Genetics and Genomics in Clinical Medicine

Raju Kucherlapati, Ph.D.
Harvard Medical School
The human genome at ten

Nearly a decade on from the completion of the draft sequence of the human genome, researchers should work with the same intensity and focus to apply the results to health.

The knowledge about the human genome and the explosion of new tools and technologies are bringing unprecedented knowledge about genes involved in human health and disease.
Significant Genomic Achievements
Decreasing Cost of Sequencing

<table>
<thead>
<tr>
<th>Year</th>
<th>Cost / Base Pair</th>
</tr>
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<tbody>
<tr>
<td>1995</td>
<td>~$1,000/genome</td>
</tr>
<tr>
<td>1998</td>
<td>$10,000/genome</td>
</tr>
<tr>
<td>2010</td>
<td>$1,000/genome</td>
</tr>
<tr>
<td>2015</td>
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</tr>
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</table>
Genetics is Changing Medical Landscape
Three Revolutions in Genetics/Genomics

Late last Century: Recognition that genetics plays a very important role in virtually all aspects of human health and disease

Last Century and early this Century: Human Genome Project provided the information and tools to rapidly identify genes in disease

Current revolution: Application of the genetics/genomics knowledge for patient care, PERSONALIZED MEDICINE
Twin Studies
The First Revolution: Role of genes in health and disease

- Many diseases run in families
- Twin studies
  - Obesity and Diabetes
    - What is the probability of developing diabetes?
    - If nobody in your family is affected – 4-5%
    - If a sibling has Diabetes – 30%
    - If you are a member of an identical twin and the other twin is affected – 90%
- Health is also affected by genes
  - Longevity
- Environment also plays an important role
FDA recommendation for genetic testing

In 2007, the Food and Drug Administration (FDA) recommended that patients starting a course of treatment using warfarin, first take a simple genetic test to help their physicians more accurately determine initial dosing levels. Patients metabolize warfarin differently depending on their unique genetic profile. Too high a dose causes severe bleeding, while a dose that’s too low can lead to dangerous blood clots. In fact, more than one in five first-time warfarin users wind up in the hospital during their first six months of treatment as doctors use “trial and error” to fine-tune dosing levels.

**FDA**

“Lower initiation doses should be considered for patients with certain genetic variations in CYP2C9 and VKORC1 enzymes.”

Medco-Mayo Clinic research published on-line in the *Journal of American College of Cardiology* in March 2010, showed hospitalization rates for patients taking warfarin dropped by approximately 30 percent when genetic information was available to doctors prescribing the drug.
February 2010

“Medco Acquires Leading Genetics Healthcare Company, DNA Direct”

June 2010

“CVS Caremark and Generation Health Outline Target Medications That Will Be the Focus of New Pharmacogenomics Partnership”

May 2010

“Walgreens said late Wednesday that it would postpone selling a personal genetic test through its drugstores after the Food and Drug Administration challenged the legality of the test, Andrew Pollack writes in The New York Times.”

Patients served: Medco  65 Million  
CVS/Caremark  50 Million
Consumer Genetics
WHO KILLED HEALTH CARE?

AMERICA’S $2 TRILLION MEDICAL PROBLEM—AND THE CONSUMER-DRIVEN CURE

REGINA HERZLINGER
Whole-Genome Sequencing in a Patient with Charcot–Marie–Tooth Neuropathy

Personal Genomes Project

Goal: Sequence 100,000 individuals and make data publicly available
Risk Assessment
Cancer Free at 33, but Weighing a Mastectomy

NY Times September 16, 2007
One Family with Breast Cancer History

Living With the BRCA Gene: One Family’s Story

Robert Minnie Price
Died of ovarian cancer at age 50.

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

Brenda Rose, 41
Treated positive for the gene, and had both ovaries removed. She has frequent mammograms and MRIs.

I know some women have their breasts removed. Yours that’s a little drastic... I’m not sure how to start treating cancer, but I’m pretty confident that we would catch it early if we ever did catch it.

Judi Denbeck, 41
After her sisters learned she had cancer, she tested positive for the gene. She gets regular mammograms and is waiting to decide whether to have a bilateral mastectomy.

