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Rethinking gene therapy development strategy: Shifting from technological acceleration to mechanism-based safety governance

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GENE THERAPY IN THE POST-ACCELERATION ERA

Decades of advancement have translated gene therapy from a theoretical experimental concept into an approved clinical reality: AAV vectors, lentiviral systems, CRISPR-based tools, and ex vivo engineered cell products are now approved or clinically established across a growing set of genetic diseases and hematologic malignancies.[1,2,3]

Against this background, a 2026 joint investigation by Science and Retraction Watch exposed systemic gaps in the field. It revealed that a 6-year-old patient, named Mei, died one week after receiving experimental base-editing therapy at Shanghai Xinhua Hospital in March 2025.[4] The first-in-human trial, led by neuroscientist Zilong Qiu, targeted Snijders-Blok-Campeau syndrome, a non-fatal, rare neurodevelopmental disorder caused by CHD3 gene mutations. This has sparked major ethical debate: trials for non-lethal conditions cannot ethically accept the same high risk as trials for life-threatening diseases.

THE XINHUA CASE: A SYMPTOM OF SYSTEMIC FLAWS, NOT AN ISOLATED SCANDAL

The public details have already been reported by Science and Retraction Watch;[3] they need not be relitigated here. The more important question is what kind of translational logic allowed a first-in-human, high-risk intervention to appear plausible when the expected benefit was uncertain, platform risk was substantial, and independent governance was insufficient (Figure 1).

Root ethical failures

These lapses are not an unavoidable tradeoff between urgency and caution for a life-threatening condition. They raise a core ethical question: does a non-fatal, non-progressive developmental disorder justify the risks of this first-in-human, high-dose intrathecal dual-AAV base-editing intervention? Disability impact alone does not make an experimental therapy ethically defensible on risk-benefit grounds; when independent experts flag insufficient preclinical data, the research team bears the full burden of proving safety.

While it is fully understandable that families facing incurable developmental conditions pursue any potential treatment, trusting and paying leading experts, the duty to assess risk tolerance for experimental interventions falls to investigators, Institutional Review Boards (IRBs), and regulators—not vulnerable families. For family-initiated, funded N-of-1 requests, institutions must transparently, formally reject proposals with insufficient preclinical evidence or poor risk-benefit balance, rather than shifting life-or-death decision pressure to families.

Indication-risk mismatch: A new category of structural risk

Indication-risk mismatch arises when a high-platform-risk intervention is paired with an indication whose natural history, severity, treatment window, or measurable benefit cannot bear that risk. This risk stems not from inherent technological flaws, but from therapy-indication pairings shaped by vector design, dosing, tissue exposure, patient selection, disease context, and an overlooked temporal dimension: target genes act either in narrow early developmental windows or across the lifespan. For example, 6-year-old Mei received CHD3 editing far past the therapy's 2–3 year effective window, raising safety risks while eliminating likely benefit. This mismatch is a practical triage tool, not an anti-tech stance: the same base editing is fully ethically justified when matched to appropriate indications, such as the 2025 FDA-reviewed trial for life-threatening CPS1 deficiency.

Family-initiated, family-funded N-of-1 trials: A distinct ethical failure

The Xinhua case—with over $800,000 in out-of-pocket family payments and a family-led study structure—demands targeted ethical scrutiny. Conventional research ethics frameworks, built for institution-led recruitment, fail to address this model's unique conflicts: overlapping investigator roles as therapy developers, care providers, and intervention gatekeepers; blurred lines between care purchase and research enrollment that distort informed consent voluntariness; and structural incentives to underreport adverse events to preserve future family access. Mandatory independent registration, full funding disclosure, and external oversight are non-negotiable; investigator self-governance is never sufficient.

Individualized therapy does not justify individualized evidence standards. If each patient becomes a unique experiment, each serious outcome must also become part of the public learning system. Notably, China's 2024 Investigator-Initiated Clinical Study Management Measures explicitly ban improper participant research charges, making this an enforcement failure, not a regulatory gap. Existing rules require independent multidisciplinary ethics review for all family-funded N-of-1 gene trials, national-level review for high-risk trials, public funding disclosure, and external indication-specific risk assessments. First-in-human high-risk platform trials for non-fatal, non-progressive conditions should be rejected without compelling evidence justifying their risk-benefit balance.

