Trends-in-Medicine

June 2005
by Lynne Peterson

SUMMARY

Prophylactic HPV vaccines are far ahead of therapeutic vaccines, with Merck's Gardasil likely to be approved in 2006 and Glaxo-SmithKline's Cervivax in 2007. ♦ Gardasil covers more strains of HPV and prevents genital warts, which could make it useful in boys as well as girls; but Cervivax has cross-protection for other HPV strains and is likely to be less expensive. The time between booster shots also could differentiate these vaccines. ♦ Uptake of any HPV vaccine will be highly dependent on a recommendation for use by the American College of Immunization Practices (ACIP), but it is expected to act quickly following FDA approval. ♦ The initial target will be adolescent girls (age 10-15), but adult women are likely to demand vaccination as well. ♦ No physician specialty has taken the lead in HPV vaccination, and a significant effort will be needed to educate doctors and parents. ♦ The link between HPV and sexuality/sexually transmitted disease is likely to be politically and socially problematic.

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Stephen Snyder, Publisher
1879 Avenida Dracaena
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

22ND INTERNATIONAL PAPILLOMAVIRUS CONFERENCE

Vancouver, Canada
May 2-5, 2005

This was the best-attended International Papillomavirus Conference (IPC) so far, with about 1,300 attendees from at least 65 countries, with about one-third of the delegates from the corporate world, which was a big increase in that contingent. A key reason for the increase in attendance was interest in the HPV vaccines that are expected to be approved within the next year or two.

HPV is a more serious problem than many people realize. About 97% of invasive cervical cancers are positive for HPV DNA, with HPV16 found in ~50% and HPV18 in ~20%. HPV6 and HPV11 cause about 90% of genital warts in men and women. With these causal relationships well established, numerous companies are attempting to develop a vaccine to prevent or treat HPV.

DIET AND HPV

HPV clearance can be affected by the serum micronutrient level diet. For instance, serum levels of vitamin E may increase the risk of acquiring HPV infection, and increased levels of several carotenoids and vitamin E may enhance the clearance of type-specific HPV. Dietary changes may hasten the clearance of HPV infection. A speaker suggested several possible mechanisms to explain this:

- The micronutrients may have an antioxidative effect, preventing damage due to oxidative stress caused by free radical molecules.
- Micronutrient levels enhance the immune response.
- Micronutrients may reduce viral load and cell proliferation.
- Micronutrients may modify the expression of genes associated with the transcriptional AP-1 complex.

HPV IN MEN

HPV is often thought of as a woman's disease, but it also affects men. In addition, both men and women get genital warts.

HPV in Men

Protective factors	Risk factors
Circumcision	Uncircumcised
Condom use	Genital warts
	Number of lifetime sexual partners
	Prostitute contact

Incidence of HPV-related Diseases in Men

Category	Incidence per 100,000 men
Penile cancer	
U.S. whites	0.4
U.S. blacks	0.6
Canada	0.6
Cuba	1.3
Puerto Rico	2.6
Uganda	4.0
Anal cancer	
White men	1.54
White women	1.83
Black men	2.19
Black women	1.92
Genital warts	
Males	162.3
Females	152.6

Among the interesting points speakers made about HPV in men were:

- Penile cancer, which is related to HPV, is a horrible disease. The rates are decreasing, but it remains a significant problem, especially for men in their 60s, 70s, and 80s.
- Anal cancer, which also is associated with HPV infection, is increasing, with a two-fold increase between 1973 and 2001.
- Genital warts are not life threatening, but there is a very high incidence associated with HPV in men and women. There was a 70% increase in the incidence of genital warts from 1998 to 2001, with the highest incidence in 20-29-year-olds. Treatment is associated with frequent visits to the doctor and high recurrence rates.
- There is an increased risk of cervical cancer among:
  - Wives of men with penile cancer.
  - Second wives of men whose previous wife died of cervical cancer.
  - Wives of men with a large number of sexual partners and/or prostitute contacts.
  - Men, who can be carriers and vectors of high-risk HPVs that increase the risk of developing cervical cancer in the female partner.
- HPV16 is the most common oncogenic type of HPV in men, which is also the case in women.
- Half of HPV infections in men appear to be low risk and non-oncogenic and half are oncogenic.
- The sites most commonly infected by HPV that experts recommend be sampled in men are: coronal sulcus/glans, penis, shaft, scrotum, and perhaps the anal canal.
- Men have a lower HPV antibody prevalence than women.
- 60.4% of men with flat penile lesions had a partner with cervical intraepithelial neoplasia (CIN).
- HPV infection in men is predominantly asymptomatic and subclinical.
- Unlike HPV infection in women, age is ***not*** associated with prevalence of HPV in men.

Potential preventive male-related strategies:

- Promote low-risk sexual behavior like abstinence and late sexual debut. A speaker pointed out that behavioral prevention options are difficult to implement.
- Promote circumcision. This was described as a theoretically useful strategy in low-resource countries.
- Consistent condom use. Again, this is a behavior prevention strategy that is difficult to implement.
- HPV vaccines. A speaker said, "The vaccines have shown excellent efficacy results in women. It is the most prominent prevention strategy for women, but we don't know yet the potential immunogenicity in men."

THERAPEUTIC HPV VACCINES

Therapeutic vaccines are primarily based on cell-mediated immune effect mechanisms. Developing a therapeutic vaccine has proven difficult.

Comparison of Therapeutic Vaccine Targets

Target	Pros	Cons
Infection/CIN-1	Most likely to be successful, High frequency of occurrence, Many potential viral targets	Not a treatable disease, Usually regresses spontaneously, Trials have to be very large
CIN-2/3	Normally treated, Accepted cancer precursor	Biologically mixed bag, CIN-3 is persistent so many may have induced tolerance or escaped immune surveillance
Cancers	Disease of ultimate interest	Least likely with current generation of vaccines to be successful, Tolerance is an issue.

PROPHYLACTIC VACCINES

Prophylactic vaccines are primarily based on the generation of virus-neutralizing antibodies. To date, successful viral vaccines are primarily prophylactic. The two leading prophylactic vaccines are Merck's Gardasil and GlaxoSmithKline's Cervivax. Three large, international, Phase III trials are underway, two with the Merck vaccine, and one with Glaxo's vaccine.

- The Merck trials include 17,800 women age 16-26 plus a cohort of 3,800 women age 24-45 and a cohort of 3,700 men age 16-24. These trials will continue through 2008, but Merck is expected to file Gardasil by the end of 2005.

