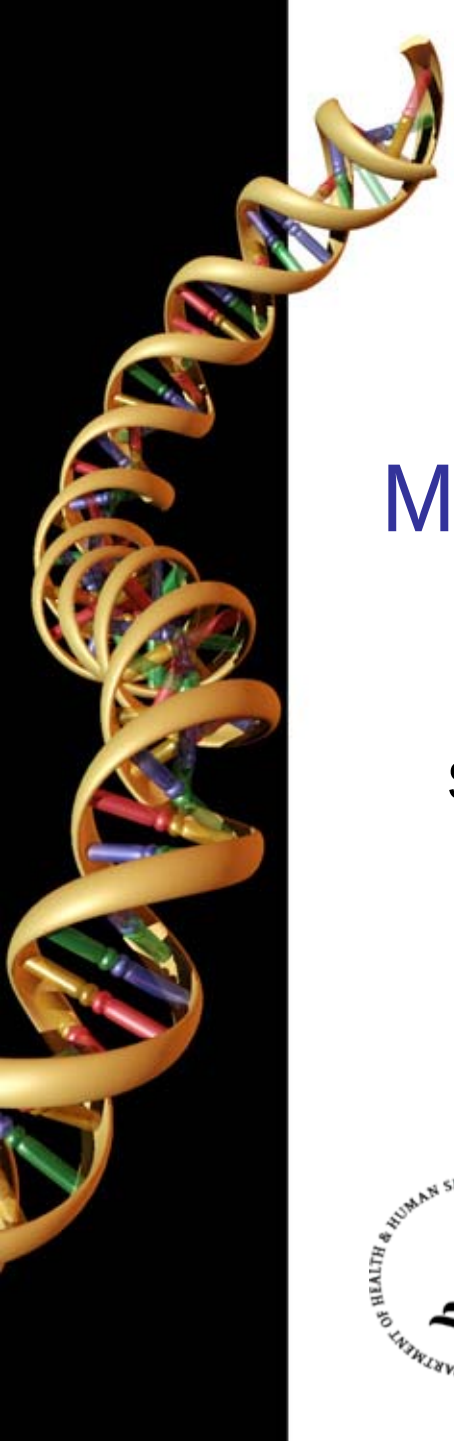
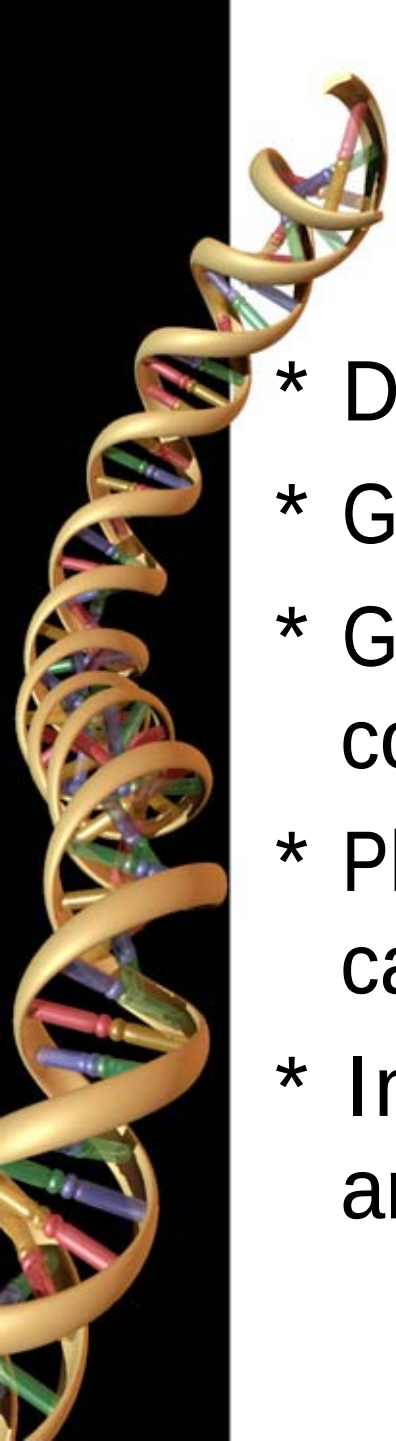


The Impact of Genomics on Medical Practice and Clinical Trials

Christopher P. Austin. M.D.
Senior Advisor to the Director for Translational Research
National Human Genome Research Institute
National Institutes of Health

NIH IPPCR Course
December 18, 2007



Outline of Talk

* Definitions
* Genetic variation
* GWAS: genetic variation causing common diseases
* Pharmacogenomics: genetic variation causing differential response to Rx
* Impact of genetics on in clinical trials and drug development

When can we expect the impact from the HGP to be realized?

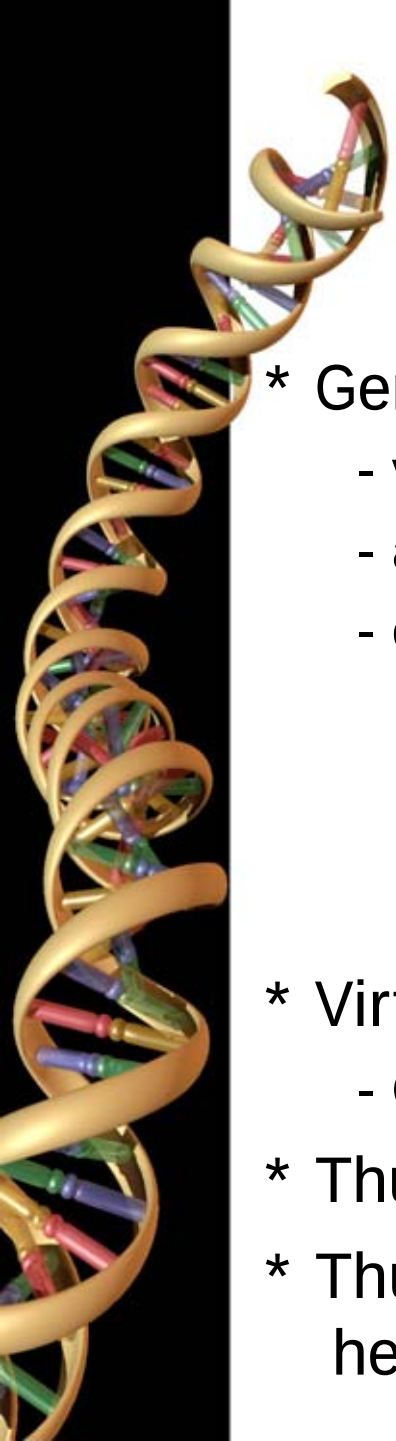
Improved understanding of biology, disease, and evolution:
0-3 years

New diagnostic tests for common diseases:
2-5 years

New therapeutics based on genomic knowledge:
4-10 years

Genetic vs Genomic Disease

* Genetic disease = Single gene causes
  - Sequence variant *causes* disease
  - e.g., Huntington's disease, cystic fibrosis
  - Known in medical practice for >100 yrs
  - Rare (<200,000 U.S. prevalence)
* Most people not directly affected
* Thus, genetics has traditionally played only a "niche" role in health care and clinical research



Genetic vs Genomic Disease

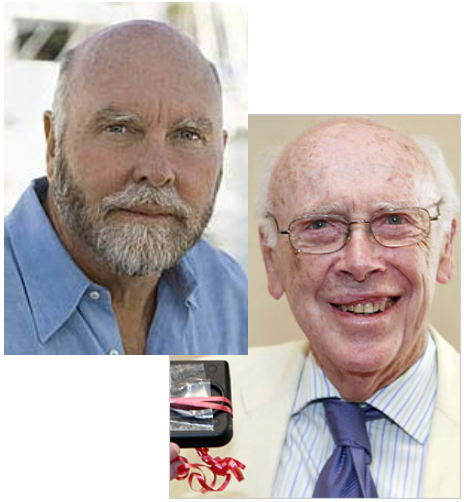
* Genomic Disease: Multiple genes change risk
  - variant *predisposes to* disease (Δ risk 5-50%)
  - a.k.a., ‘polygenic’, ‘common’, ‘complex’
  - e.g., hypertension, obesity, Alzheimer’s disease
    * ApoE (Alzheimer’s disease)
    * BRCA1 & 2 (breast & ovarian cancer)
    * Factor V (DVT)
    * PPARγ (Type 2 diabetes)
* Virtually all diseases have heritable component
  - Other component is environmental (e.g., diet, smoking)
* Thus, most people directly affected
* Thus, genetics is playing an increasingly large role in health care and clinical research

