Chapter 2
Neurofibromatosis Type 2 (NF2)
D. Gareth R. Evans

Terminology
Disease Name and Synonyms

Neurofibromatosis type 2 (NF2), Bilateral acoustic neurofibromatosis, Central neurofibromatosis. OMIM #101000. The correct name for the condition is Neurofibromatosis type 2 (NF2). The remaining names are historically due to the overlap with NF1 and previous confusion over the two conditions. The first clear description of NF2 was in 1822 by Wishart.1 NF1 was described in 1882 by von Recklinghausen. However, it was Harvey Cushing who described bilateral eighth nerve tumors developing as part of von Recklinghausen disease in 1916.2 This description is largely responsible for the confusion between the two conditions which continued for many years. Gradually over the last 20 years of the twentieth century the clear clinical and pathological differences resulted in the definition of two separate conditions, NF1, formerly known as von Recklinghausen neurofibromatosis and NF2 previously called bilateral acoustic or central neurofibromatosis. The clinical and genetic distinction between the two conditions was not fully recognized until the last three decades and reports of “neurofibromatosis” frequently included intermingled NF1 and NF2 cases.3 The conditions were eventually recognized as
separate entities with the localization of the respective genes to chromosome 17 and 22.\textsuperscript{4,5} This was followed by the formal clinical delineation at a US National Institutes of Health (NIH) consensus meeting in 1987.\textsuperscript{6}

**Diagnosis**

The Manchester (modified NIH) diagnostic criteria for NF2 are shown in Table 2.1. The original NIH criteria\textsuperscript{6} have been expanded to include patients with no family history who have multiple schwannomas and or meningiomas, but who have not yet developed bilateral 8th nerve tumors.\textsuperscript{7} The diagnosis is best confirmed using high quality MRI imaging of the brain (with 3 mm cuts through the internal auditory meati) with gadolinium enhancement. Full spinal axis imaging should also be performed. Examination of the skin for NF2 intracutaneous and deeper subcutaneous nodules is useful although, where the diagnosis is in doubt and depends on verification of a cutaneous tumor, biopsy should be considered. Ophthalmic examination with a slit lamp is also advised. NF2 is the only gene known to be associated with neurofibromatosis 2. Molecular genetic testing of NF2 that includes a combination of sequence analysis or mutation scanning and

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**Table 2.1.** Diagnostic criteria for NF2 (these include the NIH criteria with additional criteria).

<table>
<thead>
<tr>
<th>Bilateral vestibular schwannomas or family history of NF2 plus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Unilateral VS or</td>
</tr>
<tr>
<td>2. Any two of: meningioma, glioma, neurofibroma, schwannoma, posterior subcapsular lenticular opacities</td>
</tr>
</tbody>
</table>

Additional criteria: Unilateral VS plus any two of: meningioma, glioma, neurofibroma, schwannoma, and posterior subcapsular opacities

Or

Multiple meningioma (two or more) plus unilateral VS or any two of: glioma, neurofibroma, schwannoma, and cataract
duplication/deletion testing detects a mutation in most affected individuals who have a positive family history and are not the first individual in the family known to have the disorder. Identification of a pathogenic \( \text{NF2} \) mutation in blood or in two anatomically distinct tumors from the same individual confirms the diagnosis.

**Epidemiology**

NF2 is an autosomal dominant disease that usually has a 50% risk of transmission from an affected individual to their offspring. This was first confirmed in a large family reported by Gardner and Frazier in 1930. Fifty to sixty percent of patients have no family history and represent de novo mutations in the \( \text{NF2} \) gene.\(^7\) Individuals who inherit a pathogenic mutation in the \( \text{NF2} \) gene will almost always develop symptoms by 60 years of age.\(^7\) There have only been two epidemiological studies of NF2, one in North West England\(^8\) and one in Finland.\(^1\) The birth incidence of NF2 is most probably around 1:33,000 individuals,\(^10\) with disease prevalence around 1 in 60,000.\(^10\) Although the transmission rate is 50% in the second generation and beyond, the risk of transmission in an apparently isolated patient with NF2 is less than 50% due to mosaicism.\(^12\)

