Guidelines for handling HPV positivity rates

Purpose
To provide pathology laboratories, the National Cervical Screening Program (NCSP) and the Therapeutic Goods Administration (TGA) guidance on handling the HPV positivity rate quality assessment process under the *Requirements for Laboratories Reporting Tests for the National Cervical Screening Program (Second Edition 2019)*.

Background
The *Requirements for Laboratories Reporting Tests for the National Cervical Screening Program (Second Edition 2019)* (the Cervical Requirements) prescribe, *"the minimum requirements for best practice for the use of Human Papillomavirus nucleic acid testing as the primary screening method for cervical screening with reflect liquid based cytology in cases of positive oncogenic HPV types."*

The Cervical Requirements came into effect on the 27 September 2019 and replaced the First Edition (2017) Cervical Requirements.

This guidance document provides directions for laboratories on the quality assessment process for handling HPV positivity under the 2019 Cervical Requirements.

Quality assessment process for handling HPV positivity

Pathology laboratories must follow the directions outlined in the Cervical Requirements at **Standard S5.5** and **Standard S5.6** as detailed below.

Quality Measures for HPV NAT (applies to all testing settings, including screening, test of cure and self-collected specimens)

S5.5 *If a reagent batch failure is detected by a laboratory, the laboratory must investigate the cause and take appropriate remedial action.*

C5.5 *If the batch failure relates to a reagent failure with the potential to impact on the quality of testing of other providers, the laboratory must notify the TGA and NCSP immediately so that other users can be notified.*

Laboratories **must** notify the NCSP via the Australian Government Department of Health through the NCSROperations@health.gov.au inbox. A notification template laboratories can complete and submit is provided in **Attachment A.** The template outlines the required information, including the date of reagent batch failure, reagent data (lot numbers and expiry dates) and contact details.

Laboratories **must** also notify the TGA via the medical device Incident Reporting and Investigation Scheme (IRIS) through the following link: Report a medical device adverse event (medical device health professional). All relevant fields within the form must be completed in order for the notification to be accepted.

IRIS is used by the TGA to manage all reports of adverse events or problems associated with medical devices, including in vitro diagnostics. Reports are automatically entered into

the publicly searchable Database of Adverse Event Notifications (DAEN). Batch related failures may result in a recall action which would be initiated by the supplier of the product in conjunction with the TGA.

The notification to the TGA and NCSP must be undertaken **immediately** so that appropriate action can be taken (if needed).

Quality Measures for HPV NAT, screening specimens only

S5.6 *Laboratories must compare their rates of HPV detection in screening tests with the rates most recently reported by the NCSR for internal benchmarking purposes.*

C5.6(i) *The NCSR will use the routinely submitted data to produce a periodic age stratified data set (including mean and 95% confidence interval) compiled from data from all screening HPV testing throughout Australia.*

C5.6(ii) *If the laboratory's overall HPV positivity rate in screening tests is not within the 95% confidence interval, the laboratory must investigate the cause (refer to Appendix A).*

[Please note, an excerpt of Appendix A is provided in **Attachment B].**

C5.6(iii) *Monitoring of HPV positivity and investigation if required must occur at least quarterly and the results or outcomes recorded.*

a) Laboratories should consider the implementation of internal benchmarks using control charts, such as P-charts, for ongoing monitoring of the laboratory-specific positivity rate. The *Requirements for Testing of Microbial Nucleic Acids*[1] also provides additional advice on operational validation and ongoing monitoring of assays.

b) The NCSR will use the routinely submitted data to produce a periodic age stratified data set (including mean and 95% confidence interval), compiled from data from all screening HPV testing throughout Australia.

c) If a laboratory's overall HPV positivity rate in screening tests is not within the 95% confidence interval, the laboratory must investigate the cause as outlined in **Attachment B.**

d) The laboratory should compare its HPV positivity rates for the younger vaccine-eligible age cohort (born post-June 30, 1980) and older age cohorts (born pre-June 30, 1980) with the most recently available NCSR age-specific rate as described in **Attachment C.**

e) If the HPV positivity rate is **within** the 95% confidence interval for the age cohorts, the investigation does not need to proceed.

f) If the HPV positivity rate is **not within** the 95% confidence interval for one or more of the age cohorts, laboratories should investigate the device-specific ranges. Device-specific ranges are available by contacting the NCSR through the NCSRreporting@health.telstra.com inbox.

