

Glycemia measurement

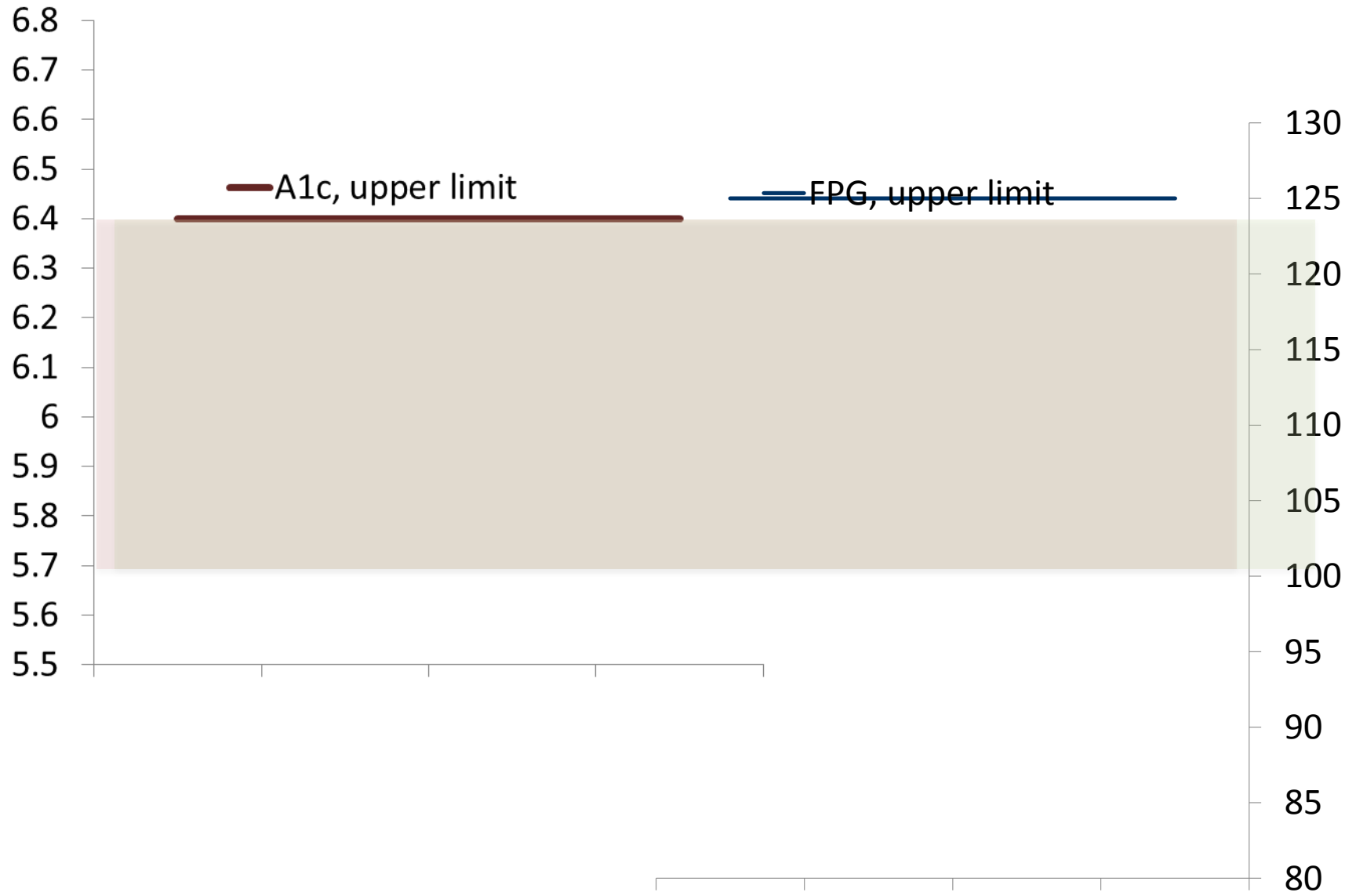
Anastassios (Taso) G. Pittas, MD MS

Michael Lewis, MD, MBA

Major recruitment challenge: High SCR-RAN ratio, partially due to sub-optimal correlation on A1c/FPG, Central Lab vs. Local Lab

