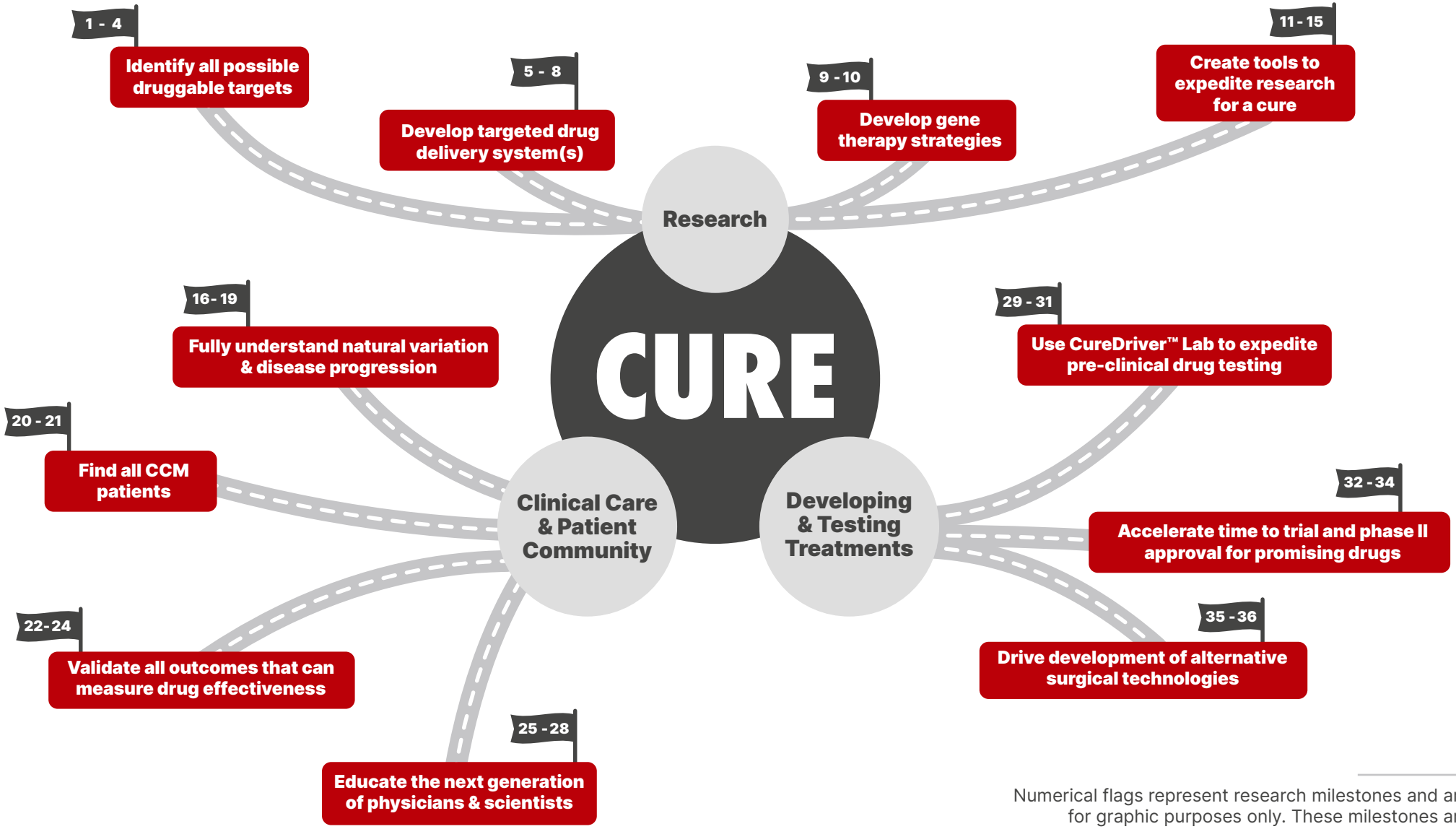
ROADMAP TO A CURE

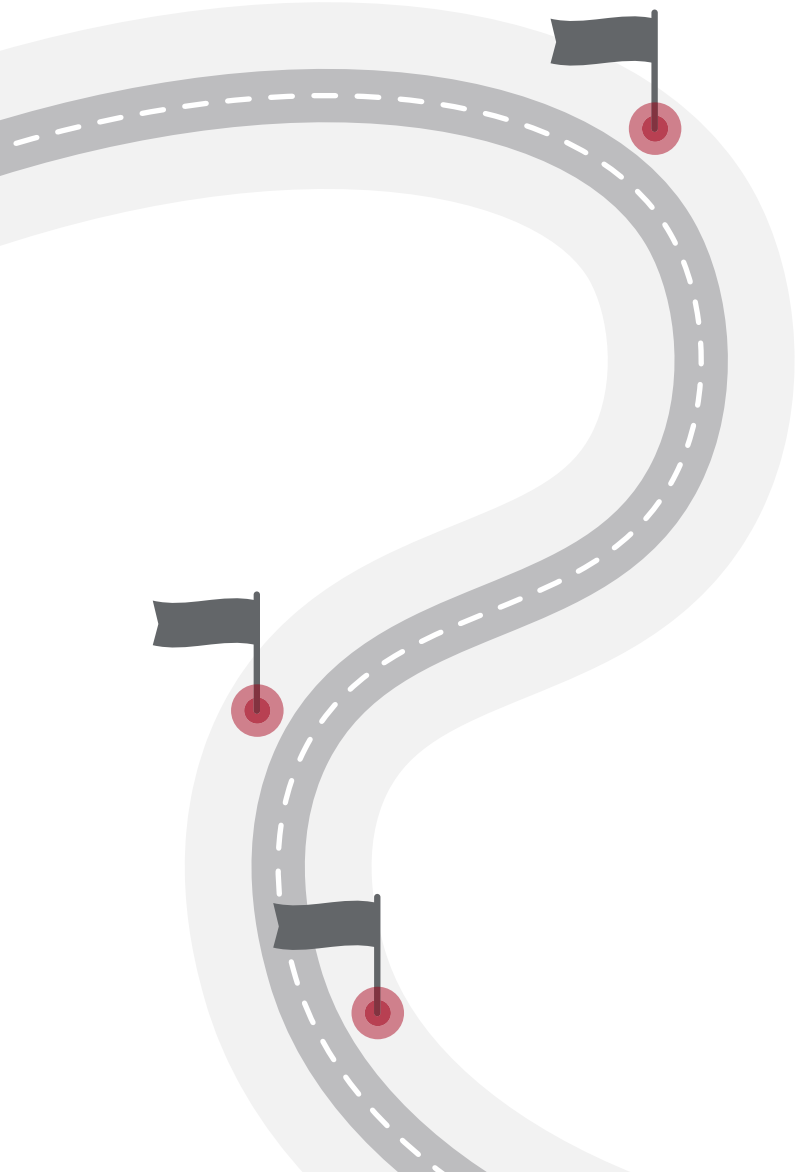
FOR **CAVERNOUS MALFORMATION** (CCM)

ALLIANCE TO CURE
CAVERNOUS MALFORMATION



Numerical flags represent research milestones and are for graphic purposes only. These milestones are non-competing and may be completed concurrently.

Research Milestones



1. Identify mechanisms involved in lesion growth, so we can target those pathways with treatments to stabilize existing lesions.

2. Understand the mechanisms involved in lesion development, so that we can develop drugs to prevent lesion genesis.
   - (Aims 1-2) Advocate and lobby for continued NIH support for academic single-disease cavernous malformation research.
   - Foster new research collaborations/consortiums.
   - Investigate new mechanisms for financial support.
   - Test promising compounds in the CureDriver™ Lab.

3. Understand the signaling mechanisms involved in seizures and neurological deficits, so that we can target those clinical outcomes in drug development.

4. Understand the mechanisms involved in clinical and non-radiologically overt hemorrhage, such that we can target all types of hemorrhage for therapeutic development.
   - (Aims 3-4) Require collaboration between clinical centers, likely development of new centers, and academic researchers.

