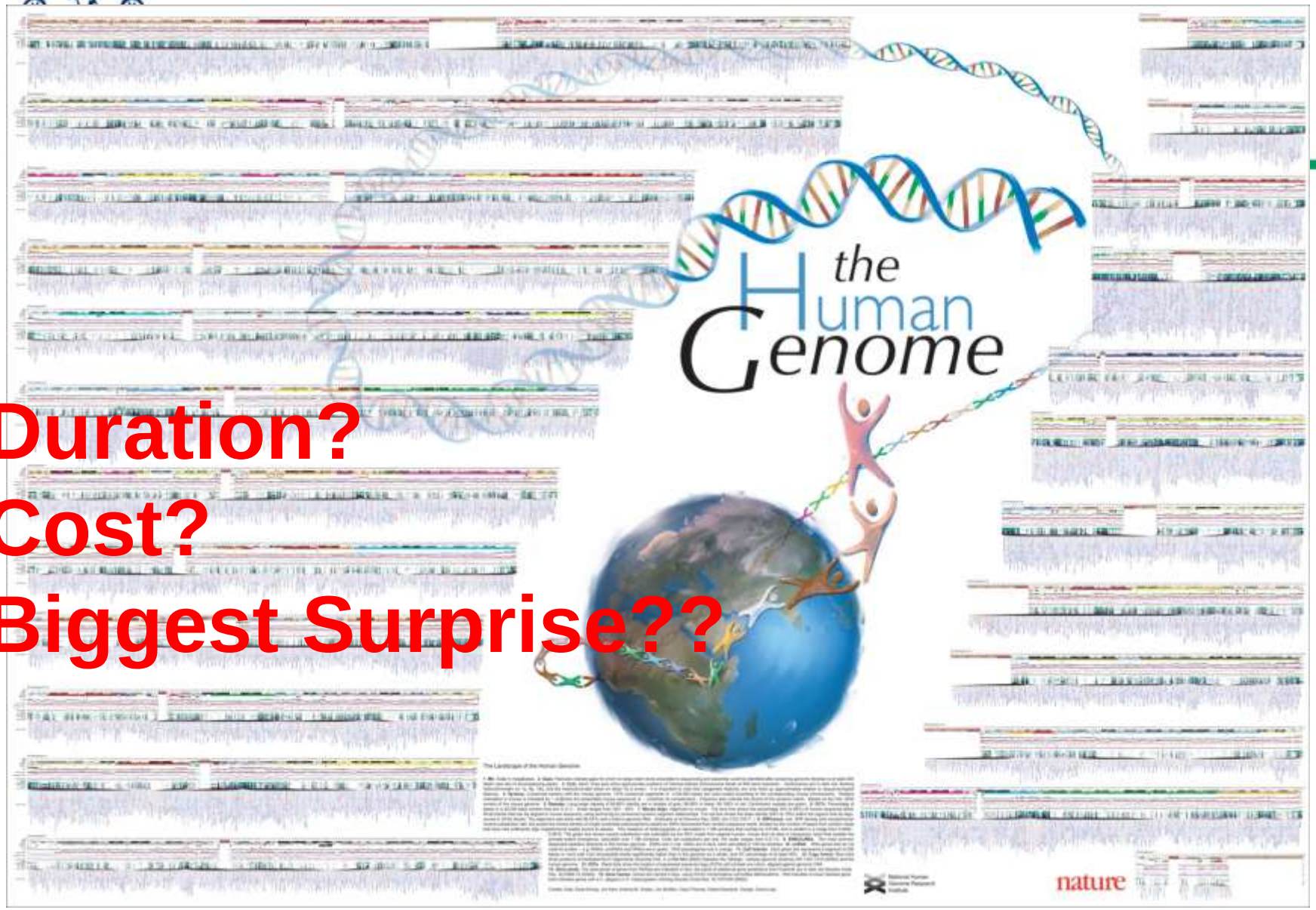
ADAM MICKIEWICZ UNIVERSITY IN POZNAŃ
Faculty of Biology

Genome Medicine



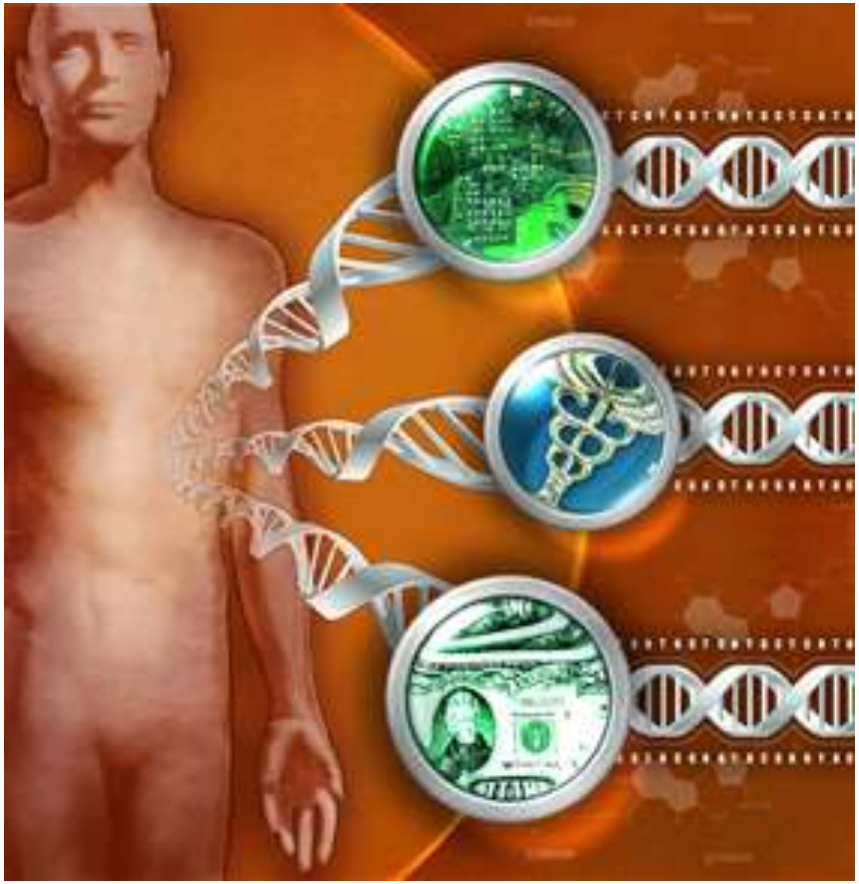
Personilized/Precision Medicine

Hans Bluyssen, 09-10-2019



Duration?
Cost?
Biggest Surprise??

Post-genome sequencing "Functional Genomics"



-translate information to different levels

-Understanding mechanisms of cell function + organism

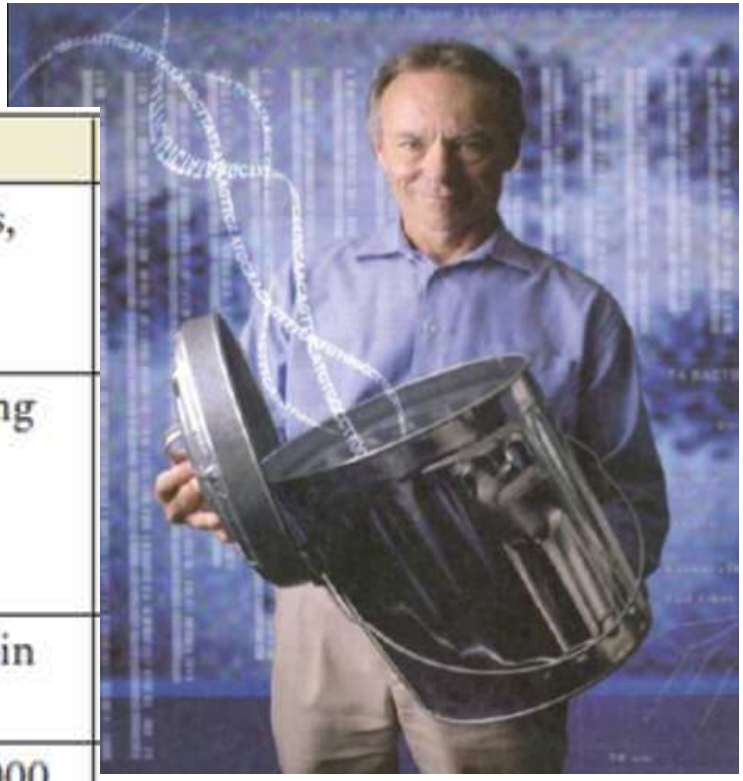
-Health care:
food and health
mechanism infectious disease
origins of multifactorial disease

-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) **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**

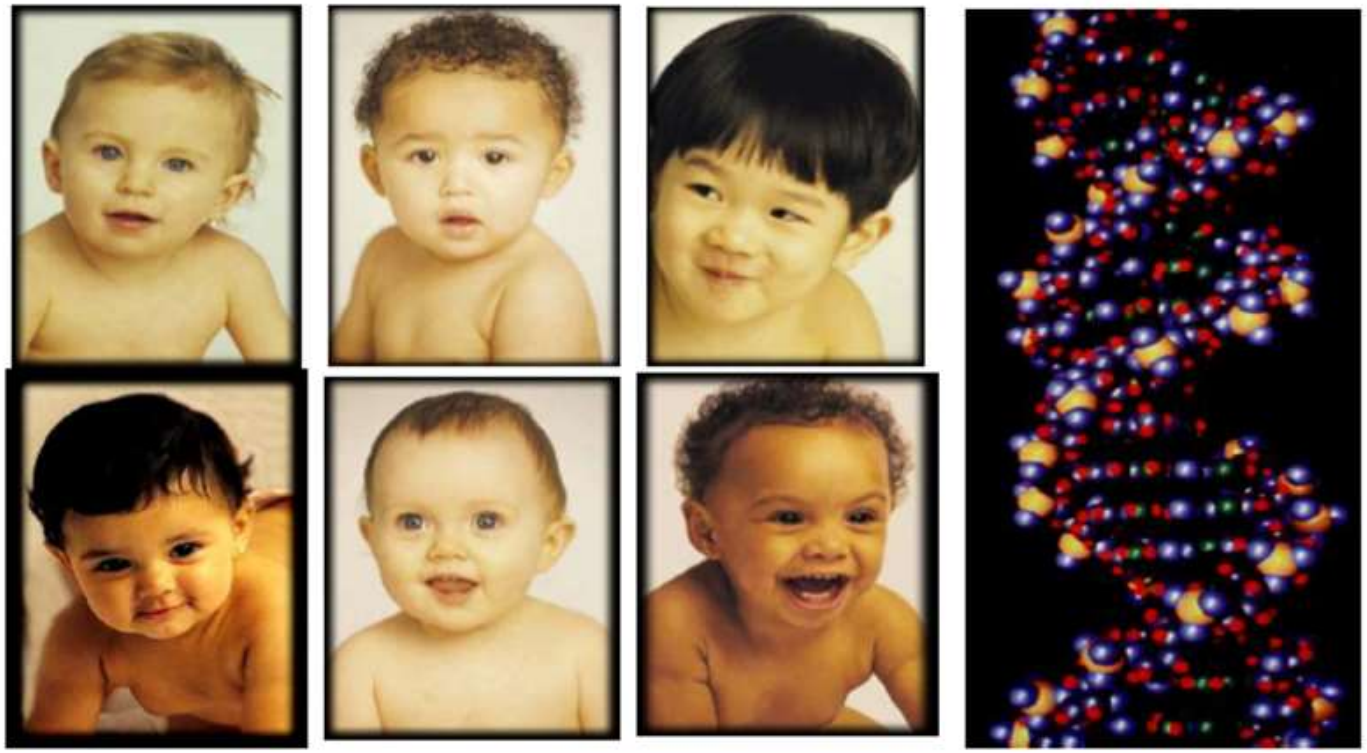


(Chan & Ginsburg, 2011)

“Personal Genome”

> 50 companies
World-wide

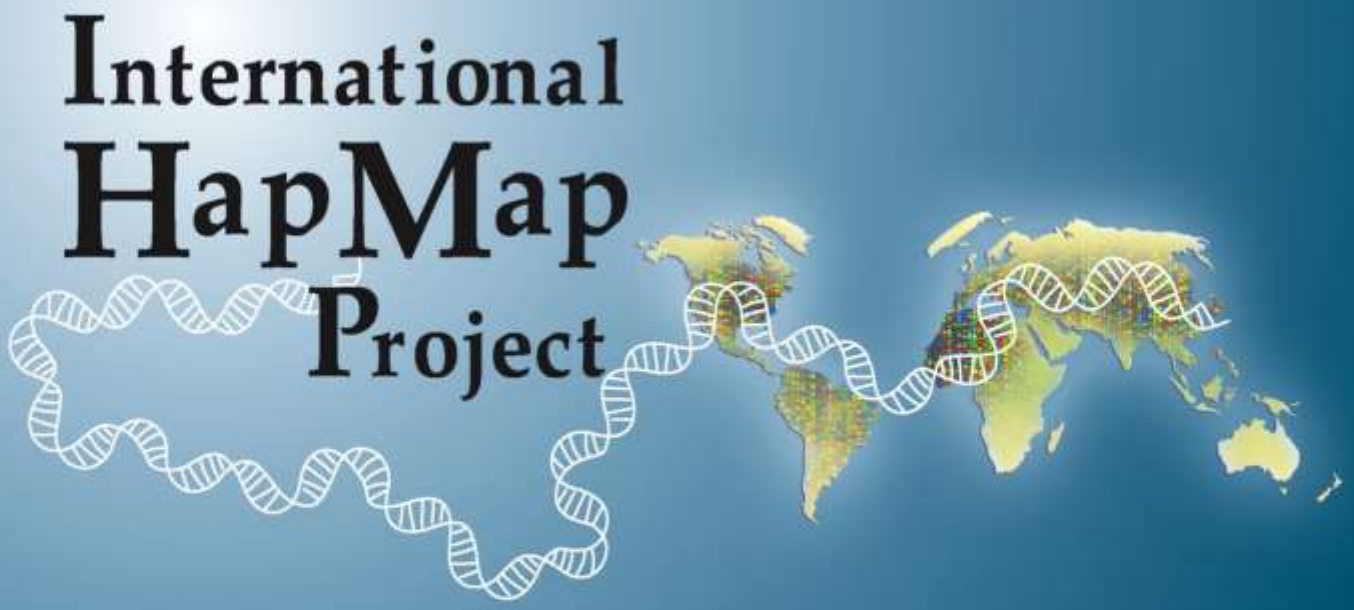
Genomics: Single Nucleotide Polymorphisms



