The Impact of Genomics on Drug Development, Clinical Research, and Medical Practice

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

NIH Introduction to the Principles and Practice of Clinical Research
January 4, 2010
Outline of Talk

- Definitions
- The Human Genome Project and its successors
- Genome variation
- Pharmacogenomics and personalized medicine
- Drug development based on the genome
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 Disease

- Single gene variant *causes* disease
  - a.k.a., ‘Mendelian’
  - Modifier genes and environment lesser contributors
- e.g., Huntington’s disease, cystic fibrosis, Tay-Sachs
- 6000 rare genetic diseases, but each is individually uncommon (<200,000 U.S. prevalence)
- Most people not directly affected
- As a result genetics traditionally played a “niche” role in health care and clinical research

Variants in multiple genes change predisposition to disease (5-50%) 
- a.k.a., ‘polygenic’, ‘common’, ‘complex’  
- Environmental contributions generally larger 
- e.g., hypertension, obesity, Alzheimer’s disease  
  - ApoE (Alzheimer’s disease)  
  - Complement Factor H (AMD)  
  - PPARγ (Type 2 diabetes)  
- Virtually all diseases have heritable component  
- Thus, most people directly affected  
- Thus, genetics is playing an increasingly large role in health care and clinical research

Stages in Deciphering the Genome

2000: First Draft

2001: Working Draft

April 15, 2003: “Finished” reference sequence

2002-2007: Defining sequence variation in populations

2007 - 2010: Defining sequence variation in a few individuals

2010 - : Defining individual genomes for medical purposes?
What can we “sequence”? (i.e., determine the presence/sequence of)

1. Reference genomes
2. SNPs
3. Haplotypes
4. Exons
5. Insertions-Deletions-Inversions
6. Transcriptomes
7. Whole genomes
Haplotypes and Tag 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)
Published Genome-Wide Associations through 6/2009, 439 published GWA at $p \leq 5 \times 10^{-8}$

NHGRI GWA Catalog
www.genome.gov/GWAStrudies
A Catalog of Published Genome-Wide Association Studies

Note: This catalog is best viewed with a screen resolution of 1280 x 1024 or higher.

The genome-wide association study (GWAS) publications listed here include only those attempting to assay at least 100,000 single nucleotide polymorphisms (SNPs) in the initial stage. Publications are organized from most to least recent date of publication, indexing from online publication if available. Studies focusing only on candidate genes are excluded from this catalog. Studies are identified through weekly PubMed literature searches, daily NHGRI-distributed compilations of news and media reports, and occasional companions with an existing database of GWAS literature (HUGENavigator).

SNP-trait associations listed here are limited to those with p-values < 1.0 x 10^-5. Note that we are now including all identified SNP-trait associations meeting this p-value threshold. Multipliers of powers of 10 in p-values are rounded to the nearest single digit; odds ratios and allele frequencies are rounded to two decimals. Standard error are converted to 95 percent confidence intervals where applicable. Allele frequencies, p-values, and odds ratios derived from the largest sample size, typically a combined analysis (initial plus replication studies), are recorded below if reported; otherwise statistics from the initial study sample are recorded. Odds ratios < 1 in the original paper are converted to OR > 1 for the alternate allele. Where results from multiple genetic models are available, we prioritized effect sizes (OR's or beta-coefficients) as follows: 1) genotypic model, per-allele estimate; 2) genotypic model, allelic estimate; 3) allelic model, allelic estimate.

Gene regions corresponding to SNPs were identified from the UCSC Genome Browser. Gene names are those reported by the authors in the original paper. Only one SNP within a gene or region of high linkage disequilibrium is recorded unless there was evidence of independent association.

