The Cure Sickle Cell Initiative

It's time to rewrite the story of Sickle Cell.

W. Keith Hoots, MD and Traci Heath Mondoro, Ph.D.

August 10, 2020

Vision and Goals

CURE SICKLE CELL.

Vision

Accelerate the development of genetic therapies aimed at curing sickle cell disease.

Goals

- Create a collaborative, patient-focused research environment.
- Engage academic researchers, private sector researchers, advocates, patients, and caregivers to develop strategies for cures.
- Determine the safest, most effective, and most readily and widely adoptable genetic therapies.
- Move newly developed genetic therapies, including gene-editing approaches, into clinical trials within five to ten years.

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Initiative Philosophy

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Key Leaders

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Dr. Gary H. Gibbons

- Director, National Heart, Lung, and Blood Institute

Dr. Edward J. Benz, Jr.

- Executive Chair, Cure Sickle Cell Initiative
- CEO Emeritus, Dana-Farber Cancer Institute

Dr. Leslie Silberstein

- Scientific Director, Cure Sickle Cell Initiative
- Director, Joint Program in Transfusion Medicine (BWH)

Time for a Cure of the First 'Molecular' Disorder

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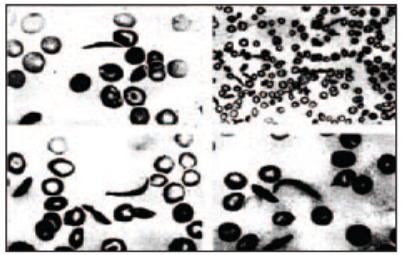
1910
Chicago physician James B. Herrick first publishes a description of sickled cells in a blood sample from 20-year-old dental student Walter Clement Noel from Grenada. Term "sickle cell anemia" coined based on paper.



Sickled cells from 1910 Herrick paper

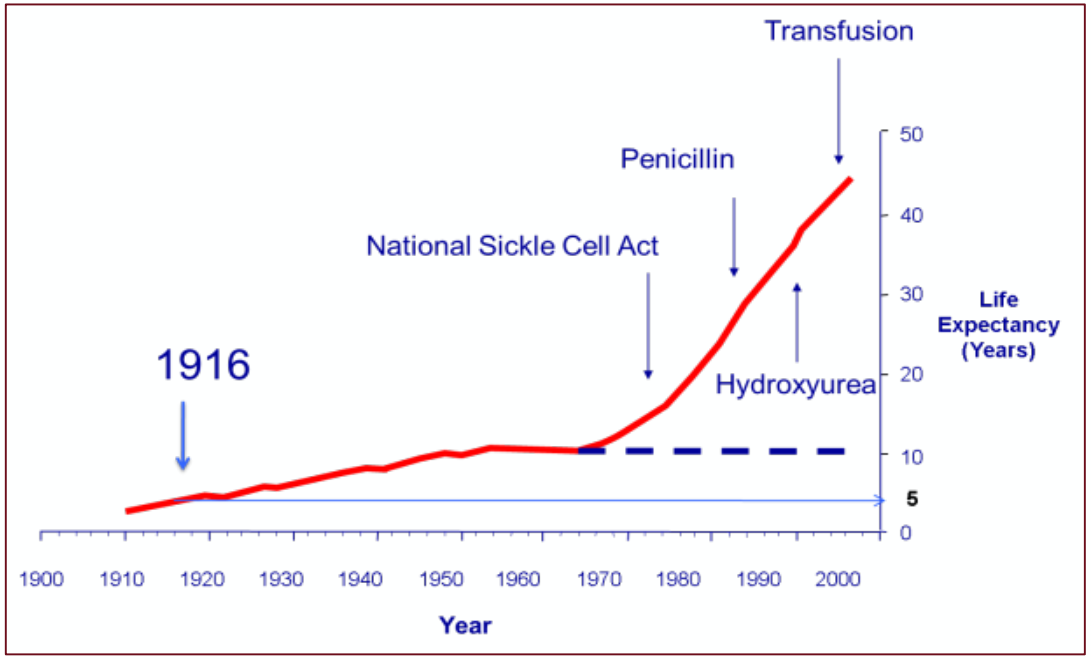
1949
Dr. Linus Pauling and others reveal that sickle cell disease due to abnormal hemoglobin protein molecule. Term "molecular disease" coined.

