Lecture 1: Introduction to Personalized Medicine
Personalized Medicine
Personalized Medicine is a general medical paradigm referring to systematic use of individual patient information to optimize patient’s health outcomes.

It is important in treating chronic diseases including hypertension, obesity, diabetes, drug abuse, cancer, HIV infection, depression and schizophrenia.

Growing interest from statistical community and other quantitative researchers is due to

- advance of biotechnology to collect individual data (Volume, Variety, Velocity)
- advance of computational algorithms and tools
- advance of clinical designs and statistical methods
Definition of Personalized Medicine

- Personalized medicine refers to “the tailoring of medical treatment to the individual characteristics of each patient”.

- Food and Drug Administration (FDA): characterization of heterogeneity of subject responses to treatment is a critical component of drug development and regulatory decision making.

- Pharmaceutical industry: targeting therapeutic intervention in a well-characterized subpopulation.

- Clinicians: use individual characteristics to guide optimal treatment and provide best clinical care for a patient.
Why Personalized Medicine?

- **Heterogeneity across patients**: what works for one may not work for another (e.g., MDD response rate 40%, Gaynes et al., 2009).

- **Temporal variability within a patient**: what works now may not work later (MDD relapse rate 50%, APA 2000).

- **Different pathologies** underlying a clinical syndrome.

- **Multiple active treatments** available (e.g., 6 main SSRIs for treating MDD).

- **Potential heterogeneity of treatment delivery** related to practical application (stage of disease, co-morbidity etc.)
Scientific Goals in Personalized Medicine

- To identify right patients for a given treatment.
- To identify right treatments for a given patient.
- Treatment is in a broad sense: type of drugs/interventions, dosage, schedules, treatment strategies and etc.

Methodology focus: To determine the optimal (dynamic) treatment regimen for a given patient using data-driven approaches (Evidence-Based Decision Making).

- Right data
- Right question
- Right method
- Right tool
Trial Evidence for Personalized Medicine

- Data from one or more clinical trials
- Data collected from sequential randomization trials
  - Adaptive Pharmacological and Behavioral treatments for ADHD (Pelham WE, 2002);
  - Sequenced Treatment Alternatives to Relieve Depression (STAR*D) (Rush, et al., 2004);
  - CATIE for schizophrenia (Schneider, et al., 2003);
  - ExTENd for alcohol dependence (Oslin, 2005);
  - Adaptive therapy for androgen independent prostate cancer (Thall et al. 2007)
- Trial evidence provides valid assessment of personalized medicine.
Challenges with Trial Evidence

- Trial data are limited in sample sizes so are usually lack of statistical power.
- Trials are not designed for personalized treatments.
- The generalizability to a broad population is questionable.
Rich data sources provide patient information: Demographics, Co-morbidity, Stage of disease, Genomic (oncology), Imaging (psychiatry), Mobile technology (neurology, psychiatry), Electronic Medical Records.
Challenges with Observational Data

- Potential confounders can invalidate results.
- High-dimensional or dynamic tailoring variables
- Noisy and poor quality data (measurement errors, missing data)
- High redundancy within data
- Infinite choices of treatment rules
- Multivariate outcomes (benefit and risk outcomes)
- Big Data size
Potential Outcome Framework
Potential Outcome Framework in Personalized Medicine

For one treatment stage with only two treatment options \{-1, 1\} and one single outcome $R$,

- **Potential outcome** $R(a)$ refers to the outcome if treated by $a \in \{1, -1\}$.
- Personalized medicine is really interested in whether $R(1)$ is larger than $R(-1)$ and the size of $R(1) - R(-1)$.

For two treatment stages and one single outcome $R$,

- **Potential outcome** $R(a_1, a_2)$ refers to the outcome if treated by $a_1$ in the first stage then $a_2$ in the second stage.
- Personalized medicine is interested in the comparisons among $R(a_1, a_2)$. 
In general, consider any treatment sequence \((a_1, a_2, \ldots)\). We let \(R(a_1, a_2, \ldots)\) be the corresponding potential outcome then personalize medicine aims to understand the difference among these potential outcomes using evidence.

- Only one possible sequence of treatments is observed for a given individual so in theory, this is an impossible task!
- One solution is to use other individuals to impute unobserved potential outcomes; however, imputation can be very questionable due to inevitable difference between individuals.
Instead of seeking individual effects, we can aim for the average effects from homogeneous individuals.