- How to cite this site: Hindorff LA, Junkins HA, Mahta J and Manolio TA. A Catalog of Published Genome-Wide Association Studies. Available at: www.genome.gov/46525384. Accessed [date of access].
- Full description of methods
- This table is also available for download in MS-Excel format. To save the file, use an .xls extension.
- For an archived Excel spreadsheet of the catalog data restricted to the most statistically significant SNP associations that were not known at the time each study was published, go to: GWAS Catalog 11-26-09
- These documents require the use of either MS-Excel or a free Excel viewer.
- Abbreviations used on this page

For questions or comments about this page, send an e-mail to: gwas_table@mail.nih.gov

Search By:

- Journal: Select Journal
- First Author: (last name)
- Disease/Trait: (string search)
- Chromosomal Region: (e.g., "1q21.31")
- Gene: (e.g., "LRP5")
- SNP: (e.g., "rs2075655")
- p-Value threshold:

Enter the exponent. For example, enter "5" for p<10^-5

Search Clear Query
How to Interpret a Genome-wide Association Study

Thomas A. Pearson, MD, MPH, PhD
Teri A. Minnok, MD, PhD

In the past two years, there has been an extraordinary increase in genomic discoveries involving complex, non-Mendelian diseases, with nearly 100 loci for as many as 40 common diseases and traits having been identified and replicated in genome-wide association (GWA) studies (T.A.M., unpublished data, 2008). These studies use high-throughput genotyping technologies to assay hundreds of thousands of single-nucleotide polymorphisms (SNPs) and relate them to clinical conditions and measurable traits. Since 2005, nearly 100 loci for as many as 40 common diseases and traits have been identified and replicated in GWA studies, many in genes not previously suspected of having a role in the disease under study, and some in genomic regions containing no known genes. GWA studies are an important advance in discovering genetic variants influencing disease but also have important limitations, including their potential for false-positive and false-negative results and for biases related to selection of study participants and genotyping errors. Although these studies are clearly many steps removed from clinical use, and specific applications of GWA findings in prevention and treatment are actively being pursued, at present these studies mainly represent a valuable discovery tool for examining genomic function and clarifying pathophysiologic mechanisms. This article describes the design, interpretation, application, and limitations of GWA studies for clinicians and scientists for whom this evolving science may have great relevance.

Figure 2. Associations in the IL23R Gene Region Identified by a Genome-wide Association Study of Inflammatory Bowel Disease

![Image of Figure 2]

Box 1. Terms Frequently Used in Genome-wide Association Studies

Alleles
Alternate forms of a gene or chromosomal locus that differ in DNA sequence
Candidate gene
A gene believed to influence expression of complex phenotypes due to known biological and/or physiological properties of its products, or to its location near a region of association or linkage
Copy number variants
Stretches of genomic sequence of roughly 1 kb to 3 Mb in size that are deleted or are duplicated in varying numbers
False discovery rate (FDR)
Proportion of significant associations that are actually false positives
False-positive report probability (FPRP)
Probability that the null hypothesis is true, given a statistically significant finding
Functional studies
Investigations of the role or mechanism of a genetic variant in causation of a disease or trait
Gene-environment interactions
Modification of disease associations in the presence of environmental factors
Genome-wide association study (GWAS)
Any study of genetic variation across the entire human genome designed to identify genetic association with observable traits or the presence or absence of a disease, usually referring to studies with a million marker density of 100,000 or more to represent a large proportion of variation in the human genome
Genotyping call rate
Proportion of samples or SNPs for which a specific allele SNP can be reliably identified by a genotyping method
Haplotype
A group of specific alleles at neighboring genes or markers that tend to be inherited together
HapMap
A genome-wide database of patterns of common human genetic sequence variation among multiple ancestral population samples
Hardy-Weinberg equilibrium
Population distribution of 2 alleles (with frequencies p and q) such that the distribution is stable from generation to generation and genotypes occur at frequencies of p^2, 2pq, and q^2 for the major allele homozygote, heterozygote, and minor allele homozygote, respectively
Linkage disequilibrium
Association between 2 alleles located near each other on a chromosome, such that they are inherited together more frequently than expected by chance
Mendelian disease
Condition caused almost entirely by a single major gene, such as cystic fibrosis or Huntington's disease, in which disease is manifested in only 1 (recessive) or 2 (dominant) of the 3 possible genotype groups
Minor allele
The allele of a biallelic polymorphism that is less frequent in the study population
Minor allele frequency
Proportion of the less common of 2 alleles in a population (with 2 alleles carried by each person at each autosomal locus) ranging from less than 1% to less than 50%
Modest effect
Association between a gene variant and disease or trait that is statistically significant but carries a small odds ratio (usually <1.3)
Non-Mendelian disease (also “common” or “complex” disease)
Condition influenced by multiple genes and environmental factors and not showing Mendelian inheritance patterns
Non-synonymous SNP
A polymorphism that results in a change in the amino acid sequence of a protein (and therefore may affect the function of the protein)
Platform
Arrays or chips on which high-throughput genotyping is performed
Polymorphic
A gene or site with multiple allelic forms. The term polymorphism usually implies a minor allele frequency of at least 1%
Population attributable risk
Proportion of a disease or trait in the population that is due to a specific cause, such as a genetic variant
Population stratification (also “population structure”)
A form of confounding in genetic association studies caused by genetic differences between cases and controls unrelated to disease but due to sampling them from populations of different ancestries
Power
A statistical term for the probability of identifying a difference between 2 groups in a study when a difference truly exists
Single-nucleotide polymorphism
Most common form of genetic variation in the genome, in which a single-base substitution has created 2 forms of a DNA sequence that differ by a single nucleotide
Tag SNP
A readily measured SNP that is in strong linkage disequilibrium with multiple other SNPs so that it can serve as a proxy for these SNPs on large-scale genotyping platforms
Trios
Genetic study design including an affected offspring and both parents
Abbreviation: SNP, single-nucleotide polymorphism.

