Empirical development of improved diagnostic criteria for neurofibromatosis 2

Michael E. Baser, PhD†[1], Jan M. Friedman, MD, PhD[2], Harry Joe, PhD[3], Andrew Shenton, BSc†[4], Andrew J. Wallace, PhD[4], Richard T. Ramsden, FRCS[5], and D. Gareth R. Evans, MD[4]

Purpose: Four sets of clinical diagnostic criteria have been proposed for neurofibromatosis 2, but all have low sensitivity at the time of initial clinical assessment for the disease among patients with a negative family history who do not present with bilateral vestibular schwannomas. We have empirically developed and tested an improved set of diagnostic criteria that uses current understanding of the natural history and genetic characteristics of neurofibromatosis 2 to increase sensitivity while maintaining very high specificity. **Methods:** We used data from the UK Neurofibromatosis 2 Registry and Kaplan-Meier curves to estimate frequencies of clinical features at various ages among patients with or without unequivocal neurofibromatosis 2. On the basis of this analysis, we developed the Baser criteria, a new diagnostic system that incorporates genetic testing and gives more weight to the most characteristic features and to those that occur before 30 years of age. **Results:** In an independent validation subset of patients with unequivocal neurofibromatosis 2, the Baser criteria increased diagnostic sensitivity to 79% (9–15% greater than previous sets of criteria) while maintaining 100% specificity at the age at onset of the first characteristic sign of neurofibromatosis 2. **Conclusion:** The Baser criteria permit early diagnosis in a greater proportion of patients with neurofibromatosis 2 than previous sets of diagnostic criteria. ***Genet Med*** **2011:13(6):576–581.**

Key Words: *neurofibromatosis 2, NF2, diagnosis, diagnostic criteria, genetic testing*

Neurofibromatosis 2 (NF2) is an autosomal dominant disease caused by heterozygous inactivating mutations of the *NF2* tumor suppressor gene.[1,2] Clinical characteristics of NF2 include vestibular schwannomas (VS), intracranial meningiomas, spinal tumors (usually schwannomas or meningiomas), peripheral nerve schwannomas, and ocular abnormalities. Early diagnosis is often difficult in patients with de novo constitutional mutations, who comprise half of people with NF2.[3] Bilateral VS occur in almost all adults with NF2, but 41% of patients with NF2 do not have bilateral VS at the time of initial clinical evaluation.[4]

Many patients with NF2 become symptomatic when tumors are relatively small, and early diagnosis can enhance clinical care in several ways: periodic magnetic resonance imaging (MRI) can be used to monitor tumor growth, and genetic counseling can be provided during the reproductive years. In some cases, surgical excision of a vestibular tumor can be undertaken before irreversible loss of hearing occurs, or decompression can be performed to allow tumor growth without damaging adjacent normal anatomy.

Four sets of clinical diagnostic criteria have been proposed for NF2 (Table 1), each based on expert opinion: criteria from a National Institutes of Health (NIH) consensus conference in 1987,[5] criteria from an internal NIH meeting in 1991,[6] the Manchester criteria of 1992,[7] and the National Neurofibromatosis Foundation (NNFF) criteria of 1997.[8] Previously, we compared these four sets of criteria using data from the population-based UK NF2 Registry[4]; none was sensitive enough to permit early diagnosis in more than 20% of patients with NF2 who present without bilateral VS and have a negative family history.

In this study, we used data from the Registry to develop an improved set of diagnostic criteria for NF2. By taking into account the clinical availability of high-quality MRI and molecular genetic testing and by incorporating new knowledge about somatic mosaicism and the natural history of NF2, these new criteria provide increased sensitivity while maintaining very high specificity.

METHODS

All the data used in this study were obtained from the UK NF2 Registry,[4] which contained 689 patients from 620 families at the time of our analysis. The Registry includes all patients who have undergone molecular diagnostic testing for NF2, usually because of single or multiple nerve-related tumors or meningiomas. It does not contain information on individuals who were tested but found not to carry an *NF2* mutation known to be segregating in the family, although all individuals testing positive for a familial mutation and all untested patients with NF2-related tumors are included.

