Full Submission for inclusion of an IVD category to the EDL

Survey response 1

Response ID
28

Date submitted
2019-01-09 12:14:24

Last page
8

Start language
en

Date started
2019-01-09 10:50:49

Date last action
2019-01-09 12:14:24

Identification

Please indicate your response ID (unique identifier given to your screening application)
62.0000000000

Name of organization supporting this application:
World Health Organization

Please enter full applicant's name
Ilbawi André; Trapani Dario

4. Typical Characteristics of IVD’s in each format in which tests in the test category are available
Papanicolaou (Pap) smear is a conventional cytological test to detect abnormal cervical cells. It is used for primary screening of cervical cancer as well as for triage testing after a positive HPV result to avoid overtreatment of cervical lesions. It is also used for follow up after treatment of cervical lesion with LEEP or cold-knife conization.

Procedure:
After visualization of the cervix with a speculum, cervical specimen is obtained with a sampling device such as wooden spatula, endocervical brush or plastic brush. The collected specimen is applied to a glass slide and fixed immediately using alcohol or spray fixative.

The glass slides are sent to a laboratory for processing and staining with Papanicolaou staining method. Reagents used for this staining are:
- 50%, 70%, 80%, 95%, 100% Alcohol
- Distilled water (running water)
- Haematoxylin
- Eosin
- Orange Gelb-6
- 0.5% Acid Alcohol
- May Grunewald Stain
- Giemsa Stain
- Methanol
- Xylene

Cytologic diagnoses follow the Bethesda classification system for reporting.

Ref.
1. WHO Comprehensive Cervical Cancer Control 2014
2. WHO list of priority medical devices for cancer management 2017

Diagnostic accuracy: Please provide typical sensitivity, specificity, PPV, NPV for each test format available. Note: Section 5 below request a summary of studies supporting performance criteria shown in this section.

1) Pap smear at the threshold of ASCUS+ for the detection of CIN 2+ and CIN 3+
   - Sensitivity
     43% to 96% (pooled 65.9% (95% CI 54.9 to 75.3)) for the outcome CIN 2+
     39% to 85% (pooled 70.3% (95% CI 57.9 to 80.3)) for the outcome CIN 3+.
   - Specificity
     86% to 98% (pooled 96.3% (95% CI 94.7 to 97.4)) for CIN 2+
     85% to 98% (pooled 96.7% (95% CI 94.6 to 98.0)) for CIN 3+

2) Pap smear at the threshold of LSIL+ for the detection of CIN 2+ and CIN 3+
   - Sensitivity
     18% to 89% (pooled 62.8%, 95% CI 46.8% to 76.5%) for CIN 2+
     64% to 80% (pooled 74.4%, 95% CI 67.8% to 80.1%) for CIN 3+
   - Specificity
     92% to 100% (pooled 97.7%, 95% CI 96.1% to 98.7%) for CIN 2+
     95% to 98% (pooled 96.9%, 95% CI 94.9% to 98.1%) for CIN 3+

REF: Koliopoulos G, Cochrane Database of Systematic Reviews 2017

Specimen types: Please provide the range of specimen types that can be used with each format for which the tests are available.

Cervical smear (cytology)

Papanicolaou staining is also used for detection of abnormal cells in the following specimen, for non-cervical cancer applications:
- Body fluids: CSF, urine, pleural and peritoneal fluids etc.
- Fine needle aspirate
- Bone marrow aspirate
- Sputum, bronchial brushings, bronchoalveolar lavage

Facility level: the kind of facility in which each test format is intended to be used. Include all that apply. [I: primary health care clinic with no laboratory]

