

Genetics and Genomics in Clinical Research

An Immersion Course for Clinical
Investigators at UAB

Introduction and Overview

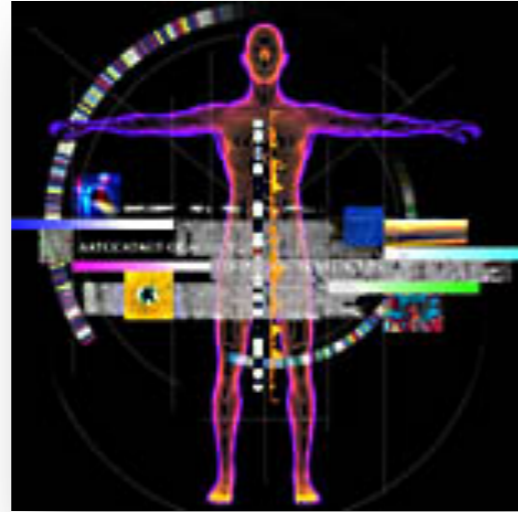
Bruce R. Korf, MD, PhD

Human “Phenome”



Monogenic

- sickle cell
- cystic fibrosis
- Huntington



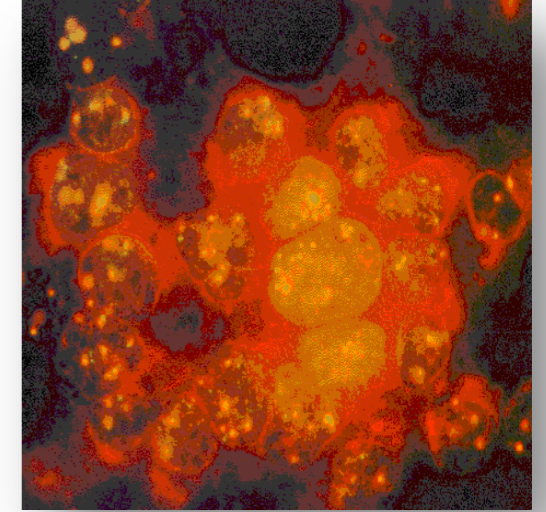
Multifactorial

- asthma
- hypertension
- diabetes



Pharmacogenomics

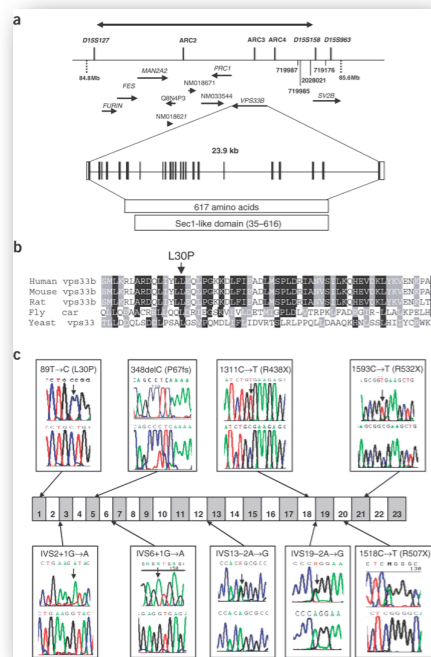
- drug metabolism
- new drug targets



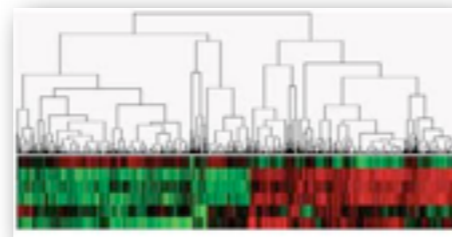
Cancer

- familial
- sporadic

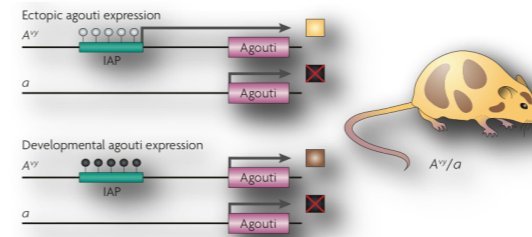
Applications of Genetics and Genomics



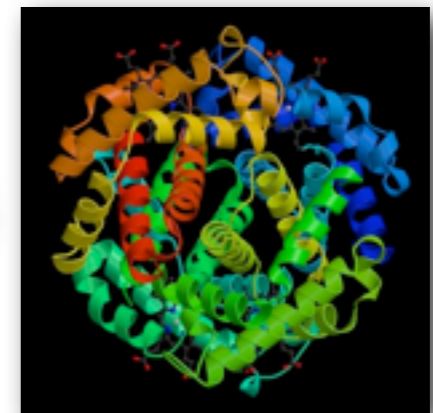
Gene Discovery



Gene Expression

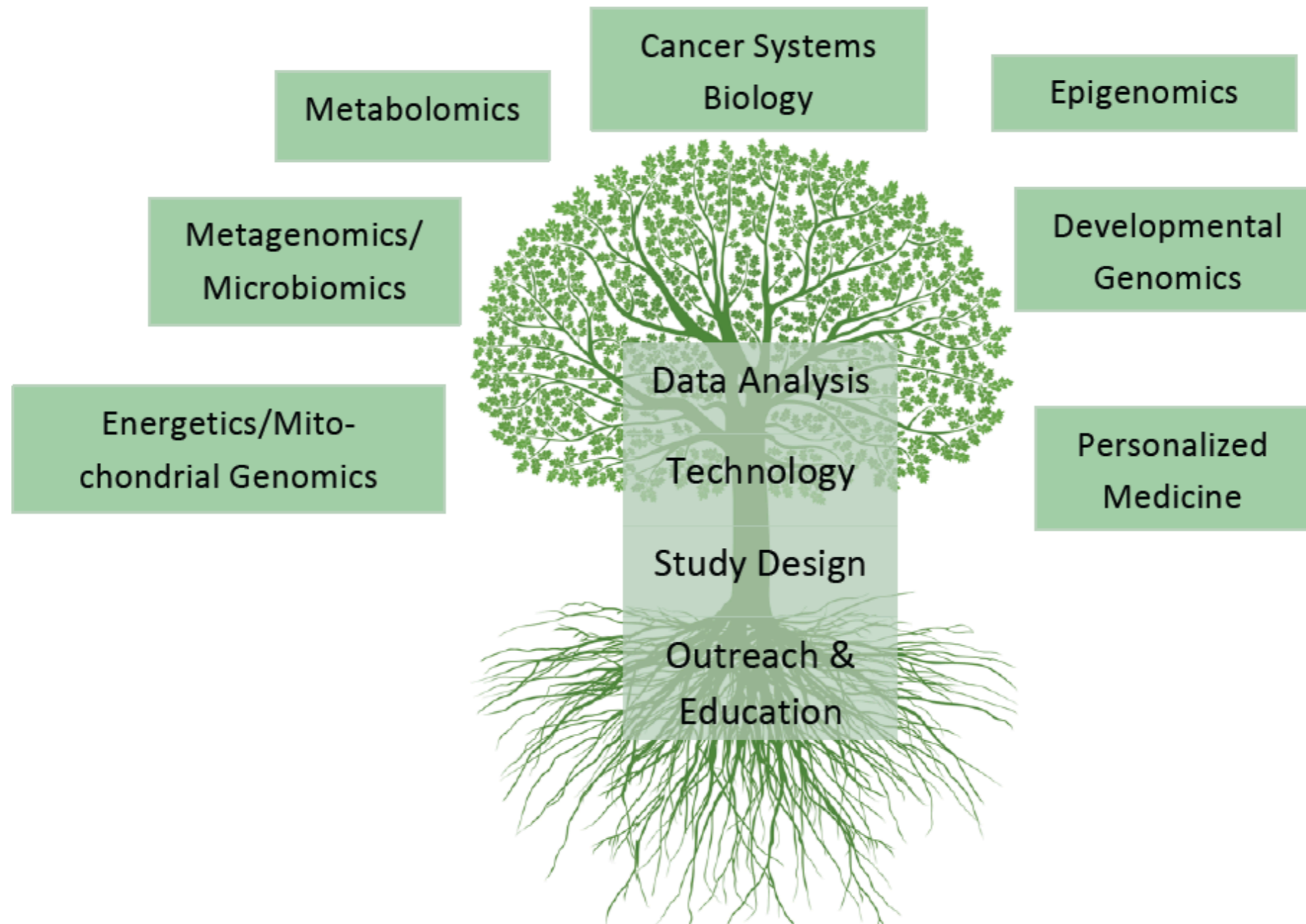


Gene Regulation



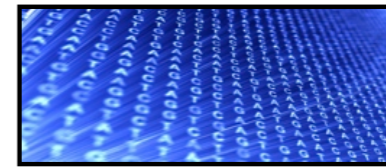
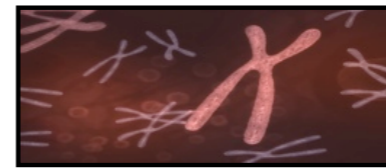
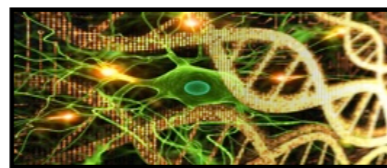
Gene Products