You can have everything taken out and it’s not like maybe you’ll catch it. There’s no denying you can’t avoid cancer.

Cherise Veide, 30
After breast cancer was diagnosed, she tested positive for the gene. She is considering prophylactic mastectomy.

When they explained that it means my daughter would not get a cancer, I was shocked.

Lori Pruch, 27
Treated negative for the gene. She is considering prophylactic mastectomy.

I just feel really happy that I don’t have to worry about this anymore.

Deborah Linde, 33
Treated positive for the gene and had a prophylactic mastectomy.

I am happy that he mastectomy was successful.

Eleanor Price Veide, 27
Has not been tested for the gene, but is assuming to be negative because her daughter has it. Ovarian cancer was diagnosed.

Jean Veide Lindon, 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 daughter needed to be treated as well.

Gloria Veide Sporesick, 59
Has not been tested.

"There’s no need to delay because it’s the situation where we would just continue to take care of ourselves extremely well.”

BRCAl Gene Testing - TVS5 - BTY6

Deborah Lindon
### Family History at Newton-Wellesley

Kevin Hughes MD

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**Have you, or has anyone in your family, have or had cancer?**

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Bloodline</th>
<th>Disease 1</th>
<th>Age Dx</th>
<th>Disease 2</th>
<th>Age Dx</th>
<th>Disease 3</th>
<th>Age Dx</th>
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<tr>
<td>Mother</td>
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<td>Kidney or Bladder Cancer</td>
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<td>Father</td>
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<tr>
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<tr>
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<tr>
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<td>Paternal</td>
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<tr>
<td></td>
<td></td>
<td>Sarcoma</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Stomach Cancer</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Thyroid Cancer</td>
<td></td>
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</tbody>
</table>

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**Avon Comprehensive Breast Care Center**

### Cancer Risk Assessment Survey

- **Patient Name:**
- **DOB:** 6/25/1948
- **Age:** 58
- **Tech:** HUGHES, KEVIN S
- **Unit #:**
- **Appt Date:** 10/29/2007

**RISK CALCULATIONS** (This analysis is only as accurate as the data entered by the patient)

<table>
<thead>
<tr>
<th>Risk of BRCA 1 or 2 Mutation</th>
<th>Risk of Hereditary Colorectal Cancer Mutation</th>
<th>Lifetime Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCAPRO 0.14%</td>
<td>CRCAPRO Combined 0.87%</td>
<td>Lifetime breast cancer risk (Per BRCAPRO) 8.88%</td>
</tr>
<tr>
<td>Myriad 3.4%</td>
<td>Myriad Combined 4.2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weijnen Combined 15.04%</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Lifetime Risk</strong></td>
<td></td>
</tr>
</tbody>
</table>

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**PARTRNERS**

**Harvard Medical School**
Early Detection
Stages of colon cancer and survival rates

- Stage 0
- Stage I
- Stage II
- Stage III
- Stage IV

Survival
- 95%
- 5%

Spread to other organs

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PARTNERS
HARVARD MEDICAL SCHOOL
Woman’s Health Initiative

Established by NIH in 1991 to address cardiovascular disease, cancer, and osteoporosis

Observational study to identify predictors of disease
  Clinical data
  Serum bank

Pre-diagnostic serum from 100 cases and 120 controls
  Cases were diagnosed with CRC within 18 months

Six laboratories assessed the plasma proteome of pools of cases and controls

Identified several proteins that have been validated in preclinical models

Human validation studies underway
Prosense imaging
Expression profiles of early stage cancers have embedded signatures that can help with prognosis.
Melanoma prognostic markers

The Path from Genetic Discovery to Patient Care
Chronic Myelogenous Leukemia (CML)
BCR-ABL translocation

The Philadelphia Chromosome

Before translocation

abilidad of chromosome #9 switches places with a piece of chromosome #22. The translocation forms an extra-long chromosome #9 (called der 9) and an extra-short chromosome #22, which is the Philadelphia chromosome that contains the abnormal, fused BCR-ABL gene.

After translocation

Philadelphia Chromosome

ABL

#9

BCR

#22

der 9

BCR

ABL
Cancer is the most frequent cause of mortality and morbidity in the US.

