Meeting of the NGSP Clinical Advisory Committee Minutes

2012 ADA 72nd Scientific Sessions
Philadelphia, PA
Sunday June 10, 8:00AM – 10:00AM

Alethea Tennill	NGSP	Judy Fradkin	NIDDK
Ann Albright	CDC	Julie Myers	Bio-Rad
Charles Peterson	TATRC	Len Pogach	VA
Craig Cartwright	Bio-Rad	Matt Peterson	ADA
David Lacher	NHANES via phone	Mayer Davidson	Charles Drew Univ.
David Leslie	Blizard Institute UK	Mike Steffes	Univ. of MN
David Nathan	MGH, Harvard	Ragnar Hanas	ISPAD
David Sacks	NGSP	Robert Cohen	Univ of Cincinnati
David Simmons	Bayer Diabetes Care	Ruth Lipman	AADE
Elizabeth Selvin	John Hopkins	Sally Marshall	Diabetes, UK
Erin Longdo	Bio-Rad	Shadi Chamany	NYC Health Dept
Hideji Hiaoka	Asahi-Kasei	Steve Hanson	NGSP
Holly Schachner	Bayer Healthcare	Sue Kirkman	ADA
Ian de Boer	Univ. of Wash	Takuji Kouzuma	Asahi-Kasei
Jennifer Knaebel	Bayer Healthcare	Zachary Bloomgarden	AACE, Mt Sinai
Joan Bardsley	AADE		

Welcome and introduction: A. Albright opened the meeting at 8:00 am and welcomed everyone. Participants introduced themselves. The 2011 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. we are starting to see more Level II labs, especially in South America
- 2011 guidelines from AACC, NACB and ADA compared to CAP HbA1c results
    1. Within Lab CV < 2%. CAP data show that many methods have CVs <2%
    2. Between-lab CVs <3.5%. Latest CAP survey shows CVs 3.5-3.9% between labs including all methods
- Is HbA1c Measurement Adequate for Optimal Clinical Use? Are CAP limits tight enough?
    1. Current CAP limit is ±7% which corresponds to ±0.5% HbA1c at 7% HbA1c
    2. If a lab consistently passes the CAP limit then it is highly likely that the lab will give results within ±0.5% at normal range or treatment target range. Is that good enough, especially for diagnosis?
    3. Based on 2012A CAP survey ≈95% of labs passed at the current limit
    4. This means a "true" HbA1c of 7% could be reported as 6.5% HbA1c or 7.5% HbA1c
- Improving 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%)
    - As of September 2012, manufacturer certification will be single sample measurements and 37/40 results must fall within 7% (relative percent)
2. Tighten CAP Survey Grading
    - 2011-2012 Acceptable limit reduced to ±7%
    - After 2012 more changes are anticipated
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 ±7% (previously ±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 ±0.5% of "TRUE" value in diagnostic and target range, but overall method CVs are not consistently ≤3.5% yet
    2. NGSP will tighten manufacturer certification criteria to be more closely aligned with CAP
    3. We are now recommending limits of ±7% for clinically significant interference from Hb variants

Discussion: D. Nathan asked how we can expect labs to be within±7% on the CAP survey when manufacturers are only expected to be within ±7% to be NGSP-certified. R. Little commented that 7% is a starting point. Our statistician, Curt Parvin did a lot of simulations; it is not that easy to compare CAP to NGSP current criteria. There are many variables and it is not a direct comparison. J. Fradkin asked if we make the numbers available publically so that customers can pick the best method. Making the results public may get more movement toward improved methods. R. Little said the actual numbers are not published. Customers can use the CAP survey results, and ask the manufacturer for their results. D. Sacks said CAP survey is more applicable, because it uses many different lots, so you can see lot-to-lot variability. CAP results are shown on NGSP website.

CAP criteria for proficiency testing: D. Sacks

- In 2007 CAP changed from peer grading to accuracy based grading using DCCT target
- ±15% was selected as the limit in 2007
- CAP has lowered this limit to ±7% over several years
- When you compare 2010 and 2012 CAP results pass rates, you see that labs have improved from 2010 to 2012

		2010 At ±8%	2010 At ±6%	2012 At ±7%	2012 At ±6%
GH2-01	**5.9%**	**95.5**	**91**	**95.6**	**95.6**
GH2-03	**7.4%**	**95.4**	**91.6**	**96.2**	**92.9**
GH2-02	**9.8%**	**95.2**	**88.6**	**94.9**	**92.5**

R. Cohen asked what caused the change. D. Sacks replied that when the CAP results are sent in they also include the lot numbers for reagents, etc. This information is sent to the manufacturers along with the results, so they can evaluate lot-to-lot variability.

