

Meeting of the NGSP Clinical Advisory Committee Minutes

2015 ADA 75th Scientific Sessions
Boston, MA
Sunday June 7, 2015 8:00AM – 10:00AM

Al Evans	Bio Rad	Maria Peluso-Lapsley	Siemens
Ann Albright	CDC	Matt Peterson	ADA
Barry Plant	Bio Rad	Myron Gross	Univ of Minnesota
Craig Cartwright	Bio-Rad	Ragnar Hanas	ISPAD
Curt Rohlfing	NGSP	Randie Little	NGSP
David Leslie	Univ of London	Robert Cohen	Univ of Cincinnati
David Nathan	MGH, Harvard	Stacye Beck	FDA
David Sacks	NIH, NGSP	Steve Hanson	NGSP
Elizabeth Selvin	John Hopkins	Takuji Kouzuma	Asahi-Kasei
Gillian Parker	Alere	Tony Prestigiacomo	Bio-Rad
Hideji Hiaoka	Asahi-Kasei	William Herman	Univ of Michigan
Judy Fradkin	NIDDK		
Karen Kemmis	AADE	By Phone	
Leonard Pogach	Veterans Admin	Elizabeth Koller	CMS

Welcome and introduction: A. Albright opened the meeting at 8:00 am and welcomed everyone. Participants introduced themselves. The 2014 NGSP Clinical Advisory Committee meeting minutes were approved.

HbA1c/NGSP Update: R. Little

- NGSP Certification
 1. The number of methods/laboratories certified seemed to level off last year but has increased again.
 2. Most laboratory certifications 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 Certification Criteria: 37/40 results must be within $\pm 6\%$
 2. CAP Survey Grading for HbA1c: $\pm 6\%$
- 2015 CAP GH5 survey data
 1. Several methods show a lot of variability while others show little, some methods show significant bias while others do not.
 2. Historically there has been considerable improvement in the comparability of results but over the last few years there has been little change.
 3. Overall pass rates were 93.3-96.3%.
 4. Two of the samples included in the survey were duplicates, for individual methods the mean absolute differences between the duplicates were $<0.2\%$ HbA1c.

5. Method-specific, between-laboratory CV's ranged from 1.3% to 8.4%.
6. Over 60% of laboratories are using methods with CVs <3% at all five HbA1c levels; over 76% of laboratories are using methods with CVs <3.5% at all five HbA1c levels.
7. Many methods are capable of between-lab CVs <2%, as recommended in the 2011 Guidelines (Clin Chem 2011; 57:793-8).
8. The 2011 Guidelines recommend between-laboratory CVs <3.5%, on the current survey the all method between-lab CVs were 3.4-3.6%.
9. Overall pass rates at the current cutoff of $\pm 6\%$ have increased since 2008.

Discussion: L. Pogach asked if it is possible to identify the best performing labs on the CAP survey. R. Little and D. Sacks noted that because duplicates were included in the current survey we can get an idea of the within-lab variation of the methods. We cannot, however, identify the individual laboratories. R. Hanas asked what information is provided to participating labs, are CVs as well as SDs provided. The labs now get a graph similar to what R. Little showed indicating the means and ranges for the individual methods as well as the sds and CVs listed in the tables. D. Sacks noted that when labs fail they can see how their method performed compared to other methods on the survey, it is probably in part because of this that there are some poor methods that have disappeared from the survey. W. Herman asked if the high CVs for some methods may be a function of having few users, or are they really just bad methods? R. Little said they seem to be bad methods, D. Sacks added that there are two new methods on the survey with few users that look very good. D. Nathan said a very low number of participating labs can affect CVs.

