

The HbA1c Network

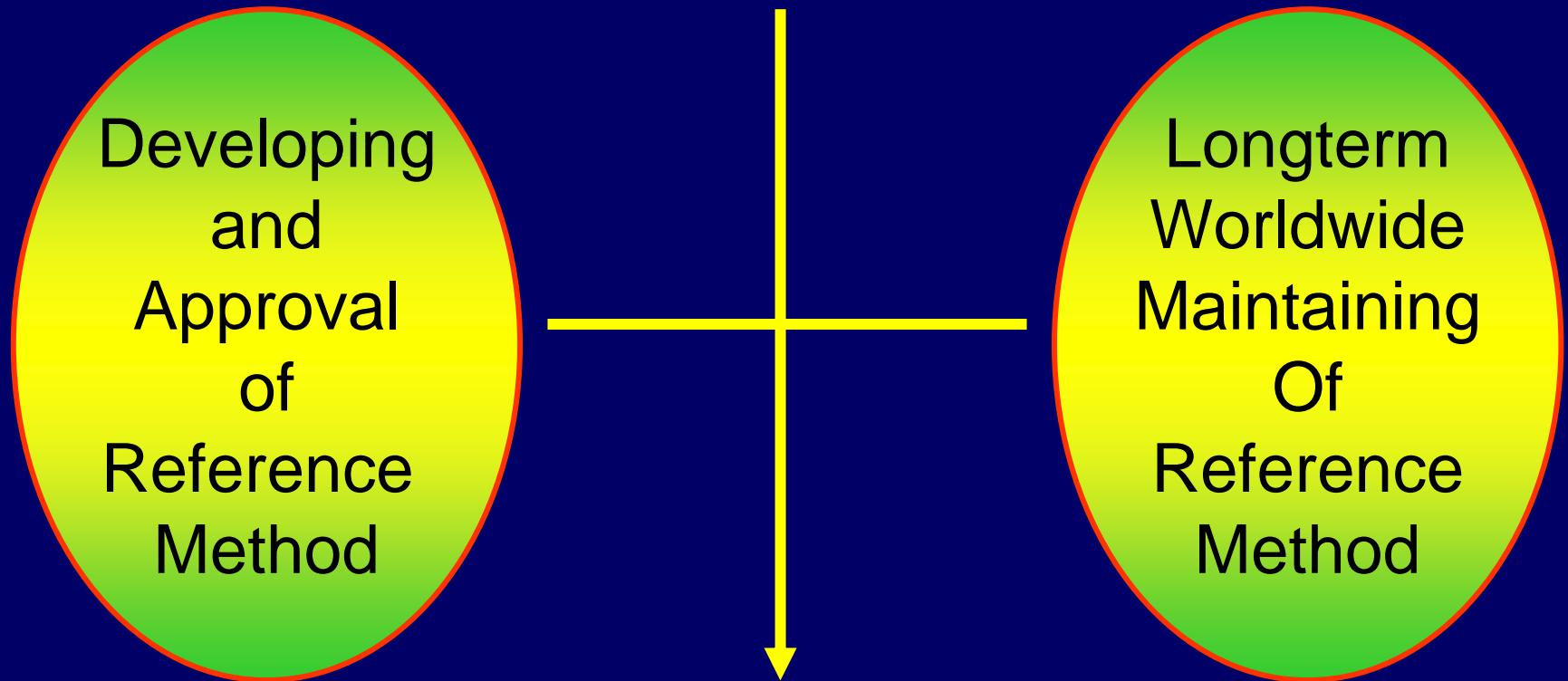
Structure, Performance and Rules

*Cas Weykamp, Network Coordinator
Queen Beatrix Hospital, Winterswijk, The Netherlands
Scientific Meeting CIRME, Milan, 6 November 2007*

