Human Papillomavirus (HPV)

HPV Type-Detect® 4.0
by Multiplex Real-Time PCR

In the 1980s, the newly developed techniques of molecular biology enabled the detection of many human papillomaviruses (HPVs) in benign and malignant lesions (1, 2). To date, there are more than 100 known HPV types. An HPV type is defined as a complete genome whose L1 gene sequence is at least 10% dissimilar to that of any other HPV type (3). Each Papillomavirus is highly tropic for a specific epithelium, and has its own degree of oncogenicity. HPV infections are associated with cancers of the head, neck and throat as well as benign lesions such as condylomas and other dermatological warts.

EPIDEMIOLOGY

HPV infection is very common, though most infected individuals immune systems clear the virus without developing clinical manifestations. Thus, very few HPV-infected individuals progress to invasive cervical cancer. HPV type is a well established risk factor determinant for progression to cervical cancer. Over 40 HPV types infect the anogenital tract, 15 of which have been classified as high-risk for development of cervical cancer, 3 as probable high-risk, 12 as low-risk and 3 as undetermined-risk (4, 5) (**Table 1**).

Table 1: Classification of HPV types by cervical oncogenicity (5).

Risk	HPV Types
High-risk	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82
Probable high-risk	26, 53, 66
Low-risk	6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, CP6108
Undetermined-risk	34, 57, 83

PREVALENCE

Prevalence of HPV infection among women around the world ranges from 2% to 40% (6). The wide variation in prevalence is due in part to the various sensitivities of the DNA-based assays used for the detection of HPV infection. **Table 2** details the prevalence of specific HPV types among females age 14 to 59 years in the United States (18). Data collected by Medical Diagnostic Laboratories (MDL) (n=40,000), demonstrated more than 40% of anogenital HPV infections consist of multiple HPV types.

Table 2. Prevalence of HPV types among females aged 14 to 59 years, NHANES 2003-2004.

Demographics	Sample Size	Prevalence % (95% Confidence Interval)	P Value*
Overall (age 14-59 years)	1921	26.8 (23.3 - 30.9)	
Age, y			
14-19	652	24.5 (19.6 - 30.5)	.003
20-24	189	44.8 (36.3 - 55.3)	
25-29	174	27.4 (21.9 - 34.2)	
30-39	328	27.5 (20.8 - 36.4)	
40-49	324	25.2 (19.7 - 32.2)	
50-59	254	19.6 (14.3 - 26.8)	
Race †			
Non-Hispanic white	837	24.2 (20.5 - 28.6)	<.001
Non-Hispanic black	533	39.2 (31.0 - 49.4)	
Mexican American	442	24.3 (19.3 - 30.6)	
Marital status			
Married	676	17.3 (14.0 - 21.5)	<.001
Widowed, divorced, separated	231	41.2 (32.3 - 52.4)	
Never married	882	31.1 (28.1 - 34.5)	
Living with partner	132	46.1 (35.2 - 60.4)	
Education ‡			
< High school	383	35.0 (29.4 - 41.7)	.006
High school and GED	380	29.7 (23.4 - 37.6)	
> High school	754	24.7 (20.9 - 29.1)	
Poverty index §			
Below poverty	503	37.5 (29.9 - 47.1)	.005
At or above poverty	1322	24.4 (21.1 - 28.4)	
Country of birth			
United States	1580	26.8 (22.8-31.6)	.30
Mexico	206	19.6 (11.4-33.6)	
Other ∫	135	30.8 (18.9-50.3)	

Abbreviations: GED, general equivalency diploma; HPV, human papillomavirus.
* By wald x^2 statistic.
† Race and ethnicity were self-reported; other race (n=109) is not shown.
‡ This analysis was limited to females older than 17 years.
§ Does not sum to 1921 because some of the responses are missing.
∫ Other includes any country other than the United States or Mexico.

In general, over 50% of sexually active women are infected by one or more HPV type. HPV-16, one of the most common types in cytologically normal women, is also the most common type among cervical cancer cases (7-12). HPV types associated with an increased risk of malignancy vary with geographic location. For example, HPV-16 is found in 77% of cervical cancers in Germany, 71% in South America, 59% in the United States, but only 33% to 39% in Japan (13-16). On the other hand, HPV-52 is found in 20% of invasive cervical cancers in Japan, but is only detected in 2% of cervical intraepithelial lesions or invasive cancer in the United States (17). It is unknown whether these geographic differences represent mutated HPV genomes, simple distribution of HPV types, genetic selection in various populations, or some other unknown mechanism.

AGE

The prevalence of HPV infection is highest in young women and coincides with initiation of sexual activity. While most studies indicate a decrease in HPV prevalence with age, a few studies conducted in several different international regions have shown a peak prevalence of HPV infection in women below age 25, a decrease among women aged 35 to 54 and a second peak after age 55 (**Figure 1**) (19). The observed increase in HPV prevalence in the older age groups could be attributed to reactivation of latent virus.

