PRE-DIABETES SCREENING TOOLS FOR ADULTS LIVING IN THE UNITED STATES

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Almost 37% of persons living in the US aged ≥ 18 years have pre-diabetes, Persons with pre-diabetes are at high risk of developing type-2 diabetes (advanced hyperglycemia) and also have a higher risk of cardiovascular disease than those with normal blood glucose levels. Furthermore, results from cross-sectional studies indicate that microvascular complications arising from hyperglycemia may begin at the pre-diabetic stage. There is evidence that progression of pre-diabetes may be halted or even reversed with lifestyle and pharmaceutical interventions. However, less than 10% of US adults with pre-diabetes are aware of their condition, which indicates that current pre-diabetes screening methods are inadequate.

US physicians need a comprehensive pre-diabetes screening tool. To this end, non-invasive screening score sets were created to screen for IFG, IGT and elevated HbA1c. Because preliminary analyses indicated that the screening accuracy of the pre-diabetes screening score sets would be enhanced by not restricting the score sets to only the pre-diabetic ranges of hyperglycemia, the pre-diabetes screening tool was designed to screen for hyperglycemia in the pre-diabetic and diabetic ranges. These hyperglycemia screening score sets have been based on a scoring system of non-invasive factors associated with hyperglycemia that are already routinely measured or assessed during a visit to the doctor. These factors were age, gender, smoking status, diabetes family history, history of cardiovascular disease, history of hypertension, height, body mass index, physical activity level (by surrogate measure of fasting

heart rate), level of alcohol consumption, history of early menarche (women only), and history of gestational diabetes (parous women only). To boost performance for the non-invasive fasting hyperglycemia score set and the non-invasive elevated HbA1c screening score set, both for use in parous women, the fasting screening score set and the HbA1c screening score set included the factor, ethnicity. The pre-diabetes tools were externally and internally validated and were also compared to other non-invasive methods that might be used to screen for hyperglycemia.

CHAPTER 1

SPECIFIC AIMS

Introduction

Almost 37% of persons living in the US aged ≥ 18 years have pre-diabetes (mild to moderate hyperglycemia (James et al, 2011), which is defined as having impaired fasting plasma glucose (IFG) (fasting plasma glucose of 100 to < 126 mg/dL), impaired glucose tolerance (IGT) (postprandial plasma glucose of 140 to 199 mg/dL) and/or HbA1c of 5.7 to 6.4% present in the blood (ADA, 2011). As its name indicates persons with pre-diabetes are at high risk of developing type-2 diabetes (advanced hyperglycemia) (ADA, 2011; Gabir et al, 2000; Zhang et al, 2010), with 5-year risks of type-2 diabetes estimated at approximately 15% - 30% in persons with IFG, 25% for persons with IGT, and 9% - 50% for persons with pre-diabetic HbA1c levels (International Expert Committee, 2009; Definition and diagnosis, n.d.). Persons with pre-diabetes also have a higher risk of cardiovascular disease than those with normal blood glucose levels (ADA, 2011; Selvin et al, 2010; Coutinho et al, 1999). Results from cross-sectional studies also indicate that microvascular complications arising from hyperglycemia may begin at the pre-diabetic stage (Rajabally, 2011; Melsom et al, 2011).

Intervention studies with pre-diabetics have demonstrated the potential to retard, halt or reverse the disease process through lifestyle and/or drug intervention programs when implemented at the pre-diabetic stage (DeFronzo & Abdul_Ghani, 2011; Perreault et al, 2009;

Horton, 2009), which indicates that the detection of pre-diabetes in US adults may help lower the mortality and morbidity rates attributable to pre-diabetes and diabetes in the US (DeFronzo & Abdul_Ghani, 2011; Horton, 2009; Hanefeld et al, 2004). Unfortunately, estimates from 2004-2005 NHANES data indicate that less than 10% of US adults with pre-diabetes are aware that they are pre-diabetic (Karve & Hayward, 2010). The extremely low percent of pre-diabetics aware of their condition strongly indicates inadequate screening for pre-diabetes and the need for improved pre-diabetes screening methods.

Asymptomatic adults can be tested for diabetes and pre-diabetes by administering the fasting plasma glucose test (FPG), which measures the fasting plasma glucose level at time of test; by administering the oral glucose tolerance test (OGTT), which measures the postprandial plasma glucose level at time of test; or by administering the HbA1c test which estimates the average blood glucose level over approximately the last month prior to the test (ADA, 2011). Because diabetes and pre-diabetes differ only in glucose level, testing for type-2 diabetes also detects pre-diabetes when present. Although the American Diabetes Association (ADA) does not provide screening guidelines specific to pre-diabetes, the ADA does provide type-2 diabetes screening guidelines for asymptomatic adults based on the recommendations of the 1997 Expert Committee Report (ADA, 2011; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003), which are as follows:

> "…testing for type-2 diabetes should begin at age 45 and every 3 years thereafter for all US adults. Testing for type-2 diabetes in asymptomatic US adults < 45 is advised when the [body mass index] is $\geq$ 25kg/cm^2 and one or more of the following factors are present: "physical inactivity; first-degree relative with

diabetes; high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander); women who delivered a baby weighing ≥ 9 lb or were diagnosed with [gestational diabetes] hypertension (≥ 140/90 mmHg or on therapy for hypertension); [high density lipoprotein] cholesterol level ≤ 35 mg/dl (0.90mmol/l) and/or a triglyceride level > 250mg/dl (2.82mmol/l); women with polycystic ovarian syndrome (PCOS); [HbA1c] ≥ 5.7%, [impaired glucose tolerance], or [impaired fasting glucose] on previous testing; other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans); and/or history of(cardiovascular disease).”” (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003)

The Expert Committee based its recommendation on the following factors: 1) the sharp increase in occurrence of type-2 diabetes is observed to begin around age 45; 2) the low likelihood that complications would occur within 3 years of a negative test result; and 3) the committee's knowledge of well documented factors associated with diabetes (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). The committee did not provide supporting documentation. The ADA screening guidelines could conceivably apply to pre-diabetes as well as for type-2 diabetes. However, the recommendations were based on factors indicating a high likelihood of diabetes, not pre-diabetes. As a result, the recommendations may not accurately predict pre-diabetes because pre-diabetes occurs earlier in the disease process. For example, pre-diabetes risk may peak (warranting universal testing for pre-diabetes) well before the age of 45. Furthermore, adults who are obese rather than severely obese may be at a high enough risk of pre-diabetes to warrant testing for pre-diabetes

even in the absence of other risk factors. For the same reasons, a screening tool originally designed to screen for or assess risk of diabetes may not be an appropriate screening tool for pre-diabetes. Unfortunately, almost all non-invasive hyperglycemia screening tools were developed to predict risk for diabetes, not screen for pre-diabetes (Nobel et al, 2011).

Extensive review of the literature does not show a pre-diabetes screening tool designed to screen for the presence of IFG, IGT and/or pre-diabetic HbA1c levels in US adults. Within the US adult population, differences observed in the prevalence of key hyperglycemic risk factors between persons with IFG, persons with IGT and persons with pre-diabetic levels of HbA1c, coupled with the low concordance between IFG, IGT and pre-diabetic HbA1c(1) indicate the need for such a screening tool. Using NHANES data, James et al reported a prevalence of IFG in US males aged $\geq$ 18 years at 33% (James et al, 2011). The prevalence of IFG in US women of the same age group was 20% (James et al, 2011). James et al also reported that the prevalence of IGT and elevated HbA1c was similar between genders (IGT – approximately 14%, HbA1c – approximately 14%)(James et al, 2011). Based on this information, US men have approximately 1.67% times the likelihood of having IFG than US women, whereas US men have about the same likelihood of having IGT or of having elevated HbA1c as US women.

James et al also provided estimates based on NHANES data (James et al, 2011) indicating that almost 30% of US adults with pre-diabetes would most likely be missed if the diagnostic test only for IFG were to be used (James et al, 2011). The estimates also indicate that over 60% of US adults with pre-diabetes would most likely be missed if the diagnostic test only for IGT or only for pre-diabetic HbA1c level were to be used (James et al, 2011). Unfortunately, clinicians rarely use more than one type of test to diagnose hyperglycemia due to the added

expense and inconvenience of using all three tests. Clinicians typically base their choice of test *only* on logistic factors such the expense of the test or the convenience of the test because no other information is available on which to base his or her decision. A non-invasive pre-diabetes screening tool the clinician can use to screen for all three conditions would provide additional information the physician can use to decide whether a diagnostic test is warranted and if so, which diagnostic test(s) should be used. Unfortunately, there is only one screening tool currently available designed to screen for pre-diabetes. This tool was designed to screen only for elevated fasting glucose in the pre-diabetic and diabetic ranges. There are no pre-diabetes screening tools for IGT or for pre-diabetic HbA1c level created to screen for those conditions.

Therefore, I developed a pre-diabetes screening tool for US adults that screens for impaired fasting glucose, impaired glucose intolerance and for elevated HbA1c in the pre-diabetic range so that the clinician can screen for all three conditions. Because preliminary analyses indicated that the screening accuracy of the pre-diabetes screening tool would be enhanced by not restricting the screening tool to only the pre-diabetic ranges of hyperglycemia, the pre-diabetes screening tool was designed to screen for hyperglycemia in the pre-diabetic and diabetic ranges. Because combined presence of fasting hyperglycemia and postprandial hyperglycemia indicates higher risk of hyperglycemic complications than when only one or the other condition is present(ADA, 2011), the hyperglycemia screening tool developed for this dissertation also includes a 4^{th} component that will screen for combined presence of fasting and postprandial hyperglycemia.

Specific Aims

Primary aim 1. To design screening tools to identify non-pregnant adults with pre-diabetes or diabetes (type unspecified), based on non-invasive measures of type 2 diabetes risk factors. The study population for Primary Aim 1 will be non-pregnant adults aged ≥ 20 years without prior diagnosis of diabetes or pre-diabetes who participated in the National Health and Nutrition Examination Survey (NHANES) 2007 – 2010. This population is defined as the training population.

Primary aim 1a*.* For fasting hyperglycemia screening in non-pregnant US adults ages ≥ 20 years without a prior diagnosis of diabetes or pre-diabetes, to develop a screening tool based on noninvasive factors routinely measured or assessed during a visit to the doctor that are also associated with pre-diabetes and/or type 2 diabetes. Fasting hyperglycemia is defined as a fasting plasma glucose ≥ 100 mg/dL.

Primary aim 1b. For postprandial hyperglycemia screening in non-pregnant US adults aged ≥ 20 years without a prior diagnosis of diabetes or pre-diabetes, to develop a screening tool based on noninvasive factors routinely measured or assessed during a visit to the doctor that are also associated with pre-diabetes and/or type 2 diabetes. Postprandial hyperglycemia is defined as a 2-hour postprandial plasma glucose ≥ 140 mg/dL.

Primary aim 1c**.** For combined presence of fasting and postprandial hyperglycemia screening in non-pregnant US adults aged ≥ 20 years without a prior diagnosis of diabetes or pre-diabetes, to develop a screening tool based on noninvasive factors routinely measured or assessed during a visit to the doctor that are also associated with pre-diabetes and/or type 2 diabetes.

Primary aim 1d. For elevated HbA1c screening in non-pregnant US adults aged ≥ 20 years without a prior diagnosis of diabetes or pre-diabetes, to develop a screening tool based on factors routinely measured or assessed during a visit to the doctor and that are associated with pre-diabetes and/or type 2 diabetes. Elevated HbA1c is defined as an HbA1c ≥ 5.7%.

Primary aim 2. To design screening tools to identify non-pregnant **women** with pre-diabetes or diabetes (type unspecified), based on non-invasive measures of type 2 diabetes risk factors. The study population for Primary Aim 2 will be non-pregnant women aged ≥ 20 years without prior diagnosis of diabetes or pre-diabetes who participated in the National Health and Nutrition Examination Survey (NHANES) 2007 – 2010.

Primary aim 2a. For fasting hyperglycemia screening in non-pregnant US women ages ≥ 20 years without a prior diagnosis of diabetes or pre-diabetes, to develop a screening tool based on noninvasive factors routinely measured or assessed during a visit to the gynecologist that are also associated with pre-diabetes and/or type 2 diabetes.

Primary aim 2b. For postprandial hyperglycemia screening in non-pregnant US women aged ≥ 20 years without a prior diagnosis of diabetes or pre-diabetes, to develop a screening tool based on noninvasive factors routinely measured or assessed during a visit to the gynecologist that are also associated with pre-diabetes and/or type 2 diabetes.

Primary aim 2c. For combined presence of fasting and postprandial hyperglycemia screening in non-pregnant US women aged ≥ 20 years without a prior diagnosis of diabetes or pre-diabetes, to develop a screening tool based on noninvasive factors routinely measured or assessed during a visit to the gynecologist that are also associated with pre-diabetes and/or type 2 diabetes.

Primary aim 2d*.* For elevated HbA1c screening in non-pregnant US women aged ≥ 20 years who are not pregnant and are without a prior diagnosis of diabetes or pre-diabetes, to develop a screening tool based on factors routinely measured or assessed during a visit to the gynecologist and that are associated with pre-diabetes and/or type 2 diabetes.

Primary aim 3. To design screening tools to identify non-pregnant **parous women** with pre-diabetes or diabetes (type unspecified), based on non-invasive measures of type 2 diabetes risk factors. The study population for Primary Aim 3 will be non-pregnant parous women aged ≥ 20 years without prior diagnosis of diabetes or pre-diabetes who participated in the National Health and Nutrition Examination Survey (NHANES) 2007 – 2010.

Primary aim 3a*.* For fasting hyperglycemia screening in non-pregnant US women ages ≥ 20 years who are without a prior diagnosis of diabetes or pre-diabetes, and who have been pregnant one or more times, to develop, a screening tool based on noninvasive factors routinely measured or assessed during a visit to the gynecologist that are also associated with pre-diabetes and/or type 2 diabetes.

Primary aim 3b. For postprandial hyperglycemia screening in non-pregnant US women aged ≥ 20 years who are without a prior diagnosis of diabetes or pre-diabetes, and who have been pregnant one or more times, to develop, a screening tool based on noninvasive factors routinely measured or assessed during a visit to the gynecologist that are also associated with pre-diabetes and/or type 2 diabetes.

Primary aim 3c. For combined presence of fasting and postprandial hyperglycemia screening in non-pregnant US women aged ≥ 20 years who are without a prior diagnosis of diabetes or pre-diabetes, and who have been pregnant one or more times, to develop a

screening tool based on noninvasive factors routinely measured or assessed during a visit to the gynecologist that are also associated with pre-diabetes and/or type 2 diabetes.

Primary aim 3d*.* For elevated HbA1c screening in non-pregnant US women aged ≥ 20 years who are without a prior diagnosis of diabetes or pre-diabetes, and who have been pregnant one or more times, to develop a screening tool based on factors routinely measured or assessed during a visit to the gynecologist and that are associated with pre-diabetes and/or type 2 diabetes.

Secondary aim 1*.* Because restriction of non-invasive factors to those routinely measured during the course of a routine visit to the doctor may lower screening ability below that of other screening methods that may currently be used, to compare screening ability of hyperglycemia screening tools to the screening ability of non-invasive impaired fasting glucose screening tools and non-invasive diabetes risk prediction/screening tools currently available. These tools are the Tool to Assess Likelihood of Fasting Glucose ImpairmenT for screening of fasting hyperglycemia, the Finnish Diabetes Risk Score (FINDRISK), and the American Diabetes Association diabetes testing guidelines for asymptomatic patients. If screening ability is lower than the currently available methods that may be used to screen for hyperglycemia, non-invasive factors associated with hyperglycemia but not routinely collected during an office visit will be added individually to the tool(s) to assess potential improvement of screening ability. These factors are ethnicity, history of kidney disease and waist circumference.

Secondary aim 2a*.* To externally validate the screening score sets for screening tools intended for use in the non-pregnant US adult population aged ≥ 20 years. The study population for Secondary Aim 2a will be non-pregnant adults aged ≥ 20 years who were

without a prior diagnosis of diabetes or pre-diabetes who participated in the National Health and Nutrition Examination Survey (NHANES) 2005 – 2006. This population is defined as the test population.

Secondary aim 2b. To externally validate screening score sets for screening tools intended for use in the non-pregnant US female adult population aged $\geq$ 20 years. The study population for Secondary Aim 2b will be non-pregnant women aged $\geq$ 20 years who were without a prior diagnosis of diabetes or pre-diabetes who participated in the National Health and Nutrition Examination Survey (NHANES) 2005 – 2006. This population is defined as the female test population.

Secondary aim 3a. To internally validate screening score sets for screening tools intended for use in the non-pregnant US adult population aged $\geq$ 20 years. Internal validation will be conducted in subgroups of the entire training population by ethnicity with ethnic subgroups defined as non-Hispanic whites, non-Hispanic blacks, Hispanics and others.

Secondary aim 3b. To internally validate screening score sets for screening tools intended for use in the non-pregnant US female adult population aged $\geq$ 20 years. Internal validation will be conducted in subgroups of the female training population by ethnicity with ethnic subgroups defined as non-Hispanic whites, non-Hispanic blacks, Hispanics and other.

Secondary aim 3c. To internally validate screening score sets for screening tools intended for use in the non-pregnant US female adult population aged $\geq$ 20 years who have been pregnant one or more times. Internal validation will be conducted in subgroups of the parous female training population by ethnicity with ethnic subgroups defined as non-Hispanic whites, non-Hispanic blacks, Hispanics and other.

CHAPTER 2

BACKGROUND AND SIGNIFICANCE

Pre-diabetes

Basic Pathophysiology of Pre-diabetes and Diabetes. Hyperglycemia occurs when the body's ability to metabolize glucose has become impaired and results in abnormally high blood glucose levels (ADA, 2011; Del Prato et al, 2002). The degree of elevation above normal blood glucose level is dependent on the degree of impairment (ADA, 2011). Glucose impairment may result in an elevated basal blood glucose (after fasting for 8 hours) (ADA, 2011), in an elevated postprandial glucose (after eating) (ADA, 2011; Schuster, n.d.) and/or in an abnormally high average blood glucose over a period of several weeks (ADA, 2011; Barrett-Conner, 2002; Schuster, n.d.). The blood glucose level at the time of blood draw can be obtained by direct measure of the level of glucose present in venous blood plasma (ADA, 2011; NHANES Laboratory Components, n.d.). If blood draw is taken at the end of a fast $\geq$ 8 hours, the measure is of the basal plasma glucose (ADA, 2011; NHANES Laboratory Components, n.d.). Because of the required fast, the basal plasma glucose measure is commonly referred to as the fasting plasma glucose test (ADA, 2011).

If the blood draw is taken after consuming carbohydrates, the measure is of the postprandial plasma glucose. The blood glucose level due to the consumption of carbohydrates (i.e. the postprandial glucose level) varies depending on the amount of carbohydrates

consumed and the length of time following consumption (Schuster, n.d.). Determining whether and/or how much the body's ability to metabolize blood glucose is impaired following the consumption of carbohydrates is more problematic than the assessment of fasting glucose. Accurate assessment of blood glucose impairment following carbohydrate consumption requires that 1) the amount and type of carbohydrate consumed is known; 2) the length of time between consumption and blood draw is known; and 3) normal and impaired blood glucose levels have already been established for the amount and type of carbohydrate consumed and the length of time following consumption (Schuster, n.d.). Because the postprandial measure of plasma glucose requires oral ingestion of a set amount of carbohydrates at a specified length of time prior to the blood draw, this measure is known as the oral glucose tolerance test (ADA, 2011; Schuster, n.d.)

A fair approximation of the average glycemic level over a period of several weeks prior to blood draw can also be determined by measuring the percent of glycolated hemoglobin A1c (HbA1c) present in the blood (ADA, 2011). Glucose binds hemoglobin A1c (i.e. the hemoglobin A1c becomes glycolated). The percent of HbA1c present in the blood can approximate the blood glucose level. HbA1c level is also affected by non-glycemic factors. For example, the percent of HbA1c present is also affected by rate of red blood cell turnover, certain hemophilic diseases, and by age with older persons having higher HbA1c levels independent of glycemic level. Ethnicity also affects HbA1c level independent of glycemic level. Blacks tend to have the highest HbA1c levels independent of glycemic level and whites of northern European descent tend to have the lowest HbA1c levels. The use of HbA1c as a diagnostic marker is somewhat controversial because HbA1c level is also affected by non-glycemic factors that can affect the

accuracy of HbA1c as a diagnostic marker for glycemic level (ADA, 2011; herman, 2009). A measure of > 5.7% HbA1c is considered abnormally high, and is defined within this dissertation as elevated HbA1c.

Hyperglycemia is a continuum, and hyperglycemia may be classified as pre-diabetes or as diabetes, with diabetes indicating a more advanced state of chronic hyperglycemia (ADA, 2011) Pre-diabetes and diabetes can both present as elevated basal (fasting) plasma glucose, elevated postprandial plasma glucose (the plasma glucose level 1 to 2 hours following consumption of carbohydrates), and/or as an above normal HbA1c level. Pre-diabetes is further classified by type of presentation: impaired fasting glucose (IFG) indicating pre-diabetes due to an elevated basal blood glucose, impaired glucose tolerance (IGT) indicating pre-diabetes due to an elevated postprandial blood glucose, and/or above normal HbA1c level in the pre-diabetic range (ADA, 2011). Conversely, diabetes is classified by its underlying cause. Type-1 diabetes is an autoimmune disorder in which the insulin-producing cells (beta cells) of the body are destroyed. In pre-diabetes and type-2 diabetes, chronic elevation in fasting and/or postprandial blood glucose occurs due to the combined effects of insulin resistance and impaired insulin secretion (ADA, 2011; Del Prato et al, 2002).

Although fasting and postprandial elevations in blood glucose are dependent on the presence of insulin resistance and impaired insulin secretion (ADA, 2011; Del Prato et al, 2002), the underlying pathologies causing the conditions differ between the two (Del Prato et al, 2002). Elevated fasting blood glucose results primarily from insulin resistance in the liver combined with reduced beta cell function and small beta cell mass (Faerch et al , 2009).

Elevation in postprandial blood glucose results primarily from insulin resistance in skeletal muscle combined with progressive loss of beta cell function (Faerch et al , 2009)

High levels of free fatty acids in plasma due to a high fat diet or an abnormally high percent of body fat (i.e., overall adiposity) cause inflammation that can contribute to insulin resistance in skeletal muscle and in hepatic tissue (Montecucco et al , 2008; Chakarova et al , 2009). High levels of free fatty acids induce insulin resistance in hepatic tissue and skeletal muscle using different pathways, which indicates that the level of insulin resistance induced by free fatty acids may differ between hepatic tissue and skeletal muscle (Montecucco et al , 2008; Chakarova et al , 2009). Inflammation resulting from an abnormally high level of body fat can also cause damage to beta cells, lowering insulin secretion (Buechler et al , 2011; Khaodhiar et al , 2009; de Ferranti & Mozaffarian , 2008). Adiposity can thus cause elevation in either or both fasting and postprandial blood glucose by inducing insulin resistance and reducing insulin secretion. The strength of the associations between adiposity and elevation in fasting blood glucose, elevation in postprandial blood glucose and elevation in the average blood glucose level over several weeks may differ because of the differing pathophysiologies between the 3 conditions. The relation between adiposity and chronic hyperglycemia is shown in Figure 1.

Classification of glycemic states*.* As shown in Figures 2a, 2b and 2c, normoglycemia, pre-diabetes and diabetes may each be defined by a range of levels with the classifications separated from one another by diagnostic thresholds along the glycemic continuum. Diagnostic thresholds for pre-diabetes and diabetes based on postprandial measures of plasma glucose require a standardized glucose challenge. Glucose challenge is defined by the type and amount of carbohydrate consumed and the length of time between consumption and blood draw. The

standardized glucose challenge has been set as a measure of plasma glucose two hours following ingestion of 75g anhydrous glucose preceded by a minimum 8 hour fast. The time of draw respective to consumption and amount and type of carbohydrate consumed were chosen to provide the most accurate assessment of postprandial glucose metabolism (Schuster, n.d.). As Figures 2a and 2b show, postprandial diagnostic thresholds are higher than diagnostic thresholds based on fasting measures of plasma glucose. The difference in diagnostic thresholds results because postprandial blood glucose is comprised of the additional blood glucose derived from consuming the anhydrous glucose as well as from the basal blood glucose. An HbA1c measure does not distinguish between hyperglycemia resulting from elevation in basal glucose level and hyperglycemia resulting from elevation in postprandial glucose level because of the nature of the measure. (i.e. an approximate average of blood glucose level over the preceding two or three weeks prior to the blood draw) (mann et al , 2010).

The current diagnostic thresholds accepted by the ADA and by the World Health Association (WHO) have been based on recommendations put forth by the International Expert Committee sponsored by the ADA in 1997 and 2003, the European Association for the Study of Diabetes, and the International Diabetes Federation in 2009 (International Expert Committee, 2009; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003) Table 1 provides the diagnostic recommendations of the expert committees as well as diagnostic guidelines adopted by the ADA and the WHO. The Expert Committees recommended the diagnostic thresholds for diabetes based on a number of factors that included increases in disease risk and cost-benefit comparisons in different populations. The primary factor the ADA and WHO used in setting diagnostic thresholds for diabetes was the level at which the risk of

retinopathy was observed to substantially increase in measures of fasting plasma glucose, 2-hour postprandial plasma glucose, and HbA1c levels (International Expert Committee, 2009). The ADA and WHO also recommended thresholds for pre-diabetes based on observed increases in disease risk and cost-benefit comparisons in different populations. The ADA and WHO also set pre-diabetic thresholds based on the level at which optimal sensitivity and specificity for predicting diabetes was achieved for each measure (International Expert Committee, 2009; Definition and diagnosis, n.d.; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003; Genuthi et al , 2003). The ADA and the WHO currently recommend the same diagnostic thresholds for diabetes using the fasting plasma glucose test and/or the 2-hour oral glucose tolerance test. The ADA and WHO also recommend the same diagnostic threshold for IGT. On the other hand the diagnostic threshold for IFG differs between the ADA recommendations and those adopted by the WHO. The ADA adopted the IFG diagnostic threshold recommended in 2003, which is based on optimal sensitivity and specificity for predicting diabetes (Genuthi et al , 2003) whereas the WHO retained the higher threshold proposed in 1997 (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003) based on clinical and public health factors more relevant to the populations they serve (Definition and diagnosis, n.d.). Although the ADA has adopted the 2009 recommendation regarding the use of HbA1c as a diagnostic measure (ADA, 2011), the WHO has not yet endorsed the use of this measure for diagnostic purposes. Reasons for the WHO's hesitancy stem from the controversy regarding its use as a diagnostic marker, and the test's limited availability world-wide (Definition and diagnosis, n.d.). As Figures 2a, 2b and 2c illustrate, the current ADA guidelines for fasting, postprandial and HbA1c glycemic diagnostic

classifications define IFG as a fasting plasma glucose of 100 mg/dL - < 126 mg/dL; IGT as a plasma glucose of 140 mg/dL - < 200 mg/dL using the OGTT as the standardized challenge test as described above; and % HbA1c of 5.7% - < 6.5% (ADA, 2011).

US Demographics of Pre-Diabetes. James et al estimated the prevalence of IFG, IGT and elevated HbA1c in the pre-diabetic range using data from 3627 adults ≥ 18 years of age who participated in the 2005-2008 National Health and Nutrition Examination Survey (NHANES) (James et al, 2011). Inclusion in the James et al study was also restricted to participants who did not have diabetes at the time of the survey either by self-report or by NHANES lab fasting plasma glucose test result ≥ 126 mg/dL or NHANES lab oral glucose tolerance test ≥ 200 mg/dL or by NHANES lab HbA1c ≥ 6.5%. NHANES is conducted by the National Centers for Disease Control and Prevention. Although data collection is ongoing, the surveys are sampled and conducted in 2-year increments. The data is cross-sectional, and consists of a questionnaire portion, an examination portion and a laboratory measures portion for each participant. The sampling scheme that NHANES uses is a complex, multi-stage probability sample design that is representative of the entire US non-institutionalized civilian population. For proper representation, NHANES data should be weighted and analyses should be performed that account for the complex sampling scheme NHANES uses. James et al used SAS and SUDAAN to accomplish this (James et al, 2011).

James et al determined that approximately 37% of US adults aged > 18 years have pre-diabetes (James et al, 2011). As Figure 3 shows, of those with pre-diabetes, approximately 72% have IFG, 38% have IGT, and 40% have elevated HbA1c in the pre-diabetic range (James et al, 2011). Figure 3 also illustrates, the low concordance between the three pre-diabetes

classifications, with 36% of pre-diabetic US adults aged ≥ 18 years with isolated IFG, 12% with isolated IGT,13% with isolated elevated HbA1c in the pre-diabetic range, and only 9% with combined IFG, IGT and elevated HbA1c in the pre-diabetic range (James et al, 2011) As noted earlier, pathophysiologies differ between elevation in fasting blood glucose and elevation in post-prandial glucose (Del Prato et al, 2002), which may explain the low concordance between IFG, IGT and elevated HbA1c. Elevated fasting blood glucose results primarily from insulin resistance in the liver combined with reduced beta cell function and small beta cell mass (NHANES Laboratory Components, n.d.; mann et al , 2010) Elevation in postprandial blood glucose results primarily from insulin resistance in skeletal muscle combined with progressive loss of beta cell function (NHANES Laboratory Components, n.d.; mann et al , 2010; Abdul-Ghani et al , 2006).

James et al observed that the prevalence of IFG differed between genders, with a prevalence of IFG in US males aged ≥ 18 years at 33%, and 20% in US women in the same age group (James et al, 2011). The prevalence of IGT was similar between genders, with approximately 14% of US men and women aged ≥ 18 years having IGT.(1) The prevalence of elevated HbA1c was very similar to that of IGT, with approximately 14% of US men and women aged > 18 years with elevated HbA1c (James et al, 2011). Based on this information, US men have approximately 1.67% times the likelihood of having IFG than US women, whereas US men have about the same likelihood of having IGT or of having elevated HbA1c as US women. Figure 4a illustrates the observed differences in prevalence.

James et al observed similar increases in the prevalence of IGT and elevated HbA1c as age increased, with the prevalence of IFG leveling off as age advanced into old age (James et al,

2011). The prevalence of IFG, IGT and elevated HbA1c in age groups 18 – 44, 45 – 64 and 65+ years was: IFG – 18.8%, 34.0%, and 31.6%; IGT – 8.4%, 15.5%, and 25.9%; and HbA1c – 6.7%, 19.3%, and 25.6%. Figure 4b reflects the changes in the prevalence of IFG, IGT and elevated HbA1c with respect to change in age (James et al, 2011), which in turn demonstrates the steeper increase in likelihood of IGT and elevated HbA1c than in IFG with increase in age.

As Figure 4c shows, James et al reported that the prevalence of elevated HbA1c in the pre-diabetic range among US non-Hispanic blacks $\geq$ 18 years was approximately double that in whites and Mexican-Americans: 25% for non-Hispanic blacks and 13% for whites and Mexican-Americans. HbA1c is higher in Blacks than in Whites even when the glycemic level is taken into account, which indicates that the higher HbA1c level James et al observed in Blacks was most likely due in part to their racial ancestry rather than an elevation in blood glucose level. Conversely, the prevalence of IGT in non-Hispanic blacks was approximately half that in whites and Mexican-Americans: 7% for non-Hispanic blacks and 14% for whites and Mexican-Americans. The prevalence of IFG in non-Hispanic blacks was 2/3 that in non-Hispanic whites and Mexican Americans: 18% in non-Hispanic blacks and approximately 27% in whites and Mexican-Americans (James et al, 2011) Based on the observed differences in the prevalence of IFG, IGT and HbA1c between ethnic groups, the likelihoods of elevated HbA1c, IFG and IGT was approximately double, half and 2/3, respectively in non-Hispanic blacks than in non-Hispanic whites or in Mexican-Americans (James et al, 2011).

Again, the difference in pathophysiologies between elevation in fasting blood glucose and elevation in post-prandial glucose (herman, 2009), may partially explain the differences in

prevalence (and resultant likelihoods) of IFG, IGT and elevated HbA1c observed between various subgroups.

Current Hyperglycemia Screening Tools Used to Screen for Pre-diabetes

The Tool to Assess the Likelihood of Fasting Glucose ImpairmentT (TAG-IT). One screening tool created to screen for impaired fasting plasma glucose is TAG-IT.(32) TAG-IT was designed using 1999 – 2004 NHANES data on non-pregnant adult NHANES participants aged 20 – 64 years with no prior diagnosis of diabetes (Koopman et al , 2008). TAG-IT was developed using logistic regression models with abnormal fasting glucose defined as a fasting plasma glucose $\geq$ 100 mg/dL as the outcome and factors associated with type-2 diabetes as covariates in the model. All continuous covariates were categorized to address linearity. Covariates were selected for inclusion in the final model if they were significant ($p < 0.05$) in the initial logistic model. Covariates chosen were age, gender, BMI, family history of diabetes, resting heart rate, and history of hypertension. Risk scores were then determined by assigning each covariate category a risk point corresponding to its odds ratio once rounded off. Odds ratios of 1 to < 1.2 were assigned a value of 0. Risk scores can then be obtained by summing the risk points corresponding to the values of the covariates in the patient of interest. TAG-IT also provides the sensitivity, specificity, and positive and negative likelihood ratios for various thresholds along the range of risk scores (Koopman et al , 2008).

The Finnish Diabetes Risk Score (FINDRISK). FINDRISK is one the most commonly used diabetes risk assessment tools worldwide. FINDRISK was developed by Lindrom and Tuomilehto using longitudinal data gathered by questionnaire and medical exam from 4615 Fins who were free of diabetes at baseline (Lindstrom & Tuomilehto , 2003). Baseline data was collected in

1987, and follow-up data collected in 1997. Logistic regression was used to create the risk score with the outcome defined as drug-treated diabetes, as listed by the Finnish nationwide Social Insurance Institution drug register. This drug register contains a list of all Finnish people who have been approved to receive free-of-charge drug treatment for certain chronic diseases, including diabetes. The following factors were defined as categorized predictors: "Age, BMI, waist circumference, history of antihypertensive drug treatment and high blood glucose, physical activity, and daily consumption of fruits, berries, or vegetables" (Lindstrom & Tuomilehto , 2003).

Although developed as a diabetes risk prediction tool, FINDRISK was assessed for screening of postprandial hyperglycemia (Franciosi et al, 2005). Franciosi et al, 2005 conducted a cross-sectional study examining the usefulness of FINDRISK as an opportunistic postprandial hyperglycemia screening tool for the physician. FINDRISK was applied to 1377 study participants aged 55 – 75 years with one or more CVD risk factors and without a prior diagnosis of diabetes. From this, the AUROC of FINDRISK was estimated when used to screen for the presence of postprandial hyperglycemia. Franciosi et al, 2005 reported an AUROC of 0.67 (95% CI 0.64 – 0.70) in the tool's screening performance. Franciosi et al, 2005 stated that one possible reason for the modest result was because of differences between the Finnish population used to create the prediction model and the Italian population from which Franciosi et al, 2005 selected their study participants (Franciosi et al, 2005).

An extensive review of the literature review did not provide evidence of a screening tool or risk prediction tool for abnormally elevated HbA1c in the general adult population.

Screening Tool Design

Screening tool design was based on the works of MacIntosh and Pepe, who are leaders in the development of classification tools based on multiple markers. MacIntosh and Pepe demonstrate that binary regression models such as logistic models produce screening tools that produce optimal results, defined as results that maximize the true positive rate when the false positive rate is held constant (McIntosh & Pepe, 2002). MacIntosh and Pepe first show that the Neyman-Pearson lemma on which hypothesis testing is based also indicates that the likelihood ratio function of multiple factors will also produce optimal screening results. They demonstrate by use of Bayes rule that a risk score based on the predicted probabilities generated by a logistic model will also produce optimal screening results in the same manner as the likelihood ratio function. Furthermore this risk score will maximize the true positive rate for its corresponding false positive rate, regardless to where the threshold is set along the risk score (McIntosh & Pepe, 2002) Hence, logistic models are very well suited for creating screening tools.

Factors Associated With Hyperglycemia

Factors associated with hyperglycemia were identified through an extensive literature search. Association between hyperglycemia and a particular factor was defined as a reported association between the two by one or more studies in which the potential for selection, information and confounder bias was adequately addressed. Associated factors were excluded from the study if they required a blood or urine sample to assess them. Routine assessment was determined by 1) a convenience sample of 10 “New Patient Packets” for various clinical and physicians’ offices (New Patient Packet, n.d.; MPMPC, n.d.; Wellspan, n.d.; Adult New Patient Packet, n.d.; Full NewPatient Packet, n.d.; Welcome to NeuroTexas, n.d.; Texas Back

Institute, n.d.; Family Doctor, n.d.; North Florida, n.d.) and 2) information provided by three medical websites on what to expect during a routine visit to the doctor (Physicians and diagnosiic procedures, n.d.; What to expect, n.d.; What does your doctor do, n.d.). Factors were selected for inclusion if they were listed in at least 8 of the 10 new patient packets or if they were listed in one of the three medical websites regarding what to expect during a routine office visit. These factors include age; BMI; level of physical activity, which may be estimated by the resting heart rate (Koopman et al , 2008); stature; smoking; level of alcohol consumption; gender; family history of type-2 diabetes; history of cardiovascular disease; stature; and history of hypertension. New patient packets from a convenience sample of 10 obstetrics/gynecology practices also indicated that age at menarche and history of gestational diabetes were routinely assessed in non-pregnant women visiting their obstetrics/gynecology doctor (Patient Forms, n.d.; UT Physicians, n.d.; New Patient Information, n.d.; Albany OB & GYN, n.d. New Patient Form, n.d.; Frisco OB & GYN, n.d.; hilltop OB & GYN, n.d.; Glens Falls OB & GYN, n.d.; Laguna Beach, n.d.; Columbia University, n.d.). Factor associated with hyperglycemia but not routinely assessed during a visit to the doctor were ethnicity, history of kidney disease, and waist circumference.

Age*.* The association between age and hyperglycemia has been well documented, which is why the ADA recommends periodic universal diabetes testing beginning at age 45 years.(2) In a cross-sectional study based on NHANES II data (1976 – 1980), Harris et al observed an increase in the prevalence of diabetes with respect to age. In white men, the prevalence of diagnosed diabetes increased from 0.5 % (age 20 – 44 yr) to 9.1% (age 65 – 74 yr) (Harris et al, 1998). The prevalence of undiagnosed diabetes in white males was very similar, increasing from

0.5 % (age 20 – 44 yr) to 10.0% (age 65 – 74 yr). Similar increases in diagnosed and undiagnosed diabetes prevalence with respect to age were also observed in black men and in women of both ethnic groups as well (Harris et al, 1998). The association between age and pre-diabetes has also been documented. James et al reported increases in the prevalence of IFG, IGT and HbA1c level with respect to increases in age (James et al, 2011). The association between IFG and age is not as strong as the association between IGT and age or pre-diabetic HbA1c level and age, with the prevalence of IFG increasing from 18.8% (age 18 – 44) to 34.0% (age 45 – 64), with no further increase in prevalence observed past age 65. Conversely, increases in the prevalence of IGT and pre-diabetic level of HbA1c with respect to age was steady: 8.4% (age 18 – 44), 15.5% (age 45 – 64) and 25.9% (age 65+) in the prevalence of IGT and 6.7% (age 18 – 44), 19.3% (age 45 – 64) and 25.6% (age 65+) (James et al, 2011).

