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PERSPECTIVE

The new screening program to prevent cervical cancer using HPV DNA: getting the balance right in maintaining quality

Suzanne M Garland[1,2,3*], Wayne Dimech[4], Peter Collignon[5,6], On behalf of the Australian Clinical Microbiologists Infectious Diseases Group[7,8,9,10,11,12,13,14,15], Louise Cooley[7], Graeme R Nimmo[8,9], David W Smith[10,11], Rob Baird[12], William Rawlinson[13], Anna-Maria Costa[1,14] and Geoff Higgins[15]

[1]*Department of Microbiology and Infectious Diseases, Royal Women's Hospital, Parkville, Australia*
[2]*Infection and Immunity Murdoch Children's Research Institute, Parkville, Australia*
[3]*Department of Obstetrics and Gynaecology, University of Melbourne, Parkville, Australia*
[4]*National Serology Reference Laboratory, Australia (NRL), Fitzroy, Australia*
[5]*Infectious Diseases and Microbiology, Canberra Hospital, Garran, Australia*
[6]*Medical School, Australian National University, Australia*
[7]*Department of Microbiology and Infectious Diseases, Royal Hobart Hospital, Hobart, Australia*
[8]*Department of Microbiology, Pathology Queensland Central Laboratory, Herston, Australia*
[9]*Department of Microbiology, Griffith University School of Medicine, Southport, Australia*
[10]*Department of Microbiology, PathWest Laboratory Medicine WA, Nedlands, Australia*
[11]*Faculty of Health and Medical Sciences, University of Western Australia, Nedlands, Australia*
[12]*Territory Pathology, Infectious Diseases, Royal Darwin Hospital, Department of Health and Families, Tiwi, Australia*
[13]*Virology, Serology and OTDS Laboratories, NSW Health Pathology, Randwick, Australia*
[14]*Department of Microbiology, The Royal Children's Hospital, Parkville, Australia*
[15]*Microbiology and Infectious Disease, South Australia Pathology, North Terrace, Australia*

**Correspondence to: Suzanne M Garland, Department of Microbiology and Infectious Diseases, Royal Women's Hospital, Locked Bag 300, Parkville, Vic 3052, Australia. E-mail: suzanne.garland@thewomens.org.au*

Abstract

Along with the reduction in human papillomavirus (HPV) infection and cervical abnormalities as a result of the successful HPV vaccination program, Australia is adopting a new screening strategy. This involves a new paradigm moving from cervical cytological screening to molecular nucleic acid technology (NAT), using HPV DNA assays as primary screening methodology for cervical cancer prevention. These assays must strike a balance between sufficient clinical sensitivity to detect or predict high-grade cervical intraepithelial lesions, the precursor to cervical cancer, without being too sensitive and detecting transient infection not destined for disease. Ensuring the highest quality HPV NAT is thus a priority in order to reduce the possibility of falsely negative screens and manage the risk associated with false positive HPV NAT test results. How to do this needs informed discussion and ongoing refinement of the screening algorithm. This is of relevance as more countries move to more sensitive HPV NAT tests for secondary prevention of cervical cancer and as more HPV assays become available.

Keywords: HPV; nucleic acid technology; quality control; quality assurance

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Introduction

Australia is leading globally the acceptance of prophylactic human papillomavirus (HPV) vaccination, with the implementation of a national government-funded, gender-neutral approach, and vaccinating all girls and boys 12–13 years of age, as an ongoing school-based program [1]. The program has been embraced by the

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community and by clinicians. This has translated into reductions in HPV vaccine-related genotype infections of ~86% in comparison with those prior to the vaccination program [2]. Clinically evident disease manifestations, such as genital warts, have been reduced by >90% [3] following the vaccination program, and high-grade cervical dysplasia (high-grade squamous intraepithelial lesion; HSIL) by 47% [4]. This is underpinned by the increasing and high vaccination coverage of 77% for three doses in young girls 12–13 years of age [5,6], 86% for one or two doses [5,6] and of approximately 65% for the catch-up program in females aged up to 26 years, which ended in 2009 [7]. Herd protection has been reported for HPV infection, exemplified by lower rates of genital warts in unvaccinated females and males [2,3,8].

