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In this Issue

Editor's Note 1

A1C Comes Into Its Own for
Diagnosis of Diabetes 2

Another Approach to the Woman
With a Negative Pap Test and
Positive High-Risk HPV 3

Are You Prepared? 5



Herman Hurwitz, M.D., F.C.A.P.
Senior Medical Director
Quest Diagnostics Philadelphia
Medical Director, Western Region

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Editor's Note:

As I noted in our spring 2009 issue, the American Diabetes Association (ADA) was developing cut-points for A1C in order to utilize A1C as a diagnostic test for diabetes. In the interim an international expert committee was assembled by the ADA, the International Diabetes Federation, and the European Association for the Study of Diabetes. The expert committee recommended A1C as the new test for the diagnosis of diabetes at the ADA 69th Scientific Sessions. The committee's findings and recommendations were published online, ahead of print, in *Diabetes Care*.

The proposal has not yet been officially endorsed by the three diabetes organizations referenced above, although the ADA has endorsed it in principle. It is widely anticipated that the recommendations will be approved and adopted. This new use of A1C has the potential to lead to a major change in the way we diagnose diabetes. At the present time, diabetes is diagnosed with the fasting plasma glucose (FPG) or an oral glucose tolerance test (OGTT). The expert committee examined the relationship between long-term glycemic exposure and complications. Following this analysis, the conclusion was that A1C, which measures average blood glucose over the preceding two to three months, may serve as a better marker of diabetes and should be used as a diagnostic test.

David M. Nathan, M.D., a diabetologist and expert committee chair, stated that A1C values show less variability than FPG results. The assay also has technical advantages over FPG.

Raymond Gambino, M.D., Chief Laboratory Officer Emeritus at Quest Diagnostics, and colleagues have previously published data that identify the potential for inaccuracies in FPG, which can occur with current collection methods in the United States. Patients also will benefit since the A1C assay does not require a fasting sample and can be collected at any time.

The committee concluded that an A1C level $\geq 6.5\%$ is sufficiently sensitive and specific to identify individuals who have diabetes. Those persons with an A1C level $\geq 6.0\%$ but less than 6.5% are at the greatest risk for developing diabetes. Is this possibly the new definition for prediabetes? The committee seems to be leaning toward eliminating that category. At the ADA 69th Scientific Sessions, Dr. Nathan pointed out that glucose impairment follows a continuum, and that people with an A1C value closer to 6.5% are clearly at higher risk of developing diabetes and complications such as retinopathy. We will keep our readership informed as the ADA prepares to publish an official statement. Stay tuned!

On a similar note, the A1C Derived Average Glucose (ADAG) Study has defined a linear relationship between A1C and average glucose. A1C results can be reported as the traditional A1C percentage together with an estimated average glucose (eAG) in mg/dL. This is analogous to reporting an estimated glomerular filtration rate with the serum creatinine. The eAG value can provide healthcare professionals and

continued on page 4

A1C Comes Into Its Own for Diagnosis of Diabetes

Historically, the measurement of glucose has been the sole means of diagnosing diabetes. While type 1 diabetes has a more characteristic clinical presentation often with very high glucose values, type 2 diabetes has a more gradual onset with slowly rising glucose values over time. This feature has required specified glucose cut-points to distinguish pathologic glucose concentrations. Early attempts to standardize the definition of diabetes relied on the OGTT. Unfortunately, the performance and interpretation of the tests were inconsistent and the number of individuals studied was small.

In 1979, the National Diabetes Data Group (NDDG) provided the diagnostic criteria that would serve as an outline for almost two decades. The NDDG relied on the distribution of glucose values, rather than the association of glucose values with complications. The diagnostic glucose values were chosen based on their association with overt or symptomatic diabetes. The NDDG identified the threshold of FPG as ≥ 140 mg/dL to diagnose diabetes. A 2-hour post 75-Gm glucose challenge (2HPG) result of ≥ 200 mg/dL was considered the gold standard for the diagnosis of diabetes. Emerging evidence, however, was beginning to show that the microvascular complications of diabetes were associated with a higher range of fasting and OGTT values.

