Systems Thinking in Personalized Medicine

Devon C. Campbell
Head, Engineering and Systems – Novartis Molecular Diagnostics
MIT SDM Systems Thinking Conference
October 25, 2011
Agenda

- Personalized medicine and the future of healthcare
- Novartis approach to personalized medicine
- Systems thinking in Rx and Dx co-development
- Systems thinking within Novartis MDx
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What will tomorrow’s health care look like?
Macroeconomic Trends

- Movement to comparative effectiveness
- Evidence based medicine
- Healthcare spending
- Development costs
- Aging populations
- Unhealthy lifestyles
- Informed Patients
- Emerging Markets
- Conservative Regulation
- Pricing and reimbursement
- “Blockbuster” models
- Variable IP rights
Macroeconomic Trends

- Movement to comparative effectiveness
- Evidence based medicine
- Healthcare spending
- Development costs
- Aging populations
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- Pricing and reimbursement
- "Blockbuster" models
- Variable IP rights

PERSONALIZED MEDICINE
Healthcare Inflection Point

- How can we capitalize on the significant advancements in medicine and be focused on the patient’s needs?

<table>
<thead>
<tr>
<th>General approach</th>
<th>Recent blockbuster era</th>
<th>Emerging targeted therapy era</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Broad therapies for large patient pools (e.g., hypertension)</td>
<td>Targeted therapies for sub-populations (e.g., c-kit pos. GIST)</td>
</tr>
<tr>
<td>B</td>
<td>Trial and error; comprehensive screening</td>
<td>Pathways, biomarkers and patient outcomes</td>
</tr>
<tr>
<td>C</td>
<td>Physician-focused sales model</td>
<td>Addressing all relevant stakeholders</td>
</tr>
</tbody>
</table>

Fundamentally, success will depend upon innovation not cost
What is “Personalized” Medicine?

**Personalized Medicine:** Use of genetic or other molecular biomarker information to improve safety, effectiveness, and health outcome of patients via more effectively targeted risk stratification, prevention, and tailored treatment management approaches.

<table>
<thead>
<tr>
<th>A. Risk stratification</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Pts more or less likely to develop disease/conditions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Inform treatment selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Is it safe?</td>
</tr>
<tr>
<td>- Is it effective</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. Inform dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Slow metabolizers vs. rapid metabolizers</td>
</tr>
<tr>
<td>- Therapeutic drug monitoring (TDM)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>D. Prognostic / Predictive tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Identify patients more likely to benefit from standard of care (e.g. adjuvant chemotherapy)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>E. Disease monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Is it safe to continue therapy or should therapy be switched?</td>
</tr>
</tbody>
</table>

| F. Improve or optimize clinical treatment pathways |
Personalized Medicine

- Systems Thinking must be patient-centric for Personalized Medicine to succeed
- Successful delivery of diagnostic test results can positively drive a company’s brand... or drive it into the ground

**HIV & HCV Test**
- 5,000 patients

**6 months incorrect results**
- 3rd party reagent

**Thousands of Patients & Doctors**

**$100M Fine**
- Billions in lost sales

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**ACTION TAKEN AGAINST HOSPITAL**

*By Walter P. Rea* Jr. | Sun Staff

Citing serious and recurring deficiencies, the national organization that just last year ranked laboratory operations at Maryland General Hospital “outstanding with Distinction” last week suspended its approval for two key testing areas at the 336-bed facility.

The College of American Pathologists in Chicago has repeatedly cited the facility’s laboratory operations, with recently issued problems complaint for a similar list of major weaknesses.

The chemistry section of the hospital is responsible for screening and prioritizing diagnostic tests. Promptness in testing is crucial to timely and accurate diagnosis and treatment.

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**AGENDA MAMMA PRINT RECALL**

June 23, 2010

The US Food and Drug Administration (FDA) announced today that it has decided to recall a blood test that has been linked to several deaths and illnesses. The test, known as the MammaPrint test, has been linked to the death of a 6-month-old baby and several cases of breast cancer.

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**THE NEW YORK TIMES**

**Quest Diagnostics Acknowledges Errors in Vitamin D Tests**

January 7, 2009

The nation’s largest medical laboratory company acknowledged today that errors in vitamin D testing have led to incorrect results for thousands of people who had their vitamin D levels tested in the last two years.

The company said that it is offering free returns to affected patients and is offering refunds for any tests that were incorrectly interpreted due to the errors.

