

**Meeting of the NGSP Steering Committee  
Minutes**

Sunday July 29, 2018 2:00 PM – 4:30 PM  
Marriott Marquis Chicago, Chicago, IL

**Participants:**

- \*David Sacks—NIH, Chair, NGSP Steering Committee
- \*Randie Little—Univ. of MO, NGSP Network Coordinator
- \*Jon Davis—Trinity Biotech
- \*Jackie Felberg—Bio Rad Laboratories
- \*Garry John—Chair, IFCC C-EUBD
- \*W. Greg Miller—Virginia Commonwealth Univ.
- \*Michael Steffes—University of Minnesota
- \*Cas Weykamp—Queen Beatrix Hospital (NL), IFCC Network Coordinator
- \***Member of the NGSP Steering Committee**

Shawn Connolly—Univ. Of MO, NGSP  
John Higgins—Mass Gen Hosp, Harvard  
Kuanys Kabytaev—Univ. of MO  
Erna Lenters—ERL;IFCC;NGSP  
Ross Molinaro—Siemens Diagnostics

Gary Myers—Myers Consulting  
Violeta Raneva—ReCCS Japan  
Carla Siebelder—Queen Beatrix Hospital (NL);IFCC;NGSP  
Curt Rohlfing—Univ. of MO, NGSP  
Hirohito Umemoto—ReCCS Japan

**Steering Committee members not present:**

Robert Cohen—University of Cincinnati  
Philippe Gillery-University Hospital of Reims (FR), IFCC Scientific Division  
David Nathan—Massachusetts General Hospital  
Curtis Parvin—Bio Rad Laboratories  
Elizabeth Selvin—Johns Hopkins University  
Hubert Vesper—CDC

**1) Welcome and Introduction—David Sacks, Chair, NGSP Steering Committee**

D. Sacks welcomed those in attendance and those present introduced themselves. D. Sacks thanked outgoing manufacturer representative Ross Molinaro for his service to the NGSP and welcomed new manufacturer representative Jackie Felberg. He also welcomed J. Higgins, noting that he is an expert in statistics who is very interested in red-cell kinetics and deformability. He recently published an excellent manuscript in Science Translational Medicine where he presents a concept to correct HbA1c for red-cell lifespan utilizing CGM data.

**2) The 2017 Steering Committee minutes were approved by the members present.**

**3) NGSP Progress Report—Randie Little , NGSP Network Coordinator**

- NGSP Network Monitoring
  - The PRLs (3) and SRLs (11) continue to demonstrate excellent comparability (May between-lab CVs were 1.04% and 0.77% for the PRLs and SRLs, respectively).
  - The SRLs are also monitored against each other using an acceptance ellipse, which is based on the IFCC network monitoring scheme. It is based on the slope and intercept of the differences between the individual SRLs results and the medians of all SRLs.
  - Monthly between-lab CVs for the NGSP network were all <1.6% over the past year.
- Long Term Quality Controls (LTQC)
  - Provides another estimate of long term consistency of NGSP results
  - 3 levels of frozen WB aliquots (prepared by ERL), ranging from 5.1 to 11.2% HbA1c.
  - Analyzed monthly by Missouri SRLs and quarterly by all SRLs
  - Results show consistency in SRL results over time since 2010.
- Certification
  - The number of certified methods continues to increase, while the number of laboratories has leveled off. This is likely due at least in part to continued consolidation of large laboratories.
  - There are >240 methods and ~140 laboratories currently certified.
  - Most certified labs are Level I and are outside of the U.S.
  - There are clusters of certified labs in Colombia SA and various locations in Asia.