Stages of Deciphering the Genome

1991-2000: First Draft

2001: Working Draft

April 15, 2003: "Finished" reference sequence



The Diploid Genome Sequence of an Individual Human

Samuel Levy[1*], Granger Sutton[1], Pauline C. Ng[1], Lars Feuk[2], Aaron L. Halpern[1], Brian P. Walenz[1], Nelson Axelrod[1], Jiaqi Huang[1], Ewen F. Kirkness[1], Gennady Denisov[1], Yuan Lin[1], Jeffrey R. MacDonald[2], Andy Wing Chun Pang[2], Mary Shago[2], Timothy B. Stockwell[1], Alexia Tsiamouri[1], Vineet Bafna[3], Vikas Bansal[3], Saul A. Kravitz[1], Dana A. Busam[1], Karen Y. Beeson[1], Tina C. McIntosh[1], Karin A. Remington[1], Josep F. Abril[4], John Gill[1], Jon Borman[1], Yu-Hui Rogers[1], Marvin E. Frazier[1], Stephen W. Scherer[2], Robert L. Strausberg[1], J. Craig Venter[1]

2007 - : Defining genome variation in individuals

2002-2007: Defining genome variation in populations

About the HapMap

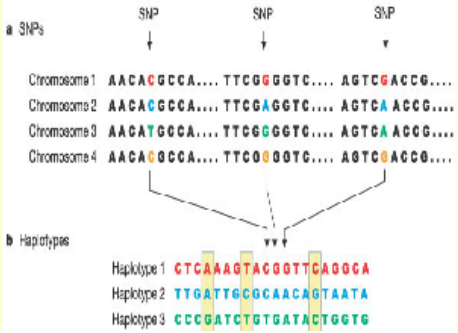
What is the HapMap?
Origins of Haplotypes
Health Benefits
Populations Sampled
Ethical Issues
Consent Forms
Community Advisory Groups(CAG)
Data Release Policy
Guidelines For Data Use
Guidelines For Referring to HapMap Populations

Project Information

About the Project
HapMap Publications
HapMap Tutorial
HapMap Mailing List
HapMap Project Participants
HapMap Mirror Site in Japan

Useful Links

HapMap Project Press Release
NHGRI HapMap Page
NCBI Variation Database (dbSNP)
Japanese SNP Database (JSNP)



What Is the HapMap?

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. The International HapMap Project is not using the information in the HapMap to establish connections between particular genetic variants and diseases. Rather, the Project is designed to provide 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.

The DNA in our cells contains long chains of four chemical building blocks -- adenine, thymine, cytosine, and guanine, abbreviated A, T, C, and G. More than 6 billion of these chemical bases, strung together in 23 pairs of chromosomes, exist in a human cell. (See http://www.dnaftb.org/dnaftb/ for basic information about genetics.) These genetic sequences contain information that influences our physical traits, our likelihood of suffering from disease, and the responses of our bodies to substances that we encounter in the environment.

The genetic sequences of different people are remarkably similar. When the chromosomes of two humans are compared, their DNA sequences can be identical for hundreds of bases. But at about one in every 1,200 bases, on average, the sequences will differ (Figure 1). One person might have an A at that location, while another person has a G, or a person might have extra bases at a given location or a missing segment of DNA. Each distinct "spelling" of a chromosomal region is called an allele, and a collection of alleles in a person's chromosomes is known as a genotype.

Differences in individual bases are by far the most common type of genetic variation. These genetic differences are known as single nucleotide polymorphisms, or SNPs (pronounced "snips"). By identifying most of the approximately 10 million SNPs estimated to occur commonly in the human genome, the International HapMap Project is identifying the basis for a large fraction of the genetic diversity in the human species.

Figure 1: When DNA sequences on a part of chromosome 7 from two random individuals are compared, two single nucleotide polymorphisms (SNPs) occur in about 2,200 nucleotides.

For geneticists, SNPs act as markers to locate genes in DNA sequences. Say that a spelling change in a gene increases the risk of suffering from high blood pressure, but researchers do not know where in our chromosomes that gene is located. They could compare the SNPs in people who have high blood pressure with the SNPs of people who do not. If a particular SNP is more common among people with hypertension, that SNP could be used as a pointer to locate and identify the gene involved in the disease.

However, testing all of the 10 million common SNPs in a person's chromosomes would be extremely expensive. The development of the HapMap will enable geneticists to take advantage of how SNPs and other genetic variants are organized on chromosomes. Genetic variants that are near each other tend to be inherited together. For example, all of the people who have an A rather than a G at a particular location in a chromosome can have identical genetic variants at other SNPs in the chromosomal region surrounding the A. These regions of linked variants are known as haplotypes (Figure 2).

In many parts of our chromosomes, just a handful of haplotypes are found in humans. [See The Origins of Haplotypes.] In a given population, 55 percent of people may have one version of a haplotype, 30 percent may have another, 8 percent may have a third, and the rest may have a variety of less common haplotypes. The International HapMap Project is identifying these common haplotypes in four populations from different parts of the world. It also is identifying "tag" SNPs that uniquely identify these haplotypes. By testing an individual's tag SNPs (a process known as genotyping), researchers will be able to identify the collection of haplotypes in a person's DNA. The number of tag SNPs that contain most of the information about the patterns of genetic variation is estimated to be about 300,000 to 600,000, which is far fewer than the 10 million common SNPs.

Genome-Wide Association Studies (GWAS)

* Method for interrogating all 10 million variable points across the human genome
* Variation inherited in groups, or blocks, so not all 10 million points have to be tested
* Blocks are shorter (so need to test more points) the less closely people are related
* Technology now allows studies in unrelated persons, assuming ~10,000 base pair lengths in common (300,000 – 500,000 markers)

2007: The Year of GWA Studies?

Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

The W

Sequence variants in the autophagy gene *IRGM* and multiple other replicating loci contribute to Crohn's disease susce

Miles Par
Mark Tre
Roland G

We followed up on 37 SNPs from 31 distinct loci, associated at $P < 10^{-5}$ on initial analysis of the WTCCC data set. Support for some of these markers diminished in the final WTCCC analysis after extensive data filtering[5]. We selected two markers for each locus where low linkage disequilibrium (LD) between associated SNPs in areas of unbroken LD suggested distinct causal variants. We genotyped SNPs in a new panel of 1,182 individuals of European descent with

Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes

John A Todd[1], Neil M Walker[1,9], Jason D Cooper[1,9], Deborah J Smyth[1,9], Kate Downes[1], Vincent Plagnol[1], Rebecca Bailey[1], Sergey Nejentsev[1], Sarah F Field[1], Felicity Payne[1], Christopher E Lowe[1], Jeffrey S Szeszko[1], Jason P Hafler[1], Lauren Zeitels[1], Jennie H M Yang[1], Adrian Vella[1,8], Sarah Nutland[1], Helen E Stevens[1], Helen Schuilenburg[1], Gillian Coleman[1], Meeta Maisuria[1], William Meadows[1], Luc J Smink[1], Barry Healy[1], Oliver S Burren[1], Alex A C Lam[1], Nigel R Ovington[1], James Allen[1], Ellen Adlem[1], Hin-Tak Leung[1], Chris Wallace[2], Joanna M M Howson[1], Cristian Guja[3], Constantin Ionescu-Tîrgovişte[3], Genetics of Type 1 Diabetes in Finland[4], Matthew J Simmonds[5], Joanne M Heward[5], Stephen C L Gough[5], The Wellcome Trust Case Control Consortium[6], David B Dunger[7], Linda S Wicker[1] & David G Clayton[1]

2007: The Year of GWA Studies?

Genome-wide association study identifies novel breast cancer susceptibility loci

Douglas
Dennis
Shahana
Christop
Suleepo
Hui-Chu
Sheila S
Børge G.
Jolanta
Daehee

A genome-wide association study identifies alleles in *FGFR2* associated with risk of sporadic postmenopausal breast cancer

David
Sholor
Nilanja
Saundı
Richar
Gilles

Common variants on chromosomes 2q35 and 16q12 confer susceptibility to estrogen receptor–positive breast cancer

Simon N Stacey[1], Andrei Manolescu[1], Patrick Sulem[1], Thorunn Rafnar[1], Julius Gudmundsson[1], Sigurjon A Gudjonsson[1], Gisli Masson[1], Margret Jakobsdottir[1], Steinunn Thorlacius[1], Agnar Helgason[1], Katja K Aben[2,3], Luc J Strobbe[4], Marjo T Albers-Akkers[5], Dorine W Swinkels[3], Brian E Henderson[6], Laurence N Kolonel[7], Loic Le Marchand[7], Esther Millastre[8], Raquel Andres[8], Javier Godino[9], Maria Dolores Garcia-Prats[10], Eduardo Polo[11], Alejandro Tres[8], Magali Mouy[1], Jona Saemundsdottir[1], Valgerdur M Backman[1], Larus Gudmundsson[1], Kristleifur Kristjansson[1], Jon T Bergthorsson[1], Jelena Kostic[1], Michael L Frigge[1], Frank Geller[1], Daniel Gudbjartsson[1], Helgi Sigurdsson[12], Thora Jonsdottir[12],

2007: The Year of GWA Studies?

