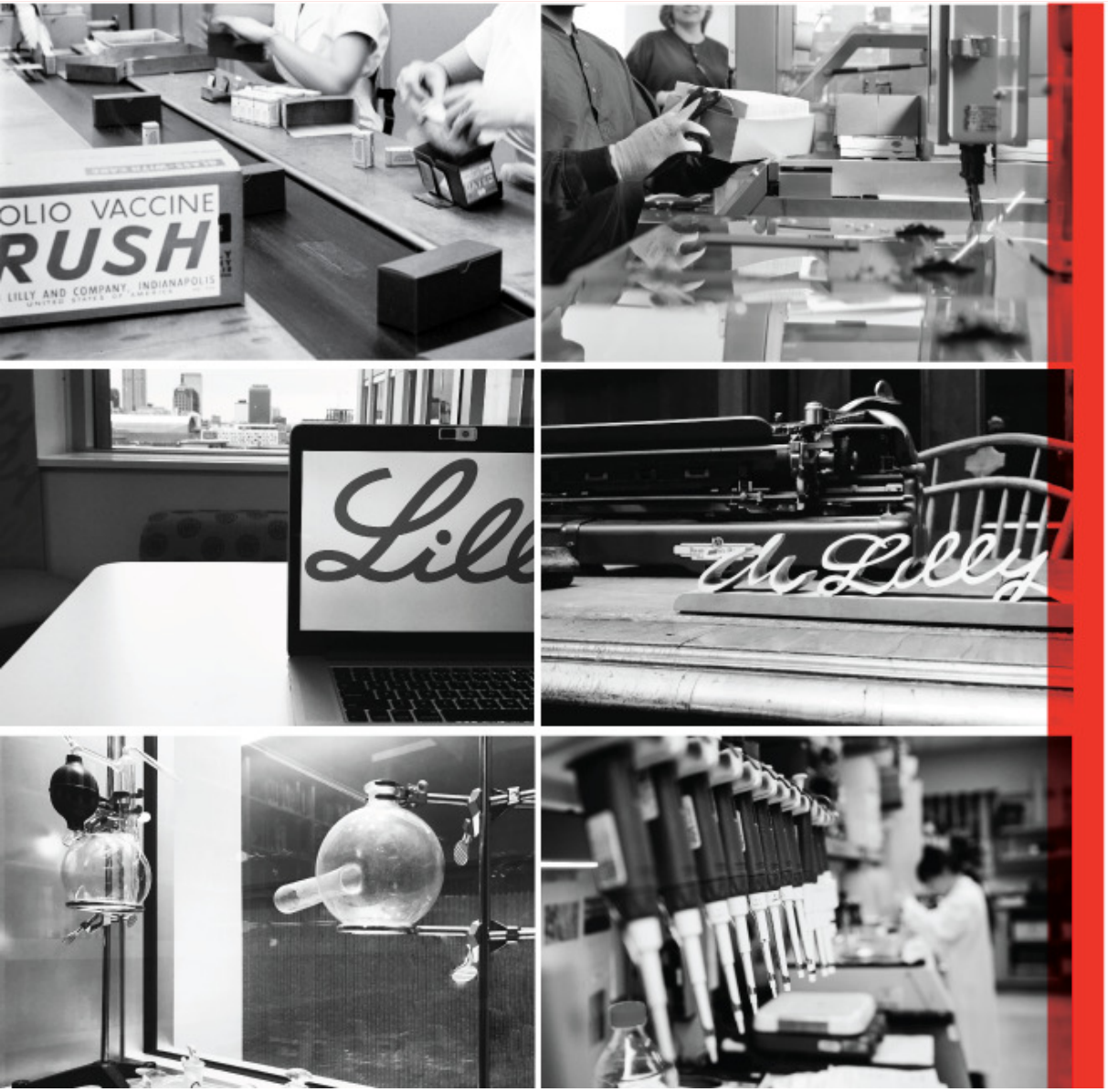


Building a Bayesian decision-theoretic framework to design biomarker-driven studies in early phase clinical development

Sep 29, 2017
Danni Yu
Eli Lilly and Company

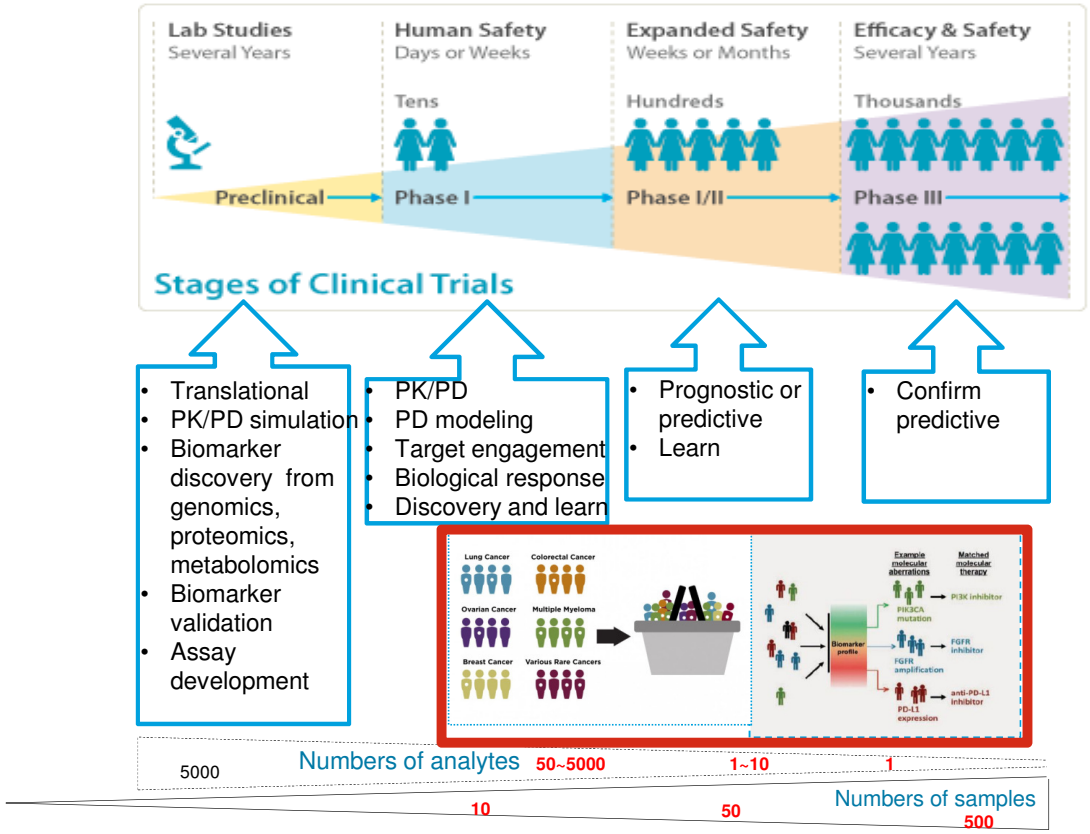
ASA webinar

Outline

- Motivation
- Introduction to Bayesian Decision Theory (BDT)
- Building the BDT framework
- Applying the BDT
- Summary

