Individualized Medicine and Biophysical System Dynamics: An Example from Clinical Practice in End Stage Renal Disease

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Three Messages

• Management of Anemia is a Critical Issue for 90% of Dialysis Patients

• System Dynamics Modeling Helped Redefine and Solve this Problem in Clinical Practice at Mayo Clinic

• System Dynamics Modeling Provides Tools for Learning in the Emerging World of Individualized Medicine
The Team

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PK/PD Simulation Modeling

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Application Development

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System Operations

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Direct Patient Care

Advisory Team Members (Not Shown):

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Steve Gudgell, Administration, Mayo Clinic

David Steensma M.D., Hematology, Harvard Medical School
Chronic Kidney Disease, Hemodialysis, and Anemia

- Chronic Kidney Disease (CKD): Any disease that leads to a permanent loss of kidney function.

- End Stage Renal Disease (ESRD): a complete/near complete failure of the kidneys to function normally.

- Hemodialysis (HD): One of several treatment options for CKD.

- 90% of HD patients require Erythropoietic Stimulating Agents (ESA) to Prevent and Control the Anemia of CKD.
Scratchpad - 406,000 Dialysis Patients in 2011 Means, Annually:

- Hemodialysis Activities Require More than 60K Person Years of Effort, Just for Patients!
- Estimated Reimbursement of $30,000 per patient = $12.2B /Yr.
Terms

• Hemoglobin
  – The Protein that Enables Transport of Oxygen to the Body and Carbon Dioxide from the Body to the Lungs

• Erythropoiesis
  – Greek: Erythro (“Red”) + Poiesis (“Making”)
  – Produces RBC’s – Red Blood Cells

• Erythropoietic Stimulating Agent (ESA)
  – A Class of Drugs Designed to Replace Erythropoietin

• Apoptosis
  – Greek: “Falling Leaves”
  – Refers to Programmed Cell Death
Anemia Among Dialysis Patients

• A Significant Quality of Life Issue for HD Patients
  – Loss of appetite
  – Sleep disturbances
  – Decreased exercise tolerance
  – Inability to concentrate
  – Generalized weakness or malaise, body aches
  – Lightheadedness, dizziness, fainting

• ESA and Iron Replacement Therapy *Can* Effectively Treat Anemia.

• However, Current Protocols do not Address “System as Cause” Issues.
Patient 2: Actual ESA Doses and Hgb Values following Standard Protocol

Day 1 to Day 721

- ESA Dose
- Hgb
- Hgb Low
- Hgb High
The Purpose of the Model: Find ESA Dosing Regimens That Stabilize a Patient’s Hgb in the Center of the Target Range

- **Hgb Too High:** Cardiovascular Damage, Thrombosis
- **Hgb Too Low:** Anemic

BTW: 10 - 13

Cyclic Period Typically 6-9 Months

Target Range

- > 13
- 10-13
- < 10

Months
Regulating The Rate of Erythropoiesis

- Increased Erythropoietin
- Decreased RBC Progenitor Apoptosis

15-20 Day Delay

Increased O₂ Carrying Capacity

O₂ Deficit

Normal Blood O₂ Level

 ESA Therapy

Increased Erythropoietin
Concept Map of Major Stocks and Flows of Erythropoiesis

Bone Marrow
- BFU Production
- Replicating CFUs
- Erythroblast Production
- Reticulocyte Development
- Reticulocyte Release
- CFU Survival
- Apoptosis

Circulation
- Maturing Reticulocytes
- RBC Production
- RBCs
- Hemoglobin
- ESA Level
- Dosing
- Eliminating
- ESA Half Life
- Feedback goes through here!

BFU: Blast Forming Unit
CFU: Colony Forming Unit
Using the Simulation Model to Study Hgb Responses to ESA Doses Recommended by Current Protocol

**Pattern 1: Oscillation**

- **X-axis:** Std Protocol Dose
- **Y-axis:** Simulated Hgb

**Pattern 2: Stabilization at Some Value**

- **X-axis:** Std Protocol Dose
- **Y-axis:** Simulated Hgb
Using the Simulation Model to Study Hgb Responses to ESA Doses Recommended by Current Protocol

Pattern 1: Oscillation

Pattern 2: Stabilization at Some Value
Patient 1: Comparison of Standard and Model Based Protocols

- **ESA Dose**
- **Hgb**
- **Hgb Low**
- **Hgb High**

D. 675

Day 1 to 1197
Patient 2: Comparison of Standard and Model Based Protocols

![Graph showing comparison of ESA Dose, Hgb, Hgb Low, and Hgb High between Standard Protocol and Model Based Protocol from Day 1 to Day 1645.](image-url)
Mayo Clinic Dialysis Services (MCDS)

