

Review Article

The Collaborative Network Approach: a model for advancing patient-centric research for Castleman disease and other rare diseases

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There are ~7000 rare diseases affecting 30 000 000 individuals in the U.S.A. 95% of these rare diseases do not have a single Food and Drug Administration-approved therapy. Relatively, limited progress has been made to develop new or repurpose existing therapies for these disorders, in part because traditional funding models are not as effective when applied to rare diseases. Due to the suboptimal research infrastructure and treatment options for Castleman disease, the Castleman Disease Collaborative Network (CDCN), founded in 2012, spearheaded a novel strategy for advancing biomedical research, the 'Collaborative Network Approach'. At its heart, the Collaborative Network Approach leverages and integrates the entire community of stakeholders — patients, physicians and researchers — to identify and prioritize high-impact research questions. It then recruits the most qualified researchers to conduct these studies. In parallel, patients are empowered to fight back by supporting research through fundraising and providing their biospecimens and clinical data. This approach democratizes research, allowing the entire community to identify the most clinically relevant and pressing questions; any idea can be translated into a study rather than limiting research to the ideas proposed by researchers in grant applications. Preliminary results from the CDCN and other organizations that have followed its Collaborative Network Approach suggest that this model is generalizable across rare diseases.

Introduction

There are ~7000 rare diseases affecting 30 000 000 individuals in the U.S.A. [1–3]. Despite major investment over the last several decades, not enough progress has been made to develop new or repurpose existing therapies for these disorders. In fact, less than 5% of rare diseases have a Food and Drug Administration (FDA)-approved treatment [4]. This striking statistic highlights the failure of traditional research approaches to overcome the unique challenges faced by rare disease research. Due to limited resources for rare disease research, traditional siloed research strategies, in which investigators work independently from one another, are not appropriate. However, this way of conducting research persists in many rare disease fields; there is often limited collaboration between researchers and physicians interested in answering the same questions. Furthermore, patients are infrequently engaged in the process. This has left many rare disease communities lacking consensus on classification, diagnostic criteria, the current state of the field, and a framework for guiding future research. Furthermore, traditional funding models are not as effective when applied to rare diseases. The traditional approach to funding research involves organizations raising funds, announcing a request for proposals (RFPs) that invite researchers to submit a research proposal (a research question, approach to answering the question, and budget) that addresses the question or area of research described in the RFP, and then awarding funds to the best proposal, as selected by a panel of experts. This system works well when the field is competitive and barriers to accessing key research material are low, given that with enough

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submissions, one or more will address a critical question and be scientifically sound. However, when the number of interested and qualified researchers in an area is limited, as in the rare disease space, it is less probable that a single proposal will both address a high-impact question and be submitted by the most qualified researcher. Therefore, rare disease organizations must hope that the right researcher with the right skill set and access to the requisite biospecimens will apply for funding. Unfortunately, this is not often the case, which can leave rare disease organization's research portfolios fragmented and uncoordinated. Adding to the complexity, the competitive nature of the RFP process can have the unintended consequence of deterring sharing of ideas and unique or limited resources, as these are commonly the assets that distinguish a researcher's proposal from others. This is especially problematic for rare disease research as patient samples are inherently scarce. Without a sufficient number of samples, meaningful insights cannot be made.

Recognizing that the traditional approach to research may not be appropriate for rare diseases, the Castleman Disease Collaborative Network (CDCN) spearheaded a new roadmap to accelerating research and treatment discovery when it was founded in 2012. Its roadmap integrated aspects employed by many other non-profit rare disease organizations and public sector organizations that have made progress toward overcoming similar challenges for other rare diseases, such as Friedreich ataxia (FA), Duchenne muscular dystrophy (DMD), chordoma, and each of the diseases included in the Rare Diseases Clinical Research Network [5]. Efforts to advance FA, DMD, and chordoma were spearheaded by patient- and/or caregiver-led networks. Each group invested heavily in generating datasets and research materials, such as natural history study data, cell lines, and animal models that can be used by the entire research community. These exemplary efforts have led to clinical trials of novel drugs, new treatment modalities, and hope for their patient communities. Inspired by the progress made by these groups, the CDCN established its mission to identify an effective therapy for every individual living with Castleman disease (CD). CD, first described in 1954, is a group of rare and poorly understood hematologic disorders with a wide range of symptoms, treatments, and disease outcomes. The most deadly subtype, idiopathic multicentric Castleman disease (iMCD) has a 50–77% 5-year overall survival rate due to frequent episodes of intense inflammation and multiple organ system dysfunction [6–9].

