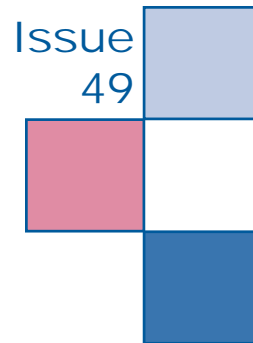
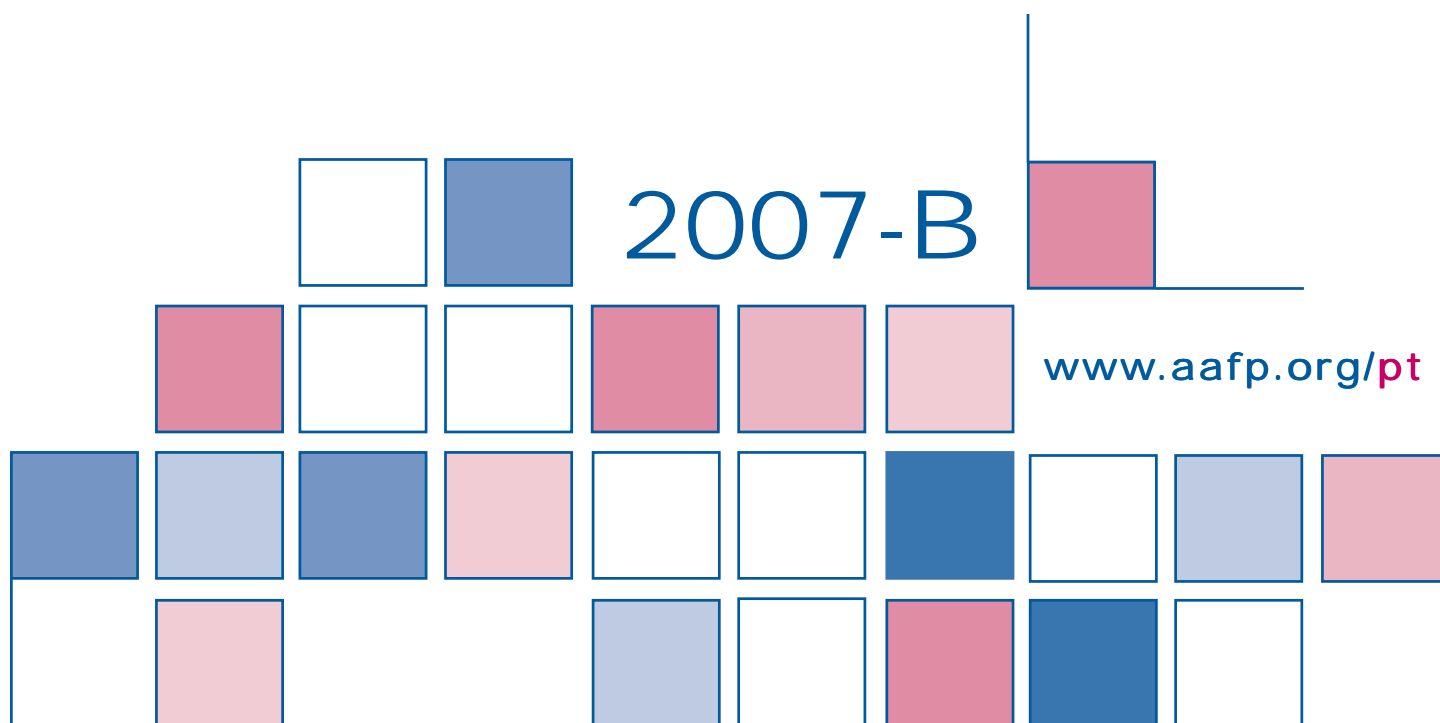


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Insight

A Continuing Education Publication for the
Physician Office Laboratory



In This Issue:

Quality Control Myths:
Part I

POL in the Courtroom

Hemoglobin A1c Testing



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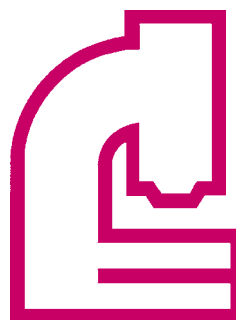



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3.	A	15.	A	27.	A
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5.	D	17.	B	29.	B
6.	A	18.	D	30.	A
7.	A	19.	A	31.	C
8.	A	20.	C	32.	D
9.	B	21.	A	33.	A
10.	C	22.	B		
11.	D	23.	A		
12.	A	24.	B		

CME Learning Objectives

Following completion of the self-instructional material, the participant will be able to:

1. Apply basic statistical concepts to laboratory quality control; recognize the “Myths of QC”; and use this understanding to determine how to establish accurate laboratory QC ranges.
2. Understand the liability issues associated with laboratory testing in the office laboratory.
3. Recognize the significance of HbA1c in the management of diabetes; identify the most common types of assays and their limitations; discuss sources of erroneous results and describe guidelines for error reduction.

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Event 2007-A	February 28, 2008	254-001-07

Quality Control Myths: Part I

By Nils B. Person, PhD, FACB
 Technical Director, Clinical Education & Support,
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The routine testing of quality control samples is required by the Clinical Laboratory Amendments of 1988 (CLIA '88) for all clinical laboratories regardless of size. It is also something we all do in the belief that it will ensure the quality of patient results. However, few aspects of day to day life in the laboratory cause more frustration and confusion for many laboratory staff than evaluating apparently out of range QC sample results. Further, misunderstandings about the statistical principles underlying our evaluation of the results obtained from quality control samples can compromise the effectiveness of the QC process. This often leads to incorrect assessment of how well the instrument is performing. In this series of two articles we will discuss the most common QC misconceptions that I call the "Myths of QC" and will discuss how applying these principles can make evaluating QC results easier and less time consuming.