Institutional pathways allowed high-risk first-in-human studies to proceed without sufficient national-level scrutiny

The Xinhua case exposes a global structural weakness in gene therapy regulation amplified by institutional incentives in China. Following the 2018 He Jiankui embryo editing incident, China built a robust regulatory framework for human gene editing: criminal law bans the illegal implantation of gene-edited embryos; 2023 regulations unified human subject ethics standards nationwide; and the 2024 investigator-initiated trial (IIT) rules directly address almost every failure seen in this case, requiring scientific and ethical review, national registry filing, and a ban on improper participant fees. All of these rules were already in effect when Mei was treated in March 2025, and the unregistered status of the study was explicitly cited in the September 2025 administrative penalty against the hospital. The problem is not a lack of existing rules, but the discretionary enforcement of rules for IITs. While the vast majority of IITs are scientifically and ethically sound, all first-in-human genome editing trials and high-dose central nervous system (CNS) AAV trials—regardless of sponsorship source—require mandatory national regulatory review.

The "world-first" incentive loop: Vanity economics and journal complicity

The underrecognized root of the Xinhua controversy is global research's obsession with "world first" breakthroughs. Before Mei's death, her team marketed an unproven base-editing procedure for neurodevelopmental disorders as a global first, fueling a cross-sector loop prioritizing prestige over safety: media chase clickbait, institutions tie funding, promotions, and rankings to high-profile firsts, nations frame them as innovation markers, and vulnerable families are sold unvetted hope.

Rewards are lopsided: success brings researchers fame and career gains, while failure leaves families to bear nearly all physical and financial costs. In Mei's case, her family paid ~$800,000 for the experimental treatment, while the hospital was fined only ~$3,600 with no penalties for the lead researcher, creating perverse incentives to cut corners.

Top journals validate this symbolic capital, publishing firsts to lift their impact factor. When Mei's family raised ethical concerns about the team's Nature paper, the journal dismissed complaints, claiming ethical oversight fell outside its data integrity remit. Despite global rules requiring ethics checks for

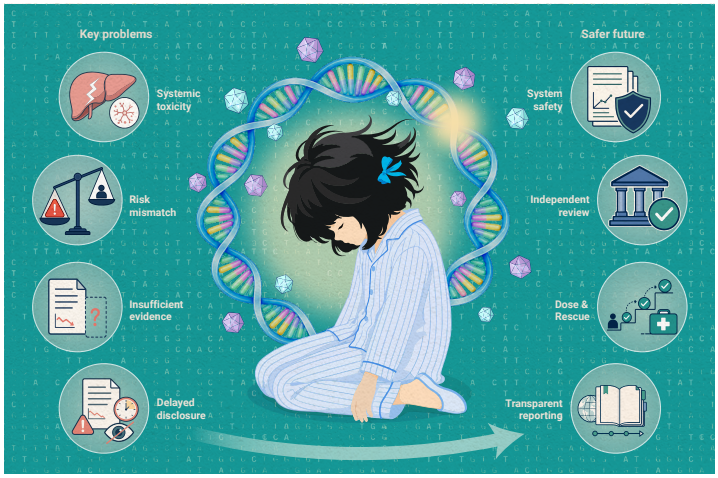

Figure 1. Gene therapy development must move from first-in-human acceleration toward mechanism-based safety governance.

human subject research, enforcement is selective: journals rarely scrutinize high-impact first papers, and even delayed retractions cannot erase already awarded prestige. This is a structural, not isolated, flaw in the high-impact journal ecosystem.

LESSONS FROM REGULATORY EVOLUTION AND APPROVED PRODUCTS

Confidence in manageable gene therapy risks stems from decades of institutional learning, not blind optimism. The 1999 death of trial participant Jesse Gelsinger spurred sweeping U.S. reforms to adverse event reporting and oversight, laying the foundation for today's field-wide safety framework. AAV-based products demonstrate that immune and organ toxicities can be managed only when monitoring and rescue plans are built into the therapeutic system. Postmarketing experience with systemic AAV products shows that platform risk can reshape indications even after approval. Ex vivo editing products show that safety depends on the entire intervention, including cell collection, editing, conditioning, engraftment, and long-term surveillance. Local delivery products show that the route can reduce systemic exposure but does not eliminate uncertainty.

