UNIVERSITÀ
DI SIENA
1240

# Il futuro della Medicina:

# dalla narrazione alla medicina di precisione

*Ranuccio Nuti*

# Clinical Hypocompetence: The Interview

FREDERIC W. PLATT, M.D.; and JONATHAN C. McMATH, M.D.; Denver, Colorado

***The interviewer failed to knock at the patient's door. He introduced himself in a hasty mumble so that the patient never had his name clearly in mind. He mispronounced the patient's name once and never used it again. The physician conducted the interview while seated in a chair about 7 feet from the patient. There was no physical contact during the interview. On several occasions the patient expressed her emotional distress. On each occasion the interviewer ignored the emotional content of her statements.***

***The physical examination was brusque, the examiner never warning his patient when painful maneuvers (for example, stroking the sole of the foot) were to be done. At the end of the examination the physician failed to comment on his findings or his plans. He said in parting, "We'll do some tests and see if we can find out just what's the matter with you," and left the room before the patient had an opportunity to question him.***

**Annals of Internal Medicine. 1979;91:898-902.**

MEDICAL WRITINGS | Words That Make a Difference **Annals of Internal Medicine**

# "What Else?" Setting the Agenda for the Clinical Interview

*Dr. A.: Well, Ms. X., it looks like that head stuffiness is just a bad virus cold and not a bacterial sinus infection, so I think we're going to have to wait it out. Antibiotics don't help with viruses and really could cause more trouble, so I don't think we'll need them.*

*(He stands and moves to the door, his hand on the doorknob.)*

*So I'm glad it wasn't anything worse. Let me know if it seems to be hanging around more than another week or if anything else develops.*

*Patient: Yes, thanks, Doctor. But before you go, there is one other thing.*

*Dr. A.: Yes?*

*Patient: Well, it's just that I've been having blood in my bowel movements. It isn't all the time, but sometimes the bowel movement is mixed with a lot of blood and I was just wondering if I should do anything about it.*

*Dr. A.: I don't believe it. Really?*

*Patient: Yes. Why? Is it something serious?*

*Dr. A.: Well, yes, it could be. And I wish you had mentioned it before. Why didn't you tell me before?*

*Patient: You didn't ask me.*

**Ann Intern Med. 2005;143:766-770.**

**Anàmnesi** (dal gr. ἀνάμνησις, der. di ἀναμιμνήσκω-ricordare; propriamente, reminiscenza, ricordo. Treccani)

Domenico di Bartolo, Governo e cura degli infermi (1440-1441)

**Familiare**
**Fisiologica**
**Lavorativa**
**Patologica remota**
**Patologica prossima**

Fredrich Friedlander The Doctor 1870

**Anamnesi sociale**
**Anamnesi farmacologica**

# LEGGI ED ALTRI ATTI NORMATIVI

LEGGE 22 dicembre 2017, n. **219**.

**Norme in materia di consenso informato e di disposizioni anticipate di trattamento.**

IL PRESIDENTE DELLA REPUBBLICA

Art. 1.

*Consenso informato*

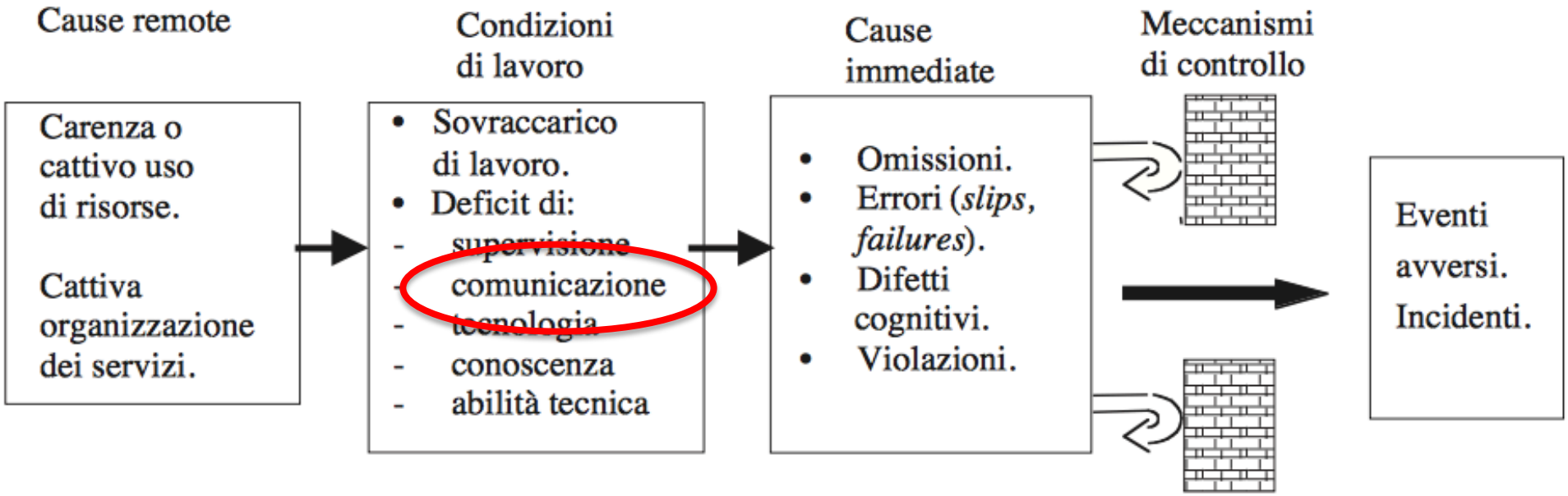
**8. Il tempo della comunicazione tra medico e paziente costituisce tempo di cura.**