We'll start by looking at the basics. What follows may seem a little abstract and theoretical, but it is important to understand these concepts before we can discuss more practical aspects of dealing with QC. In the past, many folks have avoided trying to understand the basic statistical concepts behind QC believing them to be too difficult and focused instead on the daily steps to follow. As a consequence, they are not comfortable with what to do when things don't go as expected ... and, if these principles are not applied correctly, that happens a lot. So let's spend a few minutes to understand why we do what we do. It really isn't that hard and it will make our lives easier right away.

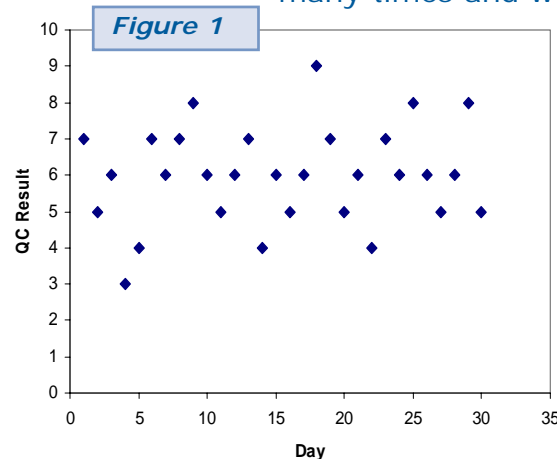
WHY DO WE TEST QC SAMPLES?

We test QC samples to detect change in system performance. QC samples are not meant to directly check accuracy. We use proficiency testing and calibration verification to document accuracy. After we have initially documented that the system is performing as expected, we run QC samples on a regular basis to detect

whether or not there has been a change in system performance. This may sound like "splitting hairs", but this seemingly trivial distinction is critical to understanding effective use of QC testing.

We detect change by comparing today's QC results to what we expect them to be. Therefore, the first step is to decide what the expected performance should be. To most sensitively detect any new changes in the performance of our one particular instrument, the expected performance **must** be based on how our particular instrument performs. We cannot base the expected performance for our instrument on data collected from a dozen or so other instruments at some time in the past (i.e., the values for mean, SD, and range in the QC material package insert).

To establish our expected performance to use as the basis for checking daily QC results, we have to create a model that will predict what results should be day to day if the system performance does not change. For any test on any instrument, if we analyze the same sample over and over many times we will get a range of values for the results of all the replicates. Let's say we analyze a QC sample many times and we get a range of



values from 1 to 10. If we graph the data in the usual way, showing the result we get each time we test the sample we get a graph like Figure 1.

If we go through the data and count up how often we get any

individual result, we get the frequency of occurrence for that value. For example, if we look at figure 1 and count up how often we got a result of 6, we find 6 occurred ten times. Similarly if we count up how often we got a result of 9, it only happened once. If we now make a new graph that shows how often we get each value on the vertical axis and over the range of results on the horizontal axis, the graph will ALWAYS look like Figure 2.



Since this pattern is always the same and follows a known pattern called Gaussian, "Normal", or "bell shaped", we can use some simple statistical tools to model or predict what the results should look like in the future if nothing changes in the performance of the instrument/method. The tools are the ones we all know and love...

mean and standard deviation (SD).

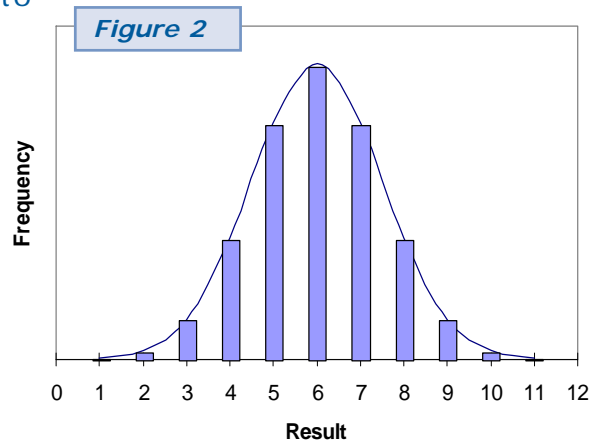
The mean indicates the center of the data and the SD indicates how far the data will spread either side of the mean. In using these statistical tools to create our expectation of what future QC results should look like, we accept certain assumptions that are an inherent part of this statistical model. Let's see how those assumptions affect how we use these expected values and what happens if we do not keep the assumptions in mind when we evaluate QC results. We will do this by looking at the "QC myth" that arises from not keeping this model and its assumptions in mind.

Myth #1:

The lab should use the mean and SD from the QC material package insert to establish acceptable QC ranges.

One of the key assumptions made by all QC protocols is that, unless something changes, the results from repeated testing of the QC sample will be evenly distributed on both sides of the mean. Remember, the mean is the average and, by definition, the average is supposed to be the middle value. This assumption will be valid only as long as the target mean used for setting up the QC range matches the actual mean of the results generated by the instrument. If, however, the QC range is set up using a target mean that does not match the actual mean for the instrument being monitored, this assumption is not valid and the effectiveness of the QC results to detect change in system performance is compromised.

