Biomarkers European Special Interest Group

Webinar
January 19th, 2023

Deepak Parashar, Nicole Krämer & Guillaume Desachy

"We are a community dedicated to leading and promoting the use of statistics within the healthcare industry for the benefit of patients."

Biomarkers Special Interest Group

“We are a community dedicated to leading and promoting the use of statistics within the healthcare industry for the benefit of patients.”

Goals:
Methods, interactions & connections

🎯 3 goals:

1. Establish advanced analytical methods to analyse biomarkers for clinical development

2. Increase interaction with other disciplines (medicine, biology, academic research)

3. Connect with other Special Interest Groups

A diverse group coming from industry & academia

👥 30+ members

😁 Strong interest in biomarkers, with a focus on clinical development

👫 Co-Leads:
Guillaume Desachy (AstraZeneca)
Nicole Krämer (Boehringer Ingelheim)

"We are a community dedicated to leading and promoting the use of statistics within the healthcare industry for the benefit of patients."

A kick-off meeting in April 2022 & 3 priority topics identified!

Kick-off meeting in April 2022 - since then, monthly meetings

Priority topics so far:

- Biomarker-based designs
- Machine Learning for Biomarkers
- Identification of publicly available biomarker datasets

A busy 1st year:
1 podcast & 1 PSI poster 😍

📻 The Effective Statistician podcast with Alexander Schacht

https://bit.ly/3rqtA4I

📰 Poster presentation at the 2022 PSI conference

Biomarkers: a whistle-stop tour

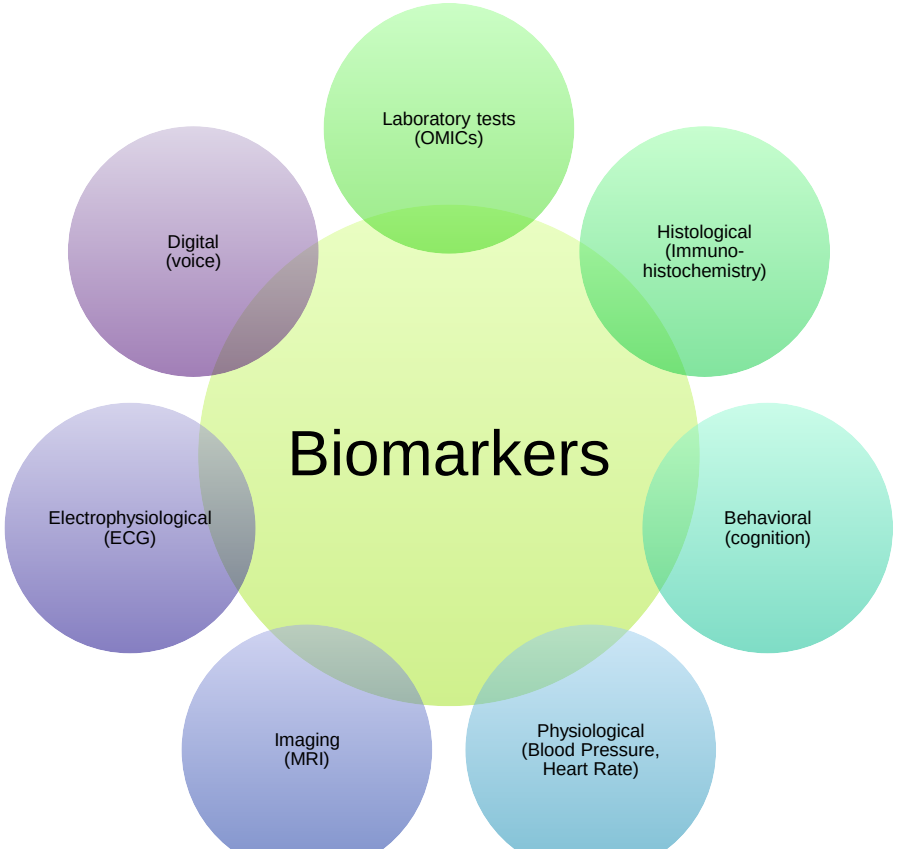
“We are a community dedicated to leading and promoting the use of statistics within the healthcare industry for the benefit of patients.”

Biomarkers: an umbrella definition

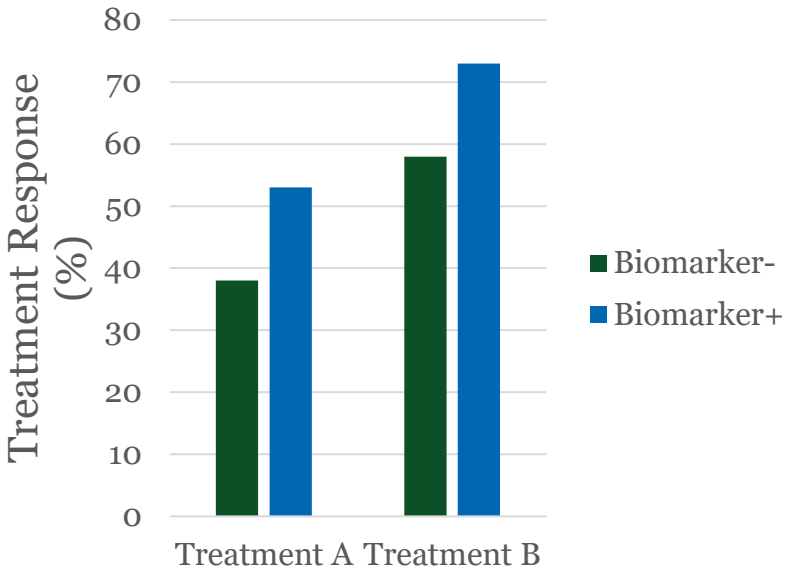
"*A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions.*"

