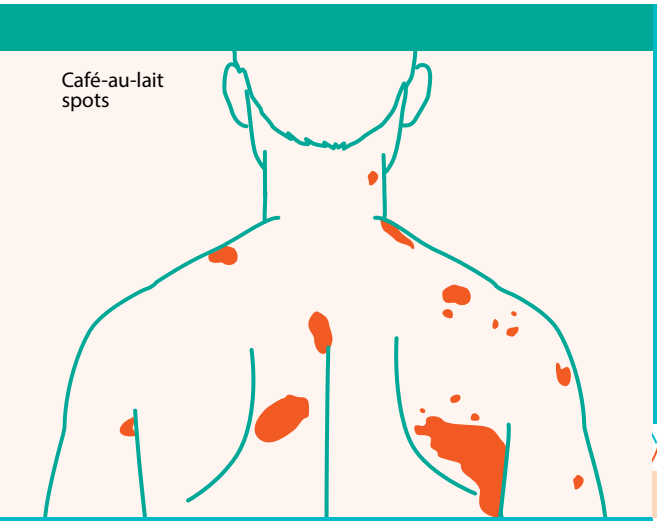
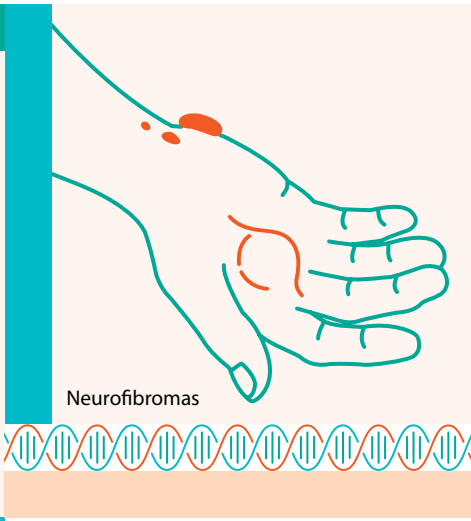
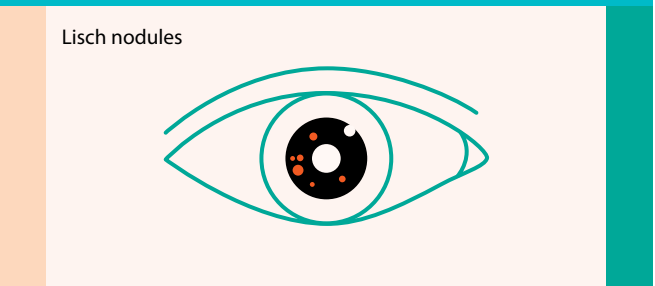
SingHealth DukeNUS
ACADEMIC MEDICAL CENTRE

Genomic
Medicine Centre

Neurofibromatosis Type 1







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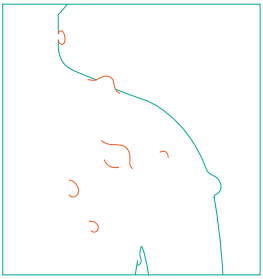
What is Neurofibromatosis type 1?

Neurofibromatosis type 1 (NF1) is a genetic condition that can affect the brain, spinal cord, nerves and skin.

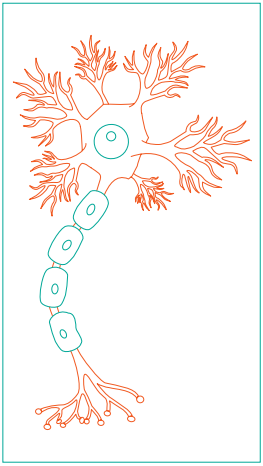
It is characterised by skin changes and the growth of tumours along the nerves in the body. These tumours are usually not cancerous.



Neurofibromas

How common is NF1?

It is estimated that **one in 3,000 people** have NF1. This condition has been observed in all racial groups and affects both genders.

