



**Meeting of the NGSP Steering Committee
Minutes**

Sunday August 4, 2019 2:00 PM – 4:00 PM
Hilton Anaheim, Anaheim, CA

Participants:

- *David Sacks —NIH, Chair, NGSP Steering Committee
- *Randie Little—Univ. of MO, NGSP Network Coordinator
- *Jon Davis—Trinity Biotech
- *Jackie Felberg—Bio Rad Laboratories
- *W. Greg Miller—Virginia Commonwealth Univ.
- *Michael Steffes—University of Minnesota
- *Hubert Vesper—CDC
- *Cas Weykamp—Queen Beatrix Hospital (NL), IFCC Network Coordinator
- ***Member of the NGSP Steering Committee**

- Shawn Connolly—Univ. Of MO, NGSP
- Kuanysh Kabytaev—Univ. of MO
- Curt Rohlfing—Univ. of MO, NGSP
- Carla Siebelder—ER, IFCC, NGSP
- Kwaku Tawiah—Univ. of MO
- Eline van der Hagen—ERL, IFCC, NGSP

Steering Committee members not present:

- Robert Cohen—University of Cincinnati
- Philippe Gillery-University Hospital of Reims (FR), IFCC Scientific Division
- John Higgins—Massachusetts Gen. Hosp.
- Garry John—Chair, IFCC 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.

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

- Recently published review: The National Glycohemoglobin Standardization Program: Over 20 Years of Improving Hemoglobin A1c Measurement. Clin Chem Jul 2019, 65 (7) 839-848.
- NGSP Network Monitoring
 - The PRLs (3) and SRLs (11) continue to demonstrate excellent comparability (May between-lab CVs were 1.38% and 1.05% for the PRLs and SRLs, respectively).
 - The SRLs are also monitored 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.
 - Monthly between-lab CVs for the NGSP network were all <1.6% over the past year.
- Long Term Quality Controls (LTQC)
 - Provides another estimate of long term consistency of NGSP results
 - Three levels of frozen whole blood (5.1%, 7.9% and 11.2% HbA1c).
 - 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. This is likely due at least in part to continued consolidation of large laboratories.
 - There are >260 methods and ~130 laboratories currently certified.
 - Most certified labs are Level I and are outside of the U.S.
- Impact of Change in Certification Criteria
 - Current limits for NGSP and CAP
 - Beginning January 2019: NGSP Manufacturer and Level II Lab Certification Criteria: 36/40 results must be within ±5% (37/40 for Level I labs)
 - CAP Survey Grading for HbA1c remain at ±6%
 - Pass Rates for NGSP certification: ±6% vs. ±5%

Certification Type	2018 $\pm 6\%$	2018 projected $\pm 5\%$	2019 Actual $\pm 5\%$
Manufacturer	92.2%	85%	92.9%
Level I Lab	95.1%	90.2%	95.9%
Level II Lab	78.6%	71.4%	69.2%

- Status of HbA1c Measurement (CAP data)
 - There has been much improvement in within and between-lab variability since 1993; improvement has been more subtle in recent years.
 - Current CAP limits (2013-2019) : Each result must be within $\pm 6\%$ of NGSP assigned target value (mean of 8 SRLs, 2 days of triplicate results from each).
 - CAP 2019A survey

- Five samples
- One sample with HbS trait was included in this survey.
- 2019A CAP Pass Rates ($\pm 6\%$) vs. Pass Rates using $\pm 5\%$

Specimen	NGSP Target (% HbA1c)	Acceptable Range ($\pm 6\%$)	Pass rate % (Low/High)	Cumulative Pass Rate %	
				$\pm 6\%$	$\pm 5\%$
GH-01	5.46	5.1-5.8	80.0/100.0	94.0	94.0
GH-02*	5.66	5.3-6.0	60.0/100.0	87.1	87.1
GH-03	9.31	8.7-9.9	86.7/100.0	96.0	93.1
GH-04	5.28	4.9-5.6	84.7/100.0	96.3	92.9
GH-05	7.41	6.9-7.9	89.6/100.0	97.9	96.1

