

State of the Art of HbA1c Measurement

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www.ngsp.org



State of the Art of HbA1c Measurement

- Background
 - ❖ Need for standardization
 - ❖ NGSP
- The Winding Road to Better HbA1c
 - ❖ Standardize to Report as HbA1c
 - ❖ IFCC vs. NGSP
 - ❖ Estimated Average Glucose (eAG)
 - ❖ HbA1c for Diabetes Diagnosis
- Current status of HbA1c measurement
- Is HbA1c Measurement good enough?
- Future Plans for Improvement

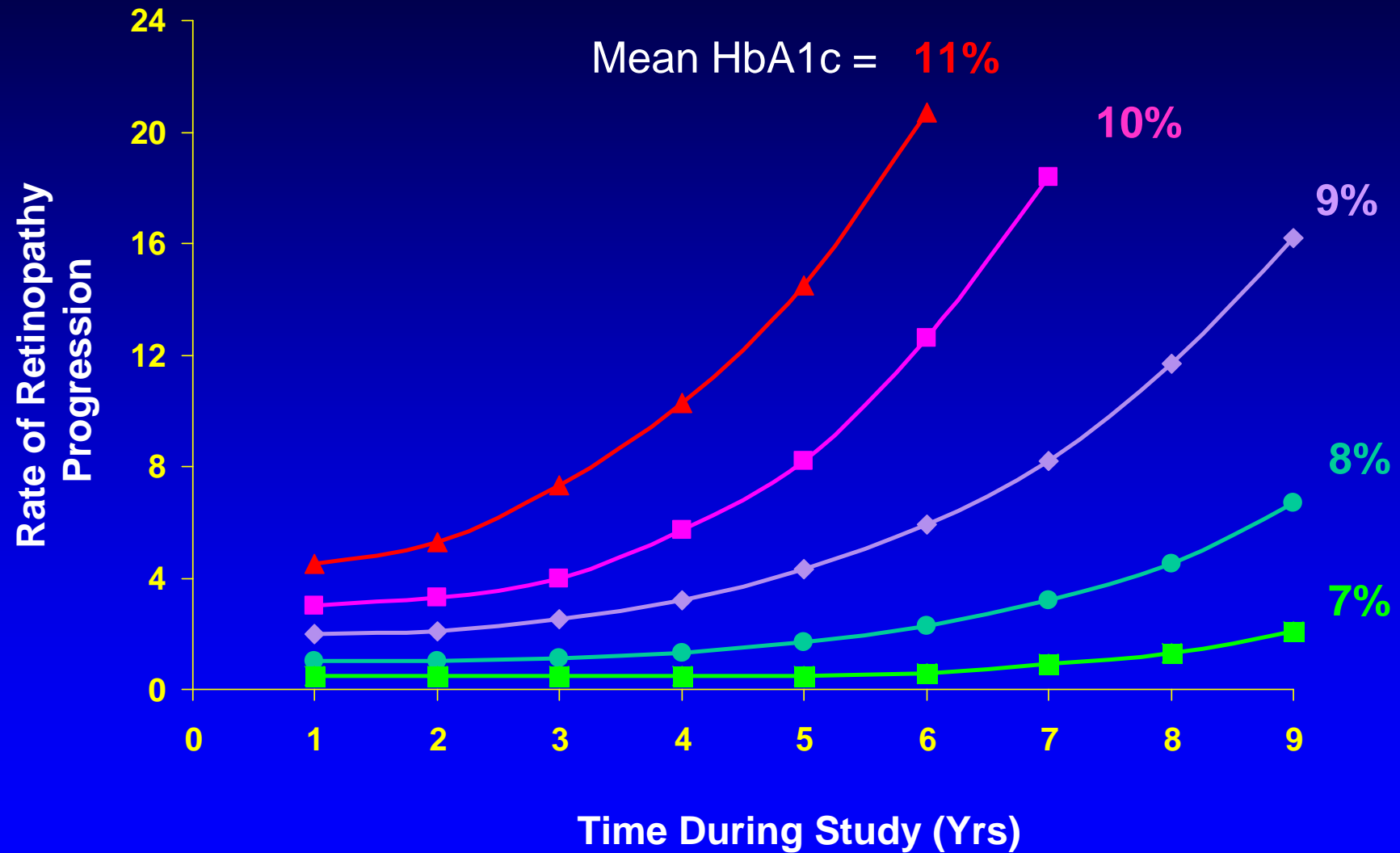
Background: Need for Standardization

- **1993:** Results from the Diabetes Control and Complications Trial (DCCT) confirmed the relationship between HbA1c and diabetes complications;
- **1994:** ADA recommended specific HbA1c goals for people with diabetes

DCCT: glucose and HbA1c

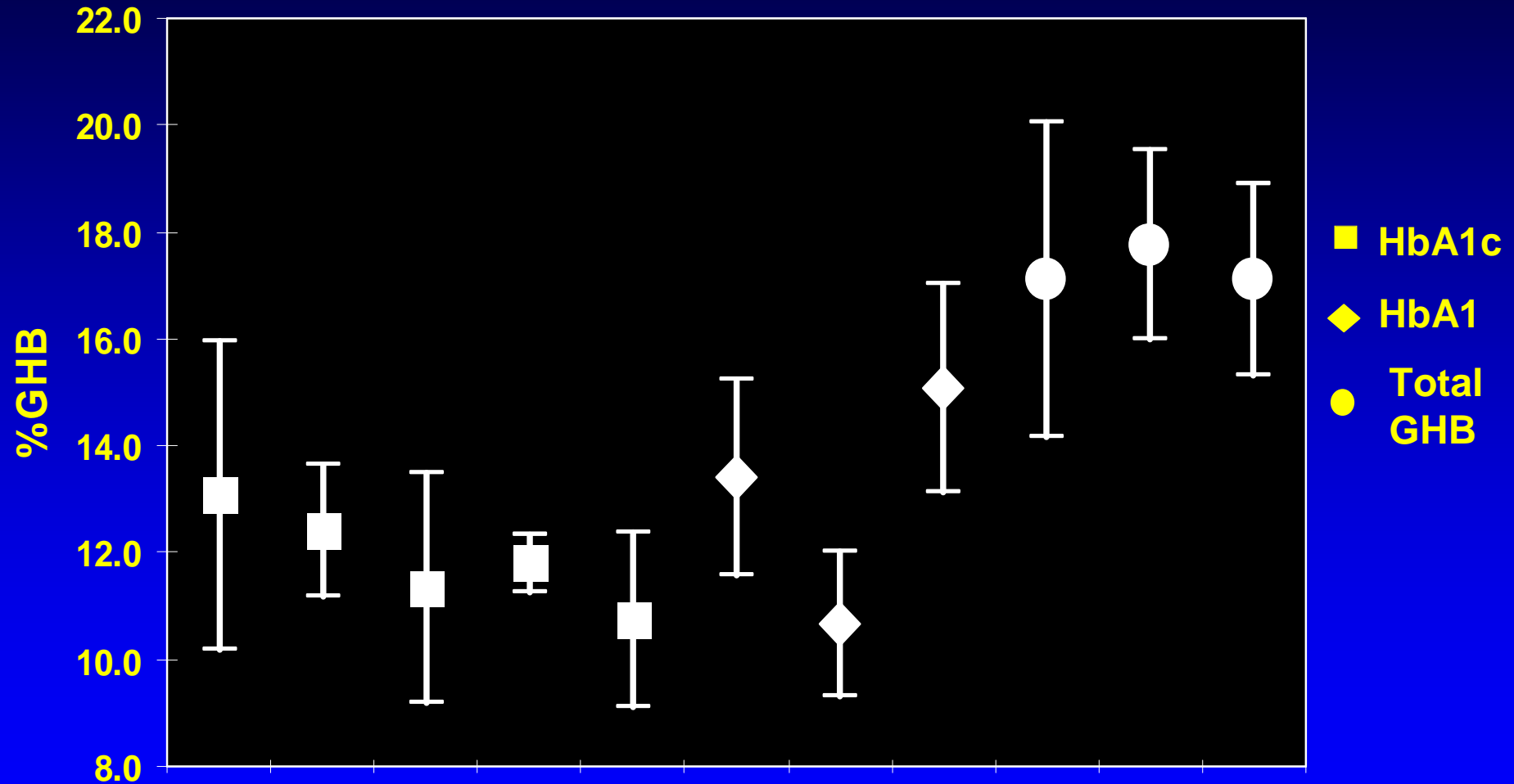
	Intensive	Conventional
Blood Glucose mmol/L (mg/dL)	8.6 (155)	12.8 (231)
HbA1c %	7.2	9.1

