Appendix A
The HPV Landscape*

Genital HPV infection is transmitted through contact with infected genital skin or mucosal surfaces/fluids. There are more than 30 types of genital HPV. Types known as "low risk" can cause genital warts, while other types, known as "high-risk," are associated with anogential cancers, the most common of which is cervical cancer in women. However, most HPV infections are asymptomatic, unrecognized, and benign. In most cases, HPV infection is transient and clears without any medical intervention (Kiviat, et al., 1999).

In the United States (U.S.), it is estimated that 20 million people have HPV, and 6.2 million new HPV infections occur annually (Gerberding, 2004; Weinstock et al., 2004). More than 50% of sexually active adults are infected with one or more genital HPV type in their lifetime (Koutsky et al, 1988; Weinstock et al., 2004), making this the most common sexually transmitted infection in the U.S. (Cates, 1999). An estimated 1.4 million Americans have genital warts (Koutsky et al., 1988), and the American Cancer Society (ACS) estimates that in 2005, over 10,000 women will develop invasive cervical cancer and more than 3,700 women will die from it (ACS, 2005a).

Understanding of the natural history of genital HPV infection and the role certain high-risk HPV types play in anogenital cancers has grown dramatically in the last 10 years. High-risk HPV (HR HPV) can lead to cervical dysplasia or cervical intraepithelial neoplasia (CIN1, CIN2, or CIN3), carcinoma-in-situ, or invasive cervical cancer, and other anogenital dysplasias and cancers (Schiffman et al, 1993; Walboomers et al, 1999; Kiviat, et al., 1999; Munoz et al, 2003; Melbye & Frisch, 1998; Unger & Duarte-Franco, 2001; Brentjens et al, 2002; ARHP, 2005). Research shows that persistent detection of HR HPV types is a strong predictor of the development of high-grade cervical precancer and invasive cervical cancer (Ho et al., 1998; Wallin et al., 1999). A recent study estimates that high-risk types of HPV are found in greater than 99.7% of cervical cancers worldwide (Bosch & Muñoz, 2000). HPV-16 and HPV-18 account for over 80% of cervical cancers (Walboomers et al., 1999; Bosch & Muñoz, 2000). A recent analysis of the U.S. National Health and Nutrition Examination Survey (NHANES) found that the antibody to HPV-16 was detected in 13% of 12-59 year-old males and females (Stone, et al., 2002).

Available studies indicate that a large proportion of anal, and a subset of vulvar, vaginal, and penile cancers are associated with HPV (International Agency for Research on Cancer, in press; Frisch et al, 1997; Bjorge et al, 1997; Maden et al, 1993; Pisani et al, 1997; Kiviat, et al., 1999). The incidence of HPV-related non-cervical cancers in the U.S. is five to ten times lower than the incidence of HPV-related cervical cancer (Reis et al, 1999), with the exception of anal cancer in homosexual men. The incidence of anal cancer in homosexual men was estimated at 12.5-36.5/100,000 before the start of the AIDS epidemic and is thought to be even higher now in homosexual and bisexual men infected with HIV (Melbye et al, 1994, Goedert et al 1998).

Cervical Cancer Screening

Most cervical cancer deaths can be prevented through detection of pre-cancerous changes within the cervix with the Papanicolaou (Pap) test (USPSTF, 1996; Gatta et al., 1999). Early detection of pre-cancerous cervical lesions with the Pap test has led to a 75% reduction in cervical cancer mortality since its introduction in the 1940s (Henson et al, 1996; Kiviat, et al., 1999). The World Health

*This section was adapted from the *Introduction* of the Battelle Report (2005), *HPV Clinician Survey: Knowledge, Attitudes, and Practices about Genital HPV Infection and Related Conditions,* submitted to CDC on May 6, 2005.

Organization estimates that annual Pap screening provides a 93.5% reduction in the incidence of cervical cancer, while a screening every two years provides a 92.5% reduction (WHO, 1986). However, many differences exist in the rate and frequency at which routine Pap screenings are performed in clinical settings, and accepted by women. Screening rates have been found to be particularly low among women who live in rural communities (Reis et al, 1999; Selvin & Brett, 2003), are medically underserved (Selvin & Brett, 2003), have minimal or no health insurance coverage (Sung et al., 2002) or who are foreign-born (Cardin et al., 2001).

HPV Testing

In the last decade, sensitive and reliable assays for detecting HPV DNA have been developed (Koutsky, 1997). Digene Corporation's Hybrid Capture 2® HPV DNA test (HC-2) is the only HPV detection assay approved by the U.S. Food and Drug Administration (FDA) for clinical use. Two new indications for HPV testing were recently approved: 1) for the management of patients with abnormal Pap smears, and 2) as an adjunct to Pap smears for cervical cancer screening of women over 30 years of age (Wright, et al, 2002).

Studies indicate that the use of the HPV DNA test for the management of patients with ASC-US Pap results is both more sensitive and more specific than a Pap test followed by colposcopic examination, or two Pap tests at an interval of six months (Wright & Schiffman, 2003; ALTS, 2003). Research also suggests that adding an HPV test to routine Pap screening in women over 30 years of age increases both the sensitivity and specificity of detection of cervical cancer or pre-cancer, compared to Pap testing alone (Petry et al., 2003). Cross-sectional and prospective studies have shown that HPV testing, in conjunction with routine Pap screening, can provide useful information about which women require follow-up evaluation such as colposcopy (Wright & Schiffman, 2003). Moreover, according to ACOG, "Because HPV DNA testing is more sensitive than cervical cytology in detecting CIN2/CIN3, women with negative concurrent results can be reassured that their risk of unidentified CIN2/CIN3 or cervical cancer is 1 in 1000" (ACOG, 2005).

