Meeting of the NGSP Clinical Advisory Committee Minutes

2018 ADA 77th Scientific Sessions
Orlando, FL
Monday June 25, 2018 2:30 – 4:30 PM

Ann Albright	CDC	Mike McPhaul	Quest
Sibyl Baladi	Bio-Rad	Matt Petersen	ADA
Richard Bergenstal	Park Nicollet/IDC	Robin Pettini	Abbott (Alere)
Brian Burke	VA	Leonard Pogach	VA
Robert Cohen	Univ. of Cincinnati	Curt Rohlfing	NGSP
Craig Cartwright	Bio-Rad	David Sacks	NIH, NGSP
Jackie Felberg	Bio-Rad	Rick San George	Abbott (Alere)
Sandip Ghosh	Birmingham SFS UK	Jane Seley	AADE
Steve Hanson	NGSP	Elizabeth Selvin	John Hopkins
Takuji Kouzuma	Asahi-Kasei	Miss Tao	Asahi-Kasei
Randie Little	NGSP	Cathinca Vargmo	Abbott (Alere)
Christine Lee	FDA	**By phone**	
David Leslie	St. Bartholomews UK	Leslie Landree	FDA

Welcome and introduction: A. Albright opened the meeting at 2:30 pm and welcomed everyone. Participants introduced themselves. The 2017 NGSP Clinical Advisory Committee meeting minutes were approved.

HbA1c/NGSP Update: R. Little

- Structure of the NGSP
    1. The NGSP Steering Committee oversees the NGSP network and meets annually at the AACC.
    2. The NGSP network consists of an administrative core, the Central Primary Reference Laboratory (CPRL), backup PRLs , and 10 Secondary Reference Laboratories (SRLs).
    3. The NGSP network labs are located in the U.S., the Netherlands, Japan and China.
    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 establishing or validating their calibration.
    2. Certification: Formal process by which manufacturers/labs perform a comparison against a SRL and must pass set criteria to obtain certification.
    3. Proficiency Testing: Used to evaluate how well methods are performing in the hands of end-users.
- 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 on six continents. There is a cluster of Level 2 labs in Columbia SA and clusters of L1 labs in several parts of Asia.

- NGSP and CAP criteria
    1. NGSP Manufacturer and Level II Lab Certification Criteria: 37/40 results must be within ±6% (38/40 for Level 1 Labs)
    2. CAP Survey Grading for HbA1c: ±6% of the target value assigned by the SRLs.
    3. In 2017, the CAP proposed changing the CAP GH5 survey grading to ±5%. The plan is to change in 2020.
    4. The NGSP criteria will be tightened in order to be comparable to the CAP criteria. Based on data analyses looking at probabilities of passing CAP and NGSP criteria, 36/40 results within ±5% will be the new limits for manufacturers and Level II labs (37/40 for Level I Labs) beginning in 2019.
    5. Since January 2018 the NGSP has provided manufacturers with educational data showing how they performed with the upcoming 2019 criteria as well as the current criteria.
    6. Based on the first six months of 2018 certification data, the pass rates for the current vs. the 2019 NGSP criteria were:

	Current	**2019**
Manufacturers	92.2%	85%
Level I Labs	95.1%	90.2%
Level II Labs	78.6%	71.4%

- 2018CAP GH5A survey data (5 samples)
    1. There has been considerable improvement in the comparability of results since 1993 when the DCCT ended. In recent years there has continued to be improvement but it has been more subtle.
    2. On the 2018 GH5A survey some methods show low between-lab CVs and small biases, however there are a few that show significant biases or high CVs.
    3. Overall pass rates were all >95%. Individual method pass rates ranged from 72.7% to 100%. The overall pass rates using limits of ±5% were a bit lower but still well over 90%.
    4. Our goal for all-method CVs is <3.5% at all HbA1c levels, CVs for the current survey were all ≤3.0% except for the lowest sample where the CV was 3.6%.
    5. All-method pass rates at the current criterion of ±6% have increased to >96%.
    6. Pass rates (at the current ±6% cutoff) have been >95% in the 5-10% HbA1c range for the last 7 surveys.
    7. Method-specific between-laboratory CVs ranged from 1.0% to 5.7%. 87% of laboratories are using methods with between-lab CVs ≤3.5% at all five HbA1c levels.
    8. Method-specific, between-laboratory CV's ranged from 1.0% (Arkray HA8180) to 4.7% (Beckman AU).
    9. 76% of laboratories are using methods with CVs<3.5% at all five HbA1c levels.

