

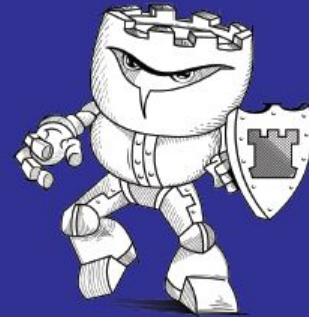
国際キャスルマン病臨床ネットワーク (CDCN)

CDCN のホームページ参照 (<http://www.cdcn.org/research-pipeline>)



CASTLEMAN DISEASE COLLABORATIVE NETWORK

2017 - 2018 COMMUNITY UPDATE



DEAR CASTLEMAN DISEASE FAMILY,



I am in awe of the dedication and passion our global community of physicians, researchers, patients, and families bring to solving Castleman disease every day. Thank you so much for all that you do and have done to advance research, diagnosis, and treatment for Castleman disease. The CDCN has made incredible progress over our first five years and are at a pivotal time in our journey. Now we need to turn our promising research into permanent cures for the thousands of patients, like me, with this awful disease.

Like many of you, I have a personal connection to the disease: it nearly killed me. During my third year of medical school, what started out as fevers and night sweats led to kidney, liver, and bone marrow failure. After three months of hospitalizations in critical condition and being read my last rites, I finally was diagnosed with idiopathic multicentric Castleman disease (iMCD). Treatment began right away, but I needed multi-agent chemotherapy before I eventually recovered — for a short time.

I returned to medical school on a mission. I published research along with Dr. Frits van Rhee in the journal, *Blood*, which initiated a paradigm shift in the disease model and established a new classification system for the disease. Dr. van Rhee and I co-founded the Castleman Disease Collaborative Network (CDCN) to accelerate research discovery internationally and find innovative treatments for the disease.

In the last five years, the CDCN has made tremendous strides, including these highlights:

- **CONNECTED** the global community of 400+ physicians and researchers through the five largest-ever Castleman disease research meetings and an online discussion board
- **ASSEMBLED** a Scientific Advisory Board of 32 experts from EIGHT countries
- **ESTABLISHED** the first-ever diagnostic criteria for iMCD
- **LAUNCHED** approximately 10 high-impact studies with collaborators around the world to investigate the cause, key cell types, and new treatment targets for Castleman disease
- **CREATED** an international registry (ACCELERATE) and biobank (CastleBank)
- **ENGAGED** the global patient community through a patient summit, online discussion board, physician referrals, and educational materials
- **MAPPED** out the collaborative network approach that we've taken, which other rare disease are following as a blueprint to accelerate research



None of us can take out Castleman disease on our own. To succeed, we need the entire community of patients, family and friends, physicians, researchers, and altruistic individuals to work together. During our 2014 Patient and Loved One Summit, our community decided that, "Castleman disease picked the wrong people to mess with," because we're going to fight back, and we're going to win!

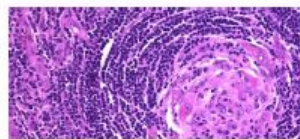
If you want to be part of an innovative research network with a roadmap to a cure, we want you in our community. I have had multiple life-threatening relapses since 2010, but, with the global community actively engaged through the CDCN, I feel more confident than ever that our work will extend my life and the lives of thousands of other patients. Join us and learn more about how your investment in this cause will help us to turn promising research into permanent cures.

Sincerely,

David Fuegenbaum, MD, MBA, MS
Co-Founder & Executive Director, CDCN
Research Assistant Professor of Medicine, University of Pennsylvania

CASTLEMAN DISEASE: THE MOST DEADLY, MOST COMMON DISEASE THAT YOU HAVE NEVER HEARD OF

Every year, thousands of patients suffer from one of the debilitating forms of Castleman disease (CD). Our focus is on bringing together all those who are working to save and extend the lives of these patients. Through advanced research and cutting edge methodology, the CDCN is accelerating the treatment of this disease on a global scale. In tandem with this vital research comes the support for those who suffer from CD, as well their families and loved ones who are also a part of this journey.



CD describes a group of inflammatory disorders that vary from a single enlarged lymph node to life-threatening multiple organ failure.