*HbS

- In general there was more variability with the HbS trait sample.
 - All-method CVs have dropped over time since 2000.
 - All-method CVs were 3.6% and 3.3% for the two samples in the 4-6% HbA1c range, 2.7% for the sample in the 6-8% HbA1c range, and 3.1% for the sample in the 8-10% HbA1c range (HbAS sample excluded).
 - Cumulative pass rates at $\pm 6\%$ have increased over time and have consistently been $>95\%$ in recent surveys.
 - Between-lab CVs by method type show that the ion-exchange HPLC methods perform well (all CVs $<2.5\%$). Two immunoassay methods have considerable variability (CVs $>3\%$), but others perform well and some were comparable to IE HPLC. The enzymatic method showed a low CV as did the affinity and CE methods. The two POC methods in the survey performed well (CVs $\leq 2.5\%$)
 - Biases by method type showed that the degrees and directions of bias were not specific to particular method types.
 - Looking at the HbAS sample compared to a HbAA sample in the same HbA1c range, two methods, the Variant II Turbo and DCA Vantage, showed more bias for the HbAS sample than would be expected based on previous variant interference studies. These two methods will be re-evaluated in the next interference study.
 - The overall pass rate for the HbAS sample was lower than for the other samples in the survey (87.1%) and the all-method CV was higher (4.4%).
 - Method-specific, between-laboratory CV's ranged from 0.9% (Arkray HA-8180) to 4.5% (Roche Integra 400) (AS excluded).
 - 89% of laboratories are using methods with CVs $<3.5\%$ at all four HbA1c levels (AS excluded).
- Hb variant interference; recent publication: Moon et al. A Genome-Wide Association Study Identifies Blood Disorder-Related Variants Influencing Hemoglobin A1c With Implications for Glycemic Status in U.S. Hispanics/Latinos (Diabetes Care 2019 Jun; dc190168).
 - Non-diabetic Hispanic/Latino adults (n= $>16,000$)
 - HBB-rs334 (causal for Sickle cell trait/disease)

- G6PD-rs1050828 (causal for G6PD deficiency)
- Both mutations associated with HbA1c but not fasting glucose
- HbA1c measured in most subjects by Tosoh G7
- HbA1c was significantly lower by 0.33% with HBB-rs334, comparable with Lacy, et al
- “On the contrary, it has also been postulated that lower HbA1c in individuals with sickle cell trait might be due to assay interference by HbS compared with those without sickle cell trait” (Rohlfing, et al letter)
- “G6PD deficiency reduces G6PD activity, results in a premature breakdown of RBCs...the shortened life span of RBCs may result lower HbA1c levels...”
- Concern is that readers may get the impression that HbA1c cannot be used in patients with HbS trait.
- Conclusions
 - The NGSP network is still doing well with very low CVs
 - The change to tighter criteria for the CAP GH survey and NGSP certification is reasonable if we want to see lower overall variability in HbA1c results for patient care.
 - Measurement of HbA1c continues to improve but there still some problems with Hb variant interference.
 - There is still a misconception that HbA1c cannot be used when Hb variants are present.

Discussion:

NGSP SRL criteria

G. Miller asked about the SRLs acceptance ellipse being based on historical data rather than goals. Is it possible to base the ellipse criteria on the performance required to become a SRL, rather than just on what the SRLs are currently doing? C. Rohlfing said the criteria were based on historical data at the time, i.e. the previous several years of SRL monitoring data. The criteria should probably be tightened since the newer SRL methods are overall performing better now. R. Little noted that the NGSP has changed the process of SRL certification. We used to perform a 100-sample comparison against the CPRL which was very cumbersome. We now use 4 months of monitoring data (n=40 samples total) from the candidate SRL and make sure their results fall within the ellipse when compared with the existing SRLs. Therefore it is not clear how the performance required of a SRL could be translated into ellipse criteria, but we can probably tighten the ellipse. G. Miller asked C. Weykamp how the IFCC certifies new network labs, he responded that they use an acceptance ellipse as well, a paper describing the process has been published. Their ellipse is based on what performance is considered achievable by the network labs. C. Rohlfing added that the criteria have to be based on the current state-of-the-art, labs cannot be expected to do better than that. C. Weykamp noted that this is a relevant issue given the recent improvements in routine lab methods, the uncertainty of value assignments is important. D. Sacks suggested consulting with J. Higgins regarding the tightening of the ellipse criteria.

