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Association of No-Cost Genetic Testing Program Implementation and Patient Characteristics With Access to Genetic Testing for Inherited Retinal Degenerations

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IMPORTANCE The benefits of no-cost genetic testing initiatives have not been characterized. The no-cost My Retina Tracker Genetic Testing Study (MRT-GTS) research registry for inherited retinal degenerations (IRDs) was launched in 2017 in the US.

OBJECTIVE To investigate the associations of MRT-GTS implementation and patient characteristics with access to genetic testing for IRDs.

DESIGN, SETTING, AND PARTICIPANTS In a cross-sectional design, analysis of new patients evaluated 12 months before (July 1, 2016, to June 13, 2017) and 12 months after (June 14, 2017, to June 30, 2018) MRT-GTS implementation at a single academic referral eye center was conducted. Participants included 369 patients with IRD. Data analysis was conducted from February to June 2020.

MAIN OUTCOMES AND MEASURES Change in rates of successfully obtaining genetic testing, odds ratios (ORs) of association between patient characteristics and obtaining testing, and days elapsed from clinic visit to reporting of results.

RESULTS Among 369 patients (mean [SD] age, 39.5 [20.8] years; 193 [52.3%] women), 144 were evaluated in the pre–MRT-GTS period and 225 in the post–MRT-GTS period. The baseline rate of successfully obtaining testing was 51.4% (95% CI, 42.6%-60.2%). The initiation of MRT-GTS was associated with a 28.9-percentage point increase in testing rate (95% CI, 16.7%-41.1%; $P < .001$). Patient characteristics that increased the odds of obtaining testing were eligibility for MRT-GTS (OR, 14.15; 95% CI, 7.36-27.24; $P < .001$) and worse visual acuity (logMAR +1.0; Snellen equivalent decrease from 20/20 to 20/200) in the better-seeing eye (OR, 1.92; 95% CI, 1.27-2.91; $P < .01$). Patients had decreased odds when identifying as Black or African American (OR, 0.10; 95% CI, 0.04-0.24; $P < .001$) or other race (OR, 0.37; 95% CI, 0.15-0.91; $P = .03$) compared with White race, and when the primary language was not English (OR, 0.13; 95% CI, 0.03-0.55; $P < .01$). The proportion of test results reported within 90 days was 81.5% (95% CI, 74.8%-86.4%) when eligible for MRT-GTS compared with 48.1% (95% CI, 35.6%-58.1%) when not eligible ($P < .001$).

CONCLUSIONS AND RELEVANCE In this study, the implementation of MRT-GTS was associated with an increase in the proportion of patients who successfully obtained testing, suggesting the potential clinical value of this approach. Patient-level demographic and clinical factors appear to be associated with decisions to pursue testing.

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Supplemental content

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Inherited retinal degenerations (IRDs) are a clinically and genetically heterogeneous group of visually debilitating disorders affecting more than 200 000 individuals in the US and millions worldwide.[1] Clinical genetic testing is an integral part of providing care for individuals with IRDs, giving a specific molecular diagnosis.[2,3] Testing may also provide relatives or prospective parents with actionable prognostic information and identify novel genetic variants to advance disease understanding.[4] In addition, testing allows access to clinical trials. Except for Leber congenital amaurosis caused by pathogenic variants in *RPE65*, treatments addressing the genetic cause of disease have not yet been developed.[5] Genetic testing is required for individuals to enroll in numerous clinical trials, including those for Stargardt disease (*ABCA4*), X-linked retinitis pigmentosa (*RPGR*), retinitis pigmentosa and Usher syndrome type 2 (*USH2A*), achromatopsia (*CNGA3* and *CNGB3*), and choroideremia (*CHM*).

