

Noninvasive Optical Detection of Impaired Glucose Tolerance: A Comparison Against FPG and A1C

Recent developments in noninvasive technology for measuring skin-AGE fluorescence have shown promise as a means for diabetes screening.

BY MARWOOD N. EDIGER, PHD, AND JOHN D. MAYNARD, MS

Diabetes is a costly national epidemic due in part to the micro- and macrovascular complications that begin years before onset.¹ Not surprisingly, screening to detect the more than 54 million undiagnosed prediabetic patients is a serious national priority. To reinforce screening to both health professionals and patients, the American Diabetes Association issued updated screening guidelines, revised its care algorithms for impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), and instituted several national direct-to-consumer campaigns.² In further support of aggressive diabetes detection, The Centers for Medicare and Medicaid Services approved diabetes screening under a National Coverage Decision—an extraordinary move as Medicare rarely extends payment for disease prevention. Finally, the recent Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) trial results provide perhaps the most important call to action—much of diabetes can be prevented, if detected early.³

IDENTIFY, TREAT EARLIER

Although the desire to identify and treat prediabetes is strong, in practice, current test methods are limited at detecting the early metabolic abnormalities of diabetes. The fasting plasma glucose test (FPG) is a poor indicator for early detection, and methods employing this metric are insensitive, missing as many as one-half of those with IGT.⁴ The oral glucose tolerance test (OGTT) is highly inconvenient, requiring fasting, consumption of a glucose load, and multiple blood draws over a 2+ hour interval.

Alternatively, advanced glycation endproducts (AGEs)

are attractive biomarkers for detecting early-stage abnormal glucose regulation. AGEs in the skin are correlated with diabetes and are predictive of future diabetes-related complications.^{5,6} Additionally, skin autofluorescence is correlated with AGE concentrations and is a marker for cardiovascular complications in people with diabetes.⁷ Recent developments in noninvasive technology for measuring skin-AGE fluorescence have shown promise as a means for diabetes screening.⁸ Accelerated AGE accumulation tracks cumulative postprandial glucose excursions in early IGT, whereas elevated fasting glucose levels are often indicative of later-stage glucose dysregulation. We hypothesize noninvasive measurement of skin AGEs is more sensitive than FPG for detecting IGT. We present an evaluation of clinical data comparing the two tests in their ability to detect IGT.

METHODOLOGY

We are developing a novel noninvasive instrument, SCOUT DS (Veralight, Albuquerque, NM), for measuring skin AGEs in vivo. The study presented here was a head-to-head evaluation of SCOUT versus FPG and A1C for detecting IGT. Although A1C is not a recognized screening test, it is often applied alongside FPG to assess glucose control in screened patients and was therefore included for comparison in this study. The naive cohort—no participants with a previous diagnosis of diabetes—consisted of 322 participants ranging in age from 21 to 88 years. All subjects also received an OGTT test, and the standard 2-hour OGTT thresholds determined “truth” for screening status (normal glucose tolerance [NGT]: 2-hour OGTT <140 mg/dL; IGT: 140 mg/dL; \leq 2-hour OGT \leq 199 mg/dL). The lower IFG

TABLE 1. STUDY DEMOGRAPHICS (N=32)

Age (years)		Gender		Ethnicity	
21-30	5.30%	Male	36.60%	White	54.70%
31-40	15.20%	Female	63.40%	Hispanic	35.10%
41-50	28.00%			Black	3.40%
51-60	25.80%			American Indian	5.00%
61-70	17.10%			Asian	0.90%
71-80	6.50%			East Indian	0.30%
81+	2.20%			Other	0.60%

threshold (FPG = 100 mg/dL) was selected as a clinically relevant criterion to establish the specificity at which the sensitivity of all three tests would be compared. The cohort demographics categorized by age, gender, and race/ethnicity are summarized in Table 1.