NGSP certifications

D. Sacks asked about the continued increase in the number of manufacturer certifications: do we know why they certify so many methods? R. Little said in many cases the same reagents are used on a number of different instruments. Manufacturers generally certify each individual platform, presumably because their customers want to see their particular instrument on the certified methods list. This is reasonable because we have seen where assays perform differently on different instruments. D. Sacks asked if all of these methods are currently commercially available, R. Little said most of them are. There is now a place on the form submitted for certification where the manufacturer specifies whether the method is currently on the market. This is important because if they fail and it is not yet available, they obviously do not need to notify customers.

Certified laboratories

C. Weykamp noted that the number of labs in China has increased significantly. D. Sacks asked C. Weykamp if any labs in Eastern Europe work with them, C. Weykamp said no. They have worked with labs in Turkey, but not Russia or the other Eastern European countries. They do have EurA1c participants in the Czech Republic and Serbia, so they may see increasing cooperation from these countries.

CAP Data

D. Sacks asked about the uncertainties of the CAP value assignments, C. Rohlfing responded that the ranges are typically ~ mean \pm 0.05% HbA1c. R. Little noted that for the HbS trait sample, there was confusion in her

lab regarding how to report this. The primary method is the G8, so this result could not be reported due to known interference, but the backup method result could not be reported either as it is a different instrument. After discussing the issue with CAP, the result was not reported and the code for unacceptable specimen was used. It is not clear what other labs running the same instrument did, they may have just reported it thinking that the interference in the 5-6% HbA1c range is minimal enough that the result is still acceptable. D. Sacks said the performance in the 6-8% HbA1c range is encouraging, the CVs have been consistently <3% since 2016. This range is important since it is around the diagnostic cutoff. C. Weykamp noted that recent improvement has been small, they see the same thing in their surveys indicating that we are probably approaching the limits of what is achievable. R. Little noted that the goal is now CV<3% at all levels and that we are close to it. D. Sacks asked about the method with the highest between-lab CV (Beckman AU). R. Little said it has been around for quite a while and has not performed well. They have new reagents for it which supposedly solve the issue of interference from HbS and HbC, this will be evaluated in the next variant study. C. Weykamp noted that the CAP results shown are consistent with what they are seeing in Europe. D. Sacks noted that the Variant II Turbo 2.0 also shows some bias with HbAS, R. Little said it showed a similar bias that was statistically significant in a previous study but it was not clinically significant. C. Weykamp said that when looking at variant interference clinical significance may be different for diagnosis versus monitoring. R. Little said the current criteria are $\pm 7\%$ at levels of 6 and 9% HbA1c, we may need to consider tightening this in the next study. J. Felberg said she was surprised to see the degree of HbAS bias for the Variant II Turbo 2.0, and said she will look into it.

