Minutes of the NGSP/IFCC Manufacturer Forum

Monday July 25, 2022 2:30—4:30 PM
Marriott Marquis, Chicago, IL

Presenters:
Randie Little—NGSP Network Coordinator
David Sacks —Chair, NGSP Steering Committee
Carla Siebelder—IFCC HbA1c Network Coordinator

Present were members of the NGSP Steering Committee and representatives from various manufacturers, laboratories and agencies.

1. **Welcome and Introduction— David Sacks, Chair, NGSP Steering Committee**
   D. Sacks welcomed those in attendance on behalf of the NGSP and IFCC.

2. **NGSP Update—Randie Little, NGSP Network Coordinator**
   - The NGSP Steering Committee oversees the administrative core and laboratory network. The laboratory network consists of the Central Primary Reference Lab (CPRL), which runs the original DCCT HbA1c method, 2 backup PRLs and 10 Secondary Reference Laboratories (SRLs) located in the U.S., the Netherlands, Japan and China.
   - The NGSP has three processes
     - Calibration: Informal process to assist manufacturers/labs with calibration of their methods.
     - Certification: Formal process where manufacturer or lab certifies against a SRL via a 40-sample comparison and must pass specific criteria.
     - Proficiency testing: CAP whole blood survey, which is accuracy-based with target values assigned by the NGSP network, shows how well the harmonization process is working.
   - The NGSP network is linked to the IFCC network via a master equation that is monitored by sample comparisons performed twice a year.
   - The network is monitored monthly via comparisons between the SRLs and CPRL using 10 fresh-frozen pooled samples.
   - NGSP network mean between-lab CVs by month were all <1.2% from May 2021 to May 2022.
   - Number of certified methods and laboratories
     - The numbers of certified methods and laboratories have increased over the years; currently there are 300 certified methods and ~140 certified laboratories.
     - The number of certified methods continues to increase while the number of certified labs has leveled off.
     - Many of the certified methods are different variations of the same basic methodology, e.g. the same reagents used on different instruments, hemolysate vs. whole blood application on the same instrument.
     - Certified laboratories are mostly Level I and outside of the U.S., and are distributed throughout the world.
   - 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 remains at ±6%
   - 2019 proposed CLIA amendment: A Roadblock to Further Improvement in HbA1c
     - CMS and CDC proposed a rule change to update proficiency testing regulations under CLIA 88
     - They proposed making HbA1c a “regulated analyte” with an acceptance limit of ±10%.

- The implication was that CAP would no longer be able to use the 6% criterion and would have to adopt 10%.
- The proposed loosening of acceptance limits (from ±6% to 10%) would reduce the effectiveness of HbA1c assays and compromise the safety of patients.

- There has been much improvement in the comparability of HbA1c results since 1993 when the results of the DCCT were reported.
- Latest CAP survey (2022 GH5A)
  - 2022A CAP Pass Rates (±6%)

Specimen	NGSP Target (% HbA1c)	Acceptable Range (±6%)	Pass rate % (Low/High)	Cumulative Pass Rate % ±6%
GH-01	8.42	7.9-9.0	87.0/100.0	97.5
GH-02	6.31	5.9-6.7	92.4/100.0	98.3
GH-03	9.05	8.5-9.6	90.7/100.0	96.9
GH-04	5.18	4.8-5.5	92.9/100.0	98.5
GH-05	6.72	6.3-7.2	92.3/100.0	98.6

  - The all-method CVs have shown an overall downward trend since 2000.
  - All-method CVs for the most recent survey ranged from 2.2 to 2.7% (2.2, 2.2, 2.5, 2.7, 2.7%).
  - Our goal for all method CVs has been <3%.
  - CV and bias by method type
    - Some individual methods had better between-lab CVs than others, but there were methods that performed well among all method types (ion-exchange, CE, affinity and enzymatic).
    - Between-lab CVs for the three POC methods that appeared on the survey were comparable to the lab-based methods.
    - Among individual methods, some of the mean biases were positive while others were negative.
- CAP data Summary (2022A)
  - Method-specific, between-laboratory CVs ranged from 1.0% to 3.5%.
  - Overall, 83% of laboratories are using methods with CVs < 3% at all five HbA1c levels.
  - All-method CVs for the most recent survey ranged from 2.2-2.7%.
  - Overall Pass rates are between 96.9 and 98.6% for the current 6% limits
- Conclusions
  - The NGSP network is still doing well with very low CVs.
  - CAP survey results show that the all-method CVs (including all laboratory results) have been <3% for the last 4 surveys. We hope to see this continue.
  - Measurement of HbA1c continues to improve but there are still a few methods with Hb variant interference.

