Meeting of the NGSP Steering Committee
Minutes
Sunday July 28, 2013 10:00 AM – 12:30 PM
Hyatt Regency Houston, Houston, TX

Participants:

*David Sacks —NIH, Chair, NGSP Steering Committee
*Randie Little—Univ. of MO, NGSP Network Coordinator
*Phillip Gillery—American Memorial Hospital (FR), IFCC Scientific Division
*Garry John—Norfolk and Norwich University Hospital (UK), Chair, IFCC Integrated Project on HbA1c (by phone)
*Curtis Parvin—Bio Rad Laboratories
*Scott Reutten—Abbott Diagnostics
*Christine Flandre—Sebia
*Michael Steffes—University of Minnesota
*Hubert Vesper—CDC
*Cas Weykamp—Queen Beatrix Hospital (NL), IFCC Network Coordinator
***Member of the NGSP Steering Committee**

Susanne Adam—Roche Diagnostics
Shawn Connolly—Univ. Of MO, NGSP
Tomoko Fujiyoshi—ReCCS Japan
Tony Prestigiacomo—Bio-Rad Laboratories
Violeta Raneva—ReCCS Japan
Curt Rohlfing—Univ. of MO, NGSP
Ben Starling—Trinity Biotech
Alexander Stoyanov—Univ. of MO

Steering Committee members not present:

Robert Cohen—University of Cincinnati
W. Greg Miller—Virginia Commonwealth Univ.
David Nathan—Massachusetts General Hospital
Elizabeth Selvin—Johns Hopkins University

1) **Welcome and Introduction—David Sacks, Chair, NGSP Steering Committee**
D. Sacks welcomed those in attendance, those present introduced themselves.

2) **The 2012 Steering Committee minutes were approved by the members present.**

3) **NGSP Progress Report—Randie Little , NGSP Network Coordinator**
- NGSP Network Monitoring
  - The PRLs and SRLs continue to demonstrate excellent comparability.
  - Monthly between-lab CVs for the NGSP network were <2% over the past year.
- Certification
  - The number of certified methods and laboratories continues to increase.
  - We are certifying more variations of the same method but also new methods, especially from Japan.
  - We are certifying more Level I and II laboratories, many of the Level I labs are part of international chains that are presumably performing clinical trials.
  - The Level 1 labs tend to use a small number of methods, mostly ion-exchange HPLC but some immunoassay methods as well.
- CAP Data
  - The CAP data show much improvement in the comparability of HbA1c results in the field between 1993 and 2013.
  - 2013A Survey
    - The method-specific means were all within 0.38 at all levels. Except for 2 methods, bias was within 0.3% HbA1c.
    - Method-specific, between-laboratory CV's ranged from 1.2% to 8.2%! All but 2 methods (<30 participants) had CVs below 5% for all 3 HbA1c levels.
    - Over 98% of laboratories were using methods that had between-lab CVs<5%. About 50% of labs use methods with between-lab CVs <3% at all three levels.
    - There appears to be room for improvement but it is getting better
    - Between-lab CVs by method type
      1) CVs for the ion-exchange methods were ≤3%.

2) Several immunoassay methods also show very good performance with low CVs while others do not perform as well.
3) CVs for the POC methods were pretty good but only a few POC methods are represented on the survey.

- Pass Rates
  1) For the low and middle HbA1c levels the ion-exchange and boronate affinity methods all showed pass rates over 90%.
  2) Pass rates for some immunoassay methods were >90% while others had lower pass rates.
  3) Pass rates:

Specimen	NGSP Target (% HbA1c)	Acceptable Range **(±6%)**	Pass Rate % (Low/High)	Cumulative Pass Rate %
GH2-01	7.11	6.6-7.6	77.5/100	95.3
GH2-02	9.32	8.7-9.9	80.0/100	94.3
GH2-03	6.07	5.7-6.5	63.6/100	93.4

