



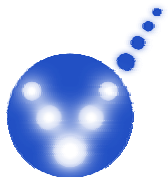
Noninvasive Fluorescence Spectroscopy for Diabetes Screening: A Clinical Case-Control Study

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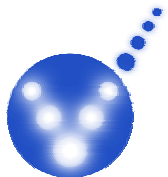
Introduction

A case-control study assessed type 2 diabetes detection using noninvasive dermal fluorescence spectroscopy. Previous work had demonstrated promise for the technique to discriminate the spectral changes in dermal chemistry occurring in the early stages of diabetes. The current study was designed to test an optical probe optimized to target dermal fluorescence and to assess the classification performance in human subjects.

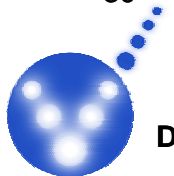
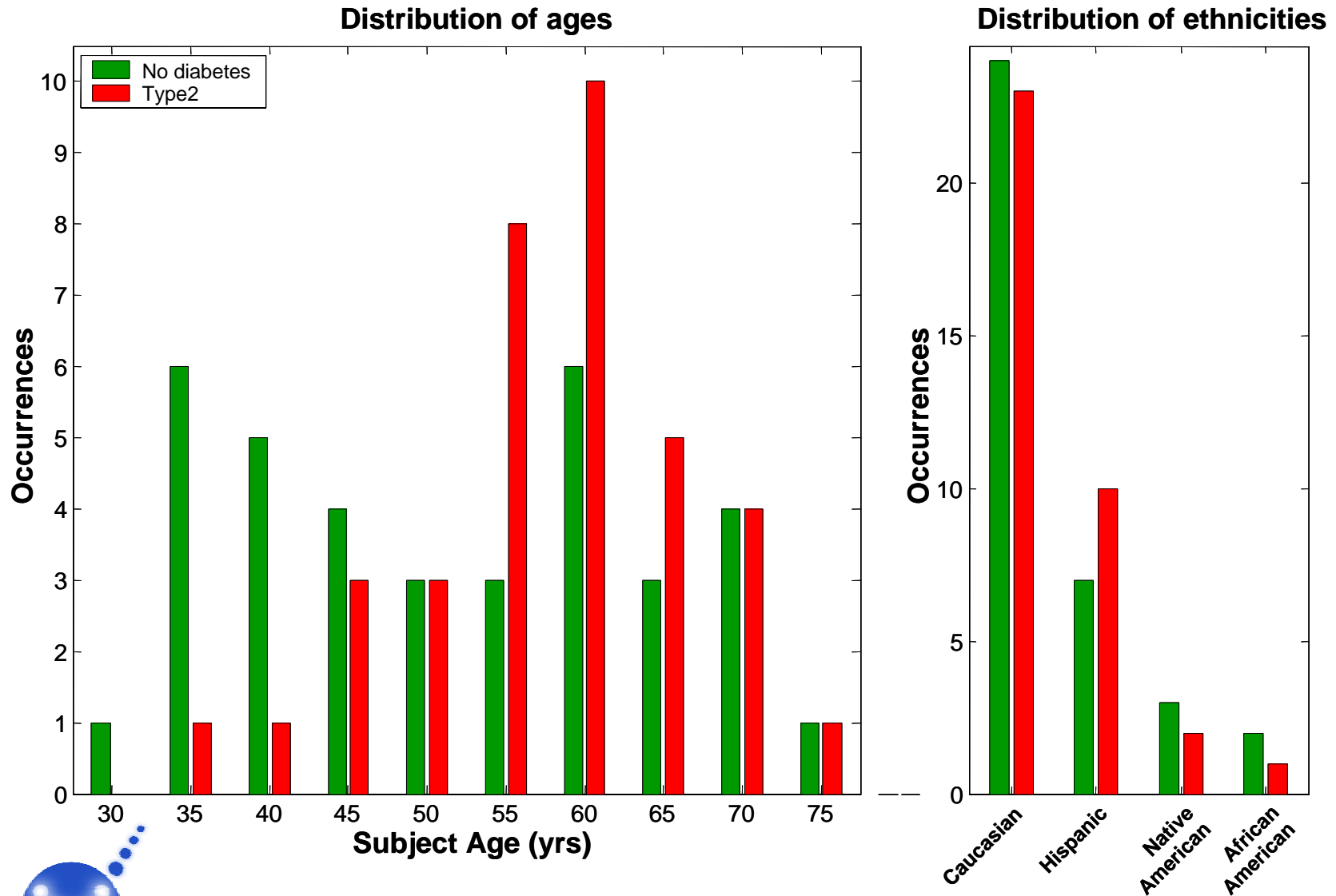


