資料6. Cancer and Central Nervous System Tumor Surveillance in Pediatric Neurofibromatosis 1のレビューワーク

Cancer and Central Nervous System Tumor Surveillance in Pediatric Neurofibromatosis 1

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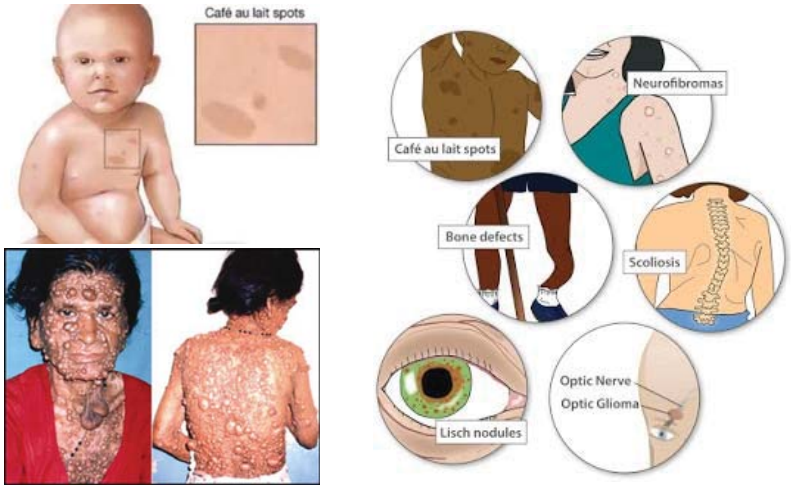
嶋田　明

神経線維腫症1型（NF1、レックリングハウゼン病）



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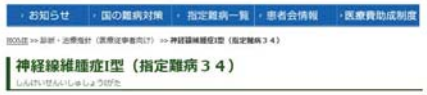


1．概要

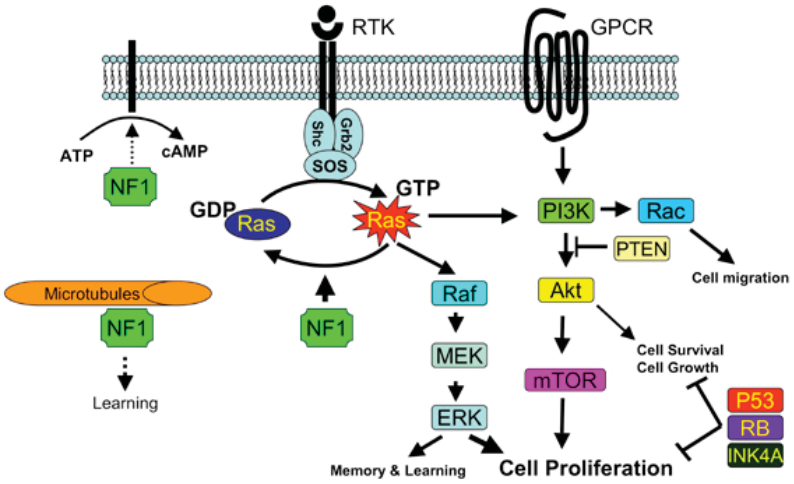
神経線維腫症I型（neurofibromatosis type1：NF1、レックリングハウゼン病）は、カフェ・オ・レ斑と神経線維腫を主徴とし、その他骨、眼、神経系、（副腎、消化管）などに多彩な症候を呈する母斑症であり、常染色体性優性の遺伝性疾患である。

