Pitfalls with HbA1c Measurements Performed on POC versus Laboratory-based Assays

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UNIVERSITY

Grady

Learning Objectives

1. Provide clinical overview of hemoglobin A1c
2. Summarize current hemoglobin A1c methodologies and understand their limitations
3. Compare hemoglobin A1c measurements at point-of-care to those in a central laboratory

No conflict of interest, nothing to disclose

Request from the Diabetic Clinic

Situation: Diabetic clinic is requesting POC A1c instrument just a floor below our core lab where we have HPLC based A1c instruments

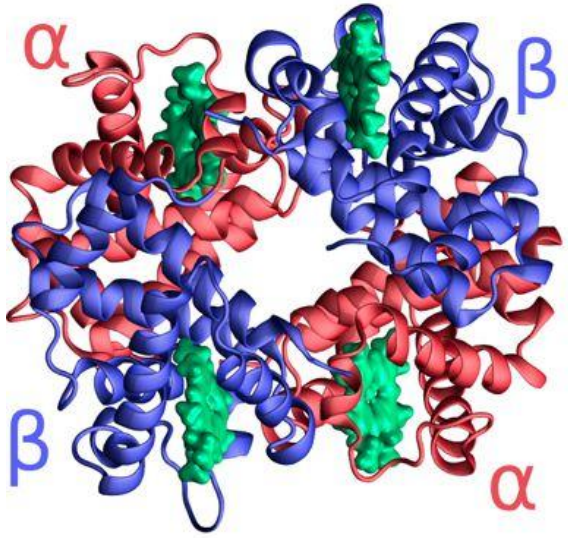
Background: Need for a faster TAT

Action: Investigate the limitations of POC A1c instruments

Recommendation: ….*tbd*

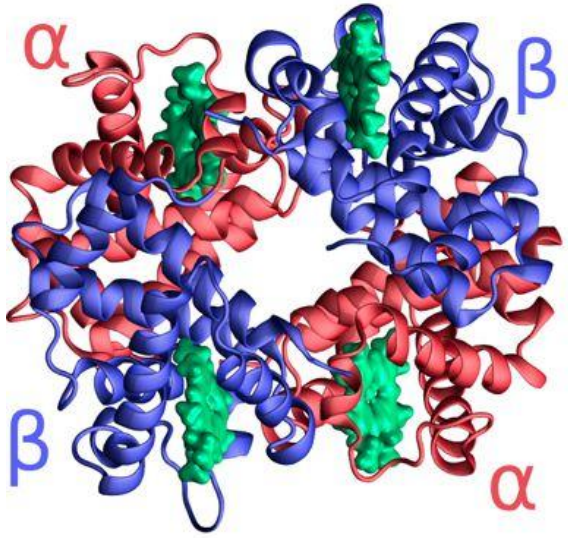
HbA1c : the blood test with a memory

- Adult Hb: 97% Hb A ($\alpha_2\beta_2$), 2.5% Hb A_2 ($\alpha_2\delta_2$) and 0.5% Hb F ($\alpha_2\gamma_2$)
  - Over 1000 Hemoglobin variants (S,C,D,E)

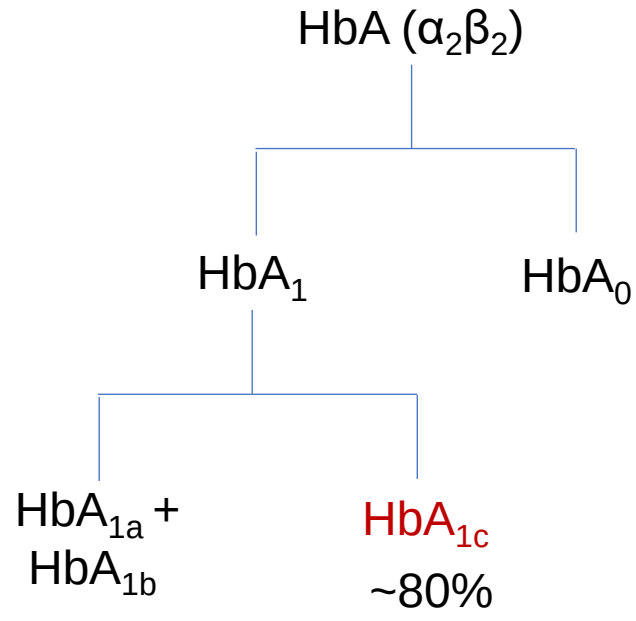


HbA ($\alpha_2\beta_2$)

HbA1c : the blood test with a memory



- Adult Hb: 97% Hb A ($\alpha_2\beta_2$), 2.5% Hb A_2 ($\alpha_2\delta_2$) and 0.5% Hb F ($\alpha_2\gamma_2$)
  - Over 1000 Hemoglobin variants (S,C,D,E)
- HbA1: series of glycated variants
- HbA1c: nonenzymatic attachment of glucose to N terminal valine of the beta chain
- HbA1c corresponds to the average blood glucose for the previous of 3 months



Criteria for the diagnosis of diabetes per ADA

Fasting Plasma Glucose*

- FPG≥ 126 mg/dL
- No caloric intake 8 hr
- Prediabetes 100-125 mg/dL

OR

2-h plasma glucose*

- 2hPG≥ 200 mg/dL during OGTT
- 75 g glucose load
- Prediabetes 140-199 mg/dL

OR

HbA1c*

- HbA_{1c} ≥ 6.5%
- **NGSP certified method**
- **Standardized to DCCT assay**
- Prediabetes 5.7-6.4%

OR

Random plasma glucose

- RPG≥ 200 mg/dL with symptoms of hyperglycemia

Or

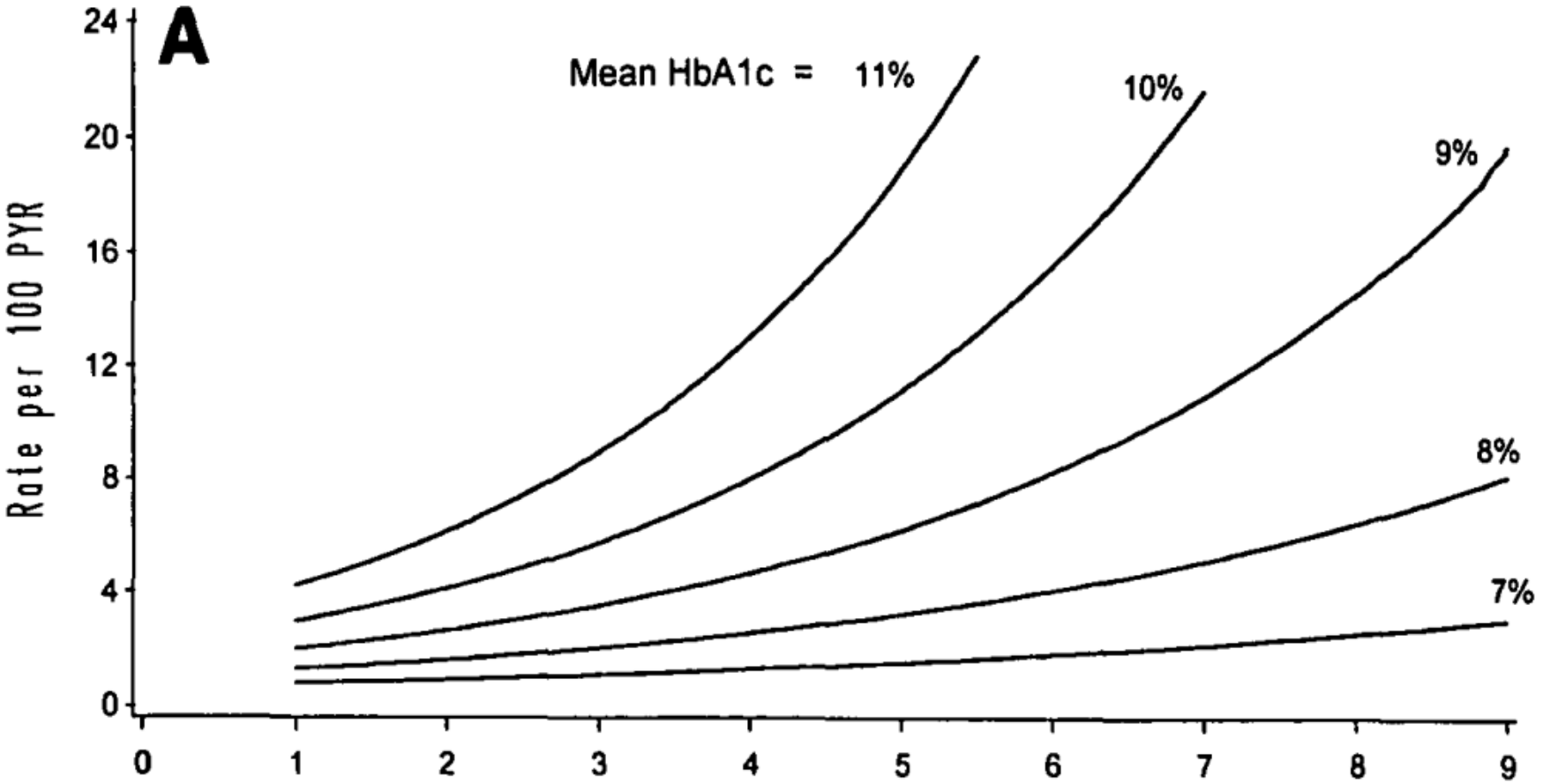
hyperglycemic crisis

*In the absence of unequivocal hyperglycemia, diagnosis requires repeat testing

ADA: American Diabetes Association
NGSP: National Glycohemoglobin Standardization Program
DCCT: Diabetes Control and Complication Trial

Diabetes control and complication trial 1983-1993

Risk of retinopathy progression as a function of A1C



DCCT Study Findings

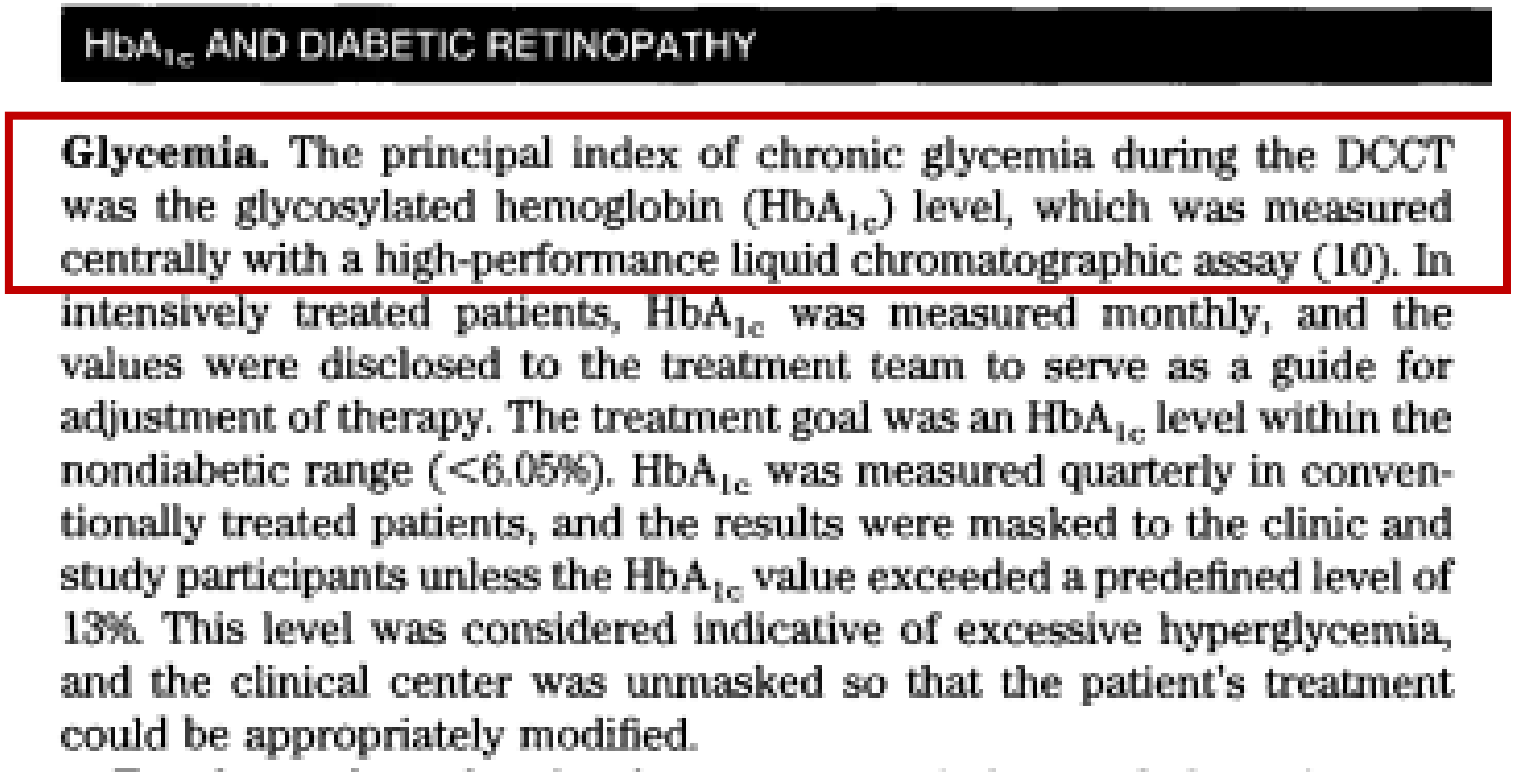
Intensive blood glucose control reduces risk of

- eye disease
  76% reduced risk
- kidney disease
  50% reduced risk
- nerve disease
  60% reduced risk

Treatment goal HbA1c <7% in most patients

Diabetes 44:968–983,1995

What A1C assay was used during DCCT?



