Genetics and Genomics in Clinical Medicine

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National Thought Leaders on Personalized Medicine

"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

- **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 BRCA1 gene that significantly raises the risk of breast and ovarian cancer. A parent who carries the defective gene has a 50 percent chance of passing it on to his or her children. In 2002, Christie Veale became the first family member to get a DNA test that revealed she had inherited the mutation from her mother. As many of her relatives followed, they have made different choices about how to manage their genetic predisposition to the life-threatening condition.

Robert Milton Price
Died of colon cancer at age 50.

Two of Robert and Eleanor's sisters died of breast cancer. Another sister died of ovarian cancer.

Eleanor Price Veith, 87
Has not been tested for the gene, but is assumed to be positive because her daughter has it. Ovarian cancer was diagnosed.

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

Rosalyn Price Pierce
Had never been tested for the gene, but must have passed it to her daughter. First developed breast cancer at age 34. Died of breast cancer in July at age 67.

Janice Price Brown
Had never been tested for the gene, but must have passed it to her daughters. Ovarian and breast cancer were first diagnosed at age 33. Died of breast cancer at age 57 in 2001.

Joan Veith Lindner, 64
Learned she had breast cancer at age 48, 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 Veith Spurlock, 59
Has not been tested.

"There's no real need to know because it is a situation where we would just continue to take care of ourselves extremely well."

Dana Pierce, 47
Tested negative for the gene.

Brenda Russo, 41
Tested positive for the gene, and had her ovaries removed. Goes for frequent mammograms and M.R.I.'s.

"I know some women have their breasts removed. To me that's a little drastic... I'm not safe from getting cancer, but I'm pretty confident that we would catch it early if we ever did catch it."

Jodi 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.

"You can have everything taken out and a few cells maybe weren't caught. There's no foolproof way to avoid cancer."

Christie Veale, 39
After breast cancer was diagnosed, she tested positive for the gene. She then had a bilateral mastecomy and later had her ovaries removed.

"I've gotten rid of the areas where it can come. I'd rather be proactive than have something chasing me."

Lori French, 37
Tested negative for the gene.

"When they explained that that means my daughter would not get it either, I was elated."

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."

Lisa Spurloc
brother has
been tested
gene. He rec
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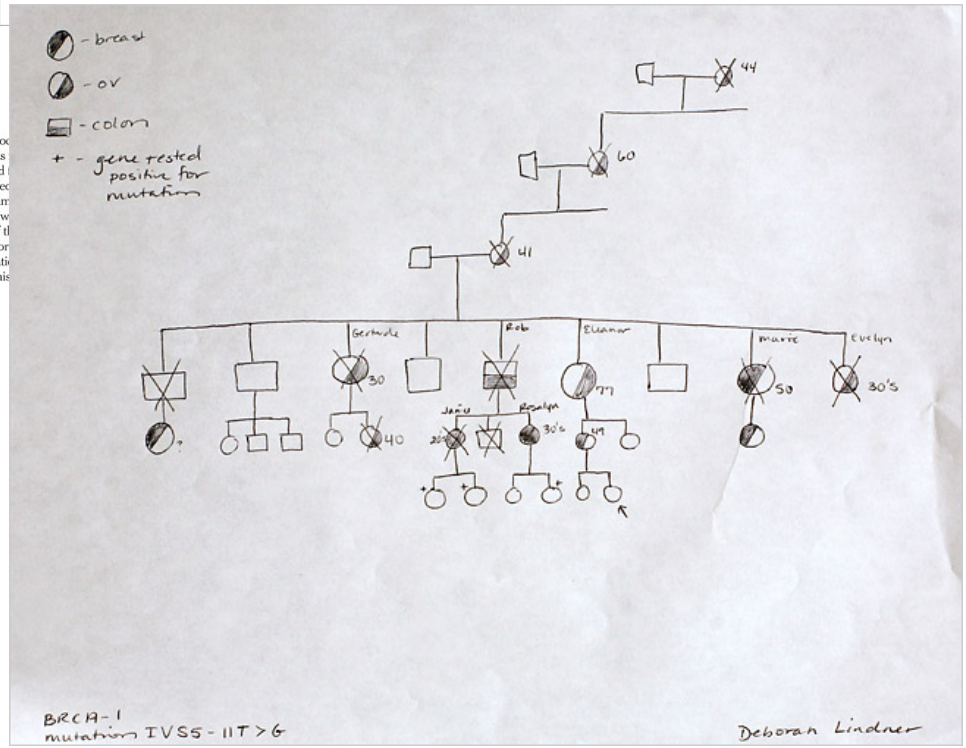
risk.



