Meeting of the NGSP Clinical Advisory Committee Minutes

2022 ADA 82nd Scientific Sessions
New Orleans, LA
Monday June 6, 2022 2:30 – 4:30 PM

Guido Freckmann	Inst for Diabetes Tech	David Sacks	NIH, NGSP
William Herman	Univ of Michigan	Elizabeth Selvin	John Hopkins
Andreas Karwath	UHB, NHS, UK	Yoshiteru Suzuki	Asahi-Kasei
Sue Kirkmann	UNC		
Takuji Kohzuma	Asahi-Kasei	*Remote Audio via Zoom*	
Randie Little	NGSP	Beena Alkolkar	NIH
David Leslie	St. Bartholomews UK	Jackie Feldberg	Bio-Rad Laboratories
Sue Manley	UHB, NHS, UK	John Higgins	Mass Gen Hospital
Michael McPhaul	Quest Diagnostics	Charles Peterson	Formerly NHLBI
Julie Myers	Bio-Rad Laboratories	Leonard Pogach	VA
Curt Rohlfing	NGSP	Michael Steffes	Univ of MN

Welcome and introduction: D. Sacks opened the meeting at 2:30 pm and welcomed everyone. Participants introduced themselves. The 2019 NGSP Clinical Advisory Committee meeting minutes were approved.

NGSP Update: R. Little

- Structure of the NGSP
    1. The NGSP network consists of an administrative core, the Central Primary Reference Laboratory (CPRL), backup PRLs , and 10 Secondary Reference Laboratories (SRLs).
    2. The NGSP network labs are located in the U.S., the Netherlands, Japan and China.
    3. The NGSP network is monitored monthly via sample exchanges.
    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
    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 comparison against a SRL using 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.
- NGSP Certification
    1. The number of certified methods continues to increase, the number of certified labs has leveled off, due at least in part to consolidation of some of the larger laboratories.

2. Certified laboratories are distributed throughout the world.

- NGSP and CAP criteria
    1. NGSP Manufacturer and Level II Lab Certification Criteria: 36/40 results must be within ±5% (37/40 for Level 1 Labs). Level 1 labs are also monitored quarterly.
    2. The CAP Survey Grading for HbA1c is still ±6% of the target value assigned by the SRLs.
    3. CAP is waiting for CMS to make a decision of whether to make HbA1c a regulated analyte, and if so what criteria they will establish, before adopting ±5%. CMS originally proposed ±10%, which has generated much opposition from the clinical and laboratory communities.
- 2022 CAP GH5A survey data (5 samples)
    1. There has been considerable improvement in the comparability of results since 1993 when the DCCT ended.
    2. Overall pass rates were 96.9% to 98.6% for the 5 survey samples. Individual method pass rates were 87% - 100%.
    3. All-method CVs on the survey have decreased between 2000 and 2022. Our goal for all-method CVs is <3.0%. CVs for the current survey were 2.2% - 2.7%.
    4. Method-specific, between-laboratory CV's ranged from 1.0% to 3.5%.
    5. Overall, 83% of laboratories are using methods with CVs < 3% at all five HbA1c levels.
- 2021 Hb variant interference publication: Clin Chim Acta 522 (2021), 31-35.
    1. Evaluated 15 assay methods for potential interferences from HbS, HbC, HbE and HbD traits.
    2. Only 3 methods, two POC (Siemens DCA Vantage and Roche b101) and one ion-exchange HPLC method (Tosoh G11), showed clinically significant interference from one or more of these variants.
    3. There is some question regarding two of these methods. A new paper was just published where the authors found that the DCA Vantage and Tosoh G11 did not show clinically significant differences (Clin Chim Acta 532 (2022):61-63). This may be due to differences in reagent lots or software.

Discussion:

Variant Interference Study

S. Manley asked whether the relationship between glucose and HbA1c for the different variants was examined in the study. R. Little said no, that would be an entirely different study. For one thing glucose could not be measured, as many of the variant samples were obtained already frozen. R. Cohen asked about hemoglobins D and E, in what populations are these found and do we have any idea of the prevalence. R. Little said they are most common in Southeast Asia and India, the prevalence of these variants can be high in specific areas, especially for E. In the U.S. we see more S and C, but we see some E and D along with other less common variants. Variants are now commonly found virtually everywhere in the world, including Japan which was previously thought to have very few. S. Manley noted that D and E are common in the UK, as are S and C. They have seen some differences in the relationships between glucose and HbA1c for individual subjects with these variants when compared to non-variant subjects. A method may not show analytical interference from these variants, but that does not mean the HbA1c/glucose relationship is the same for variant vs. non-variant patients. R. Little agreed, adding that this may apply to all patients, even among those without variants. S. Manley noted that with ion-exchange HPLC methods you can tell if a variant is present, but

for other common method types there is no way to tell. D. Sacks said the most common method types in the U.S. are ion-exchange HPLC and immunoassay. Capillary electrophoresis and enzymatic assays are becoming more common, with CE you can see if there is a variant present but with enzymatic assays you cannot. CAP includes a common variant sample (usually HbS trait) in the survey every few years. The labs do not know it is a variant prior to running the samples, so from this we get information on how the labs report variant results. Sometimes we see where a lab will report a result from a method that has variant interference but the lab using that method has no way of knowing the variant is present. Unfortunately the PT material supplier for CAP is not able to obtain a large enough sample volume to include D or E, so we have not been able to include those.

CAP Survey

D. Leslie asked what proportion of patient HbA1c results in the U.S. are generated by laboratories that participate in the CAP survey. D. Sacks responded that about 3500 labs participate in the CAP survey, roughly 10-12% are outside of the U.S. PT is required in the U.S. by law, and CAP is by far the largest PT provider in the U.S. There is another provider of HbA1c PT in the U.S. that does not use whole blood as CAP does. There is no way to know what percentage of labs use this alternative survey, and even if we knew that there is no way to determine the percentage of patients. Some large labs run thousands of patient samples a day, while other labs run small numbers. S. Manley said they have a very reliable PT provider in the UK and that PT is required by law in the UK. R. Little asked if anyone knew how many countries require PT, J. Myers said France, Germany and Australia do. R. Little noted that in the U.S. there are POC methods that are CLIA-waived, meaning that PT is not required for CLIA-waived sites using those methods and most do not. This is a problem in terms of knowing how those methods are performing in the field.