Dr. Linus Pauling

1953
Diagnostic tool developed to identify sickle cell disease and other conditions due to defective hemoglobin.

1954
Sickle cell trait found to protect against malaria. Finding explains why the prevalence of the sickle gene in Africa corresponds with regions where malaria is a major cause of death.

A Legacy of Research Excellence: Sickle Cell Disease Life Expectancy Rises



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Genetic Therapies for Sickle Cell Disease

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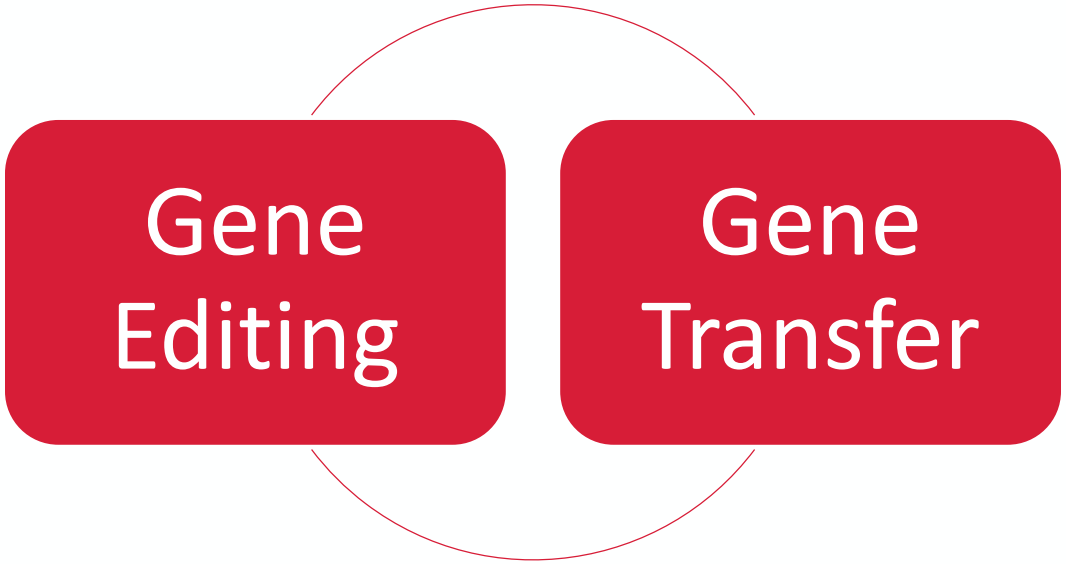
The Cure Sickle Cell Initiative aims to develop cures for all people living with sickle cell disease.

Current efforts are exploring:



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Optimizing Gene Editing/Genetic Therapies for SCD

