Meeting of the NGSP Steering Committee
Minutes
Sunday July 23, 2023 2:00 PM – 4:30 PM
Anaheim Marriott, Anaheim, CA

Participants:

*David Sacks —NIH, Chair, NGSP Steering Committee
*Carla Siebelder—IFCC HbA1c Network Coordinator
*Monica Swenson—Abbott Diagnostics
*Hubert Vesper—CDC
*Mathew Wagner—Sebia
Shawn Connolly—Univ. of MO, NGSP
Emma English—Chair, IFCC C-EUBD
Kuanysh Kabytaev—Univ. of MO
Erna Lenters—ERL, IFCC, NGSP
Kate Nyarko—Univ. of MO
Violeta Raneva—RECCS Japan
Curt Rohlfing—Univ. of MO, NGSP

Via Zoom:
Beena Alkolkar—NIH
*John Higgins—Massachusetts Gen. Hosp.
*Randie Little—Univ. of MO, NGSP Network Coordinator

Steering Committee members not present:
*Robert Cohen—Univ. of Cincinnati
*Philippe Gillery—IFCC Scientific Division
*Garry John—IFCC Scientific Division
*David Nathan—Massachusetts General Hospital
*Elizabeth Selvin—Johns Hopkins University
*Michael Steffes—Univ. of Minnesota

***Member of the NGSP Steering Committee**

1) **Welcome and Introduction—David Sacks, Chair, NGSP Steering Committee**
D. Sacks welcomed those in attendance and those present introduced themselves. D. Sacks thanked E. Noll for her service to the NGSP and welcomed new manufacturer representative Mathew Wagner to the Committee. The 2022 minutes were approved.

2) **NGSP Progress Report—Randie Little , NGSP Network Coordinator**
- NGSP Network Monitoring
  - Currently there are two PRLs the CPRL and the EPRL in Europe.
  - The PRLs and SRLs continue to demonstrate excellent comparability (May between-lab CVs were 1.24% and 0.91% 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
  - The original LTQC samples were analyzed from 2010 to 2019
  - New LTQC samples were prepared and have been analyzed from 2018 to the present
  - Analyzed monthly by Missouri SRLs and quarterly by all SRLs.
  - In all cases the mean CVs for the LTQC samples were all ≤1.5%
- NGSP Certification
  - The number of certified methods continues to increase, while the number of laboratories has leveled off.
  - There are ~330 methods and ~130 laboratories currently certified.
  - Most certified labs are Level I and are outside of the U.S.
- Variability of Level 1 Labs May 2023
  - Level 1 labs are monitored quarterly, so each month approximately 1/3 of the total number of L1 labs participate in monitoring.
  - In May, the between-lab CV for the L1 labs was 1.18% (n=27)
- Status of HbA1c Measurement (CAP data)

- Current CAP limits (2013-2023): Each result must be within ±6% of NGSP assigned target value (mean of 8 SRLs, multiple results from each).
- There has been much improvement in within and between-lab variability since 1993 as the CAP and NGSP certification criteria have been tightened over the years.
- CAP 2023A survey
  - Pass Rates (±6%)

Specimen	NGSP Target (% HbA1c)	Acceptable Range (±6%)	Pass rate % (Low/High)	Cumulative Pass Rate % ±6%
GH-01	7.58	7.1-8.1	85.1/100.0	97.0
GH-02	8.88	8.3-9.5	90.9/100.0	97.6
GH-03	5.82	5.4-6.2	93.6/100.0	98.2
GH-04	10.00	9.4-10.6	86.7/100.0	96.9
GH-05	5.24	4.9-5.6	90.0/100.0	97.4

  - Cumulative pass rates were all >96%.
  - For individual methods, pass rates ranged from 85.1% to 100%.
  - All-method CVs have dropped over time since 2000.
  - All-method CVs for the 2023A survey were all ≤3%.
  - Between-lab CVs by method type show that there are samples of all method types that perform well, and only one method showed a CV>3%. The three POC methods that appeared in the survey performed well.
  - Biases by method type showed that the degrees and directions of bias were not specific to particular method types.
  - CAP data Summary (2023A)
    1) Method-specific, between-laboratory CVs ranged from 0.7% to 3.9%.
    2) Overall, 86% of laboratories are using methods with CVs < 3% at all five HbA1c levels.
    3) All-method CVs for the most recent survey ranged from 2.4-3.0%.
    4) Overall Pass rates are between 96.9 and 98.2% for the current 6% limits
- Raw data from Manufacturers
  - We began requesting raw data from manufacturers submitting certification data for POC methods after our 2021 meeting.
  - This data are still being requested.
  - All raw data have matched data sent for certification.
  - Should we continue to ask for raw data?
- Conclusions
- The NGSP network is still doing well with very low CVs.
- CAP survey results show that the all-method CVs (including all laboratory & methods' results) have been <3% for the last 4 surveys. We hope to see this continue.