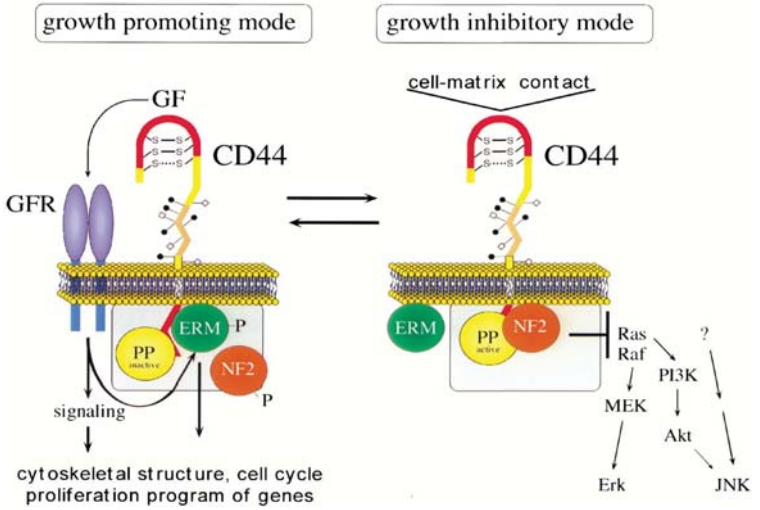
神経線維腫症II型（neurofibromatosis type2：NF2）は、両側性に発生する聴神経鞘腫（前庭神経鞘腫）を主徴とし、その他の神経系腫瘍（脳及び脊髄神経鞘腫、髄膜腫、脊髄上衣腫）や皮膚病変（皮下や皮内の末梢神経鞘腫、色素斑）、眼病変（若年性白内障）を呈する常染色体優性の遺伝性疾患である。

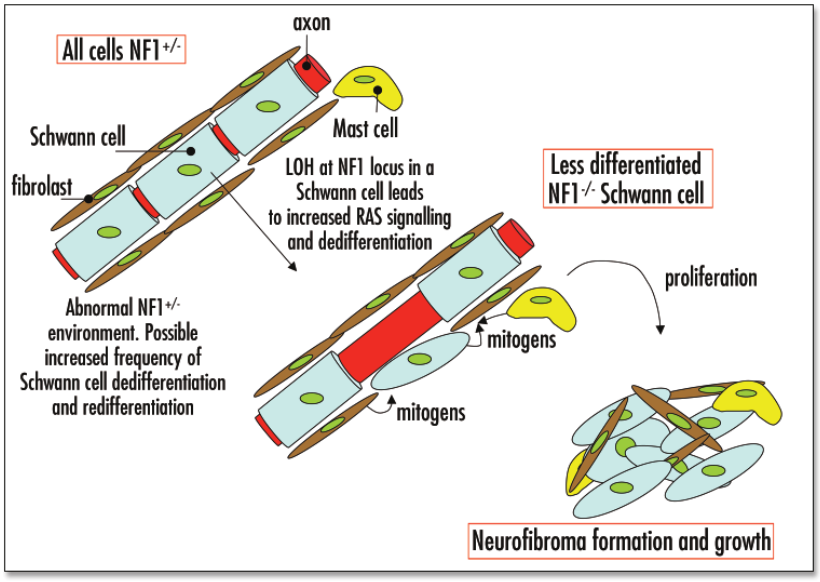
2．原因

神経線維腫症I型の原因遺伝子は17番染色体長腕（17q11.2）に位置し、その遺伝子産物はニューロフィブロミン（neurofibromin）と呼ばれ、Ras蛋白の機能を制御して細胞増殖や細胞死を抑制することにより、腫瘍の発生と増殖を抑制すると考えられている。NF1遺伝子に変異を来した神経線維腫症I型では、Rasの恒常的な活性化のため、Ras/MAPK経路の活性化とPI3K/AKT経路の活性化を生じ、神経線維腫をはじめとし、多種の病変を生じると推測されている。しかし、詳しい機構については不明な点も多い。

神経線維腫症II型の責任遺伝子は第22染色体長腕22q12に存在し、この遺伝子が作り出す蛋白質はmerlin（又はschwannomin）と名付けられている。merlinは腫瘍抑制因子として働くと考えられている。神経線維腫症II型では、merlinの遺伝子に異常が生じ、正常なmerlinができないために発症する。同様に、神経線維腫症II型以外の一般の神経鞘腫・髄膜腫・脊髄上衣腫などでもmerlinの遺伝子に異常が見つかっている。







