Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Effect of genetic diagnosis on patients with previously undiagnosed disease
Supplementary information

Methods

Seven clinical sites participate in the UDN. They include Baylor College of Medicine, Duke University School of Medicine, Harvard Medical School Teaching Hospitals (Boston Children's Hospital, Brigham and Women's Hospital, and Massachusetts General Hospital), National Institutes of Health Clinical Center, Stanford Medical Center, David Geffen School of Medicine at the University of California Los Angeles, and Vanderbilt University Medical Center.

Applications are accepted from patients located anywhere in the world. A study recommendation letter from a healthcare provider is required for the case to be considered. Cases are distributed by the coordinating center according to an algorithm developed by the UDN steering committee that is based on the patient's geographical location. The clinical site reviews the study recommendation letter and requests medical records detailing prior evaluations and testing. Cases are proposed for acceptance by the network at a biweekly interactive conference call. Individual clinical sites carry out clinical investigation of the patient. Some patients are admitted to hospitals affiliated with the clinical sites to expedite investigation.

All patients are eligible for exome or genome sequencing and for metabolomics analysis. The decision as to which tests are used is made by the clinical site. If prior workup includes genomic sequencing or metabolic screens, these data may be reviewed by the site at their discretion. Additionally, at the discretion of the clinical sites, exome or genome sequencing may be employed prior to the clinical evaluation of a patient.

Exome sequencing

Peripheral blood or extracted DNA is collected from patients and available family members. Samples are submitted from each clinical site to the Baylor Clinical Laboratory following informed consent. Patient clinical data are available through the UDN Gateway. Exome sequencing protocols, including library construction, exome capture by VCRome version 2.1, HiSeq next generation sequencing (NGS), and data analysis, are as previously described.[13] Interpretation and review are facilitated by internal annotation databases, a central in-house tracking system of all cases, and increasing automation.

For the paired-end pre-capture library procedure of the exome sequencing, genome DNA is fragmented by sonicating genomic DNA and ligating to the Illumina multiplexing PE adapters. The adapter-ligated DNA is then PCR amplified using primers with sequencing barcodes (indexes).[1] For target enrichment/exome capture procedure, the pre-capture library is enriched by hybridizing to biotin labeled VCRome 2.1 in-solution exome probes at 47°C for 64 - 72 hours.[2,3] Additional probes for over 3600 Mendelian disease genes were also included in the capture in order to improve the exome coverage. The post-capture library DNA is then subjected to sequence an analysis on Illumina HiSeq platform for 100 bp paired-end reads to achieve a mean coverage of >100X for target bases. As a quality control measure, the individual's DNA is also analyzed by a cSNP-array (Illumina HumanExome-12v1 array). The SNP data are compared with the exome data to ensure correct sample identification and to assess sequencing quality.

Data analysis and annotation were performed by the Mercury pipeline. The output data from Illumina HiSeq are converted from bcl file to FastQ file by Illumina CASAVA 1.8 software, and mapped by the BWA program to the reference haploid human genome sequence (Genome Reference Consortium human genome build 37, human genome 19).[4] The variant calls are performed using Atlas-SNP and Atlas-indel developed in-house by BCM HGSC. The variant annotations are performed using in-house developed software: HGSC-SNP-anno and HGSC-indel-anno. Variants with suboptimal quality scores were removed from consideration. Remaining variants were compared computationally to the list of reported mutations from the Human Gene Mutation Database (HGMD). HGMD variants with a minor allele frequency (MAF) of greater than 5% according to 1000 Genome Project (TGP) 18 or the Exome Aggregation Consortium (ExAC) were removed. For non-HGMD changes, synonymous variants, intronic variants more than 5 bp from exon boundaries which are unlikely to affect mRNA splicing, or common variants (MAF >1%) were also discarded.

For data interpretation, variants generated by the Mercury pipeline are analyzed according to ACMG guidelines and internal SOP[5,6] (references 5 and 6) based on existing information from public databases such as ClinVar, ExAC, the literature, and the internal knowledge base, as well as the patient phenotypes. The report contains results of variants, genes, and diseases related to the patient's clinical phenotype as well as medically actionable incidental findings (for minor and adult individuals) and carrier status (for adult individuals only) if consented. Variants on the report are confirmed by Sanger sequencing.

Genome sequencing

Extracted DNA is collected from patients and available family members and submitted from each clinical site following informed consent to the HudsonAlpha Sequencing Laboratory. Patient clinical data are available through the UDN Gateway. Whole genome sequencing (WGS) protocols, including library construction and HiSeq X next generation sequencing (NGS), are performed as previously described. Analysis and interpretation are performed using an in-house developed tool (Codicem), which makes use of variant impact and genotype to phenotype association algorithms and datasets together with internal disease curations to support rapid efficient WGS data interpretation, including structural variants. Individual clinical sites also perform parallel analyses at their local institutions.

DNA was evaluated for concentration (Picogreen) and integrity (agarose gel). DNA with poor integrity or of low concentration was re-extracted or a replacement requested. Following library construction, each library was quality controlled prior to sequencing. For passing samples, genomic DNA was fragmented by sonication and subsequently ligated to the Illumina multiplexing PE adapters. The adapter-ligated DNA was then PCR amplified using primers with sequencing barcodes (indexes) and purified. Cluster generation was performed and samples passed for sequencing. Sufficient sequencing was performed on the Illumina HiSeqX system using 150 bp paired-end reads to achieve a mean coverage of >40X over the entire genome. The sequence data were converted from bcl file to FastQ file and demultiplexed using Bcl2fastq. A variety of coverage and quality metrics were produced and tested to determine sequencing success.

Secondary analysis was performed on FastQ files using an in-house developed pipeline. Reads were mapped using BWA-mem to the reference haploid human genome sequence (Genome Reference Consortium human genome build 37, human genome 19)[4]. SAMbamba was used to fixmate, sort, and index reads. Picard was used to mark duplicates. Finally, GATK was used to recalibrate and realign the reads. Coverage of genes, transcripts, and exons was analysed using an in-house developed tool called GCAT. Small variant calling (for SNVs , insertions, deletions, and indels) was performed using GATK. Larger structural variant calling was performed using Manta (26647377). Variant annotation to tag each variants with useful data points was performed using an in-house developed software, Codicem.

Variant filtering was performed within Codicem based on a number of criteria: low quality variants, variants present on an internally curated red herring list, variants within known polymorphic repeats that are not disease associated, and variants with less than 15% of reads supporting the variant call were excluded. Variants with a MAF of greater than 5% according to ExAC, TGP, or gnomAD (unless they were identified as pathogenic or likely pathogenic in ClinVar, or identified as high confidence disease associated variants in HGMD) were also excluded. Variants were additionally excluded if they were not frameshifts, premature stops, start site alterations, read throughs, splice site altering, amino acid deletions, duplications, insertions, or indels, non-synonymous amino acid changes (regardless of NS amino acid effect predictions), unless they had previously been identified as disease associated in either HGMD or ClinVar, were identified as possible promoter disruptions in curated datasets, had an extremely high CADD score (>20), or were identified as interesting near splice variants (within 10 nucleotides of the splice site with at least a moderately high predicted splice altering score).

Variant prioritization makes use of additional datasets and algorithms and is applied according to ACMG guidelines and internal SOPs [5,6]. All variants are given precomputed ACMD codes based on their characteristics, and these are used together with genotype - phenotype associations from HGMD, Online mendelian Inheritance in Man (OMIM), ClinVar, and our in house knowledge base, as well as direct knowledge and the literature to classify each variant into pathogenicity groupings so as to identify those that are deleterious and match the patient's clinical presentation. The reports generated from Codicem contain variant, gene, and disease findings related to the patient's clinical presentation, as well as medically actionable incidental findings (for minor and adult individuals) and carrier status (for adult individuals only) if consented. Variants on the report are confirmed by Sanger sequencing.

Metabolomics

The Metabolomics Core is a collaboration between the Pacific Northwest National Laboratory (PNNL) in Richland, WA, and the Oregon Health & Science University (OHSU) in Portland, OR. Untargeted metabolomics, lipidomics, and glycoproteomics measurements are performed on plasma, urine, and cerebrospinal fluid (CSF) samples at PNNL using various separation methodologies (e.g. chromatography, ion mobility spectrometry) coupled with mass spectrometry. Oxylipid measurements are performed using a targeted mass spectrometry approach via collaboration with the Wayne State University Lipidomics Core. Metabolites, and lipids that are

identified as significantly different in UDN samples are interpreted in the context of known metabolic disease by the Oregon Health and Science University (OHSU), mapped to metabolic pathways (at both PNNL and OHSU), and mapped to patient sequencing data via collaboration with the sequencing cores.

As of May, 2017, the clinical sites submitted 191 total plasma, urine, and cerebrospinal fluid samples for analysis, corresponding to 57 probands and 43 first degree relatives.

To identify outlier molecules and associated pathways, data from UDN probands and first degree relatives are compared to corresponding data from a population of individuals with no known metabolic disease and matching the current demographics of the UDN cohort as closely as possible (e.g., primarily pediatric age range, majority Caucasian, and equal sex). When possible, samples are collected from patients at multiple times to partially account for differences in metabolic profiles due to for example circadian effects, fasting vs. non-fasting states (some patients are difficult to fast) , and symptomatic vs. asymptomatic periods.

Central biorepository

The UDN biorepository is located at Vanderbilt University Medical Center in the Division of Medical Genetics and Genomic Medicine. The biorepository serves as a centralized facility for secure storage, tracking, and distribution of biological material collected during UDN studies.

Environmental exposure

An Environmental Exposures questionnaire is implemented with electronic data entry by UDN patients (or their caretakers/family members). Previously utilized questionnaires and environmental exposure experts are utilized to develop this questionnaire. Topics covered include occupational exposures, residential exposures, drugs/tobacco/alcohol, hobbies, and parental exposures before and during pregnancy.

Model Organisms Screening Center

The MOSC (Model Organisms Screening Center) assesses whether the candidate gene variants identified in patients by the Clinical Sites and Sequencing Cores can explain the observed clinical features of the patients by performing genetic experiments in Drosophila and zebrafish. As of May, 2017, the clinical sites had submitted for consideration 157 variants in 122 genes, this representing 69 independent families from all 7 sites. Certain of these were explored through 34 fly models, 7 fish models and 2 genes modeled in both cores. The human variants are first analyzed bioinformatically using MARRVEL (http://marrvel.org/), a human and model organism database aggregation tool developed for the UDN.[7] These analyses provide a filter to select high priority genes that are then assigned to either the Drosophila or Zebrafish Core depending on the evolutionary conservation of the gene and the patient's phenotypes.

Bioinformatic analysis of genes and variants submitted to the MOSC

The variants in the gene sequences for each UDN patient are first assessed by screening public human genetics and genomics databases (OMIM, ExAC, Geno2MP, ClinVar, DGV and DECIPHER), as well as by screening

databases for homologs of seven model organisms (yeasts, worm, flies, fish, mice and rats). The MOSC developed a data mining tool named MARRVEL (Model organism Aggregated Resources for Rare Variant ExpLoration[7]) that collects useful information from these databases and outputs them in a comprehensive and integrated manner. MARRVEL displays information related to 1) whether the gene of interest has been linked to disease, 2) whether a variant of interest is found in disease or control populations, 3) a table of predicted orthologs in 7 genetic model organisms, 4) known gene function and expression information of the human gene and model organism orthologs, and 5) protein structural domain and multi-species protein sequence alignment. These data are used to assess the likelihood that the variants and their corresponding genes are responsible for the phenotype observed in the UDN patient, and also to determine the best organism and strategy to study them experimentally in vivo. The presence of a good matching ortholog of the human gene and the phenotype to be assessed determines which species is selected. In parallel, we query other private human genomic databases through collaborations with the Baylor-Hopkins Center for Mendelian Genomics[8] and Baylor Genetics[9,10] to identify additional matching cases for genotypes and phenotypes.

Experimental work in the *Drosophila* and Zebrafish Cores

The Drosophila Core primarily studies whether the specific candidate variants have functional consequences using fruit flies. If there is an apparent ortholog of the candidate gene, the case is pursued in the Drosophila Core. The standard strategy is to knock out the endogenous gene by inserting a T2A-GAL4 cassette in a coding exon of a gene based on the Trojan Exon Cassette strategy[11] using the Minos-mediated Insertion Cassette (MiMIC)[12] or CRISPR/Cas9.[13] T2A-GAL4 inactivates the function of the fly gene of interest by functioning as a gene-trap cassette, and the GAL4 that is transcribed and translated from the same locus allows replacement of the fly gene with the human cDNA driven by the Upstream Activating Sequence (UAS). By expressing the human cDNA in the proper spatial and temporal expression pattern, the loss of the fly gene function can be rescued with the human UAS-cDNA in a substantial number of cases (~70%). This strategy then allows us to test whether the variant found in the patient is able to rescue the phenotype or not. If the wild-type cDNA rescued but the mutant does not, we conclude that the variant is functional and that it is likely that the variant is pathogenic. If the variant does rescue, it can be a subtle loss of function allele, a gain of function allele, or a benign variant that is not causing the observed phenotype in the patient. Additional experiments, such as over-expression of the human cDNAs in a wild-type fly, are typically performed to distinguish among these possibilities. Because each case is unique, alternative strategies, for example, introducing a homologous variant into the fly gene by combining a mutant allele and a BAC transgene when a reference human cDNA was not able to rescue the fly T2A-GAL4 line[14], may be applied to investigate the variant of interest. If there is no obvious homologue in flies, the MOSC relies on fish genetics. The Zebrafish Core generate at least two individual knockout lines for the gene of interest using the CRISPR/Cas9 system.[15] We then cross the heterozygous animals together and assesses the phenotype in the biallelic mutant animal to minimize the influence of any potential second site hits caused by CRISPR. The advantage of zebrafish is that the phenotypes are easier to associate with the observed human phenotypes.[16,17] In some cases, rescue experiments are

attempted using reference and wild-type human cDNAs by generating stable transgenic lines or through microinjection of mRNAs into one cell stage embryos.

In one study by Chao et al. (2017)[18] , a de novo variant in EBF3 discovered in a child with global developmental delay, intellectual disability, and expressive speech disorder was submitted by the NIH-UDP. By searching additional human genomic databases, patients with overlapping phenotypes with de novo variants were found in collaboration with Baylor Genetics, Texas Children's Hospital, and NYU Langone. The two de novo variants in EBF3, the human homolog of a transcription factor first identified as knot/collier in fruit flies[19], when tested in flies behaved as severe loss-of-function alleles and failed to activate transcription in mammalian cellular reporter-based assays. In another study, Luo et al. (2017)[14] tested several dominant mutations in a specific transmembrane domain of CACNA1A associated with different neurological presentations in children identified by the Baylor Clinical Site using Drosophila. One point mutation (p.R1664Q) causes early global developmental delay whereas another variant (p.R1673P) in the same transmembrane domain is associated with similar early onset delay but also with progressive degeneration of the cerebellum in the affected patient. When tested in Drosophila, the R1664Q variant corresponds to a loss-of-function allele, whereas the R1673P variant behaved as a gain-of-function allele and caused neurodegeneration, a phenotype that likely arises from calcium excitotoxicity. Such findings across species validate the use of model organisms in testing for functional variants in human disease. Finally, the MOSC has facilitated collaborations between the UDN and other clinical genome sequencing initiatives (e.g., Centers for Mendelian Genomics) leading to the identification of a novel neurodevelopmental disorder characterized by microcephaly, profound developmental delays, intellectual disability, epilepsy, and failure to thrive.[20]

Data sharing

Data are shared as broadly as possible to increase the likelihood of making diagnoses. During the application process, patients give consent to have their data shared within and outside of the UDN. Clinical, biospecimen, and sequencing data are shared in the secure UDN Gateway environment. The UDN coordinating center, located in the Department of Biomedical Informatics at Harvard Medical School, shares de-identified participant phenotypic and genotypic data in publicly accessible databases, including the database of Genotypes and Phenotypes (dbGaP),[19] PhenomeCentral,[20] and ClinVar.[21] Through PhenomeCentral, case information is also accessible to other databases participating in the Matchmaker Exchange.[22]

Participants also have the option of making their data available on the public-facing UDN website in the form of participant pages (**Supplementary Figure 2**). The goal of sharing data on the UDN website is to identify additional patients with similar phenotypes and genomic variants, a critical aspect of the investigation of rare diseases.

Sociology study

Between January, 2015, and March, 2017, observations of the UDN served as the fieldwork for a research project in sociology on the government of genomic data and science. The method used was multi-sited ethnography. Observations in all sites except two and 83 interviews with representatives of all sites were performed.

Participant engagement

The UDN Participant Engagement and Empowerment Resource (PEER) was established to gain participant and family member perspectives on UDN research goals and participant experience. The PEER engages with UDN investigators to develop and assess participant-oriented materials and identify best practices for receiving participant input in research. Overarching goals of the PEER are to foster longstanding relationships among participants, families, and researchers; promote participant empowerment; educate participants and families on the essential dual clinical/research mission of the UDN; and encourage future engagement in research studies.

