



15 Years of Impact

ANNUAL REPORT
2020

for fiscal year ending
June 30, 2020

Accelerating the path
to a healthier world

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WHO WE ARE

Critical Path Institute (C-Path) is a nonprofit, public-private partnership with the U.S. Food and Drug Administration (FDA) created under the auspices of FDA's Critical Path Initiative in 2005.

C-Path's aim is to accelerate the pace and reduce the costs of medical product development through the creation of new data standards, measurement standards and methods standards that aid in the scientific evaluation of the efficacy and safety of new therapies. These pre-competitive standards and approaches have been termed "drug development tools" (DDTs) by FDA, which established a process for official review and confirmation of their validity for a given context of use.

C-Path orchestrates the development of DDTs through an innovative, collaborative approach to the sharing of data and expertise. We build consensus among participating scientists from industry and academia with FDA participation and iterative feedback. The process culminates with the formal regulatory review and potential endorsement of the DDT for its proposed application, defined as the context of use statement. Qualified DDTs then become open standards for the scientific community which, in turn, are assured both of the scientific rigor under which they were developed and of the FDA's understanding and acceptance of their validity.



Vision

Accelerating the path to a healthier world.



Mission

Critical Path Institute is a catalyst in the development of new approaches to advance medical innovation and regulatory science. We achieve this by leading teams that share data, knowledge and expertise, resulting in sound, consensus-based science.



Values

As an independent and trusted partner, we value collaboration, leadership, innovation, integrity, transparency and efficiency.



Impact

C-Path's successes lead to safer and better treatments, available faster for patients, creating healthier global and local communities.



**JOSEPH
SCHEEREN,**

PharmD

President and CEO, C-Path

FROM THE CEO

Dear Friends and Supporters,

I'm honored to share with you the accomplishments, connections and partnerships, progress and impact we've made over the past year at C-Path.

This year marks a momentous occasion for C-Path — 15 years of collaboration with our partners — 15 years of impact for our partners, the researchers and drug developers who offer their time and guidance and most importantly, the patients in need who share their data and voice with us.

Within this annual report, we will be sharing stories describing the impact of the work that we do. These stories inspire us and reinforce our resolve towards our mission.

At the close of our 2020 fiscal year (July 2019 - June 2020), questions and conversation about clinical trials, drug development, safety and meaningful clinical outcomes, treatments and vaccines are in the headlines, every day and across every conceivable media and social channel. The emergence and spread of COVID-19 has pushed people around the world to consider questions those of us at C-Path think about every day – whether it's in the context of the current global pandemic, or the rare life-limiting diseases that are the focus of some of our consortia and program efforts.

Throughout this time of unprecedented uncertainty, C-Path has continued to forge ahead, charting new territory and laying the groundwork for innovative drug development that will lead to treatments and cures.

While there's been no shortage of obstacles and challenges, our commitment to a healthier world remains steadfast and our work is making an impact. That's why we're taking a sharp look at where we're headed to ensure we're staying the course that will maximize the positive impact we can have in the lives of those who are counting on us.

We continue to make progress in our ongoing projects, strengthening relationships and cementing partnerships, rising to challenges, looking at new and innovative ways to operate and celebrating our successes.

Included among our most notable highlights this year:

- 01 In the fall of 2019, C-Path and the National Organization for Rare Disorders (NORD) launched the Rare Disease Cures Accelerator-Data and Analytics Platform (RDCA-DAP) with an event in Rockville, Maryland. Funded by a grant from FDA, this innovative vehicle will deliver data and analytics to increase understanding of rare diseases, inform clinical trial design and accelerate the development of new treatments.
- 02 In Europe, C-Path, Ltd. joined 30 partners from 13 countries, to launch the ERA4TB Project — an international consortium to accelerate the development of comprehensive treatments against tuberculosis. Funded by the Innovative Medicines Initiative and with a budget of over 200 million euros, ERA4TB will focus on developing a new, improved tuberculosis treatment. The partners will share their expertise, knowledge and resources to rapidly progress new candidate drugs into clinical trials.
- 03 Currently, challenges hinder the advancement of promising new pediatric devices from ideation to clinical studies, to regulatory approval, to use for children. C-Path was awarded a grant in spring 2020 to conduct stakeholder engagement to garner insights, feedback and refinement of the FDA Center for Devices and Radiological Health's (CDRH) proposed framework to enhance the pediatric medical device ecosystem and to develop a strategic plan for implementation. Funded by a cooperative agreement through FDA, C-Path is leading the efforts to build the framework and develop a strategic plan for building a viable ecosystem.
- 04 Also, in pediatrics, C-Path was awarded an FDA contract in support of ongoing development of novel clinical outcome assessments for pediatric asthma. C-Path's Patient-Reported Outcome (PRO) Consortium is carrying out this work through its Pediatric Asthma Working Group. Specifically, these assessments are intended to facilitate innovative patient-focused drug development and aid regulatory decision making by filling an unmet measurement gap. We are honored to receive FDA support and collaboration towards this exciting project.
- 05 Following the rise of the COVID-19 coronavirus to pandemic status, many concerned patients are either unable or unwilling to travel to clinical trial sites for scheduled visits, or sites have been forced to close in order to abide by social distancing measures. Representatives of ePRO Consortium and PRO Consortium member firms collaborated on the development of recommendations aimed at lessening the impact of the coronavirus-related disruption on PRO data collection at clinical trial sites. The resulting presentation, "Coronavirus Disease 2019 (COVID-19): Risk Assessment and Mitigation Strategies for the Collection of Patient-Reported Outcome Data through Clinical Sites," provides recommended risk assessment and mitigation strategies for consideration by sponsors and eCOA providers to facilitate the continued collection of PRO data in clinical trials.

06

In June, C-Path launched a partnership with FDA and the National Institutes of Health's National Center for Advancing Translational Sciences (NCATS) on the CURE Drug Repurposing Collaboratory (CDRC). CDRC is a forum for the exchange of clinical practice data to inform potential new uses of existing drugs for areas of high unmet medical need. CDRC focuses on capturing relevant real-world clinical outcome data through the FDA-NCATS CURE ID platform. In a pilot project focused on COVID-19, CDRC will use data collected via the CURE ID platform to aggregate global clinician treatment experiences to identify existing drugs that demonstrate possible treatment approaches warranting further study.

With these and a long list of other accomplishments, C-Path has become the respected authority on assembling and orchestrating dynamic, responsive and effective collaborations tasked with devising cutting-edge solutions to the world's most urgent health challenges. We take seriously the value that various foundations, organizations and others in the biopharma field have put into our work, and we are committed to increasing the efficiency and effectiveness of the toolbox with the addition of approved biomarkers, clinical outcome assessments, quantitative models and other drug development tools that will speed the search for safe and effective treatments.

C-Path is making meaningful advances in medical innovation and regulatory science every day — breakthroughs that make a difference in the lives of patients in clinical trials, in the pharmacy, at the doctor's office and at home. Each and every success opens additional doors through which we'll discover the cutting-edge science and streamlined regulatory processes needed to speed the development of safe and effective treatments for debilitating diseases.

Critically important to our work are our partners — the collaborations we build to efficiently and effectively achieve common goals. In the last year, C-Path's Predictive Safety Testing Consortium and SIGNATOPE GmbH joined together to analyze and qualify promising protein safety biomarkers in mice, rats, dogs, monkeys and humans. The Huntington's Disease Regulatory Science Consortium, along with the Clinical Data Interchange Standards Consortium, or CDISC, announced the open availability of a newly developed Huntington's Disease Therapeutic Area User Guide. C-Path and CDISC also announced the release of two Therapeutic Area Standards — one that specifies how to structure commonly collected data and outcome measurements in clinical trials for HIV, and another that describes how to use CDISC standards to represent data in research studies pertaining to clostridium difficile associated diarrhea. Critical Path Institute and the Centre for Human Drug Research (CHDR) also joined forces this year to expand global collaborations for both organizations. In addition, C-Path partnered with U.S. Pharmacopeia (USP) to develop, validate and optimize biomarkers and their associated assays in the areas of Huntington's disease, Type 1 diabetes and kidney safety.

C-Path consortia in 2019 and 2020 have launched or advanced projects with, among others, TGen North — the Pathogen and Microbiome Division of the Translational Genomics Research Institute, the Foundation for the National Institutes of Health Biomarkers Consortium Kidney Safety Biomarker Project Team and Japan's Pharmaceuticals and Medical Devices Agency.

We are grateful to have been awarded grants and contracts from FDA, Parkinson's UK, Juvenile Diabetes Research Foundation and CHDI Foundation. Our partnerships with these organizations are a reflection of the confidence they have in our mission and in our commitment to success.

At C-Path, we're engaged in accelerating medical product development, and we're committed to putting our all into the work that will help us reach our goal. But we still have a long way to go, and we know it will take a lot of hard work to get there. With the support of our partners and donors, the backing of foundations and regulatory agency advisors, collaborations with biotech and pharmaceutical companies, other key industry stakeholders and the strength of the patient voice, I am confident we are on the right path and moving in the right direction.

As we all currently navigate a temporary new normal amid the COVID-19 pandemic, we want to thank you for always remaining at a safe social distance and yet right by our side, and for your unrelenting support of our efforts.

I wish to thank all of you – our staff, our partners, collaborators and supporters around the world. It's only with your commitment and support that we are able to continue to make headway toward better health for all. Here's to the next 15 years!

Be safe and be well.

With gratitude,



Joseph Scheeren, PharmD
President and CEO



15TH ANNIVERSARY YEAR

The beginning of 2020 officially marked Critical Path Institute's 15-year anniversary, and while we are proud of our accomplishments thus far, we know that there are so many more to come.



/// 2004

FDA releases the Critical Path Initiative Report

/// 2005

FDA announces first-of-its-kind public/private partnership with C-Path and the Institute is established as a nonprofit based in Tucson led by Dr. Ray Woosley and six employees

/// 2006

C-Path's first consortium, Predictive Safety Testing Consortium (PSTC), is established

/// 2008

In a transatlantic effort with FDA and EMA, C-Path qualifies the first set of preclinical safety biomarkers

/// 2010

C-Path announces the availability of its database of 11 industry-sponsored clinical trials that include more than 4,000 Alzheimer's disease patients – the first effort of its kind

/// 2011

C-Path and CDISC release the first-ever therapeutic area common data standards for Alzheimer's disease

/// 2013

FDA and EMA reach landmark decisions on C-Path's Clinical Trial Simulation Tool for Alzheimer's disease

/// 2014

With support from a \$1 million grant from Arizona's Flinn Foundation C-Path's establishes its Data Collaboration Center (DCC)

/// 2015

WHO selects C-Path to host TB clinical trials data

C-Path launches four new consortia in one year focused on neonates, pediatric trials, Duchenne muscular dystrophy and Parkinson's

FDA and EMA qualify Total Kidney Volume Biomarker

/// 2016

TB-Platform for Aggregation of Clinical TB Studies (TB-FACTS) launched

/// 2017

C-Path receives \$1.1 million grant, partners with Arizona's TGen to advance TB research

/// 2018

University of Arizona and C-Path launch graduate certificate program in regulatory science

PSTC and FNIH Biomarkers Consortium achieve the first-ever qualification of a clinical safety biomarker

/// 2019

C-Path, Ltd. European headquarters opens

PSTC and Japan's PMDA collaborate on first-of-its-kind biomarker project

Rare Disease Cures Accelerator-Data and Analytics Platform launches

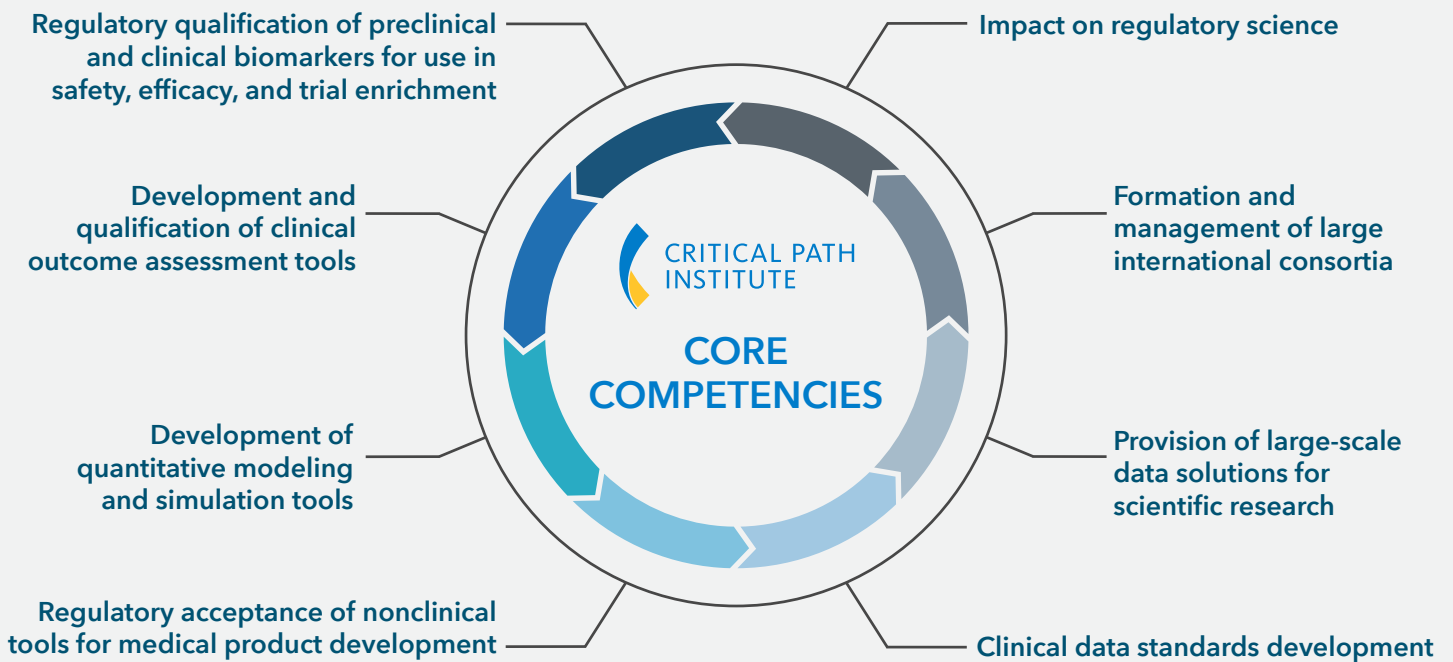
/// 2020

C-Path to lead multi-stakeholder engagement to enhance the pediatric medical device ecosystem

CURE Drug Repurposing Collaboratory launched to ID new uses of existing drugs to treat COVID-19, bringing C-Path active consortia and programs to 16

CORE COMPETENCIES

Critical Path Institute (C-Path) serves as a neutral third party to enable multiple stakeholders across the spectrum of medical product development to work together in a pre-competitive consortium model in order to drive innovative tools and methods which help to de-risk decision making in the development and regulatory review process. This makes C-Path a unique source of expertise working to achieve many of the objectives outlined in the U.S. Food and Drug Administration’s (FDA) report “Innovation / Stagnation – Challenge and Opportunity on the Critical Path to New Medical Products.”



01 Regulatory qualification of preclinical, and clinical biomarkers and novel methodologies for safety, efficacy, and trial enrichment

C-Path leads the way in regulatory qualification of biomarkers. C-Path was the first organization to qualify biomarkers with FDA, European Medicines Agency (EMA) and Japan’s Pharmaceutical and Medical Devices Agency (PMDA). The following C-Path consortia have successfully qualified biomarkers with regulatory agencies:

- The Predictive Safety Testing Consortium (PSTC): FDA, EMA and PMDA qualified six nonclinical urinary biomarkers for the detection of acute drug-induced nephrotoxicity in rodents.
- The Critical Path for Alzheimer’s Disease (CPAD): EMA qualified the baseline measurement of low hippocampal volume (atrophy) by MRI to predict whether such patients are likely to evolve to Alzheimer’s disease-type dementia during the course of an Alzheimer’s disease clinical trial. In 2015, FDA provided a Letter of Support (LOS) for Cerebrospinal fluid analytes and Hippocampal volume as exploratory prognostic biomarkers for enrichment in early-stage AD trials, and more recently, EMA gave the first-ever LOS for the pre-dementia disease progression model and clinical trial simulator that incorporates hippocampal volume.
- The Polycystic Kidney Disease (PKD) Outcomes Consortium: FDA and EMA qualified Total Kidney Volume (TKV) as a prognostic biomarker for enrichment of clinical trials in Autosomal Dominant PKD based on a quantitative disease and biomarker progression model. Subsequently, through direct interactions with the Division of Cardiology and Nephrology, TKV was designated as a reasonably likely surrogate endpoint for PKD trials.
- The Predictive Safety Testing Consortium (PSTC): FDA qualified a composite measure of six clinical urinary biomarkers, when used in conjunction with traditional measures of kidney function, for the detection of acute drug-induced nephrotoxicity during Phase 1 clinical trials.

