# Genetics and Genomics in Clinical Research

## An Immersion Course for Clinical Investigators at UAB

## Introduction and Overview

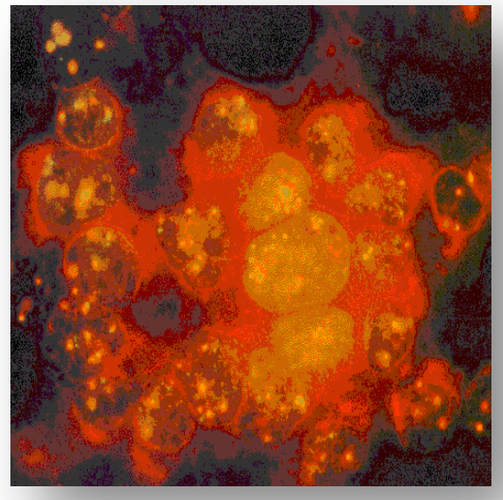
Bruce R. Korf, MD, PhD

# Human "Phenome"

**Monogenic**
- sickle cell
- cystic fibrosis
- Huntington

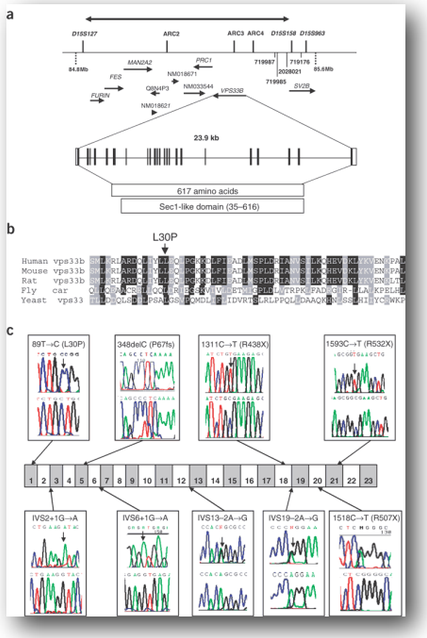
**Multifactorial**
- asthma
- hypertension
- diabetes

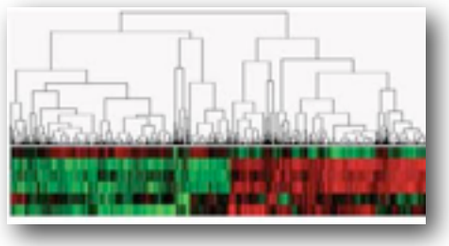
**Pharmacogenomics**
- drug metabolism
- new drug targets

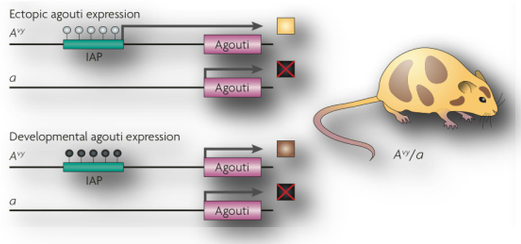


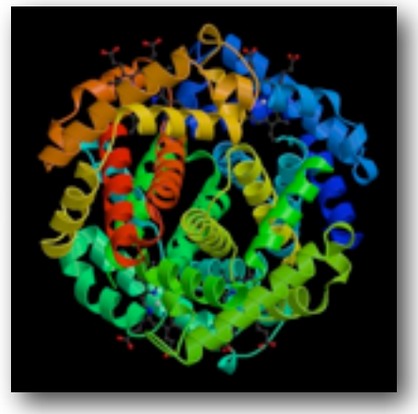
**Cancer**
- familial
- sporadic

# Applications of Genetics and Genomics



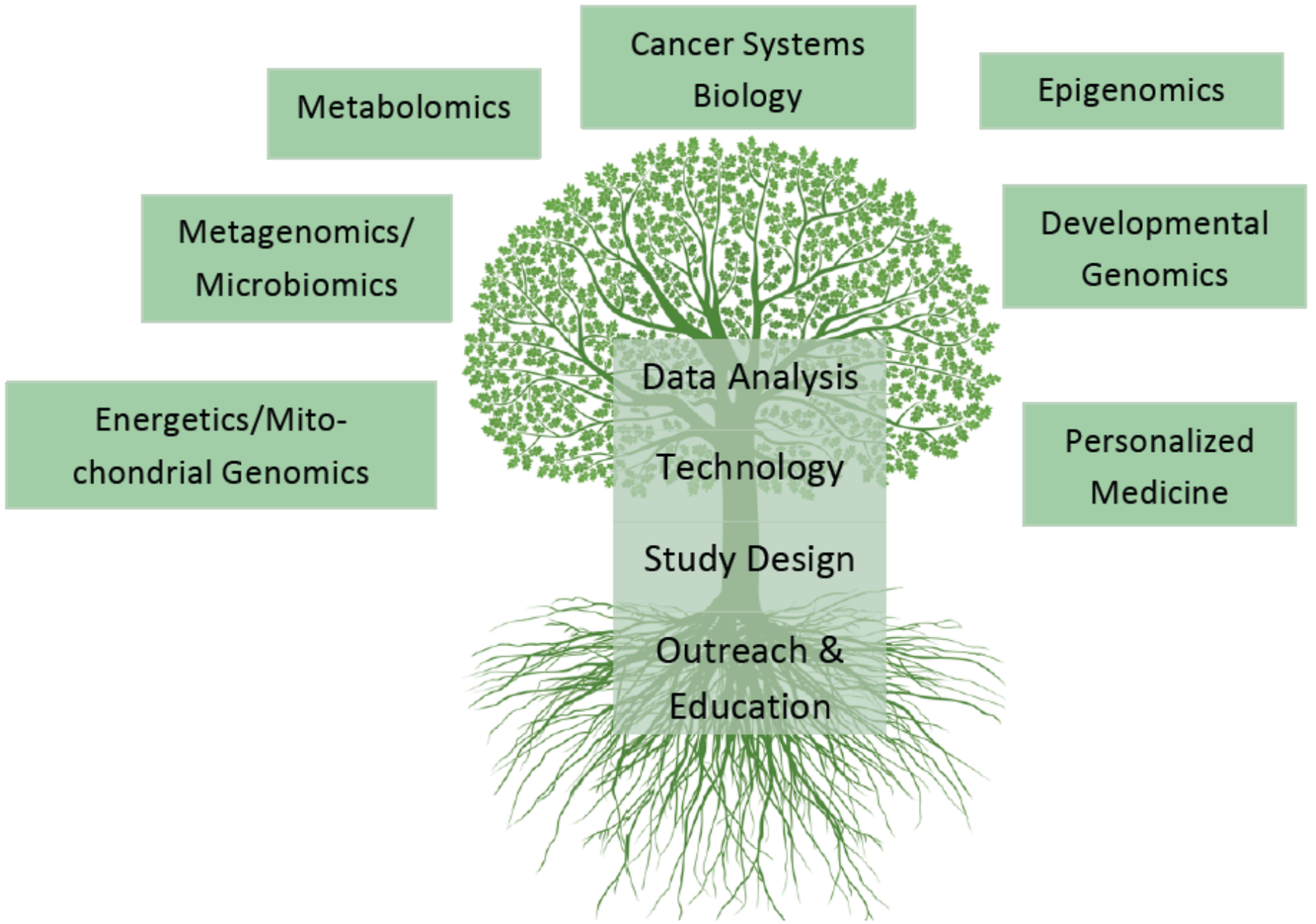





**Gene Discovery** **Gene Expression** **Gene Regulation** **Gene Products**

# Genomics at UAB



# Goals

This immersion course is intended to provide a review of the principles, major technologies, and experimental approaches in genetics and genomics through both lectures and hands-on activities. Earn up to 20 hours CME credit at no charge.

## Learning Objectives:

1. Design an approach to identification of a gene responsible for a phenotype in a family that segregates in a Mendelian manner.
2. Devise an appropriately powered case-control or transmission disequilibrium study to identify single nucleotide polymorphisms in linkage disequilibrium with a multifactorial disorder.
3. Develop a study comparing patterns of gene expression or methylation levels in normal vs. pathological tissue.
4. Formulate a protocol involved human research subjects for a genetic or genomic study to be submitted for IRB review.
5. Choose between alternative genotyping or next generation sequencing platforms appropriate for specific applications.
6. Utilize major bioinformatic databases to analyze genomic data.

# Faculty

| | |
|---|---|
| Molly Bray, PhD | Department of Epidemiology, Heflin Center |
| David Crossman, PhD | Department of Genetics, Heflin Center |
| Michael Crowley, PhD | Department of Genetics, Heflin Center |
| Bruce R. Korf, MD, PhD | Department of Genetics, Heflin Center |
| Fady Mikhail, PhD | Department of Genetics |
| Hemant Tiwari, PhD | Department of Biostatistics, Section on Statistical Genetics |

# Schedule

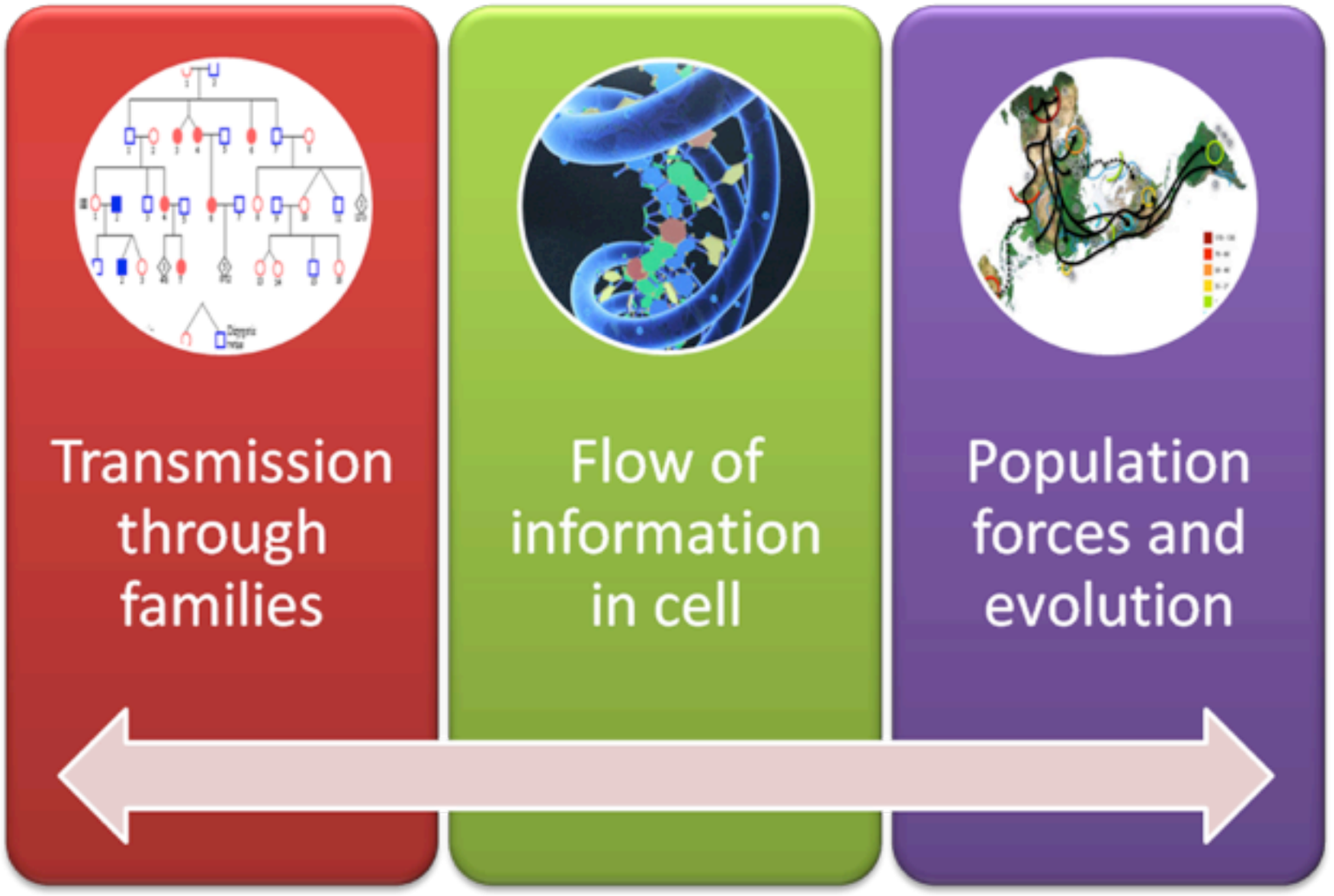
| | Mon | Tues | Wed | Thurs | Fri |
|---|---|---|---|---|---|
| 8:00 – 8:30 | Breakfast | Breakfast | Breakfast | Breakfast | Breakfast |
| 8:30-9:30 | Introduction and Pre-Test<br>*Dr. Bruce Korf* | Genotyping Technologies and Copy Number Variation Analysis<br>*Drs. Molly Bray & Fady Mikhail* | Next-Generation Sequencing<br>*Dr. Mike Crowley* | Genetic Linkage Analysis<br>*Dr. Hemant Tiwari* | Approaches to Bioinformatic Data Analysis<br>*Dr. David Crossman* |
| 9:30- 10:30 | Approaches to Gene Discovery<br>*Dr. Bruce Korf* | Microarray-Based Approaches for Gene Expression and Methylation Status<br>*Dr. Molly Bray* | Whole Genome Functional Assays<br>*Dr. Mike Crowley* | Design and Analysis of Genetic Association Studies | Bioinformtic Pathway and Ontology Analysis<br>*Dr. David Crossman* |
| 10:30- 12:30 | Case Studies/ Translational Genomics<br>*Dr. Bruce Korf* | Analysis of Microarray Data<br>*Dr. David Crossman* | Functional Genomics<br>*Dr. Mike Crowley* | Linkage Analysis, PLINK Demo | Use of Bioinformatic Databases<br>*Dr. David Crossman* |