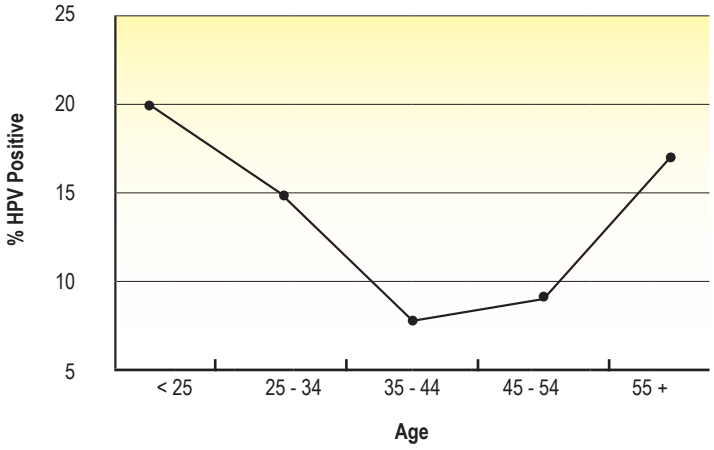

Figure 1. Age-specific prevalence of HPV (19).

GENDER

Men. Although HPV infection appears to be common in men, no data is yet available on incidence or persistence of HPV infection in men specifically. A recent Danish study has found a prevalence of 33.8% HPV infection (n=374 in male conscripts 18-29 years) by Polymerase Chain Reaction (PCR). The number of sex partners during the study was the most important risk factor for acquiring HPV. In the United States, the incidence of anal cancer among men who have sex with men is higher than the incidence of cervical cancer among women. The presence of HPV-16 DNA in penile carcinoma biopsies (n=57) was examined by PCR. Thirty-eight biopsies were HPV-16 DNA positive. This data corroborates that squamous cell carcinoma is invariably associated with HPV-16 DNA (20).

Women. For adolescents, cumulative HPV incident rates have been approximately 40% (21, 12) and prevalence rates as high as 80% (22). Of these infections, 60% to 75% are caused by high-risk viral types, with types 16, 18, and 52 being identified the most often in adolescents. Approximately 1% of HPV infections are associated with genital warts, with types 6 and 11 identified most often (23). Despite the rate of anogenital infection, very few result in cellular changes, genital warts, intraepithelial neoplasia, or cancer. Most infections (70% to 90%) are eliminated by the host immune system and become undetectable within 6 to 10 months (8, 22, 25). In adult women, HPV-16 and HPV-18 cause 60% to 70% of cervical cancers worldwide. Other HPV types are responsible for the remaining cases. Furthermore, persistent HPV infection is necessary for clinical progression to CIN 3 (24).

HPV in Children. The epidemiology of anogenital HPV infections in children is less well-delineated at the population level. The mean age at presentation of anogenital warts in case series of children has ranged from 2.8 to 5.6 years (26-28). Among eight series of 17 to 75 cases of anogenital HPV infection in children, the proportion thought to have acquired HPV from sexual abuse, range from 3% to 35% (27, 30, 31). The likelihood of sexual abuse as the means of acquisition of anogenital infection in children appears to increase with age (32). Nonsexual transmission from common skin warts appears likely to occur in some cases. Autoinoculation from a nongenital cutaneous wart to the genitalia, heteroinoculation from one individual to another, and transmission from contaminated objects (fomites) to hand and then to genital regions have been proposed as mechanisms of transmission of HPV (33-35).

CLINICAL SIGNIFICANCE

HPV in Anogenital Cancers. Tumors associated with HPV tend to occur in younger women with a past history of genital warts or cervical dysplasia and arise from the in situ lesions similar to those found in the cervix. The carcinomas are frequently of basaloid or warty type (36). Tumors not associated with HPV occur in older women and are typically well-differentiated keratinizing squamous cell carcinomas arising in a background of differentiated vulvar intraepithelial neoplasia (37). The risk factors are unknown. Cervical cancer is the second most common cancer among women worldwide, with a mean age standardized incidence rate varying from 11.3 per 100,000 women in more developed countries to 18.7 per 100,000 women in less developed countries (6). HPV infections are very common in young women and frequently resolve spontaneously. The lifetime risk to

ever contract HPV is estimated to be 80% (38). Despite the high prevalence of HPV in cervical cancer, it's a rare event occurring after a long period of viral persistence, which reflects the multi-step nature of HPV-induced cervical cancer. The progression toward cervical cancer requires additional genetic and epigenetic events. The majority of infected women appear to clear the virus by an effective immune response. Clearance of a HR-HPV infection has been linked to cytological regression (39, 40). On the other hand, a persistent HR-HPV infection appears to be a prerequisite for clinical progression and the development of cervical cancer (8, 41, 42).