Discussion:

NGSP Network

D. Sacks asked why there are only two PRLs. R. Little said the PRL in Japan is not currently working. V. Raneva said the old HPLC system used by ReCCS Japan to run the PRL method broke down, they are currently looking for a new HPLC system. E. Lenters suggested that the NGSP bias criterion of ±0.35% HbA1c should be tightened, R. Little agreed that saying previous data will need to be examined and a statistician will need to be involved. The ellipse criteria will probably need to be tightened as well. R. Little asked if the IFCC network criteria has been tightened, C. Siebelder responded that it has been tightened several times. C. Rohlfing said that for the ellipse recent monitoring data from the SRLs can be provided to a statistician to then determine reasonable tighter criteria. V. Raneva noted that for May the ASRLs and U.S. SRLs all seemed to fall toward the upper left side of the ellipse, whereas the ESRLs fell on the lower right side. In June ASRL#1 once again fell in the upper left. R. Little responded that in May ESRL#15 was actually close to the ASRLs and U.S. SRLs, and did not think that the observed patterns are consistent over time. C. Rohlfing added that there have been some months where the SRLs are bunched together near the center while

in other months they are more spread out. There is some inherent variability with all of the methods, although if patterns emerge that are consistent over time indicating possible long-term trends further investigation might be needed.

Level 1 Laboratories
E. Lenters said the variability between the L1 certified labs is significant, for example the difference between the highest and lowest values for sample 3275 was 0.45% HbA1c. R. Little replied that, given that the L1 labs run different methods and method types, this is the current state of the art that is seen when looking at CAP proficiency data. C. Siebelder noted that looking at the individual samples the variability is higher for some than for others. C. Rohlfing added that typically the higher variability is seen with the higher HbA1c levels. R. Little agreed to indicate the HbA1c levels when the slide is presented in the future.

CAP Survey
D. Sacks noted that the number of participants in the CAP survey varies substantially among methods. In many cases the methods showing poor performance have very few users. R. Little said the tables included on the CAP summary reports available on the NGSP web site include the number of participating labs for each method. D. Sacks said there is no way to know how many samples are being analyzed by each participating laboratory. Some participants are large commercial labs, others are much smaller. Some analyze hundreds of HbA1c samples a day, while others may only run 40 or 50 samples per month. He did not know any way to obtain this information, which is unfortunate because is would be useful. R. Little said that a question about how many samples the lab analyzed was included on one survey, but some labs did not put a number so the information obtained was limited. D. Sacks said CAP could try this again, he will address this with CAP.

Raw Data
C. Siebelder said she has also been requesting raw data for IFCC results from manufacturers sporadically and has also found that the data have always matched. E. Lenters was surprised. One POC method showed poor results in her laboratory, she took a video when performing the test and sent it to the manufacturer who pointed out minor factors (pipetting at 58 vs. 60 seconds, lab temperature not exactly 21 degrees C, etc.). C. Siebelder got their IFCC data and they looked fine. The problem is that the manufacturer obviously has a lot of experience running the test under what is likely very controlled conditions, but the data aren't reflecting performance in the hands of the end-users. R. Little said this illustrates the importance of having proficiency data, they are the only way of knowing how the methods are performing in the field. There are still some POC methods, and even a few lab methods, that fail NGSP certification. E. Lenters asked how many fail, R. Little said it is relatively few but did not know the percentages.

