



PRECISION MEDICINE

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DISCLOSURE - ΔΗΜΟΣΙΟΠΟΙΗΣΗ

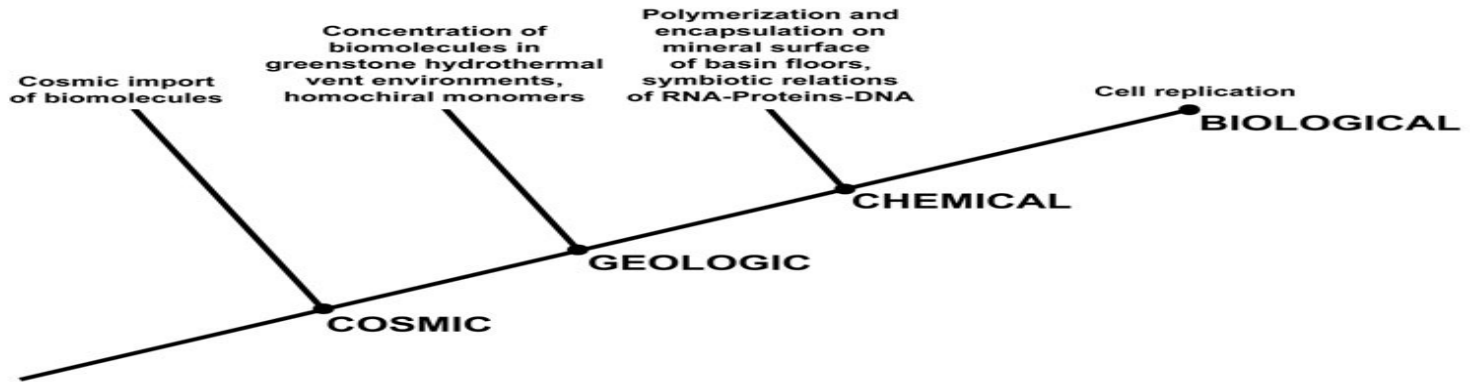
Είμαι μέλος της Εθνικής Επιτροπής «Βιοηθικής & Δεοντολογίας» για τις Κλινικές Μελέτες στην Ελλάδα, Υπουργείου Υγείας.

Δεν παίρνω αμοιβή για τις ομιλίες μου και δεν είμαι επ' αμοιβή σύμβουλος σε καμία Φαρμακευτική Εταιρεία στην Ελλάδα ή στο εξωτερικό.

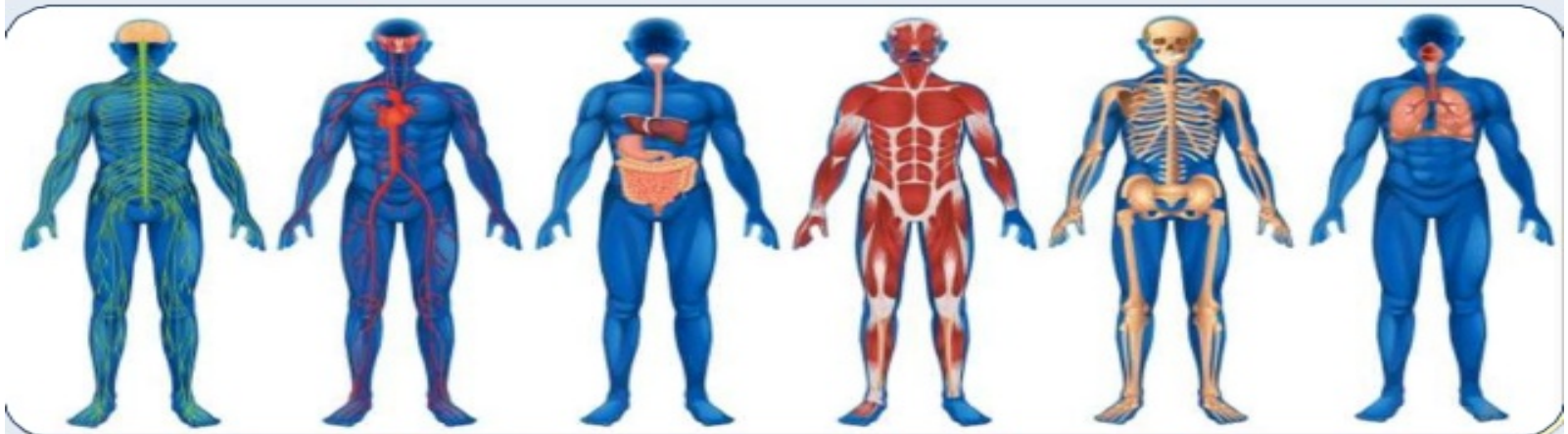
Το Εργαστήριο Πειραματικής Φυσιολογίας, το οποίο διευθύνω από το 2004, έχει τα τελευταία χρόνια χρηματοδοτηθεί με "Institutional Support" από σειρά Φαρμακευτικών Εταιρειών στα πλαίσια Ερευνητικών Προγραμμάτων και του ΜΠΣ «Μοριακή & Εφαρμοσμένη Φυσιολογία» μέσω του ΕΛΚΕ (2007-2017):

GLAXO
AMGEN
IPSEN
MENARINI
NOVARTIS
SERONO
ELI LILLY
PFIZER
ABBOTT
GENESIS
BOEHRINGER
KLOX
ELPEN

Evolution of human life on earth

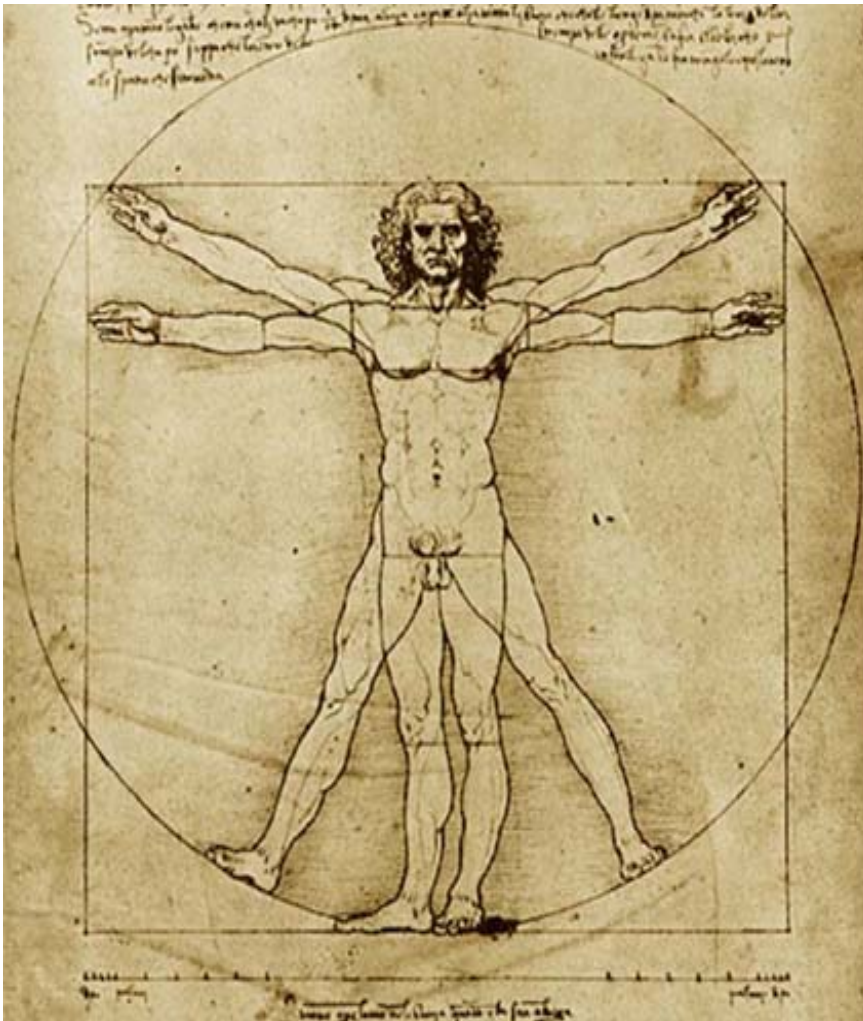


Physiology is the study of all the systems of human body & their mutual relationships.



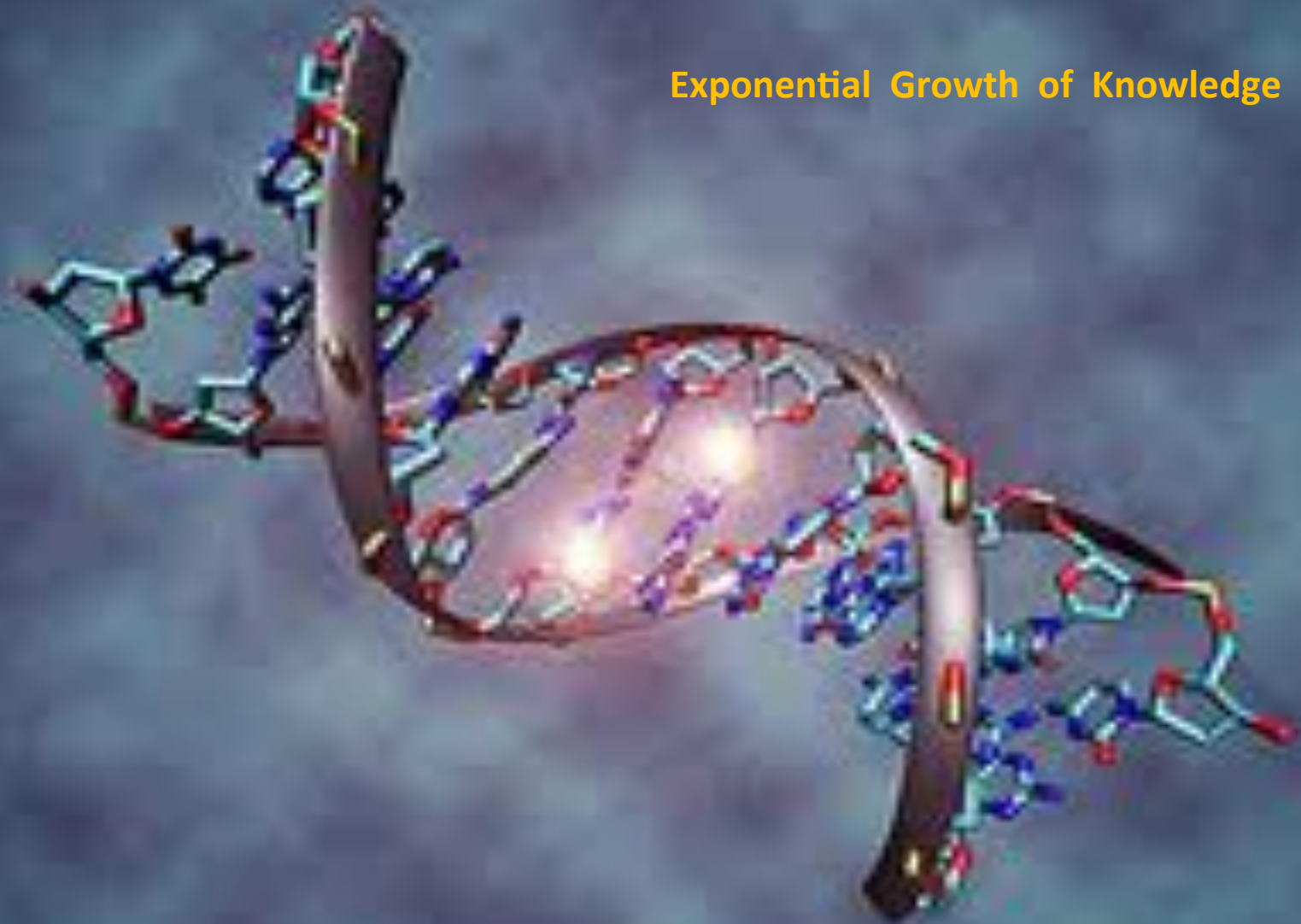
*... one day physiologists, philosophers and poets shall talk the same language ...
... "an organ is made up of its function"...*

