OMICS: WHAT IT MEANS FOR HUMAN HEALTH

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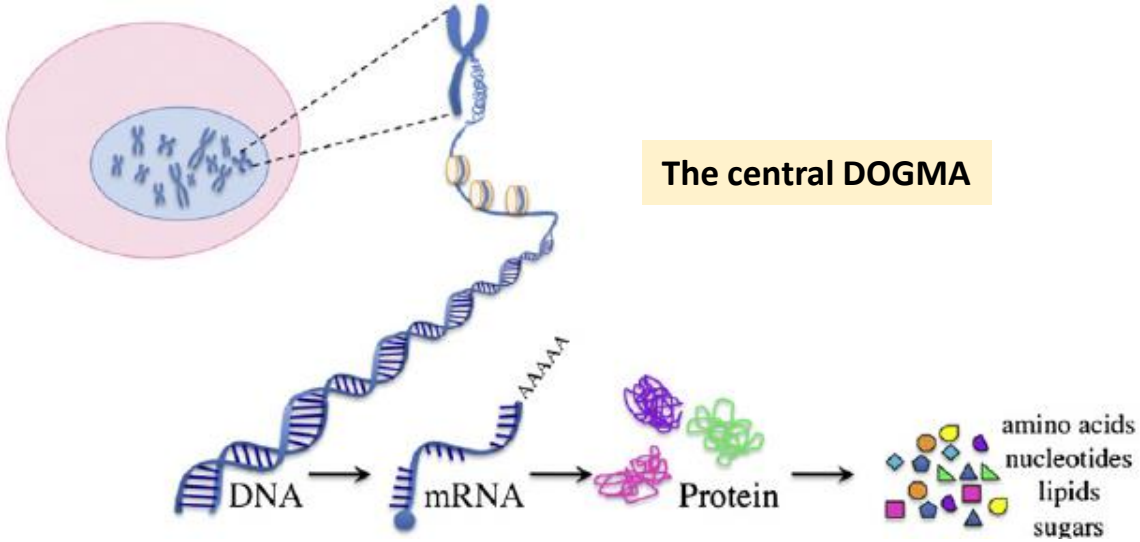
Steering Committee Member

Course-based Undergraduate Research Experiences for Students Underrepresented in Biology (CURESUB) network

What Is OMICS; Kinds of OMIC Studies; Why OMICS?



The central DOGMA

Genome | Transcriptome | Proteome | Metabolome

Genomics | Transcriptomics | Proteomics | Metabolomics

Epigenomics

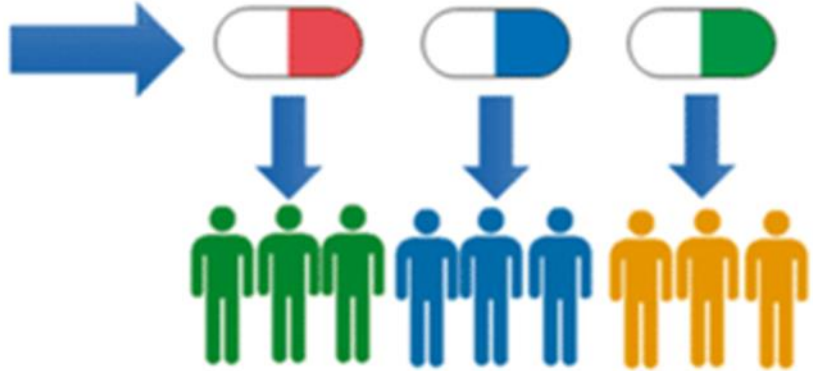
Phosphoproteomics

Lipidomics

Microbiomics

The Types of OMICS

Stratification of population based on characteristics and define a personalized signature for disease



Metagenomics: DNA Sequencing identifies species present within complex community (16S rRNA and Whole Genome Sequencing).

Metatranscriptomics: RNA Sequencing identifies species present and possible functions within complex communities (RNASeq).

Metaproteomics:
The large-scale characterization of the entire protein complement of environmental microbiota at a given point in time. Potential to unravel the **mechanistic details of microbial interactions with host / environment** by analyzing the **functional dynamics of the microbiome.**

The level of resolution is important

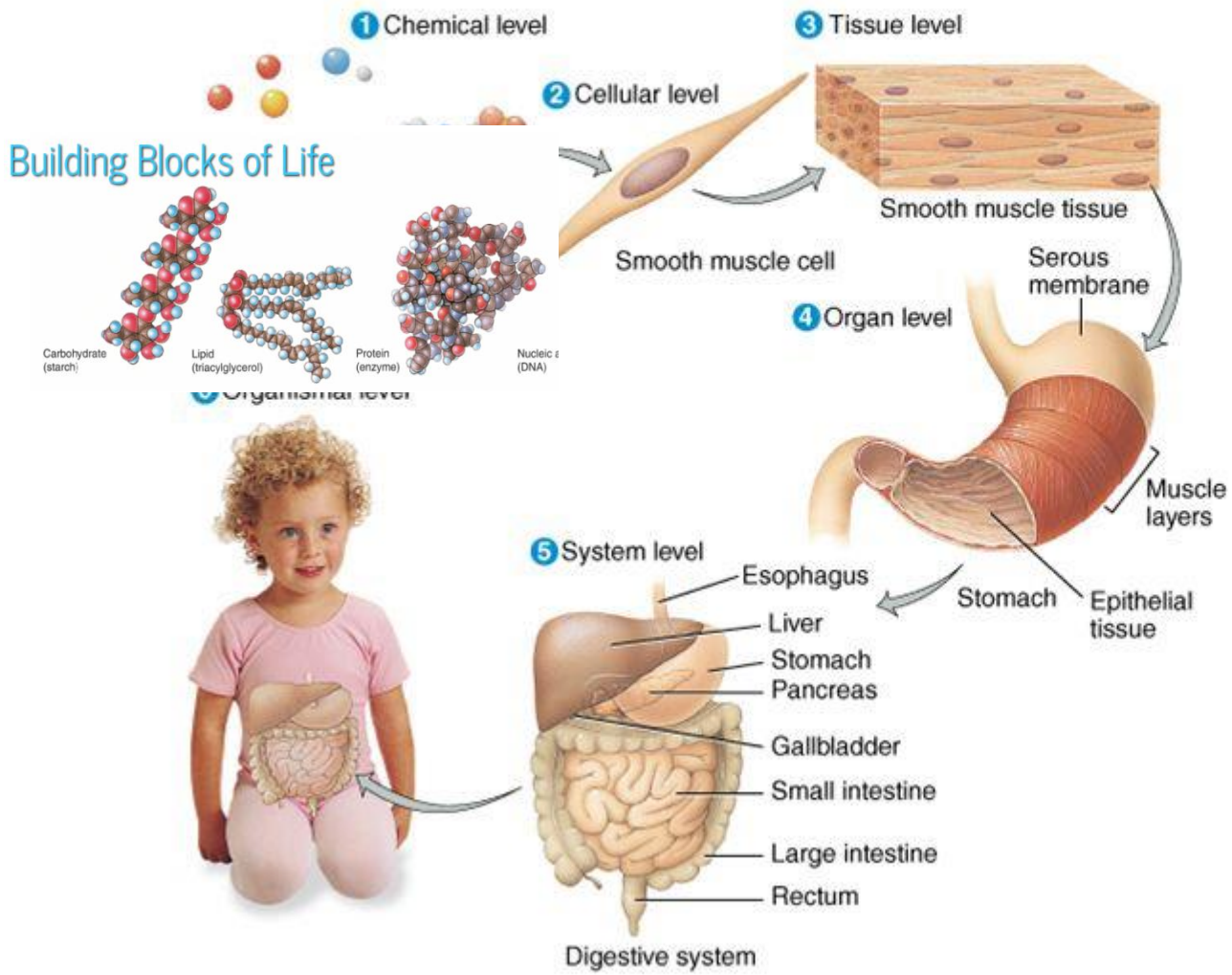
Road view is necessary when navigating to a mall

world view is necessary when navigating to a different country

Global view is necessary for weather patterns

https://www.google.com/maps/@29.2414106,-86.6099686,3.5z

Levels of Organization



- Atoms
- Molecules
- Macromolecules
- Organelles

Biochemistry

- Cells

Cell Biology

- Tissues

Molecular Biology

- Organs

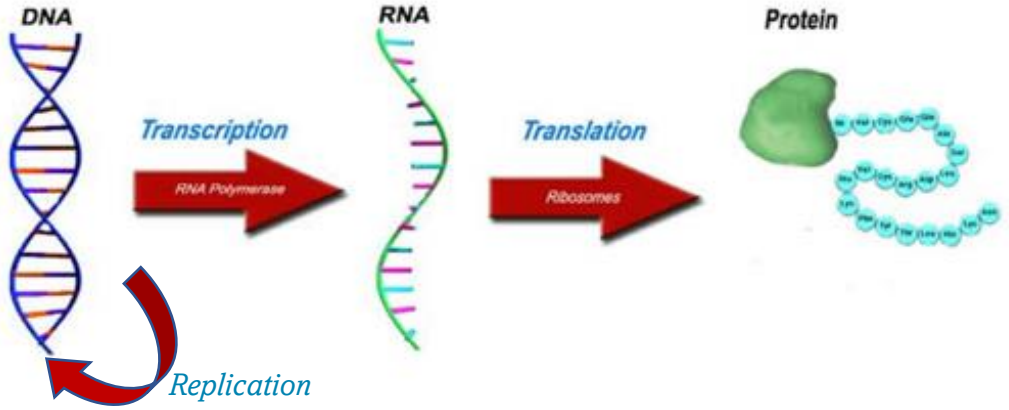
Anatomy and Physiology

Systems Biology

- Organ systems-Human Body

Basic concepts….

THE CENTRAL DOGMA



THE GENETIC CODE

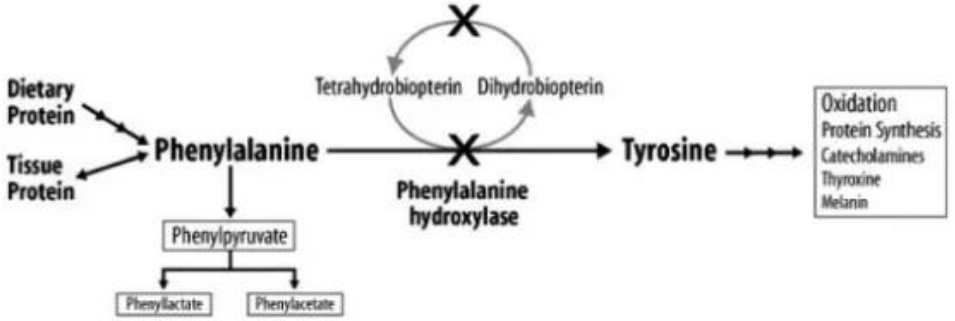
Second Position

First Position (5' end)	U	C	A	G	Third Position (3' end)
U	UUU Phe, UUC Phe, UUA Leu, UUG Leu	UCU Ser, UCC Ser, UCA Ser, UCG Ser	UAU Tyr, UAC Tyr, UAA Stop, UAG Stop	UGU Cys, UGC Cys, UGA Stop, UGG Trp	U C A G
C	CUU Leu, CUC Leu, CUA Leu, CUG Leu	CCU Pro, CCC Pro, CCA Pro, CCG Pro	CAU His, CAC His, CAA Gln, CAG Gln	CGU Arg, CGC Arg, CGA Arg, CGG Arg	U C A G
A	AUU Ile, AUC Ile, AUA Ile, AUG Met	ACU Thr, ACC Thr, ACA Thr, ACG Thr	AAU Asn, AAC Asn, AAA Lys, AAG Lys	AGU Ser, AGC Ser, AGA Arg, AGG Arg	U C A G
G	GUU Val, GUC Val, GUA Val, GUG Val	GCU Ala, GCC Ala, GCA Ala, GCG Ala	GAU Asp, GAC Asp, GAA Glu, GAG Glu	GGU Gly, GGC Gly, GGA Gly, GGG Gly	U C A G

Table 3 Genotype/phenotype correlation.

Genotype	Phenotype predicted	Phenotype observed
V388M	PKU moderate/mild	PKU classical
R261Q/V388M	PKU moderate/mild	PKU classical
R261Q/ IVS10nt-11G>A	PKU moderate/ classical	PKU classical
V388M/ IVS10nt-11G>A	PKU moderate	PKU classical

Phenylketonuria (PKU)



CRISPR/Cas9 system was found to show promising results to correct both mutated genes in the liver cells and thus heal the metabolic disorder phenylketonuria.

Genetics vs Genomics

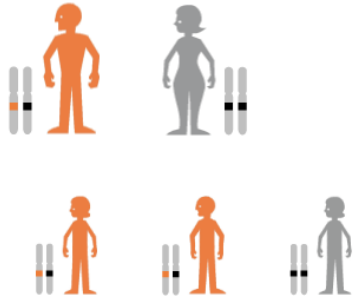
Genetics

- The study of heredity
- The study of the function and composition of single genes.
- 'Gene': specific sequence of DNA that codes for a functional molecule.