A Common Allele on Chromosome 9 Associated with Coronary Heart Disease

Ruth McPherson,[1*†] Alexander Pertsemlidis,[2*] Nihan Kavaslar,[1] Alexandre Stewart,[1] Robert Roberts,[1] David R. Cox,[3] David A. Hinds,[3] Len A. Pennacchio,[4,5] Anne Tybjaerg-Hansen,[6] Aaron R. Folsom,[7] Eric Boerwinkle,[8] Helen H. Hobbs,[2,9] Jonathan C. Cohen[2,10†]

A Common Variant on Chromosome 9p21 Affects the Risk of Myocardial Infarction

Anna Helgadottir,[1*] Gudmar Thorleifsson,[1*] Andrei Manolescu,[1*] Solveig Gretarsdottir,[1] Thorarinn Blondal,[1] Aslaug Jonasdottir,[1] Adalbjorg Jonasdottir,[1] Asgeir Sigurdsson,[1] Adam Baker,[1] Arnar Palsson,[1] Gisli Masson,[1] Daniel F. Gudbjartsson,[1] Kristinn P. Magnusson,[1] Karl Andersen,[2] Allan I. Levey,[3] Valgerdur M. Backman,[1] Sigurborg Matthiasdottir,[1] Thorbjorg Jonsdottir,[1] Stefan Palsson,[1] Helga Einarsdottir,[1] Steinunn Gunnarsdottir,[1]

Sciencexpress, 3May2007

2007: The Year of GWA Studies?

A Genome-Wide Association Study of Type 2 Diabetes in Finns Detects Multiple Susceptibility Variants

Laura
Willi
Anne
Tianl
Andr
Craig
Thom
Gonç
Jaakk

Genome-Wide Association Analysis Identifies Loci for Type 2 Diabetes and Triglyceride Levels

Diab
and

Replication of Genome-Wide Association Signals in UK Samples Reveals Risk Loci for Type 2 Diabetes

Eleftheria Zeggini,[1,2]* Michael N. Weedon,[3,4]* Cecilia M. Lindgren,[1,2]* Timothy M. Frayling,[3,4]* Katherine S. Elliott,[2] Hana Lango,[3,4] Nicholas J. Timpson,[2,5] John R. B. Perry,[3,4]

Sciencexpress, 26Apr2007

2007: The Year of GWA Studies?

Genome-wide association study of prostate cancer identifies a second risk locus at 8q24

Meredith Yeager[1,2], Nick Orr[3], Richard B Hayes[2], Kevin B Jacobs[4], Peter Kraft[5], Sholom Wacholder[2], Mark J Minichiello[6], Paul Fearnhead[7], Kai Yu[2], Nilanjan Chatterjee[2], Zhaoming Wang[1,2], Robert Welch[1,2], Brian J Staats[1,2], Eugenia E Calle[8], Heather Spencer Feigelson[8], Michael J Thun[8], Carmen Rodriguez[8],

Multiple regions within 8q24 independently affect risk for prostate cancer

Christopher A Haiman[1], Nick Patterson[2], Matthew L Freedman[2,3], Simon R Myers[2], Malcolm C Pike[1], Alicja Waliszewska[2,4,5], Julie Neubauer[2,4], Arti Tandon[2,4], Christine Schirmer[2,4], Gavin J McDonald[2,4],

Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24

Julius Gudmundsson[1,17], Patrick Sulem[1,17], Andrei Manolescu[1,17], Laufey T Amundadottir[1,17], Daniel Gudbjartsson[1], Agnar Helgason[1], Thorunn Rafnar[1], Jon T Bergthorsson[1], Bjarni A Agnarsson[2], Adam Baker[1], Asgeir Sigurdsson[1], Kristrun R Benediktsdottir[2], Margret Jakobsdottir[1], Jianfeng Xu[3], Thorarinn Blondal[1], Jelena Kostic[1], Jielin Sun[3], Shyamali Ghosh[1], Simon N Stacey[1], Magali Mouy[1], Jona Saemundsdottir[1], Valgerdur M Backman[1], Kristleifur Kristjansson[1], Alejandro Tres[4,7], Alan W Partin[5], Marjo T Albers-Akkers[6], Javier Godino-Ivan Marcos[7], Patrick C Walsh[5], Dorine W Swinkels[8], Sebastian Navarrete[9], Sarah D Isaacs[5], Katja K Aben[10], Theresa Graif[11], John Cashy[11], Manuel Ruiz-Echarri[4],

***Nature Genetics*, 1Apr2007**

2007: The Year of GWA Studies?

A Genome-Wide Association Study Identifies *IL23R* as an Inflammatory Bowel Disease Gene

26Oct2006

Richa
Mark
Them
Lisa
M. M

HTRA1 Promoter Polymorphism in Wet Age-Related Macular Degeneration

19Oct2006

Andrew DeWan,[1] Mugen Liu,[2*] Stephen Hartman,[3*] Samuel Shao-Min Zhang,[2*] David T. L. Liu,[4]
Conni
Colin

Complement Factor H Polymorphism in Age-Related Macular Degeneration

10Mar2005

Robert J. Klein,[1] Caroline Zeiss,[2*] Emily Y. Chew,[3*]

Sciencexpress

anonymized

copy number variants

CEL files

HuGENet

clustering algorithms

Q-Q plots

P3G

inversion

gene desert s

IMPUTATION

minor allele frequency

population stratification

Hardy-Weinberg deviation

epistasis

whole genome amplification

dbGaP

calling algorithm s

ancestral markers

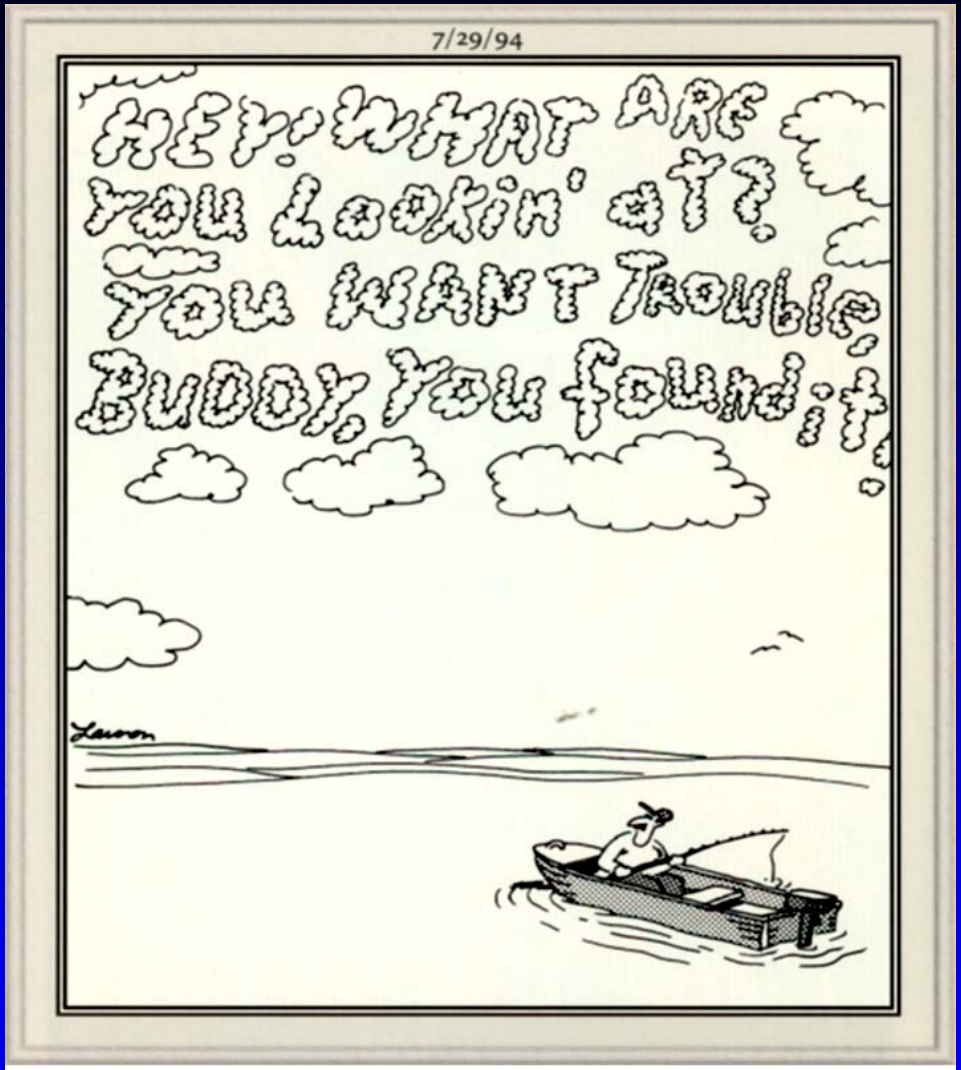
linkage disequilibrium

Bayes Factors

HapMap

gene-environment interaction

admixture



Understanding only German, Fritz was unaware that the clouds were becoming threatening.