Adiposity. The association between adiposity and hyperglycemia has been documented (Cassano et al, 1992, Meisinger et al, 2006) Cassano et al and Meisinger et al both reported that adiposity increased the risk of type-2 diabetes from the results obtained on 2 retrospective cohort studies based on data from the Department of Veterans Affairs Normative Aging Study (Cassano) and Monitoring Trends and Determinants on Cardiovascular Diseases Augsburg (Southern Germany) surveys (MONICA) (Meisinger) (Cassano et al, 1992; Meisinger et al, 2006).Using Cox proportional hazard models, Cassano et al determined that risk of IGT and type-2 diabetes (defined by fasting or postprandial glucose level) was 1.3 times higher in men with baseline BMI $\geq$ 26.88 when compared to men with BMI < 24.59 when adjusting for age, abdominal adiposity and smoking (Cassano et al, 1992).

Meisinger et al assessed the association between BMI and type-2 diabetes using Cox Proportional models, adjusting for 5-yr age group, survey number, high school education, hypertension status, dyslipidemia status, physical activity (active or inactive), current smoking status, alcohol intake (men: 0, 0.1–39.9, or ≥40 g/d; women: 0, 0.1–19.9, or ≥20 g/d), and parental history of diabetes (yes, no, or unknown) (Meisinger et al, 2006). Meisinger et al observed that risk of type-2 diabetes increased in both genders as BMI increased, with multivariable-adjusted rate ratios across quartiles of BMI of 1.0, 1.37, 2.08, and 4.15 (*P* for trend < 0.0001) in men and 1.0, 3.77, 4.95, and 10.58 (*P* for trend < 0.0001) in women (Meisinger et al, 2006). As noted earlier, adiposity greatly increases the risk of hyperglycemia because of its potential to induce insulin resistance and decrease beta cell function (Faerch et al , 2009; Montecucco et al , 2008; Chakarova et al , 2009; Buechler et al , 2011; Khaodhiar et al , 2009)

Physical Activity. The negative association between physical activity and type-2 diabetes has been documented in men and women residing in the US (Hu et al, 1992; Manson et al, 1992) Hu et al and Manson et al conducted prospective cohort studies examining the relative risk of type-2 diabetes comparing different physical activity levels in US women (Hu) and US men (Manson). Manson and Hu reported relative risks of 0.74 (women) and 0.71 (men) for developing type-2 diabetes in highly physically active US women and men compared to sedentary US women and men. The protective effects observed in both studies was independent of age and of BMI (Hu et al, 1992; Manson et al, 1992).

Smoking. The association between past and present smoking and hyperglycemia has been documented. Zhang al estimated the rate ratios of type-2 diabetes by comparing former

and current smokers to non-smokers in a 24 year-long prospective cohort study of over 100,000 nurses (Zhang et al, 2010). Using Cox proportional models adjusted for age, ethnicity, BMI, physical activity level, family history of diabetes, husband's education status, alcohol consumption and diet, Zhang et al observed that former and current smokers had higher incidence rates of type-2 diabetes than non-smokers. When compared to non-smokers with minimal exposure to passive smoke, former smokers, daily smokers of 1-14 cigarettes, 15-24 cigarettes and > 24 cigarettes had rate ratios of 1.28 (95% CI 1.12 – 1.50), 1.39 (95% CI 1.17 – 1.64), 1.68 (95% CI 1.43 – 2.01) and 1.98 (95% CI 1.57 – 2.36), respectively (Zhang et al, 2010).

Alcohol Consumption. Moderate increase in alcohol consumption appears to be protective against type-2 diabetes in abstainers and light drinkers. Joosten et al estimated the relative risk of type-2 diabetes in adults who increased their alcohol consumption compared to adults who did not in a prospective cohort study of 38,031 men who did not have diabetes or cancer in 1990 (Joosten et al, 2001). Alcohol consumption was determined by self-report at baseline and 4 years after baseline. Joosten et al observed that an increase of 7.5 g/day in alcohol consumption over a four year period was associated with lower diabetes risk among initial nondrinkers and light drinkers (< 15 g/day), with hazard ratios of 0.78 (95% CI 0.60 - 1.00) and 0.89 (95% CI 0.83 - 0.96), respectively, whereas no association was observed among men initially drinking ≥15 g/day, with a reported HR of 0.99 (95% CI 0.95 - 1.02). A similar pattern was observed for HbA1c level (Joosten et al, 2001).

In a meta-analysis of 20 studies examining the association between alcohol consumption and type-2 diabetes, Baliunas et al observed a u-curve association between level of alcohol consumed and type-2 diabetes (Baliunas et al, 2009). The lowest risk for men was

observed to occur at 22 g/day and for women at 24 g/day, with relative risks for men and women respectively of 0.87 (95% CI 0.76 – 1.00) and 0.60 RR (95% CI 0.52 – 0.69) when compared to abstaining men and women. Risk of diabetes from consumption of alcohol did not exceed that of abstainers until consumption of alcohol > 60 g/day and > 50 g/day occurred in men and women, respectively (Baliunas et al, 2009).

Gender*.* The positive association between male gender and impaired fasting glucose has been documented in more than 1 study(James et al, 2011; Harris et al, 1998; Williams et al, 2003) as well as the positive association between female gender and impaired glucose tolerance (Williams et al, 2003). Williams et al estimated the prevalence of isolated IFG (110 to < 126 mg/dL) and isolated IGT (140 to < 200 mg/dL) in men and in women in a population-based cross-sectional study conducted in Mauritius (Williams et al, 2003). Williams et al determined that men had a significantly ($p < 0.01$) higher prevalence of isolated IFG than women, whereas women had a higher prevalence of isolated IGT than men. (IFG: men – 5.1% (95% CI 4.2 – 6.0%), women – 2.9% (95% CI 2.3 – 3.5%). IGT: men – 9.0% (95% CI 7.9 – 10.2%), women – 13.9% (95% CI 12.6 – 15.1%). The difference in the prevalence of IFG and of IGT between the genders remained even when adjusting for BMI, waist circumference, waist-to-hip ratio, triglyceride and total cholesterol levels, hypertension status, beta cell function (HOMA-B) and insulin sensitivity (HOMA-S). Thus differences of the above factors between men and women cannot account for the observed differences of IFG and of IGT between genders (Williams et al, 2003).

Harris et al estimated the prevalence of IFG (110 – 125 mg/dL) and IGT (140 – 199 mg/dL) in US adults with no prior diabetes diagnosis participating in NHANES 1988 – 1994

(NHANES III) (Harris et al, 1998). For US adults aged ≥ 20 years, Harris et al estimated that the prevalence of men with IFG was higher than that of women, at 8.7% and 5.2%, respectively. For US adults aged 40 – 74 years, Harris et al estimated that the prevalence of men with IGT was lower than that of women, at 15.0% and 16.2 %.(Harris et al, 1998)

Gestational Diabetes*.* The association between gestational diabetes and hyperglycemia is well documented. Wang et al estimated the association between gestational diabetes and type-2 diabetes later in life in a prospective cohort study of 19,998 US women following pregnancy (Wang et al, 2012). Using Cox proportional hazard models adjusted for age, ethnicity and BMI, Wang et al estimated that women who had had gestational diabetes had 6.52 (95% 5.73 – 7.43) the risk of developing type-2 diabetes than women who had had normal pregnancies (Wang et al, 2012). In a systematic review of 20 studies included 675,455 women and 10,859 type-2diabetic events diabetes and type-2 diabetes, Bellamy et al estimated the association between type-2 diabetes and gestational diabetes. Using a random-effects model that pooled the unadjusted relative risks of the 20 studies, Bellamy et al estimated that women who had had gestational diabetes were 7.43 (95% CI 4.79 – 11.51) times more likely to develop type-2 diabetes than women who had always had normal pregnancies (Bellamy et al, 2009).

Family History of Type-2 diabetes*.* The association between family history of diabetes and hyperglycemia has been well documented. Langenberg et al estimated the association between diabetes and family history of diabetes in a multi-national case-cohort study of 6,887 participants (InterAct Consortium, 2013). Country-specific Prentice-weighted Cox models were used to assess diabetes rate ratios for each country and rate ratios were combined using random effects meta-analysis. A genetic risk score comprising 35 polymorphisms associated

with type-2 diabetes was also created. Adjusting for BMI, waist circumference, education level, physical activity, smoking status, diet and genetic score, Langenberg et al estimated that persons with any first-degree relative with diabetes was 2.44 (95% CI 2.03 – 2.95) times more likely to develop type-2 diabetes than persons with no family history of diabetes (InterAct Consortium, 2013).

Tan et al also estimated the association between family history of diabetes and hyperglycemia in a cross-sectional study of 4717 men living in Singapore (Tan et al, 2008). Using logistic regression models adjusted for age, sex, ethnic group and education, Tan et al observed that persons with any first degree relative having diabetes had 1.67 (95% CI 1.42 – 1.97) the odds of having impaired fasting glucose and/or impaired glucose tolerance and 2.95 (95% CI 2.36 – 3.70) the odds of having type-2 diabetes than persons with no family history of diabetes (Tan et al, 2008).

McLean et al examined the relation between diabetes family history and gestational diabetes in a retrospective study of 5850 pregnancies in which deliveries took place in Sydney, Australia (Mclean et al, 2006). As Table 2 shows, 11% of mothers with diabetic mothers only and 10% with diabetic mothers and fathers developed gestational diabetes, whereas only 5% of mothers with diabetic fathers and 3% with neither parent diabetic developed gestational diabetes(Mclean et al, 2006).

Cardiovascular Disease.The association between cardiovascular disease (CVD) and hyperglycemia is well documented. Countinho et al (Coutinho et al, 1999)performed a meta-analysis of 20 studies examining the effects of hyperglycemia on CVD. As Figure 6 shows, they observed an increase in cardiovascular events as hyperglycemia increased (Coutinho et al,

1999). Observed Increase in CVD risk was continuous across the hyperglycemic ranges, with observed increases linear or curvilinear (J-shaped) for all measures (fasting glucose, post prandial glucose and HbA1c level) (Definition and diagnosis, n.d.;Selvin et al, 2010; Coutinho et al, 1999; Barr et al, 2009) (see Figures 6 and 7).

In a retrospective cross-sectional study of 26,111 Kaiser Permanente Northwest patients, Nichols et al observed an association between macrovascular events (cardiovascular disease, stroke, peripheral vascular disease, and/or congestive heart failure) and isolated IFG and isolated IGT (Nichols et al, 2008). Nichols et al reported age and sex adjusted estimated prevalence's of 25.8%, 30.6% (IFG), and 33.9% (IGT) of macrovascular events in persons with normal glucose levels, persons with isolated IFG and persons with isolated IGT, respectively (Nichols et al, 2008).

In a prospective cohort study of 11,092 US adults, Selvin et al estimated the risk of coronary heart disease and ischemic stroke from increase in HbA1c level using Cox proportional models adjusting for age, sex, race, HDL and LDL cholesterol levels, BMI, triglyceride level, waist-to-hip ratio and status of: hypertension, diabetes family history, education level, and alcohol use (Selvin et al, 2010). Estimates of coronary heart disease risk and ischemic stroke risk increased as HbA1c level increased, with hazard ratios for coronary heart disease of 1.23 (95% CI 1.07 – 1.41), 1.78 (95% CI 1.48 – 2.15) and 1.95 (95% CI 1.53 – 2.48) and for ischemic stroke of 1.16 (95% CI 0.89 – 1.53), 2.22 (95% CI 1.60 – 3.08) and 3.16 (95% CI 2.15 – 4.64) for HbA1c levels of 5.5 - < 6%, 6 - <6.5% and $\geq$ 6.5%, respectively compared to an HbA1c of 5 - < 5.5% (Selvin et al, 2010).

Hypertension. The association between hyperglycemia and hypertension has been well established, with abnormal fasting plasma glucose and hypertension recognized as two of the conditions that tend to be present when metabolic dysfunction occurs (Alberti et al, 2005). Bower et al was also able to document an association between hyperglycemia and elevation in HbA1c in a prospective cohort study of 9603 adults (Bower et al, 2012). Using Cox proportional hazard models adjusted for age, sex, ethnicity, study site, smoking, physical activity, education, triglyceride level, BMI and waist to hip ratio, Bower et al observed hazard ratios of 1.14 (95% 1.06 – 1.23) and 1.39 (95% CI 1.20 – 1.62) for self-report of hypertension by persons with baseline HbA1c measures of 5.7 – 6.4% (pre-diabetes) and > 6.5% (diabetes) respectively compared to baseline HbA1c of < 5.7% (Bower et al, 2012).

Age at menarche. Early menarche has been shown to be associated with hyperglycemia later in life (He et al, 2010) He et al observed a negative association between age at menarche and type-2 diabetes in 2 large prospective cohorts of US nurses (He et al, 2010). Although He et al reported that much of the association was due to baseline adiposity, the association between birth weight and age at menarche indicates that some of the association between age at menarche and type-2 diabetes may also be due to shared early life factors (He et al, 2010).

Stature. Results obtained from the Lawlor et al study and the Asao study indicate an association between short stature and hyperglycemia independent of adiposity (Lawlor et al, 2002; Asao et al, 2006) Lawlor et al observed that short stature and hyperglycemia were associated independent of body mass index (BMI), with 0.89 (95% CI 0.80 – 0.99) the odds of type-2 diabetes being multiplied for every increase of 6.4 centimeters in height (Lawlor et al, 2002). Similarly, Asao et al observed that short stature and hyperglycemia were not significantly

associated independent of percent body fat. Using NHANES III data collected on 5944 US adults, Asao et al estimated the association between height and presence of IGT and of type-2 diabetes using logistic regression models adjusted for age, diabetes family history (parents), education level, physical activity, smoking status, income level, age at menarche (females only) and % body fat. Asao et al reported odds ratios of 1.10 (0.99–1.22) for presence of IGT and 1.10 (0.94–1.29) for presence of diabetes with every 6.7 centimeter decrease in height (Asao et al, 2006).

Ethnicity. The association between ethnicity and hyperglycemia is well-documented. As noted earlier on pages 17 and 18, James et al observed using NHANES 2005 – 2008 data that the prevalence of pre-diabetes differed between non-Hispanic Blacks and non-Hispanic Whites and Hispanics whether the pre-diabetes was defined by fasting glucose, by post-prandial glucose or by HbA1c (James et al, 2011) Cowie et al estimated the prevalence of pre-diabetes by ethnic group in two separate cross-sectional studies using 1999 – 2002 NHANES data and 2005 – 2006 NHANES data, respectively (Cowie et al, 2009; Cowie et al, 2006). In the first study, Cowie et al estimated the prevalence of IFG in non-Hispanic Whites, non-Hispanic blacks and Hispanics to be 27.0% (95% CI 24.1 – 30.2), 16.8 (95% CI 13.9 – 20.1) and 30.1 (95% CI 26.7 – 33.8), respectively (Cowie et al, 2009). In the second study Cowie et al estimated the prevalence of IFG and/or IGT in non-Hispanic Whites, non-Hispanic blacks and Hispanics to be 29.3.0% (95% CI 25.1 – 33.6), 25.1 (95% CI 22.0 – 28.1) and 31.7 (95% CI 24.7 – 38.7), respectively (Cowie et al, 2006).

American Indian tribes have been observed to have a higher risk of hyperglycemia than other ethnic groups in the US (Lee et al, 1995). In a cross-sectional study of 4304 native Americans , Lee et al determined the prevalence type-2 diabetes in American Indians located in

3 separate geographic locations (Arizona, Oklahoma and South and in North and South Dakoda combined). They reported that the prevalence of type-2 diabetes in the Indian population in all 3 geographic areas was several times the known prevalence in non-Hispanic whites in the US, at 65% (AZ), 38%(OK), and 33% (ND, SD) in men and 72% (AZ), 42% (OK), and 40% (ND, SD) in women (Lee et al, 1995).

Asian Indians living in the US also have a higher prevalence of type-2 diabetes compared to other US ethnic groups (Misra et al, 2010). The Misra et al study examined the prevalence of type-2 diabetes adjusted for age and gender in a randomly sampled immigrant Asian Indian population aged > 18 years (n = 1038) from 7 sites throughout the US (Misra et al, 2010). Misra et al observed that 17.4% of the Asian Indians had type-2 diabetes (Misra et al, 2010). Abate and Chandalia also note a higher prevalence of type-2 diabetes in the Asian Indians living in the US when compared to whites in their review of type-2 diabetes in Asian Indians with Abate and Chandalia reporting a prevalence of type-2 diabetes of 19% in Asian Indians and 5% in whites (Abate & Chandalia, 2001).

Kidney disease. The association between kidney disease and hyperglycemia has been reasonably well documented, even in the pre-diabetic ranges (10a). The Melsom et al cross-sectional study (the Renal Iohexol Clearance Survey) estimated the association between IFG and renal hyperfiltration (a high glomerular filtration rate (GFR)), which is indicative of kidney damage (10a). Melsom et al used data obtained from 1560 participants aged 50 to 62 years to estimate the association between GFR and fasting plasma glucose level and between GFR and HbA1c level using linear regression models adjusting for “age, sex, height, weight, current

smoking status, diastolic blood pressure, current use of ACE inhibitors or angiotensin receptor blockers" (10a).

Melsom et al observed a 3.67 (95% CI 2.29 – 5.06) and a 2.38 (95% CI 0.46 – 4.31) ml/min/1.73 m2 increase in GFR for every 18 mg/dL increase in fasting plasma glucose and every single % increase in HbA1c, respectively. As Figure 7 shows, increase of GFR in response to fasting plasma glucose was nonlinear, with increase in slope from fasting glucose levels of 5.5 mg/dL upward. Logistic regression indicated that persons with IFG had 1.56 times the odds of having hyperfiltration (defined by Melsom et al as persons in the top 10% of the GFR) when compared to persons with a normal fasting plasma glucose (10a).

Waist Circumference. The association between waist circumference and hyperglycemia has been documented. In a cross-sectional study of 537 native Hawaiians, Grandinetti et al estimated the association between waist circumference and the prevalence of impaired glucose tolerance (Grandinetti et al, 1998). They reported that for every 10 cm increase in waist circumference, the age-adjusted odds of having impaired glucose tolerance was multiplied by 1.34 (95% CI 1.08 – 1.67) and 1.70 (95% CI 1.44 – 2.02) in men and women, respectively (Grandinetti et al, 1998).

Interventions for Pre-Diabetes

There is little benefit to knowing one has pre-diabetes if the course of the disease cannot be altered. Conversely, evidence of successful lifestyle and/or pharmaceutical interventions in halting or reversing pre-diabetes demonstrates the need for a well-designed pre-diabetes screening tool.

Lifestyle interventions. Clinical trials have shown lifestyle interventions to be efficacious in delaying or preventing the progression of IGT to type-2 diabetes (Horton, 2009; McMaster University, n.d.). The McMaster University Evidenced Based Practice Center examined the effects of lifestyle changes in their meta-analysis on "The Diagnosis, Prognosis and Treatment of Impaired Glucose Tolerance and Impaired Fasting Glucose," which included 4 studies Figure 9 shows the meta-analytical results of the individual studies and their pooled results (Gillies, 2007). Although the results are promising, difficulty in sustaining lifestyle changes may limit the effectiveness of lifestyle interventions (DeFronzo & Abdul_Ghani, 2011; Horton, 2009; Gohdes, 2009). In the US Diabetes Prevention Program, participants in the lifestyle intervention group lost weight during the first year, but gradually gained weight back during the remainder of the study (Horton, 2009).

Pharmaceutical interventions. Although lifestyle interventions are efficacious in reducing the risk of diabetes in persons with IGT, pharmaceutical interventions may be more effective because they are easier to implement over long periods of time (DeFronzo & Abdul_Ghani, 2011). Pharmaceutical interventions shown effective in lowering diabetes risk include drugs to lower blood glucose (arcabose and metformin); glucagon-like peptide (GLP)-1 receptor agonists, which improve beta-cell function and reduce beta-cell damage; and weight-loss drugs, such as Orlistat, which restricts the body's absorption of fat (DeFronzo & Abdul_Ghani, 2011;Hanefeld et al, 2004; McMaster University, n.d.). Unfortunately, pharmaceutical interventions carry risks that lifestyle interventions do not, such as increased risk of heart failure, bone fractures, and pancreatitis (DeFronzo & Abdul_Ghani, 2011). As a consequence, pharmaceutical interventions which lower the risk of diabetes are recommended

only in persons at extremely high risk of diabetes (those with glucose levels close to the diabetic diagnostic level, combined presence of IFG and IGT; the presence of multiple risk factors for diabetes; or in persons for whom lifestyle interventions have proven unsuccessful (ADA, 2011) In diabetics with high blood pressure, ACE inhibitors and angiotensin receptor blockers not only lower blood pressure, but also reduce the risk of nephropathy, macrovascular events and microvascular damage independent of blood pressure (Heart outcomes prevention evaluation study investigators, 2000). Investigators of The Heart Outcomes Prevention Evaluation (Hope) study, a multinational study, estimated the efficacy of Ramipril, an ACE inhibitor in reducing risk of myocardial infarction, stroke or cardiovascular death (combined outcome) and in reducing risk of nephropathy in diabetics at high risk of a cardiovascular event (Cowie et al, 2006). Participants in the Ramipril group experienced a 25% (95% CI 12 – 36%) reduction in the combined outcome (myocardial infarction, stroke or cardiovascular death) when adjusted for change in blood pressure as well as a 24% (95% CI 3 – 40%) reduction in overt nephropathy when compared to the placebo group (Cowie et al, 2006). Possibly, persons with pre-diabetes and accompanying high blood pressure may also receive the same protection from these antihypertension drugs. Although acarbose is used to treat hyperglycemia, persons with IGT treated with acarbose reaped the additional benefit of slower progression of intima media thickness when compared to persons receiving a placebo (Hanefeld et al, 2004).

Testing for Pre-Diabetes

The ADA supports the use of the fasting plasma glucose test, the oral glucose tolerance test and the HbA1c test as viable diagnostic tests for pre-diabetes. Unfortunately, none of the three tests are sufficient to fully capture the pre-diabetic population because of low

concordance between IFG, IGT and elevated HbA1c (James et al, 2011). As noted earlier, low concordance may be due to the difference in pathophysiology of IFG and IGT (ADA, 2011). Testing for all three pre-diabetic conditions would make low concordance between the three conditions a moot point. Nevertheless, the expense and inconvenience involved in testing for all three may well make testing for hyperglycemia prohibitive for most patients. Concordance between measures is also less than 100% at the diabetic level, which is one reason the World Health Organization recommends the use of the oral glucose tolerance test over the fasting plasma glucose test in screening for diabetes (Definition and diagnosis, n.d.). The use of the oral glucose tolerance test would indicate if the person being testing had IFG and/or IGT, capturing more of the diabetic population (Definition and diagnosis, n.d.).

The ADA has favored the FPG test over the other two in the past and anticipates that HbA1c may become the test of choice by clinicians (ADA, 2011; International Expert Committee, 2009). The ADA's rationale is as follows: the fasting plasma glucose test is cheaper and easier to administer and more reproducible than the oral glucose tolerance test. The HbA1c test is easier to administer and more reproducible than the oral glucose tolerance test (International Expert Committee, 2009; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003) Table 3 illustrates the strengths and weaknesses of each test.

The Fasting Plasma Glucose Test. The most common diagnostic test used for pre-diabetes and diabetes is the fasting plasma glucose test, which measures the level of fasting plasma glucose at the time that the blood is drawn (ADA, 2011; Gohdes, 2009; Hopper, 2011). The benefits of the fasting plasma glucose test are mainly logistic: it is less costly than the other 2 tests and is more easily implemented than the oral glucose tolerance test, requiring only one

blood draw (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). Although all diagnostic tests should be re-administered to confirm diagnosis, the fasting plasma glucose test appears more likely than the oral glucose tolerance test to produce the same diagnostic result (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003; Mooy, 1996) Using a randomly selected group of 525 Whites aged 50 to 74 years who were living in the Netherlands and were participants in the Hoorn Study, Mooy et al compared the intra-individual variation between the fasting plasma glucose test and the oral glucose tolerance test. Time between first and second blood draws were between 2 and 6 weeks. Mooy et al reported that the individual coefficients of variation were 6.4% for the fasting plasma glucose test and 16.7% for the oral glucose tolerance test (Mooy, 1996).

The fasting plasma glucose test cannot identify if the person tested has IGT or elevated HbA1c.(85) The fasting plasma glucose test is also more easily influenced by day-to-day fluctuations in plasma glucose levels due to acute illness and/or stress than HbA1c (International Expert Committee, 2009) and requires that the patient fast for a minimum of 8 hours preceding the blood draw, which the HbA1c does not require (ADA, 2011; International Expert Committee, 2009).

The Oral Glucose Tolerance Test. The oral glucose tolerance test also measures plasma glucose at time of blood draw but requires 2 blood draws, the first of which must be preceded by a minimum of an 8 hour fast. Once fasting blood has been drawn, the patient consumes 75gm of anhydrous glucose, which is followed 2 hours after consumption by a second blood draw. It is this second blood draw that determines the postprandial plasma measure (ADA, 2011). The ADA tends to give more support to the fasting plasma glucose test and the HbA1c

test than to the oral glucose tolerance test because the oral glucose tolerance test produces results that are less reproducible and more expensive than the fasting plasma glucose test. The oral glucose tolerance test is also more inconvenient for patients than the other two tests as well (ADA, 2011). Nevertheless, there are several benefits to using the oral glucose tolerance test that are not common to the fasting plasma glucose test or the HbA1c test (Abate & Chandalia, 2001) First, the oral glucose tolerance test can diagnose the presence of IFG as well as IGT since fasting and postprandial blood draws are taken. As a consequence, a larger portion of persons with pre-diabetes can be detected using the oral glucose tolerance test when compared to the other 2 tests. The oral glucose tolerance test also identifies persons at extremely high risk of diabetes and higher risk of cardiovascular disease due to the combined presence of IFG and IGT (ADA, 2011; Bartoli, 2011) as well as persons with type-2 diabetes due to isolated elevated post prandial blood glucose (Definition and diagnosis, n.d.). The oral glucose tolerance test is limited in use within the US (Gohdes, 2009) because it is more expensive than the fasting plasma glucose test and is much more inconvenient to the patient than the other 2 tests (ADA, 2011; International Expert Committee, 2009; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). The oral glucose tolerance test also shares the same vulnerabilities as the fasting plasma glucose test regarding day-to-day fluctuations since both are point-of-draw measures (International Expert Committee, 2009).

The HbA1c Test. The HbA1c test measures the percent of glycolated hemoglobin A1c present in the blood at time of blood draw which in turn provides a fair approximation of the average glucose level present in the blood over the past few weeks preceding the blood draw (ADA, 2011). Because the HbA1c approximates this average, the HbA1c does not require fasting

or special diet beforehand which is more convenient for the patient than the other 2 tests (International Expert Committee, 2009). An additional benefit specific to the HbA1c test is that it is not sensitive to the day-to-day fluctuations in blood glucose level that plague the other 2 tests (ADA, 2011; International Expert Committee, 2009), and is the most reproducible of the 3 tests (International Expert Committee, 2009; Rohlfing et al, 2002). Using data obtained for a study on sucralose requiring detection of minimal change in blood glucose level, Rohlfing et al compared intra-individual variation between the HbA1c test and the fasting plasma glucose test that were used on the 48 study participants (all male, none diabetic). Blood samples were collected weekly for 12 weeks. Intra-individual variation in the HbA1c test was 1.7% and was 5.7% in the fasting plasma glucose test (Rohlfing et al, 2002).

HbA1c levels can be affected by factors other than glucose level, which can produce spurious results (ADA, 2011; International Expert Committee, 2009; herman, 2009). HbA1c levels rise with age independent of glucose level. Hypertension can also cause elevation in HbA1c level. Any condition or event that elevates or reduces the amount of hemoglobin in the blood also affects the measure of HbA1c. Ethnicity also influences HbA1c levels independent of glucose level: Blacks have been shown to have a higher HbA1c level than other ethnic groups independent of glucose level whereas whites of northern European decent have the lowest HbA1c level, again independent of glucose level (herman, 2009). The difference of HbA1c level due to age and/or ethnicity independent of glucose level has led to considerable controversy regarding the use of HbA1c as a diagnostic test (ADA, 2011; International Expert Committee, 2009; herman, 2009). Although recommendations have been made to set ethnic-specific HbA1c thresholds, the ADA has not yet included ethnic or age specific HbA1c diagnostic

thresholds for pre-diabetes and diabetes in its clinical guidelines (ADA, 2011; International Expert Committee, 2009). Because most, if not all US physicians adhere to the ADA clinical guidelines regarding diagnostic thresholds for pre-diabetes and diabetes, a screening tool designed to identify persons in the US who are at high risk of having a pre-diabetic or diabetic level of HbA1c should also adhere to the ADA clinical guidelines regarding diagnostic thresholds for pre-diabetes and diabetes . Another limiting factor of the HbA1c test is that it cannot distinguish between IFG and IGT (International Expert Committee, 2009), which would hinder the use of lifestyle and pharmaceutical treatments that may be tailored to address the underlying pathophysiology causing the pre-diabetes (NHANES Laboratory Components, n.d.; Faerch et al, 2008). The HbA1c test is also the most costly diagnostic test of the three (ADA, 2011).

Hindrances to Testing. Using 2005-2006 NHANES data on participants aged > 18 years with no history of myocardial infarction and without diabetes, either by self-report or by NHANES lab result (n = 1547), Karve and Hayward estimated that approximately 34.6% of nondiabetic US adults have IFG and/or IGT (Karve & Hayward, 2010) Of these, only about 4.8% reported having ever received a formal diagnosis of pre-diabetes from their physicians, in which pre-diabetes was defined as “borderline diabetes, pre-diabetes, impaired fasting glucose, or impaired glucose tolerance” (Karve & Hayward, 2010). The extremely small percent of pre-diabetic persons aware of their condition indicates that the current pre-diabetes screening practices of most US physicians is apparently inadequate (Karve & Hayward, 2010) One hindrance to adequate pre-diabetes screening is the lack of clear guidance regarding pre-diabetes screening available to clinicians within the US (ADA, 2011; Abdul-Ghani et al , 2006).

Currently, the ADA clinical guidelines do not provide specific criteria to identify persons that should be tested for pre-diabetes (ADA, 2011). Furthermore, there are no pre-diabetes screening tools currently available to physicians that cover IFG, IGT and elevated HbA1c. Clinical inertia, which may be defined as the continuation of clinical habits that evidence indicates should be discontinued or altered in some way, has also been cited as another possible reason for the dearth of pre-diabetes testing (Karve & Hayward, 2010). However, a set of well-designed pre-diabetes screening tools that are easy to implement in a clinical setting can provide the guidance the clinician needs regarding whether to perform a diagnostic test for pre-diabetes and if so, which test to use.

To summarize, pre-diabetes is a complex pathological condition that affects a sizeable number of US adults today, increasing their risk of diabetes and CVD as well as a host of other morbidities commonly associated with diabetes (James et al, 2011; Barr et al, 2009). Unfortunately, the presence of 2 separate pathophysiological conditions within hyperglycemia preclude the use of one diagnostic test to identify all persons with hyperglycemia (ADA, 2011; Del Prato et al, 2002). Currently, the ADA recommends the fasting plasma glucose test and the HbA1c test over the oral glucose tolerance test for the following reasons: the fasting plasma glucose test is cheaper and easier to administer and more reproducible than the oral glucose tolerance test. The HbA1c test is easier to administer and more reproducible than the oral glucose tolerance test (International Expert Committee, 2009; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). Although those factors should be taken into consideration, none of them are based on the patient's comparative likelihoods of having abnormal fasting glucose, and/or abnormal postprandial glucose, and/or having abnormally

high HbA1c due to high blood glucose. Lifestyle and pharmacological interventions may help halt or reverse progression of pre-diabetes as well as lower morbidity and mortality resulting from hyperglycemia. Unfortunately, over 90% of US adults with pre-diabetes are unaware of their condition, which indicates highly inadequate screening for pre-diabetes (Karve & Hayward, 2010). Hindrances to pre-diabetes screening include lack of guidance to the practitioner regarding pre-diabetes screening coupled with clinical inertia. For that reason a set of test-specific pre-diabetes screening tools based on information routinely collected by the physicians during an office visit could provide the practitioner with the impetus and guidance needed for proper pre-diabetes screening.

CHAPTER 3

METHODOLOGY

The objective was to develop an easy-to-use non-invasive pre-diabetes screening tool primarily designed to screen for IFG, IGT and pre-diabetic HbA1c: a pre-diabetes screening tool based on patient information collected by the physician and staff during the course of a routine office visit and that prior research had also shown to be associated with pre-diabetes or type-2 diabetes. The screening tool has been designed to screen for each pre-diabetic condition individually in a non-pregnant patient. The prevalence odds were estimated because a cross-sectional population-based study design was used, with data provided by the 2007 – 2010 National Health and Nutrition Examination Survey (NHANES).

Study Population

The study population was non-pregnant adult NHANES participants aged $\geq$ 20 years with no prior diagnosis of diabetes or pre-diabetes as determined by self-report who were surveyed between the years 2005 – 2010 inclusive for whom complete data was available. The study population was divided into two groups: The training population (n ~ 3000), which was surveyed between the years 2007 – 2010 inclusive with no prior diagnosis of diabetes or pre-diabetes as determined by self-report, and the test population (n ~ 1500), which was surveyed between the years 2005 - 2006. Data collected from the training population was used to create the screening tools. The test population was used to externally validate the tools once created

and was also used for comparative analyses. The survey years 2007 – 2010 were chosen for the training population because these survey years contained data on more predictors on which information is normally obtained during the course of a routine doctor visit than the preceding survey years. Survey years 2005 – 2006 were chosen for the test population because these survey years can be used to validate the tools created for Primary Aims 1 and 2. Study eligibility was restricted to NHANES participants who also had NHANES laboratory measures taken for fasting and postprandial plasma glucose as well as NHANES lab measures taken for HbA1c. The study population was also restricted to participants aged $\geq$ 20 years at the time of the survey because NHANES collected information on all the variables of interest only from participants aged $\geq$ 20 years. Although universal hyperglycemia testing is recommended for persons aged $\geq$ 45 years, clinicians still need guidance regarding which test would be the most appropriate to use for non-pregnant adult patients, even those $\geq$ 45 years of age. As a result, the study population was not restricted to participants aged < 45 years, but encompassed ages $\geq$ 20 years. Eligibility was restricted to NHANES participants with information available on all variables of interest for our study (i.e. no missing values). Variables of interest were: NHANES lab results of the fasting plasma glucose test, the 2-hour oral glucose tolerance test and the percent of HbA1c in the blood; diabetes/pre-diabetes status by self-report; diabetes family history; smoking status; level of alcohol consumption; hypertension status; age; gender; height; weight; heart rate; CVD status; ethnicity; waist circumference; kidney disease status; and for women only, pregnancy status at the time of the survey, number of prior pregnancies, history of gestational diabetes, and age at menarche. More information on all variables of interest has been provided below in the sections on outcome variables and on predictors. Finally, eligibility

was restricted to NHANES participants who were not pregnant at the time of the survey. Eligibility was restricted to non-pregnant participants because the pre-diabetes screening tool has been designed to screen non-pregnant US adults. The reason pregnant US adults were excluded from screening is because almost all pregnant women in the US already undergo a glucose challenge test as a normal part of their prenatal care. After hyperglycemia screening score sets were developed, verified and compared to other screening tools, 2007 – 2010 NHANES participants with a prior diagnosis of hyperglycemia but meeting all the other eligibility criteria were added to the training populations for estimates of the prevalence of undiagnosed hyperglycemic conditions within the entire US adult population.

Because many non-pregnant women within the US periodically visit an obstetrics/gynecology practice or clinic, and these practices routinely collect information regarding history of gestational diabetes and age at menarche (factors shown to be associated with hyperglycemia), screening tools intended for use by these practices have also been designed and tested. Because only parous females have the opportunity to develop gestational diabetes, two female subgroups of the training population were used. The first subgroup was the entire female training population (n ~ 1500), and the intermediate screening models using this population included the additional variable: “Age at Menarche” only. This was the population used in the screening models to create the screening tools for Primary Aim 2. For Secondary Aim1b, the test population (n ~ 750) was NHANES female participants aged $\geq$ 20 years who were surveyed between the years 2005 – 2006 inclusive with no prior diagnosis of diabetes or pre-diabetes as determined by self-report. The Secondary Aim 2b test population was used for external validation of the Primary Aim 2 screening tools. The second female

training subgroup was restricted to the parous female training population (n ~ 1200) and the screening model using this population included the additional variables, “Age at Menarche” and “Gestational Diabetes”. Because information regarding gestational diabetes was not collected on the NHANES 2005 – 2006 female participants, there was not a test population for the Primary Aim 3 screening tools. The entire training population was used for Primary Aim 1, Primary Aim 4a, and Secondary Aim 3a. The female training population was used for Primary Aim 2, Primary Aim 4b, and Secondary Aim 3b. The parous female training population was used for Primary Aim 3, Primary Aim 4c and Secondary Aim 3c. The entire test population was used for Secondary Aim 2a and the female test population was used for Secondary Aim 2b. The lack of NHANES 2005 – 2006 data on gestational diabetes precluded using the NHANES 2005 – 2006 parous female population as a test population for Primary Aim 3 screening tools. Dividing the NHANES 2007 – 2010 parous female population into two populations: one for training and one for testing, was considered. This option was rejected because of the increased potential of sparse data bias that would have been introduced by reducing the sample size of the parous female training population.

The National Health and Nutritional Examination Survey

NHANES is a population-based cross-sectional survey that is on-going in the United States (CDC, n.d.). NHANES uses a multistage sampling scheme so that over a 2-year period, a probability sample of the entire civilian non-institutionalized US population is obtained. This 2-year sample usually numbers about 10,000 persons. NHANES provides weighting and stratification variables as well as instructions on how to use them in statistical analyses. Hence, a 2-year sample or multiple 2-year samples combined into one sample can represent the entire

US civilian non-institutionalized population. When these weighting and stratification variables are properly used, NHANES data can be used to develop screening models representative of the entire non-institutionalized US population being targeted. (i.e. all non-institutionalized non-pregnant adults aged $\geq$ 20 years with no prior diagnosis of diabetes or pre-diabetes living in the US). NHANES gathers data via: a NHANES survey questionnaire administered by a trained NHANES employee, an NHANES medical examination and the taking of NHANES laboratory urine and blood samples (CDC, n.d.).

Diagnostic/Screening Modeling

Diagnostic/screening modeling differs from etiologic modeling. An etiologic model is used to estimate the effect of one factor (exposure) on another factor (outcome). However, a diagnostic/screening model is used to distinguish between those with a certain condition (i.e. "abnormal") and those without the condition (i.e. "normal"). Binary logistic models were used as screening models based on the work of MacIntosh and Pepe (McIntosh & Pepe, 2002). As discussed earlier, MacIntosh and Pepe demonstrate that screening score sets based on logistic models produce optimal screening by proving that for every false positive rate generated along the screening score continuum, its corresponding true positive rate will be at its highest possible value (McIntosh & Pepe, 2002).

Briefly, the logistic model may be expressed as Logit(p) = $e^{\mathrm{a} + \mathrm{b1x1} + \mathrm{b2x2} + \ldots + \mathrm{bixi}}$ where p is the probability of an abnormal outcome (dichotomous dependent variable - abnormal/normal gold standard test result) and x1 – xi are the predictors (independent variables). The scoring set for a particular logistic model may then be used as a test for abnormality by establishing a threshold along the continuum of $\mathrm{b1x1} +$

$\mathrm{b2x2} + \ldots + \mathrm{bixi}$ ranging from $(\mathrm{b1x1} + \mathrm{b2x2} + \ldots + \mathrm{bixi})_{min}$ to $(\mathrm{b1x1} + \mathrm{b2x2} + \ldots + \mathrm{bixi})_{max}$ generated for all values of x1, x2…xi, . Values below the threshold would be considered normal and values at or above the threshold would be considered abnormal. The sensitivity and specificity for each value of $\mathrm{b1x1} + \mathrm{b2x2} + \ldots + \mathrm{bixi}$ along the continuum can be calculated and then used to determine the most appropriate threshold for the test's intended use.