- Glaxo is testing Cervivax in 18,000 women age 15-25, including 12,000 women in a trial in Costa Rica that is being run by the National Cancer Institute. These trials will continue through 2010, but Glaxo is expected to file Cervivax in Europe in 2006 and in the U.S. by the end of 2006.

Dr. John Schiller, head of the Neoplastic Disease Section at the National Cancer Institute (NCI), offered these comments on the Merck and Glaxo vaccines:

- Both vaccines seem to be very safe with no vaccine-related serious adverse events.
- Both vaccines have shown 100% protection from type-specific persistent infection and CIN.
- Follow-up is mostly 1.5 years, but there are some 3.5 year data on HPV16.
- "The results exceed the wildest expectations of any of us. We never believed they (the vaccines) would work this well. We really are very gratified with that."
- Merck is expected to be on the market in 2007. He and other experts consider this a very fast timeline. Dr. Schiller said, "These vaccines will be upon us in a very short period of time."
- The FDA is likely to accept the reduction in persistent infection for approval but require prevention of CIN-2/3 in a Phase IV post-marketing trial.
- Supply will be the issue, not demand.

- Outstanding scientific questions about the Merck and Glaxo vaccines include:
  1. **Safety.** "The vaccines look to be very safe."
  2. **Immunogenicity.** "The vaccines are remarkably immunogenic. Almost no one doesn't respond."
  3. **Efficacy.** "They look remarkably effective in preventing HPV infection and CIN. Will they prevent cervical cancer? I personally can't imagine that cervical cancer rates won't go down."
  4. **Type-specificity.** "Probably, but a Glaxo abstract suggests there may be some type of cross-protection."
  5. **Duration of protection.** "That is one of the big outstanding questions. Merck's vaccine looks like it provides excellent protection at 3.5 years. Whether the protection is lifelong, I don't know. I've always thought we need to boost this vaccine…but if it lasts 5-10 years, it is a very feasible vaccine."
  6. **Alternative vaccines.**
  7. **Immune correlates for protection.**

MERCK'S Gardasil

A researcher reviewed the data presented recently in ***The Lancet*** on Merck's quadravalent vaccine. In the Phase II trial, Merck researchers continued to follow their patients out to 48 months, and there was still protection. A researcher said, "We've been doing natural history studies in a similar age cohort, and we found a similar rate of CIN-2/3 development (as with placebo in the trial)."

Dr. Luisa Villa of Brazil presented the results of the three-year, randomized, double-blind, placebo-controlled, Phase II trial of Gardasil administered at Months 0, 2, and 6. She said the per protocol analysis found the Gardasil dose chosen to go forward into Phase III showed a strong immune response by the third dose, then some waning out to 24 months, at which point it leveled off but was always consistently higher than placebo. The data on the HPV6 suppression were the weakest. Merck plans to follow these women for five more years, giving booster shots if needed. The impact of the vaccine in HIV positive women is still being analyzed.

Another researcher has been working on a model for studying the effect of Gardasil on cervical cancer rates. He said, "Vaccination plus screening together have a greater impact than either alone. We need to think of vaccination in combination with screening rather than as a replacement for

Comparison of Merck and GlaxoSmithKline Vaccines

Feature	Merck's Gardasil	GlaxoSmithKline's Cervivax
Targets	HPV6-11-16-18	HPV16-18
Preparation	Yeast	Baculovirus
Adjuvant	Aluminum	ASO4 (Aluminum+MPL)
FDA status of adjuvant	Approved	Not approved in U.S. (approved in Europe)
Mode of administration	IM	IM
Frequency of administration	Months 0, 1 or 2, and 6	Months 0, 1 or 2, and 6
Safety	Good	Good
Active against genital warts	Yes	No
Cross-protection	Unknown	HPV31-45-52

Comparison of Merck and GlaxoSmithKline Vaccine Trial Results

Endpoint	Merck			GlaxoSmithKline		
	Vaccine n=768	Placebo n=765	Vaccine efficacy	Vaccine n=366	Placebo n=355	Vaccine efficacy
Incidence of persistent HPV16 infection	0	41	100%	0	16	100%

screening…If only adolescents and not older women are vaccinated, there will be a lesser effect on the incidence of cervical cancer…With our vaccine, we get a dramatic drop in cervical cancer, but there is still cervical cancer – even out 40 years."

In the model, he is assuming:

- 90% efficacy.
- 50% coverage of adolescents, with a 5% per year catch-up rate.

~40-Month Results of Phase I Trial of Monovalent HPV16 Vaccine

Endpoint	Placebo	Vaccine	Vaccine efficacy
Incidence of persistent HPV16 infection	7	111	94%
CIN-2/3	0	12	100%
CIN-2	0	7	100%
CIN-3	0	6	100%
Prevention of CIN due to any type of HPV16	**Cases**	**Placebo**	**Efficacy**
CIN-1	28	38	30%
CIN-2 or worse	8	16	52%
CIN-2	6	10	N/A

Phase II Dose-Finding Study

Group	HPV6	HPV11	HPV16	HPV18	Total VLP
Placebo	0	0	0	0	0
Low dose (Gardasil formulation)	20 µg	40 µg	40 µg	20 µg	120 µg
Medium dose	40 µg	40 µg	40 µg	40 µg	160 µg
High dose	80 µg	80 µg	40 µg	80 µg	200 µg

Per Protocol Efficacy of Gardasil in the Phase II Dose-Finding Study

Measurement	Placebo n=275	Gardasil n=277	Vaccine efficacy
Received ≥1 injection	275	276	---
HPV6-11-16-18 infection, CIN or genital warts	36	4 (p<.001)	90%
HPV6-related	13	0	100%
HPV11-related	3	0	100%
HPV16-related	21	3	86%
HPV18-related	9	1	89%
Adverse events			
≥1 adverse event	92%	88%	---
With ≥1 injection site adverse event	86%	77%	---
With ≥1 systemic adverse event	69%	69%	---
Serious adverse event	1%	1%	---
Serious virus-related adverse event	0	0	---
Discontinuations due to adverse events	0	0.5%	---
Deaths	0	0	---

- No vaccination of boys. He said, "The added benefit of vaccinating boys depends on what you assume about immunity due to natural infections. If you assume no immunity from natural infections, then vaccinating both boys and girls has greater impact."

He concluded, "The (Merck) vaccine can reduce the incidence and prevalence of cervical cancer, cervical intraepithelial lesions, and genital warts. A vaccine with high efficacy can have a major impact on the epidemiology of HPV viral types. In the absence of cross immunity, screening will still have a significant role."