The Hunt for Gene Loci Associated with Complex Human Diseases

Genome wide variation!

www.hapmap.org

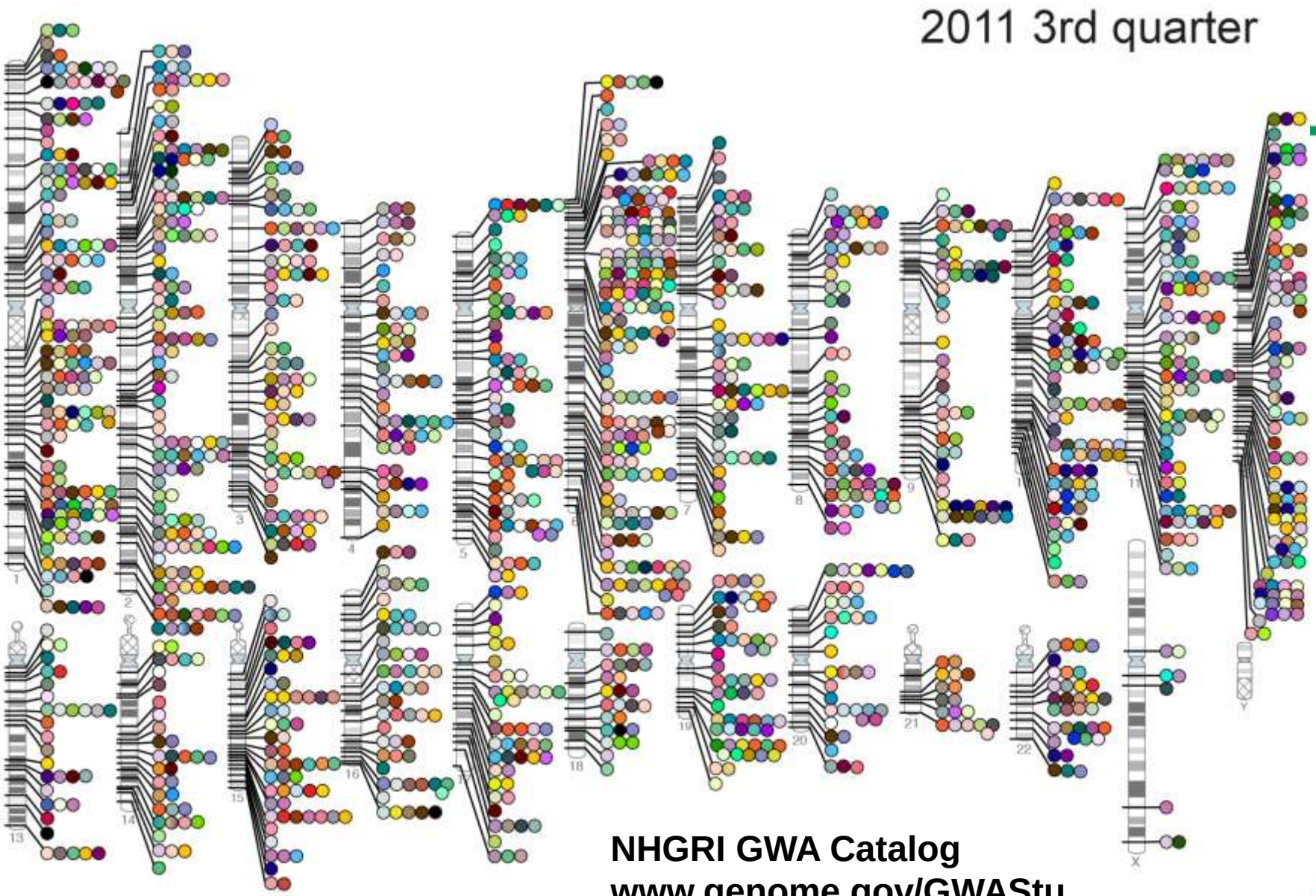


The HapMap is a catalog of common genetic variants that occur in human beings. It describes what these variants are, where they occur in our DNA, and how they are distributed among people within populations and among populations in different parts of the world.

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.

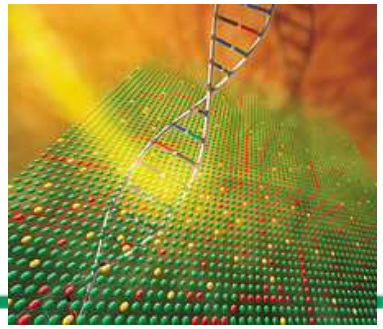
Published Genome-Wide Associations through 09/2011

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



NHGRI GWA Catalog
www.genome.gov/GWAStudies

GWAS of Disease Susceptibility



- May 2011:
  - 800 GWAS published
  - 150 diseases
  - > 2.400 SNPs with statistically significant associations + odds ratio

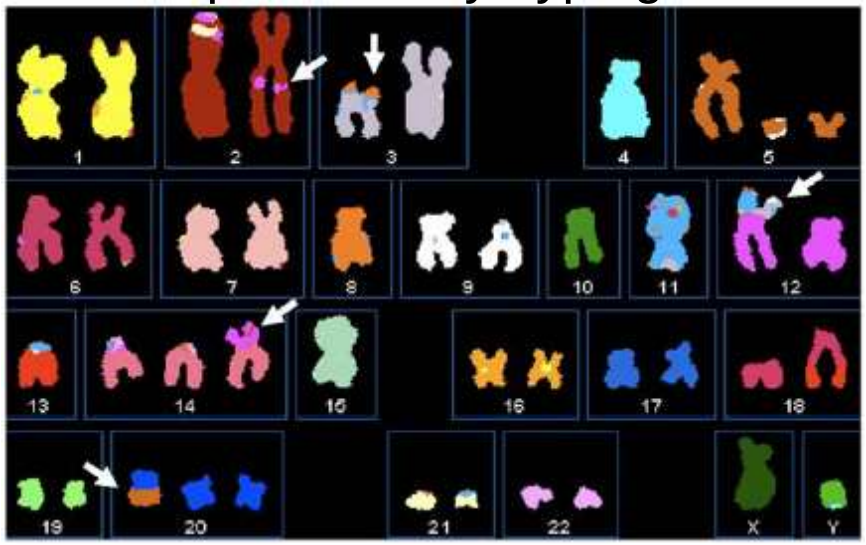
- Crohn's diseases: > 32 variants
- Type 2 Diabetes: > 20 variants
- CAD: > 200 variants

} ~ Disease risk

Next → Whole Genome Sequencing!

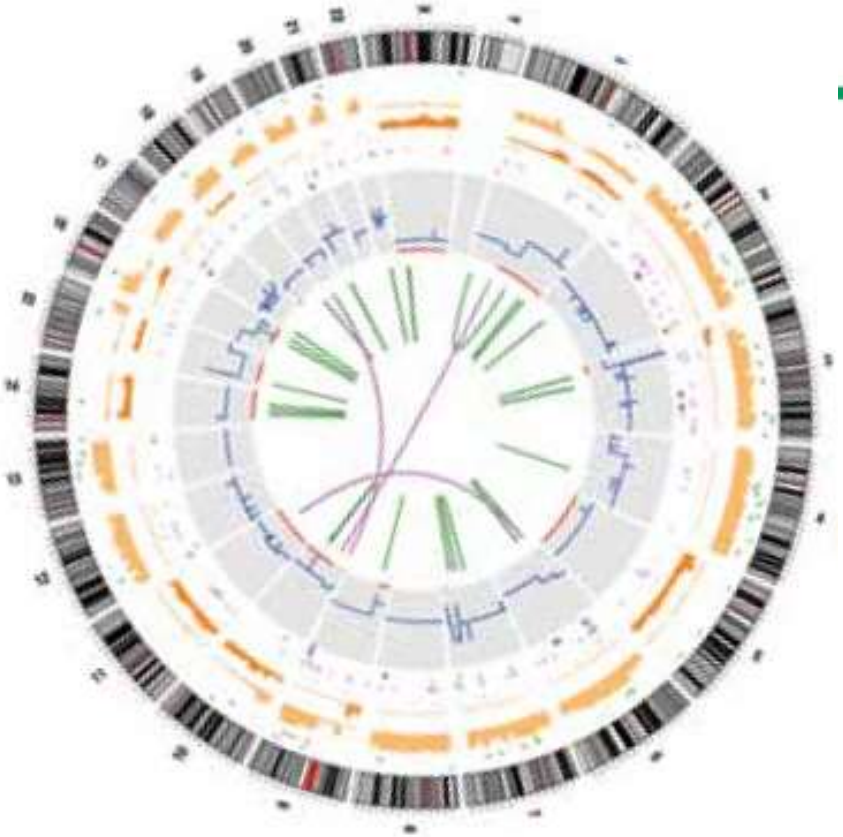
Tumor Sequencing

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.

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 | 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.

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

tés Nézet Előzmények Könyvjelzők Eszközök Súgó

l Genome Project Has a Growth...

www.technologyreview.com/view/413516/the-personal-genome-project-has-a-growth-spurt/

HOME MENU INSIDER CONNECT

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 G will soon have a lot of company. According to a report from Northwestern 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 aroun

Here's a brief description of the project from a piece I wrote last October.

> Headed by Harvard University genomics pioneer George Church, the project aims to

Microsoft PowerPoint ... The Personal Genome...

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,**

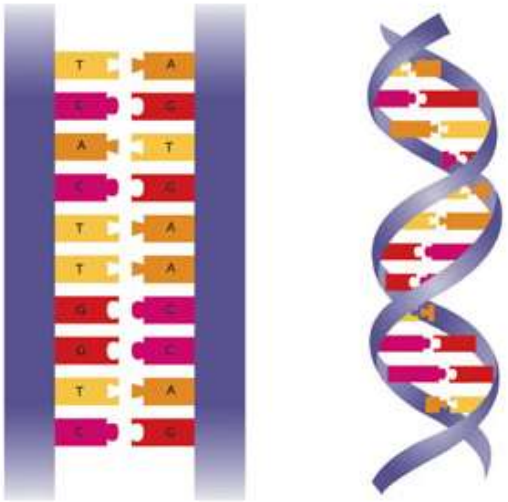
- **Aim: to understand genetic and environmental contributions to human traits.”**

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.

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

Ineffective therapies – waste money

Hypertension Drugs 10-30%

ACE Inhibitors

Heart Failure Drugs 15-25%

Beta Blockers

Anti Depressants 20-50%

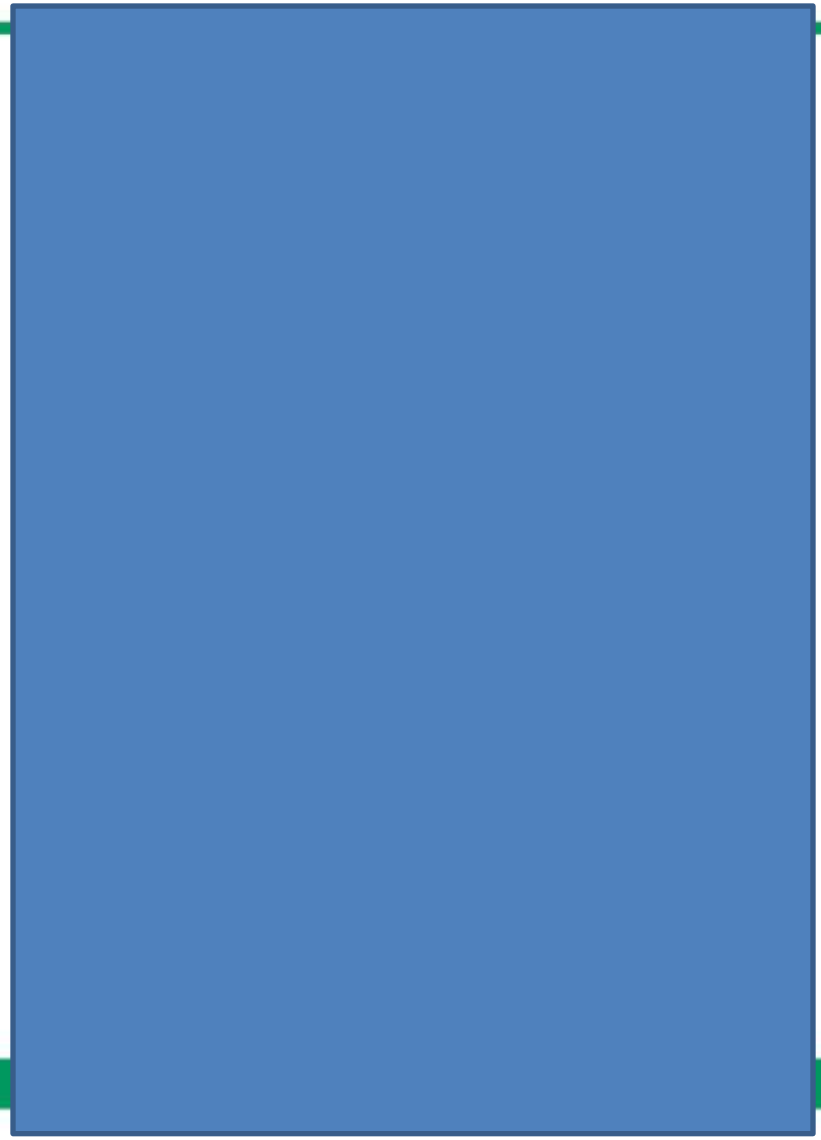
SSRIs

Cholesterol Drugs 30-70%

Statins

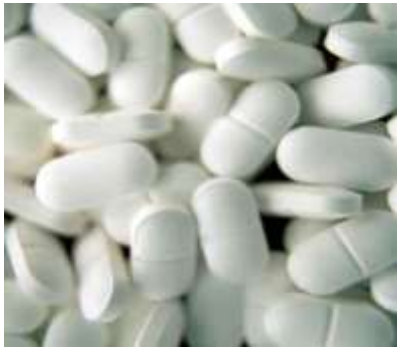
Asthma Drugs 40-70%

Beta-2-agonists



Medicine in the XX. Century

- „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!

