

117TH CONGRESS
1ST SESSION

S. 3390

To increase research, education, and treatment for cerebral cavernous malformations.

IN THE SENATE OF THE UNITED STATES

DECEMBER 14, 2021

Mr. LUJÁN (for himself and Mr. HEINRICH) introduced the following bill; which was read twice and referred to the Committee on Health, Education, Labor, and Pensions

A BILL

To increase research, education, and treatment for cerebral cavernous malformations.

1 *Be it enacted by the Senate and House of Representa-*
2 *tives of the United States of America in Congress assembled,*

3 **SECTION 1. SHORT TITLE.**

4 This Act may be cited as the “Cerebral Cavernous
5 Malformations Clinical Awareness, Research, and Edu-
6 cation Act of 2021” or the “CCM–CARE Act of 2021”.

7 **SEC. 2. FINDINGS.**

8 Congress finds as follows:

9 (1) Cerebral cavernous malformations (referred
10 to in this section as “CCM”), also known as cav-

1 ernous angioma, or cavernoma, is a devastating
2 blood vessel disease characterized by vascular lesions
3 that develop and grow within the brain and spinal
4 cord.

5 (2) Detection of CCM lesions is achieved
6 through costly and specialized medical imaging tech-
7 niques, often not accessible or convenient to patients
8 who need them.

9 (3) While CCM is a common type of vascular
10 anomaly, many individuals are not aware they have
11 the disease until the onset of serious clinical symp-
12 toms. CCM is often inherited unknowingly.

13 (4) CCM affects an estimated 600,000 people
14 in the United States.

15 (5) Individuals diagnosed with CCM may expe-
16 rience neurological deficits, seizure, stroke, or sud-
17 den death.

18 (6) Due to limited research, there is currently
19 no treatment for CCM other than brain and spinal
20 surgery, and only for certain patients.

21 (7) There is also a shortage of trained physi-
22 cians to provide skilled and timely diagnosis and ap-
23 propriate treatment for CCM.

24 (8) While the hereditary form of CCM may
25 occur among any ethnicity, the presence of a muta-

tion called the “common Hispanic mutation”, has passed through 14 or more generations of American descendants from the original Spanish settlers of the Southwest in the 1590s. New Mexico has the highest population density of CCM in the world; Texas, Arizona, and Colorado also have high rates of CCM due to the common Hispanic mutation.

(9) A second mutation (CCM2 Common Deletion) originating in the Southeastern United States before 1800 has increased rates of the illness in South Carolina, Georgia, Florida, Alabama, Mississippi, Louisiana, Texas, Oklahoma, Kentucky, Kansas, and northern California.

**SEC. 3. EXPANSION AND COORDINATION OF ACTIVITIES OF
NATIONAL INSTITUTES OF HEALTH WITH RE-
SPECT TO CEREBRAL CAVERNOUS MAL-
FORMATIONS RESEARCH.**

Part B of title IV of the Public Health Service Act (42 U.S.C. 284 et seq.) is amended by adding at the end the following:

**“SEC. 409K. CEREBRAL CAVERNOUS MALFORMATIONS RE-
SEARCH ACTIVITIES.**

“(a) EXPANSION AND COORDINATION OF ACTIVITIES.—The Director of NIH, in coordination with the directors of the National Institute of Neurological Disorders

1 and Stroke, the National Center for Advancing
 2 Translational Sciences, the National Heart, Lung, and
 3 Blood Institute, and other national research institutes, as
 4 appropriate, for the purpose of conducting research and
 5 related activities concerning cerebral cavernous malforma-
 6 tions (referred to in this section as ‘CCM’)—

7 “(1) shall strengthen and coordinate efforts of
 8 the National Institutes of Health; and

9 “(2) may award grants and cooperative agree-
 10 ments to public or nonprofit private entities (includ-
 11 ing State health departments, political subdivisions
 12 of States, universities, and other medical or edu-
 13 cational entities).

