FABRY AUSTRALIA

Understanding Fabry Disease

Fabry Disease Fact Sheet

Fabry Disease (FD) is a rare, hereditary, genetic condition. Along with other diseases, it is classified as a 'lysosomal storage disorder'. This fact sheet explores the disease presentation and clinical management.

This fact sheet is produced by Fabry Australia. It is based upon the experiences of those affected by FD, their families, and their doctors.

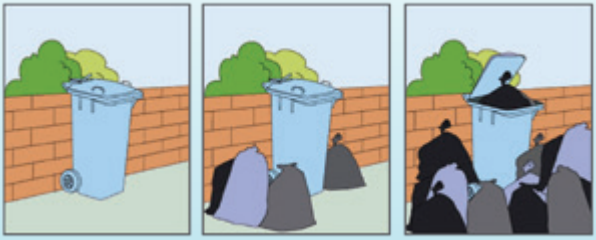
What causes Fabry Disease?

Fabry Disease is a rare, genetic disorder. Normally, in the cells of the body, there is a continuous recycling process, which consists of building new materials and breaking down old materials for disposal. Some of these processes occur in a special part of cells, called the lysosome. This process requires a series of biochemical tools, called enzymes. Enzymes can only reach the lysosomes after a special 'signal' has been attached to them.

Adults and children with FD are missing, or deficient in, an enzyme called alpha-galactosidase A (Alpha-Gal A), which is essential in the breakdown of waste products in the lysosomes, of many different types of cells within the body.

The main waste product is Globotriaosylceramide (GL-3 or Gb3). When GL-3/Gb3 waste products build up in the cells of the body, they start to cause progressive damage. Newborns show little sign of the disease, but as cells become damaged, by an accumulation of GL-3/Gb3, symptoms start to develop.

A good analogy is removing household rubbish. If this job was ineffective or non-existent, the household rubbish would take over its surroundings. This build up over time is what causes damage to the cells of the body. See diagram below.



How common is Fabry Disease?

FD is a rare disease, and the symptoms are often mistaken for other illnesses. It affects multiple organs, sometimes making accurate diagnosis difficult. It affects males, females, adults, and children.

The prevalence is estimated to be 1:117,000 among males. The condition affects people worldwide across all ethnic groups. The population-specific rates are unknown.

The prevalence may be underestimated, as many people with FD may be undiagnosed, with their organ damage not attributed to FD. It is currently estimated that FD affects approximately 5,000–10,000 people worldwide.

Can females have Fabry Disease?

Yes, females also suffer from FD, however the presentation, signs, and symptoms among females with FD is highly variable. Some females live a long life with few symptoms, others have as many symptoms and complications as a male with FD.

Diagnosis of Fabry Disease

FD encompasses a wide spectrum of clinical symptoms which may or may not appear in all individuals with this disease. This together with its rarity, often delays diagnosis. Many individuals may experience some of the symptoms that are listed here in the fact sheet, before they receive a diagnosis of FD.

Overview of Symptoms

FD often presents itself during childhood as pain and may be overlooked by a GP and misdiagnosed as 'growing pains'. The onset of signs and symptoms varies between people, even within the same family.

Symptoms include:

- Burning sensations (or pain) in hands/feet.
- Headaches.
- Vertigo / dizziness.
- Fatigue.
- Small, raised dark-red dots on the body (called angiokeratomas).
- Sweating too little (condition called hyperhidrosis).
- Intolerance to heat.
- Fever.
- Abdominal pain.
- Vomiting & diarrhoea.
- Tinnitus (ringing sound in the ears).
- Impaired hearing (sometimes hearing loss).
- Alterations in the eye, leading to clouding that can occur in the cornea (known as 'Opacity of the Cornea').
- Depression (patient studies indicate that pain does vary and can contribute to depression, fatigue, and feelings of social isolation).

Over time, patients typically develop more serious symptoms that affect the kidneys, heart, and brain.

Testing for Fabry Disease.

A genetic test can be used to confirm a diagnosis of Fabry Disease. In many cases a diagnosis of FD only occurs after another family member is found to have the disease. Therefore, it is important to advise members of your immediate and extended family, if you have a diagnosis.

A blood test to check levels of the enzyme (Alpha-galactosidase A) will determine if FD is likely, as there are lower levels than normal, in FD affected individuals.