3) NGSP certification and compliance with 21 CFR 862.1373 —Monica Swenson

- 21 CFR 862.1373 - Hemoglobin A1c test system.
  - (a) Identification. A hemoglobin A1c test system is a device used to measure the percentage concentration of hemoglobin A1c in blood. Measurement of hemoglobin A1c is used as an aid in the diagnosis of diabetes mellitus and as an aid in the identification of patients at risk for developing diabetes mellitus. The CAC is composed of representatives from major global clinical diabetes organizations.
  - (b) Classification. Class II (special controls). The special controls for this device are: (1) The device must have initial and annual standardization verification by a certifying glycohemoglobin standardization organization deemed acceptable by FDA.
  - Has the NGSP steering committee considered the regulatory implications of the special controls - and in particular with respect to timelines?
- Timelines of certification
  - Annual certification is usually tight on timeline: Example:
    - Samples received in February in two rounds (two first weeks of February)
    - Results submitted mid February
    - Certification result reported back to manufacturer 23/24 March
    - Previous certificate expires 1 April (Time from result to certificate expiration is approximately 1 week.)

- In case there is a failing result, the timeline to investigate and take actions is too short.
  - Products with diagnostic claim according to the special controls are non-compliant if certification fails and must be withdrawn from the market
  - Product withdrawal – several tasks must be done:
    1) Investigation
    2) Contract reviews
    3) Prepare customer communication
    4) Field action
- Certification timelines – how can risk be reduced?
  - The obvious: do not fail certification
  - In case of failure:
    - Perform certification more frequently (e.g. every 6 months)
      1) This will give 6 months for investigation, potential correction and new certification
      2) Will increase the testing burden for the network laboratories
    - Certification date delayed compared to time of certification measurements (certificate starts for example 4-6 months after certification measurements)
    - Temporary extension of certificate to allow time for investigation, correction and new certification measurements
    - Other proposals?

Discussion:

D. Sacks noted that the regulation states that annual standardization verification is required, so extending the certification beyond one year is not an option. R. Little said that there is no formal limit as to how early re-certification can be performed, so the manufacturer can just start the process several months before their current certification expires. Six months is probably too early, but 3-4 months ahead would be fine. The certification form has a checkbox option where the manufacturer can choose to have the new certification issued when the old one expires, but it is generally assumed that is the case unless the manufacturer specifies otherwise.

4) Clinical Advisory Committee Meeting Update—David Sacks

- The CAC met at the June 2023 American Diabetes Association annual meeting in Anaheim.
- The purpose of the CAC is to facilitate two-way communication between the NGSP and the clinical community.
- The CAC is composed of representatives from major global clinical diabetes organizations.
- Chaired by Dr. Christopher Holliday, Director of Diabetes Translation at the CDC.
- Summary
  - R. Little presented an update on NGSP progress.
  - D. Sacks presented an update on the CMS guidelines.
  - There was discussion regarding the use of GMI (Glucose Management Indicator).
    - The FDA decided not to allow companies to use the term “estimated A1c” to describe the A1c estimate derived from CGMS.
    - Thus, the term GMI was adopted for the A1c estimate.
    - The companies that manufacture CGMS put the GMI in their reports seen by patients and providers.
    - There is a question over the value of GMI when HbA1c can be easily and accurately measured.
    - Some parties in the U.S. have been pushing to replace HbA1c with GMI, there is also a push for using CGM in people with Type 2 diabetes.
    - E. Selvin gave a presentation about CGM
      1) Data from subjects who wore CGM devices from 2 different companies simultaneously.
      2) Significant differences were seen between the two CGM devices.
      3) E. Selvin could not get the manuscript published in the clinical journals; it is now published in Clinical Chemistry.
    - There was much discussion of GMI and the fact that the clinicians are often not aware of the limitations of CGM.

5) CMS Guideline Update—David Sacks

- Proficiency Testing (PT)
  - 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
  - ±15% acceptable
  - 99% of laboratories passed
- 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 ±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

- Proposed CAP PT Criterion 2020: ±5%
- CLIA Proposed PT Rule 2019 (CLIA 88 update)
  - Hemoglobin HbA1c would become a regulated analyte
  - Criterion for acceptable performance: Target ±10%
- Implications of New CLIA Proposal
  - HbA1c would become, for the first time, a regulated analyte
  - CAP is not permitted to fail a lab if it meets CLIA criteria
  - If CLIA accepts ±10%, CAP will have to loosen acceptability from ±6% to ±10%
  - CAP elected NOT to reduce criteria from ±6% to ±5% in 2020
- Response to CMS 2019 Proposal
  - Presented at CAC meeting at ADA in June 2019
  - Multiple organizations (clinical and lab) and individuals sent comments to CMS
  - Almost all the 107 comments received by CMS protested loosening HbA1c criteria
  - Delegation from ADA went to speak to CMS
  - An editorial was published in 2019 in a clinical diabetes journal criticizing the proposal (Klonoff et. al, J Diabetes Sci Technol 2019 May;13(3):424-427).
- CAP 2010, 2012, 2013 & 2022 GH2A Pass Rates at ±6% HbA1c Cutoff