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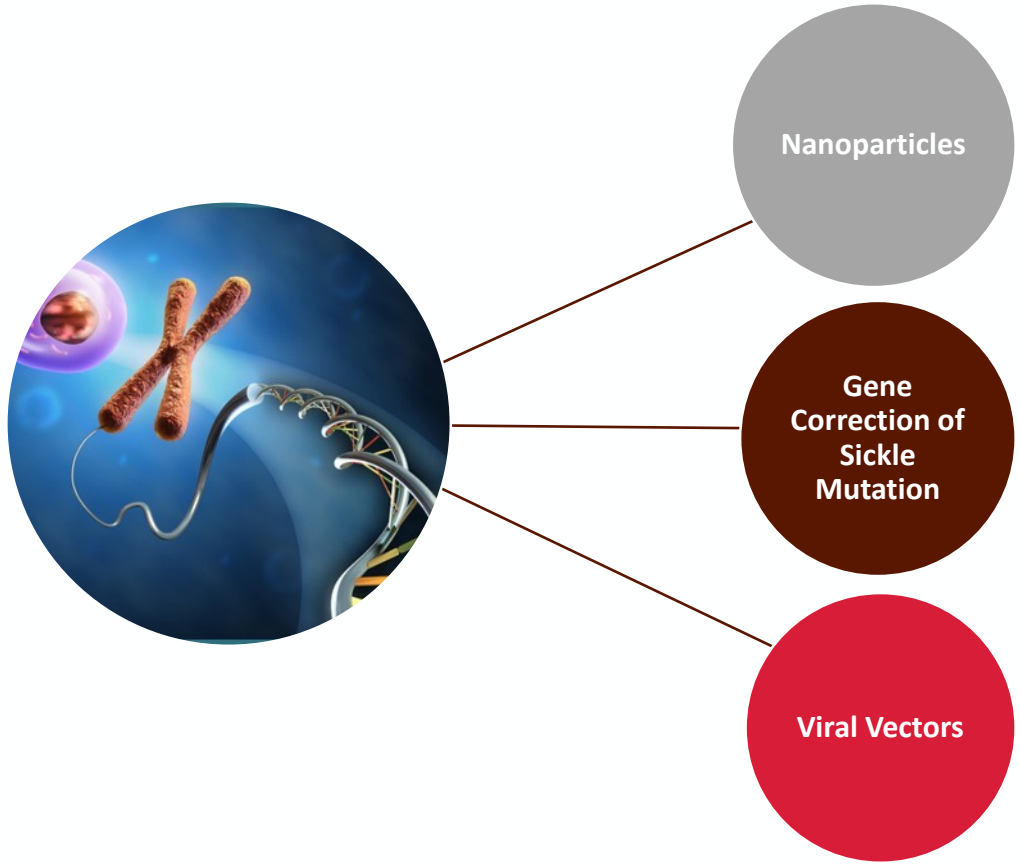
Curative Genetic Therapy Strategies



In vivo correction of β-Globin gene in mice with normalized Hb levels using nanoparticles

Targeting hematopoietic cells for gene editing using a gold nanoparticle formulation

Efficient gene correction of β–Globin gene in blood and marrow cells of patients with SCD

Lentiviral transfer of modified β-Globin gene showed remission of SCD symptoms in patient

Ricciardi et al., Nat Commun, 2018; Shahbazi Nat Mat, 2019; Park et al. Nucleic Acids Res, 2019; Ribeil et al., NEJM, 2017

