The Right Treatment for the Right Patient (at the Right Time): A Perspective on Personalized Cancer Medicine

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Personalized medicine

“The right treatment for the right patient (at the right time)”

Source of graphic: http://www.personalizedmedicine.com/
The Precision Medicine Initiative: Data-Driven Treatments as Unique as Your Own Body

Lindsey Holt
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Watch Jo Handelsman, Associate Director for Science in the Office of Science and Technology Policy, explain the Precision Medicine Initiative and its significance.

http://www.whitehouse.gov/blog/2015/01/30/

precision-medicine-initiative-data-driven-treatments-unique-your-own-body
Why is a statistician talking to you about personalized medicine?
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Because statistics is critical to achieving personalized medicine!
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**IMPACT** – Innovative Methods Program for Advancing Clinical Trials
- A *joint venture* of Duke, UNC-Chapel Hill, NC State
- Supported by NCI *Program Project* P01 CA142538 (2010–2020)
  
  http://impact.unc.edu

- *Statistical methods* for *trial design* and *data analysis* for discovery of personalized cancer medicine
The randomized controlled clinical trial

“Gold standard” for

- Evaluation of *effectiveness*
- Comparison of a *new treatment* to standard of care
- Comparison of *existing treatments* to establish new uses
The randomized controlled clinical trial

Basics of a typical trial:

- A *sample* of subjects is recruited
- Subjects are *randomized* to treatments under study
  ⇒ eliminate *bias* due to *confounding*, allow *fair* comparison
- A (primary) *outcome* is ascertained for each subject
- E.g., in *cancer* clinical trials, *OS*, *DFS*, *PFS*, *response status*...
Assessment of effectiveness:

- Comparison of a *summary measure* of outcome between/among treatments
- E.g., the *average* (or *odds ratio* or *hazard ratio*...)
Assessment of effectiveness:

- Comparison of a *summary measure* of outcome between/among treatments
- E.g., the *average* (or *odds ratio* or *hazard ratio*...)
- “*Is the average outcome if all patients in the population were to take treatment A different from (better than) that if they all instead were to take treatment B?*”
- Use *statistical methods* to evaluate the *strength of the evidence* in the data from the sample supporting a *real difference* in the population (*statistical hypothesis test*)
Thus, usually:

- Assessment of *effectiveness* (and *regulatory approval*) are based on a *summary measure* (e.g., an average) *across the entire population*
- Countless treatments have been *evaluated* on this basis
- And have *benefited* numerous patients
Thus, usually:

- Assessment of *effectiveness* (and *regulatory approval*) are based on a *summary measure* (e.g., an average) *across the entire population*
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- And have *benefited* numerous patients

However:

- All patients are *not* created equal
Patient heterogeneity

**Sources of heterogeneity:**

- Demographic characteristics
- Physiological characteristics
- Medical history, concomitant conditions

Result:

What is "best" for a patient with one set of characteristics might not be "best" for another.

Well-recognized for centuries

Subgroup analyses

Interest skyrocketed with the advent of the genomic era
Patient heterogeneity

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- Demographic characteristics
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- Medical history, concomitant conditions
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- *Subgroup analyses*
- Interest skyrocketed with the advent of the *genomic era*
A contrived example

Average outcome in the patient population:

- Larger outcomes are better (survival time)
- If all patients took treatment A = 9 months
- If all patients took treatment B = 18 months
- Treatment B is better on average
A contrived example

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Genetic mutation:
- 20% have it, 80% don’t
A contrived example

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- 20% have it, 80% don’t
- If all patients took treatment A = (0.2)(25) + (0.8)(5) = 9
A contrived example

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Genetic mutation:

- 20% have it, 80% don’t
- If all patients took treatment A = (0.2)(25) + (0.8)(5) = 9
- If all patients took treatment B = (0.2)(10) + (0.8)(20) = 18
A contrived example

Average outcome in the patient population:

- Larger outcomes are better (survival time)
- If all patients took treatment A = 9 months
- If all patients took treatment B = 18 months
- *Treatment B is better on average*

Genetic mutation:

- 20% have it, 80% don’t
- If all patients took treatment A = \((0.2)(25) + (0.8)(5) = 9\)
- If all patients took treatment B = \((0.2)(10) + (0.8)(20) = 18\)
- That is, patients *with* the mutation do much better on treatment A (25 months vs. 10 months) on average
Personalized medicine

Moral:

- While useful for *evaluation* and *approval*, summary measures are *not useful* for determining how to treat individual patients
- Ad hoc search for *subgroups* could be misleading
- May be much more complicated than finding a *single* “*mutation*” (no “*magic bullet*”)

Needed: Principled, *evidence-based* approaches
Subgroup identification and targeted treatment:

- Can we determine subgroups of patients who share certain characteristics and who are likely to benefit from a particular treatment?
- Can biomarkers be developed to identify such patients?
- In fact, can a new treatment be developed to target a subgroup that is likely to benefit?
- Can clinical trials and approval be focused on particular subgroups of patients?
Popular perspective on personalized medicine

**Subgroup identification and targeted treatment:**

- Can we determine *subgroups* of patients who share certain characteristics and who are *likely* to benefit from a particular treatment?
- Can *biomarkers* be developed to identify such patients?
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- Can clinical trials and approval be *focused* on particular subgroups of patients?

**Focus:** “The right patient for the treatment”
Popular perspective on personalized medicine

Personalised medicine: future vision

Diagnostic test positive
likely to benefit from treatment

Diagnostic test negative
Unresponsive to therapy

Source of graphic: Christoph Meinel, Hasso-Plattner-Institut Potsdam
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
- Multiple treatment options at each
- Accrued information on the patient
- Goal: Make the “best” decision(s) for this individual patient
Clinical practice: Clinicians make a series of treatment decisions over the course of a patient’s disease or disorder

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Focus: “The right treatment for the patient”
Clinical practice: Clinicians make a series of treatment decisions over the course of a patient’s disease or disorder

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Focus: “The right treatment for the patient”

This is the perspective we will consider
Acute leukemias

Two decision points:

- **Decision 1**: Induction chemotherapy (C)
- **Decision 2**: Maintenance treatment (M) for patients who respond, Salvage chemotherapy (S) for those who don’t respond
- Several options for each
- **Goal**: Prolong survival (outcome)
Clinical decision-making

How are these decisions made?

- **Clinical judgment**
- *Practice guidelines* based on *previous studies, expert opinion*
Clinical decision-making

How are these decisions made?

- Clinical judgment
- Practice guidelines based on previous studies, expert opinion
- Synthesis of all accrued information on characteristics of the patient up to the time of each decision to select a treatment from among the possible options
Clinical decision-making

How are these decisions made?

- Clinical judgment
- Practice guidelines based on previous studies, expert opinion
- Synthesis of all accrued information on/characteristics of the patient up to the time of each decision to select a treatment from among the possible options

Can we formalize clinical decision-making and make it evidence-based?
Acute leukemias

Two decision points

- **Decision 1**: Two induction chemotherapy options $C_1$, $C_2$
- **Decision 2**: Two maintenance options $M_1$, $M_2$ for patients who *respond*, two salvage options $S_1$, $S_2$ for those who *don’t*
- **Goal**: Prolong survival (outcome)
Formalizing clinical decision-making: At any decision

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

- Would like a formal rule that takes as input all available information on the patient to that point and outputs a treatment from among the possible options
- Decision 1: “If age < 50 years and WBC < 10.0 × 10^3/µl, give chemotherapy C_2; otherwise, give C_1”
Formalizing clinical decision-making: At any decision

- Would like a formal rule that takes as input all available information on the patient to that point and outputs a treatment from among the possible options
- Decision 1: “If age < 50 years and WBC < 10.0 \times 10^3 / \mu l, give chemotherapy C_2; otherwise, give C_1”

(Dynamic) treatment regime(n): Aka adaptive treatment strategy or sequential decision strategy

- A set of such rules, each corresponding to a decision point
- Can we discover rules based on data?
**First:** Focus *myopically* on a *single decision point* to fix ideas.
Single decision

First: Focus *myopically* on a *single decision point* to fix ideas

Assume:

- There is an *outcome* of interest, $Y$, e.g., survival time
- *Large* outcomes are *good*
- $X =$ all *available information* on the patient
- Set of *treatment options*, e.g., $\{C_1, C_2\} = \{0, 1\}$
Single decision

First: Focus *myopically* on a *single decision point* to fix ideas

Assume:

- There is an *outcome* of interest, \( Y \), e.g., survival time
- *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: A single *rule* of the form \( d(X) \) such that

\[
d(X) = 0 \text{ or } 1 \text{ depending on } X
\]
Treatment regime

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

Example regimes: \( X = \{\text{age, WBC}\} \)
Treatment regime

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

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

- Rule involving *cut-offs*

\[
\begin{align*}
d(X) &= 1 \text{ (C}_2\text{)} \text{ if } \text{age} < 50 \text{ and } \text{WBC} < 10 \\
&= 0 \text{ (C}_1\text{)} \text{ otherwise}
\end{align*}
\]
Treatment regime

\[ d(X) = \begin{cases} 0 \text{ or } 1 \text{ depending on } X \end{cases} \]

Example regimes: \( X = \{ \text{age, WBC} \} \)

- Rule involving \textit{cut-offs}

\[ d(X) = \begin{cases} 1 \ (C_2) \text{ if age < 50 and WBC < 10} \\ 0 \ (C_1) \text{ otherwise} \end{cases} \]

- Rule involving a \textit{linear combination}

\[ d(X) = \begin{cases} 1 \ (C_2) \text{ if age + 8.7 \log(WBC) - 60 > 0} \\ 0 \ (C_1) \text{ otherwise} \end{cases} \]
Clearly: An *infinitude* of rules/regimes $d(X)$ are possible

- Can we find the “*best*?”
- That is, “*best*” or *optimal*, regime $d^{opt}(X)$ among all possible $d(X)$?
Defining the optimal regime

Clearly: An *infinitude* of rules/regimes $d(X)$ are possible

- Can we find the “*best*”?
- That is, “*best*” or *optimal*, regime $d^{opt}(X)$ among all possible $d(X)$?
- What do we mean by “*best*”?

What we can’t do: Know the “*best*” treatment option for any patient
Defining the optimal regime

Make the “best” decision at the time a patient presents:

- For a patient with a *particular set of information* $X$, the “best decision” is to give the treatment option that leads to the *largest expected outcome* for such a patient.
Defining the optimal regime

Make the “best” decision at the time a patient presents:

- For a patient with a particular set of information $X$, the “best decision is to give the treatment option that leads to the largest expected outcome for such a patient.

Thus: Optimal rule $d^{opt}$ should satisfy

- If a patient with information $X$ were to receive treatment using $d^{opt}$, his/her expected outcome is as large as possible.
Defining the optimal regime

Make the “best” decision at the time a patient presents:

- For a patient with a particular set of information $X$, the “best” decision is to give the treatment option that leads to the largest expected outcome for such a patient.

Thus: Optimal rule $d^{opt}$ should satisfy

- If a patient with information $X$ were to receive treatment using $d^{opt}$, his/her expected outcome is as large as possible.

- And if all patients in the population were to use $d^{opt}$, the expected (average) outcome across the entire population would be as large as possible.
Defining the optimal regime

**Expected outcome:** \( A = \) treatment received

\[ E(Y|X, A) \]

is the *expected outcome* for a patient with characteristics \( X \) were s/he to receive treatment \( A \)

- *With two options \( \{0, 1\} \):*

  \[
  d^{opt}(X) = \begin{cases} 
  0 & \text{if } E(Y|X, A = 1) < E(Y|X, A = 0) \\
  1 & \text{if } E(Y|X, A = 1) > E(Y|X, A = 0)
  \end{cases}
  \]
Defining the optimal regime

Expected outcome: $A = $ treatment received

$E(Y|X, A)$ is the expected outcome for a patient with characteristics $X$ were s/he to receive treatment $A$

- With two options $\{0, 1\}$:
  
  $$d^{opt}(X) = \begin{cases} 
  0 & \text{if } E(Y|X, A = 1) < E(Y|X, A = 0) \\
  1 & \text{if } E(Y|X, A = 1) > E(Y|X, A = 0) 
  \end{cases}$$

