BIOMARKER COMMERCIALIZATION

Interreg Baltic Sea Region

EUROPEAN UNION
EUROPEAN REGIONAL DEVELOPMENT FUND

Biomarker Commercialization Review Tool

Authors:

Piia von Lode and Valérie Daussin

UNIVERSITY OF TURKU

AALBORG UNIVERSITY HOSPITAL

IMPRINT

EUROPEAN UNION

EUROPEAN
REGIONAL
DEVELOPMENT
FUND

BIOMARKER COMMERCIALIZATION (BIC) REVIEW TOOL

Designed to improve communication

The BIC Review Tool is a comprehensive checklist for selection of the most promising invention for further commercialization of IVD-applicable biomarkers.

The BIC Review Tool allows an "inventors interview"-type of approach, in addition to being a checklist for Technology Transfer Offices and Researchers. It is designed to improve communication between the stakeholders involved in the commercialization process and to facilitate collaboration. The tool is therefore in a completely different format than the Biomarker Commercialization (BIC) Guide. All introductions and explanations are missing by intention since they can already be found in the BIC Guide, Best & Pitfall Practices handbook or the Regulatory Guide.

LEAD PARTNER

Ideklinikken - Aalborg University Hospital
The North Denmark Region
Hobrovej 18-22
9100 Aalborg
Denmark

AUTHORS

Piia von Lode, Ph. D., University of Turku
Valérie Daussin, LL.M., Aalborg University Hospital

WITH THE CONTRIBUTION OF THE ENTIRE BIC CONSORTIUM

For more information: biomarker.nu

Inventors (name, affiliation): _____

Inventors' contact person and contact information: _____

Inventor disclosure/report code and topic (where applicable): _____

- ◯ Number of biomarkers: _____
- ◯ Name(s), synonym(s), acronym(s) and all different codes of the biomarker(s) at the different molecular levels: _____
- ◯ Disease/condition under investigation: _____
- ◯ Type of disease (e.g. infectious, congenital, cancer, occupational): _____
- ◯ Potentially applicable molecular forms for the current test:
  - ☐ DNA
  - ☐ mRNA
  - ☐ Modification of polynucleotide (e.g. post-transcriptional modification): _____
  - ☐ Protein
  - ☐ Modification of protein (e.g. glycovariant): _____
  - ☐ Metabolite
  - ☐ Other, which: _____

DESCRIPTION OF THE PLANNED IN VITRO DIAGNOSTIC (IVD) TEST

- ◯ Test type
  - ☐ Diagnostic
  - ☐ Prognostic
  - ☐ Predictive, for which therapy:
  - ☐ Screening
  - ☐ Risk/susceptibility
  - ☐ Companion diagnostics, for which drug: _____
  - ☐ Non-IVD applicable marker, specify type of use: _____
  - ☐ Other:
- ◯ Intended use/purpose of the test: _____

1 Biomarker discovery

TRL-1 BASIC PRINCIPLES OBSERVED

CLINICAL NEED

SIGNIFICANT, DOCUMENTED CLINICAL NEED

◯ Which important clinical question the test result answers:

_____

_____

◯ Who is the intended end user:

_____

◯ Does the important clinical question come from the intended end users and is it confirmed by them:

☐ Yes, documented contact(s):

_____

☐ Additional literature referral(s):

_____

☐ No

◯ How the test result expectedly affects the treatment or the outcome of the patient:

_____

STATISTICALLY SIGNIFICANT & CLINICALLY MEANINGFUL RESULTS ESTABLISHED

◯ Clinical study type

☐ Paired case-control study,

n (pairs) = _____

☐ Cohort study, n (controls) = _____

n (cases) = _____

◯ Statistically significant ($p < 0.05$)

☐ Yes, p = _____

☐ No

◯ Difference in affected vs. healthy people, effect size, and 95 % CI: _____

◯ RR, OR or HR (where applicable): _____

◯ Is the difference large enough to convince a clinician in routine setting?

☐ Yes, no or little overlap (in healthy vs. affected); the difference is relevant to an individual patient

☐ No, significant overlap between groups

COMMERCIAL VIABILITY

TEST RESULT AFFECTS SELECTION OF TREATMENT

◯ Is there therapy existing for the disease/condition targeted?

- ☐ Yes (specify): _____
- ☐ No
- ☐ No, but the marker provides potential for drug development
- ☐ non-IVD applicable biomarker

◯ How the test result is expected to affect the treatment of the patient:

_____

_____

_____

TEST FILLS A GAP OR OTHERWISE IMPROVES CURRENT TESTING SCHEME

◯ Is the test expected to enable detecting the disease at early stage?

