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Parent/Carer Consensus Document for the Diagnosis and Management of 22q11DS Deletion in the UK

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Max Appeal!

Registered Charity Number 1088432

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Dr Helen Baxendale
Dr Frances Bu'Lock
Dieuwertje de Waardt
Dr Helen Firth
Dr Andy Gennery
Dr Alex Habel
Dr Richard Herriot (chair of committee)
Prof Anthony Holland
Dr Claire Illingworth
Dr Dinakantha Kumararatne
Mr Nigel Mercer
Dr Merel Pannebakker
Mr Andrew Parry
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Dr Beverly Tsai-Goodman

…and the many others consulted by the panel members.

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Introduction

A Consensus (agreement) on the treatment of those diagnosed with 22q11 deletion syndrome has now been published. This was drawn up by experts across the UK and after review by Royal Colleges and other interested parties for Max Appeal and now sets a standard that can be applied and should be met across the UK.

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What does this mean to you as a parent?

Your child should be investigated for all common findings associated with the deletion, not just those relating to the initial diagnosis. Certain checks are recommended to be carried out either annually or at key stages (sometimes called transition points) of the child's development. These roughly coincide with beginning primary and secondary education and leaving secondary school for college.

If you are concerned that these checks are not being carried out you will be able to ask your paediatrician or specialist to refer to the Consensus Document and ask that the recommendations of 'best practice' are followed.

The effects of the 22q11 deletion syndrome (22q11DS) are many and varied. Not all tests need to be carried out on every person after the initial assessments have been made. You will almost certainly meet many people specialising in different aspects of the deletion syndrome.

The syndrome results from a microdeletion (i.e. a tiny part of the chromosome 22q is missing. In most cases this deletion is not inherited and results from a random happening. The rate of incidence is not properly established.

Many children are diagnosed at birth because they were born with a congenital heart condition. Children whose heart is not affected may be diagnosed later because of other problems such as speech and language delay or behavioural problems.

The great variation of the presenting symptoms and age of diagnosis resulted in the syndrome becoming known by several historical names but when a diagnostic test became available they were found to result from the same cause.

DiGeorge syndrome (DGS) and Velo-Cardio-Facial Syndrome (VCFS) are the two commonest names in use.

Dr DiGeorge was the first person to link several of the symptoms (cardiac problems, immune deficiency and neo-natal tetany) together. VCFS refers to the association of problems with the velum (palate), heart problems and the characteristic facial appearances that are seen in some but not all of those with the deletion. Unlike Down's syndrome there are no instantly recognisable features that are seen in those with 22q11DS.

The widely varied symptoms are not random happenings but are the result of a disturbance of patterning in the very early stages of the baby's development due to a missing gene in the deleted region (the TBX1 gene). Affected structures include parts of the heart (mainly the vessels leaving the heart to carry blood to the body or lungs), the thymus, the parathyroid glands and the palate.

Checks recommended to be carried out DURING INFANCY (less than 1yr):

- Ionised calcium and PTH (Parathyroid hormone)
- FBC (full blood count and differential)
- Evaluate palate
- Audiology (hearing)
- Development
- Socialisation/functioning
- Systems review

Checks recommended to be carried out PRE-SCHOOL (1 - 5yrs):

- Ionised calcium and PTH (Parathyroid hormone)
- TSH (thyroid stimulating hormone)
- FBC (full blood count and differential)
- Immunologic evaluation
- Ophthalmology (eyes)
- Evaluate palate
- Audiology (hearing)
- Cervical spine
- Scoliosis
- Dental evaluation
- Development
- Socialisation/functioning
- Systems review.

Checks recommended to be carried out SCHOOL AGE (6 - 11yrs):

- Ionised calcium and PTH (Parathyroid hormone)
- TSH (thyroid stimulating hormone)
- FBC (full blood count and differential)
- Dental evaluation
- School performance
- Socialisation/functioning
- Psychiatric/emotional/ behavioural
- Systems review.

Checks recommended to be carried out during ADOLESCENCE (12 - 18yrs):

- Ionised calcium and PTH (Parathyroid hormone)
- TSH (thyroid stimulating hormone)
- FBC (full blood count and differential
- Scoliosis
- Dental evaluation
- School performance
- Socialisation/functioning
- Psychiatric/emotional/ behavioural
- Systems review
- Genetic counselling

Checks recommended to be carried out at during ADULT LIFE (over 18yrs):

- Ionised calcium and PTH (Parathyroid hormone)
- TSH (thyroid stimulating hormone)
- FBC (full blood count and differential)
- Audiology (hearing)
- Dental evaluation
- ECG
- Socialisation/functioning
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- Development
- Socialisation/functioning
- Systems review

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- Ionised calcium and PTH (Parathyroid hormone)
- TSH (thyroid stimulating hormone)
- FBC (full blood count and differential)
- Dental evaluation
- School performance
- Socialisation/functioning
- Psychiatric/emotional/ behavioural
- Systems review.