HbA1c and the Risk of Retinopathy in the DCCT



Diabetes, 44:968-983, 1995

1993 CAP Survey (Mean +/- 2sd)

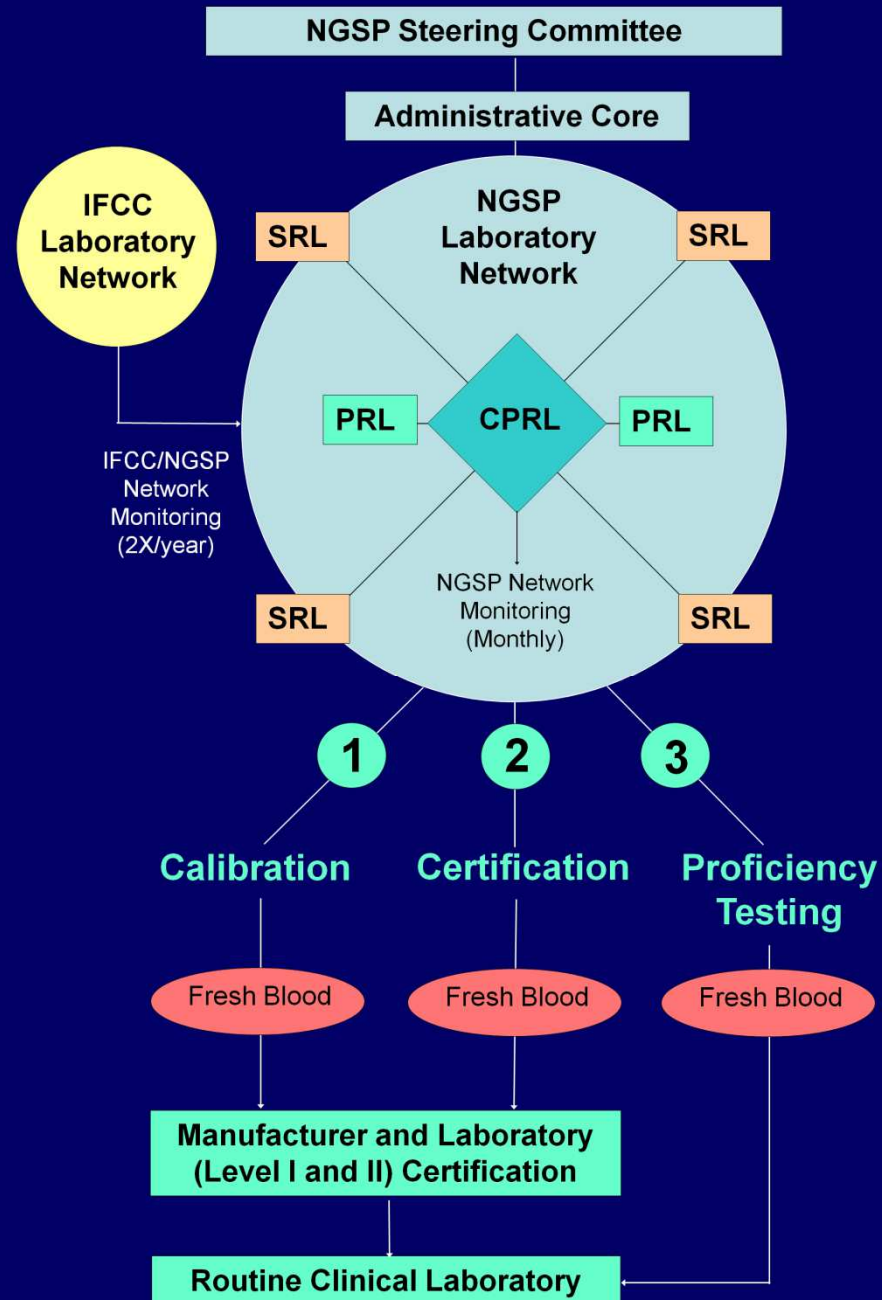


Background: NGSP



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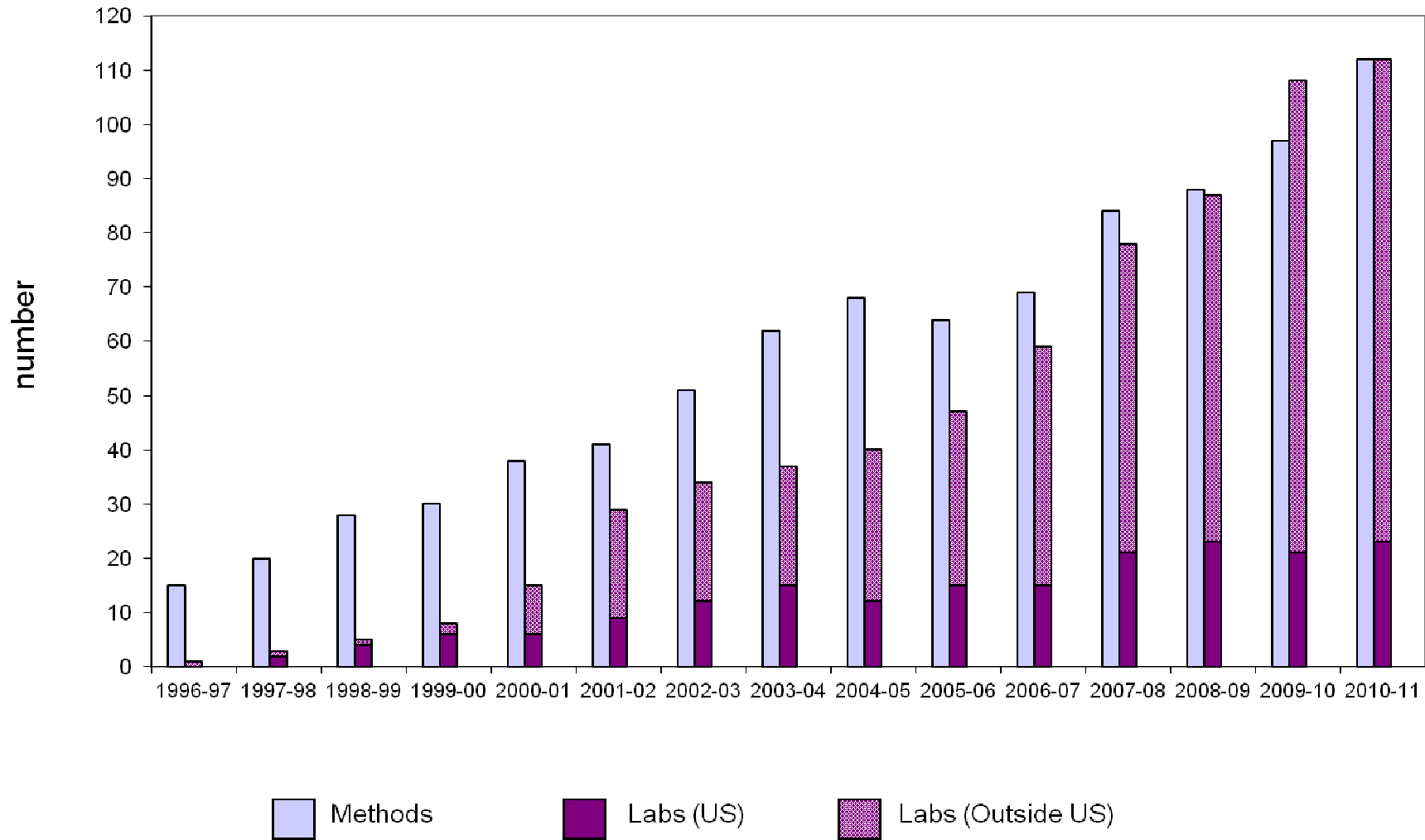
Purpose: to standardize HbA_{1c} test results to those of the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) which established the direct relationships between HbA_{1c} levels and outcome risks in patients with diabetes.



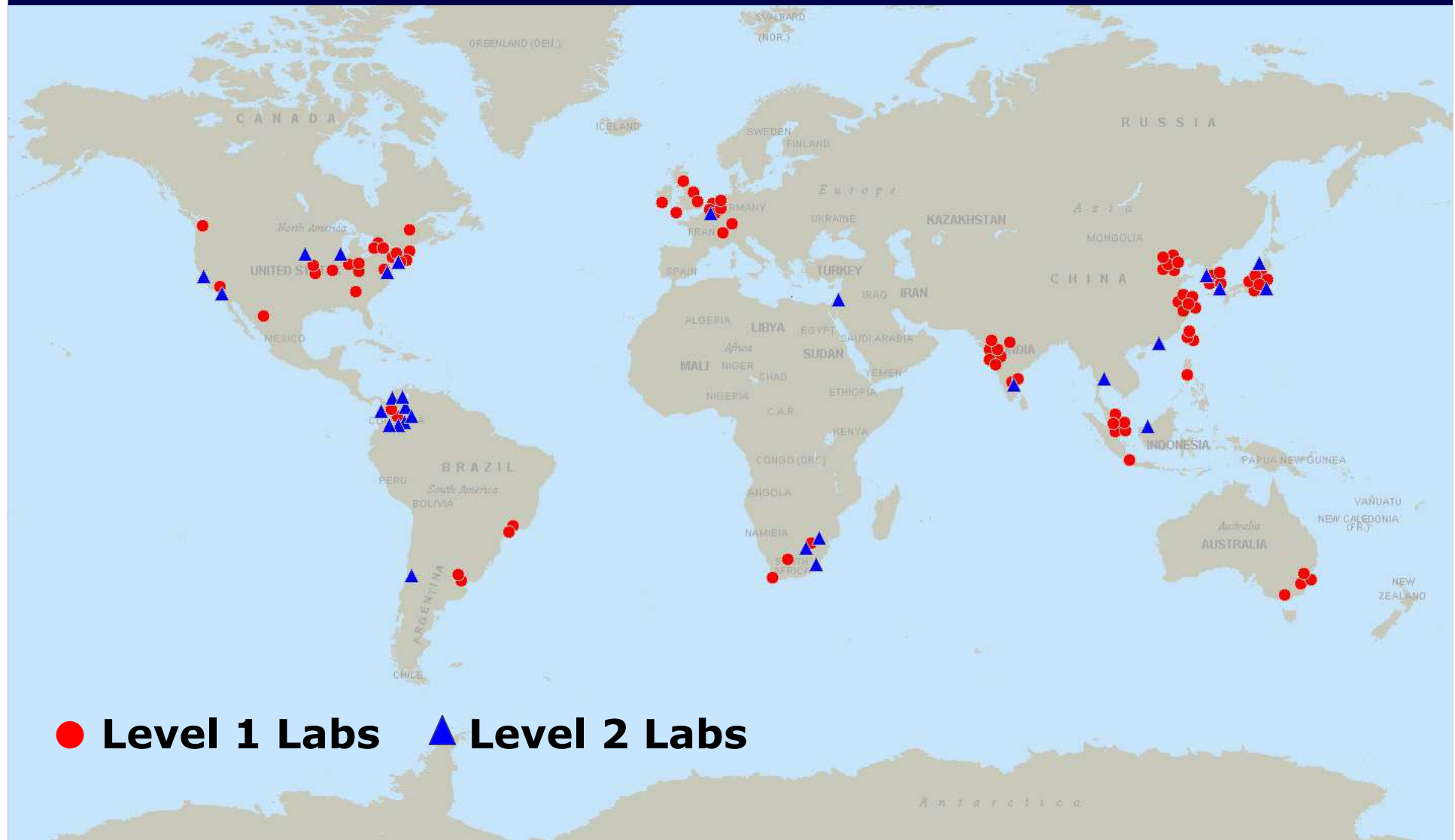
NGSP Certification

Certification Type	# samples compared	Criteria for passing	Monitoring (yes / no)	Monitoring Protocol
Manufacturer (method)	40	37 of 40 results within $\pm 7\%$	No	-
Level I Lab	40	38 of 40 results within $\pm 7\%$	Yes	10 Samples Quarterly
Level II Lab	40	37 of 40 results within $\pm 7\%$	No	-