Progression toward cervical cancer is a well orchestrated, multistep process that histologically evolves from pre-existing noninvasive premalignant lesions called cervical intraepithelial neoplasias (CINs) or squamous intraepithelial lesions (SILs). The progression from CIN I to CIN 3 and invasive cancer is associated with histological changes to the cervico-epithelial cells. There are indications that some CIN 3 lesions may develop quickly (within 2 years following normal cytology), whereas it takes another 10 to 12 years for most CIN 3 lesions to develop into invasive cervical carcinoma (43). The path toward cervical carcinogenesis and the progression from CIN I to CIN 3 is most likely HPV type-dependent, viral load dependent, host cell factors, genetic predisposition, and immune status related (**Table 3**). The quest for cellular, viral, and immune markers for the role of HPV in cervical carcinogenesis is a research objective of Medical Diagnostic Laboratories.

Vaginal, vulvar, and penile cancers are very rare, with incidence rates of about 1 per 100,000 per year. The causal relationship between HR-HPV infection and cervical cancer has become evident from epidemiological and functional studies (2, 6). HR- HPV has been detected in up to 99.7% of cervical squamous-cell carcinomas (44, 2) and 94% to 100% of cervical adeno and adenosquamous carcinomas (45, 46). HPV infection was detected in 70% to 100% of anal cancers (47, 48). In vaginal and penile carcinomas the HPV prevalence is about 60% (49) and 30% to 42% (50, 51), respectively.

POSSIBLE USES OF HPV TESTING

Triage. HPV testing could be used as a triage for women with Pap smear findings of atypical squamous cells of unknown significance (cells that are atypical but not definitively dysplastic). Those who test positive for HR-HPV types should be monitored closely or referred to colposcopy (52).

Surveillance. HPV testing could be used as a means of surveillance of women after treatment for high-grade lesions or micro-invasive cancer. Those who test positive for HR-HPV types would be monitored more closely than those who test negative (52).

Primary Screening. HPV testing could be used as a primary screening method for high-grade lesions among women aged 30 or older. Those who test positive for HR-HPV would undergo diagnosis via colposcopy (52, 6).

Vaccine. Prevention of HPV infection using vaccination is showing great promise. Large randomized controlled trials with a monovalent HPV-16 vaccine (53), and bivalent HPV-16, HPV-18 vaccine (54) showed 100% protection from HPV-16, and/or HPV-18 infection and HPV-related CIN 2 and CIN 3.

Table 3. Risk of squamous-cell cervical cancer according to HPV Type.*

HPV Type	Risk	Patients		Controls		Odds Ratio	
		No.	%	No.	%	(95% CI) †	
Negative for HPV		46	3.4	1091	84.4	1.0	
16	High	685	50.5	42	3.3	434.5	(278.2-678.7)
18	High	177	13.1	17	1.3	248.1	(138.1-445.8)
31	High	36	2.7	8	0.6	123.6	(53.5-286.0)
33	High	14	1.0	1	0.1	373.5	(46.7-2985.8)
35	High	15	1.1	6	0.5	73.8	(26.4-206.5)
39	High	8	0.6	0	0.0		--
45	High	74	5.5	9	0.7	197.6	(91.7-425.7)
51	High	13	1.0	4	0.3	66.5	(20.0-221.0)
52	High	37	2.7	4	0.3	200.0	(67.8-590.1)
56	High	9	0.7	5	0.4	45.1	(14.0-145.3)
58	High	31	2.3	6	0.5	114.8	(45.1-292.6)
59	High	17	1.3	1	0.1	419.2	(54.2-3242.4)
68	Low	2	0.2	1	0.1	53.7	(4.4-650.1)
73	High	5	0.4	1	0.1	106.4	(11.4-991.8)
6	Low	1	0.1	6	0.5	4.3	(0.5-38.4)
11	Low	1	0.1	2	0.2	11.2	(1.0-128.0)
81	Low	0	0.0	6	0.5		--
x ‡		47	3.5	34	2.6	32.9	(19.1-56.6)
Other single HR §		10	0.7	0	0.0		--
Other single LR ¶		0	0.1	19	1.5		--
16 and other LR		5	0.4	1	0.1	130.8	(14.7-1161.7)
16 and other HR		23	1.7	1	0.1	617.4	(80.8-4716.4)
16 and 18		36	2.7	3	0.2	327.2	(95.7-1119.1)
18 and other HR		21	1.5	3	0.2	187.0	(52.8-662.3)
Other - 2 infections		29	2.1	15	1.2	52.3	(25.6-106.7)
3 infections		10	0.7	4	0.3	65.4	(19.3-221.7)
4 or 5 infections		3	0.2	2	0.2	32.5	(5.1-206.8)
Total women		1356	100.0	1292	100.0		--
Multiple infections		127	9.4	29	2.2	114.9	(68.8-191.7)
Single infections		1183	87.2	172	13.3	172.6	(122.2-243.7)

* CI denotes confidence interval, HR high-risk types, and LR low-risk types. Women from Spain and Colombia have been excluded from this analysis.
† The odds ratio were adjusted for age center.
‡ HPV type X denotes specimens that were positive with the GBS +/6+ systems but that did not hybridize with any of the 33 probes.
§ This category includes HPV types 26, 66, 82, and HR.
¶ This category includes HPV types 54, 43, 40, 42, 44, 61, 70, 72, and CP6108.