- ☐ Yes, before clinical symptoms
- ☐ Yes, directly after onset of the acute disease
- ☐ No

• If no, can the disease yet be successfully treated at the time of test result?

- ☐ Yes
- ☐ No

◯ How the test expectedly improves the current testing scheme:

_____

_____

_____

FEASIBILITY & IPR

PRACTICAL ROUTINE ASSAY FEASIBLE

◯ Is the clinical concentration of the biomarker high enough to be measured by a practical routine assays?

- ☐ Yes, conc. range: _____
- ☐ No

◯ Which practical assay platform you envision for the final product: _____

◯ Which specimen types are feasible:

- ☐ Non-invasive matrices (e.g. blood, urine): _____
- ☐ Invasive matrices (e.g. CSF, biopsy):_____
- ☐ Invasive specimen is routinely taken regardless:
  - ☐ Yes
  - ☐ No, but performing the test requires one

◯ Is the biomarker stable in the (stored) clinical specimens?

- ☐ Yes, results of preliminary stability studies (e.g. freeze-thaw cycles, recovery-% etc.):

_____

- ☐ Specimen type and storage conditions: _____
- ☐ No, not tested
- ☐ No, specify: _____

◯ Is the biomarker present in fresh specimens from healthy people:

- ☐ Yes: _____
- ☐ No

◯ Does the test involve complex result interpretation?

- ☐ Yes, multiplex biomarker panel
- ☐ Yes, multiple molecular types of biomarkers
- ☐ Yes, personalized decision tree or sequential multi-parameter testing
- ☐ No

BIOMARKER OR ITS CORRELATION TO DISEASE IS A NOVEL FINDING

◯ Is/are the biomarker(s) previously known in the literature?

- ☐ No
- ☐ Yes, in the same indication (which biomarker(s)):

_____

_____

- ☐ Yes, in another indication, (which biomarker(s), which indication):

_____

_____

- ☐ If Yes, are they routinely measured in clinical settings (how and in what conc. range)?

_____

_____

2 Biomarker verification and preliminary scientific validation studies

TRL-2 PROOF OF PRINCIPLE STUDIES

CLINICAL NEED

CLINICALLY SIGNIFICANT RESULTS ESTABLISHED

◯ Description of the clinical cohort used in verification studies:

- ☐ cases: _____
- ☐ Exclusion criteria: _____
- ☐ (n) of controls = _____
- ☐ Specimen matrix = _____

◯ Is the original observation repeated with increased sample size:

- ☐ Yes, p = _____
- ☐ No, p = _____

◯ Difference in affected vs. healthy people, effect size, and 95 % CI:

_____

_____

◯ RR, OR or HR (where applicable):

_____

_____

◯ Is the magnitude of the observed difference of practical importance, i.e. clinically significant:

- ☐ Yes, how: _____

  _____
- ☐ No

◯ Have the findings been confirmed at other sites?

- ☐ Yes: _____

  _____
- ☐ No, could not be confirmed

SCIENTIFIC VALIDITY: ASSOCIATION AND SPECIFICITY TO DISEASE CONFIRMED

◯ Is the underlying biological pathway linking the biomarker to the disease known or under investigation:

- ☐ Yes: Shared molecular pathology (e.g. cellular stress) across diseases can be excluded because:

  _____

  _____
- ☐ No

COMMERCIAL VIABILITY

POSITIVE DOCUMENTED FEEDBACK FROM CLINICIANS / CLINICAL LABORATORIES

◯ What is the significant clinical question (i.e. the need) the test answers:

_____

_____

◯ Is the magnitude of the observed difference of practical importance, i.e. clinically significant:

☐ Yes, documented feedback: _____

_____

☐ Additional literature referrals: _____

_____

☐ No

LARGE TARGET POPULATION IDENTIFIED

◯ Prevalence of the disease/condition in (different) population(s):

_____

_____

◯ Who are to be tested (mark all):

☐ Entire population

☐ Specific subgroup of the population, which: _____

_____

☐ Entire affected population (with already established diagnosis)

☐ Specific population of the sick, which: _____

◯ Share amongst all sick: _____ %

☐ Newborn / children / teenagers (select)

☐ Adults with age range of:_____

☐ Elderly

☐ Female

☐ Male

☐ Specific ethnicities: _____

☐ Specific timing or other trigger: _____

◯ Contraindications for testing (which, when): _____

◯ Estimated yearly number of cases and tests for the above target group

☐ Locally: _____

☐ Internationally (specify): _____

◯ Estimated price of test: _____€

◯ Estimated maximum yearly size of the specified market (cases x €) = _____ €

◯ Is the market potential significant (profits >> patenting costs?)

