The New World of Genomics

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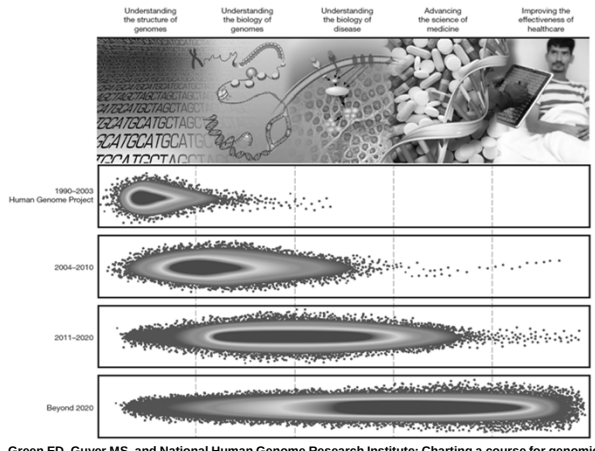
Learning Objectives

- To define genomic medicine
- To review early triumphs, and potential limitations, of genomic medicine
  - Guiding treatment
  - Risk assessment
  - Early detection/prevention
  - Diagnostics
- Applied case example: Genomic medicine approaches to hereditary breast-ovarian cancer



Green ED, Guyer MS, and National Human Genome Research Institute: Charting a course for genomic medicine from base pairs to bedside. *Nature*. 470:204-213. 2011.

Genomic Medicine aka Personalized Medicine aka Precision Medicine

- An approach to customize medical care to an individual's unique genetic makeup
- Every cell in the body contains DNA, molecules inherited from our parents that determine how the body looks and functions
- Sections of the DNA that contain information needed to make proteins are known as genes
- Variations in the DNA are associated with rare and common disease
  - Pathogenic and protective variants
- Many, if not most, human diseases have a genetic component

Precision Medicine – what it is

Precision Medicine is most simply:

- **Human genetics and genomics information integrated into clinical medicine.**

Precision Medicine more conceptually:

- **Is a paradigm shift in our concept of human disease**
- **Instead of viewing disease based only on clinical information we define it based on its genetics/genomics**
- **We are literally rewriting the textbooks of medicine**

Precision Medicine – what it is

From the top:

”Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier.”

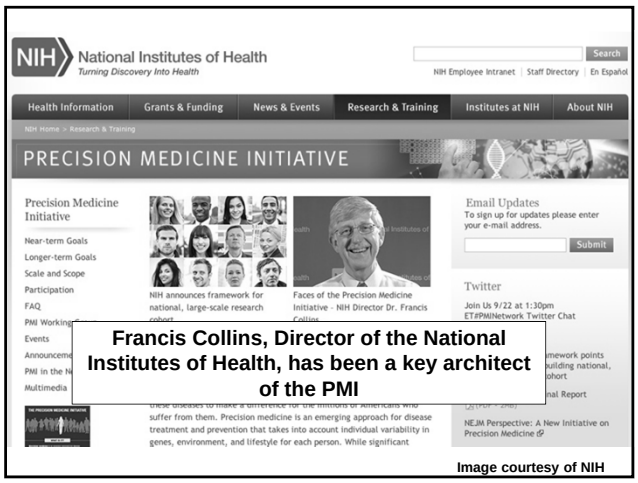
— President Barack Obama, State of the Union Address, January 20, 2015

Announcement of the NIH Precision Medicine Initiative

Image courtesy of NIH

“And that’s why we are here today, because something called precision medicine… gives us one of the greatest opportunities for new medical breakthroughs that we have ever seen!”

Image courtesy of NIH



Francis Collins, Director of the National Institutes of Health, has been a key architect of the PMI