GlaxoSmithKline's Cervivax

A researcher reviewed the results of the randomized, double-blind, placebo-controlled, Phase IIb efficacy trial (the HPV-001 trial) of Cervivax, a bivalent vaccine, conducted in 1,113 women 15-25 in the U.S., Canada, and Brazil. Women were dosed at Months 0, 1, and 6, and mean follow-up was 18 months, with up to 27-month follow-up for the earliest enrollees. This trial found the vaccine to be generally safe, well-tolerated, and highly immunogenic, with protection against HPV16 and HPV18. Prevention was:

- 91% from incident infection.
- 100% from persistent infection.
- 93% from abnormal cytology.
- 100% from cervical intraepithelial neoplasia (CIN) lesions.

He also reported on the cross-protection of Cervivax on HPV16-related (HPV31, 33, 52, and 58) and HPV18-related (45,59) strains. In these studies, there was only one biopsy-confirmed cervical lesion, a CIN-2 associated with HPV33 in the vaccine group, but he commented, "Clearly, this study was not powered to evaluate cross-protection against lesions…We see this data as providing the first evidence that a HPV16-18 vaccine may provide cross-protection against some HPV16-18-related types, particularly HPV31, 52, and 45 individually, and all high risk types combined …The real answers on cross-protection will come from the ongoing Phase III trial in which about 22,000 people have been enrolled so far…We are now doing studies to understand the mechanism of cross-protection. We speculate that the use of (our) adjuvant may contribute to this effect."

The regulatory path for HPV vaccines

The NCI's Dr. Schiller spoke at a media workshop, and he indicated the Merck vaccine is likely to be approved in 2006, and the GlaxoSmithKline vaccine in 2007. Among the other points he made about the Merck and Glaxo vaccines were:

- So far, the clinical trials have just been proof-of-concept.

- The safety data have been "exceptionally good, with no serious vaccine-related adverse events."
- Protection has also been "extremely good" with 90%-100% protection for at least 1.5 years…and Merck has 3.5 year data on a monovalent HPV16 vaccine. There is also 100% protection against cervical abnormalities by vaccine types after 1.5 years.
- No woman who has been vaccinated by these vaccines has gotten a cervical abnormality, which he called "really very dramatic."

Cervivax Phase IIb Cross-Protectivity

(Statistically significant vaccine efficacy highlighted)

Measurement	Cervivax	Placebo (500 mcg aluminum salts)	Vaccine efficacy	p-value
Number by ITT	560	553	---	---
Number per protocol	366	355	---	---
Efficacy against incident infections with HPV18-related types				
HPV31	1	10	90%	0.006
HPV45	2	4	100%	.031
HPV52	6	16	63.0%	.031
12 high risk types (except HPV16-18)	32	53	42.3%	0.011
HPV33	6	6	-0.2%	1.0
HPV35	1	3	66.5%	0.624
HPV58	5	5	0	1.0
HPV59	4	2	-100.5%	---
All HPV16-related	16	31	51.1%	---
All HPV18-related	4	7	43%	---
Efficacy against persistent infection				
HPV31	2	9	78.5%	0.03
HPV52	5	21	77.1%	0.001
All HPV16-related	11	30	65.1%	0.002
HPV33	3	5	42%	0.476
HPV35	1	1	0.4%	0.998
HPV45	1	4	75.4%	0.174
HPV58	4	6	34.1%	0.515
HPV59	3	0	---	0.083
All HPV18-related	N/A	N/A	N/A	N/A
Efficacy against typical abnormalities				
HPV52	1	11	91%	0.003
All HPV16-related	5	18	72.8%	0.005
12 high risk types (except HPV16-18)	10	30	68.2%	<.001
HPV31	1	5	80.1%	0.123
HPV33	2	4	49.9%	0.686
HPV35	0	2	100%	0.499
HPV45	N/A	N/A	N/A	N/A
HPV58	2	2	0.2%	1.0
HPV59	N/A	N/A	N/A	N/A
All HPV18-related	4	4	0.2%	1.0

Experts generally believe the FDA will approve Merck's vaccine without additional data, but it is not a slam dunk, and there are questions about the label. An expert said, "The FDA approved Sanofi-Aventis's Menactra meningitis vaccine based on antibody titers (a surrogate marker), and that is what the FDA will do for HPV as well. The FDA won't wait for CIN-2/3 data." *(NOTE: On January 17, 2005, the FDA approved Menactra.)* Another expert said, "A heated debate is going on within the FDA. I heard one official who was willing to approve it (Gardasil) prior to the CIN-2/3 data, but another official wants to wait for that data." Dr. Schiller said, "The FDA suggested it wants a hard clinical endpoint ultimately for licensure," but he was not suggesting the FDA won't approve Merck's vaccine without additional CIN-2/3 data.

A Merck investigator said the Phase III interim look at Gardasil will be this fall (September, October 2005), and after Merck evaluates that data, it will file with the FDA, which means, she said, late 2005 or perhaps early 2006. She also said there will be both persistent infection and CIN-2/3 prevention data in that interim analysis.

Labeling issues include:

- **What ages will be approved?** The vaccine was tested only in 15-25-year-old women, not girls <15, and the FDA rarely approves drugs for children that are not tested in children. However, there is a precedent for the FDA to approve – and the American College of Immunization Practices (ACIP) to recommend – use of a vaccine in children in whom it has not been tested, based on bridging studies. Merck has done bridging studies – immune response tests in girls <15 years old. A researcher said, "They responded very nicely." A Centers for Disease Control and Prevention (CDC) official agreed, saying that bridging immunogenicity studies have been used successfully with other vaccines.
- **What indication will be approved?** The question is whether Merck will be able to say only that the vaccine prevents HPV infection, or if it will be allowed to advertise something like this: "HPV causes cervical cancer. There is an HPV vaccine. Don't you want your daughter to be vaccinated?" Another expert said, "The FDA indications will make a huge difference in the first year use of the vaccine. The only data are in 15-25-year-olds. Merck has a study in women age >25, but they won't have the antibody data from that at the time of approval." Another expert said, "Doctors use drugs freely off-label, but they don't use vaccines off-label."

The marketing battle between MERCK and GLAXOSMITHKLINE

Merck's advantage is that its vaccine covers more strains of HPV (6-11-16-18) and protects against genital warts as well as HPV, so it may give boys/men a reason to take the vaccine. An expert said, "Some focus groups found that younger women are as concerned about genital warts as cervical cancer, and genital warts are more easily understood by a younger population."

The Glaxo vaccine may last longer. The adjuvant used in the Glaxo vaccine may give it longer protection. An expert said, "Glaxo will certainly market their vaccine as superior because of the adjuvant…With their vaccine, patients get higher antibody titers. They will say their vaccine will have longer protection." And the Glaxo vaccine of the future may be different from the bivalent version being discussed today.

