ANGIOMA ALLIANCE
because brains shouldn't bleed

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Dear Physician or Genetic Counselor:

As the Chief Scientific Officer and clinician members of the Angioma Alliance Scientific Advisory Board, we write to endorse the critical importance of pursing clinical genetic testing for cavernous angioma (cerebral cavernous malformations, CCM, cavernoma) patients who have a **family history** of the illness and/or **multiple cavernous angiomas**. This is an autosomal dominant disease with one of three gene loci and nearly complete clinical penetrance during a patient's lifetime. We ask that you help your patients obtain clinical genetic testing, by referral to one of the laboratories listed below, or by consulting a genetics professional or neurologist for this purpose. Identifying a patient's genotype, which may have immediate clinical implications for the patients and their kindred, is important for clinical monitoring as well as for future research endeavors, as described below.

- CCM follows an autosomal dominant inheritance pattern and therefore can affect many members of a patient's multi-generational family. First degree relatives have a 50% likelihood of sharing the disease, yet clinical screening by MRI is expensive, may require IV contrast or sedation, and may have occasional false negative results. Delay in obtaining a specific diagnosis may result in unnecessary and sometimes risky diagnostic procedures, such as angiograms or unnecessary surgery. Identifying your patients' genetic mutations will enable family screening with greater confidence, and will allow MRI screening to be targeted to other family members at risk. Once the family gene is known, a negative genetic test result for a relative is reassuring not only to that individual, but for all of that individual's descendants and will alleviate the burden and costs of imaging of unaffected relatives and their offspring.
- The different genotypes of CCM are not alike. All patients with familial CCM require monitoring and follow-up care. However, patients with CCM3 gene mutations require additional specialized care and monitoring. These patients are known to have a particularly severe and multi-systemic disease course including early age of symptom onset, high lesion burden, high hemorrhage rates and an association with meningiomas (Riant et. al 2013, PMID: 23801932). A low threshold is appropriate in these cases for aggressive screening of vascular, tumor and other pathologies in association with subtle symptoms.
- Genotypic information will be important for expediting and facilitating recruitment for future clinical trials. Identifying a drug treatment for this illness will dramatically impact the prognosis for CCM patients as well as greatly reduce the lifetime healthcare cost. Genetic information will help to define the patient population for a trial and to determine whether a given drug treatment will be effective in all forms of the illness. Early trials will likely focus on cases with a defined genotype.

Recent publications report that as many as 95% of familial CCM patients will harbor a mutation in *CCM1*, *CCM2* or *CCM3*. Mutations are identified following a tiered approach of standard gene sequencing to be followed with deletion testing, where appropriate. For reference, please see Riant et. al. 2013 (PMID: 23595507) and Schroder et. al, 2013 (PMID: 23722637). A template letter of medical necessity for insurance providers is available at: www.angioma.org/documents/ccmLMN.docx. *Clinical diagnostic genetic testing can be ordered from a variety of for-profit companies including PreventionGenetics, GeneDX, Athena Diagnostics, and ARUP Laboratories.*

Thank you very much for your support and assistance as we strive to increase awareness of the importance of genetic testing for our patients and their families. Please feel free to call Dr. Amy Akers at 757-818-0403 with any questions. She can also be reached via email at amy.akers@angioma.org. Patients, families and health care providers are encouraged to review updated scientific information about this disease, on the Angioma Alliance website at www.angioma.org.

Sincerely yours, on behalf of Angioma Alliance,

Amy Akers, PhD
Chief Scientific Officer
Angioma Alliance

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