	2010	2012	2013	2022
Low (5.1/5.6%/6.07)	91.0	95.8	93.4	98.5
Medium (6.0/7.2%/7.1)	91.6	92.9	95.3	98.3, 98.6
High (8.4/9.4%/9.3)	88.6	92.5	94.3	97.5, 96.9

- Pass Rates for CAP 2020 GH5-C: ±6% vs. ±5%

Sample ID	Target (%)	±6%	±5%
GH-11	5.5	97.9	**95.2**
GH-12	8.3	97.7	**95.4**
GH-13	5.1	97.6	**97.6**
GH-14	10.1	96.9	**95.1**
GH-15	6.0	97.6	**96.6**

- CMS Response
  - Not persuaded by comments
  - Acknowledge improvement in accuracy
  - Concerned that "…tighter criteria will limit access to testing…"
- Final CLIA Rule
  - Acceptance limits for HbA1c are 8%
  - Effective July 11, 2024
- Implications of New CLIA Regulation
  - CAP has been considering options
  - CMS indicated accreditation organizations can require labs to meet more stringent criteria
  - Can CAP require 6% for HbA1c pass?
- CAP Conundrum
  - CAP has 2 separate programs
    - PT
    - Accreditation
  - Grading of regulated analytes by PT providers must follow rules in Federal Register
  - Accrediting agency can require better accuracy for lab to remain accredited, but PT provider must grade HbA1c at 8%
  - Formal grading will have to change to 8%

Discussion:

CGMS

E. Lenters asked why the clinical journals did not want to publish the Selvin et. al manuscript. D. Sacks replied that the clinical community does not want to hear about it. For example, there was a joint ADA/AACC symposium at the ADA meeting where the use of glucose meters and CGM in hospitals was discussed. The moderator, a clinician, was shocked at the anger of several physicians present because they did not want to hear about limitations of CGM.

CMS and CAP

D. Sacks noted that CAP adopting more stringent PT requirements for accreditation than those used for formal PT grading will take time to sort out, likely years. R. Little asked if CAP would consider an educational grade, D. Sacks said they would and he will push for it. R. Little asked about the language in the CMS guideline, doesn't it indicate that CAP could adopt PT criteria more stringent than CLIA? D. Sacks clarified that it said that accreditation organizations can do this, but that does not mean it can apply to the formal PT grading, these are considered two different CAP functions. S. Connolly asked if there is any other example of this, D. Sacks said only one: neonatal bilirubin. D. Sacks said there is another problem: labs do not have to use CAP as their accrediting agency or PT provider. M. Wagner asked for clarification, CAP can require more stringent PT for accreditation, like 6%, but cannot require this for PT? D. Sacks said yes, they are considered two completely separate CAP functions. M. Wagner noted that this would be confusing for laboratories, D. Sacks agreed. H. Vesper explained that part of the accreditation is that the lab must show sufficient accuracy for their method. CAP presumably would require a laboratory to demonstrate accuracy within 6% to pass accreditation. D. Sacks