**Mosaicism**

This is a phenomenon whereby the \( \text{NF2} \) mutation is only present in some of the affected individual’s cells. A considerable proportion of NF2 patients, particularly milder cases, have mosaic disease, in which only a proportion of cells contain the mutated \( \text{NF2} \) gene. The initiating mutation occurs after conception, leading to two separate cell lineages. The proportion of cells affected depends on how early in development the mutation occurs. Recent evidence suggests that between 20% and 33% of NF2 cases without a family history of the disease are mosaic, mostly carrying the mutation in too small a proportion or none of their lymphocytes to be
detected from a blood sample. This accounts for the milder disease course in many individuals with unfound mutations, and since only a subset of germ cells (or none) will carry the mutation, there is less than a 50% risk of transmitting the disease to their offspring. However, if an offspring has inherited the mutation, they will have a typical phenotype and usually be more severely affected than their parent, since the offspring will carry the mutation in all of their cells. The mosaic mutation can be detected by analyzing tumor material from an affected individual. If an identical mutation is found in two tumors from that individual, this confirms that this is the underlying mosaic mutation even if it cannot be identified in lymphocyte DNA. Their offspring can be tested for the presence of the mutation to exclude NF2. Offspring can also be tested for NF2 if both abnormalities are identified in a single tumor to also potentially exclude the disease. The chances of mosaicism based on different ages at presentation and whether NF2 presents symmetrically is shown in Table 2.2.

Clinical Manifestations

The hallmark of NF2 is the development of bilateral vestibular schwannomas (VS) (Figs. 2.1 and 2.2). The other main tumor features are schwannomas of the other cranial, spinal (Fig. 2.3) and peripheral nerves; meningiomas both intracranial (Figs. 2.1 and 2.4) also including optic nerve and intraspinal meningiomas and intraspinal; and some low-grade central nervous system (CNS) malignancies (ependymomas). Four large clinical studies have now confirmed this clinical picture. Although the disease is still classified as “neurofibromatosis,” neurofibromas are relatively infrequent. Individuals may present with cranial meningiomas or a spinal tumor long before the appearance of a VS. Previously, there was a suggestion for two forms of the disease. The Wishart type is more aggressive with an onset commonly in the late teens or with multi tumor disease, whereas the Gardner type
Table 2.2. Chances of mosaicism and risk to offspring based on testing 402 de novo NF2 patients fulfilling Manchester Criteria.