3. 症状

①神経線維腫症I型は、以下の症状を特徴とする。

・カフェ・オ・レ斑－扁平で盛り上がりのない斑であり、色は淡いミルクコーヒー色から濃い褐色に至るまで様々で、色素斑内に色の濃淡はみられない。形は長円形のものが多く、丸みを帯びた滑らかな輪郭を呈している。小児では径0.5cm以上、成人では径1.5cm以上を基準とする。

・神経線維腫(neurofibroma)－皮膚の神経線維腫は思春期頃より全身に多発する。この他末梢神経内の神経線維腫、び漫性の神経線維腫（diffuse plexiform neurofibroma）がみられることもある。悪性末梢神経鞘腫瘍(MPNST)は末梢神経から発生する肉腫で患者の２～４%に生じる。

・その他の症候：

皮膚病変－雀卵斑様色素斑、大型の褐色斑、貧血母斑、若年性黄色肉芽腫、有毛性褐青色斑など。

骨病変－頭蓋骨・顔面骨の骨欠損、四肢骨の変形・病的骨折、脊柱・胸郭の変形など。

眼病変－虹彩小結節（Lisch nodule）、視神経膠腫など。

脳脊髄腫瘍－視神経膠腫、毛様細胞性星細胞腫、脊髄腫瘍など。

そのほかunidentified bright object（UBO）、消化管間質腫瘍（gastrointestinal stromal tumor：GIST）、褐色細胞腫、悪性末梢神経鞘腫瘍、学習障害・注意欠陥多動症などがみられる。

②神経線維腫症II型の発症年齢は様々であるが、10～20代の発症が多い。両側聴神経鞘腫と多数の神経系腫瘍が生じる。最も多い症状は、聴神経鞘腫による難聴・ふらつきで、脊髄神経鞘腫による手足のしびれ・知覚低下・脱力もおこる。その他に、頭痛、顔面神経麻痺、顔面のしびれ、歩行障害や小脳失調、痙攣、半身麻痺、視力障害、嚥下障害や構音障害などを伴うこともある。

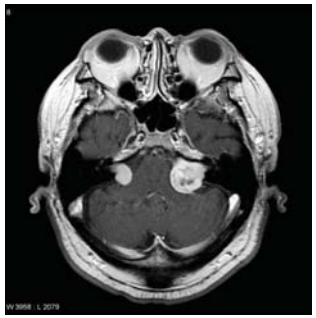
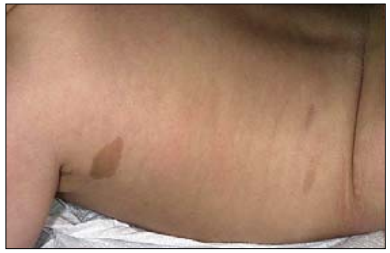
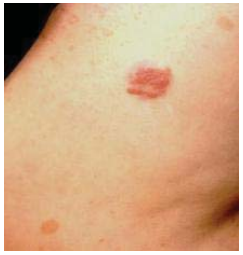


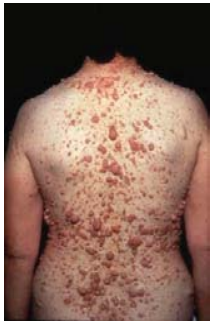
Table 1. Diagnostic criteria for NF1 (two or more must be present)