CASTLEMAN DISEASE BEFORE THE CDCN

In 2012, CDCN co-founder Dr. Fuegenbaum returned to medical school after a year of medical leave spent battling CD as a patient. His first step was to grasp the current state of CD research. He observed major gaps in our knowledge of the disease and uncovered issues that were slowing progress, including:

Challenges Within Castleman Disease Research

- Lack of collaboration between physicians and researchers.
- Inaccurate information.
- Absence of consensus criteria for diagnosing CD.
- Faulty disease model and general misunderstanding of disease.
- Precious patient samples were stored away in freezers for years with no research.

Dr. Fuegenbaum studied the rare disease research field alongside Dr. Arthur Rubenstein at the University of Pennsylvania and found systemic issues within the larger biomedical research community that were also slowing progress for CD research.

Challenges Within Biomedical Research Community

- The traditional model, which generally involves research organizations raising funds and inviting individual researchers to apply to use the funding how those researchers determine.
- Research is not done as part of an overarching strategy.
- Projects don't necessarily build on other projects.
- Competition for limited funding prevents collaboration.
- Few communication tools exist for researchers to connect with one another.
- Patients are often not included in discussions of research.

Over 90% of funds raised through CDCN go straight to research

WHAT IS CASTLEMAN DISEASE?

An immune system disorder, but more research is needed to understand the cause and mechanisms.

The Immune System Becomes Activated And Attacks Vital Organs

CD describes a rare group of three separate inflammatory disorders that share similar lymph node appearance under the microscope:

- UCD**
Unicentric Castleman Disease
- HHV-8+MCD**
HHV-8 Multicentric Castleman Disease
- iMCD**
Idiopathic Multicentric Castleman Disease

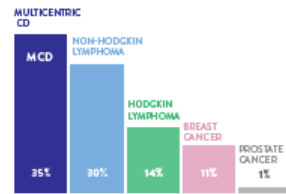
UCD is diagnosed when characteristic features are observed in a biopsied lymph node and there is only one region of enlarged lymph nodes. HHV-8+MCD is diagnosed when characteristic features are observed in a biopsied lymph node, HHV-8 is detected in the lymph node, and there are multiple regions of enlarged lymph nodes. iMCD is diagnosed using the new Fajgenbaum et al (Blood, 2017) criteria, which requires characteristic features in the biopsied lymph node, multiple regions of enlarged lymph nodes, specific distal abnormalities, and exclusion of diseases that can mimic iMCD.¹

A healthy immune system involves a complex and interconnected network of cells and inflammatory proteins called cytokines, which signal for the immune system to become activated. Lymph nodes are the home base for immune cells.

In CD patients, these inflammatory cells become activated and produce excess cytokines, particularly Interleukin-6 (IL-6). The excess cytokines lead to flu-like symptoms, lymph node enlargement, and dysfunction of vital organs including the liver, kidneys, and bone marrow.

As Deadly As Cancer

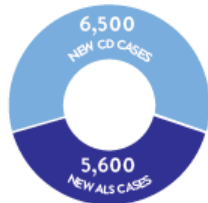
5 YEAR MORTALITY RATE



As Common As ALS

CD is diagnosed in approximately 6,500 to 7,000 patients of all ages each year in the U.S. MCD is estimated to account for 30-50% of CD cases.

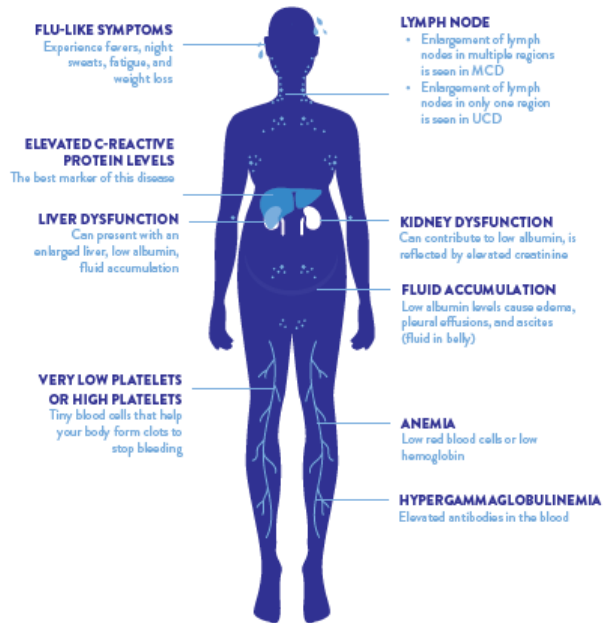
While it does not garner the same public awareness as Lou Gehrig's disease (ALS), it is estimated that a similar number of Americans are diagnosed with CD each year as with ALS, which has an incidence of 5,600 cases per year in the U.S.²