Claude Bernard

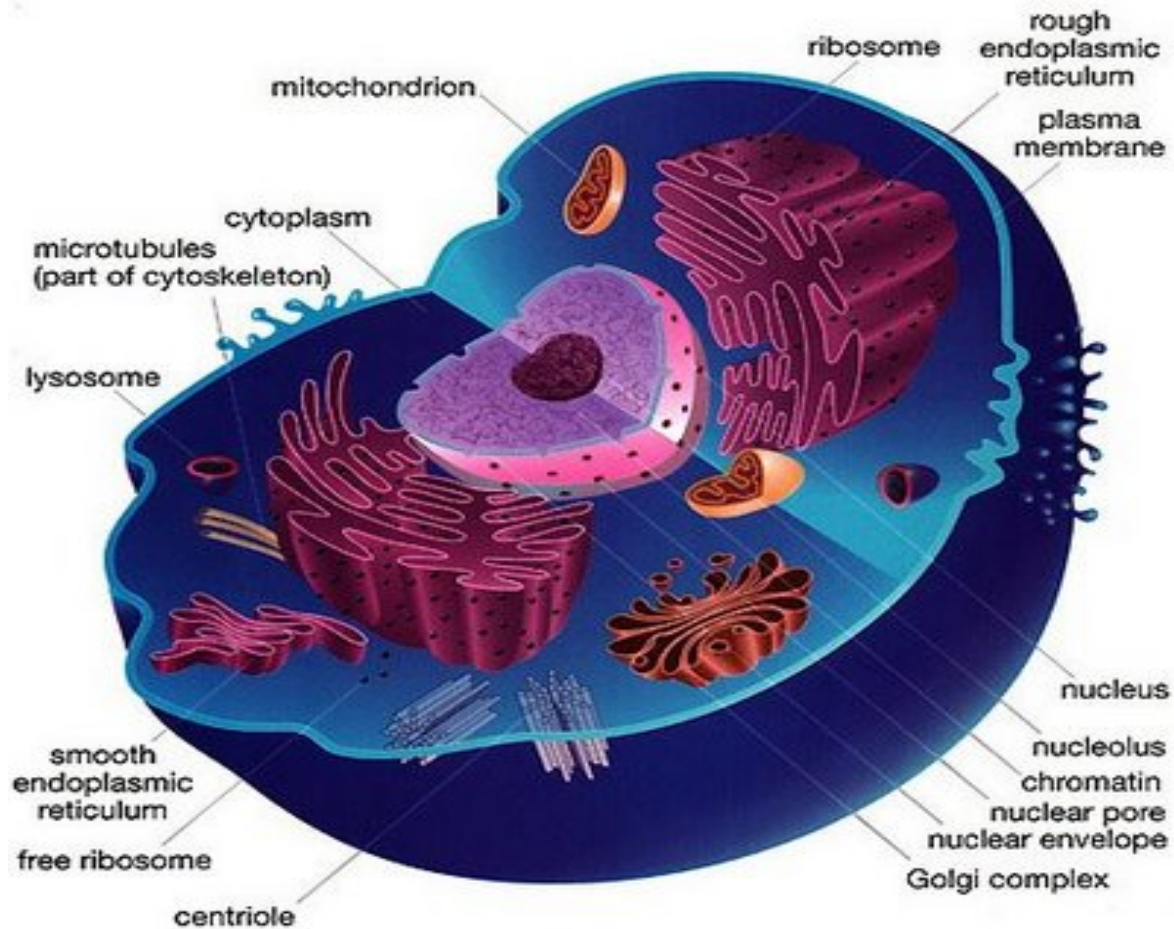




Exponential Growth of Knowledge



Cellular Physiology





DNA REPAIR



DIFFERENTIATION

PROGRAMMED CELL DEATH

TYPE I

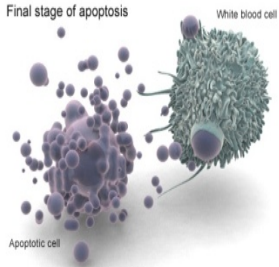
TYPE II

TYPE III

APOPTOSIS

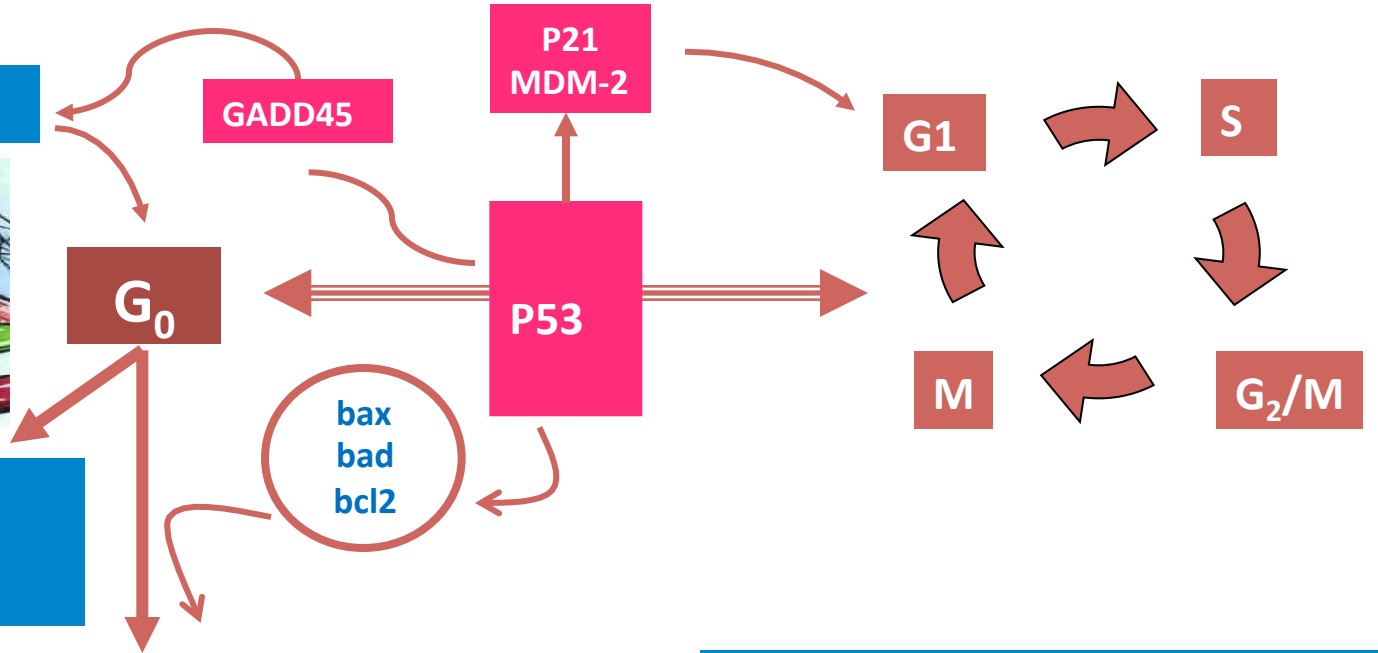
AUTOPHAGY

NON LYSOSOMAL



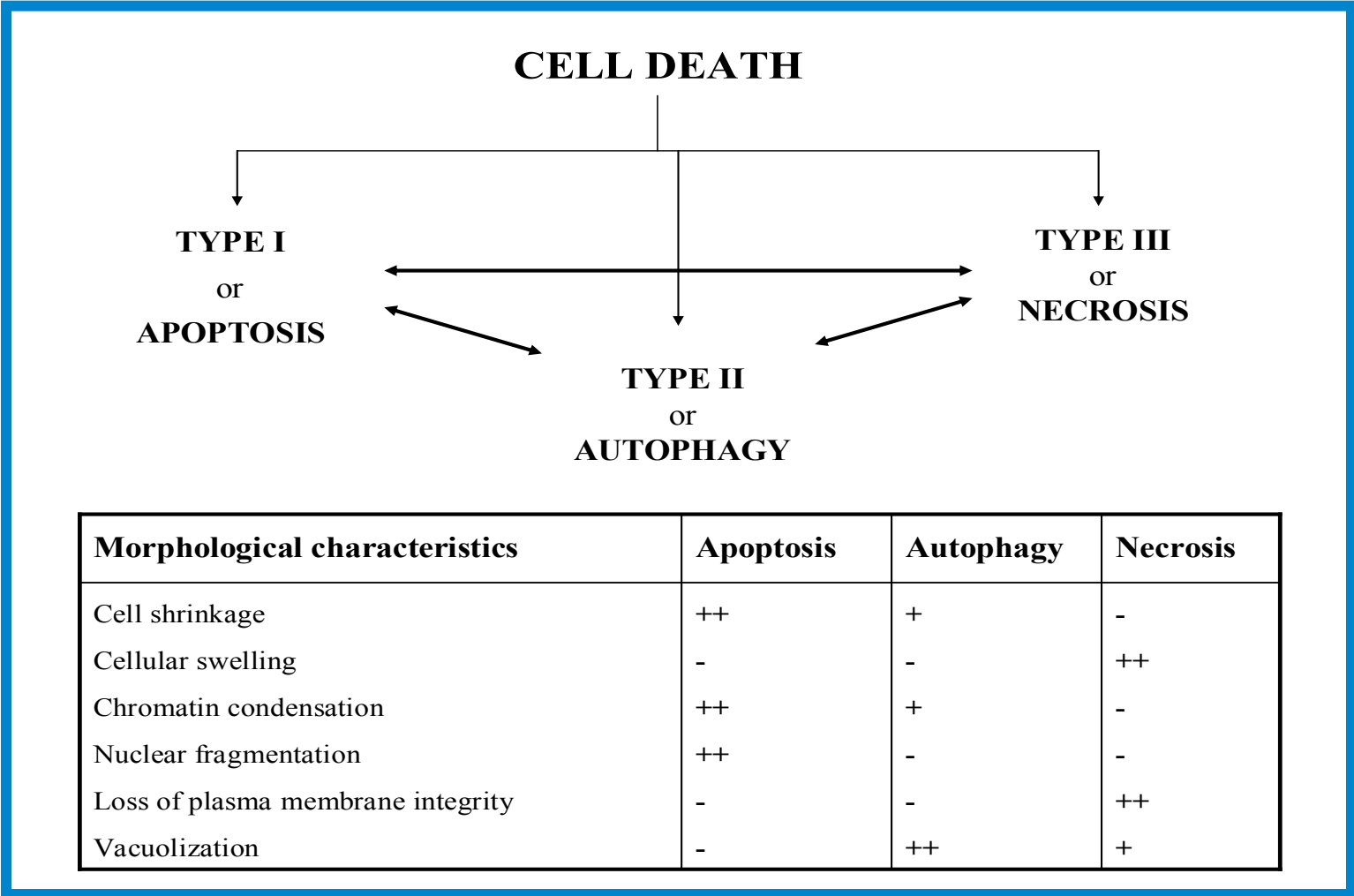
Yoshinori Ohsumi
Nobel Prize 2016
Physiology & Medicine

It is not
Type I or Type II



CELL CYCLE - MITOSIS

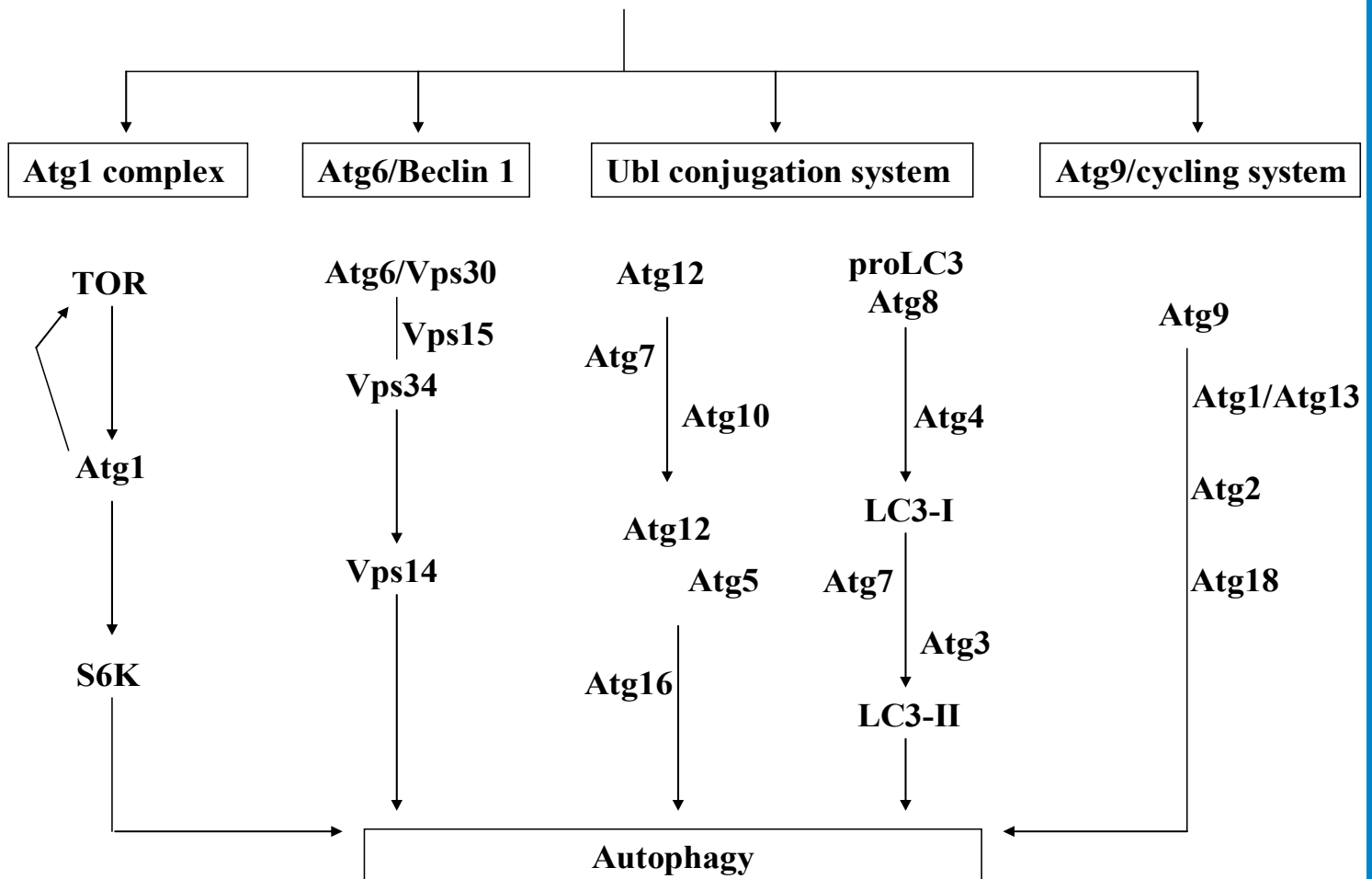


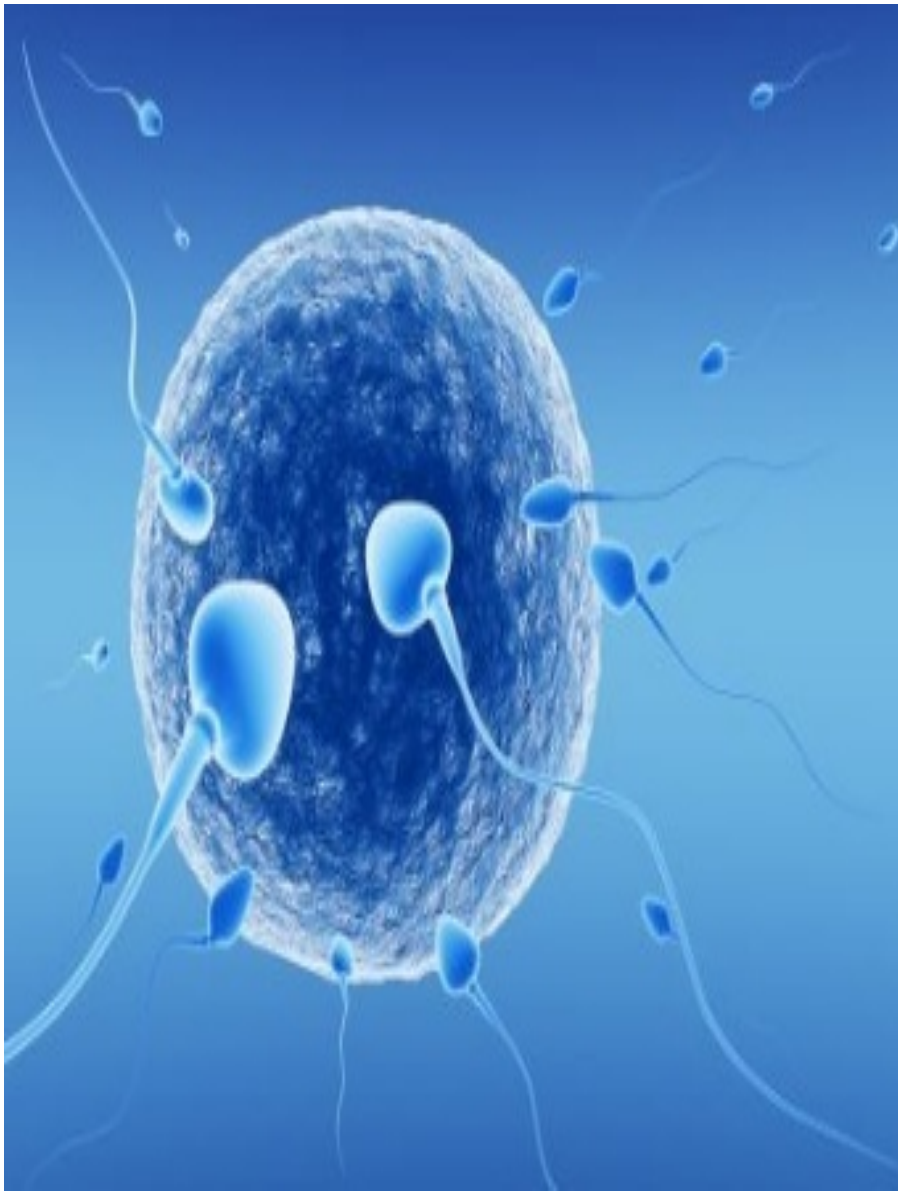


Yoshinori Ohsumi
Nobel Prize 2016
Physiology & Medicine

**Yoshinori Ohsumi, Tokyo Institute of Technology
Nobel Prize 2016
Physiology & Medicine**

Core autophagy machinery





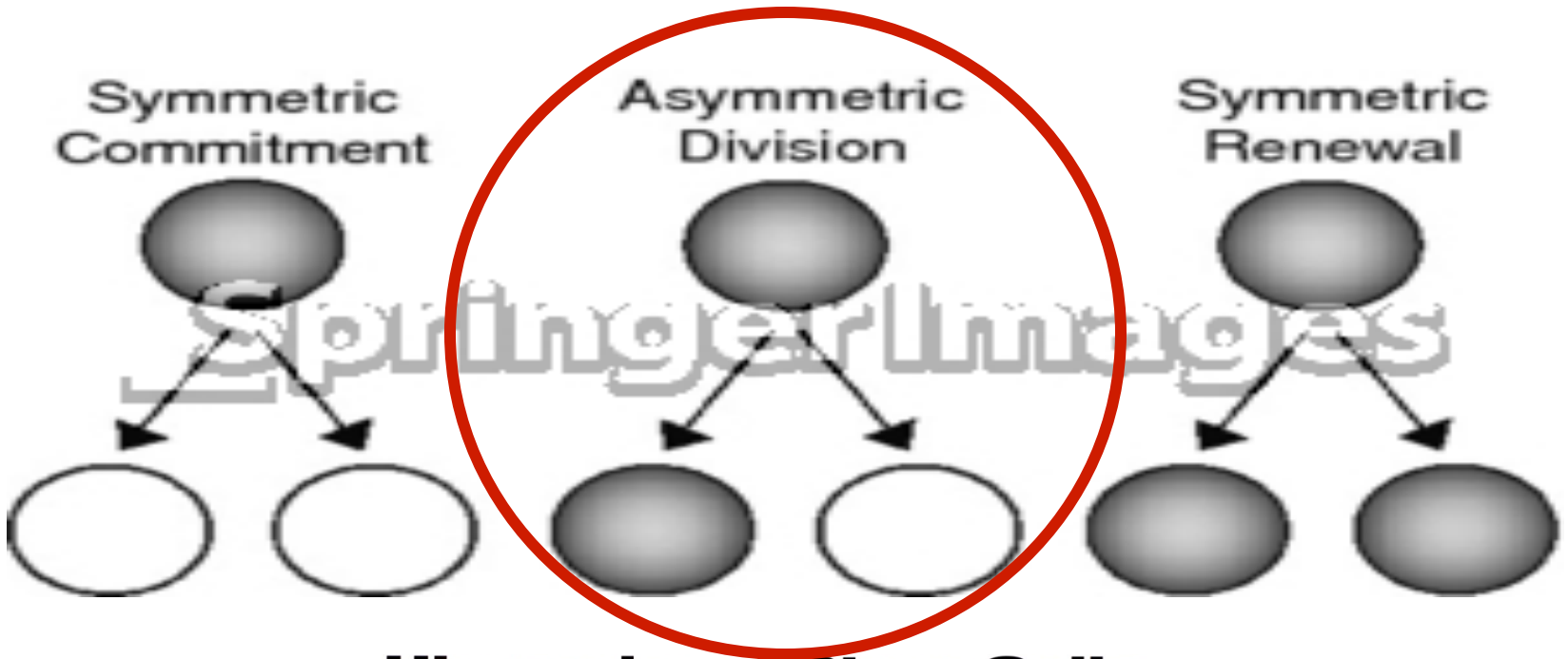
Anatomical Travelogue Home
Anatomical Travelogue Inc.

