HEREDITARY PHAEOCHROMOCYTOMA & PARAGANGLIOMA SYNDROMES (PPGL Syndromes)

Patient Information

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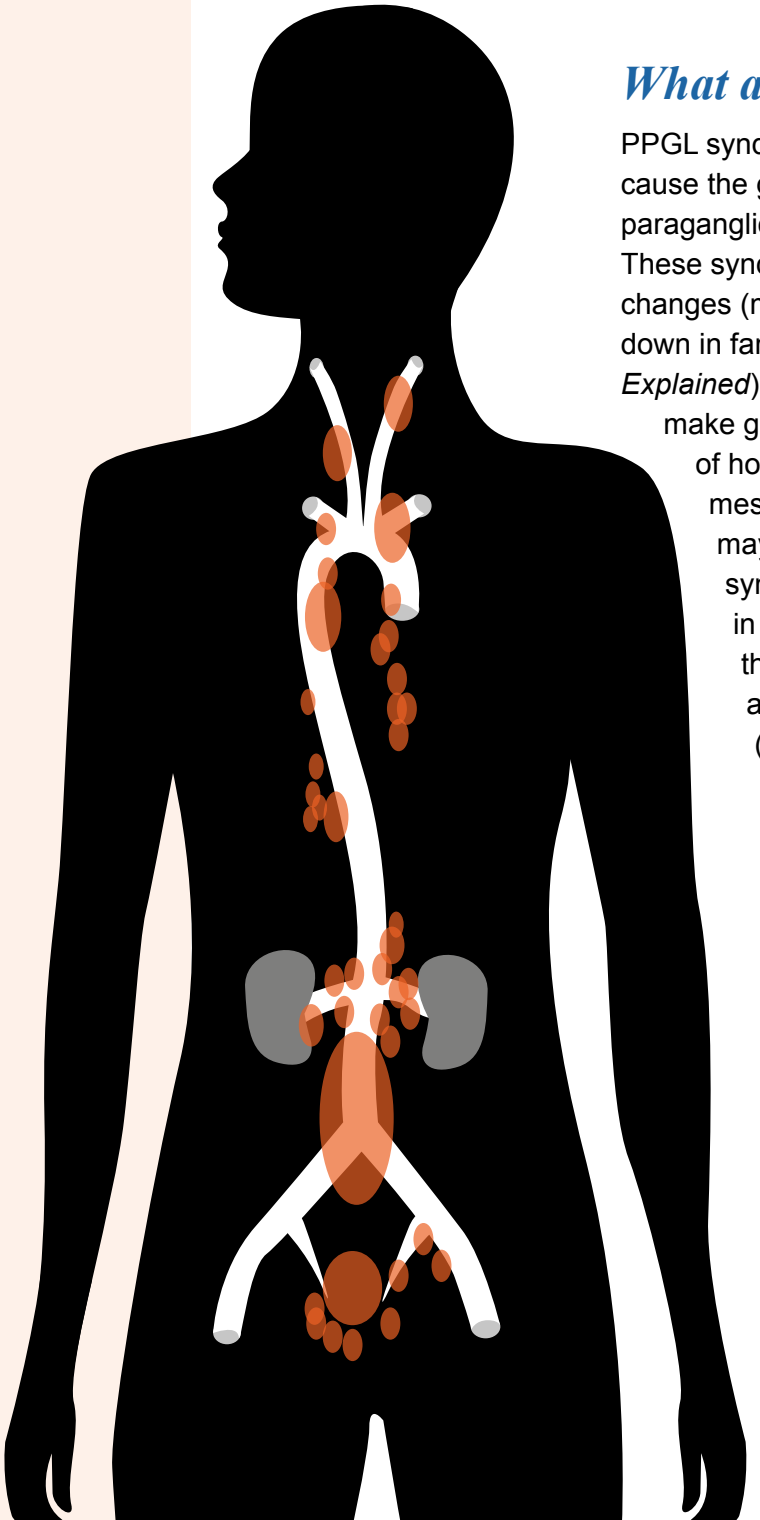
"When I was diagnosed I just wanted the facts and they were not easy to find. I think that [this book] hits the right spot...."



What are PPGL Syndromes?

PPGL syndromes are conditions that may cause the growth of multiple tumours called paragangliomas or phaeochromocytomas. These syndromes are caused by gene changes (mutations) that can be passed down in families (*see Genetic Testing Explained*). Sometimes the tumours may make greater than normal amounts of hormones, the body's chemical messengers, which in turn may cause a range of different symptoms. These tumours grow in particular cells of the body that mean that they are classed as neuroendocrine neoplasms (NEN). All the tumours in PPGL syndromes can occur alone (sporadic) and separately from an inherited syndrome.

How are PPGL Syndromes Diagnosed?

A person may be diagnosed with an inherited PPGL syndrome after being offered a gene test. Genetic testing may be offered after someone

is diagnosed with a paraganglioma or phaeochromocytoma because around 1 in 4 (25%) are caused by a genetic syndrome. It may also be offered because there is a history in your family of a PPGL syndrome, and therefore, some people may be diagnosed with a syndrome before they have developed any tumours. Not everyone diagnosed by gene test with a syndrome will actually develop any tumours in their lifetime (*see Genetic Testing Explained*).
The table below shows each type of PPGL syndrome currently known. It also shows the lifetime risk of people with each gene change (but without tumours currently) for developing different types of tumours:

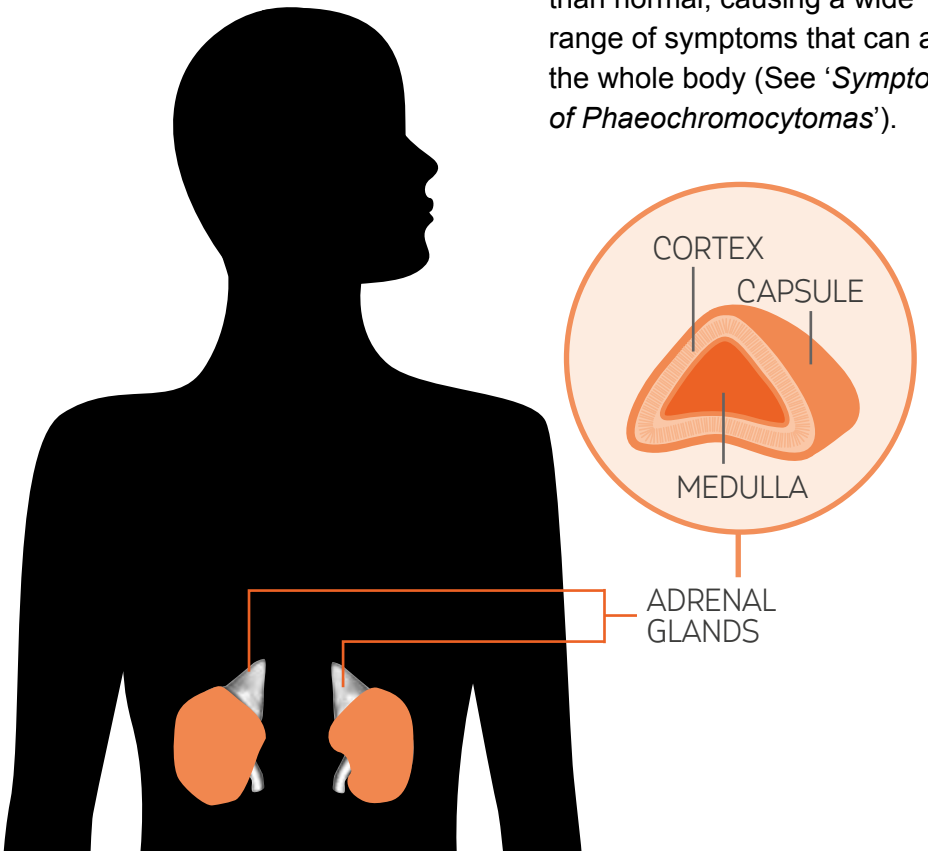
Table 1: risks of tumours in unaffected individuals with gene mutations

Gene	Risk of any tumour (lifetime)	Most likely position of tumour	Multiple tumours	Other tumours (not PGL/ Phaeo)
SDHB	25-30%	Adrenal and extra adrenal PGL	30%	Rarely GIST and renal cell carcinoma
SDHD*	50-90%	Head and neck	50%	Rarely GIST and renal cell carcinoma
SDHA	5-10%	Adrenal and extra adrenal PGL	rarely	GIST
SDHAF2**	5%	Head and neck	90%	Not reported
SDHC	up to 25%	Head and neck and extra adrenal PGL		GIST, rarely renal cell carcinoma
MAX*	30-50%	Adrenal	60%	Not reported
TMEM127*	40-60%	Adrenal	25%	Not reported

** If inherited from the father. Based on published literature and collective clinical observation including the consensus opinion of a large group of experts[3] . If inherited from the mother these gene variants rarely cause tumour development. See 'Genetic Testing Explained' for more information.*
*** Data is limited as numbers of cases are small and therefore the tumour risks are likely to be overestimates*

About Phaeochromocytomas

Phaeochromocytomas (pheochromocytomas or phaeos - 'fee-ohs'), also known as adrenal paragangliomas, are rare tumours that grow in the inner part of the *adrenal gland*. When they grow elsewhere in the body, they are called simply *paragangliomas*. The body has two adrenal glands, one on top of each kidney ('ad-renal' means 'next to the kidney'). Even though the glands are as small as a walnut, they are important as they make several important *hormones* (chemical messengers). Phaeos grow in the middle part of the adrenal gland which is called the *medulla*. The adrenal medulla makes hormones called *catecholamines* such as adrenaline and noradrenaline. These hormones help the body to keep blood pressure at the right level and to deal with sudden stress or threats. Phaeos often make more of these hormones than normal, causing a wide range of symptoms that can affect the whole body (See '*Symptoms of Phaeochromocytomas*').



Symptoms of Phaeochromocytomas

Phaeos can cause a wide range of symptoms. These are mainly due to the release of larger than normal amounts of hormones by the tumour. Symptoms can occur from time to time, often in episodes lasting only 15 minutes and may include some or all of the following:

- Sudden headaches
- Feeling dizzy
- Looking pale
- Sweating more than normal
- Fast or uneven heart rate (palpitations)
- Panic attacks / sense of doom
- Anxiety
- Weight loss
- Heat intolerance
- High (and rarely low) blood pressure (all the time or in short episodes)
- Feeling sick (with or without being sick)
- Breathlessness
- Depression
- Tiredness
- Changes in blood sugar levels

Many of the symptoms listed above are caused by the high blood pressure (*hypertension*) that can result from this tumour. It is thought that one case of high blood pressure in every 500-1000 patients is due to a phaeo. High blood pressure in patients with undiagnosed phaeos can be very difficult to control; however, once found, special drugs are widely available to help to control it well. Sometimes phaeos may be found before they have the chance to cause symptoms. This may happen when a person is having a scan for another reason. It may also be because they have a condition with a risk of phaeos, like a PPGL Syndrome, and are having regular scans or tests to look for them.

Diagnosis of Phaeochromocytomas

Phaeos can be hard to diagnose unless a patient is known to have a condition that runs in the family, such as a PPGL Syndrome, with a higher risk of developing them. This is because the symptoms are often very varied and easy to put down to a more common cause. In addition, the symptoms may occur in sudden episodes that last less than 15 minutes, meaning that it is hard for a doctor to see this happening. 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.

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. If it is possible to do the test fasting, having avoided exercise, caffeine and paracetamol on the day, this will also increase the accuracy of the test. This all helps to avoid a *false positive result*. It is important that you tell your specialist about any medicines or drugs you are taking. In many large centres, this test may also be done as a random sample in the clinic.

CT scan: a computer tomography scan gives a 3-D picture of the inside of the body. It can be used to find out the position and size of tumours.

MRI scan: a magnetic resonance

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. When you reach the time you started the test, empty your bladder for the last time collecting the urine passed in the bottle. 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.

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.

Are Phaeos Cancer?

At present there are a lack of sensitive markers to identify those phaeos that are more likely to behave as a cancer versus most phaeos which are benign. Therefore, in current practice, it is recognised that all phaeos have the *potential* to behave like a cancer (although only a minority do) and follow-up is directed accordingly.

About Paragangliomas

Paragangliomas are similar to phaeos but are much less common and grow outside of the adrenal glands. Paragangliomas arise from the extra-adrenal paraganglia. These are cells that form part of the nervous system that runs between the neck and the pelvis. Therefore, tumours can develop anywhere between these two points.

Symptoms of Paragangliomas

The type of symptoms that occur with these tumours can vary widely. They will depend on the size and location of the tumour, and whether it is making large amounts of hormones (functional tumour).