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

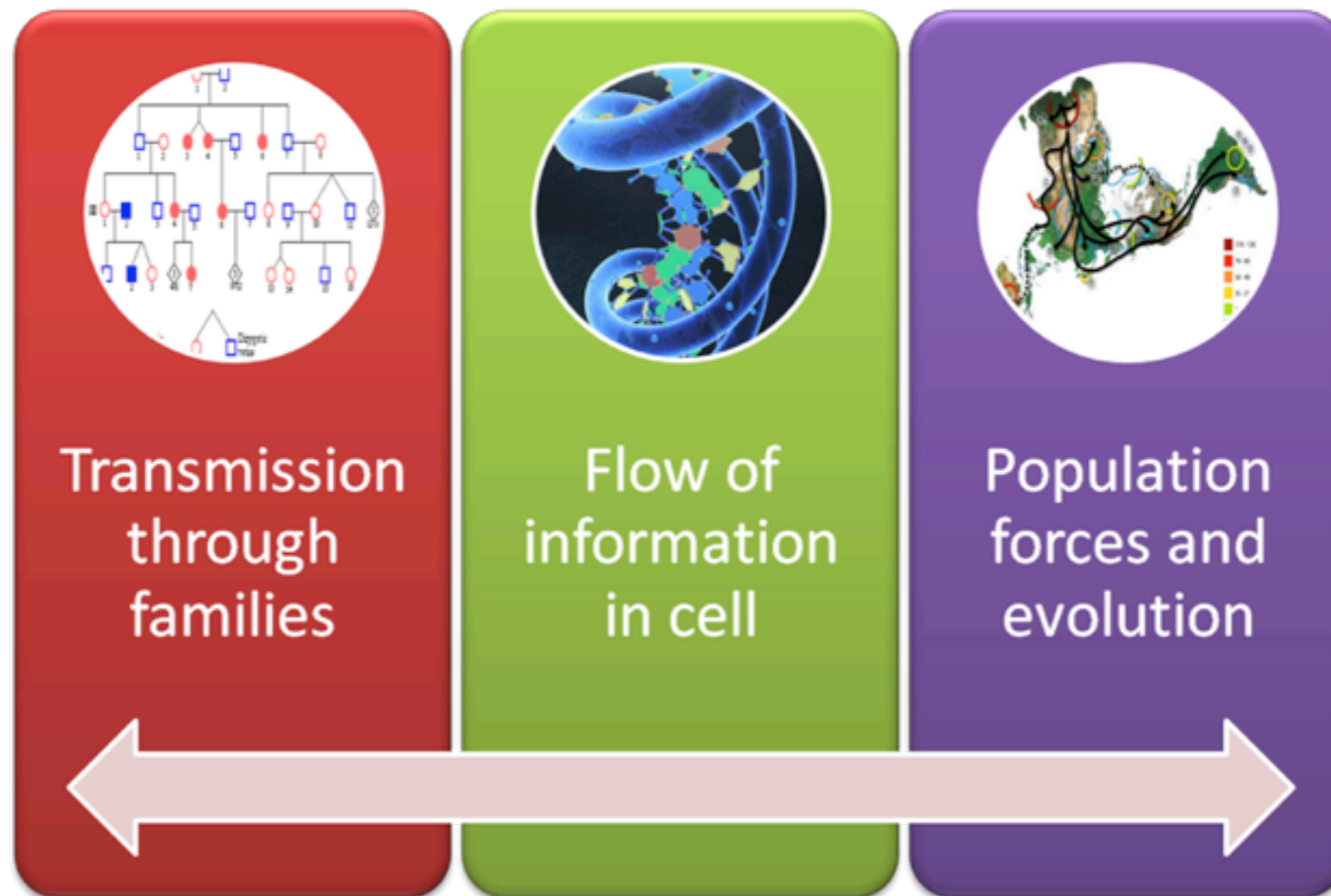
| | M O N | T U E S | W E D | T H U R S | F R I |
|--------------|---|---|---|--|---|
| 8:00 – 8:30 | Breakfast | Breakfast | Breakfast | Breakfast | Breakfast |
| 8:30-9:30 | Introduction and Pre-Test <i>Dr. Bruce Korf</i> | Genotyping Technologies and Copy Number Variation Analysis <i>Drs. Molly Bray & Fady Mikhail</i> | Next-Generation Sequencing <i>Dr. Mike Crowley</i> | Genetic Linkage Analysis <i>Dr. Hemant Tiwari</i> | Approaches to Bioinformatic Data Analysis <i>Dr. David Crossman</i> |
| 9:30- 10:30 | Approaches to Gene Discovery <i>Dr. Bruce Korf</i> | Microarray-Based Approaches for Gene Expression and Methylation Status <i>Dr. Molly Bray</i> | Whole Genome Functional Assays <i>Dr. Mike Crowley</i> | Design and Analysis of Genetic Association Studies | Bioinformtic Pathway and Ontology Analysis <i>Dr. David Crossman</i> |
| 10:30- 12:30 | Case Studies/ Translational Genomics <i>Dr. Bruce Korf</i> | Analysis of Microarray Data <i>Dr. David Crossman</i> | Functional Genomics <i>Dr. Mike Crowley</i> | Linkage Analysis, PLINK Demo | Use of Bioinformatic Databases <i>Dr. David Crossman</i> |

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)

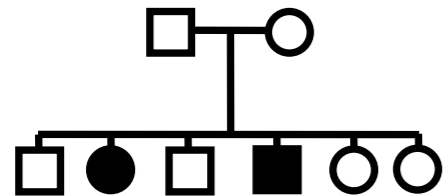


Garrod, Archibald E. 1902. The Incidence of Alkaptonuria: A Study in Chemical Individuality. *Lancet*, vol. ii, pp. 1616-1620.

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

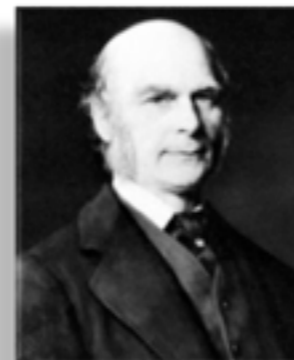


ALL THE MORE RECENT WORK on alkaptonuria has tended to show
that the constant feature of that condition is the excretion of

Mendelian Genetics

Multifactorial Inheritance

Biometry and Quantitative Genetics

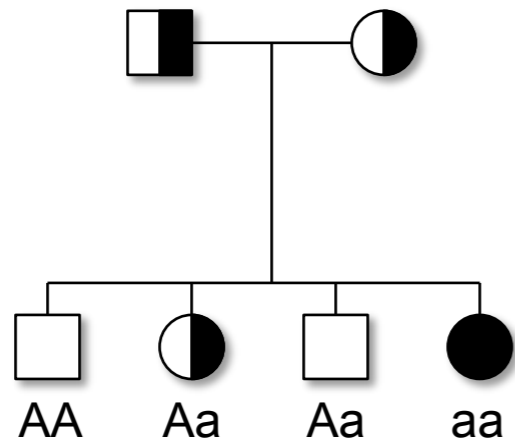


Francis Galton (1822-1911) Statistical approaches to
measurement; "eugenics"

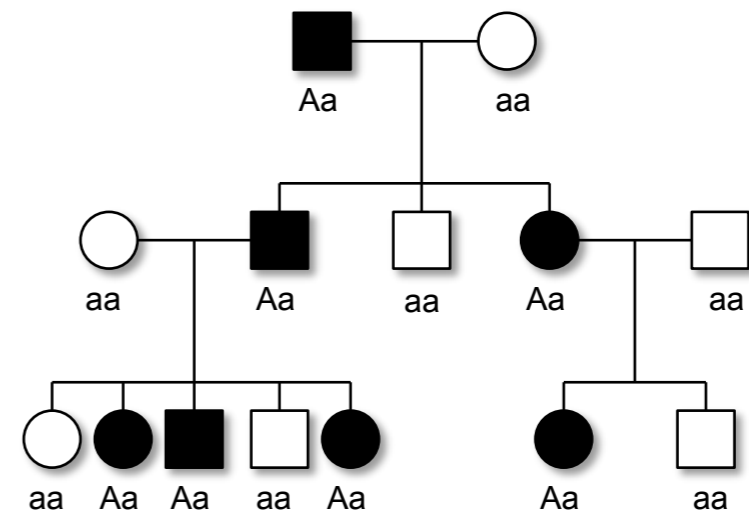
Karl Pearson (1857-1936) Mathematical statistics and
eugenics



