Phaeochromocytomas

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

PATIENT INFORMATION

AMEND

Association for Multiple Endocrine Neoplasia Disorders

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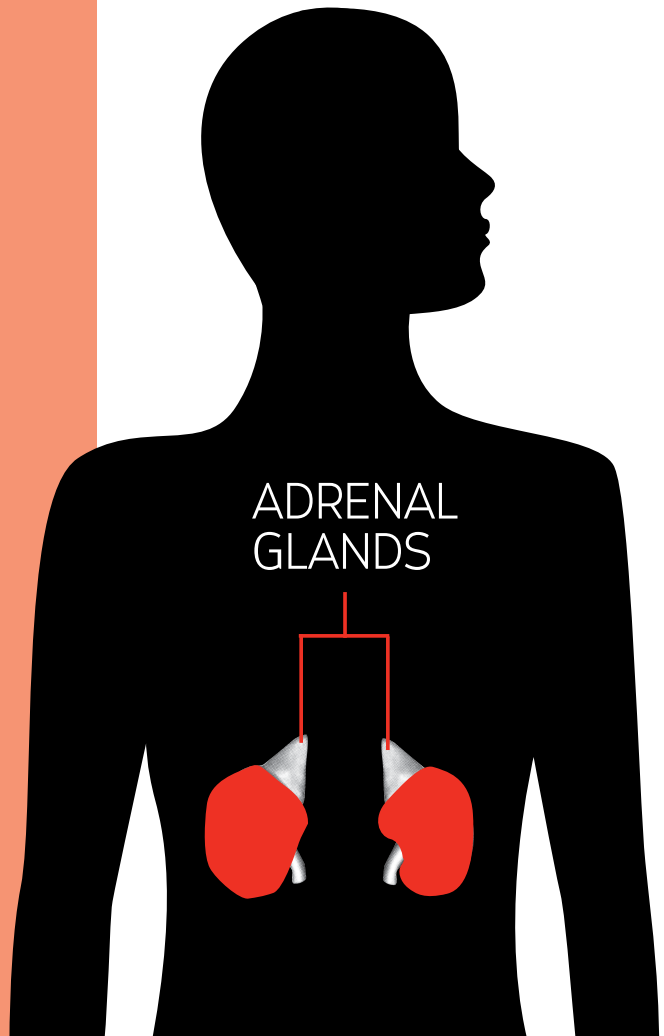
Membership is FREE

Contents

What are Phaeochromocytomas?

Phaeochromocytomas (pheochromocytomas), often known as 'phaeos' ('fee-ohs'), are rare tumours which occur in the inner part of the adrenal gland. Rarely, they can occur elsewhere in the body when they are usually called paragangliomas.



The body has two adrenal glands, one on top of each kidney ('adrenal' 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 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 may make more of these hormones than normal, causing a wide range of symptoms that can affect the whole body (See 'What are the symptoms of phaeochromocytomas?').

Phaeos can affect people of all ages, including children. Because they make hormones, phaeos are classed as a special type of tumour called a neuroendocrine tumour or neoplasm (NET / NEN).

- Phaeos are rare and occur in only around 1 per 100,000 people per year
- Most phaeos (around 8 out of 10,

or 80%) are benign tumours (i.e., not cancer)
- More than 8 in 10 or 80% of phaeos grow in the adrenal glands
- At present there are a lack of sensitive markers to identify those tumours that are more likely to behave as a cancer versus most tumours which are benign. Therefore, in current practice it is recognised that all phaeos have the potential to behave like a cancer (although only the minority do) and follow-up is directed accordingly
- The most common age for diagnosis is between 30-60 years of age, although 1 in 10 or 10% are found in children
- Phaeos occur equally in all genders and ethnicities
- Phaeos diagnosed in children are more likely to be related to a condition that runs in families than those that occur in adults, but even in adults many may be (see 'Do phaeochromocytomas run in families').

What are the 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 related to the high blood pressure (hypertension) that can be caused by this tumour. It is thought that one case of hypertension in every 500-1000 patients is due to phaeochromocytoma. Hypertension in patients with phaeos can be very difficult to control before they are diagnosed; however, once a diagnosis is made, special drugs are available to help to control it.
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, meaning that they have regular scans to look for them (See 'Do Phaeochromocytomas Run in Families?'.

How are Phaeos Diagnosed?

Phaeos can be hard to diagnose unless a patient is known to have a higher risk of developing them due to a condition that runs in the family. This is because the symptoms are often very varied and easy to put down to something more common. 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, several tests may be recommended by your doctor. These may include:

24-hour urine test (metanephrines): This test measures the level of metanephrines in urine that is collected 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.

