Minutes of the NGSP/IFCC Manufacturer Forum

Monday July 31, 2017 12:00PM-1:30PM
Marriott Marquis San Diego Marina, San Diego, CA

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

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

1. **Welcome and Introduction— Randie Little, NGSP Network Coordinator**
   - D. Sacks was chairing a symposium and ran late, so R. Little 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 an administrative core and a laboratory network consisting of Primary (3) and Secondary (10) Reference Laboratories (PRLs and SRLs) located in the U.S., the Netherlands, Japan and China.
   - The NGSP laboratory network is linked to the IFCC laboratory network via twice yearly sample comparisons.
   - 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 survey data from routine labs to evaluate how well the harmonization process is working
   - Number of certified methods and laboratories
     - The numbers of certified methods and laboratories have increased over the years; currently there are >200 certified methods and ~140 certified laboratories.
     - The number of certified methods continues to increase while the number of certified labs has leveled off, probably due to consolidation of some of the larger clinical trials labs.
     - Certified laboratories are distributed throughout the world, most are outside of the U.S.
   - Improvement in HbA1c testing.
     - There has been much improvement in the comparability of HbA1c results since 1993 when the results of the DCCT were reported.
     - CAP GH2 survey 2017A:
       - There are still several methods that show a lot of variability among laboratories but they are used by a small number of labs.
       - 2017A CAP Pass Rates

Specimen	NGSP Target (% HbA1c)	Acceptable Range	Pass rate % (Low/High)	Cumulative Pass Rate %
GH-01	6.41	6.0-6.8	75.0/100.0	**95.1**
GH-02	9.53	8.9-10.2	83.3/100.0	**96.0**
GH-03	5.34	5.0-5.7	75.0/100.0	**96.2**
GH-04	8.51	7.9-9.1	86.9/100.0	**96.3**
GH-05	7.25	6.8-7.7	68.4/100.0	**95.1**

       - Method-specific, between-laboratory CV's ranged from 1.0% to 5.7%. 87% of laboratories are using methods with CVs<3.5% at all five HbA1c levels.
       - The all-method CVs have shown a downward trend since 2000.

        - All-method CVs for the most recent survey were <3.5% (2.6-3.1%); <3.5% at all levels 5-10% HbA1c for the past 5 Surveys.
        - Pass rates (at the current ±6% cutoff) have been >95% in the 5-10% HbA1c range for the last 4 surveys.
- Update on Hb variant Interference
    - There are currently 3 methods listed on the 2017 GH5-A CAP survey report that have interference for one or more common Hb variants.
        - Beckman AU (2.7%)
        - Tosoh G7 (0.3%)
        - Tosoh G8 (11.7%)
    - ~15% of labs are using these methods *NOTE: this will decrease to 3% once the new Tosoh G8 version is FDA approved.
- Conclusions
    - There has been continuous improvement in HbA1c measurements with all-method CVs for the most recent survey <3.1%.
    - There continues to be a few methods showing poor performance on the CAP survey although these are used by a relatively small number of laboratories.
    - Cumulative pass rates have been over 95%.
    - There are still a small number of methods with interference from common Hb variants. Only ~15% of labs are currently using a method with variant (S,C,D or E) interference and this will decrease to 3% when the new version of the Tosoh G8 is FDA approved in the US.

Discussion:

Why are there so many certified laboratories in Colombia?
R. Little said there are two countries, Columbia and South Africa, where there are groups of labs that either get certified with the support of the manufacturers or they are all labs within the same network.

3. Update: IFCC Network & IFCC C-EUBD—Cas Weykamp

- Services to Manufacturers
    - Calibrators to achieve Traceability
    - Controls to check Traceability
    - Certification Programme to prove Traceability
    - Variant Samples
    - Value Assignment Specimens
    - Monitoring Master Equation IFCC – NGSP
    - Calibrators: Specifications
        - 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 (IVD Directive)
        - Eight levels of calibrators
    - Controls: Specifications
        - Low, medium and high levels
        - Medium provided with low, medium and high hemoglobin concentrations
        - 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 program
        - Panel of blind specimens
        - Analyze and send in the results
        - New certificate provides a graph based on recent paper on quality targets published by the IFCC Task Force (Clin Chem 61:5 752-759 (2015). CV (%) is plotted against bias in IFCC and NGSP units showing level of analytical performance. Total error, bias and imprecision are provided along with a grade based on the quality targets.
    - 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

- 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.

