

118TH CONGRESS  
1ST SESSION

# S. 543

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

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IN THE SENATE OF THE UNITED STATES

FEBRUARY 28, 2023

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

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## 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 2023” or the “CCM–CARE Act of 2023”.

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, although fewer than 200,000  
15       are accurately diagnosed.

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

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

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

1           (8) While the hereditary form of CCM may  
2 occur among any ethnicity, the presence of a muta-  
3 tion called the “common Hispanic mutation”, has  
4 passed through 14 or more generations of American  
5 descendants from the original Spanish settlers of the  
6 Southwest in the 1590s. New Mexico has the highest  
7 population density of CCM in the world; Texas, Ari-  
8 zona, and Colorado also have high rates of CCM due  
9 to the common Hispanic mutation.

10           (9) A second mutation (CCM2 Common Dele-  
11 tion) originating in the Southeastern United States  
12 before 1800 has increased rates of the illness in  
13 South Carolina, Georgia, Florida, Alabama, Mis-  
14 sissippi, Louisiana, Texas, Oklahoma, Kentucky,  
15 Kansas, and northern California.

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

20           Part B of title IV of the Public Health Service Act  
21 (42 U.S.C. 284 et seq.) is amended by adding at the end  
22 the following:

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

3 “(a) **EXPANSION AND COORDINATION OF ACTIVI-**  
4 **TIES.**—The Director of NIH, in coordination with the di-  
5 rectors of the National Institute of Neurological Disorders  
6 and Stroke, the National Center for Advancing  
7 Translational Sciences, the National Heart, Lung, and  
8 Blood Institute, and other national research institutes, as  
9 appropriate, for the purpose of conducting research and  
10 related activities concerning cerebral cavernous malforma-  
11 tions (referred to in this section as ‘CCM’)—

12 “(1) shall strengthen and coordinate efforts of  
13 the National Institutes of Health; and

14 “(2) may award grants and cooperative agree-  
15 ments to public or nonprofit private entities (includ-  
16 ing State health departments, political subdivisions  
17 of States, universities, and other medical or edu-  
18 cational entities).

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

21 “(1) **CLINICAL, TRANSLATIONAL, AND BASIC**  
22 **RESEARCH.**—The Director of NIH shall conduct or  
23 support, through funding opportunity announce-  
24 ments, grants, or cooperative agreements, basic, clin-  
25 ical, and translational research on CCM, including  
26 research on—

1           “(A) the identification and development of  
2 affordable imaging, plasma, and urine biomark-  
3 ers that fulfill the requirement of the Food and  
4 Drug Administration for biomarker qualifica-  
5 tion as proper measures of CCM pathogenic bi-  
6 ology, including diagnosis, response to clinical  
7 intervention, or prediction of adverse clinical  
8 events;

9           “(B) pre-clinical trials of promising CCM  
10 drug treatment candidates;

11           “(C) novel biomedical and pharmacological  
12 interventions designed to target existing lesions  
13 to reduce their size and clinical activity;

14           “(D) clinical research related to  
15 repurposing currently approved drugs for appli-  
16 cation for CCM treatment;

17           “(E) development of new non-pharma-  
18 cological treatment approaches, such as focused  
19 ultrasound, and targeted treatment delivery  
20 technology;

21           “(F) the gut-brain axis and the effects of  
22 microbiome composition on clinical  
23 symptomology;

24           “(G) the microbiome as a therapeutic tar-  
25 get for CCM treatment;

1           “(H) research related to gene therapy as a  
2 treatment for familial CCM;

3           “(I) research related to RNA-based thera-  
4 pies;

5           “(J) research related to the mechanistic  
6 overlap between CCM and other disorders, in-  
7 cluding vascular disorders and cancer;

8           “(K) research related to improving and  
9 measuring the quality of life for individuals  
10 with CCM and their families;

11           “(L) contributions of genetic variation to  
12 clinical presentation as precision medicine tar-  
13 gets for therapy;

14           “(M) clinical training programs aimed at  
15 increasing the number of scientists and clini-  
16 cians who are trained to treat patients and  
17 carry out the research described in this para-  
18 graph;

19           “(N) proteomic, pharmacological, and cell  
20 biological analysis of CCM molecules;

21           “(O) biological mechanisms for lesion gen-  
22 esis, development, and maturation;

23           “(P) biological mechanisms for lesion  
24 bleeding and symptomology;

1           “(Q) novel biomedical and pharmacological  
2 interventions designed to inhibit new lesion de-  
3 velopment, lesion growth, and lesion bleeding;  
4 and

5           “(R) continued research related to under-  
6 standing better the natural history and clinical  
7 variation associated with CCM, particularly as  
8 it relates to the development of drug develop-  
9 ment tools and clinical outcome assessments.

10           “(2) FACILITATION OF RESEARCH RESOURCES;  
11 CLINICAL TRIAL PREPAREDNESS.—

12           “(A) IN GENERAL.—The Director of NIH  
13 shall award grants and contracts to public or  
14 nonprofit private entities to fund all or part of  
15 the cost of planning, establishing, and providing  
16 basic operating support for a network of CCM  
17 Clinical Research Centers, including Coordin-  
18 ating and Participating centers regarding re-  
19 search on various forms of CCM.

