Minutes of the NGSP/IFCC Manufacturer Forum

Monday July 28, 2014 10:00AM-12:00PM
Fairmont Chicago, Chicago, IL

Presenters:
David Sacks —Chair, NGSP Steering Committee
Randie Little—NGSP Network Coordinator
Cas Weykamp—IFCC HbA1c Network Coordinator
Emma English—IFCC Task Force on HbA1c Standardization

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 Progress Report—Randie Little, NGSP Network Coordinator**
   - The NGSP is overseen by a Steering Committee and includes a administrative core and a laboratory network consisting of Primary and Secondary Reference Laboratories (PRLs and SRLs).
   - The SRLs certify manufacturers and laboratories, they are monitored against the Central Primary Reference Lab (which is the original DCCT method) monthly via sample comparisons.
   - The network is linked to the IFCC network via sample comparisons performed 2X/year.
   - The function of the NGSP is to standardize HbA1c and ensure that results from clinical laboratories match those of the DCCT.
   - The NGSP assists manufacturers with calibrating their assays, has a formal certification process and monitors performance of HbA1c testing in the field via the CAP survey which uses fresh whole blood.
   - NGSP Update
     - The numbers of certified methods and laboratories continually increased up until last year when the numbers leveled off. This may or may not have to do with the tightening of the certification criteria beginning September 2012, it will be interesting to see if it continues since the criteria were since tightened again beginning January 2014.
     - There are currently ~130 certified methods and about the same number of certified laboratories.
     - Certified laboratories are distributed throughout the world, most are outside of the U.S.
     - Current Manufacturer Certification Criteria: 37/40 individual results must be within 6% of the SRL (one SRL) mean.
     - Current CAP limits (2013-2014) :Each result must be within ±6% of NGSP assigned target value (mean of 7 SRLs, multiple results from each).
   - Status of HbA1c Measurement
     - There has been much improvement in the comparability of HbA1c results since 1993 when the results of the DCCT were reported. However, there has been little noticeable improvement since 2011.
     - There are a number of new certified methods from Japan.
     - A number of certified methods are not used in the U.S.
     - On the most recent survey (GH2-2014) there were some methods that showed signicant bias.
     - All-method CVs on the CAP surveys have dropped since 2000, the last several years they have consistently been in the range of 3.5-4%.
     - CAP GH2 survey 2014A:

- Cumulative pass rates were actually lower compared to the 2013A survey for which the acceptable limits were also ±6%.
- Pass rates:

2014A

Specimen	NGSP Target (% HbA1c)	Acceptable Range **(±6%)**	Pass Rate % (Low/High)	Cumulative Pass Rate %
GH2-01	6.49	6.1-6.9	57.0/100	88.5
GH2-02	6.97	6.5-7.4	60.7/100	89.1
GH2-03	9.65	9.0-10.3	74.5/100	94.2

2013A

Specimen	NGSP Target (% HbA1c)	Acceptable Range **(±6%)**	Pass Rate % (Low/High)	Cumulative Pass Rate %
GH2-01	7.11	6.6-7.6	77.5/100	95.3
GH2-02	9.32	8.7-9.9	80.0/100	94.3
GH2-03	6.07	5.7-6.5	63.6/100	93.4

- The method-specific bias was over 0.30% HbA1c for 7 methods for at least one level.
- Method-specific, between-laboratory CV's ranged from 0.5% to 5.6%. CVs were <5% at all levels for all but one method.
- Overall pass rates were 88.8 to 94.2% which is lower than the rates for the previous two surveys.
- The all-method CVs are still not consistently $\leq$3.5%.
- There is still room for improvement.

- Summary
  - Over 100 methods and labs have been certified in the past year. The increase in certifications may have leveled off.
  - HbA1c measurements have improved but there has been very little improvement over the last few years.
  - The NGSP recently tightened the certification criteria; we have not seen the full impact of this change yet.

