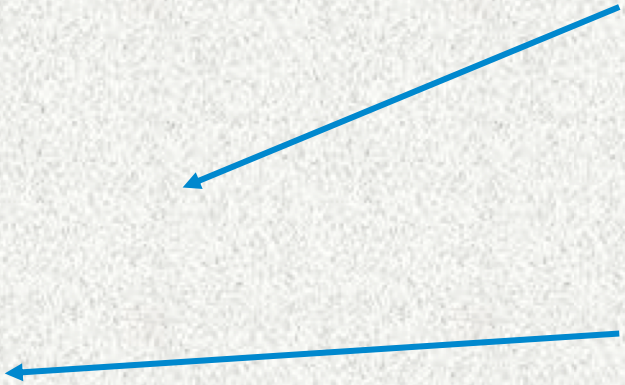
Biomarker work should begin at the end - first Why?, then How?

Lars Karlsson

Ferring

What is a biomarker?



Biomarker

Increased temperature - objectively measured

Clinical assessment

Patient feeling ill due to fever

- 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

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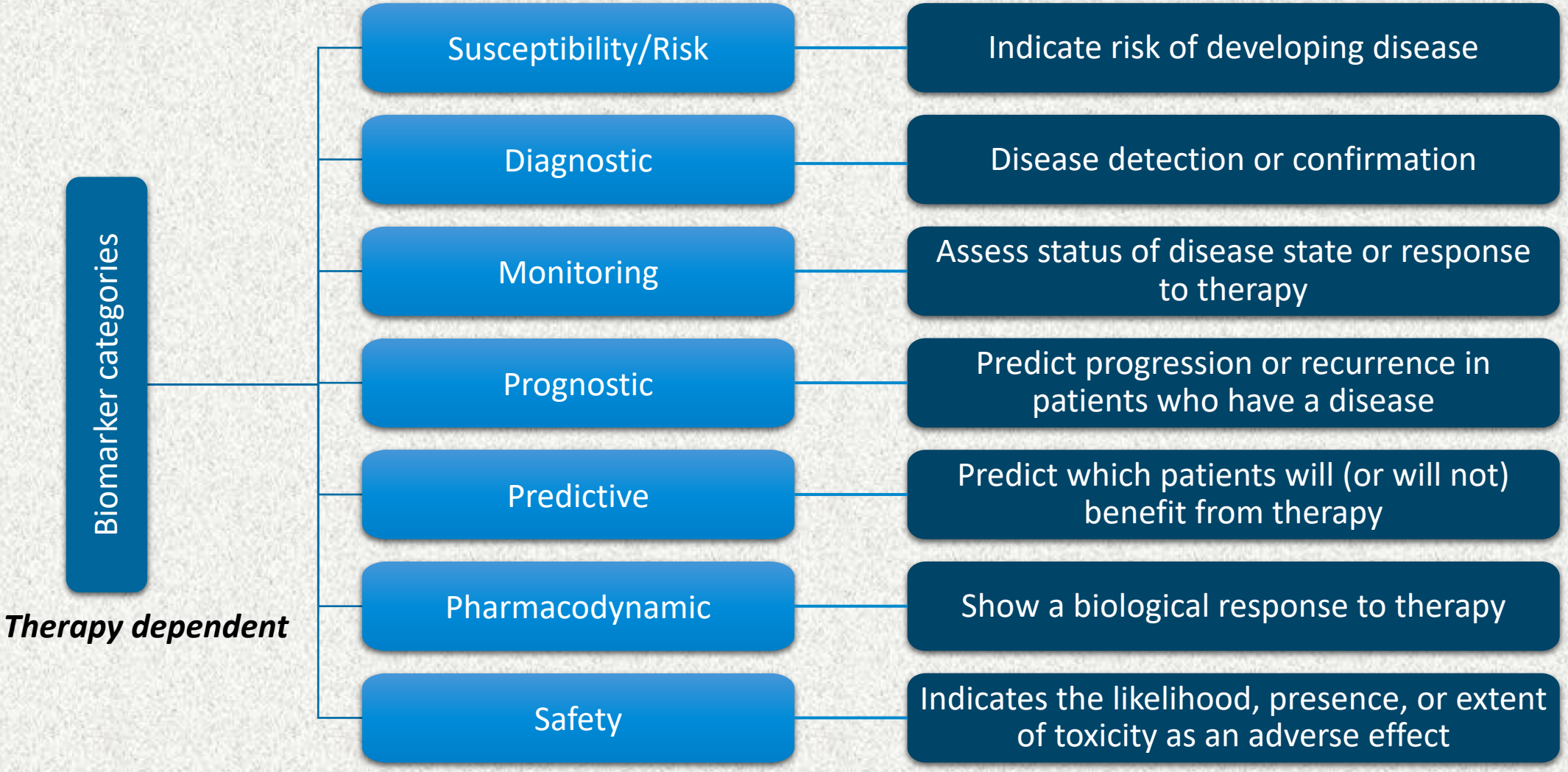
Categories of Biomarkers



