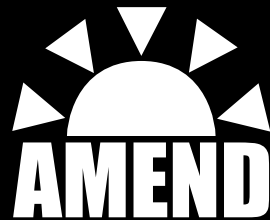


# MEN 1

**Patient Information**  
Multiple Endocrine Neoplasia Type 1



Association for Multiple Endocrine Neoplasia Disorders  
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## What is Multiple Endocrine Neoplasia Type 1?

Multiple Endocrine Neoplasia Type 1 (MEN1) is a condition that can be passed down in families. MEN1 causes more than one gland of the body's endocrine system to develop growths (tumours) known as neuroendocrine tumours (NETs). 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 growth may occur alone and separate from MEN. Multiple = more than one  
Endocrine = gland system  
Neoplasia = increase in growth of cells to form a tumour

*"AMEND has helped me so much over the past 8 years. MEN1 changed my life and at times it has been a bit of a struggle but I wouldn't have coped so well if I hadn't had the support network of AMEND!"*

## ***How is MEN1 Diagnosed?***

A person is said to have MEN1 if they have:

1. 2 or more tumours that occur in MEN1 (see What Conditions are Associated with MEN1); or
2. Only one tumour, but there is a family history of relatives with MEN1; or
3. A blood test that shows a change in a gene that is known to cause MEN1.

A patient may have a gene change that causes MEN1, but not have developed any of the tumours. This patient may be called an “MEN1 carrier” and should be offered endocrine follow-up in clinic in the same way as a patient with the MEN1 tumours.

## ***What Tumours are Associated with MEN1?***

There are three main types of tumour linked to MEN1. The tumours are usually benign (not cancer). These are found in:

1. The parathyroid glands in the neck;
2. The endocrine pancreas and gut (duodenum); and
3. The pituitary gland near the base of the brain behind the nose.

More than 8 out of 10 (80%) of MEN1 patients will have developed at least one of the tumours or have extra activity in a gland by the age of 40. This is around 4 out of 10 (40%) by the age of 20. Younger cases have been recorded. The condition varies greatly even within families, so that not everyone will have the same tumours and nor will they occur at the same age. Not all MEN1 patients will have all of the tumours detailed in this book. The first line of tests for most of the tumours linked to MEN1 is the checking of hormone levels using blood tests and scans of the head, neck and tummy area. If a tumour is found, surgery may be needed to remove just the tumour or the whole of the affected gland. The rest of this book is divided up between these tumours and explains what the current tests, treatment and medicines are.

## ***Parathyroid Tumours***

**Over-activity or tumours in the parathyroid glands cause primary hyperparathyroidism (high level of parathyroid hormone - PTH). These occur in more than 9 out of 10 (90%) of MEN1 patients by age 40.**

The parathyroid glands lie just behind the thyroid gland in the neck, although sometimes there are extra glands in the upper chest. Rarely, they may be found inside the thyroid gland.

The parathyroids are responsible for regulating the amount of calcium present in the body by releasing parathyroid hormone into the blood. This helps to keep the levels of calcium normal in the blood, bones and urine.

When tumours grow in the parathyroid glands, they lead to extra amounts of parathyroid hormone being made. This causes



calcium to be released from the bones into the blood, resulting in a rise in the level of calcium (hypercalcaemia). If left untreated this can cause osteoporosis (brittle bones) or kidney stones. These days, most patients have very few of these problems when diagnosed and treated early. High calcium levels can result in no symptoms at all, but in some people, even a small rise in the body's level of calcium can cause a wide range of symptoms:

## Testing for Parathyroid Tumours

### Blood Tests

#### Blood Calcium (serum calcium)

Simple blood test done every year (from 5-10 years)

#### Parathyroid Hormone (PTH) – even if blood calcium level is 'normal'

Simple blood tests done each year (from age 5-10 years).

### Scans

#### Sesta-MIBI (and ultrasound) of neck area

These scans may

be done, not to diagnose affected parathyroids, 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.

#### CT Scan

A computerised tomography (CT) scan uses X-rays and a computer to create detailed images of the inside of the body. In some cases you may need an injection of a contrast fluid to make the images clearer.

#### Ultrasound

A painless scan of the neck area using a probe running over the skin.

## Treating Parathyroid Tumours

Treatment involves removing the glands with tumours by surgery. These days, most surgeons will remove most of the parathyroid glands and just leave half of one gland (remnant) behind to help control the body's calcium levels

(sub-total parathyroidectomy). If the remnant does not begin to work again, the patient will need lifelong medicine in the form of activated Vitamin D (see below) which helps the body to maintain a healthy level of calcium. Decisions regarding these issues will be discussed with you when you see your surgeon. In MEN1, extra parathyroid glands may often be found in or around the thymus in the upper chest. Therefore many surgeons also perform a thymectomy (removal of the thymus gland in the upper chest) at the same time as total parathyroidectomy. Removal of the thymus may also reduce the risk of developing a thymic neuroendocrine tumour (see Other Tumours Linked to MEN1).

## 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.

**Sub-Total Parathyroidectomy** – removal of 3½ glands, leaving ½ a gland behind (remnant in situ)

### Symptoms of HYPERcalcaemia

+ calcium	++ calcium	+++ calcium
<ul style="list-style-type: none"> <li>Thirst leading to excessive urination (at night)</li> <li>Tiredness</li> <li>Aches and pains</li> <li>Indigestion</li> <li>Depression</li> <li>Mild memory problems</li> </ul>	all of the previous plus: <ul style="list-style-type: none"> <li>Muscle weakness</li> <li>Constipation</li> <li>Loss of appetite and nausea</li> </ul>	all of the previous plus: <ul style="list-style-type: none"> <li>Tummy pain</li> <li>Vomiting</li> <li>Dehydration</li> <li>Abnormal heart rhythms</li> <li>Coma</li> <li>Inflamed pancreas</li> <li>Bone pain</li> <li>Bone fractures</li> <li>Difficulty walking</li> </ul>

**Total Parathyroidectomy** – removal of all glands

**Partial Parathyroidectomy** – removal of a single gland. Not usually done in MEN1 as multiple surgeries in the same area causes scar tissue that can increase risk of nerve damage.