The most common way that this fundamental assumption is violated is by the use of QC material package insert values to establish QC ranges on a specific instrument. If the difference between the package insert mean and the actual instrument mean is more than very slight, the QC range will not effectively monitor the instrument. This is why every regulatory or standards setting organization in the US (CLIA, CAP, COLA, CLSI) states in their requirements that labs must validate their own target values for QC and have data on file to document that this was done.



Typically two things can happen when the incorrect mean is used for QC ranges and the assumption of even distribution around the mean is violated. First, a significant number of the daily QC results fall outside the expected QC range. This typically leads to much wasted effort and frustration for both the lab and the manufacturer's service folks in trying to troubleshoot a problem that doesn't exist. No cause for the "out of range" QC results can be found because **nothing is wrong** with the instrument. The only problem is inappropriately set QC ranges.

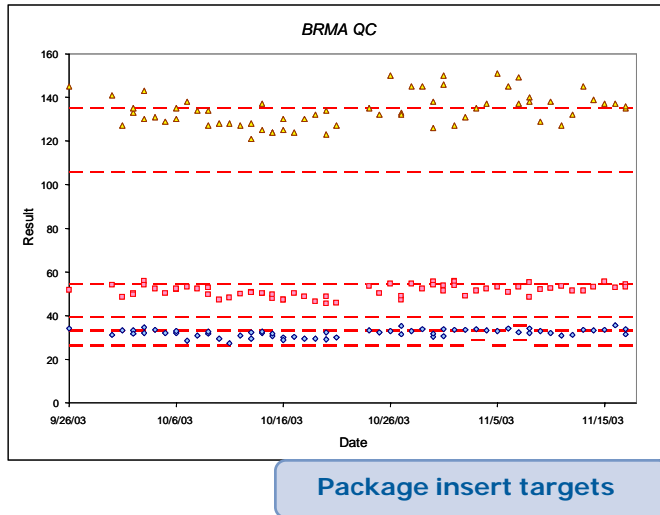
The second thing that can happen is fortunately far less common. If the QC range is not properly established, **real problems may go undetected** because the QC results are apparently in range and the operator is unaware of the problem. This happens because the QC range based on package insert values is not correct for the instrument and may not allow for effective detection of real problems. Obviously, if the difference between the package insert mean and the actual instrument mean is quite small, the impact of using the package insert mean will be minimal, but we have all dealt with situations where there have been significant differences between the mean printed on the insert and the actual mean obtained on the instrument.

The following two graphs illustrate the issue. These graphs show actual QC data from a laboratory that was frustrated because their QC, especially the highest level, was frequently out and they wanted the manufacturer to fix



the instrument as it was obviously not working correctly.

The graph on the left shows the QC data compared against 2 SD ranges based on the mean and SD contained in the QC material package insert. Note that many of the QC



results tend to be near or above the upper limit of the expected range. In contrast, the right hand graph shows exactly the same QC data compared against 2 SD ranges developed using data from the instrument being monitored. Notice that very few results fall outside the expected ranges. Also note that if there was a change in instrument performance that caused the results to shift to lower values, the ranges based on package insert would not be as quick to detect the change because the lower limit of the range is too low compared to the actual performance of the instrument. As a consequence, a true change in method performance that may affect patient results would be missed if the QC ranges were set using package insert values.

In this case, the QC material package insert ranges were established at the time the QC material was manufactured. Since then there had been changes in how the assay responds to the QC material. Since the lab did not set their expected ranges based on their own current performance, they wound up seeing a "problem" where none existed and possibly missing a real problem. Appropriately revising the QC target mean to reflect current performance of the QC material solved their "problem".

So now we understand why QC material package insert values should not be used for QC targets, but that raises two important questions ...

How do I go about setting my own QC ranges?

If I use my mean and SD to establish QC ranges how do I know the ranges are accurate and my instrument is working correctly?

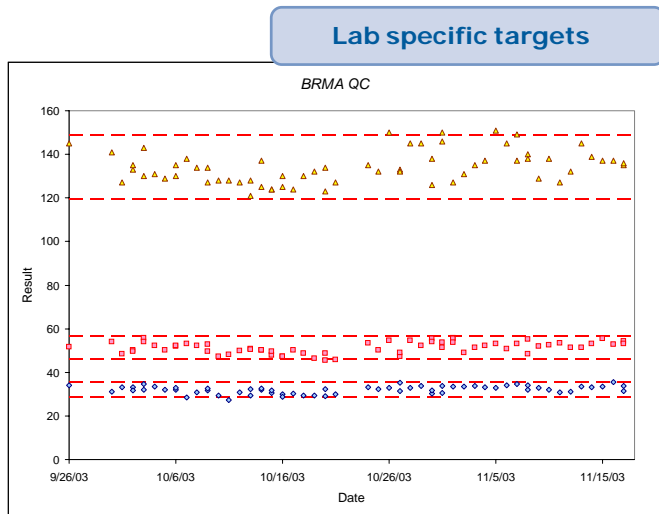
■ SETTING QC RANGES

We have established that we should be using QC targets for mean and SD based on data from our own instrument and not from a package insert or peer group, but how should we do this?

The ideal approach is to collect a minimum of 20 results for the new QC material over at least 20 days (more is always better!) and then calculate a mean and SD from that data. For a new lot of control material, the lab would order the new lot enough in advance that they can analyze the new lot side by side with the QC material in current use while they collect the necessary data. This is without a doubt the best way, but we all know it may not always be practical. We may not get the new QC lot in time or it may be a new assay or instrument. So then what?