Therapy dependent

BEST glossary - https://www.ncbi.nlm.nih.gov/books/NBK338448/

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
- “We do not know what to do – we need a biomarker!”

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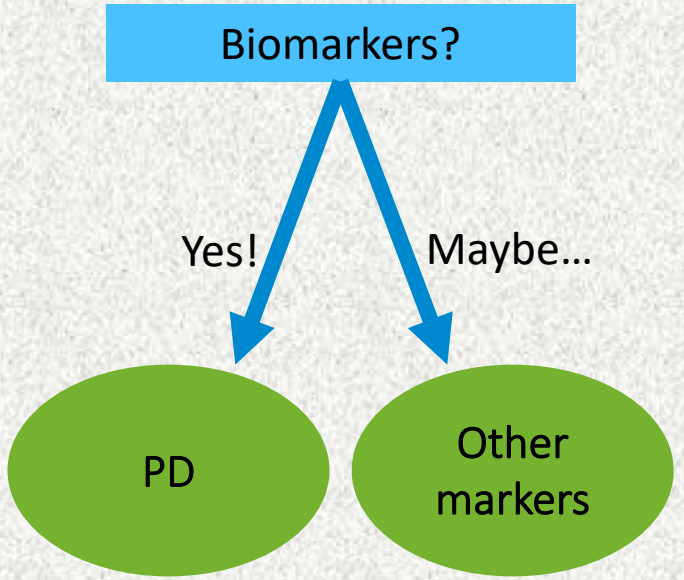
Why does the project need biomarkers?

- 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
- A ***Context of Use (COU)*** should be defined based on the target product profile (TPP)



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

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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