### Hospital Stay

Usually a few days

### Risks

The most common side effect of surgery is low calcium

(hypocalcaemia) that can be treated. Low calcium can cause tingling fingers, toes and lips and sometimes cramps. This needs top-up replacement medicine straight away which can be needed either for a short time or for much longer. There is also a possible but rare risk of nerve damage which might affect the voice.

Often there are no obvious symptoms of very mild low calcium, although some subtle signs are shown in the table below:

### Symptoms of HYPOcalcaemia

- calcium	- - calcium	- - - calcium
<ul style="list-style-type: none"> <li>Tingling of the face, fingers and toes</li> <li>Pins and needles in the face, fingers and toes</li> </ul> <p>These symptoms may be worse when crossing one's legs or sitting on the toilet for example.</p>	<p><u>all of the previous plus:</u></p> <ul style="list-style-type: none"> <li>Muscle cramps</li> <li>Clawing of hands or feet (tetany)</li> <li>Chvostek's sign -twitching of the face, mouth or nose when the facial nerves just in front of the ear are tapped</li> <li>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</li> </ul>	<p><u>all of the previous plus:</u></p> <ul style="list-style-type: none"> <li>Convulsions</li> <li>irregular heartbeat</li> <li>Difficulty breathing</li> </ul> <p>Over a long period of time, low calcium can lead to:</p> <ul style="list-style-type: none"> <li>osteoporosis</li> <li>cataracts</li> </ul>

## MEDICATION

**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** (ergocalciferol)

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 to high.

**Magnesium supplement**

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

**Calcimimetics** (Cinacalcet)

Calcimimetics are medicines that pretend to be calcium to trick the body into stopping making parathyroid hormone in order to lower blood calcium levels. This medicine may be used if the source of hyperparathyroidism cannot be found or if it is not possible for a patient to have surgery for other reasons. Calcimimetics can cause side effects including low blood calcium or nausea (and sometimes vomiting).

**Parathyroid Hormone Replacement Therapy (PTH-RT)** (Teriparatide)

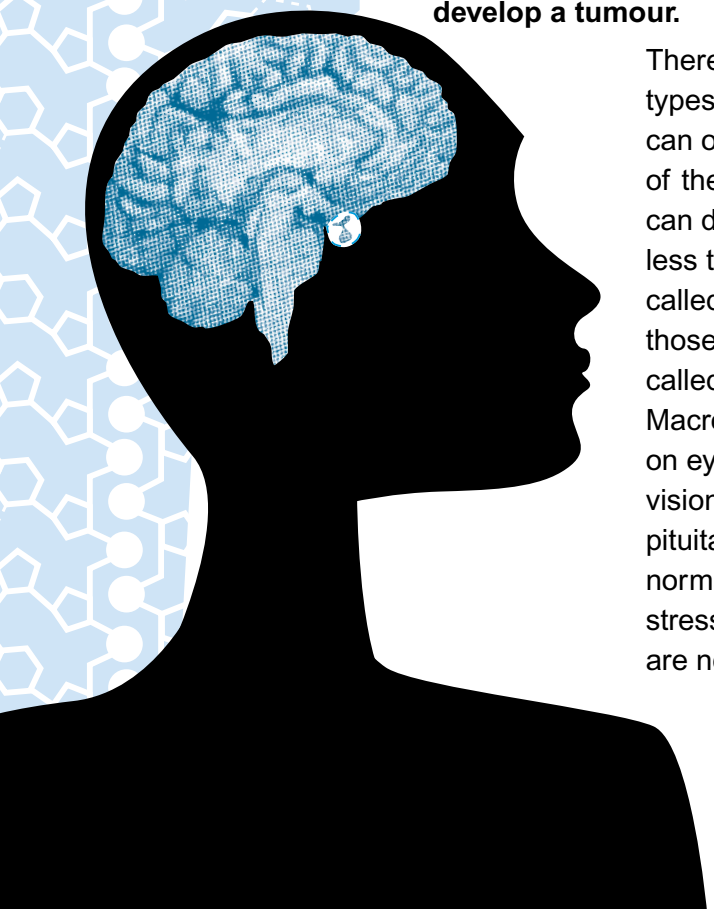
Also known as recombinant human parathyroid hormone, this is given by injection. It is a man-made hormone that acts like PTH to help keep calcium levels in the normal range. It may be given if your calcium levels cannot be controlled by using Vitamin D Analogues.

TYPE OF TUMOUR	ACTION OF TUMOUR	POSSIBLE SYMPTOMS	OTHER INFORMATION
<b>Prolactinomas</b>	Overproduces the hormone prolactin	Headaches, vision problems if the tumour is large. Women: lactation (breast milk production) without pregnancy, lack of periods, may lead to infertility Men: erectile dysfunction and infertility	Most common pituitary tumour
<b>Somatotrophinoma</b>	Overproduces the growth hormone (GH) – also called somatotropin	Causes a condition known as Acromegaly (or gigantism) which causes greater growth than normal in body parts such as the jaw, hands and feet.	Growth hormone (Somatotropin) is the main hormone required for normal growth in childhood and adolescence
<b>ACTH-producing</b>	Overproduces the hormone Adrenocorticotropin (ACTH). ACTH controls the production and release of the adrenal gland hormone cortisol, which in turn helps maintain blood pressure, blood sugar levels, helps with recovery from injury and stress, and regulates the balance of mineral salts and the water content of the body	Causes a condition known as Cushing's Disease. Symptoms include weight gain, flushing on the face and neck, excess growth of body and facial hair, change of body shape and raised blood pressure.	
<b>Non-functioning</b>	Produce no obvious hormone	May cause no symptoms. Sometimes cause headaches.	

