Meeting of the NGSP Clinical Advisory Committee Minutes

2014ADA 74th Scientific Sessions
San Francisco, CA
Sunday June 15, 2014 8:00AM – 10:00AM

Alethea Tennill	NGSP	Mayer Davidson	Charles Drew Univ.
Ann Albright	CDC	Myron Gross	Univ of Minnesota
Bruce Wolfenbuttel	Univ of Groningen	Nancy Haley	Siemens
Charles Peterson	TATRC	Ragnar Hanas	ISPAD
Craig Cartwright	Bio-Rad	Ruth Lipman	AADE
David Leslie	Blizard Institute UK	Steve Hanson	NGSP
David Nathan	MGH, Harvard	Sue Manley	Univ of Birmingham
David Sacks	NIH, NGSP	Takuji Kouzuma	Asahi-Kasei
Elizabeth Selvin	John Hopkins	Tom Kuhn	Sebia
Erin Longdo	Bio-Rad	Tony Prestigiacomo	Bio-Rad
Griffin Rodgers	NIDDK	William Herman	Univ of Michigan
Hideji Hiaoka	Asahi-Kasei		
Joan Bardsley	Medstar/AADE	By Phone:	
Judy Fradkin	NIDDK	David Aarons	VA
Ken Malamo	GI Dynamics	Elizabeth Koller	CMS
Laura McEwen	Univ of Michigan	Robert Cohen	Univ of Cincinnati
Martu Richards	Siemens		
Matt Peterson	ADA		

Welcome and introduction: A. Albright opened the meeting at 8:02 am and welcomed everyone. Participants introduced themselves. The 2013 NGSP Clinical Advisory Committee meeting minutes were approved.

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

- NGSP Certification
    1. The number of methods/laboratories certified has started to level off.
    2. Participation in the laboratory certification process is worldwide. Most laboratory certifications are outside the United States and most are Level 1 labs.
- CAP survey data
    1. Many methods are capable of between-lab CVs <2%, as recommended in the 2011 Guidelines (Clin Chem 2011; 57:793-8)
    2. On the 2014A CAP survey, between-lab, within-method CVs were <3.5% for several methods. Laboratory guidelines recommend between-laboratory CVs <3.5%.
    3. But between-lab CVs for all methods combined were 3.4-4% (including all methods). Only the high sample showed <3.5% all-method CV.
    4. There has not been much improvement in the last few years.

- Is HbA1c Measurement Adequate for Optimal Clinical Use? Are CAP limits tight enough?
    1. Current CAP limit is ±6% which corresponds to ±0.4% HbA1c at a target of 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 2014A CAP survey 89-94% of labs passed at the current ±6% limit.
- Current Limits for NGSP and CAP
    1. NGSP Certification criteria were tightened in January 2014
        - Manufacturer and Level II certification changed to 37/40 results ±6% (relative percent).
        - Level I certification changed to 38/40 results within ±6% (relative percent)
    2. CAP Survey Grading
        - Acceptable limits have been ±6% since 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
        - Tighten criteria for clinically significant interference in publications. Most recently this was ±7% (previously ±10%) at 6 and 9% HbA1c; this may be tightened further
        - Table showing Hb Variant Interferences can be found on NGSP website.
- Summary:
    1. Most Laboratories can now provide HbA1c results within ±0.5% HbA1c of "True" value in the diagnostic and target range, but overall method CVs are not yet consistently ≤3.5%.
    2. NGSP tightened manufacturer certification criteria to ±6% (relative) in January 2014.
    3. CAP criteria have been ±6% since beginning of 2013.
    4. Most recently ±7% was considered a clinically significant difference for Hb variant interference.

