

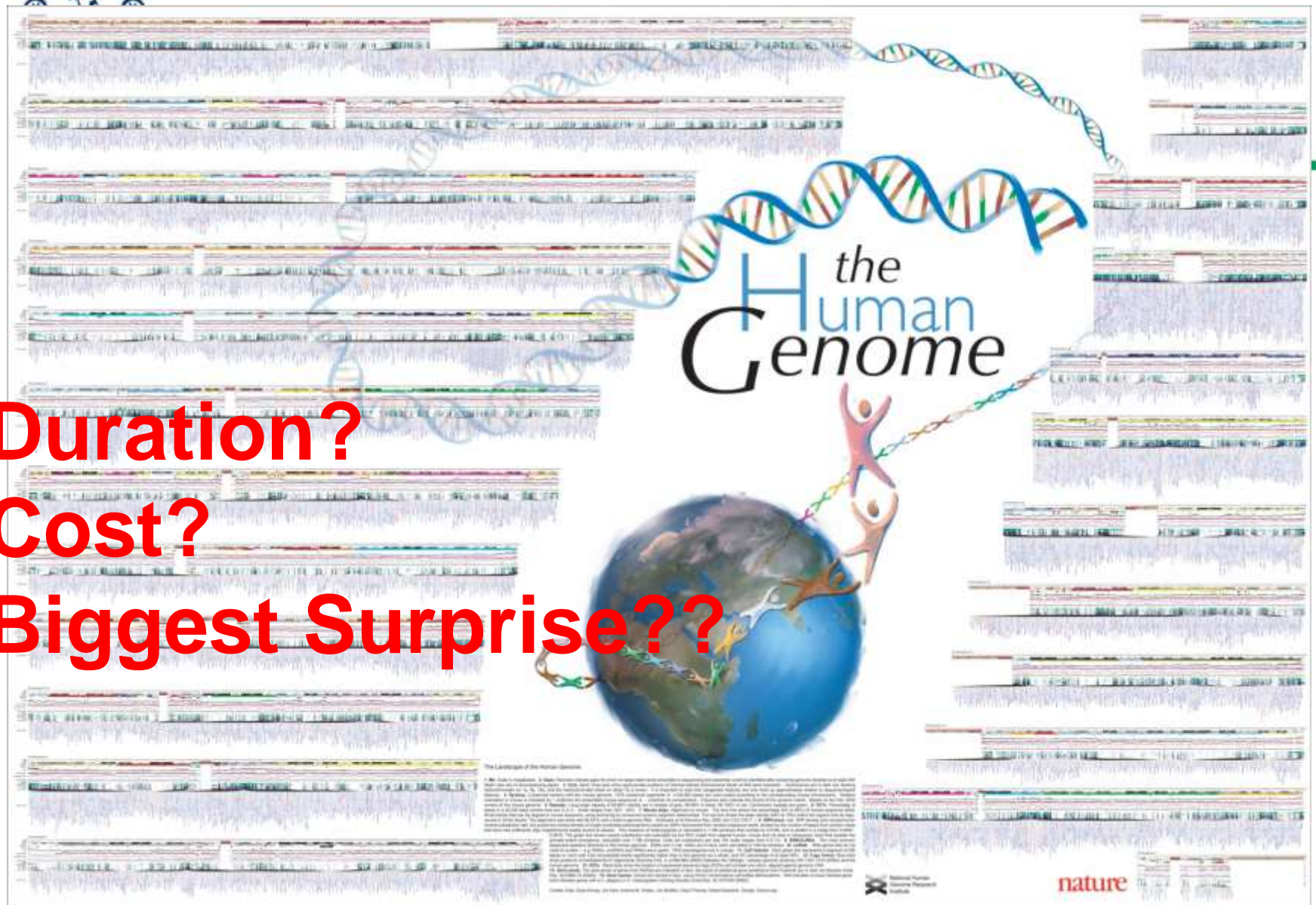
# Genome Medicine



## Personalized/Precision Medicine

Hans Bluysen, 09-10-2019

**Duration?**  
**Cost?**  
**Biggest Surprise??**

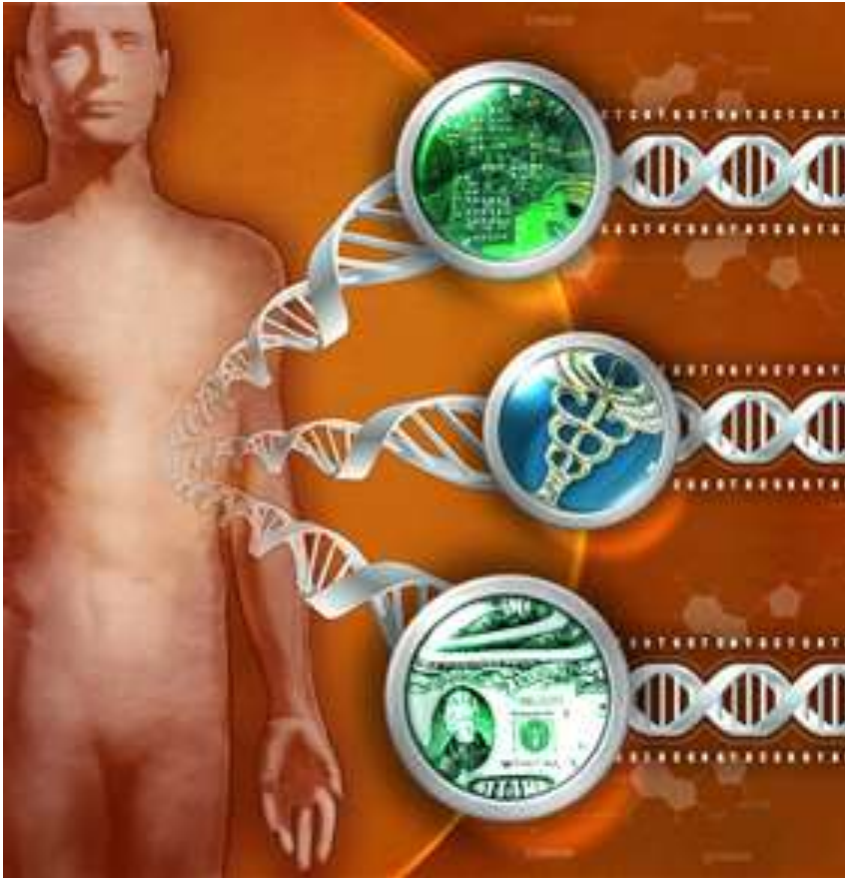






# Post-genome sequencing “Functional Genomics”

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-translate information to different levels

-Understanding mechanisms of cell function + organism

-Health care:  
food and health  
mechanism infectious disease  
origins of multifactorial disease

-Medical diagnostics/prognostics

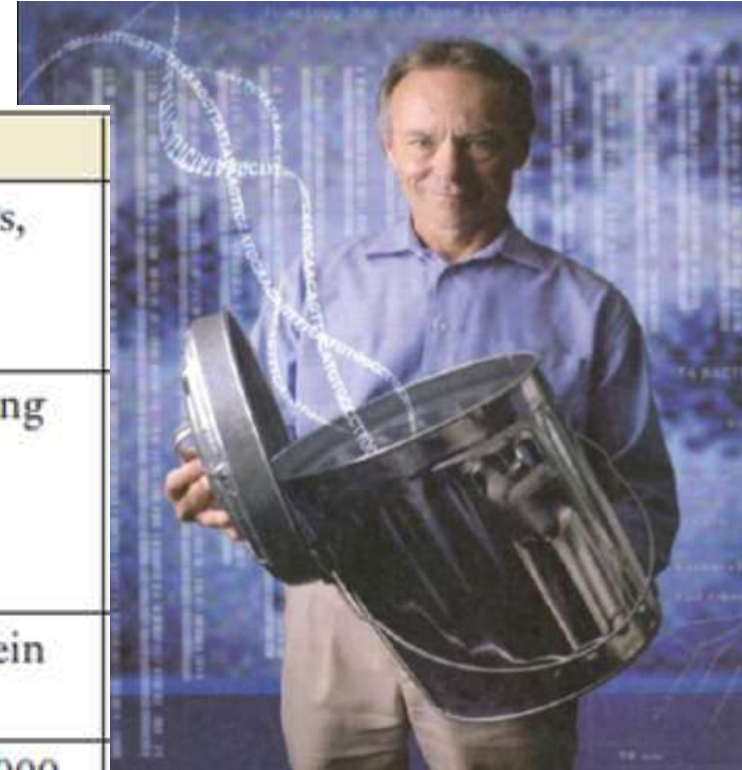
-Pharmaceutical products/  
therapeutics

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# The “Functional Genomics” Toolbox

| “-omics” approach                             | Generated information   |
|---|---|
| Human genome sequence<br>(genomics)           | Whole-genome sequence, SNPs,<br>and CNVs (~10–15 million)   |
| Gene expression profiles<br>(transcriptomics) | Microarrays and RNA sequencing<br>(~25,000 transcripts)<br><b>Transcription factor chromatin<br/>Interactions: ChIP-seq</b> |
| Proteome (proteomics)                         | Protein profiles of specific protein<br>products  |
| Metabolome<br>(metabolomics)                  | Metabolic profiles (~1,000–10,000<br>metabolites)   |
| <b>Epigenomics</b>                            | <b>DNA Methylation</b>  |



(Chan & Ginsburg, 2011)



# “Personal Genome”



> 50 companies  
World-wide

## The Road to the Personal Genome

IN THE space of a single decade, the cost of mapping all your DNA will fall from the billions of dollars to the thousands. The human genome is becoming a commodity virtually overnight. It's as if millions of households could have had dishwashers and vacuum cleaners; 10 years after James Watt built his steam engine.

DNA, the “code of life,” is the ultimate binary file, a database of 12 billion bits. The data—6 billion matching sets of either the molecules adenine (A) and thymine (T) or guanine (G) and cytosine (C)—affect everything that makes you you: the color of your eyes, whether you're moody or cheerful, and which diseases you're most susceptible to.

Today you can purchase your very own personal genome for US \$48,000 from Illumina, a San Diego biotech firm (and they'll throw in an Apple iMac). [See “The \$100 Genome,” elsewhere in this issue.] That's a bit pricey if all you want to do is check out the genetic inheritance of Saturday's dinner date. But by 2014, your genome will cost a mere \$2500, according to TSG Partners, an Atlanta-based life sciences advisory firm, so low that health insurance companies might pick up the tab just to get their hands on the data. The current head of the Personal Genome Project, George Church, thinks it will soon be far cheaper than that—perhaps even less than the dinner itself.

—Mark Anderson

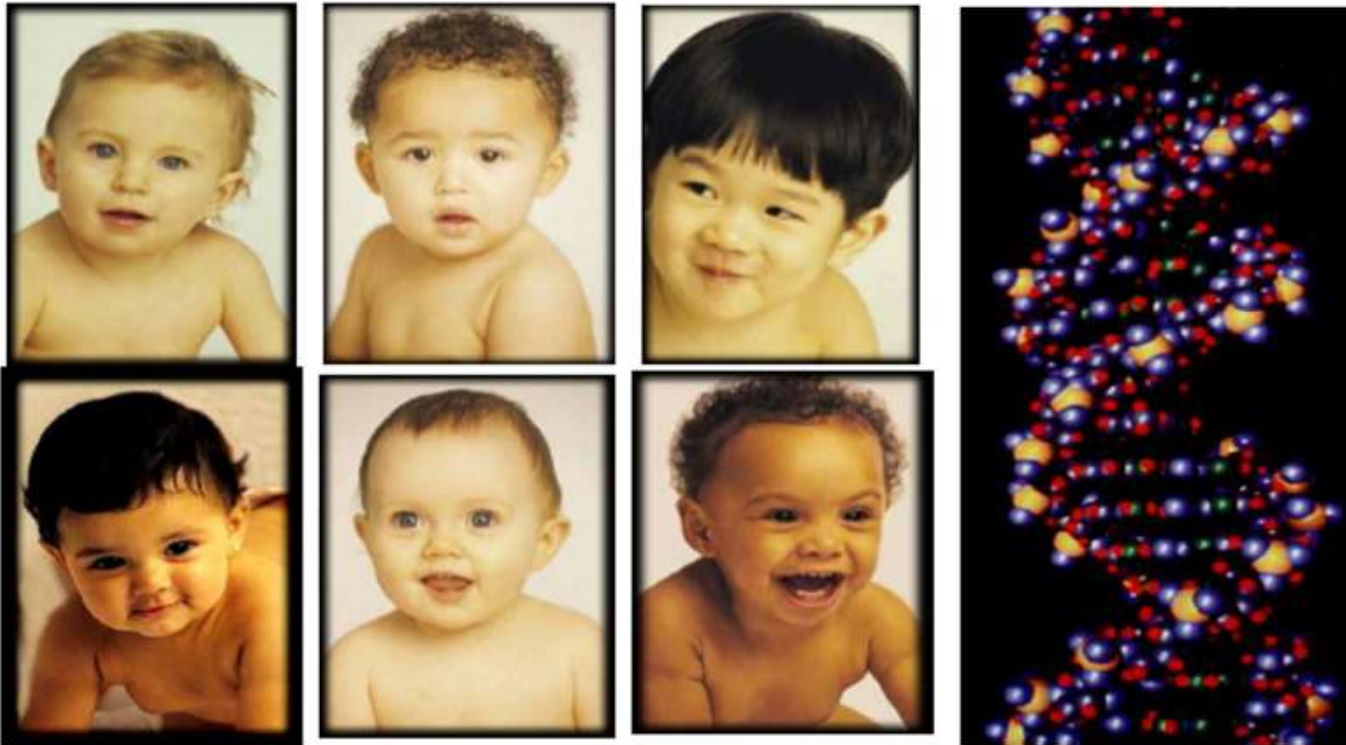
SOURCE: TSG Partners, Atlanta (projection one); George Church, Harvard Medical School (projection two).







# Genomics: Single Nucleotide Polymorphisms



The Hunt for Gene Loci  
Associated with  
Complex Human Diseases

**Genome wide  
variation!**

# International HapMap Project



The HapMap is a catalog of common genetic variants that occur in human beings. It describes what these variants are, where they occur in our DNA, and how they are distributed among people within populations and among populations in different parts of the world.