5. Provide financial support for targeted delivery mechanism research in model organisms.
   - Continue support for nanoparticle research.
   - Identify Key Opinion Leaders (KOLs) in bioengineering who may be informative and interested in researching our targeted delivery needs. Further areas of research include, but are not limited to nanoparticles, colloidal, vesicular and polymeric vesicular systems.

6. Develop an investigational consortium for research of novel targeted drug delivery modalities.
   - Ideal consortiums will include clinical and academic leaders in CCM research, as well as KOLs from academia or industry with expertise in drug delivery systems.

7. Use the CureDriver™ Lab for comparative efficacy testing of targeted delivery mechanisms.

8. Provide intellectual, financial, and administrative support, as needed, to facilitate initiation and completion of clinical trial(s) to compare the effectiveness of targeted drug delivery mechanisms in humans.

9. Develop gene therapy strategies including gene replacement and/or gene editing of *CCM1, CCM2*, or *CCM3*.
   - Support academic research as is ongoing.
   - Facilitate additional funding & collaborations, particularly industry-related collaborators.
   - With targeted delivery and an excellent safety profile, explore the possibility of treating sporadic patients in addition to familial cases.

10. Recruit industry specialists for gene therapy for research and educational support.

11. Support our research teams and work with the FDA to validate multiple clinical outcome measures to expedite drug development and efficient clinical trials.

12. Maintain and expand the CCM Biobank & Clinical Repository for the purposes of providing biological samples and patient records to basic science research.

13. Maintain and expand the Cavernous Malformation Registry as a recruitment tool and clinical research resource.

14. Develop high-throughput screening tools for preclinical treatment testing and phenotyping, included but not limited to CCM gene deficient cell lines and in vivo MRI imaging.

15. Develop our CureDriver™ Lab, a multi-platform pre-clinical treatment testing laboratory for cavernous malformation, as the premier testing facility for all CCM-related treatment testing.

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Clinical Care & Patient Community Milestones

16. Identify and contact all CCM providers in the U.S. in order to provide education and resources for their patients.

17. Improve strategies for outreach in rural communities.

18. Increase educational opportunities and participation in our Free Genetic Testing Program.

19. Identify and describe any new Founder Mutation populations, or other unique subgroups.

20. Utilize our patient registry and natural history data to understand better special considerations for individual groups including, but not limited to, pediatric and sporadic patients.

21. Utilize our patient registry and natural history datasets to provide non-medical lifestyle recommendations for patient community members.

22. Validate predictive biomarkers including, but not limited to blood, urine, and microRNAs.

23. Validate Clinical Outcome Assessments following FDA regulations including, but not limited to MRI technologies and patient reported outcome measures.