- $E(Y|X, A)$ is the regression of outcome on characteristics and treatment received (expected outcome given $X$ and $A$)
Estimating the optimal regime

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

Result: Fit a regression model to data on \((X, A, Y)\) and substitute the fitted model in the above to estimate \(d^{opt}(X)\)
Estimating the optimal regime

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

**Result:** Fit a *regression model* to data on \((X, A, Y)\) and *substitute* the fitted model in the above to *estimate* \(d^{\text{opt}}(X)\)

- For example, a *linear regression model*
  \[ E(Y|X, A) = \alpha_0 + \alpha_1 X + A\alpha_2 + \alpha_3 AX \]

- *Logistic regression model*, other *fancier* models
Data

**Required data:** Recorded \((X, A, Y)\) from \(N\) patients

- *Conventional clinical trial* comparing treatments 0 and 1, *baseline* information \(X\)
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- Exploit *statistical methods* for *regression modeling* and *fitting*
**Required data:** Recorded \((X, A, Y)\) from \(N\) patients

- *Conventional clinical trial* comparing treatments 0 and 1, *baseline* information \(X\)
- *Observational database* (e.g., epi/medical registry)
- Exploit *statistical methods* for *regression modeling* and *fitting*
- ... and adjustment for *confounding* with *observational data*
- \(X\) *must include* all characteristics that *clinicians used* in making treatment decisions
Acute leukemias

Two decision points

- **Decision 1**: Two induction chemotherapy options $C_1$, $C_2$
- **Decision 2**: Two maintenance options $M_1$, $M_2$ for patients who respond, two salvage options $S_1$, $S_2$ for those who don’t
- **Goal**: Prolong survival (outcome)
Sequential decisions

Two decisions (leukemia example):

• *Decision 1*: $X_1 =$ information available, set of *treatment options*, e.g., \{C_1, C_2\}

• $X_1$ includes age, WBC, gender, %CD56 expression, . . .
Sequential decisions

Two decisions (leukemia example):

- **Decision 1:** $X_1 =$ information available, set of *treatment options*, e.g., \{C_1, C_2\}
- $X_1$ includes age, WBC, gender, %CD56 expression, \ldots

- **Decision 2:** $X_2 =$ additional information collected, set of *treatment options*, e.g., \{M_1, M_2, S_1, S_2\}
- $X_2$ includes grade 3+ hematologic adverse event, post-induction ECOG status, WBC, platelets, \ldots
- \ldots and *responder status*
Regime: A set of rules $d = \{ d_1(X_1), d_2(X_1, A_1, X_2) \}$

- $d_1(X_1)$ dictates treatment at Decision 1 given information available at that point, $X_1$
- $A_1$ is treatment received at Decision 1 (determined by $X_1$)
- $d_2(X_1, A_1, X_2)$ dictates treatment at Decision 2 given all accrued information at that point, $X_1, A_1, X_2$
Optimal sequential-decision regime

Optimal regime: $d^{opt}$ is such that the *expected outcome* for a patient with *initial characteristics* $X_1$, if s/he were to receive *treatment at all decisions* according to $d^{opt}$, is *as large as possible*

$$d^{opt} = \{ d_1^{opt}(X_1), d_2^{opt}(X_1, A_1, X_2) \}$$
Optimal sequential-decision regime

**Optimal regime:** $d^{opt}$ is such that the *expected outcome* for a patient with *initial characteristics* $X_1$, if s/he were to receive *treatment at all decisions* according to $d^{opt}$, is *as large as possible*

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- Can we use *data* and *regression modeling* as before to *estimate* $d^{opt}$?
- I.e., consider each decision *separately* and use data from possibly *separate sources* at each?
Optimal sequential-decision regime

Optimal regime: $d^{opt}$ is such that the expected outcome for a patient with initial characteristics $X_1$, if s/he were to receive treatment at all decisions according to $d^{opt}$, is as large as possible

$$d^{opt} = \{ d_1^{opt}(X_1), d_2^{opt}(X_1, A_1, X_2) \}$$

- Can we use data and regression modeling as before to estimate $d^{opt}$?
- I.e., consider each decision separately and use data from possibly separate sources at each?
- Unfortunately not...
Complications for sequential decisions

**Delayed effects:** For example

- $C_1$ may yield higher proportion of responders than $C_2$ but may also have other effects that render subsequent maintenance treatments (M) *less effective* in regard to survival.

