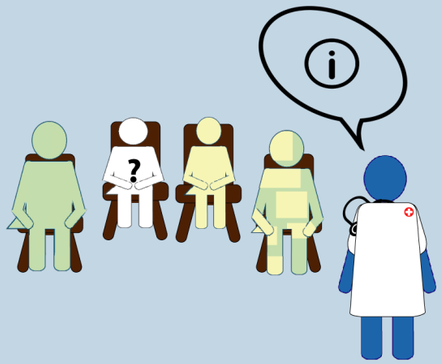
ERN GENTURIS patient journey: neurofibromatosis type 1 (NF1)

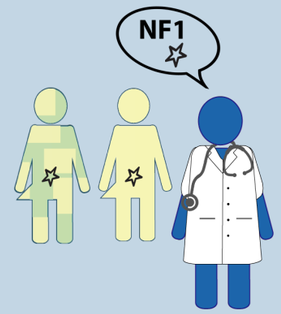
Genetic pathway

Genetic counselling and comprehensive consultation

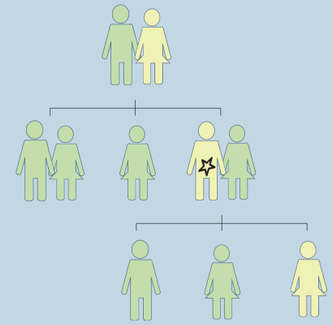


Germline genetic testing and/or tumour testing

Disclosure of the results
patient with genetically confirmed NF1



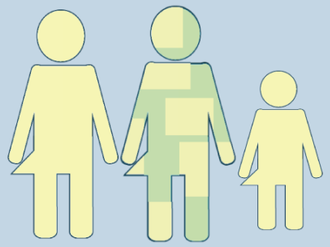
Cascade testing (testing of blood relatives with symptoms/signs)



Symptomatic person with unknown genetics

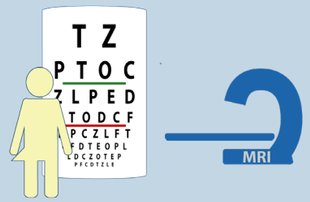
Clinical diagnosis

Patient with (clinical) NF1

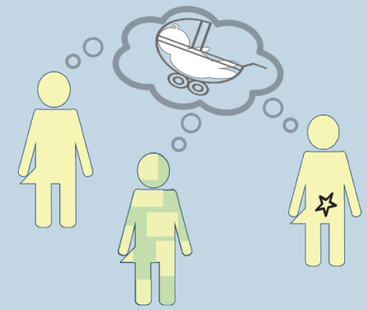


Generic surveillance on potential complications and manifestations of NF1

Manifestation- and age-specific follow-up and treatment (counselling)

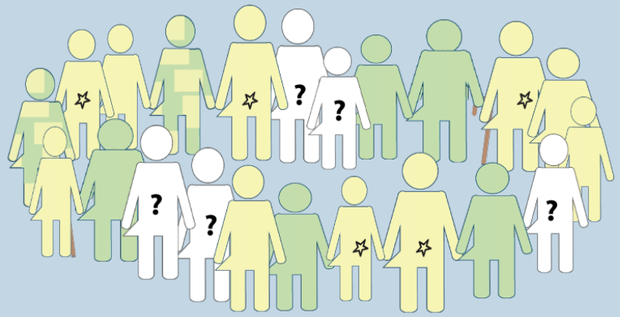


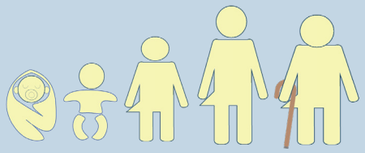
Genetic counselling regarding family planning



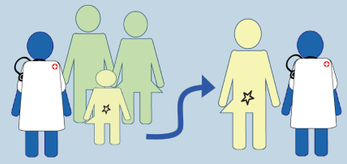
Psychosocial support for patients and families

Peer support and participation in society





NF1 care throughout life with emphasis on healthcare transition to adult care



European Reference Network

Genetic Tumour Risk Syndromes (ERN GENTURIS)

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Disclaimer: This patient journey is intended as a general overview of the clinical and diagnostic pathway for NF1 or its suspicion. It should not replace an individual clinical and genetic counselling at an expertise centre. It also does not intend to address all specific challenges of the complex condition of NF1. Specific clinical guidelines, diagnostic criteria and nomenclature may change at short notice and therefore are only referred to in this patient journey. The patient journey can be used as a guidance for the clinician to discuss the patient's detailed personal journey (personalised care).

