Rare Diseases, Common Barriers: Disparities in Pediatric Clinical Genetics Outcomes

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Abstract

Background and Objectives: Identifying a precise genetic diagnosis can improve outcomes for individuals with rare disease, though the resources required to do so may impede access and exacerbate healthcare disparities leading to inequitable care. Our objective was therefore to determine the effect of multiple sociodemographic factors on the yield of the diagnostic evaluation for genetics outpatients.

Methods: Retrospective cohort study from 2017–2019 of outpatient genetics referrals at a pediatric academic tertiary care center. Exposures included: primary language, insurance type, and neighborhood resources (via the Childhood Opportunity Index, COI). The primary outcome was identification of a genetic diagnosis within 2 years of the initial clinic visit.

Results: COI quintile was not significantly associated with the odds of diagnosis but was significantly associated with clinic attendance, with lower neighborhood resources leading to incomplete referrals. Limited English proficiency was associated with a higher odds of diagnosis, though at an older age. Public insurance was associated with increased access to genetic testing.

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Conclusion: Lower neighborhood resources are negatively associated with clinic attendance. Our findings further suggest delays in care and a referral bias for more severe phenotypes among families with limited English proficiency. Improved access to clinical genetics is needed to improve diagnostic equity.

Category of study:

Clinical

Introduction

Rare diseases affect millions of individuals in the United States and disproportionately contribute to morbidity and mortality.[1–6] Most rare childhood diseases are thought to be genetic, and identifying the precise causative change in the genome, referred to as a molecular diagnosis, can lead the way to novel treatments or therapies in addition to other improved outcomes.[7–9] However, access to the resources necessary to identify such a diagnosis are unlikely to be distributed equitably and may lead to lower rates of diagnosis in populations with historically reduced access to healthcare. Prior studies have shown that certain areas of the country have few practicing geneticists to evaluate and diagnose genetic syndromes[10,11], and access to any subspecialty care, genetics included, is limited for children who live in lower-income neighborhoods or belong to minoritized racial or ethnic groups.[12] Additionally, even if a clinical geneticist is available within a certain city or region, children who may have an underlying genetic diagnosis may not be referred for evaluation due to failure to recognize the features of a certain condition or other barriers to clinic attendance.[13] This referral bias disproportionately affects minoritized racial and ethnic groups, where syndromic features may not be recognized[14], as well as children within communities with impaired access to healthcare for socio-economic or other reasons.

Once established within the genetics clinic, families may still face additional barriers along the path to identification of a molecular diagnosis – the care cascade that has come to be known as the "diagnostic odyssey".[15] These include: lack of recognition of a genetic condition, difficulty obtaining insurance coverage for genetic testing, difficulty accessing the lab to provide samples for genetic testing, and challenges in variant interpretation due to a paucity of non-European ancestry groups in genetic reference databases.[13,16] The end result of such barriers in access to testing may be a lower diagnostic yield for families of lower socioeconomic position or from minoritized racial or ethnic groups.[16–18] However, while disparities in use of, or access to, genomic medicine have been evaluated related to many conditions primarily affecting adults or for more common diseases[19–22], the extent and nature of these disparities has not been fully defined in the pediatric rare disease community. We therefore sought to determine the influence of social determinants of health, in particular, neighborhood resources and primary language, on the genetic diagnostic odyssey at a high-volume pediatric outpatient genetics clinic.

Methods

This is a retrospective cohort study of an outpatient genetics clinic within an academic, pediatric tertiary care center in an urban community. We identified all outpatients with their first visit to genetics clinic scheduled to be in 2017 and abstracted data from the electronic health record (EHR) pertaining to the genetic evaluation for up to two years (730 days) following this initial visit date. The two year follow-up period was set for consistency in the amount of time each cohort member had for their diagnostic odyssey. Data were collected using REDCap hosted at our institution.[23] The Boston Children's Hospital Institutional Review Board reviewed and approved this analysis with a waiver of informed consent due to the nature of the study.

We developed a conceptual model related to disparities in genetic diagnosis that guided our data collection and analysis (Figure 1). The primary exposure evaluated was individual-level Childhood Opportunity Index (COI) quintile, which takes into account multiple dimensions of neighborhood resources (health, education, socioeconomic status) in order to generate a composite measure with normative levels at the metro, state, or national level.[24] State-normed COI data were used in this study due to the geographical diversity of our cohort, where many families lived outside our metro area. Our primary outcome was diagnostic yield: whether or not a molecular genetic diagnosis was identified within two years of the initial clinic visit. Other exposures assessed included: primary language, ancestry, insurance type, and reason for genetics evaluation (presenting phenotype). We also evaluated intermediate steps along the path to a genetic diagnosis such as clinic attendance, prior testing, testing planned, and testing sent. Exposure and outcome data were abstracted from our EHR by two reviewers. Further information on our exposure and outcome variables and the analysis plan is provided in the Supplement.

