1. IFCC Standardisation of HbA1c
2. Global Units for HbA1c

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Special Chemistry, Austin Health, Melbourne, Victoria, Australia

Member – IFCC Working Group on Standardisation of HbA1c
1994-2010
Diabetes

Global Epidemic

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985</td>
<td>30 Million</td>
</tr>
<tr>
<td>2000</td>
<td>180 Million</td>
</tr>
<tr>
<td>2025</td>
<td>320 Million</td>
</tr>
</tbody>
</table>

Long Term Complications

Juvenile Diabetes

- 15-20% dead in 20 years
- 40-50% dead in 30 years

Responsible for:

- 12% of all cases of blindness
- 25% of all cases of renal failure
- 40% of all non-traumatic foot and leg amputations
Major long-term complications of Diabetes

Type I Mortality
5.4 - 11.5 X ND
Average life expectancy
70% of ND

Gangrene or amputations
15-40X ND
Loss of sensation in feet
60-70% loss

Diabetic foot:
peripheral neuropathy and ischemia, foot ulcers, amputations

Autonomic neuropathy:
diarrhea, impotence

Retinopathy:
visual impairment and blindness

Macroangiopathy:
coronary heart disease
peripheral vascular disease

Nephropathy:
renal failure

Reproduction
Impotence 40% versus 5% ND
Congenital malformations in Pregnancy 2-3X ND

CVA 2-4X ND
AMI 2-4X ND
PVD 4X ND

25X ND
15X ND
HbA1c FORMATION

Glucose + β N terminal valines HbA

\[ \uparrow \quad \text{Non Enzymatic} \quad \text{Reversible} \]

Aldimine HbA1c

\[ \downarrow \quad \text{Non Enzymatic} \quad \text{Irreversible} \]

KETOAMINE HbA1c

60% Glucose binding β N valines
40% Glucose Binding is on the α N Terminal valines and the α and β side chain Lysine groups
(11 on each of 2 α and 2 β chains)
HbA1c GLYCAEMIC CONTROL PARAMETER

50% determined by MBG in past month

25% determined by MBG in prior 1 – 2 months

25% determined by MBG in prior 3 – 4 months

Reference:
   Diabetes Care 1993; 16: 1313-4. Tahara, Shima
AIM

The IFCC WG was formed in 1994 with its aim to establish a Global Reference System for HbA1c.

Specific aims were:
(a) To define the heterogenous HbA1c
(b) To prepare pure HbAO and HbA1c
(c) To develop a Reference Method
(d) To establish a Reference Laboratory Network
(e) To prepare secondary reference calibrators and controls
(f) Uniform calibration of commercial methods
(g) Method comparisons vs DCM (USA, Sweden and Japan)

Note: No mention of Global Units
IFCC HbA1c Working Group Members

<table>
<thead>
<tr>
<th></th>
<th>1994 (8)</th>
<th></th>
<th>2009 (13)</th>
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<tr>
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<td>UK</td>
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</table>
IFCC Working group for standardisation of HbA1c
HbA1c consists of 2 alpha and 2 beta subunits. 60% of glucose binding occurs on the N terminal valines of the $\beta$ chains. 40% occurs at lysine side chains on both $\alpha + \beta$ chains. Glycation is therefore heterogenous.

The IFCC WG has defined HbA1c as $\beta$N valine glycated Hb.

($\beta$N-(1-deoxy)- fructosyl Hb), a hexapeptide, representing the major glycation site of the HbA1c molecule.
PURIFICATION SCHEME FOR THE ISOLATION OF HbA1c AND HbAO

Native blood

Washing / RBC lysis / removal of cell debris

Haemoglobin

Cation Exchange Chromatography
(SP Sepharose high performance - pH 6.2)

HbA1c (crude) HbAO (crude)

Affinity chromatography
(Glycogel II Boronate - pH 8.0)

Glyc Hb Non Glyc Hb

Cation Exchange Chromatography
(SP Sepharose high performance - pH 6.2)

HbA1c (pure) >99.5% IRMM/IFCC 466
HbAO (pure) >98.5% IRMM/IFCC 467
CALIBRATORS FOR THE REFERENCE METHOD

- The calibrators are mixtures of pure HbAO and HbA1c
- A calibrator set consists of six calibrators with different HbA1c concentrations covering the clinically relevant concentration range (0, 3, 6, 9, 12, 15 % HbA1c)
- The preparation is done according to a detailed SOP
- The calibrators are stable at -70°C for at least 5 years
- A New lot is manufactured each year
  - Year 1 Checking / confirmation
  - Year 2 Used as calibrators
  - Year 3 Checking / spare calibrators
IFCC REFERENCE METHODS

