



DH03: Increasing Trend of Biomarker Analysis in Clinical Trials

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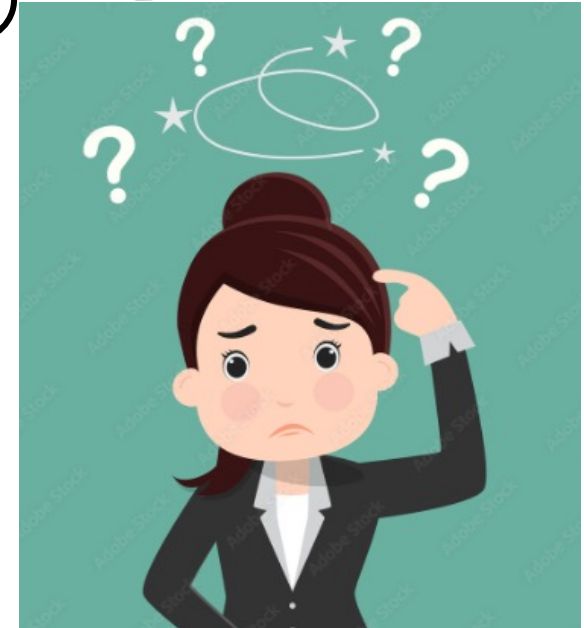
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Hey, we have a new project. Don't worry, I promise you are ABC123, fused, let's do the large biomarker component. This biomarker is exciting and we are in the right moment to take on the right components of a biomarker analysis.



Biomarker analysis, what is that? Oh great! That's a relief! I am that? Is that a new lab test? How is it different from what we do? I am so confused right now!!!?



AGENDA

- Increasing trend of biomarker analysis in clinical trials
- What is a biomarker
- The rationale behind using biomarker in clinical trials
- Different types of Biomarker
- Planning a biomarker analysis
- Examples of statistical considerations for biomarker analysis
- Some of the different outputs generated for the analysis
- Reporting biomarker analysis
- Conclusion