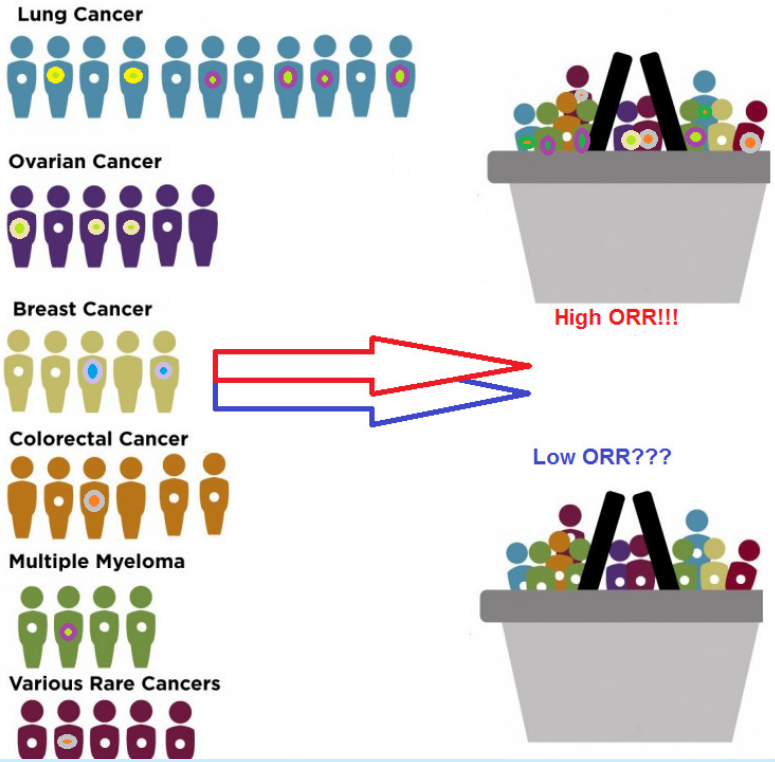
Biomarker work flow

- Traditional approach over unspecified population
- Biomarker-driven approach for precision medicine



Uncertainty and risk for clinical trial design

- ✓ How to select patients for precision medicine?
- ✓ How many patients should be selected for each subtype?
- ✓ How to select the subtype?
- ✓ How to adopt different criteria of clinical benefit in each subtype?
- ✓ How much information that we should have before running the trial?



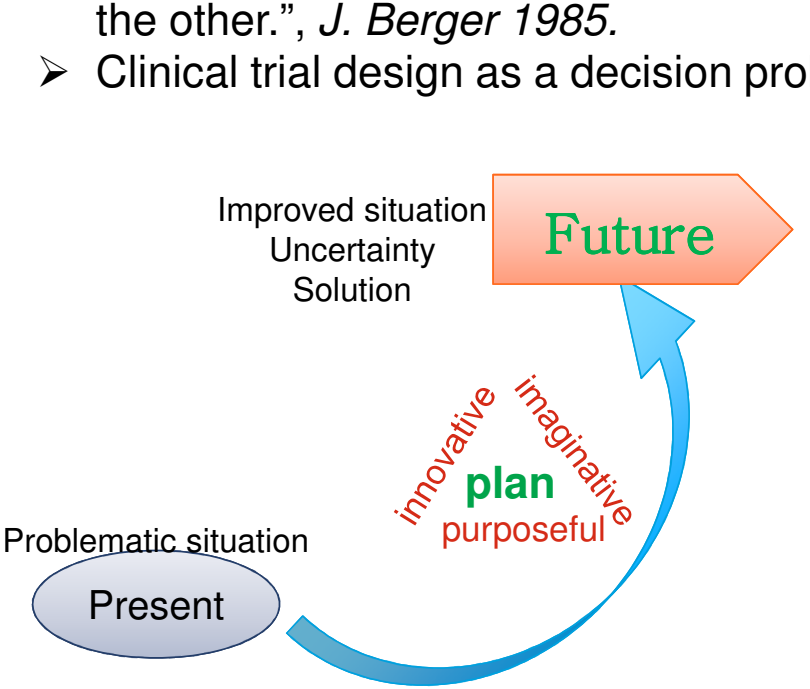
- ➢ Why are some trials so successful with high objective response rate (ORR) while the others are not?
- ➢ Are there any pitfalls before and while running the trials?
- ➢ Which biomarkers do truly help identify patients while the others might be just ambiguous?

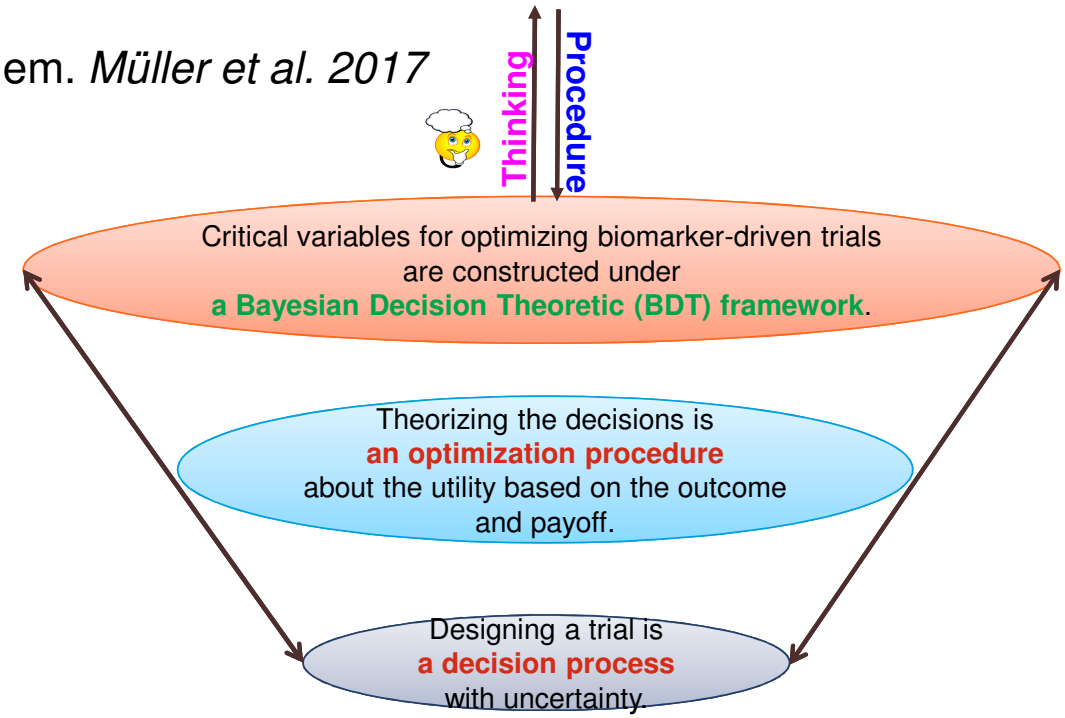
We need a method & tool to filter out unnecessary failures as early as possible.

The picture was originally copied from https://www.mskcc.org/blog/clinical-trial-shows-promise-basket-studies-drugs and then revised.

Bayes decision theory helps the process.

- "The relationships (both conceptual and mathematical) between Bayesian analysis and statistical decision theory are so strong that it is somewhat unnatural to learn one without the other.", *J. Berger 1985.*
- Clinical trial design as a decision problem. *Müller et al. 2017*





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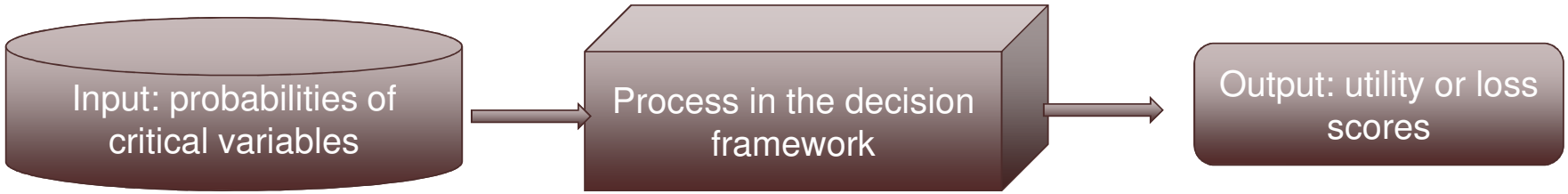
Basics of decision theory

- It includes three principle phases of problem-solving (*H. Simon 1960*):
  - Intelligence for decision recognition and diagnosis
  - Design for possible actions
  - Choice on courses of action as a goal-directed behavior
- There are two branches of decision theory (*Pratt et.al. 1995, S. O. Hansson 2005,*):
  - A normative decision theory
    - How decision **should be** made in order to be rational.
  - A descriptive decision theory
    - How decision **is** actually made.

