# Meeting of the NGSP Clinical Advisory Committee Minutes

2025 ADA 85th Scientific Sessions
Chicago, IL
Sunday June 22, 2025 8:00 – 9:30 AM

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|---|---|---|---|
| Kuanysh Kabytaev | DDL, Univ of Missouri | Guido Freckmann | Inst for Diabetes Tech |
| Brian Burke | VA | Paul Conlin | VA |
| Curt Rohlfing | DDL, Univ of Missouri | Yongjin Xu | Abbott |
| David Leslie | St Bartholomews Hospital, UK | Hongwei Zhang | Abbott |
| Elizabeth Selvin | Johns Hopkins | William Herman | Univ of Michigan |
| Irl Hirsch | Univ of Washington | Amy Rothberg | Univ of Michigan |
| Robert M Cohen | Univ of Cincinnati | Saeki Yh | Asahi Kasei |
| David Nathan | Harvard Med School | Takuji Kohzuma | Asahi Kasei |
| Julie Myers | Bio-Rad | Matthew Crowley | Duke Univ |
| David Sacks | NIH | | |

**Welcome and introduction**: C. Holliday, Director of the CDC Division of Diabetes Translation, was unable to attend so the meeting was chaired by K. Kabytaev. He opened the meeting at 8:00 am and welcomed everyone. Participants introduced themselves. The 2024 NGSP Clinical Advisory Committee meeting minutes were approved.

**NGSP/CAP Update:** C. Rohlfing
C. Rohlfing announced that longtime NGSP Network Coordinator Randie Little would retire at the end of June. He and those present acknowledged her many and important contributions to the success of the NGSP and HbA1c standardization.

- Structure of the NGSP
    1. The NGSP network consists of an administrative core, the Central Primary Reference Laboratory (CPRL), a backup PRL and Secondary Reference Laboratories (SRLs).
    2. The NGSP network labs are located in the U.S., Europe and Asia.
    3. NGSP network labs are monitored monthly via 10 fresh-frozen samples.
    4. The NGSP network is linked to the IFCC HbA1c network via an established master equation; twice-yearly sample exchanges between the networks ensure the stability of the relationship.
- NGSP Process: Consists of 3 parts
    1. Calibration: Informal process by which the NGSP works with manufacturers/laboratories to assist them in checking their calibration.
    2. Certification: Formal process by which manufacturers/labs perform a 40-sample comparison against a SRL using fresh or fresh-frozen whole blood; they must pass specific criteria to obtain certification.
    3. Proficiency Testing: Key to monitoring the progress and success of the NGSP in harmonizing HbA1c results. The CAP GH5 survey uses fresh whole blood with values assigned by the NGSP network.
- NGSP Certification: Year 1 to 28
    1. The NGSP certifies both methods and laboratories.

2. There are two types of laboratory certification: Level 1 and Level 2.
3. Most certified labs are Level 1 and most are outside of the U.S.
4. Level 1 criteria are a bit more stringent than for manufacturer or L2 certification, and they are monitored against the NGSP network quarterly.
5. The number of certified methods continues to increase (currently there are ~400), the number of certified labs has leveled off.
6. Certified laboratories are distributed throughout the world.

- Current NGSP Certification Criteria
  1. Manufacturer and Level 2 Lab Certification Criteria: 36/40 results must be within ±5%
  2. Level 1 certification: 37/40 results must be within ±5% (also quarterly monitoring)
  3. Certification must be renewed annually.
- 2025 CAP GH5A survey data (5 samples)
  1. There has been considerable improvement in the comparability of results since 1993 when the DCCT ended.
  2. CAP and NGSP criteria have been tightened over the years.
  3. The NGSP network assigns the values for the accuracy-based CAP GH-5 survey.
  4. Overall CAP accreditation pass rates (±6%) were 96.8% to 98.8% for the 5 2024 survey samples. Individual method pass rates were 88.5% - 100%.
  5. All-method CVs on the survey have decreased between 2000 and 2024. Our goal for all-method CVs is ≤2.5%. CVs for the current survey were 2.5% - 2.8%.
  6. Method-specific, between-laboratory CVs ranged from 0.4% to 4.0%.
  7. Overall, only 60% of laboratories are using methods with CVs ≤2.5% at all five HbA1c levels.
- Updated PT Regulations for 2025
  1. CMS has decided to make HbA1c a CLIA-regulated analyte.
  2. Although the CAP survey criterion has been ±6% for some time, CLIA has adopted PT criteria of ±8% effective this year.
  3. PT providers, including CAP, are not allowed to fail labs that participate in their surveys if they pass the CLIA criterion.
  4. Updated CAP PT Limits for 2025
     - CAP-accredited laboratories that use accuracy-based proficiency testing for HbA1c (e.g. GH5) are required to evaluate results based on acceptable performance criteria of ±6% in 2025.
     - The CAP now provides two evaluations for the GH5-A 2025 surveys
       - To meet CLIA regulations (±8%)
       - To meet CAP checklist (±6%) requirements for CAP accredited laboratories.

**Discussion:**

D. Sacks noted that the CAP PT overall pass rates originally presented were actually for the ±8% PT limits and not the ±6% accreditation limits (this has been corrected in these minutes). W. Herman asked about the new PT limits, why did CLIA adopt ±8% for PT when the pass rates were very high at the stricter ±6% limits? D. Sacks and C. Rohlfing noted that originally CLIA was going to adopt ±10% PT limits but later decided on ±8%. However, fortunately CAP can still require compliance with ±6% to maintain CAP accreditation.

**RBC Survival (HbA1c vs Mean Glucose):** R.M. Cohen

R.M. Cohen presented findings from a recent as yet unpublished study, many of which were presented at the current ADA Scientific Sessions (abstract below).