¹Fajgenbaum, David C., et al. "Histological evidence-based consensus diagnostic criteria for 2017 English idiopathic multicentric Castleman disease." *Blood* (2017): 1067-2016. ²ALS Association. "What you should know." <http://www.als.org/about-als/you-should-know.html> CDCN 2019-2018 Consensus Update | 5

CASTLEMAN DISEASE SIGNS AND SYMPTOMS

CD is difficult to diagnose. Patients have a wide range of symptoms that are often initially misdiagnosed as other ailments. We hope that the new diagnostic criteria that the CDCN spearheaded (Blood, 2017)¹ will speed up time to diagnosis.



¹Fajgenbaum, David C., et al. "Histological evidence-based consensus diagnostic criteria for 2017 English idiopathic multicentric Castleman disease." *Blood* (2017): 1067-2016. CDCN 2019-2018 Consensus Update | 6

ABOUT CASTLEMAN DISEASE; 3 SUBTYPES

	UNICENTRIC CASTLEMAN DISEASE (UCD)	HHV-8-ASSOCIATED MULTICENTRIC CD (HHV-8+MCD)	IDIOPATHIC MULTICENTRIC CASTLEMAN DISEASE (iMCD)
% OF CASES	50%	25%	25%
REGIONS AFFECTED	Enlarged lymph node in one region	Multiple regions of enlarged nodes	Multiple regions of enlarged nodes
COMMON AGE OF DIAGNOSIS	Mostly children and young adults, but it can occur at any age	Mostly adults 40-60 years old, but it can occur at any age	Mostly adults 40-60 years old, but it can occur at any age
GENDER	Slightly more common in females	More common in males	Slightly more common in males
SYMPTOMS	Usually has no symptoms, but there can be discomfort associated with an enlarged lymph node and occasionally "Multicentric Castleman disease-like" symptoms	Wide range from mild flu-like symptoms to severe episodes of rapid-kill, life-threatening organ failure and death	Wide range from mild flu-like symptoms to severe episodes of rapid-kill, life-threatening organ failure and death
CAUSES	The cause of the disease is unknown	HHV-8 triggers the disease, and patients are often already immunosuppressed (e.g., from HIV or organ transplantation)	The cause of the disease is unknown
TREATMENT	Surgery. UCD patients with Paraneoplastic Pemphigus need additional treatments	Can be controlled well with B-cell depletion therapy with rituximab, but cytotoxic chemotherapy is sometimes also needed	Typically involves anti-IL-6 therapy (e.g., tocilizumab approved in US, EU, and Canada; tocilizumab approved in Japan), with or without chemotherapy (e.g., cyclophosphamide, atezolizumab, rituximab)
CHANCE OF RELAPSE	Rare	With close monitoring, less common than iMCD	Common, but varies depending on treatment used
CURE	With surgical removal, most symptoms go away, and there has been no reported cases of UCD transforming into MCD	None yet. We need your help to find it!	None yet. We need your help to find it!
5-YEAR SURVIVAL RATE	95% - 1 in 20 patients die. Most UCD deaths are in patients who are also diagnosed with Paraneoplastic Pemphigus or a blood cancer.	65% - 1 in 3 patients with MCD die within 5 years (study did not separate into HHV-8-positive or negative), but new data shows a 90% 5-year survival rate for HHV-8-positive MCD patients treated with rituximab	65% - 1 in 3 patients with MCD die within 5 years (study did not separate into HHV-8-positive or negative)

¹Tsai H, Reddy S, et al. "Histological evidence-based consensus diagnostic criteria for 2017 English idiopathic multicentric Castleman disease." *Blood* (2017): 1067-2016. ²Fajgenbaum, David C., et al. "Histological evidence-based consensus diagnostic criteria for 2017 English idiopathic multicentric Castleman disease." *Blood* (2017): 1067-2016. CDCN 2019-2018 Consensus Update | 7



CDCN researchers around the world, such as Dr. Vera Krymskaya, have made groundbreaking strides in how idiopathic multicentric CD (iMCD) pathogenesis is understood and researched

TURNING PROMISING RESEARCH INTO PERMANENT CURES

Soon after Drs. Fajgenbaum and van Rhee co-founded the CDCN in 2012, they partnered with Greg Pacheco and the Castleman's Awareness & Research Effort (CARE) to join forces and merge organizations as CDCN. CDCN has made significant contributions to the ways doctors and researchers fundamentally think about CD.