Blood
  ↓ Saline wash
  ↓ Erythrocytes
    ↓ NaCl, 37°C, 4h
      ↓ Aldimine removal
         ↓ H₂O
            ↓ Haemolysate
              ↓ Endoproteinase Glu-C
                 ↓ 37°C, 18h, pH4.0
                   ↓ βN terminal hexapeptides of HbA1c and HbAO
                       ↓ Reverse phase HPLC
                          ↓ A
                            ↓ Electro spray ionisation mass spectrometry
                            ↓ B
                              ↓ Capillary electrophoresis
COMPARISON HPLC-MS VERSUS HPLC-CE
(4 MS reference labs and 6 CE reference labs)

\[ y = 0.997x - 0.005 \]

\[ R^2 = 1.000 \]
The main task of the IFCC Network is the reliable assignment of HbA1c target values to reference materials, reference panels of blood samples and control materials which are necessary for the implementation and maintenance of the system.

Each Network Laboratory has established one or both (GCMS / Cap EPG) IFCC Methods

Between lab CV%  <2.5%
# IFCC NETWORK OF PRIMARY REFERENCE LABORATORIES

<table>
<thead>
<tr>
<th>Location</th>
<th>Country</th>
<th>Type</th>
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</thead>
<tbody>
<tr>
<td>Atlanta - CDC</td>
<td>USA</td>
<td>MS CE</td>
</tr>
<tr>
<td>Colombia – University Hospital (NGSP)</td>
<td>USA</td>
<td>CE</td>
</tr>
<tr>
<td>Dusseldorf - Diabetes Institute</td>
<td>Germany</td>
<td>MS</td>
</tr>
<tr>
<td>Dusseldorf - Instand</td>
<td>Germany</td>
<td>MS CE</td>
</tr>
<tr>
<td>Kanagawa - Biopathological Medicine</td>
<td>Japan</td>
<td>CE</td>
</tr>
<tr>
<td>Kawasaki - Standard Reference Centre</td>
<td>Japan</td>
<td>CE</td>
</tr>
<tr>
<td>Malmoe - University Hospital</td>
<td>Sweden</td>
<td>CE</td>
</tr>
<tr>
<td>Milano - Technological Biomedicine</td>
<td>Italy</td>
<td>MS</td>
</tr>
<tr>
<td>Norwood – Bayer Healthcare</td>
<td>USA</td>
<td>MS</td>
</tr>
<tr>
<td>Penzberg - Roche Diagnostics</td>
<td>Germany</td>
<td>MS</td>
</tr>
<tr>
<td>Tokyo - Keio University Clinical Laboratory</td>
<td>Japan</td>
<td>CE</td>
</tr>
<tr>
<td>Winterswijk - Clinical Laboratory</td>
<td>Netherlands</td>
<td>CE</td>
</tr>
<tr>
<td>Zwolle - Clinical Laboratory</td>
<td>Netherlands</td>
<td>CE</td>
</tr>
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</table>

Total 15  6 x MS  9 x CE
IFCC NETWORK OF HbA1c REFERENCE LABS - ANALYTICAL PERFORMANCE

• The Network runs two intercomparison studies per year (6 - 10 samples, range 4 - 12 % HbA1c )

• The labs have to meet performance criteria for precision and trueness in order to be confirmed as approved IFCC reference lab.

• Excellent performance of the Network has been achieved in 20 intercomparison studies

• The Network is able to assign IFCC HbA1c values to reference materials, calibrators and control materials with a very low uncertainty
# METHOD COMPARISON STUDIES - PARTICIPANTS

## IFCC Network

<table>
<thead>
<tr>
<th>Count</th>
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<th>Laboratories</th>
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</thead>
<tbody>
<tr>
<td>11</td>
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<td>Kobold, Mosca (2x), Jeppsson, Miedema, Weykamp, Susanto</td>
<td></td>
</tr>
<tr>
<td>3 Japan</td>
<td>Hoshino, Umemoto, Takei</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 USA</td>
<td>Vesper (CDC)</td>
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<tr>
<td>4 Candidates *</td>
<td>2 Europe</td>
<td>Siekmann, Reinauer</td>
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<tr>
<td>2 USA</td>
<td>Gleeson, Little</td>
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</tbody>
</table>