Increase in Certification: Year 1 to 15



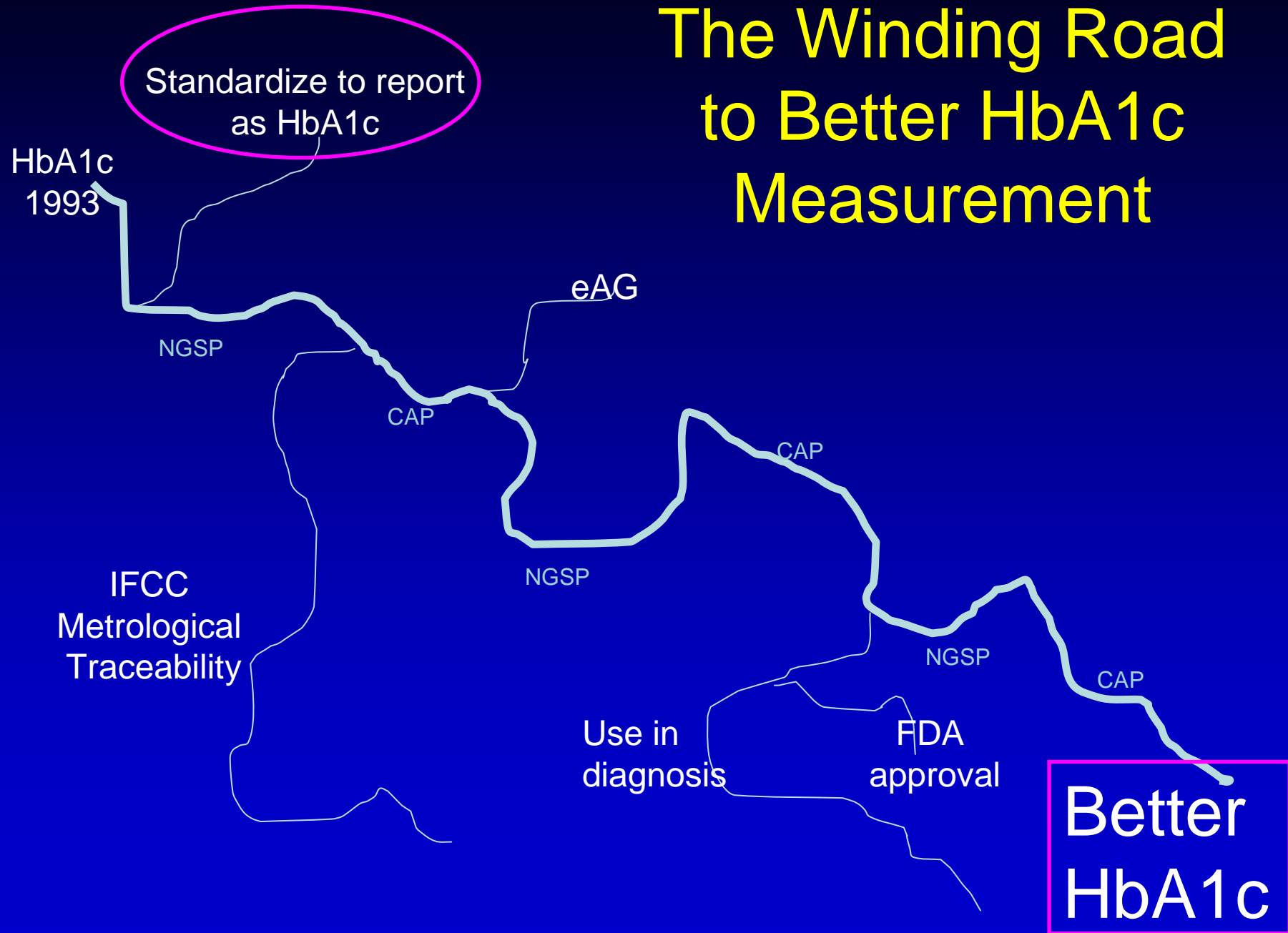
NGSP Certified Laboratories (3/12)



College of American Pathologists (CAP) HbA1c survey

- Survey samples sent twice a year
- 3 fresh pooled whole blood samples (3 HbA1c levels over a 5-10% range)
- Values assigned by NGSP (replicate analysis by 7 network labs,)
- Accuracy based laboratory assessment
- Current Pass/Fail limit is $\pm 7\%$

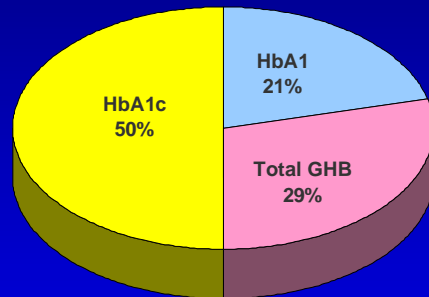
The Winding Road to Better HbA1c Measurement