Site	FPG diff		HbA1c diff	
	mean	SD	mean	SD
Atlanta	-0.45	6.80	-0.10	0.14
Baylor	7.04	7.96	-0.18	0.20
Duke	7.07	9.27	-0.14	0.16
Florida	5.70	8.60	-0.11	0.12
HealthPartners	6.93	7.06	-0.08	0.12
Kansas	-1.78	8.22	-0.08	0.17
Los Angeles	8.15	8.29	-0.22	0.17
Maine	0.98	7.25	-0.14	0.16
MedStar	1.22	8.75	-0.15	0.22
Nebraska	4.17	8.53	-0.23	0.28
New York	1.18	8.74	0.15	0.27
Northwestern	8.82	10.75	0.09	0.28
Pennington	2.93	7.84	0.07	0.11
South Carolina	3.69	13.99	0.06	0.18
Stanford	-1.40	8.31	-0.03	0.17
Tennessee	10.68	7.24	-0.14	0.17
Tufts	4.22	9.63	-0.17	0.12
UT Southwestern	4.68	18.93	-0.17	0.17
Mean	4.10		-0.09	

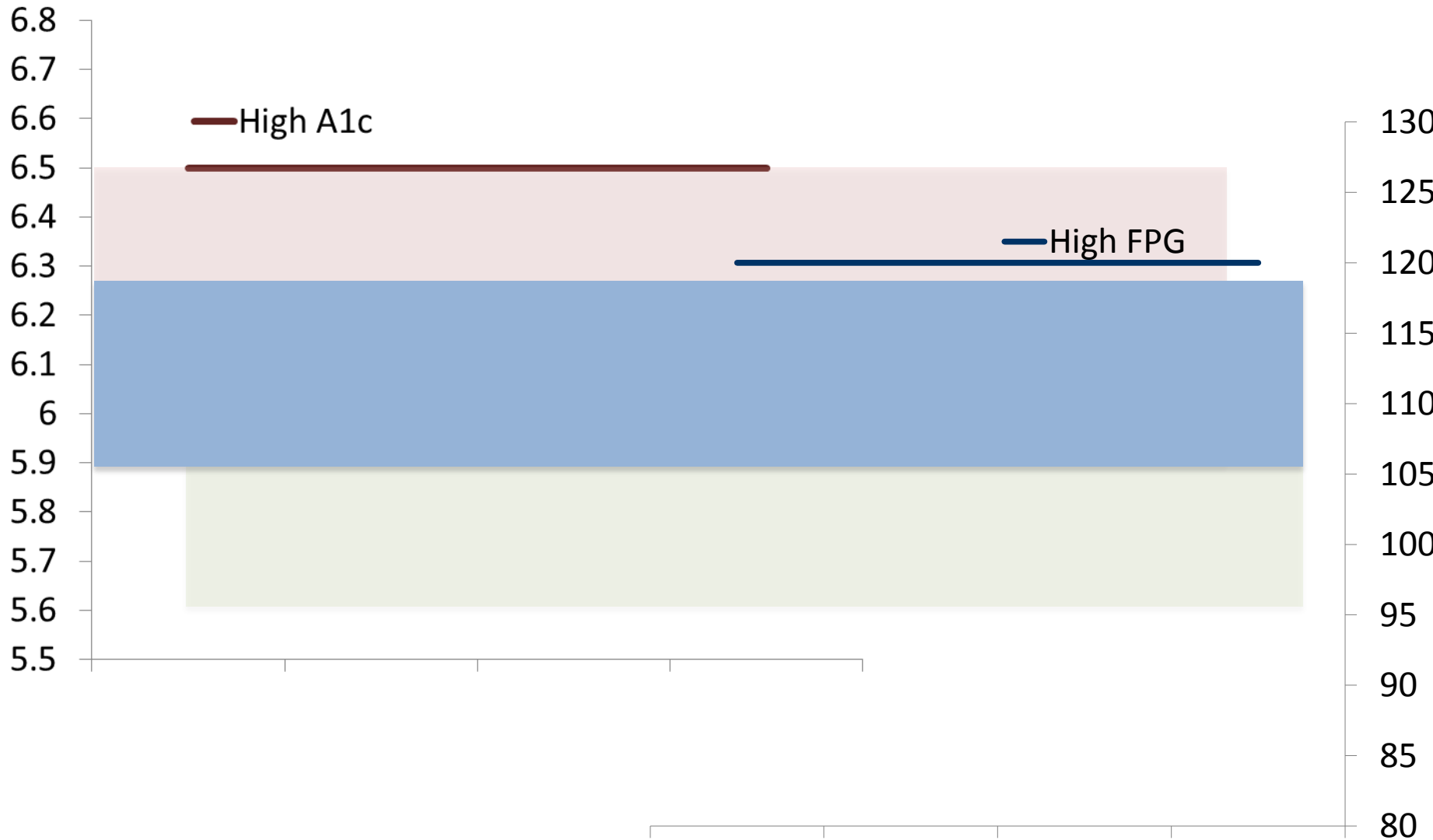
SCR-BAS Glycemia Challenge



SCR-BAS Glycemia Challenge

“Threading the Needle”

