DIAGNOSTIC TECHNOLOGY

Committee Secretary
Australian Senate Community Affairs Reference Committee
Parliament House
CANBERRA ACT 2600

# SENATE COMMUNITY AFFAIRS REFERENCES COMMITTEE

## INQUIRY INTO GYNAECOLOGICAL HEALTH IN AUSTRALIA

Thank you for the opportunity to submit a response to the petition "Gynaecology Health in Australia" tabled in the Senate in November 2005.

Diagnostic Technology Pty Ltd is the exclusive representative of Digene Corporation, a manufacturer of a molecular based high risk HPV DNA test. Over the last decade the company has been active in the introduction and utilisation of HPV DNA tests into clinical practice. The test is widely available in Australia, but is only reimbursed under a limited application. The company has been the applicant of two Medical Services Advisory Committee (MSAC) applications, "The use of HPV DNA tests for the triage of Low Grade Epithelial Abnormal Pap smears" and "The use of HPV DNA tests for screening of women for cervical cancer", both of which were unsuccessful. The company was invited to participate in an application submitted by the Public Screening Branch of the Department of Health for the use of HPV DNA testing as a test of Cure. The test of cure is now reimbursed by Medicare and has been incorporated into the NHMRC guidelines for the management of women previously treated for high grade cervical disease. The company also made submissions to the recent NHMRC review of guidelines for the screening program.

The respondent wishes to make comment on the following terms of reference listed by the Committee;

> (a) Level of Commonwealth and other funding for research addressing gynaecological cancers;
>
> (b) Extent, adequacy and funding for screening programs,

The respondent believes that there is a serious lack of research being carried out or planned, to investigate a wider utilisation of the HPV DNA test. As early as 2001, reports generated within the Department of Health and Aged Care were recommending research into the potential inclusion of HPV DNA testing into the screening program, no research has been forthcoming.

Some of the internationally recognised advantages for the inclusion include;

- Extending the period between Pap smears to a minimum of 5 years,
- improvements of cervical disease detection to levels close to 100% (currently the national program cites a 90% protection),
- clarification of potential risk of underlying disease after an initial low grade Pap smear
- reduction in screening costs.

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# An Overview of HPV and Cervical Cancer

## *HPV Test and Screening*

- Although cervical cancer is not a leading cause of cancer death, it is almost entirely preventable –
- Human papillomavirus (HPV) is recognised as the primary causative agent – HPV DNA has been found in more than 99% of cervical cancers
- A test specific for the HPV types (High Risk HPV) that are responsible for cervical cancer has been available commercially for over 8 years
- Sensitivity of a single Pap smear at best is 80%, but is generally considered to be in the range of 65-75%. The sensitivity of a single HPV DNA test is between 92-98%.
- The incorporation of HPV DNA testing into the primary Cervical Cancer Screening program has a number of potential benefits:
    - 1) It can reduce the potential of a 'false negative' result;
    - 2) It can be used as a prognostic indicator of future risk, thereby identifying who should consider more frequent testing
    - 3) It can potentially increase the interval between Pap tests for HPV negative women (from every two years to every five years)
- Key points identified in the Cancer Strategy Working Group (Commonwealth Department of Health and Aged Care) "Priorities for Action in Cancer Control, January 2001", include:

  **"It is estimated that a change in the screening interval from two to three years would potentially yield savings of $50.6 million per year"**

  **"Developments in human papilloma virus (HPV) testing are likely to have a major influence on cervical screening in the future.This virus is believed to play an important role in causing more than 95 per cent of cancers of the cervix (Walboomers et al 1999). It has been suggested that combining a test for HPV infection of the cervix with the Pap test when screening for cervical cancer could identify a very low risk group of women (those negative on both tests) who would require screening once every five years or even less frequently. Such a development could make a change in screening interval more acceptable to women and to health practitioners, but might also make the present proposal obsolete. However, further research is required before changes to screening policy could be made based on HPV testing."**
- It is estimated that Pap screening alone can, potentially, prevent 92.5% of cervical cancer cases, however, despite the 'successful' screening program, approximately 210 Australian women, or 25% of the total number, who are diagnosed with cervical cancer each year come from a group that are considered to have been adequately screening as outlined by the NHMRC. There is therefore some significant advantages to be gained with better screening tests being implemented

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- It is estimated that up to 80% of sexually active women have been **exposed to HPV** at some point in their lives
- HPV, which is usually subclinical (i.e. no symptoms), is amongst the most common sexually transmitted infections
- HPV infections are generally short-lived, but persistent infections are found in 5-10% of women 35 years of age and over. Persistent infection is associated with increased risk of neoplastic progression (i.e. epithelial abnormalities)
- Presence of HPV is not indicative of cervical disease – however, the absence of HPV is a definitive prognostic indicator of low risk (i.e. risk of developing cervical cancer if you are HPV negative is negligible)