BEST (Biomarkers, EndpointS, and other Tools), FDA – NIH, 2016

Biomarkers: very diverse kinds of data

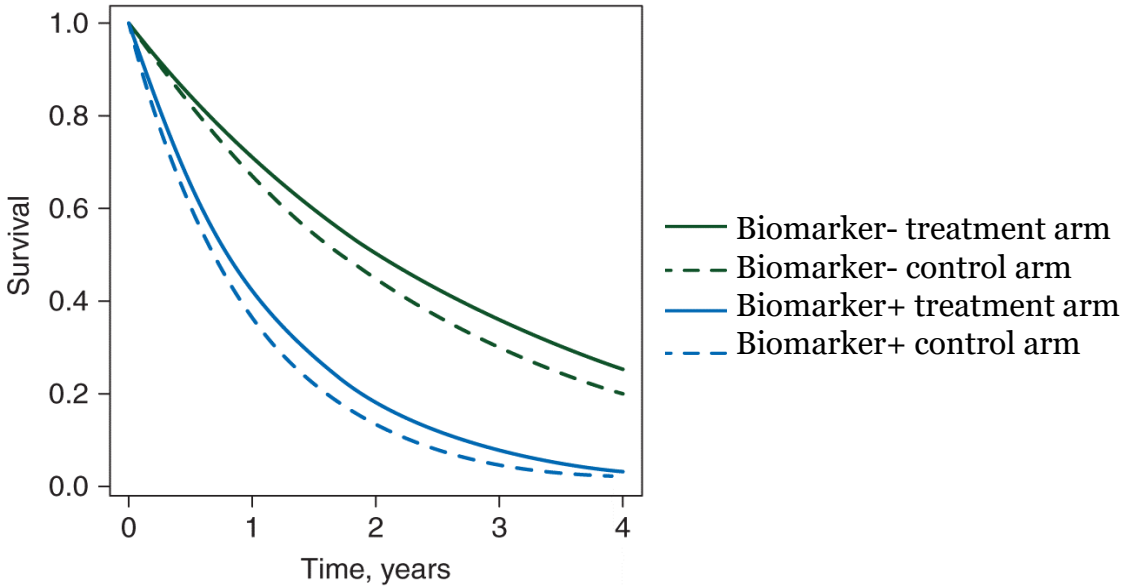


A biomarker can be prognostic



Definition: Biomarker determining the course of a disease, regardless of treatments being taken

A biomarker can be prognostic

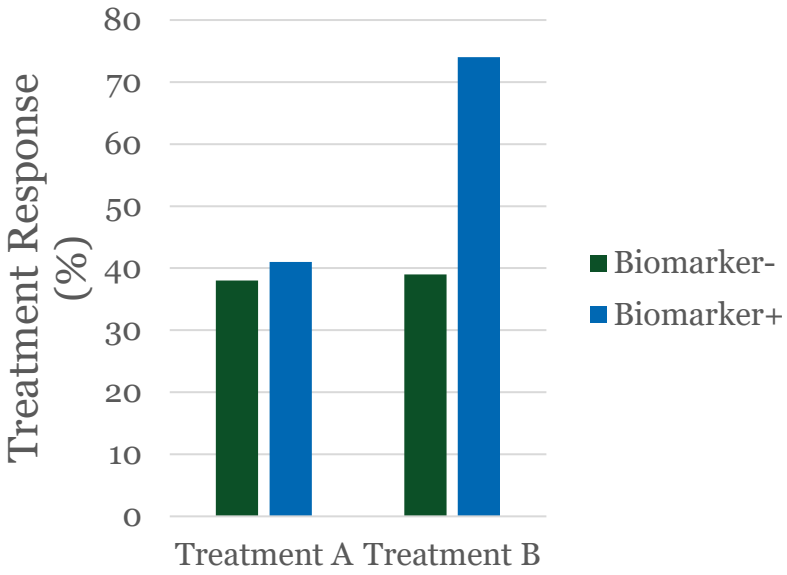


Definition: Biomarker determining the course of a disease, regardless of treatments being taken

Example (Breast Cancer): Lower survival of *hormone-receptor*+ (HR+) patients vs. HR-

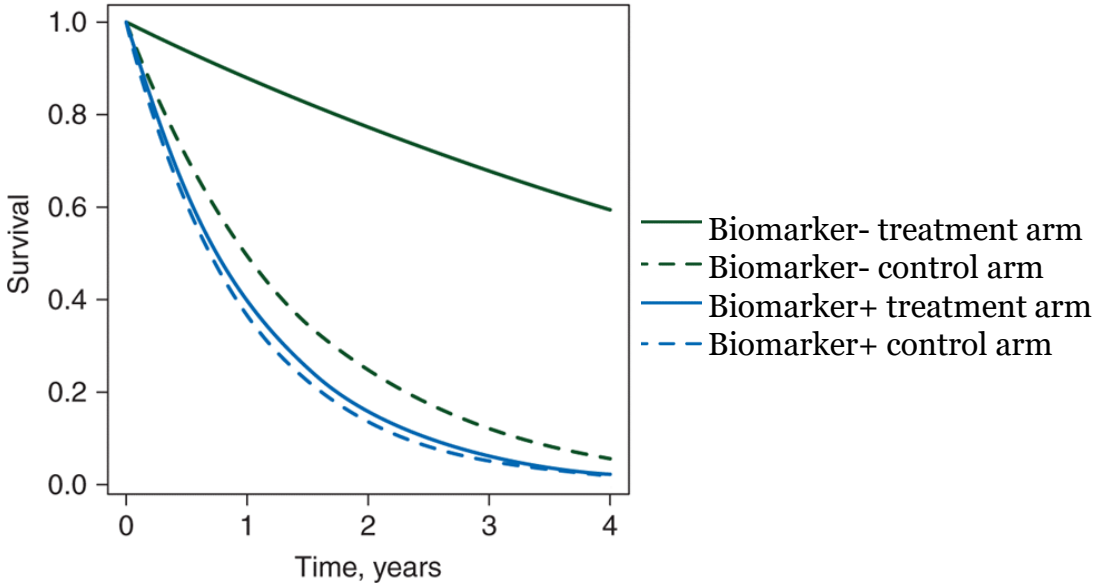
Interest in the pharmaceutical industry? Selecting patients at risk

