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Clinical Research Article

MODY Probability Calculator Is Suitable for MODY Screening in China: A Population-based Study

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Abstract

Context: Selecting appropriate individuals for genetic testing is essential due to the optimal treatment for maturity-onset diabetes of the young (MODY). However, how to effectively screen for MODY in China remains unclear.

Objective: To validate the performance of current screening strategies in selecting patients with MODY based on a nationwide type 2 diabetes cohort.

Methods: A panel of 14 MODY genes was analyzed from 1911 type 2 diabetes patients who were ages 15 to 35 years. Variants were evaluated according to the American College of Medical Genetics and Genomics guidelines. Based on this cohort, we simulated the 2 most frequently used screening strategies, including the traditional MODY criteria and the MODY probability calculator (MPC), to assess their ability to select patients with MODY.

Results: From a total of 1911 participants, 42 participants harbored pathogenic/likely pathogenic variants. The performance of the traditional criteria was sensitivity: 19.0%, specificity: 72.9%, positive predictive value (PPV): 1.6%, and missing rate: 81.0%. The optimal cut-off for MPC was 40.7%. Based on this cut-off value, the performance was sensitivity: 54.8%, specificity: 81.0%, PPV: 6.1%, and missing rate: 45.2%. Moreover, hemoglobin A1c, insulin treatment, and family history of diabetes have poor discrimination between MODY and young-onset type 2 diabetes.

Conclusion: The MPC is better than traditional criteria in terms of both sensitivity and PPV. To ensure more MODY patients benefit from optimal treatment, we therefore suggest that routine genetic testing be performed on all type 2 diabetes patients who are between the ages of 15 and35 years and have MPC probability value over 40.7%.

Key Words: MODY probability calculator, genetic testing, MODY screening, sensitivity, next-generation sequencing

Abbreviations: BMI, body mass index; FN, false negative; FP, false positive; HbA1c, hemoglobin A1c; MODY, maturity-onset diabetes of the young; MPC, MODY probability calculator; PPV, positive predictive value; TN, true negative; TP, true positive.

Maturity-onset diabetes of the young (MODY) is a group of clinically heterogeneous monogenic diabetes, accounting for 1% to 4% of young diabetes [1]. A confirmed molecular diagnosis has important implications for clinical management, disease prognosis, and genetic counselling [2-4]. However, it is estimated that more than 80% of MODY patients are undiagnosed or misdiagnosed as type 1 or type 2 diabetes [5].

The high rate of underdiagnosis is mainly caused by the expensive cost of genetic testing and the clinical heterogeneity of MODY [6, 7]. To reduce the expenditure burden, clinical screening was often conducted to identify likely MODY patients for genetic testing [8]. Such clinical screening was based on discriminative attributes such as young age of onset, family history of diabetes, and nonobesity [8]. With a clear emphasis on positive predictive value (PPV), patients

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nominated for genetic testing were often required to meet all these traditional criteria, inevitably leading to low sensitivity [9], as many MODY patients failed to meet 1 of these categorical criteria [10-13].

The MODY probability calculator (MPC) offers a quantified approach to screen individuals for genetic testing [14]. By weighting up simple discriminative clinical features, the probability of a MODY can be determined. The MPC has shown good predictive performance in European cohorts and can significantly improve the positive test rate [15]. However, when applied to other cohorts around the world, different MODY mutation pick-up rates and optimal cut-off values were observed, suggesting that the model behind the MPC needs to be fine-tuned in each country [16-20]. On this note, it has not been examined how well the MPC can perform in China, where the largest diabetes population in the world is reported [21].

With the recent advance in targeted next-generation sequencing technology, more cost-effective assays of MODY genes have been developed [22-24]. Given the increased accessibility of MODY genetic testing, the priority of clinical MODY screening has been shifted from pursuing high PPV to enhancing the sensitivity [9, 25, 26]. However, the sensitivity of applying traditional screening criteria or the MPC to a wider spectrum of patients with diabetes is poorly characterized. This is mainly due to the fact that previous studies attempting sensitivity estimation mostly relied on clinically suspected MODY individuals as their base population [5, 17, 19]. Compared to the true sensitivity in a more general population with diabetes, those estimates based on preselected individuals tend to be inflated [25]. Thus, there is an urgent need to evaluate the sensitivity of clinical MODY screening criteria in a wider population with diabetes in this era of cheaper genetic testing.

