

Biomarker Assay validation the Gold, Silver, Bronze approach

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Create clarity about intended use of data

There is an increased use of biomarkers in R&D projects

During development of a new biomarker assay, the project decisions based on the data are not always clear

The consequences may be a validation level that is:

- too high: excess use of resources
- too low: use of data of inadequate quality for critical project decisions

How to ensure that stakeholders and Bioanalysis have a common understanding of the **intended use of data** and the impact on the level of assay validation?

Workshop with stakeholders

- Bioanalysis Department
- Medical Directors
- Clinical Pharmacologist
- Scientific coordinator
- Biomarker specialist



LEAN principle
Current state

Biomarker Mapping process

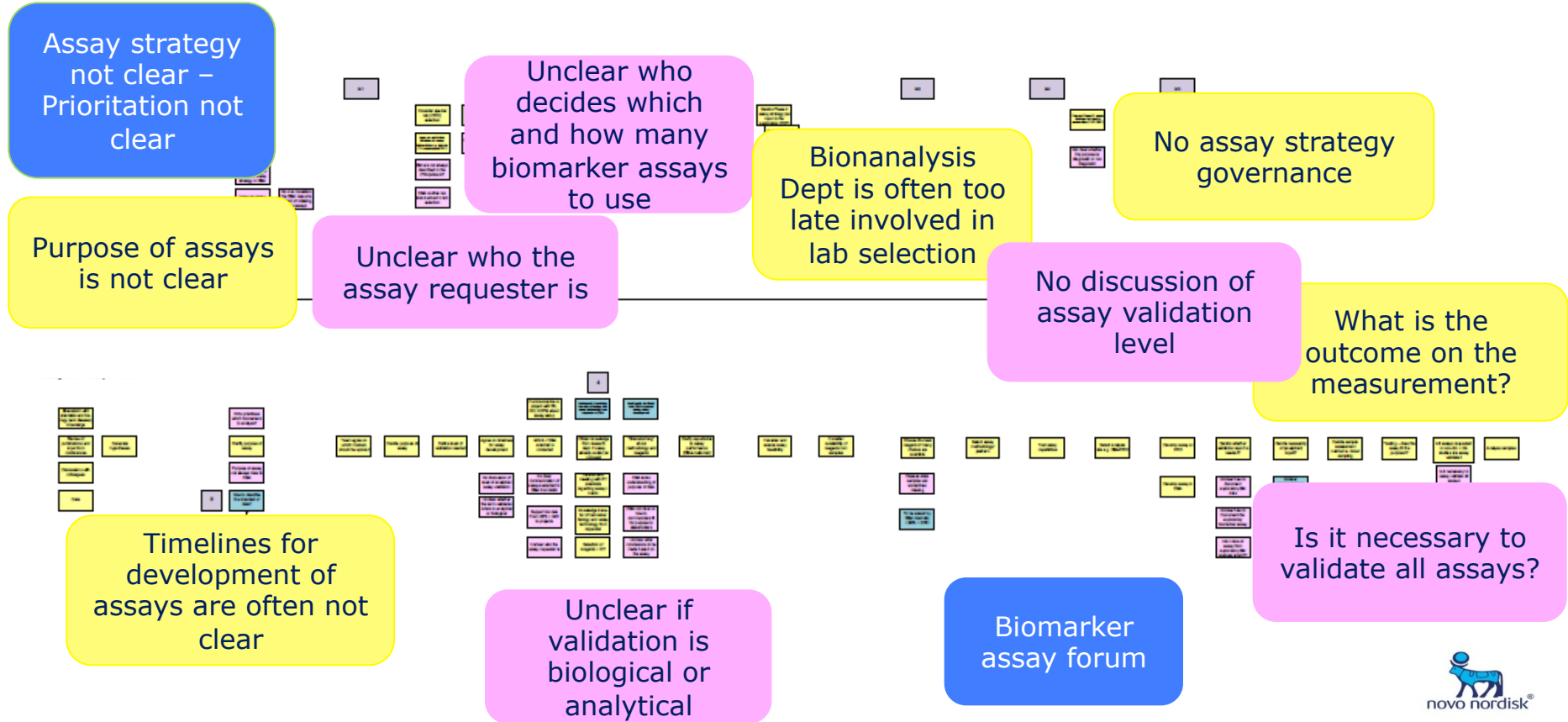
Assay strategy



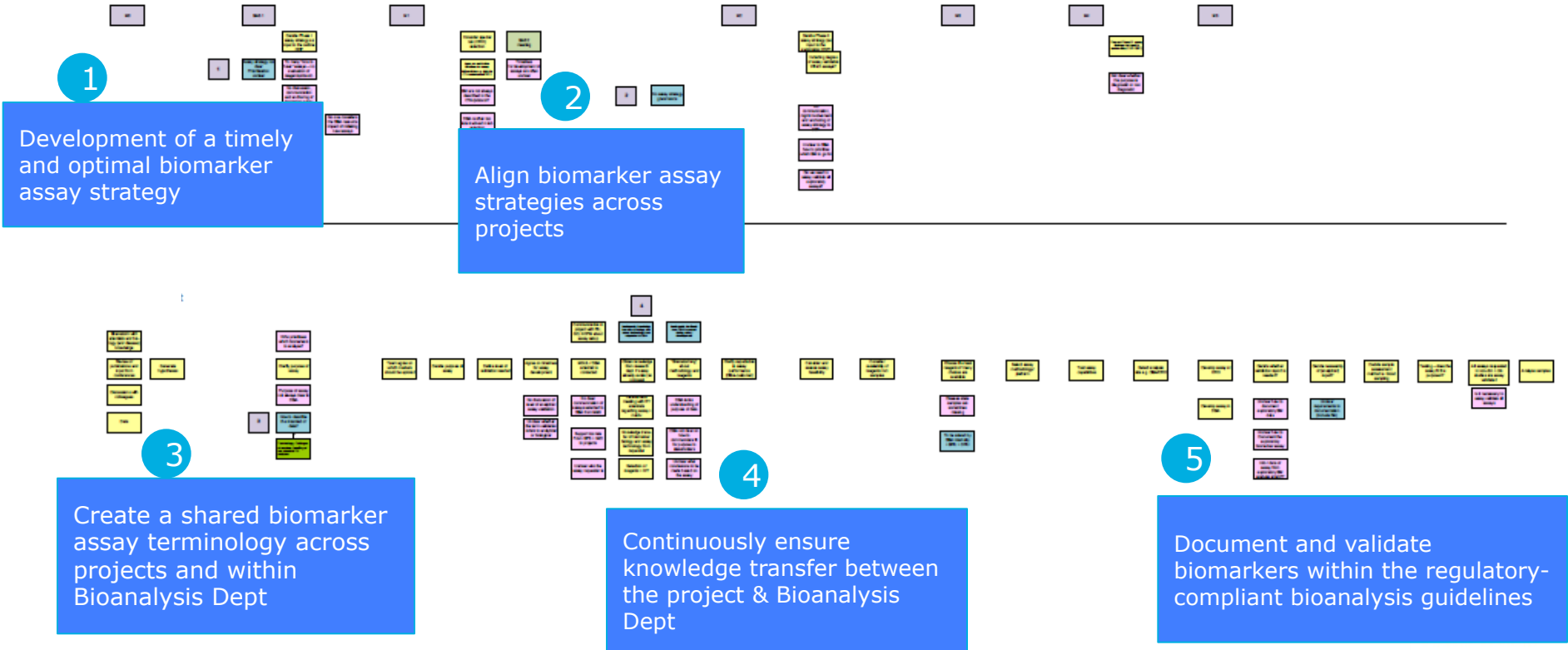
Assay Development



Assay strategy and assay development process



Identified 5 Focus Areas



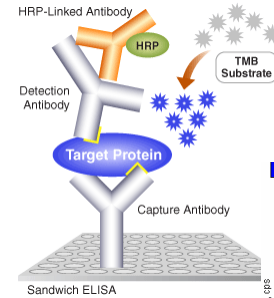
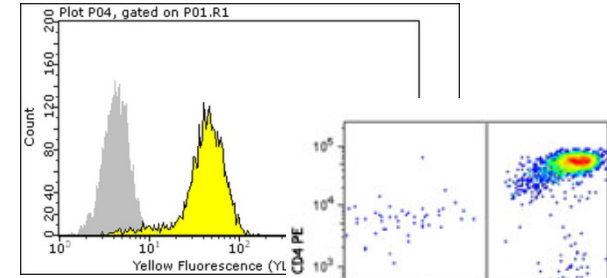
Biomarker Terminology

