

**Meeting of the NGSP Steering Committee
Minutes**
Sunday July 30, 2017 12:00 PM – 2:30 PM
Marriott Marquis San Diego Marina, San Diego, CA

Participants:

- *David Sacks —NIH, Chair, NGSP Steering Committee
- *Randie Little—Univ. of MO, NGSP Network Coordinator
- *Jon Davis—Trinity Biotech
- *Philippe Gillery-University Hospital of Reims (FR), IFCC Scientific Division
- *W. Greg Miller—Virginia Commonwealth Univ.
- *Ross Molinaro—Siemens Diagnostics
- *Curtis Parvin—Bio Rad Laboratories
- *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
- Kuanysh Kabytaev—Univ. of MO
- Curt Rohlfing—Univ. of MO, NGSP
- Scott Ruetten—Abbott Diagnostics
- Violeta Raneva-- Ref. Material Inst for Clin Chem Standards
- Amy Saenger—University of Minnesota
- Carla Siebelder—Queen Beatrix Hospital (NL);IFCC;NGSP
- Brenda Xiao—Roche Diagnostics

Steering Committee members not present:

- Robert Cohen—University of Cincinnati
- Garry John—Chair, IFCC Committee for the Educ in the Use of Biomarkers in Diabetes (C-EUBD)
- 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 and those present introduced themselves. D. Sacks thanked outgoing manufacturer representative Tony Prestigiaco for his service to the NGSP and welcomed new manufacturer representative Jon Davis.

2) The 2016 Steering Committee minutes were approved by the members present.

3) NGSP Progress Report—Randie Little , NGSP Network Coordinator

- NGSP Network Monitoring
 - The PRLs (3) and SRLs (11) continue to demonstrate excellent comparability (May between-lab CVs were 1.26% and 1.34% for the PRLs and SRLs, respectively).
 - In addition to monitoring the SRLs against the CPRL, we monitor the SRLs against each other using an acceptance ellipse which is based on the slope and intercept of the differences between the individual SRLs results and the medians of all SRLs.
 - We also test for individual within-lab and between-lab outliers.
 - Monthly between-lab CVs for the NGSP network were all <2% over the past year.
- Long Term Quality Controls (LTQC)
 - Provides another estimate of long term consistency of NGSP results
 - 3 levels of frozen WB aliquots (prepared by ERL)
 - Analyzed monthly by Missouri SRLs and quarterly by all SRLs
 - Results show consistency in SRL results over time since 2010.
- Certification
 - The number of certified methods continues to increase, while the number of laboratories has leveled off recently.
 - There are >200 methods and ~130 laboratories currently certified.
 - Most certified labs are Level I and are outside of the U.S.

- There are clusters of certified labs in South Africa, Colombia and various locations in Asia.
- CAP Data
 - There has been much improvement in within and between-lab variability since 1993
 - Current CAP limits (2013-2017) : Each result must be within $\pm 6\%$ of NGSP assigned target value (mean of 7 SRLs, multiple results from each).
 - CAP 2017A survey
 - Five samples
 - The worst methods are used by few labs (total $\sim 10\%$), 87% of labs are using methods with CVs $\leq 3.5\%$ at all five levels.
 - Individual method pass rates varied from 68.4% to 100%.
 - Method-specific between-lab CVs ranged from 1.0 to 5.7%
 - Overall pass rates were 95.1-96.3%.
 - Cumulative overall pass rates at the current cutoff of $\pm 6\%$ have increased from 2008 to 2017.
 - Cumulative overall pass rates have been $>95\%$ in the 5-10% HbA1c range for the last 4 surveys.
 - All-method CVs were $<3.5\%$ for all 5 samples.
 - All-methods CVs have been $<3.5\%$ for the last 5 surveys.
- New NGSP SRL Methods
 - ESRL13:
 - Zwolle, The Netherlands,
 - Roche Tina quant / Cobas c513
 - Replaces ESRL 9 (Integra 800)
 - ESRL14:
 - Zwolle, The Netherlands,
 - Abbott Architect c Enzymatic
 - ASRL2:
 - Shanghai, China
 - Variant II
- New SRL in China
 - Shipping of Monthly monitoring samples has now been coordinated. All ASRL#2 monitoring data has been within acceptable limits.
 - 9 methods from three manufacturers have now been certified by ASRL#2
- Update on Hb Variant Interference
 - There are currently 3 methods listed on the 2017 GH5-A CAP survey report that have interference for one or more common Hb variants.
 - Beckman AU (2.7%)
 - Tosoh G7 (0.3%)
 - Tosoh G8 (11.7%)
 - $\sim 15\%$ of labs are using these methods (this will decrease to 3% once the new Tosoh G8 version is FDA approved).
- Variant Interference: Confusion in the Literature
 - Association of Sickle Cell Trait with Hemoglobin A1c in African Americans (Lacy, et al. JAMA. 2017;317:507-515).
 - Results
 - 1) "...at the same fasting or 2-hour glucose concentration, HbA1c is statistically significantly lower among participants with vs without SCT." Mean difference was 0.30% HbA1c.
 - 2) "although the assays used in this study report no clinical significant interference in individuals with SCT, the possibility of minor interference that could potentially explain our findings cannot be ruled out."
 - Conclusions: "Among African Americans from 2 large, well-established cohorts, participants with SCT had lower levels of HbA1c at any given concentration of fasting or 2-hour glucose compared with participants without SCT. These findings suggest that HbA1c may systematically underestimate past glycemia in black patients with SCT and may require further evaluation."
 - The Tosoh 2.2 and the Tosoh G7 were used for these studies.
 - Previous NGSP variant interference studies cited in the paper showed that there were no clinically significant interferences from HbS with these methods during the time of the studies. However, there were statistically significant differences large enough to explain the findings of the study.