Here we leveraged a large, unselected type 2 diabetes cohort with the aim to (1) assess the performance of the MPC for MODY screening in China and (2) compare the sensitivity of MPC and traditional screening criteria when applied to general patients with type 2 diabetes.

Materials and Methods

Study Design

We implemented genetic testing for all 1911 type 2 diabetes patients who were recruited from 46 tertiary care hospitals and ages 15 to 35 years. Based on this cohort, we simulated the 2 most frequently used screening strategies, including the traditional screening criteria and the MPC, to assess their ability for patient selection at the time of enrollment. The screening performance was evaluated by the sensitivity, specificity, PPV, and missing rate.

Participants

The present study utilized data and samples from a nationwide, multicenter, cross-sectional survey conducted between April 2015 and October 2017, as described previously [27, 28]. The study was approved by the Ethics Committee of the Second Xiangya Hospital, Central South University in China (No. 2014032). Patients were recruited consecutively from 46 tertiary care hospitals across 24 provincial administration areas in China. The inclusion criteria were as follows: (1) diagnosed with type 2 diabetes and age 15 to35 years and (2) diabetes duration less than 1 year. The main reason for selecting patients with a disease duration of less than 1 year was that no-insulin treatment is an important discriminator for MODY and type 2 diabetes. However, Chinese patients with type 2 diabetes have significant β-cell deterioration, particularly at the early phase of diabetes. Thus, short-term intensive insulin therapy is recommended for patients with severe hyperglycemia to help restore β-cell function [13, 29].

Additionally, a wide range of clinical information, including family history, treatment, sociodemographic characteristics, and laboratory tests, as well as blood samples that could be used for genetic testing were also obtained at the time of enrollment. Finally, a total of 1911 samples were available for further analysis. All participants gave informed consent. The ethics review committee or institutional review board of each of the participating hospitals approved the study protocol. Participants age ≥18 years were asked to provide informed consent themselves, while for individuals below 18 years, approval was obtained from their parents.

Definition of Screening Strategy

The traditional MODY screening criteria was defined as have a family history of diabetes, noninsulin treatment, and age at diagnosis younger than 35 years. Only patients who met all these clinical criteria were recruited by this screening strategy.

All patients were also assessed using the MPC. Essential clinical information of age at diagnosis, sex, body mass index (BMI), ongoing treatment, hemoglobin A1c (HbA1c), family history of diabetes and current age were used as input for the MPC to calculate the probability of being MODY [14]. The patients who were recruited by the MPC should have a probability value higher than the optimal cut-offs.

Genetic Diagnosis

A panel of 14 MODY genes was sequenced by a multiple PCR based next-generation sequencing assay [30]. The design of the custom assay, library preparation, sequencing, and data analysis was conducted as previously described to an average depth of 2000X [27]. All variants were annotated using ANNOVAR and InterVar. Only rare variants (minor allele frequency <0.1% in ExAc, 1000 Genomes, and gnomAD) within the coding or splice-site regions were analyzed.

The following computational prediction tools were used in analysis: Mutation Taster [31], Sorting Intolerant From Tolerant [32], Combined Annotation–Dependent Depletion [33], PolyPhen-2 [34], Functional Analysis Through Hidden Markov Models [35], likelihood ratio test, and Mutation Assessor.

The rare variants in MODY genes were then classified into 5 categories of pathogenic, likely pathogenic, uncertain significance, likely benign, and benign based on the American College of Medical Genetics and Genomics guidelines [36]. Variants of uncertain significance should at least have PM2 and PP3 evidence items. Patients were diagnosed as MODY-positive if they carried a pathogenic or likely pathogenic MODY variant.

Statistics Analysis

Demographic and clinical variables were reported as mean (SD) for continuous variables and frequency (percentage) for categorical variables. After checking the distribution of

continuous variables with a normality test, we used *t*-test to compare continuous variables if normal distributions were not rejected and the Kruskal–Wallis test if normal distributions were rejected. Pearson's chi-square test was used to compare categorical data. All statistical analyses were performed using R, version 3.6.0 (R Programming). *P*-values < .05 were considered statistically significant, and *P*-values < .01 were considered highly significant.