We first evaluated the relationship between the above exposures and clinic attendance, comparing those who attended the first scheduled visit to those whose visit was either cancelled or was neither attended nor cancelled ("no show"). Then, focusing on the patients who attended this first clinic visit, we evaluated the relationship between these exposures and reason for clinic visit. Finally, for those who were undiagnosed at this first clinic visit, we evaluated the yield of the genetic diagnostic odyssey and the above exposures as possible predictors of this outcome. To avoid confounding in our analysis of diagnostic yield, we excluded certain reasons for referral from this analysis (Figure 2) because either a) the diagnosis was already known or had been made clinically or b) because diagnostic molecular testing was less likely to be sent for these indications or c) such testing has a yield skewing high or low. Patients were considered "diagnosed" if, over the 2 years following the initial clinic visit, a likely pathogenic or pathogenic variant was identified or a variant of unknown significance was identified that was clinically considered to be diagnostic.

Statistical analysis was performed using SPSS version 27 (IBM Corporation, Armonk, NY).

Results

Of 1859 patients with scheduled visits, 413 resulted in cancellations or no shows, leading to 1446 patients seen (Table 1). Of the attended visits, 934/1446 (64.6%) were for the purpose of diagnostic evaluation per our pre-specified criteria (Figure 2).

In comparing socio-demographic features of those who attended the first clinic visit compared to cancellation and "no shows", we identified significant variation in clinic attendance related to state-normed overall childhood opportunity by quintile (Table 2), where those in the "no show" category were more likely to live in a "Very Low" COI neighborhood and those who attended the clinic visit had a higher proportion in the higher COI quintiles. We also found significant differences in clinic attendance related to primary language and insurance plan, with the "no show" group having a higher percentage of Spanish-speaking individuals as well as those with public insurance (Table 2).

For the 1446 outpatients who attended their initial genetics clinic visit in 2017, we reviewed the reasons for referral to the genetics clinic and associated socio-demographic features. Significant differences in COI quintiles were identified for autism, possible metabolic disorder, hypermobile Ehlers-Danlos syndrome, and management of a known diagnosis, where autism had a higher proportion of individuals in the lower COI quintiles and the others had higher proportions in the higher COI quintiles. Of note, none of those presenting for pharmacogenomics evaluation and only one person presenting for hypermobile Ehlers-Danlos syndrome had limited English proficiency. (Supplemental Table S1). Supportive of our exclusions in the analysis of diagnostic yield (Figure 2) we found that hypermobility (2/87, 2%) and connective tissue evaluations (5/108, 5%) had low rates of molecular diagnosis, as did hemihypertrophy/Beckwith-Wiedemann syndrome and Neurofibromatosis 1 combined (3/79, 4%), whereas referral for an abnormal newborn screen had a relatively high yield (23/80, 29%).

We then focused on the 934 individuals who presented for diagnostic evaluation for the following indications: developmental delay/intellectual disability, autism, congenital anomalies, neurologic disease, short stature or failure to thrive, other organ system-based complaints (ophthalmologic, otologic, immunologic, dermatologic, endocrinologic, metabolic), family history of genetic disorder, or discussion of test results sent by another provider. The overall diagnostic yield was 176/934 (18.8%) including both chromosomal and monogenic conditions (Supplemental Table S2).

An analysis of demographic and clinical predictors of diagnostic yield is displayed in Table 3. No differences were found in diagnostic yield across COI quintiles. Those who had a confirmed diagnosis had a significantly lower age at first clinic visit. Additionally, there was an association between primary language and diagnostic yield, with English speakers comprising a smaller proportion of those who had a confirmed diagnosis and Spanish and Arabic speakers comprising a higher proportion compared to the undiagnosed. No differences were found across ancestry categories or by insurance status. The diagnostic yield varied by indication for evaluation, with a lower proportion of diagnoses found in those with autism and a higher proportion in those with other specific organ system