noted that this would have to be a special case that would apply to HbA1c only. Normally, CAP simply requires labs to show that they passed PT using whatever the current CAP PT criteria are. R. Little asked how labs will know this before they are inspected, D. Sacks said the accreditation criteria are written. The wording of the criteria get revised periodically based on input from inspectors. R. Little was concerned that labs will totally miss this unless it is specifically pointed out at the time the change is implemented. E. English asked if this means that the accreditation criteria will have to change to 8% until the accreditation change is formally approved and adopted, D. Sacks said yes. It has to be done, but it has to go thru a different branch of CAP. The CAP leadership will need to be convinced that the accreditation criteria need to be changed, currently some in leadership are not convinced. E. English asked if we know how the change from 6 to 8% might affect pass rates, and when labs fail do they tend to fail badly? D. Sacks said the numbers show that a few more labs will pass at 8%, he did not know the degree to which labs fail when they do. R. Little and D. Sacks noted that the concern is that labs will be less motivated to do better. D. Sacks noted that the manufacturers still have to pass NGSP certification, so it is not likely that the instruments will change, but there is a difference between what manufacturers do vs. what labs do. E. English asked if the NGSP criteria could be tightened, would that have any impact. D. Sacks did not think so, because that only addresses manufacturers and not labs. M. Wagner suggested that if CAP eventually agrees to change to 6% for accreditation it would be good to explain this as part of the educational grade, D. Sacks and R. Little agreed. E. English asked if there is a concern that this change could drive labs away from CAP accreditation and toward other accreditation providers. D. Sacks said he has not heard discussion of this, although there has been some discussion that tightening of the PT criteria might cause labs to use other PT providers. D. Sacks said the most important consideration right now is convincing CAP to adopt 6% for accreditation. H. Vesper agreed, saying this could then be added to the inspection checklist.

6) Updated Laboratory Medicine Guidelines for Diabetes Testing—David Sacks

- Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus: Initially published in both Clinical Chemistry and Diabetes Care in 2002.
- Guidelines were an ADA position statement.
- Updated guidelines were published in 2011.
- Review Process
  - Select expert committee
    - Mark Arnold
    - George L. Bakris
    - David E. Bruns
    - Andrea R. Horvath
    - M. Sue Kirkman
    - Ake Lernmark
    - Boyd Metzger
    - David Nathan
    - David B. Sacks
  - Draft document
  - Grade recommendations
    - Grading Laboratory Guidelines
      1) No accepted grading scheme for rating quality of evidence of laboratory testing
      2) ADA grading is predominantly for therapy
      3) Rita Horvath developed scheme
      4) Strength of recommendations and quality of evidence graded separately
    - Grade the Strength of Recommendations

Grade	Evidence	Experts
A Strongly recommends	High/moderate quality	Strong/very strong agreement
B Recommends	Moderate quality evidence OR Low/very low quality	Moderate agreement OR Strong/very strong agreement
C Insufficient information	Lacking, scarce or very low quality	No or very low agreement
Good practice point (GPP)	Observational/case studies, non-systematic reviews, technical documents, personal opinions, expert consensus or position	Consensus

    - Rate the Quality of Evidence

Rating	Estimate of Effect	Evidence
High	Further research very unlikely to change our confidence in the estimate of effect	High level individual studies
Moderate	Further research is likely to have an important impact on our confidence. May change recommendation.	High/moderate studies. Strength limited by studies (#, quality) OR indirect evidence
Low	Further research is very likely to have an important impact. Likely change recommendation	Low level studies with serious design flaws OR Indirect evidence
Very low	Estimate of effect is very uncertain	Insufficient to assess the effects on health outcomes

    - Post on the internet for public comment: AACC & ADA
    - Write response to each comment
    - Revise
- Review Process (ctd.)
    - Submit to committees at AACC and ADA
    - Revise
    - ADA sent for peer review - 4 reviewers, 198 comments
    - Write response to each comment
    - Revise and resubmit to committees
    - Approved by AACC Evidence Based Laboratory Medicine Subcommittee in January 2023, the AACC Academy Council in February 2023, the AACC Board of Directors in March 2023, and the ADA in March 2023
    - Submit for publication
    - Simultaneous publication in Clinical Chemistry and Diabetes Care on 20th July, 2023
    - Executive Summary also published in both journals.
- Analytes Measured in the Diagnosis and Management of Diabetes
    - Glucose
        - Blood
            1) Accredited lab
            2) Meter
        - SQ
            1) Continuous monitoring (CGM)
            2) noninvasive
        - Urine
    - Gestational Diabetes Mellitus (GDM)
    - Glycated proteins
        - Glycated hemoglobin (HbA1c)
        - Glycated albumin/fructosamine
    - Ketones: Urine/Blood
    - Genetic markers
    - Autoimmune markers (Ab): ICA, IAA, GAD, IA-2, ZnT8
    - Urine albumin
    - Insulin and precursors
- Organization
    - Recommendation
    - Supporting evidence/rationale
- Categories
    - Description/introduction/terminology
    - Use and rationale
    - Preanalytical
    - Analytical considerations
    - Interpretation
    - Emerging considerations
- Recommendations for HbA1c
    - Laboratory-based Hb A1c testing can be used to diagnose
        - diabetes, with a value ≥ 6.5% (≥48 mmol/mol) diagnostic of diabetes, and
        - prediabetes (or high risk for diabetes) with a Hb A1c level of 5.7% to 6.4% (39–46mmol/ mol).