Personalized Medicine: The Answer?

Targeted therapy:

Differentiate, diagnostics and drug co-development

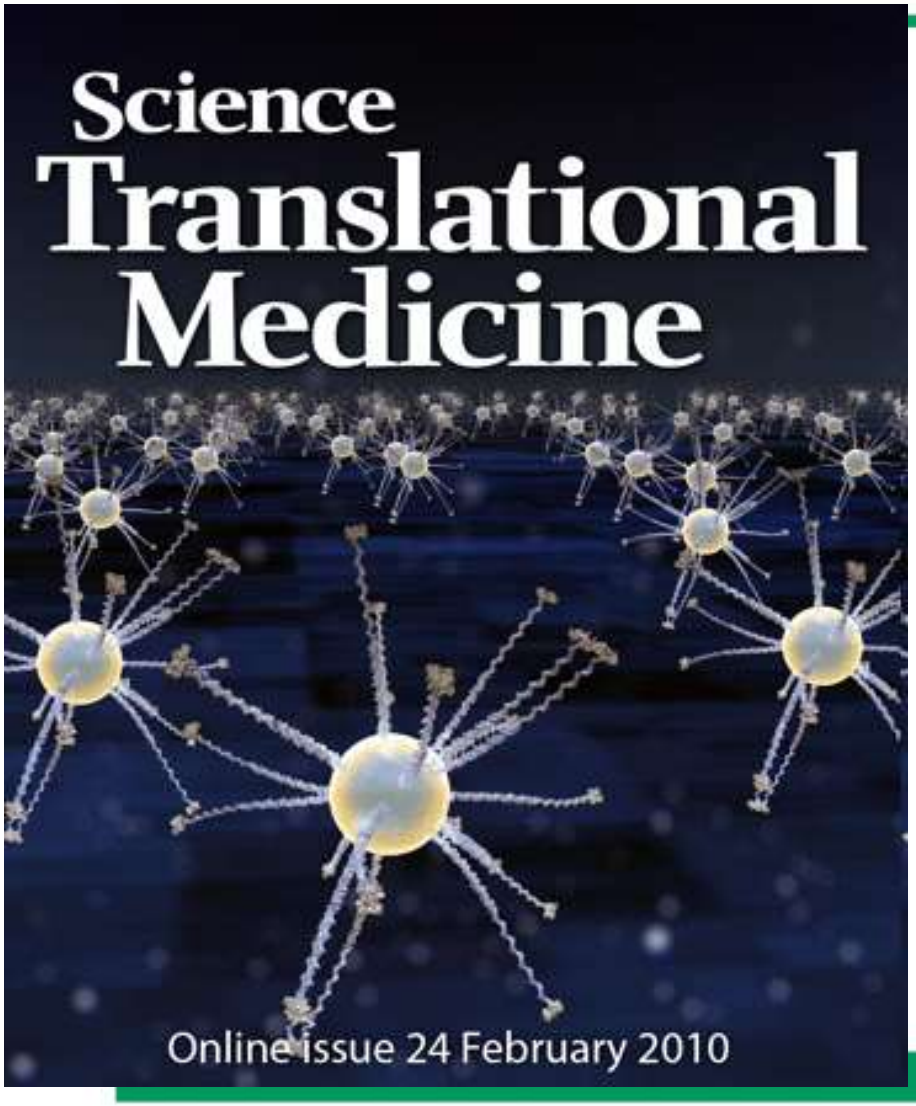
Targeted therapies help by identifying patients with the best response and least side effects

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

Drug-Diagnostics Combinations in Oncology

Cancer has a very complex biology

Development of Personalized Tumor Biomarkers Using Massively Parallel Sequencing



Mutation Details

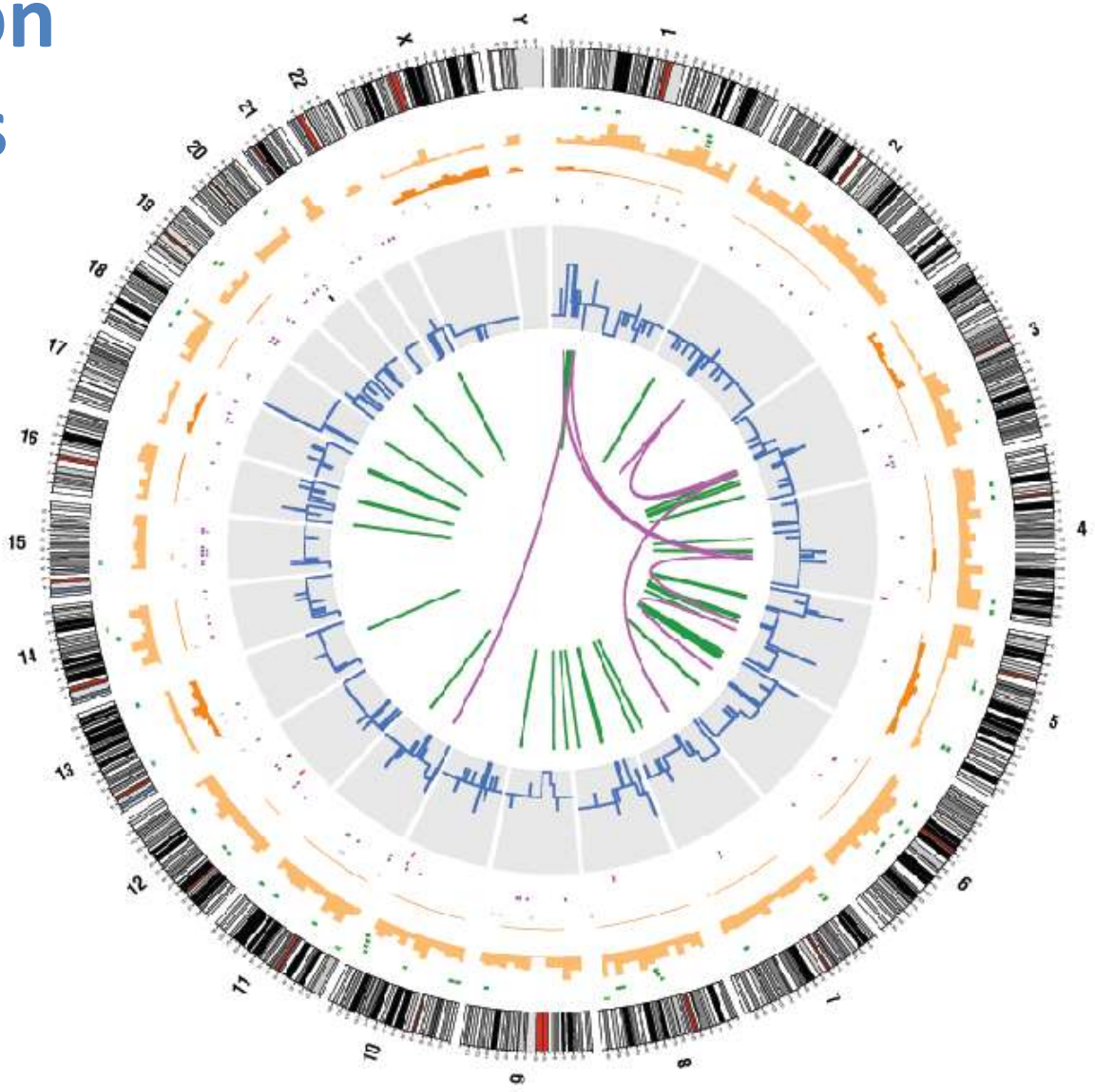
Lung Carcinoma genome

- 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.

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.*

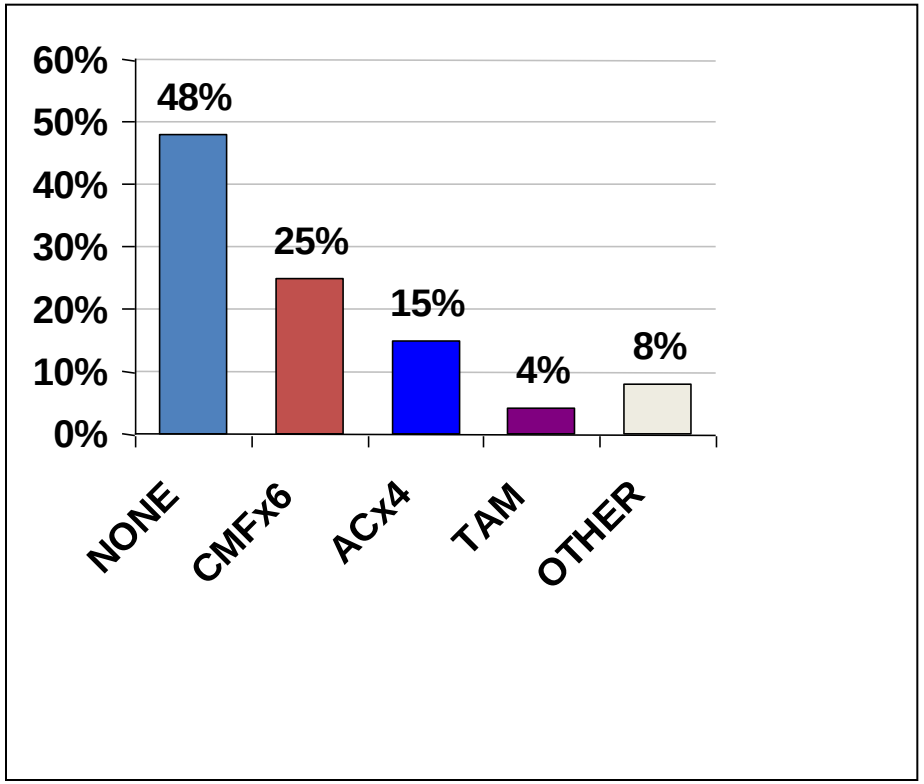
*Jørgensen JT. Expert Rev Mol Diagn 2008; 8: 689-695.

Breast Cancer: The Treatment Dilemma

61 y-old, fit, postmenopausal

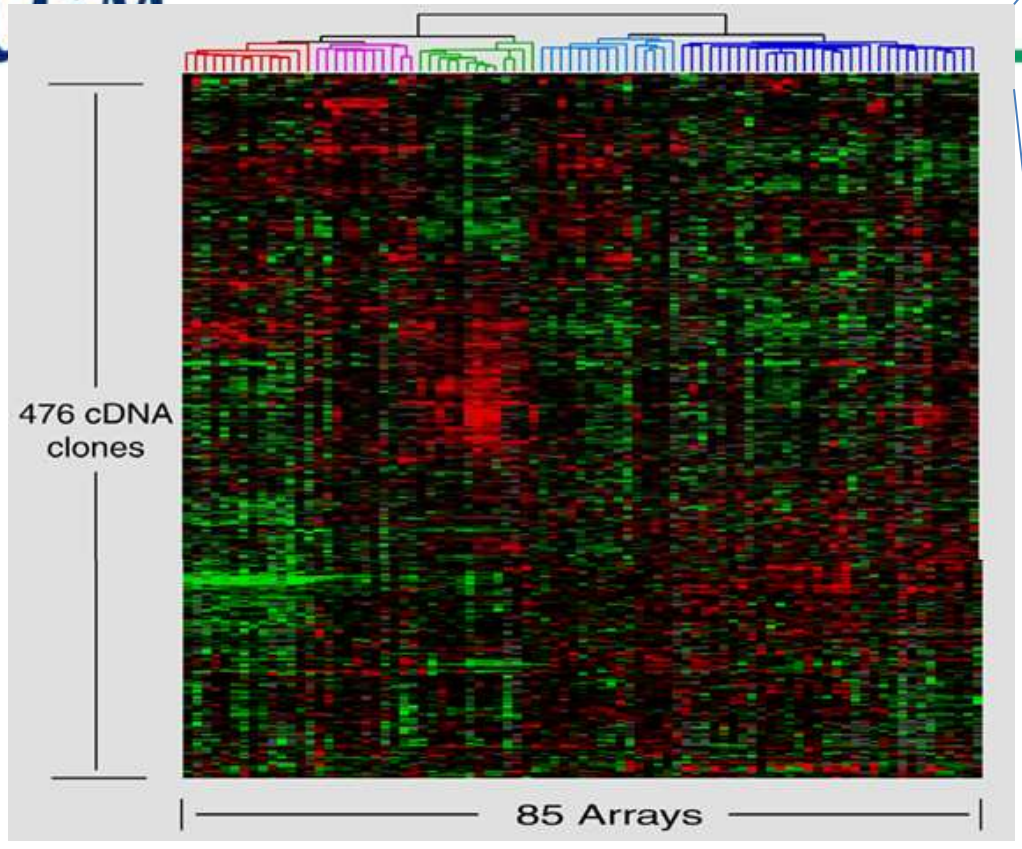
Node negative
pT = 0.9 cm
ductal cancer
ER and PR negative
HER2 negative
Grade 2