Larson, G. *The Complete Far Side*. 2003.

FOUNDATION FOR THE National Institutes of Health

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GAIN Program

GAIN HOME PAGE

- Overview
- Committees
- Partnerships
- Initial Studies
- Policies
- Instructions for Applicants
- Genotyping & Analysis
- Analysis Workshops
- Accessing GAIN Data
- Press Releases
- GAIN Glossary
- GAIN FAQs

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GENETIC ASSOCIATION INFORMATION NETWORK (GAIN)

The Genetic Association Information Network (GAIN) is a public-private partnership of the Foundation for the National Institutes of Health, Inc. (FNIH) that currently involves the National Institutes of Health (NIH), Pfizer, Affymetrix, Perlegen Sciences, Abbott, and the Eli and Edythe Broad Institute (of MIT and Harvard University). GAIN is taking the next step in the search to understand the genetic factors influencing risk for complex diseases. Through a series of whole genome association studies, using samples from existing case-control studies of patients with common diseases, GAIN will contribute to the identification of genetic pathways that make us more susceptible to these diseases and thus facilitate discovery of new molecular targets for prevention, diagnosis, and treatment.

GAIN aims to release data as broadly and rapidly as possible, with equal opportunity for access by all potential users. To promote the responsible use of the GAIN Project Datasets, investigators, and their institutions, seeking access to genotypic or phenotypic data will submit a Data Access Request Form and Data Use Certification specifying their intended use of the data and acknowledging their agreement with the terms and conditions described. All investigators, including Collaborating Study Investigators, GAIN Partners, and others, will access the GAIN Project Datasets through the same mechanism.

FNIH is actively seeking additional partners to participate in GAIN Partnerships including corporations, private foundations, and advocacy groups.

On October 10, 2006, following a rigorous five-month selection process, the FNIH's Board of Directors announced that the first six studies in common diseases have been chosen for genome-wide association analysis at the recommendation of the GAIN Steering Committee. This first phase of GAIN will genotype 18,000 samples from studies in **schizophrenia, bipolar disorder, diabetic nephropathy, ADHD, major depression, and psoriasis** (see Initial Studies). The genotype and associated deidentified phenotype information from each of the six studies (the GAIN Project Datasets) will be deposited throughout 2007 in a database managed by the National Center for Biotechnology Information (NCBI) for access by the research community.

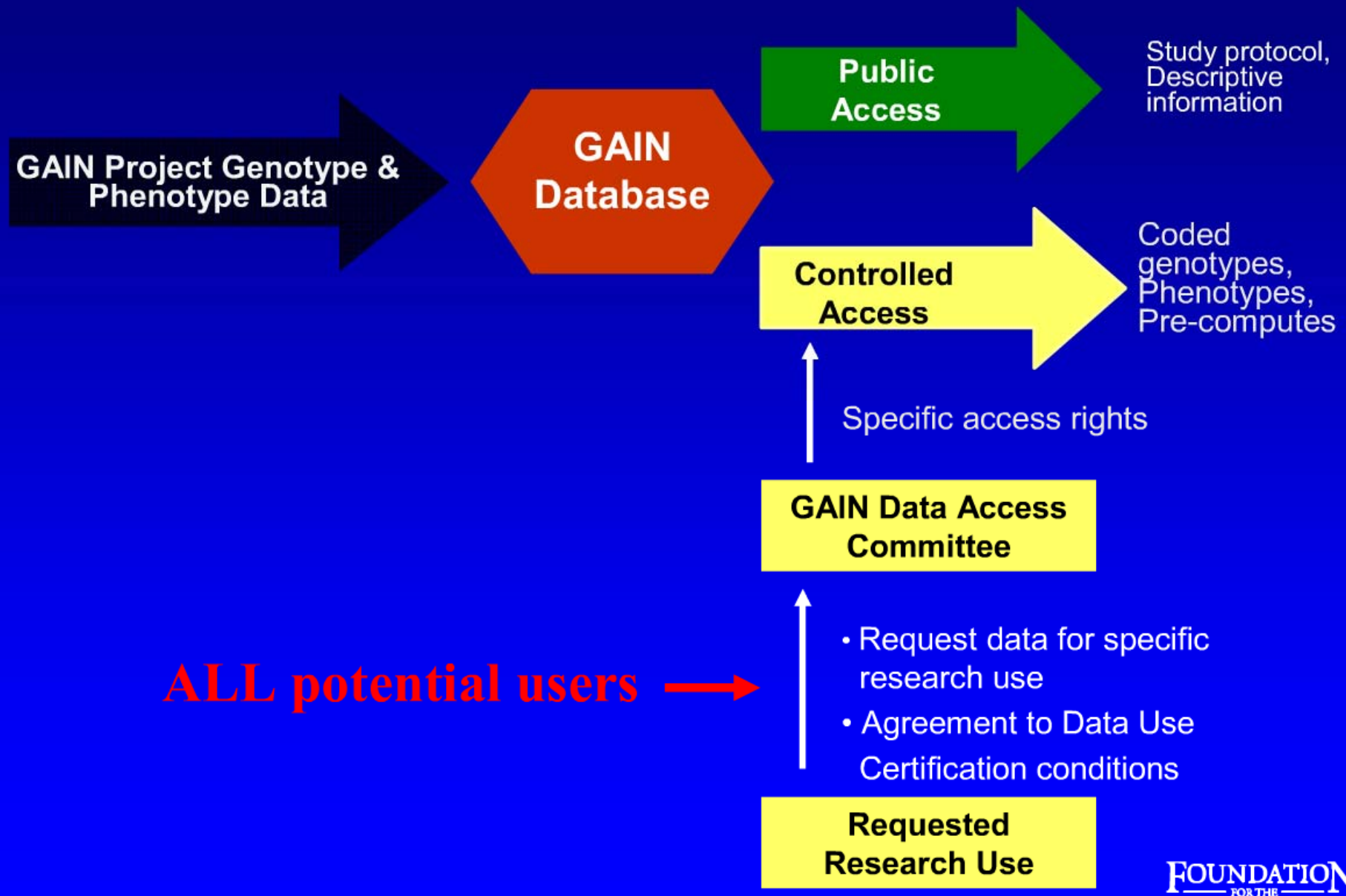
- Slide Show Presentation

GAIN First Round Awards

Disease	Principal Investigator/ Institution	Approximate Number of Samples
ADHD	Faraone SUNY Upstate	2900
Diabetic Nephropathy	Warram Joslin Institute for Diabetes	1800
Major Depression	Sullivan UNC	3850
Psoriasis	Abecasis U. Michigan	3000
Schizophrenia	Gejman Northwestern	5500
Bipolar Disease	Kelsoe UCSD	1600

FOUNDATION FOR THE National Institutes of Health

GAIN Data Access Overview



FOUNDATION FOR THE National Institutes of Health

Identifiers Excluded from GAIN Datasets

- Names
- Phone numbers
- Fax numbers
- Electronic mail addresses
- Social security numbers
- Medical record numbers
- Health plan beneficiary numbers
- Account numbers
- Certificate/license numbers
- Vehicle identifiers and serial numbers, including license plate numbers
- Device identifiers and serial numbers
- Web universal resource locators (URLs)
- Internet protocol (IP) address numbers
- Biometric identifiers, including finger and voice prints
- Full face photographic images and any comparable images
- Birth date and month
- Geographic subdivision, dates (other than complete birth dates), and "other" identifiers (e.g., outliers) MAY be permissible if relevant to the science

NATIONAL INSTITUTES OF HEALTH

Genes, Environment and Health Initiative (GEI)

Determining Genetic and Environmental Roots of Common Diseases

- GEI Home Page
- Genetics Program
- Exposure Biology Program
- Funding Opportunities
- New Training Grants

The Genes, Environment and Health Initiative (GEI)

On February 8, 2006 Health and Human Services Secretary Michael O. Leavitt announced that the President's 2007 budget proposal includes $40 million for the National Institutes of Health to plan and implement a Genes and Environment Initiative (GEI). If approved by Congress, federal funding will begin in fiscal year 2007 and continue for four years, with $26 million annually going to genetic analysis and $14 million annually designated for the development of new tools to measure environmental exposures that affect health.

The GEI will have two main components:

- The Genetics Program is a pipeline for analyzing genetic variation in groups of patients with specific illnesses.
- The Exposure Biology Program is an environmental technology development program to produce and validate new methods for monitoring environmental exposures that interact with a genetic variation to result in human diseases.

