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Editor's Note:

In this issue, we look at some updated recommendations and guidelines for two diseases—diabetes and cervical cancer.

The American Diabetes Association (ADA) has published its annual *Standards of Medical Care in Diabetes — 2008*. As noted in previous issues, diabetes and its complications are threatening the health of individuals around the world. The increase in diabetes and pre-diabetes is occurring in parallel with the worldwide epidemic of obesity.

We also discuss the use of a unique metabolite to identify patients who experience wide fluctuations of blood glucose levels, especially postmeal or prandial. Some patients who have reached their A1C goal may be at increased risk for the microvascular and macrovascular complications of diabetes as a result of these glycemic excursions. Measurement of 1,5-anhydroglucitol (1,5-AG), better known by its proprietary name as Glycomark®, allows evaluation of short-term glucose control as well as glycemic excursions. We will discuss the physiology of 1,5-AG and how it can be used to complement the A1C assay.

The long-awaited 2006 *Consensus Guidelines for the Management of Women with Abnormal Cervical Screening Tests* and the *2006 Guidelines for the Management of Women with Cervical Intraepithelial Neoplasia or Adenocarcinoma In Situ* were published by the American Society for Colposcopy and Cervical Pathology

(ASCCP) in October 2007. These guidelines reflect recent data changes from large clinical trials and advances in technology and are designed to assist clinicians of all subspecialties. This issue will only deal with highlights from the guidelines dealing with abnormal cervical screening tests.

The core recommendations for managing women with atypical squamous cells of undetermined significance (ASC-US) and low-grade squamous intraepithelial lesion (LSIL) were changed minimally. Postcolposcopy management for women with ASC-US and LSIL are now identical. A more conservative approach is recommended for the category of special populations, such as adolescents with ASC-US or LSIL. Core recommendations for managing women with high-grade squamous intraepithelial lesion (HSIL) and atypical glandular cells also underwent minor modifications. The use of high-risk (hr) human papillomavirus (HPV) DNA testing continues to evolve. Testing for hr HPV DNA is now incorporated into the management of women with atypical glandular cells following their initial evaluation with colposcopy and endometrial biopsy. The 2004 interim guidance for the use of hr HPV DNA as an adjunct to the Pap test for women 30 years of age and older was formally adopted with only very minor modifications. The reader is referred to the cited references for an in-depth discussion of all the important topics in both guidelines.

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Watch Those Excursions

The importance of tight glycemic control in preventing the complications of diabetes has been well documented. Conventional methods of assessing glycemic control, such as A1C measurement and self-monitored blood glucose (SMBG), focus on mean or fasting glucose. Many patients who may appear adequately controlled using A1C measurements may, in fact, be experiencing significant postprandial hyperglycemia. Assays such as A1C and fructosamine only reflect average glucose concentrations, potentially missing hyperglycemic excursions that may be balanced out by episodes of hypoglycemia. Therefore, an alternative marker that robustly reflects postprandial glucose (PPG) excursions could be useful in the management of patients with diabetes. Plasma 1,5-AG is a naturally occurring dietary polyol that has been proposed as a marker for postprandial hyperglycemia. An automated assay, Glycomark, has recently been approved in the U.S. as a short-term marker for glycemic control. A similar assay has been used in Japan for over a decade.

Epidemiologic studies have shown that postload glucose and PPG levels are more closely associated with all-cause, especially cardiovascular, mortality than fasting plasma glucose (FPG) values. In vitro data suggest that intermittent glycemic excursions, with its associated oxidative stress, may be more harmful to vascular endothelial cells than chronic hyperglycemia. Quantification of glycemic variability, PPG, or glucose excursions might predict macrovascular disease better than mean glucose.

Current traditional methods of

monitoring glycemic control—A1C, fructosamine, and SMBG—are embedded in the literature as the foundations for monitoring glycemic control. Advantages and deficiencies of some of these more traditional markers of glycemic control are noted below.

A1C:

- A1C is associated with the incidence of complications and is currently the most widely recognized marker for glycemic control.
- Alterations in red blood cell life span can result in misleading A1C values.
- A1C reflects mean glucose over a 3-month period. The most recent 30-day period is disproportionately represented.
- A1C is of limited value in patients with recently changing glycemic control.
- A1C does not discriminate between patients who attain adequate glycemic control with frequent hyperglycemic and hypoglycemic events, from those who achieve glycemic targets more smoothly. Therefore, an A1C value of <7% may provide false reassurance of glycemic control.
- A1C inadequately differentiates postprandial hyperglycemia from fasting hyperglycemia. In patients with moderate glycemic control, A1C cannot direct treatment decisions beyond identifying the need for further intervention.