Discussion:

D. Sacks said the progress that has been made with HbA1c standardization has been remarkable, and noted his appreciation for all of the hard work manufacturers have done to make this possible.

3. CMS Guideline Update—David Sacks, Chair, NGSP Steering Committee

- 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
- ±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

- As the CAP criteria were tightened, the comparability of HbA1c results improved dramatically.
- 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%
- Effect of Change in PT
  - True HbA1c is 6.5%
  - If criterion is ±5%, acceptable value is 6.2% - 6.8%
  - If criterion is ±10%, acceptable value is 5.8% - 7.2%
- 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
- Potential Outcome of CLIA Proposal
  - Accuracy of HbA1c assays likely to deteriorate
  - Patient care likely to suffer.
- 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).
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- 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

- What Did CMS Do? Final rule published July 11, 2022
- CMS Response
  - Not persuaded by comments
  - Acknowledge improvement in accuracy
  - Concerned that tighter criteria will limit access to testing
  - Laboratories that use non-commutable PT will be punished
  - Looser CLIA acceptance limits will not cause manufacturers to allow accuracy to deteriorate
- Final CLIA Rule
  - Acceptance limits for HbA1c are 8%
  - Effective July 11, 2024
- Implications of New CLIA Regulation
  - CMS indicated accreditation organizations can require labs to meet more stringent criteria
  - Option of using 8% and adding more stringent limit "…for educational purposes"
  - CAP will consider options
  - Plan to engage clinical community

Discussion:

CMS Final Rule

D. Sacks said that many clinicians see a change of 0.5% HbA1c as clinically significant, and FDA uses differences of 0.5% HbA1c in determining whether to approve new diabetes therapeutics. This requires a high degree of accuracy that could be compromised by loosening the PT criteria. During the comment period, CAP suggested to CMS that CAP be allowed to use 6% or 5% as their criterion since they use commutable whole blood material, while labs using other PT providers could use the 10% criterion.

When PT material is not commutable peer-group grading may be the only option.
D. Sacks agreed, you cannot use tight criteria if the material is not commutable. Recent IFCC studies where both commutable and non-commutable materials were sent to labs show a better level of performance with commutable materials.

Why did CMS suggest that loosening the criterion would allow more access to HbA1c testing? There are communities where access to medical testing and treatment is very limited, Covid exacerbated this problem.
D. Sacks agreed that limited access to testing and treatment is a major problem, however he did not think that the loosening of the HbA1c criterion would have any impact on this since there are many laboratories that provide HbA1c testing. It is possible that the thinking was that if the criterion was too tight labs might fail and this would limit access to testing, but the overwhelming majority of labs are already passing with the current CAP limits.

Now that the criterion is 5 or 6% is it necessary or even possible to make the criterion any tighter?
D. Sacks asked Erna Lenters (ISALA, The Netherlands) to discuss recent developments in Germany. E. Lenters said the situation in Germany is the opposite of the situation in the U.S. with CMS. They have decided on a criterion of 3% total error for internal controls in the lab. This means that at a level of 30

mmol/mol the limits are ±0.9 mmol/mol, this is overly strict and manufacturers are very concerned. D. Sacks felt that given the overwhelming number of labs that currently would pass at 5% that limit would be fine. It may not be feasible to go much lower than that given that there will always be some inherent variability due to various factors. There are several ways of determining how accurate a lab test needs to be. These include clinical relevance, as good as can be achieved by the current technology, biological variation and expert consensus.