14 “(b) ACTIVITIES.—The research and related activi-
 15 ties described in subsection (a) shall include the following:

16 “(1) CLINICAL, TRANSLATIONAL, AND BASIC
 17 RESEARCH.—The Director of NIH shall conduct or
 18 support, through funding opportunity announce-
 19 ments, grants, or cooperative agreements, basic, clin-
 20 ical, and translational research on CCM, including
 21 research on—

22 “(A) the identification and development of
 23 affordable biomarkers that fulfill the require-
 24 ment of the Food and Drug Administration for
 25 biomarker qualification as proper measures of

1 CCM pathogenic biology, including diagnosis, or
2 response to clinical intervention;

3 “(B) pre-clinical trials of promising CCM
4 drug treatment candidates;

5 “(C) novel biomedical and pharmacological
6 interventions designed to target existing lesions
7 to reduce their size and clinical activity;

8 “(D) clinical research related to
9 repurposing currently approved drugs for appli-
10 cation for CCM treatment;

11 “(E) the gut-brain axis and the effects of
12 microbiome composition on clinical
13 symptomology;

14 “(F) the microbiome as a therapeutic tar-
15 get for CCM treatment;

16 “(G) research related to gene therapy as a
17 treatment for familial CCM;

18 “(H) research related to the mechanistic
19 overlap between CCM and other disorders, in-
20 cluding vascular disorders and cancer;

21 “(I) research related to improving and
22 measuring the quality of life for individuals
23 with CCM and their families;

24 “(J) contributions of genetic variation to
25 clinical presentation as targets for therapy;

1 “(K) clinical training programs aimed at
 2 increasing the number of scientists and clini-
 3 cians who are trained to treat patients and
 4 carry out the research described in this para-
 5 graph;

6 “(L) continued development and expansion
 7 of novel animal models for preclinical research
 8 relating to CCM;

9 “(M) proteomic, pharmacological, and cell
 10 biological analysis of CCM molecules;

11 “(N) biological mechanisms for lesion gen-
 12 esis, development, and maturation;

13 “(O) biological mechanisms for lesion
 14 bleeding and symptomology;

15 “(P) novel biomedical and pharmacological
 16 interventions designed to inhibit new lesion de-
 17 velopment, lesion growth, and lesion bleeding;
 18 and

19 “(Q) continued research related to under-
 20 standing better the natural history and clinical
 21 variation associated with CCM, particularly as
 22 it relates to the development of drug develop-
 23 ment tools and clinical outcome assessments.

24 “(2) FACILITATION OF RESEARCH RESOURCES;

25 CLINICAL TRIAL PREPAREDNESS.—

1 “(A) IN GENERAL.—The Director of NIH
2 shall award grants and contracts to public or
3 nonprofit private entities to fund all or part of
4 the cost of planning, establishing, and providing
5 basic operating support for a network of CCM
6 Clinical Research Centers, including Coordinating and Participating centers regarding re-
7 search on various forms of CCM.
8

9 “(B) CLINICAL AND RESEARCH COORDI-
10 NATING CENTERS.—

11 “(i) IN GENERAL.—The Director of
12 NIH shall build upon the network created
13 by the U01 Clinical Trial Readiness Re-
14 search Project to identify and support the
15 development of 2 geographically distributed
16 national clinical and research coordinating
17 centers with unique clinical expertise and
18 the potential for coordinating multisite
19 clinical drug trials with respect to CCM.

20 “(ii) DUTIES.—The coordinating cen-
21 ters identified under clause (i) shall pro-
22 vide a model for the participation centers
23 described in paragraph (3), facilitate med-
24 ical research to develop a cure for CCM,

1 and enhance the medical care of individ-
2 uals with CCM nationwide, including by—

3 “(I) maintaining an institutional
4 infrastructure capable of hosting clin-
5 ical trials and facilitating translational
6 research projects and collaborations
7 for clinical trials;

8 “(II) implementing the programs
9 dedicated to patient education, patient
10 outreach, and awareness developed by
11 the Cerebral Cavernous Malformations
12 Consortium under subsection
13 (c)(3)(B);

14 “(III) developing the capacity to
15 establish and maintain communication
16 with other major CCM research and
17 care institutions internationally for in-
18 formation sharing and coordination of
19 research activities;

20 “(IV) demonstrating clinical ex-
21 pertise in the management of CCM
22 and appointing a director and support
23 staff, including a trainee and patient
24 representative, for CCM research pro-
25 gramming;

“(V) treating a sufficient number of eligible patients for participation with particular focus on unique subpopulations, such as patients with the common Hispanic mutation, Ashkenazi Jewish mutation, CCM2 Common Deletion, or CCM3 gene mutation carriers; and

“(VI) maintaining a telehealth infrastructure to support and provide clinical consultation for remote and underserved communities.