Discussion: J. Fradkin asked how clinicians knew what method their lab was using. Could we require the labs to put the interferences from the method on the patient report? R. Little responded by saying that NGSP currently certifies about 100 labs, most of which are outside the United States. There are 3500 labs on the CAP survey. NGSP has no direct communication with the labs on the CAP survey. D. Nathan commented that lab reports have different language around the results. J. Bardsley suggested that we work with AACC and have them encourage labs to put this information on the report, but understand that labs have many tests and many test methods. D. Sacks said that if labs are using HPLC methods, they can usually see a variant hemoglobin in the chromatogram and let the physician know that their patient has variant hemoglobin. But if the lab is using an immunoassay, there is no way to tell if there is a hemoglobin variant present. M. Davidson said that he knew what method his lab used, but he did not know that it had interference from HbE. Can most labs tell if a sample has a variant? D. Sacks said that most methods do not have interference from HbAS, but HbAE and HbAD still show interferences with some methods. R. Hanas pointed out that it would be more important to know the bias for each method. B. Herman asked if we could add the + or - bias to the interferences table on the NGSP website. R. Little commented that you can find that information by looking through the references, but didn't want to make the table on the website too complicated. A. Albright said that this could be a topic for a future meeting: How do labs communicate interferences with their methods to the end users?

Review of Point Of Care (POC) methods; good enough for diagnosis? R. Little

- Using POC for diagnosis
  1. Many POC methods have been NGSP certified, but these are done by the manufacturers under very controlled conditions
  2. The 2014 ADA clinical practice recommendations state: Use of POC testing for A1C provides the opportunity for more timely treatment changes.
  3. Several papers have shown that POC methods provide improvement in glycemic control and other benefits i.e. more efficient communication, more frequent intensive therapy and enhanced motivation.

- Concerns about quality of POC results for HbA1c
  1. Several papers have shown POC methods do not meet accepted lab performance criteria
  2. There is limited CAP data for most POC methods, since they are traditionally waived tests. Of the limited POC methods that appear on the CAP survey, most are likely used in hospitals by trained personnel.
- Questions concerning POC methods
  1. If POC methods are not accurate enough to use for diagnostic purposes, why are they acceptable to use for treatment decisions?
  2. Is it ok to use less accurate/precise methods for treatment than screening and diagnosis?
  3. Why not make a distinction between use of POC methods for screening vs. diagnosis?

Discussion: D. Nathan commented that there was some benefit to having the A1C result at the time of visit. But before they used the POC method they made sure that only trained personnel ran the tests after appropriate quality control samples had been analyzed. Recently one of our pediatric clinics wanted to do the same thing, and when they had anyone running the test the results were incredibly inaccurate. Only after training with a lab technician were the test results consistently accurate. Without proper training it shouldn't be used for management or diagnosis. R. Little said that scientific articles from the Netherlands stated that it was very important for the personnel running the test to be properly trained. B. Koller said that CMS has concerns about accuracy and precision and feels that in many cases the POC methods are not comparable to laboratory methods. B. Herman commented that there was a lot of confusion between screening and diagnosis. J. Bardsley said that it was good clinical practice to use a lab method for diagnosis. M. Gross said that they use POC methods only under very controlled conditions. For a study in India, POC methods were linked with lab methods that were run by lab techs. C. Peterson said that decision making is more robust if you use a 2 step process, intuitive and quantitative results. L. Selvin said the first test should be highly sensitive and the second test should be highly accurate. However, "the cat is already out of the bag". Many major institutions use POC for diagnosis.

Clinical recommendations on NGSP website: D. Aaron

- D. Aaron showed snapshots of the NGSP website showing ADA clinical recommendations for A1C and glycemic goals in adults. There are links to a wide variety of guidelines but only the ADA recommendations are actually listed on the website.
- Should the NGSP be endorsing any guidelines from any agency? Most guidelines are in agreement about the general principles, but they differ in specifics. Not all federal agencies take the same approach.