DNA analysis of a blood sample, then determines the specific change or mutation in the genetic sequence. There are many genetic mutations which result in FD.

In females, both amniocentesis and chorionic villus sampling can be used to diagnose FD in early pregnancy. However, please seek advice from your specialist and genetic counsellor, for testing during pregnancy

Testing within your family.

If you or someone in your family has been diagnosed with FD, it is possible that other members of your family may have also inherited the condition.

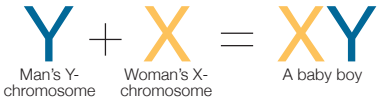
If this is the case, seek a referral from your GP to a Fabry Clinic in your State (see State Fabry Clinics listed in this brochure). This Fact Sheet may be useful to take with you, as your GP may not have heard of FD. It is important that other family members are encouraged to undergoing testing once a diagnosis of FD has been confirmed within the family. Due to the pattern of inheritance however (see below), not all members of the family will be affected.

Genetic Counselling

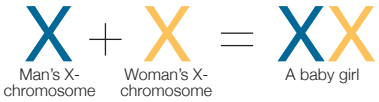
People diagnosed with FD may consider seeking advice from for genetic counsellor before having children. A counsellor will provide non-directive advice on the pattern of inheritance of FD, family planning advice, and genetic screening. The State Fabry Clinics can advise patients of how to obtain Genetic Counselling.

The inheritance pattern of Fabry Disease

We all inherit genes from our parents. These genes are contained on 46 chromosomes arranged in 23 pairs. One of these pairs determines whether an individual is male or female.

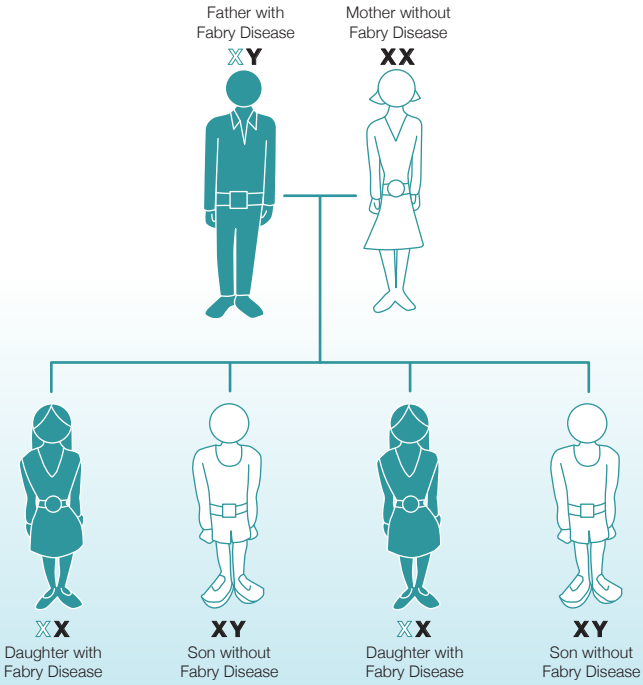


Males have a 'Y' and 'X' chromosome

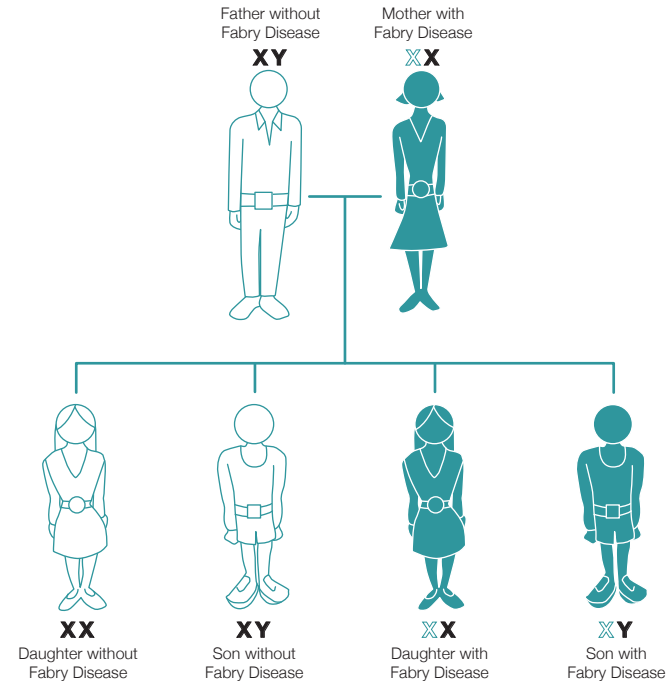


Females have two 'X' chromosomes.