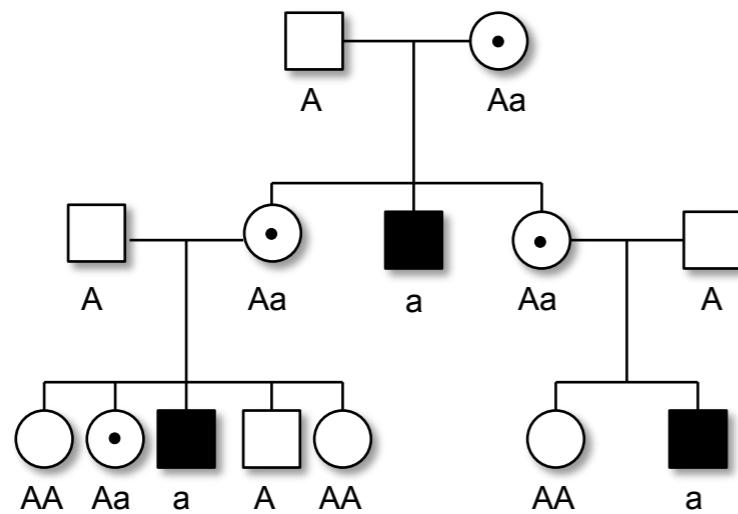
Mendelian Genetics



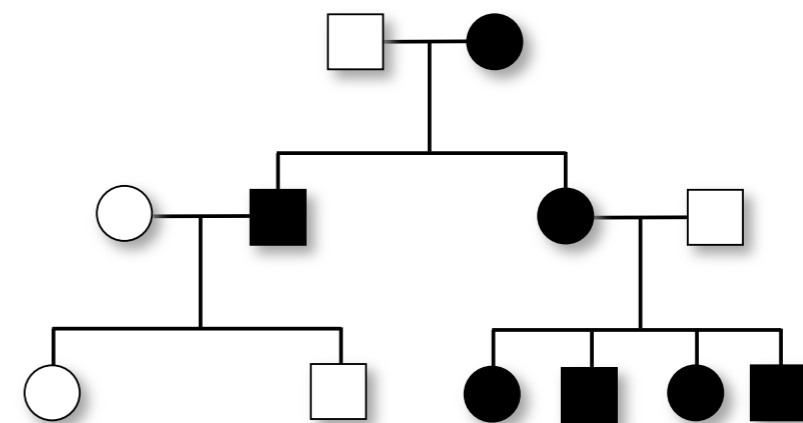
Autosomal Recessive



Autosomal Dominant

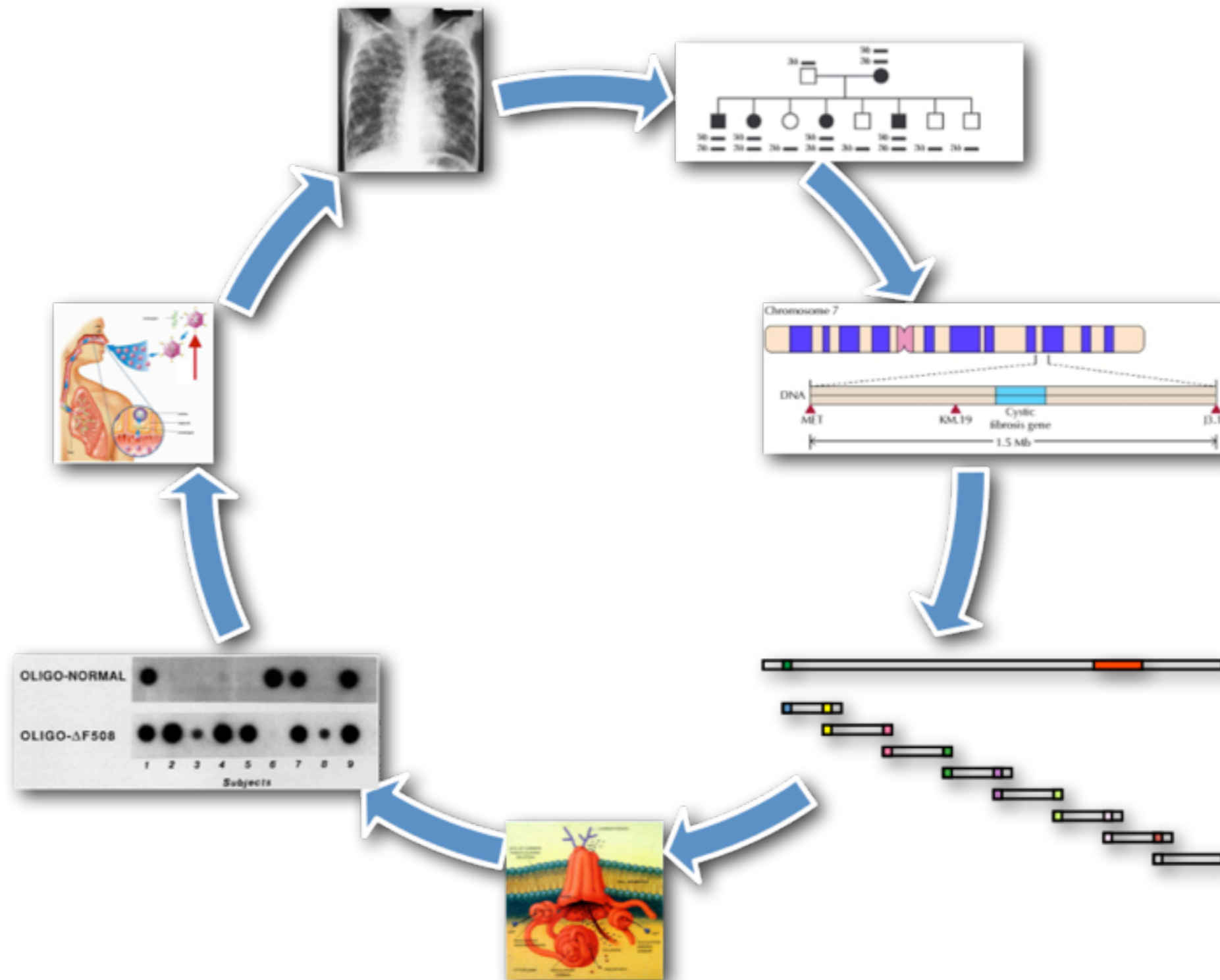


X-linked



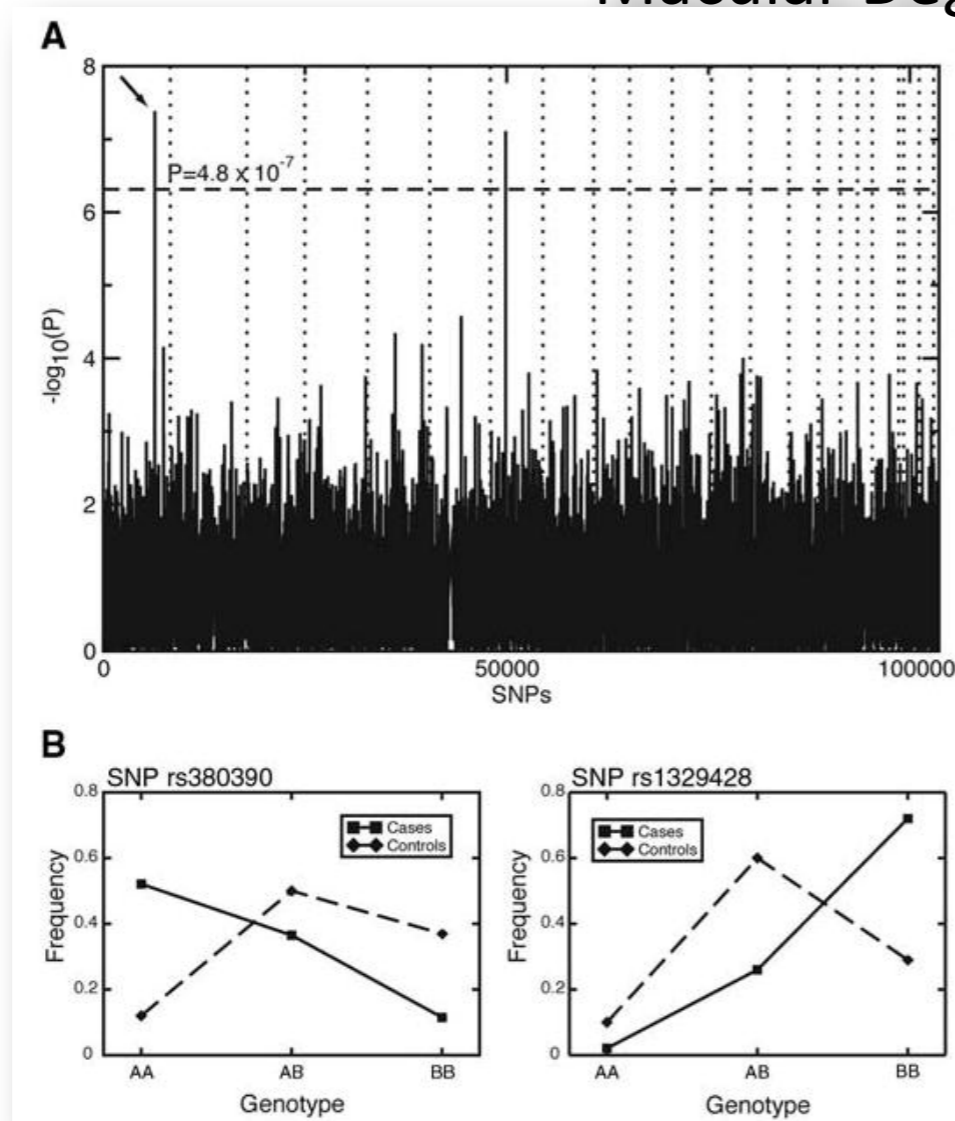
Mitochondrial

Gene Identification



Population-Based Studies

Complement Factor H Polymorphism in Age-Related Macular Degeneration

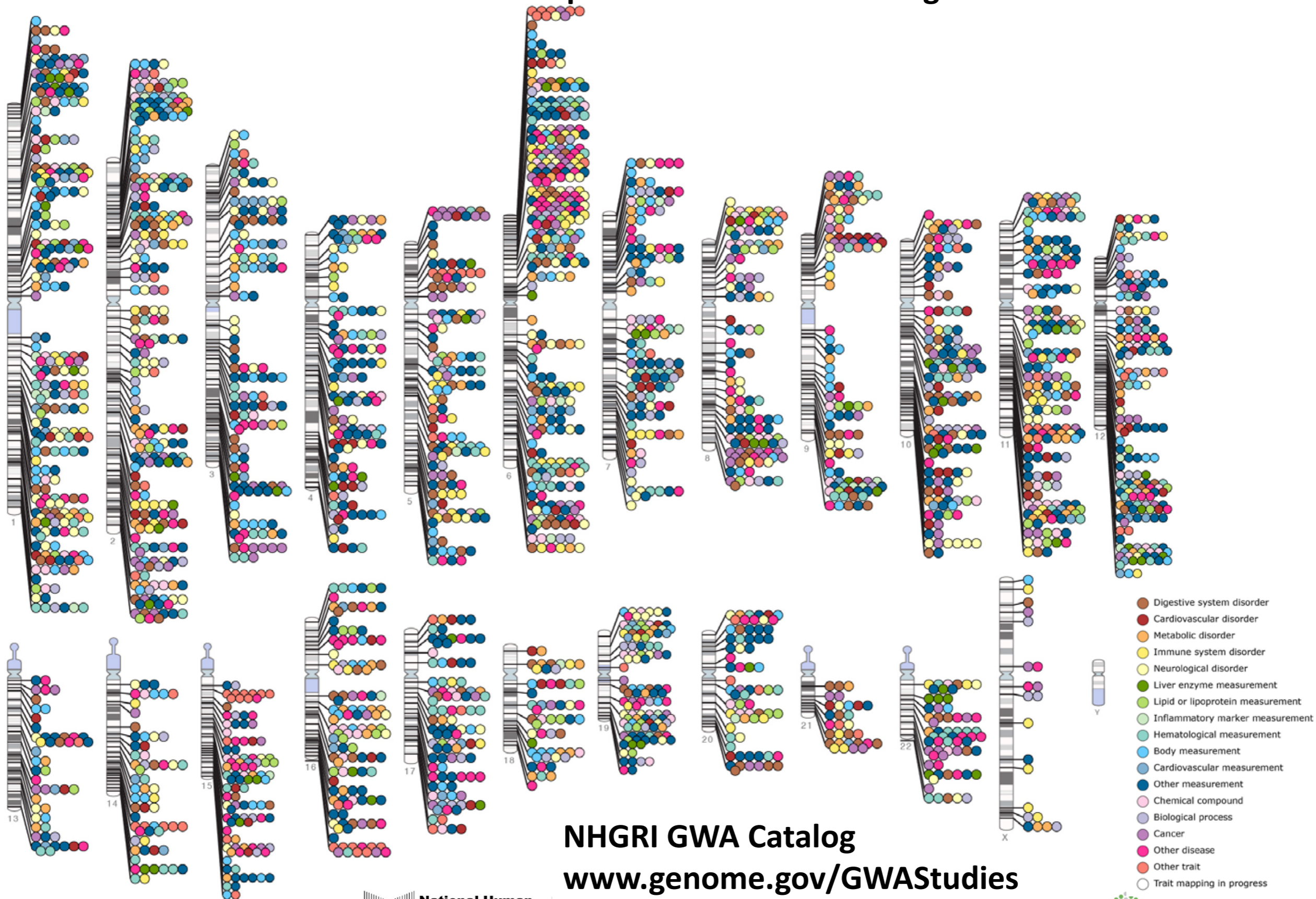


[http://www.medrounds.org/amd/
uploaded_images/fig2-757825.JPG](http://www.medrounds.org/amd/uploaded_images/fig2-757825.JPG)

[Klein et al., Science \(80- \). 2005 April 15; 308\(5720\): 385-389.](#)

Published Genome-Wide Associations through 07/2012

Published GWA at $p \leq 5 \times 10^{-8}$ for 18 trait categories



NHGRI GWA Catalog

www.genome.gov/GWAStudies

www.ebi.ac.uk/fgpt/gwas/



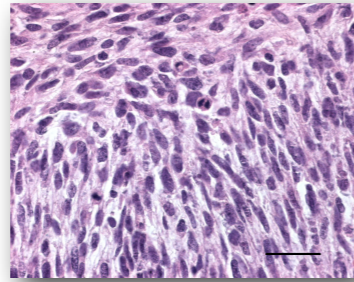
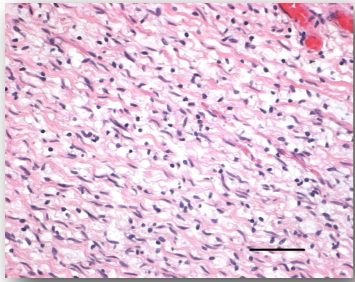
EMBL-EBI