Symptomatic person with unknown genetics

A person showing signs or symptoms (manifestations) of NF1 but who hasn't had a genetic test, or a person because they are biologically related to someone with NF1 referred for testing (NF1 is not suspected in family members without any signs for NF1).

Patient with (clinical) NF1

A **diagnosis of NF1** should be made according to the updated diagnostic criteria in 2021.

Once a NF1 diagnosis is established, the advice is to be followed by a multidisciplinary team in a NF1 expert centre. The ERN GENTURIS NF1 care pathway can be used to receive appropriate personalised care (www.genturis.eu, section thematic disease groups, NF1, care pathway).

NF1 presentation

Of note, **children younger than six years of age** may not fulfil NF1 criteria. **From birth to six months of age:** Skin abnormalities (café-au-lait spots) are often present. **More than six years of age:** diagnostic criteria are usually evident. A **parent** with mild symptoms may be diagnosed with NF1 in adulthood after their child has been diagnosed. Other conditions may also present with café-au-lait spots and need to be considered.

NF1 manifestations

The penetrance of NF1 is nearly 100%, meaning that almost all adults who carry the disease-causing gene variant will show signs of the condition. The manifestations of NF1 can vary widely from person to person, are **age-dependent** and **may progress** in severity with time. It is difficult to predict how mild or severe the impact of NF1 will be or what medical concerns will develop over time even within NF1 patients of the same family. NF1 should always be considered for a person with characteristics corresponding to the diagnostic criteria.

Genetic counselling and comprehensive consultation

Once a diagnosis of NF1 is established (or suspected in children aged less than 6 years), patients can be referred to a NF1 expert centre for more elaborate information. They will also receive information on the supervising physician for themselves and/or their child(ren).

Patients and their family need thorough information regarding:
- clinical manifestations and natural history of NF1
- surveillance and follow-up
- NF1-specific diagnostic and therapeutic approach for specific manifestations
- process of genetic and reproductive counselling and implications of germline genetic testing for themselves and their biological relatives
- possible outcomes of genetic testing
- family planning
- legal, social, insurance and financial aspects of NF1 diagnosis
- emotional support including peer support.

Germline genetic testing and/or tumour testing and disclosure of the results

General information regarding germline genetic testing:
www.coe.int/en/web/bioethics/information-brochure-on-genetic-tests-for-health-purposes
Germline genetic testing serves for:
- Confirming the diagnosis and differentiating from other conditions;
- Information to other family members;
- Deciding about reproductive counselling and reproductive options.

Germline genetic testing should at least consider *NF1* and *SPRED1* genes. When the results are negative, genetic testing of multiple tissues or tumour specimen is recommended.

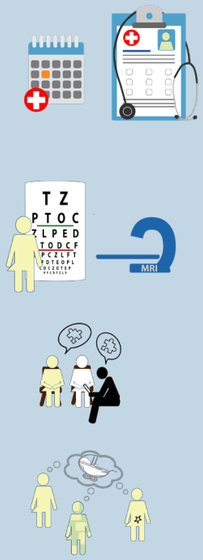
Germline genetic testing and genotype-phenotype correlation in most cases cannot predict the severity or specific complications in individual cases of NF1.
Mosaic presentations of NF1 may need individualised approach.

Genetic testing should be considered for anyone showing signs of NF1 but not fulfilling the criteria, especially any child aged less than 6 years. The disclosure of the testing results should occur only within the framework of genetic counselling.

