Biomarker work should begin at the end - first why? then how?

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What is a biomarker?

- Useful treatments have effect on *clinical outcomes* – a useful biomarker should correlate with clinical assessments.
- Biomarkers have been used a very long time in medicine (but not under that name)
- Nomenclature is exceptionally confusing
Categories of Biomarkers

- **Susceptibility/Risk**: Indicate risk of developing disease
- **Diagnostic**: Disease detection or confirmation
- **Monitoring**: Assess status of disease state or response to therapy
- **Prognostic**: Predict progression or recurrence in patients who have a disease
- **Predictive**: Predict which patients will (or will not) benefit from therapy
- **Pharmacodynamic**: Show a biological response to therapy
- **Safety**: Indicates the likelihood, presence, or extent of toxicity as an adverse effect

Therapy dependent
Some common misconceptions

- Technology drives biomarker work
  - Gene profiling, proteomics, metabolite mapping etc.
- The main biomarker challenge is to find good patient samples
- A difference in gene or protein expression is a biomarker
- Biomarkers shorten development times
Why does the project need biomarkers?

• All projects should aim to have pharmacodynamic (PD) markers available when clinical testing is initiated
  - *Biomarkers...it’s really about the PD...*

• The need for non-PD biomarkers is project dependent

• Based on the target product profile (TPP) a **Context of Use (COU)** should be defined

• **All aspects of biomarker discovery and development should be guided by the Context of Use**
  • Why is a biomarker needed?
  • What should it achieve?
PD markers

• Used to establish a PK/PD relationship
  - Essential for adequate dose selection in early clinical trials
  - Gives confidence that negative POC are not due to underdosing

• Usually based on mechanistic understanding
  - Can be proximal to target, or further downstream
  - Ideally developed in animal models and translated to humans

• PD-based decisions in early trials often based on cohort data, not individuals, but dose escalation can be stopped by individual “outliers”
  - Biologic variation often unclear
  - Assay needs to be good enough to establish a concentration-response relationship, and to avoid accidentally triggering stopping rules
What other biomarkers are needed?

- **General markers** should be used when available, if they add value
  - Development times and resource requirements limit scope for establishing new markers within pharma companies
- **Predictive biomarkers** most relevant for new development by pharma (aside from PD)
  - The main basis for precision/personalized medicine
    - Companion diagnostics - **essential** for safe and effective drug use
    - Complementary diagnostics - **inform** on improving the benefit/risk ratio
  - The need for predictive markers should always be considered
Is developing a predictive biomarker justified?

Yes

• Serious disease where giving the wrong drug has negative consequences for patients
  - Lack of efficacy of a drug will delay alternative potentially effective therapy – eg cancer treatment
  - Ineffective treatment results in irreversible damage - eg bone damage in rheumatoid arthritis
  - Need to justify treatment due to potential for severe side effects

Maybe?

• Disease where giving the wrong drug has negative consequences for society
  - Antibiotics – resistance development
  - Costly drugs where only responders should be treated

No

• Conditions where clinical responses are fast - eg pain
• Diseases where there are few long term consequences of delaying treatment - eg psoriasis where lesions are fully reversible upon successful treatment
BMx flow scheme - simplified

- Project needs
- COU(s)
- Early BMx plan
- BMx discovery
- Preclinical qualification
- Updated BMx plan
- Assay development
- Clinical testing
- Clinical confirmation
- Ready for implementation
- Clinical use (PD)

Clinical candidate
Biomarker plan

• Based on the *Context of Use* and aligned with the *TPP* and the desired *label* text
  - Clear statements of the **purpose and value** of all different markers proposed
  - Is it important to be able to include or to exclude patients? Both?
• Many / most markers are likely to have been described or suggested previously
• Biomarker discovery plan if there is a need for finding new markers
  - Experimental outline
  - Preliminary preclinical qualification plan
  - Outline of expected clinical validation
  - Timelines calculated backwards based on when the biomarker needs to be ready for use in development and/or on the market
Biomarker discovery

• Samples
  - Biobanked samples most useful for detecting DNA changes or downstream consequences of DNA changes
  - Prospective sampling allows control of patient selection specifics, timing of sampling, preanalytical sample handling etc.

• Various analytes and technologies
  - Genomic DNA, mRNA or miRNA expression, protein expression in blood, tissue etc. using immunoassays, proteomic techniques, imaging etc. ...