HbA$_{1c}$ AND DIABETIC RETINOPATHY

Glycemia. The principal index of chronic glycemia during the DCCT was the glycosylated hemoglobin (HbA$_{1c}$) level, which was measured centrally with a high-performance liquid chromatographic assay (10). In intensively treated patients, HbA$_{1c}$ was measured monthly, and the values were disclosed to the treatment team to serve as a guide for adjustment of therapy. The treatment goal was an HbA$_{1c}$ level within the nondiabetic range (<6.05%). HbA$_{1c}$ was measured quarterly in conventionally treated patients, and the results were masked to the clinic and study participants unless the HbA$_{1c}$ value exceeded a predefined level of 13%. This level was considered indicative of excessive hyperglycemia, and the clinical center was unmasked so that the patient's treatment could be appropriately modified.

HPLC

NGSP manufacturer certification process

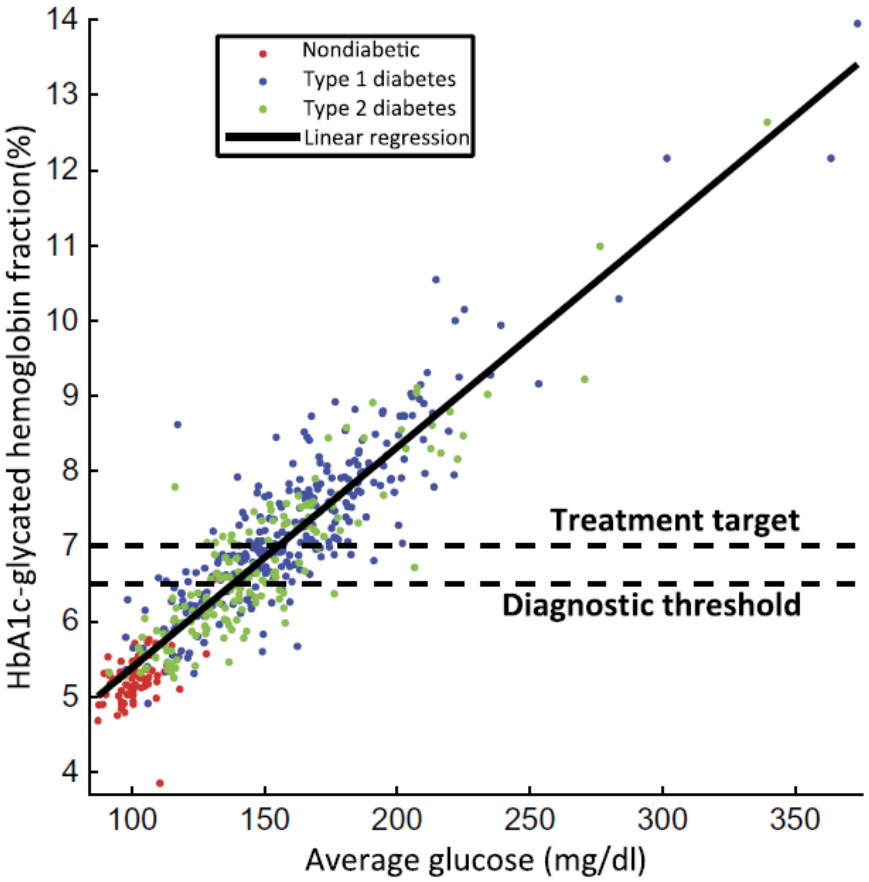
- 40 whole blood samples are compared with DCCT assay (HPLC)
- 36 of 40 single results must be within ± 5% from the manufacturer method to pass certification
- “Certification of traceability to the DCCT”
- Currently over 300 certified HbA1c methods are available *https://ngsp.org/certified.asp*

National Glycohemoglobin Standardization Program

Advantages of measuring HbA1c

- Not affected by fluctuations in blood glucose concentration
- No fasting is necessary
- Intraindividual variability is very low (<2% variation)
- Methods well standardized

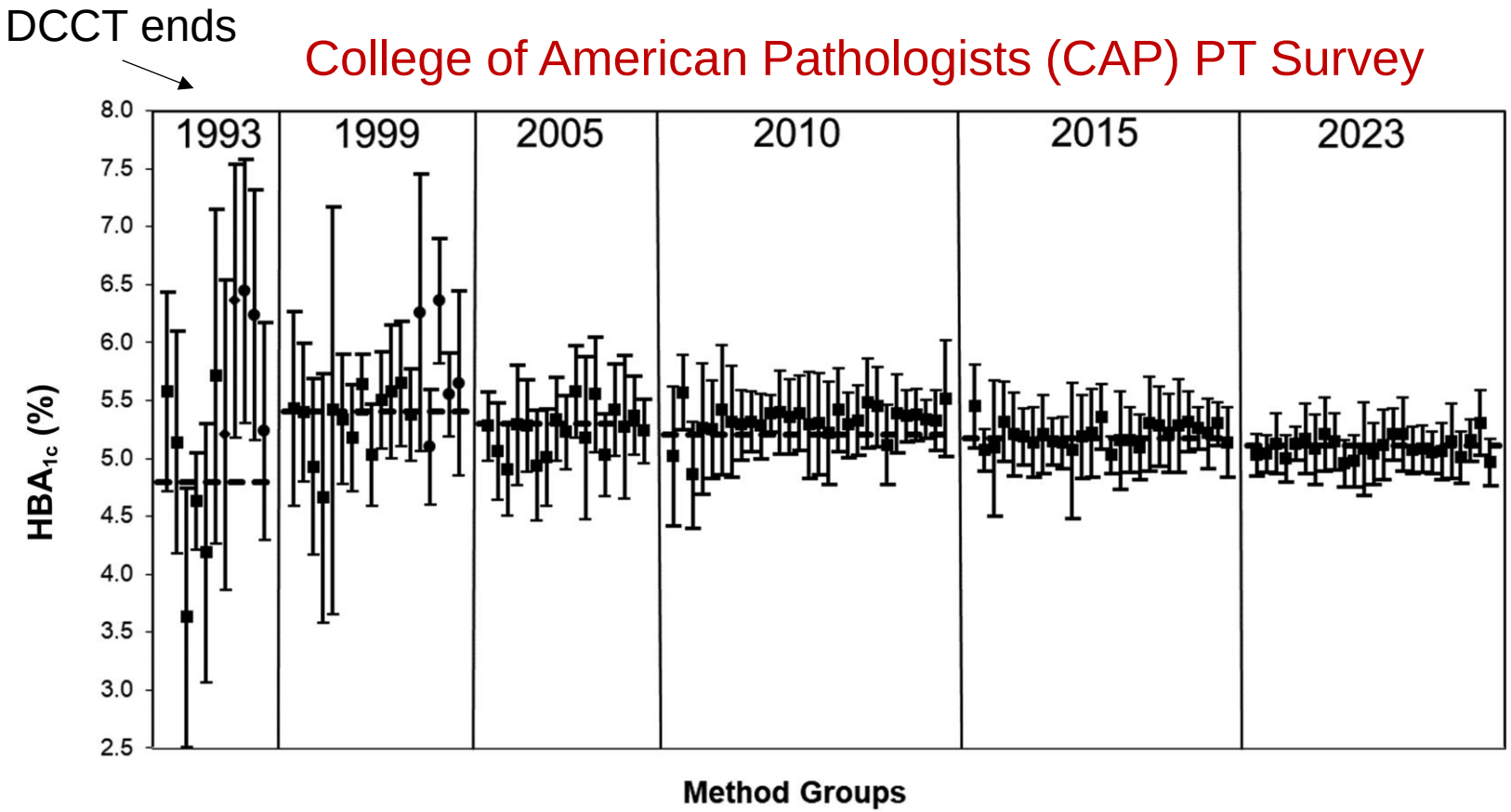
Linear relationship between AG and HbA_{1c}



Formula: 28.7 X A1C – 46.7 = eAG

Diabetes Care. 2008 Aug;31(8):1473–1478

Impact of the NGSP on HbA1c

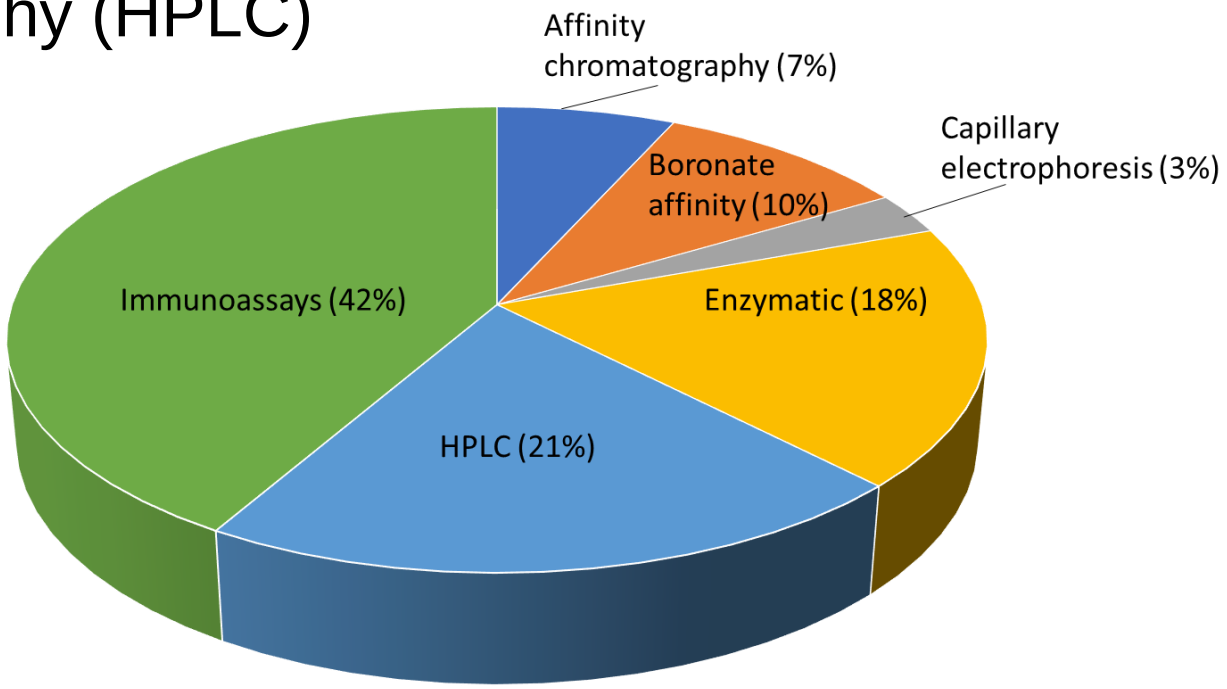


Diabetes Care. 2024;47(7):1104-1110. doi:10.2337/dci23-0040

American Diabetes Association®

How do we measure HbA1c ?