Figure 3. Genome-wide Association Findings in Rheumatoid Arthritis

![Image of Figure 3]
<table>
<thead>
<tr>
<th>Disease</th>
<th>Studies</th>
<th>Variables</th>
<th>Documents</th>
<th>Participants</th>
<th>Type of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral and Behavioral Mechanisms</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Behavioral Disorders and Activities</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cardiovascular Diseases</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Congenital, Hereditary, and Neonatal Diseases and Abnormalities</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal System Diseases</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hematological and Immunological Abnormalities</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Female Urogenital Diseases and Pregnancy Complications</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Genetic and Immunohematologic Diseases</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Immune System Diseases</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Male Urogenital Disease</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mental Disorders</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Neurodevelopment Disorders</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Obesity</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nervous System Diseases</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Neurologic and Metabolic Diseases</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oncologic Hematological Diseases</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pathological Conditions, Stasis and Synovitis</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Population: Convenience, Safety, Controls</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Psychological Phenomena and Psychoses</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Respiratory Tract Diseases</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Skin and Connective Tissue Diseases</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Lung Cancer

<table>
<thead>
<tr>
<th>Laboratories offering clinical testing:</th>
<th>Sequencing of selected exons</th>
<th>Targeted mutation analysis</th>
<th>Deletion/duplication analysis</th>
<th>Prenatal diagnostic confirmation</th>
<th>Clinical confirmation of mutations identified in a research lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Center for Human Genetics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioscience GmbH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ingelheim, Germany</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jochen Dacker, MD, PhD; Daniela Steinberger, MD, PhD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duke University</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kelley Laboratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durham, NC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michael J Kelley, MD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fox Chase Cancer Center</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Molecular Genetics Laboratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Philadelphia, PA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andrew K. Godwin, PhD; Betty A. Bove, PhD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Select all clinical laboratories

Go to research laboratories

Disclaimer: GeneTests does not independently verify information provided by laboratories and does not warrant any aspect of a laboratory's work.

Contact GeneTests


Funding Support

National Library of Medicine, NIH
National Human Genome Research Institute, NIH

Sponsoring Institution

University of Washington
Seattle, Washington

http://www.genetests.org
Genomic copy number variation, human health, and disease

Louise V Wain, John A L Amos, Martin D Tobin

Despite the long recognised effects of chromosomal structural abnormalities and completion of the Human Genome Project, much of the structural variation in the genome has gone unrecognised until recently. Deletions and duplications of DNA strands of between a few hundred bp and several million bp—collectively referred to as copy number variants—are now known to be widespread. Since 2007, rigorous and adequately powered genomewide association studies based on single nucleotide polymorphisms have yielded replicated associations to several common diseases. Some copy number variants explain rare, previously uncharacterised disorders, and they are now expected to explain some of the genetic contribution to common diseases. We review efforts to map copy number variants and discuss present and future prospects for assessment of their relation to human health and disease.

