

CRISPR Remission: A Flare-Aware Gene Editing Pathway Engine for Immune-Volatile Chronic Disease

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Infection-associated chronic conditions including Long COVID and ME/CFS present a critical unmet need in CRISPR therapeutics. These diseases are characterized by unpredictable immune flares, relapsing-remitting trajectories, and profound patient heterogeneity that render conventional static gene-editing approaches both unsafe and ineffective. While CRISPR-based therapies have achieved remarkable success in stable monogenic disorders, current development paradigms fail to account for the dynamic immune volatility, timing sensitivity, and subgroup variability that define complex chronic inflammatory states, leaving these conditions therapeutically underserved despite their growing prevalence. Driven by lived experience with relapsing-remitting chronic disease, CRISPR Remission was designed to address three fundamental barriers to safe gene editing in immune-volatile conditions: identifying stable intervention windows during fluctuating disease states, predicting flare risk across heterogeneous patient populations, and optimizing pathway selection for subgroup-specific disease severity.

This computational gene-editing pathway engine evaluates and prioritizes CRISPR therapeutic strategies under dynamically simulated immune and physiological conditions. Using large-scale synthetic cohort modeling, the system encodes baseline disease burden, multisystem symptom patterns, and immune instability metrics, then simulates longitudinal disease trajectories to map intervention safety and efficacy over time. Candidate gene-editing pathways are evaluated *in silico* using context-appropriate Cas variants, delivery modalities, and conditional regulatory logic, with quantitative scoring based on predicted flare probability reduction, remission likelihood, subgroup consistency, and off-target safety under immune instability. To enable precision evaluation across rare and high-risk populations rather than relying on population averages, we expanded the synthetic cohort infrastructure from approximately 600 million to over one billion simulated profiles stratified by age, sex, race, phenotype clusters, and baseline burden tiers. This expansion ensures robust pathway testing in historically underrepresented populations and enables detection of subgroup-specific safety signals that would be masked in aggregate analyses. Validation studies demonstrated strong predictive performance for flare-risk stratification, achieving an AUC of 0.86 with 82% sensitivity and a false-positive rate below 10%. In expanded cohort analyses spanning diverse severity tiers, IL-6R-associated pathway modulation

consistently emerged as a top-ranked intervention, reducing predicted flare probability by approximately 65% across populations. Critically, optimal pathway rankings varied systematically by baseline disease burden, demonstrating that effective remission strategies must be tailored to both immune state and disease severity rather than applied uniformly.

CRISPR Remission advances gene-editing development from mutation-centric correction toward stability-driven pathway design. By explicitly modeling the immune volatility, intervention timing constraints, and patient heterogeneity that complicate therapeutic development in chronic inflammatory disease, the system generates trial-ready pathway prioritization maps designed to improve safety profiles, reduce outcome variance, and accelerate responsible translation of CRISPR-based therapies. This platform addresses a critical gap in the CRISPR therapeutic pipeline by enabling systematic evaluation of gene-editing strategies for complex, relapsing conditions where conventional approaches have failed, opening new avenues for transformative treatment of immune-mediated chronic diseases that affect millions of patients worldwide.