- Charge difference
  - High pressure liquid chromatography (HPLC)
  - Capillary electrophoresis
- Structure difference
  - Immunoassays
  - Boronate affinity
- Enzymatic assays
- Affinity chromatography



Adapted from the CAP 2024 GH-11 (n=2986 labs)

How do we measure HbA1c ?

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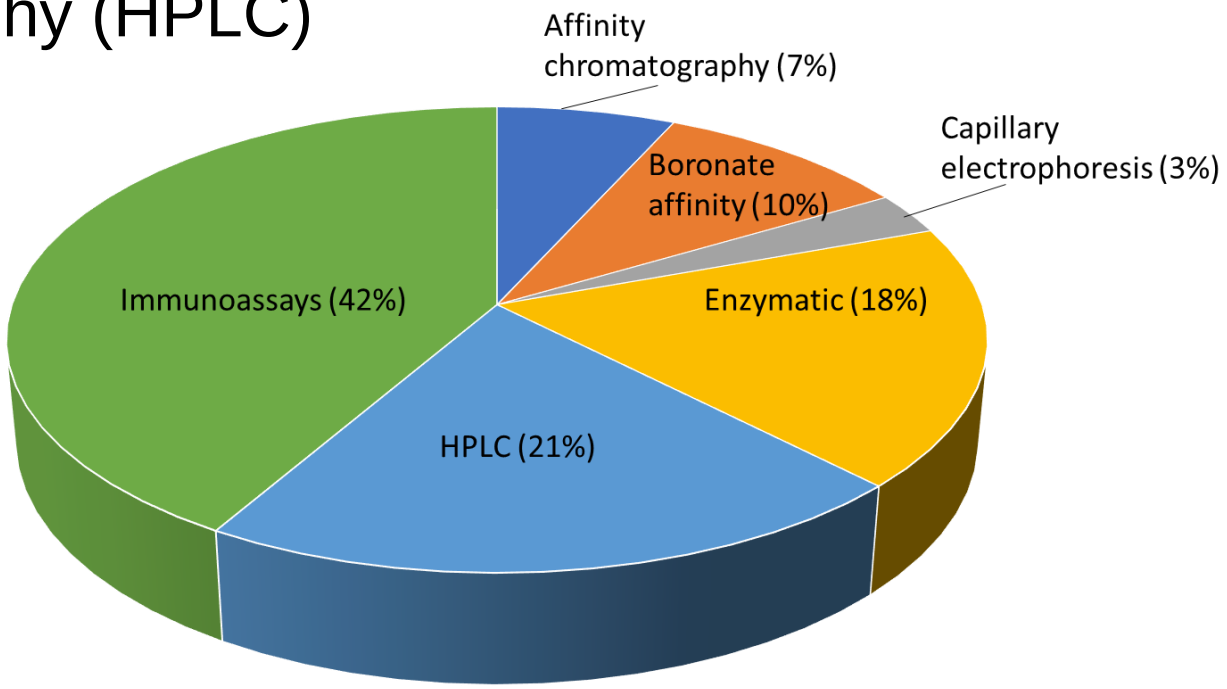
POC assays

- Enzymatic assays
- Affinity chromatography



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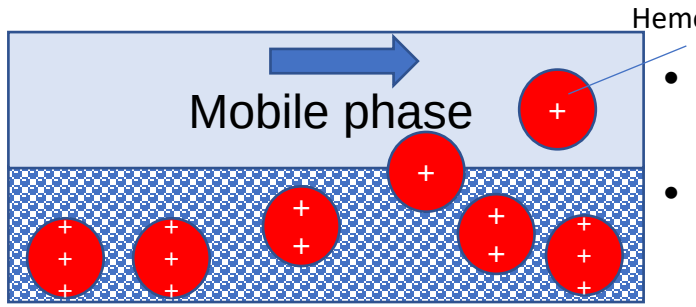
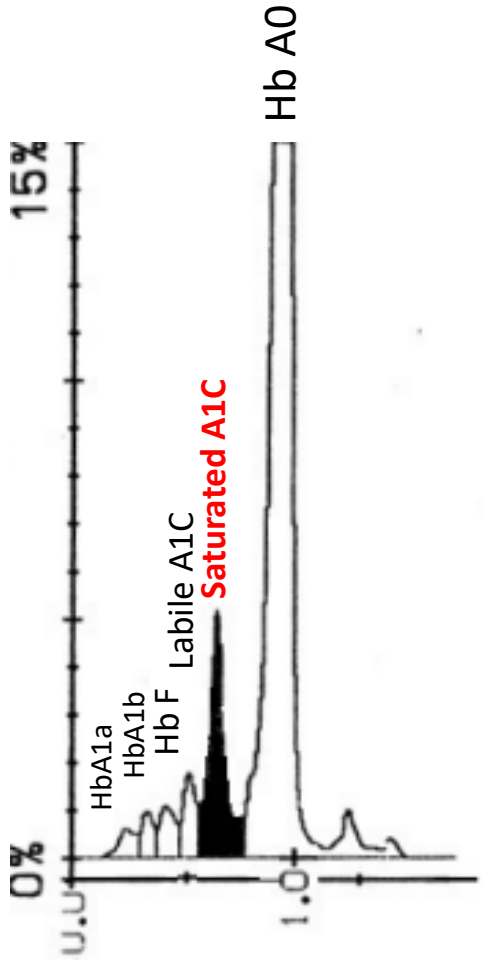
HPLC based HbA1c

- Assay based on charge difference
- Venous EDTA blood



Stationary phase negative charge

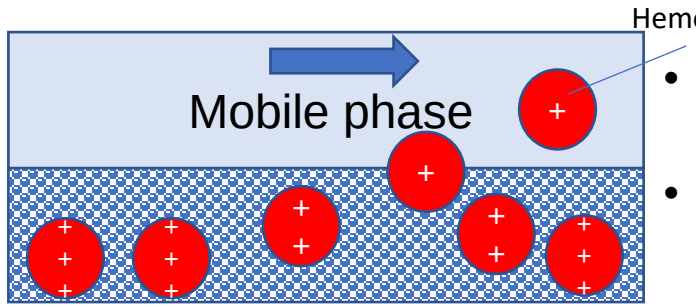
- Weakly charged Hbs elute first (A1a, A1b, HbF and A1c)
- Normal Hbs and abnormal elute next (Hb E, D, S and C)



Normal Chromatogram

HPLC based HbA1c

- Assay based on charge difference
- Venous EDTA blood
- Detects hemoglobin variant



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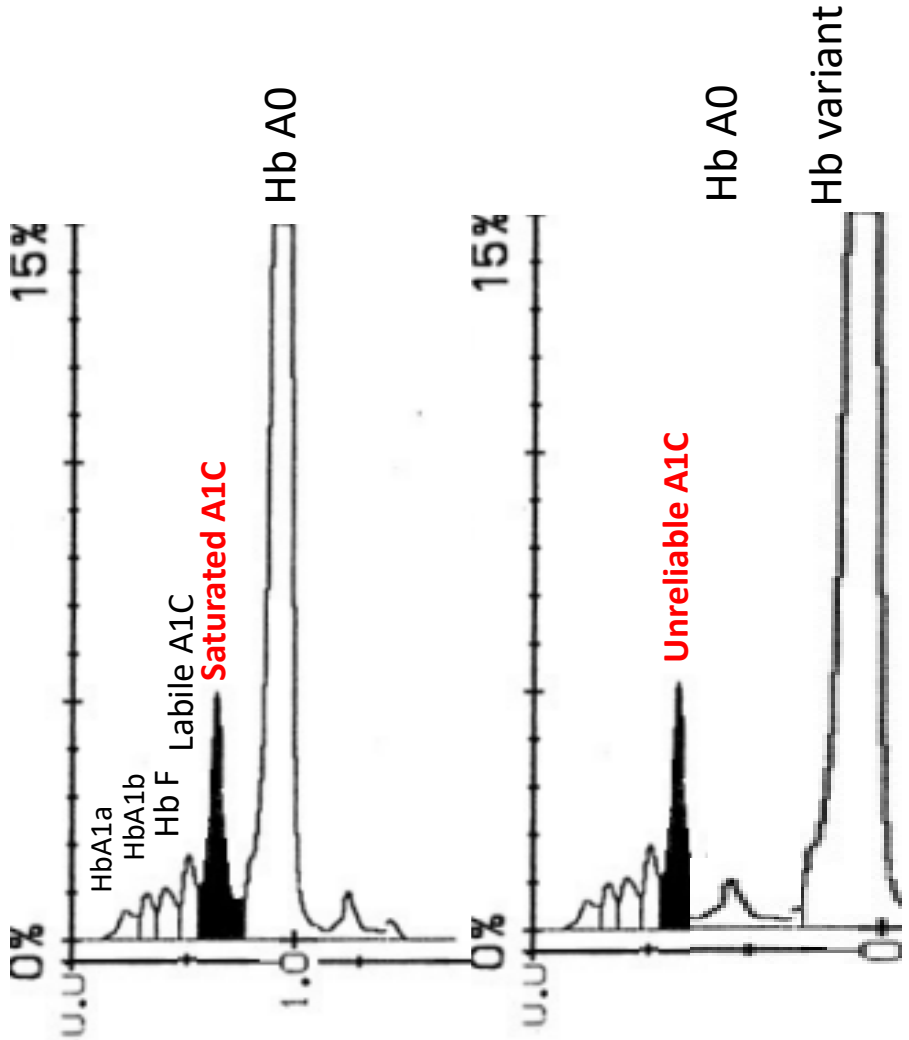
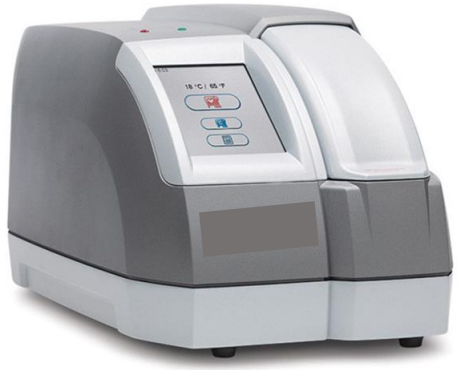


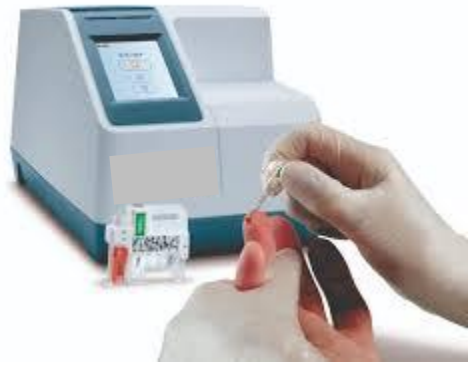
Normal Chromatogram

Variant Chromatogram

Point-Of-Care HbA1c assays - waived

- Charge difference
  - High pressure liquid chromatography (HPLC)
  - Capillary electrophoresis
- Structure difference
  - Immunoassays
  - Boronate affinity
- Enzymatic assays
- Affinity chromatography