Genomics

- The study of an organism's complete set of genetic information.
- The genome includes both genes (coding) and non-coding DNA.
- 'Genome': the complete genetic information of an organism.

Single gene inheritance

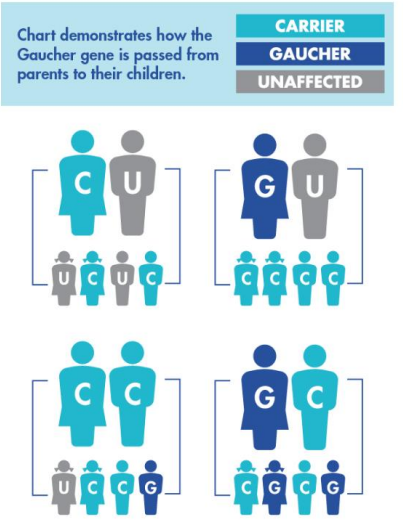


Autosomal dominant: Huntington's disease

Autosomal recessive: Phenylketonuria, Gaucher Disease, Cystic Fibrosis

https://www.gaucherdisease.org/blog/5-common-ashkenazi-genetic-diseases/

X-linked: red-green color blindness

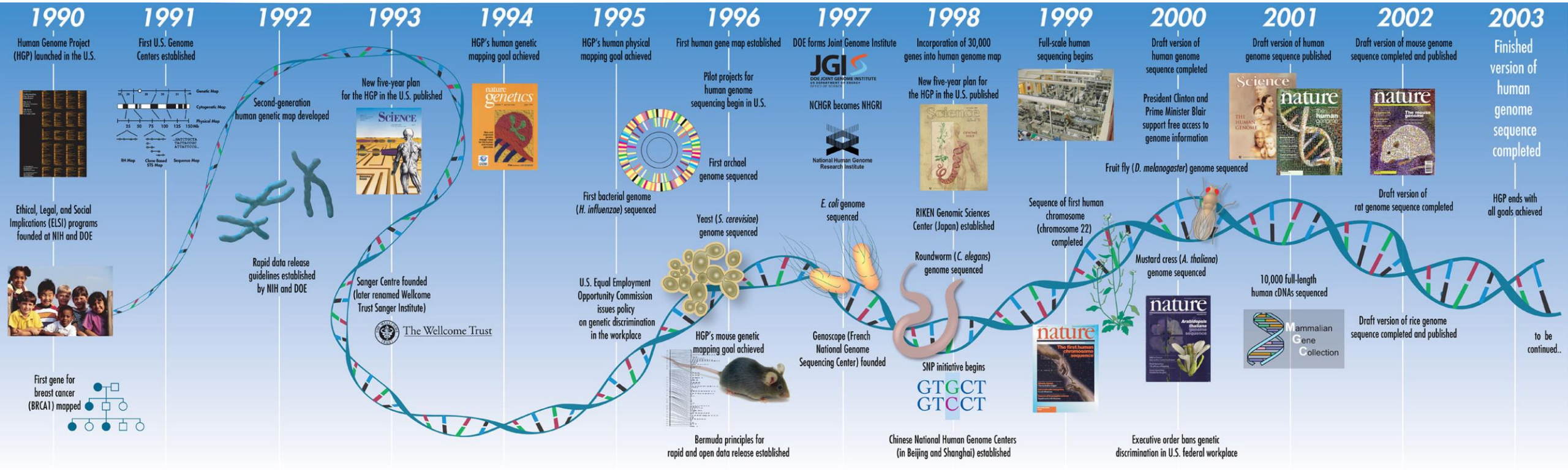


Polygenic inheritance involves multiple-genes: eye - color

Example of polygenic disorder: Inflammatory Bowel Diseases (Crohns' Disease and Ulcerative Colitis)

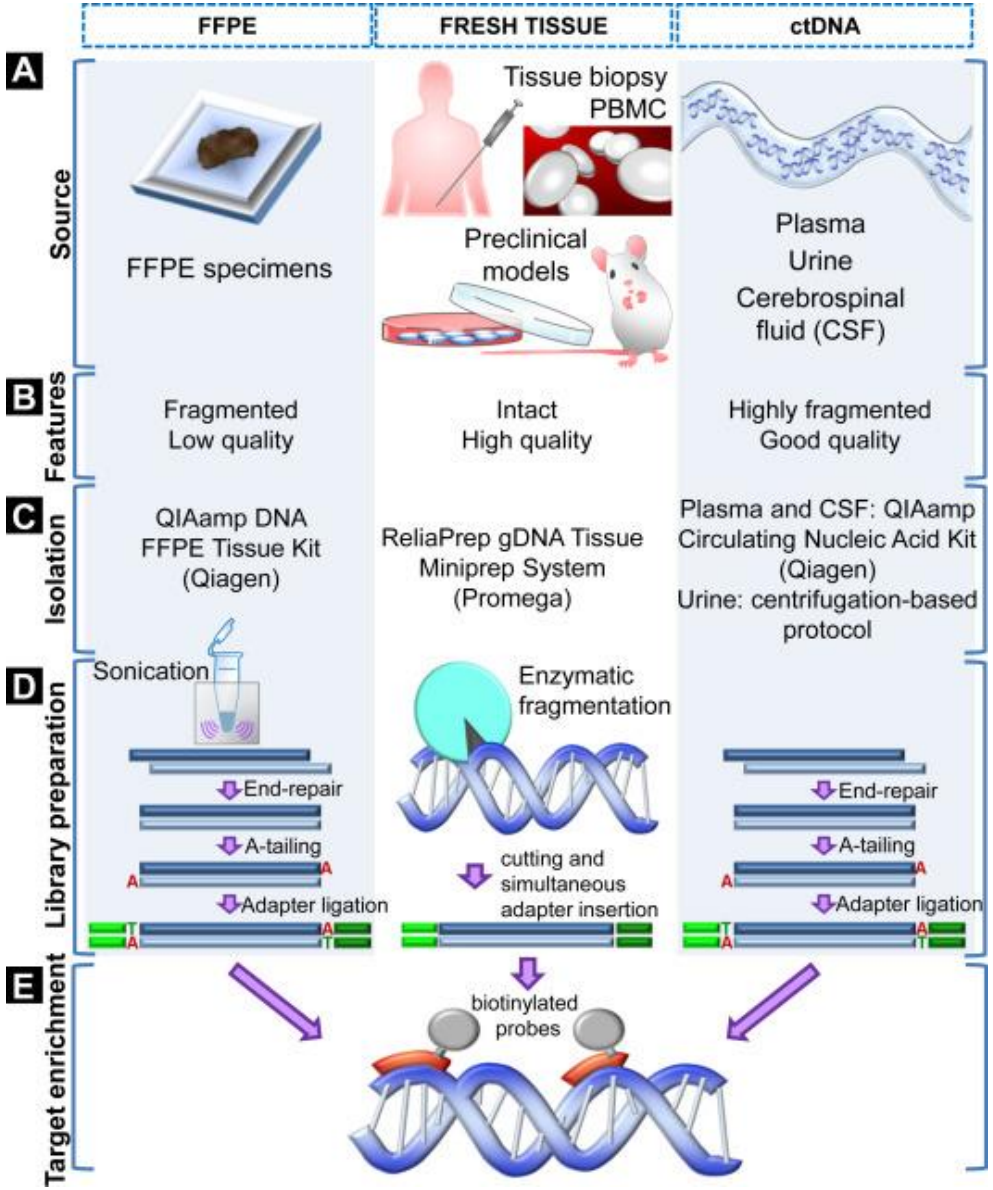
GENOMICS----

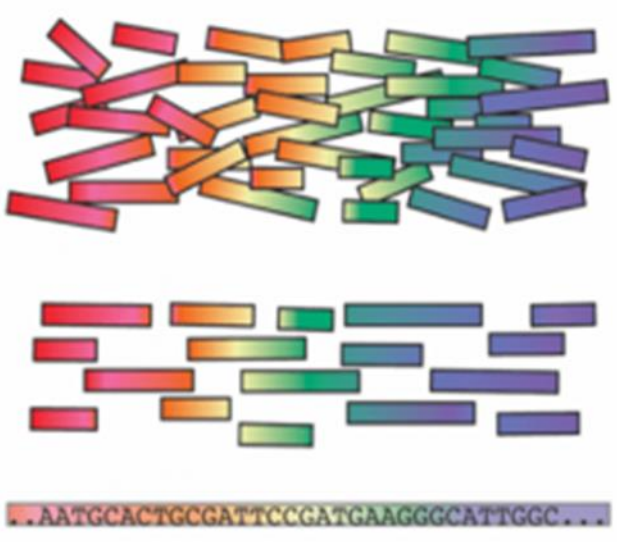
THE HUMAN GENOME PROJECT



https://www.genome.gov/human-genome-project#:~:text=The%20Human%20Genome%20Project%20was,than%20the%20original%20estimated%20budget

Genomics Workflow





Using PCR techniques, copies of the genome are made.

These copies are in the form of small DNA segments

NEXT GENERATION SEQUENCING

These segments are aligned with the reference genome that is available from the Human genome project

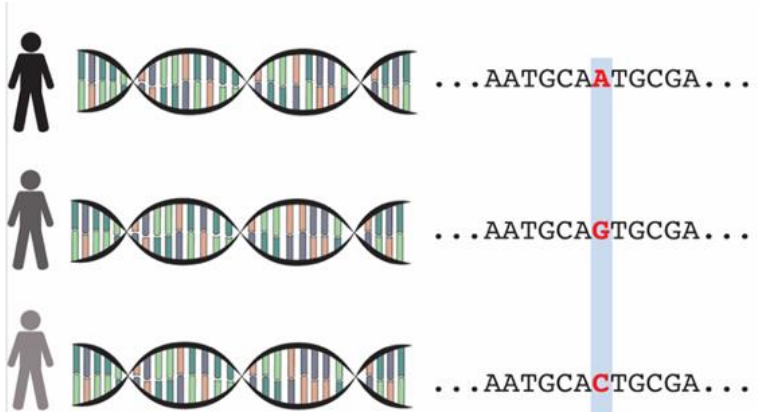
The complete genome of the sample gDNA is assembled.

Several tools are available to array / align sequences to the reference genome and identify regions of similarity that may be a consequence of functional, structural or evolutionary relationships.

Alignment of sequences from different individuals enables identification of variations at the nucleotide resolution.

Single nucleotide polymorphisms (SNPs) are alterations in single nucleotides among individuals in the population.

Several SNPs are associated with increased risk of Inflammatory Bowel Diseases (Crohns' Disease and Ulcerative Colitis)



Genomics: experimental design and application

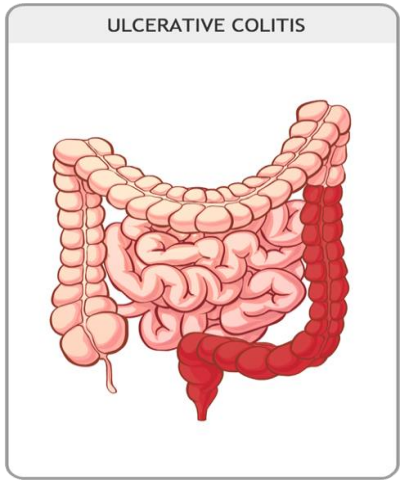
What Is Inflammatory Bowel Disease (IBD)?

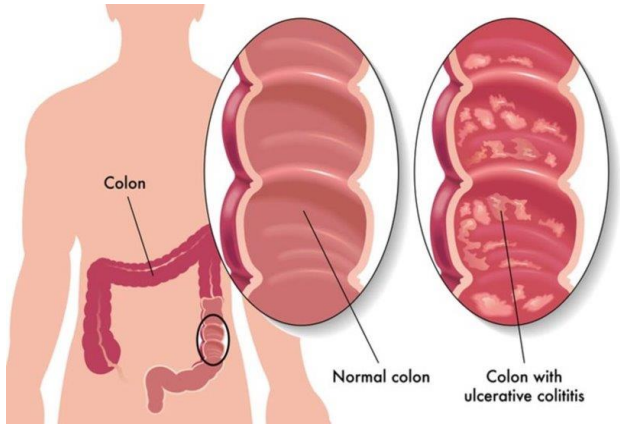
Inflammatory bowel diseases affect the intestines or bowels

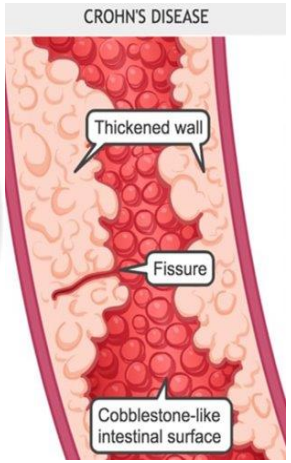
Major unmet clinical need is that no approved medications > 50% effective

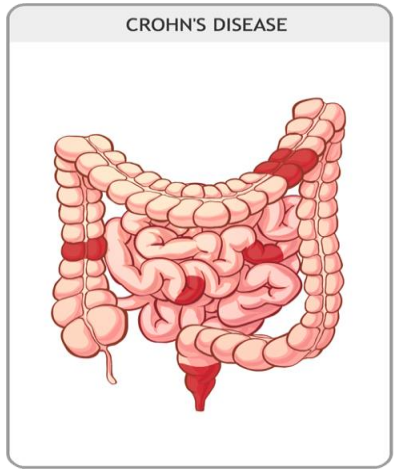
- **Ulcerative colitis**
  - Mostly affects the large intestine
  - The disease is continuous along the large intestine.
  - The inside of the intestine wall has ulcers and wounds that may have pus formation.