A 2 × 2 table was constructed to calculate the true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN). Afterward, the sensitivity, specificity, PPV, and missing rate were calculated with the following formula: sensitivity: TP/(TP + FN), specificity: TN/(TN + FP), PPV: TP/(TP + FP), missing rate: FN/(TP + FN).

For the the MPC, the receiver operating characteristic curves were plotted to determine the best cut-off points, and the area under curve was used as a measure of overall performance. Sensitivity, specificity, PPV, and the missing rate of the MPC were calculated based on the different cut-off values. The cut-off points with the highest values of the Youden index were considered the best. The Youden index was calculated as sensitivity + specificity − 1. All these analyses were performed using the pROC package [37].

Results

Patient Characteristics

The flow of subjects through the study is shown in Fig. 1. From the 1911 eligible participants, 42 were found to harbor pathogenic or likely pathogenic variants in MODY genes and were defined as the MODY-positive group; 1869 patients were defined as the MODY-negative group, including 1695 participants who were not found to harbor any rare mutation variants in MODY genes and 174 participants who were found to harbor variants of uncertain significance.

Among the 42 confirmed MODY patients, MODY1-3 accounted for 64.3% (27/42) of all MODY cases. Mutations in other rare MODY genes were responsible for 35.7% (15/42) of the cases (Fig. 1). A full description of the MODY genetic variants is available in Supplementary Table S1 [38].

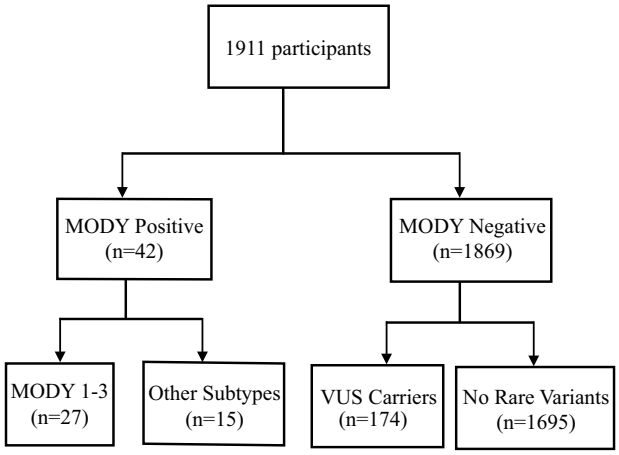


Figure 1. Participant's selection flowchart. MODY-positive = patients with pathogenic or likely pathogenic variants in 14 MODY genes; MODY-negative = patients without confirmed pathogenic or likely pathogenic variants in MODY genes.

Abbreviations: MODY, maturity-onset diabetes of the young; VUS, variants of uncertain significance.

The clinical features of the MODY-positive and MODY-negative groups are shown in Table 1. The MODY-positive group was significantly younger at diabetes diagnosis (25.24 vs 28.23 years, $P < .001$), with lower BMI (22.01 vs 25.64 kg/m^2, $P < .001$), lower fasting C-peptide (0.42 vs 0.61 nmol/L, $P = .002$), and lower plasma glucose (fasting plasma glucose 8.43 vs 9.70 mmol/L, $P = .036$; post-plasma glucose 12.87 vs 15.49 mmol/L, $P = .006$). However, as the important discriminators for MODY and type 2 diabetes, no significant difference was found in HbA1c (9.60 vs10.21, $P = .163$), family history of diabetes (31.0% vs 40.3%, $P = .285$), or insulin treatment (38.1% vs 31.5%, $P = .460$), suggesting these clinical features were not good discriminating factors in our cohort.