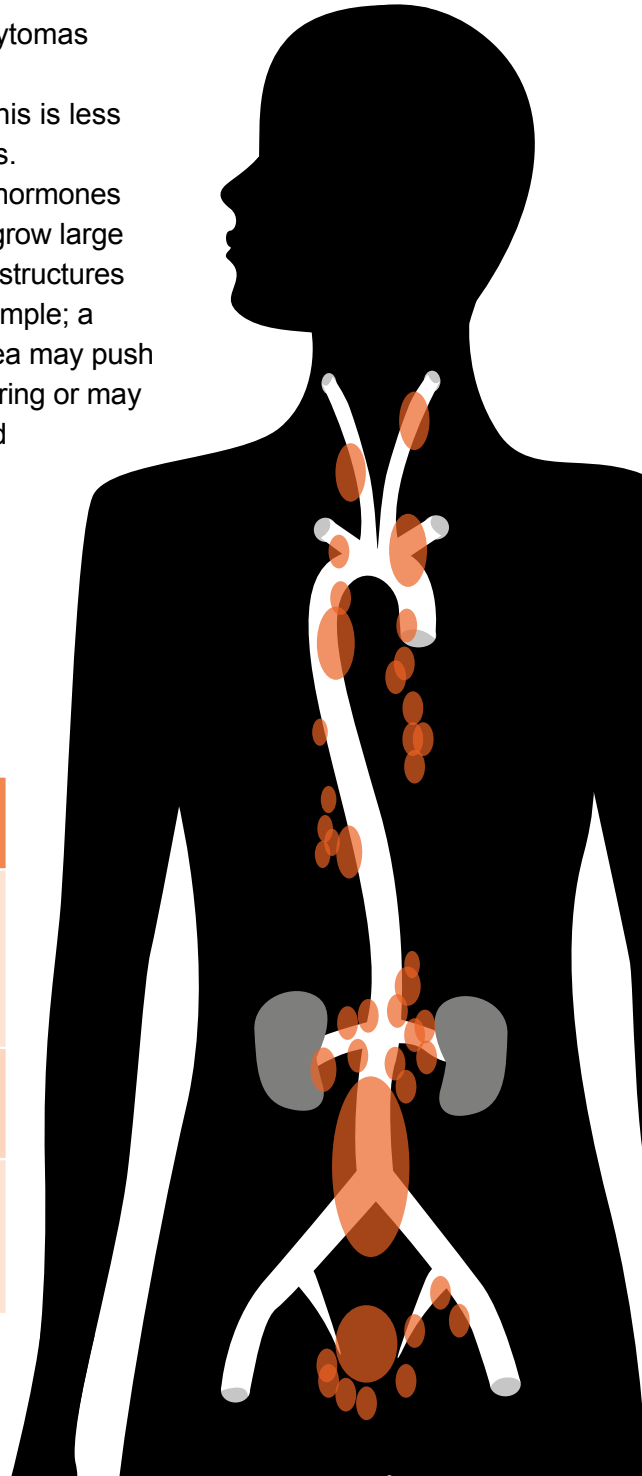
Tumours that are making large amounts of hormones (chemical messengers) may cause any of the same range of potential symptoms as phaeochromocytomas (*see previous section on Phaeochromocytomas*), but this is less common with paragangliomas.

Tumours that are not making hormones may cause symptoms if they grow large enough to push against other structures or organs in the body. For example; a paraganglioma in the neck area may push against the ear and affect hearing or may push against the windpipe and affect breathing or the voice.

Diagnosis of Paragangliomas

Diagnosis of paragangliomas relies upon scans, urine and blood tests as shown below.

Tests and scans
• MRI scan of skull base and neck, chest, abdomen and pelvis
• ^{68}GA-DOTATE-PET-CT scan;
• Blood or urine test for metanephrines and normetanephrines



Head & Neck Paragangliomas (HNPGLs)

Paragangliomas can occur in and around the head and neck and are collectively referred to as Head & Neck paragangliomas or HNPGL. Only around 1 in 10 (10%) make hormones that cause symptoms. There are four main places where the HNPGLs often grow, giving rise to their names: Carotid body, Vagal, Middle ear and Laryngeal tumours. The risk of these tumours occurring varies depending on the type of PPGL syndrome.

Symptoms of Head & Neck Paragangliomas

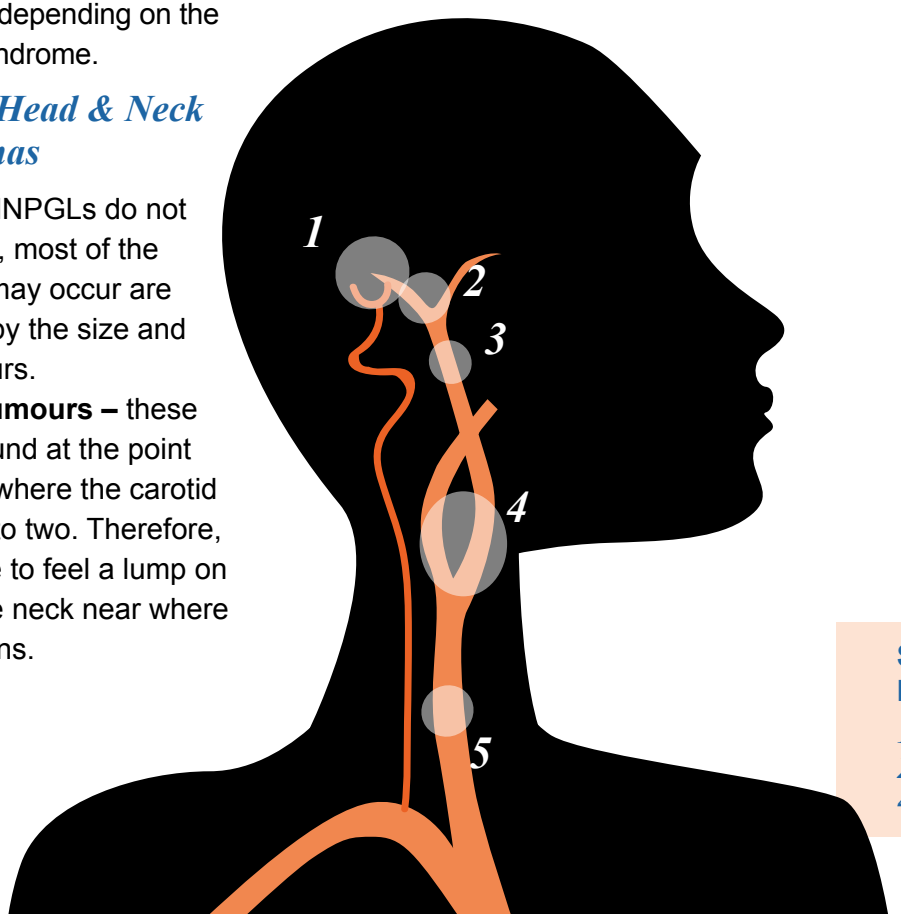
Because most HNPGLs do not make hormones, most of the symptoms that may occur are usually caused by the size and site of the tumours.

