Diabetes Management at the Point of Care

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Outline

1. • Diabetes Epidemic
2. • Guidelines/Goals for Diagnosing/Monitoring Diabetes
3. • Issues with Compliance
4. • HbA1c and glycemic control
5. • Advantages of Point-of-Care Testing
6. • Concerns Regarding HbA1c Point-of-Care Testing

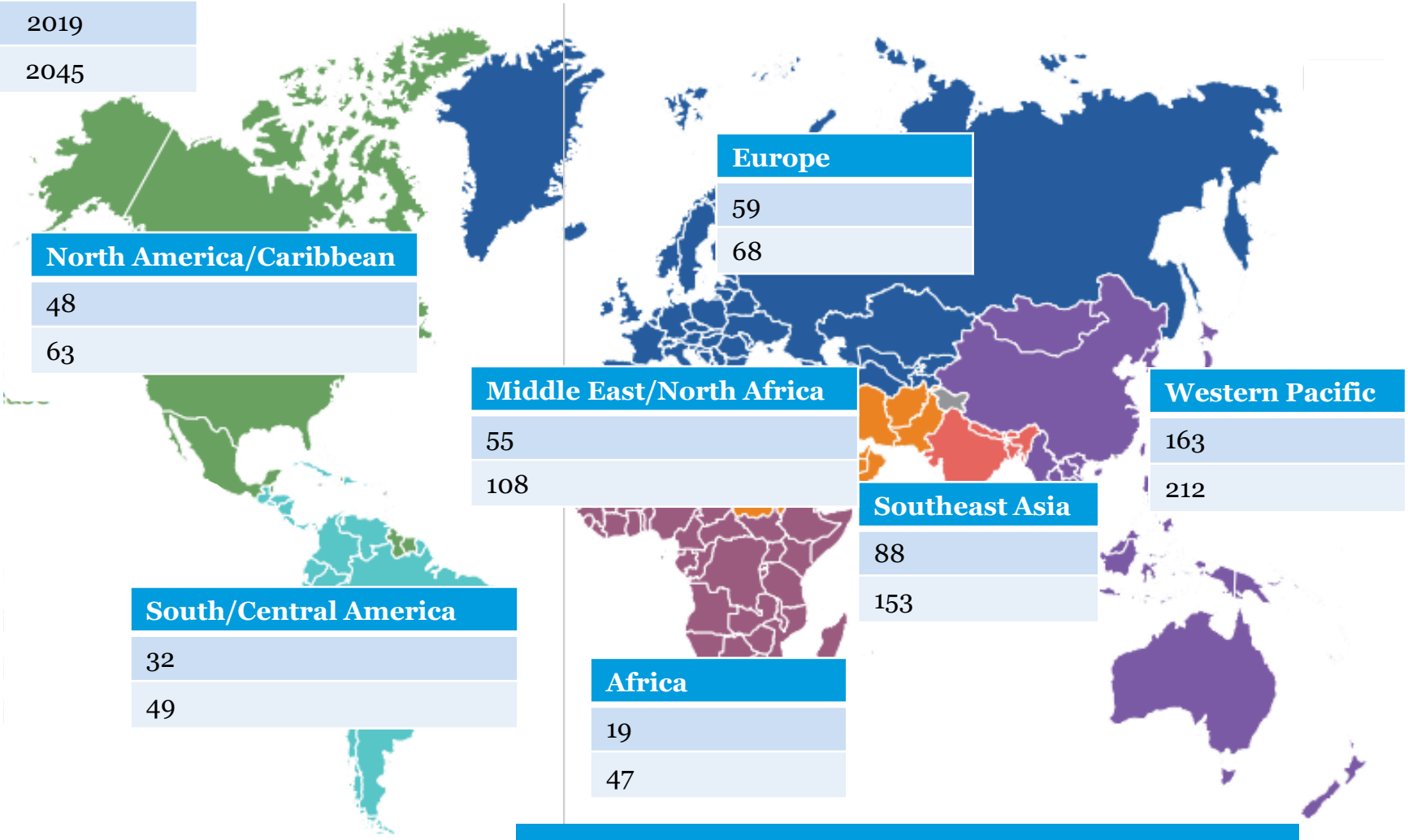
Prevalence of Diabetes in 2019

Rank	Country	Estimated Undiagnosed individuals	Estimated Diagnosed Individuals	Percentage Undiagnosed
1	China	65.2 million	116.4 million	56.0%
2	India	43.9 million	77.0 million	57.0%
3	United States	11.8 million	31.0 million	38.1%
4	Pakistan	8.5 million	19.4 million	43.8%
5	Indonesia	7.9 million	10.7 million	73.7%

~463 million adults worldwide have some form of diabetes
4.2 million adult deaths
over $760 billion in health care expenditures

IDF Diabetes Atlas, 9th Ed, 2019

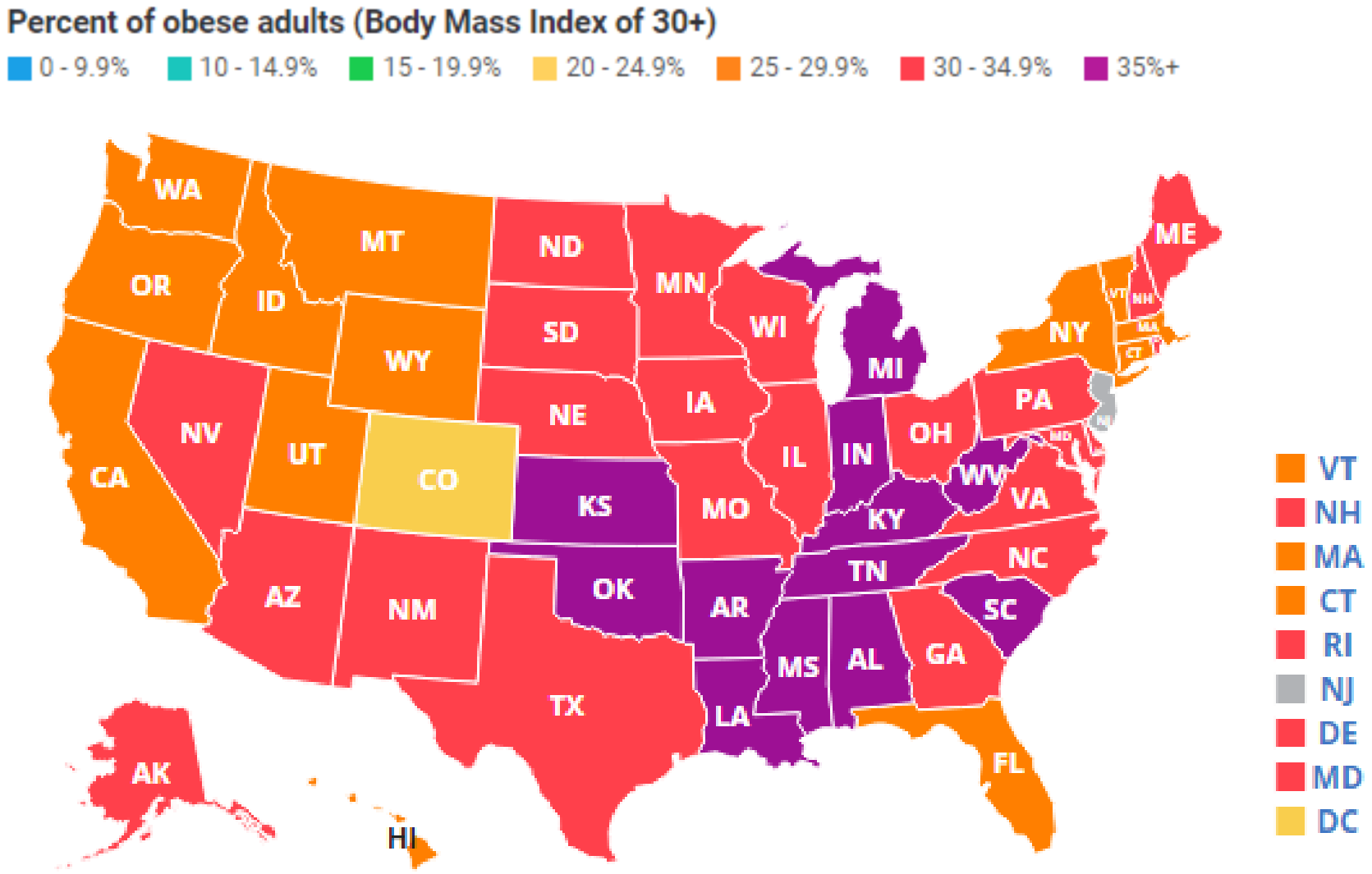
Prevalence of Diabetes in 2019
Estimated Projections for 2045



Projected to grow to 700 million by 2045

IDF Diabetes Atlas, 9th Ed, 2019

The State of Obesity: 2019



Adapted from: The State of Obesity. Trust for Americas Health. http://stateofobesity.org/adult-obesity/

Importance of Diagnosing Diabetes in a Timely Manner

Over 230 million adults worldwide are undiagnosed.

