Undiagnosed Diseases Network

QUARTERLY REPORT

SPRING 2025

UDNCONNECT.ORG | UDN@HMS.HARVARD.EDU

DATA PULLED ON 4/1/2025

WHERE WE ARE NOW

MISSION & VISION

The Undiagnosed Diseases Network (UDN) is a research study 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. Several new clinical sites are in the process of onboarding. The UDN continues to focus on sustainability efforts, UDN Phase III improvements, and collaborative partnerships with the Undiagnosed Diseases Network Foundation (UDNF) and the rare disease patient community.

RECENT PUBLICATIONS

Clinical validation of RNA sequencing for Mendelian disorder diagnostics (PMID: 40043707)

TAX1BP3 Causes TRPV4-Mediated Autosomal Recessive Arrhythmogenic Cardiomyopathy (PMID: 39963794)

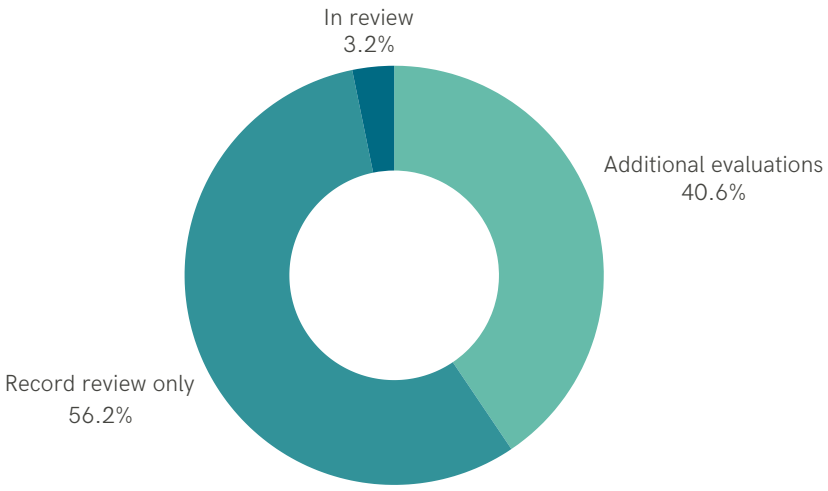
Pathogenic de novo variants in *PPP2R5C* cause a neurodevelopmental disorder within the Houge-Janssens syndrome spectrum (PMID: 39978342)

Synchronized long-read genome, methylome, epigenome and transcriptome profiling resolve a Mendelian condition (PMID: 39880924)

De novo variants in *RYBP* are associated with a severe neurodevelopmental disorder and congenital anomalies (PMID: 39891528)

LATEST NUMBERS

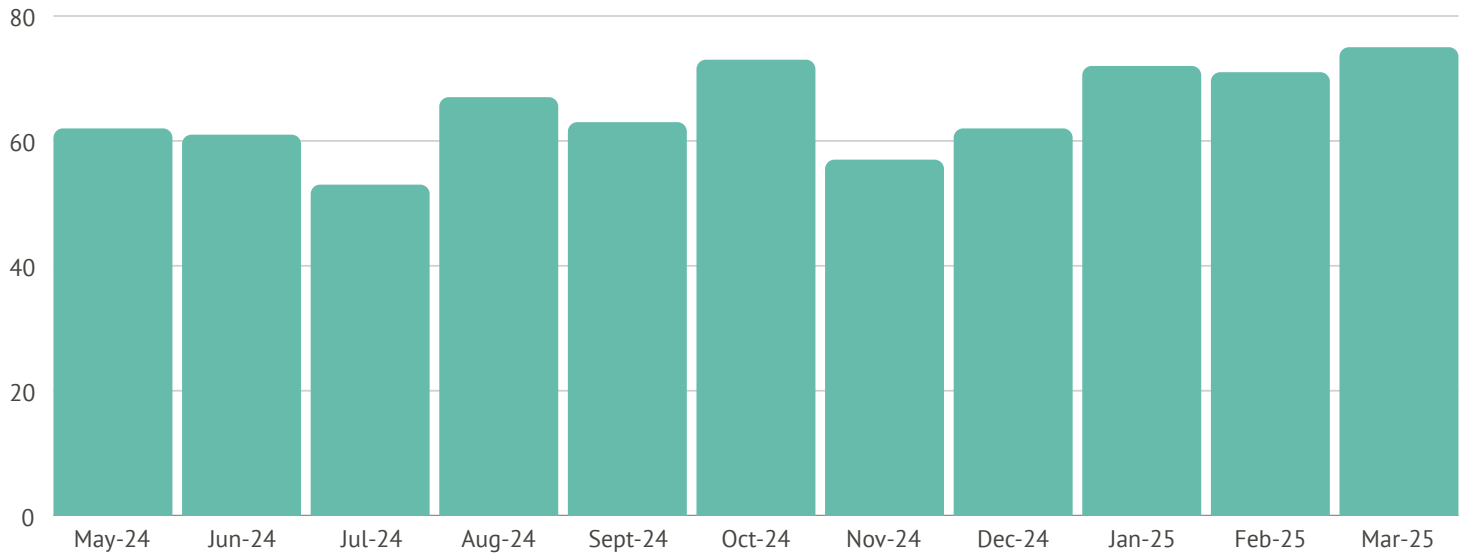
Of 7,879 cases submitted, 3,195 cases were assigned for additional telehealth, in-person, or additional research evaluations, representing all US states, the District of Columbia and more than 25 countries. Currently, there are 253 cases undergoing review. Not all participants are assigned for additional evaluations after medical record review. Participants assigned to receive medical record review only may receive useful feedback about their condition.



