Sangamo THERAPEUTICS

Developing a New Bioethical Framework to Guide the Use and Application of Genomic Medicine

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Introduction

Genomic medicines such as gene therapies, cell therapies and genome-engineered therapies have the potential to replace today's symptomatic treatments with tomorrow's cures, and even to develop therapies for diseases where no effective treatment exists today.

Sangamo Therapeutics is translating our groundbreaking genomic science and manufacturing expertise into therapies for millions of people who suffer from severe genetic diseases for which today's medicine can only offer symptom management at best.

Sangamo and others continue to advance this exciting new field of medicine, but we need more than scientific breakthroughs to realize genomic medicine's full lifesaving and life-changing potential. Our existing health care system wasn't built with this new field of medicine in mind. As such, aspects of the system need to evolve and other aspects need to be created.[1] For example, we need a robust bioethical framework to guide the use and application of genomic medicine. This framework must be acceptable to patients and health care practitioners, as well as policymakers and the greater public.

This is a rapidly developing area and one of the most exciting developments in medicine today. What does this mean for the people who will ultimately receive these therapies? That the responsibility is on each stakeholder in the healthcare ecosystem to support a patient's understanding of genomic medicine vs a traditional medicine. Genomic medicines will require a deeper partnership with patients; engaging them early and ensuring they truly grasp the benefits but also risks of these types of treatments.

If we don't address these bioethical issues, with considerations that every step of the patient journey (from diagnosis through to follow up) differs from traditional treatments, we risk future challenges with clinical trial participation, long-term data collection, commercial pathways, access systems, or other challenges that could hinder patients from receiving genomic medicines.

The diseases we seek to treat with genomic medicine are serious conditions with high unmet need. Consider how this technology can vastly improve the life of a person with a rare genetic disease:

Hemophilia is a congenital bleeding disorder caused by a lack of clotting protein and living with the complications of this disease can be challenging. Patients with severe hemophilia require frequent, life-long intravenous infusions of clotting factor to protect them from bleeding.

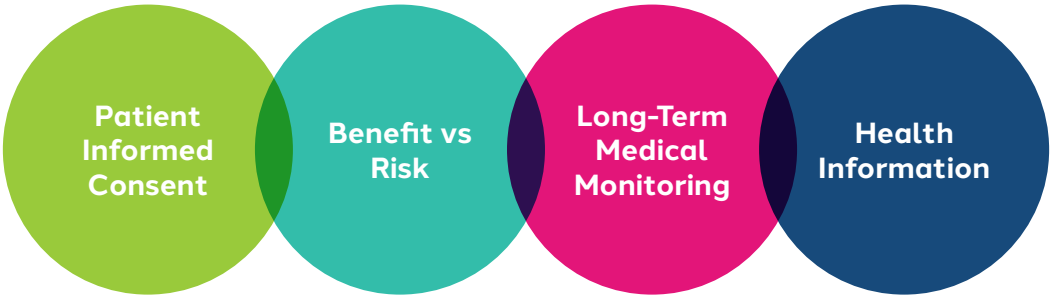
Clinical trials using gene therapy to boost the body's production of clotting factor has the potential to free patients from a lifetime of factor replacement therapy — ideally giving patients years or even decades free from daily worry about their condition.

1. Sandy Macrae, "The future of medicine is now. Are we ready?" LinkedIn, retrieved 11 January 2022 from https://www.linkedin.com/pulse/future-medicine-now-we-ready-sandy-macrae-mrcp-phd/

This is a pivotal time to address challenges and opportunities as the U.S. Food & Drug Administration (FDA) continues its strong support of innovative developments in gene and cell therapy products[2] for Americans and others around the world.

To date, the FDA has approved several gene therapy products and anticipates many more approvals in the coming years, as evidenced by the more than 900 investigational new drug (IND) applications for ongoing clinical studies in this area.

We believe there are four areas of insight where we can make progress toward developing the transparent systems needed to enable genomic medicine to fulfill its full promise to patients.



