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Minireview

Establishing a consortium for the study of rare diseases: The Urea Cycle Disorders Consortium

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ABSTRACT

The Urea Cycle Disorders Consortium (UCDC) was created as part of a larger network established by the National Institutes of Health to study rare diseases. This paper reviews the UCDC's accomplishments over the first 6 years, including how the Consortium was developed and organized, clinical research studies initiated, and the importance of creating partnerships with patient advocacy groups, philanthropic foundations and biotech and pharmaceutical companies.

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Introduction

The Rare Diseases Clinical Research Network (RDCRN) was established by the National Institutes of Health (NIH) in 2003 to facilitate collaboration among experts in many different types of rare diseases of childhood and adulthood. Although research networks or consortia have long served to advance our understanding of a number of rare diseases (e.g. PKU), such was not the case with Urea Cycle Disorders (UCD) before 2003. There had never been an attempt to develop a national collaborative approach to researching UCD. Funding of the Urea Cycle Disorders Consortium (UCDC) as part of the RDCRN over the past 6 years has addressed this gap. There is now a network of 15 clinical and research centers that provide state-of-the-art care and clinical research to patients with UCD.

The UCDC has developed a website, which was visited over 34,000 times by the lay public and by professionals in 2008. The resources available on the website include general information about UCD for lay and professional groups, diagnostic and treatment

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guidelines, a registry, and information about clinical trials and outcome. In addition, the UCDC has trained 11 geneticists who have now entered the field of inborn errors of metabolism as clinical investigators. The UCDC has established partnerships with the National Urea Cycle Disorders Foundation (NUCDF), philanthropic foundations, and biotech and pharmaceutical companies, which have contributed to the UCDC's success.

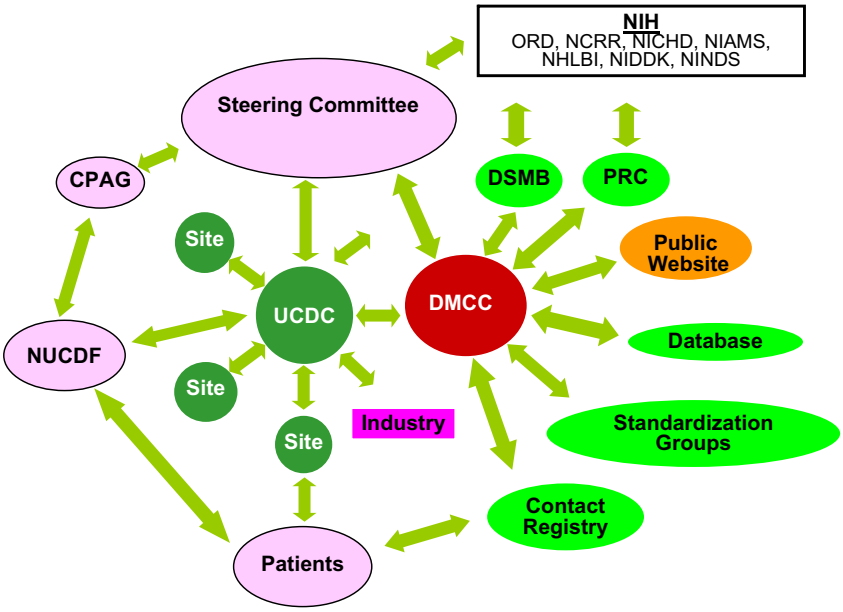
Rare diseases clinical research network

Ten consortia and a Data and Technology Coordinating Center (DTCC, now DMCC, Data Monitoring and Coordinating Center) were selected by the NIH to be a part of the original Rare Diseases Clinical Research Network, including the Urea Cycle Disorders Consortium (UCDC). In the re-competition held in 2008, this network has been expanded to 19 consortia. The RDCRN is governed by a steering committee, comprised of a principal investigator from each consortium, the director of the Data Monitoring and Coordinating Center (DMCC), NIH program and scientific officers, and a representative of the Coalition of Patient Advocacy Groups (CPAG). The steering committee and its standardization working groups develop policies, procedures, and standards for data collection, which reduces the effort each individual consortium must put forth in these efforts. The DTCC provides statistical, study implementation, data management, and monitoring support for the network. It also acts as a liaison between the consortia and the NIH-led Protocol Review Committee (PRC), which provides in depth scientific review of protocols developed by the consortia, and the Data and Safety Monitoring Board (DSMB), which monitors study protocols, ensures the safety of study participants and the integrity of studies (Fig. 1).