- Conclusion: The differences observed in the Lacy, et al paper between the non-SCT and SCT subjects are, in fact due to analytical interference with the 2.2+ and G7.
- In response:
 - A letter to the ed. was published in JAMA
 - A commentary in Practice update published on-line: <http://www.practiceupdate.com/content/sickle-cell-trait-associated-with-lower-hba1c-in-african-americans/49399/12/8/1>
- Subsequent Publications
 - www.npr.org Feb. 7, 2017: “The HbA1c test for blood sugar, a standard assay for diabetes, may not perform as well in people with sickle cell trait, a study finds.”
 - AACC Clin Lab News, April 2017: “...the relationship of HbA1c with blood glucose levels may differ between African Americans with and without SCD/SCT. This is because sickle cells have a much shorter lifespan of only 10-20 days.” “Quarterly monitoring of glycemic control using fructosamine in SCD/SCT patients will provide more reliable information than HbA1c.”
 - AACC SmartBrief, May 2, 2017: “Because sickle cell disease and sickle cell trait can interfere with traditional diabetes management, the ADA recommends fructosamine testing as an alternative to HbA1c testing.”
- Another Paper: Lewis, et al. Management of Hemoglobin Variants Detected Incidentally in HbA1c Testing: A Common Problem Currently Lacking a Standard Approach. Diabetes Care 40:e8-9, 2017
 - Vitamin D and Type 2 diabetes
 - HbA1c by Tosoh G8 HPLC
 - “HbS and HbC do not interfere with the assay”
 - Our latest variant interference study published last year shows that the G8 now shows clinically significant interference from all four common variants. Tosoh has developed a new software version that addressed the problem but it is not yet available in the U.S.
- In response to Lewis et. al
 - Letter to the Editor, Diabetes Care (in press)
 - “While the authors claim that there is no interference of these common Hb variants with the Tosoh G8 method, there is clear evidence to the contrary. Our study clearly showed a statistically and clinically significant bias in results from this method with all four common Hb variants (HbAS, AC, AD, AE).”
- Information stating that the G8 shows clinically significant interference from all four common variants, unless the lab is using the new software, is clearly posted on the NGSP web site.
- Question: How do we get people to pay more attention to the material on the NGSP website before publishing inaccurate information about Hb variant interference?
- Conclusions
 - NGSP network performance is excellent.
 - Method certification continues to increase; lab certification appears to have leveled off.
 - There has been continuous improvement in HbA1c measurements with all-method CVs for the most recent survey <3.1%.
 - There continues to be a few methods showing poor performance on the CAP survey although these are used by a relatively small number of laboratories.
 - Cumulative pass rates have been over 95%.
 - There are still a small number of methods with interference from common Hb variants.
 - Only ~15% of labs are currently using a method with variant (S,C,D or E) interference and this will decrease to 3% when the new version of the Tosoh G8 is FDA approved in the US.
 - There appears to be a lot of confusion about variant interference with commonly used methods.