https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/search.cfm

FDA database provides information on assay complexity

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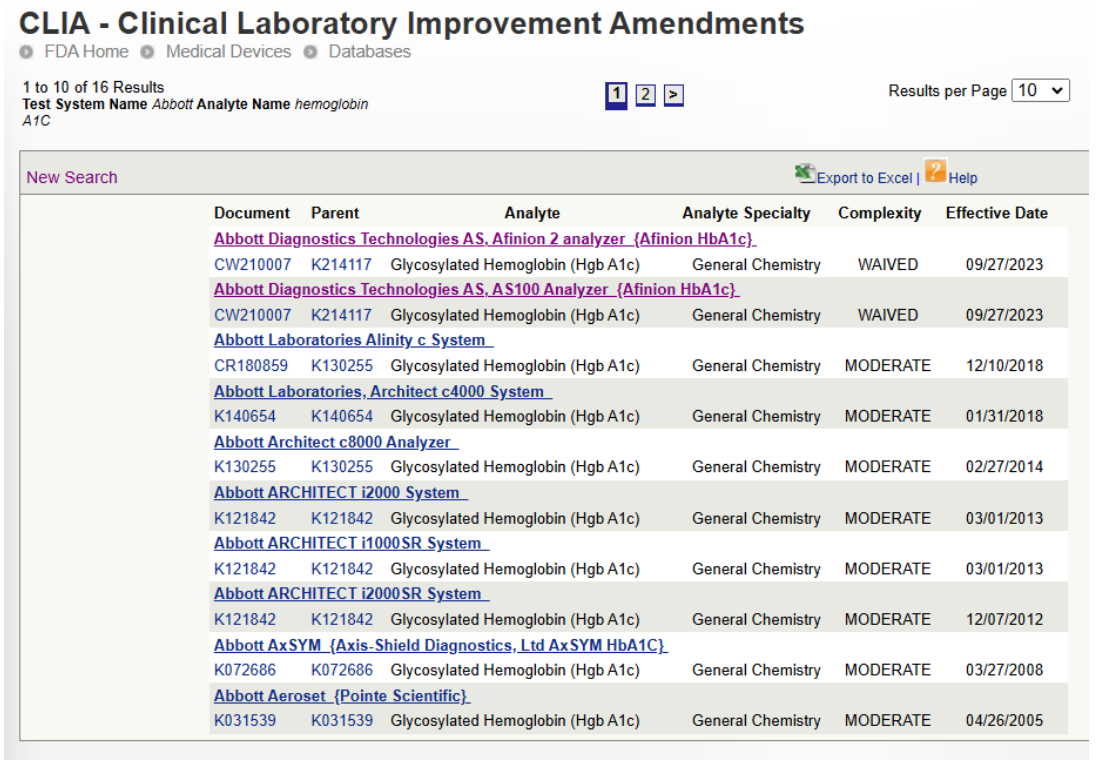
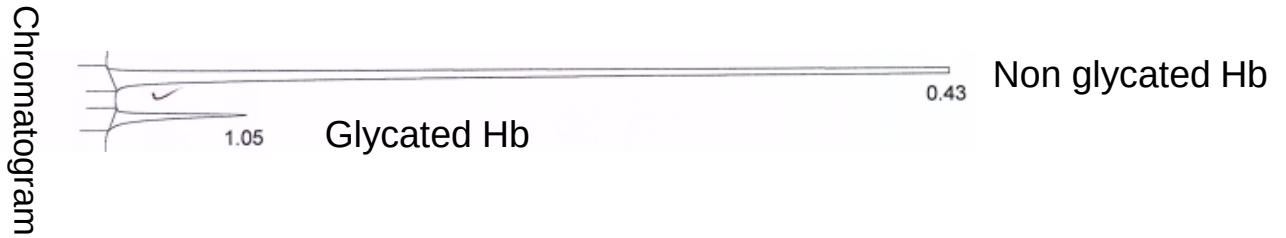
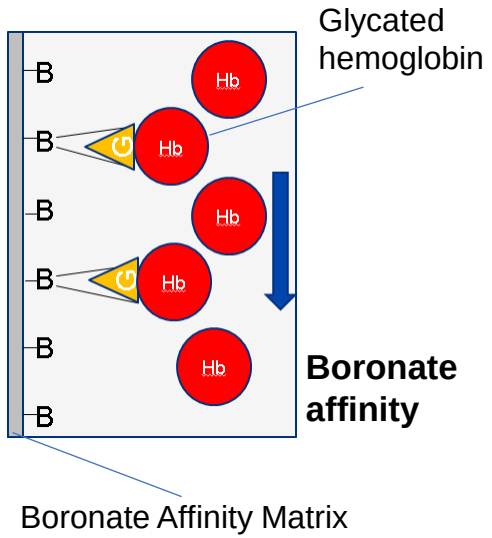


https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/search.cfm

Assays to measure HbA1c based on structure

- **Boronate affinity chromatography**
  - determines total glycated Hb (calculates HbA1c)
  - does not measure labile fractions
  - slightly overestimates A1C (binds A1a, A1b and 80% A1c)
  - unable to detect Hb variants





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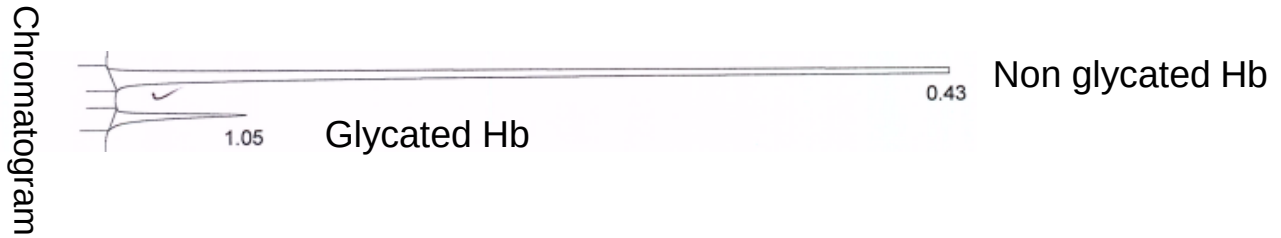
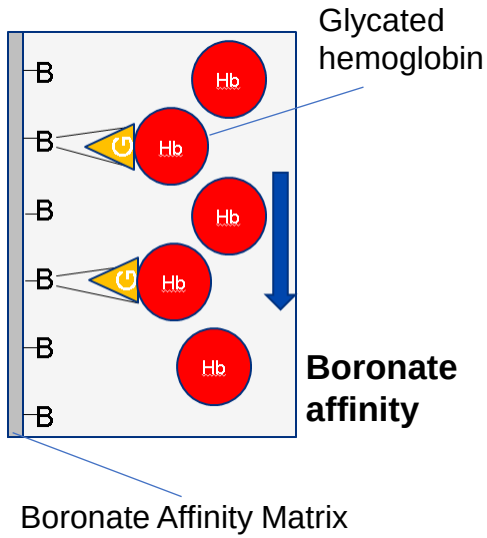
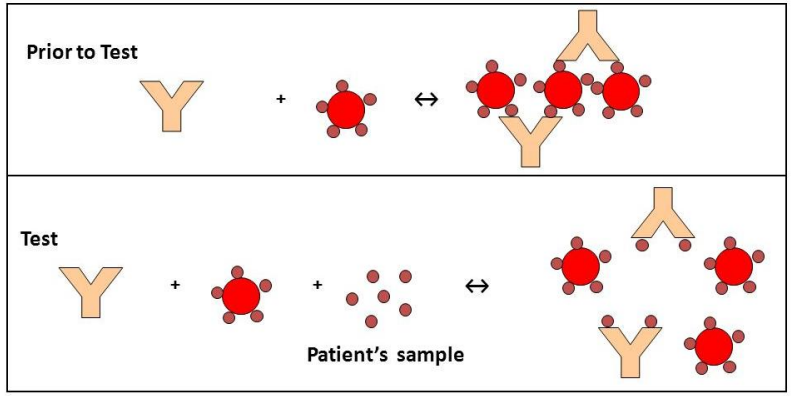




- **Immunoassay**
  - antibodies target the β-N terminal glycated amino acid (4-10 aa) (calculates A1C)
  - unable to detect Hb variants
  - interferences by rare Hb variants



What can change HbA1c?

- RBC survival (shorter life = decreased A1c)
  - Hemolytic anemia
  - Transfusion
- Iron deficiency anemia and Vitamin B12 deficiency (increased A1C)

Table 2. Conditions That Alter HbA_{1c} Independently of Glycemia

Factors Affecting HbA_{1c}	HbA_{1c} Falsely Lowered	HbA_{1c} Falsely Elevated
Erythrocyte life span	Decreased erythrocyte life span: hemolytic anemia; recent blood transfusion; splenomegaly	Increased erythrocyte life span: splenectomy
Erythropoiesis	Reticulocytosis; erythropoietin administration	Iron/vitamin B_{12} deficiency; decreased erythropoiesis
Assay interference	Severe hypertriglyceridemia	Chronic alcoholism
Glycation	High-dose vitamin C or E	Chronic kidney disease

Abbreviation: HbA_{1c}, hemoglobin A_{1c}.

JAMA. 2016;315(6):605–606.

What can change HbA1c?

- RBC survival (shorter life = decreased A1c)
  - Hemolytic anemia
  - Transfusion
- Iron deficiency anemia and Vitamin B12 deficiency (increased A1C)
- Hemoglobin variants (varies)
  - Point mutations in Hb A (i.e. Hb C,D,E and S)

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JAMA. 2016;315(6):605–606.

Hemoglobin variants

- Over 1000 hemoglobin variants (majority involves beta gene)
- Common variants AS, AC, AE, AD
- Prevalence of Hemoglobin Variants at Grady is ~10%

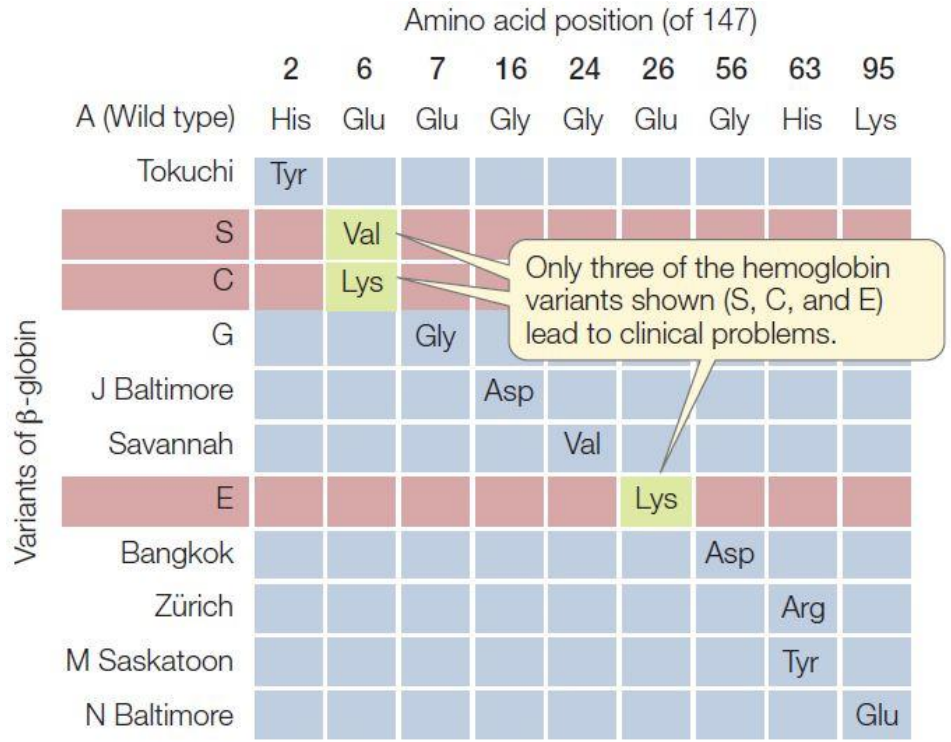


Table 1. Hemoglobin Profiles of Samples with Hemoglobin Variants

Sample	% of total Hb[a] HbA[b]	HbS	HbC	HbF	HbE
HbAA	99			<1	
HbSS		98		2	
HbCC			98	2	
HbAS	59	40		1	
HbAC	60		40	<1	
HbAE[c]	73			<1	27
HPHF	78			22	
β-Thalassemia	97			3	

[a] Glycated hemoglobin is not included.
[b] HbA, sum of HbA_0 and HbA_2.
[c] Hemoglobin profile of the subject with HbAE was determined by cation-exchange HPLC, all others by Diamat HPLC.

Clinical chemistry 39 8 (1993): 1717-23 .