The two branches of decision theory

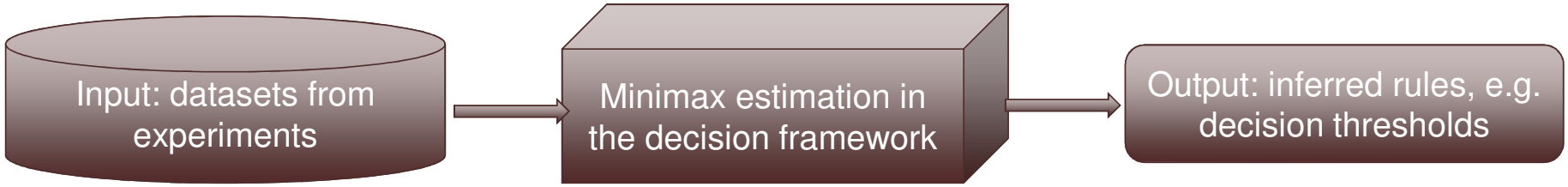
Prospective approach: selecting the best arms/cohorts for a trial that optimize the utility or minimize the loss.

Normative decision theory



Retrospective approach: inferring the decision rules according to the data of decision outcomes.

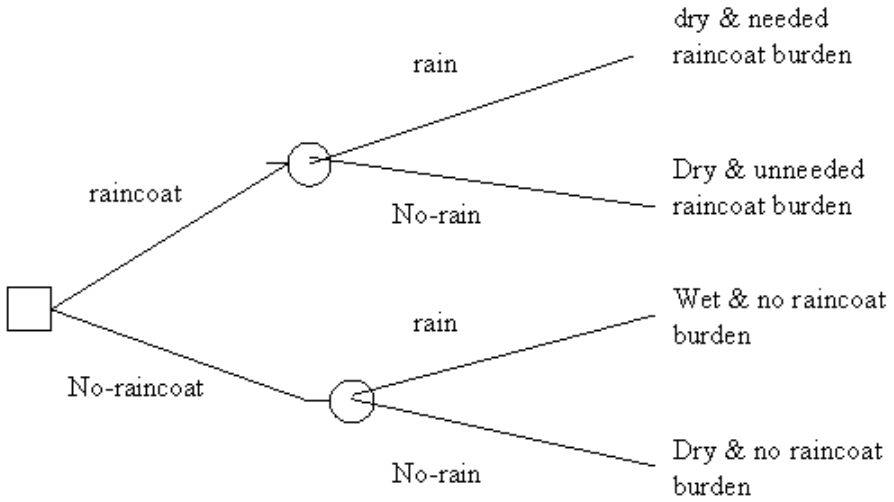
Descriptive decision theory



The four basic elements in a decision tree

A decision tree includes four basic elements.

- Acts: actions being considered by the decision makers
- Events: occurrences taking place outside the control of the decision makers
- Outcomes: results of the occurrence of actions and events
- Payoffs: values of the occurrences considered by the decision makers



✓ *Acts: taking the raincoat or not*

✓ *Events: rain or no rain*

✓ *Outcome: being dry or wet*

✓ *Payoffs: having a raincoat burden or not*

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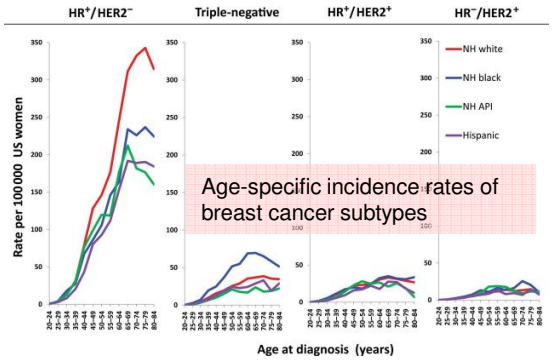
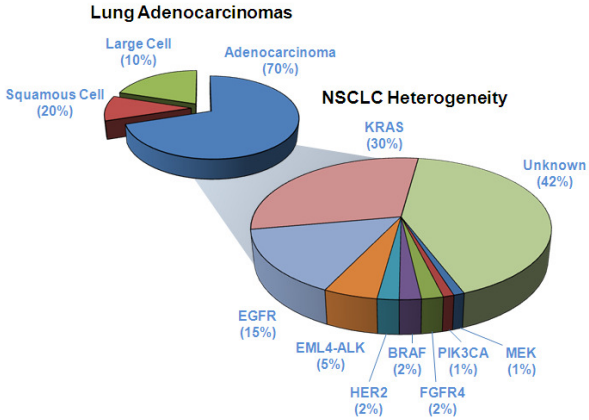
Motivation

- To facilitate decision makers prioritizing the candidate plans of biomarker-driven studies
- To construct the critical variables in a Bayesian theoretic framework
- To implement the methods and do the analysis in an interactive R/shiny app.

Critical variables in the trials with biomarkers

- ***Tumor incidence or disease prevalence*** in ***biomarker or pharmacogenomics (PGx) subtypes***, such as
  - 80-85% Chromosomal Instability (CIN), 15-20% Microsatellite Instability (MSI), 20% CpG island methylation (CIMP) in CRC.





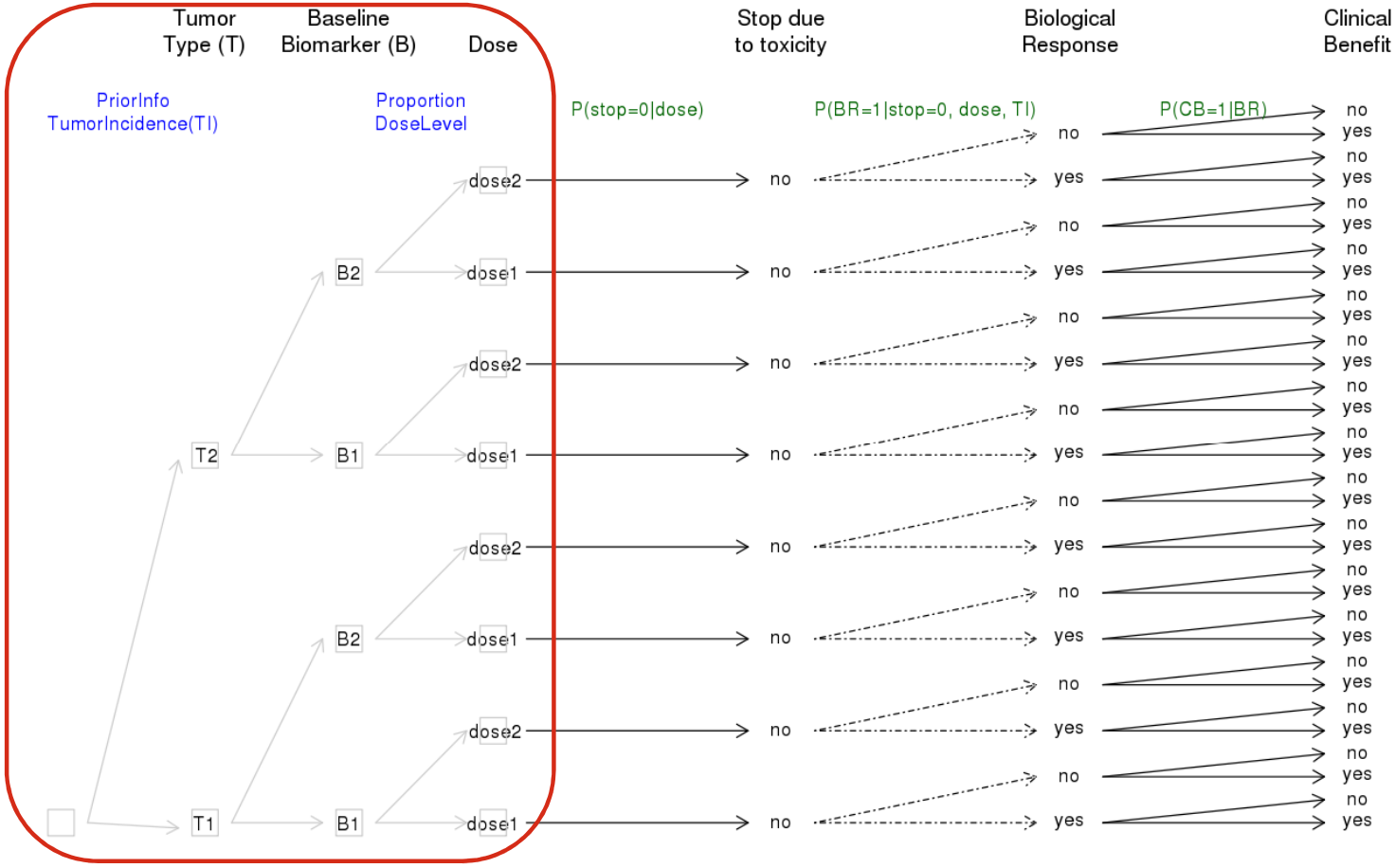
- ***Relative sample proportion or size*** in different cohorts.
- *Dropout rate:* whether stop the treatment for a patient due to toxicity.
- *Surrogate:* ***biological response*** based on pharmacogenomics biomarkers.
- *Endpoint:* ***clinical benefit*** such as ORR, PFS, OS, DFS, TTP, QOL, etc..