Image courtesy of NIH

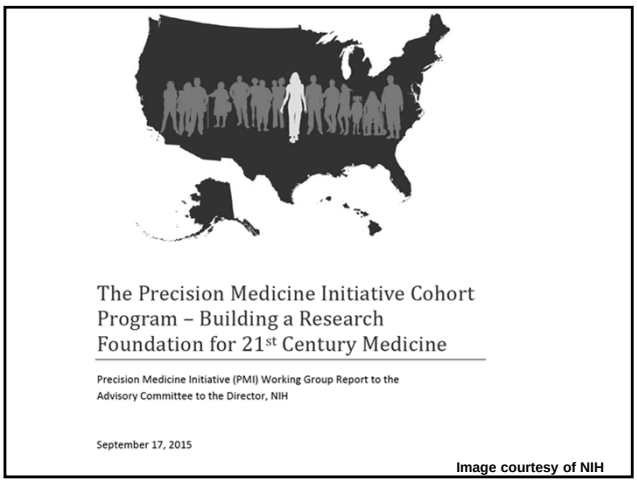


Image courtesy of NIH

Precision Medicine Initiative Details

- Large scale prospective cohort study
  - One million or more American volunteers
  - Broad diversity, all life stages
  - Begin enrollment in 2016
- Study genomic, environmental and gene-environment interactions
- More precise preventive care
  - Better risk estimates and biomarkers for range of rare and common diseases
- Fuel new targeted therapies e.g. cancer, heart disease

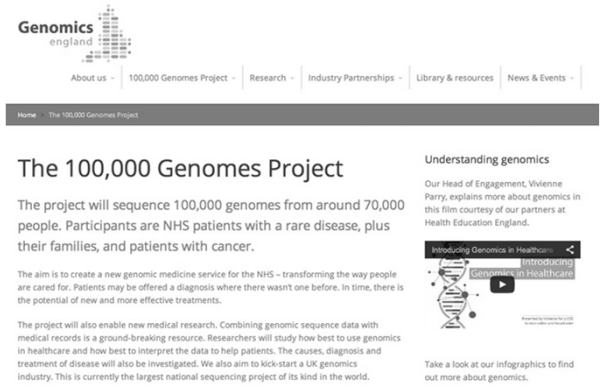
Precision Medicine Initiative Details

- Health data from EHRs and surveys
  - Physical exam
- Blood sample
  - Whole genome sequencing
- Home and mobile health (mHealth) sensors to correlate body measurements, calorie consumption and environmental exposures with health outcomes
- Participants will control how their data is shared and used in research
- Empower participants to improve own health

Precision Medicine Initiative – Integration of Genetic/Genomic Counseling

- Genetic counseling has integral role
  - Informed consent and specimen collection
  - Complexity of return of genomic based results
  - Decision making process
  - Improving health outcomes
- Service delivery models need to evolve

The UK announced the 100,000 Genomes Project in 2013



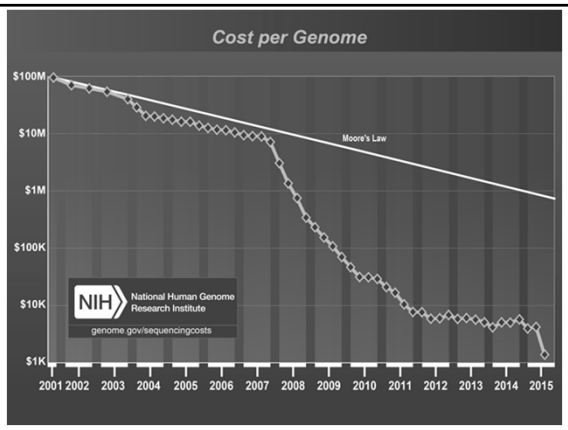
The Explosion of Human Genetics and Genomics in Clinical Practice

Driven by high throughput sequencing

- 10 years ago – challenging to routinely sequence anyone
- 5 years – 2-3 genes possible (HCM 5 – 8 genes)
- 3 years – gene panels emerging (5-20 genes)
- 2 years – larger panels (10-40; pan-cardio – 84)
- 1 year ago – clinical exome emerges
  - exome = 19,000 – 20,000 genes encoding proteins
- Now – selective clinical exome sequencing:
  - 3 or more affecteds
  - negative panel
  - insurance coverage

Sequencing a genome

- Genome refers to the entire DNA structure
  - 6 billion letters of code distributed unequally amongst 46 chromosomes
  - 3 gigabytes of data
  - ~20,000 protein coding genes (2% of the DNA code)
- Cost has dropped considerably
  - 2001: $100 million per genome
  - 2010: $30,000
  - 2015: ~$1,000



Courtesy: National Human Genome Research Institute - www.genome.gov/sequencingcosts