In FD, the defective gene is located on the 'X' chromosome.
The disease is therefore following an X-inheritance pattern.



An affected male (see diagram above) will have sons without FD, however all his daughters will have the FD gene.



In affected females (see diagram above) there is a 50% chance that a daughter will have the FD gene and a 50% chance a son will have the FD gene.

Clinical Presentation of Fabry Disease

FD encompasses a wide range of clinical symptoms which may not appear in all affected individuals. The symptoms usually worsen with age. **Not all individuals with FD will experience all the symptoms, outlined in this Fact Sheet**. Some patients also have 'atypical variants', which can alter the clinical presentation.

Pain

Pain is the most common symptom of FD and is often the symptom that most people with FD first experience. Pain due to FD may go undiagnosed during childhood and be labelled as 'growing pain'. Fabry pain is caused by the accumulation of waste products in the nerve cells. The pain can be a constant background pain or short-term severe pain. Pain can be triggered by change in temperature, episodes of stress or physical activity. Short term severe pain is often known as a 'Fabry Crisis', lasting from a few minutes to several days, and is often described as an intense burning which starts at the extremities (fingers and toes) and spreads throughout the body. Pain due to FD is often debilitating and may affect everyday activities.

Kidney Function

The accumulation of waste products in kidney cells and in the wall of blood vessels supplying the kidney, can impair kidney function over time. This may lead to reduced kidney function by early adulthood, which will be indicated by raised protein levels in the urine.

Heart

Accumulation of waste products within the cells of the heart or the walls of the coronary arteries may cause individuals with FD to develop heart problems. Some initial symptoms include shortness of breath, irregular, or fast heartbeat, enlarged heart, chest pain (angina) and increased risk of heart attack or heart failure.

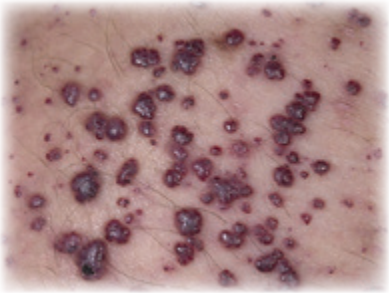
Stroke

Individuals with FD may develop a stroke. This may be a minor stroke followed by a full recovery (Transient Ischaemic Attacks or TIA's), but more severe strokes can occur. Medication to prevent stroke may be prescribed.

Eyes

The surface layer of the eye (cornea) may appear abnormal when examined by an optometrist or an eye specialist (ophthalmologist) with special equipment. This starburst, or whorling appearance, which is called 'Cornea Verticillata', does not affect vision but may increase with time. It occurs in approximately three-quarters of patients and can be a reliable indicator of FD.

Skin



Angiokeratomas are the most visible recognisable clinical feature of FD. These dark red or purple skin lesions (ranging in size from pinpoint to several millimetres in diameter) do not blanch with pressure and are usually distributed on the buttocks, groin, umbilicus, and upper thighs (bathing trunk distribution). This rash-like skin condition is not painful. It can also appear on other parts of the body such as the lips, tongue, hands, and toes. They generally start to appear in adolescence or young adulthood.

Reduced Sweating (Anhidrosis)

Many people with FD sweat less than people without the disease. They may either perspire very little or not at all. This can cause overheating, frequent fevers, and sensitivity to weather extremes. Some patients may have increased sweating (Hyperhidrosis), which is more common in females. Impaired sweating is generally caused by damage to the nerves of the sweat glands.

Nervous System

Individuals with FD may suffer from headaches, vertigo, and a ringing sound in the ears (Tinnitus). Some patients may experience a degree of hearing loss, and this can either progress over time or be quite sudden.

The Bowel

Individuals with FD may experience bowel discomfort or pain, due to the accumulation of waste products within the cells of the intestine, or the blood vessels and nerves supplying the intestine. Other possible symptoms include vomiting, nausea, and diarrhoea. Dietary changes may reduce the severity of symptoms, which can be discussed with your specialist or a dietician.