Poorly controlled diabetes leads to serious chronic complications.

A low-cost, rapid, convenient, easy and accurate way to diagnose diabetes is needed.

Current Guideline Targets: Screening & Dx Type 2 Diabetes

	ADA
	• Children, adolescents and adults of any age, overweight or obese, plus one of more additional risk factors • Testing should begin at age 45 • If test is normal, repeat it at least every 3 years
Tests	• FPG, • or 2-hr PG after 75 g OGTT criteria • or HbA1c
Prediabetes	• HbA1c 5.7% - 6.4% (39-46 mmol/umol)
Diabetes	• HbA1c ≥6.5% (48 mmol/umol)

ADA. Standards of Medical Care in Diabetes-2021. Diabetes Care 2021;44(suppl 1):S15-S33

2021 ADA Recommendations

Diagnosis of Diabetes

- FPG ≥ 7.0 mmol/L (126 mg/dL)
- 2-h PG ≥ 11.1 mmol/L (200 mg/dL) during OGTT
- A1c ≥ 48 mmol/mol (6.5%) – using a NGSP certified method standardized to the DCCT assay
- A patient with classic symptoms of hyper or hypoglycemic crisis, random plasmas glucose ≥ 11.1 mmol/L (200 mg/dL)

Definition of Prediabetes

- FPG 5.6 mmol/L (100 mg/dL) to 6.9 mmol/L (125 mg/dL)
- 2-h PG 7.8 mmol/L (140 mg/dL) to 11.0 mmol/L (199 mg/dL) during OGTT
- A1c 39-47 mmol/mol (5.7-6.4%)

ADA. Standards of Medical Care in Diabetes-2021. Diabetes Care 2021;44(suppl 1):S15-s33

Current Guideline Targets: Monitoring Diabetic Patients

Test	Frequency	Target
HbA1c	Point-of-care 2 to 4 times annually	< 7%
LDL HDL Trigs	At diagnosis and annually	< 100 mg/dL > 40/50 mg/dL(M/F) < 150 mg/dL
ACR	At least annually	< 30 mg/g
Creat/eGFR	At diagnosis and annually	≥ 60 mL/min/1.73m^2
LFT	At diagnosis and annually	Std Ref Range
BP	Every visit	< 140/90 mmHg

ADA. Standards of Medical Care in Diabetes-2021. Diabetes Care 2021;44(suppl 1):S40-S167

Current ADA Recommendations Glycemic Control Assessment

Perform HbA1c test at least two times a year in patients who are meeting treatment goals (and who have stable glycemic control).

Perform HbA1c test quarterly in patients whose therapy has changed or who are not meeting glycemic control.

Point-of-care testing for HbA1c provides the opportunity for more timely treatment changes.

ADA. Standards of Medical Care in Diabetes-2021. Diabetes Care 2021;44(suppl 1):S1-S232

Compliance With Guideline Targets is Poor

Only 26.7% of patients diagnosed with diabetes meet targets for glycemic, blood pressure, or cholesterol control

Ali MK, Bullard KM, Gregg EW, del Rio C. *Ann Intern Med*. 2014;161(10):681-9.

Only 3% of Patients Are Tested & Treated According to Guideline

- 3% of patients meet guidelines for HbA1c testing frequency AND guideline recommended antidiabetic treatment modification
- 70% of patients tested and treated according to ADA guidelines met HbA1c goals
  - Only 30% met HbA1c goals if they did not meet guidelines for either testing frequency or treatment modification

.

Outcome	Did Not Meet Either Guideline (N = 1,297)	Met Both Guidelines (N = 40)	Total (N = 1,337)
Did not achieve target HbA1c, n (%)	900 (69.4)	12 (30.0)	912 (68.2)
Achieved target HbA1c, n (%)	397 (30.6)	28 (70.0)	425 (31.8)

Lian J, Lang Y. *Curr Med Res Opin*. 2014;30(11):2233-40.

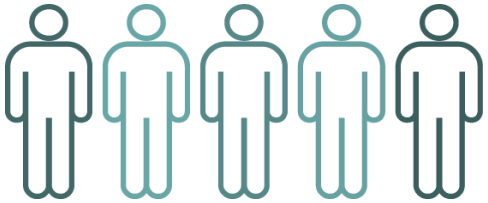
Why is Testing Compliance Poor?

Provider Time Constraints

Lost to Lab

Poor Testing Compliance

Lower Socioeconomic Status



Cultural Issues

Currie CJ, Peyrot M, Morgan CLL, et al. *Diabetes Care*. 2012;35:1279–84.
García-Pérez LE, Alvarez M, Dilla T, Gil-Guillén V, Orozco-Beltrán D. *Diabetes Ther*. 2013;4(2):175–94.