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

The small majority of participants are female (53%), and 40% are under 18 years old. Of the participants assigned for additional evaluations, 50% are female, and 61% are under 18 years old. 65% of participants assigned for additional evaluations identify as non-Hispanic white.

NEW CASES SUBMITTED 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 UDN clinical sites. In cases where participants are not able to travel to a UDN site, telehealth visits may be performed. To date, 2,798 evaluations have been completed.

31%

OF EVALUATED PARTICIPANTS HAVE BEEN DIAGNOSED

DIAGNOSES

Providing diagnoses to participants is a central goal of the UDN. Thus far, 920 certain or highly likely diagnoses (in 886 participants) have been identified. The majority of diagnoses (78%) have been made through genome-scale sequencing. Other diagnoses have been made primarily based on clinical grounds (7%) or directed clinical testing based on phenotype (9%). The remaining 6% of diagnoses were identified through other testing methods, including genome-wide assays.

88

CONDITIONS HAVE BEEN NEWLY DESCRIBED

141

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

31

PARTICIPANTS HAVE MORE THAN ONE DIAGNOSIS

EXOME SEQUENCING

472 participants (234 children and 238 adults) have undergone exome sequencing. The most common symptom category for participants undergoing exome sequencing is neurology (47%).

36%

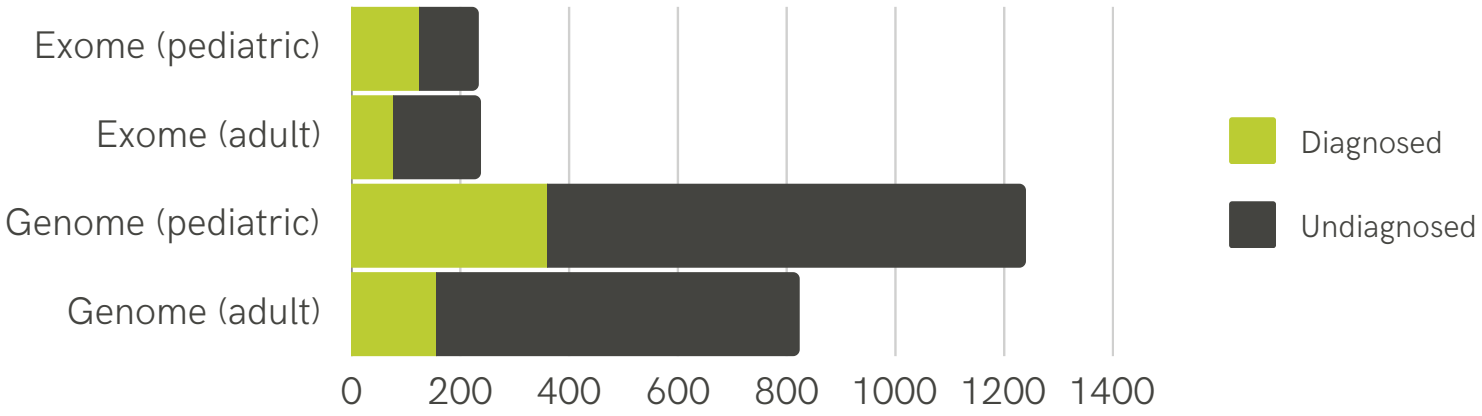
OF PARTICIPANTS WHO UNDERWENT EXOME SEQUENCING HAVE AT LEAST ONE DIAGNOSIS MADE THROUGH SEQUENCING

20%

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

GENOME SEQUENCING

2,064 participants (1,240 children and 824 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 (49%).