Conception to Birth

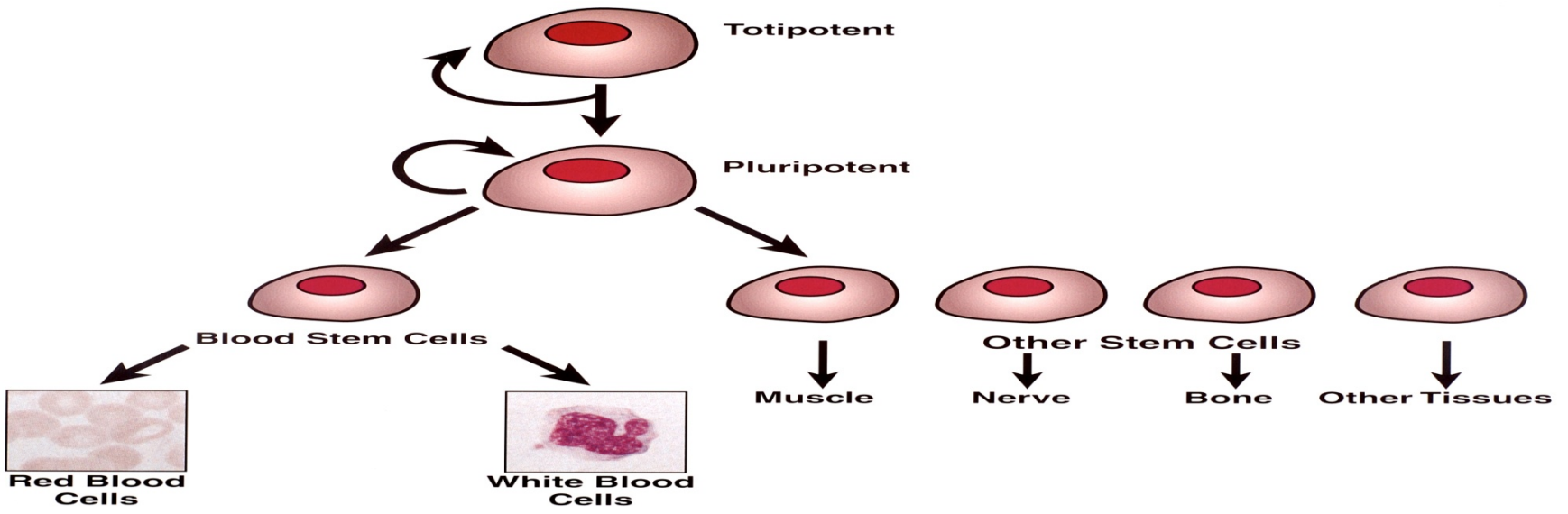
A Life Unfolds

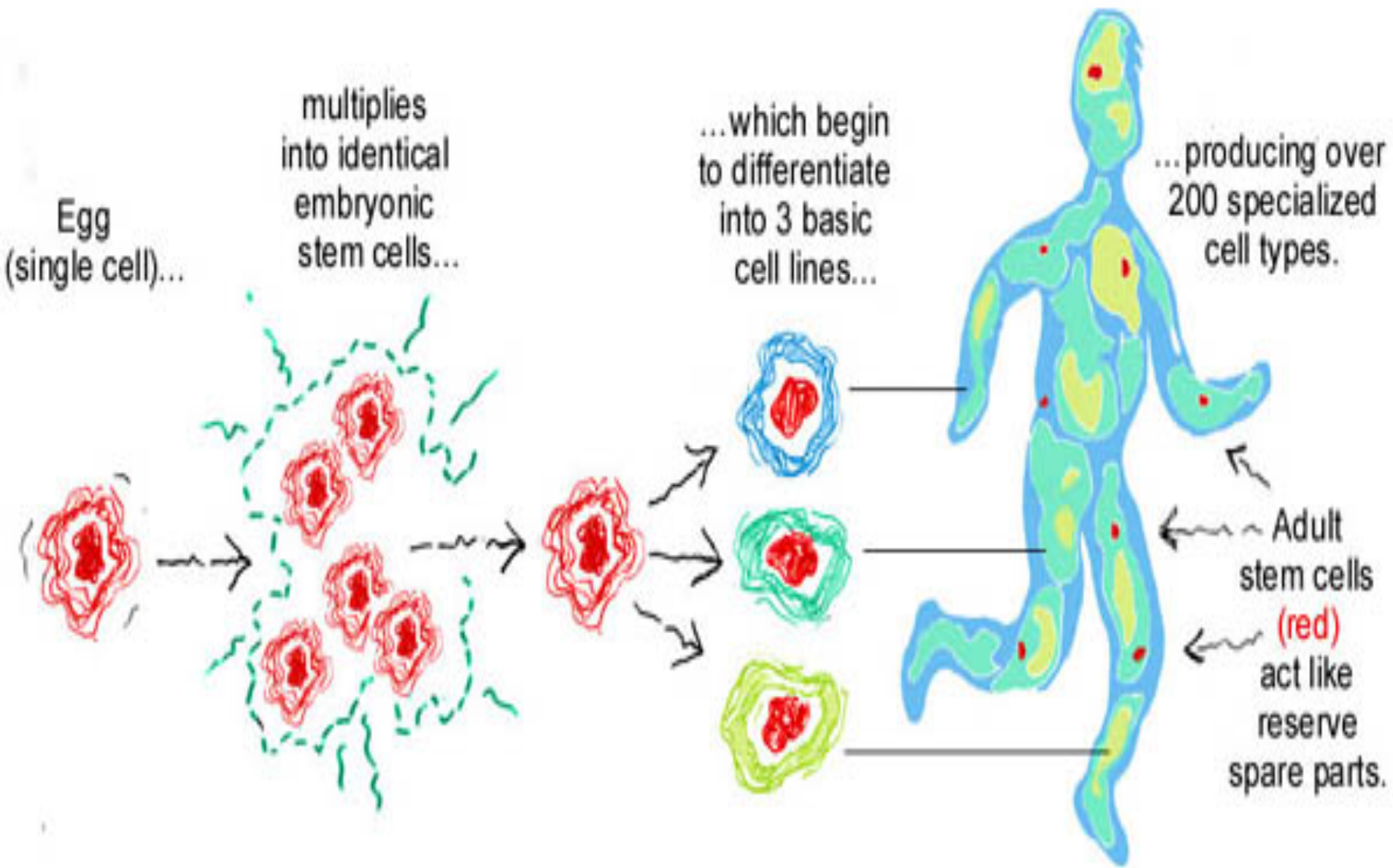
A vertical sequence of images on the right side of the slide, showing the progression of human life: a DNA double helix, a developing fetus, and a newborn baby.

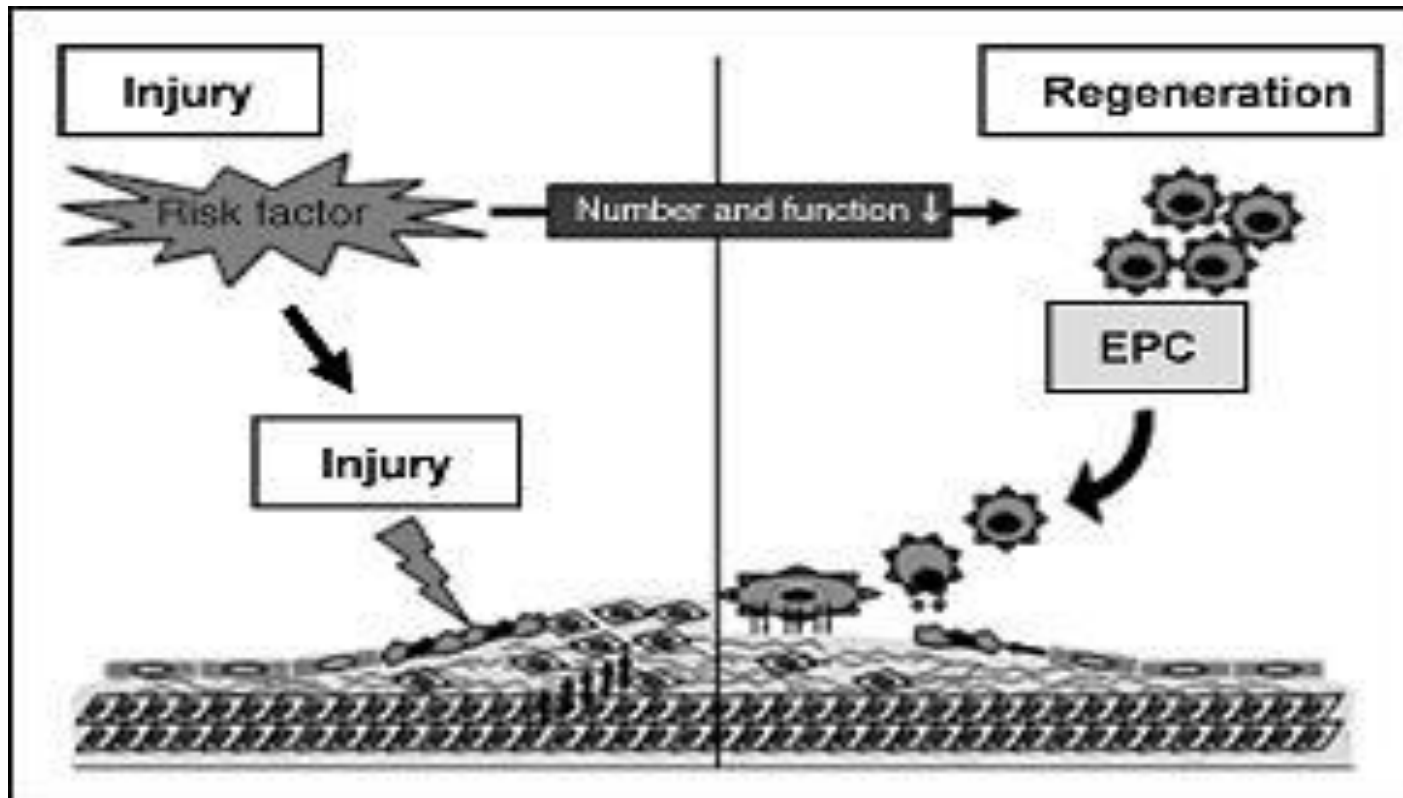
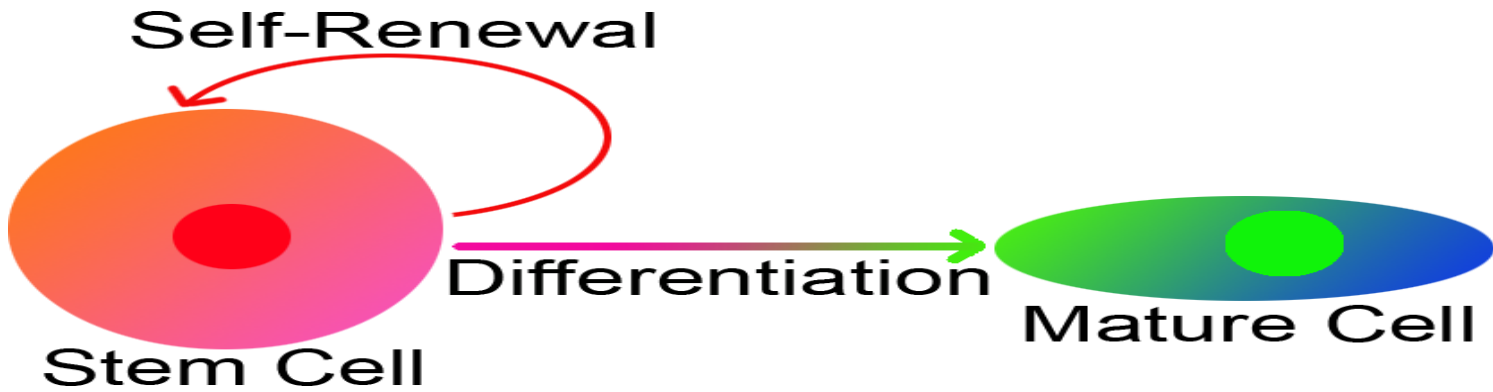
FERTILIZATION and EARLY EMBRYO	3 to 8 WEEKS	THIRD TRIMESTER	BIRTH
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Hierarchy of Stem Cells