**Raccolta dell'anamnesi**

**Metodologia di approccio al paziente**

**Corretta procedura di comunicazione**

# L'errore in Medicina




Da *BMJ Publ Group* 1995:31-54

# Corretta procedura di comunicazione

## Empatia

capacità di porsi nella situazione di un'altra persona o, più esattamente, di comprendere immediatamente i processi psichici dell'altro (Treccani)

**Tutto questo nella consapevolezza, da parte del medico, che:**

**l'insieme di gestualità e parole scelte dal medico è in grado di produrre effetti sul paziente**;

**il paziente ha bisogno di un medico che capisca la sua condizione, tratti i suoi problemi medici con competenza e l'accompagni nel percorso di malattia**

# Narrative Medicine

## A Model for Empathy, Reflection, Profession, and Trust

Rita Charon, MD, PhD

**…. Is the ability to acknowledge, absorb, interpret, and act on the stories and plights of others…. Is proposed as a model for humane and effective medical practice.**

**JAMA 286,1897-1902 2002**

# Narrative Medicine

## A Model for Empathy, Reflection, Profession, and Trust

Rita Charon, MD, PhD

**PATIENT-PHYSICIAN:**
**EMPATIC ENGAGEMENT**

**PHYSICIAN-SELF:**
**REFLECTION IN PRACTICE**

**PHYSICIAN-COLLEAGUES:**
**PROFESSION**

**PHYSICIAN-SOCIETY:**
**THE PUBLIC TRUST**

**JAMA 286,1897-1902 2002**

# Medicina Narrativa

## PATIENT-PHYSICIAN:
## EMPATIC ENGAGEMENT

**Quando una persona entra nello studio di un medico è un "qualcuno che racconta a qualcun altro che qualcosa è accaduto" (Barbara Herrnstein Smith*).**
**La malattia stessa viene raccontata secondo un andamento storico - *prima stavo bene, poi ho iniziato a stare male*…….**
**Anche la "storia clinica" è una narrazione, è la narrazione che fa il medico, costruendo una trama sulla base delle sue competenze mediche e scientifiche. I fatti narrati nella cartella clinica non sono *"sempre"* gli stessi fatti narrati dal paziente, ma non sono più o meno veri di questi.**

## Potremmo così sintetizzare le caratteristiche della narrazione:

- **Presuppone un narratore e un ascoltatore**
- **Deve essere strutturata secondo una linea temporale**
- **Riguarda il singolo individuo (è quindi un sapere idiografico)**
- **Esprime i fatti accaduti attraverso il "filtro" dalla coscienza del soggetto narrante**
- **Rivela altre informazioni oltre ai fatti accaduti**
- **Coinvolge l'ascoltatore in un processo interpretativo**

*Director of the Center for Interdisciplinary Studies in Science and Cultural Theory Duke University

**La medicina narrativa è un modello empatico in grado di favorire un'elevata aderenza al trattamento nel paziente e di offrire all'operatore una metodica per la rilevazione del vissuto soggettivo di malattia.**