anomalies. We did not identify any significant differences in diagnostic yield comparing those with or without any genetic testing performed prior to the clinic visit (62/378 [16.4%] vs 114/556 [20.5%], $p = 0.13$) or when comparing specific tests (e.g. gene panel testing). Individuals with genetic testing planned at the first clinic visit were more likely to have a diagnosis identified within the study time period, particularly if this was a single gene test – suggesting that this individual presented with a specific phenotype. Supportive of this theory is the finding that, when evaluating the relationship between number of tests sent over the two-year period and diagnosed status (excluding those who had no testing sent), those who remained undiagnosed had more testing (median 2, IQR 1–3) than those who had a diagnosis made (median 1, IQR 1–2, $p = 0.021$). No significant differences were seen across COI quintiles or language or insurance categories. The modalities leading to diagnosis were: karyotype and fluorescence in situ hybridization (8/176, 4.5%), microarray (23/176, 13.1%), single gene test (37/176, 21.0%), gene panel (47/176, 26.7%), exome sequencing (48/176, 27.3%), with other tests each contributing less than 2%. There was no significant variation in modality leading to diagnosis by COI quintile, language, or insurance type.

Considering the relationship between these predictors and diagnostic yield, we created a multivariable logistic regression model incorporating language, reason for visit, and age at first visit (Table 4). After controlling for reason for visit and age at first visit, primary language continued to be a predictor of a diagnosis, with both Arabic-speaking and Spanish-speaking families having a higher odds of diagnosis compared to English speakers.

We then evaluated the process of the genetic diagnostic odyssey related to socio-demographic factors in order to further understand the multivariable model results in an exploratory model of intermediates in the relationship between our exposures and outcome (Supplemental Figure S1). Language, insurance type, and COI quintile were all significantly associated with the likelihood of testing being planned at the first visit or sent over the two years following this first visit, where more testing was sent with those who had public insurance or from lower COI quintiles. Language was significantly associated with insurance category, where Spanish language-speaking families had a higher percentage with public insurance. This association may explain why testing was planned earlier and sent more often for those with Spanish or Arabic as the primary language and subsequently why diagnoses were more frequently identified.

We also evaluated trends across the entire cohort related to usage of exome sequencing, which is known to be high yield for diagnosis in pediatric populations with suspected genetic disease.[25] We found that those who were primarily Arabic-speaking or who had international insurance were over-represented in the group of patients who had exome sequencing while those who were Spanish-speaking or had public insurance were under-represented. Neighborhoods with "High" or "Very High" COI levels also appeared to be over-represented, though this difference was not statistically significant (Supplemental Table S3).

Due to this variation in the diagnostic odyssey and the potential impact on the time to diagnosis, we performed a survival analysis to evaluate the impact of COI quintile, language, and insurance status on time to diagnosis (Supplemental Figure S2). We found a significant

relationship between language status and time to diagnosis, with non-English speakers experiencing a shorter time to diagnosis, but time to diagnosis was not significantly different across insurance categories or COI quintiles. A Cox proportional hazards model evaluating the relationship between language status and time to diagnosis, adjusting for phenotype, demonstrated that the Spanish speaking families had a higher hazard of diagnosis over the study period compared to English-speaking patients even after controlling for phenotype (hazard ratio, HR = 2.0, 95% C.I. 1.2–3.5), $p = 0.01$, though the HRs were not significant for Arabic (HR 1.6, 95% CI 1.0–2.7, $p = 0.07$) or other languages (HR = 0.8, 95% CI 0.3–1.9, $p = 0.6$). We also found that median age at diagnosis varied between groups, with primary English-speaking patients having a younger median age at diagnosis (2.2 years, interquartile range [IQR] 0.9–6.5 years) compared to Spanish-speaking patients (5.9 years, IQR 1.0–12.6 years), Arabic (4.2 years, IQR 1.5–7.7 years) and other languages (10.4 years, IQR 2.5–21.1 years) though this difference did not reach statistical significance ($p = 0.06$). As our Arabic-speaking population was found in the prior analyses to represent a unique group with a high diagnostic yield, we then focused on the non-Arabic speaking families and identified a younger median age at diagnosis for English-speaking families (2.2 years, IQR 0.9–6.5 years) versus those who were non-English and non-Arabic speaking (7.3 years, IQR 1.8–12.3 years), $p = 0.03$.

