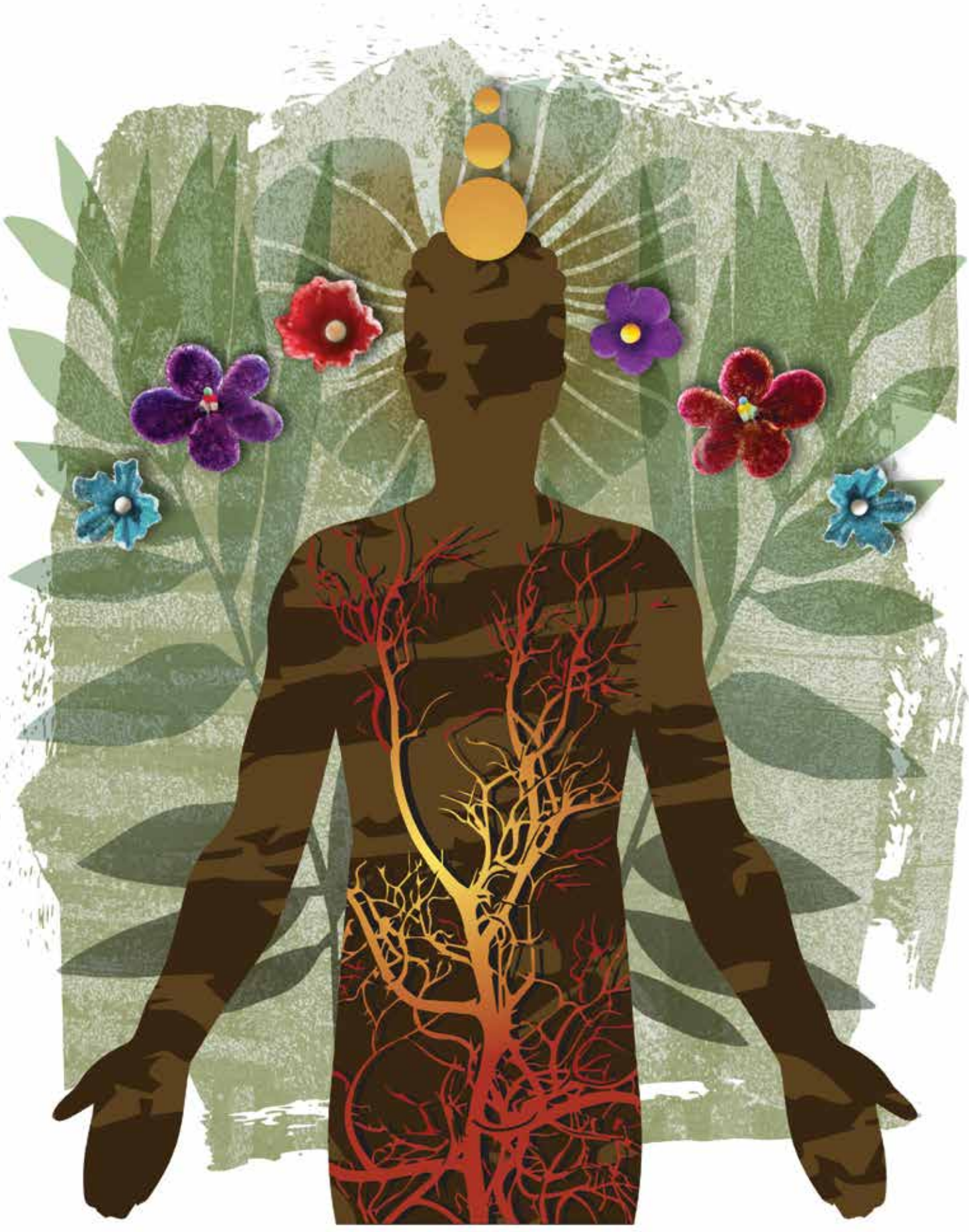

# *New Wave of Potentially Curative Treatment Offers Hope for Sickle Cell Disease:*

## *How Can We Eliminate Hurdles to Build on the Promise?*

CRAWFORD STRUNK, MD
Vice Chief Medical Officer, Sickle Cell Disease Association of America and Associate Medical Staff, Cleveland Clinic Foundation

In December 2023, more than 100,000 people in the U.S. affected by sickle cell disease received what was poised to be life-changing news: The first potentially curative gene therapies were officially approved by the U.S. Food and Drug Administration for the treatment of sickle cell disease. The sigh of relief at this new long-term treatment option was followed by a sense of widespread apprehension. With price tags in the millions, those who needed it most wondered how they could afford it. Health care systems looking to implement these therapies were entering uncharted territory. There was a new, incredible tool at our fingertips. The question was: How do we use it?

