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BIC BIOMARKER COMMERCIALIZATION

Best Practices and Pitfalls in Commercializing

IVD-Applicable Biomarkers

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LIST OF ABBREVIATIONS

AUC	Area Under Curve
BIC	Biomarker Commercialisation
BQP	Biomarker Qualification Program
BSR	Baltic Sea Region
CBA	Cost-Benefit Analysis
CDA	Confidential Disclosure Agreement
CE	Conformité Européenne (European Conformity)
CEA	Cost-Effectiveness Analysis
CEO	Chief Executive Officer
CI	Confidence Interval
CV	Coefficient of Variation
EPO	European Patent Office
EU	European Union
FDA	Food and Drug Administration
FTO	Freedom to Operate
GCP	Good Clinical Practice
GDPR	EU General Data Protection Regulation
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GSPR	General Safety and Performance Requirements
HR	Hazard Ratio
HTA	Health Technology Assessment
IP	Intellectual Property
IPR	Intellectual Property Rights
IPRP	International Preliminary Report on Patentability
ISR	International Search Report
IVD	In-Vitro Diagnostics
IVDR	European IVD Regulation 2017/746
mRNA	Messenger Ribonucleic Acid
MS	Mass Spectrometry
MTA	Material Transfer Agreement
NDA	Non-disclosure Agreement
NMR	Nuclear Magnetic Resonance
NPV	Negative Predictive Value
OA	Office Action

OR	Odds Ratio
PCR	Polymerase Chain Reaction
PCT	Patent Cooperation Treaty
POCT	Point-of-care Testing
PoP	Proof of Principle
PPV	Positive Predictive Value
QC	Quality Control
R&D	Research and Development
ROC	Receiver Operating Characteristic Curve Analysis
RR	Risk Ratio
SD	Standard Deviation
TRL	Technology Readiness Level
TTO	Technology Transfer Office
USA	United States of America
VC	Venture Capital
WIPO	World Intellectual Property Organization
WOISA	Written Opinion of the International Search Authority

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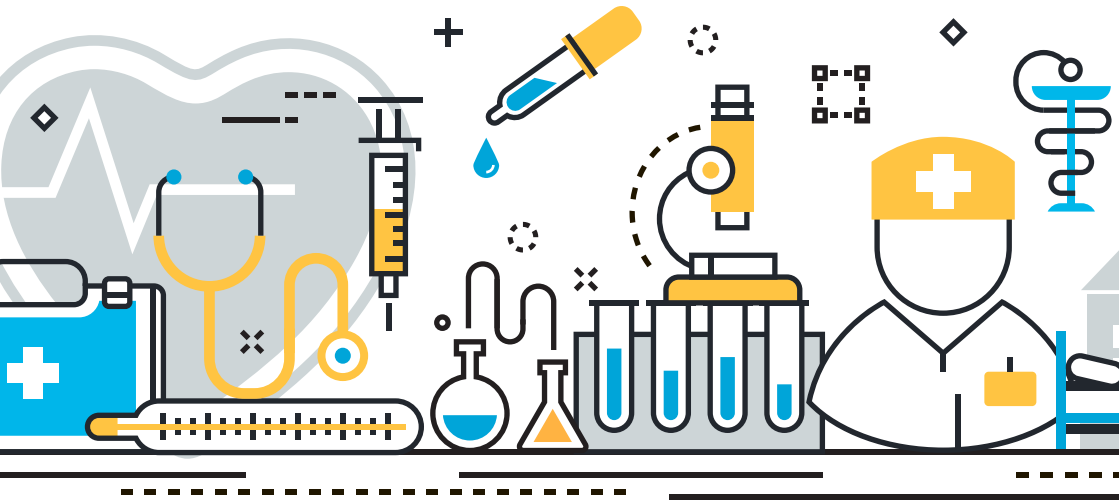
INTRODUCTION



Before biomarker discoveries made in research organizations can be commercially utilized in the clinical laboratory settings, many studies and surveys need to be completed and many questions answered. Is there a market need? Can enough scientific and clinical evidence be generated to convince the end users? Is the biomarker patent protectable? Can the invention be transferred into a practical product and produced at a scale that makes sense financially?

Although commercial product development is not the focus of academic research, understanding the requirements of the industry and real-life end users are prerequisites for the successful commercialization of new biomarker assays. According to marketsandmarkets.com, the global biomarkers market is estimated to approach 46 billion euro by 2021. The growth is mainly driven by the increasing amount of R&D funding, increasing number of diagnostic applications, increasing number of contract research organizations, and high prevalence of cancer.

This handbook collects some of the best practices and pitfalls encountered at different phases of biomarker discovery and development, as well as patent protection and technology transfer at universities, hospitals and research organizations. The handbook focuses on in vitro diagnostics (IVD)-applicable biomarkers, i.e. markers that could potentially be examined in clinical specimens to provide information on the health status of a person in the healthcare or home settings. Regulatory focus is in the European IVD Regulation 2017/746.

The input for the collection has been sought from true-life practices which have led to success; practices found in literature and taught by experts in the field; opinions, expertise and experience of the different stakeholders (incl. end users, companies, TTOs, researchers, financiers), recommendations found in guidance, regulation or laws, as well as practices learned the hard way, i.e. repeatedly failing somewhere in the process and later adapting the process for increased success.

The best practices mainly include practices that are prerequisites for successful commercialization, but also practices that have been found to promote IVD-applicable biomarker commercialization.

The pitfalls are often the reasons why the commercialization fails and are of course something that should be avoided. These can relate for example to items or data that is missing or suboptimal, typical obstacles or failures somewhere else in the process (e.g. in patenting), or pieces of advice received from the industry partners or end users.

The main target group for the handbook is people involved with technology transfer, such as the personnel of Technology Transfer Offices (TTOs). However, the presented practices are not intended to be interpreted as strict rules but rather a source of inspiration. Optimal ways to proceed with patenting and commercialization significantly vary between cases and circumstances.

2

CLINICAL IMPACTS OF IVD-APPLICABLE BIOMARKERS

2.1 Biomarker definition

A biomarker is a characteristic that can be objectively measured and evaluated as an indicator of a physiological or pathological process in an individual or an individual's response to a therapeutic intervention. The closest synonym to a clinically useful biomarker in the context of IVD is an analyte, i.e. a component (molecule) in a clinical specimen the presence, absence or concentration of which is measured in an analytical procedure such as by a laboratory test to obtain information on an individual's health status.

The biomarker (or analyte) can e.g. be a nucleic acid, protein, polysaccharide or metabolite. Alterations found e.g. by clinical inspection, physical measurement of organ functions (e.g. blood pressure, cardiogram), or microscopy of visual tissue appearance are not included in the scope of the current handbook. The scope is also narrowed down to human applications, although many characteristics and requirements are similar for veterinary applications.

In healthcare, biomarkers have been used to detect, predict and monitor disease and to selecting the best therapeutic actions. In the pharmaceutical industry, the biomarkers are utilized as versatile tools throughout the drug development process. Biomarkers enable evaluating the action of new drug candidates on their specific targets, the pharmacological and clinical efficacy of the drug candidates, as well as the anticipated safety risks such as drug-induced toxicity. This handbook, however, focuses on IVD-applicable biomarkers.

IVD-applicable biomarkers are also increasingly being used for individualizing therapies (also known as personalized medicine) so that genetic and somatic factors known to influence the patient's response to treatment are taken into account when selecting the best fitting course of treatment. Personalized medicine is all about understanding the mechanism of diseases and pairing specific drugs with specific diagnostics (also called companion diagnostic) based on the disease-specific molecular knowledge.

In all these applications, the clinical benefit and the analytical and diagnostic accuracy of the biomarker are crucial to enable efficient translation from the discovery to the use in the real-life settings. From a commercialization perspective, successful IP protection, competitiveness with existing or alternative solutions, as well as fluent interaction and collaboration between the academia, industry and end users form the other three cornerstones of successful biomarker commercialization.

2.2 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 originate 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.
- **Establish a dialogue with clinicians early on in the process** (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. Contacts with clinicians allow them to verify the clinical relevance of the biomarkers. This dialogue, preferably with 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 dialogue.** 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.

PITFALLS

- 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.
- The new biomarker threatens an existing business model. The novelty creates pressure against any change from those benefiting from the existing model.

2.3 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 will be translated 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. There might also be subpopulations in which testing is not justified e.g. due to an increased risk of false results or lack of effective treatment.
- 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 the clinicians 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.
  - addresses a significant unmet medical need (or replaces an unsatisfying existing solution) with a potentially considerable impact on public health
  - allows specific association with the disease in the target population or 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, does not involve unnecessarily complex result interpretation.

PITFALLS

- 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 models 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.

2.4 Economic evaluations

Understanding the true needs of clinical laboratories is vital. Especially because there is increasing pressure to provide cost-effective healthcare, which is based on documented guidance and defined "best practices".

In a cost-effectiveness analysis (CEA), the objective is to determine how to maximize a health benefit (e.g. life expectancy) with a (limited) budget, i.e. in a CEA one can compare the relative costs and health outcomes of different clinical care pathways. In the closely related "cost minimization analysis", the objective is to find the most inexpensive way of achieving a given output (e.g. less hospitalizations due to a specific condition). The cost-benefit analysis (CBA) is a more monetary analysis which assesses whether the health benefits achieved using a certain testing/therapy sequence (clinical care pathway) exceed its costs. The analysis takes into account the costs and consequences of testing and typically compare the costs and outcomes between new and existing clinical care pathways.

Health technology assessment (HTA) is an extensive multidisciplinary and international assessment of healthcare technologies. It can be used to develop internationally consistent practices and guidelines. HTA is needed especially when the new test is particularly expensive, particularly important for public health, or significant regional variation in use has been observed.

Mini-HTA is a narrower but similarly systematic evaluation that can be used by hospitals to assess the conditions and effects of a new method at

hospital or local level. Mini-HTA identifies the advantages and disadvantages of the test being assessed, the financial implications and the consequences for the patients and the organization.

The formulation of the question for an economic calculation varies depending on the perspective, i.e. whether the analysis is performed by the initiative of a test manufacturer, laboratory, hospital, clinician, or payer. Payer means an entity (other than the patient) that finances or reimburses the cost of health services, such as public healthcare authority, insurance company, employer or union.

BEST PRACTICES

- New IVD tests are introduced in clinical routine only when supported by a strong evidence of improving the patient outcome or reducing costs while not compromising the care of the patient.
- Economic evaluations should be made early by describing how the clinical care pathway is made more efficient by using the test. For example is the diagnostic accuracy improved so that there are fewer unnecessary hospital admissions or fewer additional tests or diagnostic procedures required.
- From the perspective of (at least) the payers, cost-efficiency often means replacing or decreasing more expensive tests or reducing the number of admissions or length-of-stay in hospitals.
- From the perspective of a clinician, a new test should provide more diagnostic sensitivity or specificity or new information that adds to the information available from existing tests and improve patient outcomes e.g. by allowing selection of the most optimal treatment.
- From the laboratory perspective, it must be possible to incorporate a new test into the routine workflow and it must be affordable to run, especially since laboratories are under huge pressure to reduce costs. A cumulative number of tests is not ideal and a new test should preferably replace an older one (where feasible).

- The decision to introduce a new IVD test will be influenced by the reimbursement policy, which differs in the several European healthcare systems. On the other hand, positive economic evaluation is key for favourable reimbursement decision. Regulators and payers are indicating that marginal improvements are less and less likely to be reimbursed in the future, but testing strategies may also differ between hospitals depending on the diseases they are specialized in.

PITFALLS

- Prospective cost-analysis and economic evaluations are difficult, slow and costly and the true impact and the far-reaching effects on clinical outcomes become better understood only with time. However, preliminary estimates concerning the economic and clinical outcomes are easier to accomplish with the help of an expert such as a commercialization consultant who is experienced in the particular field and has skills in health economics. It may yet be difficult to acquire pioneer user sites even for a highly promising and cost-effective new marker. Having a new marker introduced and reimbursed will take time.
- Even if no special chemistries or instrumentation is required, the cost of a new test may be much higher than the ones readily on the market due to the low number of tests used in the beginning and the added costs of recent IPR protection, product development, performance evaluation and registration investments. Health benefits and cost savings achieved by the new method are therefore essential. (Also see the chapter on competition analysis.)

2.5 Other impacts of testing

2.5.1 Social, psychological, ethical and legal impacts

Diagnostic testing may have consequences and impacts that reach beyond the intended purpose. Other impacts may comprise e.g. ethical, psychological, legal and social effects. Although clinical performance studies needs to be pre-approved by an ethics committee prior to start, the ethical and other considerations often span more broadly than the issues covered in the study plans.

BEST PRACTICES

- Check that the voluntary informed consent of the specimen donors (patients or their legal representatives) allows for any new (academic or commercial) use planned for the specimens or results obtained using them.
- It must be made clear to the patients what the difference is between being a subject in a clinical study and being a patient.
- Keep in track of the limitations of the biomarker and/or the assay format used. When taken to clinical use, the test providers need to clearly communicate to clinicians the limitations of use for the test and also specify what it cannot be used for.

