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

Diagnostic test: Essential Panel of antibodies for flow cytometry for leukaemia
Test purpose: As an aid to diagnosis of Acute Leukaemia
ID number: PreSubmission_ID63, FullSubmission_ID35

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
   ☐ no
Comment: While samples can be collected for analysis in the primary care setting this is unusual but testing is confined to a central facility

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: Only in so far as a central diagnostic facility can speed the appropriate diagnosis that will guide specific therapy. In an acute condition this is crucial for survival and long term outlook.

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?

   Only the extended panel of monoclonal antibodies are mentioned

   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 The list is generic ad the monoclonals are available from multiple sources

2. Which national regulatory bodies have approved these tests for market access e.g. CE IVD, US FDA, SFDA, WHO-PQ, others? Monoclonal antibody diagnosis is recognised by the regulatory bodies

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? Not applicable

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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
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? The use of monoclonal antibodies in the diagnosis and classification of the leukaemias is now the gold standard and has been in developed countries for 2 decades at least. It is used to guide appropriate therapy.

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 in variable environmental conditions e.g. temperature and humidity?

☐ yes ☒ no The conditions in how the reagents should be used has been well described.


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?)

   ☐ weak

   ☒ strong

4. Has the applicant provided pricing information for commercially available IVDs in this category? ☐ yes ☒ no See below

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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
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. Flow cytometry diagnosis is expensive because of the requirements of the machine. This has multiple uses (HIV, Immunodeficiency) and costing should not be considered for one diagnosis category alone. Once purchased the costs of an individual analysis are low and well within the budget of LMICs. Early correct diagnosis allows the use of appropriate primary treatment at a time frame that it will be of most benefit and will lead to results that are now considered the norm in high income countries.

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 See above

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? Blood and bone marrow, in general
   b. What skill level and training is required for specimen collection? Phlebotomist and haematologist or skilled nurse practitioner to obtain bone marrow in addition to blood
   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) RT for at least 24 hours, otherwise can be separated and stored frozen. Can be stored at low temperatures for more than 24 hours but early analysis is recommended if not frozen.
      ii. At what temperature is the processed specimen stored before testing (please specify if Celsius or Fahrenheit) See above
   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? 2-3 hours once analysis
starts.

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?
   A flow cytometer

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

h. How robust is the IVD? Very

i. What is the impact of an unreliable power supply, or can the IVD operate without a power supply? A reliable power supply is essential

   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

The test can only be provided at level 3 or 4 because of the cost of the flow cytometer. As this is multifunctional it can be justified because of its relevance in different conditions. It requires a significant level of skill to run and a significant throughput to guarantee the quality of the results. There are recognised quality control programmes that must be used in parallel with the diagnostic service.

Proposed answer table:

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

See comments above. Flow diagnosis in leukaemia is crucial for early and appropriate diagnosis and sub-classification which is essential for patient-centred tailored treatment. This is now the norm in developed countries and should also be available in LMICs.

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

None