

SALUTE *IN* COMUNE

La nuova era della genomica e della medicina su misura:
luci e ombre

Brescia, Palazzo Loggia, 15 Aprile 2019

Farmacologia in continua evoluzione per costruire la Società del futuro

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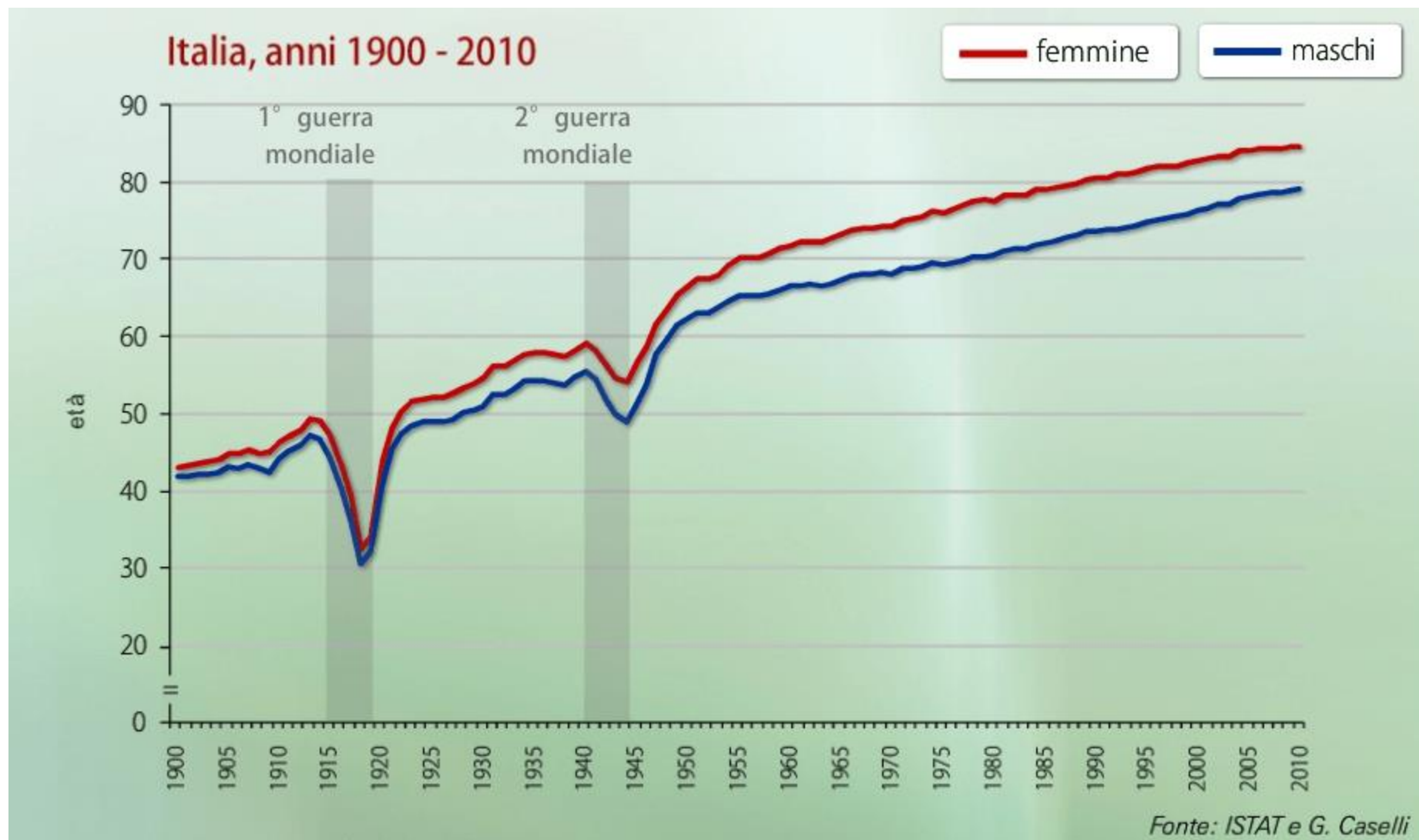


Direttore Scientifico del Centro Studi DIFF
Documentazione Informazione e Formazione sul Farmaco
Università degli Studi di Brescia

Definizioni OMS

- **Farmaco:** Sostanza o prodotto usato per modificare ed esplorare sistemi fisiologici o patologici con beneficio di chi lo riceve.
- **Salute:** Stato di completo benessere fisico, psichico e sociale e non semplice assenza di malattia

Vita media in Italia



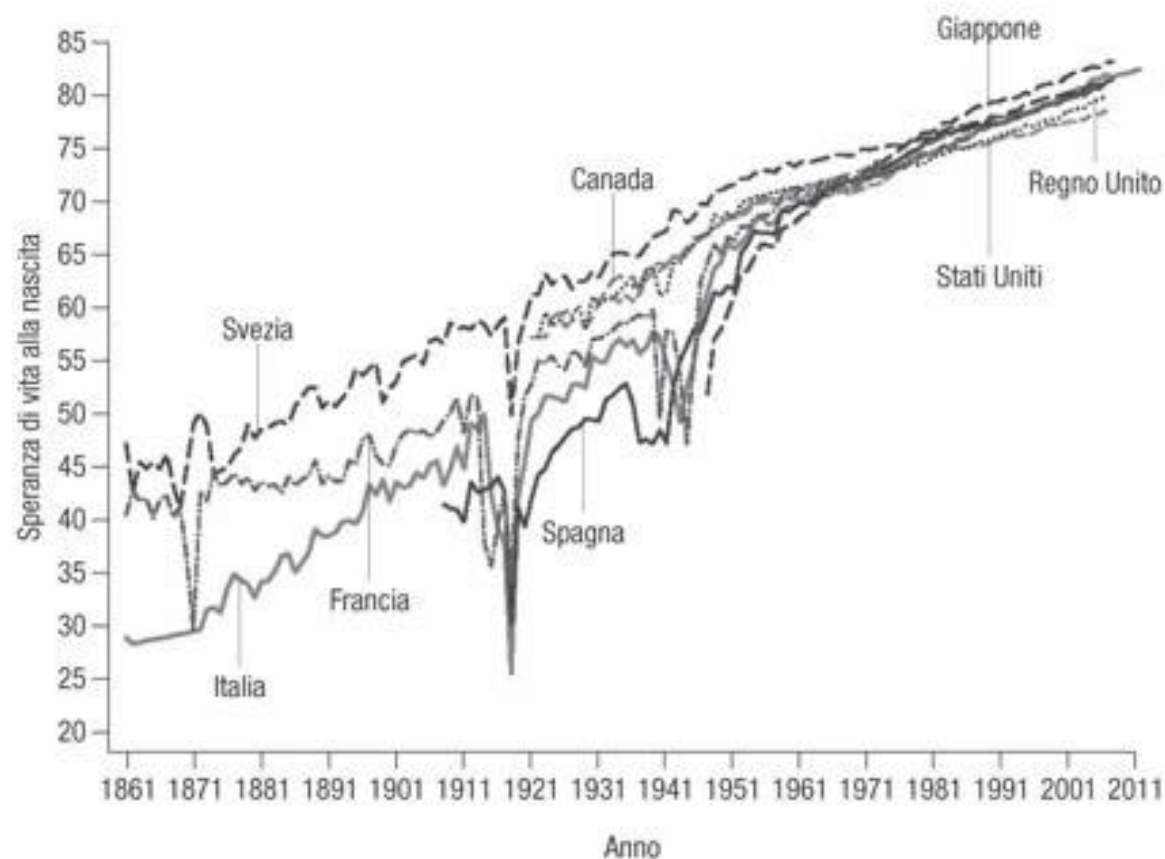
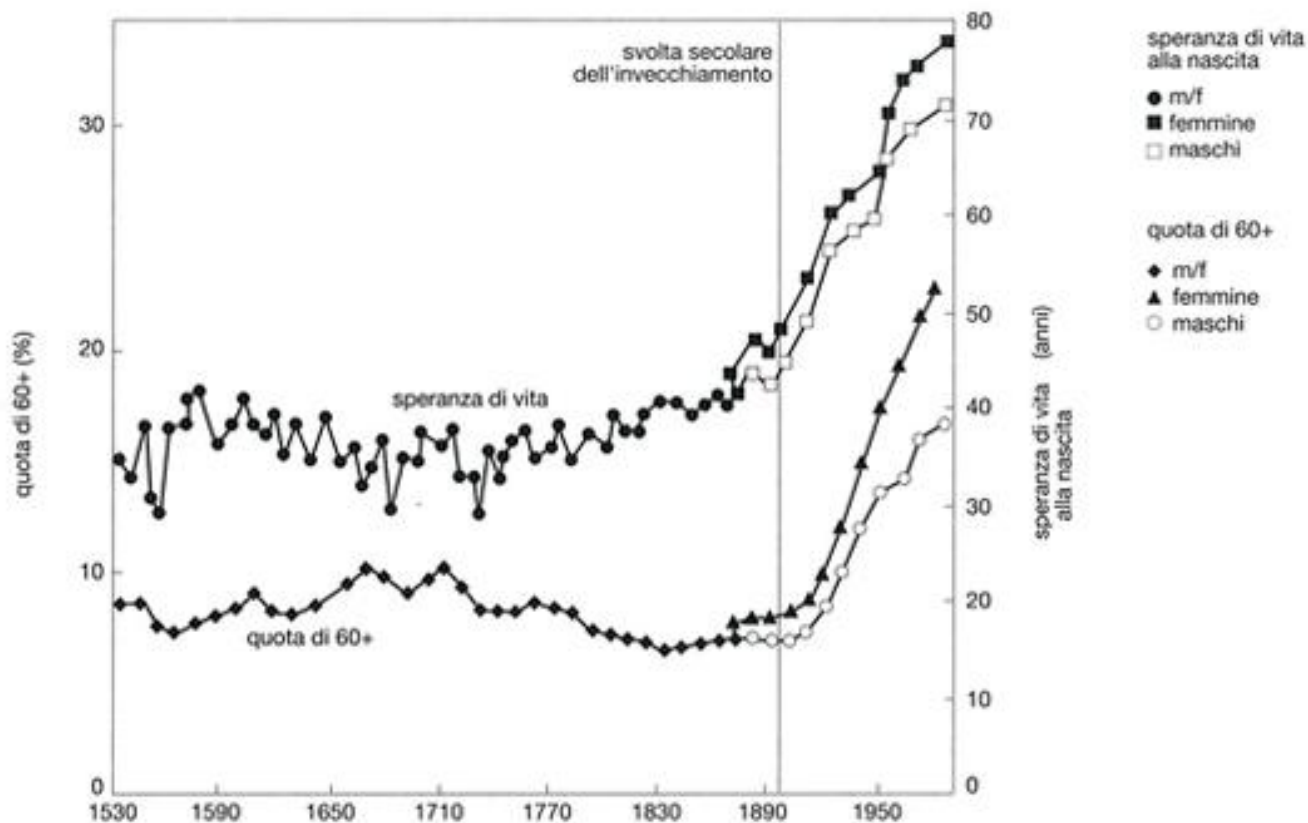
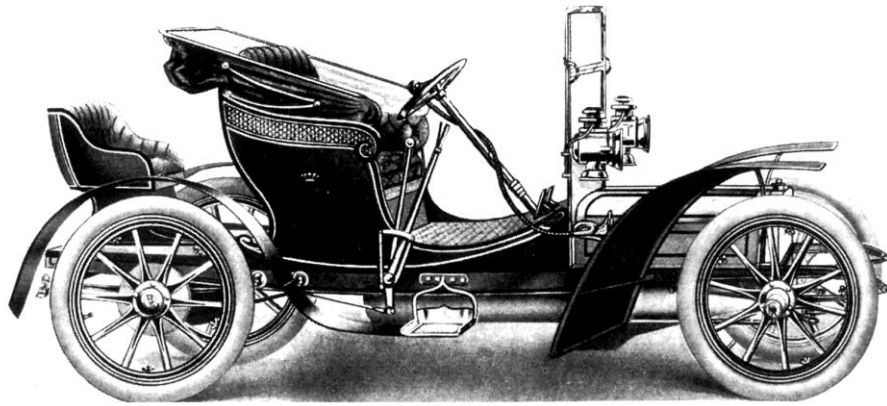
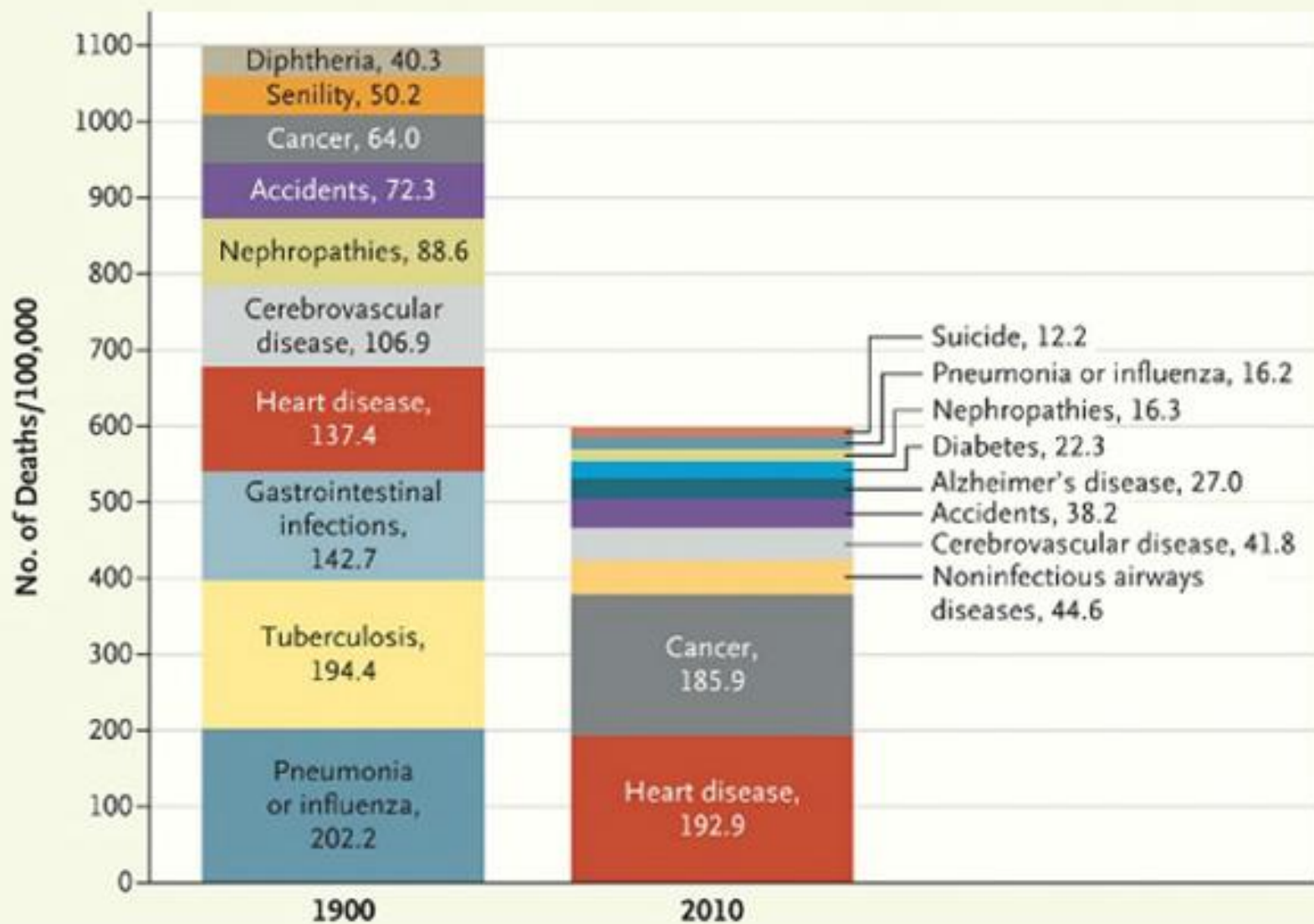


Figura 2 - La vita media in Italia a confronto col resto del mondo, 1861-oggi. Fonti: nostre elaborazioni su dati Hmd (2010) e altre fonti descritte nell'Appendice.