- CAP Data
  - There has been much improvement in within and between-lab variability since 1993; improvement has been more subtle in recent years.
  - Current CAP limits (2013-2017) : Each result must be within  $\pm 6\%$  of NGSP assigned target value (mean of 8 SRLs, multiple results from each).
  - CAP 2018A survey
    - Five samples
    - The worst methods are used by few labs (56 out of  $\sim 3300$  participating labs).
    - The cumulative pass rates were  $>95\%$  for all 5 samples
    - Pass rates for individual methods ranged from 72.7% to 100%
    - Overall CVs were  $\leq 3\%$  except for the lowest sample (CV=3.6%).
    - Cumulative pass rates at  $\pm 6\%$  have increased over time and have consistently been  $>95\%$  in recent surveys.
    - Looking at mean CVs by method and method type, overall CVs were lower for the enzymatic and HPLC assays compared to the immunoassays. However, there was variation among methods even within the same method type, resulting in some overlap between method types.
    - Method-specific mean absolute biases when compared to the NGSP target values were all 0.18% HbA1c or less.
    - Some biases were positive, others were negative.
    - Several methods had significant biases but low variability, several other has less bias but high variability.
    - Summary
      - 1) Method-specific, between-laboratory CV's ranged from 1.0% (Arkray HA8180) to 4.7% (Beckman AU).
      - 2) 76% of laboratories are using methods with CVs $<3.5\%$  at all five HbA1c levels.
      - 3) All-method CVs for the most recent survey ranged from 2.9-3.6% (3.0, 3.6, 2.9, 2.9, 3.0%)
      - 4) Pass rates (at the current  $\pm 6\%$  cutoff) have been  $>95\%$  in the 5-10% HbA1c range for the last 7 surveys.
- Hb Variant Interference
  - Methods with interference from one or more common variants:
    - Beckman AU\* (Manufacturer states current version does not show interference, but this has not yet been independently verified)
    - Bio-Rad VII Turbo
    - Tosoh G7
    - Tosoh G8 (current version in US) (Tosoh has fixed this but the new version has not yet been approved by the FDA)
  - Between 13.5% and 16.2% of laboratories are using a method with interference from one or more common variants
- Impact of the Change in Certification Criteria
  - Current limits for NGSP and CAP
    - NGSP Manufacturer Certification Criteria: 37/40 results must be within  $\pm 6\%$
    - CAP Survey Grading for HbA1c:  $\pm 6\%$
  - Future limits for NGSP and CAP
    - In 2019 NGSP Manufacturer Certification Criteria will change to 36/40 results within  $\pm 5\%$  (37/40 for Level I labs)
    - In 2020 CAP Survey Grading limit for HbA1c will be  $\pm 5\%$
    - In 2018, the NGSP and the CAP started reporting an “educational grade” using the future limits for each.
  - Each time the criteria are changed we use analyses developed by C. Parvin, originally published in 2014, to compare the NGSP and CAP criteria.
    - Plots show probabilities of passing the NGSP and CAP criteria at continuous levels of bias and imprecision at different probability levels (95%, 99% and 99.9%).
    - Based on these analyses, the Steering Committee decided 36/40 results within  $\pm 5\%$  compared best to CAP  $\pm 5\%$ .
  - Cumulative Pass Rates for CAP 2018 GH5-A:  $\pm 6\%$  vs.  $\pm 5\%$

Sample ID	±6%	±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

- Pass Rates for NGSP certification: ±6% vs. ±5%: Based on 6 months of 2018 certification data

Certification Type	Current ±6%	2019 ±5%
Manufacturer	92.2%	85%
Level I Lab	95.1%	90.2%
Level II Lab	78.6%	71.4%

- Conclusions
  - The NGSP network is still doing well with very low CVs
  - Hb variant interference is still a problem for a small number of methods...but a fair number of labs.
  - There is still a misconception that HbA1c cannot be used when Hb variants are present.
  - The change to tighter criteria for the CAP GH survey and NGSP certification is reasonable if we want to see lower overall variability in HbA1c results for patient care.

## Discussion:

### *NGSP network, CAP data*

E. Lenters asked if the scales for the PRLs and SRLs plots could be made smaller to better show the differences between the labs. R. Little agreed to do this and send the revised plots to meeting attendees. E. Lenters asked about the stability of the LTQC samples, does this mean they have stable at -80°C for almost 10 years? C. Rohlfing clarified that the main stocks of the LTQC samples are kept in liquid nitrogen tanks (-196°C), small amounts of aliquots are removed and stored in an ultralow freezer. D. Sacks asked about the slide showing the cumulative pass rates at ±6% over time, why are there some years missing. R. Little said that the criterion at that point in time was not yet ±6%. CAP went back and re-calculated the pass rates using ±6% when that criterion was being considered, but they did not provide the data for all years. We could probably obtain the data from CAP if needed.