The performance of the binary logistic model as a diagnostic/screening model can be evaluated by estimating the area under the model's receiver operating characteristic curve (AUROC). The AUROC estimates how well the diagnostic/screening model distinguishes abnormal from normal when compared to a gold standard and as one might suspect, is a function of sensitivity and specificity (Hanley & NcNeil, 1982). The receiver operating curve plots sensitivity versus 1 – specificity, with 1 – specificity ranging from 0 to 1 (Cook, 2008). Because the AUROC is the area under this curve, the AUROC estimates $\int_{(1-specificity)=0}^{(1-specificity)=1} d(sensitivity)$. The AUROC also represents the probability that if one were to randomly select two persons from the study population, with one from the abnormal group and one from the normal group, as determined by the gold standard, the diagnostic/screening model would correctly rank the two in regard to odds of abnormality (Hanley & NcNeil, 1982). In essence, the AUROC is an indication of how well the diagnostic/screening model agrees with the gold standard. An AUROC of 0.50 would indicate that the model could theoretically distinguish abnormal from normal no better than the flip of a coin. Conversely, an AUROC of 1.00 would indicate that the model could theoretically distinguish abnormal from normal perfectly (i.e. just as well as the gold standard) (Hanley &

NcNeil, 1982). When using a binary logistic model as a screening model, the AUROC represents the probability that a randomly selected subject with an abnormal gold standard test result will have a higher screening score than a randomly selected subject with a normal gold standard test result (Bewick et al, 2005).

Outcome Variables

Outcome variables were based on the diagnostic test results for the fasting plasma glucose test used to diagnose IFG and fasting diabetes (diabetes type unspecified), the oral glucose tolerance test used to diagnose IGT and postprandial diabetes (diabetes type unspecified), and the HbA1c test used to diagnose elevated HbA1c in the pre-diabetic and diabetic ranges (diabetes type unspecified). These diagnostic tests are the gold standards to which the four components of the screening tool were compared in generating the sensitivities and specificities for the components. Although the primary function of the screening tool has been designed to screen for pre-diabetes, preliminary assessment indicated that the predictive accuracy of the pre-diabetes screening tool would be enhanced by screening for fasting hyperglycemia, which screens for IFG and fasting diabetes; postprandial hyperglycemia, which screens for IGT and postprandial diabetes; and elevated HbA1c, which screens for HbA1c in the pre-diabetic and diabetic ranges. The resultant outcome variables for hyperglycemia were dichotomous and defined by the presence or absence of: 1) fasting hyperglycemia, defined as a fasting plasma glucose level $\geq$ 100mg/dL; 2) postprandial hyperglycemia, defined as a 2-hour oral glucose tolerance test result $\geq$ 140mg/dL; 3) an elevation in HbA1c, defined as $\geq$ 5.7%; and 4) a combined presence of fasting hyperglycemia and postprandial hyperglycemia. The fasting glucose level for NHANES participants was determined by a NHANES laboratory measure using

the fasting plasma glucose test. The fasting glucose was collected by venipuncture from all study participants following a 9-hour fast for the fasting plasma glucose test. The postprandial glucose level was determined by a NHANES laboratory measure using the 2-hour oral glucose tolerance test. For the oral glucose tolerance test, immediately after the fasting sample was collected, study participants drank 75 mg of glucose. Then two hours $\pm$ 15 minutes later, a postprandial glucose sample was collected by venipuncture. The HbA1c level was determined by NHANES laboratory measure of the percent of HbA1c in blood samples obtained from the NHANES participants by venipuncture (NHANES Laboratory Components, n.d.).

Predictors

Predictor Selection- Beginning Models. Predictors for beginning models were limited to factors 1) on which data was available from NHANES 2007 – 2010, 2) that prior studies have documented to be associated with pre-diabetes or type-2 diabetes, 3) which are not assessed by venipuncture or urinalysis (i.e. are non-invasive), and 4) which are measured or assessed during the course of a routine office visit. This is because the goal was to create a pre-diabetes screening tool that can be used for opportunistic pre-diabetes screening by clinicians. Opportunistic pre-diabetes screening can be defined as pre-diabetes screening that takes place during the course of a visit to the doctor's office or to a medical clinic for reasons unrelated to hyperglycemia, such as for an infectious illness or an injury. To meet this objective, predictors did not include laboratory measures that are taken by venipuncture or via a urine sample. Limiting predictors to factors that are routinely taken during the course of an office visit should benefit the physician because the screening will not require extra work on his/her part. The patient should also benefit because the screening can be performed at no additional charge to

the patient. To determine what factors are routinely collected during an initial visit to a clinic or a doctor's office, a convenience sample was taken of the first 10 new patient packets available online through utilizing google.com, using the term "new patient packet", excluding new patient packets that were not intended for the general population, such as breast cancer patients or student populations (McIntosh & Pepe, 2002; New Patient Packet, n.d.; MPMPC, n.d.; Wellspan, n.d.; Adult New Patient Packet, n.d.; Full NewPatient Packet, n.d.; Welcome to NeuroTexas, n.d.; Texas Back Institute, n.d.; Family Doctor, n.d.; North Florida, n.d.; Family Physicians, n.d.). Only factors that were addressed in $\geq$ 8 of the packets were included in the tool. Information provided by 3 medical websites on what to expect during a routine trip to the doctor was also used to identify measures that are routinely measured during the course of an office visit (Lifescape, n.d.; Physicians and diagnosiic procedures, n.d.; What to expect, n.d.). The factors thus identified upon which information is 1) routinely gathered during an initial office visit or 2) routinely measured during the course of an office visit are: age; sex; height; weight; diastolic/systolic blood pressure in millimeters of mercury (mmHg); history of hypertension; use of hypertension drugs; resting heart rate; history of cardiovascular disease; history regarding tobacco use; frequency and amount of current alcohol consumption; and a maternal/paternal/sibling history of diabetes. For use by gynecologists, to determine if age at menarche and history of gestational diabetes are also routinely assessed during a visit to an obstetrics/gynecology practice by a non-pregnant patient, a convenience sample was taken of the first 10 new patient packets available online through utilizing google.com, using the terms "new patient packet" and gynecology. It is the hope that once the screening tool is in place at a clinic or physician's office, patients can be quickly and noninvasively screened at every visit.

Characteristics and Source of Independent Variables in Initial Models. All independent variables (i.e. predictors) for initial models were obtained from NHANES 2007 - 2010. No predictors were based on invasive measures taken by NHANES (i.e. those taken by venipuncture or based on a urine sample) because invasive measures are not routinely taken during the course of a visit to the doctor. The predictor, "Gender" was a dichotomous variable (Male/Female), defined by NHANES participants' self-reported gender. The predictor, "Current Smoker" was a dichotomous variable (Current Smoker/Not Current Smoker), defined by self-report of NHANES participants. The predictor "Alcohol Consumption" was a dichotomous variable (Drinker (> 0 drinks/day)/Nondrinker (0 drinks/day)), defined by self-report of NHANES participants. "Smoker" was defined as a categorical variable (never (less than 100 cigarettes in life-time)/former (greater than 100 cigarettes in lifetime, but no longer smoking)/current), defined by participants' self-reported cigarette smoking status, as was the predicator, "Dichotomous Alcohol Consumption" (none (0 drinks/day), moderate, heavy), with moderate drinking defined as up to one drink/day in women and up to two drinks/day in men, and heavy drinking defined as above those amounts. One drink was defined as consumption of 15 g of ethyl alcohol (Alcohol and Public Health, n.d.). Each form of the factors regarding smoking and alcohol consumption, were included in alternate models, with selection of categorical over dichotomous occurring only if the categorical form **alone** met the selection criteria for model inclusion which was as follows: both categories of smokers/drinkers had odds ratios $\geq$ 1.20 when compared to the non-smokers/non-drinkers, and both categories had p-values < 0.10. The predictor, "First Degree Diabetes Family History," was a dichotomous variable (yes/no regarding presence of diabetes in mother, father and/or sibling(s)), defined by participants' self-

reported status of maternal/paternal/sibling history of diabetes. The predictor, "CVD History," was a dichotomous variable (yes/no) by participants' self-reported CVD history. History of cardiovascular disease was classified as "yes" if any of the following were reported as "yes" by the NHANES participant: "Has a doctor or health professional ever told you you had 1) congestive heart failure, 2) coronary heart disease, 3) angina/angina pectoris, 4) a heart attack, or 5) a stroke?" (Each of these factors was collected individually by NHANES). The predictor, "Hypertension," was a dichotomous variable (yes/no) defined partially by the participants' self-report and partially by NHANES blood pressure measurements for the predictor. High blood pressure was classified as "yes" if 1) the NHANES participant reported having been told more than once by a healthcare professional that he/she had high blood pressure, 2) if the participant reported taking hypertension medicine, or 3) by high blood pressure determined by NHANES blood pressure measurements. NHANES blood pressure measurements were taken 3 or 4 times for each participant. All blood pressure measurements were provided by NHANES as systolic readings and diastolic reading separately. For each participant, the systolic readings were averaged for one systolic reading and the diastolic readings were averaged for one diastolic reading. The NHANES examination measurement of blood pressure was defined as high blood pressure if the average systolic reading was $\geq$140mmHg OR the average diastolic reading was $\geq$ 90mmHg (National Heart Lung, n.d.). The predictor, "Early Menarche," was a dichotomous variable (Yes, No) determined by the female participant's reported age at menarche. Ages < 12 were defined as "Yes" and ages $\geq$ 12 were defined as "No" based on the Chumlea et al study, which estimated the median age of menarche in US female adolescents as age 12.43 based on HNANES III data (Chumlea et al, 2003). The predictor, "Gestational

Diabetes," was a dichotomous variable (yes/no) defined by female participants' self-report. Gestational Diabetes was classified as "yes" if the female participant reported that she had ever been diagnosed with gestational diabetes.

The predictor, "Age" was a continuous variable in units of year, defined by participants' self-reported age in years at time of interview/exam. The predictor, "BMI" was a continuous variable in units of Kg/m^2, defined by NHANES examination measures of standing height and weight and was a surrogate for adiposity. The predictor, "Height," was a continuous variable in units of centimeters, defined by the NHANES examination measure of standing height. Because height varies considerably between genders, the predictor "Height" was adjusted by centering height to each gender. The predictor, "Heart Rate," was a continuous variable in units of beats/minute, defined by NHANES examination measure of resting heart rate and was a surrogate for physical activity level. The decision to use resting heart rate in this manner was based on the TAG-IT team's report of similar predictive abilities between self-reported physical activity and resting heart rate and on the fact that resting heart is routinely measured during an office visit whereas level of physical activity is oftentimes not assessed (McIntosh & Pepe, 2002; New Patient Packet, n.d.; MPMPC, n.d.; Wellspan, n.d.; Adult New Patient Packet, n.d.; Full NewPatient Packet, n.d.; Welcome to NeuroTexas, n.d.; Texas Back Institute, n.d.; Family Doctor, n.d.; North Florida, n.d.; Family Physicians, n.d.).

Predictor Selection – Intermediate Models. The AUROC of a model is resistant to change from the addition or subtraction of predictors within the model (Rohlfing et al, 2002). Cook estimates that the change in AUROC from the addition of a predictor will most likely not be significant (significance – $\alpha < 0.05$) unless the beta-coefficient of the additional predictor is $\geq$

2.78 (odds ratio $\geq$ 16) (Cook, 2007). Nevertheless, Janket et al note that the additional predictor can still increase clinical relevance considerably even if the AUROC is not significantly affected (Janket, 2007). Based on this information, change in AUROC with respect to the addition or subtraction of predictors was not used for predictor selection for intermediate models. Rather, backward elimination was used to generate intermediate models, with elimination of predictors set at $p \geq 0.10$. To ensure that the results of the analyses were representative of the entire US civilian adult noninstitutionalized population and that the results of the analyses also reflected the proper variance, complex logistic regression with the proper weighting, pseudostratum and clustering variables incorporated into the analyses were used for intermediate and final model selection.

Predictor Selection – Final Models. For each intermediate model generated, factors were included in final models only if determined to have more than a negligible impact on the screening score derived from the model. Negligible impact for a predictor was set at a point estimate of an odds ratio > 0.83 (the reciprocal of 1.20) and < 1.20, based on the scoring methods used by the TAG-IT team in which an odds ratio < 1.20 was scored as '0' (Koopman et al , 2008). An estimate in change in odds of hyperglycemia with respect to a 1-unit change in age, in BMI, in heart rate or in height is unlikely to reflect more than a negligible impact on the screening score. TAG-IT addressed this by categorizing age, and heart rate by units of 10, and BMI by units of 5. Rather than categorize these variables, they were kept continuous and odds ratios for 10 unit changes in age and heart rate and a 5 unit change in BMI were estimated for final model variable selection. The TAG-IT team did not include height as a predictor in their models. However Asao and Lawlor assigned 1 standard deviation in height, as observed in their

study populations, as their relevant units of change (Lawlor et al, 2002; Asao et al, 2006). Preliminary analysis indicated that variation in height within each gender in the study population was similar, at roughly 7 centimeters. Based on the above information, odds ratios estimated for final model variable selection was based on 7 unit changes in height.

Because rounding/truncating of continuous variables would simplify the scoring sets generated from the final models, less precise variable forms were created to determine if their use in the final models could produce acceptable AUROCs when compared to the AUROCs generated from the more precise final models. The following method was used to create the less precise forms of Age, BMI, Heart Rate and Height: the variables, Age, and Heart Rate were divided by 10 and then truncated to integer form; BMI was divided by 5 and truncated to integer form and Height (centered) was divided by 7 and truncated to integer form.

For comparison of final model forms, an extensive review of the statistical software available did not reveal any methods that could be used to estimate the AUROCs that would reflect the US adult population and the proper variance for the AUROCs. As a consequence, incorporating the weights that reflected the entire US adult population yielded only the point estimates for the final models' AUROCs which precluded statistical comparison between final model forms. Although an in-depth investigation appears to indicate that clinical significance has yet to be established for comparison of screening models, the Joint Nature Conservation Committee noted that using rule of thumb, a difference of 0.05 in an AUROC could distinguish between a "good" AUROC and a "very good" AUROC (Assessing the Model, n.d.). Based on the above, a "distinguishable" difference of quality between models based on AUROCs was defined for the purposes of this dissertation as a difference of 0.050 in AUROC. For the less precise

model to be deemed acceptable for screening, its AUROC could not be lower than the more precise model by a distinguishable amount.

Linearity of continuous variables was assessed using the Box-Tidwell method (O'Connell, 2006). Briefly, for each continuous variable, X_i, an interaction term of $X_i * \ln X_i$ was entered into the model and the -2 log likelihood of the model was compared to the -2 log likelihood of the model without the interaction terms. Linearity of the variable was defined as a χ^2 p-value $\geq$ 0.05. If the Box-Tidwell method revealed non-linearity of the model, one or more splining terms were created and introduced into the model. Because inclusion of splining terms into the models would create more complex screening score sets, AUROCs of final models with and without splines were compared as described above to determine if inclusion of splining term(s) were warranted. Inclusion of splining term(s) were considered warranted if their inclusion raised the AUROC of the final model by a distinguishable amount ($\geq$ 0.05).

Characteristics and Source of Independent Variables to be Added to Final Models if Necessary. Screening score sets not comparing well to currently available hyperglycemia screening tools, as described below in the "Assessing Tool Performance" section, necessitated the addition of non-invasive predictors to their final models. Additional predictors were limited to factors 1) on which data was available from NHANES 2007 – 2010, 2) that prior studies have documented to be associated with pre-diabetes or type-2 diabetes, 3) which are not assessed by venipuncture or urinalysis (i.e. are non-invasive), and 4) which are not necessarily measured or assessed during the course of a routine office visit, but could be incorporated into a clinic's or physician's routine examination procedures. The predictor, "Ethnicity" was a categorical variable (Non-Hispanic White/Non-Hispanic Black/Hispanic/Other), defined by NHANES

participants' self-reported ethnicity. The predictor, "Waist Circumference" was a continuous variable in units of centimeters, defined by the NHANES examination measure of waist circumference. Because waist circumference varies considerably between genders, the predictor "Waist Circumference" was adjusted by centering waist circumference for each gender. The predictor "Kidney Disease History" was a dichotomous variable (Yes/No), defined by NHANES participants' self-report. History of kidney disease was classified as "yes" if the following was reported as "yes" by the NHANES participant: "Have you ever been told by a doctor or health professional that you had weak or failing kidneys? Do not include kidney stones, bladder infections or incontinence."

Characteristics of Predictors in Screening Score Sets. The characteristics of the predictors in the Screening Score Sets were based on the coding of the predictors for use during logistic regression which are as follows: Gender = 0 if female, 1 if male; 1st Degree Family History of Diabetes = 0 if not present, 1 if present; Hypertension = 0 if not present, 1 if present; Gestational Diabetes = 0 if not present, 1 if present; Current Smoker = 0 if not current smoker, 1 if current smoker; Former Smoker = 0 if not former smoker, 1 if former smoker; Alcohol Consumption = 0 if nondrinker, 1 if drinker; Moderate Drinker = 0 if not moderate drinker, 1 if moderate drinker; Heavy Drinker = 0 if not heavy drinker, 1 if heavy drinker; Age = age in years; Age Group = age in years/10, truncated to integer form; BMI = body mass index in Kg/m^2; BMI Group = body mass index in Kg/m^2/5, truncated to integer form; Heart Rate = beats/minute; Heart Rate Group = beats/minute/10, truncated to integer form; Height = standing height in cm – 151 if male, standing height in cm – 139.8 if female; and Height group = (standing height in cm – 151 if male, standing height in cm – 139.8 if female)/ 7, truncated to integer form. Ethnicity

was coded as follows: Non-Hispanic Black = 0 if not Non-Hispanic Black, 1 if Non-Hispanic Black; Hispanic = 0 if not Hispanic, 1 if Hispanic; and Other = 0 if Non-Hispanic White, 0 if Non-Hispanic Black, 0 if Hispanic, and 1 if none of the aforementioned ethnicities. Table 4 shows the values assigned to the dichotomous variables included in the final models and in the hyperglycemia score sets. Table 5 provides conversions of age, BMI, heart rate and height to their less precise group-forms.

Application

First, using the training population, SPSS was used to determine the β-coefficients for the predictors in the final binary logistic models, using the same complex analysis scheme employed in the intermediate and final model selection. To determine the viability of simplified scoring sets based on rounded β-coefficients, two forms of each final model were constructed, with □-coefficients in one model expressed to the nearest 10^{-4} and the other model with β-coefficients rounded to the nearest tenth. The AUROCs of the two forms of each model were compared, with the model form with rounded b-coefficients deemed acceptable if its AUROC was not lower by a distinguishable amount than the more precise form of the final model.

SPSS was then used to determine the screening score for each participant used to generate the final model $Score_{de} = \sum_{i=first}^{i=last} 10 * B_i X_i$ where Score is the screening score for the participant, d and e specify the outcome and model option, i specifies which predictor in the model, B is the β-coefficient generated for that predictor, and X is the value of that predictor for that particular participant.

For each scoring set, SPSS was also used to generate the sensitivity, the corresponding specificity, and the sum of the two for each point along the screening score set. SPSS was then

used to sort the sums to determine the optimal threshold for the screening score set, which was defined as the maximum value of (Sensitivity + Specificity). As noted earlier, an extensive review of the statistical software available did not reveal any methods that could be used to estimate the AUROCs that would reflect the US adult population and the proper variance for the AUROCs. As a consequence, incorporating the weights that reflected the entire US adult population, SPSS was used to determine only the point estimates for the scoring sets' AUROCs.

The above method was used for all scoring sets generated from the training population. For Primary Aim 1, which was to develop pre-diabetes screening tools for use in all types of physician practices, this consisted of 1 screening score set each for screening of: fasting hyperglycemia, postprandial hyperglycemia, elevated HbA1c and combined fasting hyperglycemia with postprandial hyperglycemia. For Primary Aims 2 and 3, which was to develop the pre-diabetes screening tools restricted to use in obstetrics/gynecology practices, for each aim, this consisted of 1 screening score set each for screening of fasting hyperglycemia, postprandial hyperglycemia, elevated HbA1c and combined fasting hyperglycemia with postprandial hyperglycemia.

Assessing Tool Performance

Tool performance for the proposed pre-diabetes screening tool should meet or exceed performance of screening tools currently in use. For fasting hyperglycemia, comparisons of AUROCs were made between AUROCs generated by the TAG-IT tool (Koopman et al , 2008) and AUROCs generated by the screening score sets developed for Primary Aims 1a, 2a and 3a. For comparison purposes, the unweighted test population and the unweighted female test population, restricted in age to < 65 years were used to generate the AUROCs based on the

TAG-IT screening score set and to generate the AUROCs for the screening score sets that were developed for Primary Aims 1a and 2a respectively, whereas generation of the TAG-IT screening score set AUROC and of the AUROCs for the screening score sets that were developed for Primary Aim 3a used the unweighted parous female training population restricted in age to < 65 years. Restriction in age was necessary because TAG-IT is not intended for fasting hyperglycemic screening of persons $\geq$ 65 years of age.

The analyses used to generate the AUROCS used the methods described below for external and internal validation: The analyses were not weighted, which eliminated the need for complex analyses to determine proper variance. This enabled the use of SPSS to generate estimates of AUROCs that included variance for all screening score sets. AUROCs were compared using the methods developed by Hanley and McNeil for the statistical comparison of AUROCs derived from the same population (Hanley & McNeil, 1983) For each screening score set of the proposed fasting hyperglycemia screening tool to be deemed acceptable, the AUROC of the proposed scoring set could not be significantly lower than the AUROC derived from the TAG-IT tool. If the proposed screening score set was not deemed acceptable, the following predictors were added to the final model from which the screening score set was derived one at a time until the screening score set was deemed acceptable or until all the following predictors had been added: Ethnicity, Waist Circumference and History or Presence of Kidney Disease. If still deemed unacceptable after predictors were added, the proposed screening score set was rejected.

Physicians may also use the ADA guidelines for diabetes testing of asymptomatic patients for fasting hyperglycemia screening. If using only non-invasive measures, physicians

would then test for fasting hyperglycemia in all patients aged ≥ 45 years and in patients < 45 years if the patient has a BMI ≥ 25 kg/m2 **and** one or more of the following risk factors: the presence of hypertension or CVD, a sedentary lifestyle defined by a resting heart rate ≥ 80 beats/min (Aetna, n.d.), a first-degree family history of diabetes, a history of gestational diabetes, and a Black, Hispanic, native American, Asian or Pacific islander ethnicity.

Because the ADA guidelines were designed to have a very high sensitivity when screening for hyperglycemia, the threshold for the fasting hyperglycemia screening score set developed for Primary Aim 1a was set to yield the closest sensitivity to that of the ADA guidelines when screening for fasting hyperglycemia in the unweighted test population (for screening adults), the unweighted female test population (Primary Aim 2a - for screening women only) and the unweighted parous female population (Primary Aim 3a - for screening parous women only). Using the fasting plasma glucose test as the gold standard, the sensitivity and specificity for the threshold of the fasting hyperglycemia screening score set developed for Primary Aim 1a was then compared to the sensitivity and specificity of the non-invasive ADA guidelines when both were applied to the unweighted test population using the extended McNemar Test combined with the use of the Youden index (Hawass, 2007) For the proposed fasting hyperglycemia screening tool to be deemed acceptable for screening of fasting hyperglycemia in which a sensitivity ≥ 0.95 is desired, the sensitivity and specificity of the screening score set thus generated could not be significantly lower than that of the ADA guidelines. The same methods as described above were used to statistically compare the sensitivity and specificity of the ADA guidelines to the female fasting hyperglycemia screening score set and to the parous female fasting hyperglycemia screening score set in the unweighted

female test population and the unweighted parous female training population, respectively. As with the screening score set developed for Primary Aim 1a, the sensitivity and specificity of the thresholds in the screening score sets for Primary Aims 2a and 3a were statistically compared to the ADA guidelines using the extended McNemar test combined with the use of the Youden index (Hawass, 2007) As before, for each fasting hyperglycemia screening score set to be deemed acceptable for screening of fasting hyperglycemia in which a sensitivity $\geq$ 0.95 is desired, the sensitivity and specificity of the screening score set could not be significantly lower than the sensitivity and specificity of the ADA test. If any of the proposed fasting screening score sets were not deemed acceptable, the following predictors were added one at a time to the final model from which the screening score set was derived until the screening score set was deemed acceptable or until all the following predictors had been added: Ethnicity, Waist Circumference and History or Presence of Kidney Disease. If still deemed unacceptable after predictors were added, the proposed screening score set was rejected, but only for screening of fasting hyperglycemia in which a very high sensitivity ($\geq$ 0.95) of the screening tool is desired.

For postprandial hyperglycemia, comparisons of AUROCs were made between AUROCs generated by the FINDRISK tool (Franciosi et al, 2005) and AUROCs generated by the screening score sets developed for Primary Aims 1b, 2b and 3b with the following modifications to the FINDRISK tool: Status regarding daily consumption of fruits and vegetables was excluded because the creators of the FINDRISK tool determined that it was not a strong predictor of diabetes (OR < 1.20) nor were its effects estimated as significant (Franciosi et al, 2005). FINDRISK's creators also estimated that the inclusion of diet increased the predictive ability of their tool by a very small amount (< 0.002). The authors' rationale for including diet in the

FINDRISK tool was based on a priori information showing diet as a risk factor for diabetes, rather than its observed predictive effects within the FINDRISK tool. A heart rate $\geq$ 80 beats/minute was used as a surrogate for sedentary behavior(106), replacing the author's definition for sedentary behavior, which was a self-report of < 4 hours a week of physical activity (Franciosi et al, 2005). For comparison purposes, the test population and the female test population, restricted in age to < 65 years were used to generate the AUROCs based on the modified FINDRISK tool and to generate the AUROCs for the screening score sets that were developed for Primary Aims 1b and 2b respectively, whereas generation of the modified FINDRISK AUROC and of the AUROCs for the screening score sets that were developed for Primary Aim 3b used the parous female training population restricted in age to < 65 years. Restriction in age was necessary because FINDRISK is not intended for screening of persons $\geq$ 65 years of age.

The analyses used to generate the AUROCS used the methods described for external and internal validation: The analyses were not weighted, which eliminated the need for complex analyses to determine proper variance. This enabled the use of SPSS to generate estimates of AUROCs that included variance for all screening score sets. AUROCs were compared using the methods developed by Hanley and McNeil for the statistical comparison of AUROCs derived from the same population (Hanley & McNeil, 1983). For each screening score set of the proposed fasting hyperglycemia screening tool to be deemed acceptable, the AUROC of the proposed scoring set could not be significantly lower than the AUROC derived from the modified FINDRISK tool. If the proposed screening score set was not deemed acceptable, the following predictors were added one at a time to the final model from which the screening

score set was derived until the screening score set was deemed acceptable or until all the following predictors had been added: Ethnicity, Waist Circumference and History or Presence of Kidney Disease. If still deemed unacceptable after predictors were added, the proposed screening score set was rejected.

Physicians may also use the ADA guidelines for diabetes testing of asymptomatic patients for postprandial hyperglycemia screening. If using only non-invasive measures, physicians would then test for postprandial hyperglycemia in all patients aged $\geq$ 45 years and in patients < 45 years if the patient has a BMI $\geq$ 25 kg/m2 **and** one or more of the following risk factors: the presence of hypertension or CVD, a sedentary lifestyle defined as a resting heart rate $\geq$ 80 beats/min (Aetna, n.d.), a first-degree family history of diabetes, a history of gestational diabetes, and a Black, Hispanic, native American, Asian or Pacific islander ethnicity.

Because the ADA guidelines were designed to have a very high sensitivity when screening for hyperglycemia, the threshold for the postprandial hyperglycemia screening score set developed for Primary Aim 1b was set to yield the closest sensitivity to that of the ADA guidelines when screening for fasting hyperglycemia in the unweighted test population (for screening adults), the unweighted female test population (Primary Aim 2b - for screening women only) and the unweighted parous female population (Primary Aim 3b - for screening parous women only). Using the oral glucose tolerance test as the gold standard, the sensitivity and specificity for the threshold of the postprandial hyperglycemia screening score set developed for Primary Aim 1b was compared to the sensitivity and specificity of the non-invasive ADA guidelines when both were applied to the unweighted test population using the extended McNemar Test combined with the Youden Index (Hawass, 2007). For the proposed

postprandial hyperglycemia screening score set to be deemed acceptable for screening of postprandial hyperglycemia in which a sensitivity $\geq$ 0.95 is desired, the sensitivity and specificity of the screening score set thus generated could not have been significantly lower than that of the ADA guidelines. The same methods as described above were used to statistically compare the sensitivity and specificity of the ADA guidelines to the female postprandial hyperglycemia screening score set and to the parous female postprandial hyperglycemia screening score set in the unweighted female test population and the unweighted parous female training population, respectively. As with the screening score set developed for Primary Aim 1b, the sensitivity and specificity of the thresholds in the screening score sets for Primary Aims 2b and 3b were statistically compared to the ADA guidelines using the extended McNemar test combined with the use of the Youden index (Hawass, 2007). As before, for each postprandial hyperglycemia screening score set to be deemed acceptable for screening of postprandial hyperglycemia in which a sensitivity $\geq$ 0.95 is desired, the sensitivity and specificity of the screening score set could not have been significantly lower than the sensitivity and specificity of the ADA test. If any of the proposed postprandial screening score sets were not deemed acceptable, the following predictors were added one at a time to the final model from which the screening score set was derived until the screening score set was deemed acceptable or until all the following predictors had been added: Ethnicity, Waist Circumference and History or Presence of Kidney Disease. If still deemed unacceptable after predictors were added, the proposed screening score set was rejected, but only for screening of postprandial hyperglycemia in which a very high sensitivity ($\geq$ 0.95) of the screening tool is desired.

For combined presence of fasting hyperglycemia and post-prandial hyperglycemia, comparisons of AUROCs were made between AUROCs generated by the screening score sets developed for Primary Aims 1c, 2c and 3c and the AUROCs generated by the TAG-IT tool(Koopman et al , 2008) as well as to the AUROC generated by the modified FINDRISK tool(Franciosi et al, 2005) For comparison purposes, the test population and the female test population were used to generate the AUROCs based on the TAG-IT tool and the modified FINDRISK tool and to generate the AUROCs for the screening score sets that were developed for Primary Aims 1c and 2c respectively, whereas generation of the TAG-IT tool AUROC and the modified FINDRISK tool and of the AUROCs for the screening score sets that were developed for Primary Aim 3c used the parous female training population. Training and Test populations were restricted in age to < 65 years for comparisons to the TAG-IT tool and to the modified FINDRISK tool. Restriction in age was necessary because TAG-IT and FINDRISK are not intended for fasting hyperglycemic screening of persons $\geq$ 65 years of age (Koopman et al , 2008; Franciosi et al, 2005)

The analyses used to generate the AUROCS used the methods described for external and internal validation: The analyses were not weighted, which eliminated the need for complex analyses to determine proper variance. This enabled the use of SPSS to generate estimates of AUROCs that included variance for all screening score sets. AUROCs were compared using the methods developed by Hanley and McNeil for the comparison of AUROCs derived from the same population (Hanley & McNeil, 1983). For each screening score set of the proposed fasting/postprandial hyperglycemia screening tool to be deemed acceptable, the AUROC of the proposed scoring set could not be significantly lower than the AUROCs derived

from the TAG-IT tool (Koopman et al , 2008) or than the AUROCs derived from the FINDRISK tool (Franciosi et al, 2005). If the proposed screening score set was not deemed acceptable, the following predictors were added one at a time to the final model from which the screening score set was derived until the screening score set was deemed acceptable or until all the following predictors had been added: Ethnicity, Waist Circumference and History or Presence of Kidney Disease. If still deemed unacceptable after predictors were added, the proposed screening score set was rejected.

Physicians may also use the ADA guidelines for diabetes testing of asymptomatic patients for screening of combined presence of fasting hyperglycemia and postprandial hyperglycemia. If using only non-invasive measures, physicians would then test for fasting hyperglycemia and postprandial hyperglycemia in all patients aged $\geq$ 45 years and in patients < 45 years if the patient has a BMI $\geq$ 25 kg/m2 **and** one or more of the following risk factors: the presence of hypertension or CVD, a sedentary lifestyle defined by a resting heart rate $\geq$ 80 beats/min (Aetna, n.d.), a first-degree family history of diabetes, a history of gestational diabetes, and a Black, Hispanic, native American, Asian or Pacific islander ethnicity.

Because the ADA guidelines were designed to have a very high sensitivity when screening for hyperglycemia, the threshold for the fasting/postprandial hyperglycemia screening score set developed for Primary Aim 1c was set to yield the closest sensitivity to that of the ADA guidelines when screening for combined presence of fasting hyperglycemia and postprandial hyperglycemia in the unweighted test population (for screening adults), the unweighted female test population (Primary Aim 2c - for screening women only) and the unweighted parous female population (Primary Aim 3c - for screening parous women only).

Using the fasting plasma glucose test combined with the oral glucose tolerance test as the gold standard, the sensitivity and specificity for the threshold of the fasting/postprandial hyperglycemia screening score set developed for Primary Aim 1c was compared to the sensitivity and specificity of the non-invasive ADA guidelines when both were applied to the unweighted test population using the extended McNemar Test combined with the use of the Youden index (Hawass, 2007). For the proposed fasting/postprandial hyperglycemia screening score set to be deemed acceptable for screening of combined presence of fasting hyperglycemia and postprandial hyperglycemia in which a sensitivity $\geq$ 0.95 is desired, the sensitivity and specificity of the screening score set thus generated could not have been significantly lower than that of the ADA guidelines. The same methods as described above were used to statistically compare the sensitivity and specificity of the ADA guidelines to the female fasting/postprandial hyperglycemia screening score set and to the parous female fasting/postprandial hyperglycemia screening score set in the unweighted female test population and the unweighted parous female training population, respectively. As with the screening score set developed for Primary Aim 1c, the sensitivity and specificity of the thresholds in the screening score sets for Primary Aims 2c and 3c were statistically compared to the ADA guidelines using the extended McNemar test combined with the use of the Youden index (Hawass, 2007). As before, for each fasting/postprandial hyperglycemia screening score set to be deemed acceptable for screening of combined presence of fasting hyperglycemia and postprandial hyperglycemia in which a sensitivity $\geq$ 0.95 is desired, the sensitivity and specificity of the screening score set could not have been significantly lower than the sensitivity and specificity of the ADA test. If any of the proposed fasting/postprandial hyperglycemia screening

score sets were not deemed acceptable, the following predictors were added one at a time to the final model from which the screening score set was derived until the screening score set was deemed acceptable or until all the following predictors had been added: Ethnicity, Waist Circumference and History or Presence of Kidney Disease. If still deemed unacceptable after predictors were added, the proposed screening score set was rejected, but only for screening of combined presence of fasting hyperglycemia and postprandial hyperglycemia when a very high sensitivity ($\geq$ 0.95) of the screening tool is desired.

Extensive literature reviews did not reveal the presence of screening tools developed to screen for elevated HbA1c. In lieu of such a screening tool, physicians may use the ADA guidelines for diabetes testing of asymptomatic patients for screening elevated HbA1c in patients. If using only non-invasive measures, physicians would then test for elevated HbA1c in all patients aged $\geq$ 45 years and in patients < 45 years if the patient has a BMI $\geq$ 25 kg/m2 **and** one or more of the following risk factors: the presence of hypertension or CVD, a sedentary lifestyle defined by a resting heart rate $\geq$ 80 beats/min (Aetna, n.d.), a first-degree family history of diabetes, a history of gestational diabetes, and a Black, Hispanic, native American, Asian or Pacific islander ethnicity.

Because the ADA guidelines were designed to have a very high sensitivity when screening for hyperglycemia, the threshold for the elevated HbA1c screening score set developed for Primary Aim 1d was set to yield the closest sensitivity to that of the ADA guidelines when screening for elevated HbA1c in the unweighted test population (for screening adults), the unweighted female test population (Primary Aim 2d - for screening women only) and the unweighted parous female population (Primary Aim 3d - for screening parous women

only). Using the HbA1c test as the gold standard, the sensitivity and specificity for the threshold of the elevated HbA1c screening score set developed for Primary Aim 1d was compared to the sensitivity and specificity of the non-invasive ADA guidelines when both were applied to the unweighted test population using the extended McNemar Test combined with the use of the Youden index (Hawass, 2007) For the proposed elevated HbA1c screening score set to be deemed acceptable, the sensitivity and specificity of the screening score set thus generated could not have been significantly lower than that of the ADA guidelines. The same methods as described above were used to statistically compare the sensitivity and specificity of the ADA guidelines to the female elevated HbA1c screening score set and to the parous female elevated HbA1c screening score set in the unweighted female test population and the unweighted parous female training population, respectively. As with the screening score set developed for Primary Aim 1d, the sensitivity and specificity of the thresholds in the elevated HbA1c screening score sets for Primary Aims 2d and 3d were statistically compared to the ADA guidelines using the extended McNemar test combined with the use of the Youden index (Hawass, 2007). As before, for each elevated HbA1c screening score to be deemed acceptable, the sensitivity and specificity of the screening score set could not have been significantly lower than the sensitivity and specificity of the ADA guidelines. If any of the proposed elevated HbA1c screening score sets were not deemed acceptable, the following predictors were added one at a time to the final model from which the screening score set was derived until the screening score set was deemed acceptable or until all the following predictors had been added: Ethnicity, Waist Circumference and History or Presence of Kidney Disease. If still deemed unacceptable after predictors were added, the proposed screening score set was rejected.

Validity of Hyperglycemia Screening Score Sets

For external validation, SPSS was used to generate an AUROC for each of the four screening score sets developed for Primary Aims 1 and 2 by the following methods: For Secondary Aim 2a, which was to externally validate each of the four screening tools developed for Primary Aim 1, screening scores for the presence of fasting hyperglycemia, post-prandial hyperglycemia, combined presence of fasting and post-prandial hyperglycemia, and elevated HbA1c were generated for all participants in the test population using the four screening score sets developed for Primary Aims 1a - 1d. Each set of screening scores generated by its corresponding screening score set was then used to generate an estimate of the screening tool's AUROC when used in the unweighted test population. The analyses were not weighted, which eliminated the need for complex analyses to determine proper variance. This enabled the use of SPSS to generate estimates of AUROCs that included variance for all screening score sets.

For Secondary Aim 2b, which was to externally validate each of the four screening tools (i.e.: screening score sets) developed for Primary Aim 2 screening scores for the presence of fasting hyperglycemia, post-prandial hyperglycemia, combined presence of fasting and post-prandial hyperglycemia, and elevated HbA1c were generated for all **female** participants in the test population using the four screening score sets developed for Primary Aims 2a - 2d. Each set of screening scores generated by its corresponding screening tool was then used to generate an estimate of the screening tool's AUROC when used in the unweighted female test population. The analyses were not weighted, which eliminated the need for complex analyses to determine

proper variance. This enabled the use of SPSS to generate estimates of AUROCs that included variance for all screening score sets.

For Secondary Aim 3, the screening score sets were also internally validated in subgroups of the training populations: For Secondary Aim 3a, which was to internally validate each of the four screening tools developed for Primary Aim 1, screening scores for the presence of fasting hyperglycemia, post-prandial hyperglycemia, combined presence of fasting and post-prandial hyperglycemia, and elevated HbA1c were generated for each ethnic subgroup of the training population using the four screening score sets developed for Primary Aims 1a -1d. Ethnic subgroups were defined as Non-Hispanic Whites, Non-Hispanic Blacks, Hispanics and Other Ethnicities. Each set of screening scores thus generated was then used to generate the estimate of the screening tool's AUROC for its corresponding training subpopulation. The analyses were not weighted, which eliminated the need for complex analyses to determine proper variance. This enabled the use of SPSS to generate estimates of AUROCs that included variance for all screening score sets. AUROCs were compared using the methods described by Hanley and McNeil for the statistical comparison of AUROCs derived from different populations (Hanley & McNeil, 1983).

