



Meeting of the NGSP Clinical Advisory Committee Minutes

2016 ADA 76th Scientific Sessions
New Orleans, LA
Monday June 13, 2016 2:30 – 4:30 PM

Ann Albright	CDC	Matt Petersen	ADA
Joan Bardsley	Medstar/AADE	Griffin Rodgers	NIDDK
Craig Cartwright	Bio-Rad	Curt Rohlfing	NGSP
Denise Furtado	Alere	David Sacks	NIH, NGSP
Myron Gross	Univ of Minnesota	Amy Saenger	Univ of Minnesota
Steve Hanson	NGSP	Rick San George	Alere
William Herman	Univ of Michigan	Elizabeth Selvin	John Hopkins
Takuji Kouzuma	Asahi-Kasei		
David Leslie	Univ of London	By Phone	
Randie Little	NGSP	Beena Akolkar	NIDDK
David Nathan	MGH, Harvard	David Aron	Veterans Admin
Gillian Parker	Alere	Robert Cohen	Univ of Cincinnati
Charles Peterson	US Army		

Welcome and introduction: A. Albright opened the meeting at 2:30 pm and welcomed everyone. Participants introduced themselves. The 2015 NGSP Clinical Advisory Committee meeting minutes were approved.

HbA1c/NGSP Update: R. Little

- NGSP Certification
 1. The number of certified methods continues to increase, the number of labs has leveled off. Some large laboratory groups are merging and consolidating.
 2. Most certified laboratories are outside the United States and most are Level 1 labs.
 3. Certified laboratories are distributed throughout the world on six continents.
- Current limits
 1. NGSP Manufacturer and Level II Lab Certification Criteria: 37/40 results must be within $\pm 6\%$ (38/40 for Level 1 Labs)
 2. CAP Survey Grading for HbA1c: $\pm 6\%$
- 2016 CAP GH5A survey data (5 samples)
 1. Historically there has been considerable improvement in the comparability of results since 1993, but over the last few years the improvement has been more subtle.
 2. On the 2016 GH5A survey several methods show high CVs, but these have small numbers of users. Most methods show low variability.
 3. Overall pass rates were 93.0-97.8%. Individual method pass rates ranged from 66.7% to 100%.

4. Our goal for all-method CVs is <3.5% at all HbA1c levels, this was achieved in the latest survey.
 5. All-method pass rates at the current criterion of $\pm 6\%$ have increased to >96%.
 6. As with the 2015 GH5A survey, two of the specimens were blind duplicates. Compared to 2015 the mean absolute differences between duplicates for the individual methods showed overall improvement; almost all were <0.15% HbA1c.
 7. Method-specific between-laboratory CVs ranged from 1.3% to 8.4%.
- HbA1c Assay Interferences
 1. We recently published new data regarding hemoglobin variant interferences (Clin Chim Acta 2016;455:80-3).
 2. Information on assay interferences is available on the NGSP web site; this information is updated regularly.
 3. Most current immunoassays do not show interference from the most common hemoglobin variants (HbAS, HbAC, HbAE, HbAD) but a few still show interference from HbAS and HbAC. The interfering variant cannot be detected with these methods.
 4. Some current ion-exchange methods do not show clinically-significant interference from the common variants but several do show interference from one or more. The presence of the interfering variant can generally be detected with these methods so as to avoid reporting an incorrect result.
 5. The current capillary-electrophoresis, boronate affinity and enzymatic methods do not show significant interference from the common variants.