Update on Evidence for Racial Differences in A1C: E. Selvin

- In January 2010, the ADA first recommended the use of A1c for diagnosing diabetes.
- Controversy re use of HbA1c for diagnosis

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. Expense and availability in some areas: HbA1c test is more expensive than glucose
4. Higher levels of HbA1c in African Americans: This has been cited repeatedly as a "limitation" of the HbA1c test for diagnosis of diabetes

- Data from NHANES III (MI Harris et al. Diab Care 1999; 22:403–408) showed higher HbA1c levels in blacks compared to whites in subjects with normal FG, impaired FG, undiagnosed diabetes, and both men and women with diagnosed diabetes in a representative U.S. population.
- Saaddine et al. Diabetes Care. 2002;25(8):1326–30: Looked at distributions of HbA1c values in NHANES III participants 5-24 YOA and showed that blacks had slightly higher HbA1c values than whites, with Mexican Americans falling in the middle of the two. The authors concluded that these differences were relatively small and "may not support the need for separate norms"
- More recent NHANES data (2009-2014) shows that, in adults without diabetes, average HbA1c was 0.11 to 0.18% HbA1c higher in blacks compared to whites depending upon the statistical model utilized.
- Based upon the data showing these racial differences, there were a number of strong statements that came out advising against the use of HbA1c for diagnosing diabetes or comparing glycemic status across racial/ethnic groups.
- Strong link between A1C and clinical outcomes
    1. Large and robust literature linking A1C with clinical outcomes: No evidence for racial differences in associations with outcomes or in clinical trials of glucose-lowering interventions (e.g. subgroup analysis in ACCORD)
    2. Most studies show higher risk of diabetes (e.g. DPP Trial) and its complications in blacks compared to whites
- Racial Differences in the Relationship of Glucose Concentrations and Hemoglobin A1c Levels (Bergenstal et. al, Ann Intern Med. 2017;167:95-102)
    1. Study design: Prospective study with 12 weeks of data collection
    2. Study population: 104 blacks, 104 whites aged 8 years or older with type 1 diabetes from 10 diabetes centers
    3. Measurements: Weighted mean glucose from ~60 days of data from a continuous glucose monitoring (CGM) device compared to single HbA1c measurement
    4. Main objective: Compare mean glucose concentration and HbA1c levels in blacks and whites with type 1 diabetes
    5. Results
        - Mean HbA1c was higher in blacks compared to whites (9.1% vs. 8.3%).
        - Mean glycated albumin and fructosamine were also higher in blacks.
        - Mean hemoglobin was lower in blacks compared to whites (133 vs. 140)
        - When compared with CGM, HbA1c values in blacks were an average of 0.4% (95% CI 0.2%-0.6%) higher than whites at the same mean glucose
        - Correlations of average glucose and HbA1c were similar in blacks and whites (r = ~0.9)
        - Hemoglobin levels were significantly lower in blacks compared to whites
        - Analyses were not adjusted for hemoglobin or other red cell parameters