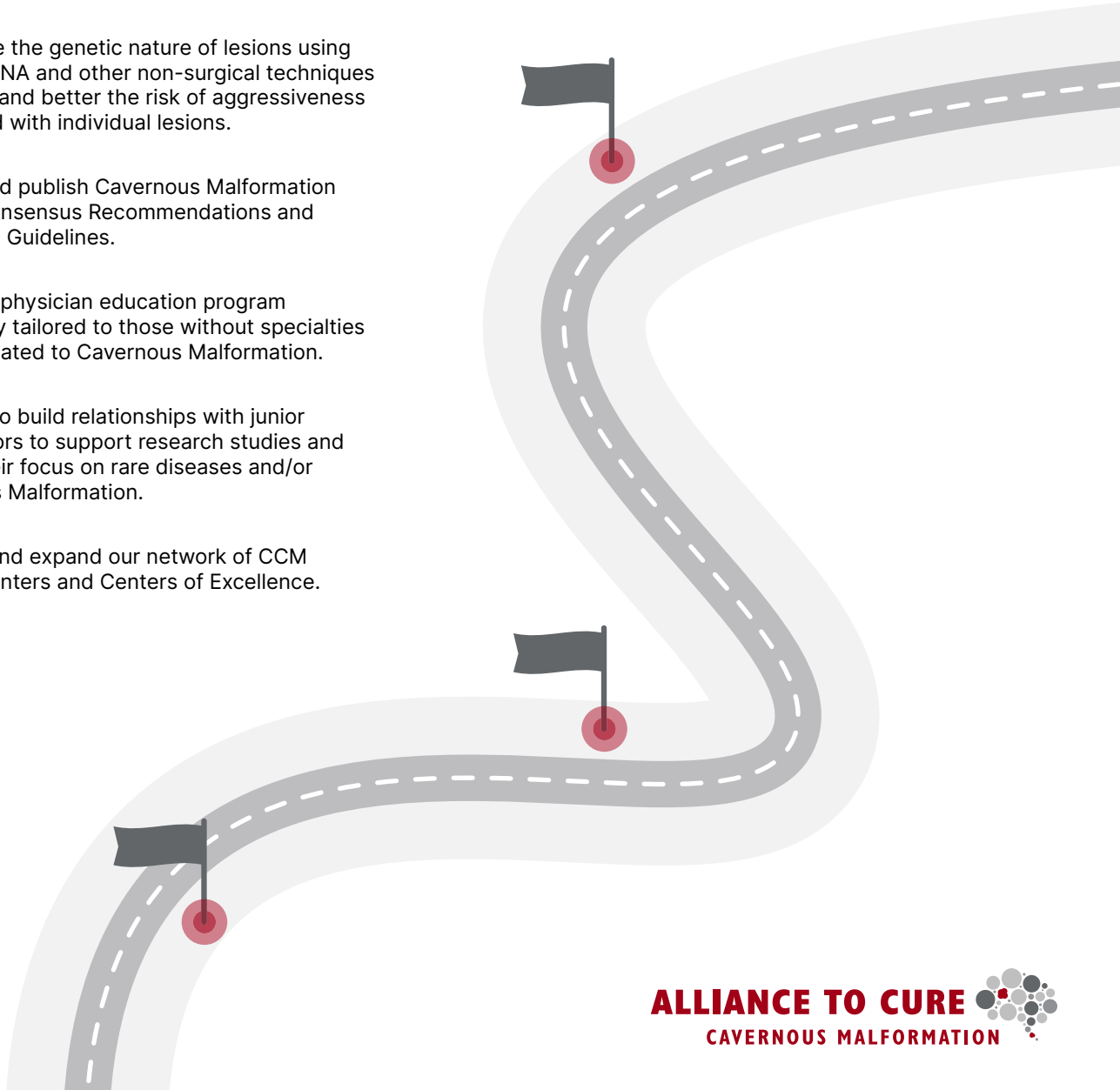
24. Investigate the genetic nature of lesions using cell-free DNA and other non-surgical techniques to understand better the risk of aggressiveness associated with individual lesions.

25. Update and publish Cavernous Malformation Clinical Consensus Recommendations and Diagnostic Guidelines.

26. Develop a physician education program specifically tailored to those without specialties directly related to Cavernous Malformation.

27. Continue to build relationships with junior investigators to support research studies and secure their focus on rare diseases and/or Cavernous Malformation.