Discussion: W. Herman asked if, where there is variant interference, it would be possible to indicate the actual values in the table on the web site to show how the results are affected. R. Little said clinically significant interference is currently defined as $\geq \pm 7\%$ at 6 and 9% HbA1c, the detailed table includes references for the original publications that show the degrees of interference. D. Sacks suggested a separate table to show this information. R. Little said the biggest issue with common variants is where a method shows interference but the presence of the variant cannot be detected and therefore an erroneous result is reported. There are methods like this in use, including POC methods, that were FDA-approved for monitoring. J. Bardsley suggested publishing the current information regarding issues with variant interferences and POC testing in the AADE journal In Practice, as many diabetes educators are unaware of these issues. R. Little asked if diabetes educators actually pay attention to what HbA1c method is used, J. Bardsley said that they mainly look at the results, there are some diverse populations where variant interferences could be a problem. Also, they are not likely to look at the NGSP web site. D. Nathan noted that physicians also lack awareness of these issues, D. Leslie agreed, they suggested publishing a new NGSP update in Diabetes Care. C. Peterson suggested for immunoassays the epitope specificity may help to be predictive of potential interference, the FDA is generally interested in that kind of information and would likely have it. R. Little said that a method only has to show that it is comparable to a previous method, and interferences have to be stated, in order to obtain FDA clearance for monitoring. D. Nathan said that we discussed this last year with the FDA, unfortunately they have to follow these guidelines which is unfortunate. C. Peterson agreed, but it would be good to address this from the regulatory side at some point if possible. R. Little said that for now our only approach is to continue to make information regarding method interferences widely available to labs and healthcare providers

CAP Update: D. Sacks

- CAP Grading
 1. Originally CAP used peer group grading for PT for HbA1c

2. In 2007 changed to accuracy grading
 3. Whole blood sent to all participants
 4. Target values obtained from analysis by NGSP SRLs; each sample analyzed in triplicate on 2 days (6 results per SRL per sample)
- PT Criteria Tightened
 1. Initially +/- 15% acceptable
 2. 99% pass rate
 3. Acceptability criterion progressively reduced from 2008
 4. Reached +/- 6% in 2013
 - Number of Labs Enrolled in CAP HbA1c PT Surveys: The number of labs participating in the surveys increased from ~800 in 1997 to ~2500 in 1998 and has leveled off at ~3500 in the last few years.

POC HbA1c: R. Little

- Data for the first POC HbA1c method were published in 1990, this was what later became the DCA2000. CVs were 2.2-4.1%, and there was no interference from common variants or labile.
- Currently there are many POC HbA1c methods available, a number of which are NGSP-certified. Not all are available in the U.S.
- Benefits/Advantages of POC for Diabetes Monitoring
 1. Significant Improvement in glycemic control: Cagliero et al 1999, Thaler, et al 1999, Miller, et al 2003 Petersen, et al 2007.
 2. Other benefits (more efficient communication, more frequent intensification of therapy, enhanced motivation): Agus et al 2010, Al-Ansary, et al (review of 7 trials) 2011
- Concerns regarding POC HbA1c
 1. Imprecision, Lack of Reproducibility and lot-to-lot variations in reagents/calibration
 - St John, et al 2005: only 1 of 4 POC devices tested were recommended for use outside of laboratory
 - Leters-Westra, et al 2009: high variability and lot-dependent results for 2 POC methods
 - Leters-Westra, et al 2010: 6 of 8 POC methods do NOT meet accepted performance criteria; there was considerable lot-to-lot variability
 - Petersen et al 2010: can be used if physicians given instrument specific reference ranges
 - Leters-Westra, et al 2014: 3 of 7 POC methods do NOT meet performance criteria
 - Dupuy, et al 2014: lot-to-lot variability for one POC method; reproducibility of reagent lot production appears inadequate.
 2. Lack of Proficiency Testing (PT) data, especially at waived sites
 - Only two POC methods appeared on the most recent CAP survey: Axis-Shield Afinion (n=57) and Siemens DCA Vantage (n=473)
 - Both methods perform well on the surveys
 - However, most if not all of the participants in the survey using these methods are likely laboratories since they are performing PT.
 - Two other POC methods appeared on the 2012 CAP survey, both of which did not perform well.
 - NGSP certification reflects performance of the method under ideal conditions in the hands of the manufacturer.