Lung cancer accounts for the most cancer deaths in the US.

Different types of lung cancer: SCLC, NSCLC and BAC.

Survival rates have not changed significantly over the years.

Treatments: Chemotherapy, Gefitinib (Iressa approved for third line therapy), Erlotinib (Tarceva, approved for second line therapy).
Iressa approved in EU with EGFR test

Iressa Phase III trials failed; FDA changes label & limits distribution

Tarceva approved based on Phase III data. Increase in median PFS 7 weeks

PFS for EGFR+ patients treated with Tyrosine Kinase Inhibitors greater than 18 months

No small molecule or biologics available

In EGFR mutation negative patients, Chemotherapy better than Tyrosine Kinase Inhibitors

EGFR mutations can predict responsiveness

K-Ras mutations and some EGFR mutations confer resistance

Some EGFR negative patients have ERBB2 mutations (therapy with Herceptin)

Some EGFR negative patients have ALK4 activation (therapy with PF-2341066)
Emerging approaches for Non-small Cell Lung Cancer
Test for mutations in EGFR, K-RAS, B-RAF, PIK3CA, HER2, EML4-ALK, and MET

EGFR sensitizing mutation

EGFR TKIs: gefitinib and erlotinib

K-ras mutant

RAF inhibitors: AZD6244

B-raf mutant

RAF inhibitors: PLX-4032

PI3KCA mutant

HER2 inhibitors: Herceptin

HER2 amplification or mutation

HER2 inhibitors: Herceptin

EML4-ALK translocation

ALK inhibitors: PF-02341066, Novartis#3-39, TAE684, BMS-359541

MET amplification

MET inhibitors: AMG208, ARQ197, GSK1363089, JNJ-38877605, MK2461, MP470

EGFR resistance mutation

Irreversible TKIs: BIBW2992, HKI-272, PF-00299804

No somatic mutation identified

ERCC1 LOW platinum (cisplatin)-based chemotherapy
RRM1 LOW gemcitabine-based chemotherapy

TS LOW pemetrexed (Alimta)-based chemotherapy
Targeted therapies: non-small cell lung cancer

TODAY

2-3 YEARS

- Tarceva
- mTOR inhibitor-1
- AZD6244-1
- AZD6244-2
- Herceptin
- AMG208
- PF02341066
### Genetic Information Saves on Unnecessary Costs in NSCLC treatment

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
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<tbody>
<tr>
<td>Patients</td>
<td>100</td>
</tr>
<tr>
<td>Cost of Tyrosine Kinase Inhibitor treatment for 6 mo.</td>
<td>$30,000</td>
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<tr>
<td>Total cost for 100 patients</td>
<td>$3,000,000</td>
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<tr>
<td>Responders</td>
<td>15%</td>
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<tr>
<td>Cost for 15</td>
<td>15 x $30,000 = $450,000</td>
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<tr>
<td>Testing for EGFR for all 100</td>
<td>$65,000</td>
</tr>
<tr>
<td>Total cost</td>
<td>$515,000</td>
</tr>
<tr>
<td>Savings per 100 patients</td>
<td>2,485,000 or 83%</td>
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The Vectibix story

Erbitux and Vectibix approved in the US
Vactibix was not approved in the EU
K-ras Mutations and Benefit from Cetuximab in Advanced Colorectal Cancer

Christos S. Karapetis, M.D., Shirin Khambata-Ford, Ph.D., Derek J. Jonker, M.D., Chris J. O’Callaghan, Ph.D., Dongsheng Tu, Ph.D., Niall C. Tebbutt, Ph.D., R. John Simes, M.D., Haji Chalchal, M.D., Jeremy D. Shapiro, M.D., Sonia Robitaille, M.Sc., Timothy J. Price, M.D., Lois Shepherd, M.D.C.M., Heather-Jane Au, M.D., Christiane Langer, M.D., Malcolm J. Moore, M.D., and John R. Zalcberg, M.D., Ph.D.*