NGSP

G. Miller commented that the information presented indicates that the program has been successful. R. Little agreed but added that the effort to standardize C-peptide is progressing much more slowly than was the case for HbA1c. K. Tawiah noted that on the map showing certified labs there are large areas where there are none, e.g. West Africa. R. Little said we do not get any requests from labs in those regions, it could be due to lack of monetary resources or other factors. D. Sacks noted that labs may be using methods that are certified by the manufacturer, even though the lab itself may not be certified. However, some labs in developing countries may use non-certified methods as they may be less costly. G. Miller added that most laboratories that obtain NGSP certification do so because they are performing research trials or studies that involve regulatory submissions, not because they are doing routine clinical testing. D. Sacks said he recently discovered that South Africa gets more NIH money than any other region outside of North America. They do a lot of clinical studies in South Africa, that may be a major reason why there are NGSP-certified labs there. It was noted that there is a large cluster of certified labs in Columbia. R. Little explained that there was an organization in Colombia that coordinated the certification of these labs, the samples were sent to them for distribution among the labs. It was also noted that there is now a large number of certified labs in Asia. R. Little said this has been facilitated in part by having SRLs in Japan and China. She also noted that the NGSP originally certifies many individual labs due to global pharmaceutical trials involving multiple labs.

3) CLIA Proposal for HbA1c/CAP Update—David Sacks

- The number of labs that participate in the CAP proficiency survey has increased since 1993 and is currently ~3500.
- Proficiency Testing (PT)
 - Evaluation of lab performance against pre-established criteria by interlaboratory comparisons
 - Also termed EQA (external quality assessment)
 - In US all labs that measure patient samples are required by law to perform PT
 - Regulated by CMS (Centers for Medicare & Medicaid Services) through CLIA
 - CAP is largest provider of PT material
- CAP Grading
 - Initially, CAP used peer group grading for PT for HbA1c
 - Subsequently, introduced whole blood PT, but maintained peer group grading
 - In 2007 changed to accuracy-based grading
 - Target values assigned by NGSP network
 - $\pm 15\%$ acceptable
 - 99% pass rate
- PT Criteria Tightened
 - In 2008 acceptability reduced to 12%

- 2009 - 10%
- 2010 - 8%
- 2011 - 7%
- 2014 - 6%
- CAP 2010, 2012 & 2013 GH2A Pass Rates at $\pm 6\%$ HbA1c Cutoff

	2010	2012	2013
Low (5.1/5.6%/6.07)	91.0	95.8	93.4
Medium (6.0/7.2%/7.1)	91.6	92.9	95.3
High (8.4/9.4%/9.3)	88.6	92.5	94.3

- CAP PT Criterion 2020: $\pm 5\%$
- Pass Rates for CAP 2018 GH5-A: $\pm 6\%$ vs. $\pm 5\%$ proposed

Sample ID	$\pm 6\%$	$\pm 5\%$
GH-01	95.9	95.9
GH-02	97.3	93.6
GH-03	96.8	95.9
GH-04	95.6	92.4
GH-05	97.1	96.1

- Summary
 - CAP progressively tightened PT grading
 - 2007 - 15%
 - 2009 - 10%
 - 2014 - 6%
 - 2020 - 5% proposed
 - Lab performance on CAP surveys improving, due to better methods
- How could CAP do this? HbA1c is not a regulated analyte
- CLIA Proposed PT Rule
 - Hemoglobin HbA1c would become a regulated analyte
 - Criterion for acceptable performance: Target $\pm 10\%$
- Effect of Change in PT
 - True HbA1c is 6.5%
 - If criterion is $\pm 5\%$, acceptable value is 6.2% - 6.8%
 - If criterion is $\pm 10\%$, acceptable value is 5.8% - 7.2%
- CAP Response to CLIA Proposal
 - CAP is not permitted to fail a lab if it meets CLIA criteria
 - If CLIA accepts $\pm 10\%$, CAP will have to loosen acceptability from $\pm 6\%$ to $\pm 10\%$
 - CAP has elected NOT to reduce criteria from $\pm 6\%$ to $\pm 5\%$ in 2020
- Potential Outcome of CLIA Proposal
 - Accuracy of HbA1c assays likely to deteriorate
 - Patient care likely to suffer.