## DCM's

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<tbody>
<tr>
<td>8 NGSP Network</td>
<td>4 USA</td>
<td>Little, Patel, Nowicki, Cole</td>
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<tr>
<td>4 Europe</td>
<td>Miedema (2x), Weykamp (2x)</td>
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<td>3 JDS</td>
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<td>1 Mono-S</td>
<td>1 Europe</td>
<td>Jeppsson</td>
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</tr>
<tr>
<td>1 Australia</td>
<td>1 Australia</td>
<td>Goodall</td>
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## Manufacturers

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<th>Approved Labs</th>
<th>Laboratories</th>
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<tbody>
<tr>
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<td>Bio-Rad, Roche, Menarini, Provalis, Axis Shield, Drew, Olympus, Thermo Electron</td>
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<td>2 Japan</td>
<td>Tosoh, Arkray (Menarini)</td>
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<tr>
<td>7 USA</td>
<td>Abbott, Bayer, Bio-Rad, BioMerieux, Beckman, Primus, Dade-Behring</td>
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* All approved as of 2005
IFCC Laboratory Network

IFCC Approved HbA1c Network Laboratories (2011)

- Germany 2
- Italy 1
- Japan 3
- Netherlands 2
- USA 3

IFCC Candidate Reference Laboratories (2011)

- China (Shanghai)
- France (Reims)
- India (Calcutta)
- South Korea (Seoul)

IFCC laboratory network website: [www.ifcchba1c.net](http://www.ifcchba1c.net)
CURRENT DESIGNATED COMPARISON METHODS
(JAPAN, SWEDEN, USA)

• All arbitrarily based on different HPLC ion-exchange methods.

• HbA1c is a % peak in a chromatogram.

• Due to interferences, all these methods define their own ‘HbA1c’ and in %HbA1c values are different for each DCM.

• All DCM’s are non specific; possible contamination of the HbA$_{1c}$ peak, while not all HbA1c elutes under the one peak, some under HbAO peak.

• HbA1c numbers are only relative (not true HbA1c values).
Traceability Chain

For HbA1c

IFCC Definition of the Analyte

Primary Calibrator
Pure HbA1c/HbA0 mix IRMM 466/467

Secondary Calibrator
Blood Panels

Manufacturer’s Working Calibrator

Manufacturer’s Product Calibrator

Patient Sample

Primary Reference MP
Gravimetry

Secondary Refer. MP
IFCC Reference Meth.

Manufacturer’s Internal MP

Manufacturer’s Standing MP

Routine MP in Lab

Network

Manufacturers

Labs

Interpretation Patient Result
CURRENT NATIONAL STANDARDISATION SCHEMES

USA
NGSP
Biorex 70 HPLC Method 1983 (DCCT)

JAPAN
JDS/JSCC
National Calibrators (1995) Tosoh / Kyoto Daiichi. HPLC mean
Now KO500 HPLC (2000) (Set to 1995 values)

SWEDEN
Swedish Clinical Chem Soc
JO Jeppsson
Mono S Cation Exchange HPLC

REST OF THE WORLD
Mainly NGSP, based on commercial methods calibrated to DCCT / NGSP and includes
Australia and New Zealand
Europe (except Scandinavia)
Asia (except Japan)
Africa, South and Central America
NGSP DESIGNATED COMPARISON METHOD

Typical Chromatograms of BioRex 70 (DCCT) Method

Reference of the method:
Hemolysate pools (≈ 25 mg Hb) prepared from red blood cells of 5 normal and 5 diabetic individuals were dialyzed vs. 0.04 M sodium phosphate, pH 6.7, and applied to (1 × 30 cm) Bio-Rex 70 columns equilibrated with the same buffer at room temperature. Minor hemoglobin components were resolved using a step gradient: 0.08 M sodium phosphate, pH 6.5 (started at column fraction 30) and 0.3 M sodium phosphate, pH 6.5 (fraction 50). Fraction size: 2.0 ml. Flow rate: 10 ml/hr. Individual fractions were dialyzed and run on 1.0 ml boronate affinity columns to determine glycosylated components indicated by the shaded area.
NGSP TRACEABILITY / UNCERTAINTY

Method
Biorex 70 Cation Exchange HPLC
Used for DCCT 1983 – 1993
Interference from abnormal Hb variants

Non Specific HbA1c
40% of HbA1c glycation
HbF
Minor Hb Forms
Carbamylated Hb (Uraemic Adduct)

Poor Separation of Peaks
HbA1a / HbA1b and HbA1c / HbF / Carb Hb

Non HbA1c peaks (HbA1a, HbA1b and HbAO) contain some Glycated Hb. Also HbA1c peak contains some Non Glycated Hb.

