



Meeting of the NGSP Clinical Advisory Committee Minutes

2013 ADA 72nd Scientific Sessions
 Chicago, IL
 Sunday June 22, 8:00AM – 10:00AM

Alethea Tennill	NGSP	Mayer Davidson	Charles Drew Univ.
Ann Albright	CDC	Myron Gross	Univ of Minnesota
Bill Herman	Univ. of Michigan	Ragnar Hanas	ISPAD
David Leslie	Blizard Institute UK	Ruth Lipman	AADE
David Nathan	MGH, Harvard	Steve Hanson	NGSP
David Sacks	NGSP	Sue Manley	Univ of Birmingham
Elizabeth Selvin	John Hopkins	Takuji Kohzuma	Asahi-Kasei Pharma
Hideji Hiraoka	Asahi-Kasei Pharma	Todd Leger	Bio-Rad
Ian de Boer	Univ. of Wash	Zachary Bloomgarden	AACE, Mt Sinai
Jane Chiang	ADA		
Judy Fradkin	NIDDK	By Phone	
Len Pogach	VA	Mark Gusack	VA
Lisa McGuire	Bio-Rad	Beena Akolkar	NIDDK
Matt Petersen	ADA		

Welcome and introduction: A. Albright opened the meeting at 8:04 AM and welcomed everyone. Participants introduced themselves. The 2012 NGSP Clinical Advisory Committee meeting minutes were approved.

HbA1c/NGSP Update: R. Little gave an NGSP update.

- NGSP Certification
 1. The number of methods and laboratories certified continues to increase
 2. Most laboratory certifications are outside the United States and most are Level I
 3. There is a cluster of Level II labs in South America and South Africa.
- 2011 Guidelines and recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus
 1. Within Lab CV < 2%. Many methods have within lab CVs <2%.
 2. Between-lab CVs <3.5%. Latest CAP survey shows CVs 3.3-3.9% between labs including all methods. The medium and high levels show all-method CV of 3.5% or below. Only the low sample shows >3.5% all-method CV.
- Is HbA1c Measurement Adequate for Optimal Clinical Use? Are CAP limits tight enough?
 1. Current CAP limit is $\pm 6\%$ which corresponds to $\pm 0.4\%$ HbA1c at 7% HbA1c
 2. In the normal range/treatment range if a lab passes current CAP limits, the method/lab is highly likely to give results within 0.5% HbA1c of the target.
 3. Based on 2013A CAP survey 93-95% of labs passed at the current limit.
- Future Plans for Improving HbA1c Measurement
 1. NGSP Certification Criteria

- Certification changed in September 2012. It changed from fixed limits to % limits, which is similar to CAP criteria.
- Manufacturer and Level II certification changed to single sample measurements; 37/40 results must fall within 7% (relative percent).
- Level I certification 38/40 results must fall within 7% (relative percent)
- 2. Tighten CAP Survey Grading
 - 2013 Acceptable limit is $\pm 6\%$
- 3. Reduce measurement interferences
 - Increase awareness of HbA1c interferences
 - Test Hb variant interference for each method
 - Encourage the use of methods that do not have interferences from Hb variants
 - Tightened acceptable limits for defining clinically significant interference in publications to $\pm 7\%$ (previously $\pm 10\%$) at 6 and 9% HbA1c.
 - Table showing Hb Variant Interferences can be found on NGSP website.
- Summary:
 1. Most laboratories can now provide HbA1c results within $\pm 0.5\%$ HbA1c of “True” value in the diagnostic and target range, but overall method CVs are not yet consistently $\leq 3.5\%$.
 2. NGSP tightened manufacturer certification criteria to be more closely aligned with CAP. CAP limits changed to $\pm 6\%$ (relative) in 2013.
 3. We are now recommending limits of $\pm 7\%$ for clinically significant interference from Hb variants.
 4. Additional tightening of certification criteria will be considered.

Discussion: D. Nathan asked what are the consequences if my lab fails CAP? D. Sacks said that laboratories must comment on why they failed and what they did to fix the problem. If they fail the next survey they are prevented from measuring the analyte until they resolve the problem. Most laboratories call the manufacturer of the lab instrument for troubleshooting to find the cause and get it fixed. R. Little commented that methods with more variability tend to disappear from the CAP survey, because the number of labs using that method decreases.