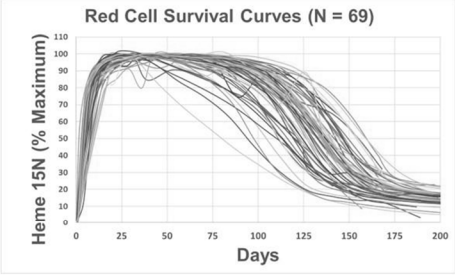
- 166-OR: Mean RBC Age (MRBC) Variation Accounts for the Predominance of Mismatch (MM) between Measured HbA1c (mA1c) and CGM-Derived Estimated HbA1c (eA1c)
  ROBERT M. COHEN; JACQUELINE CRAIG; SHAMMAH O. OMOLOLU; VERONICA TOZZO; ERIC P. SMITH; SHAHRIAR ARBABI; MATTHEW GENCO; WILLIAM ABPLANALP; DYLAN THIBAULT; CHARLES T. QUINN; CHRISTOPHER J. LINDSELL; RICHARD M. BERGENSTAL; ROBERT S. FRANCO; JOHN HIGGINS. Diabetes 2025;74(Supplement_1):166-OR https://doi.org/10.2337/db25-166-OR

  **Introduction and Objective:** Widespread use of CGM has increased awareness of discordance between mA1c and eA1c, confounding clinical decision-making, e.g. when using equations from either the A1c Derived Average Glucose or Glucose Management Indicator (GMI) studies. We test whether variation in $M_{RBC}$ (the measure of RBC survival directly determining HbA1c) in people without anemia causes most of the MM.

  **Methods:** Subjects had hematocrit≥35. The study sample was enriched with those having MM≥±0.5%. Oral $^{15}$N-glycine was used to label heme in an age cohort of emerging RBCs in vivo. Measurement of excess heme $^{15}$N over time gave RBC survival, including age-dependent removal of RBC, RBC lifespan, and $M_{RBC}$. MM was calculated using AG throughout the RBC lifespan (>4 months) with 2 mA1c near the end.

  **Results:** Fig. 1A: See wide distribution of time-dependent removal of an age cohort of RBCs. This is the largest set of human in vivo RBC labelling studies reported. Fig. 1B: correlation between HbA1c MM and $M_{RBC}$. $M_{RBC}$ is highly associated with MM ($r^{2=}$ 0.55). In the relationship between mA1c and AG (not shown), adjustment for $M_{RBC}$ improves the variance $r^2$ accounted for from 0.79 to 0.88.

  **Conclusion:** Inter-individual differences in $M_{RBC}$ account for the preponderance of mismatch observed between HbA1c and AG. This represents proof of principle that accounting for $M_{RBC}$ should simplify decision-making and potentially improve diabetes care.



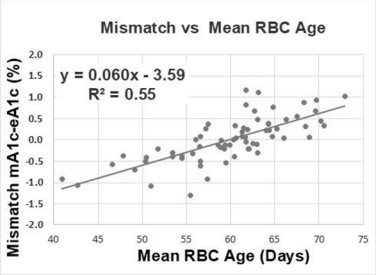




Figure 1A: Time course of $^{15}$N enrichment in heme extracted from circulating RBCs after $^{15}$N-glycine oral administration, demonstrating wide range of RBC survival. Mean $M_{RBC}$ 60±6 (1SD) days (N = 69; range 41-72). In 13 evaluable subjects studied twice 1 yr apart (not shown), the paired difference in $M_{RBC}$ averaged 1.4 days (range 0.03-2.3 days, agreement within average 2.3%). Figure 1B: Mismatch between measured and predicted HbA1c as a function of $M_{RBC}$; $r^2$ represents the fraction of variance in the mismatch that can be accounted for by $M_{RBC}$.

Funding: NIH R01 DK123330, NIH UL1TR001425 (CCTST.org), Dexcom (in kind CGM & grant)

- Background
  1. HbA1c: basis for interpreting RCT's - benefit of tight glycemic control
  2. Debate: HbA1c vs CGM in assessing complications risk

3. Discordances between HbA1c and BG: known since 1990's, Brought into focus by clinicians using CGM and GMI: GMI and mA1c frequently don't match
4. What determines HbA1c? Glucose, RBC lifespan, rate of glycation
5. This study fills a gap:
    - DATA measuring RBC Survival (as Mean RBC age or $M_{RBC}$) and relating that to relationship of A1c to AG in our population
    - What are Physiologic & Clinical Implications?

- Thank you to
    1. Our Study Subjects
    2. 3.6 Million Glucoses
    3. >1500 Phlebotomies
    4. 1700 CGM placements
    5. >83 person-years of participation
    6. Schubert Clinical Research Center Staff, Center for Clinical & Translation Science & Training (CCTST.org)
    7. Metabolic Solutions – Mass Spectrometry

Discussion:
R.M. Cohen noted that all subjects included in the study had unremarkable hemoglobin profiles. W. Herman asked about the composite graph of all subjects, what about the dips in several of the curves. R.M. Cohen replied that these were caused by single data points that did not fit the overall curve patterns. In the case of one subject they had several substantial dips in the curve so they pulled additional samples from the same study, when these were processed and analyzed these points fit the curve. So clearly there was some issue with the extraction or MS measurements. D. Nathan asked whether they had done any double labeling with $^{59}Fe$ as well as $^{15}N$, R.M. Cohen said they had not. Both noted that the results of the current study were very similar to earlier $^{59}Fe$ labeling studies that looked at very small numbers of subjects (<10). I. Hirsch asked about reticulocyte counts, R.M. Cohen said they did those. E. Selvin asked about how the corrected $M_{RBC}$ was calculated. R.M. Cohen replied that the correction was done by using the ratio of each subject's $M_{RBC}$ to the average of the entire population. What they were not able to account for was the variation in CGM, he was not able to get a good answer for this. We know that you can get different readings from different sites (e.g. arm vs. abdomen) and there can be variation between different CGMs from different manufacturers. I. Hirsch asked what meter was used in this study, R.M. Cohen said the Dexcom G6 Pro. D. Sacks asked about the mismatches before and after correction for MRBC, why is it that for many of the subjects with the lowest uncorrected mismatches (<0.5% HbA1c) the correction increases the mismatch? R.M. Cohen responded that he thought it is simply noise in the data, it could be other factors such as CGM variance. It was noted that the stability of HbA1c within individuals observed in the study is supported by data from other studies. D. Nathan asked if the group looked the possibility of using RBC indices to obtain red cell turnover, R.M. Cohen said they had not done that in this study yet.