<table>
<thead>
<tr>
<th>Diagnosis of VS&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Number of patients</th>
<th>Mutation non-mosaic</th>
<th>Mosaic found blood</th>
<th>Mosaic found tumor</th>
<th>Mosaic inferred pre blood genetic test (%)</th>
<th>Transmission risk pre blood genetic test (%)</th>
<th>Mosaic inferred post negative blood testing (%)</th>
<th>Likelihood of a missed full mutation after negative blood testing</th>
<th>Transmission risk post negative blood testing (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20 BVS</td>
<td>99</td>
<td>81 (81%)</td>
<td>5 (5%)</td>
<td>1 (1%)</td>
<td>12</td>
<td>45</td>
<td>7/13 (54%)</td>
<td>46</td>
<td>29% 1 in 3</td>
</tr>
<tr>
<td>&lt;20 UVS</td>
<td>21</td>
<td>13 (62%)</td>
<td>3 (14%)</td>
<td>3 (14%)</td>
<td>33</td>
<td>33</td>
<td>1.1/5 (22%)</td>
<td>78</td>
<td>15% 1 in 7</td>
</tr>
<tr>
<td>20–29 BVS</td>
<td>77</td>
<td>49 (64%)</td>
<td>7 (9%)</td>
<td>2 (3%)</td>
<td>30</td>
<td>36</td>
<td>4.3/21 (20%)</td>
<td>80</td>
<td>15% 1 in 7</td>
</tr>
<tr>
<td>20–29 UVS</td>
<td>28</td>
<td>5 (18%)</td>
<td>4 (14%)</td>
<td>6 (21%)</td>
<td>78</td>
<td>19</td>
<td>0.44/19 (2%)</td>
<td>98</td>
<td>6% 1 in 16</td>
</tr>
<tr>
<td>30–39 BVS</td>
<td>54</td>
<td>25 (45%)</td>
<td>9 (17%)</td>
<td>7 (13%)</td>
<td>50</td>
<td>28</td>
<td>2.2/20 (11%)</td>
<td>89</td>
<td>11% 1 in 9</td>
</tr>
<tr>
<td>30–39 UVS</td>
<td>20</td>
<td>3 (15%)</td>
<td>1 (5%)</td>
<td>6 (30%)</td>
<td>83</td>
<td>12</td>
<td>0.26/16 (2%)</td>
<td>98</td>
<td>6% 1 in 16</td>
</tr>
<tr>
<td>40+ BVS</td>
<td>59</td>
<td>18 (31%)</td>
<td>5 (8%)</td>
<td>7 (12%)</td>
<td>66</td>
<td>22</td>
<td>1.56/26 (6%)</td>
<td>94</td>
<td>9% 1 in 11</td>
</tr>
<tr>
<td>40+ UVS</td>
<td>44</td>
<td>4 (9%)</td>
<td>2 (5%)</td>
<td>8 (18%)</td>
<td>90</td>
<td>10</td>
<td>0.35/36 (1%)</td>
<td>99</td>
<td>5.5% 1 in 20</td>
</tr>
<tr>
<td>Total</td>
<td>402</td>
<td>198 (49%)</td>
<td>36 (9%)</td>
<td>40 (10%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Age at diagnosis of VS in patients fulfilling at least Manchester criteria
usually presents in an older age group with fewer tumors and perhaps only bilateral VS. In practice, classification into Gardner and Wishart type is often difficult and may vary between family members. In reality, the variation is a combination of chance, other risk factors, other genes, and the NF2 mutation type.

In the same way as sporadic VS, the majority of adults with NF2 present with hearing loss that is usually unilateral at time of onset. Nausea, vomiting, or true vertigo are rare symptoms except in late stage disease. A significant proportion of cases (20–30%) present with symptoms from an intracranial meningioma (headaches, seizures), spinal tumor (pain, muscle weakness, paresthesia), or cutaneous tumor.7,16-

**Figure 2.1.** Cranial MRI showing bilateral vestibular schwannomas and meningiomas.
Indeed, the first sign of more severe multi-tumor disease in early childhood is often a non-eighth nerve tumor (including a cutaneous tumor), an ocular presentation, or a mononeuropathy, which frequently affects the facial nerve. Some children present with a polio-like illness with wasting of muscle groups in a lower limb (amyotrophy), which usually does not fully recover. In adulthood, a more generalized symptomatic severe polyneuropathy occurs in about 3–10% of cases. 

Figure 2.2. Bilateral massive vestibular schwannomas compressing the brain stem.
of patients, often associated with an “onion bulb” appearance on nerve biopsy. Around 40% of patients will show evidence of polyneuropathy on nerve conduction studies.

Ophthalmic features are also prominent in NF2. Patients often suffer from reduced visual acuity of various causes. Many of these are amblyopias with no obvious cause. Between 60% and 80% of patients have cataracts and these may present in early life. These can be posterior subcapsular lenticular opacities or cortical wedge opacities. Optic nerve meningiomas can cause visual loss in the first years of life and extensive retinal hamartomas can also affect vision.