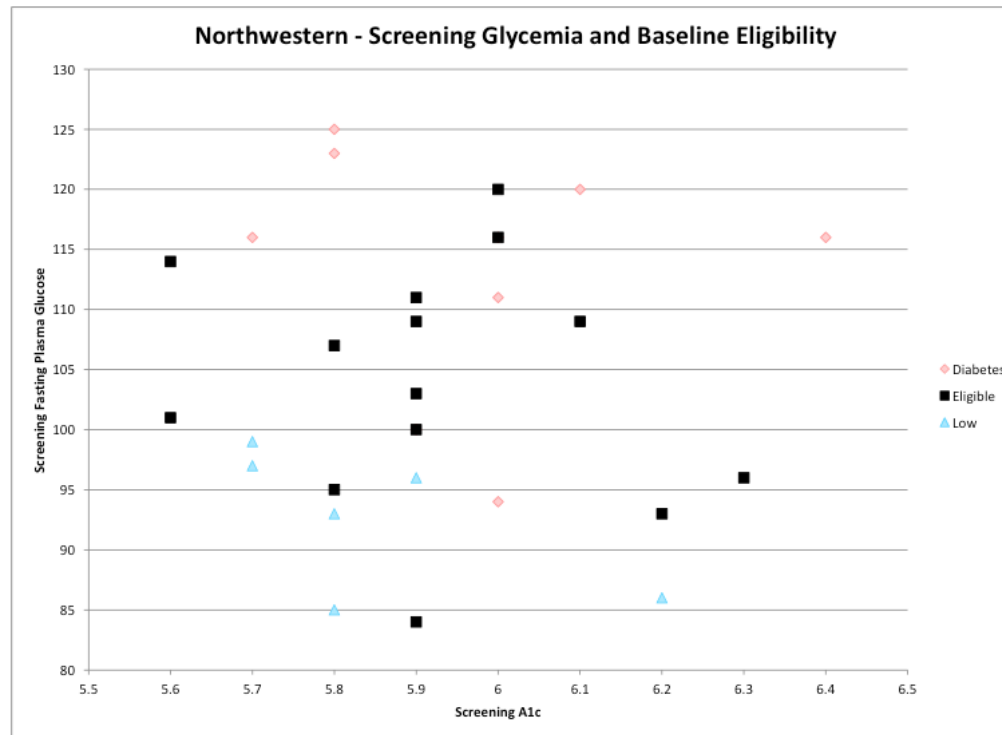
4



SCR-BAS Glycemia Challenge

site-specific data analysis, example 1

Glycemic results are continuously evaluated and site-specific algorithms are being developed and constantly updated.



