MEN 2A

Patient Information

Multiple Endocrine Neoplasia Type 2a (also known as MEN2)

AMEND

Association for Multiple Endocrine Neoplasia Disorders

Registered Charitable Incorporated Organisation no. 1153890.

MEN SUPPORT
Tel: 01892 516076
Email: info@amend.org.uk
www.amend.org.uk

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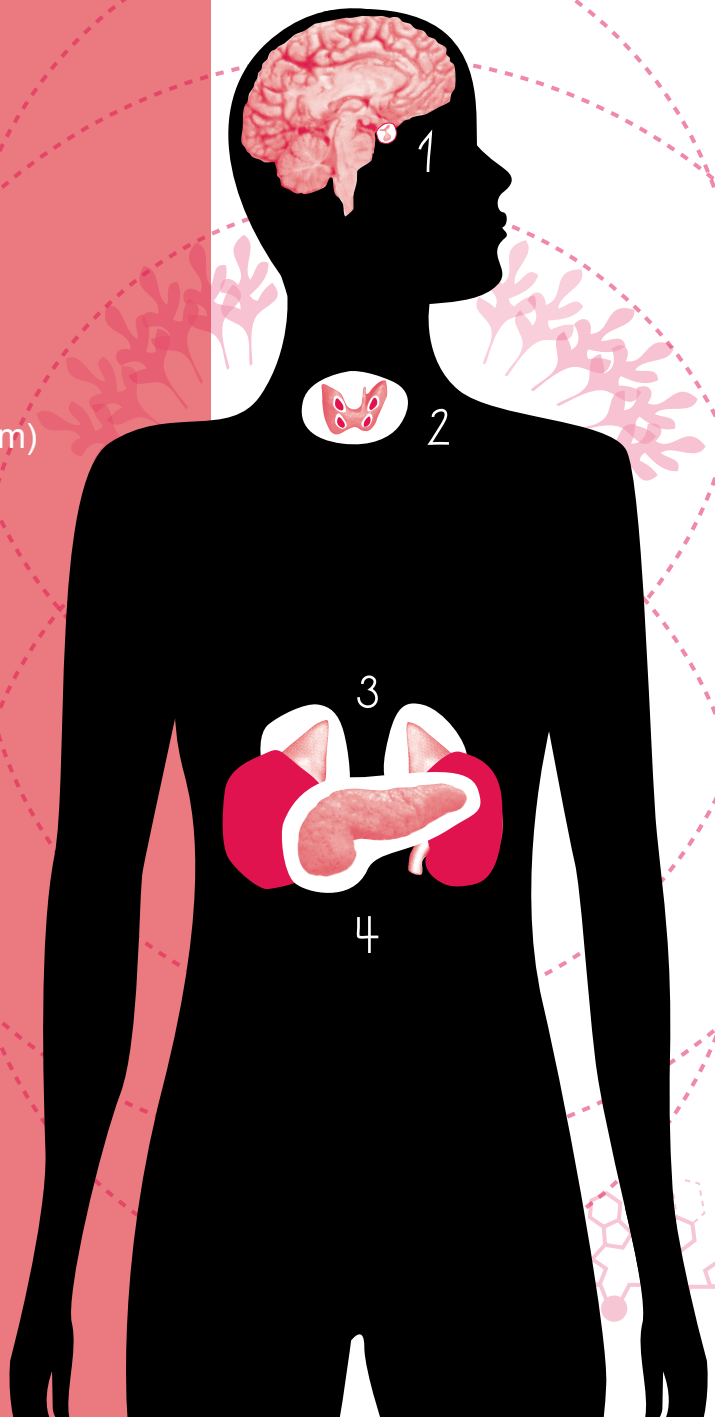

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What is Multiple Endocrine Neoplasia Type 2A?

Multiple Endocrine Neoplasia Type 2 (MEN2A) is a condition that can be passed down in families. MEN2A causes more than one gland of the body's endocrine (gland) system to develop growths (tumours). The affected glands may then make greater than normal amounts of hormones, the body's chemical messengers, which in turn cause a range of different symptoms. Each type of tumour may occur alone and separate from MEN.

Multiple = more than one
Endocrine = gland system
Neoplasia = increase in growth of normal cells (tumour)

How is MEN2A Diagnosed?

A person may be said to have MEN2A if they have:

1. 2 or more tumours that occur in MEN2A (see What Tumours Occur in MEN2A?); or
2. Only one tumour, but there is a family history of relatives with MEN2A; or
3. A blood test which shows a change in the RET gene

A patient may have the gene change that causes MEN2A, but not have developed any of the tumours. This patient may be called a "MEN2A carrier" and should be offered endocrine follow-up in clinic in the same way as a patient who does have MEN2A tumours.

What Tumours Occur in MEN2A?

There are three types of tumour that can occur in MEN2A. These are:

1. In the thyroid gland in the neck (medullary thyroid cancer)
2. In the parathyroid glands that lie close to or inside the thyroid (parathyroid adenomas)
3. In the adrenal glands that sit on top of each kidney (phaeochromocytomas).

The first treatment in MEN2A is usually for medullary thyroid cancer. This consists of removing the thyroid gland and surrounding lymph nodes. After this, management for the other tumours that occur in MEN2A involves checking hormone levels using blood and urine tests, and scans of the neck and stomach areas. Sometimes this might lead to more treatment in the form of removal by surgery of the tumour and/or the affected gland. The rest of this information book describes each tumour and explains what the current tests, treatments and medications are.

In some cases of MEN2A, the only tumour to occur in the lifetime of the patient is in the thyroid gland (medullary thyroid cancer or MTC). This was once known as Familial Medullary Thyroid Cancer (FMTC). This diagnosis is reached if there are at least four family members aged over 50 years old who are affected by MTC but not pheochromocytomas or parathyroid adenomas. Usually, the MTC occurs later in life than in other MEN2A syndromes and may be less aggressive.

The table below shows the current testing and treatment programme for MEN2A, according to their particular codon mutation of the RET gene (See Genetic Testing Explained). See specific condition sections for more details on the tests themselves.

