and present their work to the Site Directors.

NAMDC administrative core

The Administrative Core of NAMDC provides critical organizational and strategic support to assure the overall success of the Program in accordance with NIH RDCRN program objectives. As the central hub and coordinating center for all NAMDC projects, the Administrative Core manages the interactions between multiple academic departments and between the Consortium and external organizations and institutions. The Core has an Overall Program Director/Principal Investigator, a Statistical Principal Investigator, a Clinical Team Liaison, a Bioinformatician, and an Administrative Coordinator, with ultimate responsibility for the Program's scientific, clinical research, and training/educational operations. The NAMDC Executive Committee (EC) consists of these individuals plus the Chairs of the seven NAMDC Standing Committees (Data Use Committee, Biorepository Committee, Career Enhancement Program Committee, Pilot/New Project Program Committee, Publications Committee, Website Committee, and Diagnostic Committee), two NIH Representatives, and one Patient Advocacy Group representative. The EC meets regularly to assess the progress of NAMDC programs (protocols, initiatives, *etc.*), set the long-term strategic goals for the Consortium, and define the terms and rules by which the Consortium interacts with outside entities (Patient Advocacy Groups, non-NAMDC researchers, industry, *etc.*).

The Administrative Core also maintains three independent websites: (1) an internal website to manage internal documents and communications with NAMDC sites; (2) a patient remote enrollment website (www.namdc.org) recently expanded for remote enrollment in Latin America (www.namdc.org/sp); and (3) an external website coordinated with RDCRN to publicly communicate NAMDC's mission and the availability of training opportunities and core services (https://www.rarediseasesnetwork.org/cms/namdc/).

RESULTS

NAMDC clinical registry and biorepository

NAMDC is part of the Rare Diseases Clinical Research Network (RDCRN) funded by the National Institute of Health (NIH U54NS078059). NAMDC has established a network of 17 clinical centers of excellence to improve the diagnosis, natural history, and treatment of mitochondrial diseases [Figure 1]. NAMDC sites' enrollment of mitochondrial disease patients is progressing steadily with more than 1600 patients enrolled to date [Figure 2]. The proportion of female participants in the registry population is 14.6% higher than male population and there is a notable under-representation of certain patient groups - individuals over age 65 year comprise only 3% and African American subjects represent only 2.4% (see Supplementary Materials). To enhance recruitment, the NAMDC Central Coordinating Center has also implemented a remote patient recruitment system which has been successfully enrolling domestic and international patients since 2018. Data from the NAMDC Clinical Registry [Table 1] have been analyzed, and and published in the journal of Neurology Genetics (Barca *et al.*[1] 2020). A data-mining tool has been programmed to allow NAMDC site investigators to perform data queries for internal use. NAMDC is expanding the Registry to collect natural history data on all enrolled patients with select diseases. Additionally, the NAMDC Biorepository currently holds more than 330 biological samples as well as a virtual fibroblast of 185 cell lines. A Central IRB at Columbia University Medical Center has been established for this program.

NAMDC pilot program

To date, nine pilot projects have been awarded. Some of them have been completed and published[1-4], and others are in progress. The awarded projects focus on development of biomarkers, improving diagnostic tools, characterizing natural history, and testing therapies for mitochondrial diseases [Table 2].

The NAMDC career enhancement program

The NAMDC Fellowship program has been highly successful with monthly webinar meetings and didactic training of six fellows. The first three trainees who completed the program have obtained faculty positions