PITFALLS

- Information on incurable conditions is needed from the perspective of medical research and drug development. However, outside primary diagnostics, providing patients with information that cannot be used to treat them may be questionable from the perspective of ethics. It is also difficult to justify the cost of such testing in the healthcare settings.
- Testing of hereditary conditions or other severe health risks may have psychological impacts for the patient and/or the relatives.

Testing just for knowledge's sake is rarely justified but specific measures for intervention or adjusted therapy would need to be identified and engaged as a part of the clinical care pathway.

- When the procedure for definite diagnosis is invasive (such as surgical biopsy), it is not only uneconomical but also unethical to perform such procedure to a large number of people who screen positive only due to the low specificity of the screening test. Also, the compliance for an invasive operation may be low if the risk of an actual disease is low.

2.5.2 Logistical considerations

2.5.2.1 Centralized testing versus near-patient testing

The suitability of a biomarker for near-patient testing (also called point-of-care testing, POCT) depends especially on the urgency of the result but also on the turn-around-time (including specimen preparation), ease-of-use, robustness and diagnostic accuracy of the test, and whether results are available rapidly enough by other means.

It is important to carefully weigh the requirements of near-patient testing and the characteristics of a new test intended for such use. Amenability to integration into a laboratory automation system is a typical requirement for a new marker in each case.

BEST PRACTICES

- Near-patient testing is especially useful in treating patients with acute and life-threatening conditions, but also in making rapid decisions on the treatment of common infections and chronic diseases. If a new biomarker assay facilitates significant advances in treating the patients, the requirement for specialized instrumentation may be accepted more easily. However, complex, multi-step assay procedures will always have limited applicability to near-patient testing because of the requirement for either skilled (laboratory) personnel or complex instrumentation.

- During patient transport or in rural settings (e.g. outside cities or towns and in developing countries), the choice may be between near-patient testing and not testing at all. Near-patient testing may also provide benefits including reduced specimen volumes e.g. in patients who are tested daily.
- In rural settings, especially in developing countries, the prerequisite for wide use of a test is a low cost. Requirements for electricity, cold storage of reagents or professional maintenance of instrumentation may not be acceptable in settings where diseases are typically diagnosed based on clinical examination only and where many individuals remain undertreated anyway.
- The main advantage of simple manual assay devices such as immunochromatographic assays is that instrumentation is not necessarily required, but the tests can be performed anywhere by anyone. The reader-free tests are typically qualitative or semi-quantitative. Disadvantages include operator-dependency in interpreting the results. Simple readers and even phone applications are available for a more quantitative readout.
- Instrumentation intended for out-of-laboratory use must need minimal maintenance and repair. The calibration and quality control (QC) issues need to be planned carefully.
- Because most of the largest IVD manufacturers and several hundred small companies are committed to developing near-patient testing systems, the spectrum of different assay formats and systems is wide. The trend is towards full quantitative, miniaturized, homogeneous and even non-invasive testing methods in the future and there may be a high market potential for such technologies.

PITFALLS

- Increased speed of testing may not always provide a sufficient competitive edge for a new test. For the majority of tests, it is of minor importance to the patient outcome whether the test

results are received immediately or after few hours or days. Also, it may not be sensible to measure one test on-the-spot and then wait for other results from the central lab. Most tests can also be performed speedily enough in the central laboratory as STAT tests, i.e. by marking the specimens with a "STAT"-sticker and placing them in a priority lane in which the tests requested are given the highest priority for processing, analysis and reporting. ("STAT" is an abbreviation of the Latin word "statim" which means immediately, without delay.)

2.5.2.2 Self-testing and home healthcare

Self-testing and home healthcare applications are in increase. While diagnostic testing in the healthcare settings is mainly performed to detect or monitor a disease, the regular consumers are increasingly interested in their personal health and for example tests that can be purchased in the internet and rule-in or rule-out certain risks of disease even in the absence of symptoms. Home healthcare or self-testing can also be relevant for future trends in telemedicine, where no direct patient-clinician contact is necessary.

BEST PRACTICES

- Recreational tests (e.g. genetic tests that are sold directly to customers) have an increasing demand. It may not yet be sensible to perform diagnostic testing in asymptomatic population because false positives are likely to occur frequently.
- Monitoring of the treatment of already diagnosed (chronic) diseases at the home healthcare settings is increasing and has the potential of improving clinical outcomes. The home healthcare sector is likely to present a huge market for the future.

3

THE IVD-APPLICABLE BIOMARKER PIPELINE

The path from candidate discovery to translation into an IVD assay is long and complicated. FDA has recently launched standardized and comprehensive processes for developing biomarkers for use in drug development (the Biomarker Qualification Program, BQP). However, in the case of IVD-applicable biomarkers, the currently existing regulated processes rather target the end products i.e. the IVD devices (assay kits) only.

For biomarkers that pass the early discovery and the confirmatory proof-of-principle steps, the immediate next (and much more resource-intensive) phase is establishing a specific assay (prototype) for the proof-of-concept studies where the analytical and clinical performance characteristics of the prototype can be properly assessed.

3.1 Candidate discovery and biomarker verification studies

The discovery of biomarkers is increasingly performed with semi-quantitative methods that allow the analysis of differential expression of biomarkers in the investigated condition. The result of the discovery phase is a list of molecules, which are found to be differentially expressed in the case and control specimens.

Thousands of candidate biomarkers have been discovered this way and the number of publications has exploded in recent years. However, few findings enter to the specific assay development phase, pass the evaluation of analytical and clinical performance characteristics, and are eventually transformed into IVD assays.

BEST PRACTICES

- The discovery of a candidate biomarker is just the beginning of a long road. To have foreseeable commercial use, the marker (or panel of markers) needs to be practical – e.g. can be measured with a feasible technical method, in a sufficient time window, and with a sufficient throughput – and also improve the clinical care pathway in a cost-effective way.
- It has been estimated that the majority of protein biomarkers are linked to multiple diseases and that disease-specific protein markers are discovered much more rarely. It is important to consider the possibility for a shared molecular pathology across

diseases (i.e., lack of specificity) early on when evaluating a new candidate.

- The term "validation" is in regulatory and industry glossaries limited to the development of commercial products in a standardized process of establishing that the performance of a test, tool, or instrument is acceptable for its intended purpose. In IVDR, product verification and validation documentation is meant to comprise the results of all tests and studies undertaken to demonstrate the conformity of the IVD device with IVDR and the applicable general safety and performance requirements (GSPR). The performance evaluation data according to IVDR consists of three components: data demonstrating the "scientific validity" (association of an analyte with a clinical condition or a physiological state), "clinical performance" (ability of a device to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended user) and "analytical performance" (ability of a device to correctly detect or measure a particular analyte) of the test.
- To ensure long-lived patent applications with an optimal scope and focus, applications should not be filed based on the earliest findings because at this stage of discovery most findings are still very uncertain and there may not be proof of disease-specificity. Furthermore, an early invention often significantly changes along with the more targeted experiments and increased sample size: an early patent application may prevent patent protecting the most optimal form of the method or product because changes in the patent application are not allowed after the end of the first year. (Also see the chapter Patenting versus publishing: alternative protection strategies for early phase inventions.)
- If you already filed a patent application, the minimum requirement is to revisit your patent protection when new results are obtained.
- It is also important to generate knowledge on the biology of the candidate biomarker: where it is expressed, when, for how long, how many different manifestations of the molecule exist, how stable is the molecule and what is the extent of variation between individuals and different ethnicities.

PITFALLS

- Biomarkers that are linked to multiple diseases via shared molecular pathology will not facilitate disease-specific use at least as stand-alone tests.
- Biomarkers may also be expressed differentially, although they have nothing to do with the disease under investigation. For example, cellular stress is known as a major reason for detecting differences between patients and controls. Such biomarkers will not facilitate disease-specific use.
- It is important to separate candidate biomarkers and verified biomarkers to avoid filing patent applications too early. Typical signs of the earliest findings, belonging to Technology Readiness Level 1 (TRL1) include:
- All proof has been generated with a non-targeted discovery method such as proteomics or transcriptomics analysis.
- Results are presented inclusively by comparing the "sick" and "healthy" at group level, or as analysis of paired specimens.
- P-value is used to estimate the significance of the findings.
- Specimens are not representative of the population but have been heavily selected.
- In the scientific literature, the term "biomarker validation" is sometimes incorrectly used to describe the early confirmatory process. Formal validation is, however, a standardized and regulated process where typically thousands of prospectively collected specimens are analysed in a clinical performance study. Providing proof for the association of an analyte with a clinical condition is referred in the IVDR as to establishing the "scientific validity of an analyte". The term "verification" should also be relatively safe to use.

3.1.1 Clinical specimens

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 analysis.

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 needs to be performed with the same protocol. The same goes for 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.

PITFALLS

- 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.

3.1.1.1 Patient consent

When designing a new clinical study, the wording in the voluntary informed consent that the patients (or their legal representatives) sign should be formulated carefully as it dictates the future use of the specimens.

BEST PRACTICES

- Follow the format as suggested by the local ethics committee (each of which committees act in accordance with the Declaration of Helsinki for ethical principles for medical research involving human subjects), but also prepare for continuing research and utilization of the results obtained.
- Try to describe the scope and field of research at a level that is not too heavily bound on the ongoing project but rather allows use of the collected specimens in future projects involving other analysis techniques and/or targeting other molecules. The dura-

tion of storage of the specimens should be long enough to allow such continuing research.

- Also incorporate that the results obtained by using the specimens may be used for commercial purposes with the aim of producing new and more effective diagnostics and drugs for the diseases being investigated.
- Describe the anonymization process in the case that specimens are transferred between organizations. In the patient consent, include consent for such transfer.
- Consult your legal department on which requirements of the EU General Data Protection Regulation (GDPR) needs to be taken into account in your case.

3.1.2 Statistical versus clinical significance

Clinical significance refers to the practical importance of a scientific observation. It is used as a tool to quantitatively assess whether the magnitude of an observed difference is such that it is relevant to patients. In comparison, statistical significance refers to the likelihood of a difference being observed due to chance (statistical hypothesis testing). It does not give information on the scale or direction of the difference. Different measures are used to assess the clinical significance and statistical significance.

Note! Below, examples concern the analysis of group-level findings in the early discovery phase (proof-of-principle phase). For any next phase (proof-of-concept) studies, see the chapter Specific assay development for important measures like diagnostic sensitivity, diagnostic specificity, positive and negative predictive values, cut-off/reference range and AUC.

BEST PRACTISES

- Use p-value only to ensure the statistical significance of results. If $p > 0.05$, there is no need to assess the clinical significance of results.

- Case-control studies are useful for hypothesis generation, but their value in assessing the clinical significance of a new biomarker is very limited. Rather, perform a panel study preferring a specific assay platform.
- Effect size (standardized mean difference between groups) is a simple way of quantifying the difference between two groups. Effect size = ((mean of patients) – (mean of controls))/SD, where SD (standard deviation) is the spread of values in the non-affected (control) group (or both groups in case the control group does not represent the healthy population). Effect size allows assessing the significance of the result as quantitative difference without confusing it with the resolution of the difference (like p-value does). It is important to discuss whether a clinician would concern the observed absolute value (difference) clinically relevant.
- The 95 % confidence intervals (CIs) give the likely range of the effect size and allow assessing the clinical significance (e.g. of concentrations) quantitatively on the case-by-case-level. The upper 95 % CI indicates how large the difference can be at its highest.
- In the case of a new diagnostic biomarker, one is able to estimate if the difference of the biomarker concentration in the affected people is large enough to convince the clinicians. One can assess all the dots (patients) within the CI similarly – could the clinician see a difference large enough to catch his/her eye in the routine settings?
- When evaluating CIs in relation with statistically calculated values such as risk ratios, the width of the CI directly shows how precise the estimate is – the narrower the CI, the more reliable the estimate.
- Ratios are useful e.g. in making findings comparable with each other, estimating a risk for a certain outcome, or comparing the effect of different interventions.
- Relative risk or risk ratio (RR) compares the probability of an event/outcome in the selected group to the probability of the event/outcome in the control group. The further away from 1.0,

the greater the effect size, i.e. difference in probability. RR > 1 means the risk of outcome is increased (e.g. exposure causes disease) while RR < 1 means the risk is decreased (e.g. exposure decreases disease).

- Odds ratio (OR) is presented as a measure of the effect size when RR cannot be calculated (such as in the case of paired case-control specimens). OR can be used e.g. to assess how strongly a certain gene pattern is associated with a given (rare) disease in the population. The problem with OR is that it always gives a much more impressive value than RR, resulting the reader to overestimate the risk of the given event in the population assessed. Therefore, always calculate RR where feasible (i.e. when prevalence or incidence data is available) or compare ORs received with those obtained in closely related studies.
- Hazard ratio (HR) is RR averaged over the duration of the trial, i.e. it measures the effect of an intervention (or a stratification criteria) to an outcome over time. HR is used almost solely together with Kaplan-Meier (survival) curves comparing the outcome of a group with specific intervention/ stratification-pattern with a control group.
- Always avoid using a complex algorithm when you can use a simple ratio.