Fructosamine:

- Fructosamine is an established alternative to A1C, especially when

there are discrepancies between SMBG and A1C, and where short term monitoring is desired.

- Fructosamine reflects glycemia over a 1 to 2-week period.
- Fructosamine imprecisely predicts A1C in patients with otherwise stable glycemic control.
- Fructosamine is affected by variations in albumin levels.
- Fructosamine is a marker of mean glucose, and therefore has the same limitations as A1C for identifying PPG or glycemic variability.
- Fructosamine remains an established alternative to A1C for estimating short-term glycemic control as well as when A1C cannot be used due to shortened red blood cell survival.

1,5-AG dietary intake is balanced by renal excretion, with almost 100% reabsorption through the renal tubules. When glycosuria is present, tubular reabsorption of 1,5-AG is competitively inhibited in favor of glucose. When the renal threshold for glycosuria (~180 mg/dL) is exceeded, 1,5-AG is excreted almost exclusively in the urine resulting in rapid reduction in serum levels. Poor glycemic control is therefore associated with low, rather than high, serum 1,5-AG levels.

1,5-AG levels are not significantly affected by meals or activity. Certain Chinese herbal supplements may contain *Polygalae Radix*—a crude form of 1,5-AG, which can lead to artifactual increases in serum levels. Caution is advised in interpreting 1,5-AG levels in patients with renal failure, end-stage liver disease, and glomerulonephritis.

Editor's Note: This chemical interference reminds us that a patient history should always include questions about herbals, dietary supplements, and any form of complementary or alternative medicine. Patients often will not volunteer this information.

The 1,5-AG assay is not affected by changes in hemoglobin, bilirubin,

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uric acid, lipids, creatinine or ascorbic acid levels. Importantly, 1,5-AG is not affected by reductions in red blood cell life span as is A1C.

Serum levels of 1,5-AG fall rapidly with the onset of glycosuria. Upon return of good glycemic control, 1,5-AG levels recover at a rate of about 0.3 µg/dL/day independent of other patient factors. In patients with inadequate control, 1,5-AG takes approximately 5 weeks to recover following restoration of glycemic control. Changes in 1,5-AG more closely reflect changes in glycemic control than A1C or, possibly, fructosamine.

Glycemic variability is described as frequency and amplitude of glucose excursions, or as a combination of glucose excursions in the hyperglycemic and hypoglycemic range. 1,5-AG seems well suited for monitoring hyperglycemic excursions. 1,5-AG has been reported to show significant variability among diabetic patients who appeared to be well controlled using A1C values. As opposed to A1C, 1,5-AG is not affected

by hypoglycemia. Therefore, 1,5-AG appears to differentiate among patients with extensive glycemic excursions despite the similar A1C values.

PPG variations are of particular interest because their identification provides an easily identifiable means for implementing dietary or medication interventions. PPG becomes an increasingly important contributor to glycemic control as the A1C value nears 8%. Since 1,5-AG is a predictor of glycemic excursions, it would also be expected to predict PPG. The International Diabetes Federation highlighted the importance of assessing PPG and issued guidelines for its management. 1,5-AG was recognized as an emerging tool for assessing PPG. These can be accessed at <www.idf.org/webdata/docs/Guideline_PMG_final.pdf>.

In summary, the large quantity of data supporting A1C as a long-term indicator in evaluating diabetes control and predicting complications makes it unlikely that it will be replaced any time soon, if ever. Each tool for measuring glycemic control has its own

characteristics with advantages and limitations. Stay tuned as the management of diabetes and its complications continues to undergo refinement, individualization, and fine tuning!

(*Expert Rev Mol Diagn* 2008; **8**(1):9-19
— *Diabetes Care* 2004; **27**(7):1761-1773
— *Diabetes Care* 2006; **29**(6):1214-1219
— *Diabetes Care* 2008; **31**(S1):S12-S54
— *Guideline for Management of Postmeal Glucose* © International Diabetes Federation, 2007)



Desert Spring, 2006 Scottsdale, AZ

Consensus Guidelines for HPV DNA When Used for Screening

As mentioned in the Editor's Note, the 2006 Consensus Guidelines provided by the ASCCP are too extensive and detailed to be adequately described in this publication. The reader is referred to the excellent discussion as well as the useful management algorithms. The guidelines and algorithms are available at <www.asccp.org>.