g) If the HPV positivity rate is **not within** the device- and assay-specific 95% confidence interval, laboratories should continue the investigation to determine the likely cause of the variance and ensure there has been no

[1] *Requirements for Medical Testing of Microbial Nucleic Acids (Second Edition 2013)*

failure in quality.

h) If after following the above steps laboratories are still concerned, the NCSR should be consulted through the NCSRreporting@health.telstra.com inbox or the NCSR Contact Centre on 1800 627 701.

i) Monitoring of HPV positivity and investigation, if required, must occur at least quarterly and the results or outcomes of any investigation recorded.

Attachment A

Reagent Batch Failure Notification Form – NCSP Notification

Name and address of pathology laboratory	
Pathology laboratory contact details including responsible Pathologist (phone number and email)	
Date of reported reagent batch failure	
HPV test type (manufacturer and device)	
Reagent batch Lot numbers and expiry date *Please list all Lot numbers and expiry dates for any reagents used as part of this batch of tests under the general process categories listed below. Where a reagent is used at multiple steps in the process please repeat under each category.*	
1. Control kit	
2. Cellular (LBC) extraction kit	
3. Nucleic acid extraction kit	
4. Amplification kit	
5. Detection kit	
6. Wash buffer	

Attachment B

Excerpt from NPAAC Requirements

Guidance on investigating HPV detection rates (Informative) detailed in the NPACC Requirements (Second Edition 2019) in Appendix A.

If a laboratory's HPV detection rate is found to be outside of the 95% confidence interval from the mean national positivity rate, this may be a result of differences in the age distribution, high-risk population, classification of screening status or other unmeasured factors.

The laboratory should consider the implementation of internal benchmarks using control charts, such as P-charts, for ongoing monitoring of the laboratory-specific positivity rate. The *Requirements for Testing of Microbial Nucleic Acids*[2] also provides additional advice on operational validation and ongoing monitoring of assays.

This Appendix sets out the steps to be taken if the overall HPV positivity rate as monitored by the laboratory falls outside of the 95% confidence interval from the current mean national positivity rate.

1. The laboratory should compare their HPV positivity rates for the younger vaccine-eligible age cohort (born post-June 30, 1980) and older age cohorts (born pre-June 30, 1980) with the most recently available NCSR age-specific rates.
2. If HPV positivity rate is within the 95% confidence interval for the age cohorts the investigation does not need to proceed.
3. If HPV positivity rate is not within the 95% confidence interval for one or more of the age cohorts, the laboratory should investigate the device-specific ranges (contact the NCSR for these values).
4. If HPV positivity rate is not within the device and assay-specific 95% confidence interval, the laboratory should continue its investigation to determine the likely cause of the variance and ensure there has been no failure in quality.
5. If after following the above steps laboratories are still concerned, they should consult with the NCSR.

[2] *Requirements for Medical Testing of Microbial Nucleic Acids (Second Edition 2013)*

Attachment C

Comparison of the batch HPV positivity rate to the national reference range

The National Cancer Screening Register (NCSR) will produce overall and stratified national HPV positivity rates which will allow laboratories to assess their own positivity rates against the national average.

The national report will include an acceptable reference range above and below the average. An acceptable HPV positivity rate is a rate that falls within this reference range.

As the number of tests included in a batch can affect the width of the reference range, a funnel plot and a table of values will be produced which provides the reference range for each batch volume.

The laboratory can refer to the number of tests in their batch and the observed HPV positivity rate, and identify if this falls outside of the funnel plot reference range. An example funnel plot is provided below.

The most recently available national averages should be used for comparisons.

Where to find the national average, funnel plots and tables

The national average and associated tables and funnel plots are made available from the NCSR website at www.ncsr.gov.au.

