Standardizzazione dell'emoglobina A1c

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TOSOH

INCONTRO DI AGGIORNAMENTO SCIENTIFICO

"EMOGLOBINE: DIAGNOSTICA, STANDARDIZZAZIONE, PROSPETTIVE"

AULA MAGNA OSPEDALE
DESENZANO DEL GARDA (BS)
Loc. Montecroce

9 MAGGIO 2009

Agenda

- Standardizzazione HbA_{1c}
  - standardizzazione IFCC
  - lo studio ADAG
  - consensus document
  - il punto di vista dei produttori di diagnostici
  - prossimi step

Standardizzazione IFCC dell'HbA_{1c}

IFCC SD WG-SHbA1c

IFCC Reference System for HbA_{1c}

*** Definition of the analyte**
*** Preparation of pure HbA_0 and HbA_{1c}**
*** Development of reference method**
*** Installation of a Reference Lab Network**
• Preparation of secondary ref. Material

Analyte definition (1)

…, a detailed definition of the quantity to be measured constitutes an indispensable part of any analytical reference system…. In Laboratory Medicine, many hundreds different analytes are measured or determined. With regard to the implementation of traceability, it is however important to differentiate between:

– analytes which are well defined chemical entities and are traceable to International System (SI) units, called **type A** quantities, and

– analytes which are rather heterogeneous in human samples and are not directly traceable to SI units, called **type B** quantities.

M. Panteghini, J.C. Forest. Clin Chim Acta 2005

Analyte definition (2)

- Type A: more than 65 analytes (electrolytes, minerals, metabolic products (such as cholesterol, creatinine, uric acid), steroids, and vitamins.

  Test results: moles per litre.

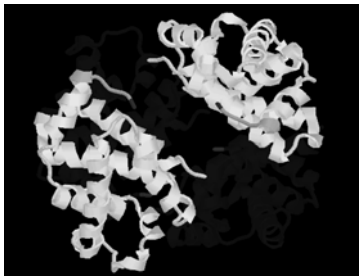
  Reference materials, reference measurement procedures: usually available, independently of routine measurement.

Analyte definition (3)

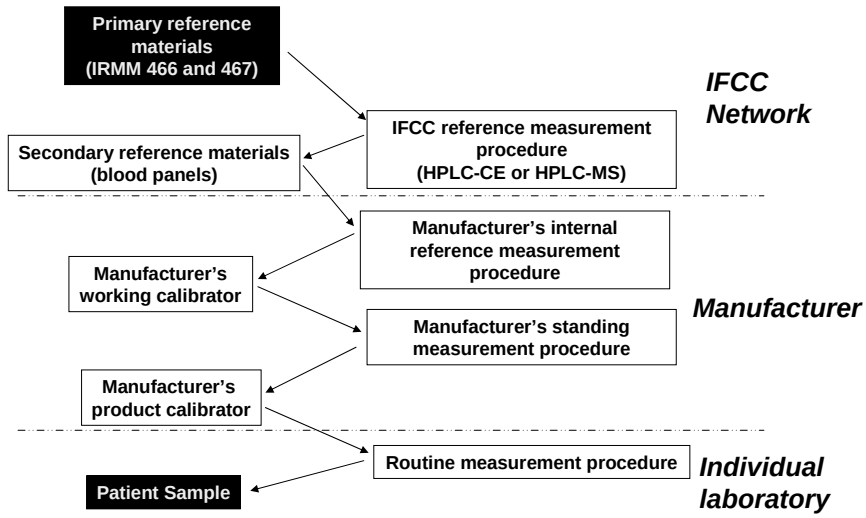
- Type B: proteins and glycoproteins (usually measured by immunochemical techniques)

  Test results: not expressed in terms of SI units (arbitrary units, e.g. WHO units or mass units of a preparation belonging to a manufacturer)