PITFALLS

- A small p-value does not necessarily have a practical impact and does not guarantee that the difference is clinically useful. Large sample sizes just give high resolution – so high that even the smallest differences between groups can often be detected. Results that are statistically significant can just as well be clinically irrelevant and have no true impact on the treatment of patients. Other assessments to judge the clinical significance are required.
- Case-control studies are inherently biased studies. The extent of sample picking needs to be decreased in the verification studies.

3.1.3 Compliance with regulatory requirements

The regulatory requirements related to commercial IVD product development set the rules for producing the proof and documentation for product registration (such as CE-marking) and meeting with the stringent quality requirements for manufacture. Complying with the regulatory requirements is the core competence of the companies productizing, manufacturing and selling IVD products.

The academic organizations rarely have resources for commercial product development and manufacture, let alone marketing and distribution. However, in the research settings it is important not only to adopt good scientific practices, but also to understand the prerequisites of IVD test development and registration issues, although the key competence in the academia would remain in finding and proving the technically and clinically optimal approaches.

BEST PRACTICES

- Proper documentation of all the experimental designs, reagents (including manufacturer, product code, lot, expiry date, storage conditions), key intermediate products and tools, exact assay conditions (e.g. instead of "RT"), replicates/repeats, instrumentation (incl. instrument qualification and calibration information and all settings and specifications) etc. early on is crucial for later registration and commercialization of a new assay concept. Even the early documentation should follow the spirit of Good Laboratory Practice (GLP).

PITFALLS

- If proper documentation of the early phases of research is missing, it will become a pain later when the regulatory submissions are topical. For example, all intermediate results and tools (such as cloning plasmids) need to be properly documented, even though they would not be needed later in the development.

3.2 Specific assay development

Research laboratories and routine clinical laboratories differ from each other to a significant extent. In research settings, more resources (such as the researcher him/herself) are available for managing the high-tech laboratory instrumentation or complex experiments, as well as for troubleshooting any technical issues arising. In a busy routine laboratory it is difficult to allocate staff for performing manual assay steps, operating non- or semi-automated instrumentation, or interpreting raw data.

An important early step of the translation process of a scientific finding into clinical test is changing the methodology used during the discovery phase for a specific, practical and up-scalable testing format. The aim is to achieve a simpler, faster, cheaper, automatable and more specifically targeted prototype assay.

3.2.1 Establishing a prototype in a specific assay platform

BEST PRACTICES

- Consider the specific testing platform early. Using an already established platform has a higher probability of success. Established platforms include e.g. immunoassays, nucleic acid amplification methods, microarrays, sequencing assays and immunofluorescence, but also other methodologies such as those based on mass spectrometry (MS) are becoming widespread (consult the intended end users).
- Converting the assay into a specific and practical prototype assay early on is important also because it may turn out difficult or even impossible to do. If you have several biomarker candidates to choose from at the proof-of-concept phase, focus on candidates that are most amenable to robust and specific assay design. It is important to ensure that the analytical sensitivity of the method is sufficient for the biomarker of interest, i.e. the clinical concentrations of the biomarker fall within the linear measuring range.

- Ensuring that raw materials needed for the assay are commercially available (or can be made available) at GMP grade from an accredited manufacturer is a part of making preparations for prototype assays that can be commercialized with reasonable efforts (also see the chapter on FTO).
- For the same reason, the need for specialized instrumentation or modified chemistries should be reasoned with an undisputed inapplicability of the more conventional tools and means, not getting stuck with the methods used in the discovery phase. Unnecessarily binding the new assay (and IPR) to a special component or method may also significantly limit the number of potential licensees.

PITFALLS

- Sticking to the use of a technical platform that is available almost only for research will delay the introduction of an assay to clinical settings.
- Other characteristics limiting the routine use of a testing platform include low-volume automatization, low throughput and batch-wise analysis (results not available on demand; only suitable for non-urgent tests).
- A rare test that requires a fast response has a low chance in finding a place in routine.
- Diagnostic methods that require complex combinations of alternative tests (i.e. a long decision-making tree) may be considered to involve too much computing, resulting in clinicians losing their touch about the decision they should take and therefore compromising their individual competences and responsibilities as experts on certain diseases. Any decision-making trees should be understandable by one look.

3.2.2 Analytical performance characteristics

Analytical performance characteristics refer to the ability of a test to conform to predefined technical specifications. There are two main types of performance characteristics: those for practicability (e.g., required skills, specimens accepted, criteria for specimen collection and handling, turn-around time) and those for reliability (e.g., accuracy of measurement (resulting from trueness and precision), trueness (i.e., bias), precision of measurement (i.e., repeatability and reproducibility), analytical sensitivity (i.e., limit of detection), limit of quantification, interference, linearity, measuring range and control of known relevant endogenous and exogenous interference and cross-reactions).

It is mainly the clinical use that dictates the requirement specifications for the analytical performance characteristics.

3.2.2.1 Practicability characteristics

The important steps in the translation of scientific findings into routine IVD assays include gaining more knowledge of the biomarkers and their characteristics, as well as changing any high-tech or non-targeted methodology used in the discovery phase into a specific, economical and up-scalable testing format such as immunoassay, PCR, or other assay format used in the clinical settings.

BEST PRACTICES

- Pre-analytical requirements for a suggested new biomarker must be thoroughly studied at an early stage.
- Use a checklist for e.g. the following practicability parameters:
  - specimen type
    - availability – is the specimen collected routinely and can the commercial sample collecting devices be used?
    - invasiveness – is it in accordance to the type of test/use of result? Is the (invasive) specimen collected in each case?
  - stability of the biomarker in the selected specimen type; appropriate specimen collection, processing and storage

protocols. Does the molecule become modified after extracting it from the circulation?
- expression of the biomarker in relation to the indication (timing, duration, concentration range, alternative manifestations of the molecule)
- scalability and amenability to automation
  - required hands-on-time
  - in case of near-patient or home tests, the required manual steps
- total turn-around-time

3.2.2.2 Reliability characteristics

Along with practicability characteristics, reliability requirements are the second type of performance characteristics that are important in the translation of biomarker discoveries into IVD assays. The reliability characteristics include parameters such as precision of measurement, limit of detection, limit of quantification (or functional detection limit), interference, linearity and measuring range.

While the reliability of the actual measurements can be significantly increased by commercial assay development, the importance of the more profound characteristics such as diagnostic accuracy naturally increase when the result has a direct effect on a medical decision. Generally, important decisions such as proceeding into surgery or biopsy should not be based on results with a high diagnostic inaccuracy, originating for example from a low number of true positives amongst a high excess of false ones, i.e. low prevalence of the biomarker. When the next step is further testing, the diagnostic sensitivity needs to be sufficient to catch most of the cases.

BEST PRACTICES

- Use a checklist for e.g. the following parameters:
  - Analytical limit of detection (typically blank + 3 SD)
  - Limit of quantification/functional detection limit/analytical sensitivity (typically CVconc < 10 -20 %)
  - Linear measuring range vs. clinically relevant concentration range (the medical decision level must lie in the linear part of the measuring range)
  - Assessment of potential hook-effect with high analyte concentrations (immunoassays)
  - Recovery in clinical specimens (spiked specimens)
  - Precision of measurement and repeatability (within-run, between-run, between-day etc.)
  - Within- and between-subject variation and whether e.g. fasting state, circadian rhythm, age, gender, ethnicity affects the results
  - Analytical specificity and cross-reactivity
  - Matrix effects and interference in clinical specimens (need for removing or blocking disturbing molecules)
  - Area-under-curve (AUC) and optimal exemplary cut-off value or reference range
  - Diagnostic sensitivity and specificity (diagnostic accuracy) using the suggested exemplary cut-off value or reference range (from apparently healthy individuals)
  - Prevalence calculations along with positive predictive value (PPV) and negative predictive value (NPV)
  - True detected PPV and NPV.

PITFALLS

- Interference by endogenous biological substances can be a complex problem in IVD assays. Both positive and negative interference can occur and be very unpredictable in nature. False results may also be caused by several other mechanisms, including cross-reactivity or low sensitivity for some molecular

forms of the analyte. It is not realistic to expect the commercialization partner to solve the problems later in the assay development process, but they should be solved earlier.

- Complex specimen preparation methods are not suitable for routine use, but the methods need to be amenable to automation as far as possible. Labour-intensive steps such as freeze/thaw cycles need to be avoided. In case of near-patient testing, any manual steps sensitive to the knowhow or experience of the operator need to be eliminated.

3.2.3 Clinical performance characteristics

Clinical performance refers to the ability of a test to detect patients with specific clinical condition or physiological state. It is about demonstrating that the biomarker is associated with the intended condition in the intended target population in an extent that positively affects treating of the patients.

BEST PRACTICES

- The criteria for the clinical performance and the appropriate study design need to be decided beforehand based on the intended use of the test. Characteristics include e.g. diagnostic (i.e. clinical) sensitivity, diagnostic (i.e. clinical) specificity, positive predictive value (PPV), negative predictive value (s), and expected values in normal and affected populations (reference range or cut-off).
- If the test does not achieve the pre-defined clinical performance criteria in the performance evaluation study (and it is not a question of optimization), further evaluation or patent protection is not required. Alternative uses of the marker can be considered (e.g. use in another related indication, such as prognostics or monitoring instead of diagnostics).

3.2.3.1 Effect of prevalence on test performance

Prevalence of the disease targeted has a high impact on the accuracy of screening tests and diagnostic tests. A new biomarker test for a rare disease would have to be extremely accurate (specific) in order to not produce many false positive results amongst the high excess of not-affected people.

For example: The prevalence of a disease is about 20 cases/100 000 individuals, all of whom belong in the target population of the test. If you use an assay with 99 % diagnostic sensitivity and test all the 100 000 individuals, you will probably catch all the 20 cases with the disease. However, if the diagnostic specificity of your assay is 99 %, you will get 1 % of false positive results, which is 1 000 cases. This means 50 false positives for each true positive case. If your diagnostic specificity is 95 %, you will get 5 % false positives, which is 5 000 cases, 250 for each true positive.

BEST PRACTICES

- Positive predictive value (PPV) and negative predictive value (NPV) take into account the prevalence of the disease when evaluating the clinical performance characteristics of new assays. In the above example (diagnostic sensitivity and specificity 99 %), the positive predictive value would be about 2 %. This means that only about 2 % of the persons testing positive are actually ill.

PITFALLS

- Assay optimization is more demanding for tests targeting rare or low-prevalence diseases due to the generation of false positive results amongst large excess of non-affected people.
- Furthermore, proper performance evaluation of the test might be problematic unless a special source (such as specialized clinic or research group) of positive specimens is identified.

3.2.3.2 Application-specific requirements

There are many types of IVD test categories.

Diagnostic assays are used to identify the presence or absence of disease in symptomatic individuals, and the desirable result is that the test is positive only in case of disease. The clinical performance of a diagnostic assay can be evaluated in a diagnostic accuracy study, where the test is compared with a reference standard and/or another assay in a patient population suspected of having the disease.

A ***prognostic*** assay is used to infer the risk for a disease-related event. The clinical performance of a prognostic marker is demonstrated by establishing the association between the biomarker and the event of interest. While a prognostic marker allows predicting the overall clinical outcome of a patient (regardless of therapy), it typically also allow to identify patients likely to benefit from more intensive therapy or at least closer monitoring.

Predictive assays help identifying patients most likely to respond to a specific intervention.

Staging biomarkers correlate with the stage of the disease in readily diagnosed patients.

Monitoring tests employ biomarkers that rapidly respond to a change in the clinical course of the disease under investigation.

Risk prediction tests will prospectively identify healthy individuals at an increased risk of developing disease.

Screening tests are used to test asymptomatic individuals for latent disease.

Companion diagnostic tests allow determining the applicability of a therapeutic drug to a specific person.

Performance requirements are slightly different from class to class, and also the strategy of incorporating the new test in the clinical care pathway affects the design of the performance evaluation studies.

3.2.3.2.1 Replacing versus add-on/complementary tests

Defining the position of the test in the clinical care pathway is one of the determinants when selecting the most appropriate strategy for the performance evaluation studies.

BEST PRACTICES

- If the new test is to replace an existing one, it is most practical and useful to directly compare the diagnostic accuracy of the new and old tests against a common standard or clinical outcome.
- If the new test is to supplement the clinical care pathway by bringing new information that will help to treat the patient the most optimal way, a comparison is required where the new combination of tests is compared with the existing test or process.
- The commercialization of an add-on test is considered more straightforward because of the lower extent of competition with the existing test providers. Even so, establishing the added clinical benefit (without a risk for over-diagnosis) is similarly important.

3.2.3.2.2 Screening tests

Biomarkers intended for screening probably face the strictest requirements amongst the many classes of test applications. High emphasis is put on characteristics like non-invasiveness, low cost, simplicity-to-perform and diagnostic accuracy -- in terms of both diagnostic sensitivity and diagnostic specificity.

For population screening to be justified, there should be little doubt of the net benefit of the program. Reductions in morbidity and mortality are to surpass the costs of screening and treatment, as well as the further processing of people who falsely screen positive.

BEST PRACTICES

- The most important requirement for a screening biomarker is to fulfil the main goal of a screening program, which is to detect the illness at a stage early enough so that treatment is

more successful and cheaper than if detected later. In many cases, early detection means year(s) before clinical symptoms arise. Establishing time-depended ROC curves (corresponding to different time lags between testing and the clinical diagnosis) can be very informative. Success of treating is mainly measured as a decrease in mortality.