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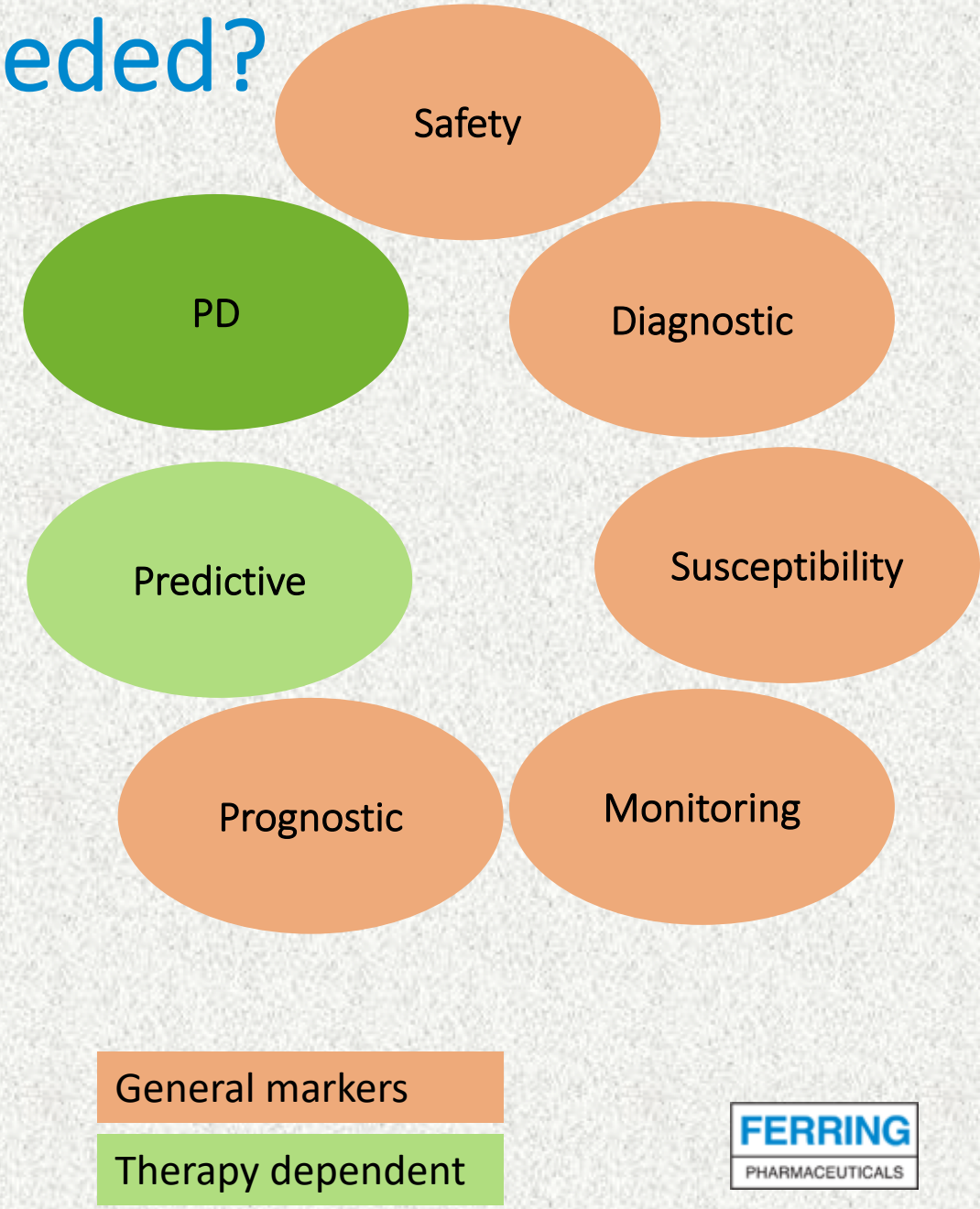
What other biomarkers are needed?

- *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



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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