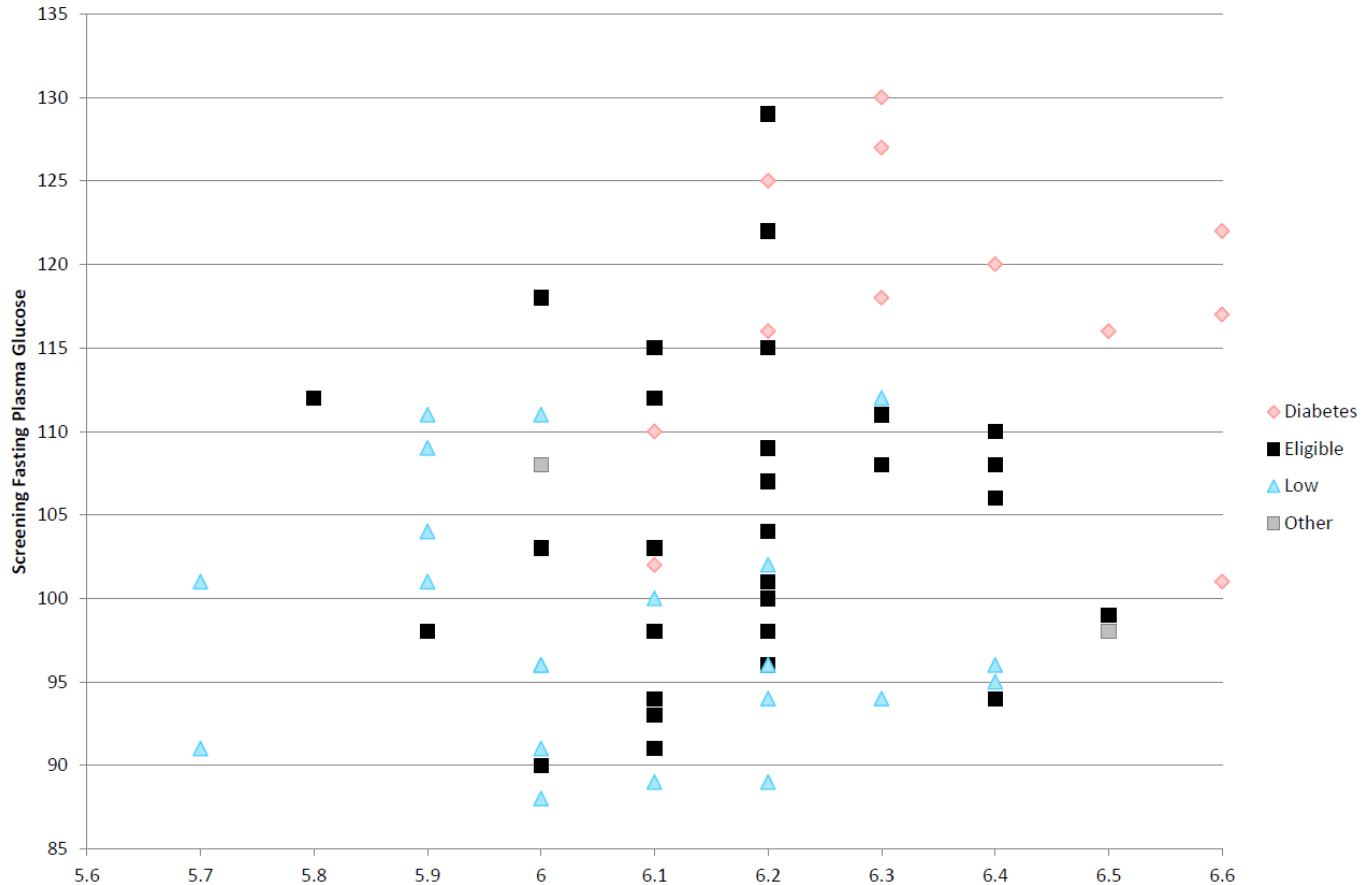
We reviewed your data and think you should consider modifying your site specific algorithm for participants to proceed to baseline if their values fall within the following range:

FPG= 85-120 mg/dL and HbA1c 5.6-6.4%

SCR-BAS Glycemia Challenge

site-specific data analysis, example 2

Nebraska VA - Screening Glycemia and Baseline Eligibility



We reviewed your data and think you should consider modifying your site specific algorithm for participants to proceed to baseline if their values fall within the following range:

FPG= 85-120 mg/dL and HbA1c 5.9-6.5%

Glycosylated Hemoglobin, HbA1c

Advantages over FPG / 2hPG

Advantages

- Captures chronic glycemia
 - fasting and post-prandial
- Correlates with complications
- Can be done anytime
 - No patient preparation
 - Not affected by acute situations (exception RBC)
- Good reliability
 - Standardized/aligned to DCCT/UKPDS
 - Stable at room temp
 - Less biological variability
- Good specificity 98% vs. Gold standard: OGTT

Disadvantages

- Affected by
 - Shortened RBC survival or decreased mean RBC age ↓
 - Hemoglobin traits [assay-specific]
 - » HbS, HbC (AA) ↓↑
 - » HbE (SE Asians) ↓↑
 - Transfusions (e.g., CABG),
 - Anemia (e.g. Iron Deficiency ↑↑)
 - Pregnancy ↓ (or↑)
 - HIV ↓
 - Vitamin C, E (inhibit glycation) ↓
 - High TG, bilirubin, uremia ↑
 - Renal failure ↓
 - EtOH, salicylates, opiate ↓↑
 - Aging ↑
 - Race (non-whites/blacks↑ vs whites↓)
- Moderate sensitivity 66% vs. Gold standard: OGTT