Even with the looser CAP criterion the methods will still have to pass NGSP and IFCC certification, so manufacturers are not likely to make changes to their methods that will impact performance, also the FDA will still effectively be using the NGSP criterion. Will it impact lab certifications, because some labs may want to maintain their quality?
R. Little agreed that manufacturers will likely not change the performance of their assays due to the need to pass certification,. The change is not likely to impact lab certifications, labs can still use the CAP survey to assess their performance against targets regardless of the actual criterion. M. Steffes said that regardless of the new CLIA rule, he cannot imagine a situation where clinicians would not support the idea of obtaining more accurate HbA1c results. Manufacturers will likely not have an incentive to put out assays that just meet the CLIA standard when their competitors are performing much better.

The NGSP web site has become and will continue to be the go to place for information regarding the CAP HbA1c survey, so it can continue to provide education regarding the CAP results.
R. Little said yes, hopefully in the worst case CAP could still provide a tighter educational grade, if so the NGSP can incorporate this information into the CAP summaries posted on the web site.

Perhaps CMS received pushback indicating that if the requirements are too strict a certain percentage of the population would be excluded from having access to testing. Is there information available regarding the percentage of people that are not being tested?
D. Sacks said the CAP does not want to fail many labs for that reason, too many lab failures would reduce access to testing. They are very aware of the number of laboratories that perform HbA1c testing and how many fail. Regarding the fraction of the population that is not being tested, there are a lot of estimates from all over the world. The IDF releases information every 2 to 3 years that has detailed diabetes statistics from all over the world. Their recent estimates show that globally about 50% of people with diabetes do not know they have it. There are estimates indicating that this number is about 20-30% in the U.S., but it is not equal in all areas and some communities are impacted more than others. However, the change to CLIA is unlikely to have any effect on this.

CMS did suggest that CAP could use more stringent criteria, does this mean they could still fail labs that do not pass their current criterion and say they are not CAP certified even if they are within the CLIA limits?
D. Sacks said that is an important question, at the moment there is uncertainty about this. The CLIA change was only announced very recently so CAP has not had time to respond. If it does turn out that CAP is not able to fail labs that fail 6% but pass 8%, CAP could potentially still reward labs that pass the stricter criterion by giving them extra recognition. Discussions will be held to consider how CAP will respond.

POC performance
E. Lenters noted that her biggest concern regarding CLIA is the waived status of POC instruments in the US. They are widely used, but because they are waived the end users do not have to participate in PT. Therefore, we do not know how they are performing in the field, and there are some that have demonstrated poor performance in her laboratory. D. Sacks agreed, there are a few POC methods that appear on the CAP survey but most do not. Those that do participate are generally in hospital or academic medical center environments where lab-based testing is also performed. Also, by law all a method has to show for FDA approval is that it performs comparably to a previously approved method ("predicate device"), which is also a problem. CMS actually decided at one point that every year they would inspect ~2% of laboratories that performed waived testing, but this was later dropped.

Would it be beneficial to perform a large study involving subjects with and without diabetes where waived POC and laboratory measured HbA1c results were compared?

D. Sacks said yes, but he did not know of anyone willing to do this kind of study There are people who suggest that waived POC is useful for diagnosing diabetes, but no one has done this type of study.