3. NGSP Publications and Meetings—David Sacks

- Change in NGSP criteria
  - A few years ago Curt Parvin presented the results of his complex statistical analyses that were used by the Steering Committee to decide on new, tighter NGSP criteria.
  - The description and results of these analyses have now been published (Clin Chim Acta 433 (2014): 259-263).
- Clinical Advisory Committee Meeting June 2014
  - The CAC meets every year in June at the American Diabetes Association annual meeting.
  - The purpose of the CAC is to allow for interaction and transfer of information between the laboratory and clinical communities.
  - The CAC includes representatives of the major clinical diabetes organizations.
  - Topics of the 2014 CAC meeting
    - Hemoglobin variants: How to better inform clinicians as to whether the HbA1c method used by their lab is affected by variants.
    - Ethnic differences in HbA1c: Do they reflect differences in mean glycemia or other factors?
    - Issues with POC testing: We request that manufacturers encourage all users of POC methods to participate in proficiency testing that uses whole blood samples with DCCT target values are used. This is the best way for POC users to assess how well their method is performing.
- Steering Committee Meeting July 27
  - Manufacturers should submit only one lot for each method to be certified (unless otherwise requested)
  - Manufacturers also need to indicate whether the method is currently being used in patient care or is new, there will be a place on the form to indicate this.

Discussion:

Proficiency Testing

Do we know how many labs are using waived POC instruments?
D. Sacks said no one seems to know. A major concern is where the POC testing is being performed, many hospital/clinical labs using POC do participate in proficiency testing, but these instruments are being used in physician and even dentist offices where PT is not being performed. One important reason why the ADA excluded POC from their diagnosis recommendations is that the vast majority of users of these methods do not participate in PT. Even though some POC methods are certified we have no way of knowing if they are being used properly in the field. If anyone has an idea how we could obtain information on how many tests are being performed using CLIA-waived vs. laboratory testing they should contact the NGSP, it would be very useful to have this information.

Are you concerned about the use of proficiency testing other than CAP?
D. Sacks said we cannot force labs to use CAP, there are concerns in terms of survey materials that are not whole blood and/or do not have assigned values that are traceable to the DCCT. The CAP has ~3500 labs participating in the GH2 whole blood survey, ~12-15% are outside of the US.

Are the CAP samples compatible with all instruments?
D. Sacks said the GH2 samples are fresh EDTA whole blood so they are matrix compatible with virtually all instruments with the exception of one POC method that shows interference from EDTA. Users of that device that participate in the survey are not graded based on the NGSP/DCCT target, peer group grading is used.

One stated quality requirement is total error of 6%, another is that the all-lab CV should be <3.5%, are these compatible?
D. Sacks said the 6% criteria are the CAP and NGSP criteria for passing when performed by individual labs. The CV goal of 3.5% is based on guidelines published by the NACB and is not a requirement of either the NGSP or CAP, also it applies to between-lab variation as opposed to within-lab.

4. IFCC Network and Integrated Project—Cas Weykamp

- Oversight of the IFCC Network is performed by the IFCC Committee on Traceability in Laboratory Medicine (metrological aspects) and the IFCC Task Force on Implementation of HbA1c Standardization (educational/clinical aspects, formerly the Integrated Project).
- IFCC Task Force on HbA1c
  - The Task Force on HbA1c is chaired by Prof. Garry John and includes members from the UK, the Netherlands, France, China, Japan and the US.
  - Aim: "To establish an interface between IFCC…and its National/Corporate Members…and the clinical users of HbA1c to enable: The implementation of a scientifically sound reporting structure for HbA1c standardised to the IFCC Reference Measurement Procedure"
  - Objectives
    - Advisory Board HbA1c Network
    - Advise Manufacturers
    - Establish Link to Professional Bodies
    - Help Implement Consensus Statement
    - Monitor Introduction of Consensus Statement Globally
    - Develop Quality Targets
  - Task Force Activities
    - Advise manufacturers on standardization
    - Publications (e.g. JAMA on links IFCC/NGSP)
    - WHO Projects
      1) Requirements for inexpensive HbA1c in developing countries
      2) Document laboratory aspects of diabetes
    - Consensus Meeting IDF Melbourne
      1) Reporting units are a national issue