Biomarkers Definitions Working Group (2001), NIH

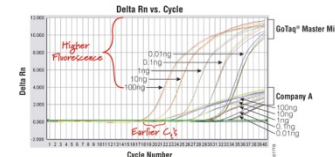
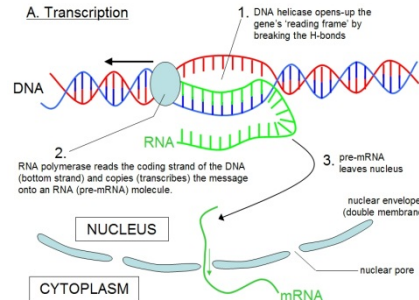
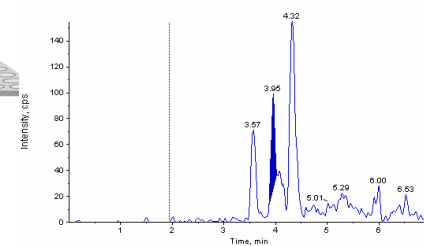
a biomarker is defined as

‘a characteristic that is objective measured and evaluated as an indicator of a biological response to a therapeutic intervention’

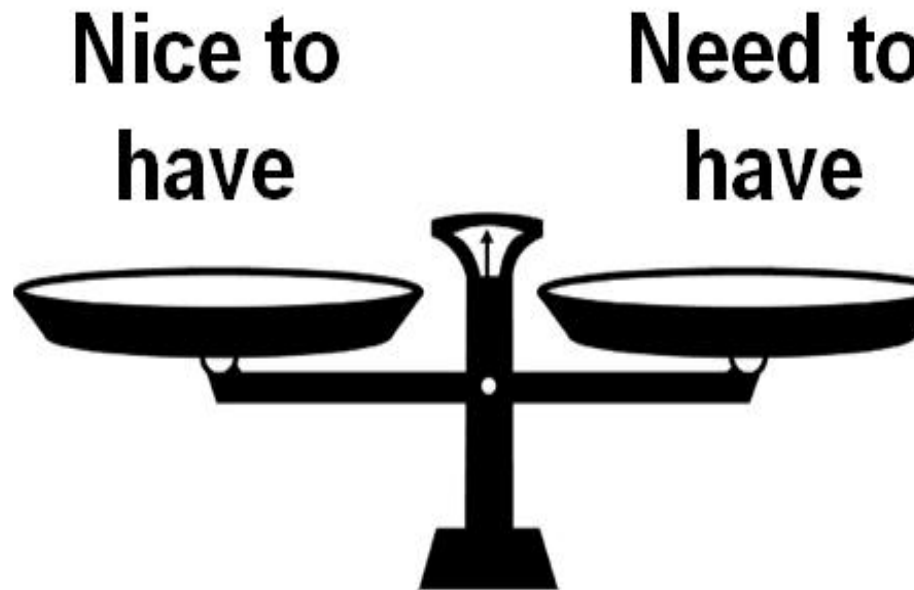
- All assay that are *not* PK-assays (drug assay)
 - Free or total target
 - Receptor occupancy
 - Functional assay
 - Drug in complexes
 - Safety markers
 - Mechanism of action markers
 - Target engagement
 - Disease markers
 - Exploratory markers
 - Pharmacodynamic markers



QC LLOQ - MNC 0113-0217 (QC) 1923.37362.amu - sample 19 of 96 from 209219_16.wiff
Area: 328.43 counts Height: 74.029 cps RT: 3.35 min



Adhere to Regulated Bioanalysis guidelines



Biomarker Assay validation

A need to make definitions for biomarker assay validation:

Fit-for-purpose

= knowledge of pre-defined criteria according to the decision requirement

- Regulatory need → “Gold”
- Key-decision making → “Silver”
- Exploratory → “Bronze”



Biomarker Assay challenge meeting

- The purpose is to create more transparency in the choice of biomarkers and having the relevant assay validation for the intended use of the data.
 - Level of assay validation
 - Resources and timing
 - Prioritisation
- The meeting should be called in for **each time a new clinical trial or Tox study** (which includes biomarkers) is in scope
- Bioanalysis Department coordinates the meeting
- Minutes are send out



Before Biomarker Challenge meeting - Questions

Why are the biomarkers selected?

Which decisions will be made upon the data?
MoA
Disease activity
Safety

Have the biomarker been measured previously?
-in-house or paper
In disease or in healthy?

Are there commercial kits available

Which matrix to collect the sample?

What are the expected levels of the biomarker?

Are there any available standard material?

Has the biomarker a CAP/CLIA certificate?