In 1997, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus reexamined the basis for the diagnosis of diabetes. In contrast to the NDDG, this group focused on the relationship between glucose levels and the presence of long-term complications as the basis for the diagnosis of diabetes. In comparing the relationship of retinopathy prevalence and glucose levels, the decision was made to lower the FPG diagnostic threshold to ≥ 126 mg/dL. They also negated the premise that the 2HPG was the gold standard

for the diagnosis of diabetes.

The 1997 report also recommended that the FPG, rather than the 2HPG, be the preferred test to diagnose diabetes because it was less costly, more convenient for patients, and more reproducible than the 2HPG. The committee also introduced the term impaired fasting glucose (IFG). A follow-up report from the same committee in 2003 lowered the cut-point for the diagnosis of diabetes to ≥ 125 mg/dL. They also refined the range for IFG from ≥ 110 mg/dL but less than 126 mg/dL to ≥ 100 mg/dL but less than 126 mg/dL.

Fast forward to 2009. Chronic hyperglycemia, which is sufficient to cause diabetic complications, is the hallmark of diabetes. Reason would suggest that laboratory measures identifying long-term glycemic exposure, specifically A1C, should provide a better marker for the presence and severity of the disease. Comparison of A1C and FPG showed a stronger and more consistent correlation of A1C with retinopathy. In 1997 and 2003, A1C was not recommended as a diagnostic test for diabetes largely because of the lack of standardization. An updated reevaluation of A1C by the present committee found that the accuracy and precision of A1C assays are at least equivalent to glucose assays.

As demonstrated by Raymond Gambino, M.D., and others at Quest Diagnostics, in-vitro glycolysis is not immediately inhibited by sodium fluoride. Additionally, the actual measurement of glucose is less accurate than many clinicians realize. A1C also demonstrates less biologic variability and is not subject to variation related to stress. The committee concluded that, compared to glucose measurement, A1C is at least as good in defining the level of hyperglycemia at which retinopathy prevalence increases and has appreciably superior technical attributes. Moreover, patient

convenience is improved by eliminating a requirement for pretest fasting. A1C is therefore a more stable biologic index than FPG.

A large volume of data from diverse populations has now established an A1C level associated with an increased prevalence of moderate retinopathy. This provides strong justification for assigning an A1C cut-point of $\geq 6.5\%$ for the diagnosis of diabetes. In making their choice of cut-point, the committee balanced the stigma and costs of mistakenly identifying an individual as diabetic against the minimal clinical consequences of delaying diagnosis in someone with an A1C level of less than 6.5%.

Importantly, the committee noted that an A1C value of $\geq 6.5\%$ should not be considered as an absolute dividing line between diabetes and nondiabetes. The decision was made to emphasize specificity over sensitivity. The group also decided to recommend effective prevention strategies for the highest risk group with an A1C value between 6.0-6.5%. Although one might consider this range a revised expression of prediabetes, the committee argues to eliminate the category of prediabetes.

Some cautions were expressed in the committee's report. It was felt that point-of-care instruments were not sufficiently accurate or precise to be used for the diagnosis of diabetes. Also, changes in red-cell turnover during pregnancy preclude the use of A1C for the diagnosis of diabetes in pregnancy. At present, glucose measurements will continue to be required for pregnant patients. Lastly, in areas where reliable A1C measurements are not available, the committee recommended the continued use of glucose testing for diagnosing diabetes.

For an in-depth and detailed discussion of the expert committee's report and rationale for their recommendations, the reader is referred to the cited references.

(Diabetes Care 2008; 31(10):1991-1996 — Diabetes Care 2009; 32(5):828-833 — Diabetes Care 2009; 32(7):1327-1334, 1344-1345 — Diabetes Dispatch June 5-9, 2009; 8)

Another Approach to the Woman With a Negative Pap Test and Positive High-Risk HPV

In the ASCCP-sponsored “2006 Consensus Guidelines for the Management of Women With Abnormal Cervical Screening Tests,” the issue of managing women 30 years of age and older who had the combination of a positive high-risk HPV DNA test and a Pap test that was negative for intraepithelial lesion or malignancy (NILM) was discussed. At the time the guidelines were released, the recommendation was to repeat both tests in 12 months. As noted in the guidelines, studies had shown that the risk of developing CIN 3 in a woman with a NILM Pap test and who was infected with HPV type 16 or 18 at enrollment was 21% and 18%, respectively. The risk for women infected with any other high-risk HPV DNA type was 1.5%. Clearly, it would be very helpful to know the HPV type of such patients in order to make

informed management decisions.