We can get a decent initial estimate of the actual mean for the new lot by running 8 to 10 replicates of the control material and using that mean. This can be done all at once in a single run. This value can be used to get started and then it can be updated after data has been collected during normal operation over 20 or 30 days. Some folks may complain of the additional cost of running these QC replicates, but we should keep in mind the costs involved in troubleshooting non-existent "problems" due to improperly set QC ranges (time and the cost of repeating the QC samples over and over), the cost of delayed patient results because time was wasted investigating an entirely preventable problem, and the potential cost of missing a real problem with instrument performance and reporting incorrect patient results because of improperly set ranges. So, it is easy to get a target mean and it makes sense to do this, but how do we know this mean is acceptable?





This is where the control material package insert, or the peer group report values come into use. We do not want to use any of these values as the QC target mean, but we can check the actual mean we get against these values to verify that our mean is acceptable. A totally appropriate way to do this is to look at the two values (our mean and the QC package insert mean) and use our judgment that the two values are as close as can be expected for this assay and the difference is not clinically significant. This is easy, but many folks are not comfortable making such a judgment and would like guidelines to go by. A good “rule of thumb” here is that our mean should be within one SD of the QC material package insert mean or the peer group mean. Always keep in mind that the QC material package insert mean may no longer be valid for a particular assay because there may have been reagent lot related changes in the assay performance with the QC material since the package insert was printed. It is always best to “validate” that the QC material package insert values are still appropriate by checking them against peer group data for the same **reagent** lot or contact the manufacturer for their current experienced mean for that **reagent** lot.

We have seen it's easy to get, and validate, an instrument specific mean to use as the target mean for QC, but what about the target SD? Establishing the SD for an instrument is tougher because it requires a lot of data and you absolutely **cannot** collect all the data in a single run or even a single day. Since the SD represents all the expected variation in performance, the data used must be collected over as many different runs / days as possible to make sure that all

normal day to day variation is included. If this is not done, the SD will be too small; the QC range will be too tight, and you will have frequent “out of range” QC results that do **not** mean anything except that the range is wrong.

If we look at statistical reference books, we learn that to calculate an SD that is within +/- 10% of the “true” SD requires more than 100 data points!! No one is going to test 100 replicates of QC material just to get data for calculating an SD, so what do you do to establish an SD to use for QC?

If you are establishing QC targets for a new lot of QC material, and you have data from a previous lot of the **same** QC material (e.g. the lot you are running right now), the best way to establish an SD for the new lot is to take the CV calculated from all the data generated using the prior lot and use that to estimate an SD for the new lot. What?

Let's try an example. We want to establish a target SD for TSH for lot 21 of ABC CONTROL level three. For the last 14 months we have been using lot 20 ABC CONTROL to monitor TSH. First we take as much of the data as we can that was collected over the last 14 months for lot 20 level three for TSH and calculate the overall CV. Let's say we get 4.5%. Now, for the new lot 21, on the instrument we are using, we get a mean for level three for TSH of 3.3. Therefore, to estimate the SD to use with ABC CONTROL lot 21, we multiply the new mean (3.3) by the CV of the prior lot (4.5 % = 0.045) and we get $3.3 \times 0.045 = 0.15$. Our initial QC targets for lot 21 for level three TSH are a mean of 3.3 and an SD of 0.15.

If you do not have data from a previous lot of the same QC material (new instrument, new assay, new brand of QC material), then the best value to use as the provisional start up SD is the QC material package insert SD. This will be a



reasonable value and will work as long as you do NOT use the QC material package insert mean as the target mean.

Remember that to properly set up statistical QC we must be sure that the QC ranges used are centered on the actual mean of the instrument being monitored. We accomplish this by using the actual mean from the instrument as the QC target mean. The SD determines how wide the acceptable range is and, in most cases, the QC material package insert SD will be a good first estimate, though usually a bit too large. This works well to get started, then the SD is updated once enough data has been collected during routine daily use.

Now we know how to properly set up effective QC targets on any instrument. When targets are established this way the frequency of "out of range" QC results is low unless there really is a problem. The next QC myth we want to address in this series is that, once set, QC targets should **never** be changed and this will bring us to deal with the dreaded lot to lot shift in QC. We will address this myth in Part 2.

Resources:

1. Brooks, Z.C. *Performance Driven Quality Control*. AACC Press, Washington, DC. 2001
2. CLSI. *C24-A3. Internal Quality Control Testing for Quantitative Measurements: Principles & Definitions: Approved Guideline*. 3rd Ed. 2006.
3. Westgard, J.O. *Basic QC Practices: Training in Statistical Quality Control for Healthcare Laboratories*. AACC Press, Washington, DC. 2001
4. www.Westgard.com



POL in the Courthouse

By Paul Fischer, MD
Family Physician in Private Practice, Augusta, GA

When you add surgery or obstetrical services to your clinical practice, your malpractice rates usually increase. Did you ever notice that this does not happen when you add laboratory services or become the director of your POL?

The difference is, in general, that there have been few malpractice cases based on laboratory services. This is true not only for family physicians but for all physicians, including pathologists. There are occasional cases of

missed diagnoses in histology but, for the most part, laboratorians do not get sued. A principal reason is that the clinician interfaces between the laboratory and the patient and is often able to figure out when a test is in error. Thus, the laboratory error rarely leads to patient harm.