Hb variants may change the RBC lifespan

- Heterozygous are clinically silent
- Homozygous can lead to hemolytic anemia and decreased RBC lifespan

Hemoglobin (Hb)	Average RBC Span (days)
Hb AA	120
Hb AS	93[12]
Hb AC	87[13]
Hb SS	17[12]
Hb SC	28[13]
Hb CC	29[12]
Hb S-Beta –thal	75[12]

https://www.mlo-online.com/continuing-education/article/13008262

Most assays in US are unaffected by Hb variants

Method	Interference from HbC	Interference from HbS	Interference from HbE	Interference from HbD	Interference from elevated HbF
Abbott Architect c Enzymatic	No	No	No	No	-
Alere Afinion	No	No	No	No	$
Arkray ADAMS A1c HA-8180V (Menarini)	No	No	HbA1c not quantified (no for ver. EU 1.41	HbA1c not quantified (no for ver. EU 1.41	No <30%
Beckman HbA1c Advanced B00389 Manual Application on DxC 700 AU AU system	No	No	No	No	$
Beckman HbA1c Advanced B93009 Online Application on DxC 700 AU	No	No	No	No	$
Beckman Synchron System Unicel DxC	No	No	No	No	$
Bio-Rad D-100 (A1c program)	No	No	No	No	-
Bio-Rad Variant II Turbo 2.0	No	No	No	No	No <25% HbF
Ortho-Clinical Vitros	No	No	No	No	$
Roche Cobas c513	No	No	No	No	$
Sebia Capillarys 2 Flex Piercing	No	No	No	No	No <15% HbF
Siemens DCA Vantage	No	Yes↑/ No*	Yes↑/ No*	No	No <10% HbF
Siemens Atellica	No	No	No	No	$
Siemens Dimension	No	No	No	No	$
Tosoh G8 ver. 5.24, 5.28	No	No	No	No	No ≤30% HbF
Trinity HPLC	No	No	No	No	No <15% HbF

Enzymatic
Boronate affinity

HPLC

Immunoassay

HPLC

Affinity chromatography
Immunoassay
Capillary electrophoresis

Immunoassay

HPLC

$ In the absence of specific method data, it can generally be assumed that immunoassay, boronate affinity and enzymatic methods show interference from elevated HbF levels (2,3).

https://ngsp.org/interf.asp

What is ADA position about variants?

- Hemoglobin variants can interfere with measurement but most assays in US are unaffected by most common variants
- If differences between plasma glucose and A1C – consider A1C variant
- For patients with increased RBC turnover- sickle cell, pregnancy, hemodialysis, blood loss or transfusion, **use only plasma glucose**

American Diabetes Association®

Why waived $A1_C$ should not be used for diagnosis

Requirement	CMS (CLIA)	The Join Commission Accreditation (TJC)	CAP Accreditation
Quality Control*	Follow manufacturer directions	Follow Comprehensive Accreditation Manual	Follow manufacturer directions (usually every shipment, lot or 30 days)
Validation*	No	No, unless required by manufacturer or organization	No, unless required by manufacturer or by organization
Proficiency Testing*	No	No	Yes, if not available perform alternative assessment
Inspection	No, unless a complaint is received	Yes, compliance to the standards	Yes, compliance to the standards

For nonwaived tests (moderate and high complexity) across all agencies:
**Two levels of QC every day of testing (or by IQCP)*
**Method evaluation is required*
**PT is required*

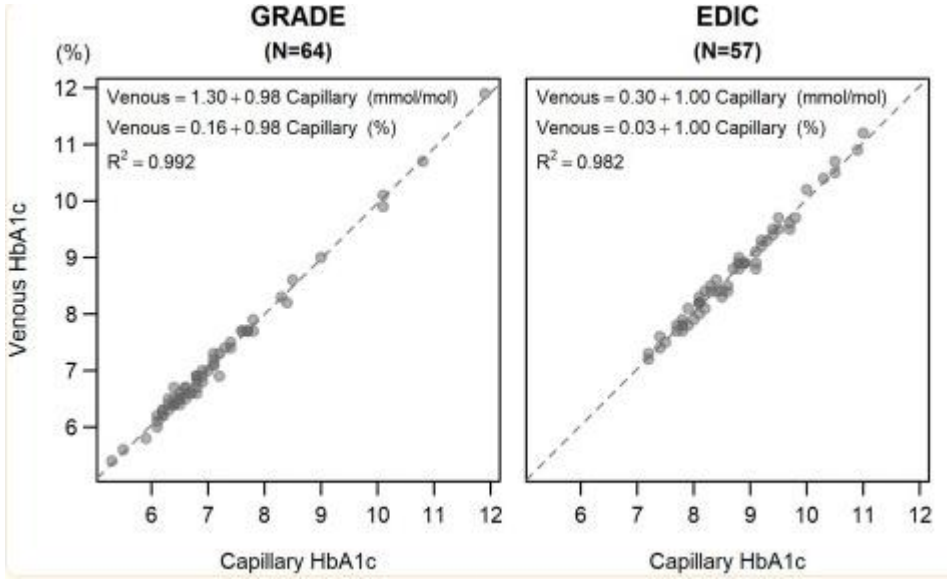
Venous vs capillary HbA1c

- Capillary blood has slightly higher hemoglobin and hematocrit values than venous blood
- HbA1c values between capillary and venous agree well

Table 4: Capillary vs. EDTA whole blood with Afinion HbA1c. Linear regression analysis data. N=number of samples, r=correlation coefficient.

No. sites	N	Regression line	r
3	74	y=0.99x + 0.07	1.00

- Capillary collections challenges
  - Preanalytical errors
    - allow alcohol to dry
    - do not wipe off capillary
    - do not use cold test cartridges
  - Insufficient blood volume
  - Pain

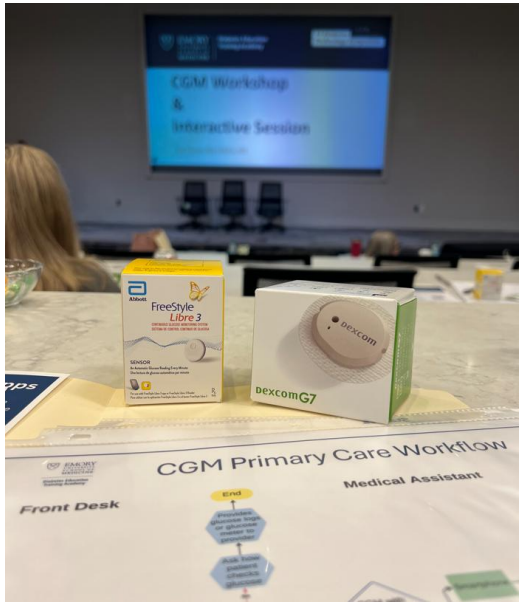


PLoS One. 2021; 16(11): e0257154.
Published online 2021 Nov 15. doi: 10.1371/journal.pone.0257154
PMCID: PMC8592405
PMID: 34780485

Comparison of central laboratory HbA1c measurements obtained from a capillary collection versus a standard venous whole blood collection in the GRADE and EDIC studies

CGM data versus A1C

- CGM used on patients treated with intensive insulin therapy or problematic hypoglycemia
- CGM correlates highly with A1C according to ADA



A1C (%)	mg/dL*
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)

CGM: continuous glucose monitoring

CGM data versus A1C

- However, there are some discrepant reports in literature regarding agreement between CGM and measured A1C
- Sensor sensitivity may decrease over time
- CGM measures interstitial glucose (may underestimate glucose by around 12-15 mg/dL)

  CGM < capillary ~ whole blood < serum/plasma [Glucose]

- Substances affecting CGM accuracy (vitamin C, acetaminophen, hydroxyurea – higher sensor reading)

CGM: continuous glucose monitoring

Comparison of A1C assays based on PT

Hemoglobin A1c - %	GH-06				GH-07				GH-08				GH-09				GH-10			
MANUFACTURER	N	MEAN	SD	CV%	N	MEAN	SD	CV%	N	MEAN	SD	CV%	N	MEAN	SD	CV%	N	MEAN	SD	CV%
Abbott Afinion 2	52	7.61	0.16	2.1	52	9.84	0.23	2.3	50	6.40	0.11	1.8	52	8.82	0.14	1.6	51	5.27	0.11	2.0
Abbott Afinion AS100	17	7.50	0.20	2.7	17	9.70	0.21	2.2	17	6.34	0.17	2.7	17	8.82	0.14	1.6	16	5.26	0.14	2.6
Abbott Alinity ci series	210	7.62	0.10	1.3	213	9.75	0.13	1.3	214	6.37	0.09	1.5	210	8.86	0.10	1.1	209	5.26	0.09	1.7
Abbott Architect c System	119	7.49	0.13	1.7	120	9.64	0.15	1.5	119	6.29	0.11	1.8	119	8.74	0.14	1.6	120	5.20	0.11	2.1
ARKRAY Adams HA-8180 series	29	7.76	0.14	1.8	29	9.94	0.14	1.4	29	6.59	0.11	1.7	29	9.04	0.12	1.4	29	5.37	0.10	1.9
ARKRAY Adams HA-8190V	16	7.74	0.09	1.2	16	9.88	0.10	1.1	16	6.59	0.11	1.6	16	9.04	0.06	0.7	16	5.39	0.09	1.6
Beckman AU HbA1c Advanced	68	7.84	0.18	2.3	69	9.84	0.22	2.2	69	6.59	0.20	3.0	67	9.00	0.22	2.4	67	5.35	0.17	3.2
Beckman AU Systems - Beckman reag.	46	7.73	0.24	3.1	45	9.74	0.28	2.9	44	6.56	0.19	2.9	45	8.88	0.26	2.9	45	5.42	0.17	3.1
Beckman UniCel DxC Synchron Systems	25	7.84	0.20	2.6	25	10.16	0.19	1.9	24	6.53	0.16	2.4	25	9.19	0.21	2.3	26	5.42	0.21	3.9
Bio-Rad D-10	70	7.83	0.18	2.3	70	10.08	0.25	2.4	72	6.64	0.14	2.1	71	9.22	0.20	2.2	70	5.25	0.12	2.3
Bio-Rad D-100	130	7.65	0.13	1.7	131	9.94	0.16	1.6	132	6.50	0.12	1.8	129	9.06	0.15	1.6	132	5.18	0.10	2.0
Bio-Rad Variant II Turbo 2.0	85	7.66	0.14	1.8	85	9.96	0.19	1.9	85	6.55	0.15	2.3	84	9.11	0.16	1.8	85	5.21	0.15	2.9
Roche cobas c311	13	7.93	0.18	2.3	13	10.08	0.29	2.8	12	6.58	0.19	2.8	13	9.21	0.19	2.1	11	5.20	0.15	2.9
Roche cobas c500 series	465	7.85	0.16	2.1	462	10.02	0.24	2.4	465	6.59	0.14	2.1	464	9.13	0.22	2.4	464	5.36	0.17	3.1
Roche cobas c513	65	7.86	0.16	2.0	65	10.03	0.20	2.0	66	6.62	0.13	2.0	65	9.13	0.19	2.1	65	5.43	0.10	1.9
Roche Hitachi Systems	10	7.92	0.18	2.2	10	10.13	0.13	1.2	11	6.69	0.09	1.4	10	9.17	0.09	1.0	11	5.48	0.09	1.6
Sebia Capillarys 2 Flex Piercing	31	7.69	0.13	1.6	29	9.64	0.09	0.9	31	6.49	0.13	2.0	31	8.93	0.13	1.5	31	5.32	0.11	2.1
Sebia Capillarys 3 (CAPI 3) Tera/Octa	44	7.65	0.09	1.1	44	9.63	0.08	0.8	44	6.50	0.08	1.2	45	8.92	0.13	1.4	45	5.30	0.07	1.3
Siemens Atellica CH	158	7.66	0.12	1.6	155	9.87	0.12	1.2	159	6.37	0.10	1.5	156	8.93	0.11	1.2	158	5.22	0.10	1.8
Siemens DCA Vantage	63	7.75	0.21	2.7	63	9.75	0.28	2.9	63	6.50	0.16	2.5	62	8.93	0.25	2.8	60	5.28	0.14	2.7
Siemens Dimension ExL	124	7.66	0.19	2.4	120	9.91	0.20	2.1	124	6.47	0.13	2.0	123	8.96	0.20	2.2	123	5.36	0.14	2.6
Siemens Dimension Vista	94	7.40	0.21	2.8	93	9.57	0.17	1.8	93	6.29	0.09	1.4	91	8.68	0.16	1.9	94	5.16	0.11	2.1
Tosoh G8 Automated HPLC	220	7.88	0.16	2.1	220	10.18	0.15	1.5	221	6.76	0.12	1.7	219	9.28	0.14	1.5	221	5.44	0.09	1.7
Tosoh G11 Automated HPLC	10	7.77	0.11	1.4	10	9.97	0.11	1.1	10	6.66	0.13	1.9	10	9.10	0.11	1.2	10	5.40	0.09	1.7
Trinity Biotech Premier Hb9210 HPLC	64	7.81	0.16	2.1	64	9.99	0.19	1.9	65	6.61	0.17	2.6	62	9.05	0.15	1.6	66	5.49	0.15	2.8
Vitros Chemistry Systems (5,1 FS; 4600; 5600; XT 3400; XT 7600)	184	7.67	0.20	2.6	183	9.69	0.26	2.7	180	6.45	0.14	2.1	184	8.84	0.24	2.7	182	5.17	0.11	2.1
Reference Method*		7.68				9.87				6.55				8.99				5.35		

* Specimens were analyzed by the National Glycohemoblobin Standardization Program (NGSP) network laboratories.

