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1240

La medicina di precisione nel metabolismo osseo

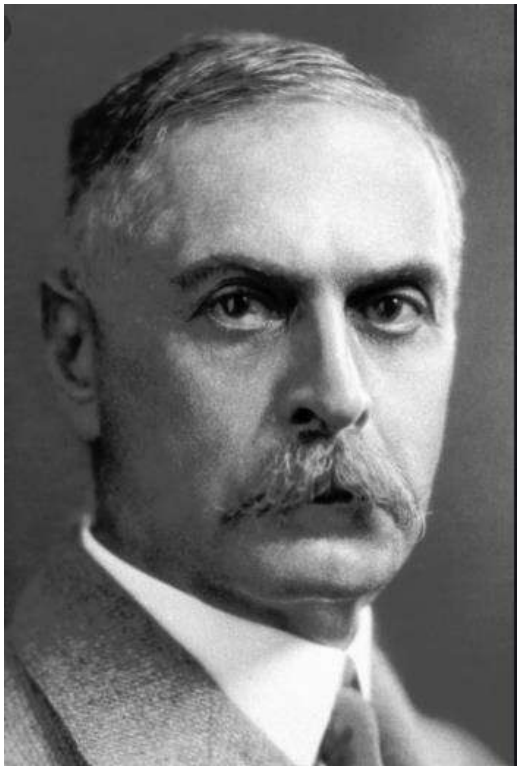
Ranuccio Nuti
Professore Emerito di Medicina Interna
Università di Siena

E’ molto più importante sapere quale tipo di paziente ha una malattia che quale malattia ha un paziente

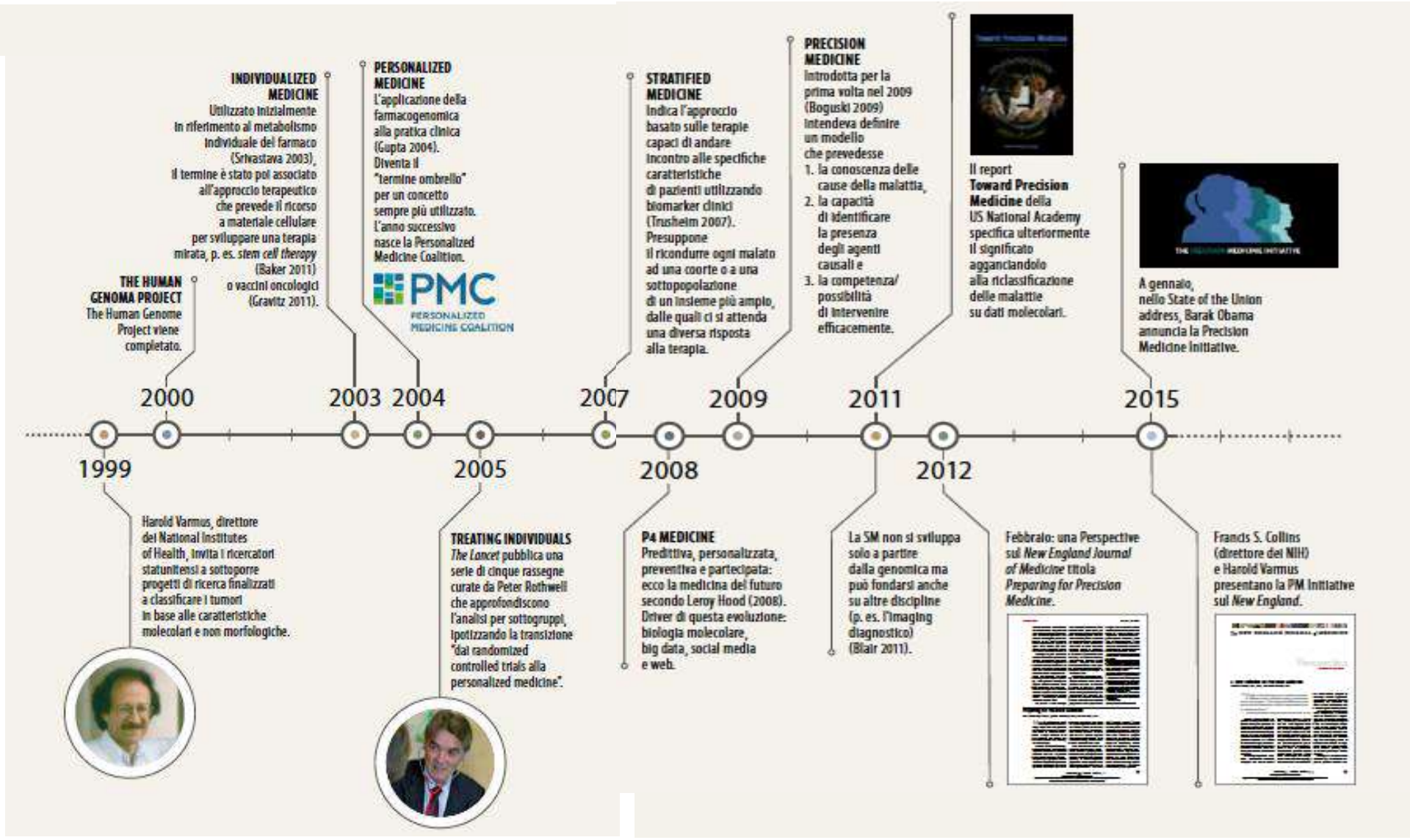
William Osler (1849-1919)

Karl Landsteiner

Identificazione delle isoagglutinine del sangue umano (1902), da cui l’utilizzo delle emotrasfusioni



Medicina di Precisione: le tappe di un percorso



THE PRECISION MEDICINE INITIATIVE®

In 2015, the president of the USA, Barack Obama, made the precision medicine initiative (PMI) announcement in his State of the Union Address.

The initiative has two major components:
a short-term focus on cancer
a long-term focus on acquiring better knowledge about health and disease.

NIH National Institutes of Health
Turning Discovery Into Health

U.S. Department of Health & Human Services

THE PRECISION MEDICINE INITIATIVE®

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.**

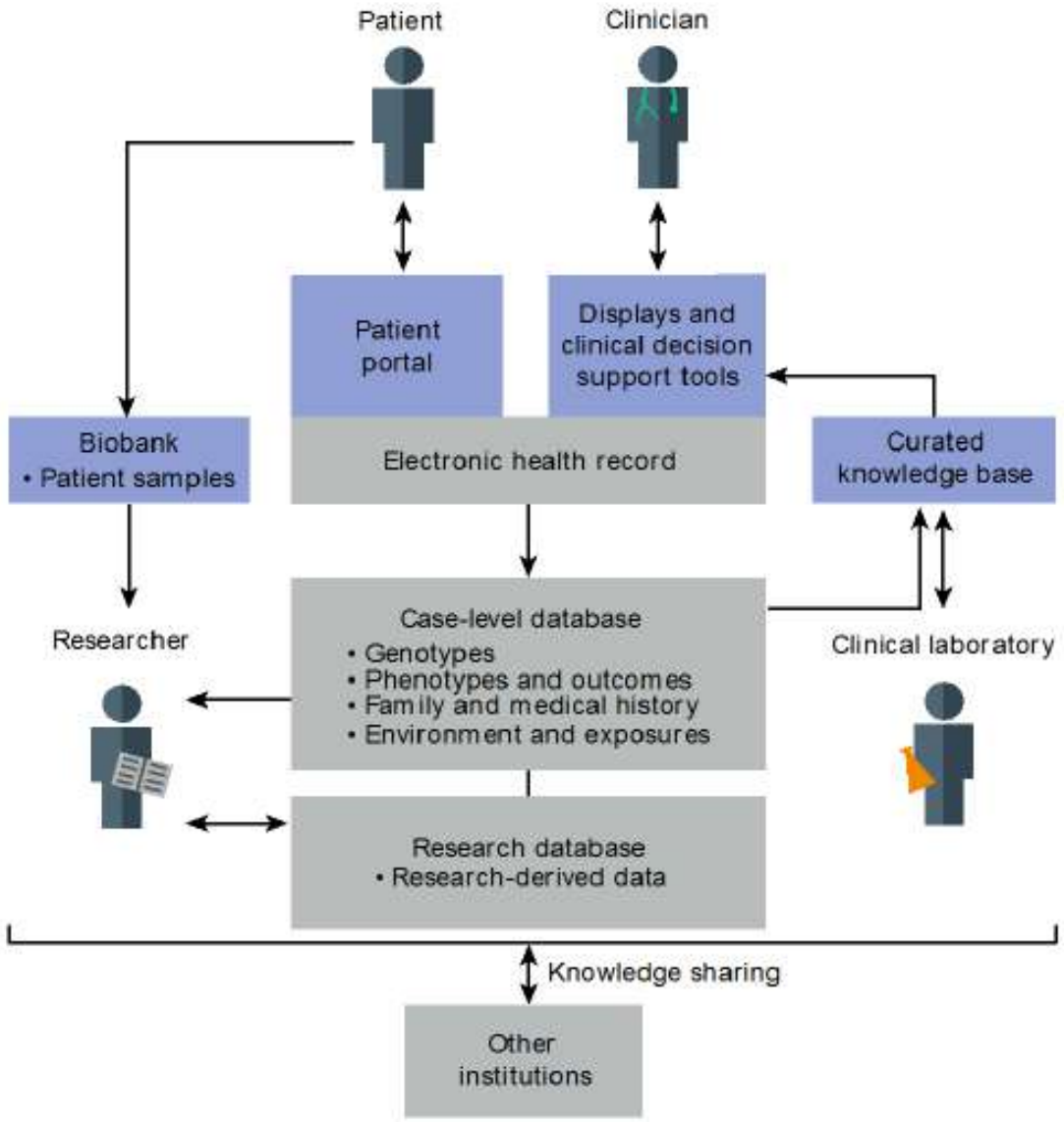
MEDICINA di PRECISIONE
Motivazioni

Sequenziamento del genoma umano

Miglioramento tecnologico dei sistemi biomedici di analisi
Epigenetica, Transcrittomica, Proteomica, Metabolomica

Nuovi strumenti per l'utilizzo di grandi dati di popolazione (big data)

Precision Medicine Ecosystem



Aronson SJ. Et al Nature. 2015; 526: 336-42.