**Pro: Should We Consider Race-based HbA1c Targets? (or at least consider the different relationship between Average Glucose Levels and HbA1c across Race) Yes:** D. Nathan

- Diabetes-Diagnosis: Glycemia is central to diabetes and its complications.
    1. Diagnosis based on glucose levels
        - Fasting plasma glucose- ≥ 126 mg/dl
        - HbA1c ≥ 6.5%, increasingly/most commonly used
        - OGTT- 2 hr after a 75 gm liquid challenge- ≥ 200 mg/dl: rarely performed clinically outside of pregnancy

- Diagnostic levels based on association with retinopathy risk (International Expert Committee Report on the Role of the A1C assay in the Diagnosis of Diabetes. Diabetes Care 32(7): 2009)

2. DETECT 2 Study
   - 44,623 patients world-wide.
   - 9 pooled studies from US (4), India (1), Australia (2), Japan (1),
   - Singapore (1).
   - Racial distribution: ?? (Not stated)
   - Retinal photographs and single measurement of glucose, OGTT and/or HbA1c available.
   - Relationship between glycemic levels and presence of retinopathy examined.
3. Relationship between Glycemia and Microvascular Complications
   - DCCT (Type 1): 44% reduction in risk for every 10% decrease in HbA1c
   - UKPDS (Type 2): 37% reduction in risk for every 1% decrease in HbA1c
4. The relationship between glycemia and diabetes-specific complications is how diabetes is defined.
   - Diagnosis
   - Epidemiology
   - Chronic glycemia (as measured by HbA1c) may now be the most common means of diagnosing diabetes
   - HbA1c also used to set glycemic treatment goals.

- Diabetes- Treatment: Glycemia is central to diabetes and its complications
  1. Risk for development of complications causally related to HbA1c levels
  2. 99% of the difference in complications between Intensive and Conventional therapy is explained/mediated by the A1c levels over time (DCCT Research Group NEJM 1993;342:381)
- Relationship between HbA1c and Mean Blood Glucose: Effect of Race on Relationship
  1. Studies

| Study | Year | Cohort | | Study period (weeks) | Number of glucose tests per patient during 4-12 w |
|---|---|---|---|---|---|
| | | Number Type | Race %W/%AA | | |
| Svendson | 1982 | 15 T1D/15 ND | 100/0 | 5 | 200-300 |
| Nathan | 1983 | 21 T1D | 100/0 | 8 | 200-300 |
| DCCT | 2002 | 1439 T1D | 96/4 | 12 | 7 |
| Hempe | 2002 | 128 T1D | 56/38 | 4 | 85 |
| Murata | 2004 | 182 T2DM | ? | 8 | 180 |
| Nathan | 2007 | 15T1/7T2/3ND | 93/7 | 12 | 24,000 (CGM) |
| ADAG/Nathan | 2008 | 268T1/159T2/80ND | 83/8 | 12 | 2700 (SMBG+CGM) |

  2. The Clinical Information Value of the Glycosylated Hemoglobin Assay. Nathan et. al, N Engl J Med 1984;310:341-6

| HbA1c (%) | MBG (mg/dL |
|---|---|
| 5 | 81 |
| 6 | 114 |
| 7 | 147 |
| 8 | 180 |
| 9 | 214 |
| 10 | 247 |
| 11 | 280 |
| 12 | 314 |

  3. Translating the A1C Assay Into Estimated Average Glucose Values. Nathan et. al, Diabetes Care 31:1473-1478, 2008.
     - Designed to provide the definitive relationship between HbA1c and MBG.

- Sponsored by ADA and EASD.
- Multinational study (10 centers): US (6), Europe (3), Africa (1).
- 507 participants: 268 Type 1, 159 Type 2, 80 Non-diabetic
- Glucose Monitoring
    - CGMS- Mean of ~2400 measurements per subject, representing a median of 13 days with CGM
    - Lifescan monitoring ~300 measurement per subject
        A. Mean of ~25 measurements per week
        B. (Goal was a minimum of 21 tests per week)
    - Total ~ 2700 measurements/patient during 12 wks: Represents a median of 51 of 84 days with either CGM or Lifescan monitoring

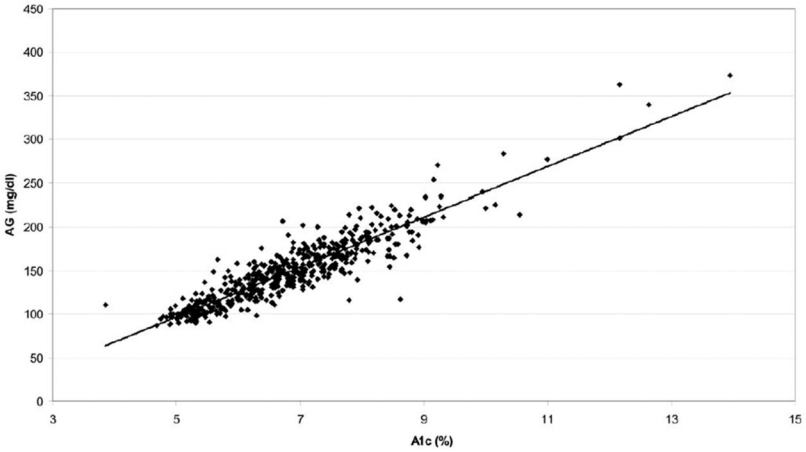



**Figure 1**—*Linear regression of A1C at the end of month 3 and calculated AG during the preceding 3 months. Calculated* $AG_{mg/dl} = 28.7 \times A1C - 46.7$ ($AG_{mmol} = 1.59 \times A1C - 2.59$) ($R^2 = 0.84$, $P < 0.0001$).