- **Crohn's Disease**
  - *It can affect the small and large intestine, but as well as other parts of the digestive system.*
  - *The disease can occur in patches*
  - *The walls become thick with cobblestone like appearance*
  - *The intestinal walls develop fissures/fistulae or openings on the sides of the wall.*

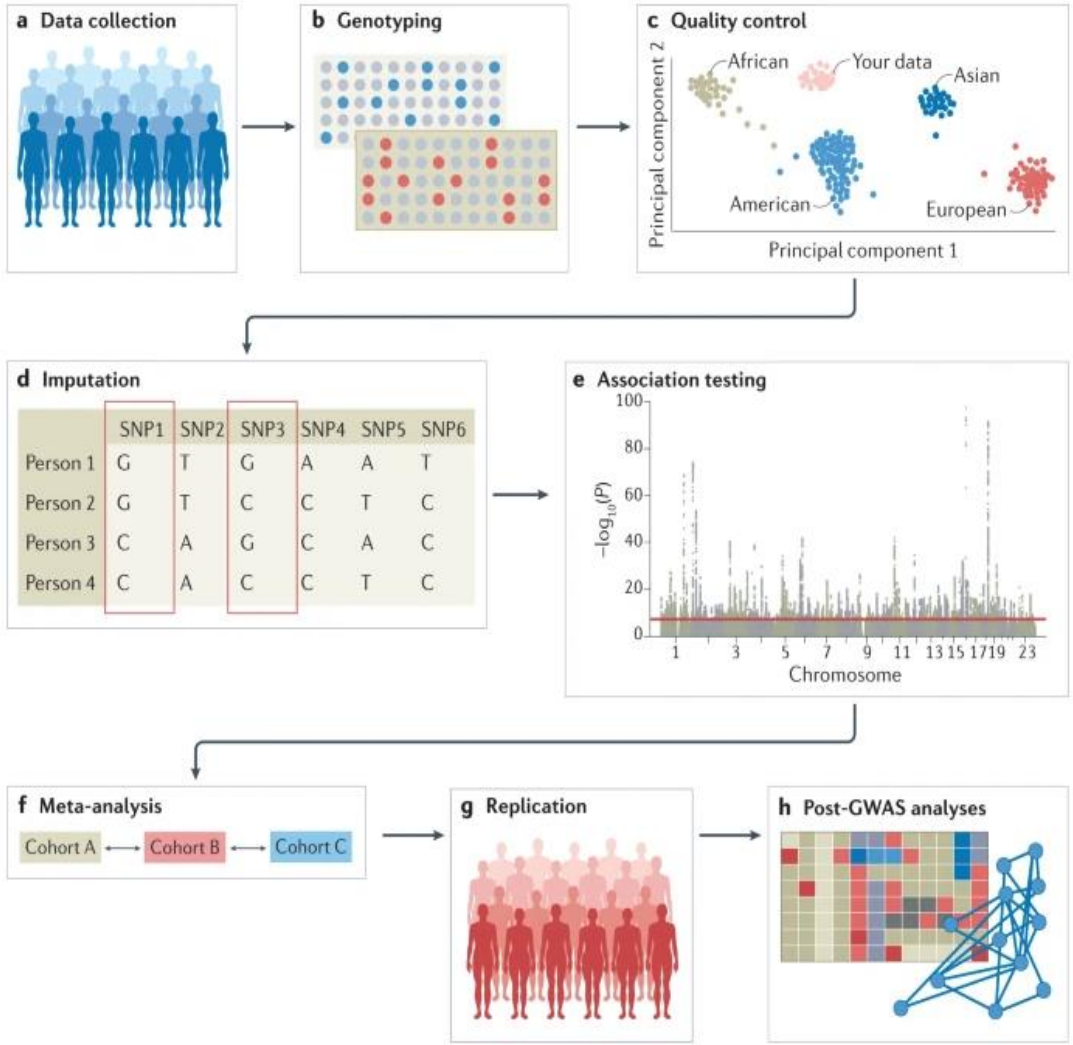






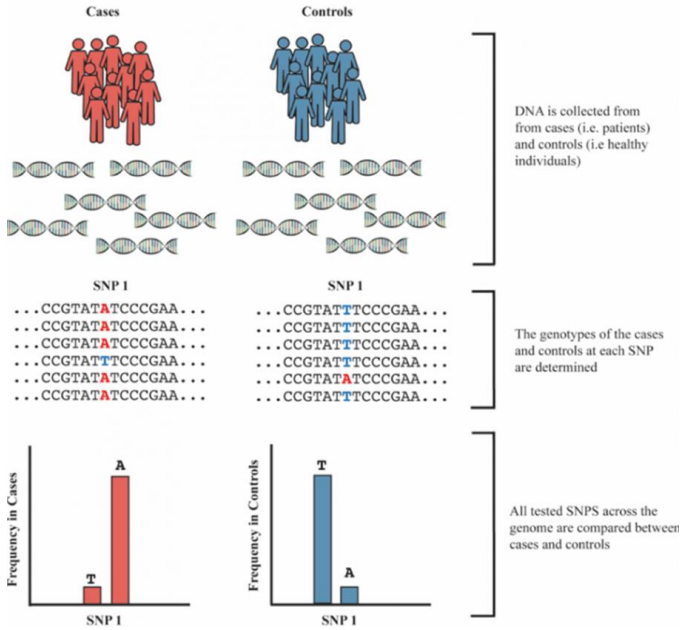


Genome-wide association studies are conducted to identify risk SNPs in population



Inflammatory bowel disease (IBD)

a polygenic disorder affects over 3 million Americans



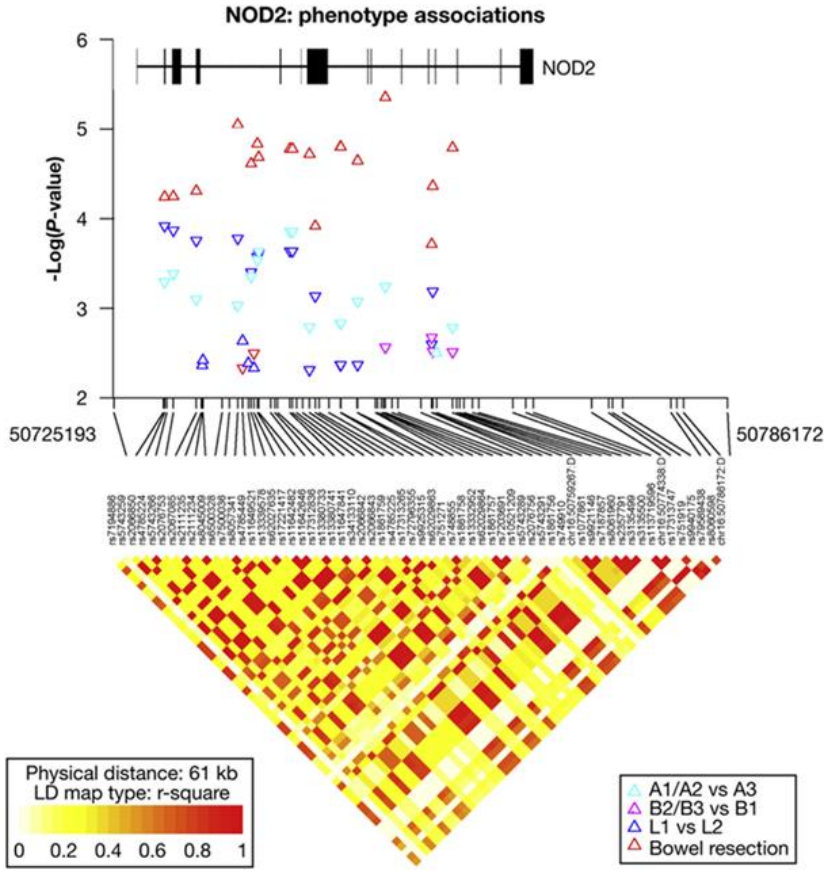
IBD Clinical data:

1. Age
2. Sex
3. Ethnicity
4. Age of disease incidence
5. Disease duration
6. Family history
7. Disease location
8. Extra-intestinal manifestation
9. Surgery
10. Smoking

After GWAS, functional hypotheses can be tested using experimental techniques such as CRISPR or massively parallel reporter assays, or results can be validated in a human trait/disease model

https://sitn.hms.harvard.edu/flash/2019/lessons-from-the-human-genome-project/

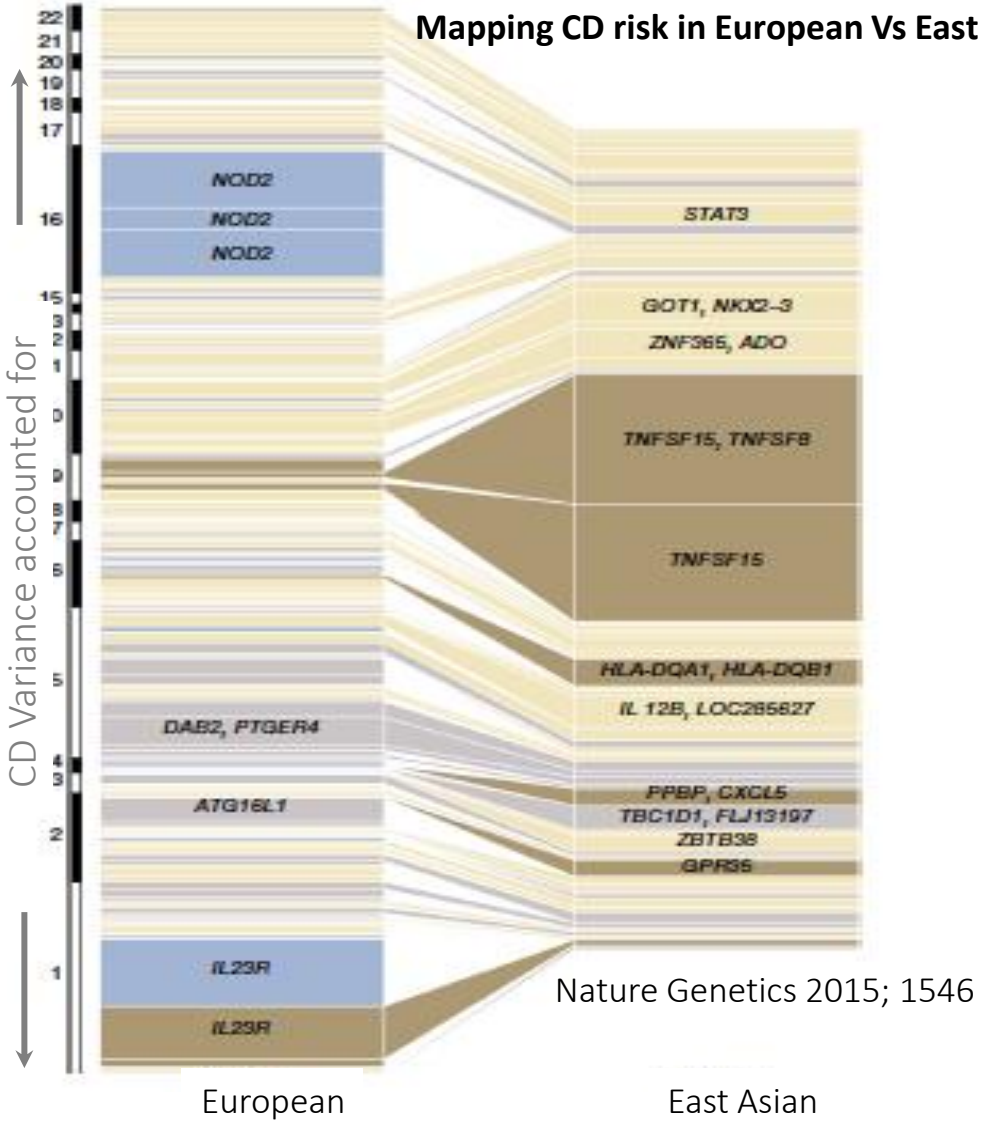
Inflammatory bowel disease (IBD) and Genetic Variants



