

Cerebral Cavernous Malformations via Sequential CCM Gene Testing

Brief Clinical Description: Cerebral cavernous malformations (CCMs) are congenital vascular anomalies of the brain that can cause significant neurological disabilities, including intractable seizures and hemorrhagic stroke. CCMs represent 5-15% of all cerebral vascular malformations and occur in ~0.5 percent of the general population. CCMs have been reported in infants and children, but the majority of patients present with symptoms between the second and fifth decades. CCMs occur in a sporadic form in which patients usually present with one or two lesions and no family history, and a familial form characterized by multiple lesions, and usually a strong family history. Perhaps 50% of “sporadic” cases with multiple lesions may in fact be members of an undiagnosed affected family. Not all patients with CCMs are clinically symptomatic. For additional information, see Zabramski et al. J Neurosurg 80: 422-432, 1994, Johnson 2006 GeneReviews (<http://www.geneclinics.org/>), and Angioma Alliance (<http://www.angiomaalliance.org/>).

Genetics: Familial CCMs show autosomal dominant inheritance. Three causative genes for CCMs have been identified: *KRIT1* (or *CCM1*) encoding a protein that interacts with the Krev-1/rap1a tumor suppressor, *MGC4607* (or *CCM2*) similar to the *KRIT1* binding partner ICAP1 α , and *PDCD10* (or *CCM3*) the programmed cell death 10 gene. Almost all causative mutations (in all three genes) are either nonsense, frameshift, splicing or deletion; missense mutations are rare. (Denier et al. Ann Neurol 60:550-556, 2006; Plummer et al. Curr Neurol Neurosci Rep 5:391-396, 2005 ; Liquori et al. Am J Hum Genet 80:69-75, 2007).

Description of This Particular Test: Sequential testing is performed in the following order. Either the *CCM2* exon 2-10 deletion (most patients) or *CCM1* exon 10 (Hispanics from the southwest) tests will be done first and billed at \$190 if positive. If the first test(s) are negative, then the *CCM1* gene is sequenced, and if a likely causative mutation is found, the testing is stopped and billed at \$940. *CCM2* gene sequencing is performed next; if a likely causative mutation in found, the testing is stopped and billed at \$1390. Finally, if both *CCM1* and *CCM2* tests are negative, *CCM3* sequencing is performed and billed at the total discounted price of \$1690.

Indications for Test: Suspected familial CCMs and/or multiple CCMs in a person without a known family history.

Sensitivity:

| <u>Test</u> | <u>Mutations Detected</u> | <u>Mutation Detection Rate</u> |
|-------------------------------------|---|---|
| <i>CCM1/KRIT1</i> “Common Hispanic” | <i>KRIT1</i> exon 10 (1363C>T) | ~70% (with American Southwest Hispanic heritage) |
| <i>CCM1/KRIT1</i> Sequencing | nonsense, splice, small indel | ~40% |
| <i>CCM2/MGC4607</i> Sequencing | nonsense, splice, small indel | ~15% |
| <i>CCM2</i> deletion testing | <i>CCM2</i> del exon 2-10, Other <i>CCM2</i> deletions | ~15% (~30% in <i>CCM1/2/3</i> mutation negative patients) ~10% (No clinical testing currently available) |
| <i>CCM3/PDCD10</i> Sequencing | nonsense, splice, small indel Currently undetectable | ~7% ~15% |

Turn Around Time: Maximum of 40 days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: *CCM2* deletion exons 2-10, *CCM1*, *CCM2*, *CCM3* gene sequencing:
\$190, \$940, \$1,390, or \$1690 (discounted ~15% from \$2,010 if ordered separately)

CPT Codes:

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|-------------------|-------|--------|----------------------------------|-------|--------|
| Ascertainment | 83890 | \$ 30 | DNA Isolation | 83891 | \$ 40 |
| Amplification X34 | 83898 | \$ 550 | Mutation Ident by Sequencing X33 | 83904 | \$ 820 |
| Separation | 83894 | \$ 110 | Interpretation and Report | 83912 | \$ 140 |

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

Ship to:

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