Since our founding in 1995, Sangamo Therapeutics has been a leader in genomic medicine research and development with a focus on putting patients first. We develop product candidates using a range of cellular and genomic engineering approaches that allows us to connect the underlying biology of the disease to the appropriate technology to create life-saving products for patients.

As we consider new bioethical guidance for genomic medicine related to Patient Informed Consent, Benefit vs. Risk, Long-Term Medical Monitoring, and Access, at Sangamo, we are driven by the question: **What does the patient journey look like?**

A Patient's Perspective

Throughout this report, we introduce you to real patients who live with the day-to-day challenges of severe conditions including Fabry disease, sickle cell anemia and Parkinson's disease. The possibility of eliminating the need for frequent, life-long treatments for the patients and families affected by debilitating diseases is what drives our work to advance the field of genomic medicine.

2. "FDA Continues Strong Support of Innovation in Development of Gene Therapy Products," U.S. Food & Drug Administration, retrieved 11 January 2022 from https://www.fda.gov/news-events/press-announcements/fda-continues-strong-support-innovation-development-gene-therapy-products

Guided by Ethical Research

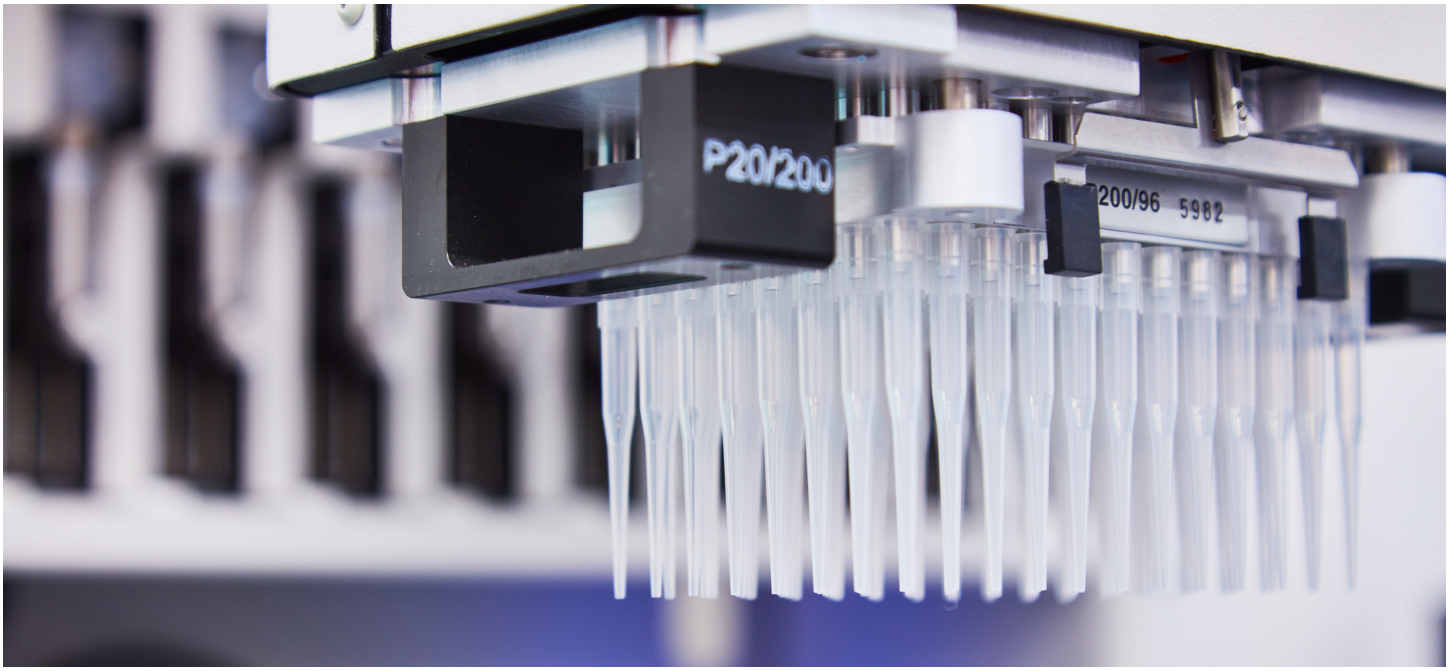
The gene and cell therapies described throughout this document refer to therapies that target somatic cells, or all cells in the body excluding reproductive (germline) cells. Therefore, any changes to genes will only affect the non-reproductive cells (somatic) of the individual's body who has received treatment.