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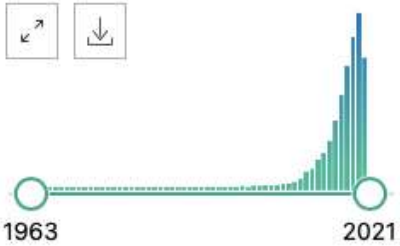

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TEXT AVAILABILITY

1 Cite Share

What is **precision medicine**?

König IR, Fuchs O, Hansen G, von Mutius E, Kopp MV.

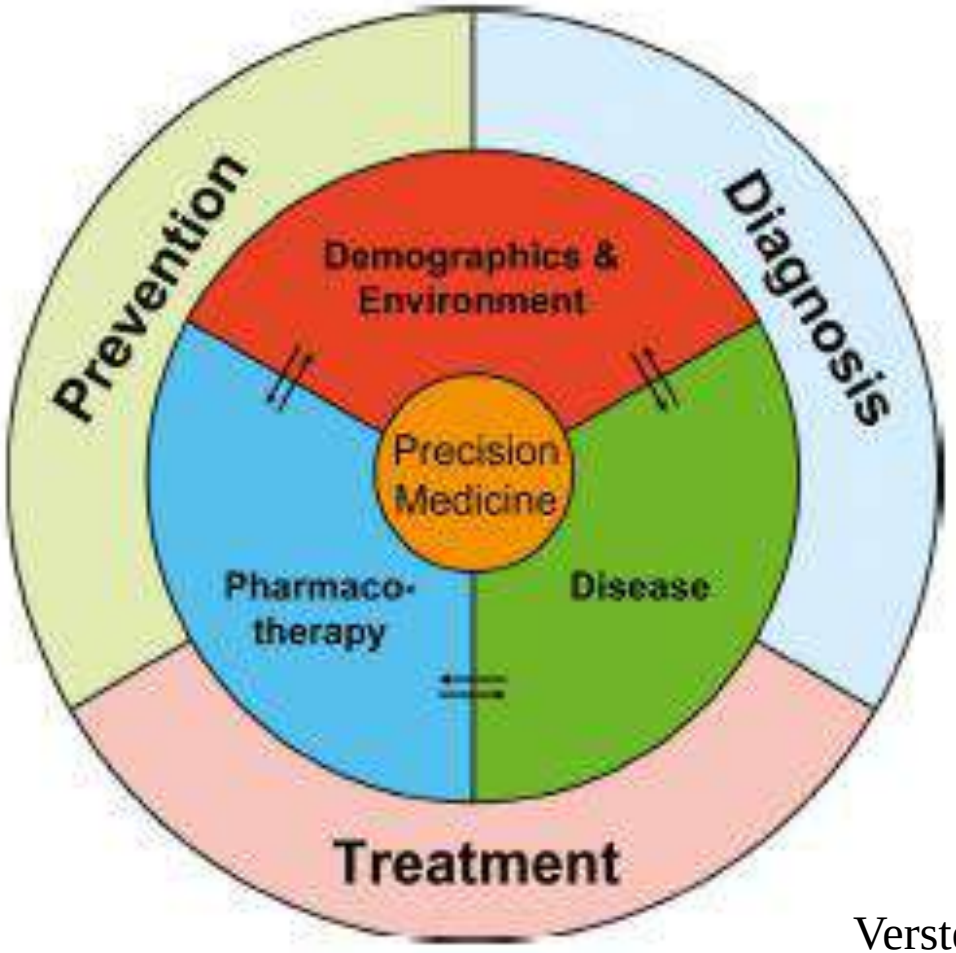
Eur Respir J. 2017 Oct 19;50(4):1700391. doi: 10.1183/13993003.00391-2017. Print 2017 Oct.

PMID: 29051268 **Free article.** Review.

The term "**precision medicine**" has become very popular over recent years, fuelled by scientific as well as political perspectives. ...For example, when does **precision medicine** begin? In which way does the stratification of patients translate into better ...

Feedback

Precision medicine can cover all phases of care: prevention, diagnostics, and treatment.
Factors that differentiate patients with the same disease from each other can be categorized in three categories: demographics and environment, disease, and pharmacotherapy



Verstegen R. et al 2019

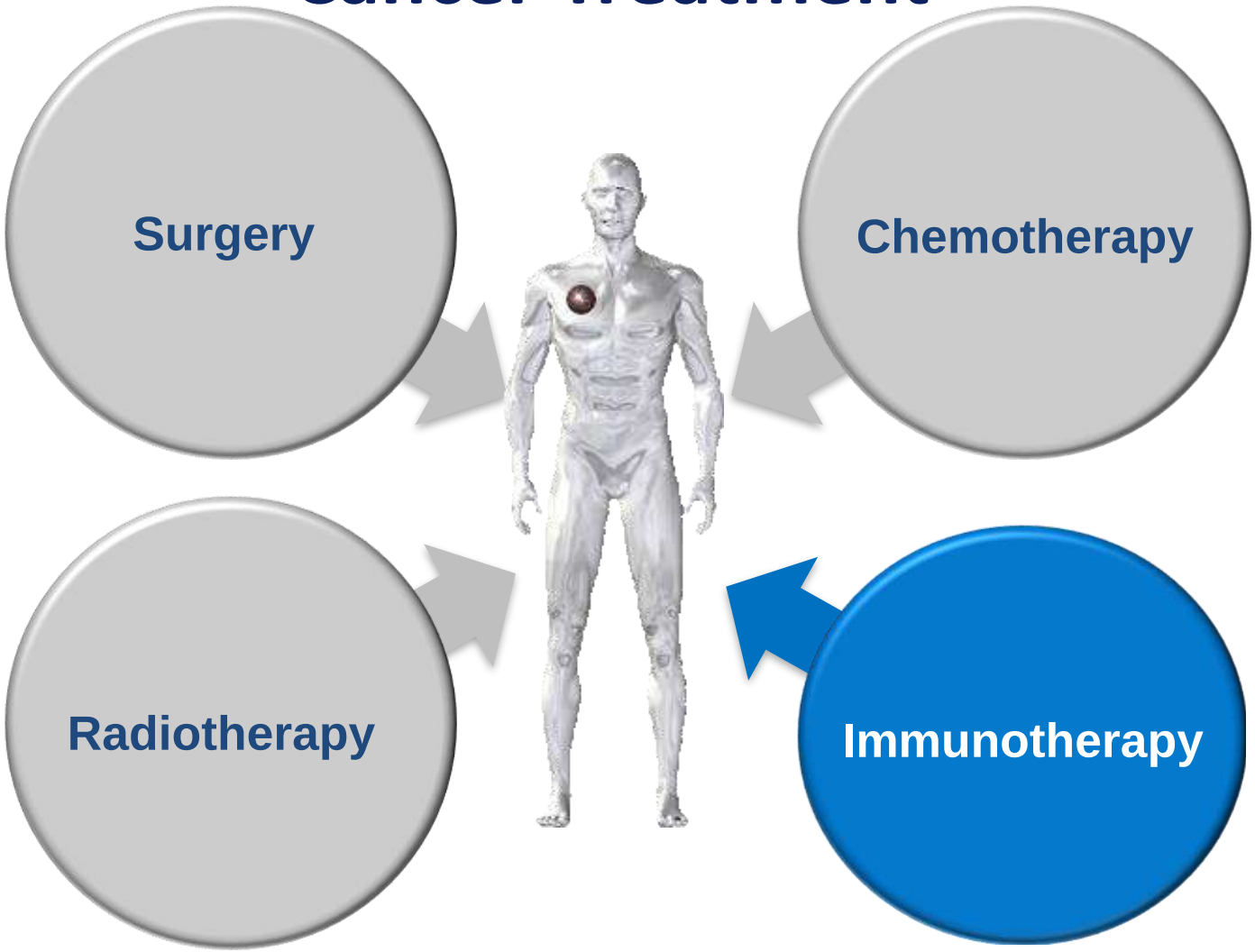
Efforts to apply precision medicine to cancer