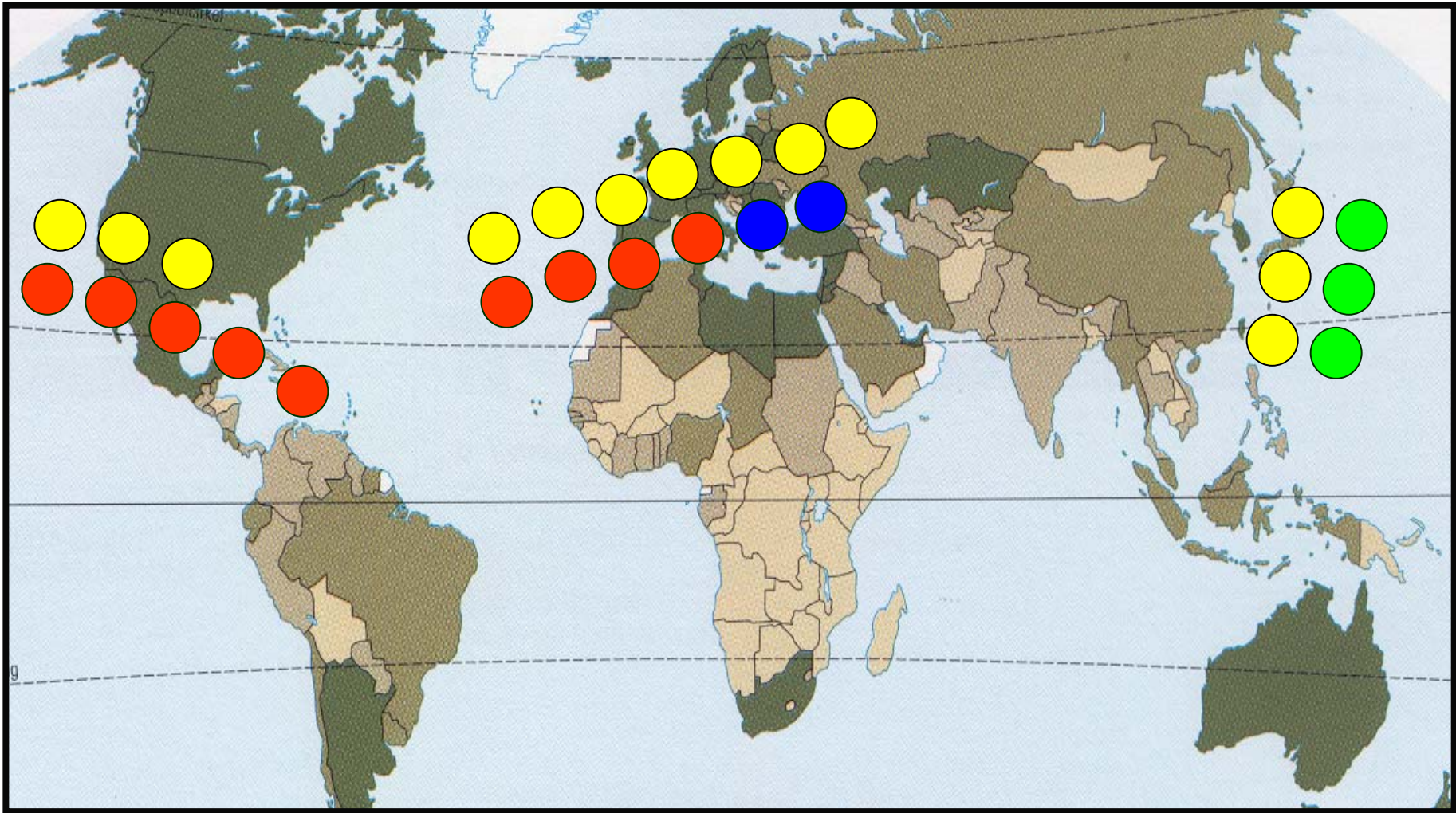


M·AGRIPPA·L·F·COS·TERTIVM·FECIT

Working Group Standardization HbA1c



Network



 **Network Labs**

DCMs



NGSP, USA (DCCT)



JDS/JSCC, Japan



Mono-S, Sweden

Traceability Chain

Definition of the Analyte

Primary Calibrator

Primary Reference MP

Secondary Calibrator

Secondary Refer. MP

Manufacturer's Working Calibrator

Manufacturer's Internal MP

Manufacturer's Product Calibrator

Manufacturer's Standing MP

Patient Sample

Routine MP in Lab

Network

Manufacturers

Labs

Interpretation Patient Result

Active Facilitation

Working Group HbA1c

Network

Continuity

Calibrators

Controls

SOP

Maintain Skills

Logistics System

Administration

Quality

Approval Network Labs

Approval Candidates

Approval Cal/Controls

Connections

DCM's

Manufacturers

EQAS Organisers

Working Group HbA1c

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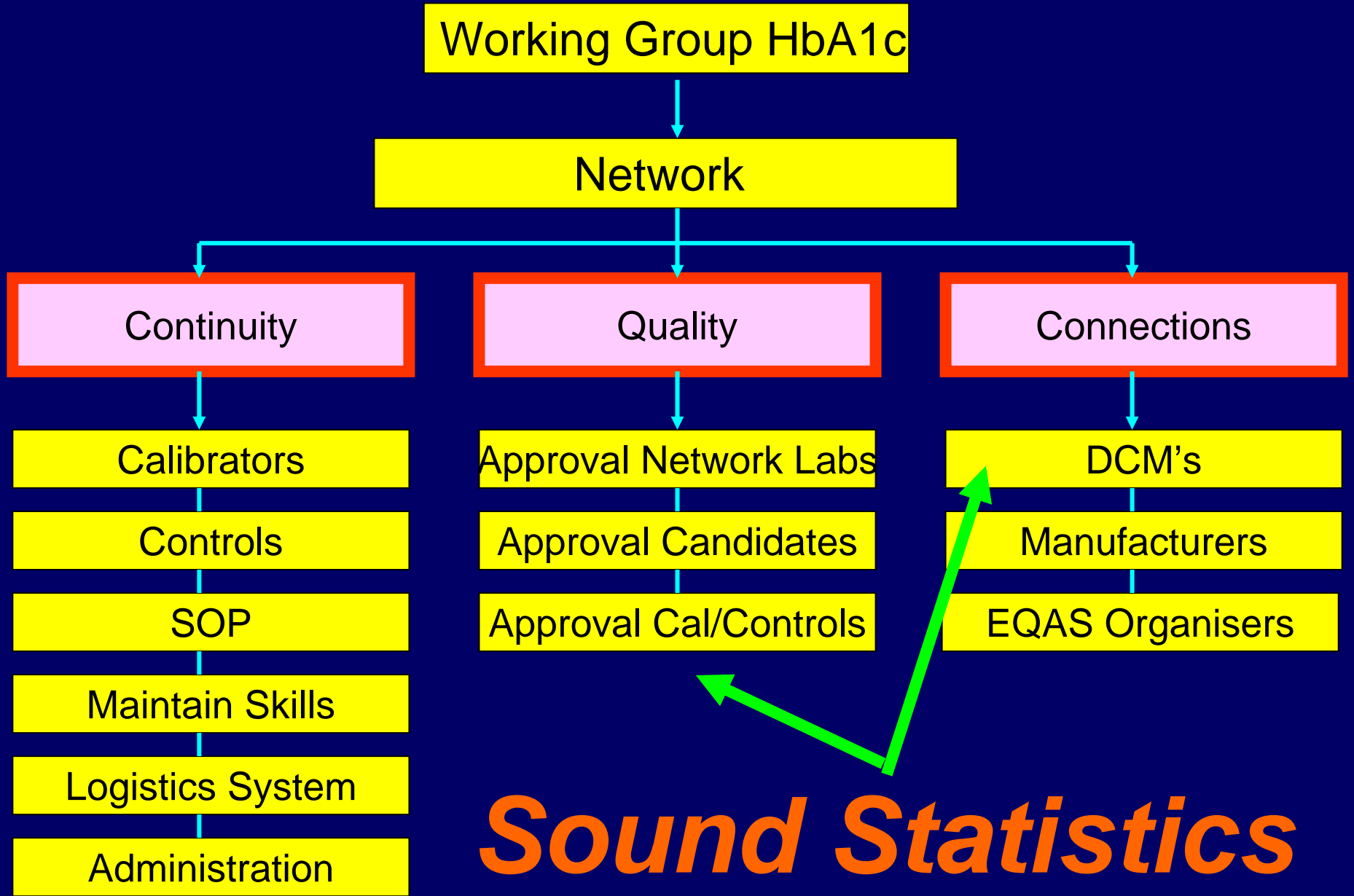
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Sound Statistics



Questions on Statistics

1. Value Assignment with a Network
How? Expanded Uncertainty?
2. Basis for Approval Network Labs?
3. Basis Approval of Calibrators/Controls?
4. Master Equation (Relation DCM's)
Statistical Basis?

Questions → Statistical Tools

Software Model

Papers

1. Value Assignment and Uncertainty

Accred Qual Assur 2006;11:319-28

2. Statistical Rules for Networks

J Test Eval 2006;34:128-34

3. Relations between Networks

Submitted

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“Intercomparison Study”

Intercomparison Study

A set with different sample types is sent to Network Laboratories And DCM Laboratories

Assay results are processed according to the Statistical Model of the Network

And evaluated

Organisations

How do they warrant Continuity?