Patient reported outcomes

Investigation of psychosocial processes and outcomes are also conducted through surveys using validated measures in order to understand better the participant's perspective on what it is like to live with an undiagnosed condition and subsequent effects on individuals of discovering a condition's etiology.

Results

Metabolomics

The metabolomics core was added to the UDN in September, 2015. Its first efforts focused on generating reference data sets from analyses of plasma, urine, or cerebrospinal fluid from 390 individuals with no known metabolic disease and matching the demographics of the UDN cohort as closely as possible. The numbers of individuals needed to construct the reference data sets were determined by statistical power analysis of historical metabolomics and lipidomics data from the PNNL Metabolomics Core and assuming an unbalanced study design of $n < 2$ for the diseased group and $n > 100$ for the unaffected group, which determined that data from 80-120 individuals with no known metabolic disease were required to detect a 2-fold change in over 90 percent of measured molecules at a type 1 error rate of $\alpha = 0.05$. Over the course of one year, a total of 1648 individual analyses were conducted on samples from the 390 individuals described above for the establishment of metabolomics and lipidomics reference datasets, the data from which are compared against corresponding data from UDN cases to identify molecules characteristic of their disease.

Analysis of NR5A1 Overexpression and the Effects of the R92W Mutation

Multiple mutations in SF-1 (NR5A1) have been implicated in human sex development, and Bashamboo et al. in 2016[21] identified patients heterozygous for a new NR5A1 allele, p.R92W. DNA binding experiments indicated

decreased interaction with target sites in vitro, and cell culture experiments suggested that NR5A1 p.R92W has a weakened ability to activate transcription. The Drosophila homolog of NR5A1, Ftz-F1, is necessary for the formation of alternate body segments in early embryos,[22,23] and NR5A1 can rescue the phenotype of Drosophila mutants,[24] providing an in vivo environment for functional analysis. Overexpression of NR5A1 at intermediate levels results in a severe pair-rule cuticle defect with loss of odd-numbered segments. In contrast, similar overexpression of NR5A1 p.R92W does not disrupt development (**Figure 1**). Yet, a further increase of NR5A1 p.R92W resulted in an intermediate pair-rule phenotype. These data provide further compelling evidence that NR5A1 p.R92W is indeed a partial loss-of-function mutant.

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Figure S1. Applicant geographic distribution

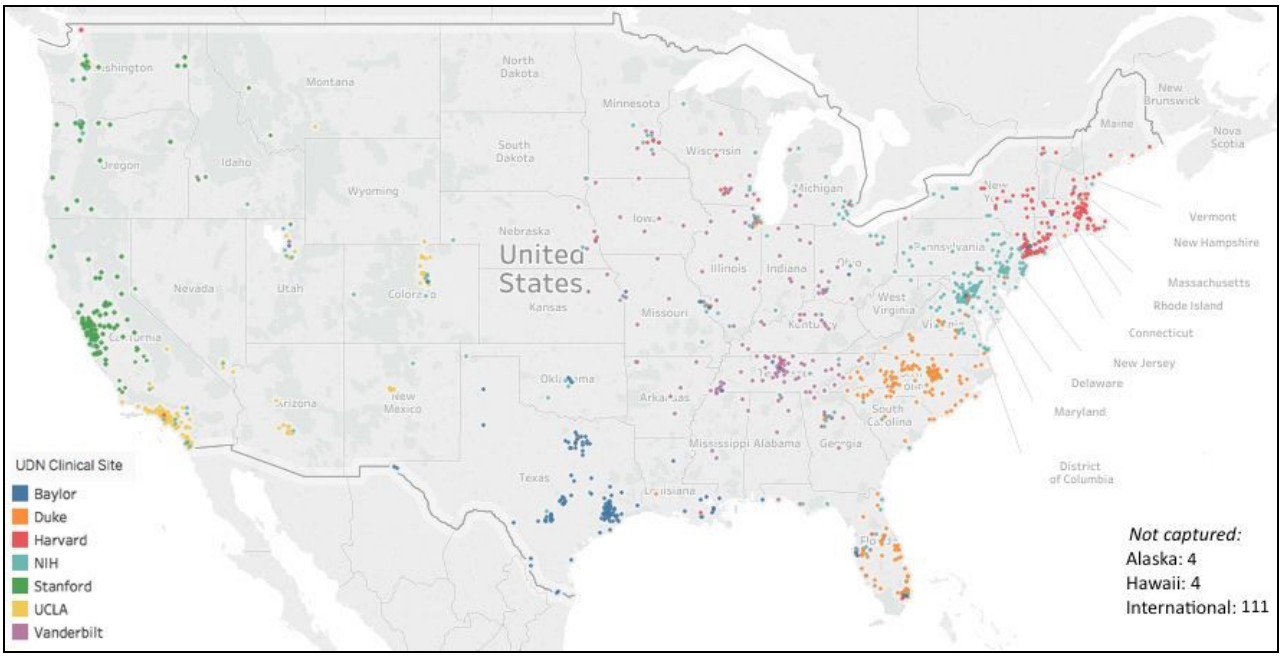

Figure S1. Applicant geographic distribution

Figure S2. Participant page

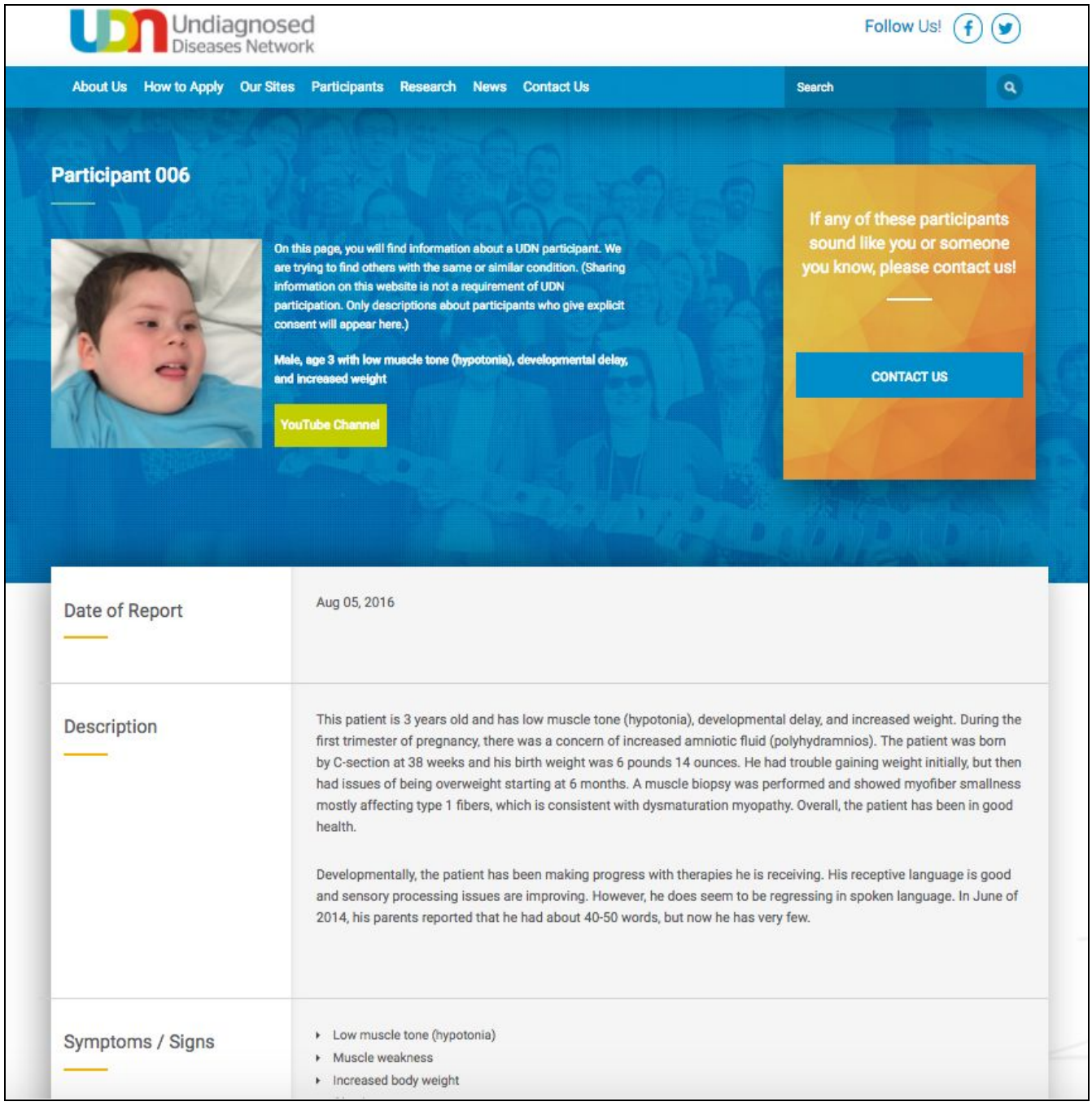

Figure S2. Example of a participant web page.

Figure S3. Metabolomic data suggesting 3-hydroxy-3-methylglutaryl-CoA lyase deficiency diagnosis

Metabolite	Proband 1	Proband 2	Proband 3	Proband 4	Proband 5	Mother	Z-Score
3-hydroxy-3-methylglutaric acid	3.83	6.87	2.94	3.09	3.74	-0.63	+ 5
L-valine	3.64	1.82	2.99	2.21	3.92	-0.87	
D-glucuronic acid	3.38	2.72	1.22	1.83	1.42	2.05	
xylitol	1.89	1.91	2.11	2.86	1.93	-1.06	
catechol	-2.61	-2.09	-0.67	-0.06	-0.29	0.77	
glycerol 3-phosphate	-2.79	0.23	-3.62	-4.70	NA	-2.97	
p-cresol	-2.83	-2.86	-2.54	-2.70	-1.89	0.94	- 5

Figure S3. Urine metabolomics suggest 3-hydroxy-3-methylglutaryl-CoA lyase deficiency. The proband has significant elevations (Z-Score >2.0) of 3-hydroxy-3-methylglutaric acid in 5 separate urine samples. Values correspond to the z-score of the difference in the level of each metabolite in comparison to the data from the reference samples. Red- positive, Blue - negative z-score. Exome sequencing subsequently revealed an exon deletion in *HMGL*.

Table S1. Applicants not accepted for evaluation

	Total (n= 589)	Pediatric applicants (n= 104)	Adult applicants (n= 485)
Sex			
Males, n (%)	264 (44.8)	57 (54.8)	207 (42.7)
Females, n (%)	322 (54.7)	47 (45.2)	275 (56.7)
Other, n (%)	3 (0.5)	0 (0.0)	3 (0.6)
Age[a]	39 +/- 21	8 +/- 5	45 +/- 16

[a]The mean age +/- standard deviation (in years) is indicated.

Table S2. UDN diagnoses and clinical actions

Diagnosis name	Gene name	Prior sequencing	Chief method used to achieve diagnosis	Type of UDN sequencing	Keys to making diagnosis	If diagnosis made on re-analysis of existing data, was the variant missed before or was the disease association not known previously?	Diagnosis category*	Brief description of management change
Mental retardation, x-linked 102	DDX3X	None	Genome-scale sequencing including genome sequencing and exome sequencing	Proband exome sequencing	Sequencing; timing	N/A	2	Testing for mitochondrial dysfunction. Clarify prognosis to prevent further unnecessary diagnostic testing or treatment.
Neurosarcoidosis	None	Proband exome sequencing	Diagnosis made primarily on clinical grounds, including aggregate assessment of non-specific test result	None	Autopsy/pathology	N/A	2	No management change; diagnosis confirmed at autopsy.
Spastic paraplegia 11	SPG11	None	Genome-scale sequencing including genome sequencing and exome sequencing	Duo exome sequencing	Research sequencing analysis	N/A	1	Suggested alterations in anti-psychotic medications that could be worsening her condition; recommended that patient contact neurology and mental health team to discuss options for reducing dose of some of her medications (baclofen, antipsychotic medications)
CACNA1A-related condition	CACNA1A	Proband exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	None	Including additional family members; research sequencing analysis; matchmaking; basic research (model organism)	Variant was not highlighted on clinical report because the phenotype did not fit the known condition, this was a phenotype expansion.	3	Treatment with acetazolamide not effective, UDN subject was started on a calcium channel blocker (flunarizine) after the UDN evaluation and the model organism data suggested gain of calcium channel function
X-linked adrenoleukodystrophy/Adrenomyeloneuropathy	ABCD1	None	Genome-scale sequencing including genome sequencing and exome sequencing	Quintet exome sequencing	Including additional family members	N/A	1	Provided risks for children of affected individuals. Referred affected individuals for appropriate screening for adrenal and brain involvement. Treatment available for certain complications- reduce baclofen, consider use of botulinum toxin injections, discontinue B6 supplementation
46,XX testicular disorder of sexual development	NR5A1	None	Genome-scale sequencing including genome sequencing and exome sequencing	Duo genome sequencing	Research sequencing analysis; matchmaking	N/A	3	No management change.
Coffin-Lowry syndrome	RPS6KA3	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Sequencing	N/A	2	Audiology assessment. Clarify prognosis to prevent further unnecessary diagnostic testing or treatment (specifically, may help guide psychiatric treatment).

Diagnosis name	Gene name	Prior sequencing	Chief method used to achieve diagnosis	Type of UDN sequencing	Keys to making diagnosis	If diagnosis made on re-analysis of existing data, was the variant missed before or was the disease association not known previously?	Diagnosis category*	Brief description of management change
DES-related condition	DES	None	Genome-scale sequencing including genome sequencing and exome sequencing	Quad exome sequencing	Sequencing	N/A	1	Other family members diagnosed. Cardiac monitoring. A recent report (Neurology 2016;87:799-805) suggested treatment with Salbutamol improved muscle function in a patient.
SCN4A-related condition	SCN4A	Proband exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	Quad genome sequencing	Sequencing; timing	Gene was associated with dominant disease. This was a new recessive condition associated with the gene that had only recently been published.	3	No management changes (self-resolving condition). Allowed recurrence risk counseling.
TRIP11-related condition	TRIP11	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Sequencing	N/A	2	Recurrence risk; provided guidance including pursuing sleep study, guidance on feeding/nutrition. Many recommendations based on having a short stature skeletal dysplasia, not necessarily specific to her condition, since there have been no reports of similar cases.
Combined oxidative phosphorylation deficiency 20	VARS2	Proband exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Research sequencing analysis; basic research	One variant was filtered out because it is intronic. Research analysis needed to highlight it for consideration for the diagnosis.	1	Recurrence risk; Confirmation that underlying defect impacts mitochondrial function, which has implications for treatment/anti-epileptic agents to use and avoid.
POMP-related condition	POMP	Proband exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	None	Matchmaking; basic research	Pathogenic variant was included on the original clinical report. At the time, though, the gene was only associated with a recessive condition, and this is a new presentation of a dominant condition associated with disease. Matchmaking and additional research was required to establish pathogenicity.	3	Reconsidering bone marrow transplant option for treatment.
Spinocerebellar ataxia, autosomal recessive 8	SYNE1	None	Genome-scale sequencing including genome sequencing and exome sequencing	Duo exome sequencing	Sequencing	N/A	1	Clarify prognosis to prevent further unnecessary diagnostic testing or treatment.
Congenital heart defect, dysmorphic facial features, and intellectual developmental disorder	CDK13	Proband exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Sequencing; timing	Disease association was not known previously.	2	Developed the first medical management guidelines for this syndrome; exploring possibility of re-purposing a known pharmaceutical (CDK13 inhibitors)

Diagnosis name	Gene name	Prior sequencing	Chief method used to achieve diagnosis	Type of UDN sequencing	Keys to making diagnosis	If diagnosis made on re-analysis of existing data, was the variant missed before or was the disease association not known previously?	Diagnosis category*	Brief description of management change
COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 31	MIPEP	Proband exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Research sequencing analysis	Disease was unknown at time of clinical proband sequencing. Disease known at time of trio exome sequencing, and single variant was highlighted. Took additional analyses and testing to confirm a deletion on the other allele.	1	Recurrence risk; Confirmation that underlying defect impacts mitochondrial function, which has implications for treatment/anti-epileptic agents to use and avoid.
17p13.3 deletion	None	Proband exome sequencing	Non-sequencing, genome-wide diagnostic assay (for example, SNP array, oligo array or karyotype)	None	Matchmaking	N/A	3	Recurrence risk (father has deletion). Sleep study performed.
Alexander disease	GFAP	None	Genome-scale sequencing including genome sequencing and exome sequencing	Duo exome sequencing	Sequencing	N/A	2	Clarify prognosis to prevent further unnecessary diagnostic testing or treatment (specifically, how to monitor/treat brain lesions).
17p13.3 deletion	None	Proband exome sequencing	Non-sequencing, genome-wide diagnostic assay (for example, SNP array, oligo array or karyotype)	None	Matchmaking	N/A	3	Sleep study & neuropsychology evaluation done.
Noonan-like syndrome	LZTR1	Proband exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Including additional family members; research sequencing analysis; matchmaking; RNA sequencing	Disease association was not known at the time of the proband exome. Disease association known at time of reporting for the UDN exome, but the condition was a phenotype expansion (recessive disease for a gene previously only described as dominant). Variant did not get included on that clinical report because of phenotype expansion. Additionally, second variant is intronic and was therefore not part of the exome analysis.	3	Recurrence risk; Consider cancer surveillance in children and carriers.
Oral-Facial-Digital syndrome, type unknown	None	Trio exome sequencing	Diagnosis made primarily on clinical grounds, including aggregate assessment of non-specific test result	Trio genome sequencing	Phenotyping	N/A	1	No change in medical management.
AGTPBP1-related condition	AGTPBP1	Duo exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	None	Reanalysis of prior sequencing data; matchmaking; basic research	Variants classified as VUS by clinical lab, disease association not known. Exome reanalyzed by UDN 5mos after initial report	4	Enabled accurate genetic counseling.