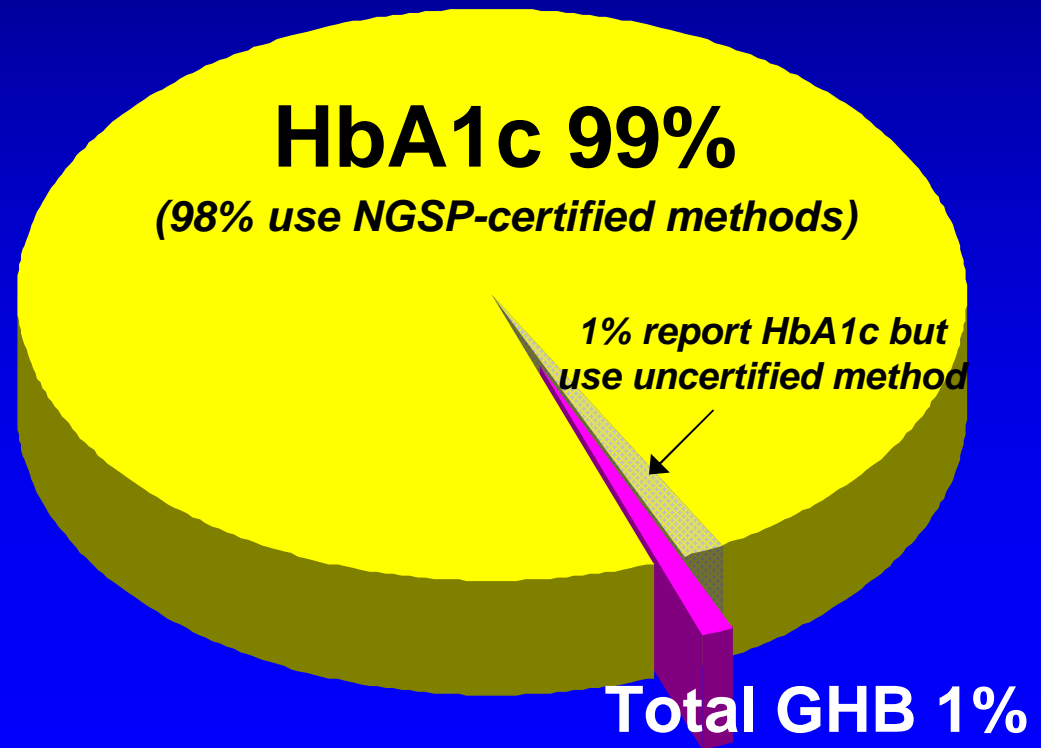
2006A CAP-GH2

% of labs reporting HbA1c

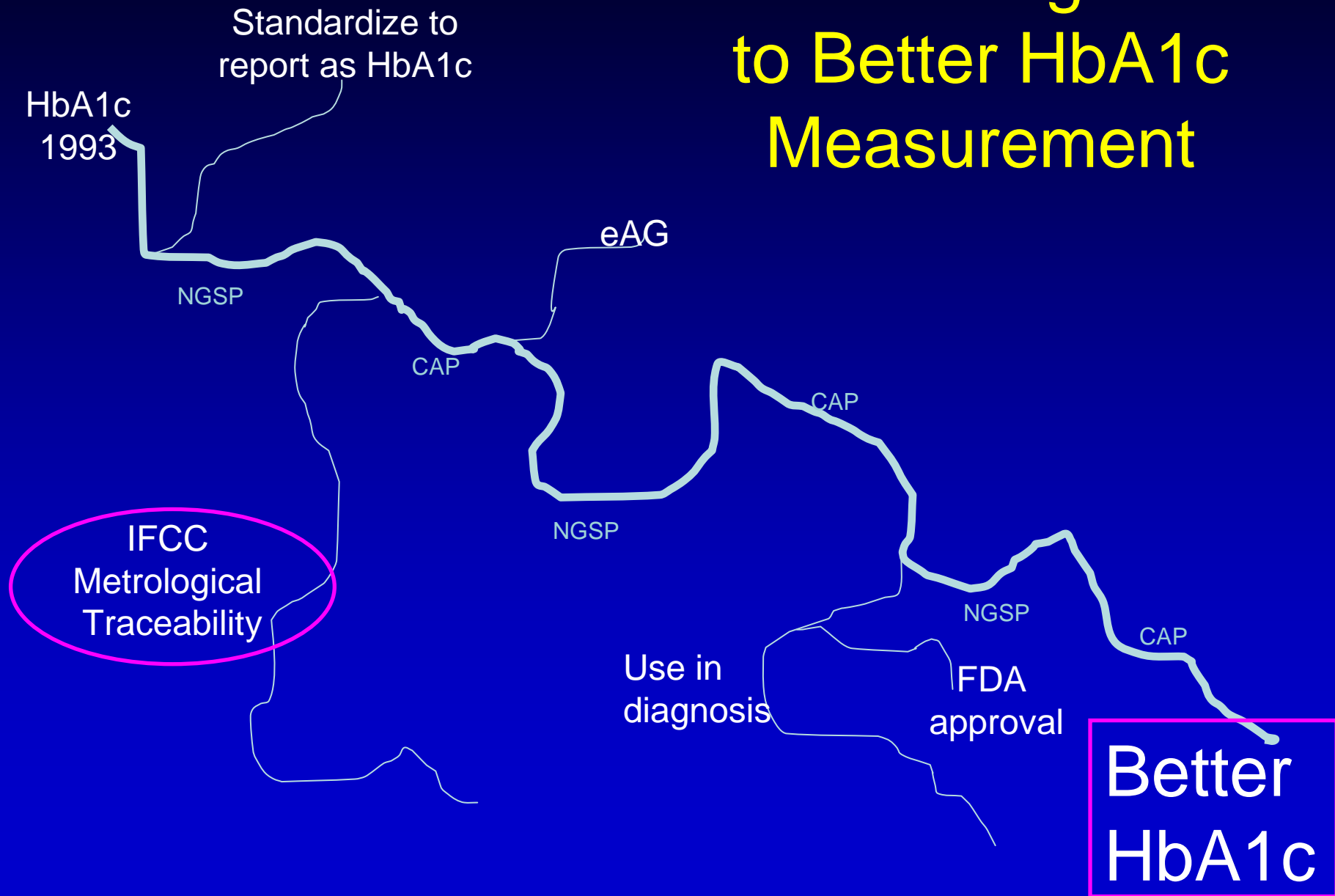
1993



2006



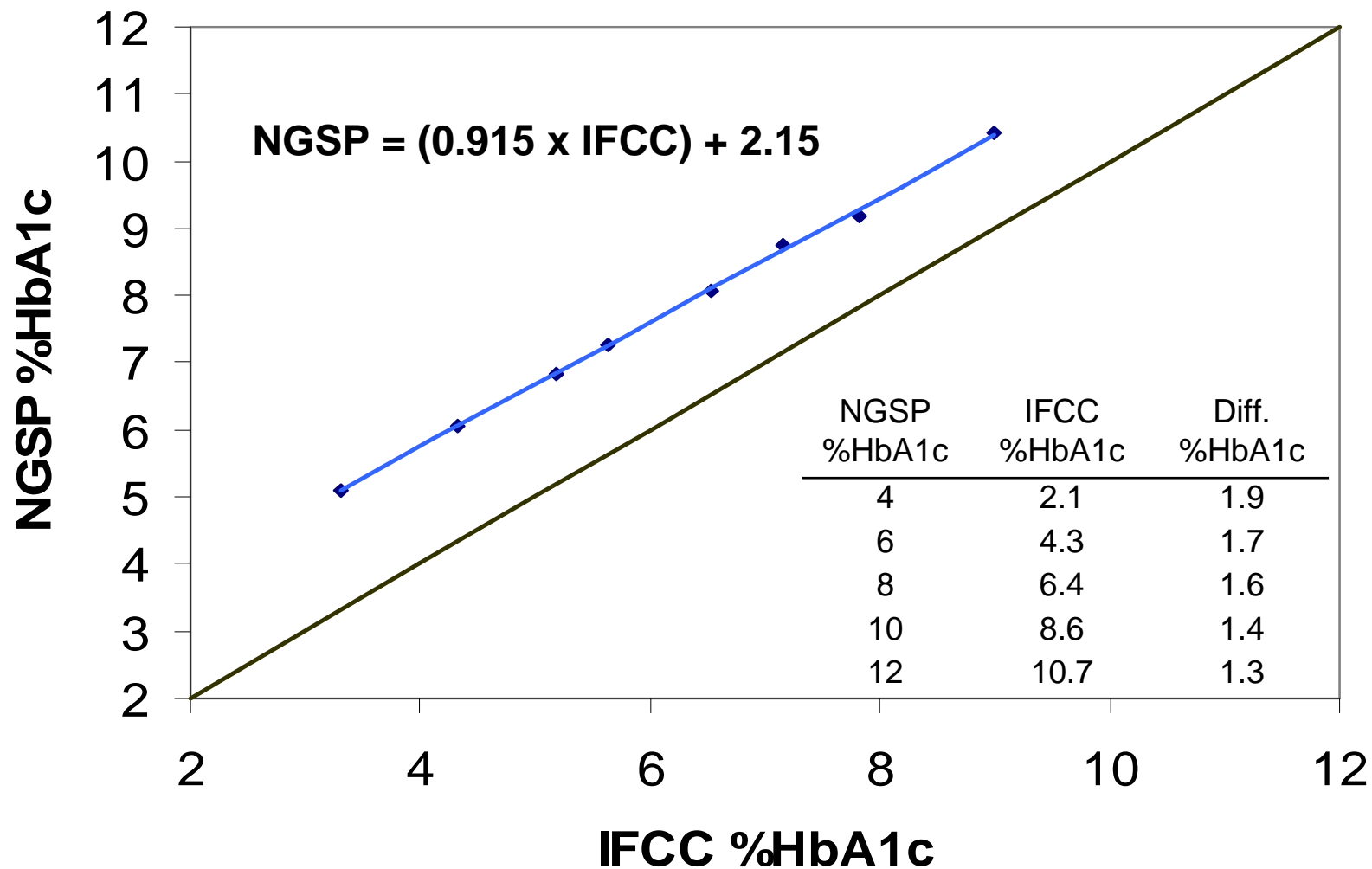
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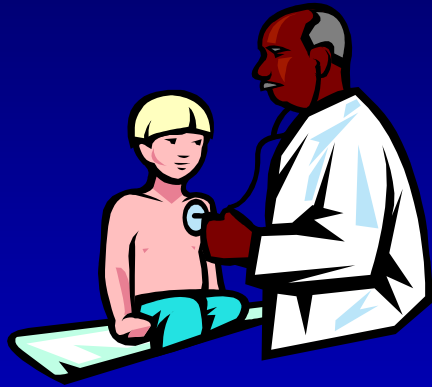
NGSP vs. IFCC

- **1995-2001:** IFCC Reference Method (higher order method) developed and approved
 - ❖ HPLC/Capillary Electrophoresis
 - ❖ HPLC/ Mass Spectrometry
- Results showed a linear relationship with NGSP but were 1.3 to almost 2% HbA1c lower

Which Numbers to Report?



The Balance



Patient Care



Traceability

NGSP vs. IFCC

- 2004: A master equation was established between the NGSP and IFCC network results:

$$\text{NGSP (\% HbA1c)} = 0.915 * \text{IFCC (\% HbA1c)} + 2.15$$

- ❖ Linear equations were also developed to describe the relationship between IFCC and the standardization schemes in Japan and Sweden
- ❖ These relationships are monitored on a regular basis to ensure traceability

IFCC vs. NGSP

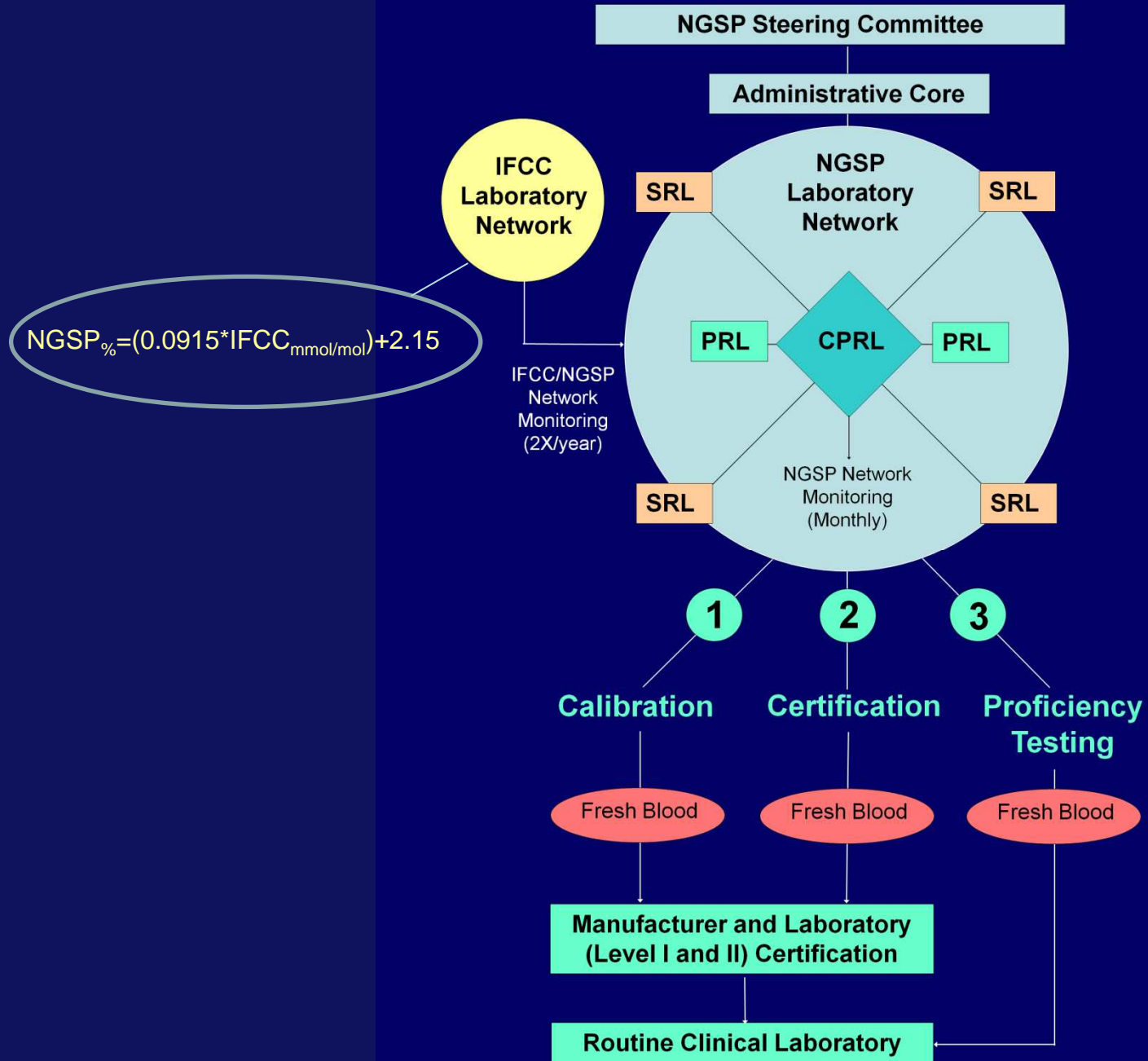
- **2007: IFCC / IDF/ EASD / ADA Consensus Statement**
- ❖ HbA1c test results should be standardized worldwide to the IFCC Reference system
- ❖ A1C results are to be reported world-wide in IFCC units (**mmol/mol**) and NGSP units (%).

NGSP HbA1c (%)	IFCC HbA1c (mmol/mol)
5	31
6	42
7	53
8	64
9	75
10	86
11	97
12	108

www.ngsp.org/convert1.asp
www.hba1c.nu/eng2.html

IFCC vs. NGSP

- **2010:** Another consensus statement on the Worldwide Standardization of the HbA1c (ADA, EASD, IFCC, ISPAD)
 - ❖ HbA1c results are to be reported in SI units (mmol/mol) and NGSP units (%)
 - ❖ Both results (IFCC and NGSP) should be reported in manuscripts



IFCC vs. NGSP: Current Status (1)

- Officially, there is worldwide consensus that HbA1c should be reported in both NGSP (%) and IFCC (mmol/mol) units.
- However, the decision on what to report is being made country by country.