Continuous Glucose Monitoring: What's New Since the 2011 ADA-AACC Laboratory Medicine Guidelines That Informs New Recommendations?: M. Sue Kirkman

- What is Continuous Glucose Monitoring?
    1. Devices that measure INTERSTITIAL (IS) glucose concentration every 5-15 minutes
    2. Interstitial glucose correlates highly with blood glucose, but can have a lag when blood glucose levels are changing rapidly
    3. Current CGMs consist of:
        - glucose sensor placed under the skin
            - transcutaneous catheter that remains in place for 1-2 weeks, or
            - free-standing device implanted into the subcutaneous space for a period of months
        - transmitter worn on the skin
        - receiver for the data
            - dedicated receiver or
            - a smart phone or smart watch
- 1st- and 2nd-Generation Interstitial or CGMs (2002-2008)
    1. GlucoWatch G2 Biographer
        - FDA approved for adults in 2001 and children 7-17 yrs old in 2002
        - When user triggered it, measured IS glucose by causing transudation across skin
    2. Dexcom: SEVEN Sensor (FDA approved for adults in 2006)
    3. Medtronic: Guardian REAL-Time Sensor (FDA approved for adults/children in 2005)
    4. Abbott: FreeStyle Navigator (FDA approved for adults in 2008)
- What Was Situation at Time of the 2011 ADA-AACC Guideline?

1. Several CGM systems on market
2. Accuracy not very high
3. FDA-approved only for ADJUNCTIVE use (user supposed to check blood glucose by meter to make decisions such as how much insulin to take for a meal)
4. One 26-week RCT of CGM vs BGM 336 people with type 1 diabetes:
    - HbA1c significantly lower in adults over age 25 years (-0.53%)
    - No significant change in A1C in children (age 8-14 yrs) or adolescents/young adults (15-24 yrs)
    - A1C reduction correlated with higher wear time in all groups (adults wore most)
    - No differences in hypoglycemia (study not powered for this)
    - Tamborlane WV at al. JDRF Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008;359:1464–1476

- 2011 Recommendations
    1. Real-time continuous glucose monitoring (CGM) in conjunction with intensive insulin regimens can be a useful tool to lower HbA1c in selected adults (age > 25 years) with type 1 diabetes. A (high)
    2. Although the evidence for HbA1c lowering is less strong in children, teens, and younger adults, real-time CGM may be helpful in these groups. Success correlates with adherence to ongoing use of the device. B (moderate)
    3. Real-time CGM may be a supplemental tool to SMBG in those with hypoglycemia unawareness and/or frequent episodes of hypoglycemia. B (low)
    4. Patients require extensive training in using the device. Available devices must be calibrated with SMBG readings and the latter are recommended for making treatment changes. GCP
- What's Changed? CGMs are More Accurate

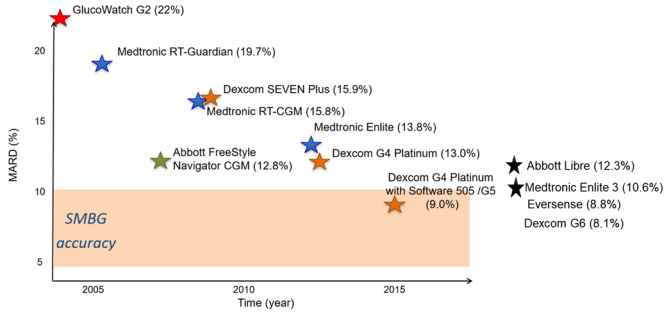
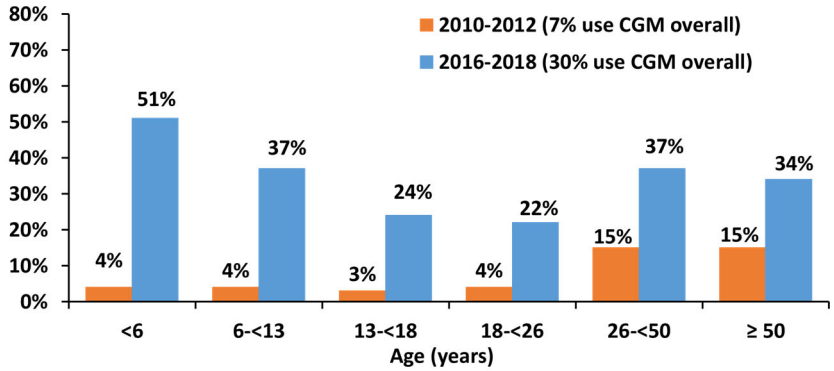


Figure 1. The accuracy timeline of CGM sensors over the last 15 years.

Faccinetti A. Sensors 2016;16:20932016

- What's Changed? FDA Approvals for "Non-Adjunctive" Use and Some Systems Factory-Calibrated
    1. RCT of adjunctive vs non-adjunctive use found no differences in A1C, hypoglycemia: Aleppo G, et al.; REPLACE-BG Study Group. REPLACE-BG: a randomized trial comparing continuous glucose monitoring with and without routine blood glucose monitoring in adults with well-controlled type 1 diabetes. Diabetes Care 2017; 40:538–545
    2. FDA now approves most systems for non-adjunctive use
    3. Several modern sensors "factory-calibrated," no calibration with meter required
    4. More/most insurance plans began to cover, at least for people on insulin
- What's Changed: CGM Use Has Increased Markedly



Wong J et al. Real-Time CGM Among Participants in the T1D Exchange Clinic Registry. Diabetes Care 2014;37:2702-09

