Meeting of the NGSP Steering Committee
Minutes
September 21, 2021 9:00 AM – 11:00 AM CST
Virtual Meeting

Participants:

*David Sacks —NIH, Chair, NGSP Steering Committee
*Randie Little—Univ. of MO, NGSP Network Coordinator
*Robert Cohen—University of Cincinnati
*Jackie Felberg—Bio Rad Laboratories
*Philippe Gillery-University Hospital of Reims (FR), IFCC Scientific Division
*John Higgins—Massachusetts Gen. Hosp.
*Garry John—Chair, IFCC Task Force on HbA1c
*W. Greg Miller—Virginia Commonwealth Univ.
*Elisa Noll—Roche Diagnostics
*Elizabeth Selvin—Johns Hopkins University
*Michael Steffes—University of Minnesota
*Cas Weykamp—Queen Beatrix Hospital (NL), IFCC Network Coordinator
***Member of the NGSP Steering Committee**

Joan Anderson-Bixby—Univ of Minnesota
Shawn Connolly—Univ. Of MO, NGSP
Kuanysh Kabytaev—Univ. of MO
Erna Lenters-Westra—ERL, IFCC, NGSP
Jennifer Peters—Univ. of Minnesota
Curt Rohlfing—Univ. of MO, NGSP
Carla Siebelder—ER, IFCC, NGSP

Steering Committee members not present:
David Nathan—Massachusetts General Hospital
Hubert Vesper—CDC

1) Welcome and Introduction—David Sacks, Chair, NGSP Steering Committee

D. Sacks welcomed those in attendance and those present introduced themselves. The minutes of the 2019 Steering Committee were approved. D. Sacks thanked outgoing manufacturer representative Jon Davis and welcomed new manufacturer representative E. Noll.

2) 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 1.03% and 0.97% 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 <1.5% 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.
  - 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.
  - There are >270 methods and ~140 laboratories currently certified.
  - Most certified labs are Level I and are outside of the U.S.
- Status of HbA1c Measurement (CAP data)
  - There has been much improvement in within and between-lab variability since 1993.
  - Current CAP limits (2013-2021) : Each result must be within ±6% of NGSP assigned target value (mean of 8 SRLs, 2 days of triplicate results from each).
  - CAP 2021B survey
    - Five samples

- 2021B CAP Pass Rates (±6%)

Specimen	NGSP Target (% HbA1c)	Acceptable Range (±6%)	Pass rate % (Low/High)	Cumulative Pass Rate % ±6%
GH-06	5.80	5.4-6.2	92.3/100.0	98.0
GH-07	9.12	8.5-9.7	90.7/100.0	97.8
GH-08	5.47	5.1-5.8	95.7/100.0	98.5
GH-09	7.25	6.8-7.7	93.6/100.0	97.9
GH-10	9.26	8.7-9.9	90.4/100.0	97.3

  - Cumulative pass rates at ±6% have increased over time and have consistently been ≥95% for the last few years.
  - All-method CVs have dropped over time since 2000.
  - All-method CVs were all ≤3% in the last two surveys. They were 2.6%-3.0% in the current survey.
  - CAP Summary (2021B)
    1) Method-specific, between-laboratory CV's ranged from 1.0% to 3.9%.
    2) Over 90% of laboratories are using methods with CVs<3.0% at all five HbA1c levels.
    3) All-method CVs for the most recent survey ranged from 2.6-3.0% (3.0, 2.6, 2.6, 2.6, 2.7%).
    4) Pass rates are between 97.3 and 98.5% with the current 6% limits.
- Hb variant interference; Rohlfing, et al. Evaluation of interference from hemoglobin C,D,E and S traits on measurements of hemoglobin A1c by fifteen methods. Clinica Chimica Acta 2021:522;31-35: Three out of 15 methods showed clinically significant interference from one or more of the common variants (HbAC, HbAD, HbAE and HbAS). The three methods were the G11, b101 and DCA Vantage.
- Conclusions
  - The NGSP network is still doing well with very low CVs.
  - CAP survey results show that all method CVs (including all laboratory results) have been <3% for the last 2 surveys and a few other previous surveys. We hope to see this continue.
  - Measurement of HbA1c continues to improve but there are still some problems with Hb variant interference.