Despite the importance of obtaining a molecular diagnosis, access to genetic testing is not available to all patients. In the US, health insurance coverage for testing varies by insurance carrier, and sometimes even among patients with the same carrier.[6] In general, policies require proof of clinical validity, an individual with symptoms or at risk of developing them, and evidence of effect on medical management.[7] The criterion regarding medical management is often contested and frequently requires insurance before authorization or appeal. The cost of next-generation sequencing (NGS) has decreased substantially,[8] but commercial pricing ranges from $250 to $2500 depending on the laboratory and test ordered. Prices remain prohibitive for many patients when testing is not covered by insurance.

To address issues of access to genetic testing, the Foundation Fighting Blindness launched the My Retina Tracker Genetic Testing Study (MRT-GTS) in 2017. The MRT-GTS allows patients to receive fully subsidized testing when enrolled in the MRT registry.[9] Through MRT-GTS, genetic testing and genetic counseling services became available at no charge to patients in the US. In the year leading up to launch of the study, testing in the IRD clinic was most commonly obtained through insurance preauthorization or out-of-pocket payment. We examined the association of MRT-GTS launch with rates of genetic testing for patients evaluated at our institution and the association of patient characteristics with odds of successfully obtaining genetic testing.

Key Points

Question Does a no-cost research registry for clinical genetic testing (the Foundation Fighting Blindness My Retina Tracker Genetic Testing Study [MRT-GTS]) increase access to testing, and are patient characteristics associated with the odds of obtaining testing?

Findings In this cross-sectional study including 369 patients with inherited retinal degeneration, analysis before and after initiation of the MRT-GTS found higher rates of patients successfully obtaining genetic testing in the post–MRT-GTS period. Eligibility for MRT-GTS and worse visual acuity were associated with increased odds of testing; Black or African American race and non–English-preferred language were associated with decreased odds of testing.

Meaning No-cost mechanisms may significantly increase patient access to testing, and patient characteristics appear to affect the odds of obtaining testing.

Methods

The MRT-GTS became available to our IRD clinic in June 2017. Therefore, retrospective medical records review included the 24 months from July 1, 2016, through June 30, 2018. The length of time was chosen to control for possible seasonal trends.[10] Data analysis was conducted from February to June 2020.

This study adhered to the tenets of the Declaration of Helsinki.[11] The MRT-GTS study and this retrospective medical records review were approved by the University of Michigan Institutional Review Board. Because the present study was a retrospective medical records review, the requirement for patient consent for study participation was reviewed and waived by the institutional review board. No compensation or incentives were offered to participants. We maintained only the components of patient data necessary for data analysis. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cross-sectional studies.

Medical records review included new patients evaluated by an expert in IRDs (including A.T.F. and K.T.J.) and determined to have a clinical presentation consistent with an IRD. Comprehensive evaluation consisted of family pedigree obtained by a genetic counselor (K.B. or D.S.), clinical examination, electroretinogram, Goldmann visual field testing, fundus photography, fundus autofluorescence, and macular optical coherence tomography. After clinical diagnosis, patients met with a genetic counselor to discuss testing options. During the study period, the same physicians and genetic counselors evaluated and counseled patients. Return visit patients were not included, even if they had not previously obtained genetic testing. We excluded 165 patients who were determined not to have an IRD, 83 patients with previous testing, 37 patients who declined to speak with a genetic counselor, 6 patients with syndromic features referred to medical genetics, and 3 patients unable to consent to genetic testing. Characteristics of patients who declined to speak with a genetic counselor and were excluded are presented in eTable 1 in the Supplement.

In the pre–MRT-GTS period, patients were offered the options of waiting for insurance preauthorization or proceeding with immediate testing with the understanding that if insurance declined coverage, out-of-pocket payment would be required. In the post–MRT-GTS period, eligible patients were offered enrollment in MRT-GTS in addition to established options. Patients were eligible if the clinical diagnosis was consistent with an IRD eligible for enrollment and if genetic testing had not been previously performed. For individuals whose preferred language was not English, in-person or phone interpreters were used. However, local institutional review board