Table 2—*Estimated average glucose*

| A1C (%) | mg/dl* | 21 T1D | 15 T1, 7 T2 3 ND |
|---|---|---|---|
| | | 1984 | 2007 |
| 5 | 97 (76–120) | 81 | 89 |
| 6 | 126 (100–152) | 114 | 120 |
| 7 | 154 (123–185) | 147 | 152 |
| 8 | 183 (147–217) | 180 | 184 |
| 9 | 212 (170–249) | 214 | 214 |
| 10 | 240 (193–282) | 247 | 247 |
| 11 | 269 (217–314) | 280 | 277 |
| 12 | 298 (240–347) | | |

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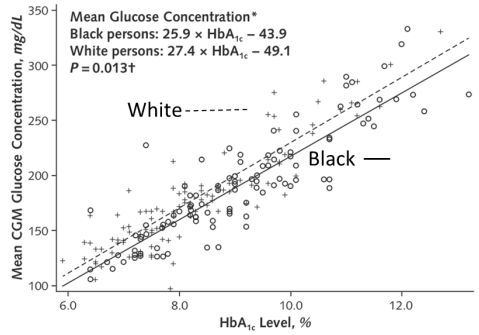
- ADAG by Race
    - Despite our best intentions to include a large enough, diverse population, the loss of power in our Cameroon site resulted in the loss of 58 samples from African participants.
    - Of 507 analyzed subjects, only 38 were African American
    - There were slope and intercept differences in the HbA1c/AG relationships between Caucasian and African/African American subjects (1.58xHbA1c-2.52 and 1.81xHbA1c-3.84 respectively, p= 0.07)

4. Bergenstal et al. Ann Int Med 2017; 167:95
    - 208 patients with Type 1 diabetes – 50% African American, 50% White with CGM and A1c
    - "For a given HbA1c level, the mean glucose concentration was significantly lower in black persons than in white persons (P = 0.013)."

*Figure 1.* Mean glucose concentration as measured by CGM versus $HbA_{1c}$ level, by race.




- Responding editorial (Selvin and Sacks, Ann Intern Med 2017;167:131-132)

5. Relationship Between Average Glucose Levels and HbA1c Differs Across Racial Groups: A Substudy of the GRADE Randomized Trial (Nathan et. al, Diabetes Care 2024 Dec 1;47(12):2155-2163)
   - 1454 total subjects, 534 NHW, 389 NHB, 327 HW, 204 other races
   - Substudy of GRADE Comparative effectiveness trial of 4 glucose-lowering medications added to metformin.
   - CGM Substudy performed in subset based on timing of usual visits.
   - Aimed to include enough representation from diverse racial/ethnic groups to address lingering questions regarding relationship of HbA1c and AG.
   - CGM for 14 days, with minimum of 10 d for primary analysis.
   - HbA1c measured with DCCT-aligned assay at beginning of CGM period and at completion of CGM (~2-weeks after start of CGM).
   - Glycated albumin measured as well.
   - Observed racial differences for both HbA1c and Glycated Albumin.

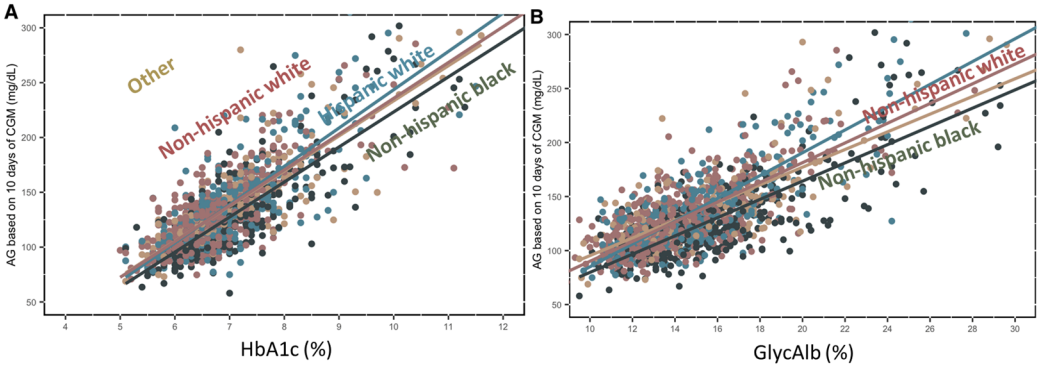



**Table 2—Racial/ethnic differences in relationship between $HbA_{1c}$ (%) and $AG_{10}$ (mg/dL) in linear regression models**

| | Unadjusted | | Adjusted for age and sex | | Adjusted for age, sex, and OGTT glucose change variable* | |
|---|---|---|---|---|---|---|
| | Intercept† | Slope‡ | Intercept† | Slope‡ | Intercept† | Slope‡ |
| Racial group | $P < 0.001$§ | | $P < 0.001$§ | | $P < 0.001$§ | |
| NHW | −90.8 (7.8) | 32.7 (1.1) | −77.8 (8.9) | 32.7 (1.1) | −80.6 (9.6) | 33.2 (1.2) |
| NHB | −96.3 (7.4) | 32.0 (1.0) | −78.0 (8.8) | 31.4 (1.0) | −75.6 (9.4) | 31.3 (1.1) |
| HW | −105.7 (9.0) | 34.9 (1.3) | −90.4 (10.0) | 34.6 (1.2) | −89.0 (10.3) | 34.5 (1.3) |
| Other‖ | −86.8 (10.9) | 32.0 (1.5) | −73.0 (11.6) | 31.9 (1.5) | −72.1 (12.0) | 31.9 (1.5) |
| *P* for pairwise comparisons | | | | | | |
| NHW vs. NHB | <0.001 | | <0.001 | | <0.001 | |
| NHW vs. HW | 0.48 | | 0.49 | | 0.73 | |
| NHW vs. other | 0.93 | | 0.83 | | 0.67 | |
| NHB vs. HW | <0.001 | | <0.001 | | <0.001 | |
| NHB vs. other | <0.001 | | 0.001 | | 0.009 | |
| HW vs. other | 0.48 | | 0.49 | | 0.61 | |