HbA1c Testing

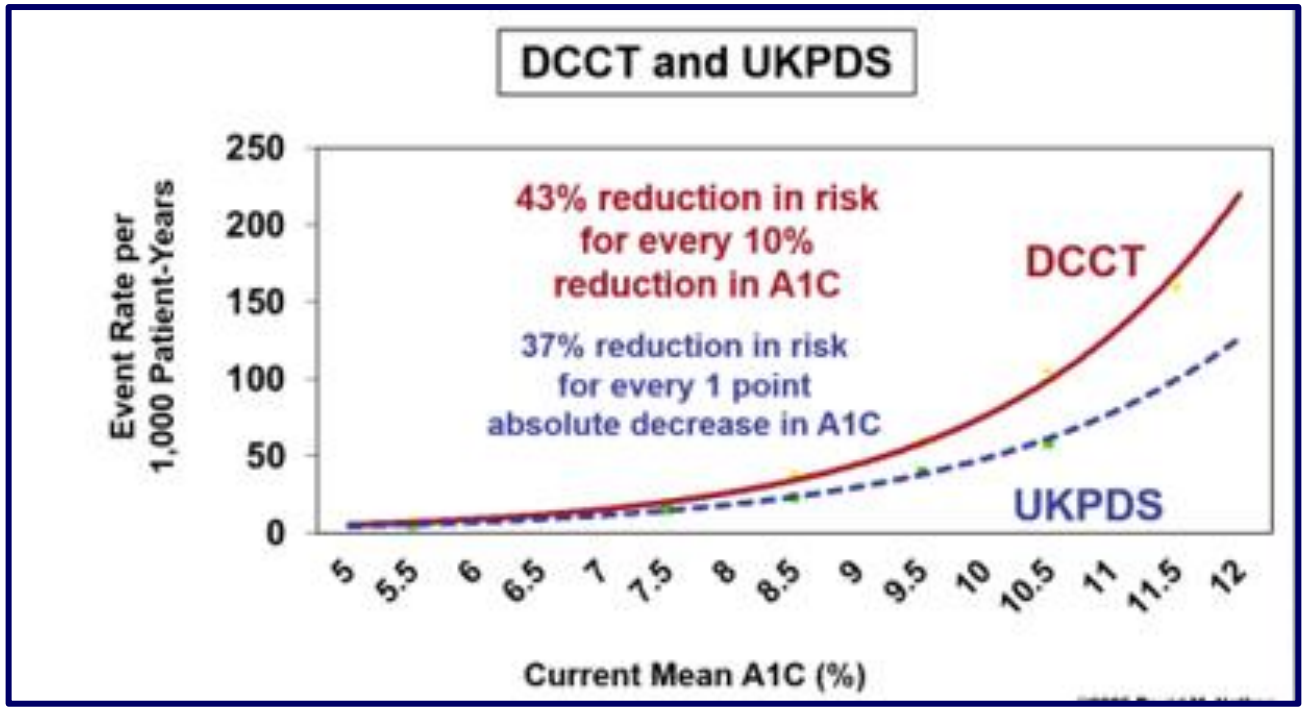
Relationship of HbA1c to SMBG

A1C, % (mmol/mol)	Mean Glucose		Mean Premeal Glucose	
	mg/dL	mmol/L	mg/dL	mmol/L
6 (42)	126	7.0	118–139	6.5–7.7
7 (53)	154	8.6	152–155	8.4–8.6
8 (64)	183	10.2	179	9.9
9 (75)	212	11.8		
10 (86)	240	13.4		
11 (97)	269	14.9		
12 (108)	298	16.5		

- Derived from 507 participants, 71% non-Hispanic white
- 3 months of data including median of 13 days of CGM and ~39 days of 7-point glucose monitoring (mean 5.1/day), for average of 2,700 glucose levels per subject
- These data show:
  - Estimated average glucose for A1c
  - Data-derived glucose targets that correlate to achieved A1c

2019 ADA Standards of Care, Diabetes Care 2019,42 (Suppl 1); S63

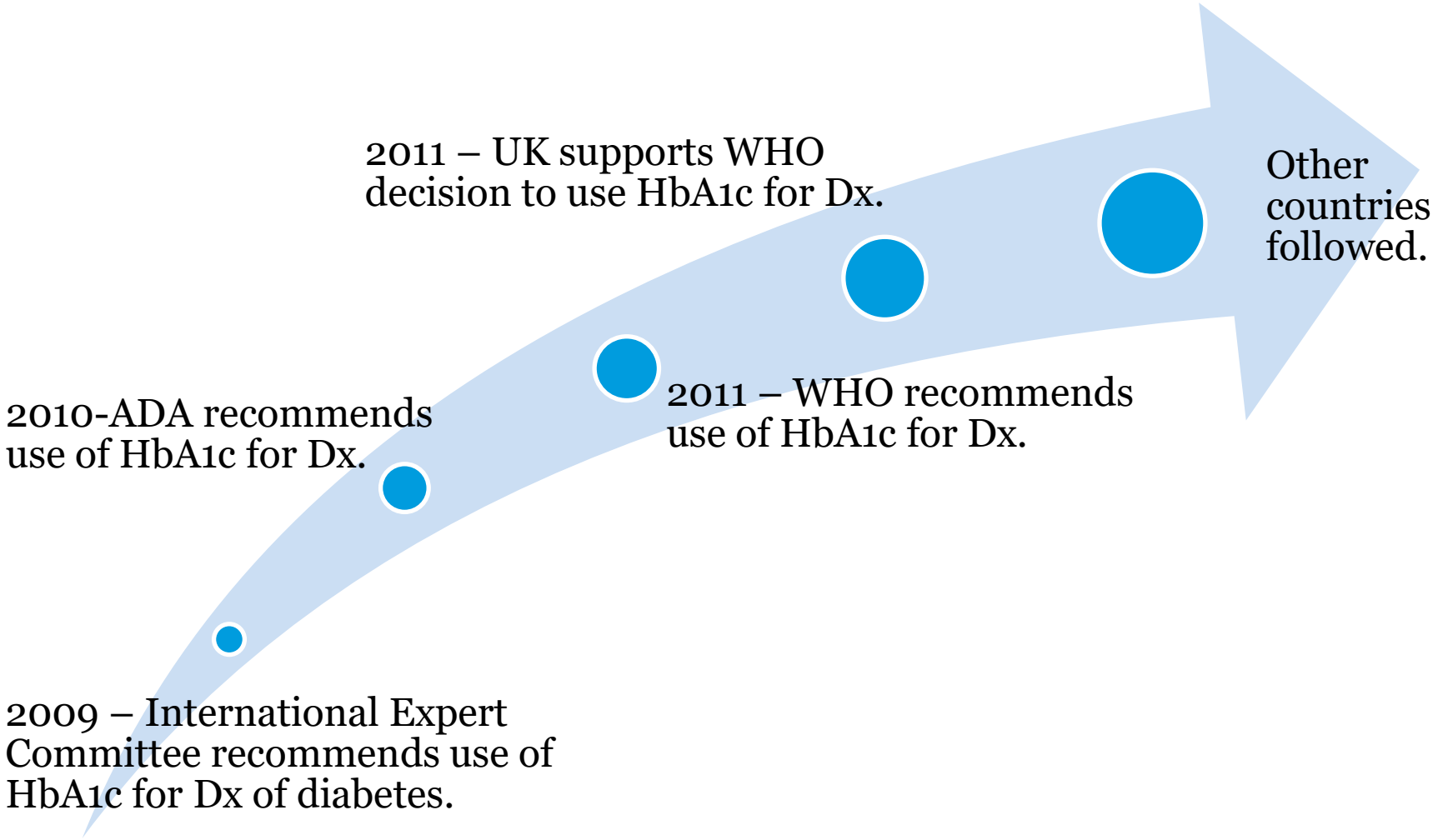
Relationship Between Glycemia and Complications



DCCT – Diabetes Control and Complications Trial
UKPDS – U.K. Prospective Diabetes Study

DCCT Research Group, Diabetes 1998,45:1289-98.
Stratton, IM, Adler AJ, Neil HA, et al. BMJ 2000;321:405-12.

HbA1c Recommended for Diabetes Diagnosis



Advantages of HbA1c for Diagnosis

- Fasting not required, can be measured any time of day
- Low biological variability
- WB sample stable in vial
- Standardized
- HbA1c measurements already used for monitoring

Issues with HbA1c Testing

The HbA1c test is an indirect measure of average glycemia and, as such, is subject to limitations.

HbA1c measurement variability.

- Variability is less on an intraindividual basis than that of blood glucose measurements,
- Clinicians should exercise judgment when using HbA1c as the sole basis for assessing glycemic control, particularly if result is near threshold that indicates a change in medication therapy

Conditions that affect red blood cell turnover may result in discrepancies between the HbA1c result and the patient's true mean glycemia.

- hemolytic and other anemias, glucose-6-phosphate dehydrogenase deficiency, recent blood transfusion, use of drugs that stimulate erythropoiesis, end-stage kidney disease, and pregnancy

Issues with HbA1c (continued)

Hemoglobin variants must be considered, particularly when the HbA1c result does not correlate with the patient's SMBG levels.

- Most assays in use in the U.S. are accurate in individuals heterozygous for the most common variants (www.ngsp.org/interf .asp).

HbA1c does not provide a measure of glycemic variability or hypoglycemia.

- For patients prone to glycemic variability, especially patients with type 1 diabetes or type 2 diabetes with severe insulin deficiency, glycemic control is best evaluated by the combination of results from SMBG or CGM and HbA1c.
- HbA1c may also inform the accuracy of the patient's meter (or the patient's reported SMBG results) and the adequacy of the SMBG testing schedule.

2021 ADA HbA1c Recommendations

To avoid misdiagnosis or missed diagnosis, the HbA1c test should be performed using a method certified by the NGSP and standardized to the DCCT assay.

Marked discordance between measured HbA1c and plasma glucose should raise the possibility of HbA1c interferences due to hemoglobin variants and consideration of using an assay without interference or plasma blood glucose criteria to diagnose diabetes.

In conditions associated with an altered relationship between HbA1c and glycemia, only plasma blood glucose criteria should be used to diagnose diabetes.