Life Cycle of a President

<u>Year 1</u>	<u>Year 2</u>	<u>Year 3</u>	<u>Year 4</u>
President Elect	President	Immediate Past President	Eminence Grise

Calibrators

How does Network warrant Continuity?

Life Cycle of a Batch Calibrators

(Calibrators are prepared from pure HbA1c and pure HbA0)

<u>Year 1</u>	<u>Year 2</u>	<u>Year 3</u>	<u>Year 4</u>
“New Calibrator”	“Calibrator”	“Old Calibrator”	“Spare”
Analysed As Sample	Calibrator Set	Analysed As Sample	
Batch Approved?	To calibrate Reference Method	Stability?	

Controls

How does Network warrant Continuity?

Life Cycle of Controls

(Controls are prepared from Whole Blood)

<u>Year 1</u>	<u>Year 2</u>	<u>Year 3</u>	<u>Year 4</u>
“Unknown Sample”	“Control”	“Control”	“Spare”
Analysed As Sample	Analysed As Sample	Analysed As Sample	
Laboratory Approved?	Stability? -Sample -Network	Stability? -Sample -Network	

Samples Intercomparison Study

Calibrators

- * Calibrator set (calibrate RM)
- * New Calibrators (approve new batch)
- * Old Calibrators (check stability)

Patient Samples

- * Unknown HbA1c (Approval Labs)
- * Known HbA1c (Controls)

Working Group HbA1c

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Calibrators 2001 – 2006

Paper with data submitted

****Number of Batches Manufactured***

10 Batches (6 HbA1c levels each)

****New Calibrators***

One occasion difference between calculated (from pure HbA1c/HbA0) and measured HbA1c exceeded criterion; batch discarded

****Old Calibrators***

Difference between calculated and measured HbA1c never exceeded criteria

***Conclusion: Calibrators can be manufactured
Reproducibly and are stable on storage***

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Controls 2001 – 2006

Paper with data submitted

*** *Number of Batches manufactured***

12 Batches ((low/High HbA1c each batch))

*** *Difference in Outcome***

Difference in measured HbA1c after 1 and 2 years storage in comparison to initial value never exceeded criterion

*** *Conclusion***

Double Conclusion: Controls are stable on storage and the Reference System is stable

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***Is updated every year in
Collaboration with and guided
By remarks of the Network Labs***

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***All Exercises are done twice
A year: this maintains skills
And proves if logistics and
Administration works well***

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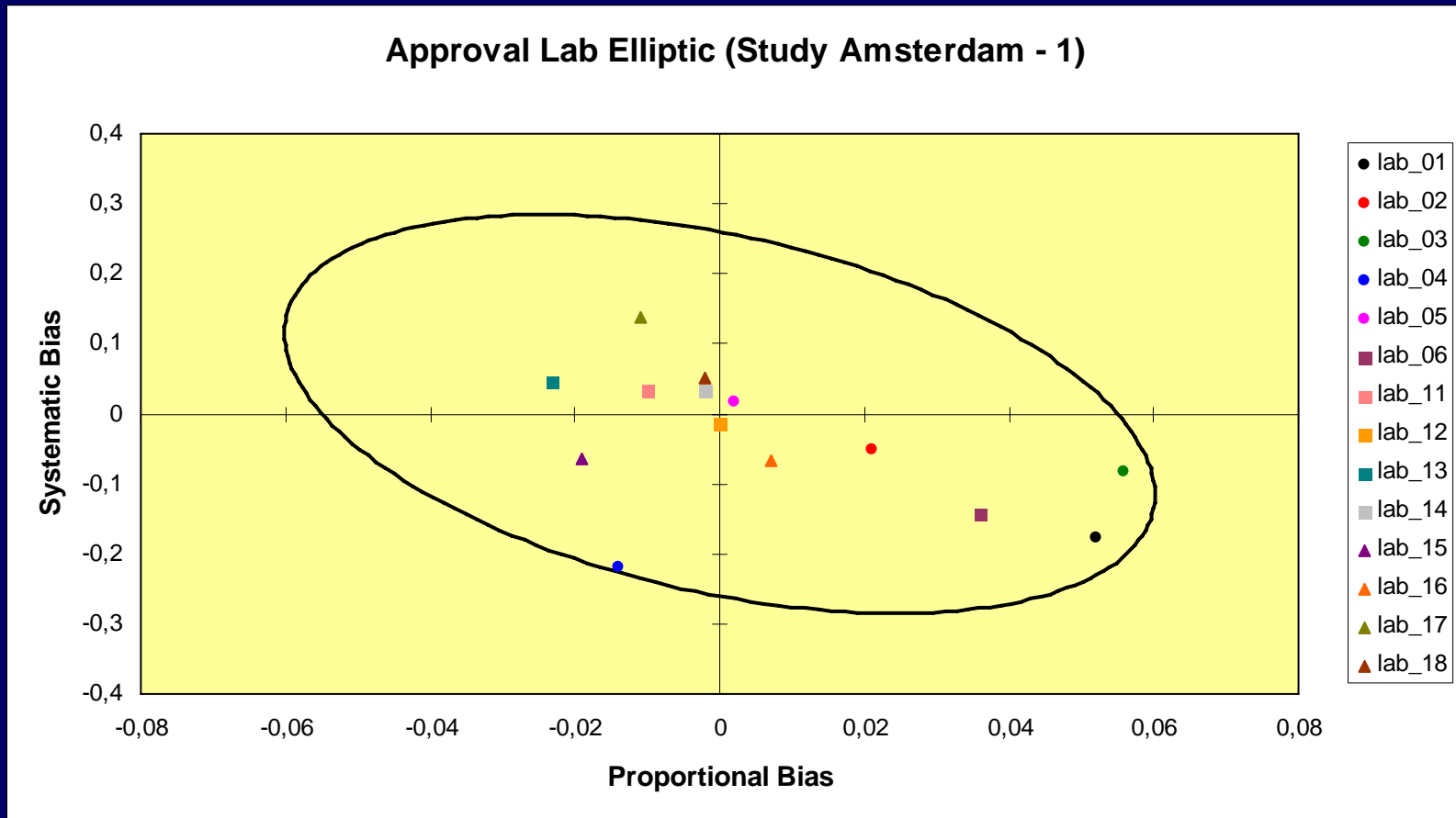
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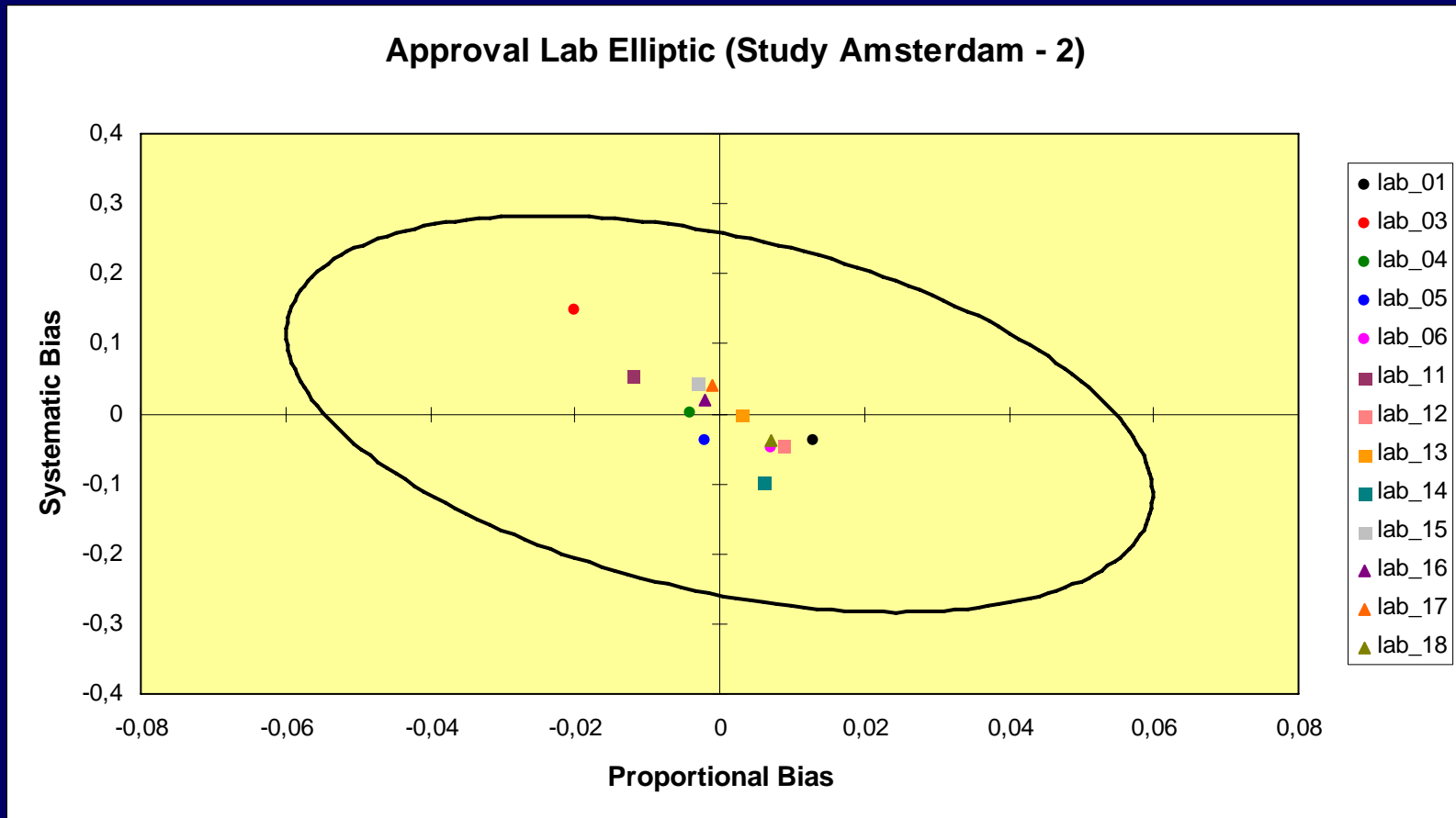
EQAS Organisers

