ADAM MICKIEWICZ UNIVERSITY IN POZNAŃ
Faculty of Biology

# Genome Medicine



# Personilized/Precision Medicine

Hans Bluyssen, 09-10-2019

**Molecular Therapies**

**Coordinator:** Hans Bluyssen

**Lecturers:** Hans Bluyssen, Joanna Wesoły, Arkadiusz Kajdasz

**Journal club:** Hans Bluyssen

**Exercises:** Arkadiusz Kajdasz, Jakub Winkler-Galicki

Natalia Lopacinska

**Language:** English

**Programme**

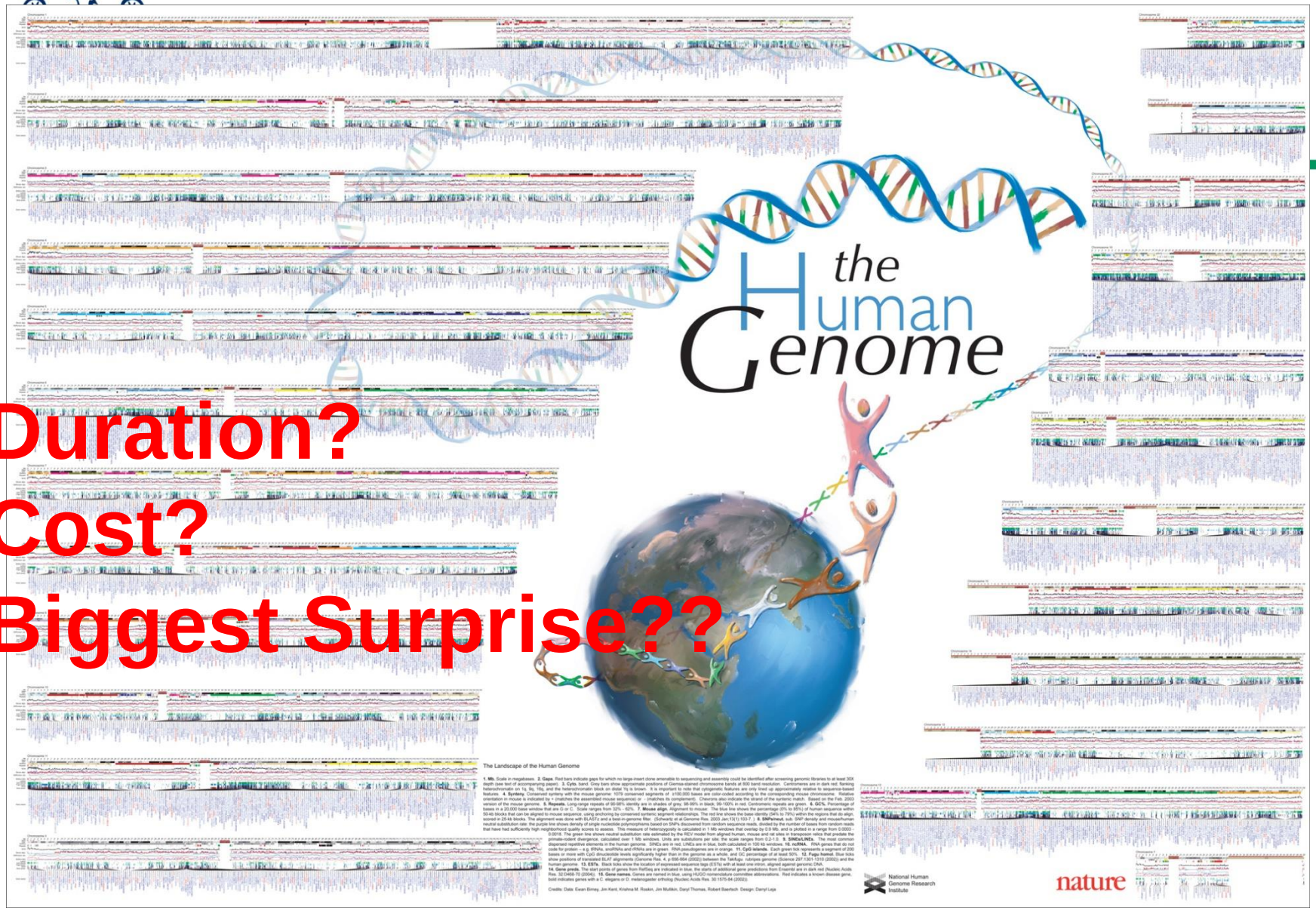
**Lectures:**

1. Genome Medicine
2. Nanotechnology & Nanomedicine
3. Immune Therapy
4. Stem Cell Research
5. RNA interference
6. Novel treatment strategies in cancer

(HB)

7. Gene-editing and therapeutic applications (AK)
8. Tissue engineering (JW)

(JW)


the Human Genome
Duration?
Cost?
Biggest Surprise??
The Landscape of the Human Genome
National Human Genome Research Institute
nature

# Post-genome sequencing "Functional Genomics"

-translate information to different levels

-Understanding mechanisms of cell function + organism

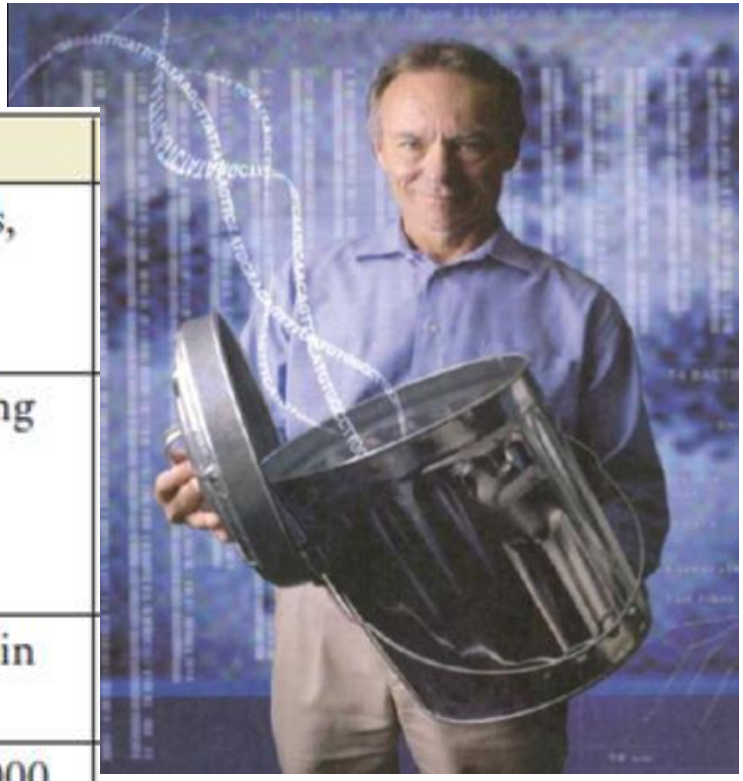
-Health care:
food and health
mechanism infectious disease
origins of multifactorial disease

-Medical diagnostics/prognostics

-Pharmaceutical products/ therapeutics

# The "Functional Genomics" Toolbox

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



(Chan & Ginsburg, 2011)

# “Personal Genome”

## 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.

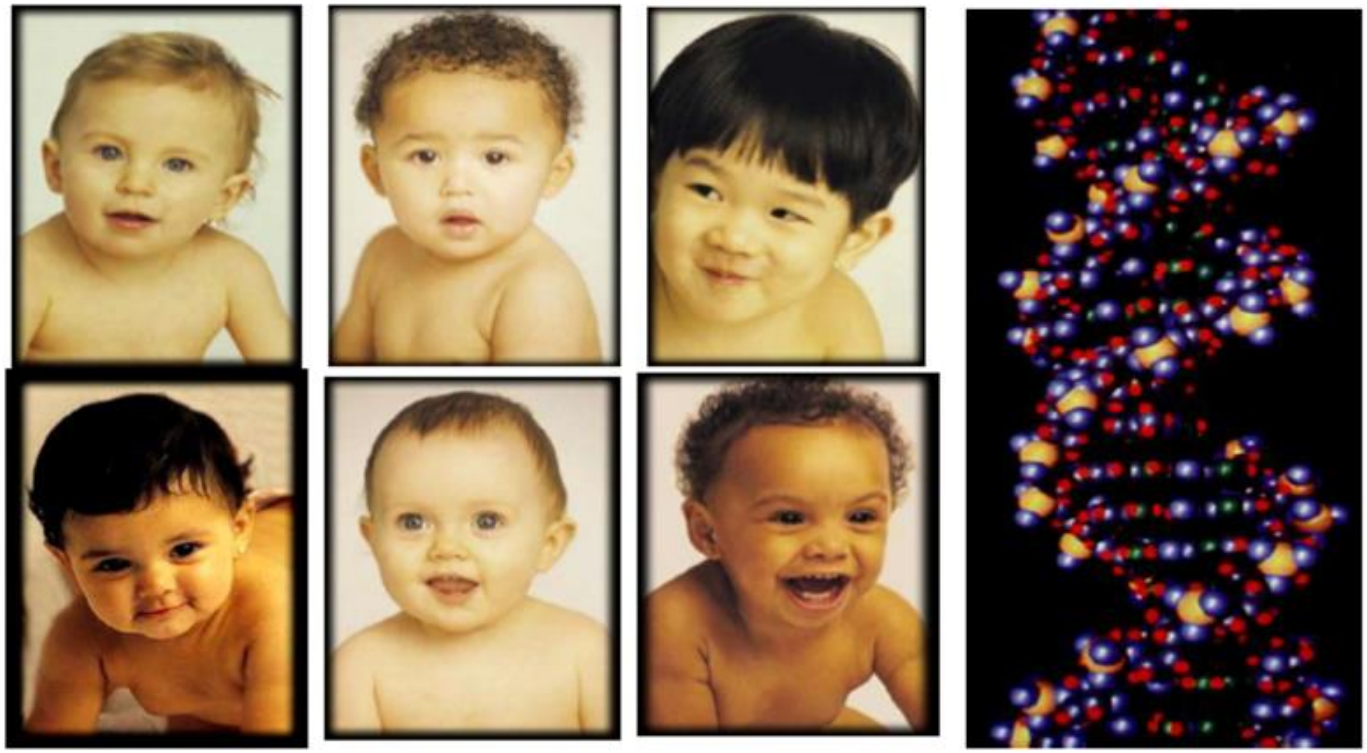
DNA, the "code of life," is the ultimate binary file, a database of 12 billion bits. The data—6 billion matching sets of either the molecules adenine (A) and thymine (T) or guanine (G) and cytosine (C)—affect everything that makes you *you*: the color of your eyes, whether you're moody or cheerful, and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

| | COST PER GENOME (US $) | GENOMES MAPPED |
|---|---|---|
| 2004 | $3 000 000 000 | 1 |
| 2006 | $60 000 000 | 1 |
| 2007 | $1 000 000 | 1 |
| 2010 | $48 000 | 75 |
| PROJECTION ONE | | PROJECTION ONE |
| 2012 | $10 000 | 5000 |
| 2014 | $2500 | 100 000 |
| PROJECTION TWO | | PROJECTION TWO |
| 2012 | $500 | 100 000 |
| 2014 | $100 | 1 000 000 |

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

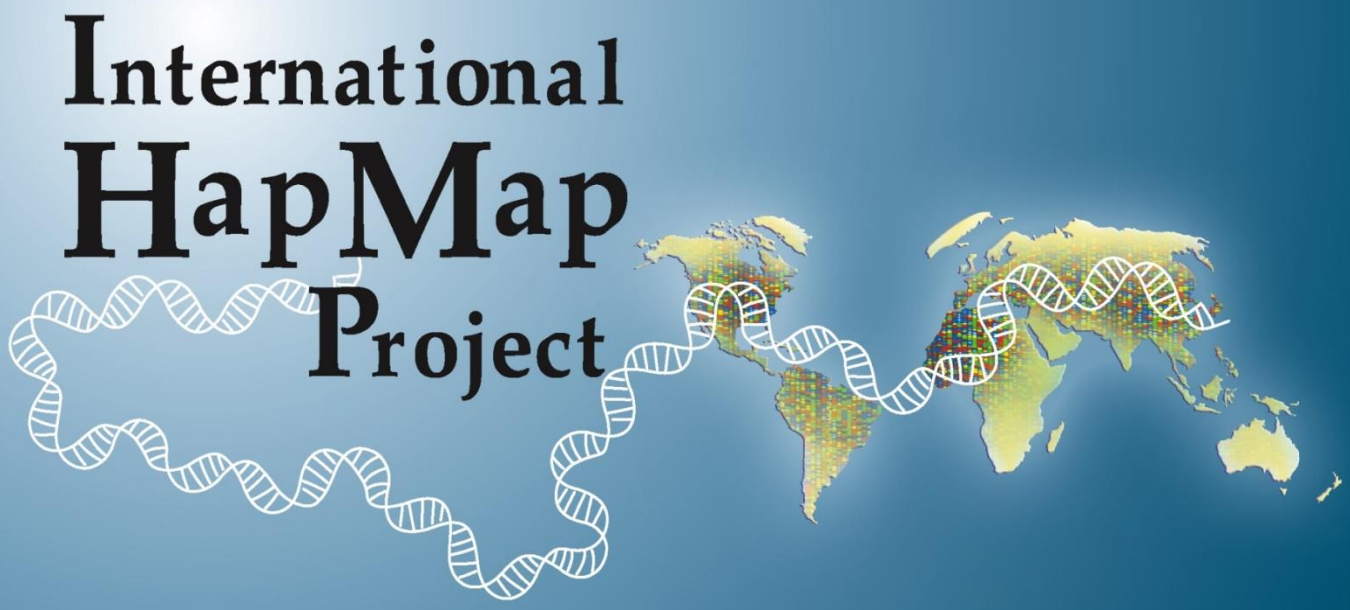
# Genomics: Single Nucleotide Polymorphisms



The Hunt for Gene Loci Associated with Complex Human Diseases

**Genome wide variation!**

# www.hapmap.org

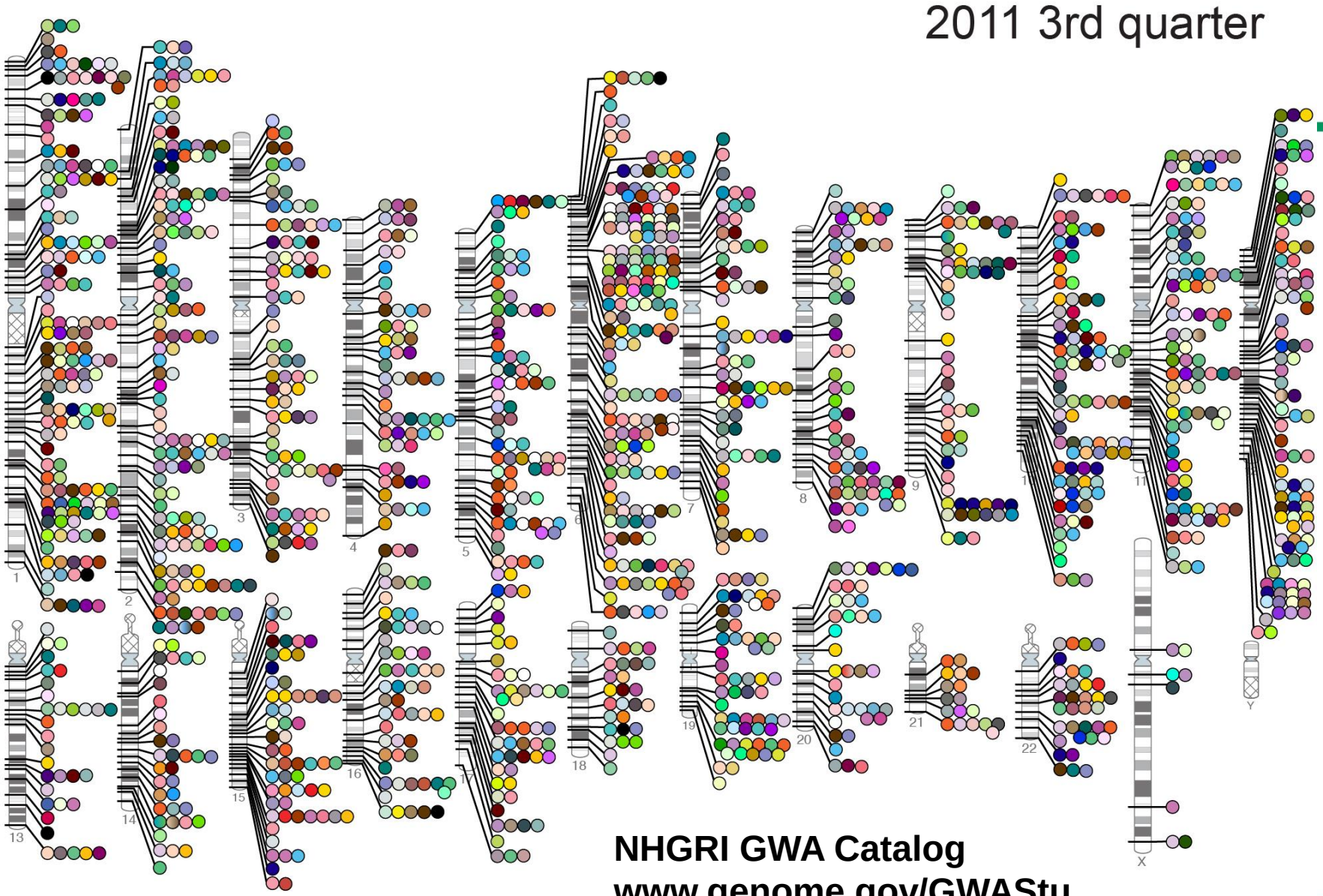



The HapMap is a catalog of common genetic variants that occur in human beings. It describes what these variants are, where they occur in our DNA, and how they are distributed among people within populations and among populations in different parts of the world.