Sources of test result variation

- **Pre-analytical**
 - Factors arising before sample arrives in the lab
- **Analytical**
 - Precision of testing method
 - Changes or differences in bias
- **Within-subject biological variation**

Minimizing pre-analytical variation

- Instruct participant to prepare same way
 - Consistency with respect to fasting status and recent exercise
- Collect and handle samples the same way
 - Well defined procedures
 - Training of staff
- Ideal – Split a single sample, or at least test samples from same blood draw

Within-subject biological variation

- Fasting plasma glucose
 - $CV_w = 5.6\%$
- HbA1c
 - $CV_w = 1.9\%$

Minimizing analytical sources of variation

- Random variation
 - Use highly precise methods
- Systematic variation (bias)
 - Use well calibrated method
 - Minimize reagent lot changes, operator changes
 - Compare results with values obtained by other labs / methods for standardized samples (external QA, or proficiency testing)
 - Participate in standardization programs (e.g., NGSP)

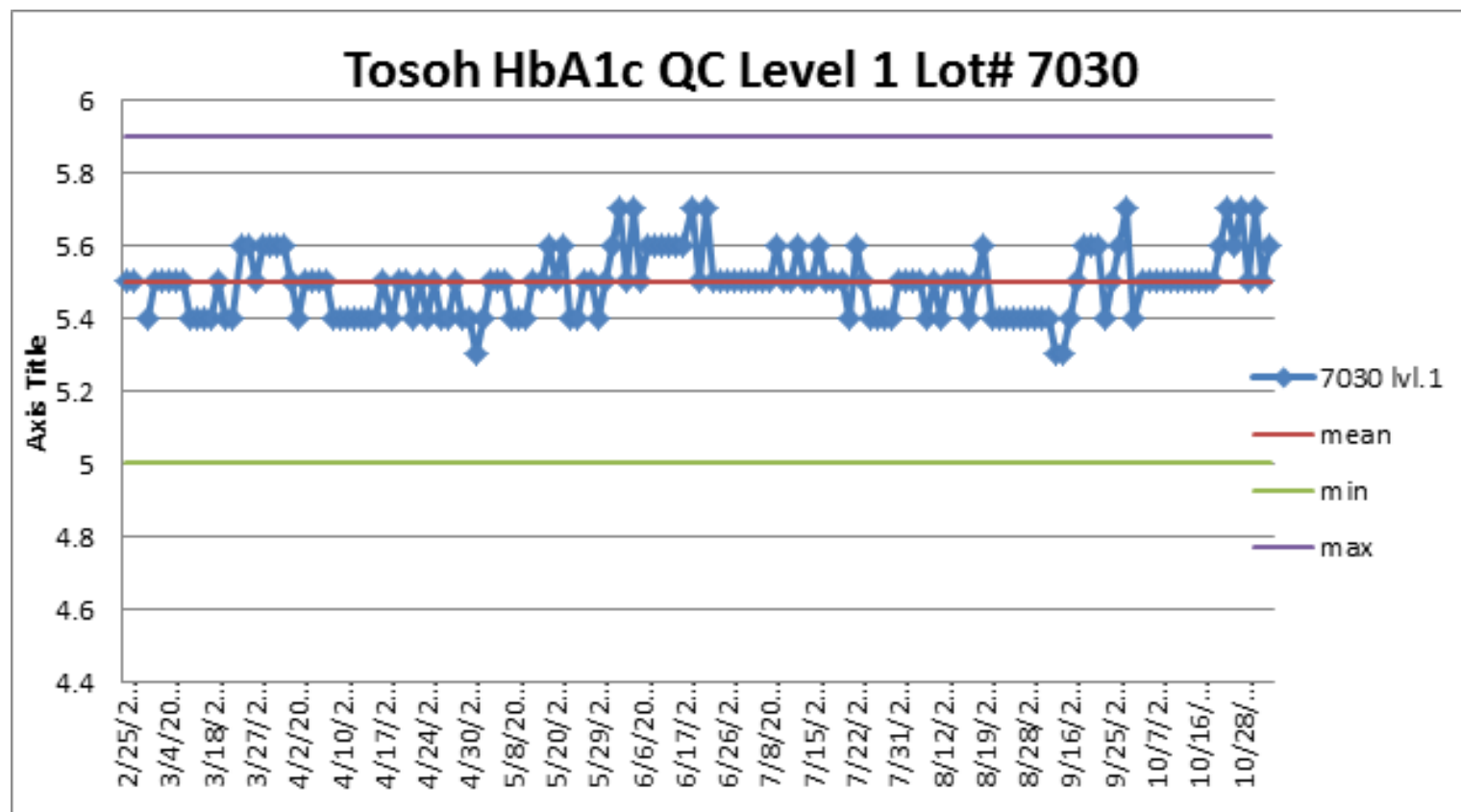
Precision of method used at Central Lab



Month: Jul 2014
Location: Colchester, VT
Site ID: Lab Clin Biochem, Univ VT
Assay Method: G8
Report Date: 08/19/2014

Specimen #	Analysis Date 1	Analysis Date 2	Result 1	Result 2	Mean Yi	Difference Y1-Y2	Di ²
2211	7/10/14	7/11/14	6.20	6.20	6.20	0.00	0.0000
2212	7/10/14	7/11/14	9.40	9.30	9.35	0.10	0.0100
2213	7/10/14	7/11/14	7.60	7.60	7.60	0.00	0.0000
2214	7/10/14	7/11/14	5.50	5.40	5.45	0.10	0.0100
2215	7/10/14	7/11/14	8.30	8.20	8.25	0.10	0.0100
2216	7/10/14	7/11/14	8.30	8.30	8.30	0.00	0.0000