P. Picasso 1897

***Il fine della Medicina Narrativa è quindi la costruzione condivisa di un percorso di cura personalizzato da cui l'integrazione con l'Evidence-Based Medicine (EBM): ciò rende le decisioni clinico-assistenziali più complete, personalizzate, efficaci e appropriate. La narrazione del paziente e di chi se ne prende cura rappresenta un elemento imprescindibile della medicina contemporanea, fondata sulla partecipazione attiva dei soggetti coinvolti nelle scelte.***

Samuel Luke Fildes The Doctor 1891

MEDICAL EDUCATION

Tuesday, March 28, 2017 | by Kim Krisberg, special to *AAMCNews*

# Narrative Medicine: Every Patient Has a Story

Every patient has a story that goes beyond the symptoms they bring into the doctor's office.

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# NARRATIVE MEDICINE

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**Medicina Narrativa (NBM)**

**Medicina Basata sull'Evidenza (EBM)**

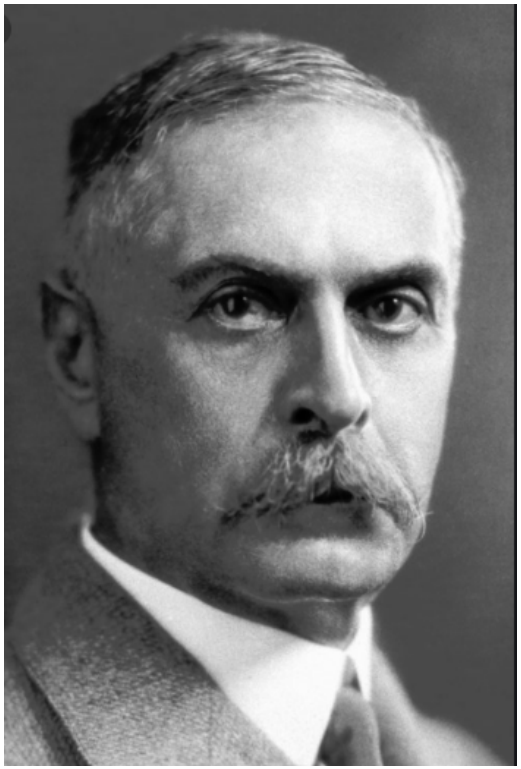
**Medicina di Precisione (PM)**

**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

**1999**

Harold Varmus, direttore dei National Institutes of Health, invita i ricercatori statunitensi a sottoporre progetti di ricerca finalizzati a classificare i tumori in base alle caratteristiche molecolari e non morfologiche.

**2000**

**THE HUMAN GENOMA PROJECT**
The Human Genome Project viene completato.

**2003**

**INDIVIDUALIZED MEDICINE**
Utilizzato inizialmente in riferimento al metabolismo individuale del farmaco (Srivastava 2003), il termine è stato poi associato all'approccio terapeutico che prevede il ricorso a materiale cellulare per sviluppare una terapia mirata, p. es. *stem cell therapy* (Baker 2011) o vaccini oncologici (Gravitz 2011).

**2004**

**PERSONALIZED MEDICINE**
L'applicazione della farmacogenomica alla pratica clinica (Gupta 2004). Diventa il "termine ombrello" per un concetto sempre più utilizzato. L'anno successivo nasce la Personalized Medicine Coalition.

PMC
PERSONALIZED MEDICINE COALITION

**2005**

**TREATING INDIVIDUALS**
*The Lancet* pubblica una serie di cinque rassegne curate da Peter Rothwell che approfondiscono l'analisi per sottogruppi, ipotizzando la transizione "dal randomized controlled trials alla personalized medicine".

**2007**

**STRATIFIED MEDICINE**
Indica l'approccio basato sulle terapie capaci di andare incontro alle specifiche caratteristiche di pazienti utilizzando biomarker clinici (Trusheim 2007). Presuppone il ricondurre ogni malato ad una coorte o a una sottopopolazione di un insieme più ampio, dalle quali ci si attenda una diversa risposta alla terapia.

**2008**

**P4 MEDICINE**
Predittiva, personalizzata, preventiva e partecipata: ecco la medicina del futuro secondo Leroy Hood (2008). Driver di questa evoluzione: biologia molecolare, big data, social media e web.

**2009**

**PRECISION MEDICINE**
Introdotta per la prima volta nel 2009 (Boguski 2009) intendeva definire un modello che prevedesse
1. la conoscenza delle cause della malattia,
2. la capacità di identificare la presenza degli agenti causali e
3. la competenza/possibilità di intervenire efficacemente.