- Clinical Data & IFCC Model Quality Targets
  - 2016 HbA1c in 19,424 clinical samples in our institution. Distribution:

	IFCC mmol/mol	NGSP %
Lowest	20	4.0%
Highest	173	18.0%
95% Results	33 – 75	5.2 – 9.0%
Median	45	6.3%

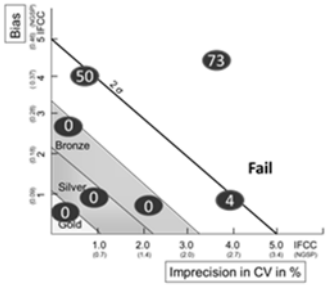
  - These data are consistent with data from 2012.
  - 95% of results were in the 33 – 75 mmol/mol (5.2 – 9.0%), thus quality focus should be on that range.
  - The ADA has defined three diagnostic categories for HbA1c
    - Low risk: <5.7%
    - Increasing risk: 5.7-6.4%
    - Diabetes: >6.4%
  - Half of the clinical samples are in the non-diabetic range
    - HbA1c is used frequently for diagnosis/screening and monitoring
    - Quality Targets should address both applications
  - 28% of the clinical samples in "Increasing Risk" range, this is a narrow window: Small analytical error will have a high impact on Interpretation
  - Clinical Interpretation HbA1c Results: Lab Queen Beatrix Hospital 2016

			Bias	
Low Risk	Incr Risk	Diabetes	Mmol/mol	% NGSP
25%	28%	47%	0	0.0
12%	33%	55%	+3	+0.28%
36%	25%	39%	-3	-0.28%

  - "What is the chance that a true HbA1c of 43 mmol/mol (6.1%) is over-estimated in the lab that much that the clinical interpretation will falsely be "diabetes"?

Bias	Imprecision (NGSP)					
Mmol/mol (NGSP %)	5% (3.4%)	4% (2.7%)	3% (2.0%)	2% (1.4%)	1% (0.7%)	0% (0.0%)
5 (0.46)	67	73	80	89	99	100
4 (0.37)	50	50	50	50	50	50
3 (0.28)	33	27	20	12	1	0
2 (0.18)	18	12	6	1	0	0
1 (0.09)	9	4	1	0	0	0
0 (0.00)	6	2	0	0	0	0

  - Chance of overestimation in relation to IFCC quality targets



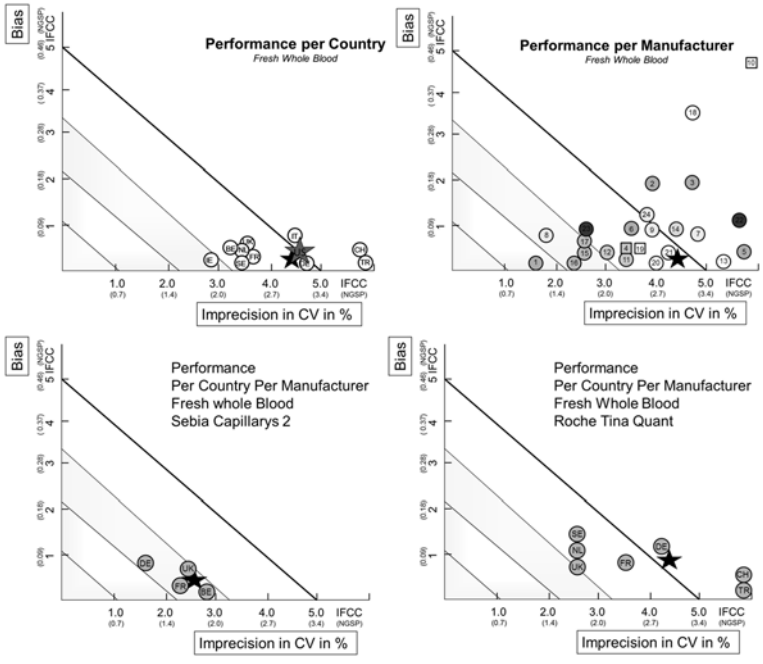
  - Summary of Clinical Data
    - HbA1c equally used for monitoring and diagnosis/screening
    - Focus Quality Management : 33 – 75 mmol/mol (5.2 – 9.0%)
    - Quality requirement for diagnosis higher than monitoring: Low bias is most important
- EurA1c
  - A Project of IFCC Education in the Use of Biomarkers in Diabetes (C-EUBD) & 15 National EQA organisers
  - Concept: Once a year the respective European EQA/PT organizers use the same 2 samples
  - Information
    - Overall performance in Europe
    - Performance per country
    - Performance per manufacturer
  - Participating countries and EQA organisers

