Model for Integration of Monogenic Diabetes Diagnosis Into Routine Care: The Personalized Diabetes Medicine Program

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OBJECTIVE

To implement, disseminate, and evaluate a sustainable method for identifying, diagnosing, and promoting individualized therapy for monogenic diabetes.

RESEARCH DESIGN AND METHODS

Patients were recruited into the implementation study through a screening questionnaire completed in the waiting room or through the patient portal, physician recognition, or self-referral. Patients suspected of having monogenic diabetes based on the processing of their questionnaire and other data through an algorithm underwent next-generation sequencing for 40 genes implicated in monogenic diabetes and related conditions.

RESULTS

Three hundred thirteen probands with suspected monogenic diabetes (but most diagnosed with type 2 diabetes) were enrolled from October 2014 to January 2019. Sequencing identified 38 individuals with monogenic diabetes, with most variants found in *GCK* or *HNF1A*. Positivity rates for ascertainment methods were 3.1% for clinic screening, 5.3% for electronic health record portal screening, 16.5% for physician recognition, and 32.4% for self-referral. The algorithmic criterion of non–type 1 diabetes before age 30 years had an overall positivity rate of 15.0%.

CONCLUSIONS

We successfully modeled the efficient incorporation of monogenic diabetes diagnosis into the diabetes care setting, using multiple strategies to screen and identify a subpopulation with a 12.1% prevalence of monogenic diabetes by molecular testing. Self-referral was particularly efficient (32% prevalence), suggesting that educating the lay public in addition to clinicians may be the most effective way to increase the diagnosis rate in monogenic diabetes. Scaling up this model will assure access to diagnosis and customized treatment among those with monogenic diabetes and, more broadly, access to personalized medicine across disease areas.

At least 0.4% of diabetes cases (and up to 6% in young people) are monogenic, caused by a highly penetrant variant in a single gene (1,2), which amounts to >100,000 individuals in the U.S. alone. Broadly, monogenic or highly penetrant single-gene diabetes encompasses maturity-onset diabetes of the young (MODY), neonatal diabetes, and syndromic forms (3). Substantial phenotypic overlap between

monogenic forms of diabetes and the more common forms of diabetes can make diagnosis based on clinical characteristics difficult. Proper diagnosis is important, because distinguishing monogenic diabetes from type 1 diabetes (T1D) or type 2 diabetes (T2D) often directly leads to more effective and less invasive treatment, most notably sulfonylureas instead of insulin for *HNF1A*, *HNF4A*, *KCNJ11*, and *ABCC8* subtypes and no treatment for the *GCK* subtype, as well as more accurate prediction of prognosis and familial risk (4–7).

Most monogenic diabetes cases are missed and consequently may receive suboptimal treatment (8), in part because of the lack of a standard protocol for identifying individuals for testing and incorporating results into medical care. Guidelines are beginning to emerge, including those incorporated into the American Diabetes Association *Standards of Medical Care in Diabetes* (9) and the International Society of Pediatric and Adolescent Diabetes guidelines (1). However, the American Diabetes Association guideline is somewhat general and could benefit from evidence-based specific algorithmic guidance, and the International Society of Pediatric and Adolescent Diabetes guidelines do not focus on adults. These international guidelines do not take into account the complexities of the heterogeneous U.S. health care system with respect to third-party payer adjudication of genetic services and testing. With the growing availability of next-generation sequencing (NGS), several investigators in countries outside the U.S. have recently reported on systematic clinical approaches to identifying and diagnosing individuals with monogenic diabetes, including in France (10), Turkey (11), China (12), Switzerland (13), and the U.K. (14).

As part of the National Institutes of Health–funded IGNITE (Implementing Genomics in Practice) network (15), we set out to develop a comprehensive approach to address challenges in diagnosing monogenic diabetes in the U.S. by designing an implementation project, the Personalized Diabetes Medicine Program (PDMP), to systematically identify individuals likely to have monogenic diabetes among the general diabetes population, perform cost-effective molecular testing using a targeted NGS panel, disclose and incorporate results into the electronic health record (EHR), and evaluate the impact on patient care, clinical, and patient-reported outcomes. We present the results of our first research question regarding the feasibility and efficiency of systematic identification and diagnosis of patients with monogenic diabetes.

RESEARCH DESIGN AND METHODS

Sites

Patients were recruited from endocrinology clinics in four distinct settings: the University of Maryland Center for Diabetes and Endocrinology (UM-CDE) (a university medical center), the Baltimore Veterans Administration Medical Center (BVAMC), the Geisinger Health System (GHS) (an integrated health system), and Bay West Endocrinology Associates (a suburban private endocrinology practice).