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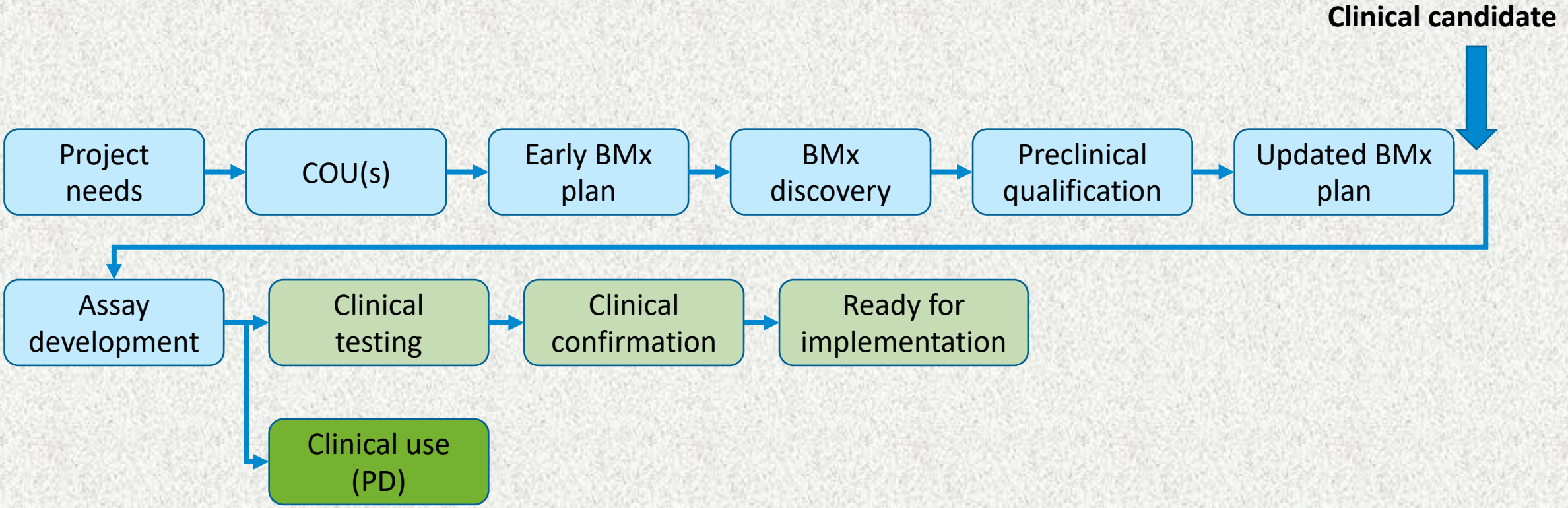
BMx flow scheme



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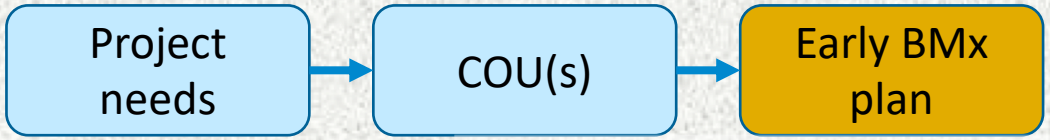
Biomarker plan



- 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

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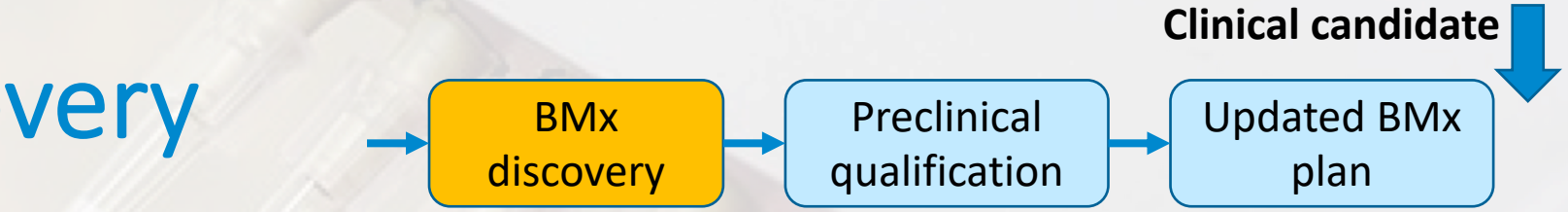
Biomarker discovery



- Samples
  - Biobanked samples useful for detecting DNA changes or downstream consequences of DNA changes, less so for proteins
  - Prospective sampling allows control of patient selection criteria, 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. …
- Dependent on technology, but should not be driven by technology
- Final clinical assays often have a different assay format