• Biomarker discovery is dependent on technology, but should not be driven by technology

• Final clinical assays often have a different assay format
Biomarker Candidate Qualification

• Identification and qualification of potential markers that *appear* to have the required properties
  - Able to separate individuals with the confidence *required for the intended clinical use*.
    • Specification of a cut-off possible
    • Limited biologic variability

• The vast majority of “biomarkers” reported in literature do not fulfil these criteria

Zeisler, NEJM 2016; 374: 13-22
Updated biomarker plan

- For preclinically qualified candidates, specification of:
  - Target population
  - Biomarker performance requirements (positive and negative predictive values)
  - Assay requirements
  - Clinical testing and validation plans
  - Data analysis plans
  - Plans for regulatory interactions

- The plan should have input from the relevant development functions (clinical, stats, bioanalysis, regulatory etc.)
Biomarker performance

• Specification of required **biomarker performance**
  • How well does the marker need to separate BMx positive vs negative? What sensitivity and specificity etc. are required? Highly dependent of the Context of Use

• Performance depends on biological variation and analytic assay quality
Clinical assay development and qualification/validation

• Development of a *Fit-for-Purpose* analytical assay – as good as needed, but not better

• A high-quality assay may require development of new analytic reagents

• Assay qualification to ensure performance in alignment with the COU
  • Limited qualification for *exploratory markers* that will not be used for decision making
    • The purpose and analysis plan should be clear
  • More extensive qualification for markers intended for *internal decision making*
  • Full validation for markers intended for *regulatory approval*
Assay qualification
- more than assay development

• Pre-analytical qualification
  - Optimize and specify processes that occur before a sample is analyzed, e.g. collection, handling, transport, storage etc.
  - Up to 75% of all testing errors occur in the pre-analytical phase

• Post-analytical follow-up
  - Reporting according to specification
  - Implementation plan
Clinical testing and confirmation

- **Prospective clinical evaluation** with adequately powered test and confirmation cohorts, sequentially or in parallel.
  - Defined endpoints aligned with the COU and required performance criteria
  - Analysis should be done blinded to the clinical outcome of the patients
  - Markers identified by post-hoc analysis should be considered as exploratory

*Diagnostic or Prognostic biomarkers*
- Clinical evaluations of investigational devices, unless exempt, must (in the US) have an approved IDE (Investigational Device Exemption) **before** the study is initiated.

*Companion diagnostics* (a subset of predictive biomarkers)
- Clinical studies usually require IND and IDE
Clinical testing and confirmation

• **Prospective clinical evaluation** with adequately powered test and confirmation cohorts, sequentially or in parallel.
  - Defined endpoints aligned with the COU and required performance criteria
  - Studies will have a separate regulatory track from therapeutics
  - Analysis should be done blinded to the clinical outcome of the patients
  - Markers identified by post-hoc analysis should be considered as exploratory

**Companion diagnostics** (a subset of predictive biomarkers) - *fastest path*

**Drug**

- Research
- NCD
- Phase 1

**CDx**

- BM Discovery
- Reag
- Assay

**Clinical Candidate**

- Phase 2a BM test
- Phase 2b BM test/confirmation
- Phase 3 BM confirmation/use
- Filing

**Diagnostic or Prognostic biomarkers – theoretical fastest path**

- BM Discovery
- Reag
- Assay

- Clinical test cohort
- Clinical confirmation cohort
- Filing
Regulatory aspects

FDA has issued several guidelines on biomarkers and strongly supports development

- Development of companion diagnostics
  - Applicable also to the co-development of markers for use in drug development
  - Considered IVDs, In Vitro Diagnostic Devices
  - Any non-approved IVD that is used to enroll, assign or manage subjects is regulated by the Investigational Device Exemption (IDE) regulation at 21 CFR Part 812
    - For most NMEs the risk would be considered “significant” and an IDE application (in addition to the IND) would be required.

- Biomarker qualification program, for establishing biomarkers useful for drug development (but not associated with specific compounds)
  - Very high bar for approval

EMA (CHMP) offers support for biomarker qualification and coordinates with the FDA

- A coming guideline for personalized medicines and companion diagnostics has been announced
Conclusions and practical considerations

• Biomarker success depends on a clearly stated Context of Use based on a well defined TPP and clear understanding of the specific intended clinical use.

• Getting a biomarker ready for use to make clinical decisions takes time.
  • For a companion diagnostic development needs to start during drug discovery and has to be ready by compound launch – companion diagnostics can usually be approved only if available at compound launch.

• Success is not a given.
  • For many complex conditions and treatments it has proved very difficult to identify clinically useful biomarkers, including predictive markers.
  • Most successful predictive biomarker tests detect malignancy based on DNA mutations.

• Biomarker development of (other than PD for internal decision making) require diagnostics expertise and are probably best done in partnership with a dedicated diagnostics developer.
My suggestions...

Insist on getting a clear written rationale for every requested analysis

• If a clear rationale is not available, do not count on there being one

• Memories are short and people leave or change jobs – without a written document the rationale for the test is often lost

• If the rationale is “Explore …”, demand to get the plan for what is going to be done with the data generated
  - How is it going to be used? Who is going to do the data analysis? What are the follow-up steps?

• “Interesting” is a dirty word – it may be interesting, but is it important? “Interesting” experiments too often lack focus or purpose

Challenge your users!

• You know the analytical challenges, they/we do not

• When you are clear on the purpose, make sure the analysis is fit-for-purpose
Thank you!