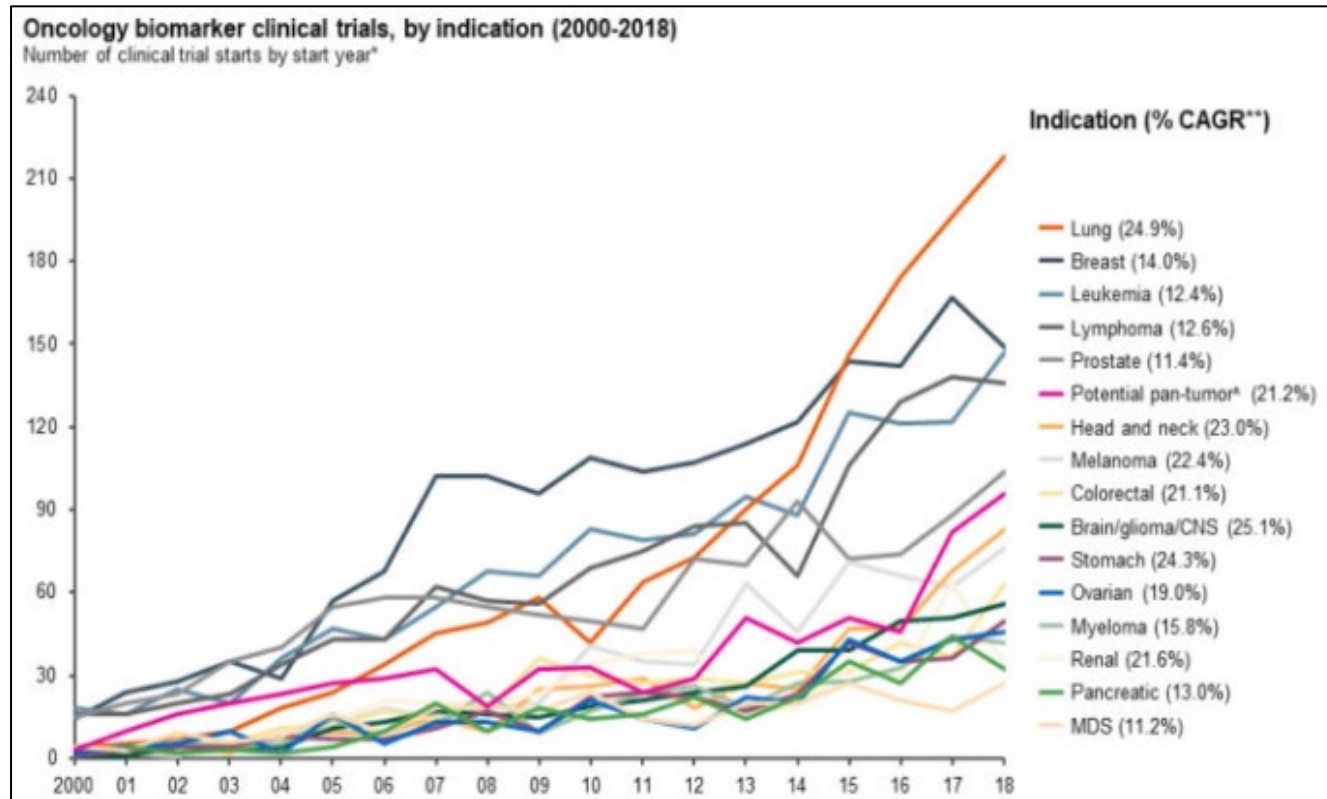


In today's day and age, is there a way to reduce the cost and time on a drug development process

14 years
\$2.7 billion



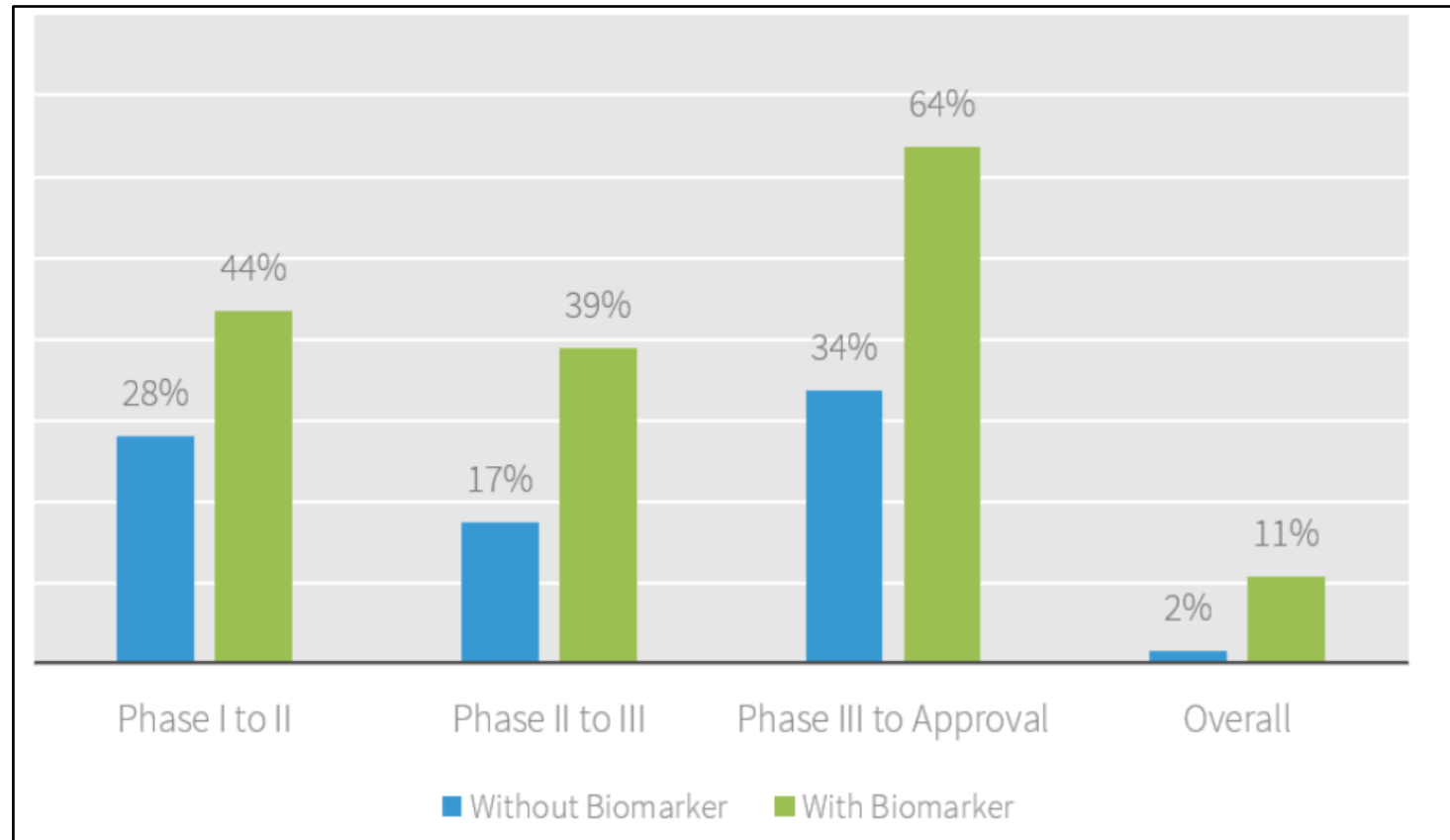
The number of oncology trials with biomarkers grew twice the rate of oncology trials overall from 2000–2018, as measured by compound annual growth rate (CAGR)