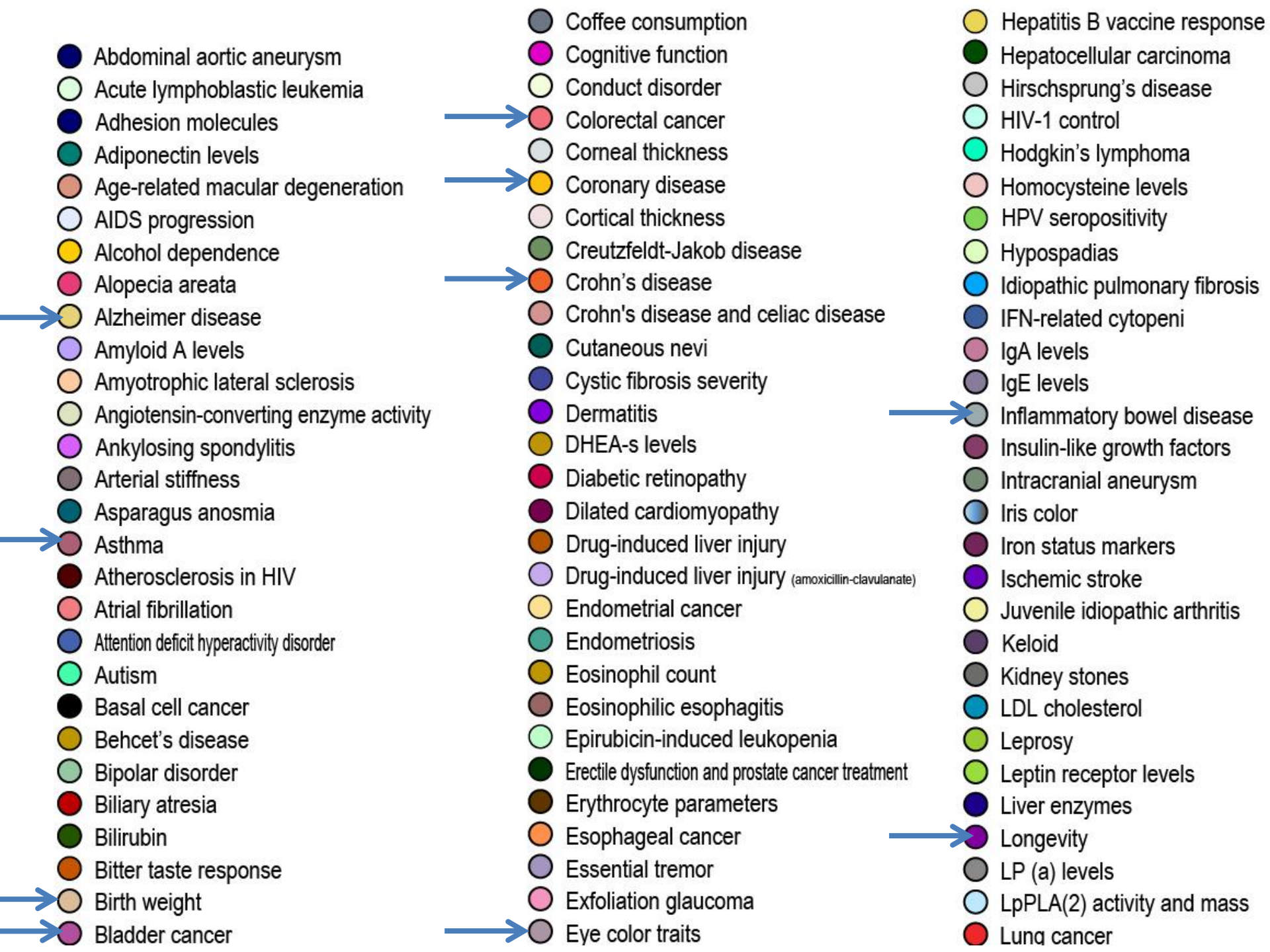
Provides information that other researchers can use to link genetic variants to the risk for specific illnesses, which will lead to new methods of preventing, diagnosing, and treating disease.

# Published Genome-Wide Associations through 09/2011

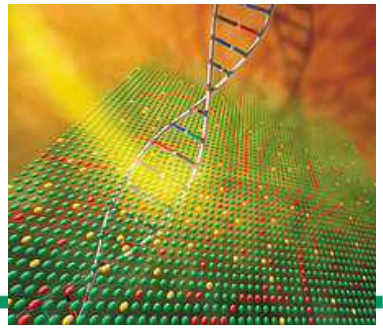
## 1,617 published GWA at $p \leq 5X10^{-8}$ for 249 traits




**NHGRI GWA Catalog**
**www.genome.gov/GWAStudies**


Abdominal aortic aneurysm
Acute lymphoblastic leukemia
Adhesion molecules
Adiponectin levels
Age-related macular degeneration
AIDS progression
Alcohol dependence
Alopecia areata
Alzheimer disease
Amyloid A levels
Amyotrophic lateral sclerosis
Angiotensin-converting enzyme activity
Ankylosing spondylitis
Arterial stiffness
Asparagus anosmia
Asthma
Atherosclerosis in HIV
Atrial fibrillation
Attention deficit hyperactivity disorder
Autism
Basal cell cancer
Behcet's disease
Bipolar disorder
Biliary atresia
Bilirubin
Bitter taste response
Birth weight
Bladder cancer
Coffee consumption
Cognitive function
Conduct disorder
Colorectal cancer
Corneal thickness
Coronary disease
Cortical thickness
Creutzfeldt-Jakob disease
Crohn's disease
Crohn's disease and celiac disease
Cutaneous nevi
Cystic fibrosis severity
Dermatitis
DHEA-s levels
Diabetic retinopathy
Dilated cardiomyopathy
Drug-induced liver injury
Drug-induced liver injury (amoxicillin-clavulanate)
Endometrial cancer
Endometriosis
Eosinophil count
Eosinophilic esophagitis
Epirubicin-induced leukopenia
Erectile dysfunction and prostate cancer treatment
Erythrocyte parameters
Esophageal cancer
Essential tremor
Exfoliation glaucoma
Eye color traits
Hepatitis B vaccine response
Hepatocellular carcinoma
Hirschsprung's disease
HIV-1 control
Hodgkin's lymphoma
Homocysteine levels
HPV seropositivity
Hypospadias
Idiopathic pulmonary fibrosis
IFN-related cytopeni
IgA levels
IgE levels
Inflammatory bowel disease
Insulin-like growth factors
Intracranial aneurysm
Iris color
Iron status markers
Ischemic stroke
Juvenile idiopathic arthritis
Keloid
Kidney stones
LDL cholesterol
Leprosy
Leptin receptor levels
Liver enzymes
Longevity
LP (a) levels
LpPLA(2) activity and mass
Lung cancer

# GWAS of Disease Susceptibility



- 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 → Whole Genome Sequencing!

# Mutation Details

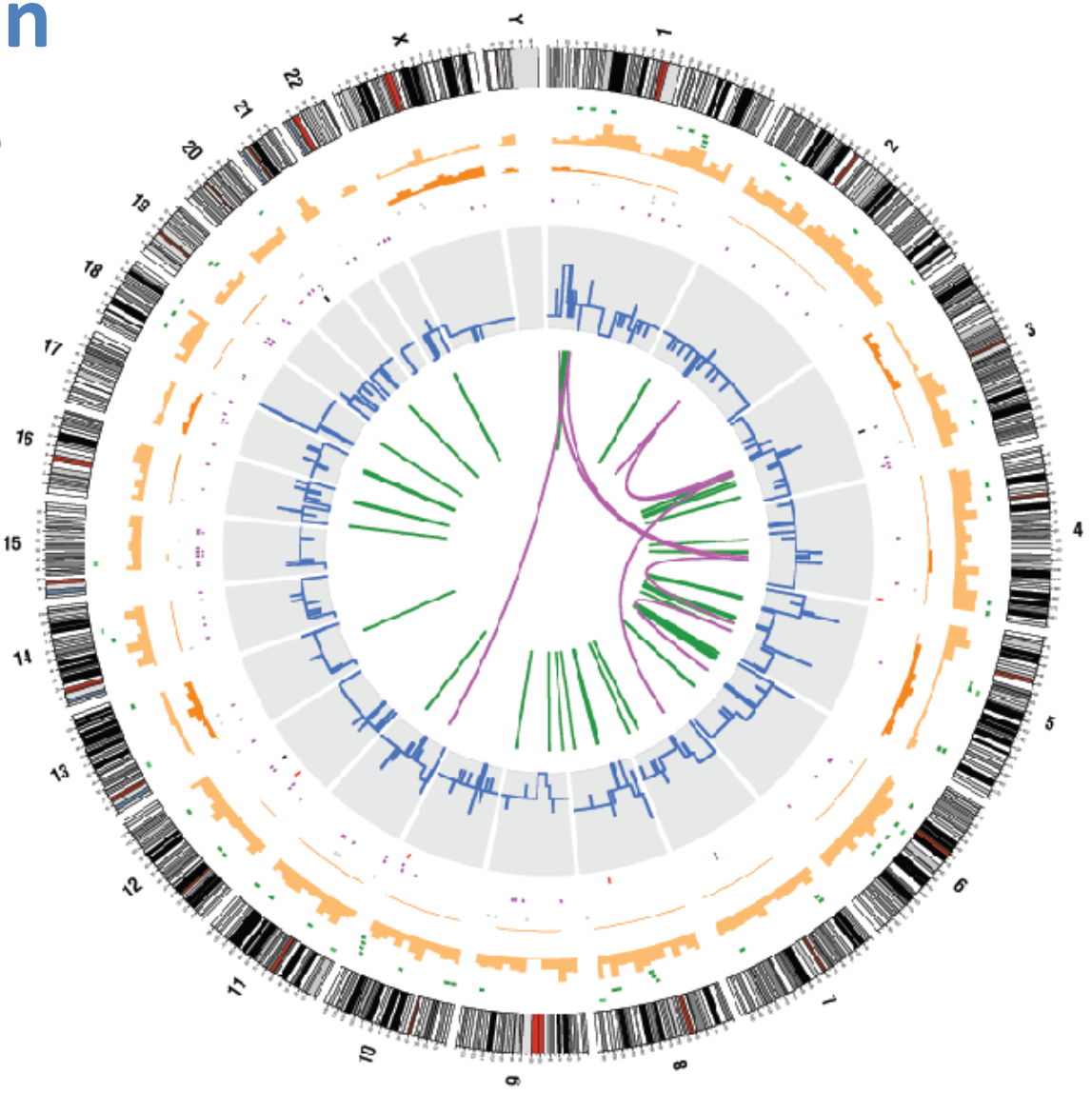
Lung Carcinoma genome

- Nature 2010 463; 184-90.

22,910 mutations

58 rearrangements

334 copy number segments



# Analysing Cancer Genomes

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"**.

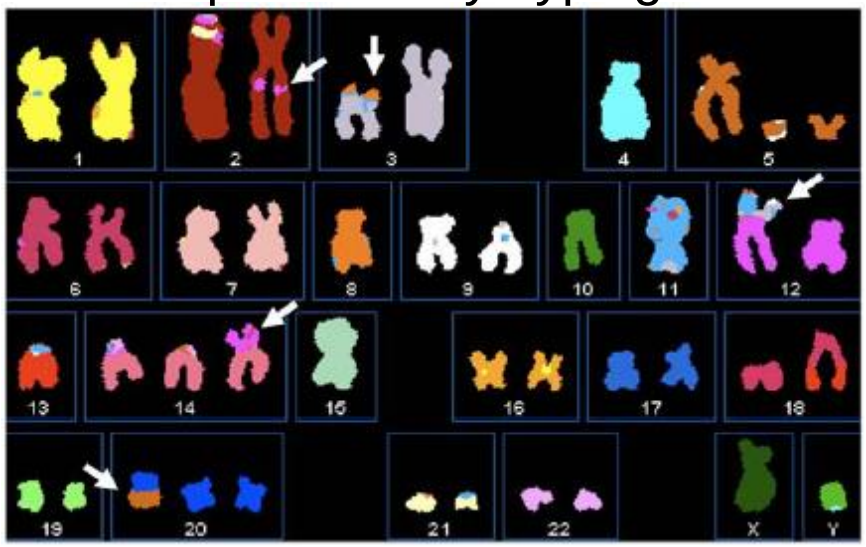
- Identifying the driver mutations will give us new targets for therapies.

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.

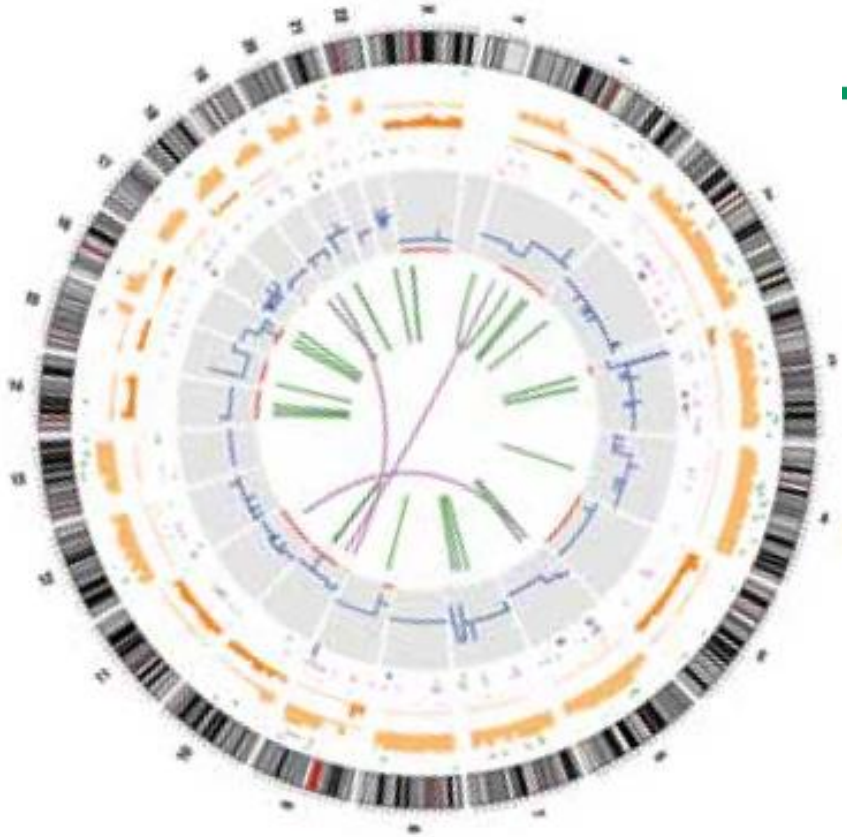
# Tumor Sequencing

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

Many cancer mutations are rare.