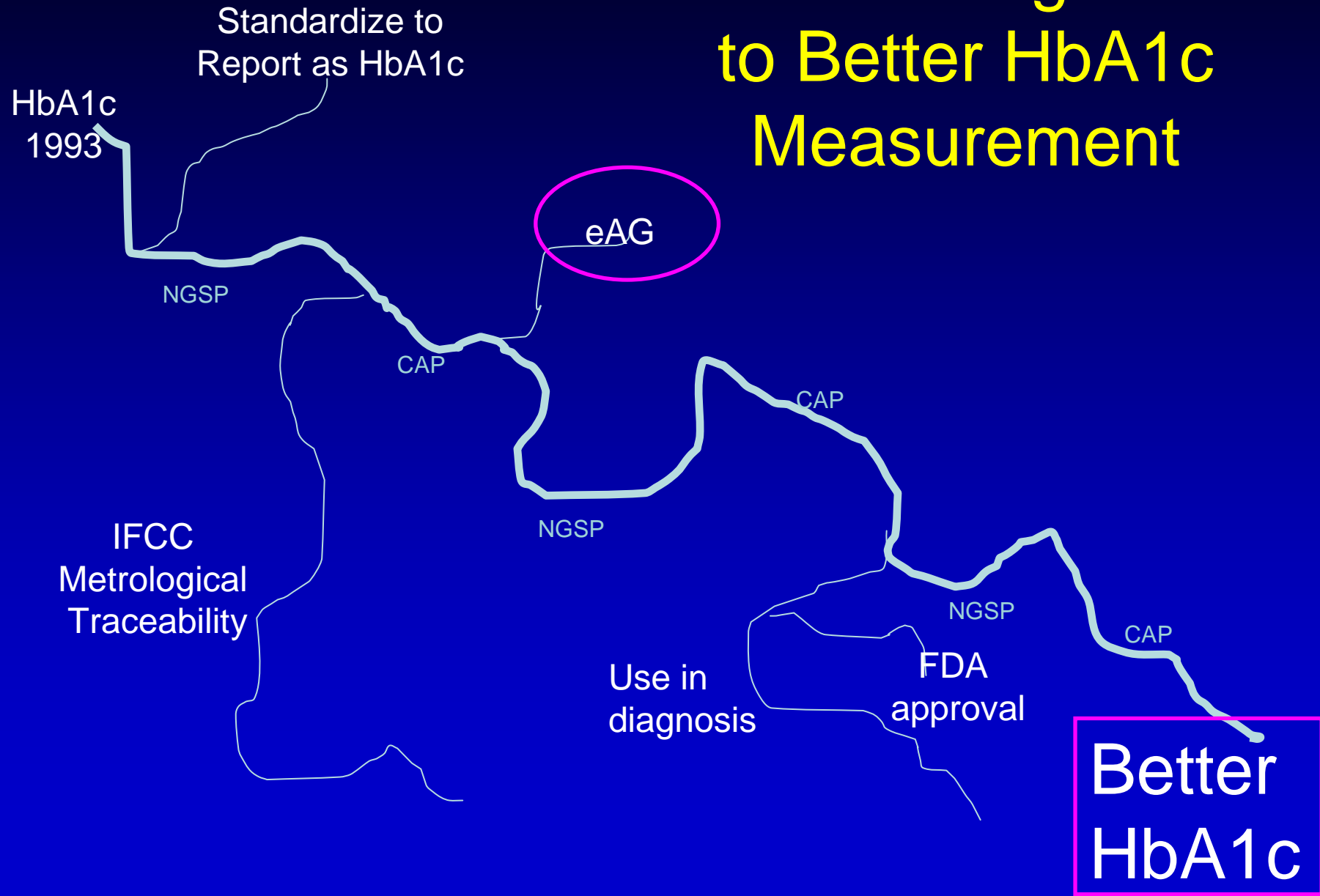
IFCC vs. NGSP: Current Status (2)

- The US will continue to report NGSP %HbA1c.
- Most other countries have decided to change to IFCC numbers in mmol/mol units.
- There is an established relationship that allows for simple conversion from NGSP to IFCC and vice-versa.

IFCC vs. NGSP: Current Status (3)

- Although the world will again be reporting different numbers, results will be traceable to IFCC numbers as well as to clinical data through linear equations that are carefully monitored.
- All relevant journals will require reporting in both units.

The Winding Road to Better HbA1c Measurement



Estimated Average Glucose (eAG)

- **2004:** ADA, EASD, IDF met to discuss the controversy in reporting units for HbA1c. They considered the possibility of reporting HbA1c as a mean blood glucose and recommended a study of mean glucose vs. HbA1c.

Estimated Average Glucose (eAG)

- **2007: IFCC / IDF/ EASD / ADA Consensus Statement**
 - ❖ HbA1c test results should be standardized worldwide to the IFCC Reference system
 - ❖ A1C results are to be reported world-wide in IFCC units (mmol/mol) and NGSP units (%).
 - ❖ If the ongoing “average plasma glucose study” fulfills it’s *a priori* specified criteria, an A1C-derived average glucose (ADAG) value calculated from the A1C result will also be reported as an interpretation of the A1C result.

Estimated Average Glucose (eAG)

- **2008:** The ADAG (A1c derived average glucose) study showed a linear relationship between HbA1c and average glucose and recommended reporting of estimated average glucose (eAG), derived from HbA1c, as an educational tool.

HbA1c vs. Mean Blood Glucose

A1C assay and estimated average glucose values

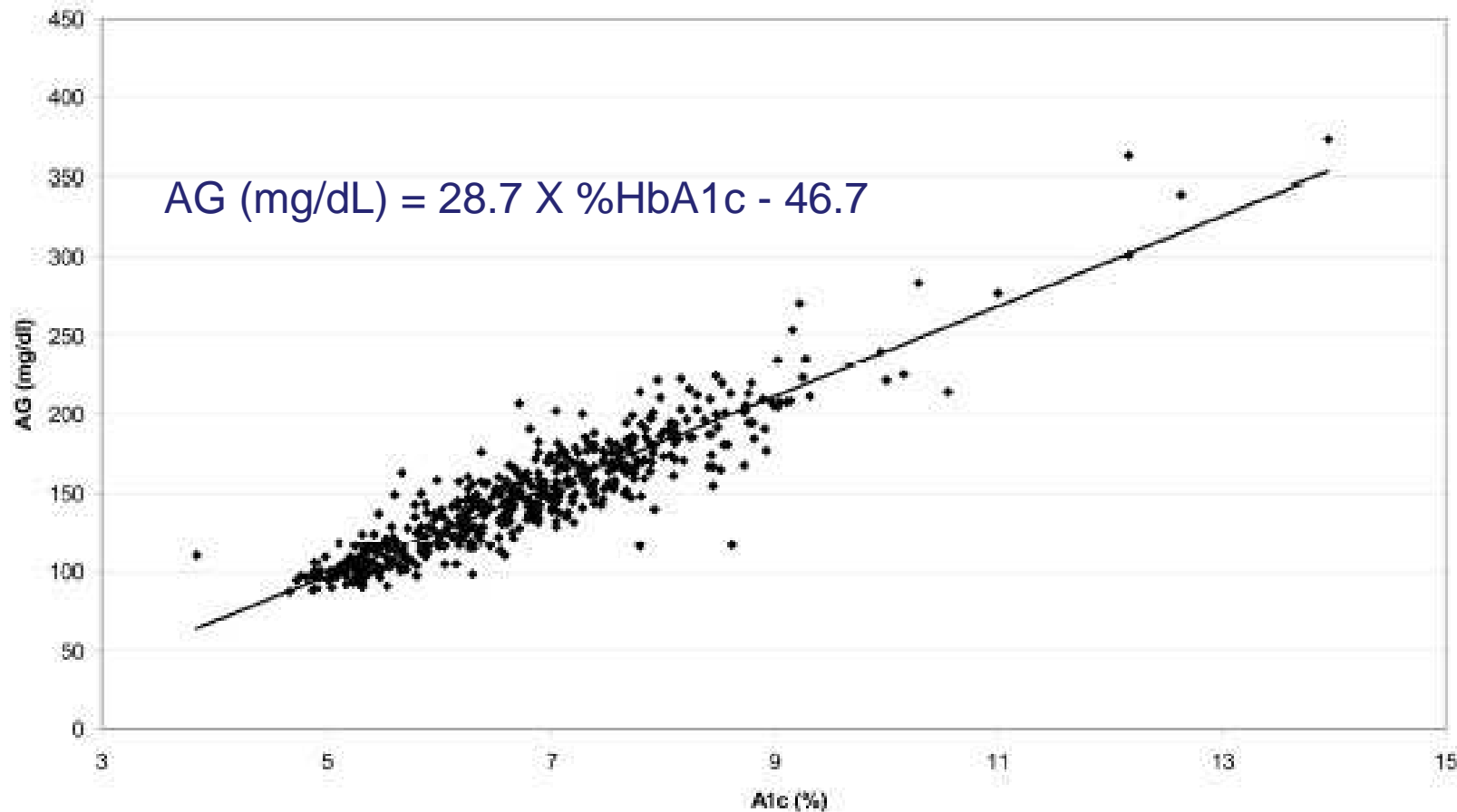
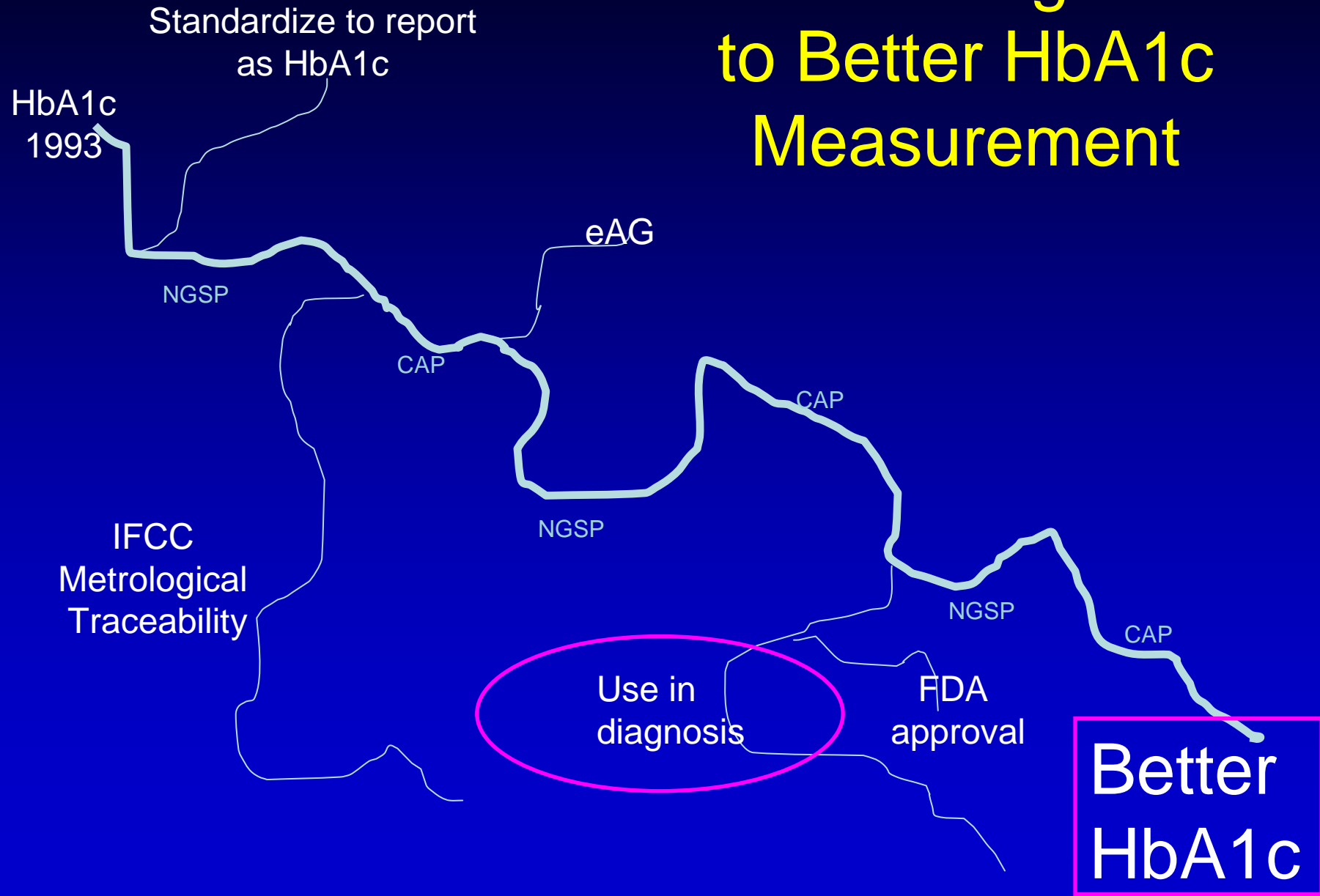