Carotid body tumours – these occur in cells found at the point in the mid neck where the carotid artery divides into two. Therefore, you may be able to feel a lump on either side of the neck near where the lower jaw joins.

Vagal tumours – these occur higher in the neck than carotid body tumours and may cause a swelling in the neck or a bulging of one of the tonsils at the back of the mouth.

Middle ear tumours – may cause pulsing tinnitus (ringing or buzzing sounds) or hearing loss.

Laryngeal tumours – may cause shortness of breath, hoarseness when talking and wheezing when breathing.



Diagnosis of Head & Neck Paragangliomas

The type of HNPGL will be identified from the symptoms listed above, as well as from scans to find its location, and various tests, including for markers that may be found in the blood (plasma metanephrines). The diagnosis of HNPGL will be confirmed by looking at the tumour under a microscope after surgery to remove it.

Tests to Locate or Identify Head & Neck Paragangliomas

All patients with HNPGLs should be assessed by an Ear, Nost and Throat surgeon (otolaryngologist) who is part of a multidisciplinary team (MDT) experienced in treating these tumours. The assessment should include:

- A look inside the ears with a medical device called an otoscope
- Feeling the neck

SITES OF HEAD & NECK PARAGANGLIOMAS

1 Middle Ear (Tympanic)
2 Jugular *3* Vagal
4 Carotid Body *5* Laryngeal

- An examination of the upper aerodigestive tract (this includes the mouth and throat and also the voice box). A long thin tube with a mini video camera built into its tip (an endoscope) is used for this procedure which takes about 30 seconds to complete in the clinic, and because it is passed through the nose, it does not tend to make patients gag.
- Hearing tests (for middle ear paragangliomas)
- MRI scan of the head and neck areas and/or whole body
- Gallium DOTATATE PET CT scan of whole body
- CT Scan of the skull base (for middle ear paragangliomas)

Treatment of Head & Neck Paragangliomas (HNPGLs)

For most patients, adopting careful active surveillance ('watch and wait') is the most appropriate and most widely recommended approach as most HNPGLs grow very slowly and do not make hormones The possibility for surgery is considered on an individual basis for patients

with HNPGLs. Considerations for surgery include; if the tumour is making hormones, if the tumour grows between scans, the presence of other tumours (tumours on the same or other side of the neck), symptoms, and the location of the specific head and neck tumour. If there is a known genetic syndrome, that may help guide the management decision. The risks of surgery and the likelihood that surgery will benefit the patient in terms of symptoms, must be carefully considered on an individual basis at an MDT.

Possible risks of Head & Neck Surgery

<u>The risks of the surgery will vary depending on the size and location of the paraganglioma.</u>

Numb skin:
The skin of the neck will be numb after the surgery. This will improve over time, but you should not expect it to return to normal.

Stiff neck:
Some people find that their neck feels stiff after surgery.

Bleeding:
Sometimes, despite a drain tube placed at the end pf the procedure, blood can collect under the skin and form a clot (haematoma). If this happens it is often necessary to return to surgery to remove the clot and replace the drains.

Chyle leak:
Chyle is the tissue fluid, which runs in lymph channels. One of these channels may leak after surgery. If this happens, lymph fluid or chyle can collect under the skin. This may mean that you will need to stay in hospital a bit longer. Sometimes you may need to return to surgery for the leak to be sealed.

Nerve Injury:
Accessory nerve – injury to this nerve may cause your shoulder to feel stiff, making lifting heavy weights, like shopping bags, a challenge.
Hypoglossal nerve – Injury to this nerve (which is very rare) may affect tongue movements and swallowing.
Marginal Mandibular nerve – injury to this nerve may make the corner of your mouth a little weak, which will be more obvious when smiling.
Vagus nerve – this nerve moves the voice box and so if it doesn't work afterwards, you may notice a change in your voice (hoarseness) or difficulties with your swallowing.

Treating Non-Functioning Paragangliomas

Surgery may be necessary if the tumour is growing, but as this is a complex area, in many cases, the doctor will simply keep these paragangliomas under surveillance or may consider some type of radiation treatment (radiotherapy).
Sometimes radiotherapy may be used to shrink tumours so that surgery becomes possible or to help to reduce symptoms. In some cases, even if the tumour is non-functioning, precautions may be taken using medicines in the same way as for functioning tumours (*see Treating Functional Tumours*).
Surgery is done under a general anaesthetic meaning that you will be asleep throughout. At the end of the surgery, you may have a drain tube coming out through the skin and stitches or skin clips to the skin. Most patients do not have much pain after the operation as this is normally well controlled by pain medicines.

Treating Functional Phaeochromocytomas and Paragangliomas

The main form of treatment for most functioning tumours is surgery. The type of surgery done depends on many factors such as the where the tumour is and its size. In the case of phaeos (adrenal paragangliomas), 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 in an attempt to avoid the need for steroids (rarely possible).

Paragangliomas are often found in the abdomen and are separate from the adrenal gland. They can be removed without taking away the adrenal gland, but they are often close to major vessels. This makes key-hole surgery harder and open surgery more common. If it is thought that your tumour might be a cancer, and it has spread nearby, then the surgeon will remove the tissues close to the tumour or adrenal gland (in the case of a phaeo) and the nearby lymph nodes. If one adrenal gland is removed, then the other gland will continue to make enough hormones and you will not need to take medicine. However, if both adrenal glands are removed, then you will need life-long medicine in the form of steroids to replace the hormones that the adrenal glands would normally make. Sometimes, if there are tumours in both adrenal glands, the doctors might recommend a partial adrenalectomy. This surgery leaves a small piece of a gland in the body in an attempt to avoid the need for steroids; unfortunately, in many cases this is not possible. No replacement is needed for loss of the hormones adrenaline and noradrenaline. 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 practise 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.

ALPHA-BLOCKERS.
An alpha-blocker such as phenoxybenzamine can cause 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. However, often, drugs with fewer side-effects, such as doxazosin, prazosin, or terazosin may be used. 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.

