Stage I: Binning Dashboard

Incidental Findings in Adults

Non-diagnostic, excludes newborn screening & prenatal testing/screening

GENE/GENE PANEL: *NF2*	**DISORDER:** Neurofibromatosis 2
HGNC ID: 7773	**OMIM ID:** 101000, 607379

ACTIONABILITY

1. **Is there a qualifying resource, such as a practice guideline or systematic review, for the genetic condition?**

☒ **YES** ☐ **NO**

2. **Does the practice guideline or systematic review indicate that the result is actionable in one or more of the following ways?**

Yes	No	
☒	☐	Patient Management
☒	☐	Surveillance or Screening
☒	☐	Family Management
☐	☒	Circumstances to Avoid

☒ **YES (≥ 1 of above)** ☐ **NO**

3. **Is the result actionable in an undiagnosed adult with the genetic condition?**

☒ **YES** ☐ **NO**

PENETRANCE

4. **Is there at least one known pathogenic variant with at least moderate penetrance (≥40%) or moderate relative risk (≥2) in any population?**

☒ **YES** ☐ **NO**

SIGNIFICANCE/BURDEN OF DISEASE

5. **Is this condition an important health problem?**

☒ **YES** ☐ **NO**

NEXT STEPS

6. **Are Actionability (Q2-3), Penetrance (Q4), and Significance (Q5) all "YES"?**

☒ **YES (Proceed to Stage II)**

☐ **NO (Consult Actionability Working Group)**

- ☐ **Exception granted, proceed to Stage II**
- ☐ **Exception not granted, STOP**

Stage II: Binning Summary

Incidental Findings in Adults

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GENE/GENE PANEL: *NF2*		**DISORDER:** Neurofibromatosis 2	
Topic		**Narrative Description of Evidence**	**Ref**
1. What is the nature of the threat to health for an individual carrying a deleterious allele?			
Prevalence of the genetic disorder		In the past, the estimated prevalence of neurofibromatosis 2 (NF2) was estimated at 1:210,000. However, a recent 2010 study estimated a higher prevalence of 1:60,000.	[1-4]
Signif/Burden of Condition	**Clinical Features**	NF2 is characterized by the development of nervous system tumors (schwannomas and meningiomas), ocular abnormalities, and skin tumors. Bilateral vestibular schwannomas occur in 95% of adult patients; vestibular schwannoma growth rates are extremely variable, both between patients and over time in the same patient. Schwannomas typically affect both vestibular nerves, leading to hearing loss and deafness, tinnitus, dizziness and imbalance. While the tumors caused by NF2 are not malignant, their anatomical location and multiplicity lead to great morbidity and early mortality.	[1-4] [1;2]
	Natural History	Average age of onset in individuals with NF2 is 18 to 24 years (range birth to 70 years). Nearly all affected individuals develop bilateral vestibular schwannomas by age 30. The average age of death is 36 years; actuarial survival from correct diagnosis is 15 years. NF2 has no racial or ethnic predilections. Childhood-onset NF2 typically presents with non-8th nerve tumors and non-vestibular symptoms, while adult-onset NF2 typically presents with vestibular symptoms. Age at diagnosis, presence of intracranial meningiomas, type of treatment center and type of *NF2* mutation are informative predictors of the risk of mortality. Age at diagnosis is, by far, the strongest single predictor.	[1] [3;4]
2. How effective are interventions for preventing the harm?			
Patient Management		At diagnosis, the following evaluations are recommended: head MRI, hearing evaluation including BAER, ophthalmologic evaluation, cutaneous evaluation, and a genetics consultation. **(Tier 4)** NF2 patients should be managed in specialty centers. NF2 patients who are managed at specialty centers have a significantly lower risk of mortality than those who are treated at non-specialty centers (relative risk 0.34, 95% CI 0.12-0.98). **(Tier 2)** Hearing preservation and augmentation are important in the management of individuals with NF2; all affected individual and their families should be referred to an audiologist. **(Tier 2)** A cervical spine scan should be performed before cranial surgery to prevent complications from manipulation under anesthesia. Lumbosacral imaging should be performed before regional analgesia is given. **(Tier 3)**	[1] [4] [5] [1]
Surveillance		MRI screening every 2 years for patients less than 20 and every 3 years for older patients should be sufficient for at-risk patients without tumors. The initial MRI scan could be at 10-12 years of age, or earlier in severely affected families. In 10% of cases, individuals with NF2 become symptomatic before 10 years of age. Once tumors are present, MRI screening should be at least annual until the individual growth rate is established. Annual audiological tests, including auditory brainstem response, may be useful. A full annual neurological examination is a wise precaution, with a spinal MRI every 2-3 years unless no tumors are present on the initial scan. **(Tier 2)**	[4;5]
Family		Effectiveness data were not provided for the family management recommendations below.	