I recently had the opportunity to serve as an expert in a malpractice case that centered on office laboratory issues. I was contacted by a lawyer defending a family physician in the Midwest. The physician had seen a 13-year-old with a sore throat and ordered a rapid strep test, which was negative. A month later, the same teenager presented with polyarthritis, weight loss, and heart failure resulting from rheumatic fever. This patient required two heart valve replacements but subsequently did well. His stress echogram, performed at the time of the court case, revealed normal cardiac function. The patient is now a healthy 18-year-old, limited only by having to avoid contact sports because of his being on Coumadin.

The central point in the case was whether the physician and his laboratory digressed from the standard of care by not following up the negative rapid strep test with a throat culture.

The process of serving as an expert for this case required about 40 hours of reading a foot-high stack of depositions, meeting with the family physician's lawyer on several occasions, being deposed by the opposing lawyer, and finally, flying to the Midwest for the trial.

The opposing legal team used a variety of approaches to prove their claim that the standard of care was not met. They produced infectious disease experts to testify that no competent laboratory in the country would fail to back up a negative strep test with a culture. They supported their claim with recommendations from the Pediatric Red Book and numerous textbooks, which stated that back-up cultures are necessary for a negative rapid strep test because of the test's low sensitivity. They argued that CLIA and COLA regulations were both violated because the package insert for the particular test that was used included comments about following up negative rapid tests with a culture. They argued CLIA, COLA, sensitivity, specificity, etc. It was enough to make a juror's head spin!



The basic clinical issue relates to the fact that rapid strep tests have very high specificity – in the 98% to 99% range. This means that patients with a positive test likely do have the disease. The sensitivity of most current rapid strep tests ranges from 90% to 95%. This means about 5% of patients with a negative rapid strep test result would test positive on bacterial culture. There have been few studies to show whether these patients with “false-negative” rapid strep tests are actually infected.

One small study showed that about 40% of such patients do, in fact, have a strep infection, as indicated by a rise in strep antibody titers. Presumably, the other 60% are non-infected strep carriers. This means that if 200 consecutive patients with sore throats presented to the office and the rapid strep test was the only method used to identify which patients had strep, only about 1 of those 200 patients would actually have strep and be missed because a follow-up culture was not done (assuming a rate of 20% strep and 80% viral pharyngitis in a typical family practice).

In the 1990s, the infectious disease community spent a great deal of energy creating “expert” opinions for family physicians, pediatricians, and internists recommending follow-up cultures for negative strep tests. At the same time, it became common practice in primary care to rely solely on the rapid strep test.

There are numerous valid reasons for not doing back-up cultures. First, cultures are inherently flawed. They have always been difficult to do and, even in the best laboratories, they have at least an 8% false-negative rate comparing paired specimens.

Additionally, the 2- to 3-day delay in test results is difficult to manage. Do you treat patients with antibiotics for a few days or make them wait and call later when they are no longer symptomatic to tell them that they now need to take antibiotics?

At the same time, the national rate for rheumatic fever has dropped precipitously. With only one to two cases a year in a typical state,

most family physicians have never even seen a patient with acute rheumatic fever.

The rapid strep test used by the family physician who was sued was, in fact, both highly sensitive (95%) and moderately complex compared with most rapid strep tests, which are CLIA waived.

Family physicians have to weigh the inconvenience of cultures, the rarity of rheumatic fever, the risks of prescribing unnecessary antibiotics, and figure out what to do with a 13-year-old with a sore throat. While there are no national statistics, it is my observation that most family physicians rely on the rapid strep test and rarely do cultures, except when the clinical problem is not clearly solved in their minds. Although textbooks still support backing up a negative rapid strep result with a throat culture, the “standard of care” in practice has evolved so that back-up cultures are not necessary . . . and that is what I argued.

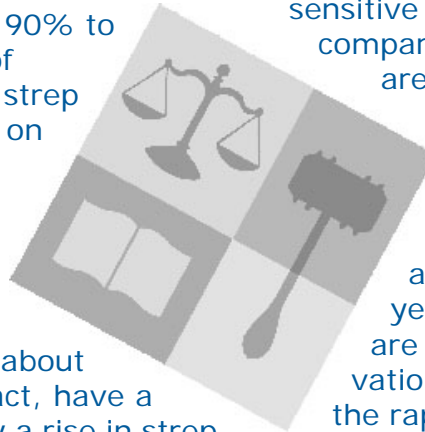
My examination on the stand lasted five hours. The next day, after only one hour of deliberation, the jury returned a 10-to-2 verdict in favor of the family physician. We won!

Ed. Note: “General Guidelines for Family Physicians Testifying as Expert Witnesses” is a free publication for Academy members. Order catalog item #314 at www.aafp.org/catalog or call (800) 944-0000.

■ Hemoglobin A1c Measurements: Fact or Fallacy?

*By Toni Clinton, PhD (BCLD), MT(ASCP)
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University of Tennessee-Memphis*

Hemoglobin A1c (HbA1c) is one of the top ten ordered laboratory tests in the United States (National Intelligence Report; 2006). HbA1c testing is performed in all clinical laboratory settings: hospital, independent commercial, and physician office laboratories. Although the utility of the assay in monitoring glycemic control of diabetic patients is well known, the technical aspects of the assay are less under-



stood. This article will discuss standardization of the assay and the most common test methods. Limitations and recommendations to reduce and limit erroneous test results will also be discussed.