FDA 2013, RS Day 2016, Morita et.al. 2017, Wilhelm-Benartzi et al.2017

https://www.ncbi.nlm.nih.gov/pubmed/24777111

https://www.dovepress.com/prevalence-and-natural-history-of-alk-positive-non-small-cell-lung-can-peer-reviewed-fulltext-article-CLEP

The prior knowledge in the BDT-framework

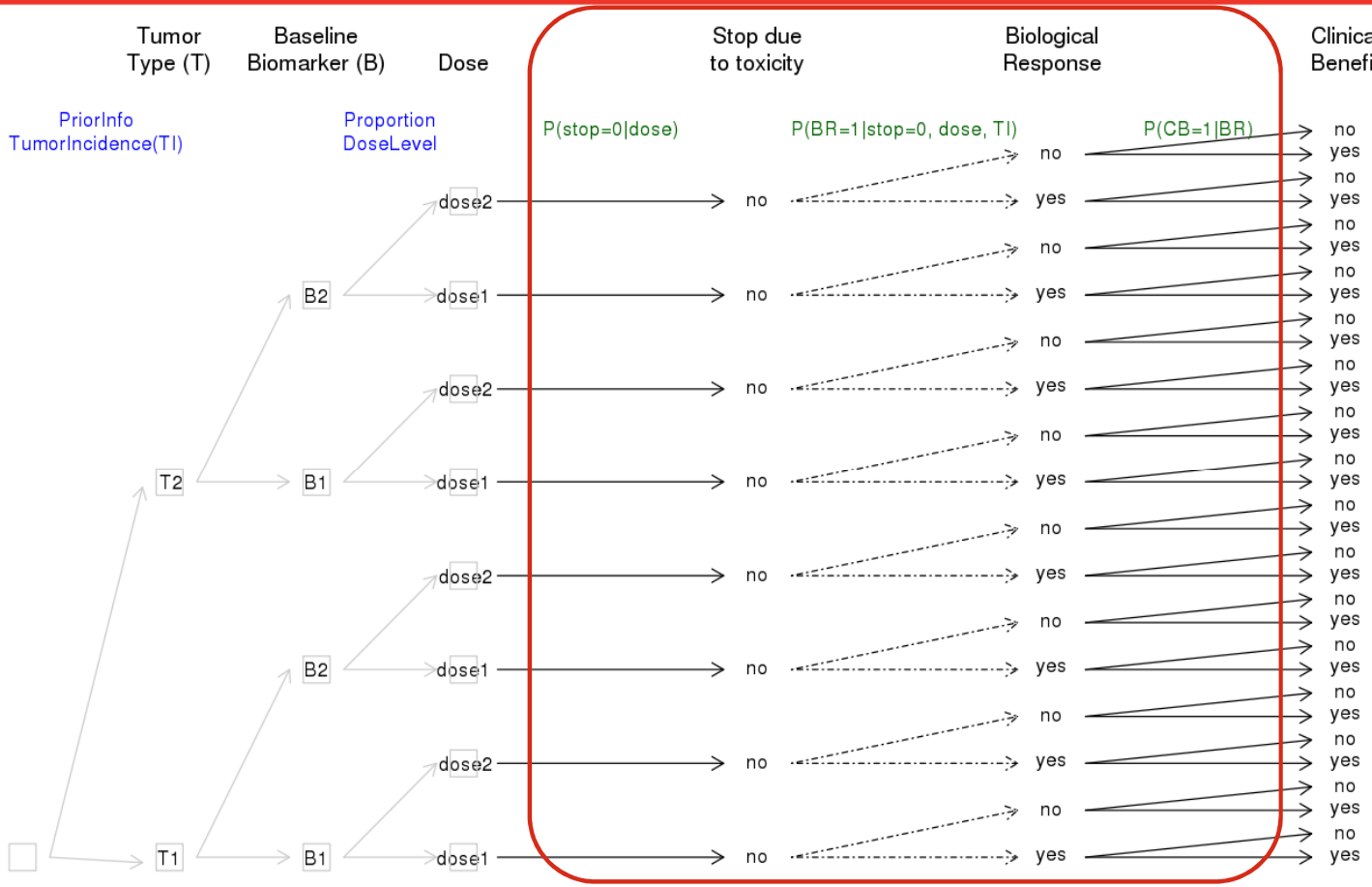


Marginal probabilities

- Occurrences of acts
- The chance for a patient to be sampled into the plan

Tumor incidence: P({T,B})
Relative proportion: P(dose)

The conditional variables in BDT-framework

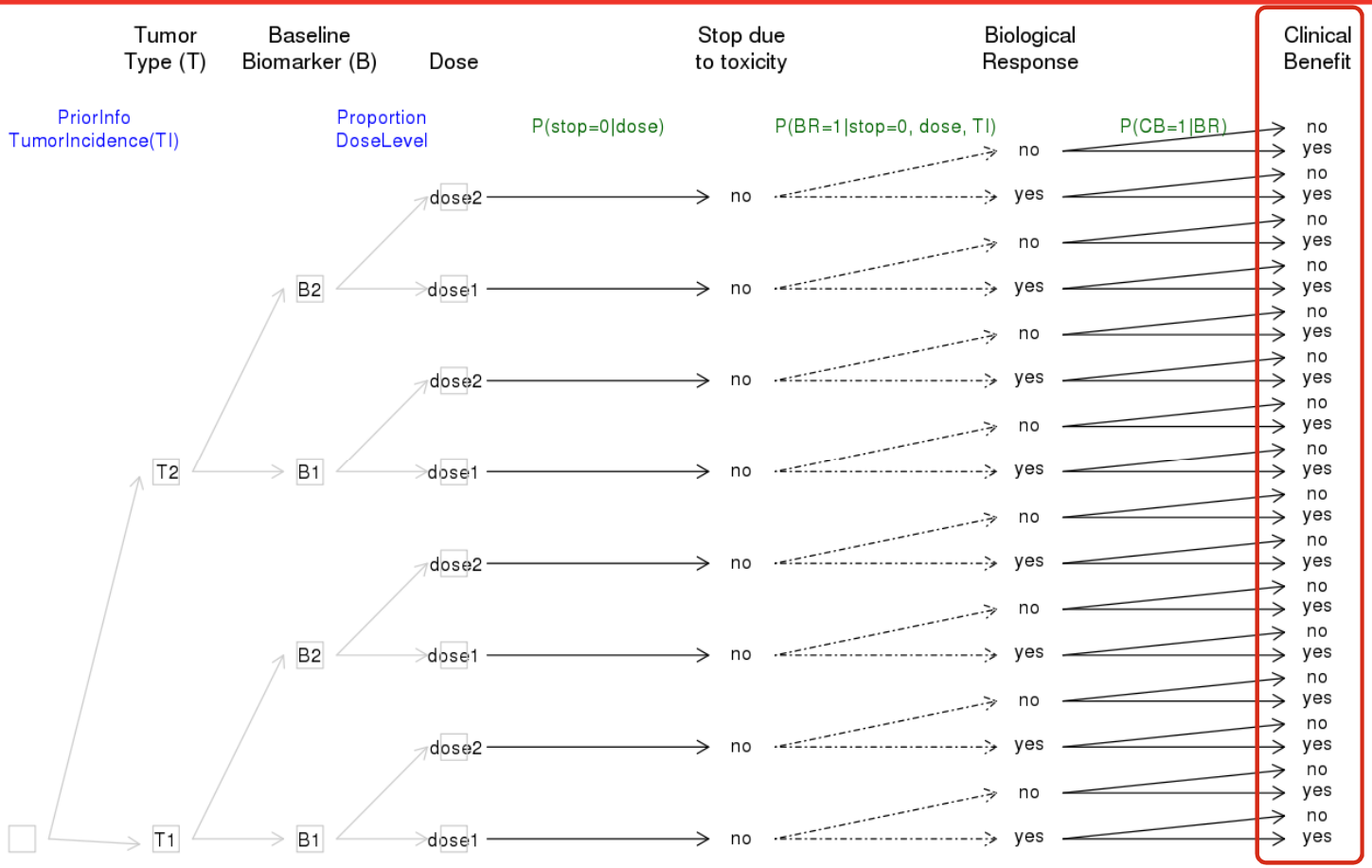


Conditional probabilities

- Occurrences of events

P(stop=0|dose)
P(BR=1|stop=0, dose, {T,B})
P(CB=1|BR)