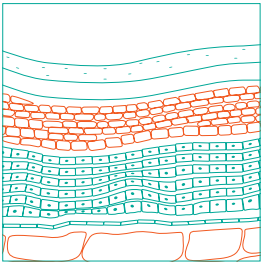


Nerves

How is NF1 diagnosed?

NF1 is generally diagnosed through a physical examination by a doctor with experience in managing NF1, who will assess if the clinical diagnostic criteria of NF1 is met.

Although NF1 is a hereditary condition that one is born with, some symptoms develop gradually over a number of years. The severity of symptoms varies from person to person. Almost all individuals with NF1 are diagnosed by adulthood.

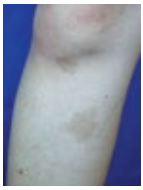


Skin

People may be diagnosed with NF1 by their doctors when they meet two or more of the following features:

1. 6 or more café-au-lait spots

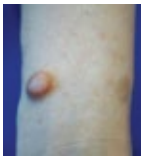
- Multiple flat, coffee-coloured patches on the skin
- These spots must be more than 5 mm in diameter in young children and more than 15 mm in diameter after puberty
- About 10-25% of the general population has café-au-lait spots



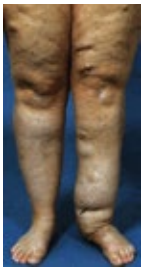
2. Freckling around the armpits or groin

3. 2 or more neurofibromas or 1 plexiform neurofibroma

- **Neurofibromas** are pea-sized bumps that can grow on the nerve tissue or under the skin. They may appear just before puberty and tend to increase in number throughout life. The number of neurofibromas in individuals with NF1 can vary greatly, from just a few to hundreds.



- **Plexiform neurofibromas** are larger and deeper tumours around the nerves. Sometimes, they cannot be seen or felt, and may be present from early childhood. They usually do not cause problems, but a few may grow quite large and cause local effects or develop into cancer.



[1]

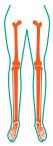
4. Optic pathway glioma

- A tumour along the main nerve of the eye that is responsible for sight
- Occurs in 15-20% of children with NF1

[1] *Adapted from Friedman JM. Neurofibromatosis 1. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews®. University of Washington, Seattle; 2019.*

5. 2 or more Lisch nodules

- The appearance of tiny tan clumps of pigment within the iris of the eyes, that do not affect vision



6. Specific skeletal changes

- The enlargement or malformation of bones in the skeletal system such as tibial dysplasia (curved lower leg bone) or sphenoid dysplasia (abnormally shaped bone around the eye)

7. Family history

- A parent, sibling (brother or sister), or child with NF1

8. A fault (i.e., mutation) in the *NF1* gene

Some children under 8 years of age may have café-au-lait spots, but no other signs of NF1. These children should be monitored carefully to see if other signs of the condition develop.

Other medical concerns related to NF1

The following problems are more common in individuals with NF1 and need to be watched for and treated if necessary:

- Learning difficulties
- Attention deficit disorder (ADD/ADHD)
- Larger head size than average
- Shorter stature/height than average
- Scoliosis (curvature of the spine)
- Early puberty
- High blood pressure
- Headaches
- Increased risk of cancer

The features of NF1 can be very different even among members of the same family.

Most people with NF1 do not have many of the health problems listed above, and live long, healthy lives.

What are the tumour and cancer risks associated with NF1?