Diabetes is estimated to affect 18 million Americans, over 6% of the total population (Winter; 2005). The vast majority of those patients have been diagnosed with Type II, or adult onset diabetes. The American Diabetes Association (ADA) recommends a HbA1c value of < 7%. Re-evaluation is recommended if the level is >8% (Sacks; 2002). In 2005, one study reported that 67% of diabetics did not meet glucose control limits as defined by HbA1c levels. The same publication reported that 20% of US diabetics have HbA1c values > 9% (McDowell; 2005).

Diabetes is a costly disease. In 2002, the estimated cost to manage a non-diabetic patient was \$2500 annually. In contrast, the cost to manage a diabetic patient was 5-fold higher (\$13,242). The costs reported in 2002 represented a 32% increase over the costs to manage the same patients in 1997 (McDowell; 2005). In 2001, approximately \$100 billion dollars was spent on managing diabetes. One dollar (1\$) out of every \$10 spent on healthcare in the US is spent on diabetes management and complications (McDowell; 2005).

Why are hemoglobin A1c measurements used to measure glycemic control? The hemoglobin A1c molecule is formed by the addition of glucose onto the beta chain of hemoglobin A. This reaction, called glycation, is the non-enzymatic addition of glucose to an amino group of a protein (hemoglobin). The rate of formation of HbA1c is directly proportional to the concentration of glucose in the patient's blood, and the reaction is irreversible. It has been demonstrated that in addition to being used as an index of glycemic control, the

reaction may also be used as a measure of risk of the development of diabetic complications (Sacks; 2002). For example, each 10% reduction in the HbA1c value equates to approximately a 45% reduction in the development of diabetic retinopathy (Sacks; 2002).

The measurement involves the determination of the relative percentage of hemoglobin A that has a glucose molecule attached (glycated). The measurement is not affected by daily glucose variations, and it will not be influenced by exercise or recent food intake. The value will however, be influenced by the life span of the red blood cells. Thus, the percent glycation of hemoglobin A will represent the blood level of glucose over the life time of a

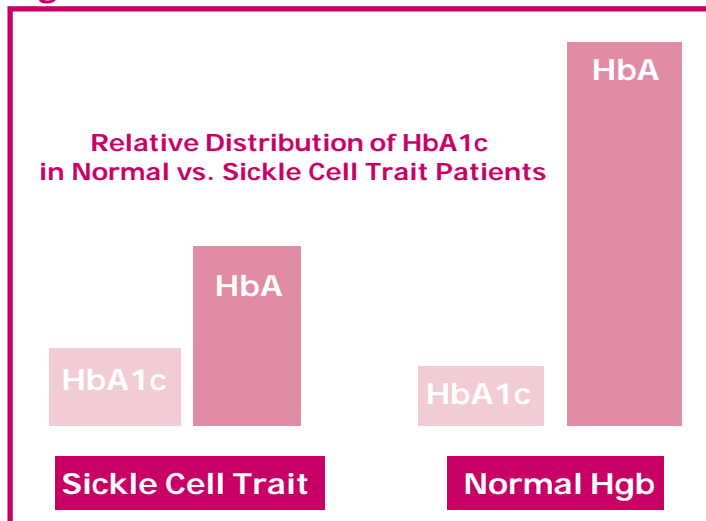
red blood cell, approximately 6 – 8 weeks. However, HbA1c determinations in patients with hemolytic anemia, or those who have undergone a recent transfusion will be inaccurate due to the shortened life span of the red blood cells.

The hemoglobin composition of a normal patient will be primarily composed of Hemoglobin A. Thus, measuring the HbA1c value (%

glycation of hemoglobin A) is an accurate representation of the glycation of the patient's hemoglobin. However, what happens if the patient's primary hemoglobin is not A? Examples would include sickle cell disease, sickle cell trait, hemoglobin C disease, and others.

The clinical utility of glycated hemoglobin was definitively demonstrated in two independent studies conducted in 1993 and 1998 respectively. The Diabetes Control and Complications Trial (DCCT; 1993) and the United Kingdom Prospective Diabetes Study (UKPDS; 1998) were prospective, randomized studies with large patient populations. The DCCT group studied patients with Type I disease, whereas the UKPDS focused on patients with Type II disease. Both studies demonstrated a strong correlation between hyperglycemia and the development of diabetic complications.

Figure 1



In 1993, the American Association of Clinical Chemistry (AACC) established a glycohemoglobin standardization committee with a stated goal to establish guidelines for HbA1c measurement that could be directly related back to the DCCT. This move was in part due to the lack of correlation between laboratory methods which prevented any meaningful interpretation of the DCCT results. The National Glycohemoglobin Standardization Program (NGSP) was organized to facilitate implementation of a measurement standardization protocol (Sacks; 2002). That program provided the ability for manufacturers to establish traceability to the DCCT through split sample testing. As a direct result of these efforts, a review of data from the 2000 CAP proficiency testing surveys indicated a marked improvement in comparability. Between laboratory CV's were <5%, and the mean HbA1c value was within 0.8% of the NGSP target (Little; 2001).

When the ADA made their recommendations for HbA1c levels, a note was made that the recommended values were appropriate only for those laboratories using methods certified by the National Glycohemoglobin Standardiza-

tion Program (NGSP) as traceable to the DCCT study (Sacks; 2002).