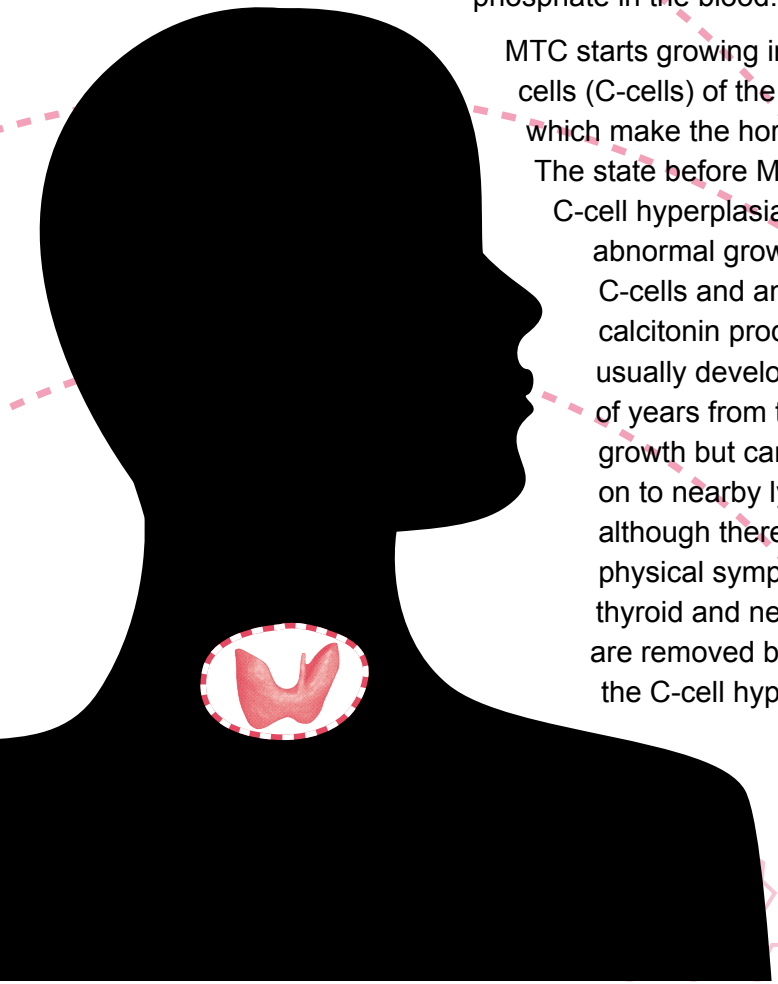
Recommended ages for tests and thyroid surgery in MEN2A

Codon number of the change in the RET gene	Gene testing	First calcitonin blood test and neck ultrasound	Surgery to remove the thyroid gland	Testing for adrenal tumours (phaeochromocytoma)	Testing for Parathyroid Hyperlasia
Moderate Risk 609, 611, 618, 620, 630, 666, 768, 790, 791, 891	By age 3-5	Age 5	From age 5 depending on test results and family history	20	20
High Risk 634	By age 3-5	Age 3	Before age 5	8	20

Medullary Thyroid Cancer (MTC)

Almost all MEN2A patients will develop medullary thyroid cancer (MTC) by the age of 40.

The thyroid gland is found at the front of the neck. This gland makes 3 hormones; thyroxine and triiodothyronine (essential for maintaining the body's metabolism and mental and physical development), and calcitonin which is involved in helping to regulate levels of calcium and phosphate in the blood.



MTC starts growing in the parafollicular cells (C-cells) of the thyroid gland which make the hormone calcitonin. The state before MTC is called C-cell hyperplasia, where there is abnormal growth of the normal C-cells and an increase in calcitonin production. MTC usually develops over a number of years from this abnormal growth but can spread early on to nearby lymph nodes, although there may be no physical symptoms. If the thyroid and nearby lymph nodes are removed by surgery while the C-cell hyperplasia or cancer is still contained inside the thyroid (total thyroidectomy and central lymph node dissection), a patient is usually cured. If calcitonin levels are still above normal after surgery, this shows that the cancer has spread (metastatic) or has not been completely removed. In this case, more surgery and other treatments may be used to control it, but sometimes it is thought reasonable just to watch-and-wait ('surveillance'). As yet there is no complete cure for metastatic MTC; however, it may often be managed well and without symptoms for many years. Symptoms that may develop can sometimes be controlled using radiotherapy and sometimes chemotherapy, or some newer 'targeted' drugs.

Due to the earlier detection of MEN2A, made possible by the genetic test, and the high chance that an MEN2A patient will develop MTC, surgery to remove the thyroid gland is now highly advised in children who carry the gene. In some cases the surgery is done before the age of 5 in order to prevent the development of the cancer (see Children and MEN2A). This course of action may be why there has been a dramatic reduction in the number of deaths in MEN2A patients from metastatic MTC. In older children, thyroidectomy is done as soon as MEN2A is diagnosed.

Testing for C-cell Hyperplasia & MTC

Below are some of the tests that you may have to confirm a diagnosis of c-cell hyperplasia or MTC:

BLOOD TESTS

Baseline Calcitonin A simple blood test to detect calcitonin levels. *[NB: once drawn, the blood must be taken immediately and on ice to a chilled centrifuge in the lab]*

SCANS/OTHER

Ultrasound Scan (US) with Fine Needle Aspiration (FNA) - a painless scan of the neck using a probe. The images then guide the insertion of a needle to sample (biopsy) areas of thyroid tissue.

How is MTC Treated?

Once a diagnosis of MTC has been made, an ultrasound scan of the neck called a 'staging ultrasound' will be done. If the lymph nodes do not look larger than normal, an operation called a 'total thyroidectomy and central node dissection' is done. If any lymph nodes do look larger than normal, then further nodes will be removed at the same time as the thyroid.

SURGERY

Total thyroidectomy + central node dissection -a small cut is made at the base of the front of the neck from which the thyroid and nearby lymph nodes can be removed. A larger cut is needed if the cervical lymph nodes need to be removed as well. Eating and drinking is possible almost straightaway after waking up from the operation.

Hospital Stay - you will probably stay in the hospital for around 3 to 5 days in total.

Risks - thyroid surgery is generally safe, but there are some possible risks that you need to be aware of. Injury to the nerves that control the vocal cords (less than 1-2%) may affect the voice. Unavoidable removal of or injury to the parathyroid glands may occur which might result in a temporary drop in calcium levels in the blood. Sometimes this may be permanent. Symptoms of low blood calcium include tingling lips, fingers and toes, and eventually cramping. All these symptoms can be corrected with medication.

