Undiagnosed Diseases Network

QUARTERLY REPORT

FALL 2025

UDNCONNECT.ORG | UDN@HMS.HARVARD.EDU

DATA THROUGH SEPTEMBER 10, 2025

WHERE WE ARE NOW

MISSION, VISION, AND VALUES

Mission: Our mission is to equitably provide diagnoses for patients with the most challenging conditions through multidisciplinary collaboration and exploration of new diagnostic approaches, advancing scientific discovery and sharing advances with the broader community.

Vision: We envision a world in which an evidence-based, collaborative approach ends the diagnostic odyssey for all with undiagnosed conditions, advances the science of disease identification, and delivers exceptional care for patients and families.

Values: Equity, Collaboration, Innovation, Partnership, Patient-centeredness, Discovery, Inclusive access, Community, Continuous improvement, Dedication, Integrity

RECENT PUBLICATIONS

Large Language Models for Rare Disease Diagnosis at the Undiagnosed Diseases Network (PMID: 40844783)

Few shot learning for phenotype-driven diagnosis of patients with rare genetic diseases (PMID: 40542121)

Disrupted diencephalon development and neuropeptidergic pathways in zebrafish with autism-risk mutations (PMID: 40460132)

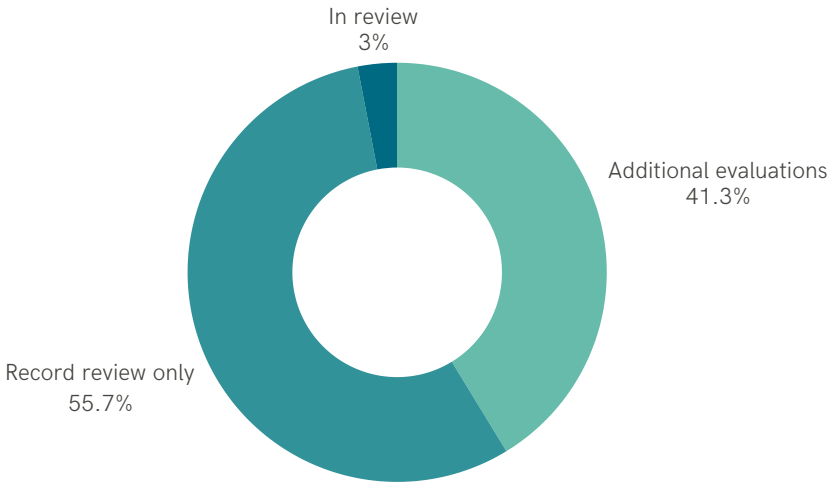
ELFN1 Deficiency: the mechanistic basis and phenotypic spectrum of a neurodevelopmental disorder with epilepsy (PMID: 40576023)

A genome-wide approach for the discovery of novel repeat expansion disorders in the Undiagnosed Diseases Network cohort (PMID: 40417743)

Integration of transcriptomics and long-read genomics prioritizes structural variants in rare disease (PMID: 40113264)

LATEST NUMBERS

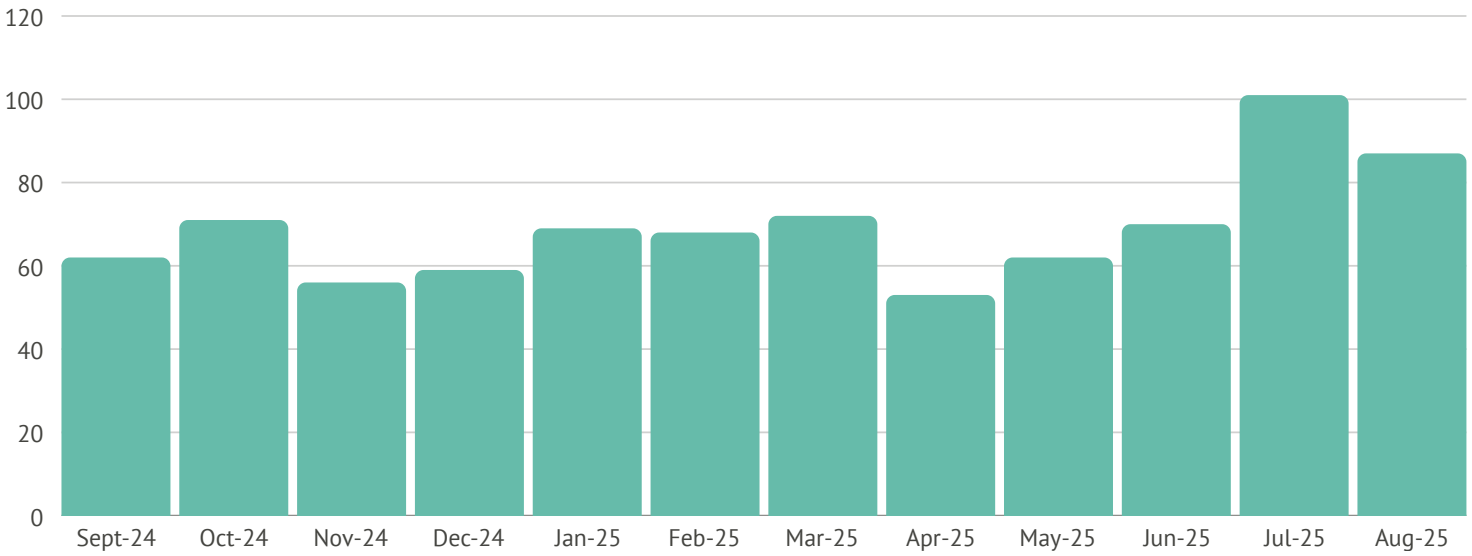
Of 8,252 cases submitted, 3,406 cases were assigned to additional telehealth, in-person, or research evaluations. UDN participants are from all US states, the District of Columbia, and more than 25 countries. Currently, there are 250 cases undergoing review. Not all participants are assigned for additional 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%).