SCOUT is a tabletop instrument that illuminates the volar forearm with near-ultraviolet and blue light. An optical probe optimized for collecting dermal fluorescence couples light emanating from the skin to a charge-coupled device (CCD) detector. The heterogeneity of skin and the inherent variations of skin absorption and scattering between individuals provide unique challenges to in vivo optical measurements. Using the diffuse reflectance signal, the instrument compensates for patient-dependent optical scattering and absorption to extract the inherent dermal fluorescence spectrum.⁹ This technique enables noninvasive fluorescence measurements in subjects with a wide range of factors such as melanin content, skin thickness, and skin surface condition. Linear-discriminant analysis was applied to the spectra to yield noninvasive classification of normal glucose tolerance versus IGT.¹⁰

Participants received two noninvasive measurements—one in the fasting state and another approximately 1-hour post-glucose load. AGE concentrations and the associated skin fluorescence should, in principle, be unaffected by acute glucose levels. Comparison of the fasting and non-fasting noninvasive measurements enabled testing of the premise that SCOUT is not influenced by acute glucose concentration. Noninvasive performance was also assessed for lighter versus darker skin color subcohorts. The instrument's measurement of white-light diffuse skin reflectance was used to objectively stratify the study population by skin color.

A total of 55 subjects screened positive for IGT by the OGTT test—a prevalence of 17.1%. FPG, A1C, and SCOUT

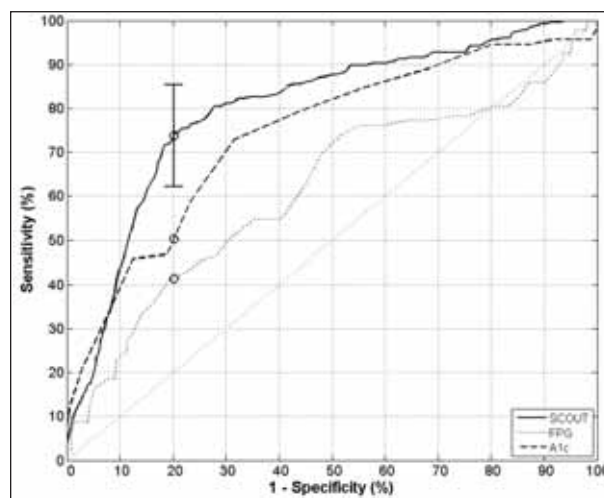


Figure 1. Receiver-operator characteristic plots of SCOUT, FPG, and A1C for detecting IGT. The critical specificity corresponding to the IFG threshold is indicated by the open circles. The error bars denote the 95% confidence interval.

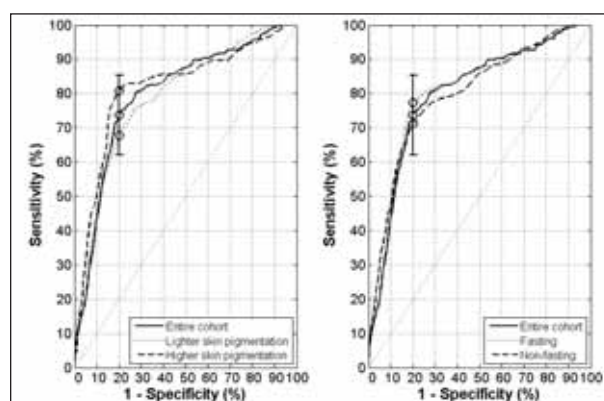


Figure 2. SCOUT IGT detection stratified by subject skin pigmentation (left) and fasting status (right).

TABLE 2. SUMMARY OF TEST SENSITIVITIES FOR DETECTING IGT

Test Sensitivity at 80% Specificity			Scout Sensitivity Advantage	
Test	Sensitivity	Threshold	Absolute difference	Relative difference
SCOUT	73.70%	51		
FPG	41.50%	100 mg/dL	32.20%	77.60%
A1C	50.20%	5.80%	23.50%	46.80%

The critical specificity (80%) corresponds to the lower IFG (FPG = 100 mg/dL). The SCOUT 95% confidence interval for sensitivity is 62.1%-85.3%.

performance for detecting IGT are presented as receiver-operator characteristic (ROC) plots in Figure 1. The IFG threshold is denoted by the open circle (sensitivity = 41.5%) on the FPG ROC curve (dashed line). This threshold corresponds to a specificity of 80%. Sensitivities of SCOUT (73.7%) and A1C (50.2%) at this same specificity are represented by open circles on their respective ROC curves. The error bars on the SCOUT ROC curve (solid line) indicate the 95% confidence interval (62.1%-85.3%). Consequently, the SCOUT sensitivity advantage for detecting IGT is statistically significant ($P < .05$). Performance values for all three tests are listed in Table 2. The sensitivity differential between SCOUT and the conventional blood assays represents large relative detection advantages. In this study, the noninvasive technology identified 77% more individuals with IGT than FPG and >46% more individuals than by A1C.