Table 1. Clinical features between MODY-positive and MODY-negative individuals

	MODY-positive	MODY-negative	*P*-value
n	42	1869	
Female, n (%)	15 (35.7)	528 (28.3)	.375
Age at diagnosis (years)	25.24 (6.02)	28.23 (5.10)	<.001
The probability value of MPC	0.42 (0.29)	0.22 (0.23)	<.001
Anthropometric factors			
Body mass index(kg/m^2)	22.01 (3.97)	25.64 (4.39)	<.001
Systolic blood pressure (mmHg)	120.20 (13.13)	122.85 (14.07)	.231
Diastolic blood pressure (mmHg)	75.98 (9.93)	79.30 (10.66)	.048
Biochemical data			
Fasting C-peptide (nmol/L)	0.42 (0.28)	0.61 (0.38)	.002
2 hours postprandial C-peptide (nmol/L)	1.19 (0.75)	1.46 (1.04)	.094
HbA1c (%)	9.60 (3.07)	10.21 (2.80)	.163
Fasting plasma glucose (mmol/L)	8.43 (3.64)	9.70 (3.89)	.036
2 hours postprandial plasma glucose (mmol/L)	12.87 (4.31)	15.49 (5.94)	.006
Questionnaire data			
Use of insulin treatment, n (%)	16 (38.1)	589 (31.5)	.460
Use of metformin treatment, n (%)	11 (26.2)	676 (36.2)	.242
Use of sulphonyl treatment, n (%)	5 (11.9)	147 (7.9)	.504
Use of acarbose treatment, n (%)	8 (19.0)	242 (12.9)	.353
Family history of diabetes, n (%)	13 (31.0)	754 (40.3)	.285
Metabolic syndrome, n (%)	16 (55.2)	1275 (86.7)	<.001

Data are presented as number (%) for categorical variables and mean (SD) for continuous variables.
Abbreviations: HbA1c, hemoglobin A1c; MODY, maturity-onset diabetes of the young; MPC, MODY probability calculator.

Performance of Traditional Criteria in Screening Patients With MODY

Of a total of 515 patients who meet all 3 traditional criteria (have a family history of diabetes, noninsulin treatment, age at diagnosis younger than 35 years), 8 patients had mutations in MODY genes, giving a sensitivity of 19.0%, a specificity of 72.9%, a PPV of 1.6%, and a missing rate of 81.0% (Table 2).

Performance of MPC in Screening Patients With MODY

The probability value of MODY was significantly higher in the MODY-positive group than in the MODY-negative group (0.42 vs 0.22, $P < .001$). The receiver operating characteristic analysis best cut-off value was set at a probability over 40.7% with an area under the curve of 0.683 (95% confidence interval .592-.774) in our cohort (Fig. 2A). Among 379 (19.93%) patients who need genetic testing, 23 (54.76%) patients had mutations in MODY genes, giving a sensitivity of 54.8%, a specificity of 81.0%, a PPV of 6.1%, and a missing rate of 45.2% (Table 2).

In a subanalysis, when the MPC was applied to distinguish the MODY1-3 patients (*HNF1A/GCK/HNF4A*) using the optimal cut-off value of 40.7%, its discriminative accuracy increased to 0.766 (95% confidence interval 664-.868), the sensitivity, specificity, and PPV were 70.4%, 80.9%, and 5.7%, respectively (Fig. 2B).

Table 2. Performance of different clinical criteria in screening patients with MODY

Screening criteria	Total (n)	Sensitivity (%)	Specificity (%)	PPV[a] (%)	Missing rate (%)
All	1911	100	100	2.2	0
Meeting traditional criteria[b]	515	19.0	72.9	1.6	81.0
MPC ≥ 40.7%	379	54.8	81.0	6.1	45.2