### *Hemoglobin Variant Interference*

D. Sacks asked how long Tosoh has had the fix for the G8 interference, hasn't it been a year or more? R. Little said yes, it has been available in Europe for some time. Her lab evaluated the new software a while ago and the data looked really good. However, E. Lenters recently found an issue with HbE trait. E. Lenters said in her previous publication she found no interference from the common variants including HbE trait, but she only ran five HbE trait samples in that study. Tosoh recently asked her to evaluate the GX for variant interference, in the process she also re-evaluated the G8. For 8 of 18 samples, HbE trait was not recognized by the G8 resulting in falsely low HbA1c results for those samples. R. Little asked if it could be a column/reagent lot issue, E. Lenters said that does not appear to be the case. When the samples are repeated the problem does not occur with the same samples each time, the problem is not consistent. There is a valley between the glycosylated E and Ao peaks that is not always recognized by the instrument. Tosoh is now aware of the issue but has not yet been able to fix the problem. G. John suggested it could be related to the age of the sample, the ability to obtain a good separation can change as a sample ages. R. Little said when her lab ran previously frozen samples they did not see this problem in any of them. When they ran fresh samples they only saw this in one of two duplicates of one sample. We will be running more samples soon. It is an important issue, a lot of labs are still reporting G8 results from variant samples, even if the interference is more evident in the higher range of HbA1c it is still a problem. E. Lenters agreed noting that the HbE issue is a big problem, especially in areas of the world where the prevalence of HbE is very high. In particular, use of the G8 to diagnose diabetes in these populations is unacceptable. How did this method get the diagnosis claim from FDA? R. Little said the method had significant interference from HbE at the time it got the claim, but it was noted in the package insert

and the presence of HbE was visible on the chromatogram. Therefore, results from these samples would not have been reported if manufacturer instructions were followed. E. Lenters questioned whether routine laboratories would even see or flag the HbE peak, especially with the latest software version where the presence of HbE trait is less obvious. C. Rohlfing said the G8 version still being used in the U.S. clearly shows a peak between the HbA1c and the HbAo peaks and labels it as an extra peak. R. Little noted that the G8 version now being used in the U.S. shows significant interference for all of the common variants. Customers have been notified by Tosoh, but many may still be reporting results from samples with the common variants. She asked M. Steffes how the University of Minnesota lab is addressing the issue. M. Steffes said they are purchasing a boronate affinity method to check samples where we have questions. In one large study, GRADE, there is a high recruitment of Asian Americans in some clinics, so HbE in particular is a big issue. Tosoh has not been very responsive to us in regards to the problem. R. Little said Tosoh has had some recent turnover in personnel, they should be able to get the problem solved but it will likely take some time. D. Sacks asked E. Lenters how Tosoh responded to her study, she said they were not happy about the results but they did agree to publish the G8 results along with those from the GX. R. Molinaro asked whether the company has had discussions with the FDA regarding the problem, D. Sacks and R. Little said they have been working with the FDA for some time now. R. Little said the FDA was wanting data from additional variant samples in different ranges, and it is difficult to obtain large quantities of these samples in the U.S. We may have to resort to getting samples from Asia. D. Sacks asked how many labs in the CAP survey use G8, R. Little said 373. D. Sacks said that is a lot of labs, one issue with the CAP survey is we do not know how many samples each lab runs. R. Little was concerned that recent articles and newsletters have been misleading and given clinicians the impression that HbA1c cannot be used in patients with hemoglobin variants, there was some talk of this at the ADA. R. Molinaro asked if manufacturers have a role to play in clearing up this misconception, also what do current guidances say? R. Little said she and D. Sacks have discussed the recent ADA guidance wording with J. Fradkin regarding this topic, it is also a bit misleading. D. Sacks read the wording from the 2018 ADA guideline:

“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).”.....

“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.”