Average treatment effects:

\[ E[R(1)] - E[R(-1)], \ E[R(a_1, a_2)] - E[R(a_1', a_2')] \]

Feature-specific average treatment effects (subgroup analysis):

\[ E[R(1) - R(-1)|X], \ E[R(a_1, a_2) - R(a_1', a_2')|X] \]

where \( X \) is a pre-defined feature variable.

Are they only comparators? The answer is NO!
We can compare

\[ E[R(\text{sign}(X))] - E[R(-\text{sign}(X))] \]

Or,

\[ E[R(D_1(X))] - E[R(D_2(X))] \],

where \( D_1 \) and \( D_2 \) are both maps from \( X \)'s domain to \( \{-1, 1\} \).

This can of interest in public health in terms of health policy decision.
Traditional comparison of average treatment effects is on fixed treatment options, i.e., what if we apply treatment option $a_1$ or $a_2$ to everyone in the study population.

Essentially, we are comparing two treatment strategies:
- Strategy 1: Everyone is treated by $a_1$.
- Strategy 2: Everyone is treated by $a_2$.

This is called **one-size-fits-all strategies**.

Similarly, the subgroup comparison is comparing two fixed treatment strategies within the subgroup.

However, personalized medicine is interested in even broader treatment strategies!
A broader treatment definition: treatment is no longer understood as some constant options but as a strategy which maps individual feature/characteristics to the domain of treatment options, i.e.,

\[ D : \text{domain of } X \rightarrow \{-1, 1\}. \]

Constant treatment options (one-size-fits-all strategies) are the special case where \( D(x) \) is a constant.

An example of \( D \):

“if patient’s age is older than 50 or his/her BMI is higher than 26, we should use drug 1; otherwise, we should use drug 2.”

Hence, personalized medicine is interested in evaluation, comparison and selection of treatment strategies.
Remarks on Treatment Strategies

- Treatment strategies are also called treatment regime, treatment policies or treatment decisions.
- A separate note: leap from treatment options to treatment strategies echoes leap from the conditional expectation of $X$ given $Y$ to the conditional expectation of $X$ given the $\sigma$-field generated by $Y$ when I teach probability and inference classes.
- Conclusion: Nothing changes dramatically or crazily, but we need a broader view.
Example 1. A patient with a particular cancer is given therapy 1 first. If his/her disease progresses, we immediately change to a more aggressive therapy 2; otherwise, we maintain the first therapy.

Example 2. A patient with a particular cancer is given therapy 1 first. If his/her disease progresses, we wait to see his/her immune responses. Depending on the responses, we decide to change to a more aggressive therapy 2 if the responses are low, otherwise, maintain the early treatment.
The average potential outcomes for the examples cannot be quantified in terms of constant treatment options, since the treatment choices depend on the intermediate outcomes for different individuals.

However, both are two different treatment strategies of practical interest and they are dynamic.

They are called dynamic treatment strategies, dynamic treatment regime, dynamic treatment policies, or adaptive treatment strategies.
Random Treatment Strategies

- Even more broader treatment definition is to allow $\mathcal{D}$ to map into a probability distribution in the domain of treatment option, i.e., we allow random treatment strategies.
- Random treatment strategies are useful when new evidence continues to come in so randomness allows to explore better strategies.
- Random treatment strategies are useful for mobile health and artificial intelligence.
- However, they are not good for practice.
- We only focus on non-random treatment strategies in this course.

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Goals and Challenges
Goals

- Evaluate a specific treatment strategy.
- Compare different treatment strategies.
- Select the optimal treatment strategies.
- Implement a specific treatment strategy.
- Validate a specific treatment strategy.
Challenges

- What designs can provide unbiased evidence?
- What assumptions ensure validity of the results?
- What methods meet the goals?
- What practical concerns remain about the results?
An Overview

- I will review traditional designs/methods for constant treatment strategies.

- I will formally introduce dynamic treatment strategies, the most interested one in personalized medicine.

- I will describe study designs for evaluating dynamic treatment strategies.

- I will introduce statistical learning methods for personalized medicine.

- Finally, I will present a number of works we have done in this area.