    - Small differences in HbA1c between groups (e.g. blacks vs whites) may be explained by hematologic differences, e.g. differences in red cell turnover or structure of Hb: Changes in RBC lifespan can affect HbA1c; known structural differences in Hb molecule that differ by race
6. Key points
    - Glucose independent race differences in HbA1c are small (difference of ~5%)
        - Likely a subgroup of individuals with a "hematologic condition" that may systematically affect HbA1c (<15 participants out of 200)
        - This condition may overlap with race but is NOT race
    - True differences in hyperglycemia far outweigh glucose-independent mechanisms in explaining HbA1c variation: ~80% of the variance in HbA1c was explained by mean average glucose (measured using CGM device) in type 1 diabetic population
    - The strong link between HbA1c and complications in both blacks and whites emphasizes the critical clinical importance for use of HbA1c
    - Race is not a precise construct; we need to move beyond "race-based analyses" to better understand non-glycemic factors that may be relevant

- ADA 2018 Practice Guidelines – Classification and Diagnosis of Diabetes
    1. "Even in the absence of hemoglobin variants, A1C levels may vary with race/ethnicity independently of glycemia (13–15). For example, African Americans may have higher A1C levels than non- Hispanic whites with similar fasting and postglucose load glucose levels (16), and A1C levels may be higher for a given mean glucose concentration when measured with continuous glucose monitoring (17)."
    2. "When using A1C to diagnose diabetes, it is important to recognize that A1C is an indirect measure of average blood glucose levels and to take other factors into consideration that may impact hemoglobin glycation independently of glycemia including age, race/ethnicity, and anemia/hemoglobinopathies."
- Where to go from here?
    1. Current evidence supports similar interpretation of A1C test results in blacks compared to whites for diagnosis and treatment of diabetes
    2. We need to move beyond "race-based" medicine to understand determinants of differences across groups (recent calls for "race-specific" cut-points for diabetes are misguided)
    3. Precision medicine: "…approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."
    4. 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
- Diagnosis of Diabetes 2018 (ADA)
    1. Current clinical practice guidelines recommend repeat testing of the same test in a new blood sample at a second time point
    2. Reduce the possibility of a false-positive diagnosis
    3. It is common for two different tests (e.g. A1C and fasting glucose) to be measured in the same blood sample
    4. Unclear if a combination of A1C and fasting glucose at a single time point provides adequate confirmation for diagnosis of diabetes
- Prognostic Implications of Single-Sample Confirmatory Testing for Undiagnosed Diabetes (Selvin et. al, Ann Intern Med. doi:10.7326/M18-0091 Jun 19, 2018)

1. Cohort study: Atherosclerosis Risk in Communities (ARIC)
2. 13,346 subjects (12,286 without diagnosed diabetes)
3. Results
    - Two tests (A1C and fasting glucose) from the same blood sample provide adequate confirmation for diagnosis
        - High positive predictive value for future diagnosis of diabetes
        - Strongly associated with complications (heart disease, CKD, death)
    - Streamlined process for diagnosis of diabetes
        - HbA1c test is used to guide treatment decisions
        - Single elevations in HbA1c or fasting glucose ("unconfirmed cases") should have tests repeated at a second time point per guidelines
    - If tests have sizable discordance, this suggests a processing problem or co-existing medication condition that may be interfering with either test

- Final thoughts
    1. More work to understand causes of racial differences in HbA1c and contribution of non-glycemic factors: Ongoing genetics work that relates to hemoglobin
    2. Race is not a precise construct and potentially a poor surrogate for differences in underlying causes of disease risk
        - "Race-based medicine" is disquieting; race is not a precise construct
        - Major causes of disparities in diabetes are not "hematological"
        - Slightly higher A1C in blacks leads to higher sensitivity of A1C – consistent with "risk-based" thresholds for biomarkers
    3. HbA1c is a useful and valid test across race/ethnic groups
        - Discouraging use of A1C in certain race/ethnic groups could worsen disparities
        - For guidelines, need to focus on specific conditions where big effects exist

Discussion:

Differences in HbA1c due to racial/ethnic or other factors

E. Selvin noted that certain pathological conditions such as liver disease may have substantial effects on HbA1c but are not addressed in the guidelines. A better understanding of what conditions can have significant effects on HbA1c, and what those effects are, is needed. S. Hanson asked about G6PD deficiency, E. Selvin said it is more common in blacks than whites and is associated with a lowered HbA1c. M. McPhaul asked what was meant when referring to potential hematological differences, changes in red cell structure/status, or something different? E. Selvin responded that the genome sequencing data will be influential, we are seeing that smaller changes in the genome may be responsible for the differences we are seeing. M. McPhaul asked if we are talking about bona-fide substitution mutations that are not some of the classic hemoglobinopathies. E. Selvin said yes, e.g. sequences of base-pair deletions. R. Cohen noted that there is evidence of variation in red cell lifespan that is not reflected in the classic hematologic parameters. The range of normal variation in red cell survival is large enough to cause clinical decision altering difference in HbA1c. The measurements of red cell lifespan have been done with labor-intensive methods, we are now trying to use these methods to validate more practical ways of looking at this that would allow us to look at this issue epidemiologically. In the shorter term looking for discordances in HbA1c and glucose when diagnosing diabetes is appropriate, but the possible causes of these discordances should be phrased more broadly. There are a number of potential causes for these discrepancies. S. Ghosh said S. Manley and other colleagues looked at potential causes of differences in HbA1c. They found suppression of HbA1c with some conditions and treatments e.g in pre-liver transplant patients. Red cell distribution width

was the parameter best correlated with differences in HbA1c. D. Leslie asked to what extent the RCDW can be an indicator of red cell lifespan. R. Cohen said there is in-vitro data from 25 years ago showing that precise fractionation of red cells by density and size can yield a wide distribution of MCVs and HbA1cs and that there was a high correlation between the two. However, no one has come up with a good way to account for this with classical hematological indices at this point. We will probably end up using some indicator of red cell size as a practical way to estimate red cell lifespan, but I am not sure we can do it with our current ways of measuring RCDW and MCV. D. Leslie asked about the relationship between iron-deficiency and HbA1c thru red cell survival. R. Cohen said J. Higgins has done some biological modeling that indicates the red cell lifespan would be predicted to be longer in cases of iron deficiency, but there has been no independent demonstration of this. L. Pogach said that he does not disagree with what was presented from an epidemiological standpoint. From a clinical perspective, it is known that African American men have lower hemoglobin than white men. These kinds of differences can cause differences in how clinicians perceive small differences in lab results. This is turn can cause differences in how we diagnose and treat patients. We all can agree that HbA1c is an indirect measurement of average glucose, and that there are factors that enter into this, not just race. This makes a difference when we add on performance measures. In the federal government there is no <8 performance measure, they have done away with it due to the potential of harm, specifically hypoglycemia. The Federal Interagency Working Group, which I co-chair, reviewed the evidence and sent out a brief that led to policy changes. To say that eAG can be used to try to manage patients poses difficulties, insulin may be used to bring the value down which can unintentionally lead to hypoglycemia. To put eAG out there, and the ADA does it with caveats, the VA says it should not be used, this does not send a clear message to clinicians. In talking to R. Little earlier she said that educators and clinicians want the eAG information posted on the NGSP web site, if so there are many other places they can get it including the ADA site. Also, the NGSP site references the ADAG study, I would suggest removing the information entirely but if you are going to link to the ADAG study there should also be a link to the Bergenstal et. al study as well. A. Albright said that she agrees that clinicians need clear direction, but it has to be within the parameters of what their particular interpretation of the literature is and what they feel is best for their patients. R. Bergenstal said he agrees with the broader notion that there is a much bigger difference within-race than between-race. It is worth noting that the use of CGM is catching on, although not for diagnosis. More people will be made aware of their average glucose, and this may not always match their HbA1c. There are ways to interpret this, it will be up to us to explain it. Thus, the more we understand about differences in red-cell lifespan, structural differences in hemoglobin, etc. the better. E. Selvin reiterated that from a guidelines perspective, focusing on the things that can cause critical differences is important. For example, a 2mm mercury shift in systolic blood pressure in a whole population can have consequences in terms of cardiovascular risks in that population. However, a 2mm difference in a clinical setting would not be considered relevant. As L. Pogach said, when making clinical decisions regarding the individual patient the clinician needs to look at all of the relevant information, including glucose, HbA1c, CGM and other test results as well as other factors relating to that patient. R. Little said she was never under the impression that eAG would be used in treatment, it was to be used as an educational tool. Even before CGM, BG monitoring was considered very important along with HbA1c, and if there are issues with hypoglycemia in trying to reach HbA1c, the goal might need to be adjusted on an individual basis. Several talks at this meeting have mentioned that you should not just look at HbA1c but also CGM/SMBG, was that not always the case? Maybe there are physicians who do not pay enough attention to glucose? D. Leslie agreed, stating that the HbA1c can tell you where you should be but does not tell you how to get there, BG is needed for that purpose. eAG is just an average or a surrogate for the HbA1c, but it still does not tell you what to actually do in order to reach goals. M. Peterson was concerned that if HbA1c and FPG are used in combination to diagnose diabetes, you