Plasma blood glucose rather than HbA1c should be used to diagnose the acute onset of type 1 diabetes in individuals with symptoms of hyperglycemia

Unchanged since 2019

FDA Approval of HbA1c methods (Monitoring)

Approved by 510(k) process as "substantially equivalent" to a legally marketed (predicate) device

Indicated to monitor long-term glucose control in individuals with diabetes mellitus

Not indicated to diagnose diabetes or prediabetes

FDA Special Controls for a Diagnostic Claim

Traceability

- Device must be certified annually

Premarket notification submission must include performance testing to evaluate precision, accuracy, linearity and interference

- Method must have little or no interference from common Hb variants.
- Level of HbF interference must be indicated

HbA1c methods FDA approved for Dx of Diabetes (2021)

*"Hemoglobin A1c measurements are used as an **aid in the diagnosis of diabetes** mellitus, as an aid to **identify patients who may be at risk** for developing diabetes mellitus, and for the **monitoring** of long-term blood glucose control in individuals with diabetes mellitus."*

- Abbott HbA1c on the ARCHITECTc 4000, c 8000 (enzymatic)
- Abbott Afinion Dx (POCT)(borate affinity)
- Abbott Allinity C
- Arkray Adams A1c HA-8189V (HPLC)
- Bio-Rad D-10, D-100 HbA1c
- Bio-Rad V II TURBO HbA1c Kit – 2.0
- Ortho-Clinical VITROS HbA1c
- Roche Cobas Integra 800 (turbidmetric inhibition)
- Roche COBAS C 501, C513Tina quant Gen.3
- Sekisui Diagnosis HbA1c Assay (enzymatic)
- Tosoh G8

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/search.cfm (last accessed 7/21/2021)

HbA1c Analytical Criteria

NGSP Certification Criteria

Certification Type	Certification Criteria
Manufacturer	36 of 40 results within ± 5%
Level I Lab	37 of 40 results within ± 5%
Level II Lab	36 of 40 results within ± 5%

CAP Criterion

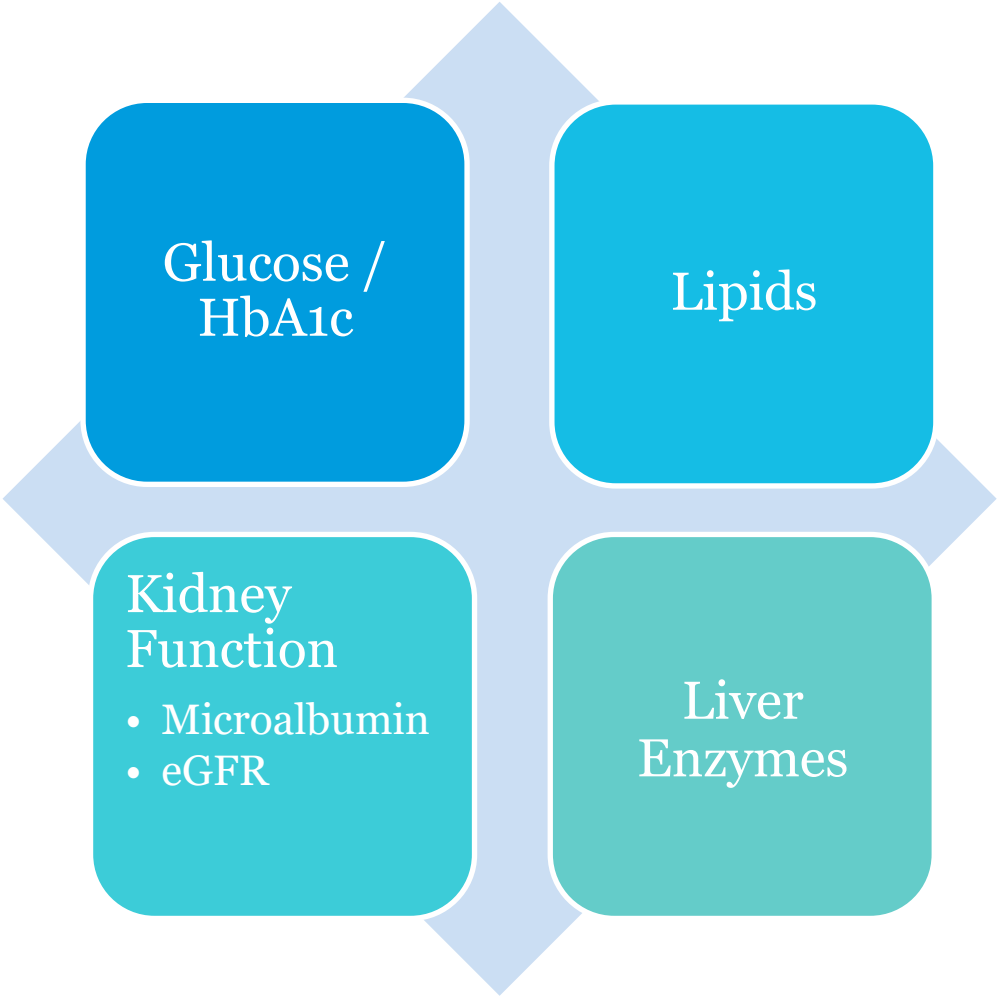
CAP GH HbA1c Survey EQA Acceptable Limits	Target ± 5%

Advantages of POC Testing

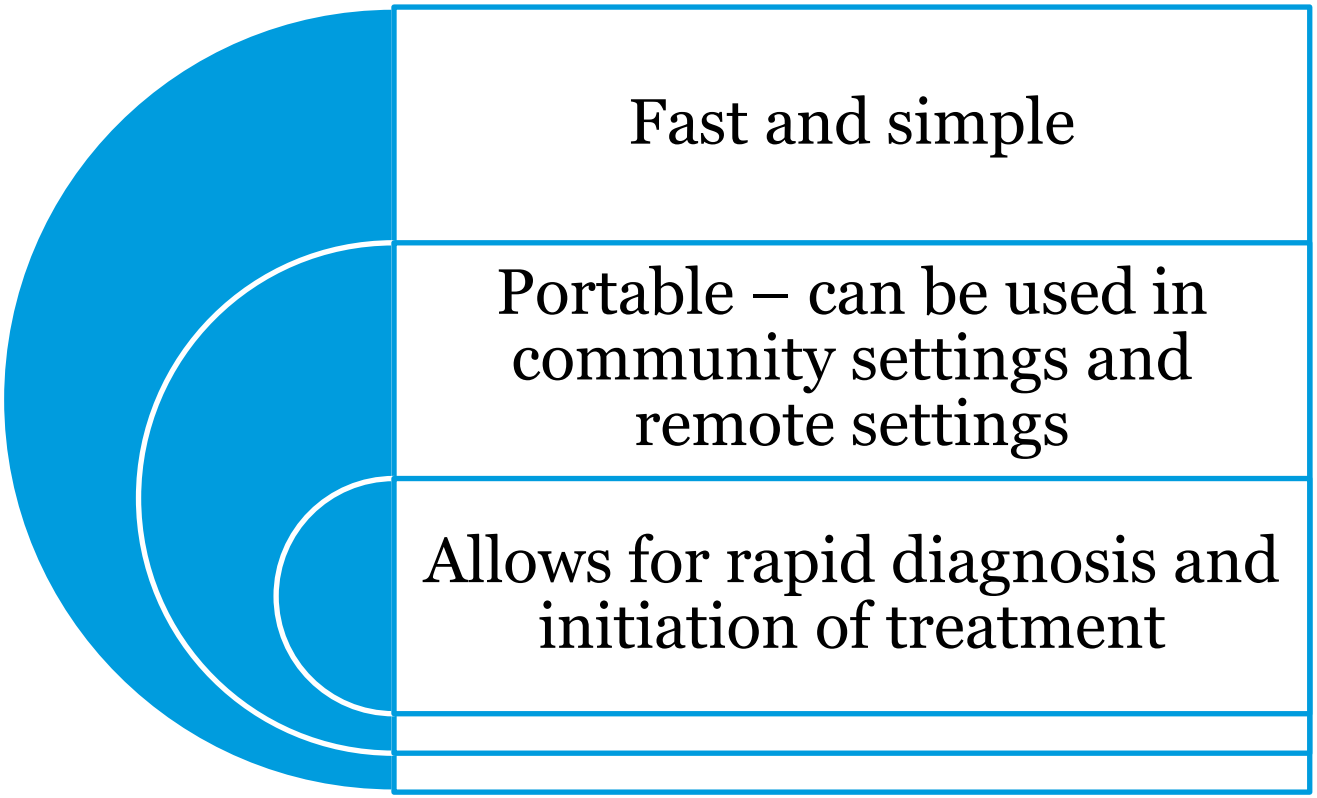
Point-of-Care Testing (POCT)

Medical diagnostic testing at or near the point of care - that is, at the time and place of patient care.