Sangamo's R&D approach is aligned with the:

- Alliance for Regenerative Medicine (ARM) Therapeutic Developers' Statement of Principles[3] the ethical use of gene editing and genetic modification, including the investigation of therapeutic applications of somatic cell gene editing.
- World Health Organization's Human Genome Editing Recommendations[4] developed by the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, to examine the scientific, ethical, social and legal challenges associated with human genome editing.

3. "FDA Continues Strong Support of Innovation in Development of Gene Therapy Products," U.S. Food & Drug Administration, retrieved 11 January 2022 from https://www.fda.gov/news-events/press-announcements/fda-continues-strong-support-innovation-development-gene-therapy-products
4. "Human genome editing: recommendations," World Health Organization, retrieved 11 January 2022 from https://www.who.int/publications/i/item/9789240030381

Patient Informed Consent



By the time a potential new medicine makes it to the clinical trial stage of research and development, it has typically gone through at least three years of preclinical testing to see if the treatment is likely to be safe and effective for use in humans. Then, clinical trials in humans must be conducted before a drug can be approved.

As with any medical treatment, participation in a clinical trial offers benefits and risks. To help a clinical trial volunteer make an informed decision, the clinical study team is required to disclose all known risks, benefits, and available alternative health care options. This is called informed consent and is an ongoing, interactive discussion to help patients make informed decisions about whether to begin or continue to participate in a clinical trial.

The potentially life-long effects of genomic medicine designed to alter the genetic instructions inside a body's cells to slow or stop the progression of disease require an enhanced approach to patient informed consent.

Unlike traditional medicine clinical trials, it is impossible for physicians to reduce the dose or stop the treatment of a genomic medicine if the effects are outside of what is expected. The effects of genomic medicine are intended to be long-term and thus the consent must be equivalent. Genomic medicine informed consent is effectively consent for life, which demands unmatched accountability and proactivity – it is the responsibility of industry to set this new bar.

Opportunities in Genomic Medicine Patient Informed Consent

Our focus at Sangamo is working to create genomic cures for patients with genetic diseases – conditions that are severe and progressive, with no known cures.

We take very seriously the notion that genomic medicine is a pioneering field and poses inherent risks that are not yet fully understood. As the industry continues to monitor the long-term effects of genomic medicines, we must be fully transparent to inform future clinical trial patients of the potentially lifelong nature of their commitment, as well as our understanding of the risks and benefits.

The informed consent process must create an environment of trust to support a patient's complete understanding of risks and potential benefits of participating in study. We work with patient advocacy stakeholders to ensure informed consent documents are developed with attention to language, literacy, and focus on what outcomes are most important to the patient.

A patient's role in a clinical trial goes beyond receiving an investigational treatment. Active participation and patient partnerships are critical for clinical trials where there is a smaller patient population, such as those researching treatments for genetic disorders.

The research community must build approaches to informed consent specific to genomic medicines that are useful and support a patient's understanding of the commitment as they decide whether to participate in a clinical trial.

A Patient's Perspective: End-Stage Renal Disease

For patients living with end-stage renal disease (ESRD), a kidney transplant often is the treatment of choice. To prevent graft rejection of the transplanted organ, patients are treated with lifelong immunosuppressive therapy. This standard-of-care therapy impacts the body's immune system and can have side effects including an increased risk of infectious complications, cancer, and other drug-related toxicities.

One patient with ESRD knew her diagnosis would mean a lifetime of dialysis or a kidney transplant and spent years learning to live with a debilitating condition, not knowing what the future held. When she received the news that her kidney function was so weak that her life was in jeopardy, she and her physicians decided a kidney transplant was the best option.