Inclusion Criteria and Algorithmic Criteria

In stage 1, only patients suspected of having monogenic diabetes were enrolled. We administered a seven-item questionnaire (Supplementary Table 1) and used the responses to identify patients possibly meeting at least one of initially six and later seven criteria (Supplementary Table 2), which were based on previously published studies and guidelines (1,9,16) available at the outset of the study of criteria with a reasonably high likelihood of identifying an individual with a monogenic diabetes variant. The questionnaire items were designed to elicit simple information about diabetes type, age at diagnosis, obesity, family history, and extra pancreatic features a patient would be expected to know that could rule out or indicate possible consistency with the criteria. The EHRs of patients recruited from the main sites were reviewed under an institutional review board–approved Health Insurance Portability and Accountability Act of 1996 waiver for prior antibody and C-peptide measures to further assess consistency with criteria.

Patients identified as possibly eligible then provided consent and were further evaluated using self-reported medical and family history and, if needed, study-obtained diabetes autoantibodies and C-peptide measures to assess final eligibility for genetic testing (Supplementary Fig. 1). Eligibility criteria for sequencing included *1*) diagnosis of diabetes before age 1 year (1,17), *2*) T1D in both participant and parent or child (1), *3*) non-T1D diagnosis before age 30 years, including IA2 antibody negativity and C-peptide positivity, based on a previous report of 25% positive predictive value (PPV) (16), *4*) nonobesity and diagnosis of T2D by age 45 years and two relatives diagnosed with diabetes by age 50 years as a starting point to try to use adiposity and family history to identify potential MODY cases in the borderline age range (18), *5*) features consistent with monogenic diabetes syndromes, *6*) impaired fasting glucose during a current or previous pregnancy and nonoverweight status before pregnancy (added later) (19), and *7*) suspicion by patient or clinician of monogenic diabetes despite not strictly meeting the other six criteria, with the research team concurring after case review.

In stage 2, we modified the inclusion criteria (Supplementary Table 2) to include any patient with diabetes or persistent mild hyperglycemia as a pilot test of the sensitivity of the algorithm while still using the algorithm to track those who would have qualified for sequencing in stage 1 and those who would not (unselected group) (Supplementary Fig. 2). In analyzing the implementation study outcomes, we combined the individuals from stage 1 with the individuals from stage 2 who would have qualified for stage 1.

Recruitment

Patients were screened in the clinic waiting room and through the GHS patient portal using a simple questionnaire (Supplementary Table 1) with yes/no questions designed to identify red flags raising suspicion of monogenic diabetes as described above. Self-referral and physician recognition, which included physician referral at all sites and manual chart review at UM-CDE, were also used to identify potential cases. The study was designed to be a regional project focusing on four health care systems, but soon after the study begun, local providers who had heard about the study as well as patients nationwide started to contact the team staff. They learned about the PDMP from other patients who had participated in the study, social media groups, and media coverage of the study and then contacted the study research coordinator by telephone or e-mail to complete the screening questionnaire. Patients using

self-referral were required to provide physician notes/records or laboratory data to support their enrollment.

Study Visits

In patients being screened for entry into the study, informed consent and detailed medical history were obtained by a study coordinator, and a three-generation pedigree focusing on details of diabetes was obtained by a certified genetic counselor. Blood was collected for measurement of GAD65 antibodies, IA2 antibodies, and C-peptide (to further characterize the diabetes and rule out T1D) (Supplementary Fig. 1), for NGS, and for banking of serum, plasma, and DNA extraction in the Clinical Laboratory Improvement Amendments–certified and College of American Pathologists–accredited University of Maryland Translational Genomics Laboratory (TGL) for future clinical variant confirmation.