The Genetics Program will be spearheaded by NIH's National Human Genome Research Institute (NHGRI). The genetic analysis would focus on the alternative spellings – called single nucleotide

http://genesandenvironment.nih.gov/

Genes, Environment and Health Initiative (GEI)

* NIH-wide initiative of the Secretary, HHS
* Aims to accelerate understanding of genetic and environmental contributions to health and disease
* Two components:
  - Genetic analyses of case-control studies of common disease ($26M per year for four years)
  - Development of innovative technologies to measure environmental exposures, diet, and physical activity ($14M per year for four years)

NCBI

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By Studies | By Diseases | Advanced Search

Study	Embargo Release	Variables	Documents	Participants	Type of Study
Collaborative Association Study of Psoriasis	August 13, 2008	35	3	2875	Case-control
Framingham SHARe	October 19, 2008	13183	123	17354	Community-based, longitudinal, family-based cohort
Genotyping the 270 HapMap samples for GAIN by Broad		-	-	-	Parent-offspring trios
Genotyping the 270 HapMap samples for GAIN by Perlegen		-	-	-	Parent-offspring trios
International Multi-Center ADHD Genetics Project	March 26, 2008	438	12	2835	Parent-offspring trios
Ischemic Stroke Genetics Study (ISGS)		74	5	485	Case-control
LEAPS		-	-	1550	Case-control
Linking Genome-Wide Association Study of Schizophrenia	August 25, 2008	-	-	5188	Case-control
Major Depression: Stage 1 Genomewide Association in Population-Based Samples	July 15, 2008	228	3	3741	Case-control
NEI Age-Related Eye Disease Study (AREDS)	June 11, 2007	174	37	600	Case-control
NINDS Parkinson's Disease	October 12, 2007	109	4	535	Case-control
NINDS Parkinsonism Study	October 12, 2007	43	5	1283	Case-set
NINDS Repository Cerebrovascular Disease/Stroke Study		40	4	870	Case-set
NINDS Repository Neurologically Normal Control Collection	October 12, 2007	66	3	2723	Control-set
Search for Susceptibility Genes for Diabetic Nephropathy in Type 1 Diabetes	July 09, 2008	54	26	1825	Case-control
Whole Genome Association Study of Bipolar Disorder	August 25, 2008	-	-	-	Case-control

Address http://www.genetests.org/servlet/access?prg=j&db=genetests&site=gt&id=8888891&fcn=c&qry=3315&res=&key=YBrqqpuFe3bfw&show_flag=c

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GeneTests

Lung Cancer

Select all clinical laboratories

Laboratories offering clinical testing:	Sequencing of select exons	Targeted mutation analysis	Deletion/duplication analysis	Prenatal diagnosis	Clinical confirmation of mutations identified in a research lab
Center for Human Genetics Bioscientia GmbH Ingelheim, Germany Jochen Decker, MD, PhD; Daniela Steinberger, MD, PhD			•	•	
Duke University Kelley Laboratory Durham, NC Michael J Kelley, MD		•			•
Fox Chase Cancer Center Clinical Molecular Genetics Laboratory Philadelphia, PA Andrew K Godwin, PhD; Betsy A Bove, PhD	•				•

Select all clinical laboratories Go to research laboratories

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National Human Genome Research Institute, NIH

Sponsoring Institution
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Seattle, Washington

http://www.genetests.org

Address http://www.pharmgkb.org/

PharmGKB

The Pharmacogenetics and Pharmacogenomics Knowledge Base

Search PharmGKB: ? Go

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The PharmGKB is an integrated resource about how variation in human genes leads to variation in our response to drugs. MORE ...

Browse:

- Genes with PharmGKB Primary Data
- Genes with Genotype Data
- Genes with Phenotype Data
- Drugs with PharmGKB Primary Data
- Diseases with PharmGKB Primary Data
- All Pathways

MORE ...

Search PharmGKB: ? Go

e.g. a gene ("ABCB1"), drug ("irinotecan") or disease ("neoplasm")

Simple Queries get customized results for top 5 most common questions

Sample query The dataset for gene ABCB1 or drug irinotecan

Genomic data, molecular and cellular phenotype data, and clinical phenotype data are accepted from the scientific community at large. These data are then organized and the relationships between genes and drugs are then categorized into the following categories:

Phenotype

- **CO** Clinical Outcome
- **PD** Pharmacodynamics & Drug Responses
- **PK** Pharmacokinetics
- **FA** Molecular & Cellular Functional Assays

- **GN** Genotype

News

- New Pharmacological Reviews (reviews: IV, V and VI)
- PharmGKB teaches a successful short course in Pharmacogenomics at the University of the Western Cape to a diverse group of students, faculty and professionals from across South Africa.

Useful Links

- Download
- Coriell Sample Sets
- Review My Genotype Submissions
- Phenotype Datasets
- Other Data Submissions
- Genotype Excel Templates
- PGRN Publications
- FAQs on Publications

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Why do I need to register?