- Another high priority for a screening test is high specificity, translating into a low false-positive rate. Each false positive subjects a person to unnecessary further testing or diagnostic procedure, which, especially when invasive, are expensive and burdening for healthcare and increase the trouble and anxiety of the patients.
- False negatives, resulting from low sensitivity, jeopardize the entire idea of the screening program and hence a very low false negative rate is typically accepted.
- The acceptable false result rates will vary with the disease, its prevalence, the work-up of people screening positive and the consequences for people screening false negative. The issues are to be addressed and discussed early on.
- The screening test itself needs to be non-invasive and inexpensive to facilitate its widespread use and compliance of the people screened. For example, a blood-based test improves the screening compliance and is likely decrease the cost of screening.
- If the biomarker discriminates well only in a certain subpopulation, it might be valuable for screening that selected population.

PITFALLS

- Cancers are often a heterogeneous group of cases ranging from aggressive and metastatic forms to minimally progressive forms. Catching and treating the slow growing forms early, before clinical manifestations, is not what is pursued by screening, as the clinical outcome of the patient is often the same. For example,

the PSA-based screening programs have been observed to catch slowly progressing cancer forms in a significant proportion.

- Similarly, a biomarker assay that misses an aggressive subgroup of cancers (e.g. a specific mutation) is not optimal for screening.
- Diseases that cannot be successfully treated (such as aggressive gliomas) are not optimal for screening, as little benefit can derived from information only. Discovery of new biomarkers can yet support drug development e.g. by allowing a tool for stratifying patients for clinical trials.
- Diseases that in the absence of a screening program would not be detected and would not cause high morbidity and mortality are not suitable for screening (such as benign tumours).
- Early diagnosis due to screening may also lead to a faulty conclusion of increased survival time. This is because survival is calculated from the time of diagnosis, which is earlier for the cases caught by screening than for those with clinical symptoms.
- A biomarker that only indicates the disease close to the time of clinical diagnosis shows low promise for screening and limited add-on value (unless existing diagnostic tool are very expensive).

3.2.3.2.3 Personalized medicine and companion diagnostics

There is an increasing interest of multiple stakeholders (including diagnostic and pharmaceutical companies, registration authorities, payers, taxpayers, hospitals, clinicians and patients) in ensuring that the clinical trials succeed and that the expensive drugs will give an effective response in the treatment of selected patients. There is an important and increasing trend in using biomarkers in personalized medicine, aiming in efficiently combining diagnostics and best fitting therapeutics.

However, the implementation of the so-called companion diagnostics is still slow-paced and requires exceptionally deep collaboration amongst many stakeholders such as the diagnostic and pharmaceutical companies, regulatory authorities, payers, healthcare providers and clinicians. In the current situation, more pitfalls than best practices has been identified from the assay developer's perspective.

BEST PRACTICES

- Introducing companion diagnostics when launching a new (expensive) drug is a new trend that comes with benefits like cost reductions for the hospitals and avoiding inefficient treatment pathways for some of the patients. When working on such an assay, enter in dialog with the drug owner as early as possible, and at least before entering the international PCT-phase of patent prosecution. This is to allow the company not only to express their interest in entering license negotiations and a (co-)development project (without which the patent may be worthless due to limitations in FTO and/or number of potential other utilizers), but also the possibility to affect the type and scope of the patent protection applied.

PITFALLS

- Differentiation between patients at routine clinical settings is needless, if you do not have the opportunity to differentiate the treatment. Such stratification does not fall within the scope of personalized medicine (but can lead to it via drug development).
- The number of different patient groups and the number of individuals in each group can be unbalanced compared to the available treatments. Developing companion diagnostics requires thorough assessment of the benefit of testing.
- For a companion diagnostic assay, close partnership (co-development) is key in the regulatory approval and commercial launch the assay and drug. The market risk for the assay developer is significantly increased due to the lack of alternative commercialization pathways and partnerships, as well as dependence on the success of the therapeutics.
- In the research settings, a test suitable for companion diagnos-

tics for a certain drug is often developed only after the drug has already entered the market. In that case many of the clinical trials have been performed without the accompanying test. A widespread introduction of a companion diagnostics test at this point requires that the level of added benefit is significant and in accordance with the financial aims of the company. If not, and if the use would be limited to singular hospitals, the patient group may not be large enough to exclude the effect of the drug on specific patients. The interest of a drug company needs to be confirmed early!

3.3 Diseases with no existing biomarkers

There remains to be a relatively long list of diseases and conditions with no existing biomarkers to test at the moment. The Handbook of Biomarkers (Jain 2017, 2nd edition, Humana Press, ISBN 978-1-4939-7430-6, doi: 10.1007/978-1-4939-7431-3) provides a good overview of this issue.

Although the commercial potential for pioneering markers is high in the long term, it is likely to take years and even decades to collect enough clinical evidence to convince the clinicians. Also, the clinical performance evaluation studies and acquiring the regulatory approvals for an IVD test that cannot be compared with an existing one are much more complex by default.

PITFALLS

- If preceding biomarkers are completely missing for a specific indication, it often significantly slows down the introduction of a pioneering biomarker both from the regulatory perspective and from the perspective of acceptance into clinical use. Significant clinical evidence is expected to change a current clinical care pathway to include the assessment of a biomarker for the first time.

- Especially in the case of some acutely life threatening conditions and traumas causing high morbidity and mortality, *in vitro* diagnostics are rarely considered accurate enough to yield definite results that could be used to guide the treatment of the severely ill patients (such as patients with traumatic brain damage). Sometimes, the tests may also be too slow to provide support for acute decisions and/or accurately reflect the current situation of the patient. Although many imaging and surgery methods are invasive for the patient and expensive for the healthcare provider, they often remain the only way to obtain direct and definite results.
- In the absence of sufficiently efficient markers, the use of biomarkers for certain indications may even be declined by the current care guidelines. Approaches that are now considered non-acceptable are likely to be too difficult to commercialize within the resources and time span available for universities and research organizations.
- In any of the above cases, protection and commercialization is most feasible for markers showing ground-breaking results that simultaneously enable sound IP protection. Even in such case, the industry and end users need to be consulted early on. It also needs to be kept in mind that the companies expect the academia to carry their weight to prove the clinical benefit of a new marker. Both the companies and the end users expect to see a lot more than a few scientific publications to be convinced.

4

COMMERCIALIZATION ASPECTS

4.1 Market research

The future customers (clinicians, hospitals, laboratories, pharmaceutical companies or other intended end users) are the best mirror for a suggested new product.

BEST PRACTICES

- Discussions with the relevant industry and end users, especially including clinicians, should be started early on to get valuable input for project planning, steering and management.
- Discussions to obtain feedback can be carried out on the non-confidential level by encoding or hiding the details of the invention. Care needs yet to be taken in all communication (also including interviews, presentations and seminars) - especially prior to submitting a patent application.
- Be prepared to listen to what the potential end users say. From the commercialization perspective, it does not really matter how significant the research is if the customer is not excited about the product.
- While the market research does not always indicate a need for the product that was first envisioned, a slightly different product might be of high interest. Having such knowledge can be worth a lot, so it is important not to become fixed with the first idea.

4.2 Market potential

Determining the market potential and the market value of a patented or patentable biomarker involves taking into account e.g. the invention's degree of readiness, the size of the market (as number of tests) and the competition situation. To ensure that the foreseeable profits exceed the high costs of patenting, the invention needs to have a significant market potential and target a growing market.

IVD tests for prevalent diseases will obviously have more extensive market potential than tests for rare diseases. From the perspective of business, tests targeting large populations have higher market potential and are

likely to be appealing to larger companies. The number of potential licensees and the expected value of license agreements increases at the same pace with the prevalence of the disease / size of the population to be tested. Development of diagnostics for rare diseases may not be attractive for the private sector, forming the main client for technology transfer. However, since some companies specialize in them, it may also be a place for good collaboration.

BEST PRACTICES

- Establishing the target population is an essential part of assessing the market potential for a biomarker assay. Who is tested and when? Everybody? Elderly? Adults? Kids? Newborn? Prenatal? Male? Female? Healthy? Sick? All sick or certain subpopulation? Before or after symptoms? Before or after diagnosis?
- Try to turn the target population into numbers and describe which share or percentage of the population could be reached by the new test nationally and internationally. (Also see chapter on prevalence.)
- Description of the potential earning model (the business case) involves assessing how to make money with the invention. Who is the customer? What is the important need of the customer/ the market to which the invention brings solution to? What is the benefit for the customer? Perspectives of the clinician, the clinical laboratory, the healthcare funding organization are interconnected and of main importance.
- Analysis of the competitive edge includes answering questions such as who are the competitors and what are the alternative solutions? Will the invention replace or supplement the existing products? What is the main advantage of the new product?
- Completely new or complementary solutions that can just be added in the testing protocol will have more value than merely alternative solutions, especially if there is a well-established product on the market that needs to be displaced.
- Once e.g. the above factors (naturally in addition to the clinical significance and benefit) are pre-established, actual market analyses can be ordered from several external actors. Contacting

the potential customers for feedback (on the non-confidential level) is an essential part of the task.

- There are different pathways for regulatory approval of a new test that can also be considered in the economic evaluation. These include producing a diagnostic kit, laboratory-developed assay, analyte-specific reagents (mainly in the USA), or research-use-only kit or reagents. The regulatory process is most stringent for diagnostic kits, but at the same time it ensures the widest use and highest return for a new test.

4.3 Competition analysis

4.3.1 Alternative biomarkers and assay formats

To have commercial use, a novel IVD test not only needs to solve a true clinical problem and be backed-up by convincing evidence, but also somehow be better compared to the competing approaches or add value to the existing testing sequence.

Furthermore, the competition analysis must span the entire spectrum of different approaches. Many diseases have multiple biomarkers due to the involvement of different biochemical pathways, and many biomarkers can be measured at different molecular expression levels.

BEST PRACTICES

- Describe the current routine testing practices (especially the golden standard) with their shortcomings.
- Literature searches (both in scientific and patent databases) for alternative (competing) approaches to solve the above shortcomings should include analysing all the alternative scientific and commercial applications for the same indication, irrespective of the biomarkers or technical platforms employed.
    - The initial searches (to be added as references to the invention disclosure) are best performed by the research team who are the best experts on the advances and limitations of

their technology.
    - TTOs will then perform the more thorough literature searches that are useful for drafting a patent application and ensuring FTO.
- It is important to recognize and describe the significant benefits of the new invention over the competing approaches. Acceptable advantages include, e.g.
    - Increased diagnostic sensitivity and specificity
    - Earlier diagnoses (less advanced diseases with less complications)
    - Earlier therapeutic actions (less costly treatment with better clinical outcomes)
    - Improved convenience and patient compliance (e.g. less invasive sampling which is also likely to result in cost savings)
    - Expected reduced number hospital admissions or length-of-stay
    - Cost savings in testing or other diagnostic procedures (by replacing or reducing more expensive testing and other procedures)
    - Decreasing the number of invasive or harmful procedures.
- If alternative applications do not exist, interviews of end users should be made and documented to ensure that the invention answers a topical and significant clinical question. Encoding or hiding the exact solution allows communication on the non-confidential level (with care). An already filed patent application gives more freedom for the presentations, but also postpones the feedback.
- Following the competition on regular (or even irregular) basis is important, because new methods are constantly invented and singular surveys may give a false impression of non-existing competition. (Note that new patent applications become public only after 18-months.)
- Once a patent application is filed, the Office Actions (OAs) from patent authorities often contain valuable analysis of alternative solutions to the problem to be solved presented in the patent application. Re-visit the competition and FTO analyses to confirm that the advantages of the new method still exceeds those of the patent examiner's findings.

PITFALLS

- Competing applications are sometimes not recognized even though they were for the exact same indication and had the same performance and practicability characteristics. This is mainly because they are executed on a different technical approach or using biomarkers belonging to a different molecular class.
- Knowledge of competing methods also emerges during the patent prosecution process. Evaluation of competing methods should be made each time the patent authorities identify applications with same technical effect. Suggested time point for thorough evaluation is before entering the international Patent Cooperation Treaty (PCT) phase (evaluation then being based on the novelty and patentability report for the priority patent application) and national phase (evaluation then being based on the International Search Report (ISR) and Written Opinion (WOISA) or (at the latest) International Preliminary Report on Patentability (IPRP) of the PCT phase). The same decision making criteria is to be used before submitting the application, i.e. a clear and relevant competitive advantage must remain.

4.3.2 Self-competition

Sometimes the own improvements made after own patent application compete with the markers and methods protected by the application. The new design is typically no longer patentable, when the inventive subject matter has become public after 18 months.

BEST PRACTICES

- In research projects spanning multiple years, postponing of patenting in the early years is recommendable if there is a high likelihood that the invention will be further developed or supplemented later (unless you already can predict the future deve-

lopments, which is not often easy in case of new inventions). This allows ensuring that the most optimal embodiments are protected and offered for commercialization. However, postponing patenting also postpones publishing and one should have a strategy in place to optimize the schedule.