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

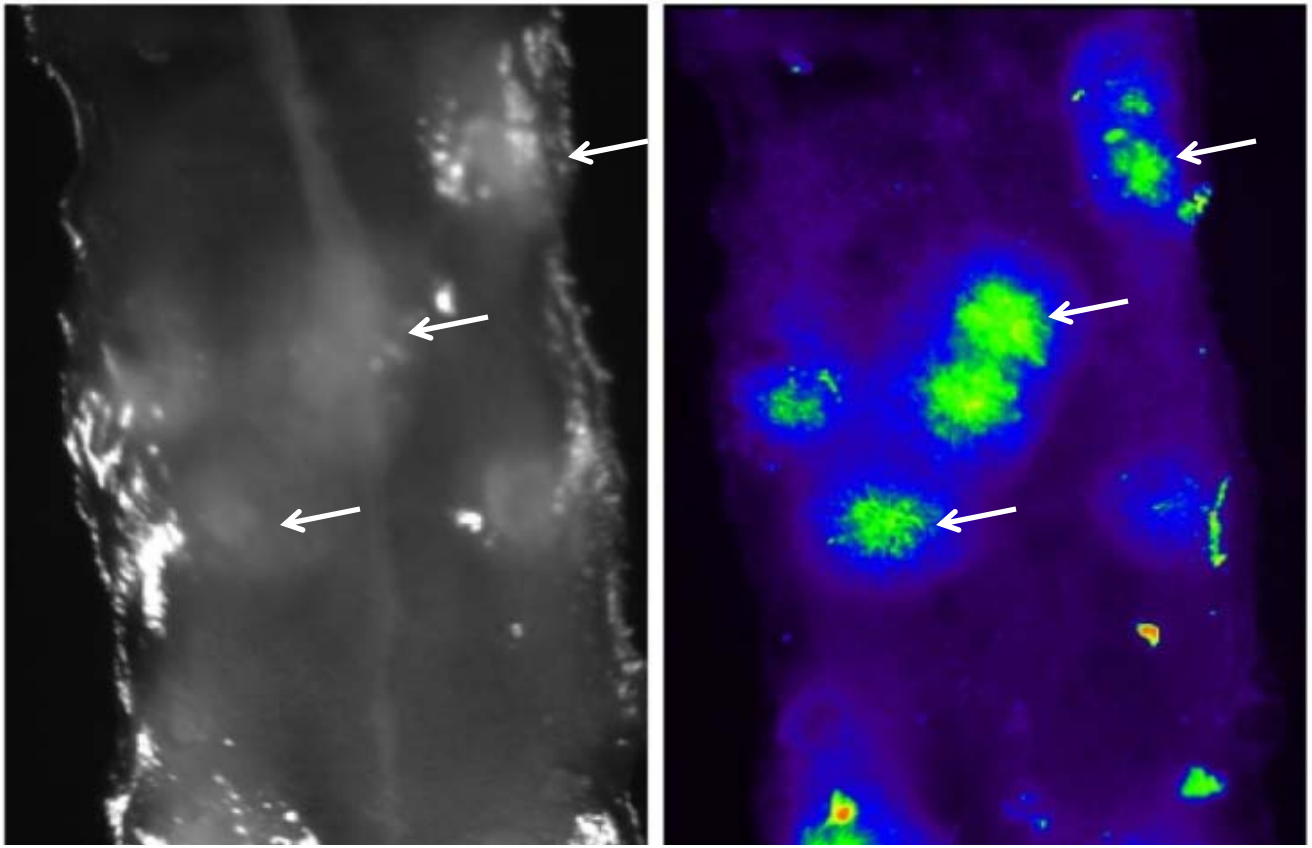
Time of diagnosis is critical

- **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

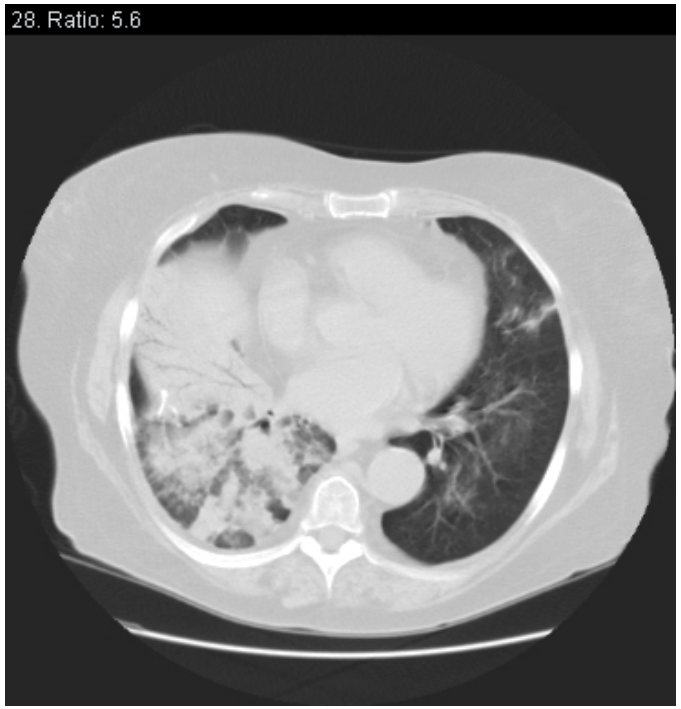
There is a need for pathway specific biomarkers