- Current CGM Systems
    1. Dexcom G6 CGM System
        - Factory calibrated
        - Approved for non-adjunctive use (don't routinely need SMBG)
        - 10 days of sensor use
        - Measures glucose every 5 min via glucose oxidase-impregnated sensor
        - Alarms for hypoglycemia and hyperglycemia thresholds and alerts for trending high or low
        - Can display glucose levels on a receiver, phone, or watch
        - CGM component of one (soon two) "hybrid closed-loop" system
        - No interference by therapeutic levels of acetaminophen
    2. Abbott FreeStyle Libre 2
        - 14-day factory-calibrated sensor; Glucose-oxidase-impregnated
        - Approved for non-adjunctive use
        - Records glucose concentration every 15 minutes
        - Patient swipes receiver or smart phone over sensor to transfer glucose data (is-CGM or "flash" CGM)
        - No alarms or alerts in original Libre (Libre 2 has optional high/low alarms but no trend alarms)
        - No interference with therapeutic levels of acetaminophen
    3. Medtronic Guardian Sensor 3/Guardian Connect
        - Measures glucose every 5 minutes (G-Ox)
        - Sensor life 7 days
        - Need to calibrate with fingerstick 2-4x/day
        - Not approved for non-adjunctive use (Medicare used to not cover; this changed early 2022)
        - Transmits to smart phone
        - Predictive alerts and alarms
        - CGM component of a hybrid closed-loop system (770G) and low-glucose-suspend (630G) Medtronic pump system (pretty much only use of this CGM)
        - Positive bias with therapeutic levels of acetaminophen
    4. Eversense E3 System
        - Sensor
            - Sensor implanted under skin of arm
            - Measures glucose every 5min through "glucose-indicating polymer"
            - Sensor labeled for 6 months in US; then must remove and place new other arm

        - Calibrate with fingerstick 2-4x/day
        - No acetaminophen interference at therapeutic doses
    - Smart transmitter
        - Non-adjunctive use
        - Rechargeable
        - On-body vibe alerts
        - On-skin adhesive
    - Mobile application
        - Transfers to smart phone/watch:
        - Trends, alerts w/predictive alerts
- Comparison of 2022 CGM Features

	Dexcom G6	Medtronic Guardian 3	Eversense E3	Libre 2
Age (FDA approved)	≥2 yrs	14-75 yrs	≥18 yrs	≥ 4 yrs
CGM or isCGM	rt-CGM	rt-CGM	rt-CGM	isCGM
Surgically Implanted	No	No	Yes	No
Sensor life	10 days	7 days	6 months	14 days
Sensor calibration	Factory	BGM 2-4x/d	BGM 2x/d	Factory
Non-adjunctive use	Yes	No	Yes	Yes
Alarms/alerts	Yes	Yes	Yes	Yes (limited)
Works with hybrid closed-loop pump	Yes	Yes	No	No

*Medicare will cover CGM approved only for adjunctive use IF used with Medtronic pump

- What's Changed? More Consistent Ways to View and Analyze CGM Data
- Consensus on Standardized CGM Metrics

METRIC	METRIC	Level
1. Number of days on CGM worn (recommend 10-14 days)	6. TAR: % of readings & time >250 mg/dL (>13.9 mmol/L)	2
2. Percentage of time CGM is active (minimum 70% of data from 14 days)	7. TAR: % of readings & time >181-250 mg/dL (>10.1-13.9 mmol/L)	1
3. Mean plasma glucose	8. TIR: % of readings & time 70-180 mg/dL (3.9-10.0 mmol/L)	In Range
4. Glucose management indicator (GMI)	9. TBR: % of readings & time 54-69 mg/dL (3.0-3.8 mmol/L)	1
5. Glycemic variability (%CV) target ≤35%	10. TBR: % of readings & time <54 mg/dL (< 3.0 mmol/L)	2

Use Ambulatory Glucose Profile (APG) for CGM report

- Consistent information on report:
    1. Average glucose and how much variability
    2. "Estimated A1C" (GMI): good for telehealth!
    3. Percent of time "in range" (TIR)
    4. Percent of time low or very low
    5. Percent of time high or very high