02

Development and qualification of clinical outcome assessments

By working with multiple stakeholders (e.g., patients, regulators, clinical advisors, industry scientists, measurement experts) in the United States and around the globe, C-Path is a leader in the development and qualification of patient-reported outcome measures and other clinical outcome assessments (COAs). C-Path’s Patient-Reported Outcome (PRO) Consortium provides a collaborative framework for the qualification of COAs that can be used to support medical product labeling claims. The Electronic Patient-Reported Outcome (ePRO) Consortium works closely with PRO Consortium to make the COAs emerging from its therapeutic area working groups available in multiple modes of data collection. While other COAs are in development or other stages of qualification, the following PRO measures have obtained FDA qualification:

- *Symptoms of Major Depressive Disorder Scale (SMDDS)*
- *Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ)*
- *Asthma Daytime Symptom Diary (ADSD) and Asthma Nighttime Symptom Diary (ANSD)*

03

Development of quantitative modeling and simulation tools

The discipline of modeling and simulation has been a key area of expertise for C-Path since its inception. The vision of C-Path’s Quantitative Medicine (QuantMed) Program is to transform drug development through methodological innovation and Model-Informed Drug Development (MIDD). C-Path’s Quantitative Medicine Program also works to drive innovation in MIDD through partnerships

with leading groups and organizations in the field, and through collaborations with societies such as the International Society of Pharmacometrics. The development of these tools is possible thanks to the standardized integration of clinical and data analytical knowledge to solve bottlenecks in the drug development process. C-Path collaborated with scientists in industry to develop the first endorsed quantitative drug development platform:

- The clinical trial simulation tool for mild-to-moderate Alzheimer's disease (first-ever quantitative drug development tool to be endorsed by FDA and qualified by EMA)
- The pre-dementia disease progression model, which incorporates HV as an enrichment biomarker (first-ever quantitative drug development tool to receive a Letter of Support from EMA)
- Development of several quantitative drug development tools for tuberculosis
- Development of the model-based qualification of total kidney volume as an enrichment biomarker of trials in polycystic kidney disease
- The clinical trial enrichment tool for early-motor Parkinson's disease utilizing dopamine transporter imaging as an enrichment biomarker

Currently, QuantMed is developing clinical trial simulation tools for Parkinson's disease, Duchenne muscular dystrophy, pre-dementia in Alzheimer's disease and Huntington's disease. Additionally, model-based biomarker qualification efforts are underway for trial optimization in type 1 diabetes prevention studies and kidney transplant trials.

04

Regulatory acceptance of nonclinical tools for medical product development

In addition to the competencies described above, C-Path also has capability in developing and providing evidence packages to regulators for *in vitro* tools and other atypical (or non-traditional) tools. *In vitro* tools are critically important in earlier phases of drug development to facilitate decision making regarding compound, dose, combination regimen selection and more.

In vitro tools can also be utilized in clinical diagnosis and pathogen detection. Surveillance of pathogen resistance is another application with which C-Path has expertise.

- C-Path's Critical Path to TB Drug Regimens Initiative (CPTR): EMA qualified the *in vitro* Hollow Fiber System of Tuberculosis to inform selection of dose and treatment regimen, including combination of two or more anti-Mycobacterium tuberculosis drugs, to maximize bactericidal effects and minimize emergence of drug resistance.
- C-Path's Critical Path to TB Drug Regimens (CPTR) has developed a Relational Sequencing TB Knowledgebase (ReSeqTB) as a knowledge platform integrating genotypic, phenotypic and clinical data to aid in surveillance of TB drug resistance, support clinical decision making for TB patient management, inform development of new diagnostics and treatment regimens. The inherent value of this platform was further developed with a new instance of this platform being developed for the World Health Organization to support its Global TB Surveillance program. The delivery of the tool occurred in April 2019.

05 Clinical data standards development

C-Path's core competency in clinical data standards development enables the effective aggregation of large datasets and helps expedite the regulatory review process. C-Path has a close and long-standing relationship with the Clinical Data Interchange Standards Consortium (CDISC). CDISC is a recognized standards-setting organization, and CDISC standards are required for new NDA and IND submissions to FDA. C-Path worked with CDISC to develop the first therapeutic area data standards and has led the efforts in many others since then including Alzheimer's disease, Parkinson's disease, polycystic kidney disease, tuberculosis, multiple sclerosis, Duchenne muscular dystrophy and others. Approved data standards are published for use by the scientific research community on CDISC's website.

06 Provision of large-scale data solutions for scientific research

C-Path's Data Collaboration Center (DCC) was instituted to provide large-scale data solutions for scientific research. The DCC team has more than a decade of experience in data standards development, platform development, platform hosting, data curation, stewardship of patient-level data privacy, data security and access control methodologies. DCC's work takes place in a neutral, non-competitive environment and utilizes appropriate data standards. C-Path has developed and continues to maintain databases for Alzheimer's disease, Parkinson's disease, polycystic kidney disease, tuberculosis, Duchenne muscular dystrophy, Friedreich's ataxia kidney safety biomarkers, multiple sclerosis and other disease areas.

Information about three different types of databases C-Path developed are listed below. For a complete list, visit the DCC Projects site.

1. Genetic sequencing of pathogens
2. Collection of nonclinical and clinical biomarker data
3. Integrating patient-level data

07 Forming and managing large international consortia

C-Path is an expert in pre-competitive collaboration and is a trusted, neutral entity in regulatory science that excels in forming, managing, and facilitating large international consortia. Stakeholders include industry, regulatory and other governmental agencies, non-governmental organizations, patient groups and academia world-wide.

C-Path's ability to drive toward focused goals is key to its extraordinary competence in overseeing large consortia through technical, scientific, legal, regulatory and project management expertise, enabling the achievement of regulatory acceptance of drug development tools or novel methodologies. Each consortium collaborator is encouraged to share data that promotes the advancement of a wide variety of cross-cutting and disease-specific drug development tools and innovative methodologies.

08

Impact on Regulatory Science

C-Path focuses on the advancement of regulatory science through multiple avenues beyond qualification. This includes the development of points to consider white papers representing consensus among experts and stakeholders within a consortium. These papers are informative to regulatory authorities as they work to develop regulatory guidance documents. Furthermore, C-Path has provided public feedback on numerous draft guidance documents released for comment by both FDA and EMA.

C-Path has been instrumental in leading the movement within the scientific community to more clearly articulate the level of evidence necessary to achieve qualification, one of the most challenging issues in the drug development tool qualification process.

In April 2016, key stakeholders including FDA Center for Drug Evaluation and Research (CDER), C-Path, and the Foundation for the National Institutes of Health Biomarkers Consortium (FNIH BC) held a workshop to develop an evidentiary criteria framework for safety biomarker qualification. The resulting white paper delineated the proposed framework and provided specific examples of its applicability to clinical safety biomarkers.

In June 2017, C-Path and the Duke Margolis Center for Health Policy held a public conference to bring together key stakeholders to discuss a draft framework outlining criteria and best practices for biomarker assay performance expectations and validation. A draft white paper was prepared in advance of the public forum, and input was solicited after the conference. Currently, the framework is being utilized by biomarker qualification stakeholders to evaluate assay acceptability in ongoing and planned biomarker qualification projects.

C-Path's Predictive Safety Testing Consortium in June 2019 released a consensus paper titled, "Points to Consider Document: Scientific and Regulatory Considerations for the Analytical Validation of Assays Used in the Qualification of Biomarkers in Biological Matrices." Once biomarkers are qualified as drug development tools (DDTs) by regulatory entities, such as the FDA's Biomarker Qualification Program, supporting information is made publicly available for use by drug development programs, which can result in increased opportunities to improve safety, efficiency and innovation in the drug development process. The points to consider document outlines PSTC-recommended scientific and regulatory considerations for the analytical validation of assays for fluid-based biomarkers qualified by regulatory agencies for use as DDTs.

NEW LEADERSHIP

Kristen Swingle Joins C-Path as Chief Operating Officer

C-Path welcomed Kristen Swingle as Chief Operating Officer in July of 2019. Swingle, who previously served as Vice President of Stem Cell Operations for Cord Blood Registry (CBR), a part of California Cryobank Life Sciences, specialized in newborn stem cell collection, processing and cryopreservation, brings nearly two decades' worth of experience in the medical and molecular sciences industry to bear in her new role as she leads the daily operations of the organization and development and implementation of C-Path's global strategy and goals.

New CSO and CPAD, INC and CDRC Executive Directors Are Selected

Long-standing Quantitative Medicine Program leader Dr. Klaus Romero was named C-Path's new Chief Science Officer (CSO) effective April 1, 2020, when former CSO Dr. Lynn Hudson entered retirement. We can't thank Lynn enough for her leadership and work in enhancing our programs and consortia in her nearly 10 years with C-Path.

In another exciting move, Dr. Sudhir Sivakumaran was promoted from Associate Director of CPAD to Executive Director, effective January 1, 2020.

In March, C-Path welcomed Dr. Kanwaljit Singh as its new International Neonatal Consortium (INC) Executive Director. Dr. Singh comes to C-Path from University of Massachusetts Medical School, where he worked for more than seven years as Instructor of Pediatric Neurology.

Marco Schito, Ph.D., was selected to lead the new CURE Drug Repurposing Collaboratory consortium as Executive Director in June. Dr. Schito previously served as Scientific Director for C-Path's Data Collaboration Center program.

Congratulations to Klaus, Sudhir, Kanwaljit and Marco.

Two New Members Appointed to Board of Directors

C-Path welcomed two new members to its Board of Directors in June 2020: James W. Newman, CPA, former Executive Chairman of Victory Pharma, Inc. and Tomas Salmonson, PhD, MSc, former Chair of the Committee for



Kristen Swingle
Chief Operating Officer



Klaus Romero
Chief Science Officer



Sudhir Sivakumaran
CPAD Executive Director



Kanwaljit Singh
INC Executive Director

Medicinal Products for Human Use (CHMP), European Medicines Agency (EMA).

James Newman is a longtime pharmaceutical executive with more than 30 years' experience in pharmaceutical company senior management, finance, information systems, facilities operations and strategic planning. He founded Victory Pharma, Inc. in 2001 and served as Executive Chairman from 2001 to 2013. In 1998, Newman founded DJ Pharma, Inc. and served as President and CEO.

As Senior Vice President of Finance and Administration for Dura Pharmaceuticals, Inc., Newman redirected the company from a biotech to a pharmaceutical sales and marketing organization. He was responsible for organizing and completing its IPO and for four secondary and three private offerings to expand the market capitalization to more than \$2 billion in six years. During his active retirement, Newman serves on the board of several charitable organizations and on the Executive Committee of the Pacific Crest Trail Association.

Dr. Tomas Salmonson has deep expertise in pharmacokinetics, bioequivalence, clinical trial methodology, clinical drug development and regulatory affairs and is currently partner at Consilium Salmonson & Hemmings. He left the Medical Products Agency in February 2019 after more than 30 years at the Swedish agency and the European regulatory network. He chaired the CHMP at the EMA between 2012 and 2018. Before that he was a member of CHMP, representing Sweden between 1999 and 2012. During his last 10 years there, he also represented the EU at the ICH Steering/Management Committee and the ICH Assembly.

Salmonson has published over 60 publications in different fields including pharmacokinetics and regulatory affairs. In 2016, he received the DIA Outstanding Contribution to Health Award, the Pharmacist of the Year in Sweden in 2017 and the TOPRA Lifetime Achievement Award in 2018.

We're fortunate to be able to add these two extraordinary and talented experts to our team.



Marco Schito
CDRC Executive Director



James Newman
Board of Directors Member



Tomas Salmonson
Board of Directors Member



IMPACT AROUND THE WORLD



C-Path's vision to accelerate the path to a healthier world has helped guide the Institute's deliberate expansion and growth outside the United States. C-Path launched its European-based headquarters, Critical Path Institute, Ltd. (C-Path, Ltd.) in Ireland, in 2017 in order to enable the Institute to increase its activity and impact in the European Union.

In early 2020, C-Path Ltd., and more than 30 partners from 13 countries, signed on to participate in the ERA4TB Project, a public-private initiative dedicated to the rapid development and testing of promising drug candidates to treat tuberculosis.

Tuberculosis is the leading cause of death by an infectious disease worldwide. According to the World Health Organization (WHO), an estimated 10 million people became ill with tuberculosis in 2018, and 1.6 million died. Even though the incidence of tuberculosis is declining, the drug-resistant form constitutes a growing threat to the safety of the world population. It is in this spirit that the UN has pledged to end the tuberculosis epidemic by 2030 through joint action of its member states.

Standard tuberculosis treatment is based on a combination regimen of four drugs that were all developed more than 60 years ago. Treatment lasts for at least six months and, in the case of resistance to the standard drugs, can be as long as two years. The current drugs are inefficient by today's standards and a new, faster-acting and safer treatment is required to reduce the length of therapy and to overcome the menace of drug-resistant strains. Until now, the development of new drugs has been slow and their incorporation into tuberculosis treatment regimens conducted in a sequential manner.

ERA4TB is set to change the paradigm of tuberculosis treatment development by abandoning the sequential approach in favor of a parallel pathway, which will allow the simultaneous investigation of more than a dozen drug candidates. By implementing a standardized approach to tuberculosis drug development that is well coordinated, with the collaborations outside Europe, ERA4TB has the potential to optimize, and more importantly, greatly reduce the development times of the new regimens needed to eliminate this epidemic.

NEW USES FOR APPROVED DRUGS

As millions of patients struggle with diseases that lack adequate treatments, there is a critical need to understand how existing drugs can be used in new ways to improve clinical outcomes. Health care professionals utilize drugs in novel ways as a potential life-saving intervention when no specific approved therapies are available. However, without the ability to share these real-world experiences in a systematic manner, the clinical and research communities cannot benefit from lessons learned.

To address the challenge, C-Path announced in June 2020 the launch of the CURE Drug Repurposing Collaboratory (CDRC) funded by FDA, in collaboration with the National Center for Advancing Translational Sciences (NCATS), part of the National Institutes of Health (NIH). A public-private partnership, CDRC provides a forum for the exchange of clinical practice data to inform potential new uses of existing drugs for areas of high unmet medical need. The Collaboratory also is working to create a network connecting major treatment centers, academic institutions and researchers, private practitioners, government facilities and health care professionals around the world to share anecdotal reports and help guide how existing drugs can be used in new ways to improve clinical outcomes for patients where no effective treatments are available.

CDRC will focus on capturing relevant real-world clinical outcome data through the FDA-NCATS CURE ID platform. Freely available on the web and as a mobile app, CURE ID serves as a centralized source of reliable, curated, clinician-submitted information. To date, more than 7,000 health care professionals have registered to use CURE ID.

In a pilot project focused on COVID-19, CDRC is using data collected via the CURE ID platform to aggregate global clinician treatment experiences to identify existing drugs that demonstrate possible treatment approaches that should be studied further in randomized trials. Critical updates have been made to the CURE ID case report form for capturing relevant details related to COVID-19.

“We are encouraging health care professionals, researchers, clinicians and prescribers to download CURE ID and submit data regularly. Clearly this is of immediate importance for global public health, and we applaud FDA and NCATS for developing the CURE ID app, which may accelerate the identification of treatments for COVID-19 and other diseases that can be further studied in randomized controlled trials,” said Joseph Scheeren, PharmD, C-Path President and CEO.

“This initiative led by C-Path, in partnership with multiple divisions and offices within FDA as well as NCATS/ NIH, will help address the scientific and regulatory challenges for drug repurposing. For COVID-19 patients, time is of the essence and the contribution of cases reported directly by health care providers, followed by rapid analysis of data from the CURE ID platform, provides a much needed accelerated strategy to generate hypotheses about the potential safety and efficacy of existing drugs and inform subsequent clinical trials.”

*–FDA Principal Deputy Commissioner
Amy Abernethy, MD, PhD*

NEW RARE DISEASE COA CONSORTIUM

C-Path announced in March 2020 a cooperative agreement to establish a Rare Disease Clinical Outcome Assessment (COA) Consortium, with funding from FDA. The new grant was awarded to C-Path with the National Organization for Rare Disorders (NORD) as a sub-awardee. The first step taken toward the establishment of the new consortium has been the creation of the Rare Disease Subcommittee within C-Path's Patient-Reported Outcome (PRO) Consortium, which will serve as an incubator for the maturation of a pre-competitive, multi-stakeholder consortium within C-Path's COA Program.