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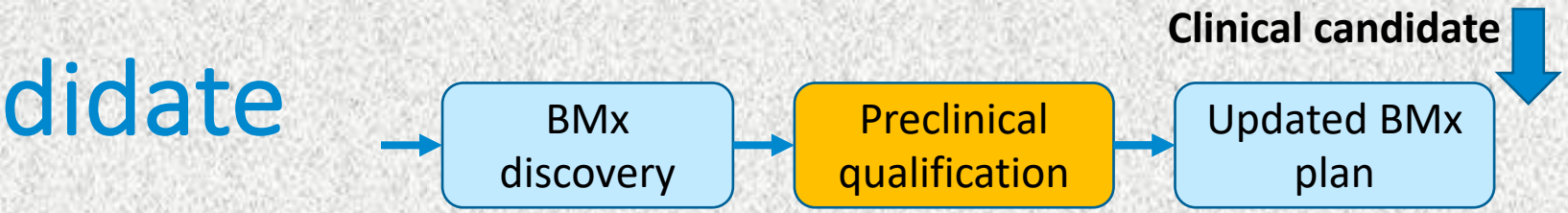
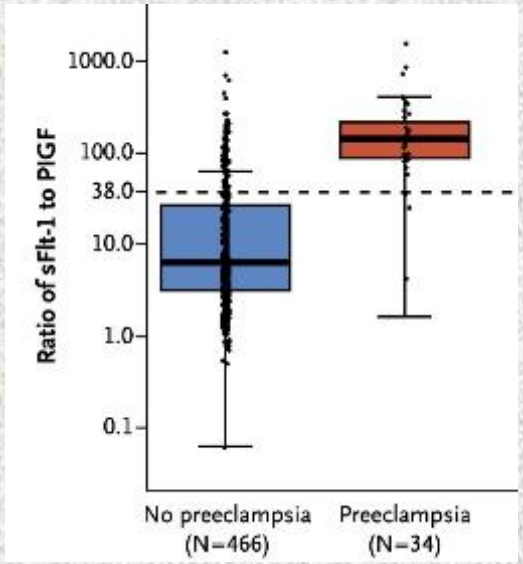
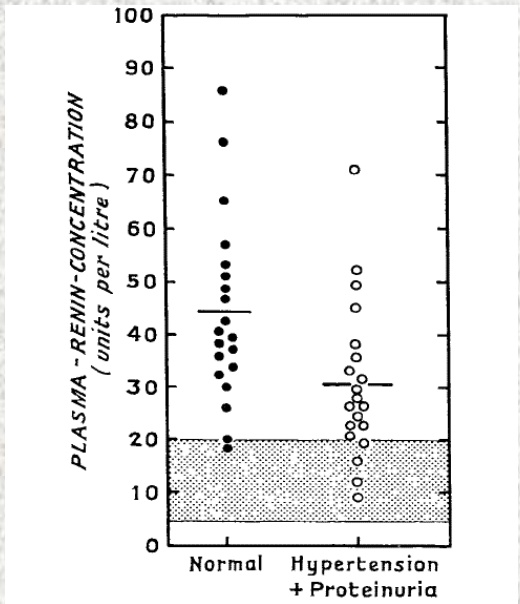
Biomarker Candidate Qualification



- 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



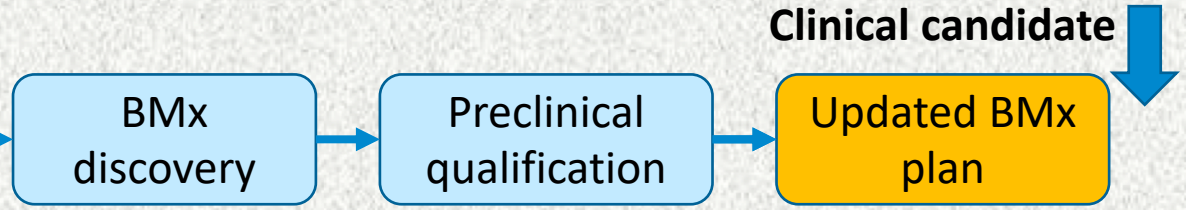
Cut-off identified



No useful cut-off

Zeisler, NEJM 2016; 374: 13-22
Weir. *Lancet*. 1973;1(7798):291-294

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.)