## *Cervical Cancer Screening*

- The primary objective of the national Cervical Cancer Screening Program is to identify individuals at greatest risk of developing cervical cancer
- The objective of the Pap Test, introduced 50 years ago, is to detect and treat high-grade pre-cancerous lesions before they progression to cancer
- Current guidelines call for routine Pap smear tests every two years for women who have no symptoms - more regular screening is recommended for women with low grade epithelial abnormalities (LSIL) as defined by a previous Pap test
- The Pap test is based on subjective (visual) assessment of cervical cell specimens and therefore requires highly trained / skilled technicians to assess specimens – abnormal or questionable samples are further referred to a qualified cytopathologist for confirmation.
- The subjective nature of assessment introduces an inherent weakness - it is estimated that approximately 30% of smears are subject to errors in sampling and interpretation (e.g. 20% of women with high grade disease have had one or more normal and no abnormal smears in the previous three years, Sung HY et al. Cancer 2000; 88: 2283-89.)
- The Pap test does not test for HPV DNA,
- The screening program also detects low-grade lesions, many of which will not progress to cervical disease / cancer, nevertheless, many will undergo further precautionary tests and procedures unnecessarily
- The Pap test is not a definitive prognostic indicator of ‘low risk’ –women, therefore, require regular Pap smears to maintain significant levels of protection.

## *HPV DNA Test*

- Digene / Diagnostic Technology has submitted two separate applications to the MSAC for the reimbursement of a HPV DNA test. The test detects the human papillomavirus, which is responsible for more than 99% of cervical cancers.
- It is the Digene / Diagnostic Technology’s contention that the HPV DNA test has the potential to improve the effectiveness of the NCSP by:

  - Providing a definitive prognostic indicator of risk, and therefore a guide to disease management, particularly in a situation of an initial LSIL Pap smear
  - Potentially increasing the screening interval, thereby delivering significant cost savings
  - Potentially reducing even further the number of women developing or dieing from cervical cancer
  - potentially increasing the current sensitivity of screening (i.e. the ability to confirm the presence of disease). Furthermore, the standardised and highly automated nature of the test introduces a reduced reliance on sample quality; is free from observer error; and is highly reproducible

- The HPV DNA test alone is not a definitive indicator of disease. However, by combining the information provided by a Pap smear and a HPV DNA test, the physician can better determine the relative risk and therefore the appropriate course of treatment
- The U.S. Food and Drug Administration has approved Digene's HPV test (Hybrid Capture® 2 HPV DNA test) for use as a cervical cancer screening test alongside the Pap smear for women over 30 years of age. This application has now also been endorsed by the American College of Obstetrics and Gynacologists, and the Amercian Cancer Society is recommended extension of screening intervals to three years This alone would reduce the number of Pap smears performed in Australia by 900,000 over a 6 year period.
- There are numerous clinical publications that support the role of HPV DNA testing, confirming that by performing both a Pap smear and a HPV DNA test together 100% of the women with serious cervical pre-cancer will be identified earlier than is currently achieved with Pap test alone.
- Low-grade lesions that return a negative HPV test result suggest a significantly reduced risk for the development of cervical cancer – such women would, therefore require a reduced frequency of Pap tests
- "The present Pap smear test is susceptible both to false positive and false negative results. A normal Pap smear does not mean that the patient can be reassured that she has no abnormality, particularly when she has symptoms e.g .discharge, bleeding etc. ***There is a place for the development of new technologies to increase the effectiveness of detection. New technologies would need to be proven within the Australian environment before being considered for widespread implementation***" (AMA Position Statement, Cervical Cancer Screening, 1999)
- Potentially HPV DNA testing as a self sample test could have major impacts on the outcomes of screening for indigenous populations.

## Medical Services Advisory Committee

In 2002, the Medical Services Advisory Committee (MSAC) completed a literature review and cost-effectiveness assessment of the Hybrid Capture-II (HC-II) test in women with a cytological prediction of low-grade abnormality. The review concluded that there was insufficient evidence about the use of this test to support public funding at the time of the review (MSAC 2002). It did however note that using HPV DNA was more sensitive for the detection of high grade disease than cytology.

**MSAC suggested however that further research into the cost-effectiveness of HPV testing in the Australian setting would be useful, particularly for older women, but this research has not been forthcoming.**

MSAC concluded that should the underlying incidence of High Grade disease in the Low Grade Pap smears be over 10%, then HPV would be more efficient. As it turns out, the 1999 data subsequently made available shows an overall rate of disease to be 9.38% after only two years of follow up. It is logical to suggest that over time the total amount of disease would be higher.