Checks recommended to be carried out during ADOLESCENCE (12 - 18yrs):

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- TSH (thyroid stimulating hormone)
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- Scoliosis
- Dental evaluation
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- Socialisation/functioning
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- Systems review
- Genetic counselling

Checks recommended to be carried out at during ADULT LIFE (over 18yrs):

- Ionised calcium and PTH (Parathyroid hormone)
- TSH (thyroid stimulating hormone)
- FBC (full blood count and differential)
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Explanation of the Recommended Assessments

Endocrinology tests: Calcium, PTH, and TSH In infancy these should be checked every 3-6 months, in childhood every 5 years and every 1-2 years thereafter although the TSH should be measured annually. Calcium levels should be checked both pre-and post-operatively and regularly during any pregnancies.

Full blood count and differential: A check on the haemoglobin levels (low levels indicate anaemia) and the total number of white cells, plus the neutrophil and lymphocyte count.

Immunologic evaluation: Immunoglobulin levels and T cell function. Flow cytometry should be done at birth and again at age 9-12 months before administering any live vaccines. Flow cytometry distinguishes between the types of lymphocyte present. The CD4 marker identifies the T helper cells that are needed to stimulate the function of other T cells.

Evaluate palate:

- In infancy: visualise the palate and evaluate for feeding problems and nasal regurgitation.
- In toddlers – adults evaluate nasal speech quality

Cervical spine: Multiple X-rays should be done: Anterior/posterior (from the front and back) Lateral (sideways) Extension (tipping the head back) Open mouth and the Base of the skull. Expert opinion is divided about the advisability of routine X-rays. Symptoms of cord suppression are an indication for urgent neurological referral.

Scoliosis exam: This checks for sideways curvature of the spine
Renal Ultrasound: Checks that both kidneys are in place and look normal but does not check how they function.

ECG: (Electrocardiogram) This tests the function by measuring the rhythm of the heart beat.

Echocardiogram: This tests the structure of the heart and valves and can show the pumping action.

Psychiatric/emotional/behavioural: Vigilance for changes in behaviour, emotional state and thinking, including hallucinations and delusions. In teens and adults assessment would include at risk behaviours (sexual activity, alcohol/drug use etc).

Deletion studies of parents: On diagnosing a child with 22q11DS both parents should be checked for the deletion.

Checks recommended to be carried out at DIAGNOSIS:

- Ionised calcium and PTH (Parathyroid hormone)
- TSH (thyroid stimulating hormone)
- FBC (full blood count and differential)
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Genetic Advice

When 22q11DS is suspected specialised tests (e.g. an array test or a FISH test) must be carried out as the deletion is too small to be seen using an ordinary microscope. If the deletion is confirmed both parents should be tested as it is possible that one may have the deletion but with only mild signs and symptoms. Genetic counselling will be offered to the family.

If neither parent has passed on the deletion it is said to be 'de novo' i.e. a new deletion that has arisen by chance. If this is the case it is rare that further children will be affected but prenatal diagnosis would usually be available in a future pregnancy if parents wish.

If one of the parents has a 22q11 deletion, there will be a one in two (or 50%) chance of a child inheriting the deletion in any pregnancy. Pre-natal diagnosis would be offered to detect the deletion but it is not possible to predict how severely and in what way a child will be affected although cardiac abnormalities may be detected at 16 or 20 week scans.

Should pre-natal tests show that a baby has the deletion; special scans should be done to look for heart defects (foetal echocardiography) and once born the baby should be seen by a senior paediatrician. The heart, calcium levels and immune system should all be checked.

When the child reaches young adulthood, genetic counselling should be given so that they can appreciate the risks of passing the deletion to a child of their own (which will be 50% in every pregnancy).

Cardiac Abnormalities

Congenital heart defects are common in 22q1DS patients. Most of these involve the arteries leaving the heart the 'conotruncal defects' although there are some children born with other defects such as a 'hole in the heart'. The conotruncal defects include an interrupted aortic arch, Tetralogy of Fallot (TOF), pulmonary atresia-ventricular septal defect (PA-VSD) and truncus arteriosus.

Surgery can be carried very soon after birth to correct most of these defects although further operations may be needed as the child grows.