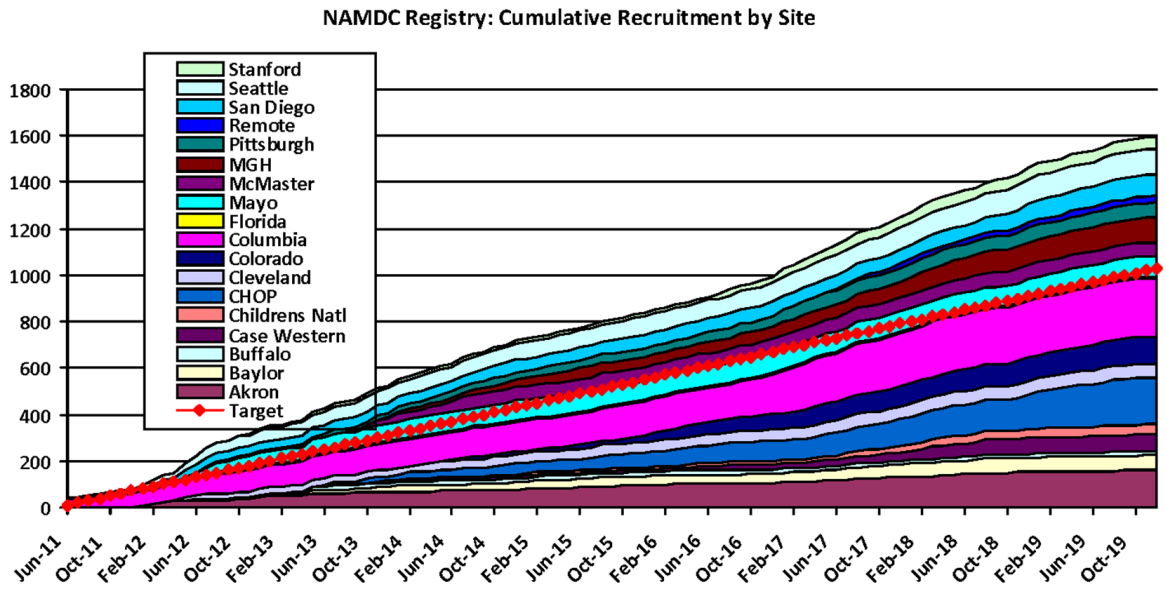

Figure 2. Actual *vs.* target recruitment. Data current as of December 31, 2019. Target Enrollment to Date: 1000; Enrolled to Date: 1634. NAMDC: North American Mitochondrial Disease Consortium

Table 1. Frequency of the various mitochondrial clinical syndromes among enrolled participants as of December 31, 2019

Clinical syndromes	Totals	Percent (%)
Alpers syndrome	23	1.5
Cardiomyopathy	12	0.8
CPEO	56	3.7
CPEO "plus"	60	3.9
Diabetes and deafness	24	1.6
Kearns-Sayre syndrome	39	2.6
LHON	42	2.8
Leigh syndrome	189	12.4
Maternal-inherited deafness	9	0.6
MELAS	109	7.1
MNGIE	18	1.2
Multi-systemic syndrome	290	19.0
MERRF	24	1.6
Myopathy	81	5.3
NARP	17	1.1
Pearson syndrome	21	1.4
Reversible infantile myopathy with cytochrome c oxidase deficiency	3	0.2
SANDO	24	1.6
Barth syndrome	3	0.2
Encephalomyopathy	95	6.2
Hepatocerebral syndrome	8	0.5
Leukoencephalopathy	9	0.6
Encephalopathy	77	5.0
Other clinical syndrome/symptoms	296	19.4

cPEO: chronic progressive external ophthalmoplegia; SANDO: sensory ataxic neuropathy with dysarthria and ophthalmoparesis; NARP: neuropathy, ataxia, and retinitis pigmentosa; MERRF: myoclonus epilepsy with ragged red fibers; MNGIE: mitochon-drial neurogastrointestinal encephalopathy; MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; LHON: Leber hereditary optic neuropathy

and are active mitochondrial disease clinician investigators. The three latest trainees are continuing their clinical training within the field of neurogenetics.

Table 2. NAMDC-funded pilot projects

RDCRN protocol number	Pilot project title	Project principal investigator/site
NAMDC7407	Prototype development of an exome variant analysis pipeline and public interface for the community-wide Mitochondrial Disease Sequence Data Resource (MSeqDR)[2-4]	Marni Falk, MD, Children's Hospital of Philadelphia
NAMDC7408	Natural history of pearson syndrome	Sumit Parikh, MD, Cleveland Clinic
NAMDC7416	Citrulline supplementation for treatment of nitric oxide deficiency in MELAS: a Phase I dose-finding and safety study	Fernando Scaglia, MD, Baylor College of Medicine
NAMDC7415	The clinical utility and a clinician's guide to new mitochondrial functional tests[1]	Johan L. K. Van Hove, MD, PhD
NAMDC7417	Activators of AMPK for Treatment of Mitochondrial Disorders	Tina M. Cowan, PhD, Stanford University
NAMDC7418	Genomic testing for molecularly undefined NAMDC Registry cases	Amel Karaa, MD, Massachusetts General Hospital
NAMDC7420	The use of amino acids to enhance the activity of enzymes involved in mitochondrial translation defects: a possible therapeutic approach	Marisa Friederich, PhD, University of Colorado
NAMDC7421	Development of Minimally Invasive Nanosensor Technology to Quantify Mitochondrial Function in Human Muscle	Zarazuela Zolkipli Cunningham, MBChB MRCP, Children's Hospital of Philadelphia

NAMDC: North American Mitochondrial Disease Consortium; RDCRN: Rare Diseases Clinical Research Network; AMPK: adenosine monophosphate–activated protein kinase; MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

NAMDC survey studies

In addition to the pilot studies, five patient surveys have been assessed through the NAMDC Registry: (1) attitudes of women carrying mitochondrial DNA mutations and healthy egg donors regarding oocyte nuclear transfer to prevent transmission of mtDNA disease; (2) nutritional supplement use in mitochondrial disease; (3) cardiovascular events in patients with metabolic diseases on chronic carnitine supplementation; (4) motivations and barriers for participation in clinical trials by individuals with mitochondrial diseases; and (5) the diagnostic odyssey of mitochondrial disease patients. Results of four of the five completed surveys have been published[5-8]. In addition, a survey of NAMDC investigators regarding the NAMDC Research Diagnostic Criteria has been completed and the results have contributed to the refinement of the NAMDC Diagnostic Criteria.

