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

Diagnostic test: Histoplasma antigen test
Test purpose: As an aid in the diagnosis of histoplasmosis
ID number: PreSubmission ID 40, FullSubmission_ID 5

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.

Draft 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
   - ☐ no

Comment:
Does the submitted test category help to increase access in any way? E.g. reduced skill required, lower cost, improved performance vs alternative options
This is a specific test with narrow range and it application is related to differentiation of AIDS related diseases.
☐ 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?
   One
   a. Does the submission include a list?
      ☐ yes
      ☒ no
   b. 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?
   None according information
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
   a. If no gold standard exists, what is your assessment of the characterisation of the studies’ specimens?

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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
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

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

Draft 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

How strong are these studies in terms of design and statistical power? (See Note above)
   - ☐ 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
   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.

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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
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

It is very specific test for the AIDS patient population

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?
      Urine

   b. What skill level and training is required for specimen collection? E.g. Phlebotomist
      Highly skilled technologist

   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)
      2-8 C
      ii. At what temperature is the processed specimen stored before testing (please specify if Celsius or Fahrenheit)
      2-8 C

   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?
      2-4 hours

   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?
      EIA-Semi-manual

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

   h. How robust is the IVD?
      Enzyme assay with the manual components, it is a robust

   i. What is the impact of an unreliable power supply, or can the IVD operate without a power supply?
      Has impact on completion of the test
      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>
</tr>
</thead>
<tbody>
<tr>
<td>Infrastructure requirements</td>
<td>N/A</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Specimen types</td>
<td>N/A</td>
<td>Urine</td>
<td>Urine</td>
<td>Urine</td>
</tr>
<tr>
<td>Testing volumes expected</td>
<td>N/A</td>
<td>Urine sample in 10ml container</td>
<td>Urine sample in 10ml container</td>
<td>Urine sample in 10ml container</td>
</tr>
<tr>
<td>Complexity of specimen handling</td>
<td>N/A</td>
<td>Highly skilled</td>
<td>Highly skilled</td>
<td>Highly skilled</td>
</tr>
<tr>
<td>Infrastructure for transporting specimens</td>
<td>N/A</td>
<td>Onsite</td>
<td>Onsite</td>
<td>Onsite</td>
</tr>
<tr>
<td>Result turn-around times required</td>
<td>N/A</td>
<td>2-4 hours</td>
<td>2-4 hours</td>
<td>2-4 hours</td>
</tr>
<tr>
<td>Reagent shipping, storage and operating conditions required</td>
<td>N/A</td>
<td>2-8 C</td>
<td>2-8 C</td>
<td>2-8 C</td>
</tr>
<tr>
<td>Instrument operating conditions required</td>
<td>N/A</td>
<td>21-25 C</td>
<td>21-25 C</td>
<td>21-25 C</td>
</tr>
</tbody>
</table>
5. **What is your recommendation to SAGE IVD?** Please summarise the key points you considered in reaching your conclusion.

Recommend approval, emphasizing the impact on very limited selective group of AIDS patients.

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

None