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

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of multianalyte panels with algorithmic analysis (MAAA) for the prediction of type 2 diabetes to be **investigational.***

Background/Overview

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. The incidence has been increasing rapidly over the last several decades, and current trends indicate that this increase will continue. 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.

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 A_{1C} (HgA_{1C}). For patients with impaired fasting glucose or impaired glucose tolerance, 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.

Other risk factors 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

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increased 1.34 times for blacks, 1.86 times for Hispanics, and 2.26 times for Asians. 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 nonglucose 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.

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 to derive the most accurate predictive model. Others, such as the Indian Risk Score and the Griffin Risk Score, use easily available clinical information without any laboratory markers to facilitate implementation as a widespread screening tool in areas of low resources.

In general, the available models have been shown to have good predictive ability, but most of them have not been externally validated. 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.

Interventions to Prevent Type 2 Diabetes
A number of intervention trials have established that both lifestyle interventions and medications are effective in preventing the onset of type 2 diabetes in high-risk individuals. These trials have selected patients at high risk for diabetes, but have used single or several clinical factors, such as impaired glucose metabolism as selection factors, rather than formal risk prediction instruments. The largest reduction in diabetes incidence has been found for intensive lifestyle interventions that combine exercise and diet. There is a lesser effect for interventions with a single component and for interventions with medications.

A Cochrane review on the efficacy of lifestyle interventions to prevent type 2 diabetes was published in 2008. This review included 8 randomized trials that compared exercise and dietary interventions to standard therapy in patients at high risk for diabetes. There was a 37% reduction in the incidence of diabetes for the intervention cohort when a combined diet/exercise intervention was used, but there were not significant effects noted for an exercise-only or a diet-only intervention.

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Another systematic review and meta-analysis evaluated the efficacy of medications for preventing progression to type 2 diabetes. This review included 10 studies of oral hypoglycemic agents and 15 studies of injectable agents. Oral hypoglycemic agents and orlistat were found to be effective in reducing progression to diabetes compared with usual care. In the largest trials with follow-up of greater than 2 years, metformin (relative risk [RR], 0.69; 95% confidence interval [CI], 0.57 to 0.83), acarbose (RR=0.75; 95% CI, 0.63 to 0.90), troglitazone (RR=0.45; 95% CI, 0.25 to 0.83), and orlistat (hazard ratio [HR], 0.63; 95% CI, 0.46 to 0.86) were efficacious in decreasing diabetes incidence compared with placebo. Evidence for other medication such as statins, fibrates, antihypertensive agents, and estrogen was inconclusive.

The largest randomized trial of preventive interventions was the Diabetes Prevention Program trial. This trial enrolled 3234 obese patients with a high risk of diabetes as defined by body mass index (BMI) level, fasting glucose, and 2-hour postprandial glucose levels. Participants were randomized to 1 of 3 groups, an intensive lifestyle intervention, a medication intervention consisting of metformin (850 mg twice per day), or a placebo control with information provided on diet and exercise. After a mean follow-up of 3 years, the incidence of diabetes was significantly reduced by 58% in the intensive lifestyle intervention group, and by 31% in the metformin group. A follow-up observational study concluded that the bulk of the benefit persisted for at least 10 years following completion of the trial.

PreDx®‡ Diabetes Risk Score
The PreDx Diabetes Risk Score™‡ (Tethys Bioscience®‡ Inc., Emeryville, CA) is a commercially available 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:

- HgA_{1C}
- Glucose
- Insulin
- C-reactive protein
- Ferritin
- Adiponectin
- Interleukin-2 receptor alpha

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 with age and gender matched controls.

As of the most recent update, the PreDx DRS is no longer commercially available.

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FDA or Other Governmental Regulatory Approval

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

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Prediction of Type 2 Diabetes

Does the PreDx Diabetes Risk Score improve the ability to predict progression to diabetes, compared with standard clinical measurements?