MEDICATION AFTER SURGERY

Levothyroxine

Levothyroxine (or thyroxine) has been used successfully for many years to replace the thyroid hormones after surgery. It must be taken life-long after thyroidectomy. Tablets are taken once a day and doses are typically between 100-150mcg for adults, but lower for children. You will need regular blood tests to make sure that you are on the right dose. A dose that is too big may cause symptoms such as a fast heartbeat, sweating, anxiety, shaking and weight loss. A dose that is too small may cause symptoms such as tiredness, a slow heartbeat, sensitivity to cold, and weight gain. Although the above symptoms may suggest a need to change your dose, the same symptoms can occur in other conditions. Therefore, only a blood test (measuring the thyroid stimulating hormone or TSH level) can help doctors be sure whether a change in dose is needed. Once your ideal dose is found, as judged by blood tests, repeat tests will only need to be done infrequently.

Calcium replacement medication *See Treating Parathyroid Tumours*

How is MTC Treated if it has spread?

Patients with MTC may have high levels of calcitonin in the blood even after surgery. However, although this shows that there are MTC cells left in the body, patients with calcitonin levels that are higher than normal, remaining the same over a period of time, or slowly increasing, often do not need further tests or treatment. This is because scans are not always able to find a site of disease outside of the neck unless calcitonin levels are very high: calcitonin alone is not proof of a growing tumour. Even so, in some patients the search for metastatic disease may involve various scans, including radioactive isotope scans and CT scans. Sometimes a camera may be used to look at the abdomen (laparoscopy). These tests may then be followed by treatment with more surgery or radiotherapy if needed.

C-cells also produce a substance called carcinoembryonic antigen (CEA) which is measured together with calcitonin to help gather more information about MTC that has spread outside the neck.

MIBG / OCTREOTIDE radioactive isotope therapy

Where surgery is no longer an option due to the extent of the disease, some expert medical

centres may use radioactive therapies called MIBG or octreotide. These have very few side effects and can help to reduce or control the spread. However, they are only used if tests suggest that they will be taken up by the tumour. The agent is attached to a radioactive substance and is given through a vein by slow injection. The patient remains radioactive for a few days and therefore must be nursed in a lead-lined room. The treatment may need to be repeated several times at 3- or 6-month intervals. Possible side effects of these therapies include feeling sick, and sometimes vomiting.

Until a complete cure is found, much of the current focus of treatment for extensive metastatic MTC is on the relief of the symptoms it causes:

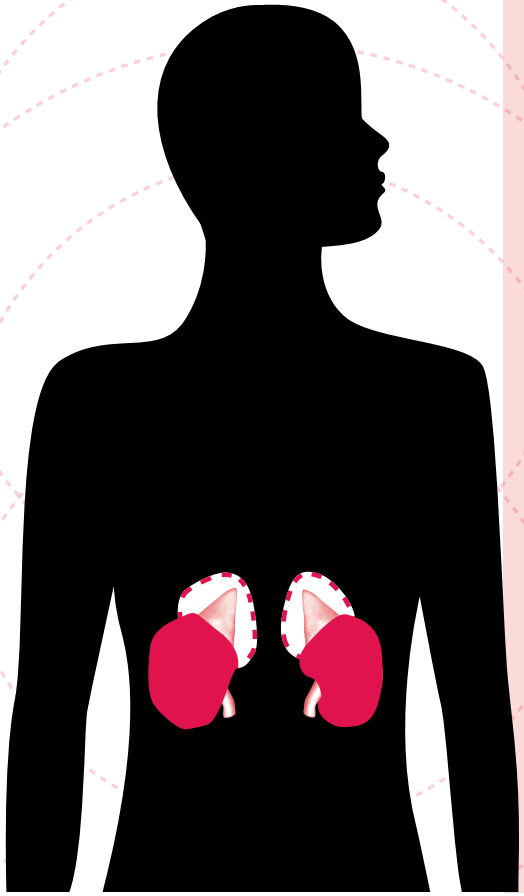
Diarrhoea - a change to the patient's diet may be needed, together with medicine such as Imodium which can help to control it. In some cases diarrhoea can also be relieved by treatment with a long-acting form of somatostatin (octreotide or lanreotide) although this is not the case for everyone. Some believe that in such cases it may also help slow down the growth of the tumour.

Flushing - medicines used to control ulcers called H2 blockers (cimetidine or ranitidine) may sometimes be used to help ease flushing.

Painful bone metastases - external radiation therapy can sometimes provide fast pain relief when MTC has spread to the bone. In all cases, pain medicine may be prescribed, and often drugs to specifically target these bone lesions.

Other Therapies for Metastatic MTC

A class of drugs called Tyrosine Kinase Inhibitors (TKIs such as cabozantinib) or more selective Inhibitors (such as selpercatinib) are available for use in metastatic MTC where other treatments do not work. These drugs are not cures but may in some people help to slow or stop the spread of MTC as well as to relieve some of the side effects of high calcitonin levels. Selpercatinib is expensive and therefore only available through the Cancer Drugs Fund (CDF). Specialists have to apply to the CDF to use this drug. You should discuss these options, the possible side effects and other issues about these therapies with your specialist. TKIs are not always suitable for everyone.



Phaeochromocytomas ('fee-oh-cromo-sy-tomers')

Phaeochromocytomas ('phaeos' – 'fee-ohs') are tumours of the adrenal glands. In MEN they are almost always benign (not cancer).

The body's two adrenal glands are normally each about the size of a whole walnut, and sit just on top of the kidneys. Phaeos grow in the inner part of the gland (medulla) and make larger than normal amounts of a group of hormones called catecholamines (such as adrenaline). Phaeos may grow for many years without causing severe symptoms, but they can start to cause serious symptoms due to events such as childbirth or surgery. Even though phaeos are almost always benign in MEN, they are still a danger to the patient due to the sudden larger than normal amounts of hormones they make. They have been known to cause strokes, heart failure and premature death. Once a patient is known to have MEN2A, regular tests should find a phaeo before

severe symptoms develop.

Possible symptoms of a phaeo may include all or some of the following: sudden headaches, palpitations, breathlessness, excessive sweating, high (or rarely low) blood pressure (either all the time or every so often), trembling, pale appearance, tiredness, depression, anxiety, and feeling sick with or without being sick.