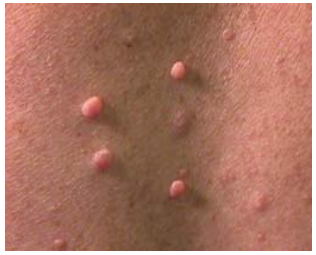
1. Six or more CAL macules, the greatest diameter of which is more than 5 mm in prepubertal patients and more than 15 mm in postpubertal patients
2. Two or more neurofibromas of any type, or one plexiform neurofibroma
3. Axillary or inguinal freckling
4. Optic glioma
5. Two or more Lisch nodules
6. A distinctive osseous lesion such as sphenoid dysplasia or pseudarthrosis
7. A first-degree relative with NF1 according to the preceding criteria

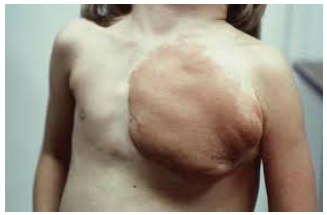


2 or more neurofibromas (fibromatous tumors of the skin), or at least one plexiform neurofibroma

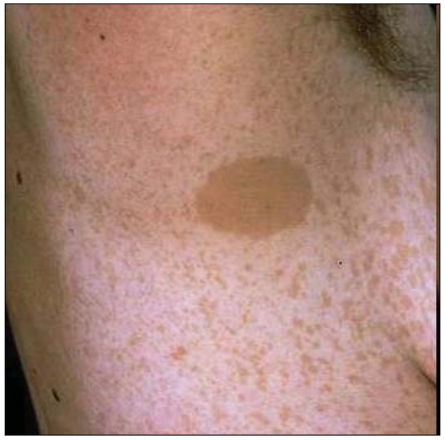


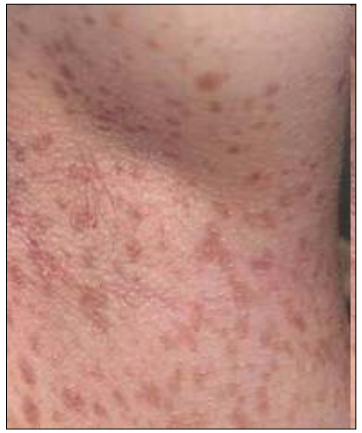






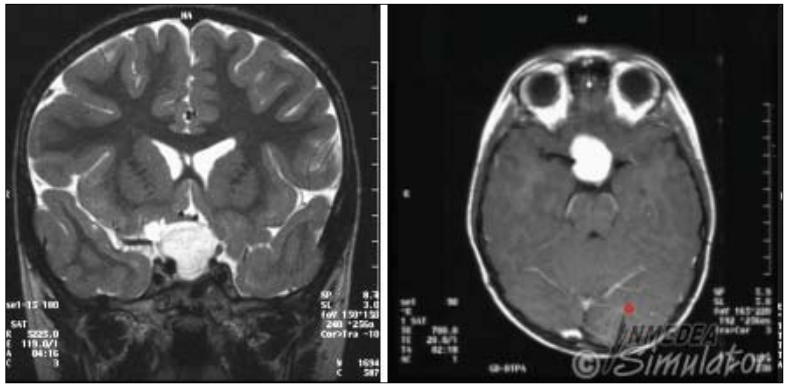
Axillary and/ or inguinal freckling





Optic glioma

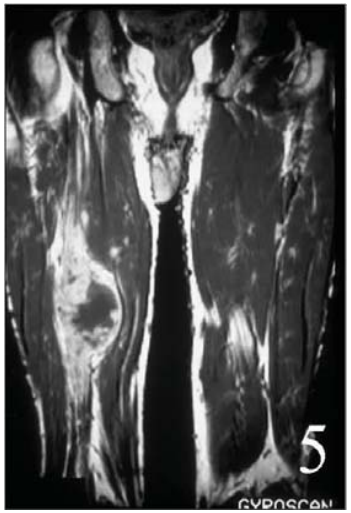
precocious puberty , visual loss



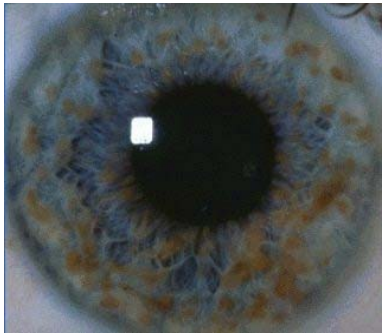
Plexiform neurofibromas

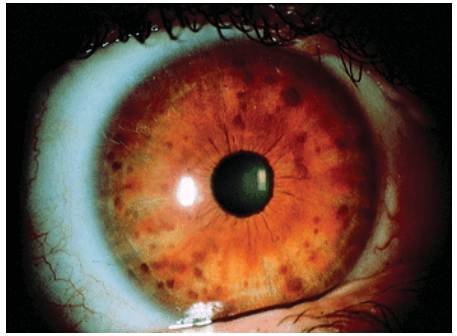
potential for transformation into malignant peripheral nerve sheath tumors (MPNST, malignant schwannomas)

FDG-PET/CTのモニタリング
有効



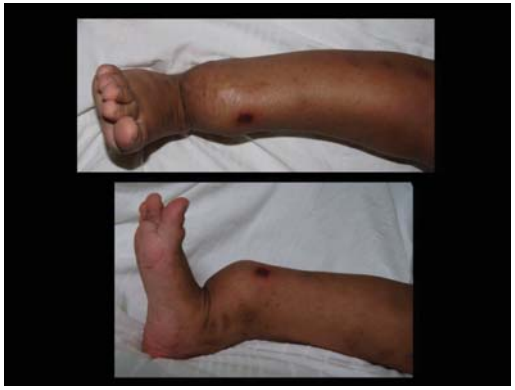
Lisch nodules

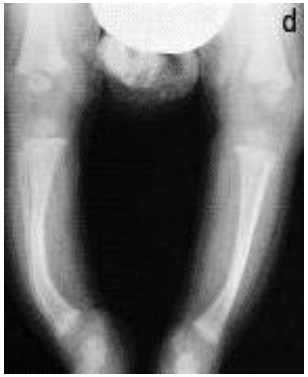




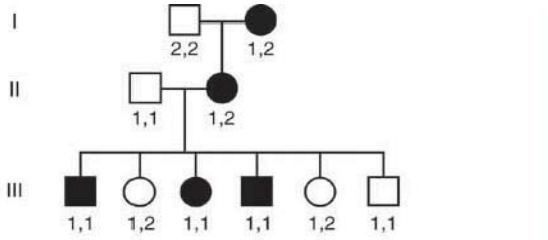
