Beyond the "Too Rare" Barrier: Platforms for Rare Mutations Leverage New Regulatory Tool

In November, Food and Drug Administration (FDA) officials introduced the Plausible Mechanism Pathway, a regulatory tool designed to make it easier to approve treatments — specifically investigational gene therapies — for rare conditions.

An article published in *The New England Journal of Medicine (1)* discussed the successful treatment of KJ Muldoon, a baby born with a rare, life-threatening liver disorder and a pathway for approval of treatments for rare diseases. This was followed by the release of the FDA's Draft Guidance for the Plausible Mechanism Pathway in February 2026. KJ received a bespoke gene-editing therapy within six months, demonstrating the value of individualized therapies and prompting the FDA to create a new pathway. For rare diseases, the population size is often too small to conduct randomized trials, but the plausible mechanism pathway helps overcome this barrier by considering a disease's underlying pathway and a therapy's mechanism of action (1).

For gene editing companies, this could mean they could use data from an initial approval to make modifications and customize the therapy for another patient with a slightly different mutation, provided it meets the plausible mechanism pathway requirements. For patients with rare diseases, this approach could eliminate the need to wait years for treatment, and companies like Aurora Therapeutics plan to make that happen.

Origins of Aurora Therapeutics

It was only two years ago that Fyodor Urnov, a professor at the University of California, Berkeley, was lecturing and writing about CRISPR's potential to treat patients with ultra-rare mutations — the barrier was not the technology, but rather companies choosing to develop these bespoke therapies and regulators approving them. Johnny Hu, a venture capitalist at Menlo Ventures with a Ph.D. in gene editing, wanted to help.

Both Urnov and Hu knew the technology was possible, but what was less certain was building a company that would actually succeed. With $16 million in seed funding from Menlo Ventures, Urnov joined forces with Nobel laureate and co-inventor of CRISPR technology, Jennifer Doudna, and formed Aurora Therapeutics.

The 11-person startup launched in January with a mission to use CRISPR to develop gene-editing treatments for patients with both rare and common mutations. They hope to start a trial in 2027.

Impact of the New FDA Pathway on Aurora and other gene therapies

In the past, existing companies have shied away from developing personalized treatments, notes Aurora's leadership; however, with the success of KJ's treatment and the new FDA pathway, a new interest has emerged. The Aurora team credits the new plausible mechanism pathway, as well as more efficient personalization and manufacturing of editors, as making startups like theirs possible.

According to the company's recent press release, a key component of its model is the emerging regulatory changes that support grouping multiple mutations within a disease into unified developmental paths, which it said could make personalized therapies economically and operationally viable.

"You can keep over 99% of the drug the same and then retarget it to each individual mutation," Hu says. While some aspects of the drugs will differ by patient, Aurora plans to use the FDA's new plausible mechanism pathway to obtain approval for the platform as a whole.

Aurora will also use artificial intelligence to design its highly personalized CRISPR-based editors for rare genetic diseases.

"Since its discovery, CRISPR has offered the promise of treating the root causes of genetic disease, but we lacked a scalable way to bring those therapies to patients with rare mutations," said Aurora co-founder Jennifer Doudna, Ph.D. "By innovating in both clinical development and approval pathways, Aurora could help address the hurdles of providing gene editing therapies for patients who were previously out of reach."

While Aurora credits the pathway with making personalized therapies economically viable by reusing most of the drug and retargeting only the guide RNA, manufacturing and quality standards for individualized products remain stringent, potentially limiting scalability for

academic or non-profit efforts. Additionally, personalized therapies often face high production costs and complex chemistry, manufacturing, and control requirements, which could strain small developers or limit access.

Another concern lies in recent FDA decisions on experimental drugs for rare conditions, which have created uncertainty and doubts about whether the agency will consistently apply the promised flexibilities of the pathway. Therapies for Duchenne muscular dystrophy, Spinocerebellar Ataxia, Mucopolysaccharidosis II, and Epstein-Barr virus–positive post-transplant lymphoproliferative disease have all received letters denying their approval. Also notable is the rejection of uniQure's Huntington's disease therapy, in which the agency required more rigorous data than expected, publicly challenged the program, and a senior FDA official anonymously questioned whether there was any therapeutic benefit. These developments have strained the FDA's relationship with the rare disease community and left companies and researchers questioning how consistently and predictably the FDA will apply this new regulatory approach.

Aurora's Lead Program: Phenylketonuria (PKU)

Aurora's lead program focuses on phenylketonuria (PKU), a rare liver disorder caused by mutations in the *PAH* gene that lead to a toxic buildup of phenylalanine in the blood. If not caught early and treated with a special diet, the disease can cause impaired brain development in children and teens. Though there are over 1,600 known PKU mutations, Aurora will start by addressing the three most common variants and expand from there, while also pursuing other genetic liver diseases.

Because PKU is well-understood biologically and has already been a target of genetic medicine, Aurora CEO Edward Kaye believes the disease perfectly fits the plausible mechanism pathway.

"We understand the proximate cause of the disease, and we know how to address it," he said. Additionally, the disease has a high unmet need, with an estimated 13,800 individuals living in the United States with PKU as of 2026.

Aurora won't be the only company looking to treat the rare metabolic disease. Kiran Musunuru and Rebecca Ahrens-Nicklas, two of the lead scientists behind Baby KJ's treatment, have a similar blueprint for PKU. While the pair is now working on urea cycle disorders — the type of rare disease KJ has — they have licensed the PKU mouse models they built to several companies. Musunuru says if PKU ends up being the next disease companies pursue, he's happy to have sparked interest from his academic work.