The development and validation of the PreDx Diabetes Risk Score (DRS) has been described in a series of manufacturer-sponsored studies. Kolberg et al first described the derivation of this risk score in 2009, using the Danish Inter99 patient cohort. This cohort consists of 61,031 subjects aged 30 to 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 with single variables and simple combinations of variables. The best single predictor was the OGTT with an AUC of 0.79, which was not significantly different from the DRS. For the other single or combined variables, the AUC varied from 0.65 to 0.75. The DRS 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. In this nested case-control design, 202 participants who progressed to type 2 diabetes were compared with 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 HgA_{1c}. 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. This was a cohort of 2770 people who were at increased risk of developing type 2 diabetes due mainly to family history. Outcome data and biomarker data were available for 2350 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% to 1.6%), which rose to 4.0% (95% CI, 2.3% to 5.7%) for patients with a moderate DRS (≥4.5 and <8), and to 12.7% (95% CI, 7.0% to 18.1%) for patients with a high DRS (≥8.0). Reclassification analysis was also performed using fasting glucose and 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.

How does the PreDx DRS compare with other diabetes risk scores in predicting the future risk of type 2 diabetes?

There is a body of literature on the comparative accuracy of different DRSs. However, the most studies that directly compare different risk scores do not include the PreDx DRS as one of the comparators. For example, Abbasi et al 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, a total of 5 risk scores were reviewed, but the PreDx score was not included. Kegne et al evaluated 12 noninvasive predictive models, not including the PreDx score, for diabetes in the EPIC-InterAct case-cohort sample, which included 27,770 individuals from 8 European countries, of whom 12,403 had incidence diabetes. The authors reported good discrimination overall, with *C* statistics ranging from 0.76 (95% confidence interval [CI], 0.72 to 0.80) to 0.81 (95% CI, 0.77 to 0.84).

Noble et al conducted a systematic review of DRSs and included the Inter99 Danish cohort study score from which the PreDx score was derived, but the authors do not specify that the PreDx score is specifically used. 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. PreDx score was compared with single markers and simple combinations of markers

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and was superior to most of these comparators. Lyssenko et al 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.

Subsequently, Rowe et al compared the PreDx score with other clinical variables used for diabetes risk prediction in a different patient population. The Insulin Resistance Atherosclerosis Study cohort was a multiethnic U.S. cohort, including 722 patients, which was designed to evaluate insulin resistance and cardiovascular risk factors and disease states in different U.S. ethnic groups and varying states of glucose tolerance. This study compared the 5-year risk of type 2 diabetes as estimated by the DRS with 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 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). It was not statistically different from the 2-hour glucose tolerance test.

SectionSummary
The PreDx DRS has been tested in 2 different prospective cohorts of patients, with reported AUCs for prediction of diabetes of 0.78 and 0.84, indicating good overall accuracy for predicting progression to diabetes. It has been evaluated in 1 U.S. cohort, but has otherwise not 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 evidence is insufficient to determine the comparative efficacy of the PreDx score compared with other diabetes risk scores. The single study that compared the PreDx score with 2 established measures (Framingham diabetes risk score, San Antonio Heart diabetes risk score) reported that the overall accuracy, as defined by AUC for predicting progression to diabetes, did not differ significantly among the 3 measures. A study in a U.S. cohort of patients suggested that the PreDx score may better predict diabetes than several individual risk factors alone. However, this comparative evidence is incomplete, and more comprehensive comparative studies are needed.

Prevention of Type 2 Diabetes
Does use of multianalyte assays (multianalyte assay with algorithm analysis) lead to targeted interventions that reduce the incidence of type 2 diabetes?