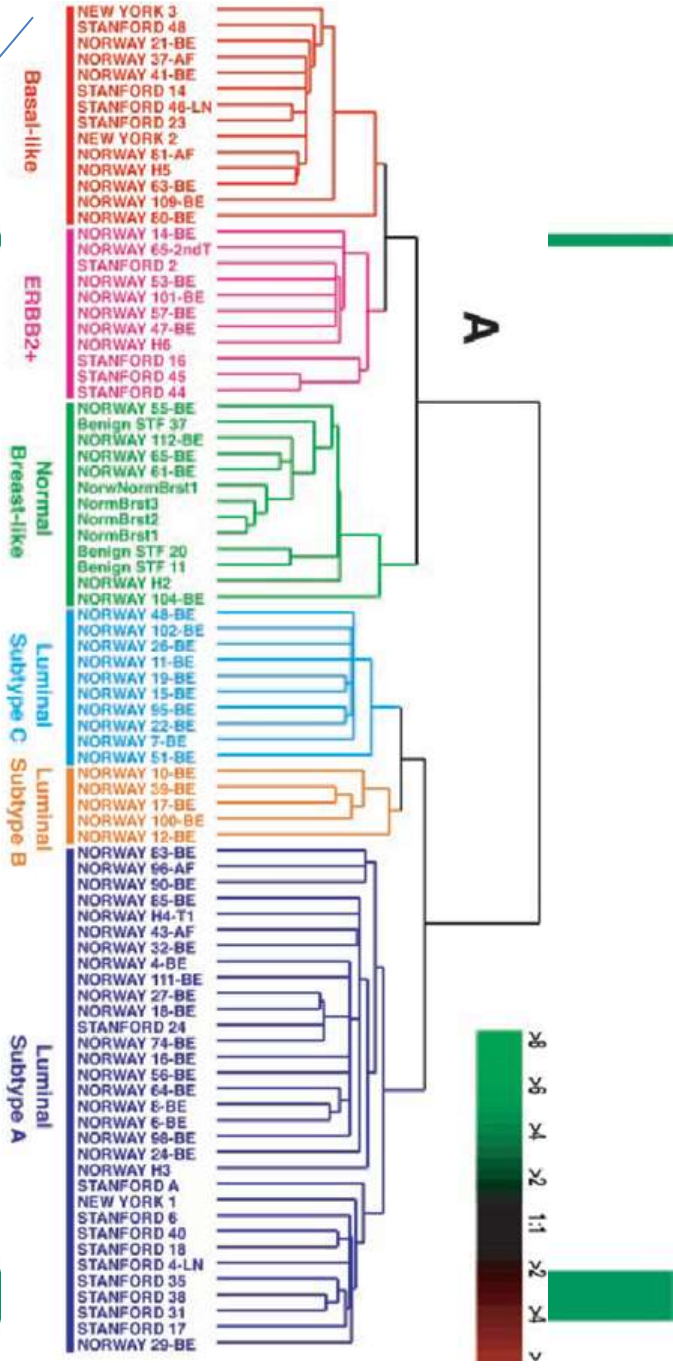
Choices of 40 experts world-wide



Courtesy: Martine Piccart

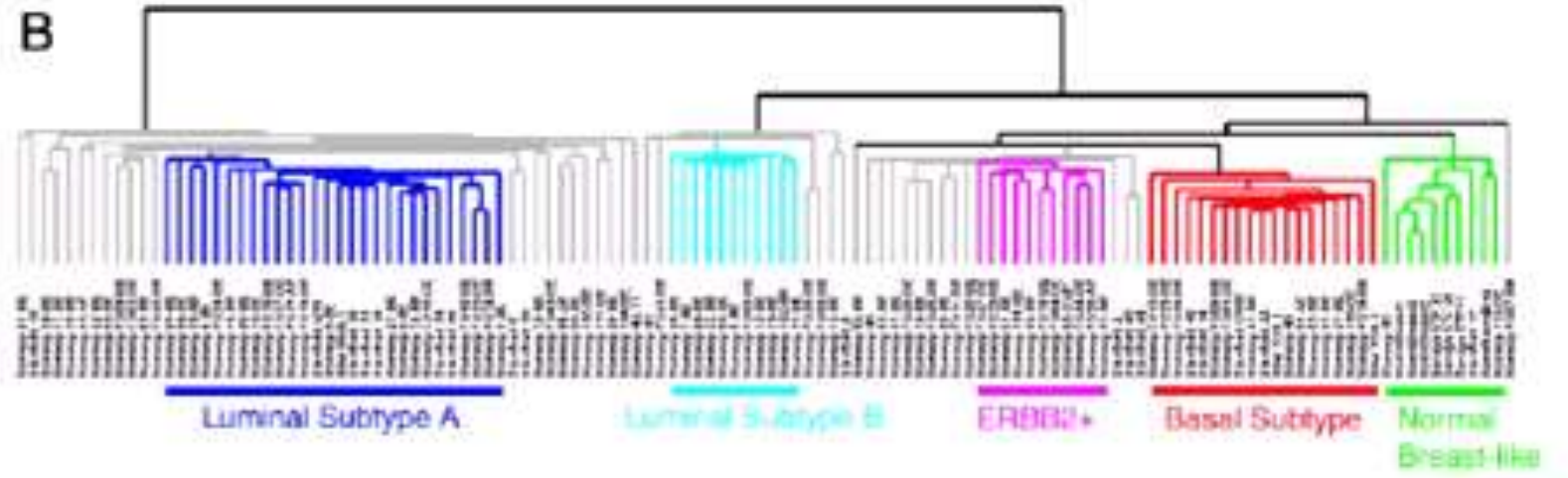
Breast Cancer Subtypes

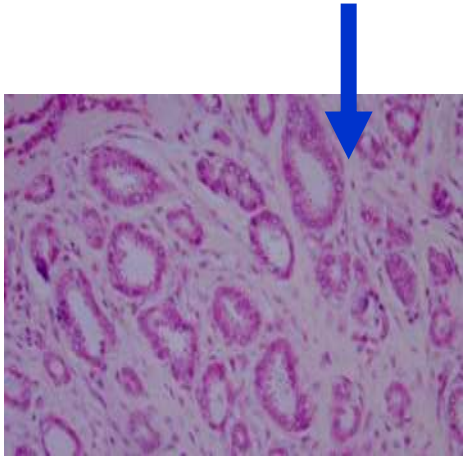




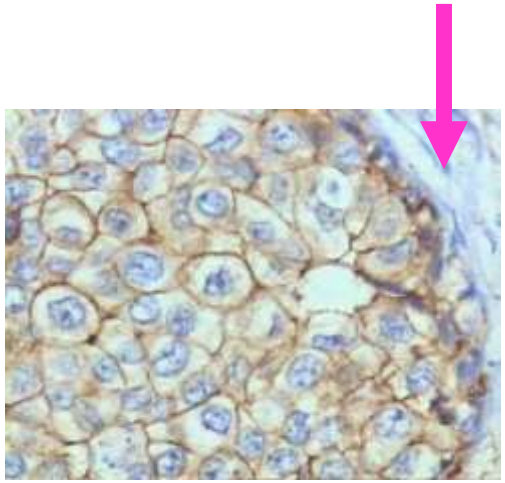
- Disease Onset + Progression
- Disease Subtyping/Classification

Sorlie *et al.* PNAS 2003

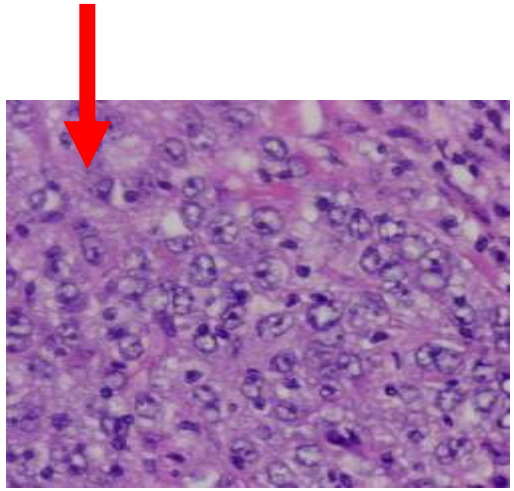




ER++, PR++, G1,2

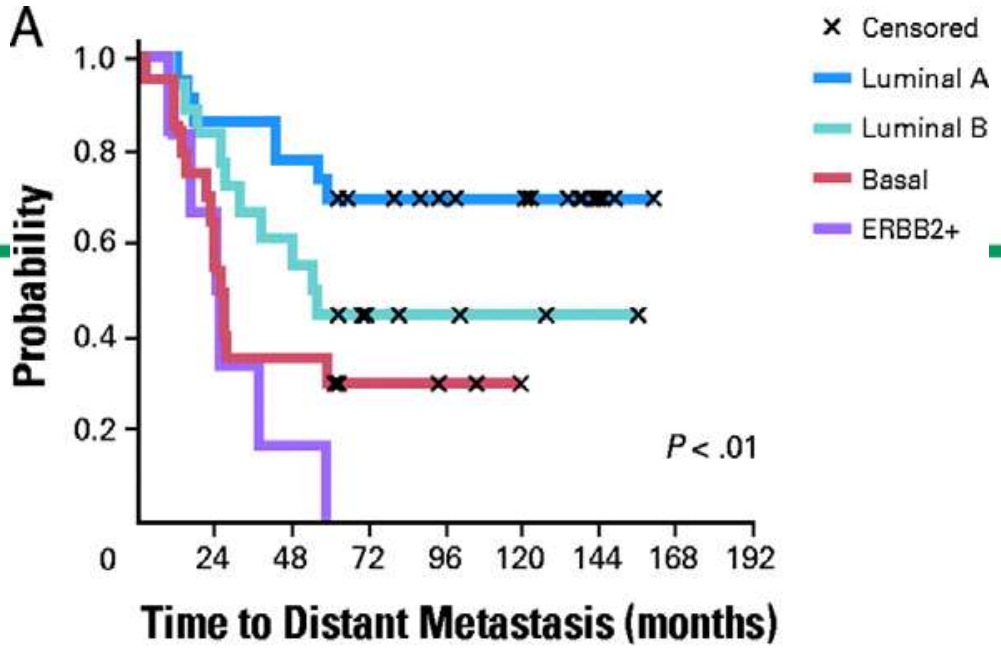


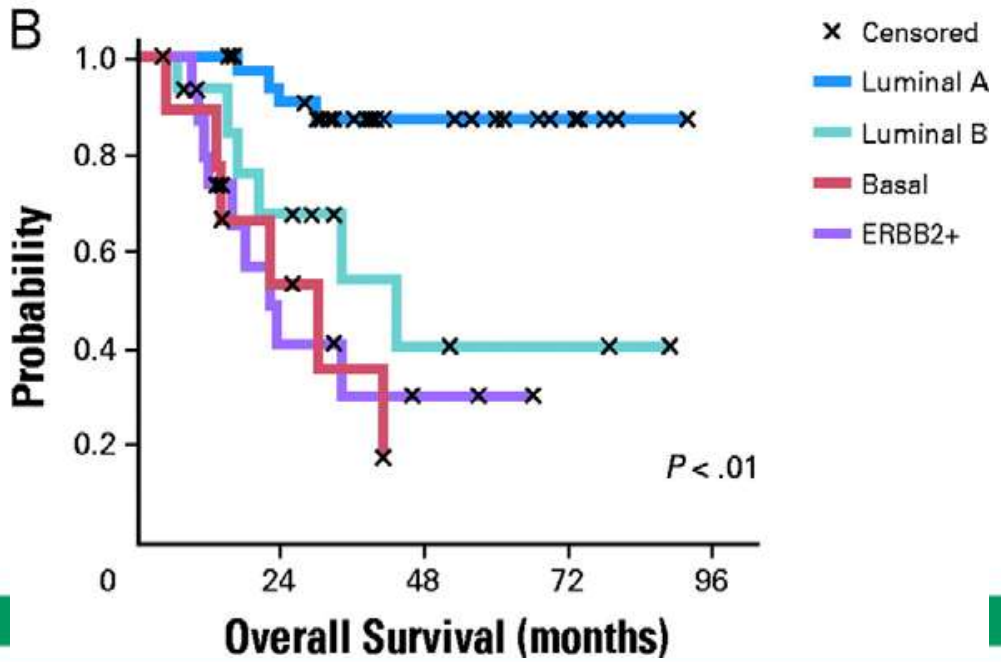
HER2 ISH pos



“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., Caroline Lohrisch, M.D., Thomas M. Suter, M.D., Josef Rüschoff, M.D., Tamás Sütő, 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 (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.