Amsterdam-1 Study



Narrow Escape for Three Network Laboratories!

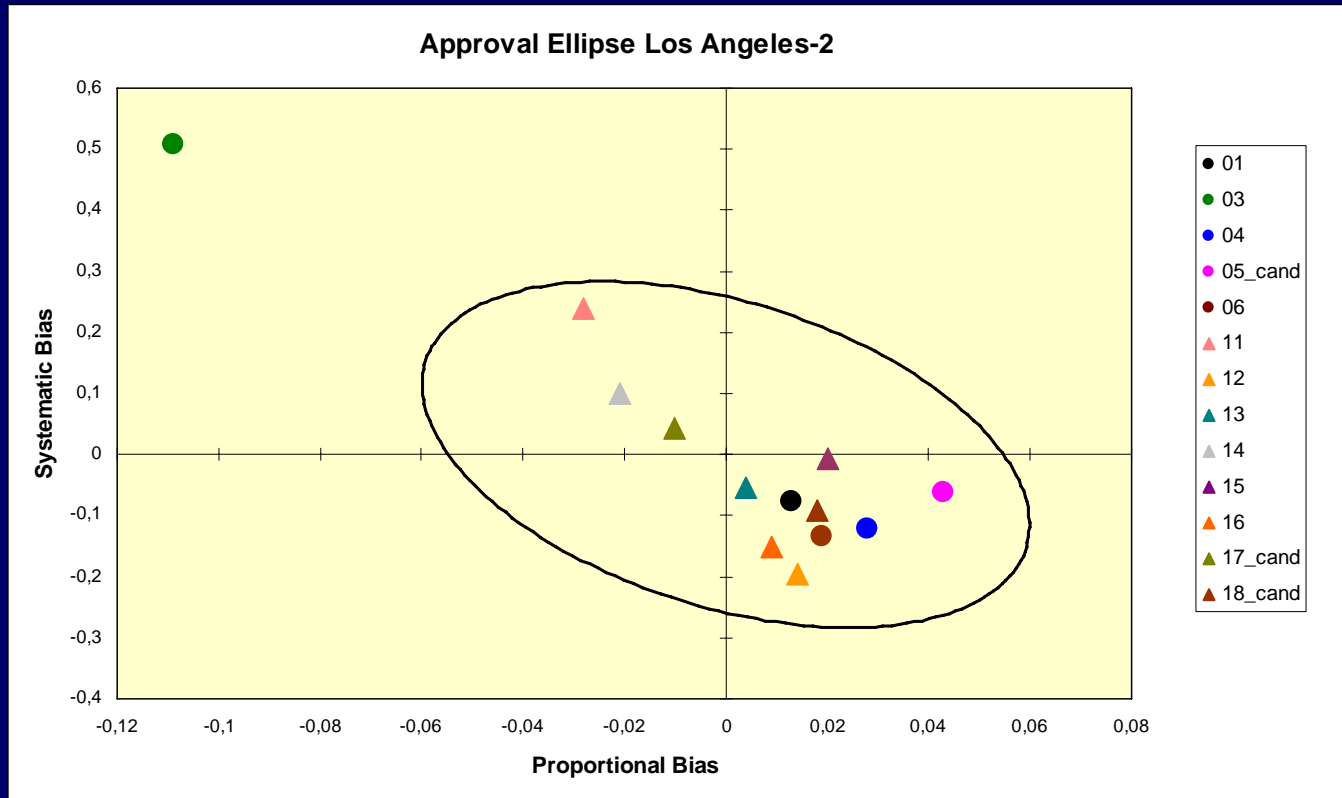
Amsterdam 2 Study



Excellent Performance of all Network Labs

Los Angeles 2 Study

Paper with these data submitted



One laboratory fails

Network Rules

- A Network Laboratory loses the status of approved laboratory when it fails (or does not submit results) in two consecutive Intercomparison Studies
- * A candidate network laboratory gets the status of approved network laboratory when it passes two consecutive intercomparison studies