Major heart defects can be detected on routine scans. However if there is a close family history of either congenital heart defects or of 22q11 DS an echocardiogram should be carried out by a cardiologist specialising in unborn babies.

Most cases of 22q11S are not linked to a family history so the majority of children are diagnosed after birth. Any child with any of the cardiac defects associated with 22q11DS should be tested for the deletion. If they are identified as having the deletion further tests will be carried out by other specialists.

Those children who undergo major cardiac surgery should have regular checks throughout their life. Any adult who has a history of the cardiac problems associated with 22q11DS should be offered a test after personal and genetic counselling as it is possible that a diagnosis of 22q11DS was never previously considered.

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How 22q11DS affects the mouth and hearing

Cleft Palate: about 1 in 10 children affected by 22q11DS will have a cleft palate that is obvious from birth and about 1 in 20 will have a more subtle defect known as a submucous cleft palate where the problem is hidden by skin.

Both types of cleft palate cause trouble with feeding and milk often leaks from the nose. Difficulty in feeding may result in poor weight gain and all babies diagnosed with a cleft should be referred to the specialist team for their region for help and advice on feeding.

No baby with either a cleft palate or VCFS should be fed through a tube leading from the nose to the stomach (nasogastric tube) without first trying oral feeding with bottles or teats designed to assist these children. Appropriate surgery will be offered in due course. Other problems affecting the child e.g. heart surgery should be dealt with first.

VPI (Velo-pharyngeal insufficiency): This is a frequent problem even when no cleft palate is detected and the speech of these children can be badly affected, with nasal sounds, because a flap at the back of the throat fails to shut and air escapes through the nose. These children should be referred to the Palate Team for assessment and Speech and Language therapy.

Facial features: Although some children with 22q11DS share characteristic facial features these are often not very obvious and may develop during childhood rather than be seen at birth.

Hearing Loss: 'Glue ear' is more common in children with a cleft palate. The use of 'grommets' has not been shown to improve hearing in the long term. Adenoids should not be removed before it is determined if the child can speak normally.

Problems with Learning and Behaviour

22q11DS children have a typical pattern of learning difficulties and this can impact on e.g. their ability to co-operate with Speech and language Therapy.

They can usually learn to read soon after starting school but begin to fall behind their classmates as they progress through primary education. They have poor understanding and reasoning abilities. However many children can cope in mainstream schooling with help on a one to one basis. 22q11DS children learn in a different way and teaching in a direct manner may be better for them rather than the methods that encourage a child to discover and learn for themselves. Computer programmes are available that can help them to learn at their own pace. They often have pleasant personalities and are willing to learn.

Unfortunately advice on education interventions is not part of the Consensus Document as it can only cover aspects of 22q11DS that are dealt with by the medical profession.

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		Infancy <1yr	Pre-School 1-5yr	School age6-11yr	Adolescence 12-18yr	Adult >18yr
Ionised calcium and PTH (Parathyroid hormone)	✓	✓	✓	✓	✓	✓
TSH (thyroid stimulating hormone)	✓		✓	✓	✓	✓
FBC (full blood count and differential) Annual check	✓	✓	✓	✓	✓	✓
Immunologic evaluation	✓		✓			
Opthalmology (eyes)	✓		✓			
Evaluate palate	✓	✓	✓			
Audiology (hearing)	✓	✓	✓			✓
Cervical spine			✓			
Scoliosis	✓		✓		✓	
Dental evaluation			✓	✓	✓	✓
Renal ultrasound	✓					
ECG	✓					✓
Echocardiogram	✓					
Development	✓	✓	✓			
School performance				✓	✓	
Socialisation/functioning	✓	✓	✓	✓	✓	✓
Psychiatric/emotional/behavioural	✓		✓	✓	✓	✓
Systems review	✓	✓	✓	✓	✓	✓
Deletion studies of parents	✓					
Genetic counselling	✓				✓	✓

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Immunologic evaluation	✓		✓			
Opthalmology (eyes)	✓		✓			
Evaluate palate	✓	✓	✓			
Audiology (hearing)	✓	✓	✓			✓
Cervical spine			✓			
Scoliosis	✓		✓		✓	
Dental evaluation			✓	✓	✓	✓
Renal ultrasound	✓					
ECG	✓					✓
Echocardiogram	✓					
Development	✓	✓	✓			
School performance				✓	✓	
Socialisation/functioning	✓	✓	✓	✓	✓	✓
Psychiatric/emotional/behavioural	✓		✓	✓	✓	✓
Systems review	✓	✓	✓	✓	✓	✓
Deletion studies of parents	✓					
Genetic counselling	✓				✓	✓

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- **Hearing problems:** Deafness resulting from 'glue ear' is common but does not usually cause long term problems. Some children may have a mild deafness due to poor development of the nerves and structure of the ear.