A living kidney donor was identified, and the transplant was successful. More than five years later, the patient works with her medical team to counteract the side effects from immunosuppressant therapy. The therapy, while not ideal, remains the standard of care until there is a better option for kidney transplant patients.

Benefit vs. Risk

The next factor of the bioethics discussion is the risk-benefit assessment. This can be viewed as three main components: 1) a biopharmaceutical company deciding to develop treatments where it believes the burden of illness is significant and potential risks to the patient are worth taking; 2) a patient receiving transparent education and independently (in collaboration with a healthcare professional) deciding to consent to the potential risk, and 3) regulatory agencies making an informed judgment as to whether the benefits (with their uncertainties) of the drug outweigh the risks.

Research and Development

At Sangamo, the diseases we are working to treat have lifelong impact on the person with the condition, and those around them.

The more we understand what is most important to people with rare diseases, their families, and caregivers, the better we can address their needs. As a company, we must be mindful of how the potential risks and possible benefits of an experimental treatment might extend beyond the immediate measures of the condition itself.

The future of genomic therapies holds great promise in treating certain diseases such as hemophilia, sickle cell disease, neurodegenerative diseases, and leukemia, among others. These therapies could offer a better quality of life for patients with serious and potentially fatal conditions.

With all emerging research, we must be transparent about the uncertainty associated with treatment such as unwanted immune system reaction, infection, or other serious risks. Genomic medicine patients contribute to the advancement of research, but often with the selfless goal of

supporting new scientific understanding that could bring relief to others who live with the same rare condition. As part of the benefit and risk discussion, our ethical bar is set higher. We must be transparent that they are among the first to test a therapy, and there is no guarantee of benefit for those who choose to participate.

Informed Patients

A continuance of the patient informed consent process is ensuring a meaningful conversation around the benefit and risk of participating in clinical trial or receiving a genomic medicine. Today's genomic medicine patients are pioneers – the first to receive these treatments. By definition, medical science doesn't have data on the lasting effects because no patient has lived a lifetime (yet) after receiving a genomic therapy.

Until longer-term medical monitoring data is available, these therapies should only be used for conditions with a compelling benefit versus risk for patients. Because there is no guarantee that a new drug in development will benefit a study participant, we must be sure that we never take a patient away from a proven treatment that could address their needs.

Ultimately, treatment decisions should be shared between a patient and health care provider to determine, with full understanding and transparency, whether the benefits of a genomic therapy outweighs the risk or burden of continuing with traditional treatments or letting the disease progress.

Regulatory Considerations

Benefit-risk assessment takes into account the extensive evidence of safety and effectiveness submitted by a sponsor in a marketing application (e.g. Biologics License Application (BLA), as well as many other factors, including the nature and severity of the condition the drug is intended to treat or prevent, the benefits and risks of other available therapies for the condition, and any risk management tools that might be necessary to ensure that the benefits of the drug outweigh its risks.

As genomic therapy research advances, the FDA has gone to great lengths to evaluate data across studies and pharmaceutical companies to improve the understanding of benefit-risk in cell and gene therapy and provide updated guidance for this field of study.

In 2021, the 70th Meeting of the FDA's Cellular, Tissue, and Gene Therapies Advisory Committee[5] convened to discuss the safety and toxicity risks of adeno-associated virus (AAV) vector-based gene therapy products. The Committee discussed ways to finetune both preclinical and clinical gene therapy research for the benefit of patient safety.

5. "70th Cellular, Tissue and Gene Therapies Advisory Committee Meeting Summary Minutes," U.S. Food & Drug Administration Center for Biologics Evaluation and Research, retrieved 11 January 2022 from https://www.fda.gov/media/154397/download

Additionally, the FDA is in the process of updating its Benefit-Risk Assessment for New Drug and Biological Products.[6] This guidance is intended to clarify for drug sponsors and other stakeholders how considerations about a drug's benefits, risks, and risk management options factor into FDA decision-making, among other considerations related to benefit-risk.