- Performance in the hands of end-users can be assessed by proficiency testing (PT) surveys (e.g. CAP), but most POC test users are not required to do PT.
- ADA Clinical Practice Recommendations
 1. 2006-Present: “Use of point-of-care testing for A1C allows for timely decisions on therapy changes, when needed.”
 2. 2010-2012: “Point-of-care A1C assays are not sufficiently accurate at this time to use for diagnostic purposes.”
 3. 2013-Present: “Although point-of-care A1C assays may be NGSP certified, proficiency testing is not mandated for performing the test, so use of POC assays for diagnostic purposes is not recommended.”

Discussion: W. Herman asked how POC is defined. D. Sacks said it can be difficult to define, it is generally a device that is not in a central lab but in settings such as bedside, a patient’s home or a physician office. D. Nathan noted that POC is not really a good term, these are really non-central lab devices. R. Little said she generally thinks of a small device where samples are analyzed one-at-a-time. A. Saenger noted that sometimes POC devices are used in a central lab. D. Nathan said central labs should have better QC standards for these devices but he is not sure if that is really true. D. Sacks and R. Little said there are definitions, we could check and see how FDA defines it.

POC HbA1c for Diabetes Diagnosis: D. Sacks

- Waived Tests
 1. Clinical Laboratory Improvement Amendments of 1988 (CLIA)
 2. “Waived tests are simple laboratory examinations and procedures that
 - Are cleared by FDA for home use or
 - Employ methodologies that are so simple and accurate as to render the likelihood of erroneous results negligible or
 - Pose no reasonable risk of harm to the patient if the test is performed incorrectly”
 3. Waived from regulatory oversight
 4. <1% of lab tests are waived; many are urinalysis
- HbA1c POCT
 1. Most (all?) are waived
 2. Not required to participate in PT
 3. Have information re performance in hands of manufacturer from NGSP certification
 4. No monitoring/assessment of performance in the hands of the user
- CAP Proficiency Testing
 1. In USA labs that perform patient testing are required by law to participate in PT
 2. Historically, CAP sent out 2 PT surveys annually for HbA1c
 3. Each survey contained 3 samples
 4. Originally artificial material
 5. Whole blood with accuracy-based grading since 2007
- HbA1c POCT for Diagnosis
 1. Alere has applied to FDA for clearance of Affinion HbA1c for diagnosis of diabetes and identifying persons at risk for diabetes
 2. “Moderate complexity”
 3. Not waived
 4. User is required to participate in PT
- FDA Meeting

1. Alere application via 510(k) - Premarket notification
2. Need only show "substantial equivalence" to device already on the market
3. FDA holding a public meeting July 22, 2016
 - o Hilton Washington DC North/Gaithersburg
 - o <http://www.fda.gov/AdvisoryCommittees/Calendar/ucm503538.htm>
 - o Thurs July 21st : PMA by Dexcom for G5 CGM use as replacement for blood glucose meter
 - o Fri July 22nd : Alere HbA1c
 - o Interested persons may present data, information or views orally or in writing, written submissions due before July 15
 - o Contact: Patricio Garcia (patricio.garcia@fda.hhs.gov, Ph: 301-796-6875)