We used statistical methods to develop a new set of diagnostic criteria, and this required a "gold standard" set of patients who definitely have NF2 and a second set of patients who definitely do not have NF2. Patients were considered to have unequivocal nonmosaic NF2 if they met either or both of the following conditions:

- Bilateral VS with onset of both tumors documented before the age of 30 years; or
- A constitutional nonmosaic pathogenic mutation of the *NF2* gene.

We defined a "pathogenic mutation" as a sequence variant that affects a conserved residue and that has not been seen in

From [1]Los Angeles, California; [2]Department of Medical Genetics, University of British Columbia and the Child & Family Research Institute; [3]Department of Statistics, University of British Columbia, Vancouver, British Columbia, Canada; [4]Academic Department of Medical Genetics, St. Mary's Hospital; and [5]Department of Otolaryngology, Manchester Royal Infirmary, Manchester, United Kingdom.

†Deceased.

Jan M. Friedman, MD, PhD, Medical Genetics Research Unit, Box 153, Children's and Women's Hospital, 4500 Oak Street, Vancouver, British Columbia V6H 3N1, Canada. E-mail: frid@interchange.ubc.ca.

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Table 1 Previous sets of diagnostic criteria for NF2

1987 NIH Criteria[5]

A patient who meets either condition A or B has NF2.

A. Bilateral vestibular schwannomas (VS)

B. 1st degree family relative with NF2
and
unilateral VS or any two of neurofibroma, meningioma, glioma, schwannoma, or juvenile posterior subcapsular lenticular opacity

1991 NIH Criteria[6]

A patient who meets either condition A or B has NF2.

A. Bilateral VS

B. 1st degree family relative with NF2
and
unilateral VS or any one of neurofibroma, meningioma, glioma, schwannoma, or juvenile posterior subcapsular lens opacity

Manchester criteria[7]

A patient who meets condition A, condition B, condition C, or condition D has NF2.

A. Bilateral VS

B. 1st degree family relative with NF2
and
unilateral VS or any two of neurofibroma, meningioma, glioma, schwannoma, or posterior subcapsular lenticular opacities

C. Unilateral VS
and
any two of neurofibroma, meningioma, glioma, schwannoma, or posterior subcapsular lenticular opacities

D. Multiple meningiomas (two or more)
and
unilateral VS or any two of neurofibroma, glioma, schwannoma, or cataract

NNFF criteria[8]

Confirmed or definite NF2:

A patient who meets either condition A or B has NF2.

A. Bilateral VS

B. First-degree family relative with NF2
and
unilateral VS <30 yr or any two of meningioma, glioma, schwannoma, juvenile lens opacity (posterior subcapsular cataract or cortical cataract)

Presumptive or probable NF2

A patient who meets either condition C or D has probable NF2.

C. Unilateral VS <30 yr
and
at least one of meningioma, glioma, schwannoma, or juvenile lens opacity (posterior subcapsular cataract or cortical cataract)

D. Multiple meningiomas (two or more)
and
unilateral VS <30 yr or at least one of meningioma, glioma, schwannoma, juvenile lens opacity (posterior subcapsular cataract or cortical cataract)

In the Manchester criteria, "any two of" refers to two individual tumors or cataract, whereas in the other sets of criteria, it refers to two tumor types or cataract.

more than 1000 control chromosomes or as the "normal" allele in more than 500 patients with NF2 with pathogenic mutations. In addition, for a variant to be considered as a pathogenic mutation, we required it either to cosegregate with the disease in at least two NF2 families, to occur with loss of the wild-type allele in an NF2-associated tumor, or to have arisen de novo in a patient with NF2 whose parents are unaffected.

Patients were considered unequivocally not to have NF2 if they met all the following conditions:

- The presence of one, but not more than one, schwannoma or of one or more meningiomas;
- No detectable pathogenic *NF2* mutation in blood; and
- No family history of typical NF2.