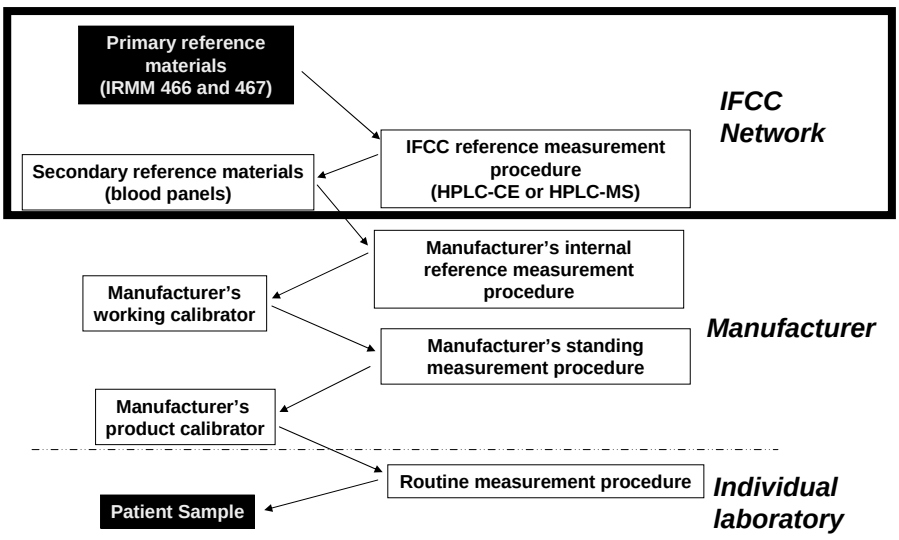
Type “B” analyte: Hb A_{1c}, βN1-deoxyfructosyl-Hb



Glucose bound to N-terminals:
- PI
- epitope
- affinity chromatography



Mosca et al, Clin Chem lab Med 2007;45:1077



CERTIFIED REFERENCE MATERIAL
IRMM/IFCC– 466

CERTIFICATE OF ANALYSIS

HAEMOGLOBIN ISOLATED FROM WHOLE BLOOD		
	Amount-of-substance fraction	
	Certified value[1] [mmol/mol]	Uncertainty[2] [mmol/mol]
HbA1c/(HbA0 + HbA1c)[3]	934	22

1) The certified value was calculated from the average of the results for the amount-of-substance fraction of HbA0 versus HbA0 plus HbA1c for three accepted datasets and converted into amount-of-substance fraction HbA1c (1000 mmol/mol – HbA0 mmol/mol). Measurements were carried out using the IFCC reference measurement procedure and were further confirmed by other methods. The certified value, expressed as mmol HbA1c per mol HbA1c plus HbA0, is traceable to the SI.
2) The certified uncertainty is the expanded uncertainty estimated in accordance with the Guide to the Expression of Uncertainty in Measurement (GUM) with a coverage factor $k = 2$, corresponding to a level of confidence of about 95 %.
3) HbA1c is defined as the beta-N-(1-deoxyfructos-1-yl) haemoglobin. HbA0 is defined as the non-glycated haemoglobin.

CERTIFIED REFERENCE MATERIAL
IRMM/IFCC– 467

CERTIFICATE OF ANALYSIS

HAEMOGLOBIN ISOLATED FROM WHOLE BLOOD	
	Amount-of-substance fraction
	Certified value[1] [mmol/mol]
HbA0/(HbA1c + HbA0)[2]	> 976

1) The certified value was calculated from the average of the results for the amount-of-substance fraction of HbA1c for two accepted datasets and converted into amount-of-substance fraction HbA0 (1000 – HbA1c mmol/mol). Measurements were carried out using the IFCC reference measurement procedure and were further confirmed by other methods. The certified value, expressed as mmol HbA0 per mol HbA1c plus HbA0, is traceable to the SI. With a 95 % probability, the true value of the material is above this level.
2) HbA1c is defined as the beta-N-(1-deoxyfructos-1-yl) haemoglobin. HbA0 is defined as the non-glycated haemoglobin.

