PROFILE OF A POTENTIAL "NOBEL PRIZE" WINNER FROM PASCO

-By Thomas Konda, M.D.

Kiran Musunuru, M.D., PhD, MPH, ML was born in New York City in 1976, while his father was undergoing postgraduate training in internal medicine and cardiology. He moved to west Pasco (FL) in 1981, where his father started a cardiology practice.

While in school, he was one of the top three national winners of "Mathcounts" (akin to spelling bee) in Washington, D.C. He wrote a computer program in genetics. Also he co-authored scientific publications about the mechanisms of actions of insulin (protein-kinase, etc.). He used to read EKG's with his father after making patient rounds. He also volunteered at the hospital fixing computers and teaching calculus to hospital employees. He also won national "Latin" essay writing competition.

At the celebration of Kiran's high school graduation arranged by his parents in an auditorium attended by family members and friends with their children, the usually shy Kiran astonished everybody with his an hour long program of music and magic (piano and advanced magic including Houdini's metamorphosis). That was the beginning of his public scientific presentations at national and international levels. He has become a star with his excellent command of language in addition to a commanding voice.

While at Harvard, as an undergraduate he started and edited "Journal of Undergraduate Sciences." Even though his major was biological sciences, he took "Advanced Engineering Calculus, Crystallography and Buddhism" as

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electives. He also co-authored a book "Cell-Cycle Regulators in Cancer" while undergraduate at Harvard.

While doing combined M.D., PhD program (on full merit scholarship) at Cornell and Rockefeller, (his thesis was in neurosciences at a molecular level) after a selected scientific presentation in California, he earned a glorified editorial in a prestigious journal "Nature Medicine" which ended with the sentence "The presentation marked Musunuru out as a future star in biomedicine". A lot of Nobel Prize winners were among the speakers and audience at that meeting. His presentation was sandwiched at the opening session between two presentations from two Nobel laureates.

While doing 2 years (instead of 3) internal medicine residency at Harvard (Brigham) he authored "Pocket Books" in internal medicine and critical care for the rest of the house staff. He received "Best Outgoing Resident Award" which is usually reserved for 3rd year resident. The director of the program described him as a "National Treasure" in writing. Also while doing residency, he worked as a consultant for a pharmaceutical company and guided them to produce new cardiovascular medicines (RNA based).

Kiran has been volunteering for American Heart Association (AHA) for decades. He has served on the leading roles for its scientific councils like clinical cardiology and functional genomics. He received national awards from AHA for his service in science; he also finds time to work with "needy students" in the inner cities.

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While doing first 2 years of interventional cardiology fellowship at Johns Hopkins, he simultaneously finished masters in public health (MPH) from Johns Hopkins School of Public Health. He later acquired masters in law (ML) covering patent, business and administration and also masters in regulatory affairs (MRA) covering drugs, devices and development, from University of Pennsylvania.

While continuing his cardiology research fellowship back at Harvard (Massachusetts General) he advanced the knowledge in 'stem cells and regenerative medicine'. He also earned "Excellence in Science Teaching" award among Harvard faculty. He was honored at white house by president Obama in person for "Presidential Early Career Award for Scientists and Engineers". He was also bestowed the most prestigious American Philosophical Society's (started by Benjamin Franklin)"Judson Daland prize for Outstanding Achievement in Clinical Investigation" at its 275th anniversary in Philadelphia, in recognition of his work discovering and therapeutically targeting cardiovascular disease genes. It carried a $50,000 prize. Kiran also collaborated with MIT and Broad Institute.

Shortly afterwards, Kiran was recruited by University of Pennsylvania in Philadelphia to become a tenured professor at a young age with his own research lab leading to many advances in gene editing. He voluntarily teaches undergraduates (biochemistry), medical students (genetics)and cardiology fellows-in-training (staying with them day and night when he is on call, developing and implementing treatment strategies for treatment of sick

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cardiac patients transferred from other hospitals. He earned "Excellence in Teaching Award" at University of Pennsylvania also.

He authored publications in many prestigious scientific journals over decades. He also served as the editor of International Circulation Journal: Genomic and Precision Medicine. He also contributed chapters in many cardiology books, including "Braunwald's Text Book of Cardiology." His latest books include "Crisper Generation" and "Genome Editing- A Practical Guide to Research and Clinical Applications", for scientists and researchers to learn the art. He conducts boot camps at national AHA meetings and he constantly preaches ethics.

At this point with all his extreme knowledge in various areas and aspects of physics, mathematics, biochemistry, computer literacy, clinical medicine, and research in genetics (well planned since his school time, as you can see) he began specializing in "gene editing" to create cures for diseases that did not have any until now, not only cardiovascular but also some metabolic (e.g.: Phenylketonuria) diseases. His latest endeavor is intrauterine gene editing to prevent damage from bad genes while baby is still in uterus.

He currently serves on NHLBI council. Collaborating with universities, NIH and pharmaceutical industry, Kiran is going to make a world of difference for the humanity all over the world.

Kiran frequently associates with Nobel Prize winners worldwide. He receives a lot of attention, appreciation and admiration from them. For example, recent 'Nobel prize winner in science' Jennifer Doudna published a book in 2017-"A crack in Creation." In the first two pages of the fourth chapter she described

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about her excitement about meeting Kiran at his lab at Harvard and marvels about his work and she writes “Kiran was already one step ahead of me about applications of “CRISPR” as a therapeutic tool” Without any doubt, he will earn a Nobel Prize for himself in the future.

Kiran dedicated his life to science and he is the self-proclaimed “Pope” for religion of “discovering cures for all kinds of diseases”. He is a down to earth humble person, very respectful to everyone, irrespective of their age or status. He is very kind to his students and researchers always giving them credit for all his own ideas, work and publications.

He is a person of many skills and talents. He is a package of brilliance, selflessness, generosity, and dedication. He encourages his parents to donate his inheritance to help the needy in addition to investing his own for the advancement of science.

Let us thank God for this gift to humanity!

Let us pray to God to bless Kiran and his parents for long healthy, happy and productive lives.

P.S. Dr. Thomas Suman Konda is a retired endocrinologist with a keen interest in academic and research medicine all his life. He has known Kiran, since Dr. T.S. Konda moved to Pasco County decades ago to support his wife (Nirmala), an excellent practicing cardiac anesthesiologist. He is also a successful stock market investor. He has always admired, enjoyed and encouraged Kiran, sharing their mutual enthusiasm and interest in medical research.

Rao,

Thanks so much for the invitation to attend Kiran's lecture on Feb 1st. I am very much impressed by his work and contributions.

I am sure he will get honored by getting a Nobel Prize one day. I always forward his lectures to my family and friends.

I congratulate you and your wife for raising such a dedicated soul. He is really a gift from God and we are so proud of him and you.

Thanks,

Sudhir Agarwal, M.D.

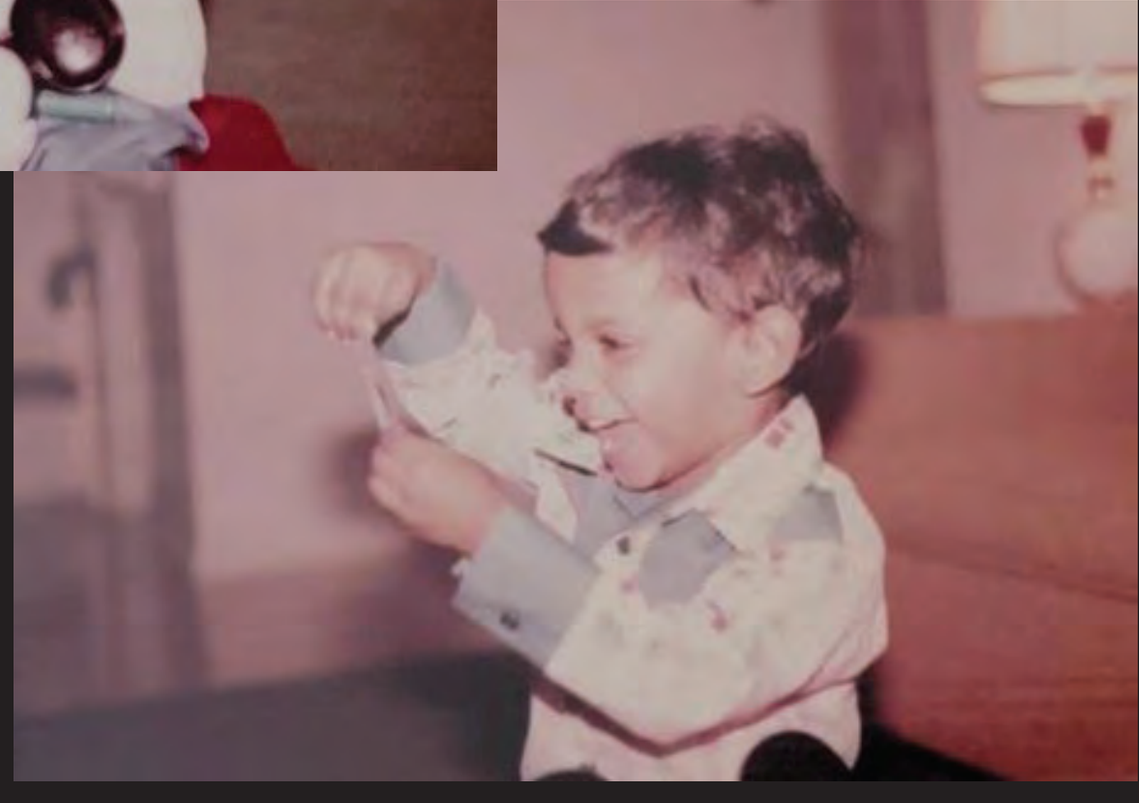
-- Personal message from a friend, 2023

From there, "wherever you go
Go with all your heart."

Kiran as an infant.

Happy young family in
New York City.
Kiran at eight months.

Kiran growing up.



A happy boy.


KIRAN

Always happy, happy.

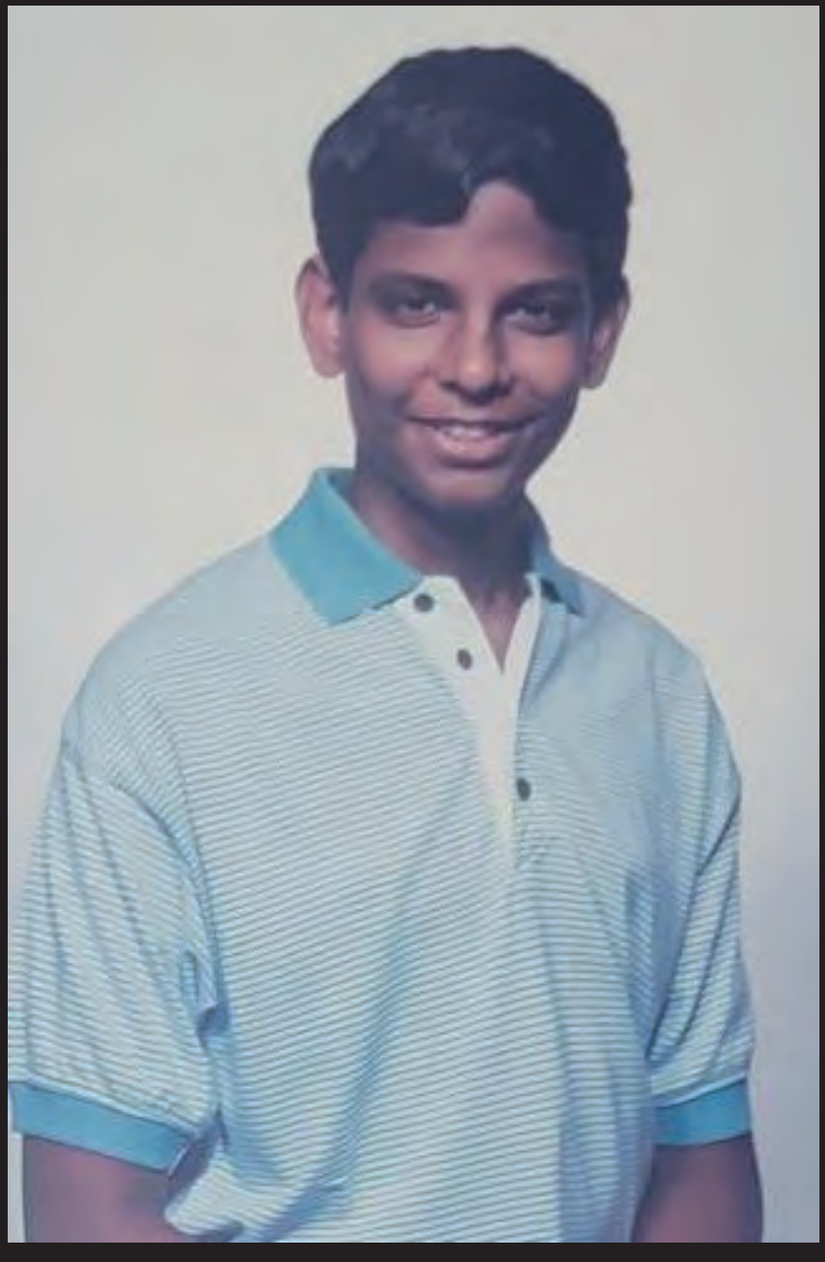
Kiran at work,
learning himself
and from his Dad.

Kiran, future teacher.

Kiran at piano.

Feeding the body,
not only the mind.

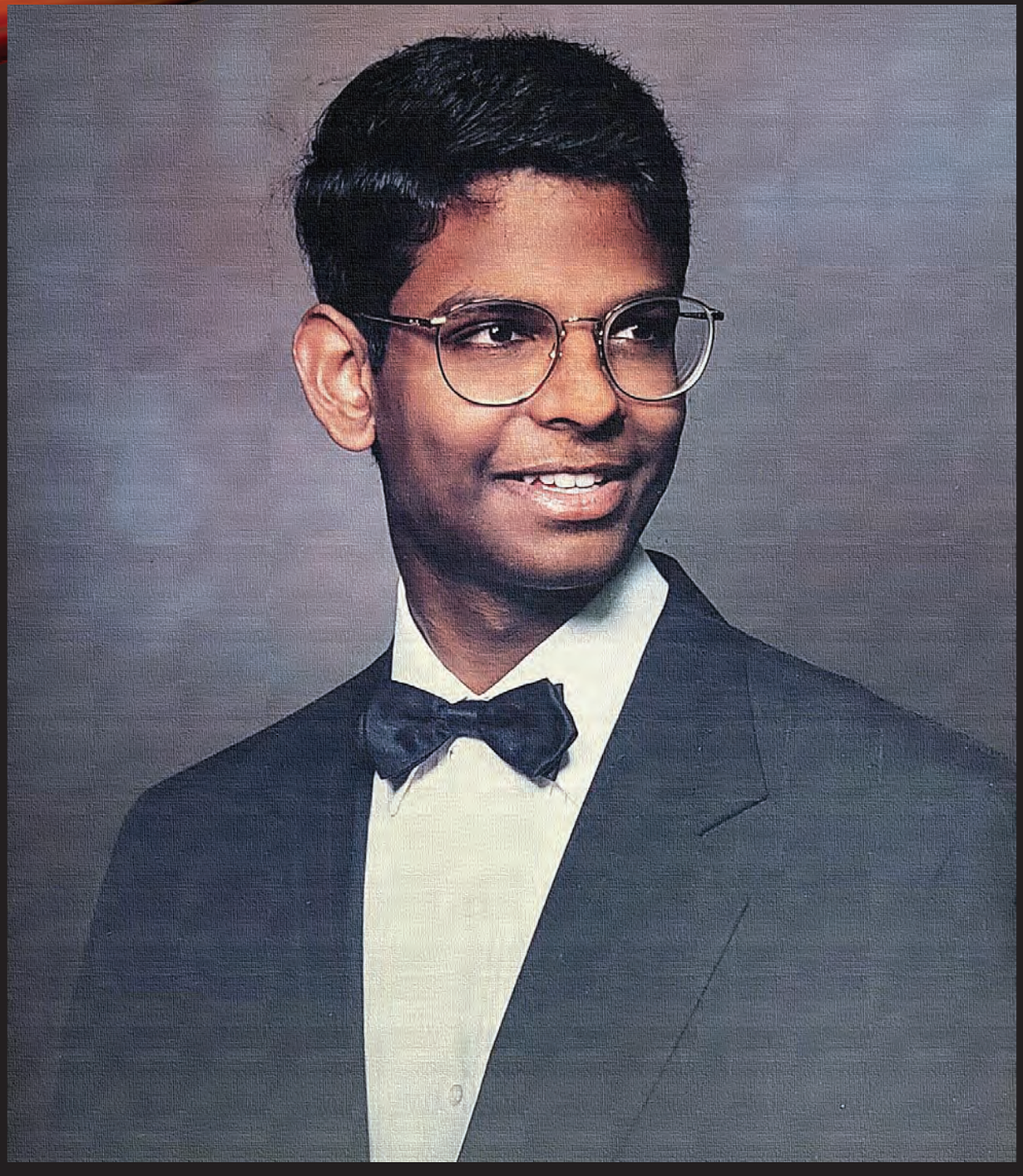
Innocence at its best.