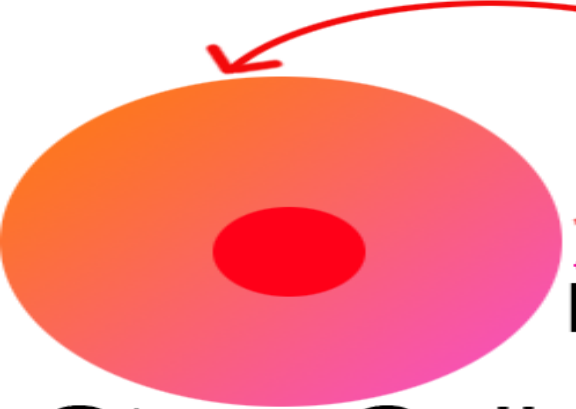






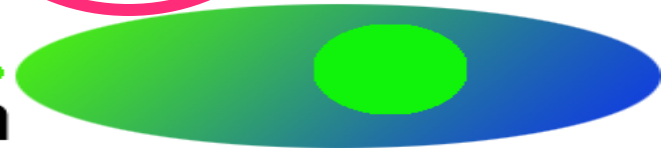


Self-Renewal

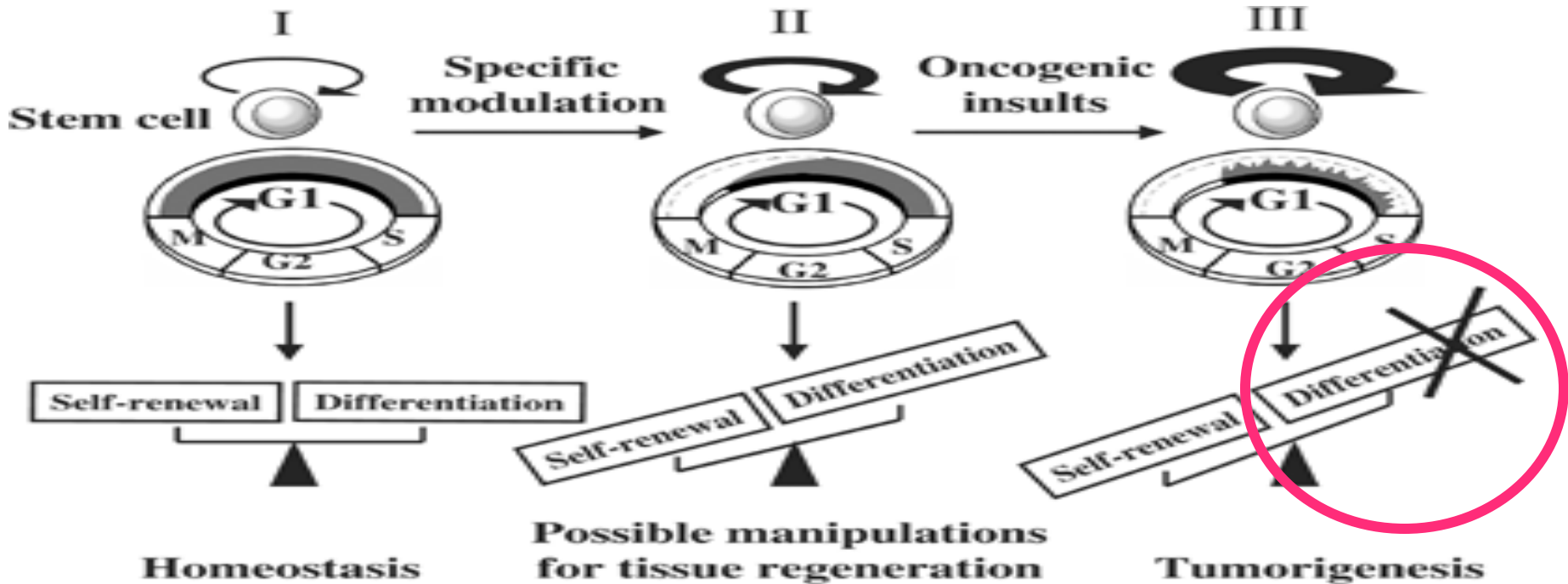
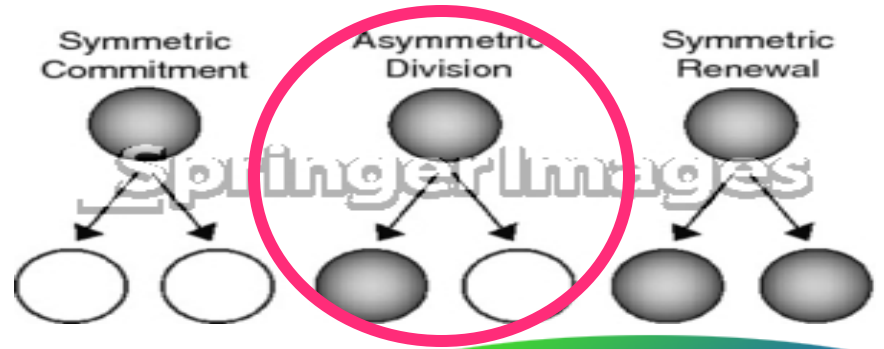


Stem Cell

Differentiation

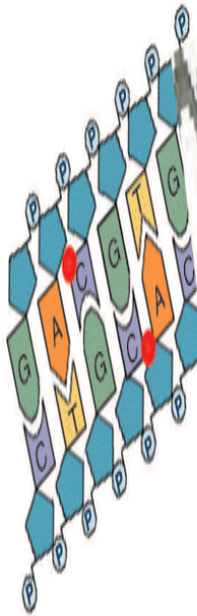


Mature Cell



TRANSCRIPTION REGULATION

1. DNA

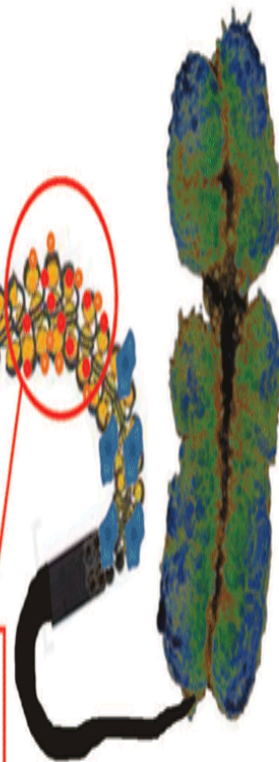


2. DNA

with histone proteins
(yellow)



3. Two meters of DNA per cell
packaged with more proteins
(blue) into chromosomes



Key to epigenetic marks

- Methyl on DNA
- Inactive marks on histones
- Active marks on histones

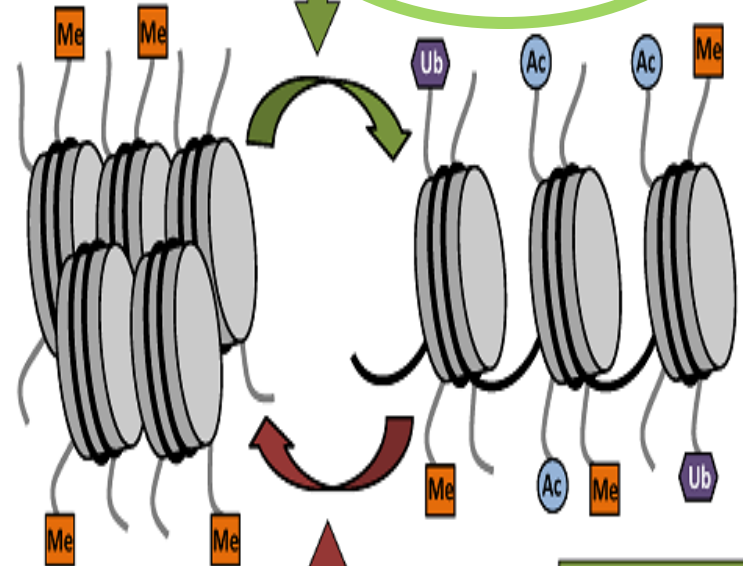
Open and active



Closed and inactive

- Development
- Environment
- Illness

Closed chromatin
DNA inaccessible
Transcription repressed



Mechanisms linked to transcriptional activation

- Acetylation (HATs)
- Lysine methylation (H3K4, H3K6, H3K79)
- Lysine de-methylation (H3K9, H3K27, H4K20)
- Mono-ubiquitination

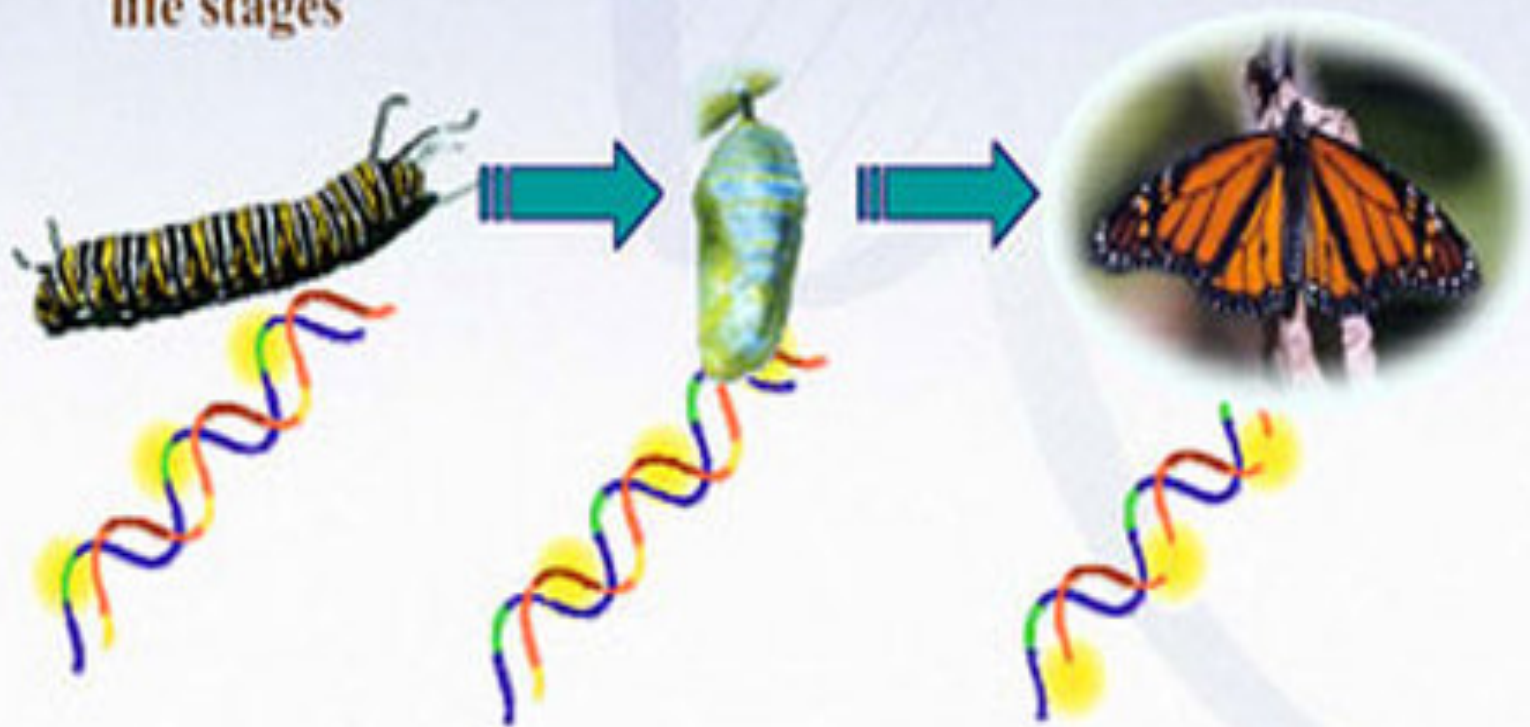
- De-acetylation (HDACs)
- Lysine methylation (H3K9, H3K27, H4K20)
- Lysine de-methylation (H3K4, H3K6, H3K79)
- De-ubiquitination (DUBs)

Mechanisms linked to transcriptional repression

Open chromatin
DNA accessible
Transcription activated

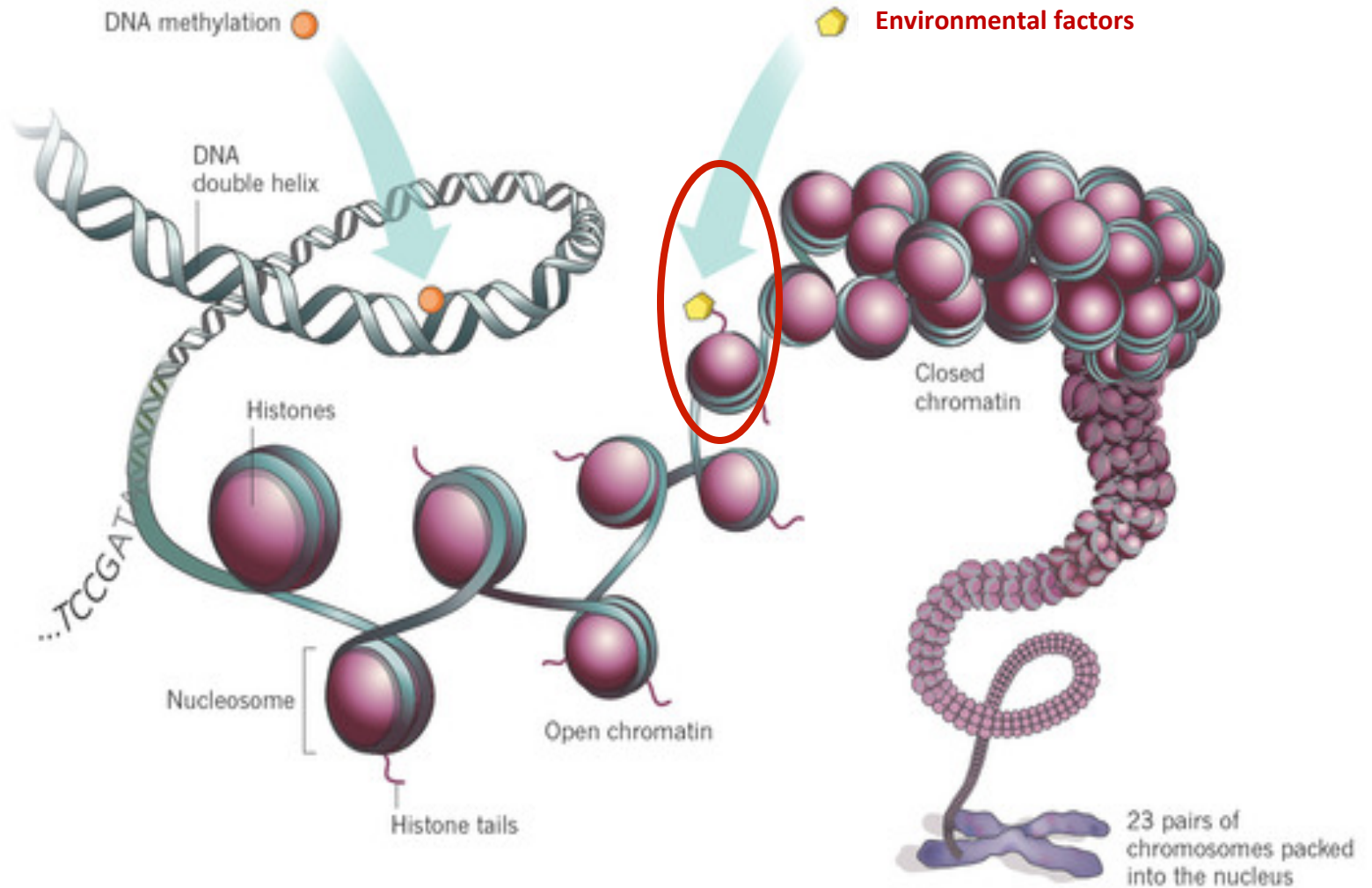
Epigenetics

Epigenetics Regulation: the same set of genes but with expressions (structures) of those genes during different life stages



POLYGAMOUS DNA

DNA works with many partners. DNA methylation, for example, influences the way that genes are expressed without changing the underlying DNA sequence, and other epigenetic factors bind to histones to control when chromatin complexes open up and allow their DNA to be read.





GENOMICS

Our genes can suggest what diseases we *might* be predisposed to, but it's an incomplete picture of human health.

PHENOTYPE

A snapshot of the current state of health that can be used to prevent, diagnose and treat disease or improve health.

LIFESTYLE/ENVIRONMENT

External factors like diet, exercise, medications, microbiota and even where we live influence our metabolic state.

THE PRECISION MEDICINE INITIATIVE®



WHAT IS IT?

Precision medicine is an emerging approach for disease prevention and treatment that takes into account people's individual variations in genes, environment, and lifestyle.

The Precision Medicine Initiative® will generate the scientific evidence needed to **move the concept of precision medicine into clinical practice.**

WHY NOW?