### ***Pituitary Tumours***

The pituitary gland sits near the base of the brain behind the nose and under part of the eye nerves in a bony hollow called the sella turcica. Even though it is the size and shape of a bean, it is the master gland of the body's endocrine system. Pituitary hormones are important for growth and development, metabolism (turning food into energy) and reproduction. **In around 30% (3 in 10) of MEN1 patients, the pituitary gland will develop a tumour.**

There are a few different types of pituitary tumour that can occur in MEN1. None of them is cancerous. They can differ in size, with those less than 10mm in diameter called microadenomas, and those of more than 10mm called macroadenomas. Macroadenomas can push on eye nerves and cause vision problems, or stop the pituitary gland from working normally. It is important to stress that pituitary tumours are not 'brain tumours'.



## Testing for Pituitary Tumours

All forms of pituitary tumour may be found using an MRI or CT scan of the head.

### PROLACTINOMAS

#### Blood Tests

**Serum prolactin** A simple blood test (annual from age 5-10 years)

**Thyroid function (to exclude other causes of increased prolactin production)** A simple blood test (annual from age 5-10 years).

#### Scans/Other

**MRI/CT scan** Annual if a tumour is being monitored or 3-5 yearly while the pituitary appears normal

**Visual Field Examination** Simple eye test to monitor possible effects of a pituitary tumour.

### SOMATOTROPHINOMAS

*Tests performed if symptoms are present.*

#### Blood Tests

**IGF-1 (Insulin-Like Growth Factor-1)** A simple blood test (if result is abnormally high, further tests will be done, as below)

**Serum Growth Hormone Day Curve** Simple blood tests done over the course of a day

#### **Oral glucose tolerance test**

Taking a drink of glucose followed by simple blood tests over 2-3 hours

#### Scans/Other

**MRI/CT scan**

**Baseline pituitary scan**

### ACTH-PRODUCING

*Tests performed if symptoms are present*

#### Blood Tests

**ACTH and cortisol** usually done first thing in the morning when ACTH levels are highest, and at midnight

**Dexamethasone suppression test (overnight or 2 days)** Taking a steroid tablet or tablets followed by simple blood and/or urine tests

#### Scans/Other

**MRI/CT scan** of the pituitary, adrenals and lung/abdomen

**Baseline pituitary scan**

**Chest x-ray**

**24 hour urine collections** Simple collections of urine over the course of 24 hours to measure cortisol levels.

## Treating Pituitary Tumours

Treatment may be in the form of medicine or surgery. This will depend upon the type of tumour and its size. Sometimes small tumours can be treated with tablets or injections. In some cases (rarely) radiotherapy is needed if surgery alone does not control the growth.

### PROLACTINOMAS

Medicine called a **dopamine agonist** (e.g. bromocriptine, cabergoline; or quinagolide), to reduce the production of prolactin. Tablet doses vary according to the size of the tumour and the amount of prolactin it makes. In some cases surgery (transsphenoidal surgery), radiotherapy, or both may be needed.

### SOMATOTROPHINOMAS

Treatment will depend upon the size of the tumour and the age of the patient. Surgical removal (transsphenoidal surgery) of the tumour is the most common treatment; however, radiotherapy

either alone or after surgery may also be used in order to reduce growth hormone levels. Treatment with injections of somatostatin analogues (octreotide or lanreotide) may also be helpful.

### ACTH-PRODUCING

Surgical removal (transsphenoidal resection) of the tumour from the pituitary gland, followed by radiotherapy if this is not completely successful. Treatment with tablets or injections may also be needed to control the hormone production from the adrenal glands caused by the ACTH

## SURGERY

### Transsphenoidal Resection

This is the most common surgery to remove the pituitary gland tumour. It is a relatively small operation carried out under general anaesthetic. The surgeon makes a small cut inside the nose. This way the surgeon can reach the pituitary gland without having to operate on the main part of your head. Patients can eat normally the following day.

### Hospital Stay

Usually 2-5 days

### Recovery Time

Recovery time from surgery is about 1-2 weeks. It may take several weeks or months for symptoms to improve.

### Risks

#### Diabetes insipidus

sometimes occurs after pituitary surgery. Although not related to diabetes, the symptoms are similar and include a great thirst and the need to pass urine more often than normal. If the condition becomes permanent, it can be treated using a drug called desmopressin. Rarely, after treatment, some patients will need long term medicine to replace other hormones (such as sex hormones, thyroid hormone, or corticosteroids), or may need other treatment in the form of radiotherapy, or a somatostatin analogue (octreotide or lanreotide).

### RADIOTHERAPY

This may be used to shrink a pituitary tumour that cannot be treated with medicines or surgery. It may also be used after surgery to decrease the chance of the tumour re-growing. An MRI scan is used to plan the radiation field, and then the treatment is given by pointing the radiation beam via 3 targets to focus on the pituitary gland. This is quite painless, and is usually given for 5 days a week over 5 weeks, giving 25 treatments altogether. Each treatment is usually over in half an hour, and most patients can carry on their normal life throughout although they may tire more easily than usual. Sometimes a different kind of targeted radiotherapy (called gamma knife therapy) may be suggested which is given in a single dose.

## Pancreatic Neuroendocrine Tumours

**Tumours of the pancreatic islet cells occur in up to 75% (3 in 4) of MEN1 patients.**

The pancreas is responsible for producing juices (digestive enzymes) to help the body to digest food. It also makes hormones to control blood

sugar levels in the body which are important as the main source of energy for the body. Some hormones made in the islet cells are:

- insulin, which lowers blood sugar levels;
- glucagon, which raises blood sugar levels;
- gastrin, which increases the amount of acid in the stomach and can cause ulcers; and
- somatostatin, which has effects on the release of growth hormone from the pituitary and on various other hormones.