POCT in Diabetes Management



Advantages of POC Testing



ADA recommendations regarding POC HbA1c testing

2006 – present: Point-of-care testing for HbA1c provides the opportunity for more timely treatment changes.

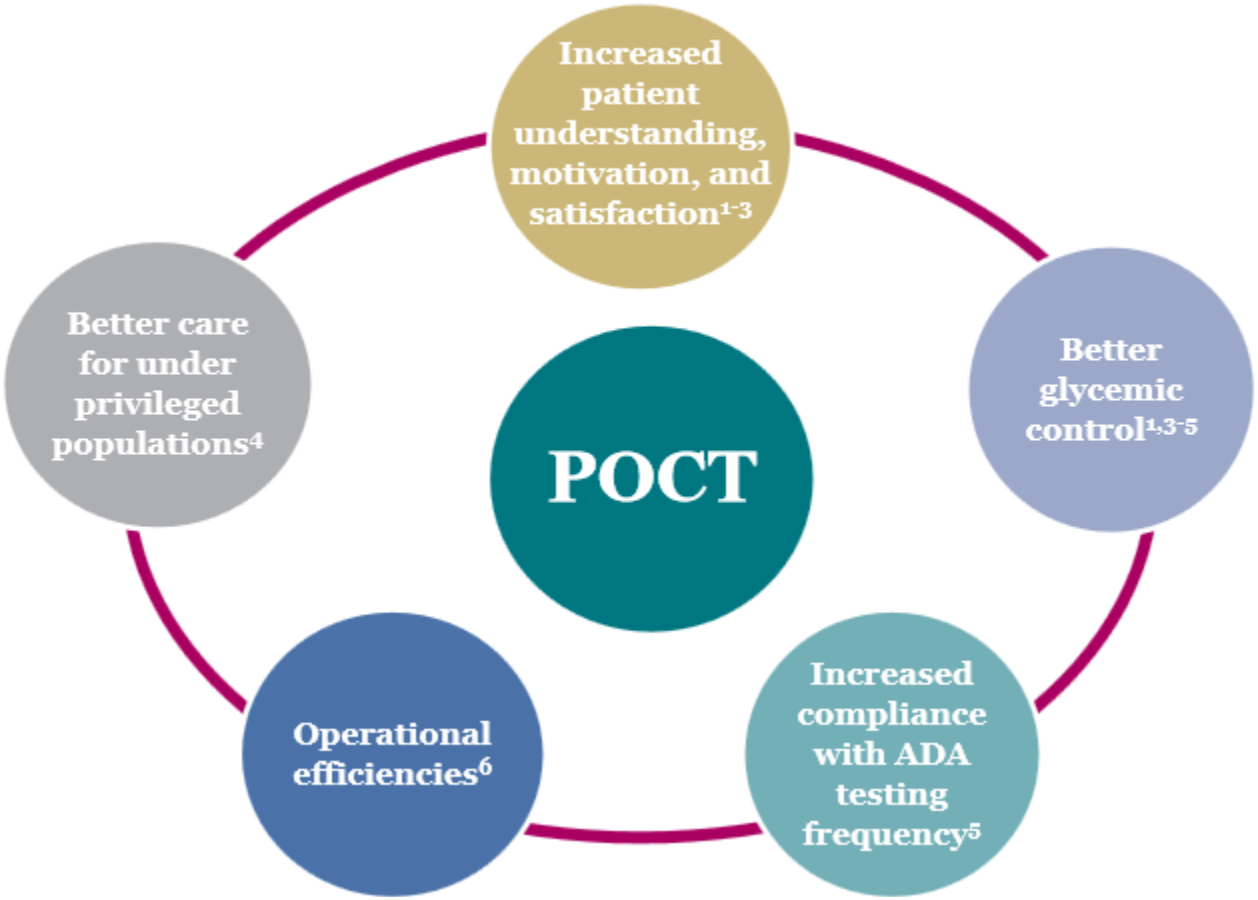
2011-2014: Point-of-care HbA1c assays are not sufficiently accurate at this time to use for diagnostic purposes.

2013-2016: "…proficiency testing is not mandated for performing the test, so use of POC assays for diangositc purposes may be problematic (and is not recommended).

2019 Point-of-care assays approved for diagnostic purposes should only be considered in settings licensed to perform moderate-to-high complexity tests.

Can POCT Help?

Advantages Observed With POCT HbA1c vs. Lab for Monitoring Diabetes



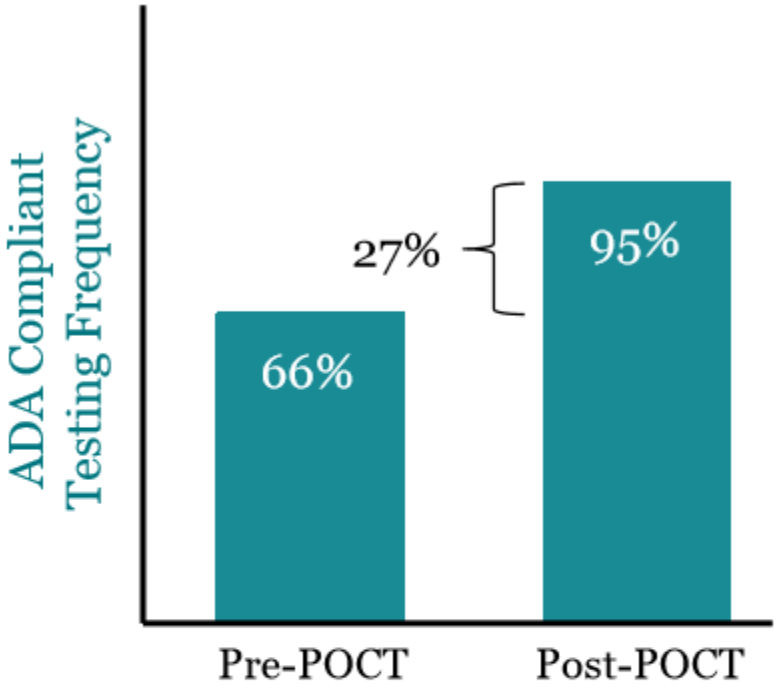
[1]Shepard MD. *Clin Biochem Rev*. 2006;27(3):161-70.
[2]Laurence CO, Gialamas A, Bubner T. *Br J Gen Pract*. 2010;60(572):e98-e104.
[3]Miller CD, Barnes CS, Phillips LS, et al. *Diabetes Care*. 2003;26(4):1158-63.
[4]Rust G, Gailor M, Daniels E, et al. Int J Healthcare Qual Assurance. 2008;21(3):325-35.
[5]Egbunike V, Gerard S. *Diabetes Educator*. 2013;39:66-73.
[6]Crocker JB, Lee-Lewandrowski E, Lewandroski N, et al. *Am J Clin Pathol*. 2014;142:640-6.

