

Meeting of the NGSP Clinical Advisory Committee Minutes

2019 ADA 79th Scientific Sessions
San Francisco, CA
Monday June 10, 2019 2:30 – 4:30 PM

Ann Albright	CDC	Sue Manley	UHB, NHS, UK
David Aron	VAHCL Diab Prog	Annemarie O'Brien	Bio-Rad
Amelita Bartolome	Bio-Rad	Shane O'Neill	EKF Diagnostics
Brian Burke	Dayton VA Med Ctr	Gillian Parker	Abbott/Alere
Craig Cartwright	Bio-Rad	Matt Petersen	ADA
Shang-Hun Chuang	Bio-Rad	Leonard Pogach	VA
Aubrey Cox	Bio-Rad	Curt Rohlfing	NGSP
Sanjoy Dutta	JDRF	David Sacks	NIH, NGSP
Jackie Felberg	Bio-Rad	Rick San George	Abbott (Alere)
Marco Flamini	Bio-Rad	Elizabeth Selvin	John Hopkins
Takuji Kohzuma	Asahi-Kasei	Yoshiteru Suzuki	Asahi-Kasei
Randie Little	NGSP	Xinran Tao	Asahi-Kasei
David Leslie	St. Bartholomews UK		

Welcome and introduction: A. Albright opened the meeting at 2:30 pm and welcomed everyone. Participants introduced themselves. The 2018 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 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 set criteria to obtain certification.
 3. Proficiency Testing: Used to evaluate how well methods are performing in the hands of end-users. All methods now listed on the CAP survey are NGSP-certified.
- NGSP Certification

1. The number of certified methods continues to increase, the number of labs has leveled off, due at least in part to consolidation of some of the larger laboratories.
 2. Most certified laboratories are outside the United States and most are Level 1 labs.
 3. Certified laboratories are distributed throughout the world. Many of the certified labs are performing clinical trials.
- NGSP and CAP criteria
 1. NGSP Manufacturer and Level II Lab Certification Criteria: Beginning in January 2019 36/40 results must be within $\pm 5\%$ (37/40 for Level 1 Labs).
 2. The CAP Survey Grading for HbA1c is still $\pm 6\%$ of the target value assigned by the SRLs.
 - 2019CAP GH5A survey data (5 samples)
 1. There has been considerable improvement in the comparability of results since 1993 when the DCCT ended.
 2. On the 2019 GH5A survey, most method means were close to the target, some methods showed little variability while others showed more.
 3. This survey included one sample with sickle-cell trait (HbAS) for educational/informational purposes, with a HbA1c target of 5.66%. When compared with the non-variant sample at roughly the same HbA1c (5.46%), means for most methods were similar in relation to the targets but some methods showed higher results in relation to the target with the HbAS sample. There was also somewhat more variability among methods with HbAS.
 4. With two exceptions, methods that showed higher results for HbAS showed differences that we would expect based on our previous variant interference studies; these differences were statistically but not clinically significant.
 5. Overall pass rates were 94.0% - 97.9% (92.9% - 96.1% at the proposed future CAP limits of $\pm 5\%$) for the non-variant survey samples and 87.1% for the HbAS sample. Individual method pass rates were 80% - 100% for the non-variant samples, 60% - 100% for the HbAS sample.
 6. All-method CVs on the survey have decreased between 2000 and 2019. Our goal for all-method CVs has been $< 3.5\%$ at all HbA1c levels, more recently $< 3.0\%$. CVs for the current survey were 2.7% - 3.6% for the non-variant samples, 4.4% for the HbAS sample.
 7. Method-specific, between-laboratory CV's ranged from 0.9% (Arkray HA-8180) to 4.5% (Roche Integra 400) (AS excluded).
 8. 89% of laboratories are using methods with CVs $< 3.5\%$ at all four HbA1c levels (AS excluded).
 9. Recent publication: The National Glycohemoglobin Standardization Program: Over 20 Years of Improving Hemoglobin A1c Measurement. R. Little, C. Rohlfing, David B. Sacks, Clin Chem 65:7;839–848 (2019).