Introduction
Human genomic variation in the form of single nucleotide substitutions has been catalogued in supplemented with association studies of copy number variation by use of existing SNP data or by the undertaking of appropriate further assays.²

Database of Genomic Variants
Genome-wide view of CNVs

Click on a cytoband to get a list of variants detected within that region.

http://projects.tcag.ca/variation

Legend: Blue bars indicate reported CNVs; Red bars indicate reported inversion breakpoints; Green bars to the left indicate segmental duplications.

- Down syndrome trisomy of chromosome 21
- Cri-du-chat syndrome del(5)p15.2 or del(5)p15.3
- β-defensin repeat unit dup(8)p23.1
- Autism spectrum disorder de-novo deletions
- Smith–Magenis syndrome del(17)p11.2
- Potocki–Shukowski syndrome dup(17)p13.2
- Di George (velo-cardio-facial) syndrome del(22)q11.2
- Williams–Beuren syndrome del(7)q11.23
- Choroid–Marie–Tooth disease neuropathy 1A (CMT1A) dup(17)q12
- Hereditary neuropathy with liability to pressure palsies (HNPP) del(17)q12
- RCCE1 module of major histocompatibility complex (including complement C4) dup(6)q21.13
- CCL3L1/CCL4L1 dup(17)q12
- Salivary amylase dup(1)q21
- FCGR3A/FCGR3B del(1)p23 or dup(1)p23

[Diagram showing genomic regions and associated conditions]
Exome Sequencing IDs Mendelian Disease Culprit

October 23, 2009
By Andrea Anderson

HONOLULU (GenomeWeb News) – Researchers from the University of Washington used exome sequencing to identify mutations causing a rare, single gene condition called Miller syndrome, attendees at the American Society of Human Genetics heard here this week.

In a plenary session on Wednesday afternoon, University of Washington genomics researcher Jay Shendure described how his team's applied whole exome sequencing to identify the mutations in the dihydroorotate oxidase gene (DHODH) in four individuals with Miller syndrome. He had presented initial findings on the research, which was covered by GenomeWeb Daily News sister publication In Sequence, last month at the Personal Genomes conference at Cold Spring Harbor Laboratory.

An estimated 80 percent of the causative mutations behind rare mendelian diseases occur in protein-coding regions of the genome, Shendure's colleague, University of Washington genetics and developmental medicine researcher Michael Bamshad, told reporters during a press briefing this week.

As such, he explained, exome sequencing holds promise for finding these mutations more quickly and affordably than whole-genome sequencing and analysis.

Shendure, Bamshad, and their co-workers recently published a paper in Nature in which they sequenced the exomes of a dozen individuals, eight from the HanMap
Genomics shifts focus to rare diseases

Disappointing genome-wide studies prompt researchers to tackle single-gene defects.

Erika Check Hayden

COLD SPRING HARBOR, NEW YORK

Genome sequencing may finally be living up to its promise of pinpointing genetic mutations that bear on treatment for individual patients. But the breakthroughs are not coming from the DNA analysis of common diseases with complex genetic origins, which has been the obsession of genomics for nearly the past decade. Instead, many genome scientists are turning back to study rare disorders that are traceable to defects in single genes, and whose causes have remained a mystery.
Complete sequencing of individuals’ genomes is likely to be technically possible for less than $1000 by 2013.

THE DNA DASH
OTHER COMPANIES RACING TO MAKE GENE SEQUENCING FASTER, CHEAPER AND MEDICALLY USEFUL.

LIFE TECHNOLOGIES
CARLSBAD, CALIF.
Formed by merger of Invitrogen and sequencing pioneer Applied Biosystems last year.

ILLUMINA
SAN DIEGO
Its new, fast machine has made it the company to reckon with in sequencing.

454 LIFE SCIENCES
BRANFORD, CONN.
One of the first of the current generation of sequencers; owned by Roche.

COMPLETE GENOMICS
MOUNTAIN VIEW, CALIF.
Has used a factory approach—send them DNA, they’ll sequence it—to finish 14 human genomes.

OXFORD NANOPORE
OXFORD, U.K.
Another nanotech entrant; has a development deal with Illumina.

ION TORRENT
GUILFORD, CONN.
New, under-the-radar company from founder of 454.