PRO Consortium's Rare Disease Subcommittee includes representatives from C-Path, NORD, FDA, the Patient-Centered Outcomes Research Institute, the National Center for Advancing Translational Sciences, and biopharmaceutical firms within PRO Consortium that are developing treatments for rare diseases. In addition, plans are underway to enable rare disease-focused biotech firms not currently members of PRO Consortium to be included in the strategic planning for the new consortium.

The Rare Disease COA Consortium aims to accelerate development of new medical products intended to safely and effectively treat people with rare diseases by creating and curating a resource of information on publicly available COAs identified as potentially fit-for-purpose endpoint measures in treatment trials for rare diseases. The premise is that existing COAs may be able to be used or modified for use across multiple diseases sharing common characteristics.

Along with planning the membership, governance and organizational structure of the new consortium,

the Rare Disease Subcommittee has launched a multi-pronged effort aimed at tackling challenges in the assessment of clinical benefit in rare disease treatment trials.

The first pilot project under this initiative is to identify COAs that can be used in children to assess activities of daily living, which is a meaningful aspect of life impacted by many rare diseases. This will be the first in a series of reviews to identify COAs aimed at symptom and functional domains that reflect important aspects of patients' lives that are impacted by rare diseases.

Concurrently, the Rare Disease Subcommittee has initiated a second pilot project that involves a literature review to explore ways in which researchers have handled heterogeneity in clinical trials including an examination of the advantages and disadvantages of the approaches to personalizing endpoints. Development of best practice recommendations for assessing clinical benefit in rare disease trials will be subsequently explored.

REGULATORY ADVANCES



MULTIPLE SCLEROSIS

The **Multiple Sclerosis Outcome Assessments Consortium (MSOAC)** received a positive Determination Letter from the FDA COA Qualification Program, accepting the consortium's Qualification Plan for use of the Symbol Digit Modalities Test to assess cognition in clinical trials to test MS therapies. Study data indicate the test can reliably assess clinically meaningful aspects of MS-related disability, which support the use of the test, alone or in combination with additional tests, as primary or key secondary endpoints in MS studies. As its next step, MSOAC plans to submit the Full Qualification Plan to the FDA's COA Qualification Program in early 2021.



DUCHENNE MUSCULAR DYSTROPHY

The **Duchenne Regulatory Science Consortium (D-RSC)** received feedback from both the FDA Fit-for-Purpose pathway and the EMA Qualification of Novel Methodologies pathway on its plans to develop a clinical trial simulation platform based on six endpoints to aid in clinical trial design for Duchenne muscular dystrophy (DMD). Modeling analysis plans were accepted, with some modifications, and work is ongoing.

C-Path's Predictive Safety Testing Consortium (PSTC) and Duchenne Regulatory Science Consortium (D-RSC) are pursuing biomarker qualification for glutamate dehydrogenase (GLDH) as a biomarker to detect drug-induced liver injury (DILI) in patients with underlying muscle damage, such as in individuals with DMD and other muscle diseases as well as in people with muscle damage caused by strenuous exercise or drug-induced muscle injury. In January 2020, FDA approved C-Path's Qualification Plan for glutamate dehydrogenase (GLDH) as a biomarker to detect drug-induced liver injury advanced to stage-two FDA review, and in May 2020 the GLDH Qualification Plan Decision Letter was accepted by FDA. If the biomarker is approved by FDA, it will serve as an additional tool for use by drug developers in teasing out more accurate and sensitive safety data in clinical trials.



TYPE 1 DIABETES

C-Path's **Type 1 Diabetes (T1D) Consortium** received a letter of support from the European Medicines Agency (EMA) encouraging the regulatory qualification of pancreatic islet autoantibodies as enrichment biomarkers capable of identifying subjects with an increased likelihood of progressing to a T1D diagnosis: insulin autoantibodies, glutamic acid decarboxylase 65, and insulinoma antigen-2 autoantibodies as enrichment biomarkers for T1D clinical trials.

In their response to the T1D Consortium Letter of Intent (LOI) and Briefing Package, the EMA stated, "Therapies that preserve endogenous β -cell function and can prevent, halt or slow T1D disease progression in a clinically meaningful way would constitute a significant advancement in T1D care. If successful, the quantitative tools proposed by this Consortium have the potential to facilitate the streamlined design, execution, and review of clinical trials targeting this goal."



IMPACT STORIES

15 Years of Impact

Critical Path for Parkinson's Consortium

Critical Path to TB Drug Regimens

International Neonatal Consortium

Patient-Reported Outcome Consortium

Polycystic Kidney Disease Outcomes Consortium

Transplant Therapeutics Consortium



Critical Path for Parkinson's Consortium

IMPACT FOR PATIENTS

CPP is leading the path to the use of remote monitoring technologies by providing novel measures that reflect what is important to patients and paving the way to decentralized clinical trials.

Biotechnology executive John Crawford knew something was not right when struggling to keep up with his hiking buddies on the Pacific Crest Trail during his long backpacking trip in 2017.

"Backpacking has been my passion for more than 50 years. Shortly before diagnosis, I was hiking on the Pacific Crest Trail in southern Washington. After several miles of hiking each day, I would start to shuffle a bit and stop to rest. The third day was more dramatic: Not finding a suitable place to stop, I slowly trudged on and came to a stop involuntarily; my feet would not move. They felt glued to the trail. It's called "gait freeze" I was to learn later. Eventually I reached the next road crossing and I hitchhiked down from the mountain to a small town. While I still did not know what the problem was, I was pretty sure that I would not be able to finish my 10-year effort to hike the 2,650-mile Pacific Crest Trail in sections."

John heroically continued to hike on despite his difficulty and has completed over 350 miles of the trail after being diagnosed with Parkinson's. One of John's passions is hiking and he has served as board member of the Pacific Crest Trail Association.

During his 30-year career, John served as a corporate officer or director in 17 early stage firms and founded two biopharmaceutical companies. John successfully completed four mergers, 15 financing transactions, and 12 strategic partnerships totaling more than \$1 billion while serving in CEO or CFO roles.

John is an inspirational, self-motivated person that has identified unique ways to manage his disease by embracing technology and personalized medicine. In the daily management of his own PD signs and symptoms, he found, *"There were too many variables to consider and each day had its unique features."* So, John developed a comprehensive spreadsheet to track his symptoms and he monitored them daily. This spreadsheet is helpful for John to monitor his medications, activities and symptoms proactively in ways that have helped him with managing his quality of life. With the advent of remote monitoring technologies, John is convinced that his tracking can be completely automated with technology. John's goal is to have custom-developed apps for smartphones that can automatically track the numerous symptoms in real time. John's vision in deploying innovative technologies for self-management of Parkinson's is aligned with the focus of Critical Path Institute's (C-Path's) Critical Path for Parkinson's (CPP) Consortium's new digital drug development tool initiative. Wearable technologies and remote monitoring devices hold tremendous promise for improving patient care, clinical trials and public health; yet collaborations amongst diverse stakeholders are critical in order to tackle challenges.



**John
Crawford**

CPP brings together the world's largest pharmaceutical companies advancing novel promising treatments for people living with Parkinson's together to collaborate as opposed to compete with one another. Additional stakeholders that participate in CPP include leading academic investigators, government agencies, patient organizations and regulatory agencies. The mission of CPP's global initiative is to share data, expertise and resources to develop tools to accelerate the development of safe and effective therapies for Parkinson's. CPP was launched in 2015 as a partnership between Parkinson's UK and C-Path, two nonprofit organizations that joined forces across the globe to make a difference. Progress to date includes development of a global integrated database consisting of data from over 9,000 people with Parkinson's from around the world. The data in this unified database has been used to achieve regulatory endorsement of the first imaging biomarker for PD clinical trials and to describe disease progression of subjects with specific genetic mutations. CPP is now focused on bringing onboard large data streams from wearable apps and remote sensors in order to model the progression of both motor and nonmotor symptoms from people with PD in their own home settings. The focus of all of CPP's efforts is aimed at listening to what is important to people living with Parkinson's. The fastest growing brain disease is Parkinson's with more than six million people affected by the disease worldwide.

Several Board members of the Pacific Crest Trail Association joined John on the last leg of his 2,650-mile hike and presented him with a completion medal at the end.





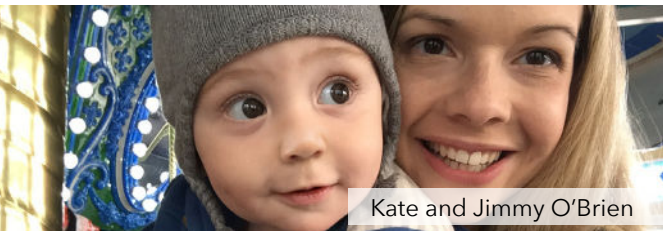
Critical Path to TB Drug Regimens

IMPACT FOR INDUSTRY

The collaborative work of the CPTR Initiative has contributed to the development of the first new drugs for TB in over 40 years, and has solidified a drug regimen development pipeline in TB.

CPTR: Revitalizing the Pipeline

In the United States, tuberculosis (TB) is easily thought of as a disease of the past. In 2018, the U.S. saw only 9,029 total cases of TB and 542 deaths.^{1,2} Globally, however, an estimated 10 million people fell ill and 1.4 million died from TB. TB is the world's leading cause of death from a single infectious agent.³ While there are encouraging trends in the global incidence and death rates (a reduction of 9% and 14%, respectively, over the last five years), TB remains a significant global health problem.



Kate and Jimmy O'Brien

Kate O'Brien, 41, is a TB survivor and advocate from the New York City area with a career in TV production. Kate was hospitalized and put into isolation for more than three months with an active TB infection in 2015, while five months pregnant. During her ordeal, Kate was astonished to learn how many people die of tuberculosis each year worldwide, and how little attention the number one infectious disease killer globally receives, especially in the U.S.






Angry at the lack of resources and awareness for the disease, Kate is now working with the National Tuberculosis Controllers Association providing community engagement & patient support through *We Are TB*, a TB Survivor advocacy organization. Adamant about leaving behind a TB-free world for her children, Kate was named a "CDC TB Elimination Champion" in 2019. "I had life and death growing in me at the same time - and life won," she's said of her diagnosis.

In 2010, first-line treatment of TB generally included a multidrug regimen of isoniazid, pyrazinamide, ethambutol and rifampin. Several alternative second line drugs were also in use; however, most were associated with significant adverse events, including permanent loss of hearing. Of the drugs available to treat TB, most were older and had been in use for many decades. For example, rifampin, the most recently approved at that time by the U.S. Food and Drug Administration (FDA) for use in TB, was approved in 1971.⁴ Despite the World Health Organization declaring TB a global public health emergency in 1993, it had been more than 40 years since any new drugs were available to treat TB.

At the same time, drug resistant, multidrug resistant (MDR), and extensive drug resistant (XDR) strains of TB were becoming increasing problems. Factors leading to drug resistance are complex and multifactorial. Treatment of TB is lengthy, often required to be at least six months in duration. The treatment course can be complicated in nature, generally consisting of a four-drug regimen for two months, followed by a longer phase of two drugs. The TB mycobacteria itself can lay dormant in the lungs, regrowing and causing reinfection despite lengthy treatment. Populations likely to be infected are from poor and rural countries with limited access to healthcare.⁵ These factors, and others, all contribute to the emergence of drug-resistant strains of TB that make treating infections even harder.

TB is one of the world's leading infectious disease killers.



OUTCOME	 Data Standards	 HFS-TB endorsement	 Model-based analyses of previous TB trials	 PBPK models	 ReSeqTB
IMPACT	Standardized terminology for TB trials, including pediatric information	Inform and streamline the development of new TB drugs and drug regimens	Improved future clinical trial design	Robust pre-clinical tools, more informed first-in-human trials	Global drug-resistance surveillance program

An urgent need existed for novel drug regimens with improved efficacy and safety profiles, as well as shorter treatment duration, to address the global health crisis in tuberculosis.

To help meet this need, the Critical Path to Tuberculosis Drug Regimens (CPTR) Initiative was launched in March 2010 by Critical Path Institute (C-Path), Bill & Melinda Gates Foundation and Global Alliance for TB Drug Development. CPTR is a public-private partnership that includes the pharmaceutical industry, academic researchers, patient advocates, and national and global regulatory and public health agencies. CPTR has worked over the last 10 years to reinvigorate the drug regimen development pipeline in TB at a time when many pharmaceutical companies were leaving the anti-infective space.

The results and impact from CPTR's work have been broad and far-reaching. In partnership with the Clinical Data Interchange Standards Consortium (CDISC), CPTR has developed standardized terminology to support TB clinical trials, including pediatric information.⁶ CPTR has also received regulatory endorsement of the hollow fiber system of TB, a preclinical model to evaluate dosing requirements for TB drugs used individually or in combination.⁷ TB-ReFLECT, a model-based analyses of several previously completed TB trials, has enabled learnings that will help the community understand study outcomes and improve the design of future clinical trials.⁸ In partnership with

Simcyp™ scientists, CPTR has developed a TB-specific set of physiologically-based pharmacokinetic models and compound files that will inform first-in-human clinical studies.⁹ CPTR has also partnered with the Translational Genomics Research Institute's (T-Gen's) Pathogen Genomics Division to whole genome sequence TB isolates with clinical and culture-based drug sensitivity data.¹⁰ This data was incorporated with similar data from the global community and able to identify drug resistance patterns across the globe. Incredibly, this is an incomplete list of CPTR's successes to date.

In 2012, bedaquiline was approved by FDA for use as part of combination therapy for MDR TB.¹¹ In 2019, pretomanid received FDA approval for use as part of a combination regimen with bedaquiline and linezolid for the treatment of XDR and MDR TB.¹² After more than 40 years of stagnation, patients around the globe have the first new drug regimens for TB. The years of collaborative work of the CPTR initiative has contributed to these approvals, and most importantly, helped solidify a drug regimen development pipeline to meet the needs of TB patients everywhere.

[Access Citations](#)

<https://c-path.org/programs/cptr/>





International Neonatal Consortium

IMPACT FOR PATIENTS

INC's work has created a paradigm shift in clinical drug development for neonatal seizures.

A 2018 publication found over 96% of neonates receive at least one off-label medication while in the neonatal intensive care unit (NICU). Off-label medications are a normal part of patient care, however their use results in more adverse drug reactions in NICU patients. For medications to be used on-label, or to be indicated, for a specific patient population, they must first be rigorously studied in that population. Unfortunately, designing drug trials in neonates is extremely difficult.

The most accepted definition of a neonate is newborns through 27 days after term birth or 27 days after expected date of delivery for preterm newborns. Neonates show significant variability that is not present in other populations. For example, while both are considered neonates, a premie may weigh as little as 1 pound, while a healthy full-term baby can weigh 10 pounds or more. A proportional difference from the average adult, weighing approximately 150 pounds, would weigh 1,500 pounds. A neonate's organs are also developing rapidly, so designing a trial that can assess a drug's physiological effects is inherently difficult. In the face of these and many other complexities, drug trials in neonatal populations have been near nonexistent.

96%

Hospitalized neonates that receive an off-label drug

12

Average number of drugs neonates born <28 weeks gestation are exposed to in the NICU

3x

More likely neonates will experience an adverse reaction to an off-label drug

With a shortage of controlled research to inform decisions, healthcare workers rely on personal or institutional experience to guide care. A lack of standardized language across the field contributes to a persistent gap in data that could otherwise be used to help inform care or translated to advance medical product development. Instead, most treatments in neonates are used off-label, exposing vulnerable patients to additional risks.

There is a persistent unmet need for safe and effective products specifically catered to and studied in neonatal populations.

In 2015, the Critical Path Institute (C-Path) launched its International Neonatal Consortium (INC), a global public-private partnership formed to forge a predictable regulatory pathway for evaluating the safety and efficacy of therapies for neonates. INC unites stakeholders from hospitals, research institutions, drug developers, patient advocacy groups, regulatory agencies and other organizations around the world to generate consensus and develop tools that accelerate medical innovation for neonates.



With its diverse group of stakeholders, INC works to curate input from parents, physicians, nurses, patient organizations and others across the field, generating broad consensus and guidelines that enhance clinician, researcher, drug developer and regulator decision making.

In 2018, INC and its partners collaborated to develop guidelines to inform the design of rigorous and efficient clinical trials for potential treatments of neonatal seizures. Neonatal seizures are the most common neurological emergency in neonates, occurring in approximately 3 in 1000 term live births, and are associated with significant mortality and neurodevelopmental disability. Trials for this condition are exceedingly difficult and face many challenges, including different diagnostic criteria in different countries, relative rarity in occurrence and the self-limiting nature of many neonatal seizures, which can make them difficult to capture in the setting of a controlled study.