- Diabetes Care. 2018;41(11):2275-2280. doi:10.2337/dc18-1581

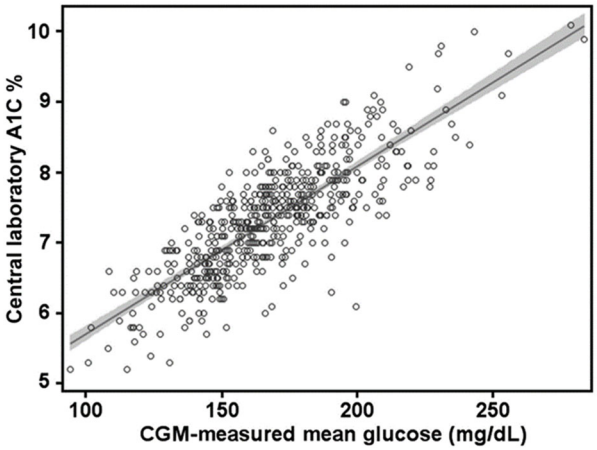
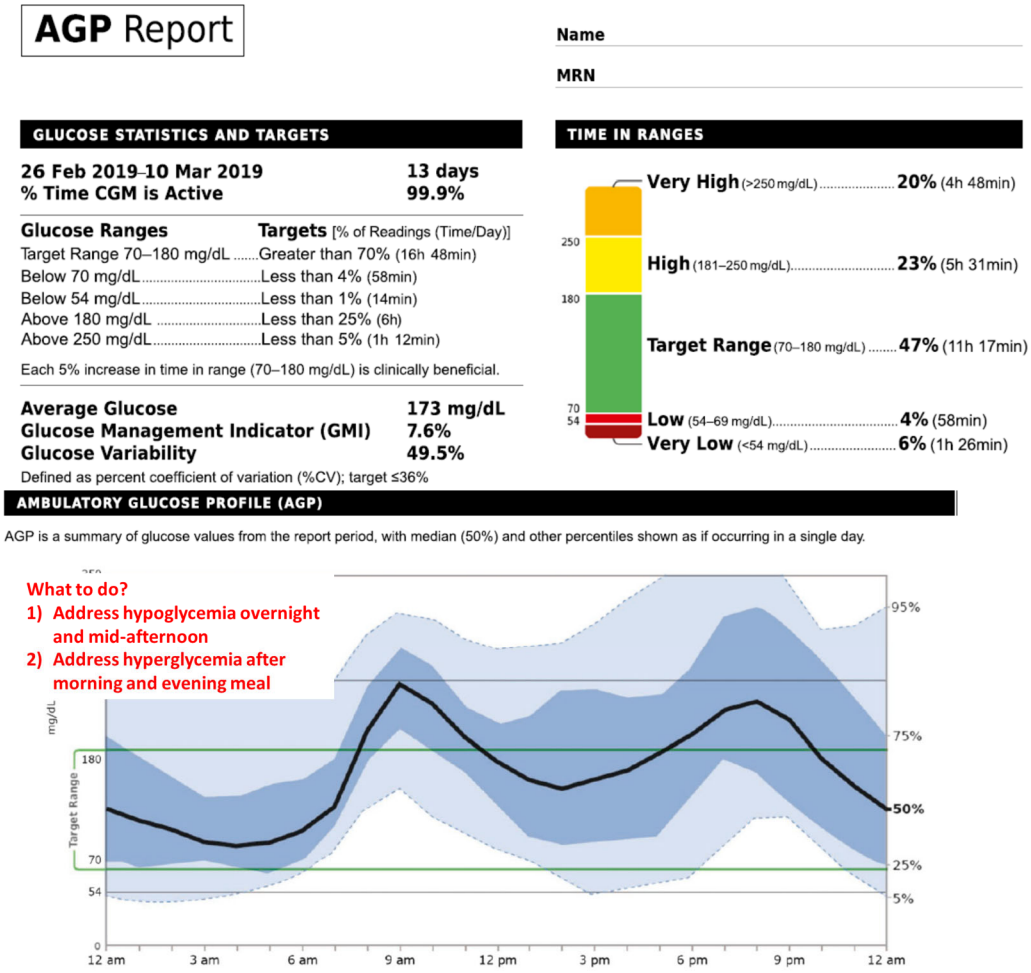


Figure Legend:
Plot of CGM-measured mean glucose concentration vs. central laboratory–measured A1C used to compute the formula to estimate GMI, combining data from four randomized trials using the Dexcom G4 sensor with 505 software (N = 528) described in the Supplementary Data. The shaded area represents the 95% CI of the regression line. The regression equation to compute GMI (%) = 3.31 + 0.02392 × [mean glucose in mg/dL] or GMI (mmol/mol) = 12.71 + 4.70587 × [mean glucose in mmol/L]. A calculator to compute GMI is available at www.jaeb.org/gmi and www.AGPreport.org/agp/links.

- Battelino T et al. Diabetes Care 2019;42:1593-1603



- Hybrid* Closed-Loop Pump Systems
    1. *Hybrid: Only controls basal rates, wearer still has to bolus for meals
    2. Medtronic 770G (Previous version (670G): First HCL System to Market)
    3. T:Slim X2 with Control IQ Early 2020
    4. T-Slim Pump and Dexcom CGM

- What Else Has Changed? A Lot More RCTs of CGM in Different Populations
    1. Benefit compared to blood glucose monitoring in:
    2. Adolescents/young adults with type 1 diabetes: Lower A1C: Laffel LM et al. JAMA 2020;323:2388-2396
    3. Older adults (> age 60 years) with type 1 diabetes and high rates of hypoglycemia: Less time in hypoglycemic range on AGP, fewer severe hypo events, lower A1C: Pratley RE et al. JAMA 2020;323:2397-2406
    4. Women with type 1 diabetes who are pregnant: Slightly lower A1C, more time in range, less hyperglycemia, better neonatal outcomes (fewer large-for-gestational age infants, NICU stays, episodes of neonatal hypoglycemia): Feig DS et al. Lancet 2017;390:2347-2359
    5. People with type 2 diabetes on insulin: Lower A1C: Beck RW et al. Ann Intern Med 2017;167:365-374
    6. And other RCTs, cohort studies. Mixed results in children.
- Recommendations in Updated ADA/AACC Guideline
    1. Use real-time CGM in conjunction with insulin as a tool to lower A1C levels and/or reduce hypoglycemia in teens and adults with type 1 diabetes who are not meeting glycemic targets, have hypoglycemia unawareness and/or episodes of hypoglycemia. A (high)
    2. Consider using intermittently scanned CGM in conjunction with insulin as a tool to lower A1C levels and/or reduce hypoglycemia in adults with type 1 diabetes who are not meeting glycemic targets, have hypoglycemia unawareness and/or episodes of hypoglycemia. B (moderate)
    3. Consider using real-time continuous glucose monitoring to improve A1C levels, time in range, and neonatal outcomes in pregnant women with type 1 diabetes. B (moderate)
    4. Consider using real-time CGM and ISCGM to lower A1C and/or reduce hypoglycemia in adults with type 2 diabetes who are using insulin and not meeting glycemic targets. B (moderate)
    5. Consider rt-CGM or is-CGM in children (less than 14 years old) with type 1 diabetes, based on FDA approval, as an additional tool to help improve glucose control and reduce the risk of hypoglycemia. B (low)
    6. Consider using professional CGM data coupled with DSME and medication dose adjustment to identify and address patterns of hyper- and hypoglycemia in people with T1D and T2D. GPP
    7. For patients using CGMs that require calibration by users, SMBG should be used to calibrate the CGM. Calibration should be done at a time when glucose is not rising or falling rapidly. For all patients using CGM, SMBG should be done during periods when CGM results are not available or when the CGM results are inconsistent with the clinical state or suspected to be inaccurate. GPP
    8. CGM data reports should be available in consistent formats that include standard metrics such as time in range, time in hyperglycemia, time in hypoglycemia, mean glucose, and coefficient of variation. GPP
- Conclusions
    1. A lot has changed with CGM since the 2011 guidelines:
    2. More accurate systems
    3. Most systems approved for non-adjunctive use
    4. Several do not require calibration by user
    5. Many more people with type 1 DM use CGM