NGS

Research-grade NGS was performed on samples from patients chosen for testing in stage 1 and all patients in stage 2 using two platforms, the Ion Torrent Personal Genome Machine for the first 271 samples and the Ion Torrent Chef System/S5 sequencer for the remaining 185 samples. Sequencing of five randomly selected samples yielded consistent results on the two platforms. A custom gene panel was used including 795 amplicons covering the coding and flanking intronic regions of 40 genes implicated in monogenic diabetes or related conditions. The panel was designed by the research team to include *1*) all known MODY genes at the time the study was initiated (2012), *2*) genes most commonly implicated in monogenic diabetes, *3*) a selection of syndromic diabetes genes that might present as seemingly isolated diabetes, *4*) genes most commonly implicated in partial lipodystrophy, which also might present as seemingly isolated diabetes, *5*) genes implicated in hyperinsulinemic hypoglycemia, which might theoretically contain variants that could cause diabetes, and *6*) monogenic obesity genes that might present as early-onset familial T2D. The panel was not meant to be comprehensive beyond the MODY genes, and consideration of additional content to include was weighed against the base-pair limitation of the platform (Supplementary Table 3). We note that although additional monogenic diabetes genes implicated in a small number of cases have been identified since the panel was designed, the panel covers all genes in which the identification of a variant has a clear impact on medical management (*HNF1A*, *HNF4A*, *GCK*, *HNF1B*, *KCNJ11*, and *ABCC8*) and that still account for most cases of monogenic diabetes and all designated MODY genes except *APPL1*, which was first reported as associated with familial diabetes in 2015 (20) and accumulation of evidence of which since has been limited (21). The sequencing methods and variant classification based on the 2015 American College of Medical Genetics (ACMG)/Association of Molecular Pathologists (AMP) standards and guidelines (22) have been described previously (23). The average depth (mean ± SD) of coverage for each nucleotide was 529 ± 225×, and an average of 91.3 ± 5.9% of the target nucleotides had a coverage depth of 100×. Variant classification into the five ACMG/AMP categories (pathogenic [P], likely pathogenic, variant of uncertain significance [VUS], benign [B], or likely benign [LB]) was performed by a team consisting of the principal investigator (T.I.P.), TGL director (L.J.B.J.), TGL genetic counselor (K.A.M.), and one to two PhD students (J.W.K./H.Z.) using the ACMG/AMP standards and guidelines as implemented through a custom interface they developed (24). Personal communication with other colleagues involved in monogenic diabetes genetic testing was sought to increase available evidence for variants with suspicion of pathogenicity.

Clinical Confirmation and Disclosure of P/LP Variants

P/LP results were confirmed by Sanger sequencing in the TGL at the University of Maryland School of Medicine before reporting them to patients and providers. A clinical report was issued to the study site physician, who then, in collaboration with the genetic counselor, disclosed the results to the patient. After the disclosure session, a physician clinic note containing recommendations for treatment based on both the genetic testing results and the patient's history, a genetic counseling letter and instructions for recruiting at-risk family members for cascade testing, and a copy of the laboratory report were mailed to the patient. These documents were also uploaded to the EHR and routed to the physician treating the patient for diabetes or mailed to the patient's physician if referred from outside the main sites.

If no variants were identified or if only benign variants, likely benign variants, or VUS were identified, the genetic counselor called the patient and reported that no clinically significant variants were found, but this should not prevent clinical testing for monogenic diabetes if indicated, because the sequencing was not performed under a clinical protocol. We note here that our assay specifically did not detect copy-number variants (CNVs) or large indels, which account for ∼50% of *HNF1B* variants (25) and a smaller percentage of variants in other genes (1.2, 1.9, and 3.5% in *HNF1A*, *HNF4A* (26) , and *GCK* (27) , respectively), which some but not all clinical laboratories detect. If one or more VUS were identified, the patient was also told that it might be useful to recruit the patient's family members to improve our understanding of the cause of diabetes. The genetic counselor then sent a letter summarizing the conversation to the participant.

Statistical Analysis

A χ^2 test was used to test whether there was a significant difference in the distribution of enrollment subsets between European and African American patients. Either χ^2 test or Fisher exact test (when one or more cell counts were fewer than five) was used to compare the performance of the questionnaire between patients with or without monogenic diabetes. A two-tailed *t* test was used to test whether there was a significant difference in the age at diagnosis between patients with or without monogenic diabetes. The test was considered statistically significant when the *P* value was <0.05.

Comparison With the MODY Probability Calculator

The University of Exeter monogenic diabetes group used its monogenic diabetes patient database to establish a tool called the MODY probability calculator (MPC) to estimate the likelihood of identifying a monogenic diabetes variant in a patient of a given age, age at diagnosis, treatment, BMI, HbA_{1c}, and parental diabetes history. An acknowledged limitation of the MPC is that it is based on a

White European population with diabetes onset before age 35 years (28). We assessed the sensitivity and specificity of the MPC in our study population.