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Gene Therapy Summary

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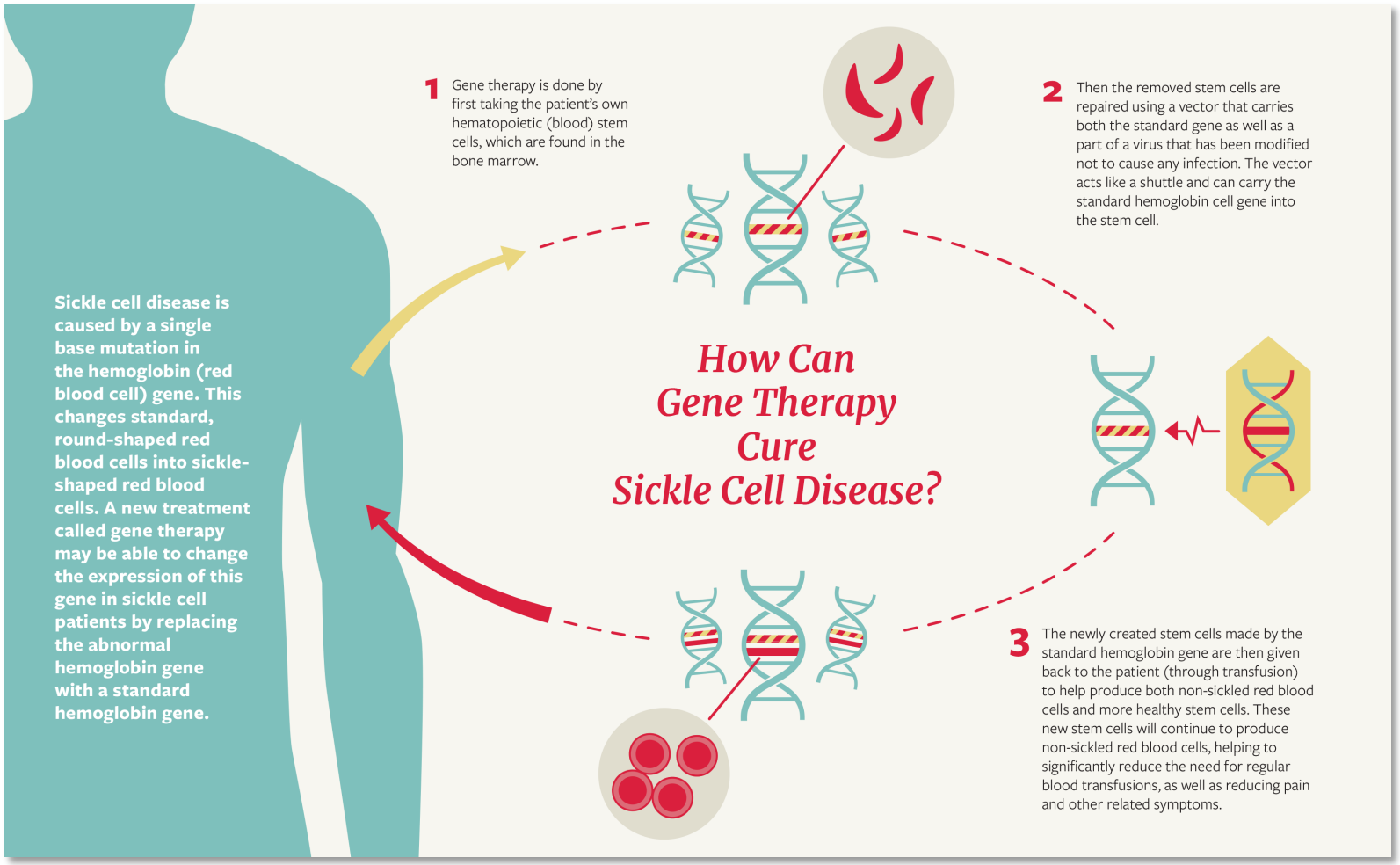

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Building a Comprehensive Approach to SCD

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- **Filling gaps** that cannot be covered by traditional funding strategies.
- **Funding research** within academia and the private sector to identify the most promising genetic therapies.
  - *NHLBI will continue to fund meritorious investigator-initiated applications focused on SCD.*
- **Partnering** with Federal agencies, academic institutions, pharmaceutical companies, professional societies, community organizations, patient representatives, and foundations.
- **Engaging communities** to inform patients, providers, and stakeholders about our work, ensuring trust and collaboration, while also educating patients and caretakers to consider participating in clinical trials.

Early Stakeholder Meeting Takeaways/Priorities

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- Conduct ***a clinical and economic impact analysis*** to evaluate whether a genetic curative strategy will lead to long-term health and clinical benefits and cost savings when compared to the lifetime cost of managing SCD.
- ***Involve patients and providers*** in advisory roles for study designs.
- Develop ***patient-centric/meaningful clinical trial endpoints*** for SCD genetic therapy trials; develop common data elements to be collected.
- Establish a ***national data resource*** for SCD gene therapy trials.