CONCLUSIONS
Patients with a colorectal tumor bearing mutated K-ras did not benefit from cetuximab, whereas patients with a tumor bearing wild-type K-ras did benefit from cetuximab. The mutation status of the K-ras gene had no influence on survival among patients treated with best supportive care alone. (ClinicalTrials.gov number, NCT00079066.)
ASCO Releases Provisional Clinical Opinion Recommending Routine KRAS Gene Testing to Guide Treatment for Metastatic Colorectal Cancer

FOR IMMEDIATE RELEASE:
January 13, 2009 6:00PM

Alexandria, Va. — In advance of the sixth annual Gastrointestinal Cancers Symposium (January 15-17 in San Francisco, CA), the American Society of Clinical Oncology (ASCO) today released its first Provisional Clinical Opinion* (PCO) on the use of KRAS gene mutation testing in patients with metastatic colorectal cancer to guide treatment with the anti-EFGR monoclonal antibodies cetuximab and panitumumab. ASCO’s PCO recommends that all patients with metastatic colorectal cancer who are candidates for anti-EFGR therapy have their tumors tested for KRAS gene mutations. If a patient has a mutated form of the KRAS gene, it recommends against the use of anti-EFGR antibody therapy, based on recent studies indicating this treatment is only effective in patients with the normal (wild-type) form of the KRAS gene. It is estimated that 40 percent of colon cancer patients have the KRAS mutation.

An economic analysis being presented at the Gastrointestinal Cancers Symposium, also embargoed until 6:00 p.m. tonight, found that routine testing for KRAS gene mutations in patients with metastatic colorectal cancer could save the U.S. health system up to $604 million per year in the cost of the drug cetuximab alone. “Personalized medicine is the next frontier in cancer care. Basing cancer treatment on the unique genetic characteristics of the tumor or the individual with cancer will improve patient outcomes and help avoid unnecessary costs and side effects for patients who are unlikely to benefit,” said Richard L. Schilsky, MD, ASCO president and Professor of Medicine at the University of Chicago Medical Center. “Using KRAS testing to guide colorectal cancer treatment is a prime example of where cancer care is heading.”
Costs of treatment for 100 patients

Average cost of treatment that includes EGFR antibodies = $30,700
Total/100 = $3,070,000
If 50% have K-RAS mutations, they should be treated with Chemo alone @ $10,000
Cost of 50 patients with Antibody therapy 50 X 30,700 = 1,535,000
Cost of 50 patients without antibody therapy 50 X 10,000 = 500,000
Total $2,035,000
Testing for K-RAS @ $450 X 100 $ 45,000
Total $2,080,000

Savings $990,000 or 9,900/patient
Total Savings/patient/full 12 wk course = $61,650 or 43% savings
Personalized Medicine at Point of Care

- Integrate patient’s genomic profile with clinical data. Ensure clinical, molecular data incorporated into medical record in usable format

- Support physician decisions
  - Guide physician to appropriate molecular diagnostics
  - Support interpretation of test results

- Draw data from other patients with similar profiles

- Provide clinical reference annotations from either external or internal databases

- Provide references to physicians for interpretation of genomic profile
Genetic data in EMR
<table>
<thead>
<tr>
<th>Date</th>
<th>Site</th>
<th>Primary Specimen</th>
<th>Indication</th>
<th>Test</th>
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<tr>
<td>12/18/2006</td>
<td>MGH</td>
<td>Blood, Peripheral</td>
<td>Cardiovascular</td>
<td>HCM-pnlA; HCM-pnlB</td>
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<tr>
<td>12/13/2006</td>
<td>BWH</td>
<td>Blood, Peripheral</td>
<td></td>
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<tr>
<td>12/04/2006</td>
<td>MGH</td>
<td>Blood, Peripheral</td>
<td>Hearing Loss</td>
<td>CX26-a</td>
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<td>11/20/2006</td>
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<td>11/14/2006</td>
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<td>Lung - Frozen Tissue</td>
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<td>2155G&gt;T (G719C), Exon 18, EGFR</td>
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</tbody>
</table>
Summary

- Genetic and genomic knowledge of cancers is increasing at a very rapid pace

- Genetic and genomic information can be used to:
  - Assess risk
  - Detect cancers early
  - Determine prognosis
  - Stratify patient populations and provide targeted therapies
  - Implementation of these principles would result in better outcomes without increasing healthcare costs