- Low signal-to-noise ratio.


How do we find the rare but important mutations?

- Sequence lots of cancer genomes.

International Cancer Genome Project: 2008

- 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 | U.S. National Institutes of Health | 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.

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

## CGA: How Will It Work?

Click here for more information

THE CANCER GENOME ATLAS

NIH NATIONAL CANCER INSTITUTE

1-800-4-CANCER | Live Chat | Publications | Dictionary

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TCGA

Program History +

TCGA Cancers Selected for

# The Cancer Genome Atlas Program

The Cancer Genome Atlas (TCGA), a landmark cancer genomics program, molecularly characterized over 20,000 primary cancer and matched normal samples spanning 33 cancer types. This joint effort between NCI and the National Human Genome Research Institute began in 2006, bringing together researchers from diverse disciplines and multiple institutions.

Over the next dozen years, TCGA generated over 2.5 petabytes of genomic, epigenomic, transcriptomic, and proteomic data. The data, which has already led to improvements in our ability to diagnose, treat, and prevent cancer, will remain publicly available for anyone in the research community to use.

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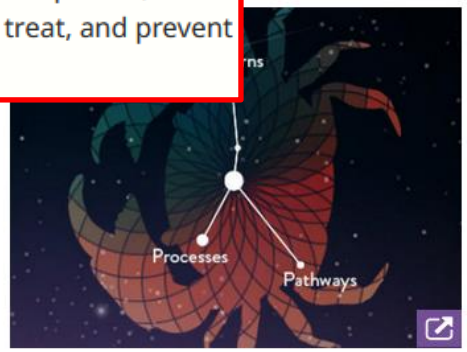
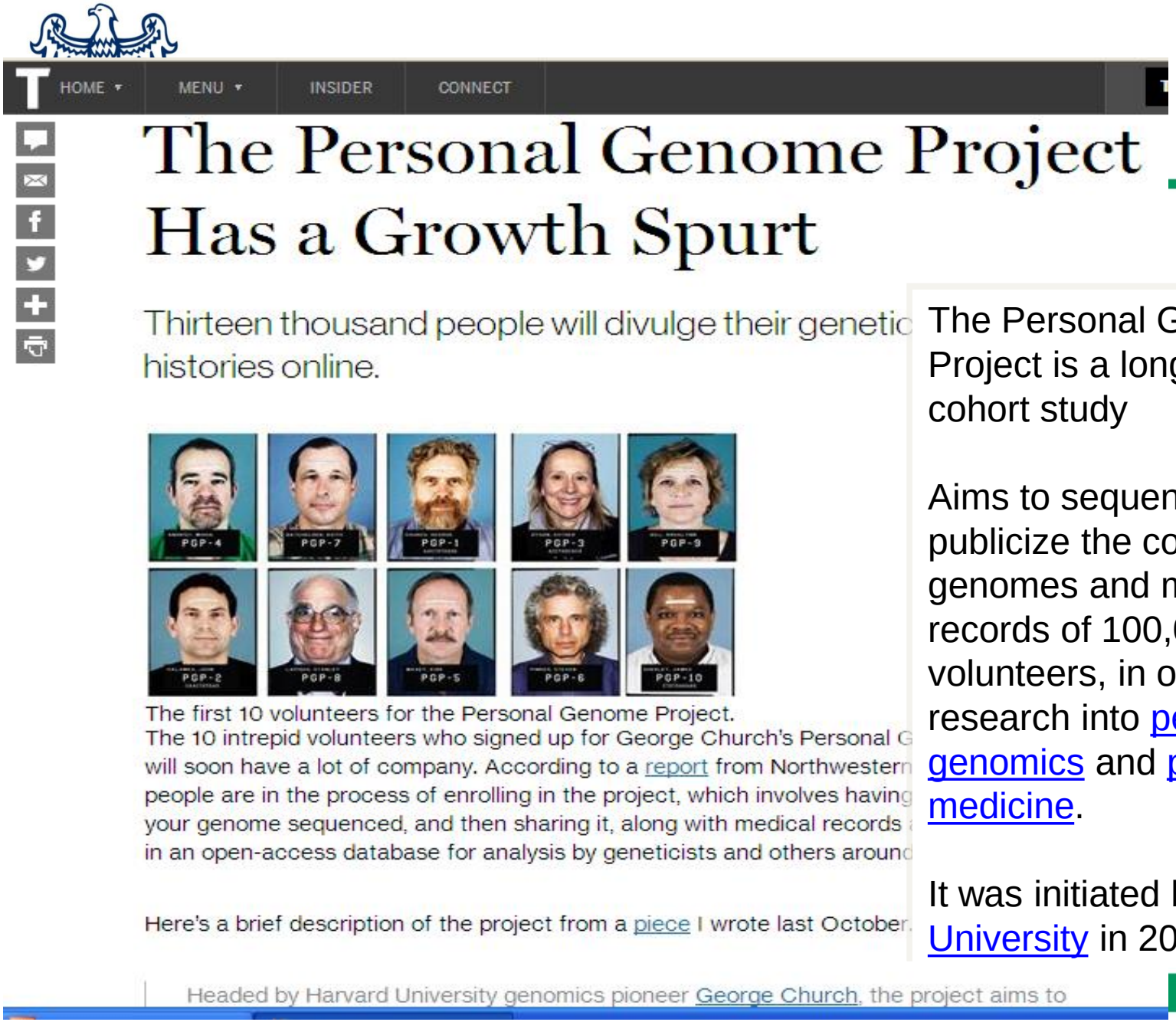
## TCGA Outcomes & Impact

TCGA has changed our understanding of cancer, how research is conducted, how the disease is treated in the clinic, and more.




## TCGA's Pan-Cancer Atlas

A collection of cross-cancer analyses delving into overarching themes on cancer, including cell-of-origin patterns, oncogenic processes, and signaling pathways. Published in 2018 at the




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.

# 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

- 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





## Part I: Genetic Material

Public data About

# 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.

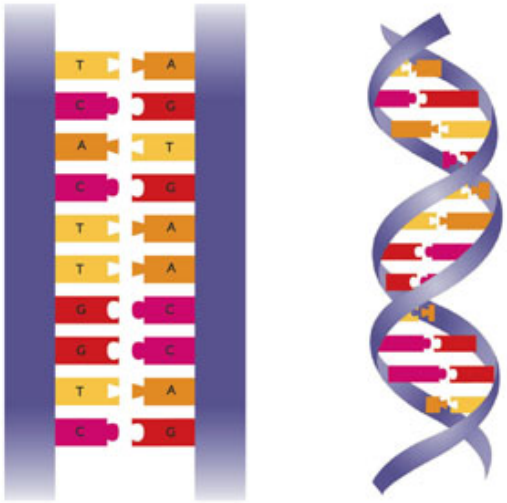
Show 10 entries Search:

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

Showing 1 to 10 of 3,262 entries

# 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...

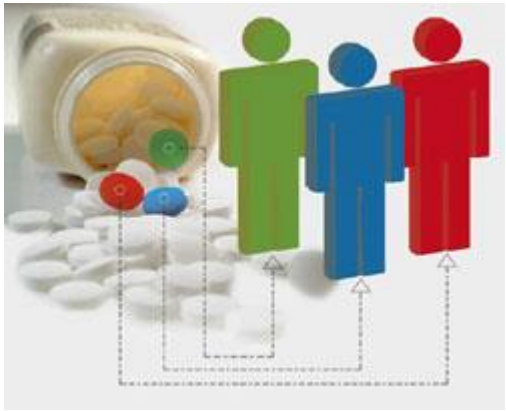
*February 17, 2014 2:31 am*

**New Healthpatch biosensor captures a wide range of information with just**

# Personalized Medicine: Definition

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

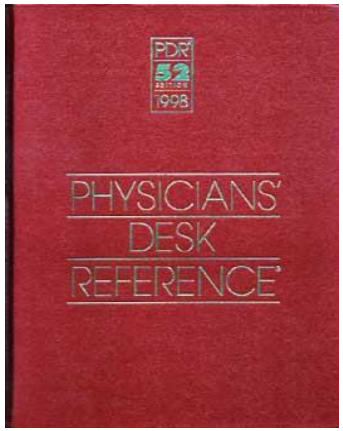
- **Stratify/classify disease**
- **select a medication**
- **provide a therapy**
- **initiate a preventative measure that is particularly suited to that patient at the time of administration**



# The paradigm of the classic treatments


Trial and error


Symptom
Diagnosis
Treatment
Dosage




Non specific
Non selective
Uniformized

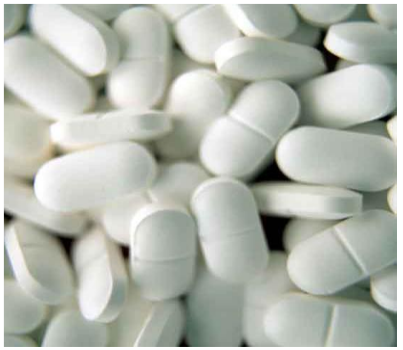
Phenotype

Does not evaluate the different therapeutic responses
- the blockbuster concept

# Medicine in the XX. Century

Institute of Genomic Medicine and Rare Disorders

- „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%

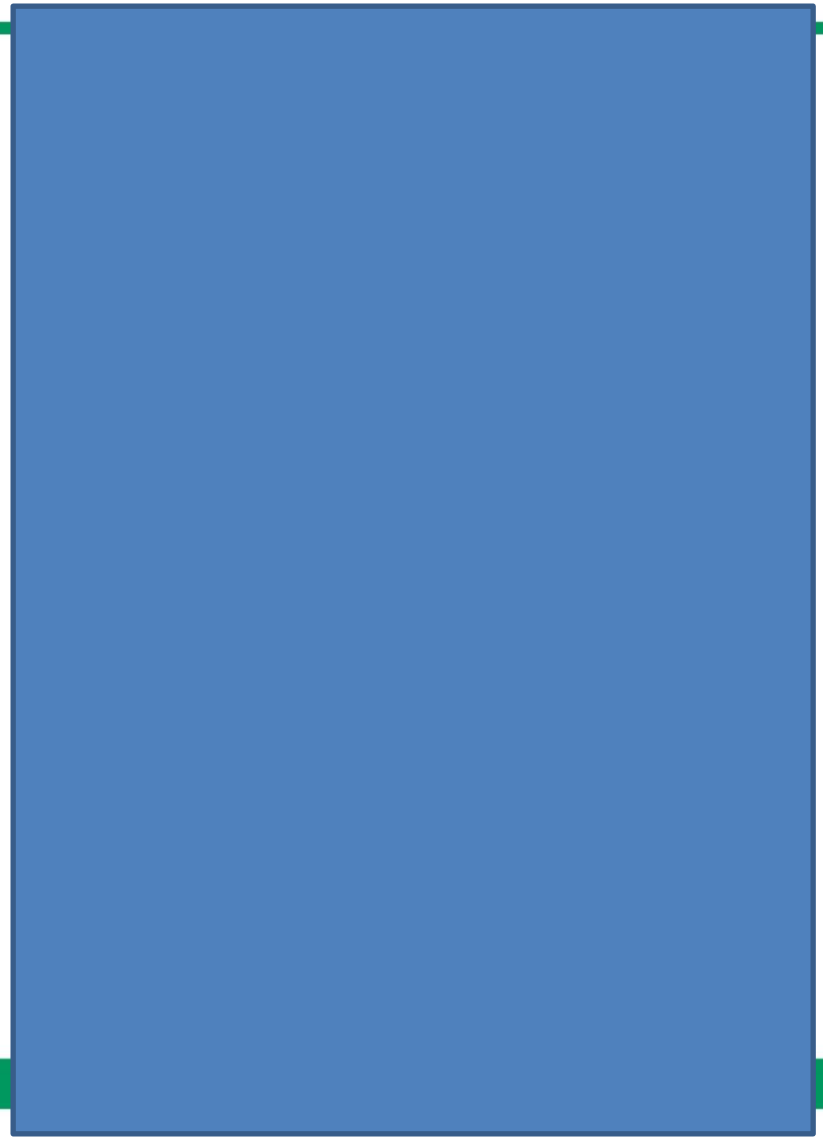
SSRIs

Cholesterol Drugs 30-70%

Statins

Asthma Drugs 40-70%

Beta-2-agonists



# Personalized Medicine: The Answer?

Institute of Genomic Medicine and Rare Disorders

## 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, wich may predict the therapeutic response to a certain drug

# Drug-Diagnostics Combinations in Oncology

- **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/ Pharmacodiagnostics

• **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.*

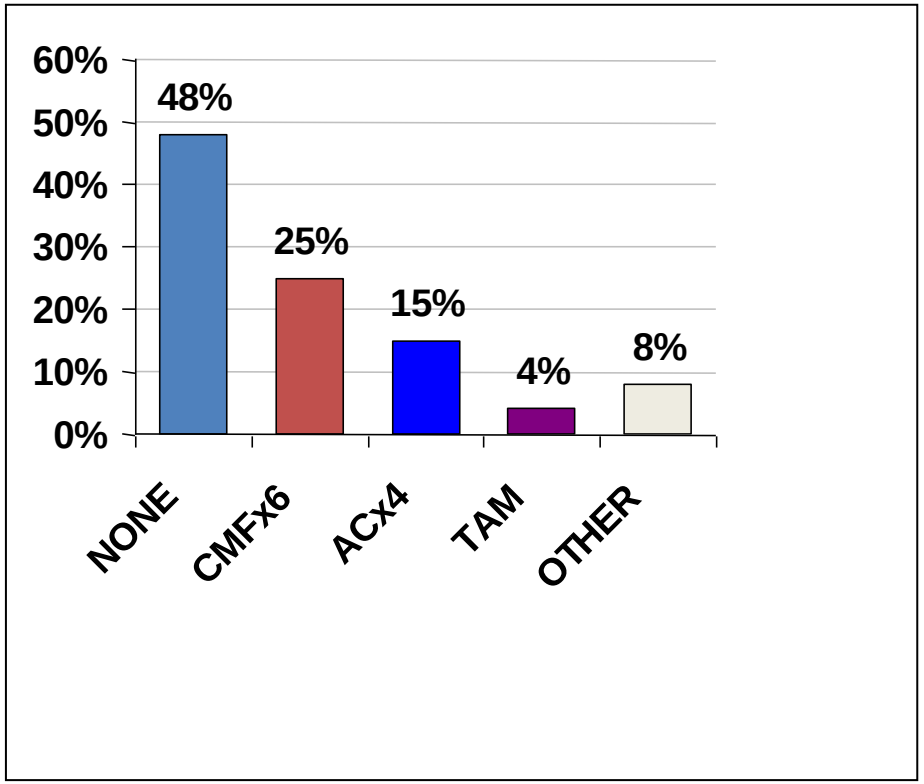
*Jørgensen JT. Expert Rev Mol Diagn 2008; 8: 689-695.