Testing for Phaeochromocytomas

If a phaeo is suspected, a number of tests may be ordered by your doctor. These may include:

24 hour urine test (metanephrines): This test measures the level of metanephrines in the urine over 24 hours. Metanephrines are breakdown products of the hormones adrenaline and noradrenaline which are made by the adrenal gland. The urine collection bottles do not contain acid.

In some places they may simply use a random collection of urine when you are seen in the clinic.

To complete a 24-hour urine test, empty your bladder completely first thing in the morning without collecting it. Note the time. Then collect your urine every time you go to the bathroom over the next 24 hours including the first time you empty your bladder the next morning. Note the time you finish the next morning on the bottle. Your doctor should give you specific instructions. Follow them carefully. Women may also receive a small, sterilised, plastic jug to help with collection.

Plasma Metanephrine Test: These days, testing the blood (plasma) for levels of the breakdown products, metanephrine and normetanephrine, is being used more widely to help diagnose phaeos. This test should ideally be done after the patient has been lying quietly in a calm, warm place for about 20 to 30 minutes. This helps to avoid a false positive result. In many large centres, this may also be done as a random sample in the clinic. It is important that you tell your specialist about any medications or drugs you are taking.

CT scan: a computer tomography scan can be used to find out the position and size of tumours.

MRI scan: a magnetic resonance imaging (MRI) scan can also help find out the position and size of tumours. It uses magnetism rather than x-rays to take pictures of the inside of the body.

^{123}I-MIBG scan: this specialised scan is done at the hospital's nuclear medicine department. MIBG (Meta-iodo-benzyl-guanidine) is a chemical that is easily picked up by many phaeos. When the MIBG is combined with a mildly radioactive agent and injected via a vein in the arm, it sticks to the tumour cells which light up on the screen as hotspots.

FDG-PET / ^{68}Ga-DOTATATE-PET-CT imaging: a PET (positron emission tomography) scan is another nuclear medicine scan similar to MIBG but which uses different agents that can either bind with or be taken up by the tumour. In many places the ^{68}Ga-DOTATATE-PET-CT scan is now the scan of choice.

How are Phaeos treated?

Treatment for phaeos is surgery. The tumour and the adrenal gland where it grows are both removed. If only one gland has a tumour then only that gland will be removed at that time. If the other gland then also develops a tumour, the surgeon may try and leave behind some of the other part of the gland to avoid needing to be on 'steroids' for life. This is because removing both glands will leave the patient needing corticosteroid drugs for the rest of their life to replace the hormones made by the glands. Doctors prefer to delay this type of drug treatment for as long as possible as the medication has its own potential drawbacks (see Bilateral Adrenalectomy).

Phaeos can cause very unstable blood pressure. To help keep

this stable during surgery, you will be given medicine (anti-hypertensive drugs) called alpha- and sometimes also beta-blockers for at least 10 days before surgery and sometimes for a much longer period. This practice of controlling the blood pressure is done even for patients with few or no symptoms in order to lessen any risk during surgery. Following surgery the blood pressure should return to normal.

While you are waiting for treatment, there are some medicines that you will need to avoid, including some that you can buy over the counter at the chemist. AMEND has produced a card to carry with you to help avoid these. The Phaeo/Para Crisis Card is available from your endocrinologist or specialist nurse.

Alpha-blockers. Alpha-blockers (phenoxybenzamine or doxazosin) have side effects such as feeling dizzy, a dry mouth and a stuffy nose. Your doctor may ask about these symptoms because it tells them that the drug is working. Men may also find that they cannot ejaculate during sex. Patients can take these drugs at home for the time before surgery. The side effects of the drugs decrease during this time as the body absorbs more salt and water to fill up the blood vessels, but you may still feel tired and become easily breathless and dizzy. The drugs are stopped after the tumour has been removed. In addition to alpha-blockade, a few patients may also need beta-blockers (propranolol or atenolol). These should only be prescribed when alpha-blockade is complete.

SURGERY

The main form of treatment for phaeochromocytomas is surgery. The type of surgery done depends on many factors such as the where the tumour is and its size. The surgery aims to remove the gland containing the tumour, in an operation called an adrenalectomy. Some tumours may be able to be removed using key-hole surgery (laparoscopic surgery) through a series of small cuts. Larger tumours may be removed using a larger single cut called an ‘open operation’.

The different types of adrenal gland tumour surgery are:

- Right hand (RH) adrenalectomy: removal of the right side adrenal gland only.
- Left hand (LH) adrenalectomy: removal of the left side adrenal gland only.
- Bilateral adrenalectomy: the removal of both adrenal glands at the same time.
- Partial adrenalectomy or cortical sparing-surgery: a small piece of the gland is left in the body to try to avoid the need for steroids (sometimes possible).

HOSPITAL STAY

Before surgery for alpha-blockade - you may need to stay in hospital for up to 7 days before surgery to make sure that the drugs are working well and that all your fluid levels are good.

After surgery - you will usually spend 2-4 days in hospital after key-hole surgery, and longer after open surgery.

Risks

Sudden surges in blood pressure during surgery could cause stroke and heart failure. However, these risks have been greatly reduced since the use of alpha-blockade and other potent drugs began. Some patients with tumours in both glands at the same time may be able to have a type of surgery which leaves a part of the outer rim of the gland behind. This needs a surgeon who is experienced with this type of surgery. You should discuss the

pros and cons of this with your surgeon and medical team.

If both glands are removed, you will need to take life-long steroid medication to replace the hormones made by the adrenals. The Addison's Disease Self Help Group (ADSHG) supports patients with Addison's Disease who also need lifelong steroids. They are a great source of information on how to deal with life on steroids (see Useful Organisations).

The two main drugs that a patient must take after both adrenal glands have been removed are hydrocortisone and fludrocortisone. They replace the hormones cortisol and aldosterone which are made by the glands. The drugs take over keeping blood sugar levels normal, aiding recovery from injury and stress, and keeping the balance of salts and water content of the body normal.

MEDICATION AFTER SURGERY

Glucocorticoids (e.g., hydrocortisone or prednisolone) - these tablets must be taken every day for life. Depending on the type of tablet prescribed, doses may either be split during the day or taken just in the morning. An increased dose should be taken at times of illness. At times of extra stress such as surgery, injury, severe vomiting and diarrhoea, extra hydrocortisone (100ml IV or IM) injected in liquid form (Efcortesol or Solucortef) is needed straight away. The injection helps to stop the risk of shock which leads to loss of blood pressure and death. For this reason, all patients should carry an emergency injection kit. They should also be shown how to self-inject before they leave hospital after surgery to remove both glands.