Study Design

- 72 subjects
 - 36 with type 2 diabetes
 - 36 not previously diagnosed with DM
- Ages ranged from 30-76 years
- Two separate visits: fasting and random
- Capillary blood glucose on each visit



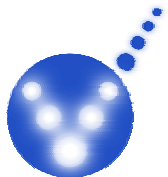
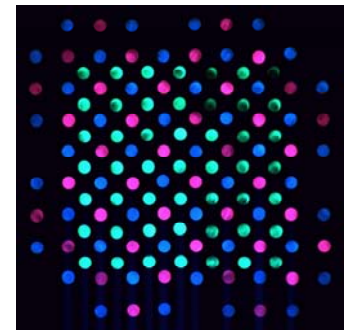
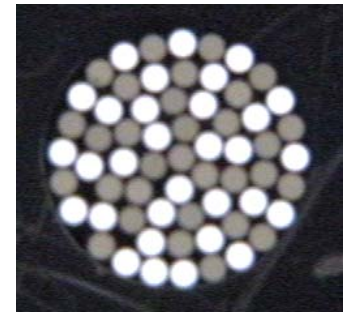
Study Demographics



Distribution of disease state by age and ethnicity for subjects participating in the case-control study

Instrumentation

- Two Jobin Yvon SkinSkan™ research-grade fluorimeters
- YSI 2700 Select Biochemistry Analyzers
- Head-to-head probe comparison:
 - **Stock fiber optic probe:**
 - Sampled various tissue depths
 - Uncontrolled source-receiver (s/r) separations
 - **Optimized probe (AGEON)**
 - Two-channel design
 - Fixed s/r separations
 - Targets dermal fluorescence