Susan McCune, M.D., director of the Food and Drug Administration's (FDA) Office of Pediatric Therapeutics, described a situation where many companies had an interest in developing new or repurposing existing therapies to treat neonatal seizures, but struggled to design appropriate clinical trials.

As a result of INC's work, consensus recommendations were developed and published to address vital aspects of neonatal seizure clinical trials, including considerations for alternative designs, inclusion and exclusion criteria, safety monitoring, appropriate outcome measures, analytical plans and more.

The INC publication, [Recommendations for the Design of Therapeutic Trials for Neonatal Seizures](#), directly facilitated FDA and other regulatory agency interactions with drug developers. According to Dr. McCune, drug developers now approach FDA with INC's publication in hand, discussing how they intend to execute clinical trials for this condition.

The publication has provided a roadmap for industry that previously didn't exist. Since it was published, several industry companies have reached out for more information on how they can begin designing clinical trials for neonatal seizures. Preliminary industry sponsored studies, intended to set the stage for future larger trials, have already begun. Despite being published less than two years ago, the field is already seeing transformative activity.

To date, INC's publication has been accessed more than 3,000 times. As INC's work spreads throughout the neonatal community, drug developers will have the resources they need to develop new medications specifically for neonatal patients. Clinicians will have more evidence-based treatment options for their patients, and patients will have better, safer and more effective therapies.

*Photos feature Annie (1lb, 15oz) and Lucy (1lb, 9oz) Beaumont
Photo credit: INC member Wakako Eklund*





Patient-Reported Outcome Consortium

IMPACT FOR PATIENTS

Patient-Reported Outcome (PRO) Consortium helps to provide drug developers with the clinical outcome assessment (COA) tools necessary to target symptoms and functional impacts that matter most to patients.

PRO Consortium: integrating voices of patients, enabling future therapies

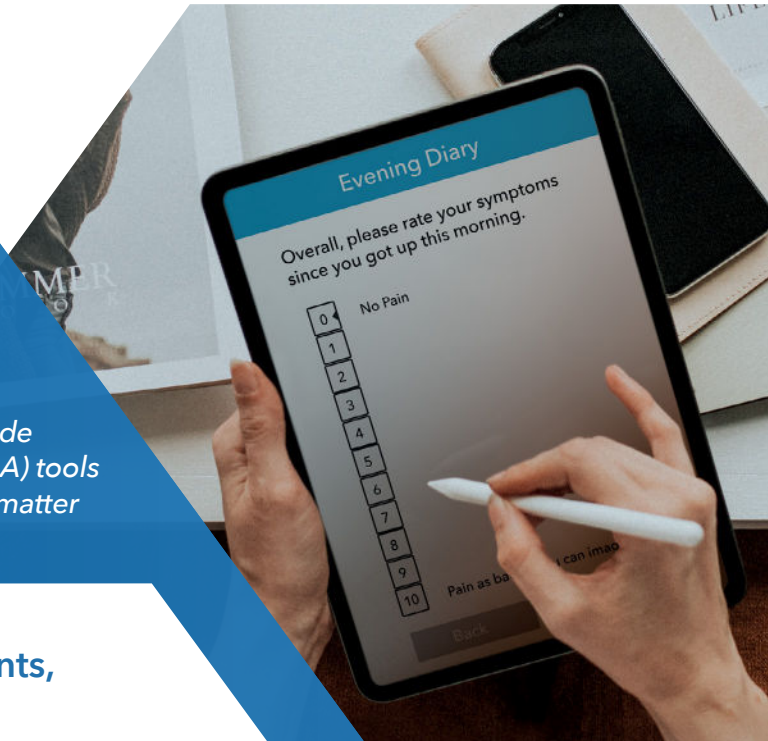
Irritable bowel syndrome (IBS) is a chronic and oftentimes debilitating collection of symptoms that occur in conjunction with disruptions in a person's bowel movements. These disruptions can include constipation, diarrhea, or both and are accompanied by symptoms that include bloating, cramping, abdominal pain and urgency.¹ IBS is one of the most common gastrointestinal (GI) disorders, impacting around 11% of the global population.² Its diagnosis is based on symptom criteria because there are no consistent and reliable diagnostic biomarkers.³

Despite its prevalence, there are still considerable gaps in our understanding of what causes IBS. IBS is categorized as a functional GI disorder, reflecting the influence that important interactions between the brain and the gut have on bowel function and associated symptoms. Research suggests many factors contribute to distinct subtypes of individuals processing food through their GI tract either too quickly (diarrhea-predominant), too slowly (constipation-predominant), or both (mixed). Although some patients have success treating IBS symptoms with changes in diet, probiotics, lifestyle changes, or mental health interventions, others rely on medication for relief from symptoms.¹

Drug development for IBS is complicated. Because of the differences in bowel disturbances across subtypes of IBS patients (i.e., diarrhea-predominant, constipation-predominant, or mixed), it is unlikely that a single potential therapy would prove successful in treating all patients. Furthermore, the severity of IBS symptoms can vary day-to-day, even with treatment, making it difficult to measure the efficacy of potential therapies across subtypes of patients. Finally, because there is no "gold standard" treatment for IBS, potential therapies must be compared to a placebo, and, importantly, because there are no reliable biomarkers associated with the disorder, assessment of symptom severity and treatment responses during clinical trials must be done using patient-reported outcome (PRO) measures.^{3,4}

These challenges stress the need for measures that are capable of monitoring symptoms that vary across time and that are sensitive enough to capture changes within a clinical trial, that capture metrics that are meaningful to patients, and that can distinguish between patients with different subtypes.

PRO Consortium was formed in 2008 by Critical Path Institute (C-Path) in



IBS impacts nearly 11% of the global population.

25-45 Million

People affected by IBS in the U.S.

20-40%

GI specialist visits are for IBS-related symptoms

6.6 Years

Average time from symptoms to diagnosis

cooperation with the U.S. Food and Drug Administration's (FDA) Center for Drug Evaluation and Research and the pharmaceutical industry. The mission of PRO Consortium is to establish and maintain a collaborative framework with appropriate stakeholders for the qualification of PRO measures and other clinical outcome assessments (COAs) that will be publicly available for use in clinical trials where COA-based endpoints are used to support product labeling claims.

Since 2010, PRO Consortium's IBS Working Group has been developing PRO measures for each of the three IBS subtypes, with the anticipation that patient responses to PRO measures would be used to generate endpoints in clinical trials for new treatments. Using structured interviews with patients to inform the process, PRO Consortium developed the Diary for Irritable Bowel Syndrome Symptoms (DIBSS) and refined the measure to reflect the experiences of patients with each of the three subtypes: constipation-predominant (DIBSS-C), diarrhea-predominant (DIBSS-D), and mixed symptom (DIBSS-M). The DIBSS was developed as a daily and event-based diary to facilitate the collection of reliable data in a condition subject to natural variability.⁵

By tailoring PRO measures for each subtype, PRO Consortium helps provide drug developers with the tools necessary to incorporate the patient's voice into the process, enables targeting of the specific symptoms that matter most to patients, and provides a means of informing novel patient-focused endpoints.

For example, FDA expanded the label for the drug LINZESS® (linaclotide) to include results of a phase 3b clinical trial conducted by Ironwood Pharmaceuticals, Inc. and AbbVie Inc. that used DIBSS-C to assess an endpoint for improved abdominal symptoms (bloating, abdominal pain, abdominal discomfort).⁶ This is the first time a PRO Consortium measure has been used to support a label claim.

C-Path and PRO Consortium orchestrate collaborative efforts across diverse groups of stakeholders to make drug development tools, like the DIBSS, publicly available. Tools like the DIBSS-C enable patients' voices to be more effectively heard and incorporated into the medical product development process and accelerate the path of novel therapies to patients in need.

"The use of patient-reported outcomes to support a treatment's label expansion reinforces FDA's commitment to the needs of the gastrointestinal illness community. It is a clear indication that patient voices are being heard and a huge win for the community as a whole. IFFGD is proud to be a part of PRO Consortium's IBS Working Group and we are excited to see the continued emphasis on meeting true patient needs by listening to patient voices."

Ceciel T. Rooker, President of International Foundation for Gastrointestinal Disorders and a participant in the IBS Working Group

[Access Citations](#)

<https://c-path.org/programs/proc/>





Polycystic Kidney Disease Outcomes Consortium

IMPACT ON INDUSTRY AND PATIENTS

C-Path as Convener, Curator, Innovator and Accelerator

The cost of developing drugs has grown dramatically over the past 10 years, reaching nearly \$1 billion for a single new drug in 2018, at times resulting in little or no access to lifesaving medicine for patients.¹ An emerging field, called regulatory or drug development science, focuses on solving this challenge by generating innovative solutions that minimize risk and facilitate decision-making throughout the drug development process. Critical Path Institute (C-Path), established in 2005, is an independent nonprofit and worldwide partner of excellence in this field. C-Path serves as a neutral third party that convenes stakeholders, curates data, generates innovative solutions and accelerates drug product development.

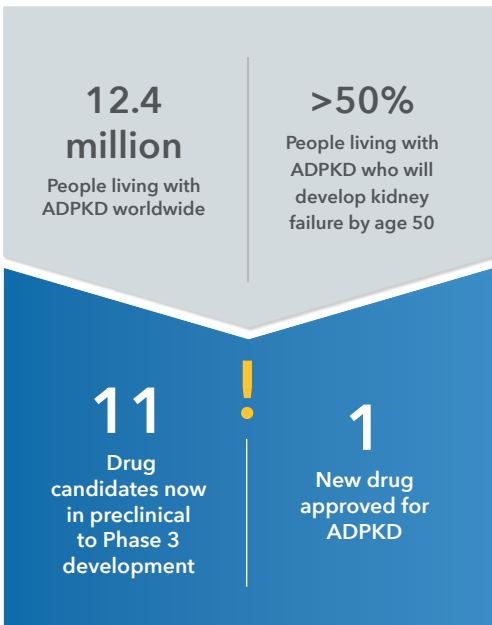
An orphan condition that has benefited from advances in drug development is autosomal dominant polycystic kidney disease, or ADPKD. ADPKD is a debilitating genetic disease which results in fluid-filled cysts developing in the kidneys.² These cysts grow larger over time, making the kidney less and less functional, ultimately leading to kidney failure.³

In 2010, no drugs were available for people living with ADPKD to prevent or slow the progression of the disease. A single drug, called tolvaptan, was under development, but many questions remained regarding how to best design adequate and efficient clinical trials for this or other drugs. These questions included how to identify which characteristics made patients optimal candidates to participate in clinical trials, how to best track the progression of the disease over the course of a trial, and how to determine whether or not the drug was working.

The first approved treatment for ADPKD is available now.

To address these challenges, C-Path launched the Polycystic Kidney Disease Outcomes Consortium (PKDOC) in 2010. PKDOC serves as convener, curator, innovator and accelerator in the ADPKD community to generate solutions that accelerate drug development science for individuals living with ADPKD.

As a convener, PKDOC has brought together stakeholders from patient advocacy groups, including the PKD Foundation, academic researchers, pharmaceutical industry companies, and representatives from regulatory and other government agencies around the world. Together, these stakeholders were able to use their knowledge, expertise and data to unlock key drug development questions in ADPKD.



As a curator and innovator, PKDOC led the development of an aggregated and integrated patient-level database of ADPKD registries and studies. These data sources included important information, like an innovative kidney imaging biomarker, called total kidney volume, or TKV. TKV is a measure of an individual's kidney size and can be used to indicate the change in kidney size over time. This metric was used as the foundation for a quantitative disease progression model, which served as the underlying evidence to support the endorsement (qualification) of the use of TKV to optimize patient selection in ADPKD clinical trials by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2016. In 2018, the evidence provided by the model also led to FDA designating TKV as capable of tracking disease progression and measuring efficacy of novel drugs in ADPKD clinical trials (i.e., a reasonably likely surrogate endpoint).

As an accelerator, PKDOC's contributions have enhanced the ADPKD drug development process. TKV was accepted as the basis of approval for JYNARQUE® (tolvaptan), the first treatment to slow kidney function decline in adults at risk of rapidly progressing for ADPKD. The designation of TKV as a reasonably likely surrogate endpoint has helped to stimulate a robust ADPKD drug development pipeline that now includes more than 10 drug candidates under evaluation from preclinical to the late clinical stages of testing. PKDOC continues its work to generate solutions that further accelerate ADPKD drug development.

The collaborative construct provided through C-Path's consortia has led to a generation of actionable solutions that enable the positive transformation of the drug development process. As a result, patients have access to better and safer drugs earlier than they otherwise would.

[Access Citations](#)

John Walsh of Albany, NY, inherited polycystic kidney disease from his mother. PKD causes cysts to grow in the kidneys, eventually causing them to lose function entirely (end-stage-kidney failure). He and his four siblings each had a 50/50 chance of having the condition passed down to them – all five of the Walsh brothers and sisters inherited it. The Walsh family has been living with the effects of PKD for more than 20 years. The progressive nature of the disease calls for the development of novel drugs to halt or delay the disease course.

While their mother died from the disease in 1993, each of the Walsh siblings has needed – and has received – a successful kidney transplant. These transplant organs have been donated by a family member, friend or even by complete strangers.

John was the sixth person in his family to undergo a kidney transplant (his niece also inherited PKD and needed one before John). When his turn came, it was John's lifelong friend, Augie Ortiz, who stepped up to help. "Think about tapping someone on the shoulder and saying, 'Hey, any chance you have two healthy kidneys and can I have one of those?' Regardless how good of a friend you are, it's a crazy thing," John said.

Through it all, John and his family have been adamant about sharing their stories and raising awareness about organ donation, and importantly, PKD research and drug development. Novel drugs that help delay or prevent end-stage-kidney failure in people living with PKD carry immense promise for this community. The Walshes all feel extremely blessed to have been able to witness and receive the generosity of others.

John (right) and his friend and kidney donor, Augie, just after the transplant in February 2019



<https://c-path.org/programs/pkd/>

Transplant Therapeutics Consortium

IMPACT FOR PATIENTS

TTC's work to qualify a reasonably likely surrogate endpoint will speed up drug development for kidney transplant patients.

Haley Jensen enjoys being active and relishes the outdoors, side effects she attributes to growing up in Evergreen, Colorado, a small town of about 10,000 people 30 miles west of Denver. The eldest of four siblings, Haley remembers her early childhood as that of any other kid from Evergreen: filled with soccer, hiking, skiing, swim team, and anything else that kept her and her siblings active.

But in high school Haley began to feel constantly fatigued. She had unexplained nose bleeds and other symptoms that drifted further and further away from that normal Evergreen childhood. Then, over Memorial Day weekend, Haley became sick enough that her dad took her to the local urgent care. The nurses struggled to measure her blood pressure, but when they did, they found it was dangerously high, and she was rushed by ambulance to the emergency room for care. With a sudden unexpectedness she describes as "a bolt of lightning," Haley's life changed forever.



Haley Jensen

100,000

People who are waiting for a kidney transplant

23,000

People who received a kidney transplant in 2019

Up to **50%**

Kidney transplants that will fail within ten years

2

Maintenance therapies approved in the last 15 years (long-term outcomes remain unchanged)

At the hospital, Haley's doctors diagnosed her with idiopathic kidney disease, kidney disease with no known cause, and she was immediately put on dialysis. Haley's doctors encouraged her to undergo peritoneal dialysis from home, and told her she would need to continue dialysis indefinitely, unless she could receive a kidney transplant.

For Haley, home dialysis was the best option by far. However, despite avoiding multiple hours-long visits to the dialysis center each week, home dialysis was still made difficult by constant physical, mental, and emotional exhaustion. Haley, with the support of her family, did her best to live a normal life. She continued to go to school and be as active as possible, at times even being wrapped up in hockey pads by her dad to keep her safe while playing soccer. She swam as much as possible, but was limited by feeling chronically unwell and fatigued. Although Haley loved to eat good food, dialysis came with severe dietary restrictions and she found she had little appetite. Worse, Haley had a constant fear of infection and there was an emotional toll from the ever-present machines in the bedroom she shared with her little sister. While at times her days could feel somewhat normal, for six months Haley had to hook up to those machines every evening, cementing the impossibility of a "normal" life.

When the call finally came that a kidney was available, she was so excited to say goodbye to her machines she didn't have time to worry about the massive surgery she was about to undergo. Thanks to Haley's amazing team at Children's Hospital Colorado, the benefits of the procedure were immediate. Haley recalls her parents saying she "looked better coming out of surgery than she had going in." After surgery, the first thing Haley did was have as much chocolate and milk as she could, something her diet didn't allow during her months on dialysis.