Discussion:

Variant interference

R. Cohen asked if the variants examined in the study were all heterozygous. R. Little said they were, only heterozygous variants were studied. E. Lenters asked if there were any explanations for the interferences observed for the DCAVantage, which have not been seen previously. Also, interference from HbAE has been noted for the b101, but the present study also shows interference from HbAC. R. Little said that in their previous study they did not see interference for the DCA Vantage. The reason it was re-examined in the current study was that on a previous CAP survey where a HbAS sample was included, the DCA showed a positive bias for the HbAS sample when compared to a non-variant sample in the same HbA1c range that was also included in that survey. She did not have an explanation for why we now see the interferences, and was not sure if Siemens knew why. This is the first time we have seen this type of change with an immunoassay; we have seen this before with ion-exchange HPLC methods. Siemens analyzed the sample for the study, we had some discussions with Siemens regarding these findings and looked at the data several different ways. E. Lenters noted that recent software changes seem to have eliminated interferences for the Tosoh G8.. R. Little agreed, and asked E. Lenters about her previous observation that the newer G8 software did not always recognize the HbAE peak properly and produced erroneous HbA1c results when that happened. E. Lenters said that this problem seems to have been resolved with the latest software update. R. Little said that is has been difficult to obtain enough heterozygous variant samples to perform these studies, and asked those present to contact her if they know of any potential sources for these samples.

Improved analytical performance

R. Cohen asked about the reason(s) continued reduction in CVs for analytical methods, is it manual technique, things the manufacturers are doing, or other factors? R. Little responded that manufacturer methods are improving, the NGSP and CAP have tried to motivate them by tightening their criteria over the years. R. Cohen asked what they do to make them better. R. Little said sometimes they make improvements to an

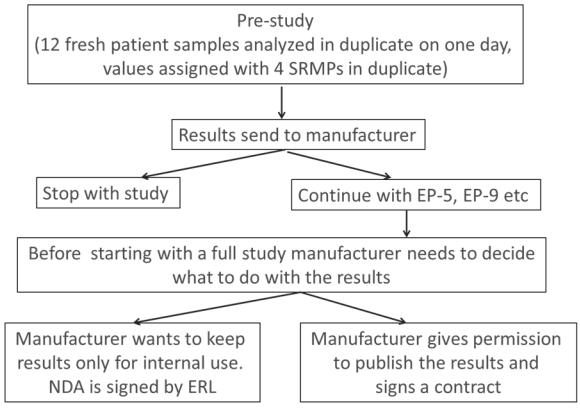
existing method, other times they come out with newer and better methods that replace the old ones. J. Feldberg agreed, saying manufacturers are always looking to improve their methods since they take part in NGSP certification and their customers take part in the CAP survey. C. Rohlfing and R. Little noted that the ion-exchange HPLC instruments in particular have always been pretty precise. Although they have improved some over the years, the most dramatic improvements have been seen with immunoassays. This is likely due to technological improvements with the assays and instruments. E. Noll agreed, noting that their company has improved the technology of their immunoassays over time and they watch the CAP surveys closely. D. Sacks said the manufacturers have been instrumental in these efforts. Between 2014 and 2021 the data show continued improvement in the performance of assays despite no change to the CAP criteria over the same time period. The manufacturers have spent a lot of effort and money to make this happen. R. Cohen asked about POC vs. laboratory methods. R. Little said a concern with POC methods is that they are generally used in CLIA-waived settings where participation in proficiency testing such as CAP is not required. There are a few that appear on the CAP survey, but it is likely that those that do appear on the survey are being used in non-waived settings.