Kiran growing up.

Kiran's personal book library during his school years. *(Part 1)*

Kiran's personal library during his school years. *(Part 2)*



Kiran,
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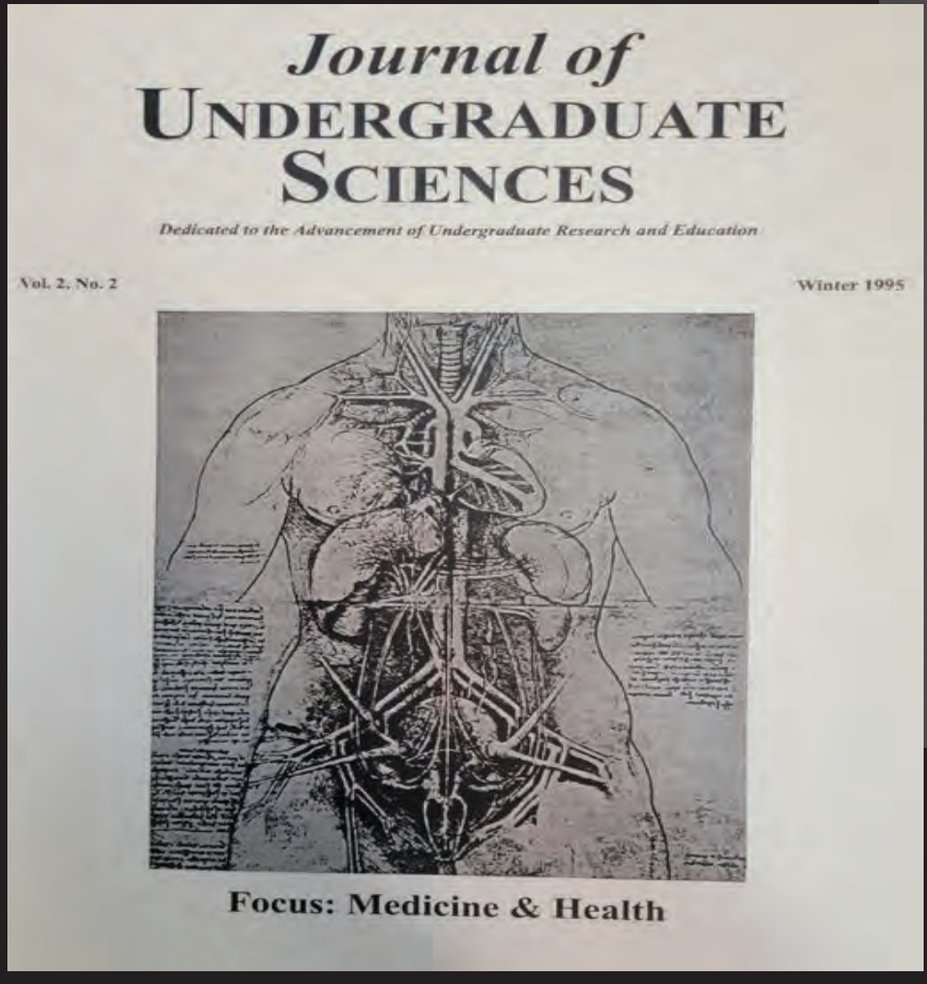
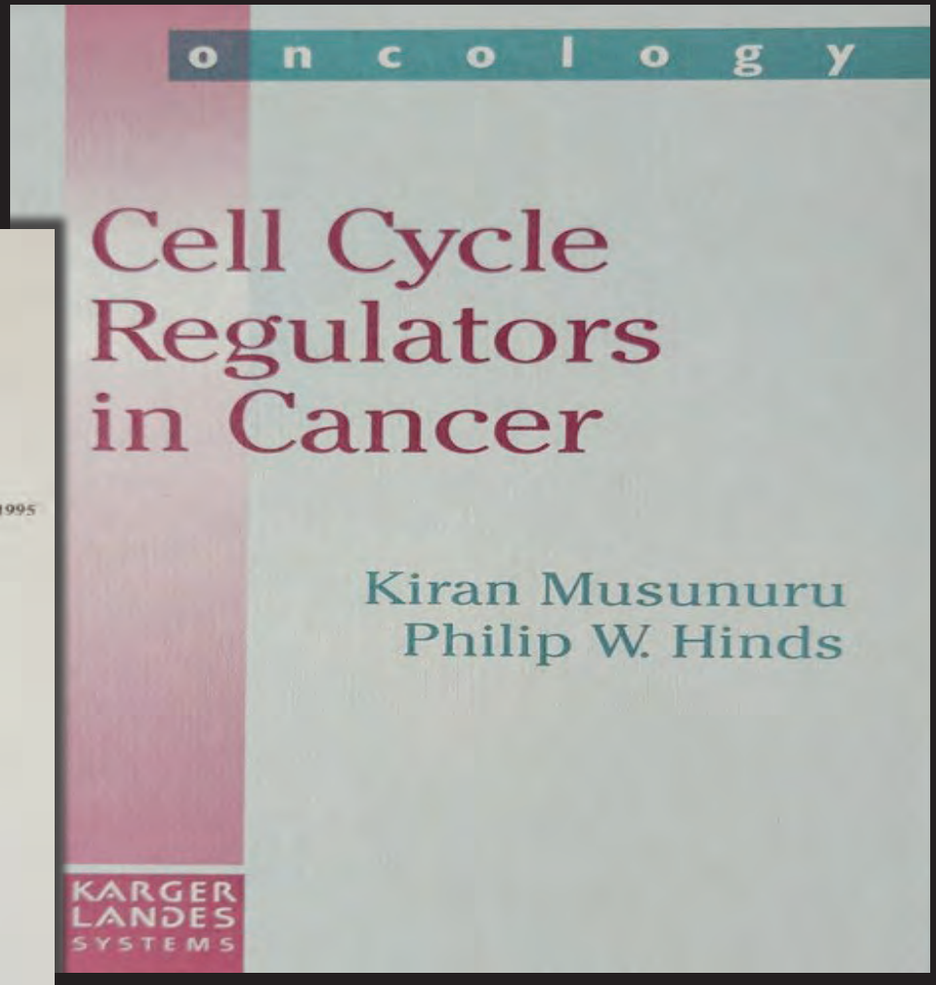
Performer

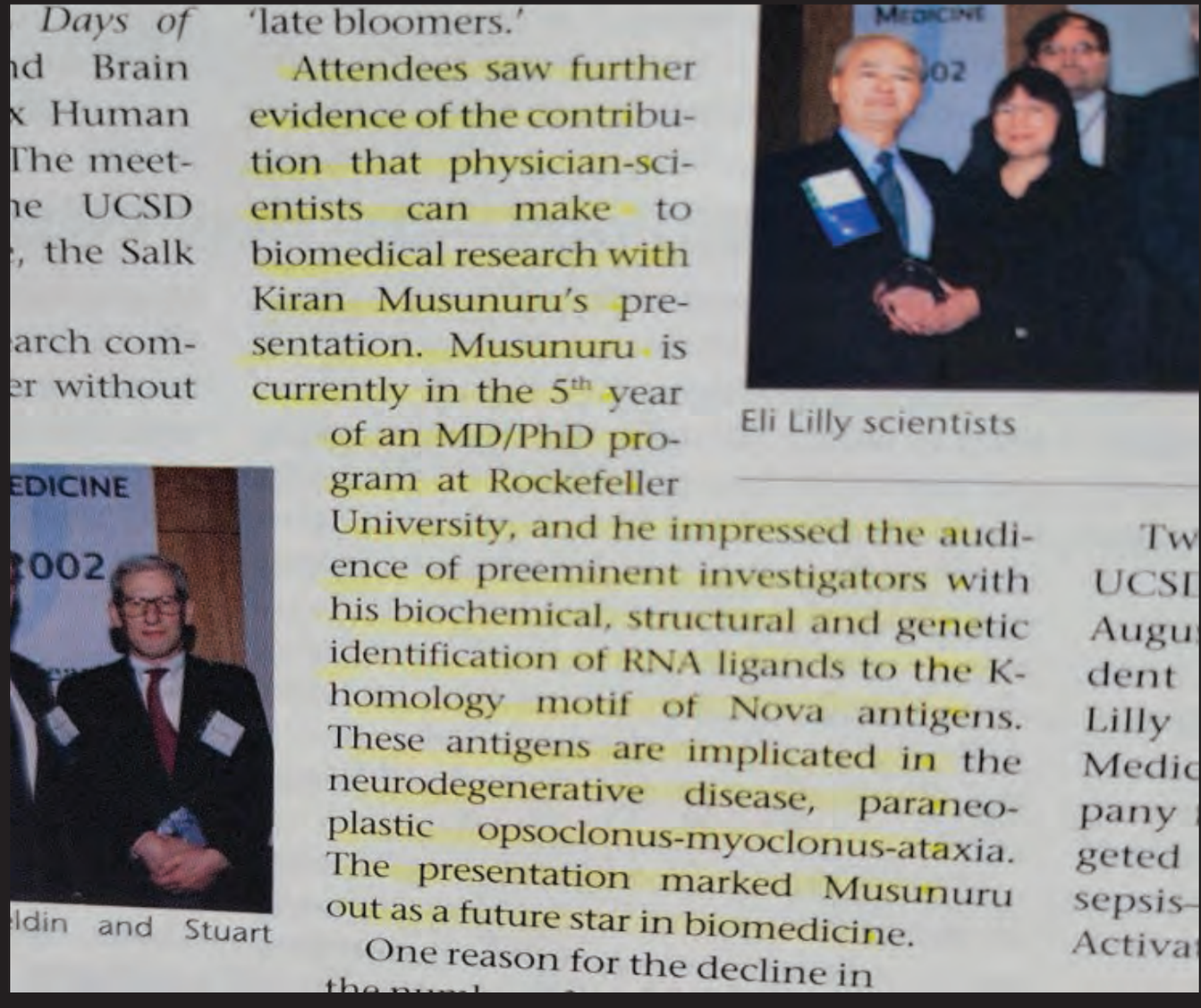
College graduation at Harvard with dad.



Kiran was the founder and first editor of this journal at Harvard while he was an undergraduate.



Kiran was the co-author for this medical book, written at age 20, while he was an undergraduate.



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Attendees saw further evidence of the contribution that physician-scientists can make to biomedical research with Kiran Musunuru's presentation. Musunuru is currently in the 5th year of an MD/PhD program at Rockefeller University, and he impressed the audience of preeminent investigators with his biochemical, structural and genetic identification of RNA ligands to the K-homology motif of Nova antigens. These antigens are implicated in the neurodegenerative disease, paraneoplastic opsoclonus-myoclonus-ataxia. The presentation marked Musunuru out as a future star in biomedicine.

One reason for the decline in

Eli Lilly scientists

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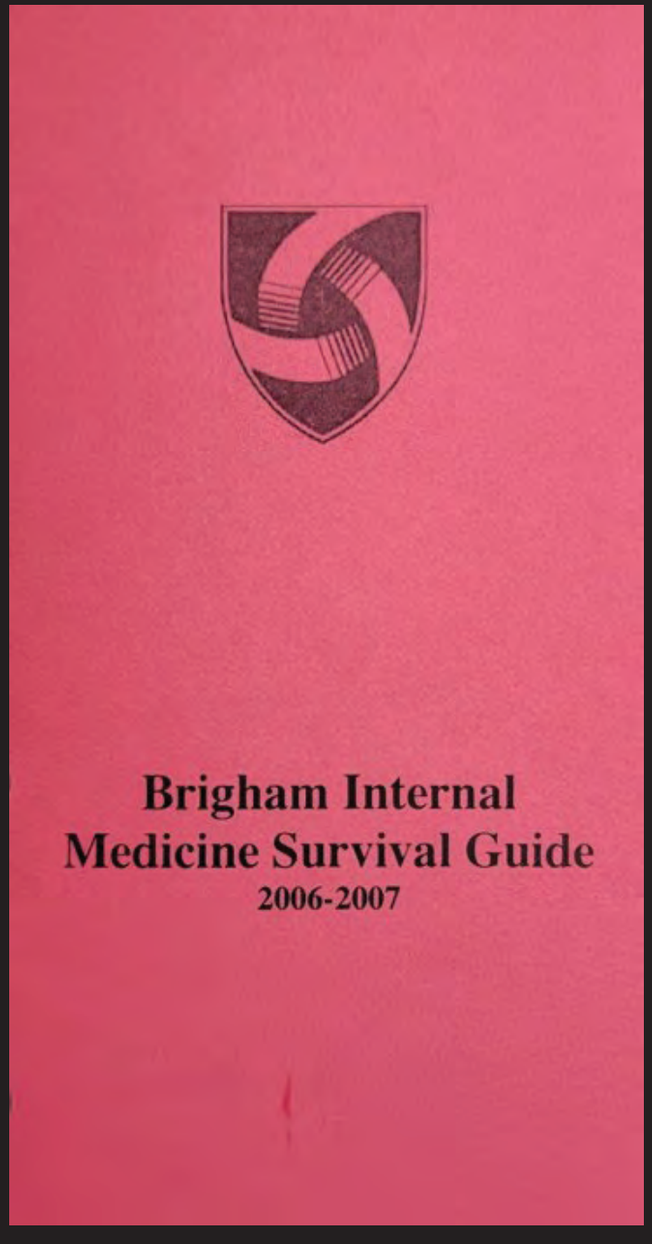
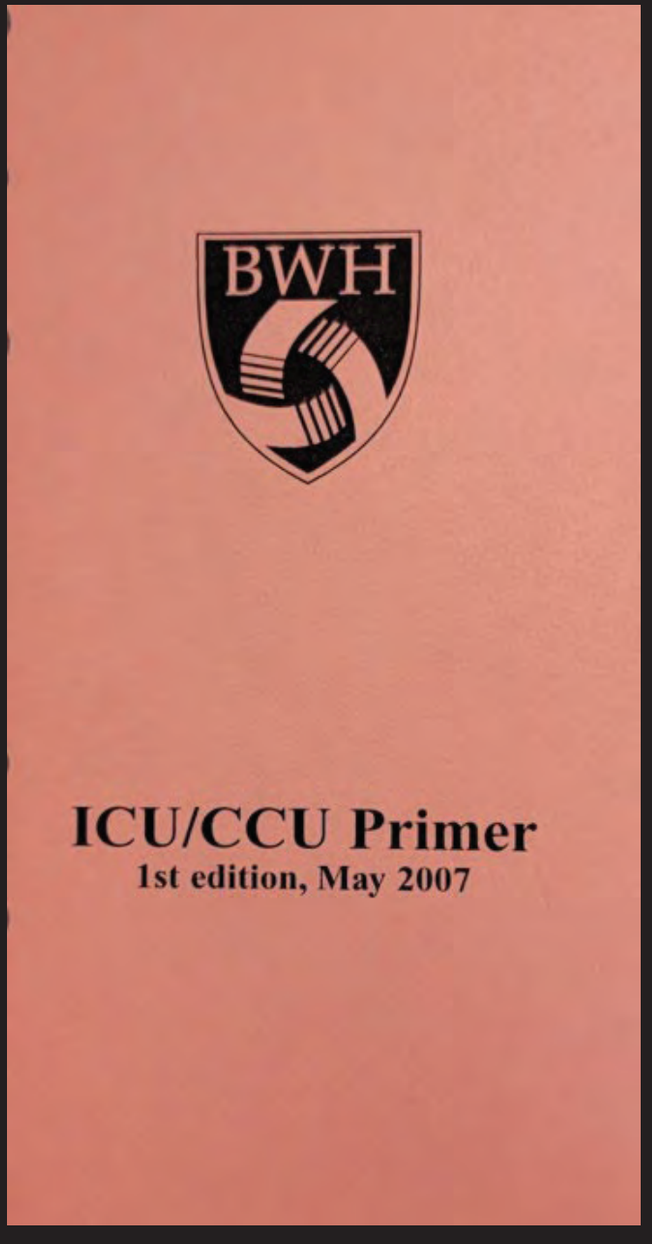
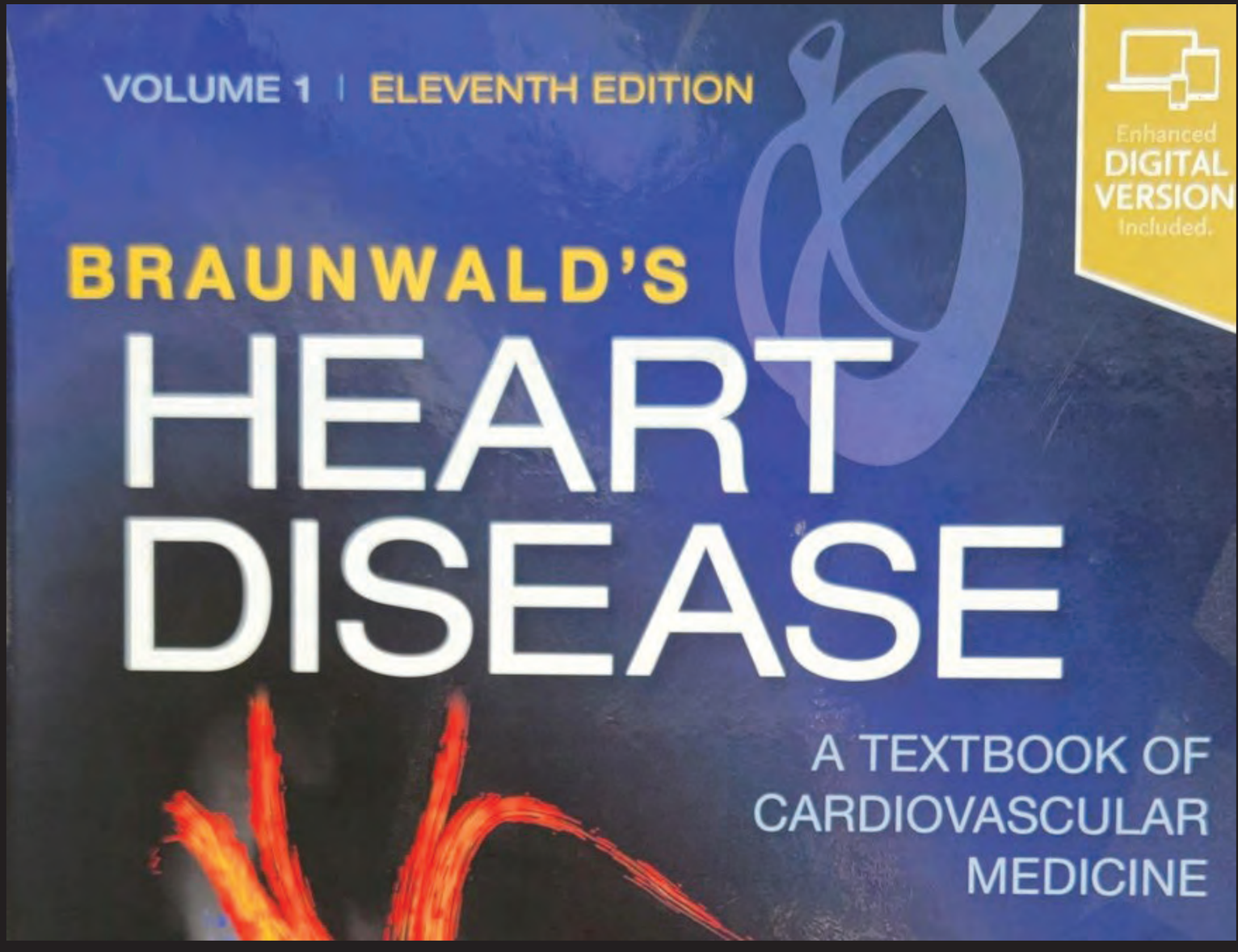
Kiran was described as a "future star" in bio-medicine during his M.D./Ph.D. program.