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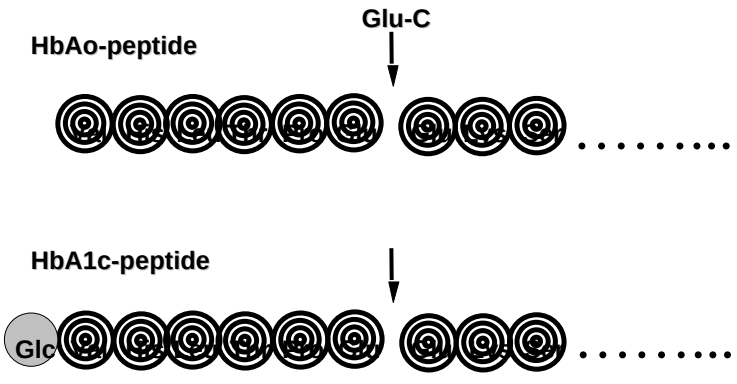
The Analytical Challenge

Proteolytic cleavage of β-chain (146 amino acids)



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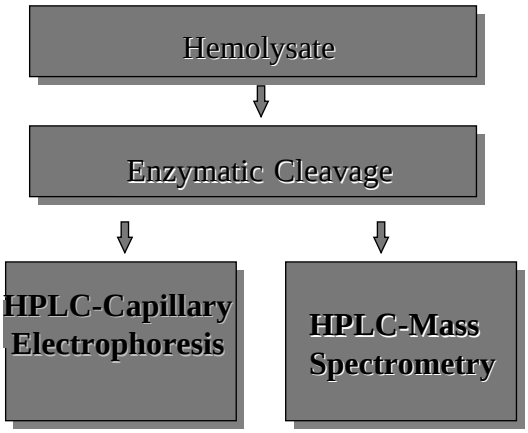
Flow Chart for Reference Methods