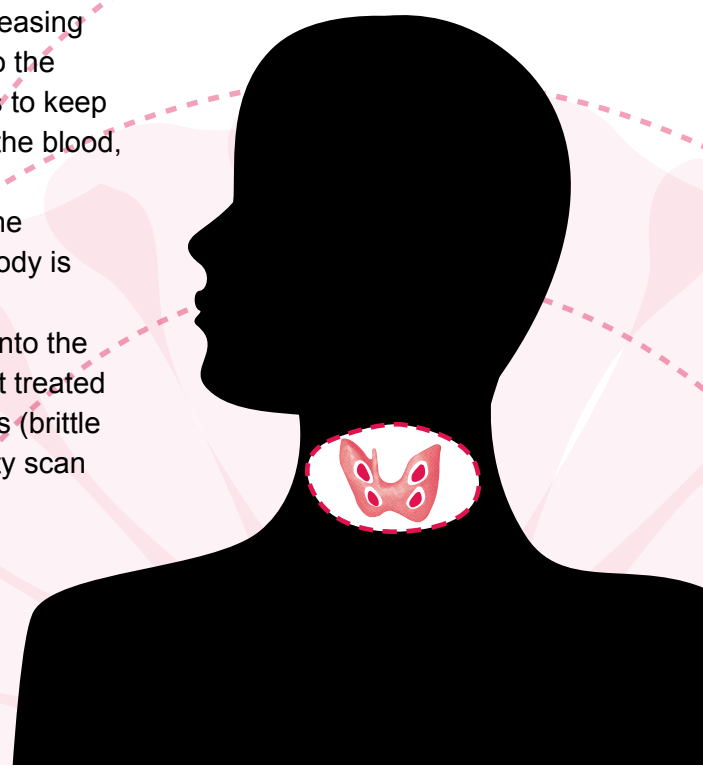
Mineralocorticoids (e.g., fludrocortisone) – these tablets must also be taken once a day for life. Tablets are taken early in the morning and doses may vary.

Regular blood tests are very important to check the levels of these drugs. This must be overseen by an experienced endocrinologist.

Parathyroid Tumours

Tumours in the parathyroid glands cause higher than normal levels of parathyroid hormone (PTH). They occur in fewer than 1 in 4 MEN2A patients.

The parathyroid glands lie just next to or are sometimes within the thyroid gland in the neck. As such they are often unavoidably removed during thyroid surgery for MTC. The parathyroids regulate the amount of calcium in the body. They do this by releasing parathyroid hormone into the bloodstream which helps to keep the supply of calcium in the blood, bones and urine normal. When tumours grow in the parathyroid glands the body is fooled into releasing calcium from the bones into the bloodstream. If this is not treated it can cause osteoporosis (brittle bones), so a bone density scan is sometimes advised. Another problem caused by parathyroid tumours is when there is too much calcium in the urine, which may lead to kidney stones. These days though, most patients have very few of these symptoms. This is particularly true when they are found and treated early.
Even a small rise in the body's level of calcium can cause a wide range of symptoms. Please note that many of these symptoms may be caused by problems other than parathyroid tumours:



Symptoms of HYPERcalcaemia		
+ calcium	**++ calcium**	**+++ calcium**
• Thirst leading to excessive urination (at night) • Tiredness • Aches and pains • Indigestion • Depression • Mild memory impairment	all of the previous plus: • Muscle weakness • Constipation • Loss of appetite and nausea	all of the previous plus: • Tummy pain • Vomiting • Dehydration • Abnormal heart rhythms • Coma • Inflamed pancreas • Bone pain • Bone fractures • Difficulty walking

Adapted from: www.patient.co.uk/doctor/hypercalcaemia.html

Testing for Parathyroid Tumours

BLOOD TESTS

Blood Calcium (serum calcium) and PTH (parathyroid hormone) – simple blood tests done each year

SCANS

Sesta-MIBI (and ultrasound) of neck area - these scans may be done, not to diagnose parathyroid tumours, but to find where they are in order to prepare for surgery. A Sesta-MIBI scan takes around 2 hours. The radioactive Sesta-MIBI is injected into the patient where it is taken up by the affected gland(s). Pictures are taken of the area straight after the injection, and then 1 hour 45 minutes to 2 hours later. The affected glands are those that are still lit up at the end of the scan. Sometimes a CT or MR scan may also be needed.

Treating Parathyroid Tumours

Treatment involves removing the gland with the tumour by surgery. If all of the parathyroid glands are affected, a patient will have all of them removed (total parathyroidectomy).
At the time of a total parathyroidectomy, some surgeons choose to transplant part of a normal gland back into the body. This is often into the neck or arm. This may help to control the body's calcium levels, and if in time this gland develops a tumour itself, it may be easier to find and remove. After total parathyroidectomy, the patient will need lifelong calcium replacement medication with a form of Vitamin D (see below). Decisions regarding these issues will be discussed with you when you see your surgeon. Occasionally, a hormone called PTH may be used instead if analogues of vitamin D are a problem.
In MEN2A, all patients will have their thyroid gland removed (see treating MTC). During this surgery the parathyroids may unavoidably be removed as well.

SURGERY

The surgeon makes a cut of about 4-5cm at the base of the throat through which to remove the affected gland(s). It is possible for the patient to be up and about, eating and drinking the same or next day.

Total parathyroidectomy - removal of all glands
Partial parathyroidectomy - removal of an individual gland

HOSPITAL STAY

You will often need to stay in hospital for a few days only

Risks

The most common side effect of surgery is low calcium (hypocalcaemia) which can be treated. Low calcium can cause tingling fingers, toes and lips and sometimes cramping. This requires top-up replacement medication straight away. There is also a possible but rare risk of voice box or nerve damage. Often there are no obvious symptoms of very mild low calcium although some subtle signs are shown in the table overleaf:

Symptoms of HYPOcalcaemia		
- calcium	**- - calcium**	**- - - calcium**
• Tingling of the face and extremities (fingers and toes) • Pins and needles in the face and extremities (fingers and toes) ` These symptoms may be worse when crossing one's legs or sitting on the toilet for example.	all of the previous plus: • Muscle cramps • Clawing of hands or feet (tetany) • Chvostek's sign - twitching of the face, mouth or nose when the facial nerves just in front of the ear are tapped • Trousseau's sign – spasm of the hand and fingers when a blood pressure cuff is applied and pumped up to a pressure sufficient to block the hand's blood supply	all of the previous plus: • Convulsions • irregular heartbeat • Difficulty breathing Over a long period of time, low calcium can lead to: • osteoporosis • cataracts

CALCIUM REPLACEMENT MEDICATION *(required if parathyroid glands are injured or unavoidably removed along with the thyroid, or are all removed due to tumours)*

Calcium Carbonate *(Calcichew, Adcal)*

This is a chalk-like tablet that has to be chewed or sucked. This is often used as a short term "top-up" after surgery, but is not always needed life-long. If the patient begins to suffer from headaches, nausea and vomiting, this may show that the dose is too high or that these tablets are no longer needed.