will essentially be diagnosing people that are farther along the risk curve. We know that the different tests by themselves have very high predictive value in terms of risk. If you require both tests to be positive you will be diagnosing fewer people even though we know that they are likely at risk if they are positive for either test. If we did decide to switch to using both, we would need to consider lowering the cutoff values, for example to 6.3 and 122. There is no question we are talking about people that are metabolically abnormal and at increased risk for microvascular disease. E. Selvin said the current guidelines say if a test is positive it has to be confirmed by repeating with a different blood sample. This can be costly and inconvenient, and the patient may be lost to follow-up. What we are suggesting is if you have a blood sample and run both tests, and they are both positive, you can make the diagnosis on the spot and initiate treatment. If one is elevated and not the other (usually this will be elevated FPG with a lower HbA1c), you can go ahead and schedule another visit to run the second test. In my opinion 6.5 is a conservative cutoff, the average glucose is going to have to get fairly high before the HbA1c gets to 6.5. I see the recommendation as a "tweak" to the guidelines rather than a change. In some since the guidelines are not entirely clear, they say that HbA1c and glucose can be used together but also you need two samples at two separate time points to confirm a diagnosis. Whether the cutoffs should be lowered is not something we addressed. B. Burke said that R. Cohen told him many years ago about the variance in HbA1c. I had no idea that this existed and that there were not distinct cutoffs, even though I went to a top medical program. I largely agree with what has been stated in terms of diagnosis, but in terms of patient management this issue has real-world consequences. When R. Cohen says I might look at this or that hematological parameter as an indicator of possible variation in HbA1c, that is not what is happening in clinical practice in the U.S. There are no guidelines regarding this from any clinical organization. I may be the only clinician in my region that follows the issue of variations in HbA1c including racial differences, etc., my colleagues are all making decisions based upon lines drawn in the sand. A. Albright said this is a problem unto itself. B. Burke said that unless this group can translate the issues being discussed into words that are meaningful to those that are caring for patients with diabetes, we can have discussions but we are not getting it. A. Albright said it is important to determine the role of this committee, it is not our role to put out campaigns around these issues, there are others that can and should be doing that. C. Lee said she went to her physician last year and her HbA1c was 6.7. The physician wanted to put me on metformin, I had to explain to her that there is a confidence interval around that number, she had no idea this was the case. Understanding how these lab tests translate into the real world is very important, I am a real-world evidence scientist, I want to make sure my research reaches patients. Having co-chaired the Hypoglycemia Interagency Work Group with L. Pogach over the past several years, we have continuously seen significant harm from hypoglycemia since the inception of the ADA National Action Plan 6 years ago. Looking at the racial difference, I agree that race may not be the only variable. However, given this difference we might tend to overtreat this group which can put them at increased risk for harm from hypoglycemia. E. Selvin noted that this small difference might actually make it a more sensitive test in terms of diagnosis, and blacks are at greater risk of complications than whites. The problems surrounding fixed cutoff are universal, as an epidemiologist I do not like the idea of dichotomizing things in general. On the other hand, you have to have cutoffs in clinical practice in order to make a diagnosis. Diabetes is a spectrum, hyperglycemia is a spectrum, we acknowledge that, but if a diagnosis cannot be made based on a classification there are implications for treatment, reimbursement, etc. Hopefully physicians understand that if a patient with a fasting glucose of 125 is not normal just because they are below the cutoff and follow-up is needed. C. Lee agreed but noted that hypoglycemia is a significant problem, and it important for clinicians to understand that the treatment cutoffs are not dichotomous. R. Cohen said when patients are diagnosed with a HbA1c well above the cutoff, as many are, we do not have these conversations. I agree with E. Selvin regarding the problems with dichotomizing, maybe the ADA should consider incorporating the idea of probabilities