It's worth noting that gene editing is not without risks, including the possibilities of off-target effects, immune responses, and unknown durability. KJ's treatment, while successful thus far, is not considered a cure and will require lifelong monitoring. Additionally, the pathway is a draft guidance, not a guaranteed fast-track, with the FDA emphasizing that the evidence must still

rule out natural variability or placebo effects. Recent FDA decisions, such as its rejection of uniQure's Huntington's disease drug, highlight the tension between the rhetoric of flexibility and demands for robust data.

Families and Foundations Driving Custom Genetic Treatments

Aurora joins other organizations working in the rare disease space that use CRISPR and other gene-editing technologies. The n-Lorem Foundation, a nonprofit organization, was founded by Dr. Stanley Crooke and provides experimental antisense oligonucleotide (ASO) based treatment to patients with ultra-rare diseases. As of the start of 2026, n-Lorem's ASOs are treating more than 50 patients.

ASO technology has also continued to evolve in the N-of-1 space, with n-Lorem's current portfolio including several allele-specific RNase H1 ASO programs, reflecting the growing importance of this approach in personalized medicine. According to the organization, many nano-rare patients carry gain-of-function mutations that can be addressed through RNase H1 technologies. In many cases, patients require an allele-selective RNase H1 strategy to preserve the function of the wild-type mRNA while degrading mutant mRNA. These strategies require extensive screening, optimization, and expertise to identify an optimized ASO for an individual patient.

While achieving this level of selectivity remains a significant challenge, recent studies have explored strategies to improve allele-specific RNA targeting, including optimizing gapmer ASO design parameters,such as mixmer ASO design and introducing mismatched nucleotides (3). Researchers have also developed engineered RNA-cleaving DNAzymes capable of allele-specific knockdown while minimizing RNase H1-mediated cleavage (4). Together, these approaches highlight ongoing efforts to improve the precision of oligonucleotide therapeutics for patients who require selective targeting of disease-causing variants while preserving expression of the normal allele.

The Valeria Association, named after Valeria Schenkel, who was born in 2018 with an ultra-rare mutation in the KCNT1 gene, collaborated with researchers from Harvard and Yale to create Valeriasen — an individualized ASO therapy — which was given to Valeria in 2020. Sadly, the little girl passed away in 2021, but the non-profit continues to work on accelerating the research, development, and implementation of individualized therapies for children with ultra-rare genetic diseases, specifically targeting neurodevelopmental disorders like KCNT1-related epilepsy. The KCNT1 Epilepsy Foundation is another non-profit with a similar goal of speeding up research into KCNT1-related epilepsy and supporting families affected by the disease.

Mila's Miracle Foundation, named after the first person — a little girl — to receive a bespoke therapy, has the mission to find and fund paths to cure devastating neurological conditions and to help grow the emerging field of individualized medicines. Mila's individualized medicine, called Milasen, was an ASO treatment targeting the mutation causing her Batten's disease.

Like many children with rare diseases, Mila has passed away, but the Foundation continues to work on making an impactful treatment platform.

Also rising from Mila's experience, the N=1 Collaborative was launched in 2021 as the first international hub, comprising a network of experts, doctors, researchers, patients, and companies working together to bring individualized treatments to patients with rare diseases. The organizing committee includes scientific leaders from around the world, such as Dr. Tim Yu, the designer of milasen, and Julia Vitarello, Mila's mother. The N=1 Collaborative and its hundreds of participants are dedicated to guiding this rapidly developing new branch of medicine

Cure Rare Disease, another nonprofit, was similarly inspired by family members seeking a cure for their child. In this case, it was Terry, who was diagnosed with Duchenne muscular dystrophy (DMD) at three years old. A treatment was created, but Terry did not live to see it. Terry's brother, Rich Horgan, however, continues to advocate for the development of genetic therapy for rare diseases.

"There are hundreds of thousands of Terrys waiting for their chance to hit back. His legacy is a future where no family has to hear, 'There's nothing we can do,'" says Horgan.

The Future of Rare Disease Therapies

There are many other Valerias, Milas, and KJs, too, because, as Hu explains, even though each individual disease is rare, combined, there are hundreds of millions of rare-disease patients. In the U.S. and Canada alone, 37 million people have a rare disease. However, while collectively large, each individual condition is a small market, raising questions about pricing, reimbursement, and whether the for-profit models will truly serve the highly rare diseases that nonprofits target. Current gene therapies often cost $1–3+ million per patient, creating barriers for patients, insurers, and global health systems and potentially exacerbating inequities, especially if overwhelming application volume strains resources. As with Baby KJ, some treatments may require lifelong surveillance, further driving costs and stretching resources.

The emergence of the FDA's plausible mechanism pathway, together with advances in CRISPR, ASO technologies, and artificial intelligence, represents a potential step forward for patients with ultra-rare diseases, though challenges remain. Companies like Aurora Therapeutics and nonprofits such as n-Lorem, N=1 Collaborative, Mila's Miracle Foundation, the Valeria Association, the KCNT1 Epilepsy Foundation, and Cure Rare Disease are translating individual tragedies into collective progress, building models that could make bespoke therapies more feasible and widely available. While not every story will have the outcome that families hope for, each effort brings the field closer to a future in which "too rare" is no longer a barrier to treatment. However, significant barriers, including safety, cost, equity, and regulatory consistency, must be addressed for these bespoke therapies to benefit more than a privileged few.

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