Specific bone lesions

Dysplasia of long bones ,
pseudoarthrosis of tibia, thinning of long bone cortex





First –degree family relative has a proven diagnosis of neurofibromatosis

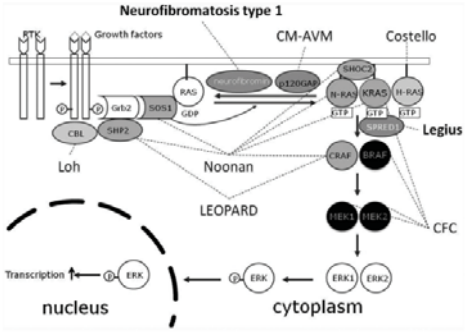


A family in which a mutation causing neurofibromatosis type 1 is transmitted in three generations. The genotype of a marker locus is shown for each pedigree member.

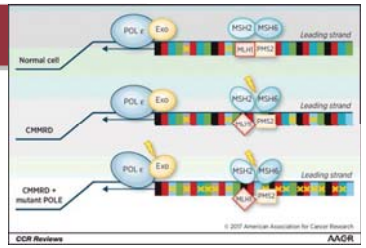
Pedigree for Neurofibromatosis Type 1

Legius syndrome

Clinicians need to be aware that a subset of individuals and families with multiple CAL macules, without other NF1 primary features, may have mutations in the SPRED1 gene, a condition called Legius syndrome



CMMRD



Biallelic mutations in any of the four mismatch repair genes *MSH2, MSH6, MLH1*, and *PMS2* result in one of the most aggressive childhood cancer predisposition syndromes, termed constitutional mismatch repair deficiency or constitutional mismatch repair deficiency syndrome (CMMRD).
The hallmark of the disease is early onset cancer, most often in childhood or young adulthood. The median age of onset of the first tumor is 7.5 years, with a wide range observed (0.4–39). The most common are malignant brain tumors, followed by gastrointestinal and hematologic malignancies.