**2011**

La SM non si sviluppa solo a partire dalla genomica ma può fondarsi anche su altre discipline (p. es. l'imaging diagnostico) (Blair 2011).

Il report **Toward Precision Medicine** della US National Academy specifica ulteriormente il significato agganciandolo alla riclassificazione delle malattie su dati molecolari.

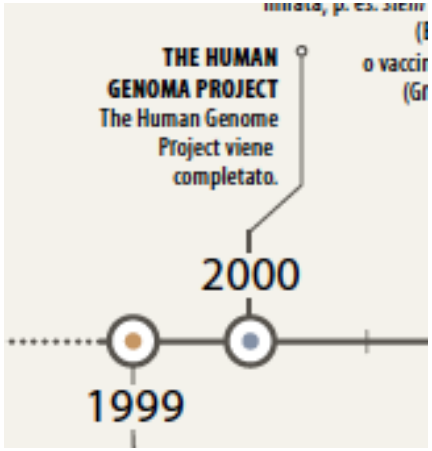
**2012**

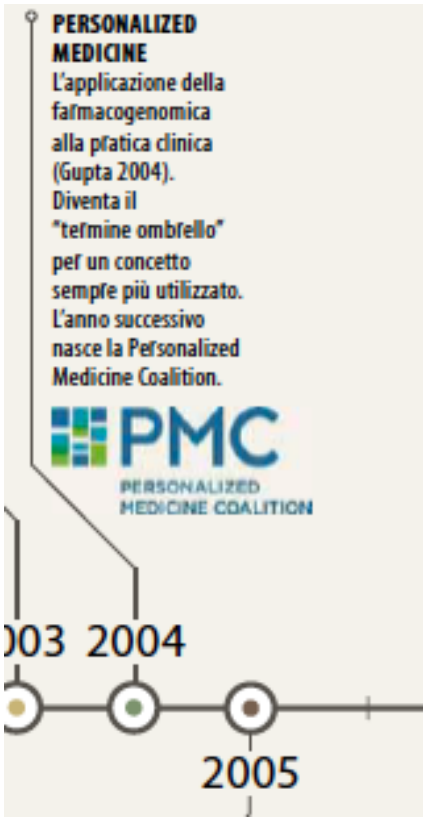
Febbraio: una Perspective sul *New England Journal of Medicine* titola *Preparing for Precision Medicine*.

**2015**

A gennaio, nello State of the Union address, Barak Obama annuncia la Precision Medicine Initiative.

Francis S. Collins (direttore del NIH) e Harold Varmus presentano la PM Initiative sul *New England*.


THE HUMAN
GENOMA PROJECT
The Human Genome
Project viene
completato.
2000
1999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PMC
PERSONALIZED MEDICINE COALITION
)03
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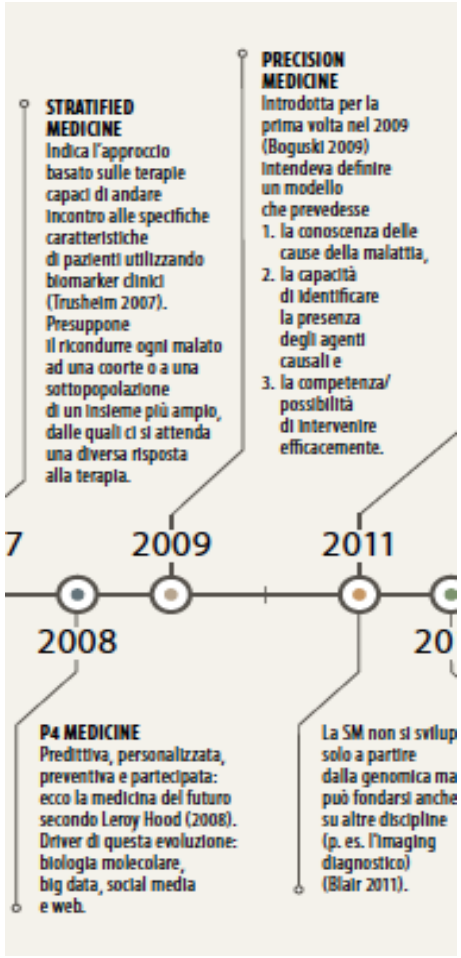
2005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7
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A gennaio, nello State of the Union address, Barak Obama annuncia la Precision Medicine Initiative.