Phaeo Para Crisis Card

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. See '*Medicines'* for a list of medicines to avoid while you have a phaeo.

Who should do the surgery?

Research has shown that the more adrenal surgeries a surgeon does in a year, the better a patient will do during and after the operation. The same is true of most types of surgery. Current treatment guidelines suggest that an experienced adrenal surgeon is one who does more than six (6) adrenal surgeries in one year. In fact, there are very few surgeons in the UK who do more than 6. Having a surgeon and anaesthetist experienced in adrenal surgery is very important because adrenalectomy can be a technically challenging

operation. In addition, tumours that make catecholamines can cause problems before and during the operation by making sudden large amounts of hormones. This sudden surge of hormones is dangerous and needs to be planned for carefully by a surgeon, anaesthetist, and hospital team (multidisciplinary team) who are used to dealing with this. Special drugs may be needed before, during and after the surgery to keep blood pressure under control.

Many (though not all) adrenal surgeons publish the number of operations they do as part of an audit run by the British Association of Endocrine and Thyroid Surgeons. You can find these lists at www.baets.org.uk/audit. Guidance for adrenal surgery from the BAETS can be found here.

What questions should I ask?

It is very important to understand why you are having surgery, what will happen during the surgery, and if your surgeon is the best one to do it. You should never be made to feel that you cannot ask questions, so do not be shy in asking the following:

1. *How many operations to remove adrenal glands do you do each year?*
   If the answer is less than 6 operations in one year, ask for a referral for a second opinion to a hospital where the surgeon does more than 6 each year.
2. *Do you have a multidisciplinary team (MDT) with whom you will discuss my treatment?*
   If the answer is 'no', ask for a referral for a second opinion to a hospital where there is an MDT with experience of treating adrenal tumours.
3. *Who will look after me after the surgery?*
   This may be the surgeon or another member of the MDT such as an endocrinologist (hormone doctor). You will be cared for by the hospital where you have your operation for a period of time and then may receive care later on from a hospital nearer to where you live.
4. *Am I at risk of adrenal insufficiency after the operation?*
   The answer will vary depending on the type of surgery you have. Having both adrenal glands removed (bilateral adrenalectomy) will mean that you become dependent upon life-long steroid medicines called glucocorticoids (e.g. hydrocortisone or prednisolone) and mineralocorticoids (e.g. fludrocortisone). An experienced surgeon will be able to tell you this immediately.

If in doubt, you can always ask AMEND or your GP for help in finding the right hospital and MDT.

Medicines

To control blood pressure, drugs called alpha-blockers are commonly used; however, other blood pressure medications may also be required.

If both adrenal glands are removed or you become deficient in the hormones released from the adrenal glands, you will require life-long treatment with replacement steroids (corticosteroids). The two main drugs that a patient must take are hydrocortisone and fludrocortisone. They replace the cortisol and another hormone called aldosterone, which are normally made by the adrenal glands. The drugs take over in the maintenance of normal blood sugar levels, the promotion of recovery from injury and stress, and the regulation of the balance of mineral salts and water content of the body. It is absolutely essential that these drugs are taken every day, as failure to do so will have very serious consequences.

If you have a phaeo or functioning paraganglioma and are waiting for treatment, you will need to avoid certain medicines that may make your symptoms worse. Some of these are listed in the table on the following page.

If you are already prescribed any of the medicines in the table, please do not stop taking them

Medicines that DO NOT need a prescription (over the counter)	
Metoclopramide	For sickness and/or vertigo
Prochlorperazine	For sickness and/or vertigo
Pseudoephedrine	For colds/flu
Medicines that DO need a prescription	
Corticosteroids (prednisolone, dexamethasone, hydrocortisone, betamethasone)	For inflammatory conditions (e.g. arthritis)
Opiates (morphine, pethidine, tramadol)	For pain
SNRI/SSRI, TCA, MAO inhibitors (amitriptyline, imipramine, paroxetine, fluoxetine)	For depression
Dopamine antagonists (sulpiride, amisulpride, tiapride, chlorpromazine)	For psychosis

unless your doctor has told you to do so. Some of the medicines listed may be used in the presence of a phaeo if absolutely essential, but only if prescribed and supervised by your doctor. In 2019, thanks to help from doctors from St Bartholomew's Hospital in London, AMEND produced a Phaeo/Para Crisis Card for patients. This can be carried by anyone awaiting treatment to show to pharmacists and doctors before being prescribed or taking any medicines.

Regular Screening in PPGL Syndromes

After any initial treatment has been done, anyone with a PPGL gene change (and therefore a PPGL syndrome) should enter a long-term screening programme. In this way, any other tumours should be found earlier before symptoms occur. This should also make treatment easier. The programme would be the same both for people who have already had treatment, and for those who are not yet affected (and may not be affected during their lifetime). Most regional genetics services would suggest the following in the table on the following page for most of the syndromes. However, if a child/adult has inherited a SDHD, SDHAF2 or MAX mutation from their mother, screening is not suggested as only mutations inherited from their father will mean that they develop tumours.

Treating Tumours that Spread or Recur

At present, due to a lack of sensitive markers, it is a challenge for doctors to predict exactly which phaeochromocytomas or paragangliomas may become cancer (*malignant*) and spread to other parts of the body. Someone with an SDHB gene mutation is more likely to have a cancerous tumour. The aim at the first surgery is to completely remove the tumour (and adrenal gland in the case of a phaeochromocytoma) and surrounding tissues, without leaving any tumour behind. However, sometimes, cells that are too small to see are left behind and may regrow in the same place (recurrence) or the disease may spread to other areas of the body (metastasis). For recurring or metastatic disease, if surgery is not possible, there are other treatments that may be used and these are discussed below.

