Reviewer’s Questionnaire for Evaluation of Submissions for EDL v3
Based on the Criteria for Selection of Essential Diagnostics for the EDL

Diagnostic test: Papanicolaou (Pap) smear
Test purpose: Primary screening of cervical cancer; triage testing after a positive HPV result to avoid overtreatment; follow up after treatment of cervical lesions with LEEP or cold-knife conisation; also detection of abnormal cells in other, non-cancer, applications
ID number: PreSubmission_ID62_FullSubmission_ID28

The selection process for essential diagnostics for the EDL will include consideration of a number of factors, including:

1. The public health and clinical need for the category of tests as determined for example, by disease burden and whether the proposed category of IVDs can help to bridge any existing gap in access to diagnostics that has been identified.

Questions:
1. Does the disease addressed by the test cause:
   ☒ a high burden of morbidity (human suffering)
   ☒ mortality
   ☒ cost on the populations and societies where it occurs

2. How strong is the evidence provided to support this?
   ☐ weak
   ☒ strong

Please complete the sub-questions below on evidence provided:

a. Disease prevalence data?
   ☒ yes
   ☐ no

b. Information on the disease impact on the quality of life of its sufferers?
   ☒ yes
   ☐ no

c. Information on the disease impact on the quality of life of the families of sufferers and the communities in which they live? E.g. patients with high care needs, orphans, spread of infection
   ☐ yes
   ☒ no

d. Impact assessments on health care resources and budgets?
   ☒ yes
   ☐ no

2. Is any information provided showing the degree of access to diagnostic testing for the addressed disease in the primary care setting?
   ☐ yes
Comment: The originators indicate this test (cervical smear) is not applicable in primary healthcare settings. Samples for cervical smears are collected by medical non-laboratory staff (such as nurses) in all settings, including primary healthcare (the collection of the sample is not laboratory related), and referred to a reference laboratory for interpretation and reporting.

3. Does the submitted test category help to increase access in any way? E.g. reduced skill required, lower cost, improved performance vs alternative options
   ☒ yes
   ☐ no
   Comment: Access at primary care settings as long as staff are trained in collection and fixation; specimen referral systems are available; and patient referral systems for management are available.

Note: Answers to the questions above will have been assessed as part of the screening application and will have been deemed acceptable. Nevertheless, information provided on these matters in the full application may be commented upon in your assessment.

2. Availability of validated commercial diagnostic tests as indicated by sound and adequate data on quality, safety, performance, and regulatory status.

Questions:
1. How many commercially available IVDs are included in the application for this category? 1
   a. Does the submission include a list?
      ☐ yes  ☒ no
   Does the application consider IVDs of all technologies ¹ that are available for the analyte² of interest?
      ☐ yes  ☒ no

2. Which national regulatory bodies have approved these tests for market access e.g. CE IVD, US FDA, SFDA, WHO-PQ, others?
   WHO endorsed

3. Have package inserts been provided showing studies demonstrating quality, safety, and performance of regulatory approved IVDs in this category?
   Quality: ☐ yes  ☒ no
   Safety: ☐ yes  ☒ no
   Performance: ☐ yes  ☒ no
   a. If so, what is your assessment of the strength of the study data described in the package inserts?

¹ Technologies: It may be that, within the IVD category, there are tests that use different technologies to measure or detect the same analyte e.g. an RDT or and EIA for HIV antibody
² Analyte: Marker that the IVDs in the category measures or detects
4. Have any independently published studies been provided, showing IVDs’ performances compared to a recognised gold standard? How strong are these studies?
☐ yes ☐ no
   a. If no gold standard exists, what is your assessment of the characterisation of the studies’ specimens?
   Studies presented compared Pap smear with HPV test, and standard cytology with liquid based cytology. HPV tests were less likely to miss cases of CIN 2+ and CIN 3+, but led to more unnecessary referrals. Pap smear led to greater chance of being falsely negative therefore requiring more frequent re-testing. Liquid based cytology showed no advantage.

5. Where relevant, have studies to demonstrate ease of use by trained lay providers been provided?
☐ yes ☐ no
What is your assessment of these studies?