Aspettativa di vita

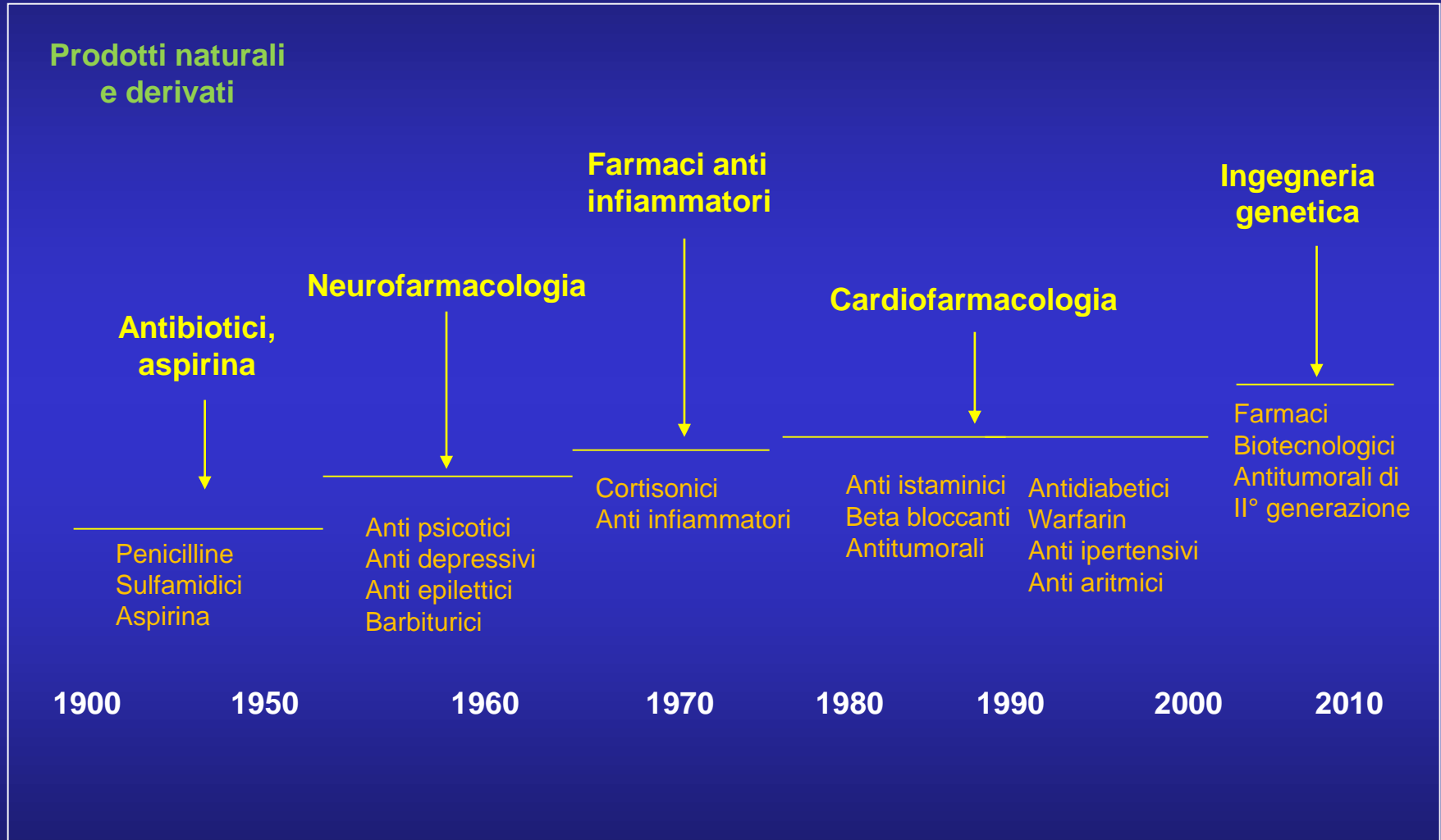






New England Journal of Medicine, 2012

CRONOLOGIA DELL'INNOVAZIONE FARMACOLOGICA



The PHARMACOLOGICAL BASIS *of* THERAPEUTICS

A Textbook of Pharmacology,
Toxicology and Therapeutics for
Physicians and Medical Students

by

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THE MACMILLAN COMPANY

NEW YORK

TABLE OF CONTENTS

Chapter	SECTION I INTRODUCTION	Page
1. General Principles		3
SECTION II CENTRAL NERVOUS SYSTEM DEPRESSANTS		
2. History and Theories of General Anesthesia		28
3. Stages of Anesthesia		35
4. Preanesthetic Medication, Technic of Anesthesia and Anesthetic Accidents		46
5. General Anesthetics		58
i. Ether and Chloroform, Divinyl Ether, Ethyl Chloride and Tri- chloroethylene		58
6. General Anesthetics		81
ii. Nitrous Oxide, Ethylene, Cyclopropane, Acetylene		81
7. Basal Anesthetics		100
Tribromethanol		100
8. The Alcohols		108
9. Hypnotics and Sedatives		126
i. The Barbiturates		126
10. Hypnotics and Sedatives		155
ii. The Bromides and Dilantin		155
11. Hypnotics and Sedatives		175
iii. Chloral Hydrate, Paraldehyde and Miscellaneous Agents		175
12. Morphine and other Opium Alkaloids		186
13. Analgesics and Antipyretics		224
i. The Salicylates, Cinchophen and Neocinchophen		224
14. Analgesics and Antipyretics		242
ii. Acetanilid and Acetophenetidin; Aminopyrine and Antipyrine		242
SECTION III CENTRAL NERVOUS SYSTEM STIMULANTS		
15. Strychnine and Picrotoxin		256
16. Metrazol, Coramine and Camphor		267
17. The Xanthines		274
Caffeine, Theophylline and Theobromine		274

CONTENTS

SECTION IV

LOCAL ANESTHETICS

Chapter	Page
18. Cocaine; Procaine and Other Synthetic Local Anesthetics . . .	286

SECTION V

DRUGS ACTING ON AUTONOMIC EFFECTOR CELLS

19. Anatomical, Physiological and General Pharmacological Considerations	317
20. Drugs Stimulating Structures Innervated by Cholinergic Nerves (Parasympathomimetic Drugs)	349
i. Choline Esters: Acetylcholine, Acetyl-Beta-Methylcholine and Carbaninoylecholine	349
21. Drugs Stimulating Structures Innervated by Cholinergic Nerves (Parasympathomimetic Drugs)	376
ii. Inhibitors of Cholinesterase: Physostigmine (Eserine) and Prostigmine	376
22. Drugs Stimulating Structures Innervated by Cholinergic Nerves (Parasympathomimetic Drugs)	389
iii. Pilocarpine, Arecoline and Muscarine	389
23. Drugs Stimulating Structures Innervated by Adrenergic Nerves (Sympathomimetic Drugs)	396
i. Epinephrine	396
24. Drugs Stimulating Structures Innervated by Adrenergic Nerves (Sympathomimetic Drugs)	423
ii. Ephedrine, Benzedrine and Miscellaneous Sympathomimetic Drugs	423
25. Autonomic Blocking Agents	460
i. Drugs Inhibiting Structures Innervated by Postganglionic Cholinergic Nerves	460
Atropine, Scopolamine and Related Synthetic Drugs	460
26. Autonomic Blocking Agents	482
ii. Drugs Inhibiting Structures Innervated by Adrenergic Nerves	482
Ergotamine and Ergotoxine	482
27. Autonomic Blocking Agents	488
iii. Drugs Inhibiting Autonomic Ganglia and Skeletal Muscles	488
Nicotine and Curare	488

SECTION VI

CARDIOVASCULAR DRUGS

28. Digitalis and Allied Cardiac Glycosides	500
29. Quinidine	538
30. The Nitrites	548

Chap
31.

32. V

33. C

34. A

35. D

D

36. O

37. Al

38. Th

39. No

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n

41. Lea

42. Me

43. Gol

M

44. Dem

As

CONTENTS

xi

Chapter	Page
31. Histamine, Thiocyanates and Miscellaneous Cardiovascular Drugs	566

SECTION VII

WATER, SALTS AND IONS

32. Water, Sodium Salts and Other Agents Affecting the Volume and Composition of the Body Fluids	578
33. Cations: Potassium, Calcium, Magnesium, Barium and Ammonium	595
34. Anions: Phosphates, Iodides, Fluorides and Other Anions	613

SECTION VIII

DRUGS AFFECTING URINE FORMATION

35. Diuretics and Antidiuretics	626
---	-----

SECTION IX

DRUGS ACTING ON THE REPRODUCTIVE ORGANS

36. Oxytocics	653
<i>Ergot, Ergot Alkaloids and Posterior Pituitary</i>	653
37. Abortifacients, Uterine Sedatives, Uterine Hemostatics and Spermatocides	673

SECTION X

GASES AND VAPORS

38. The Therapeutic Gases	677
<i>Oxygen, Carbon Dioxide and Helium</i>	677
39. Noxious Gases and Vapors	694
i. <i>Carbon Monoxide, Hydrocyanic Acid and Miscellaneous Agents</i>	694
40. Noxious Gases and Vapors	707
ii. <i>The War Gases</i>	707

SECTION XI

HEAVY METALS AND METALLOIDS

41. Lead	717
42. Mercury, Arsenic and Antimony	732
43. Gold, Silver, Thallium, Selenium, Radioactive Elements and Miscellaneous Minor Metals	751

SECTION XII

DRUGS ACTING LOCALLY ON THE SKIN AND MUCOUS MEMBRANES

44. Demulcents, Emollients, Protectives, Adsorbents, Irritants and Astringents	766
--	-----

CONTENTS

Chapter	Page
45. Gastric Antacids and Digestants	778
46. Cathartics	798
47. Emetics and Expectorants	812

SECTION XIII

ANTISEPTICS, DISINFECTANTS AND DRUGS USED IN
THE CHEMOTHERAPY OF INFECTIOUS DISEASES

48. Antiseptics, Germicides, Fungicides and Parasitocides	823
49. Drugs Used in the Chemotherapy of Helminthiasis	878
50. Drugs Used in the Chemotherapy of Malaria	903
<i>Quinine, Plasmochin and Atabrine</i>	903
51. Drugs Used in the Chemotherapy of Amebiasis	930
<i>Emetine, Chiniofon, Vioform and Carbarsone</i>	930
52. Drugs Used in the Chemotherapy of Leprosy	943
<i>Chaulmoogra and Hydnocarpus Oils</i>	943
53. Drugs Used in the Chemotherapy of Syphilis	946
i. <i>The Pharmacology and Clinical Toxicology of the Antisyphilitic</i>	
<i>Arsenicals</i>	946
<i>The Arsphenamines, Mapharsen and Tryparsamide</i>	946
54. Drugs Used in the Chemotherapy of Syphilis	978
ii. <i>Bismuth, Mercury and Iodides</i>	978
55. Drugs Used in the Chemotherapy of Syphilis	993
iii. <i>Principles of Syphilotherapy</i>	993
56. Sulfanilamide and Related Sulfonamide Drugs	1002
i. <i>The Pharmacology of Sulfanilamide</i>	1002
57. Sulfanilamide and Related Sulfonamide Drugs	1029
ii. <i>The Clinical Toxicology of Sulfanilamide</i>	1029
58. Sulfanilamide and Related Sulfonamide Drugs	1043
iii. <i>Therapeutic Uses of Sulfanilamide</i>	1043
59. Sulfanilamide and Related Sulfonamide Drugs	1065
iv. <i>Sulfapyridine and Sulfathiazole</i>	1065

SECTION XIV

DRUGS ACTING ON THE BLOOD AND
BLOOD-FORMING ORGANS

60. Drugs Effective in Iron-Deficiency Anemias	1104
<i>Iron and Iron Salts</i>	1104
61. Drugs Effective in Pernicious Anemia and Allied Anemias	1123
<i>Liver Extract and Desiccated Stomach</i>	1123
62. Miscellaneous Drugs Affecting the Blood	1140
<i>Heparin, Nucleic Acid Derivatives and Phenylhydrazine</i>	1140

SECTION XV

DRUGS OF ENDOCRINE ORIGIN

63. Thyroid	1156
-----------------------	------

Chapter

64. Pa

65. An

66. Fe

67. Ma

68. Ins

69. Ad

70. Wa

71. Wa

72. Fat

73. Fat

INDEX

CONTENTS

xiii

Chapter	Page
64. Parathyroid	1173
65. Anterior Pituitary and Anterior Pituitary-Like Hormones	1180
66. Female Sex Hormones	1192
<i>Estrogens and Luteal Hormone</i>	1192
67. Male Sex Hormones	1207
68. Insulin	1214
69. Adrenal Cortical Hormones	1229

SECTION XVI

THE VITAMINS

70. Water-Soluble Vitamins	1244
i. <i>The Vitamin B Complex, Thiamine, Riboflavin, Nicotinic Acid</i> <i>and Vitamin B₆</i>	1244
71. Water-Soluble Vitamins	1263
ii. <i>Ascorbic Acid (Vitamin C)</i>	1263
72. Fat-Soluble Vitamins	1269
i. <i>Vitamin A and Vitamin D</i>	1269
73. Fat-Soluble Vitamins	1293
ii. <i>Vitamin K and Vitamin E</i>	1293