CLIA Proposed Changes for HbA1c/CAP Update: D. Sacks

- CAP is the largest provider of proficiency testing surveys in the U.S.
- The number of labs that participate in the CAP HbA1c PT survey has increased from ~700 in 1993 to ~3500 today.
- Proficiency Testing
 1. PT is evaluation of lab performance against pre-established criteria by interlaboratory comparisons
 2. Also termed EQA (external quality assessment)
 3. In the US all labs that measure patient samples are required by law (CLIA) to perform PT
 4. Regulated by CMS (Centers for Medicare & Medicaid Services) through CLIA

5. CAP is largest provider of PT material
- CAP Grading
 1. Initially, CAP used peer group grading for PT for HbA1c
 2. Subsequently, introduced whole blood PT, but maintained peer group grading
 3. In 2007 changed to accuracy-based grading
 4. Target values assigned by NGSP network
 5. $\pm 15\%$ acceptable
 6. 99% pass rate
 - PT Criteria Tightened
 1. In 2008 acceptability reduced to 12%
 2. 2009 - 10%
 3. 2010 - 8%
 4. 2011 - 7%
 5. 2013 - 6%
 - CAP 2010, 2012 & 2013 GH2A Pass Rates at $\pm 6\%$ HbA1c Cutoff

	2010	2012	2013
Low (5.1/5.6%/6.07)	91.0	95.8	93.4
Medium (6.0/7.2%/7.1)	91.6	92.9	95.3
High (8.4/9.4%/9.3)	88.6	92.5	94.3
 - Pass Rates for CAP 2018 GH5-A: $\pm 6\%$ vs. $\pm 5\%$

Sample ID	$\pm 6\%$	$\pm 5\%$
GH-01	95.9	95.9
GH-02	97.3	93.6
GH-03	96.8	95.9
GH-04	95.6	92.4
GH-05	97.1	96.1
 - Summary
 1. CAP progressively tightened PT grading
 2. Criteria 15% in 2007, progressively tightened to 6% in 2013, plan to tighten to 5% in 2020
 3. Lab performance on CAP surveys improving, due to better methods
 - CLIA Update
 1. CMS recently presented a proposed rule to update CLIA PT requirements
 2. One of the recommendations is to establish a criterion for HbA1c of $\pm 10\%$
 - Effect of Change in PT
 1. True HbA1c is 6.5%
 2. If criterion is $\pm 5\%$, acceptable value is 6.2% - 6.8%
 3. If criterion is $\pm 10\%$, acceptable value is 5.8% - 7.2%
 - Implications of New CLIA Proposal
 1. HbA1c would become, for the first time, a regulated analyte
 2. CAP is not permitted to fail a lab if it meets CLIA criteria
 3. If CLIA accepts $\pm 10\%$, CAP will have to loosen acceptability from $\pm 6\%$ to $\pm 10\%$
 4. CAP has elected NOT to reduce criteria from $\pm 6\%$ to $\pm 5\%$ in 2020
 - Potential Outcome of CLIA Proposal

1. Accuracy of HbA1c assays likely to deteriorate
2. Patient care likely to suffer

Discussion:

Proposed CLIA PT rule for HbA1c

D. Sacks said CMS has not made a decision regarding the proposed rule yet. There was a comment period for the rule that has since passed, R. Little sent out a notice to everyone on her list about this and many comments were submitted. A number of organizations including the ADA, AACC, CAP, ISPAD submitted comments, individuals submitted comments as well. It is not clear what CMS will do with the information/comments they received, if anything. An editorial was published in the Journal of Diabetes Science and Technology (Klonoff et. al, <https://doi.org/10.1177/1932296819841699>) prior to the end of the comment period explaining why the proposed rule for HbA1c is a step backward. A. Albright noted that CMS is required to respond to every comment, and this can be very time-consuming. It would be good to know who is managing the process at CMS and if there are ways to get input to them, and why the decision was made to go to $\pm 10\%$ when it is clearly a step in the wrong direction. If there is an overwhelming number of comments arguing against the rule they would have to have a really good reason to go forward with it, there is hope. CMS is a very large organization, we need to try to find out who is managing this process and what part of the agency they are in. She asked L. Pogach if he has any insight, he responded that the only thing he has heard is that the action originated at the CDC. A. Albright said she was not aware of whether the CDC was involved and if so who at the agency is responsible but she will look into it. L. Pogach said that with the overwhelming negative comments CMS has likely received he thinks the rule will likely not go thru, but he is anxious nonetheless. D. Sacks said on the web site the day the comment period closed, about 90% of the comments they received were regarding HbA1c even though there are other analytes included in the proposed rule. CAP and AACC have some concerns about some of the other analytes as well where the criteria are too tight and a lot of labs would fail. He heard a rumor that HbA1c was brought up as a potential regulated analyte to CMS a long time ago when the criterion was 10%, and that may be where that came from. A. Albright thought that made sense, they made be working with outdated information. D. Sacks noted there is one other major HbA1c PT provider in the U.S., they use artificial material and their limits are much wider than the CAP limits. A. Albright noted that the time period for responding to comments is finite, and that the agencies are required to be open to input from the public even after the comment period is over, it is best to request an in-person meeting. If we can find out who at CMS is guiding this process, members of the relevant organizations could request meetings with them. S. Manley said that the ADA and AACC have already made their opinions known, individual comments are important but shouldn't the opinions of major organizations be able to sway CMS? A. Albright said they should, but it also depends on if there are any counter arguments, and if so who is making those arguments. L. Pogach said people at the VA tried to talk with CMS but everything just came back to public comments, they are not talking to anyone. It is possible it was some sort of mistake, sometimes in government agencies one hand doesn't know what the other is doing, you can have different, even opposing, things happening at the same time. A. Albright said if possible we would need to talk to people within CMS itself in order to find out what it going on. She will talk to colleagues at the CDC and contact people at CMS to try to find out where in the agency this is occurring and who is guiding this process. Also, they will try to find out the process for providing input post-comment period. In her experience CMS is willing to meet with stakeholders after the comment period is over. It has to be presented in terms of the stakeholders trying to better understand the process by which CMS reached their conclusions. They will not be able to tell you their position on the issue, but putting face and comment together and expressing verbally can be more compelling. D.

Sacks asked M. Peterson if the ADA would be willing to meet with them, he said yes; D. Sacks said the AACC would be as well. Finding the person/department is needed; A. Albright said if they can, there would be nothing to lose by arranging in-person meetings. D. Sacks noted that the issue is not one of labs failing, the pass rates with the current CAP criteria are very high and the labs that fail are generally using bad methods that are being phased out. A. Albright agreed, it might be different if a lot of labs were failing but that is not the case, so there is nothing to gain here and potentially a lot to lose. L. Pogach asked whether the NGSP could play a role in showing which labs perform well under the stricter criteria, even though it would not have the force of law, in the event CMS were to pass the rule. We may want to consider other strategies to inform people of which labs perform well. R. Little said the NGSP only certifies a tiny fraction of labs in the U.S., while the CAP surveys over 3000 labs that do routine patient testing. D. Sacks said one idea is if the rule passes, CAP would have to pass labs that meet 10% but maybe they could also acknowledge and identify the labs that meet the 5% criterion. He did not know if CAP would want to do this, but he could try. R. Little suggested they could continue using 5% as an educational grade. L. Pogach asked about involving patient advocacy groups. A. Albright said ADA has already responded, she was not sure about JDRF or some others, but there is not a patient advocacy group for HbA1c per se. L. Pogach said he is also referring to the public, if patients are concerned as they should be they can advocate on their own, those of us in government are limited as to what we can do while the private sector is not. M. Peterson noted that the response to CMS was overwhelming, is there really any chance they will go through with this rule for HbA1c? A. Albright agreed, stating that unless there was a large number of counter comments, which is unlikely, she cannot see it happening. It flies in the face of what the agency is trying to do in terms of ensuring and improving quality care. M. Peterson asked if there is anything else they can do, A. Albright replied that it is a matter of whether the people in CMS that are involved in the process are willing to meet with external parties. M. Peterson said ADA, JDRF and others would be happy to do this if it can happen. S. Dutta said JDRF would be willing to participate.