Interpretation will be limiting to application.
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 diabetes
- mRNA examination
  - Microarray differentiation of histologically similar lymphomas
  - Oncotype DX in breast cancer
- DNA examination
  - Germline (e.g., BRCA1/2, CFTR)
  - Somatic (in cancers, e.g., EGFR, Her2, K-ras)
SNPs in drug targets can affect drug response

<table>
<thead>
<tr>
<th>Gene polymorphism</th>
<th>Drug Response Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-lipoxygenase</td>
<td>leukotriene modifiers</td>
</tr>
<tr>
<td>LTC₄ synthase</td>
<td>montelukast, zafirlukast</td>
</tr>
<tr>
<td>β2 adrenergic receptor</td>
<td>albuterol</td>
</tr>
<tr>
<td>Angiotensin Converting Enzyme</td>
<td>ACE inhibitors</td>
</tr>
<tr>
<td>Cholesterol ester transfer protein</td>
<td>pravastatin</td>
</tr>
<tr>
<td>Interleukin 28B</td>
<td>interferon-alpha/ribavirin</td>
</tr>
</tbody>
</table>
Team Uses GWAS to ID Biomarker for Hepatitis C Treatment Response
August 17, 2009
By Andrea Anderson

NEW YORK (GenomeWeb News) – Scientists have identified a genetic marker that they said can help predict treatment response in individuals infected with one of the most common hepatitis C virus strains.

Vol 461 | 17 September 2009 | doi:10.1038/nature08309

Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance

Dongliang Ge¹, Jacques Fellay¹, Alexander J. Thompson², Jason S. Simon³, Kevin V. Shianna¹, Thomas J. Urban¹, Erin L. Heinzen¹, Ping Qiu³, Arthur H. Bertelsen¹, Andrew J. Muir², Mark Sulkowski¹, John G. McHutchison² & David B. Goldstein¹
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

Search PharmGKB:

Search for: [Go]

A rough query is: e.g., a gene ("AEBCT"), drug ("trinitoretan"), or disease ("neoplasm")

Sample query is: The dataset for gene AEBCT or drug trinitoretan

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:

CO Clinical Outcome
PD Pharmacodynamics & Drug Responses
PK Pharmacokinetics
FA Molecular & Cellular Functional Assays
GN Genotype
Customizing medication dosage, avoiding dose-related toxicity

Products
Product Detail

Amplichip CYP450 Test

Now cleared for 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 CYP3A and CYP3A5 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 whose metabolites are metabolized through these genes.

Customer Benefits

- **Broad allelic coverage**
  - High sensitivity analyzing 28 polymorphisms and mutations for the CYP3A gene and 2 polymorphisms for the CYP3A5 gene, thereby increasing the probability of more accurately determining the genotype and phenotype. Approximately genotypes over 95% of the world's population.

- **All in One**
  - Tests for 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.
Personalizing diagnosis and treatment

Herceptin: Herceptin® (Trastuzumab) is the only FDA-approved therapeutic for HER2 protein overexpressing metastatic breast cancer. Herceptin is approved for first-line use in combination with paclitaxel, and as a single agent for those who have received one or more chemotherapy regimens.

Currently Using Herceptin?
- Learn more about possible side effects and what to expect with Herceptin therapy.

How Does Herceptin Work?
- Find out how Herceptin is believed to work, including what to expect with Herceptin as a treatment option and possible benefits.

Know Your Tumor’s HER2 Status
- Knowing your tumor’s HER2 status may give you and your doctor insight into your disease and may help you make more informed decisions about your treatment.

Assessing breast cancer recurrence risk to help tailor treatment

A patient’s guide to

octype DX

Breast Cancer Assay
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. To learn more about Oncotype DX, choose from the options below.
Companies and patients are often ahead of their doctors in use of genetic data.
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; antidiabetic 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, Dymus and Tussstat). 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.
The Genetic Information Nondiscrimination Act of 2008 (GINA)

• A federal law that prohibits health insurers and employers from discriminating based on an individual’s genetic information
• Intended to allow Americans to take advantage of the benefits of genetic testing without fear of losing their health insurance or their jobs
GINA prohibits health insurers from...