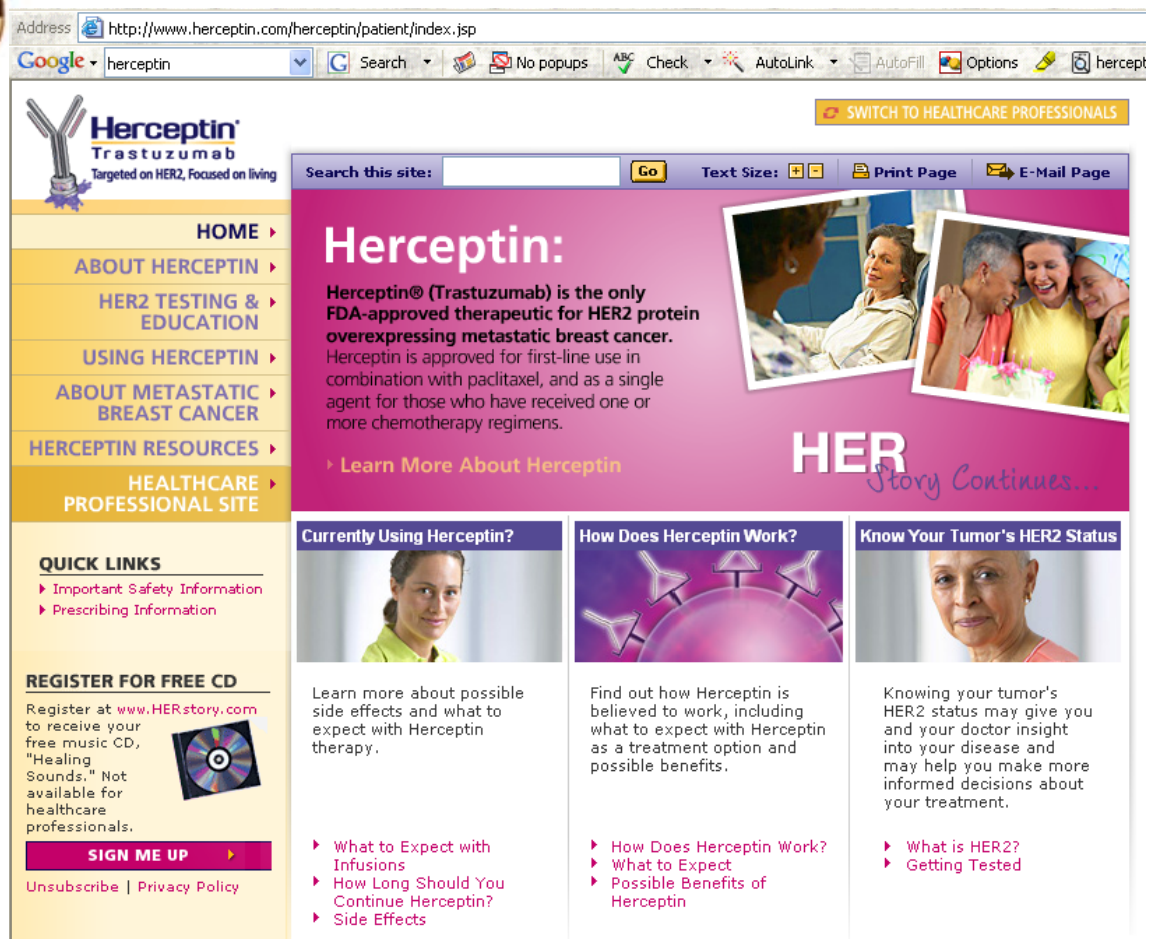
Pharmacogenomics

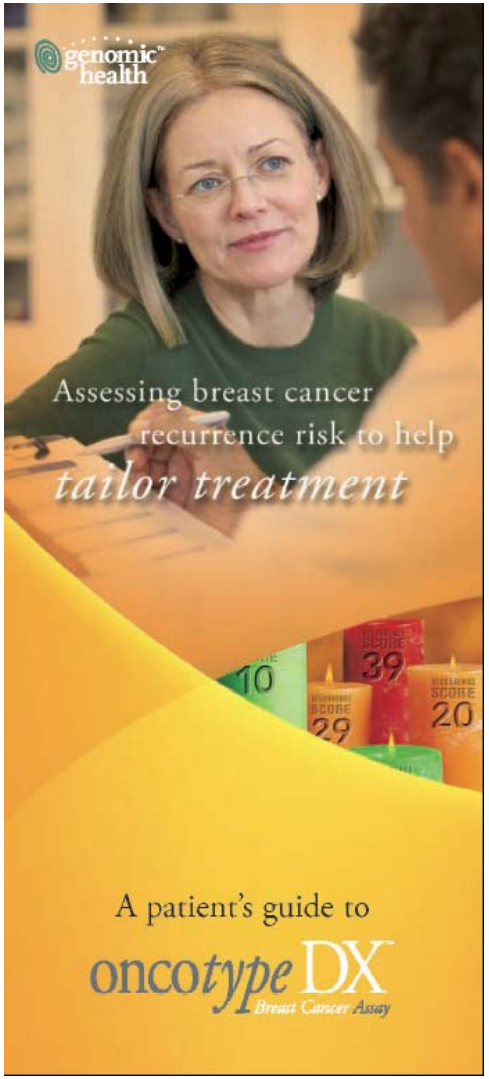
* Use of genetic differences among individual patients to
  - Identify new disease genes/targets of intervention
  - Improve specificity of diagnosis
  - Improve likelihood of response to a drug
  - Customize drug dose
  - Decrease likelihood of adverse reaction to a drug
* SNPs most useful type of genetic difference
  - Frequency ~1/300 base pairs (10M total)
  - Easily assayed
  - With HapMap, all common SNPs among individuals can be assessed with much less effort/cost than previously

Pharmacogenomics extends established concepts of “Personalized Medicine”

* Clinical history
* Physical examination
* Blood examination
    - Chemistry
    - Hematology
* Body fluids
    - Urine
    - CSF
* Organism culture and sensitivity to antibiotics
* Protein examination
    - Albuminuria in DM
* mRNA examination
    - Microarray differentiation of histologically similar lymphomas
    - Oncotype DX in breast cancer
* DNA examination
    - Somatic: Her2/neu amplification in breast cancer
    - Germline: Mutation testing for monogenic disorders (e.g., HD, CF)

Personalizing diagnosis and treatment





genomic health | oncotype DX Breast Cancer Assay

Illuminating Breast Cancer Recurrence Risk

Home | Genomic Health | Contact Us | Register |

- Healthcare Professionals
- Patients and Caregivers
- Oncotype DX Logistics

Updated ASCO Clinical Practice Guidelines Recommend Oncotype DX

For more information click here

Coming Soon ER and PR Scores in the Oncotype DX Report

Learn More

Oncotype DX Covered by Major US Health Insurance Plans

More information

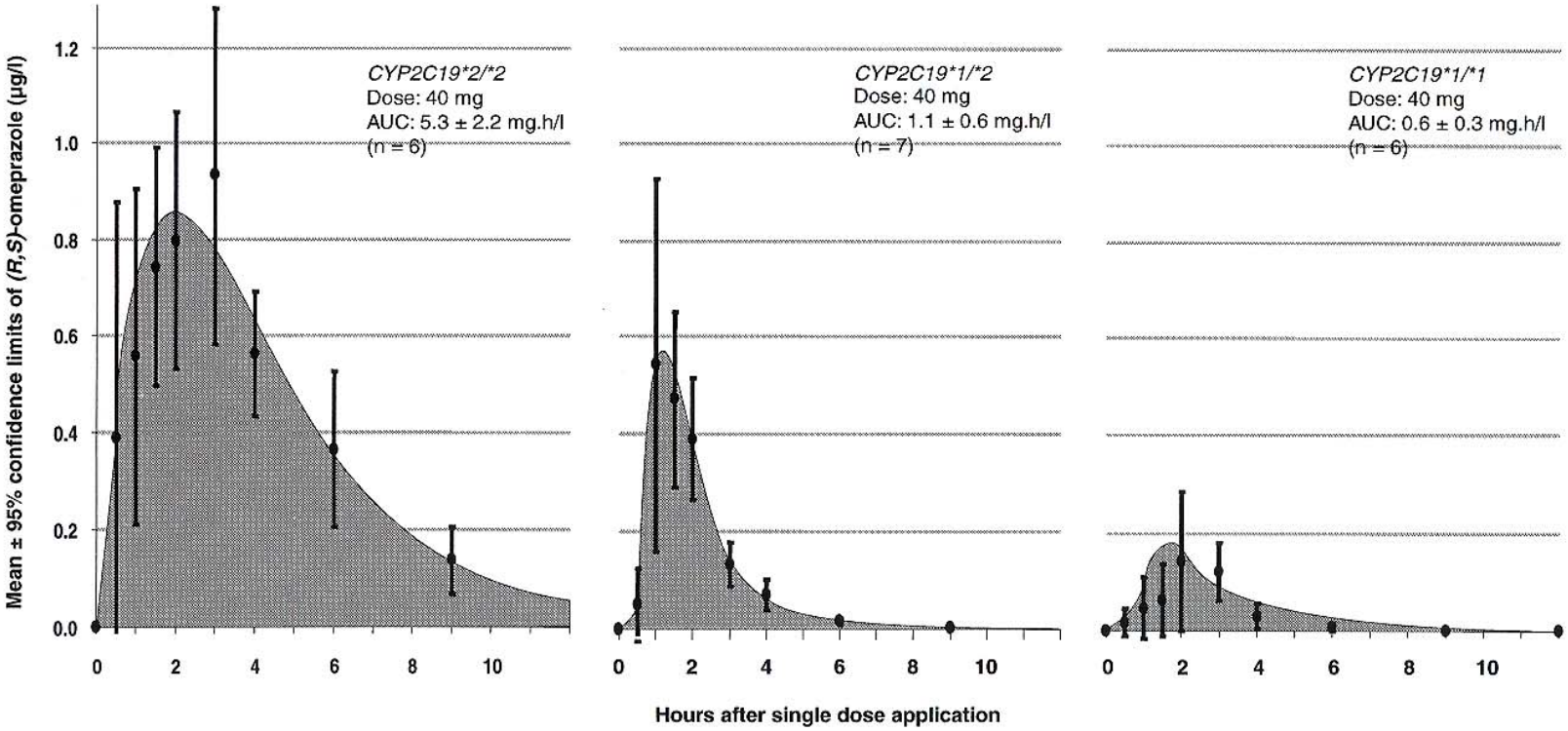
Welcome to Oncotype DX®

Oncotype DX is a clinically validated laboratory test, ordered by authorized healthcare providers, that predicts the likelihood of breast cancer recurrence in women with newly diagnosed, early stage invasive breast cancer. Oncotype DX also assesses the benefit from chemotherapy.[1] To learn more about Oncotype DX, choose from the options below.

I am a Healthcare Professional	I am a Patient or Caregiver	Oncotype DX Logistics
Click here to enter	Click here to enter	Click here to enter

- I am a Healthcare Professional
- I am a Patient or Caregiver
- Oncotype DX Logistics

Customizing medication dosage, avoiding dose-related toxicity



CYP2C19 SNP genotype produces 10-fold variation in Prilosec blood levels

Customizing medication dosage, avoiding dose-related toxicity

Address http://www.roche-diagnostics.com/products_services/amplichip_cyp450.html

Google amplichip Search No popups Check AutoLink AutoFill Options amplichip

Home

Product Detail

Diagnostics Roche

Back to Key Products

Search all Products:

Products

Product Detail

AmpliChip CYP450 Test

Now cleared for *in vitro* diagnostic use in the US and EU.

The world's first pharmacogenomic microarray designed for clinical applications.

The AmpliChip CYP450 Test is powered by Affymetrix technology. It provides comprehensive coverage of gene variations – including deletions and duplications – for the 2D6 and 2C19 genes, which play a role in the metabolism of about 25% of all prescription drugs. It is intended to be an aid for physicians in individualizing treatment doses for patients on therapeutics metabolized through these genes.

More information/related links

Customer benefits

- **Broad allelic coverage**
  High built-in sensitivity analyzing 29 polymorphisms and mutations for the 2D6 gene and 2 polymorphisms for the 2C19 gene, thereby increasing the probability of more accurately determining the genotype and phenotype. Accurately genotypes over 99% of the world's population.
- **All-in-One**
  Tests for the 31 polymorphisms and mutations, including gene deletions and duplications, on a single chip. The only test that also analyzes the functional status of gene duplications.
- **Fast results**
  Analysis can normally be completed within a single eight-hour shift.
- **Automatic Analysis**
  Automatically determines genotype and predicted phenotype when used with Roche proprietary software.
- **Gold Standard**
  Sample preparation for AmpliChip microarrays uses Roche's patented PCR technology, the gold standard in nucleic acid amplification. These microarray based assays, a new generation of diagnostic products, are built on Affymetrix's leading platform technology.