A biomarker can be predictive



Definition: Biomarker predicting the patient response to a treatment

A biomarker can be predictive

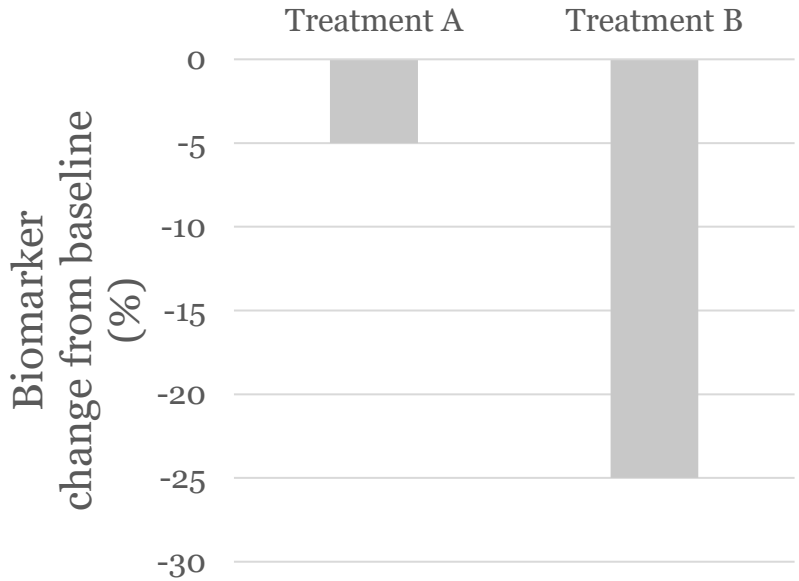


Definition: Biomarker predictive the patient response to a treatment

Example (Breast Cancer): endocrine therapies benefit only HR+ patients

Interest in the pharmaceutical industry? Find the right population of patients for a treatment

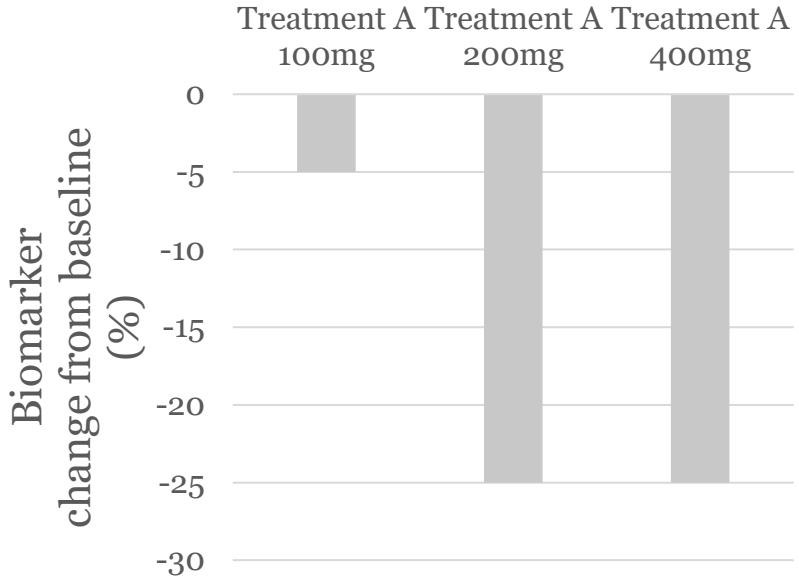
A biomarker can be pharmacodynamic



Definition: Biomarker impacted by a treatment

Example: CRP marker (marker of inflammation) can help in the dose choice

A biomarker can be pharmacodynamic



Definition: Biomarker impacted by a treatment

Example: CRP marker (marker of inflammation) can help in the dose choice

Interest in the pharmaceutical industry?

Better understand the mode of action of a compound & support the dose choice

So, what is a biomarker already?

A biomarker can be many things and can play many roles.

WARWICK

GLOBAL RESEARCH PRIORITIES
HEALTH

Enrichment designs with predictive biomarkers

Deepak Parashar

Division of Health Sciences, University of Warwick
The Alan Turing Institute for Data Science and AI

"We are a community dedicated to leading and promoting the use of statistics within the healthcare industry for the benefit of patients."

Aim: Enhance trial efficiency by selecting patient subgroups defined by biomarker signatures

Prognostic Enrichment

- Reliably include high-risk and exclude low-risk groups
- Increased absolute effect size (smaller trial)
- Relative effect size similar across groups

Predictive Enrichment

- Reliably include biomarker-positive (responders) and exclude biomarker-negative (non-responders) groups
- Increased absolute effect size (smaller trial)
- Lower relative effect size in patients without enrichment factor

Study vs. Analysis

What patients to study?	What patients to analyse?
Designs including only patients with enrichment factor (Situations where biomarker-negative info not needed or not feasible)	Biomarker-positive
Designs including patients with and without enrichment factor (Situations where there is greater uncertainty in marker cut-off)	Biomarker-positive (?)

FDA: To what extent should biomarker-negative patients be included in the study?