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Consensus Statement HbA1c

3. “HbA1c results are to be reported Worldwide in IFCC units (mmol/mol) and Derived NGSP units (%), using the IFCC-NGSP Master Equation”

Master Equation is Important:

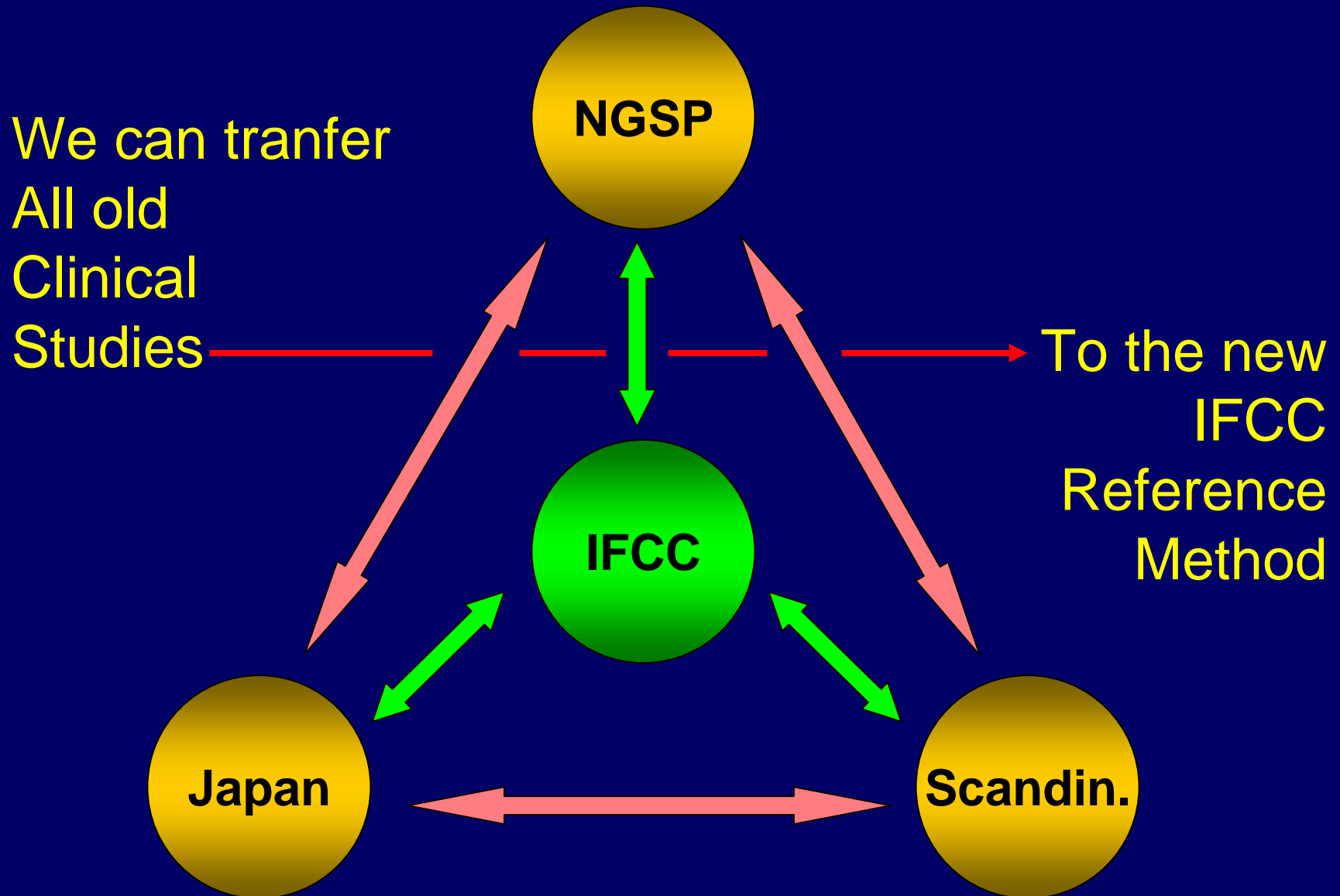
- To report according to Consensus Statement
- To relate old studies (DCCT) to new units vice versa

**Clin
Chem
2004; 50:
166-74**

**IFCC Reference System for Measurement of
Hemoglobin A_{1c} in Human Blood and the
National Standardization Schemes in the
United States, Japan, and Sweden:
A Method-Comparison Study**

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IAN GOODALL,⁶ TADAO HOSHINO,⁷ W. GARRY JOHN,⁸ UWE KOBOLD,¹ RANDIE LITTLE,⁹
ANDREA MOSCA,¹⁰ PIERLUIGI MAURI,¹¹ RITA PARONI,¹² FRANSISCUS SUSANTO,¹³
IZUMU TAKEI,¹⁴ LINDA THIENPONT,¹⁵ MASAO UMEMOTO,¹⁶ and HSIAO-MEI WIEDMEYER,⁹ on
behalf of the IFCC WORKING GROUP ON HBA_{1c} STANDARDIZATION

Master Equations



Monitoring Master Equation

Samples Intercomparison Study
are analysed by both

- The IFCC Network laboratories
- The DCM network laboratories
(NGSP network, JDS/JSCC, Mono-S