Innovative clinical trials of targeted drugs for adult, pediatric cancers

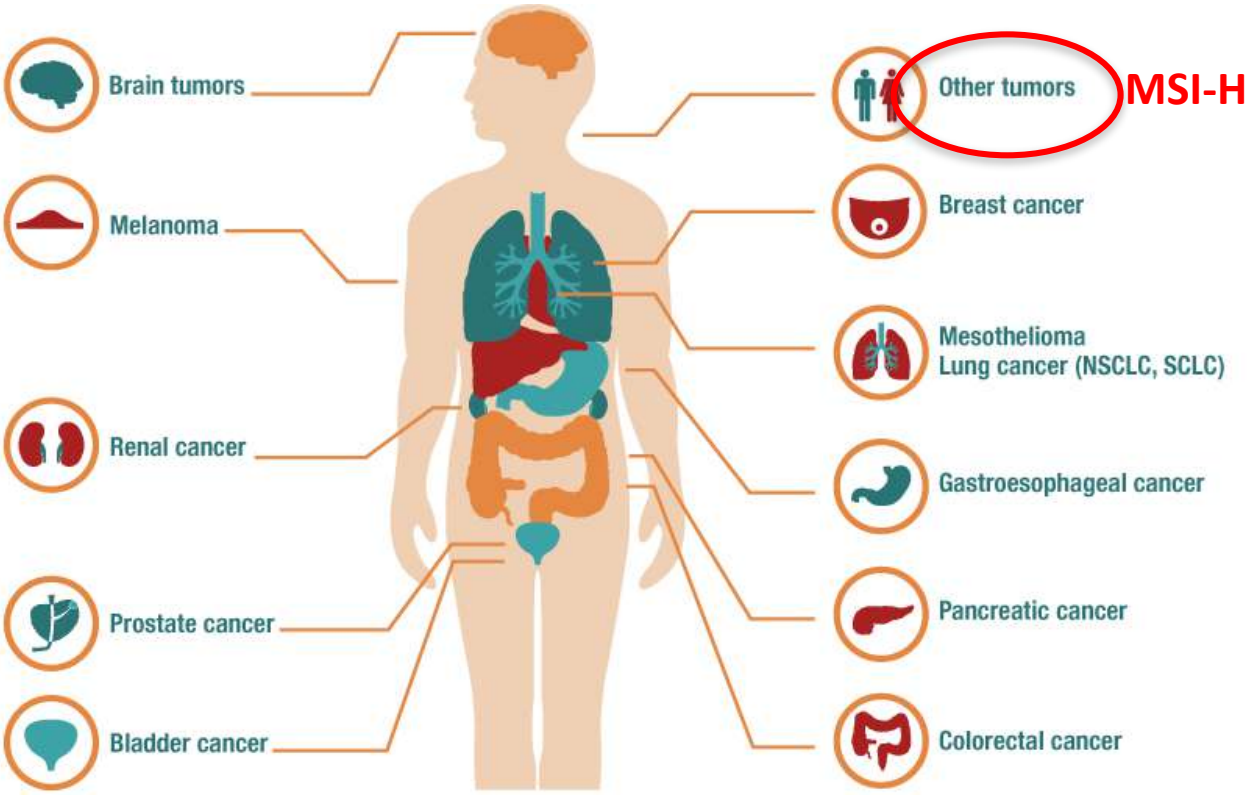
Use of combination therapies

Knowledge to overcome drug resistance

Evolving Therapeutic Options for Cancer Treatment



Immunotherapy in solid tumours with immunomodulating antibodies



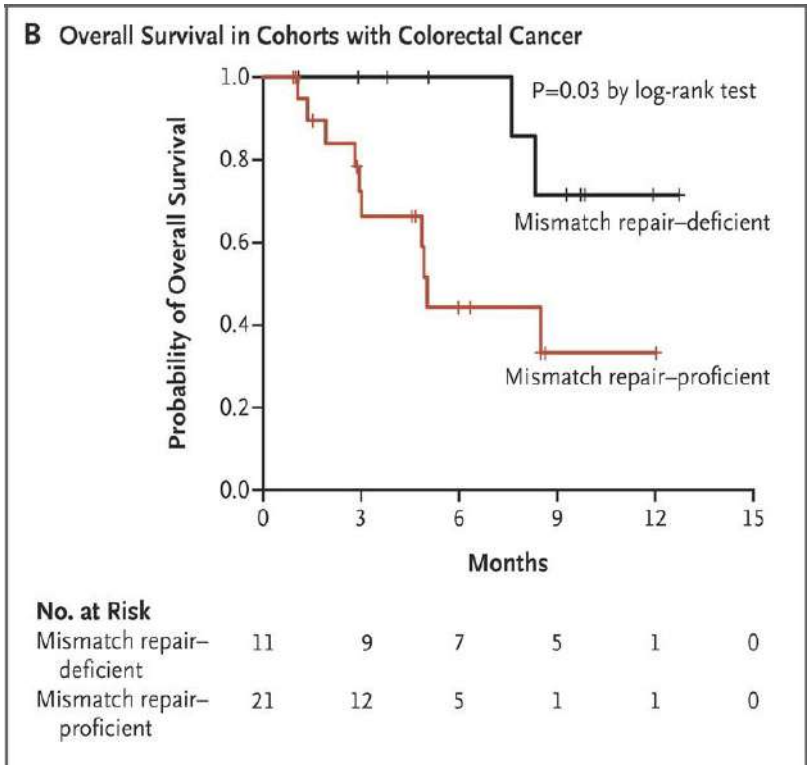
MSI-H (high level of microsatellite instability): defective mismatch repair (dMMR) system

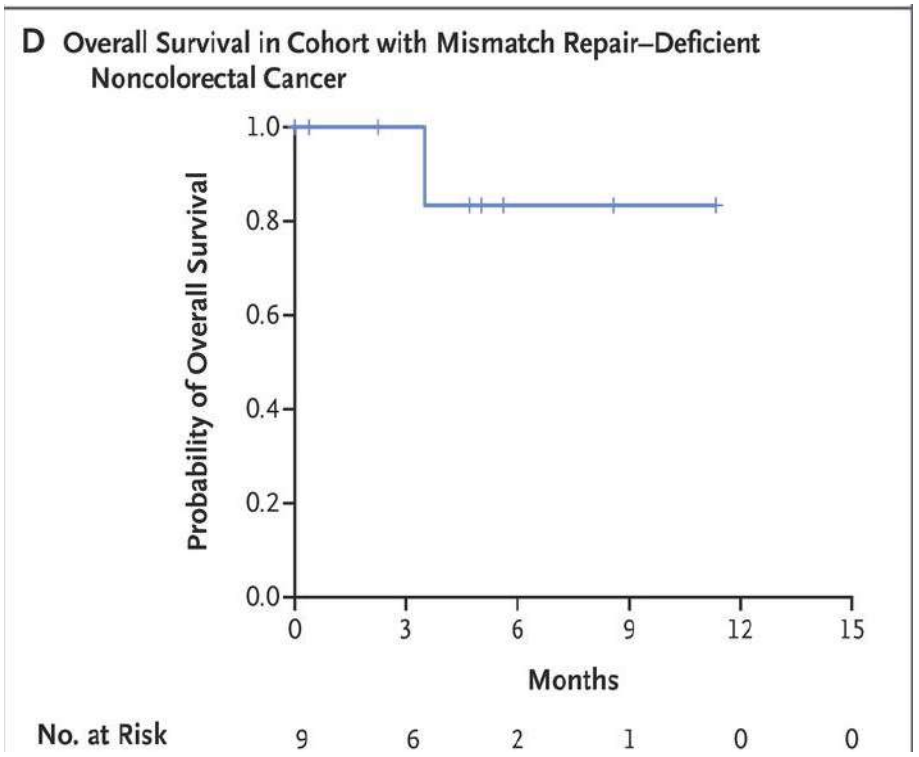
Microsatelliti: sequenze ripetute mono-, di- e tetranucleotidiche sparse in regioni codificanti e non codificanti del genoma; alterazioni in queste sequenze sono coinvolte in diverse patologie, incluso il cancro. Errori dovuti a scorretta incorporazione delle basi durante la sintesi del DNA vengono riparati principalmente dalle proteine del MMR

The NEW ENGLAND JOURNAL of MEDICINE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

Programmed Death 1 (PD-1) pathway: negative feedback system that repress Th1 cytotoxic immune responses. PD-1 blockcade: **pembrolizumab**