Identification of Risk Loci for Crohn's Disease Phenotypes Using a Genome-Wide Association Study

Gastroenterology April 2015 DOI: 10.1053/j.gastro.2014.12.030

Mapping CD risk in European Vs East Asian population



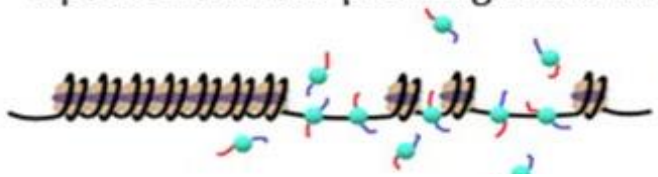
Nature Genetics 2015; 1546

- **Personalized IBD risk assessments and treatments** demand that an individual American knows their disease risk, likelihood of a treatment being effective, and risk of disease complications **as based on genetic profiles**

Epigenomics: experimental design and application

- Gene expression analysis with RNA-seq

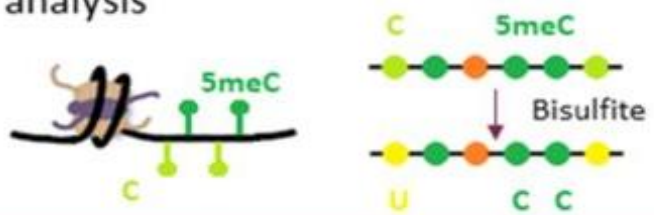
- Open chromatin profiling with ATAC-seq



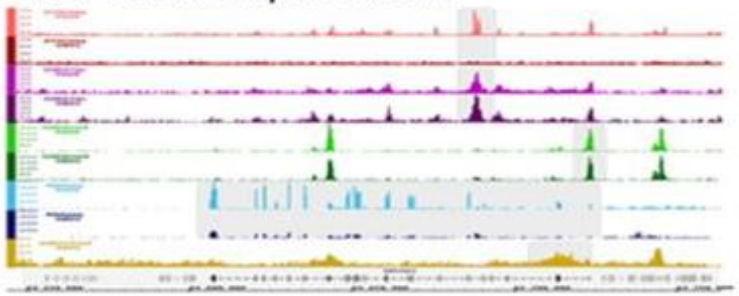
Assay for Transposase-Accessible Chromatin (Tn5 transposase tagmentation)

Genomic DNA or chromosomal DNA (Promega/ Qiagen kits)

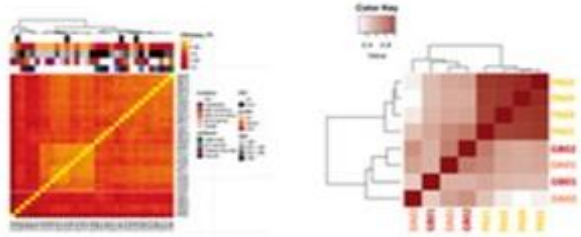
- Genome-wide DNA methylation analysis



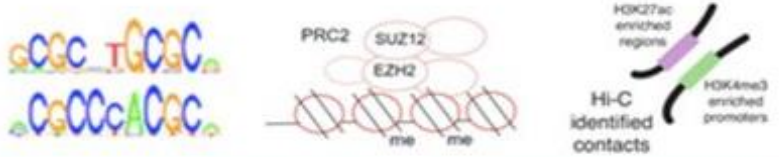
- Genome browser with coverage for each experiment



- Transcriptional and epigenomic differential analysis



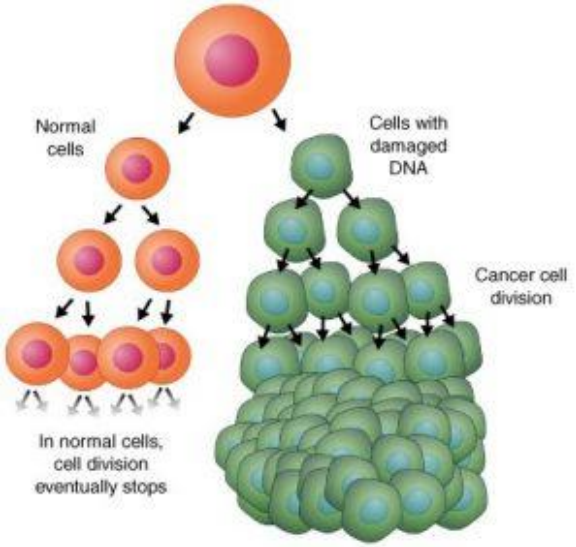
- Identification of regulatory mechanisms behind observed data



https://www.biorxiv.org/content/10.1101/867861v2

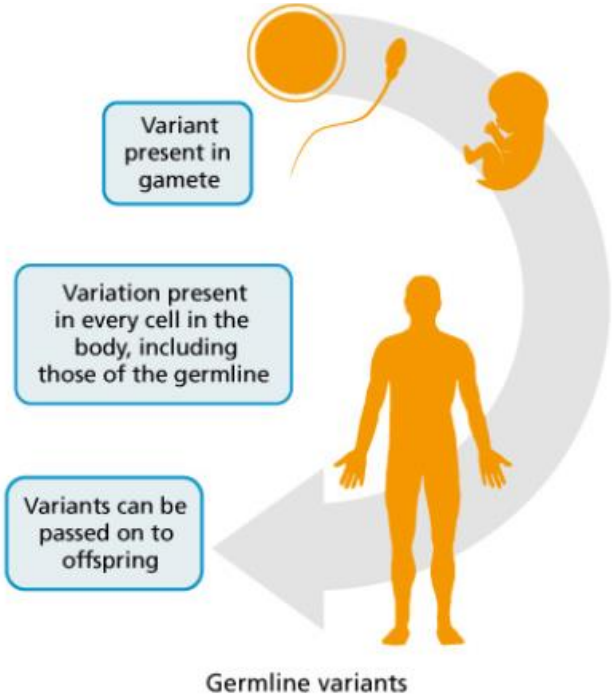
Cancer genomics

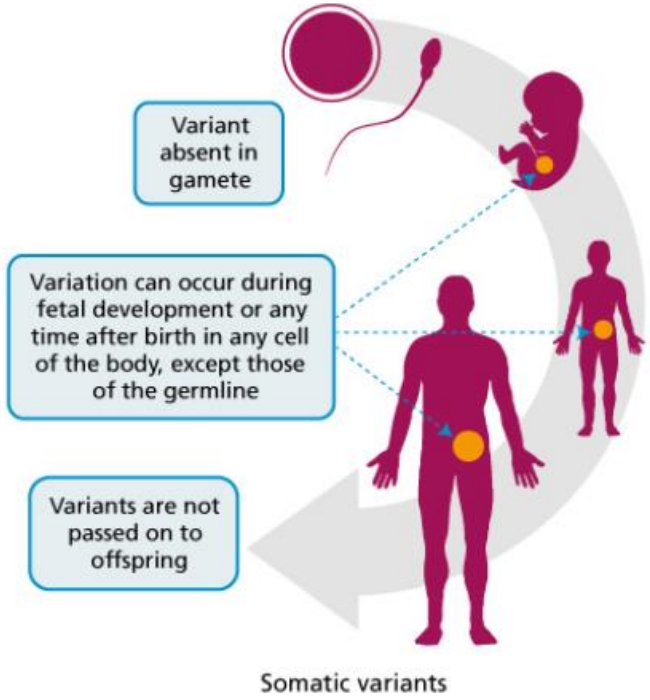
Genomic testing is increasingly being used to inform cancer diagnosis, prognosis and treatment



Characteristics of cancerous cells:

- Limitless replication potential
- Self-sufficiency in growth signals
- Evasion of programmed cell death (apoptosis)
- Insensitivity to growth-inhibitory (antigrowth) signals
- Sustained angiogenesis
- Tissue invasion and metastasis





https://www.genomicseducation.hee.nhs.uk/wp-content/uploads/2019/06/008-Gettingreadyforgenomicmedicine-GeneticsUnzipped-1.mp3

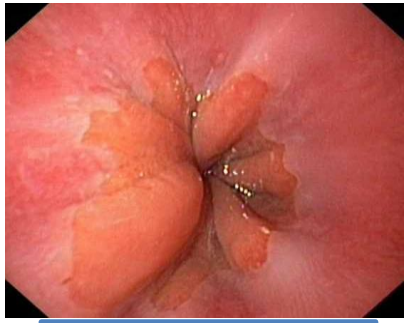
https://www.genomicseducation.hee.nhs.uk/document-library/

What is Omics?

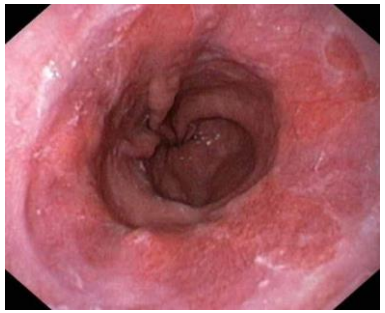
1. A field of study that focuses on one part of the body
2. A type of exercise that benefits all parts of the body
3. A type of instrument that analyzes molecules
4. A field of study that integrates collective information from all biological molecules
5. A field of study that focuses on specific biological molecules