Patients were considered to have unequivocal mosaic NF2 if they met either of the following conditions:

- Mosaicism for a pathogenic *NF2* mutation in the blood; or
- No detectable pathogenic *NF2* mutation in blood but the presence of the same pathogenic *NF2* mutation in two separate NF2-associated tumors (usually schwannomas or meningiomas).

Cataracts were defined as juvenile cortical wedge opacities or posterior subcapsular lens opacities seen on slit lamp examination. Mononeuropathy was defined as the sudden loss of function of a single nerve root, not resulting from trauma or other defined cause, with gradual, usually incomplete, recovery. Peripheral neuropathy was defined as bilateral, symmetrical, predominantly peripheral loss of motor and sensory function with slow onset and progressive course.

One hundred ninety-one Registry patients were excluded from the present analysis because (1) they could not be definitely classified as having NF2, mosaic NF2, or not NF2 as defined above; (2) information on age at onset was not available for one or more of the critical clinical features; or (3) the subject had an *NF2* mutation documented because of a known family history, but no characteristic clinical features were present. Table 2 lists the number of patients who were included in the analysis in each group.

Table 2 Patients from the UK NF2 Registry included in the study

Group	Total patients (families)	Training subset	Holdout subset
Definite nonmosaic NF2	149 (122)	82	67
Bilateral vestibular schwannoma before the age of 30 yr	115 (100)	63	52
Constitutional *NF2* mutation	125 (100)	66	59
Both	91 (78)	47	44
Definitely not NF2	315 (302)	173	142
Definite mosaic NF2	34 (34)		
Mosaicism for pathogenic *NF2* mutation in blood	13 (13)		
Same *NF2* mutation in ≥2 tumors but not in blood	21 (21)		
Total	498 (458)	255	209

Data from the patients with definite NF2 and from those who definitely do not have NF2 were used to develop the new diagnostic criteria. Data from patients with mosaic NF2 were set aside for subsequent analysis. The patients with unequivocal NF2 and those who unequivocally do not have NF2 were each randomly divided into two separate subgroups of approximately equal size. One subgroup, called the "training subset," was used to develop the new diagnostic criteria. The second subgroup, called the "holdout subset," was used to test the new diagnostic criteria that were developed.

The Registry contains information on family history, age at first recognition of 12 clinical features of the disease, and the results of *NF2* mutation testing. For the purposes of this study, we defined the age of onset of the first characteristic sign of NF2 as the youngest age at which signs or symptoms of any of the following features were noted in an individual: VS, meningioma, spinal tumor, cranial nerve schwannoma (other than VS), mononeuropathy, or peripheral neuropathy. We excluded four features (glioma, ependymoma, neurofibroma, and retinal hamartoma) because they occurred infrequently among the patients with definite NF2. The remaining features were evaluated in various combinations in the training subsets for misclassification errors between the two groups of patients. Combinations with more than six clinical features provided very little improvement over combinations of six features, so we evaluated various sets of six clinical features in detail.

The frequencies of individual clinical features were estimated at ages 0–9, 10–19, 20–29, 30–39, and 40–49 years for the NF2 and non-NF2 training subsets by means of Kaplan-Meier curves using the survival software package in R (http://www.r-project.org). Observations on patients in whom a feature had not occurred were considered to be right censored at the age of the most recent clinic visit, if alive, or at the age of death. (Survival analysis adjusts for negative observations in a consistent way, so that frequencies in different age intervals can be estimated more accurately. If a patient who is aged 15 years, for example, does not have a particular feature, two different possibilities exist: either the patient will develop the feature later in life or the patient will never develop the feature. The observation that a 15-year-old patient does not have a feature yet is said to be right censored at the age of 15 years. This means that although we know that the feature has not occurred by the age of 15 years, we do not know whether the feature will develop later in life. Survival analysis takes this uncertainty into account in estimating frequencies in each age interval.)

Probability ratios were calculated by dividing the estimated frequency in each age interval for patients with definite NF2 by the estimated frequency for patients who definitely do not have NF2.