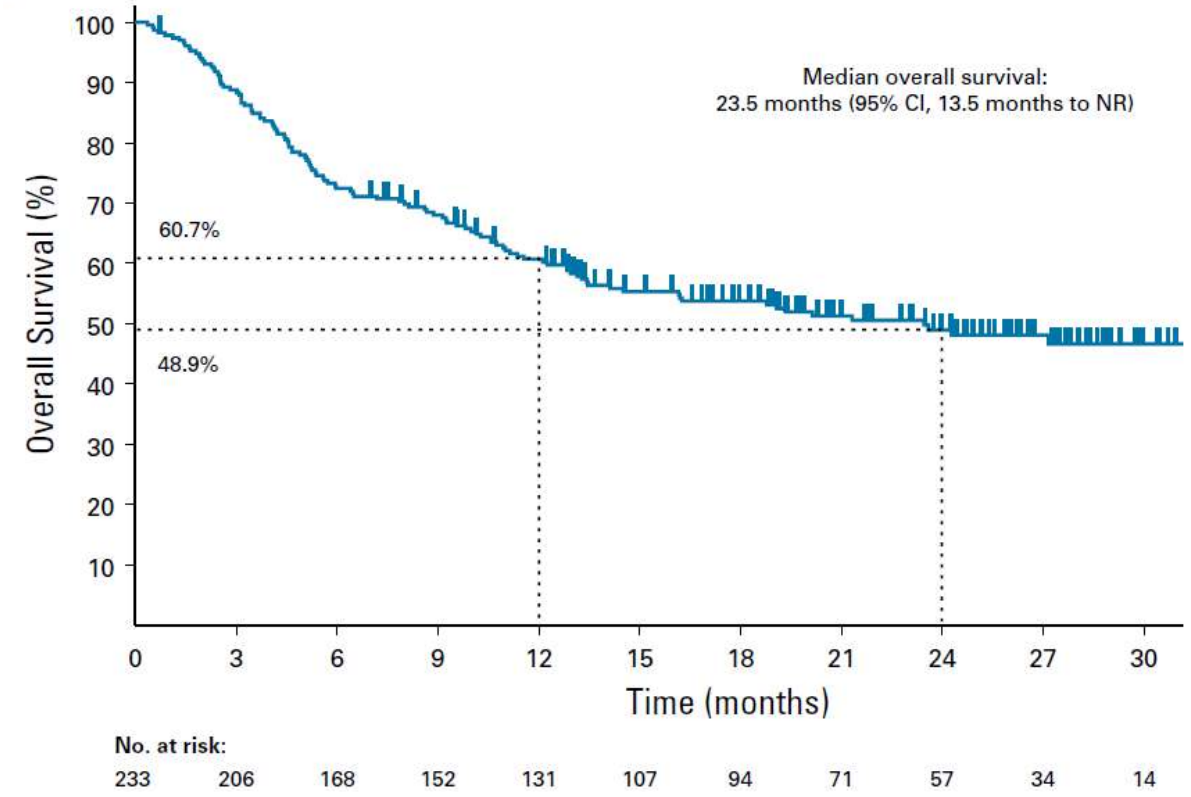


MMR-proficient tumors include those that are micro satellite stable (MSS) and MSI-low (MSI-L) or tumors with intact MMR proteins.

Le DT et al. NEJM 2015

Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/ Mismatch Repair–Deficient Cancer: Results From the Phase II KEYNOTE-158 Study

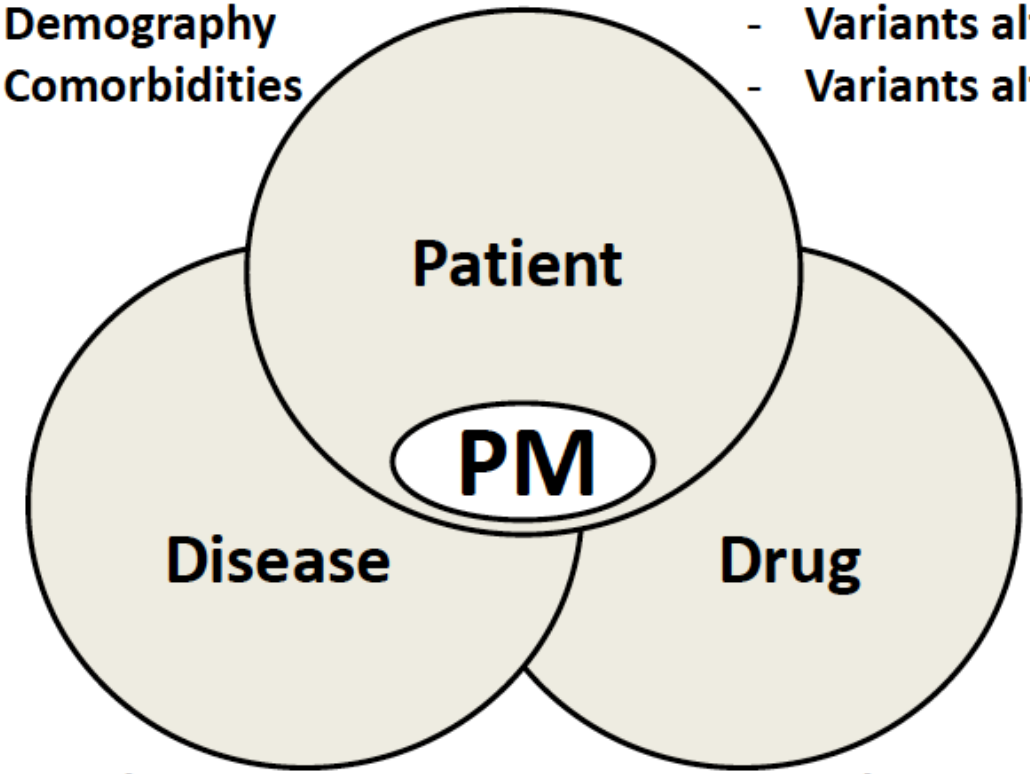
Aurelien Marabelle, MD, PhD[1]; Dung T. Le, MD[2]; Paolo A. Ascierto, MD[3]; Anna Maria Di Giacomo, MD[4]; Ana De Jesus-Acosta, MD[2]; Jean-Pierre Delord, MD, PhD[5]; Ravit Geva, MD, MSc[6]; Maya Gottfried, MD[7]; Nicolas Penel, MD, PhD[8]; Aaron R. Hansen, MBBS[9]; Sarina A. Piha-Paul, MD[10]; Toshihiko Doi, MD, PhD[11]; Bo Gao, MBBS, PhD[12]; Hyun Cheol Chung, MD, PhD[13]; Jose Lopez-Martin, MD, PhD[14]; Yung-Jue Bang, MD, PhD[15]; Ronnie Shapira Frommer, MD[16]; Manisha Shah, MD[17]; Razi Ghori, PhD[18]; Andrew K. Joe, MD[18]; Scott K. Pruitt, MD, PhD[18]; and Luis A. Diaz Jr, MD[19]



Precision Medicine
The future in Diabetes care

Phenotype
- Demography
- Comorbidities

Genotype
- Variants altering PK
- Variants altering PD

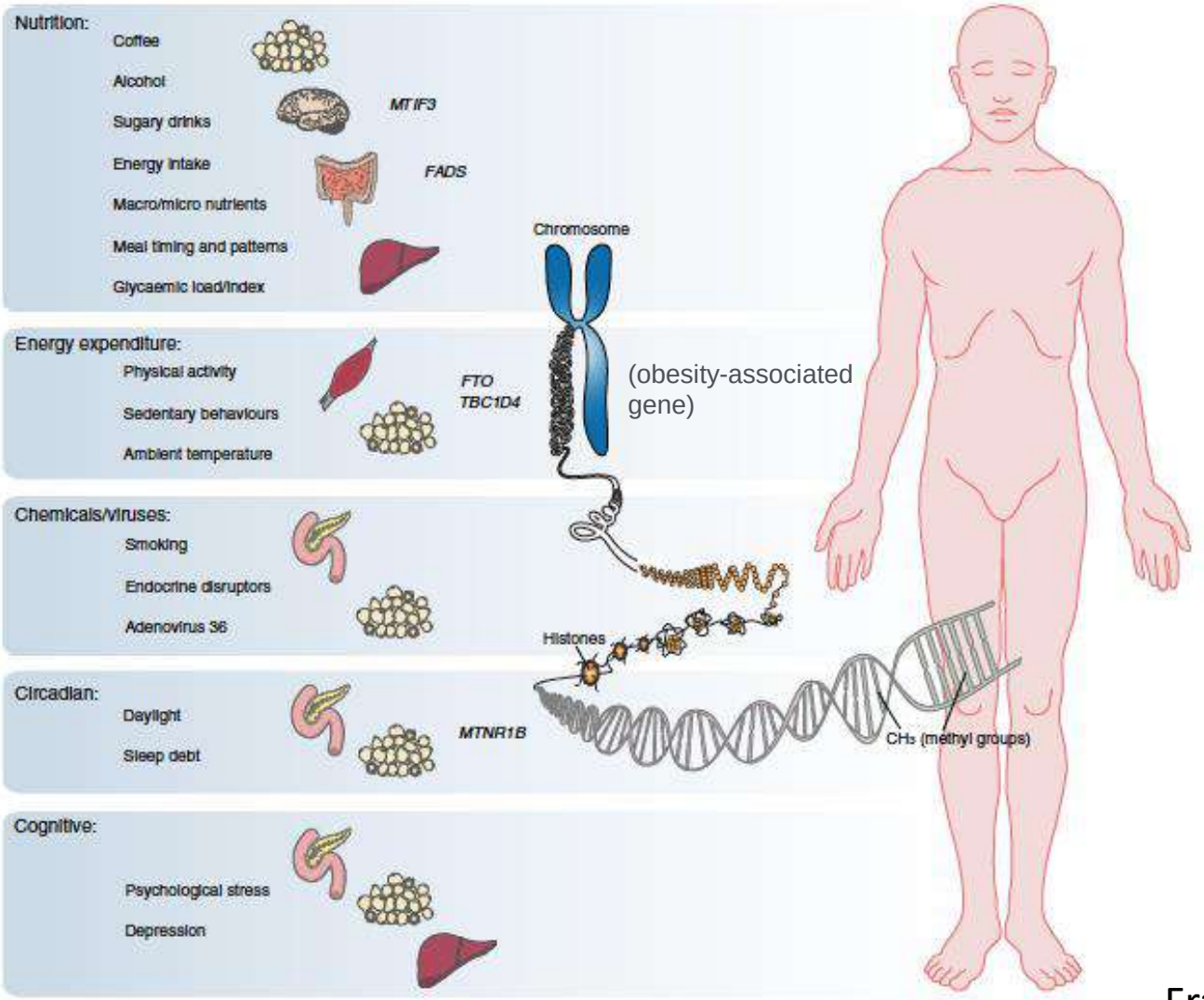


- Duration
- Severity (HbA1c)
- Fasting/postprandial
- Insulin secretion/resistance