Outcomes in the BDT-framework



Joint probabilities

- Outcome

$P(CB=1, BR, stop=0, dose, \{T,B\})$
$P(CB=0, BR, stop=0, dose, \{T,B\})$

Set the payoff values as

- U=100 if the outcome is {CB=1, BR, stop=0, dose, {T,B}}
- U= -100 if the outcome is {CB=0, BR, stop=0, dose, {T,B}}

The expected utility of a cohort or arm

- A criterion or reference used to compare plans
- A score summarizing the profit of a plan over all the possible outcomes weighted by their joint probabilities with events and acts

$$E\{U_{d,\{T,B\}}\} = \sum_{i=0}^{1}\sum_{j=0}^{1} C_j P(CB = j|BR = i)P(BR = i|stop = 0, d, \{T, B\})P(stop = 0|d) * P(d)P(\{T, B\})$$

$$where\ C_j\ is\ the\ payoff\ value\ when\ CB = j, d\ is\ a\ selected\ dose\ level.$$

- The default values of positive and negative payoff are 100 and -100. They can be changed according to decision makers' definition.
- After defining the payoff values, the plan with higher U(dose, {T,B}) is expected to be better.

The expected utilities are the scores providing comparable quantification of candidate arms/cohorts in a plan to help decision makers optimize the outcome of the plan.

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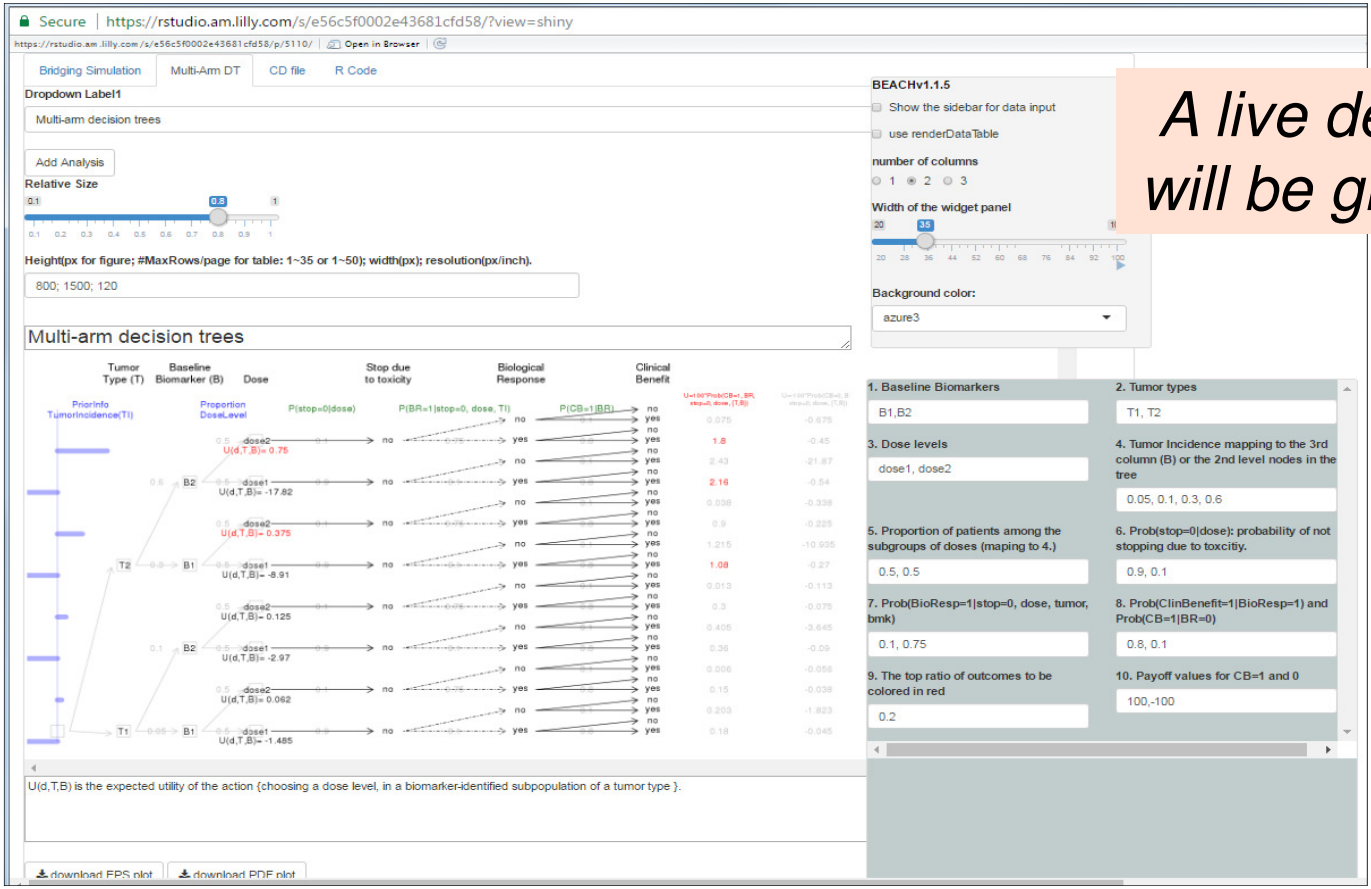
The trial evaluation tool in BEACH

Biometrics
Exploratory
Analysis
Creation
House

BEACH is a R/shiny app that provides a automation platform for interactive analyses.



A live demo will be given.