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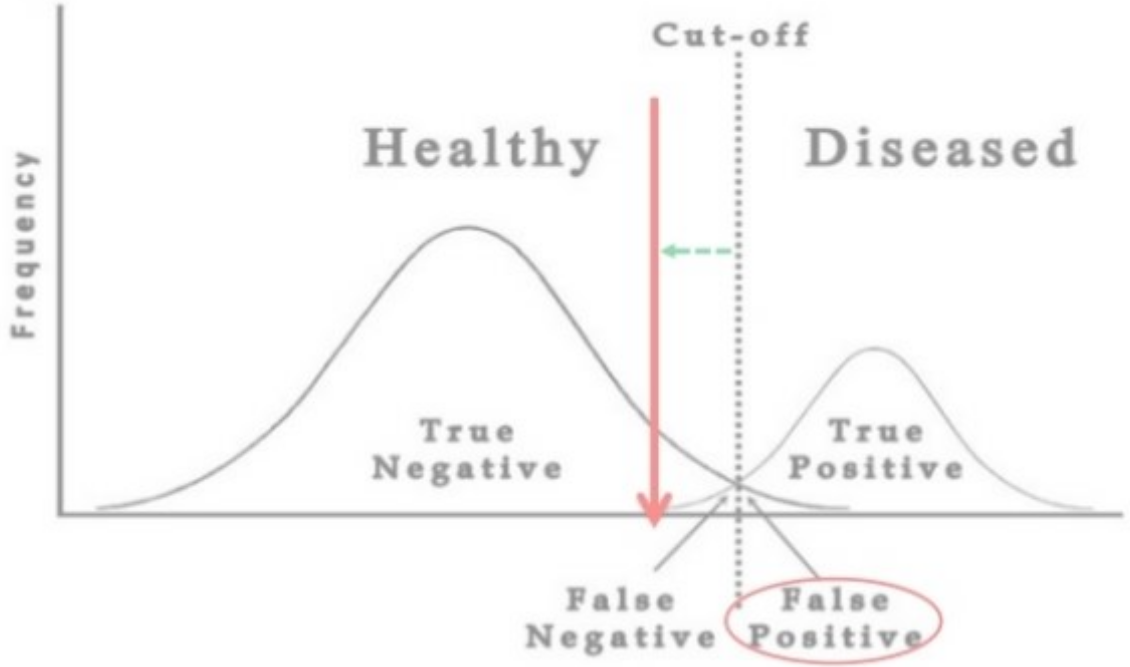
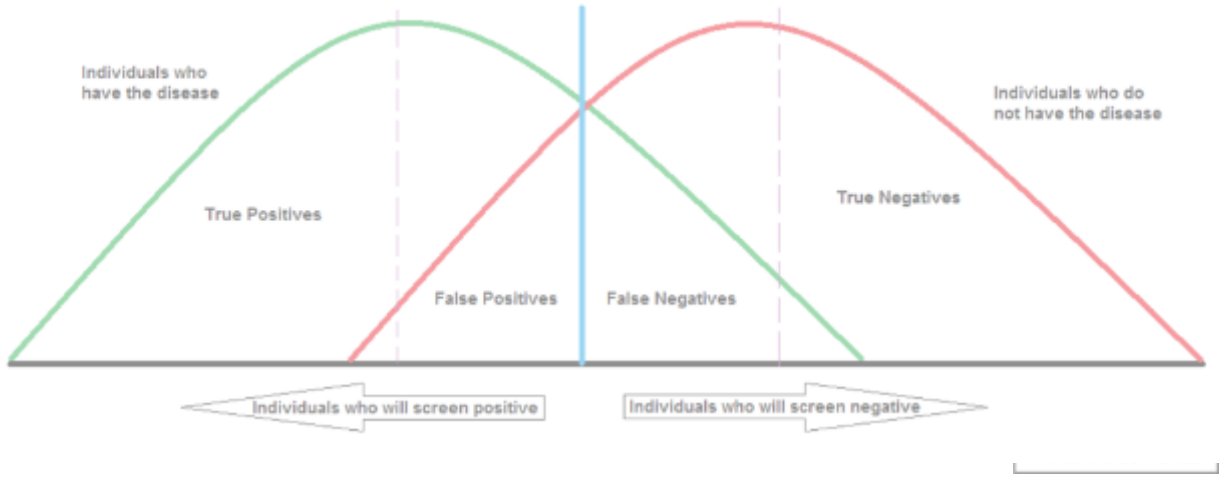
Clinical candidate