Rare Variants on the NGSP Web Site: R. Little

- The NGSP website currently lists most commonly used methods and whether or not they have interference from Hb AS, AC, AD, AE, elevated HbF. We continue to update this with new data.
- Recently we published a paper on interference of 49 rare variants using eight methods
- Would it be useful to add this information to the NGSP website along with results from other published data?
- Rare Variant Interference Study (JDST 2015)
 1. 49 rare Hb variants
 2. Trinity ultra2 boronate affinity HPLC and Roche Tinaquant immunoassay were primary and secondary comparative methods
 3. Methods evaluated were G7, G8, D-10, VII Turbo 2.0, enzymatic, and Capillars 2.
 4. Results acceptable if within the 99% prediction interval of the regression line for non-variant samples.
 5. Following manufacturer instructions, would an inaccurate result be reported?
 6. Results showed that in some cases inaccurate results could be reported even if manufacturer reporting guidelines are followed.
- Rare Variant Interference on the NGSP web site
 1. The way in which this information should be presented on the website has not yet been decided
 2. Other published data would be included; there are several papers that include small numbers of variants/methods
 3. Interest: Labs using ion-exchange HPLC or CE are noticing more and more variant peaks on their chromatograms/scans and may be interested in this information
- Other issues
 1. Few samples for most rare variants (some only n=1)

2. Results are not always clear-cut; In some cases a wrong result would have been reported for some, but not all, samples with a given method.
3. Study focused on analytical interference
 - Hb Raleigh is known to have a lower glycation rate compared to HbA
 - Other rare variants may result in altered glycation or shortened red cell lifespan that has not been well studied
4. Would this information be useful for laboratories?
5. Could presenting this information cause confusion?

Discussion: A. Evans suggested putting references for literature regarding red cell lifespan on the web site. R. Little said that the amount of information is often limited with rare variants but we could put links to what is available. W. Herman asked how rare variants are clinically recognized, R. Little said that they are usually clinically silent. In the rare variant study the variants were screened using a beta thal method then sequenced. D. Nathan noted that these unusual variants are often discovered due to HbA1c testing when the result does not match clinical impression and further hematological testing reveals the presence of the variant. R. Little said that is our main concern, variants that can cause misleading HbA1c results. D. Leslie asked what the combined frequency of rare variants is, R. Little did not know, D. Nathan said that it is likely well under one percent. W. Herman said it would be useful to know the frequencies of these variants, where they are found and if they cause discrepancies in HbA1c results. R. Little said it is important that healthcare providers be aware that a HbA1c result that does not match clinical impression may be due to a variant that is affecting the result. L. Pogach said that the NIH clearinghouse has a statement saying that there may be an interference with a HbA1c result that is at odds with clinical impression. Are there any specific ethnic groups that are known to have higher rates of rare variants? R. Little did not think so. R. Hanas noted that there are a number of conditions that can affect red cell lifespan including pregnancy. W. Herman said it would be useful to have some information regarding rare variants on the NGSP web site, others agreed.

CAP Update: D. Sacks

- Variant hemoglobins
 1. CAP works closely with NGSP
 2. Have included variant Hb in samples a few times
 3. Two samples, HbAA and HbAS, with similar HbA1c values (2012B Survey)
- 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 contains 3 samples
 4. Originally artificial, now whole blood
- Enrollment in the CAP survey has increased from ~2500 labs in 1998 to ~3500 (~15% outside the US)
- Regulated Analytes
 1. CLIA mandated 86 analytes (“regulated”) that require PT
 2. Mainly diagnostic tests regularly performed whose results are “important to health care treatment decisions”
 3. HbA1c is not included i.e., not a “regulated analyte”
- Regulated Analytes—Future
 1. CMS (Centers for Medicare and Medicaid Services) and CDC examining list of non-regulated analytes
 2. Plan to add more to mandated list requiring PT – when?