The tumours usually occur in clusters of more than one. Up to half are capable of becoming cancerous if left untreated. The varied tumours occur in differing cells of structures within the pancreas called the Islets of Langerhans and are often referred to as pancreatic neuroendocrine tumours (PNETs). About 10% (1 in 10) of MEN1 patients may develop more than one type of pancreatic tumour at one time. Most of these tumours will make greater than normal amounts of hormones, however some may not make any extra hormones and are called 'non-functioning'.



TYPE OF TUMOUR	ACTION OF TUMOUR	POSSIBLE SYMPTOMS	OTHER INFORMATION
<b>Gastrinomas</b>	Overproduces the hormone gastrin	Stomach (peptic) ulcers and diarrhoea, together sometimes referred to as Zollinger-Ellison syndrome	Most common MEN1 pancreatic tumour. Gastrinomas can also occur in the duodenum (gut).
<b>Insulinomas</b>	Overproduces the hormone insulin	Sweating and faintness due to low blood sugar levels (hypoglycaemia)	Usually located in the tail (end) of the pancreas
<b>Glucagonomas</b>	Overproduces the hormone glucagon	Skin rash and high blood sugar levels (hyperglycaemia)	
<b>VIPomas</b>	Overproduces the pancreatic protein, vasoactive intestinal peptide	Severe diarrhoea	Very rare tumour whose effects are referred to as being Verner-Morrison syndrome. Only reported in a few MEN1 patients
<b>Non-Functioning</b>	Do not appear to overproduce any hormones	None	

## Testing for Pancreatic Neuroendocrine Tumours

Many pancreatic tumours, including non-functional adenomas, may be found by a CT or MRI scan, although other types of scans may be needed if the tumours are very small. These include endoscopic ultrasound, where an ultrasound probe is passed down the throat to the gut (duodenum) on the end of a glass fibre cable, scanning with a radioactive form of somatostatin, or sampling from the veins of the liver while injecting tiny amounts of calcium into different arteries that supply the pancreas. In addition:

### GASTRINOMAS

#### Blood Tests

**Serum gastrin** A simple blood test after an overnight fast (annual from age 20 years).

#### Scans/Other

**Basal acid output** Rarely performed test where a tube is passed into the stomach (i.e. naso-gastric tube) to measure acid output.

### INSULINOMAS

#### Blood Tests

**Fasting glucose** A simple blood test after an overnight fast (annual from age 5-10 years). If a longer fast is needed (48-72 hours), this can be done in the hospital as an inpatient.

**Insulin** A simple blood test taken at the same time as the fasting glucose (annual from age 5-10 years).

#### Scans/Other

**Baseline scan** (annual or 3-yearly).

### OTHER TUMOURS

#### Blood Tests

**Chromogranin A/ Proinsulin/ Glucagon**

Simple blood tests done after an overnight fast (annual from 20 years).

#### Scans/Other

**MRI scan/CT scan/Octreotide scan or <sup>68</sup>Gallium-Dotatate PET scan** (annual or 3-yearly from age 20 years). Just for insulinomas, some centres outside the UK are offering more specific radionuclide scans. It is hoped that these may become available in the UK soon.

**Angiogram** Test done by radiologist to find the location of a tumour and its blood supply. Rarely done now unless in combination with a calcium stimulation test.

## ***Treating Pancreatic Neuroendocrine Tumours***

The treatment of pancreatic tumours will depend upon the size and type of tumour, and where it is located on the pancreas.

### **GASTRINOMAS**

Single gastrinomas may be removed by surgery; however, because they usually occur in clusters, opinion varies as to the effectiveness of surgery in this case. Indeed, the possible ulcers and diarrhoea caused by gastrinomas can be controlled in most patients using one of a number of anti-ulcer drugs called proton pump inhibitors (PPI), such as lansoprazole, and H2 blockers, such as cimetidine or ranitidine. Both types of drug aim to control the production of stomach acid,

which reduces the symptoms of ulcers. The doses of PPIs used to control the effects of gastrinomas are often much higher than the doses used in other patients.

### **INSULINOMAS**

Surgery is the main treatment in MEN1 patients with hypoglycaemia due to insulinoma. The drug diazoxide may be used to treat the hypoglycaemia while waiting for surgery, or after surgery if the tumour is hard to find.

### **OTHER (NON-FUNCTIONING) TUMOURS**

Surgery is the main treatment if and when a tumour grows to 2cm in width.

## **SURGERY AND MEDICATION**

### **Pancreatic Enucleation**

This involves the removal of only the tumour itself by either laparoscopic (key-hole) or open surgery.

#### **Hospital Stay**

About 1 week.

### **Recovery Time**

About 2-3 weeks depending on type of surgery.

### **Risks**

Inflammation of the pancreas (pancreatitis) causing severe pain in the upper abdomen and back. Leakage from the stump (pancreatic fistula) which may lengthen the hospital stay but does not usually need more surgery.

### **Medicines**

Some surgeons use octreotide treatment for a short time after surgery to reduce the risk of possible complications. No medicines long-term.

### **Distal Pancreatectomy**

This involves the removal of the body and tail of the pancreas.

#### **Hospital Stay**

About 1 week.

#### **Recovery Time**

About 1 month.

### **Risks**

Same as for pancreatic enucleation above. There is a risk that the spleen may have to be removed. If more than 80% of the

pancreas is removed, diabetes mellitus may occur.

### **Medicines**

**Pancreatic Enzymes** taken with food to aid its digestion.

**Insulin injections** to replace the insulin normally secreted by the pancreas if diabetes mellitus occurs.

### **Total Pancreatectomy**

This involves the complete removal of the entire pancreas as well as part of the duodenum and will definitely cause diabetes mellitus.

#### **Hospital Stay**

About 2 weeks.

#### **Recovery Time**

From 1-3 months.

### **Risks**

As for pancreatic enucleation. Risk of haemorrhage requiring blood transfusion.