Vitamin D3 *(cholecalciferol)*

This more common form of Vitamin D is given in capsule form but needs PTH to work to keep your calcium level normal. If this does not work, you may need to move to taking a Vitamin D Analogue.

Vitamin D Analogue *(calcitriol)*

This 'activated' form of Vitamin D may be given in a capsule form to help the body absorb calcium from the diet. It is taken once a day and is often the only life-long medicine needed after parathyroid surgery. This is used if your body cannot make parathyroid hormone (PTH) and needs more regular tests to make sure that calcium levels do not rise too high.

Magnesium supplement

This may be in the form of an injection or a tablet, but is rarely needed long-term.

Other associated MEN2A conditions

Hirschprung's Disease

Very rarely, some patients with MEN2A may also have a condition called Hirschprung's Disease (HD). This would usually occur in early childhood and is most often seen in specific gene changes (codons 609, 618 and 620). Even so, not everyone with these gene changes will have HD. The reason why some people do and others do not is still not known.

HD is a bowel condition caused by a lack of nerve cells in part of the bowel. Symptoms can include tummy pain, bloating and constipation. Children may also not weigh as much as they should. In some cases, HD might sometimes cause vomiting or diarrhoea.

HD can be seen using an x-ray. Sometimes a small piece of tissue from the bowel is removed and looked at under a microscope. This is called a rectal biopsy and may require an anaesthetic in older children.

HD can often be treated effectively by surgery in the hands of an experienced surgeon. Treatment may happen in stages over a period of several weeks or months. The section of bowel that is not working properly is removed and the two ends of the remaining healthy bowel would be joined together.

Lichen Amyloidosis

Cases of a skin condition called familial lichen amyloidosis have been seen in some families with MEN2A but this is very rare. This appears as itchy, raised, rash-like areas of skin that are slightly darker than the surrounding skin. These patches usually occur on the upper back in MEN2A and may be caused by repeated scratching (see Itchy Back below)

Itchy Back (Pruritis)

Many patients with MEN2A (codon 634) have a very itchy upper back. This often starts in childhood for reasons which are not yet understood. Repeated scratching in this area is thought to cause Lichen Amyloidosis *(see above)*.

Children and MEN2A

Deciding to have Children

There is a 1 in 2 (50%) chance that a child born to someone with MEN2A will also have MEN2A *(see genetic testing explained).* If a child is known to carry the gene change, testing and treatment plans may be set up from the start. In this way, conditions may be found and treated before serious symptoms develop.

Testing during pregnancy is available (PND) if the family's gene change is known. Pre-implantation Genetic Diagnosis (PGD) is now able to be used by people with MEN who want to start a family. PGD uses the IVF process but embryos are tested and only those that do not have the gene change are re-implanted back into the mother's womb. If families are considering PND or PGD, they should ask for a referral to one of the 23 UK clinical genetics centres before they become pregnant. PND or PGD is a personal choice, and often depends on the family's experience of the disease.

AMEND has produced a booklet called Starting a Family that can be downloaded for free from our website. The booklet expands on the information above.

Pregnancy and MEN2A

Before becoming pregnant, women with MEN2A should be tested for phaeochromocytoma. An undiagnosed phaeo can cause a life-threatening crisis during birth. Doses of medications already being taken may need to be changed during pregnancy. For example, mothers who have had both adrenal glands removed and who are taking corticosteroid medications will need extra doses for during the birth. They will also need more regular blood tests to check levels, and more regular antenatal checks.

AMEND has a private Facebook Group for those who are thinking about starting a family. Join AMEND for free and request to join the Group to meet others making similar decisions.

DNA Testing for Children

Children of a parent with a known MEN2A gene change can be offered a genetic test to find out if they also carry the gene. This is usually offered soon after birth. The test may be done using a blood sample or in some cases, using a cheek scraping or saliva sample. You should discuss this with a genetic counsellor at your Regional Genetics Services Centre.

Talking to Your Children About MEN2A

AMEND produced an information leaflet on this subject. You can download this for free from our website (www.amend.org.uk). The leaflet suggests ways in which to broach the subject of your family's MEN2A with your children, along with how much to tell them according to their age.

Explaining MEN2a to Your Children

Thanks to an award from the UK Big Lottery Fund, AMEND commissioned a kids' Medikidz™ comic on MEN2, called 'Medikidz Explain Multiple Endocrine Neoplasia Type 2: what's up with Cameron?'. Aimed at 8–12-year-olds, the comic explains MEN2A as simply as possible in an engaging way. It is a great tool to help you explain MEN2A to children in this age group. The comic is free and available through your specialist or directly from AMEND. An entertaining and simple web animation aimed at ages 5 years and up is also available to view in the children's area of the AMEND website or on our YouTube Channel (AMEND3).

Treatment and Testing Recommendations in Children

MEDULLARY THYROID CANCER (MTC)

Baseline Calcitonin - a simple blood test to detect changes in the thyroid (C-cell hyperplasia or MTC)

For a child with a known MEN2A gene change, a total thyroidectomy to prevent MTC is recommended in most children before the age of 5, depending upon the exact gene change.

PHAEOCHROMOCYTOMAS *(uncommon before age 10)*

Plasma (blood) metanephrines / normetanephrines and 24-hour urine collections (annual or 6 monthly)

Young children find the novelty of weeing into a bottle for a day rather exciting, which makes 24-hour urine tests quite easy to do.

A phaeo found on testing will need to be removed by surgery. The geneticist will be able to advise you on this.

In the hands of an experienced surgeon and team, many children cope much better with surgery than some adults.