Diagnosis name	Gene name	Prior sequencing	Chief method used to achieve diagnosis	Type of UDN sequencing	Keys to making diagnosis	If diagnosis made on re-analysis of existing data, was the variant missed before or was the disease association not known previously?	Diagnosis category*	Brief description of management change
SCN2A-related condition	SCN2A	None	Genome-scale sequencing including genome sequencing and exome sequencing	Duo exome sequencing	Sequencing	N/A	1	Adjustment to anti-epileptic medication (recommended trials of medications that target sodium channels); enabled accurate genetic counseling.
Nephronophthisis 1	NPHP1	Trio exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	Trio genome sequencing	Research copy number variant analysis	Variant was missed due to difficulty with recognizing large CNVs in exome data.	1	Enabled accurate genetic counseling.
16p11.2 deletion	STX1B	Trio exome sequencing	Non-sequencing, genome-wide diagnostic assay (for example, SNP array, oligo array or karyotype)	Trio genome sequencing	Timing	N/A	3	No change in medical management
Bainbridge-Ropers syndrome	ASXL3	None	Genome-scale sequencing including genome sequencing and exome sequencing	Duo exome sequencing	Sequencing	N/A	1	Enabled accurate genetic counseling.
Marfan syndrome	FBN1	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Sequencing	N/A	2	Enabled accurate genetic counseling.
Hyaline fibromatosis syndrome	ANTXR2	Trio exome sequencing	Directed clinical testing based on phenotype (may be molecular, including gene panels; biochemical; radiologic; or, other test type)	None	Phenotyping; targeted genetic testing	N/A	1	Enabled accurate genetic counseling.
Infantile neuroaxonal dystrophy 1	PLA2G6	Trio exome sequencing	Directed clinical testing based on phenotype (may be molecular, including gene panels; biochemical; radiologic; or, other test type)	None	Phenotyping; targeted genetic testing; basic research	N/A	1	Enabled accurate genetic counseling.
CACNA1A-related condition	CACNA1A	Trio exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	None	Phenotyping; reanalysis of targeted gene	Variant missed using research exome sequencing.	1	Possible adjustment to specific medications (vitamin B6, lamotrigine, acetazolamide or verapamil) and enabled accurate genetic counseling
Cornelia de Lange syndrome 5	HDAC8	Trio exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	Quad exome sequencing, Trio genome sequencing	Sequencing	N/A	1	Enabled accurate genetic counseling.
Mucopolysaccharidosis type IIIB (Sanfilippo B)	NAGLU	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Sequencing	N/A	1	Enabled accurate genetic counseling.

Diagnosis name	Gene name	Prior sequencing	Chief method used to achieve diagnosis	Type of UDN sequencing	Keys to making diagnosis	If diagnosis made on re-analysis of existing data, was the variant missed before or was the disease association not known previously?	Diagnosis category*	Brief description of management change
USP7-Related Condition	USP7	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Sequencing; matchmaking; basic research	N/A	4	Enabled accurate genetic counseling.
Spastic paraplegia 7	SPG7	None	Genome-scale sequencing including genome sequencing and exome sequencing	Duo exome sequencing	Sequencing	N/A	1	Enabled accurate genetic counseling.
Multiple pterygium syndrome, Escobar type	None	Quad exome sequencing	Diagnosis made primarily on clinical grounds, including aggregate assessment of non-specific test result	Quad genome sequencing	Phenotyping	N/A	1	No change in medical management.
Neurodevelopmental disorder with epilepsy, cataracts, feeding difficulties, and delayed brain myelination	NACC1	Trio exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	None	Matchmaking; basic research	Variant classified as VUS on clinical exome report, disease association not known. Reanalysis performed 6 months after initial exome	4	Enabled accurate genetic counseling.
Megalencephalic leukoencephalopathy with subcortical cysts 2B, remitting, with or without mental retardation	HEPACAM	Duo exome sequencing	Directed clinical testing based on phenotype (may be molecular, including gene panels; biochemical; radiologic; or, other test type)	None	Phenotyping	Variant classified as VUS on clinical exome report. Reanalysis performed 10 months after initial exome	1	Enabled accurate genetic counseling.
Shashi-Pena syndrome	ASXL2	Trio exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Matchmaking; basic research	N/A	4	Enabled accurate genetic counseling.
TBX2-related condition	TBX2	Quad exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	Quad genome sequencing	Sequencing; matchmaking; basic research (model organisms)	N/A	4	Enabled accurate genetic counseling.
SMARCC2- related condition	SMARCC2	None	Genome-scale sequencing including genome sequencing and exome sequencing	Duo exome sequencing	Matchmaking; basic research	N/A	4	Enabled accurate genetic counseling.
Rett syndrome	MECP2	Trio exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	Trio genome sequencing	Sequencing	N/A	1	Enabled more accurate genetic counseling; family has joined support groups; additional clinical screening based on published guidelines
IRF2BPL-related condition	IRF2BPL	Trio exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	None	Reanalysis of prior sequencing data; matchmaking; basic research	Uncertain (research exome, no formal report provided). Reanalysis was done 18 months after initial exome.	4	Enabled accurate genetic counseling.
Trigeminal trophic syndrome	None	None	Diagnosis made primarily on clinical grounds, including aggregate assessment of non-specific test result	Trio exome sequencing	Multidisciplinary approach	N/A	1	None

Diagnosis name	Gene name	Prior sequencing	Chief method used to achieve diagnosis	Type of UDN sequencing	Keys to making diagnosis	If diagnosis made on re-analysis of existing data, was the variant missed before or was the disease association not known previously?	Diagnosis category*	Brief description of management change
Lethal congenital contracture syndrome 7	CNTNAP1	None	Genome-scale sequencing including genome sequencing and exome sequencing	Quad exome sequencing	Pathology; matchmaking	N/A	2	None
Infantile neuroaxonal dystrophy 1	PLA2G6	None	Directed clinical testing based on phenotype (may be molecular, including gene panels; biochemical; radiologic; or, other test type)	None	Imaging	N/A	1	Recommended supportive care per guidelines
Mental retardation, autosomal dominant 5 (mosaic)	SYNGAP1	Trio exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing (patient fibroblasts)	Reanalysis of prior sequencing data; sequencing of DNA from different tissue types	It may have been initially overlooked because it was a mosaic finding and the condition is not associated with some of the patient's unique physical findings that were highly emphasized by her prior providers. However, a detailed review of the family history and family photos showed that all such features were familial and not felt to be related to the patient's intellectual disability.	2	Electroencephalography ordered to exclude unrecognized epilepsy, diagnosis provided to advocacy organization
GABRG2-related encephalopathy	GABRG2	Trio exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	Trio genome sequencing	Matchmaking	The variant was listed as a VUS on the patient's prior exome report, at the time this gene did not clearly fit the patient's severe epilepsy and intellectual disability phenotype, but multiple other patients with the same variant and a very similar phenotype have now been described.	3	Suggested alternative AEDs that might be helpful given genetic etiology
Epileptic encephalopathy, early infantile, 17	GNAO1	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Sequencing; team expertise	N/A	2	None
Epileptic encephalopathy, early infantile, 4	STXBP1	Trio exome sequencing	Non-sequencing, genome-wide diagnostic assay (for example, SNP array, oligo array or karyotype)	None	Targeted genetic testing	N/A	2	Patient will need to be monitored for seizures. Parents have low recurrence risk, but gonadal mosaicism has been described.
CAMK2B-related condition	CAMK2B	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Timing; matchmaking	N/A	4	Unclear what the impact of future management will be since so little is known right now. Variant was de novo, indicating low recurrence risk for family.
Schaaf-Yang syndrome	MAGEL2	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Sequencing	N/A	1	Referrals to appropriate specialists based on diagnosis; connect with research group studying the disorder

Diagnosis name	Gene name	Prior sequencing	Chief method used to achieve diagnosis	Type of UDN sequencing	Keys to making diagnosis	If diagnosis made on re-analysis of existing data, was the variant missed before or was the disease association not known previously?	Diagnosis category*	Brief description of management change
Early infantile epileptic encephalopathy 44	UBA5	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Sequencing; team expertise	N/A	1	None
Mast cell activation disorder	None	Proband exome sequencing	Diagnosis made primarily on clinical grounds, including aggregate assessment of non-specific test result	Quad genome sequencing	Multidisciplinary approach	N/A	2	Treatment- H1 and H2 antihistamines, mast cell stabilizers, leukotriene inhibitors
Hypomyelinating leukodystrophy with atrophy of the basal ganglia and cerebellum	TUBB4A	None	Directed clinical testing based on phenotype (may be molecular, including gene panels; biochemical; radiologic; or, other test type)	None	Timing	N/A	1	Suggested trial of Sinemet to help with involuntary movements associated with the disorder
Basal ganglia calcification, idiopathic, 1 (formerly Fahr disease)	SLC20A2	None	Genome-scale sequencing including genome sequencing and exome sequencing	Proband exome sequencing	Multidisciplinary approach; sequencing	N/A	1	Recurrence risk and family planning
Lewy body dementia, Parkinson's disease	None	None	Diagnosis made primarily on clinical grounds, including aggregate assessment of non-specific test result	Duo exome sequencing	Re-evaluation of clinical data	N/A	1	Prognostication and management
Peroxisomal disorder	PEX1	None	Directed clinical testing based on phenotype (may be molecular, including gene panels; biochemical; radiologic; or, other test type)	Trio exome sequencing	Multidisciplinary approach	N/A	1	Limited further diagnostic work and provided specific genes for further follow-up.
Recurrent autoimmune thrombocytopenic purpura	None	None	Diagnosis made primarily on clinical grounds, including aggregate assessment of non-specific test result	Quad exome sequencing	Re-evaluation of clinical data	N/A	1	None
Mitochondrial DNA depletion syndrome, Primary progressive multiple sclerosis	POLG	Proband exome sequencing	Diagnosis made primarily on clinical grounds, including aggregate assessment of non-specific test result	Proband exome sequencing	Multidisciplinary approach	Connection of DNA variation to disorder is challenging.	2	Initiation of new therapy (Idebenone) and mitochondrial disease support (mitochondrial cocktail), increase carbodopa/levodopa
Kohlschutter-Tonz syndrome	ROGDI	None	Genome-scale sequencing including genome sequencing and exome sequencing	Quad exome sequencing	Research sequencing analysis	N/A	1	Recurrence risk & family planning; management information
Peroxisome biogenesis disorder 14B	PEX11B	None	Genome-scale sequencing including genome sequencing and exome sequencing	Quintet exome sequencing	Research sequencing analysis	N/A	1	Recurrence risk and family planning, management information

Diagnosis name	Gene name	Prior sequencing	Chief method used to achieve diagnosis	Type of UDN sequencing	Keys to making diagnosis	If diagnosis made on re-analysis of existing data, was the variant missed before or was the disease association not known previously?	Diagnosis category*	Brief description of management change
Necrotizing myopathy due to anti-HMGCR antibodies	None	None	Diagnosis made primarily on clinical grounds, including aggregate assessment of non-specific test result	Duo genome sequencing	Multidisciplinary approach; team expertise	N/A	1	Prognostication, management, recurrence risk
Basal ganglia calcification, idiopathic, 1 (formerly Fahr disease)	SLC20A2	None	Genome-scale sequencing including genome sequencing and exome sequencing	Proband exome sequencing	Multidisciplinary approach; team expertise; sequencing	N/A	1	Recurrence risk and family planning
Congenital prion disease	PRNP	None	Directed clinical testing based on phenotype (may be molecular, including gene panels; biochemical; radiologic; or, other test type)	Proband exome sequencing	Re-evaluation of clinical data; team expertise; sequencing	N/A	1	Recurrence risk and family planning
Multiple sclerosis	None	None	Diagnosis made primarily on clinical grounds, including aggregate assessment of non-specific test result	None	Re-evaluation of clinical data; team expertise	N/A	1	Initiation of disease modifying therapy (vitamin D supplementation, vitamin B12 supplementation, metronidazole topical cream)
Hypotonia, ataxia, and delayed development syndrome	EBF3	None	Genome-scale sequencing including genome sequencing and exome sequencing	None	Re-evaluation of clinical data; sequencing; matchmaking	N/A	4	Medical management, recurrence risk and family planning
Action myoclonus-renal failure syndrome	SCARB2	None	Directed clinical testing based on phenotype (may be molecular, including gene panels; biochemical; radiologic; or, other test type)	None	Multidisciplinary approach; team expertise; sequencing	N/A	1	Recurrence risk, family planning, prognostic information
Hughes-Stovin syndrome	None	None	Diagnosis made primarily on clinical grounds, including aggregate assessment of non-specific test result	Trio exome sequencing	Multidisciplinary approach; team expertise	N/A	1	Initiation of proper precautions and therapy (Xarelto)
Leukoencephalopathy, brain calcifications, and cysts	SNORD118	None	Genome-scale sequencing including genome sequencing and exome sequencing	Quintet genome sequencing	Multidisciplinary approach; team expertise; sequencing	N/A	1	Recurrence risk and family planning
Kleefstra syndrome	EHMT1	None	Genome-scale sequencing including genome sequencing and exome sequencing	Quad exome sequencing	Multidisciplinary approach; team expertise; sequencing	N/A	1	Change in management
Basal cell nevus syndrome	PTCH1	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Multidisciplinary approach; sequencing	N/A	1	Management options, screening, family planning

Diagnosis name	Gene name	Prior sequencing	Chief method used to achieve diagnosis	Type of UDN sequencing	Keys to making diagnosis	If diagnosis made on re-analysis of existing data, was the variant missed before or was the disease association not known previously?	Diagnosis category*	Brief description of management change
Noonan syndrome	PTPN11	None	Directed clinical testing based on phenotype (may be molecular, including gene panels; biochemical; radiologic; or, other test type)	Quintet exome sequencing	Multidisciplinary approach; sequencing	N/A	1	Management of muscle symptoms, recurrence risk and family planning, start vitamin D3
ARV1-CDG	ARV1	Proband exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	None	Multidisciplinary approach; team expertise	Connection to disorder is challenging.	1	Recurrence risk, family planning
Non-TB mycobacterial infection	None	None	Diagnosis made primarily on clinical grounds, including aggregate assessment of non-specific test result	None	Multidisciplinary approach; team expertise	N/A	1	Initiation of proper therapy (Levaquin, azithromycin)
Poretti-Boltshauser syndrome	LAMA1	Quintet exome sequencing	Directed clinical testing based on phenotype (may be molecular, including gene panels; biochemical; radiologic; or, other test type)	None	Multidisciplinary approach; team expertise	N/A	1	Genetic counseling and reduction of future aggressive diagnostic testing
PURA Syndrome	PURA	None	Genome-scale sequencing including genome sequencing and exome sequencing	Quad genome sequencing	Multidisciplinary approach; team expertise	N/A	1	None
Neurodevelopmental disorder with hypotonia, seizures, and absent language	HECW2	None	Genome-scale sequencing including genome sequencing and exome sequencing	None	Multidisciplinary approach; team expertise; sequencing	N/A	1	Genetic counseling and reduction of future aggressive diagnostic testing
Hypercoagulable state secondary to prothrombin mutation	F2	None	Genome-scale sequencing including genome sequencing and exome sequencing	None	Re-evaluation of clinical data	Essentially confirmation of a pre-existing diagnosis.	1	Genetic counseling, recurrence risk
Pontocerebellar hypoplasia, type 6	RARS2	None	Genome-scale sequencing including genome sequencing and exome sequencing	Quad exome sequencing	Sequencing	N/A	1	Family specific genetic counseling for family planning
Pseudohypoparathyroidism Ib	GNAS	None	Directed clinical testing based on phenotype (may be molecular, including gene panels; biochemical; radiologic; or, other test type)	Trio exome sequencing	Targeted genetic testing	N/A	1	Family specific counseling for sporadic condition
Coffin-Siris syndrome 1	ARID1B	Trio exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	Trio genome sequencing	Research sequencing analysis	N/A	1	Referral to specialists for diagnosis-specific evaluations; Family specific genetic counseling for family planning