For Secondary Aim 3b, which is to internally validate each of the four screening tools developed for Primary Aim 2, screening scores for the presence of fasting hyperglycemia, post-prandial hyperglycemia, combined presence of fasting and post-prandial hyperglycemia, and elevated HbA1c were generated for each ethnic subgroup of the **female** training population using the four screening score sets developed for Primary Aims 2a - 2d. Ethnic subgroups were defined as Non-Hispanic Whites, Non-Hispanic Blacks, Hispanics and Other Ethnicities. Each set

of screening scores thus generated was then used to generate the estimate of the screening score set's AUROC for its corresponding female training subpopulation. The analyses were not weighted, which eliminated the need for complex analyses to determine proper variance. This enabled the use of SPSS to generate estimates of AUROCs that included variance for all screening score sets. AUROCs were compared using the methods described by Hanley and McNeil for the comparison of AUROCs derived from different populations (Hanley & McNeil, 1983).

For Secondary Aim 3c, which was to internally validate each of the four screening tools developed for Primary Aim 3, screening scores for the presence of fasting hyperglycemia, post-prandial hyperglycemia, combined presence of fasting and post-prandial hyperglycemia, and elevated HbA1c were generated for each ethnic subgroup of the **parous female** training population using the four screening score sets developed for Primary Aims 3a - 3d. Ethnic subgroups were defined as Non-Hispanic Whites, Non-Hispanic Blacks, Hispanics and Other Ethnicities. Each set of screening scores thus generated were then used to generate the screening score set's estimate of the AUROC for its corresponding parous female training subpopulation. The analyses were not weighted, which eliminated the need for complex analyses to determine proper variance. This enabled the use of SPSS to generate estimates of AUROCs that included variance for all screening score sets. AUROCs were compared using the methods described by Hanley and McNeil for the statistical comparison of AUROCs derived from different populations (Hanley & McNeil, 1983).

CHAPTER 4

RESULTS

Descriptive Analysis

The 3063 NHANES participants in the training population represented approximately 161 million non-pregnant US adults aged ≥ 20 years with no prior diagnosis of hyperglycemia who were living in the US during the years of 2007 – 2010. Using measures of fasting hyperglycemia, postprandial hyperglycemia, etc…. over half of those (54.2% - roughly 87 million US adults) were estimated to have some form of hyperglycemia. 42.9% of the non-pregnant US adult population with no prior diagnosis of hyperglycemia was estimated to have undiagnosed fasting hyperglycemia (20.1% isolated); 18.7% with undiagnosed postprandial hyperglycemia (3.5% isolated); 13.6% with a combined presence of undiagnosed fasting hyperglycemia and undiagnosed postprandial hyperglycemia; and 23.0% with undiagnosed elevated HbA1c (6.2% isolated). Table 6 shows the prevalence estimates for unspecified hyperglycemia and for each hyperglycemic condition in the non-pregnant US adult population without a prior diagnosis of hyperglycemia (years 2007 – 2010), as well as the prevalence estimates in non-pregnant US women and in non-pregnant parous US women, each population with no prior diagnosis of hyperglycemia (years 2007 – 2010). For the same three populations, Table 7 provides weighted estimates of the characteristics of factors purportedly associated with hyperglycemia. Table 6 also provides prevalence estimates for undiagnosed, unspecified hyperglycemia and for each

undiagnosed hyperglycemic condition within the full non-pregnant US adult population, which includes non-pregnant US adults *with* a prior diagnosis of hyperglycemia along with those without a prior diagnosis.

Form of Final Models

The AUROCs of all models in which age was measured in 10-year categories, BMI in 5 Kg/m^2 categories, heart rate by 10 beats/min categories, and/or height by 7 cm categories were not lower by a distinguishable amount (distinguishable = difference between AUROCs $\geq$ 0.050) when compared to models in which age was measured by year, BMI by kg/m^2, heart rate by beats/min, and/or centered height by cm (results not shown). As a consequence, the less precise form of the continuous variables (i.e. by variable group) was used in the final models.

Use of the Box-Tidwell method (O'Connell, 2006) indicated that the inclusion of splining terms for BMI might have been warranted in models developed to screen for postprandial hyperglycemia (one degree freedom $\chi^2 = 5.145$, $p < 0.05$) and for combined presence of fasting hyperglycemia and postprandial hyperglycemia ((one degree freedom $\chi^2 = 10.561$, $p < 0.05$), both for use within the US adult population. Although splining was introduced into the two models, the difference of the AUROCs between the models with splining terms and the models without splining terms were not distinguishable.(results not shown) As a result, splining terms were not included in any of the final models.

The AUROC's of models in which their β-coefficients were rounded to the nearest tenth were not distinguishably lower than AUROCs in which the β-coefficients were expressed to the nearest 10^{-4} (results not shown). As a result, β-coefficients of all final models were rounded to the nearest tenth.

The combined effects of group-terms, non-inclusion of splining terms, and the rounding of □-coefficients did not lower the AUROC of any final models by a distinguishable amount when compared to the models' most precise forms. Estimated differences in AUROCs between the most precise and least precise versions of the same models ranged from 0.001 in the model to screen for postprandial hyperglycemia in US women to 0.019 in the model to screen for combined presence of fasting hyperglycemia and postprandial hyperglycemia in US adults, lending further support for the use of the least precise models, which in turn produced the simplest, most user friendly screening score sets.

Factors selected by backward step-wise selection **and** found potentially to have more than a negligible impact on the screening scores (i.e. producing an odds ratio $\geq$ 1.20 or $\leq$ 0.83) and thus included in final models shared similarities within models with the same outcomes. Heart rate, representing level of physical activity and height were selected for final models when postprandial hyperglycemia was the outcome, but were not selected for final models when fasting hyperglycemia or elevated HbA1c were the outcomes. When the population under study contained men and women, gender was selected for final models when fasting hyperglycemia and the combined presence of fasting hyperglycemia and postprandial hyperglycemia were the outcomes but not when postprandial hyperglycemia or elevated HbA1c were the outcomes. Smoking was selected for final models when elevated HbA1c was the outcome, but not when fasting hyperglycemia or postprandial hyperglycemia were the outcomes. The factors, age and BMI were selected for final models for all outcomes in all populations, as was gestational diabetes when the population was restricted to parous women. Having a 1st degree relative with diabetes was selected for final models for all outcomes but not

in all populations. The one factor not selected for any final models for any outcomes was early menarche in women.

Comparative Results – Secondary Aim 1

Fasting Hyperglycemia. The ability of the Fasting Hyperglycemia Screening Score Set to distinguish non-pregnant US adults aged 20 – 64 years with fasting hyperglycemia from non-pregnant US adults aged 20 – 64 years without fasting hyperglycemia did not differ by a significant amount (difference in AUROC: 0.015(95% CI: -0.007 – 0.037), p = 0.184) from that of the TAG-IT tool when both were applied to the **unweighted** test population aged 20 – 64 years). The ability of the Women's Fasting Hyperglycemia Screening Score Set to distinguish non-pregnant US women aged 20 – 64 years with fasting hyperglycemia from non-pregnant US women aged 20 – 64 years without fasting hyperglycemia also did not differ by a significant amount (difference in AUROC: 0.009 (95% CI: -0.030 – 0.049), p = 0.653) when both were applied to the unweighted female training population aged 20 – 64 years. Because the Parous Women's Fasting Hyperglycemia Screening Score Set did not fare well when compared to the ADA testing guidelines for asymptomatic adults (details provided below), the screening score set was modified to enhance screening performance and the modified screening score set was compared to the TAG-IT tool. The ability of the modified Parous Women's Fasting Hyperglycemia Screening Score Set to distinguish non-pregnant parous US women with fasting hyperglycemia from non-pregnant parous US women without fasting hyperglycemia was estimated as significantly higher than that of TAG-IT when both were applied to the unweighted parous female training population. (difference in AUROC: 0.057 (95% CI: 0.026 – 0.088), p <

0.001). Table 24 provides side-by-side AUROCs for the fasting hyperglycemia score sets and the AUROCs for the TAG-IT tool, as well as the differences in AUROC between them.

The combined ability of the Fasting Hyperglycemia Screening Score Set to correctly define non-pregnant US adults with fasting hyperglycemia as having fasting hyperglycemia **and** to also correctly define non-pregnant US adults without fasting hyperglycemia as not having fasting hyperglycemia was estimated to be significantly higher than that of the non-invasive ADA testing guidelines for asymptomatic adults (Youden Index: Fasting Hyperglycemia Screening Score Set = 0.214; ADA guidelines = 0.161, $p = 0.03$) when both were applied to the test population. The combined ability of the Women's Fasting Hyperglycemia Screening Score Set to correctly define non-pregnant US women with fasting hyperglycemia as having fasting hyperglycemia **and** to also correctly define non-pregnant US women without fasting hyperglycemia as not having fasting hyperglycemia was also estimated to be significantly higher than that of the non-invasive ADA testing guidelines for asymptomatic adults (Youden Index: Women's Fasting Hyperglycemia Screening Score Set = 0.240; ADA guidelines = 0.214, $p < 0.01$) when both were applied to the female test population. However, the combined ability of the Parous Women's Fasting Hyperglycemia Screening Score Set to correctly define non-pregnant parous US women with fasting hyperglycemia as having fasting hyperglycemia **and** to also correctly define non-pregnant parous US women without fasting hyperglycemia as not having fasting hyperglycemia was significantly *lower* than that of the non-invasive ADA testing guidelines for asymptomatic adults (Youden Index: Parous Women's Fasting Hyperglycemia Screening Score Set = 0.130; ADA guidelines = 0.198, $p < 0.001$) when both were applied to the unweighted parous female training population. When the predictor, "Ethnicity" was added to

the final model and the resultant modified Parous Women's Fasting Hyperglycemia Screening Score Set was compared to the ADA guidelines, the combined ability of the modified Parous Women's Fasting Hyperglycemia Screening Score Set to correctly define non-pregnant parous US women with fasting hyperglycemia as having fasting hyperglycemia **and** to also correctly define non-pregnant parous US women without fasting hyperglycemia as not having fasting hyperglycemia was no longer significantly different than that of the non-invasive ADA testing guidelines for asymptomatic adults (Youden Index: Parous Women's Fasting Hyperglycemia Screening Score Set = 0.196; ADA guidelines = 0.198, p = 0.389). Table 24 also provides the comparative sensitivity and specificity for each of the fasting hyperglycemia screening score sets as well as the sensitivities and specificities of the noninvasive ADA clinical guidelines for testing of asymptomatic adults.

Postprandial Hyperglycemia*.* The ability of the Postprandial Hyperglycemia Screening Score Set to distinguish non-pregnant US adults aged 20 – 64 years with postprandial hyperglycemia from non-pregnant US adults aged 20 – 64 years without postprandial hyperglycemia was significantly higher than that of the modified FINDRISK tool when both were applied to the **unweighted** test population aged 20 – 64 years (difference in AUROC: 0.044(95% CI: 0.013 – 0.175), p = 0.006). The ability of the Women's Postprandial Hyperglycemia Screening Score Set to distinguish non-pregnant US women aged 20 – 64 years with postprandial hyperglycemia from non-pregnant US women aged 20 – 64 years without postprandial hyperglycemia did not significantly differ from that of the modified FINDRISK tool (difference in AUROC: 0.039 (95% CI: -0.005 – 0.083), p = 0.082) when both were applied to the unweighted female training population aged 20 – 64 years. The ability of the Parous Women's Postprandial

Hyperglycemia Screening Score Set to distinguish non-pregnant parous US women with postprandial hyperglycemia from non-pregnant parous US women without postprandial hyperglycemia was significantly higher than that of the modified FINDRISK tool when both were applied to the **unweighted** parous female test population aged 20 – 64 years (difference in AUROC: 0.045 (95% CI: 0.009 – 0.081), p = 0.016). Table 25 provides side-by-side AUROCs for the fasting hyperglycemia score sets and the AUROCs for the modified FINDRISK tool, as well as the differences in AUROC between them.

The combined ability of the Postprandial Hyperglycemia Screening Score Set to correctly define non-pregnant US adults with postprandial hyperglycemia as having postprandial hyperglycemia **and** to also correctly define non-pregnant US adults without postprandial hyperglycemia as not having postprandial hyperglycemia was significantly higher than that of the non-invasive ADA testing guidelines for asymptomatic adults (Youden Index: Postprandial Hyperglycemia Screening Score Set = 0.285; ADA guidelines = 0.164, p < 0.001) when both were applied to the test population. The combined ability of the Women's Fasting Hyperglycemia Screening Score Set to correctly define non-pregnant US women with postprandial hyperglycemia as having postprandial hyperglycemia **and** to also correctly define non-pregnant US women without postprandial hyperglycemia as not having postprandial hyperglycemia was not significantly different that of the non-invasive ADA testing guidelines for asymptomatic adults (Youden Index: Women's Postprandial Hyperglycemia Screening Score Set = 0.209; ADA guidelines = 0.192, p = 0.413) when both were applied to the female test population. Unfortunately, the combined ability of the Parous Women's Postprandial Hyperglycemia Screening Score Set to correctly define non-pregnant parous US women with postprandial

hyperglycemia as having postprandial hyperglycemia **and** to also correctly define non-pregnant parous US women without postprandial hyperglycemia as not having postprandial hyperglycemia was estimated to be significantly lower from that of the non-invasive ADA testing guidelines for asymptomatic adults (Youden Index: Parous Women's Postprandial Hyperglycemia Screening Score Set = 0.136; ADA guidelines = 0.236, p = 0.01) when both were applied to the unweighted parous female training population. Addition of the predictors, "Ethnicity", "Waist Circumference" and "Kidney Disease History" did not enhance the resultant screening tool sufficiently for the Parous Women's Postprandial Hyperglycemia Screening Score Set to be acceptable for screening of postprandial hyperglycemia in parous women when sensitivity $\geq$ 0.95 is desired (results not shown). Table 25 also provides the maximum combined sensitivity and specificity for each of the fasting hyperglycemia screening score sets as well as the combined sensitivities and specificities of the noninvasive ADA clinical guidelines for testing of asymptomatic adults.

Combined Presence of Fasting/Postprandial Hyperglycemia. The ability of the Fasting/Postprandial Hyperglycemia Screening Score Set to distinguish non-pregnant US adults aged 20 – 64 years with the combined presence of fasting and postprandial hyperglycemia from non-pregnant US adults aged 20 – 64 years without the combined presence of fasting and postprandial hyperglycemia was significantly higher than that of the TAG-IT tool (difference in AUROC: 0.059(95% CI: -0.022 – 0.096), p = 0.184) when both were applied to the **unweighted** test population aged 20 – 64 years. On the other hand when the modified FINDRISK tool was also applied to the same population, it was estimated to have similar screening ability to that of the Fasting/Postprandial Hyperglycemia Screening Score Set (difference in AUROC: 0.029(95%

CI: -0.009 – 0.092), p = 0.136). The ability of the Women's Fasting/Postprandial Hyperglycemia Screening Score Set to distinguish non-pregnant US women aged 20 – 64 years with the combined presence of fasting and postprandial hyperglycemia from non-pregnant US women aged 20 – 64 years without the combined presence of fasting and postprandial hyperglycemia was not significantly different from that of the TAG-IT tool (difference in AUROC: 0.003 (95% CI: -0.046 – 0.052), p = 0.904) and to the modified FINDRISK tool (difference in AUROC: -0.004 (95% CI: 0.073 – 0.185), p = 0.818) when all were applied to the unweighted female training population aged 20 – 64 years. Conversely, the ability of the Parous Women's Fasting/Postprandial Hyperglycemia Screening Score Set to distinguish non-pregnant parous US women with the combined presence of fasting and postprandial hyperglycemia from non-pregnant parous US women without the combined presence of fasting and postprandial hyperglycemia was significantly higher than that of the TAG-IT tool (difference in AUROC: 0.063 (95% CI: 0.018 – 0.108), p = 0.007) and of the modified FINDRISK tool (difference in AUROC: 0.051 (95% CI: 0.010 – 0.092), p = 0.016) when all were applied to the unweighted parous female training population. Table 26 provides side-by-side AUROCs for the fasting/postprandial hyperglycemia score sets, the AUROCs for the TAG-IT tool and the AUROCs for the modified FINDRISK tool as well as the differences in AUROC between them.

The combined ability of the Fasting/Postprandial Hyperglycemia Screening Score Set to correctly define non-pregnant US adults with the combined presence of fasting and postprandial hyperglycemia as having the combined presence of fasting and postprandial hyperglycemia **and** to also correctly define non-pregnant US adults without the combined presence of fasting and postprandial hyperglycemia as not having the combined presence of

fasting and postprandial hyperglycemia was estimated to be significantly higher than that of the non-invasive ADA testing guidelines for asymptomatic adults (Youden Index: Fasting/Postprandial Hyperglycemia Screening Score Set = 0.223; ADA guidelines = 0.169, $p < 0.01$) when both were applied to the test population. The combined ability of the Women's Fasting/Postprandial Hyperglycemia Screening Score Set to correctly define non-pregnant US women with the combined presence of fasting and postprandial hyperglycemia as having the combined presence of fasting and postprandial hyperglycemia **and** to also correctly define non-pregnant US women without the combined presence of fasting and postprandial hyperglycemia as not having the combined presence of fasting and postprandial hyperglycemia was similar to that of the non-invasive ADA testing guidelines for asymptomatic adults (Youden Index: Women's Fasting/Postprandial Hyperglycemia Screening Score Set = 0.211; ADA guidelines = 0.200, $p = 0.795$) when both were applied to the female test population. Unfortunately, the combined ability of the Parous Women's Fasting/Postprandial Hyperglycemia Screening Score Set to correctly define non-pregnant parous US women with the combined presence of fasting and postprandial hyperglycemia as having the combined presence of fasting and postprandial hyperglycemia **and** to also correctly define non-pregnant parous US women without the combined presence of fasting and postprandial hyperglycemia as not having the combined presence of fasting and postprandial hyperglycemia was significantly *lower* than that of the non-invasive ADA testing guidelines for asymptomatic adults (Youden Index: Parous Women's Fasting/Postprandial Hyperglycemia Screening Score Set = 0.071; ADA guidelines = 0.186, $p < 0.001$) when both were applied to the unweighted parous female training population. Addition of the predictors, "Ethnicity", "Waist Circumference" and "Kidney Disease History" did not

enhance the resultant screening tool sufficiently for the Parous Women's Fasting/Postprandial Hyperglycemia Screening Score Set to be acceptable for screening of combined presence of fasting hyperglycemia and postprandial hyperglycemia in parous women when a sensitivity $\geq$ 0.95 is desired. Table 26 also provides the maximum combined sensitivity and specificity for each of the fasting/postprandial hyperglycemia screening score sets as well as the combined sensitivities and specificities of the noninvasive ADA clinical guidelines for testing of asymptomatic adults.

Elevated HbA1c. The combined ability of the Elevated HbA1c Screening Score Set to correctly define non-pregnant US adults with elevated HbA1c as having elevated HbA1c **and** to also correctly define non-pregnant US adults without elevated HbA1c as not having elevated HbA1c was similar to that of the non-invasive ADA testing guidelines for asymptomatic adults (Youden Index: Elevated HbA1c Screening Score Set = 0.196; ADA guidelines = 0.188, $p < 0.815$) when both were applied to the test population. However, the combined ability of the Women's Fasting Hyperglycemia Screening Score Set to correctly define non-pregnant US women with elevated HbA1c as having elevated HbA1c **and** to also correctly define non-pregnant US women without elevated HbA1c as not having elevated HbA1c was significantly *lower* from that of the non-invasive ADA testing guidelines for asymptomatic adults (Youden Index: Women's Elevated HbA1c Screening Score Set = 0.155; ADA guidelines = 0.213, $p = 0.010$) when both were applied to the female test population. When the predictor, "Ethnicity" was added to the final model and the resultant modified Women's Elevated HbA1c Screening Score Set was compared to the ADA guidelines, the combined ability of the modified Women's Elevated HbA1c Screening Score Set to correctly define non-pregnant US women with elevated HbA1c as having elevated HbA1c

and to also correctly define non-pregnant parous US women without elevated HbA1c as not having elevated HbA1c was no longer significantly different than that of the non-invasive ADA testing guidelines for asymptomatic adults (Youden Index: Parous Women's Elevated HbA1c Screening Score Set = 0.245; ADA guidelines = 0.213, p = 0.320).

In like manner, the combined ability of the Parous Women's Elevated HbA1c Screening Score Set to correctly define non-pregnant parous US women with elevated HbA1c as having elevated HbA1c **and** to also correctly define non-pregnant parous US women without elevated HbA1c as not having elevated HbA1c was also significantly lower than that of the non-invasive ADA testing guidelines for asymptomatic adults (Youden Index: Parous Women's Elevated HbA1c Screening Score Set = 0.143; ADA guidelines = 0.195, $p < 0.01$) when both were applied to the unweighted parous female training population. When the predictor, "Ethnicity" was added to the final model and the resultant modified Parous Women's Elevated HbA1c Screening Score Set was compared to the ADA guidelines, the combined ability of the modified Parous Women's Elevated HbA1c Screening Score Set to correctly define non-pregnant parous US women with elevated HbA1c as having elevated HbA1c **and** to also correctly define non-pregnant parous US women without elevated HbA1c as not having elevated HbA1c was no longer significantly different than that of the non-invasive ADA testing guidelines for asymptomatic adults (Youden Index: Parous Women's Elevated HbA1c Screening Score Set = 0.188; ADA guidelines = 0.195, p = 0.613). Table 27 provides the maximum combined sensitivity and specificity for each of the elevated HbA1c screening score sets as well as the combined sensitivities and specificities of the noninvasive ADA clinical guidelines for testing of asymptomatic adults.

Hyperglycemia Screening Score Sets

Fasting Hyperglycemia.

In Non-Pregnant US Adults – Primary Aim 1a. The factors selected for the final Fasting Hyperglycemia Screening Score Set were age, BMI, first-degree family history of diabetes, history of hypertension either by self-report or detected during the NHANES examination, and gender. The AUROC of the screening score set (i.e. the ability to distinguish between US adults with fasting hyperglycemia and those without) was estimated at 0.730. Scores ranged from 18 screening points, representing a women aged 20 – 29 years with a BMI < 20 kg/m^2, no 1st degree family history of diabetes and no history of hypertension; to 80 screening points, representing a man at least 80 years of age with a BMI $\geq$ 50 kg/m^2, a history of hypertension and a 1st degree family history of diabetes. Gender was the strongest single predictor for fasting hyperglycemia, with male gender adding 10 points to the screening score in non-pregnant adults. Table 8 contains the final model from which the Fasting Hyperglycemia Screening Score Set was constructed and Table 9 shows the Fasting Hyperglycemia Screening Score Set constructed from the final model.

***In Non-Pregnant Women – Primary Aim 2a*.** The factors selected for the final Women's Fasting Hyperglycemia Screening Score Set for use in non-pregnant women only were age, BMI and 1st degree family history of diabetes. The AUROC of the screening score set (i.e. the ability to distinguish between non-pregnant US women with fasting hyperglycemia and those without) was estimated at 0.737. Scores ranged from 20 screening points, representing a woman who is aged 20 – 29 years with a BMI < 20 kg/m^2 and no 1st degree family history of diabetes; to 77 screening points, representing a non-pregnant woman who is at least 80 years of age with a

BMI $\geq$ 50 kg/m^2 and a 1st degree family history of diabetes. Having one or more 1st degree relatives with diabetes was the strongest single predictor fasting hyperglycemia, adding 5 points to the screening score when 1st degree diabetes family history was present in non-pregnant women. Table 8 contains the final model from which the Women's Fasting Hyperglycemia Screening Score Set was constructed and Table 10 shows the Women's Fasting Hyperglycemia Screening Score Set for use in non-pregnant women constructed from the final model.

In Non-Pregnant Parous Women – Primary Aim 3a. The factors selected for the final Parous Women's Fasting Hyperglycemia Screening Score Set for use in non-pregnant women who have been pregnant one or more times in the past were age, BMI, ethnicity, 1st degree family history of diabetes, and history of gestational diabetes during one or more prior pregnancies. The AUROC of the screening score set (i.e. the ability to distinguish between parous US women with fasting hyperglycemia and those without) was estimated at 0.723, which was the lowest AUROC of all the screening score sets. Scores ranged from 20 screening points, representing a non-pregnant parous woman who is aged 20 – 29 years with a BMI < 20 kg/m^2, whose ethnicity is non-Hispanic white or non-Hispanic black, has no 1st degree family history of diabetes and no history of gestational diabetes; to 92 screening points, representing a non-pregnant parous woman who is at least 80 years of age with a BMI $\geq$ 50 kg/m^2,who is Hispanic or of an ethnicity other than non-Hispanic white or non-Hispanic black, has a 1st degree family history of diabetes and a history of gestational diabetes. A history of gestational diabetes was the strongest single predictor by far for presence of fasting hyperglycemia in non-pregnant parous women, adding 10 points to the screening score when present in non-

pregnant parous women. Table 8 contains the final model from which the Parous Women's Fasting Hyperglycemia Screening Score Set was constructed and Table 11 shows the Parous Women's Fasting Hyperglycemia Screening Score Set for use in non-pregnant parous women constructed from the final model.

Postprandial Hyperglycemia.

In Non-Pregnant US Adults – Primary Aim 1b. The factors selected for the final Postprandial Hyperglycemia Screening Score Set were age, BMI, heart rate, height, alcohol consumption, and history of hypertension either by self-report or detected during the NHANES examination. The AUROC of the screening score set (i.e. the ability to distinguish between US adults with postprandial hyperglycemia and those without) was estimated at 0.750. Scores ranged from 8 screening points, representing an adult who consumes alcohol, is aged 20 – 29 years with a BMI < 20 kg/m2, a heart rate between 40 – 49 beats/min, no history or presence of hypertension and a height > 193 cm if a man or > 182 cm if a women; to 80 screening points, representing an adult who is a teetotaler at least 80 years of age with a BMI $\geq$ 50 kg/m^2, a heart rate $\geq$ 100 beats/min, a history/presence of hypertension and a height $\leq$ 157 cm if a man or $\leq$ 146 cm if a woman. A history of hypertension was the strongest single predictor for postprandial hyperglycemia, adding 6 points to the screening score when present in non-pregnant adults. Table 8 contains the final model from which the Postprandial Hyperglycemia Screening Score Set was constructed and Table 12 shows the Postprandial Hyperglycemia Screening Score Set constructed from the final model.

In Non-Pregnant US Women – Primary Aim 2b. The factors selected for the final Women's Postprandial Hyperglycemia Screening Score Set for use in non-pregnant women

were age, BMI, heart rate, height, 1st degree family history of diabetes and history of hypertension either by self-report or detected during the NHANES examination. The AUROC of the screening score set (i.e. the ability to distinguish between non-pregnant US women with postprandial hyperglycemia and those without) was estimated at 0.735. Scores ranged from 8 screening points, representing a woman who is aged 20 – 29 years with a BMI < 20 kg/m^2, a heart rate between 40 – 49 beats/min, no 1st degree family history of diabetes, no history of hypertension and a height $\geq$ 182 cm; to 71 screening points, representing a non-pregnant woman who is at least 80 years of age with a BMI $\geq$ 50 kg/m^2, a heart rate $\geq$ 100 beats/min, a 1st degree family history of diabetes, a history of hypertension and a height $\leq$ 157 cm. A history of hypertension was the strongest single predictor for presence of postprandial hyperglycemia, adding 4 points to the screening score when present in non-pregnant women. Table 8 contains the final model from which the Women's Postprandial Hyperglycemia Screening Score Set was constructed and Table 13 shows the Women's Postprandial Hyperglycemia Screening Score Set for use in non-pregnant women constructed from the final model.

In Non-Pregnant Parous Women – Primary Aim 3b. The factors selected for the final Parous Women's Postprandial Hyperglycemia Screening Score Set for use in non-pregnant women who have been pregnant one or more times in the past were age, BMI, heart rate, height, alcohol consumption and history of gestational diabetes during one or more prior pregnancies. The AUROC of the screening score set (i.e. the ability to distinguish between parous non-pregnant US women with postprandial hyperglycemia and those without) was estimated at 0.741. Scores ranged from 9 screening points, representing a non-pregnant parous woman who consumes alcohol, is aged 20 – 29 years with a BMI < 20 kg/m^2, a heart rate

between 40 – 49 beats/min, no history of gestational diabetes, and a height $\geq$ 182 cm; to 90 screening points, representing a non-pregnant parous women who is a teetotaler at least 80 years of age with a BMI $\geq$ 50 kg/m^2, a heart rate $\geq$ 100 beats/min, a history of gestational diabetes and a height $\leq$ 157 cm. A history of gestational diabetes was the strongest single predictor for presence of postprandial hyperglycemia in non-pregnant parous women, adding 8 points to the screening score when present in non-pregnant parous women. Table 8 contains the final model from which the Parous Women's Postprandial Hyperglycemia Screening Score Set was constructed and Table 14 shows the Parous Women's Postprandial Hyperglycemia Screening Score Set constructed for use in non-pregnant parous women from the final model. The Parous Women's Postprandial Hyperglycemia Screening Score Set is **not** recommended when a sensitivity $\geq$ 0.95 is desired.

Combined Presence of Fasting Hyperglycemia and Postprandial Hyperglycemia.

In Non-Pregnant US Adults – Primary Aim 1c. The factors selected for the final Fasting/Postprandial Hyperglycemia Screening Score Set for use in non-pregnant US adults were age, BMI, heart rate, height, alcohol consumption, smoking, gender, 1st degree family history of diabetes and history of hypertension either by self-report or detected during the NHANES examination. The AUROC of the screening score set (i.e. the ability to distinguish between non-pregnant US adults with the combined presence of fasting hyperglycemia and postprandial hyperglycemia and those without the combined conditions) was estimated at 0.773. Scores ranged from 10 screening points, representing a woman who consumes alcohol, doesn't currently smoke, is aged 20 – 29 years with a BMI < 20 kg/m^2, a heart rate between 40 – 49 beats/min, no 1st degree family history of diabetes, no history of hypertension and a height

≥ 182 cm; to 82 screening points, representing a man who is a teetotaler who currently smokes and who is at least 80 years of age with a BMI ≥ 50 kg/m^2, a heart rate ≥ 100 beats/min, a 1st degree family history of diabetes, a history of hypertension and a height ≤ 157 cm. A history of hypertension was the strongest single predictor for combined presence of fasting hyperglycemia and postprandial hyperglycemia, adding 8 points to the screening score when present in non-pregnant adults. Table 8 contains the final model from which the Fasting/Postprandial Hyperglycemia Screening Score Set was constructed and Table 15 shows the Fasting/Postprandial Hyperglycemia Screening Score Set constructed for use in non-pregnant US adults from the final model.

In Non-Pregnant US Women – Primary Aim 2c. The factors selected for the final Women's Fasting/Postprandial Hyperglycemia Screening Score Set for use in non-pregnant US women were age, BMI, heart rate and 1st degree family history of diabetes. The AUROC of the screening score set (i.e. the ability to distinguish between non-pregnant US women with the combined presence of fasting hyperglycemia and postprandial hyperglycemia and those without the combined conditions) was estimated at 0.783. Scores ranged from 31 screening points, representing a non-pregnant woman who is aged 20 – 29 years with a BMI < 20 kg/m^2, a heart rate between 40 – 49 beats/min and no 1st degree family history of diabetes; to 107 screening points, representing a non-pregnant woman who is at least 80 years of age with a BMI ≥ 50 kg/m^2, a heart rate ≥ 100 beats/min and a 1st degree family history of diabetes. Age was the strongest single predictor for combined presence of fasting hyperglycemia and postprandial hyperglycemia, adding 5 points to the screening score for each additional decade of life in non-pregnant women. Table 8 contains the final model from which the Women's

Fasting/Postprandial Hyperglycemia Screening Score Set was constructed and Table 16 shows the Women's Fasting/Postprandial Hyperglycemia Screening Score Set constructed for use in non-pregnant US women from the final model.

In Non-Pregnant Parous US Females – Primary Aim 3c. The factors selected for the final Parous Women's Fasting/Postprandial Hyperglycemia Screening Score Set for use in non-pregnant parous US women were age, BMI, heart rate, height, 1st degree family history of diabetes, history of gestational diabetes in one or more prior pregnancies and history of cardiovascular disease. The AUROC of the screening score set (i.e. the ability to distinguish between non-pregnant parous US women with the combined presence of fasting hyperglycemia and postprandial hyperglycemia and those without the combined conditions) was estimated at 0.779. Scores ranged from 27 screening points, representing a non-pregnant parous woman who is aged 20 – 29 years with a BMI < 20 kg/m^2, a heart rate between 40 – 49 beats/min, no 1st degree family history of diabetes, no history of cardiovascular disease and no history of gestational diabetes in one or more prior pregnancies; to 115 screening points, representing a non-pregnant parous woman who is at least 80 years of age with a BMI $\geq$ 50 kg/m^2, a heart rate $\geq$ 100 beats/min, a 1st degree family history of diabetes, a history of cardiovascular disease and a history of gestational diabetes. A history of gestational diabetes was overwhelmingly the strongest single predictor for combined presence of fasting hyperglycemia and postprandial hyperglycemia in non-pregnant parous women, adding 14 points to the screening score when present. Table 8 contains the final model from which the Parous Women's Fasting/Postprandial Hyperglycemia Screening Score Set was constructed and Table 17 shows the Parous Women's Fasting/Postprandial Hyperglycemia Screening Score Set

constructed for use in non-pregnant parous US women from the final model. The Parous Women's Fasting/Postprandial Hyperglycemia Screening Score Set is **not** recommended when a sensitivity $\geq$ 0.95 is desired.

Elevated HbA1c.

In Non-Pregnant US Adults – Primary Aim 1d. The factors selected for the final Elevated HbA1c Screening Score Set for use in non-pregnant US adults were age, BMI, smoking, and 1st degree family history of diabetes. The AUROC of the screening score set (i.e. the ability to distinguish between US adults with elevated HbA1c and those without) was estimated at 0.768. Scores ranged from 24 screening points, representing a non-pregnant adult who doesn't currently smoke, is aged 20 – 29 years with a BMI < 20 kg/m^2, and no 1st degree family history of diabetes; to 99 screening points, representing a non-pregnant adult who doesn't currently smoke and who is at least 80 years of age with a BMI $\geq$ 50 kg/m^{2}and a 1st degree family history of diabetes. Being a current smoker was the strongest single predictor for elevated HbA1c, adding 7 points to the screening score when practiced by non-pregnant adults. Table 8 contains the final model from which the Elevated HbA1c Screening Score Set was constructed and Table 18 shows the Elevated HbA1c Screening Score Set constructed for use in non-pregnant US adults from the final model.

In Non-Pregnant US Women – Primary Aim 2d. The factors selected for the final Women's Elevated HbA1c Screening Score Set for use in non-pregnant US women were age, BMI, ethnicity, smoking, and a 1st degree family history of diabetes. The AUROC of the screening score set (i.e. the ability to distinguish between US women with elevated HbA1c and those without) was estimated at 0.805. Scores ranged from 24 screening points, representing a

non-pregnant woman who doesn't currently smoke, is aged 20 – 29 years with a BMI < 20 kg/m^2, is a non-Hispanic White or of an ethnicity that is not Hispanic or not non-Hispanic Black, and has no 1^{st} degree family history of diabetes; to 103 screening points, representing a non-pregnant woman who currently smokes and who is at least 80 years of age with a BMI $\geq$ 50 kg/m^2, is a non-Hispanic Black, and has a 1^{st} degree family history of diabetes. Being a non-Hispanic Black was the strongest single predictor for elevated HbA1c in women, adding 8 points to the screening score when present in non-pregnant women. Table 8 contains the final model from which the Elevated HbA1c Screening Score Set was constructed and Table 19 shows the Elevated HbA1c Screening Score Set constructed for use in non-pregnant US women from the final model.

In Non-Pregnant Parous US Women – Primary Aim 3d. The factors selected for the final Elevated HbA1c Screening Score Set for use in non-pregnant parous US women were age, BMI, smoking, and history of gestational diabetes. The AUROC of the screening score set (i.e. the ability to distinguish between parous US women with elevated HbA1c and those without) was estimated at 0.763. Scores ranged from 17 screening points, representing a non-pregnant parous woman who doesn't currently smoke, is aged 20 – 29 years with a BMI < 20 kg/m2, is not a non-Hispanic White, a non-Hispanic Black, or an Hispanic, and who has no history of gestational diabetes; to 107 screening points, representing a non-pregnant parous woman who currently smokes and who is at least 80 years of age with a BMI $\geq$ 50 kg/m^2, is a non-Hispanic Black, and has a history of gestational diabetes. Being a non-Hispanic Black was the strongest single predictor for elevated HbA1c in parous women, adding 8 points to the screening score when present in non-pregnant parous women. Table 8 contains the final model from which the

Elevated HbA1c Screening Score Set was constructed and Table 20 shows the Elevated HbA1c Screening Score Set constructed for use in non-pregnant parous US women from the final model.

External Validation of Hyperglycemic Screening Score Sets – Secondary Aim 2

External validation of the Adult Fasting Hyperglycemia Screening Score Set, the Adult Postprandial Screening Score Set, the Adult Fasting/Postprandial Hyperglycemia Screening Score Set and the Adult Elevated HbA1c Screening Score Set indicated no distinguishable reduction in any of the screening score sets' AUROCs (i.e. in their ability to distinguish between US adults with the screened hyperglycemic condition and those without the condition) when the screening score sets were applied to the **unweighted** test population.

In like manner, none of the AUROCs of the screening score sets intended for use in the US female population were lowered by a distinguishable amount when score sets were applied to the **unweighted** female test population. Table 21 presents the test AUROCs for the hyperglycemia screening score sets created for non-pregnant US adults and for non-pregnant US women. Table 23 presents the training and test AUROCs side by side.

Internal Validation – Secondary Aim 3

All Ethnicities Combined. Internal validation of the score sets for screening of fasting hyperglycemia, postprandial hyperglycemia, combined presence of fasting hyperglycemia and postprandial hyperglycemia and/or elevated HbA1c in non-pregnant US adults indicated no distinguishable reduction in AUROCs (i.e. the ability to distinguish between non-pregnant US adults with the hyperglycemic condition and those without the condition) for any of the hyperglycemia screening score sets when score sets intended for use in non-pregnant US adults

were applied to the **unweighted** training population. The AUROCs of the hyperglycemia screening score sets were also not reduced by a distinguishable amount when score sets intended for use in non-pregnant US women were applied to the unweighted female training population; nor were the AUROCs of the hyperglycemia screening score sets lowered by a distinguishable amount when score sets intended for use in non-pregnant parous US women were applied to the unweighted parous female training population. Table 22 presents the unweighted training AUROCs for the hyperglycemia screening score sets created for non-pregnant US adults, for non-pregnant US women, and for non-pregnant parous US women when applied to the unweighted training population, the unweighted female training population and the unweighted parous female training population. Table 23 presents the training AUROCs and the unweighted training AUROCs side by side.

Ethnic Sub-Groups*.*

Non-Hispanic Whites. None of the AUROCs of the 12 hyperglycemia screening score sets were reduced by a distinguishable amount from the AUROCs derived from the weighted training population when screening score sets were applied to non-Hispanic whites in the unweighted training population, the unweighted female training population and the unweighted parous female training population. Table 22 presents the AUROCs for all hyperglycemia screening score sets when score sets were applied to non-Hispanic whites in the unweighted training population, the unweighted female training population and the unweighted parous female training population.