2) Ensure all manufacturers standardise to IFCC reference method
3) Journals must report in both SI and NGSP units

- Constructed comprehensive survey to investigate HbA1c across the globe
  1) Purpose is to determine how well the consensus statement is being implemented worldwide
  2) Undertaken under banner IFCC, IDF and WHO
  3) Sent out to national representatives IFCC and IDF
  4) Questions relating technical and clinical aspects
  5) Outcome to be published in high impact clinical or scientific journal
  6) Description of the survey (Emma English)
     - Initial survey was performed a few years ago but there were problems with the data collection.
     - A new questionnaire was developed to try to get a global perspective on how, and how well, HbA1c and glucose measurements are being used in different countries.
     - Survey questions have been devised to determine the method types, kind of standardization (if any), calibration, and proficiency testing being used.
     - These data can then be used to develop educational materials.
     - The terms standardization and calibration are often used interchangeably and incorrectly, and the preliminary survey showed that proficiency testing is not being performed in many countries.
     - This online survey will be hosted on our web site, we will own the data and there will be a dedicated e-mail address users can respond to.
     - Requests to participate will be sent out to the national clinical chemistry and diabetes organizations so that we can obtain both the laboratory and clinical perspectives.
     - In the end we want to see what units are being reported, what kind of standardization and calibration is being used and whether PT is being performed. There are also questions aimed at assessing what the barriers are to standardization and PT.
     - We expect to have the data by the beginning of 2015.
     - We plan to get the results published and use this data to devise educational support to help implement standardization worldwide.
- "Develop quality targets for the measurement of HbA1c, and on basis of these targets, and in conjunction with professional bodies, advise on the use of HbA1c for monitoring, diagnosis and screening of diabetes and glucose intolerance"
  1) As an international body we only advise, the national bodies decide.
  2) Quality targets:
     - Leading concept IFCC ⟶
     - Metrological Traceability ⟶
     - Bias & imprecision ⟶
     - Express one number ⟶
     - Criterion ⟶
       i. Classification of performance
       ii. Identify source(s) of poor performance
     - Total allowable error ⟶
       i. Clinically meaningful limits
       ii. State-of-the-art in relation to technical/economic limits
     - Criterion: Total Allowable Error
       i. Clinically (or otherwise set limits): Westgard, Sigmametrix
          a. Set criterion for allowable error (i.e. "patient result should have error <5mmol/mol")
          b. Set criterion for allowable failure
             - 2σ = in 5% of cases you will fail
             - 3σ = in 1% of cases you will fail

- i.e. "2σ is good enough; it is acceptable when 5% of results have an error >5 mmol/mol"

ii. Criteria derived from biological variation:
- HbA1c: from the "Ricos" list: intra-individual variation and inter-individual variation are 3.4 and 10.1% (in IFCC units)
- Labs are classified as "optimum", "desirable", or "minimum" performance (HbA1c: different applications can have different requirements)