- Decrease in all-method CVs over time
  1) All-method CVs were ~5% in 2000
  2) The overall trend has been downward
  3) All-method CVs have hovered around 3.5-4.0% on the last several surveys.
  4) All method CVs for the 2013A survey were 3.9%, 3.5% and 3.3% at the low, middle and high levels respectively.
  5) Our goal is to consistently achieve all-method CVs<3.5%

Discussion:

Network Labs

D. Sacks noted that the CVs between the SRLs are considerably lower than for the PRLs. R. Little said that when the CPRL started it was the most precise method available but commercial methods have greatly improved to the point where the best ones now have better precision than the CPRL. M. Steffes asked how the PRLs are calibrated. R. Little and C. Weykamp said that all of the PRLs are using the same hemolysate calibrator but the SRLs do not all use the same calibrators.

Methods

H. Vesper and M. Steffes asked about the POC method that appears to have very large biases and CVs in the first CAP graph, R. Little noted that this method has a matrix interference from EDTA blood. C. Weykamp said that among the methods the Tosoh HPLC methods still have the lowest CVs but have shown a high bias for the last few years, this is true in Europe as well as in the U.S. R. Little said that this has been noticed but the manufacturer has not yet found the root cause for this. This has not been a problem for the SRLs using Tosoh methods since they use their own calibration schemes rather than those of the method manufacturers. S. Reutten said that assays have improved over the years but recently based on the all-method CVs the improvement seems to have leveled off, as the criteria are further tightened we should see further reductions in variability. R. Little replied that we are probably getting close to the performance limits of some of the assays, we have seen some methods that do not perform well drop out over the years, it is an evolutionary process. Part of our goal is to see methods that cannot be made to perform well be phased out. However, some methods may be very good but have issues with bias.

Hemoglobin Variants

H. Vesper asked if there have been improvements with assays in terms of interference from variant hemoglobins. R. Little responded that over the years manufacturers of some assays that previously showed interference have successfully addressed this issue by changing their reagent formulations. With HPLC methods the overall situation has stayed about the same, since we have tightened our acceptance criteria for interference some methods that passed the old criteria now show significant interference based on the new criteria. Most of the new assays coming out, at least the ones that will be most widely used, will likely not have interference from common variants or at least will indicate that the interference is present. S. Reutten

noted that assays where variant interference is an issue will not be able to get a diagnostic claim. R. Little said there are many assays that are not available in the U.S. and we do not know much about interferences with some of these methods. For the HPLC methods most of them will probably continue to have interference from at least some variants, but since the interference can generally be seen it is not a problem as long as manufacturer recommendations are followed and the affected HbA1c result is not reported. H. Vesper asked if the FDA is essentially forcing assays to be interference free, R. Little replied that this is true only for the diagnostic claim, we are not sure if they will eventually require assays used only for monitoring to be free from variant interference as well. CAP included a heterozygous HbS in one of the GH2 surveys a few years ago and it showed more variability than the non-variant samples; some methods may be affected by the presence of a variant even if the differences are not large enough to be "clinically significant". C. Flandre asked if CAP plans to do this again in the future. D. Sacks responded that CAP did a voluntary challenge that included a HbC trait sample but very few labs participated (<25). The problem with including variant samples in the GH2 survey is obtaining a sufficient quantity of sample since the survey includes several thousand labs. CAP included a HbS trait sample in the GH2 survey a few years ago and in 2012. CAP will likely do so again, but for other variants it is very difficult to obtain a sufficient amount of blood.

4) Should we change the NGSP Certification Criteria?—Randie Little

- CAP tightened their acceptance limit from ±7% to ±6% for 2013, should the NGSP certification acceptance limits be tightened as well?
- Currently 37/40 results have to be within ±7% of the NGSP SRL (38/40 for Level 1 labs), the proposal is to tighten the limits to 37/40 within ±6%.
- NGSP method certifications January-June 2013
  - Of the 126 methods that applied for certification for Jan-June 2013, 10 methods (from 7 manufacturers) failed the current ±7%.
  - 21 methods (from 10 manufacturers) would have failed ±6%.
- Do we change to ±6%, and if so when should we do so?

