The Right Treatment for the Right Patient (at the Right Time): Personalized Medicine and Statistics

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Personalized Medicine

Source of graphic: http://www.personalizedmedicine.com/
So why is a statistician talking to you about personalized medicine?

My goal: To convince you that statistical science is essential in the quest for personalized medicine!
There should be a treatment for that!

Modern expectation: A *treatment* for everything

- Drugs, biologic products, medical devices, surgical procedures, behavioral interventions,…
- Cholesterol-lowering medications, anti-platelet therapies
- Anti-depressants, anti-psychotics, cognitive therapies
- Chemotherapies, tamoxifen (Nolvadex), bevacizumab (Avastin), rituximab (Retuxan)
- Antiretroviral therapies, e.g., PIs, NNRTIs, FIs
- Artificial hips, implants
How are treatments developed and evaluated?

Who decides if they “work?” How is this decided?
How are treatments developed and evaluated?

Main players
- Pharmaceutical, biotechnology, device companies
- University and government research

Who decides? And how?
- The US Food and Drug Administration (FDA)
- Safety – can people take it?
- Efficacy – does it do anything in humans?
- Effectiveness – is it better or at least as good as what is currently available?
- Do the benefits outweigh the risks?
Today, the process of deciding is highly regulated

But it wasn’t always like this...
No regulatory process

At the beginning of the 20th century, there was essentially no regulation!

- Manufacturers could advertise any product as a treatment for anything, with no evidence
- Drugs like opium, heroin, cocaine were freely available
- No requirements for labeling or a list of ingredients
- “The Wild, Wild West”
Path to the modern FDA

Little by little, legislation was enacted
- To create what is now the modern FDA (1927)
- To require evidence of safety (1938)
- To introduce the concept of a prescription (1951)

The bombshell: 1961 – Thalidomide
- Anecdotal reports of birth defects in Europe
- A FDA medical officer argued for keeping the drug off the US market ⇒ public support for stronger drug regulation
- Legislation enacted in 1962 requiring demonstration of safety and effectiveness for the first time by “substantial evidence” from “well-controlled studies”
Today

1962 to present

- The current, highly regulated process of bringing a **new treatment to market** was established

**Gold standard – the controlled clinical trial**

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

Basics of a confirmatory clinical trial

- A **sample** of subjects with the disease/disorder is recruited
- 100s to 1000s of subjects
- Subjects are **randomized** to treatments under study  
  ⇒ eliminate bias, allow fair comparison
- A **clinical outcome** is ascertained for each subject
- E.g., **survival time** in cancer, **viral load level** in human immunodeficiency virus (HIV) infection after 1 year
Effectiveness

- Compare some summary measure of clinical outcomes between/among treatments
- E.g., the average
- “Is the average outcome if all patients in the population took treatment A different from (better than) that if they all instead took 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
- Statistics is key

Success

- Countless treatments have been approved on this basis
- And have benefited numerous patients

However...

- All patients are not created equal
Patient heterogeneity
Patient heterogeneity

We’re all *different*

- Demographic characteristics
- Physiological characteristics
- Medical history
- Genetics/genomics

What works for a patient with one set of characteristics might not work for another
The genomic “revolution”

Completion of the Human Genome Project

- **Genomic** information may hold great potential

Source of graphic: http://obip.org/alumni/personalized-medicine
An (admittedly 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)
Currently

There have been some notable successes

- Genetic variation in metabolism of warfarin (Coumadin) to guide dosing
- Treatment of K-ras mutation negative colorectal cancer using cetuximab (Erbitux)
- Treatment of advanced melanoma expressing BRAF gene mutations using dabrafenib (Tafinlar) and trametinib (Mekinist)
Patient heterogeneity

Moral

- While useful for evaluation and approval, summary measures may not be useful for determining how to treat individual patients
- “One size does not fit all”
- A patient’s characteristics may play a role in which treatment option might be best for him/her

However...

- But it may be much more complicated than finding a single mutation
- Routine, fully personalized medicine may be decades away
Moving toward fully personalized medicine

- How do we do this?
- What are the challenges and possible pitfalls?
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?

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

How do we identify the “right patient?”

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 process
- Multiple treatment options at each
- Accrued information on the patient
- Goal: Make the best decisions for this individual patient

Focus on “the right treatment for the patient”

How do we identify the “right treatment?”
Cancer treatment

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
- Several options for each
- **Goal**: Prolong survival
Clinical decision-making

How are these decisions made?