- Pharmacokinetics (PK)
- Pharmacodynamics (PD)
- Cost

Diab Res Clin Pract. 2016, 117: 12–21

Lifestyle and precision diabetes medicine
Type 2 diabetes results from the complex interplay between environmental and genomic factors

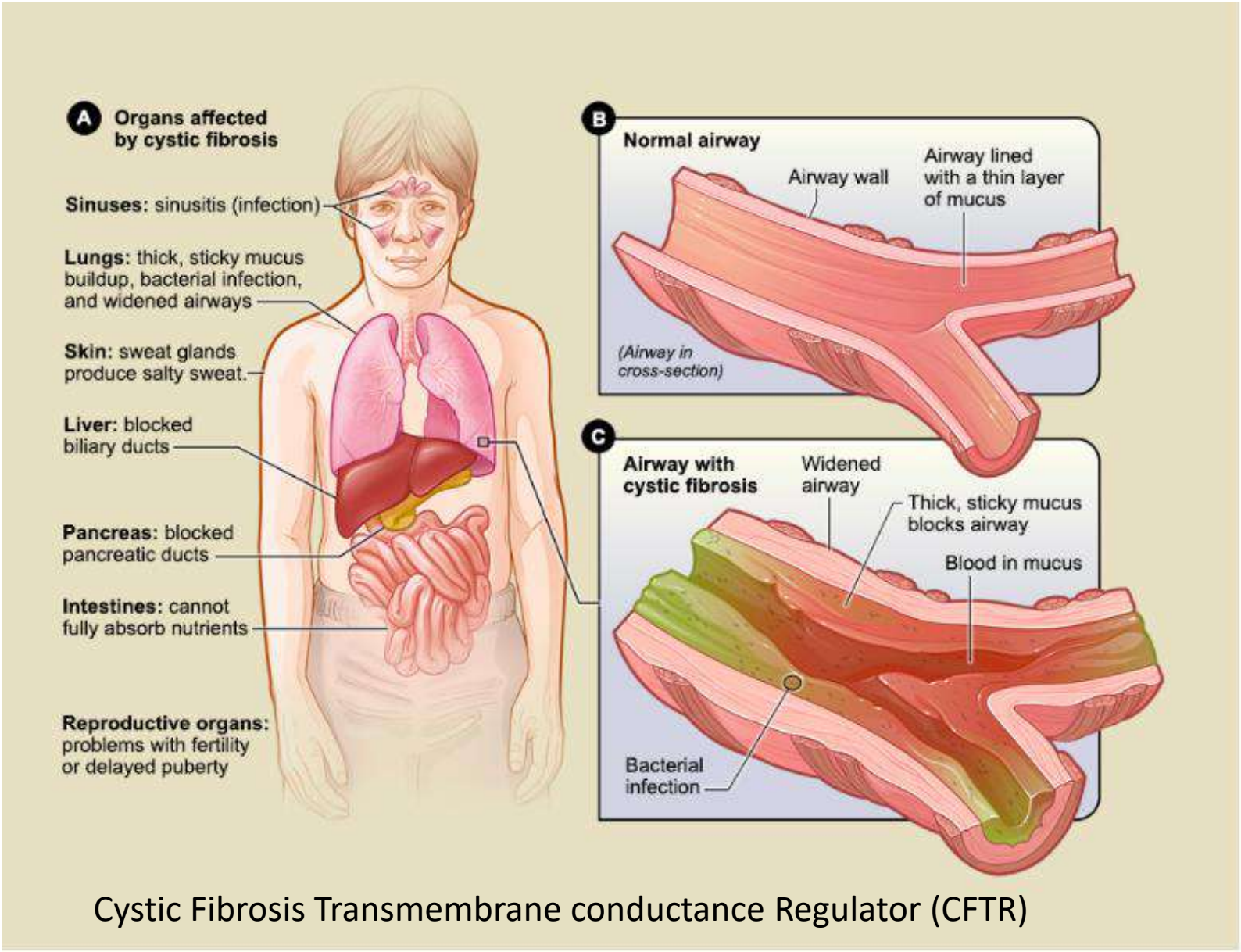


Genomics help optimise the prediction, prevention and treatment of type 2 diabetes through lifestyle therapy

Franks P. et al 2017

Fibrosi Cistica (Cystic Fibrosis)

mutazione del gene CFTR (Phe508del CFTR mutation)

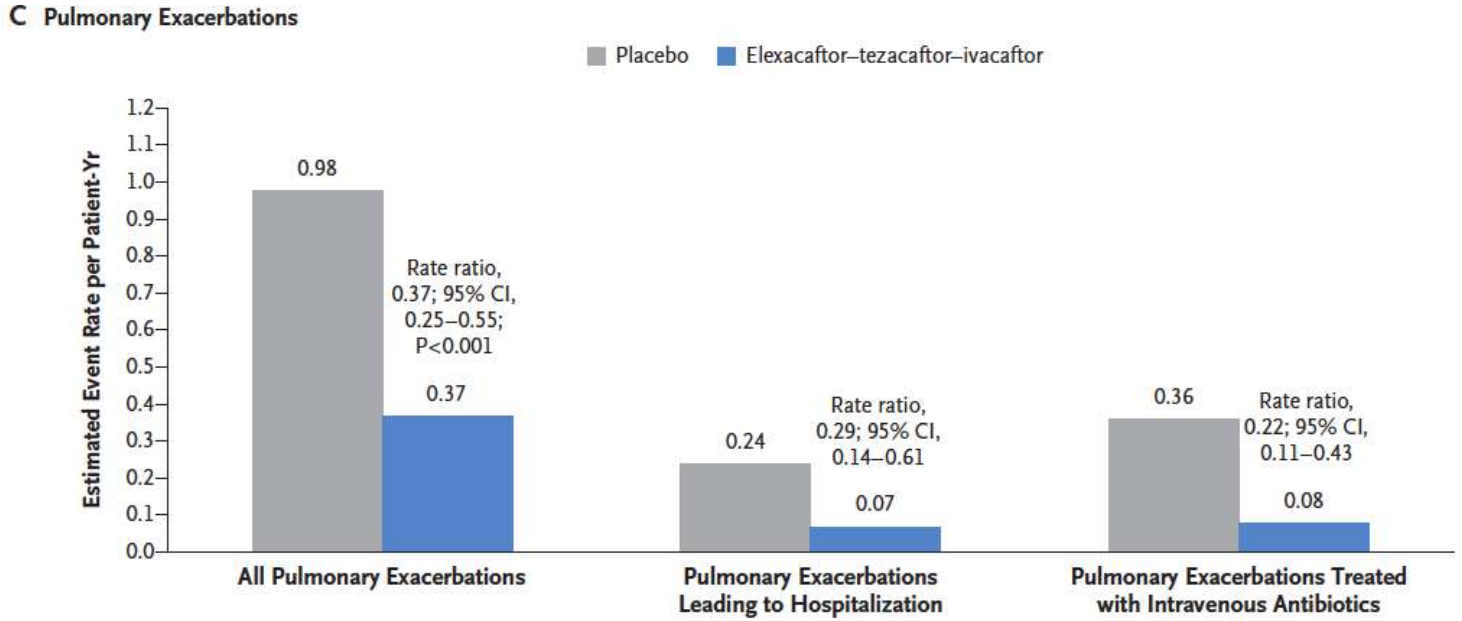


Cystic Fibrosis Transmembrane conductance Regulator (CFTR)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele



Conclusions

Elexacaftor–tezacaftor–ivacaftor was efficacious in patients with cystic fibrosis with Phe508del–minimal function genotypes, in whom previous CFTR (cystic fibrosis transmembrane conductance regulator) modulator regimens were ineffective.

Middleton PG. Et al 2019,

Precision Medicine in Bone Metabolism and Disorders

Biochemical indices

Bone Turnover Markers

BMD Evaluation

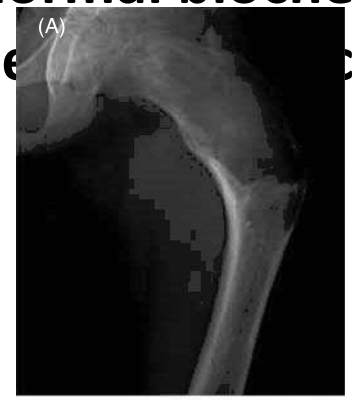
Genomic Factors

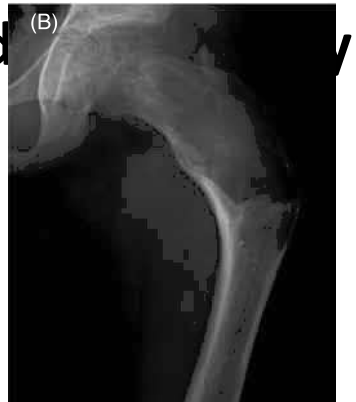
Risk factors (age, gender, underweight, parental history (of fracture), history of fragility fracture, frequent falls, early menopause, lifestyle, drugs)

Skeletal dysplasias or Osteochondrodysplasias

These disorders primarily affect musculoskeletal tissues including cartilage, bone, tendons, ligaments and muscle and are often associated with significant short stature, bone mineralization issues and early onset osteoarthritis.

