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
Test purpose: Screening for cervical cancer and for triage testing after a positive HOV results to avoid overtreatment of cervical cancer
ID number: PreSubmission_ID62_FullSubmission_ID 28

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

3. Is any information provided showing the degree of access to diagnostic testing for the addressed disease in the primary care setting?
   ☐ yes
Does the submitted test category help to increase access in any way? E.g. reduced skill required, lower cost, improved performance vs alternative options

Specimen collection and preparation can be done by trained /retrained community worker; non physician like specialized nurses, general practitioners and midwives and this ensure good quality of the Pap smear. Then the specimen referred to the laboratory for processing and results interpretations. ☐ yes
☐ no

Comment:

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?

   a. Does the submission include a list?
       ☐ yes
       ☒ no

   Does the application consider IVDs of all technologies that are available for the analyte 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?

   CE IVD, WHO-PQ,

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?

4. Have any independently published studies been provided, showing IVDs’ performances compared to a recognised gold standard? How strong are these studies?

   ☐ yes ☒ no

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1Technologies: 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

2Analyte: Marker that the IVDs in the category measures or detects
If no gold standard exists, what is your assessment of the characterisation of the studies’ specimens?

Gold standard method in detecting cervical lesion is biopsy. No studies about this gold standard were provided. The provided studies compared conventional pap with liquid base smear with HPV test. HPV tests are less likely to miss cases of CIN 2+ and CIN 3+, these tests do lead to more unnecessary referrals. However, a negative HPV test is more reassuring than a negative cytological test, as the cytological test has a greater chance of being falsely negative, which could lead to delays in receiving the appropriate treatment. No clinical difference in liquid base cytology and conventional cytology.

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?
Where relevant, have studies been provided to show the IVD’s robustness in variable environmental conditions e.g. temperature and humidity?
☐ yes ☒ no

But it is indicated that immediate fixation of specimen is needed to prevent air-drying of cells.


Questions:
1. Has the applicant provided strong peer reviewed clinical studies that demonstrate the clinical utility 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

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

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3Robustness: An IVD’s capacity to remain unaffected by small variations in method parameters, which provides an indication of its reliability during normal usage
4Clinical effectiveness: The degree to which a particular healthcare 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
5Clinical utility: The likelihood of improved outcomes from use of diagnostic tests in the IVD category
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.

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?
Specimen type is principally Pap smear of cervical exfoliated cells
b. What skill level and training is required for specimen collection? E.g. Phlebotomist highly skilled laboratory trained health care worker.
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)
Immediate fixation of specimen is needed to prevent air-drying of cells.
After fixation, glass slides must be placed in a slide storage box so that slides will not break and cells remain attached
ii. At what temperature is the processed specimen stored before testing (please specify if Celsius or Fahrenheit)
Room 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?
Time from obtaining specimen to reporting results is 2-3 weeks.
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?
After visualization of the cervix with a speculum, cervical specimen is obtained with a sampling device such as wooden spatula, endo-cervical 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

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

h. How robust is the IVD?
   fixed for long period if immediately fixed and stained

i. What is the impact of an unreliable power supply, or can the IVD operate without a power supply?
   This IVD can’t operate without power supply and unreliable power supply is one of the main reasons for high cervical cancer mortality.
   What is the minimal skill level and training required for personnel to perform this test?
   ☐ Unskilled
   ☒ Skilled
   ☒ Highly trained

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>
<thead>
<tr>
<th></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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</thead>
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<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>Result turn-around times required</td>
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</table>
5. **What is your recommendation to SAGE IVD? Please summarise the key points you considered in reaching your conclusion.**

I highly recommend addressing the Pap smear test to be included in the IVDs because:

1. Although, it has a potential risks for false positives, it has a well established benefits ranging from early detection of treatable lesions and reduction in incidence and mortality of cervical cancer.
2. Pap test is a widespread screening programs and has been conclusively shown to reduce the incidence of and mortality from the cervical cancer
3. It’s a well characterized screening approach that has a historical success in developed countries.
4. It can be of great benefits for Lower and middle income countries where other screening methods are unavailable or costly.

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