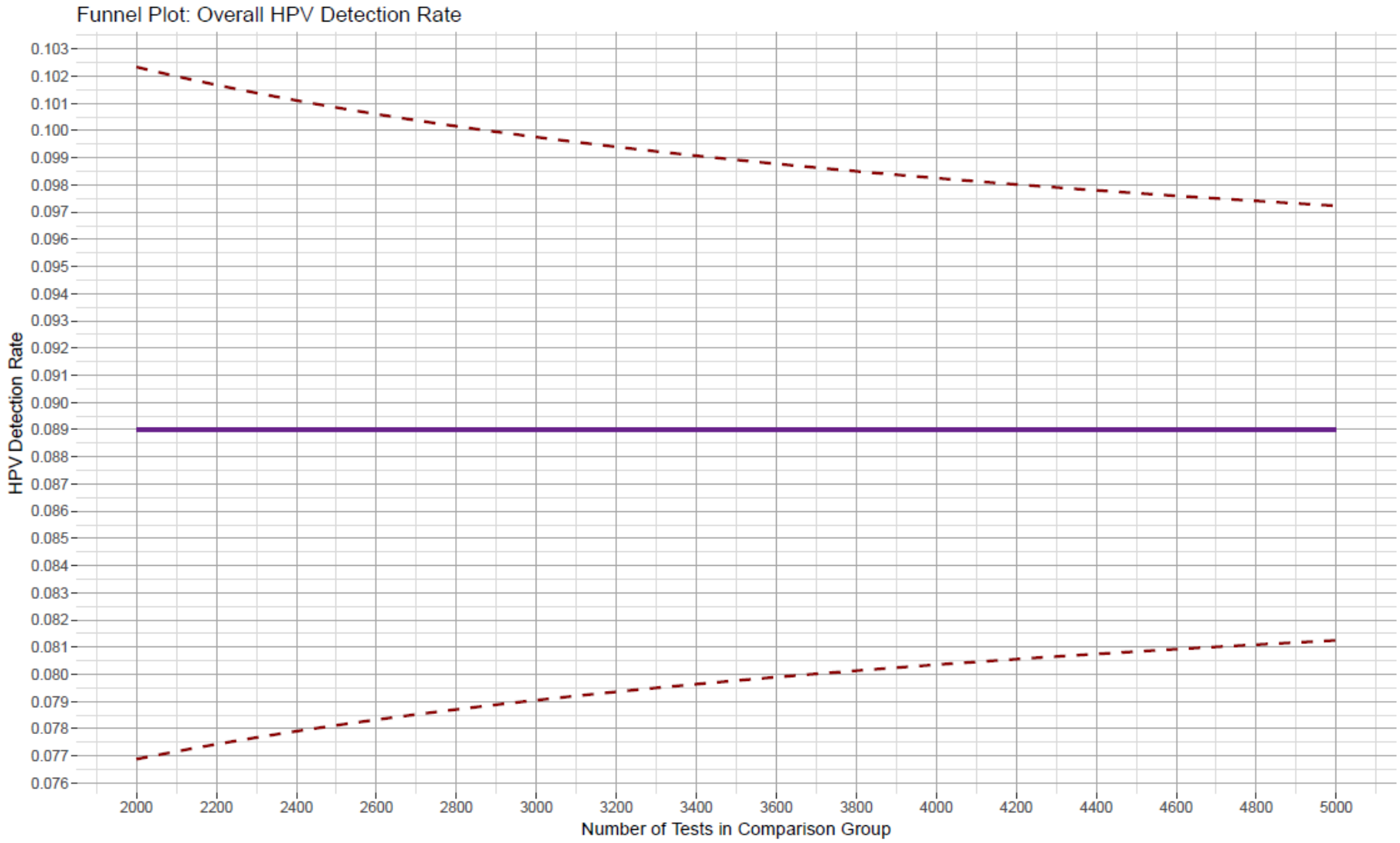
The overall and stratified national HPV positivity rates and funnel plot will be made available as a pdf and the table of reference values as either an excel or csv file. Instructions for use will also be available on the website.

How to contact the National Cancer Screening Register regarding the national reference range

Pathology laboratories may phone the NCSR Contact Centre on 1800 627 701 and ask to speak to the Epidemiology Team if there are any issues with accessing the national HPV positivity reference range.

When will the national average be available?

The national average will be calculated quarterly and pathology laboratories should use the latest published figure and associated funnel plots for comparison.


Funnel Plot: Overall HPV Detection Rate
HPV Detection Rate
0.103
0.102
0.101
0.100
0.099
0.098
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0.080
0.079
0.078
0.077
0.076
2000
2200
2400
2600
2800
3000
3200
3400
3600
3800
4000
4200
4400
4600
4800
5000
Number of Tests in Comparison Group