# Group Activities

- Monday: Case Studies in Translational Genomics
- Tuesday: Analysis of Microarray Data
- Wednesday: Functional Genomics
- Thursday: Linkage Analysis, PLINK Demo
- Friday: Use of Bioinformatic Databases

# Genetics

Scientific discipline that deals with the variability and transmission of biological traits.



# Genomics

"For the newly developing discipline of mapping/ sequencing (including analysis of the information) we have adopted the term GENOMICS. We are indebted to T. H. Roderick of the Jackson Laboratory, Bar Harbor, Maine, for suggesting the term. The new discipline is born from a marriage of molecular and cell biology with classical genetics and is fostered by computational science."

(Victor A. McKusick and Frank H. Ruddle. A new discipline, a new name, a new journal [editorial]. Genomics 1987 Sep; 1:1-2.)

# Family Studies

Archibald Garrod
(1857-1936)

Garrod, Archibald E. 1902. The Incidence of Alkaptonuria: A Study in Chemical Individuality. *Lancet*, vol. ii, pp. 1616-1620.

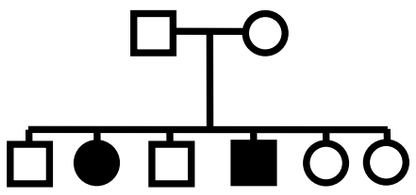
**THE INCIDENCE OF ALKAPTONURIA:**
**A STUDY IN CHEMICAL INDIVIDUALITY**

ARCHIBALD E. GARROD

Physician to the Hospital for Sick Children, Great Ormondstreet,
Demonstrator of Chemical Pathology at St. Bartholemew's Hospital

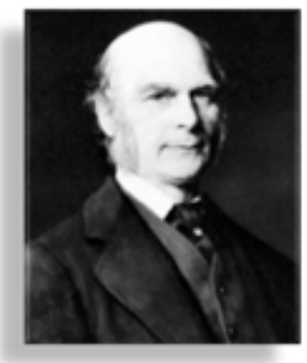
ALL THE MORE RECENT WORK on alkaptonuria has tended to show that the constant feature of that condition is the excretion of

Multifactorial
Inheritance



Mendelian
Genetics

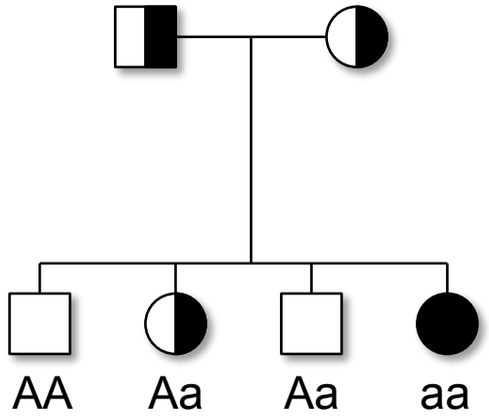
## Biometry and Quantitative Genetics



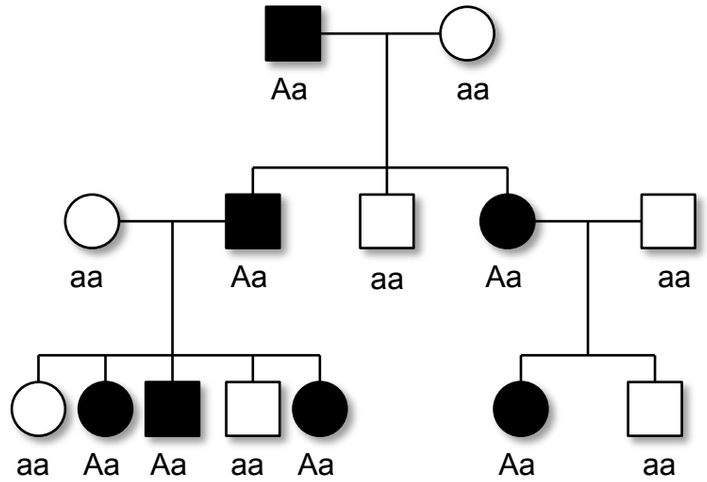
Francis Galton (1822-1911) Statistical approaches to measurement; "eugenics"