### **Medicines**

**Pancreatic Enzymes** taken with food to aid its digestion.

**Insulin injections** to replace the insulin normally secreted by the pancreas.

## Partial Pancreatectomy (Whipple's Procedure)

This involves removing the head of the pancreas, a portion of the bile duct, the gallbladder and part of the bowel and sometimes a part of the gut.

### Hospital Stay

7-10 days

### Recovery Time

2-3 months

### Risks

Internal leaks, wound infection, delayed emptying of the stomach, diabetes

### Medicines

Insulin if the surgery results in diabetes mellitus, pancreatic enzyme capsules to help absorb food.

AMEND has a separate booklet on the Whipple's Procedure which is available to download from our website or in hardcopy on request.

## Treating Metastatic Pancreatic Neuroendocrine Tumours

If MEN1 pancreatic tumours have spread outside of the pancreas (metastatic disease) and can no longer be removed by surgery alone, doctors may try a variety of different therapies to control the growth, spread and hormone secretion of the tumours. We list some of the current treatments below; however, not all of these may be available or suitable for you. You should discuss your treatment options and the possible side effects with your doctor.

## Current treatment options for Metastatic PNETs

Treatment	Information	Possible side effects
<i>Medical -Biotherapy</i>		
Somatostatin Analogues (SSAs)	Regular injections of octreotide, lanreotide or pasiriotide to control tumour growth and hormone production	Sore injection site, constipation, diarrhoea, nausea
Receptor Tyrosine Kinase (RTK) Inhibitors	Medicine in the form of a tablet that blocks a cell receptor called tyrosine kinase. E.g. sunitinib, sorafenib, imatinib and vandetanib.	Tiredness, diarrhoea, nausea, vomiting
mTOR Inhibitors	Medicine in the form of a tablet that blocks a pathway in cells called mTOR. This may help control tumour growth. E.g. everolimus	Mouth sores, skin rash, tiredness, diarrhoea, nausea, vomiting
VEGFA antibodies	Vascular endothelial growth factor A. Given as a slow injection through a drip into the bloodstream. E.g. bevacizumab	Nosebleeds, high blood pressure, headache, dry or watery eyes, dry skin
<i>Medical -Chemotherapy</i>		
Combination Chemotherapy	Chemotherapy drugs fall under 1 of 6 categories which affect different aspects of the cancer. Using combinations of chemotherapy from different categories often works best. Given by slow injection through a drip into the bloodstream. E.g. temozolomide with streptozocin or capecitabine.	Tiredness, hair loss, bruising, infection, nausea, vomiting, constipation, anaemia (low red blood cell count)
Combination Chemotherapy and Biotherapy	Combinations of chemotherapy drugs with a biotherapy such as everolimus may help control or shrink tumours.	As above
<i>Surgery</i>		
Cytoreduction	Also known as 'de-bulking surgery', it aims to reduce the amount of tumour in the body by surgery	Recovery time needed, wound infections

## Current treatment options for Metastatic PNETs

Treatment	Information	Possible side effects
<i>Radiological Treatment- Radiotherapy</i>		
External Beam Therapy (EBRT)	A machine sends beams of X-ray radiation from outside the body into the tumour	Sore skin, tiredness, nausea and loss of appetite
Radionuclide Targeted Therapy (PRRT)	Radioactive substances (Yttrium 90 or more commonly Lutetium 177) are attached to octreotide and given by slow injection through a drip into the bloodstream. This may provide relief from symptoms as well as slow or stop further tumour growth. Usually 4 cycles are given, but sometimes an extra two may be given later	Nausea, vomiting
<i>Radiological Treatment- Interventional Radiology</i>		
Radiofrequency ablation (RFA)	RFA uses electrical heat to destroy cancer cells. The electric current is given to the tumour via a probe which goes through a small cut in the skin.	Discomfort, mild pain, fever, pancreatitis
Trans-arterial embolisation (TAE)	In TAE, substances are injected directly into an artery in the liver to block or reduce the blood flow to a tumour in the liver and kill the cancer cells	Tummy pain, fever, nausea, liver infection
Trans-arterial chemoembolisation (TACE)	In TACE, a chemotherapy drug such as doxorubicin is combined with TAE (above)	Pain, fever, nausea
Selective internal radiation therapy (SIRT)	SIRT uses radioactive beads that are given to block the blood vessels of a tumour and kill it.	Fever, chills, nausea, diarrhoea, tummy pain, tiredness

Adapted from: Frost, Lines & Thakker, *Current and emerging therapies for PNETs in patients with or without MEN1*, *Nature Reviews Endocrinology*, April 2018

## Other Tumours Linked to MEN1

MEN1 patients may develop neuroendocrine tumours (NETs) in the chest or stomach area, as well as lipomas (benign tumours of fat cells), benign thyroid tumours and benign tumours of the outer layer of the adrenal gland (adrenocortical adenomas).

### OTHER NEUROENDOCRINE TUMOURS/NEOPLASMS

Less than 5% (1 in 20) of MEN1 patients may have other neuroendocrine tumours (NET/ NEN) in addition to the main tumours. These tumours make large amounts of the hormone serotonin, causing asthma-like breathing problems, attacks of flushing and diarrhoea (Carcinoid Syndrome). NETs are often found in the area of the lungs, thymus or gut. Symptoms can be relieved in most patients using somatostatin analogues (e.g. octreotide or lanreotide). Surgery, radiotherapy or chemotherapy are also

useful. The treatment for NETs of the middle gut is surgery or radionuclide therapy (MIBG, PRRT or octreotide) and/or therapies aimed directly at the liver such as embolisation or radiofrequency ablation. NETs in the thymus gland at the top of the chest affect men and cause problems from local growth of the tumour rather than hormone production and are best treated with surgery. However, about 1 in 4 (25%) of thymic tumours produce ACTH and may cause Cushing's syndrome.

### LIPOMAS

A common benign tumour of fat cells which are often found in up to one in three MEN1 patients. If they are a problem, they can usually be removed by a simple surgery under general or local anaesthetic.