☐ Yes

☐ No

FEASIBILITY & IPR

QUANTITATIVE ASSAY TECHNOLOGIES USED

◯ Assay technology(ies) used in the verification studies:

_____

_____

◯ Are the used assay technologies:

- ☐ quantitative
- ☐ target-specific
- ☐ high-throughput / up-scalable
- ☐ automatable
- ☐ currently used in routine
- ☐ sensitive (clinical concentrations fall within the linear measuring range)
- ☐ No, another assay technology to be used in prototype assay for proof-of-concept studies, which:

_____

_____

◯ Have plans and specifications been made for the prototype assay:

- ☐ Yes:
  - ☐ Reagent plan
  - ☐ Instrument plan
  - ☐ Technical specifications
- ☐ No, reason:_____

◯ Are specialized instrumentation or chemically modified reagents required in the prototype assay?

- ☐ Yes which and why:_____
- ☐ No

BIOMARKER OR ITS CORRELATION TO DISEASE IS INVENTIVE AND PATENTABLE

◯ Internal novelty and patentability survey performed:

_____

_____

◯ External novelty and patentability survey performed:

_____

_____

◯ Previous publications by inventors (incl. abstracts, posters and presentations) reviewed:

- ☐ Yes: invention not previously published by the team
- ☐ Yes: invention published and non-patentable
- ☐ No

◯ The invention is novel

- ☐ Yes, the novel features concern:
  - ☐ Singular biomarker(s)
  - ☐ Panel of biomarkers
  - ☐ Method of detection
  - ☐ Other (please specify): _____
- ☐ No

◯ Is comprehensive patent protection yet achievable?

- ☐ Yes, target of protection: _____
  - ☐ Computer algorithm
  - ☐ Sequences of binders
  - ☐ Method of producing (instead of product)
  - ☐ Other (please specify): _____
- ☐ No

◯ Is the use of the method evident in the final product?

- ☐ Yes, how: _____
- ☐ No

◯ The invention is inventive:

- ☐ Yes, the non-obvious, surprising features concern: _____
- ☐ No

3 Development of a specific biomarker assay (prototype)

TRL-3 PROOF OF CONCEPT ASSAY ESTABLISHED

CLINICAL NEED

GOOD PRELIMINARY CLINICAL PERFORMANCE

◯ Good preliminary clinical performance

o Description of clinical specimens used in setting up the prototype assay:

- ☐ Specimen matrix: _____
- ☐ Specimen preparation: _____
- ☐ Selection criteria and (n) of cases: _____
- ☐ Selection criteria and (n) of controls: _____

◯ Results obtained with prototype correlate well with the original observations:

- ☐ Preliminary cut-off concentration used: _____
- ☐ Preliminary diagnostic sensitivity: _____ %
- ☐ Preliminary diagnostic specificity: _____ %
- ☐ Other applicable measures: _____

◯ Stability of the biomarker in the matrixes studied:

- ☐ RT: _____
- ☐ -20 °C/- 70 °C: _____
- ☐ Freeze-thaw cycles: _____
- ☐ Recovery-%: _____

COMMERCIAL VIABILITY

COMPETITIVE ADVANTAGE ACHIEVED

◯ Clear purpose and need for the test has been established and verified by end-users in writing:

- ☐ Yes: _____
- ☐ No, situation has changed: _____

◯ List all competing methods (commercial or under development)

- ☐ For the same target molecule (also when different molecular class): _____
- ☐ For another target molecule: _____
- ☐ A non-biomarker based test or imaging approach: _____

◯ Advances of the new test over the competing methods:

- ☐ Increased accuracy
- ☐ Earlier diagnoses
- ☐ Earlier therapeutic actions
- ☐ Improved convenience
- ☐ Decreased number of tests of procedures
- ☐ Cost-savings due to other reasons:_____
- ☐ Other: _____
- ☐ Competing methods do not exist, reason: _____

◯ Are the results of the new test comparable to the golden standard (or equivalent) approach:

- ☐ Yes, method tested against and correlation: _____
- ☐ No, not tested because: _____