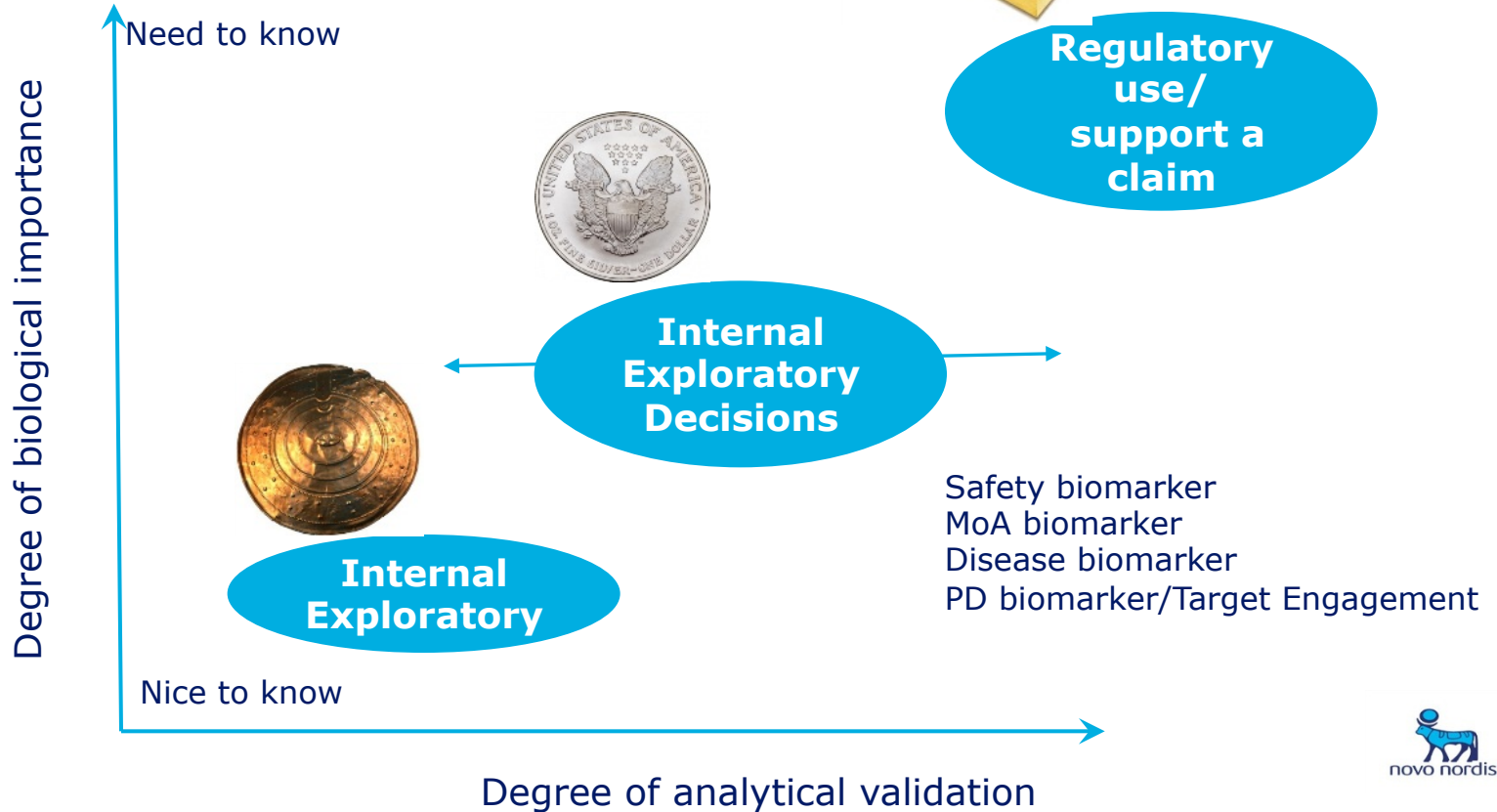
Which Assay platform will the biomarker be measured on?
ELISA, LS-MS/MS
Immunolite

Is there a CRO that has the analysis already

Do we need reports?
Validation report
Analytical report



Biomarker Assay strategy – defined upfront



Fit-for-Purpose Analytical Validation



Gold

- Support a claim
- Full validation



Silver

- Exploratory – intended for internal decisions
- Fit-for-purpose validation



Bronze

- Exploratory use
- No additional validation
/Use kit insert as it is
/If validated at CRO use this validation report