Karl Pearson (1857-1936) Mathematical statistics and eugenics

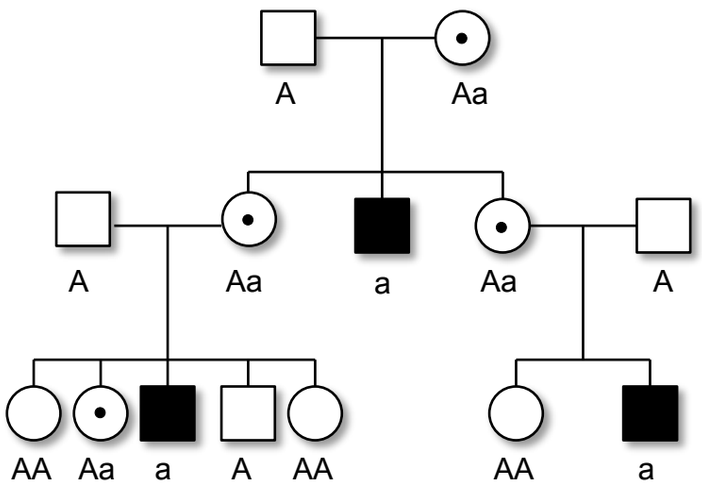
# Mendelian Genetics



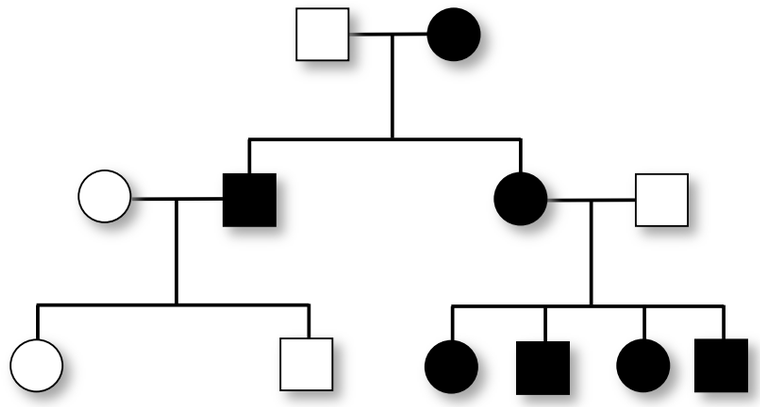

Autosomal Recessive




Autosomal Dominant

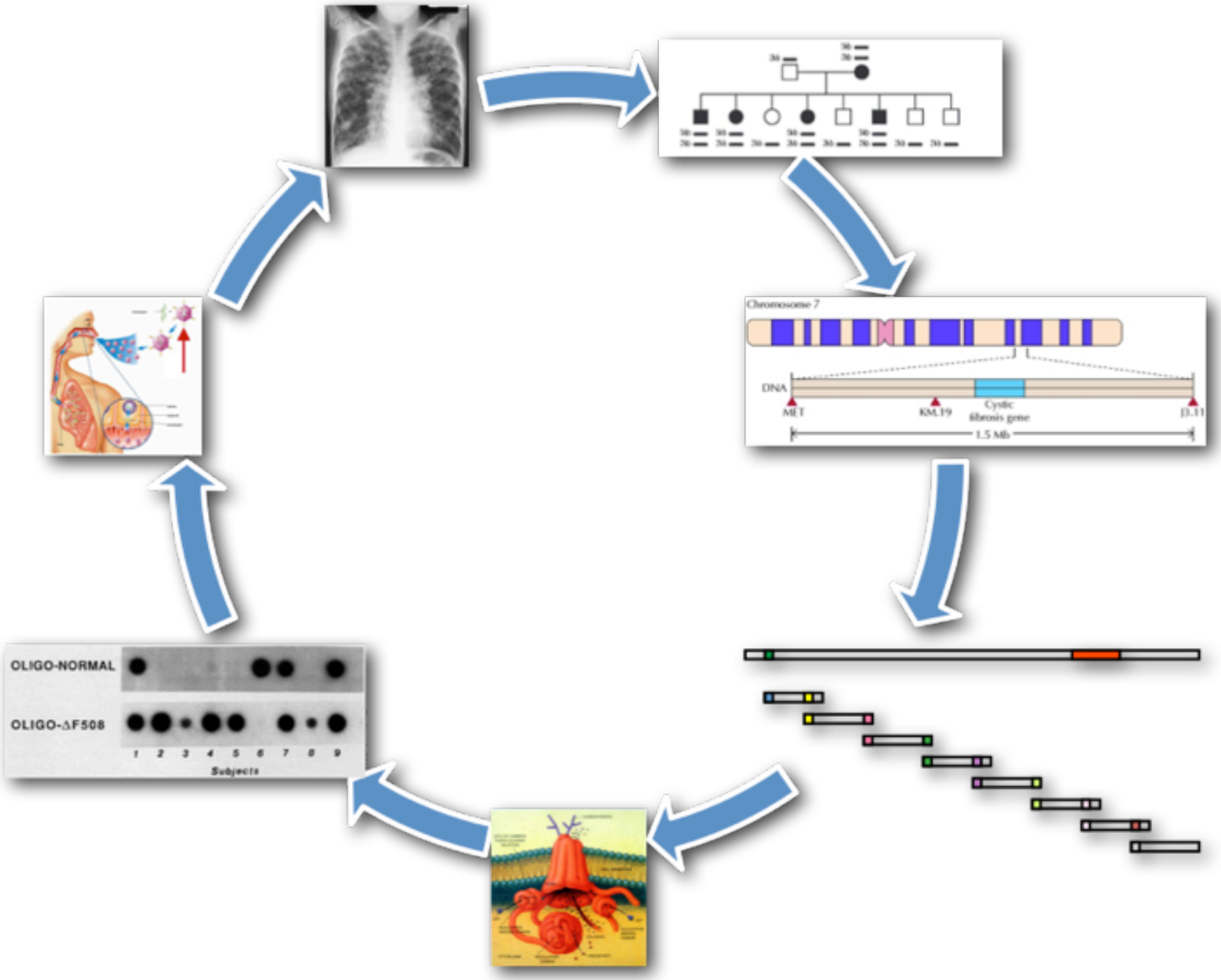



X-linked



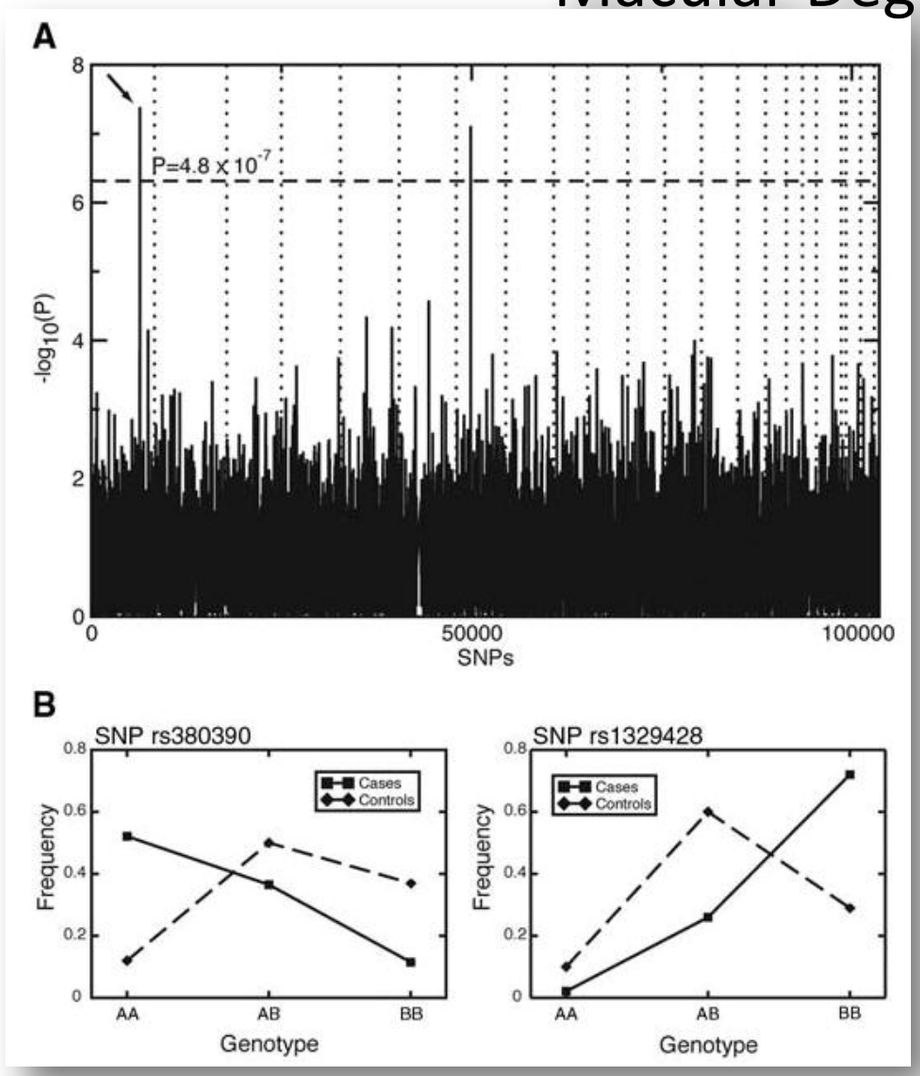
Mitochondrial

# Gene Identification

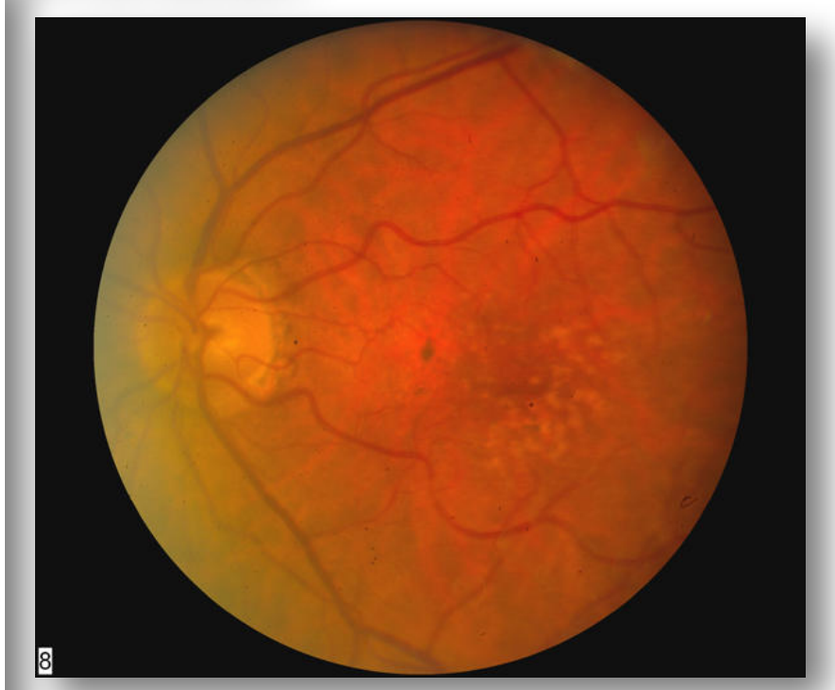


# Population-Based Studies

## Complement Factor H Polymorphism in Age-Related Macular Degeneration

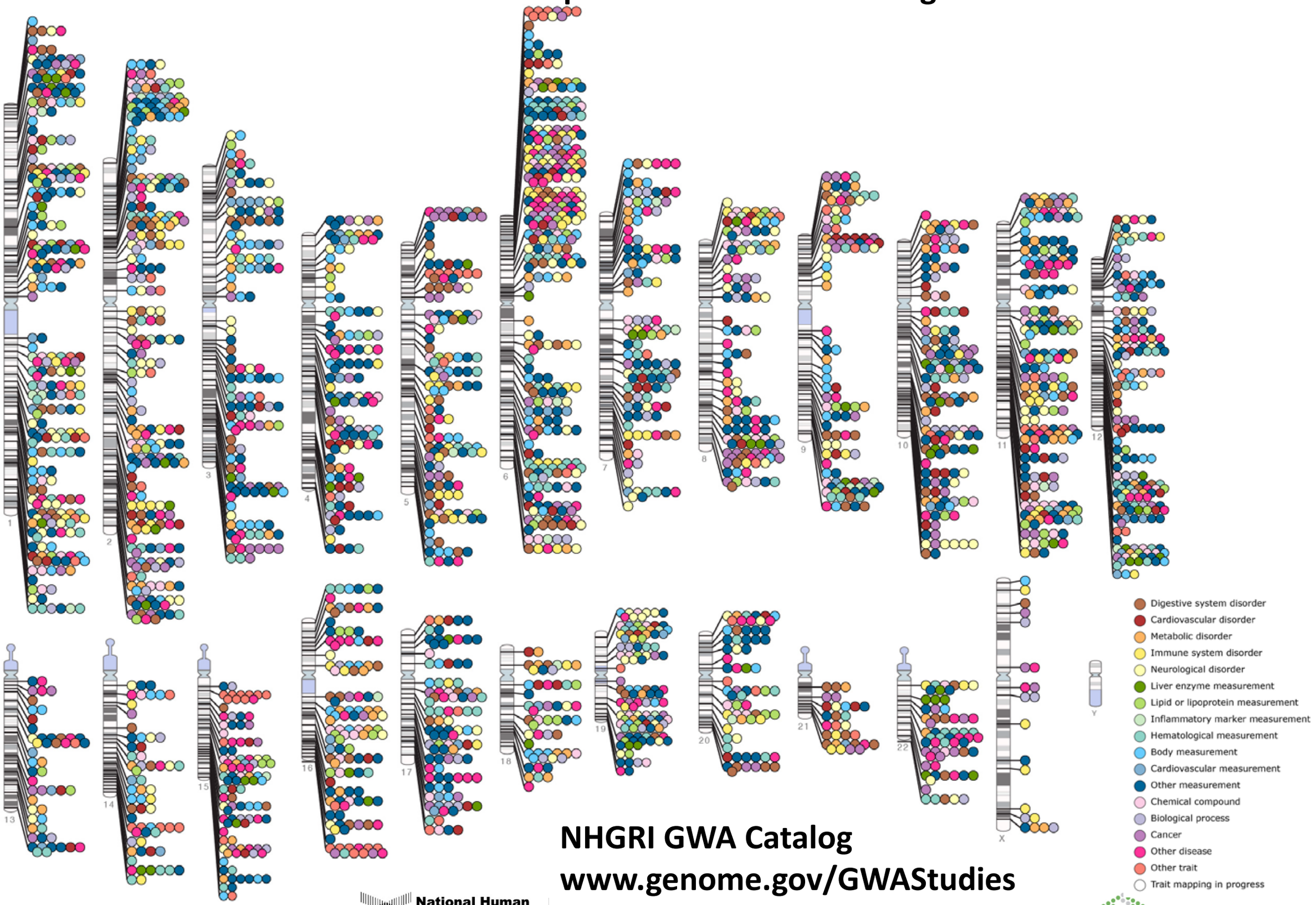



Klein et al., Science (80- ). 2005 April 15; 308(5720): 385–389.