Of the participants assigned for additional evaluations, 50% are female, and 61% are under 18 years old. 66% of participants assigned for additional evaluations identify as non-Hispanic white.

NEW CASES SUBMITTED 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 UDN clinical sites. In cases where participants are not able to travel to a UDN site or additional in person evaluations are deemed unnecessary, telehealth visits may be performed. To date, nearly 3,000 evaluations have been completed.

30%

OF EVALUATED PARTICIPANTS HAVE BEEN DIAGNOSED

DIAGNOSES

Providing diagnoses to participants is a central goal of the UDN. Thus far, 975 certain or highly likely diagnoses (in 941 participants) have been identified. The majority of diagnoses (79%) 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 5% of diagnoses were identified through other testing methods, including genome-wide assays.

89

CONDITIONS HAVE BEEN NEWLY DESCRIBED

152

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

31

PARTICIPANTS HAVE MORE THAN ONE DIAGNOSIS

MODEL ORGANISMS

The Model Organisms Screening Center (MOSC) is composed of three 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.

Between May 24, 2017 and June 30, 2023, the MOSC received 179 gene submissions and 103 were accepted for modeling in fly, worm, and/or zebrafish. Positive functional data were obtained for 54 submissions (52.4%), contributing to 22 manuscripts that describe novel disease genes, phenotypic expansions, and pathogenic mechanisms of newly identified conditions.

526

VARIANTS EVALUATED BY THE MODEL ORGANISMS SCREENING CENTER

EXOME AND GENOME SEQUENCING

2422

NUMBER OF PARTICIPANTS WITH EXOME AND/OR GENOME SEQUENCING COMPLETE

2,422 participants (1,419 children and 1,003 adults) have undergone exome and/or genome sequencing through the UDN. This figure includes both exome and genome sequencing, but is most often genome sequencing. Many participants had non-diagnostic exome sequencing prior to enrollment in the UDN.

RNA SEQUENCING

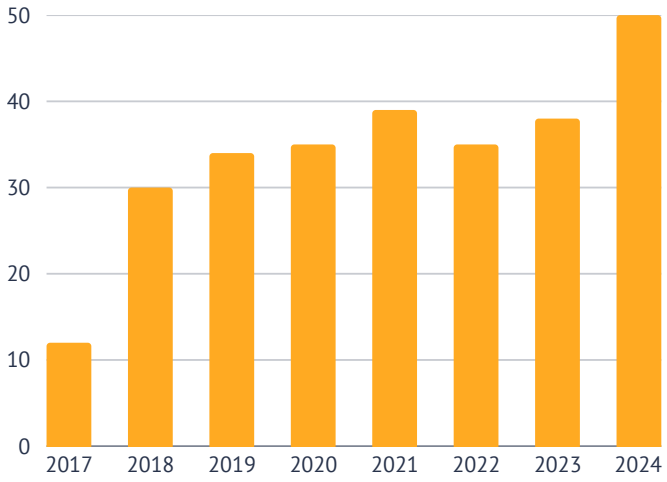
The UDN uses next-generation RNA sequencing methods to analyze the transcriptome of select UDN participants. RNA sequencing has the capability to quantify gene expression and can also facilitate the discovery of novel transcripts, identification of alternatively spliced genes, and detection of allele-specific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

789

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.

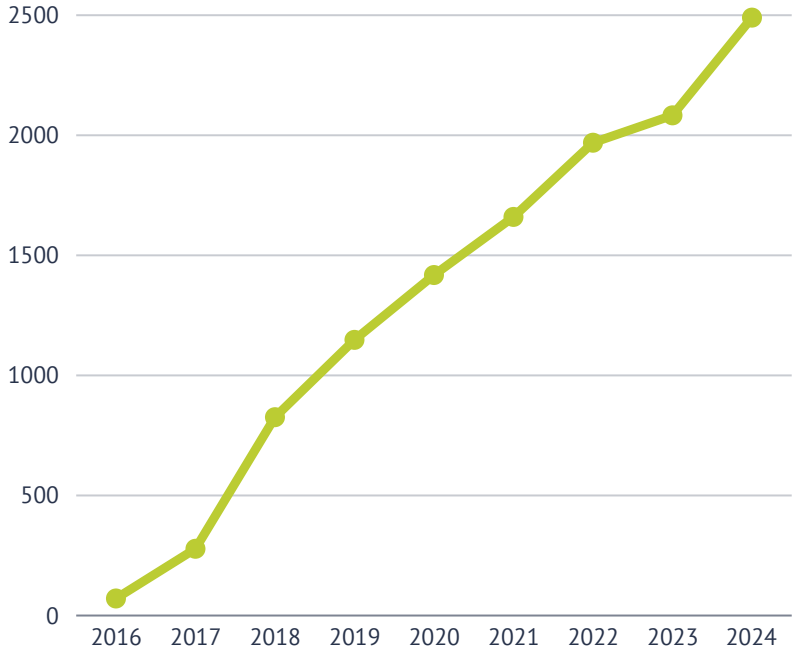
GENOMIC DATA

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



939

VARIANT INTERPRETATIONS SUBMITTED TO CLINVAR

2539

RECORDS SHARED ACROSS MATCHMAKER EXCHANGE

232

PARTICIPANT PAGES PUBLISHED ON UDN WEBSITE

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