Non-Hispanic Blacks. The ability to distinguish between non-pregnant non-Hispanic blacks with fasting hyperglycemia and non-pregnant non-Hispanic blacks without fasting

hyperglycemia was reduced by a distinguishable amount when fasting hyperglycemia screening score sets were applied to non-Hispanic blacks in the unweighted training population (AUROC: 0.672, reduction: 0.058); in the unweighted female training population (AUROC: 0.687, reduction: 0.050); and in the unweighted parous female training population (AUROC: 0.638, reduction: 0.085). The ability to distinguish between non-pregnant non-Hispanic blacks with elevated HbA1c and non-pregnant non-Hispanic blacks with normal HbA1c was also reduced by a distinguishable amount when elevated HbA1c screening score sets were applied to non-Hispanic blacks in the unweighted training population (AUROC: 0.667, reduction: 0.100) and in the unweighted parous female training population (AUROC: 0.751, reduction: 0.054). Table 22 presents the AUROCs for the hyperglycemia screening score sets created for non-pregnant US adults, for non-pregnant US women, and for non-pregnant parous US women when score sets were applied to non-Hispanic blacks in the unweighted training population, the unweighted female training population and the unweighted parous female training population.

Hispanics: The ability to distinguish between non-pregnant Hispanics with fasting hyperglycemia and non-pregnant Hispanics without fasting hyperglycemia was reduced by a distinguishable amount when fasting hyperglycemia screening score sets were applied to Hispanics in the unweighted female training population (AUROC: 0.685, reduction: 0.052). The ability to distinguish between non-pregnant Hispanics with elevated HbA1c and non-pregnant Hispanics with normal HbA1c was also reduced by a distinguishable amount when elevated HbA1c screening score sets were applied to Hispanics in the unweighted female training population (AUROC: 0.723, reduction: 0.082).

Ethnicities Other Than Non-Hispanic Whites, Non-Hispanic Blacks, or Hispanics Living in the US. The ability to distinguish between non-pregnant US adults with postprandial hyperglycemia and non-pregnant US adults without postprandial hyperglycemia was enhanced by a distinguishable amount (AUROC: 0.800, increase: 0.050) when the postprandial hyperglycemia screening score set intended for use in the non-pregnant US adult population was applied to ethnicities other than non-Hispanic whites, non-Hispanic blacks and Hispanics in the unweighted training population. Conversely, the ability to distinguish between non-pregnant parous women with fasting hyperglycemia from non-pregnant parous women without fasting hyperglycemia was reduced by a distinguishable amount when the fasting hyperglycemia screening score set intended for use in the parous female population was applied to ethnicities other than non-Hispanic whites, non-Hispanic blacks and Hispanics, such as Native Americans, Asians or Pacific Islanders in the unweighted parous female training population (AUROC: 0.656, reduction: 0.067).Table 22 presents the AUROCs for the hyperglycemia screening score sets created for non-pregnant US adults, for non-pregnant US women, and for non-pregnant parous US women when score sets were applied to ethnicities other than non-Hispanic whites, non-Hispanic blacks or Hispanics in the unweighted training population, the unweighted female training population and the unweighted parous female training population.

CHAPTER 5

DISCUSSION

Screening for Hyperglycemia

During the course of this study, the prevalence of undiagnosed hyperglycemia in the non-pregnant US adult population was estimated to be approximately 47% (Table 6); an indication that current screening methods employed by US physicians are not sufficient to the task. Those with glucose impairment (roughly 42% of the non-pregnant US adult population) have an increased risk of developing type 2 diabetes as well as increased risk of complications such as neuropathy, retinopathy, kidney disease and heart disease than that of persons with normal blood glucose levels (Zhang, 2010; Selvin et al, 2010; Coutinho et al, 1999; Rajabally, 2011; Melsom et al, 2011). If identified and addressed in the pre-diabetic stage, the likelihood of halting or reversing progression of hyperglycemia is enhanced (DeFronzo & Abdul_Ghani, 2011; Perreault et al, 2009; Horton, 2009; Hanefeld et al, 2004; Karve & Hayward, 2010; Faerch et al , 2009). Unfortunately, comprehensive identification of glucose impairment within a population can be difficult. Glucose impairment occurs when fasting blood glucose is above normal, when postprandial blood glucose is above normal or when the HbA1c level is above normal, with each condition requiring its own test for diagnosis (ADA, 2011; Schuster, n.d.; herman, 2009) Although there is some overlap with the conditions (James et al, 2011), proper screening for glucose impairment requires that each condition be screened for individually so

that the correct diagnostic test(s) corresponding to the condition(s) identified as positive by screening can be used. An extensive literature review conducted at the beginning of this dissertation did not reveal the existence of such a screening tool.

The hyperglycemia screening score sets created during the course of this dissertation were designed to screen separately for fasting hyperglycemia, postprandial hyperglycemia, the combined presence of fasting and postprandial hyperglycemia and for elevated HbA1c using non-invasive criteria routinely collected during the course of an office visit to a physician. The restriction of predictors to noninvasive information routinely collected during the course of a doctor visit should promote use of the hyperglycemia screening score sets because the score sets do not require additional data collection by the physician or the physician's staff. Score sets were also designed so that scores would be easy to tally by medical personnel or by the layperson to encourage their use.

Generally accepted rule of thumb ranking of AUROCs are as follows: 0.90 to 1.00 – Excellent, 0.80 to < 0.90 – Good, 0.70 to < 0.80 – Fair, 0.60 to < 0.70 – Poor, < 0.60 – Fail (Niche modeling, n.d.). Using this rule of thumb to evaluate the AUROCs of the screening score sets, which ranged from 0.723 – 0.805, all of the hyperglycemia screening score sets were "Fair" to "Good" in their ability to screen for hyperglycemia. External validation of all screening score sets using other US adult populations (i.e: the unweighted test populations), yielded similar AUROCs for the hyperglycemia screening score sets, with AUROCs ranging from 0.715 to 0.785: all "Fair" in screening ability (Niche modeling, n.d.). Because the hyperglycemia screening score sets were created for use in the US, score sets may not function as well in populations outside

of the US. Before use in other countries, validation studies in those countries should first be performed.

Evaluation of Screening Score Sets

Internal validation of fasting hyperglycemia screening score sets by ethnic subgroup produced AUROCs that were fair in non-Hispanic Whites, and ranged from poor to fair in ethnic subgroups other than non-Hispanic Whites, with AUROCs ranging from 0.638 to 0.736 Future improvements to the fasting hyperglycemia screening score sets should include the creation of fasting hyperglycemia screening score sets specific to ethnic subgroups other than non-Hispanic Whites for use by clinicians whose clientele are predominately ($\geq$ 95%) of a particular ethnic group other than non-Hispanic White. Internal validation of the remaining hyperglycemia screening score sets by ethnic subgroup produced AUROCs that were fair in all ethnic subgroups, with one exception: the Adult Elevated HbA1c Screening Score Set when applied to the unweighted training population when restricted to non-Hispanic Blacks, which produced an AUROC =0.667. To determine if the Adult Elevated HbA1c Screening Score Set might perform better in another US Black adult population, the score set was applied to the unweighted test population restricted to the non-Hispanic Black population, which produced an AUROC of 0.715, which is also fair. Nevertheless, to ensure that the Adult Elevated HbA1c Screening Score Set is acceptable for use in other US non-Hispanic Black populations, future improvements to the elevated HbA1c screening score sets should include the creation of an adult elevated HbA1c screening score set specific to non-Hispanic Blacks for use in clinics whose clientele are predominately ($\geq$ 95%) non-Hispanic Black.

TAG-IT (Koopman et al , 2008) is a fasting hyperglycemia screening tool very similar in design to the hyperglycemia screening score sets with one major exception: TAG-IT was designed only to screen for fasting hyperglycemia whereas the hyperglycemia screening score sets were created to screen not only for fasting hyperglycemia, but for postprandial hyperglycemia, elevated HbA1, and the combined presence of fasting hyperglycemia and postprandial hyperglycemia (Koopman et al , 2008). The prevalence estimates obtained during this study reveal that almost 10% of the non-pregnant US adult population has either undiagnosed postprandial hyperglycemia or undiagnosed elevated HbA1c but not undiagnosed fasting hyperglycemia, and that an additional 11.8% have the combined presence of undiagnosed fasting hyperglycemia and undiagnosed fasting hyperglycemia. Used as intended, TAG-IT would not screen for those hyperglycemic conditions which are present but currently undiagnosed in over 20% of the non-pregnant US adult population. The hyperglycemia screening score sets created during this study address this deficiency because they are also designed to screen for postprandial hyperglycemia and elevated HbA1c as well as for fasting hyperglycemia. Comparisons of AUROCs between the TAG-IT tool and the fasting hyperglycemia screen score sets when applied to the unweighted test population, the unweighted female test population and the unweighted parous female training population indicated that the fasting hyperglycemia screening score sets were similar to or significantly better than the TAG-IT tool in distinguishing between those with fasting hyperglycemia from those without, as shown in Table 24.

The Finnish Diabetes Risk Score (FINDRISK) is a very well-known diabetes prediction tool (Lindstrom & Tuomilehto , 2003). Although the FINDRISK diabetes prediction tool was not

originally designed for opportunistic screening of postprandial hyperglycemia, Franciosi et al, 2005 explored this option by applying the FINDRISK tool to cross-sectional data from an older population residing in Italy. While the screening performance of the FINDRISK tool was "poor" in this regard, with an AUROC of 0.67 (Franciosi et al, 2005), Franciosi established a precedent for using the FINDRISK as a screening tool for postprandial hyperglycemia. As a consequence, comparisons were made between the AUROCs of the slightly modified FINDRISK tool and the postprandial hyperglycemia screening score sets when applied to the unweighted test population, the unweighted female test population and the unweighted parous female training population. In all three instances, the AUROCs of the postprandial hyperglycemia screening score sets were higher than the AUROCs of the FINRISK tool, with two of the three AUROCs significantly higher. In short, the screening ability of the postprandial screening score sets were similar to or better than that the modified FINDRISK tool when screening for postprandial hyperglycemia, as shown in Table 25. One limitation to wide-spread use of the modified FINDRISK tool as an opportunistic postprandial hyperglycemia screening tool is the use of waist circumference as a predictor because waist circumference is rarely measured during a routine doctor visit. The postprandial screening score sets are not held to that limitation and as discussed above, have also been shown to screen for postprandial hyperglycemia as well as or better than the FINDRISK tool.

The American Diabetes Association clinical guidelines for diabetes testing of asymptomatic adults are designed to be a diabetes screening aid for health care practitioners. As Tables 24 – 27 show, estimates of sensitivity and specificity of the ADA guidelines used for screening of hyperglycemic conditions in various populations indicate that sensitivity of the

ADA guidelines is very high for all hyperglycemic conditions and in all populations. Because high sensitivity appears to be the driving force for the ADA guidelines, the threshold of each screening score set was set to produce sensitivity closest to the sensitivity of the modified ADA guidelines when both were applied to the same population and the two tools were then compared. The Youden Index was used to determine which tool was better at screening when set to a similar sensitivity and the extended McNemar test was used to determine if the observed difference in tool performance was significant. When thus compared to the modified ADA guidelines, 7 of the 12 score sets were similar to or significantly better than the ADA guidelines in screening for hyperglycemia. However, the results indicated that it was necessary to add the predictor, "Ethnicity" to the Women's Elevated HbA1c Screening Score Set, The Parous Women's Fasting Hyperglycemia Screening Score Set and the Parous Women's Elevated HbA1c Screening Score Set for those screening score sets and the modified ADA guidelines to perform at a similar level when sensitivity of the score sets and the modified ADA guidelines set to be similar as well. One limitation to the addition of the predictor, "Ethnicity" to these screening score sets is that this information is not routinely collected by physicians. Nevertheless, information on the patient's background that is routinely collected could easily be modified to include the patient's self-reported ethnicity with negligible disruption to office routine. Comparisons between the modified ADA guidelines and the Parous Women's Postprandial Hyperglycemia Screening Score Set and the Parous Women's Fasting/Postprandial Screening Score Set indicated that the modified ADA guidelines provided significantly better screening for those conditions when the sensitivities of the screening score sets were set to be similar to the modified ADA guidelines. As a consequence, *when a sensitivity $\geq$ 0.95 is desired,* it

is recommended that the modified ADA guidelines be used for non-invasive screening of postprandial hyperglycemia in parous women or for screening of the combined presence of fasting hyperglycemia and postprandial hyperglycemia in parous women. There are a couple of limitations to using the ADA guidelines for non-invasive screening of hyperglycemia. When applied to more than one condition, the ADA screening guidelines will produce the same results for all conditions thus screened. As a result, while the ADA guidelines may indicate if an adult would benefit from testing, the ADA guidelines cannot provide any information on which test might be the best to use. Because each hyperglycemia screening score set is particular to the condition and its corresponding test, the screening score sets have the capacity to provide additional information regarding which test (if any) to use. Nevertheless, in some instances the screening score sets may also not be able to provide that additional information (i.e. they may indicate testing for multiple conditions, particularly when sensitivity is set very high), because the three conditions share some of the same risk factors. In such instances, the physician may wish to compare the positive predictive values of the score sets in question. Positive predictive values of screening score sets at varying sensitivities are provided in Tables 28 – 30 to address this concern.

Application of Screening Score Sets

Screening tools such as the ADA guidelines and the hyperglycemia screening score sets are primarily used as the first stage of a two-stage hyperglycemia screening process in which invasive testing is used for the second stage. As such, a high sensitivity is preferred for the first stage of the screening process because the second stage will weed out the false positives while identifying those with hyperglycemia. Indeed, given that almost half of all non-pregnant US

adults were estimated to have hyperglycemia during the course of this study, as shown in Table 6, universal testing for adults ≥ 20 years of age may well be warranted. Unfortunately, the lack of physicians' adherence to the ADA screening guidelines strongly indicates that universal screening for hyperglycemia isn't a feasible option. The ADA screening guidelines recommend universal diabetes (hyperglycemia) testing for all persons ≥ 45 years of age, and every three years thereafter (ADA, 2011). Nevertheless, a cursory examination of the weighted training population from NHANES 2007 – 2010 showed that approximately half of the adults aged ≥ 48 years *and* having been seen by a physician at least once sometime in the three years prior to the survey had not been tested for hyperglycemia in that same three-year period.

Some physicians may balk at the high number of false positives associated with the high sensitivity of the ADA screening guidelines because of the unnecessary inconvenience and expense for a high number of the physician's patients. Unlike the ADA guidelines, the sensitivities and corresponding specificities of the hyperglycemia screening score sets created for this study are flexible, so that the physician can modify the sensitivity with its corresponding specificity (1 – specificity = the false positive rate) to best meet the needs of his or her patients under varying conditions. For example, using the Adult Fasting/Postprandial Screening Score Set (Tables 16 and 29) to screen for combined presence of fasting hyperglycemia and postprandial hyperglycemia in adults, a physician may choose to flag a threshold that would yield a sensitivity of 0.95 (threshold: 38.5, with a positive predictive value of 17%) when conducting yearly physicals on adult patients. For opportunistic screening of combined presence of fasting hyperglycemia and postprandial hyperglycemia, the same physician may decide to increase the positive predictive value of the screening score set to roughly 25% by

choosing a threshold that would yield a sensitivity close to 0.75 (threshold 49.5, with a positive predictive value of 26%) for testing, and use the threshold flagged for a sensitivity of 95% to indicate recommending lifestyle changes to the patient. To demonstrate: the physician sees patients A and B on a certain day. Patient A is female, has no first-degree relatives with diabetes, has normal blood pressure, is age 40, weighs 163 pounds, is 64 inches tall, with a heart rate of 90 beats/minute, which yields an adult fasting/postprandial hyperglycemia score of 40. Patient A is seeing the physician for her yearly physical. The physician schedules patient A for an oral glucose tolerance test in which fasting plasma glucose will also be measured.

Patient B is male, has a mother with type 2 diabetes, has normal blood pressure, is 39 years of age, weighs 225 pounds, is 72 inches tall and has a heart rate of 87 beats/minute, which yield an adult fasting/postprandial hyperglycemia score of 43. The patient is seeing the physician because he pulled his back doing yard work over the weekend. The physician does not schedule testing for the combined presence of fasting hyperglycemia and postprandial hyperglycemia, but does counsel the patient regarding the complications that can arise from elevations in fasting and postprandial blood glucose, advises the patient to lose weight and begin an exercise program, and schedules the patient for a follow-up visit in six months to determine the patient's adherence to the physician's recommendations.

The existence of different screening score sets for specific populations may be confusing to the physician and to the layperson. To address this concern, the following instructions for proper score set selection are provided: There are three groups of screening score sets, with each group intended for use within a specific population. Non-pregnant laypersons and physicians whose practices are not restricted to females should use the hyperglycemia

screening score sets intended for use in the non-pregnant US adult population with no prior diagnosis of hyperglycemia for screening of hyperglycemia in non-pregnant adults. Physicians with OB/GYN practices that include women who have never been pregnant should use the women's hyperglycemia screening score sets intended for use in the non-pregnant US adult female population with no prior diagnosis of hyperglycemia for screening their non-pregnant patients. Physicians with OB/GYN practices that are restricted to women who have been pregnant one or more times should use the parous women's screening score sets intended for use in the non-pregnant US parous adult female population with no prior diagnosis of hyperglycemia for screening their non-pregnant patients.

To facilitate use by physicians and laypersons, templates for tallying scores are provided in Appendix C. Tables of score sets' thresholds and their corresponding sensitivities, specificities and positive predictive values are also provided in Appendix C. Microsoft Excel spread sheets that will calculate patients' screening scores based on physician's choice of threshold are also available upon request.

The Screening score sets may also be utilized at the health systems level, such as within hospital systems or healthcare systems. For example, just as patients are often automatically notified of lab results, the screening score sets could be electronically embedded into hospital and healthcare systems that would then automatically notify the adult patient and his or her primary care physician if testing is warranted.

The screening scores sets can also be used as an excellent education tool for the general public. For example, just as there are blood pressure machines available for public use in many pharmacies, malls and physician offices; the screening score sets could be incorporated into

electronic devices available for public use in which the adult could enter in his or her information as prompted and based on his or her screening scores, recommendations can be provided to the adult regarding if a visit or a call to his or her primary care physician is warranted.

Limitations

There were limitations in the creation of the hyperglycemia screening score sets. The proper analysis of data collected using the complex sampling scheme employed by NHANES precluded the use of forward step-wise selection or best subset selection in choosing models, both of which may have led to improved screening models over the ones chosen using backward elimination. To address this concern, a crude sensitivity analysis was performed for model selection of screening score sets to be used in the adult population in which the weights for the training population data were divided by 52268.7 and logistic models based on the modified dataset were created in which the complex sampling scheme was *not* addressed. In this manner, point estimates were the same as when complex analyses were used, the variances produced were based on a population very similar in size to the unweighted training population, and most importantly, the -2loglikelihood of each model created this way was also made available, which allowed for a crude form of forward stepwise selection, suitable for a rudimentary comparison to the models selected using backward elimination. The models thus obtained were very similar to the models selected using backward elimination (results not shown), which indicates that any improvements that may have been occurred using forward stepwise selection (had it been available when performing complex analyses) would have most likely been slight.

Simplifying final models and their screening score sets proved problematic. The use of weighted NHANES data in model selection and screening score set design precluded statistical comparison between the AUROCs of the original final models, their simplified counterparts, and their corresponding screening score sets, which were further simplified. In addition, we were unable to clinically compare models, because clinical significance has yet to be established for hyperglycemic screening tools. To address this problem, an arbitrary difference between AUROCs of ≤ 0.050 was defined as an acceptable reduction in AUROC when simplifying the final models and their screening score sets. Because this difference is based on "rule of thumb" distinguishing a "good" AUROC from a "very good" AUROC (Assessing the Model, n.d.), rather than on scientific study, there is the possibility that simplifying the models and their corresponding screening score sets may have reduced screening performance from that of the original final models enough to noticeably affect their screening ability, even though none of the simplified models or their score sets differed in AUROC from the original final models by ≥ 0.050.

Creating a more comprehensive hyperglycemia screening tool than those currently available necessitated the creation of a hyperglycemia screening tool that is more complex that the currently available tools because they require the use of four different hyperglycemia screening score sets rather than one screening score set when screening for hyperglycemia within a population. Unfortunately, the complexity of the screening score sets may discourage their use by physicians. Encouraging use of the hyperglycemia screening score sets is a major concern. Although the ADA guidelines are simple to follow and are backed by the ADA, a cursory examination of the weighted training population indicated that approximately half of

the adults who had been to the doctor at least once in the past three years and for whom the ADA guidelines indicated diabetes testing was warranted had been tested in the past three years. Although non-adherence to the ADA guidelines may be due in part to the high number of false positives it generates, physicians may also hesitate to incorporate opportunistic hyperglycemia screening into their busy schedules. To facilitate use of the hyperglycemia screening score sets for opportunistic screening despite their complexity, it is recommended that software be created based on the hyperglycemia screening score sets that can be embedded into a physician's current software governing his or her patients' medical records which will automatically screen all patients and notify the physician if testing/counseling is warranted.

The inclusion of "Ethnicity" as a non-invasive predictor does not take into consideration that a certain percent of US adults cannot be easily pigeon-holed into one particular ethnic group, as well as the potential for these numbers to grow. Currently, it is unknown what effect, if any, this may have on the performance of the three screening score sets in which the predictor, "Ethnicity" is included. It is recommended that the performance of these three screening score sets be monitored over time to ensure that any deleterious effects can be properly addressed.

Conclusion

In conclusion, the hyperglycemia screening score sets are the only comprehensive hyperglycemia screening tool currently available to physicians. As a result, the physician is now better able to identify patients for diagnostic testing and/or counseling that the physician would have missed otherwise. Based on information routinely collected during the course of a

doctor visit, the screening score sets can be also be used by the physician for opportunistic screening without the need to collect additional information. The screening score sets were also based on information readily available in patients' medical records so that, if desired, software based on the score sets can be created that will automatically screen patients for hyperglycemia without the need to modify the score sets or collect additional information. Screening score sets may also be used to automatically screen patients' medical records at the health-system level and notify both patient and the patient's physician accordingly. Screening score sets can also be applied electronically in public venues such as pharmacies, malls and health fairs as a preventive and educational tool.

The screening score sets are not restrained to one sensitivity/specificity. As a result, the physicians can set the sensitivity very high when a high false positive rate is not a concern, or can set the sensitivity to a more moderate level when the false positive rate must be taken into consideration. To facilitate use, software and screening score set templates are also provided that the physician can use to calculate screening scores and flag patients for testing or counseling.

APPENDIX A

TABLES

Table 1: Publications Regarding Clinical Guidelines from the ADA[a] and the WHO[b]

Publication	Date	Criteria Approved	Rationale
"Expert Committee" Recommendations Regarding Diagnostic Criteria for Diabetes and Pre-diabetes			
Report of the expert committee on the diagnosis and classification of diabetes mellitus (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003)	1997	Diabetes diagnosed by fasting plasma glucose $\geq$ 126 mg/dL OR 2-hour postprandial plasma glucose $\geq$ 200 mg/dL OR diabetes symptoms AND casual glucose $\geq$ 200 mg/dL.	Measure where incidence of retinopathy begins to sharply increase
		IFG[c] diagnosed by fasting plasma glucose $\geq$ 110 mg/dL.	Level at which acute phase insulin secretion is lost in response to glucose.
			Progressively greater increase of micro and macrovascular injury observed in this range.
		IGT[d] diagnosed by 2-hour postprandial plasma glucose $\geq$ 140mg/dL.	IGT[d] lower level chosen arbitrarily, but kept because observed progressive increase in micro and macrovascular risk in this range.
		All measures to be confirmed by 2nd measure on subsequent day.	Reproducibility somewhat low for diagnostic tests, particularly for oral glucose tolerance test.
Follow-up Report on the Diagnosis of Diabetes Mellitus (mann et al , 2010)	2003	Diagnostic criteria for [c] lowered to 100 mg/dL	Higher concordance with IGT[d] Optimal sensitivity and specificity in predicting type-2 diabetes.
		Support for fasting plasma glucose test over oral glucose tolerance test for non-	Fasting plasma glucose test more reliable and less expensive than the oral

Publication	Date	Criteria Approved	Rationale
		pregnant patients	glucose tolerance test
International Expert Committee Report on the Role of the A1c Assay in the Diagnosis of Diabetes (International Expert Committee, 2009)	2009	Including HbA1c level of 6.5% as diagnostic measure of diabetes	HbA1c levels long used to monitor diabetes maintenance
			Measure at which risk of retinopathy begins to steeply increase
		Including HbA1c of 6.0% as diagnostic measure of "pre-diabetes"	Measure where diabetes risk begins to steeply increase
ADA[a] and WHO[b] Clinical Guidelines Based on the Above Recommendations			
American Diabetes Association. Standards of medical care in diabetes (ADA, 2011).	2011	All guidelines above accepted EXCEPT diagnostic measure of HbA1c set at 5.7% rather than 6.0%	Optimal sensitivity and specificity to IFG[c] lower level (using 2005-2006 NHANES data) for HbA1c of 5.7%
Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: Report of a WHO/IDF Consultation (Definition and diagnosis, n.d.).	2006	IFG[c] diagnostic criteria kept at 110 mg/dL	Increase in number of IFG[c] burdensome to poorer nations
		More support for oral glucose tolerance test than ADA[a]	Oral glucose tolerance test can identify IFG[c] *and* IGT[d]
		HbA1c not to be used to diagnose hyperglycemia	HbA1c testing expensive *and* not available world-wide

a – American Diabetes Association
b – World Health Association
c – Impaired fasting glucose
d – Impaired glucose tolerance

Table 2: Results of Gestational Diabetes Screening Program Carried Out at Blacktown Hospital in Western Sydney Australia for Deliveries Occurring Between April 2000 and May 2003 According to Family History of Diabetes

Diabetes in Parents Diabetes	n	Gestational
Neither	4672	136 (2.9%)
Father	566	31 (5.5%)
Mother	535	57 (10.7%)
Both	77	8 (10.4%)

Gestational diabetes was determined using a 2-stage testing system. At 24 – 28 weeks of pregnancy, a 1-hour non-fasting 50-g oral glucose challenge test was administered using capillary blood measure. Those with capillary blood measures $\geq$ 140 mg/dL were brought back in for a 2-hour 75-g oral glucose tolerance test. Gestational diabetes was diagnosed if the fasting capillary blood measure was $\geq$ 100 mg/dL OR the 2-hour postprandial capillary blood measure was $\geq$ 140 mg/dL.

McLean M, Chipps D, Cheung NW. Mother to child transmission of diabetes mellitus: does gestational diabetes program Type-2 diabetes in the next generation? *Diabet Med*. 2006 Nov;23(11):1213-5.(73)

Table 3: Benefits and Limitations of the Fasting Plasma Glucose Test, the Oral Glucose Tolerance Test and the HbA1c Test

FPG[a]	OGTT[b]	HbA1c
Strengths		
Least expensive test	Can detect IFG and IGT	Not influenced by day-to-day glucose fluctuations
More convenient than OGTT		Most convenient test
More reproducible than OGTT		Most reproducible test
Limitations		
Cannot detect IGT	Least convenient test	Cannot distinguish between IFG or IGT
	Least reproducible	
Easily influenced by day-to day glucose fluctuations	Easily influenced by day-to day glucose fluctuations	Nonglycemic factors affecting HbA1c can lead to spurious results
Less convenient than the HbA1c		Most expensive test

a. Fasting plasma glucose test
b. Oral glucose tolerance test

Table 4: Values of Dichotomous Variables in Final Models and Hyperglycemic Score Sets

Variable	Value
Gender	
Female	0
Male	1
Alcohol Consumption[a]	
Nondrinker	0
Drinker	1
Current Smoker	
No	0
Yes	1
1st Degree Family History of Diabetes	
No	0
Yes	1
Hypertension[b]	
No	0
Yes	1
History of Cardiovascular Disease (CVD)[c]	
No	0
Yes	1
Gestational Diabetes (Parous Females Only)	
No	0
Yes	1
Ethnicity	
Non-Hispanic Black	
No	0
Yes	1
Hispanic	
No	0
Yes	1
Other Ethnicity	
No	0
Yes	1

a. Alcohol Consumption: Drinker defined by > 0 alcoholic drinks/day by self-report
b. Presence/History of Hypertension defined by self-report of having been told more than once by a health care professional of presence of hypertension, by self-report of taking hypertension drugs, by a diastolic blood pressure measure of $\geq$ 90 mm, or by a systolic blood pressure measure > 140 mm during the course of an examination.
c. Presence/History of Cardiovascular disease defined as presence/history of congestive heart failure, coronary heart disease, angina/angina pectoris, heart attack, or stroke

Table 5: Conversion of the Continuous Variables, Age, BMI, Heart Rate, and Height to Continuous Variables, Age Group, BMI Group, Heart Rate Group, and Height Group

Age	Age Group
20 – 29 Years	2
30 – 39 Years	3
40 – 49 Years	4
50 – 59 Years	5
60 – 69 Years	6
70 – 79 Years	7
80+ Years	8
BMI	BMI Group
$\leq$ 19.99 Kg/m^2	3
20 – 24.99 Kg/m^2	4
25 – 29.99 Kg/m^2	5
30 – 34.99 Kg/m^2	6
35 – 39.99 Kg/m^2	7
40 – 44.99 Kg/m^2	8
45 – 49.99 Kg/m^2	9
50+ Kg/m^2	10
Heart Rate	Heart Rate Group
$\leq$ 49 beats/min	4
50 – 59 beats/min	5
60 – 69 beats/min	6
70 – 79 beats/min	7
80 – 89 beats/min	8
90 – 99 beats/min	9
100+ beats/min	10
Height	Height Group
Men	
$\leq$ 157 cm	0
158 – 164 cm	1
165 – 171 cm	2
172 – 178 cm	3
179 – 185 cm	4
186 – 192 cm	5
193+ cm	6
Women	
$\leq$ 146 cm	0
147 – 153 cm	1
154 – 160 cm	2
161 – 167 cm	3
168 – 174 cm	4
175 – 181 cm	5
182+ cm	6

Table 6: Prevalence[a] of Undiagnosed, Unspecified Hyperglycemia, Undiagnosed Fasting Hyperglycemia, Undiagnosed Post Prandial Hyperglycemia, Combined Undiagnosed Fasting Hyperglycemia and Undiagnosed Postprandial Hyperglycemia and Undiagnosed Elevated HbA1c in the US Adult Population

	US Adult Population	US Female Adult Population	US Parous Female Adult Population
N, weighted, in million – Population restricted to adults with no prior diagnosis of hyperglycemia	161	83	65
Non Specified Hyperglycemia, % in US adult population with no prior diagnosis of hyperglycemia	54.2	47.5	51.5
Fasting Hyperglycemia[c], %	42.9	33.1	36.6
Isolated Fasting Hyperglycemia, %	21.0	13.2	14.5
Postprandial Hyperglycemia[d],	18.7	20.9	21.3
Isolated Postprandial Hyperglycemia,	3.5	5.3	4.7
Elevated HbA1c[e],	23.0	23.1	26.0
Isolated Elevated HbA1c,	6.2	6.7	7.8
Fasting/Postprandial Hyperglycemia[f],	13.6	13.2	14.2

a. Estimates of prevalence were obtained using 2007 – 2010 NHANES data. Data was weighted to obtain prevalence of undiagnosed hyperglycemic conditions within the non-pregnant civilian non-institutionalized US population aged $\geq$ 20 years with no prior diagnosis of hyperglycemia
b. Weighted estimates in millions of non-pregnant civilian non-institutionalized US population aged $\geq$ 20 years, including those with a prior diagnosis of hyperglycemia. (Results in parentheses)
c. Fasting plasma glucose $\geq$ 100 mg/dL. (Results in parentheses)
d. 2-Hour oral glucose tolerance test result of $\geq$ 140 mg/dL
e. Fasting plasma glucose $\geq$ 100 mg/dL and 2-Hour oral glucose tolerance test result of $\geq$ 140 mg/dL
f. HbA1c $\geq$ 5.7

Table 7: Characteristics of Factors Associated with Hyperglycemia in the US Adult Population withNo Prior Diagnosis of Hyperglycemia

	All	Female	Parous Female
N[a] (weighted in millions)	161	83	65
Age (mean) Years	44	45	49
BMI(mean) Kg/m^2	28	27	28
Height (mean) cm	170	162	163
Heart Rate (mean) beats/min	71	73	73
Waist Circumference (mean) cm	96	93	94
Alcohol (%)			
Nondrinkers	17.3	22.4	22.7
Drinkers[c]	82.8	77.5	77.3
Gender (%)			
Female	51.4	---------	----------
Male	48.6	---------	----------
Early Menarche (%)			
No	---------	81.0	80.7
Yes	---------	19.0	19.3
Gestational Diabetes (%)			
No	--------	---------	94.8
Yes	--------	---------	5.2
Cardiovascular Disease (%)			
No	94.5	95.5	94.6
Yes	5.5	4.5	5.4
Hypertension (%)			
No	72.7	73.0	69.4
Yes	27.3	27.0	30.6
Family History of Diabetes[d] (%)			
No	66.8	66.1	65.8
Yes	33.2	33.9	34.2
Smoker (%)			
No	82.7	84.7	82.7
Yes	17.3	15.3	17.3
Kidney Disease (%)			
No	98.7	98.6	98.5
Yes	1.3	1.4	1.5
Ethnicity (%)			
Non-Hispanic White	70.2	71.5	71.8
Non-Hispanic Black	10.7	11.2	11.5
Hispanic	13.3	11.9	12.9
Other Ethnicity	5.8	5.3	3.8

a. Estimates were obtained using 2007 – 2010 NHANES data. Data was weighted to obtain prevalence representative of the non-pregnant civilian non-institutionalized US population aged $\geq$ 20 years without a prior diagnosis of hyperglycemia
b. Family history of diabetes: mother, father and/or sibling(s)

Table 8: Final Logistic Models with the Coefficients Rounded to the Nearest Tenth.

Hyperglycemic Conditions	Final Logistic Model	AUROC
Fasting Hyperglycemia[a]		
US Adults	1.0*Gender + 0.3*1st Degree Family History of Diabetes + 0.3*Hypertension + 0.3*Age Group + 0.4*BMI Group	0.730
US Women	0.5*1st Degree Family History of Diabetes + 0.4*Age Group + 0.4*BMI Group	0.737
Parous US Women	0.4*1st Degree Family History of Diabetes + 1.0*Gestational Diabetes + 0.4*Age Group + 0.4*BMI Group + 0.4*Hispanic + 0.6*Other Ethnicity[f]	0.723
Postprandial Hyperglycemia[b]		
US Adults	0.6*Hypertension – 0.3*Alcohol Consumption + 0.3*Age + 0.2*BMI Group + 0.3*Heart Rate Group – 0.2*Height Group	0.750
Us Women	0.3*1st Degree Family History of Diabetes + 0.4*Hypertension + 0.3*Age Group + 0.2*BMI Group + 0.2*Heart Rate Group – 0.2*Height Group	0.735
Parous US Women	0.8*Gestational Diabetes – 0.4*Alcohol Consumption + 0.4*Age Group + 0.3*BMI Group + 0.2*Heart Rate Group – 0.2*Height Group	0.741
Combined Fasting/Postprandial Hyperglycemia[c]		
US Adults	0.5*Gender + 0.3*1st Degree Family History of Diabetes + 0.8*Hypertension - 3*Alcohol Consumption + 0.4*Current Smoker + 0.4*Age Group + 0.3*BMI + 0.2*Heart Rate Group – 0.2*Height Group	0.773
Us Women	0.6*1st Degree Family History of Diabetes + 0.5*Age group + 0.3*BMI Group + 0.3*Heart Rate Group	0.783
Parous US Women	0.4*1st Degree Family History of Diabetes + 0.7*CVD + 1.4*Gestational Diabetes + 0.5*Age Group + 0.3*BMI Group + 0.2*Heart Rate Group	0.779
Elevated HbA1c[d]		
US Adults	0.4*1st Degree Family History of Diabetes + 0.7*Current Smoker + 0.6*Age Group + 0.4*BMI Group	0.768
US Women	0.4*1st Degree Family History of Diabetes + 0.5*Current Smoker + 0.7*Age Group + 0.3*BMI Group + 0.8*Non-Hispanic Black + 0.7*Hispanic	0.805
Parous US Women	0.5*Current Smoker + 0.8*Gestational Diabetes + 0.7*Age Group + 0.3*BMI Group + 0.8*Non-Hispanic Black + 0.8*Hispanic – 0.4*Other Ethnicity[f]	0.776

a. Fasting plasma glucose $\geq$ 100 mg/dL
b. Postprandial plasma glucose > 140 mg/dL
c. Combined presence of fasting hyperglycemia and postprandial hyperglycemia
d. HbA1c $\geq$ 5.7%
e. Final Models were derived and AUROCs were obtained using 2007 – 2010 NHANES data. Data was weighted to obtain prevalence representative of the civilian non-institutionalized US population aged $\geq$ 20 years
f. “Other Ethnicity” defined as ethnicity other than Non-Hispanic White, Non-Hispanic Black or Hispanic

Table 9: Score Set with Point Estimate of AUROC for [a]Fasting Hyperglycemia in US Adults Aged > 20 Years.

AUROC – 0.730	
Characteristic	Score
Gender	
Female	0
Male	10
1st Degree Family History of Diabetes	
No	0
Yes	3
History/Presence of Hypertension	
No	0
Yes	3
Age in Years	
20 – 29	6
30 – 39	9
40 – 49	12
50 – 59	15
60 – 69	18
70 – 79	21
80+	24
BMI in Kg/m^2	
15 – 19.99	12
20 – 24.99	16
25 – 29.99	20
30 – 34.99	24
35 – 39.99	28
40 – 44.99	32
45 – 49.99	36
50+	40

a. Fasting plasma glucose $\geq$ 100 mg/dL

Score set was derived and AUROC was obtained using 2007 – 2010 NHANES data. Data was weighted so as to represent the civilian non-institutionalized US population aged $\geq$ 20 years

Table 10: Score Set with Point Estimate of AUROC for [a]Fasting Hyperglycemia in US Women Aged ≥ 20 Years.

AUROC – 0.737	
Characteristic	Score
1st Degree Family History of Diabetes	
No	0
Yes	5
Age in Years	
20 – 29	8
30 – 39	12
40 – 49	16
50 – 59	20
60 – 69	24
70 – 79	28
80+	32
BMI in Kg/m^2	
15 – 19.99	12
20 – 24.99	16
25 – 29.99	20
30 – 34.99	24
35 – 39.99	28
40 – 44.99	32
45 – 49.99	36
50+	40

a. Fasting Hyperglycemia ≥ 100 mg/dL

Score set was derived and AUROC was obtained using 2007 – 2010 NHANES data. Data was weighted so as to represent the civilian non-institutionalized US female population aged ≥ 20 years

Table 11: Score Set with Point Estimate of AUROC for [a]Fasting Hyperglycemia in Parous US Women Aged ≥ 20 Years.

AUROC – 0.723	
Characteristic	Score
1st Degree Family History of Diabetes	
No	0
Yes	4
History of Gestational Diabetes	
No	0
Yes	10
Age in Years	
20 – 29	8
30 – 39	12
40 – 49	16
50 – 59	20
60 – 69	24
70 – 79	28
80+	32
BMI in Kg/m^2	
15 – 19.99	12
20 – 24.99	16
25 – 29.99	20
30 – 34.99	24
35 – 39.99	28
40 – 44.99	32
45 – 49.99	36
50+	40
Ethnicity	
Non-Hispanic White	0
Non-Hispanic Black	0
Hispanic	4
Other Ethnicity[b]	6

a. Fasting plasma glucose ≥ 100 mg/dL
b. Other Ethnicity defined as ethnicity other than Non-Hispanic White, Non-Hispanic Black or Hispanic

Score set was derived and AUROC was obtained using 2007 – 2010 NHANES data. Data was weighted so as to represent the civilian non-institutionalized parous US female population aged ≥ 20 years

Table 12: Score Set with Point Estimate of AUROC for [a]Postprandial Hyperglycemia in US Adults Aged > 20 Years.