Approved by IFCC 2001

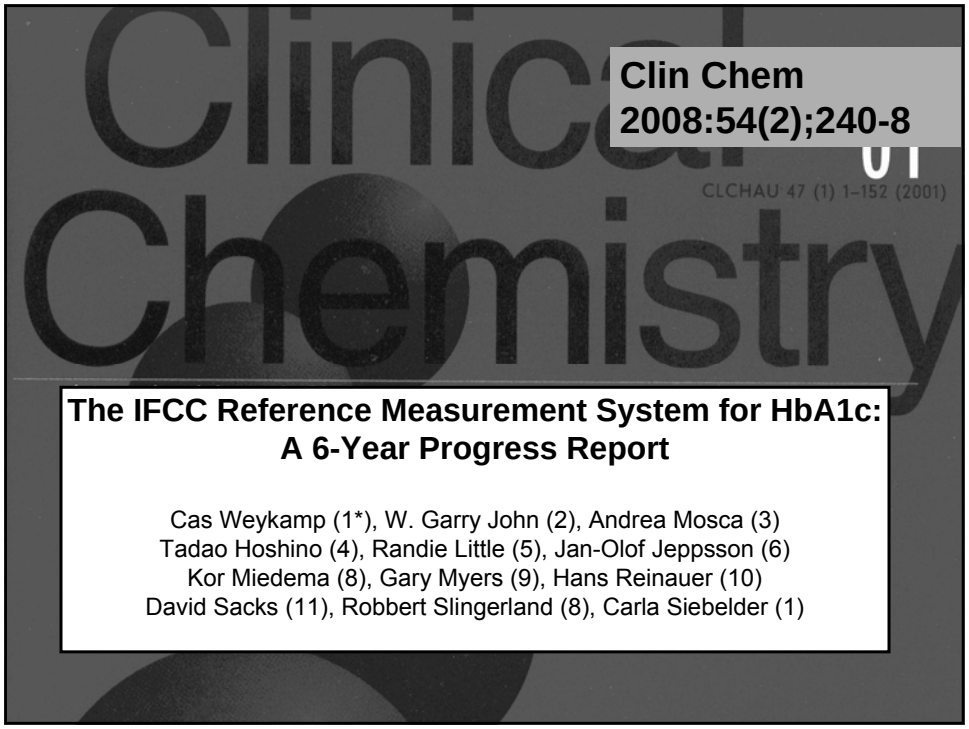
Possible interferences

- The hexapeptide represent an unique sequence
- Hb S and C
- Acetylated and carbamylated hemoglobin
- Potassium cyanide
- Sodium azid- excluded

Hemoglobinopathies in the N-terminal part

- Hb S β6 Glu → Val
- Hb C β6 Glu → Lys

• Hb Raleigh	β1 Val → Ac-Ala
• Hb Niigata	β1 Val → Leu
• Hb Deer Lodge	β2 His → Arg
• Hb Okayama	β2 His → Gln
• Hb Graz	β2 His → Leu
• Hb Agrigente	β2 His → Pro
• Hb Fukuoka	β2 His → Tyr
• Hb Tyne	β5 Pro → Ser
• Hb Warwickshire	β5 Pro → Arg
• Hb G-Makassar	β6 Glu → Ala
• Hb Machida	β6 Glu → Gln



Traceability of Manufacturers to the IFCC Reference Method for HbA1c

This certifies that ***Manufacturer X*** using ***Instrument/Method Y***, uses calibrators supplied by the IFCC Network to get traceable to the IFCC Reference Method and participates in the Monitoring Programme to demonstrate traceability. In the Monitoring Programme of 2007 the following performance was seen:

Deviation from IFCC-target	at 3 % HbA1c %	:	0.3%
	at 6 % HbA1c %	:	0.1%
	at 9 % HbA1c %	:	0.0%
Reproducibility, coefficient of variation			1.1%
Linearity, corrrelation coefficient			0.9981

Date of issue: 31 October 2007 Certification expires: 31 December 2008

IFCC units

Table 1 Suggested units and target values for HbA1c when measured with methods traceable to the IFCC reference system. A comparison with the current figures is also given.

	Current (NGSP-ADA)	**IFCC traceable method**
Reference interval (healthy)	4 – 6 %	20 - 42 mmol/mol
Target for treatment	< 7 %	< 53 mmol/mol
Change of therapy	> 8 %	> 64 mmol/mol

Panteghini et al, CCLM 2007;45:942-4

Benefits from the use of the IFCC standardised HbA_{1c} test

- New units (mmol/mol in place of %)
  No confusion when recalculating old HbA_{1c} targets in terms of new standardized IFCC numbers.
- Reduced uncertainty
- Positive impact due to change of units
  Slight changes in % units will be amplified and will be able to draw more attention
  i.e. HbA_{1c} from 8.3 % to 7.9 % → HbA_{1c} from 67 to 63 mmol/mol
- Diagnosis of diabetes
  Potential use of HbA_{1c} for the diagnosis of diabetes because of a better standardization of the analytical techniques.

Studio ADAG (A1c-Derived-Average-Glucose)

Tesi

E' possibile predire una glicemia media dei tre mesi precedenti il prelievo a partire da una misura di HbA_{1c}

ADAG study

Study Population

1. Type 1 and 2 diabetes (300 each) and 100 healthy individuals
2. Stable glycaemic control
3. Recruit diverse ethnic groups, incl. white, black, Hispanic, Asian
4. Range of HbA_{1c} concentrations