We evaluated 12 different candidate clinical features as possible diagnostic criteria by assessing their frequencies in data from subjects comprising a randomly selected "training subset" of the UK NF2 Registry. The training subset included 82 patients with definite NF2 and 173 patients who definitely do not have NF2. Kaplan-Meier curves were used to estimate the age of occurrence of each feature in each group (Table, Supplemental Digital Content 1, http://links.lww.com/GIM/A162).

We developed candidate scoring systems using various combinations of clinical features. The probability ratios for many features are much higher in younger patients, so we assigned more points to signs that occur at or before 30 years of age than to signs that occur later in life. Points were provisionally assigned to each feature based on clinical experience and then adjusted as necessary to maximize diagnostic sensitivity (data not shown). Each candidate scoring system included VS (2 points if unilateral and present at or before the age of 30 years, 6 points if bilateral and present at or before the age of 30 years, 1 point if unilateral and present after the age of 30 years, and 3 points if bilateral and present after the age of 30 years) and meningiomas (2 points for one tumor at or before the age of 30 years, 4 points for two or more tumors at or before the age of 30 years, 1 point for one tumor after the age of 30 years, and 2 points for two or more tumors after the age of 30 years) as well as four of the following additional features in various combinations:

- Spinal tumors (2 points if one or more tumors present at or before the age of 30 years and 1 point if present after the age of 30 years),
- Cutaneous schwannomas (2 points if one or more tumors present at or before the age of 30 years and 1 point if present after the age of 30 years),
- Cranial nerve schwannomas other than VS (2 points if one or more tumors present at or before the age of 30 years and 1 point if present after the age of 30 years),
- Mononeuropathy (2 points if present at or before the age of 30 years and 1 point if present after the age of 30 years),
- One or more cataracts (2 points if present at or before the age of 30 years but no points if present after the age of 30 years), or
- Peripheral neuropathy (2 points if present at or before the age of 30 years and 1 point if present after the age of 30 years).

In this preliminary analysis, a total of 4 or more points was considered sufficient to identify patients who were likely to have NF2.

RESULTS

We developed eight candidate scoring systems using various combinations of clinical features (see "Methods"). We compared the rates at which patients with definite NF2 were misclassified as being unlikely to have NF2 and the rates at which patients who definitely do not have NF2 were misclassified as being likely to have NF2 for each of the candidate scoring systems in the training subset at two different time points—the age of onset of the first characteristic sign of NF2 and the age of the most recent clinical assessment (see Methods and Table, Supplemental Digital Content 2, http://links.lww.com/GIM/A163). Patients with unequivocal NF2 were misclassified with all the candidate scoring systems as being unlikely to have NF2 in 22–29% of cases at the age of onset of the first characteristic sign of NF2, but no more than 4% of such cases were so misclassified at the most recent evaluation. The frequency with which patients who unequivocally do not have NF2 were misclassified as being likely to have NF2 was 1.7% for each of the candidate scoring systems at both time points.

Candidate scoring systems A, D, G, and H had the fewest misclassifications at the time of onset of the first characteristic sign of NF2. Because we wished to develop a system that provides earlier diagnosis of NF2, we compared the ages at which patients with definite NF2 in the training subset reached a total of 4 points for each of these four candidate scoring systems (Table, Supplemental Digital Content 3, http://links.lww.com/GIM/A164). Scoring system D had the lowest mean and median age of achieving 4 points and the largest fraction of cases that achieved 4 points before the age of 10 years and before the age of 20 years. We, therefore, formalized system D as the Baser criteria for diagnosis of NF2, as presented in Table 3 (Dr. Michael Baser was a

Table 3 The Baser criteria for diagnosis of NF2

Feature	If present at or before the age of 30 yr	If present after the age of 30 yr
First-degree relative with NF2 diagnosed by these criteria	2	2
Unilateral vestibular schwannoma	2	1[a]
Second vestibular schwannoma	4	3[a]
One meningioma	2	1
Second meningioma (no additional points for more than two meningiomas)	2	1
Cutaneous schwannoma (one or more)	2	1
Cranial nerve tumor (excluding vestibular schwannoma) (one or more)	2	1
Mononeuropathy	2	1
Cataract (one or more)	2	0