Fit-for-Purpose Analytical Validation



Full Validation

- Assay range
- Precision
- Sensitivity LLOQ
- Selectivity
Disease state
- Parallelism disease state
- Accuracy
- Sample stability
- Specificity
- Dilution linearity

Phase 2b

Fit-for-purpose Validation

- Assay range
- Precision
- Sensitivity LLOQ
- Selectivity
Disease state
- Parallelism disease state
- (stability to be considered)

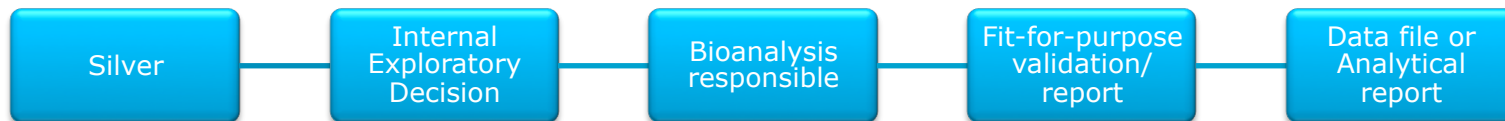
Phase 2a

Exploratory

- Assay range
- Precision

Phase 1

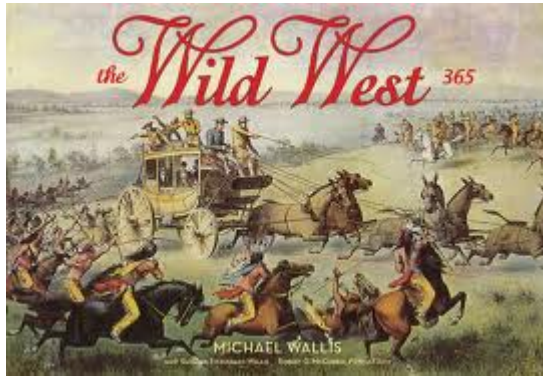
New clinical biomarker decision tree - reporting



Clinical: all data are entered into Database

Biomarker assays

- Previous: Can you measure these biomarkers?



- Granzyme B
- CXCL13
- MICA
- IL-6, IL8, IFN γ , IL-2, IL-1b, TNFa
- Trucount assay
- CRP
- RF
- Flow assay 6 color TBNK
- Flow assay Plasma B Cell panel
- Responsive genes in fractionated CD4, CD8, CD19 cells
- ANA (include IFA titer) SJC
- Total IgG SJC
- IgG isolatypes SJC
- Autoantibodies
 - Anti-dsDNA,, RNA Ab SJC
 - Sjogrens Ab SJC
- Complement factors:
 - C3 & C4, CH50 levels

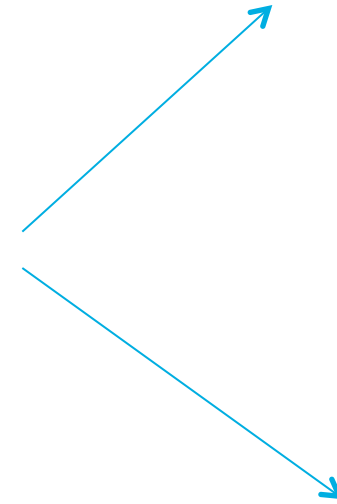
Biomarker assays

- Now: Can you measure these biomarkers?

Strategy



Meeting



Details on Biomarker assay

Biomarker	Insert Biomarker name
Technology	Insert platform (in example ELISA, ECLIA, LS-MC etc)
Matrix	Insert Serum or Plasma (EDTA, Heparin, Citrate)
Assay specificity	ELISA – specific for insert specie Volumen: insert volumen
CRO	Suggestions for CROs: insert 3 laboratory names
Assay range	insert assay range if known
Range in literature	Insert graph or data known from literature Insert reference range from from National academy of Clinical Biochemistry (NACB) if known If no reference range – write it here
Tested at Novo Nordisk	Insert experience/data , cat no, initial on person doing the assay
Intended use of data	Insert what kind of biomarker: Safety FDA requirement, MoA, disease, PD biomarker etc Insert expected outcome of measurement: up/down regulation or steady state
Responsible in Bioanalysis	Insert your initials
Decisions: Validation status	Insert Gold, Silver, Bronze: insert validation parameters Lab: insert lab name Insert Total or Free assay. Or other relevant conclusion
Reporting	Validation report ? Analytical report ?

Biomarker Assay Validation



Bioanalysis Biomarker Assay challenge meeting

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