Minutes of the NGSP/IFCC Manufacturer Forum

Monday July 24, 2023 2:30—4:30 PM
Anaheim Marriott, Anaheim, CA

Presenters:
Randie Little—NGSP Network Coordinator (virtual)
David Sacks —Chair, NGSP Steering Committee
Carla Siebelder—IFCC HbA1c Network Coordinator
Emma English—Chair, IFCC C-EUBD

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 where samples are exchanged 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 routine laboratories are performing.
   - 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 <1.6% from May 2022 to May 2023.
   - Number of certified methods and laboratories
     - The numbers of certified methods and laboratories have increased over the years; currently there are almost 330 certified methods and ~140 certified laboratories.
     - The number of certified methods continues to increase while the number of certified labs has leveled off.
     - 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%
   - There has been much improvement in the comparability of HbA1c results since 1993 when the results of the DCCT were reported.
     - In 1993 results were reported as HbA1, total GHB or HbA1c.
     - By 2004 all results were reported as HbA1c
     - The CAP HbA1c PT survey changed from peer-group to accuracy-based grading in 2004.

- Both the CAP and NGSP criteria have been tightened over time.

- Latest CAP survey (2023 GH5A)
  - 2023A CAP 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

  - The all-method CVs have shown an overall downward trend since 2000.
  - Method-specific between-laboratory CVs ranged from 0.7% to 3.9%.
  - Overall, 86% of laboratories are using methods with CVs < 3% at all five HbA1c levels.
  - All-method CVs for the most recent survey ranged from 2.4-3.0%.
  - Overall Pass rates are between 96.9 and 98.2% 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 between lab CVs >3%. https://ngsp.org/CAP/CAP23A.pdf

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

- 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

- 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%
- 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%

- Response to CMS 2019 Proposal
  - 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:

CMS Final Rule

If a lab passes the 8% for PT, CAP can still require 6% for them to be accredited?

D. Sacks said theoretically yes, if a lab passes 8% but not 6% CAP could say that their performance is not sufficient for them to be accredited. This will not be simple; it will require going through a long approval process at CAP so it will likely be years before it goes into effect. W. Greg Miller (Virginia Commonwealth University) suggested using a 6% educational grade, then the inspector could ask the lab to show their educational grade for the last 2 years and use this as the basis for enforcement. D. Sacks agreed, and also noted that the NGSP criteria for certification of methods will not be affected by the new rule.

Is this process where better performance is required for accreditation vs. PT done with other analytes?

D. Sacks said no, generally labs just have to show they passed PT and that is deemed acceptable for accreditation.

4. Updated Laboratory Medicine Guidelines for Diabetes Testing—David Sacks

- Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus: First 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
  - 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

Discussion:

D. Sacks said that the statement regarding not reporting HbA1c in individuals who do not have HbA was added to the new guidelines. The reason for this was a manufacturer representative told him that some labs that run methods that do not report HbA1c for these patients were sending the samples out to another lab running a method that would report a result, albeit a wrong one.

How do the recommendations regarding proficiency testing (GPP) and POC testing for screening and diagnosis only being performed in moderate or high complexity settings (B-low) relate to each other? It would seem that the difference between POC performed in moderate or high complexity vs. CLIA waived setting is just related to whether PT testing is performed.

D. Sacks responded that it involves more than just whether PT is performed, there are also training requirements for testing personnel in non-waived settings. PT is very important; without it the lab could be reporting inaccurate results without knowing it.

5. Update: IFCC Network—Carla Siebelder

- IFCC Roadmap: Optimum Performance HbA1c

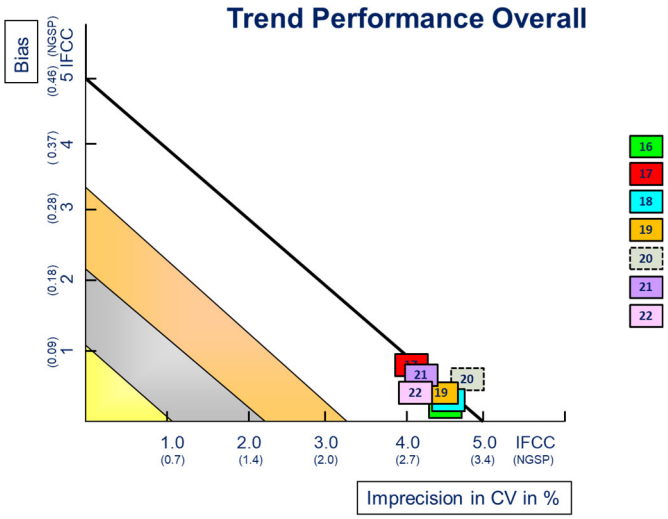
- IFCC Working Group
  - Reference Method
  - Global Network
  - Services Manufacturers
- IFCC Task Force: Model Quality Targets
- IFCC C-EUBD: Monitoring Quality in the EU and US