Gene therapy entered an already complicated treatment space. Since sickle cell disease was first described in medical literature in 1910, it has been a challenge to procure funding for research and development, overcome barriers to access and properly educate health care teams to provide consistent quality care. Understanding the difficulties faced by new advances like gene therapy — and discovering the solutions to those problems — starts by looking at the past.

### SICKLE CELL DISEASE: A (SOMETIMES PAINFUL) HISTORY

Sickle cell disease is a rare, inherited blood disorder that disproportionately affects the Black community, but occurs in all ethnicities. It causes chronic, often excruciating, pain, along with complications in every organ system from head to toe. The average life expectancy for someone with sickle cell disease is 20 years shorter than that of the general population; however, with current therapy, more than 98% of people living with the condition reach adulthood.[1]

Even though it is the most common genetic disorder worldwide,[2] in the United States, it has historically received less attention than other rare diseases. In fact, a nationwide approach to improving care and treatment was not put into place until Congress passed the National Sickle Cell Disease Control Act of 1972. This act formed the National Sickle Cell Disease Program of the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health and called for the establishment of federally funded comprehensive sickle cell centers.[3] This important bill created the necessary foundation to which we owe a great deal of

today's progress.

The first breakthrough in identification and treatment followed shortly after. In 1975, New York was the first state to mandate newborn screening for sickle cell disease.[4] This was a crucial step forward, as identification in infants allows hematologists to start education and treatment with penicillin prophylaxis early in life. By 2006, newborn screening for sickle cell disease was mandated in all 50 states, Puerto Rico and Washington, D.C., significantly decreasing the risk of mortality related to infectious complications, most often related to Strep pneumoniae.[5]

## THE NEXT WAVE OF TREATMENTS: OUR OPTIONS TODAY

Today, there are a number of effective treatments available to individuals with sickle cell disease. All of them, however, come with costs, and only one, bone marrow transplant, is accepted as a cure. Gene therapy is considered potentially curative, as it is too early to determine its long-term effects and outcomes.

In 1998, hydroxyurea became the first medicine approved by the FDA to specifically treat sickle cell disease after it demonstrated a 50% reduction in painful crises and hospitalizations.[6] Over the years, it has also demonstrated a more than 40% reduction in mortality. It has been proven to be safe and effective in patients as young as 6 months old. Hydroxyurea is FDA-approved for pediatric patients who are 2 years or older,[7] but NHLBI recommends offering it to patients as young as 9 months old.[8]

For more than 25 years, hydroxyurea has been recognized as the front-line therapy for people living with sickle cell disease. However, several barriers to its use persist. Patient concerns regarding the risk of infertility or carcinogenicity, fears of harm due to a lack of physician experience in administering the treatment, risk to the fetus in pregnant women, the frequency of required lab monitoring and a lack of perceived benefit have all led to substantially fewer patients using hydroxyurea than should be prescribed.[9]

Since hydroxyurea was introduced, other therapies have been approved. In 2017, L-glutamine, an antioxidant used in glutathione production, was approved for patients 5 years old and above.[10] In 2019, crizanlizumab, a P-selectin inhibitor, and voxelotor, a small molecule designed to reversibly lock hemoglobin in its oxygenated state, were approved for patients 16 and above (crizanlizumab) and 12 and above (voxelotor).[11] Of note, voxelotor was then approved for children age 4 and above in January 2021.[12]