- Should the criteria be tightened even further?
    1. 2011-2012 ±7%
    2. 2013 has yet to be determined

Status of HbA1c reporting outside US: D. Sacks

- Germany, the UK, Italy, Netherlands, Sweden and New Zealand now report IFCC numbers in mmol/mol.
- Australia is reporting both NGSP and IFCC and is planning on moving to mmol/mol in 2013.
- The USA, Japan and Canada are reporting NGSP numbers.

Discussion: R. Hanas stated that the most important outcome from the meeting in Dubai was that authors must report both units in journals. You can get the conversion numbers and standard deviation for each unit on the internet: www.hba1c.nu/eng2.html. S. Kirkman reported that Diabetes Care will start requiring dual reporting in their journal.

Use of HbA1c for diagnosis: D. Sacks

- WHO stated that HbA1c can be used for diagnosis; this was endorsed by IDF & EASD.
- There is no clear evidence of how many people are using HbA1c for diagnosis
- The UK is now using it for diagnosis, Sweden is not.

Laboratories reporting eAG: D. Sacks

- From 2009 until now CAP has included supplemental questions about eAG on the April CAP GH2 survey.
- In Response to the question if labs were reporting eAG the following responses were received ("n" is number of labs responding) :

Response (%)	2009	2010	2011	2012
	n=2997	n=2547	n=3190	n=3233
Yes	16.7	29.7	32.9	35.7
No	83.3	70.3	67.1	64.3

- At least half of the labs that are reporting eAG are using the correct conversion equation:

Response (%)	2009	2010	2011	2012	Comment
28.7 x HbA1c – 46.7	***28.8***	***49.9***	***51.2***	***52.1***	***Correct equation***
35.6 x HbA1c – 77.3	22.5	7.8	6.8	5.5	
Do not know	n/a	17.4	19.3	22.9	
Other	48.7	24.9	22.7	19.5	

Some of the labs in the "do not know" category may be using the correct equation.

Discussion: L. Pogach asked if the labs reported confidence interval? D. Sacks did not think any of the labs do. D. Nathan commented that we do not publish error bars around any other result. D. Simmons said that point of care (POC) units cannot meet laboratory standards, but there are still places that need POC instruments. D. Nathan commented that this becomes a question as to whether having access to HbA1c result is worth using an assay that cannot meet these criteria; is it better than having no result at all? D. Simmons said we need to make a decision about what is good enough for POC methods which cannot compete with laboratory

methods. D. Nathan asked if we should be more stringent at the manufacturer level so that methods in the field, particularly POC, will be tighter. S. Kirkman said that estimated Average Glucose at least has the word "estimated" in it. It would be nice to be able to convey to patients that the number they receive is not a hard a fast number, but a ballpark result. D. Sacks asked for input as to whether the criteria are tight enough. J. Fradkin commented that the ±0.5% is adequate for managing diabetes, but not for diagnosis. Why don't we have 2 levels of pass rates, those that are used for managing diabetes and those that can use it for diagnosis? A. Albright commented that we already have difficulty getting people to know there result and getting them to improve their glycemic status. If we add another layer it will be even tougher.

Use of Glycated Albumin in Patients with Diabetes and Renal Failure: R. Little

- In addition to tightening certification and CAP grading limits, and reducing measurement interference, we also need to better define clinical situations where HbA1c testing may not be the best way of monitoring patients. One important example is in patients with renal failure.
- At last year's meeting Ian De Boer showed a slide indicating that diabetes is the primary cause of end stage renal disease (ESRD) and better glycemic control is associated with better survival rates even with people on dialysis. So it is important to have an accurate way of monitoring their glycemic control.
- Several studies by Freedman B, et al., show that glycated albumin was more strongly associated with mortality than HbA1c.
- Peacock, et al, Kidney International 2008 showed a 1% difference in HbA1c at the same level of GA when comparing non-ESRD vs. ESRD patients.
- Inaba, et al, J Am Soc Nephol 2007 showed a 2% difference in HbA1c at the same level of GA when comparing non-ESRD vs. ESRD patients.
- Our lab looked at 121 patients with various levels of eGFR. We showed a 1.5% difference in HbA1c between patients with and without renal failure assuming that the Lucica GA assay correctly represents glycemic control.
- Usefulness of HbA1c in diabetic patients with renal failure is limited. HbA1c gives clinically significant low results. We need a better definition of when to use HbA1c and when to use something else, like GA.

