any changes in dosage schedule or contraindications, particularly if the drug to be administered is new, infrequently used, or has a narrow therapeutic range. You must always check that drugs referenced are licensed for the specified use and at the specified doses in your region.

Information included in BMJ Best Practice is provided on an “as is” basis without any representations, conditions or warranties that it is accurate and up to date. BMJ and its licensors and licensees assume no responsibility for any aspect of treatment administered to any patients with the aid of this information. To the fullest extent permitted by law, BMJ and its licensors and licensees shall not incur any liability, including without limitation, liability for damages, arising from the content. All conditions, warranties and other terms which might otherwise be implied by the law including, without limitation, the warranties of satisfactory quality, fitness for a particular purpose, use of reasonable care and skill and non-infringement of proprietary rights are excluded.

Where BMJ Best Practice has been translated into a language other than English, BMJ does not warrant the accuracy and reliability of the translations or the content provided by third parties (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages). BMJ is not responsible for any errors and omissions arising from translation and adaptation or otherwise.Where BMJ Best Practice lists drug names, it does so by recommended International Nonproprietary Names (rINNs) only. It is possible that certain drug formularies might refer to the same drugs using different names.

Please note that recommended formulations and doses may differ between drug databases drug names and brands, drug formularies, or locations. A local drug formulary should always be consulted for full prescribing information.

Treatment recommendations in BMJ Best Practice are specific to patient groups. Care is advised when selecting the integrated drug formulary as some treatment recommendations are for adults only, and external links to a paediatric formulary do not necessarily advocate use in children (and vice-versa). Always check that you have selected the correct drug formulary for your patient.

Where your version of BMJ Best Practice does not integrate with a local drug formulary, you should consult a local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing before prescribing.

Interpretation of numbers

Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

Our full website and application terms and conditions can be found here: Website Terms and Conditions.

Contact us

+ 44 (0) 207 111 1105
support@bmj.com

BMJ
BMA House
Tavistock Square
London
WC1H 9JR
UK

Contributors:

// Authors:

Sean A. McGhee, MD

Clinical Associate Professor
Stanford University, Stanford, CA
DISCLOSURES: SAMG has provided testimony as an expert in a criminal case in which immune deficiency was a concern. SAMG is a co-author of a reference cited in this topic.

Maria Garcia Lloret, MD

Assistant Professor
David Geffen School of Medicine at UCLA, Los Angeles, CA
DISCLOSURES: MGL is a co-author of a reference cited in this topic.

// Peer Reviewers:

Gabriela M. Repetto, MD

Director
Centro de Genetica Humana, Facultad de Medicina, Clínica Alemana-Universidad del Desarrollo, Santiago, Chile
DISCLOSURES: GMR is a co-author of a reference cited in this topic.

Lisa Kobrynski, MD, MPH

Associate Professor of Pediatrics
Division of Pulmonary, Allergy & Immunology, Cystic Fibrosis, and Sleep, Emory University, Atlanta, GA
DISCLOSURES: LK is an investigator in clinical trials by Baxter Bioscience. These trials do not involve patients with 22q11DS. LK is an author of a number of references cited in this topic.

Winnie Ip, BHB, MBChB, FRACP, MD(Res)

Consultant Immunologist
Department of Immunology, Great Ormond Street Hospital, London, UK
DISCLOSURES: WI declares that she has no competing interests.