20           “(B) CLINICAL AND RESEARCH COORDI-  
21 NATING CENTERS.—

22           “(i) IN GENERAL.—The Director of  
23 NIH shall build upon the network created  
24 by the U01 Clinical Trial Readiness Re-  
25 search Project to identify and support the

1 development of 2 geographically distributed  
2 national clinical and research coordinating  
3 centers with unique clinical expertise and  
4 the potential for coordinating multisite  
5 clinical drug trials with respect to CCM,  
6 including serving as United States sites in  
7 international adaptive trials.

8 “(ii) DUTIES.—The coordinating cen-  
9 ters identified under clause (i) shall pro-  
10 vide a model for the participation centers  
11 described in paragraph (3), facilitate med-  
12 ical research to develop a cure for CCM,  
13 and enhance the medical care of individ-  
14 uals with CCM nationwide, including by—

15 “(I) maintaining an institutional  
16 infrastructure capable of hosting clin-  
17 ical trials, facilitating translational re-  
18 search projects, and domestic and  
19 international collaborations for clinical  
20 trials;

21 “(II) implementing the programs  
22 dedicated to patient education, patient  
23 outreach, and awareness developed by  
24 the Cerebral Cavernous Malformations



1 Consortium under subsection  
2 (c)(3)(B);

3 “(III) developing the capacity to  
4 establish and maintain communication  
5 with other major CCM research and  
6 care institutions internationally for in-  
7 formation sharing and coordination of  
8 research activities;

9 “(IV) demonstrating clinical ex-  
10 pertise in the management of CCM  
11 and appointing a director and support  
12 staff, including a trainee and patient  
13 representative, for CCM research pro-  
14 gramming;

15 “(V) treating a sufficient number  
16 of eligible patients for participation  
17 with particular focus on unique sub-  
18 populations, such as patients with the  
19 common Hispanic mutation, Ash-  
20 kenazi Jewish mutation, CCM2 Com-  
21 mon Deletion, CCM3 gene mutation  
22 carriers, or Black and under-  
23 resourced patients; and

24 “(VI) maintaining a telehealth  
25 infrastructure to support and provide

1 clinical consultation for remote and  
2 underserved communities.

3 “(3) PARTICIPATION CENTERS.—

4 “(A) IN GENERAL.—The Director of NIH  
5 shall build upon the network created by the  
6 U01 Clinical Trial Readiness Research Project  
7 to identify and support the development of ap-  
8 proximately 6 to 10 clinical and research par-  
9 ticipation centers to facilitate medical research  
10 to develop a cure for CCM and enhance the  
11 medical care of individuals with CCM, in part-  
12 nership with the coordinating centers under  
13 paragraph (2) and other national and inter-  
14 national entities, as appropriate.

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

18 “(i) at the time of selection—

19 “(I) be affiliated with an estab-  
20 lished research network of the Na-  
21 tional Institutes of Health; and

22 “(II) have the potential to par-  
23 ticipate in a multisite clinical drug  
24 trial with respect to CCM;

25 “(ii) demonstrate—

1           “(I) the capacity to maintain  
2           communication with other major CCM  
3           research and care institutions inter-  
4           nationally for information sharing and  
5           coordination of research activities, es-  
6           pecially through health information  
7           technology; and

8           “(II) clinical expertise in CCM  
9           management or complete the CCM  
10          clinical training program under sub-  
11          section (c)(4); and

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

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

1       “(c) CEREBRAL CAVERNOUS MALFORMATIONS CON-  
2 SORTIUM.—

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

8           “(2) MEMBERSHIP.—The consortium—

9           “(A) shall include representatives of—

10           “(i) the institutions that are part of  
11           the U01 Trial Readiness Project of the  
12           National Institutes of Health, or that are  
13           part of other nationally recognized clinical  
14           Centers of Excellence; and

15           “(ii) at least 1 national CCM patient  
16           advocacy organization, which may be an  
17           entity that receives a grant or contract  
18           under subsection (b)(2)(A); and

19           “(B) may include representatives of the  
20           National Institutes of Health or the Food and  
21           Drug Administration, in an advisory or ex offi-  
22           cio role.

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

1           “(A) developing and implementing training  
2 programs for clinicians and scientists in accord-  
3 ance with paragraph (4);

4           “(B) developing patient education, out-  
5 reach, and awareness programs and materials,  
6 which may be tailored for specific regional or  
7 local needs including—

8                   “(i) a regional multimedia public  
9 awareness campaign;

10                   “(ii) patient education materials for  
11 distribution by regional physician and sur-  
12 geon offices;

13                   “(iii) an education program for ele-  
14 mentary and secondary school nurses and  
15 community health workers to facilitate  
16 early detection and diagnosis of CCM in  
17 areas in which there is a high density of  
18 cases of CCM;

19                   “(iv) regular regional patient and  
20 family-oriented educational conferences;  
21 and

22                   “(v) nationally relevant electronic  
23 health teaching and communication tools  
24 and a network of professional capacity and  
25 patient and family support; and

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

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

5           “(A) IN GENERAL.—The consortium shall  
6           establish or expand a physician training pro-  
7           gram, including information and education on  
8           advances in the diagnosis and treatment of  
9           CCM, and training and continuing education  
10          through programs for scientists, physicians,  
11          medical students, and other health professionals  
12          and care coordinators who provide care for pa-  
13          tients with CCM, telehealth, and research rel-  
14          evant to CCM, for the purpose of supporting  
15          the development of new centers through edu-  
16          cational programming to gain the expertise  
17          needed to become clinical and research centers  
18          with the potential to participate in clinical drug  
19          trials.