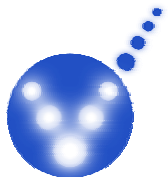


Spectroscopy

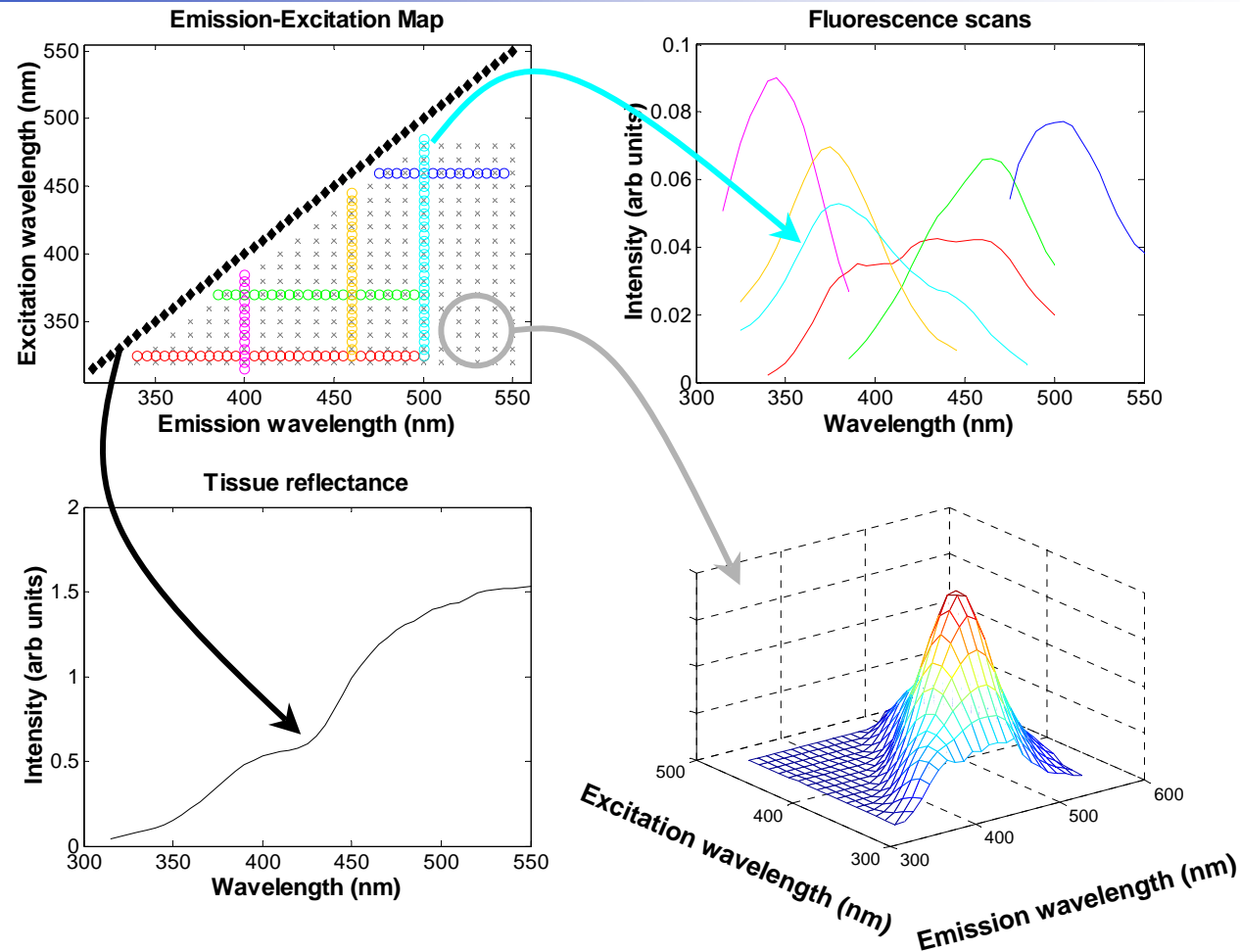
- Measured on volar forearm
 - Fluorescence
 - 3 excitation scans
 - 3 emission scans

Selected to target fluorescence peaks of advanced glycation endproducts and other major metabolic chromophores

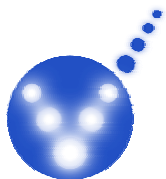
 - Excitation-emission map (EEM)
- Diffuse reflectance
 - To correct for skin optical properties



Acquired Spectra

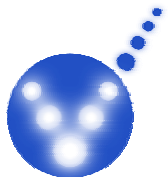


Depiction of acquired spectra - (Top-left) EEM schematic of fluorescence scans (colored circles) and comprehensive fluorescence EEM (grey x). Diffuse tissue reflectance is also depicted (black diamonds); (Top-right) Spectral shapes of representative tissue fluorescence scans, color-coordinated to scans (circles) in the EEM schematic; (Bottom-left) Representative diffuse tissue reflectance spectrum (black diamonds in schematic); (Bottom-right) Topographic surface of tissue fluorescence EEM (grey x in top left).