Diagnosis name	Gene name	Prior sequencing	Chief method used to achieve diagnosis	Type of UDN sequencing	Keys to making diagnosis	If diagnosis made on re-analysis of existing data, was the variant missed before or was the disease association not known previously?	Diagnosis category*	Brief description of management change
Epilepsy-aphasia syndrome	GRIN2A	None	Genome-scale sequencing including genome sequencing and exome sequencing	Quad exome sequencing	Including additional family members; research sequencing analysis	N/A	1	Family specific genetic counseling for family planning
Mitochondrial complex V deficiency, Nuclear type 5 (MC5DN5)	ATP5D	Proband exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	None	Research sequencing analysis; basic research (fibroblast studies, model organisms, metabolomics)	Novel gene-disease association was established by UDN team. Variants were missed on prior sequencing due to lack of gene-disease association	4	Family specific genetic counseling for family planning
Epileptic encephalopathy, early infantile, 33	EEF1A2	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Including additional family members; sequencing	N/A	1	Referral to specialists for diagnosis-specific evaluations
Metabolic encephalomyopathic crises, recurrent, with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration	TANGO2	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Timing; sequencing	N/A	1	Referral to specialists for diagnosis-specific evaluations, ongoing cardiac monitoring
Sjogren syndrome; AL amyloidosis; inclusion body myositis	None	None	Directed clinical testing based on phenotype (may be molecular, including gene panels; biochemical; radiologic; or, other test type)	Trio exome sequencing	Multidisciplinary approach	N/A	2	Referral to specialists appropriate for medical management and treatment of amyloidosis
Epileptic encephalopathy, early infantile, 47 (EIEE47)	FGF12	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Sequencing	N/A	1	Family specific genetic counseling
FOXG1 syndrome/congenital variant of Rett syndrome	FOXG1	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Sequencing; multidisciplinary approach	N/A	1	Referral to specialists based on genetic results
Marfan syndrome; Trichorhinophalangeal syndrome	FBN1, TRPS1	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Sequencing	N/A	2	Referral to specialists for long-term follow-up
Epileptic encephalopathy, early infantile, 36	ALG13	None	Genome-scale sequencing including genome sequencing and exome sequencing	Quad exome sequencing	Sequencing	N/A	1	Referred to additional research studies (including sharing of patient samples)
Mosaic GNAQ-related disorder	GNAQ	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Team expertise; targeted genetic testing	N/A	1	Referral to specialists appropriate for molecular diagnosis

Diagnosis name	Gene name	Prior sequencing	Chief method used to achieve diagnosis	Type of UDN sequencing	Keys to making diagnosis	If diagnosis made on re-analysis of existing data, was the variant missed before or was the disease association not known previously?	Diagnosis category*	Brief description of management change
Progressive myoclonic epilepsy type 3	KCTD7	None	Genome-scale sequencing including genome sequencing and exome sequencing	Quad exome sequencing	Re-evaluation of sequencing data; RNA sequencing	N/A	1	Family specific genetic counseling for family planning
Mental retardation, autosomal dominant 13	DYNC1H1	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Sequencing	N/A	1	Referral to specialists based on molecular diagnosis
Schnitzler syndrome	None	None	Diagnosis made primarily on clinical grounds, including aggregate assessment of non-specific test result	None	Team expertise; multidisciplinary approach	N/A	1	Directed clinical treatment (new medication) ((actemra (tocilizumab))
Neurodevelopmental disorder with or without anomalies of the brain, eye, or heart	RERE	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Timing	N/A	1	Referral to specialists for diagnosis-specific evaluation
TRIP12 associated autism with facial dysmorphology	TRIP12	Trio exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	Trio genome sequencing	Timing	N/A	4	Recommendations for medical surveillence for additional symptoms that may manifest later in life
Hypotonia, infantile, with psychomotor retardation and characteristic facies 2	UNC80	Trio exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	None	Timing; research sequencing analysis	Disease association not previously known.	1	No change in medical management
Achalasia-addisonianism-alacrima syndrome (AAAS)	AAAS	Trio exome sequencing	Directed clinical testing based on phenotype (may be molecular, including gene panels; biochemical; radiologic; or, other test type)	Trio genome sequencing	Multidisciplinary approach	N/A	1	No change in medical management
Primary ciliary dyskinesia, 7	DNAH11	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Sequencing	N/A	1	Recommendations to alter exposures to allergens and referral to regional center studying disease
Schaaf-Yang syndrome	MAGEL2	Trio exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	Trio genome sequencing	Timing	N/A	1	Connection with research group studying disease
IRF2BPL-related condition	IRF2BPL	Trio exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	None	Matchmaking	Disease association not previously known.	4	No change in medical management
Pseudopseudohypoparathyroidism	GNAS	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Sequencing; research sequencing analysis	N/A	1	Recommendations for altering lifestyle to prevent exacerbation of symptoms

Diagnosis name	Gene name	Prior sequencing	Chief method used to achieve diagnosis	Type of UDN sequencing	Keys to making diagnosis	If diagnosis made on re-analysis of existing data, was the variant missed before or was the disease association not known previously?	Diagnosis category*	Brief description of management change
Congenital disorder of glycosylation type 2m	SLC35A2	Trio exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	Trio genome sequencing	Research sequencing analysis; basic research	N/A	1	Referred to NIH congenital disorders of glycosylation protocol for evaluation of potential treatments
IRF2BPL-related condition	IRF2BPL	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Sequencing; matchmaking	N/A	4	Referral to specialists based on molecular diagnosis
Spinal muscular atrophy, lower extremity-predominant 1	DYNC1H1	Proband exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	Quintet genome sequencing	Including additional family members; sequencing; research sequencing analysis	N/A	2	No change in medical management
Floating-Harbor syndrome	SRCAP	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Sequencing	N/A	1	No change in medical management
Myofibrillar myopathy 8	PYROXD1	Proband exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	Quad genome sequencing	Including additional family members; timing	N/A	1	No change in medical management
Severe progeria secondary to mosaicism for ZMPSTE24 frameshift mutation	ZMPSTE24	None	Genome-scale sequencing including genome sequencing and exome sequencing	Sextet exome sequencing	Targeted genetic testing	N/A	2	Pravastatin and bisphosphonate
Coffin-Siris syndrome 1	ARID1B	None	Genome-scale sequencing including genome sequencing and exome sequencing	Quad exome sequencing	Sequencing	N/A	2	No specific therapy; care plan suggested
Congenital disorder of glycosolation	COG4	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing, Proband genome sequencing	Matchmaking; basic research (model organism)	N/A	4	Referred to NIH CDG protocol for evaluation of potential treatments
IgG4-related condition	None	None	Directed clinical testing based on phenotype (may be molecular, including gene panels; biochemical; radiologic; or, other test type)	Septet genome sequencing	Clinical testing	N/A	1	Rituximab
Diploid-triploid mosaicism; Van Maldergem syndrome 2	None, FAT4	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio genome sequencing	Team expertise; sequencing and karyotype (fibroblast DNA)	N/A	1	No specific therapy; care plan suggested
Senior-Loken syndrome 5	IQCB1	None	Genome-scale sequencing including genome sequencing and exome sequencing	Quad genome sequencing	Sequencing	N/A	1	No specific therapy; care plan suggested

Diagnosis name	Gene name	Prior sequencing	Chief method used to achieve diagnosis	Type of UDN sequencing	Keys to making diagnosis	If diagnosis made on re-analysis of existing data, was the variant missed before or was the disease association not known previously?	Diagnosis category*	Brief description of management change
Charcot-Marie-Tooth disease, axonal, type 2s	IGHMBP2	Trio exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	Trio genome sequencing	Research sequencing analysis	Reanalysis of existing whole exome data identified the VUS to be an excellent fit with the patient's phenotype. This led to genome sequence identification of the non-coding variant in trans whose proven effect on function led to the diagnosis.	2	No specific therapy; referred back to specialist in management of neuromuscular disorders
Primary pulmonology hypertension	ENG	None	Genome-scale sequencing including genome sequencing and exome sequencing	Proband genome sequencing	Reanalysis of biopsies; research sequencing analysis; basic research	N/A	1	Hydroxychloroquine and methotrexate
Brown-Vialetto-Van Laere syndrome 1	None	None	Diagnosis made primarily on clinical grounds, including aggregate assessment of non-specific test result	Trio genome sequencing	Research sequencing analysis; multidisciplinary approach	N/A	2	Pharmacologic doses of riboflavin
Limb-girdle muscular dystrophy, type 2	TOR1AIP1	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio genome sequencing	Multidisciplinary approach; research sequencing analysis; basic research	N/A	2	No specific change. Patient referred back to neurologist.
Wieacker-Wolff syndrome	ZC4H2	Trio exome sequencing	Non-sequencing, genome-wide diagnostic assay (for example, SNP array, oligo array or karyotype)	Quad genome sequencing	Targeted genetic testing	N/A	1	No specific change
Familial cold-induced autoinflammatory syndrome	NLRP3	None	Genome-scale sequencing including genome sequencing and exome sequencing	Sextet exome sequencing	Research sequencing analysis; multidisciplinary approach	N/A	2	Treatment (Anakinra) responsive (alleviated symptoms)
NADK2 deficiency	NADK2	None	Genome-scale sequencing including genome sequencing and exome sequencing	Quintet genome sequencing	Multidisciplinary approach; research sequencing analysis; basic research	N/A	3	NADPH substrate trial
Paraganglioma	SDHD	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio genome sequencing	Multidisciplinary approach; research sequencing analysis	N/A	1	Referred to NIH paraganglioma protocol for evaluation, monitoring and potential treatment
Congenital disorder of glycosylation, type Ik	ALG1	Trio exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	Trio genome sequencing	Research analysis	Diagnosis should have been made with prior sequencing, but sequencing was of poor quality in the critical regions.	1	No specific change. Patient referred back to his metabolic physician
GTP cyclohydrolase I deficiency	GCH1	None	Genome-scale sequencing including genome sequencing and exome sequencing	Quad exome sequencing	Research analysis	N/A	2	Therapy responsive (Dopa/Carbidopa)

Diagnosis name	Gene name	Prior sequencing	Chief method used to achieve diagnosis	Type of UDN sequencing	Keys to making diagnosis	If diagnosis made on re-analysis of existing data, was the variant missed before or was the disease association not known previously?	Diagnosis category*	Brief description of management change
Stormorken syndrome	STIM1	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio exome sequencing	Multidisciplinary approach; research sequencing analysis	N/A	2	Antibiotic prophylaxis for asplenia
ABCA2-related condition	ABCA2	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio genome sequencing	Research sequencing analysis	N/A	3	None
GLYR1-related condition	GLYR1	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio genome sequencing	Research sequencing analysis	N/A	3	None
SNAPC4-related inflammatory disease	SNAPC4	None	Genome-scale sequencing including genome sequencing and exome sequencing	Trio genome sequencing	Research sequencing analysis	N/A	3	None
Novel cardiac syndrome	F5, PROZ, SERPINA10, SERPINA1, PRKG1	Proband exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	Proband genome sequencing	Research sequencing analysis		3	None
Exercise-induced hyperuricemia	None	None	Diagnosis made primarily on clinical grounds, including aggregate assessment of non-specific test result	Trio exome sequencing	Phenotyping	N/A	1	The patient has been treated with Febuxostat. This treatment has successfully managed his symptoms and prevented any further episodes of hyperuricemia, even when an episode was provoked through rigorous stress testing (which had previously been able to induce episodes of hyperuricemia).
TMEM94-related condition	TMEM94	Proband exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	Duo genome sequencing	Matchmaking	N/A	4	None
Myopathy, mitochondrial, and ataxia	MSTO1	Proband exome sequencing	Genome-scale sequencing including genome sequencing and exome sequencing	Trio genome sequencing	Reanalysis of prior sequencing data; timing	Disease was not previously known	1	Referred to appropriate specialist for regular follow-up; implications for family planning
SPI1-related condition	SPI1	None	Genome-scale sequencing including genome sequencing and exome sequencing	Duo genome sequencing	Research sequencing analysis	N/A	3	None
EVIS-related condition	EVIS	None	Genome-scale sequencing including genome sequencing and exome sequencing	Duo genome sequencing	Research sequencing analysis	N/A	3	None

*Key:
1 known syndrome 2 unusual presentation of known syndrome
3 known gene/region but new syndrome 4 new gene/region, new syndrome

Table S3. Details of UDN evaluation

	Specialties consulted during in-person evaluation	Tests performed as part of in-person evaluation
1	Acupuncture, endocrinology, neurophysiology, ophthalmology	Electromyography/nerve conduction velocity, echocardiogram, electrocardiogram, computed tomography scan (cerebrum/chest/abdomen/pelvis/femur/foot/humerus/neck/radius/ulna/tibia/fibula), magnetic resonance imaging (brain), ultrasound (carotid/abdomen), bone densitometry (femur/radius/spine), lumbar puncture, skeletal survey
2	Genetics	Skin biopsy
3	Genetics, immunology, infectious disease, rheumatology	Complete blood count, chromosomal microarray, computed tomography scan (chest), immunology labs, infectious disease studies
4	Audiology, dentistry, endocrinology, genetics, neuropsychology, nutrition, occupational therapy, ophthalmology, physiatry, physical therapy	Electromyography/nerve conduction velocity, echocardiogram, electrocardiogram, ultrasound (abdomen), computed tomography scan (craniofacial), swallow study, skeletal survey
5	Audiology, dentistry, endocrinology, neurodevelopment, neuropsychology, occupational therapy, physiatry, physical therapy	Bone age, electromyography/nerve conduction velocity, electroencephalography, magnetic resonance imaging/magnetic resonance spectroscopy (brain)
6	Neurodevelopment, ophthalmology, psychiatry	Sleep study, electroencephalography, electroencephalography-evoked potential, electrocardiogram, echocardiogram, ultrasound (abdomen)
7	Neuropsychology, ophthalmology, pain and palliative care	Autonomic nervous system testing, bone densitometry (femur/radius/spine), computed tomography scan (cerebrum/chest/abdomen/pelvis/femur/foot/humerus/cervical spine/radius/ulna/tibia/fibula), echocardiogram, electrocardiogram, electromyography/nerve conduction velocity, lumbar puncture, magnetic resonance imaging (brain)
8	Genetics, neurology	Ultrasound (abdomen)
9	Immunology, genetics	Exon-level microarray on fibroblasts, immunology labs, karyotype, targeted genetic testing on fibroblasts
10	Dentistry, endocrinology, gastroenterology, neurodevelopment, neurology, nutrition, occupational therapy, ophthalmology, physiatry, physical therapy	Electrocardiogram, echocardiogram, sleep study, electroencephalography, electromyography/nerve conduction velocity, autonomic nervous system testing
11	Genetics, neuromuscular, neuropsychology	None
12	Genetics, neurology, surgery	Chromosomal microarray, creatine kinase, liver function tests, metabolomics, muscle biopsy
13	Genetics, neurology, radiology	Antibody testing
14	Genetics, neuromuscular, ophthalmology	Creatine kinase, metabolic labs
15	Cardiology, endocrinology, ophthalmology	Electromyography/nerve conduction velocity, pulmonary function tests, echocardiogram, electrocardiogram, ultrasound (liver), magnetic resonance imaging (brain), computed tomography angiography (abdomen/aorta)
16	Audiology, dentistry, genetics, neurodevelopment, neurology, neurosurgery, ophthalmology, orthopedics, radiology	Research labs, skeletal survey
17	Allergy and immunology, dentistry, dermatology, occupational therapy, physiatry, physical therapy, pulmonology	Pulmonary function tests, echocardiogram, ultrasound (neck/soft tissues), computed tomography scan (chest/lung)
18	Audiology, cardiology, gastroenterology, genetics, immunology, neurodevelopment, neurology, nephrology, ophthalmology, otolaryngology, pulmonology	Echocardiogram, electrocardiogram, electromyography, fibroblast culture, magnetic resonance imaging (brain/spine), research labs, skeletal survey
19	Genetics, immunology, neurology	Immunology labs, hematology studies, lumbar puncture, metabolic labs
20	Cardiology, radiology	Magnetic resonance angiogram (neck/chest/abdomen), ultrasound (lower extremity), echocardiogram
21	Gastroenterology, genetics, radiology	Gastrointestinal testing
22	Internal medicine, nephrology	Metabolomics, skin biopsy
23	Audiology, cardiology, genetics, neurodevelopment, neurology, ophthalmology, otolaryngology, pulmonology	Echocardiogram, electrocardiogram, fibroblast culture, research labs