There are two primary methods of glycated hemoglobin determination. One is based on charge differences and includes the individual methods of ion-exchange chromatography, high pressure liquid chromatography (HPLC), and electrophoresis. The second method is based on structural differences of the glycated hemoglobin molecule and include affinity chromatography and immunometric assays.

Ion exchange chromatography separates hemoglobin variants based on charge. A negatively charged column attracts the positively charged hemoglobin. Glycation reduces the positive charge, so the glycated and non-glycated fractions are separated. This method has the advantage of resolving all hemoglobins, including those patients with a primary hemoglobin other than A. The most common commercially available method using this technique is HPLC (Bio-Rad; TOSOH).

Immunoassay methods utilize antibodies to the HbA1c molecule. One limitation is that the antibodies do not recognize labile intermediates or variants. This is the most common methods utilized in physician office laboratories

Table 1

Condition	Hemoglobin Composition	Effect on HbA1c Value
Normal	Hemoglobin A \geq 80%	None
Sickle Cell Disease	Hemoglobin S \geq 80%	Decrease if RBC destruction; May also falsely elevate due to increase in relative distribution of glycated hemoglobin A
Sickle Cell Trait	Hemoglobin A:S ratio = 5:3 or 5:4 e.g. Hemoglobin A = 54%; Hemoglobin S = 32%	False elevation
Hemoglobin D Trait	Hemoglobin A:D ratio = 5:3 or 5:4 e.g. Hemoglobin A = 54%; Hemoglobin D = 32%	False elevation

Hemoglobin Composition of Normal Patients and Common Variants



(Bayer). Both Dade and Roche also have immunoassay methods.

Affinity chromatography is based on the principle that the glycated hemoglobin will bind to the column, and then can be eluted off. This technique will measure the total glycated hemoglobin, including HbA1c. This method will have the least interference from hemoglobin variants, but it will not detect the presence of the variants (Abbott, Primus).

Although the standardization efforts have greatly improved the correlation of laboratory to laboratory results, and there is strong data to support a direct relationship between the extent of glycation and clinical symptoms, the test does have some limitations. As mentioned previously, falsely low results may be observed in patients recovering from acute blood loss, sickle cell anemia, or suffering from hemolytic anemia. The shortened RBC lifespan and/or relative time of exposure to the patient's glucose concentration will produce spurious results.

Inaccurate results may also be seen in patients with abnormal hemoglobin composition. As mentioned, in the majority of patients the primary hemoglobin is A. Thus, using HbA1c as a measure of hemoglobin glycation is an accurate representation of the patient's physiology. However, this assumption becomes false in those patients with reduced or no hemoglobin A. Examples include hemoglobin SC disease (equal percentages of hemoglobin S and C; little or no hemoglobin A), hemoglobin C disease (primary hemoglobin is C), sickle cell disease (shortened RBC life span and primary hemoglobin is S).

Figure 1 demonstrates the relative distribution of HbA1c in a patient with a normal hemoglobin A composition compared to a sickle cell trait patient (hemoglobin S and A in a ratio of approximately 5:3). The relative percentage of glycated hemoglobin A (HbA1c) to the total concentration of hemoglobin A is much higher in the sickle cell trait patient. This is because the lower total level of hemoglobin A, rather than because of a "true" increase in the patient's percentage of glycated hemoglobin A (HbA1c). The patient's actual results will be lower than reported. Table 1 summarizes the effect of the most common hemoglobin variants on the HbA1c value.

The incidence of erroneous HbA1c result reporting can be reduced by following several guidelines:

1. Repeat measurement of all samples with results below the lower limit of normal. If the value repeats, RBC destruction and/or loss should be considered. Alternatively, the possibility of an abnormal hemoglobin interference should be considered.
2. Values of > 15% should be checked for the presence and/or history of a hemoglobinopathy – particularly in patient populations with a documented increase in certain hemoglobin variants.
3. If the HPLC method is used, reviewing any non-A or non A2 hemoglobin measured should be reviewed for the presence of an abnormal hemoglobin which may be interfering.
4. The most important way to avoid errors is to choose a method appropriate for the patient population being tested. Laboratories or physician practices with a high percentage of patients more likely to present with an abnormal hemoglobin should consider methods that will accommodate accurate glycated hemoglobin measurement.

References

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2007-B CME Questions

The material necessary to review to answer the following questions may be found in this issue of the *P.O.L. Insight* and the *AAFP-PT Handbook* or on the AAFP-PT website (<http://www.aafp.org/pt> and click on Continuing Medical Education). The Test Sheet may be found on page 16 of the *P.O.L. Insight*. The Accreditation information may be found on the inside cover of this issue.

1. True or False: Routine testing of quality control samples is not required for labs performing only waived tests.
 - A. True
 - B. False
2. QC samples are tested to detect:
 - A. Improperly collected specimens.
 - B. Changes in system performance.
 - C. Test reporting errors.
 - D. All of the above
3. True or False: QC samples are not intended to check test accuracy.
 - A. True
 - B. False
4. True or False: QC ranges should be determined by reviewing the manufacturer's package insert.
 - A. True
 - B. False
5. Plotting the frequency a result is obtained over the range of results will produce a curve known as:
 - A. Normal
 - B. Bell-shaped
 - C. Gaussian
 - D. All of the above
6. True or False: "Mean" and "standard deviation" are statistical tools used to assess variation in results.
 - A. True
 - B. False
7. True or False: "Mean" refers to the value at the center of the data range.
 - A. True
 - B. False
8. True or False: "Standard deviation" indicates how far the data spreads on either side of the mean.
 - A. True
 - B. False
9. True or False: Unless something changes, the results of repeated QC sample testing should always fall on the mean.
 - A. True
 - B. False
10. Using an incorrect mean value can cause:
 - A. Frequent out-of-range QC results
 - B. Failure to detect real problems with test performance
 - C. Both "A" & "B"
 - D. None of the above