### ADRENAL TUMOURS

Adrenal tumours in MEN1 are usually benign tumours in the outer layer (cortex) of the gland. Adrenal glands sit on

top of each kidney and make hormones important for coping with stress and illness, as well as for maintaining the water and mineral levels and thereby blood pressure in the body. In MEN1, these tumours are usually non-functioning and do not need treatment. However, if they do make too much of the hormone, cortisol, this causes a condition called Cushing's syndrome and symptoms similar to those caused by ACTH-secreting tumours of the pituitary (see Pituitary Tumour – ACTH Tumour). Treatment is by removal of the affected adrenal gland, which can usually be done by key-hole (laparoscopic) surgery. If both adrenal glands are removed, a patient would need to take lifelong steroids.

### ANGIOFIBROMAS

Small, benign, raised, red spots on the face

### COLLAGENOMAS

Small, benign, white, raised spots that may occur anywhere on the body.

## BREAST CANCER

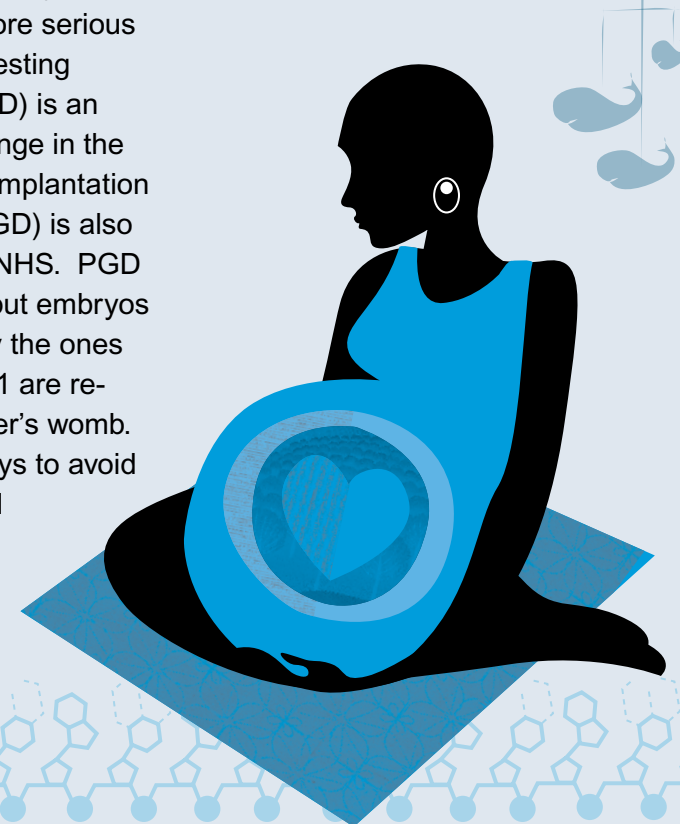
Recent research has suggested that there is a very small increase in the risk of breast cancer in women with MEN1. It may therefore be recommended that women with MEN1 start breast screening from the slightly earlier age of 40 (usually from age 50 in the UK). You should discuss this with your endocrinologist who can then help to instruct your GP.

## Children and MEN1

### Deciding to have children

**There is a 1 in 2 (50%) chance that a child born to someone with MEN1 will also have MEN1 (see Genetic Testing Explained).** Predictive gene testing in children is usually done at around 5 years of age. If a child is found to carry the gene change, testing and treatment plans may be set up early on. In this way, conditions may be found and treated before serious symptoms develop. Testing during pregnancy (PND) is an option if the gene change in the family is known. Pre-implantation Genetic Diagnosis (PGD) is also available through the NHS. PGD uses an IVF process but embryos are screened and only the ones that do not have MEN1 are re-implanted in the mother's womb. PND and PGD are ways to avoid having a child affected with MEN1. AMEND produced a separate

booklet called 'Starting a Family' which contains a great deal of information about these and other methods of conception. It is available to download from our website or in hardcopy on request. If families are considering PND or PGD, they should ask for a referral to one of the 23 UK clinical genetics services before they become pregnant. PND or PGD is a personal choice and often depends on the family's experience of MEN1.



## ***Pregnancy and MEN1***

Management during pregnancy will depend upon the particular issues in each mother with MEN1. The obstetrician and your endocrinologist should be informed as soon as a pregnancy is confirmed. Where possible it is also helpful to tell your endocrinologist that you may be trying for a baby before doing so. This is most important in mothers who already have MEN1 tumours or who are on replacement hormone medicines.

## ***Predictive Genetic Testing for Children***

Children of a parent with MEN1 caused by a known gene change (mutation) can be offered a genetic test to find out if they also carry the gene. This is usually offered at an age when biochemical testing is started at around 5-10 years of age. This could be done earlier if you are very worried about waiting this long to find out. 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 MEN1***

AMEND produced an information leaflet on this subject in 2012. It is available free to download from our website or in hardcopy on request, and suggests ways in which to broach the subject of your family's MEN1 with your children.

## ***Explaining MEN1 to Your Children***

Thanks to an award from the UK Big Lottery Fund, AMEND commissioned a Medikidz™ comic on MEN1, called 'Medikidz Explain Multiple Endocrine Neoplasia Type 1: what's up with Reuben?'. Aimed at 8-12 year olds, the comic explains MEN1 as simply as possible in an engaging way and is a tool to help you explain the disorder to children

in this age group. The comic is free and available through your specialist or directly from AMEND. An entertaining and accessible 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).

*"It's cartoons like this that will help me explain to my little boy what things he might face over his lifetime as well as help my other children understand what some of their family members have. AMEND is a special charity that has helped me in some rough times and would be lost without their support."*

## ***Treatment and Testing Recommendations***

Recommended testing programme for children with MEN1:

### **BLOOD TESTS**

#### **Parathyroids**

**Calcium:** Annual tests from ages 5 to 10 years

**Parathyroid Hormone:** Annual tests from ages 5 to 10 years

#### **Pituitary**

**Prolactin:** Annual test from ages 5-10 years

**IGF-I:** Annual test from ages 5-10 years

Opinion varies regarding the timing of surgery for MEN1 gene carriers who do not yet have symptoms. You should discuss testing and treatment in detail with a specialist doctor.