The patient is given points as shown in the table.
[a]Points are not given for unilateral or second vestibular schwannoma if age at diagnosis is more than 70 yr.
- A diagnosis of definite NF2 is established if the total number of points is 6 or more.
- *NF2* mutation testing is indicated if the total number of points is 4 or 5.
  - A diagnosis of definite NF2 is established if a constitutional pathogenic *NF2* mutation is found on mutation testing.
  - If no constitutional pathogenic *NF2* mutation is found on mutation testing:
    - A diagnosis of mosaic NF2 is established if mosaicism for a pathogenic *NF2* mutation is found in the blood or no detectable pathogenic *NF2* mutation is found in the blood but the same pathogenic *NF2* mutation is found in two separate NF2-associated tumors.
    - Otherwise, a temporary diagnosis of possible NF2 is made, pending further clarification. Clarification may occur if the patient is established to have a different condition (e.g., schwannomatosis or multiple meningiomas) by standard diagnostic criteria or if evolution of the patient's disease over time permits establishing a diagnosis of definite NF2 or mosaic NF2 according to the criteria given above.

passionate advocate for the development of an evidence-based set of diagnostic criteria for NF2. He completed an initial analysis of the data presented herein before his untimely death in December 2005. It is, therefore, appropriate to refer to this new set of diagnostic criteria as the "Baser criteria").

In recognition of the age dependence of most NF2 features, the Baser criteria assign different numbers of points to the presence of features if they occur before 30 years of age than if they occur after that age. A diagnosis of definite NF2 is established if the number of points exceeds 6. A score of 4 or more points is considered to be an indication to do NF2 molecular testing, and definite NF2 may also be diagnosed if the patient is found to have a constitutional pathogenic mutation of the *NF2* gene in the blood. A diagnosis of mosaic NF2 can be made only on the basis of compatible molecular diagnostic results—finding mosaicism for a pathogenic *NF2* mutation in the blood or, if no mutation is found in the blood, demonstrating the same pathogenic *NF2* mutation in two separate tumors. Patients who score 4 or 5 points but are not found to have a pathogenic *NF2* mutation on molecular testing are considered to have possible NF2, pending further clarification. The diagnostic algorithm by which these criteria are applied is illustrated in Figure 1.

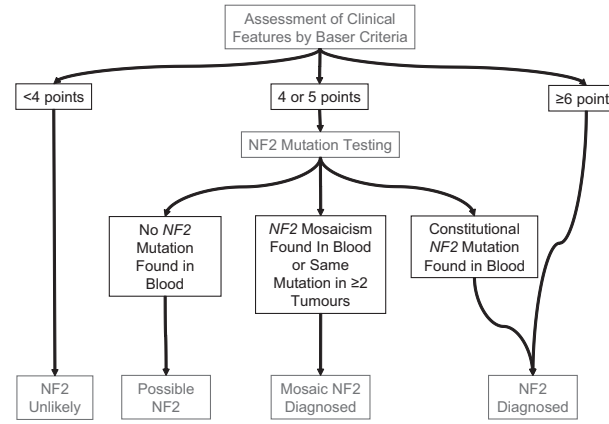

Fig. 1. Algorithm for diagnosis of NF2 using the Baser criteria.

Table 4 Proportion of cases with 4 points (indicating the need for molecular genetic testing), sensitivity, and specificity of Baser criteria for diagnosis of definite NF2 in the holdout subsets

	Patients with definite NF2	Patients who definitely do not have NF2
Number in group	67	142
Number with ≥4 points	55	4
Number with ≥6 points or with 4 or 5 points and a pathogenic *NF2* mutation in blood	53	0
Sensitivity for diagnosis of definite NF2	79%	
Specificity for diagnosis of definite NF2		100%

Calculation of sensitivity and specificity was based on numbers of patients with definite NF2 or who definitely do not have NF2 at the age of onset of the first characteristic sign of NF2.