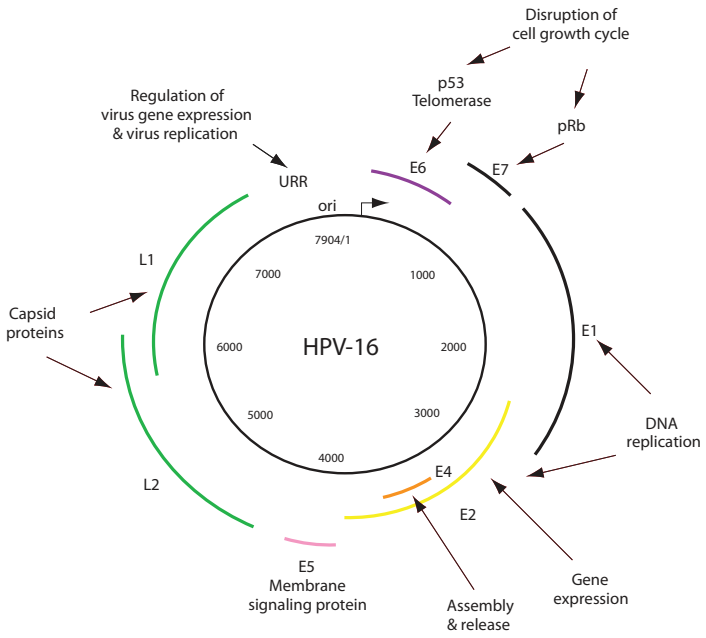

Figure 3. HPV structure and function

MOLECULAR BIOLOGY OF HPV

HPV Genome. HPVs are DNA tumor viruses whose genome is organized in three regions: the early gene (E1 to E7), the late gene (L1 and L2) regions and the upper regulatory region (URR) (**Figure 3**). The early and late gene regions are both protein encoding, but the URR is non-encoding (58). The URR possesses numerous binding sites for many repressors and activators of transcription, suggesting that it may play a part in determining the range of hosts for specific HPV types (59). E1 and E2, meanwhile, encode proteins that are vital for extrachromosomal DNA replication and the completion of the viral life cycle. The E2 also encodes two proteins: one, which inhibits transcription of the early region; and the other, which increases the transcription of the early region. A hallmark of HPV associated cervical carcinoma is loss of the expression of the viral E2 protein (60).

The E4 protein is expressed in the later stages of infection when complete virions are being assembled, and is not known to have transforming properties; however, it is considered to play an important role for the maturation and replication of the virus (61). The E4 protein also induces the collapse of the cytoplasmic cytokeratin network in human keratinocytes, a situation which may assist the release of virions from the infected cell (62). The E5 in open reading frame (ORF), meanwhile, is often deleted in cervical carcinoma cells, indicating that it might not be essential in maintaining the malignant transformation of the host cell. When present, E5 interacts with various transmembrane proteins like the receptors of the epidermal growth factor, platelet-derived growth factor and colony stimulating factor-1 (63). A study using HPV16-infected cells found the E5 protein to possess weak transforming activity (64). In the protein-encoding regions, the E6 and E7 ORF are considered to play the most major roles. These two units encode for oncoproteins that allow replication of the virus and the immortalization and transformation of the cell that hosts the HPV DNA (42, 58, 65-67). The late region units, L1 and L2 encode for viral capsid proteins during the late stages of virion assembly (58). The protein encoded by L1 is highly conserved among different papillomavirus species; therefore, antibodies against the bovine papillomavirus have been used to identify HPV capsid proteins in human tissues. The minor capsid protein encoded by L2 has more sequence variations than the L1 protein; hence, antibodies against the L2 protein have been a source of antigen for specific types of HPV antibodies.

DNA Integration. HPV DNA is usually extrachromosomal or episomal in benign cervical precursor lesions. However, in many cervical cancer cells as well as in cervical cancer cell lines and HPV-transformed human keratinocytes in-vitro, the HPV DNA is integrated in the host genome (58). Cancer tissues may contain both episomal and integrated HPV DNAs at the same time, although integration appears to occur more frequently in HPV-18-associated cervical cancer than in HPV-16-associated cervical cancer (64). During HPV DNA integration, the viral genome usually breaks in the E1/E2 region. The break usually leads to the loss of the E1 and E2 regions. The loss of E2, which encodes proteins, including one that inhibits the transcription of the E6 and E7 regions, has been known to result in uncontrolled and increased expression of E6 and E7 oncogenic proteins. Meanwhile, increased expression of E6 and E7, has been observed to lead to the malignant transformation of the host cells and to tumor formation (68-70). HPV viral integration into the host genomic DNA is associated with progression from polyclonal to monoclonal status in CIN, and these events play a fundamental role in the progression from low-grade to high-grade cervical neoplasia (71).

