Precision Medicine Through Treatment Regimes, SMARTs, and Statistics

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Precision medicine

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

Clinical decision-making:
- Key *decision points* in the disease/disorder process
- Multiple *treatment options* at each
- A *patient’s characteristics* are implicated in which *treatment options* s/he should receive
Example: Acute leukemia

Two decision points:

- **Decision 1**: Induction chemotherapy (2 options: C₁, C₂)
- **Decision 2**:
  - Maintenance treatment for patients who *respond* (2 options: M₁, M₂)
  - Salvage chemotherapy for those who *don’t respond* (2 options: S₁, S₂)
Example: Children with ADHD

Two decision points:

- **Decision 1**: Initial intervention
  (2 options: medication, behavioral therapy)

- **Decision 2**:
  - Continue initial intervention for children who *respond*  
    (1 option: continue)
  - Modify initial intervention for those who *don't respond*  
    (2 options: increase dose/intensify, add second intervention)
Clinical decision-making

How are treatment decisions made?

- *Clinical judgment, practice guidelines*
- 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 leading to the *most beneficial expected outcome* for the patient

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

- Evidence-based *decision support*
Informing clinical decision-making

At any decision point: Would like a rule that takes as input all available information on the patient to that point and outputs a recommended treatment action from among the possible options.
Informing clinical decision-making

Simplest rules: Take as input no or minimal patient information
  - E.g., acute leukemia
  - Decision 1: Give $C_1$
  - Decision 2: If response, give $M_2$, if nonresponse, give $S_1$
  - Not consistent with precision medicine

Individualized rules: More complex rules incorporating patient information
  - “Tailoring variables”
  - Consistent with precision medicine
Example of individualized rules: Acute leukemia

- **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 $S_1$, otherwise, give $S_2$
Treatment regime: Aka *adaptive treatment strategy/intervention*

- A *set of decision rules*, each corresponding to a *decision point*
- Can be *simple* or *individualized/highly tailored*
- Defines an *algorithm* for treating an individual patient

Premise:

- Development of *individualized treatment regimes* based on *data* can *inform* clinical decision-making and make it *evidence-based*
- *Precision medicine*
Single decision

Assume: There is an outcome of interest, e.g., survival time, achievement score

- *Large* outcomes are *good*
- $X =$ all *available information* on the patient
- Set of *treatment options*, e.g., $\{C_1, C_2\} = \{0, 1\}$

Treatment regime $d$: Comprises a rule $d_1(X)$ such that

$$d_1(X) = 0 \text{ or } 1 \text{ depending on } X$$

- Regime $d = \{d_1\}$
- Can be generalized to $> 2$ treatment options
Treatment regime

\[ d_1(X) = 0 \text{ or } 1 \text{ depending on } X \]

**Example regimes**: \( X = \{ \text{age, WBC, ECOG, AE, \ldots} \} \)

- Rule involving *cut-offs* or *thresholds*
  \[
  d_1(X) = 1 \text{ (C}_2) \text{ if age } < 50 \text{ and WBC } < 10 \\
  = 0 \text{ (C}_1) \text{ otherwise}
  \]
  written *mathematically* as
  \[
  d_1(X) = \mathbb{I}(\text{age } < 50 \text{ and WBC } < 10)
  \]

- Rule involving *linear combinations*
  \[
  d_1(X) = \mathbb{I}\{\text{age } + 8.7 \log(\text{WBC}) - 60 > 0\}
  \]
Defining an optimal regime

Clearly: An infinite number of rules $d_1$ and thus regimes $d$ is possible

- The class of all possible regimes $\mathcal{D}$ is infinite
- Can we find the “best” regime in $\mathcal{D}$?
- I.e., an optimal regime $d^{opt}$ among all possible $d$?
- What do we mean by optimal?

Optimal decision at the time a patient presents:

- Everything the clinician knows about a patient is contained in $X$
- Intuitively: For a patient with a particular set of information $X$, the optimal decision is to give the treatment makes the expected/predicted outcome for such a patient as large as possible
Defining an optimal regime

Can we formalize this?