# Breast Cancer: The Treatment Dilemma

61 y-old, fit, postmenopausal

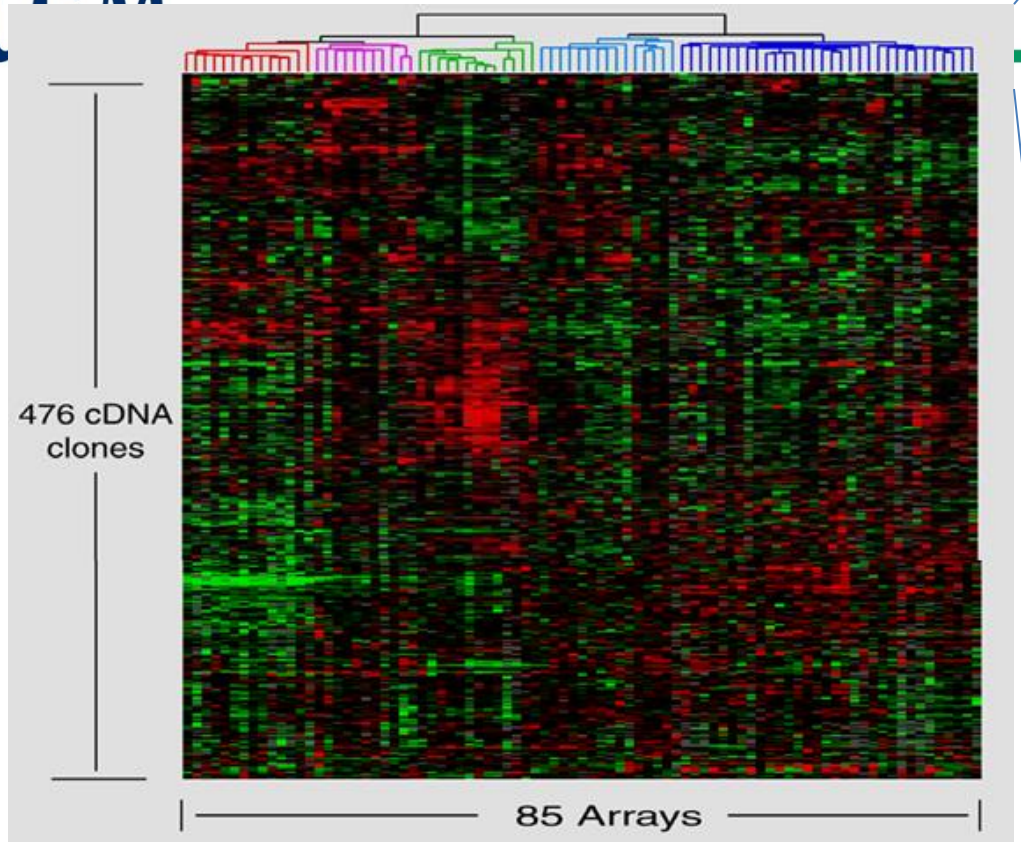
Node negative
pT = 0.9 cm
ductal cancer
ER and PR negative
HER2 negative
Grade 2

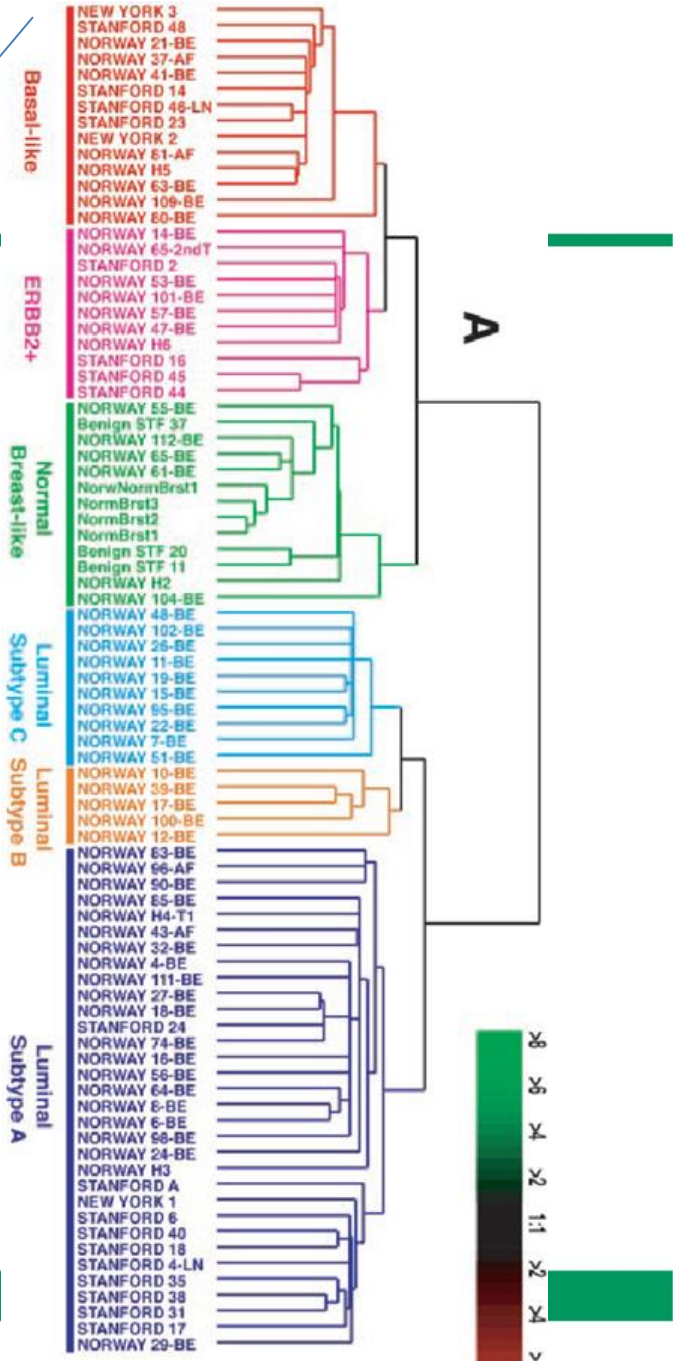
**Choices of 40 experts world-wide**




Courtesy: Martine Piccart

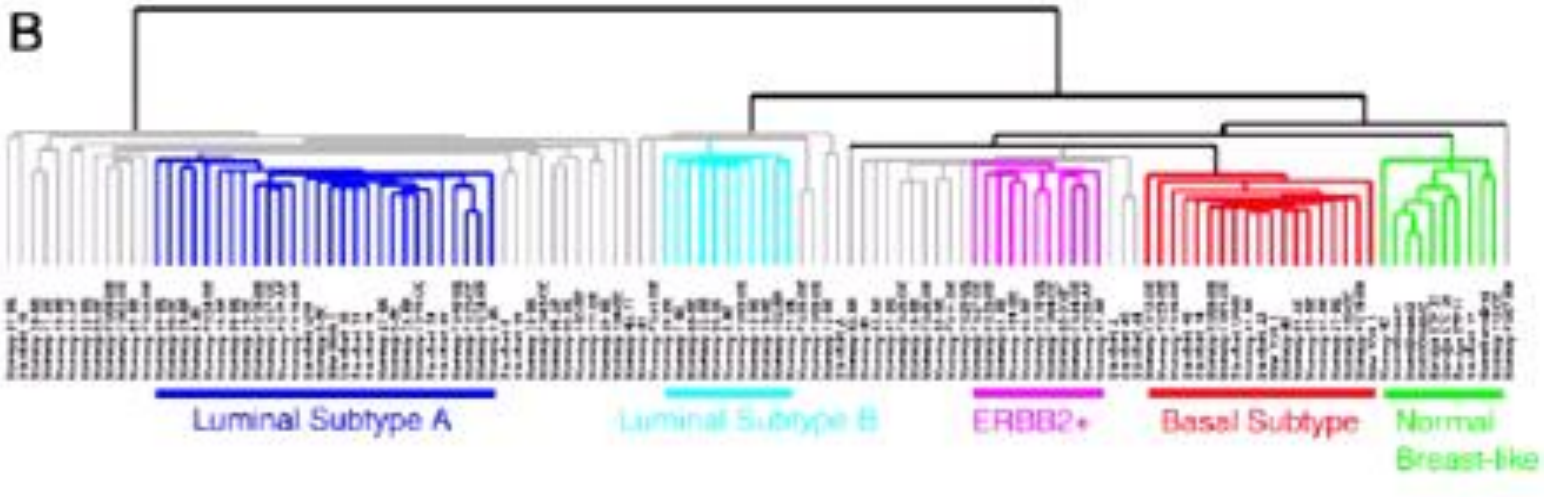
# Breast Cancer Subtypes

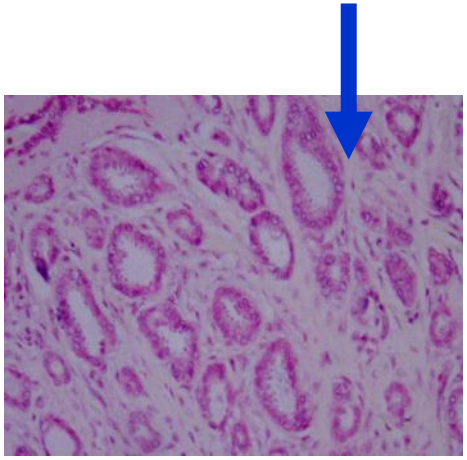


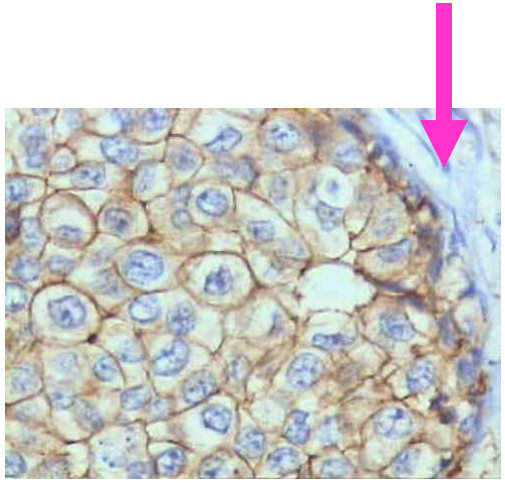

- Disease Onset + Progression
- Disease Subtyping/Classification

Sorlie *et al.* PNAS 2003

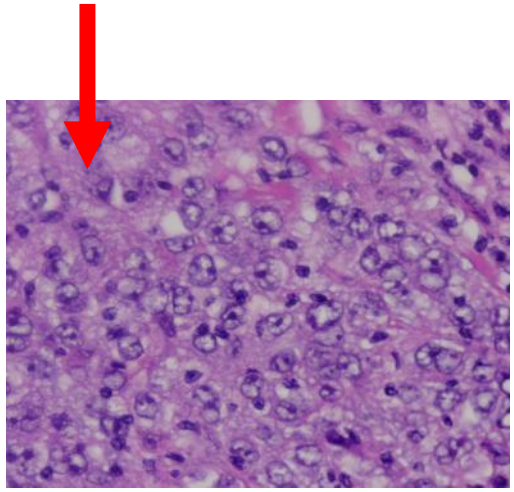


ER++, PR++, G1,2

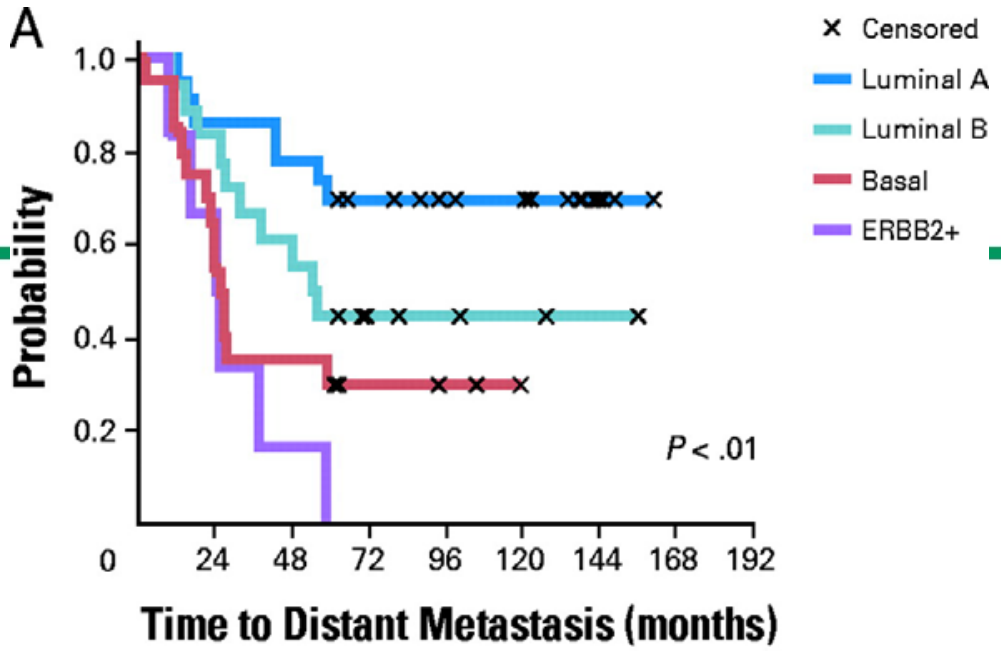


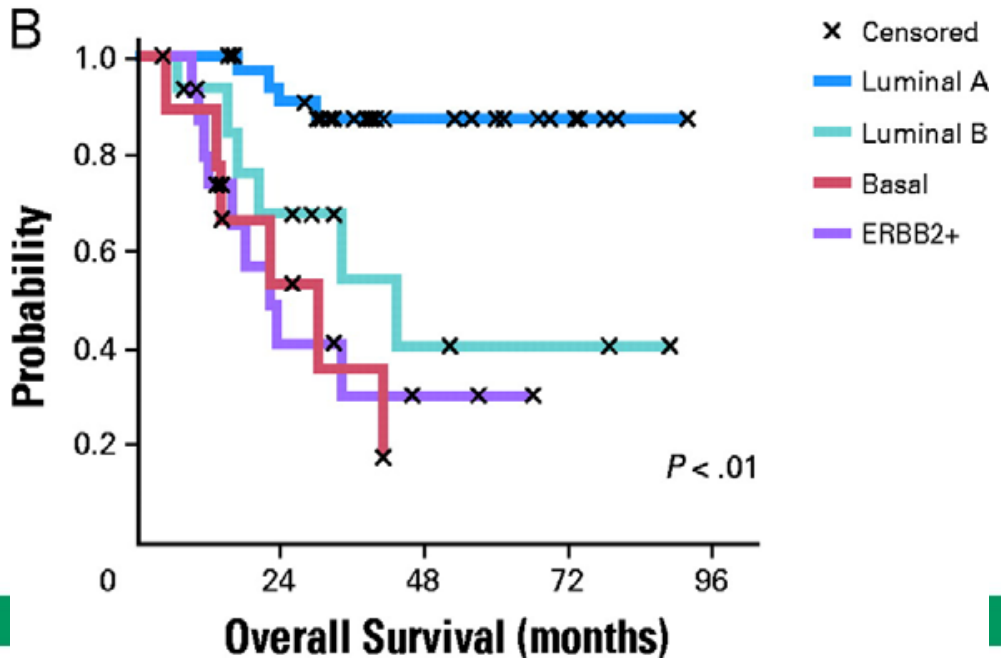
HER2 ISH pos



“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[1]

Harvey J. Lerner,[2,*] Pierre R. Band,[3,4] Lucien Israel,[5] and Benjamin S. Leung[6,7]

**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/m² 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 triphenyleth
ative with potent antiestrogen activity
mammalian species (1). It inhibits the
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.,

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.

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

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

VOLUME 26 · NUMBER 10 · APRIL 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

## 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*

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 on March 3, 2008.

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.