Prognostic Enrichment

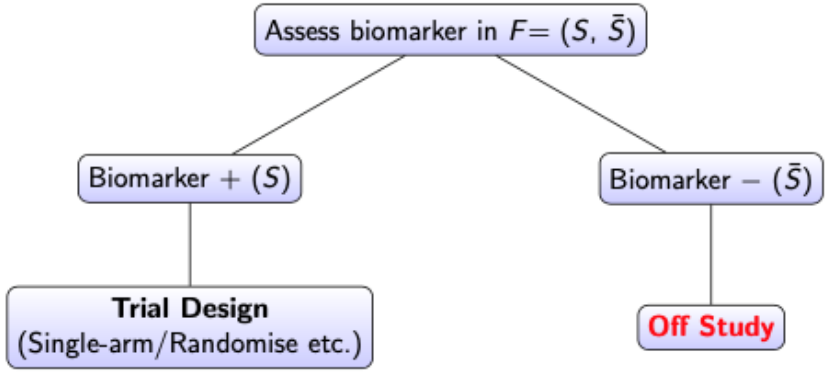
Assumption: Some treatment effect thought to be present in low-risk group

- Impractical due to large sample size.
- Deemed to be less of an issue!

FDA: To what extent should biomarker-negative patients be included in the study?

Prognostic Enrichment	Predictive Enrichment
Assumption: Some treatment effect thought to be present in low-risk group • Impractical due to large sample size. • Deemed to be less of an issue!	Assumption: Some treatment effect thought to be present in biomarker-negative group • Often uncertainty in dichotomising patients into responders and non-responders. • Some info on biomarker-negative population to assess performance is desirable! Focus for this talk!

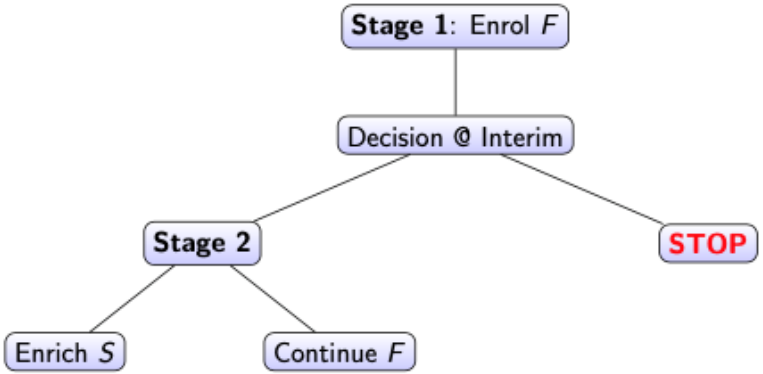
Fixed Enrichment Designs



Goal: Hypothesis test in biomarker $+$ subgroup S only.
Issue: No comparator test in the complementary subgroup $\bar{S}$.

Is the biomarker predictive?

Adaptive Enrichment Designs



Goal: Hypotheses test in S and F.
Issue: While $\bar{S}$ is included in F, no explicit testing in $\bar{S}$.

Is the biomarker predictive?

Biomarker-negatives: To test or not to test?

FDA concerns

- Design may not be efficient if drug has at least some activity in biomarker-negative patients
- Effect in biomarker-negative patients may never be known
- Study would provide no new clinical evidence w.r.t. biomarker negative patients
- Implications for Phase III

Need for testing in biomarker-positive and biomarker-negative subgroups

Example 1:
Simon two-stage enrichment design for binary endpoints

Phase II targeted cancer therapy

- Determine whether drug has activity only in target population or the general population
- Outcome is (RECIST) tumour response
- Single-arm trial
- Enrichment adaptation (with testing in biomarker-negative) based on Simon two-stage design

Parashar et. al., Pharmaceut. Statistics 2016

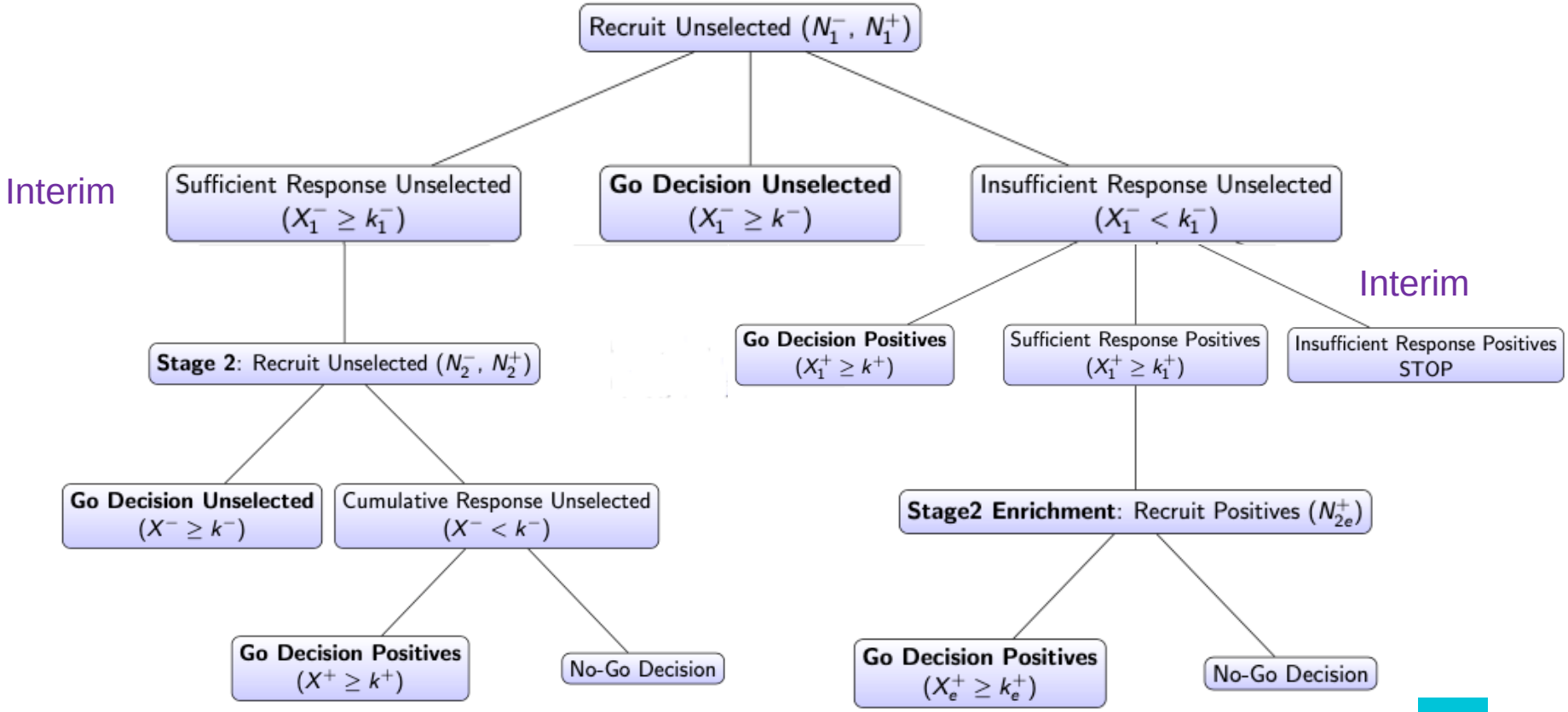
Hypotheses (group-sequential)