Validation of the Baser criteria was performed on data from an independent "holdout subset" that includes 67 patients with definite NF2 and 142 patients who definitely do not have NF2. The proportions of patients who would be diagnosed with NF2 and the corresponding sensitivities and specificities according to the Baser criteria at the age of onset of the first characteristic sign of NF2 are presented in Table 4.

Table 5 compares the sensitivity and specificity of the Baser criteria and each of the previous sets of diagnostic criteria for definite NF2 in the holdout subsets. At the age of onset of the first characteristic sign of NF2, the sensitivity of the Baser criteria is 9–15% greater than the sensitivity of the previous systems. All these diagnostic systems exhibit very high specificity. A similar analysis of 34 patients with unequivocal mosaic NF2 using the Baser criteria indicates a sensitivity of 47% (16/34) at the age of onset of the first characteristic sign of NF2 and 85% (29/34) at the time of each patient's most recent clinical assessment.

The improvement in sensitivity achieved with the Baser criteria is even greater in young patients who do not present

Table 5 Comparison of five sets of criteria for the diagnosis of NF2 in the holdout subsets

Diagnostic criteria	Sensitivity	Specificity
1987 NIH[5]	64%	100%
1991 NIH[6]	67%	100%
Manchester[7]	70%	100%
NNFF[8]	64%	100%
NNFF + molecular testing[a]	70%	100%
Baser	79%	100%

Calculation of sensitivity and specificity was based on 67 patients with definite NF2 and 142 who definitely do not have NF2 at the age of onset of the first characteristic sign of NF2.
[a]Includes cases classified as "confirmed or definite NF2" by the NNFF criteria and also cases classified as "presumptive or probable NF2" by the NNFF criteria who were found to have a pathogenic *NF2* mutation on molecular testing (see text).

with bilateral VS. All 28 patients with unequivocal NF2 in the holdout subset who presented with bilateral VS as their first characteristic sign of the disease at or before 30 years of age would be diagnosed as having NF2 by any of the sets of diagnostic criteria. Of the remaining 39 patients in the holdout subset with definite NF2, 38% would be diagnosed by the 1987 NIH criteria, 38% by the NNFF criteria, 44% by the 1991 NIH criteria, 49% by the Manchester criteria, and 64% by the Baser criteria.

Similar to the Baser criteria, the NNFF system defines a group that can be definitely diagnosed as having NF2 on the basis of clinical features alone (called "confirmed or definite NF2") and also a group for which the diagnosis is suggested but uncertain (called "presumptive or probable NF2"). In the Baser criteria, a diagnosis of definite NF2 can be established in a patient classified on the basis of clinical features as having possible NF2 by molecular demonstration of a constitutional *NF2* mutation. If the same criterion was used on patients classified as having "presumptive or possible NF2" according to the NNFF system, the sensitivity would be increased but not to the level achieved with the Baser criteria (Table 5).

DISCUSSION

In contrast to all previous sets of NF2 diagnostic criteria, the Baser criteria incorporate mutation testing, take the age of recognition of each clinical sign of the disease into account, and provide explicit standards for diagnosis of both constitutional (i.e., nonmosaic) and mosaic NF2. The use of the Baser criteria to decide when to perform *NF2* mutation testing enables molecular diagnosis to be achieved early in the course of the disease in many patients while restricting such testing to circumstances in which confirmation of the diagnosis of NF2 is likely. No *NF2* mutation is found by standard molecular diagnostic testing in $<10\%$ of patients who do not have mosaicism.[1,2] The Baser criteria permit diagnosis of these patients on the basis of clinical and imaging findings alone.

Patients in whom a diagnosis of NF2 is suspected but cannot be definitely established are considered to have "possible NF2," a temporary diagnosis that may be clarified as the disease evolves. Such patients should be followed up clinically as if they have NF2 until a definite diagnosis can be established. Some patients initially classified as having possible NF2 may subsequently be reclassified as having definite NF2 or mosaic NF2; others may be reclassified as having a different condition such as schwannomatosis[9] or multiple meningiomas.[10]

In our analysis, we only considered individuals who definitely have NF2 or who definitely do not have NF2. As a result, some patients in the UK NF2 Registry who have NF2 according to one or more of the existing sets of diagnostic criteria may have been excluded from consideration. We think that these exclusions are unlikely to have had a major effect on our results because our data are longitudinal—we were able to include many patients who fell into this "gray zone" early in their lives but who later met our standard for unequivocal NF2.