Haley says she quickly felt better after her procedure, but admits there were major adjustments. Although Haley says she "will do whatever it takes to keep her organ healthy" to avoid needing dialysis again, she has found that keeping her kidney healthy is a full-time job. In addition to needing regular specialty care from a team of clinicians, Haley must eat well, exercise regularly, stay hydrated, and live as healthy a lifestyle as possible. Most importantly, Haley says her days often seem to revolve around the regimen of at least seven different medications she takes multiple times each day as a result of her transplant. Haley takes so many medications she has had to adopt an abundance of techniques to make sure she always has medication available and remains adherent to her regimen.

Many of her medications prevent her immune system from rejecting her kidney, referred to as "immunosuppressive therapies," but many others are needed to treat the physical and emotional side effects that these life-saving therapies cause. Haley has experienced tremors, memory problems, dietary issues and many other side effects. Haley says she sometimes struggles to know if a new symptom is a side effect of her drugs or something new. Haley also carries the emotional burden of worrying about the long-term risk of life-threatening infections, skin and other rare cancers and the difficulties she will likely face having a family with her new husband.

Haley knows that even under the best circumstances, complications around her transplant will inevitably arise. "Eventually, something is going to go wrong, and something is going to happen to my transplant," Haley says. While these medications are "tremendously appreciated" and

Haley "wouldn't trade them for the world," the currently available medications have significant limitations. Better options for patients like Haley are needed. In addition to bad side effect profiles, long-term outcomes for transplant recipients who take the currently available regimens remain unacceptably poor. According to the United States Renal Disease System's (USRDS) 2019 report, graft-survival rates were 93-98% one-year after transplant, but only 34-50% by 10-years.

"This matters. Part of the reason why I have a kidney is to be able to live my life, and I want to be able to live it."

Despite the high burden of unmet needs felt by kidney transplant recipients and poor long-term outcomes, drug development for this condition has remained largely stagnant for decades. The most widely cited barrier to development is the lack of "surrogate endpoints" that would allow shorter clinical trials to predict long-term outcomes. Without this type of endpoint, clinical trials must be large and/or lengthy, and therefore expensive, in order to determine the long-term benefits of a new therapy. In the face of high costs of development, drug companies have turned their attention to other conditions, leaving patient needs unmet.



To meet this need and to help provide access to better medications for kidney transplant recipients, the Transplant Therapeutics Consortium (TTC) was co-founded in 2017 by the Critical Path Institute (C-Path), the American Society for Transplantation and the American Society for Transplant Surgeons. TTC is a public-private partnership of the transplant community, and includes the pharmaceutical industry, clinicians, academic researchers and regulatory agencies. TTC's mission is to accelerate the pace of medical product development for transplant recipients, focusing first on kidney transplantation.

Building on over a decade of work by Dr. Alexandre Loupy and the Paris Transplant Group, TTC aims to decrease the time required to bring a new product to patients by seeking regulatory endorsement of the iBox Scoring System as a surrogate endpoint capable of predicting long-term kidney transplant outcomes.

To achieve this goal, TTC is pursuing qualification of the iBox Scoring System through the Food and Drug Administration's (FDA) Biomarker Qualification Program and the European Medicines Agency's (EMA) Qualification of Novel Methodologies pathway. Qualification will require a large amount of data from a wide variety of sources. TTC leverages the pre-competitive space it creates to carry out a global data sharing effort, which now includes data from 11 clinical trial or clinical center sources, representing over 15,000 kidney transplant recipients.

The iBox Scoring System was recently accepted into FDA's Biomarker Qualification Program, bringing this tool one step closer to being publicly available for use. While formal qualification of the iBox is likely two to three years away, the transplant community's knowledge of the data supporting this tool is increasing with each monthly consortium meeting and each new shared dataset, increasing the community's confidence in the use of this tool.

The potential availability of a new surrogate endpoint has helped to reshape the drug development landscape for transplantation. For the first time in decades, multiple companies are considering clinical trials that will utilize this new surrogate endpoint, bringing hope for better treatments to kidney transplant recipients.

Haley, who was recently awarded an MBA and MPH from Boston University, says the most important message she'd like the drug development community to hear is simply, "This matters. Living with a kidney transplant is not easy, but is infinitely better than not having one at all," Haley says. "One of the many great things about having a transplant is, despite the difficulties, it's not enough to keep me from living my life and thinking about the future. Part of the reason why I have a kidney is to be able to live my life, and I want to be able to live it."





LOOKING AHEAD

As the pace of research continues to move at an increasingly faster rate, C-Path has grown into its role as a true leader in the aggregation, curation and analysis of data.

Further, the Institute facilitates data sharing. By getting the right information in front of the right teams, we are able not only to inform new research directions and catalyze new ideas and techniques, but to help shape newer and better methods to conduct and capitalize on the research that is targeting treatments for rare diseases.

With our unique operating model, which fosters collaboration among leaders from the pharmaceutical and biotech industries, universities, patient organizations and regulatory agencies around the world, C-Path is leading the charge to improve upon the ways drug development has been managed in the past and bring about a paradigm shift that is revolutionizing the ways we envision, attain and maintain good health.

The clear impact we are making, particularly in the areas of translational and regulatory science, form the

basis of a positive feedback loop, with demand from biotechnology companies, pharma companies and patient groups for C-Path participation and collaboration on projects continuing to rise. This is resulting in a period of rapid growth and expansion of the Institute to cover new disease spaces, a broader swath of the regulatory landscape and more extensive geographical regions.

In fact, C-Path has grown from seven consortia and programs to 16 in the span of five years, and our talent within the Institute has increased by 130 percent in the same timeframe. This exciting expansion has provided the scope and resources for C-Path to beneficially impact the lives of patients across an increasing number of diseases.



To ensure that this growth will build on C-Path's 15-year legacy, C-Path worked with a leading global management organization to collaborate on the development of a 5-year strategic plan. By pulling in experts from across the drug development industry and health regulatory sector, C-Path is defining an executable vision for the itself.

The work to draft a new strategic plan was divided into three phases, running from November 2019 to November 2020.

STAGE 1

Assess the current state of C-Path's strategy and aspirations through interviews with C-Path employees, the leadership team, Board members and external stakeholders.

STAGE 2

Articulate a preliminary roadmap based on the priority areas uncovered in Stage 1.

STAGE 3

Refine the preliminary findings in an iterative process with C-Path leadership to ensure the delivery of a robust final plan.

Significant progress has already been made, and C-Path is on a trajectory to increase our impact and success as we move toward completing our second decade together. Our thanks to our many stakeholders who have contributed to this project.

FINANCIAL UPDATE

With continued support from key stakeholders throughout the broader global health landscape — including patients and their families, donors, foundations, academics, biotech and pharmaceutical companies, and regulatory agency advisors — C-Path continues to home in on realizing the vision of the healthier world we are committed to making a reality.

Significant financial news this year includes:

5-year renewal of main grant with FDA

✓ Continue C-Path's Core Activities to Innovate Medical Product Development

C-Path will continue to advance its core competencies in the areas of data science, quantitative analytics, and regulatory knowledge to support the development of new approaches that further medical innovation and regulatory science to address unmet needs in the medical product development process.

Additional funding from FDA

✓ Develop a Comprehensive Model-Informed Drug Development (MIDD) Education and Training Program

C-Path will collaborate with academic partners to generate the curriculum and content for an online training course in MIDD for FDA scientists, with a focus on those without modeling and simulation expertise. C-Path will also offer post-doctoral training in MIDD, which will leverage the patient-level data from C-Path consortia to develop a clinical trial simulator/model. If possible, these fellowships will be organized in collaboration with FDA.

✓ Establish a Data and Analytics Platform (DAP) for the Rare Disease Cures Accelerator (RDCA)

Utilizing its expertise in aggregating, curating,

and analyzing patient-level data, C-Path will partner with the National Organization for Rare Diseases to establish the infrastructure for hosting, curating, standardizing, and analyzing rare disease data from a wide range of data and host a kick-off meeting of diverse stakeholders in the field of rare diseases.

✓ Enhance the Pediatric Medical Device Ecosystem

Gather input and feedback from among key stakeholder groups at the pre-consortium meeting to help advance the development of a novel ecosystem framework for pediatric medical devices; aim to produce actionable suggestions that may be used to form a new consortium that would design, advise the ecosystem, and report out meeting results through a white paper.

✓ Explore Quantitative Measures Beyond HbA1c in Diabetes Drug Development

Collaborate with stakeholders in the pediatric and adult diabetes communities to construct a patient-level database of existing continuous glucose monitoring (CGM) device data and assess methods used to analyze such data. The ultimate impact of this collaboration will be to provide regulatory grade solutions that will inform the evaluation of diabetes products related to clinically meaningful outcomes and glycemic control for diabetes patients.

✓ **Facilitate drug repurposing for diseases of high unmet medical need through the CURE ID app**

Establish the CURE Research Collaboratory, a public-private partnership to advance the collection of real-world data to generate real world evidence that can inform drug repurposing for areas of high unmet medical need, including emerging/reemerging infectious diseases, anti-microbial drug resistant infections, neglected infectious diseases, diseases in pediatric populations and pregnant women. The Collaboratory will expand to other rare diseases, including oncologic conditions, where there is little financial incentive to develop new therapies.

✓ **Establish the Acute Kidney Injury (AKI) Working Group and Optimization the Collection of Translational Biomarker Data to Develop Better Predictive Tools for Kidney Toxicity (funded with carryover)**

Utilizing its expertise in convening stakeholders, C-Path will partner with scientific leaders across the nephrology community to devise an action plan for the development of predictive tools and standards for DIKI for use in clinical investigations of novel therapies. C-Path will also optimize its approach to collecting, aggregating, curating, analyzing, and sharing of translational biomarker data using the already established Biomarker Data Repository (BmDR). This specific aim will ultimately support the development and implementation of predictive tools of AKI.

✓ **Establish a Rare Disease Clinical Outcome Assessment Consortium**

Leveraging the framework of, and expertise within, PRO Consortium, establish a pre-competitive, multi-stakeholder consortium aimed at helping

to address the unmet public health need for approved therapies to treat rare diseases. The long-term goal of this new consortium is to accelerate the development of new medical products by creating and curating a database of publicly available patient-focused endpoint measures that are potentially fit-for-purpose in assessing clinical benefit of emerging treatments for people with rare diseases.

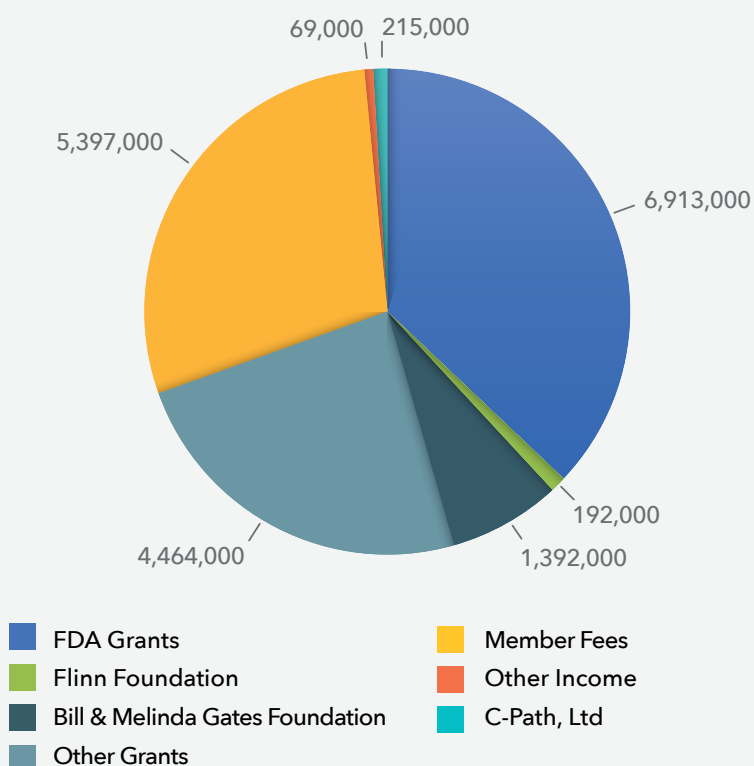
✓ **Preliminary Research to Support Qualification of an Activity Monitor-based Endpoint Measure to Evaluate Physical Activity in Persons with Chronic Heart Failure**

This project seeks to increase our understanding of the nature of physical activity carried out by persons with chronic heart failure (CHF) and characterize the level and types of physical activity identified as being important and meaningful in their daily lives. This will inform the appropriate use of wearable activity monitors (actigraphy) in CHF drug development as a complement to the traditional measures of clinical benefit in CHF treatment trials.

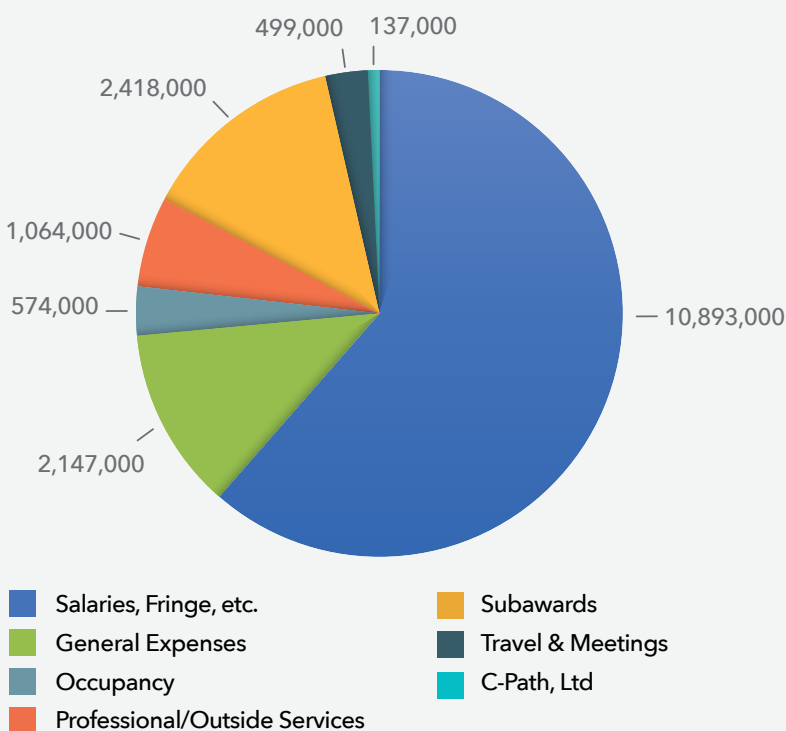
✓ **Qualification Plan Preparation to Support PROMIS Fatigue Short Form for Individuals with Multiple Sclerosis**

This project is aimed at preparing and submitting a Qualification Plan for the PROMIS® FatigueMS-8a as the next step in the CDER COA Qualification Program. The long-term result of this project will be an FDA-qualified, publicly available PRO measure for assessing fatigue severity in MS clinical trials, which will fill a critical gap in the assessment of fatigue in MS treatment trials.

