Biomarker Workshop

-Are we informed?
-Have we informed?

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Outline

- Definitions and examples
- Biomarkers in drug development process
- Project needs for biomarkers – Defining CoU and Biomarker Plan
- Conclusions and Practical considerations

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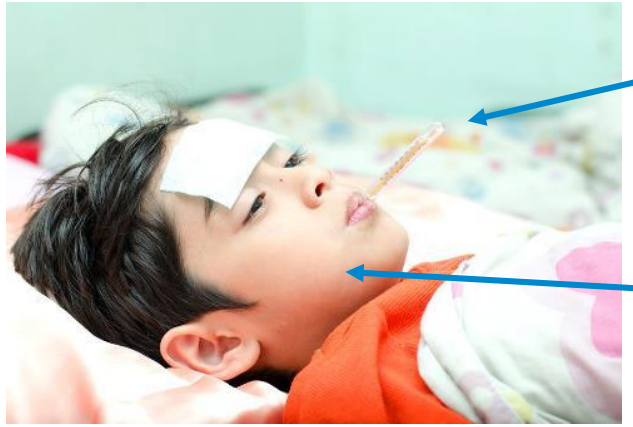
Definition – Biomarker vs Clinical Endpoint

- **Biomarker:** A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Objective indications of medical state observed from outside the patient – which can be measured accurately and reproducibly
- **Clinical Endpoint:** A characteristic or variable that reflects how a patient feels, functions or survives