http://www.medrounds.org/amd/uploaded_images/fig2-757825.JPG

# Published Genome-Wide Associations through 07/2012
# Published GWA at p≤5X10$^{-8}$ for 18 trait categories



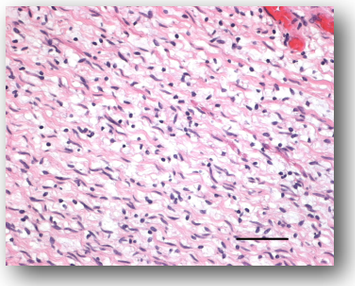

**NHGRI GWA Catalog**
**www.genome.gov/GWAStudies**
**www.ebi.ac.uk/fgpt/gwas/**

National Human Genome Research Institute

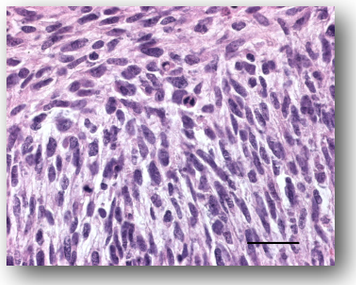
EMBL-EBI

# Cancer Genomes

Normal

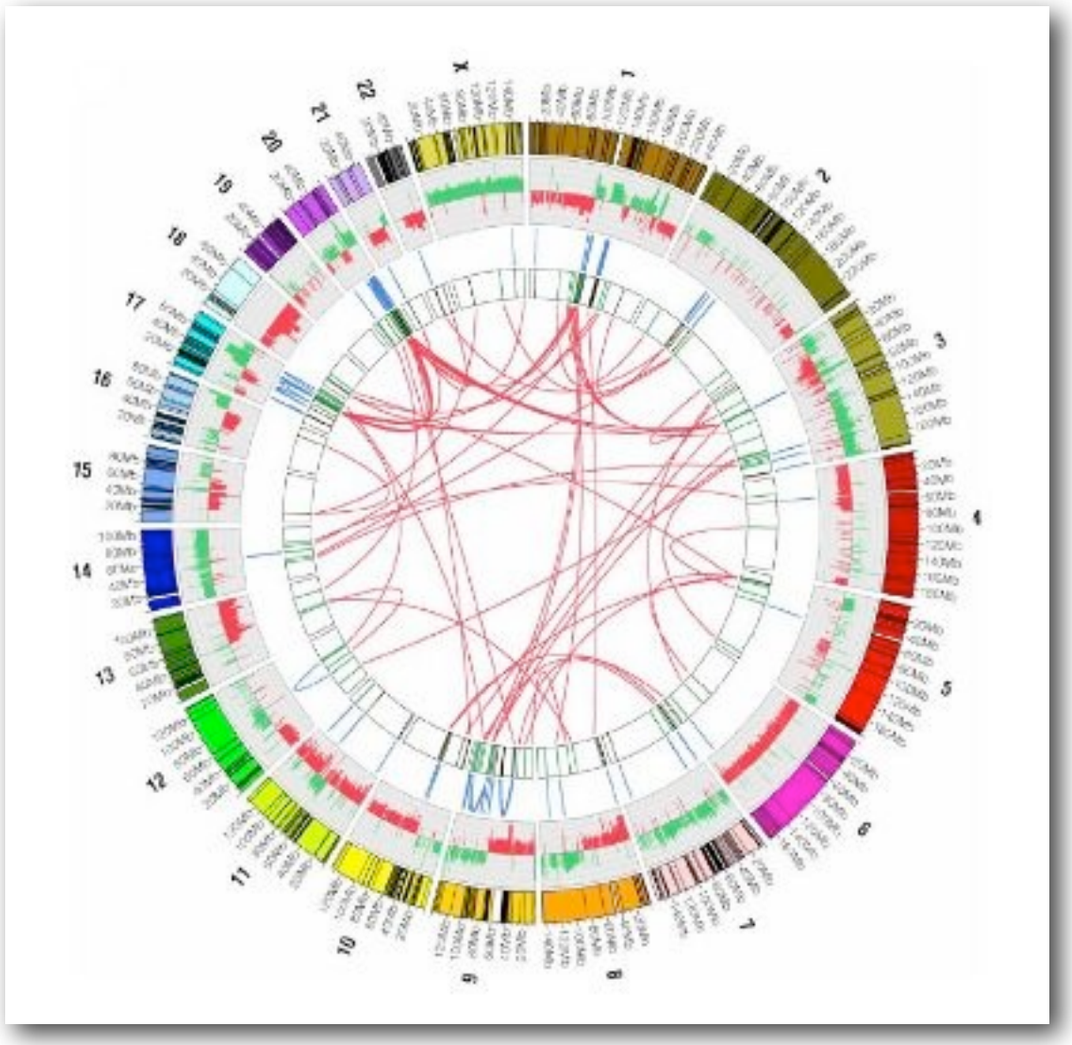


Tumor

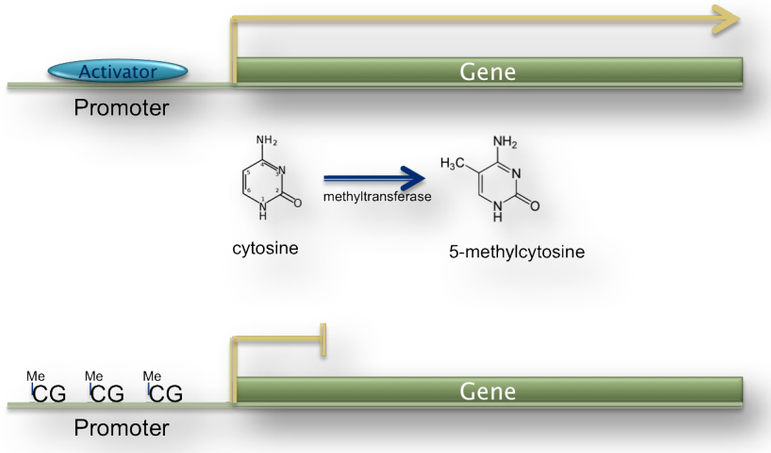


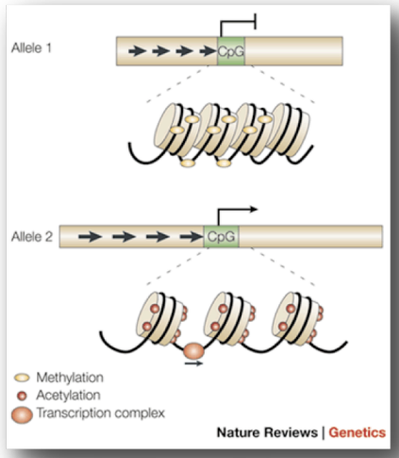
Sequence

Difference =
cancer-specific genetic
changes

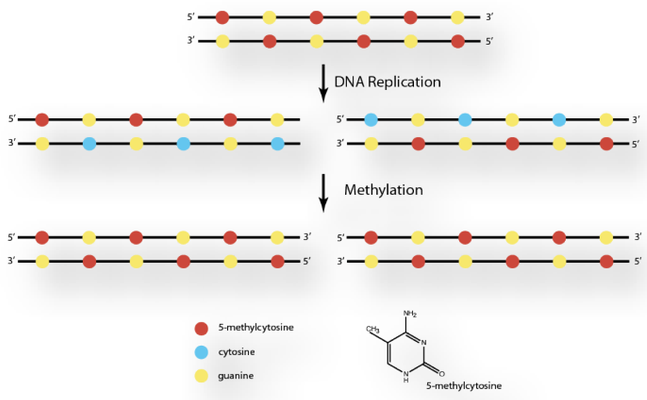


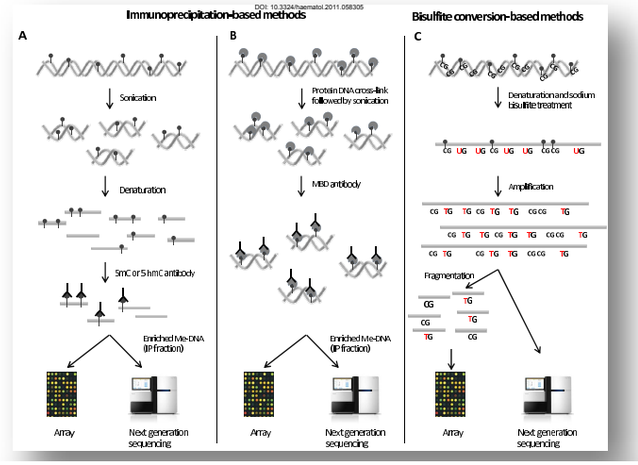
# Epigenetics



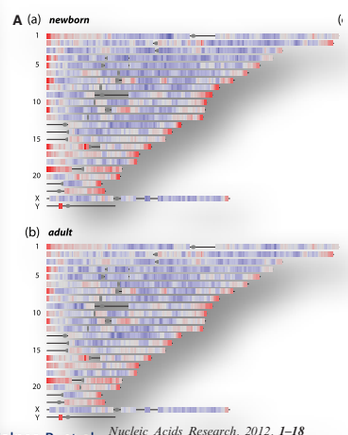




Wolf Reik & Jörn Walter
***Nature Reviews Genetics* 2, 21-32**



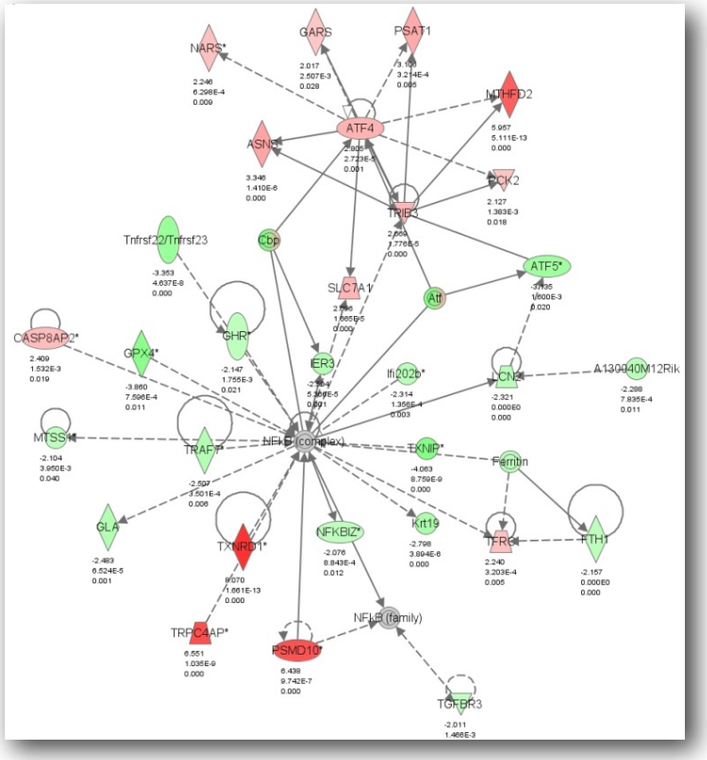



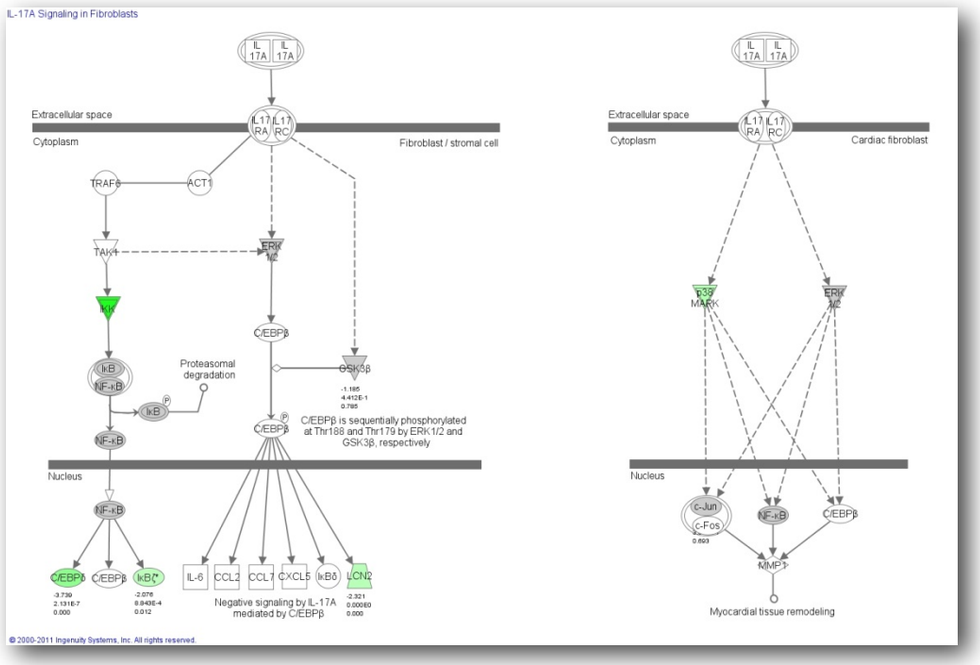

*Citation: Gronbaek K, Muller-Tidow C, Perini G, Lehmann S, Treppendahl MB, Mills K, Plass C, and Schlegelberger B. A critical appraisal of tools available for monitoring epigenetic changes in clinical samples from patients with myeloid malignancies. Haematologica. 2012; 97:xxx doi:10.3324/haematol.2011.058305*