Discussion: R. Little commented that most visitors to the NGSP website are looking for some connection to the clinical world. B. Herman said that providing the links is a good idea, but recommendations should not be endorsed. B. Koller commented that they face this issue frequently at Medicare. NGSP performs laboratory standardization and should not be endorsing any recommendations. Clinicians can look at other sites for this information. D. Nathan said that by not having this information listed are we really helping end users. Can we just say that this is not an endorsement for any recommendations? B. Koller said that CMS is on the receiving end of questions from end-users that want to be reimbursed for using POC methods for HbA1c results. There are a number of misconceptions about this. CMS has to answer all of these questions. Some people see it as an endorsement since it is on the NGSP website. So CMS feels that the link should be removed. J. Bardsley said that providing pages and links are very useful, just make it clear that you are not endorsing any recommendations. M. Peterson said it was there to provide context as to why we are standardizing A1C. Nothing that he has seen would imply that NGSP is endorsing ADA recommendations. They are the most widely followed guidelines, but adding an extra disclaimer cannot hurt anything. R. Hanas suggested that pediatric targets should be added also. J. Bardsley said that AADE was listed as a link, but NGSP is not listed on the AADE website and maybe it should be. D. Aaron said that he sees 3 separate issues that need to be addressed: a) should A1C be connected to the clinical world? b) how do you provide clinical information, a link to ADA is an endorsement, c) links that help people are great, but it should be very clear that one organization is not being preferred over another. D. Sacks said that this committee is supposed to advise the NGSP on clinical issues so what is the consensus from this group? Should NGSP link to clinical practice and diabetic recommendations, should there be a disclaimer, or no links on the NGSP website. A. Albright summarized the points raised for further discussion. Many participants seem to be in favor of the NGSP website having links to information about clinical practice recommendations and other diabetes related information. Should there be any specific guidelines posted on the website with the disclaimer that this is not an endorsement of these guidelines, but just a commonly cited set of guidelines? Or should there be no guidelines put on the website? D. Aaron thinks that people on this committee could come up with some clinically relevant information that will give some utterly non-controversial guidelines. D. Nathan said that this would just add another set of guidelines and this group does not have the same kind of process that the ADA, EASD etc., to determine these guidelines. D. Aaron suggested that we take what is common among all the guidelines. J. Fradkin said that National Diabetes Education Program (NDEP) has a process ongoing that has participation by the endocrine society, AACE, ADA, AHA and by most groups to come up with some guiding principles that take all the areas of agreement among the different guideline. Most of the professional groups have signed off on it, although VA and CMS have declined and DOD is still trying to get permission. It has been recommended that this language be used on the website. If you have any further comments please send them to Drs. Sacks or Little.

Racial/ethnic differences in HbA1c. Two papers were presented on the topic of racial/ethnic differences in HbA1c.

No Racial Differences: L. Selvin presented her paper: No Racial Differences in the association of glycated hemoglobin with kidney disease and cardiovascular outcomes. Diab Care 2013; 36:2995-3001.

- A1c vs fasting glucose

1. The advantage to using HbA1c for diagnostic test vs fasting glucose is that patient does not need to be fasting, ease of use, much less day to day variability
2. The controversy occurs due to some assay interferences from variant hemoglobinopathies, some conditions interfere with A1C test like red cell lifespan and it can be more expensive.
3. There have been reported cases of higher HbA1c in African Americans when compared to whites. Thus the claim is that HbA1c is "less valid" in African Americans than whites as a measure of hyperglycemia.
4. Why the difference if this is due to non-glycemic factors then HbA1c is falsely high in blacks and we may need race-specific targets and a race-specific diagnostic threshold

- Atherosclerosis Risk in Communities (ARIC) Study
    1. ARIC is a community based cohort of 15,000 middle-aged adults with 25% African Americans that started the study with no history of diabetes diagnosis, coronary heart disease, stroke or congestive heart failure.
    2. The study started in 1987 and is ongoing.
    3. In ARIC study there are differences between the populations in levels of A1C, triglycerides, BMI, physical activity etc. The only marker that was not significantly different was LDL.
    4. Higher HbA1c that we see in black vs. whites could be due to genetic differences that contribute to higher HbA1c and higher risk.
    5. The study found HbA1c is a risk factor for cardiovascular disease and kidney disease in both blacks and whites. HbA1c is a better predictor than fasting glucose.
    6. Racial disparities in HbA1c and other (serum) glycemic markers likely reflect the true difference in risks and hyperglycemia. If we reduce the disparity we will improve health outcomes for patients.