AUROC – 0.750	
Characteristic	Score
History/Presence of Hypertension	
No	0
Yes	6
Alcohol Consumption	
No	0
Yes	-3
Age in Years	
20 – 29	6
30 – 39	9
40 – 49	12
50 – 59	15
60 – 69	18
70 – 79	21
80+	24
BMI in Kg/m^2	
15 – 19.99	6
20 – 24.99	8
25 – 29.99	10
30 – 34.99	12
35 – 39.99	14
40 – 44.99	16
45 – 49.99	18
50+	20
Heart Rate in beats/minute	
40 – 49	12
50 – 59	15
60 – 69	18
70 – 79	21
80 – 89	24
90 - 99	27
100+	30
Height in centimeters (men)	
$\leq$ 157	0
158 - 164	-2
165 - 171	-4
172 - 178	-6
179 - 185	-8
186 - 192	-10

193+	-12
Height in centimeters (women)	
≤ 146 cm	0
147 – 153 cm	-2
154 – 160 cm	-4
161 – 167 cm	-6
168 – 174 cm	-8
175 – 181 cm	-10
182+ cm	-12

a. Postprandial plasma glucose ≥ 140 mg/dL

Score set was derived and AUROC was obtained using 2007 – 2010 NHANES data. Data was weighted so as to represent the civilian non-institutionalized US population aged ≥ 20 years

Table 13: Score Set with Point Estimate of AUROC for [a]Postprandial Hyperglycemia in US Women Aged ≥ 20 Years.

AUROC – 0.735	
Characteristic	Score
1st Degree Family History of Diabetes	
No	0
Yes	3
History/Presence of Hypertension	
No	0
Yes	4
Age in Years	
20 – 29	6
30 – 39	9
40 – 49	12
50 – 59	15
60 – 69	18
70 – 79	21
80+	24
BMI in Kg/m^2	
15 – 19.99	6
20 – 24.99	8
25 – 29.99	10
30 – 34.99	12
35 – 39.99	14
40 – 44.99	16
45 – 49.99	18
50+	20
Heart Rate in beats/minute	
40 – 49	8
50 – 59	10
60 – 69	12
70 – 79	14
80 – 89	16
90 - 99	18
100+	20
Height in centimeters (men)	
157	0
158 - 164	-2
165 - 171	-4
172 - 178	-6
179 - 185	-8
186 - 192	-10

AUROC – 0.735	
Characteristic	Score
193+	-12
Height in centimeters (women)	
≤ 146 cm	0
147 – 153 cm	-2
154 – 160 cm	-4
161 – 167 cm	-6
168 – 174 cm	-8
175 – 181 cm	-10
182+ cm	-12

a. Postprandial plasma glucose ≥ 140 mg/dL

Score set was derived and AUROC was obtained using 2007 – 2010 NHANES data. Data was weighted so as to represent of the civilian non-institutionalized US female population aged ≥ 20 years

Table 14: Score Set with Point Estimate of AUROC for [a]Postprandial Hyperglycemia in Parous US Women Aged ≥ 20 Years.

AUROC – 0.741	
Characteristic	Score
History of Gestational Diabetes	
No	0
Yes	8
Alcohol Consumption	
No	0
Yes	-4
Age in Years	
20 – 29	8
30 – 39	12
40 – 49	16
50 – 59	20
60 – 69	24
70 – 79	28
80+	32
BMI in Kg/m^2	
15 – 19.99	9
20 – 24.99	12
25 – 29.99	15
30 – 34.99	18
35 – 39.99	21
40 – 44.99	24
45 – 49.99	27
50+	30
Heart Rate in beats/minute	
40 – 49	8
50 – 59	10
60 – 69	12
70 – 79	14
80 – 89	16
90 - 99	18
100+	20
Height in centimeters (men)	
< 157	0
158 - 164	-2
165 - 171	-4
172 - 178	-6
179 - 185	-8
186 - 192	-10

AUROC – 0.741	
Characteristic	Score
193+	-12
Height in centimeters (women)	
< 146 cm	0
147 – 153 cm	-2
154 – 160 cm	-4
161 – 167 cm	-6
168 – 174 cm	-8
175 – 181 cm	-10
182+ cm	-12

a. Postprandial plasma glucose ≥ 140 mg/dL

Score set was derived and AUROC was obtained using 2007 – 2010 NHANES data. Data was weighted so as to represent the civilian non-institutionalized parous US female population aged ≥ 20 years

Table 15: Score Set with Point Estimate of AUROC for [a]Combined Presence of Fasting Hyperglycemia and Postprandial Hyperglycemia in US Adults Aged ≥ 20 Years.

AUROC – 0.773	
Characteristic	Score
Gender	
Female	0
Male	5
1st Degree Family History of Diabetes	
No	0
Yes	3
History/Presence of Hypertension	
No	0
Yes	8
Alcohol Consumption	
No	0
Yes	-3
Current Smoker	
No	0
Yes	4
Age in Years	
20 – 29	8
30 – 39	12
40 – 49	16
50 – 59	20
60 – 69	24
70 – 79	28
80+	32
BMI in Kg/m^2	
15 – 19.99	9
20 – 24.99	12
25 – 29.99	15
30 – 34.99	18
35 – 39.99	21
40 – 44.99	24
45 – 49.99	27
50+	30
Heart Rate in beats/minute	
40 – 49	8
50 – 59	10
60 – 69	12
70 – 79	14
80 – 89	16

AUROC – 0.773	
Characteristic	Score
90 - 99	18
100+	20
Height in centimeters (men)	
< 157	0
158 - 164	-2
165 - 171	-4
172 - 178	-6
179 - 185	-8
186 - 192	-10
193+	-12
Height in centimeters (women)	
< 146 cm	0
147 – 153 cm	-2
154 – 160 cm	-4
161 – 167 cm	-6
168 – 174 cm	-8
175 – 181 cm	-10
182+ cm	-12

a. Fasting plasma glucose ≥ 100 mg/dL and postprandial plasma glucose ≥ 140 mg/dL

Score set was derived and AUROC was obtained using 2007 – 2010 NHANES data. Data was weighted so as to represent the civilian non-institutionalized US population aged ≥ 20 years

Table 16: Score Set with Point Estimate of AUROC for [a]Combined Presence of Fasting Hyperglycemia and Postprandial Hyperglycemia in US Women Aged ≥ 20 Years.

AUROC – 0.783	
Characteristic	Score
1st Degree Family History of Diabetes	
No	0
Yes	6
Age in Years	
20 – 29	10
30 – 39	15
40 – 49	20
50 – 59	25
60 – 69	30
70 – 79	35
80+	40
BMI in Kg/m^2	
15 – 19.99	9
20 – 24.99	12
25 – 29.99	15
30 – 34.99	18
35 – 39.99	21
40 – 44.99	24
45 – 49.99	27
50+	30
Heart Rate in beats/minute	
40 – 49	12
50 – 59	15
60 – 69	18
70 – 79	21
80 – 89	24
90 - 99	27
100+	30

a. Fasting plasma glucose ≥ 100 mg/dL and postprandial plasma glucose ≥ 140 mg/dL

Score set was derived and AUROC was obtained using 2007 – 2010 NHANES data. Data was weighted so as to represent the civilian non-institutionalized US female population aged ≥ 20 years

Table 17: Score Set with Point Estimate of AUROC for [a]Combined Presence of Fasting Hyperglycemia and Postprandial Hyperglycemia in Parous US Women Aged ≥ 20 Years.

AUROC – 0.779	
Characteristic	Score
1st Degree Family History of Diabetes	
No	0
Yes	4
History/Presence of Cardiovascular Disease	
No	0
Yes	7
History of Gestational Diabetes	
No	0
Yes	14
Age in Years	
20 – 29	10
30 – 39	15
40 – 49	20
50 – 59	25
60 – 69	30
70 – 79	35
80+	40
BMI in Kg/m^2	
15 – 19.99	9
20 – 24.99	12
25 – 29.99	15
30 – 34.99	18
35 – 39.99	21
40 – 44.99	24
45 – 49.99	27
50+	30
Heart Rate in beats/minute	
40 – 49	8
50 – 59	10
60 – 69	12
70 – 79	14
80 – 89	16
90 - 99	18
100+	20

a. Fasting plasma glucose ≥ 100 mg/dL and postprandial plasma glucose ≥ 140 mg/dL

Score set was derived and AUROC was obtained using 2007 – 2010 NHANES data. Data was weighted so as to represent the civilian non-institutionalized parous US female population aged ≥ 20 years

Table 18: Score Set with Point Estimate of AUROC for [a]Elevated HbA1c in US Adults Aged ≥ 20 Years.

AUROC – 0.768	
Characteristic	Score
1st Degree Family History of Diabetes	
No	0
Yes	4
Current Smoker	
No	0
Yes	7
Age in Years	
20 – 29	12
30 – 39	18
40 – 49	24
50 – 59	30
60 – 69	36
70 – 79	42
80+	48
BMI in Kg/m^2	
15 – 19.99	12
20 – 24.99	16
25 – 29.99	20
30 – 34.99	24
35 – 39.99	28
40 – 44.99	32
45 – 49.99	36
50+	40

a. Elevated HbA1c ≥ 5.7%

Score set was derived and AUROC was obtained using 2007 – 2010 NHANES data. Data was weighted so as to represent the civilian non-institutionalized US population aged ≥ 20 years

Table 19: Score Set with Point Estimate of AUROC for [a]Elevated HbA1c in US Women Aged ≥ 20 Years.

AUROC – 0.805	
Characteristic	Score
1st Degree Family History of Diabetes	
No	0
Yes	4
Current Smoker	
No	0
Yes	5
Age in Years	
20 – 29	14
30 – 39	21
40 – 49	28
50 – 59	35
60 – 69	42
70 – 79	49
80+	56
BMI in Kg/m^2	
15 – 19.99	9
20 – 24.99	12
25 – 29.99	15
30 – 34.99	18
35 – 39.99	21
40 – 44.99	24
45 – 49.99	27
50+	30
Ethnicity	
Non-Hispanic White	0
Non-Hispanic Black	8
Hispanic	7
Other Ethnicity	0

a. Elevated HbA1c ≥ 5.7%
b. Other Ethnicity defined as ethnicity other than Non-Hispanic White, Non-Hispanic Black or Hispanic

Score set was derived and AUROC was obtained using 2007 – 2010 NHANES data. Data was weighted so as to represent the civilian non-institutionalized US female population aged ≥ 20 years

Table 20: Score Set with Point Estimate of AUROC for [a]Elevated HbA1c in Parous US Women Aged ≥ 20 Years.

AUROC – 0.776	
Characteristic	Score
Current Smoker	
No	0
Yes	5
History of Gestational Diabetes	
No	0
Yes	8
Age in Years	
20 – 29	14
30 – 39	21
40 – 49	28
50 – 59	35
60 – 69	42
70 – 79	49
80+	56
BMI in Kg/m^2	
15 – 19.99	9
20 – 24.99	12
25 – 29.99	15
30 – 34.99	18
35 – 39.99	21
40 – 44.99	24
45 – 49.99	27
50+	30
Ethnicity	
Non-Hispanic White	0
Non-Hispanic Black	8
Hispanic	8
Other Ethnicity	-4

a. Elevated HbA1c ≥ 5.7%
b. Other Ethnicity Defined as ethnicity other than Non-Hispanic White, Non-Hispanic Black or Hispanic

Score set was derived and AUROC was obtained using 2007 – 2010 NHANES data. Data was so as to represent the civilian non-institutionalized parous US female population aged ≥ 20 years

Table 21: External Validation[a] of Scoring Sets for Hyperglycemic Screening Tools

Hyperglycemic Condition	AUROC	(95% Confidence Intervals)
US Adults[a]		
Fasting Hyperglycemia[b]	0.715	(0.687 – 0.742)
Postprandial Hyperglycemia[c]	0.775	(0.748 – 0.802)
Combined Fasting/Postprandial Hyperglycemia[d]	0.778	(0.747 – 0.823)
Elevated HbA1c[e]	0.729	(0.699 – 0.760)
US Women[a]		
Fasting Hyperglycemia	0.732	(0.691 – 0.773)
Postprandial Hyperglycemia	0.781	(0.738 – 0.823)
Combined Fasting/Postprandial Hyperglycemia	0.785	(0.739 – 0.832)
Elevated HbA1c[e]	0.776	(0.735 – 0.818)

a. AUROCs were calculated by applying scoring systems to 2005 – 2006 NHANES non-pregnant participants aged $\geq$ 20 years without prior diagnosis of hyperglycemia. Data was not weighted.
b. Fasting plasma glucose $\geq$ 100 mg/dL
c. 2-Hour oral glucose tolerance test result of $\geq$ 140 mg/dL
d. Fasting plasma glucose $\geq$ 100 mg/dL and 2-Hour oral glucose tolerance test result of $\geq$ 140 mg/dL
e. HbA1c $\geq$ 5.7%

Table 22: Internal Validation of Scoring Systems for Hyperglycemic Screening Tools by Ethnic Group

Hyperglycemic Condition	AUROC	(95% Confidence Intervals)
US Adults		
Fasting Hyperglycemia[a]		
All Ethnicities	0.727	(0.709 - 0.744)
Non-Hispanic White	0.754	(0.731 - 0.778)
Non-Hispanic Black	0.672	(0.625 - 0.719)
Hispanic	0.719	(0.686 - 0.752)
Other Ethnicity[b]	0.681	(0.589 - 0.773)
Postprandial Hyperglycemia[c]		
All Ethnicities	0.753	(0.733 - 0.773)
Non-Hispanic White	0.755	(0.728 - 0.782)
Non-Hispanic Black	0.723	(0.668 - 0.778)
Hispanic	0.758	(0.723- 0.793)
Other Ethnicity	0.800	(0.710 - 0.890)
Combined Fasting/Postprandial Hyperglycemia[d]		
All Ethnicities	0.770	(0.749 - 0.791)
Non-Hispanic White	0.781	(0.752 - 0.810)
Non-Hispanic Black	0.756	(0.703 - 0.810)
Hispanic	0.763	(0.726 - 0.800)
Other Ethnicity	0.779	(0.667 - 0.891)
Elevated HbA1c[e]		
All Ethnicities	0.742	(0.724 - 0.761)
Non-Hispanic White	0.779	(0.753 - 0.804)
Non-Hispanic Black	0.667	(0.620 - 0.714)
Hispanic	0.745	(0.710 - 0.780)
Other Ethnicity	0.849	(0.782 - 0.916)
US Women		
Fasting Hyperglycemia		
All Ethnicities	0.716	(0.691 - 0.741)
Non-Hispanic White	0.745	(0.710 - 0.780)
Non-Hispanic Black	0.687	(0.622 - 0.751)
Hispanic	0.685	(0.638 - 0.732)
Other Ethnicity	0.736	(0.611 - 0.861)
Postprandial Hyperglycemia		
All Ethnicities	0.751	(0.724 - 0.778)
Non-Hispanic White	0.747	(0.700 - 0.794)
Non-Hispanic Black	0.755	(0.686 - 0.824)
Hispanic	0.771	(0.724 - 0.818)
Other Ethnicity	0.747	(0.616 - 0.878)
Combined Fasting/Postprandial Hyperglycemia		
All Ethnicities	0.779	(0.750 - 0.807)
Non-Hispanic White	0.784	(0.743 - 0.825)
Non-Hispanic Black	0.780	(0.713 - 0.847)
Hispanic	0.791	(0.742 - 0.840)
Other Ethnicity	0.738	(0.593 - 0.883)

Elevated HbA1c		
All Ethnicities	0.772	(0.747 - 0.796)
Non-Hispanic White	0.798	(0.776 - 0.830)
Non-Hispanic Black	0.751	(0.689 - 0.813)
Hispanic	0.723	(0.673 - 0.773)
Other Ethnicity	0.851	(0.759 - 0.943)
US Parous Women		
Fasting Hyperglycemia		
All Ethnicities	0.700	(0.672 - 0.728)
Non-Hispanic White	0.734	(0.695 - 0.772)
Non-Hispanic Black	0.638	(0.564 - 0.712)
Hispanic	0.681	(0.629 - 0.732)
Other Ethnicity	0.656	(0.486 - 0.826)
Postprandial Hyperglycemia		
All Ethnicities	0.750	(0.720 - 0.780)
Non-Hispanic White	0.742	(0.699 - 0.785)
Non-Hispanic Black	0.745	(0.665 - 0.825)
Hispanic	0.771	(0.722 - 0.820)
Other Ethnicity	0.723	(0.562 - 0.884)
Combined Fasting/Postprandial Hyperglycemia		
All Ethnicities	0.770	(0.739 - 0.801)
Non-Hispanic White	0.781	(0.738 - 0.824)
Non-Hispanic Black	0.758	(0.684 - 0.832)
Hispanic	0.779	(0.724 - 0.834)
Other Ethnicity	0.772	(0.627 - 0.917)
Elevated HbA1c		
All Ethnicities	0.754	(0.726 - 0.781)
Non-Hispanic White	0.766	(0.728 - 0.804)
Non-Hispanic Black	0.758	(0.692 - 0.824)
Hispanic	0.730	(0.667 - 0.783)
Other Ethnicity	0.779	(0.635 - 0.923)

AUROCs were calculated by applying scoring systems to 2007 - 2010 NHANES non-pregnant participants aged $\geq$ 20 years without prior diagnosis of hyperglycemia. Data was not weighted.

a. Fasting plasma glucose $\geq$ 100 mg/dL
b. Other Ethnicity defined as ethnicity other than Non-Hispanic White, Non-Hispanic Black or Hispanic
c. 2-Hour oral glucose tolerance test result of $\geq$ 140 mg/dL
d. Fasting plasma glucose $\geq$ 100 mg/dL and 2-Hour oral glucose tolerance test result of $\geq$ 140 mg/dL
e. HbA1c $\geq$ 5.7%

Table 23: AUROCs of Hyperglycemic Screening Score Sets with External and Internal Validation of Screening Score Sets

	AUROC[a]	External Validation[b] (95% CI)	Internal Validation[c] (95% CI)
US Adults			
Fasting Hyperglycemia[d]	0.730	0.715 (0.687 – 0.742)	0.727 (0.709 - 0.744)
Postprandial Hyperglycemia[e]	0.750	0.775 (0.748 – 0.802)	0.753 (0.733 - 0.773)
Fasting/Postprandial Hyperglycemia[f]	0.773	0.778 (0.747 – 0.823)	0.770 (0.749 - 0.791)
Elevated HbA1[g]	0.768	0.729 (0.699 – 0.760)	0.742 (0.724 - 0.761)
US Women			
Fasting Hyperglycemia	0.737	0.732 (0.691 – 0.773)	0.716 (0.691 - 0.741)
Postprandial Hyperglycemia	0.735	0.781 (0.738 – 0.823)	0.751 (0.724 - 0.778)
Fasting/Postprandial Hyperglycemia	0.783	0.785 (0.739 – 0.832)	0.779 (0.750 - 0.807)
Elevated HbA1c	0.805	0.776 (0.735 – 0.818)	0.772 (0.747 - 0.796)
US Parous Women			
Fasting Hyperglycemia	0.723	----------	0.700 (0.672 - 0.728)
Postprandial Hyperglycemia	0.741	----------	0.750 (0.720 - 0.780)
Fasting/Postprandial Hyperglycemia	0.779	----------	0.770 (0.739 - 0.801)
Elevated HbA1c	0.776	----------	0.754 (0.726 - 0.781)

a. AUROCs for hyperglycemic screening scores were derived from same data used to develop the screening scores: Weighted data from the 2007 - 2010 NHANES participants aged ≥ 20 years without prior diagnosis of hyperglycemia.
b. External validations of hyperglycemic screening score sets were calculated by applying scoring sets to 2005 – 2006 NHANES non-pregnant participants aged ≥ 20 years without prior diagnosis of hyperglycemia. Data was not weighted.
c. Internal Validations of hyperglycemic screening score sets were calculated by applying scoring sets to 2007 - 2010 NHANES participants aged ≥ 20 years without prior diagnosis of hyperglycemia. Data was not weighted.
d. Fasting plasma glucose ≥ 100 mg/dL
e. 2-Hour oral glucose tolerance test result of ≥ 140 mg/dL
f. Fasting plasma glucose ≥ 100 mg/dL and 2-Hour oral glucose tolerance test result of ≥ 140 mg/dL
g. HbA1c ≥ 5.7%

Table 24: Comparison of Fasting Hyperglycemia Scoring Sets to Currently Available Hyperglycemic Screening Tools

Fasting Hyperglycemia[a]	AUROC (95% CI)	Difference (95% CI)	p-value	Sensitivity + Specificity	p-value
US Adults[b]					
Fasting Hyperglycemia Screening Score Set	0.725 (0.694 - 0.756)	0.015 (-0.007, 0.037)	0.184	----------	----------
TAG-IT[c]	0.710 (0.678 - 0.741)				
Fasting Hyperglycemia Screening Score Set	----------	----------	---------	0.915 + 0.299 = 1.214[d]	0.029
Modified ADA Diabetes Screening Guidelines[e]				0.907 + 0.254 = 1.161	
US Women[f]					
Women's Fasting Hyperglycemia Screening Score Set	0.731 (0.663 - 0.764)	0.009 (-0.030, 0.049)	0.653	----------	----------
TAG-IT	0.722 (0.673 - 0.770)				
Women's Fasting Hyperglycemia Screening Score Set	----------	----------	---------	0.932 + 0.318 = 1.240	0.006
Modified ADA Diabetes Screening Guidelines				0.947 + 0.267 = 1.214	
US Parous Women[g]					
Parous Women's Fasting Hyperglycemia Screening Score Set	0.703 (0.670 - 0.736)	0.057 (0.026, 0.086)	<0.001	----------	----------
TAG-IT	0.646 (0.611 - 0.681)				
Parous Female Fasting Hyperglycemia Screening Score Set	----------	----------	---------	0.950 + 0.246 = 1.196	0.389
Modified ADA Diabetes Screening Guidelines				0.957 + 0.241 = 1.198	

a. Fasting plasma glucose $\geq$ 100 mg/dL
b. Population consisted of 2005 – 2006 NHANES non-pregnant participants aged $\geq$ 20 years without prior diagnosis of hyperglycemia. Data was not weighted. For comparison to TAG-IT only, population was restricted to persons < 65 years.
c. Tool to Assess Likelihood of Fasting Glucose ImpairmenT (TAG-IT) (Koopman et al , 2008)
d. Based on threshold that yielded a similar sensitivity as the modified ADA Diabetes Screening Guidelines when both were applied to the unweighted test population (unweighted training population for parous women)
e. ADA Screening Guidelines were restricted to noninvasive factors for which NHANES data was also available, with testing recommended if age $\geq$ 45 or if BMI $\geq$ 25 and one or more of the following are present: history of hypertension; history of cardiovascular disease; sedentary lifestyle (proxy measure of heart rate > 80 beats/min); history of gestational diabetes; one or more 1st degree relatives with diabetes; ethnicity other than non-Hispanic white.
f. Population consisted of 2005 – 2006 NHANES non-pregnant female participants aged $\geq$ 20 years without prior diagnosis of hyperglycemia. Data was not weighted. For comparison to TAG-IT only, population was restricted to women < 65 years.
g. Population consisted of 2007 - 2010 NHANES non-pregnant parous female participants aged $\geq$ 20 years without prior diagnosis of hyperglycemia. Data was not weighted. For comparison to TAG-IT only, population was restricted to parous women < 65 years.

Table 25: Comparison of Postprandial Hyperglycemia Scoring Sets to Currently Available Hyperglycemic Screening Tools

Postprandial Hyperglycemia[a]	AUROC (95% CI)	Difference (95% CI)	p-value	Sensitivity + Specificity	p-value
US Adults[b]					
Postprandial Hyperglycemia Screening Score Set	0.750 (0.713 – 0.786)	0.044 (0.013, 0.175)	0.006	----------	----------
FINDRISK[c]	0.706 (0.666 – 0.747)				
Postprandial Hyperglycemia Screening Score Set	----------	----------	----------	0.942 + 0.343 = 1.285[f]	< 0.001
Modified ADA Diabetes Screening Guidelines[e]				0.938 + 0.226 = 1.164	
US Women[f]					
Women's Postprandial Hyperglycemia Screening Score Set	0.739 (0.680 – 0.798)	0.039 (-0.005, 0.083)	0.082	----------	----------
FINDRISK	0.724 (0.665 – 0.782)				
Women's Postprandial Hyperglycemia Screening Score Set	----------	----------	----------	0.945 + 0.264 = 1.209	0.413
Modified ADA Diabetes Screening Guidelines				0.952 + 0.240 = 1.192	
US Parous Women[g]					
Parous Women's Postprandial Hyperglycemia Screening Score Set	0.732 (0.694 – 0.771)	0.045 (0.009, 0.081)	0.016	----------	----------
FINDRISK	0.687 (0.646 – 0.728)				
Parous Women's Postprandial Hyperglycemia Screening Score Set[h]	----------	----------	----------	0.966 + 0.170 = 1.136	0.012[h]
Modified ADA Diabetes Screening Guidelines				0.969 + 0.207 = 1.176	

a. 2-Hour oral glucose tolerance test result of $\geq$ 140 mg/dL
b. Population for the postprandial hyperglycemia screening score set and the ADA screening guidelines were 2005 – 2006 NHANES non-pregnant participants aged $\geq$ 20 years without prior diagnosis of hyperglycemia. Data not weighted.
c. The Finnish Diabetes Risk Score (Lindstrom & Tuomilehto , 2003), modified by using heart rate as a surrogate for exercise and by excluding daily diet of fruits and vegetables in the Diabetes Risk Score.
d. Based on threshold that yielded a similar sensitivity as the modified ADA Diabetes Screening Guidelines when both were applied to the unweighted test population (unweighted training population for parous women)
e. ADA Screening Guidelines were restricted to noninvasive factors for which NHANES data was also available, with testing recommended if age $\geq$ 45 or if BMI $\geq$ 25 and one or more of the following are present: history of hypertension; history of cardiovascular disease; sedentary lifestyle (proxy measure of heart rate > 80 beats/min); history of gestational diabetes; one or more 1st degree relatives with diabetes; ethnicity other than non-Hispanic white.
f. Population for the female postprandial hyperglycemia screening score set and ADA screening guidelines were 2005 – 2006 NHANES non-pregnant female participants aged $\geq$ 20 years without diagnosis of hyperglycemia. Data not weighted.
g. Population for the parous female postprandial hyperglycemia screening score set and the ADA screening guidelines were 2007 - 2010 NHANES non-pregnant parous female participants aged $\geq$ 20 years without diagnosis of hyperglycemia. Data not weighted.
h. Not found acceptable for screening of postprandial hyperglycemia in parous women when a sensitivity $\geq$ 0.95 is desired.

Table 26: Comparison of Combined Presence of Fasting/Postprandial Hyperglycemia Scoring Sets to Currently Available Hyperglycemic Screening Tools

Combined Presence of Fasting/Postprandial Hyperglycemia[a]	AUROC (95% CI)	Difference (95% CI)	p-value	Sensitivity + Specificity	p-value
US Adults					
Fasting/Postprandial Hyperglycemia Screening Score Set	0.773 (0.729 – 0.816)	0.059 (0.022, 0.096)	0.002	----------	----------
TAG-IT[b]	0.714 (0.669 – 0.759)				
Fasting/Postprandial Hyperglycemia Screening Score Set	0.773 (0.729 – 0.816)	0.029 (-0.009, 0.092)	0.136	----------	----------
FINDRISK[c]	0.744 (0.699 – 0.789)				
Fasting/Postprandial Hyperglycemia Screening Score Set	----------	----------	---------	0.957 + 0.266 = 1.223[d]	< 0.001
Modified ADA Diabetes Screening Guidelines[e]				0.953 + 0.216 = 1.169	
US Women					
Women's Fasting/Postprandial Hyperglycemia Screening Score Set	0.761 (0.695 – 0.828)	0.003 (-0.046, 0.052)	0.904	----------	----------
TAG-IT	0.758 (0.695 – 0.821)				
Women's Fasting/Postprandial Hyperglycemia Screening Score Set	0.761 (0.695 – 0.828)	-0.004 (-0.039, 0.031)	0.818	----------	----------
FINDRISK	0.765 (0.700 – 0.830)				
Women's Fasting/Postprandial Hyperglycemia Screening Score Set	----------	----------	---------	0.971 + 0.240 = 1.213	0.795
Modified ADA Diabetes Screening Guidelines				0.971 + 0.229 = 1.200	
US Parous Women					
Parous Women's Fasting/Postprandial Hyperglycemia Screening Score Set	0.765 (0.726 – 0.804)	0.063 (0.018, 0.108)	0.007	----------	----------
TAG-IT	0.702 (0.655 – 0.749)				
Parous Women's Fasting/Postprandial Hyperglycemia Screening Score Set	0.765 (0.726 – 0.804)	0.051 (0.010, 0.092)	0.016	----------	----------
FINDRISK	0.714 (0.668 – 0.760)				
Parous Women's Fasting/Postprandial Hyperglycemia Screening Score Set[f]	----------	----------	---------	0.982 + 0.089 = 1.071	< 0.001[f]
Modified ADA Diabetes Screening Guidelines				0.991 + 0.195 = 1.186	

a. Fasting plasma glucose $\geq$ 100 mg/dL and 2-Hour oral glucose tolerance test result of $\geq$ 140 mg/dL
b. Tool to Assess Likelihood of Fasting Glucose ImpairmenT (TAG-IT).
c. The Finnish Diabetes Risk Score, modified by using heart rate as a surrogate for exercise and by excluding daily diet of fruits and vegetables in the Diabetes Risk Score (Lindstrom & Tuomilehto , 2003)
d. Based on threshold that yielded a similar sensitivity as the modified ADA Diabetes Screening Guidelines when both were applied to the unweighted test population (unweighted training population for parous women)
e. ADA Screening Guidelines were restricted to noninvasive factors for which NHANES data was also available.
f. Not found acceptable for screening of combined presence of fasting hyperglycemia and postprandial hyperglycemia in parous women when a sensitivity $\geq$ 0.95 is desired.

Table 27: Comparison of Elevated HbA1c Scoring Sets to Currently Available Hyperglycemic Screening Tools

Elevated HbA1c[a]	Sensitivity + Specificity	p-value
US Adults[b]		
Elevated HbA1c Screening Score Set	0.960 + 0.236 = 1.196[c]	0.815
Modified ADA Diabetes Screening Guidelines[d]	0.960 + 0.228 = 1.188	
US Women[e]		
Female Elevated HbA1c Screening Score Set	0.978 + 0.267 = 1.245	0.320
Modified ADA Diabetes Screening Guidelines	0.971 + 0.242 = 1.213	
US Parous Women[f]		
Parous Female Elevated HbA1c Screening Score Set	0.968 + 0.220 = 1.188	0.613
Modified ADA Diabetes Screening Guidelines	0.971 + 0.225 = 1.196	

a. HbA1c > 5.7%
b. Population for the elevated HbA1c screening score set and the ADA screening guidelines consisted of 2005 – 2006 NHANES non-pregnant participants aged $\geq$ 20 years without prior diagnosis of hyperglycemia. Data was not weighted.
c. Based on threshold that yielded a similar sensitivity as the modified ADA Diabetes Screening Guidelines when both were applied to the unweighted test population (unweighted training population for parous women)
d. ADA Screening Guidelines were restricted to noninvasive factors for which NHANES data was also available, with testing recommended if age $\geq$ 45 or if BMI $\geq$ 25 and one or more of the following are present: history of hypertension; history of cardiovascular disease; sedentary lifestyle (proxy measure of heart rate > 80 beats/min); history of gestational diabetes; one or more 1st degree relatives with diabetes; ethnicity other than non-Hispanic white.
e. Population for the female elevated HbA1c screening score set and the ADA screening guidelines consisted of 2005 – 2006 NHANES non-pregnant female participants aged $\geq$ 20 years without prior diagnosis of hyperglycemia. Data was not weighted.
f. Population for the parous female HbA1c screening score set and the ADA screening guidelines consisted of 2007 - 2010 NHANES non-pregnant parous female participants aged $\geq$ 20 years without prior diagnosis of hyperglycemia. Data was not weighted.

Table 28: Screening Score Set Thresholds and Positive Predictive Values for Selected Sensitivities and Specificities. Screening Score Sets to be applied to US Adults

	Threshold	Sensitivity	Specificity	Positive Predictive Value
US Adults[a]				
AFG[b] Score Set Range (18 – 68)				
Maximum (Sensitivity + Specificity)	40.5	0.64	0.70	0.62
Sensitivity (Closest Approximate)				
95%	29.5	0.95	0.26	0.49
90%	32.5	0.88	0.38	0.52
80%	35.5	0.81	0.49	0.54
70%	38.5	0.72	0.61	0.58
Specificity (Closest Approximate)				
90%	47.5	0.32	0.91	0.73
80%	43.5	0.49	0.80	0.65
70%	40.5	0.64	0.70	0.62
AGT[c] Score Set Range (16 – 67)				
Maximum (Sensitivity + Specificity)	39.5	0.62	0.76	0.37
Sensitivity (Closest Approximate)				
95%	27.5	0.95	0.23	0.22
90%	30.5	0.91	0.37	0.25
80%	34.5	0.79	0.58	0.30
70%	36.5	0.71	0.65	0.32
Specificity (Closest Approximate)				
90%	45.5	0.33	0.90	0.44
80%	40.5	0.57	0.79	0.38
70%	37.5	0.67	0.69	0.33
AFG/AGT[d] Score Set Range (22 - 83)				
Maximum (Sensitivity + Specificity)	51.5	0.71	.71	0.28
Sensitivity (Closest Approximate)				
95%	38.5	0.95	0.26	0.17
90%	43.5	0.91	0.44	0.20
80%	48.5	0.79	0.62	0.24
70%	52.5	0.69	0.74	0.29
Specificity (Closest Approximate)				
90%	59.5	0.40	0.90	0.38

	Threshold	Sensitivity	Specificity	Positive Predictive Value
80%	55.5	0.55	0.81	0.32
70%	51.5	0.71	0.71	0.28
AHbA1c[e] Score Set Range (24 – 82)				
Maximum (Sensitivity + Specificity)	48.5	0.76	0.66	0.40
Sensitivity (Closest Approximate)				
95%	37.5	0.95	0.27	0.28
90%	41.5	0.91	0.41	0.31
80%	47.5	0.80	0.61	0.38
70%	50.5	0.69	0.71	0.42
Specificity (Closest Approximate)				
90%	58.5	0.38	0.90	0.53
80%	54.5	0.53	0.82	0.46
70%	50.5	0.69	0.71	0.42

a. Scoring systems were derived and AUROCs were obtained using 2007 – 2010 NHANES data. Data was weighted to obtain prevalence representative of the non-pregnant civilian non-institutionalized US population aged $\geq$ 20 years with no prior diagnosis of hyperglycemia
b. Fasting plasma glucose $\geq$ 100 mg/dL
c. 2-Hour oral glucose tolerance test result of $\geq$ 140 mg/dL
d. Fasting plasma glucose $\geq$ 100 mg/dL and 2-Hour oral glucose tolerance test result of $\geq$ 140 mg/dL
e. HbA1c $\geq$ 5.7%

Table 29: Screening Score Set Thresholds and Positive Predictive Values for Selected Sensitivities and Specificities. Screening Score Sets to be applied to US Women

	Threshold	Sensitivity	Specificity	Positive Predictive Value
US Female Adults[a]				
AFG[b] Score Set Range (20 – 69)				
Maximum (Sensitivity + Specificity)	36.5	0.79	0.58	0.48
Sensitivity (Closest Approximate)				
95%	30.5	0.95	0.29	0.40
90%	32.5	0.90	0.41	0.43
80%	36.5	0.79	0.56	0.48
70%	38.5	0.73	0.65	0.49
Specificity (Closest Approximate)				
90%	48.5	0.28	0.91	0.61
80%	44.5	0.45	0.82	0.55
70%	40.5	0.63	0.70	0.51
AGT[c] Score Set Range (14 – 60)				
Maximum (Sensitivity + Specificity)	35.5	0.69	0.71	0.39
Sensitivity (Closest Approximate)				
95%	24.5	0.95	0.20	0.24
90%	26.5	0.90	0.28	0.25
80%	31.5	0.80	0.54	0.31
70%	35.5	0.69	0.71	0.39
Specificity (Closest Approximate)				
90%	41.5	0.33	0.90	0.46
80%	37.5	0.55	0.78	0.40
70%	35.5	0.69	0.71	0.39
AFG/AGT[d] Score Set Range (34 – 95)				
Maximum (Sensitivity + Specificity)	61.5	0.81	0.65	0.26
Sensitivity (Closest Approximate)				
95%	51.5	0.95	0.31	0.17
90%	55.5	0.90	0.45	0.20
80%	61.5	0.81	0.65	0.26
70%	63.5	0.72	0.72	0.28
Specificity (Closest Approximate)				
90%	70.5	0.38	0.91	0.38

	Threshold	Sensitivity	Specificity	Positive Predictive Value
80%	66.5	0.58	0.81	0.32
70%	63.5	0.72	0.72	0.28
AHbA1c[e] Score Set Range (24 – 83)				
Maximum (Sensitivity + Specificity)	48.5	0.83	0.63	0.40
Sensitivity (Closest Approximate)				
95%	42.5	0.95	0.43	0.33
90%	45.5	0.90	0.53	0.36
80%	49.5	0.80	0.64	0.40
70%	53.5	0.70	0.75	0.46
Specificity (Closest Approximate)				
90%	61.5	0.39	0.91	0.56
80%	54.5	0.64	0.80	0.49
70%	51.5	0.74	0.70	0.43

a. Scoring systems were derived and AUROCs were obtained using 2007 – 2010 NHANES data. Data was weighted to obtain prevalence representative of the non-pregnant civilian non-institutionalized US female population aged $\geq$ 20 years with no prior diagnosis of hyperglycemia
b. Fasting plasma glucose $\geq$ 100 mg/dL
c. 2-Hour oral glucose tolerance test result of $\geq$ 140 mg/dL
d. Fasting plasma glucose $\geq$ 100 mg/dL and 2-Hour oral glucose tolerance test result of $\geq$ 140 mg/dL
e. HbA1c $\geq$ 5.7%

Table 30: Screening Score Set Thresholds and Positive Predictive Values for Selected Sensitivities and Specificities. Screening Score Sets to be applied to US Women Who Have Been Pregnant One or More Times

	Threshold	Sensitivity	Specificity	Positive Predictive Value
US Parous Female Adults[a]				
AFG[b] Score Set Range (20 – 68)				
Maximum (Sensitivity + Specificity)	41.0	0.68	0.66	0.54
Sensitivity				
95%	31.0	0.98	0.17	0.41
90%	35.0	0.93	0.32	0.44
80%	39.0	0.81	0.50	0.49
70%	41.0	0.68	0.66	0.54
Specificity				
90%	49.0	0.29	0.91	0.66
80%	45.0	0.47	0.79	0.57
70%	43.0	0.66	0.67	0.53
AGT[c] Score Set Range (13 – 68)				
Maximum (Sensitivity + Specificity)	38.5	0.69	0.70	0.38
Sensitivity[d]				
90%	30.5	0.90	0.37	0.28
80%	34.5	0.79	0.58	0.32
70%	38.5	0.69	0.70	0.38
Specificity				
90%	45.5	0.36	0.89	0.48
80%	41.5	0.56	0.80	0.43
70%	38.5	0.69	0.70	0.38
AFG/AGT[e] Score Set Range (31 – 98)				
Maximum (Sensitivity + Specificity)	61.5	0.78	0.67	0.28
Sensitivity[d]				
90%	55.5	0.90	0.47	0.22
80%	60.5	0.81	0.64	0.27
70%	62.5	0.71	0.70	0.28
Specificity				
90%	71.5	0.40	0.90	0.39
80%	66.5	0.57	0.80	0.32
70%	62.5	0.71	0.70	0.28