This allows to monitor the consistency
Of the Master Equation

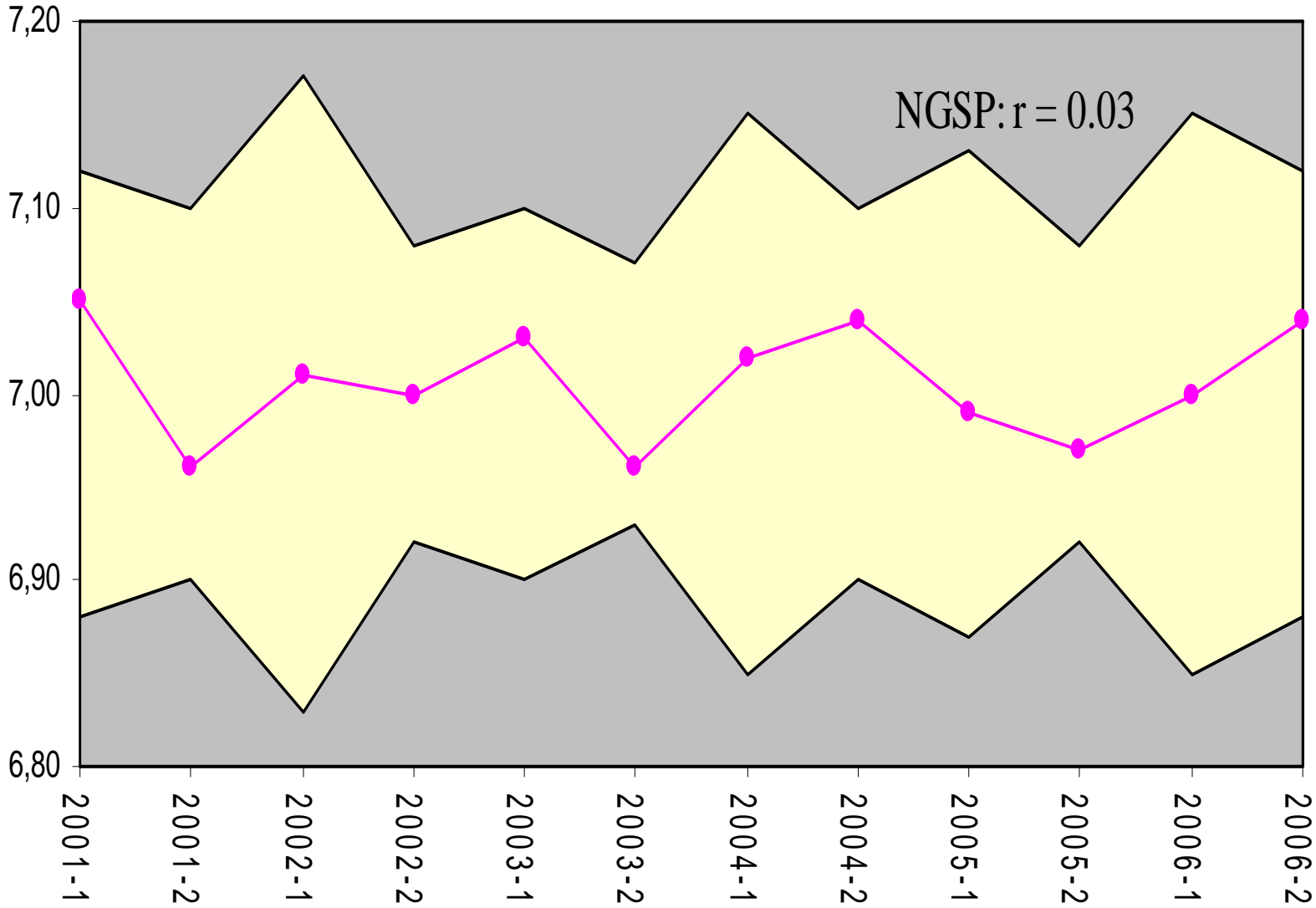
Data of 12 independant Studies

(paper with these data submitted)

$$Y = ax + b$$

Study	NGSP	JDS	Mono-S
Marrakech	$y=0.926x+2.14$	$y=0.934x+1.76$	$y=1.008x+0.90$
Chicago	$y=0.926x+2.05$	$y=0.926x+1.67$	$y=0.941x+1.09$
Kyoto-1	$y=0.906x+2.21$	$y=0.920x+1.78$	$y=1.002x+0.78$
Kyoto-2	$y=0.912x+2.17$	$y=0.943x+1.68$	$y=0.968x+1.15$
Barcelona-1	$y=0.905x+2.23$	$y=0.912x+1.78$	$y=0.964x+0.95$
Barcelona-2	$y=0.897x+2.21$	$y=0.916x+1.70$	$y=0.963x+0.92$
LA-1	$y=0.901x+2.24$	$y=0.880x+1.95$	$y=0.949x+1.10$
LA-2	$y=0.907x+2.23$	$y=0.911x+1.73$	$y=0.997x+0.91$
Orlando-1	$y=0.913x+2.15$	$y=0.892x+1.84$	$y=0.961x+1.01$
Orlando-2	$y=0.924X+2.07$	$y=0.928X+1.63$	$y=0.998X+0.81$
ME	$y=0.915+2.15$	$y=0.927x+1.73$	$y=0.989X+0.88$