- **Problems with vision:** 22q11DS children could suffer from long-sightedness and spectacles may be needed to help with reading and to help the child judge the distance, direction and location of objects. Children with 22q11DS also suffer more from conjunctivitis (pink eye).
- **Dental care:** Tooth enamel is often poor in quality leading to dental caries; teeth may be fewer in number and badly formed. Great attention should be paid to dental hygiene from the time the first teeth are developed. As well as dentists who care for children others are dedicated to care of those with special needs.

- **Neurological aspects of 22q11DS**: 22q11DS children often show clumsiness and have trouble controlling both large muscles used in walking and running and in the smaller muscles controlling e.g. fingers which make writing and using a keyboard more difficult to use. Exercises led by a therapist can help.

Behaviour and Social skills

Many 22q11DS children have behavioural problems. Their attention span can be short and they can act impulsively. They may lack confidence and find it difficult to mix with other children. They may become obsessed with a single idea and their behaviour can be like those of a child suffering from Attention Deficit and Autistic Spectrum Disorders. Children may show immature and inappropriate behaviour patterns and may need to be taught how to behave in the company of others.

Psychiatric Disorders

There is increasing evidence that many of those with 22q11DS suffer from psychiatric disorders as well as learning disabilities. This also happens in people with intellectual difficulties for other reasons.

Although much work needs to be carried out following people with 22q11 DS throughout their lives it is thought that attention deficit hyperactivity disorder (ADHD), anxiety, mood and psychotic disorders happen more often than in other groups.

Psychotic illness includes schizophrenia and this is now thought to occur in about a third of those diagnosed with 22q11DS. Treatment for this is available although it may be less effective and have more side effects than for those people who are not affected by 22q11DS.

Because of the high risk of psychiatric disorders in 22q11 DS teenagers and adults there should be an awareness of the possibility and referral to expert help should be made as soon as problems are suspected.

Endocrine aspects of 22q11 deletion syndrome

Several of the endocrine (hormone producing) glands are affected by the 22q11DS. These are the parathyroid glands as well as the thyroid gland itself. Hypo (i.e. underactive) glands are more common but an over active thyroid (hyperthyroidism) can occur.

If the parathyroid glands are underactive then low calcium levels (hypocalcaemia) in the blood may cause the muscle spasms (neo-natal tetany) seen in some new born babies with 22q11DS and which should alert clinicians to the possibility of 22q11DS even in absence of cardiac or immune problems.

Hypocalcaemia may also be seen in times of 'growth spurts' e.g. as happens in adolescence and this is one aspect of the 22q11DS that needs checking at least once a year.

Although 22q11DS children are often short for their age this is only rarely due to a lack of growth hormone. Slow growth is more likely to occur because of feeding problems. Most people affected by the 22q11DS grow to normal height catching up in the teenage years when care must be taken to prevent them becoming overweight.
Thyroid disease: All those diagnosed 22q11DS should have their thyroid function checked regularly. Although an underactive thyroid is more likely to be seen over active thyroid function may result from what is known as an autoimmune reaction when the immune system turns on the body and causes damage. (22q11DS is associated with several autoimmune diseases.)

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- **Hearing problems:** Deafness resulting from 'glue ear' is common but does not usually cause long term problems. Some children may have a mild deafness due to poor development of the nerves and structure of the ear.

- **Problems with vision:** 22q11DS children could suffer from long-sightedness and spectacles may be needed to help with reading and to help the child judge the distance, direction and location of objects. Children with 22q11DS also suffer more from conjunctivitis (pink eye).
- **Dental care:** Tooth enamel is often poor in quality leading to dental caries; teeth may be fewer in number and badly formed. Great attention should be paid to dental hygiene from the time the first teeth are developed. As well as dentists who care for children others are dedicated to care of those with special needs.

- **Neurological aspects of 22q11DS**: 22q11DS children often show clumsiness and have trouble controlling both large muscles used in walking and running and in the smaller muscles controlling e.g. fingers which make writing and using a keyboard more difficult to use. Exercises led by a therapist can help.

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Behaviour and Social skills

Many 22q11DS children have behavioural problems. Their attention span can be short and they can act impulsively. They may lack confidence and find it difficult to mix with other children. They may become obsessed with a single idea and their behaviour can be like those of a child suffering from Attention Deficit and Autistic Spectrum Disorders. Children may show immature and inappropriate behaviour patterns and may need to be taught how to behave in the company of others.