- I.e., give a precise definition of an optimal regime $d^{opt}$
- Possible through a formal \textit{statistical causal inference framework} based on \textit{potential outcomes}
- And suggests how to \textit{estimate} an optimal regime from \textit{data}
Causal inference framework

Potential outcomes: For a patient with information $X$ define

- $Y^*(1)$ is the outcome a patient would have under treatment 1
- $Y^*(0)$ similarly

- For any regime $d$ characterized by rule $d_1$, the outcome a patient would have if treatment were chosen using $d$ is

$$Y^*(d) = Y^*(1) I\{d_1(X) = 1\} + Y^*(0) I\{d_1(X) = 0\}$$

- For any regime $d$, $E\{Y^*(d)\}$ is the expected (average) outcome across the entire population if all patients were to follow $d$

- $d^{opt}$ is defined as the regime making $E\{Y^*(d)\}$ as large as possible; i.e.,

$$E\{Y^*(d^{opt})\} \geq E\{Y^*(d)\} \quad \text{for all } d \in D$$
Estimating an optimal regime

**Evidence-based:** Can we *estimate* $d^{opt}$ satisfying this definition based on *data*? 
- I.e., estimate rule $d^{opt}_i(X)$ characterizing $d^{opt}$

**Data:** $(X, A, Y)$ from $n$ patients
- $X =$ recorded *baseline characteristics*
- $A =$ treatment option *actually received*
- $Y =$ outcome *actually observed* under treatment $A$
- $Y = Y^*(A)$
Estimating an optimal regime

Data sources:

- A conventional *randomized clinical trial* comparing treatment options 0 and 1
- An *observational point exposure study* of treatments 0 and 1 satisfying the assumption of *no unmeasured confounders*
- I.e., all characteristics used by clinicians/patients to make treatment decisions are *captured in* $X$

\[ Y^*(0), Y^*(1) \perp A \mid X \]
Estimating an optimal regime

Under these conditions: Can show for any regime \( d = \{d_1\} \)

\[
E\{Y^*(d)\} = E_X\left[ E(Y|X, A = 1)\mathbb{I}\{d_1(X) = 1\} + E(Y|X, A = 0)\mathbb{I}\{d_1(X) = 0\} \right]
\]

- \( E(Y|X, A = 1) \) is the expected/predicted observed outcome for a patient with characteristics \( X \) who receives treatment \( A = 1 \)
- \( E(Y|X, A = 0) \) similarly

Optimal regime \( d^{opt} \) has rule:

\[
d_1^{opt}(X) = \begin{cases} 
0 & \text{if } E(Y|X, A = 1) \leq E(Y|X, A = 0) \\
1 & \text{if } E(Y|X, A = 1) > E(Y|X, A = 0)
\end{cases}
\]

- Chooses the option that makes expected/predicted outcome for a patient with characteristics \( X \) as large as possible
Estimating an optimal regime

\[
d_{1}^{\text{opt}}(X) = \begin{cases} 
0 & \text{if } E(Y|X, A = 1) \leq E(Y|X, A = 0) \\
1 & \text{if } E(Y|X, A = 1) > E(Y|X, A = 0) 
\end{cases}
\]

- \(E(Y|X, A)\) is the \textit{regression} of observed outcome on characteristics and treatment option received

**Suggests:** Develop a \textit{regression model} and \textit{fit} to the data

- E.g., if \(X^{(1)}, X^{(2)}\) are functions of \(X\), a \textit{linear regression} model (need \textit{not} be linear)

\[
E(Y|X, A) = \alpha_0 + \alpha_1^T X^{(1)} + A(\beta_0 + \beta_1^T X^{(2)})
\]

- Or a \textit{logistic regression} model

\[
\text{logit}\{ E(Y|X, A) \} = \alpha_0 + \alpha_1^T X^{(1)} + A(\beta_0 + \beta_1^T X^{(2)})
\]
Estimating an optimal regime

$$d_{1}^{opt}(X) = \begin{cases} 
0 & \text{if } E(Y|X, A = 1) \leq E(Y|X, A = 0) \\
1 & \text{if } E(Y|X, A = 1) > E(Y|X, A = 0) 
\end{cases}$$