TRACEABILITY - Non specific peak on a 1980’s HPLC Chromatogram

UNCERTAINTY - High
CAP SURVEY (mean ± 2SD)
MASTER EQUATIONS IFCC HbA1c v DCM HbA1c

- HbA1c-NGSP = 0.915 HbA1c-IFCC + 2.15 \ (r^2 = 0.998)
- HbA1c-Japan = 0.927 HbA1c-IFCC + 1.73 \ (r^2 = 0.997)
- HbA1c-Sweden = 0.989 HbA1c-IFCC + 0.88 \ (r^2 = 0.997)

IFCC Reference System for Measurement of Hemoglobin A₁c in Human Blood and the National Standardization Schemes in the United States, Japan, and Sweden: A Method-Comparison Study

Wieland Hoelzel, Cas Weykamp, Jan-Olof Jeppsson, Kor Miedema, John R. Barr, Ian Goodall, Tadao Hoshino, W. Garry John, Uwe Kobold, Randie Little, Andrea Mosca, Pierluigi Mauri, Rita Paroni, Fransiscus Susanto, Izumu Takei, Linda Thienpont, Masao Umemoto and Hsiao-Mei Wiedmeyer, on behalf of the IFCC Working Group on HbA₁c Standardization
COMPARABILITY OF RESULTS OF IFCC-CALIBRATED HbA1c ROUTINE METHODS

HbA1c ROUTINE METHODS

HbA1c % Mean Value IFCC-calibrated routine methods

- BioRad
- Primus
- Tosoh
- Tina-quant
- DCA
Clinical use of HbA1c

• Quality of patient care (long term monitoring)
• Outcome risk (complications)
• In USA, used for monitoring diabetes services/clinicians and programmes
• Non-diabetics – cardiovascular and stroke risk stratification
• Diabetes diagnosis (USA-ADA)
The A1C-Derived Average Glucose (ADAG) Study

International study designed to:

- Carefully look at relationship between HbA1c and average glucose
- Determine the mathematical relationship between the two for reliable conversion
- Establish that the relationship is valid across:
  - Diabetes types
  - A wide range of HbA1c levels and age
  - Different races/ethnicities

Nathan et al, Diabetes Care 31:1473, 2008
ADAG Study Centers

- Cameroon
- Denmark
- Italy
- The Netherlands

- United States
  - Boston
  - New York
  - San Antonio
  - Seattle

- India (site dropped due to specimen handling issues)
ADAG Study: Correlation of AG With HbA1c

\[ AG (\text{mg/dl}) = 28.7 \times HbA1c - 46.7 \]

\[ R^2 = 0.84 \]

\[ P < 0.0001 \]
ADAG Study Conclusion: HbA1c Correlates Highly With AG

AG (mg/dl) = 28.7 x HbA1c – 46.7
ADAG Study: Study Success

90% of cohort values fall in this range

HbA1c (%)

90% of values fell within +/- 15%
eAG Study Negatives

- Only 507 patients worldwide
  - 268 Type 1, 159 Type 2, 80 non Diabetics
- Few patients with poor control
- Very limited ethnic groups
- No children
- Correlation results show imprecision and wide scatter

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<thead>
<tr>
<th>Correlation equivalents</th>
<th>HbA1c</th>
<th>eAG</th>
</tr>
</thead>
<tbody>
<tr>
<td>ULN Level</td>
<td>6.0%</td>
<td>7.0 mmol/l</td>
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<tr>
<td>Poor Control Level</td>
<td>8.0%</td>
<td>10.2 mmol/l</td>
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</table>
Consensus Statements – Global HbA1c Units

2007 IFCC is only valid anchor for standardisation ADA/EASD/IFCC/IDF.
To report IFCC mmol/mol + NGSP/DCCT % (master equation) + ADAG (if passes criteria)