Urea Cycle Disorders Consortium

When initially funded, the UCDC consisted of five sites: Children's National Medical Center in Washington, DC (CNMC) (lead institution); Baylor College of Medicine in Houston, Texas; Children's Hospital of Philadelphia (CHOP) in Pennsylvania; University of California Los Angeles in California; and Vanderbilt University Medical Center in Nashville, Tennessee. Subsequent to receiving NIH grant funding, the UCDC received a five year matching grant from the O'Malley Family Foundation. This gift permitted the addition of two additional sites in 2004, one at Mount Sinai School of Medicine in New York City and a second at Yale University in New Haven, Connecticut. A grant from a second philanthropic foundation, the Kettering Fund, established a site at Case Western Reserve School of Medicine in Cleveland, Ohio in 2005. The UCDC consisted of these eight sites at the time the first study was activated in February 2006. It soon became apparent that the most successful mode of recruitment was by internal referral, i.e. referral to the Longitudinal Study by one of the UCDC investigators. Thus, the UCDC sought to further expand the number of sites and investigators. The O'Malley Family Foundation agreed to fund a site in Zurich, Switzerland which led to the addition of the UCDC's first international site at the University of Zurich Kinderspital in 2007. That same year, the Hospital for Sick Children in Toronto, which is funded by a Canadian philanthropist, was added to the consortium. In 2008, The O'Malley Family Foundation helped support new UCDC sites at Seattle Children's Hospital in Washington, Oregon Health & Science University in Portland, The Children's Hospital of Denver in Colorado, and the Children's Hospital Boston in Massachusetts, bringing the UCDC to its current fourteen sites. The UCDC is working to activate its 15th site at University of Minnesota in Minneapolis in late 2009, completing geographical coverage of the contiguous United States plus Alaska, Ontario and Switzerland (Fig. 2).

Each consortium site is led by a principal investigator, who is a board-certified metabolic specialist, with a team consisting of a study coordinator, a neuropsychologist, and at some sites a co-investigator, research fellow, and/or nutritionist. The UCDC also employs several staff members at CNMC for programmatic, grant management, administrative and biostatistical support. The UCDC currently consists of a total of 43 faculty investigators and 26 research staff members. The UCDC's steering committee is composed of the UCDC directors, the principal investigator from each site, the executive director of the National Urea Cycle Disorders Foundation, the NIH scientific and program officers, the DMCC director, the project manager, and the grant manager (Fig. 3).



