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

Policy # 00418
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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 A1C (HgA1C). 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 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, and 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.

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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.

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:

- HgA1C
- 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.

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.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration

approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Multianalyte assay with algorithm analysis (MAAA) tests have been developed to predict diabetes risk. The PreDx Diabetes Risk Score (DRS) is an MAAA that is intended to predict the 5-year risk of type 2 diabetes via a composite of 7 serum biomarkers that are combined via a proprietary algorithm to generate a risk score. 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.

The PreDx Diabetes Risk Score 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 DRS. 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 DRS. Therefore, the use of MAAAs to predict diabetes risk, including but not limited to the PreDx DRS, is considered investigational.

Supplemental Information

Practice Guidelines and Position Statements

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 hemoglobin A1c. None of the available guidelines discuss use of a risk score as a replacement for glucose-based screening measures.

The American Diabetes Association published guidelines in 2014 on testing for diabetes in asymptomatic patients.25 The following parameters for testing were recommended for adults:

- Testing to detect diabetes and assess future risk for diabetes should be considered in adults who are overweight or obese (body mass index [BMI] ≥25 kg/m) and who have at least 1 additional risk factor for diabetes among the following:
    - Physical inactivity
    - First-degree relative with diabetes
    - High-risk ethnicity (African-American, Latino, Native American, Asian/Pacific Islander)
    - Women with polycystic ovarian syndrome
    - Women who delivered a baby weighing >9 pounds or were diagnosed with gestational diabetes mellitus
    - Hypertension (≥140/90 or on therapy for hypertension)
    - High-density lipoprotein cholesterol <35 mg/dL and/or a triglyceride level >250 mg/dL
    - HgbA1C ≥5.7%, impaired glucose tolerance, or impaired fasting glucose on previous testing
    - Other clinical conditions associated with insulin resistance, eg, severe obesity and acanthosis nigricans)
    - History of cardiovascular disease
- Among adults without risk factors, testing should begin at age 45

The following parameters for testing were recommended for children: testing to detect diabetes should be considered for children who are overweight (BMI >85th percentile for age/sex, or weight >120% of ideal for height) and have any 2 of the following risk factors:

- Family history of diabetes in first- or second-degree relative

- High-risk race/ethnicity (African-American, Latino, Native American, Asian American, Pacific Islander)
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovarian syndrome, or small-for-gestational-age birth weight)
- Maternal history of diabetes or gestational diabetes during the child's gestation

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (USPSTF) published guidelines on screening for diabetes in adults in 2008. The following recommendations were made for screening:

- USPSTF recommends screening for type 2 diabetes in asymptomatic adults with sustained blood pressure (either treated or untreated) greater than 135/80 mm Hg (Grade B recommendation).
- USPSTF concluded that the current evidence is insufficient to assess the balance of benefits and harms of routine screening for type 2 diabetes in asymptomatic adults with blood pressure of 135/80 mm Hg or lower (I statement – insufficient evidence).

Medicare National Coverage

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

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Multianalyte Assays with Algorithmic Analyses for Predicting Risk of Type 2 Diabetes", 2.04.90, 2:2015-Archived Policy.
2. Fox CS, Pencina MJ, Meigs JB, et al. Trends in the incidence of type 2 diabetes mellitus from the 1970s to the 1990s: the Framingham Heart Study. Circulation. Jun 27 2006;113(25):2914-2918. PMID 16785337
3. Blonde L. State of diabetes care in the United States. Am J Manag Care. Apr 2007;13 Suppl 2:S36-40. PMID 17417931