_____

RISK MANAGEMENT

CLINICAL

◯ Number of false positives per each true positive (100/PPV): _____

◯ Is over-diagnostics possible? If yes, what are the consequences to a patient (especially note invasive testing or therapy steps):

- ☐ Yes: _____
- ☐ No

◯ Number of false negatives per each true negative (100/NPV): _____

◯ Is under-diagnostics possible? If yes, what are the consequences to a patient (especially note life-threatening situations):

- ☐ Yes: _____
- ☐ No

LEGAL

◯ Informed consent of patients allows commercial use (incl. patenting) of results:

- ☐ Yes
- ☐ No

◯ MTA's made allow commercial use (incl. patenting) of results:

- ☐ Yes
- ☐ No

IPR AND FTO

◯ Sufficient IP rights and FTO can be achieved:

- ☐ Yes
- ☐ No, invention non-patentable or lacks FTO: _____

FEASIBILITY & IPR

SPECIFIC AND PRACTICAL PROTOTYPE (PROOF-OF-CONCEPT ASSAY) ESTABLISHED

◯ Analytical performance (i.e. ability to correctly measure the biomarker) conforms to predefined technical specifications:

- ☐ Limit of detection: _____
- ☐ Limit of quantification: _____
- ☐ Linear measuring range: _____
  - ☐ Clinical concentrations fall within linear measuring range?
    - ☐ Yes: _____
    - ☐ No: _____
  - ☐ Hook-effect controlled?
    - ☐ Yes: _____
    - ☐ No: _____

◯ Practicability characteristics conform to predefined specifications:

- ☐ Specimens accepted: _____
- ☐ Required skills and labor in specimen preparation:
  - ☐ Low, steps: _____
  - ☐ High, steps: _____
  - ☐ Pre-analytical requirements for specimens (collection, processing, storage): _____
  - ☐ Exclusion criteria: _____
  - ☐ Total turn-around-time of assay_____

◯ Reliability characteristics conform to predefined specifications:

- ☐ Trueness of measurement (bias): _____
- ☐ Precision of measurement (repeatability, reproducibility) _____
- ☐ Recovery in spiked specimens: _____
- ☐ Interferences detected:
  - ☐ No
  - ☐ Yes: _____

FREEDOM-TO-OPERATE (FTO)

◯ In-house or IPR-free, multi-vendor commercial key components are available/can be made available economically at sufficient scale:

- ☐ Yes
- ☐ No, commercial license for following components required: _____
- ☐ No, only singular vendors exist for following components: _____
- ☐ No, following components are available only low-scale (or high-cost): _____

Describe the limiting factors and components:

_____

_____

◯ Techniques used in the prototype / proof-of-concept assay can be used without a commercial license:

- ☐ Yes
- ☐ No, commercial license is required for the following technology: _____

◯ In case of FTO hindrance, describe the geographical and temporal coverage:

_____

_____

DECISION ON PATENTING:

- ☐ Yes, patenting to be initiated
- ☐ No

Can alternative commercialization routes be considered:

- ☐ Knowledge transfer
- ☐ Material licensing
- ☐ Services-for-fee
- ☐ Database licensing
- ☐ Software licensing
- ☐ Other, specify: _____

4 Clinical performance of the prototype in laboratory settings

TRL-4 PROOF OF CONCEPT STUDIES WITH PROTOTYPE ASSAY

CLINICAL NEED

CLINICAL PERFORMANCE OBJECTIVES MET

◯ Description of the clinical cohort used in proof-of-concept studies:

- ☐ Specimen matrix: _____
- ☐ Selection criteria and (n) of cases: _____
- ☐ Exclusion criteria: _____
- ☐ (n) of controls = _____
- ☐ Are the specimens representative of the target population?
- ☐ Yes, minimal specimen picking
- ☐ No, describe the picking criteria:

_____

_____

◯ Results obtained with prototype correlate well with the condition:

- ☐ AUC (in ROC analysis): _____
- ☐ Suggested cut-off value: _____
- ☐ Diagnostic sensitivity: _____ %
- ☐ Diagnostic specificity: _____ %
- ☐ Negative predictive value (NPV): _____
- ☐ Positive predictive value (PPV): _____
- ☐ Other applicable measures, e.g. relative risk ratio, hazard ratio, etc.: _____

COMMERCIAL VIABILITY

POSITIONING IN CLINICAL CARE PATHWAY CONFIRMED

◯ Clear purpose and need for the test verified by end-users in writing:

- ☐ Yes: _____
- ☐ No, feedback obtained: _____

◯ Expected positioning in the clinical care pathway:

- ☐ Stand-alone test (preceding or confirmatory tests not required)
- ☐ Add-on test; to be incorporated in existing testing sequence
  - • Preceded by following test(s): _____
  - • Followed by following test(s):_____
- ☐ Performed simultaneously with following test(s): _____
- ☐ Replaces an existing test of: _____
- ☐ Improves an existing test of:_____
- ☐ Improvements achieved: _____

◯ Intended use settings:

- ☐ Clinical laboratory
- ☐ Near-patient testing
  - ☐ Emergency (acute testing)
  - ☐ Infectious disease
  - ☐ Chronic disease
  - ☐ Other, specify: _____
- ☐ Self-testing

EVIDENCE OF HEALTH BENEFITS AND COST-EFFECTIVENESS

◯ How the test improves the patient outcome: _____

◯ How the test improves the cost-efficiency of the clinical care pathway:

- ☐ Improved diagnostic accuracy
- ☐ Decreased need of (more) expensive tests or therapies
- ☐ Other: _____
- ☐ Does not decrease costs

FEASIBILITY & IPR

PATENTING IN PROGRESS

◯ Priority year development plan followed:

- ☐ Yes, milestones met and new experimental evidence established: _____
- ☐ No, alternative plan followed:

_____

_____

- ☐ No, new evidence not established, or it does not support the patent application:

_____

◯ Patenting with sufficient scope of patent protection seems likely based on Office Actions received

- ☐ Yes
- ☐ No, specify hindrances identified: _____

◯ IPR covers all self-made changes and improvements:

- ☐ Yes
- ☐ No, specify: _____

◯ Continuing active contribution of inventors available

- ☐ Yes
- ☐ No

◯ Based on above, proceeding to international PCT phase is feasible:

- ☐ Yes
- ☐ No

5 Pre-industrial maturation phase

TRL-5 CONFIGURATION TO INDUSTRIAL APPLICATION (BETA PROTOTYPE)

TRL-6 TECHNOLOGY DEMONSTRATED IN RELEVANT ENVIRONMENT

COMMERCIAL VIABILITY

FURTHER CLINICAL EVIDENCE ACCUMULATED IN COLLABORATION WITH CLINICIANS / INDUSTRY

◯ Description of studies conducted:

- ☐ Cohort study: _____
- ☐ Retrospective randomized trial: _____
- ☐ Prospective randomized trial: _____

◯ Clinical concentrations and reference ranges

- Healthy persons: _____
- Affected persons: _____
- ☐ Are all clinical concentrations detectable by the beta prototype:
- ☐ Yes
- ☐ No, specify: _____

◯ Within-subject variation:

- ☐ Yes: _____
- ☐ No

◯ Between-subject variation:

- ☐ Yes: _____
- ☐ No

◯ Endogeneous and/or exogeneous interference encountered:

- ☐ Yes: _____
- ☐ No

◯ Cross-reacting substances:

- ☐ Yes: _____
- ☐ No

◯ What kind of feedback is obtained from the intended end users (including modifications suggested):

_____

_____

FURTHER KNOWLEDGE OF BIOMARKER BIOLOGY

◯ Are following factors of the biomarker known:

- ☐ Where it is expressed (e.g. intracellular, intra-nuclear, excreted):_____
- ☐ When and how long it is expressed: _____
- ☐ What molecular classes can be detected, which one is preferred: _____
- ☐ How many different manifestations of the molecule exists (in selected molecular class): _____
- ☐ How stable are the molecular forms in the circulation: _____
- ☐ How the fasting state, circadian rhythm, age, gender or ethnicity affects the results: _____
- ☐ Other, specify: _____

CLINICAL NEED

ASSESSMENT OF BUSINESS MODELS

◯ Considerations for establishing a start-up (select applicable):

- ☐ High degree of readiness, reasonable amount of research and product development required
- ☐ Large size and high growth rate of market; high market share can be obtained
- ☐ Low competition, few alternative solutions in sight
- ☐ Wide scope of patent protection achieved further prevents competition
- ☐ Motivated team with entrepreneurial mindset
- ☐ Sound business plan, realistic funding options available

FEASIBILITY & IPR

BETA PROTOTYPE ESTABLISHED

◯ Documented specifications, optimizations and measured performance:

- Analytical performanc
- Clinical performance