Discussion

CLIA proposed PT rule

D. Sacks said that there was a comment period for the new CLIA rule. R. Little sent an e-mail to her contacts in the clinical and laboratory community urging them to comment. A lot of individuals and organizations sent in comments. Although there were other analytes listed in the proposed rule, almost all of the comments were about HbA1c and virtually all of them urged CMS not to adopt the rule for HbA1c. An editorial was published in the Journal of Diabetes Science and Technology by Klonoff et. al asking that the rule not be adopted. This was discussed at the Clinical Advisory Committee meeting in June. At the meeting Ann Albright noted that CMS is required to respond to every comment. It was also suggested that representatives of the clinical community could go to CMS and talk to them directly. Representatives from the ADA and JDRF plan to go to CMS. David Nathan is

also going. It will probably be in late August or September. If this rule is enacted it will be devastating, even if manufacturers do not relax their requirements, labs may do so since there will be less risk of failing PT. D. Sacks asked the manufacturer representatives for their thoughts on this. J. Felberg agreed that adoption of the rule would be moving in the wrong direction. There has been much work devoted to improving methods which has resulted in a lot of progress, loosening the PT requirements would set things back years. J. Davis agreed and added that manufacturers should strive to keep making methods better, and those that do not perform well should be called out as the NGSP has done over the years. R. Little said if the rule is adopted we could still point out which methods perform well and which do not, and asked if CAP might be able to provide an educational grade. D. Sacks responded that he has tried to explore the possibility of incorporating some kind of 5% educational criterion on the survey in the event the rule goes into effect; he would need to get approval for this. It would be a way to recognize labs that consistently fall within $\pm 5\%$. G. Miller said his impression is that the 10% proposed criterion is based on the CAP limits from years ago, once the comments are fully address there will hopefully be a recognition that the field has advanced and that 6% or 5% is more appropriate now. However, there is no way to know for sure what the decision will ultimately be. S. Connolly asked about what the other implications are if HbA1c becomes a regulated analyte. G. Miller said there are certain PT and verification requirements but these will little significance for HbA1c, the writing of the PT criterion into the law is the major issue. R. Little said if CMS decided to make HbA1c a regulated analyte at 5% it might have a significant positive impact, that would probably be the best outcome. G. Miller and D. Sacks agreed and noted that once the rule comes out it will remain that way for a long time, likely more than 20 years. H. Vesper said that CMS incorporated cost analysis into the rule change, one of their justifications is minimizing costs to laboratories. It would be good to know how the costs were calculated, it does not appear that costs to patient care were considered. D. Sacks and G. Miller noted that it will likely be at least a number of months before the final rule comes out, since CMS will have to publish responses to all of the comments. J. Felberg noted that many of the comments are likely pretty much the same. R. Little said that there was a recent article in CAP Today where they interviewed a number of experts that urged CMS not to adopt the HbA1c PT rule. H. Vesper said CMS decided not to make Vitamin D a regulated analyte because they said it could not be standardized, we have no idea who they are consulting with in making these decisions. G. Miller said there are currently a lot of regulated analytes that are not standardized. R. Little noted that for many analytes the CAP samples are processed materials and peer-group grading is used. D. Sacks said CAP got rid of their non-whole blood survey a long time ago, but CMS cannot force labs to use CAP for their PT, they can use other PT surveys that do not use whole blood and use peer-group grading. H. Vesper asked if it would be helpful to invite CMS to be a part of these meetings, so they can have a better idea of what it going on. R. Little CMS people have come to the Clinical Advisory Committee meeting before, but we do not know if they were the right people.