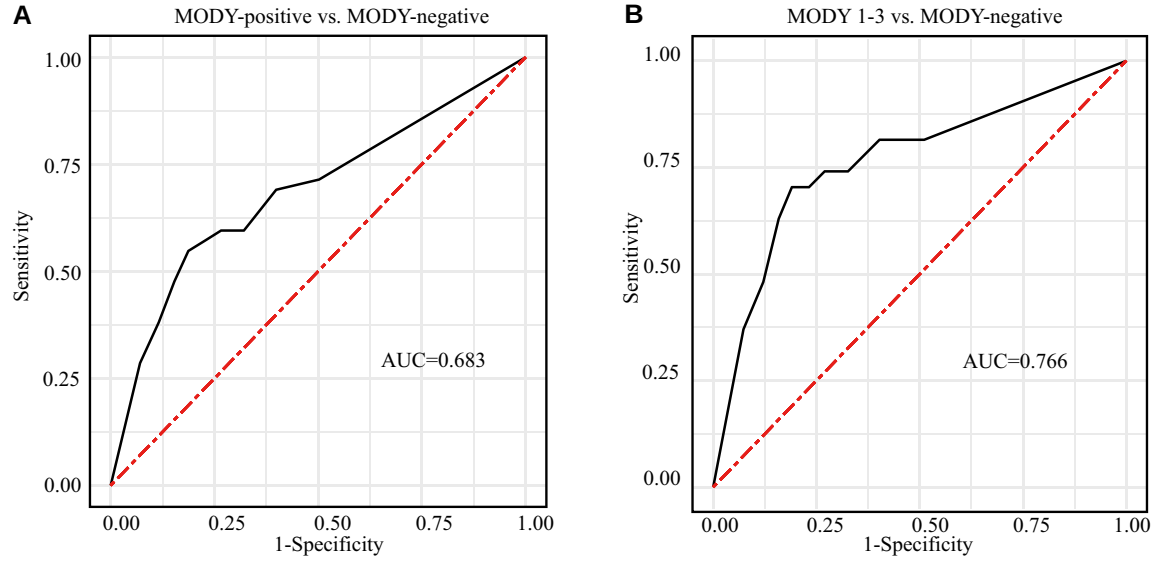
Abbreviations: MODY, maturity-onset diabetes of the young; MPC, MODY probability calculator; PPV, positive predictive value.
[a]PPV = (number of genetic positive samples)/(number needed to test).
[b]Have a family history of diabetes, noninsulin treatment, age at diagnosis younger than 35 years.

Comparison of Different Cut-offs for Screening Patients With MODY

The performance of the different cut-offs is shown in Table 3. The sum of sensitivity and specificity values was the highest at 40.7%, followed by 36% (sensitivity 57.14% and specificity 77.05%). When the cut-off value is set at 25% (as recommended by MPC developers to support the decision on genetic testing for individuals not requiring insulin within 6 months of diagnosis), the sensitivity increased to 59.52% and the specific decreased to 73.14%.

Discussion

To the best of our knowledge, this is the first study to systematically explore the effectiveness of the 2 most frequently used screening strategies for patient selection in a nationwide, multicenter, unselected type 2 diabetes cohort. Our results show



Genes	Criterion Value	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	AUC (95% CI)
MODY	≥40.7%	0.548 (0.397-0.698)	0.810 (0.792-0.827)	0.061 (0.037-0.085)	0.683 (0.592-0.774)
MODY 1-3	≥40.7%	0.704 (0.531-0.828)	0.809 (0.791-0.828)	0.057 (0.032-0.081)	0.766 (0.664-0.868)

Figure 2. Receiver operating characteristic curve analysis of the MPC for prediction of positive genetic testing for MODY. (A) MODY-positive vs MODY-negative; (B) MODY1-3 vs MODY-negative. MODY1-3 = patients with pathogenic or likely pathogenic variants in GCK/HNF1A/HNF4A genes; MODY-positive = patients with pathogenic or likely pathogenic variants in 14 MODY genes; MODY-negative = patients without confirmed pathogenic or likely pathogenic variants in MODY genes.

Abbreviations: AUC, area under curve; CI, confidence interval; MODY, maturity-onset diabetes of the young; MPC, MODY probability calculator; PPV, positive predictive value.

