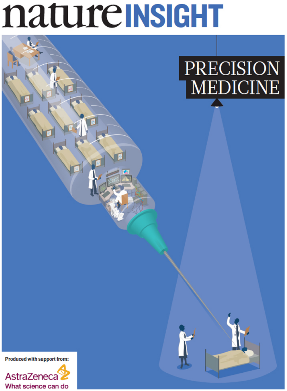
1. Introduction

Precision medicine

"The right treatment for the right patient at the right time"



Precision medicine

Patient heterogeneity:

- Genetic/genomic profile
- Demographic characteristics
- Physiological characteristics
- Clinical variables
- Environment, lifestyle factors
- Medical history, concomitant conditions
- Adverse reactions, adherence to prior treatment
- ...

Basic premise of precision medicine:

- A patient's characteristics are implicated in which treatment option(s) he/she should receive

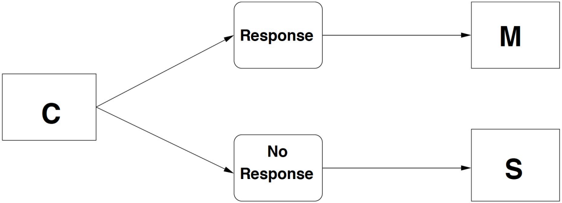
Clinical decision-making

Clinical practice: Clinicians make a series of treatment decisions over the course of a patient's disease or disorder

- Key decision points in the disease/disorder process
- Fixed schedule, milestones, events necessitating a decision
- Multiple treatment options at each decision point
- Synthesis of all information on a patient up to the point of a decision to determine next treatment action from among the feasible options
- Goal: Make the "best" decisions; i.e., leading to the most beneficial expected outcome for this patient

Precision medicine: Formalize clinical decision-making and make it evidence-based

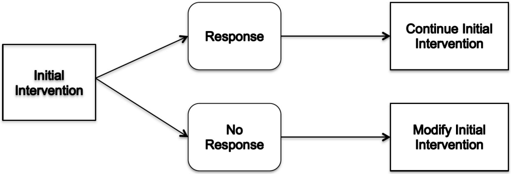
Example: Acute leukemia



Two decision points:

- *Decision 1:* Induction chemotherapy (2 options: C_1, C_2)
- *Decision 2:*
  - Maintenance treatment for patients who respond (2 options: M_1, M_2)
  - Salvage chemotherapy for those who don't respond (2 options: S_1, S_2)
- *Outcome of interest:* Disease-free or overall survival time

Example: Children with ADHD



Two decision points:

- *Decision 1:* Initial intervention
  (2 options: medication, M; behavioral therapy, B)
- *Decision 2:*
  - Continue initial intervention for children who respond
    (1 option: continue, C)
  - Modify initial intervention for those who don't respond
    (2 options: increase dose/intensify, I; add second intervention, A)
- *Outcome of interest:* Parent or teacher assessment, academic achievement measure

Multiple vs. single decision problems

Multiple decision: Aka *multistage*

- Selection of treatment over a (finite) sequence of decision points is of interest

Single decision: Aka *single stage*

- Selection of treatment at a single decision point in isolation is of interest, even if inevitable further decisions will take place
- Conventional perspective in much of clinical/pharmaceutical research

We will consider single decision problems first

- Interesting in their own right
- Foundation for the multiple decision case

What is a dynamic treatment regime?

In words:

- A set of sequential decision rules, each corresponding to a key decision point
- Each rule takes as input information on the patient to that point and returns the treatment he/she should receive from among the available, feasible options
- Formalizes the process by which clinicians synthesize information and select treatments
- Also referred to as an adaptive treatment strategy, adaptive intervention, or policy (computer science)

Optimal dynamic treatment regime: One that leads to the “best” decisions, so to the most beneficial expected outcome (defined precisely later in the course)

Dynamic treatment regimes provide a formal framework for precision medicine

Decision rules

Example: Acute leukemia (made up for illustration)

- *Decision 1:*

  If age < 50 years and WBC $< 10.0 \times 10^3/\mu l$, give chemotherapy C_2, otherwise, give C_1

- *Decision 2:*

  If patient responded and baseline WBC < 11.2, current WBC < 10.5, no grade 3+ hematologic adverse event, current ECOG Performance Status ≤ 2, give maintenance M_1, otherwise, give M_2; otherwise

  If patient did not respond and age >60, current WBC $<$ 11.0, ECOG ≥ 2 give salvage S_1, otherwise, give S_2.