2025 Criteria for Acceptable Performance

Analyte or test	Current CAP criteria for acceptable performance	New CMS criteria for acceptable performance to be implemented on January 1, 2025	Comments
Hemoglobin A1c	Target value ± 6%	Target value ± 8%	New CMS regulated analyte for 2025. *Criteria changed

Analytes regulated for proficiency testing appear in **bold** type.

*For the 2024 calendar year, the CAP criteria (Target value ± 6%) will be used.

Comparison of A1C assays based on PT

Hemoglobin A1c - %	GH-06				GH-07				GH-08				GH-09				GH-10			
MANUFACTURER	N	MEAN	SD	CV%	N	MEAN	SD	CV%	N	MEAN	SD	CV%	N	MEAN	SD	CV%	N	MEAN	SD	CV%
Abbott Afinion 2	52	7.61	0.16	2.1	52	9.84	0.23	2.3	50	6.40	0.11	1.8	52	8.82	0.14	1.6	51	5.27	0.11	2.0
Abbott Afinion AS100	17	7.50	0.20	2.7	17	9.70	0.21	2.2	17	6.34	0.17	2.7	17	8.82	0.14	1.6	16	5.26	0.14	2.6
Abbott Alinity ci series																			0.09	1.7
Abbott Architect c System																			0.11	2.1
ARKRAY Adams HA-8180 seri																			0.10	1.9
ARKRAY Adams HA-8190V																			0.09	1.6
Beckman AU HbA1c Advanced																			0.17	3.2
Beckman AU Systems - Beckn																			0.17	3.1
Beckman UniCel DxC Synchro																			0.21	3.9
Bio-Rad D-10																			0.12	2.3
Bio-Rad D-100																			0.10	2.0
Bio-Rad Variant II Turbo 2.0																			0.15	2.9
Roche cobas c311																			0.15	2.9
Roche cobas c500 series																			0.17	3.1
Roche cobas c513																			0.10	1.9
Roche Hitachi Systems																			0.09	1.6
Sebia Capillarys 2 Flex Piercin																			0.11	2.1
Sebia Capillarys 3 (CAPI 3) Te																			0.07	1.3
Siemens Atellica CH																			0.10	1.8
Siemens DCA Vantage																			0.14	2.7
Siemens Dimension ExL																			0.14	2.6
Siemens Dimension Vista	94	7.40	0.21	2.8	93	9.57	0.17	1.8	93	6.29	0.09	1.4	91	8.68	0.16	1.9	94	5.16	0.11	2.1
Tosoh G8 Automated HPLC	220	7.88	0.16	2.1	220	10.18	0.15	1.5	221	6.76	0.12	1.7	219	9.28	0.14	1.5	221	5.44	0.09	1.7
Tosoh G11 Automated HPLC	10	7.77	0.11	1.4	10	9.97	0.11	1.1	10	6.66	0.13	1.9	10	9.10	0.11	1.2	10	5.40	0.09	1.7
Trinity Biotech Premier Hb9210 HPLC	64	7.81	0.16	2.1	64	9.99	0.19	1.9	65	6.61	0.17	2.6	62	9.05	0.15	1.6	66	5.49	0.15	2.8
Vitros Chemistry Systems (5,1 FS; 4600; 5600; XT 3400; XT 7600)	184	7.67	0.20	2.6	183	9.69	0.26	2.7	180	6.45	0.14	2.1	184	8.84	0.24	2.7	182	5.17	0.11	2.1
Reference Method*		7.68				9.87				6.55				8.99				5.35		

CAP PT SURVEYS INCLUDE HB VARIANT SO LABS KNOW IF THEIR METHOD IS ACCURATE WITH A VARIANT SAMPLE

* Specimens were analyzed by the National Glycohemoblobin Standardization Program (NGSP) network laboratories.

2025 Criteria for Acceptable Performance

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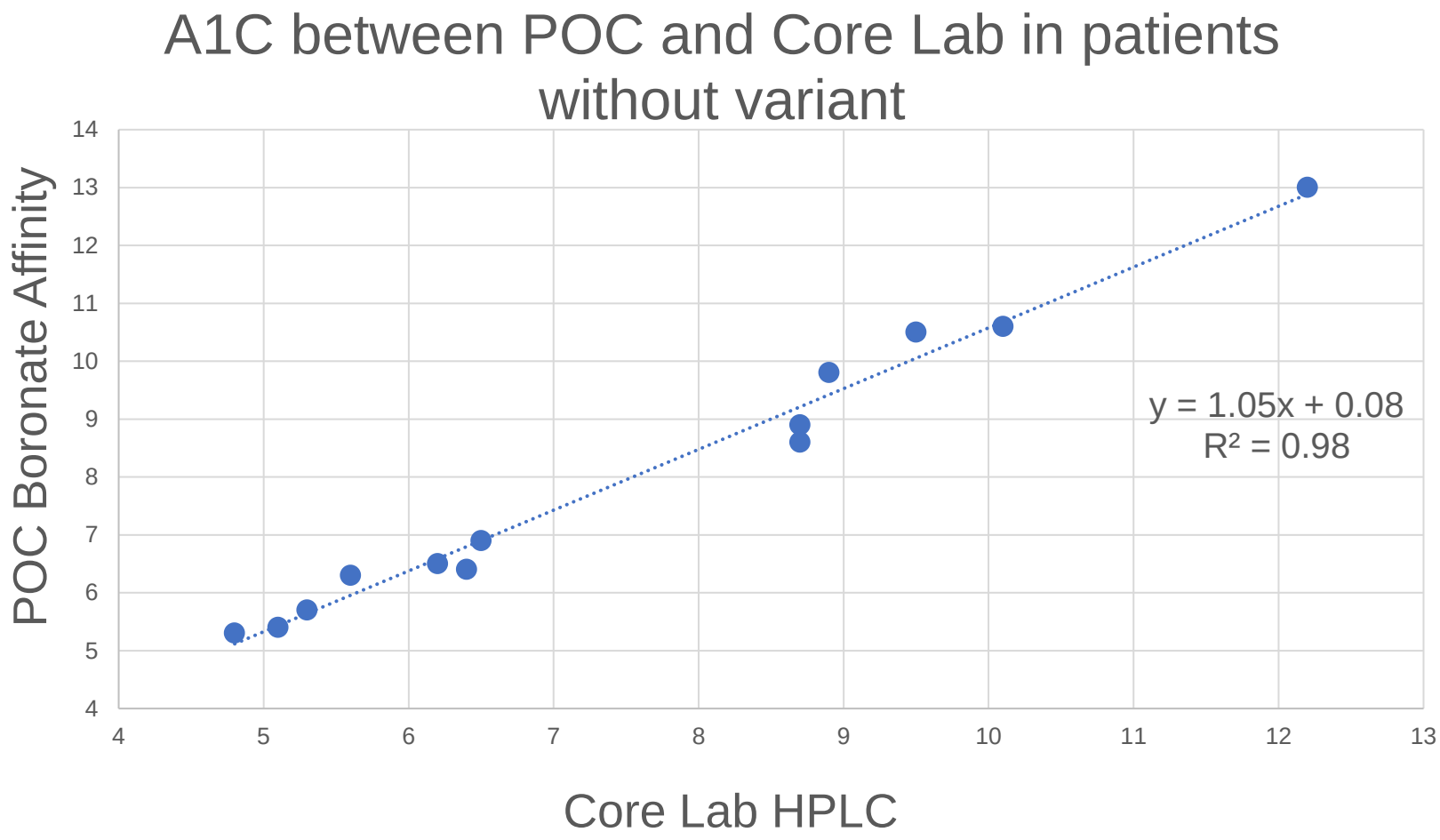
Hemoglobin A1c	Target value ± 6%	Target value ± 8%	New CMS regulated analyte for 2025. *Criteria changed

Analytes regulated for proficiency testing appear in **bold** type.

*For the 2024 calendar year, the CAP criteria (Target value ± 6%) will be used.

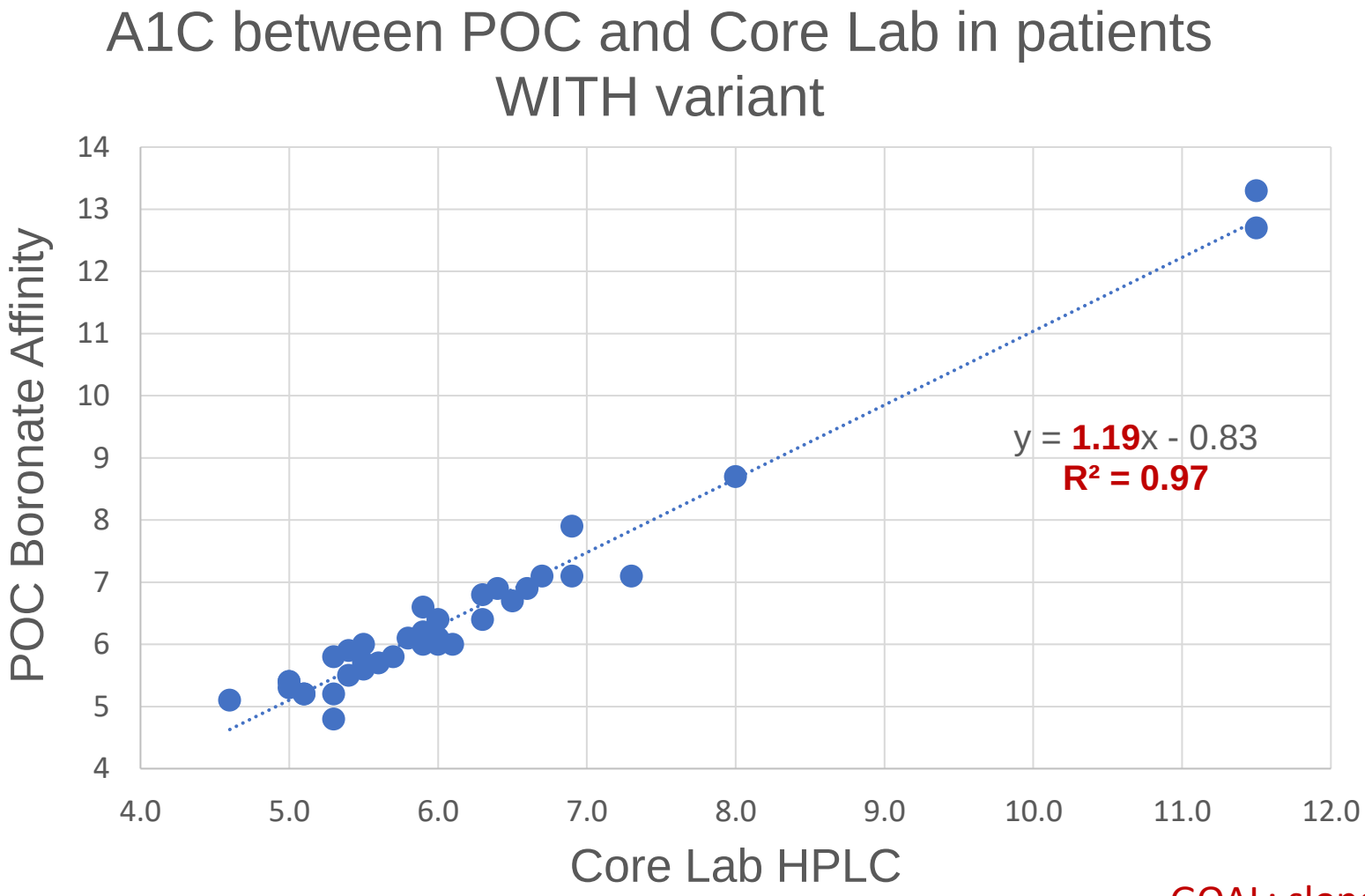
HbA1c results in patients without variants are comparable



GOAL: slope 0.9-1.1, R2 ≥0.98

Thank you Karen Smith from Grady Hospital!