***Excerpts from the Summary of the MSAC Report on HPV DNA Triage is reproduced below:***

***Effectiveness***

*…./..However, while HPV testing appeared to be more sensitive, but less specific, than cytology, the current evidence demonstrated that HPV testing cannot be recommended for widespread implementation.*

***Cost effectiveness***

*It may be appropriate fo**r further research to** be conducted to permit investigation of whether HPV testing is cost-effective in a sub-group of the overall population of women with cytological prediction of a low-grade abnormality (e.g. older women).*

Data from an internationally recognised study performed by the National Cancer Institute in the USA concluded that HPV DNA testing was more efficient and effective than cytology. This study was based on a two year follow up of women with initial LSIL Pap smears. Data from this study is reproduced below. The recent NHRMC review of the guidelines for Low grade management cited this study in the guidelines; however they used the evidence to support the fact that over time cytology detected sufficient levels of serious disease. No recognition of the fact that HPV DNA was significantly more sensitive was noted. The NHRMC guideline review process did not assess the potential of HPV DNA testing, rather they cited the fact that MSAC had reviewed this utility some 3 years before, Although more evidence had since become available yet HPV was still not considered as an option during the review process.,

**Detection of CIN 3 after ASCUS in ALTS**

| | Immediate colposcopy (IC) 1163 patients | HPV triage 1161 patients | Cytologic follow-up (CR) 1164 patients | Total CIN 3 3488 patients |
|---|---|---|---|---|
| **After initial Pap smear** | 58 (59.8%) | 76 (75.2%) | 44 (40.7%) | 178 (58.2%) |
| **During 2 years of follow up** | 14 (14.4%) | 6 (5.9%) | 22 (20.4%) | 42 (13.7%) |
| **After 2 years** | 25 (25.8%) | 19 (18.8%) | 42 (38.9%) | 86 (28.1%) |
| **Total** | 97 (100%) | 101(100%) | 108(100%) | 306 (100%) |

**Detection of CIN 3 after LSIL in ALTS**

| | Immediate colposcopy (IC) 673 patients | HPV triage 224 patients | Cytologic follow-up (CR) 675 patients | Total CIN 3 1572 patients |
|---|---|---|---|---|
| **After initial Pap smear** | 64 (62.7%) | 28 (68.3%) | 34 (36.6%) | 126 (53.4%) |
| **During 2 years of follow up** | 20 (19.6%) | 4 (9.6%) | 25 (26.9%) | 49 (20.8%) |
| **After 2 years** | 18 (17.6%) | 9(22.0%) | 34 (36.6%) | 61 (25.8%) |
| **Total** | 102 (100%) | 41(100%) | 93(100%) | 236 (100%) |

## Performance of Cytology

To highlight the inherent inadequacies of cytology one only has to review the performance standards. While Australian cytology is believed to be one of the best in the world, it is clear form the standards that the best possible accuracy that can be expected in 80%. Summary of some of the outcomes from the performance standards from 2001 are below.

***In the 2001 Performance Standards for Australian Laboratories reporting cervical cytology 15% of of the laboratories were outside the standard for reporting not more than 20% of women with a cytological diagnosis of CIN 3 where on review of a previous negative smear there were cells consistent with or suggestive of HSIL.***
***7% of laboratories (n=5, representing 52,000 smears) were outside the standard for review of preceding negative cytology in women with histological diagnosis of CIN 3***
***15% of laboratories (n=12 representing 81,000 smears) were outside the standard for reliability of cytological reporting of HSIL prediction.***
***The training and quality of Auatralian cytology is essential, however, the scope and limitations of cytology have not been taken into consideration to the modeling of HSIL and cancer detection within the LSIL follow up categories***

**It has been shown in a number of published clinical studies that a single HPV DNA test has the same relevant outcome of value of at least 3 consecutive Pap smears**

- There is some indications that there is a shift in the objectives of the screening program as stated in the 'Cervical Screening in Australia 1999–2000' report (AIHW): *i.e."* ***The National Cervical Screening Program seeks to maximise reductions in incidence of and mortality from cervical cancer.*** In, *the* 2005 budget document, the Health Department document stated that the government "reaffirmed a commitment to reduce the mortality from cervical cancer".

**NHMRC Review of the Guidelines for the management of Low Grade Abnormalities**

During the recent review of the guidelines for Cervical Cancer screening there was much debate and dissention surrounding the proposed management of women with low grade Pap smear. The review group acknowledged that the underlying rate of pre-cancer that exists in the low-grade group was not of immediate concern and that subsequent Pap smears would detect the majority of underlying pre-cancer cases.

What may be of relevance to the Committee is that some local and international epidemiology experts in cancer screening believe that the proposed management guidelines will result in a significant increase in the incidence of cancer. These experts believe that between 50-150 additional cancers would develop if the new guidelines were implemented. The annual progression of 1% for pre-cancer to cancer, in absence of any intervention is the rationale for this number.