All of these medicines demonstrated clinical benefits; however, they all have challenges related to adherence and efficacy. L-glutamine is a powder that is challenging to take at its prescribed dose. Crizanlizumab can cause infusion pain similar to a pain crisis, and voxelotor was recently pulled from the market globally because of concerns for increased risk of infectious deaths in clinical trials in Africa and increased frequency of pain episodes in post-marketing studies completed in the United States.[13]

While disease-modifying therapy is the key to living as healthy a life as possible, curative therapy for people with sickle cell disease has been a goal for several decades. In 1984, a young girl with sickle cell disease also developed acute myeloid leukemia. Because of her leukemia, she underwent a bone marrow transplant using stem cells from her sister. The transplant not only cured her of her leukemia but also her sickle cell disease.[14] Since then, more than 1,000 bone marrow transplants have been performed for people with sickle cell disease using a variety of donors (matched sibling, matched unrelated and haploidentical/partial match donors) with varying degrees of success.[15]

Currently, the only transplant approved for sickle cell disease is a matched sibling donor transplant. Other forms of transplant are still considered experimental, and each comes with its own risks and complications, including graft failure, graft versus host disease and fertility concerns, especially when using a myeloablative conditioning regimen. In addition, not every patient is eligible for a bone marrow transplant, as few patients have a matched sibling who also does not have sickle cell disease.

Moreover, because most bone marrow transplants are considered experimental, the risk/benefit ratio must be considered. Patients undergoing a bone marrow transplant must have some degree of disease severity but not be so sick that they cannot tolerate the transplant conditioning and subsequent recovery. Indeed, the only patients who meet the requirement for transplantation, even if they have no other organ toxicity, are those who have neurologic complications, including stroke, silent infarcts or neurocognitive deficits.

These advancements in treatment are exciting and life-changing for those who can access them. ... But, for many individual patients, it does not change the day-to-day reality of living with sickle cell disease. Pain is pain, and it's worse when it's an uphill battle to find relief.

## ENTER GENE THERAPY: A NEW POTENTIALLY CURATIVE OPTION

The new approval of gene therapy in 2023 meant that another transformative (and potentially curative) treatment was finally available. The two medications, bluebird bio's lovo-cel[16] and Vertex's exa-cel, were both approved for people with sickle cell disease without any qualification.[17] Even though it has been more than a year since gene therapy has been commercially available, several factors have limited its accessibility to patients.

The Centers for Medicare and Medicaid Services (CMS) and private insurance companies cover the cost of the therapy. However, there are no clear criteria to determine which patients are candidates for the therapy nationally. Several patient groups were left out of the clinical trials for the approved treatments. Patients with Hemoglobin Sickle C (HbSC) disease were excluded from both studies, and only a small percentage of patients with stroke were included in the lovo-cel study.[18] In addition, each state's Medicaid and private insurance companies have their own criteria for who would be eligible for gene therapy.

The nature of gene therapy as a cellular therapy means there are also institutional requirements for providing gene therapy. These include being Foundation for Accreditation of Cellular Therapy-certified and being chosen by the pharmaceutical company supplying the therapy to be designated as a qualified treatment center. The narrow patient criteria and the relatively few centers that are considered "qualified treatment centers" have resulted in limits to the accessibility of gene therapy.

While gene therapy has the potential to be curative for people with sickle cell disease, it does have its limitations and risks. Because myeloablative conditioning is needed to receive gene therapy, there is the risk of developing clonal hematopoiesis (genetic changes that lead to abnormal growth of blood cells) and secondary myelodysplastic syndrome (preleukemic state as a result of the transplant conditioning regimen), and potentially acute myeloid leukemia. In addition, patients are instructed to stop hydroxyurea and start chronic transfusion therapy for the time required for the cells to be manufactured. Patients also need to be admitted for a central line and stem cell collection at least once and potentially up to three times. Ultimately, the whole process can take almost a year from the time that the patient starts transfusion therapy and stops hydroxyurea to the time the patient is able to undergo conditioning and receive his/her manufactured stem cells.

