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Medical Policy Manual

Topic: Multianalyte Assays with Algorithmic Analyses for Predicting Risk of Type 2 Diabetes

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

The PreDx® Diabetes Risk Score (DRS) is a multianalyte assay with algorithmic analysis (MAAA) that is intended to predict the 5-year risk of type 2 diabetes. It is composed of 7 serum biomarkers that are combined via a proprietary algorithm. The proposed use is to identify patients at greater risk of developing type 2 diabetes, and to potentially target preventive interventions at patients with the highest risk.

Background

Type 2 diabetes mellitus is a highly prevalent disorder that is associated with an extremely high degree of morbidity and mortality. The true prevalence of type 2 diabetes in the U.S. is uncertain due to a lack of population screening, but an estimated prevalence of 8.2% was reported in 2006.[1] The incidence has been increasing rapidly over the last several decades, and current trends indicate that this increase will continue.[2] Projections have estimated that the prevalence in the U.S. will reach 11.5% in 2011, 13.5% in 2021, and 14.5% in 2031.[3]

Therefore, there is an urgent public health need to counter this trend. The potential to improve outcomes and reduce costs by preventing the onset of diabetes is vast. In order to accomplish this, accurate risk prediction methods may be helpful to identify populations with the highest risk of

diabetes. Identification of patients at high risk could then be followed by preventive interventions targeted at high-risk individuals.

Predicting Risk of Type 2 Diabetes.

There are a variety of known factors that predict risk of type 2 diabetes. The most direct are measures of glucose metabolism, such as fasting glucose, oral glucose tolerance testing (OGTT), and hemoglobin A1C (HgA1C). To date, A1C is the most widely used measure for detecting type 2 diabetes with an established cut-off of 6.5%.[4] Although this cut-off measure doesn't provide an absolute divide between normal and diabetic patients, it does provide a reasonable specificity and adequate sensitivity.[5] At 6.1%, studies have reported A1C specificity and sensitivity of 79-85% and 78-82%, respectively.[6,7]

For patients with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), there is a high rate of progression to diabetes. Approximately 10% of these patients will progress to diabetes each year, and by 10 years more than 50% will have progressed to diabetes.[8]

Other risk factors which can predict an increased risk for diabetes include family history, ethnicity, lifestyle factors, dietary patterns, and numerous different laboratory parameters. A history of diabetes in the immediate family has long been recognized as one of the strongest predictors of diabetes. Regarding ethnicity, the risk of diabetes is increased 1.34 times for blacks, 1.86 times for Hispanics, and 2.26 times for Asians.[9] A sedentary lifestyle, cigarette smoking, and dietary patterns that include sweetened foods and beverages have all been positively associated with the development of diabetes. In addition, there are numerous non-glucose laboratory parameters that are associated with the risk of diabetes. These include inflammatory markers, lipid markers, measures of endothelial dysfunction, sex hormones, and many others.[10,11]

Formal risk prediction instruments have combined clinical, laboratory, and genetic information to improve and refine upon the predictive ability of single factors. Many different formal risk prediction models have been developed. These models vary in the number and type of factors examined, and in the intended use of the instrument. For example, some prediction instruments consider the full range of clinical, biochemical, and genetic factors in order to derive the most accurate predictive model.[12] Others, such as the Indian Risk Score and the Griffin risk score, use easily available clinical information without any laboratory markers in order to facilitate implementation as a widespread screening tool in areas of low resources.[13,14]

In general, the available models have been shown to have good predictive ability, but most of them have not been externally validated against gold standard testing. There is some evidence that directly compares the predictive accuracy of different measures, but there is insufficient comparative research to determine the optimal model. There is evidence that different models have different accuracy depending on the population tested. Also, relatively simple models have performed similarly to more complex models, and genetic information seems to add little over readily available clinical and metabolic parameters.[15]