No
<table>
<thead>
<tr>
<th>Facility level: the kind of facility in which each test format is intended to be used. Include all that apply.</th>
<th>[II: district/hospital laboratory]</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facility level: the kind of facility in which each test format is intended to be used. Include all that apply.</td>
<td>[III: regional/provincial laboratory]</td>
<td>Yes</td>
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<tr>
<td>Facility level: the kind of facility in which each test format is intended to be used. Include all that apply.</td>
<td>[IV: national reference laboratory]</td>
<td>Yes</td>
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<tr>
<td>User Skill level: minimum level of training the operator undergoes to effectively perform each of the test formats.</td>
<td>highly skilled laboratory trained health care worker</td>
<td></td>
</tr>
<tr>
<td>Throughput: number of specimens tested at one time for efficient use of each test format.</td>
<td>single use</td>
<td></td>
</tr>
<tr>
<td>Time to result: length of time to report the result for each test format</td>
<td>Time from obtaining specimen to reporting result is 2-3 weeks. The read of a single slide requires at least 6 minutes. The execution of the test, collection of the specimen, is performed in the provider's office in 15-20 minutes. REF: <a href="http://apps.who.int/iris/bitstream/handle/10665/144785/?sequence=1">http://apps.who.int/iris/bitstream/handle/10665/144785/?sequence=1</a></td>
<td></td>
</tr>
<tr>
<td>Environmental stability (temperature, humidity) and shelf life for each test format.</td>
<td>Immediate fixation of specimen is needed to prevent air-drying of cells</td>
<td></td>
</tr>
<tr>
<td>Environmental stability (temperature, humidity) and shelf life for each test format.</td>
<td>After fixation, glass slides must be placed in a slide storage box so that slides will not break and cells remain attached</td>
<td></td>
</tr>
<tr>
<td>Environmental stability (temperature, humidity) and shelf life for each test format.</td>
<td>Disposal risks: risks posed by disposal of IVD components for each test format. Include all that apply.</td>
<td></td>
</tr>
<tr>
<td>Disposal risks: risks posed by disposal of IVD components for each test format.</td>
<td>[Biohazard] Yes</td>
<td></td>
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<td>[Comment] immediate fixation of specimen is needed to prevent air-drying of cells</td>
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<tr>
<td>Disposal risks: risks posed by disposal of IVD components for each test format.</td>
<td>[Storage] After fixation, glass slides must be placed in a slide storage box so that slides will not break and cells remain attached</td>
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<td>[Transport]</td>
<td></td>
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<tr>
<td>Disposal risks: risks posed by disposal of IVD components for each test format.</td>
<td>[Other]</td>
<td></td>
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<tr>
<td>Disposal risks: risks posed by disposal of IVD components for each test format.</td>
<td>[Plastic] No</td>
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<tr>
<td>Disposal risks: risks posed by disposal of IVD components for each test format.</td>
<td>[Other comment]</td>
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<tr>
<td>Disposal risks: risks posed by disposal of IVD components for each test format.</td>
<td>[Toxic to humans] Yes</td>
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<tr>
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<td>[Comment] immediate fixation of specimen is needed to prevent air-drying of cells</td>
<td></td>
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<tr>
<td>Disposal risks: risks posed by disposal of IVD components for each test format.</td>
<td>[Toxic to environment] No</td>
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### 5. Evidence summary

Summary of laboratory evaluation studies covering reliability and reproducibility, analytical accuracy (sensitivity, specificity); and analyses of potentially interfering substances, cross-reactivity, stability, sample type. All relevant studies should be reported, detailing the search strategy and eligibility criteria used, or providing a systematic review. Please indicate the organizations responsible for conducting each of the studies and provide links to full reports for each study.

Cross-contamination of epithelial cells and overlap in multiple layers is one of the technical issues related to the preparation of the traditional pap-smear. Accordingly, a thin-preparation has been introduced (Thin-Prep), using a thin-prep device. This device is able to ensure an acceptable inter-device variability, with the automatized process, with a $k=0.93$ for diagnosis and 0.85 for specimen adequacy. Cross-contamination with normal epithelial cells has been showed to be low, with 1.24 mean epithelial count in the pathological specimen. Reproducibility was fully achieved, repeating the specimen collection in the same patient multiple times ($k= 1.0$). REF: https://www.accessdata.fda.gov/cdrh_docs/pdf/p950039.pdf
Summary of studies of clinical accuracy evaluating the test in patient pathways in clinical settings covering sensitivity, specificity, and predictive values. Full evidence of all relevant studies should be reported, detailing the search strategy and eligibility criteria used, or providing a systematic review. Please indicate the organizations responsible for conducting each of the studies and provide links to full reports for each study.

In a systematic review and meta-analysis of pap-smear performance, these results were retrieved. The study included 40 studies with more than 140,000 women aged between 20 and 70 years old.

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Also, 2) Randomized controlled trial comparing the accuracy of conventional cytology with liquid based cytology for primary screening of cervical cancer.

Setting Nine screening programmes in Italy.
Participants Women aged 25-60 attending for a new screening round: 22 466 were assigned to the conventional arm and 22 708 were assigned to the experimental arm.
Interventions Conventional cytology compared with liquid based cytology and testing for human papillomavirus.
Main outcome measure Relative sensitivity for cervical intraepithelial neoplasia of grade 2 or more at blindly reviewed histology, with atypical cells of undetermined significance or more severe cytology considered a positive result. Results In an intention to screen analysis liquid based cytology showed no significant increase in sensitivity for cervical intraepithelial neoplasia of grade 2 or more (relative sensitivity 1.17, 95% confidence interval 0.87 to 1.56) whereas the positive predictive value was reduced (relative positive predictive value v conventional cytology 0.58, 0.44 to 0.77). Liquid based cytology detected more lesions of grade 1 or more (relative sensitivity 1.68, 1.40 to 2.02), with a larger increase among women aged 25-34 (P for heterogeneity 0.0006), but did not detect more lesions of grade 3 or more (relative sensitivity 0.84, 0.56 to 1.25). Results were similar when only low grade intraepithelial lesions or more severe cytology were considered a positive result. No evidence was found of heterogeneity between centres or of improvement with increasing time from start of the study. The relative frequency of women with at least one unsatisfactory result was lower with liquid based cytology (0.62, 0.56 to 0.69).
Conclusion Liquid based cytology showed no statistically significant difference in sensitivity to conventional cytology for detection of cervical intraepithelial neoplasia of grade 2 or more. More positive results were found, however, leading to a lower positive predictive value. A large reduction in unsatisfactory smears was evident.