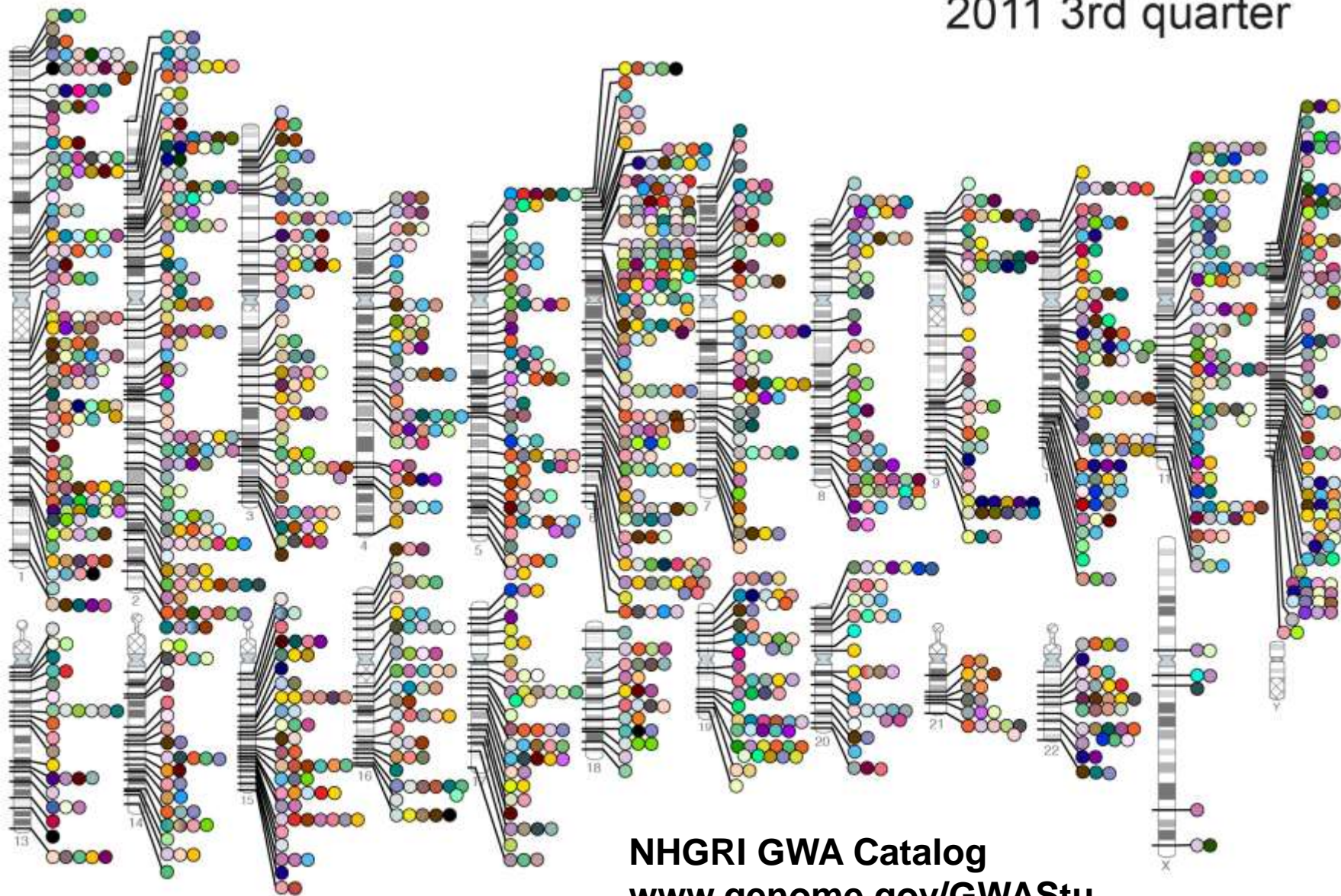
Provides information that other researchers can use to link genetic variants to the risk for specific illnesses, which will lead to new methods of preventing, diagnosing, and treating disease.



# Published Genome-Wide Associations through 09/2011

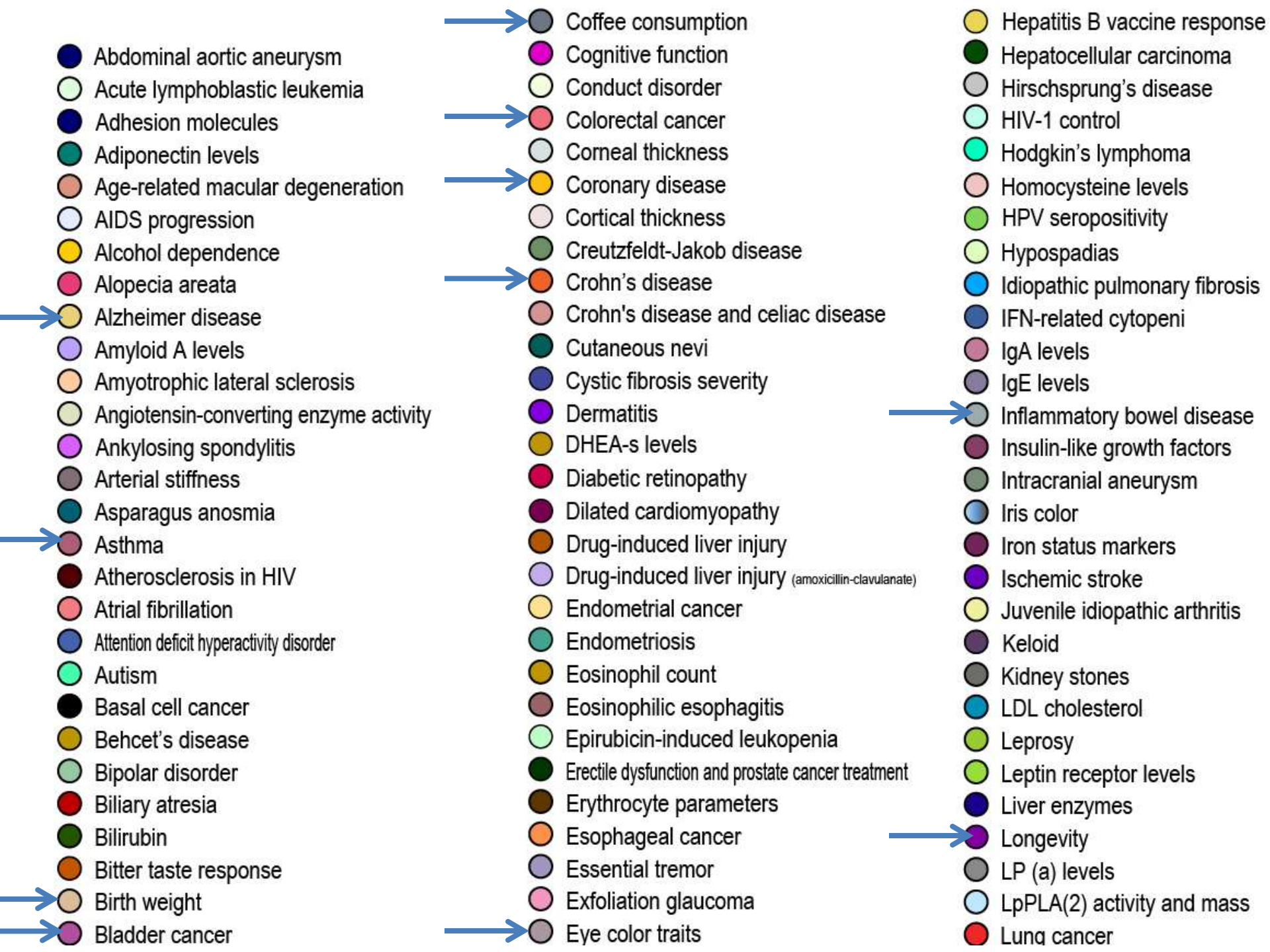
1,617 published GWA at  $p \leq 5 \times 10^{-8}$  for 249 traits

2011 3rd quarter



**NHGRI GWA Catalog**  
[www.genome.gov/GWASudies](http://www.genome.gov/GWASudies)

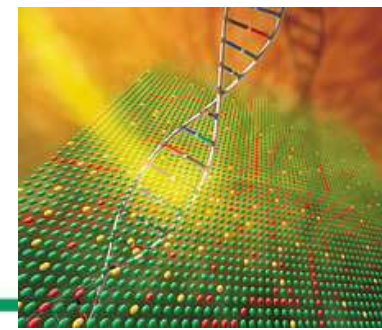






# GWAS of Disease Susceptibility

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- May 2011:
    - 800 GWAS published
    - 150 diseases
    - > 2.400 SNPs with statistically significant associations + odds ratio
  
  - Crohn's diseases: > 32 variants
  - Type 2 Diabetes: > 20 variants
  - CAD: > 200 variants
- } ~ Disease risk

Next  $\longrightarrow$  Whole Genome Sequencing!

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# Mutation Details

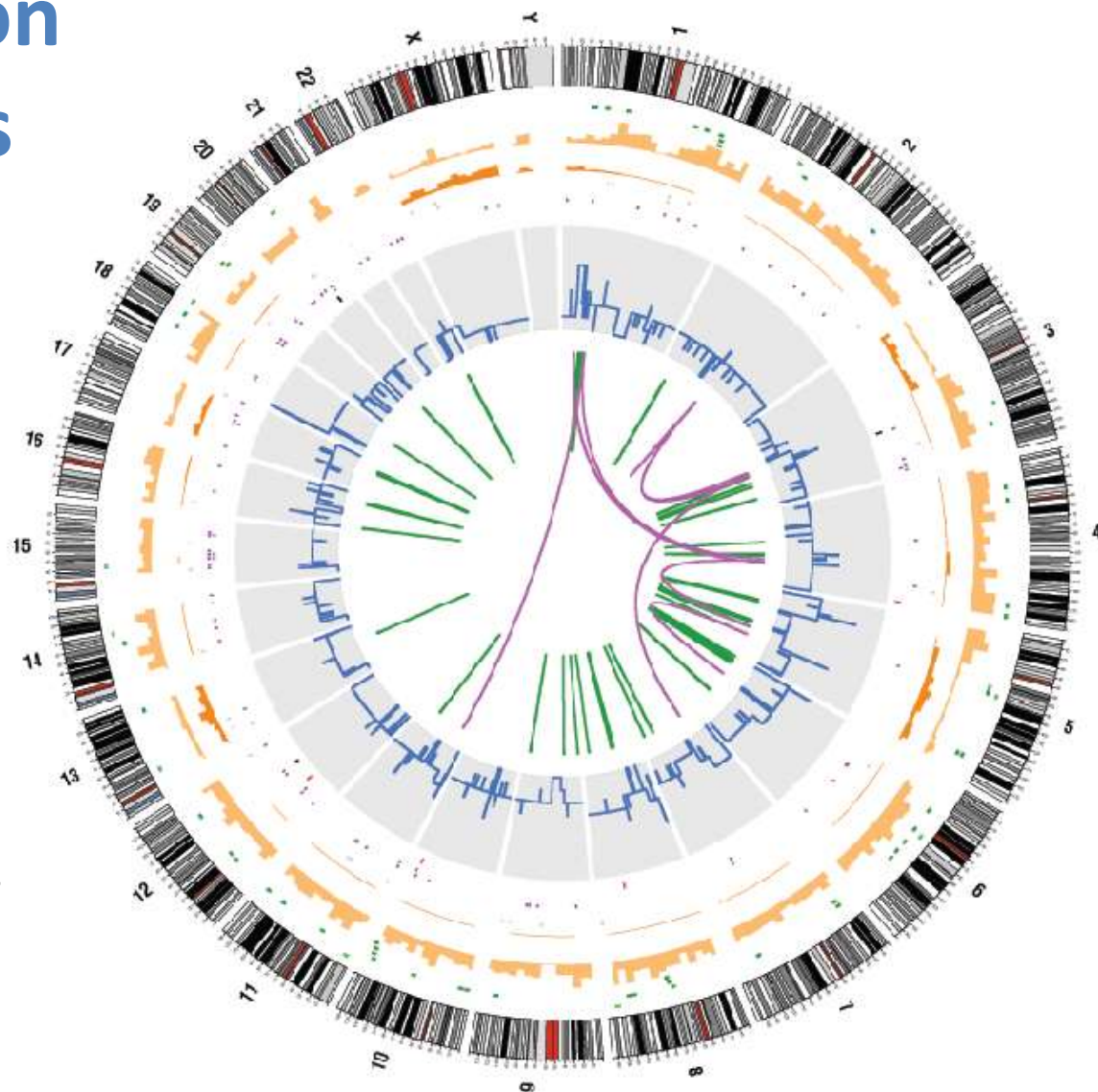
## Lung Carcinoma genome

- Nature 2010 463; 184-90.

22,910 mutations

58 rearrangements

334 copy number  
segments





# Analysing Cancer Genomes

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Cancer genomes contains a lot of genetic damage.

- Many of the mutations in cancer are incidental.
- Initial mutation disrupts the normal DNA repair/replication processes.
- Corruption spreads through the rest of the genome.

Today: Find the “driver” mutations amongst the thousands of “passengers.

- Identifying the driver mutations will give us new targets for therapies.

Tomorrow: Analyse the cancer genome of every patient in the clinic.