*Note: * Trials looking at two or more indications are repeat counted for each indication;
** % indicates CAGR 2000 – 2018*

Source: AACT; L.E.K. biomarker database

PROBABILITY OF CLINICAL TRIAL SUCCESS



Trials that use biomarkers are more likely to proceed to the next stage of development. For example, 10.7% of trials for new cancer drugs that use biomarkers obtain market approval.

Source: Using Protein Biomarkers Increases the Chances of Success in Clinical Trials | Technology Networks

WHAT IS A BIOMARKER?



- Biomarker is a biological molecule found in blood/body fluids/tissues
- Objectively measured to see how well the body responds to a treatment for a disease or condition.
- for example, protein expression level or gene mutation status in tumor tissue or protein levels in plasma or number of circulating tumor cells

RATIONALE FOR USING BIOMARKER FOR CLINICAL DATA

Findings from the biomarker analysis could be used to :

- Understand **clinical pharmacology** of the drug
- Understand the **mechanism of action of the drug**
- **Predictive of drug effect, both efficacy and safety**
- **Prognostic of disease progression**
- **Diagnostic of a Disease**
- **Companion Diagnostic**

CATEGORIES OF BIOMARKERS AND THEIR CLINICAL UTILITY

	Diagnostic		Prognostic	
<i>Predicts:</i>	Presence of a disease		Overall patient survival, independent of therapy	
<i>Time of Measurement:</i>	Before diagnosis	At diagnosis	At diagnosis	After diagnosis
<i>Clinical Utility:</i>	Allows screening of healthy patients	Distinguish benign vs. malignant; classify into subtypes	Estimate risk of disease	Allows monitoring of disease status; detects recurrence

	Predictive		Pharmacodynamic	
<i>Predicts:</i>	Response to treatment (efficacy and/or toxicity)		Drug interaction with its target	
<i>Time of Measurement:</i>	Before treatment selection		During or post-treatment	
<i>Clinical Utility:</i>	Identify treatments likely to be effective; guides initial treatment decision making.		Determines degree of drug response; guides treatment decision making in real-time.	