24-hour Urine Tests

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, noting the time you finish the next morning. Your doctor should give you specific instructions. Follow them carefully. Women may also receive a small, sterilised, plastic jug to help with collection.

Plasma Metanephrine Test: These days, testing the blood (plasma) for levels of the breakdown products, metanephrine and normetanephrine, are being used more widely to help diagnose phaeos. This test should be done after the patient has been lying quietly in a calm, warm place for about 20-30 minutes to avoid a false positive result.

It is important that you tell your specialist about any medicines or drugs you are taking.

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 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 or be taken up by the tumour. These scans are now replacing the MIBG scan, although MIBG may still be used when considering certain types of treatment.

Treating Phaeochromocytomas

The main form of treatment for most phaeos is surgery to remove the gland containing the tumour, called an adrenalectomy. The type of surgery done depends on many factors such as the where the tumour is and the size of the tumour. Most tumours can be removed by key-hole surgery (laparoscopic surgery) through a series of small cuts in the belly or in the back. Larger tumours may be removed through the belly or back using a larger single cut.

If your phaeo is thought to be cancer and it has spread locally, then the surgeon will remove the tissues immediately around the adrenal gland 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 medication. 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.

Due to the risk of sudden spikes in blood pressure caused when phaeos are handled during surgery, patients are usually given special blood pressure medicine before surgery (see 'Medicines'). This will sometimes be done as an inpatient.

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 Pheo/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.

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, 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 in the belly. 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).

Phaeos can cause very unstable blood pressure during and after surgery. To help stabilise this you will be given medication (anti-hypertensive drugs) called alpha- and sometimes also beta-blockers for at least 10-14 days before surgery and sometimes for a much longer period. This practise of controlling the blood pressure is done even for patients with little or no symptoms to minimise any risk during surgery. Following surgery, the blood pressure should return to normal.

Alpha-blockers

Alpha-blockers (phenoxybenzamine or doxazosin) have side effects such as feeling dizzy, a dry mouth and a stuffy nose. Your doctor may ask about these symptoms because it tells them that the drug is working. Men may also find that they cannot ejaculate during sex. Patients can take these drugs at home for the time before surgery. The side effects of the drugs decrease during this time as the body absorbs more salt and water to fill up the blood vessels, but the patient 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.

Who should do the surgery?

Research has shown that the more adrenal operations a surgeon does in a year, the better a patient will do during and after the operation. Current treatment guidelines suggest that an experienced adrenal surgeon is one who does more than six (6) adrenal operations in one year. In fact, there are very few surgeons in the UK who do more than 6. Having a surgeon 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 and hospital team (multidisciplinary team) who are used to dealing with this, and, in particular, the anaesthetist should have experience in this area. 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 at https://goo.gl/KNaAcd.

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 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 your GP for help in finding the right hospital and MDT.

Treating Metastatic Phaeochromocytomas

Currently, it is difficult for doctors to know which phaeochromocytomas may become cancer (malignant) and spread to other parts of the body (become metastatic). The aim at the first surgery is to completely remove the tumour and adrenal without leaving any tissue behind. However, sometimes, cells that are too small to see are left behind and may regrow in the same place (recurrence) or spread to other areas of the body (metastasis). 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 ^{131}I-MIBG is sometimes used. You may have already had an MIBG scan during the tests requested by your doctor to help assess your symptoms and make the diagnosis. If you are MIBG-positive, it means that your tumour can take up this chemical – in other words it has special receptors on its surface which take up the MIBG. If so, MIBG can also be used as a treatment, and is one of the so-called radionuclide therapies.

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.

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 although 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 can have side effects and this will be discussed in detail with you before you think about starting this therapy.

Newer Therapies

Several new 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.

Medicines

If you have a phaeo and are waiting for treatment, you will need to avoid certain medicines that may make your symptoms worse, some of which are listed below:

If you are already prescribed any of the below medicines, please do not stop taking them unless your doctor has told you to do so. In 2019, AMEND produced a *Phaeo/Para Crisis Card* for phaeo patients awaiting treatment to carry with them to show to pharmacists and doctors before taking any medicines.

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

What is a multidisciplinary team (MDT)?

Before you have any treatment, your case will be discussed by the hospital's adrenal 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 possible. MDTs are usually found in larger university training hospitals.