3. Commission on Laboratory Accreditation (LAP) suggested increased frequency of monitoring
4. Selected tests “critical to patient safety”
5. Analytes:
 - BNP/NT-proBNP
 - Troponin
 - HbA1c
6. Increased frequency of PT to 3 mailings per year, with 5 samples in each shipment
7. Require 4/5 correct (i.e., +/- 6%) to pass
8. Optional - labs can choose (either measure 3 as before or all 5)

Discussion: D. Sacks said that most labs in the last survey chose to measure all 5 samples. T. Prestigiacomo asked how the increase from 3 to 5 samples affects lab accreditation. D. Sacks said it does not matter right now since HbA1c is not currently a regulated analyte. Labs still do not like to fail, they have to document the failure and corrective actions taken, plus subsequent inspectors see their past failures. R. Little asked what happens if the lab fails and the analyte is regulated. D. Sacks said that documented corrective action is required, and if the lab fails several surveys they are no longer allowed to measure that particular analyte, at least until they can document that the problem has been resolved. R. Hanas asked if this applies to POC methods, D. Sacks said it does not since these methods are CLIA-waived. J. Fradkin asked if CAP is likely to continue including variants in the surveys, D. Sacks said he would like to, however, labs cannot be graded on these samples. R. Hanas said it would be better if POC methods were required to participate in PT. D. Sacks agreed saying that although some hospital and clinical labs using POC methods choose to participate it is voluntary. A. Albright noted that it depends upon the lab’s licensing, for example if the lab is moderate complexity they are required to participate. D. Sacks said this is true but the majority of POC HbA1c testing is not performed in laboratory settings. G. Parker noted that POC methods are not automatically excluded from the PT requirement, they must have CLIA-waived status. D. Sacks agreed but said that virtually all POC HbA1c methods currently on the market have waived status. G. Parker said that the CLIA waiver means that the method has been designated as being so simple to use that even a home user cannot get an erroneous result. R. Hanas said that we can still ask for the results to be shown. G. Parker said there are moderate-complexity labs using POC methods that do participate in CAP so we have that data. D. Sacks said this tells us how they perform in labs only, not in the hands of users in other settings. L. Pogach asked if there is a way to get larger healthcare systems that utilize these methods to participate voluntarily. A. Albright says this comes down to who will step up and do this. L. Pogach asked if NDEP, ADA and/or others can do something from a public health perspective to encourage this kind of participation. A. Albright said that perhaps one or more of these organizations could publish a statement to encourage this, but is unsure of how effective the action would be. D. Nathan agreed with L. Pogach saying this is a historic moment, we need to pay attention to this issue. R. Little said there is a cost issue, physician offices do not want to pay to participate in CAP. G. Parker said their method has been shown to perform well and she agrees that participation in PT should be encouraged. However, if POC HbA1c testing was not permitted in community health settings it could deny access to the test in underserved populations. D. Nathan responded that this is a debatable point, lack of access may be an issue in other parts of the world but not necessarily in the US. Most importantly the methods need to be good, having access to bad test results can be worse than having none. D. Sacks said some of the POC methods are very good and several perform well in the CAP survey, the problem is not knowing how they are performing in physician offices, are they being used properly? L. Pogach said in the VA POC is rarely used. In terms of encouraging participation in PT HHS needs to be a partner, but the NGSP needs to put out the message to get the discussion going, this is a patient safety

issue. It would be good to know the CMS position, the NIH clearinghouse already has a recommendation regarding this issue. J. Fradkin noted that NIH does not make formal recommendations, NIH provides information based on what others recommend. Regarding CMS, as billing gets away from fee-for-service and moves toward billing for actual care there will be an incentive toward accurate tests, payers will not want to pay for inaccurate testing. It would be good to obtain data, as healthcare changes it will be easier to obtain these kinds of data from provider networks. It was noted that it might be difficult to get simultaneous HbA1c measurements from both a POC and lab method, a study may need to be designed. G. Parker said these are the kinds of data manufacturers must provide to the FDA to get a CLIA waiver. R. Little noted that there are lots of studies comparing POC methods to lab methods, this type of study however does not show the big picture in terms of how all of the different POC methods are performing in the hands of all of the end users. This is why PT is important. R. Hanas noted that POC methods are used in international clinical studies, it is important to know how well they perform in terms of patient care but also when comparing results across different parts of the globe as part of such studies. D. Nathan agreed, studies are typically performed in controlled environments with trained staff, etc., but maybe doctors/nurses could perform the POC testing.