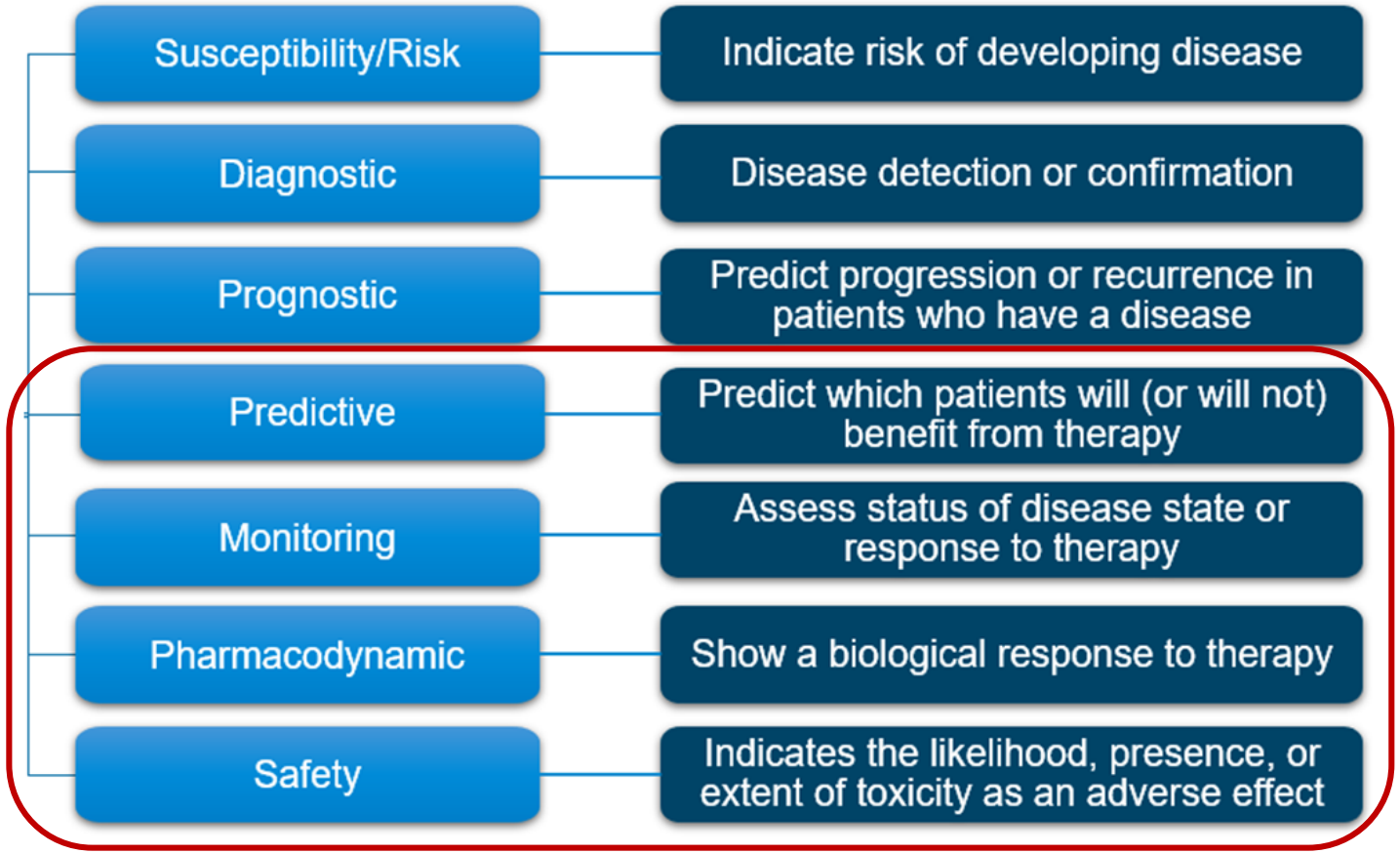


Biomarker
Increased temperature - **objectively** measured

Clinical endpoint
Patient **feeling** ill due to fever

Biomarker Categories - FDA-NIH Joint Leadership Council

Biomarker categories



Therapy dependent

*BEST: **B**iomarkers, **E**ndpoint**S**, and other **T**ools

https://www.ncbi.nlm.nih.gov/books/NBK338448/

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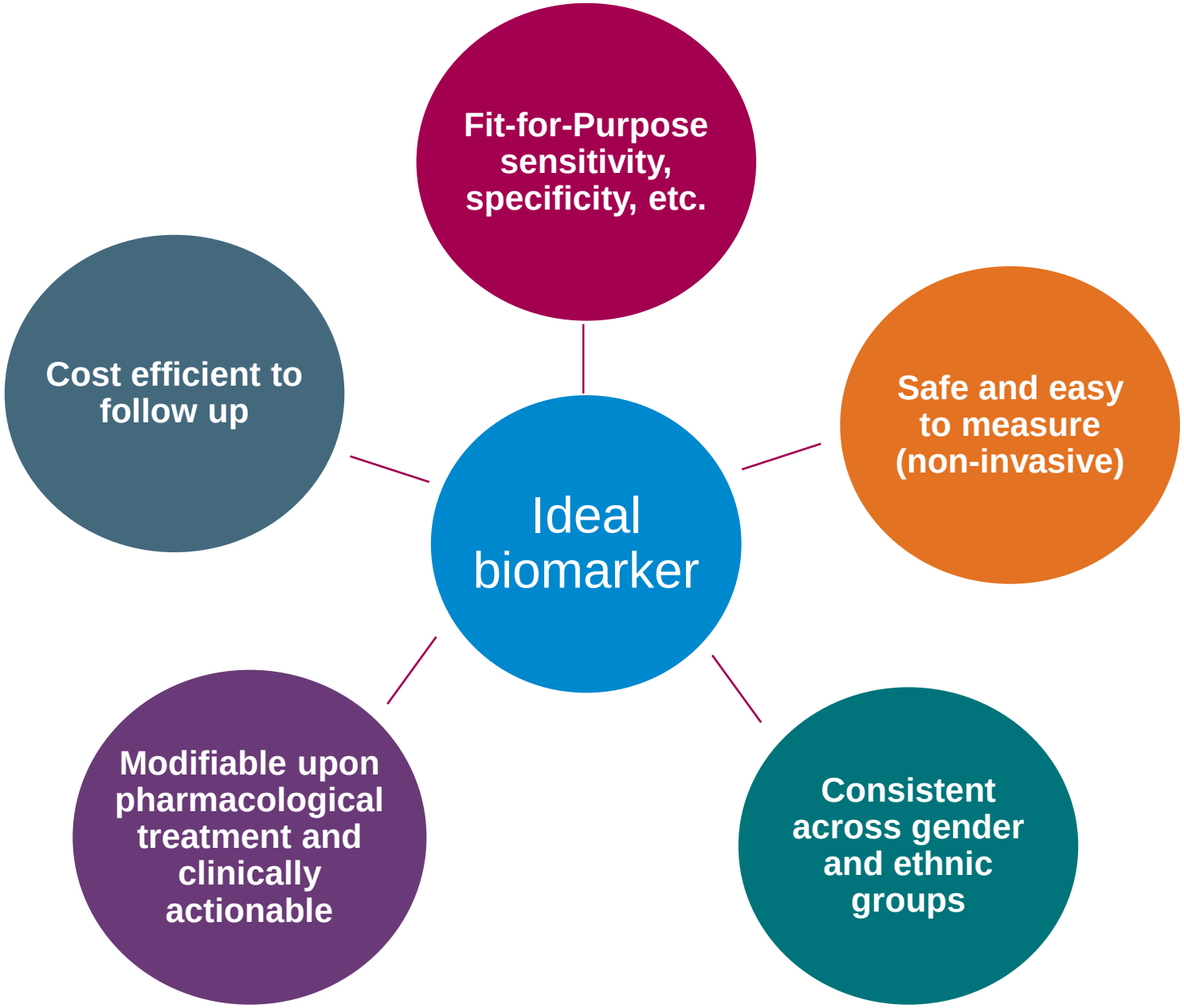
Characteristics of an ideal clinical biomarker



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Why are we interested?