The debate on how to manage women with a recognised risk of underlying pre-cancer (9.38% of all Low Grade Pap smear predictions) caused a delay in the endorsement of the guidelines. The respondent believes there are parallels to the current debate on 'available evidence' with the Senate inquiry into Hepatitis C (HCV) and the Blood Supply in Australia. In summary the inquiry report, tabled June 2004, addressed the issue of whether or not testing for HCV, a disease with high morbidity and mortality, should have been introduced.

Of particular relevance to HR HPV testing, and indeed the management of low grade disease, is the reference during this inquiry to the precautionary principle, which is predicated on the following:

*"…even if you do not know that a problem will happen the fact that it might happen means that you would err on the side of safety and make a decision to exclude that risk." (Professor Bruce Barraclough, Chairman of the Australian Council for Safety and Quality in Health Care).*

In stark contrast to the circumstances surrounding surrogate testing for HCV in the 1980s, a reliable test, which has demonstrated in numerous studies around the world to be superior to cytology in detecting women at greatest risk of developing cervical cancer, has been available for many years, yet its utility continues not to be investigated and researched.

**Screening and the Vaccine**

It must be recognised that modelling on the potential impact of the vaccines to be available shortly shows that they have the potential of reducing cancer (when no screening pre-exists) by 50%. This decrease is based on the premise that all women naïve to HPV infection have a full course of the vaccine. Therefore screening, which is currently recognised to reduce cancer by 70% must continue if we are to maintain our current levels of cancer. It has been proposed that in the future screening by cytology will not be efficient and HPV DNA testing is the logical alternative. The impact of the vaccine will not materialise for at least 20 years after its imtroduction. Continued investment in improvements in the screening program are essential.

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# Cost Effectiveness Overview

- Economic models, across studies, show that primary screening with HPV testing alone or combining HPV and Pap testing at appropriate intervals and age is cost-effective compared to annual Pap screening.

Key Comments from the Published Studies

- "For women aged 30 years and more, every 2- or 3-year screening strategy that uses either HPV DNA testing in combination with cytology for primary screening or cytology with reflex HPV DNA testing for equivocal results will provide a greater reduction in cancer and be less costly than annual conventional cytology." (Goldie et al; Obstet Gynecol 2004;103:619 –31.)
- "The cost per life year for HPV testing alone triennially is lower than for Pap smear testing alone biennially. Costs per QALY are generally lower than costs per life year (given the reported modeling assumptions and settings). Even with inclusion of patient costs, no strategies involving HPV testing cost more than $16,600 per QALY. Adoption of the ACOG Guidelines to include HPV testing with cytology as a screening option for women aged ≥30 would therefore appear to be cost-effective." (Holmes, L Hemmett, S Garfield)
- "Both HPV DNA testing strategies, HPV triage and combination testing, were more effective than each country's status quo screening policy. Incremental costeffectiveness ratios for HPV triage were less than $13 000 per year of life saved, whereas those for combination testing ranged from $9800 to $75 900 per year of life saved, depending on screening interval… HPV DNA testing has the potential to improve health benefi ts at a reasonable cost compared with current screening policies in four European countries." [Kim et al. J Natl Cancer Inst 2005;97:888 – 95

There are many potential benefits that HPV DNA testing could bring to the Australian Cervical Cancer Screening Program. Its encouraging that it has now been accepted as a test of cure, but more research needs to be done to ascertain its full potential. The HPV Vaccine offers a wonderful opportunity to reduce cancer rates, but it will not reduce the need for screening, nor the need to continually improve the outcomes from the screening program, unless research into the broader utility of HPV testing is undertaken there will be unnecessary delay in the deployment and benefits of this technology and knowledge.

**Yours sincerely**

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Some of the references


1. The NHMRC GRG 2004 Low-grade squamous abnormalities on cervical cytology: The case for cytological surveillance.
2. The ASCUS-LSIL Triage Study (ALTS) Group. A randomized trial on the management of low-grade squamous intraepithelial lesion cytology interpretations. Am J Obstet Gynecol 2003;188:1393-1400.
3. Virologic versus cytologic triage of women with equivocal pap smears: A meta-analysis of the accuracy to detect high-grade intraepithelial neoplasia. J Natl Cancer Inst 2004;96;280-93.
4. Solomon D, Schiffman M. Have we resolved how to triage equivocal cervical cytology? J Natl Cancer Inst 2004;96;250-1.
5. The ASCUS-LSIL Triage Study (ALTS) Group. Results of a randomized trial on the management of cytology interpretations of atypical squamous cells of undetermined significance. Am J Obstet Gynecol 2003;188:1383-92.