## 2015

Francis S. Collins (direttore dei NIH) e Harold Varmus presentano la PM Initiative sul *New England*.

# 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.**

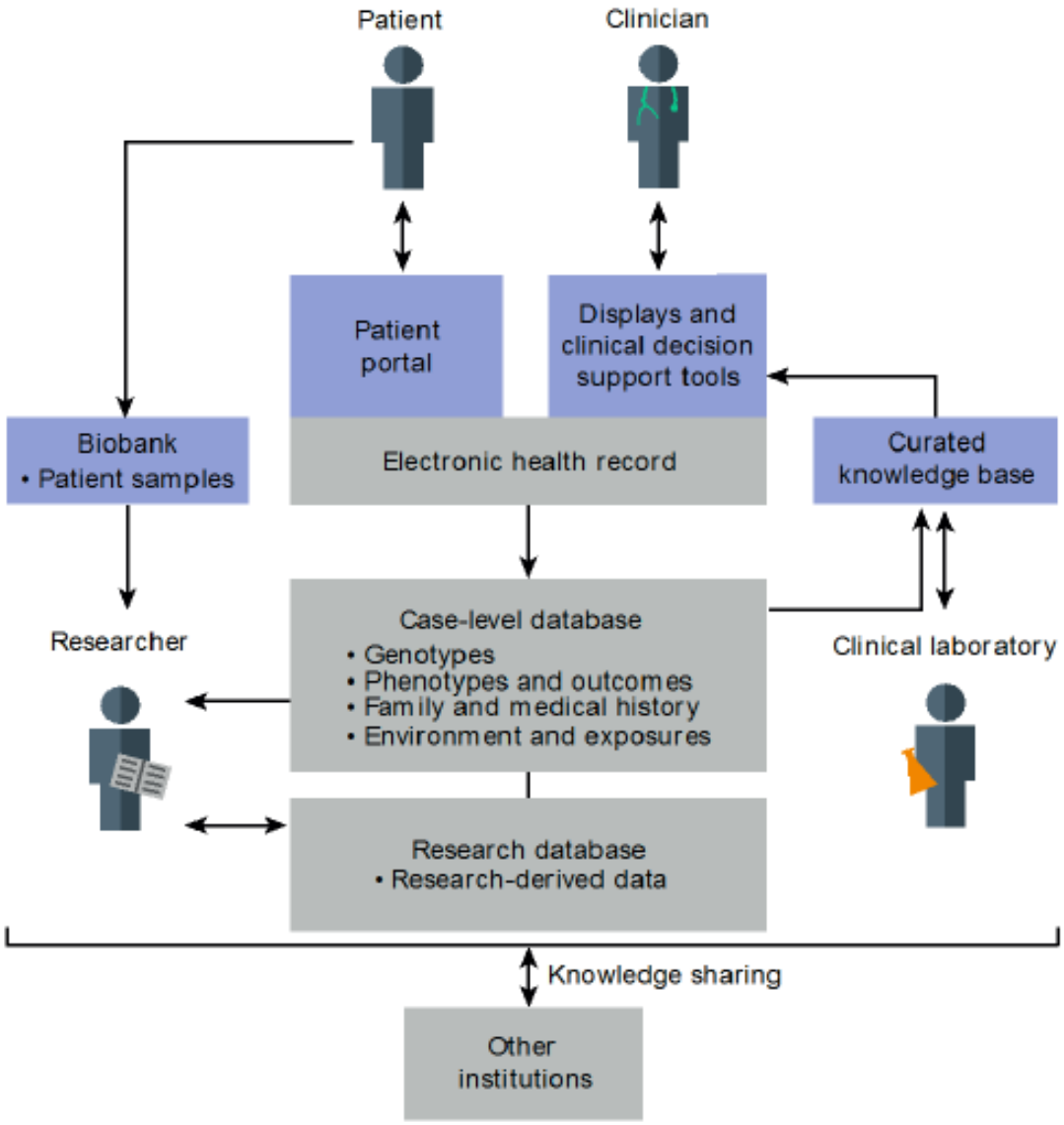
# MEDICINA di PRECISIONE
# Motivazioni

**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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**Best matches for precision medicine:**

What is **precision medicine?**
König IR et al. Eur Respir J. (2017)