The FDA has not approved HPV DNA test for use to screen for cervical cancer in lieu of cervical cytology or as a STD screening test outside the context of cervical cancer screening. In addition, the use of HPV testing in women with higher grade lesions (ASC-H, LSIL or higher) is not approved or recommended by guidelines because several studies demonstrate that most women with these higher grade lesions are HPV-infected and require colposcopy on the basis of cytologic abnormalities alone, making HPV testing of little or no added value (Wright, et al., 2004).

Current Guidelines

Currently, the American Society for Colposcopy and Cervical Pathology (ASCCP, 2004; Wright, et al., 2002), the American College of Obstetricians and Gynecologists (ACOG, 2004; 2005), ACS (2005b; Saslow, et al., 2002), and the US Preventive Services Task Force (USPSTF, 2002; 2005) guidelines state that all women should begin Pap screening for cervical cancer three years after the age of sexual onset, or at 21, whichever comes first. Pap screening is recommended yearly or every two years for women under 30 by ACOG and ACS. According to these national organizations, women over 30 should get screened every 3 years—but not more frequently, after three normal Pap results (with either the conventional or liquid-based Pap test).

The ACS and ACOG recently recommended use of the HPV DNA test in conjunction with regular Pap screening for women 30 years of age and older. One advantage to using the HPV DNA test with Pap for women over 30 years of age is the ability to extend the screening interval to three years (if both tests are normal), even in the absence of a history of normal Pap results (ACOG, 2005; ACS, 2005b;

Wright et al., 2004). There is consensus among experts at the ASCCP, the National Cancer Institute (NCI), and the ACS that women ages 30 years and older, who have a negative cytology and test HPV positive, should have both tests repeated in six to 12 months (Wright et al., 2004). Studies suggest that the extended interval would also be cost-effective over time (Goldie et al., 2004). However, it should be noted that the USPSTF found insufficient evidence to recommend for or against the routine use of HPV DNA testing as a primary screening test for cervical cancer (USPSTF, 2002; 2005).

ACOG and ASCCP recommend that HPV testing can be used to manage the care of women with borderline (ASC-US) Pap results. They also state that it can be used to test women with LSIL pap results post-treatment to determine whether HPV is still detectable, although this indication is not FDA-approved. ACOG's new guidelines strongly recommend *against* HPV testing "for triage of women with LSIL, atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesions, or atypical glandular cells cytology" (ACOG, 2005).

The recent FDA-approved indications and national guideline recommendations for the HPV test, as well as commercial marketing of the test by the manufacturer may increase the use of HPV testing in the future, both for recommended and non-recommended purposes. This is likely to have an impact on providers' counseling and clinical practices regarding at-risk patients and those with clinical manifestations of HPV infection (i.e., external anogenital warts, cervical dysplasia or other HPV-associated cancers). The use of the HPV test for cervical cancer screening may introduce emotional and interpersonal components to screening (such as anxiety, distress, fear, anger, guilt and partner suspicion; e.g., McCree & McFarlane, 2004; 2005), creating a need for patient education and counseling about HPV. Studies have shown that the way in which HPV information is communicated to patients at the time of an HPV diagnosis can influence the psychological impact of this diagnosis, as well as a woman's likelihood of following up with necessary testing or treatment (Waller et al., 2004; Waller et al., 2005). It may therefore be critical for providers to learn effective communication in this context.

Impact of HPV Testing and Recent Changes in National Guidelines on Clinical Practice

Guidelines for HPV DNA testing and changes to the interval for Pap testing are relatively new. Therefore, few research studies have assessed the knowledge, attitudes, or practices of U.S. clinicians since these changes were introduced. However, there may be several barriers to the appropriate use of the HPV test in clinical practice, such as physician (and patient) unwillingness to adopt an extended screening interval (Sirovich & Welch, 2004; Sawaya, 2005; Smith et al., 2003); unclear guidelines for managing discordant test results (Wright et al., 2004); physician fear of losing patients to follow-up; and lack of decision aids or educational materials to help patients understand the meaning and implications of HPV DNA test results.

In October 2002 and January 2003, Battelle conducted a series of 13 teleconference focus groups with physicians in the *National Breast and Cervical Cancer Early Detection Program 1* (NBCCEDP) to assess provider barriers to the extended screening intervals. The research revealed that many physicians felt the extended interval did not fit and was not followed in their practice. These providers

[1] The NBCCEDP is a CDC-funded program that provides breast and cervical cancer screening services to low-income, uninsured women.

were uncomfortable switching to a three-year screening interval due to the fear of losing patients to follow-up or patients not returning for other health maintenance exams. Those who agreed with the new guidelines tended to move some low-risk patients [defined by history of normal Pap tests, relationship status/monogamy, or older age (over 50 years)] to a longer screening interval, but continued to screen others annually. Providers who adopted the new guidelines did so because the patient population in their practice was low-risk, returned regularly for health maintenance exams, or was considered stable. (Battelle, 2003)

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