Table 1. Demographic and Clinical Characteristics

Characteristic	No. (%)		P value
	Pre-MRT-GTS (n = 144)	Post-MRT-GTS (n = 225)	
Age, mean (SD), y	37.4 (20.9)	40.9 (20.7)	.11
logMAR visual acuity, mean (SD)			
OD	0.74 (0.86)	0.81 (0.85)	.46
OS	0.72 (0.90)	0.80 (0.83)	.41
Severe visual field constriction	72 (50.0)	112 (49.8)	.97
Sex			
Female	76 (52.8)	117 (52.0)	.88
Male	68 (47.2)	108 (48.0)	
Primary language			
English	138 (95.8)	215 (95.6)	.90
Married	58 (40.3)	68 (30.2)	.051
Race			
White	120 (83.3)	169 (75.1)	.054
Black or African American	11 (7.6)	31 (13.8)	.06
Other	13 (9.0)	25 (11.1)	.51
Primary insurance			
Private	77 (53.5)	108 (48.0)	.31
Medicare	36 (25.0)	61 (27.1)	.65
Medicaid	25 (17.4)	47 (20.9)	.40
No insurance	6 (4.2)	9 (4.0)	.55
Eligible for MRT-GTS	NA	205 (91.1)	

Abbreviations: MRT-GTS, My Retina Tracker Genetic Testing Study; NA, not applicable.

regulations required that informed consent for MRT-GTS be obtained by a language-concordant health care professional, so patients with a preferred language other than English were not eligible for MRT-GTS despite the presence of an interpreter. These patients were still offered testing options available to patients in the pre-MRT-GTS period: waiting for insurance preauthorization or proceeding with immediate testing. We included these patients in the retrospective review. The Foundation Fighting Blindness partnered with Blueprint Genetics (Helsinki, Finland) to conduct testing through a 181-gene panel, which had expanded to 266 genes by the end of the study period. Blueprint Genetics is a Clinical Laboratory Improvement Amendments-certified company providing clinical-grade NGS assays able to detect single nucleotide variants, insertions, deletions, indels, copy number variants, and microdeletions or microduplications, including intronic variants in *ABCA4* and several other genes. After informed consent was obtained, saliva or blood samples were collected. Patients were defined as having successfully obtained genetic testing if a result was recorded in the patient's medical record. If testing was not obtained, the reason was documented. If no specific reason could be identified, the reason was listed as loss to follow-up.

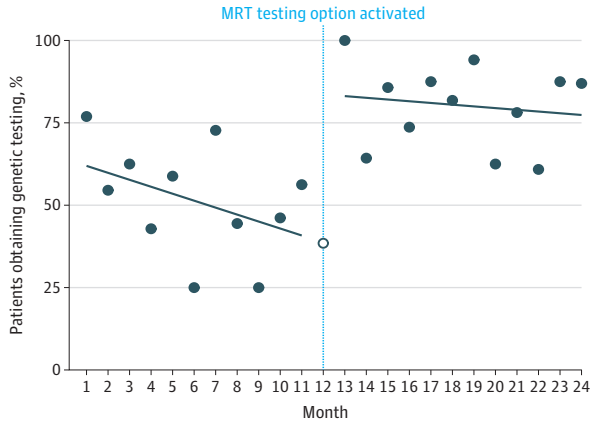
Statistical Analysis

To assess the association of MRT-GTS with rates of successfully obtaining testing, segmented regression analysis was performed using the method of Wagner et al.[10] Testing data from the month of implementation (June 2017) were excluded from analysis. Multivariate logistic regression was used to investigate the association between patient characteristics and the probability of obtaining genetic testing. Cumulative incidence analysis was used to evaluate the time elapsed between initial clinic visit and the date that a result was reported. An ideal clinical genetic test would have rapid turnaround time, allowing patients to receive a confirmatory molecular diagnosis soon after clinical diagnosis.[12] We defined time to test result reporting as the number of days elapsed between the initial clinic visit and reporting of test results by the genetic testing laboratory, including various real-world delays, such as deferred decisions to pursue genetic testing, clinic revisits to further discuss testing, and genetic testing kits obtained in the clinic and mailed from the patient's home. Statistical analyses were performed using R, version 3.6.3 (The R Foundation for Statistical Computing). Results were considered significant at $P < .05$, and all statistical tests were 2-sided.