- $C_1$ may not appear best initially but may have enhanced effectiveness over the *long term* when followed by $M_1$.

- *Result* – Require data from a *single source* in which the *same patients* are seen over the *entire sequence of decisions*. 

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Complications for sequential decisions

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- \( C_1 \) may yield higher proportion of responders than \( C_2 \) but may also have other effects that render subsequent maintenance treatments (M) *less effective* in regard to survival.
- \( C_1 \) may not appear best initially but may have enhanced effectiveness over the *long term* when followed by \( M_1 \).
- *Result* – Require data from a *single source* in which the *same patients* are seen over the *entire sequence of decisions*.

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

- \( A_1 \) = treatment received at *Decision 1*,
- \( A_2 \) = treatment received at *Decision 2*
Data: Must reflect the *entire course of decisions* of interest
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**Observational longitudinal databases:**
- Epidemiological or medical registry
- Conventional clinical trial
Data: Must reflect the *entire course of decisions* of interest

Observational longitudinal databases:
- Epidemiological or medical registry
- Conventional clinical trial
- *Challenges*
  - Confounding over time
  - Recording of $X_1, X_2$ used by clinicians to make decisions

Clinical trial for this purpose???
SMART: Sequential, Multiple Assignment, Randomized Trial

- *Randomize* subjects at *each decision* point
- Eliminates *confounding*
- Collect not only *baseline* information $X_1$ but *intervening* information $X_2$
- *Goal*: Provide *rich data* for estimation of *optimal treatment regimes*

Pioneered by Susan Murphy, Phil Lavori, and others
Schematic of a SMART: Leukemia example (*randomization at ●s*)

- Cancer
  - $C_1$
    - Response
    - No Response
      - $S_1$
      - $S_2$
  - $C_2$
    - Response
    - No Response
      - $S_1$
      - $S_2$
Sequential regression

**Estimating** $d^{\text{opt}}$: $d^{\text{opt}} = \{ d_1^{\text{opt}}(X_1), d_2^{\text{opt}}(X_1, A_1, X_2) \}$

- *More complicated* than for a single decision
Sequential regression

Estimating $d^{opt}$: $d^{opt} = \{ d_1^{opt}(X_1), d_2^{opt}(X_1, A_1, X_2) \}$

- More complicated than for a single decision
- Need specialized regression methods
Sequential regression

Estimating $d^{\text{opt}}$: $d^{\text{opt}} = \{ d_1^{\text{opt}}(X_1), d_2^{\text{opt}}(X_1, A_1, X_2) \}$

- More complicated than for a single decision
- Need specialized regression methods
- When determining $d_1^{\text{opt}}(X_1)$, must acknowledge that $d_2^{\text{opt}}(X_1, A_1, X_2)$ will be used to select treatment at Decision 2 in the future
- Backward induction, dynamic programming
- Q-learning
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 \(\{0, 1\}\)

\[
d_{2}^{opt}(X_1, A_1, X_2) =
\begin{align*}
0 & \text{ if } E(Y|X_1, A_1, X_2, A_2 = 1) < E(Y|X_1, A_1, X_2, A_2 = 0) \\
1 & \text{ if } E(Y|X_1, A_1, X_2, A_2 = 1) > E(Y|X_1, A_1, X_2, A_2 = 0)
\end{align*}
\]

- \(E(Y|X_1, A_1, X_2, A_2)\) is the *regression* of outcome on both treatments received and accrued characteristics
- Can develop and fit a *regression model*
Decision 1: Trickier

- Must take into account that the optimal rule at Decision 2 will be followed in the future.
- I.e., \( d_1^{\text{opt}}(X_1) \) must make the expected outcome as large as possible when also \( d_2^{\text{opt}}(X_1, A_1, X_2) \) will be used to determine treatment at Decision 2.
Sequential regression (Q-learning)