Current FDA guidance appropriately balances mechanistic rigor with flexible evidence standards, but requires consistent enforcement of minimum evidence thresholds, plus fixes for longstanding gaps: IRB independence, high-risk trial review capacity, and institutional-investigator conflict of interest management.

REBUILDING DEVELOPMENT STRATEGY: A MECHANISM-BASED SAFETY GOVERNANCE MODEL

Effective gene therapy reform does not rely on isolated punitive rules, but a six-part operating framework that structurally ties clinical translation speed to the rigor of mechanistic safety characterization (Figure 1).

First, reorient incentives away from the distorted "race to first-in-human dosing" metric, which rewards hasty dosing over rigorous risk assessment—exemplified by the Xinhua case, where the lead investigator celebrated a paper acceptance days before patient Mei's death, reflecting skewed rewards for high-profile milestones over incremental safety checks or transparent adverse event reporting. Without waiting for regulatory mandates, institutions, journals, and funders should tie "first-in-class" prestige to robust mechanistic evidence, manufacturing maturity, long-term safety follow-up, and full disclosure, rather than ungrounded speed.

Second, shift from isolated, target-centric safety checks to full system-level assessment, evaluating the entire therapeutic package (gene construct, vector, delivery route, dose, host immune status, manufacturing quality, adverse event rescue capacity, etc.) rather than individual components. Identical vectors produce drastically different safety profiles across delivery routes, so single-component maturity never replaces integrated system characterization.

Third, mandate a pre-specified immune-risk readiness checklist for all systemic AAV and combined CNS/systemic genome editing first-in-human trials, covering baseline testing, real-time dosing monitoring, triggered toxicity workups, and pre-planned rescue protocols. The fatal AAV-linked complications (TMA, platelet collapse, anuria) in Mei's case were well-documented risks that should have been prepared for in advance, not identified post-mortem.

Fourth, enforce dose-governed translation: require human-relevant preclinical dose-toxicity characterization, sentinel dosing, staggered enrollment, and clear escalation/stopping rules, as AAV-induced permanent anti-capsid immunity makes dose adjustment impossible after administration.

Fifth, apply indication-risk gating: conduct indication-specific pre-approval for high-platform-risk FIH trials weighing disease burden, existing care, and expected benefit against platform risks, with a conservative default for trials with uncertain treatment windows, and a presumptive ban on pay-to-participate enrollment (with independent, conflict-free fund administration for ultra-rare disease cases reliant on family support).

Finally, embed transparency in core infrastructure: mandate time-bound public reporting of all serious adverse events, jointly enforced by regulators and journals, to enable field-wide learning and prevent unreported safety failures like those in the Xinhua case.

CONCLUSION

Gene therapy needs disciplined, not diminished, ambition. Its success relies not only on technical advances in gene editing, cell engineering, and replacement, but on a rigorously governed, fully accountable ecosystem covering vector design, dosing, immune risk control, manufacturing standards, and transparent adverse event reporting.

The Xinhua case probe is no verdict on the whole field, but a chance for critical institutional recalibration. The 2025 KJ Muldoon case of individualized base editing for life-threatening CPS1 deficiency shows that rapid individualized in vivo editing can be ethically and scientifically defensible when disease urgency, regulatory review, multidisciplinary oversight, dose monitoring, and transparent disclosure are aligned.[5] Success hinges not on technology itself, but aligned governance, careful risk-benefit calibration, and radical transparency.

The field's core duty is rejecting unjustifiable first-in-human trials with indefensible preclinical risk profiles, never offloading that responsibility to desperate families, even when genetic disorders are framed as trivial, fixable "book typos".

Systemic guardrails cannot eliminate all uncertainty, but make risks anticipatable and manageable. We must end reckless rushes for "world first" headlines at the cost of rigorous evidence, and instead improve risk flagging, failure disclosure, and learning from harm. This accountability extends beyond scientists: media, university administrators, and readers clicking sensational "breakthrough" headlines all fuel the vanity economy of high-risk first-in-human trials that distorts institutional priorities.

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DECLARATION OF INTERESTS

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