Discussion

Methods that fail certification

S. Reutten asked if we have enough data to know if the 10 methods that failed the current criteria are representative of a whole year. Do we know how many methods previously failed the old NGSP criteria? R. Little said that many of the methods that failed in 2013 were new methods that the manufacturers were certifying for the first time, in some of these cases the failures were likely due to calibration issues. Others were methods that have been around for a while and had certified before but had always been borderline. B. Starling asked what proportion of methods that failed were POC, R. Little said approximately half or a bit less. D. Sacks asked if the failed methods are widely used. R. Little said there are only two methods out of the 21 that failed ±6% that actually appear on the CAP survey and they are both part of larger method groups that are lumped together; the other methods are not widely used and some are not even sold in the U.S.

NGSP vs. CAP criteria

M. Steffes asked where CAP plans to go with their criteria, D. Sacks said they will likely stay with ±6% for a while. C. Weykamp noted that CAP uses pooled samples and target values assigned by the NGSP network while individual samples and target values from a single SRL are used in NGSP certification; this makes the uncertainty larger for NGSP certification vs. CAP. R. Little said this is true but the uncertainties were taken into account in C. Parvin's calculations comparing the criteria. R. Little asked C. Parvin if he expected the proposed 37/40 ±6% NGSP criteria comparison to CAP ±6% to look the same as the 37/40 ±7% NGSP vs. CAP ±7% comparison. C. Parvin responded that he would expect them to look very similar but would not know for sure until he performed the calculations. He further noted that his calculations were based on passing all three samples on the CAP survey, compared to 2/3 passing on the survey (which is what CAP actually requires) the NGSP criteria are much stricter. C. Weykamp asked if the performance of methods on the CAP surveys corresponds with their NGSP certification performance. R. Little said she looked at this, most methods show roughly comparable performance on both but we do see differences. Sometimes, for example, one method shows consistent bias on the CAP survey that we do not see when the

method performs NGSP certification. Some of the POC methods have many lots of reagents out in the field, sometimes they fail certification and do not find any specific problem and want to attempt certification again. We now require these methods to re-certify using three lots but we do not know what goes into selecting these lots. H. Vesper noted that the CAP survey is assessing performance at the end-user level while certification performed by the manufacturer is a step higher up the metrological chain. It therefore does not make sense to have more stringent criteria for the former compared to the latter, the certification criteria should therefore be changed to be in line with CAP. However, we need to keep in mind that CMS is revising their list of regulated analytes, we do not know if HbA1c will be added to this list but if it is CAP and other PT providers may have to revise their criteria, up or down, in order to comply with regulations. R. Little asked how CMS decides their criteria, H. Vesper said he does not know but CMS has contacted PT providers including CAP for input regarding requirements for regulated analytes. R. Little asked if CMS could say the requirement is, for example, ±8%. H. Vesper said it is possible but tightening the NGSP criteria to ±6% is the right thing to do, CMS is a separate issue that will have to be dealt with when it comes up. G. John asked if we know the relationship between ±6% for NGSP and CAP, it is important to know this. D. Sacks said C. Parvin will be looking at this. C. Parvin agreed to do the calculations comparing NGSP 37/40 ±6% vs. CAP ±6% 3/3, also 36/40 and 38/40 ±6% and CAP ±6% 2/3. R. Little said we may need to consider tightening the quarterly monitoring criteria for Level 1 labs as well.