$$H_0^- : p^- = p_0^-, \qquad H_0^+ : p^+ = p_0^+$$
$$H_1^- : p^- = p_1^-, \qquad H_1^+ : p^+ = p_1^+$$

Assume $p^- < p^+$

- Conclude efficacy in full population if we reject H_0^-
- Conclude efficacy in biomarker positive if we reject H_0^+

Design Schematic



Treatment effect?

Need randomised clinical trial testing in targeted and non-targeted subpopulations

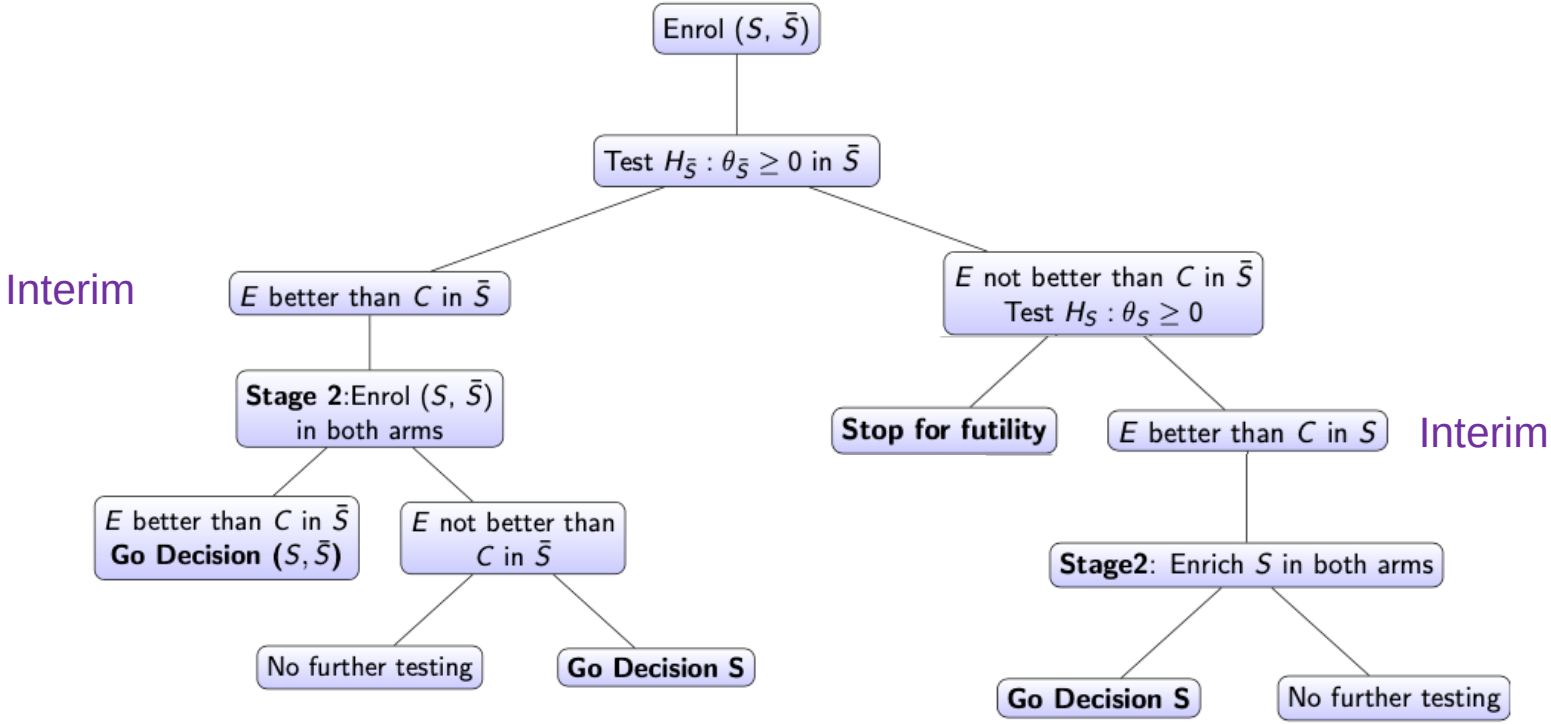
Notation

h_E	hazard using the experimental drug
h_C	hazard using the control drug
θ_S	$\log\left(h_E^S / h_C^S\right)$
$\theta_{\bar{S}}$	$\log\left(h_E^{\bar{S}} / h_C^{\bar{S}}\right)$
HR_S	hazard ratio of S
$HR_{\bar{S}}$	hazard ratio of $\bar{S}$

$$HR_S \ll HR_{\bar{S}}$$

$\boldsymbol{\theta < 0} \Rightarrow$ experimental treatment more efficient than control
$\boldsymbol{\theta \geq 0} \Rightarrow$ no improvement with experimental treatment

Example 2: Randomised Enrichment Design for Time-To-Event Endpoints



Further regulatory issues on biomarker-negative patients for predictive enrichment

- Even if treatment is a significant advance for biomarker-positive patients, questions still asked on potential effectiveness in biomarker-negative group.
- Physician's choice for critical biomarker-negative patients; important to reliably assess treatment effect in biomarker-negative group
- Our design addresses both issues
- Advanced methods (statistical, machine learning, etc.) to improve precision for biomarker-cutoff.
- Clinical relevance
- Empirical enrichment

Who said Machine Learning for Biomarkers?