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Immunology

Although severe, life threatening immunodeficiency is rare in 22q11DS. All babies diagnosed soon after birth should be checked out immediately for a functioning immune system and older children should also have some tests run when a diagnosis is made. The immune system is very complex and many cells and the 'messengers' that they release are involved in killing invading bugs. A CD-ROM explaining the immune system in cartoon form is available from Max Appeal.

The part of the immune system that fails to develop in 22q11DS children is controlled by the thymus gland. Some lymphocytes are trained by this gland and these 'T cells' in their turn can control or help other cells in the immune system to work properly.

The thymus can be badly affected by the deletion and may not be normal in size, function or in its usual place. However most of the children born with the deletion will have some thymus cells active somewhere in their body and these will eventually work properly so that the immune system will overcome the early problems.

Recurrent infections of the ears, throat and lungs can be a problem if the immune system is not working fully. If VPI (Velo Pharyngeal Insufficiency) is present it can contribute to the number of common infections of the nose and throat. Antibiotics may be offered as protection during the winter months until the child is about 5 or 6 years old.

Immunisations: 22q11DS babies should be given the primary vaccinations routinely after birth. This is to stimulate the production of protective proteins in the blood, antibodies.

Children who only have very low numbers of 'T cells' may not make antibodies but as the current UK immunisation schedule includes only inactivated vaccines they will do no harm. The only exception is BCG (protection against TB) which is offered to some families where the children are at high risk of catching TB. This should not be given to any infants without functioning T cells.

If BCG immunisation is being considered, advice should be sought from an immunologist. The MMR vaccine is not normally given until a child is a year old by which time a severe immunodeficiency will have been diagnosed.

Auto immune Diseases: These are diseases where the body scores an 'own goal' by attacking itself and rheumatoid arthritis together with autoimmune thyroid disease and some other disorders have recently been associated with 22q11DS.

Checks on the immune system: When a child is young more frequent tests will be carried out to check the numbers of cells and how well they can respond to routine vaccinations. Later it is recommended that annual checks are carried out to confirm that the immune system is working well and also that the person has no sign of autoimmune diseases.

General Paediatric Problems in 22q11DS

The sections above outline the problems associated with 22q11DS that need specialist care. Unfortunately many other problems can be associated with the syndrome and most of these can be dealt with by a general paediatrician who should refer any major problems to other specialists if necessary.

- **Breathing problems:** Wheezing may be noticed from birth and this could be caused by parts of the throat being abnormal in structure or weak. Surgery is not always needed as many problems improve with time although help may be needed to ease the problems during the first year or two. Some babies cannot prevent milk from entering the lungs instead of swallowing it. This is known as aspiration. Babies may choke or cough during feeding but 'silent' aspiration may also happen and only be noticed because of a wheeze or frequent chest infections. Tests might be needed to check if the baby can shut off the tube leading to the lungs when swallowing.

- **Feeding problems:** These may be linked to the same weaknesses that cause breathing difficulties, or to a sub mucosal (hidden) cleft palate or even to problems with the heart. GERD (Gastro-Oesophageal Reflux Disease i.e. heartburn) may result. Help and advice to overcome these difficulties can be given.

- **Constipation:** This can result from a 'lazy' gut that is too weak to move things through the intestine in the normal time and be made worse by a reluctance to eat food high in fibre or to drink adequate amounts of liquids. The team who give advice on any feeding difficulties should have plenty of suggestions to help overcome constipation although it may be necessary to use laxatives on a regular basis.

- **Growth:** This can be delayed in the pre-school years either because of problems with feeding and digestion or problems with thyroid or growth hormones. Most children catch up and when adult are normal in height but they may become overweight during their teens. Other causes of slow growth such as coeliac disease should be ruled out.

- **Problems with the bones and muscles:** Scoliosis (a sideways curve of the spine) is the most common problem and children should be checked for this as they grow. Ligaments may be weak allowing more mobility in joints than is normal. The knee caps have a tendency to become dislocated in teenagers.

- **Sleep disturbance:** Sleep may be disturbed by 'growing pains', leg pains or by 'restless legs'. Treatment will depend on the cause of the disturbance.

- **Kidney problems:** Although there may be some structural abnormalities these rarely cause any problems.

- **Genital problems:** Some boys may have the opening of the tube for the passage of urine from the bladder shifted to the underside of the penis. This may be associated with undescended testes and should be referred to a specialist.

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