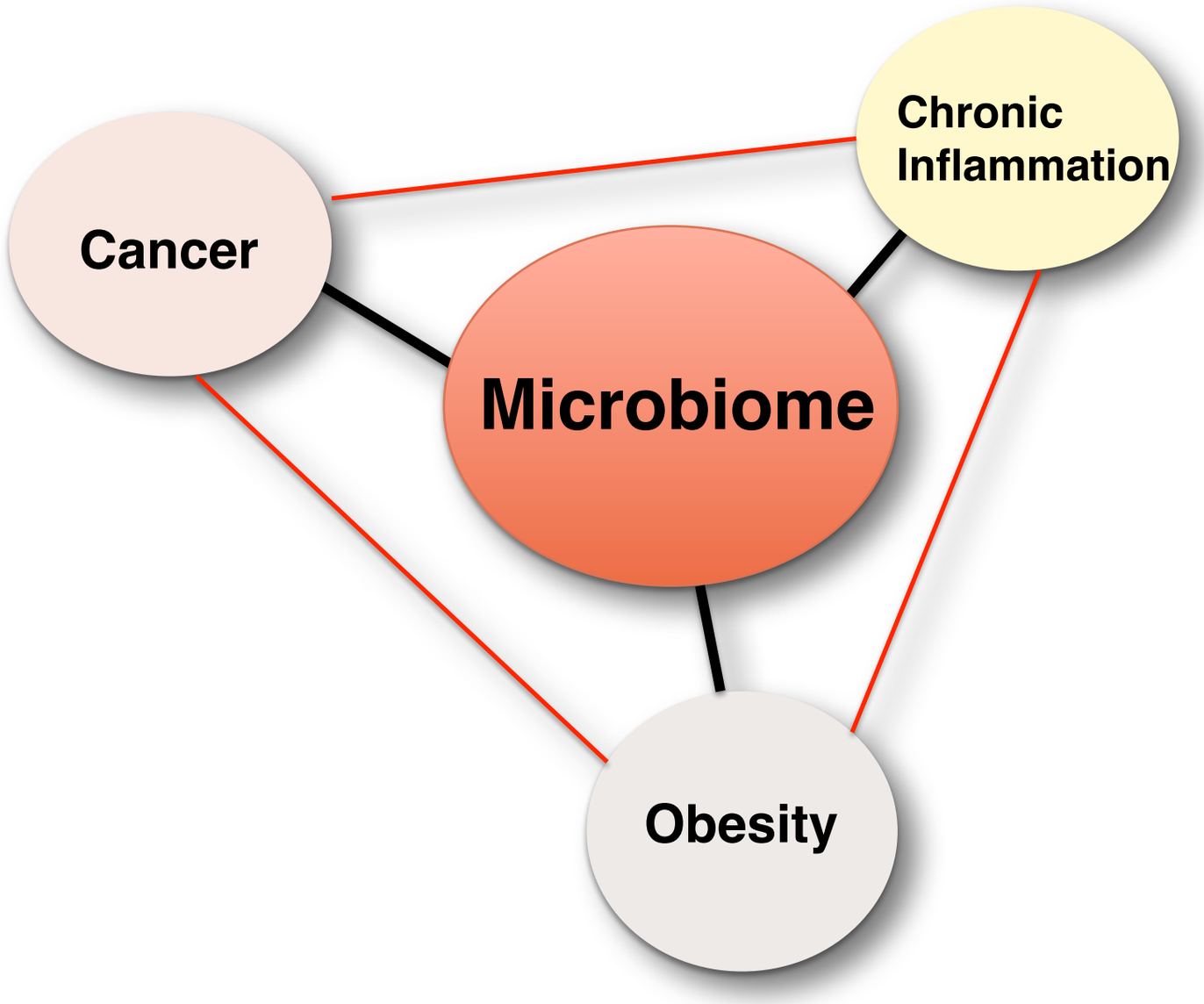

Lipea P, et al. *Nucleic Acids Research, 2012, 1–18 doi:10.1093/nar/gks312*

# Functional Genomics



# Microbiome



# Genetics in Medicine

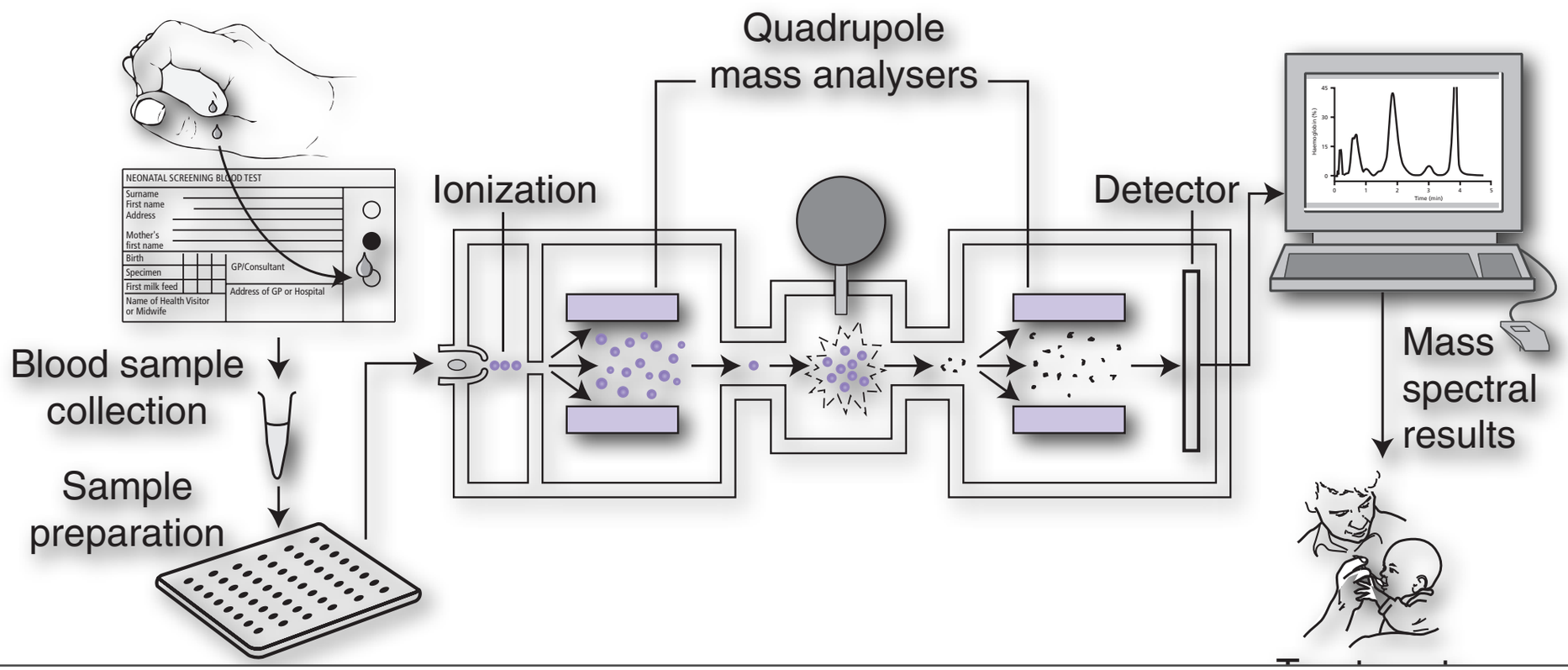
Prevention

Diagnosis

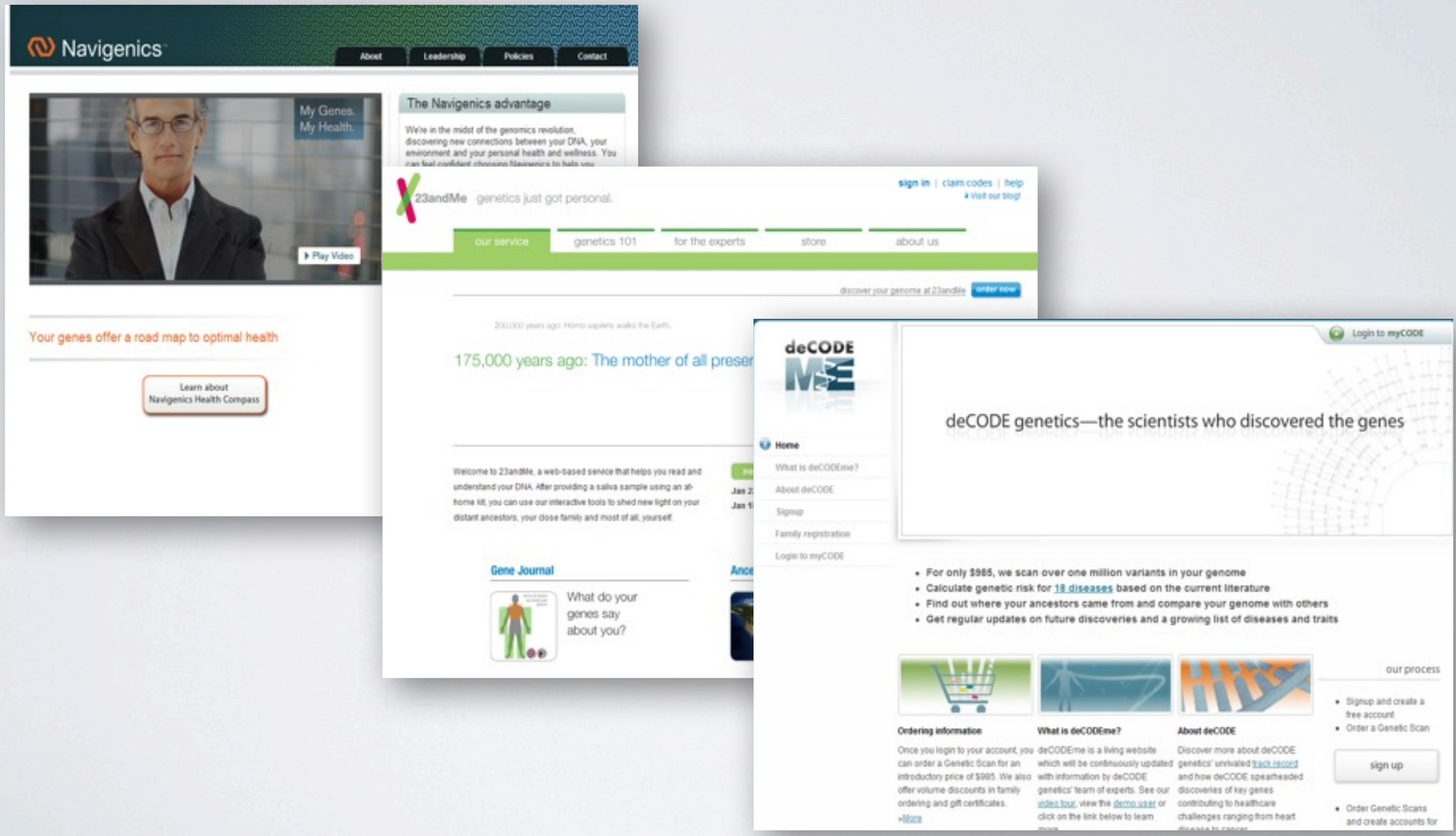
Treatment

# Prevention

# Prevention


NEONATAL SCREENING BLOOD TEST
Surname
First name
Address
Mother's first name
Birth
Specimen
First milk feed
Name of Health Visitor or Midwife
GP/Consultant
Address of GP or Hospital
Blood sample collection
Sample preparation
Quadrupole mass analysers
Ionization
Detector
Mass spectral results