TRANSCRIPTOMICS----

In-vivo Barrett's epithelial carcinogenesis

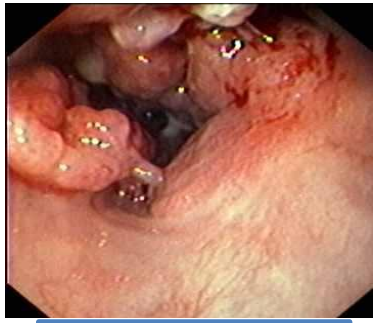


Normal EGJ



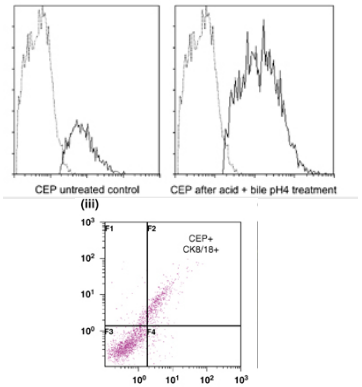
Irregular EGJ, esophagitis

Barrett's Epithelium



Adenocarcinoma

The in-vitro Barrett's epithelial carcinogenesis (BEC) model

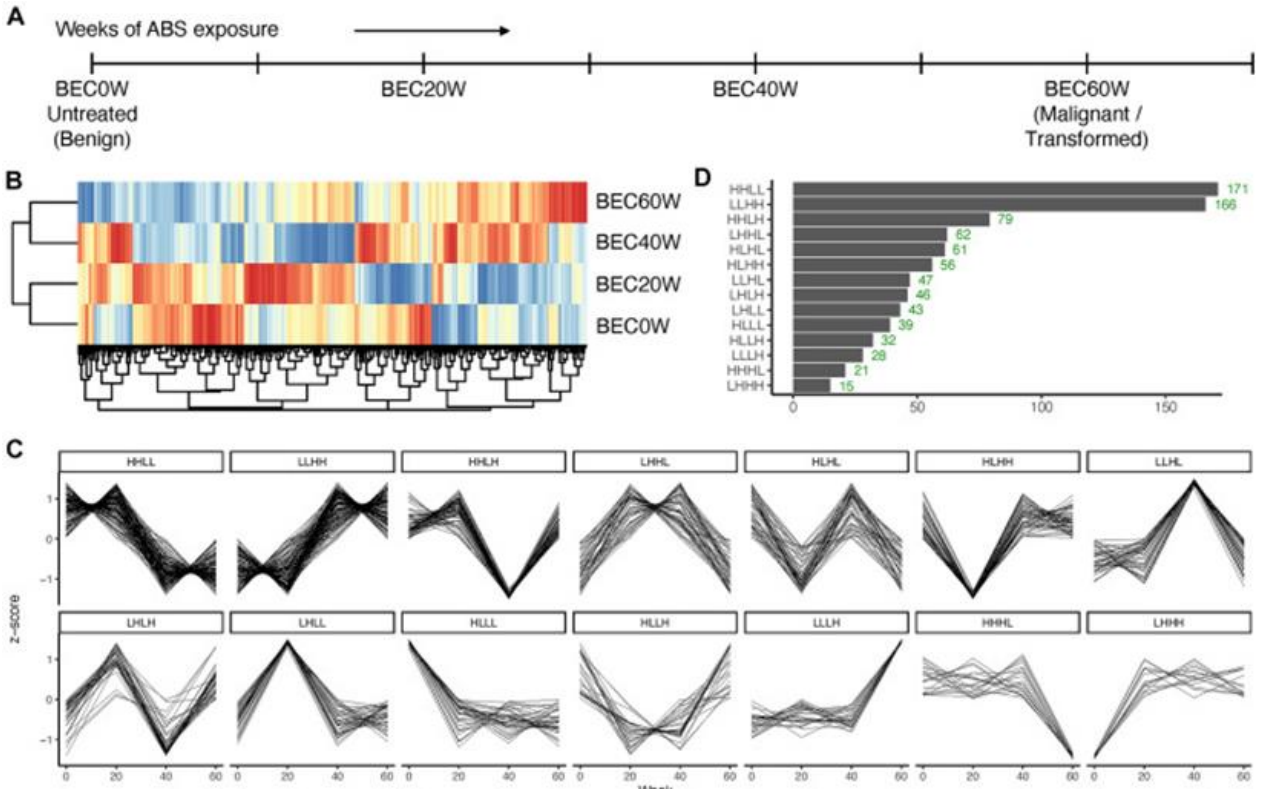


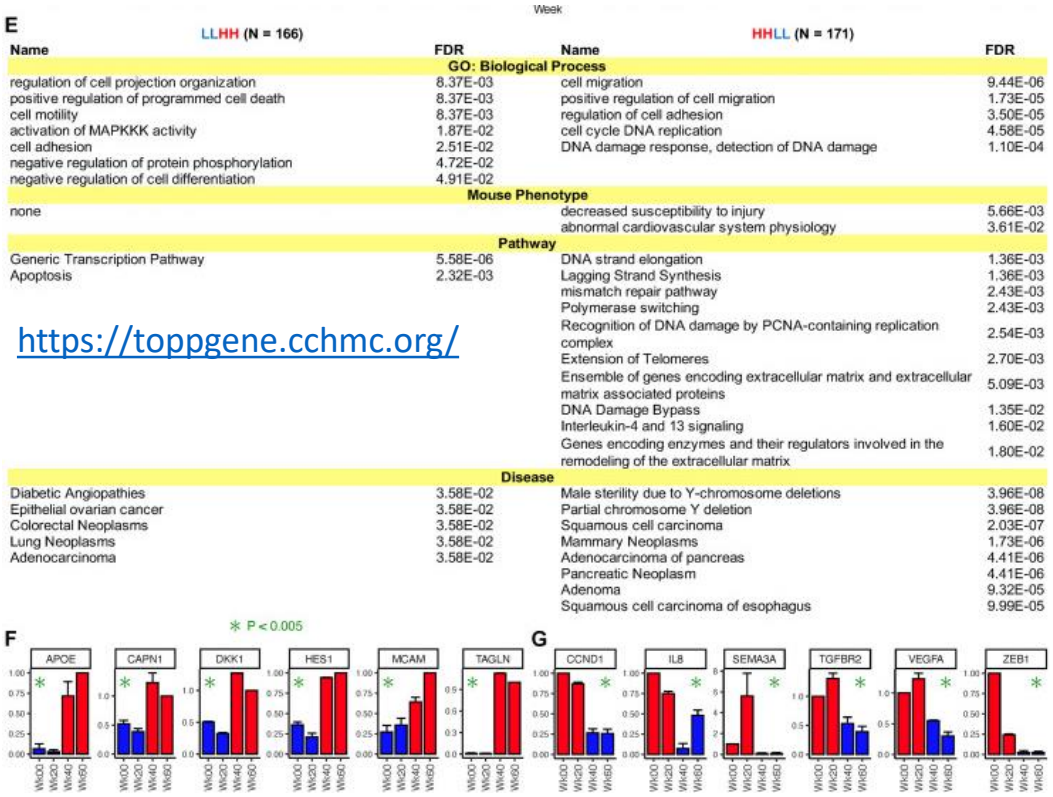
Paraffin embedded EAC tissue showing chr (2,16) fusion by FISH

Transcriptomics: experimental design and application

Barrett's Epithelium to Esophageal Adenocarcinoma: Is There a "Point of No Return"?

Front Genet. 2021 Sep 17;12:706706. doi: 10.3389/fgene.2021.706706. eCollection 2021.

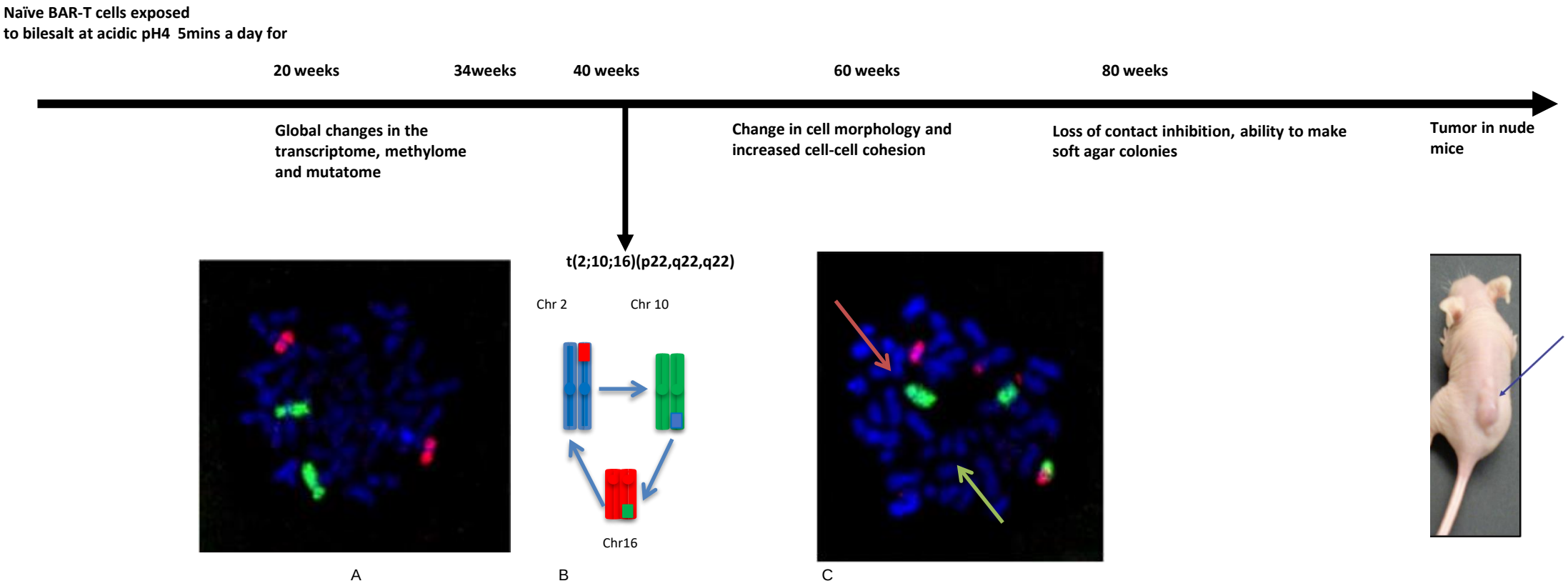




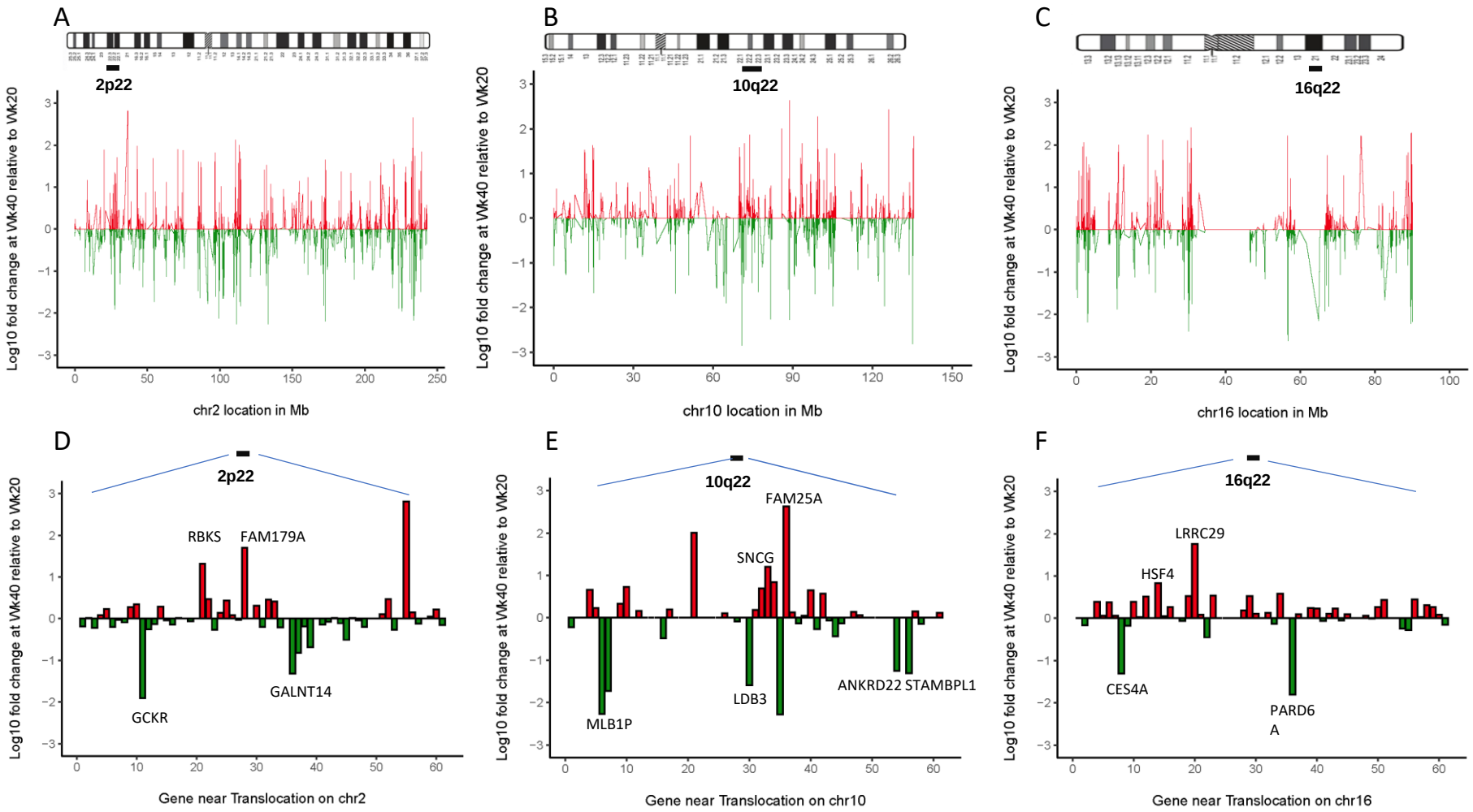
(A) The outline of the BEC model and time points selected for transcriptomic analyses. (B) Heatmap (with hierarchical clustering) of the expression data of 866 genes that showed a twofold or higher variation in expression across the four time points. (C) Classification of the genes based on whether the expression at the four time points (BEC0W, BEC20W, BEC40W, and BEC60W) are higher or lower (H/L) than the average of the four time points. (D) Number of genes in each category. (E) Biological processes, mouse phenotypes, pathways, and diseases enriched in the genes of the LLHH (left) and HHLL (right) patterns. (F,G) Confirmatory quantitative PCR for randomly selected genes from LLHH and HHLL patterns.

Prolonged exposure to acid and bile induces chromosome abnormalities that precede malignant transformation of benign Barrett's epithelium

Front Genet. 2021 Jun 9;12:674741. doi: 10.3389/fgene.2021.674741. eCollection 2021.