Funded by Amgen Inc, Thousand

Christos S.
Dongsheng Tu
Sonia

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

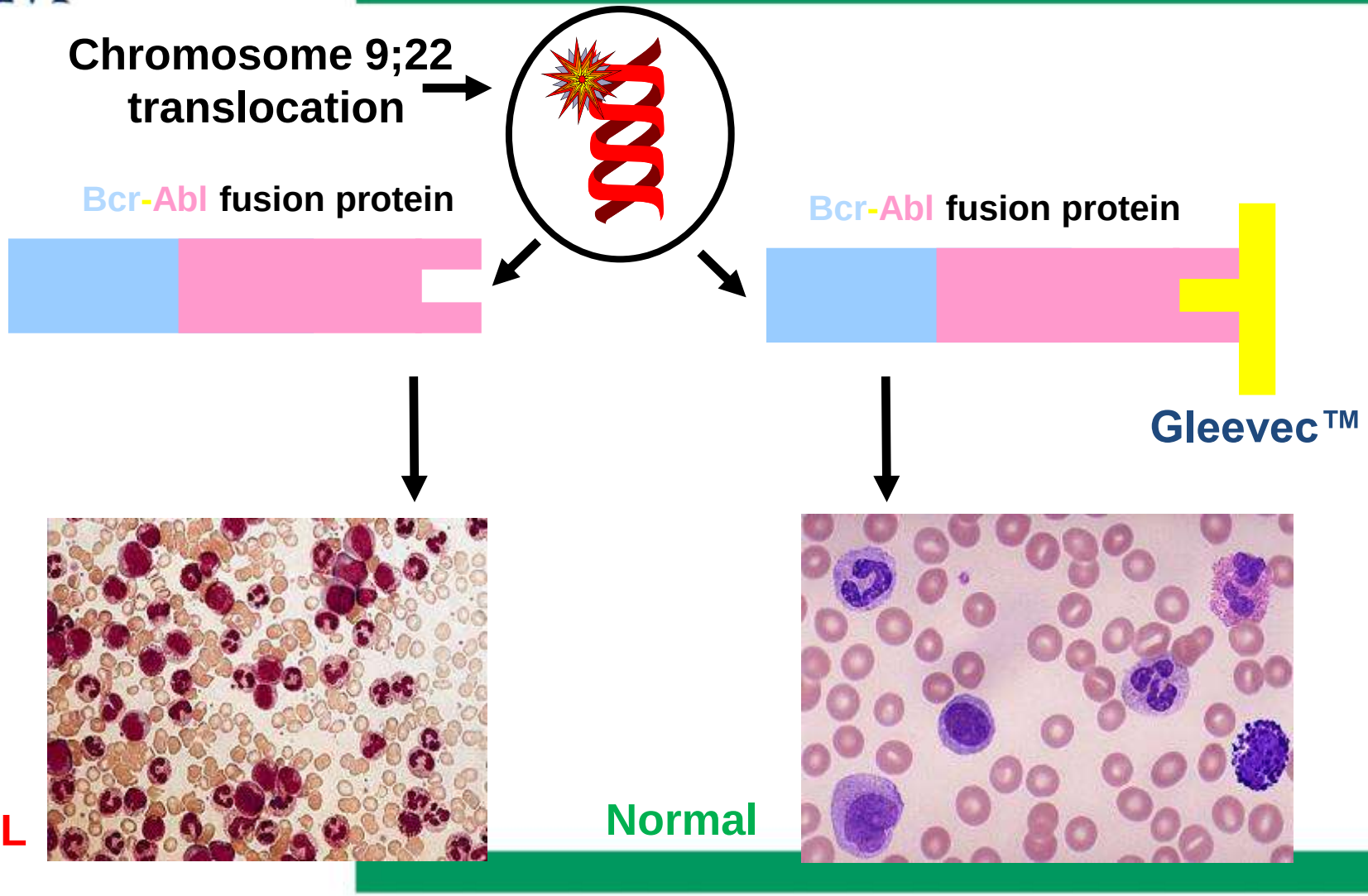
Purpose

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.

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

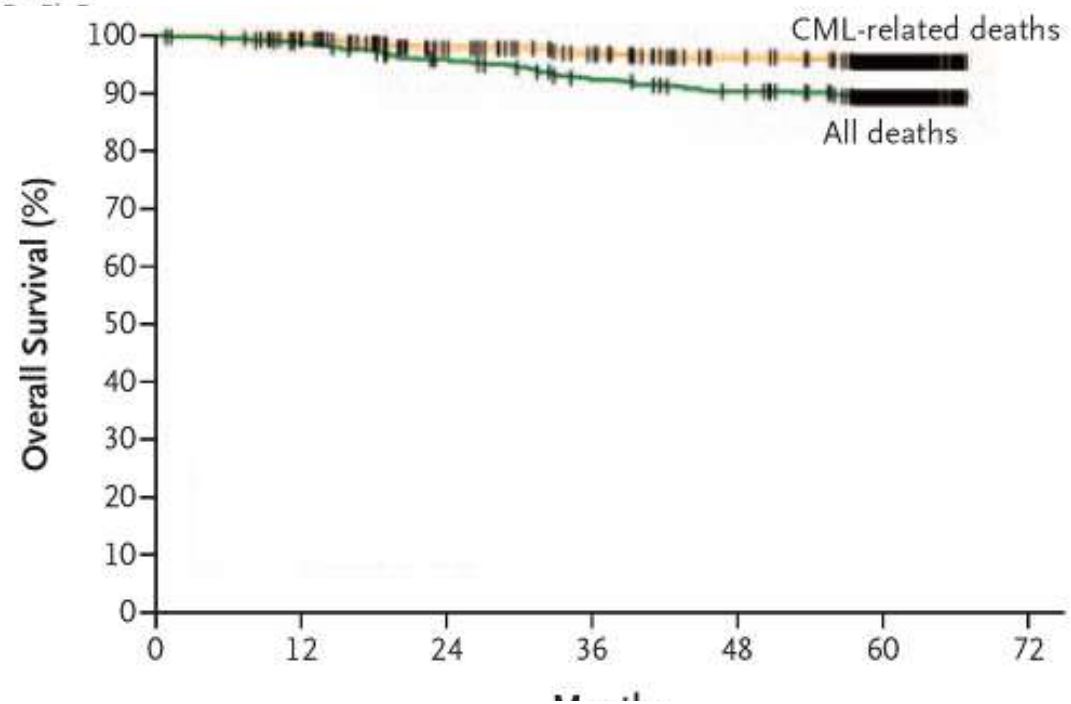


The NEW ENGLAND JOURNAL of MEDICINE

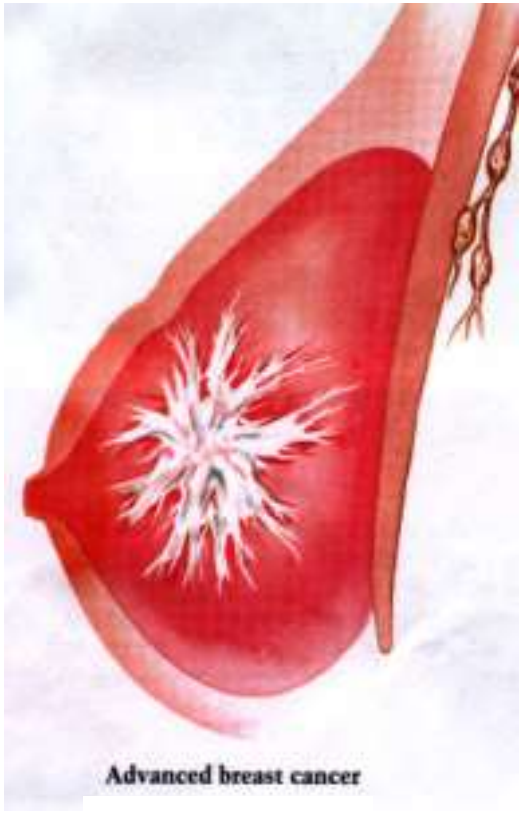
ORIGINAL ARTICLE

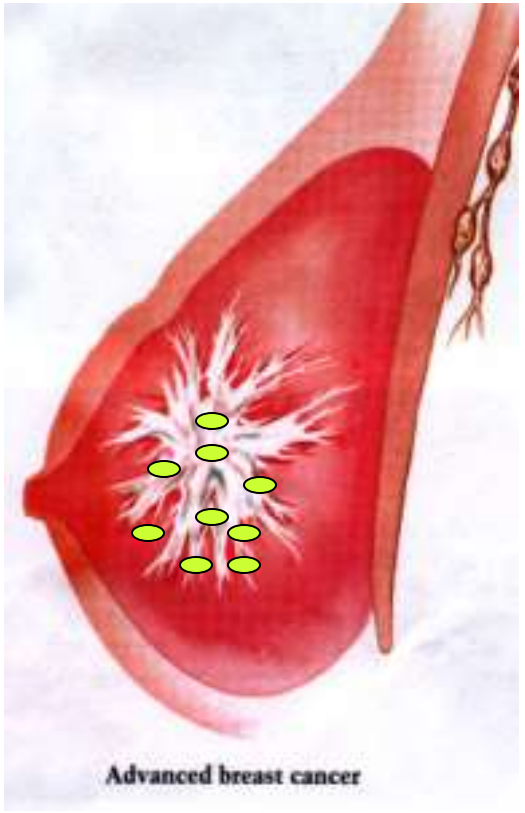
Five-Year Follow-up of Patients Receiving Imatinib for Chronic Myeloid Leukemia

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*



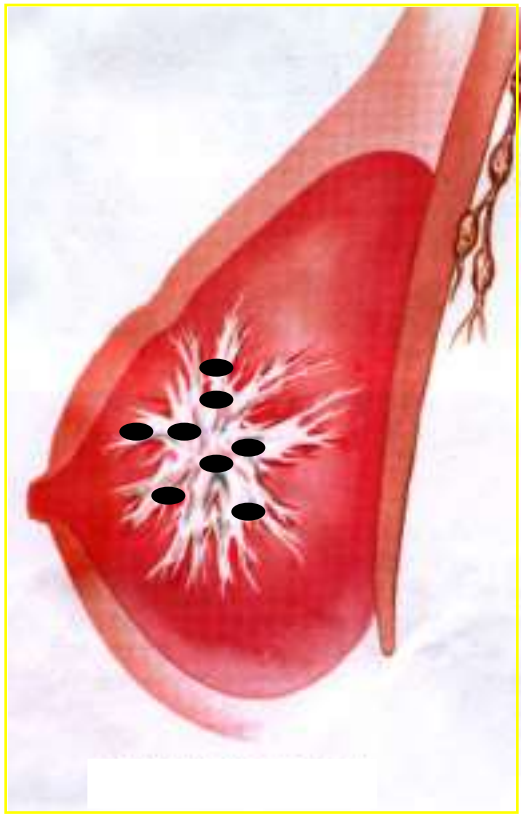
HER2 Gene Product is Overexpressed in One Third of Breast Cancers



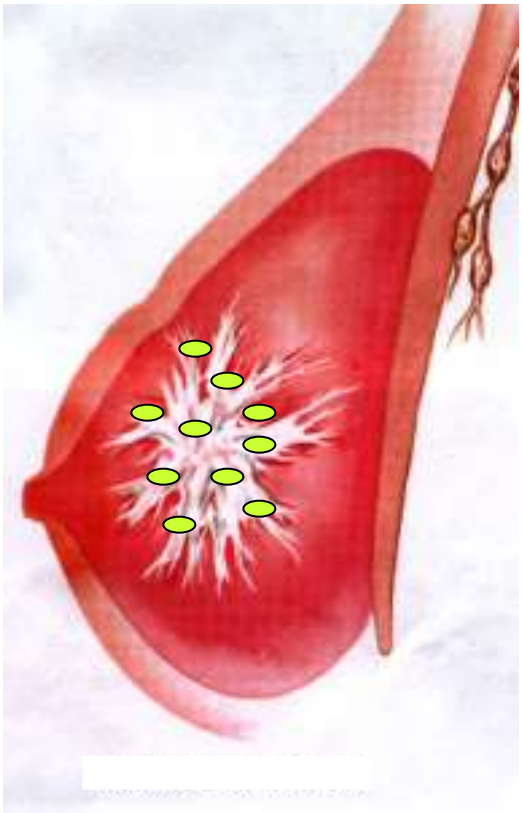


- TUMOR OVEREXPRESSING HER2
- SENSITIVE TO HERCEPTIN

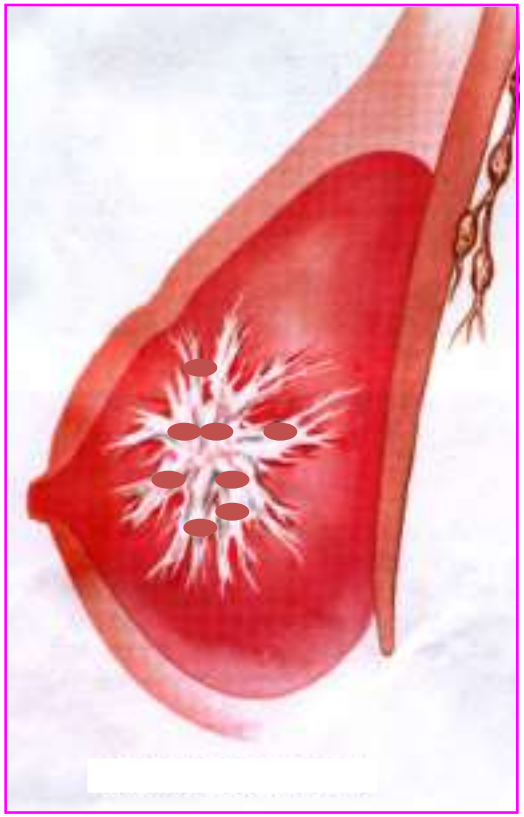
Goal: Tailoring New Drugs to Target Different Types of Breast Cancer



- TUMOR OVEREXPRESSING ?
- SENSITIVE TO ???



- TUMOR OVEREXPRESSING HER2
- SENSITIVE TO HERCEPTIN

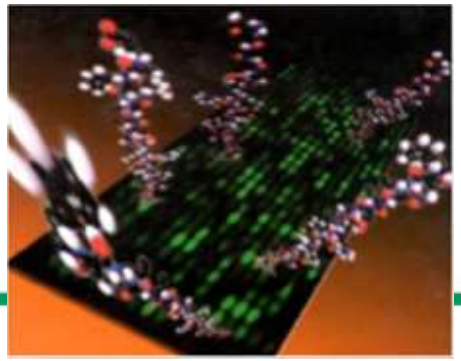


- TUMOR OVEREXPRESSING ?
- SENSITIVE TO ???