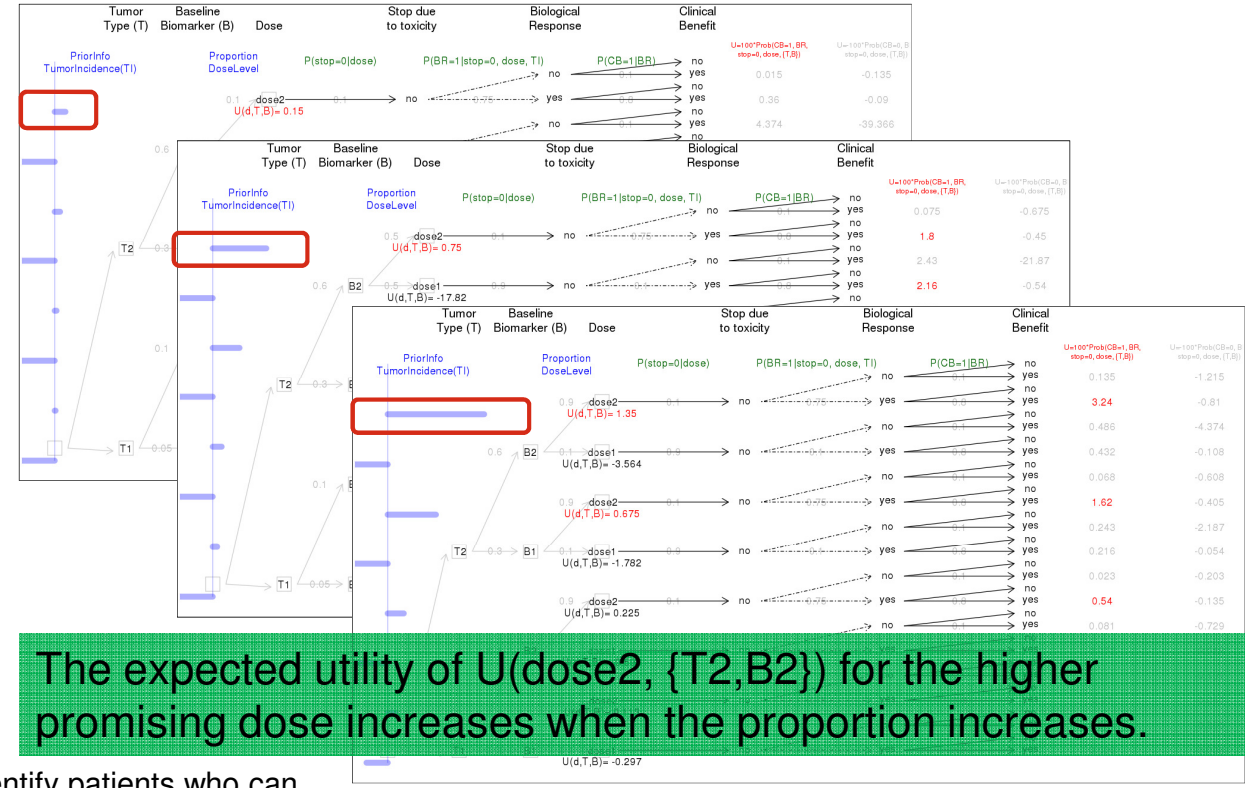
The tool is for trial plan evaluation.

- The tool will be evaluated with the following illustrated information.
  1. Changing relative sample proportion over the cohort or arm with different dosage
  2. Varying the chance of continuing the treatment without severe toxicity
  3. Varying the probability of biological response while it is not correlated with the endpoints
  4. Varying the probability of biological response while it is highly correlated with the endpoints
  5. Increasing the chance of the biological response while the tumor subtypes have low incidence

- Extension and generalization.
  - It will add the loss values of go/no-go decision rules for Critical Success Factor (CSF) analysis.
  - It will allow decision makers change the critical variables other than dose and surrogate variables.

E1: larger population size, better utility

- Changing the relative proportions between subgroups of dose
  - Changing the proportion of the subgroup with higher promising dose: P(dose2) as 0.1, 0.5, or 0.9
  - P({T1,B1})=0.05, P({T1,B2})=0.1, P({T2,B1})=0.3, P({T2,B2})=0.6
  - P(stop=0|dose1)=0.9, P(stop=0|dose2)=0.1
  - P(BR=1|stop=0, dose1, {T,B})=0.1, P(BR=1|stop=0, dose2, {T,B})=0.75
  - P(CB=1|BR=1)=0.8, P(CB=1|BR=0)=0.1

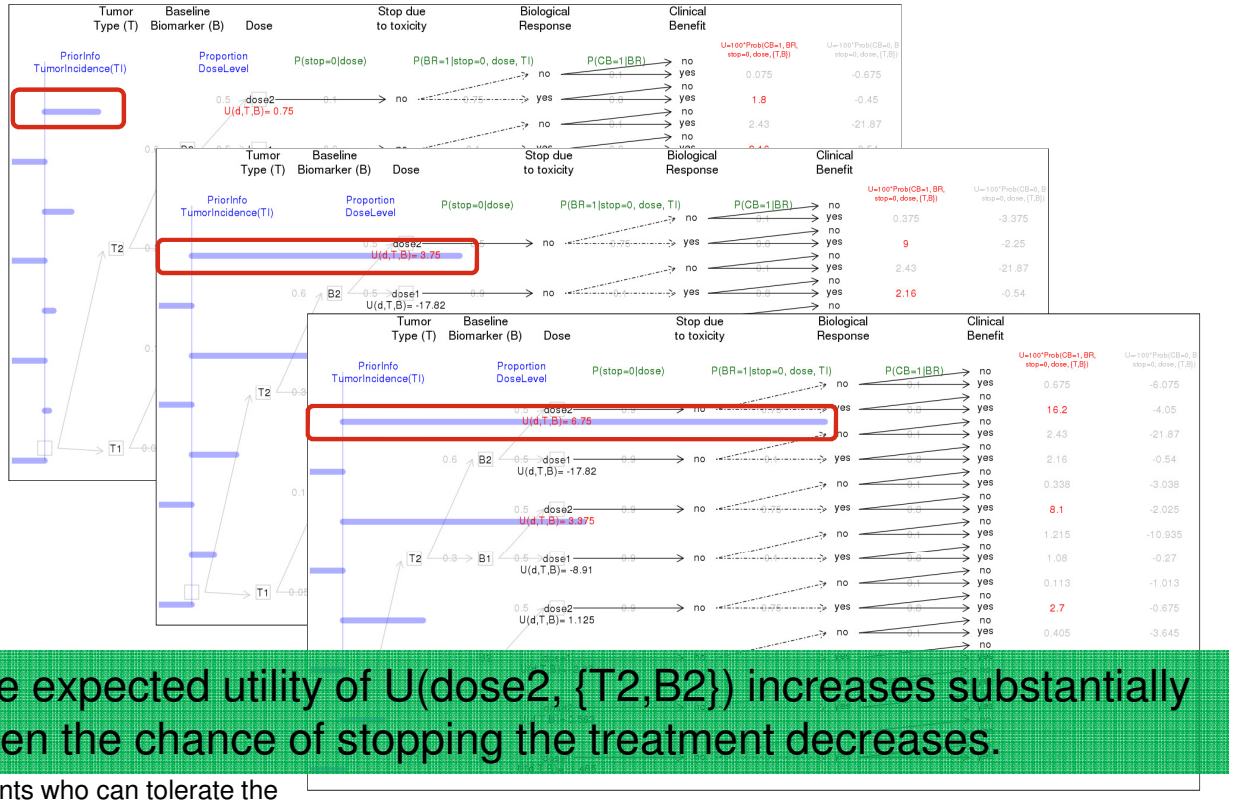


The expected utility of U(dose2, {T2,B2}) for the higher promising dose increases when the proportion increases.

Note: the toxicity biomarker should be used to identify patients who can tolerate the higher dose when P(stop=0|dose2) is quite low.

E2: less dropouts, better utility

- Varying the possibility of keeping evaluable patients
  - Varying P(stop=0|dose2) as 0.1, 0.5, or 0.9
  - P(stop=0|dose1) as 0.9
  - P({T1,B1})=0.05, P({T1,B2})=0.1, P({T2,B1})=0.3, P({T2,B2})=0.6
  - P(dose2)=0.5, P(dose1)=0.5
  - P(BR=1|stop=0, dose1, {T,B})=0.1, P(BR=1|stop=0, dose2, {T,B})=0.75
  - P(CB=1|BR=1)=0.8, P(CB=1|BR=0)=0.1