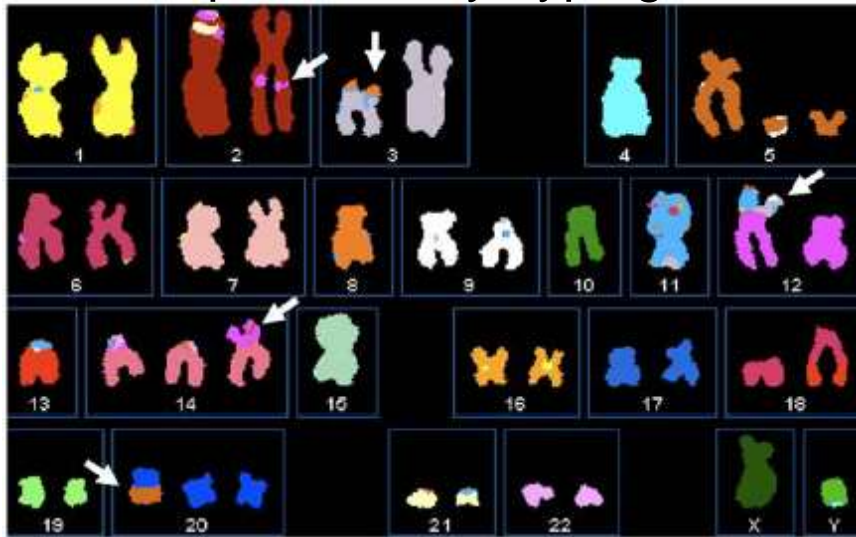
- Variations in a patient and cancer genetic makeup play a major role in how effective particular drugs will be.
  - Clinicians will use this information to tailor therapies.
-





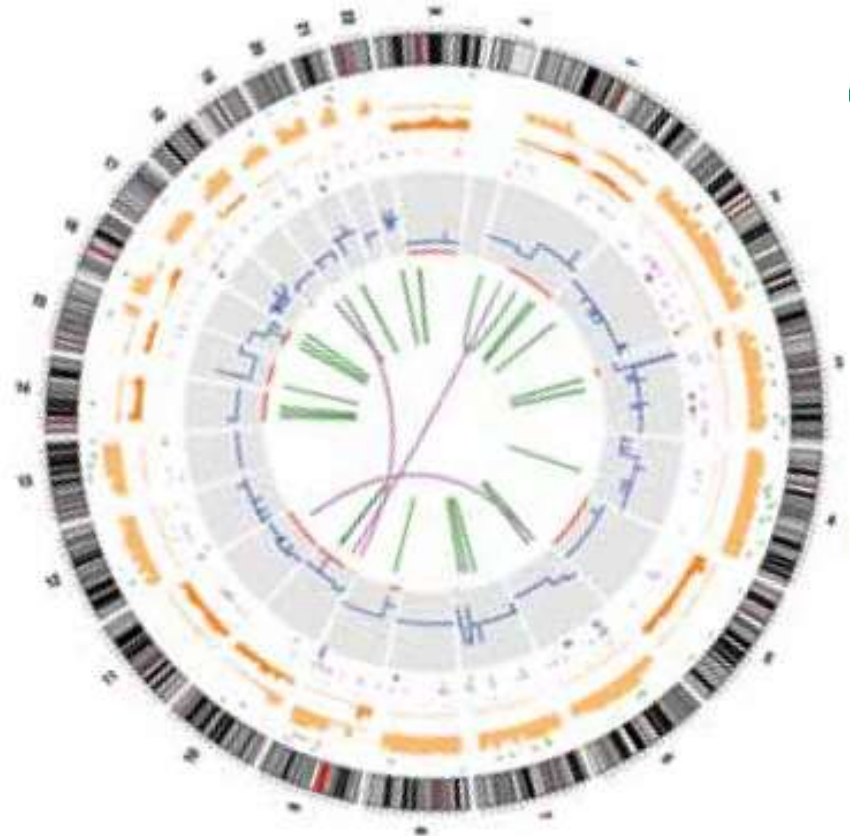
# Tumor Sequencing

## Spectral Karyotyping



Illumina (2011-2014):  
whole-genome sequencing of up to 1,500  
samples over the next three years on both  
tumor and normal genomes toward  
prostate and esophageal cancers

## Circus Plot



Paired-end sequencing  
(Indels, Substitutions, CNV, LOH,  
intra- and inter chromos. variants )



# International Cancer Genome Project

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Many cancer mutations are rare.

- Low signal-to-noise ratio.



International  
Cancer Genome  
Consortium

How do we find the rare but important mutations?

- Sequence lots of cancer genomes.

International Cancer Genome Project.

- Consortia of sequencing and cancer research centres in 10 countries.

Aim of the consortia.

- Complete genomic analysis of 50 different tumor types. (50,000 genomes).
-





# <http://cancergenome.nih.gov>

NATIONAL CANCER INSTITUTE National Cancer Institute U.S. National Institutes of Health | [www.cancer.gov](http://www.cancer.gov)

## THE CANCER GENOME ATLAS

Search  [GO](#)

[About TCGA](#) [Funding](#) [Program Components](#) [Media Center](#) [Related Initiatives](#)



### | Mission and Goal

The Cancer Genome Atlas (TCGA) is a comprehensive and coordinated effort to accelerate our understanding of the molecular basis of cancer through the application of genome analysis technologies, including large-scale genome sequencing.

[Learn more >>](#)

### | News from the Pilot Project

[National Institutes of Health to Map Genomic Changes of Lung, Brain, and Ovarian Cancers](#)

The National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI), both part of the National Institutes of Health (NIH), today announced the first three cancers that will be studied in the pilot phase of The Cancer Genome Atlas (TCGA) project. The cancers to be studied in the TCGA Pilot Project are lung, brain (glioblastoma), and ovarian. These cancers, which collectively account for more than 210,000 cancer cases each year in the United States, were selected because of the availability of biospecimen collections that met TCGA's strict scientific, technical, and ethical requirements.

### | Pilot Project to Map Three Cancers



[Click here](#) for more information

### | TCGA: How Will It Work?



[Click here](#) for more information



# The Personal Genome Project Has a Growth Spurt

Thirteen thousand people will divulge their genetic histories online.



The first 10 volunteers for the Personal Genome Project. The 10 intrepid volunteers who signed up for George Church's Personal Genome Project will soon have a lot of company. According to a [report](#) from Northwestern University, more than 10,000 people are in the process of enrolling in the project, which involves having your genome sequenced, and then sharing it, along with medical records, in an open-access database for analysis by geneticists and others around the world.

Here's a brief description of the project from a [piece](#) I wrote last October.

The Personal Genome Project is a long term, large cohort study

Aims to sequence and publicize the complete genomes and medical records of 100,000 volunteers, in order to enable research into [personal genomics](#) and [personalized medicine](#).

It was initiated by [Harvard University](#) in 2005.

Headed by Harvard University genomics pioneer [George Church](#), the project aims to



# Personal Genome Project



- The individuals agree to make their genome and their health records public.
- Volunteers... willing to share their genome sequence and many types of personal information with the research community and the general public,
- Aim: to understand genetic and environmental contributions to human traits.”







# The project publishes the

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- genotype (the full DNA sequence),
  - phenotype: medical records, various measurements, MRI images, etc.
  - all data are within the public domain
  - made available over the Internet so that researchers can test various hypotheses about the relationships among genotype, environment and phenotype.
-

# Personal Genome Project Study Guide

Welcome

About the PGP

About the Study Guide

FAQ

Contact

Credits

Part I: Genetic Material

Part II: Gene Transmission

Part III: Gene Expression

Part IV: Gene Regulation

Part V: Genetics and Society

Part VI: Project Literacy

## Part I: Genetic Material

Lesson 1: Introduction to Cells, DNA, and Genes

Lesson 2: The Structure of DNA

Lesson 3: DNA's Role in Determining Your Traits

## Participant Profiles

The participants in the PGP have volunteered to share their DNA sequences, medical information, and other personal information with the research community and the general public.

Show 10 entries

Search:

| PGP#  | participant ID           | Date enrolled | Received samples                | Health records | Relatives enrolled | Whole genome datasets | Other genetic data |
|-------|--------------------------|---------------|---------------------------------|----------------|--------------------|-----------------------|--------------------|
| PGP1  | <a href="#">hu43860C</a> | 2010-11-20    | Whole Blood, Microbiome         | Yes            | 1                  | 1                     | 1                  |
| PGP2  | <a href="#">huC30901</a> | 2010-11-20    |                                 | Yes            |                    | 1                     |                    |
| PGP3  | <a href="#">huBEDA0B</a> | 2010-11-20    | Saliva, Whole Blood, Microbiome |                |                    | 3                     |                    |
| PGP4  | <a href="#">huE80E3D</a> | 2007-04-02    |                                 |                |                    | 1                     |                    |
| PGP5  | <a href="#">hu9385BA</a> | 2010-11-20    | Microbiome                      | Yes            |                    | 4                     |                    |
| PGP6  | <a href="#">hu04FD18</a> | 2010-11-20    | Saliva                          | Yes            |                    | 1                     |                    |
| PGP7  | <a href="#">hu0D879F</a> | 2010-11-20    | Saliva, Whole Blood             |                |                    | 3                     |                    |
| PGP8  | <a href="#">huAE6220</a> | 2010-11-20    |                                 | Yes            |                    | 1                     |                    |
| PGP9  | <a href="#">hu034DB1</a> | 2010-11-20    | Saliva, Whole Blood, Microbiome |                |                    | 3                     | 2                  |
| PGP10 | <a href="#">hu604D39</a> | 2010-11-20    | Microbiome                      | Yes            |                    | 4                     |                    |

Showing 1 to 10 of 3,262 entries







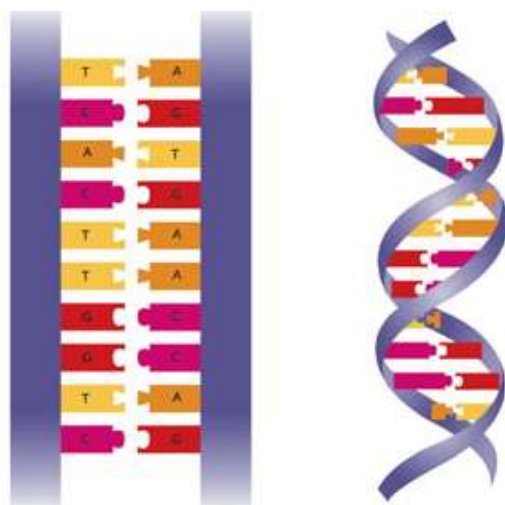
# INTERNETMEDICINE.COM

WHERE INTERNET MEETS MEDICINE

- HOME
- MEDICAL DEVICES
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- I-PATIENT
- I-HEALTH
- I-EDU
- I-SPECIALTY
- I-NEWS
- I-DAILIES

## Smartphone app enables storage, testing of DNA data

Posted by *admin* / January 31, 2013



### MEDICAL APPS NEWS »

#### Derm Consult for Inpatients? There's an App for That



SOURCE Feb 13, 2014 Diagnostic apps for dermatologists are no new smartphone...

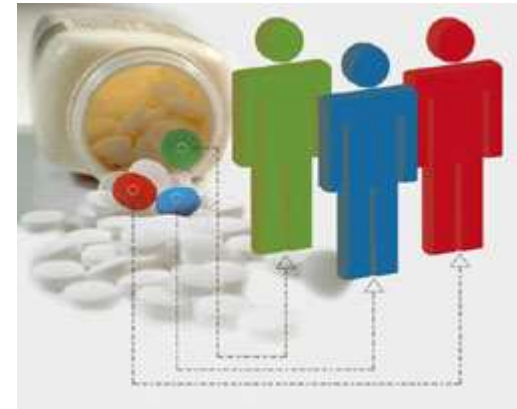
February 17, 2014 2:31 am

New Healthpatch biosensor captures a wide range of information with just adhesive, disposable patch



**The use of information and data from a patient's genotype and phenotype (level of gene expression and/or clinical information) to:**

- stratify disease
- select a medication
- provide a therapy
- initiate a preventative measure that is particularly suited to that patient at the time of administration





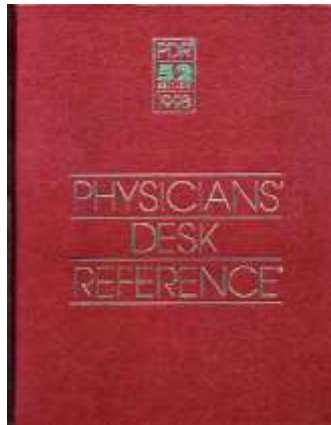
# The paradigm of the classic treatments



Trial and error



Symptom  
Diagnosis  
Treatment  
Dosage



Non specific  
Non selective  
Uniformized

Phenotype

Does not evaluate the different therapeutic responses  
- the blockbuster concept





- „One fits to all”
- The target is the **disease**
- Evidence based medicine
  - statistical approach using the rule of large numbers, resulting in statistically meaningful conclusions



## PROBLEM!



# Ineffective therapies – waste money



Hypertension Drugs **10-30%**

ACE Inhibitors

Heart Failure Drugs **15-25%**

Beta Blockers

Anti Depressants **20-50%**

SSRIs

Cholesterol Drugs **30-70%**

Statins

Asthma Drugs **40-70%**

Beta-2-agonists





# Personalized Medicine: The Answer?



## Targeted therapy:

Differentiate, diagnostics and drug co-development



Targeted therapies help by identifying patients with the best response and least side effects

Biomarkers are such diagnostic tools, which may predict the therapeutic response to a certain drug







# Drug-Diagnostics Combinations in Oncology

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- **The current efficacy of medical anti-cancer therapy is still not (far from) optimal**
  - **Rational use of drugs**
    - The right drug
    - For the right patients
    - In the right amount
    - At the right time
  - **The key elements in pharmacotherapy**
    - Pathophysiology
    - Mechanism of action of the drug
-



# Drug-Diagnostics Combinations in Oncology

**Cancer has a very complex biology**





# Companion Diagnostics/ Pharmacodiagnosics

---

- **Companion Diagnostics**

- “Match” the pathophysiology with the mechanism of action of the drug

- **Definition**

- A pre-treatment test performed in order to determine whether or not a patient is likely to respond to a given therapy. This type of test is classified as a predictive test and a prerequisite for implementation of stratified and personalized medicine.\*

\*Jørgensen JT. Expert Rev Mol Diagn 2008; 8: 689-695.