## ***Blood Tests***

There are many adults who find blood tests difficult, so no parent should be surprised if their child develops an intense dislike to them as well. For small children,

many hospitals use Ametop or Emla Cream ("magic cream") covered by plasters to numb the hands and/or arms ready for the tests. The cream takes up to an hour to work during which time the child may or may not focus on the area and possibly become distressed. In cases where a child regularly appears distressed, it is sometimes quicker and easier not to use the cream, or to use a topical anaesthetic spray instead. A phlebotomist or paediatric nurse experienced in doing children's blood tests is a must to ensure as few repeated jabs and tests and thereby as little distress to the child as possible.

### *Transition*

Transition is the process of moving from children's 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.

## *Genetic Testing Explained*

### *Chromosomes and Genes*

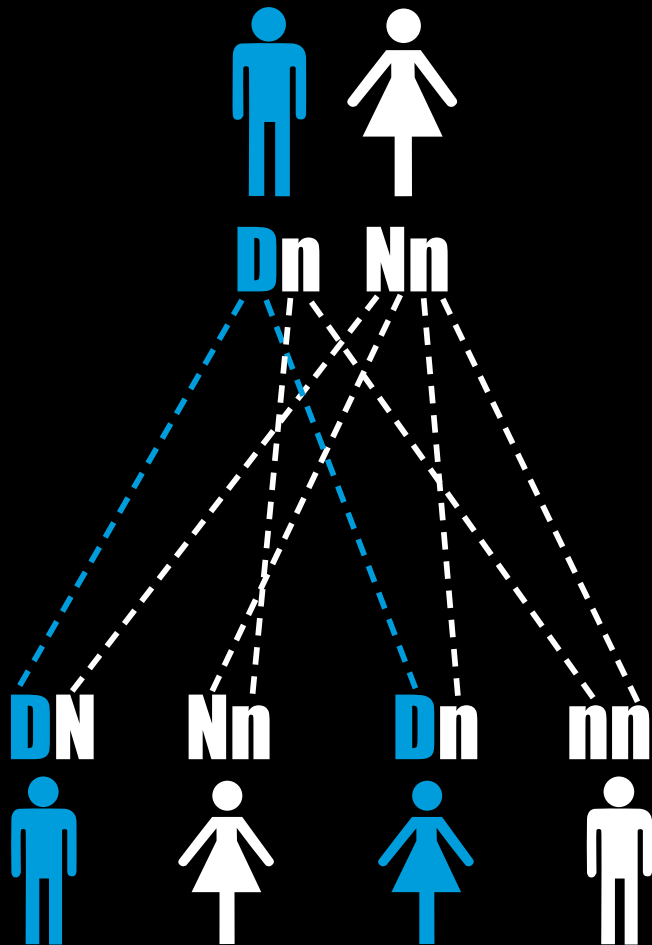
In each cell of the body there are 23 pairs of chromosomes that contain our genes. We inherit one chromosome from each pair from each parent. This means that we inherit one copy of each gene from each of our parents, thereby giving us two copies. In most people there are two normal functioning MEN1 genes. In patients with MEN1, one of this pair has a change (mutation). This can be inherited from either parent (inherited or familial) or can start in an individual for the first time (new mutation or de novo). When someone with MEN1 has children they can pass on either the normal gene or the gene change. This is entirely random, like tossing a coin. Each child therefore has a 1 in 2 or 50% chance of inheriting the gene change (coloured blue, right), and is therefore at risk of developing

the tumours in MEN1. This method of inheritance is called autosomal dominant inheritance.

### *Genetic Testing*

It is possible in some families to have a genetic test to see whether someone has inherited the gene change. However, the first step is to have a blood sample tested from someone with MEN1 in the family. With this initial test (mutation screen), the result may not be received for a number of months, and, indeed, the gene change is not always found. If the gene change is found, a 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 surrounding 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 fault 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 MEN1 parent are tested, those unaffected can rest assured that no further investigations are required. Those who have inherited the gene can be comforted by the fact that testing and monitoring patterns will determine as early as possible when intervention is required. Thanks to this early detection by DNA test, complications from ulcers, kidney stones as a result of parathyroid tumours, and advanced pancreatic islet cell cancer, may be drastically reduced.

Genetic testing and counselling is available and a referral to a genetic centre is usually made through your GP or specialist.

## *Other MEN1-Like Syndromes*

In 1 in 4 (25%) of patients with a clinical diagnosis of MEN1, no gene change can be found. In these cases, re-testing for MEN1 every few years may find a newly discovered gene change. Otherwise, there are two other syndromes that are similar to MEN1, although much rarer, that can also be tested for:

**MEN4** – in this syndrome, caused by a change in the CDKN1B gene, a person may develop parathyroid and pituitary tumours. It is thought that the tumours in MEN4 appear later in life than in MEN1.

**Familial Isolated Pituitary Adenomas (FIPA)** – in this syndrome, usually caused by a change in the AIP gene, pituitary tumours are seen to run in families. These are often prolactinomas or growth hormone producing tumours and they may occur earlier in life than in MEN1. AMEND has produced separate patient information booklets on these conditions that can be found on our website or on request from our office.

## Emotional Wellbeing

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 MEN1 diagnosis and to regain a positive vision towards dealing with it in our lives!!"*

## Life Insurance

A Code on Genetic Testing and Insurance was developed between the Government and the Association of British Insurers (ABI) on behalf of its members and describes a shared agreement on the role of genetic testing in insurance (as of 2018). The Code is based on two core principles:

1. An insurer will not need or insist that an applicant undergoes a predictive or diagnostic genetic test in order to obtain insurance.
2. The results of a predictive genetic test may be considered in an application for insurance only when both of the following conditions are met:
  - a. This Code states that the specific predictive genetic test may be considered and;
  - b. The sum assured exceeds the financial limits set out in the Code.