C-PATH 2020 FISCAL YEAR REVENUE: \$ 18,643,000



C-PATH 2020 FISCAL YEAR EXPENSES: \$ 17,732,000



Fiscal Year 2020

ASSETS

Cash and Cash Equivalents	\$ 11,266,558
Certificates of Deposit	\$ 3,143,650
Accounts Receivable	\$ 2,575,419
Property and Equipment, Net	\$ 83,834
Other	\$ 52,650

TOTAL ASSETS \$ 17,122,111

LIABILITIES AND NET ASSETS

Liabilities

Accounts Payable	\$ 615,886
Accrued Expenses	\$ 609,491
Deferred Revenue*	\$ 6,802,009
Deferred Rent	\$ 67,613

Total Liabilities \$ 8,094,999

Net Assets

Undesignated	\$ 3,748,508
Board Designated**	\$ 1,770,923
Coordinating committee designated	\$ 2,946,209
Property and Equipment	\$ 83,834
Donor Restricted	\$ 477,638

Total Net Assets \$ 9,027,112

TOTAL LIABILITIES AND NET ASSETS \$ 17,122,111

* Pre-awarded funds received for grants

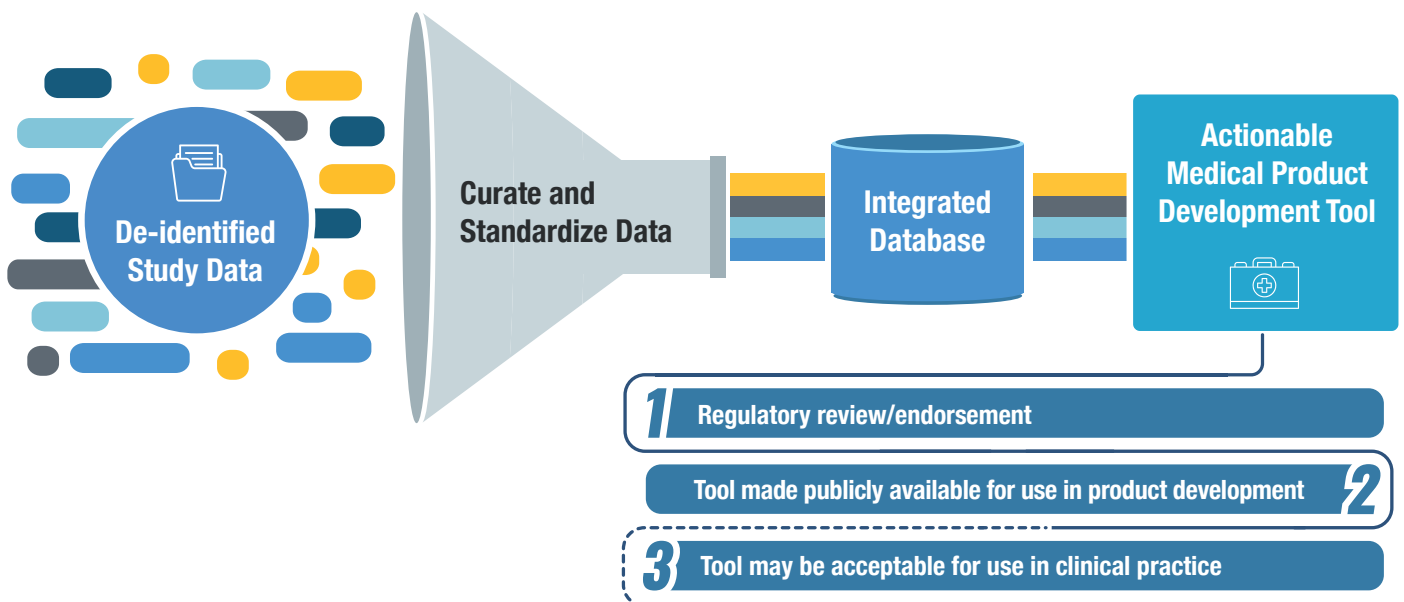
** Consortia fees managed by C-Path to support consortia activities

C-PATH INITIATIVES

Active Consortia, Programs and Public-Private Partnerships



The **Biomarker Data Repository (BmDR)**, launched by C-Path’s Predictive Safety Testing Consortium (PSTC), is a repository for data on novel translational safety biomarkers from drug development programs. Masked, de-identified data from multiple sponsors is collected and stored in a secure repository, and that data is then made available to C-Path and U.S. Food and Drug Administration staff. The data is used to support research that leads to the submission of documents to worldwide regulatory agencies to qualify novel safety biomarkers for new Context of Use (CoU) statements as well as to modify and expand existing CoU statements and to identify appropriate exploratory biomarkers to advance drug development in the future. The initial pilot focuses on kidney safety biomarkers, and the main goal of the BmDR is to provide industry with new drug development tools. Existing biomarker data could be used to significantly advance and accelerate understanding of the utility of novel biomarkers as drug development tools.





The **CURE Drug Repurposing Collaboratory (CDRC)** is a public-private partnership initiated in June 2020 by C-Path and the U.S. Food and Drug Administration (FDA) in partnership with the National Center for Advancing Translational Sciences (NCATS), part of the National Institutes of Health (NIH).

CDRC, in partnership with the FDA-NCATS CURE ID* platform, is a dedicated initiative designed to capture real-world clinical outcome data to advance drug repurposing and inform future clinical trials for diseases of high unmet medical need. The initiative includes emerging/reemerging diseases, anti-microbial drug-resistant infections and neglected infectious diseases as well as rare oncology diseases where there are limited treatment options. The Collaboratory is strongly interested in capturing data from diverse populations including pediatric and pregnant women. C-Path leads CDRC, with participation from a diverse set of global stakeholders including, but not limited to, clinicians, scientists, U.S. Health and Human Services (HHS) agencies, non-government organizations, foundations and societies.



The **Critical Path for Alzheimer’s Disease (CPAD) Consortium** was founded to create new tools and methods that can be applied to increase the efficiency of the development process of new treatments for Alzheimer’s disease (AD). Alzheimer’s disease is recognized as a major public health issue because the burden is large, the public health impact is major, and there is growing interest in intervening earlier in the disease process. This requires a robust understanding of disease progression across all stages of disease. CPAD focuses on pre-competitive sharing of high-quality industry clinical trial and observational study datasets with the ultimate goal of developing a comprehensive disease progression model across the entire continuum of AD — from the earliest stages to severe AD — providing an invaluable tool that will aid in optimizing trial design and execution, reduction of cost and time, and reduced patient burden, with significant impact on regulatory science.

2019-2020 Impact

- ✓ CPAD is developing tools that will aid in optimizing clinical trial design and execution for AD and related diseases by spearheading a C-Path industry data sharing initiative to expand the acquisition of contemporary patient-level clinical trial data that will be incorporated into a comprehensive disease progression model.
- ✓ First Quantitative Modeling Working Group (QMWG) convened in February 2020, focused on leveraging the quantitative expertise of CPAD members and the C-Path Quantitative Medicine Program to conduct meta-data and patient-level data analysis and to generate novel quantitative drug development tools across the AD continuum. CPAD has also initiated work on generation of a unified multi-modal image analysis methodology which will result in harmonized and standardized extraction of information from neuroimages.
- ✓ The AD clinical trial data repository continues to grow significantly and now contains 41 studies with 20,549 individual anonymized patient records. It has been utilized by 456 approved applicants from around the globe, covering over 150 distinct organizations from pharmaceutical industry, government agencies, nonprofit organizations, academia, and independent researchers, from more than 40 different countries.



The **Critical Path for Parkinson's (CPP) Consortium** was created in partnership with Parkinson's UK, one of the largest charity funders of Parkinson's research in EU. Parkinson's has traditionally been viewed as a disorder in which individuals don't have enough dopamine, because specific nerve cells inside the brain have died. Current research, however, indicates that the processes leading to dopamine deficit start much earlier (decades), increasing the need to understand the early stages of Parkinson's progression. CPP brings together pharmaceutical companies and academic partners working toward a common goal of sharing data precompetitively aimed to optimize and improve the design of clinical trials for Parkinson's disease. CPP is focused on accelerating drug development for patients with early motor manifestations of Parkinson's disease (PD) by quantifying disease progression along the continuum and advancing drug development tools for regulatory endorsement. Early intervention holds promise in the target population, given that delaying disease progression is a priority need as expressed by people with PD.

2019-2020 Impact

- ✓ CPP is enabling efficient paths to gene-based therapeutics
 - CPP's global integrated database consisting of 12,000 clinical studies is now being used to design the first gene based therapeutic trials in Parkinson's disease
 - The CPP integrated database has been used to demonstrate that the rate of progression of subjects carrying the LRRK2 genetic mutation is unexpectedly slower than idiopathic PD subjects. The results were published in peer review open access journal on behalf of the CPP modeling team and results include clinical trial simulations to aid sponsors in designing trials that target LRRK2 subjects. These results will serve to optimize clinical trial designs to assure the studies are powered adequately to detect meaningful treatment benefit.
 - CPP successfully recruited two new biotechnology companies pursuing gene-based therapeutic targets to join CPP as regular members. These firms have assets early in development yet there is recognition that the CPP tools and database can help to streamline their path forward to regulatory approval.

- ✓ Focus on Patient-Centered Drug Development
 - The Parkinson's disease clinical trial data repository continues to grow significantly and now contains 18 studies with 12,400 individual anonymized patient records. It is being used by clinical trialists from around the globe to optimize clinical trial designs and identify novel approaches to define patient centric clinically meaningful measures.
 - CPP is engaging people with Parkinson's directly to advance concepts and initiatives that align with the voice of the patient in all stages of drug development.
 - CPP has officially welcomed people living with Parkinson's to join CPP's working group aimed at optimizing digital health technologies that align with the needs of patients.

- ✓ CPP has gained visibility for leadership in optimizing the advancement of digital health technologies in PD clinical trials
 - CPP's 3DT project was highlighted at the 2019 Patient-Focused Drug Development workshop by the FDA as an exemplary case for open science needed to advance the use of remote technologies in PD trials. 3DT is poised to represent the first case example of acquiring digital sensor data from multiple device platforms to C-Path's Data Collaboration Center, setting a precedent to apply to other diseases.
 - A manuscript on behalf of the CPP digital drug development tool (3DT) team is featured in a dedicated special issue of a leading-peer reviewed journal entitled, "The Future of Digital Health." This manuscript outlines new paths on how worldwide collaborations can effectively align with regulatory agencies *early and often* to efficiently advance tools forward that are aligned with the voice of patients living with Parkinson's.



The **Critical Path for Sickle Cell Disease (CP-SCD)** was launched in April of 2020. It is a collaboration set up to develop community consensus on how to optimize and accelerate drug development for this rare disease. Sickle cell disease research has been limited for some time, but recent interest in the disease and novel technologies have resulted in many potential therapeutics in development, as well as the first drug approvals. However, the path to regulatory approval of these new therapeutics is challenged by limited understanding of the natural history of the disease and how to measure therapeutic effects. The mission of CP-SCD is to support collaborative development and regulatory endorsement of new medical product development tools. These tools will help to optimize and de-risk clinical trials to increase the efficiency in developing and delivering safe, effective treatments for people living with sickle cell disease.



The **Critical Path to TB Drug Regimens (CPTR)** initiative was created through a partnership between the Bill & Melinda Gates Foundation, TB Alliance and C-Path to promote innovation in regulatory science needs to accelerate development of novel drug regimens for tuberculosis (TB). Tuberculosis is a disease that still impacts one-third of the world's population, which is in desperate need of a safer, shorter-duration and more effective drug regimen. Much of this critical work is enabled by a global data-sharing initiative, funded by the Bill & Melinda Gates Foundation and led by C-Path and partner organizations, which include the World Health Organization, TB Alliance, and multiple data contributors representing industry, academia and government agencies.

2019-2020 Impact

- ✓ Through the development of new or better validated tools and methodologies, sponsors are better able to de-risk and expedite decisions related to their drug development programs.
- ✓ Completion of the CPTR quantitative medicine efforts have contributed to the establishment of a comprehensive pipeline of over twenty new drug candidates and regimens against TB.
- ✓ With the completion of the TB-REFLECT model-based meta-analysis, insights gained regarding the impact of measuring drug exposure were used to optimize the design of clinical trials to evaluate new regimens. This work contributed to the design of contemporary clinical trials, which have resulted in the approval of four new treatments against TB.
- ✓ CPTR designed and implemented the Relational Sequencing TB Data Platform (ReSeqTB), a one-stop source

for curated, aggregated, and clinically relevant genetic drug resistance data, and deployed this technology to support the tuberculosis drug resistance surveillance program at the World Health Organization.

- ✓ The TB-PACTS database now has a total of 17 datasets, with eight undergoing curation to be integrated. To date, 36 researchers have been granted access to TB-PACTS data for use in TB drug development. A bigger database maximizes the utility of each patient-level data point, and supports the generation of actionable solutions to continue to accelerate drug development against TB.



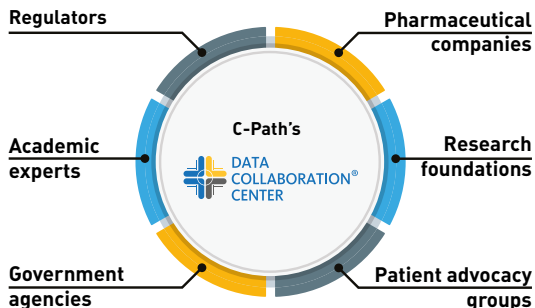
The **Data Collaboration Center (DCC)**, which built and manages C-Path's Online Data Repository (CODR), has the goal to enable multiple organizations to work together to share medical research data, in order to optimize its value in creating new insights and tools that accelerate drug development in areas with unmet medical needs. DCC supports data-sharing projects aligned with specific C-Path consortia, as well as data-sharing initiatives that are independent of C-Path consortia. All of DCC's work takes place in a neutral, precompetitive environment, utilizing appropriate data standards. DCC possesses the technical and scientific subject matter and project management expertise necessary to support advanced research efforts.

DCC solutions include: development of customized data-sharing platforms, planning and execution of multisource data aggregation and standardization, sustainable curation and administration of data and its storage, ability for teams to work together to analyze and interpret data; robust security policies and framework, and application of current regulations to ensure compliance.

2019-2020 Impact

- ✓ C-Path, in concert with NORD and funded by FDA, launched the Rare Disease Cures Accelerator Data and Analytics Platform (RDCA-DAP). The project focuses on providing a centralized and standardized infrastructure to speed up rare disease characterization and drive faster therapy development.
- ✓ In partnership with the Translational Genomics Research Institute Pathogen and Microbiome Division (TGen-North), DCC has completed the first phase of "Prevent-HAARM" (Healthcare-Associated Antimicrobial-Resistant Microbes), a pilot framework to track and respond to antimicrobial resistance in Arizona.
- ✓ Members of the Data Science team participated in a DREAM Challenge sponsored by the Cancer Moonshot initiative to create a National Cancer Data Ecosystem to collect, share, and interconnect a broad array of large datasets so that researchers, clinicians, and patients will be able to both contribute to and analyze data.

PEOPLE



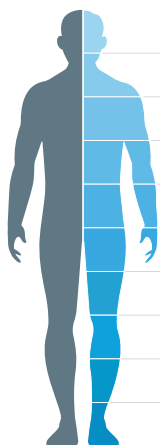
Number of bio and pharma companies

282



>1,600
scientists and
researchers
participate

DATA



- Alzheimer's disease
- Parkinson's disease
- Tuberculosis
- Solid organ transplant
- Kidney disease
- Duchenne muscular dystrophy
- Multiple sclerosis
- Type 1 diabetes
- Huntington's disease
- Friedreich's ataxia

We cover ten different therapeutic areas with clinical, genomic, phenotypic, and other data types, along with nonclinical data

163

nonclinical
trials



165

clinical
trials

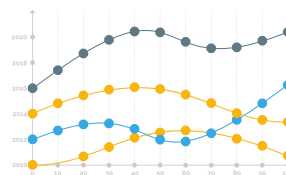
>150,000

data subjects



**>215
million**

collected data
points



IMPACT

FDA

PRO
measure

- TKV imaging biomarker
- Nonclinical kidney biomarker
- AD trial simulation tool
- AD biomarker
- PD biomarker
- Safety biomarkers

EMA

in vitro
HFS-TB

HV
imaging
for AD

7



groundbreaking quantitative
solutions for drug
development



regulatory
endorsement
of tools and
methodologies

CDISC Therapeutic Area User Guides (TAUGs)

39

developed/
published



5

in process



82
countries

Our Data Collaboration Platform has been accessed
by researchers from more than 78 countries



The **Duchenne Regulatory Science Consortium (D-RSC)** was formed in partnership with Parent Project Muscular Dystrophy (PPMD) to aggregate data and develop tools to improve clinical trial design and to accelerate the development of new therapies for Duchenne muscular dystrophy, which is an urgent unmet medical need. Duchenne is a genetic disease that causes progressive loss of muscle, cardiac issues, the inability to walk and breathe, and ultimately results in premature death. Through the integration of patient-level data from observational studies and clinical trials, D-RSC aims to generate a set of models that describe disease progression across the disease continuum, as a basis for a comprehensive clinical trial simulation tool.

This tool will improve trial protocol development and optimize the number of patients needed to demonstrate the effect of new therapies, thereby accelerating the development of the therapies for this disease.

2019-2020 Impact

- ✓ D-RSC drove alignment with global regulators around how the disease progression models may be best applied to design more optimal clinical trial protocols.
- ✓ D-RSC developed the first disease progression models of five endpoints used in DMD trials. Each model explains at least 30% of the variance in progression in the population (endpoint dependent), allowing users to design shorter or smaller trials that will demonstrate if a therapy is effective.
- ✓ D-RSC's clinical trial simulation platform allows users a user-friendly interface to simulate the results of trials of potential therapies and optimize trial protocols, reducing uncertainty about effectiveness of therapeutics.



The **Electronic Patient-Reported Outcome (ePRO) Consortium** was established to advance the science surrounding electronic collection of clinical outcome assessment data in clinical trials. ePRO Consortium provides a pre-competitive environment in which a critical mass of experts collaborates to support and conduct research, design and deliver educational opportunities, and develop and disseminate best practice recommendations for electronic collection of clinical outcome data.

