Jacques Schrenzel et al.[1]

White paper on molecular diagnostic panels in microbiology

Molecular diagnostic panels (MDx panels, thereafter panels) allow to test for several pathogens such as viruses, bacteria and parasites within a single syndromic-driven diagnostic approach. Clinicians increasingly use these tests due to their ability to rapidly evaluate patients presenting with unspecific symptoms such as diarrhoea or respiratory tract infections. Exclusion or inclusion of specific pathogens holds promises to tailor antibiotic treatments. Clinical microbiologists are therefore confronted with an increasing diagnostic demand from clinicians regarding usage of such panels. Those panels are often easy to use and reliable, based on their cartridge design, with the downside that their costs are high and that the knowledge on the diagnostic targets of these assays are often undisclosed. The Commission of Clinical Microbiology of the Swiss Society for Microbiology decided to analyse this topic in further details.

Despite tremendous diagnostic potential, the indiscriminate use of these panels could be challenging at several stages of the diagnostic process. **Pre-analytical** challenges include the high costs of many of these assays. Panel assays should therefore be carefully used in well-defined groups of patients. A key aspect of the diagnostic stewardship consists of providing recommendations towards proper assay usage in clinics. At the **analytical** stage, the parallel format of these panels implies specific quality control strategies. In the **postanalytical** part, the availability of results that are not prescribed nor even foreseen by the clinician raises additional interpretation issues. Profound knowledge on the employed panels helps to interpret unexpected positive results as well as to address the poor sensitivity for detecting specific pathogens. Finally, the clinical impact of many panels has not been evaluated in great details, to properly support their costs.

This paper will discuss the principles of competence for performing MDx assays, their clinical utility and clinical validation, their QC and results interpretation. It also underlines the urgent need for clinical studies using these panels, with a literature that remains clearly incomplete and heterogeneous, in order to assess the true performance and clinical impact of each of these multi-target assays.

1. **Competence:** by law, these assays have to be performed in an authorized microbiology laboratory. However, stat labs or core labs could be considered as adequate laboratories for performing these assays provided there are:
   i) **urgent assays** (e.g. Group B Streptococcus detection),
   ii) a **documented training** and a **QC programme**, and
   iii) that these analyses are always **under the responsibility of a microbiologist.**
2. **Qualification:** any new panel on the market should be first qualified by a laboratory/laboratories to assess its quality in terms of sensitivity and specificity. An independent publication should be available.
3. **Clinical utility:** microbiologists should advise clinicians on the best situation for using each panel in order to increase their diagnostic yield. Ideally, physicians requesting the use of panels should give adequate justification (e.g. travel abroad in regions with poor hygiene for GE panels or compromised immunity for respiratory panels). Furthermore, panels should not be used on clearly inadequate specimens (e.g. non-diarrheic stools or sputum specimens contaminated with saliva). The simultaneous presence of several pathogens in a specimen submitted should prompt a phone call to the requesting physician to discuss the results. Finally, the lower sensitivity of some assays has to be considered.
4. **Microbiological validation: introducing a CE-marked assay** requires a verification to test the own laboratory workflow and to have a positive control available in case of a problem with the test system. Many of the newest panels have assays to detect very rare pathogens. Reference laboratories should be contacted in order to assess and properly interpret such samples. At least initially, a representative number of specimens negative by non-panel assays or routine methods should be run with the panel to detect major problems of specificity. **Positive results** should be confirmed by an independent method (e.g. culture) for an adequate number of specimens in daily routine. Excessive numbers of unconfirmed results should prompt further investigations. In case of use of a invalidated transport medium, a commentary should be added to the results.
5. **Clinical validation:** only very few assays have been evaluated in large multicentre studies and have documented a clinical impact on patient management. Clinical validation should include: (i) the laboratory performance with e.g. turn around times, (ii) sensitivity and specificity comparison with the laboratory internal gold standard, and (iii) the impact of the fast test result on

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treatment change or even clinical outcomes. This yields a series of challenges – the comparison against the laboratory gold standard is often not easy – as the broad range of pathogens covered by many panels does often not allow for a single confirmation of all pathogens. Nevertheless, diagnostic laboratories should try to evaluate the impact on the clinical usage.