Historically, these 450 disorders were diagnosed primarily by history, clinical features, and radiographic findings.
Other approaches that often help classify these disorders include abnormal biochemistry (e.g., in mucopolysaccharide disorders), magne ce imaging (MRI), computerized y (CT), and DXA.





Applications of Genetic Testing for Bone Disease in Clinical Practice: Bone Genetics 101

With the explosion in genomic technologies, the underlying molecular basis of most of the skeletal dysplasias or osteochondrodysplasias has been elucidated leading to improved prediction of natural history and recurrence, and a deeper understanding of biology.

Skeletal dysplasia gene panels, exome analysis and, in some centers, genome analysis can be used to help determine the molecular basis of disease.

Lewiecki E.M. Proceedings of the 2019 Santa Fe Bone Symposium:

The genetics of osteoporosis has, over the past five decades,
evolved through five paradigms:

- **Heritability study**
- **Candidate gene study**
- **Genome-wide association study (GWAS)**
- **Polygenic Risk Score (PRS)**
- **Whole-genome sequencing**

GWAS (Genome-wide association study)

offers a hypothesis-free method of searching for putative genes in the entire genome without any assumptions about the location and functional significance of loci or their products.

The thinking behind a GWAS is actually the "common disease–common variant" hypothesis, which postulates that the genetic component of common diseases (such as osteoporosis) is made up of a large number of putative alleles that are common (>5%) in the general population.

Although it is a hypothesis-free approach, a GWAS has been successful in identifying multiple variants that are associated with BMD or fracture risk.

The Polygenic Risk Score

The PRS can be defined as a quantitative index of the genetic burden related to a specific disorder and is specific to an individual.

Operationally, there are several ways to create a PRS. The simplest approach is to assign a risk value of 0 if an individual is a noncarrier of a risk allele, 0.5 or 1 if a carrier, and 1 or 2 if homozygous for that allele, and then sum the score across variants for the individual.

The trait-associated or risk allele is defined as an allele that is more common in cases than controls. The effect size can be a regression coefficient or log OR: because the PRS is aggregated from multiple variants and effect sizes, it is likely to be unique to an individual.

Moreover the PRS can be seen as an index of an individual's genetic liability to develop a disorder.

JBMR

Infection by CagA-Positive Helicobacter pylori Strains and Bone Fragility: A Prospective Cohort Study

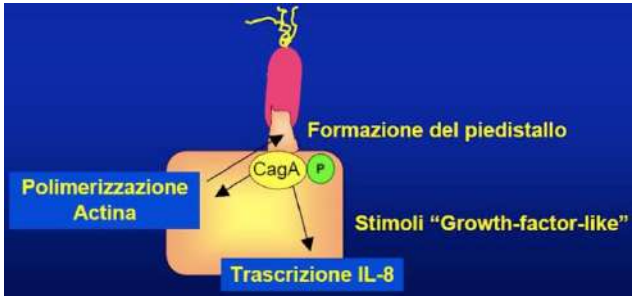
Luigi Gennari,[1] Daniela Merlotti,[1] Natale Figura,[1] Christian Mingiano,[1] Maria Beatrice Franci,[1] Barbara Lucani,[1] Tommaso Picchioni,[1] Mario Alessandri,[1] Maria Stella Campagna,[1] Sara Gonnelli,[1] Simone Bianciardi,[1] Maria Materozzi,[1,2] Carla Caffarelli,[1] Stefano Gonnelli,[1] and Ranuccio Nuti[1]

[1]Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy
[2]Department of Medical Biotechnologies, University of Siena, Siena, Italy

Table 1. General Characteristics of Subjects by HP and CagA Status

Characteristic	HP-negative	HP-positive (CagA-negative)	HP-positive (CagA-positive)
Subjects, *n* (%)	583 (51)	268 (23)	298 (26)
Males/females, *n* (%)	82 (14)/501 (86)	45 (17)/223 (83)	47 (16)/251 (84)
Fasting/feeding, *n* (%)	412 (71)/171 (29)	187 (70)/81 (30)	205 (69)/93 (31)
Age (years), mean ± SD	62.8 ± 6.5	63.4 ± 6.8	63.2 ± 6.6
Weight (kg), mean ± SD	67.0 ± 11.8	67.7 ± 12.4	65.9 ± 11.2
Height (cm), mean ± SD	162.1 ± 6.9	161.0 ± 7.2	161.8 ± 7.3
Further education, %[a]	19.0	18.6	18.1
Current smokers, %	18.0	13.4	14.8

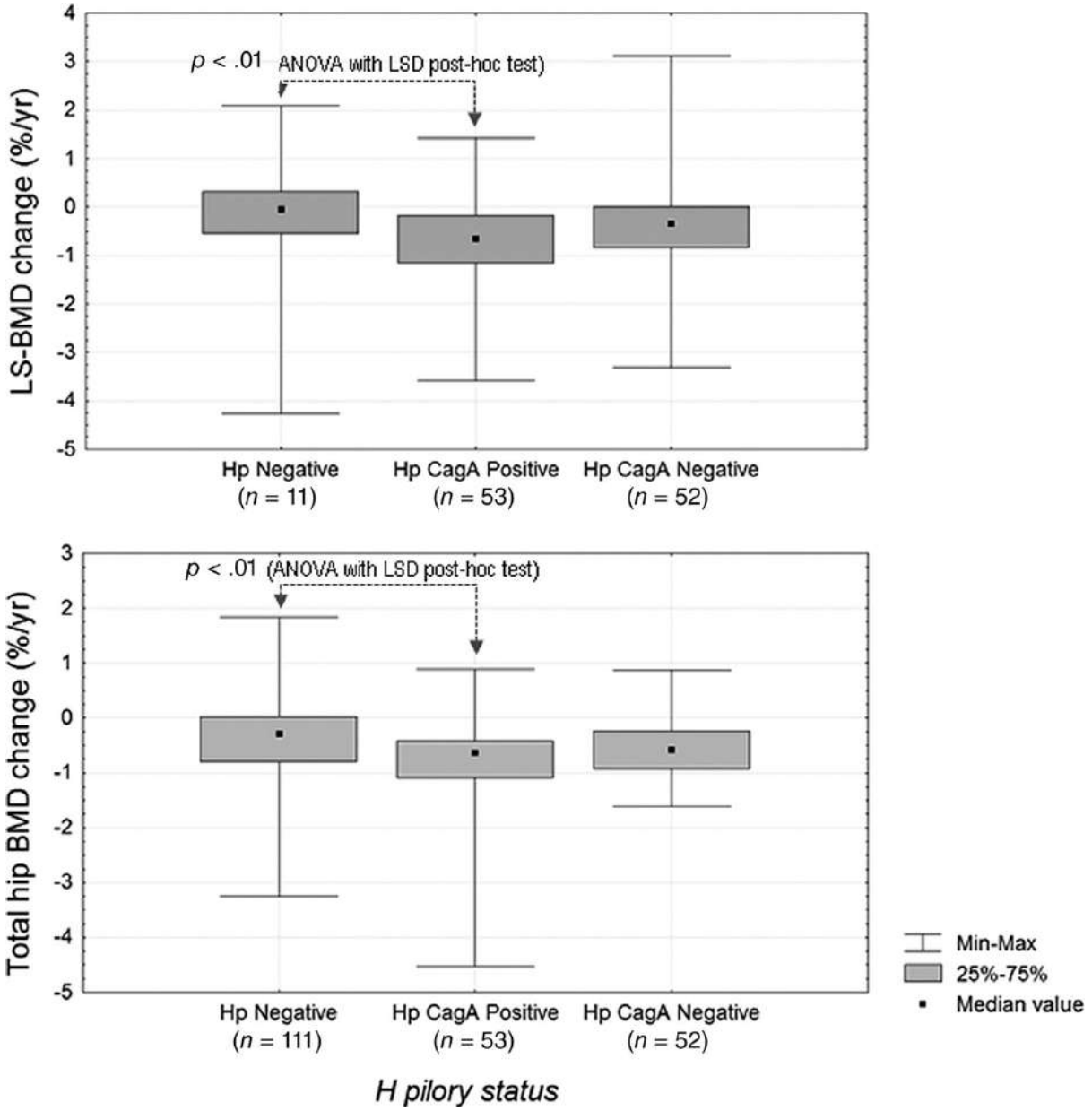
HP = *Helicobacter pylori*.
[a]Further education refers to proportion of subjects who studied beyond school level.