Other PT schemes

M. Steffes asked G. John what they see on the UK PT programs. G. John responded that it is a voluntary scheme, they see CVs <3.5%. This includes about 400 labs, there is very little POC, almost 100% are clinical laboratories. R. Little asked what methods are widely used on the UK survey. C. Weykamp said there are a higher proportion of HPLCs compared to CAP, many are Arkray. G. John added that there are two surveys, UKNEQAS uses fresh whole blood, WEQAS uses both lyophilized material and fresh blood. Each sends out three samples per month. R. Little said it would be good if CAP could do more frequent surveys, C. Weykamp asked what it costs labs to participate in CAP. D. Sacks said the problem is that CAP is not the only PT provider, if CAP tells labs they have to pay more to do a survey every month they will likely utilize another provider that does not use fresh blood. R. Little noted that CAP has another survey (Excel), but it does not provide any additional useful information regarding the performance of POC methods.

Time frame for change in criteria

D. Sacks asked manufacturers how much notice they would need if the certification criteria are tightened. S. Reutten responded that since CAP and NGSP have both been tightening their criteria there is a heightened awareness that products need to be continuously improved, but we can only respond so fast. We do not have enough data with the tightened criteria, we need another year. C. Parvin noted that the NGSP criteria are tougher on bias, so methods that have low CVs but a high bias will have a tougher time passing NGSP vs. methods that may have a higher CV but minimal bias. C. Flandre said we need to be cautious, we need to look closely at methods that would be excluded by tightening the criteria and be sure that they are not too widely used, this could cause problems. R. Little responded that this should not be a problem, at least in the U.S., because these methods are not widely used, many are not even sold in the U.S. We should not wait another year to decide on tightening the criteria since we will have to give manufacturers additional time. D. Sacks asked what additional information is needed for the committee to decide. S. Reutten said we need to see progressive improvement of methods, we need to see more data, D. Sacks replied that R. Little can just go back further to see which and how many methods failed the previous and current criteria. B. Starling asked if the NGSP has considered different criteria for POC vs. laboratory methods. R. Little said that this has been discussed before, it was decided the criteria should be the same for POC and lab methods since the results are generally used in the same way.

Analytical Requirements: Diagnosis vs. Monitoring

S. Reutten asked what the medical need is: is 4% the end goal, 2%? We would like to improve the product as much as possible but it would be good to know what the final goal is. R. Little said CAP seems to be pushing faster than NGSP, D. Sacks said it is difficult to define exactly what the medical need is. Are the medical needs for monitoring and diagnosis the same? With diagnosis bias becomes extremely important, a slight bias can increase the prevalence of diabetes considerably, you could label millions of people with diabetes who may not have it which has huge implications. We cannot get clinicians to give us a clear

answer regarding medical need. Intra-individual variation is frequently used to calculate required accuracy for analytes, but for HbA1c it is very small and assays will likely never achieve accuracy requirements based on this parameter. R. Little said we are also limited by the accuracy of the network, we cannot make limits tighter than the methods used in the network. C. Flandre asked if we are looking for more accuracy for diagnosis vs. monitoring. R. Little responded that accuracy is critical in the diagnostic range, this was one of the reasons for NGSP going to criteria based on a relative percent since this requires better performance in the lower end of the HbA1c range. It is not really different from any other diagnostic test in that if the accuracy is off the percentage of people diagnosed can change significantly. C. Flandre said the impact from the patient point-of-view is very significant because it means receiving treatment or not. R. Little said for monitoring it is not as clear cut, there is a progression, even for treatment there is pre-diabetes as well as diabetes. S. Reutten asked if diagnostic and monitoring assays need to have the same performance, M. Steffes said yes. R. Little said they have to be the same for NGSP and also the CAP survey since we cannot readily distinguish how the results are being used. D. Sacks added that although only one assay is now officially approved for diagnosis, physicians send samples to the lab without any idea what assay the lab is using and conversely the lab does not know if the results are being used for monitoring or diagnosis. Therefore the criteria must be the same for both. S. Reutten noted that this means that manufacturers who want to have a monitoring-only device is going to nonetheless be driven to approve assay performance. M. Steffes said the committee that approved HbA1c for diagnosis did not distinguish between monitoring and diagnosis. Most of the discussion concerned how well the assays are aligned. C. Weykamp asked if any manufacturers will actually market an assay for only monitoring. S. Reutten replied that there are already assays that make only that claim, currently only the Roche assay has approval for a diagnostic claim in the U.S. C. Weykamp said that it is complicated to make the distinction, if the criteria for diagnosis are more stringent than for monitoring then all assays should have to meet the criteria for diagnosis. R. Little said it is not clear at this point whether FDA will eventually apply the diagnosis criteria to monitoring as well.