Improved Glycemic Control, Appropriate Management & Operational Effectiveness with HbA1c POC Testing

Study	Findings
Rust et al.[1]	• HbA1c testing frequency increased post-POCT implementation • HbA1c levels decreased post-POCT implementation • Interventions increased significantly in post-POCT implementation period
Thaler et al.[2]	• POCT HbA1c resulted in more appropriate management
Grieve et al.[3]	• POCT HbA1c resulted in more appropriate management • Patients were more satisfied with POCT HbA1c compared to conventional testing • Patients were more likely to remember HbA1c levels if provided from POCT • HbA1c levels were lower in POCT group than conventional lab group • Patients tested with POCT had lower costs and number of visits
Shephard et al.[4]	• HbA1c contributed positively to patient care, improved the doctor-patient relationship and improved compliance and self-motivation • Post-POCT implementation — HbA1c levels decreased, there were fewer patients with poor control and a higher number achieved target HbA1c levels
Egbunike et al.[5]	• POCT HbA1c improved operational efficiencies • HbA1c testing frequency increased post-POCT implementation • HbA1c levels decreased post-POCT implementation.
Miller et al.[6]	• POCT HbA1c resulted in more appropriate management • HbA1c levels decreased with POCT

Data sourced from:
[1]Rust G, Gailor M, Daniels E. *Int J Health Care Qual Assur*. 2008;21:325-35.
[2]Thaler LM, Dunbar VG, Ziemer DC, et al. *Diabetes Care*. 1999;22:1415-21.
[3]Grieve R, Beech R, Vincent J, Mazurkiewicz. *Health Technol Assess*. 1999;3:1281-357.
[4]Shephard MDS. *Health Technol Assess*. 1999;3:1281-357.
[5]Egbunike V, Gerard S. *Diabetes Educator*. 2013;39:66-73.
[6]Miller CD, Barnes CS, Phillips LS, et al. *Diabetes Care*. 2003;26(4):1158-63.

POCT Improved Testing Frequency Compliance & Reduced HbA1c



6 months

95% of patient charts had ADA compliant HbA1c testing with significant decreases in HbA1c levels ($P = 0.008$)

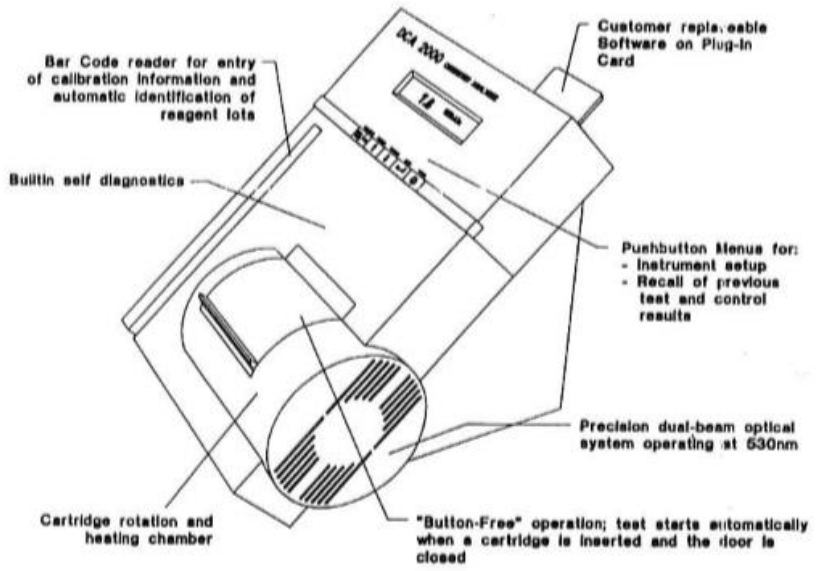
ADA-compliant testing frequency = decreased HbA1c levels.

Adapted from: Egbunike V, Gerard S. *Diabetes Educator*. 2013;39:66-73.

First POC HbA1c Method

Unitized Cartridge System for De-centralized Measurement of Hemoglobin A1c. McCloud, et al 1990

DEDICATED INSTRUMENT



CVs: 2.2-4.1%

“No interference by other hemoglobins”

“No interference by labile fraction”

FDA Cleared/NGSP-certified POC HbA1c Methods (July 2021)

Manufacturer	System	Methodology
Abbott Diagnostics	Afinion AS100, Afinion 2	Boronate affinity
EKF Diagnostics	Quo-Lab, Quo-Test	Boronate affinity
Green Cross Medis Corp	LabonaCheckA1c	Boronate affinity
OSANG Healthcare	Hemocue HbA1c 501, Clover A1c	Boronate affinity
PTS Diagnostics	A1CNow Self Check, A1C Now +	Immunoassay
Roche Diagnostics	Cobas b 101 HbA1c	Immunoassay
Sakae Corp	Medidas HbA1c on A1c GEAR	Immunoassay
SD Biosensor	SD A1cCare	Immunoassay
Siemens Healthcare Diag	DCA Vantage	Immunoassay
Skyla Corp	Skyla Hi Analyzer	Immunoassay
TaiDoc	FORA A1c	Immunoassay

More than 30 NGSP-certified POC HbA1c methods are not FDA cleared

Concerns regarding POC HbA1c

Concerns regarding POC HbA1c

Imprecision/Lack of Reproducibility for some methods

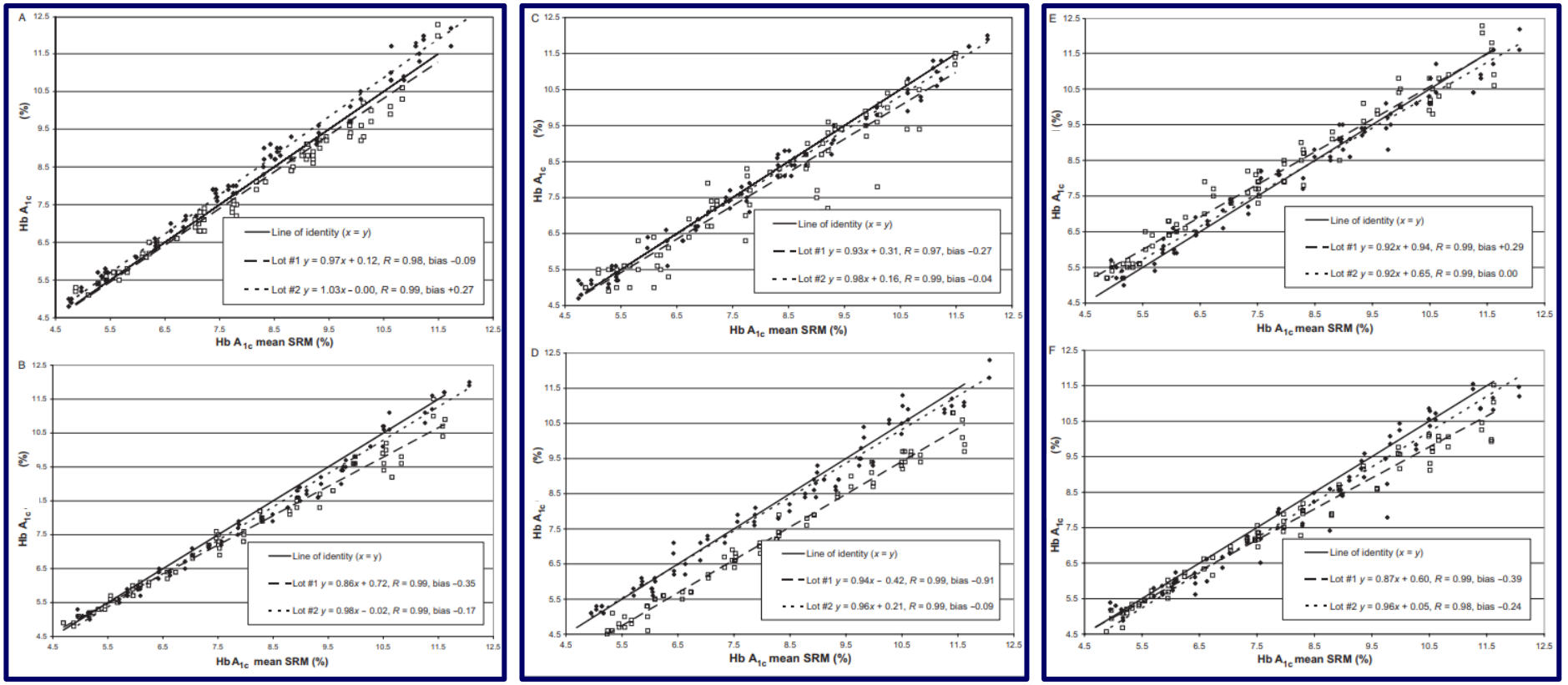
Lot-to-lot variation in reagents/calibration with some methods

PT is not required for waived testing and there is a lack of PT data for assessing performance in this setting.