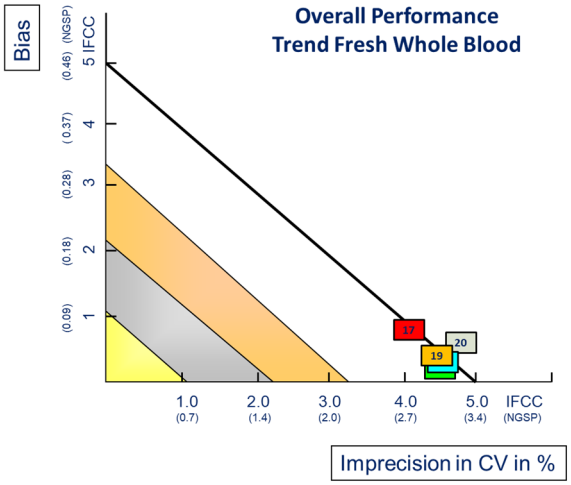
4. Update: IFCC Network—Carla Siebelder

- After working with Cas Weykamp for 30 years, I replaced him as the Network Coordinator after his retirement in 2020.
- C. Weykamp was recently presented with a Dutch royal award, Knight in the Order of the Dutch Lion, for exceptional achievements in clinical chemistry and the worldwide standardisation of blood tests for diabetes in particular
- IFCC Roadmap: Optimum Performance HbA1c
  - IFCC Working Group
    - Reference Method
    - Global Network
    - Services Manufacturers
  - IFCC Task Force: Model Quality Targets
  - IFCC Committee: Monitoring Quality in the EU and US
- Reference Method was approved in 2001, progress report was published in Clin Chem in 2008.
- Global network of reference laboratories remains in place and continues to perform well.
- Services to Manufacturers
  - Calibrators to achieve Traceability
  - Controls to check Traceability
  - Certification Programme to prove Traceability
  - Variant Samples (FDA Approval)
  - Value Assignment Specimens
  - Monitoring Master Equation IFCC – NGSP
  - Calibrators: Specifications
    - Units provided: HbA1c: IFCC (mmol/mol) and NGSP (%) Units, mmol/L, g/dL
    - Total Hb: mmol/L, g/dL
  - Controls: Specifications
    - Low, medium and high levels
    - Medium provided with low, medium and high hemoglobin concentrations
  - Certification Programme
    - IFCC studies
      a. The comparison studies have been performed every year since 2002
      b. The current study is named Kotten.
      c. Covid-19 has caused personnel, planning and logistics challenges that have altered study timelines over the past few years.
    - Certificate is provided showing how the method performed compared to quality targets.
    - There are 4 levels of acceptable method performance: Gold, silver, bronze, standard (minimum).
    - In 2021, the number of manufacturer methods that fell into each category were:
      a. Gold: 14
      b. Silver: 100
      c. Bronze: 34
      d. Standard: 23
      e. Participated (did not meet minimum standard): 14
      f. Information can be found at www.ifcchba1c.org
  - Variant samples: Collection of AS, AE, AC, AD samples in stock along with limited quantities of A2, elevated HbF and rare variants.
  - Monitoring Master Equation IFCC – NGSP
    - Master Equation: NGSP = 0.0915 x IFCC + 2.15
    - Sample comparisons between the networks are performed twice a year.
    - The ME is monitored over time and has been shown to be stable over time since 2001.

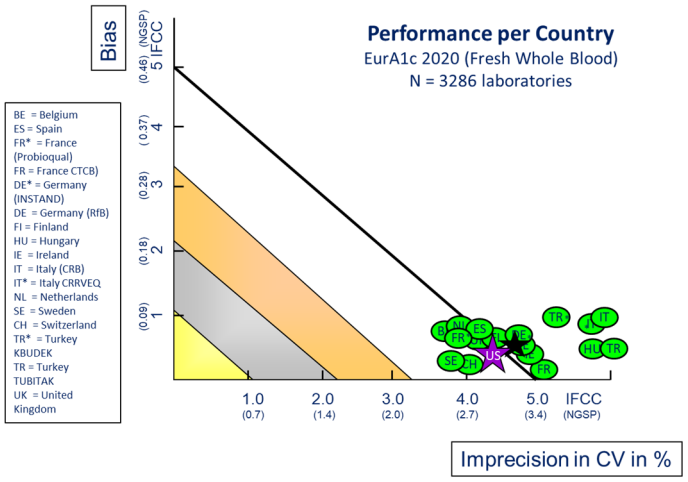
- Model Quality Targets: IFCC Task Force, published in Clinical Chemistry in 2015 (Clin Chem. 2015 May;61(5):752-9).
  - Two models were investigated, one based on biological variation, the other using Sigma metrics
    - The model selected uses Sigma metrics with a TAE of 5 mmol/mol
- Monitoring Quality— IFCC C-EUBD (IFCC Committee Education in the Use of Biomarkers in Diabetes): EurA1c
  - Basic idea: Data from national EQA/PT organisers are combined to get a global overview of the performance of HbA1c
  - International Cooperation: Once a year EQA Organisers use the same 2 samples
  - EurA1c samples
    - Fresh Whole Blood
      a. Advantage: Commutable and suitable all methods
      b. Disadvantage: Limited stability
    - Lyophilised Hemolysate
      a. Advantage: Stable
      b. Disadvantage: Not commutable for all methods, not suitable some POCT instruments
    - Choice is made by National EQA organisers based on logistics in the country
  - Number of Laboratories

