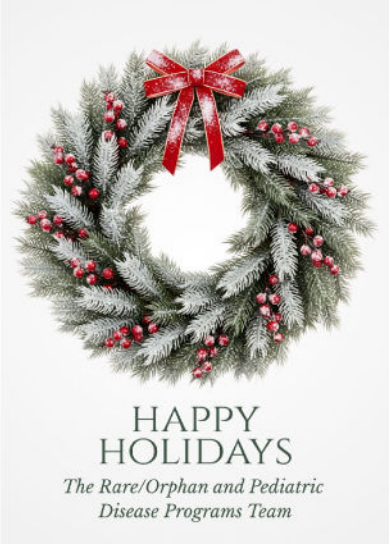
Advancing Drug Development. Improving Lives. Together.

December 5, 2025

RARE/ORPHAN AND PEDIATRIC DISEASE PROGRAMS: QUARTERLY NEWSLETTER

Welcome to the Rare/Orphan and Pediatric Disease Programs quarterly newsletter. In between major announcements, webinars and meetings, this communication serves to update you on the latest developments within C-Path's rare/orphan and pediatrics disease programs and the RDCA-DAP platform. None of C-Path's advancements are possible without the participation of our members, collaborators and data contributors. Thank you.

INTRODUCTION



As we step into the holiday season once again, we'd like to share our sincere appreciation for your connection and continued support. This year has been extraordinary thanks to the energy and enthusiasm you bring to our community.

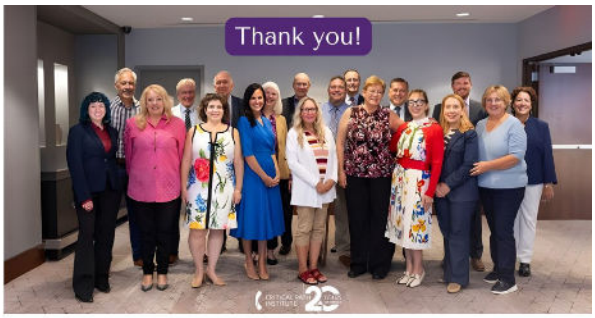
As we close out 2025, it's a great moment to revisit the highlights of the past months, acknowledge how far we've come, and set our sights on the new possibilities ahead.

We're grateful to have you with us on this journey and we look forward to creating even more together in the year to come.

Warmest wishes for a joyful holiday season and bright New Year!

SPOTLIGHT: Alpha-1 Awareness Month and CPA-1

Dedicated disease months serve to bring to light symptom awareness, preventive measures, and available resources for a specific disease. While they may not change the status of therapeutic development or clinical trials, they do offer a chance to broaden awareness of the disease in general and can serve to focus education, research, diagnostic, advocacy and fundraising efforts for greatest impact. November was Alpha-1 Awareness month and provided an opportunity to recognize those working on therapies, those with lived experience, and members of C-Path's Critical Path for Alpha-1 Antitrypsin Deficiency (CPA-1) consortium. Founded in 2023, CPA-1 is a public-private partnership comprised of industry partners, academic researchers, regulators, and patient groups working collaboratively to accelerate medical advancements for alpha-1 antitrypsin deficiency (AATD).



Importantly from a regulatory perspective, the biological mechanism of AATD is known. The disease is caused by mutations in a gene for a key inhibitor of a protease (neutrophil elastase) that is synthesized primarily in the liver and functions primarily in the lung. More than 500 mutations have been identified; less than a dozen of these are currently known to be disease-causing. Those disease-causing mutations result in a build-up of aggregated, misfolded inhibitor protein in the liver (or blood, depending on mutation) and a substantial lack of functional inhibitor in the lung. The consequences of this are more than twofold, however. While liver and lung show the primary manifestations of the disease, other body systems are affected, including the gall bladder and innate immune response to foreign pathogens in the lung. In that tissue, neutrophil elastase is activated in response to foreign pathogens. Without alpha-1 antitrypsin, the specific inhibitor of neutrophil elastase involved in AATD, elastase chews up normal healthy tissue — unopposed — contributing to emphysema, fibrosis, Chronic Obstructive Pulmonary Disease, and often lung transplant.

Fortunately, momentum is growing toward practical improvements for those waiting for treatment options, from alternate delivery systems and dosing regimens for augmentation therapy, to therapies that directly address RNA or DNA editing. Trials are ongoing, with data expected over the upcoming years. CPA-1 is actively engaged in discussions on biomarkers, endpoints, and innovation in clinical trial approaches to drive this momentum forward.

During Alpha-1 Awareness month, CPA-1 posted updates on our recent patient-focused drug development workshop. You can read those posts here and here. For more information on CPA-1 including a list of our members, visit us online.

RDCA-DAP UPDATES

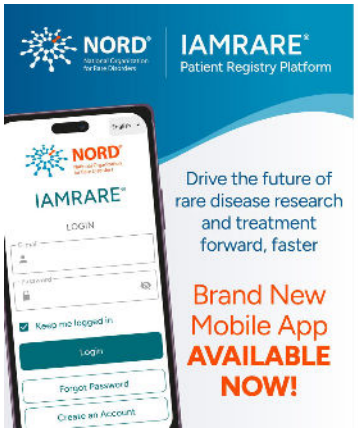
The platform currently hosts data for over 43 disease areas, including the largest database for Friedreich's ataxia. For a full list of diseases and platform engagement to date, visit Additional RDCA-DAP Resources.

NORD CORNER

NORD's IAMRARE Registry Program

NORD is thrilled to announce a request for applications for the implementation of two new patient registries on the IAMRARE® platform! Funding to create and launch a patient registry at a discounted rate is made available through RDCA-DAP®. Apply by January 10, 2026: https://rarediseases.org/rdca-dap-rfp-2026/.