Measuring Reliability of Hemoglobin A1c and Communicating Results to Clinicians at VA hospitals: M. Gusack

The VA is proposing an integrated approach to achieving excellence in health care through the application of the Clinical Laboratory Standards Institute’s concept of “Acceptable Risk” as defined in EP23: **Laboratory Quality Control Based on Risk Management.**

- Acceptable Risk for analytical error in the laboratory can be defined as that level of reliability that leads to a frequency and severity of adverse outcomes that can be tolerated by providers, their patients, and society in general.
- In the case of A1c this risk can be defined as a balance between the short term effects of hypoglycemia against the long term effects of hyperglycemia as affected by test reliability at one or more Medical Decision Points.
- Reliability of a single A1c result can be estimated by calculating accuracy and precision using Quality Control data and crafting a report for use by the provider when making a Medical Decision.

- The clinical significance between two sequential A1c test results can be determined, in part, through the generation and publication of tables that show the provider the probability that they are statistically significantly different.

Discussion: D. Nathan asked if they were doing this with all analytes? L. Pogach said that this is still in the pilot stage; they are starting with only A1c. This can be considered an educational issue that will address prevention of iatrogenic hypoglycemic events. He noted that this is an important national policy issue: The Department of Health and Human Services is preparing a national action plan for adverse drug events for several medications, including hypoglycemic agents. He also stated that the A1c accuracy was the subject of a prior Diabetes Mellitus Interagency Coordinating Committee Meeting (March 2011) and this topic is included in the NIDDK Clearinghouse on A1c that resulted from the meeting. However, it has not been actively communicated to clinicians and patients

Use of glycated albumin for patients with renal failure: *M. Davidson described a study to answer the question: Is there a stage of renal function (prior to dialysis) at which GA more accurately reflects glycemia than HbA1c levels?*

- Cross-sectional study
- HbA1c/GA ratios were measured across stages 1-5 of renal function in diabetes patients
- Adjustments for serum albumin, urinary albumin/creatinine ratio, hemoglobin
- GA was measured at Quest Labs using a boronate affinity method
- Total cohort 626 patients, mean age 54, 60% female, 78% Latino
- GA did not seem to reflect glycemia any better than HbA1c levels in pre-dialysis diabetic patients
- There was no significant difference in the HbA1c/GA ratios in the different eGFR stages

Discussion: S. Manley mentioned using fructosamine if a patient develops proteinuria and excretes a lot of protein. R. Little said the only reason glycated albumin would not work is if the kidneys excreted glycated albumin differently than albumin. M. Davidson commented that there are only a small number of patients in stages 4 and 5 of kidney failure.

Pilot Study of Glucose Variability in Advance Diabetic Kidney Disease (DKD): Ian de Boer described a planned study that will characterize glucose variability, hypoglycemia and hyperglycemia in patients with advanced DKD. The study will compare

- Patients with type 1 or type 2 diabetes, N=30. 10 patients with stage 4 or 5 CKD, 10 with ESRD on hemodialysis, 10 with ESRD on peritoneal dialysis
- HbA1c, fructosamine, glycated albumin, and glucose will be measured
- Glucose variability at days 0-6 and days 28-34 will be estimated
- Incidence of hypoglycemia
- Test correlation of different glycemia measures
- Test biomarkers of oxidative stress and systemic inflammation

Discussion: S. Manley asked if they were going to measure CBC, hemoglobin, albumin and alcohol intake. I. deBoer said yes to CBC, hemoglobin and albumin. J. Fradkin asked what the impact of anemia would have on the study. Z. Bloomgarden said that glycemic variability is greater in type 1 patients than in type 2. He suggested using one or the other, but not both type of diabetics. D. Nathan asked if he had seen the paper from Australia that was in press or just published that had done the

same type of study. I. de Boer said that he would be interested in looking at it before starting this study.