6. Where relevant, have studies been provided to show the IVD’s robustness\(^3\) in variable environmental conditions e.g. temperature and humidity?
☐ yes ☐ no
   No studies provided, but the fixed and stained Pap smear is stable for long periods of time

3. **Clinical effectiveness**\(^4\) based on published peer reviewed data, safety and comparative cost-effectiveness.

Questions:
1. Has the applicant provided strong peer reviewed clinical studies that demonstrate the clinical utility\(^5\)and effectiveness of IVDs in this category?
   clinical utility: ☒ yes ☐ no
   effectiveness: ☒ yes ☐ no
2. Are you satisfied that these studies are properly designed and sufficiently powered statistically to support their conclusions?
   ☒ yes ☐ no
3. Has the applicant provided cost effectiveness, health economics or budget impact studies demonstrating the value of IVDs in this category?
   cost effectiveness: ☒ yes ☐ no
   health economics: ☒ yes ☐ no
   budget impact studies: ☒ yes ☐ no

Cost appears to relate more to frequency of screening rather than the test itself. HPV testing leads to less frequent screening, therefore lower cost. Cost of Pap smears is given from $20 – 60; probably slightly less than an HPV test ($50 – 100).

\(^3\) Robustness: An IVD’s capacity to remain unaffected by small variations in method parameters, which provides an indication of its reliability during normal usage

\(^4\) Clinical effectiveness: The degree to which a particular health care intervention does more good than harm. It is measured by the number of lives saved, or by improvements of objective parameters of a morbid condition

\(^5\) Clinical utility: The likelihood of improved outcomes from use of diagnostic tests in the IVD category
How strong are these studies in terms of design and statistical power?
☐ weak
☐ strong

4. Has the applicant provided pricing information for commercially available IVDs in this category? ☒ yes ☐ no
   a. Is the pricing information given inclusive of instrument and service costs where relevant? ☒ yes ☐ no
      No instrument required at collection site except speculum and spatula. Microscope is required at the reading site.
   b. In your experience, based on the pricing information provided, how accessible are IVDs in this category to LMIC settings?
      accessible: ☒ yes ☐ no
      not accessible: ☐ yes ☒ no
      Please provide examples to support your conclusions.
      The main cost of a Pap smear is the cost of the pathologist. In some LMIC, middle level staff (laboratory technicians) are trained to review cytological smears and alert to abnormal smears which are checked by a pathologist. This reduces the overall cost.

5. In your experience, do you consider the cost of tests in this category (cost per test includes reagents, any amortised instrument capital expenditure and service contracts) to justify the clinical benefits. Please provide examples to support your conclusions.
   ☒ yes ☐ no

Examples

4. Appropriateness of the IVD category for use at specified levels of the laboratory or health care system.

Answer questions 1 and 2 for each IVD technology in the category. A table may help with reaching your recommendation, the characteristics of each IVD represented by one row of the table

a. What specimen type is required?
   Cervical smears

b. What skill level and training is required for specimen collection? E.g. Phlebotomist
   Trained medical staff (non-laboratory)

c. Do specimens need to be processed in any way prior to analysis? E.g. centrifugation, microscope slide staining, etc. ☒ yes ☐ no
   i. If so, for how long and at what temperature is the specimen stable before being processed (00:00:00 hours, min, seconds format)
      Sample must be spread on a glass slide and immediately fixed while wet; after this it is stable for long periods
   ii. At what temperature is the processed specimen stored before testing (please specify if Celsius or Fahrenheit)
      Ambient temperature

d. How long does it take to get a result? E.g. can a result be obtained during a consultation i.e. < 10 minutes, or while the patient is at the facility i.e. 2 – 3 hours or specimens are tested in a batch using the IVD i.e. days?
   1 week – 2 months (cytology reading)
e. Where relevant to the IVD has ease of and effective use by trained lay providers been demonstrated?
☐ yes ☒ no

f. What equipment, if any, is required to perform this type of test?
   For collection: vaginal speculum, spatula, glass slides, fixative (95% alcohol); For reading: staining reagents (Papanicolau stain: five dyes in three solutions); immersion oil, microscope

g. Do instruments need to be calibrated, maintained, or serviced on a regular basis?
☐ yes ☒ no

h. How robust is the IVD?
   Robust; stable to long periods after fixing and staining

i. What is the impact of an unreliable power supply, or can the IVD operate without a power supply?
   Microscope requires electrical power; can be operated off-grid using battery or generator power
   What is the minimal skill level and training required for personnel to perform this test?
   ☐ Unskilled
   ☒ Skilled
   ☒ Highly trained
   Skilled to collect and prepare the smear; highly skilled to read the smear