2009 ADA/EASD/IFCC/IDF/ISPAD
To report IFCC mmol/mol + NGSP/DCCT % (master equation) + eAG locally

2010 International HbA1c Consensus Committee
To report IFCC mmol/mol + NGSP/DCCT % (master equation)
To December 2011

Comparison between HbA1c values under old and new reporting units

<table>
<thead>
<tr>
<th>Current DCCT/NGSP aligned HbA1c (%)</th>
<th>New IFCC HbA1c (mmol/mol)</th>
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<tbody>
<tr>
<td>4.0</td>
<td>20</td>
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<tr>
<td>5.0</td>
<td>31</td>
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<tr>
<td>6.0</td>
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<td>6.5</td>
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<td>7.0</td>
<td>53</td>
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<td>7.5</td>
<td>59</td>
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<td>8.0</td>
<td>64</td>
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<td>9.0</td>
<td>75</td>
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<tr>
<td>10.0</td>
<td>86</td>
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<tr>
<td>12.0</td>
<td>108</td>
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HbA₁c as indicator of Diabetes Control

HbA₁c

DCCT%
4.9%

IFCC mmol/mol
30

Blood Glucose (mmol/L)
50
6.7%
8.1
9.6
11.0
12.5
13.9
15.4

90
10.4%

100
11.3%
<table>
<thead>
<tr>
<th>Country</th>
<th>Old Units %DCCT</th>
<th>Reporting of Dual Units %DCCT, mmol/mol Commencement date</th>
<th>Global Unit mmol/mol - Commencement date</th>
<th>eAG/ADAG - to be reported</th>
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<td>Austria</td>
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<td>No</td>
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<td>Denmark</td>
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<td>%DCCT</td>
<td>%DCCT</td>
<td>%DCCT</td>
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</table>

AACB website: “www.aacb.asn.au”
Footnotes to table:

* Denmark is reporting dual units (%DCCT, mmol/mol) as from 1/1/2010, together with automatic eAG to produce all three units on laboratory reports.

** Finland is reporting dual units (%DCCT, mmol/mol) as from 3/3/2010. eAG can be reported but is not mandatory. eAG must be requested separately to HbA1c.

*** The USA has not announced any changes in their HbA1c Units. They do not report any pathology in SI Units at all.

**** The USA Position on eAG is detailed as "the American Diabetes Association (ADA) and the American Association for Clinical Chemistry (AACC) have determined that the correlation (r=0.92) obtained in the ADAG study (Reference 4) is strong enough to justify reporting both an A1c result and an estimated average glucose (eAG) when a clinician orders the A1c test." Diabetes Care 2010; 33 (Supplement 1): S19 .
AACB Position Statement on HbA1c Reporting Units (2)

Conversion Formula

- DCCT/NGSP % = 0.09148 X IFCC mmol/mol + 2.152
- IFCC mmol/mol = 10.93 X DCCT/NGSP – 23.50

- DCCT target of 7.0% = 53 mmol/mol
- DCCT change of therapy level of 8.0% = 64 mmol/mol
- Old DCCT RR of 4.0-6.0% HbA1c = 20-42 mmol/mol
- GTT Diagnosis of >6.5% HbA1c = >58 mmol/mol
Clinical requirements of a HbA1c test include:

- Low individual variance
- Precision that justifies clinicians acting on differences of 0.35% to 0.5% as being significant.
- HbA1c assays with CV < 2% for combined, between and within run.

(Diabetologia 2002;38:R19-21)
Between Laboratory Variability for HbA$_{1c}$ results
HbA1c methods in use in Australia*

- Immunoassay (169 labs)
- HPLC (cation exchange) (98 labs)
- HPLC (affinity chromatography) (28 labs)

* RCPA-AACB QAP 2009
Factors Effecting HbA1c

- Average blood glucose
- Standardisation - IFCC
- Red cell life span (haemolytic anaemia)
- Precision
  - Recommendation < 2% CV, Poor >3% CV
- Interferences
  - Abnormal Hb variants
  - Homozygous Hb variants (no HbA1c)
  - HbF (HPFH)
  - Ureamic adduct (Method dependant)
HbA1c methods and Hemoglobin Variants
(Interference from HbS and HbC traits)

NGSP website (www.ngsp.org)