The skin is a useful aid to diagnosis, but cutaneous features in NF2 are much more subtle than in NF1. About 70% of

Figure 2.3. Multiple spinal schwannomas some with cystic change in NF2 as indicated by arrows.
NF2 patients have skin-related tumors, but only 10% have more than ten skin tumors. The most frequent type is a plaque-like lesion, which is intracutaneous, slightly raised and more pigmented than surrounding skin, often with excess hair (Fig. 2.5). More deep-seated subcutaneous nodular tumors can often be felt, sometimes on major peripheral nerves (Fig. 2.6). Café au lait patches are more frequent in NF2 than in the general population but are rarely as frequent as in NF1 with only 1% having six or more patches.

Screening At-Risk Individuals

Children of affected patients should be considered to be at 50% risk of NF2 and screening for NF2 can start at birth with a search for cataracts. Formal screening for VS should start at
Figure 2.5. NF2 intracutaneous plaque: slightly raised, often pigmented with excess hair.

Figure 2.6. Ulnar nerve nodular subcutaneous schwannoma separate from overlying skin.
10 years, as it is rare for tumors to become symptomatic before that time even in severely affected families. Magnetic resonance imaging (MRI) of the head and spine is the mainstay of current screening, although annual audiological tests including auditory brainstem response are still a useful adjunct to MRI. VS growth is faster in younger patients, so for asymptomatic at-risk individuals without tumors, MRI screening every 2 years for those younger than 20 years old is recommended. For those older than 20 years MRI screening every 3–5 years should be sufficient. The initial MRI scan could be at around 12 years of age, or 10 years of age in severely affected families.

In most families, it is now possible to develop a genetic test so that screening can be targeted to affected individuals only. Identifying the affected patient’s mutation not only allows testing of at-risk relatives, but may also give important indicators as to the patient’s own prognosis. As 20–33% of de novo NF2 patients are mosaic, frozen tumor should be taken at operation (with patient consent) for genetic tests. Once a mutation is known in a family, testing for the specific mutation takes 2–3 weeks. Finding the family mutation on initial search usually takes 8–10 weeks and may take longer if tumor tests need to be performed. In the occasional family, with more than one affected family member in which a mutation cannot be found, linkage tests can still be used.

**Surveillance**

Once tumors are present or a mutation has been found in an affected child, MRI screening should probably be at least annual. Spinal tumors are seen in 60–80% of NF2 patients on MRI. Nonetheless, only 25–30% of patients with spinal tumors require a spinal operation from a symptomatic tumor. Spinal MRI only every 3 years is probably sufficient unless there are new symptoms. If no tumors are present on the initial scan, a further scan 5–10 years later may be reasonable.
Managing Affected Children

NF2 is being recognized more and more frequently in childhood often before VS have developed. Recognition of the more severe disease course with early presentation and the more atypical features such as mononeuropathy are important.

Screening Individuals with Insufficient Criteria for NF2

Many individuals have two NF2-related tumors or present at very young ages with VS or meningioma, and are clearly at risk of at least having mosaic NF2. Twenty percent of patients <20 years with a sporadic VS will develop NF2 but only half of these will have a detectable mutation on blood DNA. Similarly, around 20% of apparently sporadic childhood meningioma develops into NF2. Individuals who present with a unilateral VS and other neurogenic tumors in the NF2 spectrum have a high risk of contralateral disease especially if they present at age <20 years. Five yearly MRI should probably be performed at least until 40 years of age in individuals with a sporadic VS <30 years or a meningioma <20 years of age.

Genetics

NF1 and NF2 were eventually recognized as separate genetic and clinical diseases with the localization of the respective genes to chromosome 17 and 22. This was followed by the formal clinical delineation at a National Institutes of Health (NIH) consensus meeting in the USA, in 1987. The NF2 gene was isolated by the simultaneous discovery of constitutional and tumor deletions in a gene coding for a cell membrane-related protein, which has been termed merlin or schwannomin by the two groups who isolated it. This protein is involved in the interaction between actin within the cell cytoskeleton and the cell membrane, and appears to
suppress tumorigenesis through contact-mediated growth inhibition.