relating to distance from the cutoff into the guidelines. This problem also translates into the agencies evaluating quality of care and paying for treatment, they don't understand the concept of uncertainties around a cutoff. M. Peterson noted that the guidelines already use terms like continuous variable. L. Pogach suggested the NIDDK and CDC should put out materials stating that a single HbA1c value represents a range, and also that HbA1c tests should be performed in standardized laboratory. That is consistent with the mission of this organization, all of the organizations and agencies agree with it, and it gets the message out without getting into the issue of competing guidelines. E. Selvin said the range issue applies to all tests, L. Pogach responded that HbA1c is used as a performance measure. The federal agencies have gotten rid of the treatment cutoffs, but in other organizations providers are getting judged based on these cutoffs. We need to teach people how to better understand lab tests in terms of their limitations and context in terms of the patient. A. Albright said hopefully medical schools will consider this issue. D. Sacks agreed, noting that this is a problem with medical education. There is inherent variability with all lab tests, the only way to get a really accurate result is to run the sample multiple times and use the average. Some tests are worse than others, e.g. creatinine is terrible. Many clinicians are not aware of this, but that is not the role of this committee. L. Pogach said if that is the case the NGSP should remove the web site reference to eAG, the role of the NGSP is to standardize HbA1c. R. Little said laboratories are asked to report it by clinics and hospitals. L. Pogach said hospitals can do what they want, but why have this information on the NGSP web site? R. Little said labs and manufacturers use the NGSP web site a lot and they want to know how to calculate eAG. L. Pogach suggested that at least the Bergenstal study should be included, it should now be considered the gold standard. E. Selvin noted that the Bergenstal study included only subjects with Type 1 diabetes, L. Pogach acknowledged this and said this could be acknowledged on the web site. Either present the totality of the evidence or do not present the information at all. J. Seley said it is difficult for healthcare providers to absorb and understand the issues being discussed, some of the messages make me nervous. If a patient had the two tests and one was positive while the other was negative, what would we tell that patient that is meaningful to them? They would likely say goodbye since one test was negative, and not come back. From a public health perspective I fear we would miss patients. R. Cohen said he has had that conversation many times. In these cases where you do not make a diagnosis on the spot you convey that the patient is still on the curve and at risk. J. Seley said yes, the person should be told they are at risk and that they should take preventative measures like going to a DPP program, making dietary changes or exercising. You cannot just tell them their status is uncertain and that you will retest them in a week. A. Albright noted that the minutes of this meeting are presented to the NGSP Steering Committee and therefore L. Pogach's suggestions regarding eAG on the web site will be considered.