The Molecular Biology of HPV-mediated Transformation. The first step in HPV-mediated cellular transformation is via activation of viral oncogenes E6 and E7 as a result of E2 down regulation. High-risk HPV E6 complexes, via a cellular protein E6-associated protein (E6-AP), with the tumor suppressor gene product p53, resulting in a rapid ubiquitin-dependent proteolytic degradation of p53 (72). E6 mediated interference of p53, functions together with inactivation of the pro-apoptotic Bak protein by E6, preventing cells from undergoing apoptosis, resulting in a state of genetic instability and enhancing the risk of malignant conversion (73) **(Figure 3)**.

E7 binds to and degrades the tumor suppressor pRb, thereby interfering with their control on the G1/Stransition of the cell cycle (74, 75). Inactivation of Rb by high-risk HPV E7 results in the upregulation of its upstream inhibitor p16(INK4A). Since p16(INK4A) expression is regulated by an Rb-dependent negative feedback loop, continuous inactivation of pRb by high-risk HPV E7 results in increased p16(INK4A) levels and can be detected in HPV-infected CIN lesions and cervical carcinomas (76). Hence, the detection of increased p16(INK4A) expression together with the determination of specific HPV types in urogenital specimens may provide a promising marker for the detection of HPV-mediated dysplasia with deregulated E7 expression (77) **(Figure 4)**.

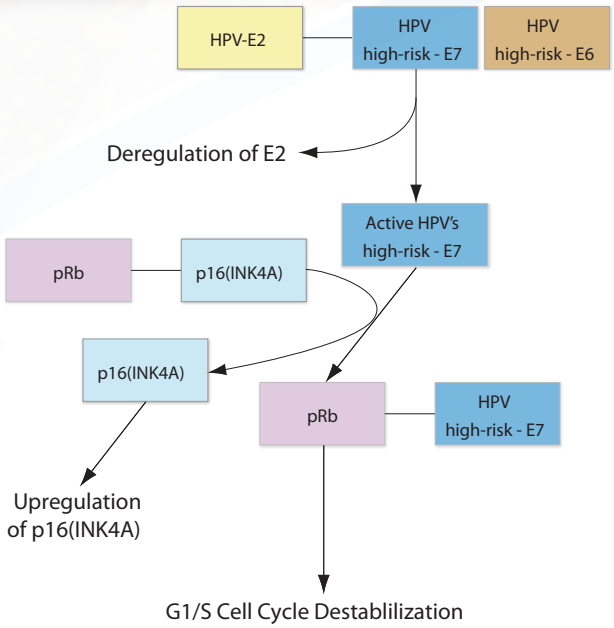

Figure 4. Effect of high-risk HPV E7 on pRb and p16(INK4A)

The demonstration of p53 and pRb tumor suppressors' inactivation by the E6 and E7 HPV oncoproteins, provides a basic explanation on how high-risk HPV types induce their oncogenic effects on cervical cells (78). When a cell suffers DNA injury or damage, p53 protein activates the transcription of genes like p21 (CIP1/WAF1) or GADD45, affecting a delay in the cell's entry into the S phase until DNA repair is accomplished. The inactivation of p53 by the E6 oncoprotein, therefore, results in the deregulation of the cell cycle and allows cellular mutations to occur (**Figure 5a**) (79). The binding of the E7 oncoprotein on pRb provides a complementary function. The binding releases transcription factor E2F that activates the expression of genes that stimulate DNA synthesis in the cell. If earlier E6 action had freed the same cell from p53 control, that cell survives into the S phase with damaged DNA and, through E7 action, is able to replicate the HPV DNA (80) (**Figure 5b**). The oncogenic properties of E6 and E7, as well as their effects on p53 and pRb, have provided the general basis for further investigations of the role of HPV in carcinogenesis in the HPV-infected cervix. Major findings in these areas are summarized in Table 3 (81). Specifically how the oncogenic effects of the HPV oncoproteins are suppressed or reversed in such conditions, and when such conditions occur physiologically, remains to be understood. DeFilippis et al recommended that strategies that inhibit the expression or activity of either E6 or E7 protein are likely to inhibit the growth of HPV-associated cancers (83).

MOLECULAR DIAGNOSIS OF HPV INFECTON

HPV diagnosis is mostly based on molecular techniques, because the virus cannot be readily cultured and the humoral immune response is detectable for many years (84). Since the natural history of HPV infection, the mode of transmission, development of persistent infection and clearance of the virus are partially known, detection and genotyping of HPV DNA in consecutive samples are essential to confirm persistent virus infection over time (85). Persistence of HPV infection is often defined as the detection of the same HPV type in consecutive samples obtained at 3 to 6 month intervals.