- Involve a patent attorney in planning the patenting strategy.

4.4 Commercialization pathways and marketing

Commercialization refers to the utilization of an invention either by starting a new company or by licensing or selling the invention and related IP to an existing enterprise. Providing paid services directly from the research unit is another alternative. The commercialization of an invention and IP is not a quick process and not all inventions sell. Commercialization of IP by sale or licensing is also referred to as technology transfer.

Although patenting may be the requirement for commercialization, patenting itself will not assure commercialization. The decision for commercial development is made by a company only after the clinical utility of a novel biomarker has been demonstrated. In addition, e.g. practical, technical, legal, financial and regulatory aspects will affect the decision.

BEST PRACTICES

- Define the type and use of the biomarker: is it e.g. a screening or a companion diagnostic assay? The routes of commercialization and the importance of early company connections significantly vary between different uses.
- To the extent that is possible, compile analyses on market potential and landscape, competitors and potential partners, freedom-to-operate and most potential paths for commercialization (start-ups, licensing, sales).
- Inventors themselves are usually the best in describing the advantages of their inventions in detailed scientific discussions

with potential partners. The commercializing discussions and agreement negotiations are handled by the TTO.

- It has been noted globally that university inventions are most successfully commercialized to actors that the inventors are already familiar with, such as project partners and competitors (companies). Cooperation between the inventors and TTO's will produce the best results in talking with the companies.
- In addition to utilizing the contacts and collaboration partners, the active marketing efforts can comprise, e.g.
  - Direct contacting of companies active in the field (with or without external commercialization consultants)
  - Attending partnering events and exhibitions (with invention-specific brochures, posters, stands etc.)
  - Virtual IPR exhibit show rooms (including TTO's own web pages)
- The TTO's need to have a budget e.g. for the external market analyses (most preferably comprising contacting businesses for feedback on the planned product) and marketing efforts, IP valuation, and travelling to partnering events and conferences, where the invention portfolio can be presented. It will also give an opportunity to talking to end users and industry representatives so that more can be learned about their needs and views.

5

INTELLECTUAL PROPERTY RIGHTS (IPR)

Most commercial partners will not consider licensing without respective intellectual property (IP) protection due to the competitive edge it provides. The existence of IP rights (IPR) is paramount, also in the eyes of investors.

Furthermore, concrete IPR allows ensuring a share of profits to both to the inventors and the research organization after the launch of the product, typically as a certain percentage of income from the sales (royalty). Also see the chapters where the agreements and business models are discussed in more detail.

5.1 IPR issues in project lifecycle

5.1.1 Patents as a source of information

It has been estimated that 70-85 % of information found in patent databases cannot be found elsewhere. Those researchers that follow the patenting field will have a significant advantage compared to those who are not up-to-date on the newest directions of commercial development.

Furthermore, the information contained in patent publications on new methods and products is much more detailed than can be found in scientific publications. From assay development perspective, patent publications can even contain direct product development tips since they often include solutions to special problems, which would otherwise only become apparent after long time of use and would be difficult to resolve without knowledge of the issue. One can also track down the main competitors in the field based on the patent publications.

BEST PRACTICES

- Offer training for researchers on the use of free patent databases (Espacenet by the European Patent Office and PATENTSCOPE by WIPO) on a regular basis.
- Guide the researchers in performing own preliminary novelty and FTO searches and interpreting patent claims where needed.
- Especially Chinese and Korean patent applications are in continuous increase. The machine translations are fairly good and

are accessible free-of-charge directly from the patent database websites.

- The patent databases can be searched e.g. by keywords, inventor, applicants, and application numbers. Patent classification codes can be used in more advanced searches.

5.1.2 Novelty of research

Producing new information will obviously have the highest impact on society. Staying aware of what other academic (or commercial) groups are doing and taking prior art and state-of-the art into account already when planning a new project will help in ensuring high standard and pioneering research and avoiding investigating again something that is known already.

BEST PRACTICES

- Carry out novelty searches utilizing both scientific and patent databases. Abstracts of relevant conferences also often give a small peek on the state-of-the-art. Searches made when planning a new project will help to ensure that one is not researching already known matter again. Searches should also be made during the research projects each time, when significant new and potentially inventive results are established. The previously published materials are referred to as 'Prior Art'.
- Patent applications give a view of the direction where the development is going. A long and expensive product development process may only be apparent by a company's patent application.
- Patent applications also give a view of the possible partners or competitors.
- While the patent slang can at first feel like a foreign language because of the specific terminology and repetitive structure of the patent publication, one will get used to it.

- The purpose of the patent publication's repetitive structure and wording is applying patent protection for an accurately and detailed defined invention in a structured and standardized format, and one will get used to the patent slang quickly.
- A patent publication describes a solution to a technical problem, whereas a scientific publication is a more neutral research report. However, both describe an invention with sufficient detail so that a professional can understand and repeat it.
- Patent claims, especially the independent patent claims (claim 1 and others that do not refer to previous claims), will determine the patent's scope of protection. The dependent claims represent the different embodiments of the invention. Patent claims are interpreted literally, with the help of the definitions given in the specification section.
- Note that patent applications become public after only 18 months from the filing date (priority date).
- It is good practice to do a complementary novelty search before entering the PCT phase.

5.1.3 Patenting versus publishing: Alternative protection strategies for early phase inventions

In the university settings, publishing is an inherent part of the work. Scientific publications and patenting are not mutually exclusive but the order matters.

Most of the inventions that are declared in invention disclosures to the university are in a very early phase. Yet, there may be significant pressure to protecting before publishing. Innovation must, however, be appropriately balanced with proof to be amenable to patenting. In the above situation, the **exemplary strategies** for protection include:

1. Not pursuing for patent protection (due to lack of sufficient amount of verification data and scientific evidence).

2. Filing a provisional (or similar non-searched) patent application using the manuscript to be published and subsequently filing a PCT patent application within one year on the condition that proof-of-concept data has been established).
3. Filing a conventional patent application based on the manuscript to be published.

The **pros** for the above situations are:

1. You have followed the criteria you have set for protection of biomarker inventions.
2. You will save in patenting costs in the case the verification studies or establishing the prototype fails. The official fees for provisional (i.e., non-searched) applications are low. Involving a patent attorney will increase the costs but also the quality of the application.
3. The new test might turn out to be a commercial success early on (although this rarely happens).

The **cons** for the above situations are:

1. The invention cannot be protected after it has been published.
2. You will not have the official novelty and patentability reports to support the drafting of the PCT patent application and patent claims. You may end up in pursuing too wide or too narrow scope of protection without a proper chance to amend the application. This can result in high patent prosecution costs.
3. There is a chance that the verification and proof-of-concept data either do not support the application or remain missing. Prepare to terminate the application process.

Alternatives to tackle the above cons:

1. Move to the next case or see 2) and 3).
2. Use provisional applications only as an alternative to saying no, i.e. instead of strategy 1). Order a novelty and patentability survey or have the application searched at the patent office (you will need to submit patent claims with the manuscript). Proceed to filing a PCT application only in case the required (and convincing) data has been generated by the end of the priority year. As there has been a clear deadline (10-11 months) for the further proof, it is a simple decision whether to proceed with patenting or not.
3. Communication of expectations combined with preparing to alternative scenarios is important. Collaborating with researchers, proceed to filing a PCT application only in case the agreed data has been generated by the end of the priority year. As there has been a clear deadline (10-11 months) for the further proof, it is a simple decision whether to continue patenting or not.

5.1.3.1 The "30-month" commercialization strategy by university TTOs

Patenting costs are significant and cumulate during the years. Especially the costs explode when the national phase is entered at 30 months (in some countries 31 months) from the priority date, i.e. the first filing date. At this point, the application exits the international PCT-phase where all communication is carried out with a single patent authority such as EPO (European Patent Office). However, patents are not granted in the PCT-phase. The granting (and the preceding further processing) is performed only by the national or regional patent authorities in the so-called "national phase".

In the national phase, the same patent application is filed separately at each selected national or regional patent office. Many national offices require translating the application to their own official language and the translation costs come on top of the official filing fees. Furthermore, the yearly payments (which will run and increase for 20 years) start running already at the time of filing rather than at the time of grant. Even with a

limited country selection, the cumulative costs after entering the national phase easily pass 50 000 €.

To restrict the investments in protecting and commercializing a single invention among the large number of inventions made yearly, the university TTOs often put a time limit at the end of the PCT-phase, which may in some cases be irrespective of achievements made in the project, or sometimes reflect point 3) in the preceding chapter. Typically, if a partner for commercial utilization has not been found during the 30 months despite a reasonable amount of marketing and commercialization efforts, even the more promising applications may be terminated.

BEST PRACTICES

- TTOs' resources for patenting are limited and estimating the commercial potential for an invention beforehand is difficult. To allow fair chances to different technologies and teams, TTOs often set milestones that need to have passed for continuing patenting either to the international PCT-phase (at 12 months) or to the hugely expensive national phase (at 30 months). The first time limit (12 months) more often reflects the success of data generation (e.g. verification results combined with further convincing scientific evidence), while the latter time limit (30 months) more reflects the existence of commercial interest by companies towards the invention.
- The typical 30-month time limit means that it must (by this point) be clearly established that the invention has significant market potential, i.e. profits are expected to notably exceed any patenting and product development costs. Having entered into serious negotiations with companies planning to commercially utilize the invention is a sign (the sign) of such potential. The existence of sole interest towards the research (in the absence of willingness to negotiate for a licence) may be a polite way of saying "no" and may not encourage to continue investing in patent protection. However, a "no" from a company with a strong "yes" from the clinicians may be related to the strategic position of the company. Perform a survey on the market size and potential. Also see the chapter Establishing start-up companies.

- Other reasons that may support the termination of patenting and commercialization activities at 30-months (or other time) include lack of progress in taking the invention closer to commercialization (by establishing a specific prototype assay), negative opinion of the patenting authority (lack of novelty or inventiveness), or the scientists leaving for other organizations (active contribution of inventors is no longer available).
- However, one rule does not fit all fields and this also applies to the 30-month rule. Especially in IVD assay development, the road from biomarker discovery to use in clinical routine is long. If the research organization wants to invest in the research of new biomarkers, other criteria for decision-making can be used instead of the patenting-derived deadlines or strict monetary restrictions. Such alternative criteria include e.g. the success rate in achieving specific milestones or the level of progress as compared to a pre-set development plan. Enthusiastic teams with good progress rate and high compliance to a development plan could be picked for continued patent prosecution process and commercialization actions.

5.1.4 Increasing the innovation activity

The majority of significant research results and inventions is published before their protection possibilities and commercial potential have been assessed and evaluated.

BEST PRACTICES

- The suggestions for increasing the awareness and activity for commercial utilization of university-based inventions include e.g.:
  - Educating researchers on IPR-related matters earlier in the project life cycle, already at the time of filing funding applications
  - Internal marketing of the services and personnel the univer-

sity has for making e.g. novelty, patentability and FTO surveys, reviewing and handling invention disclosures, and finding the best fitting commercialization paths and partners for the university-based inventions
- Bringing up success cases in internal newsletters or internal web pages
- TTO pop-up tents and stands at the campus
- Lunch meetings (or any repeating contacts) with the most innovative scientists and teams to be kept updated on recent progresses
- Invention and business idea contests
- Regular IPR training of researchers
- Classes on IPR issues incorporated in basic and graduate student's training programs
- Assigning and properly training an innovation "scout" for each faculty to educate researchers in identifying and declaring inventions.

5.1.4.1 Inventor's participation in the patenting and commercialization activities

Active participation of the researcher-inventors is crucial for successful technology transfer – the inventors cannot just give over the research completely and have nothing to do with the subsequent protection and commercialization steps. The enthusiasm and cooperation by inventors may even be a criteria of selection for starting the patenting and commercialization activities.

In the other extreme, the researchers might be heavily involved for years with the company developing a product based on the biomarker invention. While the subvention of commercial companies by taxpayers' money (i.e. work performed at the public sector for free) is not allowable, continuing support for the optimization, troubleshooting and clinical evidence building for the new biomarker assay can be arranged in the form of paid contract research when agreed with the research team.

BEST PRACTICES

- Although patenting and commercialization of an invention is to the major extent carried out by the organization's TTO and the external professionals appointed by the TTO, the inventors are expected to collaborate and give expert help to a reasonable extent in order to assist in protecting and commercializing the invention. The compensation paid by the university in the different steps of patent protecting and commercialization (as well as the share of potential future license and sales net revenues) is to cover all such endeavours so that separate fees do not need to be paid.
- The compensations paid at the different phases as well as the principle of sharing of the net income received as license or sales revenues need to be clearly specified in the organizations' guideline for inventions. The different phases of payments and the minimum sums to be paid may be in part dictated by national laws.
- The inventors' contribution to patenting comprises e.g. reviewing the documents, providing additional calculations or results (where needed), providing argumentation for the benefits of the invention, and signing the declaration and assignment documents required by the patent authorities and agents.
- The inventors' contribution to commercialization comprises e.g. participating in the scientific discussions with the industrial parties (e.g. by giving presentations and reporting results), running specimen panels provided by the companies, and active sharing of any new contact and potential partner information with the TTO.
- The inventors need also to accept to maintain secrecy and not to give to any third party information concerning the invention while the patent protection and commercialization activities are ongoing. However, in the academia, publishing the results is typically allowed after a patent application has been filed.
- A large share of the licensees of the university-born inventions are current or former collaboration partners, emphasizing the

role of the inventors in finding the best fitting commercialization partners for their inventions.