Effect of Changing HbA1c numbers in the UK: D. Sacks for Eric Kilpatrick

- United Kingdom reported only NGSP % before June 2009
- June 2009 – October 2011 UK reported both NGSP and SI units
- After October 1, 2011 UK reported SI units only.
- To determine if the HbA1c results were affected due to the change in units, they compared 20,000+ A1c values from 13,000 patients in the year immediately preceding and after the change to SI units only. The mean A1c stayed the same at 7.5% (58 mmol/mol) both before and after the switch to SI units.
- The lack of difference in change could be due to one of the following reasons: Staff adapted better than anticipated, good educational material for the switch was used during dual reporting period, the change from 7.5% to 58 mmol/mol helps to differentiate the two scales, or doctors just convert back to NGSP numbers.

Transfer to IFCC units in Sweden; Can we see any change in patient results? R. Hanas at his clinic in Sweden looked at how the change in A1c units affected the metabolic control of pediatric patients in Sweden.

- Sweden started with MonoS (HbA1c mean 8.3%)
- In 1992 switched to DCA2000 calibration with DCCT calibration (HbA1c mean 8.3% year 1 – 7.9% by year 3)
- After 1997 switched to DCA2000 with Swedish calibration (A1c 8.2% year 1 - 9.0% year 3).

IFCC/ADA/IDF/ISPAD consensus statement 2009 says: HbA1c results should be standardized worldwide and anchored to the IFCC reference system. Conversion tables for both NGSP/DCCT and IFCC/SI units should be easily accessible to the diabetes community and all scientific journals should require that manuscripts report HbA1c in both units.

- Sweden switched to IFCC numbers only in January 2011, patients still asked for Mono-S numbers
- They see a slight increase in HbA1c in adult type 1 patients since the switch
- They see a slight decrease in HbA1c in pediatric patients since the switch
- Web converter for HbA1c can be found at www.hba1c.nu/eng
- There is controversy regarding the use of HbA1c to diagnose type 1 diabetes.

Discussion: D. Nathan suggested that any effect on patient HbA1c levels might be due to the difference in scale. S. Manley commented that a lot of general practitioners do not understand IFCC numbers. Once you use IFCC numbers doctors have to change therapy based on a totally different scale. Some are converting back to NGSP numbers. D. Leslie said that some patients in UK request the DCCT/NGSP numbers. There are huge issues regarding reimbursement. The target values for the patients are the same for a patient that is 80 year old and one that is 13 years old. Patient care is being led by reimbursement not clinical considerations. R. Little said that the United States will not change unless we can see benefit for patient outcomes. R. Hanas said that we need to make sure that scientific journals require dual reporting and that the conversion table is easily accessible to everyone. D. Sacks

asked how much it costs to change the numbers. M. Petersen asked if anyone was reporting eAG numbers. There were no clear answers.

GENERAL DISCUSSION: L. Pogash was asked about giving the providers multiple numbers – result measured on the machine as well as the risk around the result depending on the CV of the lab instrument. L. Pogash commented that their report lets providers know that movement around the result may not be caused by change in the patient, but caused by variability of the method. J. Fradkin said that the slide shown by M. Gusack focused on risk, but the biggest risk is with assays that have substantial interference from hemoglobin variants. R. Little commented that many of the assays have safeguards and you can see the hemoglobin variant. D. Sacks said that manufacturers have tried to modify assays that have interferences from hemoglobin variants to eliminate the interferences. J. Fradkin suggested that we try to change the assays that labs are using that have hemoglobin interferences. Make sure that all labs are aware of the list of methods that are affected by hemoglobin variants that is on the NGSP website when they are choosing a new A1c method. L. Pogash is more concerned with Point of Care Testing since it is not regulated. D. Sacks said that WHO is going to approve POC devices for diagnosis of diabetes. He wondered about partnering with Consumer Reports to get the information out about choosing the correct method. A. Albright said that raising awareness of the issues needs to include a wide spectrum of ways to get the information out to consumers.

Ann Albright thanked everyone for their attendance, and asked for any topic discussion for next year's meeting to contact R. Little. The meeting was adjourned at 9:55 AM

Minutes prepared 7/10/2013 by A. Tennill, modified by R. Little and C. Rohlfing