Prior to the CDCN's founding, there were few advances in the understanding or treatment of CD, particularly iMCD. At that time, the CD field lagged behind many others in hematology: there was no foundation focused on advancing research; limited collaboration between researchers; no centralized registries or biobanks to collect clinical data and biospecimens; few published studies, and those available suffered from limited sample sizes; no uniform nomenclature for CD subtypes, which resulted in dissimilar stratification between studies preventing their comparison; and the etiology, cell types, and signalling pathways involved were poorly understood. Together, these barriers slowed understanding of CD and identification of new treatment targets. Clinical barriers also existed, which contributed to historically poor patient outcomes. There were no diagnostic criteria, treatment guidelines, or unique international classification of disease (ICD) code. Nevertheless, a monoclonal antibody (mAb) targeting a proinflammatory signalling molecule, interleukin-6 (IL-6), was in development in the U.S.A. and a mAb targeting the IL-6 receptor was approved in Japan. However, no other drug targets were known. With these systemic challenges in place, the CDCN decided to take a new approach to advance research and drug discovery.

The Collaborative Network Approach: leveraging the entire community to identify patient-centric research questions

The CDCN's novel strategy for advancing biomedical research is referred to as the 'Collaborative Network Approach.' Preliminary results from the CDCN and other organizations that have followed this roadmap suggest that the collaborative model is generalizable across rare diseases. At its heart, the Collaborative Network Approach leverages and integrates the entire community of stakeholders — patients, physicians, and researchers — to identify and prioritize high-impact research questions. It then identifies and recruits the most qualified researchers to conduct each study. In parallel, patients are empowered to fight back by fundraising and providing their biospecimens and clinical data for analysis in these studies. This approach democratizes research to identify the most clinically relevant and pressing questions; any idea can be translated into a study rather than limiting ideas to those conceived of by researchers in grant applications. This approach can be broken into eight critical steps and serves as a model for other rare diseases (Figure 1).



Figure 1. The eight steps of the CDCN's Collaborative Network Approach.

Step 1: build a community of physicians, researchers, patients, and loved ones

An engaged and diverse community is the foundation of the Collaborative Network Approach. Physicians, researchers, and patients each contribute key perspectives and skills and pose unique questions that set the research strategy of the organization. Without integrating the input and ideas of each of these groups, it is impossible to identify the most clinically meaningful questions and research approaches to answering them.

The CDCN established its community by first identifying physicians and researchers knowledgeable in CD through manual searches using <https://www.ncbi.nlm.nih.gov/pubmed/> and databases from associations and hospitals. Once identified, personalized emails were sent to each inviting them to join the community by signing up through an online survey that the CDCN created (<https://register.cdcn.org/register/physician>) on its website (www.CDCN.org). Tracking and maintaining this physician/researcher database has been critical to the CDCN's success. Once these individuals were identified, they were connected through a private online discussion board where important research studies, international consensus guidelines, and challenging clinical cases were posted. In addition, the CDCN organized monthly online case discussions, in-person working group meetings at the American Society of Hematology annual meeting, and quarterly research update emails. The discussion board and meetings serve as the basis for open communication and collaboration between clinicians and researchers located worldwide. Lastly, the community facilitates opportunities for interactions that would otherwise not be possible. For example, leading experts are connected on the CDCN's Scientific Advisory Board (SAB). This group currently comprises 32 experts from eight countries on five continents. Forming this community has allowed the CDCN to overcome several of the barriers that existed in the field. The community has now established consensus on the state of CD research, uniform disease nomenclature, diagnostic criteria, treatment guidelines, and a unique ICD-10 code for CD.

The CDCN has also connected patients and their loved ones, identified from existing online communities and forums (e.g. Facebook) or through direct contact with the CDCN online. Once on the CDCN's website, patients complete a registration process similar to the one completed by physicians and researchers: <https://register.cdcn.org/register/patient>. The CDCN encourages patients and loved ones who join its community to connect with one another using online platforms such as RareConnect (<https://www.rareconnect.org/en/community/castleman-disease>) and Facebook (<https://www.facebook.com/groups/403839776489587/?ref=bookmarks>). The CDCN also shares accurate and up-to-date information on treatments, research, and other patient-relevant topics. Establishment of the patient community has allowed the CDCN to provide important services to a population in need, such as patient navigation services (a full-time position within the CDCN), access to a database of expert CD physicians located around the world for clinical referrals, online educational webinars, and an annual in-person patient summit. These services and outlets are highly valued and critical to engaging the community. Interested patients are further involved in the organization through membership on the SAB, Board of Directors, volunteer leadership team, and Castleman Warriors program (more information on this program in Step 4).