Tumours / cancers	Description	Risk
Lisch nodules	Benign eye tumours	Almost 100% by adulthood; not as commonly seen in childhood
Optic nerve gliomas	Cancerous eye tumours that grow in the optic nerve	15 - 20% (~5% are symptomatic and diagnosed under the age of 6)
Malignant peripheral nerve sheath tumours (MPNST)	A type of cancer (sarcoma) that grows from the cells around nerve endings	8 - 15.8%
Gastrointestinal stromal tumours (GIST)	A type of tumour that occurs in the gastrointestinal tract, most commonly in the stomach or small intestine	6%
Female breast cancer	Cancer within the breast	Up to 20%
Astrocytoma / brainstem gliomas	Brain tumours	Up to 3%
Phaeochromocytomas (PCC)	Tumours within the adrenal gland	Up to 2%, of which 12% of these are malignant
Juvenile myelomonocytic leukaemia	Rare cancer of the blood that occurs in childhood	200- to 500-fold increase over background risk, but still rare

What are the tumour and cancer risks associated with NF1? (Continued)

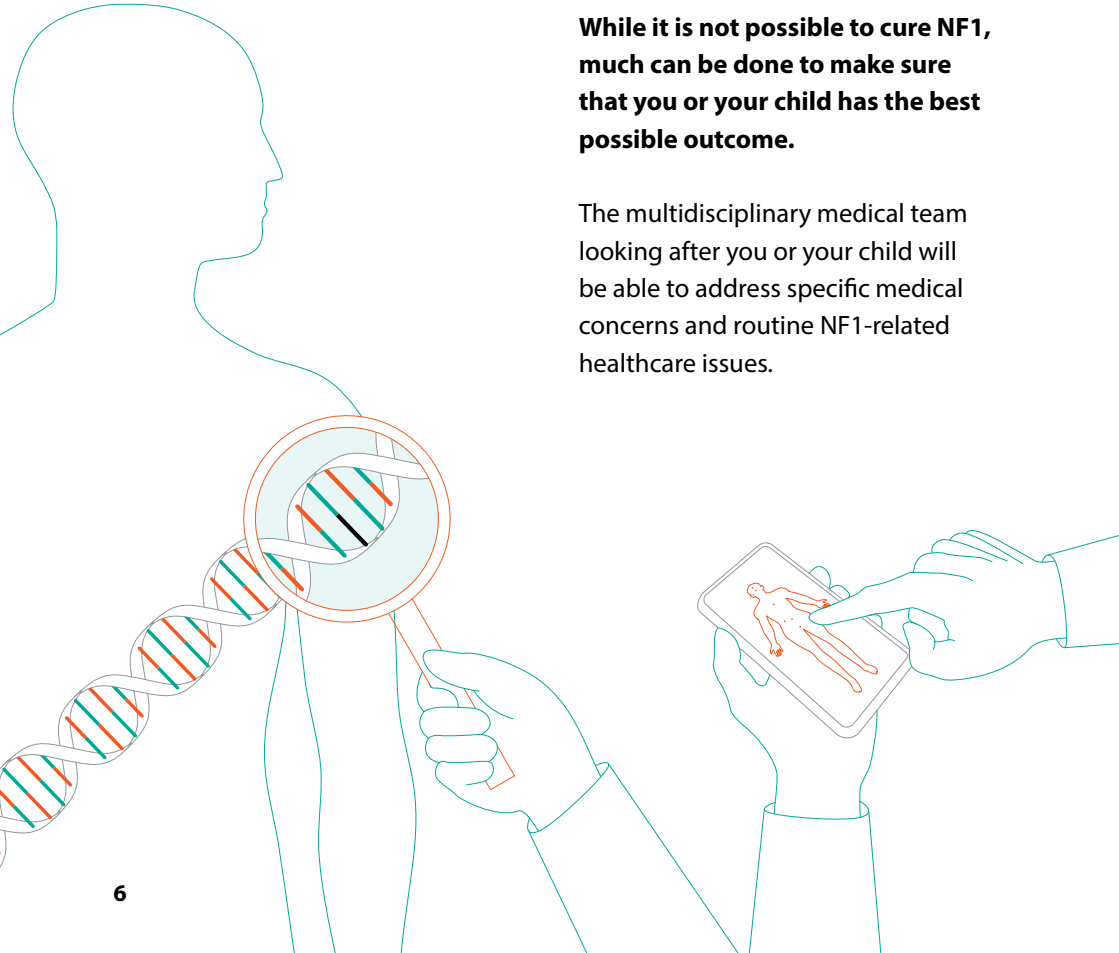
Tumours / cancers	Description	Risk
Muscle tumours	Tumours within the various muscle groups	Increased
Spinal cord tumours	Tumours found along the spinal cord	Increased

Note: The conditions associated with NF1 and their risk estimates may change as more information is available.