Figure 1—Linear regression of A1C at the end of month 3 and calculated AG during the preceding 3 months. Calculated $AG_{\text{mg/dl}} = 28.7 \times A1C - 46.7$ ($AG_{\text{mmol/l}} = 1.59 \times A1C - 2.59$) ($R^2 = 0.84$, $P < 0.0001$).

The Winding Road to Better HbA1c Measurement



HbA1c for Diabetes Diagnosis

International Expert Committee Report on the Role of the A1C Assay in the Diagnosis of Diabetes

THE INTERNATIONAL EXPERT COMMITTEE*

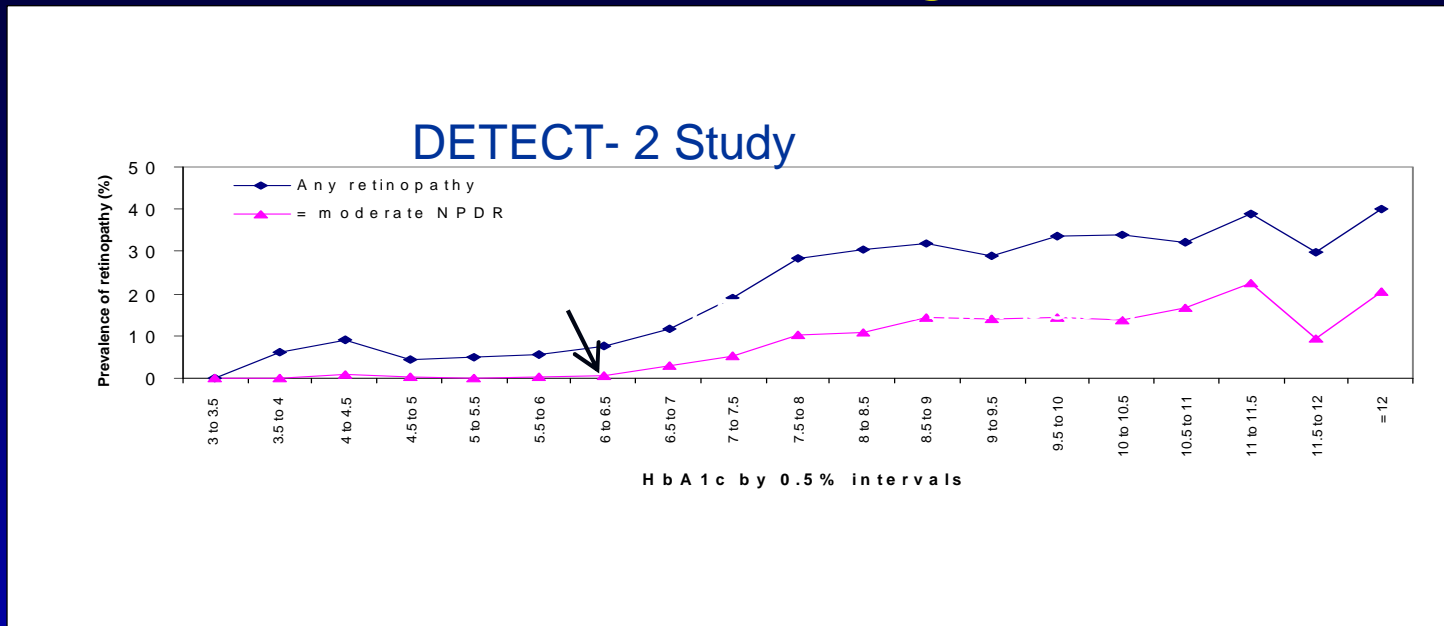
An International Expert Committee with members appointed by the ADA, EASD and IDF was convened in 2008 to consider the current and future means of diagnosing diabetes in non-pregnant persons.

Diabetes Care, VOLUME 32, Number 7, July 2009

Advantages of HbA1c Compared to Glucose: 2009 International Expert Committee Report

- Standardized and aligned to the DCCT/UKPDS; measurement of glucose is less well standardized
- Better index of overall glycemic exposure and risk for long-term complications
- Substantially less biologic variability
- Substantially less preanalytic instability
- No need for fasting or timed samples
- Relatively unaffected by acute perturbations in glucose levels
- Currently used to guide management and adjust therapy

HbA1c Cut Point for the Diagnosis of Diabetes



- Data from Detect-2 show that the level at which the prevalence of diabetes-specific “moderate” retinopathy begins to rise is at 6.5% HbA1c.
- Among those with HbA1c <6.5%, “moderate” retinopathy was virtually nonexistent.

International Expert Committee Report Recommendations

- The diagnosis of diabetes is made if the HbA1c level is $\geq 6.5\%$.
- Individuals with an HbA1c level $\geq 6\%$ but $< 6.5\%$ are likely at the highest risk for progression to diabetes.
- HbA1c tests to diagnose diabetes should be performed using clinical laboratory equipment. Point-of-care instruments have not yet been shown to be sufficiently accurate or precise for diagnosing diabetes.

2010 ADA Recommendations:

Criteria for Diagnosis of Diabetes

1. HbA1c \geq 6.5%

OR

2. FPG \geq 126mg/dl

OR

3. Two-hour plasma glucose \geq 200 mg/dl during a 75g OGTT

OR

4. Random glucose \geq 200 mg/dl in a patient with classic symptoms of hyperglycemia

2010 ADA Recommendations:

Categories of increased risk for diabetes (prediabetes)