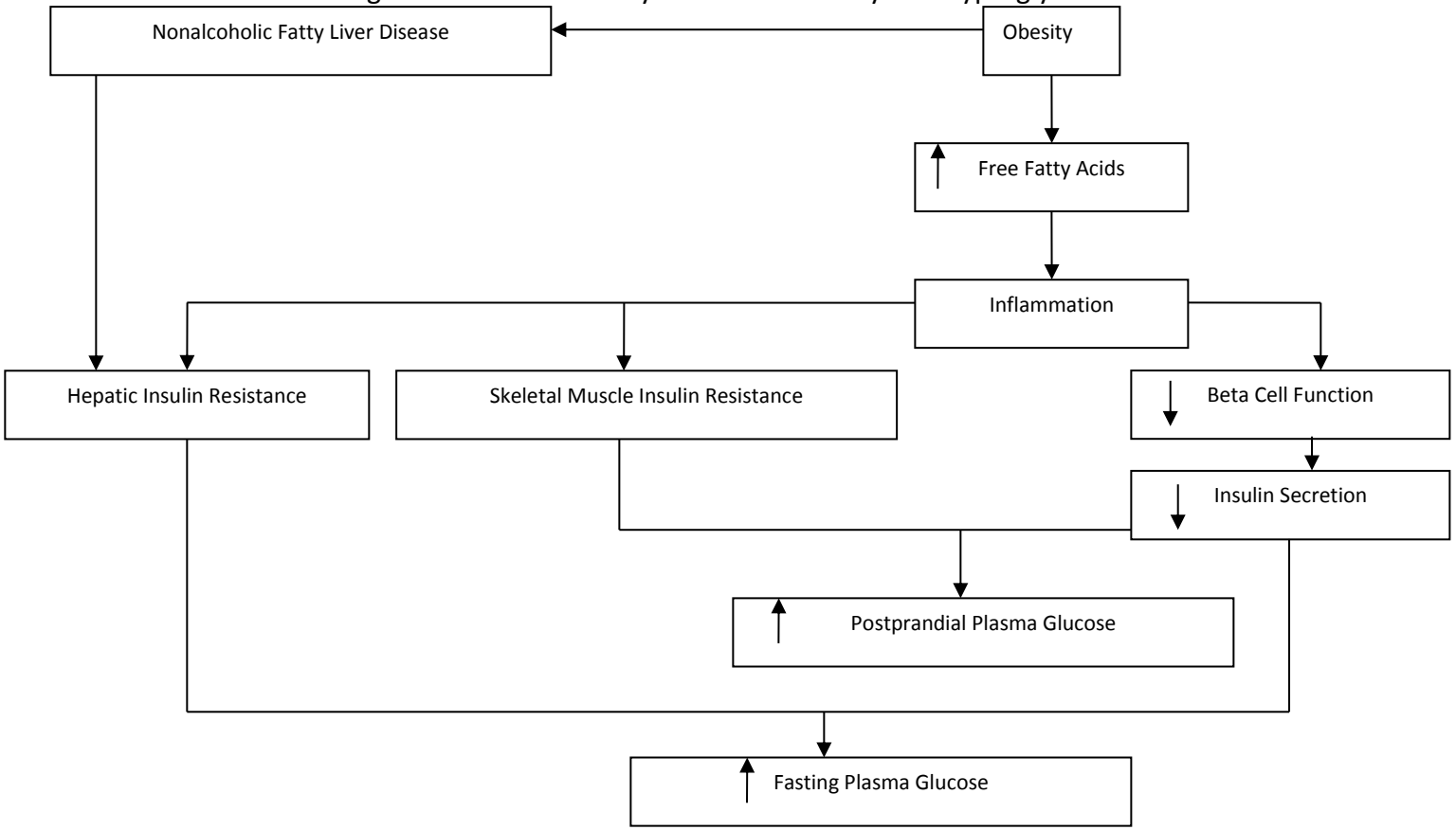
	Threshold	Sensitivity	Specificity	Positive Predictive Value
AHbA1c[f] Score Set Range (21 – 72)				
Maximum (Sensitivity + Specificity)	49.5	0.81	0.61	0.42
Sensitivity				
95%	41.5	0.95	0.34	0.33
90%	45.5	0.90	0.47	0.37
80%	49.5	0.81	0.61	0.42
70%	52.5	0.69	0.70	0.45
Specificity				
90%	61.5	0.38	0.90	0.58
80%	56.5	0.57	0.81	0.51
70%	52.5	0.69	0.70	0.45

a. Scoring systems were derived and AUROCs were obtained using 2007 – 2010 NHANES data. Data was weighted to obtain prevalence representative of the non-pregnant civilian non-institutionalized US parous female population aged $\geq$ 20 years with no prior diagnosis of hyperglycemia
b. Fasting plasma glucose $\geq$ 100 mg/dL
c. 2-Hour oral glucose tolerance test result of $\geq$ 140 mg/dL
d. Fasting plasma glucose $\geq$ 100 mg/dL and 2-Hour oral glucose tolerance test result of $\geq$ 140 mg/dL
e. Information for Sensitivity set to 95% not provided because the modified ADA Screening Guidelines are recommended for screening
   of this population when sensitivity $\geq$ 95% is desired
f. HbA1c $\geq$ 5.7

APPENDIX B

ILUSTRATIONS

Figure 1: Causal Pathways Between Obesity and Hyperglycemia



↑ Indicates "elevated", ↓ Indicates "reduced"

The American Diabetes Clinical Guideline Diagnostic Classification Recommendations (ADA, 2011)

Figure 2a: Normal and Hyperglycemic Diagnostic Classifications for Fasting Plasma Glucose

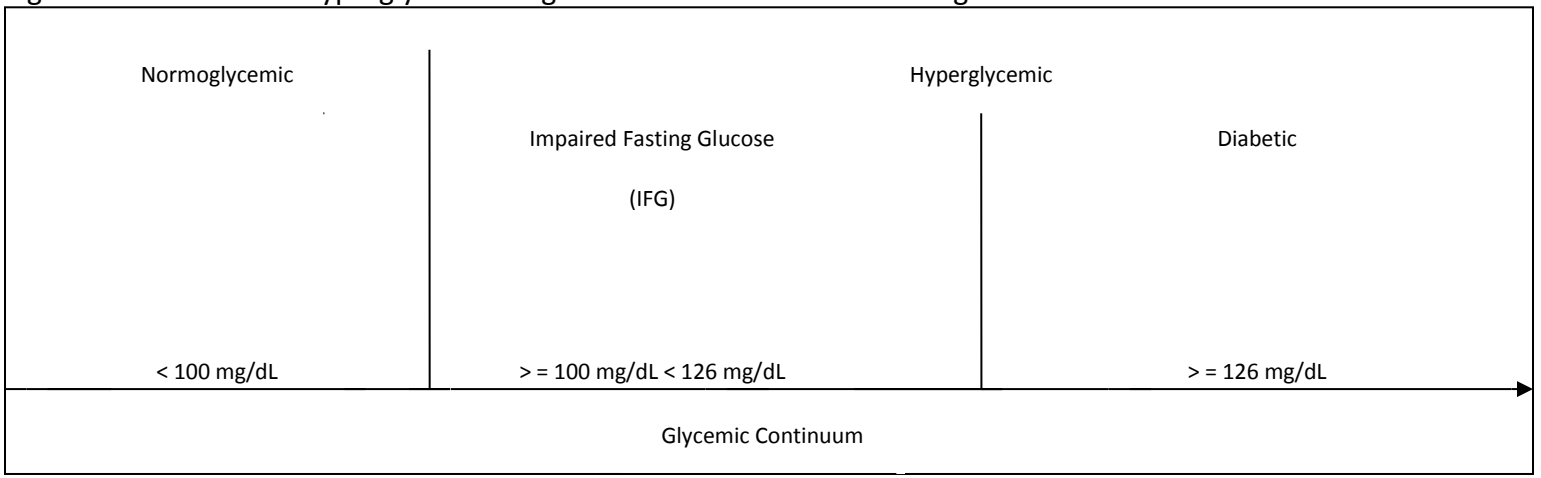


Figure2b: Normal and Hyperglycemic Diagnostic Classifications for 2 Hour Postprandial Plasma Glucose

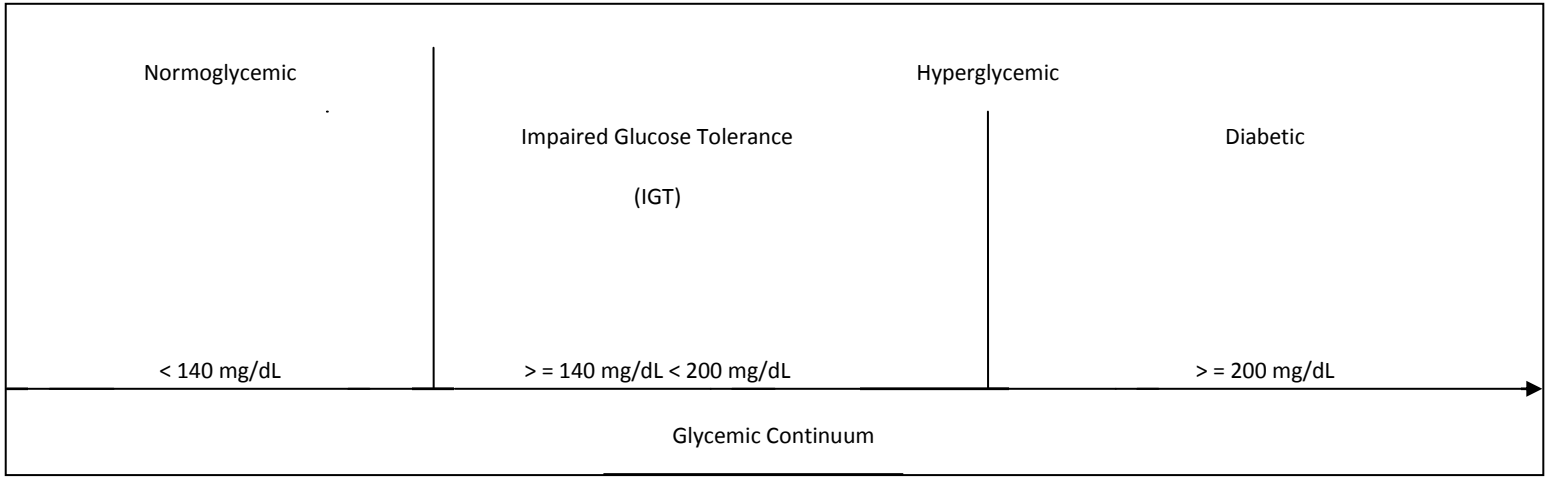


Figure 2c: Normal and Hyperglycemic Diagnostic Classifications for Percent Glycated Hemoglobin A1c

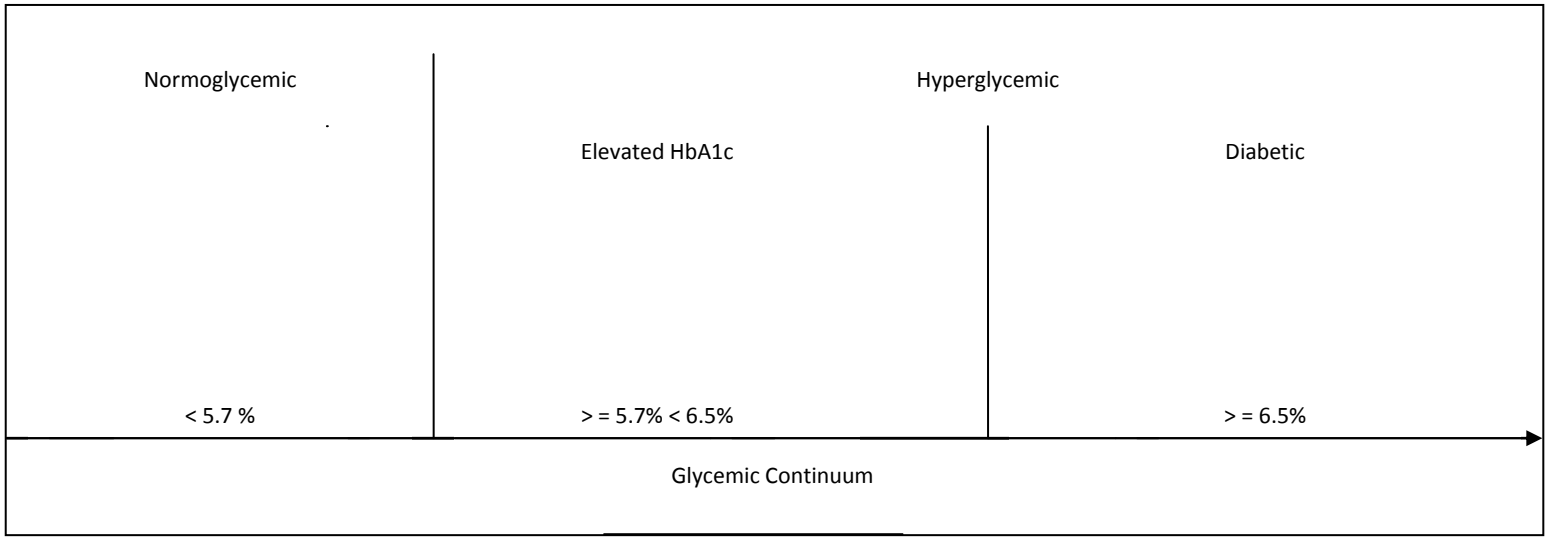


Figure 3: Classification of pre-diabetes in US adults aged ≥18 years by IFG, IGT, and HbA1c criteria, NHANES 2005-2008 (James et al, 2011).

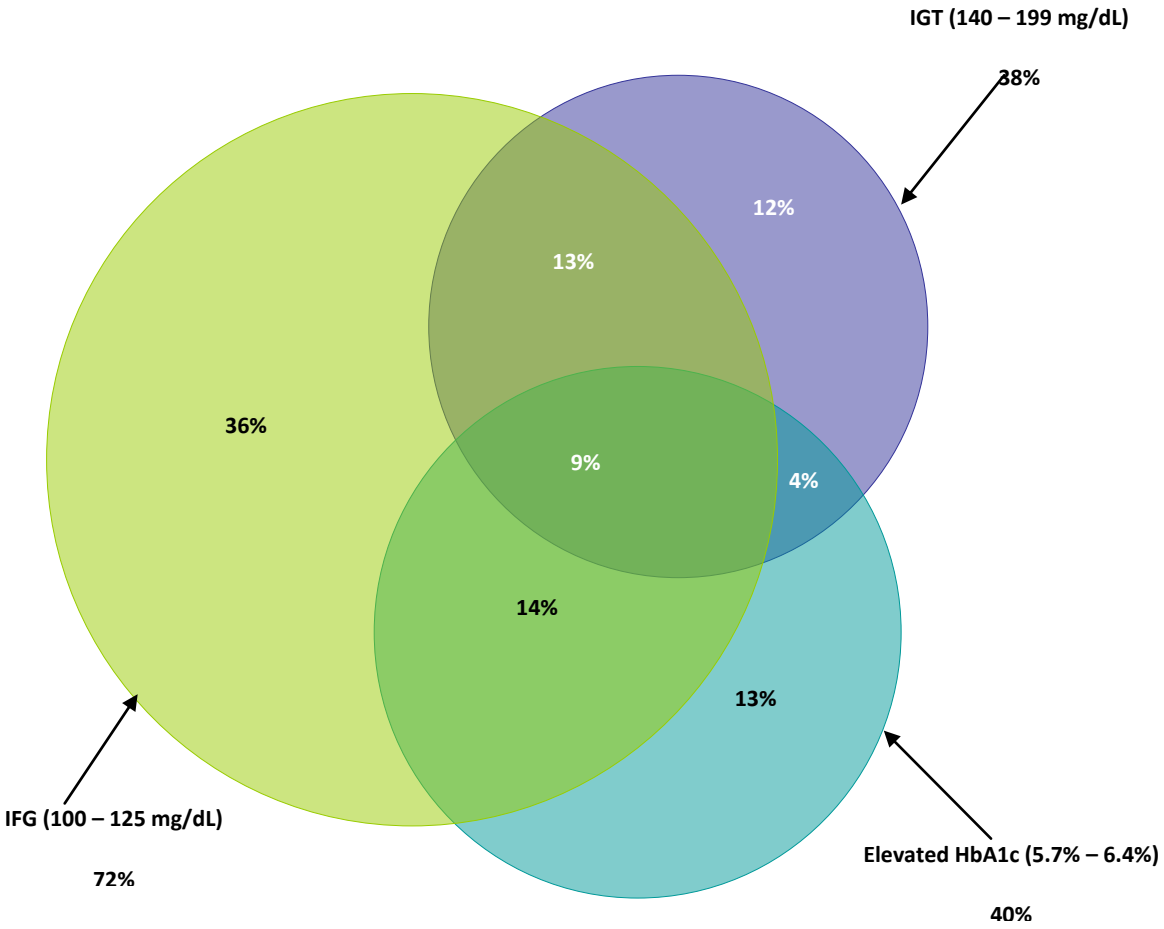
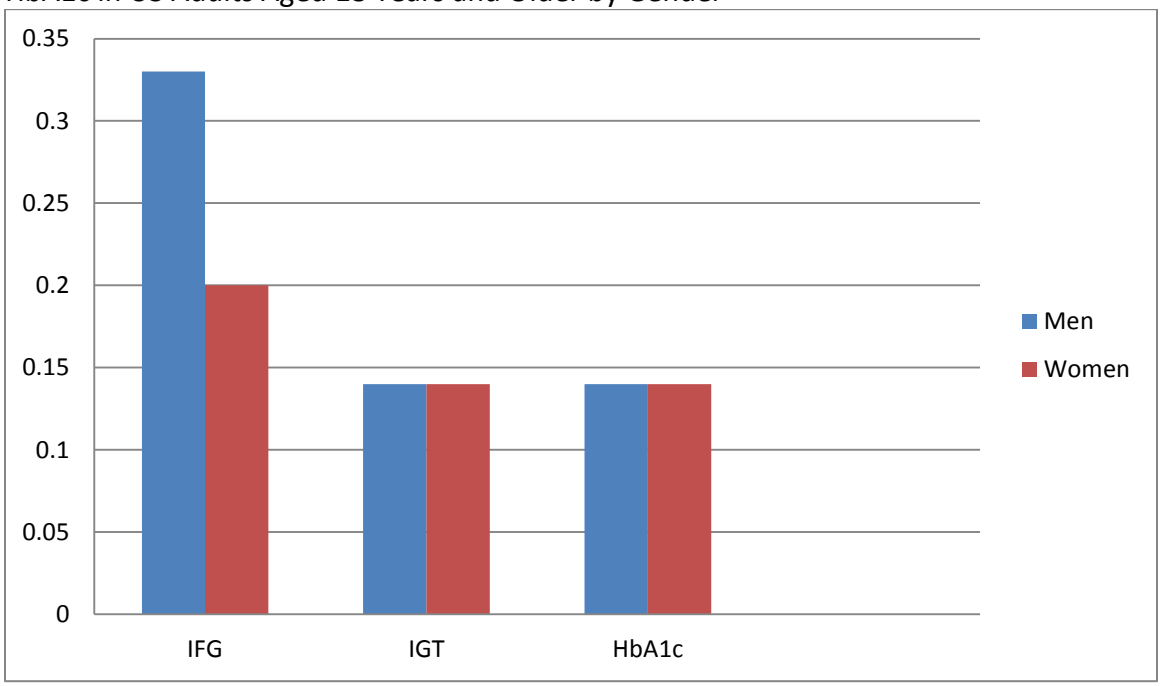
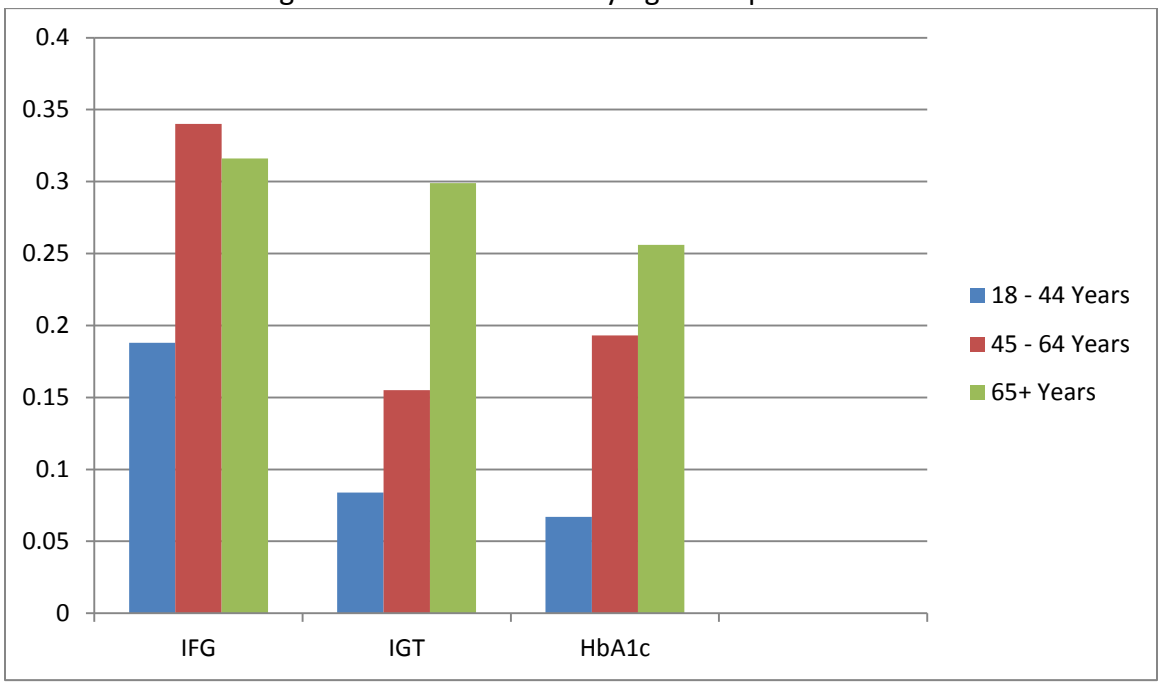


Figure 4a: Prevalence of Impaired Fasting Glucose, Impaired Glucose Tolerance and Elevated HbA1c in US Adults Aged 18 Years and Older by Gender



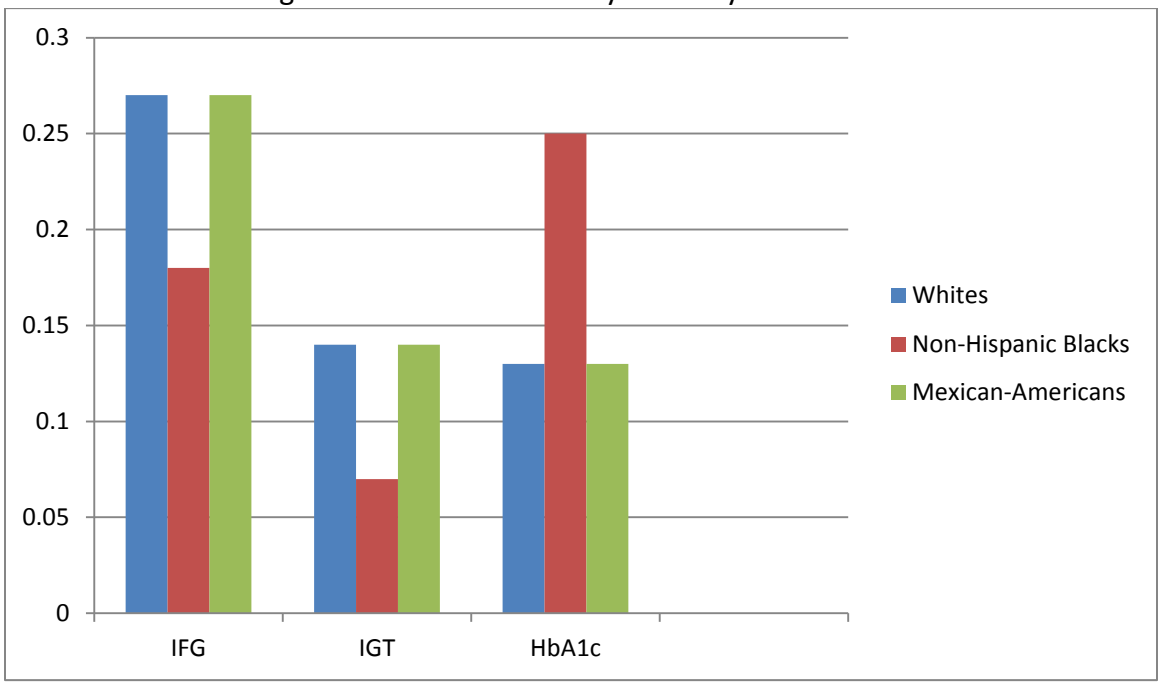
IFG – Impaired Fasting Glucose (100 to < 125 mg/dL)
IGT – Impaired Glucose Tolerance (140 to < 200 mg/dL)
HbA1c – Elevated HbA1c in the Pre-diabetic Range (5.7% to < 6.0%)

Figure 4b: Prevalence of Impaired Fasting Glucose, Impaired Glucose Tolerance and Elevated HbA1c in US Adults Aged 18 Years and Older by Age Group



IFG – Impaired Fasting Glucose (100 to < 125 mg/dL)
IGT – Impaired Glucose Tolerance (140 to < 200 mg/dL)
HbA1c – Elevated HbA1c in the Pre-diabetic Range (5.7% to < 6.0%)

Figure 4c: Prevalence of Impaired Fasting Glucose, Impaired Glucose Tolerance and Elevated HbA1c in US Adults Aged 18 Years and Older by Ethnicity



IFG – Impaired Fasting Glucose (100 to < 125 mg/dL)
IGT – Impaired Glucose Tolerance (140 to < 200 mg/dL)
HbA1c – Elevated HbA1c in the Pre-diabetic Range (5.7% to < 6.0%)

Figure 5: The Curves and 95% Confidence Limits Generated From the Coutinho et al Meta-analytical Model of 20 Studies Examining the Risk of Cardiovascular Events From Fasting and Postprandial Glucose Levels

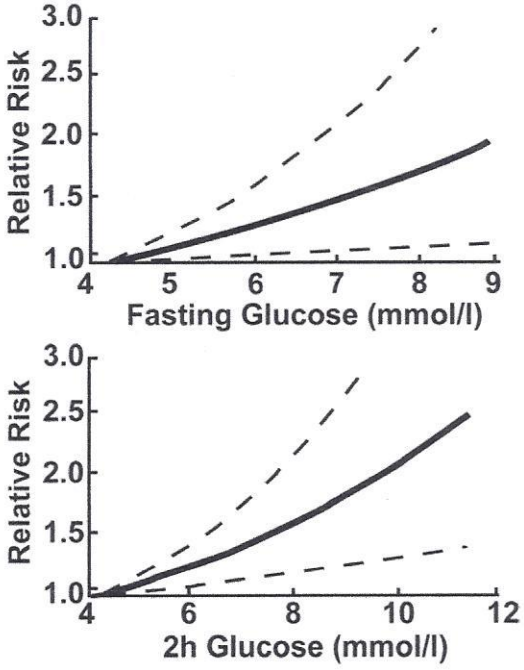
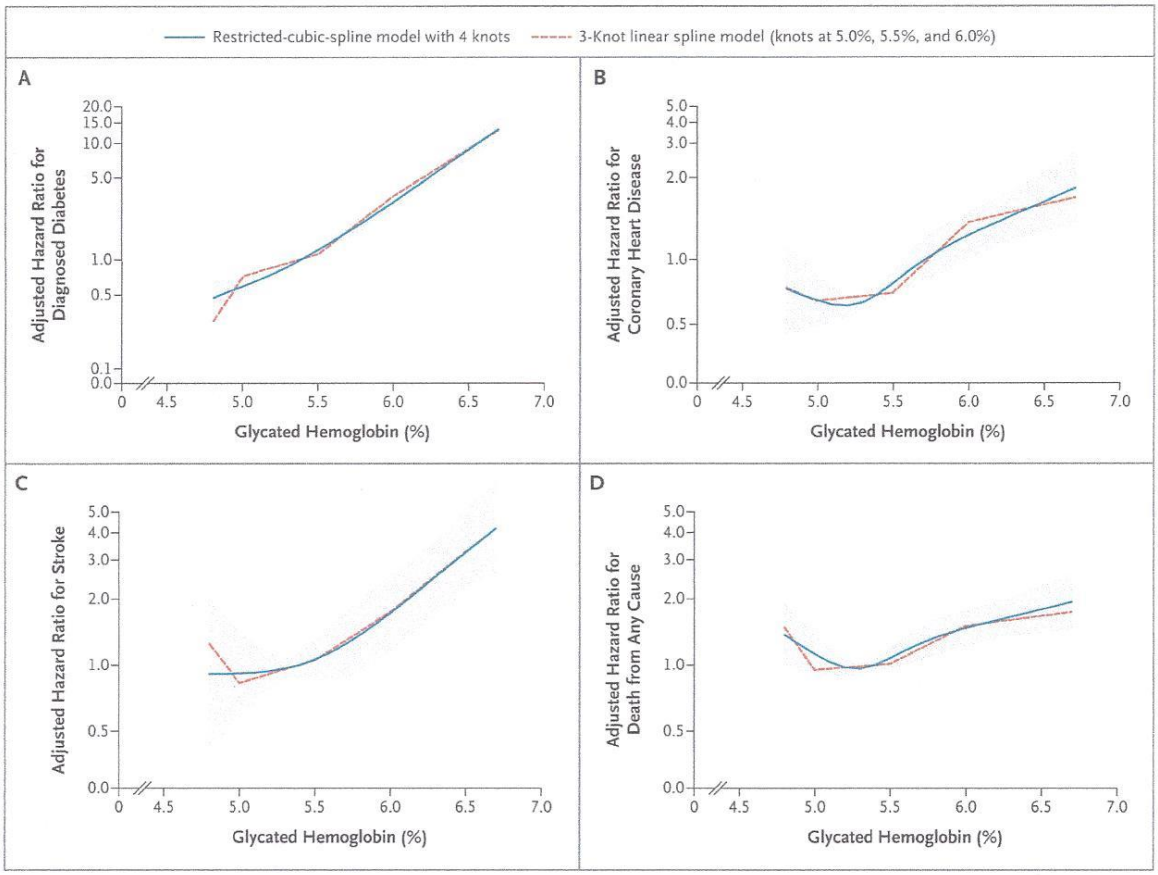


Figure 5 Originally Contained in: Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A meta-regression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care. 1999 Feb;22(2):233-40. (Coutinho et al, 1999)

Figure 6: Adjusted Hazard Ratios Observed in the Selvin et al Study for Self-Reported Diagnosed Diabetes and Coronary Heart Disease, Ischemic Stroke and Death from Any Cause, According to the Baseline Glycated Hemoglobin Value



Hazard Ratios are per each absolute increase of 1% in baseline HbA1c level. Shaded areas are 95% Confidence Limits from the Restricted Cubic-Spline Models. Models are Centered at Median (5.4%) and Plots were Truncated at 2.5th and 97.5th Percentiles of HbA1c (4.7% and 6.8%, Respectively). Hazard Ratios were adjusted for age, sex, race (Black, White), low and high density cholesterol levels, log transformed triglyceride level, BMI, waist-to-hip ratio, hypertension status, diabetes family history status, education status (no high school, high school, above high school), physical-activity index score, alcohol use and smoking status (never, ever, current – alcohol and smoking). Data is shown on natural log scale.

Figure 6 Originally Contained in: Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, Coresh J, Brancati FL. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med*. 2010 Mar 4;362(9):800-11. (Selvin et al, 2010)

Figure 7: A Nonlinear Effect of Fasting Glucose on Measured Glomerular Filtration Rate, Calculated by Local Regression Smoothing in a Generalized Additive Model (df = 3, $p < 0.0001$) and Adjusted for Age, Sex, Height, Weight, Current Smoking Status, Diastolic Blood Pressure and the Use of ACE Inhibitors or ARB (angiotensin receptor blockers).

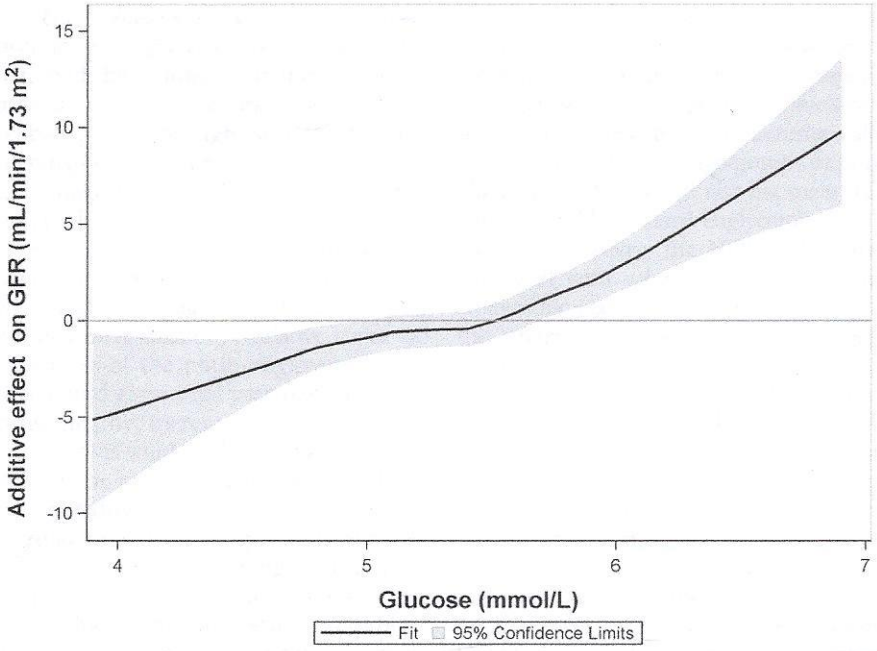


Figure 7 originally contained in: Melsom T, Mathisen UD, Ingebretsen OC, Jenssen TG, Njølstad I, Solbu MD, Toft I, Eriksen BO. Impaired fasting glucose is associated with renal hyperfiltration in the general population. *Diabetes Care*. 2011 Jul;34(7):1546-51. Epub 2011 May 18. (Melsom et al, 2011)

Figure 8: Meta-Analysis of Progression to Type-2 diabetes in Persons with IGT for Four Studies that Evaluated Combined Exercise and Diet Interventions. Pooled Overall Estimate, Presented as a Risk Ratio with 95% Confidence Interval

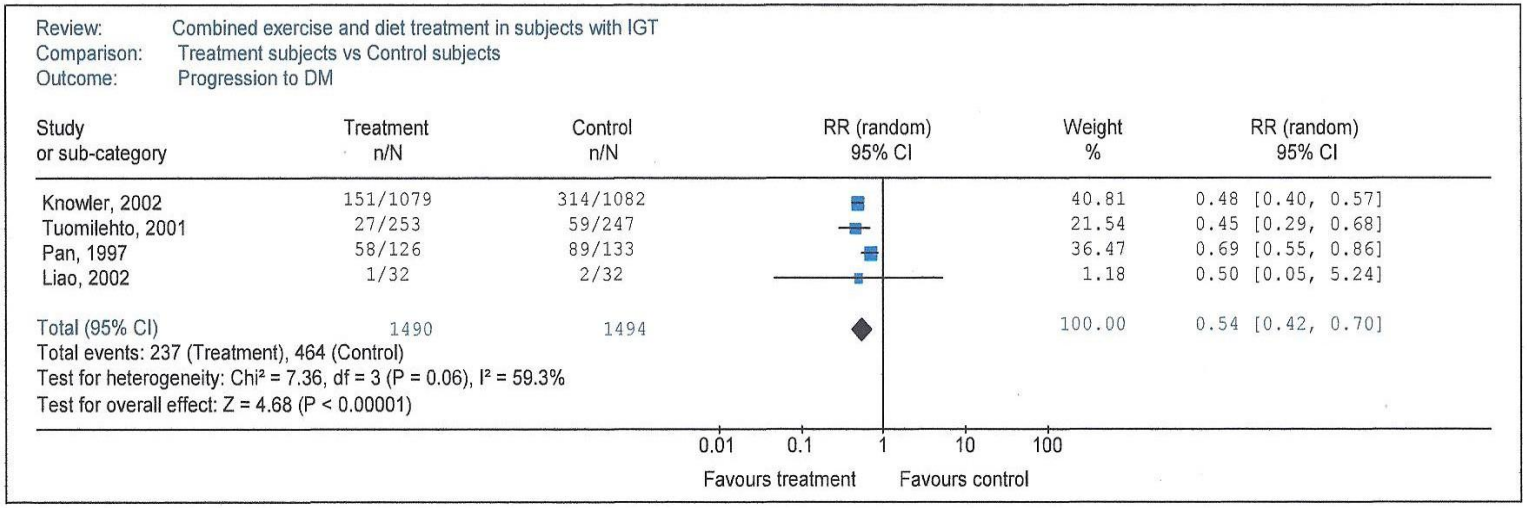


Figure 8 Originally Contained in: McMaster University Evidence Based Practice Center. Diagnosis, prognosis and treatment of impaired glucose tolerance and impaired fasting glucose. Evidence Report 128. www.ahrq.gov. (Hanley & NcNeil, 1982)

APPENDIX C

TEMPLATES FOR CALCULATING HYPERGLYCEMIA SCREENING SCORES

Adult Fasting Hyperglycemia Screening Score

For _____

Characteristic	Points	Score for Characteristic
Gender		
Female	0	
Male	10	
1st Degree Family History of Diabetes		
No	0	
Yes	3	
History/Presence of Hypertension		
No	0	
Yes	3	
Age in Years		
20 – 29	6	
30 – 39	9	
40 – 49	12	
50 – 59	15	
60 – 69	18	
70 – 79	21	
80+	24	
BMI in Kg/m^2		
15 – 19.99	12	
20 – 24.99	16	
25 – 29.99	20	
30 – 34.99	24	
35 – 39.99	28	
40 – 44.99	32	
45 – 49.99	36	
50+	40	
Total Score		

Physicians may refer to the table, "**Thresholds for Adult Fasting Hyperglycemia Screening Score Set"** to select threshold(s) for testing and/or counseling of patient

Thresholds for Adult Fasting Hyperglycemia Screening Score Set

Threshold	Sensitivity	Specificity	Positive Predictive Value
17	1	0	0.429
19.5	0.999	0.018	0.433209
21.5	0.999	0.035	0.437502
23	0.995	0.086	0.449914
24.5	0.988	0.093	0.450069
25.5	0.987	0.143	0.463888
26.5	0.981	0.171	0.470639
27.5	0.978	0.177	0.471686
28.5	0.965	0.231	0.48528
29.5	0.954	0.262	0.492697
30.5	0.945	0.273	0.494082
31.5	0.921	0.308	0.499985
32.5	0.88	0.377	0.514856
33.5	0.87	0.397	0.52015
34.5	0.86	0.431	0.531737
35.5	0.809	0.487	0.542296
36.5	0.774	0.533	0.554609
37.5	0.762	0.562	0.566552
38.5	0.717	0.614	0.582564
39.5	0.666	0.668	0.601141
40.5	0.639	0.703	0.617805
41.5	0.595	0.726	0.619989
42.5	0.535	0.776	0.642145
43.5	0.494	0.803	0.65326
44.5	0.467	0.837	0.682795
45.5	0.393	0.869	0.69268
46.5	0.351	0.885	0.696338
47.5	0.316	0.905	0.714213
48.5	0.26	0.927	0.727959
49.5	0.227	0.941	0.742973
50.5	0.2	0.949	0.7466
51.5	0.159	0.959	0.744483
52.5	0.132	0.97	0.767754
53.5	0.117	0.975	0.778572
54.5	0.092	0.98	0.775586
55.5	0.072	0.986	0.794404
56.5	0.066	0.989	0.818442
57.5	0.055	0.991	0.821153