1. Introduction

First use

Murphy, van der Laan, Robins, and CPPRG (2001):

- *Dynamic treatment regime:* “rules for how the treatment level and type should vary with time,” where “these rules are based on time-varying measurements of subject-specific need for treatment”
- *Nondynamic treatment regime:* “a special case of a dynamic treatment regime in which the treatment assignments do not vary by posttreatment observations”
- Referred to as a *static treatment regime* in later literature

Nondynamic/static regimes

Example: Antiretroviral therapy for HIV-infected patients

- Two options at each monthly clinic visit: administer therapy or not
- A static regime: Always administer therapy at each monthly visit, regardless of evolving virologic/immunologic status, side effects, drug resistance, etc
- Another static regime: Always administer therapy for 6 months after diagnosis, then do not, regardless
- A dynamic regime: Rules incorporate evolving virologic, immunologic, and other information on the patient; responsive to individual patient's disease progression

Inconsistent, confusing terminology

One perspective:

- "Dynamic" = multiple decision points
- "Nondynamic" = single decision point
- Regardless of whether or not rules incorporate patient information

Another perspective:

- "Dynamic" = multi- or single stage, rules incorporate patient information
- "Nondynamic" = multi- or single stage, rules are "static"

We adopt the second perspective in this course and often refer to a "regime" unqualified as any set of rules, dynamic or static

Problems with static regimes

In many settings: Static regimes are impossible/unethical, as in acute leukemia

- *Decision 1:* Example static rule "Give induction therapy C_1" (regardless of a patient's characteristics)
- *Decision 2:* A static rule is impossible; any reasonable rule must take account of response status
- E.g., A rule that assigns a salvage option regardless of response status would be unethical

Static regimes are of little relevance to precision medicine

Dynamic regimes

Acute leukemia example: Response status naturally incorporated

- *Decision 1:*

  If age $<$ 50 years and WBC $< 10.0 \times 10^3/\mu l$, give chemotherapy C_2, otherwise, give C_1

- *Decision 2:*

  If patient responded and baseline WBC $<$ 11.2, current WBC $<$ 10.5, no grade 3+ hematologic adverse event, current ECOG Performance Status $\leq$ 2, give maintenance M_1, otherwise, give M_2; otherwise

  If patient did not respond and age $>$60, current WBC $<$ 11.0, ECOG $\geq$ 2 give salvage S_1, otherwise, give S_2.

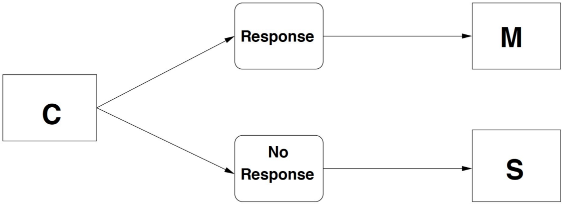
1. Introduction

Basic situation

For most of this course:

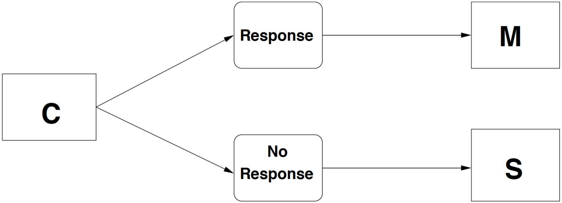
- $K \geq 1$ decision points at which a treatment must be selected from among a set of available, feasible options indexed by $k = 1, \ldots, K$
- $\mathcal{A}_k$ is the set of all available treatment options at Decision k
- a_k is an option in $\mathcal{A}_k$; i.e., $a_k \in \mathcal{A}_k$
- $\mathcal{A}_k$ contains a finite number of options, e.g., distinct therapies or interventions, specific doses of a drug ($\mathcal{A}_k$ infinite is relevant to, e.g., treatment options being doses of a drug in a continuous range of possible doses)
- Not all options in $\mathcal{A}_k$ need be feasible for all patients (to be discussed formally later)