POC HbA1c results in patients WITH variants are higher



~20% positive bias

GOAL: slope 0.9-1.1, R2 ≥0.98

Thank you Karen Smith from Grady Hospital!

One important issue with POC A1c- may report an incorrect value on a patient with sickle cell disease

Patient Age/Sex	HbA1c		D-100 Area% (Variants)	HPHENO History
	D-100	S/N 20016626 Lot # 10228788		
44/M	No value	4.4	F = 23.19, S = 64.07	Hgb SS inc. F
25/M	No value	4.2	C = 45.83, S = 44.76	Hgb SC
44/M	No value	4.2	C = 46.35, S = 44.29	Hgb SC
44/M	No value	4.2	C = 46.35, S = 44.29	Hgb SC
28/M	No value	4.4	S = 63.74	SA, inc. A2 /F
75/M	No value	4.7	S = 45.36, C = 45.21	SC
32/F	No value	4.1	S = 87.64	Hgb SS, prelim.
83/M	No value	<4.0	No value	Hgb SS

Thank you Karen Smith from Grady Hospital!

Diabetes Care Volume 45, Supplement 1, January 2022 S17

2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes—2022*

*American Diabetes Association Professional Practice Committee**

Diabetes Care 2022;45(Suppl. 1):S17–S38 | https://doi.org/10.2337/dc22-S002

What is ADA position about POCT A1c

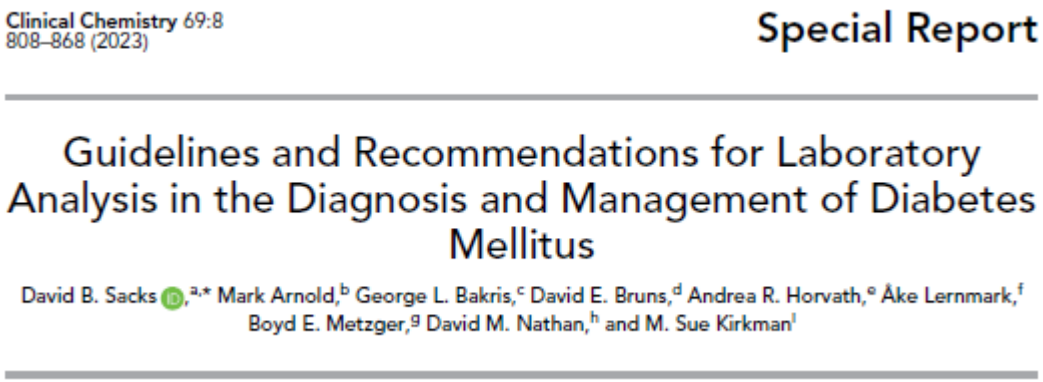
- Point-of-care A1C assays have not been prospectively studied for the diagnosis of diabetes and are **not recommended for diabetes diagnosis**; if used, **they should be confirmed with a validated measure**.
- In the U.S., point-of-care A1C assays may be more generally applied for **assessment of glycemic control in the clinic**

American Diabetes Association®

What do does NIDDK Guidelines say about A1c POCT assays?

- Diagnosis requires a laboratory test certified by the NGSP and standardized to the DCCT assay
- Some point-of-care A1C assays may be certified by the NGSP or approved by the U.S. Food and Drug Administration for diagnosis; however, they should only be considered in laboratories that are certified to perform moderate-to-high complexity tests to ensure **testing proficiency**
- POC methods are CLIA waived, and are often not performed in the same controlled setting as a laboratory

What is ADLM position about what platform to use?



Clinical Chemistry 69:8
808–868 (2023)

Special Report

Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus

David B. Sacks,[a,*] Mark Arnold,[b] George L. Bakris,[c] David E. Bruns,[d] Andrea R. Horvath,[e] Åke Lernmark,[f] Boyd E. Metzger,[g] David M. Nathan,[h] and M. Sue Kirkman[i]

- Use NGSP A1C assay that is certified to DCCT
- POCT should not be used for diagnosis
  - POCT A1C is waived so no PT is required and no evidence of nonlaboratory personnel running the test

Pros and Cons for each instrument

POCT A1c

Pros
Fast and simple
Small and portable
Low volume – finger stick
Timely treatment
Improves management
Waived in US – anyone can do it
Access to patients in resource-poor setting

Laboratory based A1c

Pros
Can recognize variant and instruct patient to have hemoglobin phenotype done
Venous collection
More accurate
DCCT method

Pros and Cons for each instrument

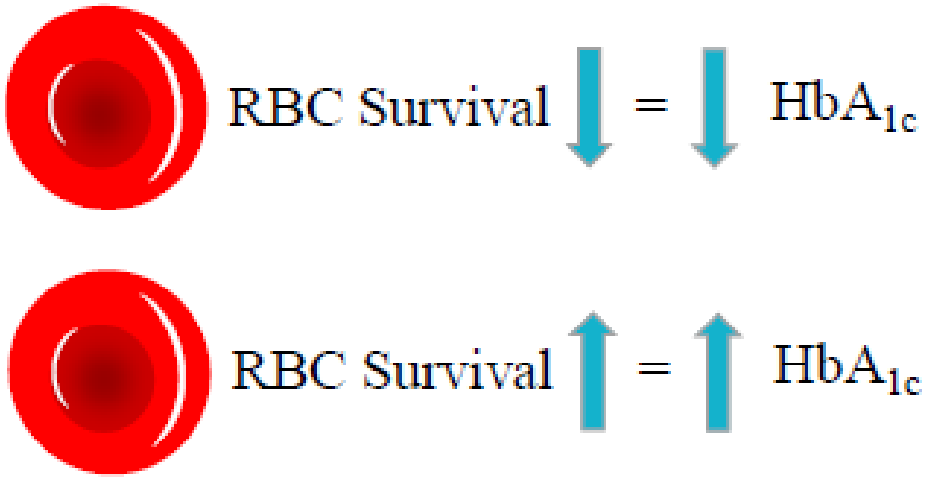
POCT A1c

Pros	Cons
Fast and simple	More expensive
Small and portable	Unable to detect variants
Low volume – finger stick	Waived – no PT required
Timely treatment	Capillary collection
Improves management	Performed by nonlaboratorians
Waived in US – anyone can do it	May report A1C in pt with hemoglobin variants
Access to patients in resource-poor setting	Slighty overestimates A1C (boronate affinity)

Laboratory based A1c

Pros	Cons
Can recognize variant and instruct patient to have hemoglobin phenotype done	Longer TAT than POCT
Venous collection	Not for POCT setting
More accurate	Prone to interference by Hb variant that co-elute with peaks of interest
DCCT method	

RBC life span will significantly impact the accuracy of any of A1c methods



Request from the Diabetic Clinic

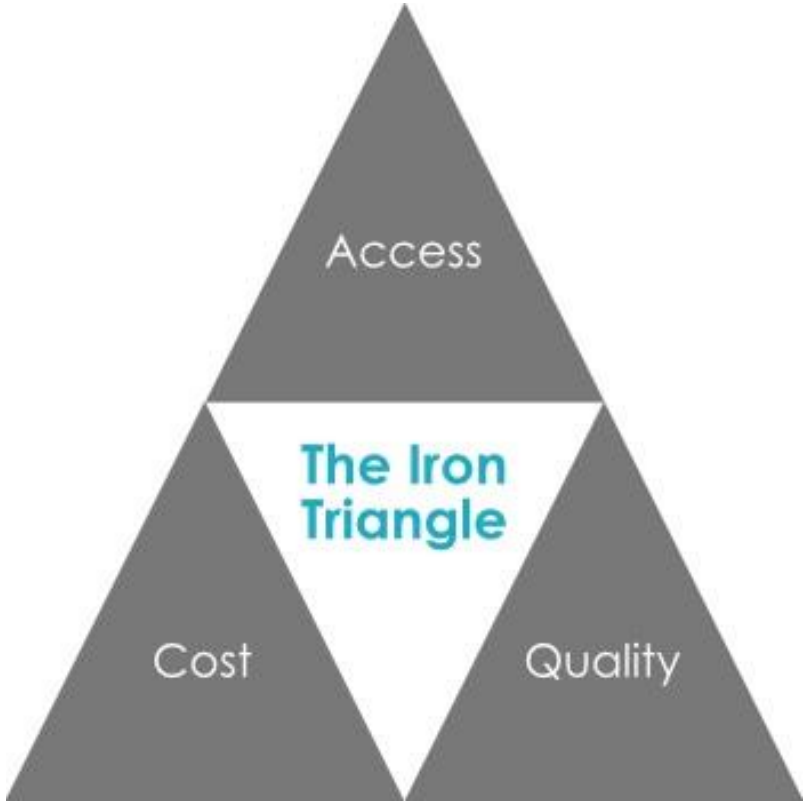
Situation: Diabetic clinic is requesting POC A1c instrument just a floor below our core lab where we have HPLC based A1c instruments

Background: Need for a faster TAT

Action: Investigate the limitations of POC A1c instruments

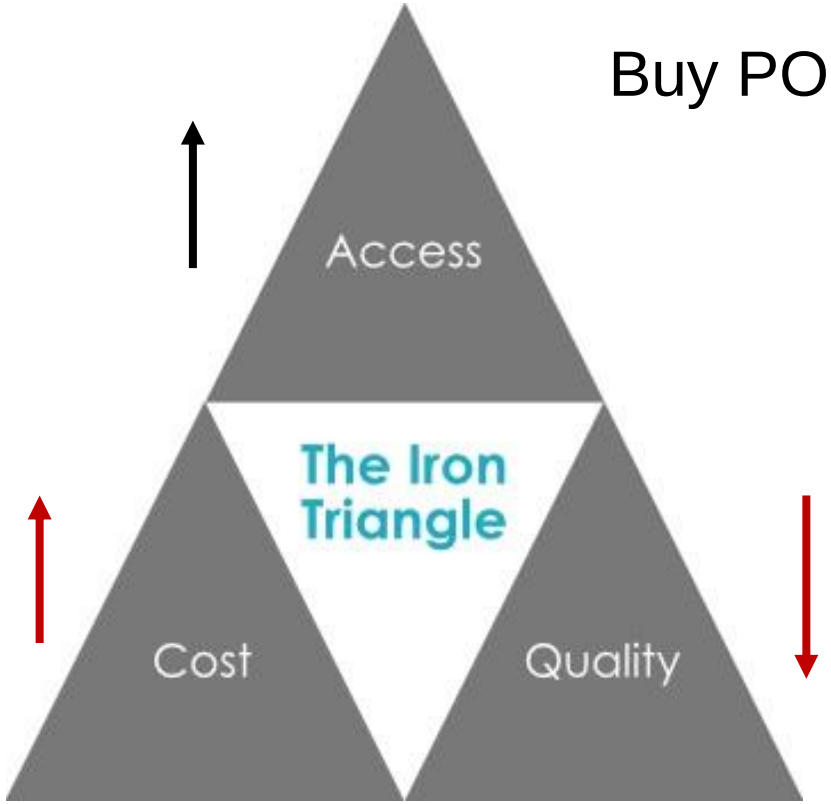
Recommendation: ….*tbd*

What do we do?
The iron triangle in healthcare debate



Model that suggests that improving one area of healthcare will likely result in worsening another

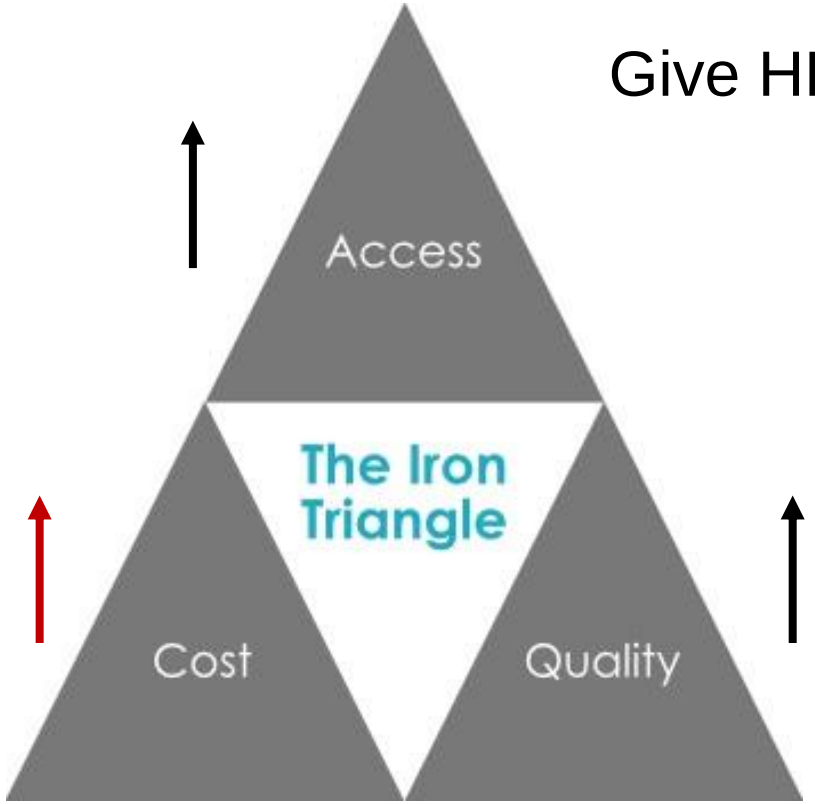
What do we do?
The iron triangle in healthcare debate



Buy POCT A1c for the clinic?