Models imply: Form of rules (algebra)

$$d_{1}^{opt}(X) = \begin{cases} 
0 & \text{if } \beta_0 + \beta_1^T X^{(2)} \leq 0 \\
1 & \text{if } \beta_0 + \beta_1^T X^{(2)} > 0 
\end{cases}$$

Estimated optimal rule: Substitute estimates for $\beta_0, \beta_1$

$$\hat{d}_{1}^{opt}(X) = I(\hat{\beta}_0 + \hat{\beta}_1^T X^{(2)} > 0)$$

Fancier models: The same idea applies to more flexible models, such as those from machine learning
Estimating an optimal regime

Other approaches:

- Restrict attention to a class of regimes with rules of a particular form \( d_1(X; \eta_1) \), e.g., acute leukemia

\[
d_1(X; \eta_1) = \mathcal{I}(\text{age } < \eta_{11} \text{ and WBC } < \eta_{12}), \quad \eta_1 = (\eta_{11}, \eta_{12})
\]

and maximize an estimator for \( E\{Y^*(d)\} \) directly in \( \eta \)

- Can choose the restricted class of regimes for interpretability, ease of implementation, etc

- Can recast this as a classification problem and use established machine learning methods to determine the form of the rule (e.g., SVM, CART)

- Estimated optimal rule is a "black box"

- Can be considered a form of artificial intelligence
Result: From any of these approaches

- An estimated *evidence-based optimal regime* based on *formal statistical principles* that can be used to inform selection of treatment
- Provides *evidence-based decision support*
- Insight on *key characteristics (tailoring variables)* that should be incorporated in decision-making
Example: Acute leukemia

Two decision points:

- **Decision 1**: Induction chemotherapy (2 options: C₁, C₂)
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  - Salvage chemotherapy for those who *don’t respond* (2 options: S₁, S₂)
Multiple decisions

Two decisions (leukemia example):

- **Decision 1:** $X_1 = \text{information available at baseline, set of treatment options, e.g., } \{C_1, C_2\}$
- **Decision 2:** $X_2 = \text{additional information collected between Decisions 1 and 2, treatment options, e.g., } \{M_1, M_2, S_1, S_2\}$
- $X_2$ includes responder status

**Regime:** A set of rules $d = \{d_1, d_2\}$

- $d_1(X_1)$ dictates treatment at Decision 1 given information available at that point, $X_1$
- $a_1$ is treatment determined by $X_1$ at Decision 1, i.e., $d_1(X_1)$
- $d_2(X_1, a_1, X_2)$ dictates treatment at Decision 2 given all accrued information at that point, $(X_1, a_1, X_2)$
Optimal regime $d^{opt}$: Intuitively, should satisfy

- If a patient with baseline characteristics $X_1$ were to receive treatment at all decisions according to the rules in

$$d^{opt} = \{d_1^{opt}, d_2^{opt}\},$$

his/her expected/predicted outcome is as large as possible.
Optimal multiple decision regime

**Defined in terms of potential outcomes:** For options $a_1$ and $a_2$ at Decisions 1 and 2

- $X_2^*(a_1)$ is the *potential information* accruing on a patient following $a_1$ at Decision 1
- $Y^*(a_1, a_2)$ is the outcome a patient *would have* following $a_1$ at Decision 1 and $a_2$ at Decision 2
- If a patient were to *follow* the rules in regime $d$
  - Treatment at Decision 1 is *determined by* $X_1$, $a_1 = d_1(X_1)$
  - Treatment at Decision 2 is *determined by* $X_1$ and $X_2^*(a_1)$, $a_2 = d_2\{X_1, a_1, X_2^*(a_1)\}$
- $Y^*(d)$ is the outcome a patient *would have* if treatments $a_1$ and $a_2$ at Decisions 1 and 2 were chosen using $d$