Select Collaborators

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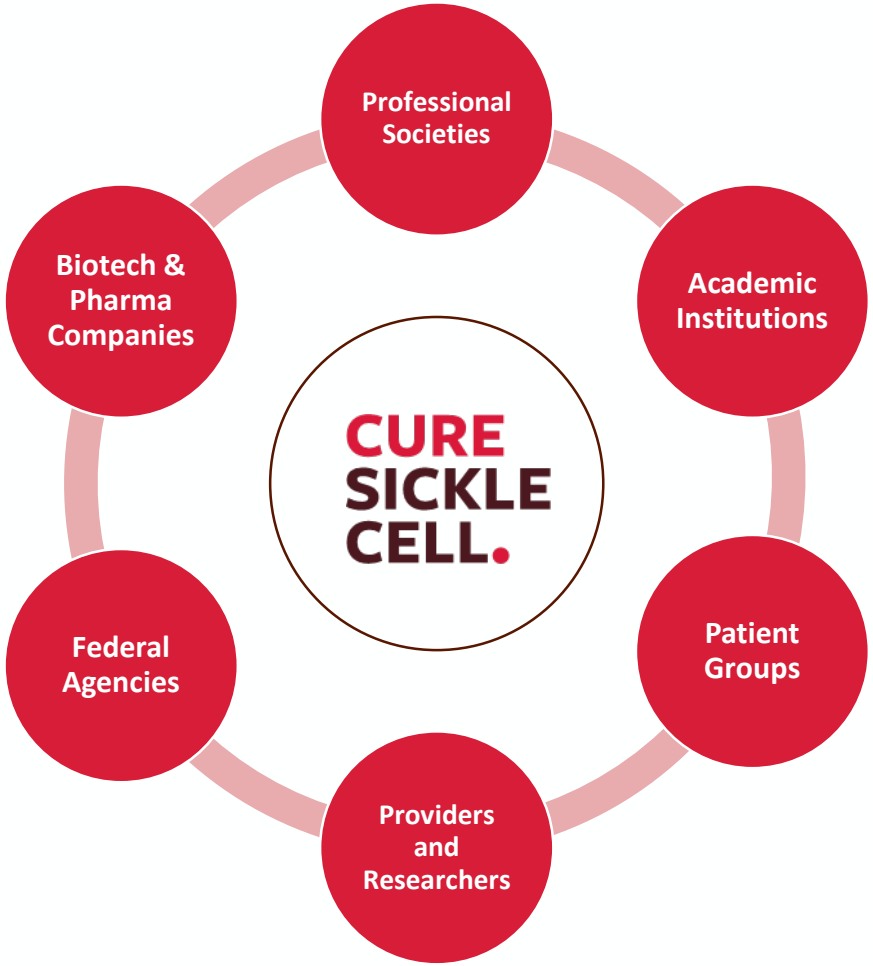

Emmes

SCDIC Sickle Cell Disease Implementation Consortium

PACT Production Assistance for Cellular Therapies National Heart Lung and Blood Program

CMS CENTERS FOR MEDICARE & MEDICAID SERVICES

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

OMH U.S. Department of Health and Human Services Office of Minority Health

CIBMTR® CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

FDA

CIRM CALIFORNIA'S STEM CELL AGENCY

NIST National Institute of Standards and Technology U.S. Department of Commerce

CDC

U.S. Department of Health and Human Services HRSA Health Resources and Services Administration

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Leveraging Key Partnerships with Federal Agencies

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The Initiative seeks to unite stakeholders from throughout the Federal government to work toward a shared vision of curing sickle cell disease.

Leveraging existing resources and relationships will allow for more efficient and effective cure identification, approval, and distribution.

Top Priorities (July-December 2020)

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1. **Engagement with Patients, Providers, and Community Organizations** – Identify and address obstacles to involvement and participation in design and performance of clinical trials. Ensure focus on quality of life and mental health outcomes.

2. **Scientific Outreach** – Engage and support broad investigator community in basic and pre-clinical translational research.

3. **Clinical Trials** - Support and/or develop assets needed to accelerate progress of clinical trials including biological resources, assays, manufacturing, and regulatory assistance.

4. **Collaborative Interface -** Establish and extend collaborative interfaces with Federal partners, ASH, CIRM, Gates and others.

5. **Data Resources** - Develop data resources focused on facilitating the application of genetic therapies in clinical practice.