- If the university decides not to continue the protection or commercialization of the invention, the inventors may be offered the possibility to reclaim the rejected invention with terms that can be negotiated separately.

5.1.5 Dealing with discrepancies

There is high competition between scientists and research groups. Unfortunately, not all the research lasts closer inspection. It is also possible that there are cultural or other differences in comprehending what kind of accuracy is expected. Sometimes, the research and the related materials move to a new organization with the principal investigator, and some institutions now require filling and signing a "customs check" type of form together with the employment contract.

BEST PRACTICES FOR THE TTOS

- Do not be afraid of asking difficult questions if you see contradictions or note that some pieces are missing, e.g. if the origin of key materials is unclear, the obtained results do not match with the methodology, data has been heavily manipulated or normalized, the statistics show distortions, or the conclusions seem unjustified.
- Ask again if there seems to be a barrier of language or other misunderstanding of the question.
- Make memorandums of meetings and phone calls and send them to all parties. They will have an opportunity to correct any misunderstandings and you will secure proper agreement between all parties. Also, summarize in writing any important piece of advice you give orally.
- Use an external consult if you think there is something that needs to be checked.

- If you already went ahead with a case that turns out rotten, consult your team, your superior, the university's legal department and the management as appropriate, and proceed according to the organizational and national guidelines (including those for research ethics). Close cases that compromise the university's reputation.
- You can neither check nor know everything. Trust is an essential part of the process. TTOs focus is in the business, not checking the validity of research methods or results. The researchers are expected to assure (e.g. by signing an invention disclosure) that all data provided is real and no mimicked, extrapolated, expected or otherwise strongly manipulated data is provided in place of actual findings.
- There are plenty of guidelines and acts on research ethics, responsible project leadership and conflict-of-interest issues, which are not within the scope of the current handbook.

5.2 Prerequisites of patenting

5.2.1 Novelty

Novelty means that an invention is different from earlier solutions disclosed in prior art. An invention cannot be patented if it has already been published by anyone, anywhere at the date of filing the patent application.

Publishing, and thereby forming an obstacle for novelty, refers to abstracts, posters, oral presentations (elsewhere than in internal closed meetings), articles, electronic and printed news, patent applications as well as brochures and marketing materials. It needs also be ensured that the data is not published accidentally (e.g. as presentation slides posted on a website after a closed meeting) or by an external party.

BEST PRACTICES

- Performing a preliminary novelty search is important (also see chapters 5.1.1 and 5.2.2). A thorough novelty and patentability

survey can be ordered from an external service provider once there is sufficient confidence based on an internal search.

- As the simplest first step, ask the researchers for their earlier publications (including abstracts, presentations etc.) as well as other closely related research by other groups. Search the researchers by name in the internet to find e.g. interviews or other public disclosures.

PITFALLS

- In academia, novelty is often destroyed by own publications that may come up only after a patent application is searched for novelty by the patent authorities. The publications (articles, abstracts, posters, public presentations) by the research team would need to be disclosed and reviewed more closely at the time of handling the invention disclosures.

5.2.2 Inventiveness

Inventiveness means a non-obvious or even surprising (1 + 1 > 2) solution to a technical problem. An invention must not be evident for a person skilled in the art or be possible to achieve with basic optimization or routine trials.

In the most optimal case, a previously unknown biomarker with clinical relevance is found, making it simpler and more straightforward to argue for both novelty and inventiveness. As this is not often the case with biomarker inventions, Figure 1 describes some alternative examples of scientific findings that might be in some cases and with some boundary conditions be considered for patenting. However, as described in the previous chapters, many other conditions than novelty and inventiveness must be met to make the decision of patenting.

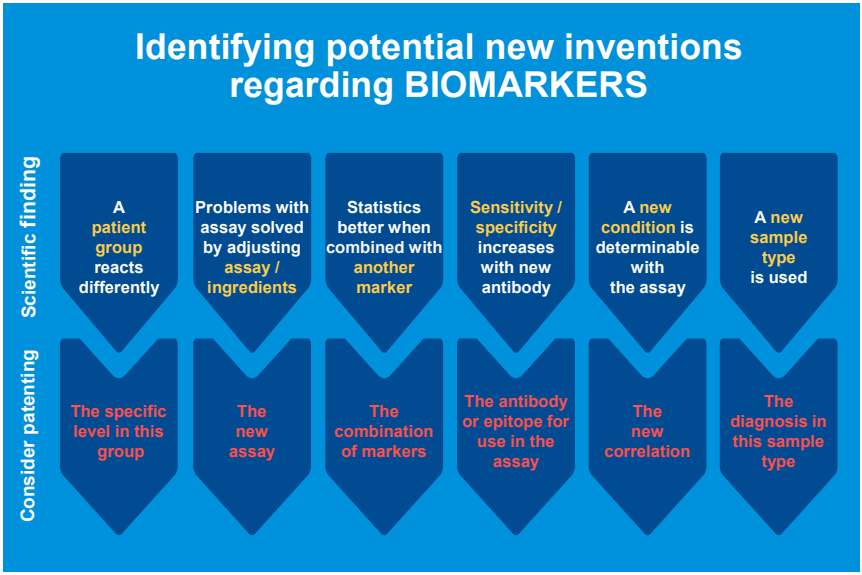


Figure 1. Examples of scientific findings that could be considered for patenting. All the examples refer to a situation where the biomarker and its correlation to a condition are already known in the prior art. The Figure is provided through the courtesy of HØIBERG European Patent Attorneys (2019).

PITFALLS

- Abstracts submitted to conferences are not considered very dangerous by the researchers if they have censored or coded the details. However, from the perspective of inventiveness, such a publication proves that a similar technical effect has been accomplished earlier. A patent application describing the invention in full may then be considered only to provide alternative markers for achieving the same technical effect than described earlier without details. This so-called non-enabling prior art is known for not destroying novelty but destroying inventiveness.

5.3 Freedom-to-operate

Freedom-to-operate means not infringing the IPR rights (almost always patents) of others and not needing licenses -- that may be costly or unavailable -- for IP owned by third parties when commercializing the invention. For example, to use reagents (such as antibodies) in a commercial kit, one needs to agree with the provider that the use of the component in a commercial product is allowed. The cost may be different. Furthermore, one needs to make a survey that there are no existing method patents that would cover the use of the reagent in the same indication.

BEST PRACTICES

- Compare the invention (as a whole) against existing patents and patent applications preferably already before generating own IPR. Pay special attention to key components that you cannot replace (such as rare antibodies).
- While FTO surveys can be purchased from several external actors, initial searches made by the inventors themselves increases their knowledge of the state-of-the-art and helps in not becoming dependent of IP owned by others in future projects. Purchased FTO surveys tend to be expensive (>10.000 €) and come therefore too late, i.e. when the product design is relatively fixed already.
- An initial FTO study should preferably be performed already after the early phase, before proceeding to assay development phase, so that obsolete or non-commercially-available (for further commercial use!) components or sequences are not used accidentally.
- Gaps in FTO detected any time before patenting may help in addressing the issue in the laboratory and in the patent application. In some cases alternative, free-to-use reagents and methods can be employed. If not, proceeding to pursue patent protection requires strong reasoning.
- Hindrances for FTO detected during patent prosecution must

also be taken into account when making decisions on the continuance. Ask your patent attorneys to also report suspected FTO issues in their reports. Although not perceived as hindrances for patenting, they can be significant hindrances for commercialization.

- The need for third-party licenses should be allowed only rarely and only for elementary patents in which case a license is needed by all competitors, too.
- Take into account the expiry date and territorial coverage of the FTO-restricting patents.
- Note that some assays (such as nucleic acid assays) and chemistries (such as labelling reagents) can easily be executed with alternative technologies and chemistries although not familiar to the researchers. In such a case, the non-commercial proof-of-concept experiments may be based on a protected assay principle or chemistry. The commercialization partner can then execute the assay using the techniques and chemistries they prefer.

PITFALLS

- An invention with restricted FTO means that the potential licensee also needs to negotiate and pay for other licenses before being able to commercialize the invention.
- For some fundamental technologies, commercial licenses may be readily available. The license fees for manufacturing and selling IVD assay kits are, however, significantly high compared to in-house or non-clinical assays such as animal or food safety testing.
- FTO may be compromised from the get-go if existing Background material is further developed in a publicly funded project where the project agreement (or MTA) limits the commercial use of so-forming Foreground materials/data. While an

industry partner may suggest to retain all the rights to materials the company is supplying for the project, including the possible improvements made, the national laws typically prohibit subsiding private property with public funds. This means that the research organizations cannot (even by agreement) automatically transfer the industrial parties the right to commercially utilize the Foreground, but utilization can be separately negotiated at a market value price. However, the industrial partners may be offered the right of first refusal, i.e., priority of entering into an agreement (at market price) before external companies have been notified or approached. Similarly to above, the commercial utilization of other reagents, materials or software used in a research project may turn out to be prohibited. All restrictions and the potential to later violate third party rights need to be identified and tackled before the project starts.

5.4 Scope of patent protection

The most important characteristic of a patent is its scope of protection, which defines whether it can be easily circumvented or not - in other words, whether potential utilizers need a license for it or not.

Broad patent claims are especially important in the case of university-based inventions for which the motivation for patenting lies in technology transfer, that is, selling or licensing the IPR for companies for a fee. This approach significantly differs from that of the industry, where the primary aim of patenting is typically not out-licensing but protecting the existing or upcoming products and/or increasing the value of the enterprise.

From this perspective, some type of biomarker inventions are difficult to patent well. A weak patent is any patent that opens up the possibility for the potential utilizer to circumvent the patent claims by replacing the least meaningful limiting feature of the independent patent claim by another solution that works similarly well.

Things that are difficult to patent well:

- Biomarker panels/patterns/signatures: The current evidence shows that many tests are likely to rely on multiple biomarkers in the future. It is, however, more complex to get regulatory approvals and solid patent protection for multiplex biomarker tests than the singular assays, as the more biomarkers that are required in the claim, the easier it will be for third parties to replace one or more of the biomarkers and thereby circumvent the patent
- Furthermore, the larger the number of markers in a combination, the easier it becomes to replace one marker with another (or several) outside the list. In the case, only a pre-defined set of biomarkers ("signature") seems be patentable, preferably only the very top marker(s) absolutely needed for the method to work should be included in the independent patent claim(s). The remaining markers should be put in a priority order and listed in dependent claim(s). If the inventors only have an unprioritized list of candidate biomarkers that work in several different combinations, unity of invention will certainly be an issue and it will be difficult to obtain strong patent protection. This is also to avoid a "lack of unity" objection, which is easily received from the patent examiners when claiming an unprioritized list of biomarkers that work in several different combinations.
- Sequences: Nucleic acid and protein sequences typically have room for minor adjustments especially around the key binding units. It is difficult to protect complex nucleic acid or peptide sequences so that all solutions that work in an assay would be covered. In the case of new biomarker findings, it is important to try to search options for protecting the new assay by the target, without strictly defining the actual binders. The exact sequences should only act as examples and be described in the dependent claims. This also applies to new antibodies against existing biomarkers. The commercial value of antibodies easily replaceable by other antibodies (with slightly different sequences) is very low relative to patenting costs. Patenting of antibodies and nucleic acid assays is feasible only when the claims permit covering virtually any binders for the same.

- Methods for production of diagnostic assay: When use of a patented production method is not evident from the diagnostic assay itself or its public documentation, infringements are difficult to monitor. The burden of proof is always at the IPR owner. The new method might result in significant savings in the manufacture of a specific product, but if the same could also be reached by other means, one could never be sure if the potential but reluctant client was already using the method or not.
- Patenting in the USA: Due to a number of Court decisions over recent years, it is currently not possible to patent naturally occurring products in the US, such as naturally occurring nucleic acids, amino acid sequences and fragments thereof. It is defined by the patent authorities as "Law of Nature". It is however possible to patent variants of such naturally occurring products/sequences.
- In addition, it is also very difficult to patent diagnostic methods in the US unless the biomarker is measured by unconventional means and/or a post-solution activity is added to the claim, usually in the form of a treatment step with a specific drug (companion diagnostic claims).
- For all the above cases it needs to be noted that patent protection by research organizations is not pursued to ensure FTO of own products but the goal is in out-licensing. It is therefore very important that the patents cannot easily be circumvented because the customer is purchasing IPR, not the final product.

Most solid form of patent protection, virtually covering *all* the different uses of a biomarker, can be achieved for biomarkers that are completely new, i.e. completely unknown in the prior art. In the current "omics" era, such findings are becoming more rare and often concern e.g. splicing variants forming previously unknown mRNA and protein sequences that cannot be deduced from the genetic code. In such a case, even all the binders later developed to detect the new marker can fall under the scope of the original patent, similarly to all related IVD products to virtually any disease indication.