Currently, very few individuals with sickle cell disease have been treated with this exciting therapy, and the numbers do not look to significantly increase anytime soon. However, with the development of *in vivo* gene therapy, which does not require collecting patients' stem cells to manufacture the cellular product, gene therapy may become more accessible. Additionally, CMS's Innovation Center has authorized the Cell and Gene Therapy Access Model,[19] which is anticipated to reduce health care spending over time by addressing the underlying causes of disease, specifically sickle cell disease. Funding would be provided through a cooperative agreement to help states cover the cost of participation in the model, including transportation and lodging.

## A POST-GENE THERAPY TREATMENT SPACE

These advancements in treatment are exciting and life-changing for those who can access them. Long term, these solutions have promising results. But, for many individual patients, it does not change the day-to-day reality of living with sickle cell disease. Pain is pain, and it's worse when it's an uphill battle to find relief.

Many individuals must occasionally seek care in the emergency department. There, they may encounter several problems, including a lack of timeliness and appropriate care, which are often a result of long-standing issues with systemic racism, implicit and explicit bias, and reluctance to provide adequate pain management amid the ongoing opioid epidemic.

A complex backdrop of other challenges complicates matters further, including the lack of effectively trained hematologists with experience and expertise in the management of sickle cell disease, the lack of a disease registry to track patient outcomes, and few, if any, well-known national advocates for the disease. Nationwide efforts led by the American Society of Hematology, the National Alliance of Sickle Cell Centers and the Sickle Cell Disease Association of America are working to correct these unmet needs.

## PAVING THE WAY TO A PAIN-FREE FUTURE

Gene therapy, while an exciting step forward, remains out of reach for most individuals with sickle cell disease. As providers dedicate themselves to learning more about this new treatment option, they must also commit themselves to ensuring patients receive adequate care outside of gene therapy.

Local hospitals and medical staff are encouraged to learn about the care of people living with sickle cell disease and should reach out to their local community-based organization or the Sickle Cell Disease Association of America for the nearest center. In addition, communication between a center of excellence and the local medical staff could be employed to improve the care of these patients. Resources could include the Agency for Healthcare Research and Quality's Project ECHO sessions,[20] designed to guide local medical staff in caring for patients with sickle cell disease; a hub-and-spoke model of care, in which a local physician can discuss care with a sickle cell expert; or referral to a sickle cell specialist.

Increasing the accessibility of new treatments like gene therapy starts with addressing old problems. Identifying how to relieve invisible barriers like systemic racism and a lack of provider education is an important step to bringing life-changing therapies out of the lab and into the lives of patients, especially in the context of sickle cell disease. Much change is needed for these patients, and the time to start is now.

**DR. CRAWFORD STRUNK** is the vice chief medical officer for the national nonprofit Sickle Cell Disease Association of America and associate medical staff at the Cleveland Clinic Foundation in the Division of Pediatric Hematology Oncology and Bone Marrow Transplant.

**NOTES**

1. Simon Pleasants, "Epidemiology: A Moving Target," *Nature* 515 (2014): https://doi.org/10.1038/515S2a; Charles T. Quinn et al., "Improved Survival of Children and Adolescents with Sickle Cell Disease," *Blood* 115, no. 17 (2010): https://doi.org/10.1182/blood-2009-07-233700.
2. Frédéric B. Piel, Dr. Martin H. Steinberg, and David C. Rees, "Sickle Cell Disease," *The New England Journal of Medicine* 376, no. 16 (2017): https://doi.org/10.1056/NEJMra1510865.
3. A. F. Manley, "Legislation and Funding for Sickle Cell Services, 1972-1982," *American Journal of Pediatric Hematology/Oncology* 6, no. 1 (1984): 67-71.
4. Cynthia S. Minkovitz et al., "Newborn Screening Programs and Sickle Cell Disease," *American Journal of Preventive Medicine* 51 (2016): https://doi.org/10.1016/j.amepre.2016.02.019.
5. Minkovitz et al., "Newborn Screening Programs and Sickle Cell Disease."
6. Dr. Samuel Charache et al., "Effect of Hydroxyurea on the Frequency of Painful Crises in Sickle Cell Anemia," *The New England Journal of Medicine* 332, no. 20 (1995): https://doi.org/10.1056/NEJM199505183322001; John Strouse and Matthew Heeney, "Hydroxyurea for the Treatment of Sickle Cell Disease: Efficacy, Barriers, Toxicity, and Management in Children," *Pediatric Blood & Cancer* 59, no. 2 (2012): https://doi.org/10.1002/pbc.24178.
7. "FDA Approves Hydroxyurea for Treatment of Pediatric Patients with Sickle Cell Anemia," U.S. Food & Drug Administration, December 21, 2017, https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-hydroxyurea-treatment-pediatric-patients-sickle-cell-anemia.
8. "Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014," National Heart, Lung and Blood Institute, September 2014, https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf.
9. Sarah L. Reeves et al., "Hydroxyurea Initiation Among Children with Sickle Cell Anemia," *Clinical Pediatrics* 58, no. 13 (2019): https://doi.org/10.1177/0009922819850476.
10. "FDA Approved L-Glutamine Powder for the Treat-

