BEST PRACTICES ON THE DEFINITION OF THE CLINICAL NEED, CLINICAL UTILITY AND CLINICAL BENEFIT

Source: extract from Best Practices handbook, BIC project

A. Clinical need

The most important requirement for a new biomarker IVD test is being able to answer a clear unmet clinical need. The need must origin from (or be confirmed by) the end users and be of type "must have", not "nice to have", because few paying customers exist for the latter kind. Wider acceptance and successful commercialization of a new biomarker test can only be gained if it fills a proven and topical need of the end users. (Also see the chapter on social, psychological, ethical and legal impacts of testing.)

Best practices:

- Establish a clear intended purpose for the test. A new biomarker test must provide an answer to an unmet clinical need which is correctly understood and confirmed by the real-life end users.
- Enter early in a dialog with clinicians (or other relevant opinion leaders or end users). Establishing the clinical need is a natural part of a non-commercial research project when the researchers are medical doctors or have other competences such as contacts to clinicians that allow them to verify the clinical relevance of the biomarkers. Otherwise dialog with relevant clinicians, preferably key opinion leaders, needs to be started as early as possible. Literature studies can only partially be employed to establish the clinical need. The feedback from the end users (or relevant industry in the field when they are the end users) needs to be documented.
- Learn from the above discussions. Listen to the opinions and potential critique of the potential customers. This will help in understanding the limitations of the technology and making better practical use of the research while turning it into something that benefits the society the most.

Pitfall practices:

- Looking for a problem to fit one's solution (rather than answering an existing, significant clinical question or need).
- Not listening to the potential customers. The need must origin from real-life end users.
- Bad market analysis: there is a need but also alternative testing methods that perform well.

B. Clinical utility and clinical benefit

Clinical utility means the ability of an IVD test to positively influence the clinical outcome when introduced in the clinical care pathway (synonyms: clinical pathway, care pathway, care model, care map, care process). The European IVD Regulation (IVDR, 2017/746) also uses the term "clinical benefit" in the context of an IVD device having a "positive impact related to its function, such as that of screening, monitoring, diagnosis or aid to diagnosis of patients, or a positive impact on patient management or public health". Only biomarkers that provide clear clinical benefits are amenable to translation into clinical use.

Best practices:

- A new biomarker test must add benefit for patients and society as compared to the existing clinical care pathway. Also the harms related to testing need to be considered, as well as populations in which testing is not justified.
- A new biomarker test must also concretely help clinicians at their work. A biomarker test must provide information that reflects the current or future situation of the patient without hindsight. The test needs to give a clear answer to a clear clinical question, for example by providing a more accurate or timely diagnosis of a disease or allowing to choose the most efficient therapy for the patient belonging to the target population.
- A new IVD test needs to be directly compatible with the clinical assessment of the patient.
- There must be a proven link between the biochemical pathway of the disease and the biomarker used for its indication.
- The expression of the biomarker needs to be specific for the indication investigated. Understanding the mechanism of disease/therapeutic effect is important.
- Patent protection of a new biomarker should be started only when a clear clinical indication and sufficient scientific evidence has been generated.
- The key criteria for a high-impact IVD-applicable biomarker include, e.g. the biomarker
    - addresses a significant unmet medical need (or replaces an unsatisfying existing solution) with a potentially considerable impact on public health
    - has specific association with the disease in the target population or allows separating patients benefiting from treatment/non-treatment (i.e., aids in medical decision making)
    - provides information that is not readily available by clinical assessment
    - determination of the biomarker will result in significant improvement in the approval or delivery of care to patients, i.e., facilitates therapeutic decisions with low risk of under- or over diagnostics
    - is present in sufficiently high levels to be measured by practical assays

- is present in the clinical specimen for a sufficiently long time window; uses a non-invasive specimen matrix
- is indicative of the present or future status of the patient
- has a high potential market size and value as the driving force for commercialization
- convinces clinicians and does not involve unnecessarily complex result interpretation.

Pitfall practices:

- Conclusions are drawn too early. Conclusions on the clinical utility are drawn based on the first observations (presence or concentration is different in the affected and healthy persons at group level or between paired specimens).
- The use of the new marker requires complex setups. The need to use complex, personalized decision trees containing multiple different markers (or even multiple molecular types of markers) in varying combinations can limit the clinical utility of new tests. When developing sequential multi-parameter testing processes, the correct use must be clear and transparent for the clinician.