Racial Differences: B. Wolffenbuttel presented his paper: Ethnic Differences in Glycemic Markers in Patients with Type 2 Diabetes. Diab Care 2013, 36:2931-2936.

- Several colleagues have contacted me about specific patients that have an HbA1c value around 7%, but when they put them on treatment the patient becomes hypoglycemic.
- Several studies have reported that HbA1c may be high in non-Caucasian patients with diabetes for a given blood glucose range. HbA1c may depend not only on glucose levels but also have a genetic component.
- The DURABLE results were used to compare eAG with SMBG to determine whether the use of eAG derived from HbA1c is acceptable and feasible in different racial ethnic groups with type II diabetes using equation from ADAG study
    1. The DURABLE trial assessed the durability of basal insulin vs. LisPro Mix in patients that had failed to reach glycemic control on oral agents alone.
    2. It was carried out on 5 continents with approximately 2000 participants.
    3. The study enrolled type II diabetic men and women between 30-80 years old with HbA1c between 7.0 and 13%
    4. Ethnicity in this study was 66% Caucasian, 16% Asian, 12% Hispanic, and 6% African descent.
    5. Patients measured SMBG pre and 2 hours post after every meal and once at 3 a.m. three times in the preceding two weeks before HbA1c was measured using NGSP certified laboratories.

6. Data from each ethnic group were calculated and show that blacks have a higher mean HbA1c than Caucasians, but lower average age, fasting, pre-meal and post-prandial glucose values.
7. A regression equation was determined for all ethnic subgroups using mean of all SMBG values and HbA1c at baseline
8. eAG was calculated from ADAG study linear equation (eAG=28.7*HbA1c-46.7) and converted to mmol/l
9. The eAG and SMBG were not found to be equal.
10. It was observed that eAG over-estimated the actual MBG <11.4 mmol/l (210 mg/dl) and it under-estimated the MBG >11.4 mmol/l
11. HbA1c values at different glucose levels differ between ethnic groups. There should be specific race treatment goals. There are racial and ethnic differences and treating them the same may lead to hypoglycemic. For a given glucose level they have a higher HbA1c and thus are at higher risk for complications.

Discussion: L. Selvin said that her group had published several papers that found a change in acetylation of alkaloids between blacks and whites. African Americans have a lower incidence of lung cancer for cigarette smoked. S. Manley commented that L. Selvin's cohort were non-treated subjects while B. Wolffenbuttel's cohort were subjects with treated T2DM. Should we think about difference between non-diabetics and diabetics separately? L. Selvin said that patients without a diagnosis of diabetes are not manipulating their HbA1c. Serum glycemic markers were the same up until diagnosis. Black/white differences are likely due to access to care. R. Hanas said that in the B. Wolffenbuttel study eAG does not match that of the ADAG study. B. Wolffenbuttel's study only used 3 SMBG measurements. The conclusions surprised him from a clinical point of view. D. Nathan commented that the ADAG study patients were mostly Caucasians due to electrical problems at several sites. If this is really an important question then we should do the ADAG study with African Americans. 7 point profiles are not enough. B. Herman commented that the DPP data did show ethnic differences in A1c based on blood glucose. D. Nathan suggested that if this is an important question and maybe worth doing; then we should repeat the ADAG study with minority populations.

Ann Albright thanked everyone for their attendance. If anyone has discussion topics for next year's meeting, contact R. Little. The meeting was adjourned at 10:05 a.m.

Minutes prepared 7/2/2014 by A. Tennill, revised by R. Little and C. Rohlfing