The majority of mutations in the NF2 gene are truncating mutations, leading to a smaller and probably nonfunctional protein product. Early studies suggested that missense mutations (which result in a complete protein product) and large deletions (which result in no protein product) both cause mild phenotypes. Larger studies of detailed genotype/phenotype correlations in multiple families have confirmed this finding.\(^ {29-36}\) The phenotype is more variable in patients with splice-site mutations, with milder disease in patients with mutations in exons 9–15.\(^ {32,35}\) This variation in disease severity is reflected in longer survival for those patients with a missense mutation compared to those with a truncating mutation.\(^ {34}\) Large scale genomic rearrangements may also occur and account for around 15% of NF2 germline aberrations.\(^ {37,38}\)

The sensitivity of genetic testing using sequence analysis and MLPA is around 92% as this is the detection rate in the second generation of NF2 families.\(^ {13}\)

**Differential Diagnosis**

The main differential diagnosis of NF2 is schwannomatosis (Table 2.3\(^ {39}\)) however some patients with multiple non-cranial schwannomas turn out to have mosaic NF2.\(^ {40,41}\) However one exclusion criteria of schwannomatosis is vestibular schwannoma, it is still not entirely clear that these do not occur in schwannomatosis. Final confirmation of schwannomatosis would involve confirming different NF2 mutations in schwannomas from the same individual or identification of a SMARCB1 mutation.\(^ {42}\) Patients fulfilling the most sensitive Manchester criteria are unlikely to be misclassified.\(^ {43}\) Care must be taken to be sure that bilateral enhancing lesions in the Cerebellopontine angle are vestibular schwannoma. These can be due to metastatic processes from choroid plexus carcinoma, lymphoma, ependymoma, or melanoma.
### Table 2.3. Diagnostic criteria for schwannomatosis.

<table>
<thead>
<tr>
<th>Definite</th>
<th>Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age over 30 years AND two or more non-intradermal schwannomas, at least 1 with histologic confirmation AND no evidence of vestibular tumor on high-quality MRI scan AND no known constitutional NF2 mutation</strong></td>
<td><strong>Age under 30 years AND two or more non-intradermal schwannomas, at least 1 with histologic confirmation AND no evidence of vestibular tumor on high-quality MRI scan AND no known constitutional NF2 mutation</strong></td>
</tr>
<tr>
<td>Or</td>
<td>Or</td>
</tr>
<tr>
<td>One pathologically confirmed schwannoma plus a first-degree relative who meets above criteria</td>
<td>Age over 45 years AND two or more non-intradermal schwannomas, at least one with histologic confirmation AND no symptoms of 8th nerve dysfunction AND no known constitutional NF2 mutation</td>
</tr>
<tr>
<td>Or</td>
<td>Or</td>
</tr>
<tr>
<td>Segmental</td>
<td>Radiographic evidence of a schwannoma and first degree relative meeting criteria for definite schwannomatosis</td>
</tr>
<tr>
<td>Meets criteria for either definite or possible schwannomatosis but limited to one limb or five or fewer contiguous segments of the spine</td>
<td></td>
</tr>
</tbody>
</table>