One of the greatest bioethical opportunities is finding a new way to evaluate benefit-risk for a treatment that is expected to have long-lasting effects. We will continue to partner with the FDA and all stakeholders to put patient safety first as this new field of medicine develops.

"For the genomic medicines we are developing at Sangamo, the challenge is understanding the lifetime risk for a small group of vulnerable patients. The clinical trials we consent patients into are, by definition, first-of-their-kind. Gene therapy technologies have been studied during the past 30 years, but only recently are the next generation forms of genomic medicine being tested in the clinic. We don't yet know the lifelong effects of a therapeutic we hope addresses the disease at its source. This is why we focus on serious medical conditions where we have the potential to make a real difference to patients' lives, and where the potential benefit significantly outweighs the risk."

– Sandy Macrae, MRCP, PhD
CEO, Sangamo Therapeutics

6. "Draft Guidance: Benefit-Risk Assessment for New Drug and Biological Products Guidance for Industry," U.S. Food & Drug Administration Center for Biologics Evaluation and Research, retrieved 11 January 2022 from https://www.fda.gov/media/152544/download

A Patient's Perspective: Fabry Disease

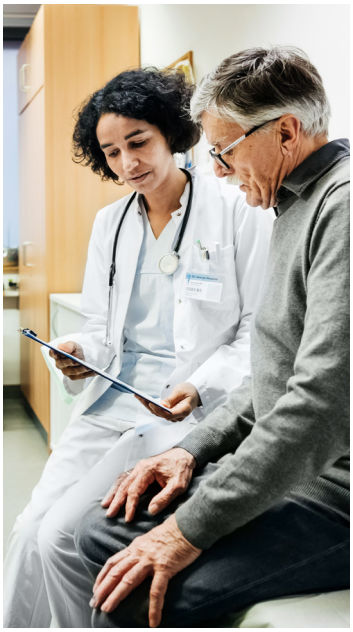
Fabry disease, a rare genetic disorder, can be challenging to manage in everyday life. It is often described as an invisible disease; a person with Fabry often looks and acts normal until they cannot.

Four members of a single family lived years with Fabry symptoms: mysterious, painful, and unresolved. The path to diagnosis was long and frustrating, with family members living with symptoms including debilitating pain in the hands and feet, and gastrointestinal issues. One family member experienced kidney failure that resulted in a kidney transplant, even though they were receiving Enzyme Replacement Therapy, an approved treatment for Fabry.

Enzyme Replacement Therapy is the most common treatment for Fabry disease. As frequently as twice per month, family members visit an infusion clinic to receive ongoing treatment.

Today, the family is on a mission to let others know a rare disease can and will attack from the inside. It may not be visible, but it is powerful.

Long-Term Medical Monitoring



Patients who receive a traditional prescription medicine are monitored by a physician for as long as they take the treatment. If or when a treatment course ends and a patient stops taking the medicine, it is no longer necessary for their physician to monitor the impact on a patient.

The treatment period for genomic medicine is very short. A patient may receive just one gene therapy treatment administered through an intravenous infusion, but the effects are expected to last in the body for years. For this reason, genomic medicine needs to be monitored for a longer period, even though it is intended to be a one-time treatment

Current guidance from the U.S. Food & Drug Administration on the design of long-term follow-up after the administration of human gene therapy products[7] suggests follow up timeframes of 5 to 15 years, depending on the type of treatment being studied.

As one component of a bioethical framework to guide the future of genomic medicine, a medical monitoring system must be established to ensure patients receive long-term monitoring to evaluate the safety and durability of genomic therapies.

Long-Term Medical Monitoring Requires Unique Approaches

We cannot overstate our gratitude to the patients who volunteer to participate in Sangamo-sponsored clinical trials and consent to long-term follow up and monitoring. As this technology progresses, it will take ongoing collaboration with all stakeholders to remain nimble and address potential challenges to effectively conduct ongoing medical monitoring. To this end, a new bioethical framework should acknowledge the lasting nature of genomic medicines vs. traditional therapies and identify pathways for medical monitoring for patients who receive a genomic therapy.