1. FPG 100-125 mg/dl (IFG)

OR

2. Two-hour plasma glucose 140-199 mg/dl
during a 75g OGTT (IGT)

OR

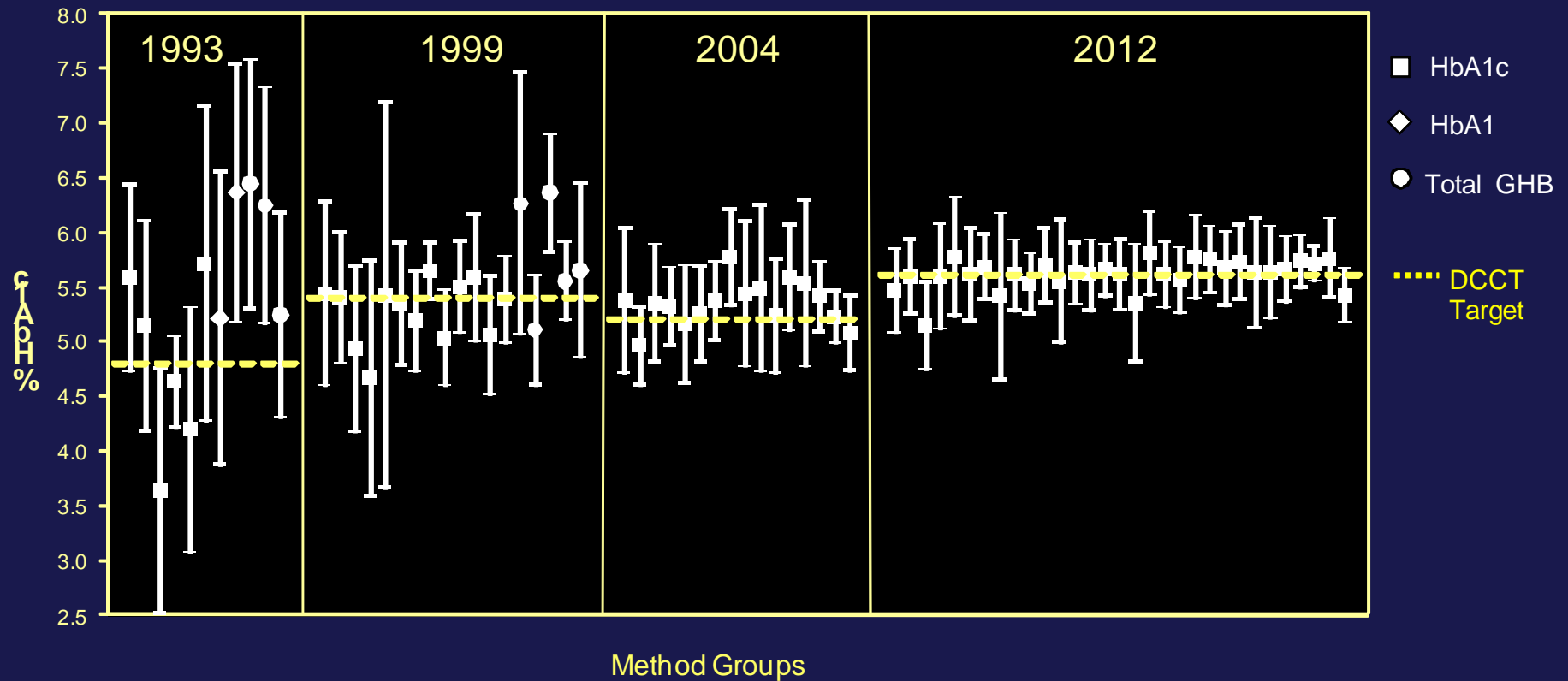
3. A1C 5.7-6.4%

The Winding Road to Better HbA1c Measurement

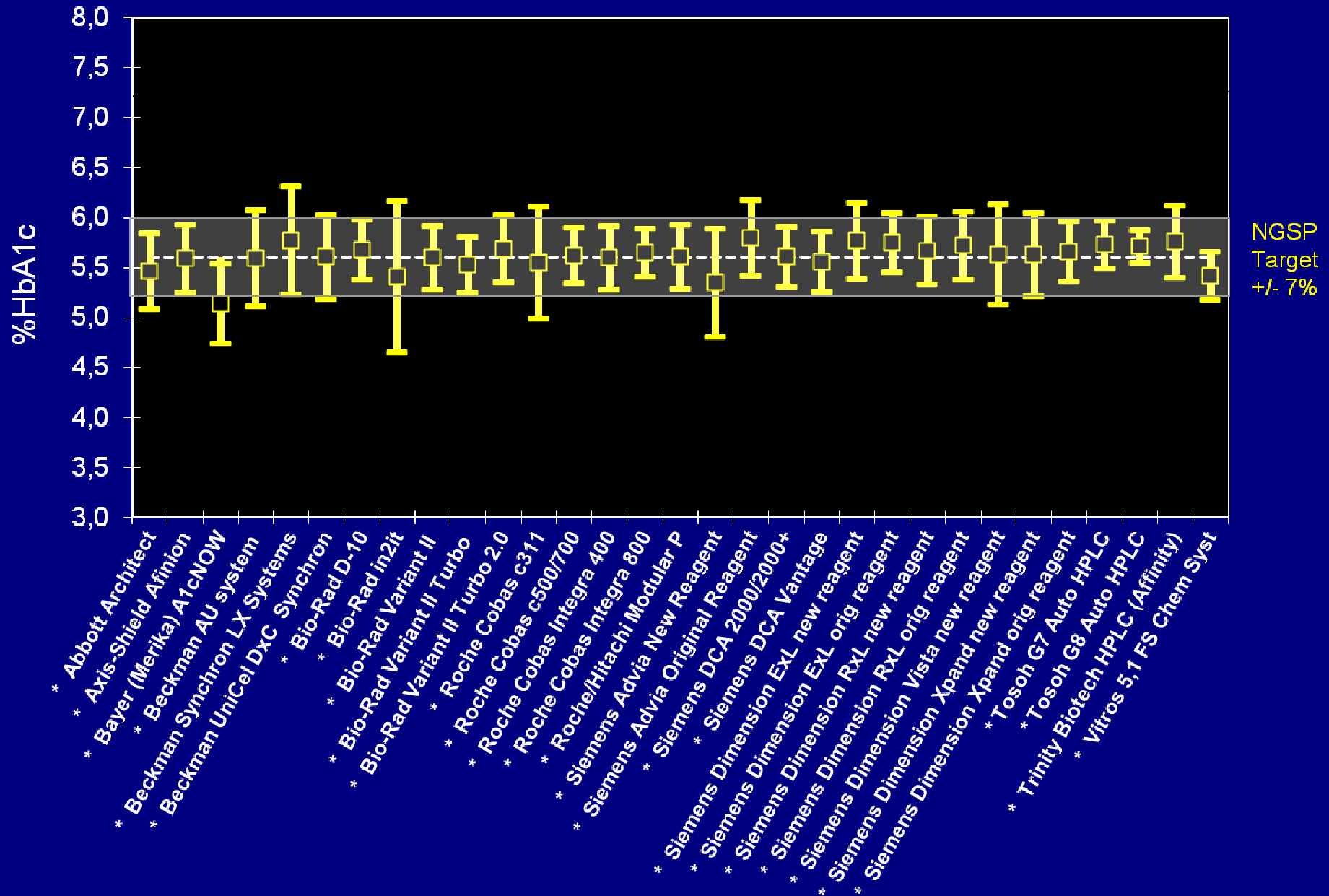


Current Status of HbA1c Measurement: From Chaos to Order

CAP Survey: Mean \pm 2sd



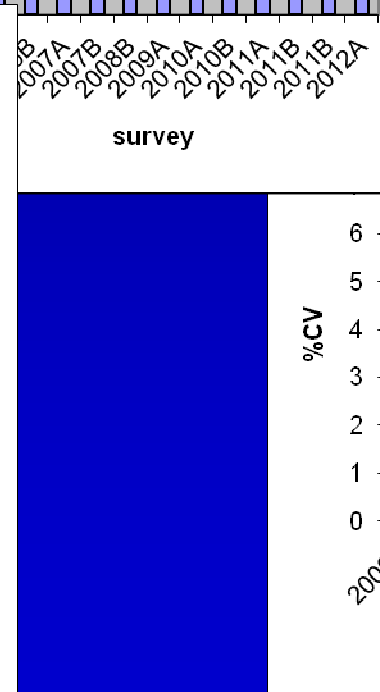
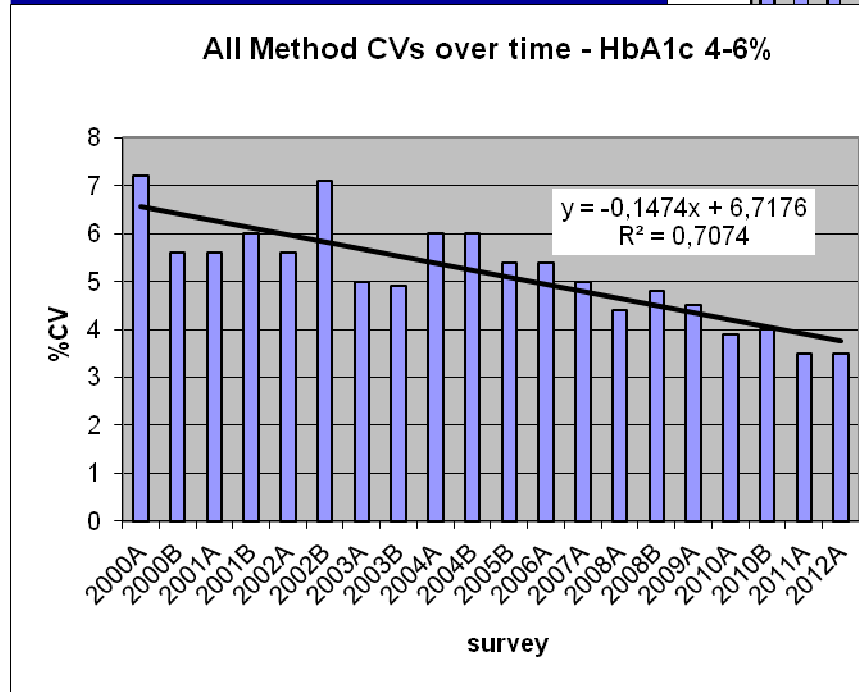
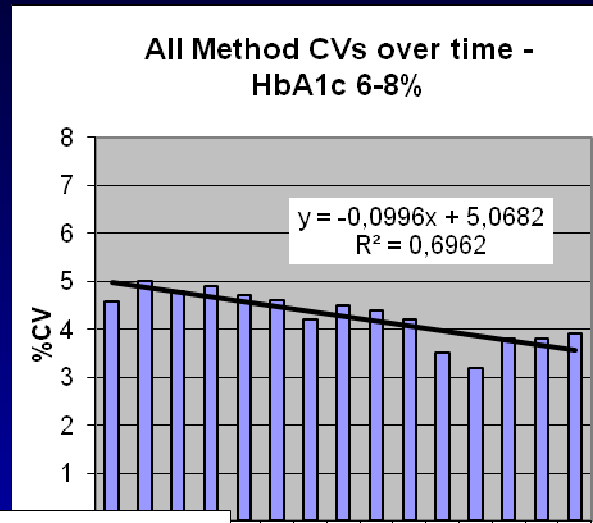
CAP GH2-A 2012 low level (mean \pm 2SD)



Point of Care (POC) Methods

- There is concern that some POC methods show high imprecision and /or high bias
- A major concern is that there is not enough proficiency testing (EQA) data on POC methods since, in the US, most users are not required to participate and choose not to do so

Decrease in All-Method CVs Over Time 2000-2012



**Is HbA1c Measurement Good
Enough?**

Is HbA1c Measurement Adequate for Optimal Clinical Use?

Consider:

1. Difference between DCCT intensive and standard treatment group only ~2% HbA1c with large decrease in risk for complications.
2. Difference in UKPDS groups <1% HbA1c, also with decrease in risk.
3. HbA1c recommended for diabetes diagnosis

How is HbA1c used for monitoring diabetes?

1. Is the patient stable, improving, or deteriorating?
2. How does the HbA1c compare to the individual's target HbA1c (e.g. 7% or 53 mmol/mol is a general target)

How Good is Good Enough?

In general, 0.5% HbA1c is considered a clinically significant change (e.g. treatment guidelines from ADA/EASD and NICE)

Diabetes Care 2009;32:193-203

<http://www.nice.org.uk/nicemedia/live/12165/44318/44318.pdf>

Are CAP limits tight enough?