Ending the diagnostic odyssey, with and without treatment ramifications

Ending the diagnostic odyssey, with and without treatment ramifications


Doctors Sift Through Patients' Genomes To Solve Medical Mysteries

Doctors Sift Through Patients' Genomes To Solve Medical Mysteries

By Rob Stein

http://www.npr.org/sections/health-shots/2012/09/25/160957147/doctors-sift-through-patients-genomes-to-solve-medical-mysteries

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North County Twins Cured After Whole Genome Sequencing By Chris Chan


North County Twins Cured After Whole Genome Sequencing

http://www.nbcsandiego.com/news/local/North-County-Twins-Cured-After-Whole-Genome-Sequencing-167426045.html

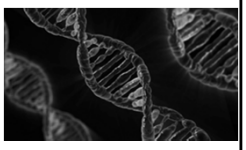
RESEARCH ARTICLE

DIAGNOSTICS

Rapid Whole-Genome Sequencing for Genetic Disease Diagnosis in Neonatal Intensive Care Units

Carol Jean Saunders,[1,2,3,4,5]* Neil Andrew Miller,[1,2,4]* Sarah Elizabeth Soden,[1,2,4]* Darrell Lee Dinwiddie,[1,2,3,4,5]* Aaron Noll,[1] Noor Abu Alnadi,[4] Nevene Andraws,[3] Melanie LeAnn Patterson,[1,3] Lisa Ann Krivohlavek,[1,3] Joel Fellis,[6] Sean Humphray,[6] Peter Saffrey,[6] Zoya Kingsbury,[6] Jacqueline Claire Weir,[6] Jason Betley,[6] Russell James Grocock,[6] Elliott Harrison Margulies,[6] Emily Gwendolyn Farrow,[1] Michael Artman,[2,4] Nicole Pauline Safina,[1,4] Joshua Erin Petrikin,[2,3] Kevin Peter Hall,[6] Stephen Francis Kingsmore[1,2,3,4,5]†

- **The use of WGS in the NICU provided differential diagnoses in a 50 hour time period**
- **WGS can shorten the time to diagnosis and quicken the move toward targeted treatment and genetic and prognostic counseling**



***Sci Transl Med* 2012**

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Clinical Diagnosis by Whole-Genome Sequencing of a Prenatal Sample

Michael E. Talkowski, Ph.D., Zehra Ordulu, M.D., Vamsee Pillalamarri, M.S., Carol B. Benson, M.D., Ian Blumenthal, B.E., Susan Connolly, M.D., Carrie Hanscom, M.S., Naveed Hussain, M.D., Shahrin Pereira, B.S., Jonathan Picker, M.B., Ch.B., Ph.D., Jill A. Rosenfeld, M.S., Lisa G. Shaffer, Ph.D., Louise E. Wilkins-Haug, M.D., James F. Gusella, Ph.D., and Cynthia C. Morton, Ph.D.

***N Engl J Med* 2012**
***Sci Transl Med* 2012**

RESEARCH ARTICLE

GENOMICS

Noninvasive Whole-Genome Sequencing of a Human Fetus

Jacob O. Kitzman,[1]* Matthew W. Snyder,[1] Mario Ventura,[1,2] Alexandra P. Lewis,[1] Ruolan Qiu,[1] LaVone E. Simmons,[3] Hilary S. Gammill,[3,4] Craig E. Rubens,[5,6] Donna A. Santillan,[7] Jeffrey C. Murray,[8] Holly K. Tabor,[5,9] Michael J. Bamshad,[1,5] Evan E. Eichler,[1,10] Jay Shendure[1]*

Analysis of cell-free fetal DNA in maternal plasma holds promise for the development of noninvasive prenatal genetic diagnostics. Previous studies have been restricted to detection of fetal trisomies, to specific paternally inherited mutations, or to genotyping common polymorphisms using material obtained invasively, for example, through chorionic villus sampling. Here, we combine genome sequencing of two parents, genome-wide maternal haplotyping, and deep sequencing of maternal plasma DNA to noninvasively determine the genome sequence of a human fetus at 18.5 weeks of gestation. Inheritance was predicted at 2.8×10^6 parental heterozygous sites with 98.1% accuracy. Furthermore, 39 of 44 de novo point mutations in the fetal genome were detected, albeit with limited specificity. Subsampling these data and analyzing a second family trio by the same approach indicate that parental haplotype blocks of ~300 kilo–base pairs combined with shallow sequencing of maternal plasma DNA is sufficient to substantially determine the inherited complement of a fetal genome. However, ultradeep sequencing of maternal plasma DNA is necessary for the practical detection of fetal de novo mutations genome-wide. Although technical and analytical challenges remain, we anticipate that noninvasive analysis of inherited variation and de novo mutations in fetal genomes will facilitate prenatal diagnosis of both recessive and dominant Mendelian disorders.