Shewhart Chart NGSP outcome in %HbA1c at IFCC-RM = 53 mmol/mol

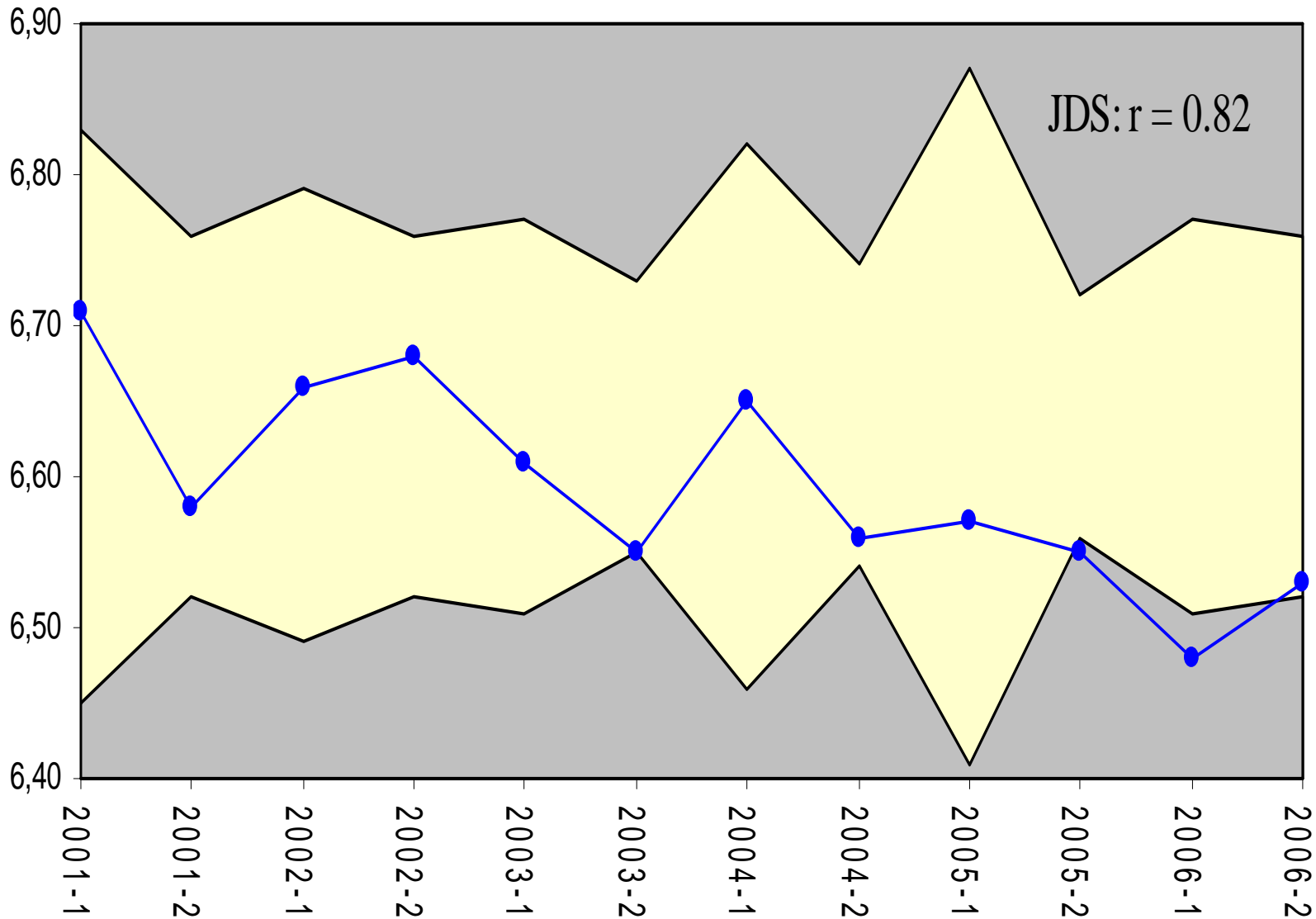


X-axis: The subsequent studies in 6 years

Y-axis: NGSP percentage HbA1c

Grey Zone: Area with significant difference from published ME

Shewhart Chart JDS/JSCC outcome in %HbA1c at IFCC-RM = 53 mmol/mol

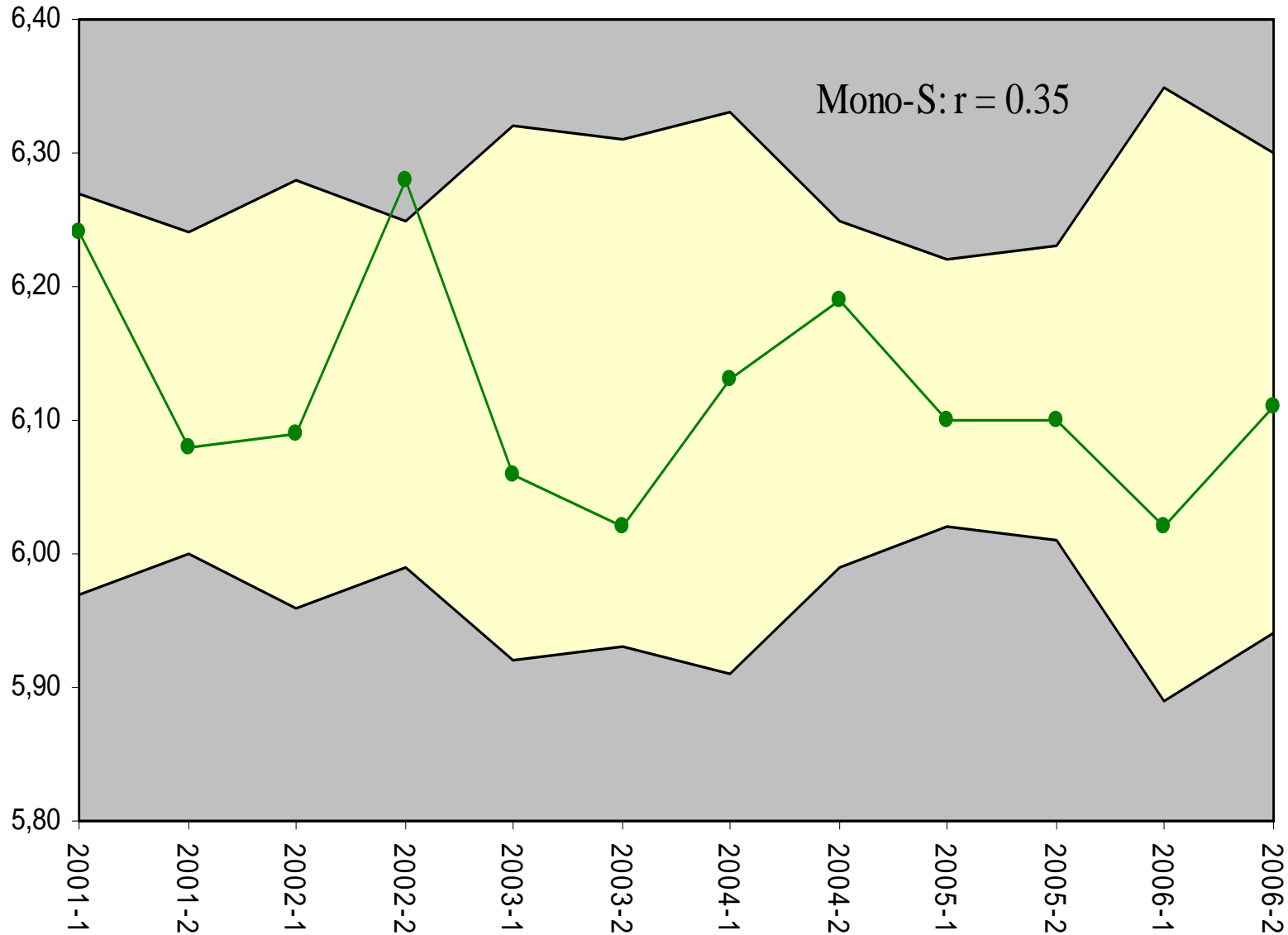


X-axis: The subsequent studies in 6 years

Y-axis: JDS/JSCC percentage HbA1c

Grey Zone: Area with significant difference from published ME

Shewhart Chart Mono S outcome in %HbA1c at IFCC-RM = 53 mmol/mol



X-axis: The subsequent studies in 6 years

Y-axis: JDS/JSCC percentage HbA1c

Grey Zone: Area with significant difference from published ME

Working Group HbA1c

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Continuity

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**The periodical
Intercomparison Study
Covers All Relevant Issues
To warrant Continuity of the
Reference Method for HbA1c**