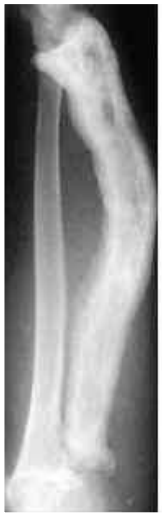
Incidence Rates and HRs for Incident Fractures by HP Status

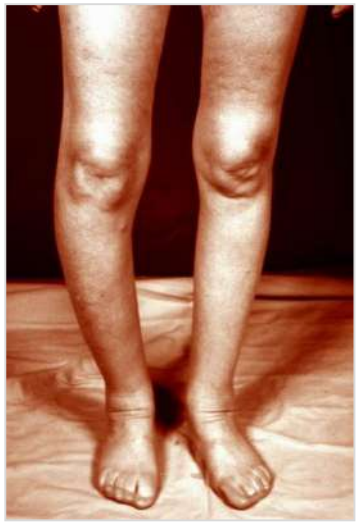
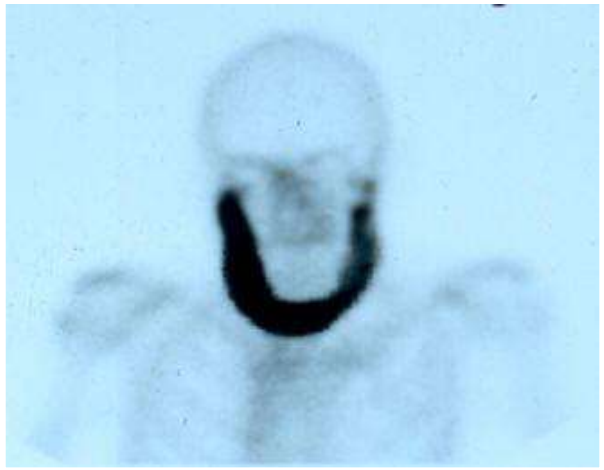
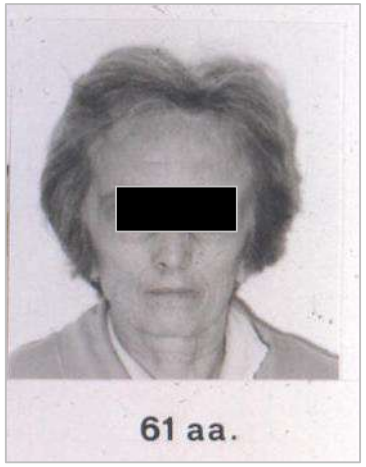
Model	HP (all)	HP (CagA-negative)	HP (CagA-positive)
Total fractures			
Crude incidence rate[a]	29.95	23.77	35.57
Unadjusted model	2.24 (1.49–3.38); $p < .0001$	1.80 (1.08–3.03); $p = .02$	2.70 (1.73–4.23); $p < .0001$
Adjusted (model 1)[b]	2.18 (1.44–3.31); $p < .0001$	1.79 (1.07–2.99); $p = .03$	2.60 (1.65–4.10); $p < .0001$
Adjusted (model 2)[c]	1.89 (1.24–2.88); $p < .01$	1.78 (1.06–2.99); $p = .03$	2.01 (1.26–3.20); $p < .01$
Clinical vertebral fractures			
Crude incidence rate[a]	10.95	7.45	14.17
Unadjusted model	3.81 (1.65–8.82); $p < .01$	2.30 (0.81–6.56); $p = .12$	5.27 (2.23–12.63); $p < .0001$
Adjusted (model 1)[b]	3.61 (1.56–8.37); $p < .01$	2.27 (0.79–6.51); $p = .13$	4.78 (1.99–11.47); $p < .0001$
Adjusted (model 2)[c]	2.87 (1.23–6.71); $p = .01$	2.36 (0.82–6.81); $p = .11$	3.20 (1.31–7.82); $p < .01$
Nonvertebral fractures			
Crude incidence rate[a]	17.73	15.52	19.69
Unadjusted model	1.81 (1.16–2.85); $p < .01$	1.56 (0.89–2.75); $p = .12$	2.09 (1.27–3.46); $p < .01$
Adjusted (model 1)[b]	1.78 (1.12–2.82); $p = .01$	1.55 (0.87–2.74); $p = .14$	2.04 (1.22–3.41); $p < .01$
Adjusted (model 2)[c]	1.54 (0.97–2.46); $p = .07$	1.53 (0.86–2.72); $p = .15$	1.59 (0.94–2.69); $p = .08$

Bone loss at the lumbar spine (A) and total hip (B), expressed as annualized percent BMD changes, in 247 females in relation to H. pylori status.

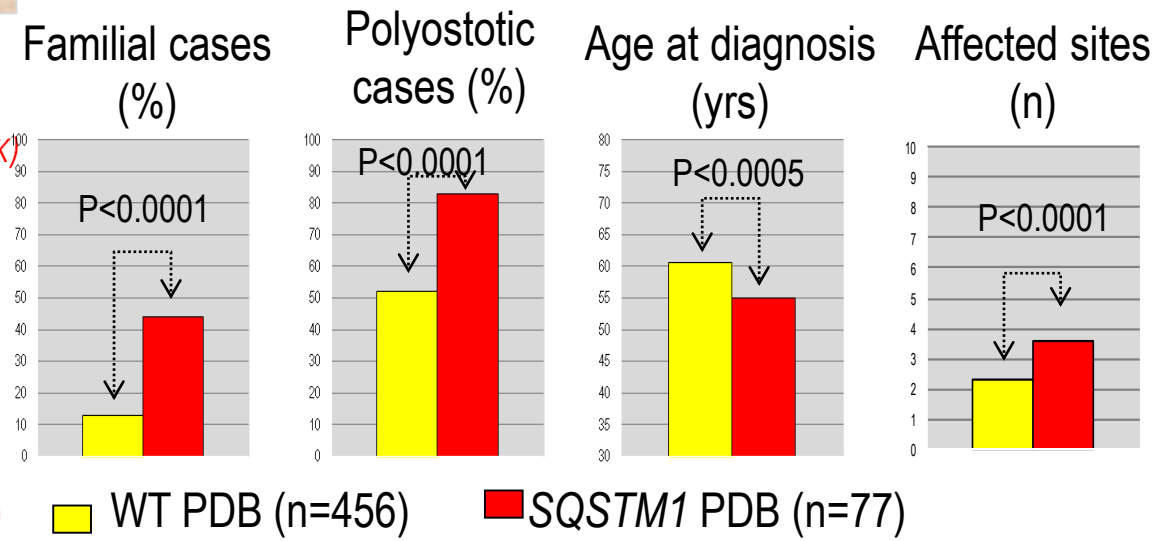


Malattia Ossea di Paget



PDB1	6p21.3	not identified
PDB2/FEO	18q22.1	*TNFSR11A (RANK)*
PDB3	5q35	***SQSTM1***
PDB4	5q31	not identified
PDB5	2q36	not identified
PDB6	10p13	not identified
PDB7	18q23	not identified
PDB/FTD/HIBM	9p13.3-p12	*VCP*
Juvenile PDB	8q24	*TNFSR11B (OPG)*



ORIGINAL ARTICLE

JBMR®

Characteristics of Early Paget's Disease in SQSTM1 Mutation Carriers: Baseline Analysis of the ZiPP Study Cohort

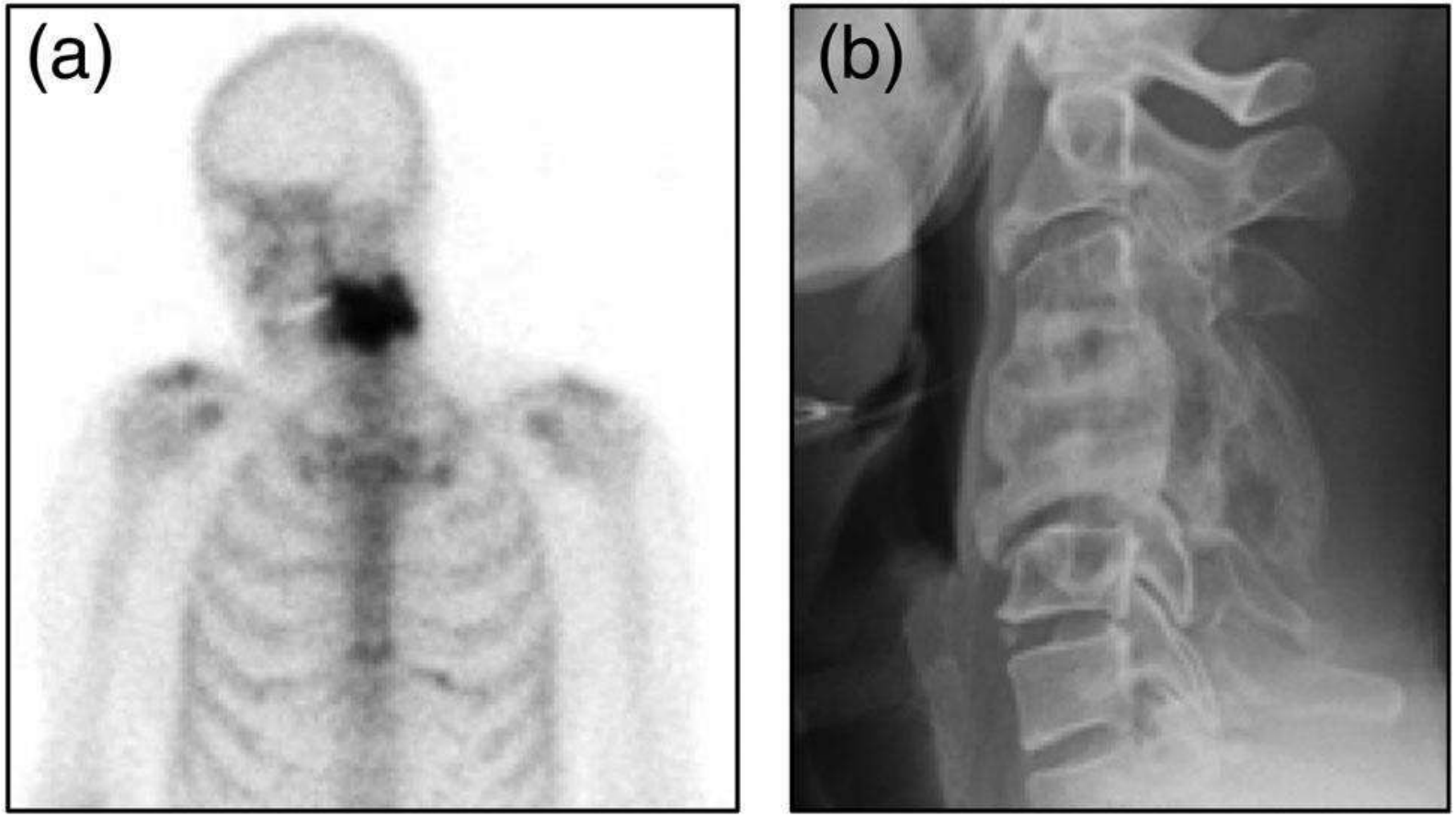
Owen Cronin,[1] Deepak Subedi,[2] Laura Forsyth,[3] Kirsteen Goodman,[3†] Steff C Lewis,[3] Catriona Keerie,[3] Allan Walker,[3] Mary Porteous,[4] Roseanne Cetnarskyj,[5] Lakshminarayan R Ranganath,[6] Peter L Selby,[7] Geeta Hampson,[8] Rama Chandra,[9] Shu Ho,[10] Jon H Tobias,[11] Steven A Young-Min,[12] Malachi J McKenna,[13,14] Rachel K Crowley,[13,14] William D Fraser,[15] Jonathan Tang,[15] Luigi Gennari,[16] Rannuccio Nuti,[16] Maria-Luisa Brandi,[17] Javier del Pino-Montes,[18] Jean-Pierre Devogelaer,[19] Anne Durnez,[19] Giovanni Carlo Isaia,[20] Marco Di Stefano,[20] Josep Blanch Rubio,[21] Nuria Guanabens,[22] Markus J Seibel,[23] John P Walsh,[24,25] Mark A Kotowicz,[26] Geoffrey C Nicholson,[27] Emma L Duncan,[28,29,30] Gabor Major,[31,32] Anne Horne,[33] Nigel L Gilchrist,[34] and Stuart H Ralston[1,3,35]