Other comments included:

- "I pray the companies don't get into a fight over who has a STD indication and who doesn't because that can kill both vaccines."
- "I would use the vaccine that covers the most strains (Merck), but if there is a $100 difference in price, I would go with the other (Glaxo)."
- "Everyone thinks we should just give young and adolescent girls the HPV vaccine. And that is a strong argument, but I think we should consider giving it to girls and boys…We shouldn't just get stuck in the rut of giving it to girls as the only option."

OTHER INTERESTING VACCINES IN DEVELOPMENT

BIOVEX'S ImmunoVex$^{HSV-2/HPV}$ prophylactic vaccine

This is a combination vaccine for HSV and HPV. Researchers presented mouse and guinea pig data showing there is complete protection against genital herpes. Preclinical studies with the combined vaccine are about to be initiated, and human clinical trials are expected to start in late 2005 or 2006.

CSL

This Australian company is developing a therapeutic HPV16 (E6-E7) vaccine for anal cancer. This vaccine is currently in a Phase I trial in Australia, and a Phase II trial in the U.S. is expected to start soon. The vaccine uses a propriety adjuvant, iscomatrix, which is not approved yet in either Australia or the U.S.

A CSL researcher said, "Merck has an advantage with the genital warts protection, but that may not necessarily be as big an advantage as some people think. It could dilute Merck's message because of the association between genital warts and promiscuity. Merck is targeting 10-12-year-olds, and doctors will say the vaccine is a cancer prevention agent, even if it is not labeled that way, which will make it a much easier sell to the parents of those adolescent girls."

In five years, there may be a more level playing field between Merck and Glaxo. A source said Glaxo's next generation HPV vaccine will have four strains, and then both companies are likely to introduced 8-strain HPV vaccines.

Glaxo's adjuvant, though not yet approved in the U.S., may have some advantages. A source said the adjuvant should not slow down Glaxo's regulatory process in the U.S. because the FDA is well aware of this adjuvant. The Glaxo adjuvant reportedly has better efficacy on cell-mediated immune systems, which could translate into the following theoretical advantages:

- **Improved efficacy.** But if Merck already has 100% efficacy, it would be hard to improve on that.
- **Longer duration of action.** Perhaps the Glaxo vaccine would need fewer booster shots or a longer time between booster shots.
- **Amount of antibody needed.** This might make the vaccine cheaper.

LARGE SCALE BIOLOGY'S rTMV

Large Scale Biology is developing vaccines grown in the leaves of tobacco plants. One of these is a treatment for Fabray's disease that is expected to enter clinical trials in about 12 months. The larger indication is a prophylactic HPV vaccine for cervical cancer, for which the company will initially seek orphan drug status to treat HPV-infected newborns, and then plans to expand to their mothers and, finally, to the general population. This vaccine may have particular appeal in less developed countries because of the ease of volume production and the anticipated low cost. The vaccine is expected to last 4-10 years and require at least two inoculations.

While the Merck and Glaxo HPV vaccines target L1, this vaccine is aimed at L2. There have been reports that L2-reactive sera can induce cross neutralization, but L2 is poorly immunogenic. Large Scale Biology believes it has found an L2 vaccine, recombinant tobacco mosaic virus (rTMV), that targets L2 and is immunogenic. In a rabbit study, researchers found good efficacy with this vaccine.

MGI PHARMA'S ZYC-101a, a therapeutic vaccine

A poster reported this plasmid given by IM injection is safe and well-tolerated. Researchers said the vaccine, which is now in Phase I/II trials, resolved CIN-2/3 lesions in women <25 and showed activity against multiple HPV types.

WYETH'S HPV16-E7E6TetM, a therapeutic vaccine

A Wyeth researcher discussed the company's early work on this multivalent vaccine. He said, "The unique part of our strategy is the delivery platform – VEE-Replicon Particles (VRPS)." The vaccine showed a robust Th1 cellular immune response and showed therapeutic efficacy in a murine model. Wyeth has developed monovalent (HPV16), bivalent (HPV16-18 and 31-33), and trivalent (HPV16-18-45) constructs.

Others:

- **HBV+HPV vaccine.** Australian researchers suggested that an HPV vaccine could be incorporated into the currently approved hepatitis B (HBV) vaccine, HBsAg. Their animal studies found that it is relatively easy to insert epitopes (one or more) into the HBV vaccine. In mice, even if the animals have been previously vaccinated with the HBV vaccine, they will still develop HPV immunity from the HPV-modified HBV vaccine. This means that the modified HBV vaccine could be given to people who had previously received the HBV vaccine, not just naïve people.

- **Intranasal HPV vaccine.** Swiss researchers reported on early work on this HPV vaccine delivery method. There does not appear to be a company working on this yet.

- **Salmonella-based prophylactic HPV vaccine.** Other Swiss researchers reported on this approach to an HPV vaccine, commenting that it is likely to be inexpensive. A Ty21a vaccine appears the most promising at this point, and a Phase I/II trial will start soon.

- **Institute Mexican del Saguaro Social's MVA-E2 therapeutic HPV vaccine for CIN-3.** A poster reported on a Phase II study in 37 women, which showed 17.6% of the 17 women who got the vaccine once a week for six weeks were free of lesions at follow-up, but 80% of the control women who had a conization were free of lesions at follow-up.

- **Prion vaccine.** German researchers reported on a vaccine with PrP L1 VLP that induces humoral immunity that is protective against PrP infection in vitro. If proven in animal models, this opens the possibility for immunoprophylactic or therapeutic intervention for incurable prion diseases. This vaccine also offers the potential of VLP-based vaccinations to overcome immunotolerance to self-antigens.

ACIP and HPV Vaccine Recommendations

Uptake of any HPV vaccine will be highly dependent on it getting a recommendation for use by the American College of Immunization Practices (ACIP). A speaker said, "With that blessing, there are other professional organizations that will bless it. Many times physicians won't use a vaccine unless their professional organization has evaluated it and says it is a good thing to put in the practice portfolio…I think there will be little vaccine sold without the recommendations."

Other sources indicated that ACIP, which meets three times a year, is planning on taking up the HPV vaccine at the first meeting after FDA approval. A New England doctor said, "I think ACIP will act quickly." Approval by the American Academy of Pediatrics (AAP) goes hand-in-hand with ACIP approval; the time delay is probably only weeks."

The ages that ACIP specifies will be important. A source said ACIP has discussed a broad recommendation – age 10-55 – as well as just recommending the studied age (15-25).