BE	WIV-ISP	Yolande Lenga
DE	INSTAND e.V.	Patricia Kaiser
GR	ESEAP	Alexander Haliassos, Kostas Makris, Otto Panagothinakis
IT	Centro di Ricerca Biomedica	Laura Sciacovelli
CZ	SEKK	Marek Budina, Marie Uhlířová
FR	Biologie Prospective	Jean-Pascal Siest
SA	Tygerberg Hospital	Rajiv Erasmus
UK	WEQAS	Annett Thomas, Samantha Jones
SE	EQUALIS	Gunnar Nordin, Carita Krook Persson
AT	ÖQUASTA	Christoph Buchta, Mathias M. Müller
ES	SEQC	Montserat Ventura, Emma Ventura
PT	Inst. Nac. de Saude Dr. Jorge	Ana Paula Faria
IE	IEQAS	Hazel Graham
CH	Universitätsspital Zürich	Roman Fried
TR	Tubitak Ume	Diler Aslan, Fatma Akcadag, Muslum Akgoz
NL	SKML	Cas Weykamp
INT	ERL	Cas Weykamp

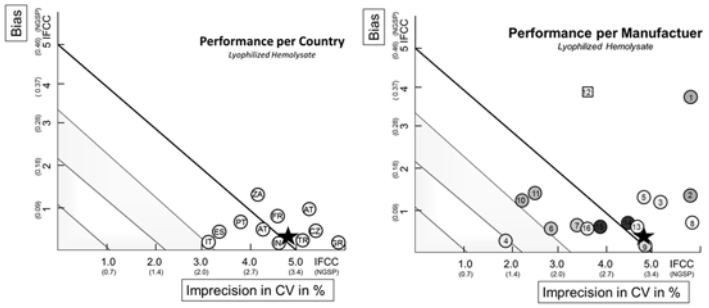
- EurA1c Samples
  - Fresh Whole Blood
    a. Advantage: Commutable and suitable for all methods
    b. Disadvantage: Limited stability
  - Lyophilized Hemolysate
    a. Advantage: Stable
    b. Disadvantage: Not commutable for all methods, not suitable some POCT instruments
  - Choice depended upon national EQA organizers, logistics in the country
  - Both sample types were made from the same pools.
- EurA1c: 15 countries - 2166 Labs

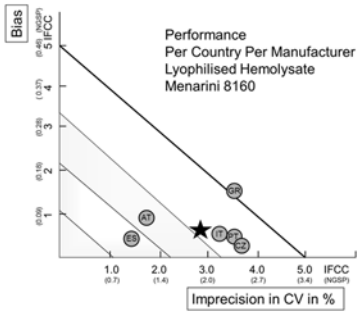
Country	Fresh Whole Blood	Lyophilized Lysate
Austria		107
Belgium	139	
Czech Republic		70
France	135	132
Germany	652	
Greece		73
Ireland	30	
Italy	84	48
Netherlands	136	54
Portugal		43
South Africa		2
Spain		76
Sweden	117	
Switzerland	29	
Turkey	48	45
United Kingdom	148	

- Results: Fresh Whole Blood



- Results: Lyophylized Hemolysate





- Conclusions EurA1c
  - IFCC created tools: Reference Method – Network – Model Quality Targets
  - EurA1c project of IFCC EUBD and national EQA organisers feasible, will be continued in 2017, possibly in years after.
  - EQA is feasible with fresh whole blood and lyophilized samples
  - At European Level:
    a. Mean Bias 2166 European Labs very good (<1 mmol/mol - <0.1%)
    b. Between laboratory variation acceptable (room for improvement)
  - At Country Level
    a. Degree of standardisation in all countries comparable (good)
    b. Between laboratory variation is different per country
  - At Manufacturer Level
    a. All major manufacturers are well standardised .
    b. Degree of between laboratory CV is variable
  - EurA1c
    a. Supplies a lot of information,
    b. Pushes labs-countries-manufacturers to improve quality and thus provide better patient care.