The main adrenal MDT will usually include:

- Specialist Adrenal surgeon (one who does more than 6 adrenal operations each year)
- 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 (to ensure that everything runs smoothly)

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 a choice of treatments
- Receive better coordinated care through 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.

Pregnancy in Patients with Phaeochromocytoma

Managing a pregnant patient with a phaeochromocytoma can be a challenge. If you have a phaeochromocytoma and are planning a family, it is advisable to wait until after treatment. If you become pregnant while you have a phaeochromocytoma, 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 in a pregnant patient as they may affect the unborn child (e.g., CT and MIBG scans and alpha-blockade). If surgery is possible, this can be done laparoscopically 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.

Do Phaeochromocytomas Run in Families?

Most phaeos are not linked to a condition that runs in families (genetic condition) and are therefore known as 'sporadic' tumours. However, nearly 1 in 2 or some 40% of phaeos are due to a gene change that has been passed down in a family, and this rises to 50% if the phaeo originates outside the adrenal. This gene change leads to an increased risk of developing a phaeo. These genetic phaeos can occur as part of a syndrome which may include additional medical problems. New genes continue to be discovered and our understanding of what patients carrying these genes can expect is growing all the time. It is generally now agreed that almost all patients with phaeos should have genetic testing.
Some of the inherited syndromes where phaeos can occur are:

1. **Multiple Endocrine Neoplasia types 2 and 3**
   Patients with MEN types 2 and 3 have a 1 in 2 (50%) risk of

phaeos and may also develop other tumours in the thyroid and parathyroid glands in the neck. (See the separate AMEND Patient Information Books on MEN2 and MEN3).

2. **Neurofibromatosis type 1 (NF1)**
   Phaeos occur in fewer than 6 in 100 people with NF1. NF1 patients may also develop problems with the skin, musculoskeletal and nervous systems.
3. **Von Hippel-Lindau syndrome (VHL)**
   As well as phaeos, people with VHL may also develop cysts and tumours of the pancreas, kidney cancer and growths in the spine, brain, and eyes.
4. **Familial paraganglioma syndromes (PPGL)**
   PPGL syndromes increase the risk of developing phaeos in the adrenal gland and phaeo-like tumours called paragangliomas throughout the body. (See the separate AMEND Patient Information Book on PPGL Syndromes or visit our website for PPGLs at www.phaeoparasupport.org.uk).

You may have this test organised by your endocrinologist or be offered an appointment with a clinical genetics service. A Clinical Geneticist or a Genetic Counsellor will explain more about possible genetic conditions that involve phaeochromocytomas and ask about your family's medical history. They may then discuss your options around genetic testing for these conditions. If a disease-causing gene change is identified, a Clinical Geneticist will be able to discuss what this means for you and possibly for other members of your family, especially children.

Do Phaeos occur in children?

In children most phaeos occur in just one adrenal gland, however, in 20% (1 in 5) of cases they can affect both glands.
About 1 in 3 young patients have tumours outside the adrenal gland with or without a tumour inside the gland.

The common early symptoms in children are like those of adults, including headache, fast heart rate and sweating. Their blood pressure is often raised. Children will have the same tests as adults to find the cause of the symptoms and to make a diagnosis.
A child with a phaeo would be a sign that they should be tested for a genetic syndrome (See 'Do Phaeochromocytomas run in families?').

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, AMEND's Counsellor is sometimes available for face-to-face sessions at our free events. See our website for more details.

AMEND has produced some specific resources that we are sure patients will find useful. 'Dealing with Diagnosis', 'Living with Uncertainty' and 'Looking after Yourself' are available to download for free from the Resources section of AMEND's website or in hard copy on request. A series of podcasts and an introductory video on the relaxation method, Mindfulness, have also been developed as part of this project and are free to access via our website and YouTube Channel (AMEND3).

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

Glossary

Adrenalectomy: surgery to remove an adrenal gland
Adrenal Cortex: The outer layer of the adrenal gland that makes hormones called glucocorticoids
Adrenal Glands: a pair of walnut-sized organs found above the kidneys 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
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
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 in urine which is measured 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
Phaeochromocytoma: a growth in the inner part of an adrenal gland which makes greater than normal levels of stress hormones

Useful Organisations

AMEND
Empowering patients with MEN and associated endocrine conditions 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

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Afterword

The aim of this book is to answer those questions, sometimes in great detail, that someone with a phaeochromocytoma may come across during diagnosis and treatment. It is not for use in self-diagnosis. It is possible that not all 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 cannot accept responsibility for any clinical decisions.

About AMEND

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

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Notes