- Requesting or requiring genetic information from an individual or their family members
- Using genetic information for decisions regarding coverage, rates, or preexisting conditions
GINA prohibits employers from...

• Using genetic information in decisions regarding hiring, firing, promotion or any other terms of employment (e.g., benefits)

• Limits the permitted scope of post-offer, pre-employment physical examinations and employer wellness programs

• Retaliating against employees who file a complaint under GINA
What GINA will not do

• Affect underwriting regarding manifest disease – someone who is already sick is not protected by GINA

• Restrict discriminatory use of genetic information in regard to life, long-term care, or disability insurance

• Extend to members of the military
The best of times, the worst of times

How to translate the genome into biological insights and therapeutics?
Developing Drugs from the Genome

- **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
Only a small % of diseases and genome-encoded targets are being addressed for drug development.

Current drug targets:
Well understood proteins

Current diseases:
Prevalent diseases that affect developed world

Human Genome
Neglected

Human Diseases
Neglected

NIH Chemical Genomics Center
The Problem of Rare and Neglected Diseases

• ~7,000 diseases affect humankind
• Only a very small fraction of diseases support commercial development of therapeutic agents
• Two types of neglected diseases:
  – Low prevalence, i.e., “rare”
    • Prevalence <200,000 in USA
    • There are >6000 rare (orphan) diseases
    • Cumulative prevalence in U.S. ~ 25 – 30 million
    • Most are single gene diseases; e.g., cystic fibrosis, Huntington disease, sickle cell disease, Tay-Sachs, OI
    • Approximately 200 have any pharmacotherapy available from the 340 products approved by FDA
  – High prevalence but “neglected”
    • Occur chiefly among impoverished and marginalized populations in developing nations who are unable to afford treatments
    • Most are infectious diseases, e.g., malaria, schistosomiasis, leishmaniasis, trypanosomiasis
Gene Therapy

• Intuitively attractive, operationally difficult
  – Access to cells to be corrected
  – Immune response to “vectors” (usually gutted viruses)
  – Cancers caused by insertion of genes next to cancer-causing genes

• So far has worked unequivocally in only a few diseases over 20 years
  – Severe combined immunodeficiency ("bubble boy")
  – Leber’s congenital amaurosis

• Unlikely to be solution to most genetic diseases
One Shot Of Gene Therapy, And Children With Congenital Blindness Can Now See

ScienceDaily (Oct. 26, 2009) — Born with a retinal disease that made him legally blind, and would eventually leave him totally sightless, the nine-year-old boy used to sit in the back of the classroom, relying on the large print on an electronic screen and assisted by teacher aides. Now, after a single injection of genes that produce light-sensitive pigments in the back of his eye, he sits in front with classmates and participates in class without extra help. In the playground, he joins his classmates in playing his first game of softball.

His treatment represents the next step toward medical science's goal of using gene therapy to cure disease. Extending a preliminary study published last year on three young adults, the full study reports successful, sustained results that showed notable improvement in children with congenital blindness.

The study, conducted by researchers from the University of Pennsylvania School of Medicine and the Center for Cellular and Molecular Therapeutics at the Children's Hospital of Philadelphia have used gene therapy to safely improve vision in five children and seven adults with a rare form of congenital blindness. Albert M. Maguire, M.D., associate professor of Ophthalmology at Penn and a physician at the Children's Hospital of Philadelphia; Katherine High, M.D., director of the Center for Cellular and Molecular Therapeutics at the Children's Hospital of Philadelphia; Investigator, Howard Hughes Medical Institute and Jean Bennett, M.D., Ph.D., professor of ophthalmology, at Penn are co-authors of the reversal of blindness in children study published in the Lancet. The gene therapy vector (shown) used in the study was manufactured at the Center for Cellular and Molecular Therapeutics at the Children's Hospital of Philadelphia.
Steps in the drug development process

1. Identify target
2. Create testing system (aka, “assay”)
3. Test >100,000 chemicals for activity on target
4. Make modifications to active chemicals to make suitable for human use
5. Test in animals for safety, effectiveness
6. Test in humans for safety, effectiveness
Two approaches to therapeutics for rare and neglected diseases

- >300,000 compounds, 10-15 yrs
- 3000 drugs
- 3 years?