Discussion:

M. McPhaul asked if, among manufacturers, they see same variations between labs in the U.S. as they see in countries in Europe. C. Weykamp said he has looked at this, for some manufacturers it is very similar but for some manufacturers it is not. Some manufacturers are not represented in Europe. M. McPhaul asked what might be driving these differences, C. Weykamp was not sure but the degree of focus on quality is different from country to country. R. Little asked if there are more good methods used in Europe compared to the U.S., C. Weykamp said that good and poor methods are used in both.

4. CAP Grading—David Sacks

- CAP Grading
  - In past, CAP used peer group grading for PT for GHb
  - In 2007 changed to accuracy grading; DCCT target used
  - +/- 15% acceptable
  - 99% pass rate

- PT Criteria Tightened
  - In 2008 acceptability reduced to 12%
  - In 2009 acceptability reduced to 10%
  - In 2010 acceptability reduced to 8%
  - In 2011 acceptability reduced to 7%
  - In 2013 acceptability reduced to 6%
- CAP GH5C 2016: Performance 6% vs 5%
  - Means and acceptable limits

GH-11	GH-11	GH-12	GH-12	GH-14	GH-14	GH-15	GH-15
9.11	9.11	6.01	6.01	5.02	5.02	7.58	7.58
8.5-9.7	8.6-9.6	5.6-6.4	5.7-6.4	4.7-5.4	4.7-5.3	7.1-8.1	7.2-8.0

  - By method

	GH-11	GH-11	GH-12	GH-12	GH-14	GH-14	GH-15	GH-15
N	9.11	9.11	6.01	6.01	5.02	5.02	7.58	7.58
	8.5-9.7	8.6-9.6	5.6-6.4	5.7-6.4	4.7-5.4	4.7-5.3	7.1-8.1	7.2-8.0
8	88.9	88.9	88.9	88.9	85.7	85.7	85.7	85.7
11	81.8	63.6	72.7	72.7	100	75	100	75
129	97.8	96.3	97.8	97.1	99.1	99.1	99.1	97.4
16	100	100	100	100	100	NA	100	NA
80	98.8	98.8	100	100	100	93.3	100	100
87	84.3	84.3	87.6	84.3	87.7	86	86.0	80.7
131	94.2	92.8	97.1	97.1	96.3	93.5	95.3	93.5
172	97.7	96	98.3	98.3	98.4	97.6	99.2	99.2
51	96.2	90.6	96.2	96.2	100	97.8	97.8	97.8
82	96.5	95.3	100	100	100	100	100	97.5
173	100	100	99.4	98.9	100	98.7	99.3	98.7
10	100	100	100	100	100	100	100	100
26	89.3	89.3	92.9	92.9	77.8	77.8	100	94.1
398	98.8	98	98.5	95.3	95.8	95.5	98.8	97.9
60	96.7	90	96.7	96.7	90.3	80.7	100	93.6
117	97.5	97.5	100	98.3	98.1	93.3	100	99.1
42	100	97.7	97.7	95.3	93.3	93.3	100	100
19	90.5	85.7	90.5	90.5	100	100	100	80
453	95.7	95.7	98.3	97.9	96.7	96.7	97.3	96.7
24	100	100	95.8	95.8	95.5	90.9	95.5	90.9
208	95.4	92.6	97.7	96.8	95.1	90.3	95.1	92.4
22	100	100	100	100	100	100	100	100
36	97.3	97.3	89.2	83.8	100	100	100	100
290	96.2	92.2	96.9	96.2	97.4	95.5	97.4	94.8
20	95.2	95.2	95.2	95.2	100	84.6	100	100
371	96.9	96.6	97.4	97.4	99.1	98.8	99.4	99.1
69	100	98.6	98.6	98.6	98.3	98.3	100	96.7
186	95.3	89.1	99.0	98.4	96.9	95	98.8	96.3
3377	96.6	95	97.4	95.9	97.1	95.7	98.1	96.4

- CAP 2016 GH5C Pass Rates at ±6% and ±5% HbA1c Cutoff

	At ±6%	At ±5%
GH-11 (9.1%)	96.6	95.0
GH-12 (6.0%)	97.4	95.9
GH-14 (5.0%)	97.1	95.7
GH-15 (7.58%)	98.1	96.4

- The CAP is considering tightening the cutoff to 5% beginning in 2019.
- In the interim surveys (4), labs would be provided with an educational 5% grading in addition to 6%.
- At the Steering Committee meeting yesterday, manufacturer representatives asked if CAP could also provide information on survey method performance to manufacturers. I will ask CAP if they are willing to share this information.