“(3) PARTICIPATION CENTERS.—

“(A) IN GENERAL.—The Director of NIH shall build upon the network created by the U01 Clinical Trial Readiness Research Project to identify and support the development of approximately 6 to 10 clinical and research participation centers to facilitate medical research to develop a cure for CCM and enhance the medical care of individuals with CCM, in partnership with the coordinating centers under paragraph (2) and other national and international entities, as appropriate.

1 “(B) ELIGIBILITY.—To qualify for selec-
2 tion as a participation center under subpara-
3 graph (A), an entity shall—

4 “(i) at the time of selection—

5 “(I) be affiliated with an estab-
6 lished research network of the Na-
7 tional Institutes of Health; and

8 “(II) have the potential to par-
9 ticipate in a multisite clinical drug
10 trial with respect to CCM;

11 “(ii) demonstrate—

12 “(I) an institutional infrastruc-
13 ture capable of hosting a clinical trial
14 site and facilitating translational
15 projects and collaborations for clinical
16 trials;

17 “(II) the capacity to maintain
18 communication with other major CCM
19 research and care institutions inter-
20 nationally for information sharing and
21 coordination of research activities, es-
22 pecially through health information
23 technology; and

24 “(III) clinical expertise in CCM
25 management or complete the CCM

1 clinical training program under sub-
 2 section (c)(4); and

3 “(iii) have a sufficient number of eli-
 4 gible patients with CCM.

5 “(C) DURATION OF SUPPORT.—The Direc-
 6 tor of NIH may provide support for participa-
 7 tion centers under this section for a period not
 8 to exceed 5 years. The Director of NIH may ex-
 9 tend the period of support for a center for one
 10 or more additional periods, not to exceed an ad-
 11 ditional 5 years, if the operations of such center
 12 have been reviewed by an appropriate technical
 13 and scientific peer review group established by
 14 the Director of NIH and if such group has rec-
 15 ommended to the Director that such period
 16 should be extended.

17 “(c) CEREBRAL CAVERNOUS MALFORMATIONS CON-
 18 SORTIUM.—

19 “(1) IN GENERAL.—The Director of NIH shall
 20 build upon the network created by the U01 Clinical
 21 Trial Readiness Research Project to convene a Cere-
 22 bral Cavernous Malformations Research Consortium
 23 (referred to in this section as the ‘consortium’).

24 “(2) MEMBERSHIP.—The consortium—

25 “(A) shall include representatives of—

1 “(i) the institutions that are part of
2 the U01 Trial Readiness Project of the
3 National Institutes of Health, or that are
4 part of other nationally recognized clinical
5 Centers of Excellence; and

6 “(ii) at least 1 national CCM patient
7 advocacy organization, which may be an
8 entity that receives a grant or contract
9 under subsection (b)(2)(A); and

10 “(B) may include representatives of the
11 National Institutes of Health or the Food and
12 Drug Administration, in an advisory or ex offi-
13 cio role.

14 “(3) RESPONSIBILITIES.—Through a con-
15 sensus-based decision-making model, the consortium
16 shall divide assignments and be responsible for—

17 “(A) developing and implementing training
18 programs for clinicians and scientists in accord-
19 ance with paragraph (4);

20 “(B) developing patient education, out-
21 reach, and awareness programs and materials,
22 which may be tailored for specific regional or
23 local needs including—

24 “(i) a regional multimedia public
25 awareness campaign;

1 “(ii) patient education materials for
 2 distribution by regional physician and sur-
 3 geon offices;

4 “(iii) an education program for ele-
 5 mentary and secondary school nurses to fa-
 6 cilitate early detection and diagnosis of
 7 CCM in areas in which there is a high den-
 8 sity of cases of CCM;

9 “(iv) regular regional patient and
 10 family-oriented educational conferences;
 11 and

12 “(v) nationally relevant electronic
 13 health teaching and communication tools
 14 and a network of professional capacity and
 15 patient and family support; and

16 “(C) preparing a biannual report to Con-
 17 gress, in accordance with paragraph (5).