APPENDIX

Principles of Prescription Writing	1305
--	------

INDEX	1327
-----------------	------

Evoluzione nella tipologia e nel concetto di malattia e terapia

CD



NCD

Stato di
sofferenza

Farmaci antidolorifici



Disabilità
funzionale

Farmaci sintomatici



Possibile e/o
asintomatica

Terapia preventiva

Evoluzione del concetto di malato



acuto

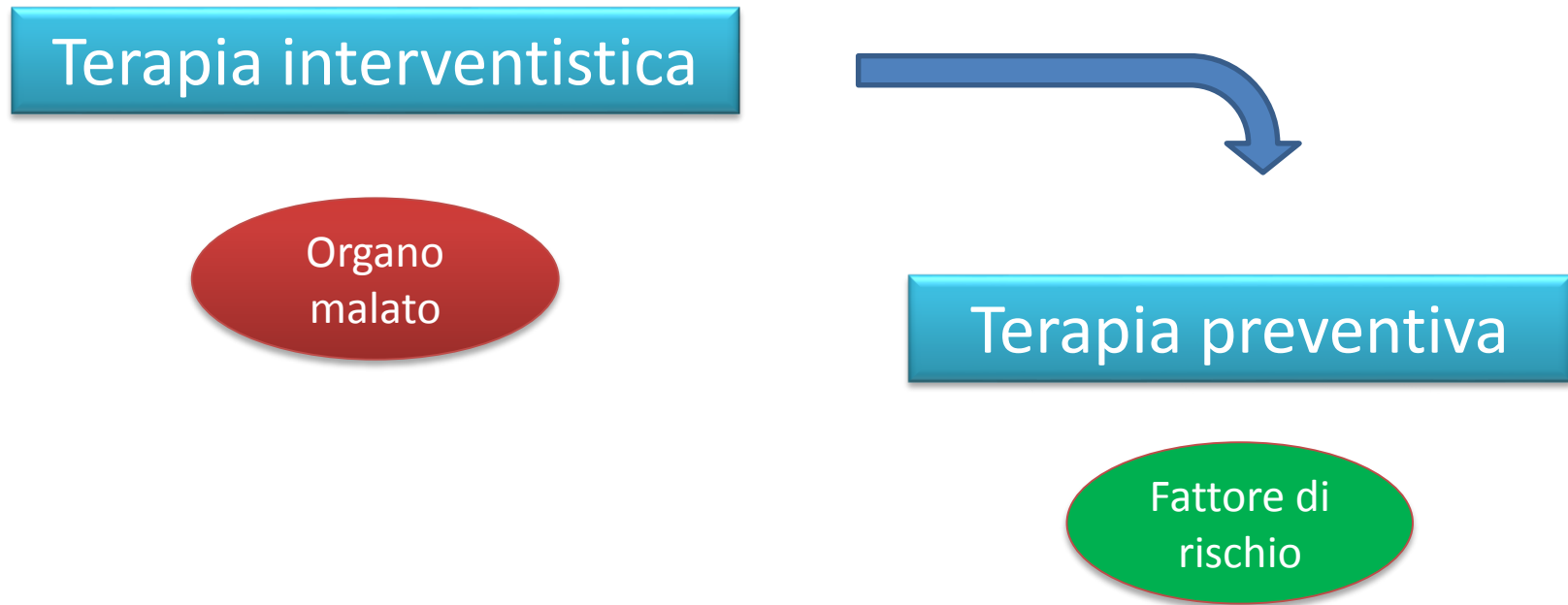


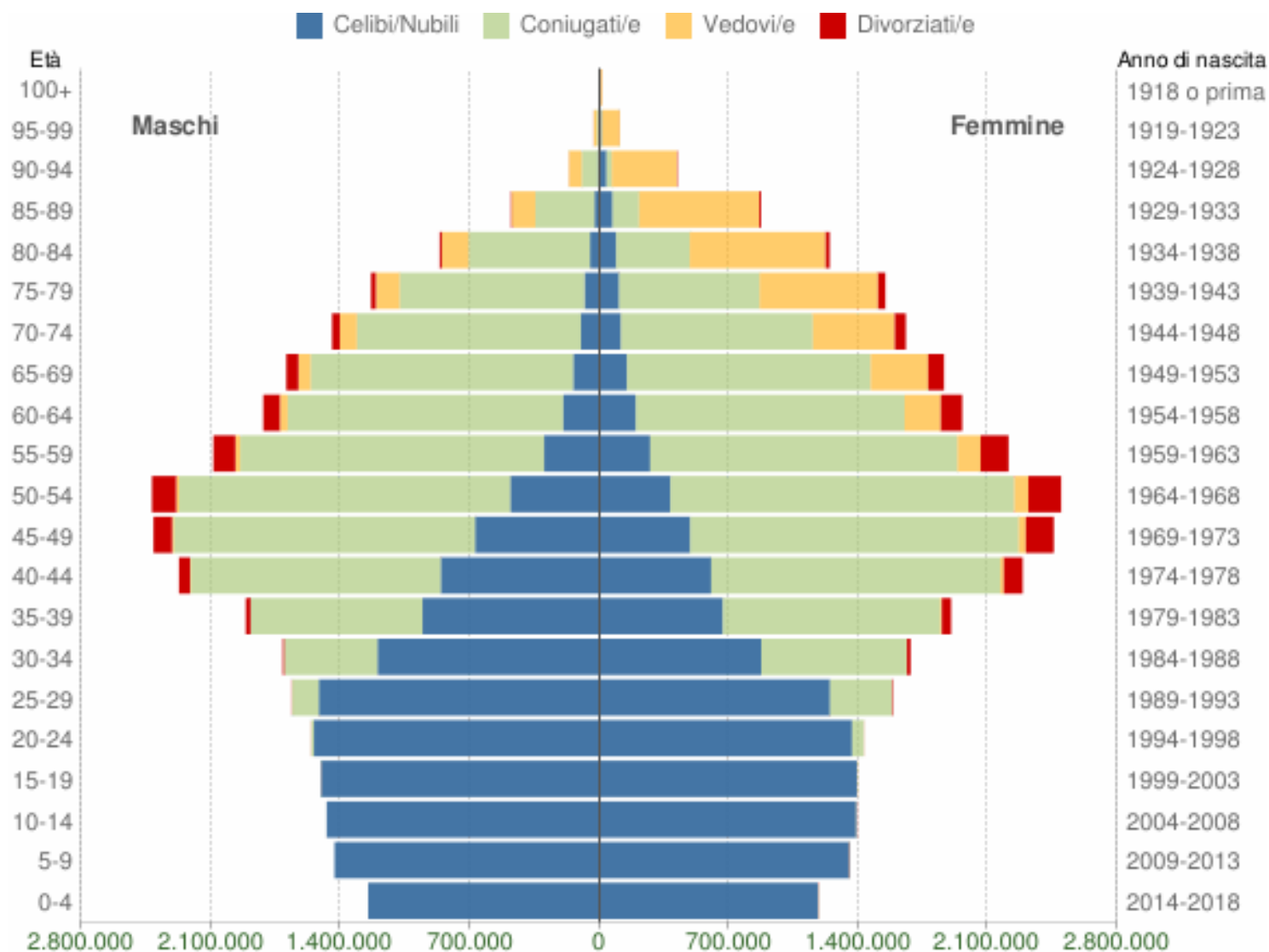
cronico



sano

Evoluzione dell'approccio terapeutico





Popolazione per età, sesso e stato civile - 2018

ITALIA - Dati ISTAT 1° gennaio 2018 - Elaborazione TUTTITALIA.IT

Over 80

29.445.741	31.143.704	60.589.445
48,6%	51,4%	
Male	Female	Tot

Tot 4.168.300

Ved 2.205.790 53%

M 1.541.109

F 2.627.191 63%

Over 100

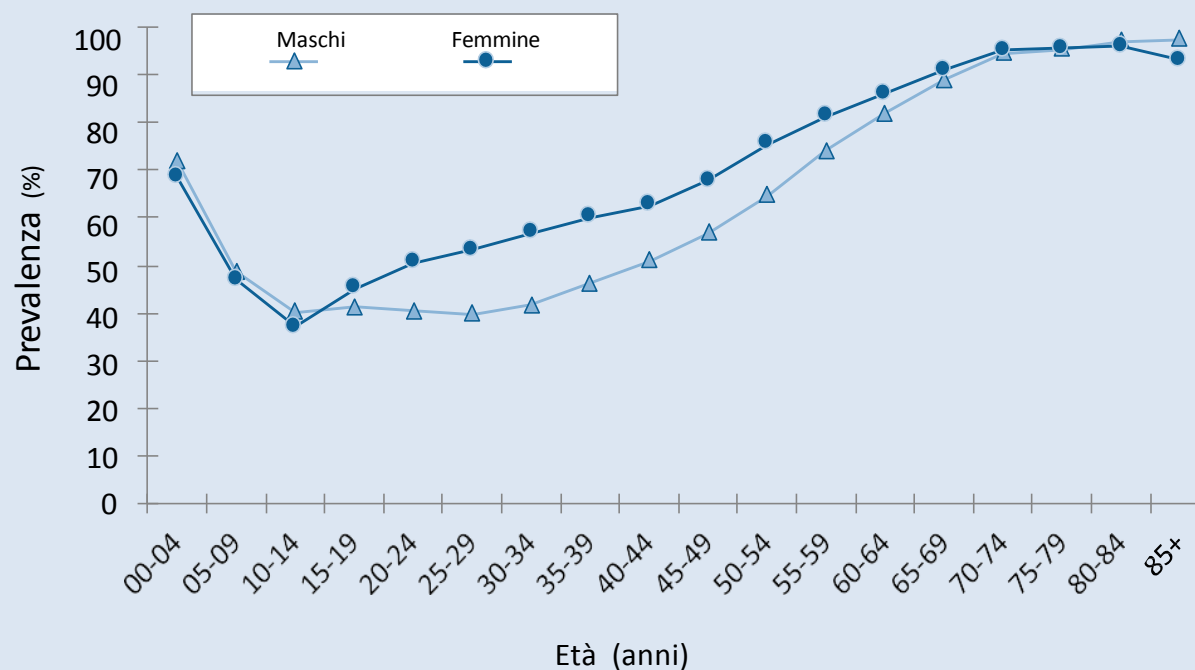
Tot 15.647

M 2.557

F 13.090 83%



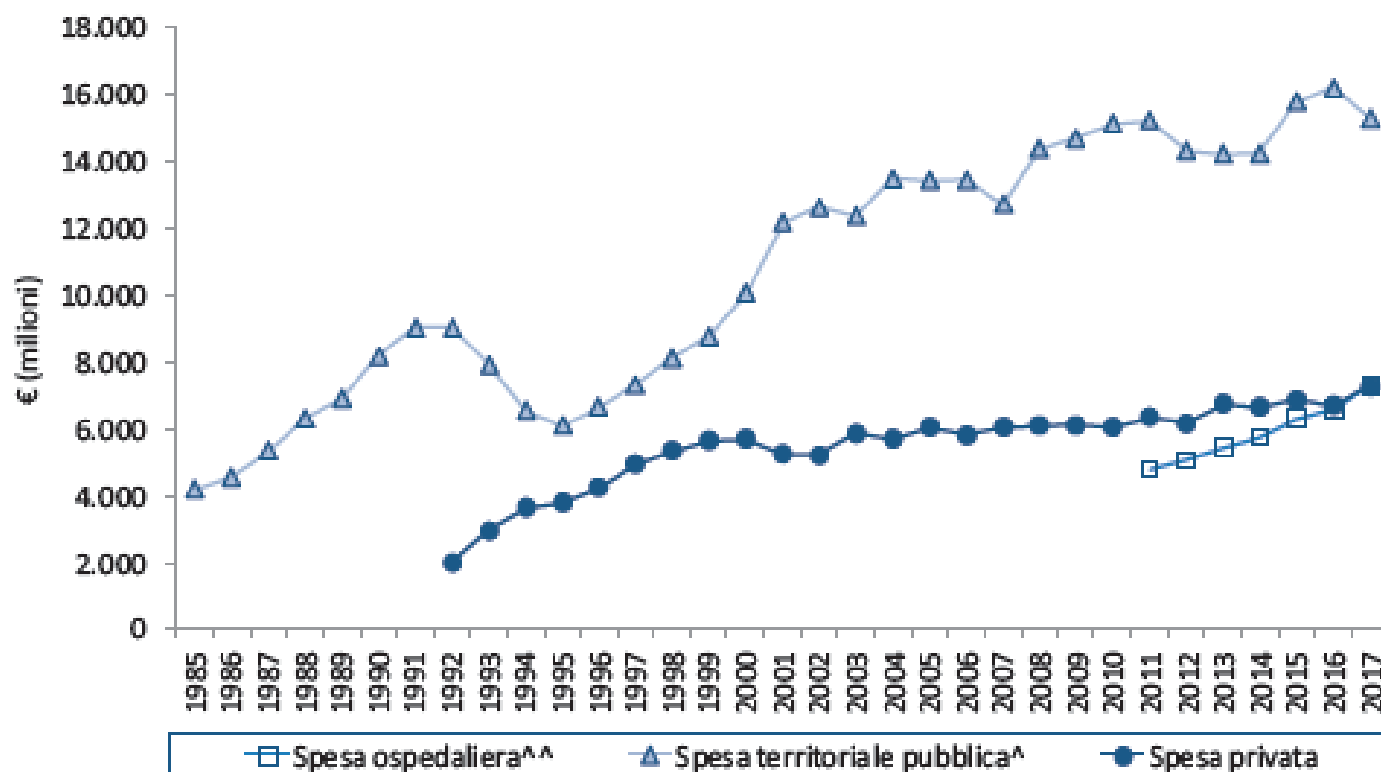
Consumo dei farmaci in Italia nel 2017: Prevalenza in funzione del genere e dell'età



Numero di farmaci assunti giornalmente dalla popolazione anziana, in Italia nel 2017

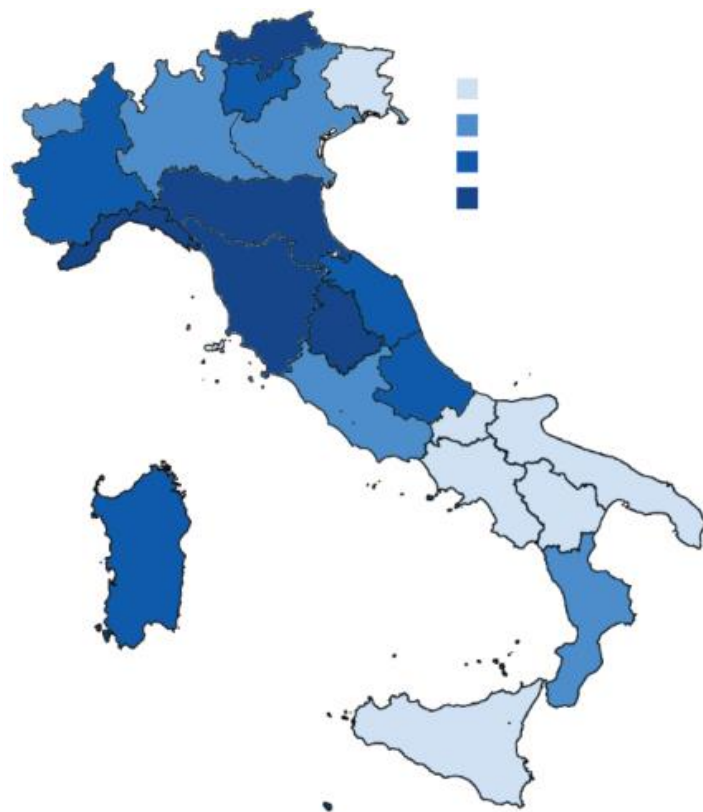
Età	Numero di farmaci (media)		
	Maschi	Femmine	Tutti
65-69	7,6	7,8	7,7
70-74	9,1	9,3	9,2
75-79	10,1	10,3	10,2
80-84	11,4	11,4	11,4
≥ 85	12,1	11,6	11,8
≥ 65	9,6	9,9	9,7

Figura 1.1.b Spesa farmaceutica nel periodo 1985 – 2017 (Figura e Tabella)