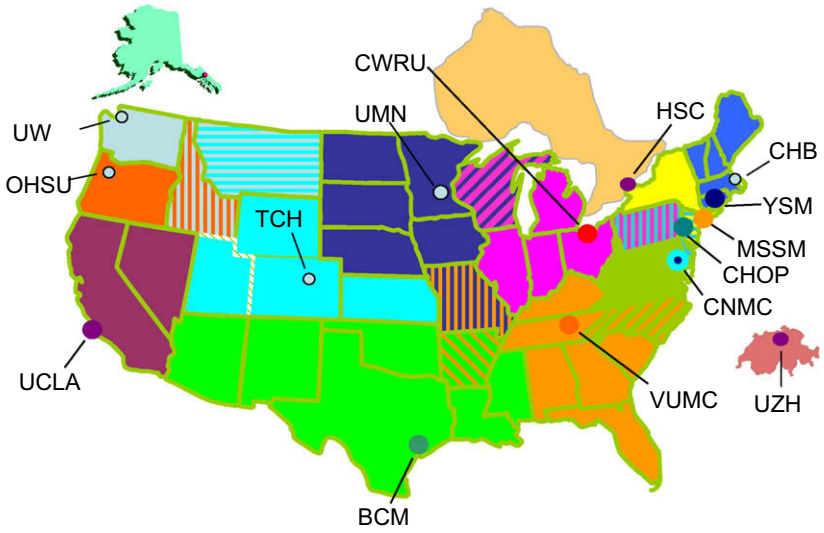


Fig. 2. UCDC Geographical Coverage CHB-Children's Hospital, Boston; YSM-Yale School of Medicine; MSSM-Mt Sinai School of Medicine; CHOP-Children's Hospital of Philadelphia; CNMC-Children's National Medical Center; VUMC-Vanderbilt University Medical Center; CWRU-Case Western Reserve University; UMN-University of Minnesota; TCH-The Children's Hospital; BCM - Baylor College of Medicine; UCLA-University of California, Los Angeles; OHSU-Oregon Health Sciences University; UW-University of Washington (Seattle Children's Hospital); HSC-Hospital for Sick Children, Toronto; UZH-University of Zurich Kinderspital.

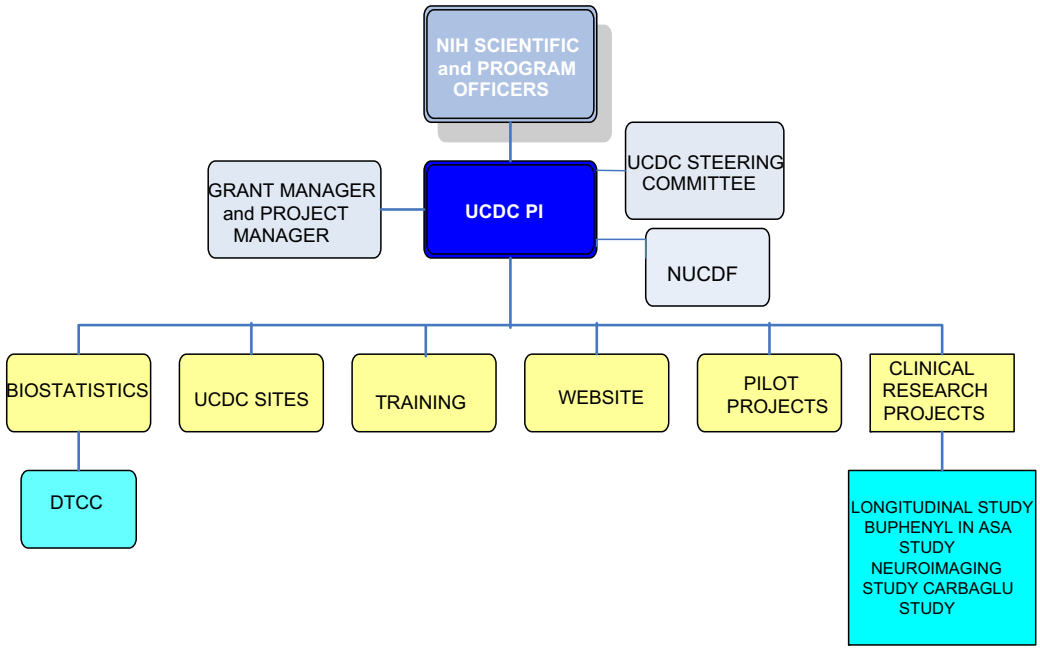


Fig. 3. Organizational structure of the Urea Cycle Disorders Consortium.

The Urea Cycle Disorders Consortium's major goals are to: (1) develop better treatments and a deeper scientific understanding of the causes and outcomes of UCD; (2) conduct clinical trials of promising new therapies; (3) develop resources with information on UCD for clinicians, researchers, and patients; and (4) train the next generation of UCD investigators. Other objectives include promoting newborn screening for UCD to aid in identification and treatment of UCD and in establishing a research contact registry for the eight UCD under study.