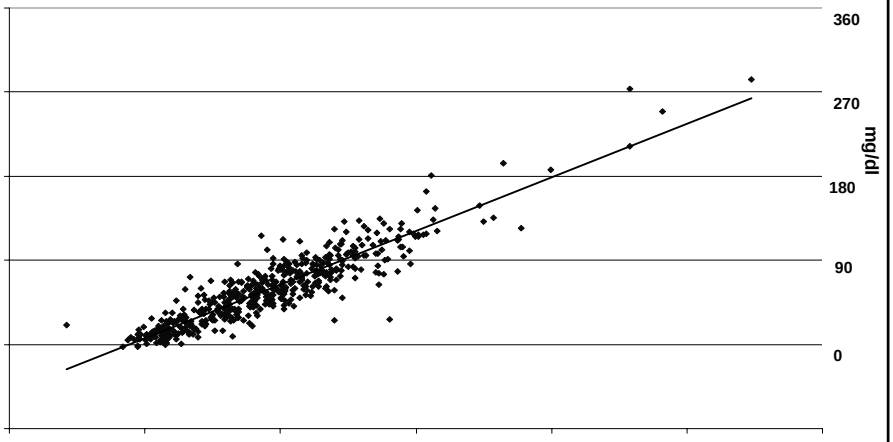
ADAG study

Trial Design

1. Measure HbA_{1c} at baseline and all monthly visits
2. SMBG (LifeScan) 4x/d at least 3 days/week
3. Continuous glucose monitoring (CGMS, Medtronic) over 48 h at 0, 4, 8 and 12 weeks
4. 8-point SMBG (Hemacue) during CGMS

ADAG study

AG over 3 months compared with HbA_{1c} at end of Month 3



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Nathan D et al, Diabetes Care 2008

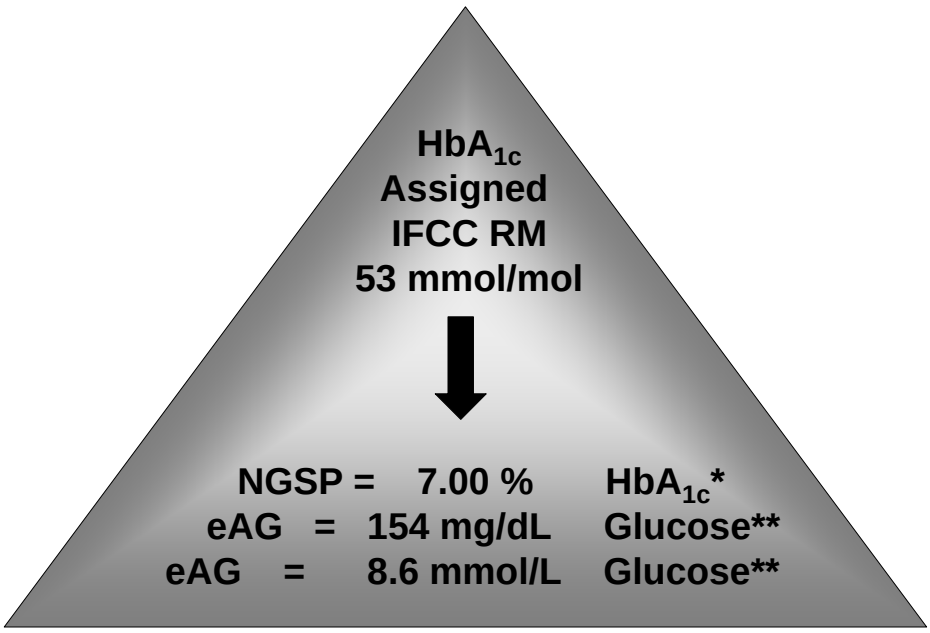
Consensus document

Consensus Statement on the Worldwide Standardization of the Hemoglobin A1C Measurement

The American Diabetes Association, European Association for the Study of Diabetes, International Federation of Clinical Chemistry and Laboratory Medicine, and the International Diabetes Federation

1. The HbA_{1c} results should be standardized worldwide, including the reference system and results reporting.
2. The IFCC reference system for HbA_{1c} represents the only valid anchor to implement standardization of the measurement.
3. The HbA_{1c} assay results are to be reported worldwide in IFCC unit (mmol/mol) *and* derived NGSP unit (%), using the IFCC-NGSP master equation.
4. If the ongoing "average plasma glucose study" fulfills its *a priori* specified criteria, an HbA_{1c}-derived average glucose (ADAG) value will also be reported as an interpretation of the HbA_{1c} result.
5. Glycemic goals appearing in clinical guidelines should be expressed in IFCC units, derived NGSP units, and as ADAG.