The success of the CDCN's Collaborative Network Approach has allowed it to build relationships with governmental agencies and industry partners, in part because it has addressed major barriers that often deter industry organizations from pursuing rare diseases, such as lack of consensus among key opinion leaders, lack of data, lack of tissue samples, and difficulty accruing patients into studies. The CDCN has had positive interactions with regulators from the FDA, who seem quite eager to meet with investigators and patients and also to contribute ideas and expertise towards study design for clinical trials. The CDCN is supporting the University of Pennsylvania with enrollment for the first clinical trial in the U.S.A. of a drug for CD directed at a target other than the IL-6 signalling pathway, which will begin enrollment in 2019. It has engaged with members of the FDA Oncology Center of Excellence who provided insightful and patient-focused guidance on several critical questions, including submission pathways, orphan drug designation, and the investigational new drug application process. In addition, the National Institutes of Health (NIH) Office of Rare Diseases Research (ORDR) has provided resources and guidance to the CDCN with regard to coordinating collaborative studies, launching clinical trials, and creating registries. The CDCN also utilizes the ORDR global unique identifier tool to link patient samples across multiple studies in a de-identified fashion. The communities of patients/loved ones and physicians/researchers that the CDCN has built have also assisted with attracting industry partners. The CDCN has forged targeted corporate partnerships with organizations that are aligned with its values and priorities to support specific studies. For example, the CDCN partnered with Medidata to collaborate on analyses of serum proteomics data from over 200 individuals. Medidata Solutions contributed bioinformatic expertise and access to proprietary machine learning software. The CDCN has also partnered with Janssen Pharmaceuticals to analyze samples collected during Janssen clinical trials, perform secondary analyses of Janssen clinical trial data, and establish the ACCELERATE Natural History Registry for Castleman disease.

Step 2: crowdsource and prioritize research studies

Once the community of physicians, researchers, patients, and loved ones is built, the next step in the Collaborative Network Approach is to crowdsource and prioritize a research agenda from the large and diverse community. Based on the belief that patient needs should be central to research and all community members' perspectives are valuable, the Collaborative Network Approach engages its full community to contribute ideas for patient-centric research. To crowdsource research questions, the CDCN distributed online questionnaires to its full community with the following three key questions: (1) What research questions are most important to answer to have the greatest impact for patients? (2) What studies are most important to be able to answer the key research questions described in (1)? (3) Who are the top researchers that you are aware of that perform the studies described in (2)? These questions were also discussed during in-person meetings at the American Society of Hematology annual meeting. Once a sufficient number of responses was obtained through crowd-sourcing, the proposed research questions and studies were inventoried into a master list and the CDCN's SAB convened through in-person and virtual meetings to discuss and prioritize the full list based on the: (1) likely impact of the work to improve patient outcome, (2) importance of the research question to furthering our understanding of CD, (3) feasibility of the project (e.g. logistically or technically), and (4) rational order within the overarching state of CD research (e.g. in-depth investigations of a particular cell type are appropriate only if the cell type has been identified as important to the disease). This process established a prioritized list of research studies that serves as the CDCN's International Research Agenda. The progress of every study and its

critical needs (e.g. lead researcher, funding, samples, etc.) are tracked and publicly available on the CDCN's website at: <https://www.cdcn.org/research-pipeline>.

To continue to monitor for patient-centric research questions, the CDCN utilizes the Codigital web platform for automated online questionnaires with separate portals for patients/loved ones and physicians/researchers. To supplement its direct crowdsourcing method, the CDCN also reviews and analyzes both discussions in the online patient communities, described in Step 1, and questions frequently posed by patients to the patient navigator, to provide an avenue of indirectly crowdsourcing research ideas and to continue to improve its understanding of patient needs.