Source: Integrating Molecular Biomarker Inputs Into Development and Use of Clinical Cancer Therapeutics - PMC (nih.gov)

HOW TO SELECT WHICH BIOMARKERS TO MEASURE

candidate-based approach

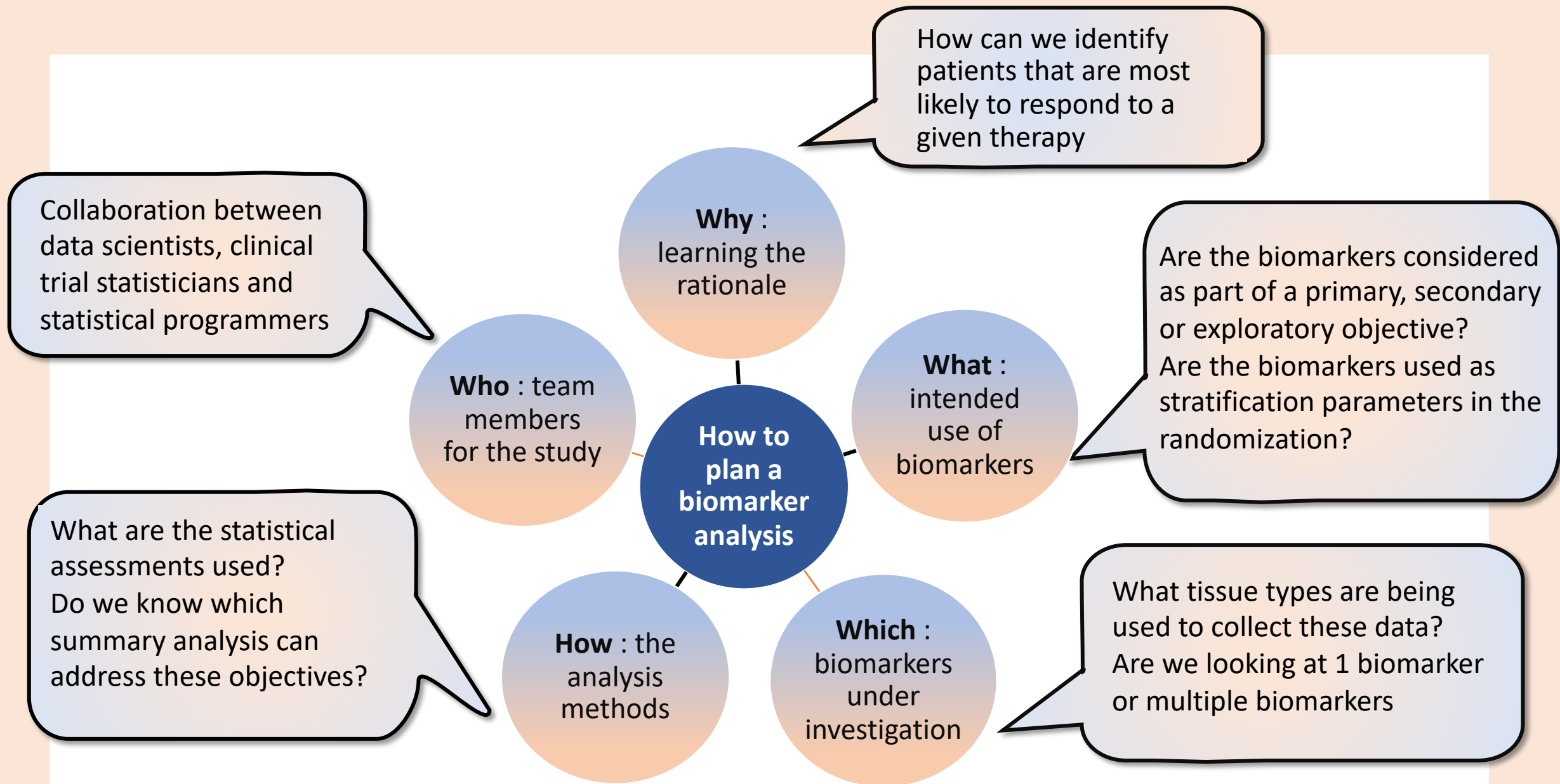
when something is already known about the marker, such as specific genes or proteins comprising the drug target signaling pathway.