Table 3. Performance of different cut-off points in screening patients with MODY

Screening criteria	TP (n)	FP (n)	TN (n)	FN (n)	Sensitivity (%)	Specificity (%)	PPV (%)	Sensitivity + specificity (%)
MPC ≥ 40.7%	23	356	1513	19	54.8	81.0	6.1	135.8
MPC ≥ 10% [14]	30	949	920	12	71.43	49.22	3.06	120.65
MPC ≥ 25% [14]	25	502	1367	17	59.52	73.14	4.74	132.66
MPC ≥ 36% [17]	24	429	1440	18	57.14	77.05	5.30	134.19
MPC ≥ 58% [18]	20	303	1566	22	47.62	83.79	6.39	131.41
MPC ≥ 60% [20]	16	224	1645	26	38.10	88.01	6.67	126.11

Abbreviations: FN, false negative; FP, false positive; MODY, maturity-onset diabetes of the young; MPC, MODY probability calculator; PPV, positive predictive value; TN, true negative; TP, true positive.

that more than 80% of MODY patients would be missed by using the traditional criteria. However, if genetic testing was limited to the MPC, more than 54.8% of patients would be detected at the optimal cut-off value of 40.7%. Moreover, HbA1c, insulin treatment, and family history of diabetes have poor discrimination between MODY and young-onset type 2 diabetes in China.

Selecting appropriate patients for genetic testing is crucial for the right treatment of MODY patients, since patients with mutations in *HNF1A* or *HNF4A* genes are sensitive to sulfonylurea [3] whereas patients with mutations in *GCK* typically do not require pharmacological intervention, except during pregnancy [39]. However, as genetic testing is high, screening strategies are needed for patient selection. Yet little is known about how to effectively screen for MODY in China. Considering that many cases would be missed using strict criteria, the best way to validate current screening strategy for finding cases of MODY is to test a large number of diabetes patients who are unselected for any risk factors. To provide an accurate and comprehensive estimate of the effectiveness of current criteria for patient selection in young-onset type 2 diabetes, genetic testing was performed on all 1911 patients who were recruited from 46 tertiary care hospitals in 24 provincial administration areas and ages 15 to 35 years. Thus, our study contributes to the existing evidence of the current strategies for identifying positive cases and investigating the number of patients who were missed.

One of our main findings is that more than 80% of MODY cases would be missed by using the traditional criteria. This figure is in accordance with previous studies estimating that more than 80% of MODY patients are misdiagnosed in the UK [5]. The low rate of correct clinical diagnoses is also seen in the SEARCH study, which found only 6% MODY meet the clinical diagnosis criteria in patients who were autoantibody negative and had fasting C-peptide >0.8 ng/mL in the United States [11]. Our study provides an accurate and robust estimate of the missing rate in China. All these results indicate that MODY is easily underdiagnosed by using traditional criteria. Failure to confirm the majority of cases is mainly due to the heterogeneity of MODY, and criteria based on absolute cut-offs have poor sensitivity. For example, we found that 38.10% of cases were not referred by traditional MODY criteria because they were treated with insulin at the onset of diagnosis. Such a high percentage of insulin treatment is most likely due to the fact that Chinese patients with type 2 diabetes have significant β-cell deterioration, particularly in the early phase of diabetes. Thus, short-term intensive insulin therapy is recommended for patients with severe hyperglycemia [13, 29]. Although a strong family history of diabetes is an important discriminating factor between type 2 diabetes and MODY, more than 69% of MODY participants had no self-reported family history of diabetes. Lack of family history is also seen in many previous studies [11, 40]. These results further indicate that a screening strategy that combines clinical criteria in a weighted manner to produce a probability of MODY may be more comprehensive.

The MPC is a quantified MODY screening tool that was developed by Shields and associates based on weighted clinical features to determine a patient's probability of having MODY. The model was developed in Europe and can be used for free worldwide [14]. However, there is no data to systematic evaluate the performance of the MPC in China. Our results show that using the MPC, a probability cut-off value over 40.7% provides relatively good specificity (81.0%) and sensitivity (54.8%) for detecting individuals with true MODY cases. Most importantly, the performance of the MPC was better than traditional criteria in terms of both the sensitivity and PPV. Furthermore, unlike traditional criteria, the decision on whether to perform genetic testing depends on the optimal cut-off value of the MPC, which would not be influenced by the clinician's experience. To ensure more MODY patients receive precise treatment, we strongly support that routine genetic testing be performed on all type 2 diabetes patients who are ages 15 to 35 years and have a MPC probability value over 40.7% in China.