**GRADE** **Bergenstal R. Ann Int Med 2017; 167:95.**

| $HbA_{1c}$, % | NHW (*n* = 534) Predicted AG (mg/dL) with 95% p | NHB (*n* = 389) | Caucasian (n=104) AG based on CGM | African American (n=104) |
|---|---|---|---|---|
| 6.0 | 105 (59, 152) | 95 (49, 142) | 115 | 112 |
| 6.5 | 121 (75, 168) | 111 (65, 158) | | |
| 7.0 | 138 (91, 184) | 127 (81, 174) | 143 | 137 |
| 7.5 | 154 (108, 201) | 143 (97, 190) | | |
| 8.0 | 170 (124, 217) | 159 (113, 206) | 170 | 163 |
| 8.5 | 187 (140, 233) | 175 (129, 222) | | |
| 9.0 | 203 (156, 250) | 191 (145, 238) | 198 | 189 |
| 9.5 | 219 (173, 266) | 207 (161, 254) | | |
| 10.0 | 236 (189, 283) | 223 (177, 270) | 225 | 215 |

- Strengths/Weaknesses of GRADE CGM Results
  - Strengths
    A. Large population.
    B. Excluded participants with potential interferences with HbA1c assay.
    C. +/- Representative of US population with T2D.
    D. Adequate number of "minorities".
    E. Careful measurement of AG with CGM.
    F. Several glycated proteins measured.
  - Weaknesses
    A. Limited period of CGM.
    B. No direct measurements of relationship between complications and glycemic levels across races.

- Implications/Conclusions of GRADE CGM Results
  1. There are differences in the relationship between HbA1c and AG levels between White and Black populations. Similar results in the two studies with adequate representation.
  2. The differences apply across at least two glycated proteins, suggesting that race-based differences in red cell lifespan/turnover are not the cause.
  3. There are insufficient data comparing the relationship of glycemia and complications across races to determine whether diagnostic criteria should be adjusted by race; however,
  4. Although the differences in AG for HbA1c are modest (~10 mg/dl per 1% A1c);
  5. Considering that we use HbA1c levels to guide BG management, ignoring differences in the translation of A1c to AG levels could result in under-treatment of Black populations and result in greater risk for complications.
- There has been much debate regarding use of race-based standards in medicine including the use of race in interpreting HbA1c
- Arguments Against Using Race-Based Adjustments/Modifications in Medicine
  1. Race is a complex construct and we risk mis-classifying individuals.
  2. "Race" has been used in harmful ways- stigmatization and worse.
  3. Race is associated with some well-understood biological factors/conditions (SC disease, other hemoglobinopathies, G6PD-deficiency, other genetic variables) that affect RBC turnover and, in turn, the relationship between AG and HbA1c.
  4. Race is an (overly) simplistic means of classifying individuals and may lead to a variety of unintended harms.
  5. However,
     - In GRADE, persons with any of the well-understood factors that interfere with the interpretation of HbA1c were excluded.

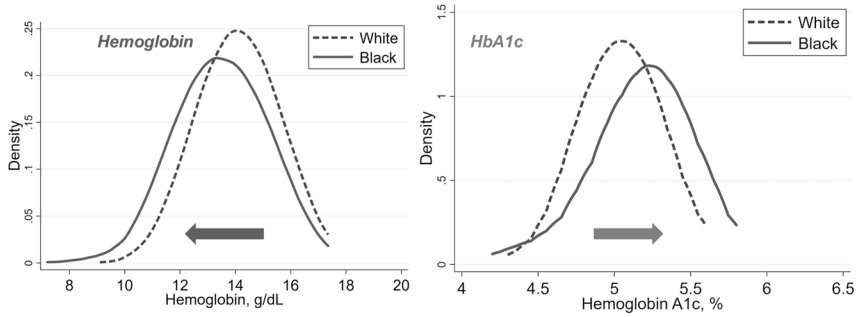
    - Moreover, the differences in glycation applied to both Hgb and albumin, suggesting that the inter-racial differences were not related to some simple construct regarding RBC kinetics.
    - The only criterion applied to racial description in GRADE was self-description, which is widely available.
    - Even if we understood better the basis of the inter-racial differences between AG and HbA1c, their measurement might not be practical or affordable. In the meantime,
    - Although the explanation for the now established differences in the relationship between HbA1c and AG levels across races is unclear, that doesn't mean that we shouldn't act on them, especially if ignoring them could lead to harm.
- A Modest Hypothesis to Explain the Inter-racial Differences between AG and HbA1c/GlycAlb
    1. Non-enzymatic glycation represents a simple mass-action phenomenon which is driven by the exposure/concentration of glucose and turnover of the protein ("available" amino groups and carbonyl of reducing sugars).
    2. The only other variable of importance is temperature (original description by Maillard).
    3. What if people with dark complexion had higher skin temperature (they do), which resulted in a modest increase in glycation of proteins at all concentrations of glucose?

**Con: Should we consider race-based HbA1c targets? No.:** E. Selvin

- Hemoglobin A1C – Fundamental to Diabetes Care
    1. Standard measure used to monitor glycemic control in persons with diabetes: Used to monitor and guide treatment
    2. Screening and diagnostic test for prediabetes and diabetes
    3. Surrogate endpoint for clinical trials of glucose-lowering therapies in type 1 and type 2 diabetes trials (FDA criteria)
- Limitations of HbA1c?
    1. Assay interferences: Some Hb traits interfere with interpretation of HbA1c assays, but this is not true for the majority of Hb variants (www.ngsp.org)
    2. Some conditions interfere with HbA1c test results: Altered red cell turnover, e.g. hemolytic anemia, transfusions, pregnancy, major blood loss
    3. Slightly higher levels of HbA1c in African Americans
        - This has been cited as a "limitation" of the HbA1c test
        - This is NOT a limitation of the HbA1c assay
            - "…the use of HbA1c levels for diagnosing diabetes mellitus or prediabetes [in African Americans] is ill-advised." Nature Reviews Endocrinology 6, 589-593; October 2010
            - "Plasma glucose level is more valid than hemoglobin A1c for diagnosing prediabetes or diabetes in black persons." Endocr Pract. 2012; 18:356-362
            - "A1c may not be valid for assessing and comparing glycemic control across racial and ethnic groups or as an indicator of health care disparities." Diab Care 2007; 30(10):2453-2457
            - "In African descent populations in the United States, the utility of HbA1c is limited in screening for glycemic status, determining care methods, assessing risk of type 2 diabetes complications, or analyzing health disparities." Prev Chronic Dis 2021;18:200365
- Race – What are we measuring?

