Genetics and Genomics in Clinical Medicine

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Partners Healthcare
“I believe we are moving into a remarkable and powerful new era in medicine and particularly in prescription drugs. I’d refer to it as an era of personalized medicine.”

Michael Leavitt, Secretary HHS
January 18, 2005
Personalized Medicine is a Disruptive Technology

Personalized Medicine will revolutionize the way medicine is going to be practiced

Some are arguing that PM is a disruptive technology that is similar to:

- Development of building automobiles for the population
- Development of color television by RCA
- Development of personal computers

It is debatable if the existing healthcare infrastructure is adequate to meet the goals of PM
What changes in Healthcare are needed

- There has to be a shift in emphasis on prevention
- There have to be strategies for early detection
- For existing drugs and treatments, it is necessary to show that incorporation of genetics and genomics in clinical decision making results in better outcomes
- There has to be a change in thinking that stratifying patient populations would provide value for all stakeholders
- Need bold steps by regulatory agencies for implementation
- Need a new framework to reimbursement
- Need a comprehensive training and education plan
Prevention is already practiced. Childhood vaccination is an example.

For adult onset disorders, prevention requires identification of at risk individuals.

Need development and utilization of risk scores.

Family histories and genotyping/full genome sequencing.
One Family with Breast Cancer History

Living With the BRCA Gene: One Family’s Story

Generations of the Price family have been affected by a mutation in the BRCA gene that significantly raises the risk of breast and ovarian cancer. A patient who carries the detectable gene has a 90 percent chance of getting it in six to ten of her children. In 2006, Christine Veidt became the first family member to get a BRCA test that resulted in a positive diagnosis. She inherited the mutation from her mother. As many of her relatives followed, they have made different choices about how to manage their genetic predisposition in the increasingly common condition.

Robert William Price
Died of colon cancer at age 50.

Eleanor Price Vahle, 67
Has not been tested for the gene, but is assumed to be positive because her daughter has it. Ovarian cancer was diagnosed.

Robert Nelson Price
Died of pancreatic cancer. One of his daughters died of breast cancer.

Brenda Price, 41
Treated negative for the gene, and had her ovaries removed. Even for frequent mammograms and MRIs, “I know some women have their breasts removed. There’s a little shoot... I’m not scared of getting cancer, but I’m pretty confident that we wouldn’t catch it early if we never did watch it.”

Robert Price, 88
Died of pancreatic cancer.

Lori Frein, 27
Treated positive for the gene. “When they explained that that means my daughter would not get it unless I was shared. I just felt really happy that I don’t have to worry about this anymore.”

Deborah Lindner, 33
Tested positive for the gene and had a prophylactic mastectomy this summer at age 33. She is planning to have her ovaries removed before she turns 40. “I just feel really happy that I don’t have to worry about this anymore.”

Christie Vodni, 28
After breast cancer was diagnosed, she tested positive for the gene. She then had a bilateral mastectomy and later had her ovaries removed. “I got rid of the areas where it can come. I’d rather be proactive than have something showing up.”

Judi Dembeck, 41
After her sister learned she had cancer, she tested positive for the gene. She gets regular mammograms and is waiting to decide whether to have a fourth child before considering surgery.

Darren Price, 47
Treated negative for the gene.

Jean Vodni, 64
Learnt she had breast cancer at age 46. Underwent chemotherapy and had her breasts and ovaries removed. She later tested positive for the gene. “When I tested positive, I knew my daughters needed to be tested as well.”

Janice Price Benson
Had never been tested for the gene, but must have passed it to her daughter. Breast cancer was diagnosed at age 56. Died of breast cancer in July at age 62.

Deanna Price, 47
Treated negative for the gene, and had her ovaries removed. Even for frequent mammograms and MRIs, “I know some women have their breasts removed. There’s a little shoot... I’m not scared of getting cancer, but I’m pretty confident that we wouldn’t catch it early if we never did watch it.”

Jeanne Vodni, 64
Learnt she had breast cancer at age 46. Underwent chemotherapy and had her breasts and ovaries removed. She later tested positive for the gene. “When I tested positive, I knew my daughters needed to be tested as well.”

Gloria Vodni Sproul, 58
Has not been tested.

“Told no one need to know because it’s a situation where we would just continue to take care of ourselves extremely well.”
Early Detection

Early detection in cancer leads better long term survival. Eg., Colon Cancer

Early detection can lead to prevent progression to diabetes. Diabetes prevention program (DPP) and Look AHEAD (Action for Health in Diabetes) for obesity, prediabetes and type II diabetes

Clinical as well as genetic and genomic information would help us with early detection
Colon Cancer Survival

Time of diagnosis is critical

If detected at Stage I, chances of survival are 95%
If detected at Stage IV, chances of survival are 5%

Early detection would be most helpful

There is a need for pathway specific biomarkers
Outcomes studies: Mrs. Baker’s response to Iressa