Results

Among 369 patients who met the inclusion criteria, 144 were evaluated in the pre-MRT-GTS period from July 1, 2016, to June 13, 2017, and 225 were evaluated in the post-MRT-GTS period from June 14, 2017, to June 30, 2018. Mean (SD) age was 39.5 (20.8) years, 193 participants (52.3%) were women, and 176 (47.7%) were men. More patients were evaluated in the post-launch period because of increased patient volume. Summary characteristics are presented in **Table 1**. Age, sex, preferred language, marital status, race, and primary health insurance coverage were similar between the prelaunch and

Figure 1. Interrupted Time Series Segmented Regression Analysis of the My Retina Tracker Genetic Testing Study (MRT-GTS) Pre- and Postlaunch Including the 24 Months From July 2016 to June 2018



Broken blue line indicates the launch of MRT-GTS, which became available locally in June 2017 (open circle), a month excluded from the regression period.

Table 2. Segmented Regression Model Analysis of MRT-GTS

Model	Genetic testing obtained, % (95% CI)	*P* value
Full model		
Baseline level (intercept)	64.1 (45.5 to 82.7)	<.001
Baseline trend	−2.1 (−4.8 to 0.6)	.15
Postlaunch change	44.9 (19.2 to 70.6)	.003
Postlaunch trend	1.6 (−2.1 to 5.3)	.40
Parsimonious model		
Baseline level (intercept)	51.4 (42.6 to 60.2)	<.001
Postlaunch change	28.9 (16.7 to 41.1)	<.001

Abbreviation: MRT-GTS, My Retina Tracker Genetic Testing Study.

postlaunch groups, as were visual acuity and proportion of patients with severe visual field constriction (defined as constriction of the III4e isopter on Goldmann visual field to the central 20° or less in both eyes). In the postlaunch period, 205 of 225 patients (91.1%) were eligible for MRT-GTS. The most common reasons for ineligibility were clinical diagnosis with an IRD ineligible for MRT-GTS (13 patients) or preferred language other than English (3 patients). eTable 2 in the Supplement lists the reasons genetic testing was not obtained. In the prelaunch period, the most common reason was insurance denial of preauthorization in 29 of 70 patients (41.4%), followed by loss to follow-up in 21 of 70 patients (30.0%). In the postlaunch period, the most commonly listed reasons were loss to follow-up in 27 of 44 patients (61.4%) and no interest in genetic testing in 7 of 44 patients (15.9%). Two patients declined MRT-GTS owing to concerns regarding privacy of personal information in a research study. One patient subsequently chose to participate in MRT-GTS after receiving a denial of insurance preauthorization, and the other subsequently declined any testing.

The results of segmented regression of interrupted time series are shown in **Figure 1** and **Table 2**. Using the method of Wagner et al,[10] coefficients for prelaunch baseline level, prelaunch trend, postlaunch change, and postlaunch trend were calculated. No statistically significant prelaunch trend or postlaunch trend change was detected. In the parsimonious statistical model, the prelaunch level of successfully obtaining genetic testing was 51.4% (95% CI, 42.6%-60.2%; *P* < .001), and the postlaunch level change was an increase of 28.9% (95% CI, 16.7%-41.1%; *P* < .001). Which physicians evaluated the patient or which genetic counselors discussed testing were not found to be significant factors. No seasonal trend was observed. The month of June 2017 was excluded from the regression because the low genetic testing rate (5 of 13 [38.5%]) during that month could have been affected by awareness of the impending availability of MRT-GTS or the logistics of implementing a new genetic testing protocol.