Stage II: Binning Summary

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Management	Children of affected patients should be considered at 50% risk of NF2 and screening for NF2 can start at birth. All NF2 patients and their families should have access to genetic testing; presymptomatic genetic testing is an integral part of the management of NF2, allowing for presymptomatic clinical screening. **(Tier 2)**	[4]
Circumstances to Avoid	No circumstances to avoid were identified.	

Description of sources of evidence:

Tier 1: Evidence from a systematic review, or a meta-analysis or clinical practice guideline clearly based on a systematic review
Tier 2: Evidence from clinical practice guidelines or broad-based expert consensus with non-systematic evidence review
Tier 3: Evidence from another source with non-systematic review of evidence with primary literature cited
Tier 4: Evidence from another source with non-systematic review of evidence with no citations to primary data sources
Tier 5: Evidence from a non-systematically identified source

GENE/GENE PANEL: *NF2*	**DISORDER:** Neurofibromatosis 2	
Topic	**Narrative Description of Evidence**	**Ref**
3. What is the chance that this threat will materialize?		
Mode of Inheritance	Autosomal dominant	
Prevalence of Genetic Mutations	Prevalence of *NF2* mutations was not identified.	
Penetrance OR Relative Risk	Penetrance is close to 100%. Virtually all individuals who have a pathogenic germline mutation develop the disease in an average lifetime. **(Tier 4)**	[1]
	Unavailable	
Expressivity	Vestibular schwannoma growth rates are extremely variable, both between patients and over time in the same patient. Growth rates are highly variable even among multiple NF2 patients of similar ages in the same family. **(Tier 3)**	[1;3; 4]
4. What is the nature of the intervention?		
Nature of Intervention	Management of NF2 requires a variety of non-invasive screening tests.	
5. Would the underlying risk or condition escape detection prior to harm in the setting of recommended care?		
Chance to Escape Clinical Detection	Regular screening (MRI, neurological, audiology) is recommended beginning at diagnosis, or earlier for family members. These screenings are above and beyond general population recommendations.	

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Final Consensus Scores						
Gene(s)	**Outcome/intervention pair**	**Severity**	**Likelihood**	**Effectiveness**	**Nature of the Intervention**	**Total Score**
NF2	Vestibular schwannoma/Surveillance	2	3B*	2B	3	10BB

*Scores where the tier of evidence recommendation of the Working Group differs from the evidence level tier in the Summary Report

To see the scoring key, please go to: https://clinicalgenome.org/working-groups/actionability/projects-initiatives/actionability-evidence-based-summaries/.

Date of Search (MM.DD.YYYY): 06.20.2014

References

[1] Evans DG. GeneReview: Neurofibromatosis 2. 8-18-2011. 6-23-2014.
Ref Type: Online Source

[2] Evans DG. Orphanet: Neurofibromatosis type 2. 6-1-2009.
Ref Type: Online Source

[3] Baser ME, DG RE, Gutmann DH. Neurofibromatosis 2. Curr Opin Neurol 2003 Feb;16(1):27-33.

[4] Evans DG, Baser ME, O'Reilly B, et al. Management of the patient and family with neurofibromatosis 2: a consensus conference statement. Br J Neurosurg 2005 Feb;19(1):5-12.

[5] Gutmann DH, Aylsworth A, Carey JC, et al. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. JAMA 1997 Jul 2;278(1):51-7.