Diagram:

1. Target
2. Screen
3. Hit
4. Lead
5. Lead Optimization
6. Preclinical Development
7. Clinical Trials
8. FDA Approval

3000 drugs

>300,000 compounds, 10-15 yrs

3 years?
Molecular Libraries and Imaging

OVERVIEW

Small molecules, often with molecular weights of 500 or below, have proven to be extremely important to researchers to explore function at the molecular, cellular, and in vivo level. Such molecules have also been proven to be valuable for treating diseases, and most medicines marketed today are from this class.

“...To empower the research community to use small molecule compounds in their research, whether as tools to perturb genes and pathways, or as starting points to the development of new therapeutics for human disease.”
The long pathway to drug development

Basic Research

NCGC, Molecular Libraries Initiative

“Valley of Death”

NIH “RAID”

Pharmas, Biotechs

NIH Clinical Center,
Academic Clinical Centers

FDA

Indefinite

3 yrs

4 yrs

1 yr

2 yrs

~3 yrs

1 yr

Identify Target

Identify chemical starting point for drug

Make many chemical modifications to give drug beneficial effect without side effects

Ph I

Ph II

Ph III

IND

Review

Patient Use
The long pathway to drug development

Basic Research

NCGC, Molecular Libraries Initiative

NIH "RAID"

Pharmas, Biotechs NIH Clinical Center, Academic Clinical Centers

FDA

Identify Target

Indefinite

Identify chemical starting point for drug

3 yrs

4 yrs

Make many chemical modifications to give drug beneficial effect without side effects

1 yr

2 yrs

Ph I

Ph II

Ph III

Review

Patient Use

1 yr

~3 yrs

IND
TRND program will bring compounds to point of clinical testing/commercial adoption

<table>
<thead>
<tr>
<th>Basic Research</th>
<th>NCGC, Molecular Libraries Initiative</th>
<th>Biotech, Pharma NIH Clinical Center CTSAs</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indefinite</td>
<td>1 yr</td>
<td>2 yrs</td>
<td>Indefinite</td>
</tr>
<tr>
<td>Target identification</td>
<td>Assay development</td>
<td>Hit to Probe</td>
<td>PK/PD (Safety)</td>
</tr>
<tr>
<td></td>
<td>Screen to Hit</td>
<td>Lead Optimization</td>
<td>In vivo Tox Formulation</td>
</tr>
<tr>
<td></td>
<td>Hit to Probe</td>
<td>Candidate Selection</td>
<td>GMP Manufacture</td>
</tr>
<tr>
<td></td>
<td>1 yr</td>
<td>Long-term Toxicology</td>
<td>Ph I (Dose finding, initial efficacy in patient pop.)</td>
</tr>
<tr>
<td></td>
<td>1 yr</td>
<td>Clinical Trials</td>
<td>Ph II (Efficacy and safety in large populations)</td>
</tr>
<tr>
<td></td>
<td>1 yr</td>
<td></td>
<td>Regulatoy review</td>
</tr>
<tr>
<td></td>
<td>2 yrs</td>
<td></td>
<td>Ph IV-V (Additional indications, Safety monitoring)</td>
</tr>
</tbody>
</table>
NIH Announces New Program to Develop Therapeutics for Rare and Neglected Diseases

Bethesda, Md. Wed., May 20, 2009 -- The National Institutes of Health is launching the first integrated, drug development pipeline to produce new treatments for rare and neglected diseases. The $115 million program jumpstarts a trans-NIH initiative called the Therapeutics for Rare and Neglected Diseases program, or TRND.

The program, unusual because TRND creates a drug development pipeline within the NIH and is specifically intended to stimulate research collaborations with academic scientists working on rare illnesses. The NIH Office of Rare Diseases Research (ORDR) will oversee the program, and TRND’s laboratory operations will be administered by the National Human Genome Research Institute (NHGRI), which also operates the NIH Chemical Genomics Center (NCGC), a principal collaborator in TRND. Other NIH components will also participate in the initiative.

A rare disease is one that affects fewer than 200,000 Americans. NIH estimates that, in total, more than 6,800 rare diseases afflict more than 25 million Americans. However, effective pharmacologic treatments exist for only about 200 of these illnesses. Many neglected diseases also lack treatments. Unlike rare diseases, however, neglected diseases may be quite common in some parts of the world, especially in developing countries where many people cannot afford expensive treatments. Private companies seldom pursue new therapies for these types of illnesses because of high costs and failure rates and the low likelihood of recovering investments or making a profit.