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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) initiative, a retrospective cohort study designed to evaluate the influence of the PreDx score on the use of interventions related to prediabetes and diabetes risk factors. The study included 30 sites across the United States, each of which retrospectively abstracted chart information for up to 50 consecutive patients who had undergone PreDx testing at a baseline visit and a follow-up visit, 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 (128 to 126.5, p=0.039), increased antihypertensive use among those with hypertension (73.1% to 77.2%, p<0.001), decreased median low-density lipoprotein (LDL) (104 mg/dL to 100 mg/dL, p=0.009), and increased median high-density lipoprotein (HDL) (48 mg/dL to 50 mg/dL, p<0.001). A similar proportion of patients received lifestyle counseling at follow-up as at baseline. The PreDx risk group was not significantly associated with changes in systolic blood pressure, antihypertensive use, or changes in LDL or HDL. However, patients with higher PreDx risk groups were more likely to undergo lifestyle counseling. Limitations of this study include a lack of standardized inclusion criteria, lack of a comparison group, and nonstandardized use of the PreDx test for clinical decision making. Any interventions were left up to physician and/or patient discretion. These limitations make it impossible to determine what changes are attributable to the PreDx test.

No other studies were identified that used the PreDx DRS as a method to select patients for interventions to prevent type 2 diabetes.

Other risk prediction instruments have been used for this purpose, demonstrating the potential for the use of risk prediction instruments to target preventive interventions. The AusDiab study used the Australian Type 2 Diabetes Risk Assessment Tool, based on 9 self-assessed measures, to evaluate the efficiency of detecting individuals at high risk of diabetes. This study used data from 5814 participants in the Australian Diabetes, Obesity, and Lifestyle Study to model 4 different screening strategies. The optimal strategy, defined as resulting in the greatest number of patients entered into preventive interventions at the least total costs, was noninvasive screening with the Diabetes Risk Assessment Tool followed by measurement of fasting plasma glucose.

Section Summary
The evidence is insufficient to determine whether the PreDx risk score can improve outcomes by targeting preventive interventions to patients who will benefit most. One study evaluated changes in cardiovascular risk factors in patients whose physicians used the PreDx score, but there are no published studies that evaluate use of the risk score to target preventive interventions. 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.

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Ongoing and Unpublished Clinical Trials
An online search of ClinicalTrials.gov in January 2015 found one unpublished trial using the PreDx risk score:

- Assessing the Risk of Developing Type II Diabetes Using Serum Biomarkers in Patients Diagnosed With Obstructive Sleep Apnea (OSA & DM) (NCT01447251): This is a randomized, open-label trial to evaluate the impact of patient receipt of information about their PreDx diabetes risk score device in patients with newly diagnosed obstructive sleep apnea requiring continuous positive airway pressure. The primary outcome is the number of participants with a change in their 7 serum biomarker panel results. Enrollment is planned for 70 subjects; the estimated study completion date was July 2014, but no published results were identified.

Summary of Evidence
The PreDx Diabetes Risk Score, a multianalyte assay with algorithm analysis (MAAA) that uses 7 biomarkers, has been evaluated in predicting risk of diabetes. In reports of 2 patient cohorts, the area under the curve for predicting progression to diabetes ranged from 0.78 to 0.84. This suggests good overall predictive ability, but conclusions about the predictive value of the diabetes risk score are limited by the lack of validation by independent research groups and testing in a wider variety of patient populations. The evidence is insufficient to determine the comparative accuracy of the PreDx DRS with other formal prediction models for diabetes.

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 instrument will perform in targeting preventive interventions to patients who will benefit the most, nor is it known how this risk score compares with other methods for selecting high-risk patients. No published literature was found on MAAAs other than the PreDx diabetes risk score. Therefore, use of MAAAs to predict diabetes risk, including but not limited to the PreDx diabetes risk score, is considered investigational.

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Policy History

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04/03/2014	Medical Policy Committee review
04/23/2014	Medical Policy Implementation Committee approval. New policy.
06/04/2015	Medical Policy Committee review
06/17/2015	Medical Policy Implementation Committee approval. No change to coverage.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
06/02/2016	Medical Policy Committee review
06/20/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
06/01/2017	Medical Policy Committee review
06/21/2017	Medical Policy Implementation Committee approval. No change to coverage.
06/07/2018	Medical Policy Committee review. Recommend archiving policy.
06/20/2018	Medical Policy Implementation Committee approval. Archived

Next Scheduled Review Date: Archived medical policy.

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81506
HCPCS	No codes

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ICD-10 Diagnosis	All related diagnoses

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
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