HPV Nucleic Acid Detection. HPV DNA can be detected

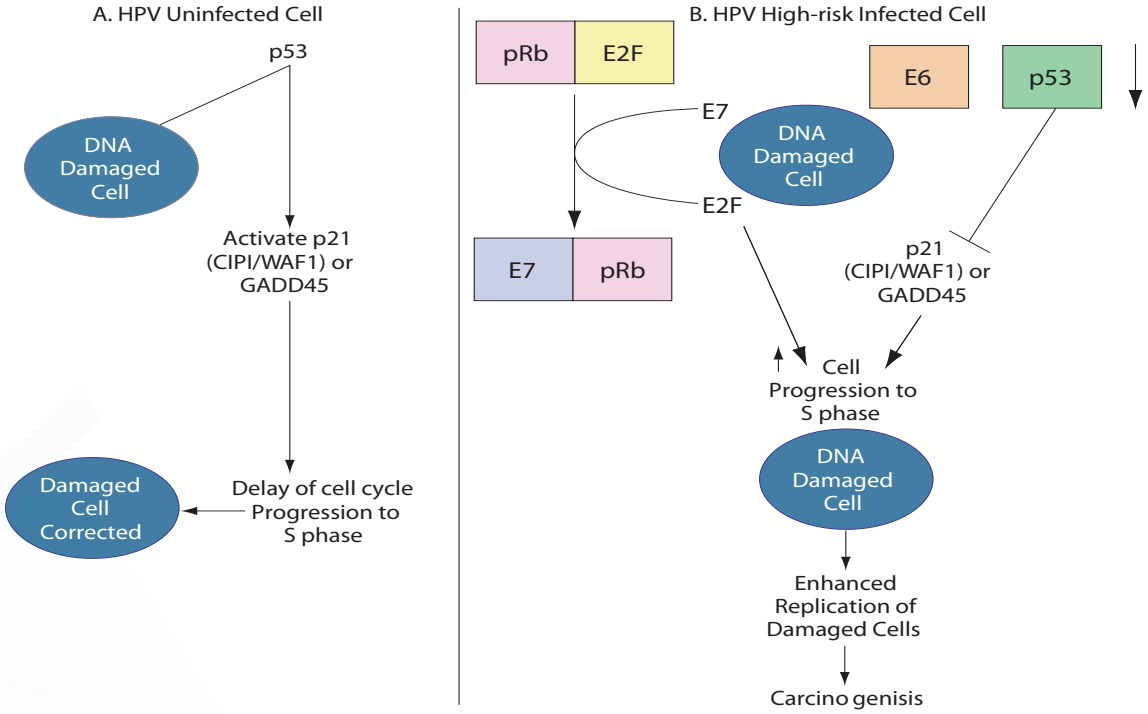

Figure 5. High-risk HPV E6 and E7 mediated cellular transformation.

in Pap smears and biopsy specimens by many nucleic acid based tests. HPV DNA assays can be performed using the same specimen as used for cytological examination and/or other STDs.

HPV Type-Detect® 4.0 by Multiplex Real-Time PCR. By utilizing updated technologies, MDL offers a diverse menu of HPV analysis with high accuracy genetic testing. MDL provides minimally-invasive, simple specimen collection methods for HPV testing using either cervico-vaginal swabs for females via the ***OneSwab***® or ThinPrep® specimen collection platforms and urethral swab for males via the ***OneSwab***® specimen collection platform.

MDL is proud to offer the following options for HPV testing:

- **Test 739: HPV Type-Detect® 4.0 by by Multiplex Real-Time PCR**

The MDL HPV Type-Detect® 4.0 assay identifies and simultaneously distinguishes between 13 different HPV types:

- **13 high-risk genotypes**: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68.

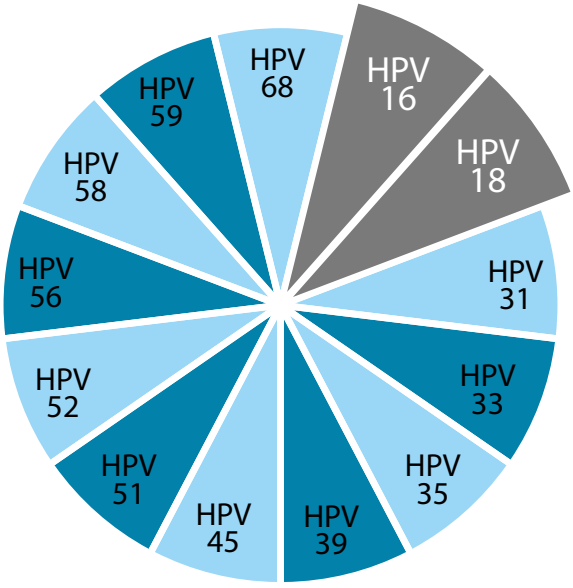

Figure 6. Types detected by MDL's HPV Type-Detect® 4.0 assay.