- IFCC Reference System for HbA1c
  - Mission of the IFCC Network is to warrant continuity of the IFCC reference measurement procedure and make HbA1c assays worldwide traceable to it.
  - Network laboratories:
    - There are approved laboratories in the US, Europe and Asia
    - There are currently three candidate laboratories (Brazil, Europe, China)
  - Traceability: The IFCC reference system has been established as the only valid anchor for worldwide HbA1c standardization to which manufacturers should show traceability.
  - Services for Manufacturers
    - Calibrators to achieve traceabililty
      1) Provided with HbA1c results in IFCC (mmol/mol Hb) and DCCT (%) units, also mmol/L and g/dL.
      2) Provided with total hemoglobin in mmol/L and g/dL.
      3) All are provided with expanded uncertainties.
    - Controls to check traceability
      1) Low, middle and high levels
      2) Middle level is provided with low, normal and elevated total hemoglobin
      3) Units provided
         - HbA1c and Total Hb
         - IFCC- NGSP Units
         - mmol/mol, %, mmol/L, g/dL HbA1c
         - mmol and g/dL Total Hb
         - All are provided with expanded uncertainties
    - Monitoring to prove traceability
      1) 24 frozen whole blood samples per year (12 blind duplicates) to be analyzed throughout the year
      2) Once a year mean deviations from the targets, imprecision and linearity are calculated
      3) Certificates of traceability are provided
      4) Many manufacturers participate
  - Questions from Manufacturers.
    - Sustainability of Calibrators: How do we know that they are stable for years, there are no batch-to-batch differences, and they are commutable? CBS (commutability, batch-to-batch, stability) test: Test every batch of calibrators.
      1) Fresh whole blood samples (n=10)
      2) Assay with 4 different methods using different principles (Menarini HA8160, Tosoh G8, Trinity Ultra^2, Roche Tina Quant)
      3) Calibrated with 4 different batches of calibrators (2009-2012)
      4) Results: All within-method and between-method means for all batches were 61-63 mmol/mol indicating commutability, batch-to batch consistency and stability.
    - What about commutability for my method?
      1) It is impossible for the network to test commutability for all methods.
      2) Manufacturers can answer this question themselves. Two options:
         - CLSI C53-P
         - Two day test
           i. Fresh whole blood
           ii. One aliquot refrigerated, the other frozen overnight
           iii. Analyze both the next day

iv. If the results are equivalent there is commutability

- The IFCC/NGSP master equation was established in 2004, could it be that the relation is drifting? If so I'm in trouble with my IFCC-traceable method when I apply for NGSP certification.
  1) ME: NGSP=(0.915*IFCC) + 2.15
  2) Monitoring validity of the ME
     - Twice a Year a Study
     - 5 Samples
     - All IFCC Network labs
     - All NGSP Network labs
     - Relation calculated
     - Relation used to calculate NGSP% at IFCC = 53 mmol/mol
     - Result is plotted over time
     - 25 Studies from 2001 to 2014
  3) Results show ME has remained stable.

Discussion:

Could you elaborate on the collaboration between the IFCC and WHO in terms of finding inexpensive methods to measure HbA1c?
C. Weykamp said they are trying to get manufacturers to supply methods that are reasonably priced in order to facilitate the use of HbA1c in developing countries. It is not easy but it might be possible to do this with subsidies.

How varied are the hemoglobin levels in the medium controls?
C. Weykamp showed that for the most recent control the range was 4.42-13.53 mmol/l (7.12-21.80 g/dl).

When performing the commutability test should it be performed at multiple levels?
C. Weykamp said 3-4 levels should be tested.

The CAP limits are +/-6%, for the IFCC medium control the uncertainty is listed as 0.14 which takes up 1/3 of the error budget.
D. Sacks noted that the uncertainty listed is for the IFCC control value assignment, CAP targets are assigned by the NGSP SRLs. C. Weykamp noted that the values for the calibrators and controls are assigned by the entire IFCC network to minimize uncertainty. D. Sacks and Curt Rohlfing said that C. Parvin previously calculated the uncertainties for the CAP value assignments using different numbers of SRLs and the uncertainties were very small. R. Little added that the uncertainties for the CAP value assignments are listed at the top of the table in each CAP summary posted on the NGSP web site. Greg Miller noted that C. Parvin's calculations looking at the probabilities of passing the CAP and NGSP criteria incorporated the uncertainties of the CAP value assignments.

There were no further questions, D. Sacks thanked everyone present for their attendance; the meeting was adjourned at 11:15AM.

Minutes prepared by C. Rohlfing 8/15/13.