Targeted radionuclide therapy
If surgery is not an option, targeted radioactive therapy using

Gene	Recommended surveillance
SDHB	• Annual hospital appointments and blood tests • Abdominal imaging* at baseline and if normal every 12-24 months • MRI/CT neck, chest at baseline and if normal every 3 years
SDHD	• Screening should only be offered to patients who have a gene change passed down from their father. • Annual hospital appointments and blood tests • Abdominal imaging* and MRI/CT neck, chest at baseline and if normal every 3 years
SDHC	• Annual hospital appointments and blood tests • Abdominal imaging* and MRI/CT neck, chest at baseline and if normal every 3 years
SDHA	• Annual hospital appointments and blood tests • Abdominal imaging* and MRI/CT neck, chest at baseline and if normal every 3-5 years
SDHAF2**	• Screening should only be offered to patients who have a gene change passed down from their father • Annual hospital appointments and blood tests • Abdominal imaging* at baseline and if normal every 3 years • MRI of neck, chest at baseline and if normal every 5 years
MAX**	• Screening should only be offered to patients who have a gene change passed down from their father • Annual hospital appointments and blood tests • Abdominal imaging* at baseline and if normal every 3 years • MRI of neck, chest at baseline and if normal every 5 years
TMEM127**	• Annual hospital appointments and blood tests • Abdominal imaging* at baseline and if normal every 3 years • MRI of neck, chest at baseline and if normal every 5 years

**MRI is the preferred method of screening but CT may be required in some instances if MRI not tolerated or unavailable. **Only if inherited from the father.*

^{131}I-MIBG is sometimes used. You may have already had an MIBG scan during the tests ordered by your doctor to help assess your symptoms and make the diagnosis. If your disease is MIBG-positive it means that your tumour is able to take up this chemical – in other words, it has special receptors on its surface which take up the MIBG. In this case, MIBG can also be used as a radionuclide therapy treatment. As 9 in 10 or 90% of functioning tumours are positive to an MIBG scan, they are often suitable for this type of therapy. MIBG is licenced for these uses in the NHS.

MIBG combined with a much higher dose of radioactivity than that used for the scan is injected into a vein in your arm via a cannula (a thin plastic tube). It takes about 40 minutes to complete the slow injection (also known as an infusion). The radioactive chemical sticks to the MIBG receptors on the tumours cells and works to kill them off while causing no harm to the healthy cells. Due to the radiation that comes out of your body following the treatment, you will need to remain in an isolation room in hospital for 4 to 7 days. You will also be given instructions about what to do when you go home to avoid exposing others to radiation. Instead of MIBG therapy, occasionally some patients have been treated with other radionuclide therapies. Increasingly, these tumours respond to a therapy known as PRRT (Peptide Receptor Radionuclide Therapy). The most common such treatment is ^{177}Lu-dotatate (*Lutathera*), which is being increasingly used. However, currently the NHS does not generally licence this treatment (although this may change).

Chemotherapy

There is a role for chemotherapy in some patients. If a phaeo is cancer and is not suitable for radionuclide therapy or where the tumour is growing more quickly than normal, chemotherapy may work better. The chemotherapy medicines used, including the oral chemotherapy called temozolomide, can have side effects and this will be discussed in detail with you before you think about starting chemotherapy.

Targeted Therapies
Several targeted therapies called multi-targeted receptor tyrosine kinase inhibitors (e.g., sunitinib, cabozantinib) are becoming more readily available for the treatment of metastatic disease. These medicines are in the form of a tablet that blocks a cell receptor called tyrosine kinase. Side effects may include tiredness, diarrhoea, nausea, and vomiting. At present, their effectiveness is limited but they may have a role in some patients.

Other Tumours in PPGL Syndromes

Particularly in the PPGL syndromes, SDHB and SDHA, other types of tumours have been seen, although rarely. These areas will be scanned as part of your care if you are being monitored due to an identified gene mutation. These other types of tumours include those detailed below.

GIST Tumours

Gastrointestinal Stromal Tumours are small cancers that grow in the soft tissues of the wall of the stomach and gut. They can grow for some time without symptoms. They occur very rarely in PPGL syndromes and therefore tests for GIST tumours are not usually done on a routine basis.
Symptoms that can occur include:

- Discomfort or pain in the stomach or gut
- Indigestion
- Nausea
- Swelling
- Bleeding from the stomach or gut (bloody stools)
- Weight gain or loss
- Fever
- Night sweats

The preferred treatment for GISTs is surgery to remove the tumours and a safe margin of tissue around the tumour. In some cases, a period of watch and wait may be advised especially if the individual is asymptomatic and the GIST has not caused any issues like bleeding. If surgery is performed, this must be done by an experienced surgeon. You can find out more about GISTs from GIST Support UK or the Paediatric and Adult Wild-Type GIST website (*see Other Useful Organisations*).

Renal Cell Carcinoma

Renal cells are found in the kidneys which make urine. Therefore, Renal Cell Carcinoma (RCC) is another term for kidney cancer. RCC can grow for some time without symptoms.
Symptoms that do occur can include:

- Blood in the urine
- Ongoing low back or side pain
- A lump or mass in the area of the kidneys
- High blood pressure
- Tiredness
- Weight loss and/or loss of appetite
- Fever and/or night sweats

Treatment for RCC will depend on the size and site of your tumour and whether it has spread to other tissues. It may include surgery or other treatments such as *ablative* or *targeted therapies*.
For more information about RCC, visit Kidney Cancer UK (*see Other Useful Organisations*).

What is a multidisciplinary team (MDT)?

Before you have any treatment, your case will be discussed by the hospital's expert multidisciplinary team (MDT). An MDT is made up of the different types of doctors and other health care workers needed to care for and treat people with rare and complex diseases. The MDT will work together to make sure that you receive the best treatment and care possible. MDTs are usually found in larger university training hospitals.

The main expert MDT will include:

- Specialist surgeon
- Endocrinologist (hormone doctor) experienced in treating adrenal disease
- Radiologist (scan doctor) experienced in adrenal scanning
- Pathologist (laboratory test doctor) experienced in adrenal disease
- Endocrine Nurse Specialist
- MDT coordinator

Other MDT members may include:

- Anaesthetist (doctor who

makes patients sleep for operations and manages pain)
- Oncologist (cancer doctor)
- Nuclear medicine doctor (doctor who performs special radioactive scans and treatments)
- Clinical geneticist (doctor who tests for diseases that can be passed down in families)
- Chemical Pathologist
- Interventional Radiologist

Why is an MDT important?

Research has shown that, in the UK, if you are cared for by an MDT, you are more likely to:

- Receive a correct diagnosis of your disease
- Receive correct staging of your disease (if and how far it may have spread)
- Be offered an appropriate choice of treatments
- Receive better coordinated care during your treatment and testing
- Be treated in line with policies and guidelines for your disease
- Be offered the right information
- Have your emotional well-being and social needs addressed.

Children and PPGL Syndromes

Screening in Children with a PPGL Syndrome

Regular screening (surveillance) using blood and urine tests, as well as scans can help to find any tumours that may develop at a very early stage. The current general guidelines for screening in children are shown below; however, guidelines are recommendations rather than rules, and parents should therefore discuss an individual child's needs with their specialist team.