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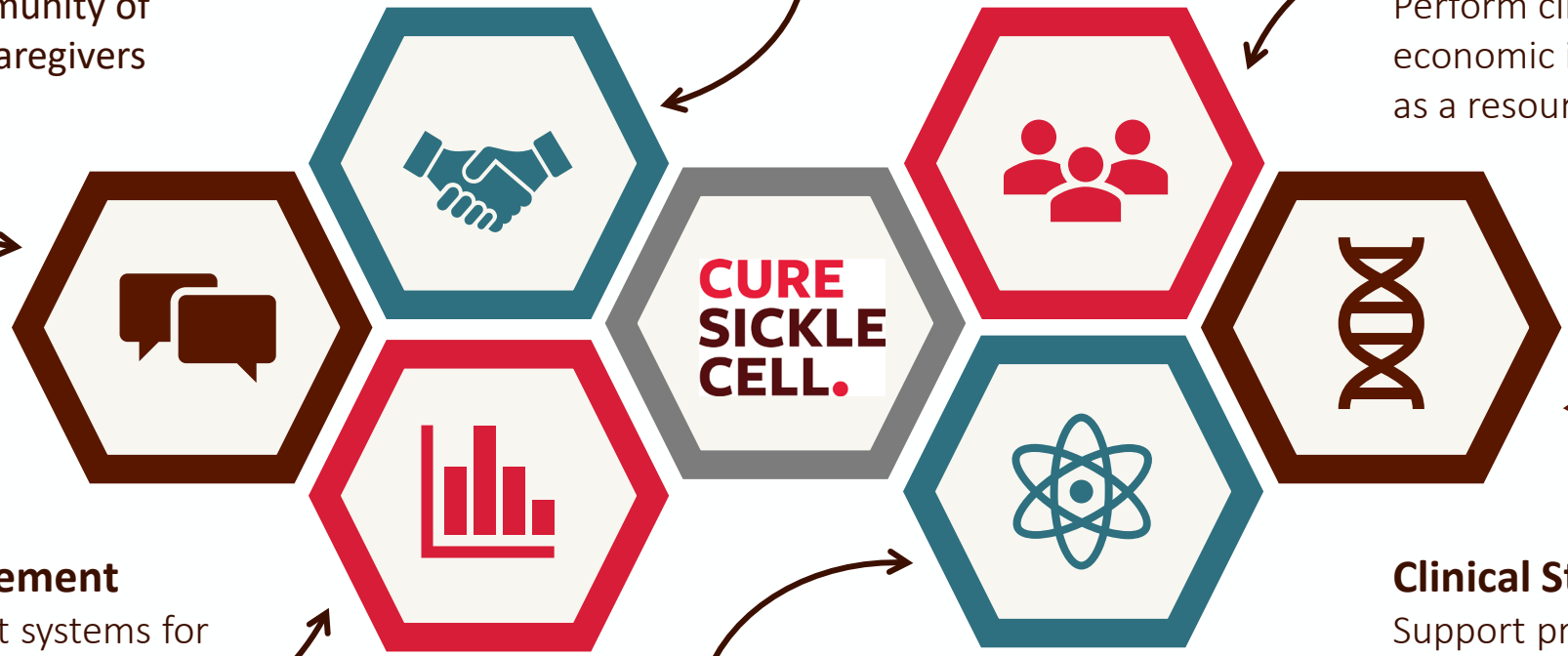
Ongoing Initiative Activities

Public-Private Partnership
Leverage networks to accelerate cures

Patient Engagement
Establish community of patients and caregivers

Patient Outcomes
Perform clinical and economic impact analysis as a resource



Data Management
Develop robust systems for patients and researchers

Biomanufacturing
Reagent manufacturing, biospecimen, regulatory resources for researchers

Clinical Strategies
Support promising research; develop meaningful endpoints for genetic therapy trials

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Committee and Subcommittee Activities

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COMMITTEE/SUBCOMMITTEE	PRIMARY ACTIVITIES
Executive Committee (EC)	Formulates and implements all policy decisions related to the conduct of the Initiative. Determines if the Initiative is meeting the needs of the sickle cell disease (SCD) community. This includes an assessment of the Initiative's contribution to and in the SCD community, the types of projects accepted by the Initiative, and progress in providing cell and gene products for clinical trials.
Steering Committee (SC)	Guides the implementation of all policy decisions related to the conduct of the Initiative. The SC receives regular reports on the activities of the subcommittees and executes the board strategies developed by the EC. The SC has the authority to form and disband subcommittees, as there is need, throughout the lifetime of the Initiative.
Communication, Outreach and Patient Engagement (COPE) SubCommittee	Provides oversight and strategic direction to guide the development, approval, and implementation of communications and engagement activities for the Cure Sickle Cell Initiative.