**Purpose**

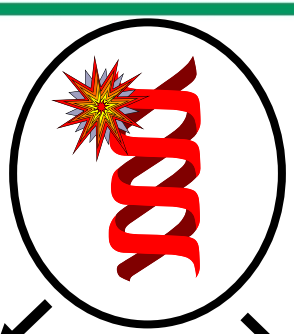
Panitumumab, a fully human antibody against the epidermal growth factor receptor (EGFR), has activity in a subset of patients with metastatic colorectal cancer (mCRC). Although activating mutations in KRAS, a small G-protein downstream of EGFR, correlate with poor response to anti-EGFR antibodies in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

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

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

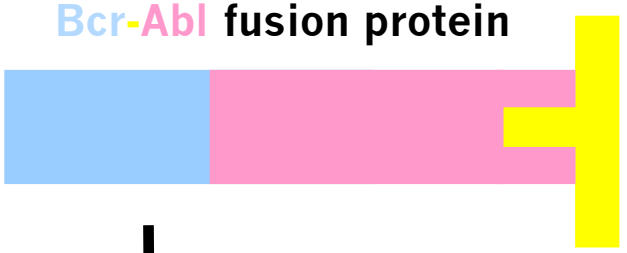
**Chromosome 9;22 translocation**



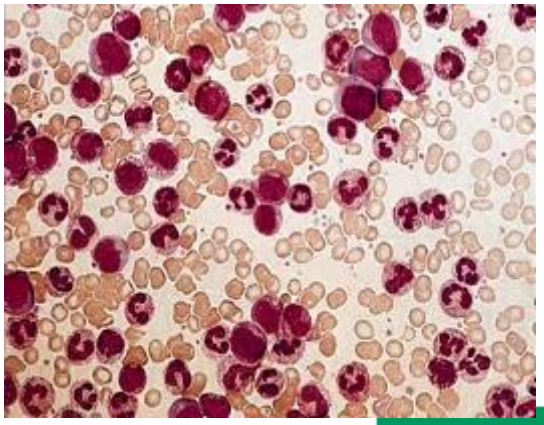
**Bcr-Abl fusion protein**

myeloid cells -- make red blood cells, platelets, and most types of white blood cells (except lymphocytes)

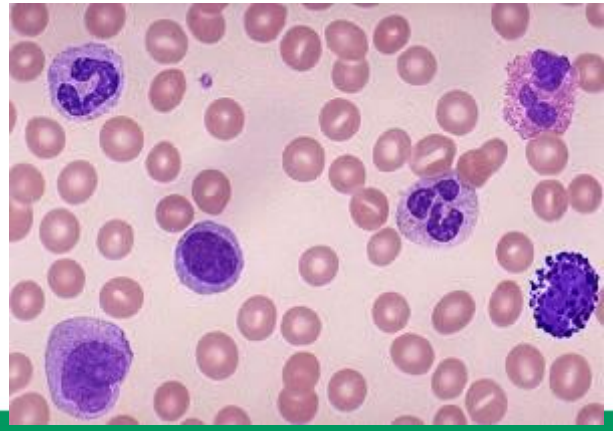
**Bcr-Abl fusion protein**



**Gleevec™**



**CML**



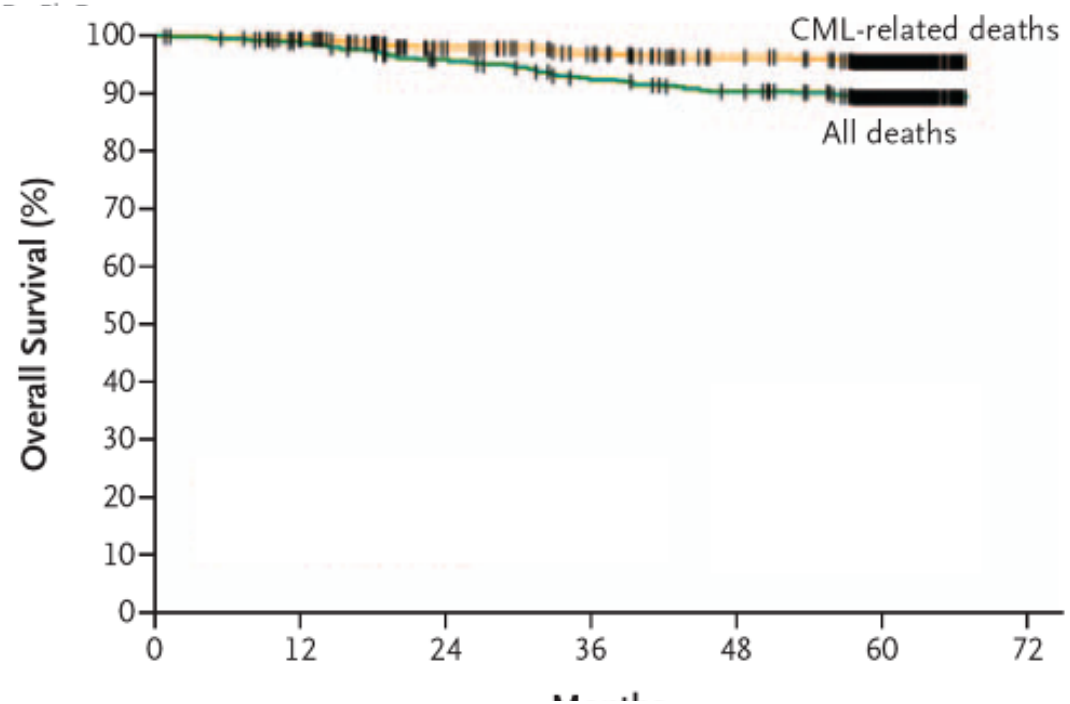
**Normal**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

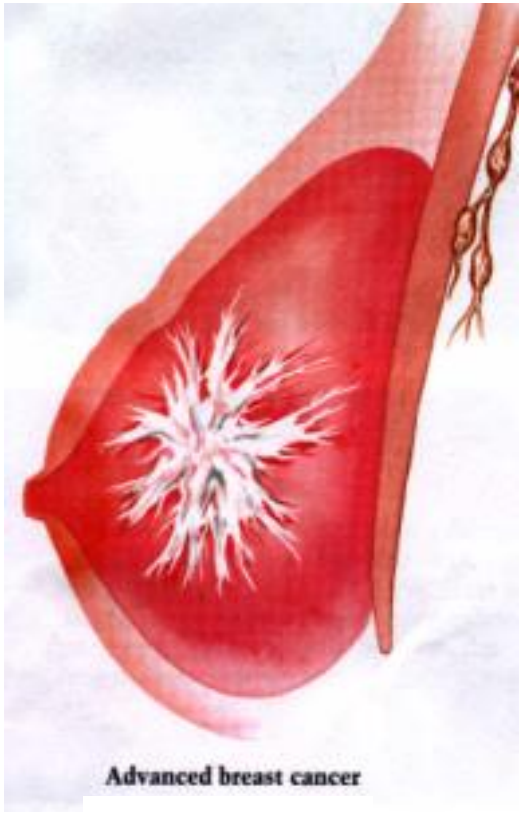
Brian J. Druker, M.D., François Guilhot, M.D., Stephen G. O'Brien, M.
Insa Gathmann, M.Sc., Hagop Kantarjian, M.D., Norbert Gatterma
Michael W.N. Deininger, M.D., Ph.D., Richard T. Silver, M.D
John M. Goldman, D.M., Richard M. Stone, M.D., Francisco Cervan
Andreas Hochhaus, M.D., Bayard L. Powell, M.D.,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

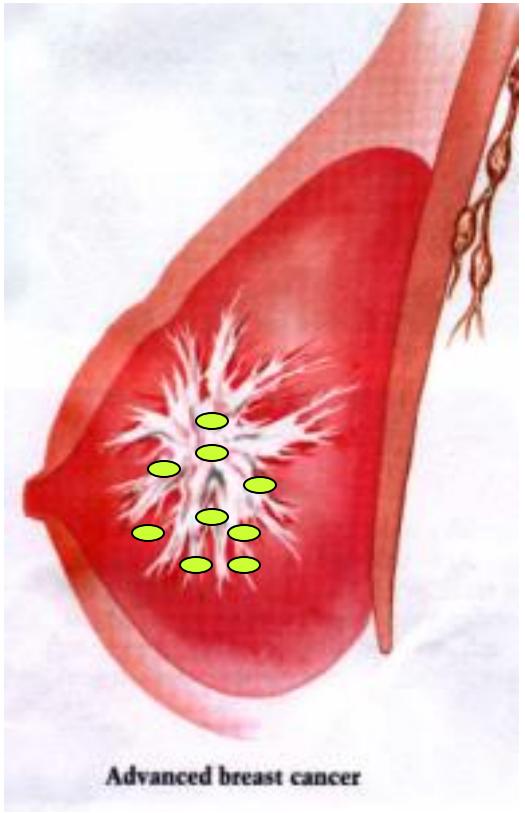


# Cost-Effective?

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

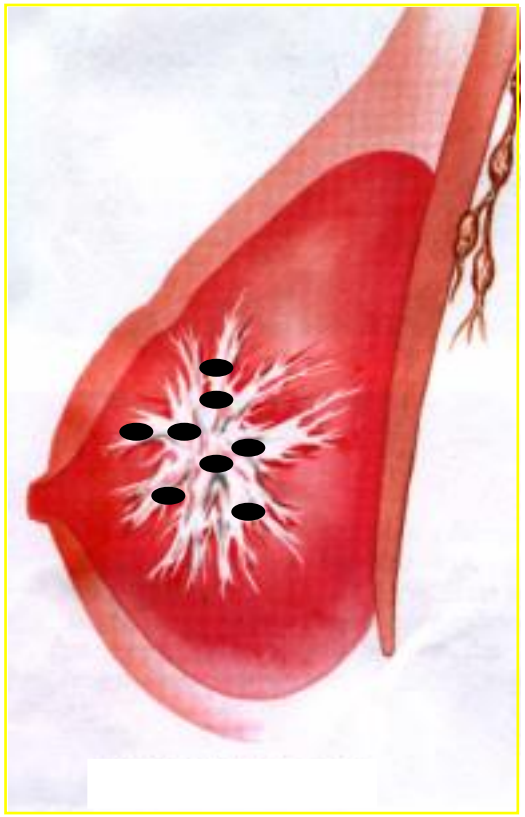
# HER2 Gene Product is Overexpressed in One Third of Breast Cancers

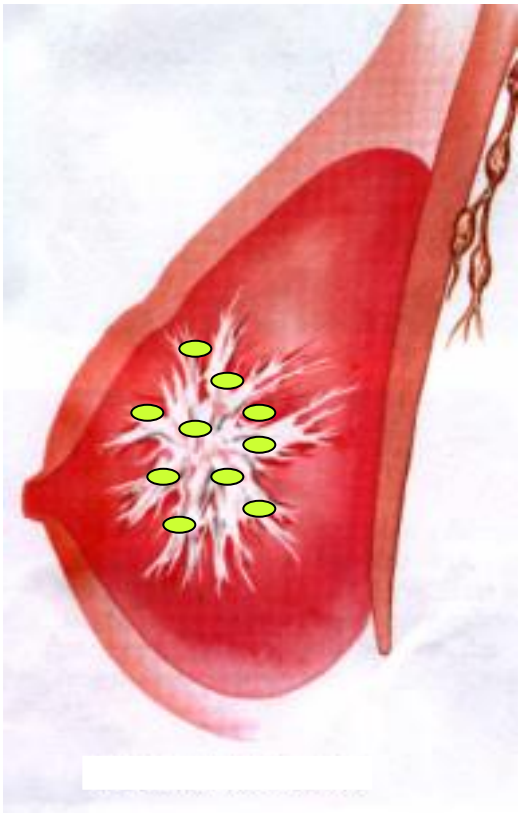


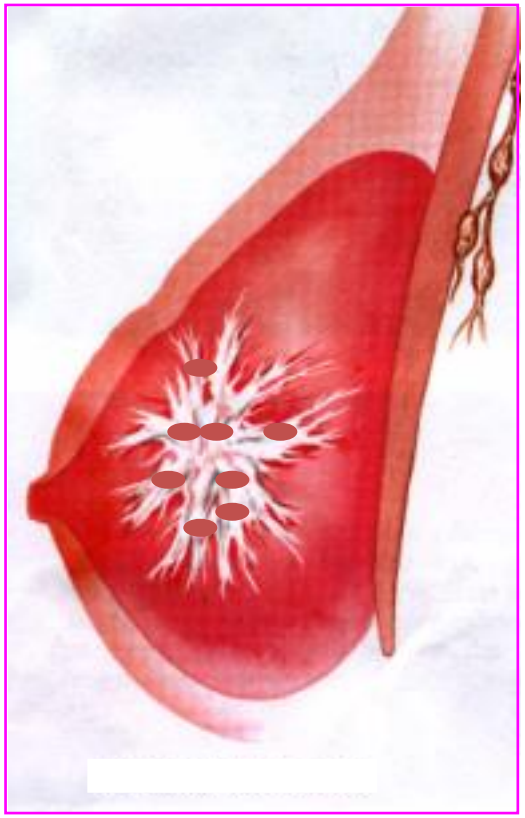




- TUMOR OVEREXPRESSING HER2
- SENSITIVE TO HERCEPTIN

# 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 the future most anti-cancer drugs will be prescribed based on the results of a companion diagnostic/pharmacodiagnostic test

The NEW ENGLAND JOURNAL of MEDICINE

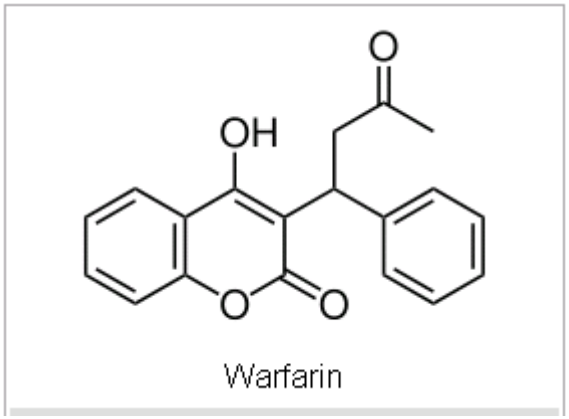
ORIGINAL ARTICLE

# 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.

N ENGL J MED 352;22 WWW.NEJM.ORG JUNE 2, 2005

# Case Study: Warfarin



Warfarin

- Most widely prescribed oral anticoagulant for preventing thrombolytic 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), 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 V*KORC1* 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: **lower dose**
- 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

↕ → **Drug Choice**

HER2 (30%↑)

(Human Epidermal growth factor receptor 2)

Blood clot prevention: Warfarin

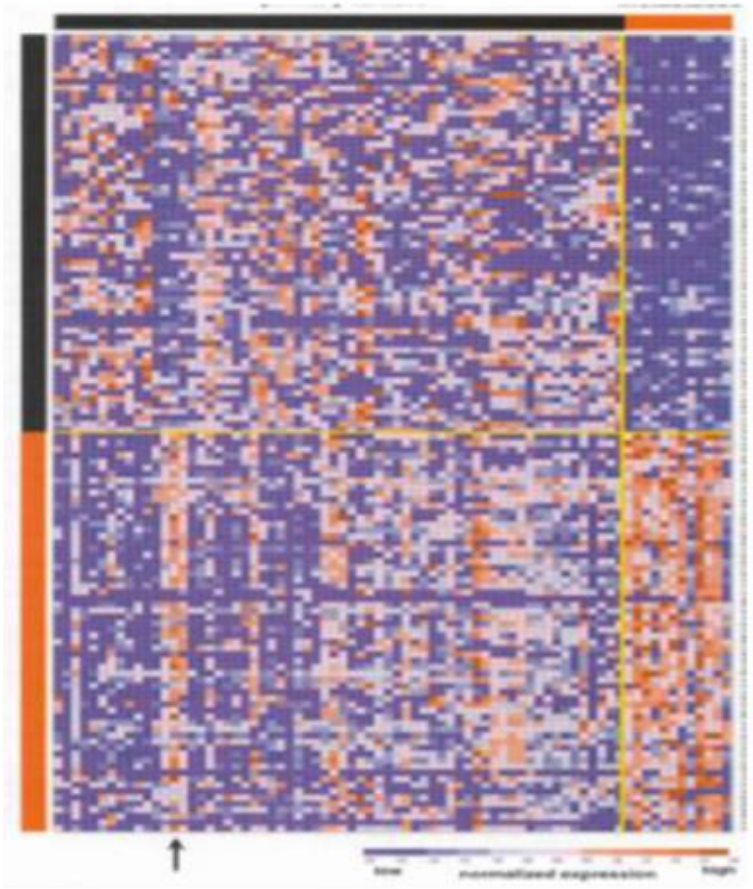
↕ → **Drug Dose**

CYP2C9

(Drug-metabolizing enzyme Variations: Adverse Drug Reactions)