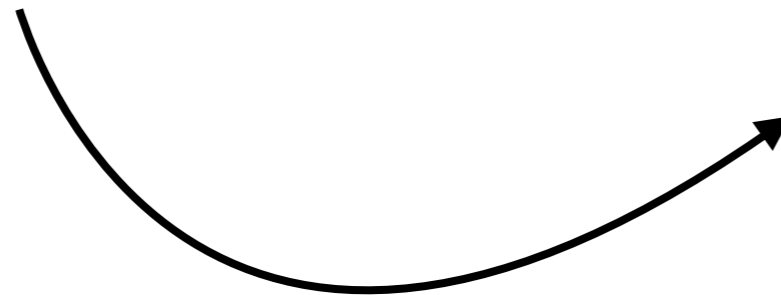
Cancer Genomes

Normal

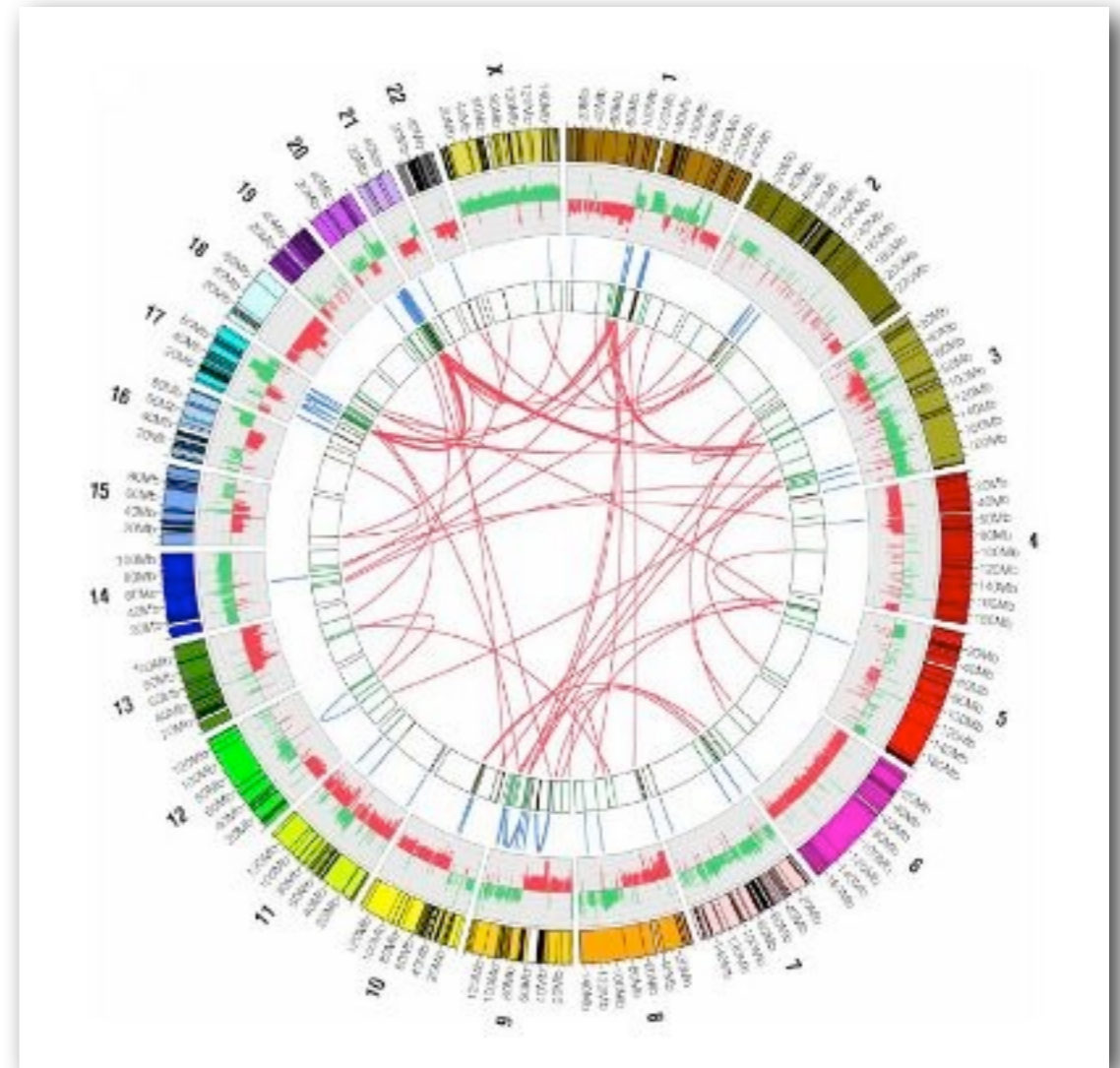
Tumor



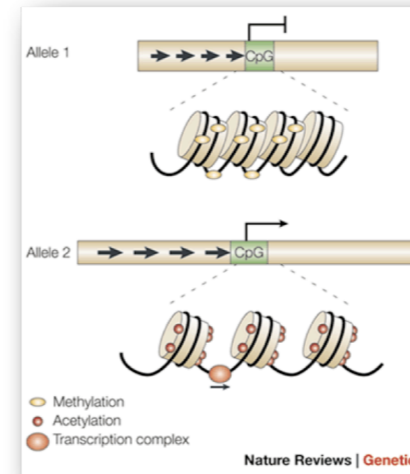
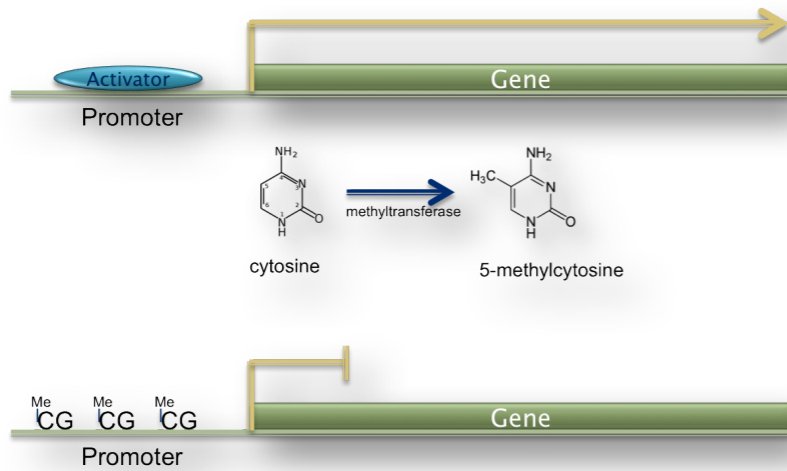
Sequence



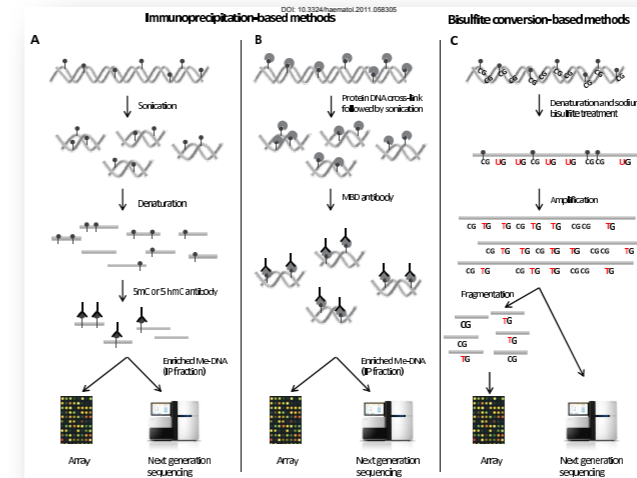
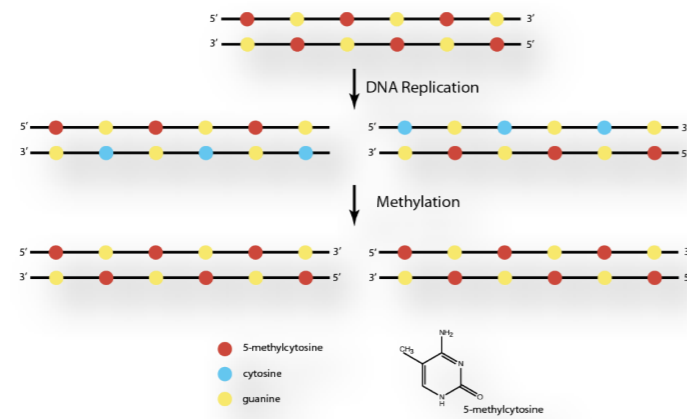
Difference =
cancer-specific genetic
changes



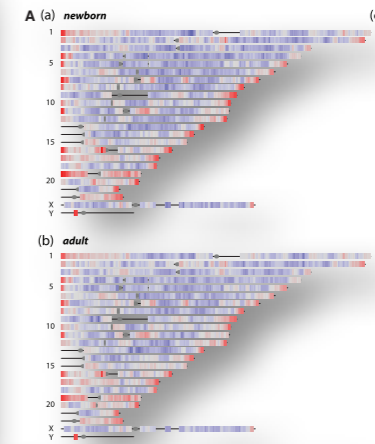
Epigenetics



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

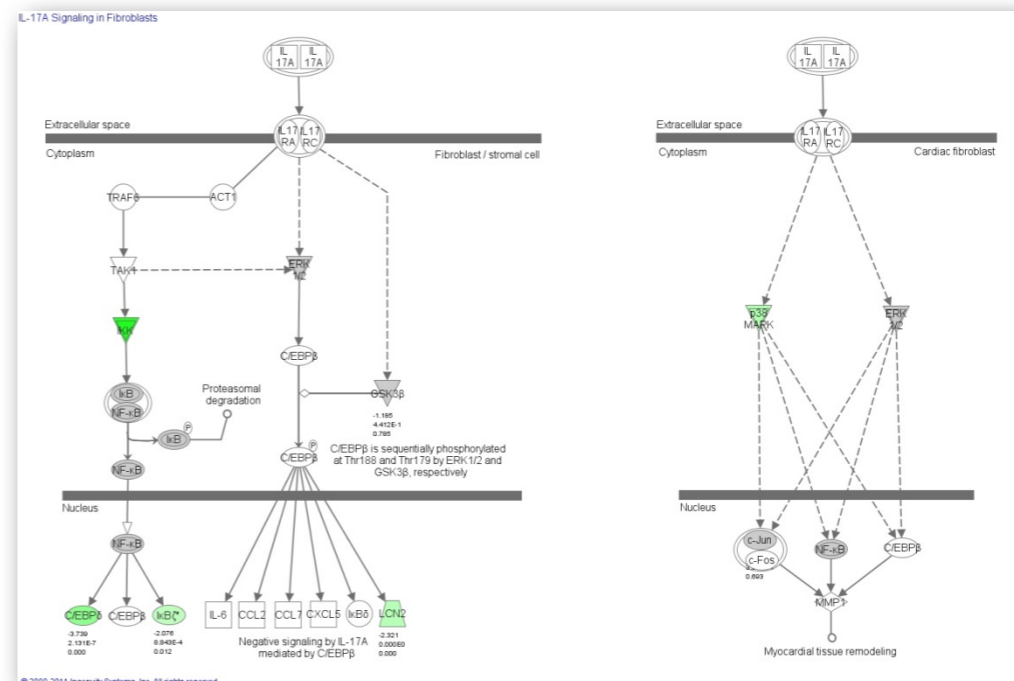
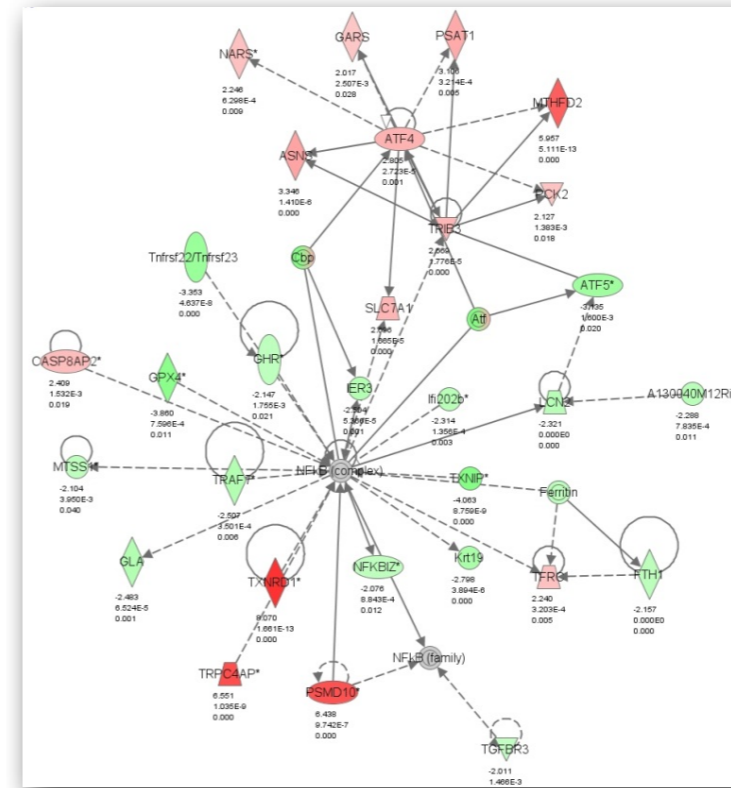