Discussion:

Change in CAP criteria

D. Sacks noted that the overall pass rates were ≥95% at the 5% cutoff, which is considered very good for a CAP survey. These percentages are actually better than what we saw from previous analyses when the criteria were tightened, e.g. from 10 to 8%. This shows how much improvement there has been in methods in recent years. In terms of individual methods, some showed little change at a cutoff of 5% compared to 6% while others showed a larger drop in pass rates.

Can there be a process mapped out for the future beyond 2019?
D. Sacks said this was done some years ago when the criteria were tightened in several steps, but at this point it is difficult to do. Years ago we did not expect to reach 5%, when the criteria were last lowered to 6% we thought that might be as low as we could go but the data now indicate otherwise. Whether we can go below 5% I do not know, it is probably not feasible at this time. One of the issues is the uncertainty of the NGSP value assignment, at a cutoff below 5% it takes up a large part of the error budget.

What HbA1c range is CAP focused on for the survey?
D. Sacks said the relevant clinical ranges may vary somewhat from one institution to the next depending upon their patient populations. CAP decided that the relevant range is up to 10%.

What is the confidence interval for the CAP value assignments?
R. Little said the CIs for each CAP sample assignment are posted on the NGSP web site. C. Rohlfing said the CIs are generally ~0.1% HbA1c. D. Sacks and R. Little noted that each SRL analyzes the samples in triplicate on two separate days, making the uncertainty very small. R. Little noted that the CI for a recent CAP sample that had an assigned value of 6.41% had a CI of 6.36-6.47%.

Are the inter-laboratory CVs versus intra-laboratory CVs the major reason why some methods show high CVs on the surveys?
D. Sacks said he thinks so, although we do not know the within-lab CVs. CAP looks at inter-laboratory CVs which vary by method, sample, etc. We give manufacturers the information from the individual labs so they can look at calibrator and reagent lots.

Will the +/-5% also apply to low HbA1c levels, e.g. below 5% HbA1c? For blood glucose the criteria widen at low levels.
D. Sacks said CAP decided to make the acceptable limits the same across the range. R. Little and C. Rohlfing said CAP samples generally do not go below 5% HbA1c, there may have been a few in the past that were in the upper 4s.

If CAP could provide information regarding method performance at 5% to manufacturers as well as laboratories it would be useful.
D. Sacks said he will check with CAP. They will probably agree to this as they have already been sharing other information with manufacturers.

Hemoglobin Variants
D. Sacks noted that several times in the past CAP has included a sample with sickle-cell trait in the survey. It is not graded but is useful in terms of showing how manufacturer methods are affected by HbS trait. CAP plans to continue to do this in the future. R. Little said it is also a good educational tool for labs to make them more aware of variant interferences.

NGSP Certification Criteria
R. Little said there has also been discussion of lowering the NGSP certification limits from +/-6% to +/-5%. We will be reviewing data in the same way as when the criteria were tightened the last time. If we decide to go to +/-5% manufacturers will be notified at least a year in advance. As before they will receive information about how their method performed at 5% as well as 6% with their certification reports during that time. D. Sacks said the analyses performed by C. Parvin the last time where the CAP and NGSP criteria were compared at 7% vs. 6% were published in a paper. The same analyses will be done looking at 6% vs. 5%, this will be the basis for the decision. There is no point in having large numbers of manufacturer methods unable to obtain certification, this would defeat the purpose of what the NGSP is trying to accomplish.

If the NGSP criteria are tightened will that also take effect in 2019?
R. Little said it would not be before then, it might be a bit after that depending upon how much time is needed to review the data.

There were no further questions, D. Sacks thanked everyone present for their attendance; the meeting was adjourned at 1:20 PM.

Minutes prepared by C. Rohlfing 9/13/17.