Table 2. Characteristics of Participants With and Without Lesions

Variable	Lesion (n = 20)	No lesion (n = 202)	p
Age (years), mean ± SD	53.6 ± 9.1	49.8 ± 9.0	.07
Gender			.95
Male, n (%)	10 (50.0)	90 (44.5)	
Female, n (%)	10 (50.0)	112 (55.4)	
Serum calcium (mmol/L), mean ± SD	2.41 ± 0.16	2.40 ± 0.11	.63
Serum 25(OH)D (nmol/L), mean ± SD	50.1 ± 26.2	52.2 ± 29.7	.76
Adjusted ALP (AU), mean ± SD	0.75 ± 0.69	0.42 ± 0.29	<.0001
Elevated ALP, n (%)	4/20 (20.0)	16/198 (8.0)	.007
uNTX/Cr (nM/mM), mean ± SD	305.5 ± 808.6	51.9 ± 51.9	<.0001
Elevated uNTX/Cr, n (%)	10/15 (66.6)	5/132 (3.8)	.0075
BAP (U/L), mean ± SD	15.1 ± 12.8	10.4 ± 7.0	.015
Elevated BAP, n (%)	1/17 (5.8)	1/186 (0.5)	.16
CTX (µg/L), mean ± SD	0.44 ± 0.26	0.32 ± 0.15	.004
Elevated CTX, n (%)	2/17 (11.7)	15/187 (8.0)	.17
P1NP (µg/L), mean ± SD	99.9 ± 84.9	53.4 ± 22.3	<.0001
Elevated P1NP, n (%)	10/17 (58.8)	35/187 (19.2)	.0001
Mutation type, n (%)			1.0
Missense	19 (94.4)	184 (91.0)	
Truncating	1 (5.6)	18 (8.9)	
Sites affected, n (%)			
1	10 (50.0)	–	
2	6 (30.0)	–	
≥3	4 (20.0)	–	

Table 1. Spectrum of Mutations in the ZiPP Study

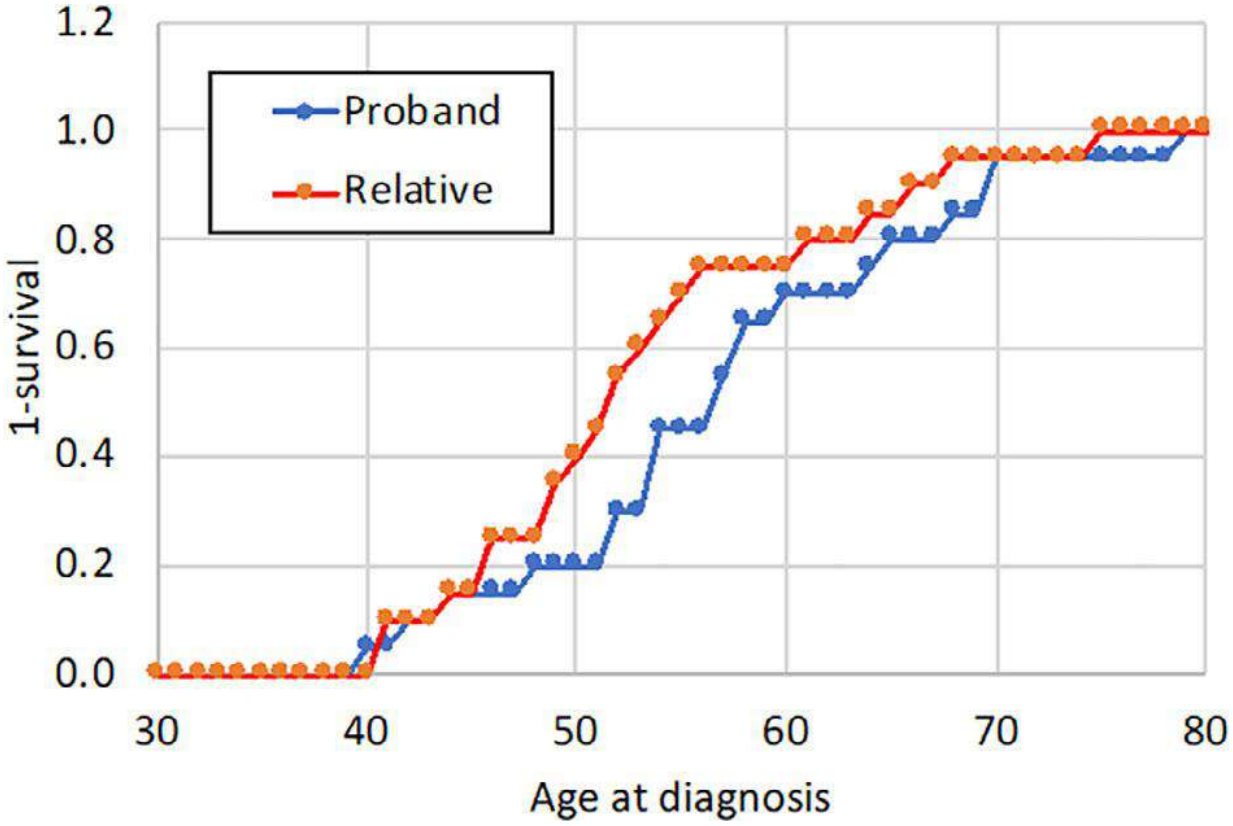
SQSTM1 variant	Mutations *n* (%)	Type of mutation
p.Pro392Leu	141 (63.5)	Missense
p.Gly425Arg	24 (10.8)	Missense
p.Met404Val	25 (11.3)	Missense
p.Gly411Ser	9 (4.1)	Missense
*aAla390**	8 (3.6)	Truncating
*p.Glu396**	3 (1.4)	Truncating
p.Thr350GlnfsX28	3 (1.4)	Truncating
p.Phe406Val	2 (0.9)	Truncating
*p.Lys378**	2 (0.9)	Truncating
*p.Gln371**	2 (0.9)	Truncating
p.Ile424Ser	2 (0.9)	Missense
*p.Glu396**	1 (0.46)	Truncating



(A) Radionuclide bone scan image showing intense tracer uptake in cervical vertebrae 4 and 5.

(B) (B) Radiograph from the same patient showing typical features of Paget's disease with expansion and fusion of C4 and C5. The patient was asymptomatic and had no

Comparison of age at diagnosis in probands with Paget's disease and their children.



The age at clinical diagnosis of Paget's disease in probands is compared with the age at which their children were diagnosed with Paget's disease through radionuclide bone scan imaging in the ZiPP study.

Conclusions

Genetic factors play a key role in the pathogenesis of PDB, and it has previously been suggested that genetic testing for SQSTM1 mutations and other susceptibility alleles might be used clinically to detect people with the disease.

The ZiPP study has confirmed the importance of SQSTM1 mutations as a genetic risk factor for PDB and has shown that a programme of genetic testing coupled to therapeutic intervention is both acceptable and feasible in the target population.

The promises of precision medicine are to dramatically change patient care via individually tailored therapies and, as a result, to prevent disease, improve survival, and extend healthspan.

However, nearly two decades after the first predictions of dramatic success, we find no impact of the human genome project on the population's life expectancy or any other public health measure, notwithstanding the vast resources that have been directed at genomics. Exaggerated expectations of how large an impact on disease would be found for genes have been paralleled by unrealistic timelines for success, yet the promotion of precision medicine continues unabated.