The **time is right** because of:

Sequencing of the human genome



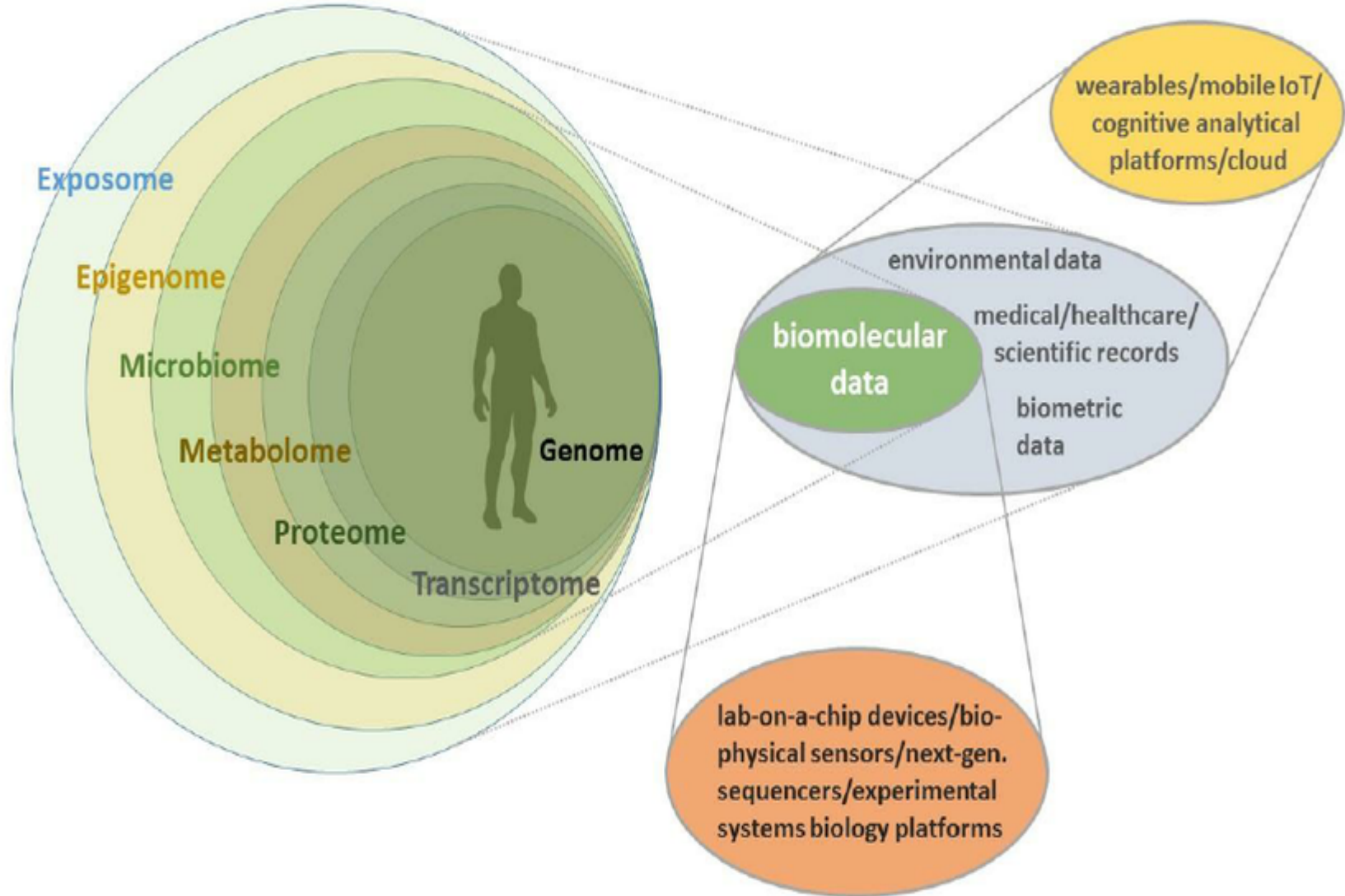
Improved technologies for biomedical analysis



New tools for using large datasets

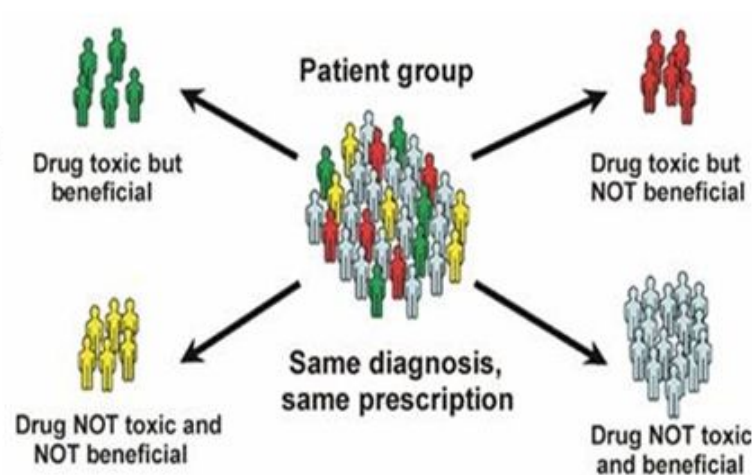


PRECISION MEDICINE

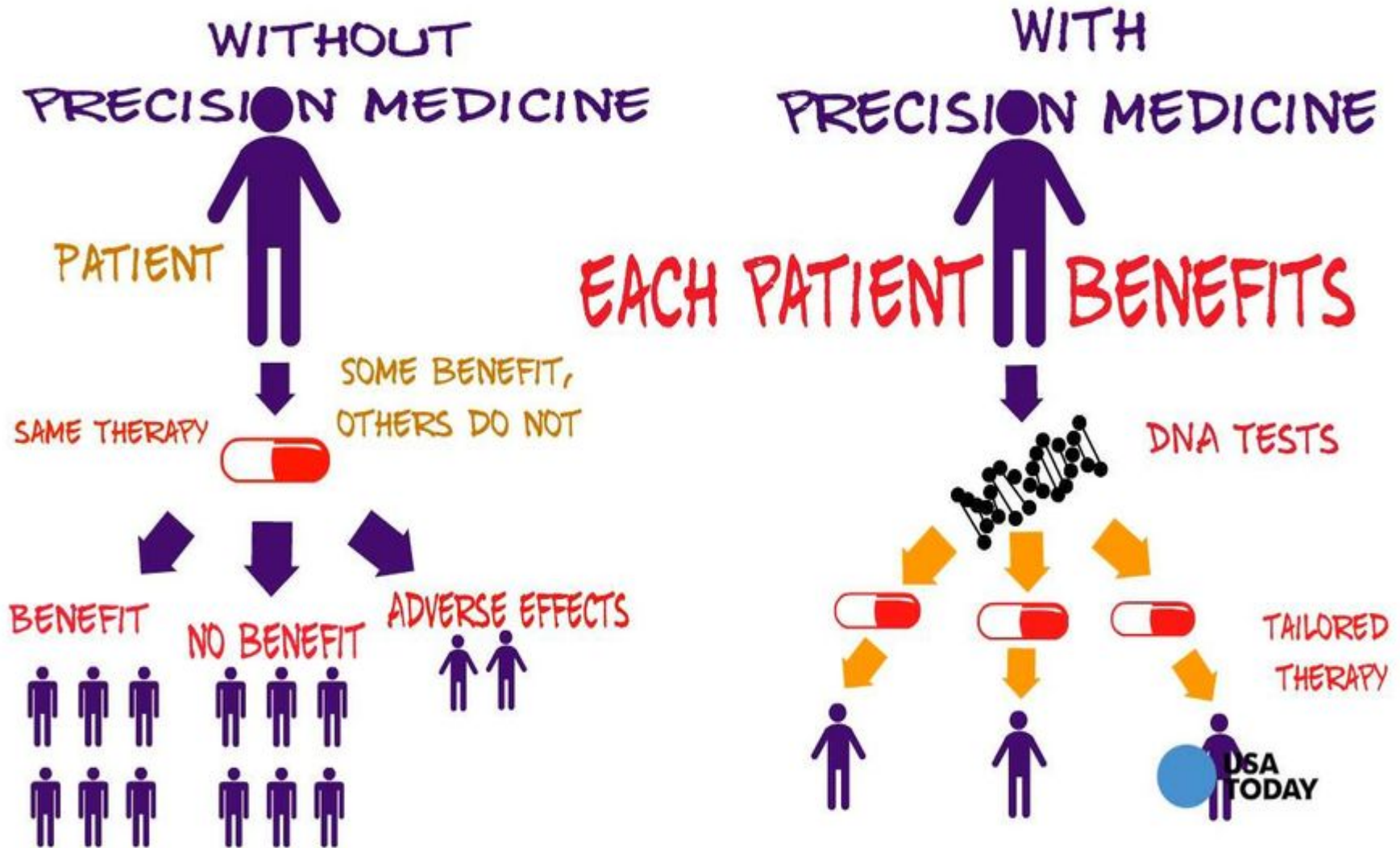


Precision medicine implies *personalization* and all its benefits

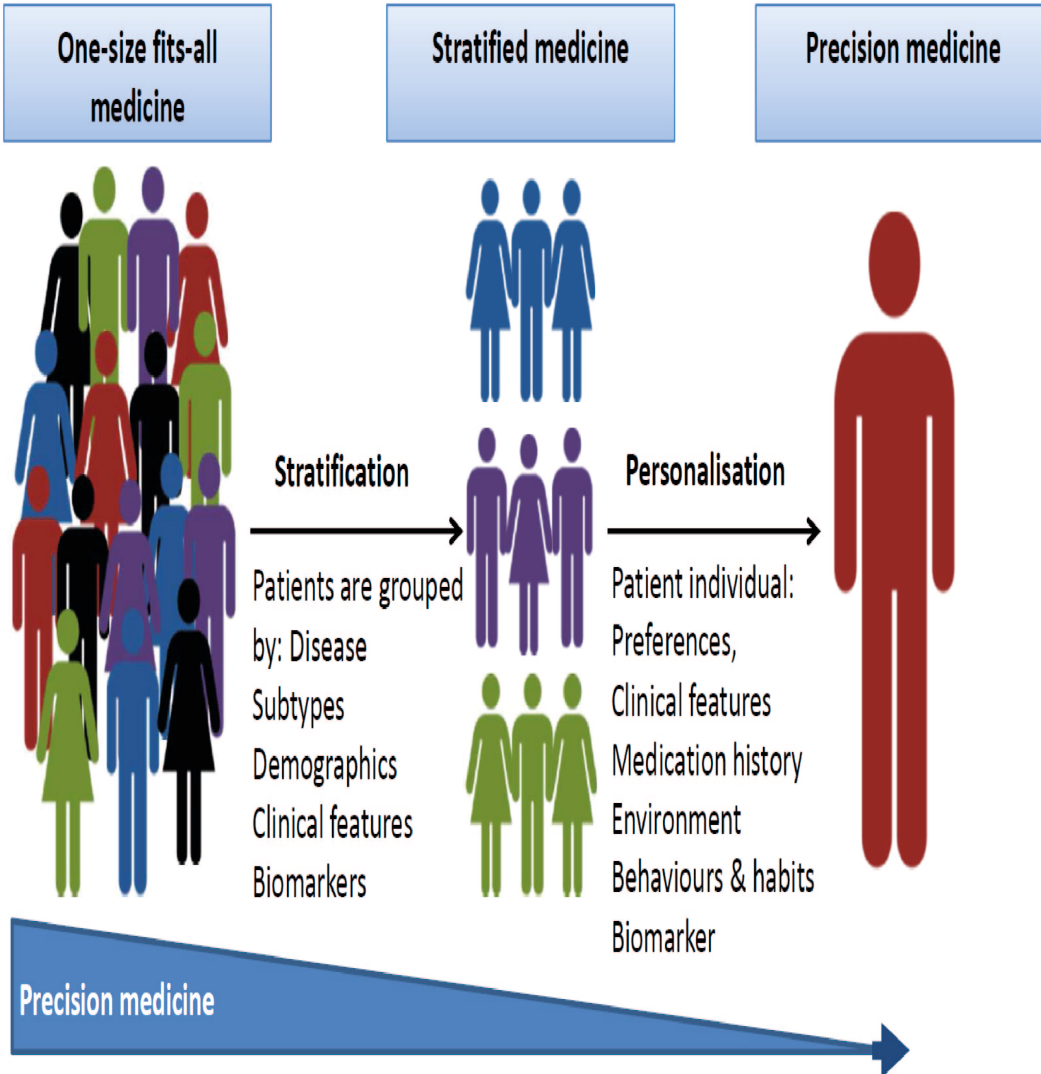
- Diagnosis predicting risk of disease
- Determining whether a treatment is working
- Monitoring healthy people to detect early signs of disease
- Producing safer drugs by predicting potential for adverse effects earlier
- Targeting groups of people most likely to benefit from a drug, while keeping its use from those who may be harmed by it
- Producing better medical products
- Ready access to information
- Decreasing health care costs