Depression / Fatigue/ Psycho-social aspect

Living with physical symptoms are one of the challenges people with FD face. Fatigue is a commonly reported symptom, which is an ‘invisible’ symptom. Fabry sufferers may also experience feelings of fear, depression, isolation, or guilt about passing the disease to children. It Is important that Fabry sufferers seek assistance for their mental as well as physical health.

Progression of Fabry Disease

There are differences between FD in childhood, adolescence, and adulthood. It is important to remember that not all individuals with FD will experience all the symptoms outlined here in this Fact Sheet and some adults with the disease will experience some of the symptoms associated with the disease in childhood and vice versa.

Children

Pain and angiokeratomas, characteristic abnormalities of the eye, gastrointestinal symptoms (such as alternating between bouts of diarrhoea and constipation), tummy pains and hearing problems are usually the only symptoms of FD in childhood. The pain is often attributed to common 'growing pains'. After diagnosis, it is important that children are given support in understanding their disease and any limitations it may present, but are also encouraged to remain positive, and to participate in normal activities with their family and peers.

Adolescents

During adolescence, many of the skin problems experienced during childhood may worsen. This is often the time when bowel and nerve pain develops. The first stage of impaired functioning of the kidney and heart can also occur at this time.

Adults

FD is slowly progressive. Symptoms result from damage to the kidneys, heart and central nervous system. Kidney problems in males with FD usually become much more severe during early adulthood. The heart becomes affected after the age of about 40 years and the risk of strokes increase.

Living with Fabry Disease

FD can be a debilitating condition, associated with many problems and shortened life expectancy. With the development of Enzyme Replacement Therapy (ERT) however, many Fabry affected individuals and families live fulfilled lives. Alleviation of symptoms often enables adults with FD to participate in day-to-day family life, sustain relationships and seek employment. Children affected by the disease can enjoy social and physical activities with their peers.

Many adults who have FD understand it is an inherited genetic condition which affects more than just themselves. Many have prematurely experienced the loss of a parent or loved one through the disease. In a significant number of cases, FD has

gone undiagnosed for a long period of time. Many affected individuals are somewhat relieved when they receive a diagnosis, as they find the cause of the unusual childhood symptoms.

For many Fabry patients, accessing funded treatment which alleviates symptoms, has greatly enhanced quality of life. This enables them to contribute and participate as full functioning individuals in society, and can have a positive effect on relationships and the family. It also allows the family to not be so restricted by the debilitating symptoms and emotional burden of living with this rare and complicated disease.

Thoughts from Fabry patients

'What a relief to know all the pain and suffering from a relatively miserable childhood was not actually something in my head but actually as a result of FD!'

'I am so glad I contacted Fabry Australia. They were a Godsend and a huge emotional and practical support to me and my family. Thank you Fabry Australia!'

'A tip to others who receive a positive diagnosis is to learn as much as you can about this complex condition and try not to panic.'

'When I was diagnosed with FD, I felt somewhat guilty that I had given this to my children. It took a while for me to accept I have this condition and so do my loved ones. But we are learning together.'

'Everyone copes differently. It is important not to let the negative comments influence you. Keeping positive is essential.'

My Dad's Story by Megan Fookes OAM

In 1994 a man (David Davie), was diagnosed with FD at the age of 48. After researching and finding very little information about such a rare fatal condition, his wife, Margaret, wrote to the *Australian Women's Weekly* with an article featuring her husband and his new predicament. As a result, many other people who had been diagnosed with this fate, reached out for support.

The first Fabry Australia meeting was held on 4th June 1994 at the Murdoch Institute, Royal Children's Hospital, Victoria with over 55 people in attendance. It was an outstanding success, and the consensus of the meeting was that a Fabry Support Group be formed. Fabry Australia was officially incorporated from 20th

June 1994. It was at this time that the Royal Melbourne Hospital Nephrology Department agreed to form a central Fabry Clinic at the Royal Melbourne hospital and to do some Genetic Research at this clinic. One of the problems of suffering a rare disease such as Fabry is that any individual doctor is likely to have limited experience in treating the condition. The setting up of the Fabry Clinic was a milestone for Fabry patients.