24	Cardiology, ophthalmology	Electrocardiogram, echocardiogram, computed tomography angiography (abdomen/thoracic aorta), computed tomography scan (cerebrum/neck/abdomen/pelvis/femur/foot/tibia/fibula), ultrasound (renal), electrocardiogram, skeletal survey
25	Genetics, neurology, neuropsychology, ophthalmology	Creatine kinase, electroencephalography, metabolic labs
26	Nephrology, ophthalmology	Electrocardiogram, echocardiogram, bone age, x-ray (knees)
27	Genetics, immunology, neurology, neuropsychology	Echocardiogram, electrocardiogram, fibroblast culture, immunology labs, research labs
28	Cardiology, genetics, hematology, immunology	Antibody testing, clotting labs, computed tomography scan (chest), echocardiogram, immunology labs, metabolic labs, hematology studies, rheumatology labs, targeted genetic testing
29	Genetics, immunology, infectious disease, neuroimmunology, ophthalmology	Electromyography, immunology labs
30	Genetics, neurology, neuropsychology	Electroencephalography, skeletal survey
31	Genetics, neurology, surgery	Metabolomics, mitochondrial studies, muscle biopsy, targeted genetic testing
32	Clinical pharmacology, dermatology, endocrinology, genetics	Complete blood count, lipid panel, liver function tests, metabolic labs, skeletal survey
33	Acupuncture, dermatology, endocrinology, occupational therapy, ophthalmology, physiatry, physical therapy, rheumatology	Skeletal survey, bone scan, nerve conduction velocity
34	Bioethics, nutrition, occupational therapy, ophthalmology, physiatry, physical therapy	DaTscan, electrocardiogram, electroencephalography, lumbar puncture, magnetic resonance imaging (brain), nerve conduction velocity, ultrasound (abdomen)
35	Endocrinology, gastroenterology, immunology, otolaryngology, rheumatology	Colonoscopy, computed tomography scan (sinus), immunology labs
36	Genetics	None
37	Genetics, neurology	Liver function tests
38	Audiology, clinical pharmacology, genetics, neurodevelopment, neurology, ophthalmology	Congenital disorders of glycosylation testing, magnetic resonance spectroscopy (cerebellum), metabolic labs, targeted genetic testing
39	Genetics	immunology labs
40	Internal medicine	immunology labs, metabolomics, RNA sequencing, skin biopsy
41	Genetics, neuropsychology, ophthalmology	Muscle biopsy
42	Audiology, genetics, neuroradiology, neuropathology, ophthalmology	Magnetic resonance imaging (brain)
43	Genetics	None
44	Audiology, cardiology, endocrinology, genetics, ophthalmology, orthopedics	Echocardiogram, electrocardiogram, magnetic resonance imaging (cervical spine), x-ray (cervical spine/forearm/elbows/pelvis)
45		Magnetic resonance imaging (spine)
46	Internal medicine, rheumatology	Immunology labs
47	Allergy and immunology, cardiology, pulmonology, rheumatology	Bronchoscopy, computed tomography scan (chest), electrocardiogram, positron emission tomography scan (torso), stress echocardiography, x-ray (chest)
48	Genetics	Magnetic resonance imaging (brain), skin biopsy
49	Cardiology, endocrinology, gastroenterology, genetics, immunology, infectious disease, neurology, nephrology, orthopedics, rheumatology	Echocardiogram, electrocardiogram, endocrine studies, renal function tests, metabolic labs, research labs, x-ray (foot)
50	Genetics, neurology, physical therapy, ophthalmology	Magnetic resonance imaging/magnetic resonance spectroscopy (brain), metabolic labs
51	Audiology, occupational therapy, ophthalmology, otolaryngology, physiatry, physical therapy, pulmonary	Magnetic resonance imaging (brain), swallow study, lumbar puncture, x-ray (chest), magnetic resonance imaging (cervical spine/thoracic spine/lumbar spine), electrocardiogram, echocardiogram
52	Occupational therapy, physiatry, physical therapy	Lumbar puncture, magnetic resonance imaging (brain)
53	Genetics, neurology	Targeted genetic testing

54	Gastroenterology, neuropsychology,nutrition, occupational therapy, ophthalmology, physiatry, physical therapy	Bone densitometry (femur), echocardiogram, electrocardiogram, electroencephalography, nerve conduction velocity, skeletal survey, ultrasound (abdomen)
55	Genetics, neurology, neuropsychology, rheumatology	Lumbar puncture, metabolomics, rheumatology labs
56	Genetics, occupational and environmental medicine	Skin biopsy
57	Audiology, dermatology, neuropsychology, occupational therapy, ophthalmology, physiatry, physical therapy	Electromyography/nerve conduction velocity, electroencephalography, electrocardiogram, echocardiogram, ultrasound (abdomen), magnetic resonance imaging (brain)
58	Neurology	Targeted genetic testing
59	Genetics	None
60	Allergy and immunology, hematology, rheumatology	Magnetic resonance imaging (brain), computed tomography scan (chest/abdomen), ultrasound (abdomen)
61	Dermatology, genetics, immunology, ophthalmology, pulmonology	Antibody testing, complete blood count, immunology labs, infectious disease studies, pulmonary function tests, rheumatology labs, x-ray (chest)
62	Ophthalmology	Echocardiogram, electrocardiogram, magnetic resonance imaging (humerus/abdomen/thighs)
63	Ophthalmology, neuropsychology	Lumbar puncture, magnetic resonance imaging (brain/cervical spine/thoracic spine), swallow study
64	Gastroenterology, infectious disease, occupational therapy, ophthalmology, physiatry, physical therapy, speech-langugae pathology	Electrocardiogram, electromyography/nerve conduction velocity, electroencephalography, endoscopy, magnetic resonance imaging (brain), lumbar puncture, x-ray (chest)
65	Endocrinology, genetics, hematology, immunology	Bone age, metabolic labs, endocrine studies, immunology labs, hematology studies
66	Audiology, endocrinology, neurology, neuropsychology, occupational therapy, ophthalmology, physiatry, physical therapy	Echocardiogram, electromyography/nerve conduction velocity, electrocardiogram, ultrasound (abdomen), magnetic resonance imaging (brain), skeletal survey
67	Genetics, nephrology, ophthalmology	Complete blood count, electrolytes, kidney function tests, metabolic labs, ultrasound (renal)
68	Neuropsychology, ophthalmology, pain and palliative care	Echocardiogram, electromyography/nerve conduction velocity, electroencephalography, electroencephalography-evoked potentional, pulmonary function tests, electrocardiogram, ultrasound (renal/abdomen), positron emission tomography scan (brain), bone densitometry (femur/radius/spine), magnetic resonance imaging (pituitary/brain/cervical/thoracic), computed tomography scan (cerebrum/abdomen/pelvis), skeletal survey
69	Genetics, neuropsychology	None
70	Genetics, neurology, neuropsychology, ophthalmology	None
71	Genetics, neurology	Metabolomics, skin biopsy
72	Genetics, neurology, nephrology, orthopedics	Magnetic resonance imaging (brain), research labs
73	Audiology, neuropsychology, occupational therapy, ophthalmology, physiatry, physical therapy	Autonomic nervous system testing, echocardiogram, electroencephalography, electromyography/nerve conduction velocity, electrocardiogram, ultrasound (abdomen), magnetic resonance imaging (brain/cervical spine/lumbar spine/thoracic spine), swallow study, lumbar puncture
74	Hematology, infectious disease, neuropsychology, ophthalmology, pulmonology	Positron emission tomography scan (torso), magnetic resonance imaging (brain), computed tomography scan (chest/abdomen/pelvis/lung), lumbar puncture
75	Neurology, ophthalmology	Chromosomal microarray
76	Audiology, neuropsychology, occupational therapy, ophthalmology, physiatry, physical therapy, pulmonology, speech-language pathology	Electromyography/nerve conduction velocity, magnetic resonance imaging (brain), lumbar puncture, swallow study, pulmonary function tests
77	Audiology, endocrinology, neurology, neuropsychology, occupational therapy, physiatry, physical therapy, speech-language pathology	Electromyography/nerve conduction velocity, electroencephalography, electroencephalography-evoked potentional, electrocardiogram, echocardiogram, ultrasound (abdomen/pelvic), skeletal survey, magnetic resonance imaging (brain), bone densitometry (femur)

78	Allergy and immunology, endocrinology, hematology, hepatology, ophthalmology	Computed tomography scan (cerebrum/pituitary), x-ray (hands/joints)
79	Dermatology, genetics, immunology, orthopedics	Skin biopsy
80	Immunology, neurology, ophthalmology, rheumatology	Environmental exposure tests, immunology labs, lumbar puncture, magnetic resonance spectroscopy, metabolomics, rheumatology labs
81	Audiology, cardiology, dentistry, genetics, neurology, neuropsychology, ophthalmology, otolaryngology, pulmonology, speech-language pathology	Echocardiogram, electrocardiogram, fibroblast culture, metabolic labs, research labs, skeletal survey
82	Genetics, ophthalmology	None
83	Allergy and immunology, audiology, dermatology, hematology, neuropsychology, occupational therapy, ophthalmology, physiatry, physical therapy, rheumatology	Electromyography/nerve conduction velocity, electrocardiogram, echocardiogram, ultrasound (abdomen), magnetic resonance imaging (brain), skeletal survey, bone age
84	Hematology, ophthalmology, rheumatology	Magnetic resonance imaging (abdomen), positron emission tomography scan (torso), ultrasound (abdomen/liver)
85	Genetics, neurology, neuropsychology, occupational and environmental medicine	Creatine kinase, electroencephalography, liver function tests, lumbar puncture, metabolic labs, muscle biopsy, magnetic resonance imaging/magnetic resonance angiogram (brain)
86	Audiology, dermatology, endocrinology, gastroenterology, neuropsychology, ophthalmology	Bone densitometry, echocardiogram, electrocardiogram, electroencephalography, electromyography/nerve conduction velocity, magnetic resonance imaging (brain), skeletal survey, ultrasound (abdomen/adrenal gland/pelvis)
87	Genetics	Skin biopsy
88	Audiology, cardiology, hepatology, neurology, neuropsychology, occupational therapy, ophthalmology, physiatry, physical therapy, speech-language pathology	Electromyography/nerve conduction velocity, electroencephalography, pulmonary function tests, electrocardiogram, echocardiogram, ultrasound (abdomen), magnetic resonance imaging (brain/cervical spine/lumbar spine/thoracic spine), swallow study, skeletal survey, bone age
89	Audiology, cardiology, dermatology, neurology, neuropsychology, occupational therapy, ophthalmology, otolaryngology, physiatry, physical therapy, speech-language pathology	Electromyography/nerve conduction velocity, electroencephalography, electrocardiogram, echocardiogram, ultrasound (abdomen), bone densitometry (femur/whole body), magnetic resonance angiogram (brain/carotids/chest/abdomen), skeletal survey, x-ray (scoliosis)
90	Genetics, neurology	Electroencephalography, metabolic labs, targeted genetic testing
91	Audiology, cardiology, dermatology, genetics, ophthalmology	Antibody testing, endocrine studies, environmental exposure tests, immunology labs, renal function tests, liver function tests, metabolic labs, plasma renin activity, targeted genetic testing, thyroid labs, urinalysis
92	Audiology, ophthalmology, otolaryngology	Lumbar puncture, magnetic resonance imaging (brain/cervical spine/thoracic spine/lumbar spine/posterior fossa/internal auditory canal)
93	Audiology, ophthalmology	Electromyography/nerve conduction velocity, magnetic resonance imaging (brain)
94	Dentistry, dermatology, genetics	Echocardiogram, endocrine studies, scalp biopsy, sweat chloride test, targeted genetic testing, ultrasound (abdomen), x-ray (teeth/spine)
95	Occupational therapy, physiatry, physical therapy	Echocardiogram, electrocardiogram, electromyography/nerve conduction velocity, pulmonary function tests
96	Endocrinology, immunology, neurology, rheumatology	Endocrine studies, immunology labs, metabolomics, mitochondrial studies, ultrasound (renal/thyroid), rheumatology labs
97	Genetics	Metabolic labs
98	Audiology, genetics, immunology, neurology, neuropsychology, occupational therapy, opthalmology, pulmonology, rheumatology	Magnetic resonance imaging (brain), research labs
99	Genetics, immunology	Immunology labs
100	Audiology, dermatology, ophthalmology	Magnetic resonance imaging (cervical spine/tibia/fibula/thighs/muscle)
101	Craniofacial, dermatology, genetics, hematology, hepatology, immunology, neurology, ophthalmology, rheumatology, speech-language pathology	Complete blood count, creatine kinase, hepatology labs, immunology labs, rheumatology labs, skeletal survey, stool studies, ultrasound (abdomen), x-ray (skull)
102	Endocrinology, genetics, neurology, neuropsychology, ophthalmology	Metabolic labs

103	Allergy and immunology, gastroenterology, ophthalmology, rheumatology	Computed tomography angiography (abdomen/aorta)
104	Genetics, neurology	None
105	None	None
106	Gastroenterology, genetics, immunology, neurodevelopment, neurology	Research labs
107	Occupational therapy, ophthalmology, physiatry, physical therapy	Electromyography/nerve conduction velocity, pulmonary function tests, lumbar puncture, swallow study, magnetic resonance imaging (brain/cervical spine)
108	Neurogenetics, ophthalmology	Congenital disorders of glycosylation testing, electromyography/nerve conduction velocity, magnetic resonance imaging/magnetic resonance spectroscopy
109	Ophthalmology	Lumbar puncture, magnetic resonance imaging (cervical/thoracic/lumbar/brain/pituitary), ultrasound (abdomen)
110	Genetics, neurology, ophthalmology, orthopedics, pulmonology	Magnetic resonance imaging (brain), research labs, skeletal survey
111	Endocrinology, neuropsychology, ophthalmology	Electromyography/nerve conduction velocity, bone scan, magnetic resonance imaging (brain/pituitary/cervical spine), computed tomography scan (abdomen/pelvis/cerebrum), swallow study, lumbar puncture
112	Cardiology, endocrinology, genetics, neurodevelopment, neurology, orthopedics, otolaryngology	Echocardiogram, electrocardiogram, research labs, skeletal survey
113	Genetics, neurology, ophthalmology	Magnetic resonance imaging
114	Audiology, infectious disease, neuropsychology, nutrition, ophthalmology, rheumatology, speech-language pathology	Electromyography/nerve conduction velocity, electroencephalography, skeletal survey, x-ray (scoliosis/pelvis), magnetic resonance imaging (brain), swallow study, ultrasound (abdomen)
115	Genetics, neurology	Metabolomics, skin biopsy
116	Audiology, cardiology, endocrinology, neurology, neuropsychology, occupational therapy, ophthalmology, physiatry, physical therapy	Electromyography/nerve conduction velocity, electrocardiogram, echocardiogram
117	Dermatology, genetics, immunology, infectious disease, nephrology, neurodevelopment, rheumatology	Immunology labs, infectious disease studies, renal function tests, research labs
118	Acupuncture, audiology, neuropsychology	Electrocardiogram, magnetic resonance imaging (brain), computed tomography scan (cerebrum/chest/pelvis/femur/foot/humerus/neck/radius/ulna/tibia/fibula), x-ray (spine), lumbar puncture
119	Cardiology, genetics, nephrology, ophthalmology, orthopedics	Echocardiogram, electrocardiogram, renal function tests, research labs, skeletal survey, ultrasound (renal)
120	Genetics, neurology	None
121	Audiology, cardiology, dermatology, endocrinology, neuropsychology, nutrition, physiatry, physical therapy, occupational therapy, rheumatology, speech-language pathology	Electromyography/nerve conduction velocity, electroencephalography, echocardiogram, electrocardiogram, ultrasound (abdomen), magnetic resonance imaging/magnetic resonance spectroscopy (brain), skeletal survey, x-ray (scoliosis), swallow study
122	Acupuncture, neuropsychology, pain and palliative care	Bone densitometry (femur/radius/spine), computed tomography scan (abdomen/cerebrum/chest/femur/fibula/humerus/cervical spine/pelvis/tibia), echocardiogram, electrocardiogram, ultrasound (carotids)
123	Audiology, endocrinology, neuropsychology, nutrition, occupational therapy, ophthalmology, physiatry, physical therapy	Electromyography/nerve conduction velocity, electroencephalography, echocardiogram, ultrasound (abdomen), magnetic resonance imaging/magnetic resonance spectroscopy (brain), skeletal survey, x-ray (scoliosis)
124	Immunology, neurogenetics, ophthalmology	Immunology labs, magnetic resonance imaging, metabolic labs
125	Audiology, endocrinology, neurology, ophthalmology, pulmonology	Fibroblast respiration studies (Seahorse), metabolomics, RNA sequencing, skin biopsy
126	Genetics, neurology	Congenital disorders of glycosylation testing, echocardiogram, exon-level microarray, magnetic resonance angiogram, magnetic resonance imaging (brain), magnetic resonance spectroscopy, skeletal survey
127	Endocrinology, genetics, neurology	Endocrine studies, metabolic labs

