Personalized Medicine: The Right Treatment for the Right Patient

Marie Davidian

Department of Statistics
North Carolina State University

January 11, 2013
“The right treatment for the right patient (at the right time)”
So why is a statistician talking to you about personalized medicine?
So why is a statistician talking to you about personalized medicine?

My goal: To convince you that the quantitative sciences, and especially statistics, are essential in the quest for personalized medicine!
Roadmap

• Some background
Roadmap

• Some background
• What is personalized medicine?
Roadmap

- Some background
- What is personalized medicine?
- Statistics, mathematics, and personalized medicine
Modern expectation
There should be a treatment for that!

“Treatments” – drugs, biologic products, medical devices, surgical procedures, behavioral therapies – are omnipresent in today’s world

- 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?

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?

Today

- US: Food and Drug Administration (FDA)
- EU: European Medicines Agency (EMA)
- Japan: Pharmaceuticals and Medical Devices Agency
- International Conference on Harmonisation (ICH)

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?
How are treatments developed and evaluated?

Main players

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

Who decides? And how? Today

- US: Food and Drug Administration (FDA)
- EU: European Medicines Agency (EMA)
- Japan: Pharmaceuticals and Medical Devices Agency
- International Conference on Harmonisation (ICH)
- 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
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 anywhere!

- 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
- A “free-for-all”
Path to modern regulatory agencies

Little by little, steps were taken

• To create what is now the modern FDA in the US (1927)
• To require evidence of safety in the US (1938)
• To introduce the concept of a prescription in the US (1951)

The bombshell: 1962 – 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 the US requiring demonstration of safety and effectiveness for the first time by “substantial evidence” from “well-controlled studies”
Today

1962 to present

- The Declaration of Helsinki was developed by the World Medical Association to set forth ethical principles for research involving human subjects (1964)
- Similarly, the Belmont Report in the US (1979)
- The current, highly regulated process of bringing a new treatment to market was established

Fundamental – the controlled clinical trial

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

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
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

- Physiological, demographic characteristics
- Medical history
- Genetic/genomic characteristics
Patient heterogeneity

We’re all different

- Physiological, demographic characteristics
- Medical history
- Genetic/genomic characteristics

What works for a patient with one set of characteristics might not work for another
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
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
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 = \((0.2)(25) + (0.8)(5) = 9\)
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 = \((0.2)(10) + (0.8)(20) = 18\)
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)
Patient heterogeneity

Moral

- “One size does not fit all”
- Use a patient’s characteristics to determine which treatment option might be best for him/her
Patient heterogeneity

Moral

• “One size does not fit all”
• Use a patient’s characteristics to determine which treatment option might be best for him/her
• Genomic information may hold great potential
• Personalized medicine
Not so fast . . .

- 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 **more likely** to do better on a particular treatment than on others?
- 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?
Subgroup identification and targeted treatment

- Can we determine subgroups of patients who share certain characteristics and who are more likely to do better on a particular treatment than on others?
- 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 finding and treating a subgroup
Popular perspective on personalized medicine

Personalised medicine: future vision

- Diagnostic test positive
  - Likely to benefit from treatment

- Diagnostic test negative
  - Unresponsive to therapy
Another perspective on personalized medicine

Can we determine how best to treat the entire population?

- Given information on any patient’s characteristics, can we determine the treatment most likely to benefit him/her?
- In fact, can we come up with “rules” that take a patient’s characteristics as input and output the best option for him/her?
Another perspective on personalized medicine

Can we determine how best to treat the entire population?

- Given information on any patient’s characteristics, can we determine the treatment most likely to benefit him/her?
- In fact, can we come up with “rules” that take a patient’s characteristics as input and output the best option for him/her?

Focus on treating everyone
Challenge

In either case

- It’s all about identifying “tailoring variables”
- Knowledge of the biology integrated with statistics
Finding tailoring variables

- Average Outcome

No Mutation | Mutation
Trt A

Trt A
Finding tailoring variables

Average Outcome

T rt A

T rt B

No Mutation  Mutation

T rt A

T rt B
Finding tailoring variables

[Graph showing the relationship between average outcome and mutation status for a treatment labeled 'Trt A'. The graph indicates that the average outcome increases with the presence of a mutation.]
Finding tailoring variables

Average Outcome

No Mutation  Mutation

Trt A  Trt B  Trt A  Trt B
Moral

- Need to identify tailoring variables
- This is a statistical problem…
Challenge, more precisely

High dimensional data!

- Must sift through 1000s of characteristics to identify the right combination of key tailoring variables
- Based on data from a sample of patients (10s, 100s, 1000s)
Challenge, more precisely

Pitfalls

- **Computational complexity**
- Chance to **miss** important characteristics
- Chance of **false discovery**
- **Statistical methods** must be used
Can we treat everyone “optimally?”