Threshold	Sensitivity	Specificity	Positive Predictive Value
58.5	0.042	0.995	0.86322
59.5	0.029	0.996	0.84489
60.5	0.022	0.997	0.846381
61.5	0.017	0.998	0.864612
62.5	0.012	0.999	0.900157
63.5	0.007	0.999	0.840235
64.5	0.006	0.999	0.818442
65.5	0.004	1	1
66.5	0.003	1	1
67.5	0.001	1	1

Adult Postprandial Hyperglycemia Screening Score

For _____

Characteristic	Points	Score for Characteristic
History/Presence of Hypertension		
No	0	
Yes	6	
Daily Alcohol Consumption		
No	0	
Yes	-3	
Age in Years		
20 – 29	6	
30 – 39	9	
40 – 49	12	
50 – 59	15	
60 – 69	18	
70 – 79	21	
80+	24	
BMI in Kg/m^2		
15 – 19.99	6	
20 – 24.99	8	
25 – 29.99	10	
30 – 34.99	12	
35 – 39.99	14	
40 – 44.99	16	
45 – 49.99	18	
50+	20	
Heart Rate in beats/minute		
40 – 49	12	
50 – 59	15	
60 – 69	18	
70 – 79	21	
80 – 89	24	
90 - 99	27	
100+	30	
Height in centimeters (men)		
≤ 157	0	
158 - 164	-2	
165 - 171	-4	
172 - 178	-6	
179 - 185	-8	
186 - 192	-10	
193+	-12	
Height in centimeters (women)		
≤ 146 cm	0	
147 – 153 cm	-2	
154 – 160 cm	-4	
161 – 167 cm	-6	
168 – 174 cm	-8	
175 – 181 cm	-10	
182+ cm	-12	
Total Score		

Physicians may refer to the table, "**Thresholds for Adult Postprandial Hyperglycemia Screening Score Set"** to select threshold(s) for testing and/or counseling of patient

Thresholds for Adult Postprandial Hyperglycemia Screening Score Set

threshold	Sensitivity	Specificity	Positive Predictive Value
15	1	0	0.186916
16.5	1	0.002	0.18722
17.5	1	0.003	0.187373
18.5	1	0.008	0.18814
19.5	1	0.015	0.189224
20.5	0.999	0.026	0.190798
21.5	0.995	0.041	0.192581
22.5	0.992	0.062	0.195572
23.5	0.985	0.083	0.198032
24.5	0.981	0.118	0.203624
25.5	0.976	0.143	0.207485
26.5	0.964	0.191	0.215027
27.5	0.954	0.229	0.221456
28.5	0.938	0.272	0.228513
29.5	0.918	0.324	0.23791
30.5	0.906	0.373	0.24935
31.5	0.874	0.43	0.260623
32.5	0.849	0.48	0.272903
33.5	0.83	0.527	0.287441
34.5	0.787	0.575	0.298587
35.5	0.748	0.61	0.305993
36.5	0.713	0.653	0.320817
37.5	0.673	0.687	0.330786
38.5	0.649	0.721	0.348428
39.5	0.622	0.755	0.368538
40.5	0.573	0.789	0.384345
41.5	0.537	0.82	0.406818
42.5	0.482	0.847	0.420025
43.5	0.442	0.867	0.4331
44.5	0.396	0.887	0.446172
45.5	0.332	0.903	0.440348
46.5	0.316	0.921	0.479042
47.5	0.271	0.931	0.474481
48.5	0.243	0.941	0.48634
49.5	0.2	0.954	0.499875
50.5	0.184	0.965	0.547212
51.5	0.15	0.972	0.551876
52.5	0.123	0.98	0.585714

threshold	Sensitivity	Specificity	Positive Predictive Value
53.5	0.101	0.984	0.592028
54.5	0.088	0.985	0.574225
55.5	0.072	0.986	0.541761
56.5	0.055	0.99	0.558376
57.5	0.038	0.993	0.55515
58.5	0.032	0.995	0.595349
59.5	0.029	0.996	0.625
60.5	0.023	0.997	0.638003
61.5	0.015	0.997	0.534759
62.5	0.009	0.999	0.674157
63.5	0.008	0.999	0.647773
64.5	0.007	0.999	0.61674
66	0.002	1	1

Adult Fasting/Postprandial Hyperglycemia Screening Score

For _____

Characteristic	Points	Score for Characteristic
Gender		
Female	0	
Male	5	
1st Degree Family History of Diabetes		
No	0	
Yes	3	
History/Presence of Hypertension		
No	0	
Yes	8	
Alcohol Consumption		
No	0	
Yes	-3	
Current Smoker		
No	0	
Yes	4	
Age in Years		
20 – 29	8	
30 – 39	12	
40 – 49	16	
50 – 59	20	
60 – 69	24	
70 – 79	28	
80+	32	
BMI in Kg/m^2		
15 – 19.99	9	
20 – 24.99	12	
25 – 29.99	15	
30 – 34.99	18	
35 – 39.99	21	
40 – 44.99	24	
45 – 49.99	27	
50+	30	
Heart Rate in beats/minute		
40 – 49	8	
50 – 59	10	
60 – 69	12	
70 – 79	14	
80 – 89	16	
90 - 99	18	
100+	20	
Height in centimeters (men)		
< 157	0	
158 - 164	-2	
165 - 171	-4	
172 - 178	-6	
179 - 185	-8	
186 - 192	-10	
193+	-12	
Height in centimeters (women)		
< 146 cm	0	
147 – 153 cm	-2	
154 – 160 cm	-4	
161 – 167 cm	-6	
168 – 174 cm	-8	
175 – 181 cm	-10	
182+ cm	-12	
Total Score		

Physicians may refer to the table, "**Thresholds for Adult Fasting/Postprandial Hyperglycemia Screening Score Set"** to select threshold(s) for testing and/or counseling of patient

Thresholds for Adult Fasting/Postprandial Hyperglycemia Screening Score Set

threshold	Sensitivity	Specificity	Positive Predictive Value
21.0000	1.000	0	0.136054
22.5000	1.000	0.001008	0.136173
23.5000	1.000	0.001567	0.136239
24.5000	1.000	0.003792	0.136502
25.5000	1.000	0.005076	0.136654
26.5000	1.000	0.008379	0.137047
27.5000	1.000	0.013292	0.137635
28.5000	1.000	0.018357	0.138247
29.5000	1.000	0.03569	0.140383
30.5000	1.000	0.042659	0.141261
31.5000	1.000	0.055313	0.142882
32.5000	.998	0.079443	0.145851
33.5000	.992	0.100991	0.148097
34.5000	.980	0.129241	0.150521
35.5000	.973	0.155685	0.153661
36.5000	.968	0.187151	0.157923
37.5000	.961	0.222991	0.162974
38.5000	.954	0.260782	0.168868
39.5000	.936	0.29014	0.171984
40.5000	.934	0.335475	0.181188
41.5000	.932	0.371528	0.189313
42.5000	.927	0.400927	0.195939
43.5000	.905	0.438459	0.202348
44.5000	.880	0.47591	0.209184
45.5000	.853	0.507826	0.214484
46.5000	.843	0.542172	0.224847
47.5000	.821	0.578061	0.234639
48.5000	.787	0.616196	0.24413
49.5000	.761	0.65254	0.256437
50.5000	.732	0.682354	0.266392
51.5000	.714	0.714207	0.282281
52.5000	.689	0.738317	0.29305
53.5000	.635	0.766198	0.29948
54.5000	.594	0.788944	0.307172
55.5000	.554	0.813463	0.318478

threshold	Sensitivity	Specificity	Positive Predictive Value
56.5000	.515	0.835815	0.330428
57.5000	.478	0.858256	0.346834
58.5000	.429	0.876942	0.354593
59.5000	.397	0.896328	0.375902
60.5000	.356	0.913517	0.393284
61.5000	.330	0.922623	0.401521
62.5000	.306	0.9338	0.421173
63.5000	.267	0.942855	0.423797
64.5000	.242	0.95318	0.44825
65.5000	.213	0.960213	0.456985
66.5000	.176	0.96738	0.459448
67.5000	.159	0.97392	0.489941
68.5000	.129	0.980023	0.503252
69.5000	.104	0.984004	0.505155
70.5000	.089	0.986161	0.503317
71.5000	.062	0.98865	0.462358
72.5000	.045	0.992655	0.490689
73.5000	.035	0.995152	0.532417
74.5000	.030	0.996074	0.543134
75.5000	.018	0.997534	0.53398
76.5000	.012	0.997959	0.476191
77.5000	.009	0.998347	0.455612
78.5000	.008	0.999561	0.749634
79.5000	.004	0.999749	0.715877
81.0000	.004	1	1
82.5000	.003	1	1

Adult Elevated HbA1c Screening Score

For _____

Characteristic	Points	Score for Characteristic
1st Degree Family History of Diabetes		
No	0	
Yes	4	
Current Smoker		
No	0	
Yes	7	
Age in Years		
20 – 29	12	
30 – 39	18	
40 – 49	24	
50 – 59	30	
60 – 69	36	
70 – 79	42	
80+	48	
BMI in Kg/m^2		
15 – 19.99	12	
20 – 24.99	16	
25 – 29.99	20	
30 – 34.99	24	
35 – 39.99	28	
40 – 44.99	32	
45 – 49.99	36	
50+	40	
Total Score		

Physicians may refer to the table, "**Thresholds for Adult Elevated HbA1c Screening Score Set"** to select threshold(s) for testing and/or counseling of patient

Thresholds for Adult Elevated HbA1c Screening Score Set

Threshold	Sensitivity	Specificity	Positive Predictive Value
23.0000	1.000	0	0.229885
26.0000	1.000	0.016723	0.232884
29.0000	.987	0.082143	0.242998
30.5000	.986	0.092324	0.24495
31.5000	.986	0.09722	0.245951
33.0000	.978	0.169873	0.260234
34.5000	.972	0.205377	0.267538
35.5000	.966	0.220598	0.270061
36.5000	.952	0.264255	0.27863
37.5000	.952	0.265996	0.279106
38.5000	.943	0.327208	0.294982
39.5000	.937	0.347426	0.300098
40.5000	.911	0.398921	0.311578
41.5000	.910	0.405392	0.313478
42.5000	.888	0.457683	0.328305
43.5000	.883	0.465001	0.329945
44.5000	.848	0.53725	0.353633
45.5000	.842	0.553154	0.36005
46.5000	.813	0.59291	0.373519
47.5000	.801	0.611982	0.381214
48.5000	.762	0.663876	0.403719
49.5000	.750	0.670268	0.404429
50.5000	.688	0.713907	0.417797
51.5000	.673	0.732026	0.428501
52.5000	.638	0.766292	0.448883
53.5000	.613	0.776513	0.450276
54.5000	.533	0.816193	0.464001
55.5000	.522	0.825531	0.471766
56.5000	.447	0.856693	0.482204
57.5000	.418	0.870196	0.490378
58.5000	.378	0.899765	0.52925
59.5000	.368	0.90559	0.537601
60.5000	.306	0.922547	0.540959
61.5000	.283	0.92622	0.533944
62.5000	.227	0.947992	0.56621
63.5000	.220	0.949981	0.567965
64.5000	.170	0.96585	0.597916
65.5000	.167	0.968145	0.609505

Threshold	Sensitivity	Specificity	Positive Predictive Value
66.5000	.123	0.976184	0.606669
67.5000	.115	0.976766	0.59658
68.5000	.072	0.98626	0.609196
69.5000	.067	0.987456	0.612792
70.5000	.050	0.989939	0.599387
71.5000	.043	0.99037	0.570226
72.5000	.020	0.993816	0.488315
73.5000	.016	0.994927	0.49221
74.5000	.013	0.997344	0.589089
75.5000	.010	0.997344	0.536154
77.0000	.008	0.997666	0.495727
78.5000	.004	0.998923	0.493928
79.5000	.003	0.998923	0.461648
80.5000	.001	0.998923	0.269727
81.5000	.001	0.999134	0.314821

Women's Fasting Hyperglycemia Screening Score

For _____

Characteristic	Points	Score for Characteristic
1st Degree Family History of Diabetes		
No	0	
Yes	5	
Age in Years		
20 – 29	8	
30 – 39	12	
40 – 49	16	
50 – 59	20	
60 – 69	24	
70 – 79	28	
80+	32	
BMI in Kg/m^2		
15 – 19.99	12	
20 – 24.99	16	
25 – 29.99	20	
30 – 34.99	24	
35 – 39.99	28	
40 – 44.99	32	
45 – 49.99	36	
50+	40	
Total Score		

Physicians may refer to the table, "**Thresholds for Women's Fasting Hyperglycemia Screening Score Set"** to select threshold(s) for testing and/or counseling of patient

Thresholds for Women's Fasting Hyperglycemia Screening Score Set

Threshold	Sensitivity	Specificity	Positive Predictive Value
19	1	0	0.331126
22	0.998	0.029	0.337228
24.5	0.988	0.137	0.361738
26.5	0.988	0.142	0.36308
28.5	0.955	0.255	0.388227
30.5	0.951	0.291	0.399047
32.5	0.898	0.4	0.425592
34.5	0.871	0.44	0.435021
36.5	0.79	0.575	0.479224
38.5	0.73	0.621	0.488105
40.5	0.631	0.702	0.511777
42.5	0.564	0.763	0.540883
44.5	0.449	0.815	0.545764
46.5	0.367	0.866	0.575524
48.5	0.281	0.912	0.612521
50.5	0.213	0.946	0.661326
52.5	0.141	0.967	0.678995
54.5	0.079	0.983	0.697018
56.5	0.055	0.987	0.67684
58.5	0.029	0.993	0.67223
60.5	0.023	0.994	0.654897
62.5	0.012	0.997	0.664452
64.5	0.01	0.999	0.831947
66.5	0.007	1	1
68.5	0.005	1	1

Women's Postprandial Hyperglycemia Screening Score

For _____

Characteristic	Points	Score for Characteristic
1st Degree Family History of Diabetes		
No	0	
Yes	3	
History/Presence of Hypertension		
No	0	
Yes	4	
Age in Years		
20 – 29	6	
30 – 39	9	
40 – 49	12	
50 – 59	15	
60 – 69	18	
70 – 79	21	
80+	24	
BMI in Kg/m^2		
15 – 19.99	6	
20 – 24.99	8	
25 – 29.99	10	
30 – 34.99	12	
35 – 39.99	14	
40 – 44.99	16	
45 – 49.99	18	
50+	20	
Heart Rate in beats/minute		
40 – 49	8	
50 – 59	10	
60 – 69	12	
70 – 79	14	
80 – 89	16	
90 - 99	18	
100+	20	
Height in centimeters (women)		
≤ 146 cm	0	
147 – 153 cm	-2	
154 – 160 cm	-4	
161 – 167 cm	-6	
168 – 174 cm	-8	
175 – 181 cm	-10	
182+ cm	-12	
Total Score		

Physicians may refer to the table, "**Thresholds for Women's Postprandial Hyperglycemia Screening Score Set"** to select threshold(s) for testing and/or counseling of patient

Thresholds for Women's Postprandial Hyperglycemia Screening Score Set

Threshold	Sensitivity	Specificity	Positive Predictive Value
13	1	0	0.209205
15	1	0.002	0.209536
17	1	0.009	0.210705
18.5	1	0.024	0.213252
19.5	0.993	0.034	0.213802
20.5	0.983	0.066	0.21779
21.5	0.983	0.078	0.220001
22.5	0.97	0.115	0.224782
23.5	0.97	0.148	0.231473
24.5	0.953	0.196	0.23872
25.5	0.937	0.228	0.243051
26.5	0.899	0.279	0.248042
27.5	0.881	0.334	0.259234
28.5	0.865	0.395	0.274438
29.5	0.845	0.449	0.288615
30.5	0.823	0.49	0.299186
31.5	0.801	0.535	0.31305
32.5	0.77	0.58	0.326603
33.5	0.739	0.623	0.341488
34.5	0.712	0.662	0.357854
35.5	0.688	0.713	0.388074
36.5	0.614	0.749	0.39289
37.5	0.553	0.78	0.399393
38.5	0.5	0.82	0.423585
39.5	0.452	0.853	0.448564
40.5	0.377	0.875	0.44379
41.5	0.331	0.899	0.464379
42.5	0.295	0.922	0.500136
43.5	0.258	0.934	0.508394
44.5	0.212	0.948	0.518896
45.5	0.172	0.956	0.508394
46.5	0.146	0.97	0.562837
47.5	0.117	0.975	0.553191
48.5	0.09	0.98	0.543478
49.5	0.081	0.984	0.572519
50.5	0.046	0.988	0.503503
51.5	0.04	0.991	0.540394

Threshold	Sensitivity	Specificity	Positive Predictive Value
52.5	0.034	0.993	0.562355
53.5	0.028	0.993	0.514139
54.5	0.018	0.997	0.613497
55.5	0.012	0.998	0.613497
56.5	0.004	0.999	0.514139
58.5	0.004	1	1

Women's Fasting/Postprandial Hyperglycemia Screening Score

For _____

Characteristic	Points	Score for Characteristic
1st Degree Family History of Diabetes		
No	0	
Yes	6	
Age in Years		
20 – 29	10	
30 – 39	15	
40 – 49	20	
50 – 59	25	
60 – 69	30	
70 – 79	35	
80+	40	
BMI in Kg/m^2		
15 – 19.99	9	
20 – 24.99	12	
25 – 29.99	15	
30 – 34.99	18	
35 – 39.99	21	
40 – 44.99	24	
45 – 49.99	27	
50+	30	
Heart Rate in beats/minute		
40 – 49	12	
50 – 59	15	
60 – 69	18	
70 – 79	21	
80 – 89	24	
90 - 99	27	
100+	30	
Total Score		

Physicians may refer to the table, "**Thresholds for Women's Fasting/Postprandial Hyperglycemia Screening Score Set"** to select threshold(s) for testing and/or counseling of patient

Thresholds for Women's Fasting/Postprandial Hyperglycemia Screening Score Set

Threshold	Sensitivity	Specificity	Positive predictive Value
33.0000	1.000	0	0.131926
35.5000	1.000	0.0029	0.132259
38.0000	1.000	0.01502	0.133669
39.5000	1.000	0.017037	0.133906
41.0000	1.000	0.041907	0.136907
42.5000	1.000	0.049472	0.137846
43.5000	1.000	0.090271	0.143143
44.5000	.989	0.09283	0.142149
45.5000	.989	0.11703	0.145478
46.5000	.975	0.160919	0.15015
47.5000	.965	0.171009	0.1503
48.5000	.965	0.195286	0.154135
49.5000	.965	0.239726	0.161688
50.5000	.953	0.264024	0.164411
51.5000	.951	0.310319	0.173181
52.5000	.929	0.338508	0.175836
53.5000	.924	0.375147	0.183474
54.5000	.909	0.412657	0.190413
55.5000	.895	0.445923	0.197184
56.5000	.894	0.48011	0.207121
57.5000	.871	0.51002	0.212768
58.5000	.860	0.546888	0.223789
59.5000	.850	0.581276	0.235741
60.5000	.837	0.605951	0.243966
61.5000	.809	0.647111	0.258473
62.5000	.771	0.680296	0.268169
63.5000	.722	0.718647	0.28051
64.5000	.658	0.758353	0.292649
65.5000	.628	0.78552	0.307864
66.5000	.579	0.809215	0.315622
67.5000	.523	0.836226	0.326653
68.5000	.471	0.85494	0.330628
69.5000	.422	0.879471	0.347084
70.5000	.375	0.906056	0.377609
71.5000	.358	0.919193	0.402644
72.5000	.342	0.931529	0.431704
73.5000	.289	0.945419	0.445688
74.5000	.234	0.955036	0.441959
75.5000	.208	0.961065	0.447649

Threshold	Sensitivity	Specificity	Positive predictive Value
76.5000	.172	0.969985	0.466005
77.5000	.150	0.973632	0.463291
78.5000	.129	0.981919	0.520441
79.5000	.112	0.987779	0.581652
80.5000	.087	0.989445	0.55645
81.5000	.083	0.990353	0.56537
82.5000	.047	0.990585	0.431229
84.0000	.038	0.992749	0.441455
85.5000	.025	0.994021	0.384893
86.5000	.022	0.998745	0.725995
87.5000	.019	1	1
88.5000	.013	1	1
92.0000	.006	1	1

Women's Elevated HbA1c Screening Score

For _____

Characteristic	Points	Score for Characteristic
1st Degree Family History of Diabetes		
No	0	
Yes	5	
Current Smoker		
No	0	
Yes	5	
Age in Years		
20 – 29	12	
30 – 39	18	
40 – 49	24	
50 – 59	30	
60 – 69	36	
70 – 79	42	
80+	48	
BMI in Kg/m^2		
15 – 19.99	12	
20 – 24.99	16	
25 – 29.99	20	
30 – 34.99	24	
35 – 39.99	28	
40 – 44.99	32	
45 – 49.99	36	
50+	40	
Ethnicity		
Non-Hispanic White	0	
Non-Hispanic Black	8	
Hispanic	7	
Other Ethnicity	0	
Total Score		

Physicians may refer to the table, "**Thresholds for Women's Elevated HbA1c Screening Score Set"** to select threshold(s) for testing and/or counseling of patient

Thresholds for Women's Elevated HbA1c Screening Score Set

Threshold	Sensitivity	Specificity	Positive Predictive Value
22.0000	1.000	0	0.230947
24.5000	1.000	0.02	0.234555
26.5000	.998	0.072	0.244115
27.5000	.998	0.074	0.244513
28.5000	.998	0.077	0.245113
29.5000	.998	0.109	0.2517
30.5000	.998	0.143	0.259099
31.5000	.992	0.152	0.259969
32.5000	.990	0.16	0.261407
33.5000	.987	0.209	0.272574
34.5000	.985	0.22	0.274955
35.5000	.985	0.245	0.281497
36.5000	.982	0.276	0.289426
37.5000	.979	0.309	0.298473
38.5000	.979	0.322	0.302465
39.5000	.977	0.344	0.309032
40.5000	.958	0.396	0.322633
41.5000	.956	0.418	0.330332
42.5000	.949	0.431	0.333712
43.5000	.927	0.474	0.346079
44.5000	.920	0.51	0.360544
45.5000	.903	0.527	0.364394
46.5000	.879	0.548	0.368683
47.5000	.847	0.608	0.393522
48.5000	.832	0.63	0.403081
49.5000	.803	0.644	0.403826
50.5000	.774	0.684	0.423812
51.5000	.742	0.707	0.431976
52.5000	.723	0.726	0.442088
53.5000	.695	0.751	0.455986
54.5000	.639	0.798	0.487169
55.5000	.628	0.814	0.503455
56.5000	.610	0.832	0.521617
57.5000	.537	0.854	0.524834
58.5000	.503	0.861	0.520774
59.5000	.489	0.868	0.526622
60.5000	.439	0.883	0.529803
61.5000	.391	0.908	0.560686

Threshold	Sensitivity	Specificity	Positive Predictive Value
62.5000	.382	0.914	0.571531
63.5000	.342	0.921	0.565224
64.5000	.301	0.939	0.597068
65.5000	.269	0.945	0.594935
66.5000	.262	0.949	0.60672
67.5000	.230	0.958	0.621857
68.5000	.182	0.971	0.653337
69.5000	.158	0.976	0.664089
70.5000	.146	0.976	0.646246
71.5000	.104	0.983	0.647531
72.5000	.090	0.985	0.643087
73.5000	.086	0.986	0.648469
74.5000	.056	0.99	0.6271
75.5000	.035	0.992	0.567813
76.5000	.029	0.995	0.635268
77.5000	.014	0.995	0.45677
78.5000	.010	0.996	0.428816
79.5000	.004	0.998	0.375235
80.5000	0.001	0.999	0.230947
81.5	0	0.999	0
83.5	0	0.999	0

Parous Women's Fasting Hyperglycemia Screening Score

For _____

Characteristic	Points	Score for Characteristic
1st Degree Family History of Diabetes		
No	0	
Yes	4	
History of Gestational Diabetes		
No	0	
Yes	11	
Age in Years		
20 – 29	8	
30 – 39	12	
40 – 49	16	
50 – 59	20	
60 – 69	24	
70 – 79	28	
80+	32	
BMI in Kg/m^2		
15 – 19.99	12	
20 – 24.99	16	
25 – 29.99	20	
30 – 34.99	24	
35 – 39.99	28	
40 – 44.99	32	
45 – 49.99	36	
50+	40	
Ethnicity		
Non-Hispanic White	0	
Non-Hispanic Black	0	
Hispanic	4	
Other Ethnicity[b]	6	
Total Score		

Physicians may refer to the table, "**Thresholds for Parous Women's Fasting Hyperglycemia Screening Score Set"** to select threshold(s) for testing and/or counseling of patient

Thresholds for Parous Women's Fasting Hyperglycemia Screening Score Set

Threshold	Sensitivity	Specificity	Positive Predictive Value
19	1	0	0.3663
22	0.998	0.01	0.368171
26	0.997	0.067	0.381833
29	0.979	0.157	0.401659
31	0.979	0.17	0.4054
33	0.932	0.314	0.439876
35	0.929	0.318	0.440522
37	0.813	0.499	0.484006
39	0.813	0.503	0.486009
41	0.675	0.661	0.53509
43	0.661	0.666	0.533572
45	0.472	0.79	0.565066
47	0.449	0.817	0.586476
49	0.29	0.914	0.660923
51	0.264	0.919	0.653255
53	0.133	0.965	0.687161
55	0.115	0.969	0.681966
57	0.055	0.984	0.665215
59	0.045	0.987	0.666765
61	0.025	0.992	0.643666
63	0.015	0.997	0.742942
65	0.009	1	1
67	0.008	1	1

Parous Women's Postprandial Hyperglycemia Screening Score

For _____

Characteristic	Points	Score for Characteristic
History of Gestational Diabetes		
No	0	
Yes	8	
Alcohol Consumption		
No	0	
Yes	-4	
Age in Years		
20 – 29	8	
30 – 39	12	
40 – 49	16	
50 – 59	20	
60 – 69	24	
70 – 79	28	
80+	32	
BMI in Kg/m^2		
15 – 19.99	9	
20 – 24.99	12	
25 – 29.99	15	
30 – 34.99	18	
35 – 39.99	21	
40 – 44.99	24	
45 – 49.99	27	
50+	30	
Heart Rate in beats/minute		
40 – 49	8	
50 – 59	10	
60 – 69	12	
70 – 79	14	
80 – 89	16	
90 - 99	18	
100+	20	
Height in centimeters (women)		
< 146 cm	0	
147 – 153 cm	-2	
154 – 160 cm	-4	
161 – 167 cm	-6	
168 – 174 cm	-8	
175 – 181 cm	-10	
182+ cm	-12	
Total Score		

Physicians may refer to the table, "**Thresholds for Parous Women's Postprandial Hyperglycemia Screening Score Set"** to select threshold(s) for testing and/or counseling of patient

The Parous Women's Postprandial Hyperglycemia Screening Score Set is not recommended for use when sensitivity $\geq$ 95% is desired. It is recommended that physicians use the American Diabetes Association Testing

Guidelines for Asymptomatic Adults to screen for postprandial hyperglycemia in parous women (ADA guidelines provided below).

American Diabetes Association Screening Guidelines for Asymptomatic Adults

Age $\geq$ 45?	If yes, then test, screening is complete
BMI $\geq$ 25?	If no and age < 45, do not test, screening is complete
Sedentary?	If yes and BMI $\geq$ 25 kg/m^2 then test
First-degree relative with diabetes?	If yes and BMI $\geq$ 25 kg/m^2 then test
African-American?	If yes and BMI $\geq$ 25 kg/m^2 then test
Latino?	If yes and BMI $\geq$ 25 kg/m^2 then test
Native American?	If yes and BMI $\geq$ 25 kg/m^2 then test
Asian American?	If yes and BMI $\geq$ 25 kg/m^2 then test
History of Gestational Diabetes?	If yes and BMI $\geq$ 25 kg/m^2 then test
History of giving birth to a child weighing $\geq$ 9 pound at birth?	If yes and BMI $\geq$ 25 kg/m^2 then test
Receiving treatments for hypertension?	If yes and BMI $\geq$ 25 kg/m^2 then test
Blood Pressure > 140/90 mmHg?	If yes and BMI $\geq$ 25 kg/m^2 then test
History of cardiovascular disease?	If yes and BMI $\geq$ 25 kg/m^2 then test
History of polycystic ovarian syndrome?	If yes and BMI $\geq$ 25 kg/m^2 then test
High density lipoprotein cholesterol < 35 mg/dL?	If yes and BMI $\geq$ 25 kg/m^2 then test
Triglyceride > 250 mg/dL?	If yes and BMI $\geq$ 25 kg/m^2 then test
Presence of acanthosis nigricans?	If yes and BMI $\geq$ 25 kg/m^2 then test
Severely obese?	If yes then test

Thresholds for Parous Women's Postprandial Hyperglycemia Screening Score Set

Threshold	Sensitivity	Specificity	Positive Predictive Value
12.0000	1.000	0	0.21322
14.0000	1.000	0.001948	0.213547
15.5000	1.000	0.01029	0.21496
16.5000	1.000	0.011799	0.215217
17.5000	1.000	0.021379	0.216867
18.5000	.991	0.039427	0.218476
19.5000	.991	0.052788	0.220877
20.5000	.991	0.071234	0.22428
21.5000	.980	0.086301	0.225204
22.5000	.971	0.0985	0.225989
23.5000	.968	0.115765	0.228841
24.5000	.966	0.134741	0.232293
25.5000	.946	0.174718	0.237044
26.5000	.946	0.20839	0.244659
27.5000	.928	0.246974	0.250307
28.5000	.912	0.271732	0.253312
29.5000	.910	0.310603	0.263489
30.5000	.897	0.367984	0.277745
31.5000	.872	0.419973	0.289387
32.5000	.844	0.462978	0.298805
33.5000	.824	0.488108	0.303641
34.5000	.794	0.537535	0.317671
35.5000	.754	0.577209	0.32596
36.5000	.720	0.607528	0.331949
37.5000	.709	0.659866	0.360887
38.5000	.693	0.699381	0.384391
39.5000	.640	0.739125	0.399162
40.5000	.601	0.768785	0.413388
41.5000	.562	0.795022	0.426456
42.5000	.509	0.819107	0.432461
43.5000	.485	0.849589	0.466124
44.5000	.436	0.86704	0.47065
45.5000	.363	0.893051	0.479146
46.5000	.324	0.91477	0.507104
47.5000	.287	0.931052	0.529671
48.5000	.257	0.934567	0.51528
49.5000	.229	0.949381	0.550309
50.5000	.184	0.958575	0.546394

Threshold	Sensitivity	Specificity	Positive Predictive Value
51.5000	.175	0.967021	0.589634
52.5000	.154	0.972379	0.601963
53.5000	.115	0.978696	0.593714
54.5000	.090	0.981872	0.573758
55.5000	.060	0.982803	0.486178
56.5000	.044	0.986769	0.476281
57.5000	.036	0.989933	0.493739
58.5000	.027	0.989933	0.4243
59.5000	.024	0.991955	0.443492
60.5000	.014	0.994757	0.426725
61.5000	.014	0.997455	0.59366
62.5000	.011	0.997632	0.567955
65.5000	0.000	0.998931	0

Parous Women's Fasting/Postprandial Hyperglycemia Screening Score

For _____

Characteristic	Points	Score for Characteristic
1st Degree Family History of Diabetes		
No	0	
Yes	4	
History/Presence of Cardiovascular Disease		
No	0	
Yes	7	
History of Gestational Diabetes		
No	0	
Yes	14	
Age in Years		
20 – 29	10	
30 – 39	15	
40 – 49	20	
50 – 59	25	
60 – 69	30	
70 – 79	35	
80+	40	
BMI in Kg/m^2		
15 – 19.99	9	
20 – 24.99	12	
25 – 29.99	15	
30 – 34.99	18	
35 – 39.99	21	
40 – 44.99	24	
45 – 49.99	27	
50+	30	
Heart Rate in beats/minute		
40 – 49	8	
50 – 59	10	
60 – 69	12	
70 – 79	14	
80 – 89	16	
90 - 99	18	
100+	20	
Total Score		

Physicians may refer to the table, "**Thresholds for Parous Women's Fasting/Postprandial Hyperglycemia Screening Score Set"** to select threshold(s) for testing and/or counseling of patient

The Parous Women's Fasting/Postprandial Hyperglycemia Screening Score Set is not recommended for use when sensitivity $\geq$ 95% is desired. It is recommended that physicians use the American Diabetes Association Testing Guidelines for Asymptomatic Adults to screen for the combined presence of fasting hyperglycemia and postprandial hyperglycemia in parous women (ADA guidelines provided below).

American Diabetes Association Screening Guidelines for Asymptomatic Adults

Age $\geq$ 45?	If yes, then test, screening is complete
BMI $\geq$ 25?	If no and age < 45, do not test, screening is complete
Sedentary?	If yes and BMI $\geq$ 25 kg/m^2 then test
First-degree relative with diabetes?	If yes and BMI $\geq$ 25 kg/m^2 then test
African-American?	If yes and BMI $\geq$ 25 kg/m^2 then test
Latino?	If yes and BMI $\geq$ 25 kg/m^2 then test
Native American?	If yes and BMI $\geq$ 25 kg/m^2 then test
Asian American?	If yes and BMI $\geq$ 25 kg/m^2 then test
History of Gestational Diabetes?	If yes and BMI $\geq$ 25 kg/m^2 then test
History of giving birth to a child weighing $\geq$ 9 pound at birth?	If yes and BMI $\geq$ 25 kg/m^2 then test
Receiving treatments for hypertension?	If yes and BMI $\geq$ 25 kg/m^2 then test
Blood Pressure > 140/90 mmHg?	If yes and BMI $\geq$ 25 kg/m^2 then test
History of cardiovascular disease?	If yes and BMI $\geq$ 25 kg/m^2 then test
History of polycystic ovarian syndrome?	If yes and BMI $\geq$ 25 kg/m^2 then test
High density lipoprotein cholesterol < 35 mg/dL?	If yes and BMI $\geq$ 25 kg/m^2 then test
Triglyceride > 250 mg/dL?	If yes and BMI $\geq$ 25 kg/m^2 then test
Presence of acanthosis nigricans?	If yes and BMI $\geq$ 25 kg/m^2 then test
Severely obese?	If yes then test

Thresholds for Parous Women's Fasting/Postprandial Hyperglycemia Screening Score Set

Threshold	Sensitivity	Specificity	Positive Predictive Value
30.0000	1.000	0	0.142045
32.0000	1.000	0.000805	0.142144
33.5000	1.000	0.002591	0.142362
34.5000	1.000	0.00482	0.142635
35.5000	1.000	0.007851	0.143009
36.5000	1.000	0.010577	0.143346
37.5000	1.000	0.013591	0.143721
38.5000	1.000	0.031261	0.14596
39.5000	1.000	0.044553	0.147691
40.5000	1.000	0.060412	0.14981
41.5000	.997	0.071769	0.150948
42.5000	.997	0.09666	0.154464
43.5000	.984	0.11314	0.15513
44.5000	.984	0.131958	0.157962
45.5000	.984	0.15575	0.161694
46.5000	.984	0.185219	0.166568
47.5000	.984	0.206175	0.170216
48.5000	.969	0.242776	0.174826
49.5000	.969	0.271526	0.180481
50.5000	.967	0.31991	0.190479
51.5000	.939	0.349232	0.192875
52.5000	.923	0.380962	0.19796
53.5000	.921	0.413099	0.206162
54.5000	.909	0.44634	0.213774
55.5000	.903	0.474553	0.221539
56.5000	.893	0.500238	0.22826
57.5000	.881	0.536162	0.239145
58.5000	.842	0.568823	0.244261
59.5000	.810	0.606409	0.254126
60.5000	.805	0.64323	0.271932
61.5000	.777	0.671057	0.281235
62.5000	.711	0.701816	0.28298
63.5000	.683	0.726972	0.292885
64.5000	.632	0.755383	0.299686
65.5000	.590	0.777135	0.304639
66.5000	.566	0.800755	0.319971
67.5000	.536	0.824555	0.335734
68.5000	.484	0.839444	0.332938

Threshold	Sensitivity	Specificity	Positive Predictive Value
69.5000	.436	0.863228	0.345568
70.5000	.419	0.879741	0.365987
71.5000	.395	0.897296	0.388886
72.5000	.335	0.911545	0.385159
73.5000	.317	0.925291	0.412967
74.5000	.283	0.934847	0.418011
75.5000	.255	0.951127	0.463541
76.5000	.218	0.96194	0.486464
77.5000	.203	0.967722	0.510548
78.5000	.161	0.970383	0.473103
79.5000	.140	0.975746	0.487895
80.5000	.119	0.977992	0.471549
81.5000	.098	0.97886	0.433415
82.5000	.085	0.979908	0.411317
83.5000	.077	0.989835	0.556843
84.5000	.063	0.993269	0.607382
85.5000	.063	0.996847	0.767573
86.5000	.056	0.997941	0.817687
87.5000	.041	0.997941	0.769314
88.5000	.032	0.999261	0.878759
89.5000	.025	0.999261	0.847202
90.5000	.010	1	1
94.5000	.007	1	1

Parous Women's Elevated HbA1c Screening Score

For _____

Characteristic	Points	Score for Characteristic
Current Smoker		
No	0	
Yes	4	
History of Gestational Diabetes		
No	0	
Yes	7	
Age in Years		
20 – 29	12	
30 – 39	18	
40 – 49	24	
50 – 59	30	
60 – 69	36	
70 – 79	42	
80+	48	
BMI in Kg/m^2		
15 – 19.99	9	
20 – 24.99	12	
25 – 29.99	15	
30 – 34.99	18	
35 – 39.99	21	
40 – 44.99	24	
45 – 49.99	27	
50+	30	
Ethnicity		
Non-Hispanic White	0	
Non-Hispanic Black	8	
Hispanic	8	
Other Ethnicity	-4	
Total Score		

Physicians may refer to the table, "**Thresholds for Parous Women's Elevated HbA1c Screening Score Set"** to select threshold(s) for testing and/or counseling of patient

Thresholds for Parous Women's Elevated HbA1c Screening Score Set

Threshold	Sensitivity	Specificity	Positive Predictive Value
28.5000	1.000	0.043	0.26828
29.5000	1.000	0.056	0.270973
30.5000	1.000	0.069	0.273721
31.5000	.993	0.089	0.276652
32.5000	.993	0.093	0.277533
33.5000	.993	0.131	0.286196
34.5000	.988	0.145	0.288488
35.5000	.988	0.158	0.291643
36.5000	.986	0.184	0.297741
37.5000	.980	0.216	0.304878
38.5000	.980	0.227	0.307881
39.5000	.980	0.245	0.312924
40.5000	.960	0.306	0.326764
41.5000	.948	0.339	0.334763
42.5000	.929	0.352	0.334678
43.5000	.917	0.402	0.349826
44.5000	.908	0.453	0.368066
45.5000	.898	0.469	0.372405
46.5000	.893	0.502	0.386196
47.5000	.842	0.565	0.404467
48.5000	.825	0.596	0.417426
49.5000	.814	0.61	0.422747
50.5000	.746	0.658	0.433544
51.5000	.718	0.689	0.447533
52.5000	.690	0.704	0.449922
53.5000	.666	0.736	0.469543
54.5000	.612	0.772	0.485021
55.5000	.597	0.789	0.498185
56.5000	.571	0.809	0.511947
57.5000	.505	0.835	0.517816
58.5000	.485	0.849	0.529852
59.5000	.467	0.859	0.537492
60.5000	.429	0.879	0.554371
61.5000	.384	0.902	0.578924
62.5000	.373	0.905	0.579417
63.5000	0.333	0.916	0.581761
64.5000	0.281	0.932	0.591828
65.5	0.241	0.938	0.576969

Threshold	Sensitivity	Specificity	Positive Predictive Value
66.5	0.228	0.943	0.583942
67.5	0.199	0.951	0.587627

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