The Baser criteria's explicit consideration of molecular genetic testing results is especially valuable for younger patients, who often do not present with bilateral VS, and for older patients, in whom knowledge of when various features developed is unavailable. The default assumption in a patient older than 30 years who does not know the age of occurrence of a feature that is currently present is that the feature developed after the age of 30 years.

A combination of sequence analysis or mutation scanning and duplication/deletion testing can achieve a detection rate of more than 90% for pathogenic mutations in patients with inherited NF2.[1,2] The detection rate is approximately 60% in de novo (simplex) cases because 25–30% of such cases are mosaic.[11,12] Some clinical laboratories may use less sensitive methods for detecting pathogenic mutations of the *NF2* locus; this would delay the diagnosis of NF2 in a few patients until it can be made on the basis of clinical features alone.

NF2 mutation carriers within an affected family can be identified by mutation analysis regardless of age or clinical status if the causal mutation has been previously identified in the family.[13,14] Patients who do not have NF2 would not be expected to have a constitutional pathogenic *NF2* mutation in their blood, although individual sporadic schwannomas usually, and meningiomas often, have *NF2* mutations in tumor tissue.[15,16]

All five sets of diagnostic criteria had 100% specificity in the 142 patients in the holdout subset who definitely do not have NF2. Only four (2.8%) of these patients scored 4 points, indicating a need for NF2 molecular testing according to the Baser criteria. These four patients all had multiple meningiomas, but we are aware of another family (not included in this study) in which two children who did not inherit an *NF2* mutation from their affected mother were found to have cataracts, which had been inherited as an autosomal dominant trait from their father. These two children would not be diagnosed as having NF2 by the Baser criteria, although they would meet the 1991 NIH diagnostic criteria for NF2.

Bilateral VS occur in almost all adults with NF2, but these tumors often are not present in patients with early-onset NF2 at the time of initial clinical presentation.[4] NF2-associated VS may become symptomatic although still relatively small, before they are apparent on routine head MRI examination. Visualization of small VS requires thin-slice gadolinium-enhanced T1 imaging of the internal auditory canal using a special MRI protocol designed for this purpose.[17,18] Deterioration of hearing is not correlated with rate of VS tumor growth in NF2,[19] and careful monitoring of both hearing and tumor growth is necessary in patients with NF2.[1,2]

The UK NF2 Registry is population based and has several sources of ascertainment,[4] so it is likely to be more similar to the overall NF2 patient population than if the subjects had been identified through a single clinic or hospital. However, both the training and holdout subsets were drawn from the same source, so if subjects in the Registry differ from the NF2 patient

population as whole, both subsets are likely to share similar biases. We would welcome the opportunity to test the Baser criteria on other large longitudinal clinical and molecular genetic data sets from patients with NF2.

Since 1997, when the most recent set of diagnostic criteria were proposed, the natural history of NF2 has become more clearly defined,[19–24] and management of the disease has improved.[1,2,25–27] Molecular testing for *NF2* mutations has become clinically available,[1,2,26,28,29] and somatic mosaicism has been found to occur in 25–30% of de novo NF2 patients.[11,12] Schwannomatosis has been defined as a distinct clinical entity,[9] excluded from the NF2 locus,[30] and shown to be related to mutations of the SMARCB1 locus in some patients.[31–34] Most importantly, we have begun to understand the molecular pathogenesis of NF2,[1,35–37] and this is permitting the development of novel therapeutic initiatives.[25,38–41] Both NF2 and other conditions with which it may be confused clinically are being recognized more frequently,[42] probably because of the availability of high-quality MRI. Adoption of the Baser criteria as the clinical standard for diagnosis of NF2 is, therefore, both opportune and important for optimal patient care.

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