Discussion

We present an analysis of socio-demographic factors related to the genetic diagnostic odyssey in the outpatient setting. Our main finding was that the primary source of inequity in access to a genetic diagnosis was access to the genetics clinic, where lack of neighborhood resources was negatively associated with clinic attendance. Variation in the reason for referral was also observed, with important implications for referral patterns and evidence of referral bias, where conditions such as hypermobile Ehlers-Danlos syndrome should not be concentrated in those with higher neighborhood resources, though referrals for these conditions were enriched in this way. Our results are also consistent with prior research that has shown that people who attend a genetics clinic visit tend to have higher levels of education and income, and are less likely to identify with a minoritized population[26]. Engagement in research studies for genetic diagnosis has also been found to be lower for populations with historically poor access to healthcare.[27]

Once in the clinic, there was no difference in diagnostic yield related to COI quintile, though there was significant variation related to primary language, where those who spoke Arabic or Spanish as a primary language had a higher odds of diagnosis compared to English speakers, even when considering other factors such as age and reason for visit. Although we had hypothesized that families with limited English proficiency would have more difficulty navigating the diagnostic odyssey, associations between intermediate factors related to access to genetic testing were identified that may explain this finding. We observed that Spanish speaking patients in our study were more likely to have public insurance, which may facilitate access to genetic testing in our clinic as prior authorization is not typically pursued (since the patient cannot be balance-billed). Thus, a child with public insurance may be more likely to have testing planned and ordered on the day of the first visit, while a child with private insurance would have to await insurance authorization which may not

be successful. Indeed, insurance authorization has been identified as a substantial barrier to outpatient genetic testing[28,29]. While prior studies of adult patients have found that genetic testing is more easily accessed for those with private insurance compared to Medicaid[17], a recent analysis focusing on pediatric patients found that insurance prior authorization denials were less frequent with public compared to private payers[29]. Furthermore, of all prior authorization requests that were either approved or determined to not require prior authorization in this study, 26% did not proceed to actual testing, supporting our hypothesis that ordering and sending a genetic test on the same day of the initial clinic visit greatly facilitates access to a diagnosis[29]. However, the improved access to testing that we observed with public insurance did not carry over to exome sequencing, where inequities were identified.

Another factor driving diagnostic yield, which is more difficult to quantify, is the underlying likelihood of a genetic diagnosis among those presenting to clinic. It may be that the children seen in clinic who were from families of limited English proficiency had more severe or extreme presentations and a higher pre-test probability of a diagnostic test result. Similarly, a higher diagnostic yield for patients from minoritized populations compared to white individuals via gene panel testing for RASopathies (Noonan syndrome and related disorders) was identified at a molecular diagnostic laboratory[16] and also may reflect bias in recognition of genetic syndromes in minoritized populations and subsequent referral for testing - where white patients might have had testing for a milder phenotype. We found that children from families with limited English proficiency were older at diagnosis, suggesting a delay in referral and supporting our conclusion that a major disparity in identifying a genetic diagnosis relates to access to a genetics clinic. Additionally, many of the Arabic-speaking families were from communities with higher rates of consanguinity and may be at higher risk for recessive conditions, although de novo dominant conditions are still frequently identified in these populations[30]. It is difficult, however, to draw conclusions regarding language and the likelihood of a diagnosis from a biological standpoint, as both Spanish-speaking and Arabic-speaking families represent diverse ethnic identities and ancestral backgrounds. Shared language was not intended to serve as a proxy for shared ancestry in our stud, rather, we considered limited English proficiency as a potential barrier in access to care.

Though we were unable to evaluate the impact of structural racism on identification of a genetic diagnosis within our cohort due to lack of data within our EHR, prior work has shown that white individuals are concentrated in neighborhoods with higher levels of childhood opportunity, while those who are Black or Hispanic are concentrated in neighborhoods of lower childhood opportunity, a phenomenon known as "opportunity hoarding".[31] We found a negative association between COI quintile and clinic attendance suggesting a possible racial and ethnic bias in referral for which COI might be a proxy. A distinct, though somewhat related, issue relates to genetic ancestry, where interpretation of variants of uncertain significance may be more challenging in populations that are poorly represented in genetic reference databases.[16] We did not detect significant differences in diagnostic yield related to self-reported ancestry in our study. Many rare diseases are caused by de novo variants, and thus, determination of the pathogenicity of these variants may not be as reliant upon population reference databases as are inherited variants such as those

seen in genes related to cancer predisposition or cardiomyopathy or evaluation of complex traits, where lack of diversity in population databases makes diagnosis challenging.[16,19,22,32] While we support diversification of reference databases, our results suggest that directing resources towards addressing referral bias and providing support for patients to attend clinic is equally important, albeit not unique to genetics as a subspecialty.