$K = 2$: Acute leukemia



- *At baseline:* Information x_1, history $h_1 = x_1 \in \mathcal{H}_1$, e.g., x_1 = { demographic, physiologic, and clinical variables; prior medical history; genetic and genomic information; etc }
- *Decision 1:* Set of options $\mathcal{A}_1 = \{C_1, C_2\}$, rule $d_1(h_1)$, $d_1 : \mathcal{H}_1 \to \mathcal{A}_1$
- *Between Decisions 1 and 2:* Additional information x_2, including responder status; e.g., x_2 = { updated measures of clinical variables, evolving marker values, indicators of occurence of and timing of adverse events, response status }

$K = 2$: Acute leukemia



- *Accrued information/history:* $h_2 = (x_1$, therapy at Decision 1, $x_2) \in \mathcal{H}_2$
- *Decision 2:* Set of options $\mathcal{A}_2$ = {M$_1$,M$_2$,S$_1$,S$_2$}, rule $d_2(h_2)$, d_2: $\mathcal{H}_2 \rightarrow \mathcal{A}_2$ such that

$$d_2(h_2) \text{ takes values in } \{\text{M}_1,\text{M}_2\} \ (h_2 \text{ indicates responder}),$$

$$d_2(h_2) \text{ takes values in } \{\text{S}_1,\text{S}_2\} \ (h_2 \text{ indicates nonresponder})$$

- *Treatment regime:* $d = \{d_1(h_1), d_2(h_2)\} = (d_1, d_2)$

K decision treatment regime

In general:

- *Baseline information* $x_1 \in \mathcal{X}_1$, *intermediate information* $x_k \in \mathcal{X}_k$ between Decisions $k-1$ and k, $k = 2, \ldots, K$
- *Treatment options* $\mathcal{A}_k$ at Decision k, elements $a_k \in \mathcal{A}_k$, $k = 1, \ldots, K$
- *Accrued information* or *history*

$$
\begin{aligned}
h_1 &= x_1 \in \mathcal{H}_1 \\
h_k &= (x_1, a_1, \ldots, x_{k-1}, a_{k-1}, x_k) \in \mathcal{H}_k, \quad k = 2, \ldots, K,
\end{aligned}
\tag{1.1}
$$

- *Decision rules* $d_1(h_1), d_2(h_2), \ldots, d_K(h_K)$, $d_k : \mathcal{H}_k \rightarrow \mathcal{A}_k$
- *Treatment regime*

$$
d = \{d_1(h_1), \ldots, d_K(h_K)\} = (d_1, d_2, \ldots, d_K)
$$

“Overbar” notation

Convenient later: Define

$$\overline{x}_k = (x_1, \ldots, x_k), \quad \overline{a}_k = (a_1, \ldots, a_k), \quad k = 1, \ldots, K$$

- $\overline{x}_k \in \overline{\mathcal{X}}_k = \mathcal{X}_1 \times \cdots \times \mathcal{X}_k$
- $\overline{a}_k \in \overline{\mathcal{A}}_k = \mathcal{A}_1 \times \cdots \times \mathcal{A}_k$
- $\overline{x} = \overline{x}_K$, $\overline{a} = \overline{a}_K$
- $h_k = (\overline{x}_k, \overline{a}_{k-1})$

Problems with static regimes, revisited

In many settings: Static regimes are impossible/unethical, as in acute leukemia ($K = 2$)

- *Decision 1:* Example static rule "Give induction therapy C_1" (regardless of a patient's characteristics)

$$d_1(h_1) = \mathrm{C}_1 \quad \text{for all } h_1$$

- *Decision 2:* A static rule is impossible; any reasonable rule must take account of response status; i.e.,

$$d_2\colon \mathcal{H}_2 \rightarrow \{\mathrm{M}_1, \mathrm{M}_2\} \text{ (h_2 indicates responder)},$$

$$d_2\colon \mathcal{H}_2 \rightarrow \{\mathrm{S}_1, \mathrm{S}_2\} \text{ (h_2 indicates nonresponder)}$$