6. More logical and consistent ways to collate and analyze large amounts of data from CGM
7. CGMs are critical part of hybrid closed-loop insulin delivery systems and movement towards fully "artificial pancreas"
8. Updated guidelines will reflect these changes

Discussion:

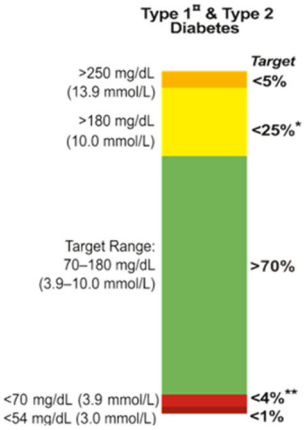
CGM use

E. Selvin asked about the Eversense system, is it widely used? S. Kirkman responded that they do not use it at all in their clinic, there are some Endocrinologists who like it but she did not think it was as widely used as some other CGM systems. Some do not like the fact that the sensor has to be implanted under the skin, then removed and another inserted every 6 months. S. Kirkman said that many of the same people that did not like the idea of estimating mean glucose from HbA1c favor GMI, which is just basically using the equation the other way around. E. Selvin and R. Little asked about the GMI study design, how and where was HbA1c measured? What type of subjects were included in the study? S. Kirkman did not know about the HbA1c measurements or exactly what type of patients were included, but she surmised that they are probably all type 1 patients and it is likely not a very ethnically diverse population. At least the ADAG study included people without diabetes and with pre-diabetes as well as some Type 2 subjects. E. Selvin said that the equation from the study has not been extensively validated, and it does not necessarily perform well outside of the context of the study population. S. Manley asked which CGMs were used in the GMI study, S. Kirkman said they were all Dexcom G4s. S. Manley noted that in the UK they have found differences in the CGM/HbA1c relationships in different ethnic populations. E. Selvin agreed, noting that data show that the GMI equation does not perform well in different populations. She has tried to get the data published but so far has not been able to. W. Herman said in their practice they have found that GMI and actual HbA1c are sometimes very close to each other, but other times they are discordant. E. Selvin asked about discordant results, in these cases how do you know which result is correct? R. Cohen said you do not know. There are underlying issues with both measurements, there are people that have belief systems that one or the other is correct but we are not at a point where we know which is correct and under what circumstances. W. Herman said he generally assumes that there is an issue with the HbA1c. R. Cohen said there are problems with CGM, including effects of pressure on the sensor site, altered blood flow, and intermittent periods of non-measurement. We are still in a learning phase, and are not at a point where we can say the HbA1c is necessarily wrong. S. Kirkman noted that only 72 hours of CGM data are required to obtain the GMI result. S. Manley said they have also had trouble publishing papers on this topic. HbA1c and CGM are not the same thing. S. Kirkman agreed noting that the fact that the two are expressed in the same units has the potential to cause confusion. E. Selvin agreed, saying that HbA1c has limitations but they are well understood, this is not currently the case with CGM. We do know that there is a lot of variability among CGMs that has nothing to do with HbA1c, and there may be other underlying physiological factors that cause variability in the measurements. S. Kirkman said that CGM is clinically useful in terms of showing time-in-range and when hypo and hyperglycemia is occurring, this is something that HbA1c will not tell you. She tends to look at that more than average glucose. Often people that are hypoglycemic at night are not aware that it is occurring, CGM is especially useful for detecting this. D. Leslie agreed, noting that it provides so much more information than just a high HbA1c, in addition to detecting nocturnal hypoglycemia it is also useful for detecting high post-prandial levels. S. Kirkman said it has been shown that some patients experience anxiety when starting CGM, they discover how high their post-prandial levels

actually are. W. Herman said this is not necessarily surprising, given that most patients in the U.S. are on a single shot of long-acting insulin per day.

Standardization of Glucose Monitoring: Guido Freckmann

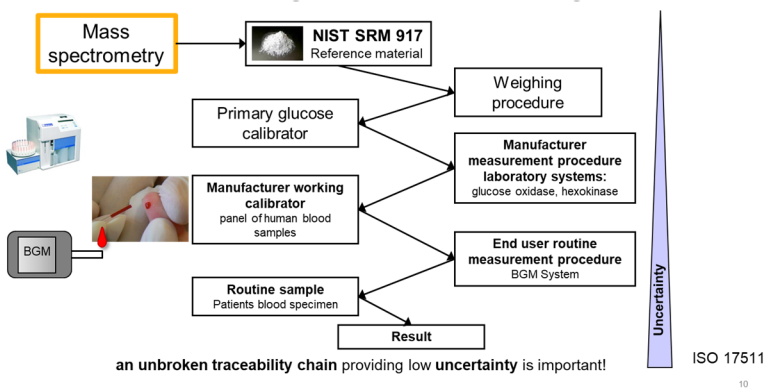
- Recent History: ADA and FDA
    1. Working Group on Continuous Glucose Monitoring (CGM): IFCC Scientific Division created a Working Group on Continuous Glucose Monitoring (WG-CGM) to define standard procedures for assessment of the analytical performance of CGM systems:
        - traceability, measurand, matrix, including the measurement uncertainty
        - evaluation procedures, including study procedures
        - metrics & corresponding minimum acceptance criteria
        - https://www.ifcc.org/ifcc-scientific-division/sd-working-groups/wg-cgm/
    2. Increased Use of CGM - Clinical Targets
        - CGM derived parameters used as clinical targets:
            - Average Glucose
            - Glucose Variability
            - Glucose Management Indicator (GMI) (~A1c)
            - Time above Range - TaR
            - Time in Range - TiR
            - Time below Range - TbR
        - Battelino et al. 2019 Diabetes Care



