Optimizing Statin Treatment Decisions for Diabetes Patients in the Presence of Uncertain Future Adherence

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INFORMS Annual Meeting, Austin, TX
November 8, 2010
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Supported by the Agency for Health Care Research and Quality (R21HS017628)
Diabetes

- The American Diabetes Association estimates 23.6 million people have diabetes in the U.S.
  - 8% of the population
  - 90-95% of diabetic patients have type 2 diabetes

- Two out of three people with diabetes will die from either stroke or coronary heart disease (CHD)

- Statins are a first line treatment for preventing CHD events and strokes
Adherence

- Medical adherence is the extent to which patients take their medication as prescribed by their doctor.

- Measures: self reporting, review of prescription refills through pharmacy claims, and electronic monitors on pill canisters.
Long-Term Nonadherence

![Graph showing the probability of nonadherence over time from Statin initiation. The y-axis represents the probability ranging from 0 to 0.5, and the x-axis represents time from Statin initiation in years, ranging from 0 to 20. The graph shows an increasing trend in probability as time increases.]
Drugs don’t work in patients who don’t take them

Reasons for poor adherence:
- poor understanding of how medication works
- cost of medication
- forgetfulness
- busy schedule
- side effects

Downsides of poor adherence:
- unnecessary disease progression
- disease complications
- lower quality of life
- death
Interventions

- Since poor adherence has a large affect on patient outcomes, interventions may be very useful.

- A *medical intervention* is any measure whose purpose is to improve health or alter the course of disease.
Interventions

- Clarification of the benefits of the medication (a longer visit with your doctor, an email, a phone call, or a mailing)
- Reinforcement of message with a close family member or friend
- Efforts to reduce medication cost or impact on lifestyle
Machine Maintenance Literature

- Klein 1962, Derman 1963
- Markov decision process models to find the optimal time to perform maintenance
- Inspection is used to gain information about the machine’s state
Active vs. Inactive Surveillance

- *Inactive Surveillance*: involves a simple rule for when to have an intervention

- *Active Surveillance*: intervening when a patient’s adherence rate for a medication falls below a certain percentage

- Prescription refills monitored through pharmacy claims can be used to actively monitor a patient’s adherence rate
MDP Model

Time Horizon

- \( T = \{0, 1, 2, \ldots, N\} \)
- patients begin medical treatment at time 0

States

- adherence level \( \ell \in L = \{1, 2, \ldots, A\} \)
- health status \( s \in S = \{1, 2, \ldots, M\} \), death \( s = M + 1 \)

Decision

\[
D_{(\ell,s)} = \begin{cases} 
\{ W, I \} & \text{for } \ell \in L, \forall s \neq M + 1, \text{ and } t = 1, \ldots, N - 1, \\
\{ W \} & \text{for } s = M + 1 \text{ or } t = N 
\end{cases}
\]
State Transition Diagram

Beginning Treatment
State Transition Diagram

Beginning Treatment

HIGH
MED
LOW
NON

0 1

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State Transition Diagram

Beginning Treatment

- HIGH
- MED
- LOW
- NON

Transition Diagram:

0 1 2
State Transition Diagram

Beginning Treatment

HIGH
MED
LOW
NON

Intervention
HIGH
MED
LOW
NON

0 1 2 3

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Reward Function:

\[
r(\ell, s, d') = \begin{cases} 
R_0 q(\ell, s, d) - C^T & \text{for } \ell \in L, s \neq M + 1, d = W, \\
R_0 q(\ell, s, d) - C^T - C' & \text{for } \ell \in L, s \neq M + 1, d = I, \\
0 & \text{for } s = M + 1 
\end{cases}
\]

<table>
<thead>
<tr>
<th>Probabilities</th>
<th>Source</th>
</tr>
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<tbody>
<tr>
<td>Transitions among adherence states</td>
<td>Ingenix</td>
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<tr>
<td>Transitions among health states</td>
<td>Mayo Clinic</td>
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<tr>
<td>Probabilities of CHD or Stroke</td>
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<td>Probability of death from other causes</td>
<td>CDC Mortality Tables</td>
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</table>
Optimality Equations

\[ v_t(\ell, s) = \max_{d \in D(\ell, s)} \left\{ r(\ell, s, d) + \lambda \sum_{\ell' \in L, s' \in S} p_t(\ell', s' | \ell, s, d) v_{t+1}(\ell, s) \right\}, \]

\[ \forall \ell \in L, s \in S, t = 1, \ldots, N - 1 \text{ where } \lambda \in [0, 1) \text{ is the discount factor per stage.} \]
Theorem:
Assuming deterministic cholesterol, the optimal policy for interventions is monotonic with respect to the patient’s adherence state. There exists a state $\bar{\ell}$ such that if an intervention is optimal for $\ell = \bar{\ell}$ then it is optimal for all $\ell > \bar{\ell}$.
Theorem 4.7.5 [Puterman 1994] provides the sufficient conditions for this property:

- Rewards are nonincreasing in $\ell$
- Superadditivity of rewards and sums of probabilities
- Empirically observe the Increasing Failure Rate property
Types of Interventions

Perfect Intervention
When the intervention occurs, every patient improves to perfect adherence over the next year.

Imperfect Intervention
When the intervention occurs, each patient’s adherence either stays the same or improves, according to the first year adherence probabilities.
Inactive Surveillance: Imperfect Interventions for Females

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Inactive Surveillance: Imperfect and Perfect Interventions for Females
Active Surveillance

- Preliminary results show there is a threshold policy in both the adherence state ($\ell$) and time ($t$).

- Intervention policies vary significantly depending on the underlying health states.
Active Surveillance: Imperfect Interventions for Females
Main Findings

- The optimal policy for interventions with deterministic cholesterol states is monotonic with respect to adherence states.

- Numerical experiments show the monotonic policy also holds with stochastic cholesterol states.

- There is a tradeoff between frequency of interventions and quality of interventions.

- Use of Active Surveillance is likely not cost effective.
Future Work

- Prove the threshold policy for the general case with stochastic underlying health states
- Explicitly consider the partially observable nature of adherence
Thank You

Questions?
Theorem 4.7.5

Suppose for $t = 1, \ldots, N - 1$ that

1. $r(\ell, d)$ is nonincreasing in $\ell$ for all $d \in D_\ell$,
2. $q_t(k|\ell, d) = \sum_{j=k}^{A} p(j|\ell, d)$ is nondecreasing in $\ell$ for all $k \in L$, all $d \in D_\ell$, and all $t$,
3. $r(\ell, d)$ is a superadditive function on $L \times D$,
4. $\sum_{j=0}^{M+1} p_t(j|\ell, d) \nu(j)$ is a superadditive function on $L \times D$ for nonincreasing $\nu$, and
5. $r_N(\ell)$ is nonincreasing in $\ell$.

Then there exist optimal decision rules $d_t^*(\ell)$ which are nondecreasing in $\ell$ for $t = 1, \ldots, N$. 