ACIP also is considering establishing an Adolescent Vaccine Platform that will begin with Menactra (meningitis vaccine) and an HPV vaccine. An expert explained, "This will in part take away from each disease individually, encouraging parents to think about vaccinations for life – infant, adolescent, and then adult vaccines. One way to do this is to require the adolescent vaccine to enroll in school. If meningitis is a part of this, it would be easier for people to accept the platform…It takes the emphasis from each disease and de-emphasizes them…An adolescent platform will make it easier for pediatricians to prescribe the HPV vaccine. It would be a huge blessing to the HPV world."

The issue for ACIP is the cost of an Adolescent Vaccine Platform. There is a federal program that covers vaccinations for children. An Adolescent Vaccine Platform would be covered by this free program. Thus, the question for the ACIP will be whether the federal budget can accommodate this new platform. An expert said, "That will be the issue, not science or STD vs. cervical cancer."

A CDC official outlined the process used by ACIP to make a decision about vaccines, including the HPV vaccine. ACIP is a U.S. federal advisory committee that is coordinated and organized by CDC. It meets three times a year in Atlanta. There are 15 voting members, appointed for 2-4 year terms, plus eight non-voting members from government (DOD, FDA, NIH, etc.), and non-voting liaison members from professional organizations – AAP, American College of Obstetricians and Gynecologists (ACOG), and the American Medical Association (AMA).

ACIP has two functions:

1. Develop recommendations and publish written guidelines for use of vaccines. Those guidelines address:
   - Routine target age groups
   - Safety
   - Contraindications
   - Need for booster doses
   - Simultaneous administration with other vaccines
2. Make recommendations for the Vaccines for Children (VFC) program. This program provides free vaccines for eligible children <19 years of age (Medicaid, Indians, parents whose insurance doesn't cover vaccines, etc.).

Funding for new vaccines occurs through a vote by ACIP, and then the federal government establishes a contract with the manufacturer. Currently, the VFC program provides 42% of funding for childhood vaccines (5% from states, 9% from grants, and 44% from parents and private insurers). How an ACIP recommendation is worded affects whether or not it is covered by VFC.

ACIP has ~14 different working groups, with ≥2 voting ACIP members in each working group, plus CDC staff, consultants, and others. The first ACIP HPV Vaccine Working Group met a little more than a year ago "to review data and monitor the progress in HPV vaccine development." This working group also has CDC staff, other ACIP members, and consultants. It considers safety, efficacy, duration of protection, potential target groups, vaccine acceptability, and cost. The working group will develop background material and recommendation options and draft ACIP recommendations. Then, the full ACIP will consider the recommendations in condensed version, vote on them, and approve the final written recommendations. The CDC official said, "The working group has been considering the two vaccines (Merck and Glaxo). They are very similar, but they have significant differences…ACIP only makes recommendations for licensed vaccines…so it will just make recommendations for the first one approved and then revise them later when another is approved."

Among the options the ACIP can recommend are:

- **Routine use.**
- **Permissive use.** This means doctors can give the vaccine, but routine inoculation is not recommended.
- **Specific groups only.** For example, the hepatitis B vaccine was initially recommended only for healthcare workers.

The CDC official described the challenges for HPV vaccine recommendations, commenting, "The over-arching challenge is that the HPV vaccine world is new to ACIP, and many members are not as aware of this as they are of other infectious diseases, and this is a challenge everyone is facing."

- **Data on duration of protection.** She said, "There will be some but limited information on this…There is a precedent for vaccines to be recommended with limited data at first licensure."
- **Target age groups.** There are scientific and social issues here, including:
  - Duration of protection impacts this.
  - Pre-adolescents and older adolescents are hard to reach.
  - Older age groups also need to be addressed.
- **Vaccination of males.** She predicted this would be "a very challenging issue."
- **Acceptability.** She noted that there needs to be more education and research in this area, "Education may increase acceptability, but we do need more information on this."
- **Cost-effectiveness and the impact on outcomes.** She said, "There are no guidelines for cost-effectiveness, but ACIP will want to see data on this." In 1985, it cost $45 to fully immunize a U.S. child. By 1990, that had increased to $114, and in 2004 it was about $472 (most of the increase due to the addition of the pneumonococcal vaccine). Menactra will cost about $70 per child, but if the HPV vaccine costs ~$300, adding these two vaccines would nearly double the cost of immunizing an American child. It will be interesting to see what Merck and Glaxo are doing in this area. Are they being as proactive as Johnson & Johnson was with its Cypher drug-eluting stent in terms of cost-effectiveness data? Can cost-effectiveness data be obtained prior to the CIN-2/3 data in Merck's Phase III trial?

The ACIP guidelines will not recommend any indication not approved by the FDA, and the ACIP will not make any recommendations about cervical cancer screening or school immunization laws, which are the responsibility of the individual states. The HPV vaccine needs to be considered, the CDC official said, in the context of the overall childhood and adolescent immunization schedule in the U.S. And she pointed out that there are three potential vaccines targeted at pre-adolescents: HPV, Menactra (meningitis), and diptheria-tetanus-pertussis (Tdap).

WHO WILL GET THE HPV VACCINE WHEN IT IS AVAILABLE?

In the U.S.

In descending order of importance, according to the NCI's Dr. Schiller, there are:

- **10-13-year-old girls**, who are the ultimate target group.
- **Young women**, since some may not have been exposed to these viruses yet.
- **Adolescent boys and men** – if the vaccines are shown to prevent infection. Dr. Schiller pointed out, "There have been no efficacy trials in boys or men yet. The companies are currently conducting trials. At the moment, we are talking about vaccinating girls until there are demonstrations that the vaccines work in men."

This meeting was primarily attended by HPV researchers, not clinicians, but there were some clinicians there. U.S. doctors estimated that one year after the first vaccine is approved here, it will be used by:

- **20% of girls <age 15.**
- **20% of girls age 15-25.** A family practice doctor said, "30% of girls under 25 in my practice will get the HPV

vaccine, but other primary care doctors, especially male doctors, will give it to <5% of their girls that age." A New England family practice doctor said, "HPV vaccinations are very challenging. Whether it is presented as a prevention for cancer or an STD will make a difference. The marketers and clinicians speaking about it need to be clear…Half of the adolescent girls will get it simply because I recommend it; they won't know what they are getting." Another doctor said, "I don't think third party payors will cover the vaccine the first year."

- **17% of females >age 25.**
- **A negligible number of boys.** A doctor said, "I don't think even physicians will make the connection to boys, and as a man, I can't see getting a vaccine for cervical cancer. I'll vaccinate my two daughters, though."