***N Engl J Med* 2012**
***Sci Transl Med* 2012**

MEDICINE

Whole-Genome Sequencing: The New Standard of Care?

Whole-genome sequencing may dramatically alter medicine, but there are obstacles to broad implementation.

Liam R. Brunham[1] and Michael R. Hayden[2]*

Science 1 June 2012: 336 (6085), 1112-1113.

Science June 2012

Having the Genetic Code is not enough

- >99% of the DNA sequence identical
  - Several million genetic "variants" per person
  - Some variants (aka mutations) increase susceptibility to a specific disease
  - Some variants provide protection
  - Most variants remain beyond our understanding
- Large scale genomic studies have failed to identify all variants for common disease
  - 30+ variants (Type 2 diabetes; RR 1.2-1.4) explain 10% of disease heritability
  - Heart disease, schizophrenia, HTN

The current state of genomic risk assessment for CHD

Janssens and van Duijn: An epidemiological perspective on the future of direct-to-consumer personal genome testing. Investigative Genetics 2010, 1:10.

The current state of genomic risk assessment for CHD

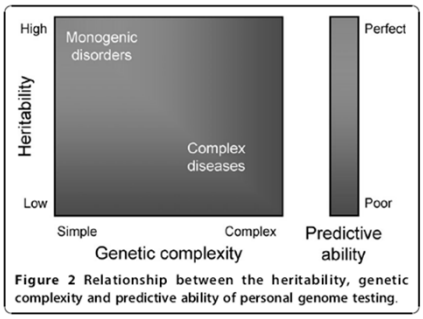


Figure 2 Relationship between the heritability, genetic complexity and predictive ability of personal genome testing.

Janssens and van Duijn: An epidemiological perspective on the future of direct-to-consumer personal genome testing. Investigative Genetics 2010, 1:10.

EGAPP Recommendations: Genomics profiling to assess CV risk

- Found insufficient evidence to recommend testing for the 9p21 genetic variant or 57 other variants in 29 genes to assess risk for cardiovascular disease (CVD) in the general population, specifically for heart disease and stroke
- Found that the magnitude of net health benefit from use of any of these tests alone or in combination is negligible
- Discourages clinical use unless further evidence supports improved clinical outcomes

Genetics in Medicine 2010

The New World of Genomics

Kevin Sweet, MS, LGC
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The Ohio State University Wexner Medical Center

Genomic Medicine – Early Triumphs

- **Diagnosis:** for some types of heart disease, detection of a gene mutation can lead to diagnosis and treatment to prevent sudden cardiac death before any symptoms occur
- **Guiding treatment:** instead of classifying cancers by the tissue where first detected, now beginning to categorize by genomic characteristics
  - select individualized treatments based on different *somatic* tumor signatures
- **Early detection/prevention:** individuals with *germline BRCA* mutations at higher risk of developing breast (and other) cancers

Early Triumphs - Diagnosis

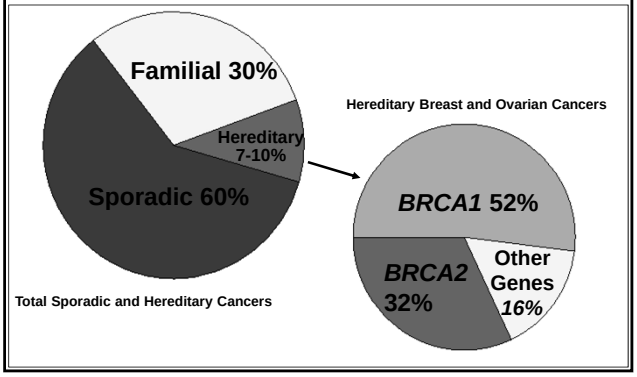
- **>6,000 inherited (Mendelian) diseases**
- **Collectively afflict more than 25 million Americans**
- **Large scale sequencing, ever decreasing cost, increasing data accumulation**
  - **As of Feb 2015, 2,937 genes underlying 4,163 Mendelian phenotypes discovered**