Consumo di farmaci

Antidepressivi



Antinfiammatori

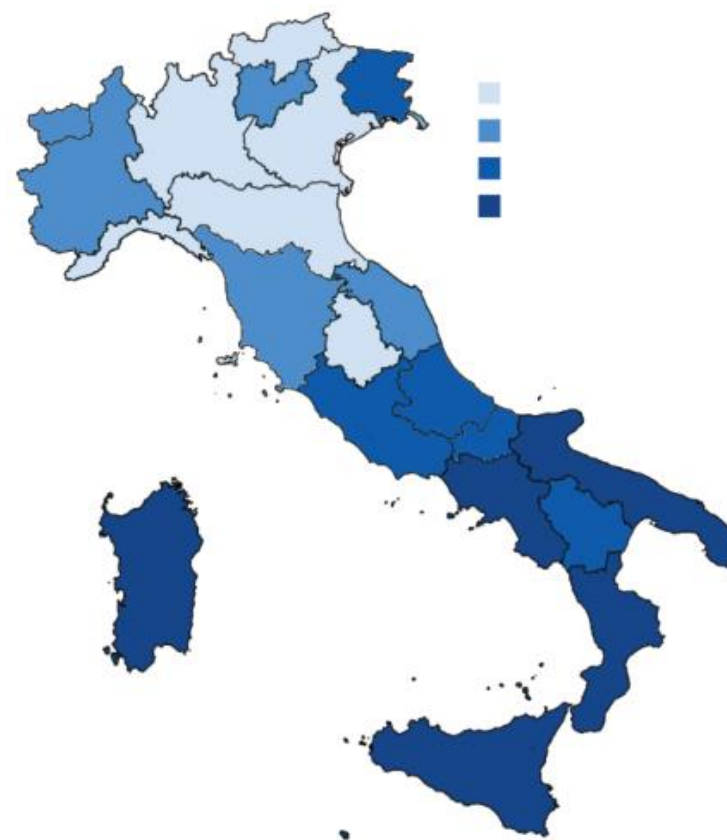


Tabella 1.4.4. Primi trenta principi attivi per consumo in età pediatrica nel 2017

ATC	Principio attivo	Confezioni (per 1000 ab.)	Consumi (%)*	
			Maschi	Femmine
J	amoxicillina/acido clavulanico	401,9	53,6	46,4
R	beclometasone	151,0	54,4	45,6
J	amoxicillina	127,5	52,4	47,6
J	cefixima	104,7	51,1	48,9
H	betametasone	101,7	56,7	43,3
J	azitromicina	86,5	53,2	46,8
R	salbutamolo	94,1	60,0	40,0
J	claritromicina	86,7	53,9	46,1
A	colecalfiferolo	68,6	49,5	50,5
R	cetirizina	68,6	59,4	40,6
N	acido valproico	58,4	62,4	37,6
R	budesonide	56,3	56,2	43,8
R	fluticasone	44,4	61,4	38,6
J	cefepodoxima	43,9	52,8	47,2
R	montelukast	42,6	63,2	36,8
J	ceftriaxone	37,7	53,7	46,3
R	salbutamolo/ipratropio	36,1	55,1	44,9
J	cefaclor	26,1	50,5	49,5
H	somatropina	18,5	62,1	37,9
J	acidovir	17,3	51,2	48,8
R	flunisolide	17,0	54,5	45,5
R	levocetirizina	17,0	63,3	36,7
H	levotiroxina	14,9	37,0	63,0
N	carbamazepina	13,6	55,0	45,0
H	prednisone	13,6	53,6	46,4
N	levetiracetam	13,3	46,3	53,7
R	salmeterolo/fluticasone	13,0	66,2	33,8
P	mebendazolo	12,5	47,6	52,4
R	desloratadina	11,7	61,2	38,8
B	sodio cloruro	11,2	54,3	45,7

* calcolato rispetto al totale dei consumi in età pediatrica

Tabella 2.8 Primi trenta principi attivi per spesa convenzionata di classe A-SSN: confronto 2017-2016

ATC	Principio attivo	Spesa (milioni)	%*	Spesa lorda pro capite	Rango 2017	Rango 2016
A	pantoprazolo	277,9	2,7	4,59	1	1
C	rosuvastatina	244,8	2,3	4,04	2	2
C	atorvastatina	234,5	2,3	3,87	3	3
A	colecalfiferolo	233,9	2,2	3,86	4	6
C	ezetimibe/simvastatina	186,8	1,8	3,08	5	8
A	lansoprazolo	180,4	1,7	2,98	6	4
J	amoxicillina/acido clavulanico	173,7	1,7	2,87	7	7
A	omeprazolo	163,5	1,6	2,70	8	9
R	salmeterolo/fluticasone	161,3	1,5	2,66	9	5
A	esomeprazolo	149,2	1,4	2,46	10	11
C	bisoprololo	130,3	1,3	2,15	11	17
R	beclometasone/formoterolo	124,0	1,2	2,05	12	19
B	enoxaparina sodica	124,0	1,2	2,05	13	13
G	dutasteride	123,1	1,2	2,03	14	10
C	ramipril	122,4	1,2	2,02	15	16
C	ezetimibe	113,8	1,1	1,88	16	26
C	omega 3	112,3	1,1	1,85	17	21
A	mesalazina	104,3	1,0	1,72	18	22
A	insulina lispro	103,9	1,0	1,71	19	23
C	simvastatina	103,8	1,0	1,71	20	20
N	pregabalin	101,5	1,0	1,67	21	15
R	fluticasone/vilanterolo	96,6	0,9	1,59	22	35
R	tiotropio	96,4	0,9	1,59	23	18
C	amlodipina	93,7	0,9	1,55	24	24
C	olmesartan/amlodipina	92,6	0,9	1,53	25	28
A	insulina aspart	89,6	0,9	1,48	26	25
A	metformina	87,8	0,8	1,45	27	29
N	levetiracetam	85,9	0,8	1,42	28	32
A	rifaximina	84,2	0,8	1,39	29	30
C	nebivololo	83,0	0,8	1,37	30	31
Totale		4079,0	39,1			
Totale spesa classe A-SSN		10.418,9				

*calcolata sul totale della spesa convenzionata

Tabella 3.4.2. Primi venti principi attivi di classe C con ricetta a maggiore spesa nel 2017

ATC	Principio attivo	DDD/1000 ab die	Spesa (milioni)	%*	Δ% 17-16
N	paracetamolo	4,6	143	5,0	10,7
G	tadalafil	0,6	121	4,2	5,3
N	lorazepam	10,2	111	3,8	4,0
N	alprazolam	8,7	105	3,6	8,5
G	sildenafil	0,7	87	3,0	14,9
G	drospirenone/etinilestradiolo	6,1	73	2,5	-3,0
D	gentamicina/betametassone	3,5	64	2,2	11,3
N	lormetazepam	13,0	53	1,8	8,2
N	zolpidem	4,1	49	1,7	16,4
N	bromazepam	1,4	47	1,6	7,4
R	acetilcisteina	4,4	46	1,6	9,0
N	delorazepam	2,3	41	1,4	10,2
M	tiocolchicoside	0,6	39	1,4	0,1
N	triazolam	3,3	37	1,3	8,0
G	gestodene/etinilestradiolo	6,2	37	1,3	-5,9
N	levoacetilcarnitina	0,7	35	1,2	7,8
N	betaistina	2,1	34	1,2	12,6
G	varafenafil	0,2	33	1,1	-11,4
G	etonogestrel/etinilestradiolo	2,1	32	1,1	8,8
S	desametassone/tobramicina	1,4	31	1,1	8,5

* calcolata sul totale della spesa

Pharma giant Pfizer pulls out of research into Alzheimer's

Wed, Jan 17, 2018

WaltaHealth

Drug company Pfizer has announced it is pulling out of research into drugs to treat Alzheimer's disease. The US-based pharmaceutical giant said it would be ending its neuroscience discovery programmes following a review, and 300 jobs would be lost.

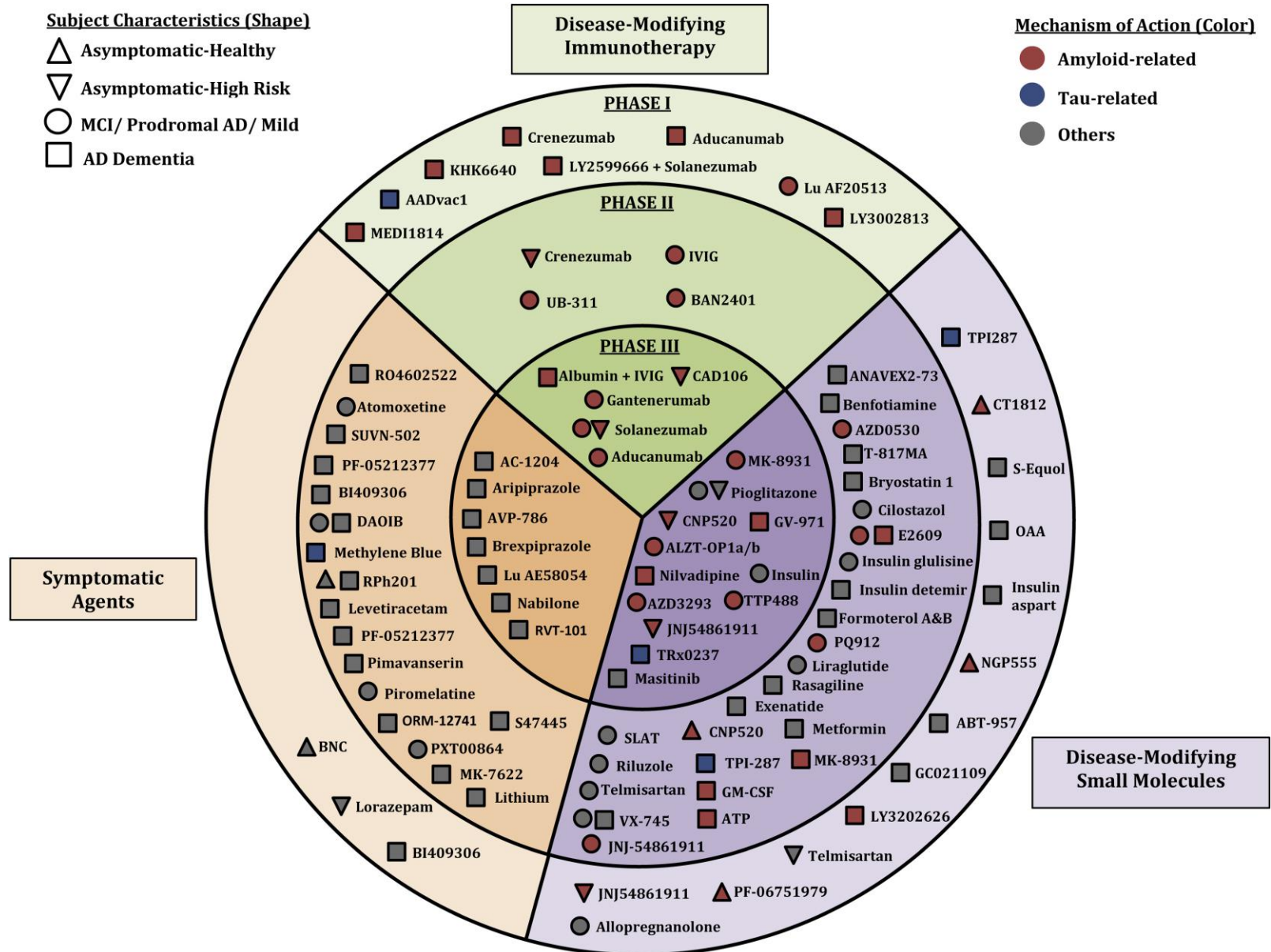
The Alzheimer's Society called the news "disappointing" and a "heavy blow" to those living with dementia. Companies should be encouraged to invest in research into neuroscience, Alzheimer's Research UK said.

The move means Pfizer will also stop looking for treatments for Parkinson's disease, but the company said it planned to create a new fund dedicated to neuroscience research in the future.

A statement from the company said: "We have made the decision to end our neuroscience discovery and early development efforts and re-allocate funding to those areas where we have strong scientific leadership and that will allow us to provide the greatest impact for patients."

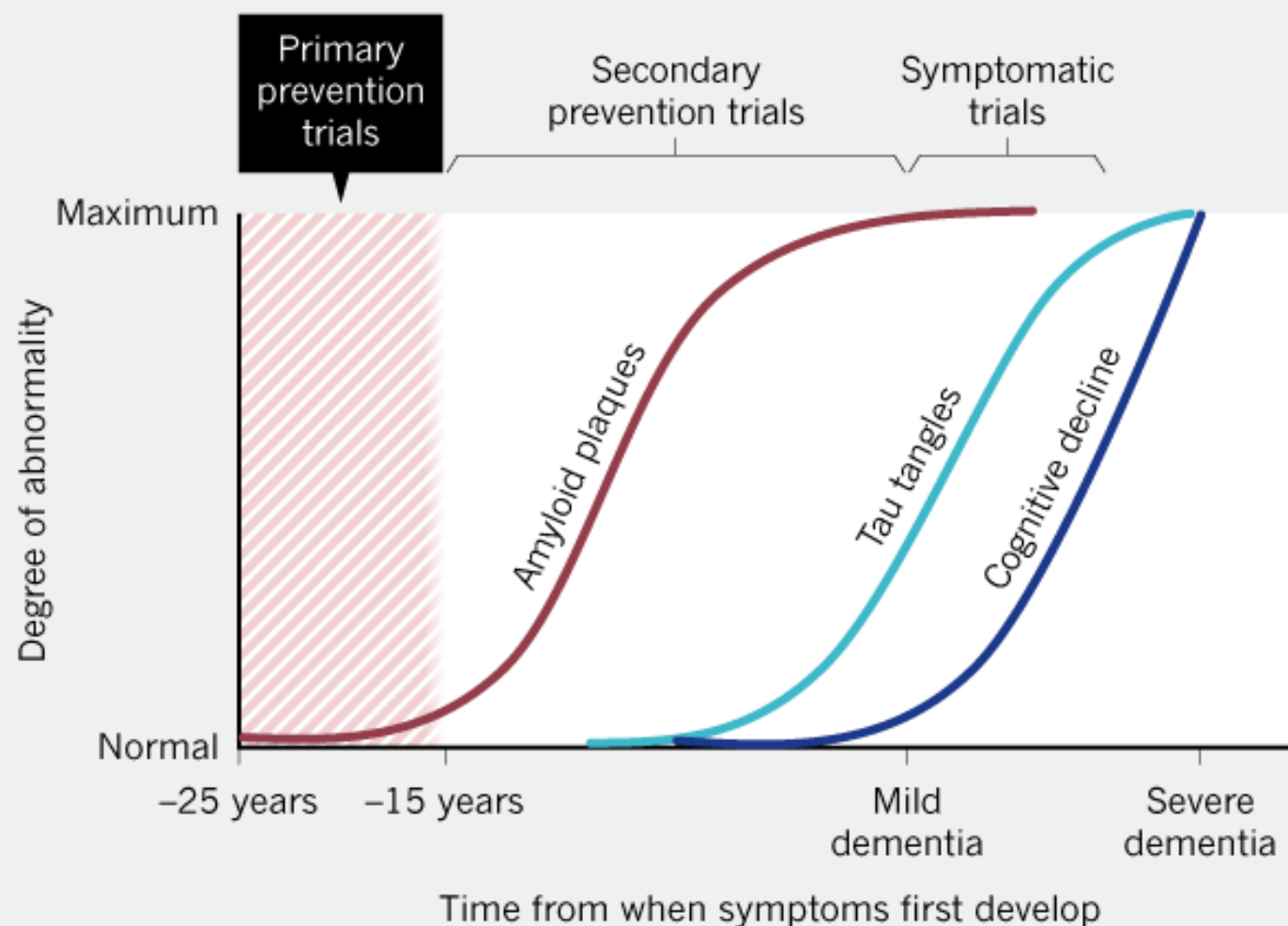


Esplorazione nuovi potenziali trattamenti (Clinical trials 2016)