Scientific Subcommittee Activities

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COMMITTEE/SUBCOMMITTEE	PRIMARY ACTIVITIES
Assay Development (AD) Subcommittee	Surveys the problems associated with the current assays being used clinically to identify cell/gene therapy efficacy to identify important assays to pursue/develop. Further identify projects/investigators that could be recommended to NHLBI for additional support to move their work forward.
Gene Editing and Gene Therapy (GE/GT) SubCommittee	Identifies barriers from bench to more practical areas, which can include lack of access to appropriate reagents, or technologies, or even more practical, standardized approaches, which will further the field of gene modification. Helps build a consensus regarding which projects would be most beneficial for NHLBI to help facilitate progress.
Clinical Trial Design (CTD) SubCommittee	Identifies barriers to the design of clinical trials, assists with identifying appropriate endpoints and common data elements, discusses long term follow up strategies, considers immunology/fertility, and encourages patient engagement.
Apheresis for SCD Working Group	Understanding and improving access to novel therapies as they relate to stem cell collections, red cell exchange, red cell transfusion, vascular access, iron overload and apheresis instruments.

Special Interest Groups

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CONSORTIUMS	PRIMARY ACTIVITIES
Clinical and Economic Impact Analysis	Performs a landscape analysis to inform simulation models for clinical care of individuals with SCD. Create robust models to estimate the costs of care and impact of treatments. Disseminates study results.
Data Consortium	Identifies, documents, collects, and where feasible, harmonizes SCD datasets (e.g., clinical study phenotype and genotype data) to support secondary analyses. Establishes or links with registries of SCD patients and collects/integrates a core set of data to support future clinical studies.

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CEIA Consortium: Projected Activities

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The CEIA Consortium has defined *four primary phases* to perform the proposed study.

Phase 1	Landscape Analysis and Assessment of MarketScan Database
Phase 2	Analysis of Public -CMS MAX- and Private Payer Databases
Phase 3	Model Coding and Development
Phase 4	Results Generation and Dissemination of Study Outcomes

Consortium Goals: Determine **burden of disease** and **develop simulation models** that assess the clinical and economic impact of care and treatment for SCD from both the payer's and societal perspective.

Two separate publicly available simulation models will be developed and made publicly available.

Early publishable results available within 6-9 months. Full study to be completed in three years.

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Advising and Guiding Initiative Efforts

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Key advisors to the Initiative will include:

- **Community Input Panel**—patient advocates, patients, and parents of children with sickle cell disease.
- **External Scientific Panel**—physicians and scientists who are not funded by the Initiative or associated with any Subcommittee.

Multiple Approaches to Benefit All

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The Cure Sickle Cell Initiative will:

- Support different scientific strategies so there are multiple options depending on the presentation of the disease.
- Assemble a large body of preclinical and clinical data on different approaches (or variations of few approaches).
- Focus efforts on addressing and proving safety for pediatric populations, so young children can be cured before any irreversible organ damage occurs.

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Moving Therapies Forward

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The Cure Sickle Cell Initiative is currently exploring:

- Safety and risks
- Potential off-target effects
- Technology hurdles and bottlenecks
- Best practices and methods to:
  - **Develop assays to ensure that therapies work**
  - **Create standard operating procedures to isolate and modify cells**
  - **Produce common data elements**
  - **Design patient-centric clinical trials with meaningful endpoints**
  - **Assess the clinical and economic impact of genetic therapies on patients**

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What We Are Funding

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- Manufacturing studies designed to test new emerging therapies in the laboratory to evaluate their potential for safety and efficacy prior to the start of a clinical trial.
- Development of non-genotoxic conditioning regimens.
- Diagnostic tools (such as an MRI scale, for example, to confirm that there haven't been changes in a child's brain, or risk of stroke after a curative therapy).
- A prospective study to collect data on the long term clinical and meaningful patient reported outcomes in people who have undergone curative allogeneic transplants, curative genetic therapies.
- A national cell bank resource that will provide investigators access to critical biosamples needed for testing of new gene editing approaches.
- Advancement of robust and reliable laboratory assays to be used for testing changes to red blood cells before and after curative therapies for sickle cell disease.