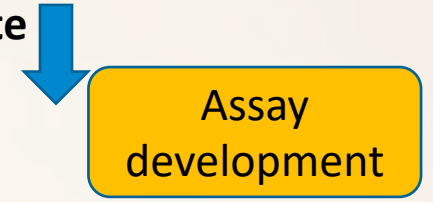
Assay development

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

- The assay should be ***Fit-for-Purpose*** - ie be able to support the intended clinical use
- Available assays may, or may not, be fit for purpose
  - An assay intended to measure an analyte increase may not be suited to measure a decrease in the concentration
  - Different matrices may require different assays for the same analyte
  - A high-quality assay may require development of new analytic reagents
- As the compound progresses in development the accuracy and precision of the assay need to be refined
  - Loose criteria for exploratory markers, strict criteria and full validation for markers intended for regulatory approval

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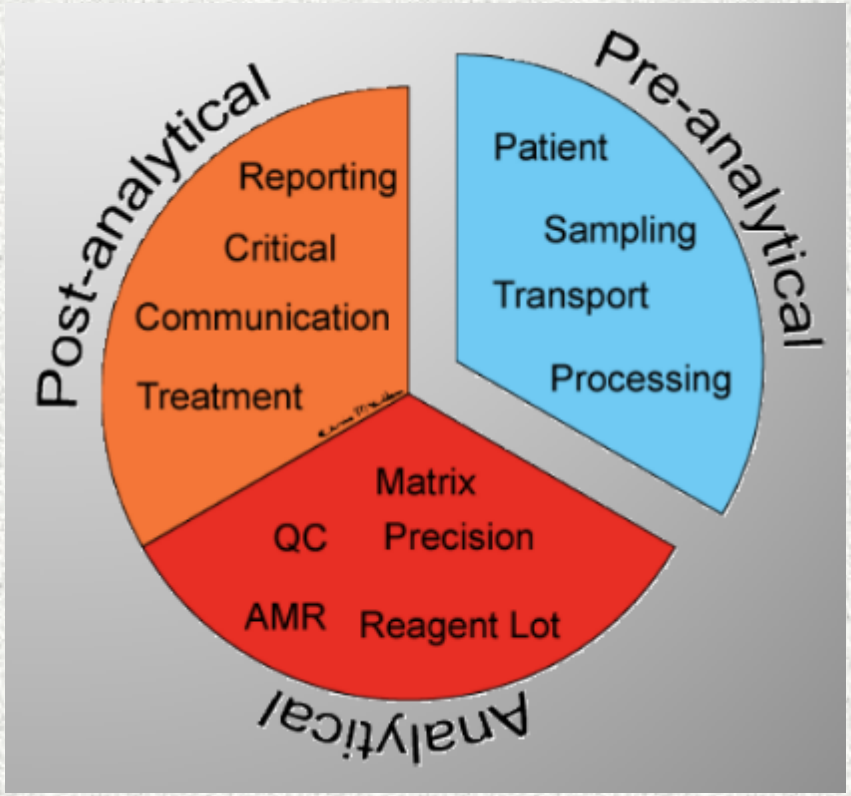
Clinical candidate