Blood Tests in Children

There are many adults who find blood tests difficult, so no parent should be surprised if their child does too. 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 become stressed. In cases where a child regularly appears

Gene(s)	Age to start Screening	Clinical Review	Blood and Urine Tests	Scans
SDHx (SDHA, SDHB, SDHC and SDHD inherited from the father)	SDHB – from 5 years SDHA, SDHC and SDHD inherited from the father – from 10 years	Annual clinical symptoms and/or signs review and blood pressure check from the time of presentation or from age 5-10 years	Annual blood or urine tests of metanephrine levels Annual blood test for levels of 3-methoxytyramine	MRI of neck, chest, abdomen and pelvis every 2-3 years
TMEM127	10-15 years	Annual clinical symptoms and/or signs review and blood pressure check from the time of presentation or from age 10-15 years	Annual or 6-monthly blood or urine tests of metanephrine levels	MRI of neck, chest, abdomen and pelvis from age 15-18 years; if negative, imaging may be repeated every 2-3 years (abdomen and pelvis) and 3-5 years (neck and chest). Longer intervals may be considered after several years of uneventful follow-up
MAX	10 years	Annual clinical symptoms and/or signs review and blood pressure check from the time of presentation or from age 10 years		MRI of neck, chest, abdomen and pelvis every 2-3 years from presentation or from age 15 years; longer intervals may be considered after several years of uneventful follow-up
SDHAF2 (inherited from the father)	18 years	Annual clinical symptoms and/or signs review and blood pressure check from the time of presentation or from age 18 years		MRI of the neck every 3-5 years from presentation or from the age of 18 years. Longer intervals may be considered after several years of eventful follow-up. Imaging of chest, abdomen and pelvis not routinely needed unless symptoms or tests suggest a PPGL

**Adapted from Table 5, 'Surveillance strategies for asymptomatic carriers of PPGL predisposition genes in childhood'[9]*

stressed, it is often 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 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. The transition process should also include a clinical genetics appointment to ensure that the young adult understands the genetic condition and implications for family planning.

Deciding to have children

There is a 1 in 2 (50%) chance that a child born to someone with a PPGL Syndrome will also inherit the gene change (see Genetic Testing Explained).

Depending on which gene change you have, predictive gene testing in children is usually done at between 5 to 10 years of age after an appointment at your Regional Clinical Genetics Centre. If a child is found to carry the familial gene change, testing and treatment plans may be set up from about 5 years of age. In this way, conditions may be found and treated before symptoms develop. Testing during pregnancy, known as Pre-Natal Diagnosis (PND) is an option if the gene change in the family is known. Pre-implantation Genetic Testing (PGT) is available through the NHS for families with known SDHB gene changes. PGT uses an IVF process, but embryos are screened and only the ones that do not have an SDHB gene change are re-implanted in the mother's womb. PND and PGT are ways to avoid having a child affected with a PPGL Syndrome.

AMEND has written 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 PGT, they should ask for a referral to one of the 23 UK clinical genetics services before they become pregnant. PND or PGT is a personal choice and often depends on the family's experience of their condition.

Pregnancy and PPGL Syndromes

Management during pregnancy will depend upon the particular issues in each mother with a PPGL Syndrome. 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 tumours.

If you are thinking about starting a family and want to know more

about your options, download the free AMEND resource, 'Starting a Family: Your Choices'.

Pregnancy in Patients with Functional Phaeo/Para

Managing a pregnant patient with a phaeochromocytoma or paraganglioma that is making increased quantities of hormones (functional tumour) can be a challenge. If you have a functional tumour and are planning a family, it is advised to wait until after treatment. If you become pregnant while you have a functioning tumour, you must tell your doctor as soon as possible. Endocrinologists, surgeons and obstetricians will all need to work together to keep both mother and baby safe during tests and treatment. Many tests and treatments cannot be used on a pregnant patient as they may affect the unborn child (e.g. CT, MIBG and PET scans). If surgery is possible, this can be done by key-hole surgery by an experienced surgeon in the 2nd trimester of pregnancy (months 4-6). Sometimes, the phaeo can be managed until a few weeks after the birth when it will be removed by surgery.

Predictive Genetic Testing for Children

Children of a parent with a known gene change (mutation) causing an inherited paraganglioma syndrome 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, depending on the gene change. The gene test may be done using a blood sample or in some cases, using a cheek scraping or saliva sample. You should discuss this at your appointment at the Regional Genetics Service.

Talking to Your Children About PPGL Syndromes

AMEND produced an information leaflet on this subject for families with MEN syndromes 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 genetic syndrome with your children. While it will be adapted in due course, it is still useful for families with PPGL Syndromes even in its current form.

Explaining PPGL Syndromes to Your Children

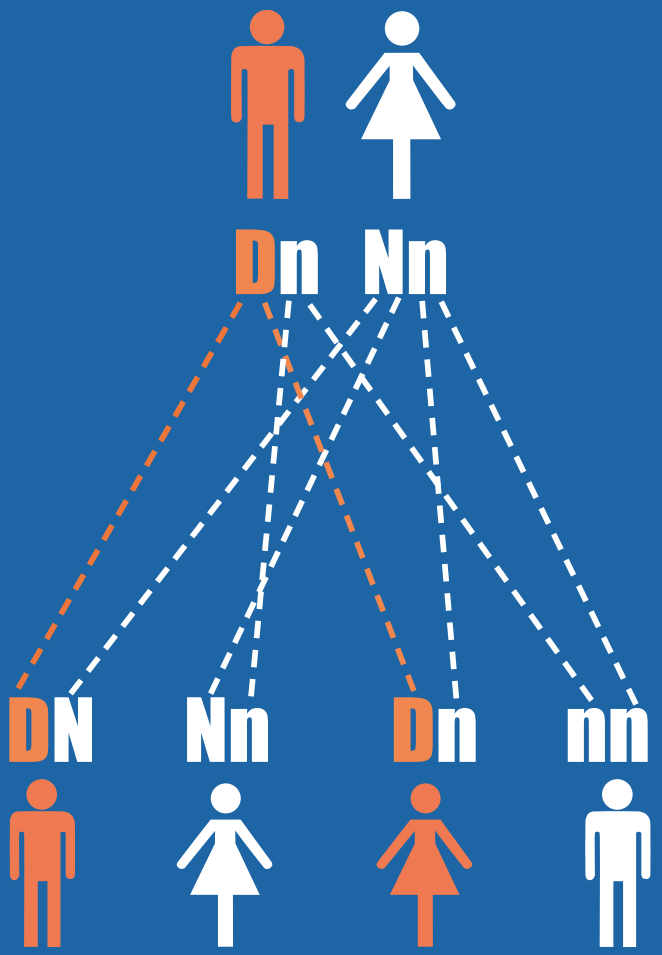
AMEND has developed a cartoon for children about PPGL syndromes. It is suitable for children from age 5 and can be used to help parents explain the syndrome in simple terms. It is free to access on our website.