**Optimal regime:** $d^{opt}$ makes $E\{Y^*(d)\}$ as large as possible
Can we estimate $d^{opt}$ from data?

- Can we use *data* and *regression modeling* at *each decision point* as before?
- I.e., consider each decision *separately* and use data from *separate* studies comparing the options at each?
- *Not quite*...
Complications for multiple decisions

Delayed effects: For example

- \( C_1 \) may not appear best initially in terms of response but may have enhanced effectiveness over the long term for survival when followed by \( M_1 \)
- Result – Must use data from a single study (same patients) reflecting the entire sequence of decisions

Required data: \((X_1, A_1, X_2, A_2, Y)\) recorded from \(n\) patients

- \( A_1 \) = treatment actually received at Decision 1
- \( A_2 \) = treatment actually received at Decision 2
- \( X_2 \) = intervening information actually observed
- \( Y \) = outcome actually observed
- \( Y = Y^*(A_1, A_2) \)
**Longitudinal observational study:**

- Records baseline, intervening information and treatments actually received
- **Challenge:** All characteristics used by clinicians/patients to select treatment options *at all decisions* must be captured in $X_1, X_2$
- Must satisfy a *no unmeasured confounders* assumption at *every* decision point

**Clinical trial?**
SMART: Sequential, Multiple Assignment, Randomized Trial

- Randomize subjects at each decision point
- Record treatments $A_1$ and $A_2$ received
- Collect not only baseline information $X_1$ but intervening information $X_2$

Advantages:

- Allows evaluation of simple regimes (treatment sequences)
- Yields rich data for estimation of an optimal treatment regime

Pioneered by Susan Murphy, Phil Lavori, and others
Acute Leukemia: Randomization at $s$

SMART

Cancer

$C_1$

$C_2$

Response

No Response

Response

No Response

$M_1$

$M_2$

$S_1$

$S_2$
Two decision points:

- **Decision 1**: Initial intervention
  (2 options: medication, behavioral therapy)

- **Decision 2**:
  - Continue initial intervention for children who *respond*
    (1 option: continue)
  - Modify initial intervention for those who *don’t respond*
    (2 options: increase dose/intensify, add second intervention)
Children with ADHD: Randomization at

**ADHD**

- **Medication**
  - Response
    - Continue Medication
  - No Response
    - Increase Medication Dose
    - Add Behavioral Therapy

- **Behavioral Therapy**
  - Response
    - Continue Behavioral Therapy
  - No Response
    - Intensify Behavioral Therapy
    - Add Medication
Embedded regimes in a SMART

Leukemia SMART: *Embeds* 8 simple regimes/sequences

1. *Give C*$_1$ followed by *M*$_1$ if response, else *S*$_1$ if nonresponse
2. *Give C*$_1$ followed by *M*$_1$ if response, else *S*$_2$ if nonresponse

7. *Give C*$_2$ followed by *M*$_2$ if response, else *S*$_1$ if nonresponse
8. *Give C*$_2$ followed by *M*$_2$ if response, else *S*$_2$ if nonresponse
Embedded regimes in a SMART

**ADHD SMART:** Similarly *embeds* 4 simple regimes

1. *Medication followed by increased dose if nonresponse, else continue*
2. *Medication followed by added behavioral therapy if nonresponse, else continue*
3. *Behavioral therapy followed by intensified behavioral therapy if nonresponse, else continue*
4. *Behavioral therapy followed by added medication if nonresponse, else continue*

- In a SMART, *randomization* guarantees there will be subjects whose *actual treatments received* are *consistent with* following *all* of the embedded regimes
- Allows evaluation and comparison of *treatment sequences*
Estimating an optimal regime

Data sources, again:

- **SMART**: Collection of extensive, detailed information at baseline and intermediate to Decisions 1 and 2 supports estimation of an optimal regime
- **Longitudinal observational study**: Depends on quality of information available

Estimating $d^{opt}$: $d^{opt} = \{ d^{opt}_1(X_1), d^{opt}_2(X_1, A_1, X_2) \}$

- Start at the final decision and work backward
- Backward induction
Sequential regression (Q-learning)

