Press release
Evry (France), Bergamo (Italy) - November 5, 2026

Crigler-Najjar Syndrome: Gene Therapy Maintains Its Efficacy Four Years After Treatment

The trial conducted at Papa Giovanni XXIII Hospital in Bergamo as part of the international CureCN consortium, promoted by Généthon, demonstrates the long-term benefits of gene therapy for an extremely rare and potentially life-threatening liver disease that forces patients to undergo phototherapy every night and may require a liver transplant.

On November 5, 2026, the *New England Journal of Medicine* published a study on the long-term efficacy of AAV8-mediated gene therapy (GNT0003) in patients with Crigler-Najjar syndrome. The clinical trial was sponsored as part of the international CureCN consortium by Généthon, a unique non-profit organization specializing in gene therapy research and development, founded by the French Muscular Dystrophy Association (AFM-Téléthon).

Crigler-Najjar syndrome is an extremely rare congenital liver disorder affecting approximately 500 people in Europe. It is caused by a deficiency of UGT1A1, an enzyme required for bilirubin metabolism. The accumulation of this substance can lead to irreversible neurological damage and, in the most severe cases, death. To date, patients have relied on blue-light phototherapy to control their bilirubin levels. Liver transplantation is the only definitive curative treatment option, but it carries a risk of complications. GNT 0003 is a gene therapy aiming at restoring UGT1A1 expression in the liver and correcting bilirubin levels in patients,

Lorenzo D'Antiga, Director of the Paediatrics Department at Papa Giovanni XXIII Hospital, and his co-authors documented the persistence of treatment benefits four years after administration in the three patients who received the therapeutic dose at the hospital in Bergamo, Italy. Two of them were able to discontinue phototherapy, while the third maintained a partial response, requiring lower exposure to phototherapy. In all three patients, bilirubin levels remained significantly below the threshold associated with the risk of neurotoxicity.

The investigators also observed a sustained normalization of alanine aminotransferase (ALT) levels, a liver enzyme that is a key marker of liver health and function, **in the three patients treated at the highest dose**, an effect that had never been achieved with phototherapy alone.

One of the patients also successfully completed a pregnancy without complications following gene therapy and gave birth to a healthy baby.

This latest publication follows the results of the phase 1-2 CureCN trial, published in the *New England Journal of Medicine* in 2023. Those results demonstrated the safety of the treatment and its ability to correct the disease, enabling patients who received the therapeutic dose to discontinue phototherapy (*NEJM* 2023;389:620-631).

The pivotal part of the trial, which began in January 2023, aims to confirm the observed effect in a larger patient population, including children aged 10 years and older, as this is the age at which the liver reaches maturity.

"The results of this clinical trial open a new path toward the correction of genetic liver diseases that affect both children and adults and would otherwise be incurable. Until now, adeno-associated virus (AAV) vector gene therapy has shown clinical efficacy in patients with hemophilia A and B. There is now also a clear signal of its efficacy in Crigler–Najjar syndrome. Offering real hope of a cure to patients with severe rare diseases is the greatest reward for physicians and researchers in this field. At Papa Giovanni XXIII Hospital in Bergamo, we continue our commitment to clinical research with passion and dedication, bringing to the bedside innovative therapies that may one day be available to all patients with diseases that currently lack a definitive treatment" says **Lorenzo D'Antiga,** Director of the Paediatrics Department at Papa Giovanni XXIII Hospital and principal investigator of the study.

"These four-year follow-up results confirm the potential of GNT0003 to change the management of Crigler-Najjar syndrome in the long-term. They confirm not only the safety of our approach but, above all, its potential for sustained efficacy over time. The teams at Genethon have devoted considerable effort to this project, from initial design of the treatment to clinical trial, and we are very happy of these results, which pave the way for the treatment of other metabolic diseases. This study and those to come also reflect our long-term commitment to finding therapeutic solutions for rare and ultra-rare diseases." says **Giuseppe Ronzitti**, from Généthon's Immunology and Gene Therapy for Liver Diseases team.

D'Antiga L, et al. New England Journal of Medicine 2026;395:1870-1872. DOI: 10.1056/NEJMc2603129
Durability of Gene Therapy in Patients with Crigler–Najjar Syndrome

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About Genethon

A pioneer in the discovery and development of gene therapies for rare diseases, Genethon is a non-profit laboratory created by the AFM-Telethon. The first gene therapy drug, to which Genethon contributed, has been approved for marketing for spinal muscular atrophy. With more than 240 scientists and professionals, Genethon's goal is to develop innovative therapies that change the lives of patients suffering from rare genetic diseases. Fifteen gene therapy products resulting from Genethon's research, or to which Genethon has contributed, are currently undergoing clinical trials for diseases of the liver, blood, immune system, muscles, and eyes. Others are preparing for clinical trials over the next five years. www.genethon.com

About Papa Giovanni XXIII Hospital

One of the country's leading hospitals, providing a comprehensive range of medical and surgical specialties. A modern, high-technology hospital, it is internationally recognised for its expertise in organ transplantation and was the first hospital in Italy to offer all types of transplantation for both adults and children. Its Paediatrics Department is a European reference centre for rare liver diseases and paediatric liver transplantation, and is a full member of two European Reference Networks: ERN RARE-LIVER, dedicated to rare hepatological diseases, and ERN TRANSPLANT-

CHILD, focused on paediatric transplantation. Combining highly specialised clinical care with research, the Department has also been developing innovative research programmes in liver gene therapy in recent years, contributing to the advancement of new treatments for rare and potentially life-threatening liver disorders. www.asst-pg23.it

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Press contact :

Généthon: Stéphanie Bardon – communication@genethon.fr / +33 (0)6 45 15 95 87

Ospedale Papa Giovanni XXIII – Davide Cremaschi – comunicazione@asst-pg23.it
+39 348 080 9251