Undiagnosed Diseases Network

QUARTERLY REPORT

SPRING 2022

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

UDN sites continue to evaluate participants and support research into undiagnosed and rare conditions. Since NIH Common Fund support for the UDN ends in June 2022, we are working on sustainability strategies, including the development of a foundation, to support the work of the network. We aim to make the transition from the current UDN to a sustainable model seamless and smooth for patients and families. If you are interested in partnering with the UDN on sustainability efforts, please contact UDN@hms.harvard.edu.

RECENT PUBLICATIONS

Genome sequencing reveals novel noncoding variants in *PLA2G6* and *LMNB1* causing progressive neurologic disease (PMID:35247231)

Lord of the fruit flies: an interview with Hugo Bellen (PMID: 35302163)

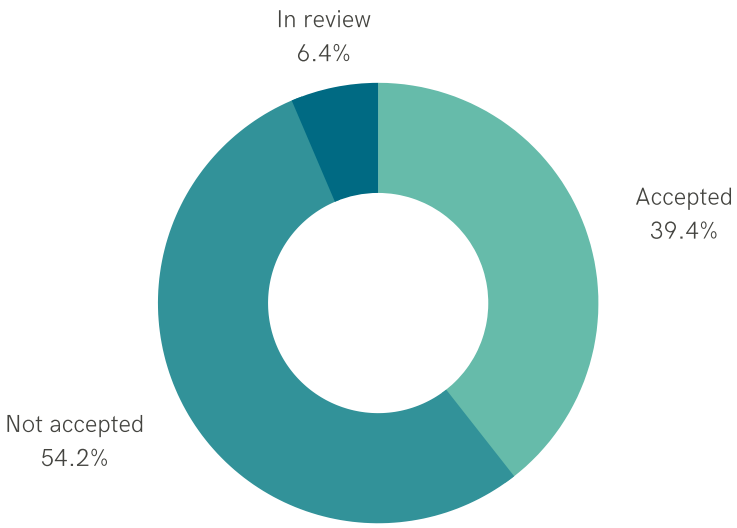
ModelMatcher: a scientist-centric online platform to facilitate collaborations between stakeholders of rare and undiagnosed disease research (PMID: 35224820)

PRUNE1 c.933G>A synonymous variant induces exon 7 skipping, disrupts the DHHA2 domain, and leads to an atypical NMIHBA syndrome presentation: case report and review of the literature (PMID: 35194938)

Loss of *IRF2BPL* impairs neuronal maintenance through excess Wnt signaling (PMID: 35044823)

LATEST NUMBERS

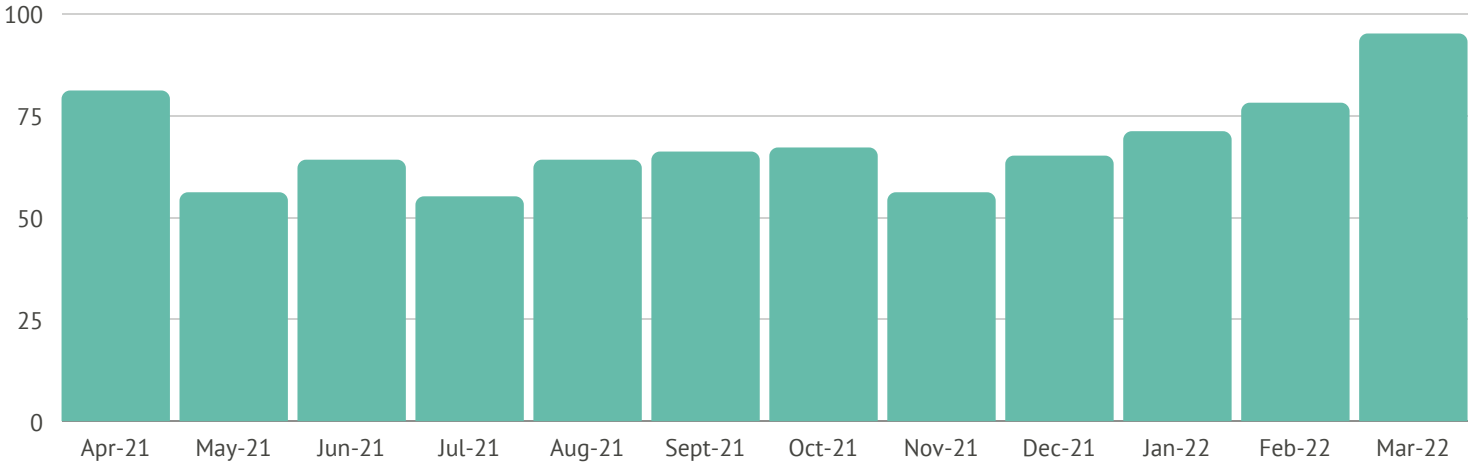
Of 5,700 applications received, 2,246 have been accepted, representing all US states, the District of Columbia, and more than 25 countries. Currently, there are 366 applications undergoing medical record review. Applicants are not accepted for a variety of reasons, including lack of objective findings. 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 small majority of applicants are female (53%), and 41% are under 18 years old. Of the applicants accepted for participation in the study, 50% are female, and 62% are under 18 years old. The majority of applicants (69%) and accepted participants (64%) identify as Non-Hispanic white.