Primer written for colleagues by Kiran as a first-year resident at Harvard.





Primer written for fellows by Kiran as a second-year resident at Harvard.



Kiran wrote three chapters in this textbook of cardiovascular medicine.

INNOVATION NEEDS RESPONSIBILITY

In January 2009, I wrote a guest column in the *Tampa Tribune* titled "Unraveling Genome Has Great Potential, But We Are Not There Quite Yet."

Little did I know then that, by 2015, we would be there!

We have known for a long time that in humans, life is transmitted through 23 pairs of chromosomes in each cell, half of each pair contributed by each parent. The chromosomes are made of DNA, which is encoded into various genes.

In 1953, James Watson and Francis Crick unveiled the structure of DNA, cracking the code of life. Decades later, the entire human genome (all of the DNA sequences in a single cell) was mapped, made of billions of nucleotides (the chemical alphabet). The scientists then focused on identifying the tiny portions of the gene that are responsible for various functions and dysfunctions.

For a while, scientists toyed with the idea of altering DNA (the basic units of the gene), finally resulting in genetic engineering with recombinant DNA (cut and paste - cut the nucleotides from the genes of one organism and paste them into the genes of another) to introduce desired traits.

For example, by altering the genes of bacteria, large quantities of hormones (insulin, for instance), antibiotics and clot-busting medications were manufactured for human medical treatment, saving millions of lives. Similar benefits were achieved from transgenic animals.

For the past couple of decades, the technique was also used to produce transgenic crops called GMOs (genetically modified organisms) by splicing genes from one species into a different species to improve productivity and to enrich their quality.

For the past few years, scientists have embarked on the idea of "gene editing," a process that nature does all by itself to protect bacteria from viruses. The scientists observed it, learned from it and duplicated it in animals and humans.

When a bacterium is invaded by a virus, it keeps a genetic record of the virus in memory and when re-invaded by the same virus, it produces a powerful enzyme that effectively snips the virus out (a molecular scissor). Scientists named the process "CRISPER" and the enzyme "Cas9."

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This process of gene editing, which can be done on any living organism, has enormous potential in infinite ways to improve on nature. The applications can range from cancer research to curing diseases, production of vaccines to eliminating mosquito-borne illnesses, production of fuel and electricity to disposal of plastic and production of super crops to save endangered species.

This new genome-editing technique (deleting, altering or rearranging DNA) is precise, relatively quick and easy, and inexpensive. A CRISPER kit can be commercially bought for $130.

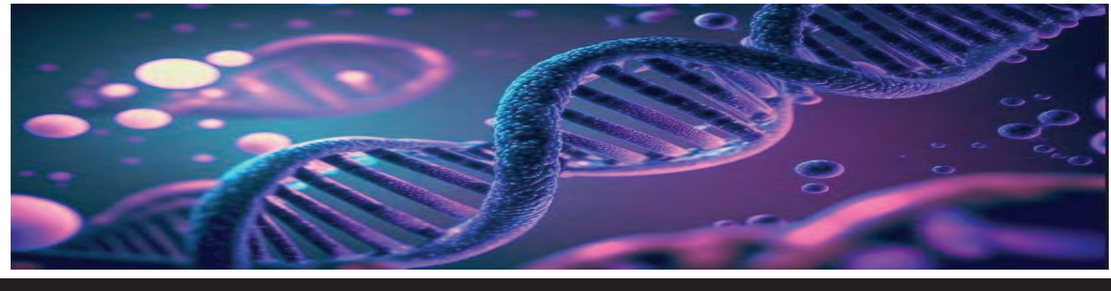
The story is all rosy, until one thinks of using this technique to edit germ-line cells (sperm, egg, embryo). The resulting change can be passed on to future generations forever. What might be the long-term unintended consequences of altering the genes permanently? A rogue scientist could go beyond the ethical, moral and legal limitations, producing designer babies, superior humans and super bugs.

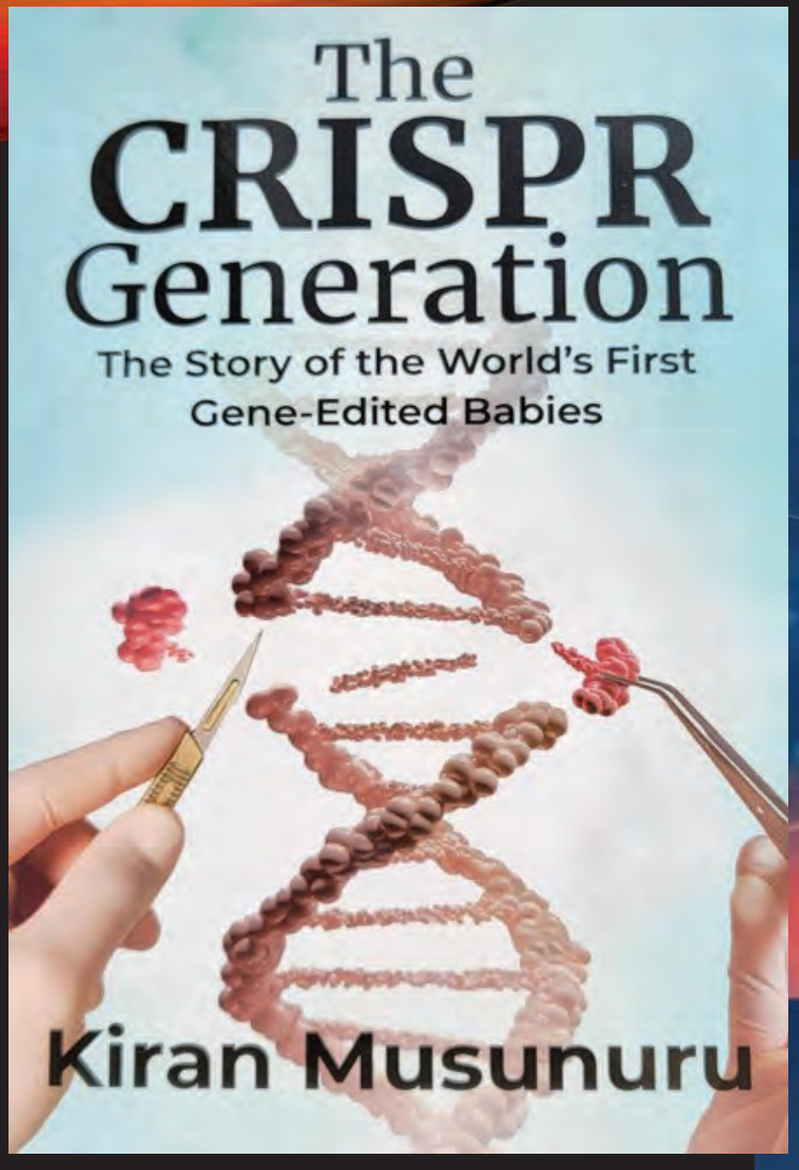
Are we trying to play God? I wouldn't even venture to go there in this column. However, I cannot help but wonder why the creator is empowering humans with super-intelligence to decode all the secrets of creation and the means to alter it in no small measure. What is the creator's ultimate plan? Only God knows.

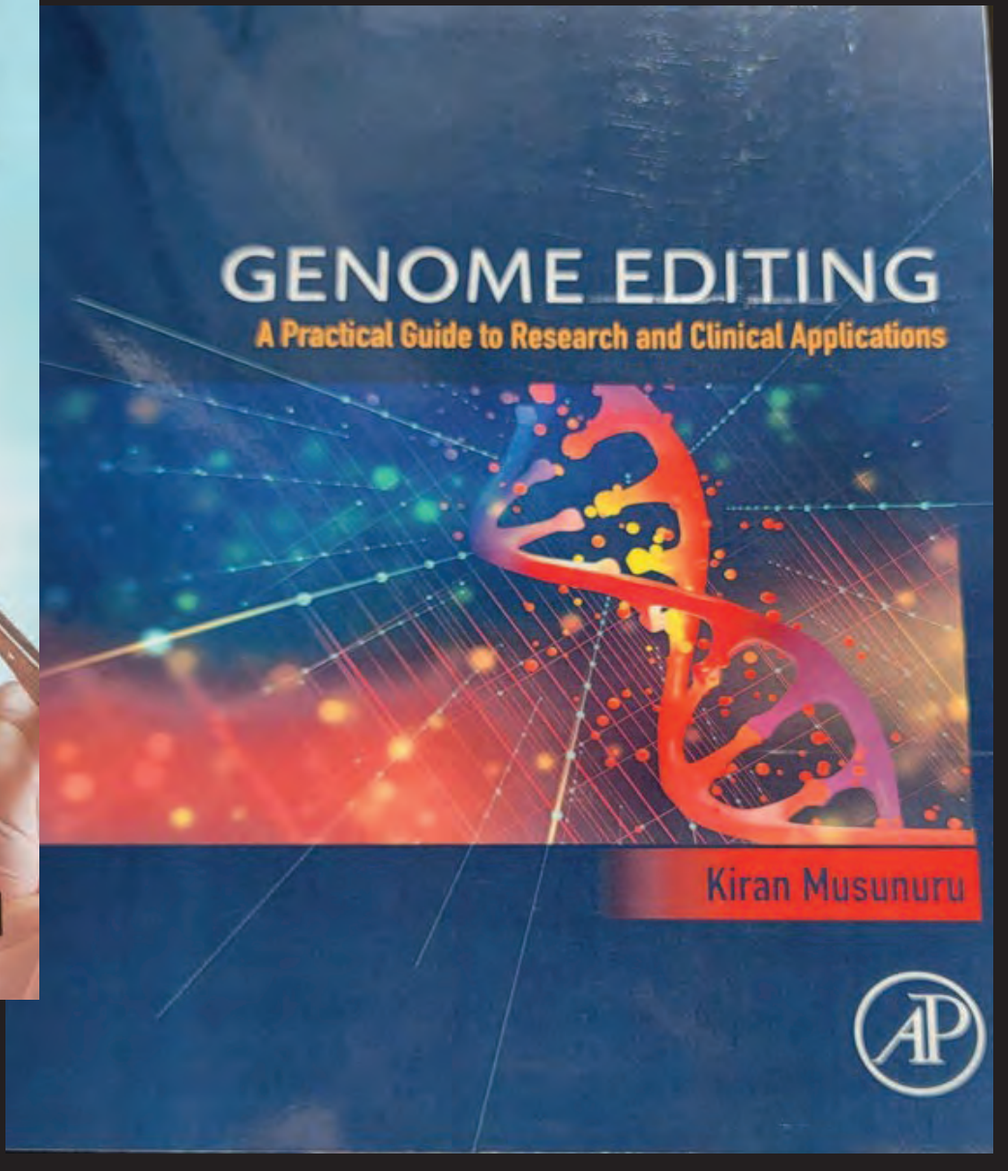
But the genie is out of the bottle, and gene editing is here to stay. This technology is one of the biggest things since nuclear energy. We can only hope that it will be put to good use.

Guest Column, Published Tampa Bay Times, September 23, 2016.

P.S. My son Kiran Musunuru, a nationally and internationally celebrated cardiologist from Harvard and University of Pennsylvania, is currently working with gene-editing techniques to find cures for several diseases that do not have any treatment or cure at this time.







More books written by Dr. Kiran Musunuru

Indeed, not too far in the future, the standard of cardiovascular care may look quite different from current practices. Patients would undergo whole-genome sequencing at birth, thereby allowing so-called primordial prevention by assessing the genetic determinants of an individual's lifetime risk for cardiovascular disease and institution of appropriate counseling—starting with lifelong exercise and dietary habits and, as the patient advances in age, individually tailored preventive medications and therapies that address all the individual's various validated, causal genetic risk factors for disease. If cardiovascular disease should nevertheless emerge at some point in the patient's life, he or she would receive the specific therapies that have been demonstrated to be most efficacious and safest for individuals with that genetic profile, both in the acute setting and in the long term for secondary prevention. This standard of care would represent an important step toward ensuring that people everywhere enjoy longer lives free of cardiovascular disease.

Kiran's remarks from Braunwald's textbook of cardiology.

Kiran Musunuru-Wikipedia

Kiran Musunuru is an American cardiologist who is a Professor of Medicine at the University of Pennsylvania Perelman School of Medicine. He researches the genetics and genomics of cardiovascular and metabolic diseases. Musunuru is a leading expert in the field of gene-editing.

Early life and education

Musunuru is the son of Rao and Prameela Musunuru; he was born in New York City and grew up in Florida. His father is a renowned cardiologist who moved to the US from India in 1976.

Musunuru obtained a degree in Biochemical Sciences from Harvard College in 1997. He later obtained a PhD in Biomedical Sciences from Rockefeller University in 2003, and an MD from Weill-Cornell Medical College in 2004. Musunuru also graduated with a Masters of Public Health (MPH) in Epidemiology from the Johns Hopkins Bloomberg School of Public Health in 2009, and an ML in Law from the University of Pennsylvania Law School in 2019.

Musunuru was interested in heart disease early in his medical career, first training in Internal Medicine at Brigham and Women's Hospital and then in Cardiovascular Medicine at Johns Hopkins Hospital. He also undertook postdoctoral work at the Massachusetts General Hospital, as well as the Broad Institute.

Research and career, Awards and honors, References- see-
https://en.wikipedia.org/wiki/Kiran_Musunuru


TIME 100 TALKS
PRESENTING PARTNER
American Heart Association.
100 YEARS
Bold Hearts

‘80% of Cardiovascular Disease Is Preventable’: Health Experts Reimagine Heart Care

BY **CHANTELLE LEE** JUNE 25, 2024

More than 184 million people—about 61% of U.S. adults—are likely to have some type of cardiovascular disease by 2050, the American Heart Association (AHA) reported earlier this month. That will lead to a tripling in the costs related to heart disease. It’s a statistic that TIME senior health correspondent Alice Park cited to begin her discussion about the future of healthcare with AHA CEO Nancy Brown; cardiologist Kiran Musunuru; and Andres Acosta, associate professor of medicine at Mayo Clinic, for a TIME100 Health panel in New York on Tuesday.

The event was sponsored by AHA and is part of the TIME100 Talks series. The TIME100 Health list includes the most influential people in the health industry around the world.