PHASE 1 & 2 Build Community & Prioritize Research

- Connected the global community of 400+ physicians and researchers.
- Assembled Scientific Advisory Board of 32 experts from eight countries.
- Engaged patients through various platforms like the leadership team, and online discussion boards.
- Established the current state of medical knowledge for CD through an article published in the top hematology journal, *Blood*.
- Determined high-priority research projects for the International Research Agenda (IRA).

STATUS: COMPLETE



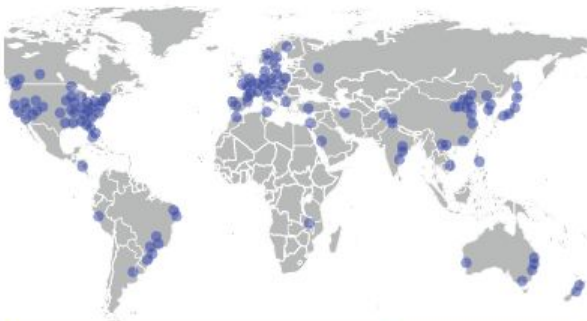
PHASE 3 & 4 Execute Research & Identify / Track Treatments

- Engaging patients and loved ones to fight back against CD by raising money and awareness for research through the Castleman Warrior program.
- Building a global patient registry for CD through a major collaborative partnership.
- Engaging leading experts to conduct the high-priority projects in the IRA.
- Collecting patient samples for research.
- Recruiting top researchers to conduct CD research.

STATUS: ONGOING

¹Tsai H, Reddy S, et al. "Histological evidence-based consensus diagnostic criteria for 2017 English idiopathic multicentric Castleman disease." *Blood* (2017): 1067-2016. ²Fajgenbaum, David C., et al. "Histological evidence-based consensus diagnostic criteria for 2017 English idiopathic multicentric Castleman disease." *Blood* (2017): 1067-2016. CDCN 2019-2018 Consensus Update | 8

OUR GLOBAL RESEARCH NETWORK



OVER **420** CD RESEARCHERS AND PHYSICIANS

39 COUNTRIES



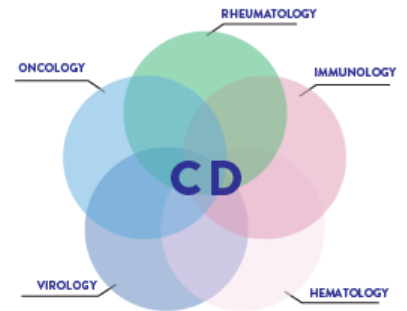
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OPPORTUNITIES FOR RESEARCHERS

CD research sits at the intersection of hematology, oncology, virology, rheumatology, and immunology. It is also positioned on the frontier of medicine, as the pathogenesis and etiology of most cases of CD is poorly understood.

We seek to fund further research to find answers to the toughest questions about this disease. By focusing on CD, researchers could uncover aspects of its etiology and pathogenesis and be published in high-impact medical journals.

If you are interested in conducting research and/or collaborating, please reach out to info@castlemannetwork.org or visit CDCN.org for more information on our next round of research grant funding.