Prosense Imaging

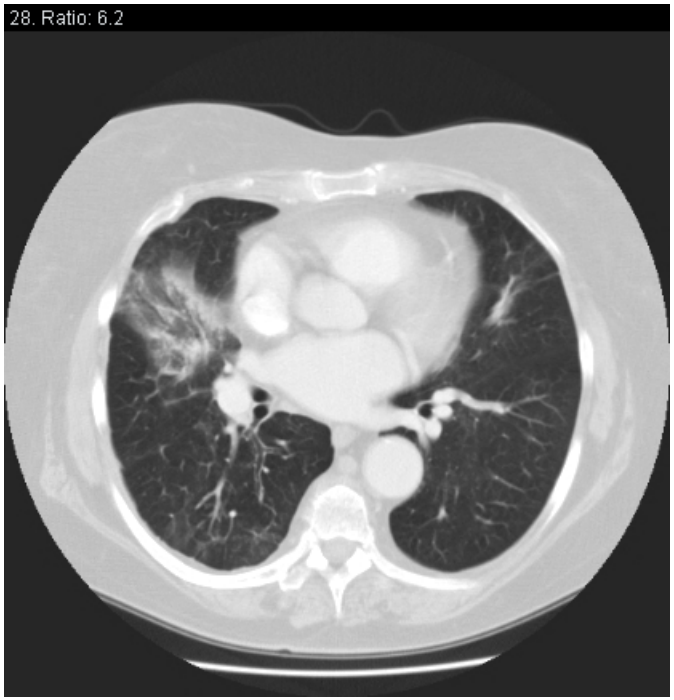


Outcomes studies: Mrs. Baker's response to Iressa

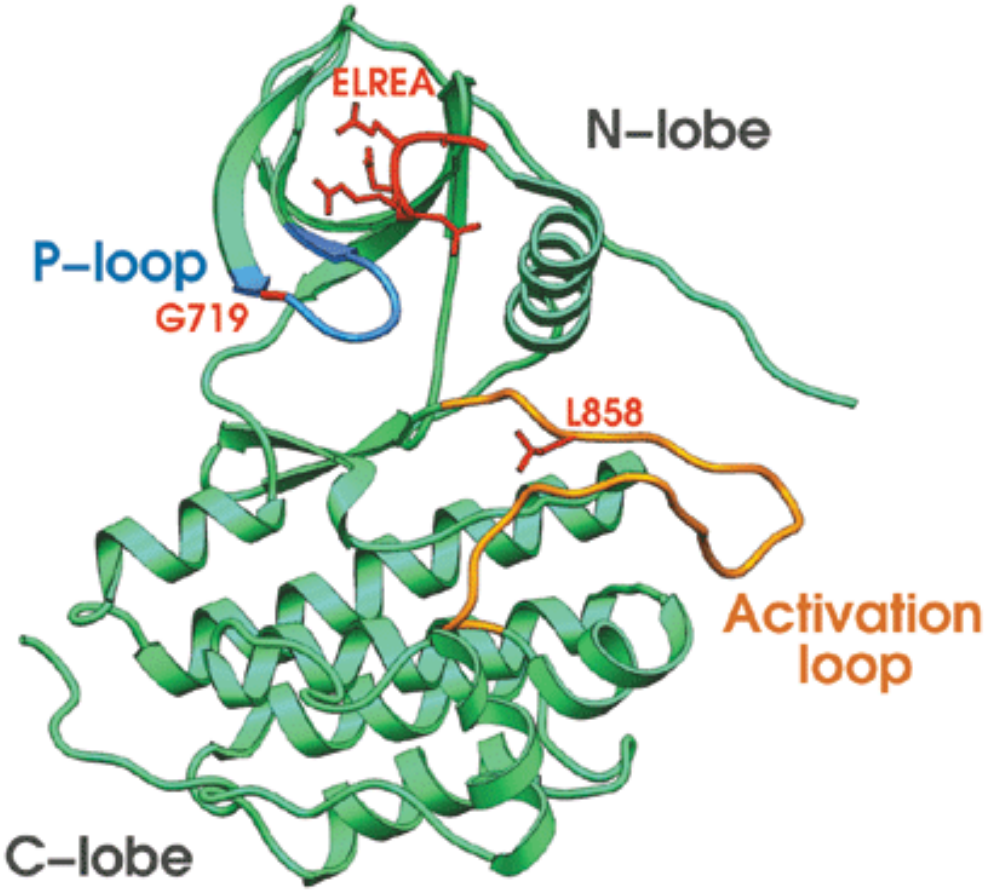
Before



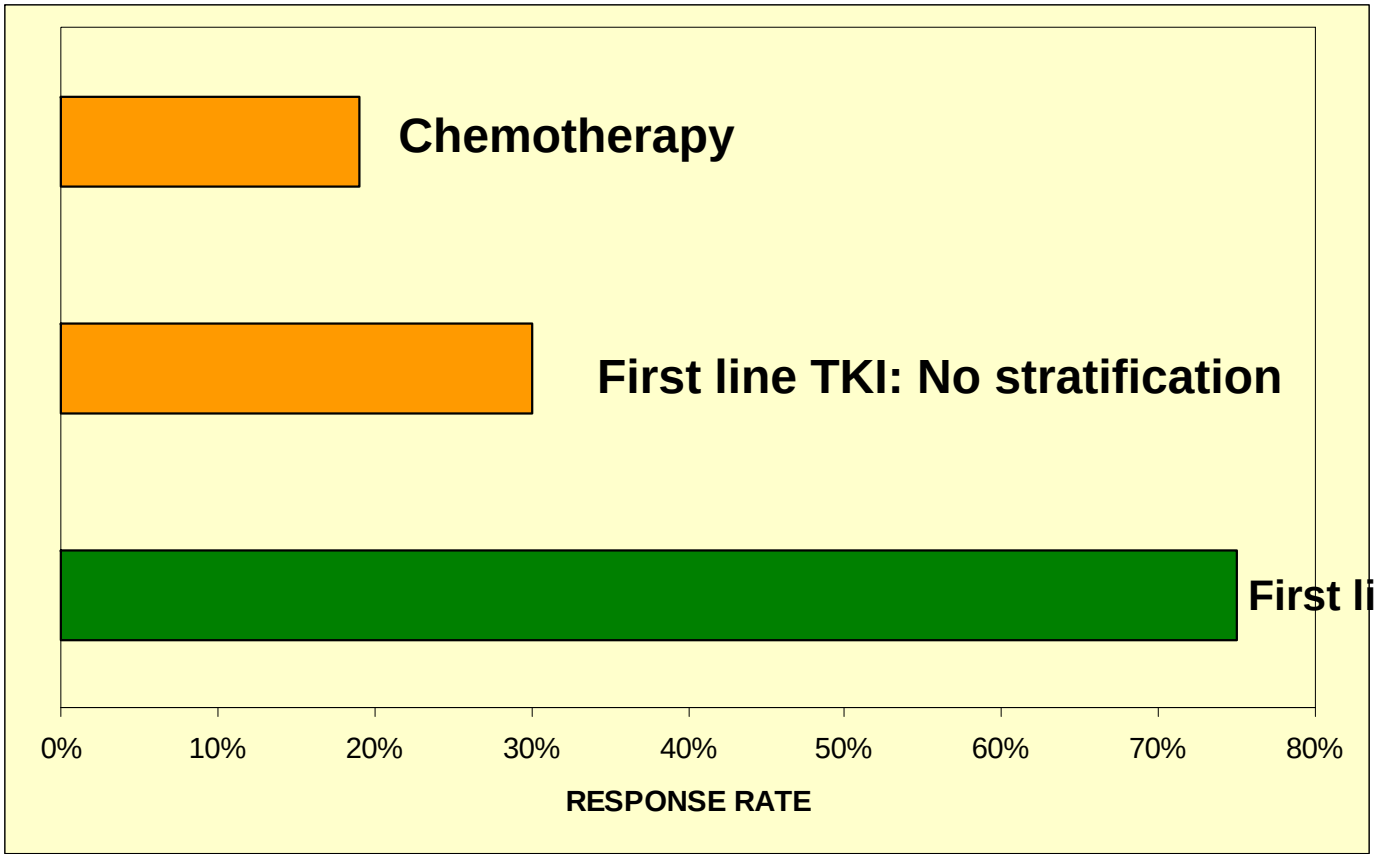
Two months later



EGFR Mutations



Appropriate clinical trial design may result in improved outcomes



Asahina, et al., 2006 Br J Ca 95(8):998.
Inoue, et al., 2006 JCO 24(21):3340.
Lee, et al., 2005 CCR 11(8):3032.
Niho, et al., 2006 JCO 24(1):64.
Lin, et al., 2006 Lung Cancer 54(2):193.

Reck, et al., 2006 Clin Lung Cancer (6):406
Suzuki, et al., 2006 Br J Cancer 94, 1599.
Kimura, et al., 2006 J Thorac Oncol. 1(3):260
Giaccone, et al., 2006 CCR 12(20 Pt 1): 6049.
Schiller, et al., 2002 NEJM 346(2):92

Molecular Stratification for First-Line Gefitinib

	N	RR	DCR	OS (months)	PFS (months)	1-YR SURVIVAL
Molecular Stratification of first line gefitinib						