        - Diabetes Care: Standards of Medical Care in Diabetes, 2020.
    3. Are TiR & GMI already replacing HbA1c?
        - 82nd ADA Scientific Sessions: Is Time in Range the Gold Standard in Glucose Management?
        - Euromedlab 2021: Which future for HbA1c as biomarker of diabetes monitoring?
    4. Do we need Standards for CGM Accuracy?
        - Results from different CGM systems must be comparable
        - We need a CGM standard
    5. Standardization – Accuracy evaluation
        - BGM for SMBG
            - ISO 15197:2013: Standard for BGM Systems used for SMBG
            - FDA Guidance: "Self-Monitoring Blood Glucose Test Systems for Over-the Counter Use"
        - CGM
            - CLSI - POCT05-A performance metrics (2008 – adjunctive use)

- CLSI - POCT05 2nd Edition performance metrics for CGM (Nov/2020)
- FDA – iCGM Criteria (2018 intraoperable CGM - semi closed loop / AID systems)
- International standard is missing…

6. CGM Guidelines
   - CLSI Requirements:
     - Study procedures incl. reference measurements
     - Data collection
     - Point accuracy
     - Trend accuracy
     - Threshold alert and alarms
     - Stability and reliability
   - Gaps:
     - Traceability & Acceptance criteria for reference measurements
     - Specific requirements
     - for distribution of glucose concentrations and rates of change
     - for procedures & evaluation metrics: many metrics, graphs, tables…
     - Minimum acceptance criteria
   - US FDA Requirements for iCGM → metrics & acceptance criteria (intraoperable CGM used eg. in semi closed loop / AID systems)
7. Working Group on Continuous Glucose Monitoring (CGM): Traceability, measurand, matrix, including the measurement uncertainty
8. Traceability Chain – BGM Systems



9. Effect of Different Comparators

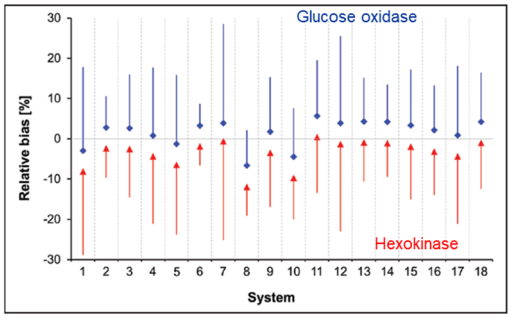
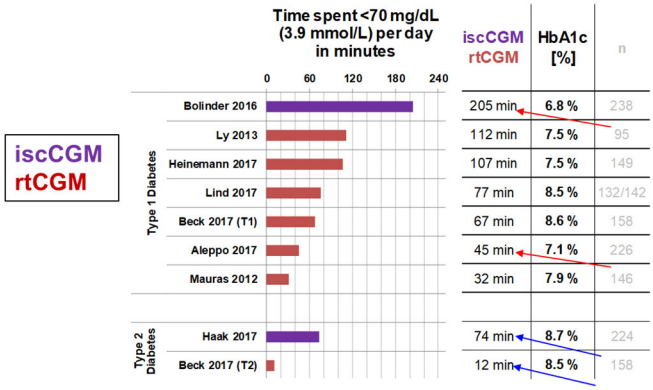


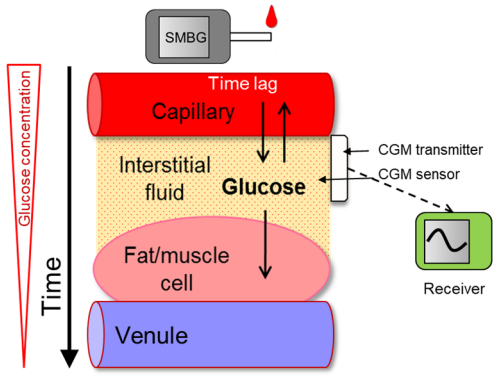
Figure 1. Relative bias according to Bland and Altman[29] for each test strip lot. The relative bias evaluated by using the glucose oxidase (GOD) method is shown in blue diamonds with the upper 95% limits of agreement; the bias evaluated by using the hexokinase (HK) method is shown in red triangles with the lower 95% limit of agreement.

- BGM system accuracy is dependent on the reference measurement procedure: harmonization / standardization of reference measurement procedures …
- Impact of Two Different Reference Measurement Procedures on Apparent System Accuracy of 18 CE-Marked Current-Generation Blood Glucose Monitoring Systems. Freckmann et. al, J Diabetes Sci Technol. 2020 Aug 19;1932296820948873. doi: 10.1177/1932296820948873.

10. Different CGM - Systematic Differences?

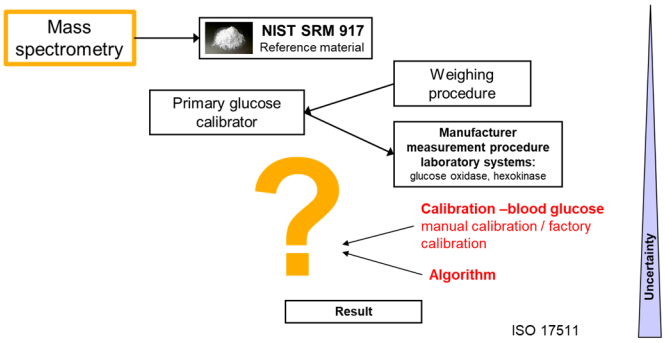


11. Different CGM System – Different Decision?
    - Choice of Continuous Glucose Monitoring Systems May Affect Metrics: Clinically Relevant Differences in Times in Ranges. Freckmann et. al, Exp Clin Endocrinol Diabetes. 2022 May;130(5):343-350.
    - Head-to-Head comparison:
        - 24 subjects with T1DM for 7 days
        - 2 CGM systems: Freestyle Libre (arm) and Dexcom G5 (abdomen)
        - TiR was comparable between the devices
        - For 11 subjects, difference in TbR (G5-4%, FL 8%) would mean different therapeutic recommendations (international consensus target <4%).
12. CGM Differences
    - Current CGM are more accurate! But are they better comparable?
    - What are the reasons for differences?
        - comparator / reference device?
        - device used for calibration?
        - measurement procedure?
13. Analogy: Weighing yourself on Mars
    - CGM is like weighing yourself on Mars with an ordinary scale in order to find out your weight on Earth
    - The scale reading will not be the same, there are two things you can do to obtain the same reading
        - Implement a reference procedure on Mars (difficult)
        - Calculate compensation algorithms based on knowledge about Mars and use this in the scale
    - This is what the companies are doing with CGM (glucose in blood vs. interstitial fluid).
14. Compartment – Calibration Procedure