Important: A negative DNA result does not rule out NF1. A **diagnosis of NF1** should be made according to the updated diagnostic criteria in 2021.

Cascade testing (testing of blood relatives with symptoms/signs)

Cascade testing is the process of performing genetic counselling and germline genetic testing of blood relatives at risk for inheriting NF1. First-degree offspring have a 50% chance of having NF1.
The penetrance of NF1 is nearly 100%, meaning that almost all adults who carry the disease-causing gene variant will show signs of the condition. Disease-causing variants may not be inherited from a parent but occur for the first time (de novo) in the genetic material of a patient with clinical NF1. NF1 is not suspected in family members without any signs for NF1.



Generic surveillance on potential complications and manifestations of NF1

NF1 increases the risk of tumours, may cause manifestations in other organs (e.g. bone, cardiovascular), and can cause difficulties in cognitive abilities and social functioning. For this reason, specific surveillance (regular monitoring) programs exist for persons with NF1. These might differ between countries. Patients should ask their physician or contact expert centre about recommendations in their country. Current recommendations at a European level regarding follow-up (what, by whom,which frequency and when to refer) can be found in the ERN GENTURIS NF1 care pathway. These include:
- Tumour screening/identification in individuals with NF1 (ERN GENTURIS NF1 pocket guide: www.genturis.eu - "Guidelines and pathways").
- Surveillance of non-tumour manifestations (ERN GENTURIS NF1 care pathway: www.genturis.eu - "Guidelines and pathways").
- Surveillance for psychological and social-emotional manifestations in NF1.

Manifestation- and age-specific follow-up and treatment (counselling)

To be performed by a specialist, in collaboration with a NF1 expert centre. Manifestation specific follow-up should be personalised according to the specific conditions and needs.
Current recommendations at European level regarding follow-up (what, by whom, which frequency and when to refer) can be found in the ERN GENTURIS NF1 care pathway (www.genturis.eu - "Guidelines and pathways").
Not all symptoms need specific treatment, some changes may only need close follow-up.

Psychosocial support for patients and families

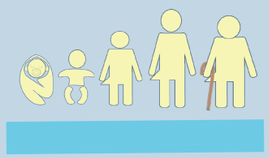
Patients and their family need psychoeducation to understand and cope with the diagnosis and available treatment options. Psychoeducation should proactively be offered to the patient and a psychologist is part of the multidisciplinary team.
Patients and their family might seek support repeatedly, at different timepoints e. g. at the time of new cancer diagnosis, family planning, decision-making for treatment.

Genetic counselling regarding family planning

At reproductive age, patients should receive genetic consultation for information about family planning and reproductive options.
Prenatal testing and preimplantation genetic testing can be discussed, but differences between countries exist based on legal and ethical issues.

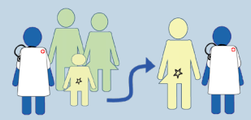
Peer support and participation in society

Support during education and work: It's advised to offer children repeatedly neurocognitive assessment to detect learning difficulties (50% of people with NF1 will experience some difficulties with learning). Memory, attention, visual-motor function, and spatial orientation are the areas that are commonly affected. There can be problems processing information and trouble with executive functioning skills, which include planning, management, attention, organisation and social interaction. Working with a individual's teachers or supervisors at work to address these concerns is vital and can have a big impact and positive rewards.
Peer support: Support can also be obtained via peers. Patient organisations can be of great importance as they often have support programs, offer peer to peer support and in some countries they can offer financial support. Patient organisations can provide families with the opportunity to become active for a better future of people living with NF1. Patient organisations can be found on:
https://www.genturis.eu/l=eng/patient-area/patient-associations.htmlww.genturis.eu.



NF1 care throughout life with emphasis on healthcare transition to adult care

NF1 is a variable presenting condition over time, but has a progressive nature with increased risks for medical complications lifelong. A dedicated clinician and a structured Healthcare Transition program are imperative for effectively transitioning adolescents and young adults with NF1 from a paediatric to an adult care model. The overarching goal is to foster independence, enhance quality of life, and mitigate associated medical complications.



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