11. Ideally, establishing instrument-specific target values involves collecting data for:
 - A. A single sample on the initial day of testing
 - B. 5 samples over 5 days
 - C. 10 samples over 10 days
 - D. 20 or more samples over at least 20 days
12. True or False: Establishing, validating, and documenting lab-specific target values is a regulatory requirement.
 - A. True
 - B. False
13. True or False: An initial estimate of the mean for a new lot number of QC material can be done in a single day with 8-10 replicate tests
 - A. True
 - B. False
14. The established QC values should be within _____ of the package insert or peer mean.
 - A. 1 SD
 - B. 2 SD
 - C. 5%
 - D. 10%
15. True or False: The SD for a new lot of QC material can be estimated using the CV of the previous lot.
 - A. True
 - B. False
16. The real "costs" of not setting lab-specific QC values for each instrument include:
 - A. Time & expenses associated with troubleshooting a non-existent problem
 - B. Delayed patient results
 - C. Erroneous patient results
 - D. All of the above
17. True or False: Becoming a Laboratory Director will often increase the physician's malpractice insurance rates.
 - A. True
 - B. False
18. Preparing to serve as an expert witness in a malpractice case may involve:
 - A. Reading depositions and being deposed by opposing lawyers
 - B. Traveling to appear in court
 - C. Literature review
 - D. All of the above
19. True or False: Rapid Strep antigen tests are 98-99% specific and 90-95% sensitive in detecting infections.
 - A. True
 - B. False
20. Diabetes affects an estimated _____ Americans.
 - A. 5 Million
 - B. 13 Million
 - C. 18 Million
 - D. 22 Million
21. True or False: Hemoglobin A1c is one of the top 10 tests ordered in the U.S.
 - A. True
 - B. False



22. The American Diabetes Association recommends a HbA1c value of:
 - A. <3%
 - B. <7%
 - C. <9%
 - D. <12%
23. True or False: HbA1c is formed by the addition of glucose onto the beta chain of hemoglobin A.
 - A. True
 - B. False
24. True or False: The glycation reaction is reversible over time.
 - A. True
 - B. False
25. True or False: The amount of HbA1c is a measure of risk of development of diabetic complications.
 - A. True
 - B. False
26. HbA1c measurement is not affected by:
 - A. Recent food intake
 - B. Recent blood transfusion
 - C. Exercise
 - D. "A" & "C" only
27. True or False: The primary composition of hemoglobin in normal patients is Hemoglobin A.
 - A. True
 - B. False
28. True or False: The clinical utility of HbA1c measure was confirmed by 2 independent studies in the US & UK.
 - A. True
 - B. False
29. True or False: Lack of test method standardization did not affect the interpretation of the DCCT study results.
 - A. True
 - B. False
30. True or False: The National Glycohemoglobin Standardization Program was organized to facilitate implementation of measurement standardization protocol.
 - A. True
 - B. False
31. Methods for glycated hemoglobin measurement are based on differences in:
 - A. Charge
 - B. Molecular structure
 - C. "A" & "B"
 - D. None of the above
32. Falsely low HbA1c results due to shortened RBC lifespan may be observed in patients who:
 - A. Are recovering from acute blood loss
 - B. Have sickle cell disease
 - C. Suffer from hemolytic anemia
 - D. All of the above
33. True or False: HbA1c results will be inaccurate for patients with hemoglobinopathies.
 - A. True
 - B. False



AAFP-PT CME Test Answer Sheet

ALL INFORMATION MUST BE COMPLETED TO OBTAIN CREDIT

2007-B (submit by May 31, 2008 to obtain credit)

Fill in the circles for the correct answers:

Please print:

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Select one if you are a physician:

- FP IM
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 Other

Select one if you are laboratory personnel:

- MT MLT Nurse Practitioner
 RN LPN Physician Assistant
 Med. Assist. Laboratory Manager
 Laboratory Consultant Other

	A	B	C	D
1.	○	○	○	○
2.	○	○	○	○
3.	○	○	○	○
4.	○	○	○	○
5.	○	○	○	○
6.	○	○	○	○
7.	○	○	○	○
8.	○	○	○	○
9.	○	○	○	○
10.	○	○	○	○
11.	○	○	○	○
12.	○	○	○	○
13.	○	○	○	○
14.	○	○	○	○
15.	○	○	○	○
16.	○	○	○	○
17.	○	○	○	○
18.	○	○	○	○
19.	○	○	○	○
20.	○	○	○	○
21.	○	○	○	○
22.	○	○	○	○
23.	○	○	○	○
24.	○	○	○	○
25.	○	○	○	○
26.	○	○	○	○
27.	○	○	○	○
28.	○	○	○	○
29.	○	○	○	○
30.	○	○	○	○
31.	○	○	○	○
32.	○	○	○	○
33.	○	○	○	○

Evaluation: please fill in bubble between 1 & 5 – 1 denotes poor, 5 denotes excellent:

1. To what extent were the objectives achieved?
poor ① ② ③ ④ ⑤ *excellent*
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poor ① ② ③ ④ ⑤ *excellent*
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