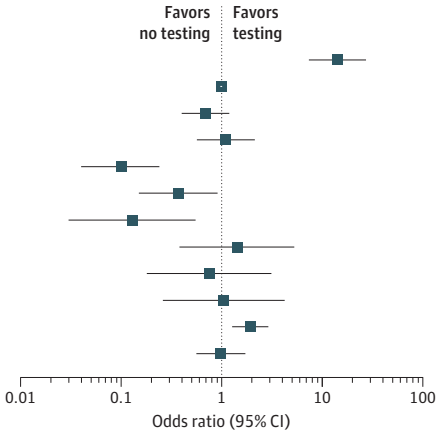
Associations between likelihood of successfully obtaining testing and patient demographic and clinical characteristics are shown in **Figure 2**. The most positively associated factor was eligibility for MRT-GTS, which significantly increased the odds of obtaining testing (OR, 14.15; 95% CI, 7.36-27.24; *P* < .001). Another factor associated with increased odds was worse visual acuity (logMAR +1.0; Snellen equivalent decrease from 20/20 to 20/200) in the better-seeing eye (OR, 1.92; 95% CI, 1.27-2.91; *P* < .01). Patients had decreased odds of obtaining testing when self-identifying as Black or African American (OR, 0.10; 95% CI, 0.04-0.24; *P* < .001) or other race (OR, 0.37; 95% CI, 0.15-0.91; *P* = .03). Patients also had lower odds of obtaining testing when the preferred language was not English (OR, 0.13; 95% CI, 0.03-0.55; *P* < .01). We found no association between the odds of obtaining testing and age, sex, marital status, type of health insurance coverage, or presence of severe visual field constriction. Characteristics of patients who successfully obtained genetic testing are reported in eTable 3 in the Supplement.

Cumulative incidence time analysis for patients who obtained genetic testing found a significant difference in time to test result reporting based on MRT-GTS eligibility (**Figure 3**). At 60 days, the proportion of patients with completed testing reports was 120 of 178 (67.4%; 95% CI, 59.8%-73.6%) in the MRT-GTS eligible group and 27 of 77 (35.1%; 95% CI, 23.5%-44.9%) in the noneligible group (*P* < .001). At 90 days, the proportion of patients with completed reports was 145 of 178 (81.5%; 95% CI, 74.8%-86.4%) in the eligible group and 37 of 77 (48.1%; 95% CI, 35.6%-58.1%) in the noneligible group (*P* < .001).

There was no statistically significant difference in the probability of a positive test result between the prelaunch (38 of 64 [59.4%]) and postlaunch (86 of 138 [62.3%]) groups (*P* = .81). A positive test result was defined as the finding of 1 or more pathogenic variants in a gene explaining the clinical phenotype for X-linked or autosomal-dominant disease, and 2 or more pathogenic variants explaining the clinical phenotype for autosomal-recessive disease. A total of 151 patients had positive results. During the study period, genetic diagnoses were made in 47 different genes. The most common molecular diagnoses were due to pathogenic variants in *ABCA4* (n = 29), *USH2A* (n = 17), *RPGR* (n = 13), *RHO* (n = 9), *CRB1* (n = 6), *BEST1* (n = 5),

Figure 2. Patient Characteristics Independently Associated With Odds of Successfully Obtaining Genetic Testing

Variable	Odds ratio (95% CI)
Eligible for MRT-GTS	14.15 (7.36-27.24)
Age	0.99 (0.97-1.01)
Male	0.69 (0.40-1.19)
Married	1.10 (0.57-2.15)
African American	0.10 (0.04-0.24)
Other race	0.37 (0.15-0.91)
English not preferred language	0.13 (0.03-0.55)
Private insurance	1.42 (0.38-5.27)
Medicare	0.75 (0.18-3.12)
Medicaid	1.05 (0.26-4.23)
logMAR +1.0 in better-seeing eye	1.92 (1.27-2.91)
Severe visual field constriction	0.98 (0.56-1.72)



For individuals of African American and other races, odds ratios are reported in relation to those of the White race. For private insurance, Medicare, and Medicaid, odds ratios are reported in relation to no insurance. For logMAR +1.0 value, the Snellen equivalent decrease is from 20/20 to 20/200. MRT-GTS indicates My Retina Tracker Genetic Testing Study.