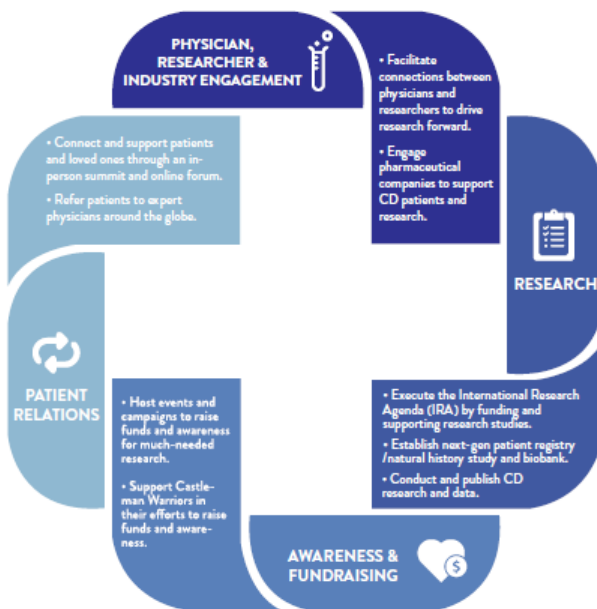
OUR TOP FUNDING PRIORITIES FOR 2017

Funds Needed For Research



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THE CDCN'S PATIENT-CENTERED PROGRAMS



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FINDING A CURE FOR PATIENTS LIKE KATIE

Blazing A Path To A Cure

We work every day to find the answers to questions that make treatment decisions difficult and slow progress to a cure such as:

- What triggers the immune response in UCD and IMCDP?
- Which cell type is the problem cell, or the "Castleman cell," where the disease originates?
- What cellular signaling pathways are activated?
- What are all of the inflammatory proteins being secreted by these activated cells?
- What role does genetics play in CD?

The CDCN works with experts from around the globe and a community of patients fighting back to answer these questions and eliminate this disease.



5-year-old Katie has been battling UCD since she was 1. We need to find a cure for Katie!

ACCELERATE Patient Registry

The CDCN has created the first-ever global patient registry and natural history study of CD, called ACCELERATE. A collaborative partnership with a pharmaceutical company and major academic medical center, ACCELERATE is an observational, web-based registry that combines data from physicians and patients around the world to better understand this deadly disease and facilitate future research. The registry uses an innovative design developed by our Scientific Advisory Board and will provide insights into diagnosis, treatment, and outcomes. Dr. Fajgenbaum serves as the Principal Investigator. ACCELERATE was launched in November 2016 and patient enrollment is ongoing.

Our Top Four Projects Include:

- MEASURING the levels of 1,129 proteins and inflammatory messengers in the blood of patients.
- SEARCHING for pathogens that may trigger CD.
- IDENTIFYING cells and/or activated intracellular pathways that drive the disease.
- UNDERSTANDING the role of genetics in CD.

2012 Worked with experts from around the world to develop an International Research Agenda (IRA) that inventories and prioritizes high-impact research projects.

Identified and built the global research community in order to establish what was currently known about the disease, prioritize high-impact research studies, and encourage top researchers to conduct CD research.

2012 | 2014

2015 Funded studies in collaboration with more than 12 universities around the world that directly impact patient care and help doctors get the right drugs to their patients.

Invest enough funds into high-impact research studies and projects to uncover how the disease works and identify treatments that are effective for each subtype of CD.

2017 & BEYOND

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WE NEED YOUR HELP TO FIND THE CURE

Now that the CDCN has connected the research community and created a blueprint for curing the disease, we know exactly which projects need funding. With your support, we can make major advances to solve this disease.

How You Can Make A Difference

Major progress has been made, but research is urgently needed to improve patient care. If you are a patient, loved one, or someone who cares about advancing treatments, we need your help:

- DONATE**
Fund high-impact research
- BECOME A CASTLEMAN WARRIOR**
Raise awareness, funds, and support for patients/loved ones
- HOST**
Hold fundraising events in your community (with the support of the CDCN)
- CONNECT**
Meet other patients and loved ones through our online community
- REGISTER**
CDCN patients can enter the registry and contribute tissue (old biopsies, blood draws) for research
- JOIN**
Work with the CDCN leadership team as a volunteer (e.g. help with creating educational materials, refining our social media strategy to raise awareness)

BECOME A WARRIOR!

The Castleman Warrior program is an international campaign that gives patients and loved ones the opportunity to fight back against CD by raising funds and awareness for research.



IN
2
MONTHS



9
WARRIORS

RAISED
\$40,000
AND FUNDED
RESEARCH STUDIES

Join the fight and become a Castleman Warrior at
<http://www.cdcn.org/get-involved>



After seeing our Castleman Warrior logo during a CDCN event, one of our patients had the Castle Man tattooed on his shoulder. If this is not patient engagement, we don't know what is!