Step 3: identify the most qualified researchers to perform the prioritized studies

Once an International Research Agenda is established, it is critical to identify and recruit the most qualified experts to perform the community-prioritized studies. Although identifying the most qualified individuals is not easy, the CDCN has found success employing two approaches. One approach involves a targeted method in which the CDCN sends information about a high-priority research project it plans to conduct to its complete physician/researcher database, including its SAB, and solicits suggestions for experts. The CDCN also performs extensive literature reviews to find leading experts. The identified candidates are then engaged by the CDCN through telephone and in-person meetings to gauge their interest and expertise. If a candidate is determined to be a strong fit, then the researcher and CDCN work together to define the scope of work and deliverables. Once agreed upon, a 'strategically-directed research grant' is awarded to the researcher for the express purpose of completing the research project. The CDCN has also found success identifying qualified researchers by melding this non-traditional approach with the more traditional competitive RFP processes: the CDCN posts an RFP announcement for a community-prioritized research project and shares information about it with its complete physician/researcher database and its SAB to identify possible experts who may be interested in applying. Candidate researchers are engaged by the CDCN through telephone and in-person meetings to inform them of the opportunity and to gauge their interest and expertise. If a researcher is determined to be a strong fit, they are encouraged to submit a research proposal. However, engagement is not a pre-requisite to apply; any researcher may submit a proposal for these competitive grants. A panel of peer reviewer experts then reviews all proposals and selects the awardee for recommendation to the CDCN Board of Directors, which can reject or accept the recommendation of the panel — similar to the NIH's two-tiered system of review. Both of these mechanisms have allowed the CDCN to identify the experts needed to execute its International Research Agenda. However, the CDCN also recognizes that research is ever-changing and that important new questions may arise that are not part of its International Research Agenda. Therefore, the CDCN also provides a third mechanism for identifying experts to answer high-impact research questions, 'investigator-initiated research proposals,' which can be focused on any topic at the researcher's discretion. The applications are collected on a rolling basis via email (grant@castlemannetwork.org) and reviewed by a sub-committee of the CDCN's SAB before being presented to the CDCN Board of Directors for a final decision.

Step 4: raise funds to perform the prioritized studies

Step 4 of the Collaborative Network Approach involves fundraising to support the high-priority research projects of the International Research Agenda. The CDCN raises funds for specific studies through multiple channels. It hosts events and campaigns and directly interacts with individual donors. Several signature events are held each year, including the Quest for a Cure Gala and World Castleman Disease Day. In these venues, the CDCN takes a targeted approach. It fundraises by informing potential donors of the exact research study that their funds will enable. This strategy helps donors feel more connected to the impact of their contribution. For example, at one fundraising event, potential donors were given the opportunity to provide funding in proportion to the cost of analysis of each sample in the experiment. They then knew that their funds enabled a set number of samples to be assayed, allowing them to recognize their direct contribution. The CDCN also established the Castleman Warrior Program. In addition to raising awareness and allowing patients to support one another, this program facilitates fundraising for research. Warriors are encouraged to share their stories with one another through monthly teleconferences, host local community events, and create a personalized donation page on the CDCN's website. These donation pages are shared with the Warriors' personal networks as a grassroots funding stream.

The CDCN's website uses a merchant services partner to allow online donations via credit card as well as receiving check donations by mail or gifted securities. After donations are received, the CDCN distributes to donors personalized thank-you letters, tax information, and information regarding the status of its research projects via personalized research updates, events, web content, newsletters, and social media. Such transparency and efficiency promote confidence in and connection to the cause.

Step 5: procure samples and enroll patients for the prioritized studies

With the optimal researcher and necessary funding in place, the next step in the Collaborative Network Approach is the identification of the proper study subjects, in the case of a clinical trial, or research biospecimens, in the case of a laboratory study. Historically, rare disease research has been plagued by conflicting results that arise from research on biospecimens with poor correlative clinical information, improperly stratified experimental cohorts, and small sample sizes. To avoid these pitfalls, the CDCN invests heavily in selecting the ideal samples for its research collaborations. Each study on the International Research Agenda has a detailed strategy to obtain samples (e.g. blood, saliva, lymph node tissue, etc.). To execute these strategies, the CDCN leverages its patient/loved one and physician/researcher databases (Step 1). Direct-from-patient sample procurement is facilitated by personalized outreach. Interested patients are asked to complete a questionnaire to express their desire to donate a sample (<https://www.cdcn.org/samples>). Responses allow CDCN personnel to determine if the patient may be eligible for enrollment in any current research studies. To support wider and future research efforts, the CDCN recently established a biobank for collection and sharing of biospecimens with the entire research community. It has also launched the ACCELERATE Natural History Registry, which allows patients anywhere in the world to consent online (www.CDCN.org/ACCELERATE) for medical record acquisition and extraction. Together, its biobank and ACCELERATE allow the CDCN to collect and correlate key clinical information with biospecimens. The CDCN also procures biospecimens through collaborations with physicians, researchers, and corporate partners. Collaborations with corporate partners have resulted in the acquisition of samples and related clinical data collected as part of previous clinical trials.