Can NF1 be cured?

While it is not possible to cure NF1, much can be done to make sure that you or your child has the best possible outcome.

The multidisciplinary medical team looking after you or your child will be able to address specific medical concerns and routine NF1-related healthcare issues.



What are the medical issues to look out for in childhood and how are they managed?

Medical issue	Treatment
Hypertension	· Regular blood pressure checks
Developmental delay	· Early intervention therapies
Behavioural issues (e.g., ADD)	· Behavioural therapies · Involvement of a developmental paediatrician
Scoliosis, curved lower leg	· Early care by an orthopaedist (a doctor specialising in bones)
Neurofibromas	· If painful or irritating, they can be removed
Plexiform neurofibromas	· Watch carefully; if growing rapidly or causing pain, seek medical attention
Optic gliomas	· Regular eye exams

Sun protection, such as the use of sunscreen, is also recommended.

What causes NF1?

NF1 is caused by a fault (i.e., mutation) in the *NF1* gene. Genes are instructions for cells to make proteins in the body. The *NF1* gene is a tumour suppressor gene which normally produces a protein that blocks the development of tumours and cancer. When faulty, it leads to a diagnosis of NF1 and an increased risk of tumours/cancer.

You can undergo genetic testing to understand if you have a faulty *NF1* gene. As genes are shared among family, if you have a faulty *NF1* gene, it may indicate that other family members may have inherited the faulty gene too and may also be at increased risk of tumours/cancer.

How is genetic testing done?

Genetic testing is typically a one-time blood test. If a blood sample cannot be taken, other sample sources (e.g., skin or saliva) may be explored.

What are the possible results of genetic testing?

There are 3 types of results you may receive:

Positive

Faulty gene(s) identified

Increased risk of developing certain tumours and cancers (depends on faulty gene(s) involved)

Your family (parents, siblings, children and extended relatives) may have inherited the faulty gene(s) and should consider genetic testing to clarify this

Variant of Uncertain Significance (VUS)

Uncertain gene change(s) identified, unclear if these change(s) increase risk for tumours and cancers

May be clarified by testing other family members

May be reclassified over time as 'positive' or 'negative' when more information is known

Negative

No faulty gene(s) identified

If you have been clinically diagnosed with NF1, you may still have an increased risk of certain tumours and cancers. Your doctors will personalise a screening and management plan for you accordingly.

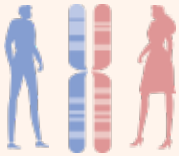
Test limitations will be explained in the context of your personal and family history of clinical features

How is NF1 inherited?

NF1 follows a **dominant inheritance pattern**. This means that having one faulty copy can cause features of NF1.

About half of all people with NF1 have inherited the faulty gene from a parent. The other half have it because of a new and spontaneous change (mutation) in their gene.

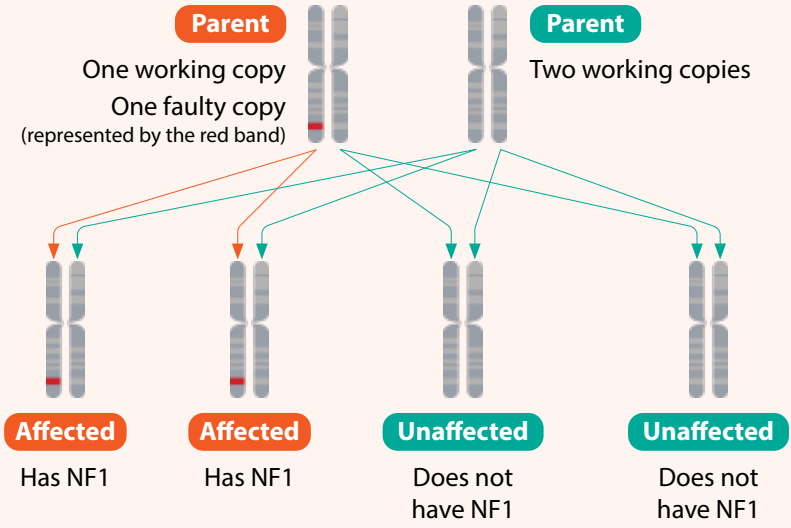
Everyone has 2 copies of each gene in their body's cells:



1 copy comes from our father

1 copy comes from our mother

Dominant inheritance pattern



- A parent with a faulty gene(s) has a 50% chance of passing down their faulty gene(s) to their children.
- A child, sibling or parent of a family member with a faulty gene(s) has a 50% chance of also inheriting the same faulty gene(s).
- Extended relatives may also inherit the faulty gene(s).

Who should undergo genetic testing for NF1?

If you or your family members meet the following criteria, genetic testing should be considered to confirm the diagnosis of NF1.

- Individuals who exhibit features of NF1 and would like to confirm the diagnosis of NF1
- Individuals who have family members with a previously identified faulty *NF1* gene
- Individuals with NF1 who are planning for a family and are interested in assisted reproductive technologies

How can your genetic test result help you?

Personalised management

The genetic test result may help to personalise management options based on one's tumour/cancer risk.

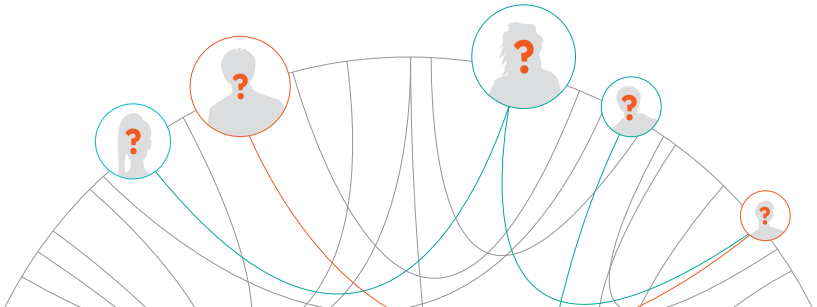
If you have a cancer diagnosis

- Can help guide and personalise treatment options
- Can help understand what other tumours/cancers you are at risk of and how to manage these risks

If you are currently cancer-free

- Can guide relevant screening options to detect tumours and cancer at their earliest, most treatable stage
- Can help individuals with NF1 to consider dedicated reproductive options when planning to have children

A genetic test result can also help one to understand if other family members are at risk of NF1. Family members can then consider their own testing (predictive testing) to clarify carrier status and determine their tumour/cancer risks.



What can I do to manage my/my child's increased risk of tumours and cancer?

< 18 yr

Screening and management recommendations for individuals below 18 years

General

- Annual physical examinations (which include skin and neurological examinations, blood pressure, height, weight and pubertal development)

Optic nerve pathway gliomas

- Regular eye examinations

Malignant peripheral nerve sheath tumours (MPNST)

- Annual clinical review with an NF1 specialist
- Further imaging of tumours may be recommended on a case-by-case basis

Neurofibromas

- Options for removal (if needed) are surgical excision, laser removal and electrodessication

Phaeochromocytomas

- Usually from the age of 10 onwards
- Annual blood pressure checks
- Blood tests and/or urine tests (if needed)

Juvenile myelomonocytic leukaemia

- Surveillance for children with xanthogranulomas (a type of skin lesion)
- Blood tests may be ordered if certain features are observed (e.g., prolonged fever, weight loss, loss of appetite)

≥ 18 yr

Screening and management recommendations for individuals 18 years and older

Optic nerve pathway glioma

- Regular eye examinations on a case-by-case basis

Breast cancer

- Maintain breast awareness
- Annual breast mammograms and/or breast magnetic resonance imaging (MRI) scans