Our first step comes with informed consent and the diligence to explain the complex science to patients, including the potential benefits and risks and nature of the lifelong commitment prior to agreeing to participate in a clinical trial. The success of a trial and the science is dependent on the ongoing and active partnership of the patient, their loved ones, and health care providers.

Circumstances such as a patient moving out of state, or the retirement of a treating physician will continue to pose challenges with ongoing monitoring. We must identify paths for the data to follow the patient, regardless of changes in proximity to treatment providers or milestones in life.

7. "Long Term Follow-Up After Administration of Human Gene Therapy Products, Guidance for Industry," U.S. Food & Drug Administration Center for Biologics Evaluation and Research, retrieved 11 January 2022 from https://www.fda.gov/media/152544/download

In partnership with rare disease patient advocacy organizations, we are looking at the possibilities of using real-world evidence as a mechanism for long-term medical monitoring. This could include observational studies, patient registries, or databases to track follow-up, in addition to ongoing conversations with both patients and providers to support understanding related to long-term monitoring.

At Sangamo, we prioritize our relationships with patient advocacy organizations through a dialogue to ask questions, listen to the needs of patient communities and incorporate the patient voice throughout our development process.

From a bioethics perspective, we have legal and regulatory obligations we must meet. But as an individual pharmaceutical company addressing unmet needs and replacing today's treatments with tomorrow's cures, we want to do more than what is required – we want to do what is right for the patients we serve.

An example of a patient registry that could support long-term medical monitoring for rare diseases is the National Organization for Rare Disorders (NORD) IAMRARE Natural History Study Patient Registry. This registry program brings rare disease communities together and collects data which could be used to study interventional outcomes, support the design of clinical trials for new treatments and improve the quality of life for patients.

More information at https://rarediseases.org/iamrare-registry-program/

A Patient's Perspective: Parkinson's Disease

Parkinson's disease is a neurodegenerative disease marked by progressive symptoms including slow movement, rigidity, unstable posture, tremors, loss of smell, sleep disorders, and neuropathic pain. In the US, Parkinson's disease impacts more than one million patients, with 50,000 newly diagnosed patients each year. There are treatments that target some of the movement symptoms, but these therapies don't slow the underlying disease progression.

In his late 30s, one patient started to notice small, almost imperceptible changes in his movement. His physician ran tests and mentioned Parkinson's, but both patient and doctor dismissed the possibility. He was too young and healthy; he didn't look like a typical Parkinson's patient. Additional tests and an MRI followed, and a neurologist delivered the devastating Parkinson's diagnosis.

Staying engaged and finding support has helped him come to terms with the disease and how it could progress in the future. He's a member of an early onset Parkinson's group, finding comfort in others who share his concerns and questions about how the disease has impacted their lives.

Health Information

Genomic medicines have life-changing potential for those facing serious or rare illnesses and are among the fastest-growing areas of research. Another important component of a bioethical framework is supporting a patient's access to individual health information.

Access to Individual Health Information

As patients take greater ownership of their health and health outcomes, we support their desire to better understand the research in which they took part and see and use the data gathered about their health.

Sangamo is aligned with global efforts aimed at data sharing and clinical trial transparency to make appropriate information available to the scientific community, academic researchers, practitioners, and most importantly for patients.

Our first milestone toward this effort begins at the end of 2021 when the European Union Clinical Trial Regulation becomes effective. This is in addition to current guidance that requires clinical trial sponsors to provide summary results of clinical trial findings to participants in easy-to-read, non-technical language.

Our longer-term goal is to provide some level of individual clinical trial data back to participants. Returning individual research results to study participants is not a currently a widespread practice and is not always possible in clinical research. A variety of individual-level data return programs are being piloted in the United States and Europe in partnership with clinical trial sponsors.

These programs are looking at opportunities to share personal health information with secure delivery directly to patient volunteers or integrated into a patient's electronic medical record. One of the ideas behind this concept is to help clinical trial participants avoid enduring multiples of the same test or repetitive invasive procedures.