Advantages Network

- * **Backbone to get a RM started**
- * **Continuity**
- * **Quality**

***In the Development of a Reference System
.....a network is the Backbone of Research:***

- Stimulus of a group***
- Finding Resources (Sponsors, EU)***
- Coordination Executive Work***

***..... And thus the best guarantee of Success
In creating a such a reference system***

Quality

- Prevention of Blunders

(if a network assigns a value, blunders are excluded)

- Lowest Uncertainty in top Traceability Chain

(uncertainty decreases when n increases)

- Systematic (re) approval of labs

(Intercomparison Studies with sound statistical rules)

- Central batchmanagement calibrators

(Manufacture and Validity check)

Continuity

For global, reliable, long-lasting standardisation continuity of the reference system is essential

A Network meets this requirement of Continuity

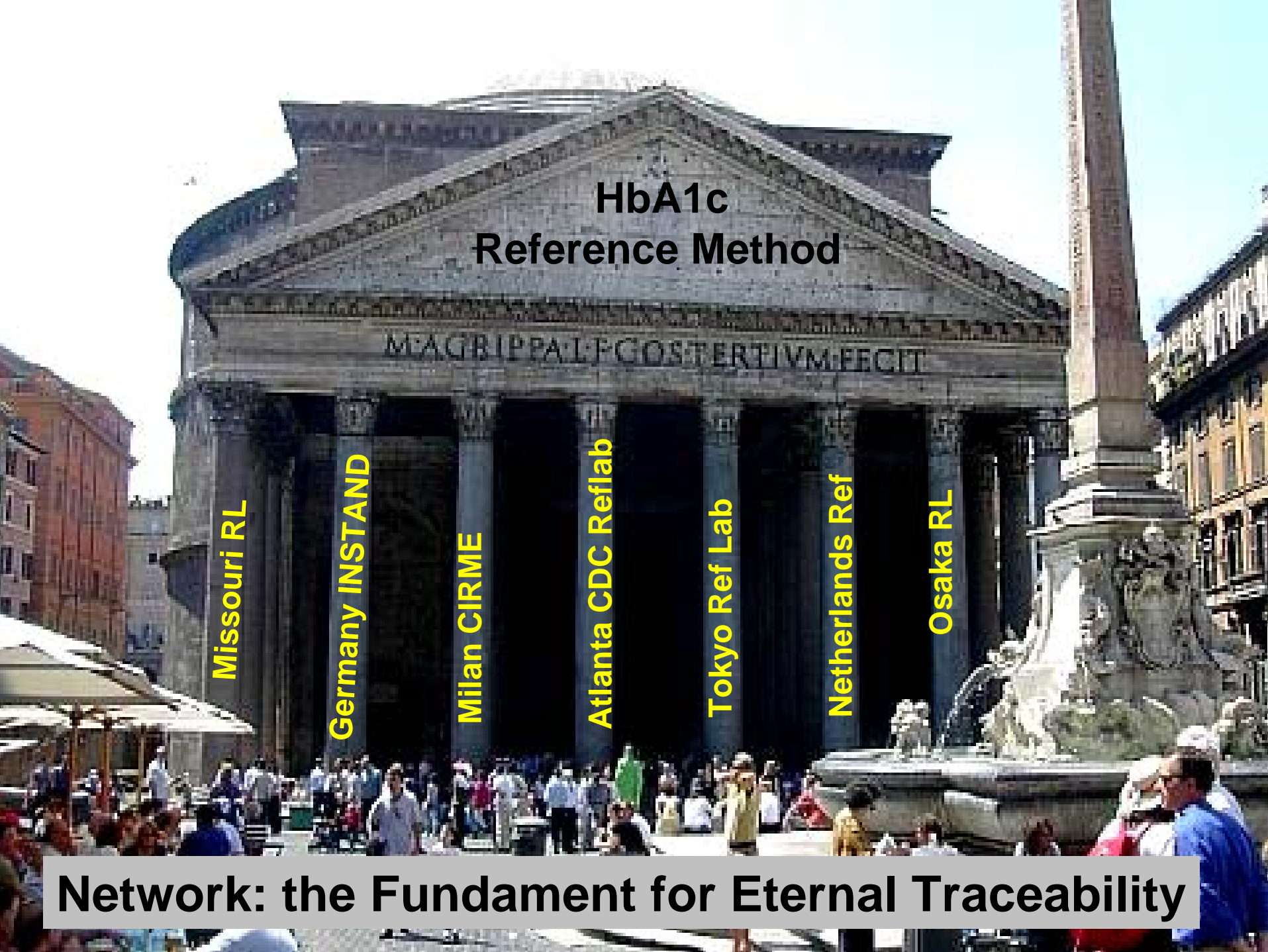
- No problem when some labs stop in a network of 15 labs*
- Guaranteed availability of calibrators from central stock*
- Updated SOP*
- Maintenance of specific skills*
- Logistic and Administrative System*



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**HbA1c
Reference Method**



The image shows the Pantheon in Rome, Italy, with a large crowd of people in the foreground. The Pantheon's facade features a pediment with the inscription "M·AGRIPPA·L·F·COS·TERTIVM·FECIT". Several vertical labels are overlaid on the columns, listing reference methods for HbA1c. The labels are: Missouri RL, Germany INSTAND, Milan CIRME, Atlanta CDC Reflab, Tokyo Ref Lab, Netherlands Ref, and Osaka RL. A large obelisk is visible on the right side of the Pantheon.

HbA1c Reference Method

Missouri RL

Germany INSTAND

Milan CIRME

Atlanta CDC Reflab

Tokyo Ref Lab

Netherlands Ref

Osaka RL

Network: the Fundament for Eternal Traceability

Thanks to the Network of HbA1c Reference Laboratories:

- Germany Prof. Hans Reinauer and Dr. Patricia Kaiser, INSTAND, Düsseldorf
Dr. Uwe Kobold, Roche, Penzberg
Dr. Franziscus Susanto, DDZ, Düsseldorf
- Italy Prof. Andrea Mosca, Dr. Renata Paleari and
Prof. Donatella Caruso, CIRME, Milan
- Japan Dr. Tadao Hoshino, IBM, Kanagawa
Dr. Masao Umemoto, SRC, Kawasaki
Prof. Izumi Takei, SKMU, Tokyo, Japan
- The Netherlands Dr. Robbert Slingerland, IKW, Zwolle, The Netherlands
Dr. Cas Weykamp, SKB, Winterswijk
- USA Dr. Hubert Vesper, CDC, Atlanta, GA
Dr. Cindy Deng and Dr. Jim Albarella, Siemens MS, Norwood
Dr. Randie Little, UMSM, Missouri