Assay development

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



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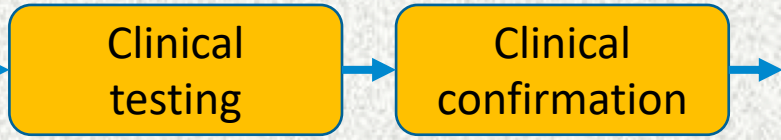
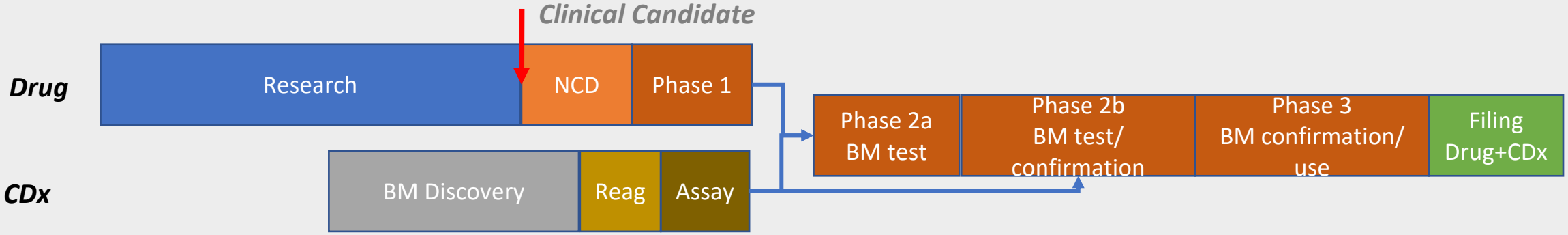
Clinical testing and confirmation

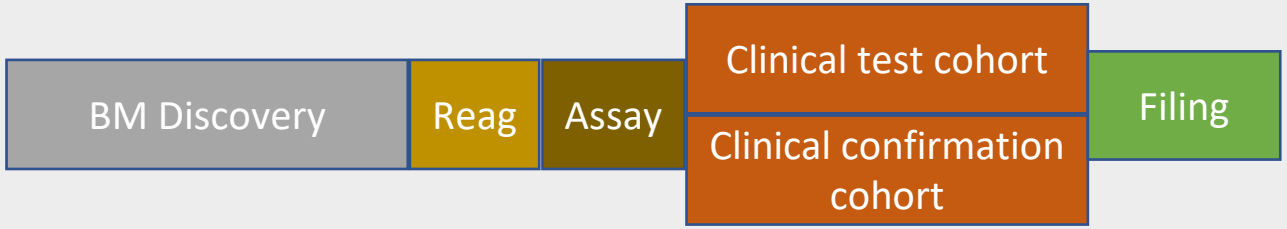


- **Prospective clinical evaluation** with adequately powered test and confirmation cohorts, sequentially or in parallel.
  - Defined endpoints aligned with the COU and required performance criteria
  - Studies will have a separate regulatory track from therapeutics
  - Analysis should be done blinded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

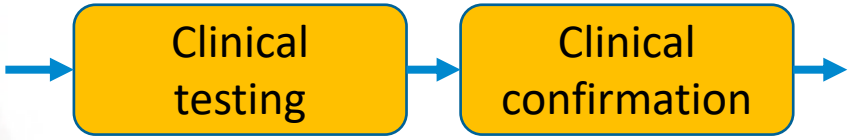
Companion diagnostics (a subset of predictive biomarkers) - *fastest path*



Diagnostic or Prognostic biomarkers – theoretical fastest path



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

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Conclusions and practical considerations

- Context of Use is essential
  - Based on a well defined TPP and clear understanding of the specific intended clinical use
- Start in time
  - 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
- Partner
  - 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

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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

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Thank you!

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