- Capillary reference measurements possible (SMBG)
- ISF reference measurements currently not feasible
- Current CGM algorithms calculate a "hybrid-glucose" based on tissue and blood glucose values (venous or capillary) used for calibration
- Study data needed for development

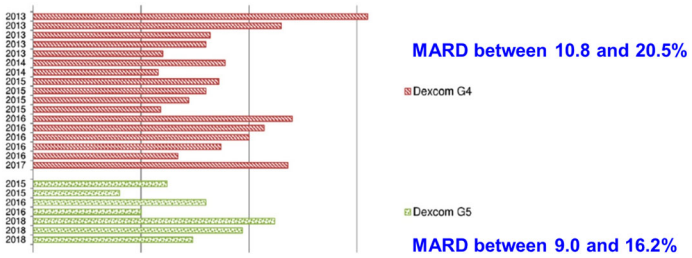
15. Traceability Chain – CGM ?



16. Working Group on Continuous Glucose Monitoring (CGM): Traceability, measurand, matrix, including the measurement uncertainty
    - To be defined:
        - Measurand (capillary or venous)
        - Reference measurement procedure
        - Algorithm (time lag reduction, etc.)
        - Evaluation procedures, including study procedures
        - Metrics & corresponding minimum acceptance criteria
    - Standardization process of continuous glucose monitoring: Traceability and performance. Freckmann et. al, Clinica Chimica Acta 515 (2021) 5–12.
17. Minimum Acceptance Criteria for Comparator Devices
    - Definition based on biological variation (EFLM database): Same approach was used before (Sacks 2011, Westgard QC), currently in CLSI POCT12
    - Updated with recent results

	Imprecision	Bias	Total analytical error
Minimum	<3.8%	<3.6%	<9.8%
Desirable	<2.5%	<2.4%	<6.5%
Optimum	<1.3%	<1.2%	<3.3%

18. CGM Accuracy: MARD – Study Procedures



→ **Study design and evaluation should be defined**

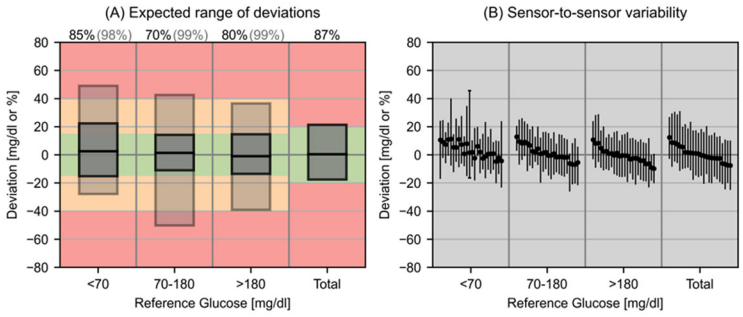
- Heinemann et al. JDST 2020;14(1):135-150

19. Study Procedures: Definition of:
    - Duration based on CGM sensor lifetime, sample size, study population
    - Distribution of glucose values and rates of change
    - Reference measurement procedure
    - Pairing of CGM and reference values
    - Evaluation: Metrics/parameters
20. FDA iCGM Requirements: Metrics & acceptance criteria

CGM glucose range	<70 mg/dl	70-180 mg/dl	>180 mg/dl	Total
Requirement 1 for agreement rate*	>85%	>70%	>80%	>87%
Limit 1	±15 mg/dl	±15%	±15%	±20%
Requirement 2 for agreement rate*	>98%	>99%	>99%	-
Limit 2	±40 mg/dl	±40%	±40%	
Requirement 3	No reference above 180 mg/dl	-	No reference below 70 mg/dl	-

** Lower bound of one-sided 95% confidence interval*

    - No specific information on the direction of deviation (bias) and imprecision
    - Lower bound of 95%CI: Marks a shift in comparison to BGMS acceptance criteria →Incorporation of statistical uncertainty
21. Metrics & Visualization



IfDT unpublished data

22. Conclusion
    - CGM derived parameters are used for clinical decisions
    - It is important that results from different devices are comparable
    - WG-CGM is working on basic definitions to support an international standard for CGM
    - An international standard for CGM accuracy evaluation is needed

Discussion:

CGM Use

G. Freckmann noted that there has been much debate regarding whether TIR as measured by CGM will eventually replace HbA1c as the gold standard for diabetes management. S. Kirkman said although there are some zealots who think that HbA1c is no longer needed, she thinks that most clinicians think that they are complementary. D. Leslie, W. Herman and S. Kirkman noted that there is a push for insurance to cover CGM for people with T2 diabetes, but the evidence that it leads to improved control in these patients is less clear than is the case with T1. W. Herman said that studies have generally shown slight improvement in HbA1c for T2 subjects with CGM, e.g. from 7.0% to 6.8%, but those patients at 9.0% tend to stay there. D. Leslie said physicians need to be skeptical when industry pushes for the widespread use of CGM in these patients.

CGM Standardization

G. Freckmann said that in any case there is a need to standardize CGM as has been done with HbA1c. For BG meters we have an ISO standard and a FDA guidance that is more strict than ISO. M. McPhaul asked whether the study presented, two different CGMs on the same patient, is the way to standardize, i.e. are "standard patients" needed instead of "standard samples"? G. Freckmann said this is a problem with CGM, we need patients with comparative measurements over time. Companies use different algorithms due to sensors having different time lags, these algorithms are generally based on studies where venous blood glucose was measured. A recent study of healthy subjects showed that capillary blood glucose is on average 20% higher compared to venous blood glucose. This could be one reason for the observed differences. S. Manley asked if anyone has done studies where different systems were randomized among patients and looked at the results. G. Freckmann said a good comparison study requires funding. E. Selvin said companies will not participate in studies where different devices are compared. G. Freckmann said their group performed a study four years ago where the Libre and Dexcom devices were compared and the study was actually funded by Roche. D. Leslie said his impression is that the Libre system reads lower than Dexcom. G. Freckmann said that has been his impression.