Life insurance companies and underwriters need to know what

they are covering and if you are taking out a life insurance policy in excess of £500,000 (or Critical illness insurance in excess of £300,000; or Income protection in excess of £30,000), they may ask for further information from your GP, or even want you to have a medical examination. This is standard practice and allows the insurer to correctly set your premiums. You can request a copy of the report your GP sends to the company; however, this can sometimes delay your policy. With long-term medical conditions, you may wish to provide details of your medical specialist too. This may help to speed up your application.

- It is vital that you are honest and upfront about your medical conditions.
- Remember, insurers are allowed to ask for details of your family history.
- Try to answer the questions as accurately as possible as withholding information may affect the final claim on the policy.

- Always check your policy documents.

There are only a few insurance companies that specialise in insuring people with pre-existing medical conditions. The best way of finding a company that is likely to offer the best terms is to find an experienced Independent Financial Adviser (IFA). Insurance companies who have signed up to the Code should not ask for the results of genetic testing for either the individual being insured or other family members.

Further information can also be found through Genetic Alliance UK ([www.geneticalliance.org.uk](http://www.geneticalliance.org.uk)).

## *Useful Information*

**FREE PRESCRIPTIONS:** In the UK, you are entitled to free prescriptions for all your medicines if you need to take lifelong insulin for diabetes mellitus or are prescribed the following medicines:

- Hydrocortisone
- Thyroxine
- Desmopressin
- Testosterone
- Oestrogen replacement
- Growth hormone

You should obtain a FP92A leaflet from your doctor and fill in parts 1 and 2. Your doctor will then sign it and send it on. You will then receive a Medical Exemption Certificate, 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/exemption-certificates/medical-exemption-certificates](http://www.nhsbsa.nhs.uk/exemption-certificates/medical-exemption-certificates)

### **MEDICALERT Emblem®:**

AMEND recommends that anyone taking lifelong medicines obtain and wear a MedicAlert® identification emblem. The emblem contains summary 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 helps emergency medical staff to give treatments in full knowledge of your underlying condition and current medicines. 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 online at [www.medicalert.org.uk](http://www.medicalert.org.uk). Other medical identification products are available.

## *Useful Organisations*

### **The Pituitary Foundation**

Tel: 0870 774 3355  
[www.pituitary.org.uk](http://www.pituitary.org.uk)

### **Diabetes UK**

Tel: 020 7424 1000  
[www.diabetes.org.uk](http://www.diabetes.org.uk)

### **NET Patient Foundation**

Tel: 0800 434 6476  
[www.netpatientfoundation.org](http://www.netpatientfoundation.org)  
The NET Patient Foundation is an excellent resource for more detailed information on sporadic pancreatic and other neuroendocrine tumours.

### **Parathyroid UK**

Tel: 01342 316315  
[www.parathyroiduk.org](http://www.parathyroiduk.org)  
An excellent resource regarding parathyroid issues

## Glossary

**ACTH:** Adrenocorticotrophic Hormone made by the pituitary gland to tell the adrenal glands how much hormone (cortisol) to make

**Adenoma:** A benign growth that is not cancer

**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

**Benign:** Not cancer

**Carcinoid Syndrome:** Large amounts of the hormone, serotonin, causes asthma-like breathing problems, attacks of flushing and diarrhoea

**Chemotherapy:** Cancer treatment using chemicals

**Chromosomes:** Cell structures that contain genes

**Codons:** Sections of genes where mutations (changes) 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

**Diabetes Insipidus:** Not related to diabetes, but it does share some of the same signs and symptoms such as the need to pee often and increased thirst. Caused by the loss of a hormone called vasopressin, which may occur after pituitary surgery in MEN1

**Diabetes Mellitus:** Type 1 diabetes caused by the loss of insulin, which may occur after pancreatic surgery in **MEN1**

**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 into the bloodstream to affect the activity of other organs

**Gene:** Structures made of DNA. A change in the normal gene structure results in a variant (mutation) which may be disease-causing

**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

**Neoplasia:** Abnormal level of growth in cells to form a tumour

**Neuroendocrine tumours (NETs):** A body system consisting of nerve and gland cells that make hormones and release them into the bloodstream

**Malignant:** Cancer

**Metastasis:** Cancer that has spread to other sites in the body

**Osteoporosis:** A condition caused by having altered calcium levels in the blood over a long time period making bones break more easily than normal

**Pancreas:** An organ that sits behind the stomach and makes hormones and juices that help with food digestion

**Pancreatitis:** Painful swelling of the pancreas

**Parathyroid glands:** Four small organs found in the neck that make parathyroid hormone (PTH).

People with MEN1 may have more than 4 parathyroids

**Pituitary gland:** The bean-sized 'master gland' that sits under the brain and behind the nose and makes many different 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

**Thymus gland:** Sits in the chest between the lungs making hormones and white blood cells that help fight infections in the body

**Transition:** Period of time when a child gradually moves from paediatric to adult healthcare services

**Ulcer:** A painful sore on or inside of the body

## *AMEND Medical Advisory Team*

**AMEND would like to thank the following for their help and support in producing and updating this and all our other AMEND patient information titles:**

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## *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 MEN1. It is not for use in self-diagnosis. It contains detailed information on tests, surgery and potential symptoms associated with MEN1. 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.

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## *About AMEND*

AMEND is a charity registered in England and Wales (number 1153890). It provides support and information services to families around the world who are affected by multiple endocrine neoplasia and other rare endocrine tumours. AMEND encourages research into the conditions by awarding annual medical prizes and research grants. It hosts a patient information event 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](http://www.amend.org.uk)

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