2017 Planned Budget

REVENUES

Campaign/Contribution Income:	
CARE/CDCN Events	\$136,000
Castleman Warrior Program	\$40,000
Individual Annual Giving	\$40,000
Restricted Grants (top individual donors)	\$50,000
Grant Sponsorships	\$115,000
Total Projected Revenue for 2017	\$381,000
Restricted funds from prior years	\$67,801

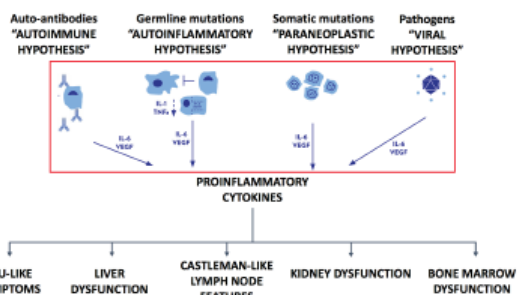
EXPENSES

General Operations/Administrative		\$26,905
Program Expenses:		
Patient and Physician Symposia	\$65,000	
Communications and Development	\$62,900	
Total Program Expenses	\$127,900	
Research Expenses:		
Research Operations:		
BioBank - Precision for Medicine	\$30,000	
Bioinformatics	\$50,000	
West-Lab Research	\$50,000	
Two UPenn/CDCN Biomedical Leadership Fellowships	\$36,000	
Strategically-directed Research Grants		
HUNT I: Columbia Hunt Pathogen Study	\$21,725	
FAST III Study	\$50,000	
Columbia HUNT II RNA Sequencing	\$85,000	
SPEED IE Proteomics Study	\$103,000	
New Investigator CD Pilot Projects	\$45,000	
Antibody-mediated-reactive T-cell Study	\$50,000	
Genomics Study	\$70,000	
Next-gen Studies (C ₂ TGF/IMiB)	\$50,000	
Clinical Trial Support	\$50,000	
Annual OOC Invited Grant Process	\$30,000	
Total Research Expenses	\$720,725	
Total Expenses	\$875,530	
Net Operating Income for 2017	\$494,530	
Net Operating Income for organization at end of 2017	\$113,271	

Existing and Planned Studies

The CDCN worked with experts from around the world to develop an International Research Agenda that prioritized high-impact research projects. We have provided the current model for how we think the disease works below (immune system becomes activated, inflammatory proteins or "cytokines" are released by an unknown immune cell, and organ dysfunction occurs). Our studies listed on page 10 target every aspect of this model to uncover all of the unknowns of CD.

Several hypothesis have been proposed



Research Questions That Need To Be Answered:

- What causes the release of inflammatory proteins?
- What cells are releasing the inflammatory proteins?
- What are the cellular signalling pathways responsible for the inflammatory protein release?
- What approved or novel treatments could help to treat or cure this disease?

CDCN Leadership



David Fajgenbaum, MD, MBA, MSc, Executive Director; Jason Roth, PhD, Chief Scientific Officer; Helen Partridge, MSc, Chief of Staff; Mary Zaccaro, MBA, Managing Director of Development; Dustin Shilling, PhD, Senior Research Advisor; Caitlin Poljansek, Managing Director of Communications

Board of Directors

Since 2007, CARE has been led by a dedicated Board of Directors, which took over leadership of the CDCN in 2012, when the two organizations merged.

- Greg Pacheco, Co-Founder & Board President; Vice President of Operations at BH & F Inc. Greg is a CD survivor.
- IC DiPasquale, Board Vice President; Wine-maker at Hope Family Winery; IC is a close family friend of Greg Pacheco and was a member of the founding Board.
- Charlyn Pacheco, Co-Founder & Board Secretary; Charlyn is Greg Pacheco's wife and has helped to lead several CD fundraising efforts in Paso Robles, CA.
- Michael Stief, Board Treasurer; Operations Manager at Black's Hardware & Turkey Farm; Michael is a close family friend of Greg Pacheco.
- Sam D'Amico, Board Member & Founder of the inaugural ELKESTRONG Run for a Cure; Sam is the brother of Ellyn D'Amico, who sadly passed away battling CD when she was only 13 years old.
- David Fajgenbaum, MD, MBA, MSc; Board member; Co-Founder & Executive Director of the CDCN; Research Associate Professor of Medicine in the Division of Hematology & Oncology at the University of Pennsylvania. David is a CD survivor.
- Bette Jacobs, PhD; Board member; Professor of Health Systems Administration at Georgetown University; Distinguished Scholar and Co-Founder at the ONall Institute for National and Global Health Law; Fellow and Visiting Professor at Campion Hall at University of Oxford.
- Karin Silk, JD; Board member; Associate, Decker LLP.