Dermal fluorescence

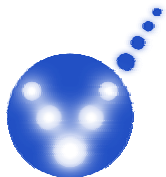
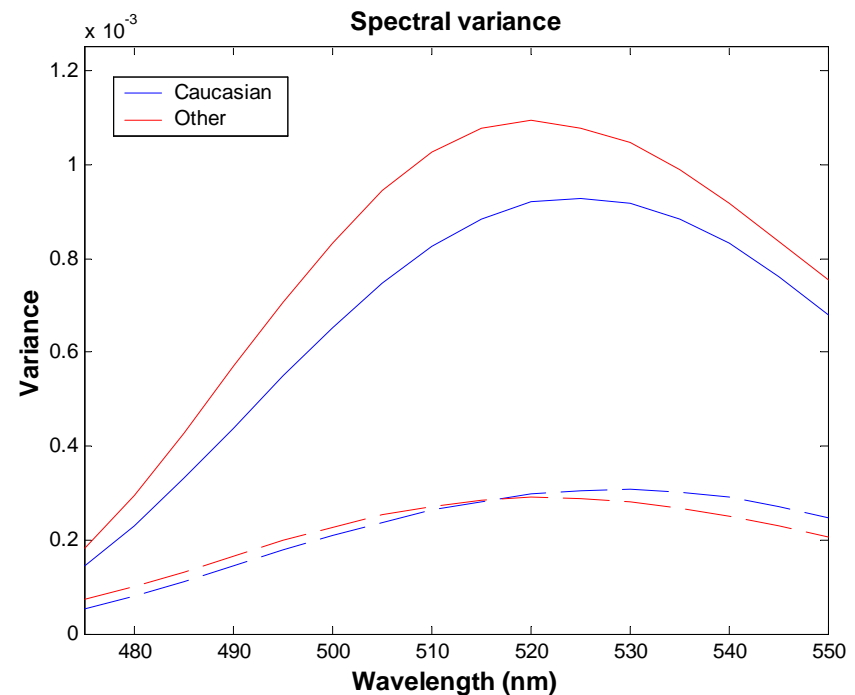
- Dermal fluorescence distorted by skin optical properties
- Correct for skin color, blood content and scattering to extract dermal signal from measured spectrum
- Diffuse reflectance used to compute dermal fluorescence correction factor