2019-2020 Impact

- ✓ In collaboration with C-Path's PRO Consortium, ePRO Consortium developed a presentation, posted publicly in April 2020, that provided sponsors and eCOA providers with guidelines and recommendations for capturing PRO data originally intended to be collected electronically from study participants during in-person visits to study sites. This information enabled sponsors and eCOA providers to implement alternative data collection strategies to allow clinical trials to continue despite the challenges posed by COVID-19 and the resulting public health precautions and study subject concerns.
- ✓ ePRO Consortium conducted an electronic implementation assessment of patient (child) and observer diaries that are in development within PRO Consortium's Pediatric Asthma Working Group under an FDA BAA contract, providing important feedback to enhance the suitability of these measures for electronic implementation in future research and clinical trials.

FA-ICD

The **Friedreich's Ataxia Integrated Clinical Database (FA-ICD)** is designed to catalyze and accelerate Friedreich's ataxia (FA) research and drug development by curating and standardizing FA clinical trial and natural history data into CDISC format and making this data publicly available to qualified researchers. These researchers can access and analyze data in aggregate, or filter and view de-identified patient-level data from four clinical trials and a large FA natural history study. The initiative represents a collaborative partnership between the Friedreich's Ataxia Research Alliance (FARA) and C-Path, with a goal of expanding the FA-ICD platform by engaging with other data contributors to secure additional datasets.

2019-2020 Impact

- ✓ FA-ICD has shared data with ten companies interested in FA drug development who have accessed the data to inform their future clinical trial design.
- ✓ FA-ICD data was used to support new analyses of the Friedreich's ataxia rating scale to optimize the measure for use in clinical trials.
- ✓ FA-ICD data is being used by RDCA-DAP to help design the new data and analytics platform to ensure that data is accessible, interpretable and able to be analyzed by users.



The **Huntington's Disease Regulatory Science Consortium (HD-RSC)** was created in partnership with the CHDI Foundation, a nonprofit biomedical research organization exclusively dedicated to collaboratively developing therapeutics that will substantially improve the lives of those affected by Huntington's disease. Huntington's disease is an autosomal-dominant inherited neurodegenerative disorder characterized by motor impairment, cognitive decline, and neuropsychiatric disturbances, making it imperative to optimize the understanding of disease progression. With the goal of improving the efficiency of development, review and approval of emerging therapeutics for Huntington's disease, this global initiative aims to facilitate interaction between biotech and pharmaceutical industry partners with regulatory agencies to work towards the regulatory acceptance of drug development tools, biomarkers and better clinical outcome assessments. HD-RSC will also collect and standardize natural history and clinical trial data from HD patients around the world to develop an integrated database of patient-level data, which will be used to gain a better understanding of disease progression dynamics and work towards model-informed drug development to de-risk HD programs and accelerate the global regulatory approval of urgently needed HD therapies.

2019-2020 Impact

- ✓ Several new members have joined HD-RSC, bringing the total number to 36 stakeholders. This growth has expanded the consortium's reach throughout the global HD community.
- ✓ Jointly with D-RSC, HD-RSC has published a manuscript on the value of standardized data structures in rare diseases in the journal *Clinical and Translational Science*.

- ✓ HD-RSC has now acquired five observational datasets and data from three interventional clinical trials (one placebo-arm only) and has in-house approximately 18,000 individual anonymized patient records. This data is being used to develop a clinical trial simulation tool to study natural disease progression across multiple clinical outcome measures.
- ✓ HD-RSC outlined a biological-based disease framework for use in HD clinical research. The framework represents a paradigm shift in conceptualization of the disease on a biological continuum, beginning with the presence of the causative gene rather than the onset of clinical signs and symptoms that occur later in life.



The **International Neonatal Consortium (INC)** is a global collaboration forging a more predictable regulatory path to evaluating the safety and effectiveness of therapies for neonates. Due to reasons related to a complex and rapidly changing physiology, lack of reference standards (e.g., unknown laboratory value reference ranges, an unsystematic adverse event reporting system, etc.), and differences in perception of the importance of neonatal research between key stakeholders, drug development in neonates remains a perpetual challenge. The last drug that significantly impacted survival in preterm neonates was approved over 30 years ago. Clinical trial activity in the neonatal population remains minimal (<1% of currently registered trials are in neonates), and the vast majority of drugs (>90%) in this population are used off-label, which greatly impacts an objective evaluation of safety and efficacy of the drugs. INC aims to accelerate the development of safe and effective therapies for neonates. INC engages the global neonatal community—families, neonatal nurses, academic scientists, regulators, pharmaceutical investigators, advocacy organizations, and funders—to focus on the needs of the neonate. Through teams that share data, knowledge, and expertise, INC develops tools that can be incorporated into clinical trials for neonates.

2019-2020 Impact

- ✓ Hemodynamic Adaptation - Standardizing measurements of Blood Pressure (BP) in neonates: Current gold standard methods of accurately measuring BP in neonates usually involve invasive methodologies such as intra-arterial catheters. INC's Hemodynamic Adaptation workgroup provided recommendations based on a systematic review and analysis of published literature on methods of measuring BP in neonates. These recommendations (site of measurement: right vs. left upper arm vs. lower limb;

types of methods: oscillometric vs. intra-arterial catheter) will form the basis of a standardized BP measurement protocol in neonates, reduce variability as well as improve routine clinical care.

- ✓ Neonatal Adverse Event Severity Scale - An effort to standardize safety assessment and reporting in neonatal clinical trials: Recognition and classification of adverse events in the neonatal population is challenging because of complex physiology, multi-organ system involvement, and symptoms not similar to classification systems in adults and older children. INC utilized Delphi approach to develop a 5-grade, 35-point neonatal terminology and a neonatal adverse event severity scale that are now widely available and used standards, providing an important and easy-to-use method for standardizing the adverse event reporting in clinical trials. This scale has been published on the NCI/NIH website, translated into Japanese, and adopted by regulatory agencies for safety reporting in neonatal clinical trials.



The **Multiple Sclerosis Outcome Assessments Consortium (MSOAC)** collects, standardizes, and analyzes data about multiple sclerosis (MS) that have been generated over several decades, with the goal of qualifying a new measure of disability as a primary or secondary endpoint for future trials of MS therapies. MS is a demyelinating disease in which a specific layer of nerve cells in the brain and spinal cord are damaged. This damage disrupts the ability of parts of the nervous system to exchange information, resulting in variety of signs and symptoms, requiring the optimization of outcome measures to capture these relevant aspects of disease. MSOAC works on the development of such optimized outcome measures by bringing together members from academia and industry, regulatory authorities, patient advocacy groups and individuals living with multiple sclerosis, aiming to speed the development of new therapeutic options for this disease.

2019-2020 Impact

- ✓ The EMA issued a positive qualification opinion that will improve trial design by offering sponsors more flexibility and choice of performance outcome measures.
- ✓ The use of a control arm MS database was extended to 47 qualified researchers, facilitating a range of studies on MS disease progression.
- ✓ MSOAC received a positive Determination Letter from FDA accepting the Qualification Plan, moving one step closer to qualification at FDA and facilitation of improved clinical trials using COAs in MS.



The **Polycystic Kidney Disease Outcomes Consortium (PKDOC)** brings together leading nephrologists and other scientists from academia, industry, and government to spur the development of new therapies for patients with polycystic kidney disease (PKD). PKD is a disorder that affects the kidneys, in which collections of fluid (cysts) develop, interfering with the kidney's ability to filter waste products from the blood. The growth of cysts causes the kidneys to become enlarged and can lead to kidney failure. PKDOC's mission is to develop drug development tools and methods to promote research that will lead to the development of treatments for PKD and improve the lives of all it affects. PKDOC has developed CDISC data standards for PKD and aggregated clinical data from Autosomal Dominant Polycystic Kidney Disease patients collected over many years in patient registries and observational studies. These data enabled the development of a disease-biomarker progression model that provided the support necessary for the U.S. Food and Drug Administration and European Medicines Agency to qualify an imaging biomarker, Total Kidney Volume, for use as an enrichment strategy in drug development trials. PKDOC continues to work on alternative endpoints and clinical trial designs.

2019-2020 Impact

- ✓ A new TKV modeling proposal has been initiated. This effort will result in the development of tools to optimize clinical trial design for PKD therapies (from patient selection, to endpoint optimization, to sample size and power calculations, to attrition, to frequency of observations).
- ✓ The consortium has maintained monthly meetings to serve as an effective forum for informing the PKD community about important activities such as quantitative imaging, composite endpoints, eGFR trajectory, genetic studies for autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic disease (ARPKD), and biomarker surrogacy.



The **Patient-Reported Outcome (PRO) Consortium** brings together drug developers, measurement scientists, patients, clinicians and regulators to collaborate on effectively incorporating the voice of the patient into the drug development process. Its primary goal is to obtain regulatory qualification of patient-reported outcome measures and other clinical outcome assessments (COAs) for use in clinical trials where

COAs can, and should, be used to evaluate patient-focused clinical benefit. In addition to the four PRO measures previously qualified by FDA, PRO Consortium had 15 COAs in FDA's COA Qualification Program at the end of this fiscal year.

2019-2020 Impact

- ✓ Sixteen licenses have been issued for use of the Myelofibrosis Symptom Assessment Form (MFSAF) v4.0 in treatment trials.
- ✓ Twenty-three licenses have been issued for use of the *Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ)* in treatment trials.
- ✓ Nine licenses have been issued for use of the *Symptoms of Major Depressive Disorder Scale (SMDDS)* in treatment trials.
- ✓ Four licenses have been issued for use of the *Asthma Daytime Symptom Diary (ADSD)* and the *Asthma Nighttime Symptom Diary (ANSD)* in treatment trials.



Despite considerable advances in medicine and technology, many of the tests used to evaluate drug safety have not changed in decades. The mission of the **Predictive Safety Testing Consortium (PSTC)** is to bring together pharmaceutical companies to share and validate innovative safety testing methods to accelerate drug development under advisement of the U.S. Food and Drug Administration, European Medicines Agency and Japan's Pharmaceutical and Medical Devices Agency. PSTC does this by developing and implementing scientific research strategies in a neutral, pre-competitive environment, thereby allowing members to share expertise, resources, data and internally developed approaches, which improves both the speed and precision of the drug development process. PSTC's efforts are intended to develop drug development tools that assist pharmaceutical companies and regulatory agencies in making better-informed decisions, all of which ultimately benefit patients. Currently, PSTC is engaged in the qualification of novel translational safety biomarkers (nonclinical and clinical safety biomarkers) across several organ systems for application in the development of drugs.

2019-2020 Impact

- ✓ FDA accepted Qualification Plan for glutamate dehydrogenase (GLDH) as a biomarker to detect drug-induced liver injury in clinical trials. This fills a gap in drug development to discriminate liver injury from muscle injury in patients with underlying muscle disease.
- ✓ FDA advanced a Letter of Intent to stage two review for qualification of drug-induced skeletal muscle injury biomarkers, a qualification that will permit the detection of muscle injury earlier and with higher specificity than the current standards in clinical trials.
- ✓ With the Japan National Institute of Health Sciences (NIHS), PSTC signed a collaboration agreement with the objective of qualifying GLDH with PMDA to facilitate better global harmonization of acceptable safety biomarkers.



The work of the **Quantitative Medicine Program (QuantMed)** focuses on the development and innovation of quantitative solutions for medical product development and clinical needs, with the aim of improving population and individual health by transforming drug development through methodological innovation. The program goal is to leverage knowledge from a network of experts in industry, academia, non-profit and regulatory sciences combined with data acquired from multiple sources to develop quantitative methodologies in pharmacometrics, statistics, systems pharmacology, artificial intelligence and digital data analytics. The solutions developed by QuantMed are often formally reviewed by regulatory agencies as fit-for-purpose in a drug development context. Because QuantMed’s philosophy is one of open science, solutions developed are publicly available as open-source platforms. The QuantMed program is highly collaborative, seeking to advance the development of novel treatments for patients with unmet medical needs.

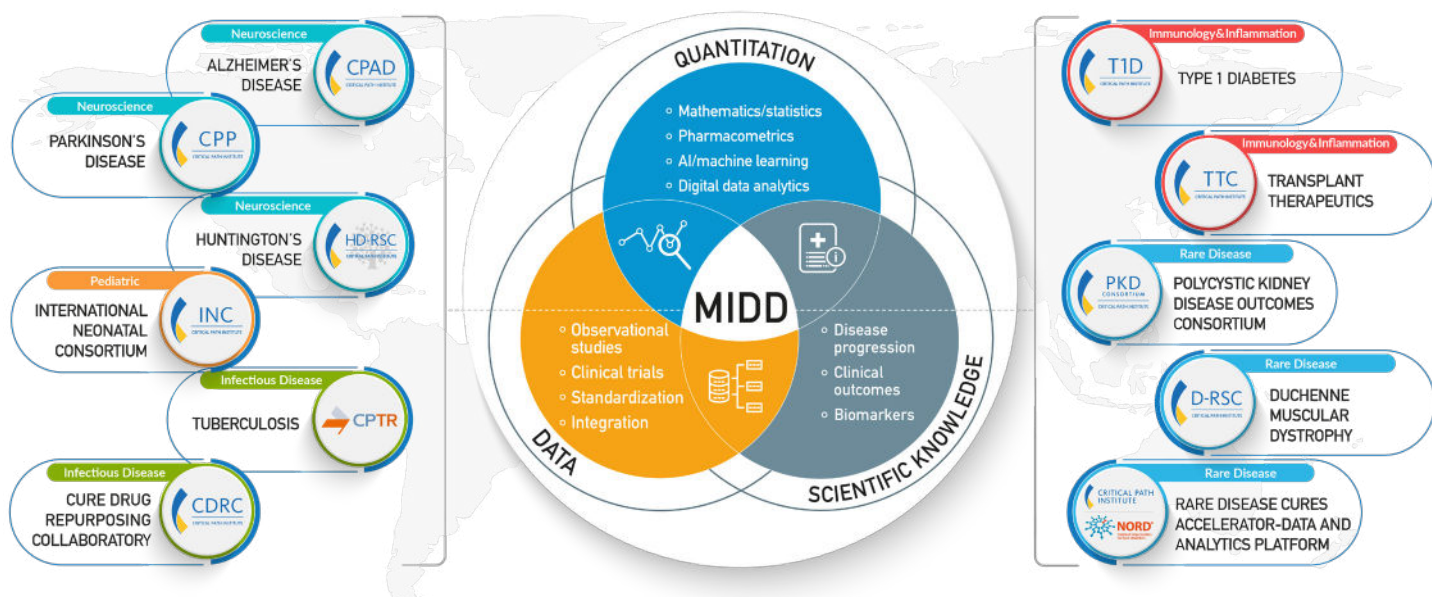
2019-2020 Impact

- ✓ The Rare Disease Cures Accelerator-Data and Analytics Platform (RDCA-DAP) was represented at an FDA rare disease day, providing deepening collaboration and engagement with FDA on MIDD to enable improvement of rare disease drug development.

- ✓ A strategic partnership with the Office of Clinical Pharmacology is facilitating steps towards realizing the immense potential for MIDD to improve drug development across the landscape of diseases through Prescription Drug User Fee Act (PDUFA) VII negotiations.
- ✓ A developing partnership between RDCA-DAP and the European Joint Program on Rare Diseases is strengthening the ability to extend the vision of RDCA-DAP to the EU.
- ✓ The RDCA-DAP workshop highlighted QuantMed’s efforts in developing a predictive model for kidney failure in polycystic kidney disease, providing a basis for sponsors to effectively design trials in PKD.
- ✓ QuantMed team members have driven the development and completion of regulatory submissions for Type 1 diabetes, Parkinson’s disease, and Duchenne muscular dystrophy that will help optimize trial design in these diseases.

QuantMed team members are initiating quantitative analyses for the Real-World Data (RWD) and Real World Evidence (RWE) awards, focusing on the evaluation of source data via quality metrics that assess the suitability of these sources for fit-for-purpose quantitative evaluations and generation of quantitative tools to generate actionable real-world evidence for unmet medical needs in neonatal drug development (INC) and infectious diseases (CDRC).

Creating solutions for drug development through Model-Informed Drug Development (MIDD)



RDCA-DAP

The **Rare Disease Cures Accelerator-Data and Analytics Platform (RDCA-DAP)** is an FDA-funded initiative that provides a centralized and standardized infrastructure to support and accelerate rare disease characterization, with the goal of accelerating therapy development across rare diseases. This platform is made possible through a collaborative grant from the FDA and in partnership with the National Organization for Rare Disorders (NORD).

RDCA-DAP promotes the sharing of existing patient-level data and encourages the standardization of new data collection. By integrating such data in a regulatory-grade format suitable for analytics, RDCA-DAP accelerates the understanding of disease progression (including sources of variability to optimize the characterization of subpopulations), clinical outcome measures and biomarkers, and facilitates the development of mathematical models of disease and innovative clinical trial designs. RDCA-DAP is positioned to generate solutions to drug development bottlenecks. As such, the utility of the patient-level data is maximized, and data may be used to develop tools that will be accessible to the community in order to optimize and accelerate drug development across rare diseases.