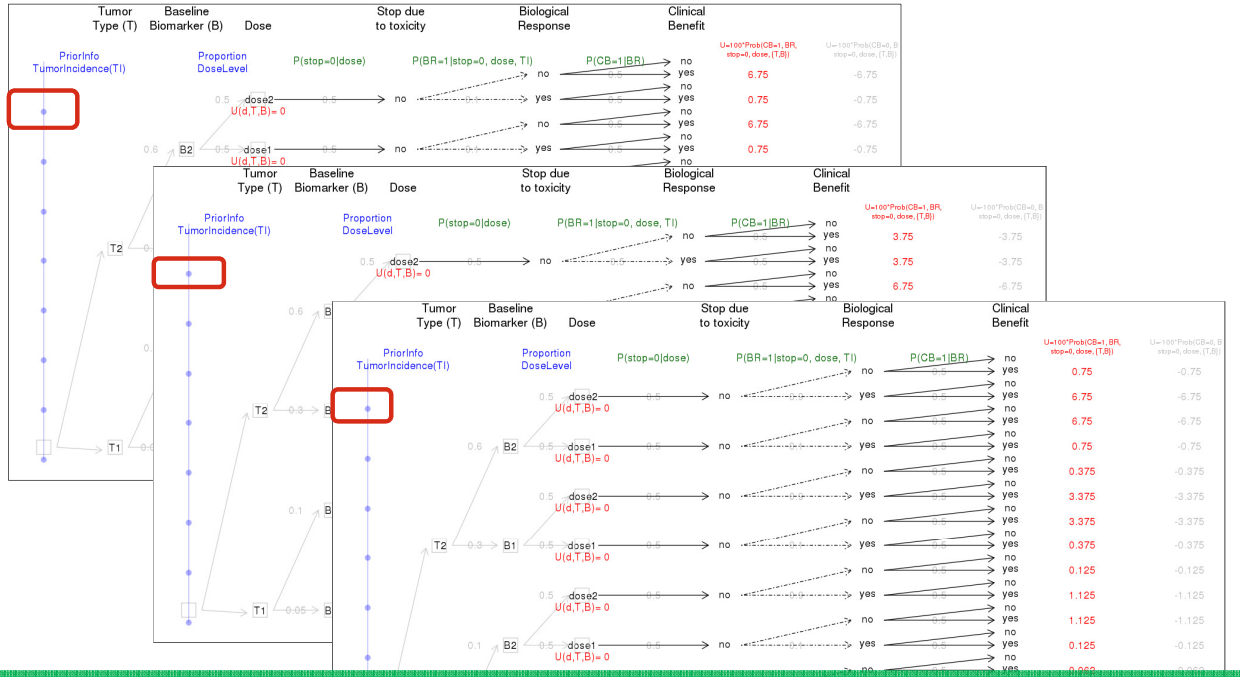


The expected utility of U(dose2, {T2,B2}) increases substantially when the chance of stopping the treatment decreases.

Note: the toxicity biomarker should be used to identify patients who can tolerate the higher dose when P(stop=0|dose2) is quite low.

E3: irrelevant surrogate, worse utility

- Varying the chance of biological response (surrogate variables) non-correlated with clinical benefit.
  - Varying P(BR=1|stop=0, dose2, {T,B}) as 0.1, 0.5, 0.9
  - P(BR=1|stop=0, dose1, {T,B})=0.1
  - P(stop=0|dose2)=0.5
    P(stop=0|dose1)=0.5
  - P({T1,B1})=0.05, P({T1,B2})=0.1,
    P({T2,B1})=0.3, P({T2,B2})=0.6
  - P(dose2)=0.5, P(dose1)=0.5
  - P(CB=1|BR=1)=0.5,
    P(CB=1|BR=0)=0.5



The expected utility of U(dose2, {T2,B2}) is always 0 when the clinical benefit and biological response are independent and P(CB=1)=0.5

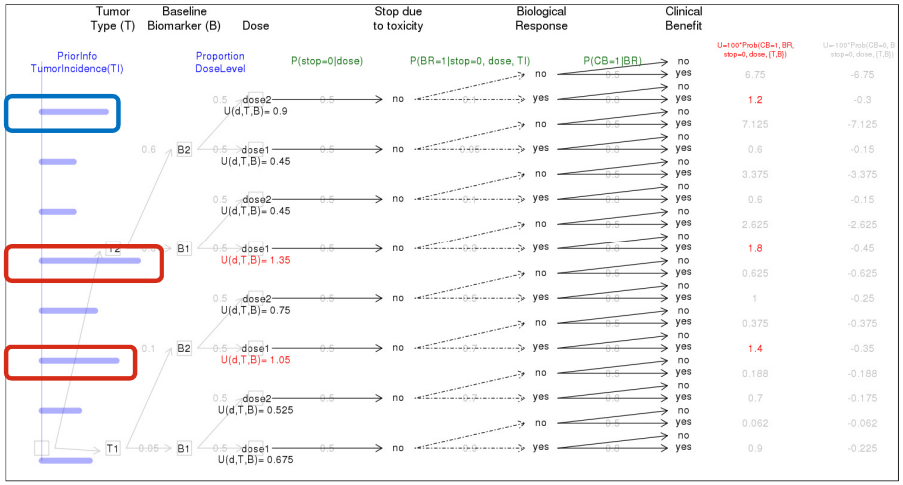
E4: correlated surrogate, better utility

- Varying the chance of having biological response (surrogate) while the dependence of CB over BR is high
  - Varying P(BR=1|stop=0, dose2, {T,B}) as 0.1, 0.5, 0.9
  - P(BR=1|stop=0, dose1, {T,B})=0.1
  - P(stop=0|dose2)=0.5
    P(stop=0|dose1)=0.5
  - P({T1,B1})=0.05, P({T1,B2})=0.1,
    P({T2,B1})=0.3, P({T2,B2})=0.6
  - P(dose2)=0.5, P(dose1)=0.5
  - P(CB=1|BR=1)=0.8,
    P(CB=1|BR=0)=0.5

The expected utility of U(dose2, {T2,B2}) is substantially increased with higher biological response rate when P(CB=1|BR=1) is high.

E5: low incidence needs high ORR

- When the biological response is much higher in biomarker tumor subtypes with low incidence
  - P(BR=1|stop=0, dose2, {T1,B1})=0.9
    P(BR=1|stop=0, dose2, {T1,B2})=0.7
    P(BR=1|stop=0, dose2, {T2,B1})=0.1
    P(BR=1|stop=0, dose2, {T2,B2})= 0.05
  - P(BR=1|stop=0, dose1, {T1,B1})=0.7
    P(BR=1|stop=0, dose1, {T1,B2})=0.5
    P(BR=1|stop=0, dose1, {T2,B1})=0.3
    P(BR=1|stop=0, dose1, {T2,B2})= 0.1
  - P(stop=0|dose2)=0.5, P(stop=0|dose1)=0.5
  - P({T1,B1})=0.05, P({T1,B2})=0.1
    P({T2,B1})=0.3, P({T2,B2})=0.6
  - P(dose2)=0.5, P(dose1)=0.5
  - P(CB=1|BR=1)=0.8, P(CB=1|BR=0)=0.5



When biological response and P(CB=1|BR=1) have relatively high values in the biomarker subtypes with relatively low incidence, the expected utility for the subtypes may also be relatively high.

Extension and generalization

Given the tumor type or indication T_i, the biomarker B_j, and the number of responders θ_{ij}, it is defined that

$$\theta_{ij} = \sum_{k=1}^{n_{ij}} X_{ijk} \sim Binomial(\pi, n_{ij}), \text{ where}$$

The prior $\pi \sim Beta(1 + \alpha_{ij}, 2 - \alpha_{ij})$

where α_{ij} can be assumed either the disease prevalence or a flat prior so that π~Uniform(0,1).

The posterior $\pi_{ij}^* = p|\overrightarrow{X_{ij}} \sim Beta(1 + \alpha_{ij} + \sum_{k=1}^{n_{ij}} x_{ijk}, 2 - \alpha_{ij} + n_{ij} - \sum_{k=1}^{n_{ij}} x_{ijk})$

The posterior $\theta_{ij}|\overrightarrow{X_{ij}} \sim \text{Binomial}(\pi_{ij}^*, n_{ij})$

The loss function given the decision rule $\delta_{ij}$is defined as (*J. O. Berger 1985*):

$$\text{L}(\theta_{ij}, A_0) = \begin{cases} \theta_{ij} - \delta_{ij}, & if \theta_{ij} > \delta_{ij} \\ 0, & if \theta_{ij} \leq \delta_{ij} \end{cases} \quad \text{and L}(\theta_{ij}, A_1) = \begin{cases} 0, & if \theta_{ij} > \delta_{ij} \\ \delta_{ij} - \theta_{ij}, & if \theta_{ij} \leq \delta_{ij} \end{cases}$$

The expect loss is

$$E\left[L(\theta_{ij}, A_0)\right] = \sum_{\delta_{ij}+1}^{n_{ij}} \left(\theta_{ij} - \delta_{ij}\right) P(\theta_{ij}|\overrightarrow{X_{ij}}) \quad and \; E\left[L(\theta_{ij}, A_1)\right] = \sum_{0}^{\delta_{ij}} \left(\delta_{ij} - \theta_{ij}\right) P(\theta_{ij}|\overrightarrow{X_{ij}})$$