RESULTS

Target Population

Over 3.5 years, 2,190 individuals were screened by questionnaire across four sites, including 598 at UM-CDE, 252 at BVAMC, 1,061 at GHS, and 278 at Bay West (Supplementary Table 4). In addition, there were 222 patients recognized by physicians either as individual physician referrals (both within and outside the sites) or by manual chart review by one of us (E.A.S.) of patients coming in for clinical visits at UM-CDE. Finally, there were 110 self-referrals. Further information about the study population can be found in Supplementary Tables 5 and 6.

Enrollment

During stage 1, 479 individuals in whom there was suspicion for monogenic diabetes based on the initial screen were invited to enroll in the study, and 274 were enrolled. During stage 2, 474 individuals were invited regardless of suspicion for monogenic diabetes, and 233 were enrolled. Of the 507 (274 + 233) enrolled, 313 were found to meet algorithmic criteria and were sequenced, and 51 were not tested after team review of laboratory results and medical history at stage 1. An additional 143 individuals enrolled at stage 2 not meeting algorithmic criteria and were sequenced for the sensitivity pilot. African American individuals invited to participate were less likely to enroll (Supplementary Table 7).

Genetic Testing

In total, 456 (223 meeting algorithmic criteria in stage 1, 90 meeting algorithmic criteria in stage 2, and 143 not meeting algorithmic criteria in stage 2) of 507 enrolled patients underwent genetic testing (34 enrolled but ultimately not meeting algorithm criteria and 17 enrolled but refusing further testing in stage 1 were not sequenced). The numbers of screened enrolled patients at stage 1 and stage 2 and total number of genetically tested patients are illustrated in Fig. 1. Table 1 describes participant demographics.

After filtering for coding and consensus splice-site variants with <5% frequency in 1000 Genomes, ExAC, and the National Heart, Lung, and Blood Institute Exome Sequencing Project, a total of 449 missense variants, three nonsense variants, nine splice-site variants, and 17 small (<20 bp) insertions/deletions were analyzed according to the ACMG/AMP guidelines for variant interpretation (Supplementary Tables 8 and 9).

Monogenic Diabetes Diagnosis

Thirty-eight patients were discovered to have 35 P/LP variants in target genes (Supplementary Table 10). A comparison of screening question responses between those with and without P/LP variants is shown in Table 2. Most variants were in *GCK* (21 individuals with 20 different variants) or *HNF1A* (seven individuals with six different variants) (Supplementary Table 10). The remaining variants were found in *HNF4A* (two individuals with the same variant), *HNF1B* (one), *INS* (two), *KCNJ11* (one), *LMNA* (two), *MC4R* (one), and *WFS1* (one).

We were able to identify P/LP monogenic diabetes variants in 12.1% (38 of 313) of individuals suspected of having monogenic diabetes: 25 (11.2%) of 223 from stage 1 and 13 (14.4%) of 90 from stage 2 (Table 3). P/LP variants were not identified in any of the 143 individuals not suspected of having monogenic diabetes sequenced in stage 2. The likelihood of identifying a P/LP variant was strongly dependent on the recruitment method, as described below.

Clinic Screening

Clinic screening of 1,904 individuals yielded 130 (6.8%) individuals meeting algorithmic criteria for monogenic diabetes. Four (3.1%) had P/LP variants, comprising 5.1% (four of 78) of screened patients meeting algorithmic criterion 3 (non-T1D diagnosed by age 30 years).

EHR Portal Screening

Nineteen (6.6%) of 286 individuals screened electronically in the MyGeisinger portal met algorithmic criteria and were tested. One (7.7%) patient meeting algorithm criterion 3 (non-T1D before age 30 years) had a P/LP variant.

Physician Identification of Patients

Participating physicians identified patients for the PDMP in two ways: direct referral by physicians at four sites and manual chart review by E.A.S., at UM-CDE.

Referral. Overall, of 108 patients referred by their own physicians and meeting final algorithmic criteria, 19 had P/LP variants, for a hit rate of 17.6% in physician-referred cases. Of these 19, just over half (10 [52.6%] of 19) qualified on the basis of non-T1D diagnosed by age 30 years (algorithmic criterion 3), and the remainder (nine [47.4%] of 19) met no criteria other than clinical suspicion (algorithmic criterion 7). Of these nine patients who did not meet prespecified criteria, five had prediabetes but not frank diabetes by age 30 years. Reasons for referral of the other four included: T2D with normal BMI at age 45 years and family history of mild hyperglycemia, antibody-negative T1D picked up incidentally on a routine screen, gestational diabetes at age 29 years and T2D at age 43 years with near-normal BMI, and suspected lipodystrophy.