Discussion: D. Sacks noted that the CAP survey now offers a five-sample whole blood survey three times a year for HbA1c, but since HbA1c is not yet a CLIA-regulated analyte they still give labs the option of participating in a 3-sample twice yearly survey as before. HbA1c may soon become a CLIA-regulated analyte; if so, labs will be required to participate in the former. D. Nathan asked why the device is being submitted to FDA as moderate complexity, is this in order to get the diagnostic claim? R. San George responded that it must be submitted as moderate complexity in order to get the diagnostic claim. D. Nathan suggested that the whole idea of a test being considered moderate complexity for diagnosis vs. waived for monitoring is absurd, for the latter you are using the results as a basis for treatment that often involves the use of pharmaceuticals. W. Herman noted that with monitoring you at least generally have other results to look at, including a previous HbA1c and glucose results, and for diagnosis false positives or negatives can have implications. D. Nathan responded that there is often other data available around the time of diagnosis as well, physicians generally trust HbA1c, more so than other tests including patient self-monitoring. A. Saenger said that it can be confusing, when a test is ordered it is difficult to know how the physician is using it. D. Nathan said this distinction is being applied due to the FDA, D. Sacks said it depends upon how the company applies. D. Leslie said that he could not think of another example where this situation applies. In one case you are deciding yes or no, in the other case there is a continuum. G. Parker and R. San George clarified that they also had to first apply under moderate complexity to get the monitoring claim as well, this is the process for a new device or intended use. Once approved under moderate complexity there is a whole separate application process to obtain waived status. D. Sacks said that one important distinction between moderate complexity and waived status is that moderate complexity places a higher bar on the end-user, there are requirements in terms of training and qualifications. B. Herman asked if there is an example of a POCT that includes a requirement for PT testing, if PT were required for a POC HbA1c method to be used for diagnosis how would this be implemented in physician offices? D. Sacks said CMS is the organization that does the monitoring of PT testing, CAP does the lab inspections but CMS oversees this and sometimes they do their own inspections. He asked if manufacturers have to report to anyone when a device is sold to a facility such as a physician office. G. Parker said that manufacturers do not have to report which labs are doing which tests, CLIA-waived labs are required to report results in CLIA-waived settings. If the test is being used as moderate-complexity they are required to have a CLIA license and participate in PT. D. Sacks said he does not know how one could determine exactly how a test is actually being used in different physician offices. D. Nathan agreed, thousands of physician offices that are using these tests for monitoring are probably also using them for diagnosis. A. Saenger and R. Little agreed, they have probably been doing this for some time. R. Little said the only issue is getting the test paid for, but her understanding is that there are ways around it. If a POC method that is already CLIA-waived for monitoring gets a diagnostic claim under moderate complexity, this can be designated on the labeling but who knows how it is actually being

used in a given setting? W. Herman noted that this is problematic; we do not know how well these tests are being run in physician offices since they do not participate in PT. D. Nathan noted that studies of POC methods done in his lab as well as by others have shown that some can perform well, but these were performed in the lab by trained laboratory technicians, not in physician offices. D. Furtado asked what a “comfortable” number of participating labs is on a CAP survey for an individual method in terms of showing that the method performs well. R. Little responded that it is not so much the number of labs as it is the setting. Presumably all or almost all end-users of POC methods that participate in CAP are in laboratory settings. D. Furtado acknowledged this, waived Alere Afinion users generally do not participate in CAP due to cost, a number of CLIA-waived users (~400) do participate in other PT surveys such as API where the cost is much less. D. Sacks said these surveys do not use whole blood so we do not know how to interpret the data. D. Furtado said the majority of the 57 users that appeared on the most recent CAP survey were actually in waived, non-med tech settings. R. Little noted that information on the setting is included in the CAP survey data but it can be difficult to interpret. Also, this is out of thousands of users, so it’s hard to know if this sample is representative, and that they are doing PT even though they are not required to. D. Sacks said that according to CMS it is impossible to have a waived test “un-waived” without an act of Congress. R. San George said each method should be judged by its own merits, POC methods should not all be lumped together. We have data showing that the method performs well in the hands of non-laboratory personnel including nurses and produces accurate results in non-laboratory settings. D. Sacks asked if Alere intends to eventually apply for waived status for diagnosis if it is approved under moderate complexity. R. San George responded yes, that is the intention, and noted that FDA has set a higher bar for waiver approvals. Many of the POC methods currently on the market were given waived status prior to 2007-2008 when the requirements were not as strict. Just because a method was granted waived status for monitoring 10 years ago does not mean that it would be approved today. W. Herman asked if the Alere method has any interferences, R. San George said since it is boronate affinity it is unaffected by common interference including variants, with the exception of some interference from elevated HbF. D. Nathan asked if it would be possible to obtain data from PT surveys other than CAP. R. Little and D. Sacks said the results from these surveys are hard to interpret, they do not use whole blood so there are matrix effects, plus they are peer-group graded so there is no way to know if the method as a whole has a bias. D. Sacks further noted that the pass rates are wider than CAP, there is no law stating requirements for pass rates, many labs that cannot pass CAP may use these surveys to ensure they will pass. R. Little said the Afinion looks very good on the CAP survey, the question is whether the 50+ sites on the survey are representative of the thousands of sites using the method. D. Sacks said we do not even really have a good idea of how many POC devices are being used in the U.S. R. San George said there is no evidence of harm that has emerged from the use of these methods, R. Leslie responded that absence of evidence is not evidence of absence. R. Little noted that there are still some POC methods on the market that perform poorly. A. Albright noted that it is possible that harm caused by the use of a poor method may be attributed to something else. A. Saenger said that the participants in CAP are likely labs that are licensed and therefore take more care in performing the test whether the method is waived or not, but we cannot get this kind of detail from CAP. G. Parker noted that there is data from their POC market surveys showing that ~97% of the U.S. POC HbA1c market is split between the Afinion and the DCA, so the high-performing POC methods are dominant in the U.S. There are approximately 10,000 of these instruments in use. R. Little said it is encouraging that these two methods are the dominant POC methods. W. Herman said that the ADA guidelines currently say POC should not be used for diagnosis, if the door is opened to POC perhaps the specific method(s) to be used should be stated. A. Albright noted that more oversight might be needed. M. Petersen suggested that the ADA Standards of Care could state the specific POC methods to be used. G. Parker suggested that since the FDA has raised the bar for methods seeking a diagnostic claim, the ADA could state that