3) CAP Update—David Sacks

- The Clinical Advisory Committee normally meets annually at the American Diabetes Association Meeting, but they have not met since 2019.
- Proposed CLIA update
  - Background
    - CAP has gradually tightened the pass/fail criteria for HbA1c over the years, it is currently ±6%.
    - CAP was able to tighten the criteria because HbA1c is not a CLIA-regulated analyte.
    - Several years ago, CMS decided to update the list of regulated analytes.
  - CMS issued a draft proposal that HbA1c be added to the list of regulated analytes, with a pass rate of ±10%.
  - CAP would be required by law to loosen their HbA1c PT criterion to ±10% if the proposal is adopted.
  - We do not currently know where the 10% number came from or who suggested it.
  - If adopted, this would have a negative impact on patient care.
  - This proposal generated much discussion, the overwhelming majority of comments sent to CMS expressed opposition to adopting the 10% criterion for HbA1c.
  - The pass rate for laboratories is over 95% using the current CAP criterion of ±6%.
  - CMS has not stated if or when the proposal will be changed or adopted.
  - CAP had intended to tighten the criterion to ±5%, but decided not to do so after the proposal was introduced.
  - Based on the CAP surveys where an educational grade of ±5% was included in the reports, the number of labs that would have failed using this criterion was only slightly higher compare to ±6%.
- Inclusion of a hemoglobin variant in the CAP HbA1c PT survey.
  - CAP periodically includes a variant sample in the survey.
  - Purpose is to see how variant results are affecting HbA1c results and how they are being reported.
  - The results are not graded for methods that have interference with variant samples and labs that use these methods are not punished.
  - CAP will continue to periodically include variant samples in the survey.

4) Concerns about certification of POCT instruments—Erna Lenters-Westra

- Original published study of POC instruments: Six of eight hemoglobin A1c point-of-care instruments do not meet the general accepted analytical performance criteria. Clin Chem. 2010 Jan;56(1):44-52.
- Published method evaluations can have significant impact upon manufacturers, so we have developed a formal protocol for evaluations.
- Method evaluations: Current Procedure



- Recent POC method evaluation
  - Manufacturer product insert
    - Method comparison against in-house HPLC method: r^2=0.9528
    - Intra and inter-lot precision claims are both CV≤10%
  - Analyzer showed acceptable performance in the IFCC certification program.
  - Methods is also NGSP certified.
  - Recent method evaluation performed at Isala: Pre-test results
    - Method involves pipetting and mixing steps as well as timing requirements.
    - Comparison with means of all 4 IFCC SRLs using 24 samples: r^2=0.9196
    - Accuracy: Average bias was -10.97 mmol/mol
    - Precision: CV=9.94%
    - Performance clearly did not perform in accordance with IFCC or NGSP requirements.
  - When the manufacturer was contacted, possible explanations included minor deviation in room temperature, pipetting technique, and minor timing issues during analysis.
  - There is no clear explanation as to the discrepancy between the method evaluation performance vs. performance in IFCC and NGSP certification.
  - Proposal: Communicate to manufacturers by email and on the website that, for NGSP certification, manufacturers may randomly be asked for "raw" printed data from the POCT instrument with results, time and date.

Discussion

CAP

J. Feldberg said it is very disappointing that CMS would propose criteria that would actually set back the standardization effort. D. Sacks agreed, noting that the current pass rates over 95% are probably actually higher, given that many failures on CAP are due to transcription error and not analytical error.

Concerns about POC HbA1c

E. Lenters noted that POC testing is often performed by healthcare providers that lack the laboratory experience she has. If a method performs poorly in her lab it is highly unlikely that it can be performed better by those with little or no laboratory training. The discrepancy between certification and method evaluation performance begs the question of whether data being submitted by manufacturers is legitimate, especially if they also have a precise laboratory analyzer on site. R. Little agreed and noted these results are disappointing. She is concerned not only about POC methods but some lab methods as well. In particular, there is a lab method that always shows little or no bias on certification, but almost always shows a bias on the CAP survey. With this particular method, the kits come from the U.S. but values are assigned outside of the U.S., it is unclear as to whether this may be part of the issue. For POC methods it is true that some manufacturers have in-house laboratory methods, and when she gets data from their POC methods she cannot say for certain that their data came from the POC rather than lab method. We do advise laboratories that, when choosing a method, they first look to see if the method is certified but then also look at how the method is performing on the CAP surveys. E. Lenters said that she asked the manufacturer to include R&D people in future virtual meetings, as the people she has been speaking to are from marketing and may not fully understand the technical issues. R. Little asked if this particular method appears on any PT surveys, V. Raneva said