It is a big issue in the U.S., members of Congress are aware of it. G. John said there are misconceptions around the globe regarding when HbA1c can and cannot be used. Manufacturers can and are helping with educational efforts. R. Molinaro asked if part of the issue is that the guidances are somewhat vague. D. Sacks said yes, we have been talking with J. Fradkin regarding the ADA guidance to try to make the wording clearer. Part of the problem is that there are currently no definitive answers to some of the questions. R. Little said the Lacey et. al article we discussed last year, which stated that there was a difference in HbA1c results between black subjects with and without sickle cell trait. We know this was due to analytical interference with the HbA1c method that was used, but NPR and other news outlets ran stories on the article and so it received a lot of publicity. WG Miller said in his mind he’s struggling with the difference between analytical interferences in the laboratory and interferences due to shortened red cell lifespan, this is where people are getting confused. D. Sacks and R. Little agreed. WG Miller said this makes it difficult to make clearly worded guidelines, this is where our laboratory background could be helpful in the writing of these guidelines. D. Sacks suggested contacting the writing committee. J Higgins noted that the recent paper by Beck, Bergenstahl et. al showed a small difference in HbA1c results between black and white subjects. G. John said that now that we have very precise ways of measuring HbA1c, other factors that influence HbA1c have become more visible. Educational efforts are really important in addressing these issues. D. Sacks asked M. Steffes if he thought the writing committee would be willing to listen to input, M. Steffes said he had never served on a writing committee. He served on the expert committee that ultimately recommended HbA1c for diagnosis, then the writing committee actually wrote the guidance.

*NGSP and CAP criteria*

WG Miller asked about how the plots showing the probabilities of passing CAP and NGSP criteria relate to the CAP 2018 B survey data. R. Little and C. Rohlfing noted that it is difficult to make direct comparisons because the data from the survey represents all labs/methods while the NGSP/CAP model shows the probabilities of a single manufacturer method passing. R. Little said the tightening of the criteria are needed, there are still a few methods with high imprecision in use. Bias can generally be addressed by the manufacturers, but imprecision generally cannot be fixed, the poorly performing methods just need to go away. E. Lenters was concerned about tightening the NGSP criterion to 5% given that NGSP certification samples are individual samples, while CAP samples are pools. There are some samples where we see differences of as much as 5% between two SRL methods that are due to the sample matrix and have nothing to do with the bias or imprecision of the methods. Maybe it would be better to allow 0.3% HbA1c difference below a certain HbA1c level? At 4% HbA1c 5% corresponds to a difference of 0.2% HbA1c, we even occasionally see that much difference between SRL duplicates. R. Little said this might be why the 2018 manufacturer pass rates dropped from 92 to 85% when going to 5%. We generally compare manufacturer methods to a SRL that is the same method type, so that helps to address at least some of the individual sample matrix issues. Also, if there is an outlier it is generally investigated. In practice we generally see when methods fail is not one or two outliers. We generally see either a consistent bias, often with a slope, and/or a lot of scatter even when the method is compared to a SRL of the same method type. Also, 36/40 have to be within 5%, which allows for several samples to be outside this range. In general the methods that look good on the CAP survey also look good on the certification. E. Lenters said that some POC methods they have evaluated do not show good performance, but nonetheless obtained NGSP certification, how is this possible? POC manufacturers may also have a good HPLC method in their laboratory that they use to check the sample results. R. Little agreed, saying there are ways that manufacturers can “cheat” on certification but it is difficult for labs to cheat on the CAP survey. This is why the CAP survey is so important. E. Lenters suggested occasionally asking manufacturers for the raw data, C. Rohlfing asked how this would work with single-use POC methods where the device is used once and discarded. E. Lenters said most all POC methods have a way to print out the results. C. Rohlfing said the idea of using only samples  $\geq 5\%$  HbA1c has been discussed; R. Little said we will go ahead and adopt this policy unless there are objections (there were none). C. Weykamp asked about the uncertainties of the assigned values. In the case of the CAP survey the values are assigned by multiple SRLs performing multiple measurements, in the case of NGSP certification it is duplicates performed by a single SRL. R. Little said that C. Parvin incorporated the uncertainties of both the CAP and SRL value assignments into the model based on historical data. D. Sacks said C. Parvin told him that the influence of the additional uncertainty for NGSP as opposed to CAP was minimal.