Manual Chart Review. Two (10.5%) of 19 individuals selected for sequencing after manual chart review at UM-CDE had P/LP variants. One was diagnosed with T1D at age 15 months, had a parent with diabetes (criterion 2), and was found to have a variant in *KCNJ11*. One had been diagnosed with T1D and T2D at different ages, was born with only one kidney (criterion 5), and was found to have a variant in *HNF1B*. An additional four patients were identified by both their physician and manual chart review at UM-CDE as meeting criteria, but none had P/LP variants.

Self-referral

Twelve (32.4%) of 37 of the self-referring patients meeting algorithmic criteria had P/LP variants. Seven of 12 met algorithmic criterion 3 (non-T1D diagnosed by age 30 years). Of the remaining five cases who met algorithmic criterion 7 (clinical suspicion) only, two were diagnosed at older ages (one at age 54 years and one at age 65 years but with recollections of mild hyperglycemia in her 20s), two were diagnosed with prediabetes before age 30 years, and one had T1D with periods of noninsulin dependence.

Comparison of the Screening Algorithm With the MPC

Our approach identified 38 people with monogenic diabetes or obesity. Retrospectively, we considered how useful the MPC would have been in identifying

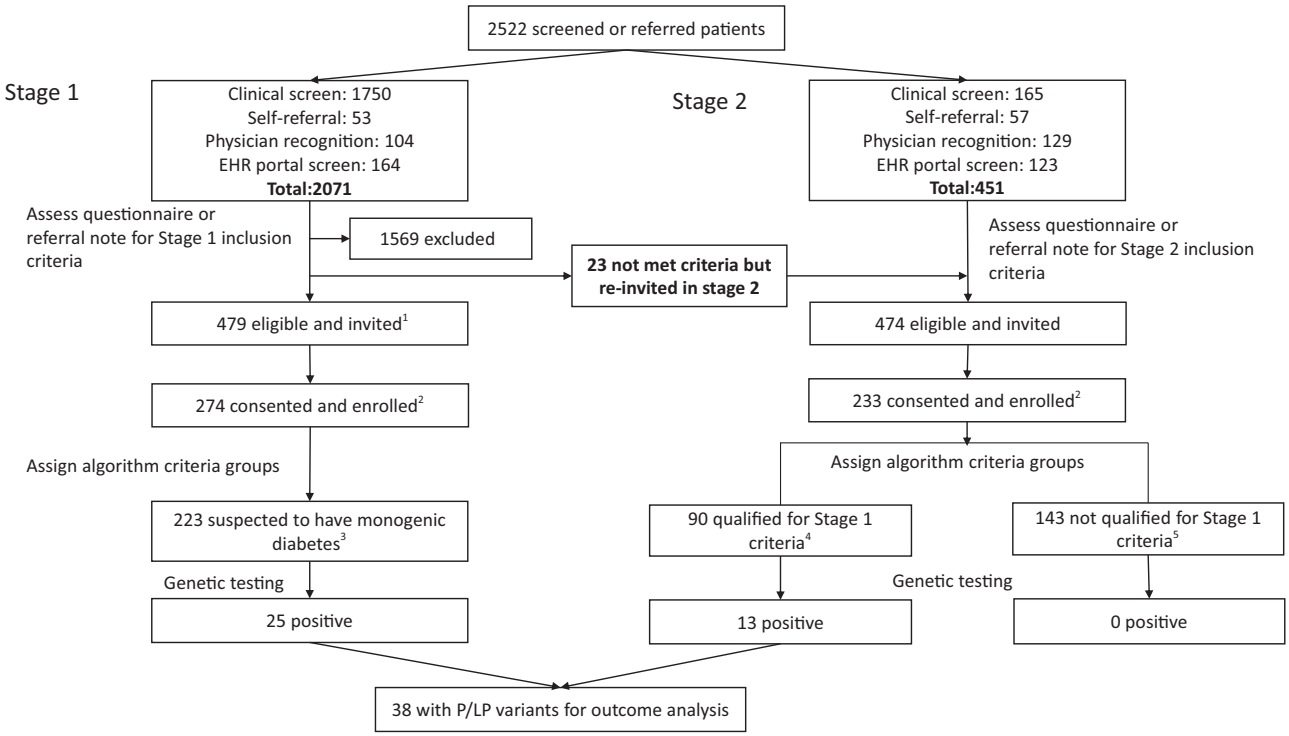

Figure 1—Flowchart showing numbers of patients at each step during enrollment. During stage 1, 2,071 patients were screened, 479 were invited into the study based on inclusion criteria, and 274 patients suspected of having monogenic diabetes were enrolled. Twenty-three of the excluded patients in stage 1 were reinvited to join the study during stage 2. In addition to 451 newly screened patients, a total of 474 eligible patients in stage 2 were eligible based on inclusion criteria and were invited. Of these, 90 patients who were suspected of having monogenic diabetes and 143 patients who were not suspected of having monogenic diabetes were enrolled. Overall, 456 patients went through genetic testing, including 313 patients suspected and 143 patients not suspected of having monogenic diabetes. Finally, 38 of the 313 suspected patients tested positive for P/LP variants in eight genes. [1]Total of 1,569 excluded (1,528 did not meet inclusion criteria; 41 unable to assess questionnaire). [2]Total of 205 dropped (97 unreachable; 11 declined participation; 50 no showed; 30 assessed to be not suspicious for monogenic diabetes; 17 refused to test). [3]Total of 51 assessed to be not suspicious for monogenic diabetes based on lab results and medical history. [4]Total of 92 dropped (20 unreachable; 23 declined participation; 48 no showed; 1 refused to test). [5]Total of 149 dropped (111 unreachable; 11 declined participation; 27 no showed).