An error in the testing process led to incorrect results for hundreds of patients. An error in the testing process led to incorrect results for hundreds of patients.

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**ABBOT LABORATORIES ENTERS INTO CONSENT DECREE WITH FDA**

ABBOT, a big of its sort, announced today that it has reached an agreement with the US Food and Drug Administration to have a consent decree entered which will settle issues involving the lab, located in Lake County, Ill.

The decree was signed by the US Department of Justice and the FDA. The decree requires Abbott to perform a series of corrective actions to ensure the quality of its products. The decree also imposes significant financial penalties on Abbott.

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**NEWS**

**Breast Cancer Testing Scandal Shines Spotlight on Black Box of Clinical Laboratory Testing**

By Karen Dale

A breast cancer testing company has been accused of violating federal law by using a flawed testing process that led to incorrect results for patients.

The company, which is based in California, has been using a testing process that was not approved by the FDA. The testing process was flawed and led to incorrect results for patients.

The company has been accused of violating federal law by using a flawed testing process that led to incorrect results for patients.

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**PERSONALIZED MEDICINE**

9 | Systems Thinking in Personalized Medicine | Novartis Molecular Diagnostics | MIT Systems Thinking Conference | October 2011
Why is Personalized Medicine important?

Personalized Medicine can save Money
Why is Personalized Medicine important?

PERSONALIZED MEDICINE can save Lives

- D. PROGNOSTIC BIOMARKER TESTS
- D. PREDICTIVE BIOMARKER TESTS
- A. RISK STRATIFICATION
- B. INFORMED TREATMENT SELECTION
- C. INFORMED DOSAGE SELECTION
- F. INFORMED CLINICAL TREATMENT PATHWAY
- E. INFORMED DISEASE MONITORING
## Personalized Medicine: Leukemia

- Expanded mental models lead to improved Leukemia survival

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Mental Model</th>
<th>Resolution</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 years ago</td>
<td>1 classification</td>
<td>“Disease of the Blood”</td>
<td>~ 0%</td>
</tr>
<tr>
<td>80 years ago</td>
<td>2 classifications</td>
<td>Leukemia or Lymphoma</td>
<td></td>
</tr>
<tr>
<td>60 years ago</td>
<td>~ 5 classifications</td>
<td>Chronic Leukemia, Acute Leukemia, Preleukemia, Indolent Lymphoma, Aggressive Lymphoma</td>
<td></td>
</tr>
<tr>
<td>Today</td>
<td>~ 38 Leukemias, ~ 51 Lymphomas</td>
<td>Too many to list</td>
<td>~ 70%</td>
</tr>
</tbody>
</table>

5 Year Survival

PERSONALIZED MEDICINE
Personalized Medicine: CML

- Winning the fight against CML in the last decade through targeted therapy

![The New York Times](image)

**January 19, 2010**

**PERSONAL HEALTH**

**Living With a Formerly Fatal Blood Cancer**

**By JANE E. BRODY**

In December 2005, a series of mysterious symptoms — night sweats, easy bruising, swollen ankles and breathlessness upon exertion — prompted Barry to see his doctor. Only six months earlier, a physical exam had found nothing abnormal. But now Barry’s white blood cell count was through the roof.

Before 2000, fewer than half of C.M.L. patients survived seven years; now nearly 90 percent are alive seven years after diagnosis and, like Barry, lead relatively normal lives. (The basketball star Kareem Abdul-Jabbar announced in

<table>
<thead>
<tr>
<th></th>
<th>Before 2000</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Course</strong></td>
<td>Fatal</td>
<td>Indolent</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Poor</td>
<td>Excellent</td>
</tr>
<tr>
<td><strong>Median survival, yrs</strong></td>
<td>3-6</td>
<td>Potentially multi-decade</td>
</tr>
<tr>
<td><strong>Frontline treatment</strong></td>
<td>Allogeneic SCT, IFN alfa</td>
<td>TKIs</td>
</tr>
<tr>
<td><strong>Second-line treatment</strong></td>
<td>Not established</td>
<td>Allogeneic SCT</td>
</tr>
</tbody>
</table>

### Personalized Medicine: Addt’l successes

#### Example

- **HER2+ testing for Herceptin**

#### Type

- Predictive Companion Dx to select patient population for Herceptin
- Detection/Prognostic Dx test for IBD that differentiates Crohn’s disease from ulcerative colitis
- Entocort EC is used to treat Crohn's disease only
- Prognostic Dx that indicates likelihood of distant recurrence to inform clinicians in determining best course of breast cancer treatment
- Detection Companion Dx test for presence of mutated BRAF gene supporting personalized treatment of metastatic melanoma
- Patients take the drugs only after test shows they have the mutation.