POC A1c for diagnosis: What is sufficient evidence for CLIA waiver?: R. San George

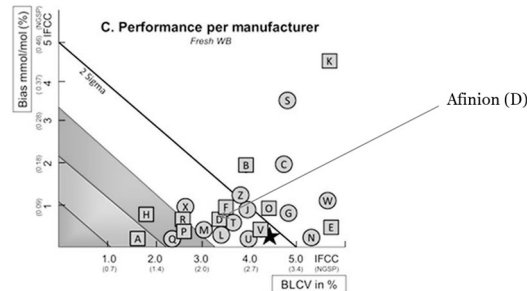
- The Problem

1. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the U.S.
 - 30.3 million in the U.S. (9.4 million) have diabetes
 - 23.1 million are diagnosed, 7.2 million (23.8% of people with diabetes) are undiagnosed
 - Incidence and prevalence of diabetes varies by region, those with the highest tend to coincide with higher numbers of ethnic minorities and lower socioeconomic status
 - An estimated 33.9% of U.S. adults aged 18 and over (84.1 million people) had prediabetes in 2015, nearly half (48.3%) of adults 65 and older had prediabetes
 - Among adults with prediabetes, 11.6% reported being told by a healthcare provider that they had this condition.
 - The total direct and indirect estimated total cost of diagnosed diabetes in the U.S. in 2012 was \$245 billion.
 - The average medical expenditures for people with diagnosed diabetes were about \$13,700 per year. About \$7900 of this was attributed to diabetes.
 - Diabetes Diagnosis and Control: Missed Opportunities to Improve Health (based on the 2018 Kelly West Award Lecture). Diabetes Care 2019;42:994–1004 <https://doi.org/10.2337/dci18-0047>
 - WHAT CAN POINT-OF-CARE HbA1c DIAGNOSTICS OFFER?

- Potential to identify people with previously undiagnosed diabetes and prediabetes, especially in underserved communities
 - A. By helping to address health disparities in diabetes: racial, ethnic, geographic, socioeconomic
 - B. Through hospital outreach, wellness, urgent care and POL screening programs
 - Potential to reduce healthcare costs and burden
 - A. By bringing people into the health care system for treatment, education and prevention
 - B. By providing timely feedback on lifestyle, diet, medication and follow-up
- Recent History: ADA and FDA
 1. ADA Guidelines Regarding POC HbA1c
 - ADA guidelines recommend the use of point-of-care HbA1c methods for use in monitoring of glycemic control.
 - The ADA guidelines have endorsed the use of HbA1c for diagnosis of diabetes since 2010.
 - The ADA guidelines have recommended against the use of point-of-care HbA1c methods for diagnosis of diabetes.
 - Standards of Medical Care in Diabetes 2015 and 2016: “Although point-of-care A1C assays may be NGSP certified, proficiency testing is not mandated for performing the test, so use of point-of-care assays for diagnostic purposes is not recommended.”
 2. FDA Actions
 - In late 2015 Alere (now Abbott) submitted a 510(k) application to FDA to obtain a clearance for the Afinion HbA1c Dx product to be as an aid in the diagnosis of diabetes and as an aid in identifying patients who may be at risk for developing diabetes. For use in clinical laboratories and moderate complexity point-of-care settings.
 - July 22, 2016: Clinical Chemistry and Clinical Toxicology Devices Panel k153726 Afinion HbA1c Dx test system
 - We have the following discussion questions for the panel to address during the Advisory Committee Meeting.
 - A. In their “Standards of Medical Care in Diabetes” practice guidelines, the American Diabetes Association recommends against the use of POC HbA1c tests for the diagnosis of diabetes.
 - B. Does the panel have any concerns about risks to health regarding the use of POC HbA1c devices in general for the diagnosis of diabetes? If so, please describe these concerns. **Unanimous no**
 - C. Does the Afinion HbA1c Dx test system, with an intended use in moderate complexity POC settings, raise any new concerns about risks to health? If so, please describe these concerns. **Unanimous no**
 - D. If the panel has concerns about risks to health for a or b above, what mitigations, if any, may be implemented to address those concerns?