UCDC studies

The UCDC initiated a research contact registry, four clinical protocols, and two pilot studies during the initial 6-year funding per-

Urea Cycle Disorders are described in this review article. The other UCDC studies, which are described in separate articles in this symposium issue, include:

- Assessing Neural Mechanisms of Injury in Inborn Errors of Metabolism Using Structural MRI, Functional MRI and Magnetic Resonance Spectroscopy (MRS) (Gropman article in this supplement). This project studies cognitive and motor dysfunction in patients who are female carriers of ornithine transcarbamylase (OTC) deficiency or are males with late onset presentation of OTC deficiency, utilizing state of the art MRI (magnetic resonance imaging). This project seeks to improve our understanding of the underlying neural mechanisms that contribute to metabolic, cognitive, sensory and motor abnormalities in urea

- Measuring Urea Production in Patients with Urea Cycle Defects (Yudkoff article in this supplement). The overall purpose of this study is to develop a novel method to assess the in vivo rate of ureagenesis by administering [1-13C]acetate to humans and using mass spectrometry to measure the rate of appearance of label in [13C]urea.
- A Randomized, Double-Blind, Crossover Study of sodium phenylbutyrate and low-dose arginine (100 mg/kg/day) Compared to high-dose arginine (500 mg/kg/day) Alone on liver function, ureagenesis and subsequent nitric oxide production in patients with argininosuccinate lyase (AL) deficiency (Lee article in this supplement). This study focuses on determining if using sodium phenylbutyrate in the treatment of patients with AL deficiency improves outcome as measured by the frequency and severity of hyperammonemic crisis and transaminase levels. This is done by treating patients with sodium phenylbutyrate (Buphenyl-TM), an FDA-approved drug labeled for the treatment of other urea cycle disorders (ornithine transcarbamylase deficiency and citrullinemia).
- *N*-Carbamylglutamate treatment of *N*-Acetyl Glutamate Synthetase Deficiency (NAGS) (Tuchman article in this supplement). This study focuses on the effect of *N*-Carbamylglutamate on the incorporation of [15 N] ammonia into urea as a measure of restoration of ureagenesis capacity in patients with inherited NAGS deficiency diagnosed by DNA testing. The hypothesis is that *N*-Carbamylglutamate will restore deficient ureagenesis capacity and ameliorate the hyperammonemia in patients with inherited NAGS deficiency.

Research contact registry

In March 2005, the UCDC, in collaboration with the DTCC, launched an on-line research contact registry. As of July 31, 2009, 295 individuals with UCD have self-registered. Of those, 250 (85%) live in the U.S. Subjects enrolled in the registry receive information from the DTCC about UCDC studies via email bi-annually. The subject can then contact one of the UCDC sites to learn more about the studies and arrange for enrollment if they are deemed eligible to participate. March 2009 estimates show that 34% of the contact registrants are enrolled in one of the DSMB approved UCDC studies. About 45% of registrants that live within 200 miles of a UCDC site are enrolled in a study, and 51% of subjects who live within 100 miles of a UCDC site are enrolled in a study. This is slightly above average for the use of contact registries in general and for the RDCRN specifically [1].

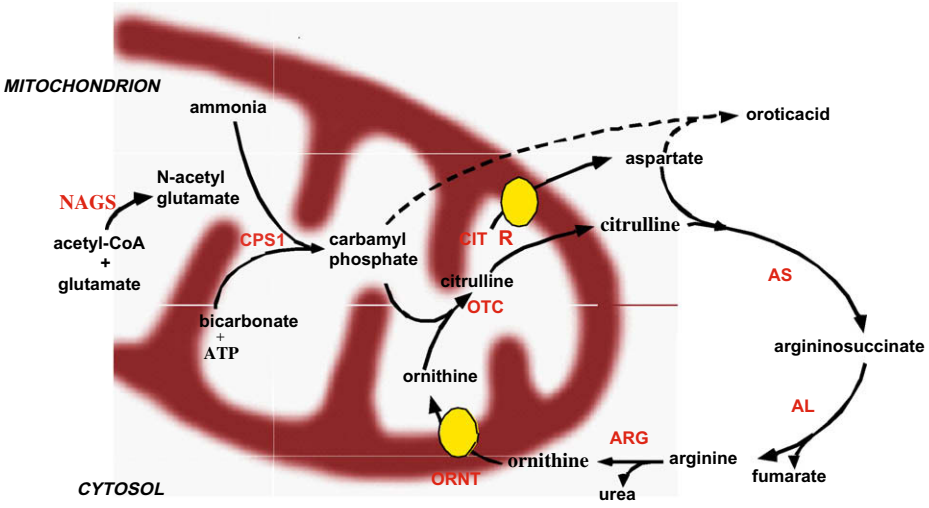
Longitudinal study of urea cycle disorders