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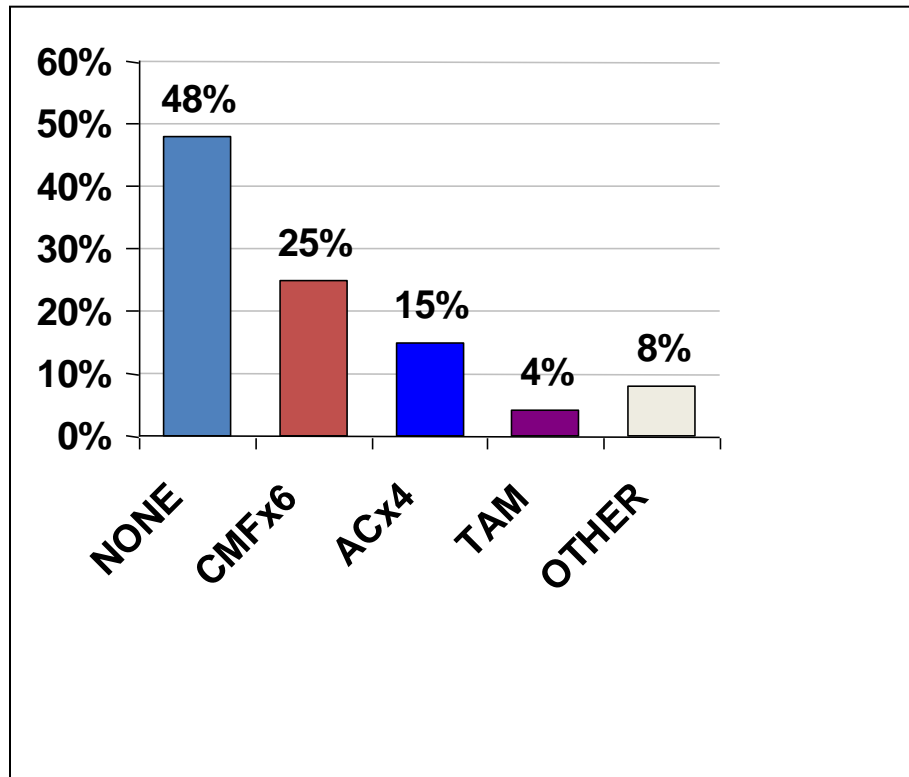


# Breast Cancer: The Treatment Dilemma

## Choices of 40 experts world-wide

61 y-old, fit,  
postmenopausal

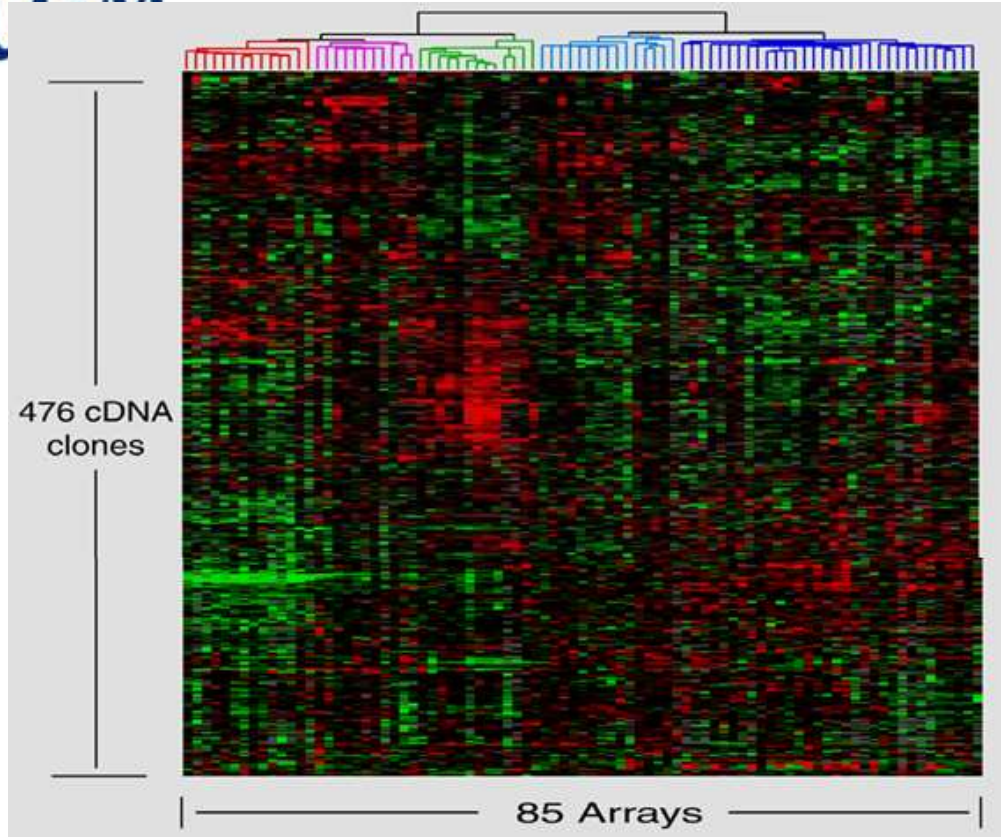
Node negative  
pT = 0.9 cm  
ductal cancer  
ER and PR negative  
HER2 negative  
Grade 2



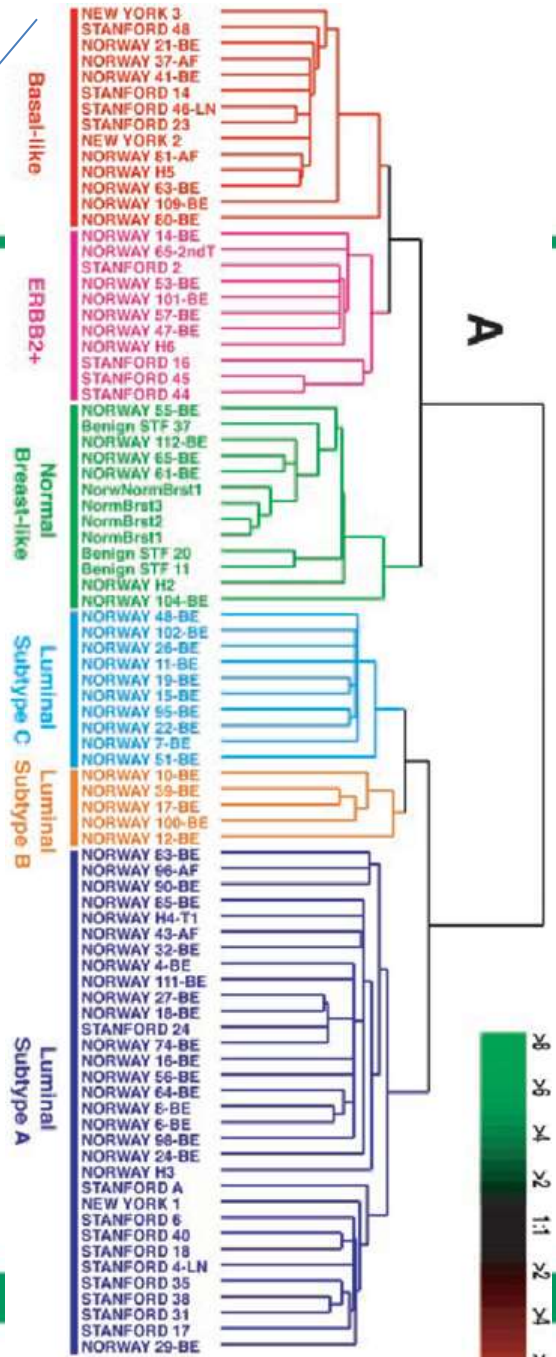
Courtesy: Martine Piccart

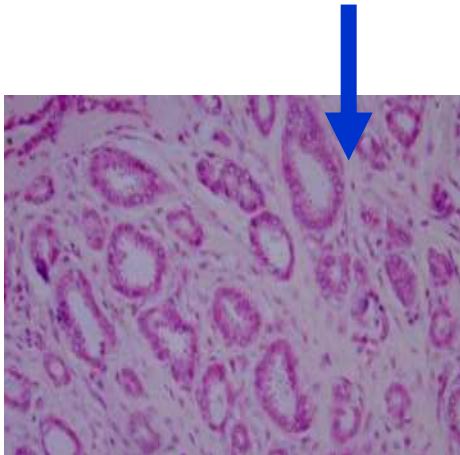
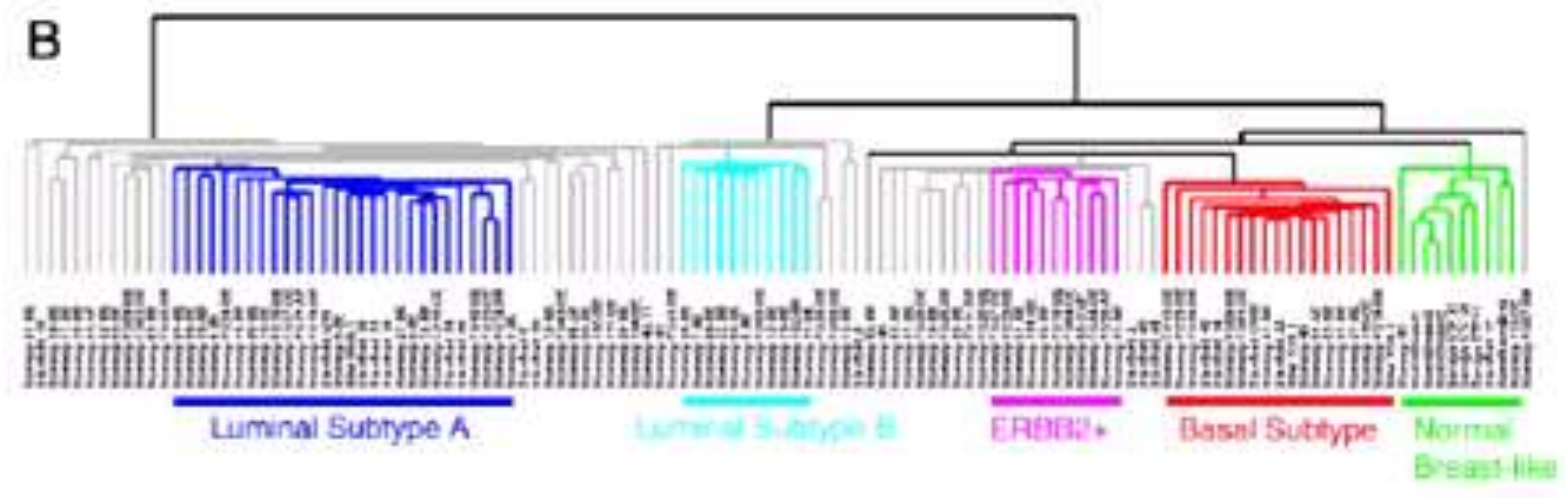


# Breast Cancer Subtypes

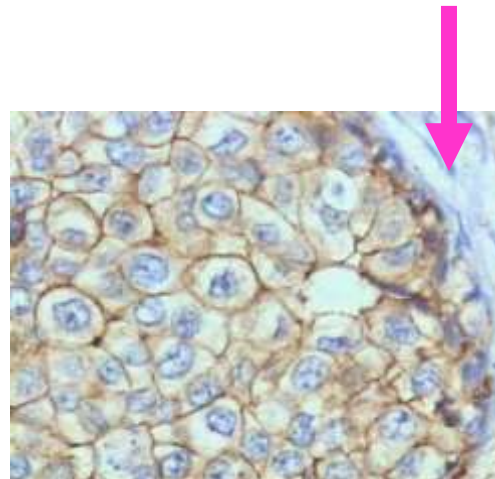


- Disease Onset + Progression
- Disease Subtyping/Classification

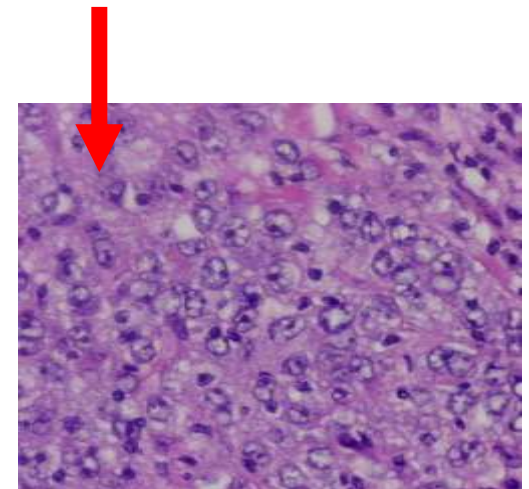




ER++, PR++, G1,2



HER2 ISH pos



“triple neg,” CK5/6+

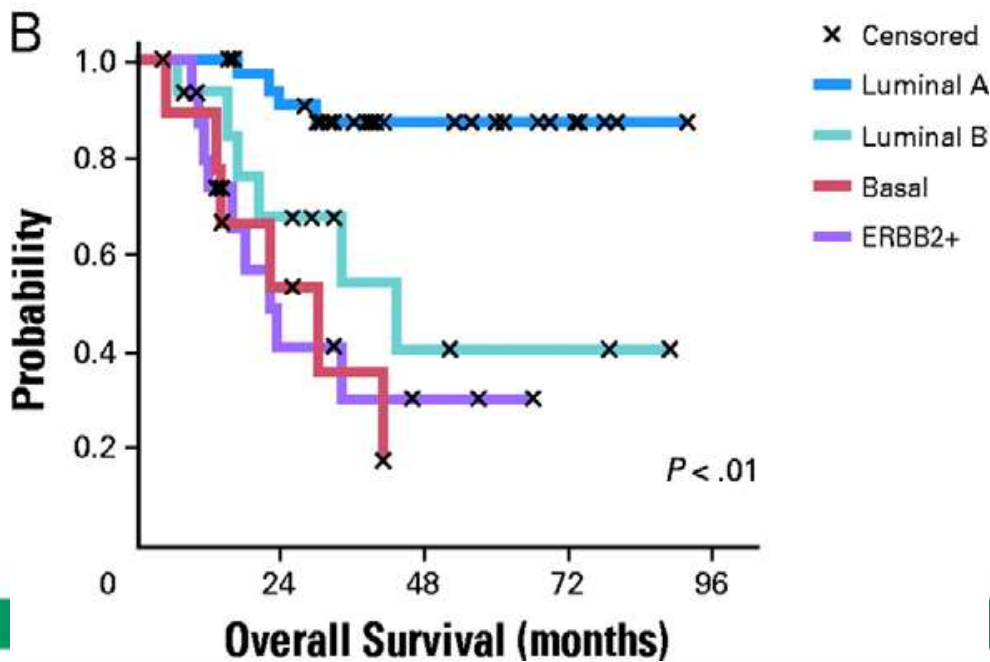
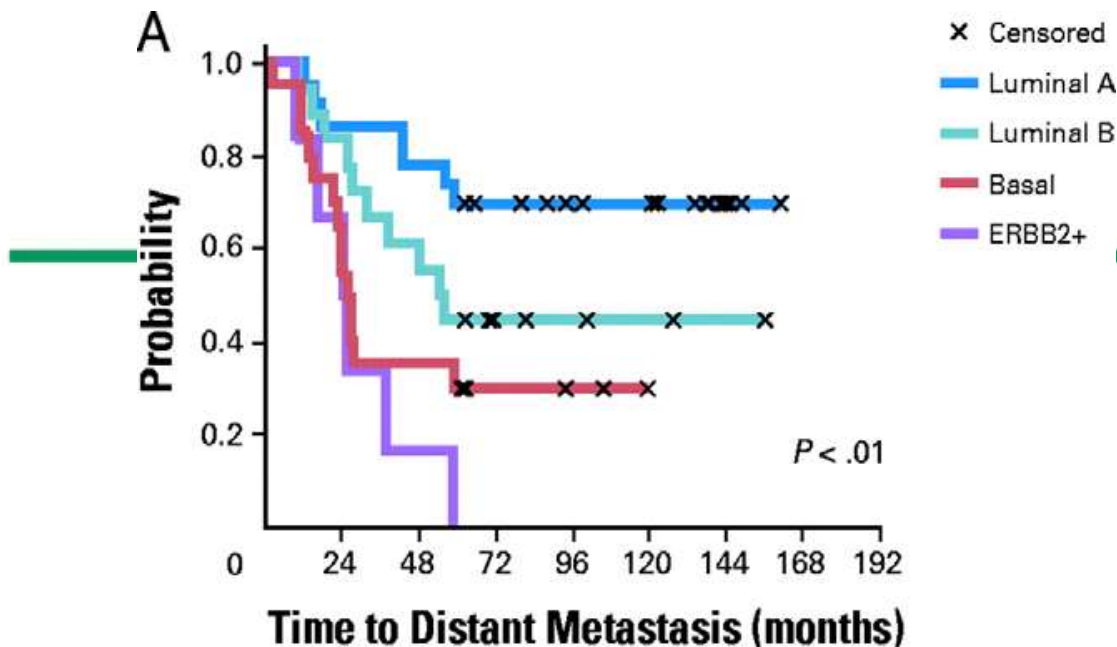




# Breast Cancer Subtype

~

# Clinical Outcome





# Tamoxifen (Nolvadex®) - ER

## Phase II Study of Tamoxifen: Report of 74 Patients With Stage IV Breast Cancer<sup>1</sup>

Harvey J. Lerner,<sup>2,\*</sup> Pierre R. Band,<sup>3,4</sup> Lucien Israel,<sup>5</sup> and Benjamin S. Leung<sup>6,7</sup>

### SUMMARY

Tamoxifen (NSC-180973), a synthetic antiestrogen, was studied for efficacy and toxicity in patients with metastatic breast adenocarcinoma. Two dose levels were used, 10 mg bid and 15 mg/m<sup>2</sup> bid, in separate groups. In the 10-mg bid dosage group, 30 of the 31 patients were considered evaluable for efficacy. Five complete

**Tamoxifen (NSC-180973), a synthetic antiestrogen, was studied for efficacy and toxicity in patients with metastatic breast adenocarcinoma. Two dose levels were**

thrombocytopenia, nausea, and fluid retention. A high degree of correlation between response and positive estrogen-receptor assay suggests the value of the test as a means to select patients for tamoxifen treatment. The conclusion from this study is that tamoxifen used as a single agent is an effective drug with minimal toxicity for treatment of metastatic breast adenocarcinoma.