Patient data return is gaining momentum within the industry and has generated a consortium of pharmaceutical companies working toward a standardized approach to data return to share data back to patients in a responsible manner that is standardized across pharmaceutical companies. The Patient Data Access Initiative (PDAI) has a goal to help companies implement data sharing with patients while they are still participating in the clinical trial.

Those who participate in a Sangamo-sponsored clinical trial receive a patient information letter containing details of the study in which they participated. This includes specifics related to the genomic medicine they received, how the therapy is expected to work in the body, and, depending on the type of genomic medicine being studied, the exact sequence of the gene that may have been inserted into a patient's cells. This letter is intended to become part of a study participant's medical records.

Patients are asking us for access to their own data, however, barriers and challenges exist for industry – including lack of clear guidance from the FDA and ensuring approval from the Institutional Review Boards who monitor and approve communication from the trial sponsor to the patient participants.

We will continue to advocate for access initiatives that put patients at the center of the development process, acknowledges their contributions to research and enables them to work with health care providers to make more informed decisions about their own health, including a variety of treatment options.

"As a society, we've never had more access to information than we do now. Part of Sangamo's commitment to patients is to work with other industry leaders to develop a standardized approach to returning an individual's health data during and after a clinical trial, and in the case of genomic therapies, as monitoring data is understood in the long-term. We must work toward cross-industry best practices that protect patient privacy, puts patients in control of the information they wish to receive, and offers information in a contextual manner that is easy to understand by patients or their health care providers – all while maintaining clinical trial integrity and government and regulatory requirements."

– Christeen Moburg
Vice President of Patient Advocacy and Government Relations

A Patient's Perspective: Sickle Cell Anemia

One patient, now in her 40s, was diagnosed with sickle cell anemia at 11 months old. At the time, the life expectancy for people living with sickle cell anemia was 21 years. Her parents knew they had no time to lose to learn more about the disease and advocate for their daughter's care.

This hereditary disease can cause episodes of extreme pain, lasting a few hours to a few weeks. sickle cell anemia accounts for 200,000 emergency room visits a year, a significant burden of disease. In her lifetime, this patient has endured countless trips to the ER, received 500+ pints of transfused blood and experienced several minor strokes that weakened her left side.

Now an advocate for herself and others, she speaks regularly to doctors, nurses, and the public about life with this invisible and painful disease, putting her years of experience to work helping others make the most out of living with sickle cell anemia.

Conclusion

Genomic medicine won't reach its potential in one huge leap. The science advances step by significant step. Progress is rapid but in the context of medical history, we're still in the early days of genomic medicine. We're building Sangamo to last so that our unique platform and deep expertise can drive genomic medicine advances for years to come and, most importantly, play our part in ensuring genomic medicine delivers on the promise it holds for patients.

We in the industry must take the lead – starting conversations, raising issues, and asking hard questions. We must collaborate among ourselves, with patients, patient advocacy organizations and organizations like Alliance for Regenerative Medicine and Biotechnology Innovation Organization (BIO) to develop solutions and pioneer change.

- Sangamo leadership is proud to be on the forefront of these discussions as part of the Alliance For Regenerative Medicine's Gene Editing Task Force[8] and the BIO Cell and Gene Therapy Committee.

The same collaboration, focused effort and strategic investment that brought us the interstate highway system, the internet and any number of life-changing systems can be applied to genomic medicine. Our technology is life altering for sure, and for many patients, potentially lifesaving.

This new field of medicine has the potential to change the way serious diseases are treated or even cured. We must also be clear-eyed that a new field of medicine will bring new challenges to our existing health care framework. We are just beginning to consider how to create the infrastructure that will put these advances to work – and need to make sure that our system can evolve to keep up with the science.

Sangamo THERAPEUTICS

8. "ARM Committees & Task Forces," Alliance for Regenerative Medicine, retrieved 11 January 2022 from https://alliancerm.org/committees/