128	Dentistry, dermatology, gastroenterology, genetics, hematology, nephrology, neurodevelopment, ophthalmology	Research labs, skeletal survey, skin biopsy, targeted genetic testing, ultrasound (renal)
129	Endocrinology, genetics	Computed tomography scan (pelvis), endocrine studies, magnetic resonance imaging, targeted genetic testing
130	Genetics	None
131	Genetics, neurology	Pulmonary function tests
132	Genetics, neurology	Skin biopsy
133	Genetics, immunology, neurology	Environmental exposure tests, muscle biopsy, thyroid function tests, x-ray (hand/spine)
134	Endocrinology, genetics, neurology	Audiology testing, radiology testing
135	Audiology, endocrinology, genetics, neurodevelopment, neurology, opthalmology	Magnetic resonance imaging (brain), research labs
136	Occupational therapy, ophthalmology, physiatry, physical therapy	Lumbar puncture, swallow study, magnetic resonance imaging (brain/cervical spine/lumbar spine/thoracic spine), ultrasound (abdomen), electromyography/nerve conduction velocity
137	Genetics, neurology, neurodevelopment	Research labs, targeted genetic testing
138	Genetics, neurology, neurodevelopment, neuropsychology	Echocardiogram, electrocardiogram, research labs
139	Audiology, neurodevelopment, neurology, nutrition, occupational therapy, ophthalmology, physiatry, physical therapy	Skeletal survey, swallow study, bone age, bone densitometry, x-ray (chest), magnetic resonance imaging/magnetic resonance spectroscopy (brain), ultrasound (abdomen), electroencephalography, electromyography/nerve conduction velocity
140	Allergy and immunology, audiology, endocrinology, neurodevelopment, nutrition, occupational therapy, physiatry, physical therapy	Skeletal survey, swallow study, bone densitometry, magnetic resonance imaging/magnetic resonance spectroscopy (brain), ultrasound (abdomen), echocardiogram, electrocardiogram, electroencephalography, electromyography/nerve conduction velocity, autonomic nervous system testing
141	Allergy and immunology, hematology	Computed tomography scan (abdomen/chest/sinuses)
142	Nutrition, occupational therapy, ophthalmology, physiatry, physical therapy, speech-language pathology	Swallow study, computed tomography scan (cerebrum), echocardiogram, electrocardiogram, electroencephalography, electromyography/nerve conduction velocity, lumbar puncture, magnetic resonance imaging (brain/lumbar spine/cervical spine/thoracic spine), ultrasound (abdomen), x-ray (chest)
143	Audiology, neurodevelopment, neurology, nutrition, occupational therapy, ophthalmology, physiatry, physical therapy, speech-language pathology	Skeletal survey, swallow study, magnetic resonance imaging/magnetic resonance spectroscopy (brain), bone densitometry, ultrasound (abdomen), electrocardiogram, echocardiogram, electroencephalography, electromyography/nerve conduction velocity
144	N/A	None
145	Audiology, neurodevelopment, nutrition, occupational therapy, physiatry, physical therapy, speech-language pathology	Skeletal survey, swallow study, bone age, magnetic resonance imaging/magnetic resonance spectroscopy (brain), ultrasound (abdomen), electrocardiogram, echocardiogram, electroencephalography, sleep study, autonomic nervous system testing, electromyography/nerve conduction velocity
146	Audiology, endocrinology, gastroenterology, neurodevelopment, nutrition, ophthalmology, recreational therapy	Skeletal survey, bone age, magnetic resonance imaging (brain/pituitary), magnetic resonance spectroscopy (brain), ultrasound (abdomen), electrocardiogram, echocardiogram, electroencephalography, autonomic nervous system testing, electromyography/nerve conduction velocity
147	Genetics	Metabolomics, RNA sequencing, skin biopsy, targeted genetic testing
148	Audiology, dentistry, gastroenterology, neurodevelopment, nutrition, occupational therapy, ophthalmology, pain and palliative care, physiatry, physical therapy, recreational therapy, speech-language pathology	Skeletal survey, bone age, swallow study, ultrasound (abdomen), magnetic resonance imaging/magnetic resonance spectroscopy (brain), electroencephalography, electromyography/nerve conduction velocity, sleep study
149	Occupational therapy, ophthalmology, physiatry, physical therapy	Lumbar puncture, magnetic resonance imaging (brain/spine), ultrasound (abdomen), electromyography/nerve conduction velocity

150	Dermatology, occupational therapy, ophthalmology, physiatry, physical therapy, recreational therapy	Computed tomography scan (chest), echocardiogram, electromyography/nerve conduction velocity, lumbar puncture, magnetic resonance imaging (brain/muscle/cervical spine/lumbar spine/thoracic spine), pulmonary function tests
151	Neuropsychology, occupational therapy, ophthalmology, physiatry, physical therapy, speech-language pathology	Swallow study, lumbar puncture, magnetic resonance imaging (brain), electroencephalography, electroencephalography-evoked potentional, electromyography/nerve conduction velocity
152	Ophthalmology, physiatry, physical therapy	Echocardiogram, electromyography/nerve conduction velocity, magnetic resonance imaging (brain/cervical spine/lumbar spine/thoracic spine)
153	Genetics, neurology	Chromosomal microarray, magnetic resonance imaging, metabolomics, nerve conduction velocity
154	Endocrinology, genetics, nutrition, occupational therapy, ophthalmology, physiatry, physical therapy, pulmonology, speech-language pathology	Swallow study, computed tomography scan (chest), magnetic resonance imaging (brain), perfusion lung scan, bone densitometry, ultrasound (veins/abdomen), electrocardiogram, echocardiogram, pulmonary function tests, electromyography/nerve conduction velocity, electroencephalography
155	Endocrinology, genetics, hematology, immunology, neurology	Bone marrow biopsy, metabolic labs, endocrine studies, immunology labs, metabolomics, pancreatic function tests, skeletal survey, ultrasound (abdomen)
156	Dentistry, neuropsychology, ophthalmology	Lumbar puncture, magnetic resonance imaging (brain/cervical spine/lumbar spine/thoracic spine), ultrasound (liver), electromyography/nerve conduction velocity
157	Dermatology, hematology, nephrology, occupational therapy, ophthalmology, pain and palliative care, physiatry, physical therapy, rheumatology	Echocardiogram, positron emission tomography scan (torso), ultrasound (abdomen/renal), x-ray (hands/knees/shoulders/spine)
158	Ophthalmology	Metabolomics
159	Audiology, dentistry, genetics, ophthalmology, physiatry, physical therapy	Skeletal survey, magnetic resonance imaging (brain), ultrasound (abdomen), electrocardiogram, echocardiogram
160	Dermatology, endocrinology, hematology, nephrology, occupational therapy, ophthalmology, physiatry, physical therapy	Echocardiogram, electrocardiogram, positron emission tomography scan (torso), ultrasound (liver/renal), x-ray (chest)
161	Cardiology, genetics, neurology	Echocardiogram, electrocardiogram
162	Genetics	None
163	Gastroenterology, genetics, neurology, nephrology, ophthalmology, orthopedics	Research labs, skeletal survey, ultrasound (renal)
164	Cardiology, genetics, immunology, nephrology, neurology, neuropsychology, otolaryngology	Computed tomography scan (abdomen/renal), echocardiogram, electrocardiogram, electromyography, immunology labs, renal function tests, research labs
165	Dentistry, endocrinology, neurology, occupational therapy, ophthalmology, physiatry, physical therapy, speech-language pathology	Bone age, electromyography/nerve conduction velocity, magnetic resonance imaging/magnetic resonance spectroscopy (brain), skeletal survey, swallow study
166	Genetics	Exon-level microarray, renal function tests, metabolic labs, metabolomics
167	Allergy and immunology, audiology, gastroenterology, infectious disease, neurology, nutrition, occupational therapy, otolaryngology, physiatry, physical therapy, recreational therapy, speech-language pathology	Swallow study, electroencephalography, x-ray (abdomen/spine/cervical/thoracic), bone age, skeletal survey, magnetic resonance imaging (brain/abdomen/orbits/pituitary), magnetic resonance angiogram (carotids), ultrasound (abdomen)
168	Genetics, neurology	Skin biopsy, metabolomics
169	Gastroenterology, genetics, neurology, neuropsychology, ophthalmology, otolaryngology, speech-language pathology	Research labs
170	Dentistry, infectious disease, ophthalmology	Computed tomography scan (mandible/neck/chest/abdomen/pelvis), echocardiogram, magnetic resonance imaging (brain/orbits/pituitary), positron emission tomography scan (torso), x-ray (long bones/chest)
171	Audiology, dentistry, neurodevelopment, nutrition, occupational therapy, ophthalmology, physiatry, physical therapy, speech-language pathology	Swallow study, bone age, skeletal survey, computed tomography scan (cerebrum), ultrasound (abdomen), echocardiogram, electrocardiogram, electroencephalography, autonomic nervous system testing, electromyography/nerve conduction velocity, sleep study

172	Audiology, endocrinology, genetics, nephrology, neurodevelopment, neurology, ophthalmology, orthopedics	Endocrine studies, renal function tests, research labs, skeletal survey
173	Nephrology, ophthalmology, occupational therapy, physiatry, physical therapy, speech-language pathology	Swallow study, electroencephalography, electroencephalography-evoked potentional, electromyography/nerve conduction velocity, lumbar puncture, magnetic resonance imaging/magnetic resonance spectroscopy (brain/lumbar spine/cervical spine/thoracic spine), x-ray (chest)
174	Genetics	Nasal brush biopsy
175	Occupational therapy, ophthalmology, physiatry, physical therapy	Lumbar puncture, magnetic resonance imaging/magnetic resonance spectroscopy (brain), magnetic resonance imaging (cervical spine/thoracic spine/lumbar spine), echocardiogram, autonomic nervous system testing, electromyography/nerve conduction velocity
176	Endocrinology, genetics, neurology, nutrition	Bone age, bone densitometry, calorimetry, endocrinology labs, metabolomics
177	Neurology, ophthalmology	Metabolomics
178	Audiology, cardiology, neurology, neurodevelopment, ophthalmology	Echocardiogram, electrocardiogram, electroencephalography
179	Cardiology, genetics, neurogenetics, neurology, ophthalmology	Mitochondrial studies
180	Genetics, neurology	Skin biopsy
181	Audiology, dentistry, endocrinology, gastroenterology, genetics, nephrology, neurology, neuropsychology, orthopedics	Endocrine studies, renal function tests, magnetic resonance imaging (brain), research labs, skeletal survey
182	Endocrinology, gastroenterology, genetics, immunology, infectious Disease, neurology, neuropsychology, ophthalmology, psychiatry, rheumatology, speech-language pathology	Electroencephalography, endocrine studies, hepatology labs, immunology labs, infectious disease studies, magnetic resonance imaging (brain/spine), research labs, ultrasound (bladder/liver)
183	Genetics	Metabolic labs
184	Cardiology, hematology, ophthalmology, rheumatology	Positron emission tomography scan (torso), x-ray (pelvis)
185	Endocrinology, immunology, neurogenetics, occupational and environmental medicine, rheumatology	Environmental exposure tests, lumbar puncture, immunology labs, metabolomics, mitochondrial studies, muscle biopsy
186		Lumbar puncture, metabolomics, skin biopsy
187	Genetics, neurology	Metabolomics, skin biopsy
188	Cardiology	Metabolomics, skin biopsy
189	Genetics, neurology	None
190	Genetics	Induced pluripotent stem cell/cardiomyocyte studies, metabolomics, skin biopsy
191	Occupational therapy, ophthalmology, physiatry, physical therapy	Computed tomography scan (abdomen/cerebrum/chest/femur/fibula/foot/humerus/cervical spine/pelvis/radius/ulna/tibia), electrocardiogram, electroencephalography-evoked potential, electromyography/nerve conduction velocity, lumbar puncture, magnetic resonance imaging (brain)
192	Genetics, neuromuscular, neuropsychology	Electroencephalography, endocrine studies, lipid panel, skeletal survey, thyroid labs, uric acid
193	Genetics, neurology, ophthalmology	Antibody testing, metabolic labs
194	Occupational therapy, ophthalmology, physiatry, physical therapy	Lumbar puncture, computed tomography scan (cerebrum), magnetic resonance imaging (brain), electromyography/nerve conduction velocity
195	Genetics, neuromuscular, neuropsychology	None
196	Allergy and immunology, audiology, genetics, neurology, neuropsychology, nutrition, occupational therapy, ophthalmology, otolaryngology, physiatry, physical therapy, recreational therapy	Magnetic resonance imaging/magnetic resonance spectroscopy (brain), bone densitometry, ultrasound (abdomen), electrocardiogram, echocardiogram, electromyography/nerve conduction velocity, sleep study, autonomic nervous system testing
197	Genetics, neurology, neuromuscular, ophthalmology	Electroencephalography-evoked potential, magnetic resonance imaging (brain)
198	Dentistry, genetics, pulmonology, ophthalmology	None

199	Dermatology, neuropsychology, occupational therapy, ophthalmology, physiatry, physical therapy, recreational therapy, rheumatology, speech-language pathology	Lumbar puncture, computed tomography scan (chest/lung), magnetic resonance imaging (brain/cervical spine/lumbar spine/thoracic spine), ultrasound (abdomen), electromyography/nerve conduction velocity
200	Audiology, dentistry, dermatology, neurodevelopment, neurology, nutrition, occupational therapy, ophthalmology, otolaryngology, physiatry, physical therapy, speech-language pathology	Bone age, skeletal survey, x-ray (chest), magnetic resonance imaging/magnetic resonance spectroscopy (brain), ultrasound (abdomen), echocardiogram, electrocardiogram, electromyography/nerve conduction velocity, electroencephalography-evoked potential
201	Cardiology, dentistry, genetics, occupational therapy, neurology, ophthalmology, orthopedics, physiatry, physical therapy, recreational therapy, rheumatology	Bone age, skeletal survey, computed tomography scan (heart), ultrasound (abdomen), electrocardiogram, echocardiogram, electromyography/nerve conduction velocity
202	Genetics, neurology	Electromyography/nerve conduction velocity
203	Cardiology, genetics, immunology, neurology, ophthalmology	Antibody testing, complete blood count, echocardiogram, electrocardiogram, electroretinography, hair biopsy, immunology labs
204	Audiology, dentistry, gastroenterology, genetics, neurodevelopment, neurology, neuropsychology, ophthalmology	Magnetic resonance imaging (brain), research labs
205	Cancer genetics, genetics, neuroimmunology, occupational and environmental medicine	Antibody testing, electromyography/nerve conduction velocity, environmental exposure tests, infectious disease studies, skin biopsy, targeted genetic testing
206	Endocrinology, genetics, neurodevelopment, neurology, neuropsychology, ophthalmology, orthopedics, speech-language pathology	Endocrine studies, neurology labs, research labs, skeletal survey
207	Genetics, immunology, nephrology, pulmonology, rheumatology	Echocardiogram, computed tomography scan (chest), immunology labs, renal function tests, pulmonary function tests, rheumatology labs, skin biopsy, stress test, ultrasound (renal), x-ray (chest)
208	Bioethics, cardiology, dentistry, genetics, endocrinology, ophthalmology, rheumatology	Bone age, skeletal survey, computed tomography scan (crebrum), magnetic resonance imaging (brain/cervical spine/lumbar spine/thoracic spine), ultrasound (abdomen), echocardiogram, electrocardiogram, electromyography/nerve conduction velocity
209	Hepatology, physiatry, physical therapy, rheumatology	Computed tomography scan (chest), pulmonary function tests, x-ray (chest)
210	Neuropsychology, ophthalmology	Lumbar puncture, computed tomography scan (cerebrum/chest/abdomen/pelvis/femur/foot/humerus/neck/radius/ulna/tibia/fibula) magnetic resonance imaging (brain/spine), bone densitometry, ultrasound (abdomen), electrocardiogram, echocardiogram, electromyography/nerve conduction velocity
211	Cardiology, internal medicine, neurogenetics, neuropsychology, ophthalmology	Complete blood count, chromosomal microarray, electrocardiogram, electromyography/nerve conduction velocity, lumbar puncture, magnetic resonance imaging/magnetic resonance spectroscopy (brain), metabolomics
212	Audiology, occupational therapy, ophthalmology, physiatry, physical therapy, recreational therapy, speech-language pathology	Lumbar puncture, magnetic resonance imaging (brain/cervical spine/lumbar spine/thoracic spine), ultrasound (abdomen), electroencephalography-evoked potential, electromyography/nerve conduction velocity, autonomic nervous system testing
213	Audiology, genetics, neurology, neuropsychology, ophthalmology, speech-language pathology	Magnetic resonance imaging (brain), research labs
214	Genetics, neurology, neuropsychology, ophthalmology	Complete blood count, creatine kinase, echocardiogram, magnetic resonance imaging (brain), metabolic labs
215	Genetics	None
216	Cardiology, endocrinology, genetics, hematology, nephrology, neurology, ophthalmology	Echocardiogram, electrocardiogram, pulmonary function tests, electroencephalography, electromyography/nerve conduction velocity, magnetic resonance imaging (brain/spine/orbits), magnetic resonance spectroscopy (brain), ultrasound (renal)
217	Cardiology, hematology, pain and palliative care, occupational therapy, physiatry, physical therapy, pulmonology	Autonomic nervous system testing, computed tomography scan (chest), magnetic resonance imaging (brain), echocardiogram, electrocardiogram, pulmonary function tests, x-ray (chest)