Early Triumphs - Guiding Treatment

- **Match advanced tumor alterations with specific targeted therapies, clinical trials**
  - **FoundationOne®: 315 somatic tumor pathway genes plus 28 common gene rearrangements**
  - **Doesn't predict response to chemotherapy or recurrence (e.g. Oncotype)**
- **OSU CCC prospective single-arm trial***
  - **37 breast tumors**
    - **192 tumor alterations, median of five *per* patient**
    - **97% matched with at least one FDA-approved treatment or clinical trial**
    - **65% of patients (n=24) with an FDA-approved breast cancer therapy**

2014 San Antonio Breast Cancer Symposium

Early Triumphs – Detection and Prevention



Highly Penetrant Gene Variants

- Hereditary breast and ovarian cancer (HBOC)
- Caused by *BRCA1* or *BRCA2 germline* mutation
  - Repairs double stranded DNA breaks
- Incidence
  - 1 in 500 women, in the general population
  - 2% of all individuals of Ashkenazi Jewish ancestry
  - 25% of all Ashkenazi Jewish women with ovarian cancer

Features That Indicate Increased Likelihood of *BRCA* Mutation

- Multiple cases of early onset breast cancer
- Ovarian cancer (with family history of breast or ovarian cancer)
- Breast and ovarian cancer in the same woman
- Bilateral breast cancer
- Ashkenazi Jewish heritage
- Male breast cancer along with female breast cancer in a family

HBOC-associated cancer risks

- Increased lifetime risk of multiple tumor types
  - Breast cancer (females):50-85%
  - Contralateral breast cancer risk (female) depends on age of 1st diagnosis
  - Breast cancer (males): 6-16%
  - Ovarian cancer: 20-40%
  - Other tumors: pancreatic, melanoma, prostate

Pathological Features of HBOC Cancers

- **Breast cancer**
  - ***BRCA1*: ~80% are ER/PR/Her2/neu (triple) receptor negative**
  - ***BRCA2*: more likely to be ER/PR (+)**
  - **Prognosis appears to be the same as for sporadic breast cancer**
- **Ovarian cancer**
  - **Predominantly papillary serous**
  - **Can be mucinous but not as often**
  - **Not typically associated with tumors of low malignant potential or borderline tumors**
  - **Prognosis may be better than for sporadic ovarian cancer**

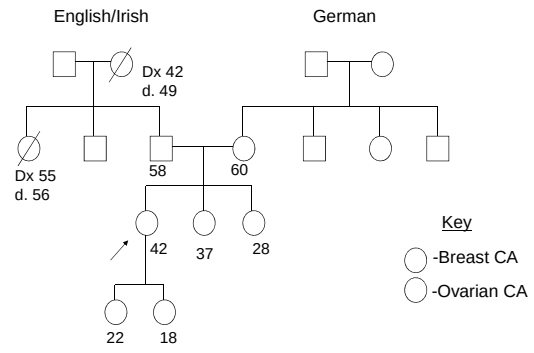
Sometimes used in treatment decisions: genomic based PARP inhibitors

- **PARPs work at molecular level to repair single strand DNA breaks**
- **Inhibition of PARP leads to the accumulation of defects, which leads to double-stranded breaks**
  - ***BRCA*-associated tumors lack effective homologous-recombination DNA repair**
  - **Results in selectively-induced cytotoxicity in tumor cells while sparing normal cells in patients with *BRCA*-associated tumors**
- **Dec 2014: FDA approved Lynparza (olaparib) for women with advanced ovarian cancer associated with defective *BRCA* genes**

Applications of genomic tumor analysis

- **Ruth: 42 year old female recently diagnosed with metastatic breast cancer**
- **Age at diagnosis alone = NCCN referral!**
- **Some of the alterations in Ruth's breast tumor:**
  - **ERBB2 amplification**
    - **Trastuzumab is effective in a subset of ERBB2 amplified breast cancers**
  - ***BRCA2* 617delAT (present in >80% of tumor cells)**
    - **May also identify true germline (hereditary) mutations**