Diabetes Care 2007;30:2399



* According to Clin Chem 2004;50:166-174
** According to Presentation ADAG Study at EASD Meeting, Amsterdam 18 September 2007 (Provisional Results)

eAG: a favore

1. Pazienti e medici, utilizzando la misura dell'emoglobina glicata, possono riferirsi direttamente alla glicemia media
2. Non c'è confusione con i nuovi numeri
3. Data la correlazione lineare tre eAG ed HbA_{1c} si può subito trasformare l'HbA_{1c} in eAG
4. I clinici sono già abituati all'utilizzo di parametri calcolati (eGFR, eLDL-c)

eAG: contro

1. Lo studio ADAG non include bambini, donne in gravidanza, nefropatici, soggetti di origine asiatica
2. Le elaborazioni sono state effettuate unendo insieme soggetti non diabetici, paz. con diabete t1 e t2
3. Gli intervalli fiduciari della eAG sono molto ampi
4. La glicemia media stimata riduce il peso delle fluttuazioni glicemiche (ampiezza e frequenza)
5. Non è detto che i dati del singolo paziente siano identici a quelli della media della popolazione

Predicting mean glucose from HbA_{1c}

HbA_{1c} (%)	eAG (mg/dL)	int. fid. 95 %
5	97	(76 – 120)
6	126	(100 – 152)
7	154	(123 – 185)
8	183	(147 – 217)
9	212	(170 – 249)
10	240	(193 – 282)
11	269	(217 – 314)
12	298	(240 – 347)

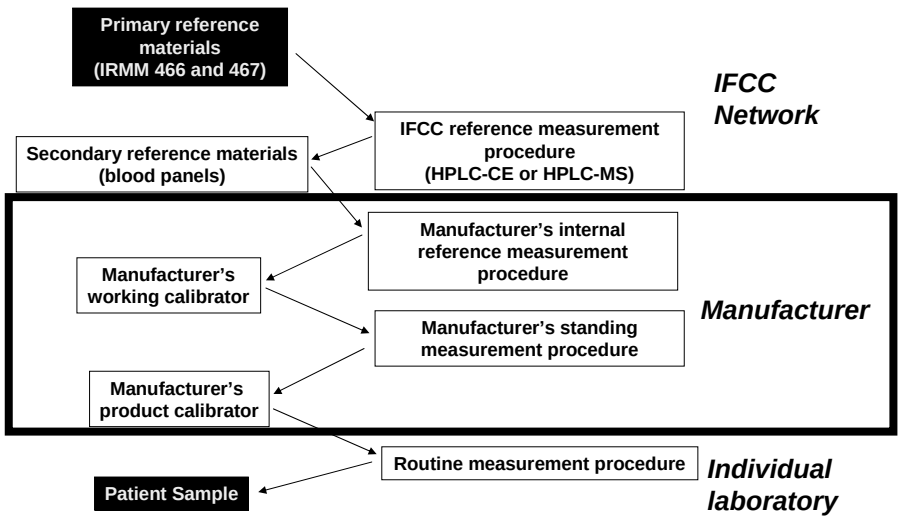
The Diabetes Research in Children Network (DirecNet) Study Group

'For any given HbA_{1c} level, mean sensor glucose levels differed by …. 50 mg/dL or more, making the conversion of HbA_{1c} levels into mean glucose equivalents as suggested by a recent ADA consensus statement tenuous at best.'