ment of Sickle Cell Disease," U.S. Food & Drug Administration, August 18, 2017, https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approved-l-glutamine-powder-treatment-sickle-cell-disease.
11. Mariam Barak et al., "Current and Future Therapeutics for Treating Patients with Sickle Cell Disease," *Cells* 13, no. 10 (2024): https://doi.org/10.3390/cells13100848.
12. Allison Inserro, "Voxelotor for Sickle Cell Disease Wins FDA Nod for Patients as Young as 4," AJMC, December 17, 2021, https://www.ajmc.com/view/voxelotor-for-sickle-cell-disease-wins-fda-nod-for-patients-as-young-as-4.
13. Julie Kanter et al., "Expert Consensus on the Management of Infusion-Related Reactions (IRRS) Presenting with Pain in Patients Receiving Crizanlizumab," *HemaSphere* 7, no. S1 (2023): https://doi.org/10.1097/01.HS9.0000928196.80128.ee.
14. Courtney D. Fitzhugh et al., "Hematopoietic Stem Cell Transplantation for Patients with Sickle Cell Disease: Progress and Future Directions," *Hematology/Oncology Clinics of North America* 28, no. 6 (2014): https://doi.org/10.1016/j.hoc.2014.08.014.
15. Monica Bhatia and Sujit Sheth, "Hematopoietic Stem Cell Transplantation in Sickle Cell Disease: Patient Selection and Special Considerations," *Journal of Blood Medicine* 6 (2015): https://doi.org/10.2147/JBM.S60515.
16. It should be noted, however, that lovo-cel did receive a black box warning secondary to the fact that two patients on the trial developed myelodysplastic syndrome and later died of acute myeloid leukemia.
17. Matt Hoffman, "FDA Approves Bluebird Bio's Lovo-Cel Gene Therapy for Sickle Cell Disease," AJMC, December 10, 2023, https://www.ajmc.com/view/fda-approves-bluebird-bio-s-lovo-cel-gene-therapy-for-sickle-cell-disease; "FDA Approves First Gene Therapies to Treat Patients with Sickle Cell Disease," FDA, December 8, 2023, https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapies-treat-patients-sickle-cell-disease.
18. Dr. Haydar Frangoul et al., "Exagamglogene Autotemcel for Severe Sickle Cell Disease," *The New England Journal of Medicine* 390, no. 18 (2024): https://doi.org/10.1056/NEJMoa2309676; Julie Kanter et al., "Lovo-Cel Gene Therapy for Sickle Cell Disease: Treatment Process Evolution and Outcomes in the Initial Groups of the HGB-206 Study," *American Journal of Hematology* 98, no. 1 (2022): https://doi.org/10.1002/ajh.26741.
19. "Cell and Gene Therapy (CGT) Access Model," Centers for Medicare & Medicaid Services, https://www.cms.gov/priorities/innovation/innovation-models/cgt.
20. "Project ECHO," Agency for Healthcare Research and Quality, https://www.ahrq.gov/patient-safety/settings/multiple/project-echo/index.html.

JOURNAL OF THE CATHOLIC HEALTH ASSOCIATION OF THE UNITED STATES www.chausa.org

HEALTH PROGRESS®

Reprinted from *Health Progress*, Summer 2025, Vol. 106, No. 3