Heart disease has been the leading killer of Americans since 1950. Brown, who has been CEO of the AHA since 2008, said

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the number of people in the U.S. living with the risk of heart disease—and the resulting cost—is "staggering." Part of the issue, she said, is the lack of equal access to healthcare and to social determinants of health, such as healthy food and a living wage. But another issue is the way the U.S. healthcare system approaches these types of medical conditions.

"I think that this country focuses a lot on treating conditions," Brown said. "But we're not focusing enough on prevention and helping people earlier in their lives understand the power of things that make a difference in their life. You know, 80% of cardiovascular disease is preventable."

Musunuru, a professor of cardiovascular medicine and genetics in the Perelman School of Medicine at the University of Pennsylvania, said cardiovascular disease can be attributed to about half genetics and about half environment or lifestyle. There are ways to reduce risk factors for developing cardiovascular disease, such as cholesterol levels, blood pressure, and even obesity. The challenge, he said, is that these risk factors develop over time. And the country's current healthcare system attempts to cope with

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chronic disease with chronic treatment. While there can be merits to that approach, Musunuru said, it also puts "an outsized burden" on patients.

He suggested the healthcare system shift its focus to preventing chronic diseases, starting at an early age—like we do with vaccines to prevent infectious diseases.

"You're not going to eliminate heart disease, but can you push off heart attack and stroke by decades?" Musunuru said. "Instead of suffering a bad heart attack at age 60, maybe dying from it, it happens at age 100 and you enjoy 40 years of life you might not have otherwise had."

Acosta, who codirects the Nutrition Obesity Research Program and directs the Precision Medicine for Obesity Program at Mayo Clinic, discussed how some treatments can also help with reducing the risk of other diseases. Obesity, for instance, is one of the major risk factors for heart disease, and weight loss drugs like Wegovy and Zepbound are having a significant impact on treating it. AHA previously reported that people taking Wegovy decreased their risk of heart attack, stroke, or death from cardiovascular issues by

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20%, compared to those taking a placebo. Acosta said this data was a “game changer” and marked a “new era” in the management of obesity and cardiovascular disease.

The panelists also highlighted the importance of genetic testing. Few people have their genetics tested, Brown said, and a priority for the AHA is encouraging people to do so.

Musunuru researches the genetics of heart disease and aims to identify genetic factors that protect against disease. Having genetic information, he said, can help medical practitioners know early on what patients’ risks are for developing certain diseases and can allow patients to take a “proactive” approach to their health.

“Your genes are the same on the day you’re born as the day you die,” Musunuru said. “If you know what’s in your genes at the time you’re born, that gives you a forecast of what your life will look like as it unfolds.”

TIME100 Talks: Reimagining the Future of Healthcare was presented by the American Heart Association.

AMERICAN KAHANI

COMMUNITY, LEAD STORIES

The Gene Editor-in-Chief: Dr. Kiran Musunuru's Race to Save a Baby With a Rare Genetic Disorder Affecting One in a Million

May 16, 2025

The Indian American researcher's race against time is said to stand as a testament to what becomes possible when scientific innovation meets human compassion.

In the predawn hours of a February morning in 2025, Dr. Kiran Musunuru stood anxiously in a hospital room at Children's Hospital of Philadelphia. Before him lay six-month-old KJ Muldoon, sleeping peacefully in the same crib that had been his home since birth. As a clear liquid flowed through an IV into the infant's tiny veins, Dr. Musunuru felt a conflicting surge of emotions.

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"I was both excited and terrified," recalls Dr. Musunuru, the Barry J. Gertz Professor for Translational Research at the University of Pennsylvania's Perelman School of Medicine.

What KJ received that morning was unlike any treatment given to a patient before — a personalized gene-editing therapy created specifically to correct the single DNA letter in his genetic code that had caused a rare, life-threatening condition. That infusion would make medical history and potentially open the door to treating thousands of other genetic diseases that have long been considered untreatable.

The Midnight Email

The story began on August 8, 2024, when Dr. Musunuru received an urgent email from Dr. Rebecca Ahrens-Nicklas at Children's Hospital of Philadelphia. A newborn boy had been diagnosed with CPS1 deficiency, a rare genetic disorder affecting just one in 1.3 million babies.

CPS1 deficiency prevents the body from properly processing ammonia, a toxic byproduct of protein metabolism. If left untreated, the condition can cause severe brain damage or death. Half of all babies with the disorder die within their first week of life. In her email, Dr. Ahrens-Nicklas's asked if Dr. Musunuru can save the baby's life considering that most babies don't survive unless they get liver transplant at 3 years of age.

"At this point, the clock starts in my mind," Dr. Musunuru said, as reported by The New York Times. "This is real life. This is not hypothetical."

For the Muldoon family — parents Kyle and Nicole — the diagnosis was devastating. Doctors initially offered "comfort care," acknowledging the grim prognosis. But the Muldoons decided to give their son a fighting chance.

For the Muldoon family — parents Kyle and Nicole — the diagnosis was devastating. Doctors initially offered "comfort care," acknowledging the grim prognosis. But the Muldoons decided to give their son a fighting chance.

Dr. Musunuru wasn't a newcomer to the field of gene editing. As the Barry J. Gertz Professor for Translational Research in Penn's Perelman School of Medicine, he had dedicated years to studying how gene editing could be used to treat genetic conditions. He is also a professor of Cardiology, Professor of Genetics and professor of Pediatrics at University of Pennsylvania school of medicine. Incidentally, Dr. Musunuru has designed gene therapy for the enzyme PCSK9 that decreases high cholesterol that is undergoing stage 2 clinical trials. If approved it will change the treatment of coronary heart disease. It's like vaccine for heart attacks.

According to the Penn Medicine report, Dr. Musunuru and Dr. Ahrens-Nicklas had been collaborating since 2023 to study the feasibility of creating customized gene editing therapies for individual patients. Both are members of the NIH-funded Somatic Cell Genome Editing Consortium, which supports collaborative genome editing research.

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Their focus had been on urea cycle disorders — precisely the category of disease affecting baby KJ. But developing a personalized treatment would typically take years, time the infant simply didn't have.

"Developing a gene editor to treat patients is a deliberate process that can take years," noted the New York Times report. "But KJ did not have years to wait — perhaps as few as six months before a mounting risk of severe brain damage or death."

The Race Against Time

What followed was an unprecedented scientific sprint. Dr. Musunuru assembled a team that included Dr. Fyodor Urnov at the University of California, Berkeley, and reached out to Danaher Corporation and other biotechnology companies to help produce the treatment.

Their approach used a refined CRISPR technique called "base editing," which precisely changes a single letter in the DNA sequence without cutting the DNA strand. This method, invented in David Liu's Harvard laboratory, reduces the risk of unintended genetic modifications.

The team worked around the clock. In Berkeley, as Dr. Urnov told The New York Times, "scientists burned a vat of midnight oil on this the size of San Francisco Bay." He added, "such speed to producing a clinic-grade CRISPR for a genetic disease has no precedent in our field. Not even close."

Dr. Liu himself described the timeline as "astounding."

"These steps traditionally take the better part of a decade, if not longer," he said.

Within just six months — lightning speed in the world of medical development — Musunuru's team had designed, tested, and manufactured a treatment ready for human use. The FDA expedited the regulatory approval process, recognizing the urgency of KJ's condition.

The Breakthrough

On February 25, 2025, KJ received his first infusion of the experimental therapy, followed by additional doses in March and April. The results were remarkable. Within two weeks of the first treatment, KJ was able to eat normal amounts of protein — something that would have been dangerous before. When he contracted typical childhood illnesses, which would normally have caused dangerous spikes in ammonia levels, he "sailed through them," according to Dr. Ahrens-Nicklas.

Now 9½ months old, KJ is growing well and meeting developmental milestones. His weight has increased from the 7th percentile to the 40th percentile for his age. While he still requires some medication, the dosage has been greatly reduced, and his doctors are preparing to discharge him from the hospital — allowing him to go home with his family for the first time in his life.

"We've been in the thick of this since KJ was born, and our whole world's been revolving around this little guy and his stay in the hospital," his father, Kyle Muldoon, told Penn Medicine News. "We're so excited to be able to finally be together at home so that KJ can be with his siblings, and we can finally take a deep breath."

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Beyond One Patient

For Dr. Musunuru, saving KJ's life is just the beginning. The implications of this treatment extend far beyond one rare disorder.

"We want each and every patient to have the potential to experience the same results we saw in this first patient," Dr. Musunuru explained to Penn Medicine News. "And we hope that other academic investigators will replicate this method for many rare diseases and give many patients a fair shot at living a healthy life."

More than 30 million Americans suffer from one of over 7,000 rare genetic diseases. Many of these conditions are so uncommon that pharmaceutical companies have little financial incentive to develop treatments. But the approach used for KJ — essentially creating a molecular GPS that can be reprogrammed to target different genetic mutations — offers a template that could be adapted for countless other conditions.

The cost of development, while significant, was comparable to that of a liver transplant — the standard treatment for CPS1 deficiency in older children. As the process becomes more refined, Musunuru believes costs will decrease further.

"As we get better and better at making these therapies and shorten the time frame even more, economies of scale will kick in and I would expect the costs to come down," he told ABC News.

The Future of Personalized Medicine

The breakthrough represents what Dr. Peter Marks, who recently resigned from his position overseeing gene-therapy regulation at the FDA, called "one of the most potentially transformational technologies out there."

The methodology could eventually be applied to more common genetic disorders like sickle cell disease, cystic fibrosis, Huntington's disease, and muscular dystrophy.

"The promise of gene therapy that we've heard about for decades is coming to fruition," Dr. Musunuru said, "and it's going to utterly transform the way we approach medicine."

For the Muldoon family, the significance is measured in simpler terms — in milestones met and moments shared.

"Any time we see even the smallest milestone that he's meeting – like a little wave or rolling over – that's a big moment for us," Nicole Muldoon told ABC News.

As KJ prepares to leave the hospital and experience the world beyond his crib for the first time, Dr. Musunuru's race against time stands as a testament to what becomes possible when scientific innovation meets human compassion — and a reminder that behind every medical breakthrough are the very real lives hanging in the balance.

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BRIEF REPORT

Patient-Specific In Vivo Gene Editing to Treat a Rare Genetic Disease

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SUMMARY

Base editors can correct disease-causing genetic variants. After a neonate had received a diagnosis of severe carbamoyl-phosphate synthetase 1 deficiency, a disease with an estimated 50% mortality in early infancy, we immediately began to develop a customized lipid nanoparticle–delivered base-editing therapy. After regulatory approval had been obtained for the therapy, the patient received two infusions at approximately 7 and 8 months of age. In the 7 weeks after the initial infusion, the patient was able to receive an increased amount of dietary protein and a reduced dose of a nitrogen-scavenger medication to half the starting dose, without unacceptable adverse events and despite viral illnesses. No serious adverse events occurred. Longer follow-up is warranted to assess safety and efficacy. (Funded by the National Institutes of Health and others.)

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PROGRAMMABLE GENE-EDITING TECHNOLOGY BASED ON CLUSTERED regularly interspaced short palindromic repeats (CRISPR)–CRISPR-associated protein 9 (Cas9)[1] has matured into therapeutic approaches that are improving the lives of patients with various diseases, such as sickle cell disease, β-thalassemia, and hereditary angioedema.[2-4] Precise, corrective CRISPR-Cas9 technology — namely, base editing (which can effect cytosine-to-thymine changes [cytosine base editing[5]] or adenine-to-guanine changes [adenine base editing[6]]) and prime editing[7] (which can produce any single-nucleotide change or small insertion or deletion) — can potentially address more than 90% of pathogenic variants in genetic diseases that, although rare individually, collectively affect hundreds of millions of people worldwide.[8] However, drug-development efforts have largely focused on recurrent variants in a few relatively common genetic diseases on account of the extensive resources needed to develop and bring to market any given therapy.[9]

We developed a workflow for the rapid development of customized, corrective gene-editing therapies for patients with ultrarare or unique "N-of-1" variants (Fig. 1). More specifically, we developed a base-editing therapy, delivered in vivo to hepatocytes through lipid nanoparticles, for a single patient who at birth received

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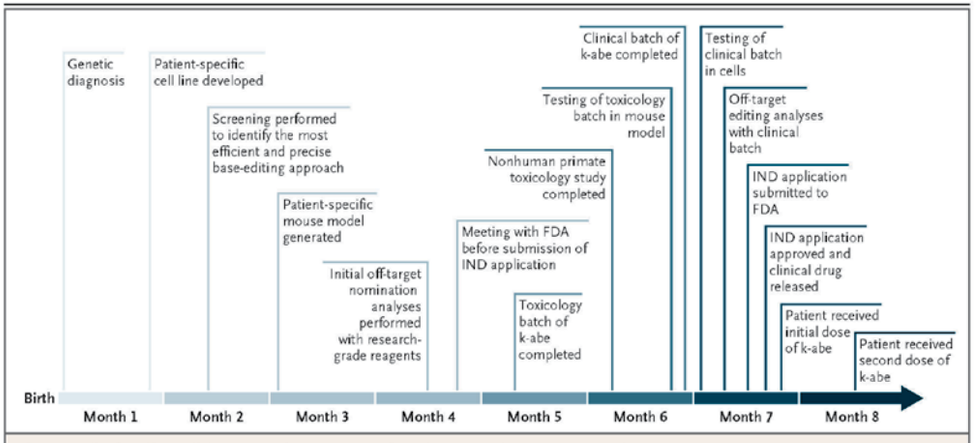

Figure 1. Timeline from Birth to Second Treatment with Kayjayguran Abengcemeran (K-abe).
FDA denotes Food and Drug Administration, and IND Investigational New Drug.

a diagnosis of neonatal-onset carbamoyl-phosphate synthetase 1 (CPS1) deficiency, an ultrarare inborn error of metabolism affecting the urea cycle. CPS1 deficiency affects 1 in 1,300,000 persons[10] and has an estimated mortality of 50% in early infancy.[11] Liver transplantation provides a functional urea cycle and improves outcomes.[12,13] However, hyperammonemic crises and irreversible neurologic injury often occur in infants before they grow large enough to undergo transplantation.[14-16] We administered the customized therapy to our patient twice, at approximately 7 and 8 months of age, with the goal of providing protection against hyperammonemia.

METHODS

STUDIES FOR INVESTIGATIONAL NEW DRUG APPLICATION

Full descriptions of cellular studies, studies in animals, and off-target assessments are provided in the Supplementary Appendix 1, available with the full text of this article at NEJM.org. The institutional animal care and use committee at the University of Pennsylvania and at AmplifyBio approved the studies in mice and nonhuman primates, respectively. Genome-sequencing data from the patient and blood-derived genomic DNA samples from the patient's father were obtained under a human subjects research protocol that was approved by the institutional review board at the University of California, Berkeley.

CLINICAL STUDY

Because the therapy (kayjayguran abengcemeran, or k-abe) was administered as part of clinical care under a single-patient expanded-access Investigational New Drug application, the clinical protocol was reviewed by the institutional review board at Children's Hospital of Philadelphia (CHOP) through alternative procedures. After the initial regulatory review by the Food and Drug Administration (FDA), we received authorization from the FDA to obtain concurrence by the CHOP chairperson of the institutional review board, who then reviewed and approved the study. The patient's parents provided written informed consent. Clinical activities were overseen by a multidisciplinary oversight committee comprising physicians from the CHOP metabolism, hepatology, immunology, gene therapy, and medical ethics services. The investigators vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol, available at NEJM.org.

RESULTS

CLINICAL PRESENTATION

Symptoms of CPS1 deficiency, including lethargy and respiratory distress, developed in the patient

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(a male neonate) within the first 48 hours of life. Measurement of blood ammonia revealed a level greater than 1000 μmol per liter (1703 μg per deciliter; reference range, 9 to 33 μmol per liter [15 to 56 μg per deciliter]). Continuous renal-replacement therapy was initiated promptly. Plasma amino acid profiling revealed a critically elevated level of glutamine, undetectable citrulline, and a normal level of urinary orotic acid, findings suggestive of a proximal urea-cycle defect. Rapid targeted analysis of the patient's genome identified two truncating *CPS1* variants: c.1003C→T (p.Gln335Ter, referred to as Q335X, on the paternal allele) and c.2140G→T (p.Glu714Ter, referred to as E714X, on the maternal allele). The Q335X variant is absent in the Genome Aggregation Database but has been reported in a case of neonatal-onset CPS1 deficiency.[17]

The patient was weaned from continuous renal-replacement therapy and transitioned to long-term therapy that included nitrogen-scavenger medication (glycerol phenylbutyrate), citrulline supplementation (at a dose of 200 mg per kilogram of body weight per day, which remained unchanged throughout his clinical course), and a protein-restricted diet (given as a 1:1 mix of natural protein and essential amino acid formula). The patient had the expected infantile "honeymoon" period[14] from days 50 to 100, after which his biochemical status worsened, leading to a further reduction in protein intake and an increase in the dose of glycerol phenylbutyrate to manage the elevated ammonia and glutamine levels. Each hyperammonemic episode incurred a risk of permanent neurologic damage and death. Given the severity of his disease, the patient was listed for liver transplantation at 5 months of age.