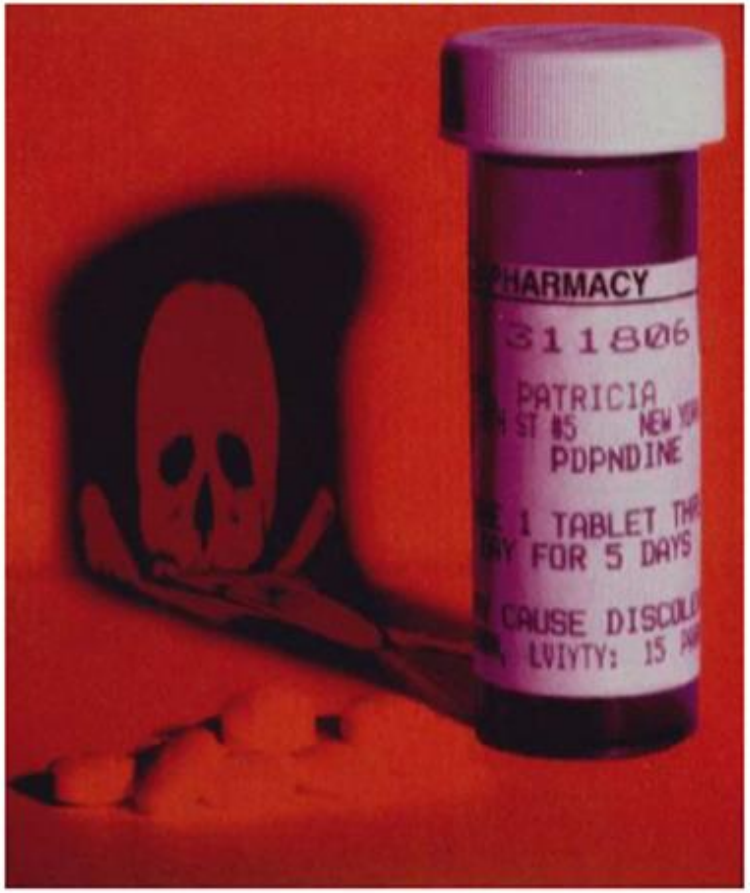
# From Pharmaceuticals to Pharmasuitables

**Disease Subtyping:**



**Right Rx for Right Disease**

**Individual Variation and AE risk**




**Right Rx for Right Patient**

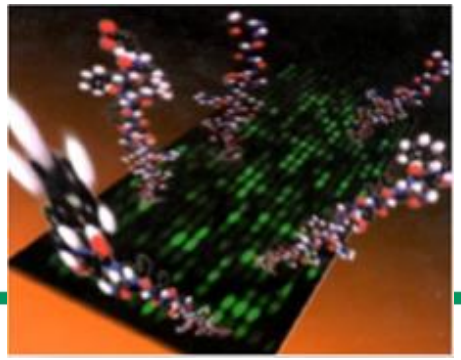
# BIDIL


November 2005

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

"For African Americans Only"

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

(Chan & Ginsburg, 2011)

# AmpliChip

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


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

**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.

# Multiplex Tests are Already Starting to Have an Impact

Institute of Genomic Medicine and Rare Disorders

## 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

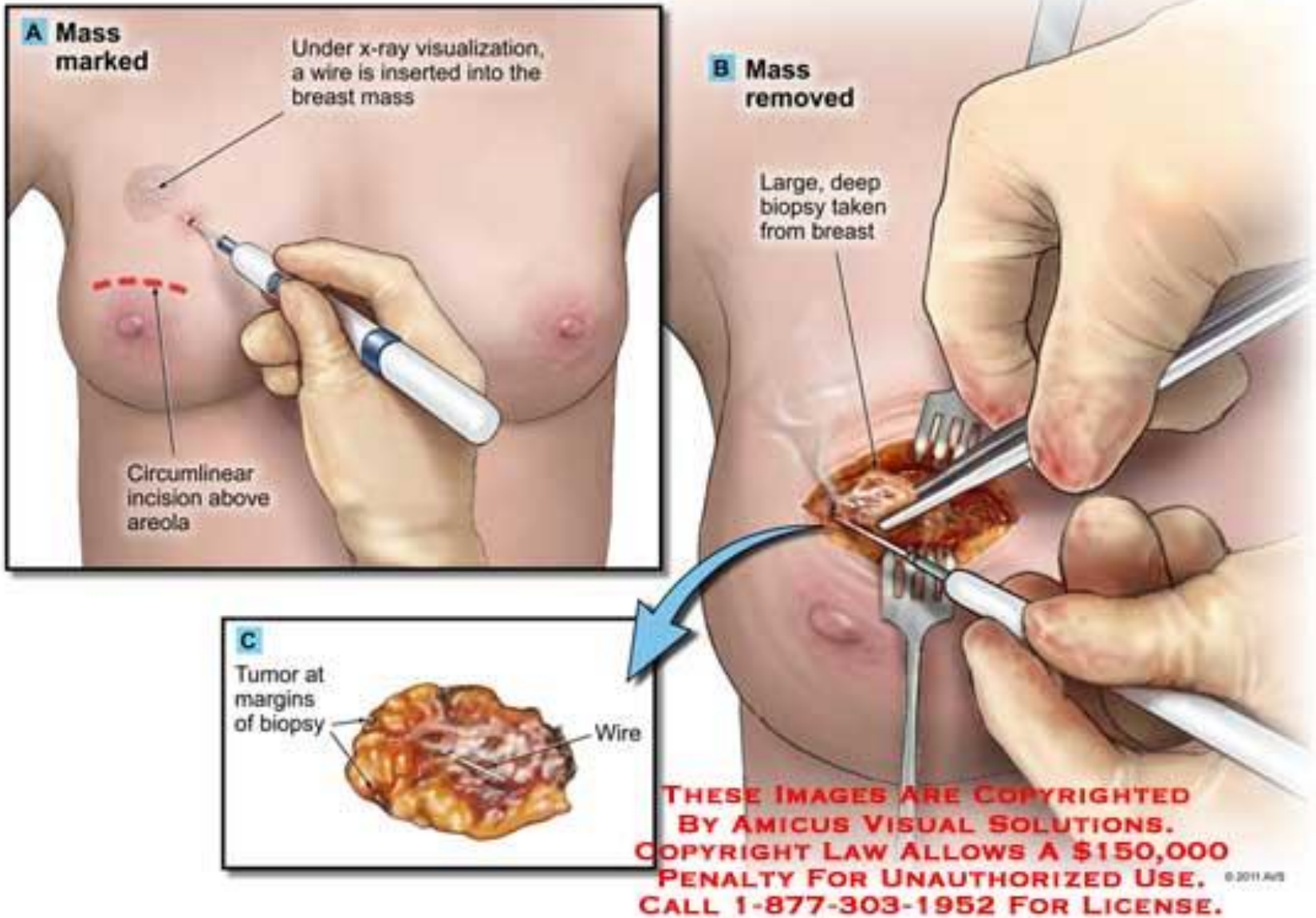
## AlloMap

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

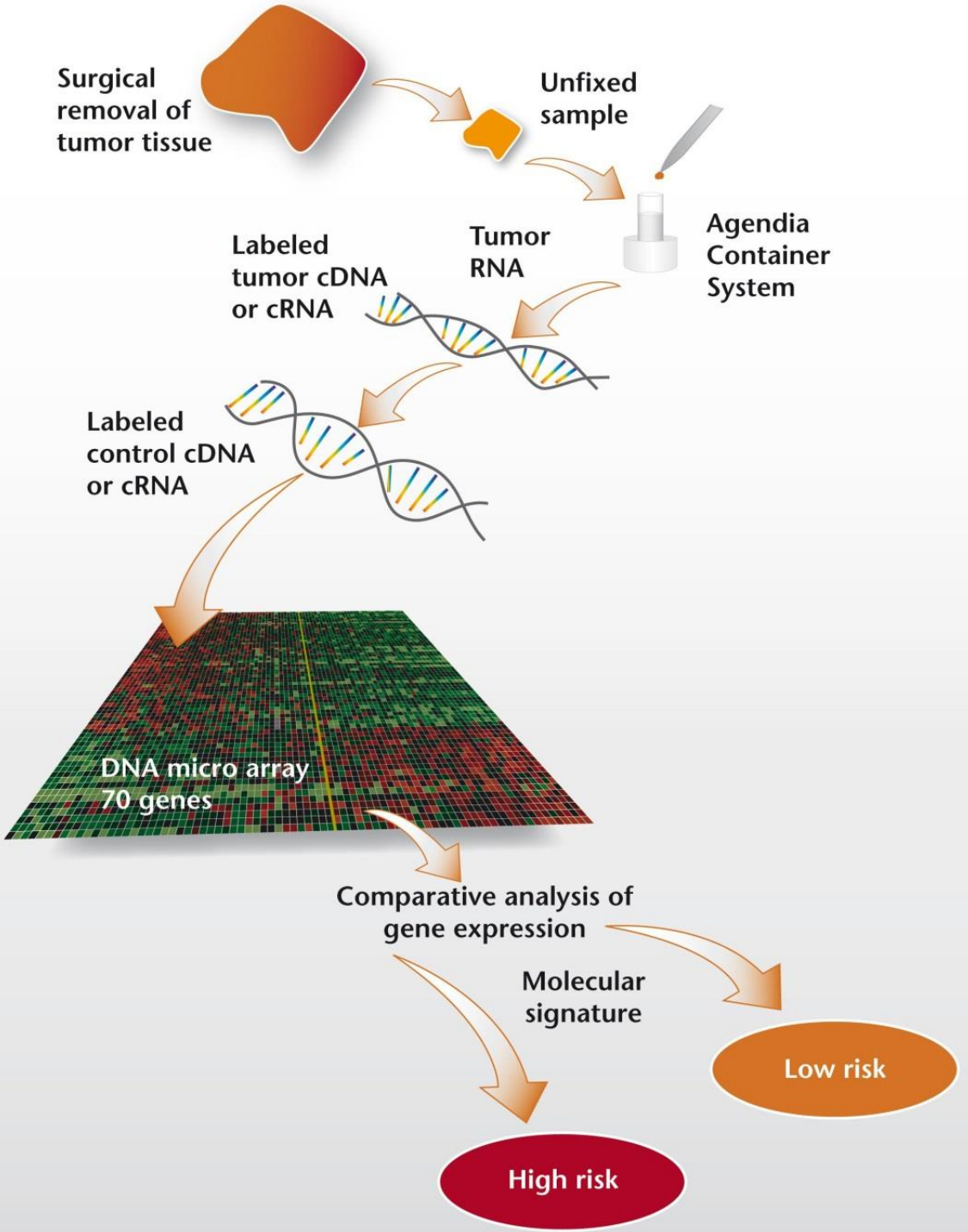
# [redacted]'s 11/19/01 Right Breast Biopsy

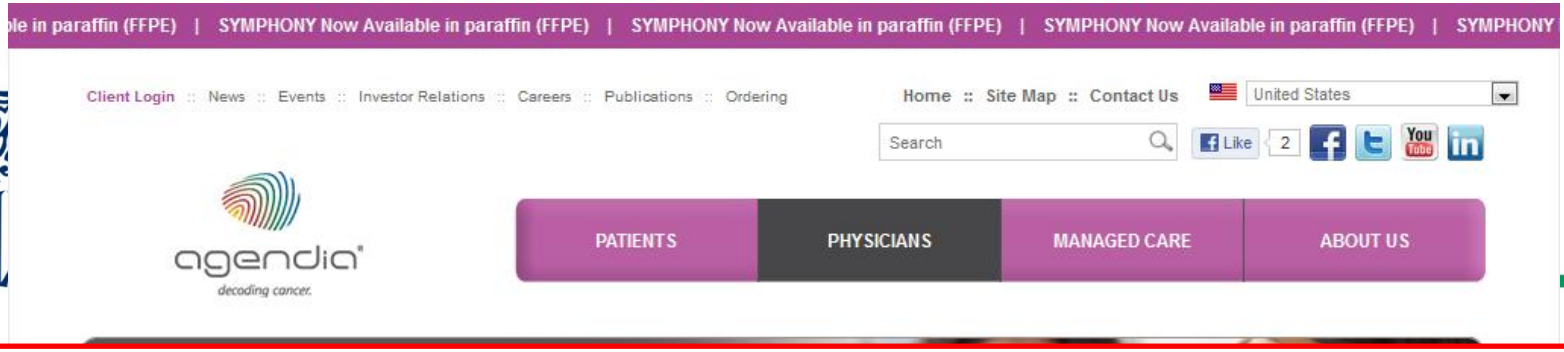


agendia®

decoding cancer.

mammaprint



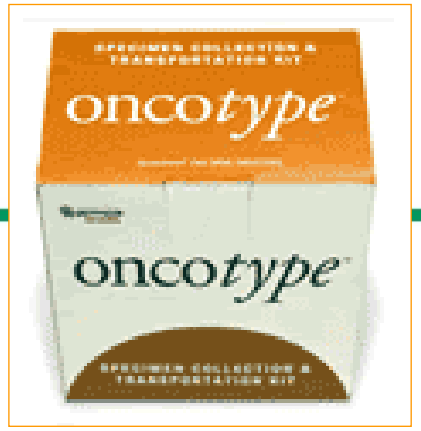



MammaPrint is the first and only FDA-cleared IVDMIA breast cancer recurrence assay. The unique 70-gene signature of MammaPrint provides you with the unprecedented ability to identify which early-stage breast cancer patients are at risk of distant recurrence following surgery, independent of Estrogen Receptor status and any prior treatment.

Unlike previous generation genomic tests, MammaPrint interrogates all of the critical molecular pathways involved in the breast cancer metastatic cascade. It analyzes 70 critical genes that comprise a definitive gene expression signature and stratifies patients into two distinct groups — low risk or high risk of distant recurrence. With MammaPrint, there are no intermediate results.

Hormonal therapy alone (e.g. Tamoxifen) may be sufficient to further reduce her risk if your patient is Low Risk by MammaPrint, when combined with traditional risk factors. Conversely, if she is High Risk by MammaPrint and has additional risk variables, more aggressive therapy including chemotherapy may be recommended.

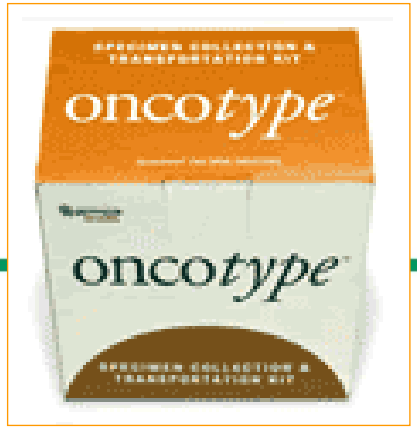
With MammaPrint, you gain vital insights into the aggressiveness of your patient's tumor allowing you to tailor your treatment protocol to your patient's individual needs.