# DIRECT-TO-CONSUMER TESTING



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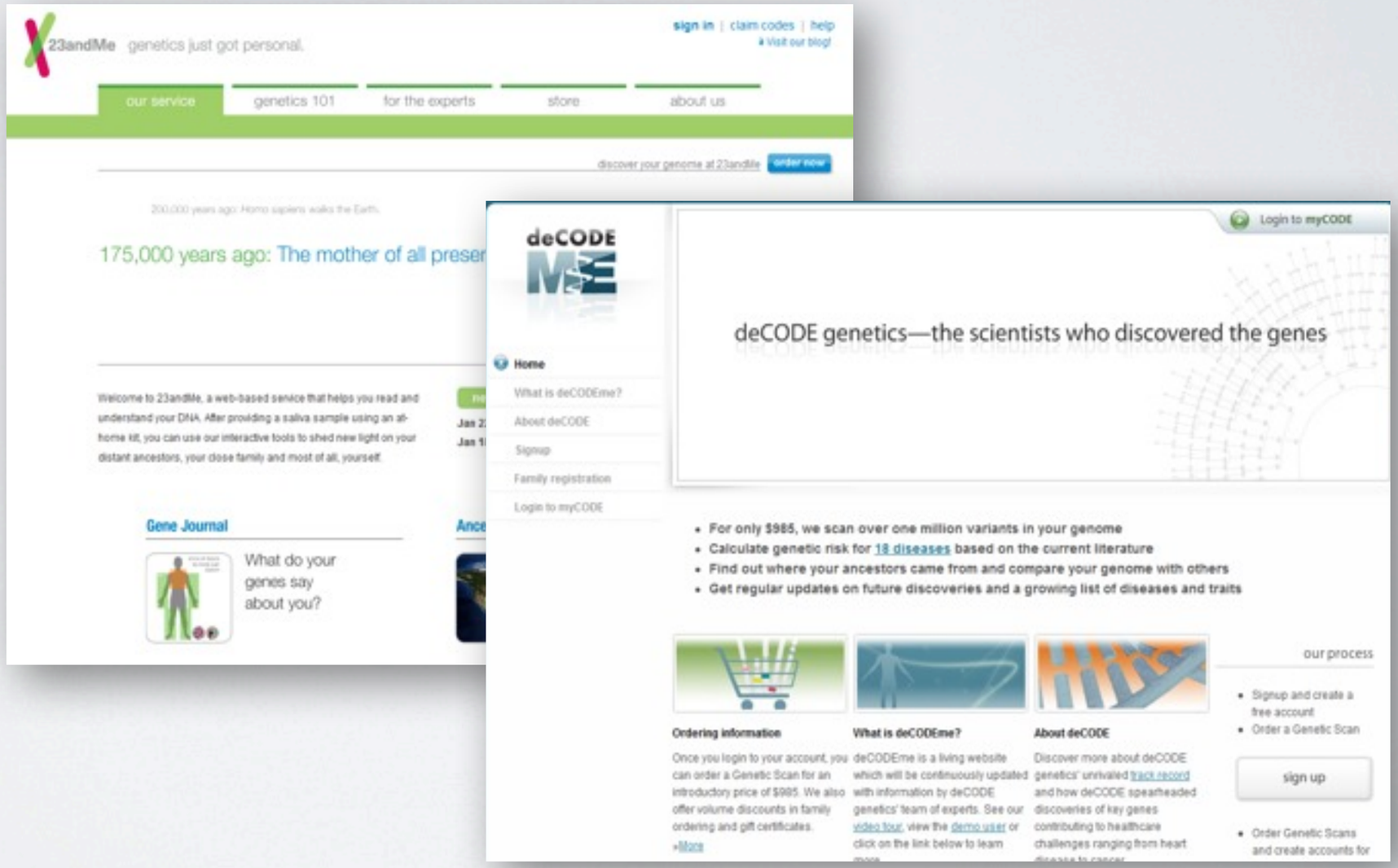

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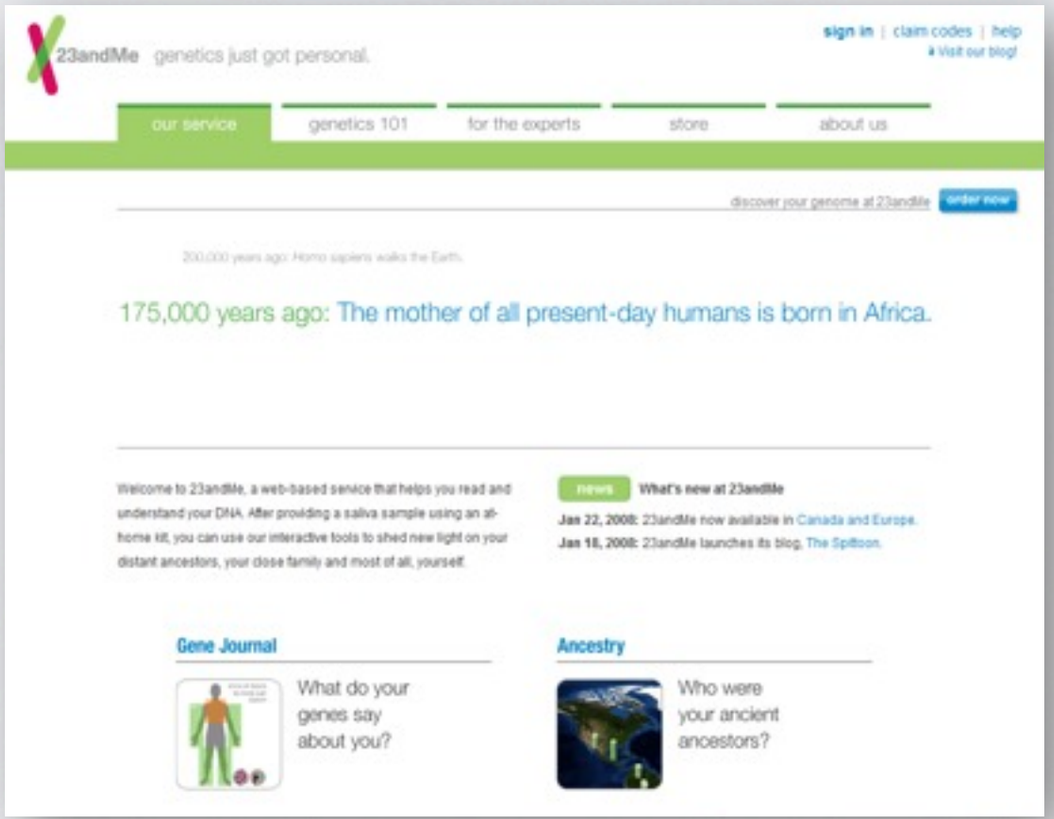
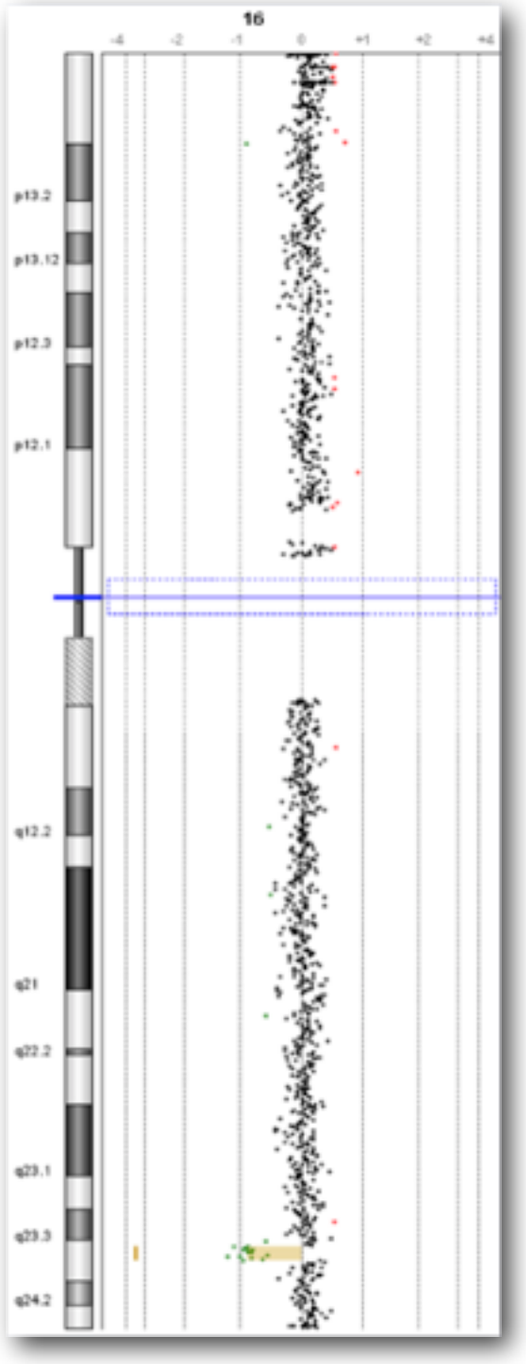
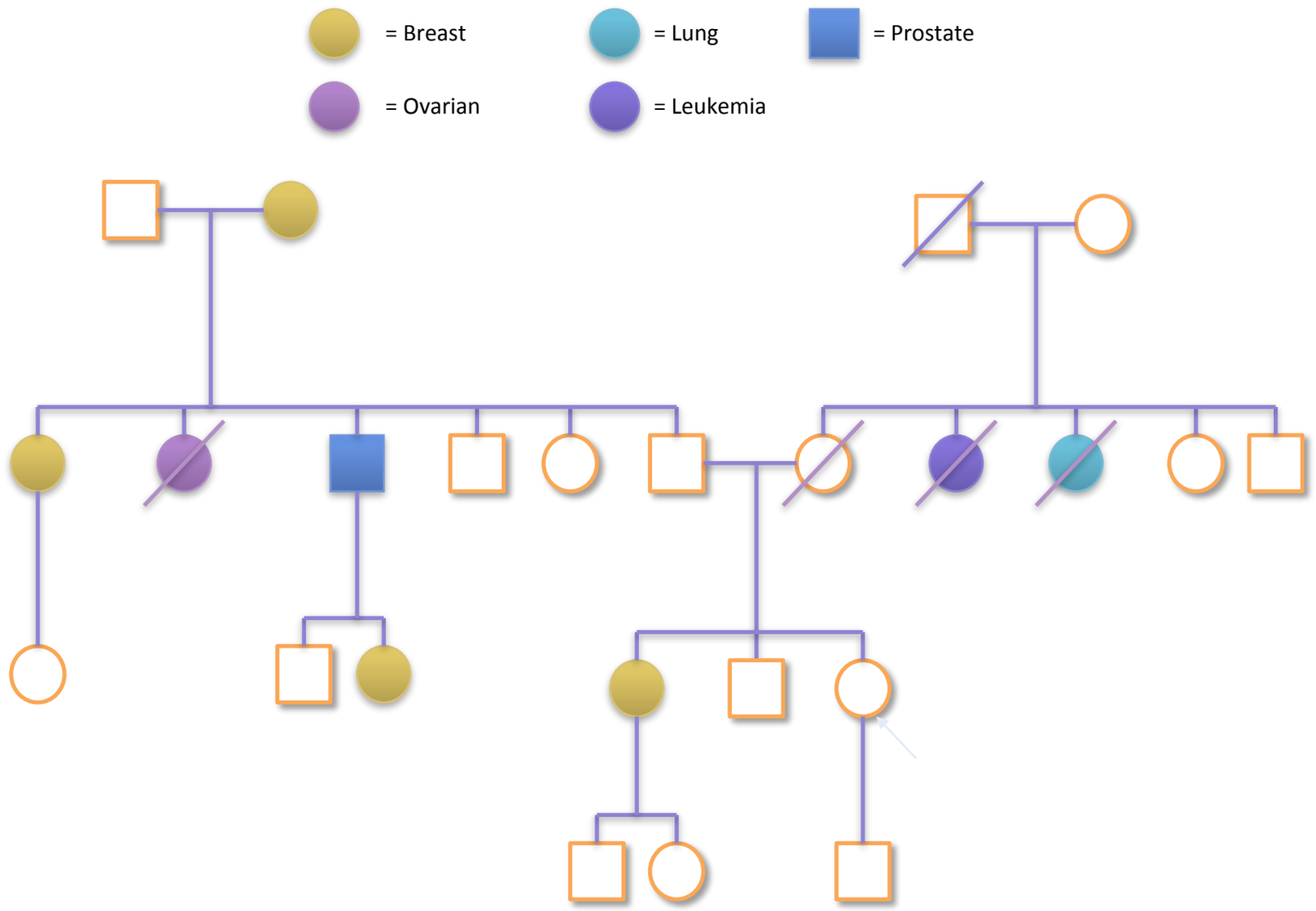