[Cancer Treat Rep 60:1431-1435, 1976]

**The high degree of correlation observed between response rate and positive ER assay suggests the value of this test as a means to select patients for tamoxifen treatment.**

Tamoxifen is a synthetic triphenylethylene derivative with potent antiestrogen activity in mammalian species (1). It inhibits the binding of estradiol to uterine receptors from various experimental animals (2) and exerts an inhibitory effect on the growth of the DMBA-induced rat mammary tumor (3). In man, tamoxifen inhibits the binding of estradiol to receptors from normal endometrium (4) and adenocarcinoma of the breast and uterus (5,6).

with evaluable disease. Except for nine patients, all had undergone prior mastectomy and approximately half had at least one course of non-hormonal chemotherapy.

The criteria for patient inclusion were: histologically proven breast adenocarcinoma with metas-



# Trastuzumab (Herceptin®) - HER2 Breast Cancer

Human Epidermal  
growth factor  
receptor 2

The New England

*The* NEW ENGLAND  
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

OCTOBER 20, 2005

VOL. 353 NO. 16

## Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer

Martine J. Piccart-Gebhart, M.D., Ph.D., Marion Procter, M.Sci., Brian Leyland-Jones, M.D., Ph.D., Aron Goldhirsch, M.D., Michael Untch, M.D., Ian Smith, M.D., Luca Gianni, M.D., Jose Baselga, M.D., Richard Bell, M.D., Christian Jackisch, M.D., David Cameron, M.D., Mitch Dowsett, Ph.D., Carlos H. Barrios, M.D., Günther Steger, M.D., Chiun-Shen Huang, M.D., Ph.D., M.P.H., Michael Andersson, M.D., Dr.Med.Sci., Moshe Inbar, M.D., Mikhail Lichinitser, M.D., István Láng, M.D., Ulrike Nitz, M.D., Hiroji Iwata, M.D., Christoph Thomssen, M.D., Caroline Lohrisch, M.D., Thomas M. Suter, M.D., Josef Rüschoff, M.D., Tamás Sittler, M.D., Ph.D.

### BACKGROUND

Trastuzumab, a recombinant monoclonal antibody against HER2, has clinical activity in advanced breast cancer that overexpresses HER2. We investigated its efficacy and safety after excision of early-stage breast cancer and completion of chemotherapy.

in advanced breast cancer that overexpresses HER2. We investigated its efficacy and safety after excision of early-stage breast cancer and completion of chemotherapy.

Bordet Institute, Blvd. de Waterloo 125, 1000 Brussels, Belgium, or at martine.piccart@bordet.be. The authors' affiliations are listed





# Cetuximab (Erbix®) Panitumumab (Vectibix®) - EGFR/*K-ras*

VOLUME 26 • NUMBER 10 • APRIL 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

ES

## Wild-Type *KRAS* Is Required for Panitumumab Efficacy in Patients With Metastatic Colorectal Cancer

Rafael G. Amado, Michael Wolf, Marc Peeters, Eric Van Cutsem, Salvatore Siena, Daniel J. Freeman, Todd Juan, Robert Sikorski, Sid Suggs, Robert Radinsky, Scott D. Patterson, and David D. Chang

### A B S T R A C T

#### Purpose

Panitumumab, a fully human antibody against the epidermal growth factor receptor (EGFR), has activity in a subset of patients with metastatic colorectal cancer (mCRC). Although activating mutations in *KRAS*, a small G-protein downstream of EGFR, correlate with poor response to anti-EGFR antibodies in mCRC, their role as a selection marker has not been established in randomized trials.

#### Patients and Methods

#### Purpose

Panitumumab, a fully human antibody against the epidermal growth factor receptor (EGFR), has activity in a subset of patients with metastatic colorectal cancer (mCRC). Although activating mutations in *KRAS*, a small G-protein downstream of EGFR, correlate with poor response to anti-EGFR antibodies in mCRC, their role as a selection marker has not been established in randomized trials.

From Amgen Inc, Thousand Oaks, CA; Ghent University Hospital, Ghent, Belgium; University Hospital Gasthuisberg, Leuven, Belgium; and the Ospedale Niguarda Ca' Granda, Milan, Italy.

Submitted October 1, 2007; accepted November 20, 2007; published online ahead of print at [www.jco.org](http://www.jco.org) on March 3, 2008.

Funded by Amgen Inc, Thousand

tions are found at the end of this article.

weeks for panitumumab and 7.3 weeks for BSC. Response rates to panitumumab were 17% and 0%, for the WT and mutant groups, respectively. WT *KRAS* patients had longer overall survival

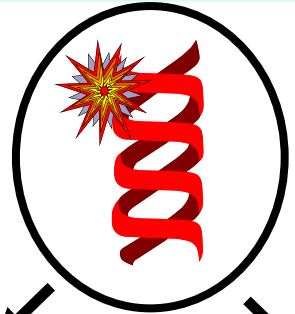
Christos S.  
Dongsheng Tu  
Sonia





# Imatinib (Gleevec™) – Specifically Targets An Abnormal Protein, Blocking Its Ability To Cause Chronic Myeloid Leukemia

Chromosome 9;22  
translocation



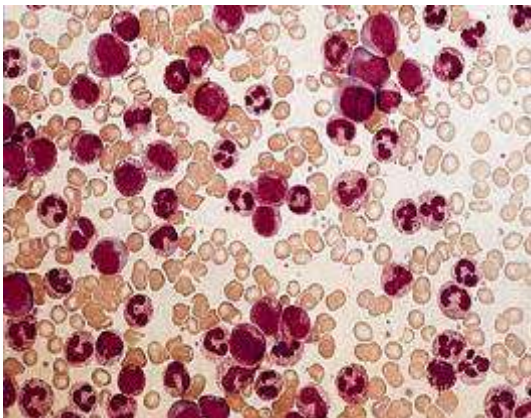
Bcr-Abl fusion protein



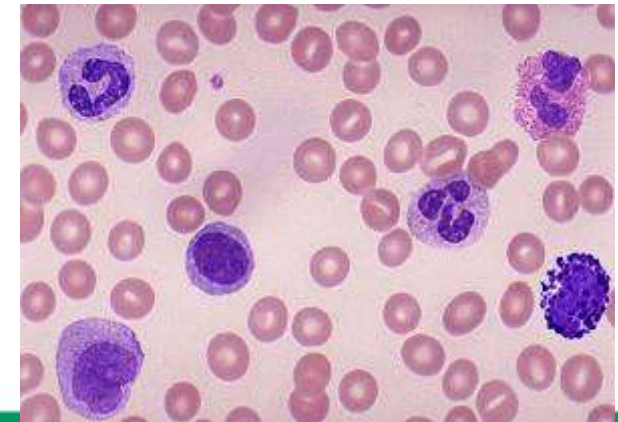
Bcr-Abl fusion protein



Gleevec™



CML

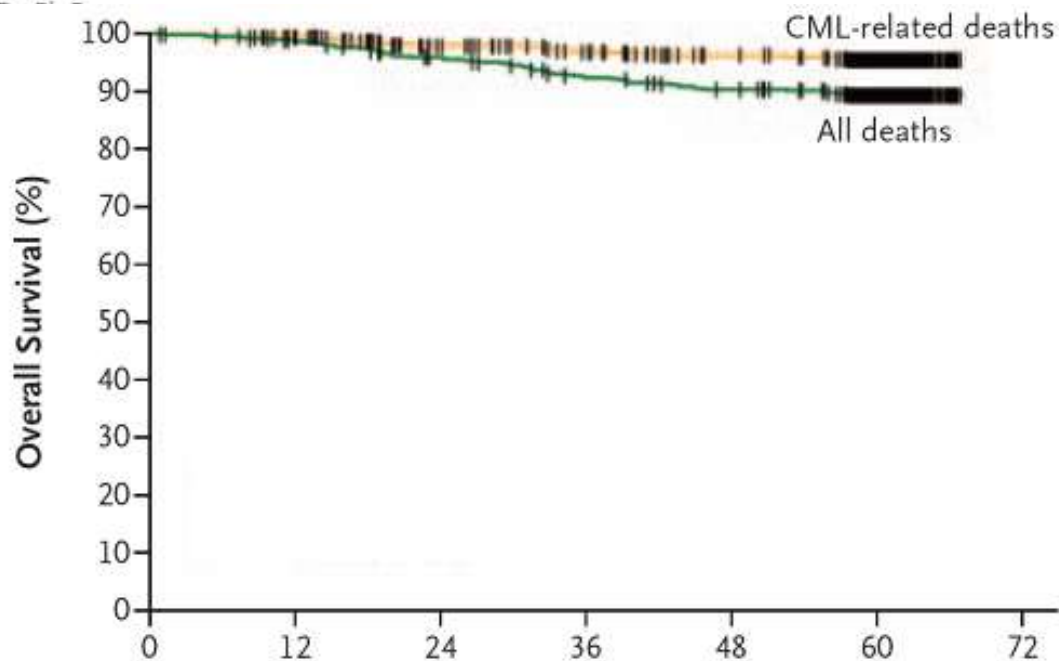


Normal

ORIGINAL ARTICLE

## Five-Year Follow-up of Patients Receiving Imatinib for Chronic Myeloid Leukemia

Brian J. Druker, M.D., François Guilhot, M.D., Stephen G. O'Brien, M.D., Insa Gathmann, M.Sc., Hagop Kantarjian, M.D., Norbert Gattermaier, M.D., Michael W.N. Deininger, M.D., Ph.D., Richard T. Silver, M.D., John M. Goldman, D.M., Richard M. Stone, M.D., Francisco Cervantes, M.D., Andreas Hochhaus, M.D., Bayard L. Powell, M.D., Janice L. Gabrilove, M.D., Philippe Rousset, M.D., Josy Reiffers, M.D., Jan J. Cornelissen, M.D., Timothy Hughes, M.D., Hermine Agis, M.D., Thomas Fischer, M.D., Gregor Verhoef, M.D., John Shepherd, M.D., Giuseppe Saglio, M.D., Alois Gratwohl, M.D., Johan L. Nielsen, M.D., Jerald P. Radich, M.D., Bengt Simonsson, M.D., Kerry Taylor, M.D., Michele Baccarani, M.D., Charlene So, Pharm.D., Laurie Letvak, M.D., and Richard A. Larson, M.D., for the IRIS Investigators\*





# Cost-Effective?

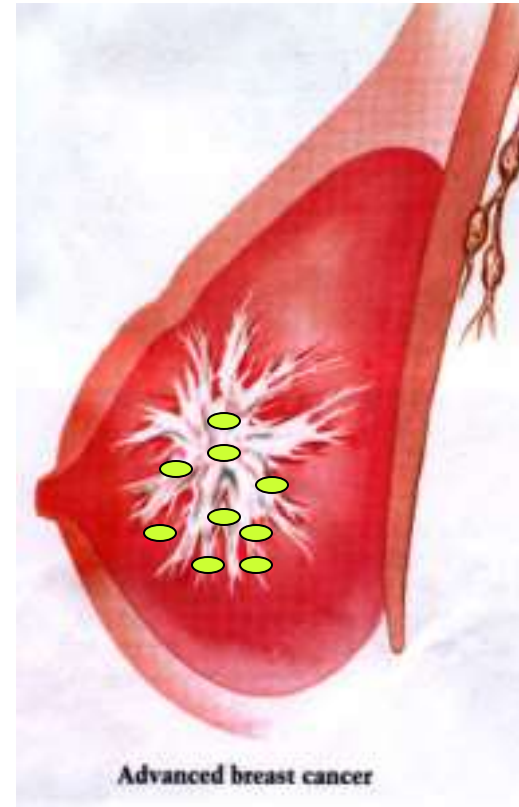
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- Gleevec as 1<sup>st</sup> line therapy for CML
  - 6 years increased survival over interferon-alpha therapy
  - \$43,100/per life-year saved
-