        - An NGSP-certified method should be performed in an accredited laboratory
        - A (moderate)
    - Point-of-care Hb A1c testing for diabetes screening and diagnosis should be restricted to FDA-approved devices at CLIA-certified laboratories that perform testing of moderate complexity or higher. B (low)
    - Treatment goals should be based on American Diabetes Association recommendations which include maintaining Hb A1c concentrations <7% (<53 mmol/mol) for many nonpregnant people with diabetes and more stringent goals in selected individuals if this can be achieved without significant hypoglycemia or other adverse effects of treatment. (Note that these values are applicable only if the assay method is certified by the NGSP as traceable to the Diabetes Control and Complications Trial reference.) A (high)
    - Higher target ranges are recommended for children and adolescents and are appropriate for individuals with limited life expectancy, extensive comorbid illnesses, a history of severe hypoglycemia, and advanced complications. A (high)
    - During pregnancy and in preparation for pregnancy, women with diabetes should try to achieve Hb A1c goals that are more stringent than in the nonpregnant state, aiming ideally for <6.0% (<42 mmol/mol) during pregnancy to protect the fetus from congenital malformations and the baby and mother from perinatal trauma and morbidity owing to large-for-date babies. A (moderate)
    - Laboratories should be aware of potential interferences, including hemoglobin variants that may affect HbA1c test results depending on the method used. In selecting assay methods, laboratories should consider the potential for interferences in their particular patient population. GPP
    - HbA1c measurements in individuals with disorders that affect red blood cell turnover may provide spurious (generally falsely low) results regardless of the method used, and glucose testing will be necessary for screening, diagnosis, and management. GPP
    - Assays of other glycated proteins, such as fructosamine or glycated albumin, may be used in clinical settings where abnormalities in red blood cell turnover, hemoglobin variants, or other interfering factors compromise interpretation of Hb A1c test results, although they reflect a shorter period of average glycemia than Hb A1c. GPP
    - HbA1c cannot be measured and should not be reported in individuals who do not have Hb A, e.g., those with homozygous hemoglobin variants, such as HbSS or HbEE; glycated proteins, such as fructosamine or glycated albumin, may be used. GPP
    - Laboratories should use only Hb A1c assay methods that are certified by the NGSP as traceable to the Diabetes Control and Complications Trial reference. The manufacturers of Hb A1c assays should also show traceability to the International Federation of Clinical Chemistry and Laboratory Medicine reference method. GPP
    - Laboratories that measure Hb A1c should participate in an accuracy-based proficiency testing program that uses fresh whole blood samples with targets set by the NGSP Laboratory Network. GPP
    - The goals for imprecision for Hb A1c measurement are intra-laboratory CV <1.5% and inter-laboratory CV <2.5% (using at least 2 control samples with different Hb A1c concentrations) and ideally no measurable bias. B (low)
- Acknowledgements
    - All the members of the scientific review committee
    - ADA
        - William Cefalu
        - Robert Gabbay
        - Malaika Hill
        - Mindy Saraco
    - AACC: Stefanie Kleinman