these individuals. Twelve individuals were missing information (BMI, HbA_{1c}, or parental diabetes history) necessary to apply the calculator. An additional five individuals were diagnosed after age 35 years (range, 43–65), making the calculator inapplicable, including three with *GCK*, one with *HNF4A*, and one with *LMNA* variants. Of the remaining 21 individuals, 18, 16, and 16 had a score $>$20, $>$50, and $>$62.4%, respectively. The three patients with scores $<$20% had variants in genes other than the top three MODY genes (*HNF1B*, *MC4R*, and *WFS1*). Of the 18 patients who would have been selected by an MPC value of $\geq$20%, 16 had variants in *HNF1A*, *HNF4A*, or *GCK.* Therefore, a cutoff of 20% picked up all calculable individuals with variants in the three main MODY genes, including two non-White individuals. One of these would have been missed with a cutoff of 50%. Numbers are too small to draw conclusions as to the overall performance of the calculator in non-White individuals, one of our chief concerns, but we note that distributions of scores were similar among individuals not found to have a P/LP variant (data not shown). In evaluating additional performance metrics of the MPC in our study population, we note that in the 181 total patients who were both diagnosed before age 35 years and had all variables needed for the MPC, a cutoff score of 62.4% maximized sensitivity and specificity combined at 76.2 and 86.9%, respectively. Although our selection criteria had 100% sensitivity in identifying the 21 patients with computable scores, specificity was only 34.2%.

CONCLUSIONS

Systematic screening and referral review effectively narrowed down a group of $>$2,500 patients with diabetes to a subset in which sequencing yielded a 12% positivity rate for monogenic diabetes. We are observing all cases for changes in management and glycemic outcomes, as well as offering cascade testing of relatives, and will report the impact in the future. The *KCNJ11* variant identified in one PDMP participant was previously reported in one individual who transitioned from insulin to high-dose sulfonylureas (29), and this participant has already successfully done the same after 9 years of insulin therapy. In stage 2 of our study, we sequenced individuals who were not suspected to have monogenic diabetes to pilot evaluation of the sensitivity of our selection process. Although the sample size was too small to draw any hard conclusions about sensitivity, our algorithm and selection process picked up all cases with P/LP variants in patients who met criteria but did not identify any variants in those not meeting criteria.

Our questionnaire screening strategy would potentially be more scalable than training all practitioners to