5) NGSP/IFCC Relationship: Randie Little

- Master Equation
  - NGSP (%)=0.0915 IFCC (mmol/mol) + 2.15.
  - Monitored twice yearly with 5 pooled samples.
- There has been a trend over the last 3 exchanges where the NGSP network has moved progressively higher compared to the IFCC network.
- The last exchange showed NGSP =7.15% HbA1c at IFCC=53mmol/mol compared to NGSP=7% HbA1c for the original ME.
- This difference was outside the confidence interval for the relationship.
- The long-term QC samples that have been analyzed by the NGSP SRLs quarterly since 2009 do not show any significant trends.
- The IFCC network runs previous calibrators and samples in each exchange and they do not see any apparent trends.

Discussion

C. Weykamp noted that based on the 90% confidence interval the relationship in the last exchange is statistically significantly different although the actual difference is small. C. Rohlfing noted that a 95% interval would be wider. C. Weykamp said the IFCC also compares with the Japanese and Swedish systems and these relationships were within their confidence intervals. V. Raneva said the IFCC values for the JDS 2002 samples in the last exchange were about 3% (relative) lower than their original assigned values, this may be why the NGSP values seem higher relative to IFCC. C. Weykamp said the IFCC checks (previous calibrators and samples) did not show this trend. The JDS samples are 12 years old, also the IFCC network mean was very slightly lower than present at the time of the original value assignment. R. Little noted that the actual differences are very small. C. Weykamp asked about the trend in the normal range in the NHANES study, R. Little and M. Steffes said that was performed by a single SRL. The shift was small, ~0.1-0.15% HbA1c, when we investigated we could not find anything in the NGSP monitoring or QC data that showed a shift, this may have been due to inadequate sensitivity to detect such a small difference. M. Steffes added that the shift caused an apparent shift in the frequency of pre-diabetes and

diabetes, it is a case of using numbers beyond their meaning. R. Little said this is the problem with using exact cutoffs. M. Steffes said that the NGSP is based around the same CPRL with the same resin and the same calibrator over a very long term. If there is a small amount of deterioration this might cause a slight shift in the system. R. Little and C. Rohlfing said the SRLs are somewhat independent from the CPRL, although we do make sure they do not drift too far apart. H. Vesper noted that the statistical limits are based on the particular survey and based on a 90% CI there is a 10% chance of going outside the limits. T. Prestigiacomo asked if it would be helpful to get data from the manufacturers. We run correlations internally using both IFCC and NGSP value assignments, we see differences, the data might be useful. H. Vesper asked if a previous set of samples could be re-analyzed to determine if the bias in the relationship is consistent. Is there a set of 2011-2 samples left that could be re-analyzed. R. Little said re-analysis by the IFCC network would be very time-consuming, C. Weykamp noted that one previous sample from 2011 was analyzed in the last exchange and the result was 35.3 mmol/L vs. 35.8 mmol/L in the original study. R. Little and C. Rohlfing asked if there is still whole blood available from the 2011 study that has not been thawed so that the NGSP SRLs can analyze these samples, C. Weykamp will check.