2019-2020 Impact

- ✓ Meetings and webinars were held with the wider rare disease community and RDCA-DAP has met with over 100 groups one-on-one to disseminate the concept of the platform and to encourage data sharing.
- ✓ A prototype of the data interrogator tool was built; it allows basic queries and statistical analysis of data for use in demonstrating how the platform will look and what it will be able to do.
- ✓ RDCA-DAP has put processes in place to bring in the first rare disease datasets into the platform.



The **Type 1 Diabetes (T1D) Consortium** is a public-private partnership initiated in March 2017. Current membership is composed of the following industry and members: JDRF, the Leona M. and Harry B. Helmsley Charitable Trust, Janssen Research & Development, LLC, Novo Nordisk and Provention Bio. Membership is also comprised of academic partners and advisors from the National Institutes of Health (NIH). Type 1 diabetes is a condition in which the insulin-producing cells of the pancreas are damaged

by antibodies generated by the body's own immune system (autoantibodies). In order to optimize the drug development process for novel T1D treatments, it is crucial to understand how the presence of the autoantibodies affects the risk of reaching a T1D diagnosis. As such, the primary goal of T1D Consortium is to qualify islet autoantibodies as enrichment biomarkers to be used in the development of therapies for the treatment, and ultimately prevention of type 1 diabetes. The islet autoantibodies of interest include insulin autoantibodies (IAA), glutamic acid decarboxylase 65 (GADA), insulinoma antigen-2 (IA-2) and zinc transporter 8 (ZnT8) autoantibodies.

2019-2020 Impact

- ✓ The Trial Outcome Markers Initiative (TOMI) was initiated in late 2019 and convened stakeholders in 2020 in response to T1D community drug development needs. The engagement from multiple industry, academic, and diabetes charity organizations shows the T1D community's commitment to addressing outcomes in new-onset T1D and overcoming recent failures in disease modification trials.
- ✓ With FDA funding, T1D Consortium began comprehensive assessment to understand the relationships between CGM measures and established measures of glycemic control. Understanding of these relationships is a clear unmet need in T1D drug development that must be addressed if data from CGM devices are to be used in diabetes product evaluations.
- ✓ Initiation of the islet AA assay modernization project is helping the drug development community assess the status of assay platforms under development with the goal of streamlining future study design and obtaining consensus on necessary and sufficient criteria for new islet AA assays.



The **TB Platform for Aggregation of Clinical TB Studies (TB-PACTS)** is designed to catalyze and accelerate tuberculosis (TB) research by curating and standardizing TB clinical trial data and making this data publicly available to qualified researchers. These researchers can access and analyze data in aggregate, or filter and view individual patient-level data from 17 clinical trials, including REMoxTB, RIFAQUIN and OFLUTBU. This initiative represents a collaborative partnership between the Special Programme for Research and Training in Tropical Diseases (TDR), the TB Alliance, St. George's University of London, Case Western University, the British Medical Research Council and C-Path. The partnership continues to expand the scale of the TB-PACTS platform by engaging with other TB clinical data contributors to secure additional datasets. This and other C-Path TB data platforms will be leveraged in the new IMI-funded European Regimen Accelerator for TB consortium.



The **Trial Outcome Markers Initiative in T1D (TOMI-T1D)**, formed in May 2020, is a JDRF and Diabetes UK-funded international partnership between researchers from academic institutions, pharmaceutical industry and independent non-profit organizations. TOMI's mission is to accelerate drug development and optimize immune intervention trials in T1D through the development of a composite outcome measure which 1) improves clinical interpretability and patient acceptability, 2) shortens the time to primary outcome and 3) minimizes the number of participants required in trials.



The **Transplant Therapeutics Consortium (TTC)** convenes diverse stakeholders (industry, academia, and government agencies) to optimize the development of medical products for transplant patients. Solid organ transplantation can be the treatment of choice for many people with end-stage conditions. The development of novel medicines that can maximize the lifespan of a transplanted organ will improve quality of life and reduce mortality, which requires optimized clinical trial designs, based on tools that provide a robust quantitative understanding of predictors of clinically relevant endpoints. TTC supports collaborative development and regulatory endorsement of such drug development tools for solid organ transplantation, which, in turn, may help to shorten the time needed to deliver safe, effective therapies for transplantation patients. The consortium achieves this by bringing together key stakeholders in the transplant community with the primary goal of identifying and addressing the regulatory challenges that impact the development and approval of new therapies in transplantation.

2019-2020 Impact

- ✓ A Letter of Intent (LOI) in support of a reasonably likely surrogate endpoint (RLSE) to streamline clinical trials and open accelerated approval pathways for novel immunosuppressive drugs was accepted into the FDA Biomarker Qualification Program, moving the field one step closer to providing a qualified RLSE for industry.
- ✓ Continued engagement with the EMA is helping ensure harmonization of an acceptable RLSE across the major regulatory bodies.

- ✓ Creation is underway of an aggregated patient-level database using real-world evidence and historical clinical trial data. This database will support the construction of novel and publicly available drug development tools that facilitate the development of novel immunosuppressive therapies for use in kidney transplantation.
- ✓ Work is ongoing to develop a quantitative “drug-trial-disease model” (DTDM) that will inform clinical trial endpoint selection, entry criteria, and size, duration, and design considerations.



C-PATH COLLABORATORS

ACADEMIC INSTITUTIONS

- Baylor Scott & White Research Institute
- Binghamton University
- Brigham and Womens Hospital
- Brighton and Sussex Medical School
- Case Western Reserve University
- City University, London
- Cleveland Clinic
- Colorado State University
- Duke University
- Emory University
- Fraunhofer SCAI
- George Washington University
- Harvard University
- Helmholtz Centre Munich
- Imperial College London
- Indiana University School of Medicine
- Johns Hopkins University
- Karolinska University
- Leiden University Medical Center
- Lund University
- Mayo Clinic
- McGill University
- Mt. Sinai
- Icahn School of Medicine at Mount Sinai
- Newcastle University
- New York University
- North Shore University Health System
- Northwestern University
- OULU Finland
- Paris Descartes University, Necker Hospital
- RIKEN Institute
- Stanford University
- State University of New York, Buffalo
- Stony Brook Medicine
- Tampere University
- Tufts University
- University College London Institute of Neurology
- University of Alabama, Birmingham
- University of Arizona
- University of Bristol
- University of British Columbia
- University of California, Davis
- University of California, Irvine
- University of California, San Francisco
- University of Cambridge
- University of Cape Town
- University of Chicago
- University of Colorado, Denver
- University of Florida
- University of Genoa
- University of Glasgow
- University of Hasslet
- University of Helsinki
- University of Illinois
- University of Iowa
- University of Kansas
- University of Leicester (UK)
- University of Leuven
- University of Liverpool
- University of Ljubljana
- University of Lübeck
- University of Maryland
- University of Massachusetts
- University of Munich
- University of Oxford
- University of Pittsburgh
- University of Pennsylvania
- University of Rochester
- University of Sheffield
- University of St. Andrews
- University of Texas
- University of Turku
- University of Utah
- University of Virginia
- University of Washington
- VU University Medical Center
- Washington University
- Western Washington University

PHARMACEUTICAL COMPANIES

- Abbott Molecular
- AbbVie
- Actelion Pharmaceuticals Ltd
- Alere
- Allergan
- Amgen, Inc
- Astellas
- AstraZeneca Pharmaceuticals LP
- Avrobio
- Baxter Healthcare Corporation
- Bayer Pharma AG
- Becton Dickinson Diagnostic Systems
- Biogen
- BioMérieux
- Biophytis
- Boehringer Ingelheim Pharmaceuticals, Inc
- Bristol-Myers Squibb Company
- Catabasis Pharmaceuticals
- Celgene
- Cepheid
- Chiesi
- Commonwealth Biopharma
- CTI BioPharma
- Cydan Development
- Daiichi Sankyo
- Denali Therapeutics Inc
- Edgewise Pharmaceuticals
- Eisai, Inc
- Eli Lilly and Company
- EMD Serono
- Ferring Research Institute
- Galápagos
- Genentech, Inc
- GE Healthcare
- Gilead Sciences
- GlaxoSmithKline Corporation
- Goldfinch Biopharma, Inc
- Hansa Medical
- Healx
- Hoffmann-La Roche, Inc
- Horizon Pharma, Inc.
- IBM
- Inception Sciences Canada
- Ironwood Pharmaceuticals, Inc
- Infant Bacterial Therapeutics
- Innate Immunotherapeutics
- Ixico
- Kadmon Corporation
- Johnson & Johnson Pharmaceutical Services
- Lundbeck
- Mallinckrodt Pharmaceuticals
- Metabolic Solutions Development Co.
- Merck Sharp & Dohme Corporation
- Millenium: The Takeda Oncology Company
- Mitsubishi Tanabe Pharma Corporation
- Neuramatrix
- Nuredis
- Novartis Pharmaceuticals Corporation
- Novo Nordisk
- NS Pharma
- Ocello (NL)
- Otsuka
- Palladio Biosciences
- Pfizer, Inc
- PharmaStat
- Prilenia
- PTC Therapeutics
- Qiagen
- Reata Pharmaceuticals
- Regulus Therapeutics
- Relay Therapeutics
- Sage
- Sanofi
- Santhera Pharmaceuticals, Inc
- Sarepta Therapeutics, Inc
- Sequella, Inc
- Shire Pharmaceuticals, Inc
- Summit (Oxford) Limited
- Sunovion Pharma, Inc
- Takeda Pharmaceutical Company
- TEVA Pharmaceutical Industries, Ltd
- Therabron
- Thermofisher
- Transplant Genomics
- Triplet Tx
- UCB Pharma
- uniQure
- Vaccinex
- Veloxis
- Vertex Pharmaceuticals
- Voyager Therapeutics
- Wave Life Science

PATIENT GROUPS

- Alzheimer's Association
- Alzheimer's Drug Discovery Foundation
- Alzheimer's Research UK
- Bill and Melinda Gates Foundation
- CHDI Foundation
- Cure Parkinson's Trust
- Davis Phinney Foundation
- European Huntington Association
- Graham's Foundation
- Huntington's Disease Society of America
- Huntington Society of Canada
- Huntington Study Group
- Italian MS Society
- JDRF
- KHI Patient Family Partnership Council
- March of Dimes
- Michael J. Fox Foundation
- Movement Disorder Society
- National Multiple Sclerosis Society of Canada
- National Multiple Sclerosis Society
- National MS Society of UK
- National Organization for Rare Disorders
- Parent Project Muscular Dystrophy
- Parkinson's Disease Foundation
- Parkinson's UK
- PKD Charity
- PKD Foundation
- PMD Alliance
- USAgainstAlzheimer's

OTHER

- ADPKD Paediatric Registry
- Alberta MS Research Foundation
- .assisTek
- American Society of Transplantation (AST)
- American Society of Transplant Surgeons (ASTS)
- American Society for Clinical Pharmacology and Therapeutics (ASCPT)
- Bambino Gesù Children's Hospital
- Benaroya Research Institute
- BLISS
- Centre for Human Drug Research (CHDR)
- Children's Hospital of Philadelphia
- Cincinnati Children's Hospital Medical Center
- Clinical Ink
- COINN
- Consortium of MS Centers
- Drink Clinical Trial
- EFCNI
- ERT
- European Joint Programme for Rare Diseases
- FIND
- ICON
- International Society of Pharmacometrics
- IQVIA
- Istituto Mario Negri
- Japan National Institute of Health Sciences
- Kessler Foundation
- MedAvante
- Medidata Solutions
- NANN
- NEC Society
- PATH
- PhRMA
- Preemie Parent Alliance
- Scientific Institute H.S. Raffaele, Italy
- Signant Health
- TB Alliance
- TB Clinical Diagnostics Research Consortium
- Terasaki Research Institute
- The Leona M. and Harry B. Helmsley Charitable Trust
- The Transplantation Society
- Treatment Action Group
- Working Group on New TB Drugs (Stop TB Partnership)
- Y-Prime

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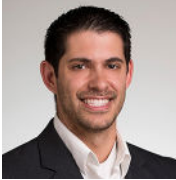
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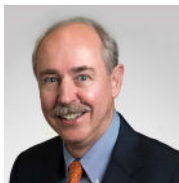
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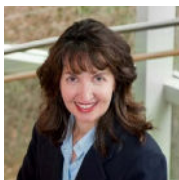
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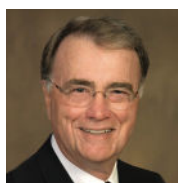
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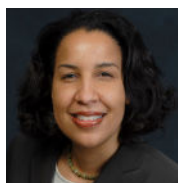


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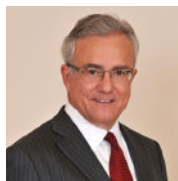


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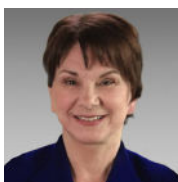
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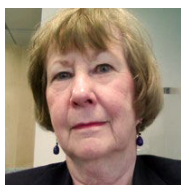
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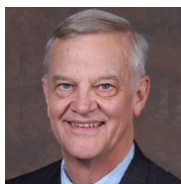
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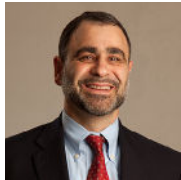
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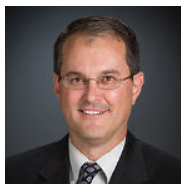
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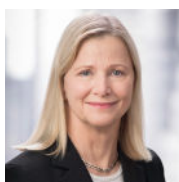
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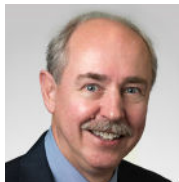


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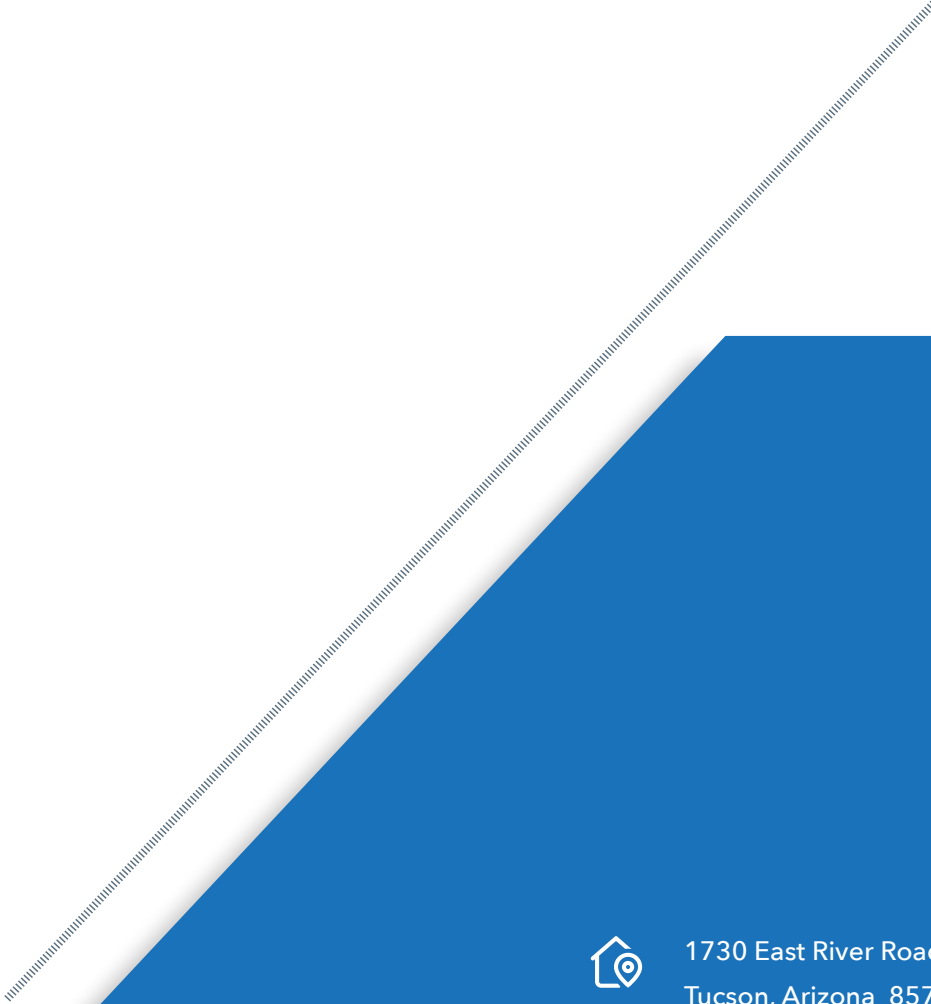


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