4. Mainous AG, 3rd, Baker R, Koopman RJ, et al. Impact of the population at risk of diabetes on projections of diabetes burden in the United States: an epidemic on the way. Diabetologia. May 2007;50(5):934-940. PMID 17119914
5. Schwarz PE, Li J, Lindstrom J, et al. Tools for predicting the risk of type 2 diabetes in daily practice. Horm Metab Res. Feb 2009;41(2):86-97. PMID 19021089
6. Shai I, Jiang R, Manson JE, et al. Ethnicity, obesity, and risk of type 2 diabetes in women: a 20-year follow-up study. Diabetes Care. Jul 2006;29(7):1585-1590. PMID 16801583
7. Liu S, Tinker L, Song Y, et al. A prospective study of inflammatory cytokines and diabetes mellitus in a multiethnic cohort of postmenopausal women. Arch Intern Med. Aug 13-27 2007;167(15):1676-1685. PMID 17698692
8. Meigs JB, Hu FB, Rifai N, et al. Biomarkers of endothelial dysfunction and risk of type 2 diabetes mellitus. JAMA. Apr 28 2004;291(16):1978-1986. PMID 15113816
9. Noble D, Mathur R, Dent T, et al. Risk models and scores for type 2 diabetes: systematic review. BMJ. 2011-11-28 12:18:32 2011;343.
10. Balkau B, Lange C, Fezeu L, et al. Predicting diabetes: clinical, biological, and genetic approaches: data from the Epidemiological Study on the Insulin Resistance Syndrome (DESIR). Diabetes Care. Oct 2008;31(10):2056-2061. PMID 18689695
11. Mohan V, Goldhaber-Fiebert JD, Radha V, et al. Screening with OGTT alone or in combination with the Indian diabetes risk score or genotyping of TCF7L2 to detect undiagnosed type 2 diabetes in Asian Indians. Indian J Med Res. Mar 2011;133:294-299. PMID 21441683
12. Griffin SJ, Little PS, Hales CN, et al. Diabetes risk score: towards earlier detection of type 2 diabetes in general practice. Diabetes Metab Res Rev. May-Jun 2000;16(3):164-171. PMID 10867715
13. Zhang L, Zhang Z, Zhang Y, et al. Evaluation of Finnish Diabetes Risk Score in screening undiagnosed diabetes and prediabetes among U.S. adults by gender and race: NHANES 1999-2010. PLoS One. 2014;9(5):e97865. PMID 24852786
14. Abbasi A, Peelen LM, Corpeleijn E, et al. Prediction models for risk of developing type 2 diabetes: systematic literature search and independent external validation study. BMJ. 2012;345:e5900. PMID 22990994
15. Orozco LJ, Buchleitner AM, Gimenez-Perez G, et al. Exercise or exercise and diet for preventing type 2 diabetes mellitus. Cochrane Database Syst Rev. 2008(3):CD003054. PMID 18646086

16. Padwal R, Majumdar SR, Johnson JA, et al. A systematic review of drug therapy to delay or prevent type 2 diabetes. Diabetes Care. Mar 2005;28(3):736-744. PMID 15735219
17. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. Feb 7 2002;346(6):393-403. PMID 11832527
18. Diabetes Prevention Program Research G, Knowler WC, Fowler SE, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet. Nov 14 2009;374(9702):1677-1686. PMID 19878986
19. Kolberg JA, Jorgensen T, Gerwien RW, et al. Development of a type 2 diabetes risk model from a panel of serum biomarkers from the Inter99 cohort. Diabetes Care. Jul 2009;32(7):1207-1212. PMID 19564473
20. Lyssenko V, Jorgensen T, Gerwien RW, et al. Validation of a multi-marker model for the prediction of incident type 2 diabetes mellitus: combined results of the Inter99 and Botnia studies. Diab Vasc Dis Res. Jan 2012;9(1):59-67. PMID 22058089
21. Urdea M, Kolberg J, Wilber J, et al. Validation of a multimarker model for assessing risk of type 2 diabetes from a five-year prospective study of 6784 Danish people (Inter99). J Diabetes Sci Technol. Jul 2009;3(4):748-755. PMID 20144324
22. Kengne AP, Beulens JW, Peelen LM, et al. Non-invasive risk scores for prediction of type 2 diabetes (EPIC-InterAct): a validation of existing models. Lancet Diabetes Endocrinol. Jan 2014;2(1):19-29. PMID 24622666
23. Rowe MW, Bergman RN, Wagenknecht LE, et al. Performance of a multi-marker diabetes risk score in the Insulin Resistance Atherosclerosis Study (IRAS), a multi-ethnic US cohort. Diabetes Metab Res Rev. Sep 2012;28(6):519-526. PMID 22492485
24. Shah BR, Cox M, Inzucchi SE, et al. A quantitative measure of diabetes risk in community practice impacts clinical decisions: The PREVAIL initiative. Nutr Metab Cardiovasc Dis. Nov 1 2013. PMID 24374006
25. Chen L, Magliano DJ, Balkau B, et al. Maximizing efficiency and cost-effectiveness of Type 2 diabetes screening: the AusDiab study. Diabet Med. Apr 2011;28(4):414-423. PMID 21392062
26. American Diabetes Association. Standards of Medical Care in Diabetes—2014. Diabetes Care. January 1, 2014 2014;37(Supplement 1):S14-S80.

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27. U. S. Preventive Services Task Force. Screening for type 2 diabetes mellitus in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. Jun 3 2008;148(11):846-854. PMID 18519930

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
02/07/2019	Medical Policy Committee review
02/20/2019	Medical Policy Implementation Committee approval. Brought back to active status.
02/06/2020	Medical Policy Committee review
02/12/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 02/2021

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
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. Food and Drug Administration (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
    3. Reference to federal regulations.

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