Limitations to our study include the observational nature and sample size, and that this analysis represents the workflow within a single academic institution. Though our overall cohort was large, the proportion diagnosed was smaller and presented challenges to analysis adjusting for multiple factors such as language, reason for visit, and COI. We were also unable to elaborate on inequities in referral patterns due to the study design, thus future analyses are needed in order to explore the outcomes for patients who did not attend their clinic visit. Due to the timeframe of the study, we were also unable to evaluate the impact of telehealth, though our data may provide a helpful benchmark for future analyses of the landscape of outpatient genetics referrals incorporating such visits, which improve access if transportation to clinic is a major barrier, but not if other factors such as time off from work to attend a visit are the primary barriers. As telehealth practices were rapidly incorporated into our practice in 2020 and have evolved substantially since then, future research is needed to evaluate the impact of this change to clinic structure once enough time has passed to evaluate the telehealth diagnostic odyssey.

Overall, our results demonstrate significant variation in the genetic diagnostic odyssey related to sociodemographic characteristics and suggest that access to the genetics clinic is the most salient barrier to obtaining a diagnosis for children with rare disease. Our results represent a balance of many interacting features relating to detection of a genetic diagnosis, where this outcome depends on two important factors – whether or not the patient has an underlying diagnosis (unmeasurable, but potentially predictable), and whether or not testing was sent (measured in this study). Our patients with historically greater access to healthcare due to English language, insurance type, or higher neighborhood resources may have presenting phenotypes that were less extreme or severe and less likely to be genetic, leading to a lower yield. Conversely, those with limited English proficiency, public insurance, or lower neighborhood resources, may have had more extreme or severe phenotypes because of decreased access to healthcare and increased likelihood of missing a genetic phenotype in minoritized individuals, thus leading to a higher yield once they do present. The rise of exome sequencing availability, even during the study period, may impact access to a diagnosis, though this will be contingent upon equitable access to this test.[33] Our results suggest that improved engagement with primary care physicians and other providers responsible for outpatient genetics referrals would be helpful to address these disparities that we have identified, and that additional insight into the factors driving delayed or incomplete referrals is critical. Future studies incorporating implementation science and equity-focused quality improvement are needed to continue to explore issues of access within clinical genetics in order to identify and address inequities in care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

Data Availability:

To protect patient privacy, the dataset generated and analyzed during the current study may be available from the corresponding author on reasonable request contingent on a data use agreement.

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Impact:

- The resources required to identify a genetic diagnosis may impede access and exacerbate healthcare disparities leading to inequitable care.

- In an analysis of pediatric outpatient genetics referrals, we observed a significant association between neighborhood resources and clinic attendance but not diagnostic yield for those attending, and a higher diagnostic yield for families with limited English proficiency, suggesting referral bias for more severe phenotypes.

- Thus, the primary barrier to finding a genetic diagnosis was initiation of care, not the ensuing diagnostic odyssey.

- Further research efforts should be directed at increasing access to clinical genetics evaluations for children with rare disease.
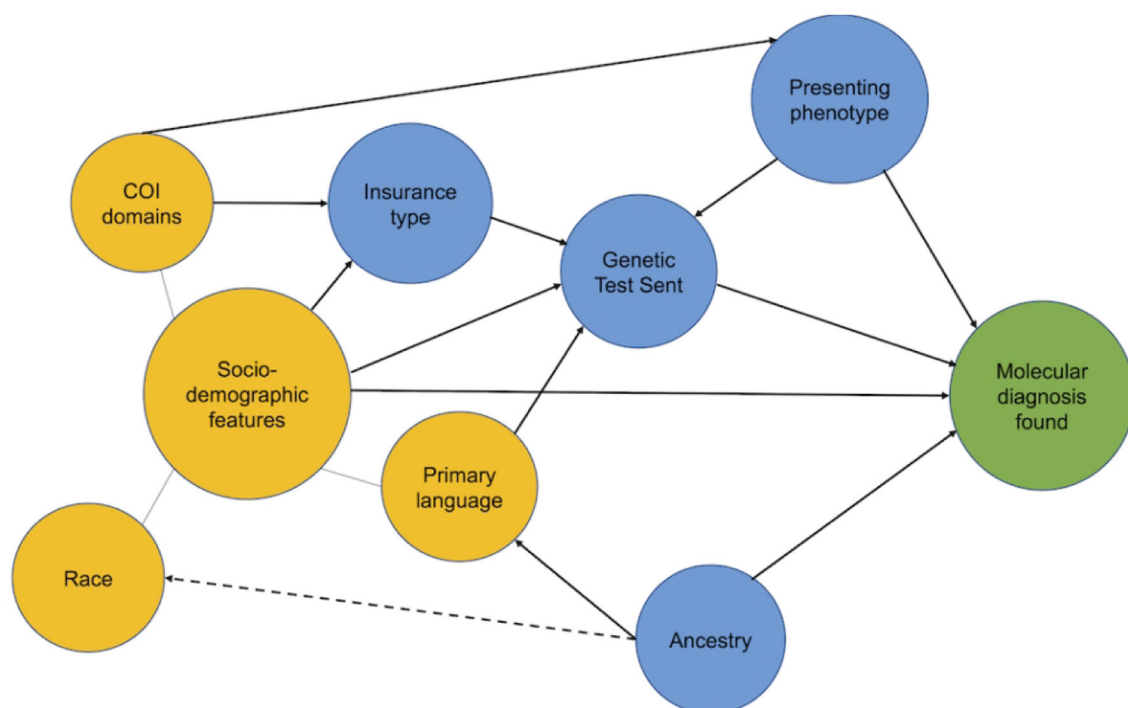
Figure 1. Conceptual model.