Discussion: M Davidson commented that patients with ESRD may be spilling albumin and so the difference may be even greater than has been shown. D. Nathan said that until they measure CGMS we will not know the true result. How many patients were on EPO or had transfusions? R. Cohen commented that CGMS studies need to done and the questions about EPO use need to be determined. R. Little commented that there are already some studies showing the effect of proteinuria on GA and also the effect of EPO on HbA1c. She also commented that HbA1c in the normal range doesn't seem to be that different between the 2 groups and this is a bit puzzling. S. Marshall commented that the relationship between the two groups is not going to stay constant; if you increase hemoglobin concentration then you decrease %HbA1c. T. Kouzuma commented that the Lucica GA does not yet have FDA approval in the U.S.

NHANES HbA1c D. Lacker (via phone)

- An increase in the proportion of HbA1c results between 5.7 and 6.4% was noted in NHANES 2007-2010 when compared to 1996-2006. This is important due to the use of HbA1c for diagnosis of diabetes.

- This shift was not seen in the glucose data.
- NHANES 2007-2010 data were temporarily withdrawn until the cause of the shift could be evaluated.
- NHANES HbA1c laboratories from 1999- present participated in the NGSP as secondary reference labs. (1999-2004 used Primus CLC 330, 2005-2006 used Tosoh 2.2+, 2007-2010 used Tosoh G7)
- Internal and external quality controls were evaluated to determine if the reason for the increase was due to laboratory method changes. Nothing was found during the evaluation that could determine that the laboratory methods were related to the increase.
- The participant data and HbA1c data were re-released without changes to the data. The user is cautioned to carefully consider the information presented when analyzing HbA1c data from 1999-2010.

NIDDK A1C Fact Sheet – J. Fradkin

- The A1C Test and Diabetes fact sheet has been published to help alleviate some of the confusion as to when to use the test, what constitutes pre-diabetes and diabetes, etc.
- It also gives some general information on the use of A1C.
- Thank you to all those that contributed to the fact sheet.

Reporting of HbA1c at the VA – L. Pogach

- The VA has almost 1 year's worth of calibration and control data for all HbA1c tests.
- This data will be used to make a decision as to whether they will hold the local laboratories to a tighter level than what CAP is doing in the private sector.
- Will use the Acceptable Risk Document EP23 to help make this determination.
- The next question is how to disseminate this information to clinicians.
- We want to use performance goals to assess populations and sub groups: tighter control for younger patients, not so tight control in older patients, etc.

Discussion on last 3 topics: D. Simmons congratulated Dr. Lacher on his effort and suggested that perhaps this is a real biological phenomenon which is consistent with a wide array of studies that have come out since the diagnosis recommendations. We have known for decades that the pre-analytic variability for OGTT is huge. R. Little said that it is good to understand from an epidemiological standpoint that an increase in HbA1c of 0.1 or 0.2% will affect millions of patients and their diagnosis. A. Albright mentioned that the issue CDC has with running the nation's surveillance system is that it does get complicated when you look at various ways to determine the prevalence of diabetes.
D. Sacks asked for some feedback from the group as to whether CAP needs to tighten their criteria. M. Steffes said that for the epidemiologists and NHANES the criteria need to be tightened, but he is not sure that we can get much tighter using the current technology. R. Cohen commented that the error bars around the different methods for the CAP survey are clearly very different; some methods are capable of detecting smaller differences, some are tighter than others. R. Little noted that it is not just ion-exchange HPLC that is able to achieve low variation; with a new SRL in Japan, we have seen some very tight relationships between HPLC and immunoassays. We do not have performance data on those methods because they are not sold in the U.S. D. Sacks asked if we can expect CAP to be tighter than NGSP. R. Little commented that both are getting tighter, they just may not always be in the right order. D. Nathan said that you can't expect the end user to be tighter than the manufacturer. A limit of 6% as shown by D. Sacks in his presentation will not decimate the clinical laboratories. If this group does not move to tighter criteria, it will not get done. Do we need to move to a 2 tier system for POC

testing? D. Simmons commented that we might need a 3 tier system, because NHANES demands may be tighter than for the clinical diabetes lab, and POC provides to a different community to service their demands and the advantages are going to be different. You can tighten anything enough given enough money. R. Hanas said that it was discussed in Sweden with clinical chemists who said that it could and should be tightened. If you ask for it you will eventually get it.

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 10:00 AM.

Minutes prepared 6/26/2012 by A. Tennill, reviewed by C. Rohlfing, R. Little, D. Sacks