- Reference Method was approved in 2001(published 2002), progress report was published in Clin Chem in 2008.
- Global network of reference laboratories remains in place and continues to perform well. Currently there are 20 approved laboratories and one candidate laboratory.
- 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
    - Eight level frozen whole blood panel
    - 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).
    - TAE of 5 mmol/mol
    - In 2022, the number of manufacturer methods that fell into each category were:
      a. Gold: 4
      b. Silver: 86
      c. Bronze: 91
      d. Standard: 38
      e. IFCC criteria not met: 20
      f. Information can be found at www.ifcchba1c.org (login required)
  - 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
    - After 20 years the calculated mean NGSP value at IFCC 53 mmol/mole (7.0% NGSP) is NGSP=7.015%.
- 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
  - Model incorporates both bias and imprecision
- Monitoring Quality— EurA1c: A Project of the IFCC C-EUBD and EQA/PT organisers

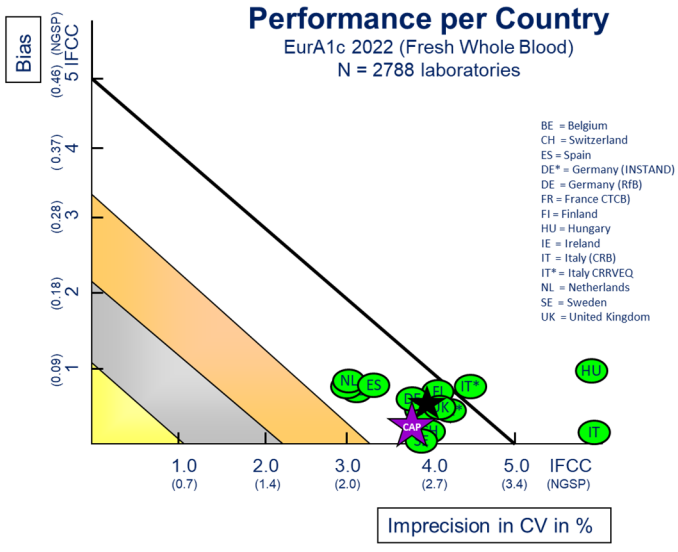
- International Cooperation: Once a year EQA Organisers use the same 2 samples
- Data combined to get a global overview of the performance of HbA1c
- First survey was in 2016 (published 2018)
- Participants can choose to analyze fresh whole blood or lyophilized hemolysate
- Number of Laboratories

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
2021	4077	2524	1553
2022	4325	2788	1537

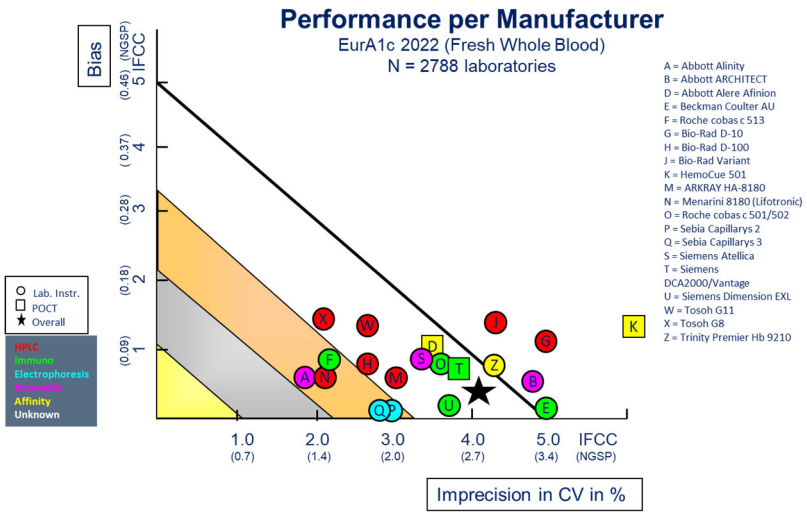
- EurA1c 2022: 22 countries - 26 EQA - 4325 laboratories
- EurA1c 2022 (preliminary) results
  - Overall Performance (2016-2022)



  - Performance Per Country 2020



  - Performance per Manufacturer



- Also examine performance per manufacturer/method per country
- Ultimate goal: Contribute to Optimum Patient Care
  - Lots of information on the performance of many HbA1c tests
  - Pressure to improve

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.