PATIENT-SPECIFIC CUSTOMIZATION OF BASE-EDITING THERAPY

Reliable assessment of base editing of the *CPS1* Q335X variant would ideally use human hepatocytes with the variant; however, human hepatocytes were not available. Therefore, we used the cultured human HuH-7 cell line as a proxy. We synthesized a cassette harboring a 100-bp human genomic segment spanning the *CPS1* Q335X variant, as well as 100-bp segments spanning the patient's other *CPS1* variant and two reference variants in *PAH* to serve as positive controls (Fig. S2A in the Supplementary Appendix 1 [all supplementary figures and tables are available in Supplementary Appendix 1]). We transduced HuH-7 cells with a lentiviral vector containing the cassette, thereby inserting the cassette into the genome. This process was completed 1 month after the patient's birth.

To develop a patient-specific, bespoke gene editor, we screened various adenine base editors (ABEs) with guide RNAs (gRNAs) tiling the site of the Q335X variant in the lentivirus-transduced HuH-7 cells (Fig. S2B, S2C, and S2D and Fig. S3). We identified an ABE with a preference for NGC protospacer-adjacent motifs, termed NGC-ABE8e-V106W, and a gRNA with the target Q335X adenine in the eighth position of its protospacer sequence as the most efficient and precise base-editing approach; although there was bystander editing of neighboring adenines, all such edits were synonymous (Figs. S4 through S7). This process was completed 2 months after the patient's birth. We named the gRNA used in the lipid nanoparticle therapy (Table S1) "kayjayguran," the messenger RNA (mRNA) encoding the ABE (Fig. S1 and Table S2) "abengcemeran," and the therapy "k-abe" (for short).

PRECLINICAL STUDIES

After the initial regulatory review by the FDA, we manufactured a toxicology batch of k-abe (i.e., the batch used for toxicologic testing) and undertook a limited safety study in cynomolgus monkeys to characterize single-dose toxicity of the lipid nanoparticle therapy. A total RNA dose of 1.5 mg per kilogram of body weight was administered intravenously. No clinical signs of toxic effects were present, and there were transient elevations in alanine aminotransferase and aspartate aminotransferase levels to several times the upper limit of the normal range — findings that are consistent with the results of previous studies (Fig. S12).[18,19] Two weeks after treatment, plasma levels of lipid excipients had fallen more than 99.5% from the peak levels, a development that supported readministration of the therapy at intervals greater than 2 weeks (Fig. S13). The results of the study in cynomolgus monkeys (completed 5 months after the patient's birth) indicated that a dose of 0.1 mg per kilogram was a potentially safe initial clinical dose for the patient.

On learning of the patient's genetic diagnosis, we immediately started generating mouse models to assess the in vivo editing efficiency of k-abe. To maximize the chance of success, we used estab-

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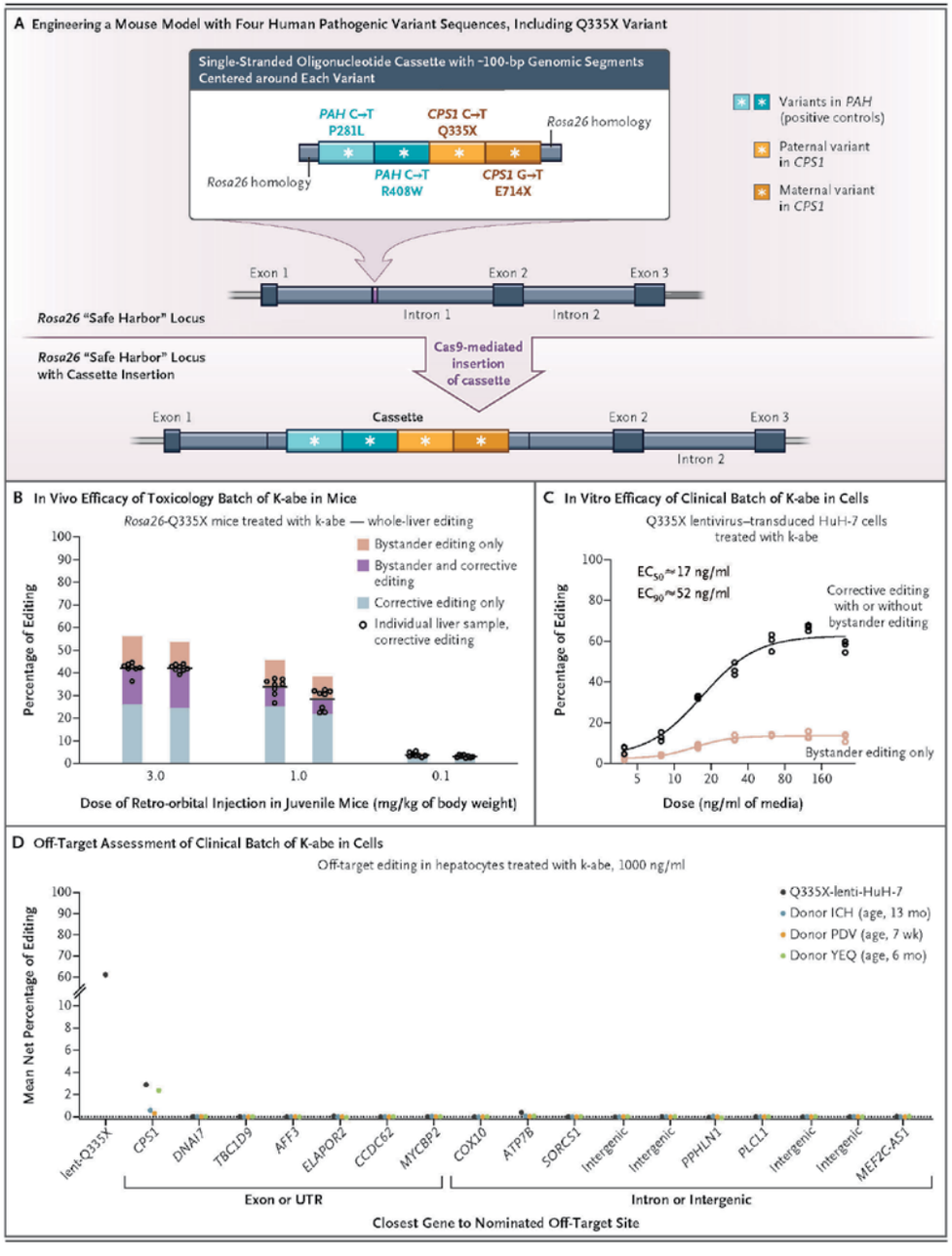

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Figure 2 (facing page). Preclinical Studies.
Panel A shows the contents of the single-stranded DNA oligonucleotide cassette inserted into the endogenous mouse *Rosa26* locus in mouse zygotes. Panel B shows the extent of whole-liver corrective adenine base editing of the *CPS1* Q335X variant in *Rosa26*-Q335X mice. Several days after administration of a single dose of k-abe from the toxicology batch, we obtained multiple samples distributed throughout the liver of each juvenile mouse on necropsy. We assessed the extent of editing in eight samples per mouse by sequencing the *Rosa26*-Q335X cassette. The two bars at each dose level (3.0, 1.0, and 0.1 mg per kilogram of body weight) represent two mice. Across the three dose groups, no more than 1% insertional or deletional mutagenesis occurred at the target site. Panel C shows corrective adenine base editing of the *CPS1* Q335X variant in lentivirus-transduced HuH-7 cells treated with k-abe. Editing was determined 3 days after treatment at the stated dose (concentration after dilution with cell medium). The best-fit agonist response curve with variable slope (four-parameter logistic regression) and 50% effective concentration (EC_{50}) and 90% effective concentration (EC_{90}) values were calculated with GraphPad Prism. Panel D shows the evaluation of a high-priority subset of nominated off-target sites for any adenine-to-guanine editing through individual-site targeted amplicon sequencing in the Q335X lentivirus–transduced HuH-7 cells (Q335X-lenti-HuH-7) and in primary human hepatocytes from three male donors (donor ICH [13 months of age], donor PDV [7 weeks of age], and donor YEQ [6 months of age]) after treatment with k-abe at 1000 ng per milliliter of media, as compared with untreated cells. Of 21 high-priority nominated off-target sites, 16 were successfully sequenced and shown here. Cas9 denotes clustered regularly interspaced short palindromic repeats–associated protein 9, and UTR untranslated region.

lished CRISPR reagents in mouse zygotes to insert a cassette harboring a 100-bp human genomic segment spanning the *CPS1* Q335X variant into the *Rosa26* "safe harbor" locus (the same cassette used for the lentivirus-transduced HuH-7 cells) (Fig. 2A). At 5 months after the patient's birth, we performed a limited dose–response study in which the toxicology batch of k-abe was used in a small number of *Rosa26*-Q335X mice. In this study, we observed up to 42% whole-liver corrective editing, along with the expected synonymous bystander editing (Fig. 2B and Figs. S10 and S11A). Editing was evident at the lowest dose (0.1 mg per kilogram), which further supported that dose as the initial clinical dose for the patient. Subsequent validation of in vivo corrective editing in a second mouse model in which the Q335X variant was introduced into the endogenous mouse *Cps1* locus is described in Figures S9 and S11B.

With the clinical batch of k-abe that was produced 5 months after the patient's birth, we performed a dose–response potency assessment in lentivirus-transduced HuH-7 cells (Fig. 2C and Fig. S8). To assess off-target editing, we performed ONE-seq[18] and CHANGE-seq-BE assays[20] using recombinant NGC-ABE8e-V106W protein and kayjayguran, as well as a modified GUIDE-seq[21] assay using a nuclease version of the editor (Figs. S14 through S18, and see Supplementary Appendix 2), during months 4 and 5. The ONE-seq assay was performed with a synthetic library that had been designed with the patient's genome as the reference genome. The CHANGE-seq-BE assay was performed with genomic DNA obtained from the patient's father, who carried the Q335X variant (we were unable to obtain enough genomic DNA from the patient). We prioritized the on-target *CPS1* site and 21 nominated off-target sites for verification with individual-site targeted amplicon sequencing (Fig. 2D and Tables S3 through S6). We exposed lentivirus-transduced HuH-7 cells and primary human hepatocytes from three donors to a supersaturating dose of k-abe. Low-level synonymous bystander editing was evident at the endogenous wild-type *CPS1* genomic site in all four cell lots, a finding that is consistent with the gRNA (kayjayguran) having a 1-base mismatch to the wild-type sequence (the HuH-7 cells retained endogenous wild-type *CPS1* alleles in addition to the transduced *CPS1* Q335X variant sequence). We observed a low level of off-target editing at an intronic site in *ATP7B* in the HuH-7 cells but not in the three primary human hepatocyte lots. *ATP7B* encodes a copper transporter and was not considered to represent biologic risk because its loss of function has not been linked to carcinogenesis.[22] Subsequent analysis of a larger set of nominated off-target sites detected no off-target editing in the treated primary human hepatocytes (Fig. S19).

TREATMENT OF THE PATIENT

A single-patient, expanded-access Investigational New Drug application was submitted to the FDA when the patient was 6 months of age, which was approved 1 week later. The patient was presumed to have no cross-reactive immunologic material, and out of concern for the potential development

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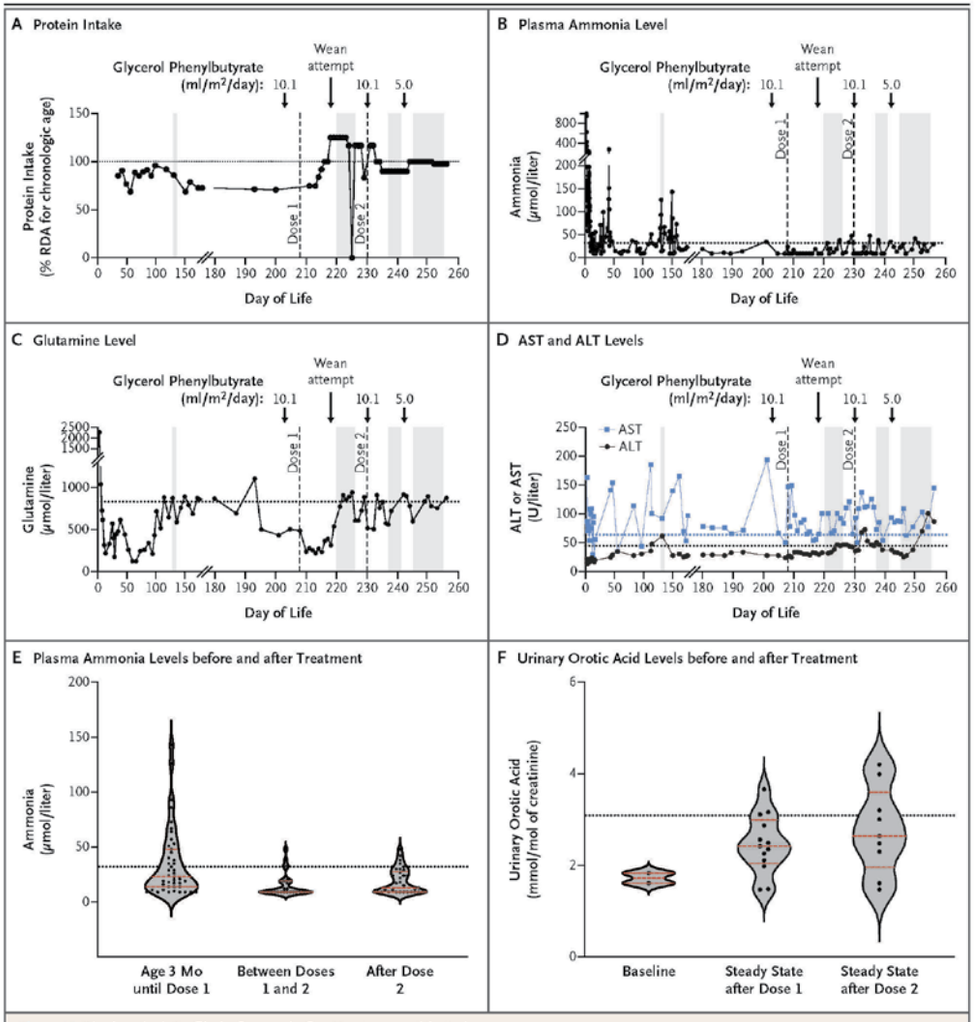

Figure 3. Biochemical Profile before and after Treatment with K-abe.

Shown are the timelines of protein intake (Panel A) and levels of plasma ammonia (Panel B), glutamine (Panel C), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (Panel D). The gray bars from left to right indicate periods of rotavirus-positive gastroenteritis before treatment, rhinovirus-positive upper respiratory tract infection after dose 1, and two viral illnesses after dose 2 (gastroenteritis followed by a new rhinovirus or enterovirus infection with associated viral transaminitis). In Panels B through F, the dotted horizontal lines indicate upper limits of the normal range for the laboratory value. Panels E and F show violin plots of plasma ammonia levels and urinary orotic acid levels, respectively, before and after treatment. Inside the plots, the red dashed line indicates the median, and the red dotted lines indicate the upper and lower quartiles. The clusters of dots indicate the individual data points. To convert the values for ammonia to micrograms per deciliter, divide by 0.5872. To convert the values for glutamine to micrograms per deciliter, divide by 68.42. RDA denotes recommended dietary allowance.

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of an immune response to full-length CPS1 protein, prophylactic immunosuppression with sirolimus and tacrolimus was initiated on days 205 and 209, respectively, after the patient's birth. We selected this steroid-sparing regimen because corticosteroids can trigger hyperammonemia in patients with CPS1 deficiency. On day 208 after birth, the patient received an intravenous infusion of k-abe at a total RNA dose of 0.1 mg per kilogram. After treatment, it was possible to increase his dietary protein intake. Because the patient was born at 35 weeks' gestation, his prescribed protein goal was sometimes above the recommended daily allowance for chronologic age (Fig. 3A). The patient recovered from a viral respiratory infection without the occurrence of an illness-associated hyperammonemic crisis; however, he received intravenous fluids, which is standard during illness, and was on a protein-free diet for 1 day (day 225 after birth). We were unable to wean him from glycerol phenylbutyrate; we had reduced the dose from 10.1 to 8.1 ml per square meter of body-surface area per day but then restored the original dose because of rising glutamine levels.

Given the incomplete biochemical correction in the patient — and according to the clinical protocol — he received a second dose of k-abe (0.3 mg per kilogram) 22 days after receipt of the first k-abe infusion. The patient had a coughing episode during the second infusion that resolved with nasal suctioning. Transient elevations in alanine aminotransferase and aspartate aminotransferase levels occurred a few days after the second k-abe infusion and recurred a few weeks later during the course of viral illness (Fig. 3D). At 2 weeks after the second infusion, the patient was able to receive a reduced dose of glycerol phenylbutyrate to half the starting dose (from 10.1 to 5.0 ml per square meter per day) without unacceptable adverse effects.