Older Children

Older children of a newly diagnosed parent should be tested straight away due to the high chance of having MTC in MEN2A.

Blood Tests

There are many adults who find blood tests difficult, so no parent should be surprised if their child develops a strong dislike of them too. For small children, many hospitals use a cream covered by plasters to numb the hands and/or arms ready for the test. The cream takes up to an hour to work during which time the child may focus on the area and become distressed. It is often quicker and easier either not to use the cream at all or to use an anaesthetic spray instead. A phlebotomist experienced in doing children's blood tests is important to ensure as few jabs and as little distress for the child as possible.

Transition

Transition is the process of moving from children to adults' specialist healthcare services. It refers to the full process including initial planning, the actual transfer between services, and the support required throughout. A good transition is essential to make sure that young people do not 'fall out' of healthcare services, in order to keep them as healthy as possible.

Young people and their parents or carers will all be involved in discussions with the doctor to decide when to begin transition and to manage expectations. Transition may often begin as early as around 11 years old. However, in young people with learning disabilities, this may be much later, or they may remain in children's services. At the beginning of the process, young people should expect to be assigned a key, named worker, be given a Transition Care Plan

and a Personal Transition Folder containing important contact details, medical details, education/ social care needs, future goals and emergency plans.
During the process, a doctor from adult services may attend the children's services hospital appointments and vice versa. This helps a young person become familiar with the staff who will be caring for them in adult services, even if these will be in a different hospital. Between ages 16-25 they should be seen in a Young Adult service, usually based in the adult services. For the first couple of appointments, they should see the same doctor so that they settle in well to adult services environment.
AMEND has developed some resources including videos for young adults that can be found on our website. In addition, we have 2 moderated peer support WhatsApp Groups for ages 13-17 and 18-30 where your young people can meet others in similar situations. You can find more information about the Groups on our website.

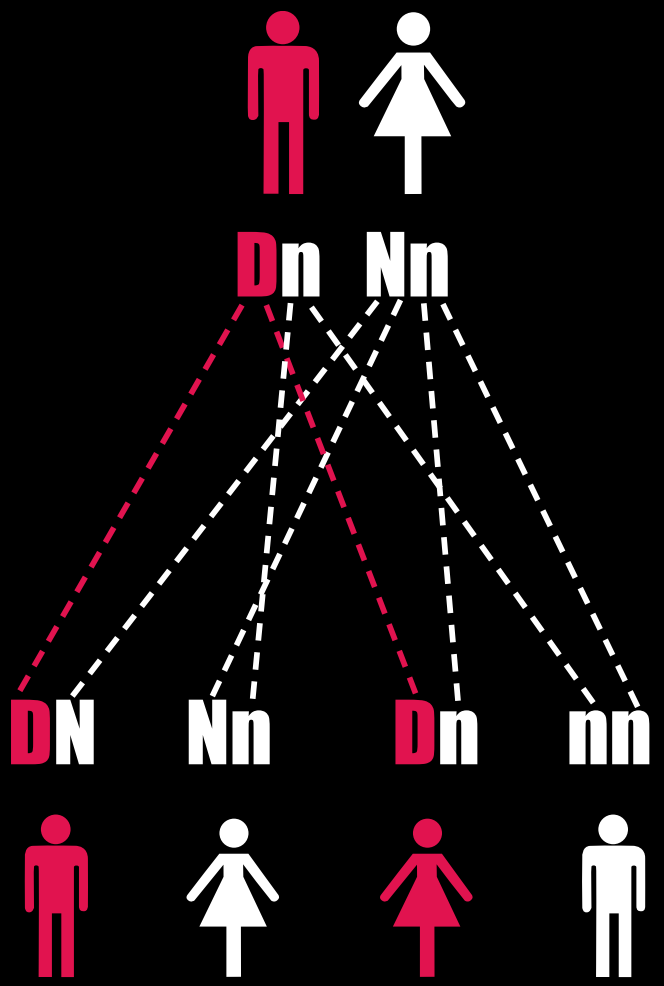
Genetic Testing Explained

Chromosomes and Genes

n each cell of the body there are 23 pairs of chromosomes that contain our genes. We inherit one chromosome from each pair from each parent. This means that we inherit one copy of each gene from each of our parents, thereby giving us two copies.

In most people there are two normal functioning MEN2A (RET) genes. In patients with MEN2A, one of this pair has a change.

When someone with MEN2A has a child, they can pass on either the normal gene or the gene with the change. This is random, like tossing a coin. Each child of a parent with MEN2A thus has a 1 in 2 or 50% chance of inheriting the RET gene change (coloured red, over page). This child would then be at risk of developing the tumours of MEN2A. This method of inheritance is called autosomal dominant inheritance.



What are codons and why do they matter?

There are a number of different changes at different positions in the RET gene. The position of the change (e.g., codon 634) may help to predict the course of disease in a person. In some cases, this can help doctors to plan tests and treatments, including for example, the age of prophylactic thyroidectomy (see 'Recommended ages for tests and thyroid surgery in MEN2A' on page 5).

Genetic Testing

It is possible in some families to have a genetic test to see whether someone has inherited the RET gene change. The first step is to have a blood sample tested from someone with MEN2A in the family. With this test (mutation screen), the result may not be received for some weeks or even longer. Sometimes the gene change may not always be found. If the gene change is found, another blood test (predictive genetic testing) may then be offered to other members of the family. The results from predictive genetic testing are received normally within several weeks. There are a number of issues with predictive genetic testing particularly in relation to children and as such, all patients should be seen and counselled by a consultant
clinical geneticist. If the gene change cannot be found or if a blood sample from an affected person cannot be obtained then predictive genetic testing cannot be done.
Having children tested is a very individual decision, however; if children of a known MEN2A parent are tested, those who have not inherited the gene change can rest assured that no further tests are required. Those who have inherited the gene change can be comforted by the fact that testing and treatment plans will show as early as possible when treatment is required. Thanks to this early detection by genetic test, complications from advanced MTC, high blood pressure, stroke and heart failure due to phaeos, and kidney stones as a result of parathyroid tumours, may be greatly reduced.
Genetic testing and counselling is available at 23 regional genetic centres throughout the UK (www.bsgm.org.uk).
A referral to a genetic centre is made through your GP or specialist.