if a POC method is used for diagnosis it needs to be FDA cleared for this purpose. D. Nathan said the ADA guidelines were based on the recommendations of the Expert Committee which did not recommend POC for diagnosis due to concerns about accuracy and lack of PT. W. Herman agreed noting that PT is the best way to ensure consistent accuracy. D. Nathan felt that we should stay with the current ADA guideline and it should really apply to monitoring as well. R. Little asked why a method can be considered good enough for monitoring but not diagnosis. The reason for the FDA's higher bar for diagnosis is that it was their opportunity to make more stringent criteria since it was a new intended use.

Fructosamine and Glycated Albumin: R. Little

- The reaction pathway for the synthesis of glycated proteins is basically the same as for hemoglobin glycation
- Glycated Serum Proteins (fructosamines)
 1. Shorter half-life compared to lifespan of erythrocytes
 2. Reflect mean glycemia over prior 2-4 weeks
 3. No standardization
 4. No specific treatment or diagnostic cutoffs
- Glycated Serum Proteins (GSP) & Glycated Albumin Methods
 1. Nitroblue Tetrazolium (NBT) reduction by fructosamines – “fructosamine assay”
 2. Enzymatic assay measuring total GSPs
 3. Enzymatic assay measuring glycated albumin specifically
- Glycated Albumin
 1. Assay first described by Kohzuma, et al (Clin Chim Acta 2002;324:61-71)
 2. Within and between-run CVs <1% (Kohzuma, et al JDST 2011;5:1455-62)
 3. Data showing high correlation with HbA1c and fructosamine, and risk for complications
- Use of shorter term markers of glycemic control
 1. In cases where a shorter timeframe of mean glycemia would be useful
 2. When HbA1c cannot provide an accurate assessment of glycemic control (e.g. renal failure)
- Interferences with GSP and GA

Interference	Effect on GSP/GA*
Nephrotic syndrome	Lower
Smoking	Lower
Obesity	Lower
Cushing's Syndrome	Lower
Hyperuricemia	Lower
Hyperthyroidism	Lower
Hypothyroidism	higher
- Issues to consider
 1. How will assay results be interpreted given the lack of clinical guidelines and standardization
 2. Need to check assay performance before selecting a method
 3. Does the patient have an interfering condition