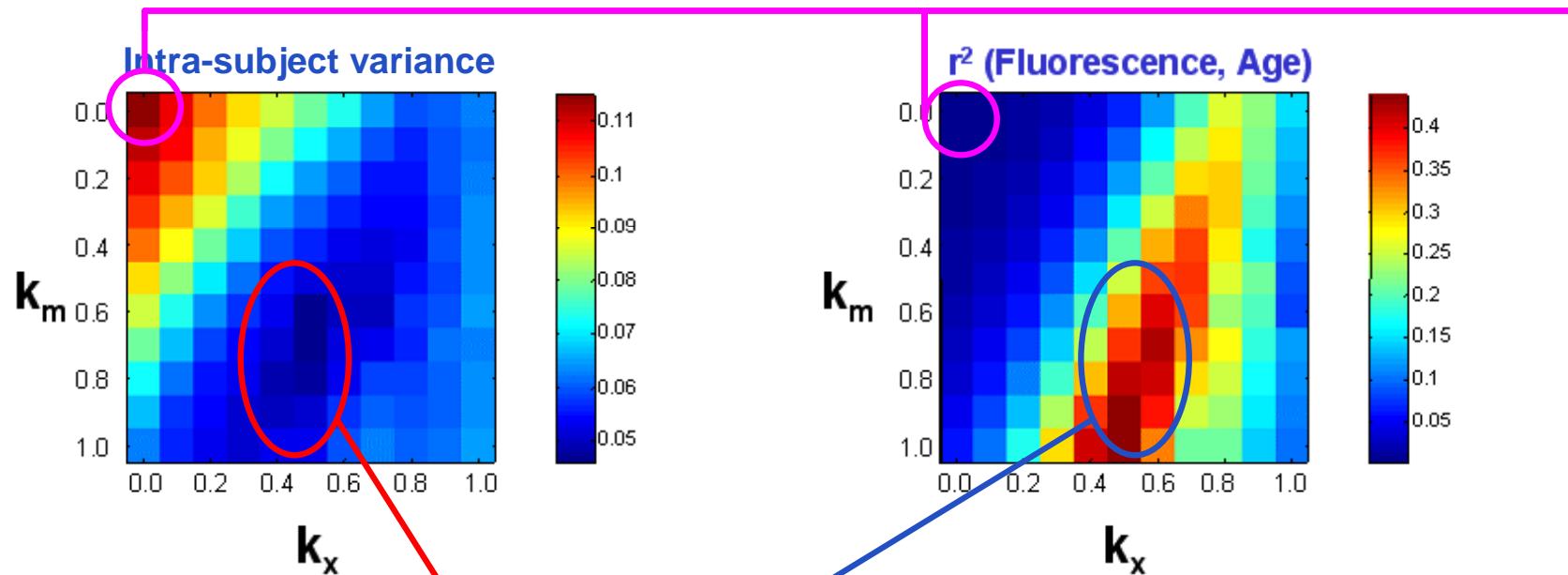
Fluorescence Correction

$$f_{mx} = \frac{F_i}{R_{im}^{k_m} R_{ix}^{k_x}}$$

(Above) Expression for dermal fluorescence correction that estimates dermal fluorescence, f , given the measured fluorescence, F , and the tissue reflectance at both the excitation (R_x) and emission (R_m) wavelengths. Exponents (k) minimize intra-subject spectral variance. **(Right)** Emission scan spectral variance ($\lambda_x = 460$, $\lambda_m = 475-550\text{nm}$) for broad skin color categories. Dermal fluorescence correction substantially reduces overall variance and diminishes the difference in spectral variance between skin types.



Fluorescence Correction (2)



Example 1) $k_m = 0.7$; $k_x = 0.5$:

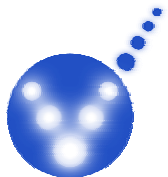
Minimizes intra-subject variance

Maximizes correlation between fluorescence and age in non-DM subjects

Example 2) $k_m, k_x = 0$:

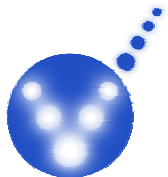
Maximizes intra-subject variance and minimizes fluorescence-age correlation

Maps of intra-subject variance and the fluorescence/age correlation coefficient for corrected fluorescence, f , over the full range of k values