20          “(B) STIPENDS.—The Director of NIH  
21          may provide stipends for health professionals  
22          who are enrolled in the training programs de-  
23          scribed in subparagraph (A).

24          “(5) REPORT TO CONGRESS.—The consortium  
25          shall biennially submit to the Committee on Health,

1 Education, Labor, and Pensions of the Senate and  
2 the Committee on Energy and Commerce of the  
3 House of Representatives a report that describes the  
4 research, education, and other activities on CCM  
5 conducted or supported through the Department of  
6 Health and Human Services. Each such report shall  
7 include—

8 “(A) a research plan;

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

19 “(C) recommendations for particular  
20 projects or types of projects that the national  
21 research institutes or other entities in the field  
22 of research should conduct on inherited or non-  
23 inherited forms of CCM based on patient-identi-  
24 fied priorities.

1       “(d) **PRIORITIZE CCM FUNDING FOR BIOTECH.**—  
 2 The Director of NIH, in coordination with the directors  
 3 of the National Institute of Neurological Disorders and  
 4 Stroke, the National Center for Advancing Translational  
 5 Sciences, the National Heart, Lung, and Blood Institute,  
 6 and other national research institutes, as appropriate,  
 7 shall prioritize the provision of grant funding for small  
 8 biotechnology entities that are working to develop treat-  
 9 ments for CCM.”.

10 **SEC. 4. CENTERS FOR DISEASE CONTROL AND PREVEN-**  
 11 **TION CEREBRAL CAVERNOUS MALFORMA-**  
 12 **TIONS SURVEILLANCE AND RESEARCH PRO-**  
 13 **GRAMS.**

14       Part B of title III of the Public Health Service Act  
 15 (42 U.S.C. 243 et seq.) is amended by inserting after sec-  
 16 tion 317U the following:

17 **“SEC. 317V. CEREBRAL CAVERNOUS MALFORMATIONS SUR-**  
 18 **VEILLANCE AND RESEARCH PROGRAMS.**

19       “(a) **IN GENERAL.**—The Secretary, acting through  
 20 the Director of the Centers for Disease Control and Pre-  
 21 vention, may award grants in such sums as may be nec-  
 22 essary and cooperative agreements to public or nonprofit  
 23 private entities (including State health departments, polit-  
 24 ical subdivisions of States, universities, and other medical  
 25 or educational entities) for the collection, analysis, and re-



1 porting of data on cerebral cavernous malformations (re-  
2 ferred to in this section as ‘CCM’).

3 “(b) NATIONAL CEREBRAL CAVERNOUS MALFORMA-  
4 TIONS EPIDEMIOLOGY PROGRAM.—The Secretary shall  
5 award grants and cooperative agreements, including tech-  
6 nical assistance, to public or nonprofit private entities  
7 for—

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

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

16 “(c) NATIONAL SURVEILLANCE PROGRAM.—The  
17 Secretary shall—

18 “(1) provide for a national surveillance program  
19 for the purpose of carrying out epidemiological ac-  
20 tivities regarding CCM, including collecting and ana-  
21 lyzing information on the number, incidence, cor-  
22 relates, and symptoms of cases of CCM and the clin-  
23 ical utility (including costs and benefits) of specific  
24 practice patterns; and



1 and treatment efficacy in an effort to expedite clinical  
2 trials for cerebral cavernous malformation.

3 (b) CLINICAL OUTCOME ASSESSMENT QUALIFICA-  
4 TION.—The Secretary of Health and Human Services, act-  
5 ing through the Commissioner of Food and Drugs, shall  
6 coordinate with clinical centers, investigators, and advo-  
7 cates to support the qualification of newly developed pa-  
8 tient reported outcome measures for quality of life as a  
9 clinical outcome in an effort to hasten the pace of clinical  
10 trials for cerebral cavernous malformation.

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

20 (d) ADAPTIVE TRIAL DESIGN AND EXPEDITED RE-  
21 VIEW PATHWAYS.—The Secretary of Health and Human  
22 Services, acting through the Commissioner of Food and  
23 Drugs, shall coordinate with clinical centers, investigators,  
24 and advocates to support domestic and international  
25 adaptive trial designs for rare disease research and expe-

1 dited peer review mechanisms for including orphan drug  
2 designation, fast track, breakthrough therapy designation,  
3 and priority review or accelerated review, where appro-  
4 priate, in an effort to hasten the pace of clinical trials for  
5 cerebral cavernous malformation.

○