Advisory Council Members

- Marc Bocanegra, Philadelphia, PA
- Arthur Blumenthal, Philadelphia, PA
- Ajay Raju, Philadelphia, PA
- Berale Pressencia, Philadelphia, PA
- Louis Matti, Connecticut
- Marjorie Raboin, New York, NY
- Ryan Hannon, Philadelphia, PA
- Tony Fortis, Philadelphia, PA
- Albert Salvetti, Philadelphia, PA
- Maria Kruger, New Jersey
- Paul Kruger, New Jersey
- Eric Okamoto, MD, PhD, Imperial College London
- David Simpson, BSc, MChB, FRACR, FRCD, New Zealand
- Gordana Skolovic, MD, PhD, Michigan State University
- Peter Northon, MD, USC; Co-Founder of Cancer Center
- Eris van Roon, MD, PhD, MRCGP (UK), FRCP (UK); Co-Founder CDCN
- Raymond Wong, MChB, MD, MRCGP (UK), FRCR, FRUKAM (Canada); Hong Kong
- David Wu, MD, PhD, University of Washington
- Kazuyuki Yoshitaki, MD, PhD, Japan

Leadership Team

The CDCN has made major strides with the guidance of a leadership team composed of more than 55 patients, loved ones, medical students, recent MD graduates, PhD students and recent graduates, and MBA students and recent graduates.

Scientific Advisory Board

The CDCN's first priority was to assemble the top global experts on CD onto a Scientific Advisory Board that sets the overall direction of the CDCN and prioritizes research. Currently the CDCN includes 32 members representing eight countries including the United States of America, United Kingdom, Brazil, Norway, Japan, France, New Zealand, and China.

- Corey Casper, MD, MPH; University of Washington
- Amy Claiborne, MD, FCAP; Cornell University
- Shantaraman Chakravartan, MD; Cincinnati Children's Hospital
- Claudia Colliani, MD, PhD; Sao Paulo, Brazil
- Angela D'Amico, MD; Mayo Clinic
- Dick D'Amico, PhD; UNC School of Medicine
- Ahmed Dogan, MD, PhD; Memorial Sloan Kettering Cancer Center
- David Fajgenbaum, MD, MSc; University of Pennsylvania
- Koji Hamada, MD, PhD; University of Pennsylvania
- Alexander Foxon, MD, PhD; Ohio State University Hospital
- Elaine Jaffe, MD; National Institutes of Health
- Makoto Iida, MD, PhD; Takamatsu Red Cross Hospital in Japan
- Raj Jayaraman, MD; Texas Children's Hospital
- Derrick Kalliker, MD, FRCP, FRCP, FRCSd, FTCD; London
- Vera P. Kryazheva, PhD, MBA; University of Pennsylvania
- Russell Kuznetsov, MD; UC San Diego Moores Cancer Center
- Mary Jo Lechowicz, MD; Emory University
- Megan Linn, MD, PhD; University of Pennsylvania
- Sunita Nataru, MD; University of Pennsylvania
- Eric Okamoto, MD; Imperial College London
- Jean-Francois Rossi, MD, PhD; Montpellier, France
- Arthur Rubenstein, MBBCh; University of Pennsylvania
- Jason Roth, PhD; Director of Translational Research at the CDCN
- Serey Serey, MD; Imperial College London
- David Simpson, BSc, MChB, FRACR, FRCD; New Zealand
- Gordana Skolovic, MD, PhD; Michigan State University
- Tom Uldrick, MD; NIH National Institutes of Health
- Peter Northon, MD, USC; Co-Founder of Cancer Center
- Eris van Roon, MD, PhD, MRCGP (UK), FRCP (UK); Co-Founder CDCN
- Raymond Wong, MChB, MD, MRCGP (UK), FRCR, FRUKAM (Canada); Hong Kong
- David Wu, MD, PhD; University of Washington
- Kazuyuki Yoshitaki, MD, PhD; Japan