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 for antibodies for flow cytometry for leukemia
Test purpose: As an aid in the diagnosis of acute leukemias
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

3. 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
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?
   N/A
   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?
   US FDA, EMA (European Medicine’s Agency), National Agencies of Health and Public Health Ministries of each individual country
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?
      Yes.
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 publications for the diagnosis of acute leukemia are very strong and well established.

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?
The diagnostic criteria for acute leukemia are very clearly defined (Dohner et al).

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


Questions:
1. Has the applicant provided strong peer reviewed clinical studies that demonstrate the clinical utility and effectiveness of IVDs in this category?
clenital 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
   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 diagnostics of leukemia is standard. For proper diagnosis, flow cytometry is basic, but state-of-the-art assays based on sequencing, genetics and molecular biology are important

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
as they play key roles in prognosis, as well as in targeted therapy (e.g. FLT3 mutation for TKI therapy and transplantation).

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

**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?
   - Peripheral blood samples / bone marrow blood smear.

b. What skill level and training is required for specimen collection? E.g. Phlebotomist
   - Highly trained healthcare professional familiar to modern protocols for flow cytometry and molecular biology are required.

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)
   for the basic diagnosis – 24 hours.
   ii. At what temperature is the processed specimen stored before testing
   (please specify if Celsius or Fahrenheit)
   normal centrifugation at room temperature and afterwards staining with monoclonal antibodies.

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?
   24 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?
   - protein immunofixation and electrophoresis

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

h. How robust is the IVD?
   - Very robust.

i. What is the impact of an unreliable power supply, or can the IVD operate without a power supply?
   - It is not reliable.
   - 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:

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<th>Regional hospitals/lab</th>
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4. **What is your recommendation to SAGE IVD? Please summarise the key points you considered in reaching your conclusion.**

I highly recommend flow cytometry and molecular biology for the basic protocols in diagnosis and follow-up for acute leukemia.

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

Flow cytometry
Molecular biology laboratory
Normal laboratory protocols (pipettes, centrifuge);
Highly trained staff.