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 2020 most anti-cancer drugs will be prescribed based on the results of a companion diagnostic/pharmacodiagnostic test

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

(Chan & Ginsburg, 2011)

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

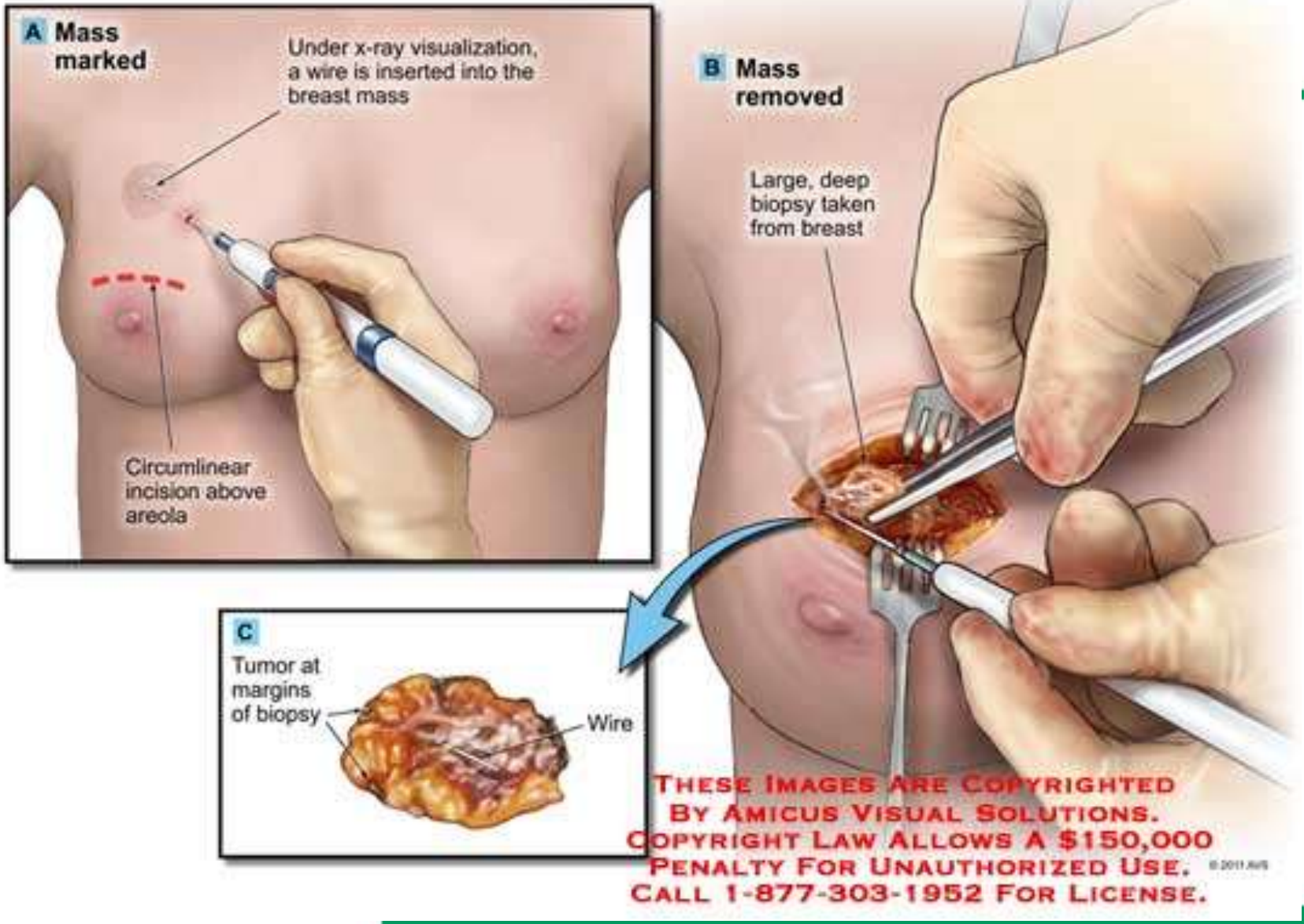
AlloMap

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

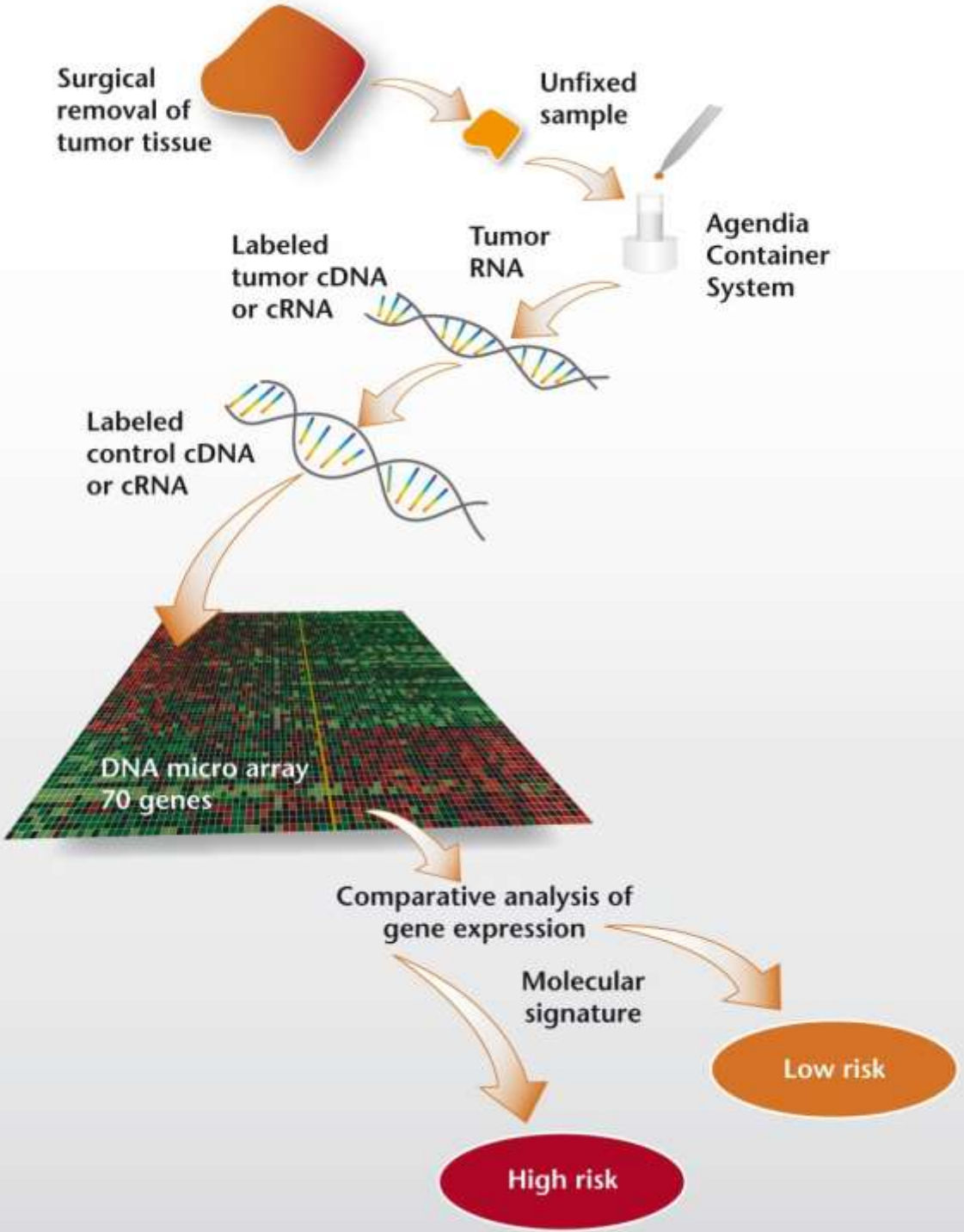
[redacted]'s 11/19/01 Right Breast Biopsy



agendia®

decoding cancer.

mammaprint



Oncotype DX®: A Genomic Assay

Recurrence tumor after surgery
Decision-making about treatment

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

The Recurrence Score® Result Uses Key Genes Linked to Critical Molecular Pathways

16 Breast Cancer related genes

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

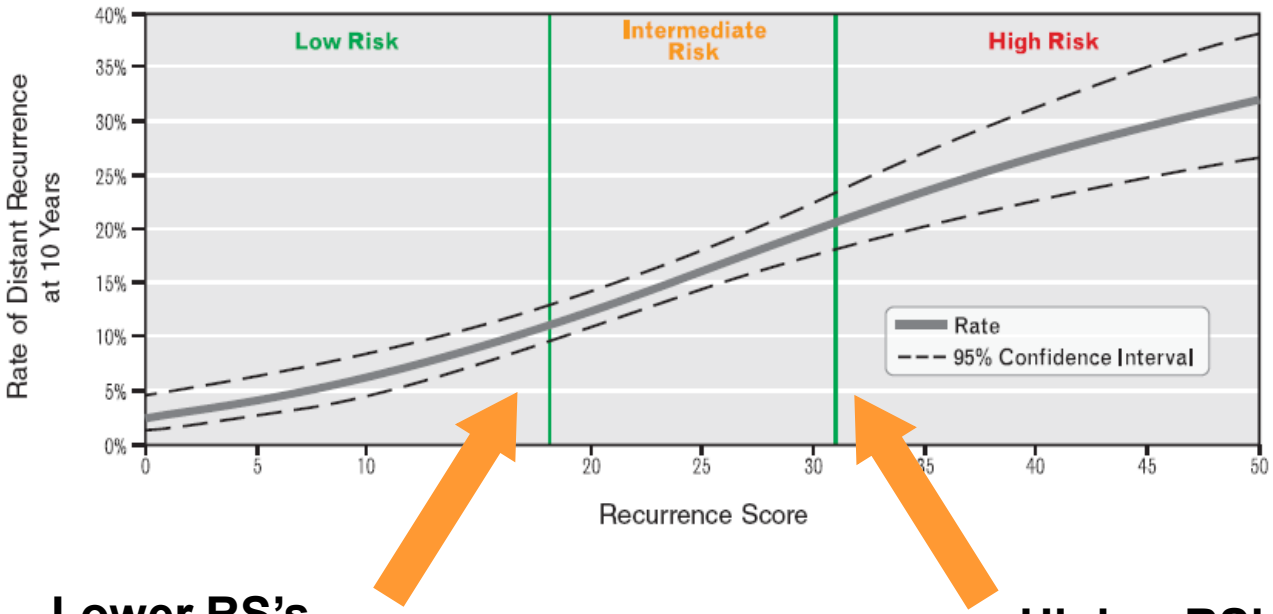
5 Reference genes

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

Conclusions

- 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

AlloMap®

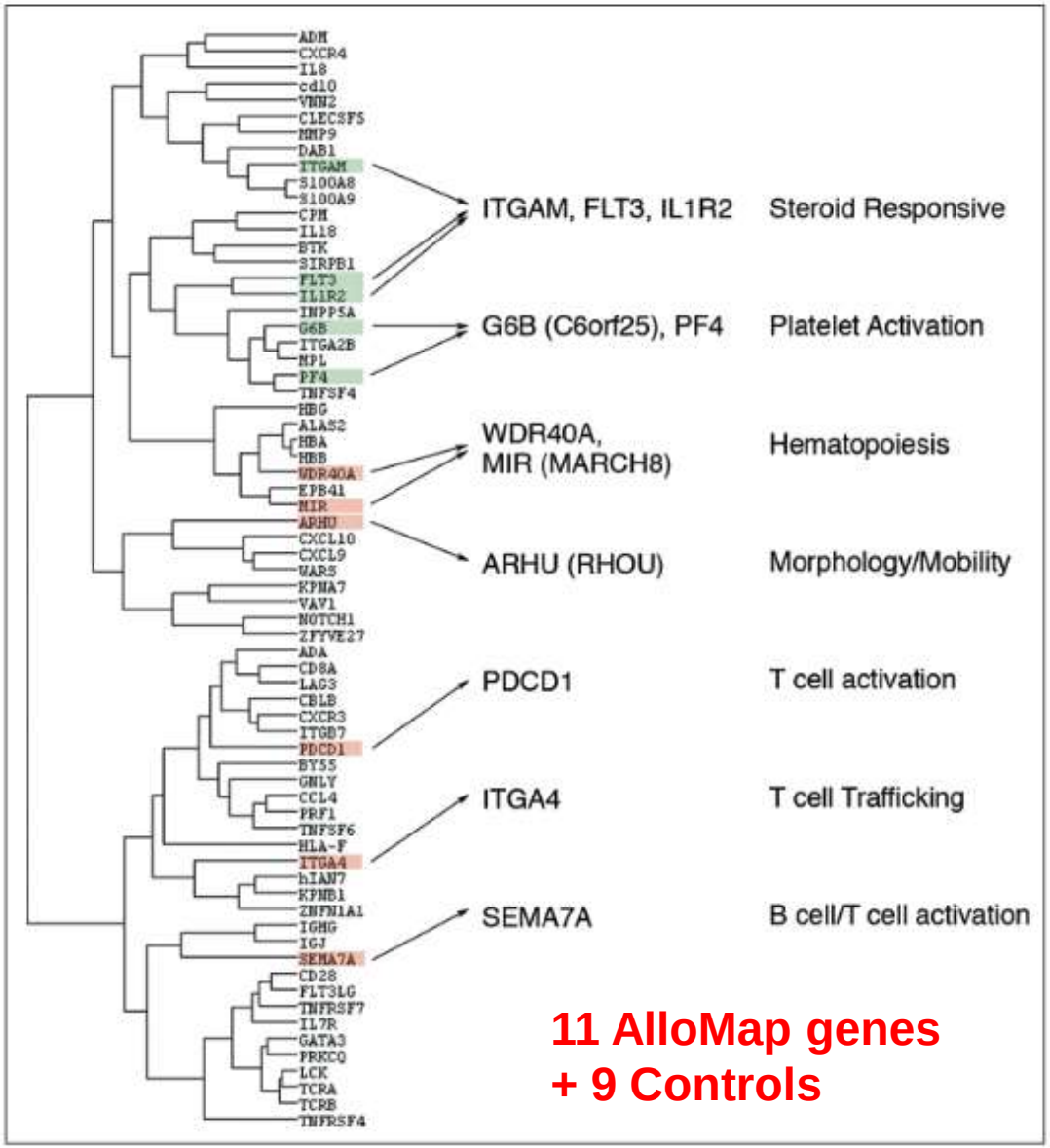
Personalizing Care for Heart Transplant Patients