Alteration in gene expression as a result of chromosomal rearrangement

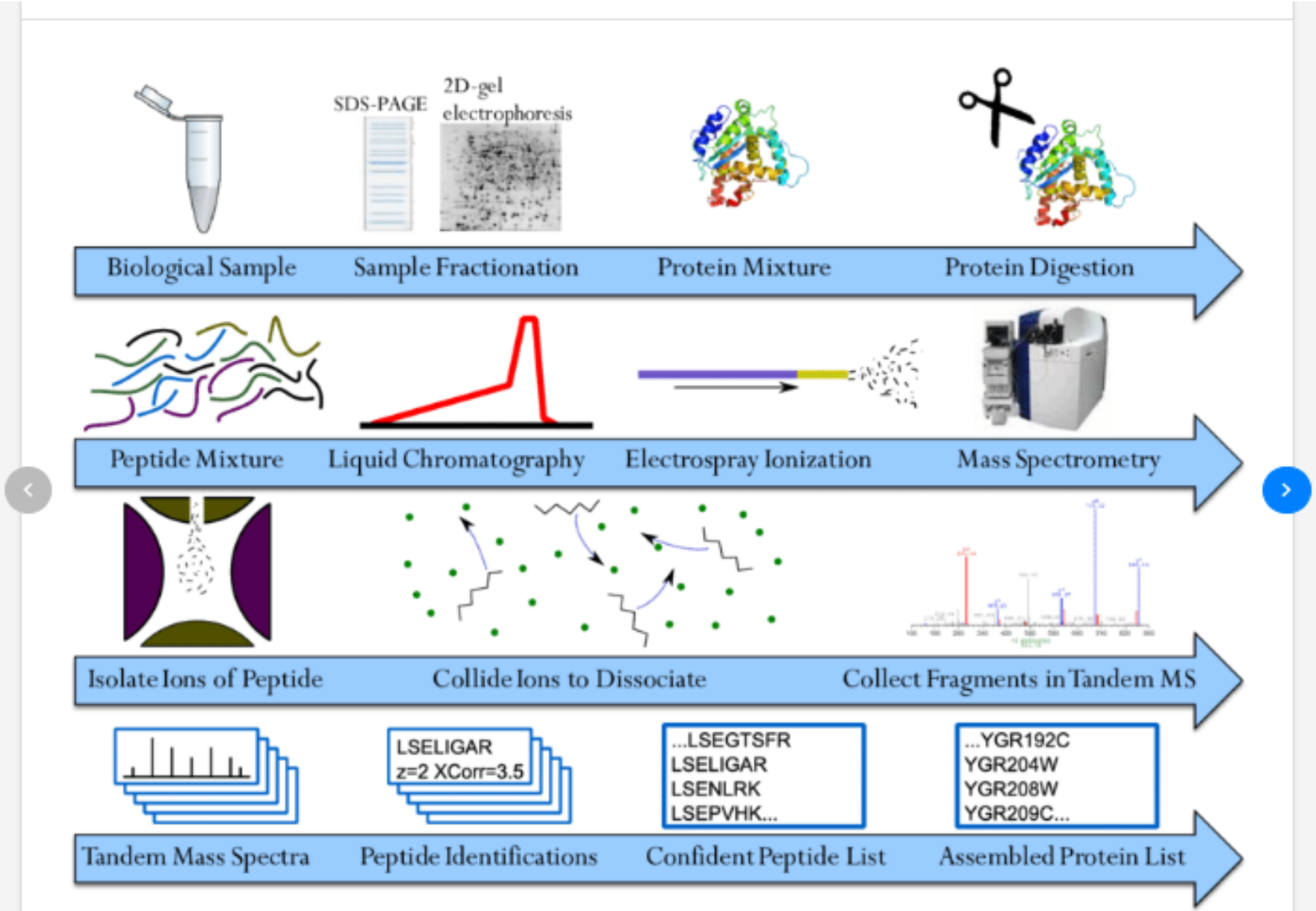


Altered transcriptional landscape of Barrett's epithelial cells as result of translocations between chromosomes 2, 10 and 16 in BEC40W compared to BEC20W cells

Front Genet. 2021 Jun 9;12:674741. doi: 10.3389/fgene.2021.674741. eCollection 2021.

PROTEOMICS----

Proteomics Workflow

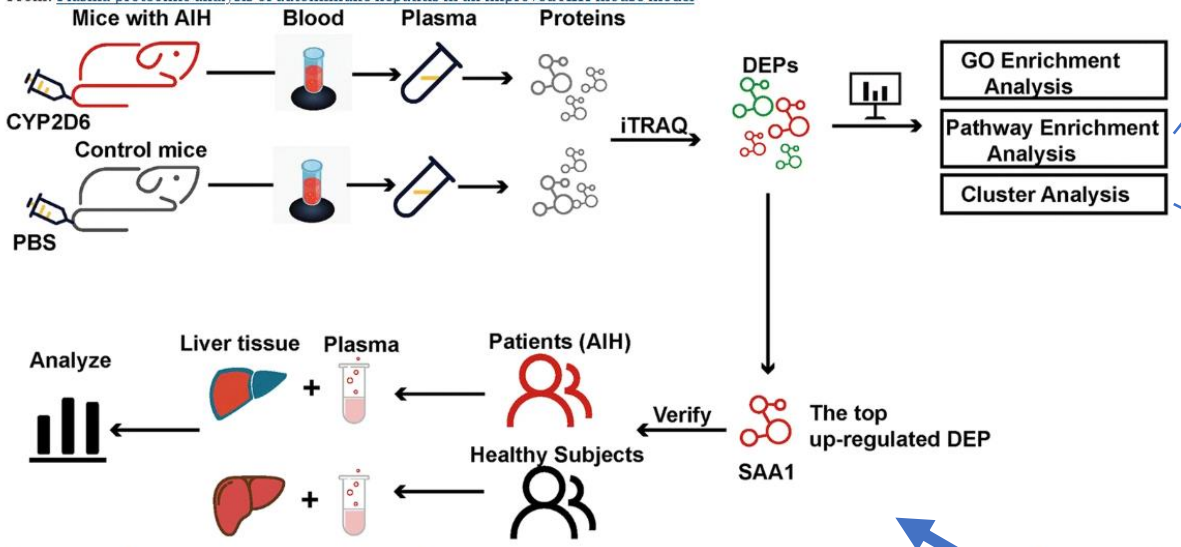


Proteomics: experimental design and application

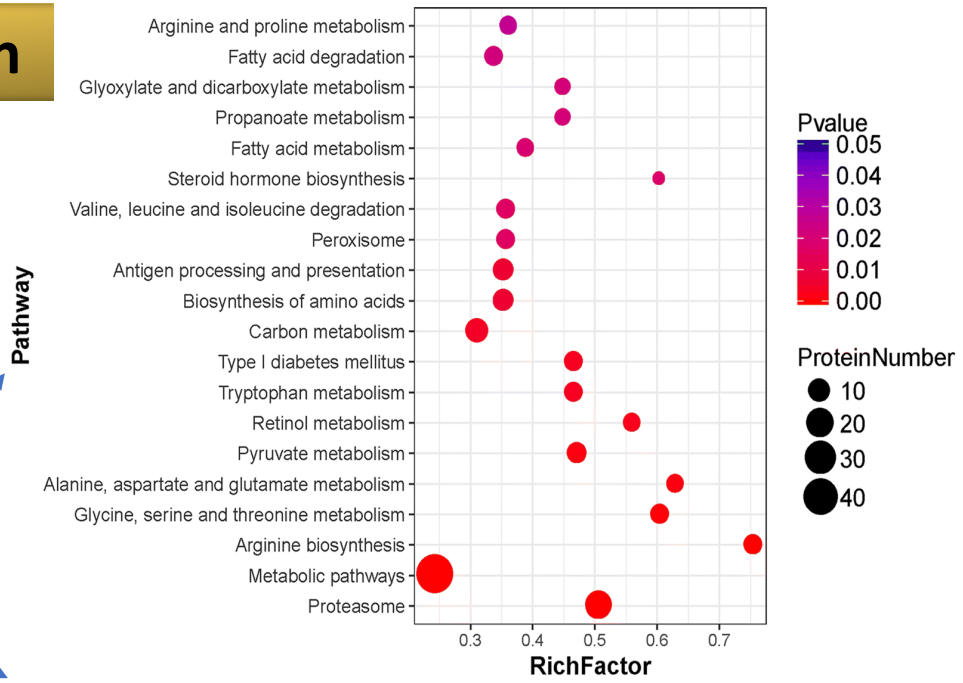
Plasma Proteomic Analysis of Autoimmune Hepatitis

https://translational-medicine.biomedcentral.com/articles/10.1186/s12967-019-02180-3#Abs1

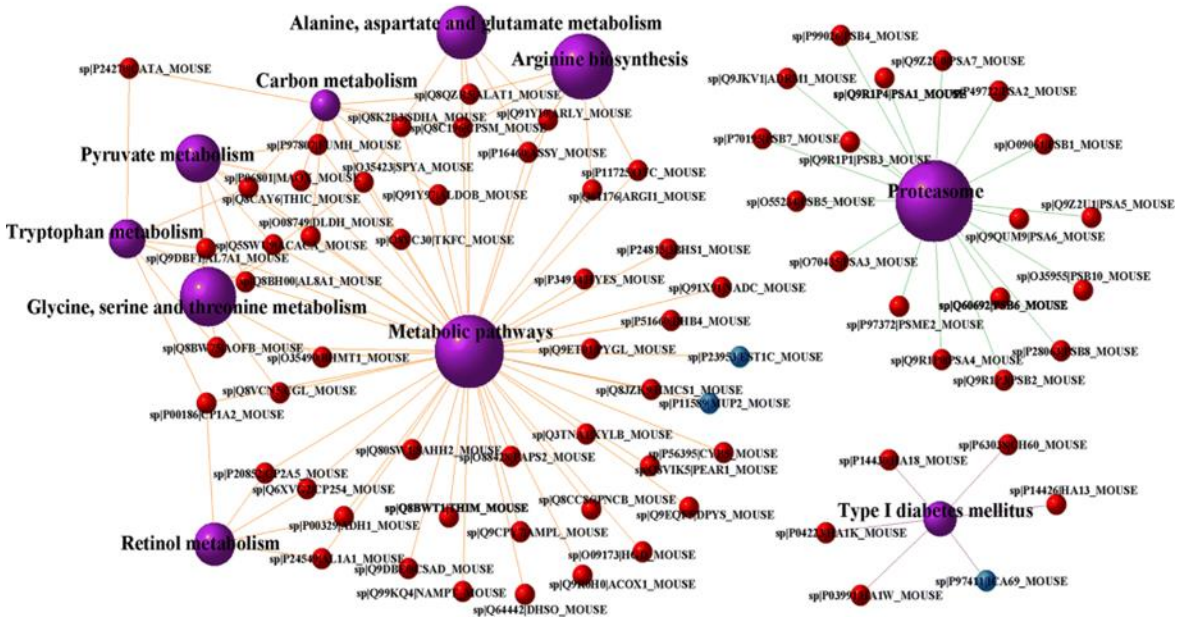
From: Plasma proteomic analysis of autoimmune hepatitis in an improved AIH mouse model



The schematic diagram of the experiment design. *CYP2D6* cytochrome P450 2D6, *AIH* autoimmune hepatitis, *DEPs* differentially expressed proteins, *iTRAQ* isobaric tags for relative and absolute quantitation, *SAA1* serum amyloid A 1, *GO* gene ontology



differentially expressed proteins (DEPs)



METABOLOMICS---

LIPIDOMICS---

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7149616/

Metabolomics/ Lipidomics Workflow

Sample Preparation

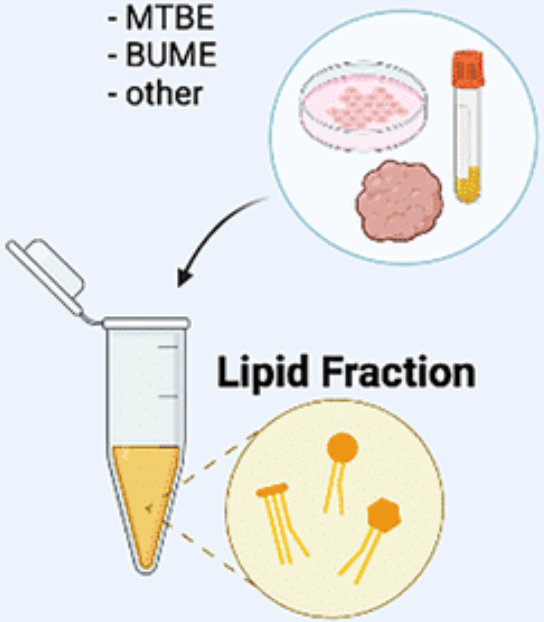
Sample Collection:

- Cells
- Serum
- Tissue

} Flash-frozen

Lipid Extraction:

- Bligh & Dyer
- Folch
- MTBE
- BUME
- other



MS-Detection

Analyte Separation:

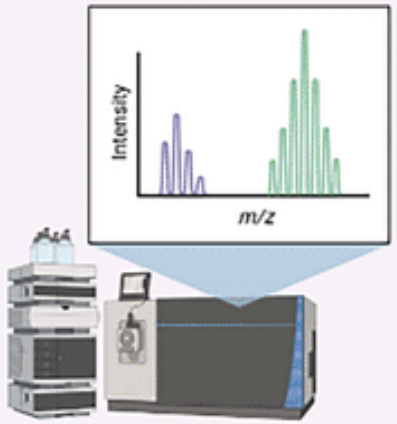
- Liquid-chromatography (LC)
- Gas-chromatography (GC)

Ionization:

- ESI
- MALDI
- APCI
- DESI
- APPI
- SIMS
- other

Mass-spectrometry:

- MS
- Tandem MS/MS



Data Analysis

Analyte Annotation:

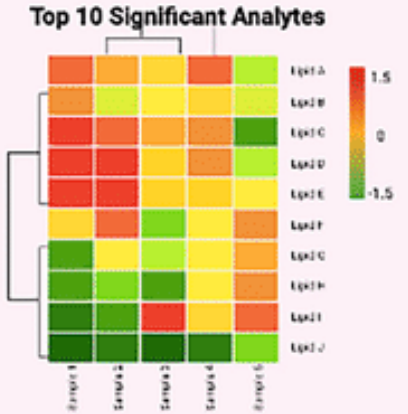
- Annotation Software (e.g. MassHunter)

Data Normalization:

- Sample-based (e.g. protein)
- Data-based (e.g. Log)