218	Dentistry, genetics, neuropsychology, ophthalmology, psychiatry, recreational therapy, speech-language pathology	Bone age, magnetic resonance imaging/magnetic resonance spectroscopy (brain), skeletal survey, swallow study
219	Audiology, dentistry, endocrinology, neurodevelopment, neurology, nutrition, occupational therapy, ophthalmology, otolaryngology, physiatry, physical therapy, recreational therapy	Bone age, bone densitometry, echocardiogram, electromyography/nerve conduction velocity, skeletal survey, swallow study, x-ray (chest)
220	Genetics, neuropsychology	Metabolic labs, skeletal survey
221	Audiology, cardiology, genetics, neurology, orthopedics, otolaryngology, physical therapy, pulmonology, speech-language pathology	Echocardiogram, electrocardiogram, electromyography, fibroblast culture, muscle biopsy, research labs, skeletal survey
222	Allergy and immunology, gastroenterology, infectious disease, neurology, neurosurgery, pulmonology, rheumatology	Cytokine profiling, gastric emptying study, immunology labs, metabolomics, muscle biopsy, positron emission tomography/computed tomography scan, RNA sequencing, skin biopsy
223	Audiology, dentistry, endocrinology, neurodevelopment, physiatry	Magnetic resonance imaging/magnetic resonance spectroscopy (brain), skeletal survey, bone densitometry, ultrasound (abdomen)
224	Cardiology, neurology, ophthalmology	Echocardiogram
225	Internal medicine	Metabolomics
226	Endocrinology, genetics, neuromuscular	Antibody testing, bone age, complete blood count, creatine kinase, electrolytes, endocrine studies, targeted genetic testing, thyroid function tests, vitamin D
227	Genetics, neurodevelopment, neurology	Magnetic resonance imaging (brain), optical coherence tomography, research labs
228	Genetics, hematology, ophthalmology	Magnetic resonance imaging (brain/femurs/spine/thighs/femurs), skeletal survey, ultrasound (renal)
229	Endocrinology, ophthalmology	Lumbar puncture, magnetic resonance imaging (brain)
230	Genetics, neurology	Cytokine profiling, skin biopsy
231	Genetics, neurology, ophthalmology	Muscle biopsy
232	Allergy and immunology, dentistry, endocrinology, gastroenterology, hematology, neurology, physiatry	Bone age, magnetic resonance imaging (brain/pituitary), ultrasound (abdomen)
233	Genetics, neurology, ophthalmology, surgery	Complete blood count, chromosomal microarray, environmental exposure tests, magnetic resonance imaging/magnetic resonance spectroscopy, metabolic labs, mitochondrial studies, muscle biopsy
234	Neurology, ophthalmology, pain and palliative care, rheumatology	Swallow study, magnetic resonance imaging (brain/spine), skeletal survey, ultrasound (abdomen)
235	Cardiology, endocrinology, genetics, neurodevelopment, neurology	Echocardiogram, electrocardiogram, research labs, skeletal survey
236	Cardiology, genetics	Skin biopsy
237	Cardiology, genetics, neurology, neuropsychology, ophthalmology, orthopedics, physical therapy, pulmonology	Echocardiogram, electrocardiogram, electromyography, magnetic resonance imaging (heart), research labs
238	Genetics, ophthalmology	Electrocardiogram, metabolomics
239	Genetics, immunology, neurology	immunology labs
240	Dermatology, endocrinology, genetics, immunology, neurogenetics, neurology, ophthalmology, rheumatology	Chromosomal microarray, immunology labs, magnetic resonance imaging, nerve conduction velocity, skin biopsy, somatosensory evoked potential testing
241	Dermatology, gastroenterology, hematology, immunology, nephrology, neurology, ophthalmology, pulmonology	Computed tomography scan (head), immunology labs, magnetic resonance imaging (brain), metabolic labs, positron emission tomography scan, skeletal survey, ultrasound (abdomen)
242	Allergy and immunology, audiology, cardiology, dentistry, endocrinology, hematology, neurodevelopment, neurology, occupational therapy, ophthalmology, physiatry, physical therapy, speech-language pathology	Swallow study, bone densitometry (femur), echocardiogram, electrocardiogram, electromyography/nerve conduction velocity, holter monitor, magnetic resonance imaging/magnetic resonance spectroscopy (brain), metabolic cart, skeletal survey, ultrasound (abdomen), x-ray (pelvis/skull/spine)

243	Allergy and immunology, audiology, endocrinology, hematology, nephrology, nutrition, occupational therapy, otolaryngology, physiatry, physical therapy, rheumatology	Computed tomography scan (femur/chest/abdomen/pelvis/sinuses/tibia/fibula), echocardiogram, electrocardiogram, endoscopy, positron emission tomography scan (extremities/torso), bone densitometry (radius/femur/spine), octreascan, skeletal survey, skin biopsy, ultrasound (renal), x-ray (chest)
244	Genetics, neurology, ophthalmology	Computed tomography scan (head), electromyography/nerve conduction velocity, oral riboflavin challenge, targeted genetic testing
245	Genetics, neurogenetics, neurology, ophthalmology	Bone age, skeletal survey,
246	Genetics, immunology, neurology, neuropsychology	Bone densitometry, electromyography, endocrine studies, targeted genetic testing
247	Endocrinology, genetics, neurology, ophthalmology	Endocrine studies, metabolic labs
248	Gastroenterology, neurogenetics, neuroimmunology, ophthalmology	Liver function tests, metabolic labs, metabolomics, ultrasound (abdomen)
249	Dentistry, genetics, hematology, neuropsychology	Bone marrow biopsy, magnetic resonance imaging (brain), metabolic labs
250	Genetics, ophthalmology	None
251	Cardiology, dermatology, genetics, immunology	Cytokine profiling, skin biopsy
252	Genetics, neuropsychology	None
253	Cardiology, genetics, neurology, pulmonology	Complete blood count, creatine phosphokinase, echocardiogram, electrocardiogram, magnetic resonance imaging (lower extremities), muscle biopsy, pulmonary function tests
254	Nephrology	Skeletal survey, ultrasound (abdomen)
255	Audiology, dentistry, neurodevelopment, neurology, occupational therapy, ophthalmology, otolaryngology, physiatry, physical therapy, speech-language pathology	Autonomic nervous system testing, swallow study, bone age, electromyography/nerve conduction velocity, electroencephalography, electrocardiogram, ultrasound (abdomen), magnetic resonance spectroscopy/magnetic resonance angiogram (brain), magnetic resonance imaging (brain/cervical spine/lumbar spine/thoracic spine), computed tomography scan (cerebrum), skeletal survey, sleep study, x-ray (forearm/scoliosis)
256	Genetics, pathology	Cytokine profiling, lumbar puncture, RNA sequencing
257	Genetics, immunology	Chromosomal microarray
258	Dermatology, endocrinology, nutrition, occupational therapy, ophthalmology, physiatry, physical therapy, rheumatology	Bone scan, echocardiogram, lumbar puncture, magnetic resonance imaging (brain/cervical/thoracic), positron emission tomography scan (extremities/torso), ultrasound (renal)
259	Genetics, immunology, neurology, ophthalmology	Congenital disorders of glycosylation testing, clotting labs, complete blood count, electroencephalography, exon-level microarray, renal function tests, hematology studies, ultrasound (renal)
260	Genetics, neurology, neuropsychology, ophthalmology, radiology	Electroencephalography, research labs
261	Genetics, neurology	None
262	Cardiology, endocrinology, genetics, neurology, pulmonology, rheumatology	Electromyography, magnetic resonance imaging (brachial plexus/heart/pelvis), research labs
263	Genetics, neurology, neuromuscular, neuropsychology	None
264	Neurology, neuropsychology, ophthalmology	Metabolomics
265	Dermatology, hematology, infectious disease, neurology, occupational therapy, otolaryngology, pain and palliative care, psychiatry, pulmonology, rheumatology, surgery, tracheostomy, transfusion medicine, urological surgery, vascular access	Bone marrow aspiration/biopsy, bronchoscopy, cathetergram, chest physiotherapy, chest tube placement, computed tomography scan (abdomen/ankle/cerebrum/cervical spine/chest/fibula/foot/pelvis/sinuses/tibia), echocardiogram, electrocardiogram, endoscopy, magnetic resonance angiogram (brain), magnetic resonance imaging (brain, thighs), mechanical ventilation, metabolic cart, positron emission tomography scan (torso), skin biopsy, spontaneous breathing trial, vapotherm, ultrasound (arm veins/leg veins/liver/right upper quadrant), x-ray (abdomen/chest)
266	Genetics, neurology, ophthalmology	High resolution SNP array, metabolic labs, muscle biopsy
267	Genetics, neurology, neurology, ophthalmology	Metabolic labs, skeletal survey

268	Genetics, neuromuscular, neuropsychology	Magnetic resonance imaging (brain)
269	Genetics, neurology	Magnetic resonance imaging/magnetic resonance spectroscopy (brain), magnetic resonance imaging (spine), video electroencephalography monitoring
270	Dentistry, dermatology, endocrinology, gastroenterology, genetics, hepatology, neuropsychology, ophthalmology	Magnetic resonance imaging (brain), research labs
271	Endocrinology, hematology, immunology, genetics, neurology	Bone marrow biopsy, metabolic labs, endocrine studies, immunology labs, metabolomics, pancreatic function tests, skeletal survey, ultrasound (abdomen)
272	Dermatology, genetics, pathology	Flow cytometry, infectious disease studies
273	Audiology, neuropsychology, occupational therapy, ophthalmology, physiatry, physical therapy	Electrocardiogram, electromyography/nerve conduction velocity, lumbar puncture, magnetic resonance imaging/magnetic resonance spectroscopy (brain), ultrasound (abdomen)
274	Gastroenterology, genetics, neurology, neurology, neuromuscular	Allergy testing, electroencephalography, electromyography/nerve conduction velocity, enzyme testing, magnetic resonance imaging/magnetic resonance spectroscopy (brain), metabolic labs, skin biopsy
275	Audiology, dentistry, endocrinology, neurodevelopment, occupational therapy, ophthalmology, physiatry, physical therapy, speech-language pathology	Swallow study, bone age, electromyography/nerve conduction velocity, electroencephalography, ultrasound (abdomen), magnetic resonance imaging/magnetic resonance spectroscopy (brain), skeletal survey, sleep study
276	Genetics, neurology	None
277	Genetics, neuropsychology	immunology labs, magnetic resonance imaging (spine), skeletal survey
278	Endocrinology, hepatology, neurology, neuropsychology, nutrition, occupational therapy, ophthalmology, physiatry, physical therapy, speech-language pathology	Autonomic nervous system testing, swallow study, electroencephalography, electromyography/nerve conduction velocity, echocardiogram, electrocardiogram, ultrasound (abdomen), bone densitometry (femur), magnetic resonance imaging/magnetic resonance spectroscopy (brain), lumbar puncture, skeletal survey, sleep study, x-ray (skull/chest/scoliosis)
279	Genetics, pathology	None
280	Genetics	Congenital disorders of glycosylation testing, RNA sequencing, skin biopsy
281	Neuropsychology, ophthalmology	Electromyography/nerve conduction velocity, bone densitometry (femur/radius/spine), magnetic resonance imaging (brain), computed tomography scan (tibia/fibula/radius/ulna/neck/humerus/heart/foot/chest/abdomen/pelvis)
282	Neuropsychology, nutrition, occupational therapy, ophthalmology, physiatry, physical therapy, speech-language pathology	Echocardiogram, electroencephalography, electromyography/nerve conduction velocity, ultrasound (abdomen)
283	Audiology, dentistry, dermatology, gastroenterology, genetics, neurodevelopment, neurology, nutrition, occupational therapy, ophthalmology, physiatry, physical therapy, rheumatology, speech-language pathology, vascular access	Echocardiogram, electrocardiogram, electromyography/nerve conduction velocity, electroencephalography, electroencephalography-evoked potential, metabolic cart
284	Neurogenetics, ophthalmology	Magnetic resonance imaging/magnetic resonance spectroscopy
285	Genetics, hepatology, immunology, neuromuscular, ophthalmology, rheumatology, surgery	Antibody testing, clotting labs, complement deficiency workup, immunology labs, rheumatology labs
286	Genetics, neurology, neuropsychology	Magnetic resonance imaging (brain), skeletal survey, targeted genetic testing
287	Allergy and immunology, audiology, endocrinology, neuropsychology, occupational therapy, ophthalmology, physiatry, physical therapy	Autonomic nervous system testing, bone age, bone densitometry (radius/femur/spine/whole body), echocardiogram, electrocardiogram, electroencephalography, eectromyography/nerve conduction velocity, pulmonary function tests, ultrasound (abdomen), skeletal survey, sleep study, x-ray (scoliosis)
288	Cardiology, genetics, ophthalmology	Complete blood count, chromosomal microarray, bone density, echocardiogram, congenital disorders of glycosylation testing, magnetic resonance imaging/magnetic resonance angiogram (cardiac), skin biopsy
289	Genetics	None
290	Neurogenetics	Antibody testing, congenital disorders of glycosylation testing, rheumatology labs, steroid testing
291	Genetics, neurology	Karyotype, lumbar puncture, metabolomics, targeted genetic testing

292	Genetics, ophthalmology	Skin biopsy
293	Genetics, neurology, ophthalmology	None
294	Allergy and immunology, audiology, dermatology, genetics, rheumatology	Complete blood count, metabolic labs, rheumatology labs, skin biopsy, urinalysis
295	Genetics, neuromuscular, neuropsychology	Creatine kinase, muscle biopsy
296	Audiology, neurodevelopment, neurology, nutrition, occupational therapy, ophthalmology, physiatry, physical therapy	Bone age, bone densitometry (femur), echocardiogram, electroencephalography, electromyography/nerve conduction velocity, magnetic resonance imaging/magnetic resonance spectroscopy (brain), skeletal survey, swallow study, ultrasound (abdomen)
297	Dermatology, genetics	Metabolomics, skin biopsy, targeted genetic testing
298	Dentistry, dermatology, genetics	Bone age, bone density, endocrine studies, skeletal survey, skin biopsy
299	Allergy and immunology, dentistry, dermatology, otolaryngology, rheumatology	Computed tomography scan (neck), magnetic resonance imaging (neck)
300	Audiology, cardiology, genetics, neurodevelopment, neurology, ophthalmology, orthopedics	Echocardiogram, electrocardiogram, electroencephalography, magnetic resonance imaging (brain), skeletal survey, research labs
301	Audiology, dentistry, hematology, neuropsychology, ophthalmology	Computed tomography scan (craniofacial), echocardiogram, electrocardiogram, ultrasound (abdomen), magnetic resonance imaging/magnetic resonance spectroscopy (brain), skeletal survey, x-ray (scoliosis)
302	Genetics, neurology, nutrition, ophthalmology	Enzyme testing, nutrition assessment, vitamin D
303	Endocrinology, genetics, neurology, neuropsychology	endocrine studies, magnetic resonance imaging (abdomen), metabolic labs, targeted genetic testing, thyroid function tests
304	Audiology, occupational therapy, ophthalmology, pain and palliative care, psychiatry, physiatry, physical therapy	Echocardiogram, electromyography/nerve conduction velocity, pulmonary function tests, ultrasound (abdomen), magnetic resonance imaging (brain/muscle/cervical spine/thoracic spine/lumbar spine), lumbar puncture
305	Genetics	Creatine kinase, targeted genetic testing
306	Audiology, dentistry, endocrinology, neurodevelopment, nutrition, occupational therapy, ophthalmology, otolaryngology, physiatry, physical therapy	Swallow study, bone age, computed tomography scan (abdomen/chest/neck/pelvis), echocardiogram, electrocardiogram, electromyography/nerve conduction velocity, electroencephalography, ultrasound (abdomen/lower extremities) magnetic resonance imaging/magnetic resonance spectroscopy (brain), magnetic resonance imaging (pituitary/cervical/thoracic/elbow), skeletal survey, sleep study, x-ray (abdomen/scoliosis)
307	Audiology, dentistry, endocrinology, gastroenterology, neurodevelopment, neurology, occupational therapy, ophthalmology, otolaryngology, physiatry, physical therapy	Bone age, electrocardiogram, metabolic cart, ultrasound (abdomen/scrotum/testicle), skeletal survey, x-ray (chest/abdomen/kidneys/ureters/bladder)
308	Cardiology, genetics, immunology, ophthalmology, orthopedics	Echocardiogram, electrocardiogram, research labs
309	Genetics, neurology	Metabolomics, RNA sequencing, skin biopsy, splicing assay
310	Genetics	None
311	Allergy and immunology, dermatology, infectious disease, rheumatology	Electrocardiogram
312	Dermatology, genetics, hematology, ophthalmology, otolaryngology, pain and palliative care, psychiatry, physiatry, physical therapy, speech-language pathology	Swallow study, computed tomography scan (heart), echocardiogram, electrocardiogram, magnetic resonance angiogram (brain/lower extremities), pulmonary function tests, magnetic resonance imaging (thighs), skeletal durvey, x-ray (scoliosis)
313	Audiology, gastroenterology, hematology, neurodevelopment, nutrition, ophthalmology, speech-language pathology	Echocardiogram, electrocardiogram, electroencephalography, ultrasound (abdomen), magnetic resonance imaging (abdomen), computed tomography scan (cerebrum), skeletal survey, sleep study, x-ray (scoliosis)
314	Internal medicine	Cytokine profiling, metabolomics, skin biopsy
315	Genetics, neurodevelopment	Research labs
316	Allergy and immunology, audiology, dentistry, endocrinology, neurodevelopment, neurology, occupational therapy, ophthalmology, physiatry, physical therapy, speech-language pathology	Autonomic nervous system testing, echocardiogram, electrocardiogram, electromyography/nerve conduction velocity, metabolic cart, ultrasound (abdomen), skeletal survey, x-ray (scoliosis)