Malignant peripheral nerve sheath tumours (MPNST)

- Annual clinical review and physical examination with an NF1 specialist
- Encourage early reporting of symptoms
- Further imaging of tumours may be recommended on a case-by-case basis

Phaeochromocytomas

- Annual blood pressure checks
- Blood tests and/or urine tests (if needed)

Neurofibromas

- Options for removal (if needed) are surgical excision, laser removal and electrodessication

Your managing doctor(s) will discuss screening recommendations with you and your child (if needed) in greater detail. The age and onset of screening may depend on the personal and/or family history of NF1. Screening guidelines may change as more information is known.

Other screening and management recommendations

Hypertension

- Further imaging may be recommended to understand the cause of hypertension

Bone problems

- Clinical evaluation of the back
- Management of scoliosis (curved spine) and/or osteoporosis
- Vitamin D supplementation

Neurological or psychiatric conditions and pain

- Screening assessments
- Medications, physical therapy and surgery

These issues may not be encountered by most individuals with NF1. Screening, management or treatment of these problems are offered on a case-by-case basis and will be discussed in greater detail by your managing doctors.

Frequently Asked Questions (FAQs)

Q: Is NF1 always inherited?

A: No, this condition is just as often a spontaneous change as it is inherited from a parent. This is possible as *de novo* (new) changes in the gene can occur in the egg or sperm cell of an unaffected parent, or at conception of an embryo.

Q: Is NF1 contagious?

A: No, you cannot catch NF1 like how you would catch common colds/flus. NF1 is a condition one is born with and is not contagious.

Q: What are the chances that I will have another child with NF1 if neither my spouse nor I have it?

A: In about 50% of cases, NF1 is the result of a spontaneous change (*de novo*) in the genetic material of the sperm or egg at conception, in families with no previous history of the disease. In such cases, the risk of having another child with NF1 is low (< 1%).

Q: What should someone do if they think they have NF1?

A: Only a trained healthcare professional familiar with NF1 can make the diagnosis of this condition. Please approach a doctor/healthcare professional if you think you or your child has NF1.

Q: Is NF1 considered a disability?

A: No, many people with this diagnosis can still live long, healthy and fulfilling lives. As the manifestation of symptoms differs between individuals, the complications faced will vary in severity.

Support Groups

NCCS Support Group

At the National Cancer Centre Singapore (NCCS), we provide a holistic approach to supporting you and your loved ones in cancer management. It is open to all cancer patients, survivors and caregivers in Singapore.

For more information and registration:

Tel: 6436 8668 (Patient Support Line)
6225 5655 (Cancer Helpline)
Email: patientsupport@nccs.com.sg
Website: www.nccs.com.sg/patient-support-programme
www.nccs.com.sg/support-groups

Club Rainbow Singapore

Club Rainbow Singapore supports and empowers children with chronic illnesses and their families by providing relevant compassionate services in their journey.

Tel: 6377 1789
Email: contact@clubrainbow.org
Website: www.clubrainbow.org

If you have any questions, please contact:

Cancer Genetics Service,
National Cancer Centre Singapore
30 Hospital Boulevard, Singapore 168538
Mondays to Fridays: 8.30am to 5.30pm
Weekends and Public Holidays: Closed

Tel: **6436 8000**
Email: **cgsgroup@nccs.com.sg**
Website: **www.nccs.com.sg/patient-care/specialties-services/cancer-genetics-service**

Cancer Helpline

Tel: **6225 5655**
Email: **cancerhelpline@nccs.com.sg**

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If you wish to support the Cancer Genetics Service's education, research and patient support efforts, please scan the QR code to make a donation.

Acknowledgements

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Sengkang General Hospital
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National Cancer Centre Singapore
6436 8088
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National Heart Centre Singapore
6704 2000
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www.nni.com.sg

Singapore National Eye Centre
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