Discussion:

Hemoglobin variant interference

G. Miller asked if the NGSP could contact the FDA regarding the current Tosoh variant interference issue and see if there is a way to accelerate the approval of the new software. D. Sacks agreed. R. Little said the FDA is requiring the same variant interference data that was required for the original diagnostic claim. G. Miller noted that there are already data showing that the issue has been resolved, if this were brought to the attention of the FDA there might be a way to accelerate the process. The FDA can be a bottleneck in terms of getting

improved methods into the U.S. market because of the regulatory process. If we can get their attention maybe the process can be streamlined. R. Molinaro suggested contacting Tosoh to ask how the NGSP could help, they are familiar with the challenges of the regulatory process. R. Little said we have already been working with them to help them get the data they need and they have not asked for anything else, but we could try contacting the FDA. M. Steffes said that manufacturers need to be forthcoming about these kinds of issues, Tosoh has not been, communication has been lacking. A. Saenger said turnover at the company has been part of the problem. R. Little said they have tried to minimize the issue by stating that the interference is mainly at the high end of the HbA1c range. C. Weykamp noted that the FDA is requiring variant samples with percentages of the variant that do not physiologically exist. For example, HbE of 30%, this may be the result on a HPLC method but on CE where the separation is better the results are actually ~25%. R. Little said she has talked to the FDA regarding this, explaining that the % variant results are not standardized, we may need to have further discussions with them. At one time they were wanting various levels of the variants down to very low levels, we explained that they do not exist that way in patients. For example, they wanted data showing that HbE could be detected down to 5% or lower, but there is no point in detecting these levels. S. Ruetten said there are supposed to be Tosoh technical people attending the meeting, R. Little said she has been in contact with them. They are having to supply variant samples as we mainly see S and C. There was an extra set of frozen variant samples left from our previous variant study but for some reason they wanted fresh samples. D. Sacks asked R. Little if her lab has evaluated the new software. R. Little said yes, we have already analyzed our samples from the previous variant study and the new software has fixed the problem. The new software is already being used in Europe. S. Ruetten noted that it is useful to manufacturers to have variant samples available in case these issues come up.

Confusion over Variant Interferences

R. Little said the JAMA paper received a lot of attention, and there has been a lot of resulting confusion as reflected by the reports on NPR and the AACC reports. The ADA does not recommend fructosamine as an alternative to HbA1c in patients with SCT, they only recommend it in cases where HbA1c cannot be used. A. Saenger said the Lewis et. al paper recommended reporting the specific variant along with the HbA1c result. The Minnesota lab as well as many other labs currently just report that there is a variant but do not report the specific variant since the HbA1c assay is not a confirmatory test for identifying variants. R. Little said small differences that may not necessarily be clinically significant can affect the results of studies like the one published in JAMA. D. Sacks asked if there could be a statement on the NGSP web site saying that clinically significant differences may not apply to population-based studies. R. Little said that we should probably say something, and suggest that the actual papers should be reviewed when the interference studies are cited. All of the references are currently listed on the NGSP web site. G. Miller said the fundamental problem is that people do not know that the information is readily available on the NGSP web site so they don't check it prior to making statements regarding interferences. There is no good way to address this other than to publish letters with the correct information. C. Weykamp asked if CAP could put a statement regarding variant interferences in the CAP report, referencing the NGSP web site. G. Miller said CAP could probably do this, just as a reminder that variant interferences can be an issue with some methods and the NGSP web site has information regarding this. However, very few people are likely to pay attention to the statement. It is a bit disturbing that whoever wrote the misleading information on behalf of the AACC did not check with experts prior to publication. The information published in AACC newsletters is probably reviewed by trained clinical chemists, it may be that the clinical chemist in this case was not sufficiently knowledgeable in this particular field. These are news articles as opposed to journal articles, but nonetheless when the AACC puts out wrong information they need to be informed. They should then consider future corrective action.

CAP survey

H. Vesper asked about POC devices on the CAP survey, R. Little said there are only a few on the survey since POC methods are waived and users therefore don't have to participate in CAP. POC for diagnosis is still up in the air. S. Ruetten asked if there is any tracking of the investigations performed by manufacturers when a method performs poorly on the CAP survey. R. Little said manufacturers are generally aware of how their methods perform on the surveys, a summary of each survey is posted. It is up to them to pursue corrective action. D. Sacks added that CAP sends each manufacturer the raw data for their methods including lot numbers, etc. that they can use in troubleshooting.