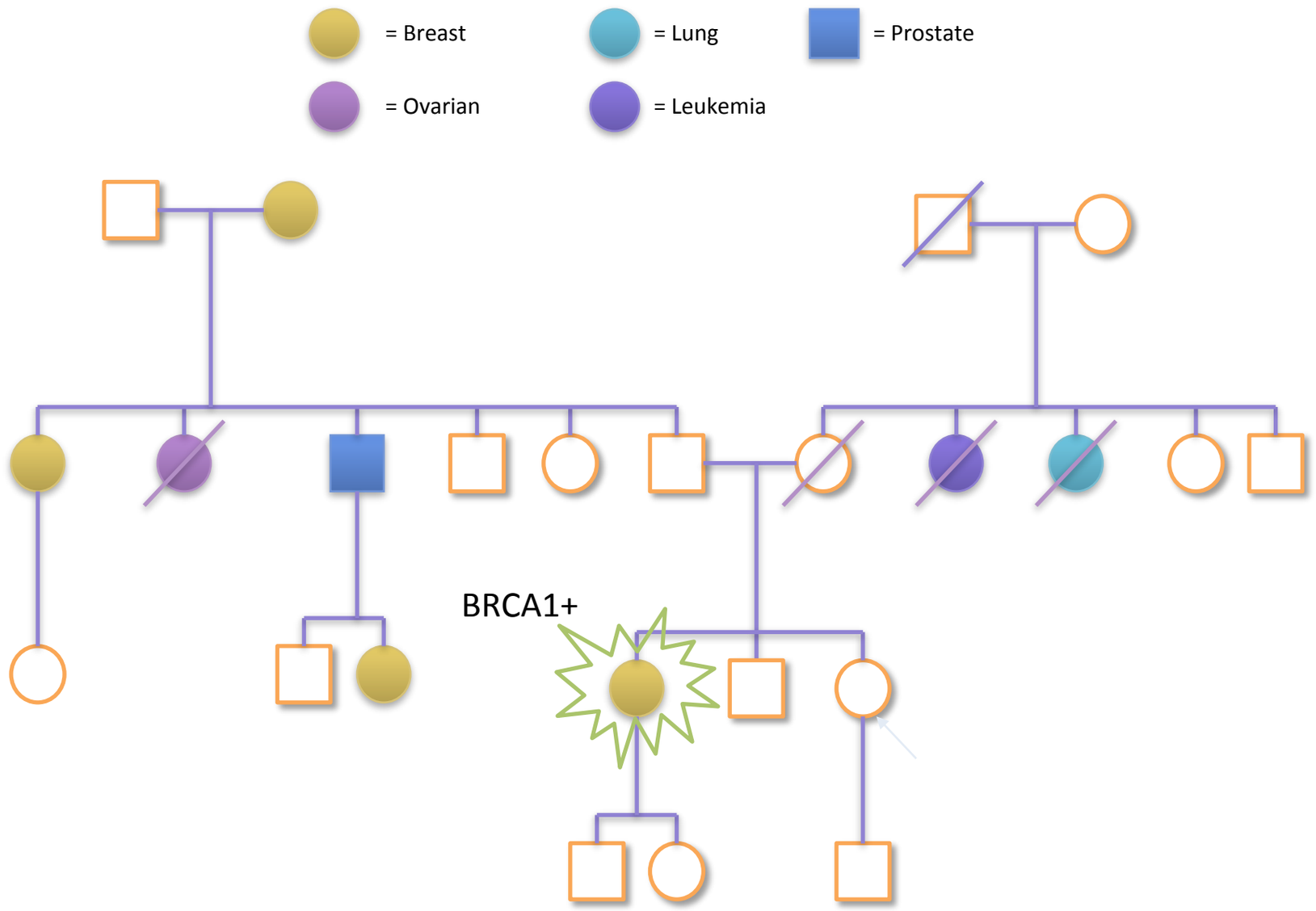
# Diagnosis



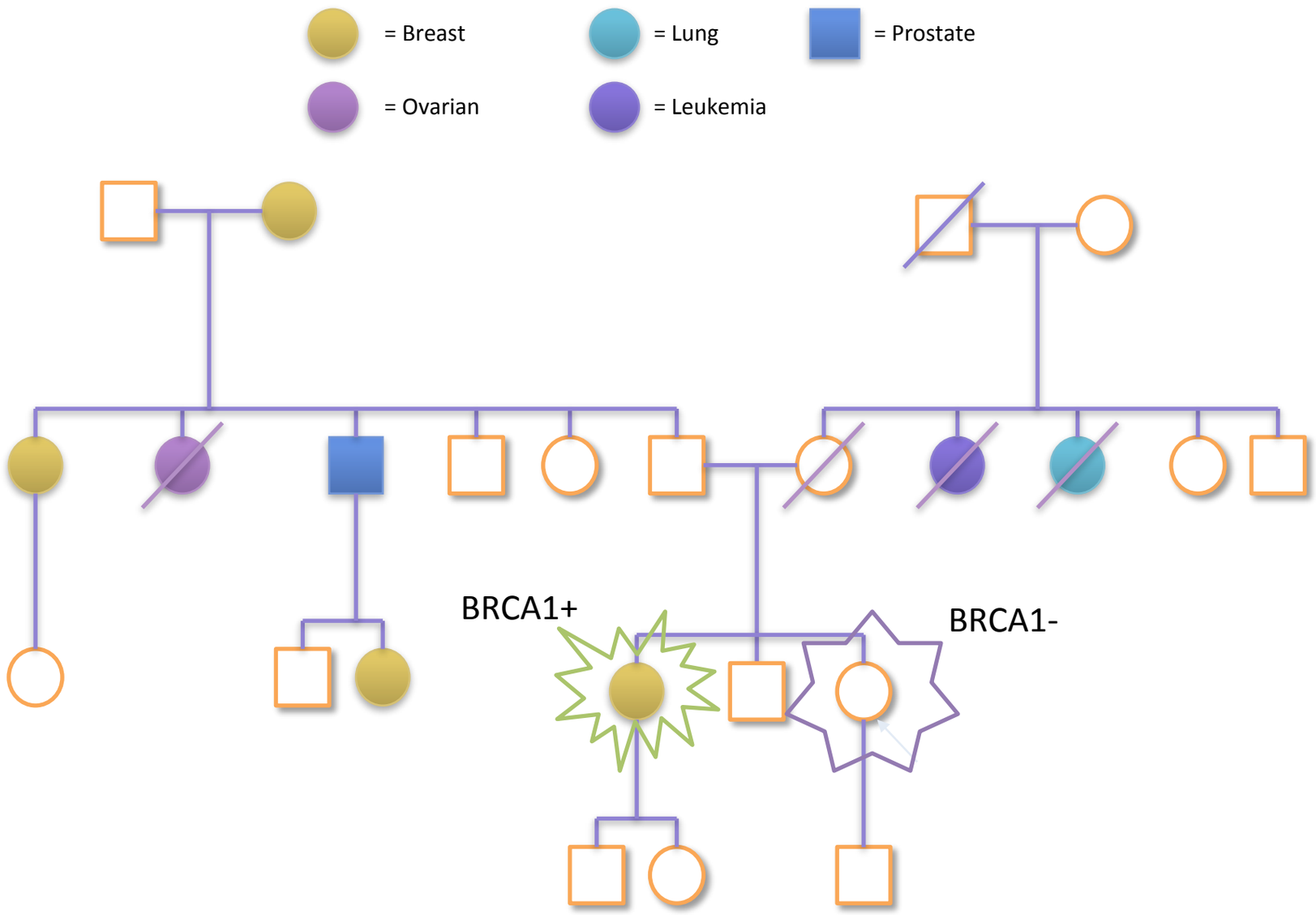

# Presymptomatic Diagnosis



# Presymptomatic Diagnosis

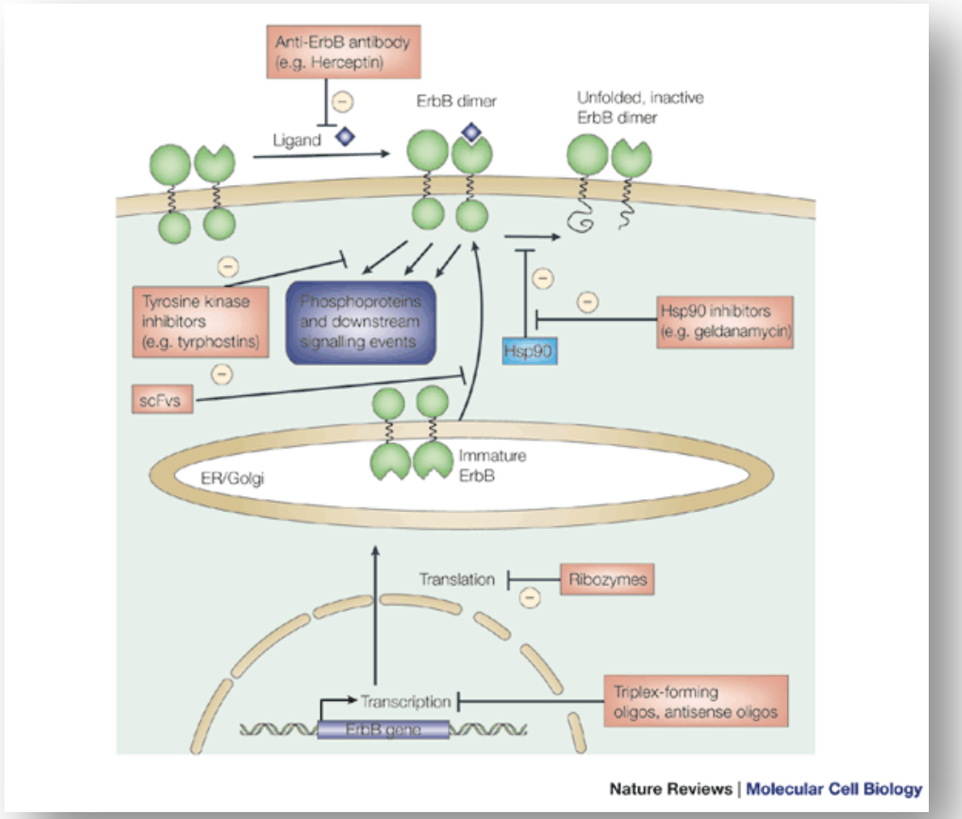


# Presymptomatic Diagnosis



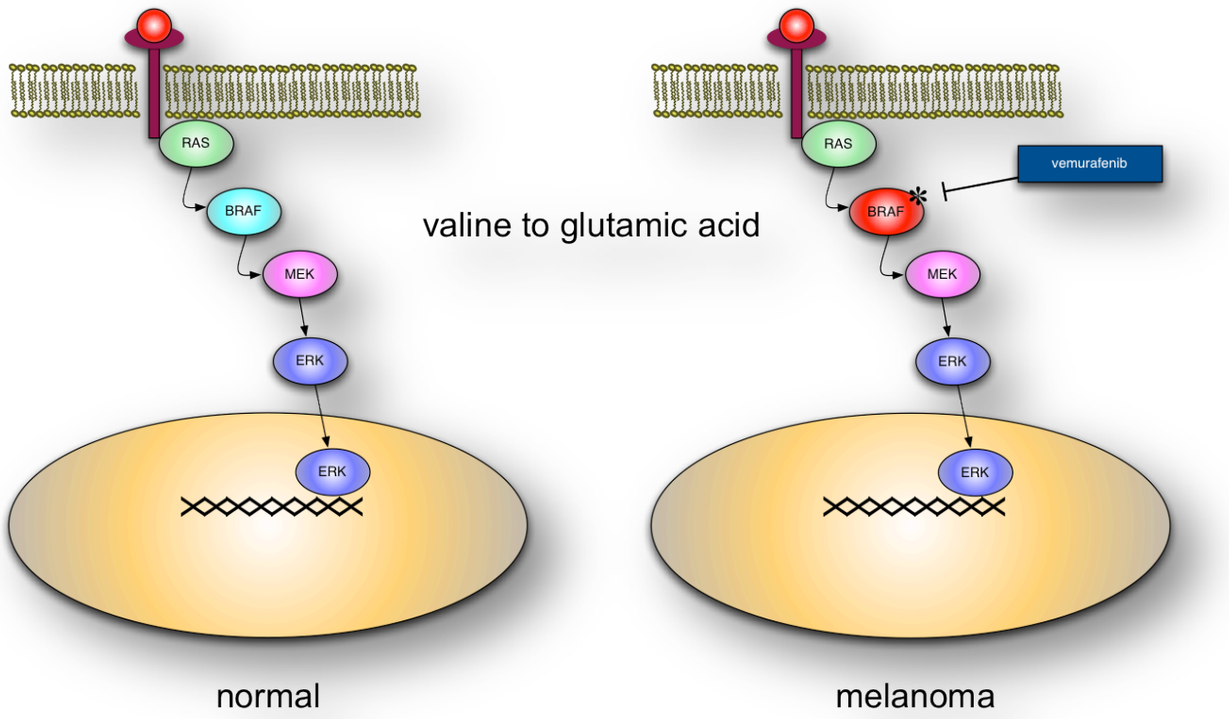
# Therapeutics

## Herceptin

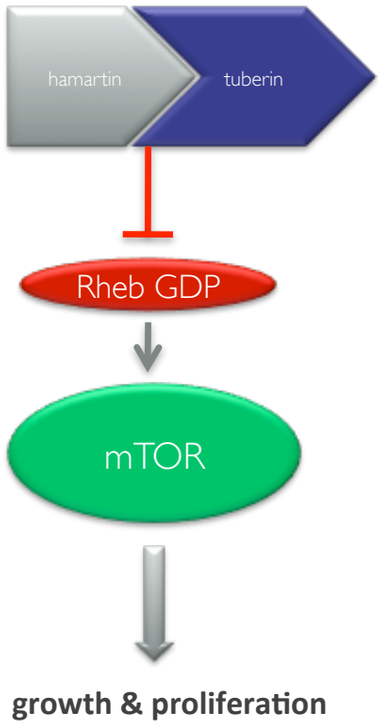


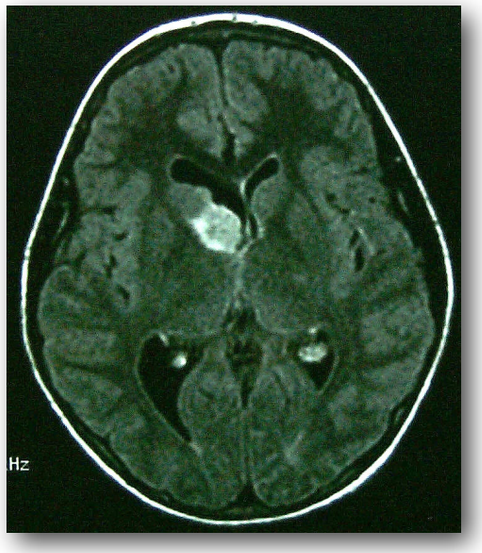

*Nature Reviews Molecular Cell Biology* **2**, 127-137 (2001)

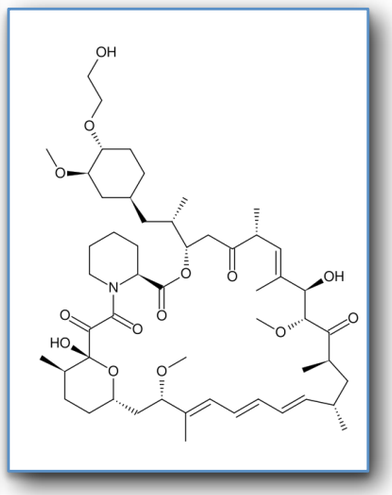
## BRAF V600E in Melanoma

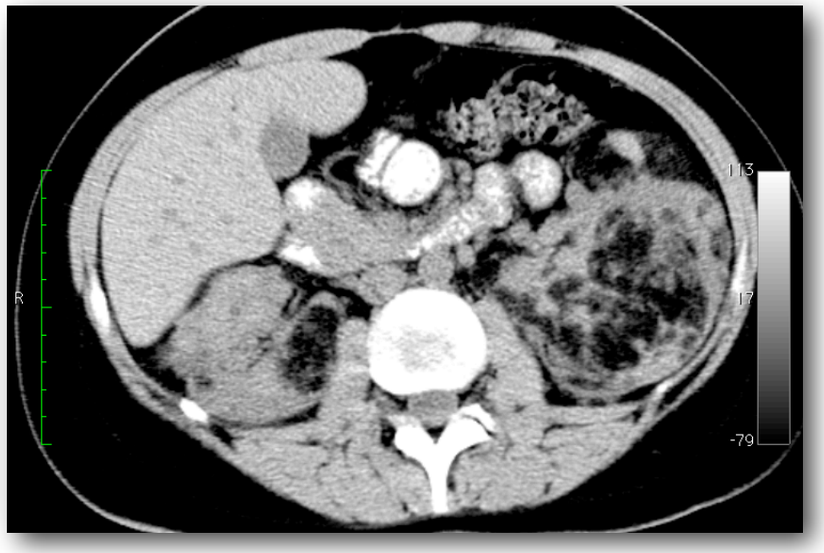


# Everolimus and Tuberous Sclerosis



# Genomics at UAB

University of Alabama at Birmingham
Heflin Center for Genomic Science

HUDSONALPHA
INSTITUTE FOR BIOTECHNOLOGY


- Pilot studies
- Study design
