Undiagnosed Diseases Network

QUARTERLY REPORT

FALL 2020

UDNCONNECT.ORG | UDN@HMS.HARVARD.EDU

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WHERE WE ARE NOW

MISSION & VISION

The Undiagnosed Diseases Network (UDN) is a research study that is funded by the National Institutes of Health Common Fund with the purpose of bringing together clinical and research experts from across the United States to solve the most challenging medical mysteries using advanced technologies.

Through this study, we hope to both help individual patients and families living with the burden of undiagnosed diseases, and contribute to the understanding of how the human body works.

CURRENT STATUS

Despite significant challenges brought by COVID-19, the UDN continues to make progress towards its goals to provide diagnoses to patients and advance knowledge of rare disease. The UDN sites rapidly implemented new workflows, including protocols for remote work and telemedicine, to ensure continuity of UDN research activities. We look forward to continuing to make advances in rare and undiagnosed conditions in the coming months and years.

RECENT PUBLICATIONS

Alternative transcripts in variant interpretation: the potential for missed diagnoses and misdiagnoses (PMID: 32366967)

Missed Diagnoses: clinically relevant lessons learned through medical mysteries solved by the Undiagnosed Diseases Network (PMID: 32730690)

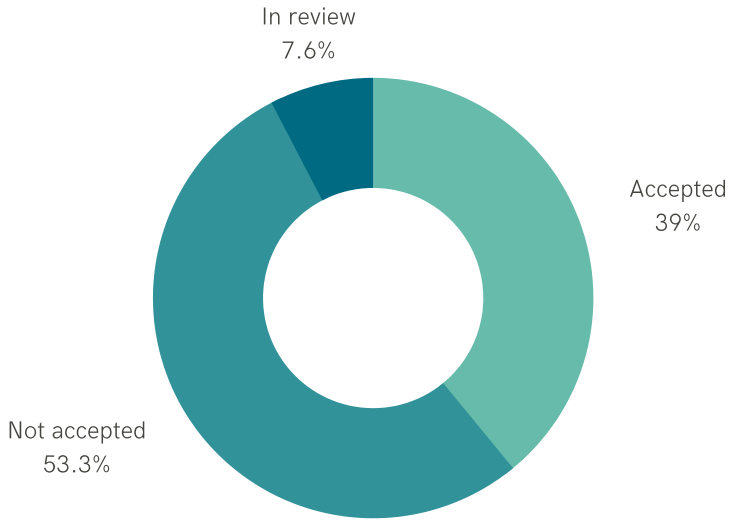
De novo variants in the ATPase module of *MORC2* cause a neurodevelopmental disorder with growth retardation and variable craniofacial dysmorphism (PMID: 32693025)

A relatively common homozygous *TRAPPC4* splicing variant is associated with an early-infantile neurodegenerative syndrome (PMID: 32901138)

Clinical sites of the Undiagnosed Diseases Network: Unique contributions to genomic medicine and science (in press)

LATEST NUMBERS

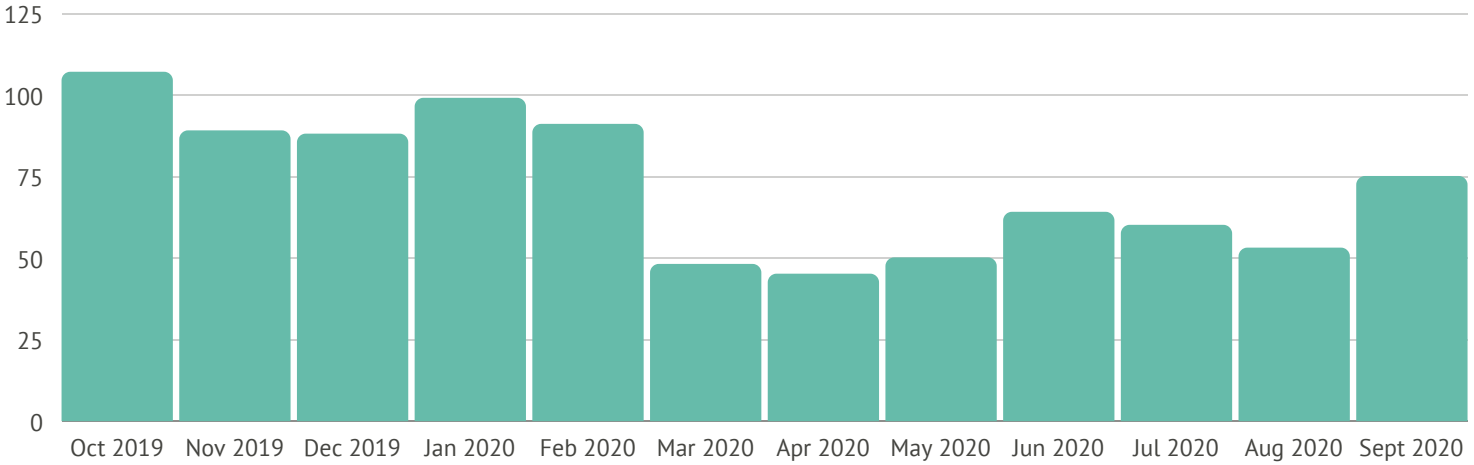
Of 4,582 applications received, 1,789 have been accepted, representing all US states, the District of Columbia, and more than 25 countries. Currently, there are 350 applications under medical record review. Applicants are not accepted for a variety of reasons, including lack of objective findings. Applicants who are not accepted may receive recommendations for additional tests or evaluations during the review process.