NF1 is associated with highly elevated risks of ***juvenile myelomonocytic leukemia***, ***rhabdomyosarcoma***, and ***malignant peripheral nerve sheath tumor*** as well as substantial risks of noninvasive ***pilocytic astrocytoma***, particularly ***optic pathway glioma (OPG)***, which represent a major management issue.

Although, cancer risk is not the major issue facing an individual with NF1 during childhood.

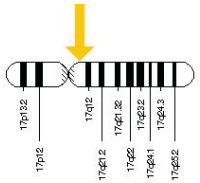
Table 2. NF1: tumor features, with typical ages at presentation and childhood risk

Disease feature	Frequency (pediatric risk) in %			Age of presentation
Series	**Huson (15)**	**McGaughran (16)**	**Update for key tumors[a]**	
Patients in series	135	523	1,500	
Peripheral neurofibromas	>99	60 (20–60)		≥7 years
Plexiform neurofibromas				
All plexiforms	30	15 (15)		0–18 years
Large lesions of head and neck	1.2	6 (6)		0–3 years
CNS tumors				
Optic glioma (symptomatic)	1.5	5 (5–6)	6%	Childhood
Other CNS tumors	1.5	2.0 (1)	2%	Lifelong
Spinal neurofibromas	1.5	2.0 (0.2)	0.2%	Lifelong
Malignancy				
Malignant peripheral nerve sheath tumors	1.5	5 (0.2)	0.2%[b]	Lifelong
Embryonal rhabdomyosarcoma	1.5	0.2 (0.2)	0.3%	0–5
Gastrointestinal tumors[c] (neurofibromas and GISTs)	2.2	2.0 (0)	0%	Lifelong
Pheochromocytoma	0.7	0.4 (0.2)	0%	≥10 years
Duodenal carcinoid	1.5	2 (0.1)	0%	≥10 years
Glomus tumors in nail beds	0	0.2 (0.1)	0%	Adults (usually)

Abbreviation: GIST, gastrointestinal stromal tumor.
[a]Update based on 1,500 NF1 patients in the Manchester register.
[b]0.5% by age 20 years.
[c]Frequency of GIST in adulthood has been found to be as high as 6%, but this may reflect MRI surveillance detecting asymptomatic tumors.

NF1-gene , chromosome 17 (17q11.2)

- Genetic code of neurofibromin synthesis. Regulation of signal –transduction -protein RAS
- GTPase activation
- 62 coding exons spread over 282kb.
- There are multiple NF1 pseudogene in the genome that ca complicate mutation analysis.
- Neurofibromin, 2,839 amino acid cytoplasmic protein
- Whole gene deletion (2-7%)
- Nontruncating mutation
- In-frame deletion (c2970_2972 delAAT) cause CAL macules-only type of NF1 similar to Legius syndrome