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 functioning copies of most genes. In patients with a PPGL Syndrome, one of a pair of genes has a change (mutation) so that it does not work in the right way. 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 a PPGL syndrome 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). If the child has inherited the gene change, they may be at risk of developing the phaeochromocytoma or paraganglioma. This method of inheritance is called autosomal dominant inheritance.

Although SDH gene changes are inherited in the autosomal dominant manner, individuals with SDHAF2, SDHD and MAX mutations will generally only develop paragangliomas if the change is inherited from their father. They can inherit the mutation from their mother but will very rarely develop paragangliomas. They can still pass it to their children. Therefore, if a man inherits a gene change from his mother, he will only rarely develop paragangliomas, but if he then passes that gene change to a child of either sex, that child will be much more likely to develop tumours.



Genetic Testing

It is possible in some families to have a genetic test to see whether someone has inherited the gene change. The first step is to have a blood sample tested from someone with a paraganglioma or phaeochromocytoma. With this first test (mutation screen), the result may not be received for a number of months, and, indeed, a gene change is only found in about 4 in 10 or 40% of cases, but up to 8 in 10 or 80% in children and teenagers. A gene change is more likely if there is a family history of paraganglioma or if an individual has more than one tumour. If a 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 usually received 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 in the regional genetics service. If a gene change is not found, then predictive testing is not needed. If a blood sample from an affected person cannot be taken, then predictive genetic testing cannot be done.

Having children tested is a very individual decision; however; if children of a parent with a known gene change that causes a PPGL syndrome are tested and do not have that gene change, they can rest assured that no further tests are needed. Those who have inherited the gene can be comforted by the fact that a screening plan will find and treat any tumours as early as possible. In this way, problems caused by the tumours in PPGL syndromes may be greatly reduced.

Genetic consultations are available through the NHS and a referral to your Regional Genetics Service is usually made through your GP or specialist.

Emotional Wellbeing

Living with a rare disease 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, our Counsellor is sometimes available for face-to-face sessions at our free events. See the AMEND 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 our 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 (www.youtube.com/AMEND3).

"Really great help, we are very grateful to [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!!"

Glossary

Ablative therapy minimally invasive procedure to destroy abnormal tissue

Adrenalectomy surgery to remove an adrenal gland

Adrenal Cortex The outer layer of the adrenal gland that makes hormones called glucocorticoids

Adrenal Glands a walnut-sized organ found above each kidney that make stress hormones

Adrenal Medulla The inner layer of the adrenal gland that makes the stress hormones, adrenaline and noradrenaline ('fight or flight' hormones)

Alpha-blockade a special blood pressure drug that widens the blood vessels to help control high blood pressure

Benign a lump or tumour that is not cancer

Beta-blockade a commonly used blood pressure control drug that is also used to keep heart rhythms normal

Catecholamine a class of stress hormones made by the adrenal glands

Chemotherapy cancer treatment using chemicals

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

False Positive Result a test result that shows a person has a disease or condition when they do not

GIST Gastrointestinal Stromal Tumour. Soft tissue cancer found in the stomach and/or gut

Glucocorticoids A class of steroid hormones (e.g. cortisol), made in the adrenal cortex, that regulate many systems in the body, such as metabolism and the immune system. When both adrenal glands are removed, they are replaced using the drugs hydrocortisone or prednisolone

HNPGL Head and neck Paraganglioma

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

Hypertension blood pressure that is higher than normal

Laparoscopic surgery surgery using long instruments inserted into the body through a few small cuts

Malignant a medical word for cancer

Metanephrines a substance which is measured in urine and/or blood to help diagnose a phaeochromocytoma

Mineralcorticoids a class of steroid hormones (e.g. aldosterone), made in the adrenal cortex, that regulate fluid and salt levels in the body. When both adrenal glands are removed, they are replaced using the drug, fludrocortisone

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

Paraganglioma a tumour like a phaeochromocytoma that develops in areas of the body outside of the adrenal glands in cells near blood vessels and nerves

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

PGL Paraganglioma

PPGL Phaeochromocytoma and Paraganglioma (syndrome)

Targeted therapy Use of drugs to find and attack specific cancer cells

Useful Organisations

AMEND

Empowering patients with MEN and PPGL syndromes through information, support and friendship
Tel: 01892 516076
www.amend.org.uk

Neuroendocrine Cancer UK

National charity supporting and educating patients and families affected by neuroendocrine tumours
Tel: 0800 434 6476
www.neuroendocrinecancer.org.uk

GIST Support UK

National charity supporting and educating patients with gastrointestinal stromal tumours
Tel : 0300 400 0000
www.gistsupportuk.com

Paediatric and Adult Wild-Type GIST

www.pawsgistclinic.org.uk

Kidney Cancer UK

Support and Information for UK patients with kidney cancer
Tel : 0800 002 9002
www.kcuk.org.uk

Human Fertilisation & Embryology Authority (HFEA)

Information on UK regulations for use of Pre-implantation Genetic Testing (PGT) in SDHB
www.hfea.gov.uk

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Afterword

The aim of this book is to answer those questions, sometimes in great detail, that someone with a PPGL syndrome may come across during diagnosis and treatment. It is not for use in self-diagnosis. 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 may have carefully with your specialist. Every care has been taken to ensure that the information contained in this book is accurate, nevertheless, AMEND does not accept responsibility for any clinical decisions.

About AMEND

Members have access to all the membership benefits of AMEND, including the free Counselling Service, resources and events, as well as to a dedicated website at www.phaeoparasupport.org.uk.

AMEND is a Charitable Incorporated Organisation registered in England and Wales (number 1153890). It provides support services and information resources to families affected by multiple endocrine neoplasia and inherited paraganglioma syndromes. AMEND hosts regular free patient information events each year and runs social media forums connecting patients for peer support. We rely entirely upon donations in order to provide all our resources and services for free.

How we can Help

AMEND provides a free counselling service for members. AMEND can also put you in contact with others who have PPGL Syndromes to offer support through sharing their experience.

If you have found this resource useful, please visit our website for more information on AMEND or to make a donation: www.amend.org.uk

Membership, resources and services are FREE for affected families

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