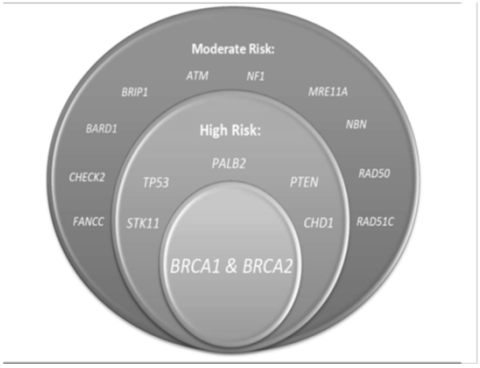
Ruth's pedigree



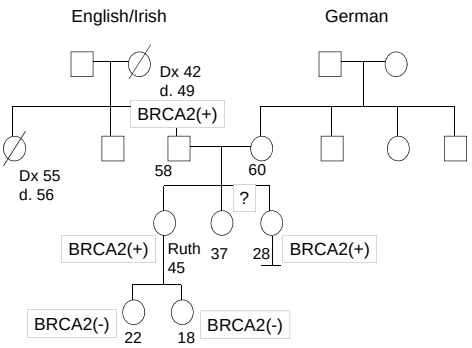
Misconceptions Regarding Family History

- **Cancer on the father's side doesn't count**
  - **Half of all women with HBOC inherited it from their father**
- **Ovarian cancer not a factor in breast cancer risk**
  - **Ovarian cancer is an important indicator of hereditary risk, although it is not always present**
- **The most important thing in the family history is the number of women with breast cancer**
  - **Age of onset of breast cancer is more important than the number of women with the disease**

Clinical Testing – Cancer Panels



Post-test



Impact of results: medical management

Ruth tests positive for germline *BRCA2* 617delAT

- **Recommend oophorectomy(w/ fallopian tubes)**
- **Eligible for specific clinical trials e.g. PARP Inhibitors**

Ruth's daughters (both *BRCA2* mutation negative)

- **General population risk, follow ACS guidelines**
- **Cannot pass familial *BRCA2* mutation to children**

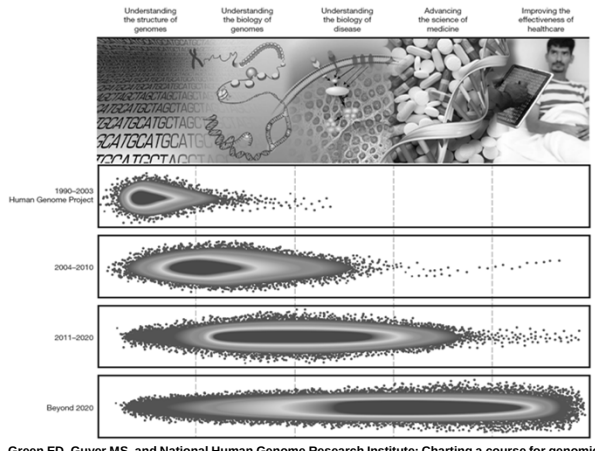
- **Ruth's sister (*BRCA2* mutation positive)**
  - **Consider increased breast cancer screening +/- chemoprevention OR mastectomy and ovarian cancer screening OR oophorectomy (after child-bearing,<40)**

Impact of results: medical management

- **Ruth's other sister (mutation status unknown)**
  - **Recommend screening as if mutation positive, until proven otherwise through testing**
  - **Same for other *at-risk* females in family**
- **Ruth's father (obligate carrier)**
  - **Annual clinical exam; increased awareness**
  - **Annual prostate cancer screening**
  - **Follow ACS guidelines**

All Disease is Complex Disease

- **Predisposed to certain diseases because of our genes**
- **Not only genes that determine our health**
- **Microbiome: ecosystem of microorganisms that live on and in the human body**
  - **Degree influenced by environmental factors**
  - **Some degree of genetic influence of the host**
- **Lifestyle, habits, environment may cause some genes to be switched on and off, or even altered**
  - **<u>Epigenetics</u>: stable and heritable changes in gene *expression* NOT caused by changes in the DNA code**



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