DirecNet Study Group. Diabetes Care 2008; 31:381-385

Standardizzazione IFCC dell'HbA_{1c}

- il punto di vista dei produttori di diagnostici-



Clin Chem Lab Med 2008;46(4):573–574 © 2008 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2008.090

Report

Implementation of standardization of HbA_{1c} measurement

Summary of the meeting with manufacturers held in Milan, Italy, December 12, 2007

IFCC officers:
Prof Mauro Panteghini, Chair of the IFCC Scientific Division (SD)
Dr Garry John, Chair of the IFCC SD WG on Standardization of HbA1c (WG-HbA_{1c})
Prof Andrea Mosca, Secretary of the IFCC SD WG-HbA_{1c}
Dr Cas Weykamp, Coordinator of the IFCC Network of Reference Laboratories for HbA_{1c}

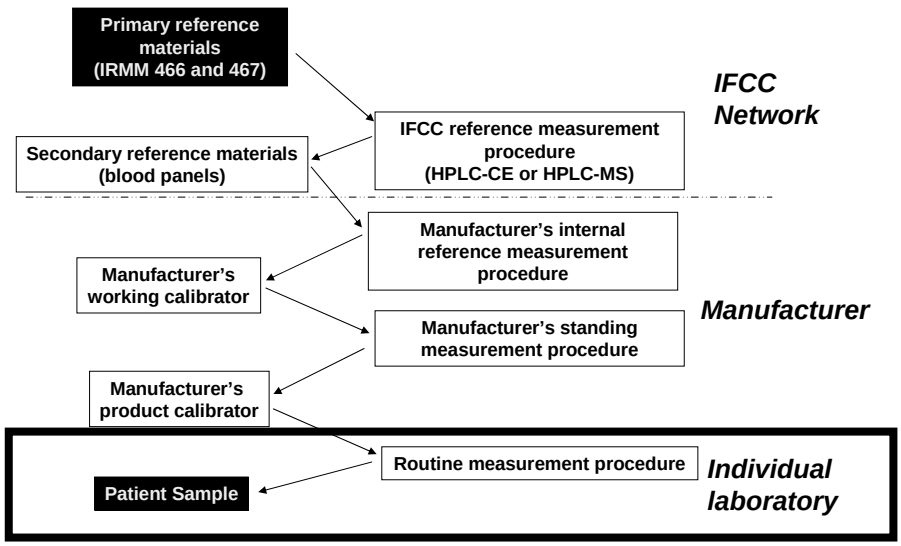
Representatives of manufacturers:
David Ambruster, Lieselotte Lennartz (Abbott); Beate Saeger, Takeshi Takagi (Arkray); Cathinca Vargmo, Kjersti Grimsrud (Axies-Shield and Vogt); Ben Irvin (Bayer); Elisabetta Della Dea (Beckman Coulter); Tamara Davis, Gianni Bertoli, Laura Madia (Bio-Rad Laboratories); Chistiane Wernz, Alexandra Lein (Dia Sys Diagnostic Systems); Nick Mayor (Genzyme); Francesco Caggiano (Menarini); Bernd Vögt (Roche Diagnostics); Geneviève Hennache (Sebia); Takuya Yotani (Sekisui Chemical Co.); Mary Lou Gantzer (Siemens); Nancy Van Bijlen (Tosoh Bioscience).