A broad-based approach

does not rely on a biological hypothesis and is generally used in discovery. It allows to analyze different markers at once.

TYPES OF BIOMARKERS AT EACH MOLECULAR LEVEL AND ASSOCIATED TECHNOLOGY

	PROTEIN	RNA	DNA			CELLULAR
TECHNOLOGY	Protein Expression	Gene Expression	Gene Sequencing	Gene Copy Number	Chromosome Changes	
IHC	X					
RT-PCR		X				
RNA Sequencing		X				
Next Generation Sequencing			X	X	X	
Circulating Tumor Cells						X



STATISTICAL CONSIDERATIONS FOR BIOMARKER ANALYSIS

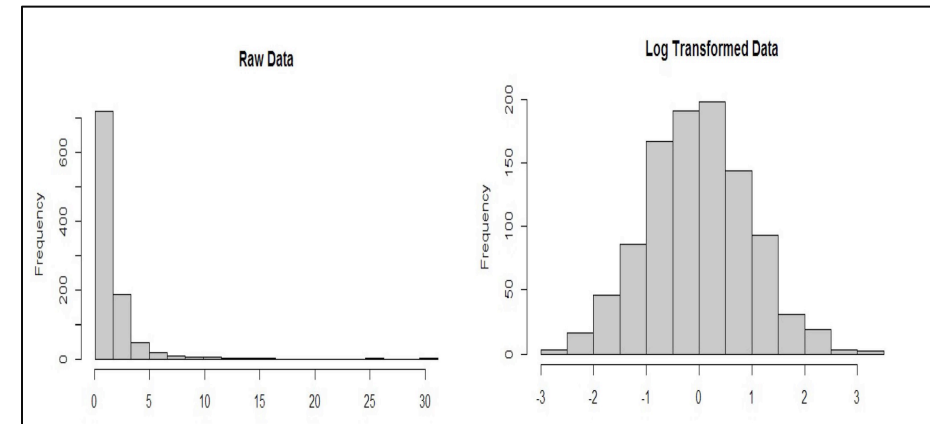
At Planning analysis :

- Pharmacodynamic assessments, predictive modeling
- Combining data across studies: meta-analysis approach
- multivariate model using multiple biomarkers