I would like to review the recommendations regarding the

appropriate use of hr HPV DNA testing. As we have noted in previous issues, gynecologic cytology, or the Pap smear, is still the best cancer-screening test to date—reducing the incidence of invasive cervical cancer by over 70%. The Pap test using liquid-based collection, improved collection devices, and computer-assisted screening has helped to improve the sensitivity and reduce the false-negative proportion even

further. In spite of this true medical success story, cytology has limitations, including limited sensitivity.

The shortcomings of the Pap test have led to considerable interest in utilizing a combination of cytology and hr HPV DNA testing to further improve cervical cancer screening. The FDA has approved the use of hr HPV DNA as an adjunct to the Pap test for cervical cancer screening in women 30 years of age and older. A newly acquired HPV infection, which frequently occurs shortly after a woman's first sexual encounter, often clears spontaneously. The high prevalence of HPV infection, which peaks in

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adolescents and women in their 20s, drops significantly over time as the immune system clears the infection. Therefore, hr HPV DNA should not be used for routine cervical cancer screening before the age of 30.

The consensus document updates the studies that compared the use of gynecologic cytology alone, hr HPV DNA testing, and a combination of gynecologic cytology and hr HPV DNA testing. The use of hr HPV DNA testing was significantly more sensitive as a screening tool than gynecologic cytology alone. A recent review of screening studies from North America and Europe reported that the pooled sensitivity and specificity of hr HPV DNA testing for the detection of high-grade cervical disease and cancer (CIN 2+) in women 35 years and older is 95% and 93%, respectively. By contrast, pooled sensitivity and specificity at a threshold of ASC-US are 60% and 97%, respectively. Sensitivity using a combination of hr HPV DNA testing and gynecologic cytology is higher than either test alone with a negative predictive value of 99% to 100%.

Editor's Note: Translated, a positive Pap test or persistent hr HPV DNA result both have good sensitivity in this age group; that is, the likelihood of a positive result predicting significant cervical abnormality is high.

Conversely, a negative Pap test alone—conventional or liquid-based with its relatively low specificity—is more likely to represent a false-negative result, which can have serious consequences. This is most likely to occur if the patient does not adhere to the recommended Pap test screening interval or harbors a lesion that sheds only a small number of abnormal cells. This latter situation is one which can lead to successive false-negative Pap tests.

The American Cancer Society (ACS) concluded in its 2002 *Guidelines for the Early Detection of Cervical Neoplasia and Cancer* that it is “reasonable to consider” the use of hr HPV DNA testing with cytology in women 30 years and older. The ACS also concluded that the frequency of combined cytology and hr HPV DNA testing should not be more than every 3 years provided that both tests are negative. Likewise, the American College of Obstetricians and Gynecologists (ACOG) has recommended that use of a combination of cervical cytology and hr HPV DNA testing is appropriate for screening of women 30 years and older. The ACOG publication also stated that although combining hr HPV DNA testing will improve the sensitivity of screening for cervical cancer, there remains insufficient data to prove that the combination improves outcomes or will reduce the cost of screening.

The 2006 Consensus Guidelines formally reviewed and modified the 2003 Interim Guidelines on how to manage women with different combinations of screening results using combined cytology and hr HPV DNA testing. The following were two controversial areas:

- When should women who are negative by both tests be rescreened?
- How to manage cytology-negative, hr HPV DNA-positive women?

Women who are negative by both tests have a less than 1 in 1,000 risk of having CIN 2+. Additionally, prospective follow-up tests have shown that the risk of developing CIN 3 during a 10-year follow-up period are low. Women who are hr HPV DNA positive require counseling regarding their risk for subsequent CIN 2, the source of

their infection, and their infectivity. In a study from the Northern California Kaiser Permanente group, 6.5% of 213,000 women were hr HPV DNA positive. A total of 58% of the hr HPV DNA-positive women had a concurrent negative cytology. The risk of having an undetected CIN 2+ in women with this combination ranges from 2.4% to 5.1% in screened populations. Additionally, even in women who are 30 years of age and older, most hr HPV DNA-positive women become negative during follow-up. In one study, 60% of hr HPV DNA-positive women became negative after a median follow-up of 6 months. Therefore, it is reasonable to repeat cytology and hr HPV DNA testing at 12 months for cytology-negative, hr HPV DNA-positive women.