### NF2 Management

#### Surgery

VS surgery in NF2 presents unique technical and decision-making challenges. Schwannomas in the cerebellopontine angle may have multifocal components from the eighth nerve as well as from adjacent cranial nerves – facial, trigeminal, and the lower cranial nerves. As a result, the facial
nerve may pass through the middle of the tumor mass and be difficult to identify. The principle of surgery is to limit the burden of neurological deficit as far as is possible. Facial nerve preservation is very important in the presence of bilateral disease. Facial paralysis threatens the health of the eye by loss of blink and lacrimation (loss of intermedius nerve function), and if combined with trigeminal damage is a serious threat to vision. Risk is minimized by leaving fragments of VS on the facial nerve and if possible by not removing a coexistent facial schwannoma. The patient should be considered holistically. If the vision on the contralateral side is poor (not an infrequent finding in NF2), then surgery should be very conservative. Similar arguments apply to the management of the lower cranial nerves to avoid the problems of bilateral bulbar palsy. “Do not remove a tumor just because it is there!” Usually a VS with good hearing will be treated conservatively until there is a neurosurgical need to remove it. However, there are occasions, when early removal of small tumors will be advised if it is felt possible to preserve hearing or at worst the cochlear nerve for subsequent cochlear implantation. Surgical results are certainly far better when managed by an experienced team.\textsuperscript{24,44-47} There is clear evidence of a reduction in mortality with a significantly increased life expectancy for NF2 patients managed at three specialty centers in the UK (OR 0.34).\textsuperscript{47} All other craniospinal axis tumors should also be managed conservatively with a goal of preserving function. The removal of asymptomatic tumors should only be undertaken if there is evidence of rapid growth and inevitable loss of function without surgery.\textsuperscript{24} All NF2 patients should be managed in the context of a multidisciplinary team with a minimum of an NF2 physician, ENT surgeon, Neurosurgeon, and neuroradiologist.\textsuperscript{24}

**Radiotheraphy**

The use of radiotherapy is controversial in patients with NF2 although it may be useful in some situations. The same tumor considerations make treatment results worse in NF2 than in
sporadic disease.\textsuperscript{48} It has a role in patients who have particularly aggressive tumors, who are poor surgical candidates or who refuse surgery. This should be weighed against control rates of only 50\% compared to a control rate in sporadic VS of 95\%.\textsuperscript{48,49} In addition, there is a greater risk of malignant change in NF2 patients compared to sporadic VS.\textsuperscript{50,51} Forty percent of patients retain pretreatment hearing for at least 3 years. The upper limit of size for radiotherapy is generally a maximum intracranial diameter of 3 cm.\textsuperscript{48} It is important to be able to offer both radiotherapy and surgery, and both options should be discussed in a balanced fashion. Surgeons should use clinical judgment as to when to recommend radiation therapy.\textsuperscript{24,48}

**Hearing Rehabilitation**

Hearing preservation surgery in patients with NF2 is extremely difficult. Patients often become bilaterally profoundly deaf as a result of the disease or treatment of the disease. Teams experienced in the positioning of brainstem implants can offer partial auditory rehabilitation to those who are deaf, although results are still behind those achievable for cochlear implants. In a few patients, it may be possible to rehabilitate hearing successfully with a cochlear implant if the cochlear nerve is left intact after surgery. However, this is not always possible even in the presence of an intact nerve as its blood supply may be damaged. The Auditory Brainstem Implant (ABI, Cochlear Nucleus Implant) has allowed most recipients to appreciate environmental noise and to enhance their lip reading skills. A small number are able to achieve good open set sentence scores, but as yet the factors that predict outcome are not fully understood.

**New Therapies**

The NF2 protein appears to impact on multiple intracellular signaling pathways. These pathways include the PI3-kinase, mTOR, Akt, and Raf/MEK/ERK pathways.\textsuperscript{52}
The progress being made in cellular research especially with regard to pathways in which the NF2 gene product interacts raises the hopes of targeted therapy. Targeting the ERK1/2, AKT, integrin/focal adhesion kinase/Src/Ras signaling cascades, PDGFβ, phosphatidylinositol 3-kinase/protein kinase C/Src/c-Raf pathway, VEG-F, and other pathways\cite{52} means that drugs such as bevacizumab, erlotinib, lapatinib, and sorafenib\cite{53} may well bear fruit. Indeed, a recent report on ten patients showed objective radiological improvement in eight VS with bevacizumab.\cite{54} A further small report on two German patients treated with bevacizumab backs up the promise of drug treatments.\cite{55}