Table 1—Demographics of individuals sequenced by 40-gene panel

Characteristic	UM-CDE	GHS	Bay West	BVAMC	Total
Monogenic diabetes suspected	(*n* = 195)	(*n* = 78)	(*n* = 34)	(*n* = 6)	(*N* = 313)
Age ± SD, years	38.6 ± 17.9	47.1 ± 19.5	46.8 ± 10.7	47.3 ± 14.3	42.5 ± 16.8
Female sex	62.6 (122)	62.8 (49)	85.3 (29)	0	63.9 (200)
Race/ethnicity					
Hispanic	2.6 (5)	1.3 (1)	0	0	1.9 (6)
African American	40.0 (78)	0	17.6 (6)	66.7 (4)	28.1 (88)
White	54.9 (107)	98.7 (77)	79.4 (27)	33.3 (2)	38.1 (213)
Asian	4.0 (8)	0	2.9 (1)	0	2.9 (9)
Pacific Islander	0	0	0	0	0
Native American	1.0 (2)	0	0	0	0.6 (2)
Other	0	1.3 (1)	0	0	0.3 (1)
Monogenic diabetes not suspected (stage 2 only)	(*n* = 64)	(*n* = 52)	(*n* = 23)	(*n* = 4)	(*N* = 143)
Age ± SD, years	34.7 ± 20.5	47.1 ± 18.2	44.4 ± 11.3	57.5 ± 14.1	39.9 ± 21.5
Female sex	57.8 (37)	69.2 (36)	60.9 (14)	25.0 (1)	61.5 (88)
Race/ethnicity					
Hispanic	0	0	0	0	0
African American	32.8 (21)	0	13.0 (3)	75.0 (3)	21.1 (27)
White	50.0 (32)	100 (52)	69.6 (16)	0	69.9 (100)
Asian	12.5 (8)	0	17.4 (4)	0	8.4 (12)
Pacific Islander	0	0	0	0	0
Native American	3.1 (2)	0	0	25.0 (1)	2.1 (3)
Other	1.5 (1)	0	0	0	0.7 (1)

Data are presented as percentage (*n*) unless otherwise indicated.

recognize suspicious cases by clinical judgment. Unfortunately, we were unable to achieve a high PPV with our questionnaire as a whole. However, sequencing all individuals diagnosed with non-T1D by age 30 years (algorithm criterion 3) had a PPV of 5.1% (four of 78) when picked up through clinical screening and an overall PPV of 15.0% (22 of 147) when physician referral and self-referral were included. This criterion was included in the algorithm based on previous work providing evidence of a 25% PPV in individuals with clinically diagnosed T2D by age 30 years regardless of obesity/metabolic syndrome status (16). Notably, with the rising prevalence of childhood obesity and T2D, differential diagnosis of diabetes in childhood and adolescence has become increasingly challenging. Our data underscore the importance of including monogenic diabetes in the differential. The high prevalence of childhood obesity suggests that BMI is no longer an effective discriminator of monogenic diabetes versus T2D status, and indeed, monogenic diabetes P/LP variants were previously found in as many as 4.5% of children with overweight or obesity with clinically diagnosed T2D (8,23,30). In the case of the PDMP, six of 15 young adults with P/LP variants, including two in *GCK*, had BMIs in the overweight or obese

Table 2—Screening questionnaire responses of patients with and without monogenic diabetes

PDMP screening questions	Monogenic diabetes	No monogenic diabetes	*P*
1) Were you diagnosed with diabetes or high blood glucose before age 1 year?	0.0 (0/38)	2.4 (11/467)	1.00
2) Were you diagnosed with diabetes or high blood glucose at age ≥30 years? How old were you when you were diagnosed?	81.6 (31/38)	59.8 (278/465)	0.27
3) Were you extremely overweight when you were diagnosed?	2.9 (1/35)	23.4 (102/436)	0.01
4) As a child, did/do you have hearing or vision problems, intellectual disability (for example, learning disabilities, mental retardation, or autism), birth defect(s), or kidney disease?	13.2 (5/38)	27.5 (129/469)	0.18
5) Do you have T1D (if unsure, were you on insulin at diagnosis and have been ever since)?	7.9 (3/38)	32.1 (150/467)	0.01
6) Do you have a parent or a child with T1D?	14.7 (5/34)	14.2 (61/431)	1.00
7) Do you have two or more people related to you by blood with diabetes? If yes, please list relationship, age at diagnosis, and type of diabetes.	89.2 (33/37)	83.5 (391/468)	0.89

Data are presented as percentage (*n*/*N*).