Approval of Methods by the FDA: R. Little

- A Recent FDA Approved Method
 1. 510(k) for a POC method (immunoassay) used for diabetes monitoring.
 2. Package insert states: "Samples containing the following hemoglobin variant have been shown to interfere with this assay: Hemoglobin C, Hemoglobin D, Hemoglobin E, Hemoglobin F(>10%), and Hemoglobin S" "All variant tested were shown to interfere with this device."
 3. Inaccurate results will be reported for all patients with the four most common Hb variants. This translates to a lot of inaccurate results being reported that can lead to improper treatment.
 4. Is there any way of curtailing FDA approval of methods that show such obvious interference where there is no way to detect the presence of the interfering variants?

Substantial Equivalence and HbA1c Assays: S. Beck

- Agenda
 1. Introduction to 510k Program
 2. Performance for Monitoring vs. Diagnostic Claims
- FDA Regulation
 1. Risk Based Regulation- Class I, II, or III
 2. According to section 513(f) of the FD&C Act, a new (i.e., post-amendments) device is automatically in Class III and must undergo premarket approval or reclassification before it can be marketed, unless it is a type of device that was in commercial distribution prior to May 28, 1976, and is Substantially Equivalent (SE) to another such device; or it is within a type of device introduced after May 28, 1976, that has been reclassified into Class I or II and is SE to another device within such classification.
 3. When FDA determines under sections 510(k), 513(f)(1), and 513(i) of the FD&C Act that a new device is SE to a legally marketed (predicate) device, the new device is classified into the same class and subject to the same requirements as the predicate device.
- Premarket Notification: 510(k)
 1. HbA1c assays are considered class II medical devices.
 2. 510(k) submission required of most class II devices.

3. A 510(k) is a premarket submission made to FDA to demonstrate that the new device to be marketed is “substantially equivalent” to a legally marketed device which is not subject to PMA.
 4. Submission has 90 day review clock.
 5. Summary of FDA’s review and basis for decision is posted on the FDA website.
- Substantial Equivalence
 1. What substantial equivalence to predicate device means:
 - Similar intended use
 - Similar performance characteristics
 - Similar fundamental scientific technology
 2. What substantial equivalence may not mean
 - Identical technology
 - Substantial Equivalence is a comparative standard, meaning that you compare the performance of your device to the performance of a predicate device.
 - Effectively, the substantial equivalence process means that as long as a new device performs as well as one already on the market, it is deemed, substantially equivalent.
 - Regulatory Information: Regulation Section and Product Code
 1. 862.1373 –Diagnosing Diabetes (PDJ)
 2. 864.7470 –Monitoring Diabetes (LCP)
 - Diagnostic Claim Indications for Use: A Hemoglobin A1c Test system is a device used to measure the percent concentration of hemoglobin A1c in blood. Measurement of hemoglobin A1c is used as an aid in the diagnosis of diabetes mellitus and as an aid in the identification of patients at risk for development of diabetes mellitus.
 - Diagnostic Claim: Special Controls: In addition to the general controls of the FD&C Act, a diagnostic claim hemoglobin A1c test system is subject to the following special controls:
 1. The device must have initial and annual standardization verification by a certifying glycohemoglobin standardization organization deemed acceptable by FDA.
 2. The premarket notification submission must include performance testing to evaluate precision, accuracy, linearity and interference, including the following:
 - What Additional Performance Data are Needed for HbA1c Devices That Are Currently Cleared For a Monitoring Claim Versus Devices Seeking Both Monitoring and Diagnosis Claim?
 - Similar Studies for Both Claims
 1. Linearity: Evaluate the linearity of the proposed device across the claimed measuring range of the assay; resource: current CLSI EP-6A protocol.
 2. Traceability: Device must have and maintain yearly certification
 3. Stability: Stability Protocols, Value Assignment and Acceptance Criteria needed for review in 510(k) submission.
 4. Endogenous and Exogenous Interferents:
 - Resource: CLSI EP07-A
 - Test a minimum of ten replicates (diagnostic) of each sample, including concentrations of HbA1c of ~6.0% and greater than or equal to 8.0% HbA1c in the test and control samples.
 - Compounds to test include (but are not limited to) bilirubin, triglycerides, total protein, rheumatoid factor, acetylsalicylate, ascorbic acid, and hemoglobin derivatives (carbamylated hemoglobin, HbA0, HbA1a+b, Acetylated Hb, Glycated Albumin, Labile HbA1c)