The relationship between various social determinants of health and the primary outcome of genetic diagnosis. Yellow circles indicate exposures analyzed as possible predictors of the outcome (green circle). Blue circles indicate possible confounders. The dashed arrow reflects that race is a social construct that may overlap with genetic ancestry.
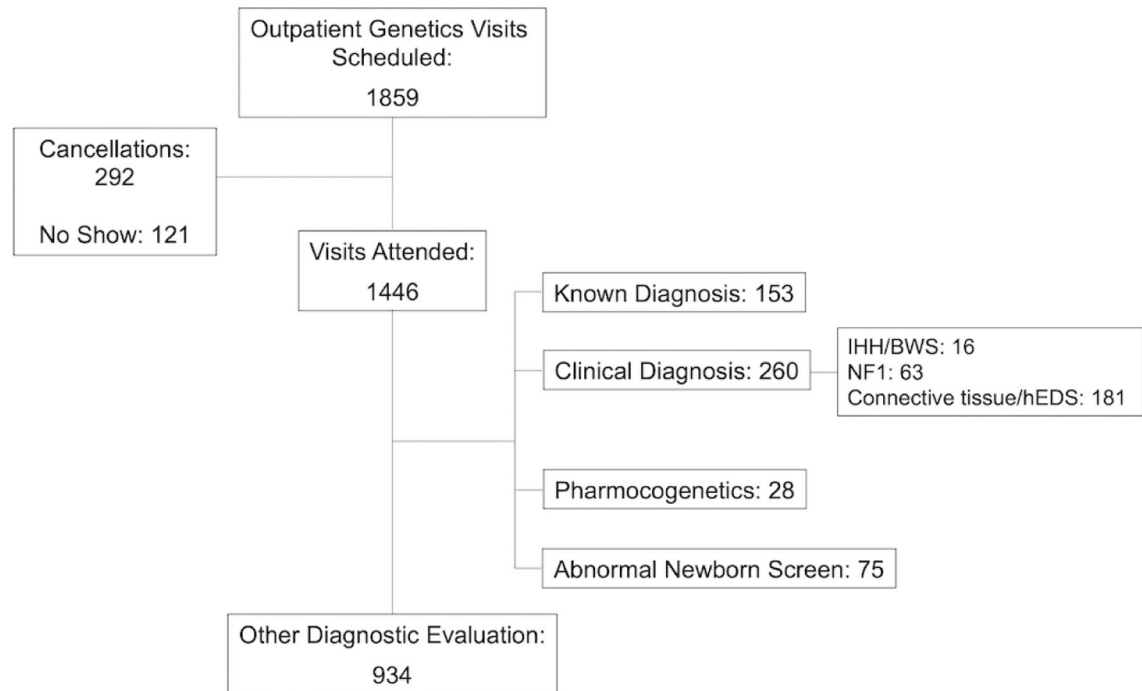
Figure 2. CONSORT-style diagram.
Of the attended visits, certain indications for genetics visit were excluded from further analysis (indications are not mutually exclusive, and individuals with one excluded diagnosis and one included diagnosis were included in the analysis). CONSORT, **Con**solidated **S**tandards **o**f **R**eporting **T**rials, IHH/BWS, isolated hemihyperplasia/Beckwidth-Wiedemann syndrome; NF1, Neurofibromatosis 1; hEDS, hypermobile Ehlers-Danlos syndrome.