4) CAP Meeting Report: Changes in Certification Criteria—David Sacks, NGSP Steering Committee Chair

- CAP Grading
 - In past, CAP used peer group grading for PT for GHb
 - In 2007 changed to accuracy grading; DCCT target used
 - +/- 15% acceptable
 - 99% pass rate
- PT Criteria Tightened
 - In 2008 acceptability reduced to 12%
 - In 2009 acceptability reduced to 10%
 - In 2010 acceptability reduced to 8%
 - In 2011 acceptability reduced to 7%
 - In 2013 acceptability reduced to 6%
 - Considering reducing to 5%
- CAP GH5C 2016: Performance 6% vs 5%

- Means and acceptable limits

GH-11	GH-11	GH-12	GH-12	GH-14	GH-14	GH-15	GH-15
9.11	9.11	6.01	6.01	5.02	5.02	7.58	7.58
8.5-9.7	8.6-9.6	5.6-6.4	5.7-6.4	4.7-5.4	4.7-5.3	7.1-8.1	7.2-8.0

- By method

N	GH-11	GH-11	GH-12	GH-12	GH-14	GH-14	GH-15	GH-15
	9.11	9.11	6.01	6.01	5.02	5.02	7.58	7.58
	8.5-9.7	8.6-9.6	5.6-6.4	5.7-6.4	4.7-5.4	4.7-5.3	7.1-8.1	7.2-8.0
8	88.9	88.9	88.9	88.9	85.7	85.7	85.7	85.7
11	81.8	63.6	72.7	72.7	100	75	100	75
129	97.8	96.3	97.8	97.1	99.1	99.1	99.1	97.4
16	100	100	100	100	100	NA	100	NA
80	98.8	98.8	100	100	100	93.3	100	100
87	84.3	84.3	87.6	84.3	87.7	86	86.0	80.7
131	94.2	92.8	97.1	97.1	96.3	93.5	95.3	93.5
172	97.7	96	98.3	98.3	98.4	97.6	99.2	99.2
51	96.2	90.6	96.2	96.2	100	97.8	97.8	97.8
82	96.5	95.3	100	100	100	100	100	97.5
173	100	100	99.4	98.9	100	98.7	99.3	98.7
10	100	100	100	100	100	100	100	100
26	89.3	89.3	92.9	92.9	77.8	77.8	100	94.1
398	98.8	98	98.5	95.3	95.8	95.5	98.8	97.9
60	96.7	90	96.7	96.7	90.3	80.7	100	93.6
117	97.5	97.5	100	98.3	98.1	93.3	100	99.1
42	100	97.7	97.7	95.3	93.3	93.3	100	100
19	90.5	85.7	90.5	90.5	100	100	100	80
453	95.7	95.7	98.3	97.9	96.7	96.7	97.3	96.7
24	100	100	95.8	95.8	95.5	90.9	95.5	90.9
208	95.4	92.6	97.7	96.8	95.1	90.3	95.1	92.4
22	100	100	100	100	100	100	100	100
36	97.3	97.3	89.2	83.8	100	100	100	100
290	96.2	92.2	96.9	96.2	97.4	95.5	97.4	94.8
20	95.2	95.2	95.2	95.2	100	84.6	100	100
371	96.9	96.6	97.4	97.4	99.1	98.8	99.4	99.1
69	100	98.6	98.6	98.6	98.3	98.3	100	96.7
186	95.3	89.1	99.0	98.4	96.9	95	98.8	96.3
3377	96.6	95	97.4	95.9	97.1	95.7	98.1	96.4

- CAP 2016 GH5C Pass Rates at $\pm 6\%$ and $\pm 5\%$ HbA1c Cutoff

	At $\pm 6\%$	At $\pm 5\%$
GH-11 (9.1%)	96.6	95.0
GH-12 (6.0%)	97.4	95.9
GH-14 (5.0%)	97.1	95.7
GH-15 (7.58%)	98.1	96.4

5) Possible Change in NGSP Certification Criteria—Randie Little , NGSP Network Coordinator

- Current Manufacturer Certification Criteria (2014-2017): 37/40 individual results must be within 6% of the SRL (one SRL)
- Current CAP limits (2013-2017): Each result must be within $\pm 6\%$ of NGSP assigned target value (mean of 8 SRLs, multiple results from each).
- Impact of a Change from $\pm 6\%$ to $\pm 5\%$:
 - Manufacturer certifications Aug 2016-July 2017

- 256 methods were submitted
- 95.7% passed with >37/40 results within $\pm 6\%$
- 89.1% would have passed at $\pm 5\%$
- Level I Laboratory certifications Feb-July 2017
 - 129 lab methods were submitted
 - 89.9% passed with >38/40 results within $\pm 6\%$ (2 passed Level II)
 - 82.2% would have passed at $\pm 5\%$ (7 passed Level II)
- Level II Laboratory certifications Feb-July 2017
 - 54 lab methods were submitted
 - 85.2% passed with >37/40 results within $\pm 6\%$
 - 61.1% would have passed at $\pm 5\%$ 129 lab methods were submitted

Discussion:

Possible Changes in CAP, Certification Criteria

D. Sacks said that each time the CAP was going to change criteria, labs were notified in advance how they would perform with the tightened as well as the current criteria on their reports. The analyses show that a change in the CAP criterion from 6% to 5% would have very little impact on individual labs as the drop in overall pass rates is very small. At the 5% cutoff 2016C pass rates were still $\geq 95\%$. The CAP has not decided whether to go to 5%, the issue is--will the CAP and NGSP be out of sync since they both now use 6% limits? G. Miller asked whether the methods that show substantial changes in pass rates for 6% vs. 5% are the ones that perform poorly on the CAP survey. D. Sacks said yes, virtually all of them are methods that show significant biases. R. Little noted that these methods are also used by a small number of labs. G. Miller suggested that this means that labs that would presumably be penalized if the criterion is changed are labs that should be considering changes to their methodology anyway, D. Sacks and R. Little agreed. S. Ruetten said we are getting to a point where how the reference values are assigned are critical, we need to consider the total error of the value assignments. The distribution of the reference value assignments, i.e. from low to high, is also important. D. Sacks agreed. R. Little noted that the NGSP calculates the uncertainty of the CAP value assignments and they are included in the summary reports on the NGSP web site. Multiple SRLs analyze the samples in triplicate on two different days, the uncertainty is therefore very small, less than 2%. R. Molinaro asked about the timeline if the change is made, D. Sacks said that in the past it has been 1-2 years but we will get input from manufacturers. D. Sacks asked C. Parvin if the uncertainty of the value assignments were included in the calculations he performed previously when the criteria were changed, C. Parvin said they were. The probabilities of a lab passing the criteria at different levels of bias and imprecision given the imprecision of the reference value assignments were determined using simulations. S. Ruetten asked how low you can go given the limitations of the current reference methods and value assignments. C. Parvin noted that the reference value assignment can be improved by adding replicates, this might be needed as the limits get narrower. R. Little said it is possible to obtain more replicates. However, there is very little variation in the replicates within each SRL, most of the variation is between the SRLs. C. Weykamp noted that there are differences between CAP and NGSP certification. For the CAP multiple SRLs/methods are used to assign the values, NGSP certification is performed using a single SRL. Also, CAP samples are pools, whereas NGSP certification is performed using single samples. This means that differences between individual patients that can result in small differences in results between methods would be more pronounced with NGSP certification. The uncertainties of the value assignments for the CAP survey are very low as they are assigned by multiple SRLs and pooled samples are used, it is unavoidable that the uncertainties of the value assignments for the manufacturer certifications will be higher. G. Miller said another important question is whether the current state of the art in HbA1c testing is sufficient to meet clinical needs in terms of monitoring patients and diagnosing diabetes. If it has reached an adequate level of performance then we may not need to worry about improving the performance of the test, if not then we need to go further. C. Weykamp said he has data demonstrating that the current state of the art is likely not good enough. G. Miller said that with NGSP certification the SRL could have a small bias at the time the certification is performed, this could affect whether a method passes or fails. S. Ruetten agreed, noting that if the total error budget is 5% and the SRL error is 1.2% that consumes over 20% of the total error budget. R. Little said it is possible that a method could fail with one SRL and pass with another, but in cases where a method fails and tries again using a different SRL they generally fail the second time as well. The methods that passed over the past year but would have failed with 5% were borderline methods. D. Sacks said that certified methods and certified labs are two different things that do not necessarily have to be linked, you could change the criteria for one and not the other. C. Weykamp said it does not appear that a change from 6% to 5% would have much impact on the CAP survey, but it would likely