The longitudinal study follows the natural history of participants with congenital deficiencies in any of the six enzymes and two membrane transporters involved in urea biosynthesis (see Fig. 4). The specific disorders and estimated prevalence [2,3] are noted below:

- Ornithine transcarbamylase deficiency (OTCD) (1:14,000)
- Argininosuccinate synthase (AS) deficiency (Citrullinemia) (1:57,000)
- Carbamyl phosphate synthase I (CPSI) deficiency (1:62,000)
- Argininosuccinate lyase (AL) deficiency (Argininosuccinic aciduria) (1:70,000)
- Arginase (ARG) deficiency (Argininemia) (1:350,000)
- *N*-acetylglutamate synthase (NAGS) deficiency (unknown)
- Citrullinemia type II (mitochondrial aspartate/glutamate carrier deficiency-CITR) (1 in 21,000 in Japan)
- Hyperornithinemia, hyperammonemia, homocitrullinuria (HHH) syndrome (or mitochondrial ornithine carrier deficiency-ORNT) (unknown)

As of July 31, 2009, after 3.5 years of recruitment, the longitudinal study has enrolled 352 eligible participants (Fig. 5). The recruitment goal is to enroll 440 participants in the study by February 2011. Recruitment from UCDC site metabolic clinic patient populations has proven to be the most effective recruitment mechanism representing 69% of enrolled participants, followed by referrals from the patient advocacy group, NUCDF (13%), referrals from other physicians (8%) and referrals of small numbers of participants from other study participants, the research contact registry, and the internet.

In early publications [4,5] interim cross-sectional analysis of the first 183 participants enrolled during the initial 22 months of this study were presented. The current publication updates these findings for 352 eligible participants. Using the baseline assessment data provided at the time of enrollment through participant interview and review of medical records, characteristics of each type of



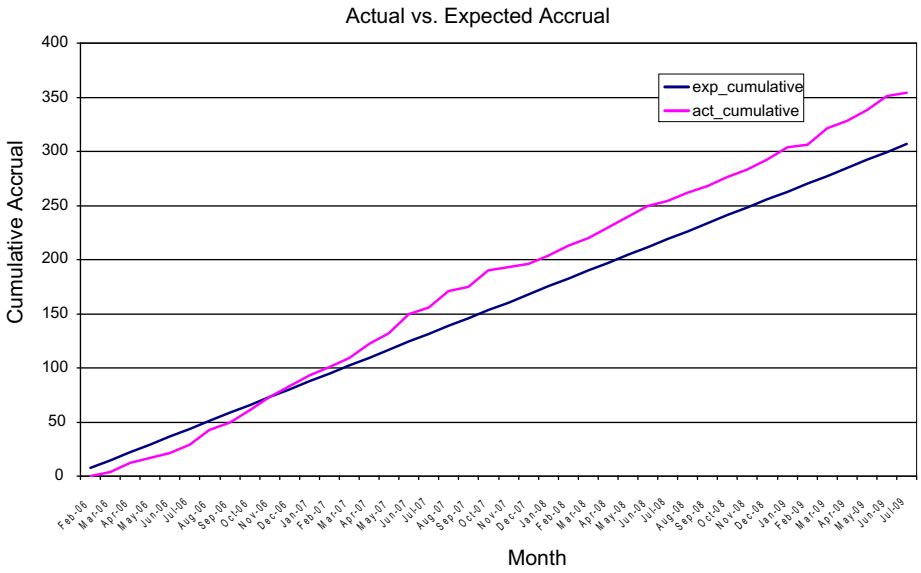


Fig. 5. Actual accrual vs. expected accrual per longitudinal study. Data current as of July 31, 2009. Target enrollment to date: 294; enrolled to date: 352.