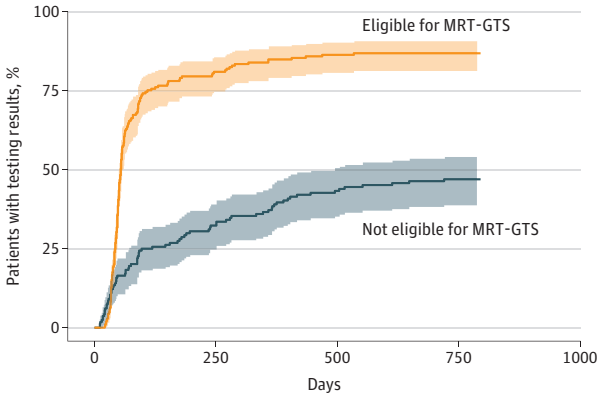
RS1 (n = 4), *RP2* (n = 4), and *PRPH2* (n = 4). Of the patients diagnosed during this time period, 11 were enrolled in research studies or clinical trials and an additional 2 patients were treated with an approved gene therapy, voretigene neparvovec-rzyl.[5]

Discussion

This study showed an association between implementation of a no-cost genetic testing program and access to genetic testing. Implementation of MRT-GTS was followed by a substantial and sustained increase in the rates of successfully obtaining testing. In addition, this study identified patient characteristics affecting the likelihood of obtaining testing, with individuals who identified as Black or African American or other race and those whose preferred language was not English having decreased odds of testing. These findings suggest the potential role of programs such as MRT-GTS in increasing access to testing for patients with genetic diseases and highlight how decisions to undergo testing are influenced by systems and individual factors.

Increasing access to genetic testing is important for developing new therapies. Molecular confirmation of the clinical diagnosis advances knowledge and identifies individuals eligible for clinical trials. Our results demonstrated that a successful partnership between a nonprofit organization (Foundation Fighting Blindness) and a commercial clinical laboratory (Blueprint Genetics) increased access to testing and decreased turnaround time. Interest in testing was similar in the prelaunch and postlaunch periods, suggesting that the main mechanism by which MRT-GTS increased access to testing was by subsidizing costs. In 2007, Stone[12] proposed that an ideal clinical test for IRDs should cost less than $500, have a greater than 50% chance of producing a clinically meaningful result, produce a clear and standardized report, and have a turnaround time of 8 weeks or less. Between 2006 and 2015, the National Institutes of Health provided no-cost testing through the National Ophthalmic Disease Genotyping Network (eyeGENE).[13] However, turnaround times for eyeGENE ranged

Figure 3. Cumulative Incidence Analysis Comparing the Time From Initial Clinic Visit to Laboratory Reporting of Genetic Test Results for All Study Patients, Stratified by Eligibility for My Retina Tracker Genetic Testing Study (MRT-GTS)



Shaded areas represent 95% CIs.

from 4 months to several years. In 2016, Spark Therapeutics briefly sponsored a no-cost testing initiative called ID Your IRD.[14] At one academic medical center, 48 of 66 (73%) patients consented to testing through the ID Your IRD 31-gene panel. The initiative was limited by the number of genes tested and low yield of 12 of 48 (25%) patients testing positive for a disease-causing genotype. Our data showed that MRT-GTS was associated with an increased proportion of patients with completed test reports at 60 and 90 days. There were insufficient data to determine which specific factors were associated with an increased time to result reporting or whether an association existed between insurance denial of preauthorization and the rates of obtaining testing. MRT-GTS provided a separate research-based mechanism for genetic testing, bypassing potential insurance-related issues.