During the 4 weeks after the second infusion of k-abe, two viral infections, each with accompanying vomiting and diarrhea, developed in the patient. In contrast to a gastroenteritis infection that had occurred in the patient before the administration of k-abe, he recovered from the viral infections without a hyperammonemic crisis and was able to continue his full-protein diet during the course of his illnesses. The median blood ammonia levels before the first k-abe dose (23 μmol per liter [39 μg per deciliter]; interquartile range, 14 to 48 μmol per liter [24 to 82 μg per deciliter]), between the first and second doses (9 μmol per liter [15 μg per deciliter]; interquartile range, 9 to 19 μmol per liter [15 to 32 μg per deciliter]), and after the second dose (13 μmol per liter [22 μg per deciliter]; interquartile range, 9 to 28 μmol per liter [15 to 48 μg per deciliter]) support the occurrence of a treatment-related reduction (Fig. 3E). CPS1 contributes to orotic acid synthesis, and patients with CPS1 deficiency often have urinary orotic acid levels at the lower end of the normal range (median level in our patient before the first k-abe dose, 1.7 mmol per mole of creatinine; interquartile range, 1.6 to 1.8); after receipt of the two doses of k-abe, the levels in our patient were often at the high end of the normal range (2.4 mmol per mole of creatinine; interquartile range, 2.0 to 3.0) or above the normal range (2.6 mmol per mole of creatinine; interquartile range, 2.0 to 3.6) (Fig. 3F). The patient's weight increased from 7.14 kg (the 9th percentile) at 207 days after birth (before the first dose), to 8.17 kg (the 26th percentile) at 256 days after birth (the end of the 7-week follow-up period), and his neurologic status was stable.

DISCUSSION

In this study, we describe a personalized base-editing therapy wholly developed in the 6-month span after a patient's birth. The patient was able to receive an increased amount of dietary protein and a reduced dose (to half the starting dose) of a nitrogen-scavenger medication, despite the "stress tests" presented by consecutive viral infections. The short follow-up is a limitation of this study; longer follow-up is needed to assess the safety and efficacy of k-abe, as well as the patient's neurologic health. Liver biopsy to assess for corrective *CPS1* editing was deferred because it posed an unacceptable risk to the infant. The potential for germline editing with k-abe could not be evaluated, although a study of a different lipid nanoparticle gene-editing drug did not detect editing in sperm samples from nonhuman primates nor germline transmission of gene edits in female mice to offspring.[19]

An advantage of lipid nanoparticle therapies is the potential for readministration,[23] which is contraindicated with adeno-associated virus–delivered therapies, given the immunogenicity of the vec-

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tor. We opted to start with a very low initial dose of k-abe to evaluate safety, which was followed by a moderately higher second dose. In principle, the patient could receive additional and higher doses of k-abe in the future, if needed.

Therapies similar to k-abe could be developed for hundreds of hepatic inborn errors of metabolism. Similar to antisense oligonucleotide therapy,[24,25] corrective gene editing lends itself to rapid customization for individual patients owing to the platform nature of the technology.[9] Shared components among gene-editing therapies could include the same lipid nanoparticle formulation and mRNA, with the gRNA customized to each patient's variant.

We assessed k-abe for editing efficiency in mice and for safety in nonhuman primates. Such studies might not be necessary for future patient-specific treatments; perhaps cell-based studies would be sufficient. Although k-abe was developed under emergency conditions for a devastating neonatal-onset metabolic disorder, we anticipate that rapid deployment of patient-specific gene-editing therapies will become routine for many genetic diseases.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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REFERENCES

1. Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E. A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. Science 2012;337:816-21.
2. Frangoul H, Locatelli F, Sharma A, et al. Exagamglogene autotemcel for severe sickle cell disease. N Engl J Med 2024;390:1649-62.
3. Locatelli F, Lang P, Wall D, et al. Exagamglogene autotemcel for transfusion-dependent β-thalassemia. N Engl J Med 2024;390:1663-76.
4. Cohn DM, Gurugama P, Magerl M, et al. CRISPR-based therapy for hereditary angioedema. N Engl J Med 2025;392:458-67.
5. Komor AC, Kim YB, Packer MS, Zuris JA, Liu DR. Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage. Nature 2016;533:420-4.
6. Gaudelli NM, Komor AC, Rees HA, et al. Programmable base editing of A•T to G•C in genomic DNA without DNA cleavage. Nature 2017;551:464-71.
7. Anzalone AV, Randolph PB, Davis JR, et al. Search-and-replace genome editing without double-strand breaks or donor DNA. Nature 2019;576:149-57.
8. Nguengang Wakap S, Lambert DM, Olry A, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet 2020;28:165-73.
9. Urnov FD. Give Cas a chance: an actionable path to a platform for CRISPR cures. CRISPR J 2024;7:212-9.
10. Summar ML, Koelker S, Freedenberg D, et al. The incidence of urea cycle disor-

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ders. Mol Genet Metab 2013;110:179-80.
11. Nettesheim S, Kölker S, Karall D, et al. Incidence, disease onset and short-term outcome in urea cycle disorders — cross-border surveillance in Germany, Austria and Switzerland. Orphanet J Rare Dis 2017;12:111.
12. Bates TR, Lewis BD, Burnett JR, et al. Late-onset carbamoyl phosphate synthetase 1 deficiency in an adult cured by liver transplantation. Liver Transpl 2011;17:1481-4.
13. Pritchard AB, Izumi K, Payan-Walters I, Yudkoff M, Rand EB, Bhoj E. Inborn error of metabolism patients after liver transplantation: outcomes of 35 patients over 27 years in one pediatric quaternary hospital. Am J Med Genet A 2022;188:1443-7.
14. Ah Mew N, Krivitzky L, McCarter R, Batshaw M, Tuchman M, Urea Cycle Disorders Consortium of the Rare Diseases Clinical Research Network. Clinical outcomes of neonatal onset proximal versus distal urea cycle disorders do not differ. J Pediatr 2013;162(2):324-9.e1.
15. Choi Y, Oh A, Lee Y, et al. Unfavorable clinical outcomes in patients with carbamoyl phosphate synthetase 1 deficiency. Clin Chim Acta 2022;526:55-61.
16. Posset R, Garbade SF, Gleich F, et al. Severity-adjusted evaluation of liver transplantation on health outcomes in urea cycle disorders. Genet Med 2024;26(4):101039.
17. Kido J, Matsumoto S, Sugawara K, Sawada T, Nakamura K. Variants associated with urea cycle disorders in Japanese patients: nationwide study and literature review. Am J Med Genet A 2021;185:2026-36.
18. Musunuru K, Chadwick AC, Mizoguchi T, et al. In vivo CRISPR base editing of PCSK9 durably lowers cholesterol in primates. Nature 2021;593:429-34.
19. Lee RG, Mazzola AM, Braun MC, et al. Efficacy and safety of an investigational single-course CRISPR base-editing therapy targeting PCSK9 in nonhuman primate and mouse models. Circulation 2023;147:242-53.
20. Lazzarotto CR, Malinin NL, Li Y, et al. CHANGE-seq reveals genetic and epigenetic effects on CRISPR-Cas9 genome-wide activity. Nat Biotechnol 2020;38:1317-27.
21. Tsai SQ, Zheng Z, Nguyen NT, et al. GUIDE-seq enables genome-wide profiling of off-target cleavage by CRISPR-Cas nucleases. Nat Biotechnol 2015;33:187-97.
22. Song L, Nguyen V, Xie J, et al. ATPase copper transporting beta (ATP7B) is a novel target for improving the therapeutic efficacy of docetaxel by disulfiram/copper in human prostate cancer. Mol Cancer Ther 2024;23:854-63.
23. Koeberl D, Schulze A, Sondheimer N, et al. Interim analyses of a first-in-human phase 1/2 mRNA trial for propionic acidaemia. Nature 2024;628:872-7.
24. Kim J, Hu C, Moufawad El Achkar C, et al. Patient-customized oligonucleotide therapy for a rare genetic disease. N Engl J Med 2019;381:1644-52.
25. Kim J, Woo S, de Gusmao CM, et al. A framework for individualized splice-switching oligonucleotide therapy. Nature 2023;619:828-36.

Baby Is Healed With World's First Personalized Gene-Editing Treatment

The New York Times

05-15-2025

KJ Muldoon was born with a rare genetic disorder, CPS1 deficiency, that affects just one in 1.3 million babies. Credit...Muldoon Family

The technique used on a 9½-month-old boy with a rare condition has the potential to help people with thousands of other uncommon genetic diseases.

By Gina Kolata

- May 15, 2025

Something was very wrong with Kyle and Nicole Muldoon's baby.

The doctors speculated. Maybe it was meningitis? Maybe sepsis?

They got an answer when KJ was only a week old. He had a rare genetic disorder, CPS1 deficiency, that affects just one in 1.3 million babies. If he survived, he would have severe mental and developmental delays and would eventually need a liver transplant. But half of all babies with the disorder die in the first week of life.

Doctors at Children's Hospital of Philadelphia offered the Muldoons comfort care for their baby, a chance to forgo aggressive treatments in the face of a grim prognosis.

"We loved him, and we didn't want him to be suffering," Ms. Muldoon said. But she and her husband decided to give KJ a chance.

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Instead, KJ has made medical history. The baby, now 9 ½ months old, became the first patient of any age to have a custom gene-editing treatment, according to his doctors. He received an infusion made just for him and designed to fix his precise mutation.

The investigators who led the effort to save KJ are presenting their work on Thursday at the annual meeting of the American Society of Gene & Cell Therapy, and are also publishing it in the New England Journal of Medicine.

The implications of the treatment go far beyond treating KJ, said Dr. Peter Marks, who was the Food and Drug Administration official overseeing gene-therapy regulation until he recently resigned over disagreements with Robert F. Kennedy Jr., the secretary of health and human services. More than 30 million people in the United States have one of more than 7,000 rare genetic diseases. Most are so rare that no company is willing to spend years developing a gene therapy that so few people would need.

But KJ's treatment — which built on decades of federally funded research — offers a new path for companies to develop personalized treatments without going through years of expensive development and testing.

Illnesses like KJ's are the result of a single mutation — an incorrect DNA letter among the three billion in the human genome. Correcting it requires pinpoint targeting in an approach called base editing.

To accomplish that feat, the treatment is wrapped in fatty lipid molecules to protect it from degradation in the blood on its way to the liver, where the edit will be made. Inside the lipids are instructions that command the cells to produce an enzyme that edits the gene. They also carry a molecular GPS — CRISPR — which was altered to crawl along a person's DNA until it finds the exact DNA letter that needs to be changed.

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One of the syringes of KJ's treatment.Credit...Kiran Musunuru

While KJ's treatment was customized so CRISPR found just his mutation, the same sort of method could be adapted and used over and over again to fix mutations in other places on a person's DNA. Only the CRISPR instructions leading the editor to the spot on the DNA with the mutation would need to be changed. Treatments would be cheaper, "by an order of magnitude at least," Dr. Marks said.

The method, said Dr. Marks, who wrote an editorial accompanying the research paper, "is, to me, one of the most potentially transformational technologies out there."

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It eventually could also be used for more common genetic disorders like sickle cell disease, cystic fibrosis, Huntington's disease and muscular dystrophy.

And, he said, it "could really transform health care."

The story of KJ's bespoke gene-editing treatment began on the evening of Aug. 8, when Dr. Kiran Musunuru, a gene-editing researcher at the University of Pennsylvania got an email from Dr. Rebecca Ahrens-Nicklas at the Children's Hospital of Philadelphia. A baby had been born, and genetic testing showed he had CPS1 deficiency.

Could he save the baby?

Dr. Musunuru had begun investigating the use of gene editing for fairly common gene mutations.

Developing a gene editor to treat patients is a deliberate process that can take years. But KJ did not have years to wait — perhaps as few as six months before a mounting risk of severe brain damage or death.

"At this point, the clock starts in my mind," Dr. Musunuru said. "This is real life. This is not hypothetical."

KJ's disease is caused by an inability to rid the body of ammonia, a byproduct of protein metabolism. Ammonia builds up in the blood and crosses into the brain. His doctors put him on a diet that severely restricted protein — just enough for him to grow. He also had a medicine, glycerol phenylbutyrate, that helped remove the ammonia in his blood. But he still was at high risk for brain injury or death. Any illness or infection could make his ammonia levels soar and cause irreversible damage to his brain.

KJ lived at the hospital under 24-hour care.

Building a gene-editing system for the Muldoons' baby and testing it was not easy.

"There was a lot of shooting from the hip," Dr. Musunuru said.

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Dr. Kiran Musunuru, a gene-editing researcher at the University of Pennsylvania, left, and Dr. Rebecca Ahrens-Nicklas at the Children's Hospital of Philadelphia.Credit...Children's Hospital of Philadelphia

He began working with Fyodor Urnov at the University of California, Berkeley, who made sure there were no unexpected and deleterious gene edits elsewhere in the DNA. Dr. Urnov is a part of an academic collaboration with Danaher Corporation, a company capable of producing the gene editor for KJ at a standard that would allow it to be used in a patient.

Danaher in turn collaborated with two other companies it owned, two additional biotechnology firms and another research institute, said Sadik Kassim, its chief technology officer for genomic medicines.

"At every step of the process, we were always expecting someone to say, 'No, sorry,'" Dr. Kassim said. "And that would be the end of the story." But

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his fears were unfounded. Danaher and the other companies charged only for the raw materials to make the drug, he added.

The F.D.A. also smoothed regulatory approval of the treatment, Dr. Ahrens-Nicklas said.

Dozens of researchers put all else aside for months.

In Berkeley, Dr. Urnov said, "scientists burned a vat of midnight oil on this the size of San Francisco Bay." He added that "such speed to producing a clinic-grade CRISPR for a genetic disease has no precedent in our field. Not even close."

David Liu of Harvard, whose lab invented the gene-editing method used to fix KJ's mutation, said the speed was "astounding."

"These steps traditionally take the better part of a decade, if not longer," he said.

Only when the gene-editing solution was in hand and the F.D.A. approved the researchers' work did Dr. Ahrens-Nicklas approach KJ's parents.

"One of the most terrifying moments was when I walked into the room and said, 'I don't know if it will work but I promise I will do everything I can to make sure it is safe,'" she said.

On the morning of Feb. 25, KJ received the first infusion, a very low dose because no one knew how the baby would respond. He was in his room, in the crib where he had lived his entire life. He was 6 months old and in the seventh percentile for his weight.

Dr. Musunuru monitored the two-hour infusion, feeling, he said, "both excited and terrified."

KJ slept through it.

Within two weeks, KJ was able to eat as much protein as a healthy baby. But he still needed the medication to remove the ammonia from his blood — a sign that the gene editor had not yet corrected the DNA in every affected cell.
The doctors gave him a second dose 22 days later.

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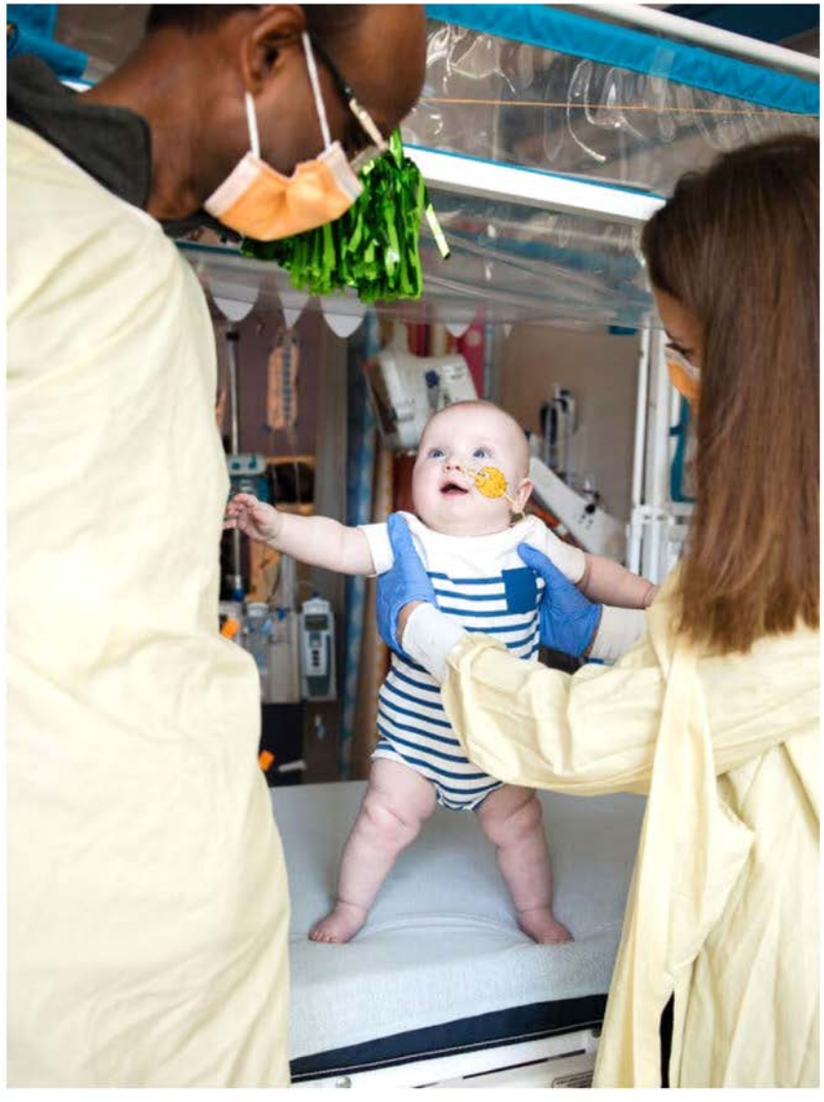

KJ is now well enough for the team to start planning to discharge him from the hospital and live at home, and he is meeting developmental milestones.Credit...Children's Hospital of Philadelphia

They were able to halve the medication dose. He got a few viral illnesses in that time, which normally would have triggered terrifying surges in his ammonia levels. But, Dr. Ahrens-Nicklas said, “he sailed through them.”