# Oncotype DX®: A Genomic Assay

## Recurrence tumor after surgery
## Decision-making about treatment

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




The Onco*type* DX® 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

Onco*type* DX® Recurrence Score assay shows consistent results across multiple independent studies

# The Recurrence Score® 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 |

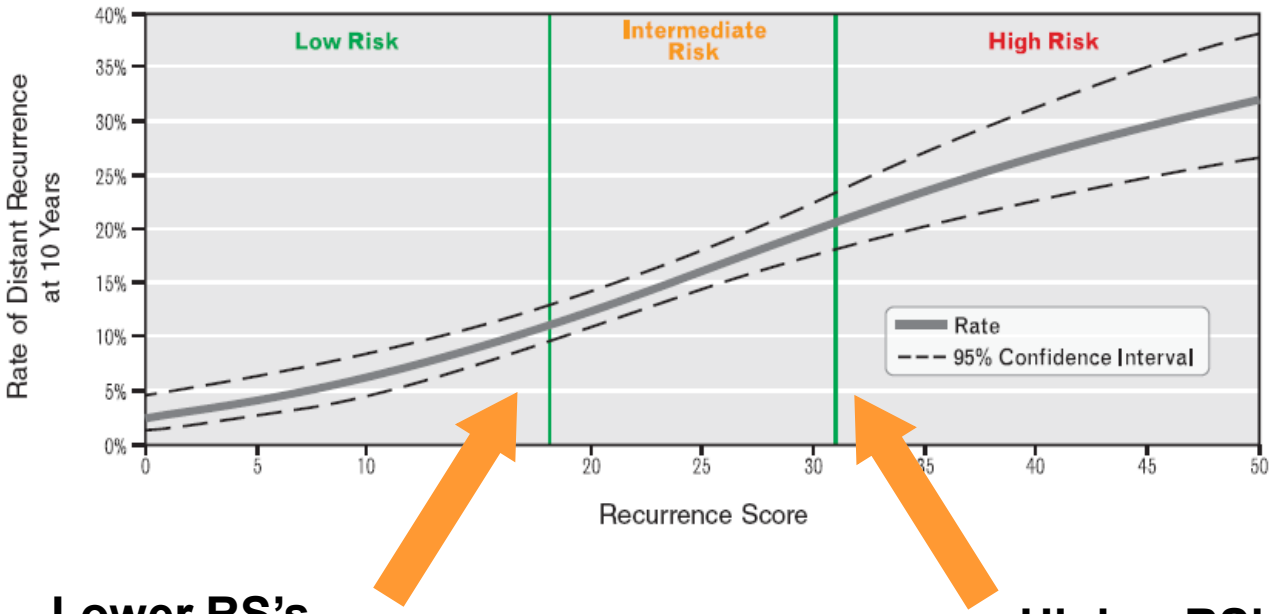
## 5 Reference genes

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

Paik et al. *N Engl J Med.* 2004;351:2817-2826.

# Oncotype DX® is a Standardized and Quantitative Assay

## Recurrence Score® 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

AlloMap®



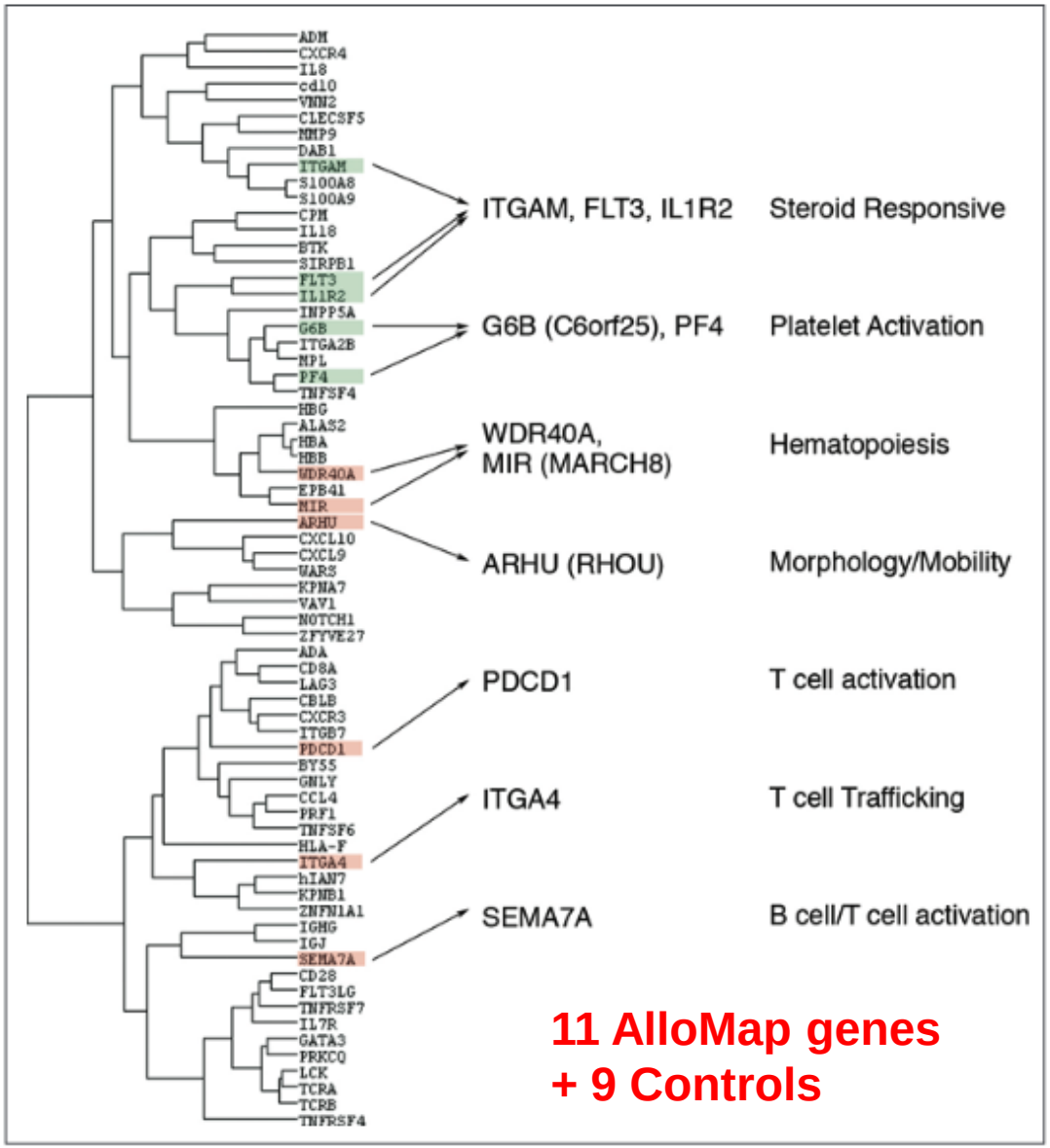

# Personalizing Care for Heart Transplant Patients

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

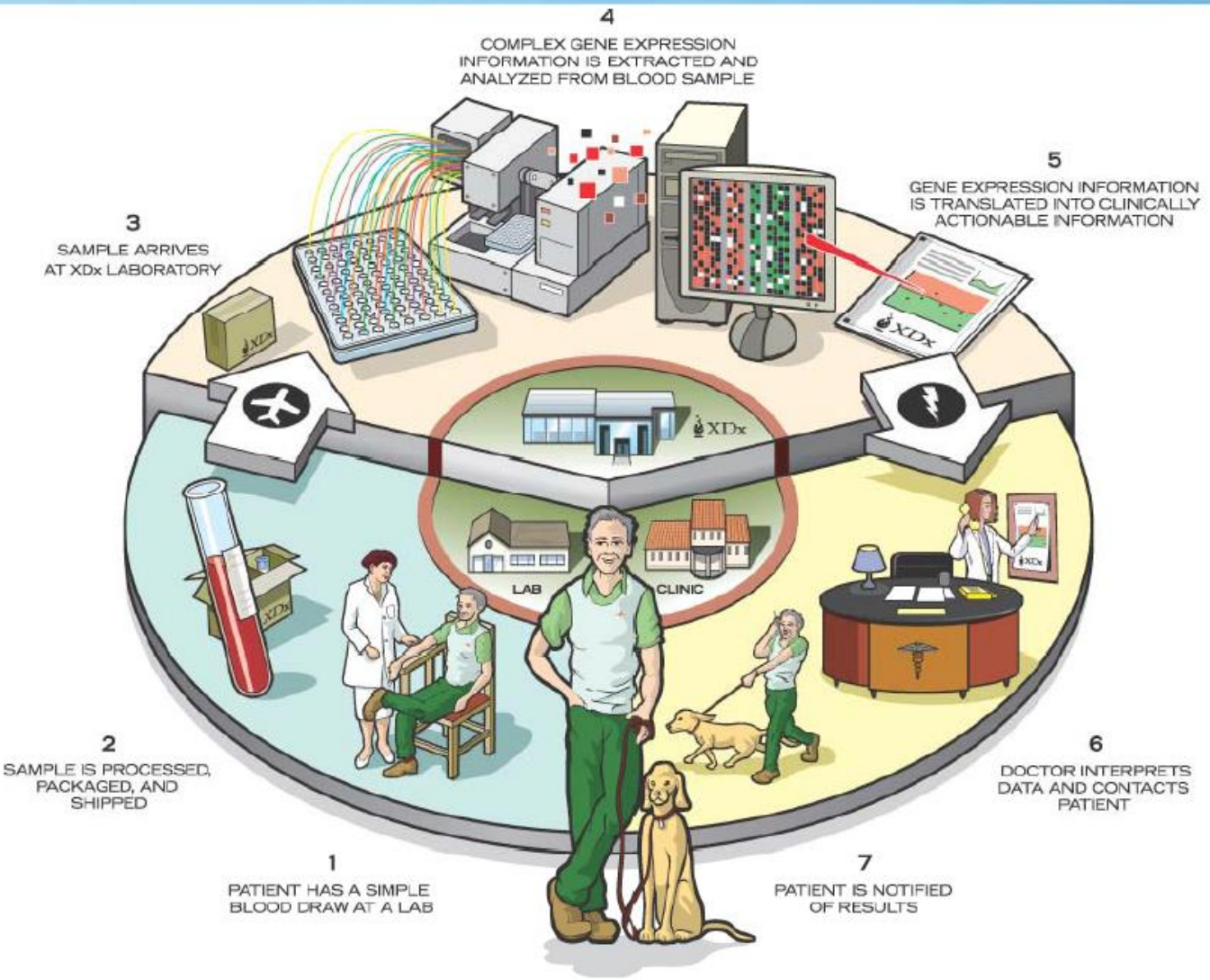



Using linear discriminant analysis, the expression levels of 11 genes were selected for the calculation of the AlloMap score (integer 0–40). This set of genes best distinguished between the presence and absence of rejection in the development of the AlloMap test.

### Differential Expression of AlloMap Genes in Rejection Samples

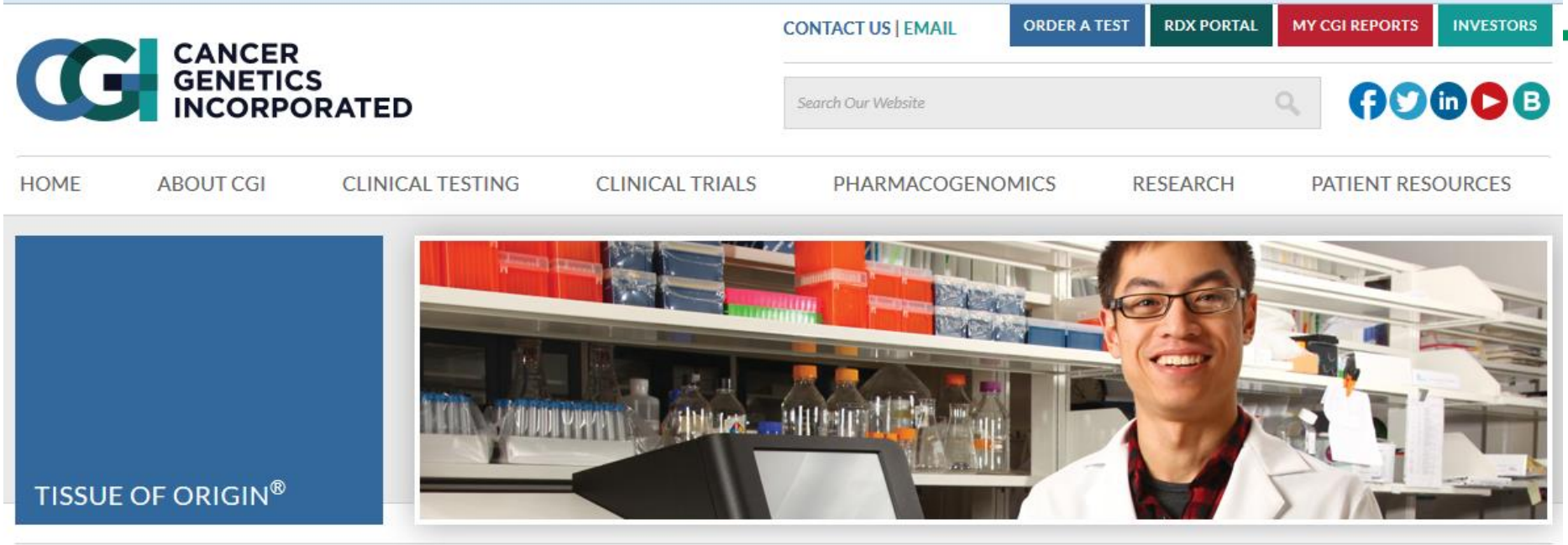
| Pathway and Gene | Gene Expression Level |
|---|---|
| **T cell priming** | |
| ***ITGA4*** **Integrin alpha-4** α subunit of VLA-4; involved in T cell trafficking and adhesion | ↑ |
| ***PDCD1*** **Programmed cell death** T cell costimulatory molecular (inhibitory); CD28 family | ↑ |
| **Proliferation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

# AlloMap Workflow




XDx
EXPRESSION DIAGNOSTICS

# 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® 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[1]
- Extensive analytical and clinical validation.
- Statistically significant improvement in accuracy over other methods, including IHC[2]
- Leads to a change in treatment 65% of the time.

# “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.

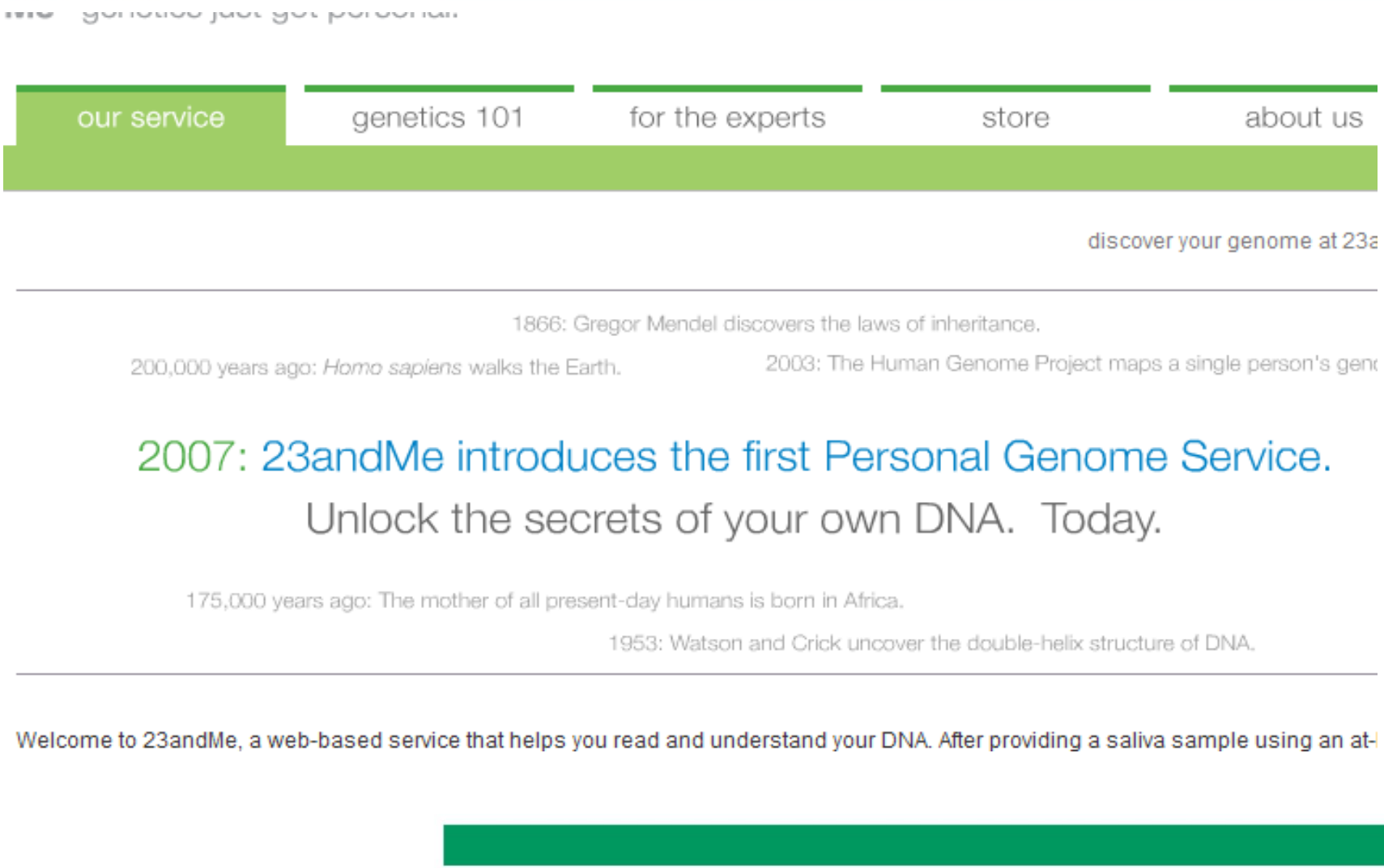
DNA, the "code of life," is the ultimate binary file, a database of 12 billion bits. The data—6 billion matching sets of either the molecules adenine (A) and thymine (T) or guanine (G) and cytosine (C)—affect everything that makes you *you*: the color of your eyes, whether you're moody or cheerful, and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

| | COST PER GENOME (US $) | GENOMES MAPPED |
|---|---|---|
| 2004 | $3 000 000 000 | 1 |
| 2006 | $60 000 000 | 1 |
| 2007 | $1 000 000 | 1 |
| 2010 | $48 000 | 75 |
| PROJECTION ONE | | PROJECTION ONE |
| 2012 | $10 000 | 5000 |
| 2014 | $2500 | 100 000 |
| PROJECTION TWO | | PROJECTION TWO |
| 2012 | $500 | 100 000 |
| 2014 | $100 | 1 000 000 |