# HER2 Gene Product is Overexpressed in One Third of Breast Cancers

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- TUMOR OVEREXPRESSING **HER2**
  - SENSITIVE TO **HERCEPTIN**
-

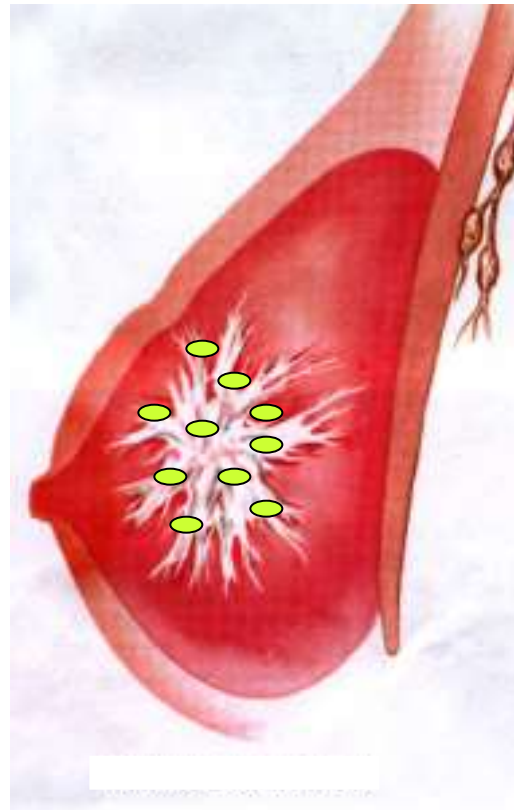




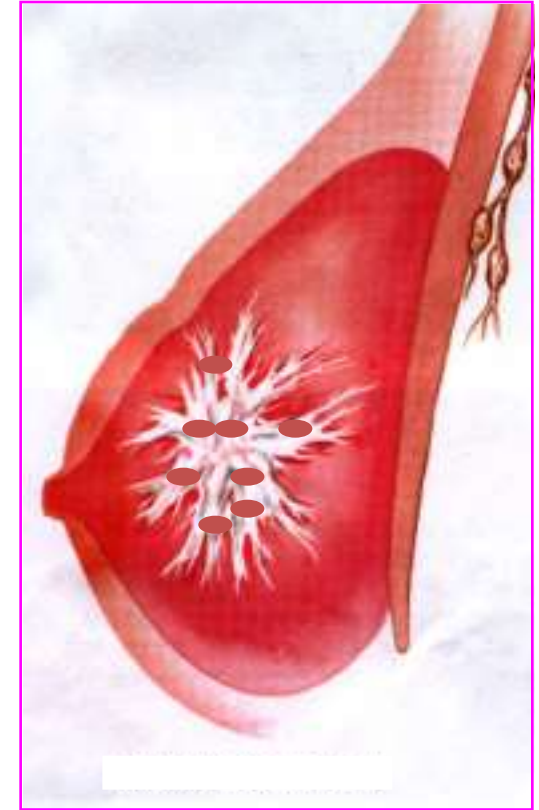
# Goal: Tailoring New Drugs to Target Different Types of Breast Cancer



- TUMOR OVEREXPRESSING ?
- SENSITIVE TO ???



- TUMOR OVEREXPRESSING **HER2**
- SENSITIVE TO **HERCEPTIN**



- TUMOR OVEREXPRESSING ?
- SENSITIVE TO ???



# Drug-Diagnostics Combinations in Oncology

---

- The improvement of future medical anti-cancer therapy will come from our increased understanding of the molecular pathophysiology and drug mechanisms of action
  - The key driver in this process will be the molecular analytical methods and molecular diagnostics
  - Parallel drug-diagnostic co-development will be the standard development model for new anti-cancer drugs
  - Future medical anti-cancer therapy will be more individualized compared with today's knowledge
  - In 2020 most anti-cancer drugs will be prescribed based on the results of a companion diagnostic/pharmacodiagnostic test
-



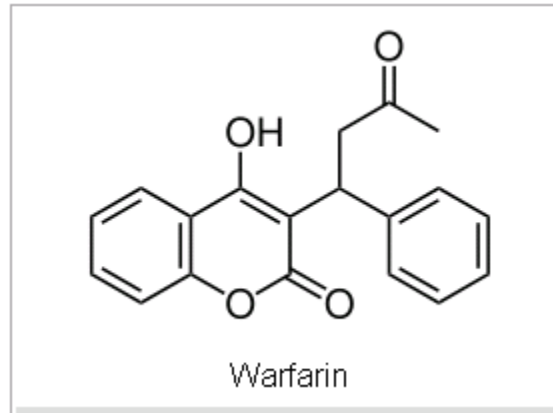
ORIGINAL ARTICLE

# Effect of *VKORC1* Haplotypes on Transcriptional Regulation and Warfarin Dose

Mark J. Rieder, Ph.D., Alexander P. Reiner, M.D., M.P.H.,  
Brian F. Gage, M.D., M.Sc., Deborah A. Nickerson, Ph.D., Charles S. Eby, M.D.,  
Howard L. McLeod, Pharm.D., David K. Blough, Ph.D.,  
Kenneth E. Thummel, Ph.D., David L. Veenstra, Pharm.D., Ph.D.,  
and Allan E. Rettie, Ph.D.



# Case Study: Warfarin



- Most widely prescribed oral anticoagulant for preventing thrombotic events, despite its narrow therapeutic range
- Problematic dosing due to patient's diet, age, and other medications
- Second most common drug implicated in adverse drug reaction-linked emergency room visits

Sources: US FDA ([www.fda.gov](http://www.fda.gov)), Warfarin Information; Rettie et al. *Molecular Interventions* 2006; 6(4):223-227; Flockhart et al. *Genetics in Medicine* 2008; 10(2):139-150





# Personalized Warfarin Dosing

## Drug-metabolizing enzyme Variations

---

- One-third of thrombosis patients metabolize their warfarin dose differently than expected due in large part to variations of *VKORC1* and *CYP2C9*
  - *VKORC1* SNPs, such as the 1639G>A allele, indicate that a patient will respond well to a lower dose of warfarin
  - *CYP2C9*\*2 and *CYP2C9*\*3 alleles encode SNP variants of *CYP2C9* with reduced efficiency in degrading warfarin
  - Warfarin labeling suggesting genetic testing of *VKORC1* and *CYP2C9* is the first indication of personalized dosing being approved by the FDA
-



# Companion Diagnostics

Breast cancer: Herceptin



HER2 (30%↑)

(Human Epidermal growth factor receptor 2)

→ **Drug Choice**

Blood clot prevention: Warfarin



CYP2C9

(Drug-metabolizing enzyme)

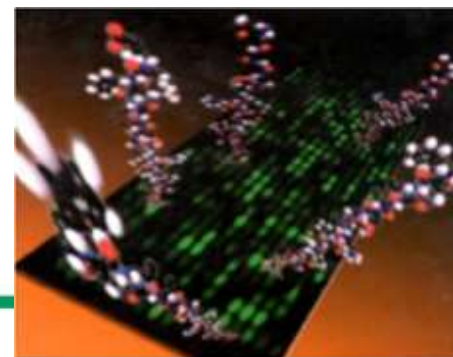
Variations: Adverse Drug Reactions)

→ **Drug Dose**





# Clinically Available Molecular Diagnostics



Diagnostic Kits  
Laboratory-developed-tests (LDTs)

| Time point in clinical decision making | Cancer   |   | Cardiovascular disease   |  |
|--|--|---|--|--|
|  | Test   | Indication  | Test   | Indication   |
| Risk/susceptibility →                  | <i>BRCA1, BRCA2</i><br><i>HNPCC, MLH1, MSH2</i><br><i>TP53, PTEN</i>   | Breast<br>Colon<br>Sarcomas   | <i>KIF6, 9p21</i><br>Familion <sup>®</sup> 5-gene profile                                      | CAD<br>LQTS  |
| Screening                              | HPV genotypes  | Cervical  | Corus <sup>™</sup> CAD   | CAD  |
| Diagnosis →                            | Lymphochip   | Lymphoma  | Corus CAD  | CAD  |
| Prognosis →                            | Oncotype DX <sup>®</sup> (21-gene assay)<br>MammaPrint <sup>®</sup> (70-gene assay)<br>Her2/neu, ER, PR                        | Breast  | TnI, BNP, CRP  | ACS  |
| Pharmacogenomics →                     | Her2/neu<br><i>UGT1A1</i><br><i>KRAS</i><br><i>EGFR</i><br>Amplichip <sup>®</sup> ; DMET <sup>™</sup><br><i>CYP2D6/CYP2C19</i> | Herceptin<br>Irinotecan<br>Cetuximab<br>Erlotinib, gefitinib<br>Various others<br>(see Table 2) | <i>KIF6, SLCO1B1</i><br>Amplichip; DMET <sup>™</sup><br><i>CYP2D6/CYP2C19</i><br><i>VKORC1</i> | Statins<br>Warfarin<br>Various others<br>(see Table 2) |
| Monitoring                             | CTCs   | Tumor recurrence or progression →   | AlloMap <sup>®</sup> gene profile  | Transplant rejection                                   |



# AmpliChip

**A range of drug metabolism phenotypes is observed for individuals based upon the particular cytochrome P-450 genes they possess.**

## **Analysis of CYP2D6 and CYP2C19 genes**

Comprehensive detection of gene variations – including deletions and duplications – for the CYP2D6 and CYP2C19 genes, which play a major role in the metabolism of an estimated 25 percent of all prescription drugs. This test helps clinicians determine therapeutic strategy and treatment dose for therapeutics metabolized by the CYP2D6 or CYP2C19 gene product.



*Source: Caraco, Y., N Engl J Med, 2004*





# Multiplex Tests are Already Starting to Have an Impact

---



## OncoType DX

Analyzes by qPCR, mRNA expression of a panel of 21 genes within a tumor to determine a Recurrence Score

## MammaPrint

Microarray-based prognostic breast cancer mRNA expression profiling test of 70 genes

## AlloMap

qPCR-based expression profile of 11 genes to assist physicians in managing heart transplant patients for potential organ rejection

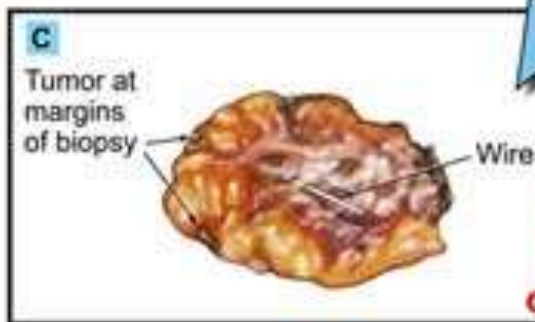
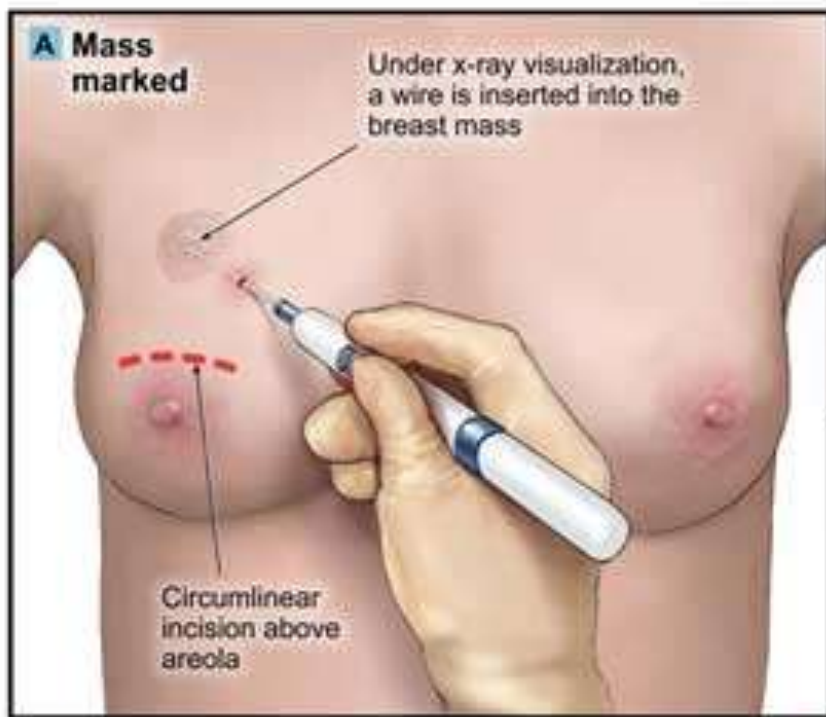
## Tissue of Origin

Microarray technology considers 15 common malignant tumor types, including bladder, breast, and colorectal tumors based on mRNA expression on 1,550 genes

---



# 's 11/19/01 Right Breast Biopsy



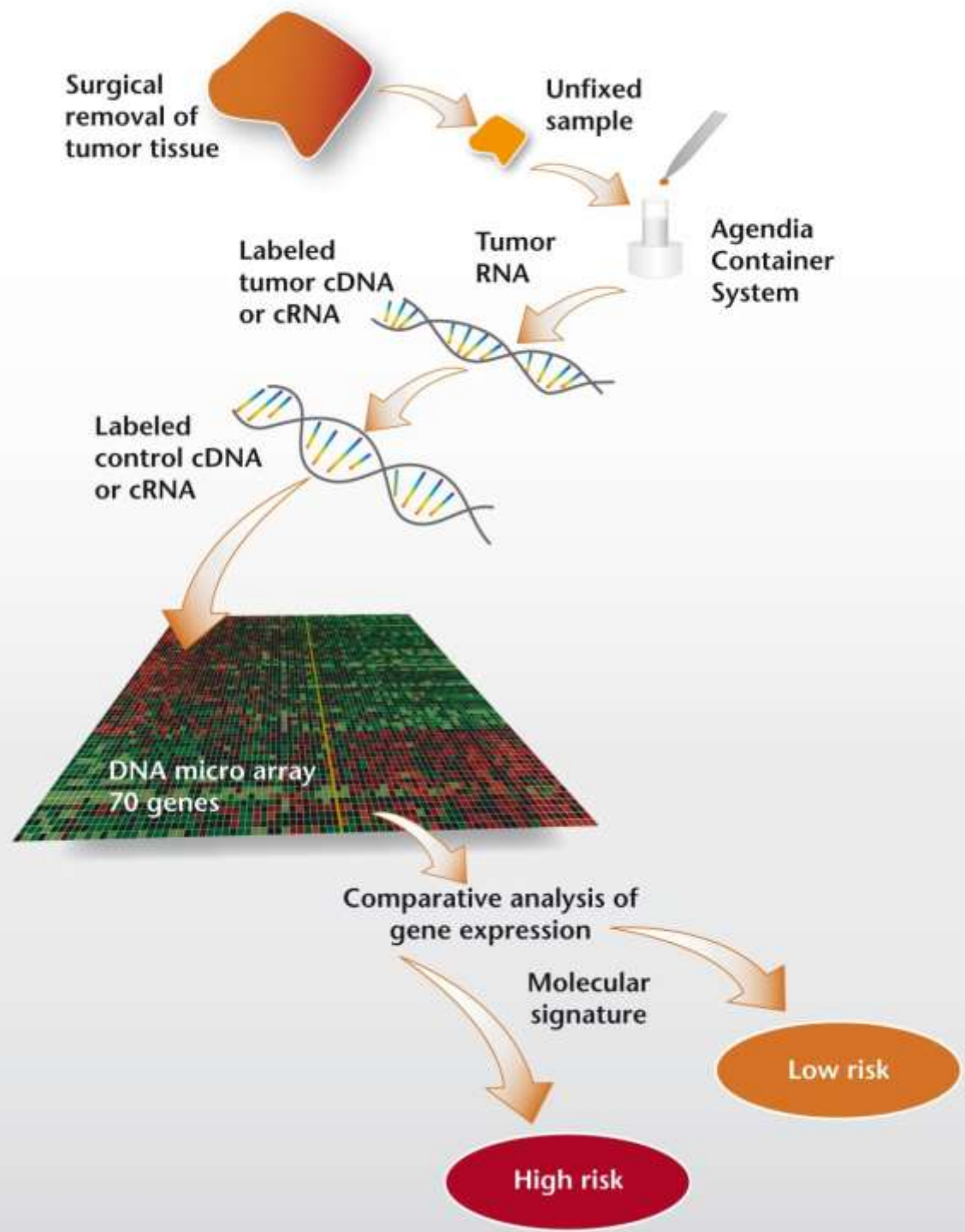
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agendia<sup>®</sup>  
*decoding cancer.*