However, the much more common type of invention describes a new correlation between a known biomarker (or a group of known biomarkers) and a condition (see Figure 2 left panel). In many cases, successfully protecting such new correlation provides a relatively wide coverage of related IVD products.

However, in the case that the correlation is known from prior art (see Figure 2 right panel), the biomarker invention might relate to providing more accuracy for assessing the condition in question. In such a case, competition and FTO analyses become increasingly important. Hindrances for FTO (due IPR owned by others) must be taken into account when making decisions on patenting. Although not preventing patenting, lack of FTO is a significant hindrance for commercialization.

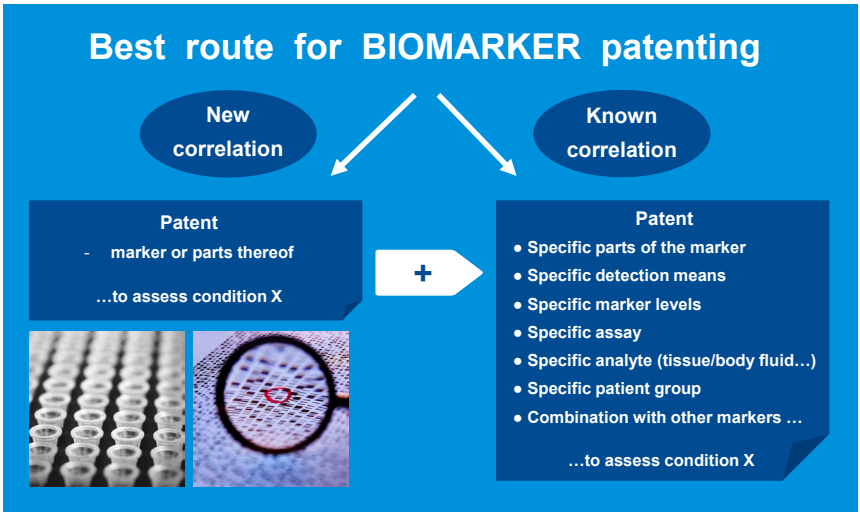


Figure 2. Patenting new correlations versus improvements to known correlations between a biomarker (or a group of biomarkers) and a condition of interest. The Figure was provided through the courtesy of HØIBERG European Patent Attorneys (2019).

BEST PRACTICES

- To ensure that the university-owned IPR becomes interesting to companies, it is not enough to have an invention patented – it needs to be patented well and with broad enough patent claims so that the scope of protection is proper for the technology. Companies will only pay for rights they really need.
- If the intention is to form a start-up, the viewpoint of protecting the planned products can be emphasized somewhat more.
- Also, make a plan for the relevant territorial coverage of the patent family.

5.5 Other forms of IP and commercialization without IPR

Patent is the most important form of IPR at research organizations and most of technology transfer is based on licensing the patents to companies. However, not all inventions can and needs to be protected with a patent.

In some cases, a patent may be impossible to get (e.g. due to lack of novelty/inventiveness or non-technical nature of the invention) or the foreseeable scope of the patent may too narrow to justify the high costs of patenting. Furthermore, to obtain a patent means that the invention must be fully revealed in the patent application, including detailed descriptions of materials and methods required to set the assay up. The patent application (unless withdrawn) will become public in 18 months and it is no longer possible to keep the invention as trade secret after that.

In case of IVD-applicable biomarker assays, patents remain to be the decisive form of IPR in technology transfer. In most cases, it would anyway be difficult to keep secrecy of the analytes measured. In the healthcare settings, clinicians would rarely rely on "black box" tests without a possibility to understand the results obtained. Furthermore, the submissions for regulatory approvals are in some respects public.

IVD assays are naturally also launched and sold without patent protection. Other forms of IPR such as registered trademarks may help a company to achieve a foothold on the market, but competition for the underlying

technology is then free and it is not likely that any single company reaches a monopoly for an important marker.

From the perspective of technology transfer, non-patent IP transfer strategies can include, for example:

- Knowledge transfer – e.g. instructions, recipes, results and other documents specified in a license agreement
- Database licensing – e.g. access to clinical data, raw data and/or results database
- Copyright – e.g. computer software
- Trade secrets – e.g. complex algorithms in connection with biomarker signatures
- Material licensing – e.g. cell lines and antibodies.

Providing services-for-fee directly from the unit is another means for commercializing special knowhow.

5.6 Termination of protection and commercialization activities

Many research organizations file a double-digit number of new patent applications yearly. The maintenance of a patent portfolio is a resource-intensive, long and costly process. The rules and timing of termination when a partner for utilization has not been found with reasonable efforts need to be transparent and understandable.

BEST PRACTICES

- At a TTO, establish basic rules when patenting and commercializing activities are to be terminated, e.g.
  - required evidence has not been established within the priority year, or it shows low clinical utility

- patent protection with sufficient scope of protection is not possible
- active contribution of inventors is needed but it is no longer available
- the commercial potential of the invention proves to be lower than was expected (e.g. due to limitations in FTO or target population)
- a partner for utilization has not been identified by the time of national phase of patent prosecution (the 30-month strategy)

- After the decision to terminate, the inventors can be offered the opportunity to acquire the rights from the university with terms negotiated separately.

6

BUSINESS MODELS, AGREEMENTS AND OTHER LEGAL VIEWPOINTS

6.1 Material transfer agreements (MTAs)

6.1.1 MTA-in

While the ownership of a university-based invention (or other intellectual property or knowhow) is determined at each organization according to the national laws that take into account e.g. the type and terms of funding, it is important to also know about other engagements the researchers have made related to the invention.

Special attention needs to be paid, for example, to the use of third party materials under a material transfer agreement (MTA). MTAs are made by researchers constantly and sometimes without reading the terms before signing. It is not the rarest situation that a compulsory license is granted based on an existing MTA. This is especially problematic if other licensees are blocked or non-existent.

BEST PRACTICES

- Educate researchers to consult the university legal department when drafting any documents with companies or when modifying the organizations MTA templates.
- Educate researchers in how to interpret terms and conditions and to understand the main principles (background and foreground results, ownership of results).
- Educate researchers to think ahead about potential inventions, knowhow and other IP that may arise.
- Secure the ownership of results obtained using a material provided under MTA. The material cannot be used commercially, but the obtained results should be (e.g. in a patent application or marketing materials).
- The principal investigators also need to educate their teams on the binding terms of the MTAs made. They also need to reserve time for reporting as agreed in the MTA.

PITFALLS

- Materials should not be obtained from companies under a strict MTA if the same material is also commercially available (with a reasonable price).
- An MTA made with a company remains to be in force although the material becomes commercially available from another source without restrictions.
- Researcher accepts company MTA instead of using the MTA of his own organization and without consulting the legal department.
- In the worst-case scenario, an invention made using the material belongs to its provider in full.
- In some cases, even publishing may require the permission of the provider. If the confidentially obligations are not followed and results are published, the organization may end up in court for a breach of agreement.

6.1.2 MTA-out

The new EU General Data Protection Regulation (GDPR; 2016/679; enforcement date 25.5.2018), is designed to harmonize data privacy laws across Europe, protect all EU citizens' data privacy and give form to the way research organizations and industry approach data privacy. It sets more stringent requirements for the processes related to transferring clinical specimen materials and needs to be taken into account in related MTAs.

BEST PRACTICES

- The new EU-regulations need to be taken into account in all MTAs that relate to patient specimen materials so that the following processes are described:

1. De-identification of the information of donors so that tracing back by the Receiver becomes impossible
2. Informing the receiver of any restrictions relating to the use (or further transfer) of the materials
3. Maintaining the chain-of-custody of the materials
4. Ensuring there are no restrictions of using the material for the purpose intended. The patient consent must allow using specimens for the purpose (in a wider sense) and the Provider must have the right to transfer the material.
5. Ensuring that unused materials are properly disposed of in accordance with applicable laws and related ethical approvals.

6.2 Non-disclosure agreements (NDAs)

A Non-Disclosure Agreement (NDA) is an agreement of keeping confidential information secret according to terms and duration described in the agreement. It is the same as CDA (Confidential Disclosure Agreement).

BEST PRACTICES

- An unprotected invention or other unprotected intellectual property or knowhow should only be presented to business partners after making a NDA. An NDA will be needed if the upcoming negotiations or discussions will contain information that is not published or publicly available, not already known (by the company) and is not IP protected.
- For initial discussions and feedback, however, the invention or knowhow can often be coded so that first presentations can be given on the non-confidential level (the same with the potential end users). For example, you can tell that you found protein or genomic markers A and B that, when existing in a clinical specimen together, will indicate with 90 % diagnostic accu-

racy (or any of the real calculations you have) that the disease is aggressive and the patient will benefit from surgery. Make yet a notification that the material is for internal use only and not meant to be distributed.

- NDA's are is force typically 2-5 years (or less if the invention is published).

6.3 Business models

6.3.1 Licensing versus sales of IPR

When selecting between feasible agreement models, at least the following variables are to be reviewed:

- Degree of readiness: the amount of product development contributions needed; possibilities for refining the invention in-house (e.g. further proof-of-concept studies)
- Size and growth rate of the market: what is the share that could be obtained
- Competition analysis: what are the alternative solutions, how significant the invention is
- Scope of patent: coverage (extent) of the patent claims, possibilities for circumventing
- Circumstances in which the invention was made and the terms of funding (contract research)
- Number of companies interested (or parties in contract research)

Licensing of IPR may be more advantageous when:

- The research continues and the invention can be used as background material (must be taken into account in the terms*)
- Multiple licensing agreements are expected (e.g. via different territories or fields of use), increasing the potential cash flow

Sales of IPR may be more advantageous when:

- When unreasonably large patenting costs are expected compared to the foreseeable income
- When the number of potential licensees is very limited
- When it facilitates establishing a new business activity or start-up by the research team.

* When there are prospects for further research, the primary commercialization path is non-exclusive licensing wherein the university retains the right of ownership and further utilisation rights. However, whether this is possible depends on the possible project agreement, the invention and the utilization parties. When the rights to an invention have been sold exclusively, the invention can no longer act as background material when applying for public research funding.

6.3.2 Negotiations with alternative term sheets

The companies often wish for more transparent negotiations for the university-IPR licenses and the availability of alternative agreement models from the company to choose from depending e.g. on the market risk and other financial considerations.

BEST PRACTICES

- In situations where several alternative agreement models are feasible, provide the potential licensee with the selected models for review e.g. in the form of a term sheet. Include at least the following specifics and variables:
  - Licensor, licensee, date
  - Technology: name or description
  - The exact IPR: invention disclosures, patent/patent application(s), trademarks, knowhow, materials etc.
  - Territory
  - Field of use
  - Type of agreement: sales or licensing (exclusive, sole or non-exclusive), or if these are alternative models
  - The different balances between up-front payments, royalties and/or annual fees
  - Ownership of rights (transferred or remain with the licensor)
  - Patenting costs (who pays, in what extent and when)
  - Decision maker in patent procurement issues
  - Sublicensing issues (right to grant; payments/royalties)
  - Infringements
  - (Duration, diligence requirements, milestone fees etc. case-by-case)
- Also define the target and scope of the agreement properly, i.e. whether it comprises a method (e.g. invention disclosure or patent application for a biomarker assay) and/or materials (e.g. clone for producing a specific antibody). Also describe any possible specimen materials transferred (also see chapter on MTA-out).

6.3.3 Establishing start-up companies

If the invention is significant and targets a growing market, the researchers might themselves be motivated to form an entrepreneur team. However, the circumstances, ownership of inventions and opportunities for funding

differ between countries and are to be taken into account. Where feasible, having ownership of the respective IPR may play an important role in creating value for a new start-up company and in the acquisition of funding for the first rounds.

BEST PRACTICES

- Establishing a new company can be justified if:
  - The researchers have or can acquire ownership (or licence) to the IPR
  - There is an important market need that the invention brings a solution to
  - The protection of the invention is proving successful
  - The expected product development contributions are reasonable / in-scale with comparable approaches
  - The founders have endurance to undertake all the labour-intensive tasks of e.g. product development, quality assurance, transfer-to-production, registration & approvals, marketing, production, sales and distribution, understanding that at the maximum of 10 % of the work is done at the end of a research project (with a prototype or proof-of-concept assay).
  - The business plan is sound enough to make external funding realistically possible
  - The business potential is sufficient to provide not only a decent livelihood for researchers, who are becoming full-time or part-time entrepreneurs, but also a growing cash flow that will later cover new product development – very few enterprises are successful with one product only
  - Conflict-of-interest issues are taken into account, i.e. the business does not compete with the main employee (in case of part-time entrepreneurs)
  - A business-oriented CEO has been identified
- While the law prohibits subsiding private property with public funds (in other words meaning that the universities cannot offer corporations any services, materials or IPR below the market value), the universities are in many case open for negotiation to share the market risk in the early years of operation of a start-up.

When feasible (e.g., no other industrial parties have the priority to negotiate for commercial utilization), the universities with entrepreneurial mind-set may courage the new enterprises by offering them the ownership of the IP rights with flexible terms, including alternatives for directing the remuneration from down payments towards royalties. (Also see chapter on Agreements and Terms.)

- Universities may in some cases also participate as stakeholders in a new company and IPR can be transferred as an investment-in-kind contribution.

