NGSP Clinical Advisory Committee

ADA 71st Scientific Sessions 2011
San Diego, CA
Sunday June 26, 8:00AM – 10:00AM

Alethea Tennill	NGSP	Joan Bardsley	AADE, MEDSTAR
Ann Albright	CDC	John Sperzel	Axis-Shield
Bill Herman	Univ of Michigan	Judy Fradkin	NIDDK
David Aron	Dept of Vet. Affairs	Laura Madia	Bio-Rad
David Nathan	MGH, Harvard	Lorna Lampert	MGH, Harvard
David Sacks	NGSP	Matt Peterson	ADA
David Simmons	Bayer Diabetes Care	Mayer Davidson	Charles Drew Univ.
Dr. V. Mohan	MDRF, India	Mike Steffes	Univ. of MN
Elizabeth Selvin	John Hopkins	Phillip Home	UK Newcastle
Ian de Boer	Univ. of Wash	Ragnar Hanas	ISPAD
Jeff Durban	Becton Dickinson	Randie Little	NGSP
		Zachery Bloomgarden	AACE, Mt Sinai

Welcome and introduction: A. Albright opened the meeting at 8:00 am and welcomed everyone. Participants introduced themselves. The 2010 NGSP Clinical Advisory Committee meeting minutes were approved.

HbA1c variability and Hb Variant Interference: R. Little gave an NGSP update.

- NGSP Certification (July '10 – June '11)
    1. 106 methods (most sold globally)
    2. 109 laboratories; 93 were Level I, 16 were Level II
    3. 20 certified labs were from the US; 89 were from outside the US
- There has been considerable improvement in the quality of HbA1c testing over time.
    1. The CAP shows marked reduction in the variability of HbA1c since 1993.
    2. Between-lab CVs have shown decreasing trends since 2000. There are 3000 labs using the CAP survey and are now showing ~3.5% CV at all HbA1c levels
- 2011 guidelines from AACC, NACB and ADA recommend
    1. Within Lab CV < 2%.
    2. Between-lab CVs <3.5%
- Is HbA1c Measurement Adequate for Optimal Clinical Use?
    1. Difference between DCCT Intensive and Standard groups was ≈2% HbA1c with a large decrease in risk for complications.
    2. Difference between UKPDS groups was ≈1% with a decrease in risk for complications.
    3. The recommendation for diabetes diagnosis is ≥6.5% HbA1c
    4. Typically 0.5% HbA1c is considered a clinically significant change in the patient
    5. CAP Limits
        - Current limit is ±7% CV
        - This is a limit of ±0.5% at 7% HbA1c

        - If lab consistently passes CAP limit then it is highly likely that the lab will give results within ±0.5% HbA1c in the normal or treatment target range
        - Based on 2011A CAP survey ≈93-95% of labs passed at the current limit
- Is ± 0.5% HbA1c tight enough? This means a "true" HbA1c of 6% could be reported as 5.5% HbA1c or 6.5% HbA1c
- Ways to Improve HbA1c Measurement
    1. Tighten NGSP Manufacturer Certification Criteria
        - Current criteria: Assessment of Agreement --95% CI of differences must be within ±0.75% HbA1c (HbA1c range 4-10%)
        - More changes are anticipated in 2012
    2. Tighten CAP Survey Grading
        - Current acceptable limit reduced to ±7%
        - Expect more changes in 2013
    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
        - Tighten the clinical significance level for interference used in publications (currently this is ±10% at 6 and 9% HbA1c)
    4. Define clinical situations where HbA1c testing may not be ideal for monitoring patients, e.g. renal failure and iron deficiency anemia

CAP criteria for proficiency testing: D. Sacks

- In 2007 CAP changed from peer group grading to accuracy based grading using DCCT target
- ±15% was the acceptable limit; the pass rate was 99%
- CAP has progressively lowered the acceptable limit, it is currently ±7%.
- CAP 2010 GH2A pass rates at ±6% and ±8% cutoffs

		At ±8%	At ±6%
GH2-01	**5.10%**	**95.5**	**91**
GH2-03	**6.00%**	**95.4**	**91.6**
GH2-02	**8.40%**	**95.2**	**88.6**

- Future plan for grading targets
    1. 2011-2012 ±7%
    2. 2013 has yet to be determined

Status of HbA1c reporting outside US: D. Sacks

- Czech Republic and Croatia are reporting IFCC numbers in %
- Most European countries report IFCC numbers in both mmol/mol and %
- UK is moving to using mmol/mol this year
- Germany is reporting IFCC mmol/mol
- Sweden is reporting IFCC mmol/mol,

D. Nathan commented that EASD journals must report both units. P. Home commented that UK did switch to IFCC numbers but the patients and doctors were still using NGSP numbers so the change has been delayed. D. Sacks said that DCCT/NGSP numbers will be reported in US. Some of the other countries have started dual reporting. R. Hanas stated that Sweden has a

website www.hba1c.se that discusses the differences and converts units from one group to another, i.e. Mono S to IFCC. The idea was to report both units. Z. Bloomgarden commented that it would be interesting if CAP reported results in both NGSP and IFCC units. R. Little commented that the US is concerned about the confusion if more than one number is used. The US would switch if there was a benefit to the patients, but what is the benefit? D. Nathan asked why change units if there is no benefit to the patients. D. Simmons commented that we are asking people to do something different without showing a benefit to the patient. V. Mohan said that in the developing world they have been working on getting the doctors to understand the test and the numbers currently used. 60% of all diabetics live in Asia. Suddenly changing to IFCC numbers will just add more confusion the mix.