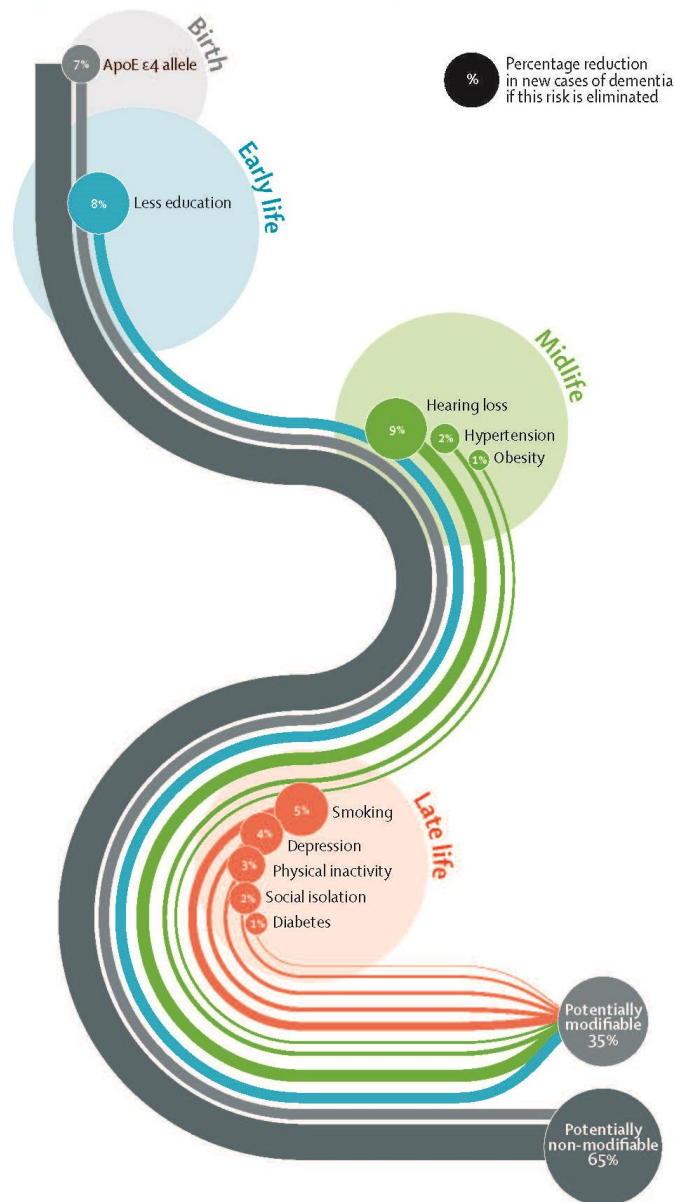
STAYING AHEAD

Primary prevention trials would investigate drugs designed to treat Alzheimer's disease before brain pathology, such as amyloid- β plaques and tau tangles, or cognitive symptoms develop.



Risk factors for dementia

The Lancet Commission presents a new life-course model showing potentially modifiable, and non-modifiable, risk factors for dementia.



Potentially modifiable risk factors for Dementia

Less education 8%

Hearing loss 9%

Hypertension 2%

Obesity 1%

Smoking 5%

Depression 4%

Physical inactivity 3%

Social isolation 2%

Diabetes 1%

The Lancet Commissions. Lancet On Line, July 20, 2017



Mass media power



Bill Gates announces \$30 Million investment to support AD research

Tuesday 17 July 2018



On 17 July, Microsoft co-founder and billionaire philanthropist Bill Gates announced his next investment in AD with the launch of the Diagnostics Accelerator - a "venture philanthropy" fund backed by Bill Gates and Alzheimer's Drug Discovery Foundation (ADDF) co-founder Leonard Lauder.

They are joined by other philanthropists, including the Dolby family and the Charles and Helen Schwab Foundation. This coalition of philanthropists has committed more than \$30 million to accelerate innovative new ideas for earlier and better diagnosis of AD and related dementias.

JANUARY 18, 2010

Joe Klein:
The CIA's
Afghan Disaster

Yemen: The
New Center
Of Terror

Why the Recession
Hasn't Been Cool
To Teens

TIME

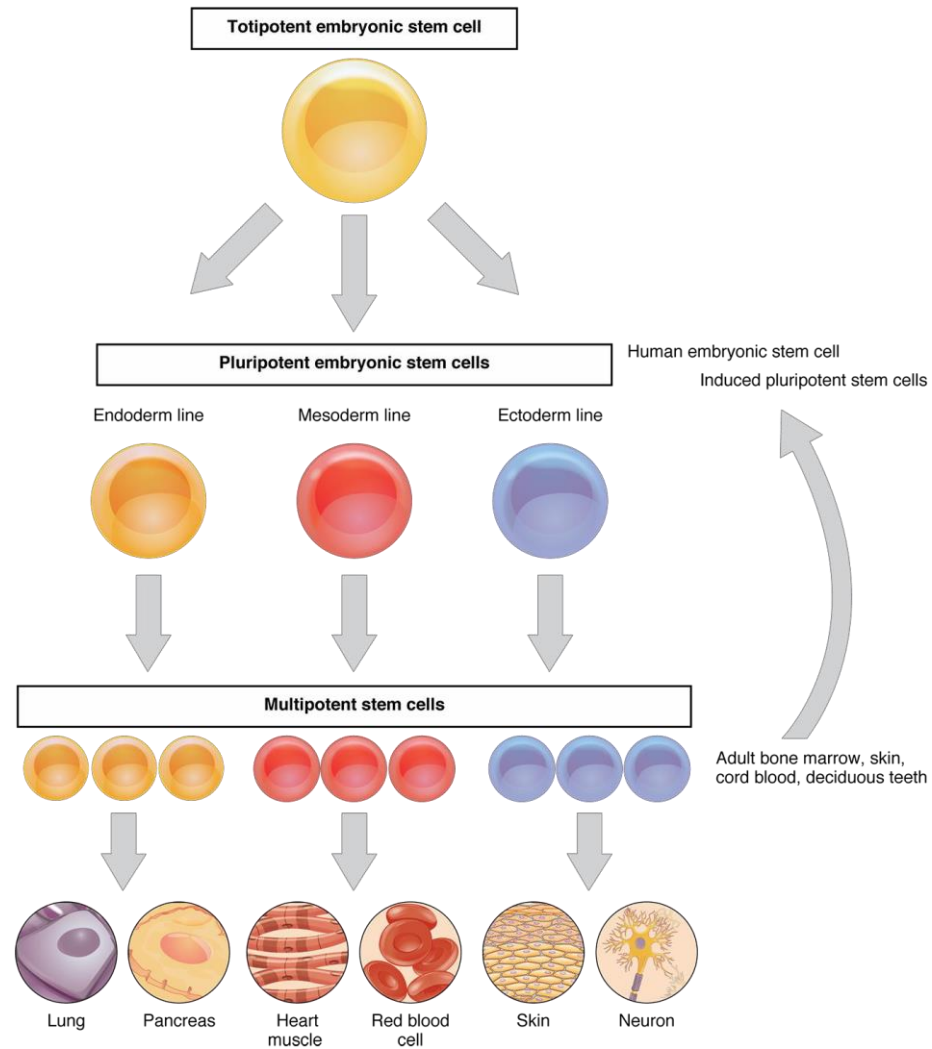
WHY YOUR DNA ISN'T YOUR DESTINY

The new science of epigenetics
reveals how the choices you
make can change your genes
—and those of your kids

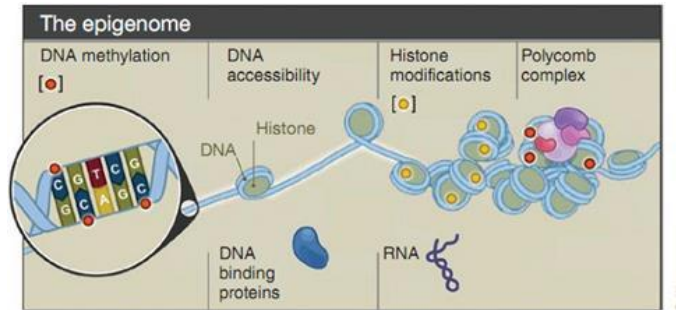
BY JOHN CLOUD

WWW.TIME.COM

200 different cell types ----- Only 1 genome



Epigenoma



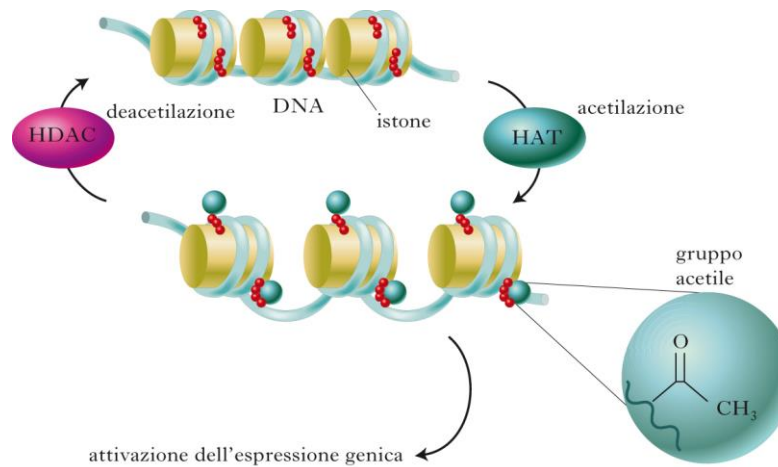
E' il risultato del processo attraverso il quale si determina l'attivazione di specifici set di geni in specifiche cellule.

Il programma del profilo di espressione genica è definito «epigenoma».

L'epigenoma è ereditabile, auto- conservante e reversibile

L'epigenoma è composto da due moduli:

- i) una componente parte integrante e covalente del DNA, le citosine metilate localizzate nelle regioni ricche in CG
- ii) una componente non –covalente costituita dalla cromatina e gli enzimi regolatori degli istoni



L'epigenomica è regolata da fattori intrinseci (processi di attivazione trascrizionale programmata) o fattori estrinseci

I fattori estrinseci possono essere **segnali sensoriali** o **sostanze esterne**

Epigenetics and the Agouti Yellow Mouse:

How the Maternal Environment Influences Disease in Offspring



Pregnant Mouse

Normal Diet



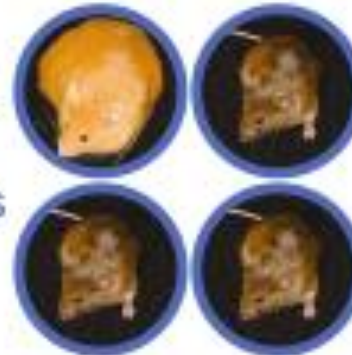
Offspring



Mainly:

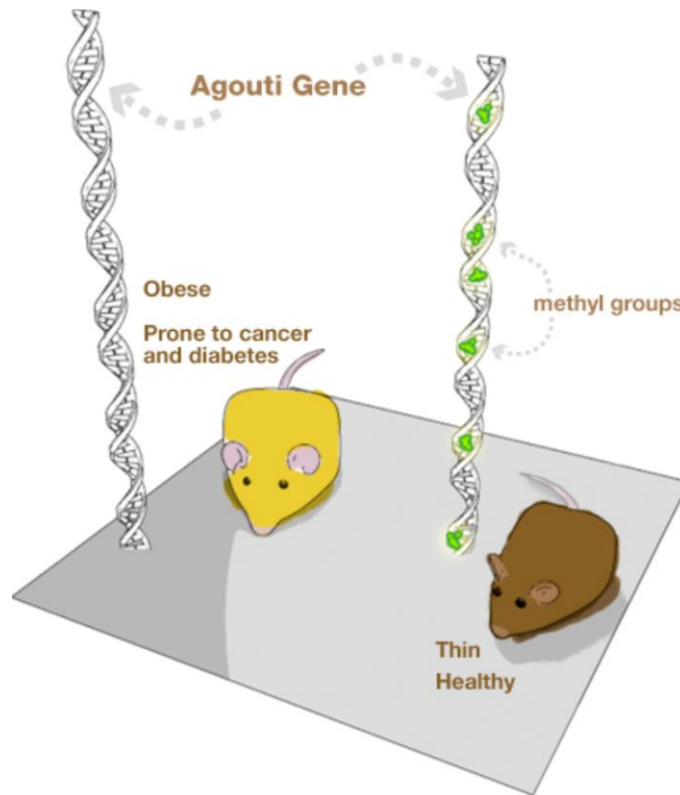
- Yellow
- Obese
- Prone to disease

Diet Rich in Methyl Groups

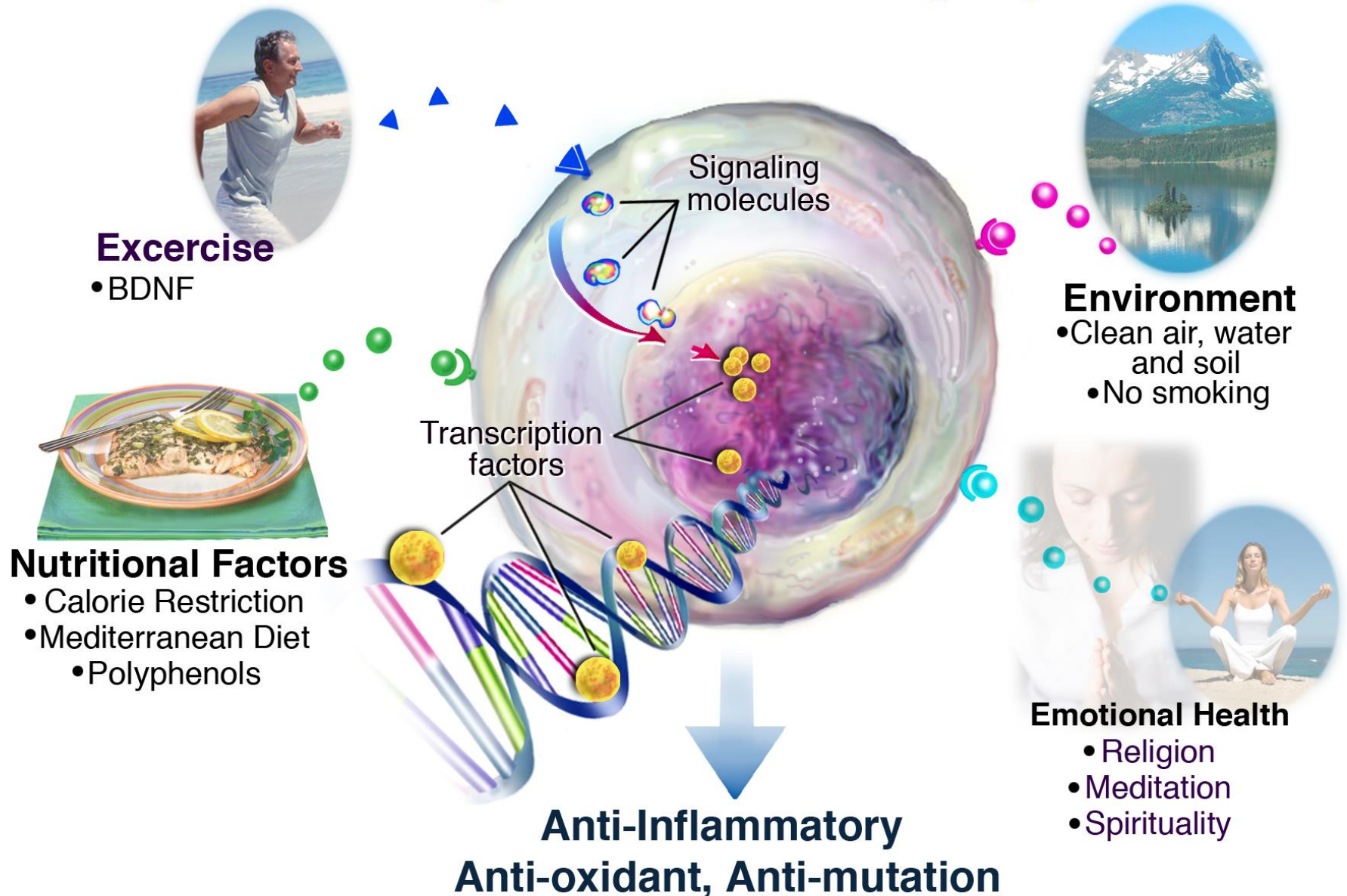


- Brown
- Lean
- Not prone to disease

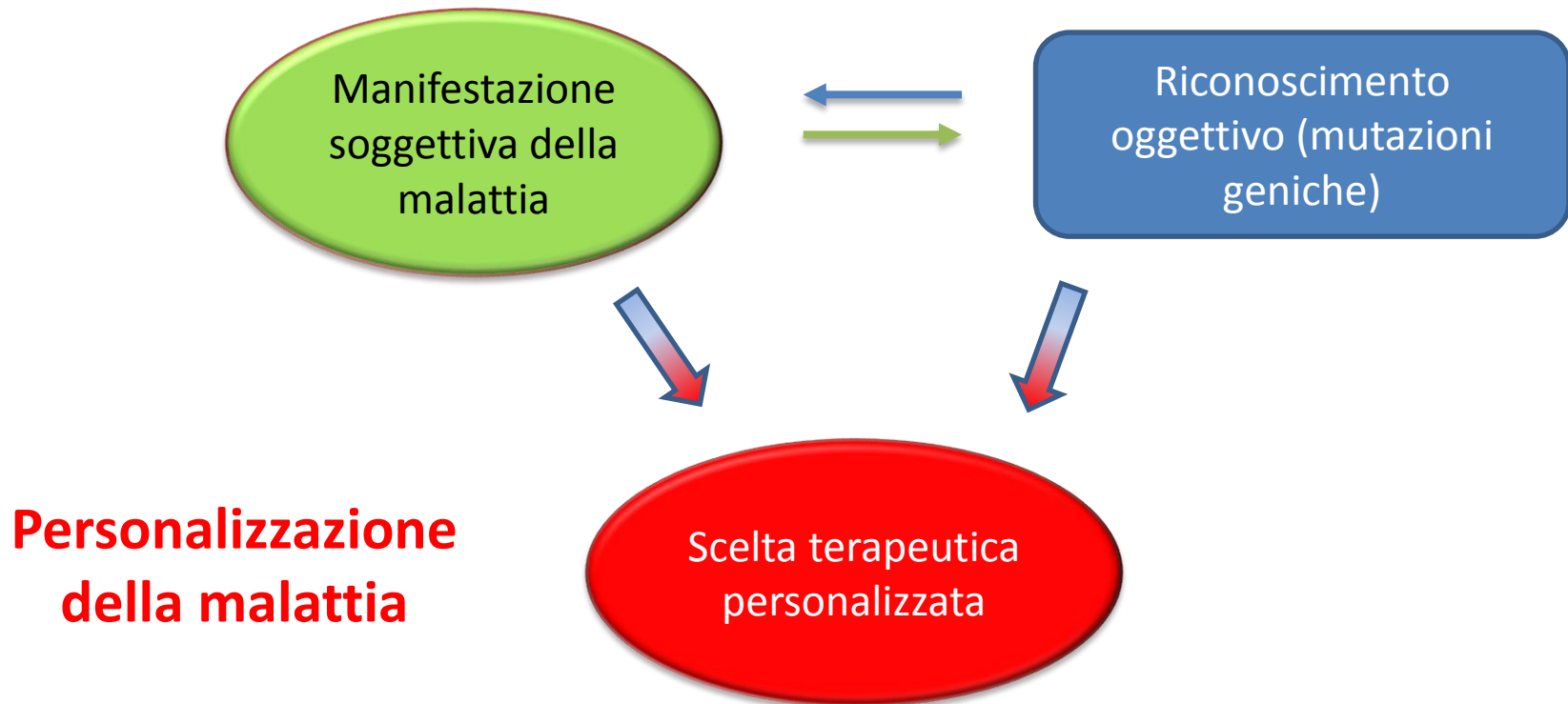
Experiments in mice show just how important a mother's diet is in shaping the epigenome of her offspring



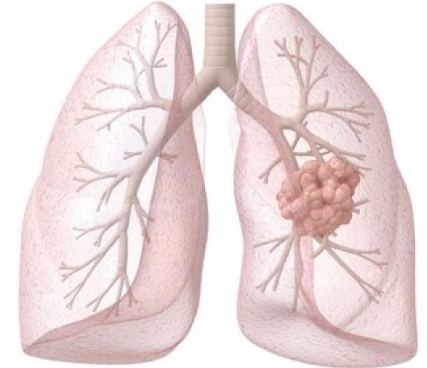
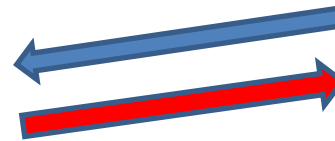
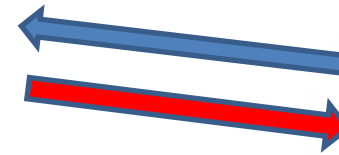
Epigenetics and Gene Activation for Improved Health and Longevity



Il rapporto reciproco e interattivo tra patrimonio genetico individuale, epigenetica e malattia genera un nuovo modello di «malato»



Individuo con malattia

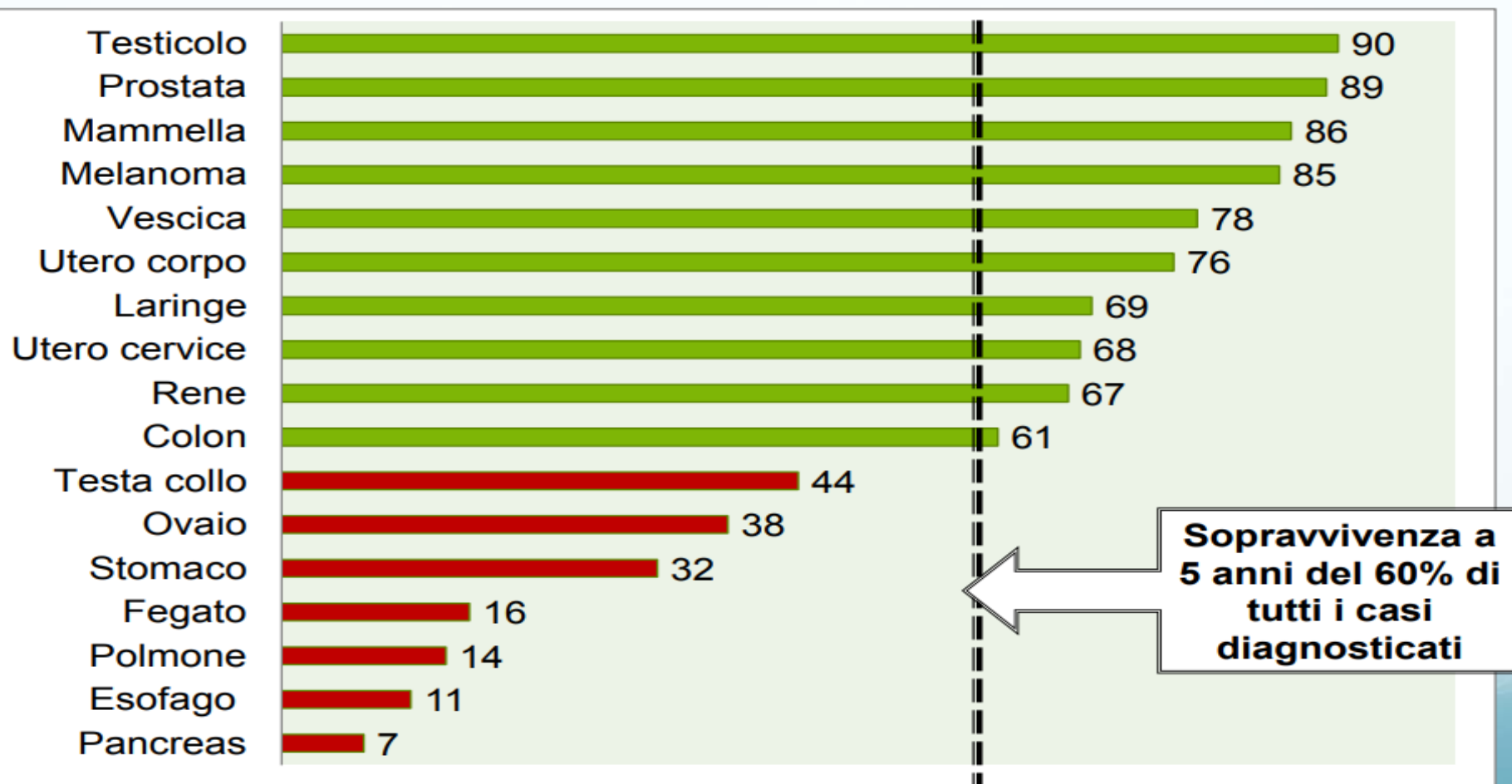


La sopravvivenza dai tumori in Italia

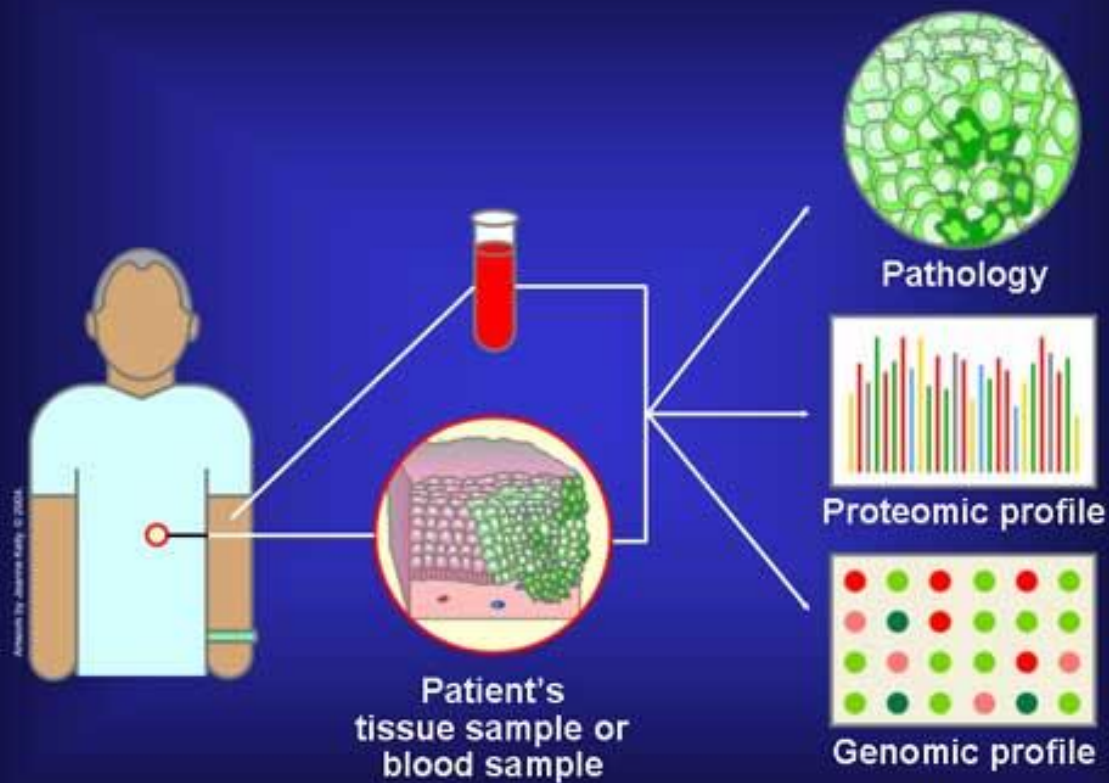
- In Italia, la sopravvivenza media a cinque anni dalla diagnosi di un tumore maligno è **del 57% fra gli uomini e del 63% fra le donne**.
- **La sopravvivenza è aumentata nel corso del tempo** e cambia, migliorando, man mano che ci si allontana dal momento della diagnosi.
- È particolarmente elevata la sopravvivenza dopo un quinquennio in **tumori frequenti** come quello del seno (87%) e della prostata (91%).
- Il cancro è ancora la seconda causa di morte (il 30% di tutti i decessi) dopo le malattie cardiovascolari, ma chi sopravvive cinque anni dalla diagnosi ha, per alcuni tumori (testicolo, corpo dell'utero, ma anche melanoma, linfomi di Hodgkin e in misura minore colon-retto), **prospettive di sopravvivenza vicine a quelle della popolazione che non ha mai avuto una neoplasia**.