PITFALLS

- Sold IPR is the property of the new owner. Assigning IPR to a start-up typically means that the rights cannot be returned to the university in case the commercialization fails or the company goes bankrupt (as a contrary to licensed IPR). On the other hand, liability issues and patenting costs are transferred to the new owner as well. However, you can try to make a clause in the agreement on returning IPR to the university in case the company fails, but the typical risk is that the IPR will anyway be counted as property of the estate and sold to cover the losses of the creditors (unless you set a clause that allows predicting the bankruptcy well in time, e.g. lack of sufficient turnover). Other problems sometimes encountered relate to significant changes in the scope of the patent made during the patent prosecution process (to better cover the products of the company, but making the patent less useful for others). Also, having already seen the commercialization endeavours fail, the university may not be enthusiastic to have the possible termination discussions with the original inventors that may not have been involved with the IPR ever since, or who may not work at the university any longer. In other words, it all depends in the case and the value/adaptability of the invention.

- When the payments are directed strongly from front payments to royalties (paid from the sales of products), the market risk may remain at the IPR seller for a long period of time. Public funding is tax-payers' money and the university cannot therefore carry the entire risk of entrepreneurship without applying e.g. time limits, diligence requirements and/or yearly payments.
- Accepting equity as a replacement for a cash is a somewhat controversial issue and is not allowed by the IPR policy of the research organization. National differences may also exist. The pros include getting a share of any success of the company (also from other products than the licensed one) and that equity usually only replaces the down payment, not royalty. The cons concern the strong dilution of ownership after several rounds of investments, the non-liquidity of the possession, and labour-intensiveness related to participation in board and general meetings, agreements etc.

6.3.3.1 Connections with investors

An investor is a person/group of people/company who invests in a start-up company, which usually carries an economic benefit. Since investors appear in different ways and pursue different investment strategies, they are often divided into different groups. Founders with a need for venture capital are often faced with the question of what kind of investors they should approach. The choice is usually between a private investor, a business angel or a venture capital company, but also other options exists). All provide capital, but differ in many other ways.

Private investors are a good option for capital seekers who do not want to grant a say in company decisions. They either participate as silent partners or provide the company with an interest-bearing loan. This group of investors is a good choice for start-ups that are still in their early stages as their focus is on the return potential and they can be promised a disproportionate multiplication of the investment in the first few years. The investment volume of a private investor depends on its financial possibilities. In general, private investors could invest anything from a thousand euros up to several hundred thousand euros.

Business Angels are successful businessmen (or women) or former entrepreneurs. They not only provide venture capital, but also usually want to actively participate in the company. There are now numerous business angel networks and pitching events for start-ups. As a rule, business angels participate in very early business phases, sometimes even in the start-up phase, in order to contribute their knowledge and experience (industry know-how, large network, important contacts) as early as possible. This enables inexperienced founders in particular to avoid critical mistakes. Business angels are rather short- to medium-term oriented investors and participate in those phases where the investment risk is still highest and risk capital is very difficult to access for capital seekers. Their goals are to successfully position the company in the market and increase its value, and then to sell their shares profitably to a strategic investor or venture capital company after approximately two to five years. In contrast to private investors, business angels demand higher company shares. Depending on the level of investment, which averages between 50 000 and several hundred thousand euros , as well as the business model and company status, capital seekers should be prepared to sell 5 to 35 % of their company shares (usually with granting a say in company decisions). Founders and business angels should therefore be on the same wavelength and share similar views.

Venture capital companies are among the first port of call for many capital seekers. But especially for early-stage start-ups that do not yet have a proof-of-concept, they may not be the right kind of investors. Venture capital (VC) companies place high investment demands on capital seekers. Seeking to generate high profits, they want to avoid risks as far as possible. Capital seekers who can already demonstrate initial success and have a demonstrably functioning and scalable business model are suitable for approaching venture capital companies. The investment level of venture capital companies starts usually at least 250 000 euros, depending on the company, but can also be several million euros. Before the initial approach, start-ups should inform themselves about the industry focus and investment criteria of the venture capital companies in order not to address the wrong investors. In contrast to private investors or business angels, no individual decides on a capital commitment, but the decision is made by an investment committee. If founders attach great importance to their entrepreneurial freedom, they are not necessarily in good hands with a VC company. These usually have a far-reaching effect on the decision-making processes of start-ups. VC companies are a good choice for founders who

can get involved and want a financially strong and professional partner with a large network at their side. Start-ups planning to finance through a VC company should start the VC acquisition in good time and bring a lot of patience with them, because it can take up to twelve months until the final contract is signed and payment is received.

BEST PRACTICES

- When planning to establish a start-up and to search external funding from investors, have the first contact with early stage investors as early as possible, i.e. right after the IPR and ownership questions have been discussed with the university. No agreements need yet to be finalized, but there should be an understanding of the alternative models of IPR transfer together with prices (e.g. in the form of a term sheet).
- Present the investors the medical need and the development plan. As investors undertake multiple project valuations at a time, the development plan has to be clear.
- The team seeking for funding needs to have good knowledge of the limitations and competition in the field. In the case of new IVD assays, the current gold standards used in hospitals need to be presented and compared to.
- Project valuation can and should be performed with several different investors to get a reliable assessment of the required investment.
- If available, prefer an investor who is familiar with the field and able to develop the technology further.
- Especially the following aspects are relevant for an investor for decision-making:
  - Strong and credible team
  - Innovative technology or business model from a high-tech industry
  - Market prospects (need to be above average)
  - Risks foreseeable in the realization phase
  - IPR, other guarantees

- Existence and location of the company
- Rights for participation in and control of the company (not on the scientific R&D level as the team has competence there)
- Fit in the existing portfolio (diversification or synergy effects; networking)

- The investors' favourite patenting countries in the field include e.g. Germany, France, UK, USA and Japan.

7

CONCLUSIONS

The high discovery rate and low commercialization rate of university born biomarker inventions highlight the need for selecting the best practices, or at least avoiding the pitfalls, when dealing with reviewing, protection and commercialization of IVD-applicable biomarker inventions.

The current collection of best practices and pitfalls aims in its part to help in ensuring that the research, patent protection and technology transfer processes at universities and research organizations are managed in a manner that supports their commercialization, taking seriously into account the needs and requirements of the companies and end users.

The common goal of all the stakeholders, after all, is to give rise to technically and economically practical, clinically informative IVD assays that can be commercialized with reasonable efforts and which ultimately lead to new and improved diagnostics.

8

GLOSSARY

The purpose of the Glossary is to define the terms that might have different meanings and to clarify how we use them in BiC. Any other definitions are used as they are presented in the IVDR glossary.

Analyte is a chemical substance that is the subject of (bio)chemical analysis (1); used in the definition of biomarker (1).

Biomarker is a molecular characteristic that can be objectively measured and evaluated as an indicator of a physiological or pathological process in an individual or an individual's response to a therapeutic intervention. The closest synonym to a clinically useful biomarker in the context of in vitro diagnostics (IVD) is an analyte, i.e., a component (molecule) in a clinical sample the presence, absence or concentration of which is measured in an analytical procedure such as by a laboratory test to obtain information on an individual's health status. The biomarker (or analyte) can e.g. be a nucleic acid, protein, polysaccharide or metabolite (2, 3, 4). Alterations found e.g. by clinical inspection, physical measurement of organ functions (e.g. blood pressure, cardiogram), or microscopy of visual tissue appearance i.e. digital biomarkers are not included in the scope of the current handbook. The scope is also narrowed down to human applications although many characteristics and requirements are similar for veterinary applications.

Biomarker commercialization (BiC) is the name of the current EU-project which formed by 9 partners from the Baltic Sea Region (BSR). The main object of BiC is the development of new practical tools to support the different phases of IVD-applicable biomarker development and commercialization process (5), assessing the maturity level of the biomarker inventions and emphasizing the industry expectations. The ultimate goal is that the new tools will improve the understanding and collaboration between academia and industry and lead increased development of new and effective IVD diagnostics.

Biomarker signature is "the smallest set(s) of molecular quantities that are able to predict a given outcome (target) with maximal predictive performance" (6). Synonym: panel of biomarkers. Examples include transcriptomic, proteomic or metabolomic profiles of a disease. The concept was introduced by the advent of the new spectroscopic technologies such as liquid-chromatography mass-spectrometry or nuclear magnetic resonance spectroscopy. FDA introduces the term of composite biomarker consisting of "several individual biomarkers that are combined in a stated algorithm to reach a single interpretive readout" (7).

Clinical significance refers to the practical importance of a scientific observation (8). It is used as a tool to quantitatively assess whether the magnitude of an observed difference is such that it is relevant to patients. Measures include e.g. effect size and risk ratios. In comparison, **statistical significance** refers to the likelihood of a difference being observed due to chance. It does not give information on the scale or direction of the difference.

Feasibility study is an analysis and evaluation of a proposed project to determine if it (1) is technically feasible, (2) is feasible within the estimated cost, and (3) will be profitable. Feasibility studies are typically conducted before companies decide to invest in new product development (9).

GxP is a general abbreviation for the "good practice" quality guidelines and regulations. The "x" stands for the various fields of ”good practice” (e. g. Good Manufacturing Practice, GMP; Good Laborabory Practice, GLP; Good Clinical Practice, GCP).

Health Technology Assessment (HTA) is a comprehensive, systematic assessment of the background for and the consequences of applying health technology. The purpose of HTA is to improve the basis for decisions about prioritisation and planning in the health area. HTA evaluates treatment methods to disseminate knowledge on the best use of health technologies. HTA contributes to quality development and efficient resource utilisation in any national health service (10).

***In vitro* diagnostics (IVD)** refers to tests (assays) used for in vitro examination of clinical specimens derived from the human body to provide information on the health status of the subject. IVDs are essential tool in the everyday medical practice and most treatment decisions are based on the IVD results.

***In vitro* diagnostic medical device regulation (IVDR)** is the EU REGULATION 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on in vitro diagnostic medical devices (11).

Patent Cooperation Treaty (PCT) phase is the international patent prosecution phase managed by the World Intellectual Property Organization (WIPO). The PCT system facilitates the launch of the patent application in all the PCT member countries (now 152). Typically this phase starts at the end of the priority year (i.e. first year after filing the first national or

areal patent application for the same invention). At the end of the PCT process, the patent authority provides an International Preliminary Report on Patentability (IPRP). Patents are not, however, granted during the PCT phase but the prosecution process is continued in national and areal patent offices.

Payer means an entity (other than the patient) that finances or reimburses the cost of health services, such as public healthcare authority, insurance company, employer or union.

Product is generally "something that is made to be sold, usually something that is produced by an industrial process or something that is cultivated" (12). In the BIC project the term refers to a physical IVD test (i.e. assay) kit for measuring biomarker(s) (i.e. analyte(s)) in selected clinical settings (including home and near patient testing).

Proof of concept (PoC) is an "experimental work intended to verify that the concept works as expected in clinical setting or in real-life setting." (13). POC studies are performed using a practical and targeted (specific) testing platform that could be commercialized and used with reasonable efforts.

Proof of principle (PoP) relates to the early biomarker development studies performed before the proof of concept phase. The methodology employed at this stage may be qualitative or semi-quantitative in nature and use instrumentation mainly available at research settings only. The clinical samples used in these early studies are typically heavily selected (e.g. paired samples of healthy and sick).

Stakeholders in BiC include e.g. research organizations, health care providers (e. g. hospitals and clinical laboratories), clinicians, patients, IVD industry, investors, and health insurance companies.

Technology Readiness Level (TRL) analysis is the assessment of the maturity of a discovery established by European regulations; it is based on an established scale, referring to whether it is a basic research, applied research, proof-of-concept, performance evaluation of prototype, integration/implementation, commercial design, or fully commercial deployment (13, 14, 15, 16).

User, also **End User** or **Intended User**, means any healthcare or medical industry professional or lay person supposed to use the in vitro diagnostic medical device.

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Before biomarker discoveries can be commercially utilized in clinical laboratories, many studies and surveys need to be completed and many questions answered. Is there a market need? Is there enough scientific and clinical evidence to convince the end users? Is the biomarker patentable? Is the translation into a practical product feasible?

Although commercial product development is not the focus of academic research, the route to reach the patients will almost always require a professional commercialization process. Understanding industry and end-user requirements is essential for the successful commercialization of new biomarker assays.

The current handbook collects some of the best practices and pitfalls encountered at different phases of biomarker discovery, development, patent protection and technology transfer at universities, hospitals and research organizations. The focus is on *in vitro* diagnostics (IVD)-applicable biomarkers, i.e. markers intended to provide information on the health status of a person.

The input for the collection has been sought from true-life practices:

- practices found in literature or taught by experts in the field;
- opinions and expertise of different stakeholders (end users, companies, technology transfer professionals, researchers, financiers);
- recommendations, regulation and laws;
- as well as practices learned the hard way, i.e. repeatedly failing somewhere in the process and later adapting the process for increased success.

The main target group of the handbook comprises professionals working in Technology Transfer Offices (TTOs). The presented practices are yet not intended to be interpreted as strict rules but rather as a source of inspiration. Optimal ways to proceed with patenting and commercialization significantly vary between cases and circumstances.

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