My husband is so special

Fabry Australia is very fortunate to have a lot of support from its members and some quiet 'heroes' like Merle the 'coat hanger queen' who has lost 2 daughters and a husband from FD. Merle worked hard to hand craft items, such as covered coat-hangers and clothed children's teddy bears, with a message attached saying 'all proceeds go to Fabry Research'. Merle's fundraising supported several medical students to research FD. Today, supporting research into FD continues to be a high priority, and Fabry Australia are grateful for the continued fundraising efforts of our members.

Current Treatments for Fabry Disease

There are several symptomatic and protective/preventative treatments recommended for FD. Current treatments for FD which are government funded, Include Enzyme Replacement Therapy, and Chaperone Therapy. At the time of printing, further treatments are undergoing trials. Please discuss the best option with your Fabry Specialist.

Enzyme Replacement Therapy (ERT)

Enzyme Replacement Therapy (ERT) for FD is designed to replace the missing or malfunctioning enzyme, Alpha A, in individuals with FD. The enzyme is manufactured from cultures of cells which have been genetically engineered to express the human enzyme. This enzyme is given by intravenous infusion each fortnight to stabilize and reduce FD symptoms.

Treatments are administered in a local hospital or via home infusion, administered by a nurse, and some patients infuse themselves. The first 12 treatments are usually co-ordinated at the State Fabry Clinic.

The principle underlying this treatment is that the enzyme that is missing or not functional may be partially replaced by infusing this therapeutic form of the enzyme. The enzyme used in treatments contains a particular chemical 'address' on its surface, that allows it to be taken up by cells from the blood and transferred to the lysosome of the cell, where it carries out its work in breaking down the storage material Gb3 (GL-3). The aim of the treatment is to help relieve symptoms and to prevent progression of damage to important organs, like the kidney and heart. Criteria have been devised for the initiation of therapy and are based on the responsiveness of various organs to treatment. In Australia, criteria are based around changes in the heart, brain and kidneys or pain and gastro-intestinal symptoms which affect quality of life.

Chaperone Therapy.

Some FD mutations result in a “functional deficiency” in enzyme function, where the enzyme is present, but is a poorly functioning. This mutated Alpha Gal-A enzyme may be unable to fold and configure in the correct 3-dimensional manner. This prevents the enzyme from entering the lysosome of the cells of the body, where it is needed to break down the ‘substrate’ (GL-3/ Gb3) that is the cause of Fabry disease. Chaperone therapy is an oral therapy, which binds to the enzyme already present in the patient’s body and ‘chaperones’ the enzyme into the lysosome of the cell, where it is required. Once in the lysosome, it detaches from the enzyme, leaving the enzyme free to fulfil its function.

Chaperone therapy will not work for all FD patients, and the success of this treatment depends on the type of mutation present. To determine if a patient could benefit from chaperone therapy, you must know the mutation they have. Mutations that chaperone therapy is suitable for are often called “amenable” mutations.

Emerging Treatments...

At the time of printing, new treatments are undergoing clinical trials, including ‘Substrate reduction therapy’ and ‘Gene Therapy’.

For many years, Australian Fabry patients have enrolled in clinical trials. Patients are needed to collect data required by the Australian government, to demonstrate that a medicine is safe and effective. Results from trials can lead to the development of medicines to further improve lives of people suffering from FD. For further information regarding Clinical Trials, please discuss with your Fabry treating specialist or go to **medicinesaustralia.com.au/issues-information/clinical-trials.**

How is treatment for Fabry Disease funded?

FD treatments are approved and funded by the Federal Health Department under the Life Saving Drugs Program (LSDP). Treatment is available only to those who qualify and meet criteria for approved therapy. Further information can be found at: **https://www.health.gov.au/initiatives-and-programs/life-saving-drugs-program. Speak to** your State Fabry doctor about treatment options.

How often do I go to the Fabry clinic?

It is recommended that FD patients visit their clinic for review approximately every 6-12 months. Any changes of signs or symptoms should be reported to the Fabry doctor, as FD is progressive. Ask to participate in the FD Registry. Registries are important to further assist FD experts in the clinical management of patients.

Tracking symptoms of Fabry Disease

It is useful to keep a diary of symptoms for you or your child such as pain, gastro symptoms, illness, dizziness, fatigue, fever – see Fabry Australia for a Fabry Diary.