317	Genetics, neurology, ophthalmology	Congenital disorders of glycosylation testing, echocardiogram
318	Cardiology, dermatology, gastroenterology, genetics, immunology, neurology, ophthalmology	Antibody testing, echocardiogram, electrocardiogram, immunology labs, infectious disease studies
319	Dentistry, genetics, neurology, neuropsychology	Computed tomography scan (craniofacial), echocardiogram, electrocardiogram, electroencephalography, magnetic resonance imaging/magnetic resonance spectroscopy (brain), sleep study, x-ray (wrist/hands/spine)
320	Rheumatology	Bone marrow aspiration/biopsy, bone scan, computed tomography scan (chest), magnetic resonance imaging (brain/humerus/pelvis), positron emission tomography scan (extremities/torso), pulmonary function tests
321	Genetics, neuroendocrinology	Endocrine studies
322	Occupational therapy, physiatry, physical therapy	Electromyography/nerve conduction velocity, magnetic resonance imaging (cervical spine/thoracic spine/lumbar spine), magnetic resonance imaging/magnetic resonance spectroscopy (brain), ultrasound (abdomen), lumbar puncture
323	Audiology, genetics, hematology, ophthalmology	Swallow study, computed tomography scan (cerebrum), echocardiogram, electrocardiogram, electromyography/nerve conduction velocity, ultrasound (abdomen), magnetic resonance imaging/magnetic resonance spectroscopy (brain)
324	Neurogenetics	Exon-level microarray, metabolic labs, metabolomics
325	Genetics	Research labs
326	Genetics, infectious disease, internal medicine, neurology, ophthalmology, pathology, pulmonology	Antibody testing, computed tomography scan (chest), infectious disease studies, magnetic resonance imaging (brain/spine), positron emission tomography/computed tomography scan, viral tests
327	Genetics, neuromuscular, neuropsychology	Magnetic resonance imaging (full body)
328	Audiology, ophthalmology, otolaryngology	Electromyography/nerve conduction velocity, electrocardiogram, magnetic resonance imaging (brain/cervical spine/lumbar spine/thoracic spine/posterior fossa/internal acoustic canal/hip), lumbar puncture, x-ray (hip/knee)
329	Cardiology, genetics, neurology, neuropsychology	Magnetic resonance imaging (brain)
330	Cardiology, genetics, ophthalmology	Congenital disorders of glycosylation testing, echocardiogram, electrocardiogram, skeletal survey
331	Audiology, dentistry, neuropsychology, ophthalmology	Computed tomography scan (craniofacial), echocardiogram, electrocardiogram, electroencephalography, electroencephalography-evoked potential, electromyography/nerve conduction velocity, pulmonary function tests, ultrasound (abdomen), skeletal survey, sleep study, swallow study, x-ray (scoliosis)
332	Genetics	Skin biopsy
333	Allergy and immunology, audiology, dermatology, nephrology, neurodevelopment, occupational therapy, ophthalmology, physiatry, physical therapy, speech-language pathology	Bone age, computed tomography scan (chest), echocardiogram, electrocardiogram, electromyography/nerve conduction velocity, magnetic resonance imaging/magnetic resonance spectroscopy (brain), swallow study, ultrasound (abdomen/renal/thyroid)
334	Audiology, genetics, neurodevelopment, neurology, ophthalmology	Research labs
335	Allergy and immunology, audiology, neurodevelopment, neurology, nutrition, ophthalmology, physiatry, physical therapy, occupational therapy	Bone age, echocardiogram, electrocardiogram, electroencephalography, electromyography/nerve conduction velocity, magnetic resonance imaging/magnetic resonance spectroscopy (brain), skeletal survey, swallow study, ultrasound (abdomen), x-ray (chest)
336	Neurogenetics, neuropsychology, ophthalmology	Sleep study
337	Allergy and immunology, genetics, neurology, ophthalmology, pulmonology, rheumatology	Autonomic nervous system testing, computed tomography scan (chest), electrocardiogram, electroencephalography, electromyography/nerve conduction velocity, magnetic resonance imaging (brain), skeletal survey
338	Audiology, cardiology, endocrinology, gastroenterology, genetics, neurodevelopment, neurology, ophthalmology, orthopedics	Echocardiogram, electrocardiogram, research labs, ultrasound (liver)
339	Genetics, neuropsychology, ophthalmology	Echocardiogram, endocrine studies, magnetic resonance imaging (brain), ultrasound (abdomen)

340	Allergy and immunology, occupational therapy, ophthalmology, pain and palliative care, physiatry, physical therapy, speech-language pathology	Swallow study, echocardiogram, electromyography/nerve conduction velocity, electroencephalography-evoked potential, lumbar puncture, magnetic resonance imaging (brain/cervical/thoracic), ultrasound (abdomen), pulmonary function tests
341	Dentistry, genetics, neurology, neuropsychology	Bone density, metabolic labs
342	Occupational therapy, ophthalmology, physiatry, physical therapy, speech-language pathology	Swallow study, echocardiogram, electroencephalography, electroencephalography-evoked potential, electromyography/nerve conduction velocity, lumbar puncture, magnetic resonance imaging (cervical/thoracic), magnetic resonance imaging/magnetic resonance spectroscopy (brain), pulmonary function tests
343	Dentistry, dermatology, endocrinology, immunology, pulmonology	Computed tomography scan (chest), flow cytometry, pulmonary function tests, skin biopsy, targeted genetic testing
344	Genetics, neuroimmunology, rheumatology	Targeted genetic testing
345	Endocrinology, gastroenterology, genetics, neurology - sleep disorders, neuromuscular, nutrition, ophthalmology	Bone age, hearing test, lumbar puncture, metabolic labs, magnetic resonance imaging/magnetic resonance spectroscopy, skeletal survey
346	Audiology, neurodevelopment, neurology, physiatry, rheumatology	Audiology testing, swallow study, bone densitometry, echocardiogram, electrocardiogram, electromyography, lumbar puncture, nerve conduction velocity, skeletal survey, skin biopsy, sleep study, sweat chloride test
347	Endocrinology, genetics, neurology, ophthalmology, orthopedics	Complete blood count, electrolytes, endocrine studies, liver function tests, sleep study, thyroid labs
348	Genetics, neurogenetics, neurology, ophthalmology	Magnetic resonance imaging/magnetic resonance spectroscopy (brain), magnetic resonance imaging (spine), video electroencephalography monitoring
349	Genetics, immunology, neurology, pain and palliative care, rheumatology	Bone density, immunology labs, lumbar puncture, rheumatology labs
350	Audiology, genetics, neurology, speech-language pathology	Electroencephalography, feeding study, magnetic resonance imaging (brain), research labs
351	Endocrinology, genetics, ophthalmology, neuropsychology	Bone age, functional magnetic resonance imaging, ultrasound (renal)
352	Dermatology, gastroenterology, genetics, neurodevelopment, neurology, orthopedics	Endocrine studies, magnetic resonance imaging (brain), research labs, skeletal survey
353	Endocrinology, neurodevelopment, neurology, nutrition	Computed tomography scan (cerebrum), electroencephalography, electromyography/nerve conduction velocity, lumbar puncture, skeletal survey, skin biopsy, sleep study, ultrasound (abdomen)
354	Audiology, genetics, neurology, ophthalmology	Audiology testing, echocardiogram, magnetic resonance imaging, metabolic labs, mitochondrial studies, muscle biopsy, RNA sequencing, skleletal survey, ultrasound (abdominal)
355	Gastroenterology, genetics, hematology	Autonomic nervous system testing, bone densitometry (femur/radius/spine), computed tomography scan (cerebrum/chest/abdomen/pelvis/femur/foot/humerus/cervical spine/radius/ulna/tibia/fibula), echocardiogram, electrocardiogram, electromyography/nerve conduction velocity, lumbar puncture, magnetic resonance imaging (brain)
356	Gastroenterology, neuropsychology, physiatry	Echocardiogram, electromyography, magnetic resonance imaging (brain), swallow study, skin biopsy, ultrasound (abdomen), x-ray (chest)
357	Endocrinology, genetics, neurology, neuromuscular, ophthalmology	Audiology testing, autonomic nervous system testing, electromyography/nerve conduction velocity, magnetic resonance imaging, mitochondrial studies, muscle biopsy
358	Infectious disease, rheumatology	Cytokine profiling, metabolomics, skin biopsy
359	Audiology, genetics, neurodevelopment, neurology, opthalmology, physical therapy, speech-language pathology	Lumbar puncture, metabolic labs, research labs
360	Gastroenterology, genetics, immunology, metabolism	Fasting study, metabolic labs
361	Audiology, gastroenterology, genetics, neurodevelopment, neurology, ophthalmology, otolaryngology	Lumbar puncture, research labs
362	Genetics	None

363	Endocrinology, neurology, neuropsychology, nutrition, physiatry, psychiatry	Glucose tolerance test, electrocardiogram, lumbar puncture, magnetic resonance imaging (brain/pituitary), skeletal survey, skin biopsy, sleep study
364	Cardiology, genetics, neurology, ophthalmology, pediatrics	Electrocardiogram, electroencephalography, metabolomics, metabolic labs, mitochondrial studies, skeletal survey
365	Ophthalmology, rehabilitation consult, social work	Electromyography/nerve conduction velocity, lumbar puncture, magnetic resonance imaging (brain), skin biopsy, swallow study, ultrasound (abdomen)
366	Genetics	Echocardiogram
367	Genetics	Metabolomics
368	Genetics	Research labs
369	Gastroenterology, neuropsychology	Magnetic resonance imaging (brain/cervical spine), electromyography/nerve conduction velocity, lumbar puncture
370	Cardiology, gastroenterology, genetics, metabolism, neurosurgery, ophthalmology	Echocardiogram, electromyography, exon-level microarray, metabolic labs, metabolomics, targeted genetic testing, thryoid function tests
371	Genetics, neuromuscular	Hematology studies, pulmonary function tests, x-ray
372	Genetics, ophthalmology	Skin biopsy
373	Neuromuscular, ophthalmology	Echocardiogram, electromyography/nerve conduction velocity, magnetic resonance imaging (lower extremities), pulmonary function tests, swallow study
374	Genetics, ophthalmology	Metabolic labs, targeted genetic testing, urinalysis
375	Neurogenetics	Chromosomal microarray, echocardiogram, electrocardiogram, magnetic resonance imaging
376	Audiology, genetics, neurology, ophthalmology	Research labs
377	Allergy and immunology, dermatology, genetics	Karyotype, chromosomal microarray, immunology labs, skin biopsy, targeted genetic testing
378	Cardiology, genetics, neurology, ophthalmology	Environmental exposure tests
379	Audiology, genetics, neurodevelopment, neurology	Lumbar puncture
380	Genetics, neurology, ophthalmology	Magnetic resonance imaging/magnetic resonance spectroscopy (brain), electromyography, targeted genetic testing
381	Genetics, neuromuscular, neuropsychology, physical therapy, pulmonology	Electromyography/nerve conduction velocity, mitochondrial studies, muscle biopsy, pulmonary function tests
382	Genetics	Complete blood count, creatine phosphokinase, magnetic resonance imaging, metabolic labs, hematology studies

Table S4. Applicant demographic characteristics and primary symptom category

	Total applicants[1] (n= 1519)	Pediatric applicants (n= 615)	Pediatric applicants accepted (n= 350)	Adult applicants (n= 904)	Adult applicants accepted (n= 251)	Significance
Sex						
Males, n (%)	704 (46.3)	318 (51.7)	170 (48.6)	386 (42.7)	109 (43.4)	#
Females, n (%)	811 (53.4)	297 (48.3)	180 (51.4)	514 (56.9)	141 (56.2)	#
Other, n (%)	4 (0.3)	0 (0.0)	0 (0.0)	4 (0.4)	1 (0.4)	
Age (Years) [a]	29 +/- 22	8 +/- 5	8 +/- 5	43 +/- 16	39 +/- 16	
Race						
White, n (%)	1178 (77.6)	452 (73.5)	259 (74.0)	726 (80.3)	197 (78.5)	#
Asian, n (%)	82 (5.4)	41 (6.7)	24 (6.9)	41 (4.5)	14 (5.6)	
Black or African American, n (%)	73 (4.8)	28 (4.6)	18 (5.1)	45 (5.0)	13 (5.2)	
Multiracial, n (%)	65 (4.3)	34 (5.5)	16 (4.6)	31 (3.4)	7 (2.8)	
American Indian or Alaska Native, n (%)	3 (0.2)	1 (0.2)	0 (0.0)	2 (0.2)	0 (0.0)	
Native Hawaiian or Other Pacific Islander, n (%)	1 (0.1)	1 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	
Other, n (%)	117 (7.7)	58 (9.4)	32 (9.1)	59 (6.5)	20 (8.0)	
Ethnicity						
Hispanic or Latino	156 (10.3)	110 (17.9)	64 (18.3)	46 (5.1)	19 (7.6)	#
Not Hispanic or Latino	1133 (74.6)	424 (68.9)	237 (67.7)	709 (78.4)	185 (73.7)	#
Unknown/Not Reported	230 (15.1)	81 (13.2)	49 (14.0)	149 (16.5)	47 (18.7)	

Primary symptom category						
Neurology, n (%)	607 (40.0)	285 (46.3)	171 (48.9)	322 (35.6)	112 (44.6)	^#
Musculoskeletal and orthopedics, n (%)	148 (9.7)	63 (10.2)	43 (12.3)	85 (9.4)	25 (10.0)	
Allergies and disorders of the immune system, n (%)	104 (6.8)	28 (4.6)	15 (4.3)	76 (8.4)	17 (6.8)	#
Gastroenterology, n (%)	99 (6.5)	38 (6.2)	15 (4.3)	61 (6.7)	7 (2.8)	
Rheumatology, n (%)	86 (5.7)	12 (2.0)	10 (2.9)	74 (8.2)	18 (7.2)	#
Cardiology and vascular conditions, n (%)	52 (3.4)	21 (3.4)	12 (3.4)	31 (3.4)	13 (5.2)	
Endocrinology, n (%)	43 (2.8)	17 (2.8)	11 (3.1)	26 (2.9)	5 (2.0)	
Pulmonology, n (%)	31 (2.0)	11 (1.8)	3 (0.9)	20 (2.2)	6 (2.4)	
Hematology, n (%)	26 (1.7)	8 (1.3)	3 (0.9)	18 (2.0)	6 (2.4)	
Infectious diseases, n (%)	20 (1.3)	1 (0.2)	0 (0.0)	19 (2.1)	1 (0.4)	#
Dermatology, n (%)	16 (1.1)	2 (0.3)	1 (0.3)	14 (1.5)	4 (1.6)	
Nephrology, n (%)	15 (1.0)	6 (1.0)	4 (1.1)	9 (1.0)	5 (2.0)	
Oncology, n (%)	11 (0.7)	4 (0.7)	1 (0.3)	7 (0.8)	1 (0.4)	
Dentistry and craniofacial, n (%)	9 (0.6)	4 (0.7)	2 (0.6)	5 (0.6)	1 (0.4)	
Ophthalmology, n (%)	8 (0.5)	3 (0.5)	2 (0.6)	5 (0.6)	3 (1.2)	

Psychiatry, n (%)	5 (0.3)	2 (0.3)	1 (0.3)	3 (0.3)	1 (0.4)	
Toxicology and environmental medicine, n (%)	3 (0.2)	0 (0.0)	0 (0.0)	3 (0.3)	0 (0.0)	
Urology, n (%)	3 (0.2)	1 (0.2)	1 (0.3)	2 (0.2)	0 (0.0)	
Gynecology and reproductive medicine, n (%)	2 (0.1)	1 (0.2)	1 (0.3)	1 (0.1)	0 (0.0)	
Other, n (%)	231 (15.2)	108 (17.6)	54 (15.4)	123 (13.6)	26 (10.4)	

[a]The mean age +/- standard deviation (in years) is indicated.

[1] The number of applications reviewed or withdrawn by May 23, 2017 totaled 1203. At that time, 316 applications were still under review by the clinical sites.

Characteristics of those who applied and those who were accepted into the Undiagnosed Diseases Network since its inception. Percentages shown in parentheses. P values <0.01 for comparisons (Fisher's exact test) * pediatric applicants vs pediatric accepted; ^adult applicants vs adult accepted; # adult applicants vs pediatric applicants

Contributions

The entire network contributed to the results presented here. EA, KS & CE analyzed the data. EA wrote and revised the draft with help from co-authors.

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