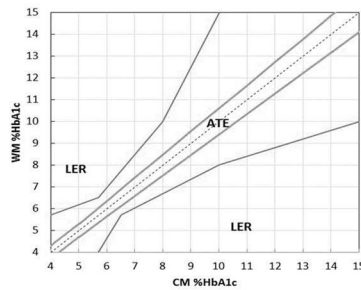
- 510K clearance (diagnostic claim) was granted to the for Afinion HbA1c Dx on Afinion As100 Analyzer in May 2018 and for the Afinion2 Analyzer in November 2018.
 - Data from 510(k) decision summaries show that the performance of the Afinion systems at the diagnostic cutoff of 6.5% is comparable to laboratory analyzers. Recent CAP survey data also show that the Afinion performance is comparable to laboratory analyzers.
- 3. 2019 ADA Standards of Medical Care Statement on POC Systems: “The A1C test should be performed using a method that is certified by the NGSP (www.ngsp.org) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. Although point-of-care A1C assays may be NGSP certified or U.S. Food and Drug Administration approved for diagnosis, proficiency testing is not always mandated for performing the test. Therefore, point-of-care assays approved for diagnostics purposes should only be considered in settings licensed to perform moderate-to-high complexity tests.”
- What about CLIA Waiver?
 1. CLIA requires that tests performed by laboratories with a Certificate of Waiver be "simple."
 2. Appropriate fail-safe mechanisms and failure alert mechanisms help assure that a test has “an insignificant risk of an erroneous result.”
 3. To demonstrate that your device is “accurate” in the hands of the intended operator, we recommend that you perform prospective clinical studies of the device proposed for waiver using patient samples collected in the intended testing environment.
 4. Quality assurance in the absence of proficiency testing in waived settings
 - Appropriate fail-safe mechanisms
 - Robust system design
 - Instrument self-test and diagnostics
 - Factory calibration of instruments and cartridges
 - Mitigations against potential operator errors
 - Demonstrated through internal flex studies
 - Demonstrated through external clinical studies
 - Robust quality management systems
 - QA tracking of 10 years of production lots
 - Complaint management
 - Post-market surveillance
 - “an insignificant risk of an erroneous result.”
 - Post-market surveillance
 - Participation in eQA and PT programs by Abbott
 - A. Noklus (Norway) – 4 distributions/year, fresh whole blood, target assigned by an IFCC HbA1c Integrated Network Laboratory, The Netherlands (SRL to NGSP)
 - B. Equalis (Sweden) – 10 distributions /year, fresh whole blood, target assigned by , target assigned by Swedish reference method and an IFCC HbA1c Integrated Network Laboratory
 - C. The Netherlands Neqas (UK) – 6 distributions /year, fresh whole blood, target assigned by an IFCC HbA1c Integrated Network Laboratory

- Participation in eQA and PT programs by Customers
 - A. CAP (US) – 4 distributions /year, fresh whole blood, target assigned by 8 NGSP SRMs
 - B. MQ Zurich (CH) – 4 distributions/year, stabilized whole blood, target assigned by the IFCC HbA1c Integrated Network Laboratory, The Netherlands
 - C. Neqas (UK) – 10 distributions/year, fresh whole blood
 - D. RCPA (Australia) – 3 distributions/year, , fresh whole blood
- EurA1c: The European HbA1c Trial to Investigate the Performance of HbA1c Assays in 2166 Laboratories across 17 Countries and 24 manufacturers by Use of IFCC Model for Quality Targets (Clinical Chemistry 64:8, 1-10, 2018)



- FDA recommended that Abbott discuss clinical study proposals with outside experts in the clinical community to ascertain whether they believe the studies would address the clinical concerns raised by the advisory committee at the clinical chemistry and toxicology devices panel meeting on July 22, 2016.
- Accordingly, Abbott reached out to several members of the diabetes clinical community and among them assembled an advisory panel made up of experts specializing in diabetes care and research that included clinicians from the American Diabetes Association (ADA), representatives of the laboratory medicine community and an expert in diagnostics regulatory affairs.
- FDA CLIA Waiver Guidance 2008: Key Study Design Elements
 - Minimum of 360 patient samples
 - From intended use population
 - Span the measurement range of the Waived Method (WM)
 - Minimum of 3 test sites
 - Representative of intended use population and intended operators
 - 1 to 3 operators per site, at least 9 operators total
 - Patient samples as equally distributed among operators as possible
 - Test period of about 1 month
 - At least 2 weeks
 - Comparative Method (CM)
 - Type A Reference method or Type B Traceable Method
 - Error Grid Analysis
 - 95% of WM results within ATE zone relative to CM; Zero results within LER zones
 - Total Analytical Error calculation
- Plan to greatly exceed minimum requirements
- Goal to generate overwhelming amount of compelling evidence

○ Error Grid Analysis



ATE zone:

CM \leq 5.0% HbA1c: WM must be within CM \pm 0.3 %HbA1c

CM $>$ 5.0% HbA1c: WM must be within CM \pm 6.0% (relative units)

LER zone :

defined by the following coordinate pairs:

CM (%HbA1c)	WM (%HbA1c)
5.70	4.00
6.50	5.70
10.00	8.00
15.00	10.00
4.00	5.70
5.70	6.50
8.00	10.00
10.00	15.00

● Acceptance Criteria

- A. 95% of Waived Method (Afinion) results compared to the Comparative Method (Trinity Premier) need to fall within the ATE zone
- B. Zero of Waived Method (Afinion) results compared to the Comparative Method (Trinity Premier) need to fall within the LER zones

○ Additional study designs for consideration

- Non-inferiority of untrained vs. trained operators
- Enroll intended use population of at-risk individuals to screen for and identify undiagnosed prediabetes and diabetes
- Distribution of A1c values to be mostly in the 5% to 7% A1c range
- Compare Afinion HbA1c Dx results obtained by untrained CLIA waived operators with trained laboratory operators and to NGSP reference method
- Evaluate for non-inferiority of results from untrained operators to those of trained operators in classification of individuals into normal, prediabetes and diabetes categories
- Power study for non-inferiority end-point
- Compute Bland-Altman difference analysis to determine mean bias between untrained and trained operators
- Proficiency Testing of CLIA waived installed base
- Prepare three “proficiency test” samples at low, medium and high A1c levels
- Fresh whole blood pooled, aliquotted, stored and shipped at refrigerated temperature
- Ship to 100(?) CLIA waived sites running Afinion HbA1c assay in routine use
- Randomly selected sites, willing to participate
- Ship sample aliquots to NGSP lab for assignment of target values
- From results calculate overall mean A1c and 2SD range.
- Compare overall mean to NGSP target
- Compare individual site results to overall mean and NGSP target
- Establish grading criteria and apply
- POC A1c for Diagnosis: What is Sufficient Evidence for a CLIA Waiver?
 1. Robust system design
 2. Appropriate fail-safe mechanisms

3. Strong mitigations against potential operator errors
4. Robust QMS
5. Post-market surveillance of global eQA and PT data
6. Clearly demonstrated accuracy in hands of intended use operators in intended use settings--compared to NGSP reference method with error grid analysis
7. Maximize benefits, minimize risks

Discussion:

POC for Diabetes Diagnosis

R. San George asked those present for their input in terms of what is sufficient for a CLIA waiver. D. Sacks said he does not think waived tests should be used for diagnosis, the consequences of getting a wrong result can be very serious. All of the countries in Europe require POC devices to run PT. How many of the Afinion devices are there in use in the U.S, and how many users participate in PT? R. San George said there are thousands, a few hundred of which participate in PT. R. San George noted that PT alone does not assure quality, it is important but CLIA-regulated labs do more than PT. There are other things, even in a waived environment, that can assure quality. The PT data show some lab values that are not good, but no one is saying do not use lab values. D. Sacks noted that fingerstick glucose is waived, but no one is proposing that fingerstick glucose be used to diagnose diabetes in the U.S. R. San George agreed but said that this is because the fingerstick methods do not perform as well as lab methods, the Afinion does. G. Parker said that fingerstick glucose is widely used for screening to identify individuals that can then be referred to their physician for further testing if needed. We hear from customers, including employers that screen and urgent care centers, that they would like to use HbA1c for this purpose rather than glucose due to the challenges associated with glucose. Sometimes urgent care centers are the only place people interact with the medical community. R. San George said they are wanting to maximize benefits and minimize risk. The benefits are clear, and we also know what the risks are, they have been clearly stated. Hopefully we will get that balance right, and others will agree that we have. The question of presumptive diagnosis was discussed, R. Little said the idea would be that the first POC HbA1c would be confirmed with a lab value. R. San George said a number is not a diagnosis. The operator does not make the diagnosis, the diagnosis can only be made by a physician who will look at the CLIA-waived number and decide whether they believe it or not, or whether they should act on it. They will make a decision based on the overall clinical presentation, and may decide to do further confirmatory testing. It mitigates against the risk, there is a shared responsibility, the manufacturer has a responsibility to assure that the test result is accurate but there are others that share in the responsibility in terms of assuring quality patient care. L. Pogach said there has been a lot of discussion of racial differences in HbA1c and what to do about them. Use of CGM to get a better idea of what the individual patient's HbA1c should be has been suggested, it is a complex ecosystem. Screening is ubiquitous, the bottom line is a screening result needs to be confirmed. I don't see a need for an initial screening test to be diagnostic as you would be referred to a healthcare provider anyway. A result of 6.6 can have implications in terms of insurance. R. San George said the need was shown in his first slide, there are a lot undiagnosed people. L. Pogach said screening for diabetes and pre-diabetes is now widespread, including in pharmacies, some of which are in rural areas that may not have a physician. If the result comes back as 8 you need to see a doctor, as the pharmacy isn't going to do anything to treat the patient. The issue is access to care. What is the value added? At the VA DOD, due to racial differences we want the result to be confirmed and allow a budget because if the value is 6.6 and this is confirmed with a second result, that person is now labeled as having diabetes which has implications. R. San George agreed but noted that this is true whether the initial value came from a lab or a POC device, the person needs follow-up that may include fasting glucose if