UCD and associations with various factors were investigated. The questions posed included the following:

What is the relative frequency of proximal vs. distal UCD defects and of neonatal onset vs. late onset disease? Table 1 illustrates the relative frequency of the various UCD among enrolled participants and those who have registered in the research contact registry. We examined relative frequencies in OTC deficiency (as a proximal defect) vs. AS/AL deficiencies (as distal defects). Thus far, the distribution of frequency among eligible and registered participants appears to be consistent with prior estimates [6,7]. OTC deficiency is by far the most common disorder among the UCD, accounting for more than half of all participants, followed by AL and AS deficiencies which together account for slightly less than a third of the participants. It is expected that the proportional frequency of these latter two disorders will increase in the near future as infants diagnosed with AS/AL deficiencies by expanded newborn screening using tandem mass-spectrometry [8] are enrolled, while most other UCD, especially CPS1 and OTC deficiencies cannot yet be identified by this screening method.

Among longitudinal study participants with OTC deficiency, 11% are neonatal onset, presenting clinically within the first month of life, and 89% are late onset, presenting after 1 month of age. Thirty-six percent are asymptomatic heterozygous females; 37% are manifesting heterozygous females; 24% are symptomatic males; and 3% are asymptomatic males. Although the neonatal onset presentation comprises the smallest subgroup for OTC deficiency, the majority of participants with AS and AL deficiencies (56%) are neonatal onset, possibly reflecting greater survival of these participants. Based on prior studies, it was assumed that the proportion of participants with neonatal onset OTC deficiency presentation would be at least equal to those with late onset disease [9]. However, here the proportion of neonatal onset participants is much smaller. This difference may be due to failure to recruit severely affected patients before they died or those who underwent liver transplantation soon after their initial presentation. If this hypothesis is correct, as the study enrolls more participants soon after their initial clinical presentation, the proportion of neonatal cases should increase. As of July 31, 2009, only four out of 352 participants in the Longitudinal Study have died compared to a much higher proportion of deaths reported in earlier studies [10]. A retrospective analysis of data from deceased patients, including those with OTC deficiency, has been added to the study to further evaluate this question.

Table 1
Frequency of the various urea cycle disorders among eligible participants in the longitudinal study and those who have registered with the research contact registry. Data current as of July 31, 2009.

Diagnosis	Registered in research contact registry	Longitudinal study participants (eligible)
OTC	162	202
AL	47	55
AS	31	52
CPS	17	8
Diagnosis pending	13	8
ARG	8	12
CITR	6	2
HHH	4	3
NAGS	4.	0

Are there ethnic/racial differences in UCD prevalence? Table 2 shows the ethnic/racial origin of the participants. Although still preliminary, a marked difference is observed between the proportion of African–Americans enrolled in the study (4%) and their proportion in the general population (12%) [11]. Hispanics/Latinos who represent a similar proportion of the general population as African-Americans accounted for 15% of enrolled participants. While this could reflect a true difference in disease prevalence, it is more likely to be related to disparity in access to information about the study, location of UCDC sites, and/or mistrust of research due to past abuses [12].

What are the triggers for hyperammonemic episodes? Previous studies show that the number and severity of hyperammonemic episodes impact outcome [13]. As of July 31, 2009, there were a total of 1084 episodes of hyperammonemic crises reported in 189 of the 352 participants. The participants and/or guardians were asked to provide information on perceived triggers that preceded each recorded hyperammonemic episode. They identified several precipitants, noted in Fig. 6. Not surprisingly, an intercurrent infection was the most frequently cited trigger, followed by a recent change in diet. There were several dozen other triggers listed, however, none of them was implicated in an appreciable frequency. In the majority of cases there was no specific precipitant identified. As these participants are followed prospectively in the Longitudinal

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