Merck and Glaxo are expected to do a lot of direct-to-consumer advertising, and that could boost first-year usage. The message is expected to be:

1. HPV causes cancer.
2. Wouldn't you like to prevent HPV in your daughter?
3. This is a vaccine to prevent HPV.

A source added, "I'm worried about adding 'prevention of external genital warts' would dilute the cancer message."

HPV vaccination is unlikely to be universal, but it may become mandatory by some schools or states. An expert said, "Two states still don't require any vaccinations."

Outside the U.S.

Clinicians offered the following comments about the outlook for use of these two vaccines outside the U.S.:

- *Germany #1:* "I expect about 10% of eligible girls in Germany would be vaccinated the first year. It definitely will be used."
- *Germany #2:* "There won't be much use in Germany if it is handled by pediatricians. Merck said they were going to OB/GYNs, suggesting they bring it up at a girl's first visit (generally for birth control pills), which would let them cover prevention – pregnancy and HPV…I have two daughters, but I think I would wait five or six years after the vaccine is approved before getting it for them – until there are more data, especially if they will need a booster every three years."
- *U.K.:* "There will be a very small percentage of British children getting these (Glaxo and Merck) vaccines because of the cost, and virtually no boys."
- *Cameroon:* "We would choose the Glaxo vaccine over the Merck vaccine because of price. The only critical need is prevention of cervical cancer, not genital warts…But there will be very little use unless there is a much lower price for developing countries."
- *India:* "Only 1%-3% of the eligible females will get this vaccine unless the price is very low. Rich families will pay for it, but there will be no widespread use, even if the vaccine is discounted from the U.S. price…I'm sure companies will develop generic versions, but those are 10 years away."

Challenges in Implementing an HPV Vaccination Program

Getting an HPV vaccination program underway will not be simple, speakers insisted. A Canadian family practice doctor said, "I'm amazed at the amount of work needed to implement HPV testing." Another expert said, "There is a myth that the vaccine will be accepted just because it is a good vaccine. There is a complex transition from a vaccine to a program. It will be a gradual process – scientific and political."

Challenges to implementing HPV vaccination include:

Educating doctors

A survey of 939 Canadian physicians found that doctors had limited knowledge about HPV, about the link between HPV and cervical cancer, and about HPV transmission. Only 37% of respondents offer cervical screening consistent with guidelines. Physicians were more likely to offer cervical screening to women under age 40, if they had been in practice less than 10 years, and if they were not solo practitioners.

Which medical profession will lead the way

One of the big questions is which doctors will lead the use of HPV vaccines. In fact, there may be something of a turf war over this. A speaker said, "We need experts from many fields, unfamiliar one with the other, to work together." An OB/GYN said, "Who will counsel young girls and boys is a contentious issue, to put it mildly…Everyone has a piece of the pie. Until someone comes forward, there will be a variety of doctors involved, and, unfortunately, they may provide misinformation. We will have an incredible treatment, but no physician group leading the way…I feel strongly that a lot of usage will be patient-driven."

- **Pediatricians** see adolescent girls (and boys), but sources agreed they will not prescribe the HPV vaccine without an ACIP recommendation.
- **Family practice doctors.** Most sources think only a small percentage of HPV vaccinations will be given by primary care doctors – at least at first.
- **OB/GYNs** know more about HPV and have more experience with it, but adolescent girls generally don't see OB/GYNs, and parents may be reluctant to take their daughters to these specialists that young. OB/GYNs conceivably could encourage parents to have their daughters

vaccinated, but they may not want to spend the time on this. A source said, "The reality of HPV is that it takes an inordinate amount of time to counsel patients – to go over the natural history of the disease, how it is treated, and the consequences. The problem is there is not enough time to educate patients. Realistically, if you suggest an HPV vaccine, it will open a can of worms that doctors don't want to do from a time standpoint." Another expert said, "OB/GYNs are critically placed to provide vaccines to women. They are the primary or sole healthcare provider for many women aged 25-45. They already provide routine cytology-based cervical cancer prevention. They already utilize HPV DNA testing for ASCUS (atypical squamous cells of undetermined significance) management and primary screening. And they have had years to learn the education message and place the risks into perspective…But we need to educate OB/GYNs. Many are not very informed about the vaccines and the potential benefits. But OB/GYNs know the vaccine is coming."

- **Planned Parenthood** and other clinics.

Educating women and adolescents

Sources generally agree that a huge education effort will be needed to encourage use of the vaccine. Asked why so little is currently known about HPV, a family practice doctor said, "HPV is still not in the health curriculum of middle schools… When we put sexuality with this, we close people's minds…HPV is not transmitted by bodily fluids – not semen or urine. This is not like HIV. It doesn't stay inside your body. It is a virus that lives in the skin outside of us, in the top 1 mm of skin…Skin-to-skin contact is required to spread it." Another speaker said, "Physicians are extraordinarily reluctant to talk about this because of the sexual connotation…The physician population is very reluctant to educate patients, and those who do state many untruths." An OB/GYN said, "The amount of information being disseminated is enormous, and any community physician will recognize it is hard to stay abreast...and the sexual connotation even magnifies the difficulty…The barriers are largely centered on the STD nature of the virus…But mothers may be cautious about the vaccine. There would be hysteria if a mother promoted a vaccine in an adolescent daughter, and she incurred an adverse event."

Morality issues

A speaker said, "When we educate people about HPV, our job is to present the facts – and leave the moral implications to them." Another speaker said, "We have to be honest that the vaccines are for STDs. We can't sweep that under the rug and focus only on cancer." A third expert commented, "Parents need to preach abstinence but teach protection."

Should the vaccine be positioned as a cancer or STD preventive?

An expert urged, "I think we have to focus on the STD prevention feature of the vaccine, not cancer prevention."

Parental attitudes

The National Vaccine Advisory Committee (NVAC), of the National Vaccine Program Office (NVPO), meets three times a year. The next meetings are June 7-8 and September 27-28, 2005. The members are expected to take up the issues of who will offer vaccinations and adolescent vaccines in general. The meeting is open to the public, and CDC, which is organizing the meeting, is reaching out to a broad group of stakeholders.

A poster reported on a study by University of Washington and Indiana University researchers on parental acceptability of HPV vaccination. They surveyed 1,600 parents of 8-12-year-olds, using a 3-item, 11-point scale to measure the likelihood of vaccine acceptance. Most of the parents were white, married females with some college. The NCI's Dr. Schiller said, "With a little education, about 75% of parents of girls 10-15 would be willing to give their daughters the vaccine. Before reading that (HPV) information sheet, about 50% were willing to have their daughters vaccinated."