Nicole Krämer[1],
in collaboration with Ali Farnoud[1] & Holly Tovey[2]

[1]Boehringer Ingelheim GmbH & Co KG
[2]The Institute of Cancer Research

Machine Learning -The ~~usual suspects~~ backbone

What?

- (Causal) Random Forests
- Boosting
- Penalized regression methods
- Neural networks
- …

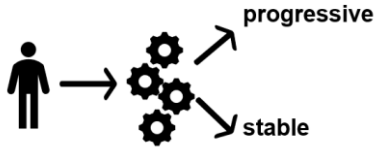
What for?

- Prognostic effects
- Predictive effects
- Pharmacodynamic effects
- Biomarker selection
- …

Is this it? Let us look at three more examples.

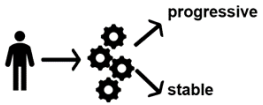
Example 1:
Explainable Machine Learning

- Case study: Identification of patterns distinguishing between progressive and stable Mild Cognitive Impairment in early Alzheimer's disease (Bloch et al, 2022)
- Multimodal data
  - Imaging biomarkers (MRI – magnetic resonance imaging)
  - Socio-demographic features
  - Genetic risk factor (APoEε4)
  - Cognitive test results



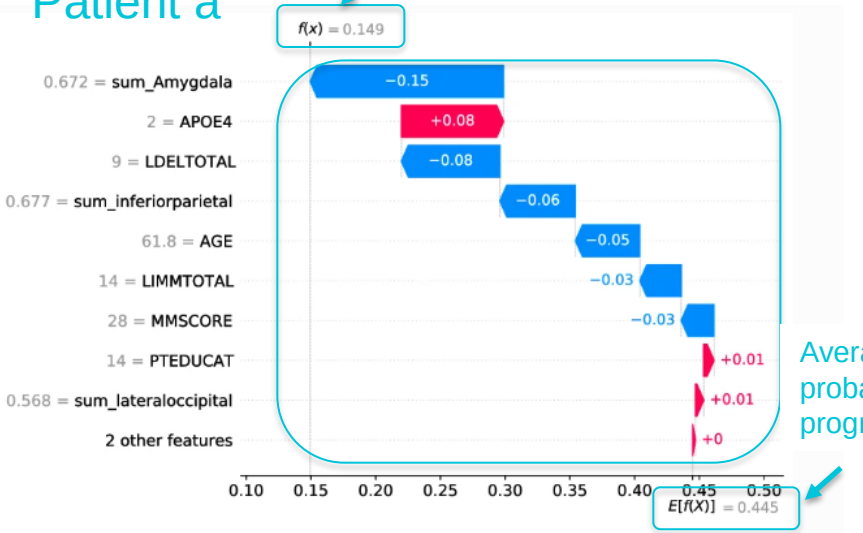
- The black box: **= feature selection + random forest**