4) Clinical Advisory Committee Meeting Update—David Sacks

- The CAC is composed of representatives from major global clinical diabetes organizations. The purpose is to facilitate communication between these organizations and the lab. They advise the NGSP on clinical aspects of HbA1c and report back to their organizations.
- The 2019 CAC meeting took place in San Francisco at the ADA meeting in June.
 - Chaired by Ann Albright of the CDC.
 - R. Little presented an update on NGSP progress.
 - Len Pogach of the VA argued that HbA1c results should be reported as a range rather than a single number, and announced a new DHHS-VA diabetes numeracy literacy campaign.
 - Rick San George of Alere (now part of Abbott) spoke about why they feel their POC instrument should be used for diagnosing diabetes.
 - They have been lobbying the FDA for a diagnostic claim for their CLIA-waived device (Afinion).
 - Eventually they decided on a two-tiered approach
 - 1) Alere obtained FDA approval for a diagnostic claim, but only when the device is used in moderate complexity settings (PT and personnel requirements).
 - 2) There are now trying to obtain a diagnostic claim for use in waived settings as well.
 - This would basically mean that the device could be used for diagnosis virtually anywhere with no PT or testing personnel requirements.
 - If FDA gives the approval for diagnosis in waived settings, other manufacturers could then obtain this approval using the Afinion as a “predicate device”.

Discussion:

Diabetes Numeracy Literacy Campaign

R. Little said the diabetes health literacy campaign that was announced by L. Pogach is focused on helping clinicians and patients to better understand what the numbers mean. For example, if a HbA1c is 7.3 it does not mean that result is exact, there is a confidence range associated with that number. He is also very focused on the problem of hypoglycemia, especially among older patients, and a better understanding of the numbers is part of addressing this issue.

POC HbA1c for Diagnosis

R. Little said that manufacturers applying for a diagnosis claim for waived POC instruments would still have to go through the process for obtaining a FDA diagnostic claim. These criteria are more stringent than for monitoring. J. Felberg said that is true, but they would not have to go through the two-step process as Alere is doing, which would make it easier to get the claim. D. Sacks said the main concern is the lack of PT; we would have no way of knowing how the method is performing in the hands of the end-users. R. Little said we do get some PT data for the Alere method, but these data come from laboratories where PT and personnel requirements apply. D. Sacks was more concerned about bias than imprecision, since for diagnosis the test is supposed to be repeated. He asked C. Weykamp if PT is required for POC methods in Europe. C. Weykamp did not know; the rules can and do vary from country to country. R. Little asked about diagnosis and POC in the Netherlands. C. Weykamp said the guidelines do not say anything about it. E. van der Hagen said that in the Netherlands testing is generally done by laboratories, even much of the physician office testing is controlled by labs, and they are required to participate in PT. D. Sacks said the number of POC devices used for HbA1c in the U.S. probably exceeds the number of laboratory instruments. G. Miller said the practical reality is that we as laboratorians have no way of knowing how physicians are using the results we are providing. It is a reasonable assumption that HbA1c results are being used for diagnosis regardless of if the method is FDA approved for that purpose. R. Little agreed and added that in many cases they probably only use one HbA1c despite the guidelines saying the test should be repeated. D. Sacks said a lot of clinicians were using HbA1c for diagnosis long before it was officially recommended for that purpose. He would ask primary care providers what cutoff they were using and they would generally be vague in their answers. Once the guidelines came out there at least was a universal cutoff value. G. Miller said our job is to try to hold standards to an acceptable level for the best patient care and safety. We can try to influence the field through guidelines and providing information, hopefully the conscientious practitioners will follow the recommendations. Because of HbA1c harmonization efforts, the quality of HbA1c testing is now at a level where good medical decisions are being made in almost all situations. D. Sacks said that manufacturers have been an important part of this process, they have spent much time and money to improve the quality of their methods.

Position at the University of Missouri

R. Little announced that she is planning to eventually retire, so there is an Associate Laboratory Director position open at the University of Missouri. It is now listed with the AACC and in other places. She asked those present to refer any qualified candidates that might be interested. D. Sacks noted that the position has good security with the NGSP ongoing as well as the EDIC which is ongoing and tied to the UM laboratory. M. Steffes noted that the EDIC will continue for at least five years and probably longer, the participation rate among the study patients remains very high.

*D. Sacks thanked everyone for their attendance, the meeting was adjourned at 3:50 PM.
Minutes prepared by C. Rohlfing 8/22/2019. Modified by R. Little 08/23/2019.*