Parental Acceptance of HPV Vaccination

Feature	Control n=800	Intervention n=800	p-value
Information provided	Paragraph on HPV	Paragraph on HPV plus 2-page HPV information sheet	---
Effect of intervention on parental knowledge assessment score	4.17	5.57	<.001
Mean vaccination acceptability score	6.28	6.56	0.17

Researchers found:

- Receipt of an HPV information sheet increased parental knowledge of HPV but did not significantly increase parental acceptability of the vaccine.
- HPV vaccine strategies should focus on increasing parental perceptions about these vaccines, overcoming general barriers to vaccines rather than on providing general information about HPV.

Researchers said the key factors in vaccine acceptance, in descending order of importance, were:

- Belief in personal and society benefits of vaccination.
- Peer influences.
- Belief a child is at risk for HPV.
- Willingness to follow a doctor's recommendation.

- Personal experience with genital warts.
- Female child.

Attitudes differ by country

The entire link between the HPV vaccine and sexuality is likely to be problematic, particularly outside the U.S. An expert said, "This vaccine is not an easy sell in developing countries."

The level of parental openness about sexuality varies by country. A study of 320 women and ~60 young girls (age 9-17) in Canada, France, Italy, Germany, and India found that barriers to dialog on sexuality are strong, and the key issue is embarrassment by both mother and daughter. A researcher said, "Mothers fear saying too much, not the right thing, not the right way, and inducing boredom, stress, or early sexual activity. The perception (by the mother) is that it is too early (for this talk), and there is rebellion and a lack of interest by daughters. The drivers that encourage mothers to talk to their daughters are: (1) It is very important for the daughter to be aware of potential risks, (2) They want an open relationship with their daughter, and (3) They want to be a good mother…Overall, a 'proper' dialogue between mother and daughter on sexually transmitted diseases generally does not take place."

Mother and Daughter Discussion of Sexual Issues

Timeframe	Mothers	Daughters (age 9-17)
Childhood	Answers questions	Very open, asks questions, forgets
Pre-puberty	May initiate conversations on puberty	Specific questions requiring short answers
Puberty	Initiate or answer questions. Shock for the mother	Catch-up if knowledge gaps (in India especially)
Post-puberty	Does not initiate conversation	Embarrassed. Stops talking to mother. Prefers friends
Late teens	First serious boyfriend has an effect. Mothers compelled to initiate dialog, advise contraception, and discuss STDs (not India)	Daughters may be willing to discuss with the mother again (not in India)

Among the various attitudes the study found were:

- *Italy* – closed attitudes, a feeling that parents should take the lead, but they find it very difficult, and sex is a taboo subject. Italian mothers were described as "full of inhibition" and would rather talk about the dangers of drug addiction than sexually transmitted diseases.
- *France* – mixed attitudes, with more openness among the affluent and better educated. Mothers generally believe puberty is the right time to talk about sexuality.
- *Germany* – open but not necessarily comfortable discussing sexual topics. Mothers felt they could talk about sexually transmitted diseases throughout development, but it is easier during pre-puberty.
- *Canada* – encourage dialogue but find it easier to talk to daughters <11 years old. Mothers felt they could talk about sexually transmitted diseases throughout development, but it is easier during pre-puberty.
- *India* – girls are afraid of parental anger. Mothers thought puberty was the right time for discussion, but the topic of sexually transmitted diseases is avoided.

Researchers reported that the key sources of information about sexuality for young girls are: Teen magazines, friends, and schools, in that order – but not mothers. They also found cancer is a much easier topic for mothers to discuss with their daughters than STDs or sexuality – but there are many misconceptions about cervical cancer. And in Europe and India, the study found that some mothers didn't know where or what a cervix is. Some French women confused cervical cancer and colon cancer. Mothers often believe that it is not their responsibility but a doctor's role to talk about cervical/female cancer. The link between HPV and cervical cancer came as a shock to many of the mothers in the study, though less so in Canada. A speaker said, "The typical reaction was, 'How can we not know about this thing?' They wanted more information, and they started to panic. They wanted to see a gynecologist tomorrow." The researchers concluded that the lesson for HPV vaccine makers is that they need to recognize cultural differences and manage expectations carefully.

Impact on Pap smears

HPV vaccines will ***not*** replace Pap screening, speakers insisted. Pap smears are ~80% effective, and vaccinations only protect about 70% of women. However, vaccines will substantially reduce the number of:

- Abnormal Paps.
- Follow-up re-tests, colposcopies, and biopsies.
- Surgeries to remove pre-malignant cervical lesions.
- Cervical cancer rates.

A speaker cautioned, "Vaccines cannot replace Pap smear screening…The vaccine alone will not do as good a job as Pap smears, so clearly we have to keep doing Paps…Less frequent screening might be cost effective, but the potential problem with decreased compliance is that women may no longer feel they need to have a Pap smear based on a misconception of how complete the (vaccine) protection is and a misconception of the prevalence (of cervical cancer)."

Vaccines have the greatest potential for impact in less developed countries without effective Pap screening programs, but their uptake will be slow in those countries because of cost. In countries with Pap screening programs, people who get the HPV vaccine might get by with fewer (less frequent) Pap smears and delayed onset of screening (to a later age). However, this depends on whether or how frequently the vaccines will need a booster shot – and on the cost. A source said, "Vaccination and screening are independent, but screening absolutely doesn't need to be annual."

Lack of long-term data

Programs targeted at adolescents will take years – probably at least two decades – before they significantly slow the rate of cervical cancer. An expert said, "If we start vaccinating adolescents…we will have a 20 year lag before we see an impact on invasive cervical cancer."

Should boys be vaccinated?

A speaker said, "We don't know if the vaccine works in boys or men. We need trials before we vaccinate them. We shouldn't give the vaccine to boys until women are vaccinated."

Should vaccination be mandatory?

An expert predicted, "Vaccination won't be mandatory in the U.S. because of the sexually-transmitted component and the religious right…It is almost impossible in the current U.S. climate to make it mandatory to be vaccinated for something that could be prevented by abstinence."

Should adult women be vaccinated?

Speakers agreed that the initial focus in HPV vaccination will be adolescent girls (age 12-14), but they also warned that adult women are likely to want to be vaccinated. NCI's Dr. Schiller said, "It makes sense to vaccinate just women…There is no evidence of protection in men. Men may not be protected as well as women, but inclusion of genital warts (protection) would make the vaccine more attractive to men." Another speaker said, "It will be difficult to deny a safe and highly effective vaccine to older, sexually active women…We need to consider vaccinating adult women…Adult immunization has not received the same emphasis as childhood vaccines… And I think women are going to ask for vaccination."