Clinical practice: Treatment decisions over time

- Fixed schedule
- Event(s) necessitating a decision

Clinical decision-making

- Clinical judgment used to synthesize all information available, make a “personalized” treatment decision
- Can this be formalized?
- That is, can we construct decision rules?
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
Sequential decision-making

- **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
Sequential decision-making

- **Decision rule 1**: Genetic/genomic profile, demographics, physiological characteristics, medical history, \ldots \implies \text{which of 2 chemotherapies C to use}
- **Decision rule 2**: Previous info + responder status, intermediate physiological/clinical measures, side effects, \ldots \implies \text{which of 2 maintenance therapies M (responders) or 2 salvage chemotherapies S (non-responders) to use}
• **Decision rule 1:** “If age < 50, progesterone receptor level < 10 fmol, RAD51 mutation, then give C₁, else, give C₂”
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, CA 15-3 > 25 units/mL, then give S₁, else, give S₂”
Construct (estimate) rules from data

- At each decision, identify the tailoring variables and the right function of them to give a decision rule
- **Goal**: Find the decision rules that would lead to best expected outcome if followed by all patients
- Each rule must take account of what might happen later when deciding what to do now
- **How to do this**: Statistical modeling, dynamic programming
47 year old male goes to the ER

- 102.5 °F fever, headache, nausea/vomiting, rash, . . .
- MSM, recent unprotected sex, . . .
- Tests for cytomegalovirus (CMV), Epstein-Barr virus (EBV), influenza negative
- HIV test positive
- HIV RNA (viral load) > 750,000 copies/ml
- CD4+ T cell count = 432 cells/µL
47 year old male goes to the ER

- 102.5 °F fever, headache, nausea/vomiting, rash, ...
- MSM, recent unprotected sex, ...
- Tests for cytomegalovirus (CMV), Epstein-Barr virus (EBV), influenza negative
- HIV test positive
- HIV RNA (viral load) > 750,000 copies/ml
- CD4+ T cell count = 432 cells/µL

Diagnosis – Acute HIV infection
Treatment of acute HIV infection
Should this patient be started on antiretroviral therapy (ART)?

Disadvantages:
- Cost
- Side effects
- Eventual drug resistance
- Limit future ART options

Advantages:
- "Train" the immune system through cycles of treatment "interruption" – cycles of treatment and viral exposure may allow patient to maintain control of virus

More generally:
- Can we determine the "best" way to use ART to manage the infection and prolong time to AIDS?
Treatment of acute HIV infection

Should this patient be started on antiretroviral therapy (ART)?

- **Disadvantages:** Cost, side effects, eventual drug resistance, limit future ART options
- **Advantages:** “Train” the immune system through cycles of treatment “interruption” – cycles of treatment and viral exposure may allow patient to maintain control of virus

More generally

Can we determine the “best” way to use ART to manage the infection and prolong time to AIDS?
Treatment of acute HIV infection

Should this patient be started on antiretroviral therapy (ART)?

- Disadvantages: Cost, side effects, eventual drug resistance, limit future ART options
- Advantages: “Train” the immune system through cycles of treatment “interruption” – cycles of treatment and viral exposure may allow patient to maintain control of virus

More generally

- Can we determine the “best” way to use ART to manage the infection and prolong time to AIDS?
Mathematical modeling

HIV dynamic model

• Represent mechanisms involved in virus-immune system interaction mathematically
• System of differential equations
• Over-simplification of complex biology, but can be useful
• Predict viral load, CD4 count at any time under any ART strategy
Dynamical system model
Dynamical system model

\[ \dot{T}_1 = \lambda_1 - d_1 T_1 - \{1 - \epsilon_1 u(t)\} k_1 V_l T_1 \]
\[ \dot{T}_1^* = \{1 - \epsilon_1 u(t)\} k_1 V_l T_1 - \delta T_1^* - m_2 ET_1^* \]
\[ \dot{T}_2 = \lambda_2 - d_2 T_2 - \{1 - f \epsilon_1 u(t)\} k_2 V_l T_2 \]
\[ \dot{T}_2^* = \{1 - f \epsilon_1 u(t)\} k_2 V_l T_2 - \delta T_2^* - m_2 ET_2^* \]
\[ \dot{V}_l = \{1 - \epsilon_2 u(t)\} 10^3 N_T \delta (T_1^* + T_2^*) - cV_l \]
\[ - \{1 - \epsilon_1 u(t)\} \rho_1 10^3 k_1 T_1 V_l \]
\[ - \{1 - f \epsilon_1 u(t)\} \rho_2 10^3 k_2 T_2 V_l \]
\[ \dot{V}_{NI} = \epsilon_2 u(t) 10^3 N_T \delta (T_1^* + T_2^*) - cV_{NI} \]
\[ \dot{E} = \lambda_E + \frac{b_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_b} E - \frac{d_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_d} E - \delta_E E \]
Model-based treatment

Add statistics

- Fit the model to data on many subjects using statistical methods
- Use the fitted model + control theory to design ART interruption strategies
- Use the model to study the consequences of different ART interruption strategies on “virtual patients” (simulation)
- Study the promising ones on real patients in a clinical trial
Model-based treatment
Model-based treatment
The goal of truly personalized medicine is still elusive.

But it is attainable!

Combining quantitative sciences (statistics, mathematics, computer science,…) with biological, biomedical sciences is one key that will pave the way.
2013 – the International Year of Statistics

http://statistics2013.org