About Fabry Australia

Fabry Australia (formerly known as Fabry Support Group Australia) was founded in 1994. It is a not-for-profit Patient Organisation founded and operated by people with a direct connection to Fabry Disease. A volunteer committee undertakes to further the mission of the organization, 'Uniting and supporting the Australian Fabry Community'.

The goals of Fabry Australia are to:

1. Promote patient advocacy.
2. Share information, knowledge, and resources.
3. Promote and support research and development.
4. Encourage active involvement with patients, medical community, partners, and industry groups
5. Raise awareness and understanding of Fabry within the Community.
6. Maintain financial and resource viability.

Fabry Australia connects with over 450 individuals including patients, families, carers, and professionals. Fabry Australia works in collaboration with a range of stakeholders such as the Fabry State Clinics, Health Professionals, Allied Health Professionals, Pharmaceutical Companies and Government Departments, in relation to issues surrounding access to appropriate health care, services, and treatment of Fabry Disease in Australia.

Fabry Australia offers a range of services and implements projects to further support its members and fulfil our goals. Fabry Australia has received grants from various pharmaceutical companies with an interest in FD. Fabry Australia also appreciates the support and fundraising efforts of individuals, with donations gratefully received. Fabry Australia is a registered charity with Direct Gift Recipient (DGR) status thus allowing all donations over $2 (AUD) to be tax deductible. For further information about the work of Fabry Australia and its services please contact us directly, or go to our website to donate, www.fabry.com.au.

Please note this Fact Sheet is not intended to replace medical advice or care.

Australian Fabry Clinics

Adult Clinics

Royal Melbourne Hospital (VIC & TAS)
Dr Kathy Nicholls
Nephrologist
Ph: 03 9342 7143

Royal Adelaide Hospital (SA)
Associate Prof Ian Chapman
Internal Medicine
Ph: 08 8222 4162

Royal Brisbane and Women's Hospital (QLD)

Dr Charles Denaro
Internal Medicine & Aged Care
Ph: 07 3646 7678
or 07 3646 8346

Royal Perth Hospital (WA)
Dr Mark Thomas
Nephrologist
Ph: 08 9224 2550

Westmead Hospital (NSW & ACT)
Dr Michel Tchan
Metabolic Clinic
Department of Genetic Medicine
Ph: 02 9845 9780

Paediatric Clinics

Royal Children's Hospital (VIC)
Dr Heidi Peters
Clinical Metabolic Services
Ph: 03 9345 6251

Women's and Children's Hospital (SA)
Dr Drago Bratkovic
Metabolic Clinic
Ph: 08 8161 6726

Royal Children's Hospital, Brisbane (QLD)
Dr Jim McGill
Metabolic Medicine
Ph: 07 3646 8111

King Edward Memorial Hospital (WA)
Associate Professor Nicholas Pachter
Genetic Services of Western Australia
Ph: 08 6458 1525

The Children's Hospital at Westmead (NSW)
Assoc Prof Carolyn Ellaway
Genetic Metabolic Disorders Service
Sydney Children's Hospital Network
Ph: 02 9845 3654

Fabry Australia

Fabry Australia is a patient lead non-profit membership patient organisation founded in 1994. Fabry Australia is a registered charity supported by voluntary donations, educational grants, fundraising and is managed by the members themselves.

Our Aims

- Improve contacts, information and support to people affected by FD and their families.
- Bring about more public awareness of FD
- Improve medical services to Fabry patients in Australia.
- Promote and support research into FD.
- Share information on FD, ongoing management and care available treatments/therapies to Fabry patients.
- Build links with families, clinicians, researchers, support groups to strengthen and support local knowledge about FD.
- Co-operate and collaborate with other Fabry related groups and individuals interested in rare diseases to promote common interests.
- Help raise money to support these aims.

Services include:

- Website
- Social Media
- Australian Fabry Expert Meetings
- State Fabry Patient Meetings
- Fabry Australia Newsletters
- Fabry Disease Advocacy
- Educating families and doctors
- Funding Fabry research
- Fabry Educational Materials
- Visiting international Fabry Experts
- Fundraising activities
- Fabry Awareness Month Campaigns
- Fabry Australia Membership Retreats

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FABRY AUSTRALIA

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