Concerns regarding POC HbA1c

Authors	Year	comments
St John, et al	2005	Only 1 of 4 POC devices recommended for use outside laboratory
Lenters-Westra, et al	2009	high variability and lot-dependent (2 POC methods)
Lenters-Westra, et al	2010	6 of 8 POC methods do NOT meet accepted performance criteria; lot-to-lot variability
Lenters-Westra, et al	2014	3 of 7 POC methods do NOT meet performance criteria
Dupuy, et al	2014	lot-to-lot variability for one POC method

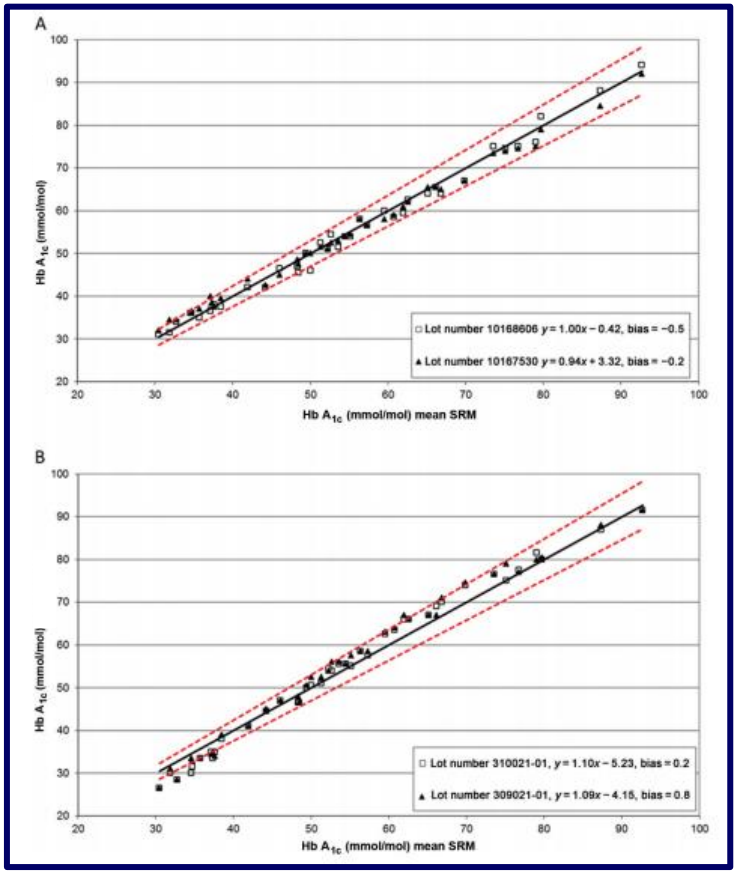
Research Studies:
Lot-to-lot Variability

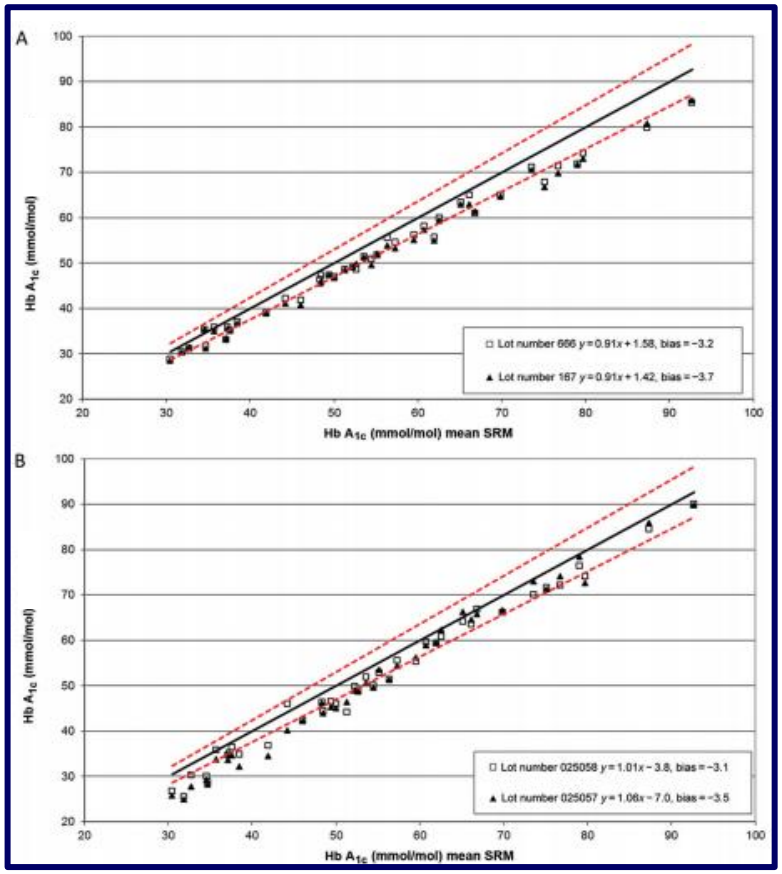


All methods showed significant differences between lots

Lenters-Westra E, et al. Clin Chem. 2010;56:44-52

Research Studies: Accuracy





Some methods (4) were accurate compared to NGSP/IFCC while others (3) showed poor correlation

Lenters-Westra E, et al. Clin Chem. 2014;60:1062-72.

Multicenter assessment of a hemoglobin A1c point-of-care device for diagnosis of diabetes mellitus

Philip M. Sobolesky[a,*], Breland E. Smith[b], Amy K. Saenger[c], Karen Schulz[d], Fred S. Apple[c,d], Mitchell G. Scott[e], Alan H.B. Wu[f], Randie R. Little[g], Robert L. Fitzgerald[b]

Method	Mean (%HbA1c)	N	# of Sites	Between Day RMS CV	Between Run RMS CV	Within Run RMS CV	Total CV
Bio-Rad Variant II	5.4	136	2	1.68%	1.39%	1.02%	2.39%
	6.6	140	2	1.61%	0.80%	0.60%	1.87%
	11.5	140	2	0.59%	0.18%	0.56%	0.83%
Roche Tina-quant	5.2	152	2	0.38%	0.48%	1.81%	1.89%
	6.6	152	2	0.00%	0.43%	1.23%	1.28%
	9.2	152	2	0.32%	0.80%	1.30%	1.55%
Siemens Dimension Vista	5.1	72	1	1.27%	0.00%	3.23%	3.23%
	6.7	72	1	1.22%	0.82%	1.39%	1.96%
	8.5	72	1	0.77%	0.00%	1.27%	1.44%
Affinion AS100	5.3	359	5	0.55%	0.47%	1.34%	1.46%
	6.5	363	5	0.31%	0.32%	1.24%	1.35%
	9.8	368	5	0.31%	0.13%	0.80%	0.85%

https://doi.org/10.1016/j.clinbiochem.2018.09.007.

Assessing Performance of POC Methods

NGSP certification reflects performance of the method under ideal conditions in the hands of the manufacturer.

Performance in the hands of end-users can only be assessed by EQA (PT) surveys, e.g., CAP, BUT most POC test users (in waived settings) are not required to perform PT.