Table 3—Hit rate by recruitment methods and algorithmic criteria

	Criterion, *n*/*N**									Total		Screened	
	1	2	3a	3b	3a and 3b	4	5	6	7	*n*/*N*	Hit rate, %	*n*/*N*	Hit rate, %
Physician recognition	0/7	1/1	8/19	2/21	10/40	0/11	1/5	0/2	9/61	21/127	16.50	21/222	9.50
Self-referral	—	—	4/9	3/7	7/16	0/4	0/1	—	5/16	12/37	32.40	12/109	11.00
Clinical screen	0/1	0/9	3/20	1/58	4/78	0/29	0/2	0/1	0/10	4/130	3.10	4/1904	0.20
EHR portal screen	—	—	0/4	1/9	1/13	0/6	—	—	—	1/19	5.30	1/286	0.30
Total	0/8	1/10	15/52	7/95	22/147	0/50	1/8	0/3	14/87	38/313	12.10	38/2522	1.50
Hit rate, %	0.00	10.00	28.80	7.40	15.00	0.00	12.50	0.00	16.10				

*Criteria: *1*, diagnosed with diabetes age ≤1 year; *2*, diagnosed with T1D, parent or child with T1D, IA2 negative, and C-peptide positive; *3*, diagnosed with non-T2D age ≤30 years; 3a, not on insulin and IA2 negative; 3b, on insulin, IA2 negative, and C-peptide positive; *4*, diagnosed with T2D age <45 years, two or more relatives in same lineage diagnosed age ≤50 years, IA2 negative, and C-peptide positive; *5*, hearing, visual, or cognitive impairment, birth defects, or kidney disease in childhood; *6*, no diabetes but with fasting glucose >100 mg/dL during current or past pregnancy, prepregnancy BMI <25 kg/m^2, IA2 negative, and C-peptide positive; and *7*, clinical suspicion.

range. The 5.1% PPV for young-onset non-T1D in the clinical screening is likely an underestimate, because the awareness raised around this study among local referring clinicians likely took some candidates out of the screening pool. Nevertheless, it demonstrated that screening can pick up cases missed by providers. Physician referrals had an overall hit rate of 18.3% (which may not be generalizable given their familiarity with the study), but the most successful strategy for identifying cases came from sequencing self-referral, with 32.4% of sequenced self-referrals found to have a P/LP variant. It is also worth noting that manual chart review by an endocrinologist/geneticist, as a supplement to physician referral on site, was able to pick up two cases of less common types of monogenic diabetes, emphasizing the unique perspectives of different physicians when evaluating atypical diabetes. Consistent with the success of this approach, Riddle et al. (31) proposed establishing a regional center with specialized expertise to support additional case identification through systematic chart review. Although the self-referral group had the highest positivity rate, relying solely on this method is likely to exacerbate health disparities (32). Therefore, it is important to develop a system in which monogenic diabetes is considered strongly on the differential diagnosis. The MPC may be a useful tool as part of this process with a cutoff score of 20%, even in a multiethnic population, but comprehensive screening and diagnostic approaches must consider the possibility of monogenic diabetes in individuals with later-onset diabetes or diagnosis of diabetes, which is not compatible with the use of the calculator.

Limitations

The sensitivity of our NGS panel was limited in that it did not have the capacity to pick up CNVs or large indels. We also elected not to include the m.3243A>G variant in order to avoid ethical complications around consent in a broad panel for automatic disclosure of mitochondrial variants to other relatives, but instead, we considered mitochondrial diabetes testing for suspected cases. The NGS panel was also limited in size by practical considerations and by the knowledge of monogenic diabetes at the time of the study and panel design. The number of known monogenic diabetes genes has increased since then and continues to increase (3,33); therefore, any list becomes out of date quickly. In any case, we do not view this as a major limitation to the study, because *1*) we included all established MODY genes, including those that account for most cases of monogenic diabetes and/or have clear implications for medical management (*HNF1A*, *HNF4A*, *GCK*, *HNF1B*, *INS*, *KCNJ11*, and *ABCC8*), and *2*) the focus of our study was less on epidemiology than on the feasibility and outcomes of implementing monogenic diabetes testing in clinical care, which was achieved. The high impact shown by our study is expected to continue to increase as new genes continue to be discovered and comprehensive sequencing and CNV evaluation of monogenic diabetes genes become increasingly feasible.

Recommendations

For easily implemented selection criteria in a clinical setting, our study was only powered enough to contribute to the growing body of evidence that non-T1D or autoantibody-negative C-peptide–positive diabetes diagnosed before age 30 years should prompt evaluation for monogenic diabetes, with 15% of individuals in this category having P/LP variants. In addition, the high hit rate of physician referral was consistent with the suggestion from the monogenic diabetes expert forum that training health care providers and having centers of expertise will benefit the diagnosis of monogenic diabetes (31). Finally, the finding that approximately one-third of sequenced self-referrals tested positive emphasizes the importance of educating the patient population on diabetes heterogeneity. Equipping patients with information may facilitate conversations with providers around atypical types of diabetes and enable correct and timely diagnosis.

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