The Australian Government has embraced new data collection systems for cervical cancer prevention strategies due to the reductions in HSIL abnormalities in vaccinated women [4,9], with a change to bring in the more sensitive nucleic acid technology (NAT) for HPV DNA for primary screening. The 'Renewal' program [10] recommended changing from cervical cytology (first described by Dr. Papanicolaou in 1928 [11], and used since that time [12]) to NAT screening. NAT is more sensitive and less subjective, particularly in vaccinated cohorts, where there are fewer infections and consequently less disease. 'Renewal' was introduced on 1 December 2017. Netherlands was the first country to adopt HPV DNA primary screening and did so in early 2017 [13]. They did so by combining the number of laboratories into five national laboratories, with all being required to use the same HPV DNA assay (the Cobas 4800; Roche Diagnostics, Indianapolis, IN, USA), in combination with a completely harmonized laboratory workflow. The Dutch have an organized quality assurance program (QAP) that has been set up centrally for HPV testing in the Dutch cervical cancer screening program (Dr. Rob Schuurman, Senior Clinical Microbiologist and National Reference Officer HPV for the Dutch Cervical Cancer Screening Program, personal communication). Other countries worldwide are planning implementation [14,15].

Prior to 'Renewal', general practitioners were surveyed through the Royal Australian College of General Practitioners (RACGP) [16]; nurse practitioners through the Australian College of Nurse Practitioners (ACNP) [16]; obstetricians and gynecologists through the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) [17]; and the general public through the Young Female Health Initiative (YFHI) study [18]. These groups expressed concerns about the potential impact of the delay in screening age, the decline in attendance for sexually transmitted infection screens and the change to 5-year gap in screening [14–18]. These findings highlighted gaps in knowledge among health practitioners and young women that need to be addressed to ensure this paradigm shift is fully embraced.

'Renewal' examined the latest evidence-based data on cervical cancer prevention strategies, taking into account the effects of HPV prophylactic vaccination [10]. It recommends that cervical screening be delayed until 25 years of age, with high risk (HR) HPV NAT including specific identification of genotypes HPV16 and HPV18 being performed every 5 years until 74 years of age irrespective of HPV vaccination status. Those positive for HR-HPV are to be followed up in accordance with an algorithm of care, utilizing reflex cytology and/or colposcopy, where indicated [19]. This approach is based on a large body of evidence from randomized controlled trials, which have shown that primary HPV NAT assay screening is more sensitive than cervical cytology in recognizing women at risk of cervical cancer and its precursor lesions [20–22]. In Australia, given the relatively high coverage of vaccine in the catch-up cohort, females eligible for the vaccine are now 38 years or younger. As a result, it is timely to change to HPV NAT primary screening, as the screened populations will now include many vaccinated individuals with varying HPV prevalences and age-group profiles. The recently published COMPASS pilot study has already demonstrated the value of NAT screening in the population that is age-eligible for vaccination in Australia, showing that a positive HPV DNA NAT test is significantly more sensitive in detecting HSIL than cytology [23].

The National Pathology Accreditation Advisory Council (NPAAC) sets standards for all laboratory tests in Australia [24,25], and those for the performance of NAT have been in place for many years, and emphasize the importance of quality assurance (QA) and quality control (QC). These have allowed the establishment of high-quality NAT tests for the diagnosis of a wide range of organisms, while also ensuring that they can be delivered appropriately and efficiently across a range of population groups. However, the more recently introduced standards for NAT for HPV DNA tests have added the requirement that only laboratories testing a minimum of 2000 samples per batch period should perform HPV NAT screening [24]. The batch period is determined by the specimen storage times as specified by the manufacturer of each of the HPV tests for the type(s) of collection medium used and/or expiry time for liquid-based cytology (LBC) medium, whichever is shorter, thus allowing

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for retesting of the 2000 samples if required. This approach is unique, in that a mandated minimum number of samples has not been found necessary for any other infectious disease NATs, including Class 4 organisms such as HIV. This requirement increases the burden on laboratories carrying out testing, increases the cost of testing, restricts the ability to adjust testing workflows to best meet the service requirements, and threatens test availability and timeliness. We believe alternative measures are available, as detailed below, to ensure the accuracy and precision of NAT for HPV. There might be an argument for HPV DNA testing to be preferentially undertaken by larger laboratories that have the option of triaging with cytology, but purely for practical, economical, and efficiency reasons given the requirements for various QC and QA. However, stipulating 2000 samples for DNA NAT tests per batch does not have a good rational basis. The important factor is whether there is appropriate clinical sensitivity and acceptable imprecision in the assay used that is sufficient to minimize the risk of missing high-grade lesions.