18 “(4) TRAINING PROGRAM FOR CLINICIANS AND
 19 SCIENTISTS.—

20 “(A) IN GENERAL.—The consortium shall
 21 establish or expand a physician training pro-
 22 gram, including information and education on
 23 advances in the diagnosis and treatment of
 24 CCM, and training and continuing education
 25 through programs for scientists, physicians,

1 medical students, and other health professionals
2 and care coordinators who provide care for pa-
3 tients with CCM, telehealth, and research rel-
4 evant to CCM, for the purpose of supporting
5 the development of new centers through edu-
6 cational programming to gain the expertise
7 needed to become clinical and research centers
8 with the potential to participate in clinical drug
9 trials.

10 “(B) STIPENDS.—The Director of NIH
11 may provide stipends for health professionals
12 who are enrolled in the training programs de-
13 scribed in subparagraph (A).

14 “(C) ELIGIBILITY.—To be eligible to par-
15 ticipate in the training program, an individual
16 shall be affiliated with an entity that is in an
17 existing clinical research network of the Na-
18 tional Institutes of Health.

19 “(5) REPORT TO CONGRESS.—The consortium
20 shall biennially submit to the Committee on Health,
21 Education, Labor, and Pensions of the Senate and
22 the Committee on Energy and Commerce of the
23 House of Representatives a report that describes the
24 research, education, and other activities on CCM
25 conducted or supported through the Department of

1 Health and Human Services. Each such report shall
2 include—

3 “(A) a research plan;

4 “(B) provisions specifying the amounts ex-
5 pended by the Department of Health and
6 Human Services with respect to various forms
7 of CCM, including those affected by the com-
8 mon Hispanic Mutation, Ashkenazi Jewish mu-
9 tation, CCM2 Common Deletion, CCM3 gene
10 mutations, and other familial and sporadic
11 forms of cerebral cavernous malformation and
12 patients who identify as Black or African Amer-
13 ican; and

14 “(C) recommendations for particular
15 projects or types of projects that the national
16 research institutes or other entities in the field
17 of research should conduct on inherited or non-
18 inherited forms of CCM.

19 “(d) PRIORITIZE CCM FUNDING FOR BIOTECH.—
20 The Director of NIH, in coordination with the directors
21 of the National Institute of Neurological Disorders and
22 Stroke, the National Center for Advancing Translational
23 Sciences, the National Heart, Lung, and Blood Institute,
24 and other national research institutes, as appropriate,
25 shall prioritize the provision of grant funding for small

1 biotechnology entities that are working to develop treat-
 2 ments for CCM.”.

3 **SEC. 4. CENTERS FOR DISEASE CONTROL AND PREVEN-**
 4 **TION CEREBRAL CAVERNOUS MALFORMA-**
 5 **TIONS SURVEILLANCE AND RESEARCH PRO-**
 6 **GRAMS.**

7 Part B of title III of the Public Health Service Act
 8 (42 U.S.C. 243 et seq.) is amended by inserting after sec-
 9 tion 317U the following:

10 **“SEC. 317V. CEREBRAL CAVERNOUS MALFORMATIONS SUR-**
 11 **VEILLANCE AND RESEARCH PROGRAMS.**

12 “(a) IN GENERAL.—The Secretary, acting through
 13 the Director of the Centers for Disease Control and Pre-
 14 vention, may award grants in such sums as may be nec-
 15 essary and cooperative agreements to public or nonprofit
 16 private entities (including State health departments, polit-
 17 ical subdivisions of States, universities, and other medical
 18 or educational entities) for the collection, analysis, and re-
 19 porting of data on cerebral cavernous malformations (re-
 20 ferred to in this section as ‘CCM’).