PRECISION MEDICINE



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www.cancer.gov

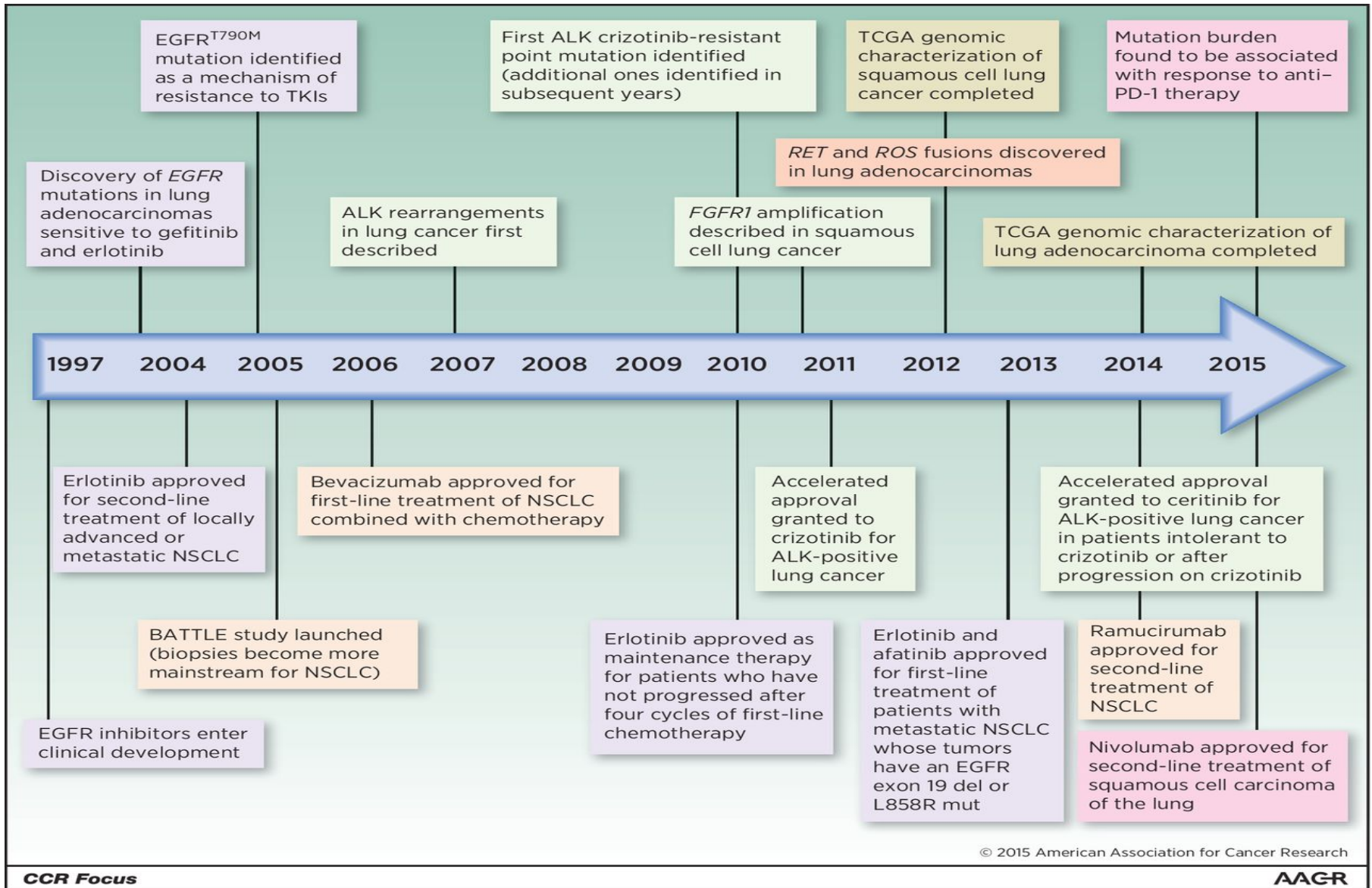


PRECISION MEDICINE

Table 1. Examples of Conditions in Which Precision Medicine Has Been Used.*

Medical Field	Disease	Biomarker	Intervention
Cancer	Chronic myeloid leukemia	BCR-ABL	Imatinib ⁴
	Lung cancer	EML4-ALK	Crizotinib ³
Hematology	Thrombosis	Factor V Leiden	Avoid prothrombotic drugs ⁵
Infectious disease	HIV/AIDS	CD4+ T cells, HIV viral load	Highly active antiretroviral therapy ⁶
Cardiovascular disease	Coronary artery disease	<i>CYP2C19</i>	Clopidogrel ⁷
Pulmonary disease	Cystic fibrosis	<i>G551D</i>	Ivacaftor ⁸
Renal disease	Transplant rejection	Urinary gene signature	Antirejection drugs ⁹
Hepatology	Hepatitis C	Hepatitis C viral load	Direct-acting antiviral agents ¹⁰
Endocrine disease	Multiple endocrine neoplasia type 2	<i>RET</i>	Prophylactic thyroidectomy ¹¹
Metabolic disease	Hyperlipidemia	LDL cholesterol	Statins ¹²
Neurology	Autoimmune encephalitis	CXCL13	Immunotherapy ¹³
Psychiatry	Alcohol-use disorder	<i>GRIK1</i>	Topiramate ¹⁴
Pharmacogenomics	Smoking cessation	<i>CYP2A6</i>	Varenicline ¹⁵
Ophthalmology	Leber's congenital amaurosis	<i>RPE65</i>	Gene therapy ¹⁶

PRECISION MEDICINE





VITAL STATISTICS:

Personalized Medicine



> 25

genes that are “actionable targets” (that means they have been shown to be important in drug response, and there are guidelines for using this information clinically). These include:

GENE	DRUG (Condition)
CYP2D6, CYP2C19	Amitriptyline (tricyclic antidepressant)
CYP2D6	Codeine (pain)
DPYD	Capecitabine (breast and colon cancer)
CYP2C19	Clopidogrel (antiplatelet)
CYP3A5	Tacrolimus (immunosuppressant)
HLA-B	Carbamazepine (seizures)
TPMT	Mercaptopurine (leukemia)
VKORC1, CYP2C9	Warfarin (anticoagulant)
IFNL3	Peginterferon (hepatitis C)
DPYD	Fluorouracil (cancer)
SLCO1B1	Simvastatin (cholesterol)

60%

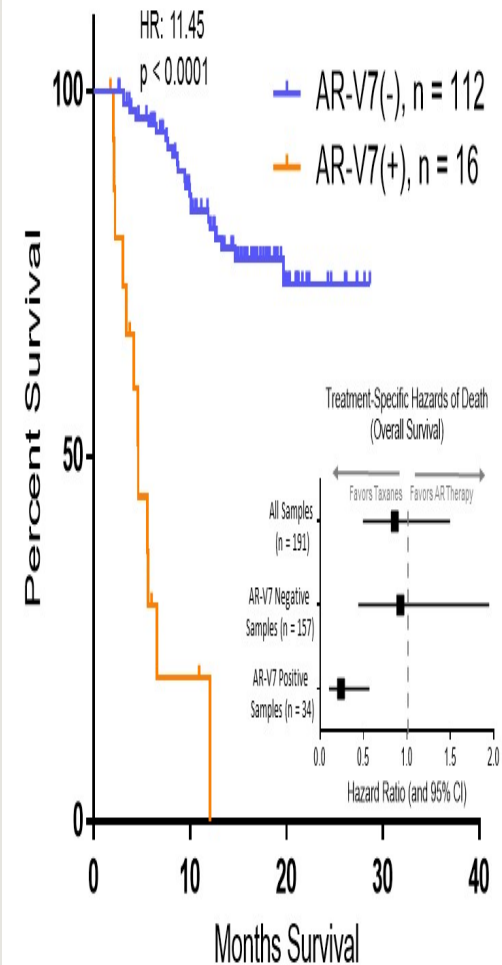
of patients admitted at UAB receive prescriptions for at least one drug that has an actionable gene target

Precision Medicine and the Paradigm Shift

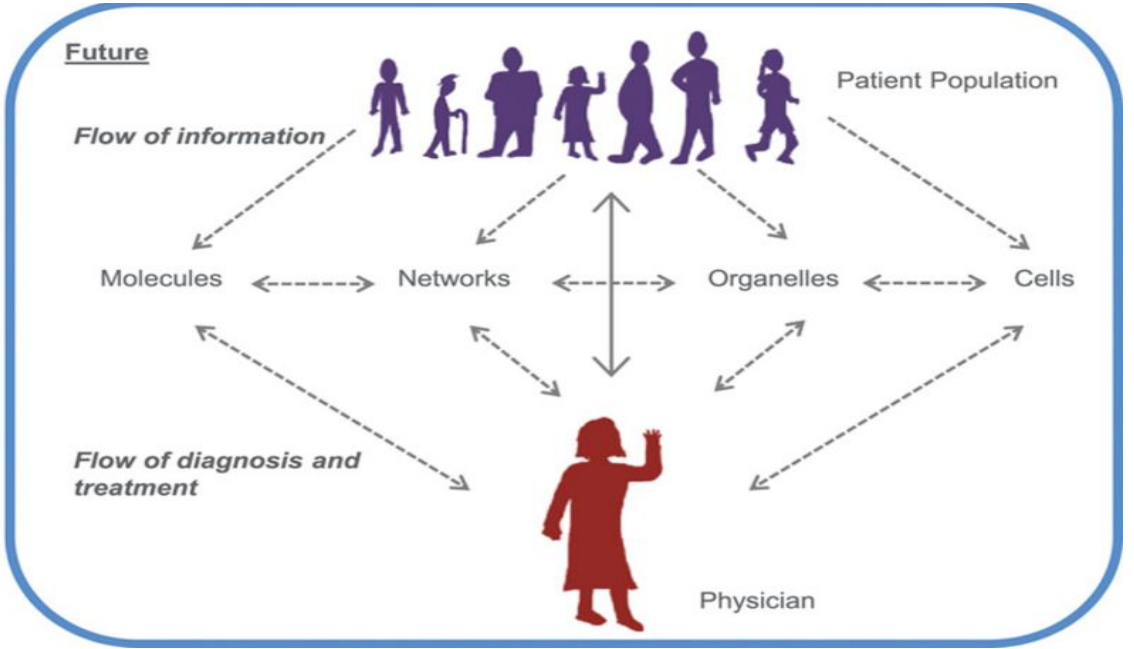
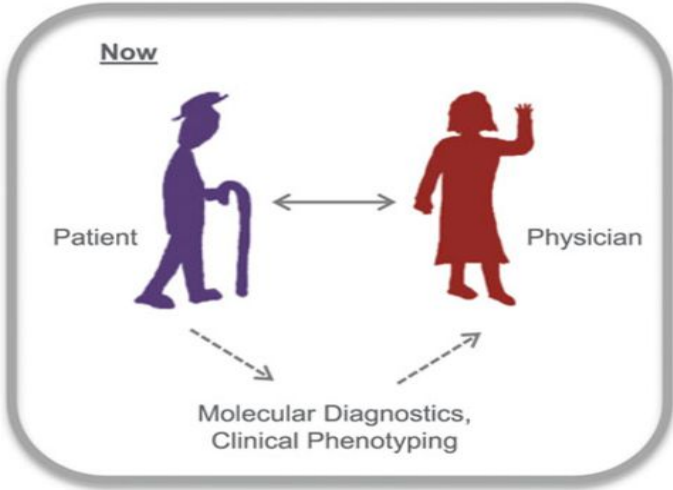
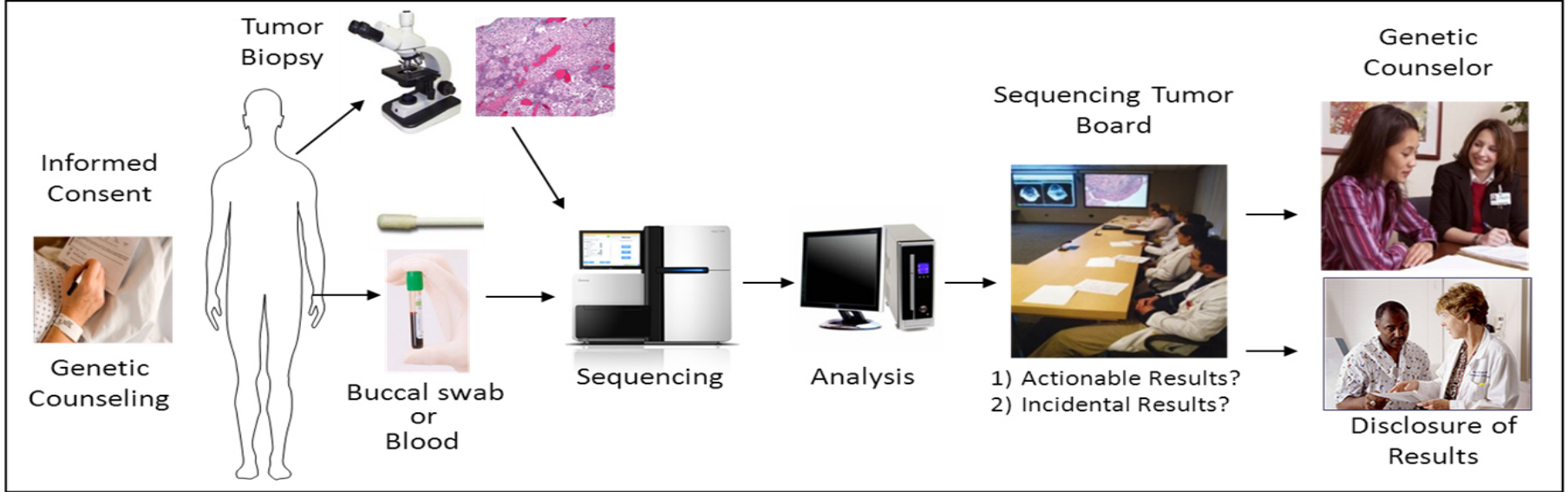


Treatment landscape in prostate cancer. Courtesy of William K. Oh, MD.

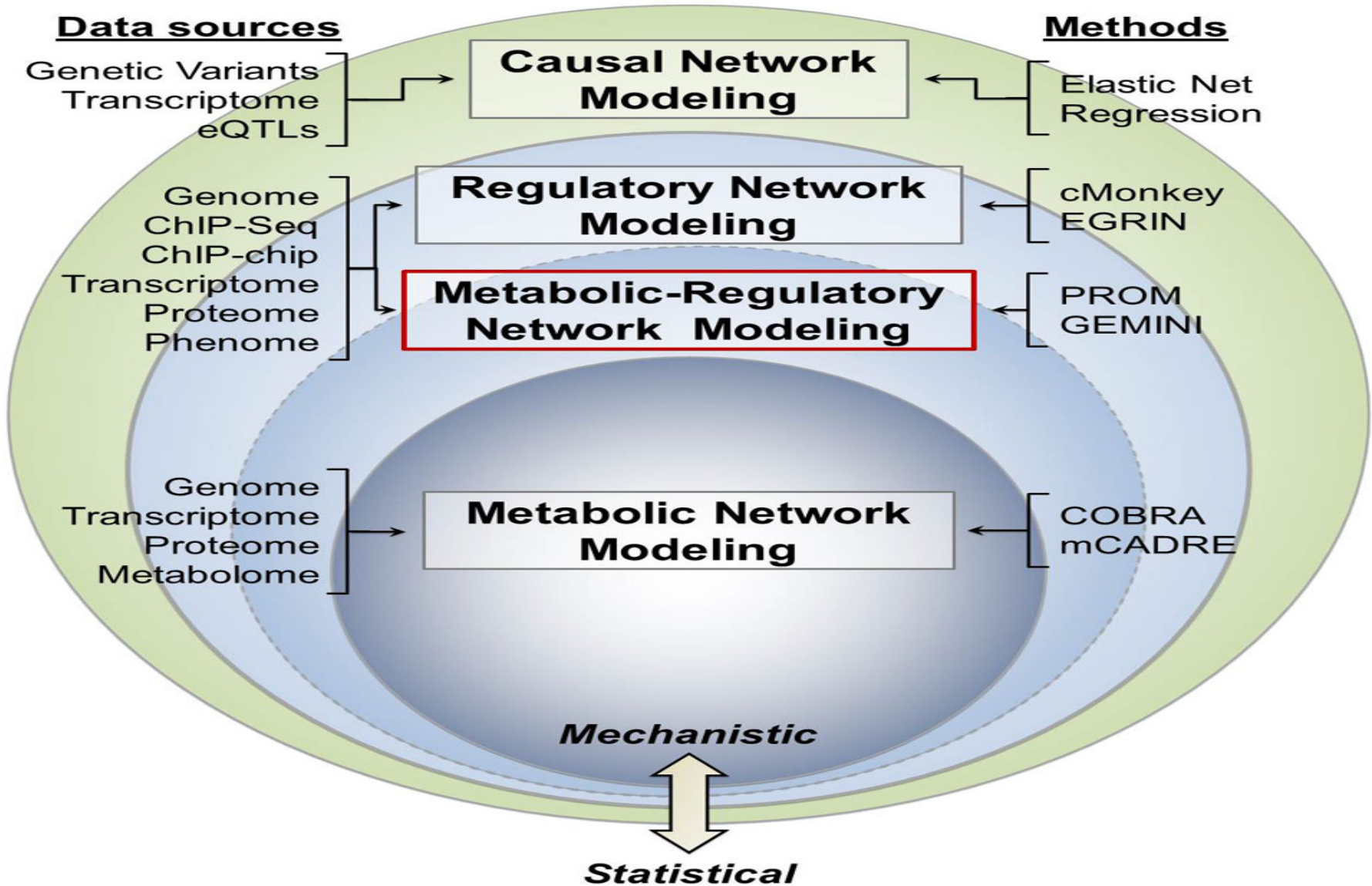
Overall Survival:
Pre-AR Signaling Inhibitor Samples