Analysis/Statistics:

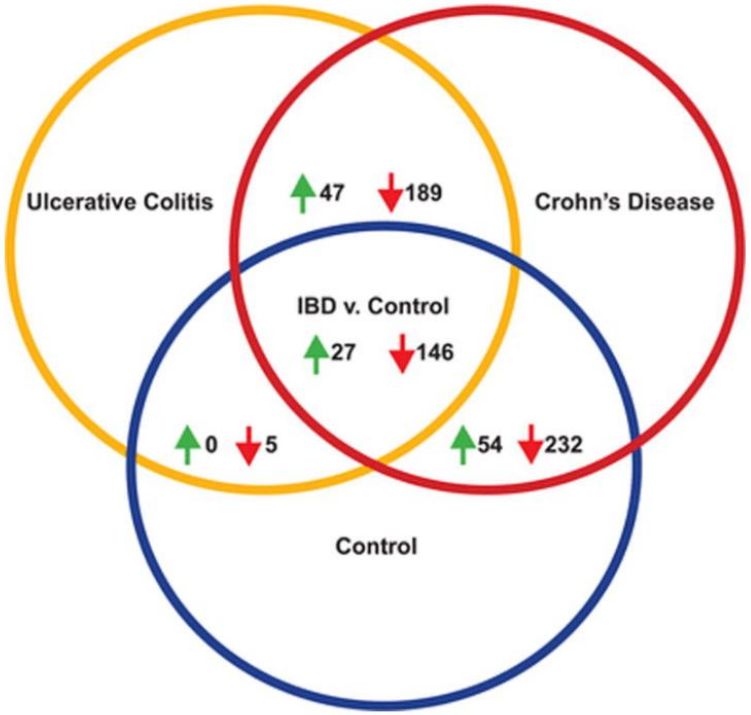
- ANOVA, t-test, SAM, EBAM
- Heatmap
- Lipid Ontology Enrichment
- Pathway Analysis

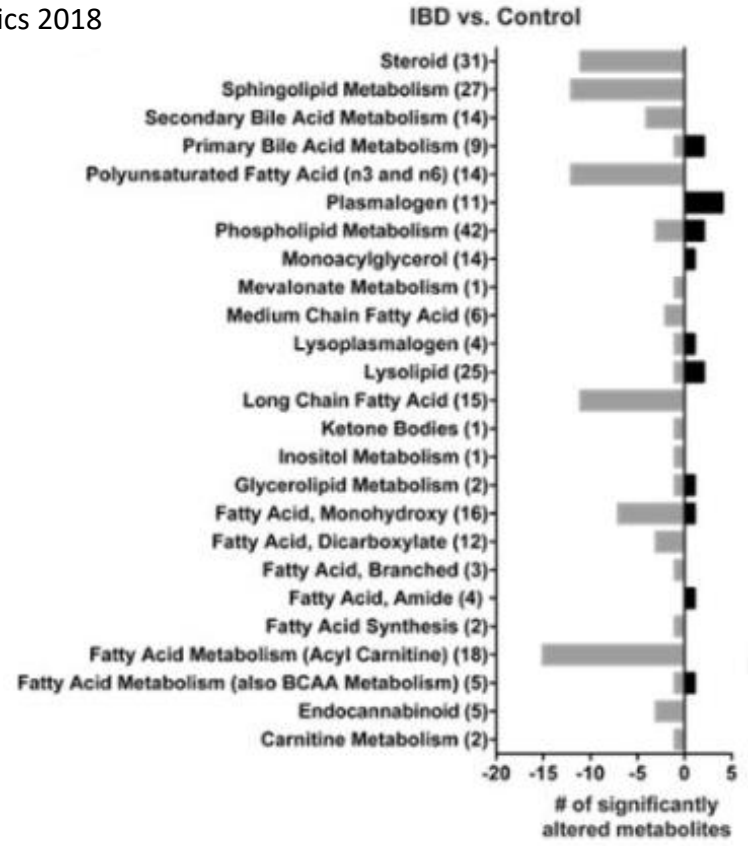


Metabolomics and Lipidomics : experimental design and application

Alterations in Lipid, Amino Acid, and Energy Metabolism Distinguish Crohn's Disease from Ulcerative Colitis and Control Subjects by Serum Metabolomic Profiling

Scoville et.al. Metabolomics 2018

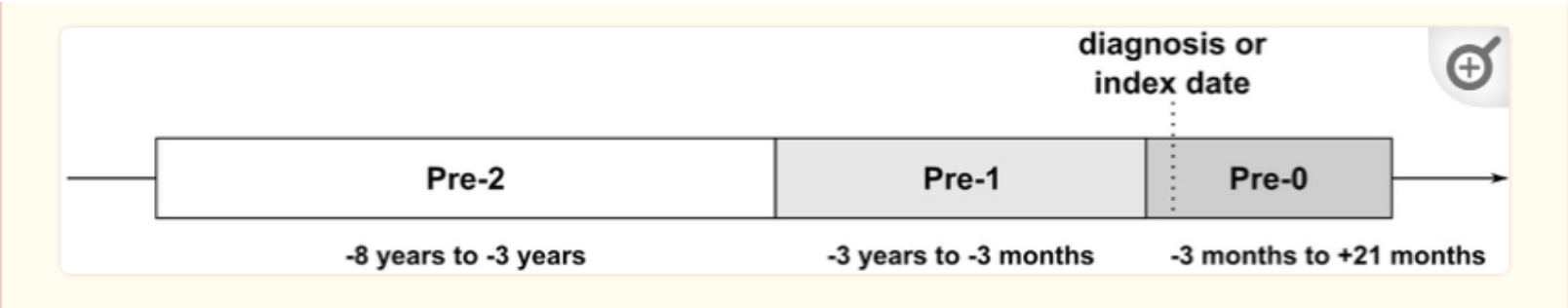




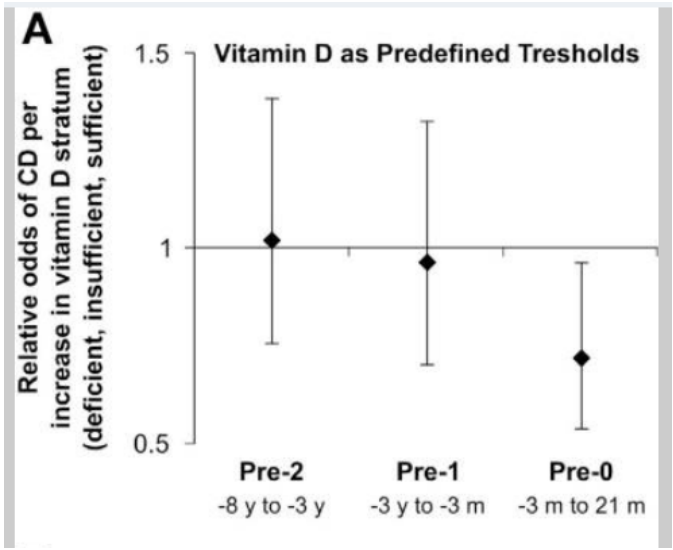
Multiple metabolites were significantly altered between UC, CD, and control subjects

Lipid related metabolic pathways are altered in IBD compared control subjects

Metabolomics and Lipidomics to find causation of disease:

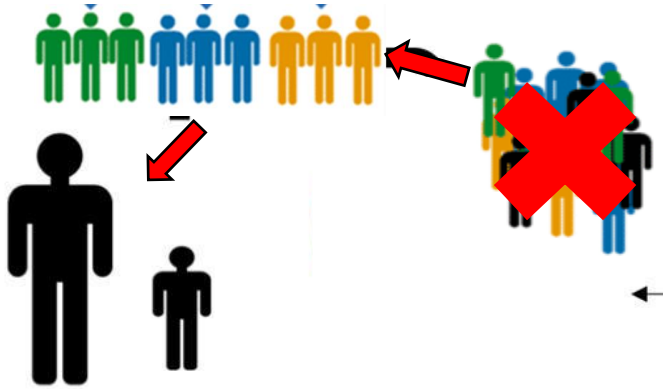


Serum sample collection and experimental design



Levels of Vitamin D Are Low After Crohn's Disease Is Established But Not Before

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7163919/



Personalized medicine

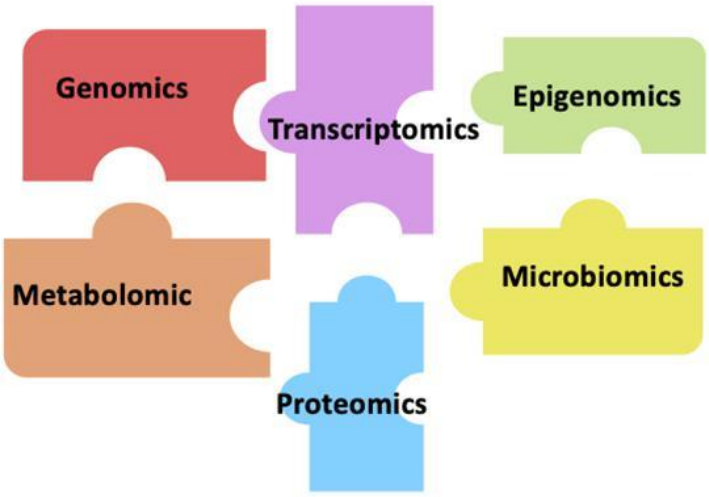
To Improve patient health

to understand the biology of diseases

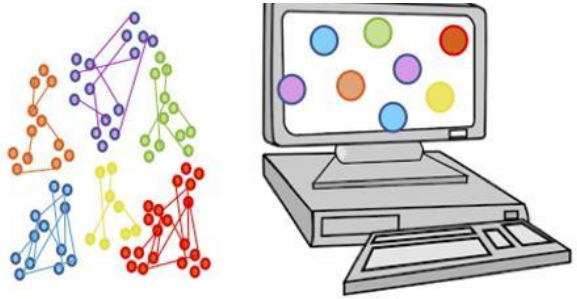
To improve diagnostics and therapies

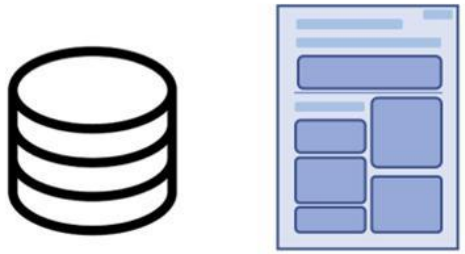
Application of OMICS in Human Health

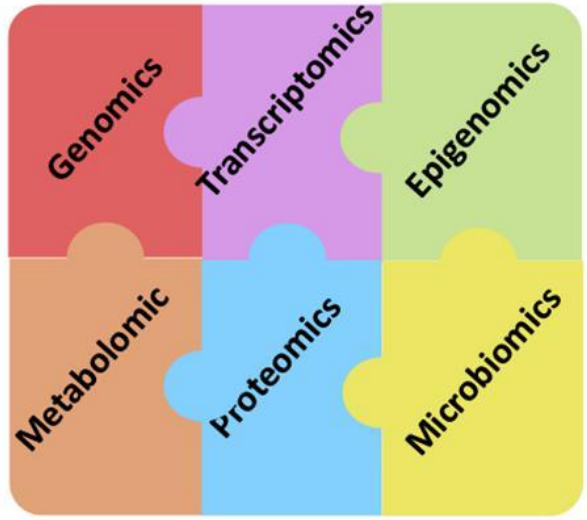
Combinatorial machine learning approaches



Single Omics



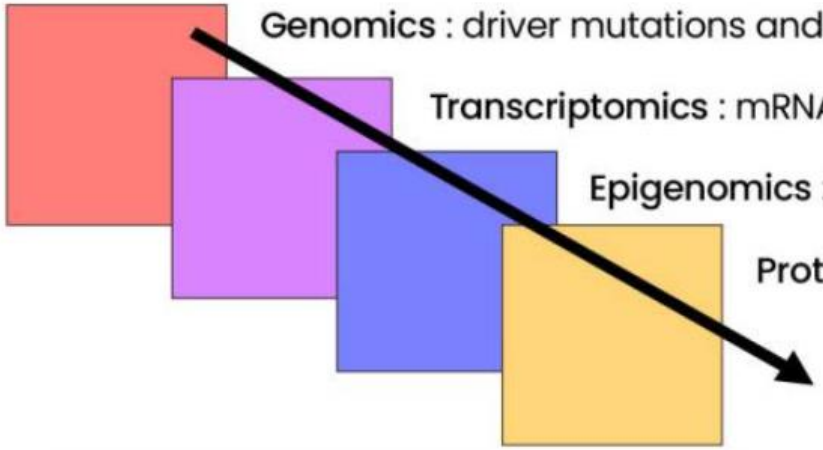




Multi-omics

Multi-Omics in Personalized Cancer treatment

Biological Features in Multi-omics Approaches



Genomics : driver mutations and genes, copy-number alterations

Transcriptomics : mRNA quantification, co-expression network, gene ontology

Epigenomics : CpG patterns, transcription regulation

Proteomics : driver proteins, protein abundance, post-translational modification

Clinical Features Found in Multi-omics Approaches

Lung Cancer

- Proteogenomic signature for patient subtypes
- Revealed a novel KEAP1/NFE2L2 network
- APOBEC signature in young female