Optimal treatment regime

Again: The goal of a clinician is make the " best" decisions leading to the most beneficial expected outcome for a patient

- For a given problem with K decision points, there is an infinitude of possible regimes d
- $\mathcal{D}$ = class of all possible K decision treatment regimes
- A key goal of precision medicine is thus to identify an *optimal treatment regime*

$$d^{opt} \in \mathcal{D}$$

  among all regimes in $\mathcal{D}$, where the rules in d^{opt} lead to the "best" decisions, so to the most beneficial expected outcome
- Required: a formal definition of an optimal regime d^{opt}

Will distinguish later between: Best decisions vs. best treatment options

1. Introduction

Conventional evaluation of treatments

Goal: Given a health outcome of interest, single decision

- What is the expected outcome if a treatment option were used to treat the entire patient population?
- How does it compare to the expected outcome for a competing option? Is there a clinically meaningful difference?
- Given suitable *data*, estimate this expected outcome for each option and compare (using statistical methods)
- *Causal inference*

Data sources:

- A *clinical trial* in which subjects are *randomized* to each option – the “gold standard” data resource
- An *observational study* in which options are selected at physician or patient discretion – likely misleading due to *confounding*; e.g., sicker patients are more likely to receive one option over the other

Evaluation of treatment regimes, $K \geq 1$

Goal: Given a specific health outcome of interest

- What is the expected outcome if the entire patient population were to receive treatment according to the rules in a regime d?
- How does it compare to the expected outcome for a competing regime d', say?
- Given suitable data, estimate the expected outcome of any regime and compare (using statistical methods)
- *Causal inference*

Optimal regime:

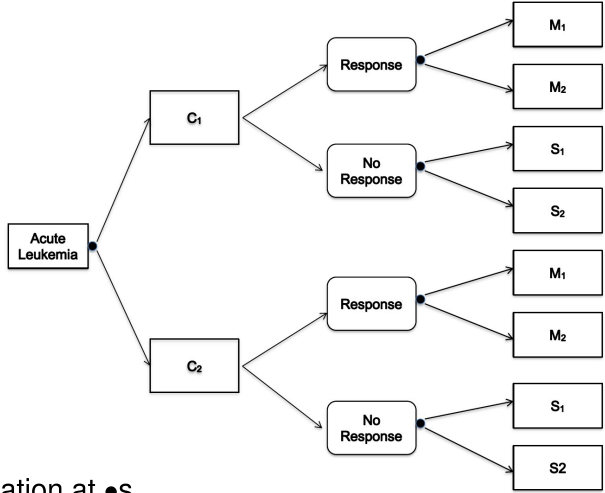
- Intuitively: If the entire patient population were to receive treatment according to the rule(s) in an optimal regime, the expected outcome should be most favorable
- Goal: Estimate an optimal regime satisfying this and the associated expected outcome from suitable data

Evaluation of treatment regimes, $K > 1$

What are suitable data when $K > 1$?

- Cannot "piece together" data from separate trials or observational studies at each decision point – treatment options administered at earlier decisions may have "delayed effects"
- That is, early treatments may have effects that do not manifest immediately and thus have implications for selection of later treatments
- Accounting appropriately for delayed effects requires data on the same set of subjects through all K decisions
- Data from longitudinal, *observational studies* involve *time-dependent confounding* (later)
- An appropriate *clinical trial*: Sequential multiple assignment randomized trial (SMART) – subjects are *randomized* at each decision point

Example: SMART for acute leukemia



Randomization at •s

Plan for the course

- Review of causal inference in the simplest setting of a point exposure study
- Development and evaluation of single decision regimes, including characterization and estimation of optimal regimes
- Development and evaluation of multiple decision regimes, including including characterization and estimation of optimal regimes
- Design and analysis of SMARTs
- Statistical inference on optimal regimes, additional topics

Disclaimer

Simplification:

- To avoid having measure-theoretic considerations distract from appreciation of the conceptual foundations in theoreical arguments, we often treat random variables that may be continuous or discrete as discrete without comment
- The arguments of course can be generalized under appropriate conditions