The Hybrid Capture® 2 HPV DNA Test, Digene Corp., USA. The Hybrid Capture® 2 (HC2) test identifies 18 clinically significant HPV types. The HC2 kit consists of a Dacron® swab and a transport tube packaged in a cardboard container supplied by the manufacturer. The sample is collected from the endocervix and ectocervix with the swab, which is then placed in the proprietary transport medium. The specimen is denatured in the laboratory, and the liberated single-stranded DNA is hybridized in a solution with an RNA probe mix consisting of five (5) low-risk genotypes (6, 11, 42, 43 and 44), and 13 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68). The resulting bound DNA-RNA "hybrids" are reacted with an antibody directed against the hybrids. A chemiluminescent substrate, which binds to the antibody, is added and a signal output is recorded. Most recent studies have evaluated HC2 as an intermediate screening test in women with abnormal cytologic findings rather than as a primary screening test. A highly significant correlation appears to exist between a positive test and the finding of CIN or invasion on histologic examination (86). One study of 311 women with a cytologic diagnosis of LSIL, HSIL or cancer found that when used alone, the HC2 test had a sensitivity of 74% for the detection of CIN; sensitivity increased to 91% when a positive HC2 test was coupled with an abnormal Pap smear (LSIL, HSIL or cancer) (87). Among the age of 30 to 35 years or older, the sensitivity of a single lifetime HC2 test for detection of high-grade dysplasia has been about 80% to 90%, and specificity of 57% to 89% (53, 88, 89). In 44 women with ASCUS, 6 of the 10 women with high-grade lesions were identified by HC2 HPV testing. In 96 women with LSIL on Pap smear, 29 of the 37 high-grade lesions were detected by the HC2 HPV test. This 60% to 76% sensitivity is somewhat higher than the 58% sensitivity previously reported for repeating the Pap smear alone (90).

The HC2 assay limitations:

- HC2 assay cannot identify type specific HPV.
- The detection limit of HC2 assay is about 5,000 HPV genome equivalents, which makes it less sensitive than PCR (92, 93). Cross-reactivity of the two probe cocktails may reduce the clinical relevance of a positive result (93, 94).
- Patients with cervical cancer may have poor recovery of HPV because of tumor necrosis and bleeding which may alter the test results.
- Unable to detect HPV-HR Type 66.

HPV VACCINES

The immune system normally controls viral infections by neutralizing a virus with a specific antibody or by killing virally infected cells. HPV infection does not cause a systemic infection; it does not kill keratinocytes and it induces no response, or a poor slow local inflammatory response. Humoral immunity does not appear to be as important as cell-mediated immunity in clearing HPV infection, but rather is important in protecting an individual from becoming infected. In natural infection, only around 50% of those becoming HPV DNA positive show a neutralizing antibody response.

Currently, there are two different types of vaccines: prophylactic vaccines that would elicit an antibody response and prevent infection, and therapeutic vaccines which would induce a specific and cell-mediated response leading to regression of already preexisting lesions. In June 2006, the quadrivalent HPV vaccine types 6,11,16,18 (Gardasil®, manufactured by Merck and Co., Inc., Whitehouse Station, New Jersey) was licensed for use among females aged 9 to 26 years and is the first vaccine developed to protect against most HPV-type-related cervical cancer, cervical cancer precursors, vaginal and vulvar cancer precursors,

and anogenital warts. This prophylactic vaccine works by preventing four HPV types: HPV 16 and 18, which cause 70% of cervical cancers, and HPV 6 and 11, which cause 90% of genital warts. The vaccine has no therapeutic effect on HPV-related disease, so it will not treat existing diseases or conditions caused by HPV.

The licensed HPV vaccine is composed of the HPV L1 protein, the major capsid protein of HPV. Expression of the L1 protein in yeast using recombinant DNA technology produces noninfectious virus-like particles (VLP) that resemble HPV virions. The quadrivalent HPV vaccine is a mixture of four HPV type-specific VLPs prepared from the L1 proteins of HPV 6, 11, 16, and 18 combined with an aluminum adjuvant. Clinical trials indicate that the vaccine has high efficacy in preventing persistent HPV infection, cervical cancer precursor lesions, vaginal and vulvar cancer precursor lesions, and genital warts caused by HPV types 6, 11, 16, or 18 among females who have not already been infected with the respective HPV type. No evidence exists of protection against disease caused by HPV types with which females are infected at the time of vaccination. However, females infected with one or more vaccine HPV types before vaccination would be protected against disease caused by the other vaccine HPV types. In a Phase II clinical trial 276 women who received the quadrivalent vaccine, the efficacy for prevention of persistent infection was with HPV 6, 11, 16 or 18 was 89.5%. In a Phase III clinical trial of 5,442 women aged 16 to 23 years, vaccine efficacy was 100% for prevention of any grade CIN related to HPV types 6, 11, 16 or 18 (95).

GlaxoSmithKline filed in early 2007 for approval in the United States for a similar preventive HPV vaccine, known as Cervarix®. It is designed to prevent infection from HPV types 16 and 18; however, some cross-reactive protection against virus strains 45 and 31 were shown in clinical trials. Cervarix® is created using the L1 protein of the viral capsid which induces the formation of neutralizing antibodies. A double blind, multi-centre, randomized, placebo-controlled Phase II clinical trial of 1113 women between 15 to 25 years of age in the United States and Brazil demonstrated vaccine efficacy of 91.6% against incident infection and 100% against persistent infection with HPV types 16 and 18 (96).

Therapeutic vaccines are very much in the infancy compared with prophylactic vaccines. Most of these vaccines focus on the main HPV oncogenes, E6 and E7 whose expression is required for promoting the growth of cervical cancer cells and cells within warts. Therapeutic vaccines may be able to elicit immune responses against these two oncogenes thereby eradicating established tumors. A number of these vaccines have been studied in phase I/II clinical trials in humans, including women with CIN, vulvar intraepithelial neoplasia (VIN) and advanced cervical cancer.