Use of HbA1c for diagnosis D. Sacks

- In January, 2011 WHO stated that HbA1c can be used for diagnosis.
- In March 2009, 2360 HbA1c tests were analyzed in his lab. 32% of results were <6%, 52% < 6.5%
- In May 2010, 3018 HbA1c tests were analyzed in his lab. 44% were <6%, 61% were <6.5%
- The total number of assays increased by 28% between March 2009 and May 2010; the number of HbA1c results <6.5% increased 18%

Discussion: D. Aron commented that if you are paid for performance than increasing the number of tests below 6.5% improves your results. D. Nathan commented that there is an increase in patients with psychological problems being tested using HbA1c (due to effects of treatment medications).

Laboratories reporting eAG: D. Sacks

- From 2009 to 2011, CAP has included supplemental questions about eAG on the GH2 HbA1c survey
- In Response to the question of whether or not labs were reporting eAG, the following responses were received:

Response (%)	2009	2010	2011
	n=2997	n=2547	n=3190
Yes	16.7	29.7	32.9
No	83.3	70.3	67.1

- However many labs are using the incorrect conversion equation

Response (%)	2009	2010	2011	Comment
28.7 x HbA1c – 46.7	***28.8***	***49.9***	***51.2***	***Correct equation***
35.6 x HbA1c – 77.3	**22.5**	**7.8**	**6.8**	
Do not know	**n/a**	**17.4**	**19.3**	
Other	**48.7**	**24.9**	**22.7**	

Discussion: D. Sacks is wondering how to get labs to use the correct equation. D. Nathan said physicians need to be educated to understand that eAG is a best guess for average glucose. D. Simmons commented that HbA1c is an analyte the physicians use to manage diabetics and populations

"at risk". D. Aron said the HbA1c is special because it is only used every 3-6 months, and major treatment decisions are based on HbA1c.

Measuring Glycemic Control in Patients with Renal Failure: I. deBoer

- There are several causes of End Stage Renal Disease (ESRD): Diabetes, hypertension, glomerulonephritis and cystic kidney, with diabetes being the leading cause
- The population characteristics are: aging, comorbidity, sedentary, high mortality rate
- The goals of dialysis are to facilitate quality of life, keep access open, keep volume under control
- Then the test results are considered: HbA1c, Hgb, iron, Ca etc
- Factors affecting glucose metabolism in ESRD include:
    1. Increased insulin resistance, uremia, decreased insulin secretion and dialysate glucose raise glucose
    2. Decreased renal and hepatic insulin catabolism, decreased renal gluconeogenesis, anorexia and dietary restrictions lower glucose metabolism
- ESRD affects the glucose – HbA1c relationship:
    1. Increased RBC turnover due to blood loss and erythropoietin use
    2. Altered glycation or carbamylation rate
    3. There is a lack of careful studies testing these issues
- Alternative measurements:
    1. Fructosamine – independent of RBC turnover, reflect changes in 2-3 weeks, correlates less well with mean glucose
    2. Glycated Albumin- independent of RBC turnover, reflect changes in 2-3 weeks, lower with obesity, correlates with vascular calcification and stiffness
- Peacock, TP etal, Kidney Int 2008 showed that glycated albumin correlated well with glucose independent of ESRD, hemoglobin and EPO while HbA1c was lower with dialysis and EPO
- Summary/Conclusions: ESRD fundamentally changes goals of diabetes care, glucose and insulin metabolism, ascertainment of glycemia and associations of HbA1c outcomes. The role of HbA1c is unclear.

VHA-DoD guidelines for use of HbA1c in Clinical Practice: D. Aron

- 2010 VHA-DoD guidelines update reemphasizes clinical awareness of HbA1c test, accuracy and precision and addresses emerging evidence of racial differences.
- The VA/DoD diverges from ADA in the diagnosis of diabetes and target goal setting
- Diabetes is determined by an A1c>7% on 2 occasions using a clinical lab method or a A1c$\geq$6.5% with a confirmed FPG $\geq$126 mg/dl or FPG $\geq$126mg/dl on at least two occasions
- Pre-diabetes is determined by FPG <126 mg/dl and $\geq$ 100 mg/dl on two occasions or A1c $\geq$5.7% and <6.5% with FPG $\geq$100 mg/dl and <126 mg/dl
- The target range for glycemic control should be individualized, based on the provider's appraisal of the risk-benefit ratio and discussion of the target with the individual patient
- Providers should recognize the limitations of the HbA1c test as they make therapeutic changes
- Without consideration of precision and accuracy of the test result used to guide therapeutic changes, there is concern over inappropriate intensification of treatment (e.g. reported value higher than actual) to "achieve a target", especially for patients receiving insulin
    1. The VHA-DoD Tool Kit is under development. It discusses interpretation of A1c precision and accuracy of the tests and sources of error in reporting
    2. The range of uncertainty for a HbA1c result depends upon the overall assay error.

3. Depending on the performance among methods and labs establishing each reporting range may not be practical.
4. So there is a consensus recommendation to report A1c with a 95% confidence interval for precision and accuracy. This is being tested in a small number of labs.

Discussion: R. Little asked how bias and CV were calculated. Are different lot numbers taken into account? D. Aron will check on this. D. Nathan commented that if you give them a range to aim for they will be happy with the higher number.

A. Albright thanked everyone for their attendance. The meeting was adjourned at 10:00 AM.

Minutes prepared 7/11/11 by A. Tennill, modified by C. Rohlfing and R. Little.