that it is difficult for ASRL#1 to ship samples to China, where this method is, so it would not have been in their surveys. It is her understanding China was supposed to conduct their own PT surveys, but she was not sure if this method would have been included. R. Little said she will contact ASRL#2 in China and see if they might have some PT data from China. E. Lenters asked about her proposal; if printouts of raw data could be obtained that include the result, date and time, you can at least know that the data came from the POC instrument and not their in-house HPLC method. G. John noted that the manufacturer did not make inaccurate claims about the performance of their method in their package insert. E.Lenters agreed but noted that when the manufacturers deal with laboratories they generally show their certificates, not their package inserts. C. Siebelder and C. Weykamp said they are planning to add a statement to the IFCC HbA1c web site that is based on the proposal, just to add a safeguard against fraud. J. Feldberg said that at Bio-Rad they have looked at some POC methods and seen a wide variety of performance among them. If printouts are required, they could still use their in-house HPLC to tell them what the values should be, then run the samples on their POC method when needed until they get a result that closely match the HPLC. R.Cohen expressed this concern as well. E. Lenters said that the inclusion of date and time on the printouts should be able to indicate when/if this happens. We cannot prove that a delay between results is due to repeated reanalyses of the samples, and this checking of printouts cannot be 100% effective, but it can put manufacturer on notice. She was concerned, because a lot of POC method evaluations in her laboratory have been stopped by the manufacturers after the pre-study due to performance issues. Nonetheless some are NGSP certified and have IFCC certificates. C. Siebelder and C. Rohlfing noted that there are PT data for laboratory methods, so if there is manipulation with the certification data at least we can see when field performance does not match certification performance. With most POC methods there are no PT data, so there is no way to know. R. Little said this is a concern regarding FDA approval of POC for diagnosis. If they are approving a method for diagnosis as compared to monitoring there is a lot more involved. Nonetheless methods can change over time, and without PT data available it is hard to know how the method is performing in the field. Regarding the proposal, it would be more work for the NGSP but it is probably doable. D. Sacks thought it was a good way of reducing the likelihood of fraud. He asked E. Lenters what percentage of manufacturers stop evaluations after her initial analyses. E. Lenters said she would need to look back at the data to obtain a definitive number, but it is probably ~10%. In some cases the manufacturers see that the performance is not good and want to work with their lab to improve the method, others are new and not yet on the market. In these cases, the lab works with the manufacturers to improve the method. However, there are some that are already on the market and in use, and there is no indication that the method will be improved. D. Sacks wondered about the signed non-disclosure agreements with manufacturers that prevent E. Lenters from sharing this information about methods with the NGSP, IFCC or other relevant parties. This is important information and poor methods have a negative impact on patient care, is it necessary to sign these agreements? E. Lenters replied that it is frustrating, but it is necessary in order to work with manufacturers rather than push them away, we want to work with them and help them improve their methods. In some cases, we have told them the method is so bad it needs to be removed from the market, and in some cases they have done so. R. Little said that it would probably be too expensive to just purchase the methods instead of working directly with the manufacturer, but that would avoid the nda issues. E. Lenters agreed that this would be a good idea, but it is expensive. If money could be provided, she would be happy to do the testing. R. Little said that for variant studies their lab does not have agreements so that the data can be published, although for methods still in development the results aren't published if the manufacturer objects to it. In the past we have found laboratories running the methods that analyze the samples when the manufacturer cannot or does not wish to run them. D. Sacks asked if E. Lenters could send an e-mail to him outlining what the project would cost. E. Lenters said she can, it would depend upon whether it would involve just an initial small study (pre-test) or a full evaluation including EP-5, EP-9, etc. The former would be much less time-consuming and less expensive, and might be sufficient. R. Little said there may be manufacturers who would be willing to help fund the study. E. Lenters said she is now working with an organization, FIND, that is trying to make POC HbA1c available at low cost to low and middle-income countries. They sent out applications to many manufacturers to participate, she has proposed that participating manufacturers provide instruments for her lab to perform small studies to assess the performance of the methods. R. Little asked if this data will be published, E. Lenters said FIND does not want the data to be published. D. Sacks said it is an unfortunate situation, the data are important but if they are not in the public domain very few people will be aware of the information. He asked R. Cohen for a clinical perspective. R. Cohen said he is one of two endocrinologists out of 10 in their group that does not use POC HbA1c because of these kinds of uncertainties. These methods are generally not used in lab settings, and it can be unclear as to how well they are performing. He understands the limitations involved in gaining access to the necessary materials but is concerned about the lack of public access to the information, it is a conundrum. R. Little asked if R. Cohen knew how the POC results are being used (monitoring, diagnosis). If they are using them to diagnose diabetes and the result is high, do they verify it by repeating the test on a laboratory method? R. Cohen