PreDx® Diabetes Risk Score

The PreDx® Diabetes Risk Score™ (Tethys Bioscience®, Inc., Emeryville, CA) is a commercially available multianalyte assay with algorithmic analysis (MAAA) that is intended to determine the 5-

year risk of developing type 2 diabetes. The risk score is based on 7 biomarkers that are obtained by a peripheral blood draw:

Glucose Metabolism Biomarkers

- HgA1C
- Glucose
- Insulin

Inflammation and Atherosclerosis Biomarkers

- C-reactive protein
- Ferritin
- Interleukin-2 receptor alpha

Adipose Function Biomarkers

- Adiponectin

The results of these biomarkers are combined with age and gender to produce a quantitative risk score that varies from 0 to 10. Results are reported as the absolute 5-year risk of developing type 2 diabetes and the relative risk compared to age and gender matched controls.

Regulatory Status

The biomarkers included in the PreDx® Diabetes Risk Score are not subject to U.S. Food and Drug Administration (FDA) approval. Laboratories performing these tests are subject to Clinical Laboratory Improvement Amendment (CLIA) standards for laboratory testing.

MEDICAL POLICY CRITERIA

The use of multianalyte panels with algorithmic analysis (MAAA) for the prediction of type 2 diabetes is considered **investigational**.

SCIENTIFIC EVIDENCE

Validation of the clinical use of any diagnostic test focuses on 3 main principles:

- Technical performance for such testing may compare test measurements with a gold standard and may also compare results taken on different occasions (test-retest).

- Diagnostic performance (i.e., sensitivity, specificity, and positive and negative predictive value) is evaluated by the ability of a test to accurately predict the clinical outcome in appropriate populations of patients. The sensitivity of a test is the ability to detect a disease when the condition is present (true positive). The specificity is the ability to detect the absence of a disease or outcome when the

disease is not present (true negative).

- Clinical utility is established when the evidence demonstrates that the diagnostic information obtained from a test can be used to benefit patient management and improve health outcomes.

Literature Appraisal

Technical Performance

- The development and validation of the PreDx® Diabetes Risk Score (DRS) has been described in a series of manufacturer-sponsored studies.[16-18] Kolberg et al. first described the derivation of this risk score in 2009, using the Danish Inter99 patient cohort.[16] This cohort consists of 61,031 subjects aged 30-60 years-old and was intended to estimate the 5-year risk of progression to type 2 diabetes. The authors identified 64 candidate biomarkers that had support in the literature and that met study quality control indicators. They applied multiple logistic regression approaches to select the biomarkers with the greatest predictive ability. Validation of the model with the same cohort was performed by the bootstrapping method.

  The final model included 6 biomarkers: glucose, insulin, C-reactive protein, ferritin, adiponectin, and Interleukin-2 receptor alpha. The area under the curve (AUC) for the final fitted model was 0.78, and the bootstrapping estimate for AUC was similar at 0.76. The risk score was compared to single variables and simple combinations of variables. The best single predictor was the oral glucose tolerance test with an AUC of 0.79, which was not significantly different from the diabetes risk score (DRS). For the other single or combined variables, the AUC varied from 0.65 to 0.75. The diabetes risk score was superior to other single or combination variables, except for the 2-hour insulin level, which was not significantly different.

  In a separate publication by the same research group using the same overall population of the Inter99 cohort, the model was validated in a different way.[18] In this nested case-control design, 202 participants who progressed to type 2 diabetes were compared to 597 controls randomly selected from all participants who did not progress. The PreDx® logistic model in this study consisted of the previously derived 6 biomarkers with the addition of HgA1C.

  The AUC of the fitted model was 0.84. This was superior to single biomarkers, which had AUCs that ranged from 0.70 to 0.77, and was also superior to a noninvasive clinical model that had an AUC of 0.77. The absolute 5-year risk of progression to diabetes for patients with a low DRS (<4.5) was 1%, which rose to 7% for patients with a moderate DRS (≥4.5 and <8), and to 24% for patients with a high DRS (≥8.0).