Asahina, et al., 2006 Br J Ca 95(8):998.	16	**75.0%**	81.0%	NR	8.9	
Inoue, et al., 2006 JCO 24(21):3340.	16	**75.0%**	88.0%		9.7	
No stratification of first line gefitinib						
Niho, et al., 2006 JCO 24(1):64.	40	**30.0%**		13.9		55.0%
Lin, et al., 2006 Lung Cancer 54(2):193.	53	**32.1%**	52.8%	9.4	3.2	41.5%
Reck, et al., 2006 Clin Lung Cancer (6):406.	58	**5.0%**	45.0%	29 weeks	7 weeks	
Suzuki, et al., 2006 Br J Cancer 94, 1599.	34	**26.5%**	50.0%	14.1		58.2%
No stratification of first line erlotinib						
Giaccone, et al., 2006 CCR 12(20 Pt 1): 6049.	53	**22.7%**	53.0%	391 days	84 days	
Chemotherapy						
Schiller, et al., 2002 NEJM 346(2):92	1155	**19.0%**		7.9		33.0%

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

Measure	Base	With marker (3 scenarios)		
Market size (pts)	200k	50k	50k	50k
Response rate	25%	50%	75%	90%
Peak share	20%	80%	80%	95%
Patients Rx'd Responders (Rs) Non-Rs	40k 10k 30k	40k 20k 20k	40k 30k 10k	47.5k 42.75k 4.75k
Total cycles: (6 per R, 2 per Non-R)	120k	160k	200k	266k
Price per cycle	$1k	$1k	$1k	$1k
Peak sales	$120m	$160m	$200m	$266m
		+33%	+66%	+122%

Extent 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

Regulatory Activity

WSJ.com THE WALL STREET JOURNAL. ONLINE

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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

FDA Approves Label Change for Warfarin

FDA Approves Genetic Testing Labeling For Blood-thinning Drug

August 18, 2007

"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

Cost/Benefit Analysis for Warfarin testing

"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

Reimbursement systems

- **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