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

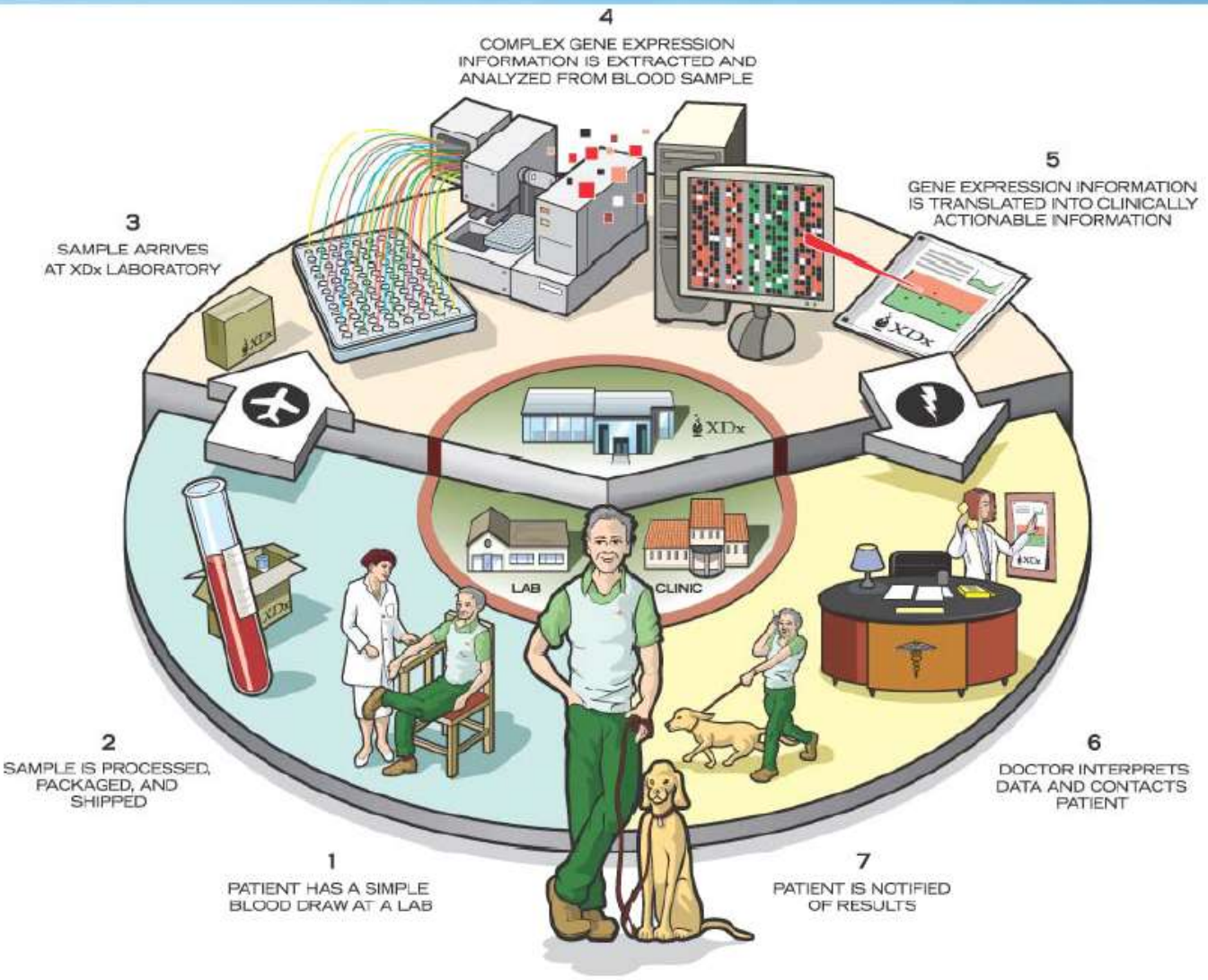


Using linear discriminant analysis, the expression levels of 11 genes were selected for the calculation of the AlloMap score (integer 0–40). This set of genes best distinguished between the presence and absence of rejection in the development of the AlloMap test.

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

Tissue of Origin

CANCER GENETICS INCORPORATED

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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.

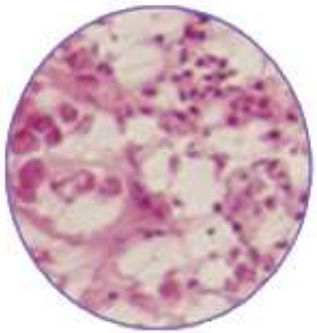
Methodology

CGI processes the specimen, runs the Tissue of Origin and reports the results to the ordering physician. Proprietary analytics are used to interpret the data, and a report is generated that provides clear, objective information on the Similarity Score for each of 15 tumor types, uniquely enabling the healthcare provider to rule in or rule out specific tumor types.

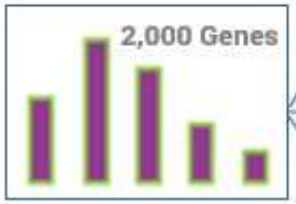
- Bladder
- Breast
- Colorectal
- Gastric
- Hepatocellular
- Kidney
- Melanoma
- Non-Hodgkin's Lymphoma
- Non-Small Cell Lung
- Ovarian
- Pancreas
- Prostate
- Sarcoma
- Testicular Germ Cell
- Thyroid

Each report includes a pathologist's interpretation of the test results.

How the Test Works



PATIENT RNA PROFILE GENERATED



PATIENT PROFILE COMPARED WITH KNOWN TISSUE PROFILES GENERATED

Similarity Scores Generated	
Colorectal	**88.2**
Pancreas	4.4
Non-small Cell Lung	2.3
Breast	2.1
Gastric	1.2
Kidney	0.6
Hepatocellular	0.3
Ovarian	0.3
Soft Tissue Sarcoma	0.1
Non-Hodgkin's Lymphoma	0.1
Thyroid	0.1
Prostate	0.1
Melanoma	0.1
Bladder	0.1
Testicular Germ Cell	0.0

Tissue of Origin® Overview

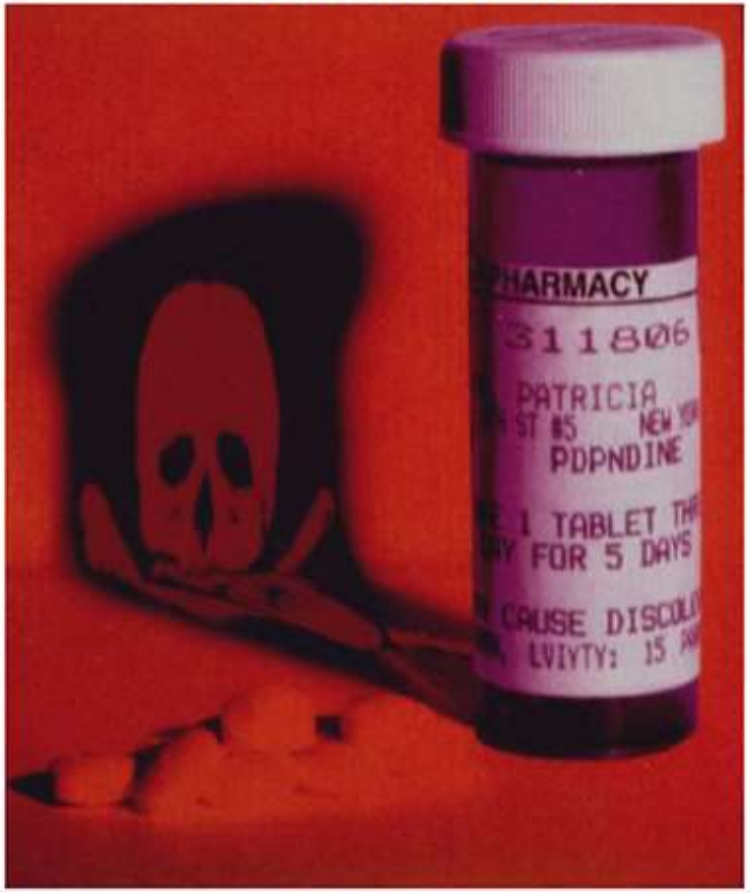
- The Tissue of Origin reports the most likely tissue of origin from 15 of the most common tumor types, representing 58 morphologies.
- 2000 genes, covering 15 tumors types and 90% of all solid tumors[1]
- Extensive analytical and clinical validation.
- Statistically significant improvement in accuracy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

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 22nd century.

Personalized Medicine: Could the dream become a nightmare?

Betty's story gone wrong

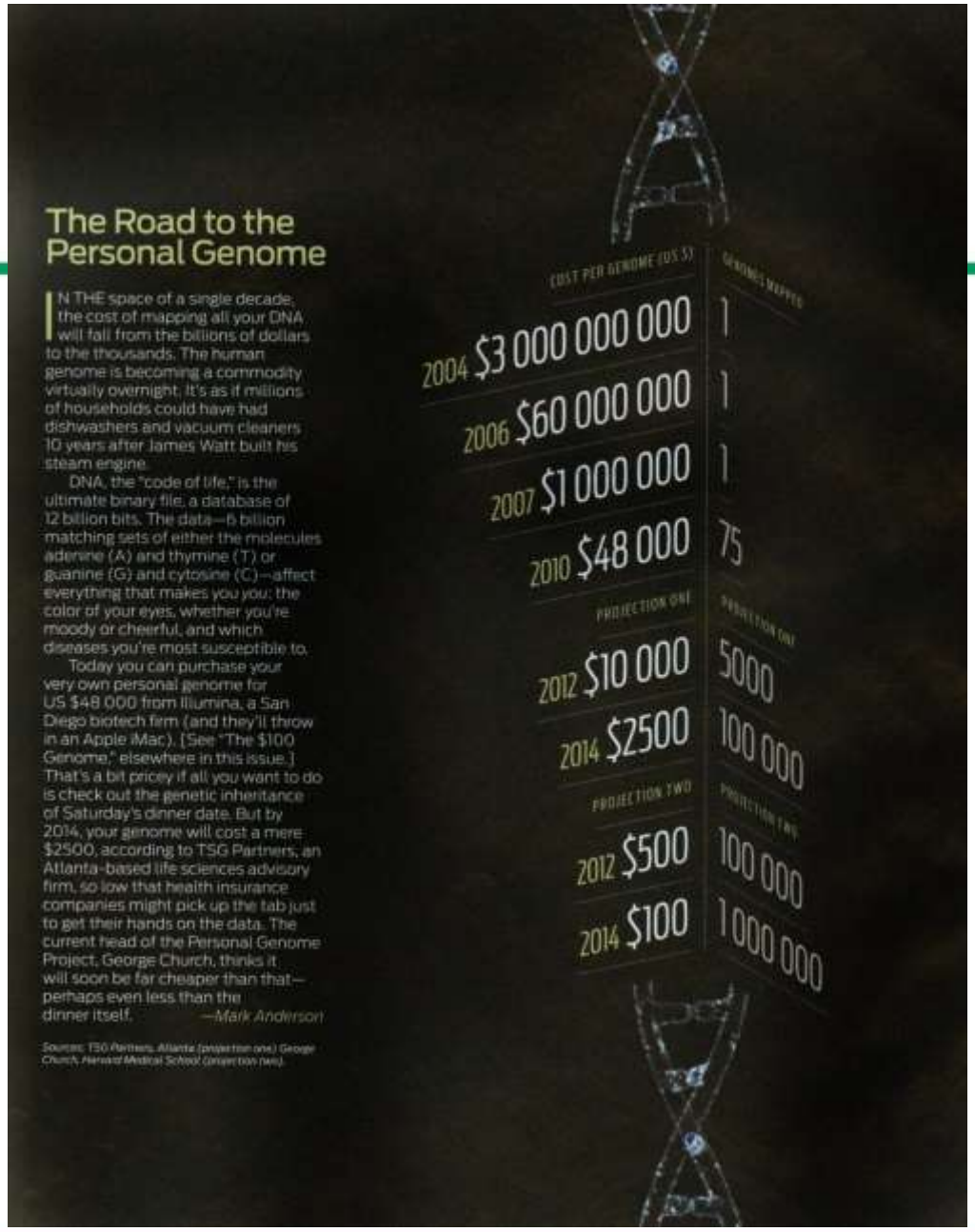
- Betty never learns about her family history, educational efforts for the public and health care providers were defunded, community efforts never got off the ground, and Betty's PA and MD thought genetics was irrelevant to practice.
- Betty hears about genome sequencing, but after seeing her brother 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.

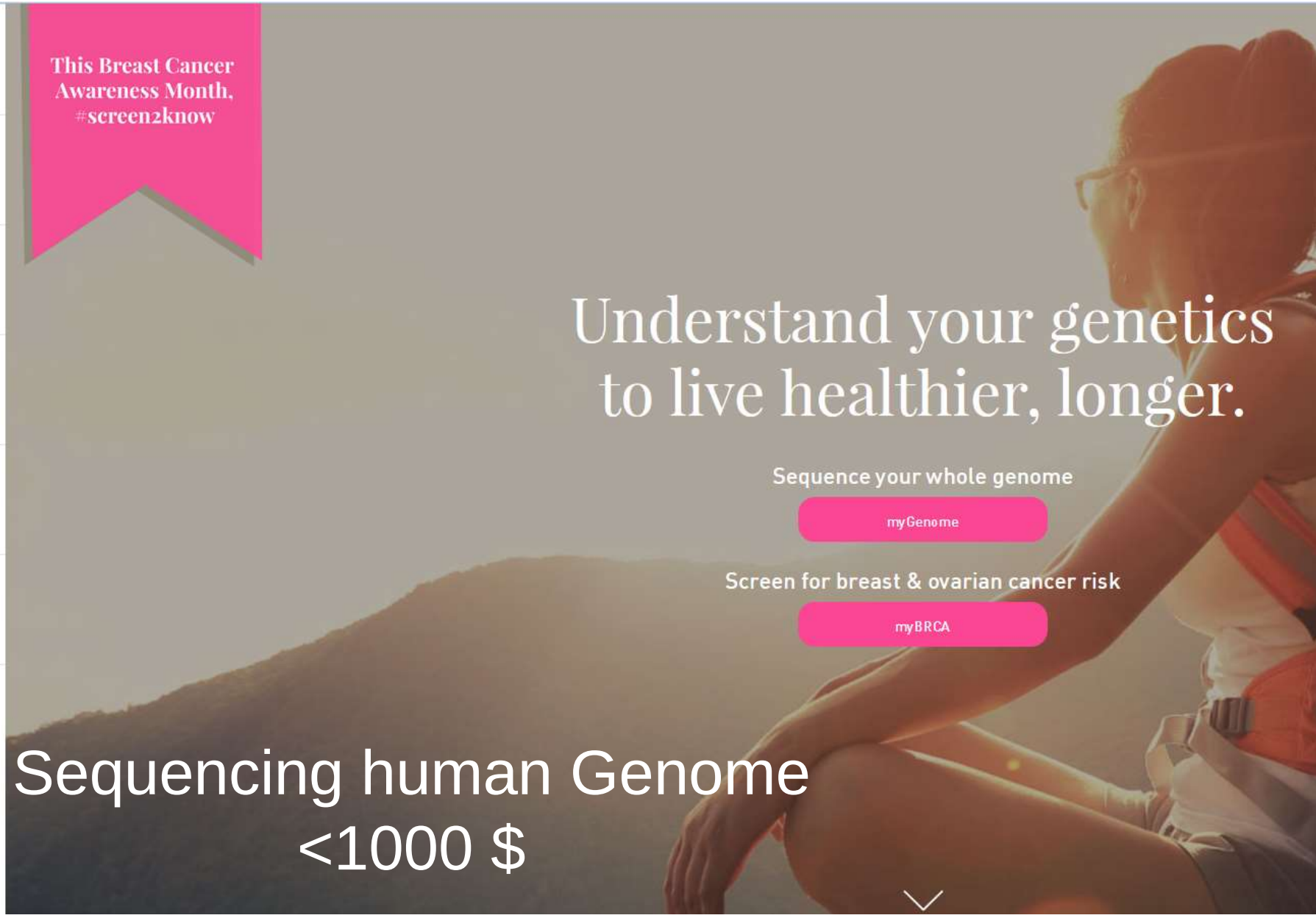
Betty's story gone really wrong

- 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.