Citation: Gronbaek K, Muller-Tidow C, Perini G, Lehmann S, Treppendahl MB, Mills K, Plass C, and Schlegelberger B. A critical appraisal of tools available for monitoring epigenetic changes in clinical samples from patients with myeloid malignancies. *Haematologica*. 2012; 97:xxx
doi:10.3324/haematol.2011.058305

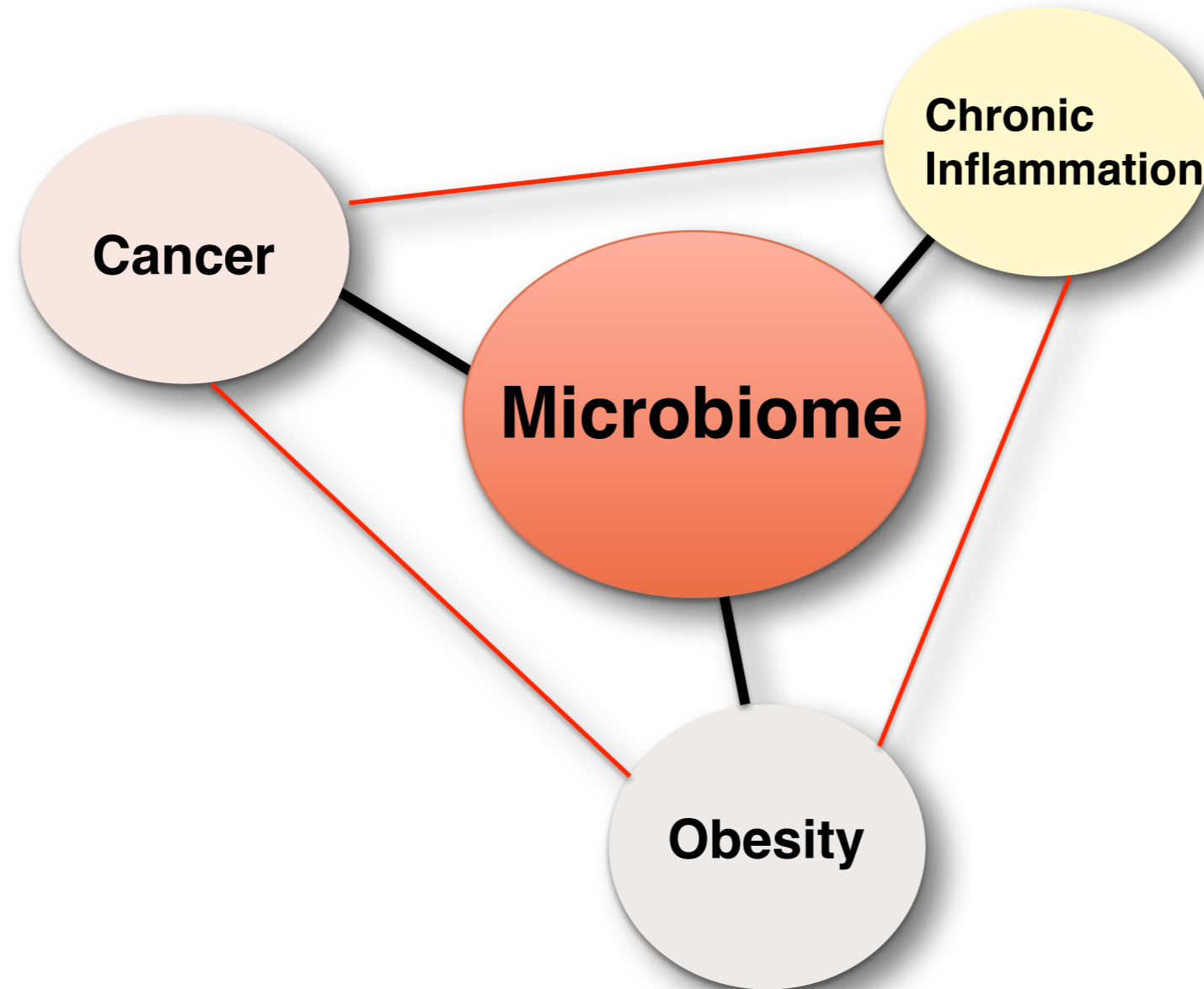


Alpea P, et al. *Nucleic Acids Research*, 2012, 1-18
doi:10.1093/nar/gks312

Functional Genomics



Microbiome



Genetics in Medicine



Prevention



Diagnosis

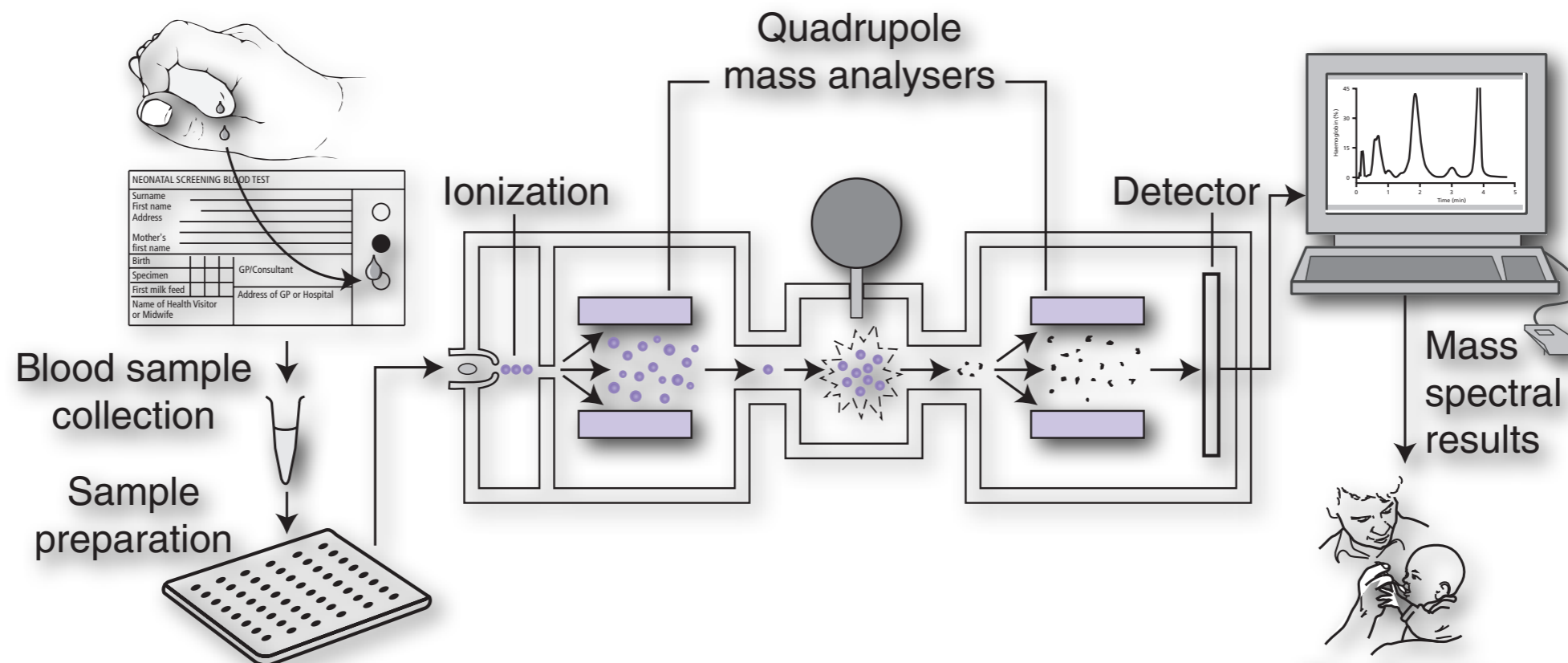


Treatment

Prevention



Prevention



DIRECT-TO-CONSUMER TESTING

The image displays three overlapping screenshots of genetic testing websites:

- Navigenics:** The top-left screenshot shows the Navigenics website header with the logo and navigation links (About, Leadership, Policies, Contact). Below is a video player with a man's face and the text "My Genes. My Health." and "Play Video". A main heading reads "Your genes offer a road map to optimal health" with a "Learn about Navigenics Health Compass" button.
- 23andMe:** The middle screenshot shows the 23andMe website with the tagline "genetics just got personal." and navigation links (our service, genetics 101, for the experts, store, about us). A main heading reads "175,000 years ago: The mother of all present" and includes a "Gene Journal" section with the question "What do your genes say about you?".
- deCODEME:** The bottom-right screenshot shows the deCODEME website with the tagline "deCODE genetics—the scientists who discovered the genes". It features a navigation menu (Home, What is deCODEme?, About deCODE, Signup, Family registration, Login to myCODE) and a list of benefits: "For only \$985, we scan over one million variants in your genome", "Calculate genetic risk for 18 diseases based on the current literature", "Find out where your ancestors came from and compare your genome with others", and "Get regular updates on future discoveries and a growing list of diseases and traits". It also includes an "our process" section with a "sign up" button.

DIRECT-TO-CONSUMER TESTING

The image shows two overlapping website screenshots. The background screenshot is for 23andMe, featuring a green navigation bar with links for 'our service', 'genetics 101', 'for the experts', 'store', and 'about us'. The main content area includes a headline '175,000 years ago: The mother of all present' and a 'Gene Journal' section with an illustration of a person and the text 'What do your genes say about you?'. The foreground screenshot is for deCODEME, with a white background and a blue navigation bar. It features a 'Home' menu with links for 'What is deCODEme?', 'About deCODE', 'Signup', 'Family registration', and 'Login to myCODE'. The main content area has a headline 'deCODE genetics—the scientists who discovered the genes' and a list of bullet points: 'For only \$985, we scan over one million variants in your genome', 'Calculate genetic risk for 18 diseases based on the current literature', 'Find out where your ancestors came from and compare your genome with others', and 'Get regular updates on future discoveries and a growing list of diseases and traits'. Below this is a 'our process' section with a 'sign up' button and a list of steps: 'Signup and create a free account' and 'Order a Genetic Scan'.

23andMe genetics just got personal. [sign in](#) | [claim codes](#) | [help](#) | [Visit our blog](#)

[our service](#) | [genetics 101](#) | [for the experts](#) | [store](#) | [about us](#)

discover your genome at 23andMe [order now](#)

200,000 years ago: Homo sapiens walks the Earth.

175,000 years ago: The mother of all present

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.