Applicants present with a wide variety of symptoms, with neurologic symptoms being the most common clinical presentation (40%).

The slight majority of applicants are female (52%), and 42% were under 18 years old at the time of application. Of the applicants accepted for participation in the study, 50% are female, and 62% were under 18 years old at the time of application. The majority of applicants (68%) and accepted participants (62%) identify as Non-Hispanic white.

APPLICATIONS PER MONTH



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EVALUATION PROCESS

As part of the UDN evaluation process, multiple specialists are consulted to provide input on each individual case. Often, participants are evaluated by these specialists at one of the 12 UDN clinical sites. In cases where participants are not able to travel to a UDN site, telemedicine visits may be performed. To date, 1,433 evaluations have been completed.

29%

OF EVALUATED PARTICIPANTS HAVE BEEN DIAGNOSED*

DIAGNOSES

Providing diagnoses to participants is a central goal of the UDN. Thus far, 445 certain or highly likely diagnoses have been identified. The majority of diagnoses (81%) have been made through exome or genome sequencing. Other diagnoses have been made primarily based on clinical grounds (6%) or directed clinical testing based on phenotype (9%). The remaining diagnoses were identified through a genome-wide assay such as chromosomal microarray or karyotype. Regarding the 81% of diagnoses made through exome or genome sequencing, multiple variant types were observed, including single nucleotide variants (87%) and copy number variants (7%).

27

CONDITIONS HAVE BEEN NEWLY DESCRIBED

69

DIAGNOSES HAVE BEEN MADE BASED ON CLINICAL GROUNDS OR THROUGH DIRECTED CLINICAL TESTING

13

PARTICIPANTS HAVE MORE THAN ONE DIAGNOSIS

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*Some participants have been diagnosed but not evaluated. 445 diagnoses have been identified in 431 participants. 416 of these participants have completed evaluations.

EXOME SEQUENCING

452 participants (228 children and 224 adults) have undergone exome sequencing. The most common symptom category for participants undergoing exome sequencing is neurology (47%), followed by multiple congenital anomalies (10%).

32%

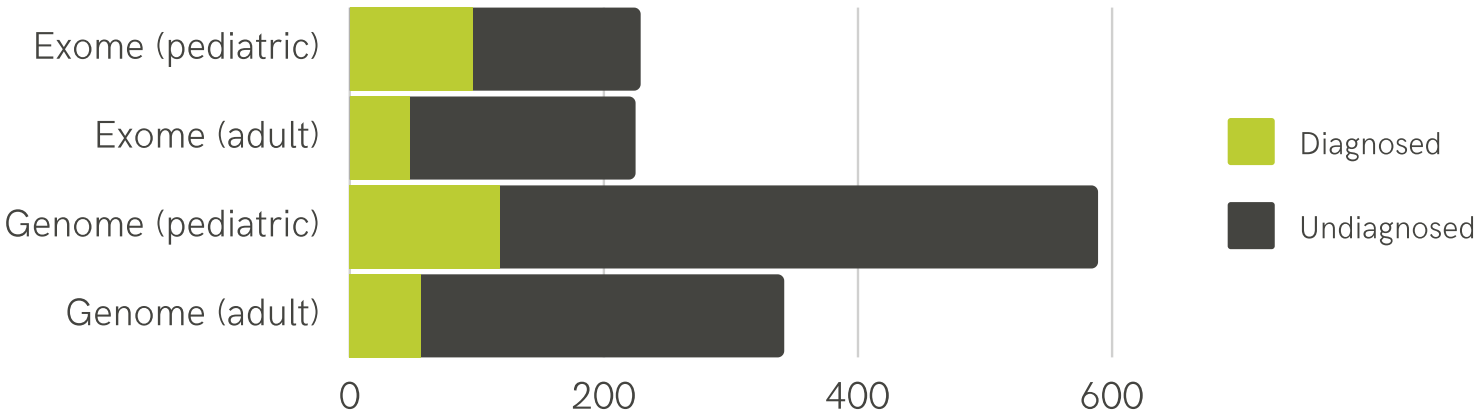
OF PARTICIPANTS WHO UNDERWENT EXOME SEQUENCING HAVE AT LEAST ONE DIAGNOSIS MADE THROUGH SEQUENCING

19%

OF PARTICIPANTS WHO UNDERWENT GENOME SEQUENCING HAVE AT LEAST ONE DIAGNOSIS MADE THROUGH SEQUENCING

GENOME SEQUENCING

929 participants (588 children and 341 adults) have undergone genome sequencing. Many of these participants had non-diagnostic exome sequencing prior to enrollment in the UDN. The most common symptom category for participants undergoing genome sequencing is neurology (50%), followed by multiple congenital anomalies (10%).