PRECISION MEDICINE

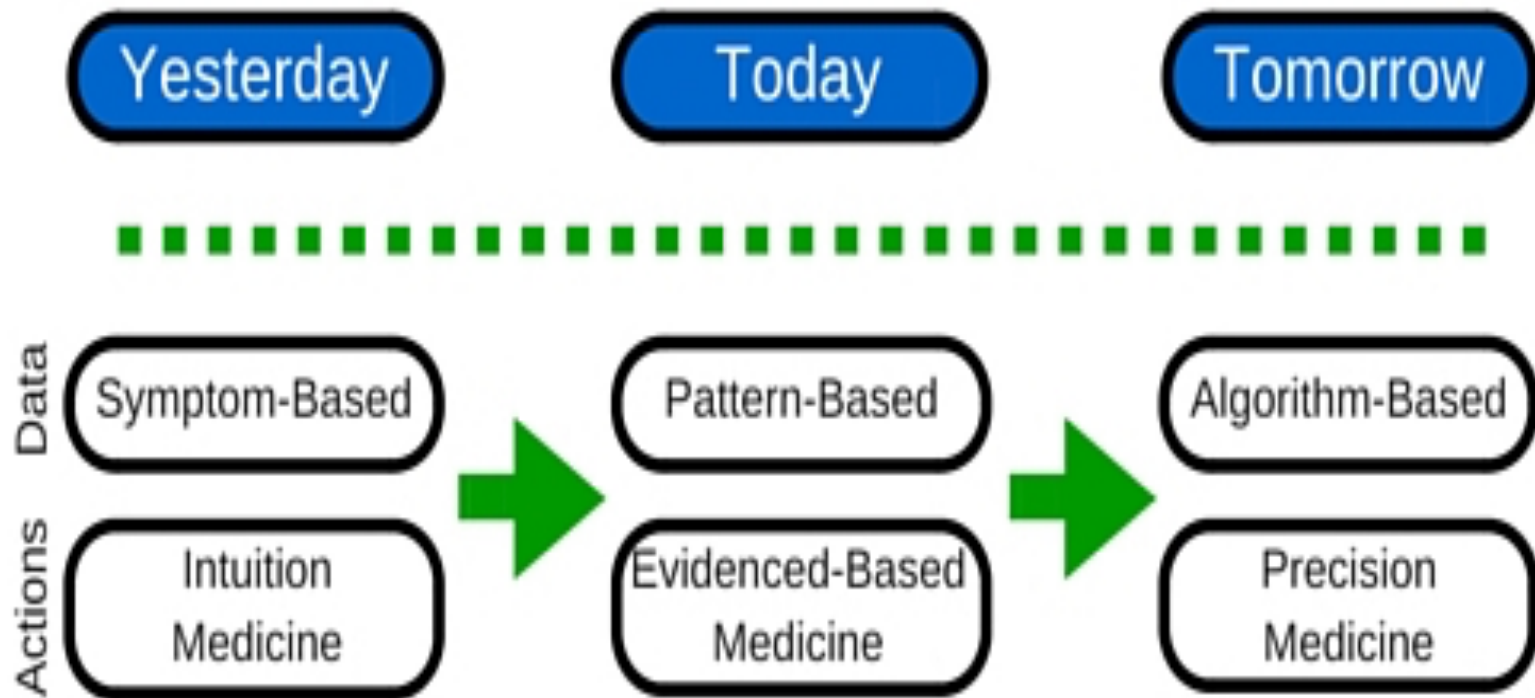


PRECISION MEDICINE



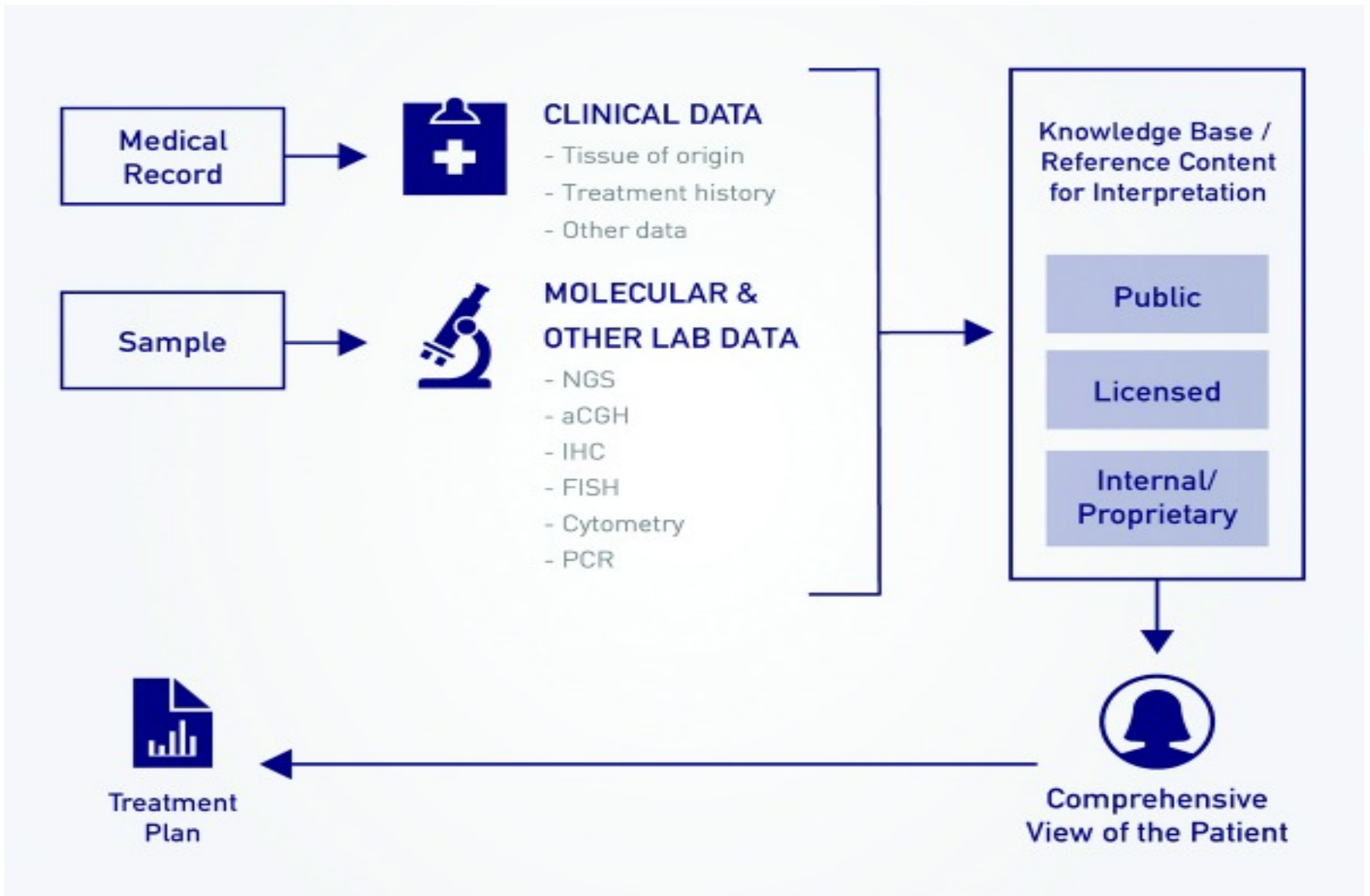


Precision Medicine - Paradigm Shift



Application of rules, algorithms and reference database enables actionable clinical decision support and precise, efficient care

PRECISION MEDICINE

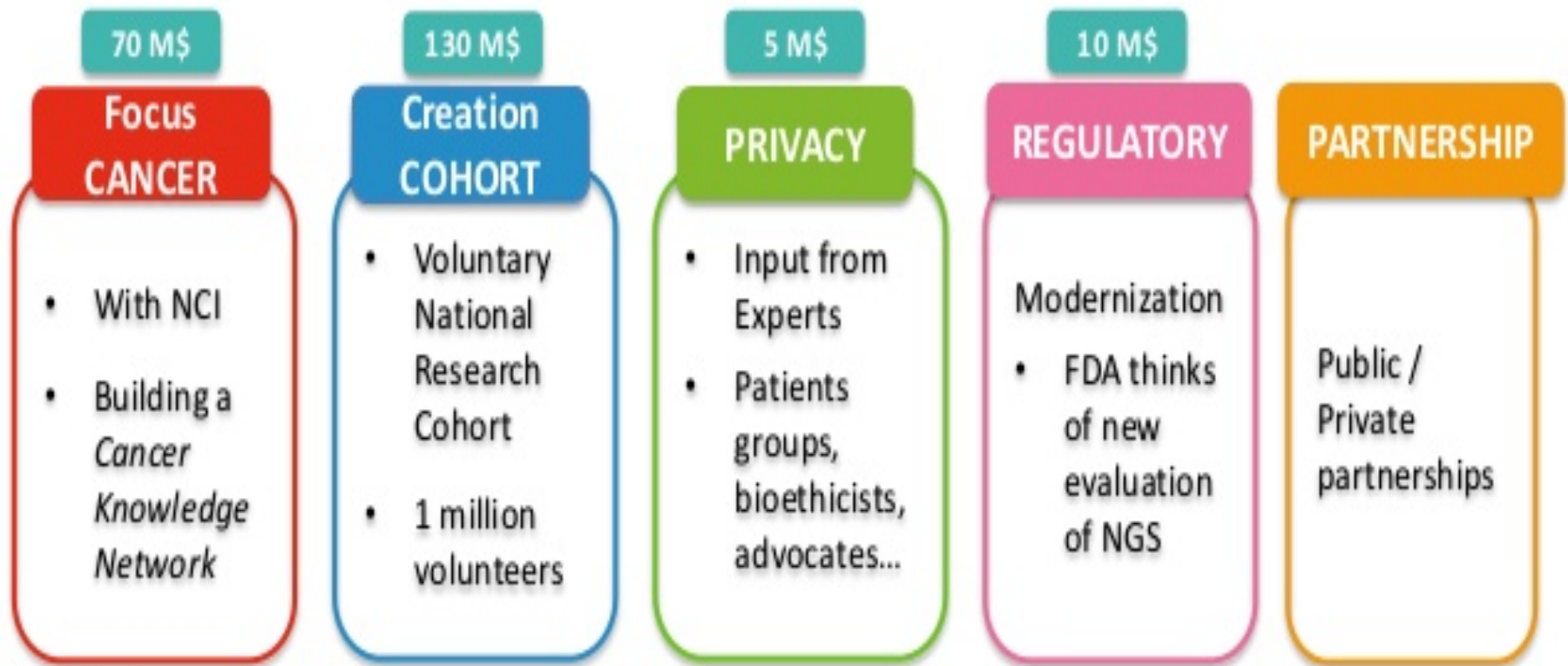




President Obama's Precision Medicine Initiative

State of the Union Address, 20 January 2015, USA — Budget :

215 M\$



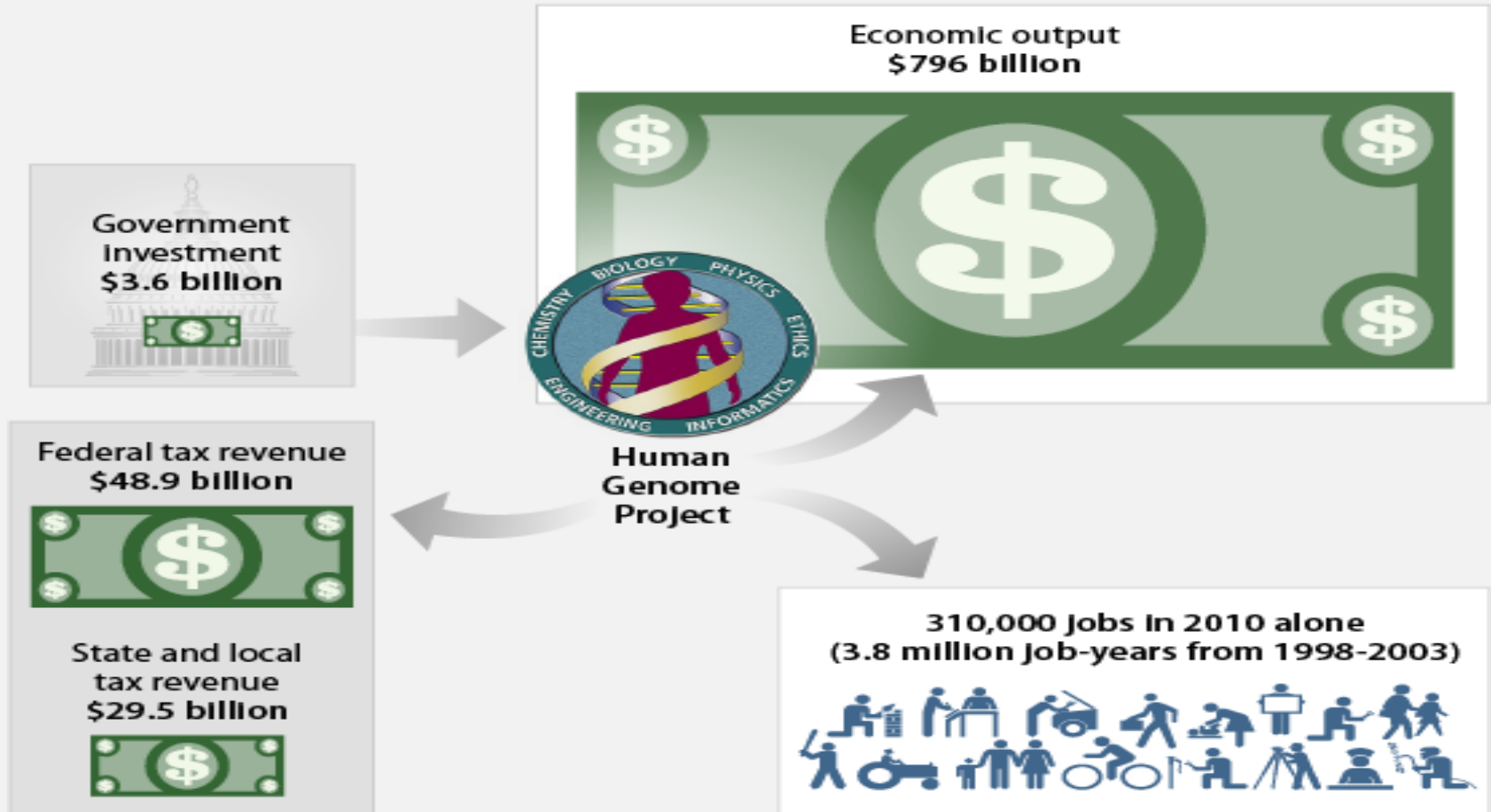
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Economic Impact of the Human Genome Project, 1988-2003

The Human Genome Project yielded a 14,000% return on investment over the 23 years of its life in terms of economic output and a 1,250% return on investment in terms of federal tax revenue alone



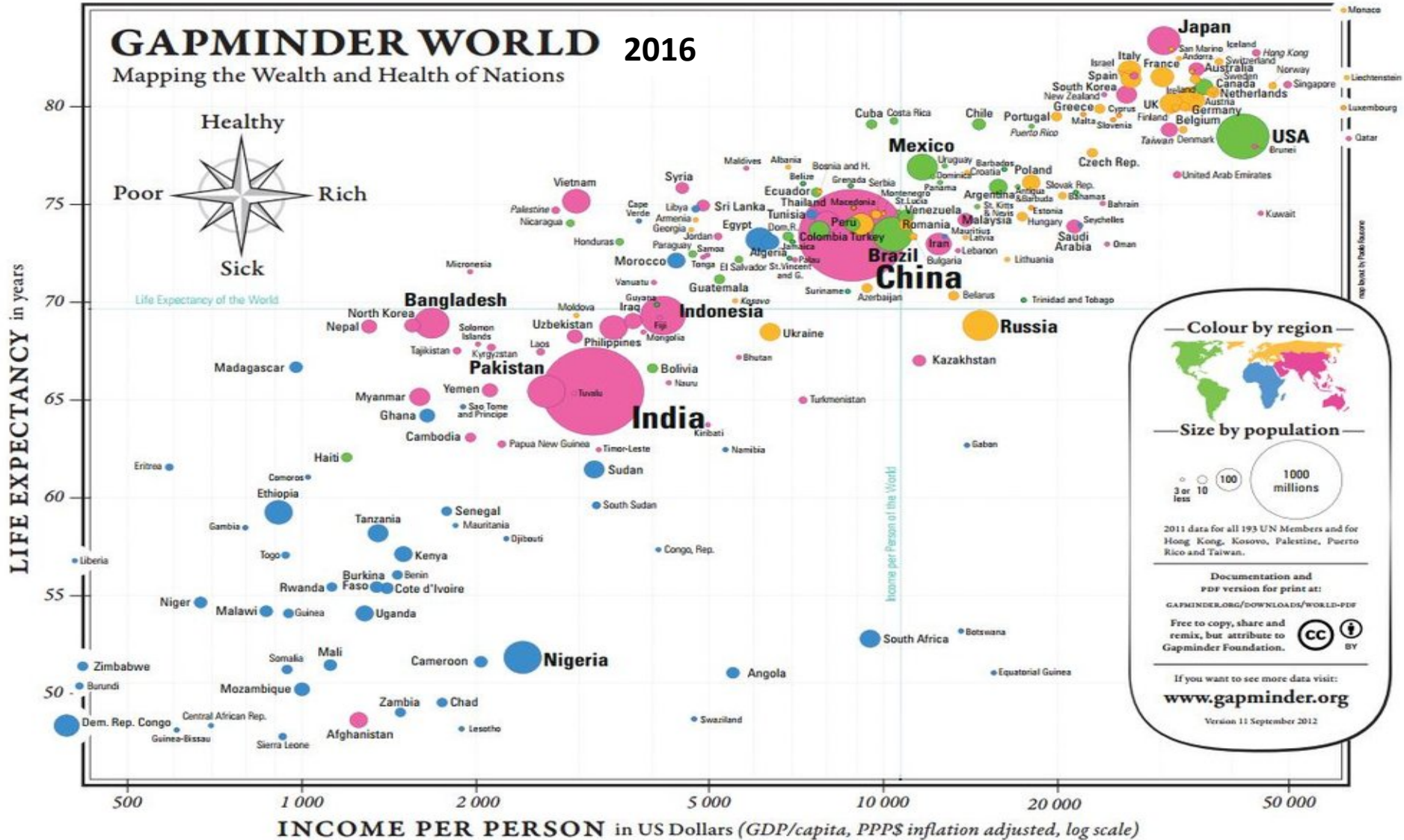
Source: Science Progress with data from "Economic Impact of the Human genome Project," Battelle Technology Partnership Practice, May 2011.