Key questions in Early Clinical Development

- Does the compound reach the target, cause intended pharmacological effects, and show clinically relevant effects in the target population?
- What doses are associated with pharmacological activity?
- How long should exposure be maintained to obtain the desired response?
- Does the compound exhibit a therapeutic window for the proposed indication?
- Which patients are most likely to respond?

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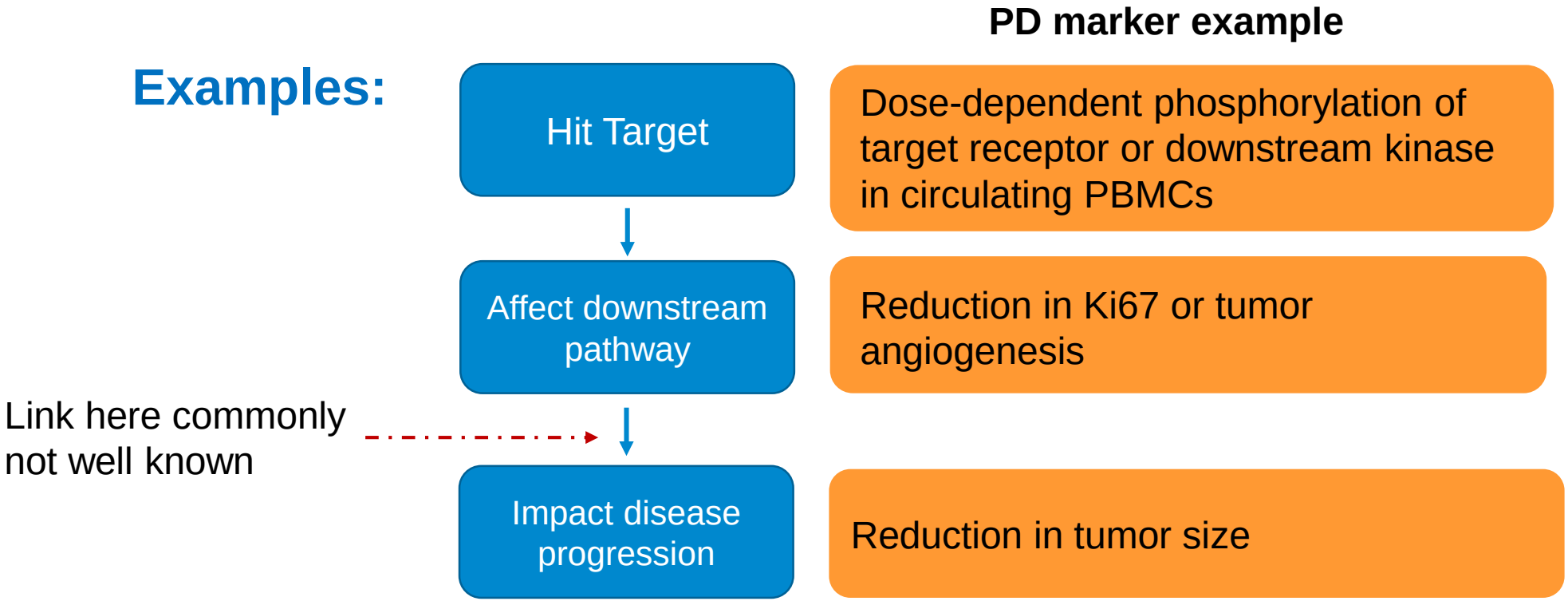
Pharmacodynamic (PD) markers

Used to establish a PK/PD relationship

- Essential for adequate dose selection in early clinical trials
- Gives confidence that negative PoC is not due to under-dosing
- Assay needs to be good enough to establish a concentration-response relationship, and to avoid accidentally triggering stopping rules

Examples:



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What other biomarkers are needed?

