

IFCC Standardization of HbA1c

REFERENCES

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- **Comparability of Results**
- **Traceability**

Information on the IFCC Standardization of HbA1c

The Diabetes Control and Complication Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that the risk for complications in patients with diabetes is directly related to glycemic control, as measured by glycohemoglobin (GHB).^{1,2,3}

Method accuracy and precision, comparability of results and traceability to the highest order are essential. Although HbA1c is used as a diagnostic marker throughout the world, results still vary between laboratories as routine methods based on different analytical principles may give different results. Therefore, the need for harmonization is well recognized.

Three national standardization programs already exist, NGSP in the USA and most European countries, JDS in Japan, and Mono S in Sweden. They are all based on designated comparison methods.

To provide comparable results across routine HbA1c methods, a uniform standardization of all HbA1c routine assays is needed, anchored on a metrologically sound international reference measurement system. The IFCC Working Group on HbA1c has developed such a reference system.

The “Main Characteristics of the NGSP and IFCC Programs” chart describes the NGSP and IFCC programs in detail.

Main Characteristics of the NGSP and IFCC Programs

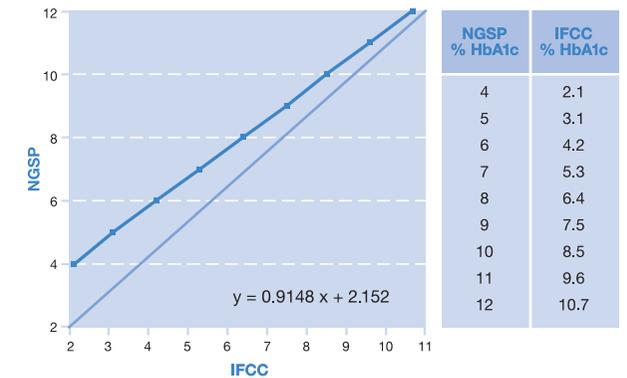
	NGSP		IFCC
Formation	1996 – The NGSP (previously known as the National Glycohemoglobin Standardization Program) is formed.	Formation	1995 – The International Federation of Clinical Chemistry (IFCC) formed a Working Group (WG) on HbA1c Standardization.
Mission	Standardize glycohemoglobin test results so that clinical laboratory results are comparable to those reported in the Diabetes Control and Complications Trial (DCCT) where relationships to mean blood glucose and risk for vascular complications have been established.	Mission	Development of a reference system for international standardization of all routine assays measuring HbA1c in human blood. The reference measurement system consists of a reference method and reference materials allowing traceability to higher metrological order. ^{6,7}
Principle	HbA1c is defined and measured as a peak of the chromatogram of the chosen designated comparison method. The anchor is ion-exchange HPLC using Bio-Rex® 70 resin according to the HPLC method used in the DCCT.	Principle	HbA1c is defined by its molecular structure and specifically measured with a reference method. This includes isolation and hemolysis of erythrocytes, enzymatic cleavage of the hemoglobin, separation, and analysis by HPLC-ESI/MS or HPLC-CE. ^{6,7,8}
Calibration	Calibration for standardization was initially based upon the set-point used in the DCCT using frozen whole blood calibrators.	Calibration	Primary reference materials of pure HbA1c and HbA ₀ were developed and are used for preparing calibrators.
Network	NGSP has established a network consisting of a central primary reference laboratory, back up primary reference laboratories, and secondary reference laboratories (SRLs) throughout USA and Europe. SRL methods include ion-exchange HPLC, affinity HPLC, capillary electrophoresis and immunoassay. All of these laboratories must perform precision testing according to NCCLS EP5-A guidelines and are monitored on a monthly basis. ^{4,5}	Network	The IFCC has established a network designated to maintain the IFCC reference system and to transfer the system to manufacturers, EQAS and other interested parties. The network consists of a minimum of six and a maximum of 15 approved reference laboratories with representative geographic distribution. The laboratory's performance is monitored on a regular basis to prove their ability to operate the reference method according to quality criteria.
Services	Manufacturers and laboratories can participate in a certification process consisting of the assessment of both, precision and bias versus the NGSP to establish traceability to the DCCT. Over 97% of laboratories worldwide now meet acceptable standards through this program.	Services	Provides secondary reference materials to manufacturers for calibration allowing higher order traceability due to increased specificity. The IFCC network offers control materials with assigned values to manufacturers. Manufacturers can participate in an optional monitoring program to ensure traceability according to the IVD Directive. ^{9,10}

NOTE: DCCT Bio-Rex® 70 HPLC method and IFCC HPLC-ESI/MS or HPLC-CE methods are not clinical applications.

Relationship

HbA1c results generated using the IFCC reference method are significantly different than the results obtained using the NGSP method. IFCC results are lower throughout the range of values compared to NGSP results due to increased specificity.

The relationship between HbA1c results from the NGSP network and the IFCC network has been evaluated and a master equation has been developed:



The Master Equation

$$(NGSP A1C) = 0.9148 (IFCC A1C) + 2.152$$

$$(IFCC A1C) = 1.093 (NGSP A1C) - 2.350$$

Regulatory Requirements

The new European IVD (in-vitro diagnostic) Directive 98/79/EC requires: “The traceability of values assigned to calibrators and/or control materials must be assured through available reference measurement procedures and/or available reference materials of a higher order.”

All manufacturers of glycated hemoglobin diagnostics must comply with the IVD Directive in order to supply HbA1c tests to the European market.

Traceability

NGSP

NGSP glycohemoglobin test results are standardized to the Diabetes Control and Complications Trial (DCCT) by the NGSP network, thus traceable to clinical outcomes. DCCT demonstrated the importance of glycemic control. DCCT/NGSP values are required for NGSP certification.

IFCC

The IFCC reference method allows traceability to the highest order reference. The IFCC Reference System for HbA1c was accepted by the national member societies of the IFCC in 2002. It allows a manufacturer of an HbA1c assay to trace the value assignment of an HbA1c calibrator to an accepted reference method and material in accordance with the IVD Directive and the upcoming Standard on Traceability (ISO 17511).

Bio-Rad's Approach

Bio-Rad's HbA1c methods are NGSP certified and IFCC standardized. Bio-Rad offers NGSP HbA1c calibrator values. Bio-Rad's HbA1c calibrators are traceable to the IFCC and DCCT reference systems by the following method:

The approved IFCC reference method is used to assign IFCC values to the secondary reference materials. These secondary materials are used to value assign product calibrators and determine product calibration parameters through use of the IFCC/NGSP master equation.

Now that laboratory standardization has essentially been achieved, diabetology groups will determine if and how IFCC values will be adopted clinically.

NOTE: For Bio-Rad product-specific calibration information, please see your instructions for use.