1. Race is a social construct
2. “Race is an unscientific, societally constructed taxonomy that is based on an ideology that views some human population groups as inherently superior to others on the basis of external physical characteristics or geographic origin. The concept of race is socially meaningful but of limited biological significance.” – Williams et al, 1994
3. “[…] present-day inequalities between so-called “racial” groups are not consequences of their biological inheritance but products of historical and contemporary social, economic, educational, and political circumstances.” – American Anthropological Association, 1998
4. Williams D et al, Public Health Rep. 1994; American Anthropological Association Statement on Race. Adopted May 17, 1998. Available at: https://www.americananthro.org/ConnectWithAAA/Content.aspx?ItemNumber=2583&RDtoken=47501&userID=6944

- Race and Ancestry: Subcontinental genetic variation in the All of Us Research Program: Implications for biomedical research. Gouveia et. al, Am J Hum Genet 2025 Jun 5;112(6):1286-1301
    1. “Race and ethnicity are poor proxies for genetic ancestry; therefore, biomedical research should adjust directly for ancestries estimated from genetic data rather than relying on self-identified race or ethnicity,” Charles Rotimi, scientific director of the National Human Genome Research Institute
    2. “The clear message here is that these are two distinct constructs, they mean different things, and they should not be used interchangeably.” Luisa Borrell, CUNY School of Public Health
- Racial disparities in diabetes in the US: Racial disparities in diabetes and its complications are primarily driven by historical factors:
    1. Slavery
    2. Segregation
    3. Jim Crow laws
    4. Redlining and other racist policies
    5. Environmental exposures
    6. Differences in the built environment and food availability
    7. …other social determinants of health and health care
- Distributions of hemoglobin and HbA1c in young, healthy adults (NHANES): Difference in HbA1c between Black and White Adults: ~0.2 %-points




- Strong link between A1C and clinical outcomes
    1. Large and robust literature linking HbA1C with clinical outcomes
    2. No evidence for racial differences in associations with outcomes or in clinical trials of glucose-lowering interventions (e.g. subgroup analysis in ACCORD)
    3. Most studies show higher risk of diabetes (e.g. DPP Trial) and its complications in Black adults and other racial or ethnic minority groups compared to White adults

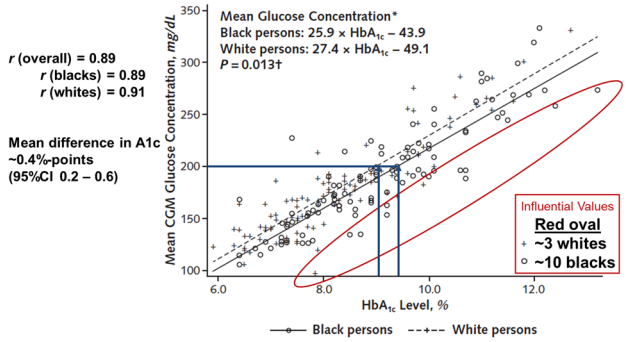
4. No racial differences in the correlations of HbA1c with average glucose (via CGM) or with fasting glucose -- Bergenstal et al 2018, Ann Int Med

- Why are there small but systematic differences in HbA1c by race?
    1. Glucose-independent race differences in HbA1c are small
        - ~0.2 %-points in HbA1c
        - In diabetes, any non-glycemic determinants will typically be dwarfed by differences in true hyperglycemia
    2. Small differences in HbA1c between groups (e.g. Black vs White adults) may be explained by "hematologic differences" in a subgroup: Emerging data suggest genetic differences in a subgroup may underlie small differences in HbA1c that are independent of glycemia
    3. Selvin et al Ann Int Med 2011; Selvin et al Diabetes Care 2013; Selvin Diabetes Care 2016
- There is a growing body of literature describing genetic differences in HbA1c in subgroups of the population. The groups where the effect is large are rare.
- Genetic differences ≠ Race differences
    1. Some of the emerging genetic variations associated with hemoglobin and HbA1c vary by race/ethnicity
    2. Race is associated with genetic ancestry and therefore indirectly related to genetic variants that may affect HbA1c
    3. Likely a subgroup, i.e. not ALL adults who self-identify as Black
    4. Uncommon genetic variations are likely driving race differences in distributions of hemoglobin and HbA1c in the population
    5. Conditions that affect red cell turnover, hemoglobin, and/or HbA1c may overlap with race but are NOT race
- When to consider race in medical decision making?
    1. For screening? Is it ok to use a non-causal risk factor to identify high-risk groups?
    2. For treatment decisions?
        - We should NOT use a non-causal risk factor for treatment decisions
        - High risk of individual misclassification
        - Race is a poor surrogate for differences in underlying causes of disease risk
- Screening criteria for diabetes or prediabetes, ADA 2025
    1. Testing should be considered in adults with overweight or obesity (BMI ≥25 kg/m2 or ≥23 kg/m 2 in individuals of Asian ancestry) who have one or more of the following risk factors:
        - First-degree relative with diabetes
        - **High-risk race, ethnicity, and ancestry (e.g., African American, Latino, Native American, Asian American)**
        - History of cardiovascular disease
        - Hypertension (≥130/80 mmHg or on therapy for hypertension)
        - HDL cholesterol level <35 mg/dL (<0.9 mmol/L) and/or triglyceride level >250 mg/dL (>2.8 mmol/L)
        - Individuals with polycystic ovary syndrome
        - Physical inactivity
        - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans, metabolic dysfunction–associated steatotic liver disease
- Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes—2025: "Historically, a correction factor for muscle mass was included in a modified equation [for

kidney function] for African American people; however, race is a social and not a biologic construct, making it problematic to apply race to clinical algorithms."

- Why race-specific cut points for A1C won't help
    1. Race does not reliably reflect individual genetic or other biological information
    2. Using race or a race-based adjustment to guide treatment will result in misclassification of individual patients.
    3. Race adjustments may line up populations on average but can result in substantial misclassification of the individual
    4. Bergenstal et al. Ann Int Med 2017; 167:95

*Figure 1.* Mean glucose concentration as measured by CGM versus $HbA_{1c}$ level, by race.