#### 4) Clinical Advisory Committee Meeting Update—David Sacks

- The CAC is composed of representatives from major clinical diabetes organizations. The purpose is to facilitate communication between these organizations and the lab. They advise the NGSP on clinical aspects of HbA1c and report back to their organizations.
- The 2018 CAC meeting took place in Orlando at the ADA meeting in June.
  - Chaired by Ann Albright of the CDC.
  - R. Little presented an update on NGSP progress.
  - E. Selvin gave a presentation summarizing recent studies of racial/ethnic differences in HbA1c.
    - Studies have shown higher HbA1c results in black compared to white subjects
    - Beck and Bergental study published last year
      - 1) Concluded that HbA1c results in black Type 1 patients were slightly higher than those of white patients at equivalent CGM levels.
      - 2) However, there were significant differences among individuals in both groups, resulting in considerable overlap.
    - This topic has generated a lot of discussion
    - A sub-study of the GRADE study is currently looking at the racial differences issue.
  - L. Landree from the FDA gave a presentation by phone regarding POC HbA1c for diabetes diagnosis.
    - The FDA hosted a meeting in 2016 in Washington DC to discuss the topic.
    - Alere has a POC device, the Afinion, that is CLIA-waived, meaning users do not have to participate in proficiency testing (PT).
    - The FDA recently approved the Afinion for diabetes diagnosis, but under moderate complexity, not as waived. This means that users must participate in PT. There are personnel, training and QA/QC requirements, and the labs are inspected on-site every two years.

- Alere has acknowledged that their eventual goal is to have the waived version approved for diagnosis.
- L. Pogach of the VA requested the Committee to consider removing the information regarding estimated average glucose (eAG) from the NGSP web site.
  - It is used by some clinicians in the U.S.
  - The ADA position is that clinicians can use it with their patients if they find it useful.
  - Some labs in the U.S. report eAG along with HbA1c, if the clinicians request it. Other labs do not report it.
  - R. Little has been told by some clinicians and diabetes educators that they find the eAG information presented on the NGSP web site to be useful.
  - L. Pogach is concerned about hypoglycemia and overtreatment of diabetes in order to reach target levels, and feels the eAG information could be misleading and compounds the problem.

## Discussion

### *Racial/ethnic Differences in HbA1c*

D. Sacks mentioned that D. Nathan had indicated that the results of the GRADE study of racial differences would likely be coming out next year. J. Higgins said yes, unfortunately they are only doing two weeks of CGM for the study. M. Steffes said the study has been bogged down by legal issues centered around obtaining assay instrumentation needed to complete the study.

### *POC HbA1c for Diagnosis*

D. Sacks said that Alere states that the moderate-complexity Afinion method uses different cartridges than the waived instrument that cannot be used on the latter, and that sales of the moderate-complexity test are restricted to labs that are designated as such. The idea that anyone could run a test to diagnose diabetes is disconcerting. G. John asked if there are any waived POC tests that are used for diagnosis in the U.S. D. Sacks responded yes, there are a few, two examples are pregnancy and HIV.