- Precision
 1. Monitoring: Evaluate low, middle and high decision HbA1c levels
 2. Diagnostic: Evaluate the entire measurement range of the assay to include: 5%, 6.5%, 8%, ~10-12% and greater if needed to cover entire claimed range of assay.
 3. Present results for repeatability, between-run, between-day, and between-lot components for each instrument separately.
 4. Monitoring: Evaluate according to CLSI EP5-A2
 5. Diagnostic: Include a minimum of 3 lots and 3 instruments.
 6. Special Control: Performance testing of device precision must, at a minimum, use blood samples with concentrations near 5.0%, 6.5%, 8.0% and 12% hemoglobin A1c. This testing must evaluate precision over a minimum of 20 days using at least 3 lots of the device and 3 instruments, as applicable.

- Hemoglobin Variants
 1. Special Control: Performance testing must demonstrate that there is little to no interference from common hemoglobin variants, including Hemoglobin C, Hemoglobin D, Hemoglobin E, Hemoglobin A2 and Hemoglobin S.
 2. Special Control: When assay interference from Hemoglobin F or interference with other hemoglobin variants with low frequency in the population is observed, a warning statement must be placed in a black box and must appear in all labeling material for these devices describing the interference and any affected populations.
 3. Variants and Concentrations to be tested:

Hemoglobin Variant	Concentration (%)
A2	6
S	40
C	40
E	30
HbD (Punjab or Los Angeles)	35
F	30

- Method Comparison
 1. Special Control: Performance testing of device accuracy must include a minimum of 120 blood samples that span the measuring interval of the new device and compare results of the new device to results of the standardized test method. Results must demonstrate little or no bias versus the standardized method.

2. Sample distribution

Hemoglobin A1c level	Number of samples	Percent of samples
≤ 5%	5	4.2%
5 – 6%	15	12.5%
6 – 6.5%	30	25.0%
6.5 – 7%	30	25.0%
7 – 8%	20	16.7%
8 – 9%	10	8.3%
> 9%	10	8.3%
Total samples	120	100%

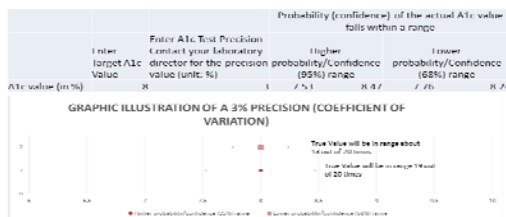
3. Provide results of the regression analysis for this evaluation. Select a regression method that accounts for the random measurements errors associated with your new method and the reference method (i.e., the method used by the standardization program), such as weighted Deming regression or Passing-Bablok regression.
4. Special Control: Total error of the new device must be evaluated using single measurements by the new device compared to results of the standardized test method, and this evaluation must demonstrate a total error less than or equal to 6%.