**Decision 2:** *Given* the patient’s *accrued history to this point*, determine the *optimal rule* to be used *now*

- **Decision 2 options coded** \{0, 1\}; can show

\[
d_2^{opt}(X_1, A_1, X_2) =
\begin{cases} 
0 & \text{if } E(Y|X_1, A_1, X_2, A_2 = 1) \leq E(Y|X_1, A_1, X_2, A_2 = 0) \\
1 & \text{if } E(Y|X_1, A_1, X_2, A_2 = 1) > E(Y|X_1, A_1, X_2, A_2 = 0)
\end{cases}
\]

- **\( E(Y|X_1, A_1, X_2, A_2) \)** is the *regression* of outcome on both treatments and all accrued characteristics

- Can develop and fit a *regression model* and *estimate* \( d_2^{opt}(X_1, A_1, X_2) \) as before
Sequential regression (Q-learning)

Decision 1: Trickier

- Decision 1 options coded \{0, 1\}
- Must take into account that the *optimal rule* at Decision 2 will be followed *in the future*
- I.e., \(d_1^{opt}(X_1)\) must select treatment at Decision 1 to make the *expected/predicted outcome* as large as possible *acknowledging that* \(d_2^{opt}(X_1, A_1, X_2)\) will be used to determine treatment at Decision 2
- Best explained by *illustration*
Sequential regression (Q-learning)

Illustration:

- Develop a *regression model* for Decision 2, e.g.,

\[
E(Y|X_1, A_1, X_2, A_2) = \alpha_{20} + \alpha_{21}^{T}X_1^{(1)} + \alpha_{22}^{T}X_2^{(1)} + \alpha_{23}^{T}X_1^{(1)}A_1 \\
+ A_2(\beta_{20} + \beta_{21}^{T}X_2^{(2)} + \beta_{22}A_1),
\]

*fit* to the data \((X_1, A_1, X_2, A_2, Y)\) from \(n\) subjects, and *estimate*

\[
\hat{d}_{2}^{opt}(X_1, A_1, X_2) = I(\hat{\beta}_{20} + \hat{\beta}_{21}^{T}X_2^{(2)} + \hat{\beta}_{22}A_1 > 0)
\]

- For each subject, obtain

\[
\tilde{A}_2 = \hat{d}_{2}^{opt}(X_1, A_1, X_2),
\]

the estimated *optimal treatment option* at Decision 2 (*may or may not be the same* as \(A_2\) actually received by the subject)
Sequential regression (Q-learning)

Illustration:

- For each subject, form $\tilde{Y}$, the estimated predicted outcome s/he would have if the optimal option $\tilde{A}_2$ were received at Decision 2

$$
\tilde{Y} = \tilde{\alpha}_2 + \tilde{\alpha}_2^T X_1^{(1)} + \tilde{\alpha}_2^T X_2^{(1)} + \tilde{\alpha}_2^T X_1^{(2)} A_1 + \tilde{A}_2 (\tilde{\beta}_2 + \tilde{\beta}_2^T X_2^{(2)} + \tilde{\beta}_2 A_1)
$$

- Develop a regression model for Decision 1 with $\tilde{Y}$ as the “outcome,” e.g.,

$$
E(\tilde{Y} | X_1, A_1) = \alpha_{10} + \alpha_1^T X_1^{(1)} + A_1 (\beta_{10} + \beta_{11}^T X_1^{(2)}),
$$

fit to the “data” $(X_1, A_1, \tilde{Y})$ from $n$ subjects, and estimate

$$
\hat{\alpha}_1^{opt} (X_1) = I(\hat{\beta}_{10} + \hat{\beta}_{11}^T X_1^{(2)} > 0)
$$

- Fancier models are possible (e.g., flexible machine learning)
Estimating an optimal regime

Other approaches:

- Restrict attention to a class of regimes with rules of a particular form $d_1(X_1; \eta_1)$ and $d_2(X_1, A_1, X_2; \eta_2)$ and maximize an estimator for $E\{ Y^*(d) \}$ directly in $\eta$
- Can choose the restricted class of regimes for interpretability, ease of implementation, etc
- Can recast estimation at each decision as a classification problem and use established machine learning methods to determine the form of the rules at each decision (e.g., SVM, CART)
- Estimated optimal rules are “black boxes”
- Can be considered a form of artificial intelligence
Evidence-based decision support

Result: From any of these approaches

- An *evidence-based regime* based on *formal statistical principles* that can be used to inform selection of treatment at each decision point
- Provides *evidence-based decision support*
- Insight on *key characteristics (tailoring variables)* that should be incorporated at each decision point
How best to use behavioral interventions to manage cancer patients’ pain?

- **Pain Coping Skills Training (PCST)** – can be *brief* (1 session) or *full* (5 sessions); which is better!
- Further intervention for *responders*? Maintain or intensify for *nonresponders*?
- **Ideally**: Use more *time- and resource-intensive interventions* only for those who need them
- What is the best *intervention sequence*?
- **Optimal intervention regime**?
Optimizing behavioral cancer pain intervention

Figure 1. Trial Design with Focus on Randomization Pattern. (Figure 2 includes full assessment scheme.)

R01 CA202779, PI: Tamara Somers, Duke University Psychiatry and Behavioral Sciences
Optimizing behavioral cancer pain intervention

Eight embedded regimes: First four intervention sequences

1. Start with PCST-Full, PCST-Plus (augment) if nonresponse, PCST-Full maintenance (continue) if response
2. Start with PCST-Full, PCST-Plus (augment) if nonresponse, nothing further if response
3. Start with PCST-Full, PCST-Full maintenance (continue) if nonresponse, PCST-Full maintenance (continue) if response
4. Start with PCST-Full, PCST-Full maintenance (continue) if nonresponse, nothing further if response

Aims:

- Primary analysis: Compare Decision 1 treatments (PCST-Full vs Brief) based on response
- Secondary analysis: Compare embedded regimes on the based on final outcome(s)
- Exploratory analysis: Estimate an optimal regime
I-SPY 2+ platform trial in breast cancer

How to treat women with locally advanced breast cancer who do not respond to initial therapy?

- **I-SPY 2**: Adaptive phase II platform trial, *collaborative effort* of NCI, FDA, industry (FINH Biomarkers Consortium)

- *Adaptive randomization*: Assign as many participants as possible to better options based on data from previous participants

- **I-SPY 2+**: Incorporate *SMART* with repeated randomization of nonresponders
I-SPY 2+ platform trial in breast cancer

P01 CA210961, PI: Laura Esserman, UCSF
Parent messaging and student attendance

October to Mid-December

At Risk Child

Basic Informational Messaging I

Basic Informational Messaging II

Business As Usual (Control)

No Response

Response

Continue BIM I

Augment BIM I

Intensify BIM I

No Response

Response

Continue BIM II

Augment BIM II

Intensify BIM II

January to June

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Precision Medicine Through Regimes/SMARTs/Statistics
Issues

- Flexibility versus interpretability? Machine learning approaches lead to “black boxes” but interpretability may sacrifice performance.
- What if more than one outcome is of interest? E.g., balancing efficacy and toxicity in cancer treatment?
- Design principles (e.g., sample size, primary analysis) for SMARTs? How to do adaptive randomization in a SMART?
- Assessment of uncertainty (e.g., standard errors)?
- Once an optimal regime is estimated, should it be compared to standard of care in a conventional clinical trial?
- Real-time regimes (mHealth)?
Discussion

- *Statistical research* is ongoing to address all of these issues (and is *way ahead* of what is actually being done in practice)
- Thinking in terms of sequential treatment decision making is *gaining acceptance*
- SMARTs and estimation of optimal treatment regimes are *becoming commonplace*

Treatment regimes and SMARTs to develop them are one major approach to achieving precision medicine
Available December 2019
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- Supported by NCI *Program Project* P01 CA142538 (2010–2020)

http://impact.unc.edu

- Statistical methods for *precision cancer medicine*
Thought leaders

Susan Murphy and Jamie Robins