Limited EQA Performance Data for POC Methods

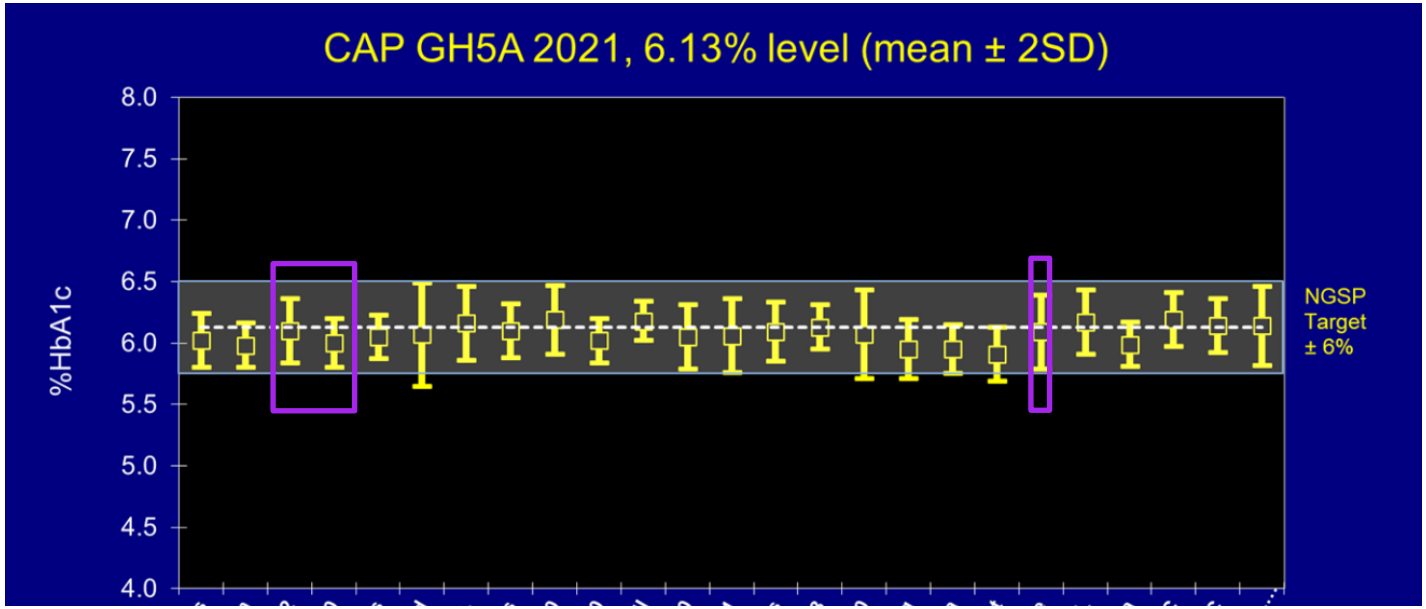
CAP Survey Data

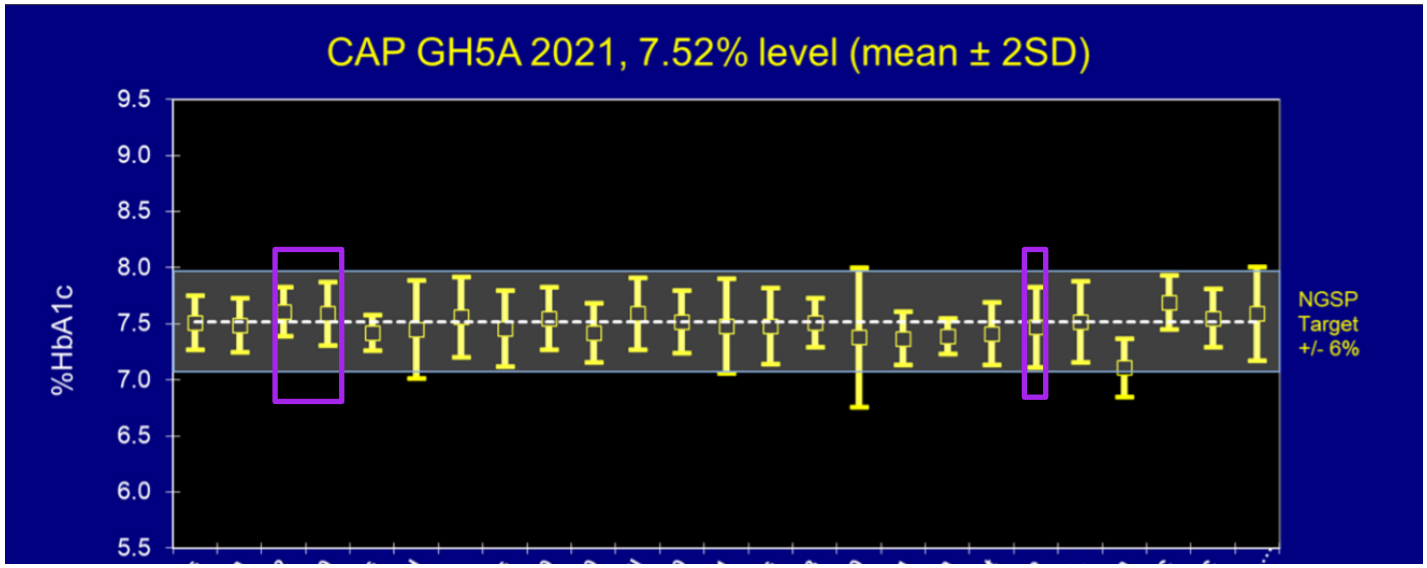
		2021 GH5-04			2021 GH5-03		
NGSP %HbA1c Reference		6.13			9.39		
	No Labs	Mean % HbA1c	Mean bias	% CV	Mean % HbA1c	Mean bias	% CV
POCT Method 1	100	6.10	-0.03	2.1	9.30	-0.09	2.0
POCT Method 2	105	6.00	-0.13	1.7	9.21	-0.18	1.9
POCT Method 3	321	6.09	-0.04	2.5	9.46	+0.07	3.1

However

		2012 GH2-01			2012 GH2-02		
NGSP %HbA1c Reference		5.6			9.4		
	No Labs	Mean % HbA1c	Mean bias	% CV	Mean % HbA1c	Mean bias	% CV
POCT Method 4	28	5.14	-0.46	3.8	8.49	-0.91	6.3
POCT Method 5	10	5.41	-0.19	7.0	9.01	-0.39	3.0

Some POCT Methods Perform as well as Lab Based Methods





Performance of HbA1c POCT Instruments in GP Offices

6 years of Norwegian NOKLUS EQA data

1288 GP offices; 52 hospital laboratories

Both the DCA and Afinion showed acceptable performance in pediatric clinic settings in each EQA survey.

- Quality Specifications, trueness ≤ 6.0%, inaccuracy ≤2.0% at 2 levels in each EQA survey

Slovik UO, Roraas T, Christensen NG, Sandberg S. Clin Chem. 2013;59:1790-801.

Summary

Pros	Cons
Services need for a low cost, rapid test	Repeat testing required for diagnosis (slows speed) Is the cost really much lower for the patient?
Small test volume from fingerstick	Small test volume possible for some lab testing (capillary collection vials)
Some methods are accurate & precise	Some methods are not accurate nor precise and have lot-to-lot variability
PT for some methods shows good performance (same level as lab testing)	Limited PT data, mostly from non-waived settings.

Benefits of POC Testing

Operational Benefits

- Reduced staff time
- Fewer orders to central lab
- Fewer patients lost to follow-up

Clinical Benefits

- Increased patient understanding
- Faster implementation of medication modification
- Lower HbA1c levels

Economic Benefits

- Fewer phone calls
- Less appointments
- Increased patient satisfaction

POCT improves diabetes management in a world with more diabetes

Conclusions

Increased Quality

- Improved clinical outcomes including lowered HbA1c have been achieved with point-of-care testing

Operational Efficiency

- Rapid tests allow for lean processes and reduce staff time spent in chasing lab results and relaying them to patients

Patient Satisfaction

- The teachable moment not only leads to better patient understanding but can strengthen the relationship between patients and provider

Lian J, Lang Y. *Curr Med Res Opin*. 2014;30(11):2233-40.
Crocker JB, Lee-Lewandrowski E, Lewandroski N, et al. *Am J Clin Pathol*. 2014;142:640-6.
Point-of-Care Testing in General Practice Final Report Jan 2009.

Questions?

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