Table 1.

Demographic features of genetics outpatients with initial clinic visit in 2017.

	N = 1859
Sex (female)	884 (47.6%)
In state	1379 (74.2%)
Race	
White	959 (50.5%)
Black	97 (5.2%)
Asian/Pacific Islander	62 (3.4%)
Native American	6 (0.3%)
Other	274 (14.7%)
Unknown	482 (25.9%)
Language	
English	1594 (85.7%)
Spanish	109 (5.9%)
Arabic	87 (4.7%)
Other [a]	69 (3.7%)
Insurance Plan	
Private	1132 (60.9%)
Public	622 (33.5%)
International	74 (4.0%)
Self-pay	27 (1.5%)
Unknown	4 (0.2%)
COI Overall	N = 1682
Very low	290 (17.2%)
Low	285 (17.0%)
Moderate	308 (18.3%)
High	377 (22.4%)
Very High	421 (25.0%)

COI, childhood opportunity index, state-normalized data. a) Other languages included Albanian (2), Cape Verde Creole (6), Chinese (10), Haitian Creole (7), Hindi (1), Indian (1), Italian (1), Korean (1), Polish (1), Portuguese (16), Russian (7), Sign Language (6), Somalian (5), Urdu (1), Vietnamese (3), unspecified (1). Further details on "Other" race are generally not available in our electronic medical record.

Table 2.

Relationship between socio-demographic features and clinic attendance.

	Attended N = 1446	Cancelled N = 292	No Show N = 121	*p*
Female sex	681 (47.1%)	151 (51.7%)	52 (43.0%)	0.21
In state	1093 (75.6%)	184 (63.0%)	102 (84.3%)	<0.001
Language				0.03
English	1247 (86.2%)	249 (85.3%)	98 (81.0%)	
Spanish	81 (5.6%)	14 (4.8%)	14 (11.6%)	
Arabic	66 (4.6%)	19 (6.5%)	2 (1.7%)	
Other	52 (3.6%)	10 (3.4%)	7 (5.8%)	
Insurance Plan				<0.001
Private	912 (63.1%)	181 (62.2%)	39 (32.8%)	
Public	453 (31.3%)	91 (31.3%)	78 (65.5%)	
International	58 (4.0%)	14 (4.8%)	2 (1.7%)	
Self-pay	22 (1.5%)	5 (1.7%)	0 (0%)	
Unknown	1 (0.1%)	1 (0.3%)	2 (1.7%)	
COI Overall	N = 1304	N = 263	N = 114	<0.001
Very low	207 (15.9%)	43 (16.3%)	40 (35.1%)	
Low	206 (15.8%)	51 (19.4%)	28 (24.6%)	
Moderate	252 (19.3%)	44 (16.7%)	12 (10.5%)	
High	310 (23.8%)	49 (18.6%)	19 (16.7%)	
Very High	329 (25.2%)	76 (28.9%)	15 (13.2%)	

COI, Childhood Opportunity Index (state-normalized data). Patients with cancellations or no shows that then rescheduled and attended in 2017 were counted as attended visits with the date of the first attended visit used as the index date

Table 3.