If the woman is still hr HPV DNA positive after 12 months, she would be considered persistently positive and should undergo colposcopy, even if the repeat cytology is still negative. Women who are negative on both tests after 12 months can be rescreened in 3 years. Women who demonstrate a cytologic abnormality at the 12-month follow-up should be managed according to the ASCCP guidelines.

Finally, a word about HPV genotyping. Data suggest that infection with different types of hr HPV do not carry the same risk for development of CIN 2+. Of the 13 HPV types considered oncogenic, 3 of them—16, 18, and 45—are responsible for 77% of all cervical cancers. HPV-18 is found in association with 32% of cervical adenocarcinomas.

One of the greatest obstacles to incorporating hr HPV DNA testing into the screening of women 30 years of age and older is physician uneasiness and patient anxiety over the management of women with

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Editor's Note

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I frequently receive calls questioning an unexpected normal or abnormal test result. After reviewing patient history and physical findings, preanalytic variables, and positive or negative predictive value related to disease prevalence, the caller and I can usually come to a reasonable conclusion about the test results. I would like to bring the reader's attention to what I feel is a good reminder of how we all should use laboratory tests and data.

In an editorial appearing in the February 2008 issue of the *American Journal of Medicine*, the editor describes a scenario where a patient was misdiagnosed as having had a myocardial infarction. An elevated serum troponin level occurred following a therapeutic misadventure related to administration of general anesthesia. This "label" caused the patient much grief when she was subsequently denied coverage for life insurance. A second review of the

patient's hospital chart caused the insurance company's medical officer to agree that the patient had suffered a minor myocardial injury secondary to an untoward reaction to anesthesia—not an acute myocardial infarction.

The editor's take-home message: "a laboratory test by itself rarely, if ever, establishes a clinical diagnosis. Careful collection of other clinical information such as history, physical findings, and associated diagnostic studies . . . are almost always required in combination with laboratory tests . . . in order to establish a rational and reproducible clinical diagnosis."

Finally, everyone of us at Quest Diagnostics takes great pride in announcing that *Fortune* magazine has selected Quest Diagnostics to the 2008 list of "America's Most Admired Companies." The list is compiled from interviews with 3,700 executives, directors, and securities analysts of

companies they admire most in their industry based on eight criteria including Innovation; Quality of Management; Social Responsibility; Use of Corporate Assets; Long Term Investment; People Management; Financial Soundness; and Quality of Products and Services.

"Our ranking as one of the most admired companies in America is a tribute to the quality and dedication of our employees and the trust we have earned from patients and physicians as a provider of outstanding diagnostic testing services," said Surya Mohapatra, Ph.D., Chairman and Chief Executive Officer. "Our ranking as the only diagnostic testing company on the list of Most Admired Companies reinforces our industry leadership and reputation."

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cytology-negative, hr HPV DNA-positive screening results. Several studies have shown that HPV types 16 and 18 account for most cases of CIN 2,3, which are subsequently identified in women with cytology-negative, hr HPV DNA-positive screening results.

In the Kaiser Permanente study noted above, 10-year follow-up results showed that CIN 3 was identified in 21% and 18%, respectively, of women who were HPV-16 or HPV-18 positive at the time of study enrollment. Significantly, the risk of CIN 3 was only 1.5% in women infected with other HPV types. These findings suggest that HPV genotyping would be a useful adjunct to the decision-making process in cytology-negative and hr HPV-positive women on initial screen.

Genotyping assays to identify specific hr HPV types have not been cleared

by the FDA at the time of this writing. The consensus guidelines' authors state that once FDA clearance has been obtained for HPV typing assay(s), it would be reasonable to apply HPV genotyping to samples from cytology-negative and hr HPV DNA-positive women. Women whose samples are HPV types 16 or 18 positive would be referred for colposcopy. Women whose samples are not HPV types 16 or 18 positive would be advised to return in 12 months for repeat cytology and hr HPV DNA testing. As time goes on and additional enhancements to the best cancer-screening test yet devised appear, the incidence of invasive cervical cancer will, likely, continue to be reduced.

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