Genetic Counseling and Prenatal Counseling

Mode of Inheritance

Neurofibromatosis 2 (NF2) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a Proband

Around 50\% of individuals with NF2 have an affected parent, and 50\% have NF2 as the result of a de novo mutation. However, 25–33\% of individuals who are simplex cases (i.e., individuals with no family history of NF2) are mosaic for an NF2 mutation.\cite{13,14}

Recommendations for the evaluation of parents of a proband with an apparent de novo mutation include a clinical history and, if any suspicion of NF2 exists, an MRI scan. A parent can be excluded as having NF2 if his/her offspring is shown to be mosaic, but absence of a mutation detected in the child does not eliminate the possibility of mosaicism in the parent. Because the age of onset of symptoms is consistent within families, it is usually not necessary to offer surveillance to asymptomatic parents.
Sibs of a Proband

The risk to the sibs of the proband depends on the genetic status of the parents.

- If a parent of the proband is affected, the risk to the sibs is 50%.
- If neither parent of an individual with NF2 is symptomatic, the risk to the sibs of the affected individual is extremely low because the age of onset of symptoms is relatively uniform within families.
- However, a single case of germline mosaicism in a clinically normal individual has been reported.\(^\text{17}\)

Offspring of a Proband

Each child of an individual with NF2 has up to a 50% chance of inheriting the mutation:

- If the proband has other affected family members, each child of the proband has a 50% chance of inheriting the mutation.
- If the proband is the only affected individual in the family, two possibilities exist:
  - The proband may have somatic mosaicism for the disease-causing mutation. Offspring of an individual who is mosaic will have less than a 50% risk chance of inheriting the disease-causing mutation. The proband may have a de novo germline mutation (i.e., present in the egg or sperm at the time of conception). Each offspring of an individual with a de novo germline mutation has a 50% chance of inheriting the mutation.
  - Persons with somatic mosaicism and bilateral vestibular schwannomas have <50% chance of having an affected child. If a point mutation is detected in DNA from multiple tumors, but not in DNA from leukocytes, the risk to offspring is probably less than 5%.\(^\text{13}\)
Other Family Members of a Proband

The risk to other family members depends on the genetic status of the proband’s parents. If a parent is found to be affected, his or her family members may be at risk, depending on the family structure.

Predictive Testing

At-risk relatives whose genetic status is unknown can be tested for presence of the NF2 mutation (either constitutional or somatic mosaic) identified in an affected relative such as the proband. In the rare instance in which an NF2 mutation cannot be identified, linkage analysis can be used in families with at least two affected family members of different generations or tumor DNA can be used to exclude at least half of children as being at risk.

Offspring of a sporadic case in whom molecular genetic testing of a tumor has revealed loss of heterozygosity (LOH) can be reassured if testing of their lymphocyte DNA shows that they have inherited the allele that was lost in the parental tumor, because this allele is unlikely to have a disease-causing mutation.13,14

Prenatal diagnosis/preimplantation genetic diagnosis (PGD) for at-risk pregnancies requires prior identification of the disease-causing mutation in the family. There is a limited but clear demand for this in some families.

Complications That Require Referral to National NF Centers

All NF2 patients should be managed under the auspices of a national center. Auditory brain stem implantation should only be carried out by an experienced team within a national
Some especially milder cases of NF2 can have their main management carried out by a multidrug therapy (MDT) in a peripheral center with regional review annually by the Regional MDT.

**Conclusions**

NF2 continues to be a condition with considerable morbidity and increased mortality. Multidisciplinary management with early diagnosis is vital for management. Hopefully, new targeted therapies will revolutionize the outcomes in this condition.

**References**

Chapter 2. Neurofibromatosis Type 2 (NF2)


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2011, XVII, 162 p. 40 illus., 20 illus. in color., Softcover