All *in vitro* diagnostic devices (IVDs) used for medical testing, including diagnostic molecular tests for HPV, require a range of QA processes to ensure they are fit for purpose. In Australia, IVDs must be registered on the Therapeutic Goods Administration's Australian Registry of Therapeutic Goods (ARTG) under one of four classes [26]. Currently, HPV NAT assays are classified as Class 3 devices, which are tests for conditions having a moderate public health risk or high personal risk. Manufacturers or sponsors must demonstrate the IVD is fit for purpose and conforms to the essential principles. Once registered on the ARTG, the IVD can be used for diagnostic testing in Australia. Laboratories using the IVD must be accredited to standard (ISO 15189) and the NPAAC guidelines, as assessed by the National Association of Testing Authorities/Royal College of Pathologists of Australasia (NATA/RCPA). Laboratories achieve NATA/RCPA accreditation for the particular test by verifying the IVD in their laboratory prior to implementation, and their staff must demonstrate competency and successful participation in a range of QA processes.

First, all IVDs should have appropriate positive and negative controls provided by the kit manufacturer and for every run the results for these tests must be within the manufacturer's predetermined limits before results can be released [24].

Second, participation in an external quality assessment scheme (EQAS)/QAP is mandatory for laboratories accredited to quality standard ISO 15189 [25]. The RCPA distributes a biyearly or quarterly HPV NAT QAP to laboratories throughout the Pacific region [27]. Annually, this QAP comprises a total of 12 samples consisting of a mixture of negative or 'no sample', low-risk HPV, high-risk HPV (including HPV16 and HPV18) and 'other' HPV types. In addition, the National Serology Reference Laboratory, Australia (NRL), provides the HPVN435 EQAS where, three times each year, participating laboratories receive a panel of five samples consisting of a mixture of positive and negative samples, including high-risk HPV16 and HPV18/45. For both programs, laboratories test the samples and report the reactivity and the genotype to the QA provider. The results are analyzed and compared with the reference or consensus results and a report is issued to the participating laboratory. It is essential that these programs are utilized to ensure appropriate accuracy, precision, and detection limit of the NAT assay [24]. Participation in an EQAS/QAP is mandatory and participation and performance are monitored by NATA/RCPA as part of the ongoing laboratory assessment process. While the selection of the provider of the program is voluntary, laboratories are encouraged to participate in more than one. However, EQAS/QAPs are periodic and only provide a snapshot in time, not continuous monitoring of test performance.

Lastly, continuous monitoring of testing and participation in a real-time QC program, similar to programs used to monitor testing for other infectious disease agents (e.g. HIV), is required under the draft NPAAC guidelines [24]. Laboratories test an externally sourced QC sample, which has reactivity close to the assay's lower cutoff or limit of detection, with each test run and monitor the reactivity of that sample over time to ensure consistency of performance. The results from a participating laboratory can be compared with those from other laboratories using the same assay and QC sample. This process provides real-time monitoring of assay sensitivity by the QC provider, and results that exceed expected limits can be immediately investigated [28,29]. Daily use of an externally sourced nonmanufacturer supplied control is also mandated in the draft standard [24].