- A second validation study used a separate cohort from the prospective Botnia study.[17] This was a cohort of 2,770 individuals who were at increased risk of developing type 2 diabetes, due mainly to family history. Outcome data and biomarker data were available for 2,350 individuals.

  The AUC for the validation set was 0.78, which was lower than the AUC of 0.84 obtained for the training set. The absolute 5-year risk of progression to diabetes for patients with a low DRS (<4.5) was 1.1% (95% CI: 0.5-1.6%), which rose to 4.0% (95% CI: 2.3-5.7%) for patients with a moderate DRS (≥4.5 and <8), and to 12.7% (95% CI: 7.0-18.1%) for patients with a high DRS (≥8.0). Reclassification analysis was also performed using fasting glucose and oral glucose tolerance testing (OGTT) as baseline. The net reclassification index of 0.20 indicated that the DRS performed

better than glucose and OGTT. The main advantage of the DRS was in reclassifying patients with abnormal glucose and OGTT into lower risk levels after application of the DRS.

Conclusion

The PreDx® diabetes risk score (DRS) has been tested in 2 different prospective cohorts of patients, with reported AUCs of 0.78 and 0.84, indicating good overall accuracy for predicting progression to diabetes. However, DRS validation studies do not appear to predict the risk of type 2 diabetes any better than current, more simple tests such as the oral glucose tolerance test. In addition, the DRS test has not been validated by independent research groups, nor has it been tested in a wide range of patient populations. As a result, there is some uncertainty in the predictive accuracy and generalizability of the risk score. The DRS did appear to improve reclassification of patients into lower risk categories, which may have implications for patient medication and treatment planning, although this was not demonstrated.

Diagnostic Performance

There is a body of literature on the comparative accuracy of different diabetes risk scores. However, the majority of studies that directly compare different risk scores do not include the PreDx® diabetes risk score as one of the comparators. For example, Abbasi et al.,[15] performed a systematic review and independent validation of 12 different risk models identified in the literature, but did not include the PreDx® score. In another publication evaluating the validity of different risk models,[8] a total of 5 risk scores were reviewed, but the PreDx® score was not included. Noble et al. conducted a systematic review of diabetes risk scores and included the Inter99 Danish cohort study score from which the PreDx ® score was derived, but the authors do not specify if the PreDx ® score was used.[19] The authors make no direct comparisons between risk scores, noting that direct comparisons are precluded by heterogeneity in the patient populations, clinical outcomes reported, and intended context of use, among other factors.

- Within the manufacturer-sponsored validation studies, there were limited comparisons of the PreDx® score with other risk models.[17,18] The PreDx® score was compared to single markers and simple combinations of markers and was superior to most of these comparators. Lyssenko et al.[17] compared the performance of the DRS with 2 other risk prediction scores, the Framingham score and the San Antonio Heart risk score. The Framingham score had an AUC of 0.76 while the San Antonio score had an AUC of 0.77, neither of which were significantly different from the DRS, which had an AUC of 0.78.

- Recently, Rowe et al. compared the PreDx® score to other clinical variables used for diabetes risk prediction in a different patient population.[20] The Insulin Resistance Atherosclerosis Study (IRAS) cohort, was a multi-ethnic US cohort including 722 patients. This study was designed to evaluate insulin resistance, cardiovascular risk factors, glucose tolerance and disease states in different US ethnic groups. The 5-year risk of type 2 diabetes as estimated by the DRS and compared to other risk assessment tools, including fasting glucose, BMI, fasting insulin, the homeostasis model assessment-estimated insulin resistance (HOMA-IR) index, and the OGTT. Test performance was assessed by receiver operator characteristic curve analysis, with AUC reported. In the whole cohort, the PreDx® disease risk score (DRS) had a significantly higher AUC than fasting glucose alone (0.762 vs 0.711, P=0.003), fasting insulin alone (0.690, P=0.003), HOMA-IR (0.716, P=0.03), and BMI (0.671, P<0.001). However, the PreDx® DRS was not statistically different from the 2-hour glucose tolerance test.