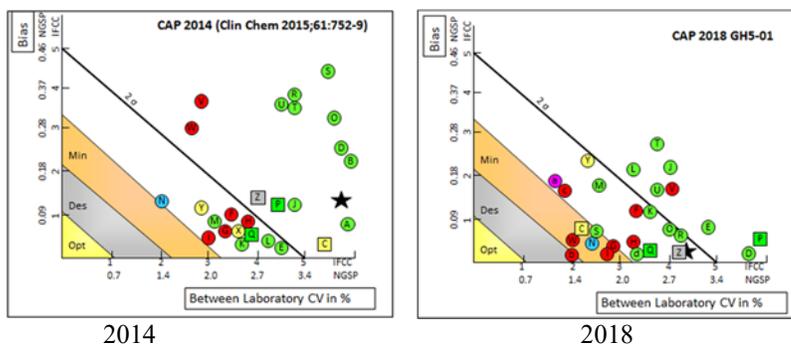
### *eAG on the NGSP Web Site*

R. Little said we do not make recommendations to use eAG on the web site. Rather, if clinicians are requesting it and labs are reporting it, the labs should know what it means. The NGSP web site is geared toward laboratories, we are providing them with information. G. John noted that he was on the committee that drafted the international consensus recommendations. eAG was discussed in the first statement but removed from the second; the Committee decided the correlation between eAG and HbA1c was not good enough to have confidence in eAG. The recommendation was that clinicians can access eAG and use it with patients if they want to, but labs should not report it. Very few labs outside of the U.S. are reporting it. D. Sacks noted that the wording is careful on the NGSP web site, we do not recommend the use of eAG. M. Steffes asked G. John if they report eGFR, G. John said they do although with reservations as there are problems with it. D. Sacks said in the U.S. many clinicians carry in their pockets a card relating average glucose to HbA1c. Originally, this was based on data from the DCCT. The DCCT was never designed for this purpose, the ADAG study was and the ADAG equation is different. Some years ago a question was put on the CAP survey asking if labs were reporting eAG and if so which equation they were using. It turned out about half of the labs that reported it were reporting it using the old, incorrect DCCT equation. Once an explanation was provided on the CAP survey, the number of labs using the incorrect equation dropped dramatically. By putting the correct ADAG equation on the web site, we are providing the correct information to labs. M. Steffes said he favored keeping the information on the web site. WG Miller agreed, noting that we are providing the correct information to labs versus having them search for it elsewhere on the internet, which might lead them to incorrect information. G. John agreed that it is better to have the correct information readily available. J. Higgins commented that we do not want to state that there is a “correct” linear equation, but the information and concept is helpful. As far as the EGFR comparison, eAG is probably closer to true average glucose than EGFR is to GFR. With EGFR you have to correct for race and gender, and it makes a number of assumptions about body weight. WG Miller commented that where there is concern over hypoglycemia, the insulin dosing protocols, which are likely based on POC glucose, should be examined. There was general agreement that the use of treatment targets, and clinicians assuming that a lab result represents an exact number, can be problematic; however, this is a problem in terms of educating clinicians as to the proper use of these tests. G. John said that years ago when the 7% target was introduced in the UK, there were problems with physicians overtreating some patients without taking factors such as their age into account. D. Sacks said the major clinical organizations are now moving toward individualized

treatment goals in their guidelines. D. Sacks asked the Committee to vote on whether to remove the eAG information from the web site. The vote was unanimous to keep the information on the web site.

#### 4) EU Monitoring Quality—Cas Weykamp, IFCC Network Coordinator

- “EurA1c”
  - Concept: Once a year the respective European EQA/PT Organizers use the same 2 samples
  - Information
    - 1) Overall performance in Europe
    - 2) Performance per country
    - 3) Performance per manufacturer
    - 4) Performance per country per manufacturer
    - 5) Progress Quality
  - Manuscript is available online and will be published in the August issue of Clinical Chemistry along with an accompanying editorial by Eric Kilpatrick
- Monitoring in the U.S.
  - CAP performance improved between 2014 and 2018



- Several of the worst-performing methods in 2014 are gone from the market and better methods have replaced them.

#### Discussion:

G. John said that the improvement in bias is striking, D. Sacks agreed. C. Weykamp said another interesting aspect is the performance of the tests in different countries, and in Europe compared to the US. The performance of methods varies significantly among countries. The number of participating labs has increased since 2016 from ~2100 to ~3000. D. Sacks asked C. Weykamp if he knows why there are these differences among countries, C. Weykamp responded that there are different attitudes toward quality in different countries. For example, in Germany the PT limits for HbA1c were  $\pm 18\%$  until recently. Also, manufacturers pay more attention to quality in countries that pay more attention to quality. Also, when there is pressure on technicians to process large numbers of samples, there is less attention to quality. R. Little asked if the 18% in Germany was due to the use of processed material. C. Weykamp and G. John said that a big factor is that when labs in Germany fail a survey they cannot get reimbursement for the test for one year. Thus, they are afraid to fail labs. C. Weykamp said he suggested at a conference several years ago that these wide limits are unacceptable, Germany is now lowering the requirement to 8%, and they are using fresh whole blood. G. John said the data are interesting, countries you think would perform well do not necessarily do so, and vice-versa. M. Steffes suggested that it would be interesting to see how methods in the U.S. perform in individual states. E. Lentes asked if HbA1c will still be used in 10 years, or will it be replaced by CGM. D. Sacks said it depends upon whom you ask, CGM is getting a lot of attention, but it is still expensive technology. G. John said in the UK CGM is provided free to patients with T1 diabetes, but only up to 18 years of age. D. Sacks said there are other issues with CGM, there has to be a lot of healthcare personnel involved. D. Sacks said HbA1c will not go away any time soon, G. John agreed.

*D. Sacks thanked everyone for their attendance, the meeting was adjourned at 4:00 PM.  
Minutes prepared by C. Rohlfing 8/24/2018.*