Year	Total	Fresh Whole Blood	Lyophilised Hemolysate
2016	2166	1517	649
2017	2647	1809	838
2018	3980	2875	1105
2019	4575	3038	1537
2020	5120	3286	1834

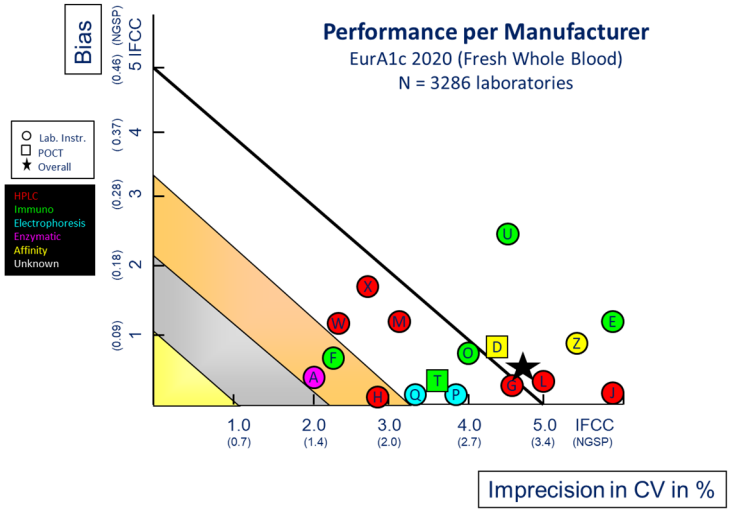
  - Results of 2016 EurA1c have been published (Clin Chem. 2018 Aug;64(8):1183-1192)
  - EurA1c 2020: 22 countries - 27 EQA - 5120 laboratories
  - Due to Covid blood could not be obtained from diabetic patients, so 2 samples from non-diabetic subjects were included in 2020.
  - EurA1c Results
    - Overall Performance (2016-2020)



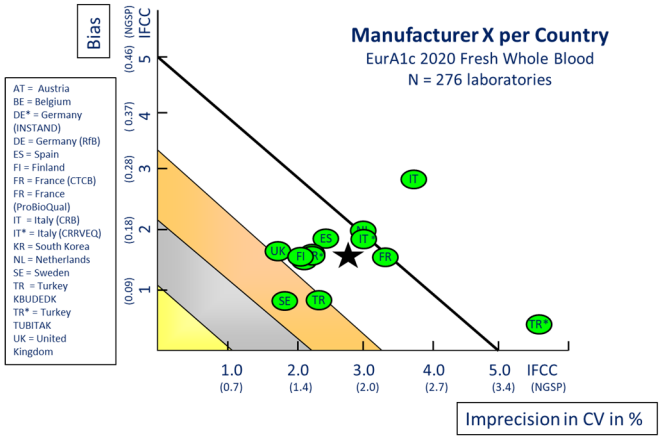
    - Performance Per Country 2020



- Performance per Manufacturer



- Manufacturer X per Country



- EurA1c
  - Supplies a lot of information about the performance of many HbA1c tests
  - Pushes labs - countries - manufacturers to improve quality and thus provide better patient care

Discussion:
C. Siebelder noted that overall bias was minimal indicating that the methods are well standardized. However, imprecision is still a significant issue for some methods. Performance varies among methods and among countries.

Discussion:

ADA Guidelines

What does the ADA suggest to do when there is a discrepancy between HbA1c and glucose results? Which result should be trusted?
R. Little said they suggest investigating both the HbA1c and glucose results. D. Sacks noted that there is a common perception among clinicians that HbA1c is not a good test because there are some things that can cause interferences with the results. These concerns were amplified after the ADA recommended the use of HbA1c for diabetes diagnosis. The idea is that glucose is the gold standard. M. Steffes said in most cases results from both are basically concordant and both can be trusted. One argument against glucose is the pre-analytical variation, which is not an issue for HbA1c. HbA1c is affected by red cell lifespan, there is a recent paper by J. Higgins that goes into detail on this. D. Sacks agreed, stating that there are issues with glucose that clinicians are often not aware of. Looking at the literature, HbA1c is a better predictor of microvascular complications than glucose.

D. Sacks thanked everyone present for their attendance; the meeting was adjourned at 4:30PM.

Minutes prepared by C. Rohlfing 09/28/2022.