Discussion: S. Beck noted that the FDA is legally tied to substantial equivalence, as long as a method is shown to be substantially equivalent to one previously cleared for the same intended use they must clear it even if the method being compared to is older technology. However, the diagnostic claim was deemed a new intended use and they were therefore able to raise the bar in terms of requirements for clearance. J. Fradkin asked what good it is to have a black box warning when it is not known that a patient has a hemoglobin variant. S. Beck acknowledged that this is a problem, unfortunately there are predicate devices that showed interference from hemoglobin variants and therefore they have to clear new devices for monitoring that show interference. For the diagnostic claim this is not the case since they were able to adopt new special controls for the new intended use. J. Fradkin expressed concern that devices cleared for monitoring may be used “off label” for diagnosis. L. Pogach said this is an issue of patient safety, the NGSP should put a notice on the web site regarding this and other methods with black box warnings. R. Little said the method mentioned is not widely used and it will be added to the web site since the manufacturer has acknowledged these interferences. L. Pogach said that even if not many people are actually affected there is “proof of concept” in terms of the NGSP public health mission, so it is important that the information is made available. T. Prestigiaco said that he does not defend the performance of this particular method but probably 90% of the methods listed on the NGSP web site have interferences of one kind or another. Several of those devices now have diagnostic as well as monitoring claims. At some point the onus has to be on the laboratory, that is why the black box warnings are there, laboratories that use these devices need to accept the responsibility for knowing the limitations of their method. S. Beck agreed and added that physicians also need to look at the entire clinical picture when interpreting results. R. Little said that the important distinction is not just whether the method has an interference but rather if an inaccurate result would be reported, this is what we focused on with the rare variant study. We need to make it clear when, for a given method and variant, inaccurate results are likely to be reported. T. Prestigiaco said the NGSP already provides information regarding variant interference based on numerous studies, the NGSP probably does not want to go so far as deciding whether to certify methods based on variant interferences. R. Little said this has come up before, one problem is that we cannot possibly evaluate all of the methods that are certified. D. Nathan noted that the FDA issue with substantial equivalence is a problem with medications as well. A. Albright noted that it would literally take an act of Congress to resolve this problem.

A1c Laboratory Reporting and Health Numeracy in the VHA: L. Pogach

- Website: <http://www.qualityandsafety.va.gov/>
- VHA Choosing Wisely Hypoglycemia Safety Initiative (HSI): Foster shared, informed decisions between the clinician, Veteran and family/care givers
 1. National Components
 - Choosing Wisely Task Force
 - Health and Human Services National Action Plan
 - Education efforts and solicitation for volunteers – virtual presentations, QSV site with provider- and patient-facing information, HSI Toolkit
 - Veteran Service Organizations
 2. VISN Champion –Aid in Implementation/Communication--Patient Aligned Care Team: emphasis on shared decision making, health literacy (including numeracy)/Population and POC management
 3. Clinical Reminder designed to gather data, and prompt a discussion with patients about their goals (Clinical Decision Support)
 4. VISN Data Warehouse report to generate lists of high risk patients and allow providers facilities to track results

- 5. Template and/or Reminder
 - o Hypoglycemia screening questions and section to document care plan
 - o Responses generate health factors
- 6. Meaningful Use Stage 3 Informatics
 - o Point-of-care: CPRS Reminder
 - o Clinical Decision Support
 - o Registries
 - o A1c range calculator (under development)
- NIDDK DIABETES CLEARING HOUSE
 1. Interpreting Laboratory Results
(<http://diabetes.niddk.nih.gov/dm/pubs/comparingtests/>)
 2. When interpreting laboratory results health care providers should
 - o consider that all laboratory test results represent a range, rather than an exact number
 - o be informed about the A1C assay methods used by their laboratory
 - o send blood samples for diagnosis to a laboratory that uses an NGSP-certified method for A1C analysis to ensure the results are standardized
 - o consider the possibility of interference in the A1C test when a result is above 15% or is at odds with other diabetes test results
 - o consider each patient’s profile, including risk factors and history, and individualize diagnosis and treatment decisions in discussion with the patient
- VHA Laboratory Result Comment
 1. In support of the VA’s new “Choosing Wisely” –Hypoglycemic Safety Initiative (CW-HSI), Pathology and Laboratory Medicine Services (PLMS) have been asked to make some additions to our hemoglobin A1C test reports to complement the materials Veterans and providers are receiving.
 2. We are being asked to append the following comment to all of our A1c reports (including both lab and POC tests):
 - o “An understanding of A1C test result accuracy is essential if clinicians are to interpret results for screening and for treatment goals and options through the process of Shared Decision Making.
 - o Contact <include instructions on facility’s/laboratory’s preferred method of communication> for performance characteristics of this assay.”
 3. Citing performance measures or non-VA decision support comments, (such as ADA recommendations) should be removed as may not be consistent with the individualized patient target approach advocated by the VHA Campaign
 4. Beta spreadsheet:



- CMS Public Comment on A1c Accuracy and A1c Performance Measures

1. The Centers for Medicare and Medicaid Services entered a public comment to NQF recommending that the 0729 Composite measure <8% measure be retired.
 2. "A safer and more patient-centric proposal could consider an A1c level <8% units limited to adults <75 years if accompanied by exclusion criteria: a) the absence of major co-morbid disease that reduces life expectancy, b) the absence of co-morbid disease that increases the risk of adverse drug events (not limited to hypoglycemia), and c) insulin use. Over-treatment for all patients should be avoided."
 3. CMS also notes that A1c levels delineated above are contingent on the use of levels obtained at NGSP certified laboratories and not via point-of-care (POC) systems because of accuracy concerns. The NGSP permissible coefficient of variation allows a single A1c test to have a range of +/- 6% (relative) www.ngsp.org.asp. POC-testing is less accurate. Inaccurate results can result in inappropriate intervention and patient harm.
- Recommendations
 1. Recommend an ad-hoc committee, chaired by Chair, Clinical Advisory Committee, to review federal agency and private sector policy recommendations that are dependent upon the accuracy of A1c measurement, including accuracy of Clinical Laboratory and POC for performance measurement.
 2. Recommend an ad-hoc committee to develop an education program on A1c measurement with modules for health systems, laboratory directors, patients, educators.
 3. Recommendations would be reviewed by membership by email and non-F2F conference calls as necessary.

Discussion: L. Pogach noted that there is much misinformation regarding treatment goals, many physicians are misinformed about HbA1c target levels and do not understand the concept of results representing a range rather than an exact number. Overtreatment can lead to hypoglycemic episodes which can have serious consequences for patients. Many VA patients in particular have co-morbid conditions which need to be considered. The VA is no longer recommending specific HbA1c targets like <7%, we are also developing a range calculator to help healthcare providers understand the concept of results as a range based on the variability of the assay method. For example, Coumadin results are interpreted based on a range. D. Nathan said he is sympathetic to the notion that point estimates are just that, we are delusional in thinking that reported lab test results represent exact numbers. However, in terms of patient safety a concern is that the range goes both ways. For example if the actual reported number happens to fall on the low end of the range the range itself will extend even lower, potentially leading to unintended consequences for safety. A second issue is that the DCCT data were generated using high quality assays and the resulting treatment goals have tangibly improved the health of patients with diabetes even taking into account safety considerations. Reporting results as a range may be mathematically accurate but it could cause confusion and chaos for physicians and patients. L. Pogach responded that there are many people in the US that are sick and/or elderly for which a goal of 7.0% HbA1c is nowhere near appropriate. We have data showing that hypoglycemia is now a bigger problem than hyperglycemia. Of the people in the VA who are 65-75 years of age and have chronic co-morbid conditions, about 2/3 have HbA1c <8% and about half of those have HbA1c <7%. There is no doubt there is an epidemic of hypoglycemia, HHS has expressed concern, the Medicare Inspector General has reported on overtreatment in nursing homes. A goal of <8% may be appropriate for seniors who are relatively healthy, the problem is that after a long period of undertreatment we have gone too far the other way. We have to recognize that there are many sick elderly people who are overtreated and conversely there are young healthy people that are not treated adequately. D. Nathan said that no one disagrees with some modification of goals on an