have greater impact on NGSP certification because of the uncertainty in the value assignments. R. Little noted that 256 methods were certified over the year, but only a small number of them appear on the CAP survey. The ones that do appear are mostly the better-performing methods. The methods that failed were mainly either one of several methods submitted by one of the major manufacturers or methods that are relatively obscure. D. Sacks asked if the methods being certified are good enough, are we certifying methods that should not be certified? R. Little felt that it would not be a bad thing if the methods that passed 6% but failed 5% were failed; these methods showed significant scatter and/or bias. Some failed 5% because of bias at the low end, where it is important to be accurate. The good methods pass 5%. C. Weykamp noted that the failure rate would rise from 4% to 11%, which is pretty significant. It was his opinion that the NGSP criterion should not change due to the uncertainty in the value assignments. R. Little thought it seemed backward to have looser criteria for a method to be certified than for a lab to pass CAP. G. Miller said it is not really “looser”, C. Weykamp agreed adding that when value assignment criteria are not the same, pass/fail criteria do not need to be the same. C. Rohlfing said that when C. Parvin previously did the analyses looking at CAP compared to NGSP criteria, it was noted that the number of samples affects the probabilities of pass/fail. NGSP certification is performed with 40 samples, CAP surveys consist of 3, or more recently 5, samples. G. Miller said C. Parvin’s earlier analyses supported tightening of the NGSP criterion to 6%; can the analyses be performed again to look at 5%? C. Parvin recalled that in the analyses curves were constructed comparing the NGSP and CAP criteria at different probabilities of passing. The focus was on trying to make them match in the middle part of the curves, moving out toward the outer edges the NGSP criteria were more strict than CAP. This would be consistent with the idea of methods with significant bias having a lower chance of passing NGSP certification. What is the possibility of the NGSP using more than one SRL to assign values to certification samples? R. Little said it would be difficult for SRLs that only have one method, which includes the SRLs in Japan, China and Minnesota. In the case of the SRL in China in particular, the whole reason for adding them was the difficulty in shipping samples to China. S. Adam asked if there is a need to further tighten the criteria. R. Little said at the ADA Clinical Advisory Committee meeting we hear examples where an inaccurate HbA1c result was reported from a lab. Also, some physicians expect the HbA1c result to be an exact number, it is difficult to know what is “reasonable”. C. Weykamp was asked to present recent data looking at the performance of methods in a recent survey compared to IFCC quality targets.

7) Clinical Data and IFCC Model Quality Targets

- 2016 HbA1c in 19,424 clinical samples in our institution. Distribution:

	IFCC mmol/mol	NGSP %
Lowest	20	4.0%
Highest	173	18.0%
95% Results	33 – 75	5.2 – 9.0%
Median	45	6.3%

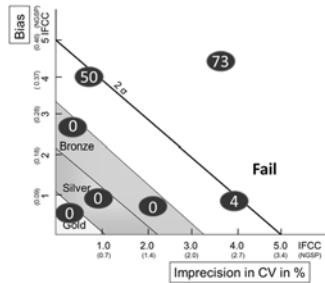
- These data are consistent with data from 2012.
- 95% of results were in the 33 – 75 mmol/mol (5.2 – 9.0%), thus quality focus should be on that range.
- The ADA has defined three diagnostic categories for HbA1c
 - Low risk: <5.7%
 - Increasing risk: 5.8-6.4%
 - Diabetes: >6.4%
- 25% of our results were in the low risk range, 53% were in either the low or increasing risk range.
- Impact of bias on categorization

Bias				
Low Risk	Incr Risk	Diabetes	Mmol/mol	% NGSP
25%	28%	47%	0	0.0
12%	33%	55%	+3	+0.28%
36%	25%	39%	-3	-0.28%

- “What is the chance that a true HbA1c of 43 mmol/mol (6.1%) is over-estimated in the lab that much that the clinical interpretation will falsely be “diabetes”?”

Bias Mmol/mol (NGSP %)	Imprecision (NGSP)					
	5% (3.4%)	4% (2.7%)	3% (2.0%)	2% (1.4%)	1% (0.7%)	0% (0.0%)
5 (0.46)	67	73	80	89	99	100
4 (0.37)	50	50	50	50	50	50
3 (0.28)	33	27	20	12	1	0
2 (0.18)	18	12	6	1	0	0
1 (0.09)	9	4	1	0	0	0
0 (0.00)	6	2	0	0	0	0

- Chance of overestimation in relation to IFCC quality targets



- In terms of the chance of over or underestimation causing incorrect categorization, bias is more important than CV.

Discussion:

R. Molinaro said the data show the importance of knowing the uncertainty of target value assignments given the impact of bias. G. Miller said the data tell us that if we can come up with a scheme to further improve bias among the different methods, as much as it is technically possible, it improves the ability to properly classify patients. C. Weykamp noted that the results of the recent EurA1c survey showed that several manufacturers performed very well. However, several performed poorly and had significant bias, efforts to reduce bias will put a lot of pressure on those manufacturers. G. Miller said this is consistent with CAP survey results; there are a few manufacturers with significant biases. It seems reasonable to tighten the CAP survey criteria to encourage these manufacturers to either improve the poorly-performing methods or get them out of the market. Methods that are already performing well would not be punished. C. Weykamp noted that survey data indicate that the notion that POC instruments do not perform well does not always hold true. S. Ruetten said we clearly want to avoid misclassification of patients, but with a pre-diabetes range of 5.7-6.4% it appears we already have a built-in “grey zone”, why do we have this? M. Steffes said the ranges and cutoffs were derived from epidemiological studies where retinopathy was plotted versus HbA1c. The primary study was one from Australia which was very well done. The risk of retinopathy rises sharply with HbA1c. The numbers were arrived at based on consensus at WHO and ADA, there was quite a bit of overlap between the groups however. Clinicians need to make decisions based on the numbers and the patient. Too many times clinical decisions are made based on lab results without considering the patient. D. Sacks said it would seem that this group seems to approve of tightening the CAP criteria but there are concerns about tightening the NGSP manufacturer certification criteria. We will see if C. Parvin previously did the analyses for 5%, if not perhaps he can do it. C. Parvin said that if he still has the program he probably can do the calculations. R. Little asked if the potential tightening of the NGSP criteria should be discussed with manufacturers at the Manufacturer Forum. G. Miller said the manufacturers should be informed that tightening of the CAP and NGSP criteria are being considered and ask for their input, R. Molinaro agreed. D. Sacks asked if those present believe that the CAP criterion should be tightened, there was agreement that it should be. R. Molinaro asked about the timeline, D. Sacks responded that the CAP has discussed tightening the criterion in 2019. S. Ruetten asked if CAP can provide manufacturers as well as individual labs with information on how well they perform at both 6% and 5% on surveys prior to the change. D. Sacks said he would have to clear this with CAP but felt that this can be done. G. Miller said it is good to provide labs and manufacturers with these data to give them time. M. Steffes supported the idea of NGSP tightening to 5% based on C. Weykamp’s data. As the DCCT laboratory they have found that they have to adjust their calibrator values based on their interactions with the Missouri lab, as they have seen bias in the manufacturer value assignments. S. Ruetten said he would like to see data showing the distribution of value-assignment results from all of the SRLs, if any one of the SRLs is at one of the extremes relative to the SRLs this could consume over 1% of the 5% total error budget. R. Little said the problem is that the NGSP monitoring and CAP samples that are analyzed by all of the SRLs are pooled rather than single-donor samples. Certification samples, which are single-donor, are not analyzed by all of the SRLs. So is there agreement that the CAP criterion can be tightened, but there is not agreement to change the NGSP certification criteria at this point until the committee has reviewed C. Parvin’s analysis? The committee agreed to this. D. Sacks noted that CAP can provide performance data at 6% and 5% to manufacturers going forward, and can also provide them with the previous data he showed earlier. The CAP change is not yet definite but the CAP Committee thought it seemed feasible and reasonable, and if this committee approved it could go forward but it would not happen before 2019.

8) Clinical Advisory Committee Meeting Update—David Sacks

- The CAC is composed of representatives from major clinical diabetes organizations. The purpose is to facilitate communication between these organizations and the NGSP. They advise the NGSP on clinical aspects of HbA1c and report back to their organizations.
- The CAC met at the ADA in June 2017.
 - Chaired by Ann Albright of the CDC.
 - R. Little presented an update on NGSP progress.
 - Discussion of sickle-cell trait and HbA1c
 - R. Little spoke about the recent JAMA and Diabetes Care studies.
 - NIDDK/NIH is concerned about hemoglobin variant interferences, they even receive inquiries from members of Congress regarding these issues.
 - Racial differences in HbA1c: Recent paper published in the Annals of Internal Medicine
 - Elizabeth Selvin and I wrote an accompanying editorial.
 - Two of the authors, Richard Begental and Roy Beck, gave a presentation.
 - Subjects with Type 1 diabetes.
 - Excluded any subjects with hemoglobinopathies
 - After exclusions there were 104 white and 104 black subjects.
 - Performed CGMS and HbA1c
 - Compared mean glucose based on CGMS to HbA1c
 - Found lower mean HbA1c in white compared to black subjects
 - After correcting for the lower mean glucose values in white compared to black subjects, there was still a difference of ~0.4% HbA1c between the groups.
 - They also compared mean glucose to fructosamine and glycated albumin and found no significant differences between the groups.
 - Concluded that the difference in HbA1c between the groups was due to non-glycemic factors.
 - There is much ongoing debate in the U.S. as to the cause of these differences and whether they are clinically important.
- - POC methods for diabetes diagnosis
 - Alere has applied for a diagnostic claim for the Afinion which is a POC HbA1c method.
 - Current ADA guideline is that POC methods are not to be used for diagnosis.
 - The method is NGSP certified and widely used for monitoring.
 - Since it is CLIA-waived there is no requirement to perform proficiency testing.
 - Plan is to submit to FDA for diagnostic claim as a moderate-complexity test, then later obtain waived status for the diagnostic claim.
 - There was no one from FDA at the CAC meeting.
 - The FDA held a meeting with an expert panel (Clinical Chemistry and Toxicology Device Panel) in Gaithersburg, MD July 22nd to discuss the Alere diagnostic claim application.
 - 1) Various speakers from ADA, Alere and others
 - 2) Panel was able to ask questions
 - 3) Panel advises FDA but their conclusions are not binding
 - 4) Conclusions were that they had no concerns about the moderate-complexity application, but there were more concerns about use of a waived test.
 - R. Little gave a presentation about fructosamine and glycated albumin.