SCOUT detection performance stratified by skin color and fasting status is presented in the left and right panels, respectively, of Figure 2. The solid ROC curve in each panel is that of the entire cohort in Figure 1. In the left panel, SCOUT IGT detection performance for light and dark skin subcohorts, as delineated by diffuse optical reflectance, are depicted. SCOUT performance for nonfasting and fasting measurements are compared to the full cohort in the right panel. In both cases, the subcohort results fall well within the confidence intervals. Hence, these results suggest that the noninvasive technology effectively compensates for skin color and that SCOUT IGT detection performance is independent of fasting status.

IMPLICATIONS FOR CARE

The superior sensitivity of the prototype SCOUT instrument, combined with the convenience of the test method, create a device with the potential for opportunistic screening in both traditional health care environments and in nontraditional, more accessible care settings. The noninvasive test creates no biohazards or patient discomfort, and independence from fasting enables testing any time of day.

SCOUT provides immediate results that encourage prompt follow-up. SCOUT is portable (about 10 lbs), and the test does not require a reference lab or highly trained operators, so testing can be performed practically anywhere.

SCOUT reports a value from 0 to 100 that represents a patient's likelihood of having IGT. To facilitate interpretation of these results, future SCOUT clinical trials will develop guidelines referenced against comparable thresholds on the FPG and OGT continuums.

SCOUT is currently being tested in the United States in a large multicenter study that will be completed later this year. If the data are deemed adequate by the US Food and Drug Administration, SCOUT will be well suited to replace FPG as the mainstay for diabetes screening, providing a new tool in the quest for earlier diabetes detection and intervention. ■

Marwood N. Ediger, PhD, is the Chief Technology Officer for Verelight. He may be reached at woody.ediger@verelight.com; phone: 505-272-7539; or fax: 505-272-7112.

- Ramlo-Halsted BA, Edelman SV. The natural history of type 2 diabetes. Implications for clinical practice. *Prim Care*. 1999;26:771-789.
- Nathan DM, Davidson MB, DeFronzo RA, et al. Impaired fasting glucose and impaired glucose tolerance. *Diabetes Care*. 2007;30:753-759.
- Gerstein HC, Yusuf S, Bosch J, et al for the DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial. *Lancet*. 2006;368:1096-1105.
- Engelgau MM, Narayan KM, Herman WH. Screening for Type 2 diabetes. *Diabetes Care*. 2000;23:1563-1580.
- Monnier VM, Bautista O, Kenny D, et al for the DCCT Skin Collagen Ancillary Study Group. Skin collagen glycation, glycooxidation, and crosslinking are lower in subjects with long-term intensive versus conventional therapy of type 1 diabetes: relevance of glycated collagen products versus HbA1c as markers of diabetic complications. *Diabetes*. 1999;48:870-880.
- Genuth S, Sun W, Cleary P, et al for the DCCT Skin Collagen Ancillary Study Group. Glycation and carboxymethyllysine levels in skin collagen predict the risk of future 10-year progression of diabetic retinopathy and nephropathy in the diabetes control and complications trial and epidemiology of diabetes interventions and complications participants with type 1 diabetes. *Diabetes*. 2005;54:3103-3111.
- Mulder DJ, Water TV, Lutgers HL, et al. Skin autofluorescence, a novel marker for glycemic and oxidative stress-derived advanced glycation endproducts: an overview of current clinical studies, evidence, and limitations. *Diabetes Technol Ther*. 2006;8:523-535.
- Maynard JD, Rohrschreib M, Way JF, et al. Noninvasive type 2 diabetes screening: superior sensitivity to fasting plasma glucose and glycosylated hemoglobin, accepted for publication in *Diabetes Care*. May 2007.
- Hull EL, Ediger MN, Unione AHT, et al. Noninvasive, optical detection of diabetes: model studies with porcine skin. *Optics Express*. 2004;12:4496-4510.
- Brown CD, Davis HT, Ediger MN, et al. Clinical assessment of near-infrared spectroscopy for noninvasive diabetes screening. *Diabetes Technol Ther*. 2005;7:456-466.