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A week and a half ago, the team gave KJ a third dose.

It is too soon to know if he can stop taking the medication completely, but the dosage is greatly reduced. And he is well enough for the team to start planning to discharge him home from the hospital. He is meeting developmental milestones and his weight is now in the 40th percentile for his age, but it is not yet known if he'll be spared a liver transplant.

The result "is a triumph for the American peoples' investment in biomedical research," Dr. Urnov said.

The researchers emphasized the role government funding played in the development.

The work, they said, began decades ago with federal funding for basic research on bacterial immune systems. That led eventually, with more federal support, to the discovery of CRISPR. Federal investment in sequencing the human genome made it possible to identify KJ's mutation. U.S. funding supported Dr. Liu's lab and its editing discovery. A federal program to study gene editing supported Dr. Musunuru's research. Going along in parallel was federally funded work that led to an understanding of KJ's disease.

"I don't think this could have happened in any country other than the U.S.," Dr. Urnov said.

Those who worked on saving KJ were proud, Dr. Urnov said.

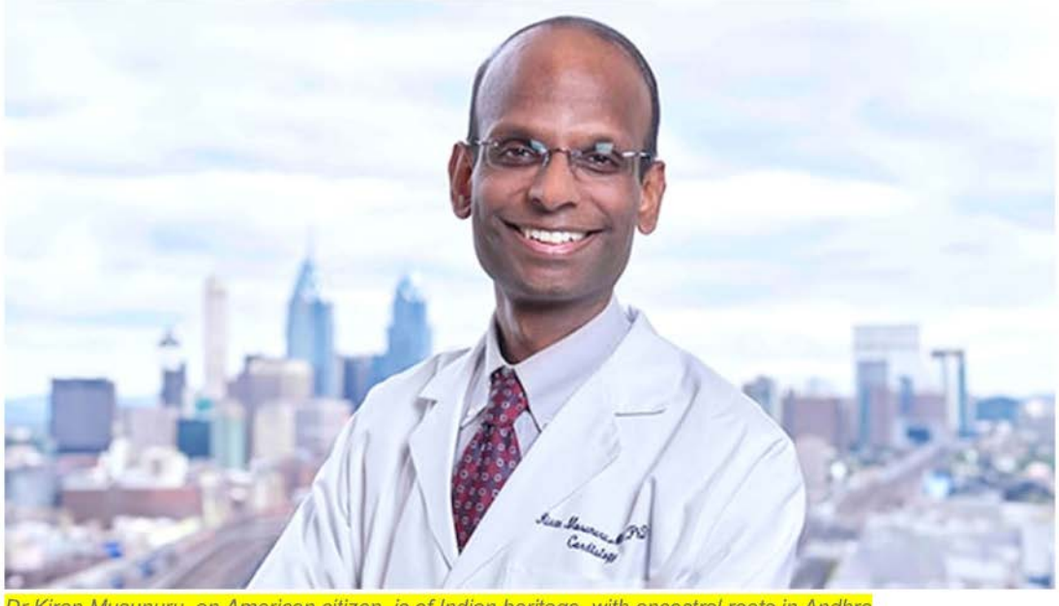
"We all said to each other, 'This is the most significant thing we have ever done.'"

INDIA TODAY

News / World / US News / Baby healed in world's 1st gene-editing therapy; Indian-origin doc plays key role

Baby healed in world's first gene-editing therapy; Indian-origin doctor plays key role

An Indian-origin cardiologist, Kiran Musunuru, played a key role in a groundbreaking medical milestone, helping treat a nine-month-old baby boy with a rare genetic disorder using customized gene-editing therapy. Musunuru was born to Telugu parents who migrated to the US from India.



Dr Kiran Musunuru, an American citizen, is of Indian heritage, with ancestral roots in Andhra Pradesh. (Photo: National Library of Medicine, US)

India Today World Desk
New Delhi,UPDATED: May 16, 2025, 21:30 IST
Written By: Gaurav Kumar

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A nine-month-old baby boy, who was born with a rare and life-threatening genetic disease, **was successfully treated with an customized gene-editing treatment** made just for him. Indian-origin cardiologist Kiran Musunuru was in the team of doctors who became the first to treat the baby using the customized gene-editing therapy. The baby was diagnosed with a severe genetic disorder that typically proves fatal for about half of affected infants in early life.

The nine-month-old baby, identified as KJ, was born with severe CPS1 deficiency -- a condition that affects only one in 1.3 million people -- was treated by Rebecca Ahrens-Nicklas, a senior physician, and Doctor Kiran Musunuru.

The doctors at the Children's Hospital of Philadelphia and the University of Pennsylvania began work immediately after the boy's diagnosis, completing the complex design, manufacturing, and safety testing of the personalized therapy within six months.

The baby was just seven months old when he received the experimental treatment in February 2025.

He was born with a severe condition called carbamoyl phosphate synthetase 1 (CPS1) deficiency, a disorder so rare it affects only one in a million births. The disease is caused by a faulty gene in the liver, leading to dangerous build-ups of ammonia in the blood, which can cause brain damage, coma, or even death if not managed properly.

Dr Kiran Musunuru used the CRISPR base editing technique, which meant he carefully changed one tiny part of the baby's DNA without cutting it, to fix the gene causing the disease.

WHO IS DOCTOR KIRAN MUSUNURU?

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Kiran Musunuru is a heart disease expert and Associate Professor of Cardiovascular Medicine and Genetics in the Perelman School of Medicine at the University of Pennsylvania. He is a principal expert in genetic research and medicine.

He was born to Indian immigrant parents who settled in the US. His father, Dr Rao Musunuru, is also a renowned cardiologist who moved from Andhra Pradesh and built a distinguished medical career in the United States.

Dr Kiran graduated in Biochemical Sciences from Harvard College in 1997.

Later, he completed a PhD in Biomedical Sciences at Rockefeller University in 2003, followed by a medical degree from Weill Cornell Medical College in 2004.

In addition to his medical and scientific training, the 48-year-old doctor has pursued extensive interdisciplinary education to support his work at the intersection of science, public health, and policy.

He earned an MPH in Epidemiology from the Johns Hopkins Bloomberg School of Public Health in 2009, followed by an ML in Law from the University of Pennsylvania Law School in 2019.

Most recently, in 2024, he completed an MRA in Regulatory Affairs from the Perelman School of Medicine at the University of Pennsylvania.

His research focusses on the genetics of heart disease and seeks to identify genetic factors that protect against disease and use them to develop therapies to protect the entire population, according to Dr Kiran's website.

In his recent work, he has been using gene editing to create a one-shot "vaccination" against heart attacks.

HONOURS AND AWARDS FOR GROUNDBREAKING WORK

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Kiran Musunuru has received numerous prestigious honours in recognition of his groundbreaking contributions to science and medicine.

Among them is the Presidential Early Career Award for Scientists and Engineers, presented to him at the White House by former US President Barack Obama—one of the highest honours given by the US government to early-career researchers.

His accolades also include the American Heart Association's Award of Meritorious Achievement, the American Philosophical Society's Judson Daland Prize for Outstanding Achievement in Clinical Investigation, the American Federation for Medical Research's Outstanding Investigator Award, and Harvard University's Fannie Cox Prize for Excellence in Science Teaching.

In addition to his research and teaching roles, Musunuru recently served as Editor-in-Chief of Circulation: Genomic and Precision Medicine, a leading peer-reviewed journal in the field, reflecting his leadership in advancing precision medicine and cardiovascular genetics.

Published By:

Gaurav Kumar

Published On:

May 16, 2025

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IN THE LAB

CRISPR is used in landmark treatment to correct genetic misspelling of a single patient

Treatment of baby with rare disease could usher in era of personalized genome editing

Baby KJ with two of the researchers who treated him, Kiran Musunuru (left) and Rebecca Ahrens-Nicklas. Children's Hospital of Philadelphia

By Jason Mast May 15, 2025

General Assignment Reporter

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For the first time, scientists say they have reached into the genome of a severely ill child and rewritten the unique misspelling in his DNA.

The results, published in the New England Journal of Medicine on Thursday, are a landmark in the 50-year quest to read and repair the code of life. The boy, a now 9.5-month-old named KJ, was diagnosed days after birth with an ultra-rare disease that impairs his liver's ability to process ammonia, which can build up and cause permanent brain damage or death.

KJ had been living in the hospital, waiting until he was old enough to receive a liver transplant. Instead, at 6 months, doctors administered the first dose of the gene editing treatment. They have since been able to loosen a strict low-protein diet and reduce his daily ammonia-lowering medications by half.

Plans for a transplant have, for the moment, been scrapped, although investigators remain cautious about declaring success.

"It is still early days to be able to make definitive statements about how well this worked," said Rebecca Ahrens-Nicklas, the Children's Hospital of Philadelphia physician who administered the therapy. "I think we can say this has been shown to be safe and well tolerated, and there's hints that this has been a benefit to him, but we just need more time."

Some outside researchers were less reserved. Clinical trials using CRISPR gene editing have been underway for nearly a decade. But like most trials, they focused on broad groups of patients. If early findings hold up, KJ's therapy will mark the first time CRISPR has been successfully calibrated to fix a single patient's unique genetic typo.

"It's terrific work," said Erik Sontheimer, a gene editing researcher at UMass Chan Medical School. "It truly brings CRISPR genome editing into the n-of-1 regime."

The results may offer hope of treatment for thousands of patients with deadly or disabling mutations that are unique or too rare to interest traditional for-profit drug developers.

At the same time, they will ignite long-simmering questions about how to safely and equitably scale personalized treatments.

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In their paper, Ahrens-Nicklas, University of Pennsylvania geneticist Kiran Musunuru, and the other researchers behind KJ's treatment concluded patient-specific genetic surgery "will become routine for many genetic diseases." Eventually, perhaps. But KJ's treatment was a remarkable endeavor, requiring collaboration of researchers and companies working at breakneck speed, for free or reduced rates in Philadelphia, Boston, North Dakota, California, Maine, and Vancouver, British Columbia. No one will say how much it cost.

Applying it to more than a tiny handful of patients may require not just scientific advances, but sweeping changes to how the U.S. regulates and pays for genetic medicine.

Chasing CRISPR's promise

Both the need and the possibility for such concierge DNA repair emerged a few years ago, as gene editing tools became more precise. Early on, CRISPR was best at breaking genes, not fixing them. But in the late 2010s, Harvard biochemist David Liu debuted two CRISPR-based tools, base editing and prime editing, that allowed researchers to swap individual letters and make other small changes to DNA.

If early CRISPR was a molecular scissors, base and prime editing was like taking a pencil and eraser to the genome.

The challenge is that single genetic diseases can be caused by up to thousands of different mutations. Companies were not going to spend tens of millions of dollars developing a therapy for each. Musunuru began warning about "mutational discrimination": a world in which only patients with the most common and lucrative variants for a particular disease receive treatment.

There was an alternative path, though. Since 2018, academics and nonprofits have been crafting treatments calibrated to children's particular mutations using antisense oligonucleotides (ASOs), small stretches of DNA or RNA that change how genes function without changing the genome itself.

Some in the n-of-1 movement, as it's called, wanted to use gene editing as well. ASOs required lifetime treatment, but CRISPR could provide a permanent fix. And whereas ASOs were used primarily for neurological diseases, gene editing could help patients with liver and blood conditions, the easiest organs to reach with CRISPR.

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"This is the critical next step we've been waiting for," said Julia Vitarello, whose late daughter Mila became the first patient to receive an n-of-1 ASO and who has since been working on making such medicines broadly available.

A nurse's hunch

Nicole and Kyle Muldoon's fourth child was born at the University of Pennsylvania premature but seemingly healthy. After birth, Nicole went for a surgery to deal with a complication and Kyle went to watch his other three kids, leaving KJ in the NICU.

Within two days, though, a nurse showed Kyle his son's arm. When you lifted it, the arm stayed rigid, shuddering on its way down, a possible sign of sepsis or meningitis. But one nurse thought to also check ammonia levels. They should have been under 40. KJ's were in the thousands.

He was rushed across the street to CHOP, where doctors put him on dialysis to clear the ammonia in time, hopefully, to prevent brain damage. Ahrens-Nicklas had his genome sequenced. The test showed CPS1 deficiency, one of the most severe of a cluster of conditions, called urea cycle disorders, that prevent the liver from breaking down ammonia.

Kyle and Nicole tried to learn all they could. It was "trauma," he told reporters, "parenthood trauma."

Ahrens-Nicklas, meanwhile, sent the sequence to Musunuru. The two had been collaborating for three years, preparing, with support from the National Institutes of Health, for a moment like this. But for now, she told the family nothing.

"I was very nervous about giving any false hope," she said.

'What diseases would we tackle?'

KJ's wasn't the first mutation Musunuru and Ahrens-Nicklas tried to solve. Soft-spoken, lanky, and supremely confident, Musunuru had spent much of the 2010s trying to convince the world of a single idea: CRISPR could be used to break cholesterol genes in perhaps billions of people, staving off the heart disease he saw as a practicing cardiologist.

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Around 2020, investors finally started listening and backed a company, Verve Therapeutics, he co-founded to take the idea into clinical trials. In summer of 2021, Musunuru returned from a sabbatical there itching for a new challenge.

He wanted to focus on fixing, instead of breaking, genes. The same summer, the first human data emerged proving you could deliver CRISPR to the liver with lipid nanoparticles, the same tiny soap bubbles used in mRNA vaccines. He reached out to Ahrens-Nicklas, who specializes in treating children with inborn errors of metabolism.

"We started brainstorming, you know, if we make any change we want in the liver, what diseases would we tackle?" he said.

They eventually homed in urea cycle disorders. The need felt particularly acute. The disorders were generally quite rare and severe. Many patients would need to be treated as infants, meaning researchers would have to craft an editor in a number of months.

Musunuru and Ahrens-Nicklas began running what they called "time trials." Ahrens-Nicklas picked a variant, informed by her clinical experience, and they tested to see how fast they could design an editor.

The first one took over a year. But over five or six tries, the team got faster and faster.

The six-month sprint

When Musunuru got the sequence, one evening in early August, it kicked off a stripped-down, hair-on-fire version of a process that usually takes years and tens of millions of dollars.

KJ had two mutations, one from each parent. One was amenable to prime editing, which is versatile but cumbersome. The other was amenable to base editing, which is limited but simpler. Musunuru would likely be able to craft a base editor, but several pins would have to be lined up immediately if it was going to be ready for KJ in time.

The editor would have to be tested in mice bearing KJ's mutation. But mice need time to be born, so they immediately placed an order from the Jackson Laboratory in Maine. The drug, they believed, needed to be tested in monkeys for safety. But waiting lists for lab

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monkeys can resemble queues for a rent-controlled apartment in New York City. So they reserved them immediately.

They needed to manufacture the drug at human quality and confirm that it didn't accidentally also nick another part of KJ's DNA in a location that could cause cancer or other issues. For that, Musunuru emailed, among others, Fyodor Urnov, a director at the University of California-Berkeley's Innovative Genomics Institute, who had become the country's most vocal advocate for pushing custom gene editors into patients.

Urnov had struck a partnership with Danaher, a $134 billion biomedical conglomerate, to fund and provide services for his institute to create such treatments for blood disorders. Both now agreed to help.

"We've been preparing this, full time, for the past few years of our lives," said Urnov.

Back at Penn, a graduate student, Sarah Grandinette, created cell lines bearing KJ's mutations. Base editors contain two parts — a letter-swapping enzyme, called the editor, and a homing sequence, called guide RNA — and she created 30 different combinations to test. She picked one after four weeks and then swapped it out for a better one, built with machine learning at Harvard.

The following months were chaotic, nerve-wracking, but largely hitch-free. There were no significant off-target edits. The monkeys, dosed around month 5 with funds from the NIH, appeared unharmed. The editor was shown to work in mice around the same time.

The FDA authorized a trial a week after submission. Because it was for a single, desperate patient, some testing could be skipped. KJ's therapy was produced in Fargo, N.D., with a guide RNA supplied from California and lipid nanoparticles brought from Vancouver. Vials were flown, frozen, to Philadelphia.