Discussion: R. Little said a study published by their group in 2013 showed that at a given level of glycated albumin, HbA1c results for subjects with renal failure were ~1.5% HbA1c lower compared to normal subjects. This suggests that HbA1c results may be artificially lowered in renal failure patients, probably due to lower average erythrocyte lifespan. Several present suggested that there can also be issues with albumin turnover, how do we know that the GA result is accurate? R. Cohen said the problem in the case of renal failure is while there are issues with red-cell turnover, there are also issues

with albumin turnover. Are there studies looking at glycated albumin vs. CGM? There seems to be little data looking at substantial populations. R. Little said there is a study underway of patients with renal disease where glycated albumin, fructosamine, HbA1c, CGM and other analytes will be measured. Since there are interferences with GA it is important to look at the individual patient. Also, the new GA assay is not yet FDA-approved. R. Little asked if there is a clinical use for GA. D. Leslie said yes, although he is nervous about fructosamine based on past experience but if the new assay is improved it could be more useful. R. Little said there is still an issue of whether the fructosamine results should be adjusted for total protein or total albumin. E. Selvin said that when they looked at this in a community-based population it did not seem to make a difference. D. Nathan said they measured fructosamine in thousands of stored samples, it correlated well with HbA1c and complications, the issue is clinical utility. The assay is easy to perform but we never really found a use for it. However, now that we have CGM and investigators are looking at models that would facilitate making more rapid changes in treatment, it may be more useful. In particular it may be useful in pregnancy. D. Leslie agreed, their institution uses it for pregnant patients as they are looking for shorter-term changes. R. Little asked about protein turnover changes in pregnancy, D. Leslie acknowledged that this is a concern. W. Herman said given that we know that there are interferences with both HbA1c and glycated protein, it is good to be able to have another measure of mean glycemia in cases where, for example, an interference with HbA1c is suspected. E. Selvin noted that there are large cohort studies where there are no fasting samples and HbA1c also cannot be measured but they would like to identify diabetes. If fructosamine/GA could be standardized it could be very useful for this purpose. D. Leslie asked if it would be useful in studies where subjects may have iron-deficiency, E. Selvin said yes, also in populations with variants or anemia or where you do not have HbA1c available. Also it could be useful in short-term feeding studies and other trials where the study is not long enough to see changes in HbA1c. R. Little asked if the lack of FDA approval of the GA assay is an issue, E. Selvin said not for research studies. D. Nathan noted that glycated protein is very stable, they measured it in samples that were 25 years old. A. Albright noted that if it were to be used to identify diabetes in these studies there would need to be an established diabetes cutoff which means it would need to be standardized; E. Selvin agreed. A. Saenger said that standardization may not be much of an issue, there are only two assays on the current CAP survey, Roche and Diazyme. R. Little said it is not used much right now, the question is will it be used more. E. Selvin noted that life insurance companies now are all using fructosamine on their initial screen as they do not analyze whole blood. If it is high they then measure HbA1c. R. Little asked T. Kouzuma if the Lucica GA will be compared to fructosamine as part of obtaining FDA clearance, he responded that they would be doing this. D. Sacks asked about an effort to standardize GA in Japan, T. Kouzuma said there is one. D. Leslie noted that the correlation coefficient between GA and HbA1c in D. Nathan's study was 0.75 which is pretty good. R. Cohen said that when you look at populations as a whole you may see correlations of 0.75 but when you look at within-individuals you see higher correlations, it would be good to design studies to look at this more closely it may help us decide how to interpret the test.

A. Albright thanked everyone for their attendance, the meeting was adjourned at 4:05 PM.

Minutes prepared by Curt Rohlfing 06/30/2016. Modified by Randie Little 7/5/2016 and David Sacks 7/7/2016.