* Adjusted for age (intercept and slope). Age was centered at 30.9 y (the mean age in the data set).
† Two-degree-of-freedom test for difference in slope and intercept simultaneously.

- Key points
    1. The strong link between HbA1c and complications in both Black and White adults ▶ critical clinical importance for use of HbA1c
    2. Race is an extremely poor proxy for unknown genetic variation
    3. Need to move beyond "race-based analyses" related to HbA1c
    4. Need to better understand non-glycemic factors that may be relevant and reduce real disparities in diabetes
- Implications of Racial Differences in HbA1C
    1. Current evidence supports similar interpretation of HbA1c test results across all race and ethnic groups for diagnosis and treatment of diabetes
    2. Calls for "race-specific" cut-points for diabetes draw attention away from real health disparities
    3. In the absence of an understanding of the full genetic determinants of HbA1c any "race-specific" approaches will be WRONG
    4. Discouraging use of HbA1c in certain race or ethnic groups could worsen diabetes disparities
- Where to go from here?
    1. More work to understand contribution of non-glycemic factors to HbA1c--E.g., ongoing genetics work that relates to hematologic genetic variants
    2. Race is not a precise construct and a poor surrogate for differences in underlying causes of disease risk
    3. Do not use race-specific cut-points – could do more harm than good
        - Risk of misclassification/misdiagnosis
        - Major causes of disparities in diabetes are not "hematological"
        - Ignores individuals of mixed heritage
- HbA1c is a Useful and Valid Test Across Race/ethnic Groups

1. Genetic differences ≠ Race differences
2. For clinical cut-points and medical decision-making, we need to understand underlying causes of group-level differences and focus on objective, biological measures
3. In the short term and from a pragmatic standpoint, we can use a combination of fasting glucose and HbA1c to diagnose diabetes and pay attention to any discordance

**Update on Diabetes and Kidney Disease:** I. Hirsch

- Introduction: The BLOSSOM Study
    1. BLOod Sugar Sensing On Maintenance dialysis (BLOSSOM) cohort study, which enrolled 420 participants with kidney failure treated with maintenance dialysis
    2. Parent study: 263 with, 157 without diabetes
    3. We used the Dexcom G6 Pro worn concurrently, to ascertain glycemia (and GMI)
    4. GMI, HbA1c, GA, and fructosamine measured at baseline, 3 weeks, 3 months and 12 months after enrollment
    5. Journal of the American Society of Nephrology ():10.1681/ASN.0000000693, March 21, 2025. | DOI: 10.1681/ASN.0000000693

| | Overall (N = 251) | HD (N = 233) | PD (N = 18) |
|---|---|---|---|
| Age, years | 60.8 (13.7) | 60.6 (13.4) | 63.4 (16.9) |
| Male sex | 143 (57%) | 134 (58%) | 9 (50%) |
| Race | | | |
| American Indian/Alaska Native | 6 (2%) | 5 (2%) | 1 (6%) |
| Asian | 12 (5%) | 11 (5%) | 1 (6%) |
| Black | 41 (16%) | 38 (16%) | 3 (17%) |
| Multiracial | 11 (4%) | 11 (5%) | 0 (0%) |
| Native Hawaiian/Pacific Islander | 10 (4%) | 10 (4%) | 0 (0%) |
| White | 122 (49%) | 110 (47%) | 12 (67%) |
| Other/prefer not to answer | 49 (20%) | 48 (21%) | 1 (6%) |
| Hispanic ethnicity | 70 (28%) | 66 (28%) | 4 (22%) |
| Dialysis vintage, years | 3.1 (3.5) | 3.3 (3.6) | 1.5 (1.5) |
| Diabetes type | | | |
| No diabetes | 92 (37%) | 84 (36%) | 8 (44%) |
| Type 1 | 5 (2%) | 4 (2%) | 1 (6%) |
| Type 2 | 154 (61%) | 145 (62%) | 9 (50%) |
| ESA use | 192 (76%) | 179 (77%) | 13 (72%) |

**Figure 1. Mean glucose vs GMI, sub panels are HD and PD**

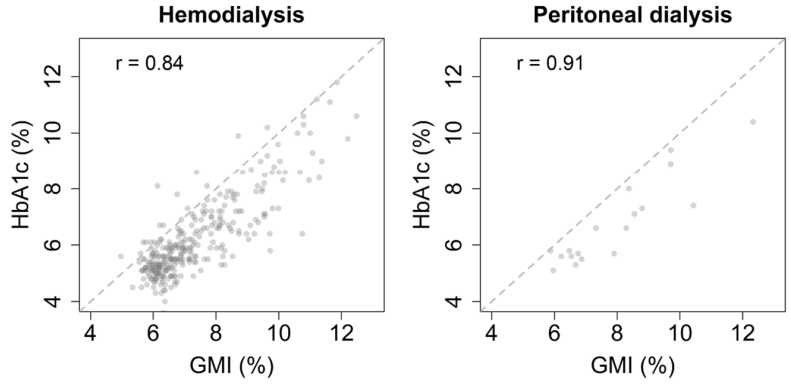



**Table 3. Measures of correlation, variability, and accuracy of glycemia markers for GMI, overall and by dialysis modality (across all time points)**

| | Overall | | | HD | | | PD | | |
|---|---|---|---|---|---|---|---|---|---|
| | HbA1c | GA | Fruct. | HbA1c | GA | Fruct. | HbA1c | GA | Fruct. |
| N | 323 | 323 | 323 | 305 | 305 | 305 | 18 | 18 | 18 |
| Metric | | | | | | | | | |
| Pearson r | 0.85 | 0.87 | 0.71 | 0.84 | 0.88 | 0.74 | 0.91 | 0.81 | 0.84 |
| Spearman r | 0.77 | 0.84 | 0.66 | 0.77 | 0.86 | 0.69 | 0.84 | 0.67 | 0.75 |
| Absolute residuals, median (IQR) | -0.0 (-0.4-0.4) | -0.2 (-1.8-1.5) | -5.6 (-44.3-37.8) | -0.0 (-0.4-0.4) | -0.2 (-1.8-1.4) | -3.4 (-40.1-34.3) | -0.1 (-0.4-0.3) | 0.0 (-2.0-1.9) | 10.6 (-17.5-27.2) |
| p10 (%) | 63 | 55 | 41 | 63 | 54 | 41 | 72 | 44 | 56 |
| p20 (%) | 91 | 88 | 75 | 90 | 88 | 77 | 100 | 78 | 83 |
| p30 (%) | 98 | 96 | 93 | 98 | 97 | 94 | 100 | 94 | 94 |