#### Clinical and/or Economic Significance

- Significant increase of total life years
- High impact on Herceptin sales
- Five fold sales increase in four years after introduction of Dx test
- Less chemotherapy leads to improved quality of life for patients and lower overall cost of treatment
- High margins, high reimbursement rate
- Offers the opportunity for significantly more effective treatment for patients
- Gained early FDA approval two months ahead of its PDUFA date.
Personalized Medicine: Mental Model Expansion

- Subpopulation differentiation for treatment provides a logical starting point for thinking about the boundaries of systems thinking mental models.
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To enable Personalized Medicines of their drugs, Pharma are taking three general approaches

- Leverage existing but *separate* internal Dx and Rx businesses

Examples:
- Abbott
- Roche

**SEPARATE DIVISION GOALS / MOTIVATION**

**DESIRE TO UTILIZE LEGACY PRODUCTS**

**REGULATORY DIFFERENCES**

**DIFFERENCES IN CORP. CULTURE**
To enable Personalized Medicines of their drugs, Pharma are taking three general approaches

- **Leverage existing but separate internal Dx and Rx businesses**
- **Outsource most CDx development by partnering with Dx companies**

Examples:
- Amgen: Dxs
- BMS, OSI: Dako
- Merck: Celera
- AZ: Dako
To enable Personalized Medicines of their drugs, Pharma are taking three general approaches:

- Leverage existing but *separate* internal Dx and Rx businesses
- Outsource most CDx development by partnering with Dx companies
- Establish internal, fully integrated MDx capability

Example:
- Novartis MDx
Novartis approach to Personalized Medicine

- **Novartis Background***
  - Leading market position of our healthcare business portfolio
  - One of 20 largest companies by market capitalization
  - Most new US drug approvals in the industry since 2000
  - One of the industry’s biggest investors in research
    - ~16% net sales reinvested in R&D

- **Novartis MDx**
  - Unique Structure:
    - Stand alone business unit within Novartis Pharma
  - Operating Philosophy:
    - Internal capability and external partners
    - Take the Regulatory high road with FDA
    - Hire “rock star” talent
  - Global Reach

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* 2010 NVS Annual Report
Novartis approach to Personalized Medicine

- The Novartis system for delivering on the promise of Personalized Medicine recognizes strength in diversity

**NVS Biomarker Discovery and Translational Medicine**

- Long standing research efforts
- Specialized skills in:
  - Pathways and genetics
  - Research assay development
- **Produces biomarkers of clinical utility for a medicine**

**MDx Diagnostic Development and Commercialization**

- Specialized Diagnostic skills in:
  - Regulatory
  - Intellectual Property
  - Technical Development
  - Analytical & Clinical Validation
  - Reagent Manufacturing
  - Channel and reimbursement
- **Produces consistent, regulated, widely available diagnostic tests**
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Dx Development is an FDA regulated, stage-gate process requiring specialized skills.

**Phase 0**
- Concept
  - Confirms whether the business case for a new product idea warrants further investment.

**Phase 1**
- Feasibility & Planning
  - Confirms that project risks are sufficiently understood and that plans and requirements are realistic.

**Phase 2**
- Design & Development
  - Confirms that product development is complete and ready for validation.

**Phase 3**
- Launch Readiness
  - Confirms that the product and organization are ready for market launch.

**Phase 4**
- Commercialization
  - Confirms that operations are stable enough to transfer to sustaining operations.

**System Design & Development**

**Voice of Market**

**Requirement Decomposition**
- Sensitivity
- Specificity
- Turn Around Time
- Costs
- Etc...

**Instrument mfg & validations**
- Reagent mfg & validations
- Software mfg & validations
- Regulatory Submissions

**Analytical Performance**
- Producing a reliable single result
- Robustness
- Accuracy
- Precision (Repeatability/Reproducibility)
- Sensitivity (LOD)
- Specificity (Interference factors)
- Performance around the cutoff
- Sample type/matrix
- Potential for carryover, cross hybridization
- Stability

**Clinical Performance**
- Clinical sensitivity
- Clinical specificity
- Positive/Negative Predictive Value
- Likelihood Ratio’s
Dx Development becomes even more complicated when performed in parallel with Rx Research and Development.
There are two primary Rx/Dx Co-development options