- An Academic, Non-profit Institution
- Service Arm of Mayo Clinic Department of Nephrology and Hypertension
- 17 Dialysis Care Facilities
- 625-650 Prevalent Hemodialysis Patients
- 15 Physicians; 7 Allied Staff - 2 PAs, 2 NPs, 3 RNs
- Common Policies & Procedures
- Shared Dialysis Database
# Implementation Timeline

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reporting and Process Improvement Project Initiated</td>
<td>1Q 2007</td>
</tr>
<tr>
<td>Observation of Meaningful Dynamic Patterns</td>
<td>1Q 2008</td>
</tr>
<tr>
<td>Erythropoietic Simulation Model Ready for Testing</td>
<td>2Q 2008</td>
</tr>
<tr>
<td>Two Pilot Studies Complete</td>
<td>4Q 2008</td>
</tr>
<tr>
<td>Organization-Wide Rollout Complete</td>
<td>3Q 2009</td>
</tr>
<tr>
<td>90% of Patients Stabilized in Target Range of 10-13</td>
<td>2Q 2010</td>
</tr>
<tr>
<td>75% of Patients Stabilized in Target Range of 10-12</td>
<td>3Q 2010</td>
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</tbody>
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Sample Behavior Over Time (BOT) Chart

- Actual Hgb
- Projected Hgb
- Simulated Historical Hgb
- Iron
- TFS
- Actual Iron Dose
- Recommended ESA Dose
- Actual ESA Dose
Improved Healthcare Value Delivery

• Patient Quality of Life

• Staff Productivity

• Dramatic Cost Reductions
% Patients with Hgb < 10, BTW 10-13, > 13, and BTW 10-12

- < 10
- BTW 10-13
- > 13
- BTW 10-12

- May-07: 3%
- Aug-07: 3%
- Nov-07: 3%
- Feb-08: 3%
- May-08: 3%
- Aug-08: 3%
- Nov-08: 3%
- Feb-09: 3%
- May-09: 3%
- Aug-09: 3%
- Nov-09: 3%
- Feb-10: 3%
- May-10: 3%
- Aug-10: 3%
- Nov-10: 3%
- Feb-11: 3%
- May-11: 3%

- June-07: 32%
- Jul-07: 32%
- Aug-07: 32%
- Sep-07: 32%
- Oct-07: 32%
- Nov-07: 32%
- Dec-07: 32%
- Jan-08: 32%
- Feb-08: 32%
- Mar-08: 32%
- Apr-08: 32%
- May-08: 32%
- Jun-08: 32%
- Jul-08: 32%
- Aug-08: 32%
- Sep-08: 32%
- Oct-08: 32%
- Nov-08: 32%
- Dec-08: 32%
- Jan-09: 32%
- Feb-09: 32%
- Mar-09: 32%
- Apr-09: 32%
- May-09: 32%
- Jun-09: 32%
- Jul-09: 32%
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- Sep-09: 32%
- Oct-09: 32%
- Nov-09: 32%
- Dec-09: 32%
- Jan-10: 32%
- Feb-10: 32%
- Mar-10: 32%
- Apr-10: 32%
- May-10: 32%
- Jun-10: 32%
- Jul-10: 32%
- Aug-10: 32%
- Sep-10: 32%
- Oct-10: 32%
- Nov-10: 32%
- Dec-10: 32%
- Jan-11: 32%
- Feb-11: 32%
- Mar-11: 32%
- Apr-11: 32%
- May-11: 32%
Before and After Distribution of Hemoglobin Values

Target Range

Percentage of Patients

- < 9.0
- 9.0-9.49
- 9.5-9.99
- 10.0-10.49
- 10.5-10.99
- 11.0-11.49
- 11.5-11.99
- 12.0-12.49
- 12.5-12.99
- 13.0-13.49
- 13.5-13.99
- > 14

Jan-07 vs. May-11
## Observed Reductions in Hospitalizations

(Currently Under Study)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Before</th>
<th>After</th>
<th>% Change</th>
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<tbody>
<tr>
<td>Discharges per Patient Year</td>
<td>3.14</td>
<td>2.28</td>
<td>-27%</td>
</tr>
<tr>
<td>Days Hospitalized per Patient Year</td>
<td>12.2</td>
<td>8.52</td>
<td>-30%</td>
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A Generalized Methodology for Biophysical System Dynamics

• “... applies to all of medicine.”

• “... could revolutionize medical care.”

• “... asks exactly the right questions ... which are not being asked in medical schools.”

• “... effectively addresses a fundamental issue at the core of medical care: homeostasis.”

• “Places us in grave danger of actually learning something!”
Future Applications and Development

- Extensions to the Erythropoietic Model
- Methadone dosing learning environment
- Antibiotics
- Immunosuppressants
- Anticoagulants
- Collaboration with Emerging “Departments of Systems Biology”
- Biophysical System Dynamics SIG
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