Step 6: study execution

Once all pieces are brought together, the study is ready to begin. However, since many of the research projects that the CDCN leads have multiple collaborators, the CDCN continues to stay involved throughout the study execution phase, assisting with project management and scientific advice. By fostering connections between the multiple collaborators, the CDCN promotes cooperation that improves outcomes and increases the speed of project completion.

Step 7: data analysis/identify treatments

Once the research project has been completed, the next step in the Collaborative Network Approach is data analysis. The exact nature and complexity of the data analysis step vary based on the experimental platform. For some projects, analysis can be rather straightforward. In such instances, the CDCN collaborates directly with the researchers who conducted the work. However, other datasets may require sophisticated bioinformatics approaches to interpret the results and an intimate clinical knowledge of CD to translate the findings into improved patient outcomes. For such projects, the CDCN repeats Steps 3 and 4 to identify and support experts in the analysis of these datasets. As in Step 6, the CDCN stays involved throughout the process and collaborates with its network of physicians through teleconferences and in-person meetings to understand the clinical significance of results and translate them into improved patient outcomes.

As part of its approach to data analysis, the CDCN places special emphasis on identifying new drug targets for treating CD. To do this, it directs investigators who analyze the datasets to leverage bioinformatic strategies specifically tailored to this task. One such strategy is aimed at identifying FDA-approved drugs as candidates for off-label use in CD. This approach has the benefit that these drugs' safety profiles are already understood and they are commercially available; they may be able to be used off-label in the near-term if an appropriate clinical scenario arises. When off-label drugs are administered to CD patients, the use of these existing treatments is captured in the ACCELERATE Natural History Registry to gain insights into how effective they are in a real-world setting. When promising drugs are identified through the ACCELERATE Natural History Registry or the CDCN physician network, the CDCN plans to support their rigorous assessment through clinical trials.

Step 8: knowledge dissemination

A final and critical step in the Collaborative Network Approach is prompt dissemination of study outcomes to the global community of physicians/researchers, patients/loved ones, and other rare disease organizations. The CDCN accomplished this by collaborating with the lead researcher of a project and other members of the CDCN research community to prepare the findings of a study for presentation at scientific meetings and for publication in scientific journals. Once published, the CDCN actively distributes the articles to its community of physicians/researchers and patients/loved ones via its discussion boards, email lists, and monthly online case discussions. This final step ensures that the community, described in Step 1, is well informed about scientific progress and therefore better able to identify and prioritize the next round of high-impact research. After disseminating findings throughout the community, the cycle continues: more individuals join, new research ideas are shared (inspired by the findings), and greater progress towards the CDCN's mission is accomplished.

The CDCN's governance and organizational structure

In addition to its volunteer leadership team, there are several other components to the CDCN organizational model (Figure 2). The CDCN is a registered 501(c)3 non-profit organization that relies on donations to achieve its mission. The Board of Directors manages the CDCN's resources from a fiduciary, financial, and legal standpoint. The SAB prioritizes the International Research Agenda and develops consensus guidelines. The Advisory Council leverages the expertise and networks of influential leaders across business, medicine, media, law, and finance to drive awareness and fundraising strategies. The CDCN's very low operating costs help it to maximize the impact of every dollar it raises; it is largely sustained by a skilled and experienced workforce of volunteers. However, without a full-time staff, the organization is tasked with constantly attracting and retaining volunteers. The primary location of the CDCN in Philadelphia affords the benefit of students and professionals in health and medicine, which has helped to meet the need for talented and motivated volunteers.

