BEST PRACTICES ON CLINICAL SPECIMENS

Source: extract from Best Practices handbook, BIC project

The means for ensuring a high quality of specimens used in biomarker studies should be included in the project plan and be an essential part of risk management of the project. Specimen integrity is one of the factors of highest importance when making conclusions from the clinical performance analyses.

Pairing or matching case and control specimens is often performed at the discovery stage because the disease prevalence is often low, because random selection could result in imbalance of some factors varying between individuals and specimens, and because the throughput of the discovery analysis methods is typically low. The extent of specimen picking needs to be gradually decreased when the research proceeds.

Best practices:

- Prepare a specimen management plan spanning e.g. the sampling, handling, stability, preservatives, storage, shipping, de-identification, chain-of-custody (an action audit trail that contains information when the specimens have been used, by whom, for what purpose etc.), patient consent, ethical approval, restrictions-for-use and disposal issues following the spirit of good clinical practice (GCP).
- Many retrospective specimens are stored frozen or fixed and you need to know something about the stability of the candidate biomarkers in the storage conditions early on.
- In the case of pathological specimens the origin of the tissue needs to be taken into account. Control specimens have to show the same localization and the same characterization (e.g., age, ethnicity, environmental conditions), and the form of preservation of the pathological and healthy specimens need have been performed with the same protocol. The same goes with specimens received from a biobank.
- The probability of making an erroneous conclusion decreases with the increased sample size and decreased extent of specimen picking. Although strictly selecting specimens with hindsight is necessary in the early phase of discovery, conclusions of the ability of a biomarker to discriminate between disease and non-disease should be made on specimens better representing the target population, i.e., individuals that have been or would be tested for the presence of disease. At this stage, many of the findings that first showed a good discrimination ability disappear, a natural phenomenon in the biomarker discovery pipeline.

- Blinding of specimens during the test process avoids bias especially in case of marginally positive subjects and is a required element in the later verification studies.

Pitfall practices:

- Diagnostic sensitivity, diagnostic specificity, AUC (Area Under Curve in ROC, i.e. Receiver Operating Characteristic curve analysis), NPV (Negative Predictive Value) and PPV (Positive Predictive Value) calculations are not to be made on heavily selected specimens due to the strong bias.