POC Hemoglobin A1c devices used in the Diagnosis of Diabetes: L. Landree

- Regulatory History HbA1c
    1. Since before 1976, HbA1c assays were cleared for use in monitoring diabetes control in patients already diagnosed with diabetes.
    2. In 2010, the ADA recommended HbA1c for the diagnosis of diabetes.
    3. In response the FDA created a separate regulation for HbA1c tests intended for use in diagnosing diabetes as a way of identifying assays that demonstrate adequate performance for diagnostic use.
    4. The first diagnostic HbA1c test was approved by FDA in 2013, since then a number of assays have been cleared for diagnostic use.
- Regulations

1. 21 CFR 864.7470 – Monitoring Diabetes (LCP): Measurement of hemoglobin A1c is used to monitor long term blood glucose control in patients previously diagnosed with diabetes.
2. 21 CFR 862.1373 – Diagnosing Diabetes (PDJ): Measurement of hemoglobin A1c is used as an aid in the diagnosis of diabetes mellitus and as an aid in the identification of individuals who may be at risk of developing diabetes mellitus

- HbA1c Testing Environments
    1. HbA1c is analyzed in a wide variety of environments including central laboratories, physician office laboratories, emergency rooms and community health clinics.
    2. Devices include:
        - Assays for large clinical chemistry analyzers in central laboratories
        - Benchtop devices for POC use
        - Handheld devices for POC laboratories
- POC HbA1c for diagnostic use: Advisory Panel Meeting: July 22, 2016 meeting of the Clinical Chemistry and Clinical Toxicology Devices Panel
    1. Although a number of POC devices have been cleared for monitoring, no POC assays had been cleared for diagnostic use until very recently.
    2. Alere had applied for the first POC diagnostic claim for the Afinion
        - The method had been previously cleared for monitoring
        - ADA 2016 Guidelines: "…use of point-of-care assays for diagnostic purposes is not recommended."
    3. The topic of discussion was whether approval of a CLIA-waived device for diagnostic use in moderate complexity settings would be acceptable to the panel.
    4. POC testing refers to the use of a IVD test outside of the central laboratory setting near to the patient
        - Physician office laboratories
        - Operating rooms
        - Emergency departments and ICUs
        - Community health screenings
        - Diabetes clinics
    5. CLIA and POC settings
        - Some POC settings such as community health clinics are CLIA-waived, meaning that anyone can perform the testing.
        - Other POC settings, such as emergency departments, that are part of a hospital are moderate-complexity under CLIA which means there are requirements for training personnel and performing proficiency testing.
    6. Clinical Laboratory Improvement Amendments (CLIA)
        - Ensure quality laboratory testing
        - Any laboratory that performs testing on human specimens (e.g. blood, urine, tissue) for the purpose of diagnosis, prevention, or treatment of disease, or assessment of health, must be certified under the CLIA regulations
        - Every in vitro diagnostic test falls into one of three CLIA categories:
            - Waived
            - Moderate Complexity
            - High Complexity
        - The type of CLIA certificate determines the complexity of tests a lab is allowed to run

7. CLIA Complexity—Laboratories
    - Waived
        - No proficiency testing requirements
        - No personnel requirements
        - Only QA/QC requirement is to follow manufacturer's instructions
        - Onsite inspection of ~2% of labs each year
    - Moderate and high complexity
        - Proficiency testing required 3 times/year
        - Personnel training requirements
        - QA/QC requirements
        - Onsite inspection of all labs every 2 years.
8. Proficiency Testing
    - … determines and compares the performance (e.g., accuracy, precision) of individual laboratories on unknown test samples provided by a proficiency testing program (e.g., the CAP survey)
    - … is designed to ensure ongoing quality of test results
    - … evaluates test performance in a realistic clinical environment
    - … should be performed at least 2x per year to verify test accuracy
    - … is only required in moderate and high complexity labs