Main meeting outcomes

1. **Deadline for implementing traceability to the IFCC reference system is December 31, 2009.**
2. **After January 1, 2011 all new instruments will report both SI units (mmol/mol) and NGSP derived units (%).**
3. **The implementation of HbA_{1c} result in terms of eAG will not be an issue of the analytical systems.**
4. **EQA programmes will have to use commutable control materials with target values assigned using the IFCC reference measurement procedure, together with a clear definition of the clinically allowable total error.**
5. **The IFCC WG-HbA_{1c} is willing to review the proposed manufacturer's traceability chain.**

Standardizzazione IFCC dell'HbA_{1c}

- i prossimi step-



Global standardization of HbA_{1c} - results reporting -

Country	IFCC numbers	NGSP numbers	eAG	other	timeline *(starting from)*
USA	no	yes	yes	nd	2008 August
Sweden	yes	yes	yes	Swedish numbers	(?)
Japan	yes	no	no	JDS numbers	(?)
UK	yes	yes	no		2009 June 1st (dual reporting up to June 1st 2011)
Germany	yes*	yes	(?)		(?)
IFCC Network	yes	no	no		2008 August

* Only for EQAS organizers and manufacturers

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Diabetes UK

NHS National Diabetes Support Team

The Association for Clinical Biochemistry

HbA_{1c} Standardisation
For Clinical Health Care Professionals

Diabetes UK

NHS National Diabetes Support Team

The Association for Clinical Biochemistry

HbA_{1c} Standardisation
For Laboratory Professionals

Diabetes UK

NHS Diabetes

The Association for Clinical Biochemistry

A change in reporting your HbA_{1c} results.
Information for People with Diabetes

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seconda bozza (versione 14 marzo 2009)
confidenziale

Raccomandazioni per l'implementazione della standardizzazione internazionale dell'emoglobina glicata in Italia

Documento prodotto dal Gruppo di Lavoro GLAD (Gruppo di Lavoro A1c Delegati)

Componenti del Gruppo di Lavoro

Prof. Andrea Mosca (delegato SIBioC, Università degli Studi di Milano) [coordinatore]
Sig.ra Maria Teresa Branca (delegato OSDI,...)
Dott.ssa Mariarosa Carta (delegato SIMeL, Az. Osp. di Vicenza)
Dott.ssa Maria Ludovica Genna (delegato AIPaC, Az. Osp. RN Cardarelli, Napoli)
Dott. Carlo B. Giorda (delegato AMD, ...)
Sig.ra Rosangela Ghidelli (delegato OSDI, Az. Osp. S. Anna, Como)
Sig.ra Germana Ghislandi (delegato FAND,...)
Prof. Dario Iafusco (delegato SIEDP/ISPED,...)
Prof.ssa Annunziata Lapolla (delegato SID, Università degli Studi di Padova)
Dott.ssa Vera Buondonno Lombardi (delgato FAND,...)
Dott. Carlo Augusto Lovagnini Scher (delegato AMD,...)
Dott. Maurizio Marra (delegato SIMeL, INRCA IRCCS, Ancona)
Dott. Gerardo Medea (delegato SIMG, Az. Osp. di Brescia)
Dott. Franco Meschi (delegato SIEDP/ISPED, IRCCS H. S. Raffaele, Milano)
Dott. Andrea Pizzini (delegato FIMMG, ASL Torino 2, Torino)
Dott.ssa Antonella Radice (delegato SIMeL, Az. Osp. S. Carlo, Milano)
Dott. Francesco Rossi (delegato AIPaC, Az. Osp. RN Cardarelli, Napoli)
Dott. Raffaele Scalpone (delegato AID,..)
Dott. Gianni Tofini (delegato AID,...)
Prof.ssa Mariella Trovati (delegato SID, Università degli Studi di Torino)
Dott.ssa Martina Zaninotto (delegato SIBioC, Az. Osp. di Padova)

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Conclusioni (HbA_{1c})

- la standardizzazione IFCC ha sviluppato un sistema di riferimento adeguato e robusto per un analita di classe B (eterogeneo)
- Il sistema di riferimento è già implementato per la calibrazione dei produttori di diagnostici, deve esserlo per i professionisti di laboratorio
- la standardizzazione è un processo collaborativo lungo che coinvolge diversi livelli di responsabilità e di azioni concertate di tipo trasversale