INCIDENZA E SOPRAVVIVENZA TUMORI

Sopravvivenza (%) a 5 anni per sede tumorale in Italia

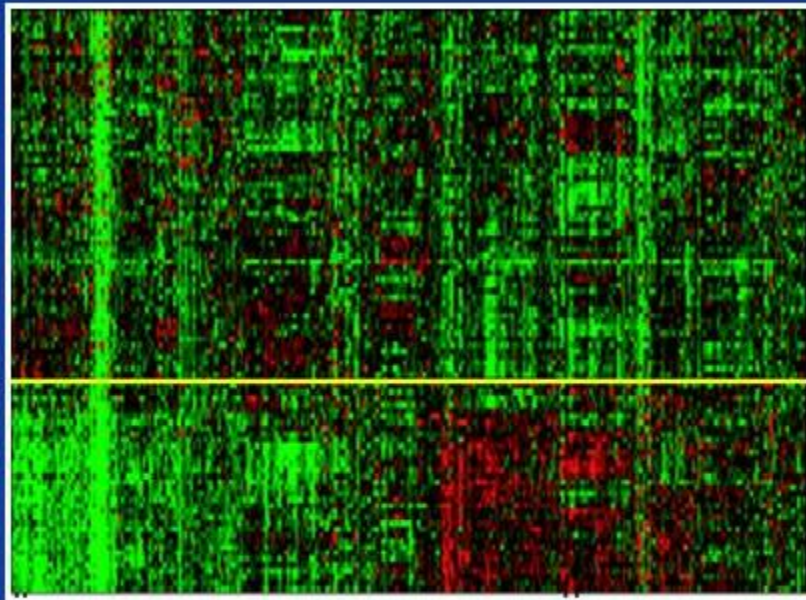


Biopsy

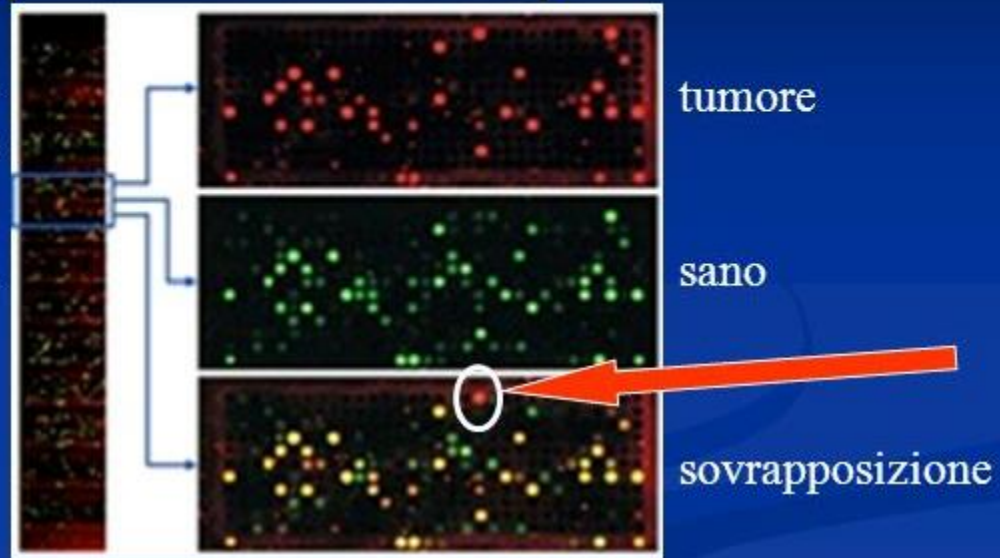


microarray o DNA chip

consente di analizzare **migliaia di geni** di un tumore, per identificare quali geni con potenziale attività tumorale sono attivi nelle cellule di un paziente



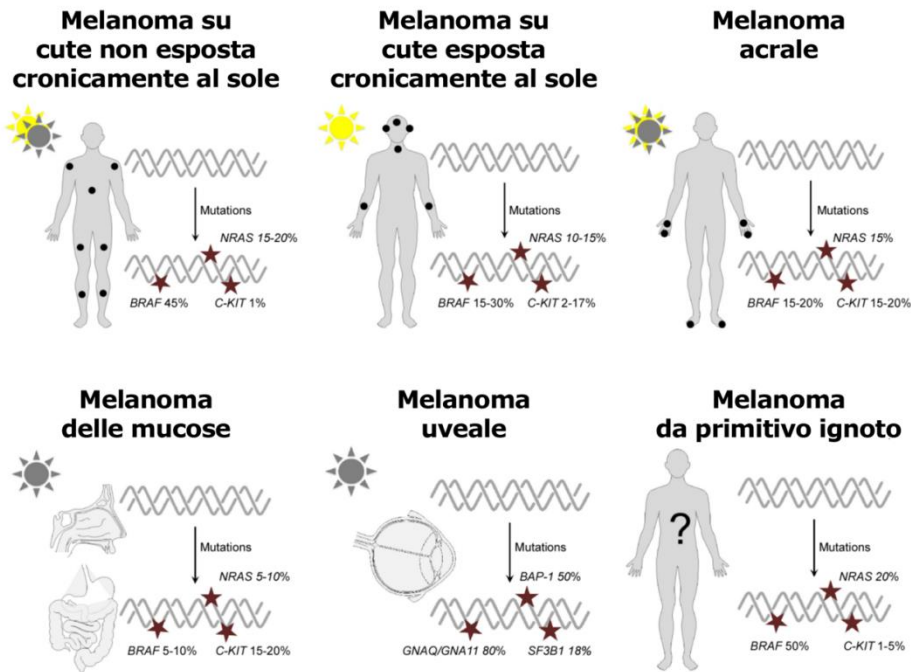
Esempio di “microgriglia”



Viene fatto il cosiddetto

“profilo molecolare” di un cancro

Diagnosi molecolare dei tumori



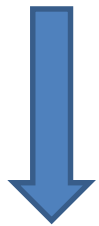
Le più importanti innovazioni degli ultimi anni hanno riguardato il trattamento del melanoma avanzato.

I principali traguardi sono stati l'approvazione di nuovi farmaci specifici:

- Inibitori della proteina BRAF (terapia mirata)
- Inibitori di MEK (terapia mirata)
- Inibitori dei checkpoint immunitari (immunoterapia).

Personalized therapy for personalized tumour

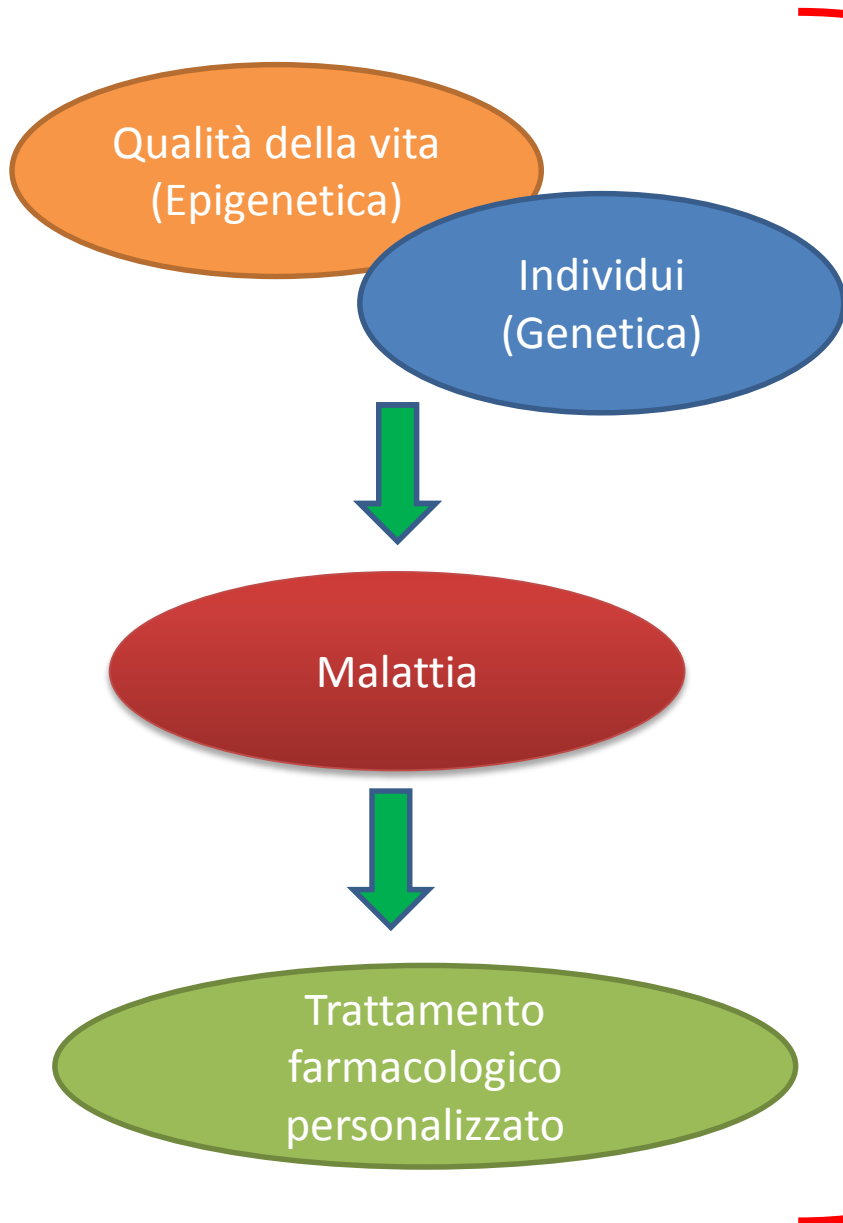
- Non tutti i tumori sono
 - PD1 positivi
 - HER positivi
 - ER positivi
 - etc



Numero di
pazienti da
trattare

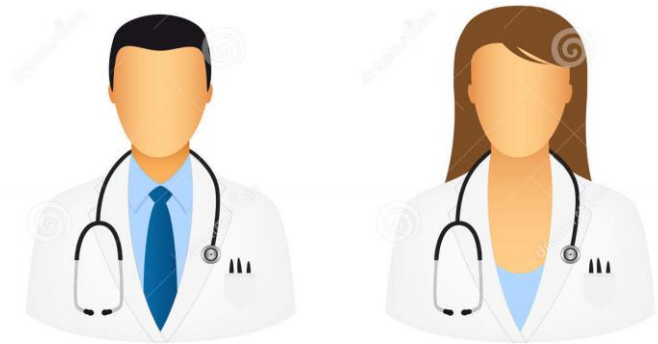


La possibilità di successo:
sopravvivenza "libera da
malattia a cinque anni»



La medicina personalizzata comporta la necessità di

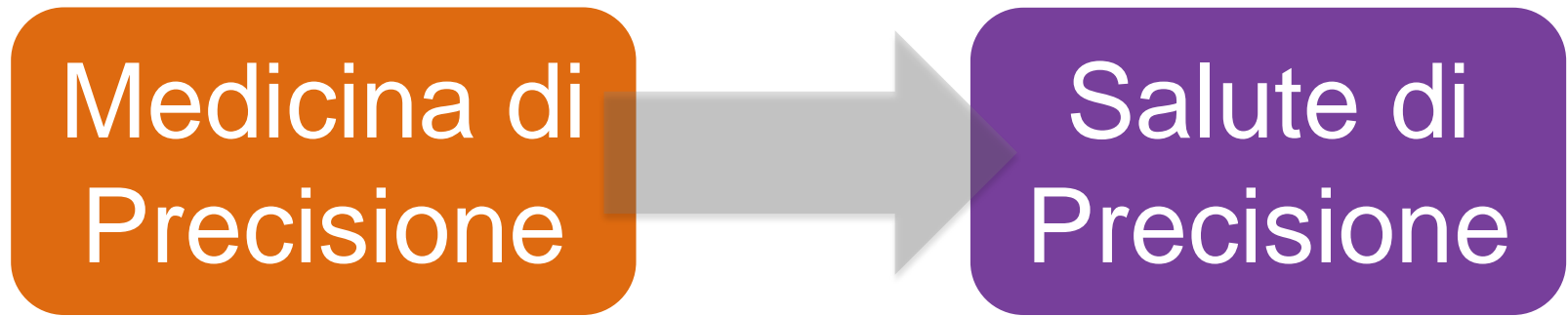
- acquisizione di notevoli informazioni
- elaborazione dei dati attraverso algoritmi validati



La medicina personalizzata potrà generare

- una maggiore percentuale di successo terapeutico
- una minore discrezionalità del medico

Il Passaggio incombente



Salute: Stato di completo benessere fisico, psichico e sociale e non semplice assenza di malattia (Definizione OMS)

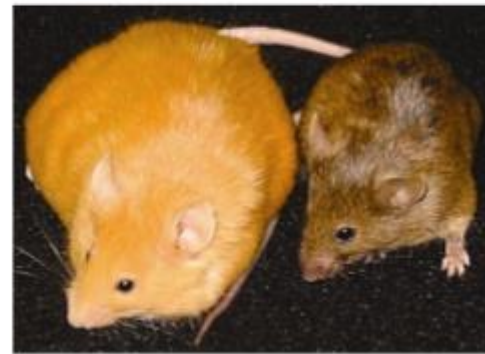
Maternal Diet Affects Epigenetic Gene Regulation in Isogenic Offspring (A^{vy}/a)

Young Mice

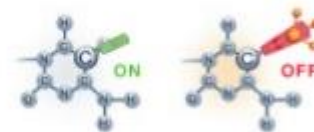
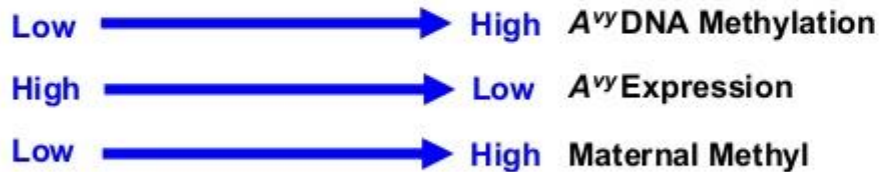