6. Committee on Education in the Use of Biomarkers in Diabetes (EUBD) Activities—Emma English

- Who are the EUBD?
  - Chair: Emma English
  - Full Members
    - E. Van Der Hagen
    - A. Sato
    - J. Shrha
    - E. Kilpatrick
  - Consultant Members
    - D. Sacks
    - E. Lenters-Westra
    - C. Siebelder
  - Corresponding Members
    - 15 members nominated by national associations
    - 6 members nominated by corporate organisations
- What do we do?
  - To maintain and further develop the network of reference laboratories for the measurement of HbA1c (through collaboration with C-TLM and any other appropriate IFCC committee)
  - To work in partnership with national and international recognised bodies, associated with diabetes care, to promote the appropriate clinical and analytical use of biomarkers for diabetes
  - To work with industry partners, to promote the appropriate clinical and analytical use of biomarkers for diabetes (for example in the support of meeting national and international regulatory guidance)
  - To support the development of national and internationally recognised quality criteria for POCT IVDs for biomarkers of diabetes in a range of clinical settings (where these differ from laboratory methods).

- To monitor the literature on current and emerging biomarkers and advise on best practice in relation to laboratory aspects of diabetes.

- Project Highlights
  - WHO prequalification of POCT HbA1c IVD and BGM
    - Purpose—WHO states: The aim of WHO prequalification of in vitro diagnostics (IVDs) is to promote and facilitate access to safe, appropriate and affordable in vitro diagnostics of good quality in an equitable manner. The focus is on IVDs for priority diseases that are appropriate for use in resource-limited settings.
    - Progress: POC HbA1c IVD
      a. Draft written (completed)
      b. Expert consultation (completed)
      c. External public review (completed)
      d. Final draft revisions
    - Progress: BGM
      a. Draft written (completed)
      b. Expert consultation (completed)
      c. External public review
      d. Final draft revisions
  - Modelling impact of biological and analytical variation: The risk of clinical misinterpretation of HbA1c: Modelling the impact of biological variation and analytical performance on HbA1c used for diagnosis and monitoring of diabetes. Weykamp et. al Clin Chim Acta 2023 Aug 1;548:117495. doi: 10.1016/j.cca.2023.117495. Epub 2023 Jul 20.
  - CGM versus HbA1c
    - How does CGM correlate with HbA1c?
    - What happens when there is discordance?
    - What is GMI?
    - How is GMI generated?
    - What is the quality of CGM devices and how do you assess it?
    - We are working with a major Clinical Diabetes Journal to answer these questions.
  - Glycated Albumin
    - What is the current state of the art of GA methods and how was standardization achieved?
    - What is the clinical utility of GA – systematic review
- Next steps
  - Back to anaemia
  - Ketones
  - Educational Events
- Contact: Emma.English@ice.cam.ac.uk

Discussion:

EUBD

E. English noted that the EUBD currently has 6 corporate corresponding members, any companies not currently represented should contact her if they wish to add a representative. She conducted an online Mentimeter poll to obtain input from those present. The first question asked what the main topics of interest to the manufacturers. High-priority responses included variants, glycated albumin and POC. The next question asked what they would like to see the EUBD do next. This elicited a variety of responses including POC, anemia, glycated albumin, variants, access to testing, markers in pregnancy and red cell lifespan issues. E. English noted that these are topics that the EUBD is focusing on but would like to focus on them more. She will take this data and the committee will use it in thinking about what issues they will prioritize. They will then reach out to manufacturers again and try to drill down to get more specific regarding the topics and how best to address them. The committee can then develop responses as to how they will address each of these issues, and if there are some, they cannot address they will explain why.

D. Sacks thanked everyone present for their attendance; the meeting was adjourned at 4:10 PM.

Minutes prepared by C. Rohlfing 09/22/2023.