Predictive biomarkers

- Most relevant for Pharma (aside from PD markers)
- Used to identify subpopulations of patients most likely to respond, or suffer harm, to a given therapy
- 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**

General markers

- Used when available, if they add value
- Development times and resource requirements limit scope for establishing new markers within pharma companies

Pharmacodynamic

Predictive

Diagnostic

Prognostic

Monitoring

Susceptibility/Risk

Safety

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Justification for developing a predictive biomarker

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 – e.g. cancer treatment
- Ineffective treatment results in irreversible damage – e.g. 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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Biomarker discovery and evaluation

Target identification	Lead identification	Lead optimization	Candidate nomination	PhI, II, III clinical trials	Launch
CoU/TPP • **Biomarker Class** • **Purpose of biomarker**	Biomarker Discovery	Biomarker confirmation Assay development	Biomarker assay validation	Clinical validation	Regulatory Approval
	Candidate BM ID Test hypotesis Proteomic Genomic Metabolomic	Integrated technologies Multi-analyte assays	Prototype clinical assay Test set ⇔ specific detection of analyte ⇔ robust, reproducible assay Clinical assay development		Analytical and clinical validated assay

Number of analytes

Number of samples

Biomarker plan – a living document

- Based on the **Context of Use** and aligned with the ***TPP*** and the desired **label** text

- **Biomarker Discovery Plan** if there is a need for finding new markers
  - Preliminary preclinical validation plan
  - Outline expected clinical validation and quality criteria

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

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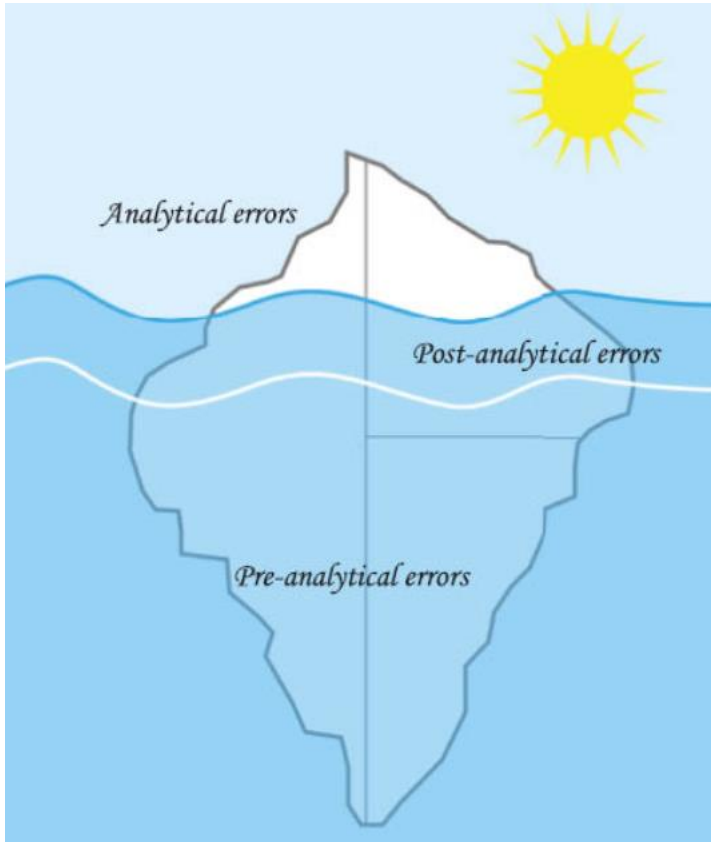
Pre-analytical considerations

~70% of testing errors occur in the pre-analytical phase



- **Right patient**
  - Heterogeneity (ethnicity, environmental factors, medication etc.)
  - Participation bias
- **Right sampling and specimen - well defined and documented**
  - Home sampling or at clinic
  - Tissues, cells, whole blood, plasma, serum, saliva, faeces
  - DNA/RNA, cfDNA, miRNA, images, MRI, recordings of uterine contractions
- **Right transport**
  - Ensure cold-chain is kept
- **Right storage and processing**
  - Temperature (-80°C, N_2)
  - Storage medium (paraffin-embedded, PFA-fixed, RNAlater, collection vials (EDTA, heparin, P-100) ; downstream analysis

=> In case the use of the samples collected is not specified upfront there is a high risk that the sample will not be useful several years down the line

Patient considerations

- **Informed consent**
- **Purpose of sample collection needs to be clearly stated**
- **Typically, only a portion of the individuals who consent to donate specimens actually donate them**
- **Risk of interfering with patient recruitment**
- **Consent limits time samples can be used**
- Mandatory or optional collection
- Individuals of European descent consent to donate DNA specimens for biobanking purposes at higher rates than individuals of minority backgrounds
- Men consent more frequently than women
- Participants in clinical studies appear to donate more readily than healthy individuals
- Donations of saliva, urine etc. are made more easily than donations of whole blood
- Separate consent required for acquiring genomic samples and for RNA
- Individuals can withdraw consent at any time

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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 (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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Take home message

➢ 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 biomarker assay is often lost
- If the rationale is “Explore …”, demand to get the plan for what is going to be done with the data generated

➢ 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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