6) Manufacturer Certification Failures: Randie Little

- July thru Dec 2012, Jan thru July: 21 methods (from 10 manufacturers) failed certification.
- Seven were POC methods.
- All manufacturers were given the NGSP protocol information on what they needed to do to re-certify assuming their methods were already on the market.
- The NGSP protocol states: "In the event that a method fails certification, the manufacturer must determine and document the reason(s) for this failure prior to a subsequent attempt to obtain certification. Subsequent changes to the method must be documented and there must be a description of how these changes will be applied to end-users. In the case of a point of care method, any adjustment in calibration or other change must be documented and certification testing must be repeated with 3 different lots of reagents."
- Of the 21 methods that failed, seven subsequently passed certification
- No further correspondence for 10 of the 21 failed methods (6 manufacturers)
- One method failed again twice (it was unclear whether or not the method was on the market at the time)
- Of the seven of the methods that subsequently passed
  - 3 were POC and the manufacturers performed testing with 3 lots.
  - One was claimed to be due to instrument error (due to instrument move) and possibly sample handling issue.
  - One claimed bias due to calibration factors; changed the way value is assigned to bulk reagents.
  - One reported revised internal product specifications.
  - One had not been sold in the US or Europe (but possibly Japan) and did not give any explanation.
- Issues:
  - Should there be a time limit to attempt certification again after a failure if there is no specific cause determined and no corrective action taken?
  - Based on e-mail correspondence, it was decided that they could re-certify but they needed to wait ~6 months. Should this be 6 months from their previous certification attempt? Or 6 months from when their data was sent or analyzed?
  - One re-certified without explanation (i.e. they slipped thru); e.g. some methods are certified by different manufacturer/ distributors and it is difficult to keep track.

Discussion:

S. Reutten asked how the Steering Committee decided on 6 months. If the manufacturer does not do the right things (corrective action, effectiveness check) it could be much longer than 6 months, the timing would seem to be irrelevant. D. Sacks responded that 6 months is a minimum that was decided based on e-mail correspondence among the committee. R. Little said it was decided that manufacturers in the situation where they fail certification and no specific cause can be determined should get another chance but there should be a minimum time between attempts. Sometimes the

explanation for the failure can be unclear. Is it OK if there is no explanation and 6 months later they pass? Should we wait 6 months regardless of if there is an explanation? B. Starling said that for a new device coming on the market 6 months seems reasonable. However, if there is a scenario where a method that has been previously certified fails for whatever reason, is there a case for allowing an immediate re-certification attempt? R. Little said it is sometimes hard to know if the method is on the market, it may not be in the U.S. but available elsewhere, or it may be sold by a distributor under another name. Another concern is that if a manufacturer method fails under presumably the best conditions then subsequently passes, what does this say about how the method is performing in the hands of end-users? C. Flandre said we need to distinguish between the distributor and manufacturer, R. Little said this is sometimes difficult, that manufacturer may not even know that the distributor is also selling the product. C. Flandre said the manufacturer is responsible for the quality of the product in the hands of end-users, if there is misuse of the product or the transportation conditions are not right due to the distributor, the manufacturer must take action. R. Little said there was a recent case where the manufacturer did not know that a distributor was certifying the same product. H. Vesper said there are two sides, one is that the manufacturer needs time to figure out what the problem is, make adjustments and do the proper documentation. On the other hand the NGSP has to have a limit, otherwise a manufacturer can continuously re-apply until they finally pass by chance. Also, the NGSP workload in terms of processing the certifications needs to be considered. D. Sacks asked what the implications are for manufacturers when a method fails. If the problem is solved in one week, what are the implications for having to wait six months to re-apply? S. Reutten said NGSP certification is required to obtain a diagnostic claim from the FDA, but if a product is not certified the manufacturer should know this prior to launch of the product and should investigate to determine the cause. C. Flandre suggested consideration of a maximum rather than minimum limit, if the manufacturer finds the cause of the problem quickly and documents corrective action they could re-apply immediately, even when performed by the manufacturer there is always a possibility of instrument failure. Six months could then be a maximum time allowed for the manufacturer to fix the problem and re-apply. G. John suggested that the time frame is irrelevant, the major issue is that all corrective actions must be documented thoroughly, some companies may be able to do this quickly while others may take longer. All changes need to be documented and the robustness of the system ensured. T. Prestigiacomo noted that due to regulations, if a manufacturer certification fails and cannot re-certify for six months the manufacturer may have to pull the method from the market because the claim is that it is NGSP-certified. Additionally, if the manufacturer is unable to determine the root cause of the problem and take corrective action within 6 months the method probably should be pulled from the market. C. Flandre agreed and reiterated that there should be a maximum time allowed for correcting the problem. R. Little said there should be a minimum time as well. C. Weykamp noted that if a method fails and is not re-certified for 6 months it would not meet ADA requirements. R. Little cited a recent case in which a company outside the U.S. attempted to certify their method and failed. They re-analyzed the samples with a different calibration and passed, so they want to make another attempt using this new calibration. I explained that they also have to explain how this will affect their customers, they need to explain how the change will translate to end-users. D. Sacks said this is a clear-cut case where the company did not adequately determine the cause of the problem and therefore should not be allowed to attempt another certification. What manufacturers are saying is that putting a blanket six-month moratorium on a company if they do due diligence and figure out the problem in a few weeks is not fair. S. Reutten said the if the method failed and could not re-attempt certification for six months, even if the company investigated and corrected the problem within a few weeks, the method would effectively be off label claim for six months which could mean pulling it from the market. C. Flandre added that normally when something goes wrong with a method the manufacturer gets indications from sources including customers and may already be working on the problem based on this information. S. Reutten said the company should also know internally that there is a problem, T. Prestigiacomo said NGSP Level I labs will tell the manufacturer if they see a problem. R. Little asked if there should be no minimum and no maximum, D. Sacks said there is probably no need for a maximum since method certification expires after one year. Each case needs to be evaluated based on its merits. S. Reutten agreed saying that we need to emphasize to manufacturers that the NGSP will be carefully evaluating due diligence in these cases. There was a consensus that there will be no minimum or maximum time limit for re-attempting certification after a failure, but adequate