Should we vaccinate women with a prevalent infection?

A speaker said, "This is a dilemma…and it will become more and more of an issue. Currently, there are no good treatment options for these women. Waiting won't be satisfactory to these women…It will be difficult to deny these women a safe vaccine, even if the vaccine did nothing for the current infection. But there are three things it might do:

- Prevent new infections by other (HPV) types for which the corresponding VLPs are in the vaccine.
- Prevent successive rounds of auto-inoculations and thus potentially decrease or inhibit progression.
- Render women non-infectious to new partners by neutralizing their shed virions. No one has studied this yet.

However, the HPV vaccine probably won't do anything to alleviate a lesion a woman already has. A speaker said, "Most of us feel the vaccine will do nothing to get rid of established lesions."

Cost

Eighty percent of cervical cancers occur in developing countries, but the Merck and Glaxo vaccines are likely to be too expensive for widespread use in those countries. Dr. Schiller said, "I think it will be difficult to develop a sustainable vaccine program with the current vaccines because they are:

1. Expensive to produce.
2. Expensive to distribute because they require needle injection and cold chain.
3. Complex logistics, with three injections over six months."

Developing countries may find more utility in second generation vaccines, which should be easier to administer, less expensive, and offer protection against more types (of HPV). Dr. Schiller said, "The best for second generation vaccines are manufacturers in countries of intermediate development, such as India, Brazil, China, or Indonesia…In the U.S. and developed countries, there will be a cohort of 12-year-olds that get vaccinated every year, and initially, there will be a bolus of adult women. Once that bolus is over, then the manufacturers could use the capacity for less developed countries – at a cheaper price, perhaps."

DIAGNOSTICS

A CDC poster reported on HPV testing in the U.S. in 2004. Researchers sent surveys to 5,388 healthcare providers after the new HPV guidelines were approved by ACOG and the American Cancer Society. Those guidelines called for:

- HPV should be collected at the time of Pap testing in women age ≥30.
- Women with a normal Pap plus positive HPV test should have more frequent Pap tests.
- Women with a normal Pap and a negative HPV test could have an extended Pap interval (≤3 years).

The response rate was very high, with 82% of the surveys returned. Of these, 3,364 met the criteria for participation. Among the findings: 78% use liquid cytology, and 35.4% use conventional with or without liquid cytology.

CDC Study on HPV Testing in the U.S. in 2004

Question	OB/GYN	Family practice doctors	Physician assistants	Internal medicine	Nurse midwives	Overall
HPV test used for Pap abnormalities	91%	53%	60%	37%	85%	57%
HPV as adjuvant (run simultaneously with Pap test)	37.3%	19.3%	N/A	10.2%	26.0%	20.8%

CDC Study on HPV Testing in the U.S. in 2004

Question	Overall response
Type of cytology used	
Liquid	78%
Conventional with or without liquid	35.4%
HPV Test used for Pap abnormalities	
ASCUS	98%
ASC-H	90% *
LSIL	78% *
HSIL	68% *
HPV as adjuvant test by age	
Women <30	55% **
Women ≥30	29%
Patient Consent	
Seek patient consent before HPV testing	28%-36%
Tell patients about HPV test	48%-59%
Explain relationship of HPV test to Pap test	58%-63%
Explain HPV test detects an STD	59%-64%

* The guidelines call for these women to go immediately to colposcopy instead of having an HPV test.

** This is contrary to guidelines.

There was an undercurrent of concern about Digene and its marketing practices at the meeting. Sources predicted Digene is incurring problems with professional organizations, opinion leaders, even government agencies over the print and broadcast advertising campaign that it is running in three cities (Atlanta, Baltimore, and Philadelphia) for its Hybrid Capture 2 HPV assay. The ads have headlines like:

- "You are not failing your Pap smear, but it might be failing you."
- "If you are a gambling woman, then getting a Pap test is just fine."

In the fine print, the ads go on to explain the benefits of doing both a Pap smear and HPV testing at the same time. However, the concern is that the ads will send the wrong message, that they will lessen confidence in Pap tests and/or encourage women to believe HPV testing should be used instead of a Pap smear.

Comparison of Roche and Digene HPV DNA Assays

Feature	Digene Hybrid Capture 2	Roche Amplicor HP	Roche Linear Array HPV
Types of HPV measured	13	13	37
Liquid cytology sample	4 ml	.025 ml	.025 ml
Grayson	Yes	No	N/A
FDA status	Approved	Expected to be submitted to FDA in late 2005	Expected to be submitted to FDA in late 2005
European status	CE Mark	CE Mark	CE Mark expected in 2Q05
Method	Hybrid capture	PCR	PCR

A Digene sales rep defended the ads, saying focus groups told them this approach is what would get the attention of women. She called the ads "disease-state education" designed to "raise awareness." She added, "I don't think they will decrease Pap use. We are not suggesting our HPV test replace the Pap test…ACOG has endorsed using the two tests together in women ≥30 years old."

Roche's HPV typing test is expected to be approved in the U.S. in late 2005, but the market is big enough for two players. According to a CDC survey, only about 21% of eligible women are getting both a Pap smear and an HPV test at the same time. Sources at both Digene and Roche predicted that it will be "years" before HPV vaccination affects the volume of HPV testing.

Asked what the advantages are of Digene's test over the Roche test, a Digene sales rep said, "Our test avoids the contamination issue with PCR. We don't need unidirectional workflow. *(NOTE: This would mean the Digene test is faster to run.)* We have more clinical data than Roche, and we have a reputation in HPV."

MISCELLANEOUS

BIOMAS'S AS-101 [ammonium-trichloro (dioxyethylen-0,0') tellurate]

This Israeli company has developed a topical cream to treat perianal and genital warts. An open label, multicenter, Phase II trial in Israel of 20% AS-101 in 31 patients found the cream cured a significant number of patients, and there was a low recurrence rate (5.5%). The company hopes to get an IND and start a U.S. Phase II trial by the end of 2005. The cream would compete with 3M's Aldara (imiquimod), which currently is the only FDA-approved topical treatment for these conditions.

Phase II Trial of AS-101

Measurement	Genital warts n=21	Perianal warts n=15
Complete cure rate	78.0%	68.0%
Treatment failures	11.0%	23.0%
Withdrew	11.0%	9.0%
Recurrence		
1-3 months	0 of 16	0 of 5
3-6 months	0 of 7	2 of 5
6-9 months	0 of 4	0 of 4
9-12 months	0 of 2	0 of 1
Total	0 of 21	2 of 15
Duration of complete cure		
Mean duration	32 days	63 days

♦