- Recent 510(k) Clearance
    1. Addition of a diagnostic claim to a POC device with an existing claim for monitoring
    2. Indications for use: "… test is to be used as an aid in the diagnosis of diabetes and as an aid in identifying patients who may be at risk for developing diabetes. The measurement of % HbA1c is recommended as a marker of long-term metabolic control in persons with diabetes mellitus."
    3. Intended for moderate complexity POC laboratories
- Diagnostic HbA1c tests: Performance must be equivalent to the performance of a legally marketed diagnostic HbA1c device
    1. Devices must be precise
    2. Devices must be accurate: the total error compared to a standardized method cannot exceed 6%
    3. Devices must have little to no chance of giving false test results for samples containing common hemoglobin variants (HbC, HbD, HbE, HbA2, HbS)
    4. Devices must maintain annual certification with a glycohemoglobin standardization organization (e.g., NGSP)
    5. Intended for use with capillary and venous whole blood samples
        - Method comparison
        - Precision
        - Total error calculations
    6. CLIA Categorized as moderate complexity

Discussion:

POC for Diabetes Diagnosis

R. Cohen noted that the total error requirement of 6% corresponds to ~±0.4% HbA1c at the diagnostic cutoff of 6.5. Given this fact it is not necessarily a bad thing if someone has to come back for a second test to confirm a life-changing diagnosis. L. Pogach agreed but expressed concern about the potential

for false positives. A diagnosis of diabetes has many implications such as for insurance, 6.1-6.9% is too wide of a confidence interval. This also assumes that the test is being performed properly in a moderate-complexity laboratory. I do not see the problem with sending a diagnostic test to a laboratory, I am concerned about POC coming into this realm. The current NIDDK educational materials, based on ADA guidelines and FDA approvals, state that the test should be performed in a standardized facility, i.e. laboratory. I do not see how an urgent public health problem is being addressed by taking this step. R. Little said that the FDA ±6% limits used to evaluate POC methods are the same as those used to evaluate laboratory methods, and asked L. Landree whether the FDA requirement will be tightened when NGSP and CAP change to ±5%. L. Landree replied that if they were to change it they would have to change the special control, but it will be considered. D. Sacks asked if there is some limitation as to who can buy these POC devices, can they be sold only to moderate-complexity labs or can others buy them? L. Landree said they should only be marketed to moderate-complexity labs, not waived labs, and if a waived lab is inspected and found to be using one of these devices they will be cited. D. Sacks noted that only 2% of waived labs are inspected every year, is there any way of preventing a lab from purchasing one of these devices and cartridges and using it in a waived environment? L. Landree said not that she is aware of. R. San George said that cannot happen with the Afinion, instruments used in a waived setting do not have the software that would allow the diagnostic test to run. The diagnostic instruments are only sold to labs that are certified as moderate complexity. R. Little asked R. San George to discuss their future intentions. He said they eventually intend to try to obtain clearance for the test to be used for screening for undiagnosed diabetes in CLIA-waived settings, especially where these people are currently not being identified and brought into the health care system. In the ideal world the test could then perhaps be confirmed by a test performed in a laboratory. We do want to address what would be necessary that the system is sufficiently robust such that it can be used by anyone and still have an extremely low risk of producing an erroneous result, and would like input from this group regarding this.

Topics for the next meeting

A. Albright noted there is not sufficient time to discuss the Alere request now but this could be a topic for next year's meeting. R. Little asked the group what other topics they might want to discuss in the next meeting, and also are there other people that may not know about this meeting that might want to come? A. Albright noted that it is an open meeting, R. Bergenstal said he was not clear on this but he knows of people that have expressed interest. J. Seley suggested reaching out to relevant groups that might not currently be participating. No topics were suggested, A. Albright asked those present to contact R. Little if they think of any relevant topics.

A. Albright thanked everyone for their attendance and discussion, noting that everyone's goal is what is best for patients. The meeting was adjourned at 4:30 PM.

Minutes prepared by Curt Rohlfing 07/13/2018. Modified by Randie Little 7/16/2018.