- Clinical judgment
- Practice guidelines based on combining results of previous studies and expert opinion

Can such clinical decision-making be formalized and made evidence-based?
In either case

- The key is to identify all “tailoring variables”
Tailoring variables

Average Outcome

No Mutation  Mutation

Trt A
Tailoring variables

Average Outcome

No Mutation  Mutation

Trt A

Trt B

Trt B

Trt A

28/47
Tailoring variables

Average Outcome

No Mutation  Mutation

Trt A

29/47
Tailoring variables

- Average Outcome

- Trt A
- Trt B

- No Mutation
- Mutation

30/47
Need to identify the best combination of all tailoring variables

- Knowledge of the biology integrated with...
Challenges

High dimensional data
- Must sift through 1000s of characteristics to identify the important tailoring variables
- From data on a sample of patients (10s, 100s, 1000s)

Complex relationships
- Even with only a few characteristics, must describe the relationship between outcome, tailoring variables, and treatment selection correctly
Challenges

Pitfalls

- Computational intensity
- Chance to miss important characteristics
- Chance of false discovery
- Chance of incorrect models for relationships

Statistics!
Can we formalize clinical decision-making?

- Can we make what clinicians do in practice evidence-based?
- Can we come up with decision rules that take a patient’s characteristics as input and output the best option for the patient given those characteristics?

Evidence-based = based on data
Cancer treatment

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
- Several options for each
- Goal: Prolong survival
Decision rule 1: Genetic/genomic profile, demographics, physiological characteristics, medical history, . . . ⇒ which of 2 chemotherapies C to use

Decision rule 2: Previous info + responder status, intermediate physiological/clinical measures, side effects, . . . ⇒ which of 2 maintenance therapies M (responders) or 2 salvage chemotherapies S (non-responders) to use
Example decision rules

- **Decision rule 1:** “If age < 50, progesterone receptor level < 10 fmol, RAD51 mutation, then give C₁, else, give C₂”
- **Decision rule 2:** “If patient responds, age < 60, CEA > 10 ng/mL, progesterone receptor level < 8 fmol, give M₁, else, give M₂; if does not respond, age > 65, P53 mutation, CA15-3 > 25 units/mL, then give S₁, else, give S₂”
Treatment regime

- A set of formal decision rules, each corresponding to a key decision point
- Lots of possible rules at each decision point
- Lots of possible regimes – is there a “best” regime? How do we define “best?”
Optimal treatment regime

The “best” treatment regime

- Suppose large outcomes are better (survival)
- Optimal treatment regime: If an individual patient were to receive treatment according to this regime, his/her expected (average) outcome would be as large as possible given the information available on him/her
- And thus would lead to the largest expected (average) outcome for the population of patients

Challenge

- Can we use data to determine an optimal regime?
- What kind of data do we need?
Studies for developing optimal regimes

**SMART:** Sequential, Multiple Assignment, Randomized Trial

- Randomize subjects at each decision point and record treatment received
- Collect baseline information before the first decision and intervening information between decisions
- Collect outcome
- Goal: Rich data for estimation of optimal treatment regimes

Pioneered by Susan Murphy, Phil Lavori, and others
Schematic of a SMART: Cancer example (randomization at •s)
Given data from a SMART

- We can use specialized **statistical methods** to estimate an optimal regime
- **Statistical modeling** of outcomes at each decision point
- *...and methods to identify the combinations of tailoring variables* that should be involved
Single decision

- Regime is a single rule
- Optimal regime/rule leads to largest expected (average) outcome for a patient with characteristics $X$
- (Regression) model for the expected (average) outcome in terms of characteristics $X$ and treatment received
- For any given $X$, the estimated optimal regime chooses the predicted outcome from this model the largest
More than one decision

- **Regression models** for expected (average) outcome in terms of the **accrued information** and treatment received at each decision
- Models must take account of what might happen **later** when deciding what to do **now**
- **Backward induction, dynamic programming**
- ...adapted to the setting of **human data** and **statistical modeling**
Wrap-up

• The goal of truly personalized medicine is still elusive
• But it is attainable!
• **Statistical science** will be a critical ingredient
Recognition

2013 MacArthur Fellow Susan Murphy
All things statistics

/http://www.worldofstatistics.org/