APPLICATIONS PER MONTH



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, telehealth visits may be performed. To date, 1,873 evaluations have been completed.

28%

OF EVALUATED PARTICIPANTS HAVE BEEN DIAGNOSED*

DIAGNOSES

Providing diagnoses to participants is a central goal of the UDN. Thus far, 572 certain or highly likely diagnoses (in 549 participants) 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 4% of diagnoses were identified through other methods, including transcriptome sequencing and chromosomal microarray. Regarding the 81% of diagnoses made through exome or genome sequencing, multiple variant types were observed, including single nucleotide variants and insertions/deletions (87%) and copy number variants (7%).

49

CONDITIONS HAVE BEEN NEWLY DESCRIBED

84

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

21

PARTICIPANTS HAVE MORE THAN ONE DIAGNOSIS

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*Some participants have been diagnosed but not evaluated.

EXOME SEQUENCING

462 participants (231 children and 231 adults) have undergone exome sequencing. The most common symptom category for participants undergoing exome sequencing is neurology (47%), followed by multiple congenital anomalies (9%).

33%

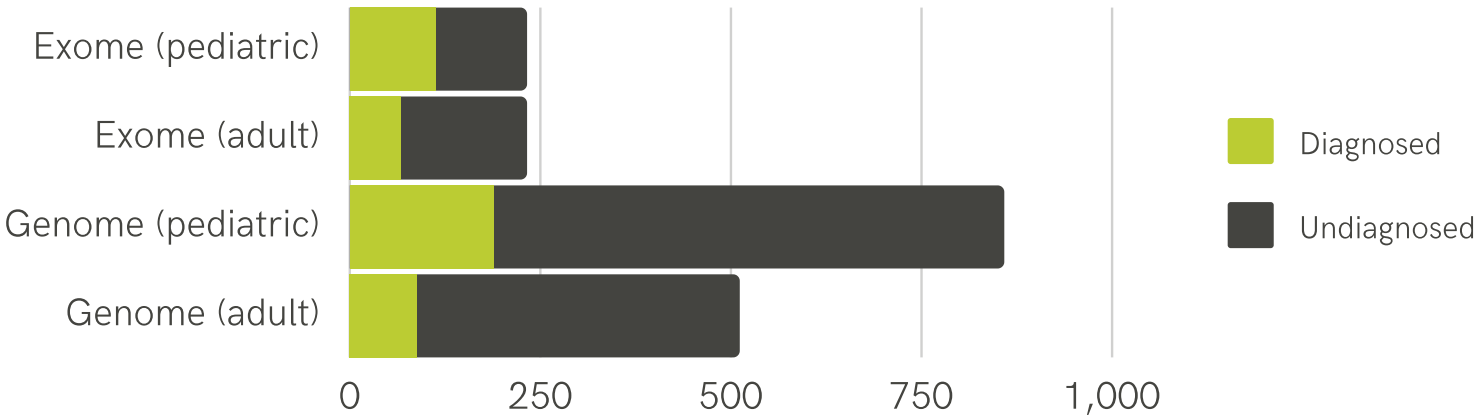
OF PARTICIPANTS WHO UNDERWENT EXOME SEQUENCING HAVE AT LEAST ONE DIAGNOSIS MADE THROUGH SEQUENCING

17%

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

GENOME SEQUENCING

1,367 participants (857 children and 510 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 (9%).