DISCUSSION

Mitochondrial diseases are challenging because they may be the most diverse human disorders at every level: clinical, biochemical, and genetic. Some are confined to the nervous system but most are multi-systemic, often affecting the brain, heart, liver, skeletal muscle, kidney, endocrine, and respiratory systems. Although severity varies, largely these are progressive and often crippling disorders. They frequently cause weakness, exercise intolerance, fatigue, seizures, mental retardation, dementia, hearing loss, blindness, and premature death.

The challenge lies in the extraordinary clinical spectrum of mitochondrial diseases, which all too often leads practitioners to either underdiagnose ("what is this complex disorder?") or to overdiagnose ("this disorder is so complex that it must be mitochondrial!"). The diagnostic difficulty is reflected in the diagnostic odyssey encountered by patients; in our survey study utilizing the RDCRN Contact Registry, subjects reported seeing, on average, more than eight clinicians before being given the diagnosis of mitochondrial disease[4]. Given this heterogeneity of mitochondrial disorders, it is essential to apply common, agreed-upon standards to the diagnosis and classification of patients. Further, given the variety of clinical and biochemical phenotypes, effective research on any given subset depends on aggregating relatively large numbers of patients.

These exigencies make clear that two prerequisites are necessary before effective clinical research can take place: (1) a clinical patient registry/longitudinal study to evaluate and expedite subsequent research with available patients; and (2) uniform diagnostic criteria for mitochondrial diseases. NAMDC was established with the goal of addressing these essential elements. After 8 years of continuous support of a U54 RDCRN cooperative agreement, NAMDC has built a basic infrastructure, established a robust clinical

registry, expanded the NAMDC Biorepository, plans to implement a registry-wide Natural History study for more common mitochondrial disorders, continues support of pilot projects, and plans to expand the career enhancement program to train new mitochondrial disease investigators. Furthermore, NAMDC plans to collaborate in the international data-harmonization efforts aiming to provide users with access to a comparable view of data from global mitochondrial registries. As NIH funding of projects has a finite lifespan, NAMDC leadership is implementing innovative and cost-effective alternatives such as remote enrollment and is assembling a patchwork of funding sources by ensuring industrial support and strategic collaboration with the UMDF non-for-profit enterprise. Through this approach, NAMDC aims to build a critical infrastructure and performance level to support a resource-efficient and sustainable plan for future mitochondrial disease research in North America and in collaboration with international partners.

DECLARATIONS

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Authors' contributions

Provided participant data, data analysis, regulatory compliance, manuscript preparation, communication among centers, and study design and implementation: Rosales XQ
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Provided participant data and directed career enhancement program: Haas R
Provided participant data and directed the pilot project program: Van Hove JLK
Provided participant data and directed the new projects program: Karaa A
Critical data review: Krotoski D
Provided participant data: Engelstad K
Database curation and data set preparation: Buchsbaum R
Data analysis, study design, and critical data review: DiMauro S
Data analysis, manuscript preparation, communication among centers, study design and implementation, and critical data review: Hirano M

Availability of data and materials

NAMDC sends Registry data to the RDCRN annually to be made available to qualified researchers through a controlled-access public website such as the database of Genotypes and Phenotypes (dbGAP) as required by the federal funding agency.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

The Columbia University Institutional Review Board (CU CIRB) has been designated as the central IRB for the NAMDC Consortium. The CU CIRB is responsible for the continuing review of all sites participating

in the NAMDC Registry and biorepository and the oversight of those aspects of Consortium Studies that are within the purview of an IRB. Columbia University, as the lead institution, is responsible for ensuring that each NAMDC member site has IRB approval to participate in the NAMDC Patient Registry and Biorepository. Columbia University maintains copies of all IRB approval notices from each member site. In order to participate in the NAMDC Registry and Biorepository, patients must provide consent in writing by signing the appropriate CU CIRB approved consent/assent form according to age. The NAMDC member sites retain the original consent form, upload a copy to the NAMDC centralized database, and provide a full copy to the patient for their records.

Consent for publication

Not applicable.

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