Explaining individual predictions



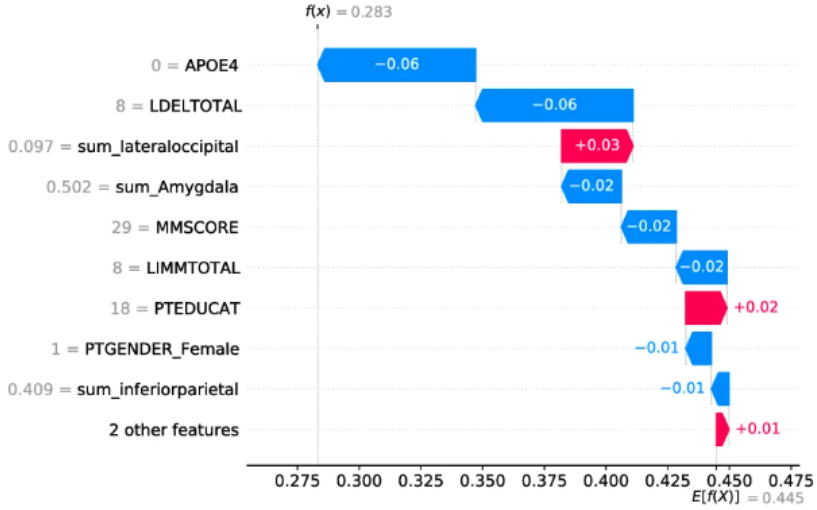
Estimated probability to progress

Patient a



Average estimated probability to progress

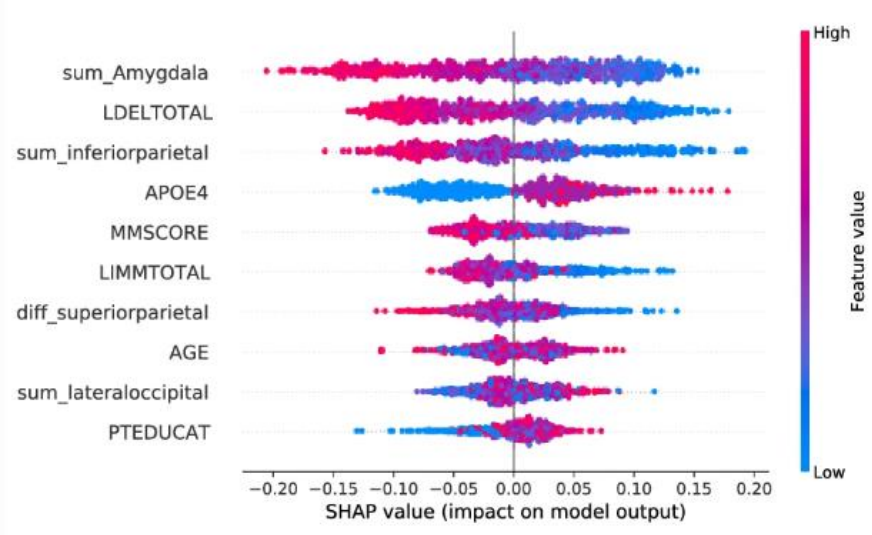
Patient b



SHAP values = local, additive contributions of each feature to the prediction of this patient

Graphs taken from Bloch et al (2022)

Investigate feature importance

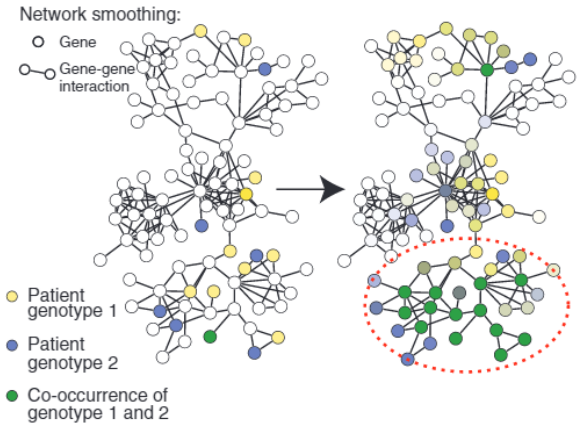


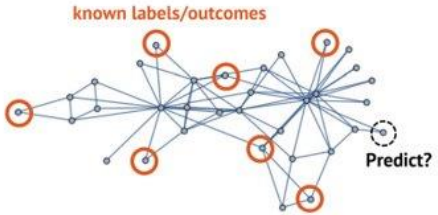
- Many other refined model interpretations are possible.
- As an example, you can cluster patients based on how similar the **reason for their predicted outcome** is.

Example 2:
Use network information

Let us make use of the rich biological information from literature and data bases!

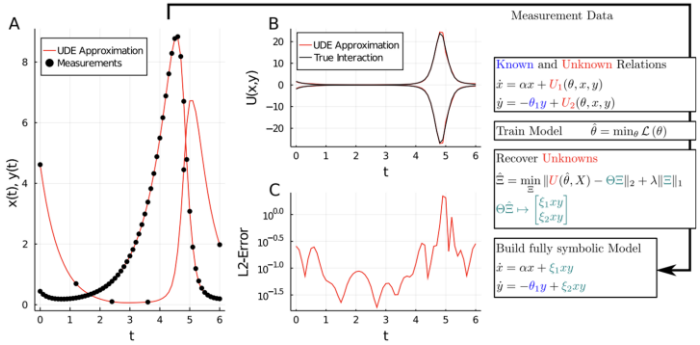
- Incorporate a known network structure into a machine learning model, e.g. via **network smoothing** (Hofree et al, 2013)
- Use **regularized** regression with a penalty matrix that is defined by the graph structure, see e.g. Dirmeier et al (2018)
- **Neural network** approaches, e.g. Benson (2021)





Example 3:
Scientific Machine Learning

- Next generation pharmacometrics modeling using AI is successfully used.
- Universal differential equations (UDEs) combine the advantages of mechanistic modeling and AI.
- Rackauckas et al (2020) in a nutshell
  - (1) Identify known parts of a model
  - (2) Train the unknown parts using neural networks
  - (3) Use symbolic regression to build a model.



Are there success stories? Yes!

- FDA approved (Benjamens et al, 2020)
  - Diagnostic software for lesions suspicious for cancer
  - MRI brain interpretation
  - ECG monitoring
  - …
- AI/ML in FDA submissions (Liu et al, 2022)
- From the past: data-driven patient stratification
  - Consensus molecular subtypes in colorectal cancer
  - Cell-of-origin subtypes in diffuse large B-cell lymphoma

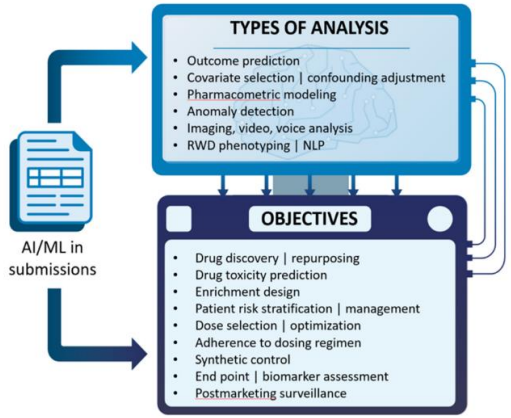


Figure 2 Common type of applications of AI/ML in drug development. AI/ML, artificial intelligence / machine learning; NLP, natural language processing; RWD, real-world data.