When they were sure a committed group was in place, Ahrens-Nicklas had informed Kyle and Nicole. It "was such a foreign concept," said Kyle. But it was compelling compared to the invasiveness of a liver transplant. And they trusted Ahrens-Nicklas.

They named the drug kayjayguran abengcemeran, or k-abe, after KJ. It was injected into KJ's IV bag mid-morning in late February. He lay sleeping as a crowd watched in excitement and fear.

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Ahrens-Nicklas and Musunuru picked an ultra-low dose to minimize risk, and the first shot showed little efficacy. But after a second treatment, they saw results. KJ has now received his third — and final — dose, though researchers have not yet reported whether that's allowed him to fully come off daily medicines. Ahrens-Nicklas said she would consider KJ to have a "milder form" of his disease, not cured.

Researchers won't know exactly how well they were able to edit the liver. To do so, they would need to biopsy KJ's liver, which would be unsafe given his condition. But outside researchers were impressed.

It's "groundbreaking," said Julien Baruteau, who develops treatments for urea cycle disorders at the University College of London.

Nicole, KJ's mom, has her own measure of efficacy: walking into his hospital room one morning and seeing him sitting up in his crib. "We didn't know if that was going to be something he was able to do," she said.

KJ, in his father's lap, with his mother and siblings. Children's Hospital of Philadelphia

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Will there be more n-of-1s?

Researchers dearly want to correct the genetic misspellings in other children like KJ, but the hurdles are high. It's not just cost. Several technical factors made KJ's mutation particularly easy to treat. Other treatments may require further customization, though researchers may save time in other ways.

Although Ahrens-Nicklas and Musunuru wanted to run through as much of the usual drug development process as possible for the first patient, they hope to eventually be able to treat new mutations after just testing cells in a lab. The goal would be to build a "platform" where you can develop an editor for one mutation, prove it works, and then tweak it slightly to go after the next mutation.

Under longtime biologics chief Peter Marks, the FDA had shown openness to that idea. But Marks' forced resignation in March casts doubt over the future of the agency's efforts. So, too, do the Trump administration cuts at the NIH, which has been spending hundreds of millions of dollars to enable gene-targeted treatments.

Researchers involved in KJ's therapy were eager to underline the government's involvement. "This is what the engine of American innovation does for American health care," said Urnov.

Musunuru and Ahrens-Nicklas are planning to return to the agency in the next couple years to start a "platform" trial, going after multiple mutations in a more common rare disease. In the meantime, they hope KJ's case will encourage others to try curing another child with an n-of-1 disease.

Sontheimer, the UMass gene editing researcher, said he assumes the pair are already working on the next patient. "I'm willing to bet that there are already other patients," he said.

HEALTH

Gene editing helped a desperately ill baby thrive. Scientists say it could someday treat millions

BY LAURA UNGAR
Updated 2:25 PM EDT, May 15, 2025

A baby born with a rare and dangerous genetic disease is growing and thriving after getting an experimental gene editing treatment made just for him.

Researchers described the case in a new study, saying he's among the first to be successfully treated with a custom therapy that seeks to fix a tiny but critical error in his genetic code that kills half of affected infants. Though it may be a while before similar personalized treatments are available for others, doctors hope the technology can someday help the millions left behind even as genetic medicine has advanced because their conditions are so rare.

"This is the first step towards the use of gene editing therapies to treat a wide variety of rare genetic disorders for which there are currently no definitive medical treatments," said Dr. Kiran Musunuru, a University of Pennsylvania gene editing expert who co-authored the study published Thursday in the New England Journal of Medicine.

The baby, KJ Muldoon of Clifton Heights, Pennsylvania, is one of 350 million people worldwide with rare diseases, most of which are genetic. He was diagnosed shortly after birth with severe CPS1 deficiency, estimated by some experts to affect around one in a million babies. Those infants lack an enzyme needed to

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help remove ammonia from the body, so it can build up in their blood and become toxic. A liver transplant is an option for some.

MORE STORIES

Clownfish shrink their bodies to survive ocean heat waves

For kids with autism, swim classes can be lifesaving

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Tradition and change intertwine to create beauty at a century-old arboretum

Knowing KJ's odds, parents Kyle and Nicole Muldoon, both 34, worried they could lose him.

"We were, like, you know, weighing all the options, asking all the questions for either the liver transplant, which is invasive, or something that's never been done before," Nicole said.

"We prayed, we talked to people, we gathered information, and we eventually decided that this was the way we were going to go," her husband added.

Within six months, the team at Children's Hospital of Philadelphia and Penn Medicine, along with their partners, created a therapy designed to correct KJ's faulty gene. They used CRISPR, the gene editing tool that won its inventors the Nobel Prize in 2020. Instead of cutting the DNA strand like the first CRISPR approaches, doctors employed a technique that flips the mutated DNA "letter" — also known as a base — to the correct type. Known as "base editing," it reduces the risk of unintended genetic changes.

It's "very exciting" that the team created the therapy so quickly, said gene therapy researcher Senthil Bhoopalan at St. Jude Children's Research Hospital in Memphis, who wasn't involved in the study. "This really sets the pace and the benchmark for such approaches."

In February, KJ got his first IV infusion with the gene editing therapy, delivered through tiny fatty droplets called lipid nanoparticles that are taken up by liver cells.

While the room was abuzz with excitement that day, "he slept through the entire thing," recalled study author Dr. Rebecca Ahrens-Nicklas, a gene therapy expert at CHOP.

After follow-up doses in March and April, KJ has been able to eat more normally and has recovered well from illnesses like colds, which can strain the body and exacerbate symptoms of CPS1. The 9 ½-month old also takes less medication.

Considering his poor prognosis earlier, "any time we see even the smallest milestone that he's meeting – like a little wave or rolling over – that's a big moment for us," his mother said.

Still, researchers caution that it's only been a few months. They'll need to watch him for years.

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"We're still very much in the early stages of understanding what this medication may have done for KJ," Ahrens-Nicklas said. "But every day, he's showing us signs that he's growing and thriving."

Researchers hope what they learn from KJ will help other rare disease patients.

Gene therapies, which can be extremely expensive to develop, generally target more common disorders in part for simple financial reasons: more patients mean potentially more sales, which can help pay the development costs and generate more profit. The first CRISPR therapy approved by the U.S. Food and Drug Administration, for example, treats sickle cell disease, a painful blood disorder affecting millions worldwide.

Musunuru said his team's work — funded in part by the National Institutes of Health — showed that creating a custom treatment doesn't have to be prohibitively expensive. The cost was "not far off" from the $800,000-plus for an average liver transplant and related care, he said.

"As we get better and better at making these therapies and shorten the time frame even more, economies of scale will kick in and I would expect the costs to come down," Musunuru said.

Scientists also won't have to redo all the initial work every time they create a customized therapy, Bhoopalan said, so this research "sets the stage" for treating other rare conditions.

Carlos Moraes, a neurology professor at the University of Miami who wasn't involved with the study, said research like this opens the door to more advances.

"Once someone comes with a breakthrough like this, it will take no time" for other teams to apply the lessons and move forward, he said. "There are barriers, but I predict that they are going to be crossed in the next five to 10 years. Then the whole field will move as a block because we're pretty much ready."

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Ungar covers medicine and science on the AP's Global Health and Science team. She has been a health journalist for more than two decades.

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The Philadelphia Inquirer

ALWAYS ASKING, ALWAYS PHILLY

New Jersey takes lead role in birthright defense

The state's solicitor general called on the Supreme Court to reject Trump's Day 1 executive order on citizenship.

By Jeff Gammage
Staff Writer

New Jersey led the legal argument against President Donald Trump's effort to end birthright citizenship on Thursday, its solicitor general urging the Supreme Court to bring clarity to the matter through a nationwide ruling.

It was not immediately evident what such a decision might say, but a majority of justices were concerned about the impact of even temporarily allowing the Trump administration to deny citizenship to children born to people who are in the country without official permission.

Trump has asked the court to rule that lower, federal district court injunctions can apply only to the

Kiran Musunuru (left), director of the Penn Cardiovascular Institute's Genetic and Epigenetic Origins of Disease Program, and Rebecca Ahrens-Nicklas, director of the Gene Therapy for Inherited Metabolic Disorders Frontier Program at Children's Hospital of Philadelphia, with KJ Muldoon at CHOP. Courtesy of Children's Hospital of Philadelphia

A baby with a rare metabolic disease

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DAILY NEWS

FRIDAY MAY 16, 2025

LITTLE MIRACLE

THANKS TO GENETIC EDITING, CHOP AND PENN DOCTORS HAVE BABY KJ ON THE MEND PAGE 3

KJ Muldoon smiles while in treatment at Children's Hospital of Philadelphia. KJ was diagnosed with a rare genetic disorder and has been successfully treated with customized gene editing therapy. Courtesy of Children's Hospital of Philadelphia

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SENATE PANEL REJECTS STATE STORE WEED PROPOSAL PAGE 6

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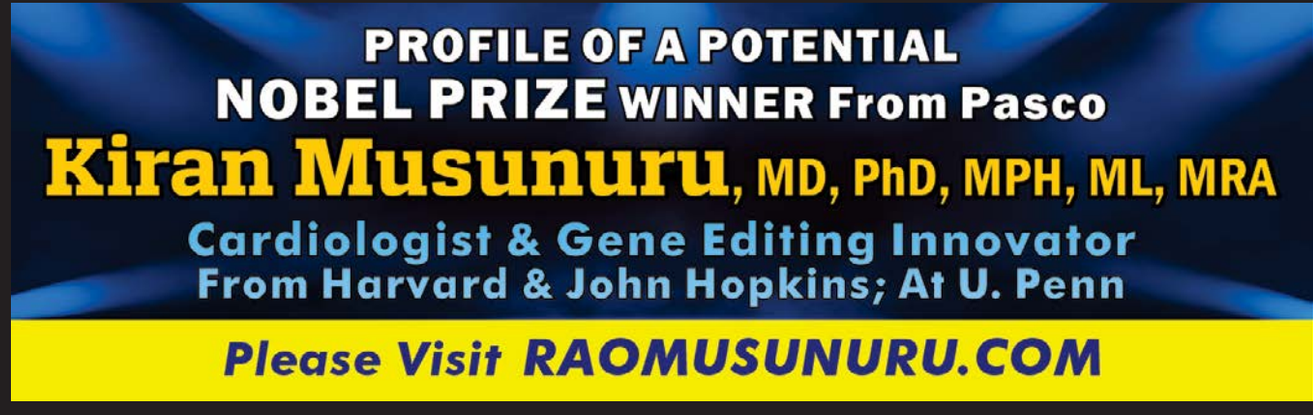
PROFILE OF A POTENTIAL
NOBEL PRIZE WINNER From Pasco
Kiran Musunuru, MD, PhD, MPH, ML, MRA
Cardiologist & Gene Editing Innovator
From Harvard & John Hopkins; At U. Penn
Please Visit RAOMUSUNURU.COM

PROFILE OF A POTENTIAL "NOBEL PRIZE" WINNER FROM PASCO

-By Thomas Konda, M.D.

Kiran Musunuru, M.D., PhD, MPH, ML was born in New York City in 1976, while his father was undergoing postgraduate training in internal medicine and cardiology. He moved to west Pasco (FL) in 1981, where his father started a cardiology practice.

While in school, he was one of the top three national winners of "Mathcounts" (akin to spelling bee) in Washington, D.C. He wrote a computer program in genetics. Also he co-authored scientific publications about the mechanisms of actions of insulin (protein-kinase, etc.). He used to read EKG's with his father after making patient rounds. He also volunteered at the hospital fixing computers and teaching calculus to hospital employees. He also won national "Latin" essay writing competition.

At the celebration of Kiran's high school graduation arranged by his parents in an auditorium attended by family members and friends with their children, the usually shy Kiran astonished everybody with his an hour long program of music and magic (piano and advanced magic including Houdini's metamorphosis). That was the beginning of his public scientific

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presentations at national and international levels. He has become a star with his excellent command of language in addition to a commanding voice.

While at Harvard, as an undergraduate he started and edited "Journal of Undergraduate Sciences." Even though his major was biological sciences, he took "Advanced Engineering Calculus, Crystallography and Buddhism" as electives. He also co-authored a book "Cell-Cycle Regulators in Cancer" while undergraduate at Harvard.

While doing combined M.D., PhD program at Cornell and Rockefeller, (his thesis was in neurosciences at a molecular level) after a selected scientific presentation in California, he earned a glorified editorial in a prestigious journal "Nature Medicine" which ended with the sentence "The presentation marked Musunuru out as a future star in biomedicine". A lot of Nobel Prize winners were among the speakers and audience at that meeting. His presentation was sandwiched at the opening session between two presentations from two Nobel laureates.

While doing 2 years (instead of 3) internal medicine residency at Harvard (Brigham) he authored "Pocket Books" in internal medicine and critical care for the rest of the house staff. He received "Best Outgoing Resident Award" which is usually reserved for 3rd year resident. The director of the program described him as a "National Treasure" in writing. Also while

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doing residency, he worked as a consultant for a pharmaceutical company and guided them to produce new cardiovascular medicines (RNA based).

Kiran has been volunteering for American Heart Association (AHA) for decades. He has served on the leading roles for its scientific councils like clinical cardiology and functional genomics. He received national awards from AHA for his service in science; he also finds time to work with "needy students" in the inner cities.

While doing first 2 years of interventional cardiology fellowship at Johns Hopkins, he simultaneously finished masters in public health (MPH) from Johns Hopkins School of Public Health. He later acquired masters in law (ML) covering patent, business and administration and also masters in regulatory affairs (MRA) covering drugs, devices and development, from University of Pennsylvania.

While continuing his cardiology research fellowship back at Harvard (Massachusetts General) he advanced the knowledge in 'stem cells and regenerative medicine'. He also earned "Excellence in Science Teaching" award among Harvard faculty. He was honored at white house by president Obama in person for "Presidential Early Career Award for Scientists and Engineers". He was also bestowed the most prestigious American Philosophical Society's (started by Benjamin

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Franklin)"Judson Daland prize for Outstanding Achievement in Clinical Investigation" at its 275th anniversary in Philadelphia, in recognition of his work discovering and therapeutically targeting cardiovascular disease genes. It carried a $50,000 prize. Kiran also collaborated with MIT and Broad Institute.

Shortly afterwards, Kiran was recruited by University of Pennsylvania in Philadelphia to become a tenured professor at a young age with his own research lab leading to many advances in gene editing. He voluntarily teaches undergraduates (biochemistry), medical students (genetics)and cardiology fellows-in-training (staying with them day and night when he is on call, developing and implementing treatment strategies for treatment of sick cardiac patients transferred from other hospitals. He earned "Excellence in Teaching Award" at University of Pennsylvania also.

He authored publications in many prestigious scientific journals over decades. He also served as the editor of International Circulation Journal: Genomic and Precision Medicine. He also contributed chapters in many cardiology books, including "Braunwald's Text Book of Cardiology." His latest books include "Crisper Generation" and "Genome Editing- A Practical Guide to Research and Clinical Applications", for scientists and researchers to learn the art. He conducts boot camps at national AHA meetings and he constantly preaches ethics.

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At this point with all his extreme knowledge in various areas and aspects of physics, mathematics, biochemistry, computer literacy, clinical medicine, and research in genetics (well planned since his school time, as you can see) he began specializing in "gene editing" to create cures for diseases that did not have any until now, not only cardiovascular but also some metabolic (e.g.: Phenylketonuria) diseases. His latest endeavor is intrauterine gene editing to prevent damage from bad genes while baby is still in uterus.

He currently serves on NHLBI council. Collaborating with universities, NIH and pharmaceutical industry, Kiran is going to make a world of difference for the humanity all over the world.

Kiran frequently associates with Nobel Prize winners worldwide. He receives a lot of attention, appreciation and admiration from them. For example, recent 'Nobel prize winner in science' Jennifer Doudna published a book in 2017-"A crack in Creation." In the first two pages of the fourth chapter she described about her excitement about meeting Kiran at his lab at Harvard and marvels about his work and she writes "Kiran was already one step ahead of me about applications of "CRISPR" as a therapeutic tool" Without any doubt, he will earn a Nobel Prize for himself in the future.

Kiran dedicated his life to science and he is the self-proclaimed "Pope" for religion of "discovering cures for all kinds of diseases". He is a down to earth humble person, very respectful

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to everyone, irrespective of their age or status. He is very kind to his students and researchers always giving them credit for all his own ideas, work and publications.

He is a person of many skills and talents. He is a package of brilliance, selflessness, generosity, and dedication. He encourages his parents to donate his inheritance to help the needy in addition to investing his own for the advancement of science.

Let us thank God for this gift to humanity!

Let us pray to God to bless Kiran and his parents for long healthy, happy and productive lives.

P.S. Dr. Thomas Suman Konda is a retired endocrinologist with a keen interest in academic and research medicine all his life. He has known Kiran, since Dr. T.S. Konda moved to Pasco County decades ago to support his wife (Nirmala), an excellent practicing cardiac anesthesiologist. He is also a successful stock market investor. He has always admired, enjoyed and encouraged Kiran, sharing their mutual enthusiasm and interest in medical research.