Yellow Slightly mottled Mottled Heavily mottled Pseudo-agouti

Adult Mice

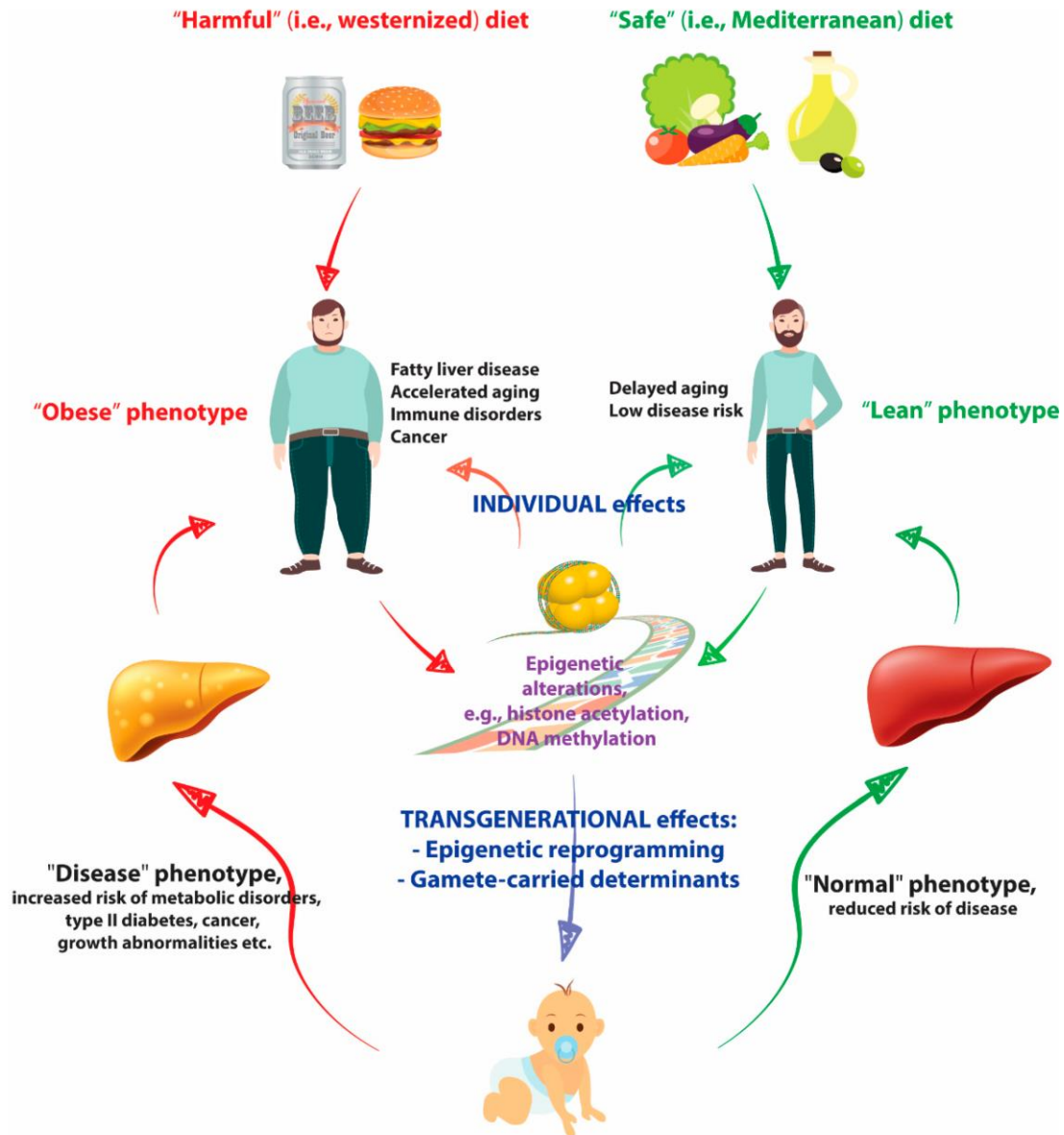


Obese Lean

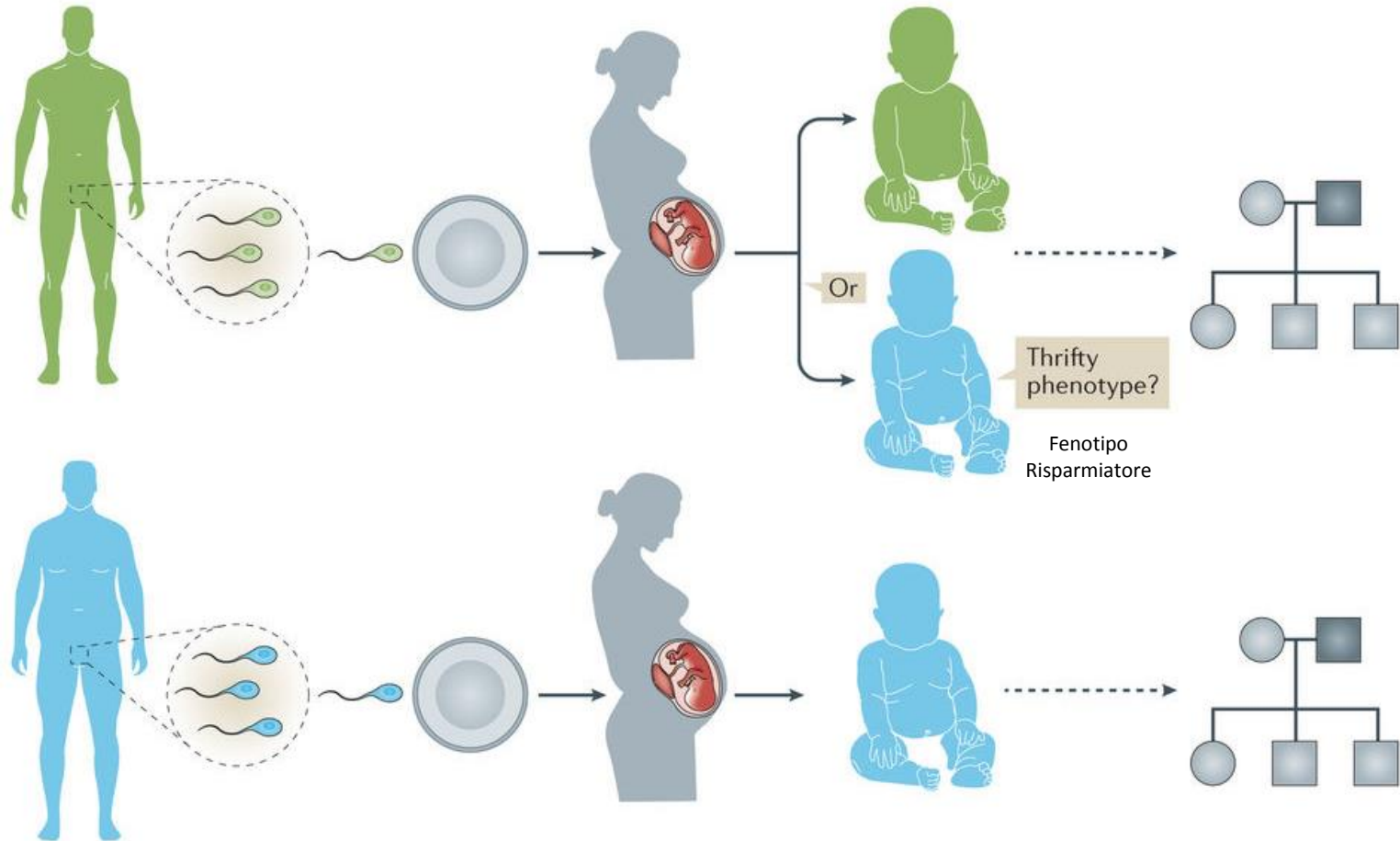


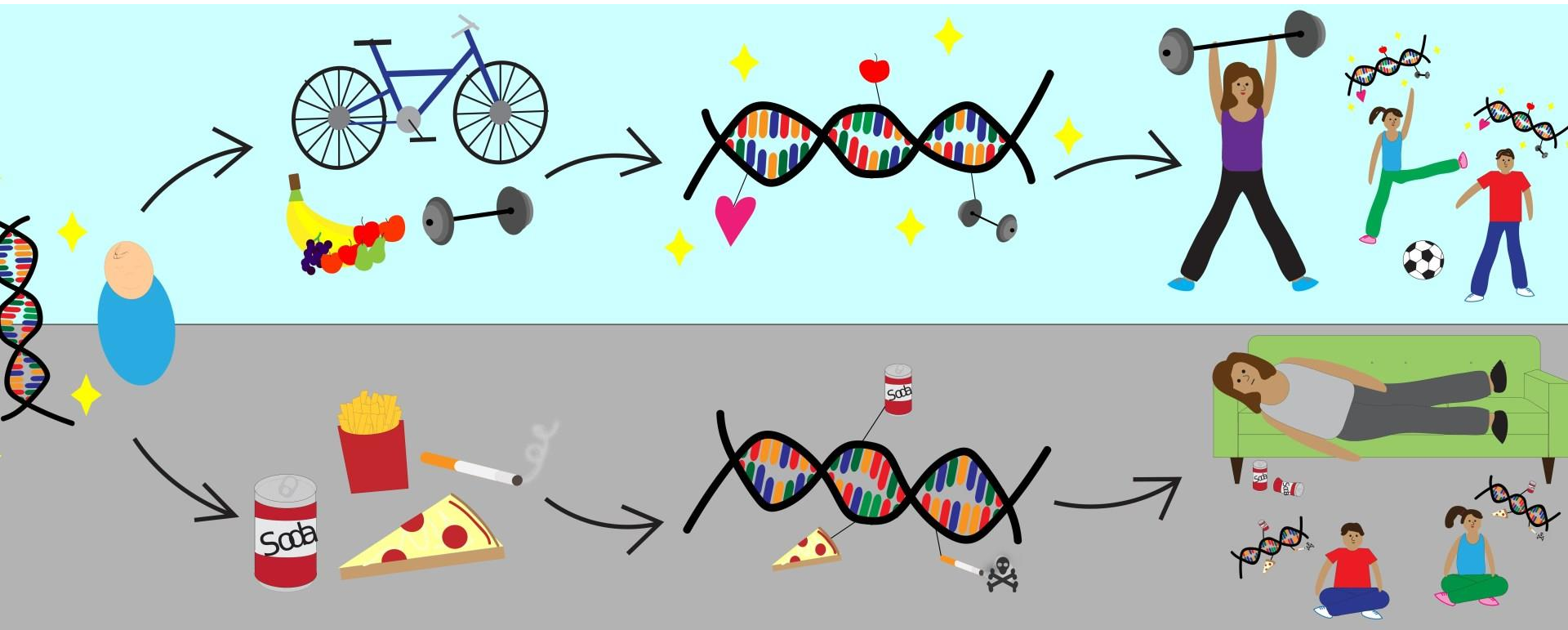
CAVAT

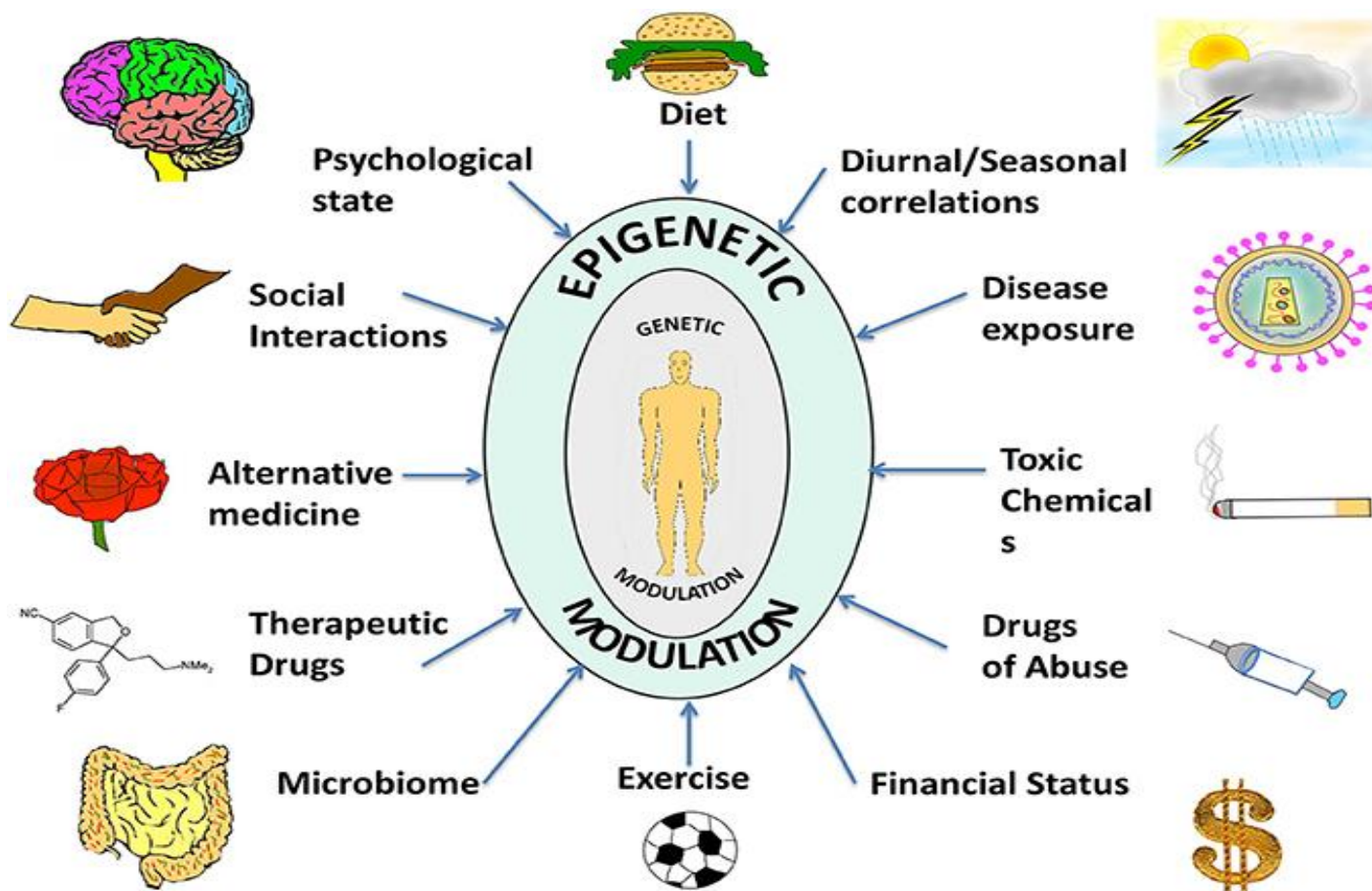
Randy Jirtle Duke
Waterland MCB 2003



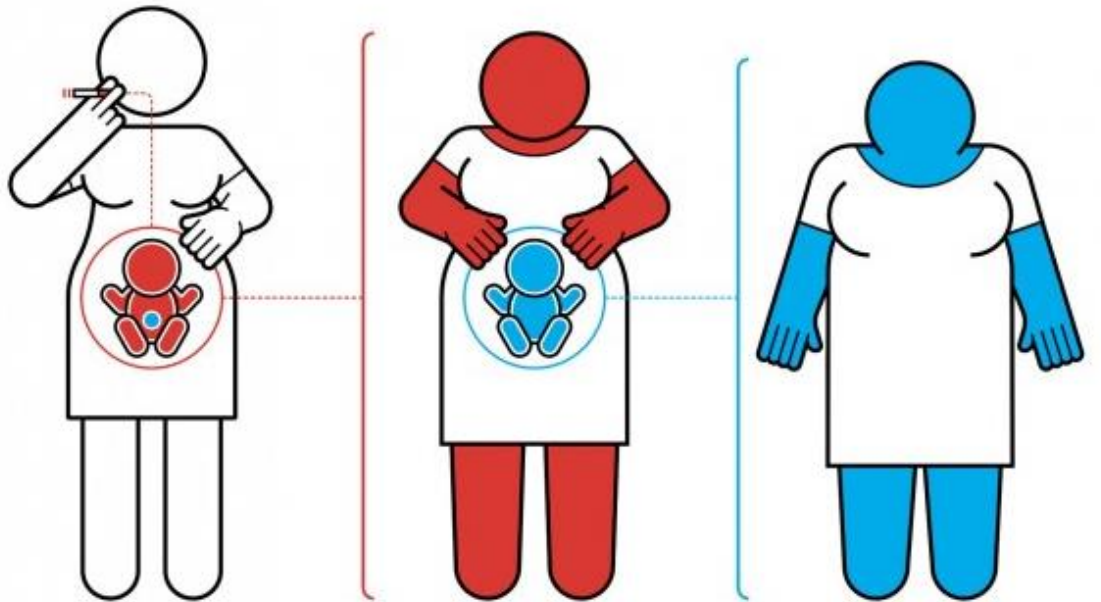
Effetti genitoriali dell'Esercizio e dell'Obesità sulla predisposizione alle malattie metaboliche







L'Eredità Epigenetica



I Generazione

II Generazione

III Generazione

I corretti Stili di Vita (soprattutto l'esercizio fisico e la dieta) hanno il potenziale di modificare l'epigenoma delle cellule riproduttive e potrebbero avere un effetto senza precedenti sulla salute delle future generazioni, influenzando la salute e il rischio di malattie delle generazioni successive.