Company-internal success stories

- Feature selection
- Identification of gene signatures
- Exploration of digital biomarkers
- …

FDA and Machine Learning / AI (Liu, 2022)

Focus Area Artificial Intelligence

Evaluation of Machine Learning Applications

Context of use

Risk-based

Generalizability / fairness / performance guarantees

Transparency / explainability

AI / Machine Learning in Office of Clinical Pharmacology

Machine Learning review team

Landscape analysis

Methodology research

Applications

FDA and Machine Learning / AI (Liu, 2022)

Source: Artificial Intelligence and Machine Learning (iqconsortium.org)

Landscape Analysis

- Application of Machine Learning in Drug Development and Regulation: Current Status and Future Potential. (PMID: 31925955)

Methodology

- Long short-term memory recurrent neural network for pharmacokinetic-pharmacodynamic modeling (PMID: 33210994)
- A novel approach for personalized response model: deep learning with individual dropout feature ranking. (PMID: 33104924)
- Application of machine learning based methods in exposure-response analysis. (PMID: 35275315)

Applications

- Ongoing research: Use ML to predict the treatment outcome (both efficacy and toxicity)
- Medical Imaging data for precision medicine (in collaboration with CDRH, CBER and OCE)

EMA and Machine Learning / AI

Source: Artificial intelligence in European medicines regulation (nature.com)

Initiatives

- EMA task forces on data analytics and methods, and on digital transformation
- EMA Analytics Centre of Excellence to build regulators' understanding of AI and apply it to support regulatory processes
- 2021 Joint HMA/EMA Workshop on Artificial Intelligence in Medicines Regulation
- …

Considerations

- Clear framework for medicines whose benefit–risk ratio relies on digital technologies, including AI.
- Risk categorization for digital technologies that impact a medicinal product's benefit–risk ratio.
- Regulatory access to the underlying algorithms and datasets
- The post-authorization management of medicines may need updating.
- …

Build trust in Machine Learning for Biomarkers

Provide in-house trainings

Show use cases and share success stories

Publish more on this topic!

Get rid of the misconception that Machine Learning is heuristics and algorithms only

- Provide quantification of uncertainty
- Provide error control guarantees e.g. via knock-offs (Sechidis et al, 2021)
- Apply proper model validation and quantification

How to increase Machine Learning applications

Provide templates to colleagues

e.g., work flows for feature selection

Identify promising use cases

"high risk & high benefit" – something that could not be solved without machine learning, and/or

"look, Machine Learning is very similar to what we already do"

Incorporate analysis into clinical decision making

e.g., adaptive designs, proper pre-specification and model validation in the Statistical Analysis Plan

"Biomarker analysis will be exploratory only and may include multivariate methods."

Summary – what's next?

- Machine learning is here to stay.
  - The high dimensionality and the complexity of biomarkers call for advanced methods.
  - Education, research and collaboration are key.
- There is so much more to explore.
  - Digital biomarkers – an exciting new field!
  - Pre-training models on external data (as it is often used for image analysis)
  - Federated learning – learning from decentralized data sources
  - …
- We, the Biomarker SIG, want to provide a platform to learn and collaborate.

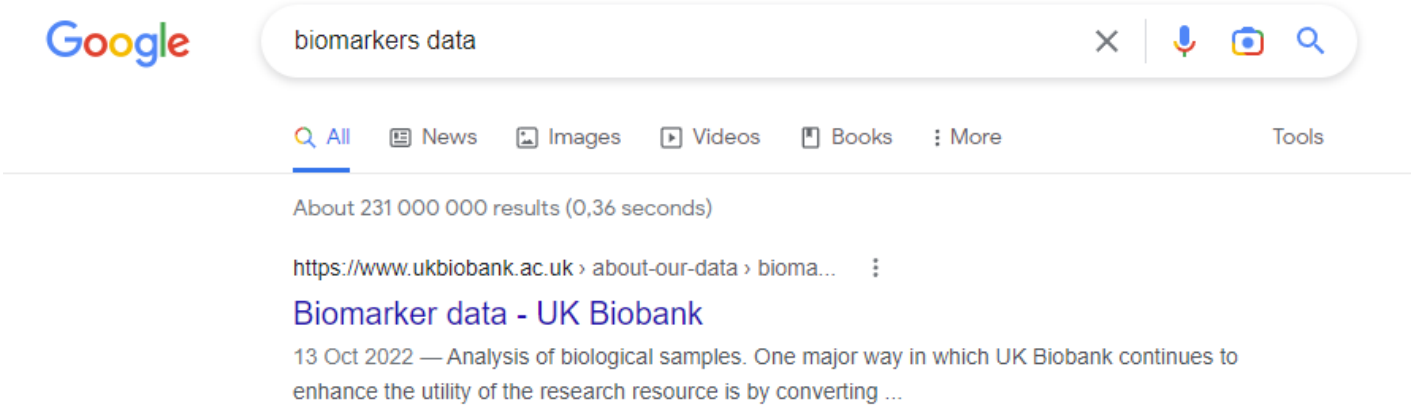
But where is the data?

Guillaume Desachy

Early Biometrics & Statistical Innovation, Data Science & Artificial Intelligence,
R&D, AstraZeneca, Gothenburg, Sweden

Let’s look for data!

Lesson 1: Let's not reinvent the wheel!



Existing data repositories? They don't meet our needs. 😢

"I need to have access to different kinds of biomarkers!"

"I need datasets to assess if a biomarker is prognostic or predictive!"

"I need a dataset with a lot of variables to be able to test this new machine learning technique!"

Our goal:
Create a collection of biomarker datasets

Biomarkers data type

Data generation platform

Data description

Data location

Disease indication

"We are a community dedicated to leading and promoting the use of statistics within the healthcare industry for the benefit of patients."

The long-term goal: make it interactive!

And you, what is your favorite biomarker dataset? 😀

bit.ly/bm-sig-data

What's next?

"We are a community dedicated to leading and promoting the use of statistics within the healthcare industry for the benefit of patients."

2023?
Another exciting year for the SIG! 😍

- 🔦 Biomarkers Session @ PSI 2023 (June 11th-14th)
- 💻 Another webinar (Q3 2023)
- 🔎 Working on the priority topics
  - White papers
  - Collborating with the Data Visualization SIG for a Wonderful Wednesday

Biomarkers SIG Co-Leads

https://www.linkedin.com/in/dr-nicole-kraemer/

https://www.linkedin.com/in/guillaume-desachy/

Back ups

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