2217	7/10/14	7/11/14	5.40	5.40	5.40	0.00	0.0000
2218	7/10/14	7/11/14	9.70	9.70	9.70	0.00	0.0000
2219	7/10/14	7/11/14	7.40	7.40	7.40	0.00	0.0000
2220	7/10/14	7/11/14	6.40	6.40	6.40	0.00	0.0000
Mean Di						0.03	

Sample Central Lab QC data



Major recruitment challenge: High SCR-RAN ratio, partially due to sub-optimal correlation on A1c/FPG, Central Lab vs. Local Lab

Site	FPG diff		HbA1c diff	
	mean	SD	mean	SD
Atlanta	-0.45	6.80	-0.10	0.14
Baylor	7.04	7.96	-0.18	0.20
Duke	7.07	9.27	-0.14	0.16
Florida	5.70	8.60	-0.11	0.12
HealthPartners	6.93	7.06	-0.08	0.12
Kansas	-1.78	8.22	-0.08	0.17
Los Angeles	8.15	8.29	-0.22	0.17
Maine	0.98	7.25	-0.14	0.16
MedStar	1.22	8.75	-0.15	0.22
Nebraska	4.17	8.53	-0.23	0.28
New York	1.18	8.74	0.15	0.27
Northwestern	8.82	10.75	0.09	0.28
Pennington	2.93	7.84	0.07	0.11
South Carolina	3.69	13.99	0.06	0.18
Stanford	-1.40	8.31	-0.03	0.17
Tennessee	10.68	7.24	-0.14	0.17
Tufts	4.22	9.63	-0.17	0.12
UT Southwestern	4.68	18.93	-0.17	0.17
Mean	4.10		-0.09	

Context for variation data: External QA (proficiency testing) data
 comparing various instruments vs. “all method mean”
 (grand mean FPG = 88.69)

Instrument	FPG diff (mean-inst)
Beckman UniCel DxC glucose oxidase	-1.12
Vitros 250,350	-3.77
Vitros 5.1	-4.29
Siemens Dimension	2.36
Abbott Architect	0.46
Beckman AU	0.41
Beckman UniCel DxC hexokinase	0.11
Roche cobas c500	1.09
Roche cobas Integra	1.48
Roche modular	1.35
Siemens Advia	-0.55
Siemens Dimension UV	2.40
Siemens Dimension Vista	0.65

Context for variation data: External QA (proficiency testing) data
 comparing various instruments vs. reference method
 (reference method HbA1c = 6.49%)