"NIH is eager to begin the work to find solutions for millions of our fellow citizens faced with rare or neglected illnesses," said NIH Acting Director Raynard S. Kington, M.D., Ph.D. "The federal government may be the only institution that can take the financial risks needed to jumpstart the development of treatments for these diseases, and NIH clearly has the scientific capability to do the work."

Developing Drugs

The drug development process is time-consuming and expensive. Studies suggest that it currently takes more than 10 years and hundreds of millions of dollars to take a potential drug from discovery to the marketplace. And the failure rate is high.

"This initiative is really good news for patients with rare or neglected diseases," said ORDR Director Stephen C. Groft, Pharm.D. "While Congress has previously taken important steps to help these patients, such as providing incentives for drug companies under the Orphan Drug Act, this is the first time NIH is providing support for specific, preclinical research and product development known to be major barriers preventing potential therapies from entering into clinical trials for rare or neglected disorders. While we do not underestimate the difficulty of developing treatments for people with these illnesses, this program provides new hope to many people worldwide."

Typically, drug development begins with academic researchers studying the underlying cause of a disease discover a new molecular target or a chemical that may have a therapeutic effect. Too often, the process gets stuck at the point of discovery because few academic researchers can conduct all the types of studies needed to develop a new drug. If a pharmaceutical company with the resources to further the research does get involved, substantial preclinical work begins with efforts to optimize the chemistry of the potential drug. This involves a series of chemical modifications and tests in increasingly more complex systems - from cell cultures to animal tests - to refine the potential medicine for use in people. Only if these stages are successful can a potential treatment move to clinical trials in patients.

Unfortunately, the success rate in this preclinical process is low, with 80 to 90 percent of projects falling in the preclinical phase and never making it to clinical trials. And the costs are high: it takes 2 to 4 years of work and $10 million, on average, to move a potential medicine through this preclinical process. Drug developers colloquially call this the "Valley of Death."

TRND will work closely with disease-specific experts on selected projects, leveraging both the in-house scientific capabilities needed to carry out much of the preclinical development work, and contracting out other parts, as scientific opportunities dictate. Its strategies will be similar to approaches taken by pharmaceutical and biotechnology companies, but TRND will be working on diseases mostly ignored by the private companies. Importantly, TRND will also devote some of its efforts to improving the drug development process itself, creating new approaches to make it faster and less expensive.

If a compound does survive this preclinical stage, TRND will work to find a company willing to test the therapy in patients. There are several stages to the clinical trials process that can take several years before the safety and efficacy of a new drug is determined. FDA will only approve a drug for general use after it passes these trials. The clinical trials process is also expensive, but the failure rate is lower at this stage.

"NIH traditionally invests in basic research, which has produced important discoveries across a wide range of illnesses," said NHGRI Acting Director Alan E. Guttmacher, M.D. "Biotechnology and pharmaceutical companies have enormous strength and experience in drug development, but to maximize return on investment work primarily on common illnesses. TRND will develop promising treatments for rare diseases to the point that they are sufficiently "de-risked" for pharmaceutical companies, disease-oriented foundations, or others, to undertake the necessary clinical trials. NIH's goal is to get new medications to people currently without treatment, and thus without hope."
NIH’s new programs to translate genes into drugs

Traditional NIH basic research

Roadmap Molecular Libraries Program
NIH Chemical Genomics Center (NCGC)

Therapeutics for Rare and Neglected Diseases (TRND) Program

Biotech, Pharma

NIH Clinical Center

Identify target → Create testing system (a.k.a., “assay”) → Test >300,000 chemicals for activity on target → Make modifications to active chemicals to make suitable for human use → Test in animals for safety, effectiveness → Test in humans for safety, effectiveness
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”!
My contact information

Christopher P. Austin, M.D.
Senior Advisor to the Director for Translational Research, NHGRI
Director, NIH Chemical Genomics Center

austinc@mail.nih.gov

http://www.ncgc.nih.gov/about/caustin.html