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MODEL ORGANISMS

The Model Organisms Screening Center (MOSC) is composed of two centers that use fruit fly (*Drosophila melanogaster*), nematode worm (*C. elegans*) and zebrafish (*Danio rerio*) genetics to evaluate the impact and function of genetic variants identified through the UDN.

304

VARIANTS EVALUATED BY THE MODEL ORGANISMS SCREENING CENTER

172

NUMBER OF PARTICIPANTS WITH METABOLOMICS ANALYSES COMPLETE

METABOLOMICS

The Metabolomics Core provides comprehensive analytical methods, analyses, technologies, and metabolomics expertise to the UDN to aid in clinical diagnosis and investigate potential mechanisms underlying phenotypic changes in participants.

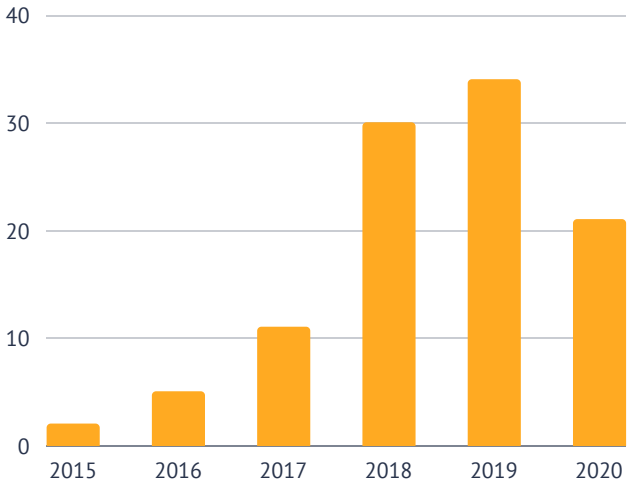
RNA SEQUENCING

The UDN uses next-generation RNA sequencing methods to analyze the transcriptome of select UDN participants. RNA sequencing has the capability to quantify gene expression and can also facilitate the discovery of novel transcripts, identification of alternatively spliced genes, and detection of allele-specific expression.

373

NUMBER OF PARTICIPANTS WITH RNA SEQUENCING COMPLETE

DATA SHARING



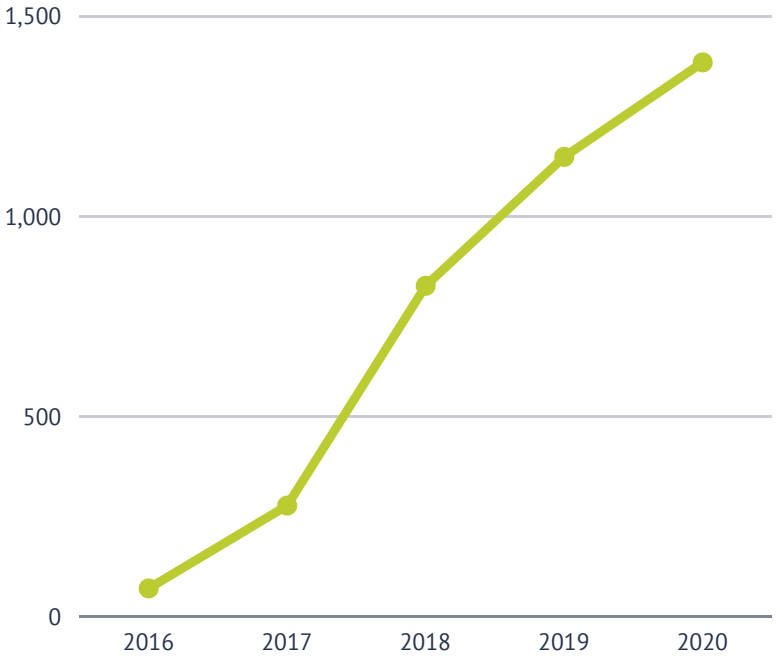
The UDN is committed to collecting and sharing data in useful, sustainable, and responsible ways. In addition to sharing data in relevant research repositories as described below, for those participants who would like to do so, the UDN shares their information via participant pages on the UDN website to identify other similar patients. Investigators also disseminate UDN research by publishing in the scientific literature. The graph on the left shows the number of UDN publications per year.

GENOMIC DATA

Genomic data are shared in the database of Genotypes and Phenotypes (dbGaP) under accession phs001232.

VARIANT-LEVEL DATA

Variant-level data are submitted to ClinVar, shared across the Matchmaker Exchange, and posted on the UDN website to facilitate collaborations and connections among researchers and families. The graph on the right shows the number of participant records shared across the Matchmaker Exchange over time.



461

VARIANT INTERPRETATIONS SUBMITTED TO CLINVAR

1,385

RECORDS SHARED ACROSS MATCHMAKER EXCHANGE

174

PARTICIPANT PAGES PUBLISHED ON UDN WEBSITE

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