Furthermore, the guidelines stated that it would be reasonable to apply genotyping tests to women with a combination of a NILM Pap test and a positive high-risk HPV DNA test in a manner similar to the way that high-risk HPV DNA tests are used to triage an ASC-US Pap test result. At the time of publication, there was no FDA-approved HPV genotyping assay available and the guidelines did not endorse such a course of action. Since that time, an FDA-approved assay has become available. This test specifically detects HPV 16 and HPV 18 and is approved for use with ThinPrep liquid-based samples.

The ASCCP has now updated its guidelines to include an algorithm using HPV genotyping to manage women with a NILM Pap test and a

positive high-risk HPV DNA test result. A positive genotype result for HPV 16/18 in this case would require follow-up colposcopy. A negative genotype result for HPV 16/18 would require repeating both the Pap test and high-risk HPV DNA test in 12 months. Currently, both options—genotyping for HPV 16/18 or repeating both tests in 12 months—are acceptable. The ASCCP has noted that when data from the pivotal trial of the HPV genotyping assay, which led to FDA approval, as well as data from other companies seeking FDA approval for other HPV genotyping assays are available, changes in management guidelines may be necessary. Stay tuned!

(J Lower Gen Tract Dis 2007; 11:201-222 — HPV Genotyping Clinical Update, Copyright © 2009 American Society for Colposcopy and Cervical Pathology)



Vibrant Summer Lilies

Longwood Gardens, Pennsylvania, 2009

Editor's Note

continued from page 1

patients with a more meaningful index of chronic glycemia. Patients who self-monitor their glucose levels in mg/dL can relate better to the eAG values expressed in the same measurement units. For example, an A1C value of 6% corresponds to an eAG of 126 mg/dL.

Quest Diagnostics offers the option of reporting A1C as a percentage together with an eAG in mg/dL. The ADA provides an on-line calculator for converting A1C values to eAG values and vice versa. <http://professional.diabetes.org/GlucoseCalculator.aspx>

HPV DNA testing has improved the sensitivity of screening for cervical cancer. The addition of HPV 16/18 genotyping enhances the screening sensitivity. The clinical utility of HPV genotyping assays was discussed at the 2006 American Society of Colposcopy and Cervical Pathology (ASCCP) consensus conference. No FDA-approved molecular HPV genotyping tests were available at that time. The consensus conference members recognized that FDA approval would likely occur in a relatively short period of time. Therefore, recommendations were made contingent on anticipated FDA approval. The expected FDA action has now occurred. This test specifically detects HPV 16 and HPV 18 and is approved for use with ThinPrep® liquid-based samples.

Women 30 years of age or older who present with a positive high-risk HPV DNA test and a Pap test result that is negative for intraepithelial lesion or malignancy (NILM) can be triaged based on their HPV 16/18 genotype results. In this issue we will discuss how patients with that combination of findings can be further evaluated and managed based on the HPV 16/18 genotype results.

The new 2009 H1N1 influenza virus

strain, also known as swine flu, seemed to appear out of nowhere. Just as the seasonal influenza incidence should have been winding down in North America, we began to hear dire warnings about the spread of a previously unseen combination of animal and human strains that appeared to originate in some communities in Mexico. Sure enough, cases began to be reported in large areas of the United States. The World Health Organization has now declared swine flu a worldwide, high level pandemic as cases continue to be reported from around the globe. As of June 2009, the Centers for Disease Control and Prevention (CDC) estimated that as many as one million Americans have been infected with the novel 2009 H1N1 influenza virus.

The original media reports about swine flu occurred over a weekend. I remember arriving at my office on a Monday morning and walking into an absolute buzz saw as questions poured in from anxious and concerned patients and physicians. How do I submit samples? Which test should I order? What is the turnaround time? By this time Quest Diagnostics had partially implemented its own Pandemic Flu Emergency Preparedness Plan.

Some of our suppliers soon began to ration supplies as demand from many sectors threatened the supply of collection devices and test kits. It soon became apparent that rapid influenza immunoassay tests were not the best choice since no one, including the CDC, had been able to validate that test system with this new strain of influenza virus.