- Low – high throughput studies
- Genetic Epidemiology
- Investigator Education

- High throughput analysis
- Next Generation Sequencing
- RNA Seq

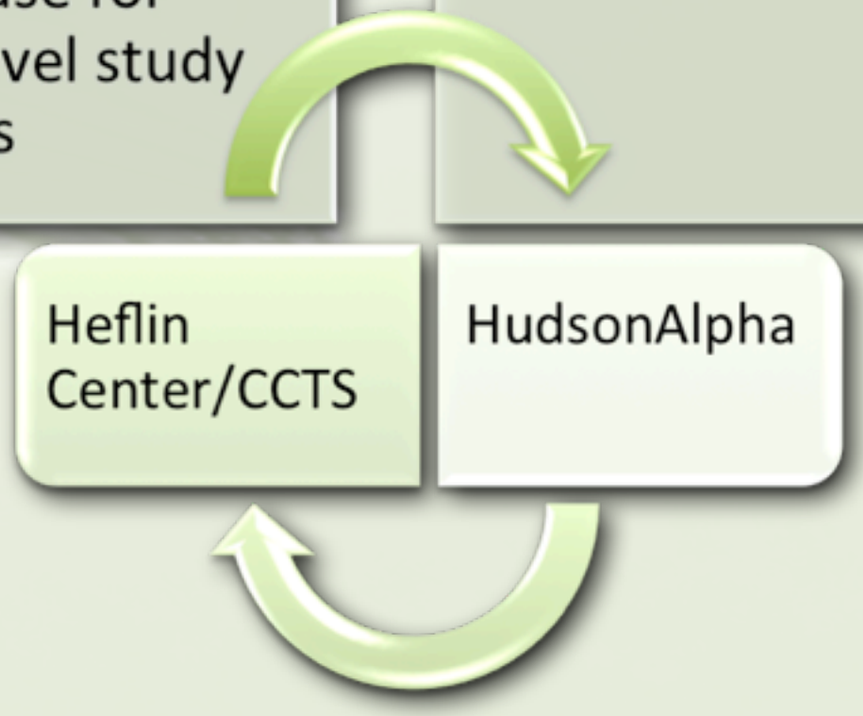
# UAB Program in Genomics & Proteomics

**Genomics & Proteomics Study Navigator**

- Consultation service
- Inventory
- Needs assessment
- Genomics & proteomics roadmap
- Business case for master's level study consultants

**Genomics & Proteomics Educational Coordinator**

- Education & outreach program
- Innovative educational offerings



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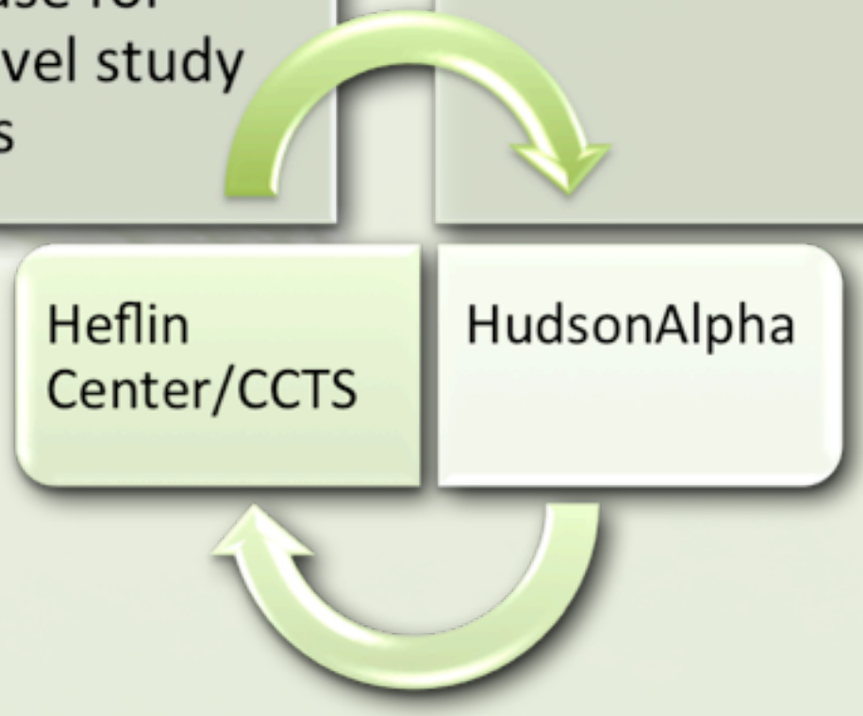


www.heflingenetics.uab.edu

genomics@uab.edu


The best way to predict the future is
to invent it.
Alan Kay
Computer Scientist