Discussion:

Rare variants

C. Weykamp said that if the difference in HbA1c between the two ethnic groups were due to differences in glycation, we would expect to see this with other glycated proteins as well. D. Sacks agreed, noting that this is mentioned in the accompanying editorial. R. Little and D. Sacks noted that there is significant overlap between the groups, and there are a few outliers that could be having some effect on the relationship.

9) 5th 2016 PT in Japan and Asia (Korea)—Violeta Raneva

- Performed in cooperation with Katsuhiko Kuwa, Ph.D. at the Japan Reference Measurement Institute.
- 3 Whole Blood Specimens, single donors, sent refrigerated to participants in Japan, and frozen to Korea's participants.

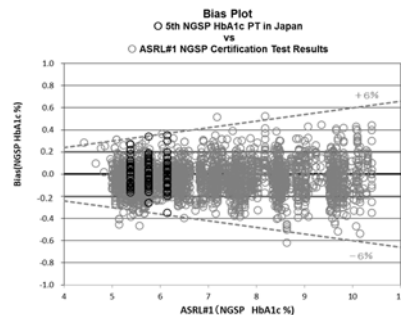
- Participants were mostly manufacturers, some end-users were also included.
- Target Values set by mean values of SRLs (frozen whole blood samples)
- Target values (CVs): 5.384 (1.4%), 5.757 (0.8%), 6.148 (1.3%)
- 54 methods participated, 49 in Japan and 5 in Korea.
- 39 methods were NGSP-certified (35 in Japan, 4 in Korea)
- Measurements were performed in duplicate on one day.
- Results

Specimen	NGSP Target ±ts/√n	Total Mean	Mean	Mean	Acceptable Range NGSP (±6%)	Pass Rate % at ±6% All	Acceptable Range JDS (±5%)	Pass Rate % at ±5% All	Pass Rate % at ±5% In Japan	CVs %	CVs %
	(% HbA1c)	All	In Japan	In Korea					In Japan	All	In Japan
1	5.384 ± 0.058	5.399	5.400	5.390	5.06 – 5.71	100.0	5.12 – 5.65	100.0	100.0	1.9	1.9
2	5.757 ± 0.034	5.779	5.783	5.740	5.41 – 6.10	100.0	5.47 – 6.05	98.1	100.0	2.0	1.7
3	6.148 ± 0.060	6.156	6.157	6.150	5.78 – 6.52	100.0	5.84 – 6.46	96.3	100.0	2.0	1.7

- Results by method type

Type of Method		HPLC		Affinity		Immunoassay		Enzymatic		Asia (Korea)	
54 Participants (16 POCTs)		22 (3)		2 (2)		23 (10)		7 (1)		5 (2)	
Specimens	NGSP Target ±ts/√n (% HbA1c)	Mean	CVs (%)	Mean	CVs (%)	Mean	CVs (%)	Mean	CVs (%)	Mean	CVs (%)
1	5.384 ± 0.058	5.40	1.6	5.48	3.2	5.38	2.1	5.46	1.9	5.39	2.7
2	5.757 ± 0.034	5.82	1.4	5.73	5.6	5.73	1.7	5.84	2.6	5.74	3.9
3	6.148 ± 0.060	6.17	1.5	6.13	0.6	6.12	2.2	6.25	2.3	6.15	4.5

- The distribution of the PT results was very similar to that of the results of certifications performed by ASRL#1.



Discussion:

D. Sacks asked if 5% is the JDS acceptable limit, V. Raneva said that it is. The 6% criterion was included because it is the current NGSP limit. R. Little asked if there is PT testing of individual laboratories in Japan, V. Raneva said yes but freeze-dried materials are used. Also, the target values are the averages of the participants, they are not assigned by reference laboratories. R. Little asked if there is a pass/fail limit, V. Raneva was not sure. G. Miller noted that the data seem to be consistent with the CAP data, D. Sacks agreed. R. Little suggested that it might be useful to make a bias plot similar to the one presented by V. Raneva where the individual CAP survey results are plotted with an overlay showing the individual SRL value assignment results to show how narrow the SRL results are relative to those of the survey participants.

D. Sacks thanked everyone for their attendance, the meeting was adjourned at 2:15PM.

Minutes prepared by C. Rohlfing 9/6/17. Modified by R. Little 9/8/17 and D. Sacks 9/12/17.