Vaccination will not eliminate the need for cervical cancer screening in the United States because not all HPV types that cause cervical cancer are included. It is not a substitute for routine cervical cancer screening, and vaccinated females should have cervical cancer screening as recommended.

Treatment

The Centers for Disease Control and Prevention (CDC) recommendations for the treatment and management of patients as outlined below, can be found in the Centers for Disease Control and Prevention (CDC) Morbidity and Mortality Weekly Report (MMWR) 2015 edition Sexually Transmitted Diseases, Treatment Guidelines. MMWR 64:72-75.

Table 4: CDC's 2015 CDC Treatment Guidelines Pocket Guide Summary (97).

Recommended Regimens For External Genital & Perianal Warts (Patient-Applied)
★ Imiquimod 3.75% or 5%[a] cream See complete CDC Guidelines ***OR***
Podofilox 0.5%[a] solution or gel See complete CDC Guidelines ***OR***
Sinecatechins 15% [a, b] ointment See complete CDC guidelines
Recommended Regimens For External Genital & Perianal Warts (Provider–Administered)
Cryotherapy apply small amount, dry, apply weekly if necessary **OR**
Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80%–90% ***OR***
Surgical removal
Recommended Regimens For External Genital & Perianal Warts [Provider–Administered (Alternatives)]
★ Podophyllin resin 10%–25% in compound tincture of benzoin may be considered for provider-administered treatment if strict adherence to the recommendations for application ***OR***
Intralesional interferon ***OR***
Photodynamic therapy ***OR***
Topical cidofovir

a No definitive information available on prenatal exposure
b These creams are oil-based and may weaken latex condoms and diaphragms. Refer to product labeling for further information
★ Indicates update from the 2010 CDC Guidelines for the Treatment of Sexually Transmitted Diseases

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* Test Results

Patient Information:	**SSN:** N/A	**DOB:** 2/28/1976 (Age:45)	**Ordering Physician/Lab:**	**NPI:** 2121212121
DOE, JANE 123 LIBERTY DR WILLOWBROOK, FL 60527 Sex: Female			**JOHN DOE MD1** **JOHN DOE, MD** 21 QUAKERBRIDGE ROAD SUITE 200 DAYTON, NJ 08810 **Tel: (345) 262-7171** **Fax: (609) 245-7645**	

Patient ID: Date Received: **8/27/2021** Date Reported: **8/27/2021**

Test	Specimen	Date Collected / Comment	Results: Normal	Results: Abnormal	Reference/Units/Comments
HPV Type-Detect 4.0 by Real Time PCR High Risk Types Only * 739 Verified 8/27/2021	*Thin-Prep - 1*	8/26/2021 Cervical		**Detected**	**Types HPV: 16, 18, 31. See explanation below.**

*This test was developed and its performance characteristics determined by the laboratory. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.

Thin-Prep-1;739:HPV Type-Detect 4.0 by Real Time PCR High Risk Types Only

HPV-16 is the most common type among cervical cancer cases. It accounts for about half of all cases of squamous cell carcinoma worldwide. It is also the second most prevalent type in patients with cervical adenocarcinomas. The presence of HPV-16 places a woman at 38 times the risk for the development of cervical cancer compared to those who are HPV negative. In accordance with ACOG recommendations, women with a negative cytology screen who test positive for HPV-16 should have another cytology screen, and HPV test in 6 to 12 months. The following were tested: High Risk: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.

Thin-Prep-1;739:HPV Type-Detect 4.0 by Real Time PCR High Risk Types Only

HPV-18 is the second most common type found in patients with cervical squamous cell carcinoma. It is the most prevalent type of infection in patients with cervical adenocarcinomas. In accordance with ACOG recommendations, women with a negative cytology screen who test positive for HPV-18 should have another cytology screen, and HPV test in 6 to 12 months. A vaccine that prevents persistent infection with this virus is now commercially available. The following were tested: High Risk: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.

Thin-Prep-1;739:HPV Type-Detect 4.0 by Real Time PCR High Risk Types Only

HPV-31 is the fourth most common type detected in patients with cervical squamous cell carcinoma. Occasionally it is found in mixed infections with other HPV types, notably HPV-16. In accordance with ACOG recommendations, women with a negative cytology screen who test positive for HPV-31 should have another cytology screen, and HPV test in 6 to 12 months. The following were tested: High Risk: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.

A positive result is provided for bacteria, virus, parasites, and/or fungal species when PCR amplification (real-time PCR), sequence information (Pyrosequencing), and/or sequencing analysis occurs above cut-off levels established by the laboratory. Pertinent reference intervals for the tests reported above are available from the laboratory upon request.

View:	M				
Mail:	Ye s	USPS	Fax:	Yes	*Manual*
	Al l	Yes		All	No

Medical Director, Mats Sanden, M.D.

MDL#: 11833564 40979
9/16/2021
PATH Final