Gene Journal

What do your genes say about you?

deCODEME

Home

- What is deCODEme?
- About deCODE
- Signup
- Family registration
- Login to myCODE

deCODE genetics—the scientists who discovered the genes

- For only \$985, we scan over one million variants in your genome
- Calculate genetic risk for **18 diseases** based on the current literature
- Find out where your ancestors came from and compare your genome with others
- Get regular updates on future discoveries and a growing list of diseases and traits

our process

- Signup and create a free account
- Order a Genetic Scan

[sign up](#)

Ordering information

Once you login to your account, you can order a Genetic Scan for an introductory price of \$985. We also offer volume discounts in family ordering and gift certificates. [+More](#)

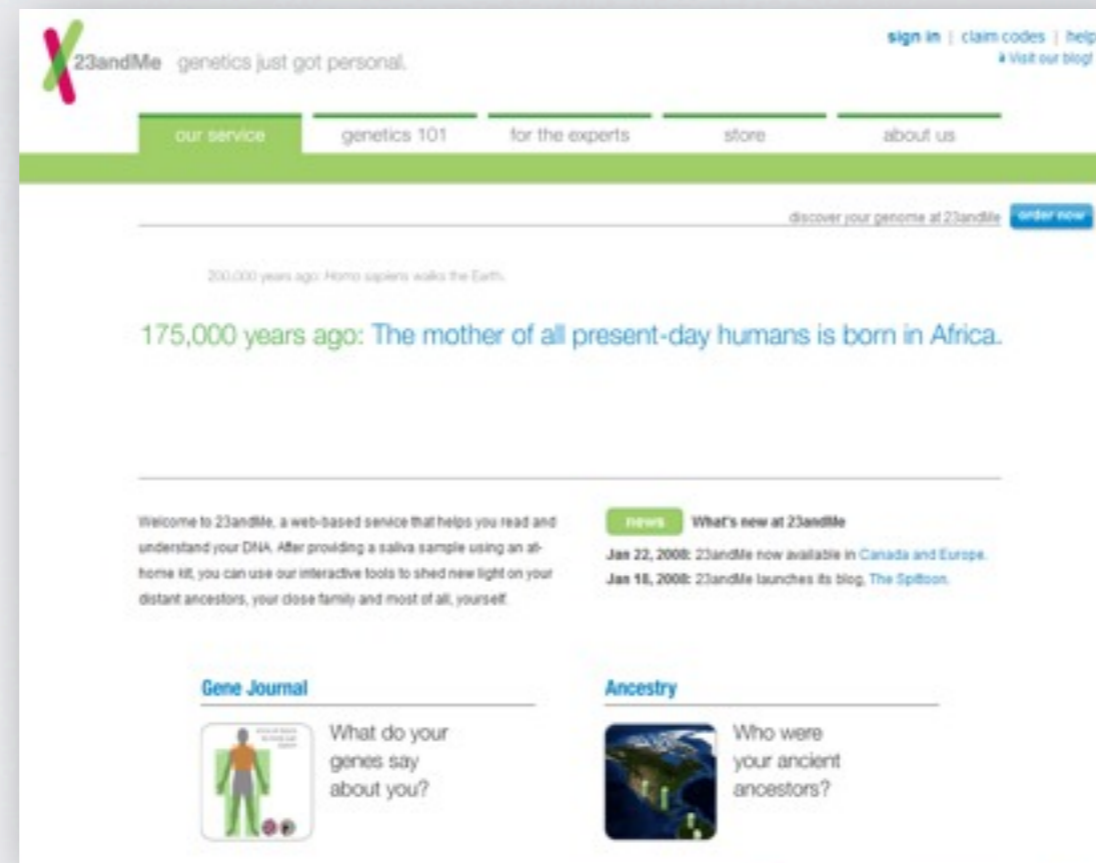
What is deCODEme?

deCODEme is a living website which will be continuously updated with information by deCODE genetics' team of experts. See our [video tour](#), view the [demo user](#) or click on the link below to learn more.

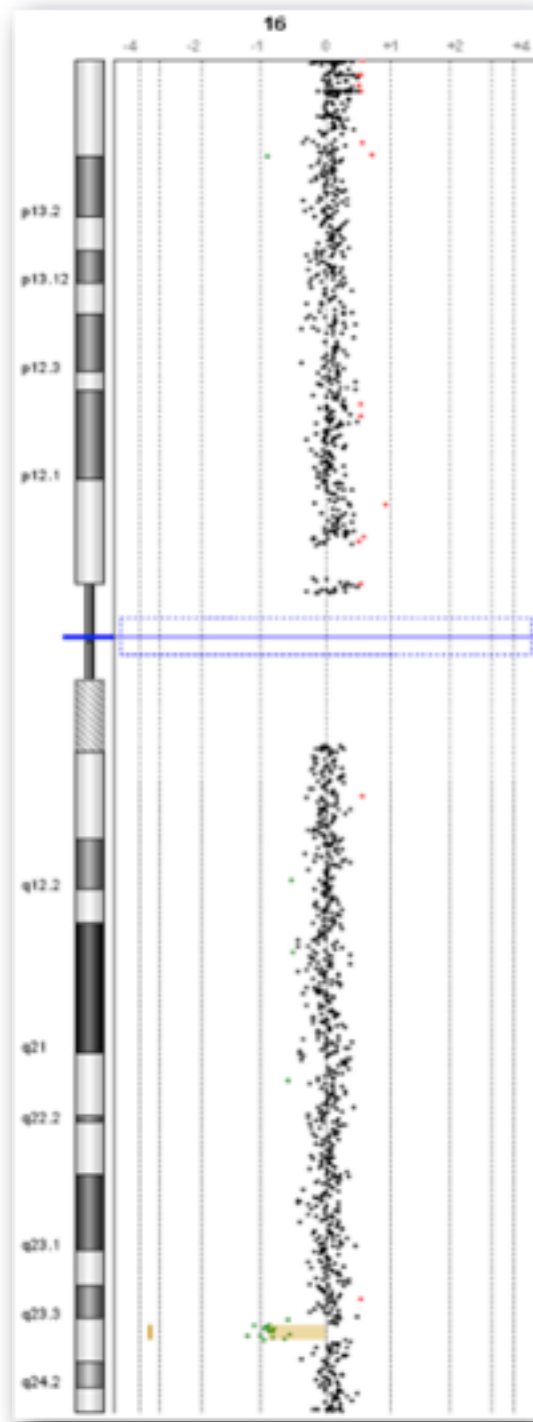
About deCODE

Discover more about deCODE genetics' unrivaled [track record](#) and how deCODE spearheaded discoveries of key genes contributing to healthcare challenges ranging from heart disease to cancer.

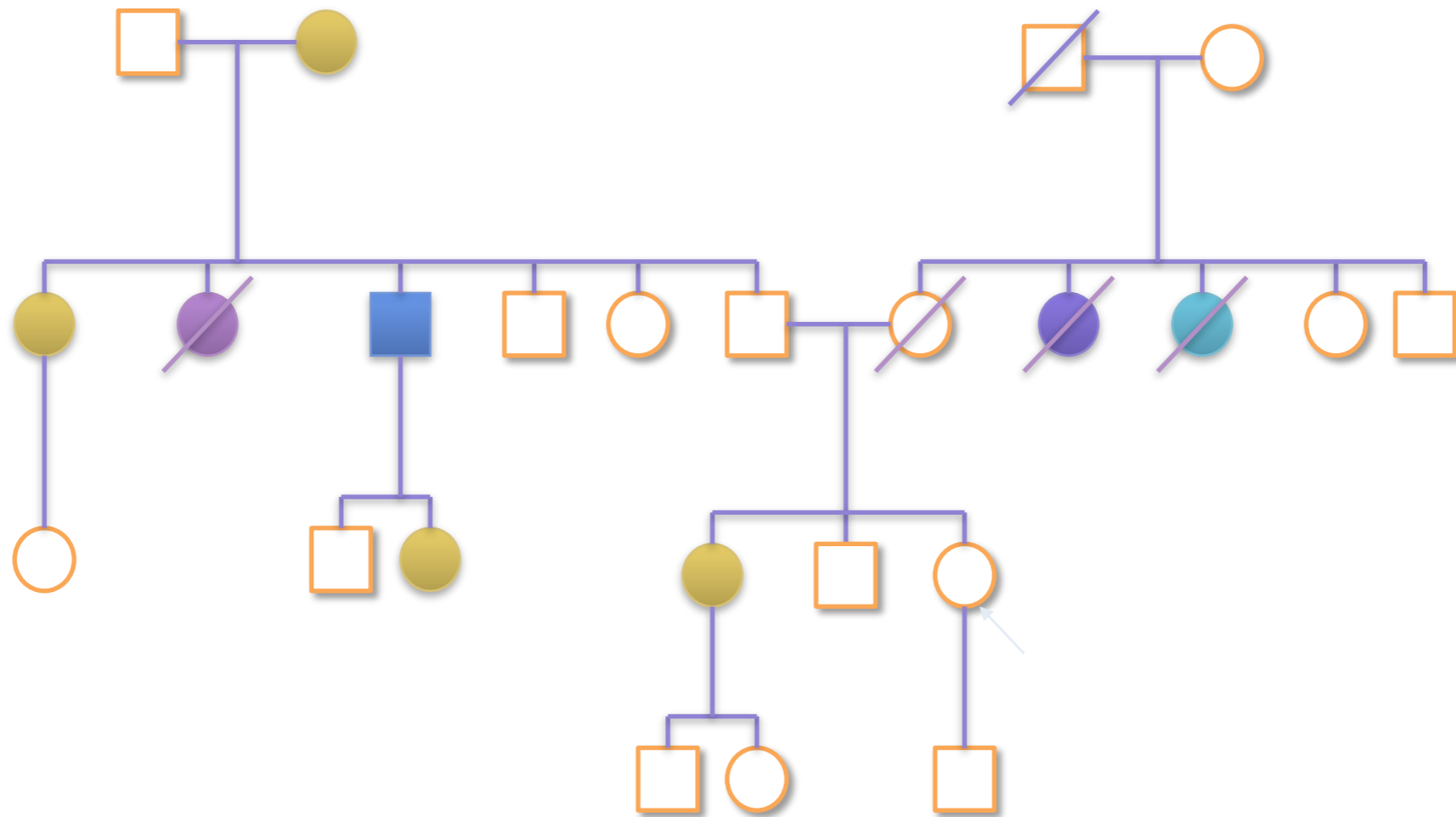
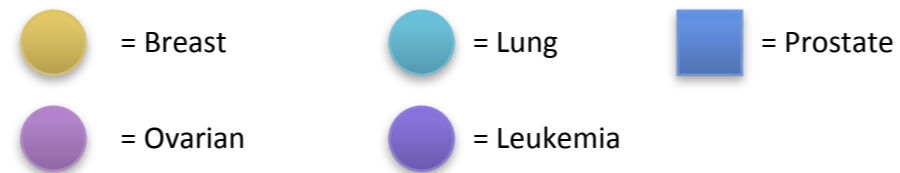
DIRECT-TO-CONSUMER TESTING