Demographic and clinical predictors of a genetic diagnosis

	Total 934	Diagnosis Found 176	No Diagnosis 758	p
Female sex	402 (43.0%)	80 (45.5%)	322 (42.5%)	0.50
Age at first clinic visit, years (median, IQR)	3.1 (0.9–7.8)	2.1 (0.5–7.4)	3.4 (1.1–7.8)	0.003
In state	706 (75.6%)	129 (73.3%)	577 (76.1%)	0.44
Ancestry				
African continent	69 (7.4%)	12 (6.8%)	57 (7.5%)	0.87
Asia/Pacific Islands	70 (7.5%)	17 (9.7%)	53 (7.0%)	0.26
Middle East	91 (9.8%)	23 (13.1%)	68 (9.0%)	0.12
Latin America	179 (19.2%)	36 (20.5%)	143 (18.9%)	0.67
North America	180 (19.3%)	34 (19.3%)	146 (19.3%)	>0.99
Europe	522 (55.9%)	95 (54.0%)	427 (56.3%)	0.61
Unknown	130 (13.9%)	21 (11.9%)	109 (14.4%)	0.47
Language				0.04
English	789 (84.4%)	139 (79.0%)	650 (85.8%)	
Spanish	55 (5.9%)	15 (8.5%)	40 (5.3%)	
Arabic	56 (6.0%)	17 (9.7%)	39 (5.2%)	
Other	34 (3.7%)	5 (2.8%)	29 (3.9%)	
Insurance Plan				0.58
Private	551 (59.0%)	96 (54.5%)	455 (60.0%)	
Public	319 (34.2%)	67 (38.1%)	252 (33.2%)	
International	47 (5.1%)	9 (5.1%)	38 (5.0%)	
Self-pay	17 (1.8%)	4 (2.3%)	13 (1.7%)	
Overall COI Level	N = 830	N = 157	N = 673	0.34
Very low	146 (17.7%)	26 (16.6%)	120 (18.0%)	
Low	127 (15.3%)	31 (19.7%)	96 (14.3%)	
Moderate	145 (17.5%)	30 (19.1%)	115 (17.1%)	
High	207 (25.0%)	32 (20.4%)	175 (26.0%)	
Very High	205 (24.7%)	38 (24.2%)	167 (24.8%)	
Reason for visit				
DD/ID	283 (30.3%)	59/283 (21.0%)	224/283 (79.2%)	0.32
Autism	149 (16.0%)	11/149 (7.4%)	138/149 (92.6%)	<0.001
Congenital anomalies	231 (24.7%)	45/231 (19.5%)	186/231 (80.5%)	0.77
Neurologic	199 (21.3%)	42/199 (21.1%)	157/199 (78.9%)	0.36
Metabolic disease	129 (13.8%)	18/129 (14.0%)	111/129 (86.0%)	0.15
Other	305 (32.7%)	81/305 (26.6%)	224/305 (73.4%)	<0.001
Genetic testing recommended at first visit	318 (34.0%)	77 (44.0%)	241 (31.8%)	0.003
Type of test				
Karyotype	43 (4.6%)	12 (6.8%)	31 (4.1%)	0.16
CMA	187 (20.0%)	31 (17.6%)	156 (20.6%)	0.40
Single gene	50 (5.4%)	23 (13.1%)	27 (3.6%)	<0.001

	Total 934	Diagnosis Found 176	No Diagnosis 758	*p*
Gene panel	88 (9.5%)	21 (11.9%)	67 (8.9%)	0.25
Exome sequencing	13 (1.4%)	2 (15.4%)	11 (84.6%)	>0.99
Fragile X	75 (8.0%)	6 (3.4%)	69 (9.1%)	0.01

IQR, interquartile range; DD/ID, developmental delay or intellectual disability; CMA, chromosomal microarray.

Table 4.

Multivariate model: the effect of multiple predictors on diagnosed status:

Exposure		Unadjusted Odds Ratio (95% C.I.)	*p*	Adjusted Odds Ratio (95% C.I.)	*p*
Primary language					
	English	(ref)		(ref)	
	Spanish	1.8 (0.9–3.3)	0.08	2.3 (1.2–4.5)	0.01
	Arabic	2.0 (1.1–3.7)	0.02	1.9 (1.0–3.5)	0.05
	Other	0.8 (0.3–2.1)	0.66	0.9 (0.3–2.3)	0.79
Age, years*		0.8 (0.8–0.9)	0.001	0.8 (0.7–0.9)	0.001
Insurance	Private	(ref)		n/a	
	Public	1.3 (0.9–1.8)	0.19		
	International or self-pay	1.2 (0.6–2.3)	0.57		
COI levels				n/a	
	Very low	(ref)			
	Low	1.5 (0.8–2.7)	0.18		
	Moderate	1.2 (0.7–2.2)	0.53		
	High	0.8 (0.5–1.5)	0.56		
	Very high	1.1 (0.6–1.8)	0.86		
Reason for visit:					
	DD/ID	1.2 (0.8–1.7)	0.30	1.8 (1.2–2.7)	0.008
	Autism	0.3 (0.2–0.6)	<0.001	0.4 (0.2–0.8)	0.008
	Congenital anomalies	1.1 (0.7–1.5)	0.78	1.1 (0.7–1.7)	0.69
	Neurologic	1.2 (0.8–1.8)	0.36	1.3 (0.8–2.0)	0.23
	Metabolic disease	0.7 (0.4–1.1)	0.13	1.0 (0.5–1.9)	>0.99
	Other	2.0 (1.5–2.8)	<0.001	2.3 (1.5–3.6)	<0.001

COI, Childhood Opportunity Index, DD/ID, developmental delay or intellectual disability.

*
Log-transformed.