- The current $\pm 7\%$ CAP limit corresponds to a limit of $\sim \pm 0.5\%$ HbA1c at a target of 7% HbA1c.
- In the normal range or treatment target range, if a lab consistently passes the CAP limit, then the lab/method is highly likely to give results that are within 0.5% HbA1c of the target.
- Based on the 2012A CAP survey, $\sim 95\%$ of laboratories pass at the current $\pm 7\%$ CAP limit.

2012A CAP Pass Rates

Specimen	NGSP Target (% HbA1c)	Acceptable Range ($\pm 7\%$)	Pass Rate % (Low/High)	Cumulative Pass Rate %
GH2-01	5.6	5.2-6.0	72.7/100	95.6
GH2-02	9.4	8.7-10.1	81.8/100	94.9
GH2-03	7.2	6.6-7.8	89.4/100	96.2

Future Plans for Improvement

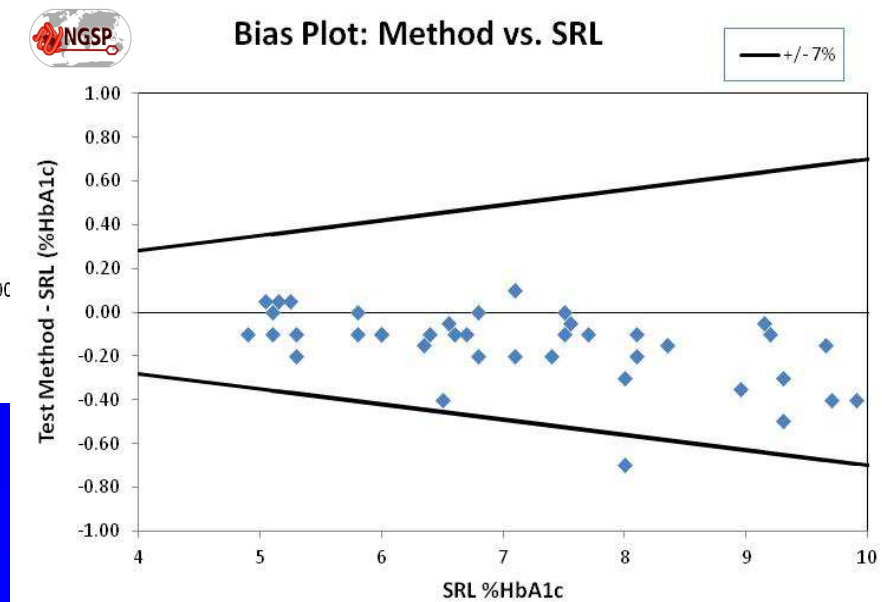
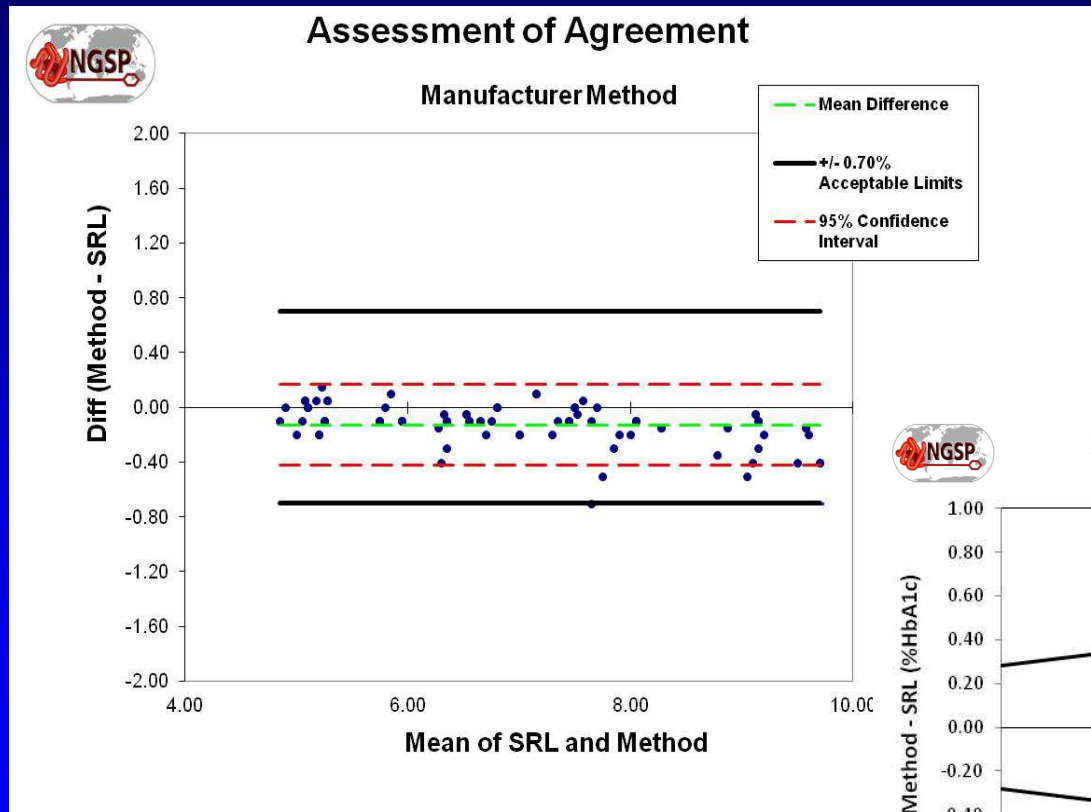
1. Tighten NGSP Manufacturer Certification Criteria (currently limit is 37/40 within 7%)
2. Tighten CAP Survey Grading for HbA1c (current limit is 7%; 6% is planned for 2013)
3. Reduce assay interferences

Improving HbA1c Measurement

1. Tightening of NGSP Manufacturer Certification Criteria:

- **1996:** Initial criteria based on CLSI EP9 (bias) and EP5 (precision); HbA1c range 4-14%
- **1999:** Changed from EP9 bias assessment to Bland/Altman assessment of agreement (95% CI of differences within $\pm 1\%$ HbA1c)
- **2002:** Tightened precision criteria from $\leq 5\%$ to $\leq 4\%$
- **2007 :** Tightened assessment of agreement criteria from $\pm 1\%$ to $\pm 0.85\%$ HbA1c (and narrowed the HbA1c range to 4-12%)
- **2010:** Tightened assessment of agreement criteria from $\pm 0.85\%$ to $\pm 0.75\%$ HbA1c (and narrowed the HbA1c range to 4-10%).
- **September 2012:** Tightened criteria from $\pm 0.75\%$ HbA1c to 37/40 results within 7% (relative percent)

Change in Certification Criteria: September 2012



Improving HbA1c Measurement

2. Changes in CAP Survey Grading for HbA1c

- **2007**: Survey began accuracy based grading with $\pm 15\%$ acceptable limit
- **2008**: Acceptable limit was reduced to $\pm 12\%$
- **2009**: Acceptable limit was reduced to $\pm 10\%$
- **2010**: Acceptable limit was reduced to $\pm 8\%$
- **2011-2012**: Acceptable limit reduced to $\pm 7\%$
- **After 2012**, the plan is to tighten to $\pm 6\%$

Improving HbA1c Measurement

3. Reducing Interferences

- Increasing awareness of HbA1c interferences
- Testing for interference from Hb variants and adducts for each method
- Encouraging use of methods without these interferences
- Tightening criteria for a clinically significant interference (recently tightened from $\pm 10\%$ to $\pm 7\%$ at 6 and 9% HbA1c)

Common Hb Variants

- HbS
- HbE
- HbC
- HbD
- &
- Elevated HbF

Interferences (>7% bias at 6 & 9% HbA1c)

Method	Interference from HbC	Interference from HbS	Interference from HbE	Interference from HbD	Interference from elevated HbF
Abbott Architect/Aeroseet	Yes	Yes	@	@	\$
Arkray ADAMS A1c HA-8180V (Menarini)	No	No	HbA1c not quantified	HbA1c not quantified	No
Axis-Shield Afinion	No	No	No	No	\$
Bayer A1cNOW	Yes	Yes	No	No	\$
Beckman AU system	Yes	Yes	No	No	\$
Beckman Synchron System	No	No	No	No	\$
Bio-Rad D-10 (A1c program)	No	No	No	No	Yes >10% HbF
Bio-Rad Variant II NU	-	-	No	No	Yes >10% HbF
Bio-Rad Variant II Turbo	No	No	Yes	Yes	Yes >5% HbF
Bio-Rad Variant II Turbo 2.0	No	No	No/Yes (conflicting)	No	Yes >25% HbF
Bio-Rad in2it	Yes	No	Yes	No	\$
Ortho-Clinical Vitros	No	No	No	No	\$
Roche Cobas Integra Gen.2	No	No	No	No	\$
Roche/Hitachi (Tina Quant II)	No	No	No	No	\$
Sebia Capillarys 2 Flex Piercing	No	No	No	No	-
Siemens Advia HbA1c (original)	Yes	Yes	@	@	\$
Siemens Advia A1c (new version)	No	No	@	@	\$
Siemens DCA 2000	No	No	No	No	Yes >10%
Siemens Dimension	No	No	No	No	\$
Tosoh G7	Yes	No	Yes	No	No
Tosoh G8	No	No	Yes	No	No
Trinity (Primus) HPLC (affinity)	No	No	No	No	Yes >15% HbF

@ assumed no for all immunoassays

\$ assumed yes >10-15% for all boronate affinity methods

Summary (1)

- HbA1c measurements have improved considerably since the DCCT ended in 1993.
- Although results are not be reported in the same units worldwide, there is an established relationship that allows for conversion between NGSP % and IFCC mmol/mol.
- eAG is being reported along with HbA1c in the US
- HbA1c is now recommended for diagnosing diabetes (ADA, WHO).

Summary (2)

- In an effort to further decrease the variability in HbA1c measurement, the NGSP will continue to tighten manufacturer certification criteria and the CAP may continue to tighten its PT criteria for laboratories.
- There will be ongoing monitoring of the impact of these measures.

Summary (3)

- Interference from Hb variants is still of concern but at the present time most laboratories are using methods that show no interference from the most common variants.
- The NGSP will continue to evaluate new methods for interference from the most common Hb variants and will likely tighten criteria for interference.

Thank you!

Questions?

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