**Decision 1:** Trickier

- 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 make the *expected outcome* as large as possible when *also* $d_2^{opt}(X_1, A_1, X_2)$ will be used to determine treatment at Decision 2
- Best explained by illustration
Sequential regression (Q-learning)

Implementation:

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

\[
E(Y|X_1, A_1, X_2, A_2) = \alpha_0 + \alpha_{11}X_1 + \alpha_{22}X_2 + \alpha_{23}A_1 X_1
\]
\[
+ A_2(\beta_{20} + \beta_{21}X_2 + \beta_{22}A_1),
\]

*fit* to the data, and *estimate* \(d^\text{opt}_2(X_1, A_1, X_2)\) by *substitution*
Sequential regression (Q-learning)

Implementation:

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

$$E(Y|X_1, A_1, X_2, A_2) = \alpha_{20} + \alpha_{21}X_1 + \alpha_{22}X_2 + \alpha_{23}A_1X_1 + A_2(\beta_{20} + \beta_{21}X_2 + \beta_{22}A_1),$$

*fit* to the data, and *estimate* $d_{2}^{opt}(X_1, A_1, X_2)$ by *substitution*

- For each subject, form $\tilde{Y}$, the *predicted expected outcome* with the *Decision 2 optimal treatment* determined by the estimated $d_{2}^{opt}(X_1, A_1, X_2)$ *substituted* for $A_2$ actually received, i.e.,
Sequential regression (Q-learning)

Implementation:

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

\[
E(Y|X_1, A_1, X_2, A_2) = \alpha_{20} + \alpha_{21}X_1 + \alpha_{22}X_2 + \alpha_{23}A_1X_1 \\
+ A_2(\beta_{20} + \beta_{21}X_2 + \beta_{22}A_1),
\]

*fit* to the data, and *estimate* \(d_{2}^{opt}(X_1, A_1, X_2)\) by *substitution*

- For each subject, form \(\tilde{Y}\), the predicted expected outcome with the Decision 2 optimal treatment determined by the estimated \(d_{2}^{opt}(X_1, A_1, X_2)\) substituted for \(A_2\) actually received, i.e.,

\[
\tilde{Y} = \hat{\alpha}_{20} + \hat{\alpha}_{21}X_1 + \hat{\alpha}_{22}X_2 + \hat{\alpha}_{23}A_1X_1 \\
+ \hat{A}_{2}^{opt}(\hat{\beta}_{20} + \hat{\beta}_{21}X_2 + \hat{\beta}_{22}A_1)
\]
Sequential regression (Q-learning)

Implementation:

- Develop a *regression model* for Decision 1 using the *predicted outcomes*, e.g.,

\[
E(\tilde{Y}|X_1, A_1) = \alpha_{10} + \alpha_{11} X_1 + A_1 (\beta_{10} + \beta_{11} X_1),
\]

fit to the data, and estimate \(d_{opt}^1(X_1)\) by substitution.
Sequential regression (Q-learning)

Implementation:

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fit to the data, and estimate \( d_1^{opt}(X_1) \) by substitution
• An approach exists for estimating optimal treatment regimes from *appropriate data*
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• *So why isn’t everyone doing this?*
Challenges:

• Needed *longitudinal information* is often *not captured* in observational databases
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- But much less so in *chronic diseases* like cancer, CVD, HIV infection (with *notable exceptions* . . .)
- *In fact*, trials with *two randomizations* have been commonplace in leukemia for some time (but *not for this purpose*)
Issues

- What if *more than one outcome* is of interest? E.g., balancing *efficacy* and *toxicity*?
- *Design principles* (e.g., sample size) for *SMARTs*?
- Once an optimal regime is estimated, should it be compared to *standard of care* in a conventional clinical trial?
- *mHealth* – can *real-time* regimes be developed?
• *Statistical research* is ongoing to address all of these (and many other) issues...
Next steps

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- ...and is *way ahead* of what is actually being done in practice
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- Must *challenge* the conventional clinical trial paradigm *and* myopic view of treatment
- Must ensure *all* relevant longitudinal data are *recorded*
- Will require *collaboration* among statisticians, clinicians, registrars, trialists,...
Thought Leaders

2013 MacArthur Fellow Susan Murphy and Jamie Robins