Patient characteristics appeared to affect the odds of obtaining genetic testing. We observed decreased odds of testing for IRDs in Black or African American individuals. Decreased rates of testing among Black or African American

patients have been described in cancer genetics. Armstrong et al[15] reported that African American women at risk for inherited breast and ovarian cancer had lower rates of attending genetic counseling appointments and subsequently testing for *BRCA1/BRCA2*. McDonald et al[16] surveyed African American adults and found that the main barriers to participation in cancer genetics research were distrust of researchers' motives and concerns about exploitation. Substantial ophthalmic health disparities also exist for African American individuals for cataract, glaucoma, and diabetic retinopathy.[17-19] In addition, we found decreased odds of testing for individuals identifying as other race and those whose preferred language was not English. Health and eye care disparities have been reported to exist for immigrant populations.[20,21] Another possibility is that benefits of genetic testing could not be adequately communicated to patients through in-person or phone interpreters. Non-English-speaking patients at our institution were ineligible for MRT-GTS owing to regulations. Future implementation of additional mechanisms to enroll non–English-speaking patients would help address existing inequalities in insurance coverage and access to health services for this demographic. The reasons for decreased odds of testing in these groups warrant further investigation. These findings are concerning because individuals who do not obtain testing become disadvantaged in 2 ways: foregoing information that could help determine risk to family members or future children and missing opportunities to participate in clinical trials.

We found an association between increased odds of obtaining genetic testing and increase in logMAR visual acuity, suggesting that individuals with worse vision are more likely to obtain testing. This association was weak compared with other factors. We hypothesize that individuals with worse vision might be motivated to seek a molecular diagnosis that could allow enrollment in clinical trials. Health state utility values have previously been associated with visual acuity in the better-seeing eye.[22] We found no association with age, sex, marital status, type of health insurance coverage, or presence of severe visual field constriction.

Rates of positive testing were similar in the prelaunch and postlaunch periods. Testing through MRT-GTS returned a result explaining the retinal disease phenotype in 86 of 138 (62%) of individuals, similar to reported diagnostic yields in the literature. For example, Ellingford et al[23] reported a yield of 51% using a 105-gene NGS panel on 537 patients and Consugar et al[24] document a 51% yield using a 257-gene NGS panel on 192 patients. Stone et al[25] reported a 76% yield using a tiered testing strategy for 1000 patients. Two possible advantages of the nontiered NGS approach are that less time is needed to reach a molecular diagnosis and high-quality results can be generated by the laboratory independent of guidance from an expert ordering clinician. However, we caution that any form of genetic testing should be ordered by a clinician or genetic counselor who is adequately prepared to interpret testing reports and provide counseling.

Limitations

This study has limitations. The quasi-experimental design does not allow determination of causality. Accuracy of data are limited by the retrospective nature of the study. We caution against overinterpretation of reasons that genetic testing was not performed (eTable 2 in the Supplement) because patients who were lost to follow-up may have chosen to cease care for reasons not documented. To mitigate potential selection bias from loss to follow-up, patients lost to follow-up were included in the analysis as not having obtained testing. There were 37 patients excluded because of declining to speak with a genetic counselor, and it would be useful to understand why individuals would decline further discussion after receiving a clinical diagnosis. Some patient factors that might be associated with the odds of obtaining genetic testing, such as level of education and socioeconomic status, were not routinely documented. The data reflect findings from a single academic center in the suburban US, which may not be representative of other academic centers, especially those located in more rural or urban areas.

Conclusions

Results of this cross-sectional study suggest that a no-cost genetic testing program increases access to testing and that the positive association of the program with increased access to testing persisted. Increased access to testing may help patients receive more specific diagnoses, facilitate patient enrollment in clinical trials, and advance medical knowledge on disease-causing variants and genotype-phenotype correlations. Further research is needed to understand the barriers to testing in specific patient populations.

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Concept and design: Zhao, Schlegel, Fahim, Jayasundera.
Acquisition, analysis, or interpretation of data: Zhao, Branham, Fahim.
Drafting of the manuscript: Zhao.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Zhao.
Supervision: Branham, Fahim, Jayasundera.

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