Summary of evidence of the impact of using tests in clinical practice on diagnoses, treatment, and patient outcomes. Please summarise model based evaluations and empirical studies where available and provide links to full reports.

From the 15,145 screened citations, 27 papers (24 studies) were included; five older studies located in a United States Preventive Services Task Force review were also included.

A randomized controlled trial in India showed even a single lifetime screening test significantly decreased the risk of mortality from and incidence of advanced cervical cancer compared to no screening (mortality: risk ratio 0.65, 95% confidence interval 0.47, 0.90; incidence: relative risk 0.56, 95% confidence interval 0.42, 0.75). Cytology screening was shown to be beneficial in a cohort study that found testing significantly reduced the risk of being diagnosed with invasive cervical cancer compared to no screening (risk ratio 0.38; 95% confidence interval 0.23, 0.63). Pooled evidence from a dozen case–control studies also indicated a significant protective effect of cytology screening (odds ratio 0.35; 95% confidence interval 0.30, 0.41). This review found no conclusive evidence for establishing optimal ages to start and stop cervical screening, or to determine how often to screen; however the available data suggests substantial protective effects for screening women 30 years and older and for intervals of up to five years.


Summary of available non-clinical data (appraisal of evidence of quality manufacturing, ease of use and test disposal) and links to any relevant references.

Train and re/train has been demonstrated to be an important way to ensure good quality of the pap smear, from collection to specimen preparation. In particular, a role delegation model has been proposed for the collection of the specimen, where community workers or non/physician providers like specialized nurses, general practitioners in some settings and midwives are trained for the procedure, achieving a reliable reproducibility and performance. The procedure is considered to be easy to learn, and in some settings, like gyn/ob specialists, to be a basic skill for the professionist.

Please attach relevant documents. Documents should be published in the last 5 years, except when not available.

6. Societal impact information

Ethical issues: please detail any important ethical consideration by the type of test and consequences

Counseling should be provided to all women undergoing cervical cancer screening.
Ref. WHO Comprehensive Cervical Cancer Control

Equity and human rights issues: please indicate if it reduces inequities or increase equity and accessibility

Pap smear is widely used as a method for cervical cancer screening. Increased participation rate in screening and early treatment of precancerous lesions have been proven to reduce cervical cancer incidence, which is generally higher in vulnerable populations including lower socioeconomic groups and women who are HIV+.

Acceptability: please indicate the acceptability by patient or by health care worker, benefits and harms

PAP smear is generally well tolerated and acceptable to patients when conducted in an appropriate manner with pre- and post-test counseling. (Ref: WHO Comprehensive Cervical Cancer Control)

https://www.liebertpub.com/doi/abs/10.1089/152460902753668466

7. Budget and resources impact
A Microsimulation economic model was retrieved from the literature, for the purpose.

Background: Recommended screening policies for cervical cancer differ widely among countries with respect to targeted age range, screening interval, and total number of scheduled screening examinations (i.e., Pap smears). We compared the efficiency of cervical cancer-screening programs by performing a cost-effectiveness analysis of cervical cancer-screening policies from high-income countries.

Methods: We used the microsimulation screening analysis (MISCAN) program to model and determine the costs and effects of almost 500 screening policies, some fictitious and some actual (i.e., recommended by national guidelines). The costs (in U.S. dollars) and effects (in years of life gained) were compared for each policy to identify the most efficient policies.

Results: There were 15 efficient screening policies (i.e., no alternative policy exists that results in more life-years gained for lower costs). For these policies, which considered two to 40 total scheduled examinations, the age range expanded gradually from 40–52 years to 20–80 years as the screening interval decreased from 12 to 1.5 years. For the efficient policies, the predicted gain in life expectancy ranged from 11.6 to 32.4 days, compared with a gain of 46 days if cervical cancer mortality were eliminated entirely. The average cost-effectiveness ratios increased from $6700 (for the longest screening interval) to $23 900 per life-year gained. For some countries, the recommended screening policies were close to efficient, but the cost-effectiveness could be improved by reducing the number of scheduled examinations, starting them at later ages, or lengthening the screening interval.


https://academic.oup.com/jnci/article/94/3/193/2520059