2. Considering a 4-tier laboratory system, with the following levels:
   i. Primary care
   ii. District hospitals/laboratories
   iii. Regional hospitals/laboratories and
   iv. National hospitals/Reference laboratories

in your judgement, which level would be best suited to handle the required complexity of the relevant IVD?? Please include your answer in the table based on the likely availability of the following at district, regional and national laboratory level:

   a. Infrastructure requirements e.g. instrument size and complexity, biosafety requirements
   b. Specimen types
   c. Testing volumes expected (sample throughput required)
   d. Complexity of specimen handling e.g. biosafety level required, centrifugation or complex protocols requiring highly skilled laboratory technicians
   e. Availability of infrastructure for transporting specimens
   f. Result turn-around times required
   g. Reagent shipping, storage and operating conditions required
   h. Where relevant, instrument operating conditions required
   i. Required qualifications, training and skill levels needed for test performance and result interpretation e.g. non-laboratory personnel for a simple rapid test, trained laboratory technician to perform routine testing, medically trained personnel for result interpretation, Ph.D. level scientist required for highly complex and variable methodologies
j. Quality management requirements based on complexity of facilities & support required to perform the test

Proposed answer table:

<table>
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<th>Collection = X</th>
<th>Primary care</th>
<th>District hospitals/lab</th>
<th>Regional hospitals/lab</th>
<th>National hospitals/Reference lab</th>
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<tr>
<td>Infrastructure requirements</td>
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<tr>
<td>Specimen types</td>
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<td>Testing volumes expected</td>
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<td>Complexity of specimen handling</td>
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<td>Result turn-around times required</td>
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<td>Reagent shipping, storage and operating conditions required</td>
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<tr>
<td>Instrument operating conditions required</td>
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<td>Required qualifications, training and skill levels</td>
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<tr>
<td>Quality management requirements</td>
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<td>X</td>
<td>XY</td>
<td>XY</td>
</tr>
</tbody>
</table>

5. What is your recommendation to SAGE IVD? Please summarise the key points you considered in reaching your conclusion.

I recommend Pap smears to be included in the IVD List for screening for cervical cancer and pre-cancer.

Pap smears are an old, trusted method of screening for cervical cancer and pre-cancer, and are still widely recommended in many national programmes, especially in resource-limited countries, where HPV testing is generally not available in public facilities.

HPV is the test of choice for screening for cervical cancer globally. Due to its higher sensitivity, rescreening is not required as frequently as for Pap smears (about every 5 years), thus reducing cost and possibly improving compliance. However, the HPV test requires laboratory-based testing with the requirement of test kits and (often) instrumentation, which are frequently not available in government facilities in resource-limited countries. Point of care HPV tests are not yet widely available and are still complex (Xpert technology).

Pap smears remain an effective alternative, and are still recommended by many ministries of health. Due to their reduced sensitivity, rescreening must be done at more frequent intervals (3 years - all screening procedures need to be performed more frequently in HIV positive women). Constraints include lack of proper spatulas and fixative, expertise to read the smears, return of results and loss
of patients to follow up. In some countries, middle level staff (cytotechnologists) are trained to screen smears at intermediate laboratory level, and refer possible abnormal smears for confirmation (to cytopathologists), thus reducing cost and turnaround time. Another advantage is that cervical smears serve as a permanent record.

Constraints to referral of specimens and waiting for return of results apply equally to HPV and cervical smears. Only visual inspection with acetic acid (VIA) is a point of care test and many nurses in primary facilities are trained in this procedure, but VIA is not recommended for patients >50 years and an alternative method must be used.

Referral for further evaluation and treatment is the overall limiting factor and applies to all screening methods. Colposcopy is usually not available in public facilities in resource-limited settings except at national level. Cryotherapy and other treatments are often not available outside national and major regional centres in resource limited countries.

6. Please list the items that require further clarification from the originator of this submission.