Conclusion

The evidence is insufficient to determine the comparative efficacy of the PreDx® score compared to other diabetes risk scores. The study that compared the PreDx® score to two established measures (the Framingham diabetes risk score, and the San Antonio Heart diabetes risk score) reported that the overall accuracy did not differ significantly among the 3 measures. The second study indicated that the PreDx® disease risk score (DRS) may be more effective than several individual risk factors in predicting type 2 diabetes; however, no difference was observed between the two-hour glucose tolerance test and the DRS in predicting risk. Overall, more comprehensive comparative studies are needed.

Clinical Utility

In 2013, Shah et al. published results from the industry-sponsored Provision of Evidence-based Therapies Among Individuals at High Risk for Type 2 Diabetes (PREVAIL) retrospective study. The study was designed to evaluate the influence of the PreDx® score on the use of interventions related to pre-diabetes and diabetes risk factors.[21] The study included chart reviews of 50 consecutive patients at 30 sites for a total of 913 patients. The PreDx® test score was stratified into low, moderate, and high risk groups. From baseline to follow-up, all patients demonstrated small reductions in systolic blood pressure (from 128 to 165.5, P = 0.039), increased antihypertensive use among those with hypertension (from 73.1% to 77.2%, P<0.001), decreased median low-density lipoprotein (LDL) (from 104 mg/dL to 100 mg/dL, P=0.009), and increased median high-density lipoprotein (HDL) (from 48 mg/dL to 50 mg/dL, P<0.001). A similar proportion of patients received lifestyle counseling at follow-up. The PreDx® risk group was not significantly associated with changes in systolic blood pressure, antihypertensive use, or changes in LDL or HDL. However, patients in higher PreDx® risk groups were more likely to undergo lifestyle counseling. Limitations of this study included a lack of standardized inclusion criteria, lack of comparison group, and non-standardized use of the PreDx® test for clinical decision making. Any interventions were left up to physician and/or patient discretion. These limitations restrict conclusion regarding which changes would have occurred in the absence of any intervention or with routine medical care only. Therefore, this study provides little evidence to support using the PreDx® score as a means of establishing risk or selecting patients for diabetes-related interventions.

There were no other studies identified that used the PreDx® diabetes risk score (DRS) as a method to select patients for interventions to prevent type 2 diabetes.

Conclusion

The evidence is insufficient to determine whether the PreDx® risk score can improve outcomes by targeting preventive interventions to patients who will benefit most. It is not known whether the PreDx® risk score is as good as or better than other methods for identifying individuals at high risk for diabetes.

Clinical Practice Guidelines

There are no clinical practice guidelines that specifically address the use of diabetes risk scores such as the PreDx® score. However, there are a number of clinical practice guidelines that address screening for diabetes in high-risk individuals. These guidelines specify that screening is performed by glucose-

based measurements, either by fasting glucose, oral glucose tolerance test, or HgA1C. None of the available guidelines discuss use of a risk score as a replacement for glucose-based screening measures.

Summary

The evidence is insufficient to determine the comparative accuracy of the PreDx® diabetes risk score with other formal prediction models for diabetes. Additionally, there is a lack of evidence on the clinical utility of the PreDx® score. No published studies were identified that used the risk score to select patients for preventive interventions. As a result, it is not known how this risk assessment tool will perform in targeting preventive interventions to patients who will benefit the most, nor is it known how this risk score compares to other methods for selecting high-risk patients. Therefore, use of the PreDx® diabetes risk score (DRS) is considered investigational.

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CROSS REFERENCES

None

CODES	NUMBER	DESCRIPTION
CPT	81506	Endocrinology (type 2 diabetes), biochemical assays of seven analytes (glucose, HbA1c, insulin, hs-CRP, adiponectin, ferritin, interleukin 2-receptor alpha), utilizing serum or plasma, algorithm reporting a risk score
HCPCS	None	