there may be a racial difference involved. L. Pogach said he believed that the VA currently recommends that a HbA1c ≥ 6.5 be confirmed with a fasting glucose. M. Peterson said the ADA changed their guideline this year to state that a HbA1c ≥ 6.5 can be confirmed with a fasting glucose from the same blood sample with no need to subsequently repeat either test. L. Pogach reiterated that he did not see a need for this method to be a diagnostic test. R. Little asked him if he is opposed to more screening, he said he is not in favor of it being a diagnostic test. It might be useful for screening if it is better than what the pharmacy chains are using, he was not sure what that was, CVS is using their house brand. G. Parker said that CVS is using their private label A1cNow, it is an OTC product. L. Pogach asked why a HbA1c test needs to be sold to patients. S. Manley said that in the UK the number of fasting glucose tests ordered has dropped by half while the number of HbA1cs ordered has doubled since they officially recommended HbA1c for diagnosis. Her group recently published a paper in Diabetic Medicine showing that in pre-liver transplant patients, HbA1c was lowered by $\sim 2\%$ DCCT across the range of values. We are looking at the effects of other kidney disorders on HbA1c. With alpha 1 antitrypsin disorder and with thalassemia HbA1c can be elevated by 1-2% DCCT. These effects are much larger than the race/ethnicity effects that have been reported. Results will be affected regardless of whether a POC or lab method is used. It does not mean that HbA1c is not a good diagnostic test, these are a small percentage of people being tested, but healthcare providers that are seeing these results may not be aware that the results are being affected in these cases. D. Sacks said he has run POC testing at NIH and before that Brigham and Womens Hospital. At these institutions and many other hospitals, there is a lab person that oversees POC testing, the nurses are trained and every year they are evaluated, and every POC result goes into the computer and is monitored by medical technologists. Even so they still see disasters, there are fingerstick glucose results that make no sense, some of the nurses have to be re-trained. These are nurses in a supervised environment, yet they still get huge errors that can adversely affect patient care. This is why he has concerns regarding waived testing in an unsupervised environment. G. Parker said this is why studies have to be performed in order to get a CLIA waiver, you have to show that when operators mess up, and they will, you do not get a result but rather you get an error code. Just as all lab tests are not the same, all POC methods are not the same, our system is very robust. M. Peterson said we've been having discussions regarding whether HbA1c should be used for diagnosis and the limitations of HbA1c for years. This is no different other than that it is related to POC. In the end the method will get approved for diagnosis or not, and the method will be used for diagnosis or not, it seems beyond debate at this point. R. Little said that the FDA suggested consulting the clinical community to see if there are issues that they feel need to be addressed, this is part of that process. M. Peterson said they have shown that the method is accurate and robust, the issues put to them are not really things they can address, there is nothing different other than the fact that this is a POC device. S. Manley noted that POC devices are improving all the time, in their hospital POC is run in a laboratory environment that includes participation in EQA. She did not have a good picture of how their POC would perform in the hands of untrained users versus in the laboratory; would there be differences in the results? R. Little said there is no way for us to know since there is no PT requirement. R. San George said more studies need to be done, he has proposed some, Dr. Nathan's group did a study that was just published in JDST. He had his best laboratory technician analyze 300 samples on the Afinion and compared those results to those from the laboratory method. The results were very good, he then repeated the study with 400 samples analyzed by eight different untrained operators (medical assistants, nurses, fellows, etc.) and also got very good results. That was one study done in one location, we would like to find others that would perform these kinds of studies. Results of studies we perform are met with skepticism. S. Manley asked if anyone in the U.S. is using POC HbA1c in a laboratory setting. R. Little and D. Sacks said yes, the participants on the CAP survey. L. Pogach asked if CDC could eventually state that HbA1c methods used for screening should be NGSP certified. A. Albright responded that CDC does not set standards,