Emotional Well-being

Living with a rare genetic disorder is not always easy. Some people cope better than others, but most people will have periods of low mood at some point along the way. It is now better recognised that overall health depends upon both physical and emotional health. For this reason, AMEND offers a free telephone counselling service to registered members. In addition, AMEND's Counsellor is sometimes available for face-to-face sessions at our free events. See our website for more details.
AMEND has produced some specific resources that we are sure patients will find useful. 'Dealing with Diagnosis', 'Living with Uncertainty' and 'Looking after Yourself' are available to download for free from the Resources section of AMEND's website or in hard copy on request. A series of podcasts and an introductory video on the relaxation method, Mindfulness, have also been developed as part of this project and are free to access via our website and YouTube Channel (AMEND3).

"Really great help, we are very grateful to [AMEND's Counsellor] and her support. She was exactly what we needed to help us cope with the diagnosis and to regain a positive vision towards dealing with it in our lives!!"

Useful Information

FREE PRESCRIPTIONS

n the UK, if you need to take lifelong hydrocortisone or levothyroxine, you are entitled to free prescriptions for all medicines. You should obtain a FP92A application form from your doctor and complete parts 1 and 2. Your doctor will then sign it and send it on. You will then receive a Medical Exemption Card, which you must show to your pharmacist when collecting medicines. You can find more information on Medical Exemption Certificates on the following website: www.nhsbsa.nhs.uk/HealthCosts/2095.aspx

MEDICALERT®

AMEND recommends that anyone taking lifelong medications obtain and wear a MedicAlert® identification emblem. The emblem contains summarised information of your medical condition and a 24-hour Helpline number for emergency medical staff to call in order to obtain detailed information on your medical condition from the MedicAlert database. This enables emergency medical staff to give appropriate treatment in full knowledge of your underlying condition and current medications. Emblems come in a range of styles so that there is something for everyone, even children. Telephone AMEND for an order form and brochure or join and order online at www.medicalert.org.uk. Other medical identification products are available.

Useful Organisations

The British Thyroid Foundation
Tel: 0870 770 7933
www.btf-thyroid.org

Addison's Disease Self Help Group (ADSHG)
Tel/Fax: 01483 83073
www.adshg.org.uk

Parathyroid UK
Tel: 01342 316315
www.parathyroiduk.org

You and Your Hormones (Society for Endocrinology)
www.yourhormones.info/

Glossary

Adrenal Glands a pair of walnut-sized organs found above the kidneys that make stress hormones.

Autosomal Dominant Inheritance when the child of a parent with a genetic condition has a 50% or 1 in 2 chance of inheriting that condition from the affected parent

Calcitonin a hormone made by the C-cells of the thyroid gland that has no known action in healthy people

Catecholamine a class of stress hormones made by the adrenal glands

CEA short for carcinoembryonic antigen; a substance that can be measured as a marker for MTC

Chemotherapy cancer treatment using chemicals

Chromosomes cell structures that contain genes

Codons sections of genes where mutations may occur to cause disease

De novo a new gene change that starts in that person and which has not been passed down from a parent

DNA short for deoxyribonucleic acid; the carrier of genetic information, stored in every cell in the body

Endocrine Glands organs in the body that make and release hormones which affect the activity of other organs

Gene structures made of DNA. A change in normal gene structure results in a mutation (i.e. RET gene mutation in MEN2)

Hormones chemical messengers in the body which drive different processes by controlling the function of many different organs

Hypercalcaemia a state of having too much calcium in the blood

Hypocalcaemia a state of having too little calcium in the blood

Medulla the central part of an organ

Metanephrines a substance in urine which is measured to help diagnose a phaeochromocytoma

Neoplasia abnormal level of growth in cells to form a tumour

Neuroendocrine tumours a body system consisting of nerve and gland cells that produce hormones and releases them into the bloodstream

Osteoporosis a condition caused by having hypocalcaemia over a long time period making bones break more easily than normal

Pancreatitis painful swelling of the pancreas

Parathyroid Glands four small organs found in the neck that make parathyroid hormone (PTH)

Phaeochromocytoma a growth in the inner part of an adrenal gland which makes greater than normal levels of stress hormones

PGD short for preimplantation genetic diagnosis; the screening out of embryos with a genetic disorder prior to implantation using an IVF-like procedure

PND short for prenatal diagnosis; the testing of a baby for genetic disorders before it is born

Radiotherapy a form of cancer treatment that uses X-ray radiation to destroy cancer cells

RET the name of the gene that, if containing a change, can cause MEN2A and MEN2B

Thyroid Gland a butterfly-shaped organ found in the neck that makes and releases hormones called thyroxine and triiodothyronine

Ulcer a painful sore on or inside of the body

AMEND UK Medical Advisory Team

- **Professor Rajesh Thakker**, University of Oxford, Oxford Centre for Diabetes,Endocrinology & Metabolism
- **Dr Caroline Brain**, Consultant Paediatric Endocrinologist, UCLH & GOSH, London;
- **Professor Ashley Grossman**, Royal Free Hospital, London
- **Professor Maralyn Druce**, Consultant Physician and Endocrinologist, Bart's Health NHS Trust, London
- **Dr Fiona Lalloo**, Consultant Clinical Geneticist, St Mary's Hospital, Manchester;
- **Mr David Scott-Coombes**, Department of Surgery, University Hospital of Wales, Cardiff;

Afterword

This book has been written for MEN patients by MEN patients with the help of a medical advisory team. The aim of this book is to answer those questions, sometimes in great detail, that one may come across during a lifetime of living with MEN2A. It is not for use in self-diagnosis. It contains detailed information on tests, surgery and potential symptoms associated with MEN2A. However, it is possible that not all of this information will be relevant to you. This book is not intended to replace clinical care decisions and you should always discuss any concerns you have with your specialist. Every care has been taken to ensure that the information contained in this book is accurate, nevertheless, AMEND cannot accept responsibility for any clinical decisions.

About AMEND

AMEND is a Charitable Incorporated Organisation registered in England and Wales (number 1153890). It provides support and information services to families affected by multiple endocrine neoplasia and related endocrine tumours. AMEND encourages research into the conditions by awarding annual medical prizes and research awards. It hosts regular free patient information events every year and runs social media forums connecting patients from around the world.

Please visit our website for more information on AMEND or to make a donation: www.amend.org.uk

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Follow us on Twitter (@AmendInfo)

Scan to go to our website:

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