<table>
<thead>
<tr>
<th>Method</th>
<th>Interference from HbS</th>
<th>Interference from HbC</th>
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<td>Abbott Architect/Aeroset</td>
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<td>Bayer (Siemens) Advia</td>
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<td>Beckman Synchron System</td>
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<td>Bio-Rad D-10</td>
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<td>Bio-Rad Variant A1c</td>
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<td>Bio-Rad Variant II A1c</td>
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<td>Dade Behring Dimension</td>
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<td>Metrika A1cNOW</td>
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<td>Olympus AU system</td>
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<td>Ortho-Clinical Vitros</td>
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<td>Primus HPLC (affinity)</td>
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<td>Roche Cobas Integra *</td>
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<tr>
<td>Roche Cobas Integra Gen.2</td>
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<td>Roche/Hitachi (Tina Quant II)</td>
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<td>Tosoh A1c 2.2 Plus</td>
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<td>Tosoh G7 Auto HPLC</td>
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*This method will be replaced by the Roche Cobas Integra Gen 2 by the end of 2007
Germany

Enacted a law which states that HbA1c assays must be reported only in SI units

1/1/2009   DCCT $\rightarrow$ DCCT + IFCC
1/1/2010   DCCT + IFCC $\rightarrow$ IFCC (mmol/mol)

eAG NOT to be reported
Consensus Meeting ACB, London 23/1/2008
Convened by Dr Sue Roberts, National Director for Diabetes, UK Department of Health
19 Associations (Medical/Scientific/Diabetes/QC)
ACB/Assoc Clin Path/ Ass Brit Diabetologists/ Dept of Heath/
Diabetes UK/ Eur Fed Clin Chem/ IDF/ IFCCLM/ Medicine/ AACB/
Prim Care Diab Soc/ RC Path/ RC Phys/ RCGP/ RC Nursing/ RC Obstrets and Gynaec/ UK NEQAS/ Wales WEQAS
1/6/2009   DCCT  \rightarrow  DCCT + IFCC
1/6/2011 \rightarrow  IFCC (mmol/mol)
eAG NOT to be reported
New Zealand (No Meetings)

NZSSD – NZ Society for Study of Diabetes
All professionals involved in the care of people with diabetes, 250 members
- Diabetes physicians, specialist nurses, podiatrists, dieticians, ophthalmologists, general physicians, family doctors, community health, allied industries, medical scientists.

1/8/2009 DCCT → DCCT + IFCC
1/8/2011 → IFCC (mmol/mol)

eAG NOT to be reported
Italy

Working Group (20 Delegates/National Associations) meeting in Milan (2009)
Ital Soc Clin Bio/Clin Molec Biol (SIBioC) (Umbrella Org)
Publication – CCLM 2010; 48: 625-6
Changes in reporting units/new units
Relationship old vs new units
Timeline for Changes
Definition of analytical goals
1/1/2010 DCCT → DCCT + IFCC
1/1/2012 → IFCC (mmol/mol)
eAG NOT to be reported
Netherlands

Several meetings 2009. Ten associations
6/4/2010 DCCT → DCCT + IFCC
1/1/2011 → IFCC (mmol/mol)
eAG NOT to be reported
70,000 Euro from government
Sweden

Collaboration between clinical chemists and five medical associations, diabetic nurses association and diabetes patients association.

1/9/2010 Mono S $\rightarrow$ Mono S + IFCC
1/1/2011 $\rightarrow$ IFCC (mmol/mol)

eAG NOT to be reported

Note- Dual Units only for four months
Japan


% JDS \rightarrow JDS + 0.4 \% \rightarrow IFCC

(JDS + 0.4\% = DCCT/NGSP)

Will report in % JDS in clinical practice

15/5/2011 JDS to report HbA1c as JDS + 0.4\% and IFCC (mmol/mol)

No dates of implementation
Australia

- Teleconferences and emails
- [www.aacb.asn.au](http://www.aacb.asn.au) – AACB website - Position Statement
  - Home page → Resources (bottom left) then → Position Statement (upper right)

Approx. 4/7/2011 DCCT → DCCT + IFCC
4/7/2013 → IFCC (mmol/mol)

eAG NOT to be reported

USA

- No Changes to current % DCCT units
- USA does not use any SI units
- eAG to be reported with every HbA1c
- Diabetes Care 2010, 33 (supp. 1): 519-
- ADA/AACC have determined that the correlation (r=0.92) obtained in the ADAG (eAG) study is strong enough to justify both an A1c result and an eAG whenever a clinician orders the A1c test
Typical Plan of Action

• Convene a working group of official representatives, preferably representing National Associations (diabetes clinicians, scientists, pathologists, diabetes organisations and Department of Health etc.)