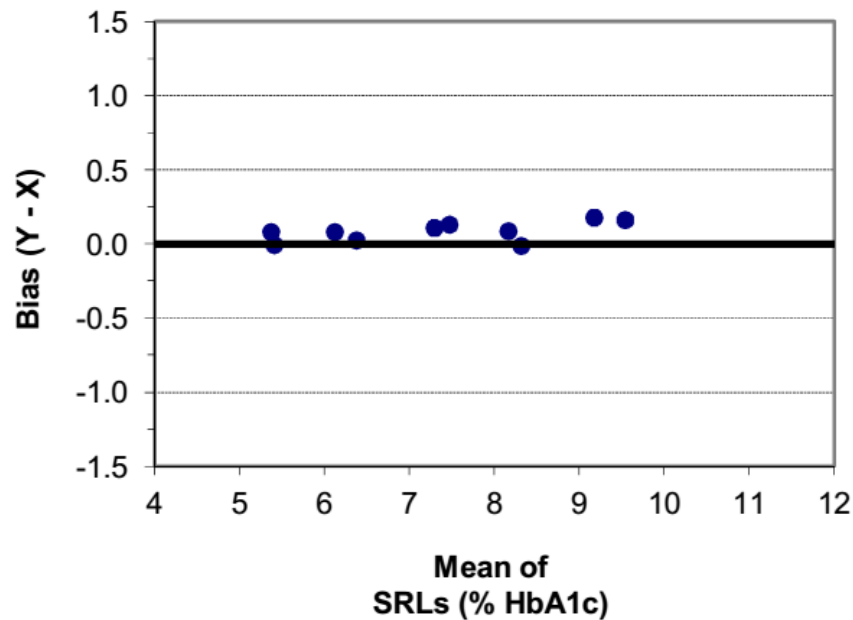
Instrument	HbA1c diff (ref-inst)
Beckman Unicel DxC	-0.01
Bio-Rad D-10	-0.09
Bio-Rad Variant II Turbo	-0.08
Bio-Rad Variant II Turbo 2.0	0.04
Roche cobas c500	-0.03
Roche cobas Integra 800	-0.08
Siemens DCA Vantage	0.03
Siemens Dimension ExL	-0.36
Siemens Dimension Vista	-0.35
Tosoh G7	-0.32
Tosoh G8	-0.28
Vitros 5,1	0.12
Mean	-0.12

Standardization data: NGSP HbA1c data
comparing Central Lab vs. reference method

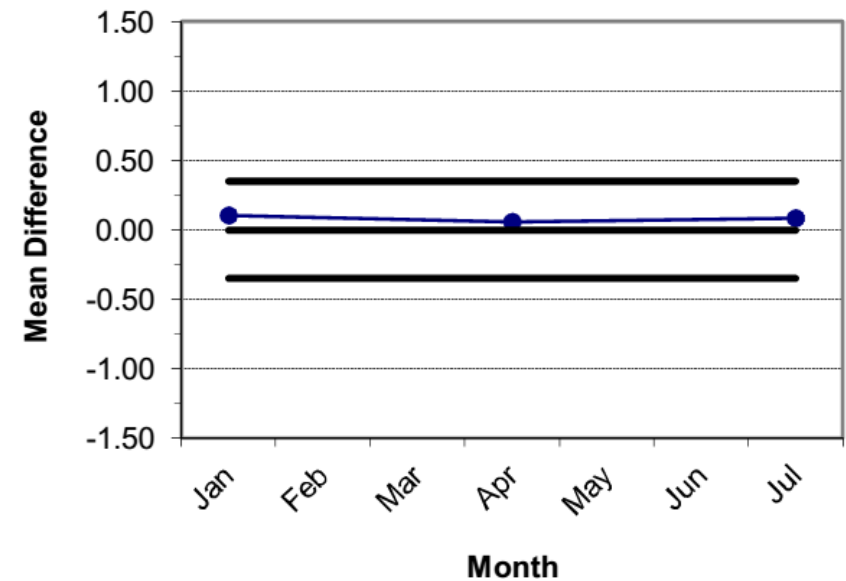
		Lab Clin Biochem, Univ VT				Comments
Specimen #	Mean of SRLs	Y1	Y2	Mean Y	Mean Y - Mean X	
2211	6.12	6.20	6.20	6.20	0.08	
2212	9.17	9.40	9.30	9.35	0.18	
2213	7.47	7.60	7.60	7.60	0.13	
2214	5.37	5.50	5.40	5.45	0.08	
2215	8.16	8.30	8.20	8.25	0.09	
2216	8.31	8.30	8.30	8.30	-0.01	
2217	5.40	5.40	5.40	5.40	0.00	
2218	9.54	9.70	9.70	9.70	0.16	
2219	7.29	7.40	7.40	7.40	0.11	
2220	6.37	6.40	6.40	6.40	0.03	
Mean	7.32	7.41			0.09	