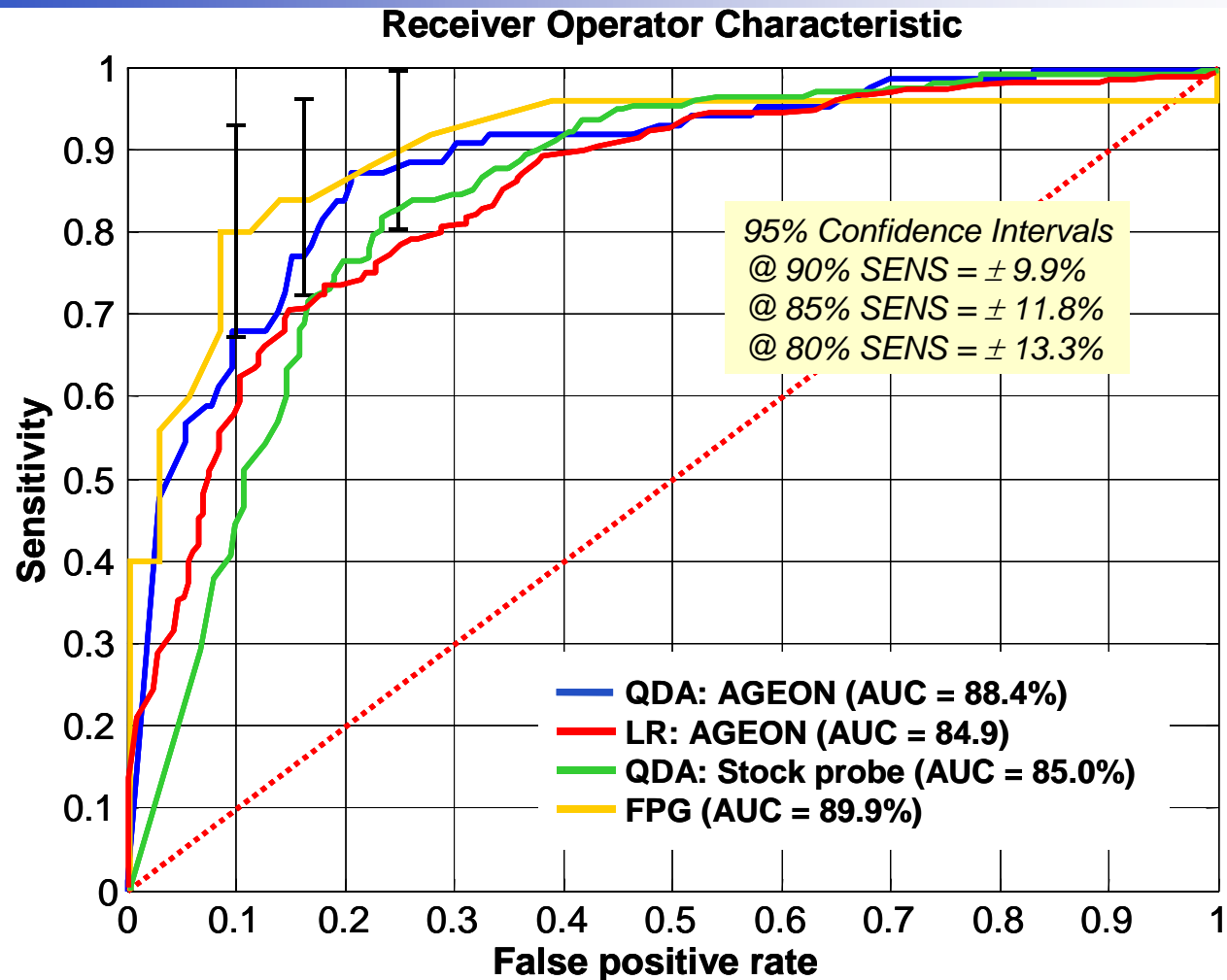


Noninvasive disease classification

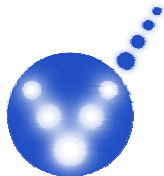
Quadratic Discriminant Analysis (QDA) and Logistic Regression (LR) were applied to the fluorescence data to assess disease classification performance in subject-out cross-validation for the entire cohort



Noninvasive disease classification (2)

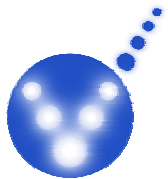


Classification performance via receiver operator characteristics for analysis of optical spectroscopy (QDA & LR) vs. FPG including 95% confidence intervals at selected sensitivities. Area-under-the-curve (AUC) shown in legend for each method. Within the power of this study, noninvasive classification performance utilizing the AGEON probe via QDA in cross-validation is comparable to that of FPG.



Extending the Study

- Additional findings
 - Identification of key spectral regions
 - Signal/noise limitations
 - Spectral resolution requirements
- Prospective classification
 - True validation was evaluated 5-6 months following calibration for a post-study group of 25 subjects without diabetes and 4 subjects with type 2 diabetes. In this group:
 - Sensitivity: 75%
 - Specificity: 88%



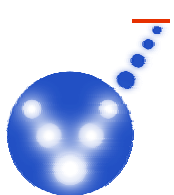
Summary

- Conclusions

- Noninvasive classification in case-control (QDA of AGEON spectra in cross-validation) is comparable to that of FPG
- AGEON outperforms the stock probe

- Next steps

- Large study currently underway in an ‘at-risk’ population, utilizing AGEON and a new, higher signal/noise instrument
- An in vivo ‘source of signal’ study



Summary (2)

- Published work
 - Brown et al., “Clinical Assessment Of Near-Infrared Spectroscopy For Noninvasive Diabetes Screening,” *Diabetes Technology and Therapeutics*, 7(3), 456-466 (2005).
 - Hull et al., “Noninvasive, optical detection of diabetes: model studies with porcine skin,” *Optics Express*, 12(19), 4496-4510 (2004).
- This work was supported by the NIH/NIDDK under grant R41 DK068969-01