STATISTICAL CONSIDERATIONS FOR BIOMARKER ANALYSIS

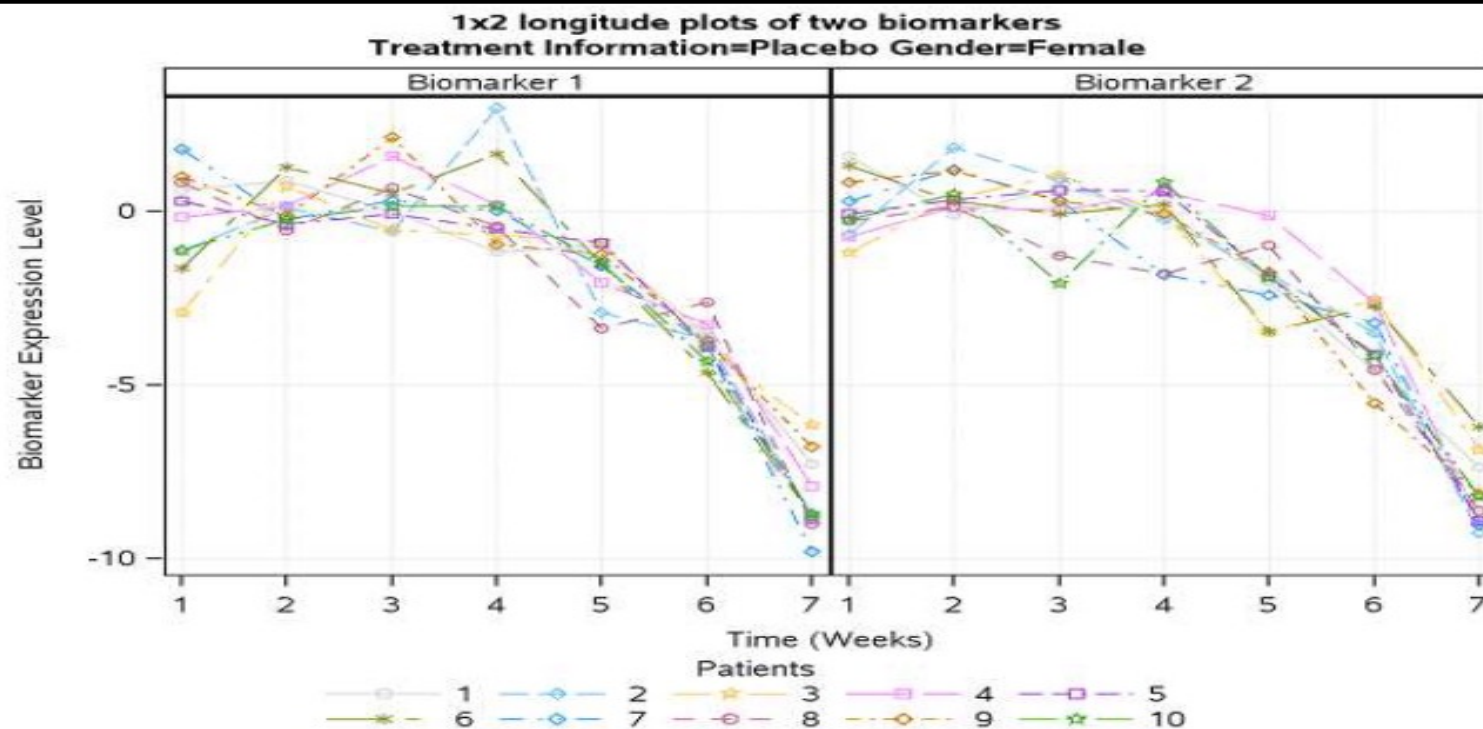
At Programming stage :

- Handling data with values below the lower limit of quantification
- Unscheduled/missing measurements
- Summarized measures : Quantitative vs Qualitative replicates
- Visualizing the log transformed data



OUTPUTS FOR VISUALIZING BIOMARKER DATA

Example of Longitudinal plots to display patient profiles across two lattice variables (biomarker type, gender)



REPORTING BIOMARKER DATA

- Biomarker data can be submitted as part of the CSR:
 - **Primary objective** : when biomarker is the primary endpoint or is used as a stratification parameter in the randomization.
 - **Secondary Objective** : strong prior evidence about the use of the biomarker under investigation from either pre-clinical models or patient samples.
- An additional exploratory biomarker analysis can be submitted in the form of an abstract/report or HAQ's : The results are of interest and either complement the CSR or influence the clinical program as a whole
- Exploratory analysis for additional related studies or research

KEY TAKEAWAY

“Ultimately, biomarker-driven therapy approaches will lead to

- better patient outcomes by enabling early detection;
- identifying treatment responders;
- monitoring treatment, response, and targeted therapeutic effect.

Further, we anticipate these methods will expand to other therapeutic areas. For the immediate future, all signs point to cancer care will be profoundly influenced by biomarkers to guide researchers and physicians at every stage, from drug development to disease management.”

*Source : The Evolution of Biomarker Use in Clinical Trials for Cancer Treatments,
The Journal of Precision Medicine*

Know your
biomarkers.
Know your
options.



Biomarkers are the
signposts on the path
to personalized medicine.

HTG

THANKYOU



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