SNPs in drug targets can affect drug response

Gene polymorphism	Drug Response Affected
5-lipoxygenase	leukotriene modifiers
LTC_4 synthase	montelukast, zafirlukast
β2 adrenergic receptor	albuterol
Angiotensin Converting Enzyme	ACE inhibitors
Cholesterol ester transfer protein	pravastatin
Potassium channels	drug-induced QT prolongation

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Drug Reaction Testing

Do not alter the dosage amount or schedule of any drug you are taking without first consulting your medical provider or pharmacist.

Genelex will be happy to mail information to you or to your healthcare provider on your behalf, simply complete the **request form**.

Research shows that of all the clinical factors such as age, sex, weight, general health and liver function that alter a patient's response to drugs, genetic factors are the most important. This information becomes even more crucial when you consider the fact that adverse reactions to prescription drugs are killing about 106,000 Americans each year -- roughly three times as many as are killed by automobiles. This makes prescription drugs the fourth leading killer in the U.S., after heart disease, cancer, and stroke.

We currently offer CYP2D6, CYP2C9, CYP2C19, NAT2 and CYP1A2 screens that can help your physician or pharmacist predict your particular response to many prescription, OTC (over-the-counter) and herbal medicines including those used to treat depression, anxiety, seizures and psychoses; blood pressure, anticoagulation and other heart medicines; anti-diabetic agents, and many pain relievers. These include such important medications as Coumadin (warfarin), Prozac, Zoloft, Paxil, Effexor, hydrocodone , amitriptyline, Claritin, cyclobenzaprine, Haldol, metoprolol, Rythmol, Tagamet, tamoxifen, Valium, carisoprodol, diazepam, Dilantin, Premarin, and Prevacid (and the over-the-counter drugs, Allegra, Dytuss and Tusstat). **Click here to view a more complete list of drugs processed through these pathways.**

Approximately half of all Americans have genetic defects that affect how they process these drugs. There are four different types of metabolizers, and we all fall into one of these categories for the variable pathways in Cytochrome P450 (this Cytochrome is responsible for creating the enzymes that process chemicals of all kinds through our bodies.) The easiest way to understand this is to picture a two lane highway.

Printer-Friendly

**Questions?
Ready to Order?
Call 800-523-3080 to speak with a DNA Testing Consultant.**

Adverse Drug Reaction Standard Panel
2D6, 2C9, and 2C19
Price: $600.00
Add to Shopping Cart

Adverse Drug Reaction Extended Panel
2D6, 2C9, 2C19, 1A2, and NAT2
Price: $1000.00
Add to Shopping Cart

I just wanted to call and tell you that my physician switched my medications based on my test results, and I cannot describe how much better I feel. You have made a believer out of me, my family, and my physician. I hope this testing becomes routine before anyone is placed on long term medication.

23andMe genetics just got personal.

sign in | help
have a claim code?

our service | genetics 101 | for the experts | store | about us

discover your genome at 23andMe **order now**

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 use our interactive tools to shed new light on your distant ancestors, your close family and most of all, yourself.

news My Genome, Myself: Seeking Clues in DNA, *New York Times*, November 2007

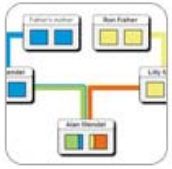
Gene Journal

What do your genes say about you?

Ancestry

Who were your ancient ancestors?

Family Inheritance



Do you have your mother's sense of taste?

Genome Labs

Would you like to search your genome?

how the process works

Getting Started with 23andMe

Saliva Kit

Joining 23andMe is easy - once you've placed your order and signed our online consent form, all you do is spit in a plastic tube included with the kit we ship to you. Each kit is labeled with the name of the person it is designated for along with a claim code. Just use the kit's pre-paid, pre-addressed shipping envelope to send your sample to our contracted laboratory. Our service is currently available in the United States.

Genotyping

After receiving your sample, lab professionals extract DNA from cells in your saliva. Your DNA is then chopped up into shorter strands and copied many times via a process called amplification. Next, your DNA is washed over a small microchip-like device that contains short strands of synthetic DNA. The synthetic DNA fragments latch onto the pieces of your DNA that are a complementary match. Then a laser-scanning step reveals which strands of synthetic DNA are stuck to your DNA to determine your genotype. The chip used in our process is the Illumina HumanHap550+ BeadChip, which reads more than 550,000 SNPs (single nucleotide polymorphisms) plus a 23andMe custom-designed set that analyzes more than 30,000 additional SNPs. What this means is that the laboratory process reads nearly 600,000 data points on your genome. Find out more about our genotyping process.

Your 23andMe Personal Genome Account

Your personal journey of genetic discovery starts when 23andMe receives your genetic data from the laboratory and uploads it to a secure database. With your own private login, you can then use our web-based interactive tools to explore your genome. You can discover your origins, learn what the latest genetic findings may mean for you, and connect genetically with friends, family, and others across the globe.

Questions

How does 23andMe genotype my DNA?

What is the difference between genotyping and sequencing?

More Info

scientific excellence

considerations

Genes vs. Drugs

* Numbers
  - Human genes ~20,000
  - Human proteins (targets) > 250,000
  - Current drug targets: <500
  - ∴ >95% remain
* Gene identification only start to determining function and any therapeutic potential
* “Validation”
  - Definition of sequence function, role in disease
  - Demonstration of manipulability of gene product
  - Transforms gene product into drug target

Development of a novel drug

Product Surveillance

Introduction
Registration

15

Ph IV-V

1

Ph III

2

Clinical Tests
(Human)

Ph II

2-5

Development

5 cmpds

Ph I

Years

Preclinical Tests
(Animal)