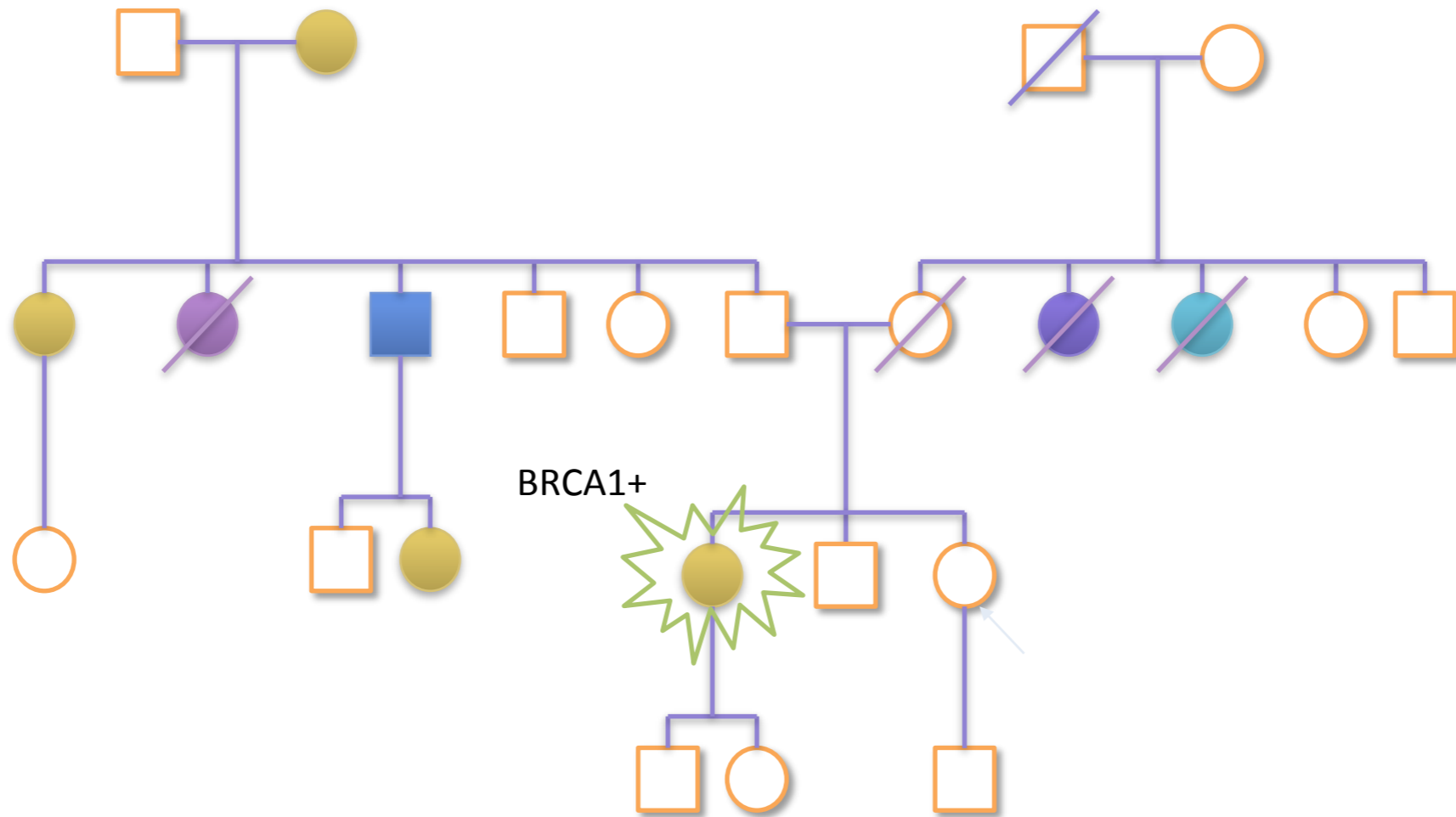
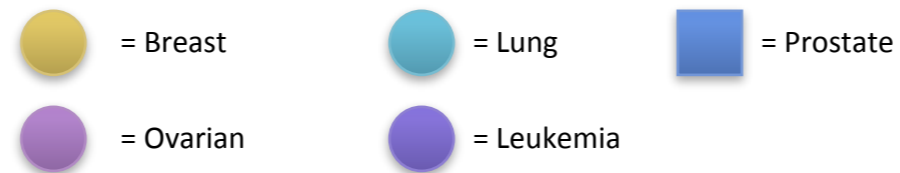
Diagnosis



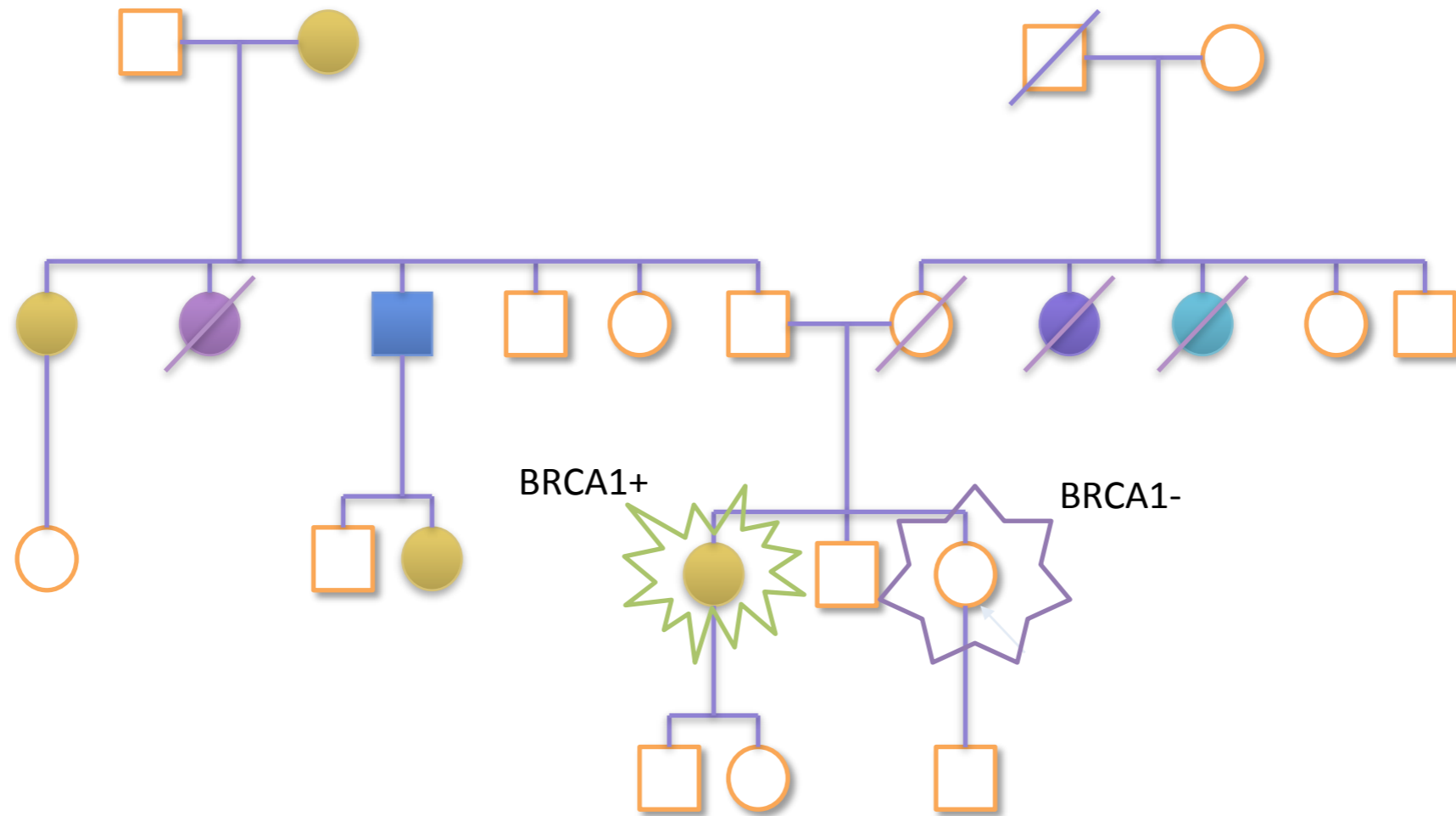
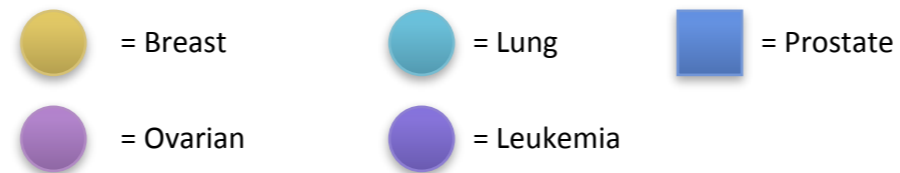
Presymptomatic Diagnosis