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Research Opportunity Announcements

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Current Research Opportunity Announcements (ROAs) include:

OTA-19-005:

Preclinical and Clinical Studies for Curative Therapies for Sickle Cell Disease

The NHLBI is soliciting applications for preclinical and clinical projects focused on curative strategies for sickle cell disease in the areas of gene therapy (replacement) and gene editing. Proposed projects may also be focused on developing or refining activities that improve the safety or efficacy of the clinical protocol for gene therapy or gene edited autologous hematopoietic transplantation (e.g., improved bone marrow conditioning regimens, better stem cell mobilization and harvesting).

For more information, visit www.curesickle.org.

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Regulatory Assistance

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The Cure Sickle Cell Initiative collaborates with the ***Production Assistance for Cellular Therapies (PACT)*** program, an NIH-wide resource, to provide regulatory assistance to investigators who may require support with the following services:

- **Guidance for pre-IND INTERACT discussions with FDA**
- **INTERACT meeting package preparation**
- **Guidance for pre-IND discussions with FDA**
- **Pre-IND meeting package preparation**
- **Pre-clinical study design**
- **Chemistry, Manufacturing and Controls (CMC) development**
- **Initial Investigational New Drug (IND) preparation**

For more information, visit www.curesickle.org.

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Engaging the Patient Community

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People impacted by sickle cell disease have built the foundation of this effort and will continue to be involved in ongoing efforts to identify curative genetic therapies. They have/will:

- **Participate in focus groups and advisory groups (including young adults).**
- **Inform the work of the Subcommittees.**
- **Help to identify specific ways to seize scientific opportunities.**
- **Guide the development of materials for the patient community.**
- **Share insight on the development of clinical trials.**
- **Provide guidance on barriers to clinical trial participation to support education and recruitment.**

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Focus Group/Community Engagement Sessions

Since December 2017 we have conducted Community Engagement Sessions to hear directly from people living with SCD and those providing care and support.

- Conducted 7 site visits: 27 provider interviews, 19 patient interviews, and 2 group interviews throughout the U.S.
- Objectives:
  - **Identify barriers to treatment and care**
  - **Engage with the community**
  - **Build relationships**
  - **Better understand views on clinical trial participation**

Insights from the SCD Patient Community

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- Developing curative strategies is more than completing regulatory requirements.
- The patient community must be involved early in the process of developing therapeutic strategies.
- Clinical trials have the best chance of succeeding if the endpoints are ones that will be accepted by patients, as well as the FDA.
- Minimizing disruption of daily life for the patient and the patient's family should be a high priority during study design. Patient outreach should begin during protocol development.
- A dissemination plan of the results to the trial participants would minimize feelings of abandonment in the post-trial period.

How Patients Feel About New Therapies

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- Investigators from the NIH's National Human Genome Research Institute (NHGRI) published a survey in 2018 on **patient attitudes and beliefs toward genome editing.**
- The responses from the participants confirm that **the patient community is skeptical regarding new curative strategies** based on past disparities in access to medical care and in societal treatment.
- Conclusion:
  - **"The advent of genome editing has renewed hope for the SCD community, but caution tempers this optimism."**
- The intent moving forward is to maintain and invigorate this optimism with evidence of **listening** and **acting** on the promising science.

Source: Persaud A, et al. A CRISPR focus on attitudes and beliefs toward somatic genome editing from stakeholders within the sickle cell disease community. Genet Med. 2019; 21(8):1726-1734

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Questions?

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