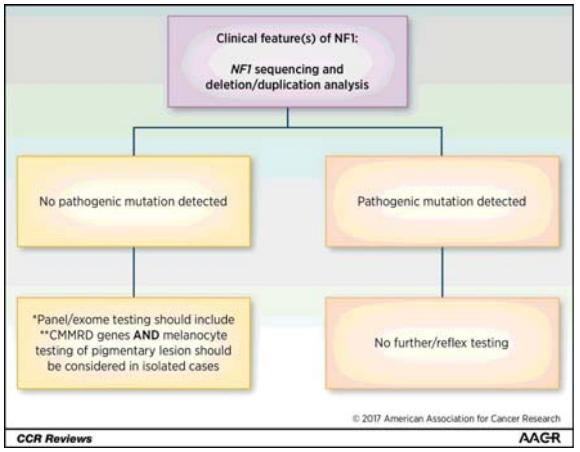


A variety of syndromes have overlapping features with NF1

Some examples include pigmentary abnormalities due to mutations in *SPRED1*,
CMMRD due to biallelic *MLH1*, *MSH2*, *MSH6*, or *PMS2* mutations,
RASopathy syndromes (such as LEOPARD/Noonan) due to mutations in *PTPN11*, or
McCune–Albright syndrome due to mutations in GNAS

Cancer/Tumor Screening/Surveillance Protocol

Most centers begin genetic testing with the NF1 and SPRED1 genes !



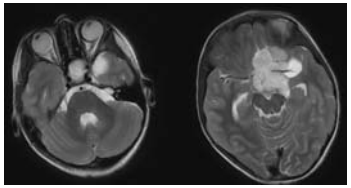
Next-generation sequencing panel/focused exome should include at least GNAS, MLH1, MSH2, MSH6, NF2, PMS2,PTPN11, SOS1, and SPRED1 (if not already tested) and either reflex to, or include, deletion/duplication analysis of each gene.

Summary of recommendations for childhood management

1. Genetic testing: Children considered at risk of NF1 especially with 6t CAL macules or diagnosed with NIH criteria should ideally have genetic testing of the NF1 gene with an RNA-based approach and testing of SPRED1 if pigmentary features only
2. Genetic testing: Those testing negative should be considered for a panel of genes including GNAS, MLH1, MSH2, MSH6, NF2, PMS2, PTPN11, SOS1, and SPRED1 (if not already tested)
3. General: Annual history and physical exam (including skin and neurologic exam and also blood pressure, height, weight, and pubertal development) Tumor surveillance
4. OPG: Children with NF1 should have 6–12 monthly ophthalmic assessments from birth to 8 years. One baseline assessment of color vision and visual fields should be undertaken when the child is developmentally able.

5. MPNST: Assess with history and clinical examination annually for typical signs of MPNST: any nondermal neurofibroma with rapid growth, loss of neurologic function, or increasing pain or change in consistency
6. JMML: Assess for risk of JMML in NF1 in children with juvenile xanthogranulomas
7. Internal burden: A baseline whole-body MRI should be considered between ages 16 and 20 years to assess internal tumor burden to determine adult follow-up regimen
8. Routine MRI: MRI surveillance is not currently recommended unless symptomatic or with an already diagnosed tumor. Specific biochemical or imaging surveillance for tumors with absolute risks in childhood below 1% is not recommended such as for pheochromocytoma, neuroendocrine tumors, MPNST, or non-optic glioma.

Especially, in children



OPG does not affect overall survival of children with NF1 (unlike in children with sporadic OPG), and little is known about the natural history of OPG.

Nonetheless, there is a clear need to make an early diagnosis of OPG before significant loss of vision occurs.

As the greatest risk of developing OPG is during childhood (especially in children <7 years ofage), ophthalmologic exams should start when the NF1 diagnosis is established and continue throughout childhood.

Recommendation for transition to adulthood

- Young adults with NF1 should be counseled on the future risk of MPNST and the cardinal signs.
- Women ages 30 to 50 should be advised of the increased breast cancer risks of 4- to 5-fold and to access extra breast screening according to guidelines for moderate (20%) lifetime risk or high risk if additional family history of breast cancer.
- NF1-affected individuals with high internal tumor burden and/or whole gene deletions should be referred to a specialist NF1 network clinic for long-term follow-up and surveillance.
- All adults with NF1 should have at least annual blood pressure checks and access to specialist clinics if they develop cardinal features of MPNST, gastrointestinal stromal tumors, or other NF1-related major complications.