For the continues response variables

- Assuming the continues response variable (i.e. time-to-event) follows a lognormal distribution

$$X \sim Lognormal(\mu_0, \sigma_0^2)$$

- Considering the conjugate prior as a Normal distribution with known variance. The posterior distribution is

$$\mu|X \sim Lognormal\left(\frac{\frac{\mu_0}{\sigma_0^2} + \frac{\sum_{k=1}^{n} \ln(x_k)}{\sigma^2}}{\frac{1}{\sigma_0^2} + \frac{n}{\sigma^2}}, \frac{1}{\sigma_0^2} + \frac{n}{\sigma^2}\right)$$

Adding the benchmark reference

- While X is a discrete variable following a Binomial distribution,
  - the distribution ω of the difference such as in the response rate $\pi_{trt} - \pi_{ref}$ is estimated by sampling π_{trt} from the Beta posterior distributions,

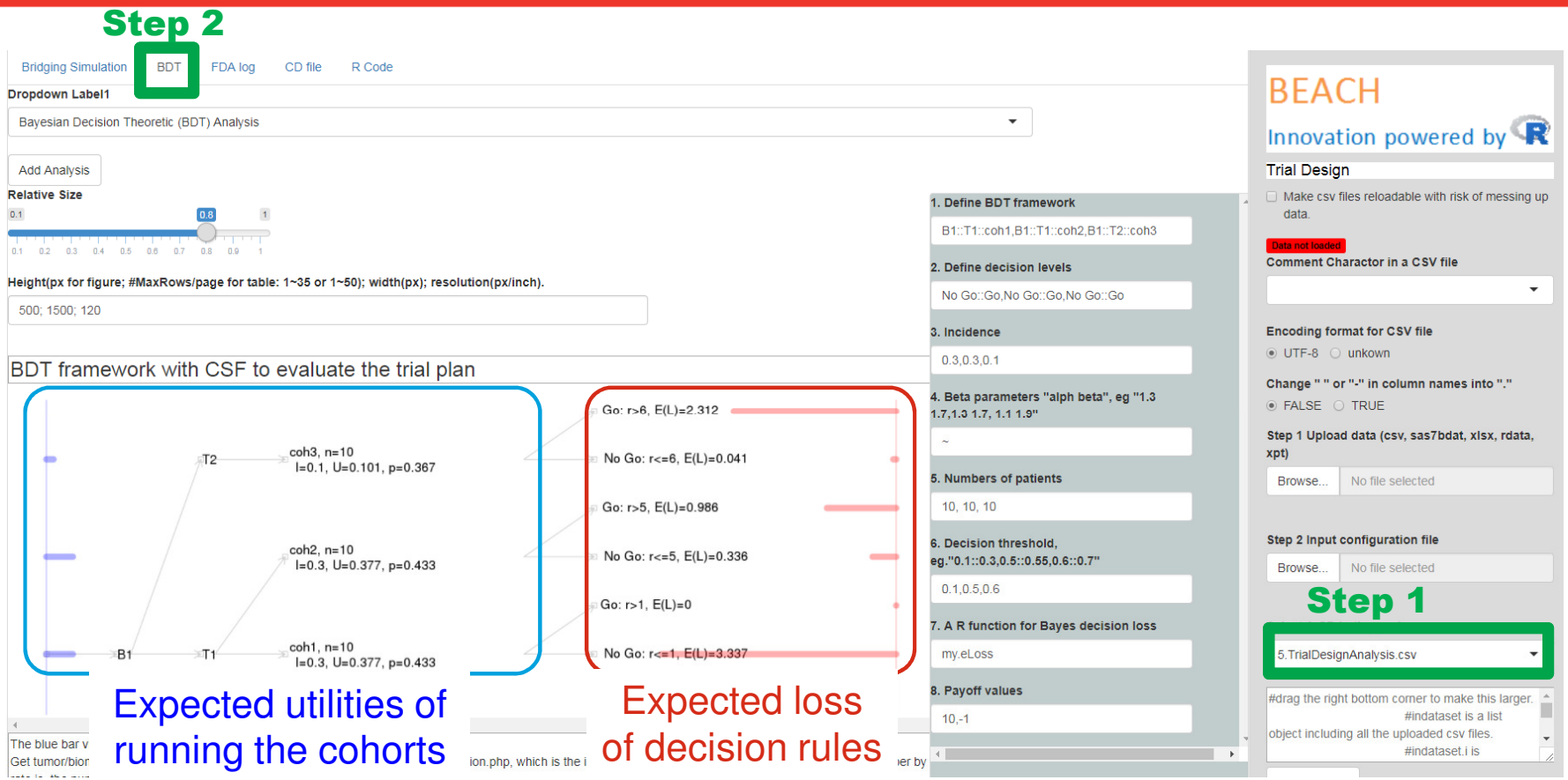
$$\pi_{ij}^{*} = p|\overrightarrow{X_{ij}} \sim Beta(1 + \alpha_{ij} + \sum_{k=1}^{n_{ij}} x_{ijk}\,, 2 - \alpha_{ij} + n_{ij} - \sum_{k=1}^{n_{ij}} x_{ijk}).$$

  - $P(\pi_{trt} - \pi_{ref} \geq \gamma| \ldots)$ is then obtained from ω and it replaces P($\pi_{trt}|\ldots$) in the utility functions.
- While X is a continues variable following a Lognormal distribution,
  - the distribution ω of the difference such as in the time-to-event $\mu_{trt} - \mu_{ref}$ is estimated by sampling μ_{trt} from its own Lognormal posterior distributions,

$$\mu|X \sim Lognormal\left(\frac{\frac{\mu_0}{\sigma_0^2} + \frac{\sum_{k=1}^{n} \ln(x_k)}{\sigma^2}}{\frac{1}{\sigma_0^2} + \frac{n}{\sigma^2}}, \frac{1}{\sigma_0^2} + \frac{n}{\sigma^2}\right).$$

  - $P(\mu_{trt} - \mu_{ref} \geq \tau| \ldots)$ is then obtained from ω and it replaces P($\mu_{trt}|\ldots$) in the utility functions.

The analysis tool for the BDT-framework



Live Demo (~ 30 min)

- https://github.com/DanniYuGithub/BEACH
- library(shiny); runGitHub("BEACH", "DanniYuGithub");

README.md

Biometric Exploratory Analysis Creation House (BEACH) is a shiny app that provides automation platform for users.

Before running BEACH, please make sure your computer is connected to internet and the following packages are installed.

dep.packages <- c("shiny", "DT", "haven", "xtable", "rtf", "plyr", "sas7bdat", "WriteXLS", "SASxport", "rJava"); na.packages <- dep.packages[!dep.packages %in% installed.packages()] if (length(na.packages)>0) install.packages(na.packages);

if(!"sas7bdat.parso" %in% installed.packages()) devtools::install_github('BioStatMatt/sas7bdat.parso', force=TRUE)

Please set up your default internet browser as google chrome Then, in your R console, please run the following code to run BEACH locally.

library(shiny); runGitHub("BEACH", "DanniYuGithub");

To install the package from R cran, please check the link https://cran.r-project.org/web/packages/BEACH/index.html
library(shiny); library(DT); library(BEACH); runBEACH()

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Summary

- The Bayesian Decision Theoretic (BDT) framework is proposed as a guidance and methodology for decision makers to prioritize clinical trial plans.

- A R/shiny app tool structured in BEACH automation platform is provided for implementing the proposed analyses.
  - The tool implements the proposed method under the BDT framework.
  - It is extended to critical success factor analysis with expected loss.
  - It is generalized as enabling user-defined variables under the framework.

Acknowledgement

- Sponsors
  - Pandu Kulkarni and Yanping Wang
- Other thought leaders sharing insightful ideas and discussions
  - Michael Man about biomarker-driven studies and Critical Success Factor (CSF) analysis
  - Karen Price and Michael David Sonksen about Bayes' theorem
  - Christopher Kaiser about designing early phase clinical trials

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