6. **EQC:** to compare labs, by using test probes that are provided independently from the manufacturers. To be ideally run twice a year on 8 to 12 samples, based on what is commercially available. Each separate EQC will not test all targets of the MDx panel but one expects the EQC to ultimately assess each target, after several EQC distributions.
7. **IQC:** to assess assay robustness under routine conditions, IQC should be rotated on the various slots of the device to ensure similar performance. To be performed for each new lot (or for each delivery, if transportation could affect robustness). Assess cartridge stability using the last cartridge of the lot, in case of bad storage only.
8. **Data interpretation:** as usual, predictive positive and negative values are closely related to the prevalence of the targeted disease. This aspect is of peculiar importance here, due to the parallel nature of the panel that can deliver unexpected positive results. The latter should therefore be interpreted in the light of the prevalence of the disease, to translate these results into meaningful positive predicted value.
9. **Post-market surveillance:** users should be encouraged to rapidly notify to the company any problem encountered with such panels, so that unexpected events (false positive, false negative) could be accessible to all users, through an open communication to and from the manufacturers.
10. The following elements should be carefully considered when using MDx panels:
    a. The **prevalence** of a disease may vary markedly across time and geography. The same panel contains probes for diseases of markedly different frequencies (e.g. rare cholera and frequent Campylobacter in Switzerland), leading to very heterogenous performance due to highly different a priori probabilities.
    b. The limitations mentioned above are typically considered by a physician when ordering an assay. The use of a panel biases this risk balance, as evidenced by the – much too frequent – reporting of EHEC, that are simply not clinically relevant and that were not thought of or even requested by the physician.
    c. Finally, each assay on a MDx panel has its biological performances that should be known by the microbiologists.
    d. Interpreting a result from a molecular panel represents therefore a tricky task, that has to integrate the clinical a priori probability and the assay performance, for returning meaningful and medically actionable decisions.

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A more complete version, including examples and references is available online:
www. sulm.ch/d/pipette -> Aktuelle Ausgabe (Nr. 1-2019)

«D'Esthi isch die Beschti»

Seit den Geburtswehen der «pipette» 2003, der Geburt, den Jahren als Säugling, Kleinkind und jetzt pubertierende Erwachsene war Esther Meyle mit dabei. Sie hat für die «pipette», die SwissMedLab, die SULM viel getan und generell zur gesamten Labormedizin in der Schweiz sehr viel beigetragen. Immer fröhlich, positiv, nichts war zu viel, um mit dem teils ungestümen Chefredaktor Volldampf voraus zu fahren. Ihr und auch ihrem Ehemann David gebührt ein riesiger Dank, denn beide haben stets bescheiden, im Hintergrund arbeitend, vieles für unsere Fachgesellschaft getan. Zeitgerecht hat Esther immer geschaut, dass die Autoren ihre Artikel ablieferten, dass neue Ideen aufgenommen wurden, die Homepage aktualisiert und vor allem, dass meine Editorials «meylesiert» wurden. Will heissen, so umgeschrieben wurden, dass sie noch (fach)gesellschaftlich verträglich blieben, aber an ihrer Bissigkeit nicht viel verloren.

Ohne sie (sic! Esther und nicht die Editorials) wäre die «pipette» nicht, was sie ist, wäre die SULM nicht, was sie ist, und wäre auch die SwissMedLab nicht, was sie ist. Esther und David waren für uns eine enorme Bereicherung. Für mich persönlich eine wertvolle, freundschaftliche, kameradschaftliche und vor allem herzliche Beziehung. Ich wünsche jedem Chefredaktor eine solche Unterstützung, Beziehung und Freundschaft. Denn nur so gelingen Dinge, die allen zugutekommen. Auch sind wir froh, dass Jacqueline Geser die Geschäfte von Esther und David Meyle übernommen hat. Wir begrüssen sie ganz herzlich in unseren Kreisen.

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