PRECISION MEDICINE

GAPMINDER WORLD 2016

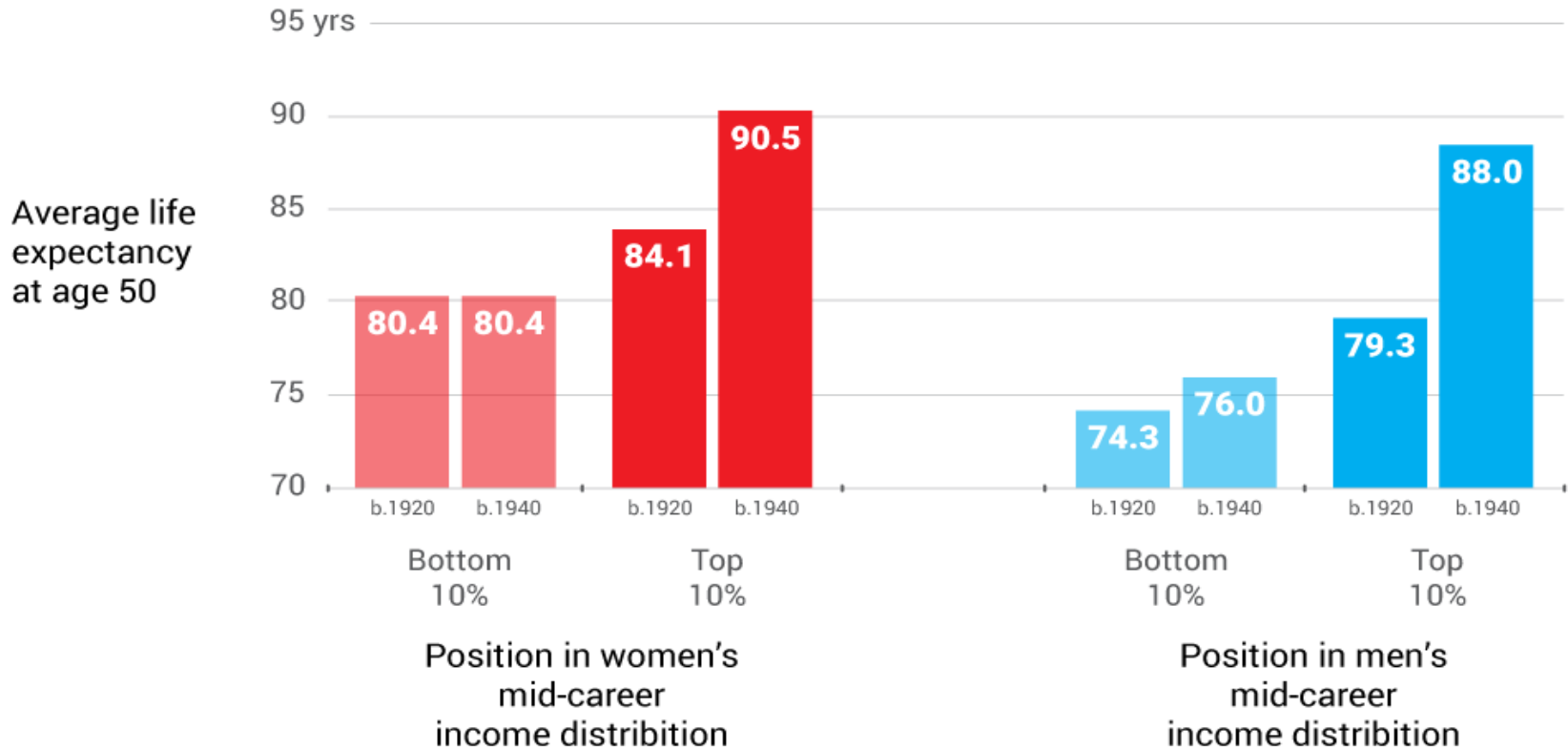
Mapping the Wealth and Health of Nations

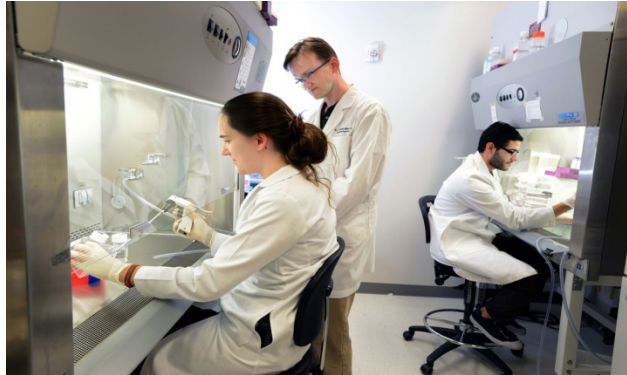




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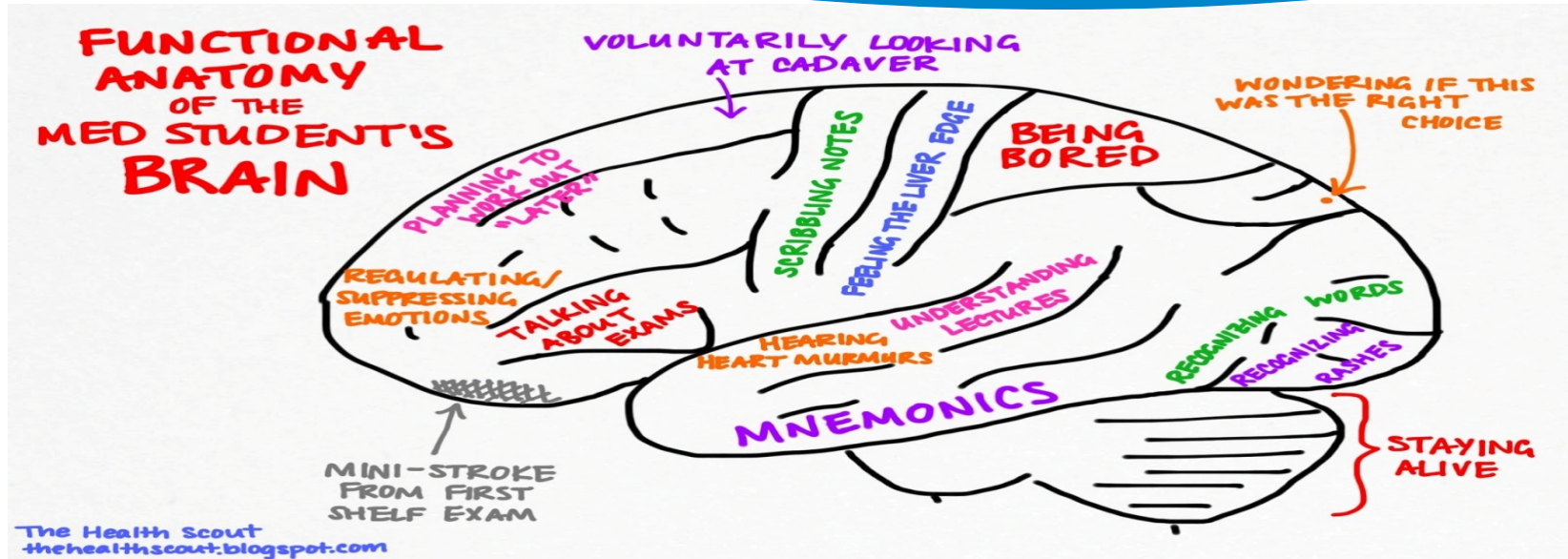
Americans making more money are living longer than those earning less
This means gaps in life expectancy by income have grown over time.







Exponential Growth of Knowledge



1950 = 50 yrs

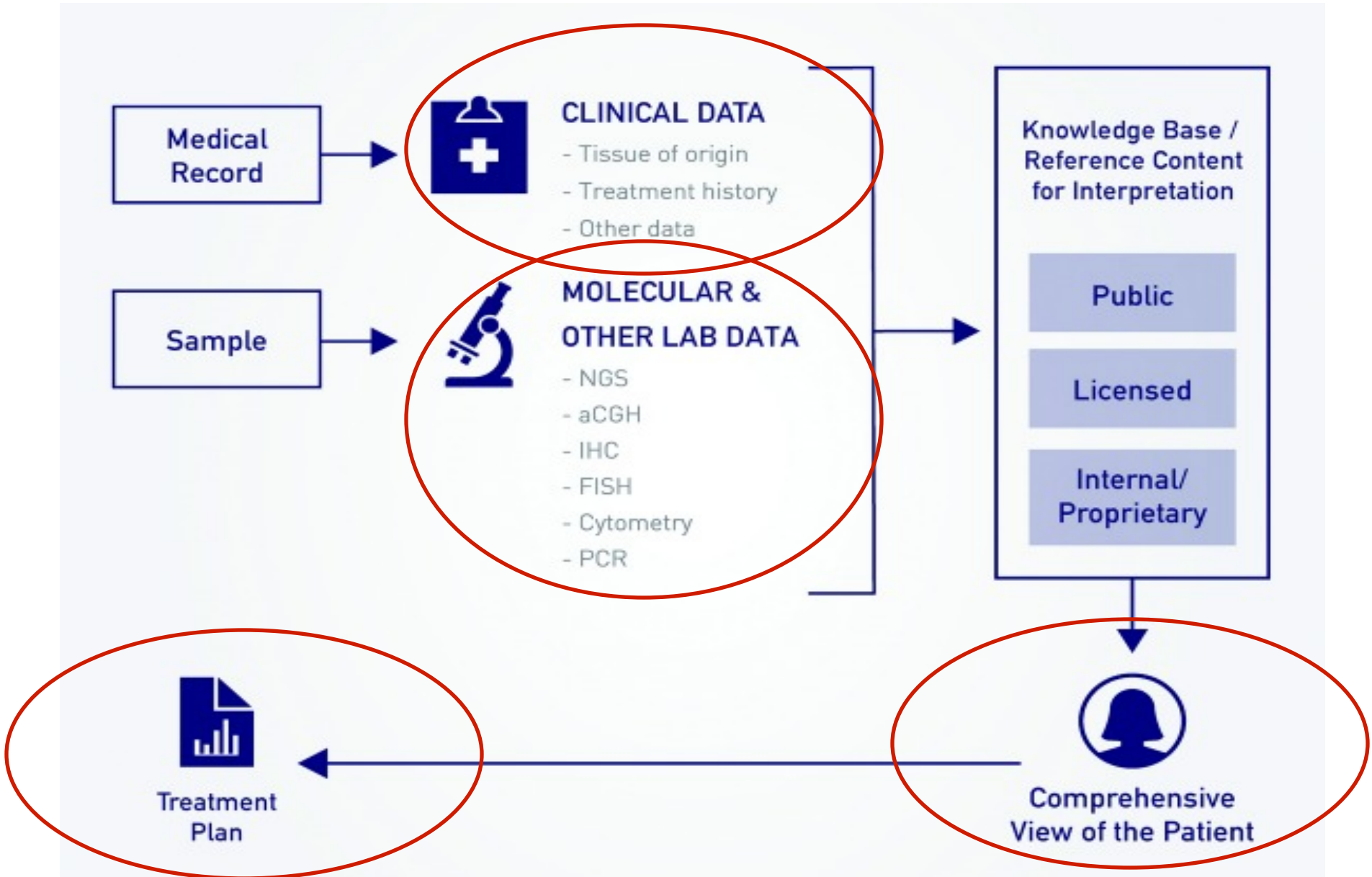
1980 = 7 yrs
1 doubling

2010 = 3.5 yrs
2 doublings

Doubling Time Of Medical Knowledge

2020 = 0.2 yr = 73 days
4 doublings/yr

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PRECISION MEDICINE

Uncertainty in the Era of Precision Medicine

David J. Hunter, Dept. of Epidemiology, Harvard Medical School
N Engl J Med 375; 8:711-712, 2016

... such analysis provides evidence on the risk of disease development/recurrence but no direct evidence regarding whether specific therapies are more or less effective within a risk categories ...

... the new tests add to, but not replace, the information from the prior clinical tools, such as (immunohistochemistry, tumor markers and clinical prognostic indexes) ...

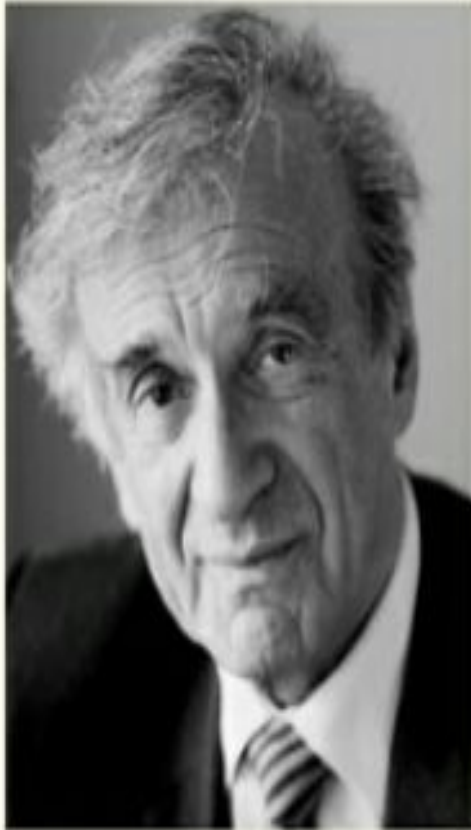


PHASES OF LIFE TIME



Μια αστραπή είναι η ζωή αλλά προλαβαίνουμε ...
Νίκος Καζαντζάκης

HUMAN RIGHTS & PRECISION MEDICINE



“You who are so-called illegal aliens must know that no human being is illegal. That is a contradiction in terms. Human beings can be beautiful or more beautiful, they can be fat or skinny, they can be right or wrong, but illegal? How can a human being be illegal?”

Elie Wiesel, writer, Nobel Peace Prize winner and Holocaust survivor.