Limitations

It is important to highlight several limitations of the CDCN's approach. First, reliance on identifying qualified volunteers to serve as key personnel is very challenging and creates issues with turnover. It may not be feasible

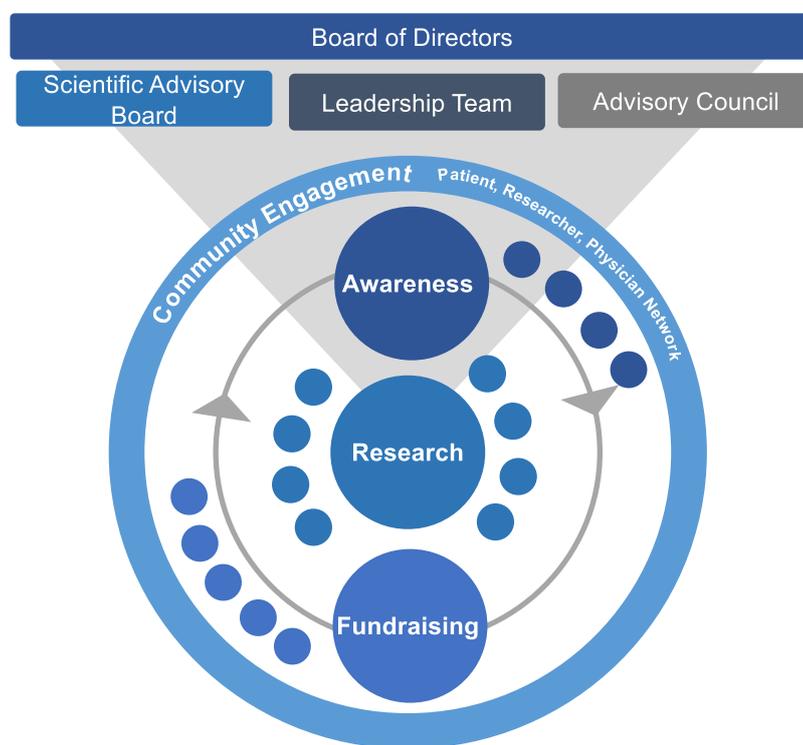


Figure 2. The CDCN's governance and organizational structure.

for many disease fields to rely on volunteers for a variety of reasons, such as patient and caregiver exhaustion. Second, researchers within a given rare disease may be reluctant to follow the scientific direction determined by crowdsourcing consensus among physicians and researchers and coordinated by a patient-led foundation. Third, the CDCN's dependence on private donations, philanthropy, and fundraising may not be scalable to the 7000 rare diseases as resources and public support may become exhausted over time.

The CDCN's impact

The CDCN's mission is to identify an effective therapy for every individual living with CD. Through its Collaborative Network Approach, the CDCN has made incredible progress toward this goal. Since its founding in 2012, the CDCN has connected and engaged over 500 physicians and researchers and over 10 000 patients and loved ones. It has leveraged these communities to develop and execute an International Research Agenda. This effort has supported 23 research projects with samples, study coordination, and/or data analysis, funded 19 projects, and facilitated major steps forward for CD, such as publication of over 20 research papers, including a new model of iMCD pathogenesis and a uniform CD classification system [11], multiple case series describing over 400 patients [12–15], the first-ever iMCD diagnostic criteria [16], a retrospective analysis of laboratory tests associated with response to anti-IL6 therapy in iMCD [17], and the first-ever iMCD treatment guidelines [18]. Additionally, CDCN members served as investigators on the clinical trials that led to the first-ever FDA-approved therapy for iMCD [19]. Based on these successes, other rare disease fields, including deficiency of ADA2, fibrous dysplasia/McCune-Albright syndrome, SYNGAP-1, and Curing Retinal Blindness have reported that they have begun integrating aspects of the Collaborative Network Approach. We believe that this roadmap has the potential to accelerate progress for many other rare diseases.

Summary

- 95% of rare diseases do not have a single FDA-approved therapy.
- Pioneered by the Castleman Disease Collaborative Network, the Collaborative Network Approach is a novel strategy for advancing biomedical research.
- This approach democratizes research, allowing the entire community to identify the most clinically relevant and pressing questions.
- The approach has the potential to accelerate progress for many other rare diseases.

Abbreviations

CD, Castleman disease; CDCN, Castleman Disease Collaborative Network; DMD, Duchenne muscular dystrophy; FA, Friedreich ataxia; FDA, Food and Drug Administration; ICD, International Classification of Disease; IL-6, interleukin-6; iMCD, idiopathic multicentric Castleman disease; ORDR, Office of Rare Diseases Research; RFP, request for proposals; SAB, Scientific Advisory Board.

Competing Interests

DCF has received research funding from Janssen Pharmaceuticals.

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