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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.

383

VARIANTS EVALUATED BY THE MODEL ORGANISMS SCREENING CENTER

244

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.

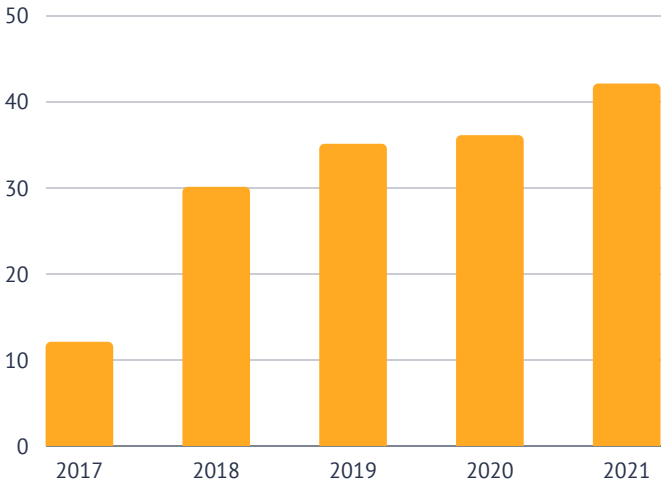
RNA SEQUENCING

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.

505

NUMBER OF PARTICIPANTS WITH RNA SEQUENCING COMPLETE

DATA SHARING



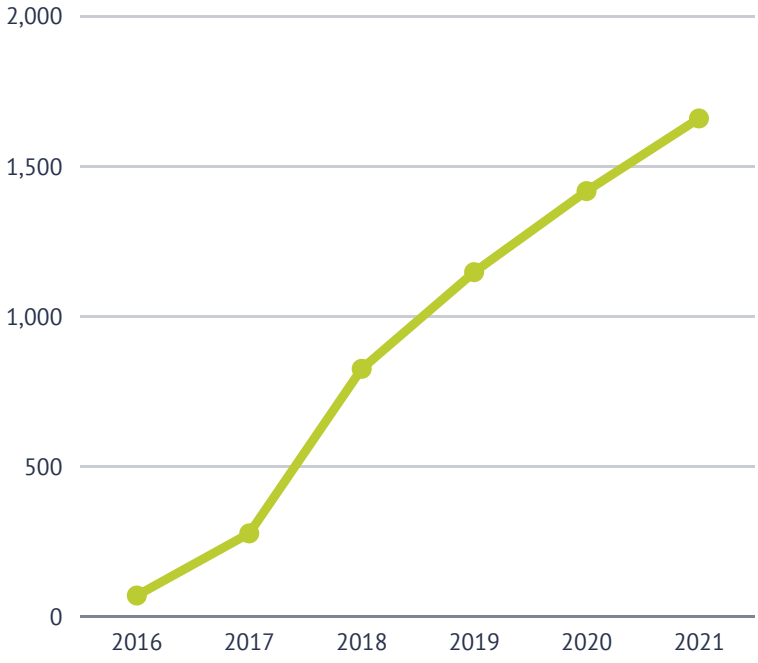
The UDN is committed to collecting and sharing data in useful, sustainable, and responsible ways. In addition to sharing data in relevant research repositories as described below, for those participants who would like to do so, the UDN shares their information via participant pages on the UDN website 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.



572

VARIANT INTERPRETATIONS SUBMITTED TO CLINVAR

1,736

RECORDS SHARED ACROSS MATCHMAKER EXCHANGE

196

PARTICIPANT PAGES PUBLISHED ON UDN WEBSITE

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