Breast Cancer

- Proteogenomic signature in ERBB2 subtypes
- RB response to CDK4/6 Inhibitor Therapy
- Acetylproteome-specific patient group for metabolism

Gastric Cancer

- Patients subtypes for driver gene and kinase activities
- Proteogenomic signature in early-onset patients
- Phosphorylation in cellular signaling pathway

Glioblastoma

- Mesenchymal subgroups for transcription factors
- Phosphoproteomes signature in ceullar and growth factors
- Patient subtypes with the phosphosite S38 of *STMN1*

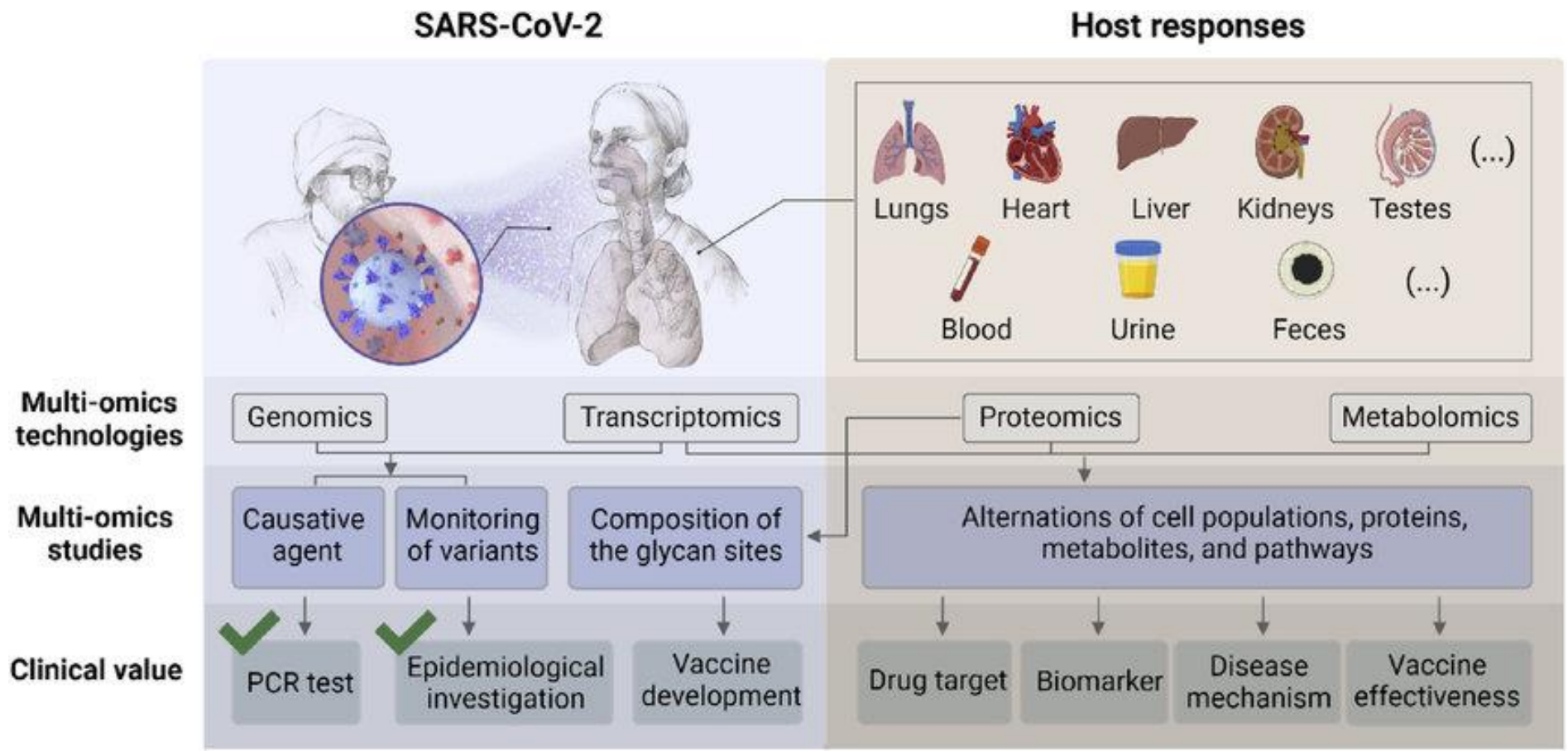
Acute Myeloid Leukemia

- CpG patterns related to driver mutations
- Subtypes for *IDH1* / *IDH2* mutations and methylation
- Patients subtypes for gene fusions

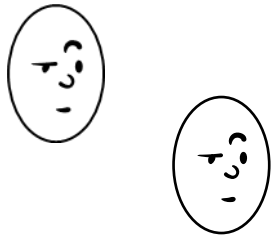
Pancreatic Ductal Adenocarcinoma

- Patients subtypes for *KRAS* mutational heterogeneity
- Multi-omics modules related to tumor purity and gene expression signatures

Multi-omics studies on SARS-CoV-2 and host response

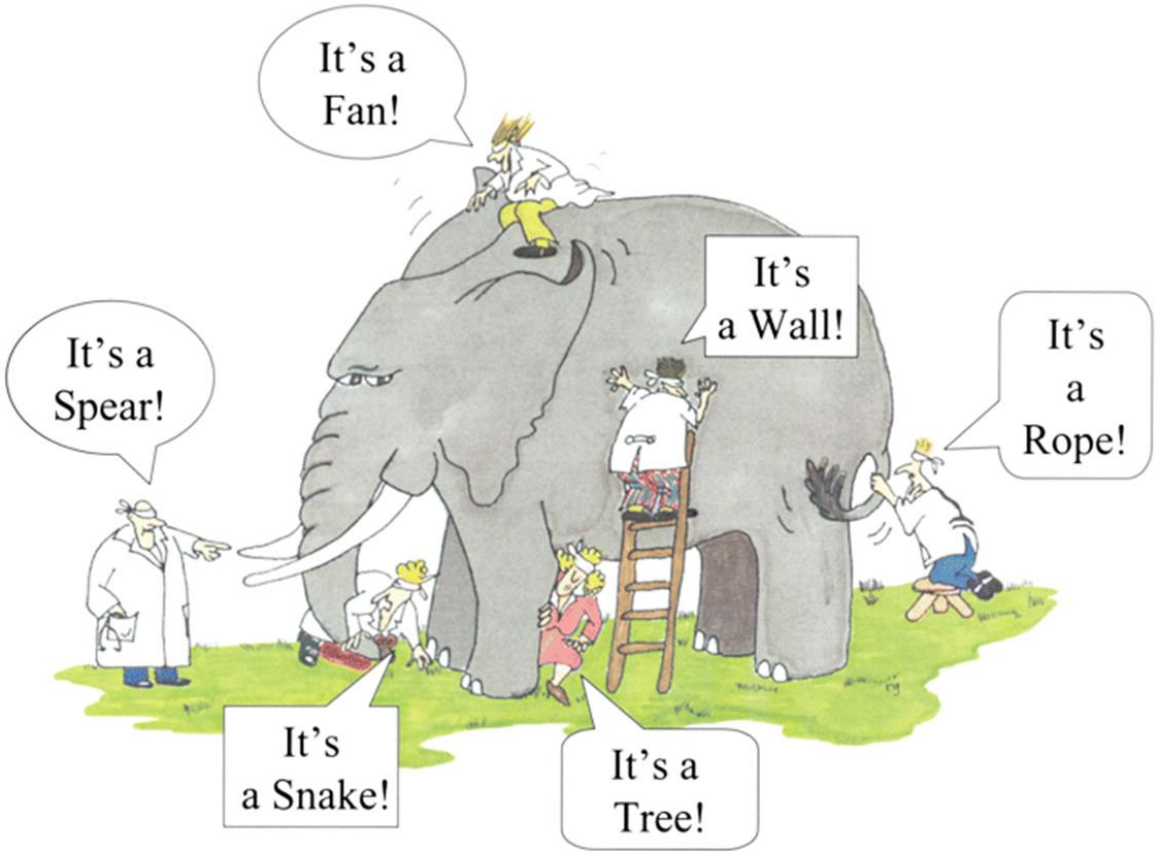


Mechanisms of SARS-CoV-2 Variants of Concern,'' by BioRender.com (2022). Retrieved from https://app.biorender.com/ biorender-templates



Challenges for Multi-omics

- Validation of observations
- Refining the technological tools
- Appropriate expertise
- Ethical issues
- Social issues
- Legal issues
- Cost
- Time



Central Dogma of Biology

SUMMARY

'Omics

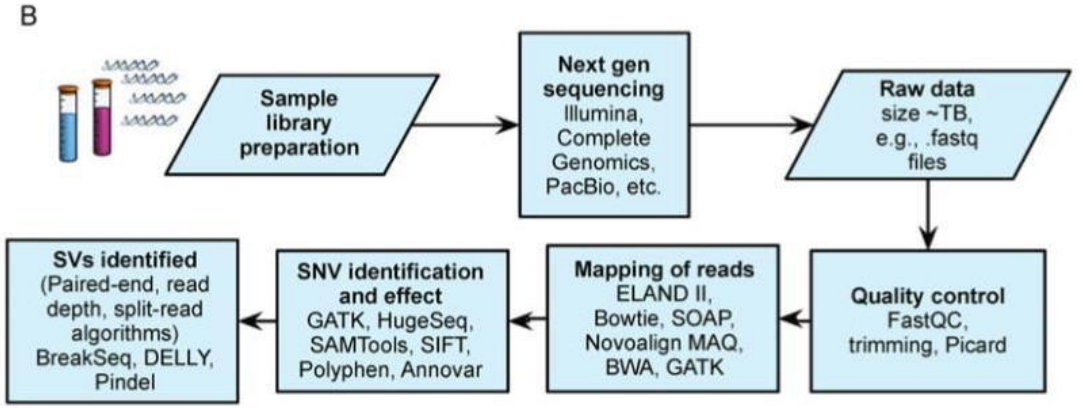
DNA → Genomics

Transcription

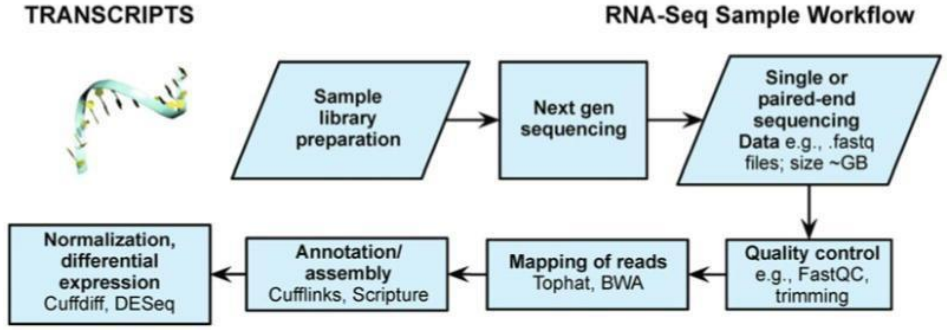
RNA → Transcriptomics

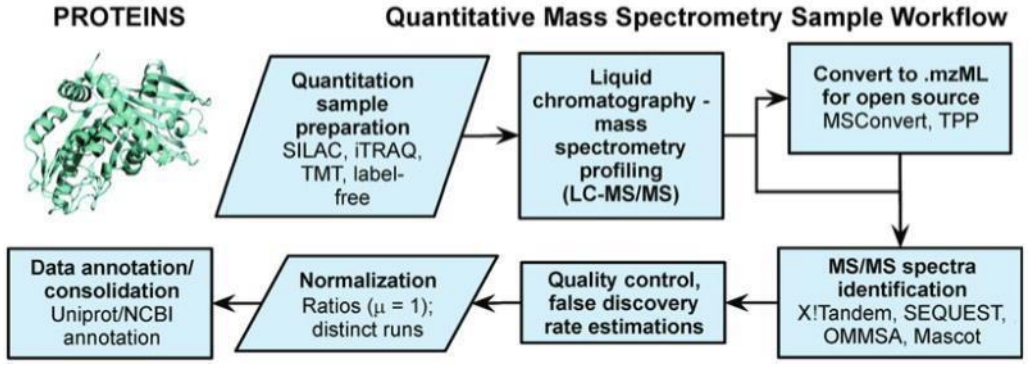
Translation

Protein → Proteomics



Mias and Snyder, Quant Biol. (2013) 1(1): 71–90. doi: [10.1007/s40484-013-0005-3]





https://wildlifesnpits.wordpress.com/2015/11/18/transcriptomics-for-conservation/