**Ideal Rx/Dx Co-Development**

**Prospective Clinical Trial Validation with IVD Test**
- Develop IVD
- Rx Registration Trial

**Bridging Strategy using Clinical Trial Assay (CTA) & IVD**
- Develop CTA
- Rx Registration Trial
- Compare CTA & IVD Results
- Develop IVD

**Rx AND Dx CO-DEVELOPMENT**

12-18 mos

Rx AND Dx CO-DEVELOPMENT

Rx/Dx Co-Development
Taking a holistic perspective of the system, there are several key questions we can ask while keeping the END in mind...

1. What analytical platform is needed for the Dx?
2. What will be the Rx biomarker analytical platform in discovery and early development and how different is it from #1?
3. How should we align to minimize variance in platform/assay selection?
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Diagnostics Development

- As mental models are extended, the sources of variation explode:
  - Biomarkers selection, data management
  - Sample integrity
  - Platform technologies, Dx partner selection
  - Bridging study performance

- Due to the complexity of the Rx/Dx co-development arena, successful development demands a system perspective capable of identifying and mitigating variation
Managing Variance

- Robust CDx performance is critical for Rx approval

All steps have an inherent variation...

Error budget stacking can lead to shifting clinical results

Over time……
- Reagent lot changes
- New lot of plastic in disposable
- Formulation changes
- Instrument changes

Systems thinking used to minimize variance

... and variance is cumulative
Managing Variance: Data Integrity

- Is your biomarker real or has there been a data mgmt problem?
- Simple errors can cause havoc
  - Excel cut & paste errors
  - Inadvertent use of duplicate samples
  - Reversed sample labels
  - Incorrect tables & figures
  - Incorrect gene lists
  - Experimental data sets confounded by nonrandom factors
## Managing Variance: Sample Integrity

<table>
<thead>
<tr>
<th>Procedure*</th>
<th>*Variability impacts on...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient posture</td>
<td>Blood volume, biomarker density, selective isolation of specific sizes of biomarkers</td>
</tr>
<tr>
<td>Venipuncture site</td>
<td>Composition of biomarker</td>
</tr>
<tr>
<td>Syringe or needle type</td>
<td>Gas permeability, platelet activation, hemolysis</td>
</tr>
<tr>
<td>Tube additives</td>
<td>Composition on biomarkers, side reactions between biomarkers &amp; additives</td>
</tr>
<tr>
<td>Tube fill volume</td>
<td>Hemolysis, concentration of tube additives</td>
</tr>
<tr>
<td>Tourniquet duration</td>
<td>Blood volume, biomarker density, selective isolation of biomarker sizes</td>
</tr>
<tr>
<td>Storage conditions</td>
<td>Platelet activation, stability of components</td>
</tr>
<tr>
<td>Freeze thaw</td>
<td>Platelet activation, hemolysis, genomic &amp; proteomic stability</td>
</tr>
</tbody>
</table>

*Lim et al Analytical Chem. 2011, 83 8-13

- **Is your biomarker real or is there a sample problem?**
  - Apparent biological variation of the biomarker may be due to collection errors, storage variation, etc...

**FDA THINKS IT’S IMPORTANT**
Managing Variance: Balancing Assay & Device

- Strive to simultaneously prevent both biological (biomarker) variability and platform variability.
  - Use similar platform technologies for biomarker qualification and CDx development
  - Use known, characterized platform technologies
  - Apply DFSS tools and system modeling wherever possible throughout assay and system development

\[ \text{Total program technical risk} = \text{sum of all risks} \]
Managing Variance: Multivariate Modeling

- Expansion of mental models to include multiple, simultaneous factors leads to better informed models and improved system performance
Managing Variance: MDx Example

- Standardization of an assay providing greater intra- and inter-lab reproducibility

**Lab Developed Tests**

- Non-standardized kits
- Non-GMP; minimal QA assurance standards
- Sample preparation and PCR in two separate steps; increased risk of PCR contamination
- Complex; prone to human error
- Variable

**MDx/Partner Standardized Test**

- Standardized IVD kit
- Pegged to international standards
- Highly reproducible
- All testing steps combined within one input device; elimination of PCR contamination
- Simple; automation minimizes human errors
- GMP-quality; highly reproducible
- Modular platform expands market access
Summary

- Personalized medicine and the future of healthcare
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Questions

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