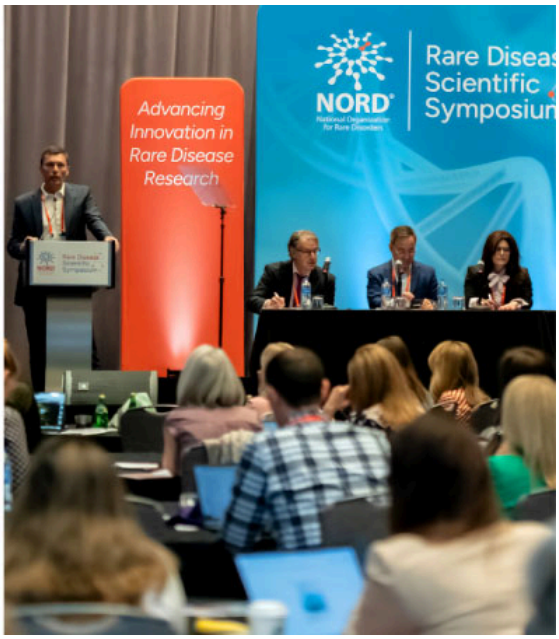
Introducing Our New Mobile App



Patient registries are an important tool to address the unique challenges for advancing research in rare diseases. NORD's IAMRARE® Registry Program is an easy-to-use system that allows patients and organizations to inform and shape medical research. With the addition of our new mobile app, sharing and collecting data is even easier. **Learn more about the IAMRARE platform and the benefits of partnering with NORD at iamrare.org**.

Save the Date for the 2026 NORD Rare Disease Scientific Symposium, April 14-15

Prepare to join the National Organization for Rare Disorders (NORD), representatives from our NORD Rare Disease Centers of Excellence, and leading biopharmaceutical researchers at the 2026 NORD Rare Disease Scientific Symposium, to be held **April 14-15 in Arlington, Va**. Learn more and access recordings of the 2025 Symposium by visiting nordscience.org.



WEBINAR SERIES 2025

Thursday December 11, 12 PM ET | Register now for our upcoming webinar: 'From Vision to Reality: 6 Years of RDCA-DAP, Driving Drug Development Solutions and Innovations in Data Sharing'

On Demand Webinars

October 30: Addressing the Lack of Standardized Laboratory Reference Ranges in Neonatal Trials: Pilot GUI Launch

C-Path's International Neonatal Consortium (INC) provides an overview and demo of their Neonatal Lab Values Graphical User Interface (GUI). This interactive tool enables exploration of real-world neonatal laboratory data to support clinical trial planning, safety assessments, and regulatory science. The GUI displays harmonized reference ranges and distributions for key laboratory parameters across gestational ages and postnatal timeframes, helping users to understand variability in neonatal lab values. Please visit our INC Lab Values project page to learn more: c-path.org/inc.

May 22: RDCA-DAP and NORD's IAMRARE Platform to Platform Federation: Lessons Learned

RDCA-DAP and NORD present an overview of their collaborative work enabling a direct connection of the RDCA-DAP to the NORD IAMRARE registry platform. Key highlights included lessons learned from the collaboration in data formatting and standardization and

how these lessons helped enhance the RWD collected by IAMARE, as well as a robust discussion with concrete examples on how RWD is improved to make it more fit for use.

April 17: ACE Inhibitors as a Cardioprotective Treatment in Dystrophinopathies

Dr. Karim Wahbi discusses the use of ACE inhibitors as a cardioprotective treatment in dystrophinopathies, detailing their effectiveness in preventing heart failure and improving survival. The variety panelists, which included PPMD committee members Colin Werth and Pat Furlong, Parent Project Italy Founder Filippo Buccella, Lead Product Developer at Cumberland Pharmaceuticals Dr. Ines Macias-Perez, and Dr. Jonathan Soslow of Vanderbilt Pediatric Heart Institute, emphasized the importance of early treatment, ideally by the age of 10 years, and the call for better dissemination of these recommendations. The group highlighted the need for better understanding and care for Duchenne and Becker muscular dystrophy carriers, particularly mothers and sisters, and the importance of regular check-ins for carriers to address their overall well-being.

February 20: Vivli and RDCA-DAP: Data Platform Partnerships to promote Rare Disease

C-Path collaborator Julie Wood, Chief Operating Officer at Vivli, led this webinar, highlighting Vivli's mission as an independent nonprofit dedicated to global data sharing and analytics. She explored how Vivli and RDCA-DAP are working together to advance data sharing in rare diseases. Following her presentation, panelists from Vivli and C-Path engaged in a dynamic discussion on platform-to-platform collaboration and strategies to enhance data accessibility, concluding with a live Q&A. C-Path participants included Richard Liwski, Alexandre Bétourné, and Ramona Walls.

You can view all 2024 ROPD Webinars on demand here.

For more information about Rare/Orphan and Pediatric Disease Programs, visit: https://c-path.org/area-of-focus/rare-and-orphan-diseases/.

ANNOUNCEMENTS AND CONSORTIUM NEWS

November 24: C-Path Consortium Adds Gene Editing and Advanced Imaging Leaders to Accelerate Alpha-1 Research

November 18: C-Path's International Neonatal Consortium Launches Groundbreaking Neonatal Lab Values GUI Tool to Standardize Reference Ranges in Neonatal Trials

November 11: In Memoriam: C-Path Remembers Dr. Gil L'Italien's Legacy of Science, Compassion, and Collaboration

CRITICAL PATH INSTITUTE

1840 E River Rd, Suite 100 | Tucson, AZ 85718 | (520) 547-3440 | info@c-path.org

c-path.org

FDA Acknowledgment