individual or even a group basis, but that is different from changing the entire concept of how results are reported which may result in unintended consequences. L. Pogach said from the VA and HHS perspective reporting results as a range is appropriate. R. Cohen noted that vast majority of people with severe renal disease have a different relationship between blood glucose and HbA1c, some with HbA1c values of 6.5% or 7.0% will be at risk of hypoglycemia while others will not. There are a lot of people that do not know how to deal with patients with co-morbid conditions where there can be a “mismatch” of results, that gets lost in these discussions about specific goals, etc. L. Pogach said the accuracy of assays is an important issue. There are very accurate assays, but as long as we have assays such as some POC that are not as good, and physicians do not understand the potential inaccuracy of these tests, there is risk of overtreatment. E. Koller said that from the CMS perspective, they want the right treatment for the right patient at the right time. We are very concerned about the accuracy of HbA1c assays, particularly POC assays, not only in terms of direct patient care but also how the results are used in performance measures. Sometimes healthcare providers end up treating a number instead of the patient. We want to see accurate HbA1c assays, and also make sure that physicians have some understanding of the assays and how they are applied in clinical care. E. Selvin said that the issue of variability in lab tests is universal, HbA1c is one of the best tests, why is it being singled out? Is there discussion of reporting other lab tests as a range? L. Pogach said it is not being singled out. This is the NGSP, also there is the HHS National Action Plan and CMS statement. I would like to extend this to other analytes. Years ago things that affect the interpretation of results like analytical variation, ethnic differences, etc. were widely discussed but it’s a lost art, we’ve become obsessed with specific targets, performance measures, etc. E. Selvin and D. Nathan asked if there are any data supporting the notion that reporting results as a range improves patient care. L. Pogach responded that there are data showing that for example treating renal patients with erythropoietin based on a number (Hb results) can cause harm. D. Nathan said you cannot fix bad care by changing the way lab results are reported. D. Leslie said that the concept of a range is important and many physicians do not understand it. Physicians do need to be educated in this concept, however, do we know that reporting individual results as a range will change physician behavior? L. Pogach responded that the VA can use the data they have available to monitor this in real time. R. Little asked if the VA could therefore be a test case for this concept, L. Pogach said no. The VA is moving ahead, the relevant government agencies have signed off. The ADA and NIDDK have been pushing the target of 7 which has resulted in overtreatment, the VA and other agencies are simply swinging the pendulum back the other way. D. Leslie noted that the hypoglycemia problem has been recognized and the recommendations regarding targets have already been changed, we now need to do analysis with the changed targets. L. Pogach said the VA has this but he cannot share it. It is up to the NGSP to decide whether and how to be engaged in this issue. D. Sacks said with cystatin C, for example, there can be a 20% difference in results between instruments. HbA1c is one of the few analytes that is standardized, why doesn’t the government focus efforts on standardizing/harmonizing other analytes rather than “fine-tuning” a test that is already standardized? L. Pogach said that not every test is used as a performance measure. For example, the VA has already done away with targets for LDL as it incentivizes going below the target level. The goal is patient safety. R. Little asked what the NGSP should do, L. Pogach said get a gentle message out that everyone can agree to, it could be done by the CDC or NGSP.

R. Little showed the former and current clinical use page from the web site. Based on concerns expressed by L. Pogach we have made some recent changes to better reflect the current recommendations, including links to other recommendations in addition to ADA. Proposals for further changes, including links to the National Diabetes Information Clearinghouse and possibly the new NDEP guiding principles, were presented. L. Pogach said the proposed changes represent a good start, especially linking to NDIC. R. Little said the proposed changes will be discussed at the NGSP Steering

Committee meeting at the AACC. E. Koller said that neither the VA nor CMS signed off on the last NDEP recommendations due to concerns about the goals presented, this should be considered when deciding what to put on the NGSP web site. R. Little said that when the minutes of this meeting go out they will be sent to former as well as current participants, she will ask for additional comments and then present everything to the NGSP Steering Committee.

A. Albright said there had been good discussion of issues surrounding POC and the desire for more PT in clinical settings. We all want safe treatment of diabetes where hypoglycemia is minimized while maintaining control to the extent possible. We all need to participate in the ongoing discussions. She thanked everyone for their participation, the meeting was adjourned at 10:00 AM.

Minutes prepared by Curt Rohlfing 07/10/2015.