mammaPrint






## Oncotype DX<sup>®</sup>: A Genomic Assay

Recurrence tumor after surgery  
Decision-making about treatment

a 21-Gene Assay for N-, ER+, Tam+ Patients







# The Recurrence Score<sup>®</sup> Result Uses Key Genes Linked to Critical Molecular Pathways

## 16 BREAST CANCER RELATED GENES

| Estrogen                   | Proliferation                                    | HER2         | Invasion                      | Others                |
|----------------------------|--|--------------|-------------------------------|-----------------------|
| ER<br>PR<br>Bcl2<br>SCUBE2 | Ki-67<br>STK15<br>Survivin<br>Cyclin B1<br>MYBL2 | GRB7<br>HER2 | Stromelysin 3<br>Cathepsin L2 | CD68<br>GSTM1<br>BAG1 |

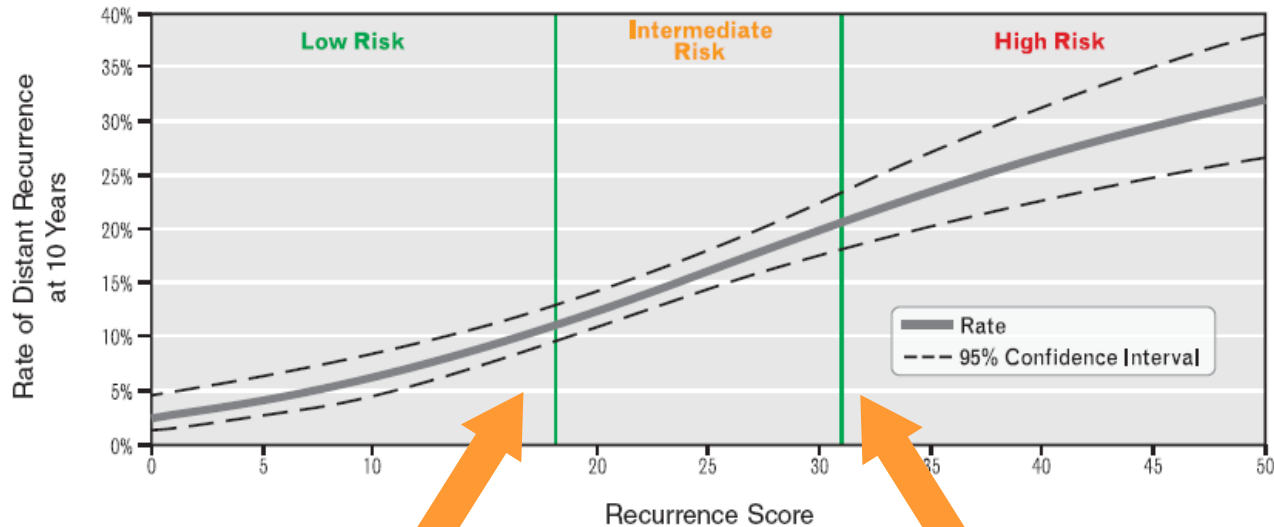
## 5 REFERENCE GENES

|            |       |       |     |      |
|------------|-------|-------|-----|------|
| Beta-actin | GAPDH | RPLPO | GUS | TFRC |
|------------|-------|-------|-----|------|



# Oncotype DX<sup>®</sup> is a Standardized and Quantitative Assay

## Recurrence Score<sup>®</sup> in N-, ER+ patients



### Lower RS's

- Lower likelihood of recurrence
- Minimal, if any, chemotherapy benefit

### Higher RS's

- Greater likelihood of recurrence
- Clear chemotherapy benefit

1) Paik et al. *NEJM* 2004, 2) Habel et al. *Breast Cancer Research* 2006

3) Paik et al. *JCO* 2006, 4) Gianni et al. *JCO* 2005



# Conclusions

---

- The *Oncotype DX*<sup>®</sup> Recurrence Score assay predicts the likelihood of adjuvant chemotherapy benefit
  - It also is a prognostic assay for the risk of distant recurrence at ten years assuming five years of adjuvant tamoxifen treatment
  - *Oncotype DX*<sup>®</sup> Recurrence Score assay shows consistent results across multiple independent studies
-



Non-invasive.  
Improved  
quality of life.

## Personalizing Care for Heart Transplant Patients

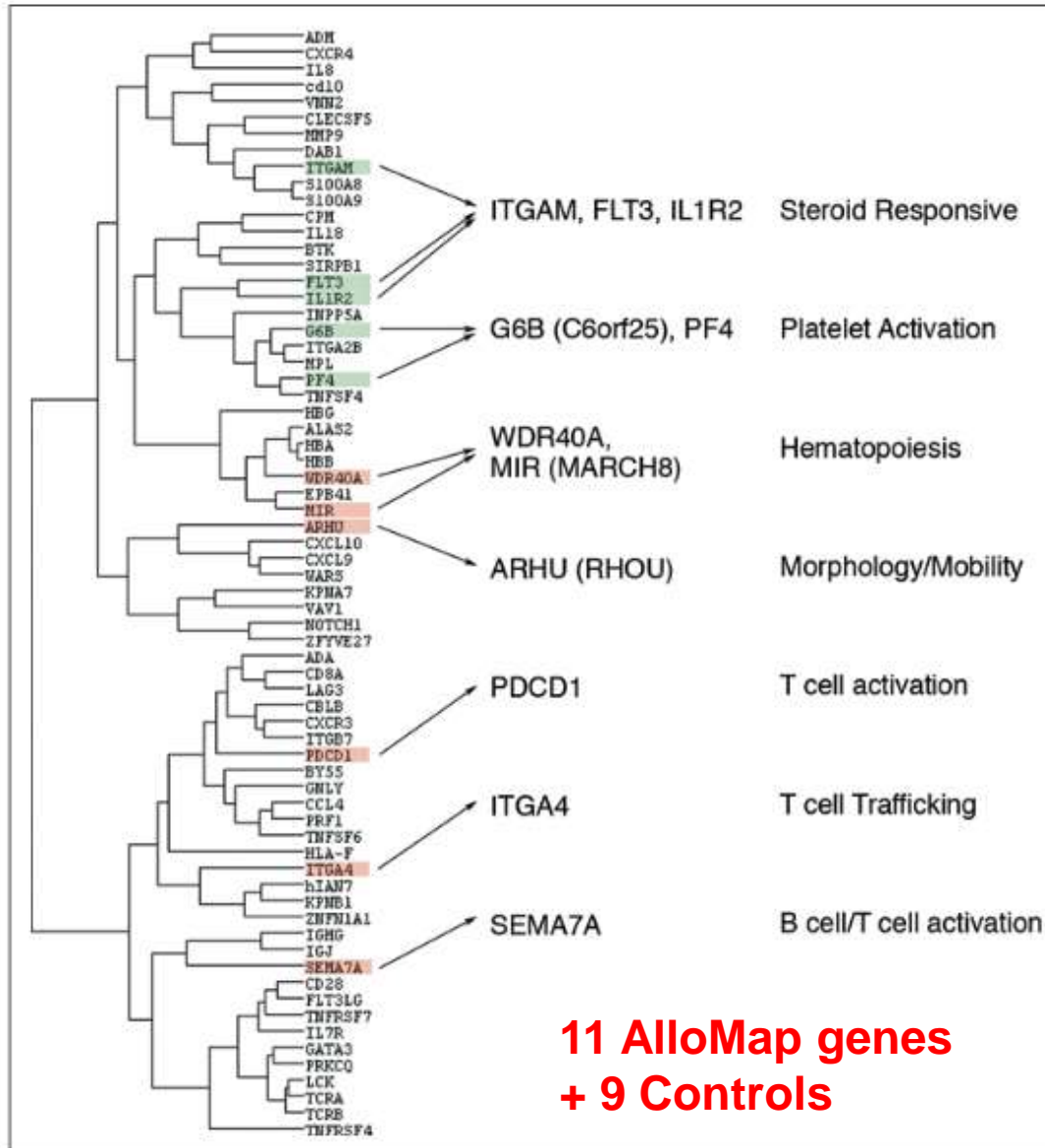
AlloMap® is a non-invasive blood test for heart transplant patients. AlloMap is the first and only non-invasive test with a rapid turnaround time that helps physicians identify the risk of acute cellular rejection in heart transplant recipients.

Since its introduction in 2005, AlloMap has helped to:

- Reduce patients' pain, anxiety, and risk caused by biopsies through a simple, non-invasive method of blood sample collection
- Give providers accurate information on the risk of acute cellular rejection in their patients following heart transplant



## Targeting Specific Genes for the AlloMap Test

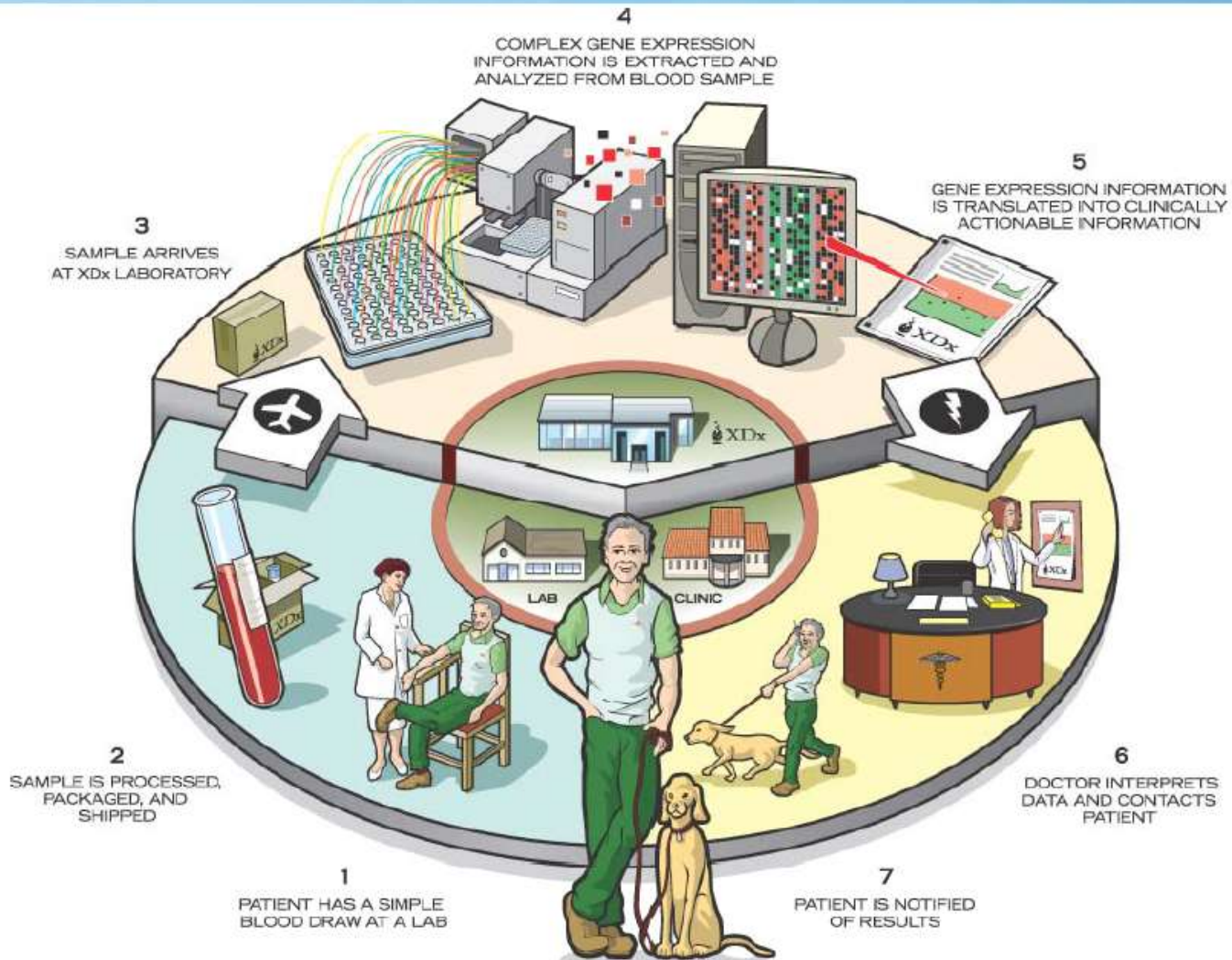


Using linear discriminant analysis, the expression levels of 11 genes were selected for the calculation of the AlloMap score (integer 0–40). This set of genes best distinguished between the presence and absence of rejection in the development of the AlloMap test.