Before Two months later

28. Ratio: 5.5

28. Ratio: 6.2
EGFR Mutations
Appropriate clinical trial design may result in improved outcomes

**Chemotherapy**


**First line TKI: No stratification**

- Schiller, et al., 2002 NEJM 346(2):92

**First line TKI: Target Group**

75% RR
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>RR</th>
<th>DCR</th>
<th>OS (months)</th>
<th>PFS (months)</th>
<th>1-YR SURVIVAL</th>
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</thead>
<tbody>
<tr>
<td>Molecular Stratification of first line gefitinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Asahina, et al., 2006 Br J Ca 95(8):998.</td>
<td>16</td>
<td>75.0%</td>
<td>81.0%</td>
<td>NR</td>
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<td>Inoue, et al., 2006 JCO 24(21):3340.</td>
<td>16</td>
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<td>88.0%</td>
<td></td>
<td>9.7</td>
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<tr>
<td>Niho, et al., 2006 JCO 24(1):64.</td>
<td>40</td>
<td>30.0%</td>
<td></td>
<td>13.9</td>
<td>55.0%</td>
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<tr>
<td>Lin, et al., 2006 Lung Cancer 54(2):193.</td>
<td>53</td>
<td>32.1%</td>
<td>52.8%</td>
<td>9.4</td>
<td>3.2</td>
<td>41.5%</td>
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<tr>
<td>Reck, et al., 2006 Clin Lung Cancer (6):406.</td>
<td>58</td>
<td>5.0%</td>
<td>45.0%</td>
<td>29 weeks</td>
<td>7 weeks</td>
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<tr>
<td>Suzuki, et al., 2006 Br J Cancer 94, 1599.</td>
<td>34</td>
<td>26.5%</td>
<td>50.0%</td>
<td>14.1</td>
<td></td>
<td>58.2%</td>
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<tr>
<td>No stratification of first line erlotinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Giaccone, et al., 2006 CCR 12(20 Pt 1): 6049.</td>
<td>53</td>
<td>22.7%</td>
<td>53.0%</td>
<td>391 days</td>
<td>84 days</td>
<td></td>
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<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Schiller, et al., 2002 NEJM 346(2):92</td>
<td>1155</td>
<td>19.0%</td>
<td></td>
<td>7.9</td>
<td></td>
<td>33.0%</td>
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Stratifying patient populations

Some of the strategies are developed by Pharmaceutical companies. Eg., Herceptin

Some strategies are required by regulatory agencies. Eg., Panitumimab and EMEA

Some strategies are suggested by regulatory agencies. Eg., Genetic testing for warfarin dosing by FDA

Some strategies are being developed by Pharma and Biotech companies. Eg., New class drugs for Tarceva resistant lung tumors

A new value proposition for drug developers
Drug Marketability and Value
(From Lechleiter of Lilly)

Benefits

Using markers to identify target patients results in smaller possible market.

But likely market is greatly increased, since higher response rate drives:
• Greater, faster uptake
• Increased cycles delivered by capturing all responders.

Also protects non-responders from drug related adverse events.

Example: Peak sales increase for marker with 25% frequency

<table>
<thead>
<tr>
<th>Measure</th>
<th>Base</th>
<th>With marker (3 scenarios)</th>
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</thead>
<tbody>
<tr>
<td>Market size (pts)</td>
<td>200k</td>
<td>50k</td>
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<tr>
<td>Response rate</td>
<td>25%</td>
<td>50%</td>
</tr>
<tr>
<td>Peak share</td>
<td>20%</td>
<td>80%</td>
</tr>
<tr>
<td>Patients Rx’d</td>
<td>40k</td>
<td>40k</td>
</tr>
<tr>
<td>Responders (Rs)</td>
<td>10k</td>
<td>20k</td>
</tr>
<tr>
<td>Non-Rs</td>
<td>30k</td>
<td>20k</td>
</tr>
<tr>
<td>Total cycles: (6 per R, 2 per Non-R)</td>
<td>120k</td>
<td>160k</td>
</tr>
<tr>
<td>Price per cycle</td>
<td>$1k</td>
<td>$1k</td>
</tr>
<tr>
<td>Peak sales</td>
<td>$120m</td>
<td>$160m</td>
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Extant of benefits depends on frequency of and response rate with marker.
Reimbursement

Insurance companies and CMS will reimburse if:

• Use of genetic information in clinical decisions is shown to be effective
• If the FDA requires the use of such treatment
• If treatment guidelines suggest use of genetic information
• If there is a good cost/benefit ratio
A Prospective Randomized Clinical Trial

Creating an optimal warfarin dosing nomogram (CROWN)

Nomogram development phase (500 patients)

Randomized controlled clinical trial (1,200 patients) with relevant clinical endpoints and a cost-effectiveness analysis.

Participating hospitals

- Brigham and Women’s Hospital
- Massachusetts General Hospital
- Newton-Wellesley Hospital
- NSMC
- Faulkner Hospital
PERSONAL DOSE
In Milestone, FDA Pushes Genetic Tests Tied to Drug Agency Seeks to Tame Risks of Blood Thinner; Some Doctors Protest
By ANNA WILDE MATHEWS
August 16, 2007; Page A1
"Today's approved labeling change is one step in our commitment to personalized medicine. By using modern science to get the right drug in the right dose for the right patient, FDA will further enhance the safety and effectiveness of the medicines Americans depend on,"

Andrew C. von Eschenbach, M.D.
Commissioner of FDA
“We estimate that formally integrating genetic testing into routine warfarin therapy could allow American warfarin users to avoid 85,000 serious bleeding events and 17,000 strokes annually. We estimate the reduced health care spending from integrating genetic testing into warfarin therapy to be $1.1 billion annually, with a range of about $100 million to $2 billion.”

Andrew McWilliam, Randall Lutter and Clark Nardinelli
Office of Policy and Planning at the FDA
AEI-BROOKINGS JOINT CENTER FOR REGULATORY STUDIES November 2006
Current reimbursement systems in the US do not provide incentives for development or implementation of diagnostics for diagnosis or treatment decision.

Develop value propositions about how reimbursement can benefit all parties

Models for thinking about a revamped reimbursement systems

Experiments with Payor, Providers and Government
Education

Educating Healthcare professionals
Incorporating genetics into clinical training
Educating the public
Incorporating genetics into curricula