• Convene a national meeting, teleconference, or email correspondence.

• Discuss concepts of units (IFCC or DCCT) and select units and future dates for implementation.

• Prepare educational material for laboratories, clinicians and patients
IFCC Reference System for HbA1c

• New precise definition of HbA\textsubscript{1c}
  • The IFCC has defined HbA\textsubscript{1c} as (β-N-(1-deoxy)-fructosyl Hb), a hexapeptide, representing the major glycation site of the HbA1c molecule.

• Preparation of primary reference materials
  – HbA\textsubscript{0} and HbA\textsubscript{1c}, six calibrators with 3-15% HbA\textsubscript{1c}

• IFCC reference methods
  – Electrospray ionisation MS or capillary electrophoresis detection
  – Unanimous adoption as Approved IFCC Reference Method

• IFCC National Reference Laboratories
  – 15 laboratories, 6 countries, 2 reference methods (MS/CE)

Adapted from Hoelzel \textit{et al} Clin Chem 2004; \textbf{50}: 166-74
Scientists and clinicians have been working for more than 10 years to produce a gold-standard, interference free method for HbA$_{1c}$.

The new calibration method, without interferences, gives values approximately 1.5% lower than the DCCT values.

Unfortunately the two numbers are still similar enough in appearance to cause confusion, so a decision has been taken to change the units of reporting the new values in order to avoid any problems.

The new ‘IFCC standardised’ results will be written in units of mmol/mol.
International Consensus Statement: 2007
ADA/EASD/IFCC/IDF

1. HbA\textsubscript{1c} results should be standardised worldwide including the reference system and results reporting
2. The new IFCC reference system represents the only valid anchor to implement standardisation of the measurement
3. HbA\textsubscript{1c} results are to be reported worldwide in IFCC units (mmol/mol) and derived NGSP units (%)
4. If the ongoing average plasma glucose study fulfils its a priori specified criteria an HbA\textsubscript{1c}-derived average glucose (ADAG) value calculated from the HbA\textsubscript{1c} result will also be reported
5. Glycaemic goals appearing in clinical guidelines should be expressed in IFCC units, derived NGSP units and as ADAG

\textit{Diabetologia} 2007; 50: 2042-3
UK Consensus Statement Summary (2008)

• HbA$_{1c}$ test results should be standardised using the IFCC reference method (already completed by manufacturers)
• Extensive education programmes should be developed for all healthcare professionals (completed)
• HbA$_{1c}$ results should be reported in IFCC (mmol/mol) units and DCCT (%) units
• Parallel reporting will start from June 2009 and continue for 2 years (commenced)
• After this time it is envisaged that laboratories will report only IFCC units (planning under way)

Ann Clin Biochem 2008; 45: 343-4
International Consensus Statement 2010
ADA/EASD/IFCC/IDF

1. HbA$_{1c}$ results standardised worldwide
   - Reference system and results reporting

2. IFCC reference system is the only valid anchor for standardisation

3. HbA$_{1c}$ reported in IFCC (mmol/mol) and derived NGSP (%) units

4. HbA$_{1c}$ conversion tables (IFCC-NGSP) easily accessible

5. Editors to recommend publication in both IFCC and NGSP units

6. Reportable term is HbA$_{1c}$
   - Other terms (e.g. A1C may be used in guidelines and educational material

7. Further discussion at IDF meeting in December 2011

Note: Estimated average glucose (eAG) not included in statements.
Recognize may add value to consultation process. Local decision on implementation

Ann Clin Biochem 2010; 47: 290-1
Why is HbA1c so important?

DCCT showed that HbA1c is the best long-term marker of diabetes control.

Better control of HbA1c leads to better outcomes in people with diabetes:
- Deaths related to diabetes: 21%
- Microvascular complications: 37%
- Myocardial infarction: 14%

INTERLABORATORY VARIABILITY

International, National and between Provinces / Cities / Laboratories

• Both accuracy and precision are ultimately and totally dependent on routine laboratory assays in every laboratory.

• There are very good and very poor commercial assays.

• Good assays are good everywhere, poor assays are poor everywhere.

• HbA1c assays need tight precision and high specificity.

• The choice of HbA1c instrumentation and assays is crucial in all laboratories.