Use of these three different types of QC material provides a robust mechanism by which to monitor the analytical performance of the molecular assays. However, the standard goes beyond this and requires the participating laboratories to provide HPV positivity rates to a national database for comparison of the detection rates of HPV. If the HPV detection rates are more than two standard deviations (SDs) outside the mean for an age-stratified reference population, retesting of samples is required irrespective of the results of

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the NAT QC and QA data. The report states that a sample size of 2000 is required to make meaningful comparisons of HPV positivity rates. However, this ignores the effect of differing HPV prevalences between populations being tested. This will vary with sexual behavior, age [30], and whether public health HPV vaccination programs are in operation and need to be taken into account in assessing screening performance [31]. These are important in determining the risk of false positive or false negative results, and it is routine laboratory practice to take into account these potential differences in pretest probability and adjust the test interpretation accordingly. The additional requirements in place for the HPV DNA NAT mean that, even if the analytical performance of the test is satisfactory, testing laboratories that have percentage positive findings outside a defined range will be considered to have a testing 'anomaly'. They will be required to record this as an 'anomaly'/disparity and to carry out further investigations even if the test is actually performing according to expectation. The requirement does not take into account that the 'defined range' may not be appropriate for the population group being tested. The consequence is unnecessary resources being devoted to the investigation and possibly repeat testing on their batch of over 2000 stored samples, resulting in a substantial additional drain on resources. More importantly, this approach may create a false impression of poor test performance, leading to a loss of health practitioner and public confidence in the testing by the public. It is worth noting that no other country has set an absolute number of specimens/tests that a laboratory must perform in order to be permitted to undertake HPV DNA NAT screening.

Laboratories already use three methods of QC and QA, and include an external QC sample each time they carry out a batch of testing. Under these circumstances, the requirement for initial testing of 2000 samples before commencing the screening service, the need to retain the last 2000 samples, and the setting of target detection rates are unnecessary, wasteful, and possibly detrimental to the reputation of the screening program. If combined with the implementation of a national system that could rapidly identify any loss of sensitivity of the assay, we would suggest that the requirement for retention of 2000 samples for retesting if the HPV prevalence rates are outside of two SDs is excessive.

It will be important to review findings with these new technologies with time and modify guidelines accordingly. This is particularly so as there are multitude of HPV tests currently available on the market [32]. What is critical in the performance of any HR-HPV test as a primary cervical screen is its ability to detect viral infections associated with lesions that are cervical intraepithelial neoplasia (CIN) grade 2 or worse (CIN2+), and thus to be able to separate cervical lesions requiring further clinical intervention from transient infections that just require follow up. Guidelines and minimum requirements have been established by Meijer *et al* [33] for novel HPV tests with respect to sensitivity, specificity, and reproducibility relative to the clinical performance of two clinically validated tests: Hybrid Capture 2 (HC2 – Qiagen, Gaithersburg, MD, USA) and GP5+/6+ polymerase chain reaction (PCR) enzyme immunoassay (GP5+/6+ PCR EIA, Diassay, Rijswijk, The Netherlands) [33]. Of the large number of HPV tests available and increasing on the market, very few have been validated according to these criteria. One step toward addressing this situation is the evaluation being undertaken by an international initiative, VALGENT (VALidation of HPV GENotyping Tests). The VALGENT framework was created to support the clinical performance evaluation of HPV tests, including those with genotyping capabilities [34,35].

Conclusion

Australia is leading the way in introducing a comprehensive public health HPV vaccine program for young people, as well as implementing surveillance that allows us to measure vaccine impact and effectiveness in a real-world setting.

Australia is also a leader in moving to a more sensitive cervical cancer prevention strategy, using HPV NAT for primary screening. It is imperative that we adopt the best QA and QC measures to accompany the introduction of these new assays. The best QA measures must include continuous testing for low level clinically relevant positive HPV test results, which are ideally monitored continuously by the laboratory doing the test and by external QA bodies. In order to achieve optimal outcomes, we certainly need the added skills and expertise of clinical microbiologists. NPAAC mandates a combined report by both specialties [24]. Working closely together, the two specialties should achieve the best outcomes for screening for underlying risk of cancer development, and the best standard of care for the women of Australia.

Ethics approval was not required for this paper as no study subjects were used, and no patient data was accessed. This article is the opinion expressed by all authors in relation to new changes to screening for

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cervical precancer by utilizing HPV DNA assays from a microbiological viewpoint.

Author contributions statement

SG, WD, and PC constituted the core writing team, who conceived the idea and drafted the manuscript as an opinion piece. The rest of the authors' contributions included review and critique of the various manuscript versions and all approved the final version.

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