500 Compounds

MedChem
HTS

Research

500,000 Compounds

Assay

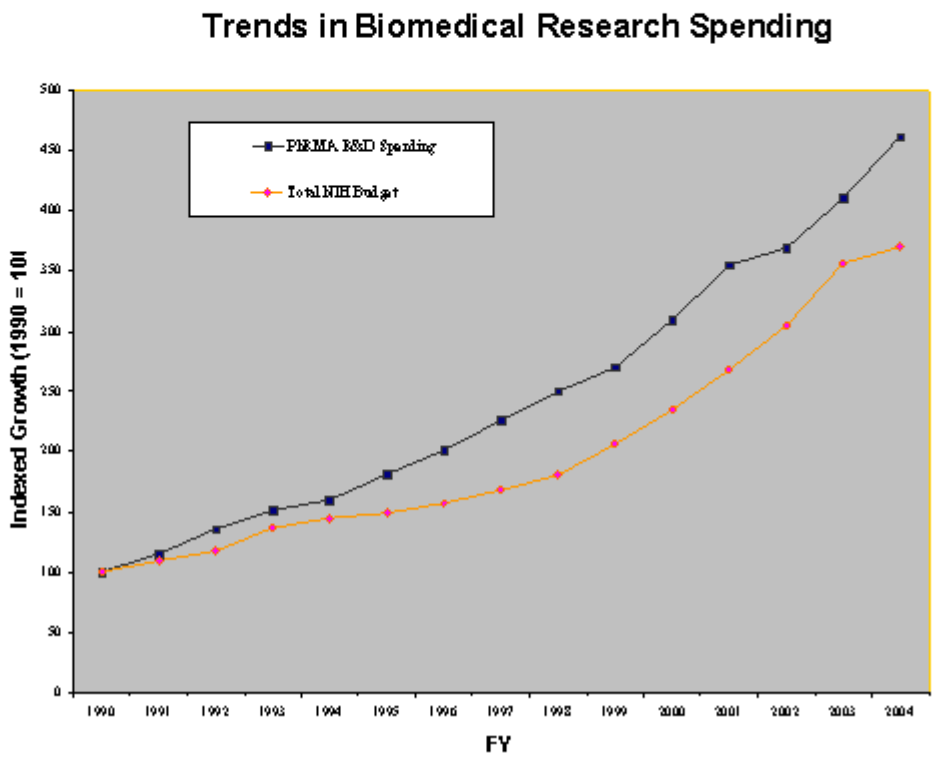
Target
validation

0

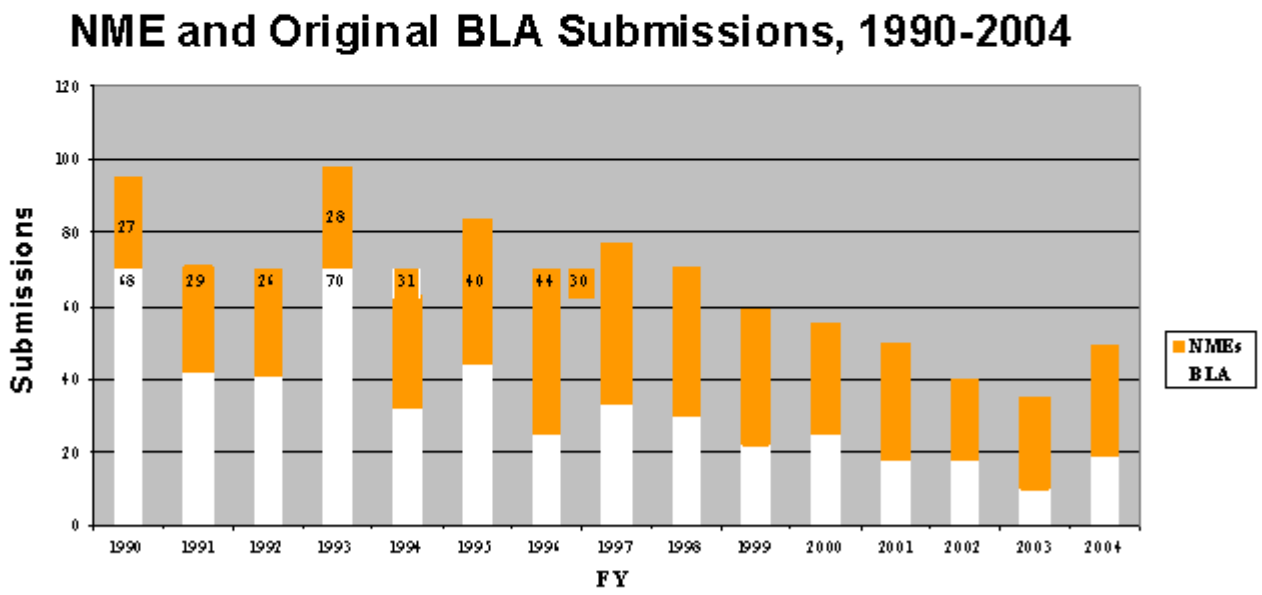
The Human Genome Project

25,000 genes/500,000 proteins

Despite Increasing Investments in Biomedical Discovery …..



… We are Not Seeing the Expected Payoff in New Medical Products



The Challenge

- 8% of compounds entering Phase 1 will make it to market, down from 14% fifteen years ago.
- Costs of development are increasing.
- Phase 3 failure rate reported to be 50%, up from 20% 10 years ago.

The Diagnosis

- Investment and progress in basic biomedical science has far surpassed investment and progress in the medical product development sciences.
- The scientific development process – the critical path to patients – is becoming a serious bottleneck to delivery of new products.
- We are using the evaluation tools and infrastructure of the last century to develop this century's advances.

The Prescription

- Bring scientific advances to the medical product development process (e.g., simulation models, validated biomarkers, new trial designs, novel rapid pathogen identification).
- Stimulate development of robust applied research programs in critical path scientific areas, to develop techniques that remove specific obstacles in product development.
- Modernize regulatory standards to reflect the best science, intensify FDA involvement.

FDA's Critical Path Initiative

About Critical Path

The Critical Path Initiative is FDA's effort to stimulate and facilitate a national effort to modernize the scientific process through which a potential human drug, biological product, or medical device is transformed from a discovery or "proof of concept" into a medical product. More.

- *New!* Janet Woodcock, Deputy Commissioner and Chief Medical Officer Commentary on Critical Path
- Frequently Asked Questions

Critical Path Opportunities

Reports

- *New!* Critical Path Opportunities for Generic Drugs
- Critical Path Opportunities Initiated During 2006
- Critical Path Opportunities Report - March 2006 [PDF 447 KB]
- List [PDF 486 KB]
- Challenges and Opportunities Report - March 2004 (PDF)

Upcoming Events

- Workshop on In Vitro Analyses of Cell/Scaffold Products, Dec. 6-7, 2007

Past Events

- Workshop on Improving the Quality of Cancer Clinical Trials, Oct. 4-5, 2007
- Accelerating Anticancer Agent Development and Validation Workshop, June 20-22, 2007
- FDA Commissioner testifying on Critical Path at the University of Utah --, June 1, 2007
- BIMO Workshop, May 10-11, 2007
- Public Hearing: Should prescribing information be distributed electronically?-- April 27, 2007
- Hepatotoxicity Special Interest Group: Issues and Controversies in Drug-Induced Liver Injury (DILI), January 24 and 25, 2007
- Part 15 hearing - Electronic Submission of Regulatory Information, Dec. 18, 2006
- Sex Differences and Critical Path Initiative, Nov. 13, 2006
- Part 15 hearing - Conduct of Emergency Clinical Research, Oct. 11, 2006
- AAMC-FDA Conference on Drug Development Science, Jan. 13-14, 2005
- Medical Imaging as a Drug Development Tool: An FDA/DIA Workshop

Faces Behind Critical Path

- Interview on Warfarin

Did You Know?

- *New!* FDA Announces Public-Private Partnership with Duke to Modernize Clinical Trials
- Need for Veterinarians in Biomedical Research
- Quality in FDA-Regulated Clinical Research
- FDA and NIH Seek Information on Establishing an Electronic Platform
- FDA Helping to Develop Artificial Pancreas
- Nanotechnology: No Small Issue at FDA!

Contact Us

http://www.fda.gov/oc/initiatives/criticalpath

http://www.fda.gov/cder/genomics/

Genomics at FDA

December 10-12, 2007
Workshop co-sponsored by FDA, DIA, PhRMA, and Bio:
Biomarkers and Pharmacogenomics in Drug development and Regulatory Decision Making. Information and registration

- Genomics Overview
- What's New and Upcoming Events
- Genomic Data Submission
  - Decision Tree for Genomic Data Submission
  - Voluntary Genomics Data Submission (VGDS)
  - Quick Reference Guide
- Interdisciplinary Pharmacogenomics Review Group (IPRG)
- Regulatory Information
  - Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels
- Frequently Asked Questions
- Background Information on Genomics
  - Pharmacogenomics
  - Education
- Drug Development and Drug Interactions
- Publications by FDA Staff
- Presentations
- Related Links
- Contact Information

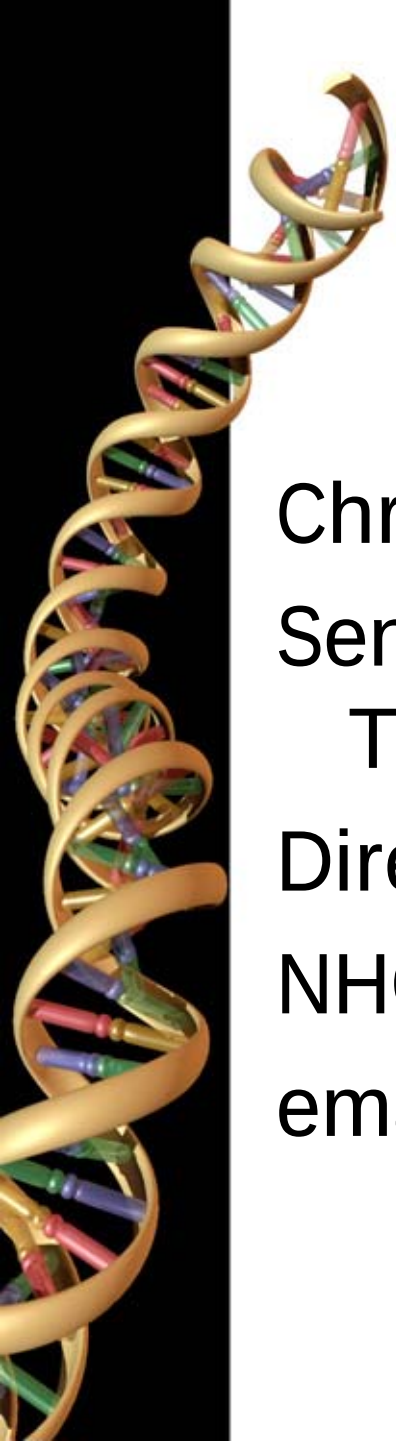
Genomics Overview

Pharmacogenomics allows us to identify sources of an individual's profile of drug response and predict the best possible treatment option for this individual. The use of genomic information, accelerated by the sequencing of the human genome and the advent of new tools and technologies, has opened new possibilities in drug discovery and development. Consequently, regulatory science and regulations need to be set in place appropriately.

FDA recognizes the importance of pharmacogenomics and encourages its use in drug development. This is reflected in the FDA white paper "Stagnation or Innovation? – Challenge and Opportunity on the Critical Path to New Medical Products," which identifies pharmacogenomics as a key opportunity for the Critical Path.

Genomics is changing how drugs are developed in the clinic

* Genetically defined subpopulations for clinical trials
  - greater power with reduced n
* Smaller patient populations eligible for treatment upon drug approval
  - Better efficacy data improves chance of formulary acceptance
  - Financial success of drugs for genetically defined populations suggests more “targeted” drugs will be entering trials
    * Herceptin
    * Gleevec
    * Avastin
    *Cerezyme
*ALL diseases may eventually be “rare”!



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