Standardization data: NGSP HbA1c data comparing Central Lab vs. reference method

Bias Plot

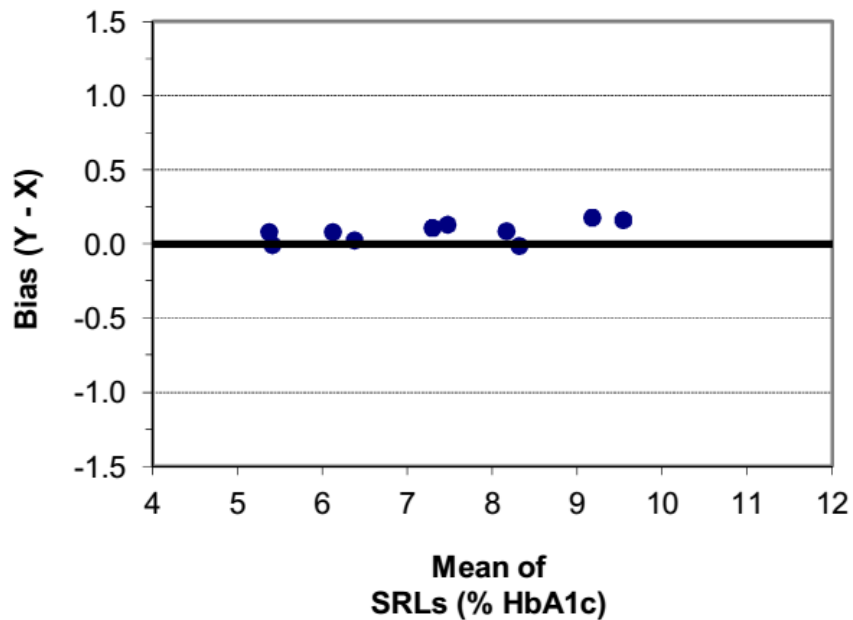


Bias Monitoring Chart

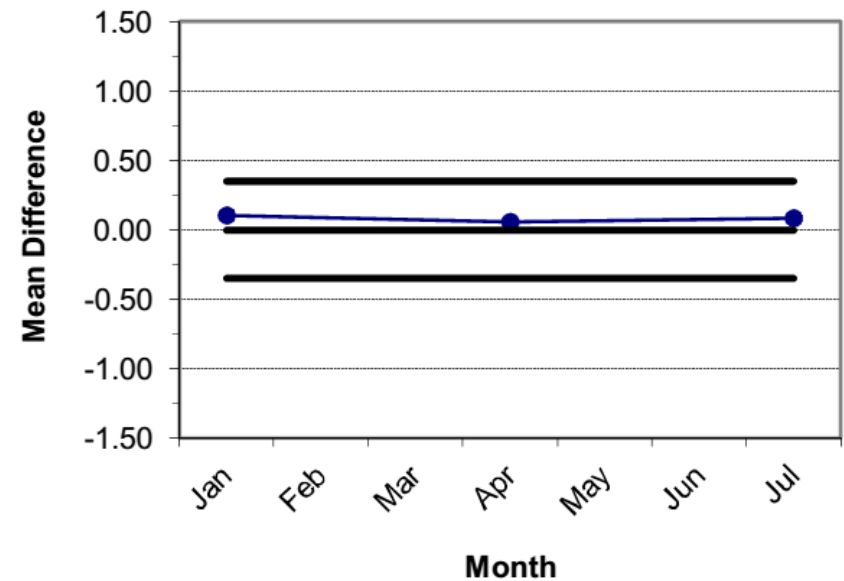


Standardization data: NGSP HbA1c data comparing Central Lab vs. reference method

Bias Plot



Bias Monitoring Chart



Standardization data: NGSP HbA1c data comparing Central Lab vs. reference method

- Annual NGSP Level I recertification challenge
- 40 samples tested at reference lab
 - Must have 38/40 within 6% of reference lab results
 - Our performance: 40/40 within 4%
- Fewer than 20 NGSP Level I certified labs in USA at present; only a few dozen worldwide

Summary

- Study organizers and central lab have taken multiple steps to assure consistency of results from central lab and to reduce the impact of variation on recruitment.
- The central lab is willing to work with any site's staff and/or affiliated lab to help enhance consistency.
 - Data sharing
 - Consultation