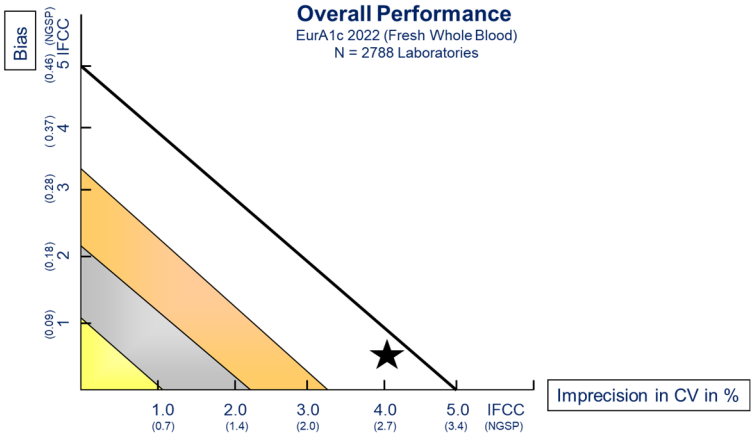
Discussion

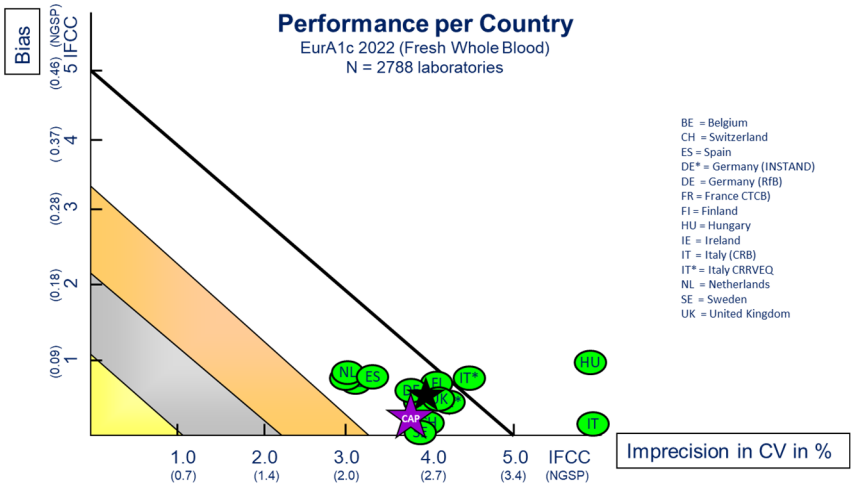
D. Sacks noted that the new guidelines are available for free online. He noted that an important premise for the guidelines is that none of the recommendations can differ from ADA Standards of Care where there is overlap. The recommendation that HbA1c should not be reported in patients without HbA was not included in the previous guidelines because it seemed obvious. However, some laboratories that use HPLC or CE have apparently been sending samples without HbA out to labs using other methods, such as immunoassay, so they can get a result. E. Lenters asked about the assignment of values to the HbA1c PT survey in the U.S. that is not

the CAP survey, and how many methods on the CAP survey have inter-lab CVs >2.5%. D. Sacks said the other survey does not assign values, the survey does not use whole blood and peer group grading is used. D. Sacks and R. Little said there are a few methods on the CAP survey with inter-lab CVs>2.5%, they are the same methods from one survey to the next. D. Sacks added that these are recommendations, labs cannot be forced to adopt methods with inter-lab CVs<2.5%, but the goal is to encourage method improvement. He noted that the new guidelines generated intense interest immediately after publication, altmetrics showed the third highest score of any Clinical Chemistry publication to date and it was picked up by numerous news outlets. R. Little suggested that the CAP summaries posted on the NGSP web site could mention the methods with inter-lab CVs>2.5% citing the new guidelines. D. Sacks agreed that this would be a good idea and noted that he would comment on this in the commentary portion of the CAP results sent to labs.

7) Update IFCC Network—Carla Siebelder

- There are currently 20 approved laboratories and 1 candidate laboratory in the IFCC laboratory network. They are spread around the globe and include labs in the U.S., Europe, South America and Asia.
- The IFCC/NGSP master equation is still being monitored via sample comparisons between the two networks performed twice a year. The equation remains very stable, after 20 years the calculated mean NGSP value at IFCC 53 mmol/mole (7.0% NGSP) is NGSP=7.015%.
- EurA1c 2022 Preliminary Data
  - A project of the IFCC C-EUBD and EQA/PT organisers
  - Once a year EQA Organisers use the same 2 samples
  - 2022: 22 countries - 26 EQA - 4325 laboratories
  - Model is based on the IFCC quality targets with a TAE of 5mmol/mol
  - Country EQA organizers have the option of whole blood or lyophilized materials.