S. Kirkman noted that in addition to clinical ramifications, CGM is used a lot in research studies. Different meters are used in different studies, which is a problem. With HbA1c we feel comfortable comparing results across studies because of standardization. The worry with CGM is that people will compare studies where, for example, the data were obtained using Dexcom for one study and Libre for another. R. Little said people assume they are the same, this is also a problem with C-peptide. E. Selvin noted that algorithms change, for example Libre I and Libre II are different. R. Cohen asked G. Freckmann if he is suggesting standardizing CGM devices to capillary or venous glucose, Also, even if the chemistries were to be somewhat standardized there are differences in terms of transfer from the capillary thru the capillary membrane into the interstitial space. These macro-physiological differences present challenges in terms of being able to compare "apples to apples" when looking at results from different CGM devices. G. Freckmann responded that the CGM devices are being calibrated to read as capillary values, since that is how the patient is calibrating them and that is what is being used to make therapeutic decisions. The problem is that the studies that produce the data submitted to FDA and other regulatory bodies utilize venous glucose, as that is what the regulatory bodies want to see. In his opinion it is more appropriate to use capillary glucose as the reference for GGM use, although it might be different in the case of CGM in hospital intensive care units. The manufacturers are also trying to reduce the lag time between the capillary and ISF values. R. Cohen said we measure the capillary or the ISF values because that is what is accessible. However, for the most part we are assessing what the

impact will be on the brain. You are extrapolating based upon what the patient thinks, but it's also how the information will be applied. G. Freckmann said we have all of this physiology going on between the capillary and venous, the best way might be something in between, but we do not really know. The problem is right now we have a sort of averaging going on, which is not really working. R. Cohen said that in addition to the chemistry, there is the issue of physiology and all of the things that involve going from the chemistry to the macro data on integrating glucose and looking at excursions and average glucose over time. We are doing two sorts of reasoning, one is avoiding the consequences of acute hypoglycemia and the other is making long term projections of complications risk. There are still some things that are not clear concerning the inter-instrument differences and susceptibilities to location and why some of the decisions were made concerning calibration. Some were chosen for arm or abdomen based on convenience for the patient, we do not know to what extent things such as potential altered blood flow are being considered. G. Freckmann agreed that there is much we still do not know. S. Manley asked about variation using the same device in different locations within and among individuals. G. Freckmann said he has seen data where the same device was used on the abdomen and arm and the MARDs were different, but there is very little published on the topic. D. Sacks said this is not surprising, as it has been shown that with BG meters different results are obtained when capillary glucose is sampled from the finger vs. the abdomen. G. Freckmann said the algorithms are optimized using special study groups, if you apply them in different groups, e.g. ICU subjects, they are not optimized for that. It might also be true of different locations, but it is not easy to study this. J. Higgins said that from the perspective of maximizing the integration of HbA1c with CGM, the CGM value that would be most important would be the GMI. In that context, it seems that the device bias would need to be separated from the MARD, it is confusing that the manufacturers lump the bias in with the MARD. If you average values from the Libre for example, where you are getting 100 values/day, the imprecision becomes irrelevant but a significant bias will really confuse the picture. The bias needs to be stated separately, and we also need to know how much it varies from sensor to sensor. G. Freckmann agreed, noting the the bias is very important and it might vary from sensor to sensor, and also from device to device and among glucose ranges. The problem is for this purpose we need a reference. S. Manley asked if these variations are the reason the CGM devices do not work as well in children. G. Freckmann said it could be, the problem is there is little accuracy data for children because it is difficult to do accuracy studies in children. M. McPhaul suggested that a study using 6 sensors placed across the body might be needed. G. Freckmann said a standard group of patients is what is needed, it may be the only way to achieve the goal. D. Sacks said even if you can do this, if there is a bias between devices how do you know which one is correct? G. Freckmann did not know. R. Little asked if there is an accepted reference for BG monitoring. G. Freckmann said it is not clearly defined, what they are working on is linking to the NIST standard which will reduce bias, but then the problem is how to link that to CGM. The companies are doing a good job, the problem is that every company is doing their own job. D. Sacks asked if the FDA asks manufacturers what equation they are using or how they are converting their numbers. E. Selvin said they do not, they just compare the numbers to a table. M. McPhaul said it is important to highlight these issues with CGM, in the current context it is bad if people are suddenly thinking that it is better than HbA1c. E. Selvin said there is a whole group of people that think that. D. Sacks noted that in a talk on gestational diabetes there was the suggestion that the problem of diagnosing it can be solved by having pregnant women wear CGM for a week. S. Kirkman said the technology is useful but it is wrong to treat average glucose as measured by CGM as if it is a "gold standard" compared to HbA1c. E. Selvin added that there is variability around the calculated mean glucose. M. McPhaul suggested an editorial in a clinical journal, perhaps Diabetes Care, presenting these issues is needed, otherwise these perceptions are going to continue. E. Selvin agreed, stating that the editorial would need to be aimed at a clinical audience. S. Manley suggested contacting the editors of Diabetes Care, E. Selvin noted that she will be a Diabetes

Care editor starting in July. S. Manley said the editorial should discuss the issues surrounding the use of CGM and HbA1c, and emphasize that they both have a role. E. Selvin said the issues around CGM are currently not being well communicated, D. Leslie noted that physicians have a tendency to simply look at a result and believe it.

D. Sacks thanked everyone for their attendance and the discussions. The meeting was adjourned at 4:35 PM.

Minutes prepared by Curt Rohlfing 07/18/2022.