responded that they use it for diagnosis as well as monitoring, and in the real world there is often no distinction between lab and POC results. It is fine to use POC in screening setting where you are looking for a A1c of 9 vs. normal, but when you are trying to distinguish 6.5 from 6.0 or 7.0 it is probably pressing the limits in terms of the CVs of some of these methods. R. Little said there are some POC methods that perform well and could probably get thru the CLIA-waiver process that includes non-trained users. However, we still would not know if the method changes over time. She suggested they might be able to get students to do some of the work in their institution, but there would still need to be funding. There is the issue of trained lab personnel performing the test vs. the users that would actually perform it in the field. E. Lenters agreed, noting that for some methods it has been shown that there is no difference, but there are POC methods that involve pipetting, etc. where the test would be less reliable in the hands of users with little or no lab training. However, most POC methods are fairly foolproof. R. Cohen reiterated the importance of obtaining real-world data for these methods in clinical settings with the actual end-users. E. Selvin proposed the alternative of a consortium approach, where groups of labs that already have the instruments could gather the data, then pool their results for publication. Either way it would take a lot of leadership and effort. Where funding is concerned, there are groups that facilitate interactions with industry where they obtain money and then make it available in the form of grants. It would require finding the right partners. J. Feldberg offered to inquire about funding at her company, and suggested approaching other manufacturers as well. E. Lenters noted that there are so many POC methods available that we cannot test all of them. The ones that appear on PT surveys are not a major concern, but the vast majority do not. R. Little said it would be good to get data from other countries including PT surveys in order to try to get a sense of which methods are widely used and try to focus on those. C. Rohlfing added that it also be best to focus on those which are IFCC and/or NGSP certified. D. Sacks said with glucose meters David Klonoff's group periodically monitors the performance of them but focuses upon those that are the most commonly used. D. Sacks returned to E. Lenters proposal regarding requests for data printouts from manufacturers. R. Little agreed to compose something to send out to the entire committee. J. Feldberg and E. Noll agreed to approach their companies re. possible funding for the POC studies. D. Sacks expressed appreciation for this, noting that it is very important information.

EurA1c, IFCC study

C. Siebelder said that they are continuing with the EurA1c project, the latest study included over 5,000 participants. The IFCC intercomparison studies are also continuing, this year the samples could not be sent out in March due to Covid, but samples were sent out in July. She also reminded those present of the upcoming IFCC symposium in honor of the retirement of C. Weykamp.

D. Sacks thanked everyone for their attendance, the meeting was adjourned at 10:40 AM CST.
Minutes prepared by C. Rohlfing 10/14/2021.