documentation of corrective action and explanation of how the changes will impact end-users is required.

7) Clinical Advisory Committee Meeting Update—David Sacks

- The CAC is composed of representatives from major clinical diabetes organizations. The purpose is to facilitate interchange between these organizations and the NGSP.
- The CAC met at the ADA in June 2013.
  - R. Little presented an update on NGSP progress.
  - Glycemic control in patients with renal failure was discussed.
    - Mayer Davidson spoke about a recent study evaluating glycated albumin and HbA1c as measures of mean glycemia in these patients.
    - Ian de Boer of EDIC discussed a study being planned to look at glucose variability in patients with diabetes and ESRD that will include CGMS measurements along with other measures including HbA1c and glycated albumin.
- Mark Gusack of the Veteran's Administration gave a presentation on how the VA is planning to report HbA1c results with additional information on accuracy and precision.
- A summary of findings from a study conducted by Eric Kilpatrick, et al. looking at the impact of changing from NGSP to IFCC numbers in the UK was presented (the manuscript is in-press and will be published in Clin Chem).
  - There has been controversy over whether switching the number scale for reporting HbA1c results can adversely impact glycemic control in patients with diabetes.
  - The UK dual reported HbA1c results (IFCC and NGSP) before switching to only IFCC.
  - The group looked at mean HbA1c results from the diabetes registry in Hull (n>20,000) for the year before and after the switch to reporting IFCC results only.
  - The data showed no difference in mean HbA1c results before and after the switch indicating that there was no impact on glycemic control.
- Findings from another study (unpublished) from Sweden looking at the impact of changing the reporting scale for HbA1c were presented by Ragnar Hanas.
  - The n's were small, the findings are preliminary
  - Study of patients with Type 1 diabetes.
  - Results showed a slight increase in HbA1c in adults after the switch to IFCC numbers and a slight decrease in pediatric patients.

Discussion:

D. Sacks noted that R. Hanas and D. Leslie of the UK indicated that patients are still asking for results in % and asked C. Weykamp if they see this in the Netherlands. C. Weykamp responded that this is always some opposition to any change, but they are not seeing this in the Netherlands. Proper education is very important. D. Sacks reiterated that the findings of Hanas et. al are preliminary and there will be more studies looking at the impact of changing the numbers on glycemic control. One strength of the Kilpatrick study was that all of the assays were performed in a single lab. S. Reutten asked what the significance of the findings are given that it is just a change in the number scale. R. Little and D. Sacks said that it does not just involve the physicians but also how patients interpret the results.