Discussion

IFCC Laboratory Network

D. Sacks asked how many laboratories will be allowed into the IFCC network, C. Siebelder responded that the current number is the maximum. C. Siebelder noted that the EurA1c data show very little bias overall indicating that HbA1c is well-standardized, but there is still room for improvement in imprecision (overall CV is ~4%). Performance also varies among countries with CVs ranging from 3% to well over 5%. D. Sacks asked if we know why there is such variation, C. Siebelder responded that it is difficult to know for sure, education could be a factor. E. Lenters asked about logistics, could there be issues with sample degradation due to shipping times/storage? C. Siebelder said it is possible in the case of Italy when whole blood is used. E. Lenters asked if it might be possible to send both lyophilized and whole blood samples to countries that performed poorly, in order to see if shipping/storage might be the issue. C. Siebelder said it can be considered, but there are costs involved and it would require the participating labs to analyze additional samples. The data have also been analyzed in more depth including looking at manufacturer per country, this can indicate if the problems are only with certain methods/manufacturers. Also, there is the question of if the EQA organizers might play a role. M. Swenson asked why Norway is not included, C. Siebelder replied that they did not choose to participate. C. Siebelder noted that overall performance on the CAP survey, which is mainly US labs, was very comparable to EurA1c overall performance. H. Vesper asked if the differences between countries might be driven in part by differences in the number of manufacturers in each country, i.e. are there countries where one manufacturer might be dominant? C. Siebelder did not think so. E. English noted that manufacturer distribution networks vary by country, there are countries where more tests are sold directly to the consumer. H. Vesper said it seems like there are a few less countries compared to the 2016 EurA1c, C. Siebelder said that Covid presented significant challenges. Turkey is not included in the current data but they are participating again using lyophilized materials. Some countries that had used whole blood switched to lyophilized due to these issues, but they might be convinced to go back to using whole blood. R. Little asked which CAP survey was used for the comparison with EurA1c, C. Siebelder said the CAP data that were available in December 2022, a sample with the same level as the EurA1c samples was selected. M. Wagner recalled that earlier EurA1c data seemed to show differences among manufacturers and at least a few of them were in the bronze region. C. Siebelder said the more detailed data looking at individual manufacturers will be presented at the Manufacturer Forum.

Hb Variants

M. Wagner asked about occasionally including a HbS trait sample in future CAP surveys. It would be useful to see how the labs running different methods deal with it and it could also be an educational tool. The labs could be asked if information regarding the presence of a variant would be passed on to the clinician or if the result is simply reported if it is a non-interfering variant. D. Sacks noted that CAP has done this in the past. There were instances where labs were not aware that their method had interference from HbS trait, the labs and manufacturers were then informed. The labs automatically passed regardless as this was done strictly for educational purposes. However, since HbA1c will now become a regulated analyte, CAP would not be able to include a variant sample in with the regular survey samples. The only way it could be done would be to send it as an extra sample where lab participation would be voluntary. Someone would have to pay for this, either labs would have to voluntarily pay extra for a sample that would not be graded or CAP would have to find another way to cover the cost. The costs associated with providing a variant sample to all of the labs is much greater than for a non-variant sample. R. Little added that the labs would already know that there is a variant present. M. Wagner asked if an alternative would be to include a question in the dry lab portion of the survey. D. Sacks said in the US there is also an ethical question of whether you are essentially performing a genetic test without patient permission. So many labs will not do anything as far as informing the clinician, others might pass the information along to the clinician, in any case many would likely be unwilling to answer the question. R. Little asked if it could be included before HbA1c becomes a regulated analyte, D. Sacks replied that there is not enough time. H. Vesper asked if NGSP could look at variants since CAP cannot, maybe as part of certification NGSP could request data on variants along with the sample comparisons. R. Little said NGSP already performs and publishes periodic interference studies looking at various methods. It would be very difficult for NGSP to provide sufficient quantities of variant samples to evaluate interferences in individual certifications. H. Vesper asked if manufacturers could be required to provide the variant samples, the manufacturer representatives present indicated that it would not be feasible for them to do so. E. Lenters noted that HbA1c values for the variant samples is another issue, obtaining variant samples from diabetic patients is much harder than obtaining them from non-diabetic patients. It is not unusual to see more interference at higher levels than is the case at normal levels, so you need to check the entire clinically relevant range. R. Little said the inclusion of a variant sample in the CAP survey is really more for educational purposes, you cannot really draw conclusions about the

degree of variant interference based on a single sample. We have to rely on the lab's due diligence in knowing whether their method has an interference, and even then some labs will not know a variant is present depending upon what method they are using.

Glycated albumin
M. Wagner noted that there was an article in the new CLN that is very critical of glycated albumin.

D. Sacks thanked everyone for their attendance, the meeting was adjourned at 4:35PM.
Minutes prepared by C. Rohlfing 8/24/2023.