*P10(%): percentage of a biomarker that falls within 10% for the predicted mean of that level of CGM glucose

| Covariate determinants of bias of glycemic markers with mean CGM glucose | HbA1c (N = 251) | | Glycated albumin (N = 251) | | Fructosamine (N = 251) | |
|---|---|---|---|---|---|---|
| | % difference (95% CI) | p-value | % difference (95% CI) | p-value | % difference (95% CI) | p-value |
| Age (per 10 yr increment) | -0.3 (-1.2, 0.6) | 0.46 | 0.7 (-0.6, 2.0) | 0.32 | 0.0 (-1.8, 1.7) | 0.96 |
| Male sex | -2.1 (-4.9, 0.8) | 0.15 | 1.3 (-2.3, 5.2) | 0.48 | 2.6 (-2.3, 7.7) | 0.31 |
| Race/ethnicity | | | | | | |
| Black | 0.1 (-3.4, 3.6) | 0.98 | 1.7 (-2.6, 6.2) | 0.45 | 0.5 (-6.3, 7.8) | 0.88 |
| Other | -1.4 (-4.6, 1.9) | 0.40 | 1.5 (-2.6, 5.8) | 0.47 | 0.7 (-4.3, 6.0) | 0.79 |
| Hispanic ethnicity | 3.1 (-0.6, 7.0) | 0.10 | 2.0 (-1.9, 6.0) | 0.33 | 0.8 (-4.4, 6.4) | 0.76 |
| Dialysis vintage (per year increment) | 0.0 (-0.4, 0.4) | 0.96 | **0.8 (0.1, 1.4)** | **0.02** | **1.4 (0.8, 2.1)** | **< 0.0001** |
| Diabetes | | | | | | |
| Type 1 | 3.1 (-7.1, 14.5) | 0.57 | 16.3 (-2.6, 38.9) | 0.09 | 11.4 (-11.8, 40.7) | 0.37 |
| Type 2 | 1.8 (-1.7, 5.4) | 0.32 | **7.2 (2.9, 11.7)** | **0.0009** | **8.6 (2.9, 14.6)** | **0.003** |
| ESA use | -2.8 (-6.2, 0.6) | 0.11 | -2.4 (-7.0, 2.4) | 0.32 | 2.4 (-3.0, 8.1) | 0.38 |
| ESA dose (per 100 microgram increment) | **-3.3 (-5.5, -1.1)** | **0.004** | 0.5 (-1.5, 2.7) | 0.61 | 1.6 (-1.2, 4.5) | 0.27 |
| IV iron use | -2.6 (-5.4, 0.2) | 0.07 | -1.2 (-4.5, 2.2) | 0.49 | 4.5 (-0.1, 9.4) | 0.06 |
| PO iron use | 2.8 (-0.5, 6.1) | 0.10 | -1.4 (-6.2, 3.7) | 0.59 | -6.2 (-13.3, 1.4) | 0.11 |
| BMI (per 5 kg/m2 increment) | **1.6 (0.7, 2.6)** | **0.0007** | **-2.5 (-3.6, -1.5)** | **< 0.0001** | **-2.2 (-3.5, -0.8)** | **0.002** |
| Hemoglobin (per 1 g/dL increment) | **2.4 (1.2, 3.5)** | **< 0.0001** | -0.5 (-2.0, 1.1) | 0.55 | 0.7 (-1.1, 2.5) | 0.44 |
| Serum albumin | | | | | | |
| 3.8 - < 4.2 g/L | **6.9 (2.5, 11.4)** | **0.002** | -2.9 (-7.9, 2.4) | 0.28 | 3.3 (-2.7, 9.7) | 0.28 |
| ≥ 4.2 g/L | **7.2 (2.8, 11.9)** | **0.001** | -2.6 (-7.6, 2.6) | 0.32 | **7.6 (0.8, 14.9)** | **0.03** |

**Table 2. Within-person repeatability of glycemia markers and GMI**

| | 3 weeks | | 3 months | | 12 months | |
|---|---|---|---|---|---|---|
| N | 31 | | 28 | | 13 | |
| Median (IQR) days from initial measurement | 18 (12-36) | | 105 (92-135) | | 368 (365-376) | |
| | Within-person correlation | Correlation of change in biomarker with change in CGM mean glucose | Within-person correlation | Correlation of change in biomarker with change in CGM mean glucose | Within-person correlation | Correlation of change in biomarker with change in CGM mean glucose |
| HbA1c | 0.90 | 0.35 | 0.93 | 0.16 | 0.95 | -0.19 |
| Glycated albumin | 0.94 | 0.55 | 0.92 | 0.49 | 0.77 | 0.91 |
| Fructosamine | 0.87 | 0.32 | 0.86 | 0.07 | 0.46 | 0.39 |
| GMI | 0.93 | -- | 0.90 | -- | 0.87 | -- |

- Conclusions: In our BLOSSOM Study with dialysis patients with and without diabetes
    1. There is good correlation within individuals for all biomarkers
    2. We see the expected bias of HbA1c with GMI in this population.
    3. There is not as good correlation with the change in all biomarkers with the change in GMI
    4. Some biases were expected, others not

**Discussion:**

D. Leslie noted that there was a paper in the Journal of Human Genetics a few years ago that examined the relationship between HbA1c and the insulin receptor gene in Greenland Inuits which might be relevant to the BMI data observed in the study.

*K. Kabytaev thanked everyone for their attendance and the discussions. The meeting was adjourned at 9:45 AM.*

*Minutes prepared by Curt Rohlfing 7/17/2025.*