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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.

511

VARIANTS EVALUATED BY THE MODEL ORGANISMS SCREENING CENTER

METABOLOMICS

338

NUMBER OF PARTICIPANTS WITH METABOLOMICS ANALYSES COMPLETE

The Metabolomics Consultation Service 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

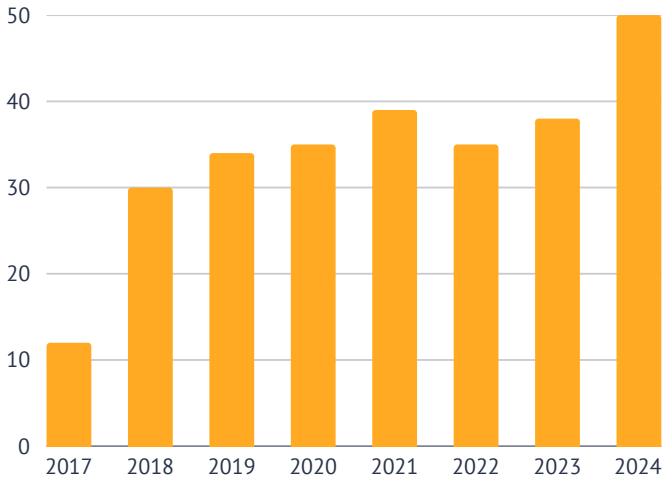
The UDN uses next-generation RNA sequencing methods to analyze the transcriptome of select UDN participants. RNA sequencing has the capability to quantify gene expression and can also facilitate the discovery of novel transcripts, identification of alternatively spliced genes, and detection of allele-specific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

777

NUMBER OF PARTICIPANTS WITH RNA SEQUENCING COMPLETE

DATA SHARING

NUMBER OF UDN PUBLICATIONS PER YEAR



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.

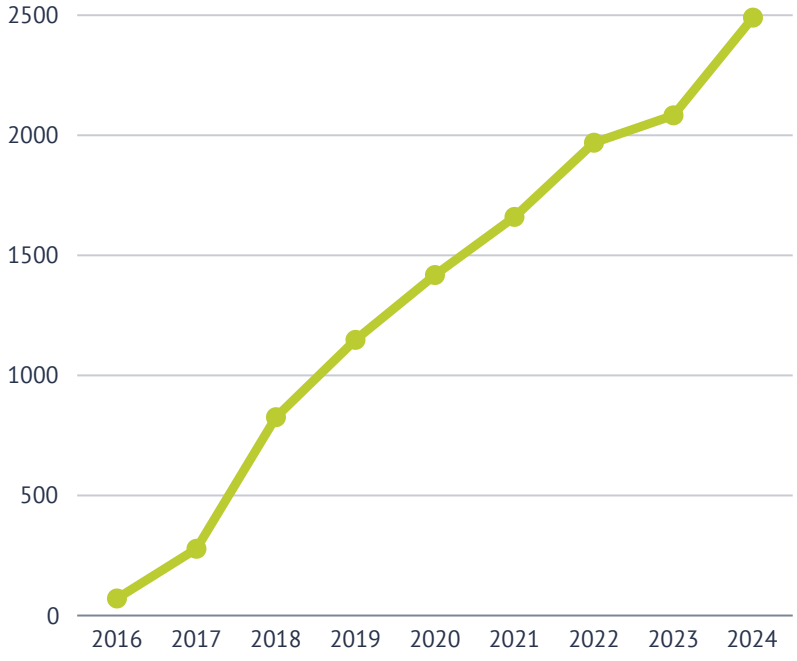
GENOMIC DATA

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.

NUMBER OF PARTICIPANT RECORDS SHARED TO MATCHMAKER EXCHANGE



911

VARIANT INTERPRETATIONS SUBMITTED TO CLINVAR

2539

RECORDS SHARED ACROSS MATCHMAKER EXCHANGE

230

PARTICIPANT PAGES PUBLISHED ON UDN WEBSITE

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