they do have people they work with that try to get people into interventions, but it is their decision what tests they use. R. Little asked whether the ADA recommendations will change if the waiver is approved, will they state that the second confirmatory test must be a lab test? M. Peterson said that is a possibility, it would be up to their Professional Practice Committee. A. Albright reiterated that Alere/Abbott is looking for people to step up and be willing to participate in studies in their institutions. R. San George said they would welcome that and thanked the Committee.

DHHS-VA Diabetes Health Literacy/Numeracy Campaign: L. Pogach

- According to the people that came up with a National Action Plan, numeracy is a part of literacy, but it is often neglected.
- Numeracy is not necessarily computational.
- Diabetes is a disease of numbers, and it is important that patients get their numbers right.
- Numbers are difficult for a lot of people.
- We are not just talking about lab tests, but also other parameters such as nutrition and exercise.
- HbA1c and SMBG are important, along with understanding elements of risk.
- HbA1c
 1. A HbA1c result represents a range
 2. Often patients hear that their result should be less than x, and performance measures have been based on this.
 3. Ever since DQIP came out our group has stressed the importance of considering co-morbid conditions, life expectancy and other factors when interpreting HbA1c results.
 4. We try to educate our clinicians that if a value exceeds a goal by 0.1 or 0.2% HbA1c, there is no need to be concerned and increase or add medications.
 5. Many healthcare providers treat a result as if it is an actual number when it is not, it actually represents a range.
 6. We want to educate healthcare providers and patients so that they can better understand this concept, we want to get this information out.
 7. The information is already available for patients who ask for it, we plan to make it more widely available.
 8. We hope to get this rolling out in November during Diabetes Month.

Discussion:

A. Albright asked if there is web site people can go to in order to learn about the Literacy/Numeracy Campaign. L. Pogach said they are working on a web site devoted to the campaign, they would like to have blogs and podcasts as part of the campaign. Also the National Care Commission has recommended that by 2021, the various federal agencies involved should use common educational materials. A. Albright noted that the National Care Commission was authorized by Congress, it includes federal organizations involved with diabetes as well as selected external people, every meeting they have is open to the public. There are three subcommittees, anything they can share publicly will be made available on the NCC web site. They are due to submit a report to Congress in 2021. A number of things are being discussed, everything from what the various federal agencies are doing to where there are gaps/issues in diabetes. Her hope is that the NCC will come up with something more robust that will advance diabetes as a health issue in this nation. We want people to be aware of the NCC and encourage them to stay tuned for any information that is being made publicly available. Dr. William Herman is the chair of the NCC. L. Pogach noted that there will be interesting discussions on their web site on October 31st. R. Little asked about numeracy, isn't this what diabetes

educators work on? They work with insulin doses, dietary issues, etc., wouldn't this fall under diabetes education? A. Albright said it does, L. Pogach agreed and noted that B. Burke just got a grant for a novel delivery system for the VA, we are working on materials addressing nursing and nutritional needs and will try to incorporate numeracy as well. A. Albright noted that Dr. Ed Gregg, head of the Epidemiology and Statistics Branch at the CDC, has retired and they are looking for qualified candidates. The announcement should come out on jobs.gov soon. There is exciting work going on in this area, we are finally seeing a leveling of prevalence and incidence of diabetes. At the same time we are concerned about the increased incidence and aggressive complications of T2 diabetes in youth and young adults.

A. Albright thanked everyone for their attendance and discussion, noting that she and others will try to get to the bottom of the issue of the proposed CLIA 10% criterion. The meeting was adjourned at 4:20 PM.

Minutes prepared by Curt Rohlfing 06/28/2019. Modified by Randie Little 07/01/2019.