## Differential Expression of AlloMap Genes in Rejection Samples

| Pathway and Gene  | Gene Expression Level |
|---|-----------------------|
| <b>T cell priming</b>   |                       |
| <i>ITGA4</i><br>Integrin alpha-4<br>α subunit of VLA-4; involved in T cell trafficking and adhesion   | ↑                     |
| <i>PDCD1</i><br>Programmed cell death<br>T cell costimulatory molecular (inhibitory); CD28 family   | ↑                     |
| <b>Proliferation and mobilization of erythrocytes</b>   |                       |
| <i>MARCH8</i><br>Cellular mediator of immune response (MIR)<br>E3 ubiquitin ligase  | ↑                     |
| <i>WDR40A</i><br>WD repeat domain 40A<br>Uncharacterized protein of the WD-repeat protein family  | ↑                     |
| <b>Platelet activation</b>  |                       |
| <i>PF4</i><br>Platelet factor 4<br>Chemokine-like molecule expressed in platelets   | ↓                     |
| <i>C6orf25</i><br>G6b inhibitory receptor<br>Putative inhibitory receptor of the Ig superfamily expressed in platelets                      | ↓                     |
| <b>Steroid response</b>   |                       |
| <i>IL1R2</i><br>Interleukin-1 receptor type II<br>IL-1 decoy receptor inhibits cytokine signaling; steroid-dependent expression             | ↓                     |
| <i>ITGAM</i><br>Integrin alpha-M<br>α subunit of MAC-1; involved in cell trafficking  | ↓                     |
| <i>FLT3</i><br>FMS-like tyrosine kinase<br>Signaling molecule expressed in monocytes  | ↓                     |
| <b>Unknown role</b>   |                       |
| <i>SEMA7A</i><br>Semaphorin 7A<br>Expressed by T cells, B cells, and immature granulocytes  | ↑                     |
| <i>RHOU</i><br>Ras homolog gene family, member U<br>Member of the Rho GTPase family involved in the modulation of cytoskeleton organization | ↑                     |

# AlloMap Workflow





# Tissue of Origin



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TISSUE OF ORIGIN®



## Tissue of Origin®

The Tissue of Origin test, formally a Pathwork test, is a microarray-based gene expression test that aids in identifying challenging tumors, including metastatic, poorly differentiated, and undifferentiated cancers. TOO is the **ONLY** FDA-cleared test of its type and is a Medicare-reimbursed test.





# Tissue of Origin<sup>®</sup> Overview

---

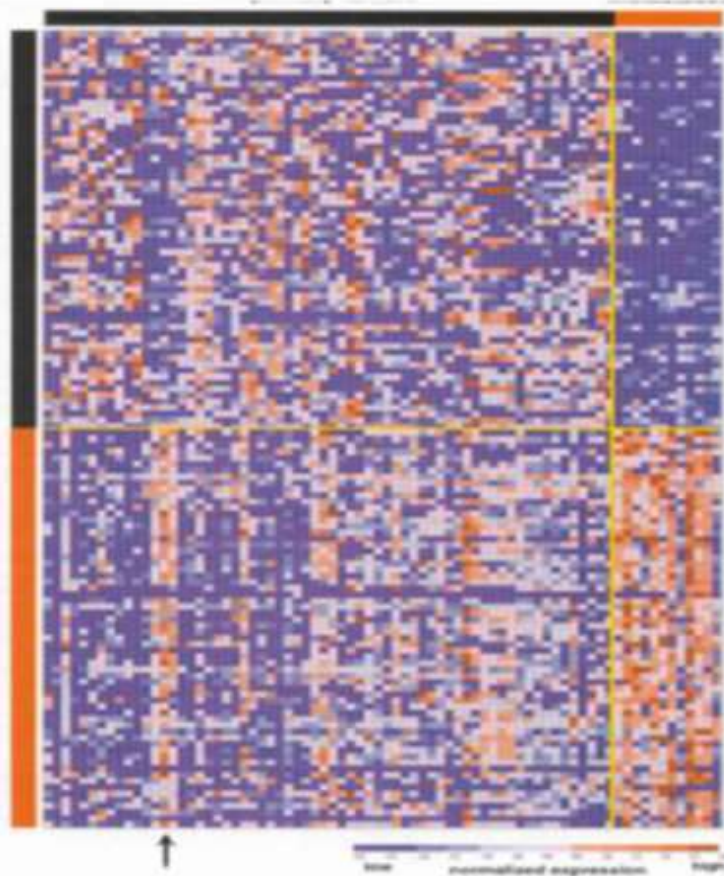
- The Tissue of Origin reports the most likely tissue of origin from 15 of the most common tumor types, representing 58 morphologies.
  - 2000 genes, covering 15 tumors types and 90% of all solid tumors<sup>1</sup>
  - Extensive analytical and clinical validation.
  - Statistically significant improvement in accuracy over other methods, including IHC<sup>2</sup>
  - Leads to a change in treatment 65% of the time.
-





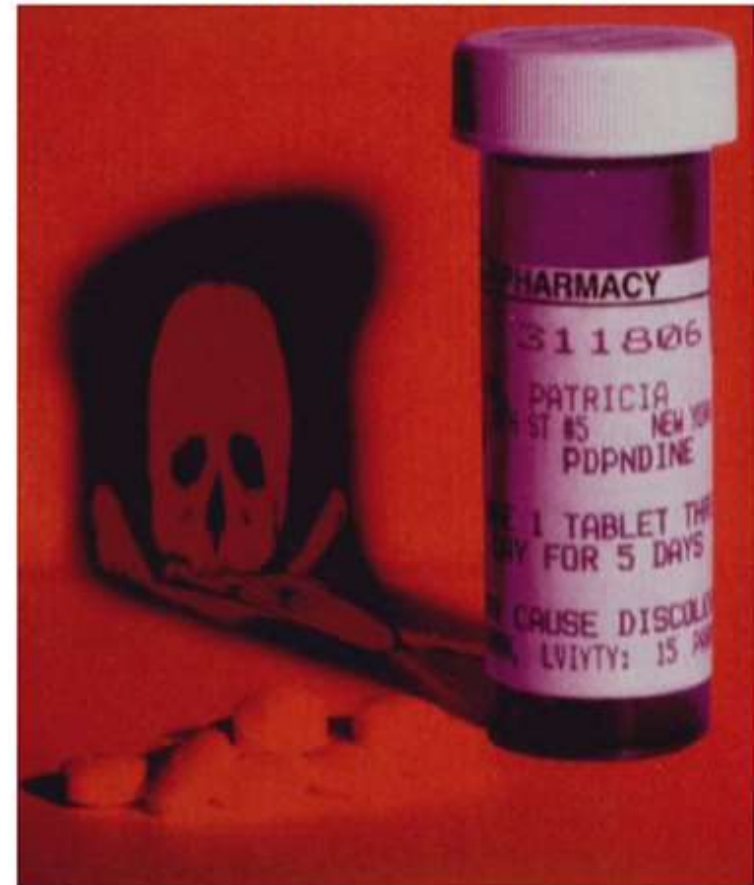
# From Pharmaceuticals to Pharmasuitables

**Disease Subtyping:**



**Right Rx for Right Disease**

**Individual  
Variation and AE risk**



**Right Rx for Right Patient**



# BIDIL



November 2005

First drug approved by  
FDA  
that comes with a  
race-specific label:

“For African Americans Only”



---

# Personalized Medicine: A future dream





# Betty's story in 2017

---

- Betty completes the Surgeon General's family history tool at age 25, learns of uncles with early heart disease.
  - She consults her PA, who works in a practice that has made an effort to stay informed about genomic medicine. She suggests complete genome sequencing for \$1000.
  - Betty inquires about the risk of genetic discrimination, but effective legislation has outlawed this.
  - She is found to have three gene variants that have been shown conclusively in well validated studies to increase her risk of early heart attack 4-fold.
  - She and her PA design a program of prevention based on diet, exercise, and medication precisely targeted to her genetic situation.
-





# Betty's story continues

---

- Betty does well until age 75.
  - She develops left arm pain that she assumes is due to gardening, but her care providers know her higher risk and diagnose an acute MI.
  - Referring to her genome sequence, the PA and MD choose the drugs that will work best to treat her.
  - She survives and is alive and well in the 22<sup>nd</sup> century.
-



# **Personalized Medicine: Could the dream become a nightmare?**





# Betty's story gone wrong

---

- Betty never learns about her family history, educational efforts for the public and health care providers were defunded, community efforts never got off the ground, and Betty's PA and MD thought genetics was irrelevant to practice.
  - Betty hears about genome sequencing, but after seeing her brother lose his health insurance from this information, she decides not to.
  - Betty eats an unhealthy diet, gains weight, and develops high blood pressure.
  - While tests to predict which drug would be most effective for Betty have been proposed, they have never been validated, and are not reimbursed.
-



# Betty's story gone really wrong

---

- Betty's hypertension is treated with a drug that causes a hypersensitivity reaction, so she stops treatment.
  - After 10 years of uncontrolled hypertension, Betty develops left arm pain at age 50.
  - Unaware of her high risk, her PA assumes this is musculoskeletal and prescribes rest.
  - Betty returns to the ER a few hours later in cardiogenic shock.
  - The absence of her genome sequence information prevents immediate optimum choice of therapy.
  - Betty dies in the ER.
-





# “Personal Genome”



> 50 companies  
World-wide

## The Road to the Personal Genome

IN THE space of a single decade, the cost of mapping all your DNA will fall from the billions of dollars to the thousands. The human genome is becoming a commodity virtually overnight. It's as if millions of households could have had dishwashers and vacuum cleaners 10 years after James Watt built his steam engine.

DNA, the “code of life,” is the ultimate binary file, a database of 12 billion bits. The data—6 billion matching sets of either the molecules adenine (A) and thymine (T) or guanine (G) and cytosine (C)—affect everything that makes you you: the color of your eyes, whether you're moody or cheerful, and which diseases you're most susceptible to.

Today you can purchase your very own personal genome for US \$48,000 from Illumina, a San Diego biotech firm (and they'll throw in an Apple iMac). [See “The \$100 Genome,” elsewhere in this issue.] That's a bit pricey if all you want to do is check out the genetic inheritance of Saturday's dinner date. But by 2014, your genome will cost a mere \$2500, according to TSG Partners, an Atlanta-based life sciences advisory firm, so low that health insurance companies might pick up the tab just to get their hands on the data. The current head of the Personal Genome Project, George Church, thinks it will soon be far cheaper than that—perhaps even less than the dinner itself.


—Mark Anderson

SOURCE: TSG Partners, Atlanta (projection one); George Church, Harvard Medical School (projection two).





# Challenge: Premature Translation “Genomics and Personalized Health”



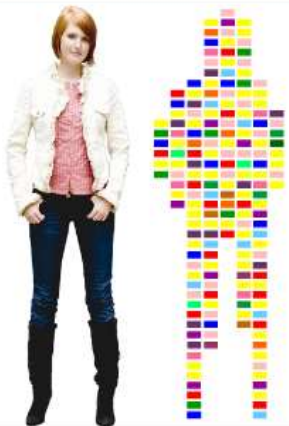
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deCODE genetics  
the pioneers in gene discovery

deCODEme  
the most comprehensive genome scan  
with information on more diseases and genes

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Join deCODEme today.

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- For only \$985 we scan over one million variants in your genome
- Calculate genetic risk for [17 diseases](#) based on the current literature
- Find out where your ancestors came from
- Invite friends and family, compare your genomes
- Get regular updates on future discoveries and a growing list of diseases and traits



### Ordering information

For a low introductory price of \$985 you can order a Genetic Scan of over one million variants across the genome. In 2-3 weeks after we receive your sample you will have access to your personal genome profile.

[»More](#)



### What is deCODEme?

deCODEme is a living website which will be continuously updated with information by deCODE genetics' team of experts. Now you can study your genome profile in an easy manner guided by the scientists who discovered the genes.

[»More](#)



### About deCODE

Discover more about deCODE genetics' unrivaled [track record](#) and how deCODE spearheaded discovery of key genes contributing to healthcare challenges ranging from heart disease to cancer.

[»More](#)

### sign up now

- 1 Create an account and place your order for Genetic Scan.
- 2 Receive our sample collection kit and mail back a sample in the enclosed self addressed stamped envelope.
- 3 Receive a notification from deCODE me and access your CODE on a personalized and secure website.

sign up



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## Welcome to Navigenics

We are in the midst of an exciting era of discoveries about the connections between our individual genetic composition and our personal health and wellness. These discoveries are providing a detailed map of thousands of genes that instruct the body how to grow, live and thrive – and a better understanding of how variations in these genes may influence our health over time.

But how will you know what to do with this information and how it can help you? Navigenics will tell you your genetic health profile and help you develop a plan for wellness and prevention – so you can be even more in control of your health and live a longer, more active life.

Your genes offer a road map to optimal health



# Challenge: Premature Translation “Genomics and Personalized Health”

the genetics just get personal.

our service

genetics 101

for the experts

store

about us

discover your genome at 23andMe

1866: Gregor Mendel discovers the laws of inheritance.

200,000 years ago: *Homo sapiens* walks the Earth.

2003: The Human Genome Project maps a single person's genome.

**2007: 23andMe introduces the first Personal Genome Service.**  
Unlock the secrets of your own DNA. Today.

175,000 years ago: The mother of all present-day humans is born in Africa.

1953: Watson and Crick uncover the double-helix structure of DNA.

Welcome to 23andMe, a web-based service that helps you read and understand your DNA. After providing a saliva sample using an at-home kit, you can explore your genetic heritage, discover health-related insights, and connect with relatives.





# “My Genome, Myself: Seeking Clues in DNA”

A. Harmon, New York Times, Nov 17, 2007

## TRACKING SNPS

Using the Web site of 23andMe, a company that queried 550,000 SNPs in a sample of her DNA, the reporter determined that her genotype for adult lactose intolerance is GG (she is lactose intolerant). Some of her other genotypes are below:

| SNP        | Location | Genotype | Genotype associated with                            |
|------------|----------|----------|---|
| rs662799   | APOA5    | AA       | Tendency to gain weight when eating fatty foods     |
| rs174575   | FADS2    | CC       | Higher I.Q. if breast fed for nine months as infant |
| rs6920220  | 6q23     | GG       | Low risk of rheumatoid arthritis                    |
| rs17070145 | KIBRA    | CC       | Relatively poor verbal memory                       |
| rs1801260  | CLOCK    | AA       | Early rising  |
| rs1953558  | OR11H7P  | CC       | Sensitivity to smell of sweat                       |
| rs17822931 | ABCC11   | CC       | Wet earwax  |

**"I am convinced that within five years every college-educated person in America is going to have a profile like this. You cannot afford not having this."**

**Kari Stefansson, DeCode Genetics-April 1, 2008**



Veritas  
Genetics

This Breast Cancer  
Awareness Month,  
#screen2know



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Understand your genetics  
to live healthier, longer.

Sequence your whole genome

myGenome

Screen for breast & ovarian cancer risk

myBRCA

Sequencing human Genome  
<1000 \$





# Clear, simple, powerful.

From answering specific questions to giving you the most comprehensive view of your genetic make-up, our goal is to empower you to make smarter decisions so you can live healthier, longer.