28. Maintain and expand our network of CCM Clinical Centers and Centers of Excellence.



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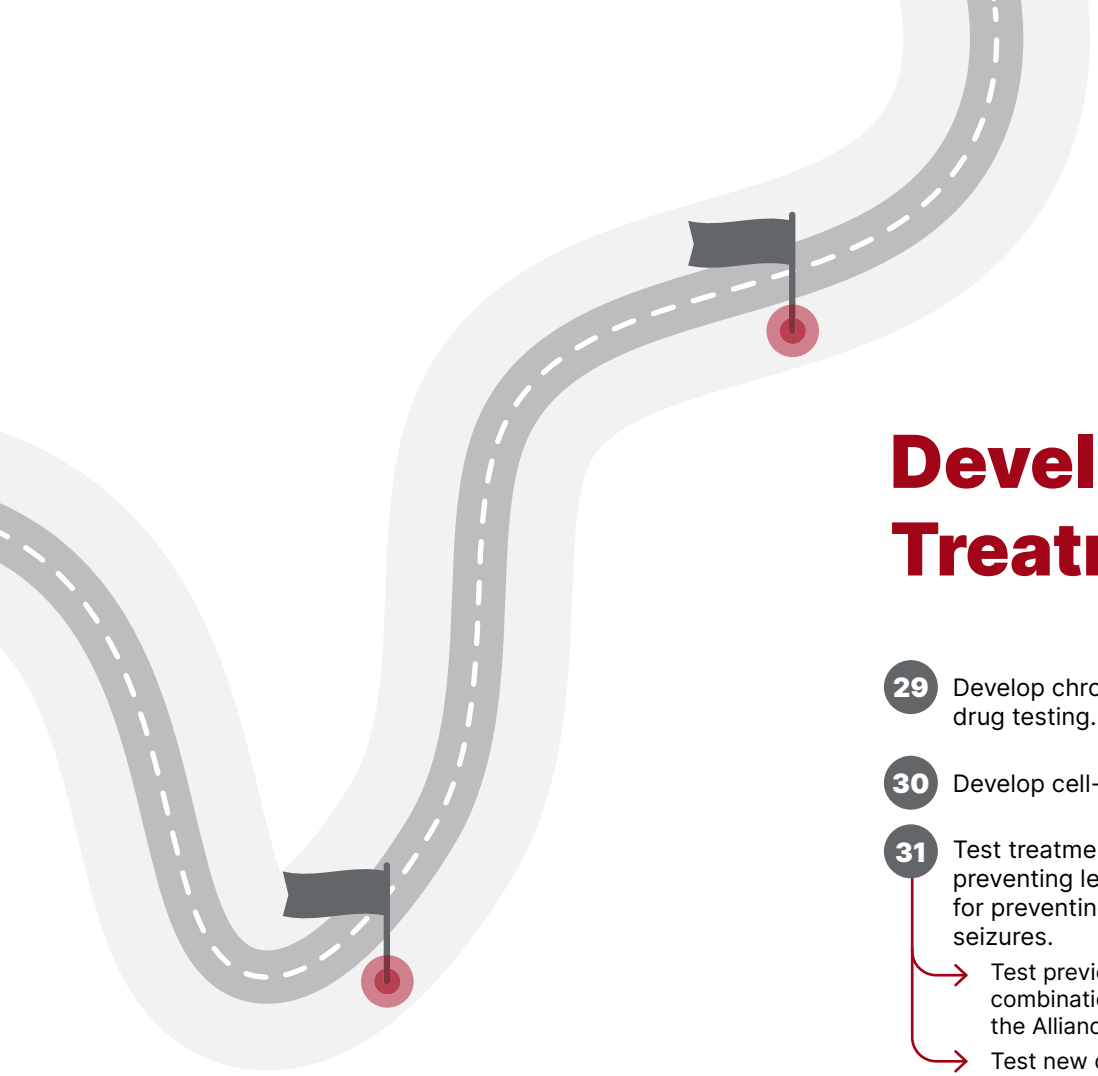

Developing & Testing Treatments Milestones

29 Develop chronic conditional murine models for drug testing.

30 Develop cell-based models for drug testing.

31 Test treatments for shrinking lesions, for preventing lesion formation and stabilization, for preventing hemorrhage and, for preventing seizures.

- Test previously approved compounds and/or combinations of compounds as determined by the Alliance's selection criteria.
- Test new chemical entities or repurposed as a contracted resource for academic or industry partners.

32 Facilitate platform trial design, implementation & rapid recruitment to compare the effects of previously tested drugs and/or new chemical entities.

33 Maintain, expand, and optimize our network of CCM Clinical Centers and Centers of Excellence.

34 Maintain and expand the Cavernous Malformation Registry as a tool for trial recruitment.

35 Facilitate study design & recruitment for nonsurgical interventions including but not limited to focused ultrasound treatment.

36 Provide logistical, administrative, and project management support to launch potential treatment studies and trials.

37 Provide logistical, administrative, and project management support to recruit and retain study participants and ensure successful trial completion.