When genetic testing was restricted to MODY1-3, the specificity was 80.9% and the sensitivity increased to 70.4%. It is unsurprising, since this prediction model was only validated for these 3 common subtypes. In contrast to previous studies, our study proposes a lower sensitivity. Ang et al showed the sensitivity and specificity of the MPC were 76.9% and 60.3% in a South Asian population [19]. According to Santos et al, the Portuguese cohort's sensitivity and specificity were 76.3% and 74.4%, respectively [17]. Still, our data might be more robust, since the results from previous studies were based on individuals who were sent for genetic testing because they had a clinical suspicion of having MODY and the sensitivity and specificity were likely overestimated. Moreover, it should also be noted that criteria relying on absolute binary cut-offs would miss a majority of cases.

The cut-off value of 40.7% showed the highest value of sensitivity and specificity in our cohort. This value was higher than 25%, which was suggested by Shields et al for individuals not requiring insulin within 6 months of diagnosis [14]. Although lower cut-off values result in higher sensitivity, this could be accompanied by compromised specificity. The optimal

threshold value may depend on both sensitivity and specificity. Additionally, other studies also propose higher cut-off values in non-Caucasian populations. Da Silva et al found that a probability cutoff of 36% provides the best discriminatory value for detecting individuals with MODY in Portugal [17]. Santomauro et al suggested that the cutoff point of the MPC that resulted in the best sensitivity and specificity in Brazilians was 60% [20]. All these findings suggest that higher cut-off values should be considered in non-Caucasian populations.

Although the minimum MODY cases would be missed by using the MPC, nearly 45% of patients were still not detected. In addition, the PPV in our cohort demonstrates that less than 1 in 10 individuals referred for genetic testing with a MPC cut-off value above 40.7% will have monogenic diabetes. The low PPV and missed cases indicate that there is still some room for the MPC to be improved to better suit our population. For example, the probability of MODY would be high in patients with lower BMI, younger age at diagnosis, lower HbA1c, and positive family history of diabetes. However, we found no significant difference in family history and HbA1c between MODY-positive and MODY-negative groups (Table 1), making it difficult to discriminate between MODY and type 2 diabetes. In addition, participants with confirmed MODY mutations had lower C-peptide and lower plasma glucose than those without these variants. Further studies are still needed to explore whether incorporating fasting C-peptide and plasma glucose (including fasting plasma glucose and postprandial plasma glucose) into the model would effectively improve the diagnostic ability in type 2 diabetes in China.

There are also some limitations in our study. First, we had small numbers of patients with MODY from which to evaluate the performance of the MPC in our cohort. It is mainly due to the low prevalence of MODY in type 2 diabetes; Second, family history of diabetes and current treatment data were from a questionnaire, which may have some ascertainment bias. Third, panel sequencing was focused on single nucleotide variants in exons, which might miss potential nonexonic or copy number variants, especially the HNF1B, which was characterized by cooy number variants. Additionally, carriers of uncertain significance were defined as MODY-negative individuals since we found they have similar clinical features to those with type 2 diabetes (Supplementary Table S2) [38].

In conclusion, using a nationwide, multicenter, unselected type 2 diabetes cohort, we found the MPC is effectively screening MODY in China. Due to the heterogeneity of MODY patients, criteria based on absolute cut-offs would miss a majority of cases. In order to effectively manage these patients, we therefore suggest that genetic testing be performed on all patients who have a MPC probability value ≥40.7% in newly diagnosed type 2 diabetes who are age 15 to 35 years in China. However, further studies are still needed to refine the model to better suit our population.

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Author Contributions

K.Z., Z.Z., T.X., and X.L designed the study and provided overall supervision. J.Z. and Y.C. performed the analyses and prepared the manuscript. J.Z., Y.C., and H.S. interpreted the data. L.Z., F.M., and Y.L. reviewed the manuscript. All authors contributed to the article and approved the submitted version.

Disclosures

The authors declare that they have no competing interests.

Data Availability

The data generated during the current study are available from the corresponding author on reasonable request.

Statement of Ethics

The study was approved by the Ethics Committee of the Second Xiangya Hospital, Central South University in China (No. 2014032). The ethics review committee/institutional review board of every participating hospital approved the study protocol. Participants aged ≥18 years were asked to provide informed consent for themselves, while for individuals <18 years, approval was obtained from their parents.

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