“Personal Genome”

> 50 companies
World-wide

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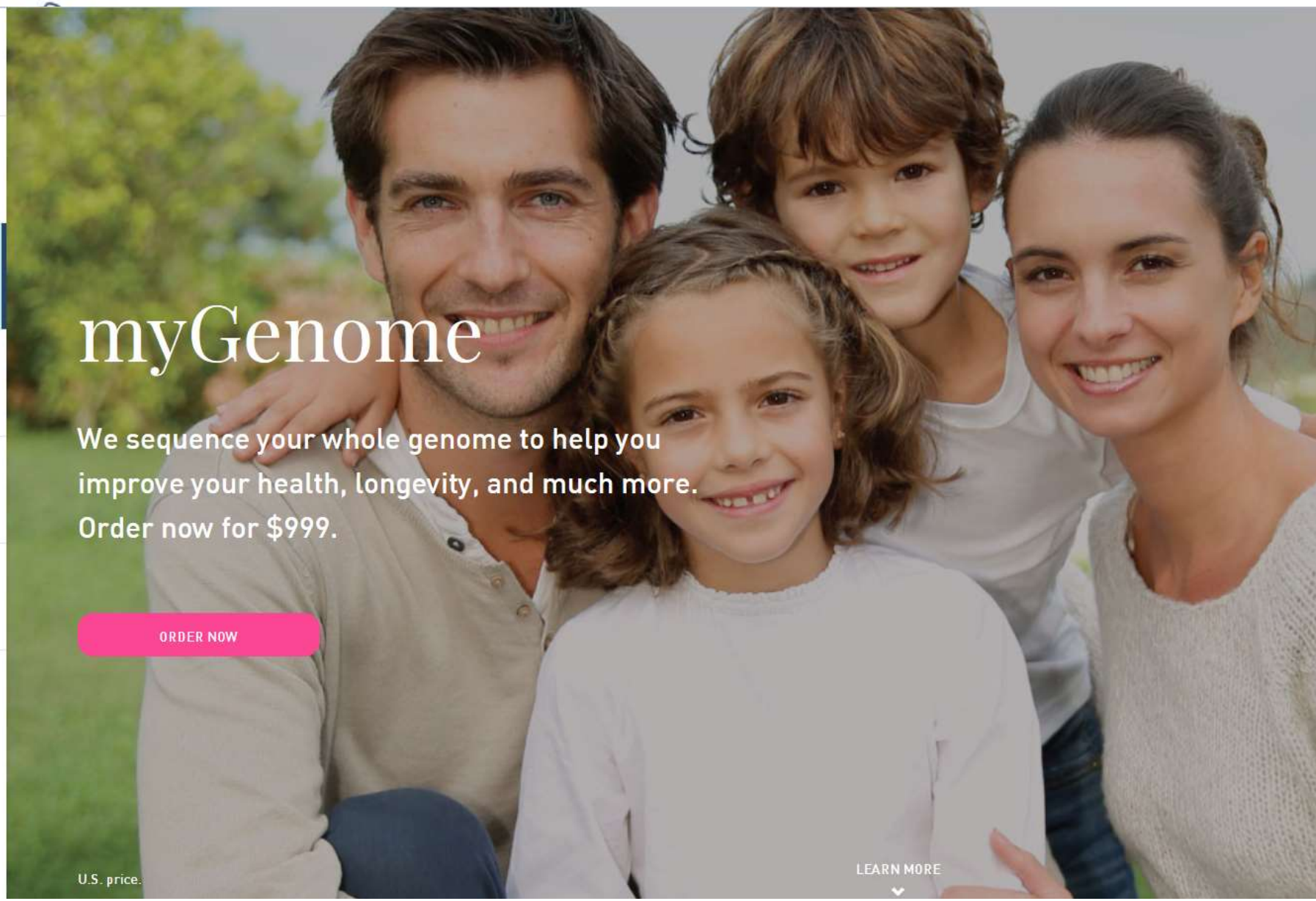
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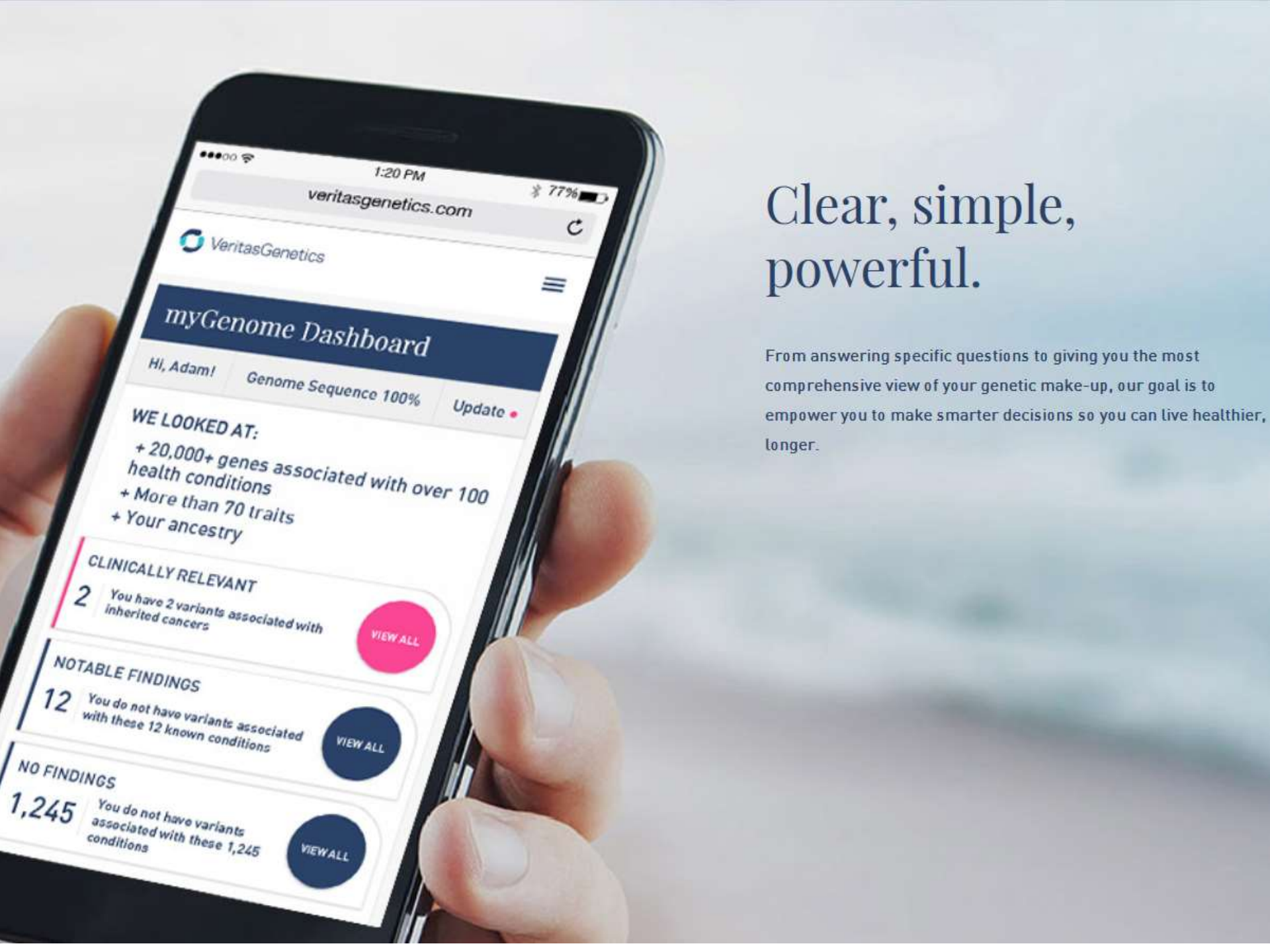


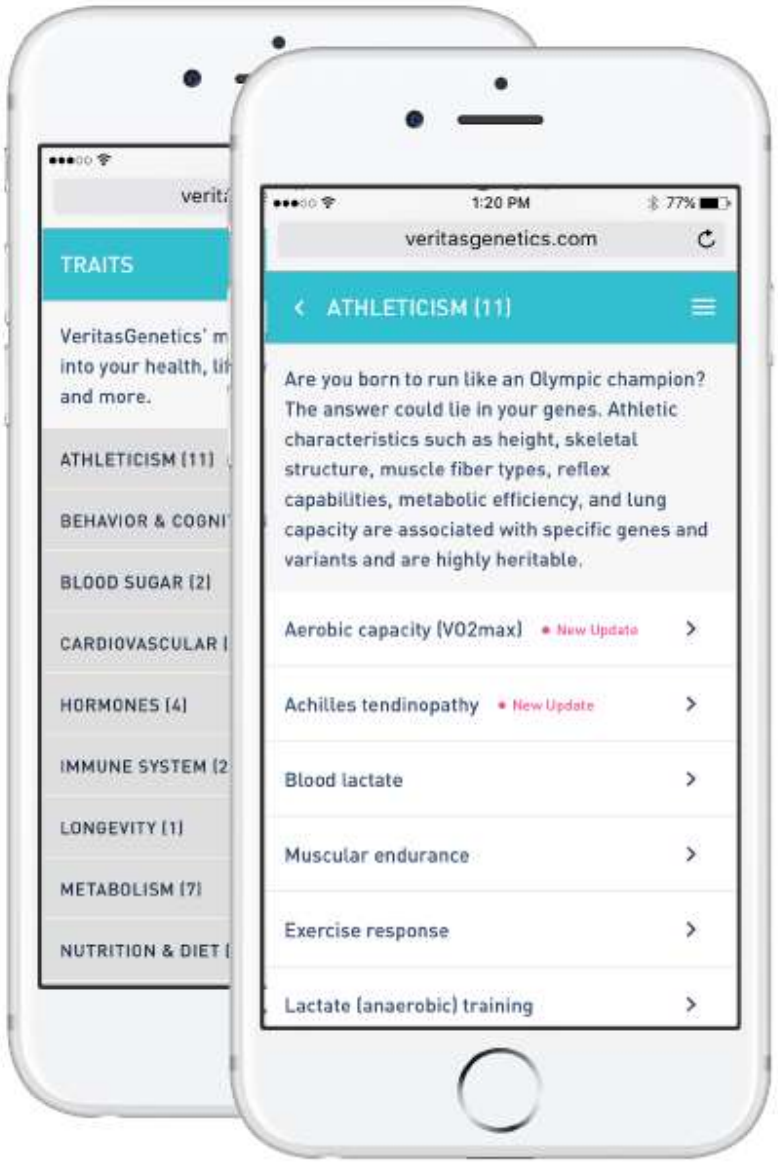
Clear, simple, powerful.

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.

Understand your disease risks

myGenome provides insights relevant to you from over 100 inherited diseases in categories including:

- Inherited cancers (incl. breast cancer, ovarian cancer, colorectal cancer)
- Cardiovascular diseases (incl. hypertension, coronary artery disease)
- Immune disorders (incl. rheumatoid arthritis, Crohn's disease)
- Endocrine & metabolic syndromes (incl. diabetes, obesity)
- Neurological disorders (incl. Alzheimer's, Parkinson's, Dementia, Autism)
- Mental & mood disorders (incl. schizophrenia, anxiety, depression)
- Organ health (incl. cataract, glaucoma)
- Reproductive / Carrier (incl. conditions relevant to family planning)



Insights to live healthier, longer

We look at traits related to

- Athleticism (incl. aerobic capacity (VO2max), muscle strength)
- Behavior & Cognition (incl. memory, snacking behavior)
- Blood sugar (incl. blood sugar, fasting glucose)
- Cardiovascular (incl. blood pressure, HDL/LDL cholesterol)
- Hormones (incl. menopause age, testosterone levels)
- Immune System (incl. IL6 levels, norovirus resistance)
- Longevity (incl. telomere length)
- Metabolism (incl. diet response, weight gain, weight response to exercise)
- Nutrition & Diet (incl. lactose intolerance, omega-6, omega-3)
- Physical Appearance (incl. BMI, body weight, childhood growth)
- Sensory Perception (incl. nearsightedness (myopia), pain sensitivity)
- Substance Reaction (incl. alcohol flush reaction, caffeine metabolism)

Family plan, with confidence

myGenome provides you with insights about your family history and inherited diseases. Learn if you are a carrier of a genetic condition and what you could pass on to your children. In addition, our genetic counselors will help you understand your results.