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

# Challenge: Premature Translation
# "Genomics and Personalized Health"



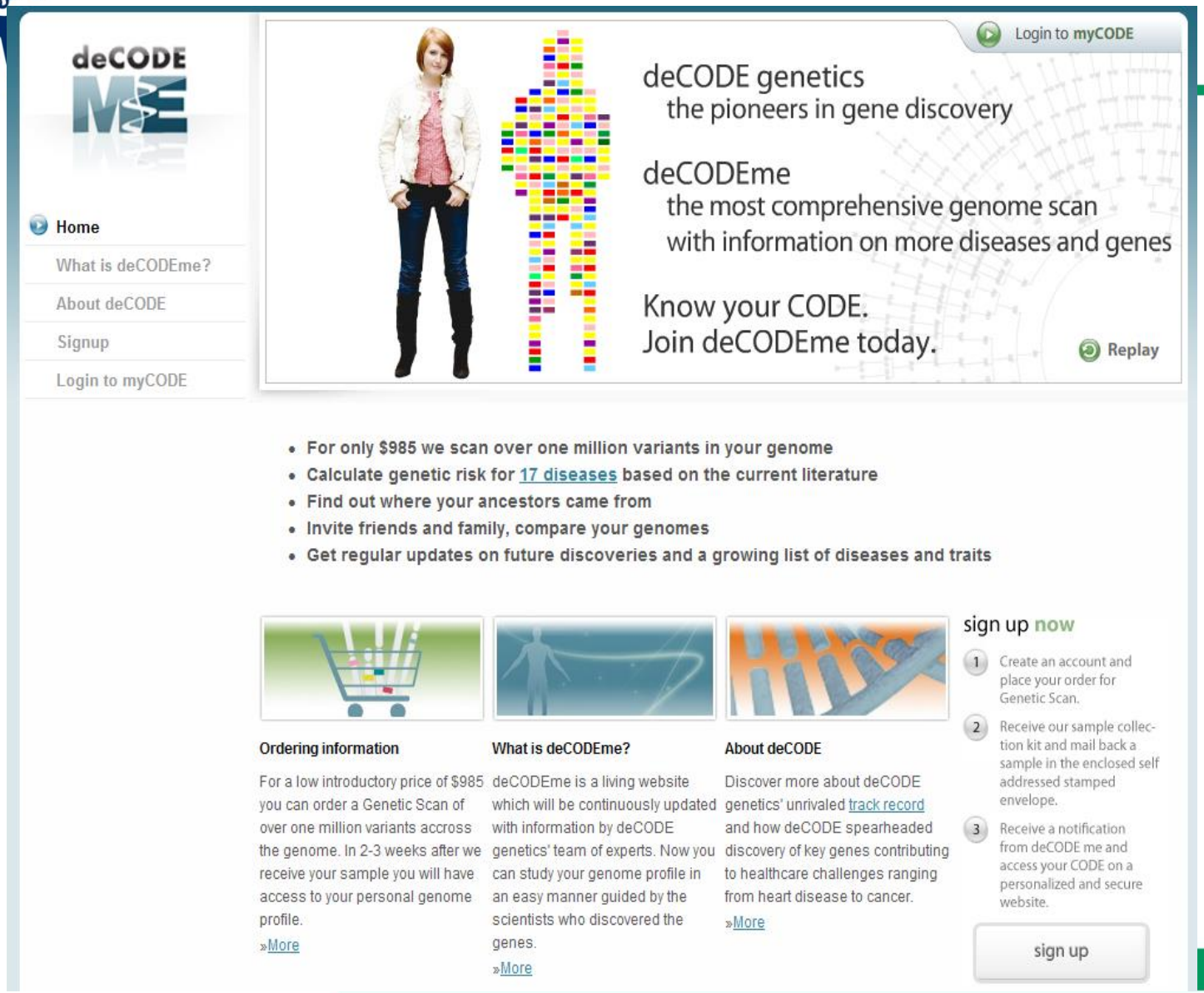
Anne Wojcicki

The most popular and one of the “oldest” personal genetics company, established in 2006, offers easy and affordable access to genetic information. Its name comes from the fact that human DNA is organized into 23 pairs of chromosomes. The Mountainview-based 23andme has already built up the biggest database of patients’ DNA information with more than 5,000,000 customers and one billion phenotypic data points!

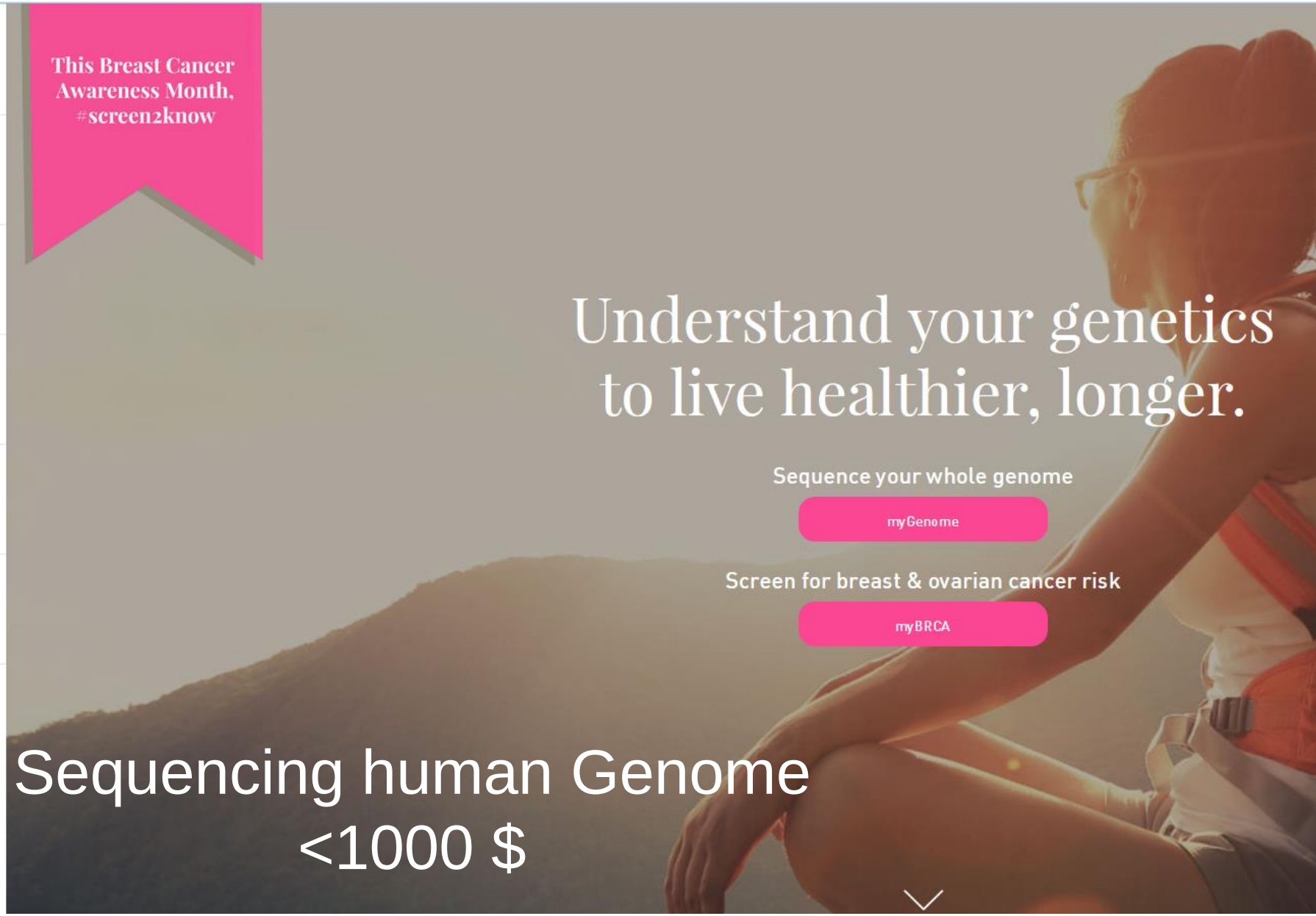
https://youtu.be/zeo7zPzZwIk

https://medicalfuturist.com/top-companies-genomics/

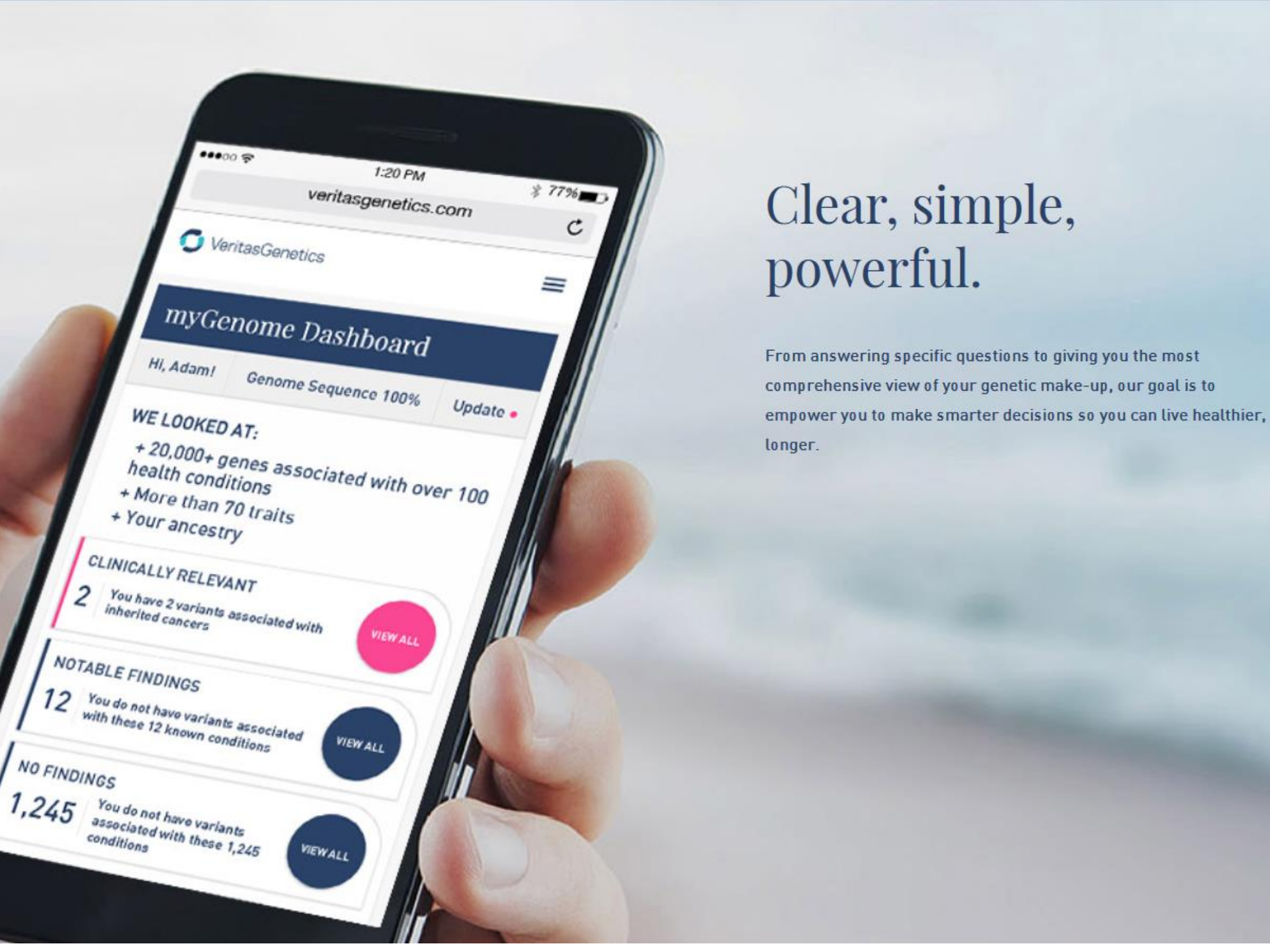
# Challenge: Premature Translation "Genomics and Personalized Health"



# Challenge: Premature Translation "Genomics and Personalized Health"




# Sequencing human Genome
# <1000 $




# Clear, simple, powerful.

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**Our Lab Detects Your Unique Genetic Code and Extracts the Health Information Which No One Can See**


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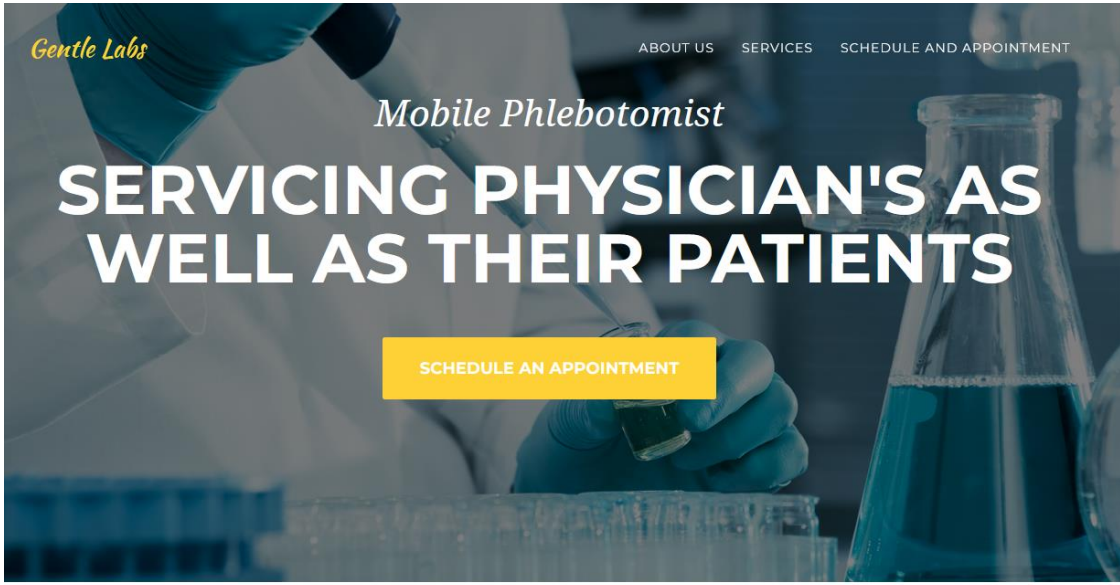
using artificial intelligence to build a new universe of life-saving genetic therapies

PATHWAY GENOMICS®




illumina

Aim: <100$

GENTLE LABS IS A MOBILE CLINICAL LABORATORY

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# 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 22nd 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.