Model that suggests that improving one area of healthcare will likely result in worsening another

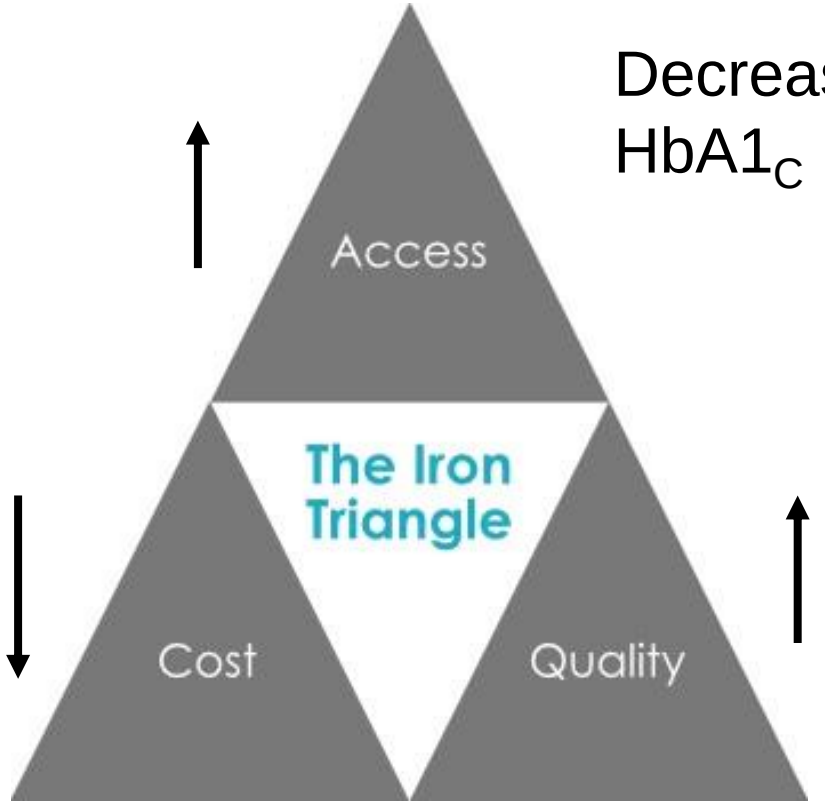
What do we do?
The iron triangle in healthcare debate



Give HPLC instrument to the clinic?

Model that suggests that improving one area of healthcare will likely result in worsening another

What do we do?
The iron triangle in healthcare debate



Decrease turn-around-time for $HbA1_C$ results?

Model that suggests that improving one area of healthcare will likely result in worsening another

Monitor TAT for A1C from Diabetic Clinic after implementing changes to the workflow

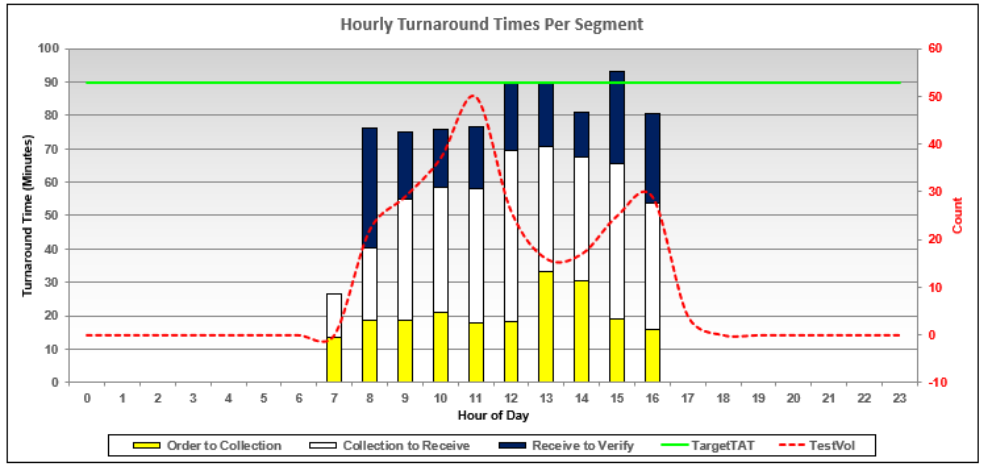
Verify Date: November 2024 [Monthly]

Filters:
Day(s): Mon,Tues,Wed,Thur,Fri
Test: Hb A1c - Hb A1c
(HB A1C is the representative result code)
Patient Locat 2 - Diabetic Clinic

Count: 255
Activity Being Counted: Tests

1st Time Segment: Order to Collection
2nd Time Segment: Collection to Receive
3rd Time Segment: Receive to Verify

Performance Summar	Turnaround Time (minutes) Average	Median	90% Completion	Outliers (above target) n	% of Total
Overall Target	90.0	90.0	90.0		
Total	84.4	75.0	127.0	81	31.8%
Order to Collectior	24.1	16.0	38.0		
Collection to Rece	38.0	34.0	68.0		
Receive to Verify	23.5	18.0	35.5		



TAT from order to verify 127 min

Order to collection

- Draw patient as soon as possible

Collection to receive

- Location to pneumatic tube station
- No batching of the samples

Receive to verify

- Treat samples STAT (use different color bags)
- Receive samples at the A1c station

Monitor TAT for A1C from Diabetic Clinic after implementing changes to the workflow

Verify Date: November 2024 [Monthly]

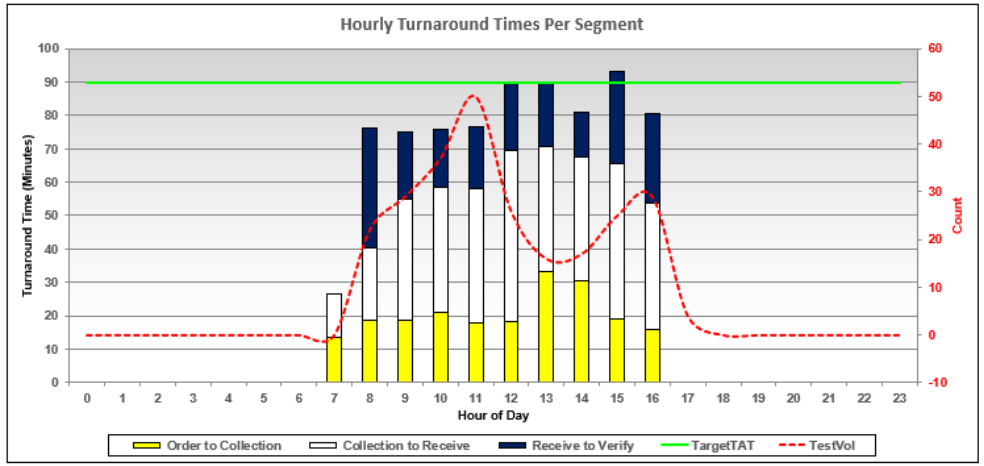
Filters:
Day(s): Mon,Tues,Wed,Thur,Fri
Test: Hb A1c - Hb A1c
(HB A1C is the representative result code)
Patient Locat 2 - Diabetic Clinic

Count: 255
Activity Being Counted: Tests

1st Time Segment: Order to Collection
2nd Time Segment: Collection to Receive
3rd Time Segment: Receive to Verify

Performance Summar — Turnaround Time (minutes)

	Average	Median	90% Completion	Outliers (above target) n	% of Total
Overall Target	90.0	90.0	90.0		
Total	84.4	75.0	127.0	81	31.8%
Order to Collectior	24.1	16.0	38.0		
Collection to Rece	38.0	34.0	68.0		
Receive to Verify	23.5	18.0	35.5		



TAT from order to verify 127 min

verify Date: February 2025 [Monthly]

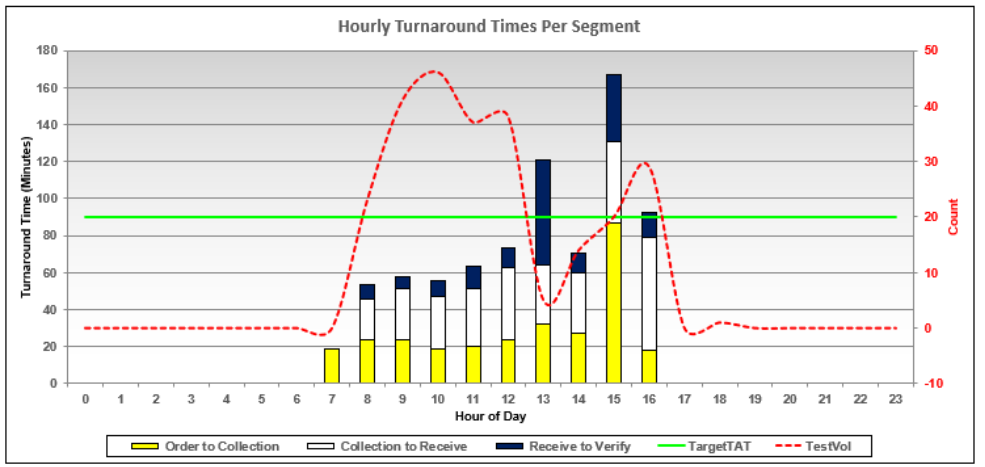
Filters:
Day(s): Mon,Tues,Wed,Thur,Fri
Test: Hb A1c - Hb A1c
(HB A1C is the representative result code)
Patient Locat 2 - Diabetic Clinic

Count: 254
Activity Being Counted: Tests

1st Time Segment: Order to Collection
2nd Time Segment: Collection to Receive
3rd Time Segment: Receive to Verify

Performance Summar — Turnaround Time (minutes)

	Average	Median	90% Completion	Outliers (above target) n	% of Total
Overall Target	90.0	90.0	90.0		
Total	69.1	63.0	106.7	52	20.5%
Order to Collectior	28.0	19.0	41.2		
Collection to Rece	34.0	28.0	72.0		
Receive to Verify	15.1	8.5	27.0		



Current TAT from order to verify 107 min

Request from the Diabetic Clinic

Situation: Diabetic clinic is requesting POC A1c instrument just a floor below our core lab where we have HPLC based A1c instruments

Background: Need for a faster TAT

Action: Investigate the limitations of POC A1c instruments

Recommendation:

- Monitor the TAT and continue discussions with diabetic clinic
- Attach a comment to POCT A1c
  - that this test should not be used for diagnosis of diabetes
  - always confirm POCT diabetes diagnosis with venous laboratory testing (same applies to glucose meter – confirm glucose in the lab)

Conclusion

- There are many methods that measure HbA1c that are standardized and NGSP certified (waived and moderate complexity)
- Waived A1c use immunoassays or boronate affinity methodology
  - PT is not required for waived tests (unless CAP accreditation)
  - Cannot detect hemoglobin variants
- Hemoglobin variant may affect RBC lifespan and subsequently affect the accuracy of A1c result
- Results from POC instruments should be confirmed with laboratory assays

EMORY

Grady

Thank you for listening!

kgalior@emory.edu

What to do if the HbA1c is not reliable?

- Fructosamine
  - Assesses glycemic control over the past 3 weeks
  - Measures primarily glycated albumin
  - Colorimetric assay (RI= 200 – 285 µmol/L)
  - Clinical assays sensitive to interferences
  - Affected by changes in protein concentrations and half-life