21 “(b) NATIONAL CEREBRAL CAVERNOUS MALFORMA-
 22 TIONS EPIDEMIOLOGY PROGRAM.—The Secretary shall
 23 award grants and cooperative agreements, including tech-
 24 nical assistance, to public or nonprofit private entities
 25 for—

1 “(1) the collection, analysis, and reporting of
2 data on CCM; and

3 “(2) epidemiological activities, including encour-
4 aging consistency in ICD–10 coding, adoption of
5 ICD–11 coding, collecting, and analyzing informa-
6 tion on the number, incidence, correlates, and symp-
7 toms of cases and the clinical utility of specific prac-
8 tice patterns.

9 “(c) NATIONAL SURVEILLANCE PROGRAM.—The
10 Secretary shall—

11 “(1) provide for a national surveillance program
12 for the purpose of carrying out epidemiological ac-
13 tivities regarding CCM, including collecting and ana-
14 lyzing information on the number, incidence, cor-
15 relates, and symptoms of cases of CCM and the clin-
16 ical utility (including costs and benefits) of specific
17 practice patterns; and

18 “(2) wherever possible, ensure that the surveil-
19 lance program is coordinated with the data and sam-
20 ple collection activities of the National Institutes of
21 Health under section 409K.

22 “(d) TECHNICAL ASSISTANCE.—In making awards
23 under this section, the Secretary may provide direct tech-
24 nical assistance, including personnel support.

1 “(e) COORDINATION WITH CLINICAL CENTERS.—
 2 The Secretary shall ensure that epidemiological informa-
 3 tion is made available to clinical centers as supported by
 4 the Director of the National Institutes of Health under
 5 section 409K.

6 “(f) AUTHORIZATION OF APPROPRIATIONS.—There
 7 are authorized to be appropriated such sums as may be
 8 necessary to carry out this section.”.

9 **SEC. 5. FOOD AND DRUG ADMINISTRATION CEREBRAL CAV-**
 10 **ERNOUS MALFORMATIONS CLINICAL TRIAL**
 11 **PREPAREDNESS AND SUPPORT PROGRAM.**

12 (a) BIOMARKER QUALIFICATION PROGRAM.—The
 13 Secretary of Health and Human Services, acting through
 14 the Commissioner of Food and Drugs, shall coordinate
 15 with clinical centers, investigators, and advocates to sup-
 16 port the qualification of appropriate surrogate biomarkers
 17 for diagnosis and measuring pathology and treatment effi-
 18 cacy in an effort to expedite clinical trials for cerebral cav-
 19 ernous malformation.

20 (b) CLINICAL OUTCOME ASSESSMENT QUALIFICA-
 21 TION.—The Secretary of Health and Human Services, act-
 22 ing through the Commissioner of Food and Drugs, shall
 23 coordinate with clinical centers, investigators, and advo-
 24 cates to support the qualification of newly developed pa-
 25 tient reported outcome measures for quality of life as a

1 clinical outcome in an effort to hasten the pace of clinical
2 trials for cerebral cavernous malformation.

3 (c) INVESTIGATIONAL NEW DRUG APPLICATION.—
4 The Secretary of Health and Human Services, acting
5 through the Commissioner of Food and Drugs, shall co-
6 ordinate with clinical centers, investigators, and advocates
7 to support appropriate investigational new drug applica-
8 tions under section 505(i) of the Federal Food, Drug, and
9 Cosmetic Act (21 U.S.C. 355(i)) in an effort to hasten
10 the pace of clinical trials for cerebral cavernous malforma-
11 tion.

12 (d) ADAPTIVE TRIAL DESIGN AND EXPEDITED RE-
13 VIEW PATHWAYS.—The Secretary of Health and Human
14 Services, acting through the Commissioner of Food and
15 Drugs, shall coordinate with clinical centers, investigators,
16 and advocates to support appropriate adaptive trial de-
17 signs for rare disease research and expedited peer review
18 mechanisms for including orphan drug designation, fast
19 track, breakthrough therapy designation, and priority re-
20 view or accelerated review, where appropriate, in an effort
21 to hasten the pace of clinical trials for cerebral cavernous
22 malformation.

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