Additionally, previous experience had shown that the rapid immunologic assays were not as sensitive as viral culture, polymerase-chain reaction

(PCR), or direct fluorescent antibody (DFA) tests. As time went on, it became apparent that a negative rapid immunoassay result did not ensure that a patient was not infected with H1N1 type A influenza. We informed our clients that the best choice of an initial detection test was a rapid culture or DFA test. In viral culture, rapid is a relative term (24-48 hours versus 4-6 days for a traditional viral culture).

Initially, the presence of the 2009 H1N1 influenza virus could only be confirmed by the CDC and the samples had to be submitted through state health departments. Later, state health departments were given the CDC PCR technology to do the confirmatory testing for the 2009 H1N1 influenza virus. Many state health departments rapidly became overwhelmed by demand and instituted limited conditions for testing positive samples.

In the meantime, Focus Diagnostics, the infectious disease center of excellence at Quest Diagnostics, marshaled its resources and developed and validated a PCR test in record time for the detection of the 2009 H1N1 influenza virus. This test confirms the presence of the 2009 H1N1 influenza virus strain from nasal or nasopharyngeal samples. Focus Diagnostics provides PCR-confirmation results within 24 hours of sample receipt. The Focus Diagnostics' test name is Influenza A H1N1 (2009) Real Time RT-PCR.

Lastly, in this issue, we discuss some resources that a physician's office can utilize in order to be prepared and to deal with an outbreak of epidemic influenza or any other infectious disease epidemic. An upsurge of the 2009 H1N1 influenza virus is predicted to be a distinct possibility when seasonal influenza recurs.

Are You Prepared?

Family physicians are on the front line during an infectious disease outbreak. Pandemic influenza is potentially the most catastrophic infectious disease epidemic that family physicians may face. For years, the World Health Organization experts worried about the pandemic risk of an H5N1 avian influenza virus. The recent outbreak of the novel 2009 H1N1 influenza virus (swine flu) in Mexico, the United States, and now the rest of the world reinforced the need for family physicians to be prepared.

While we currently have no reason to believe that a 2009 H1N1 influenza virus pandemic will rival the great pandemic of 1918/1919, physicians may want to keep in mind that a significant pandemic would likely overwhelm family physicians as well as the healthcare system in the United States. Potentially effective viral neuraminidase inhibitors, such as oseltamivir and zanamivir, are still in short supply. Critical shortages of equipment, supplies, and oxygen are likely to occur. No one is sure of the effect on transportation and essential services. Quest Diagnostics, even with a well-established supply chain and emergency preparedness plan, had to scramble to obtain adequate numbers of collection supplies and test kits during the recent 2009 H1N1 influenza virus outbreak.

Family physicians play a critical role in the detection, management, and prevention of infectious diseases. If you do not have a detailed plan for responding to a medical emergency of this magnitude, now is the time to

develop one. Underlying principles are the same regardless of whether you are preparing for pandemic influenza, severe acute respiratory syndrome (SARS), extensively drug resistant tuberculosis or a bioterrorism event. The purpose of this communication is to outline measures necessary to prepare you and your office, and provide resources that you can use to develop an individual, detailed plan. According to the *Family Practice Management* article, "Preparing Your Office for an Infectious Disease Epidemic," your plan should address the following issues in writing:

- Education and training for both patients and staff
- Systems to triage, cohort, diagnose and treat patients
- Availability of equipment and supplies
- Protection of staff, non-epidemic patients and families (including, but not limited to, the use of personal protective equipment, for example, masks)
- Communication with staff, patients and consultants
- Coordination with local and state public health authorities
- Business continuity
- Recovery and reconstitution of the office practice.

The following list of resources can assist you in developing a practical and workable preparedness plan, including an office checklist and telephone triage process, as well as test ordering information.

<http://www.aafp.org/online/en/home/clinical/disasterprep/swine-flu.html>

<http://www.aafp.org/online/en/home/publications/journals/afp/preprint/influenza-telephone-triage.html>

http://www.aafp.org/online/etc/medialib/aafp_org/documents/clinical/bt/fpfluchecklist.Par.0001.File.tmp/PanFluChecklist.pdf

<http://www.cdc.gov/h1n1flu/>

<http://www.QuestDiagnostics.com/patient/swineflu.html>

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Herman Hurwitz, M.D., *Executive Editor*
Patricia Mellon, *Senior Editor*

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Telephone: 215.442.7673

Email: herman.s.hurwitz@questdiagnostics.com

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