Presymptomatic Diagnosis

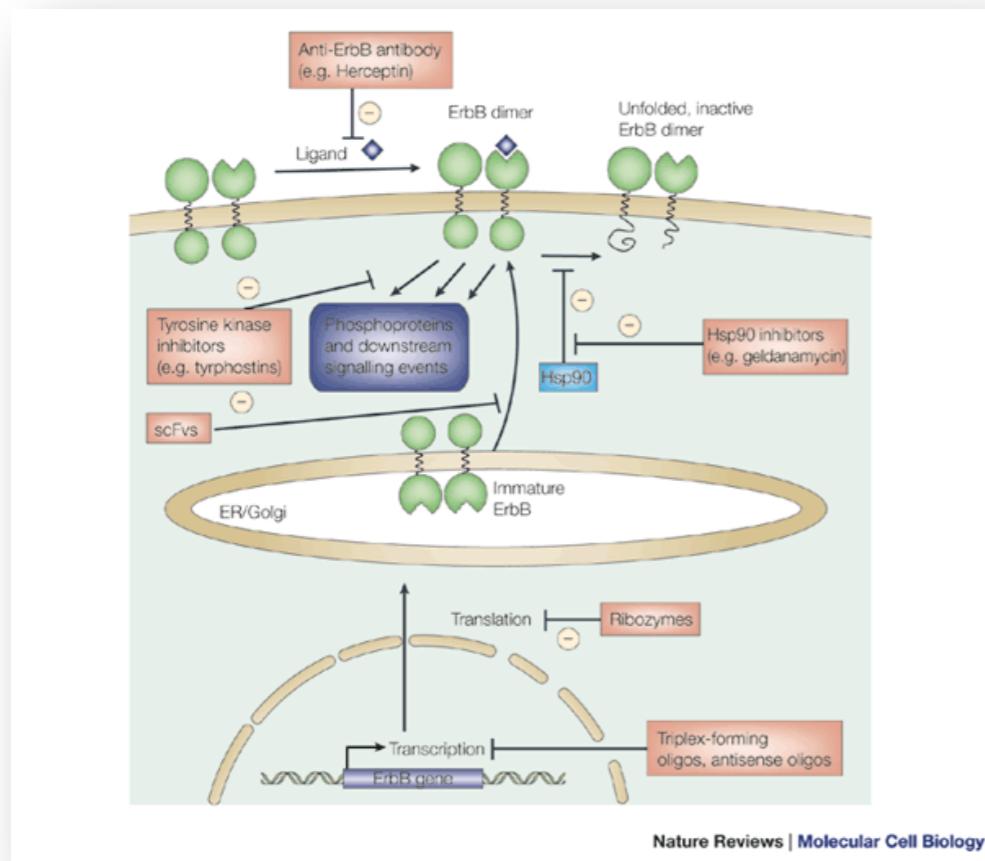


Presymptomatic Diagnosis

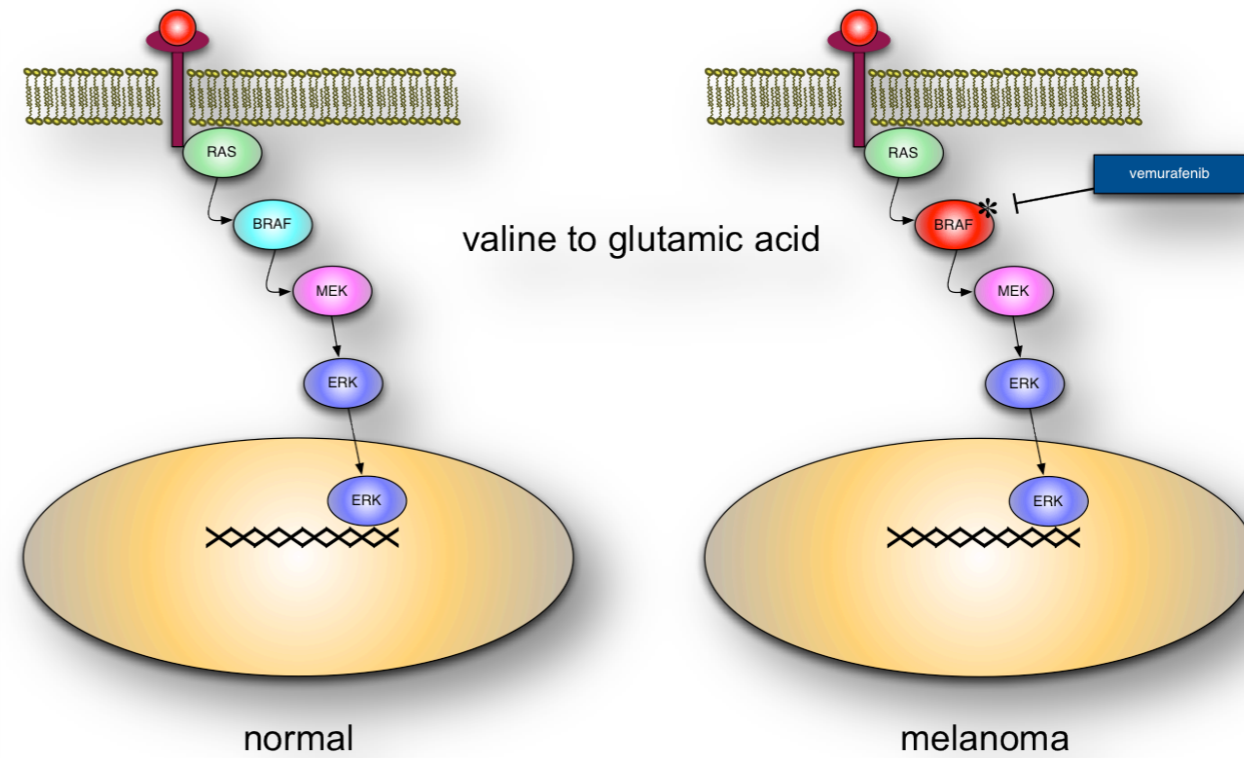


Therapeutics

Herceptin

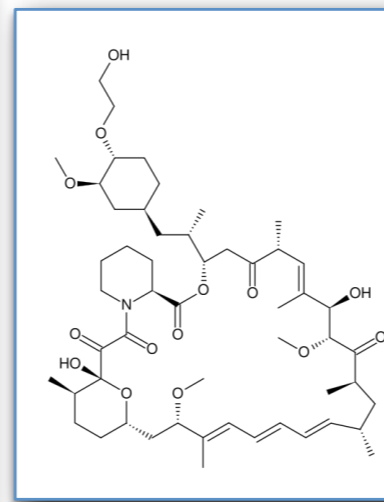
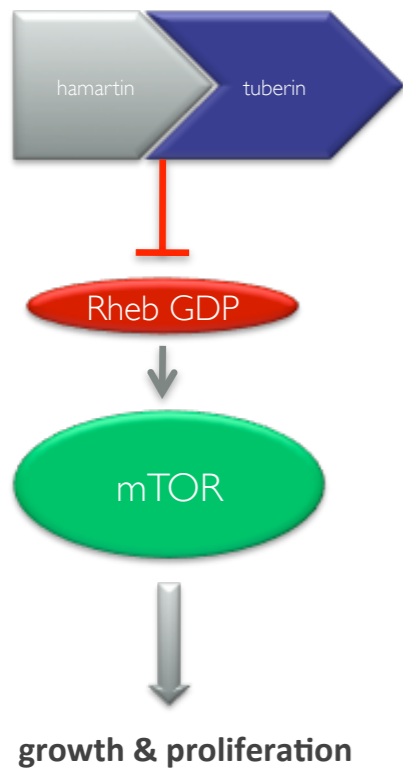


BRAF V600E in Melanoma



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

Everolimus and Tuberous Sclerosis



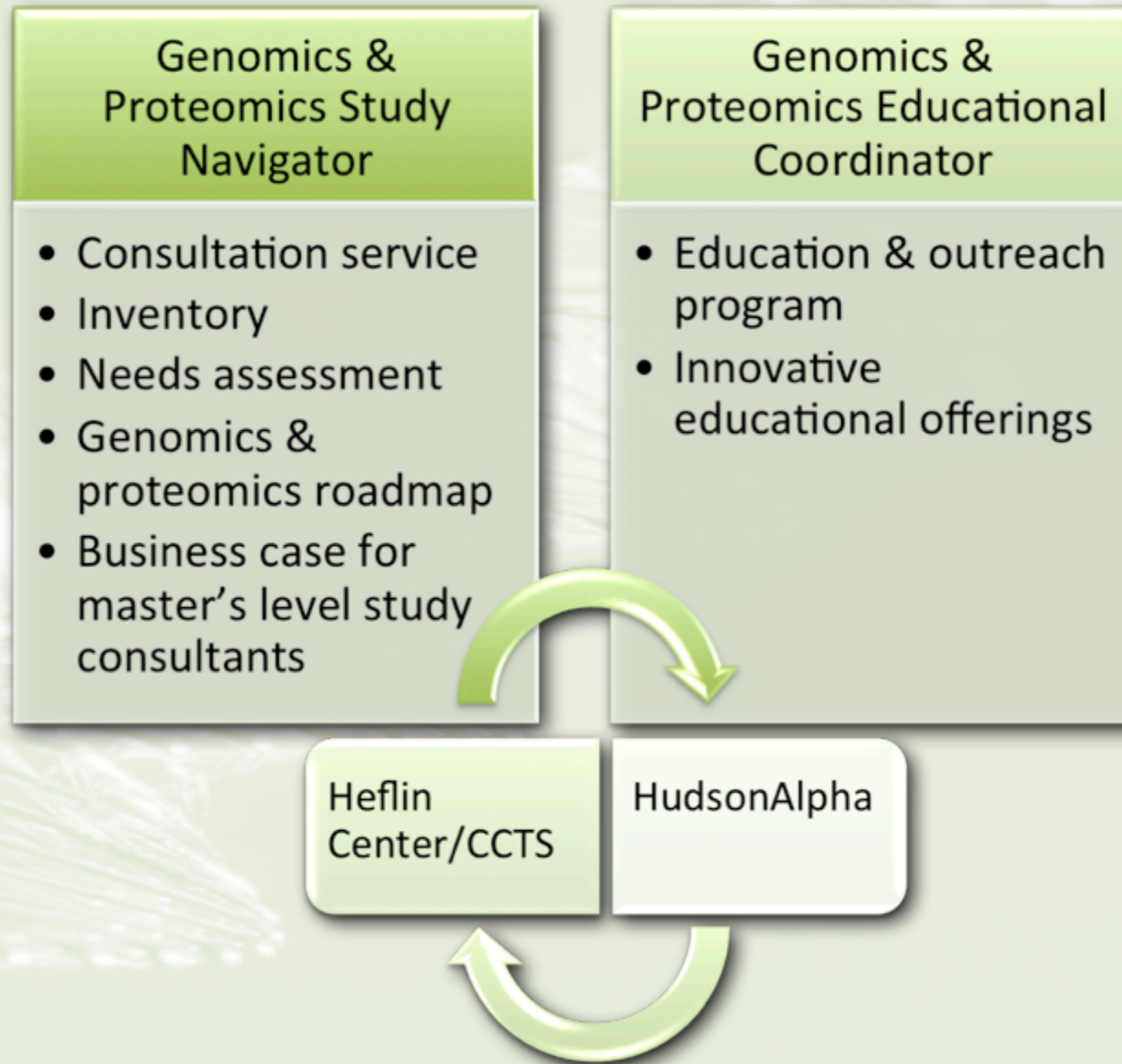
Genomics at UAB



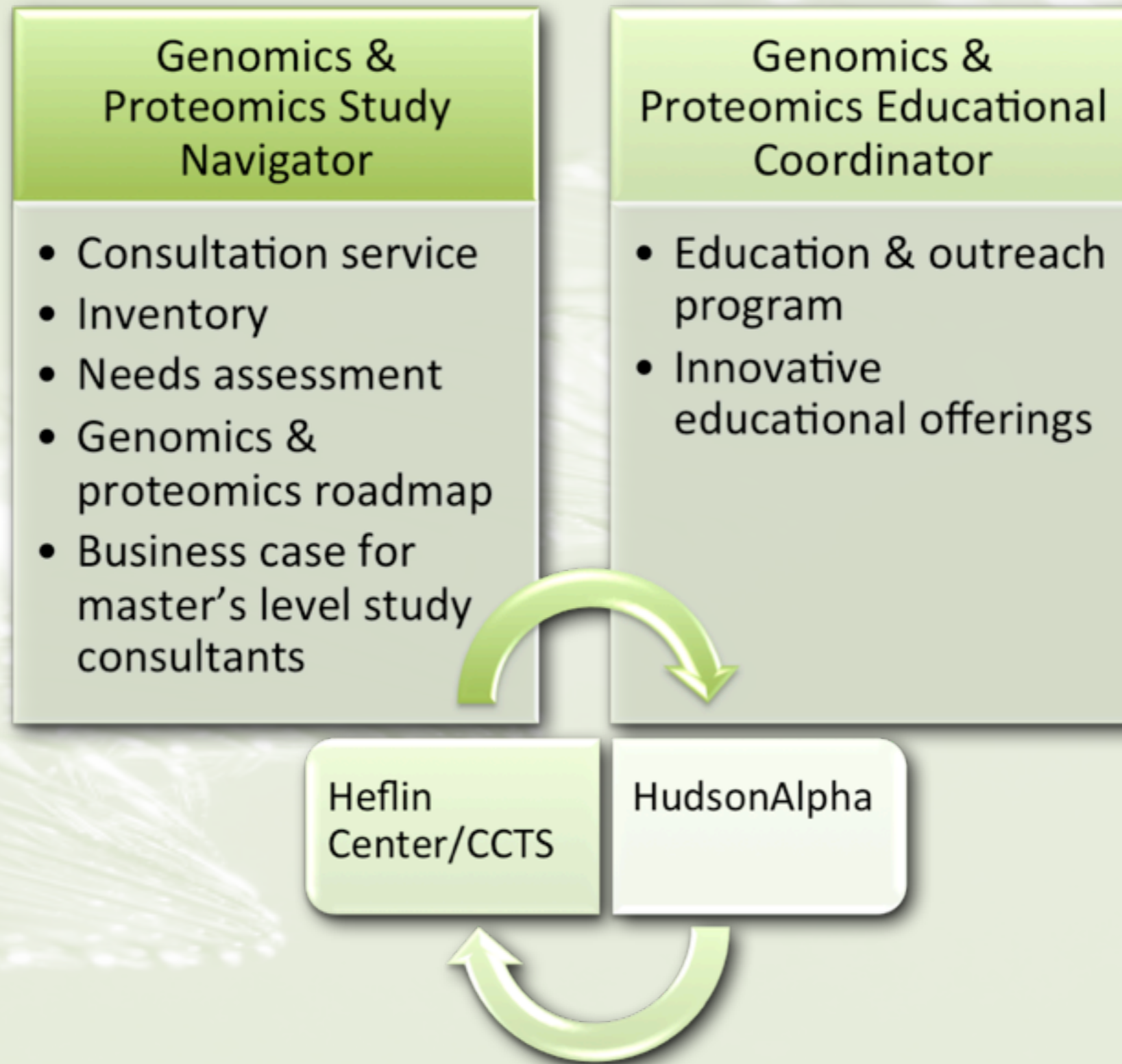
- Pilot studies
- Study design
- Low – high throughput studies
- Genetic Epidemiology
- Investigator Education

- High throughput analysis
- Next Generation Sequencing
- RNA Seq

UAB Program in Genomics & Proteomics




UAB Program in Genomics & Proteomics



www.heflingenetics.uab.edu

genomics@uab.edu



The best way to predict the future is
to invent it.

Alan Kay
Computer Scientist