8) IFCC Integrated Project Update: David Sacks

- The IFCC IP essentially replaced the IFCC Working Group on HbA1c Standardization.
- The purpose of the IFCC IP is to establish an interface between the IFCC and clinical organizations and end-users, and also act as an advisory board to the IFCC laboratory network.
- The group met in May at Euromedlab.
  - A survey has been developed to gather information on how HbA1c is used worldwide.
  - Hopefully the results of the survey will be presented next year.

9) FDA Claim for Diagnosis Update: David Sacks

- Clinicians have been using HbA1c for diabetes diagnosis for some time.

- The FDA has decided that manufacturers must submit a new application in order to make a diagnostic claim for HbA1c on their package inserts.
- A meeting was held in Washington DC last August that included representatives from the FDA and manufacturers to discuss the requirements for obtaining a diagnostic claim.
- A representative from the FDA will be at the NGSP/IFCC Manufacturer Forum.

10) Japan PT: Violeta Raneva

- Proficiency testing in Japan is organized by the Reference Material Institute for Clinical Chemistry Standards (ReCCS, ASRL#1) and the Japan Reference Measurement Institute (JMRI).
- At present, both HbA1c JDS and NGSP units are reported in Clinical Practice in Japan.
- In the future, JDS (Japan Diabetes Society) has decided to use only NGSP HbA1c units starting from April, 2014.
- JDS recommends limits of less than ±5% (NGSP units), whereas CAP Survey pass limits were ±7% in 2012 and ±6% in 2013.
- 2012 HbA1c (NGSP) Japan (Asia) PT
  - 36 NGSP-certified methods participated (28 in Japan, 6 in China and Korea
  - 5 samples (4 individual whole blood, 1 pooled and hemolyzed)
  - Target values were set by ASRL#1 and SRL#9
  - Survey was voluntary
  - Results
    - Overall pass rates were 93% to 100%
    - Between-laboratory CVs ranged from 2.2% to 3.7%.
    - All but 6 (of 34) methods had bias less than ±5%.
    - Overall means were very close to Target Values (within ±0.1 HbA1c%).
    - Method-specific, between-laboratory CVs ranged from 1.1% to 4.5%.
    - Method-specific means were very close to target values (within ±0.18 HbA1c%) except for sample No.5 (enzymatic assay + 0.385 HbA1c%).
    - Mean overall differences between laboratory analyzers and POCT methods ranged from +0.09 HbA1c% to -0.278 HbA1c%.
    - POCT CVs were slightly higher compared to laboratory analyzers but all were ≤4.44%.

Discussion:

R. Little asked if the participants were manufacturers rather than individual labs and how many of the methods are used only in Japan. V. Raneva replied that the participants were all manufacturers, she was not sure exactly how many methods are used only in Japan but some (Tosoh, Arkray, Beckman Coulter) are used in other countries. C. Weykamp asked if they see a high bias with the Tosoh HPLC on the Japan PT as is the case in Europe and the US. V. Raneva said they see some high bias for the G9 at the high HbA1c levels but otherwise they do not see it. R. Little noted that we do not see the bias at the manufacturer level on NGSP certification, C. Weykamp said this is also true of the IFCC monitoring program. S. Reutten asked if the results of the survey were made available to manufacturers but there was no penalty for not passing. D. Sacks asked what the future plans are for PT in Japan, will it be expanded to individual labs or regulated by organizations in Japan? V. Raneva was not sure.

D. Sacks thanked everyone for their attendance, the meeting was adjourned at 12:25 PM.

Minutes prepared by C. Rohlfing 8/14/13. Modified by R. Little 8/19/13 and D. Sacks 9/3/13.