**Precision medicine** in pediatric oncology.
Forrest SJ et al. Curr Opin Pediatr. (2018)

Human genomics projects and **precision medicine.**
Carrasco-Ramiro F et al. Gene Ther. (2017)

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## Search results

**Items: 1 to 20 of 43084**

<< First < Prev Page 1 of 2155 Next > Last >>

1. Cases in **Precision Medicine**: APOL1 and Genetic Testing in the Evaluation of Chronic Kidney Disease and Potential Transplant.
Neugut YD, Mohan S, Gharavi AG, Kiryluk K.
Ann Intern Med. 2019 Oct 8. doi: 10.7326/M19-1389. [Epub ahead of print]
PMID: 31590185
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2. From computational genomics to systems metabolomics for **precision** cancer **medicine** and drug discovery.
Alberghina L, Piccialli G.
Pharmacol Res. 2019 Oct 4:104479. doi: 10.1016/j.phrs.2019.104479. [Epub ahead of print] No abstract

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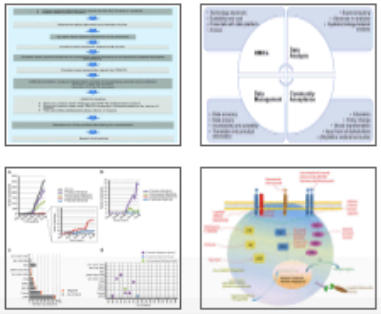
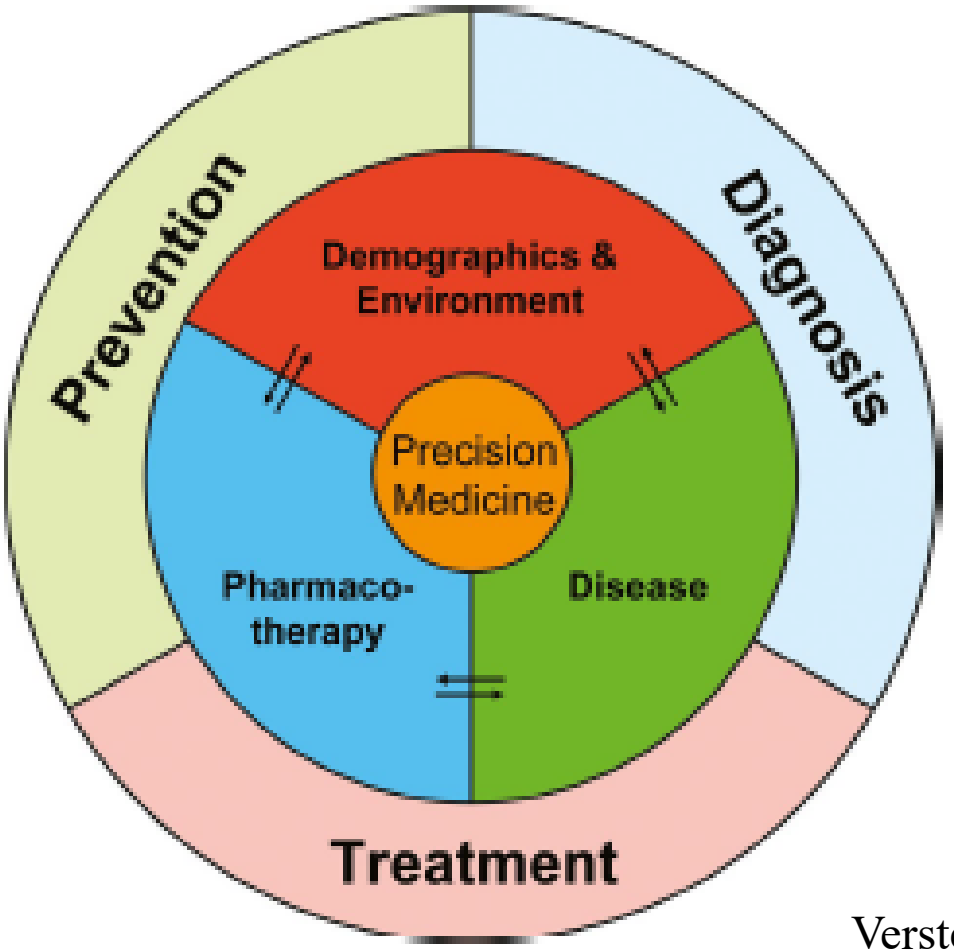
**PMC Images search for *precision medicine***



**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

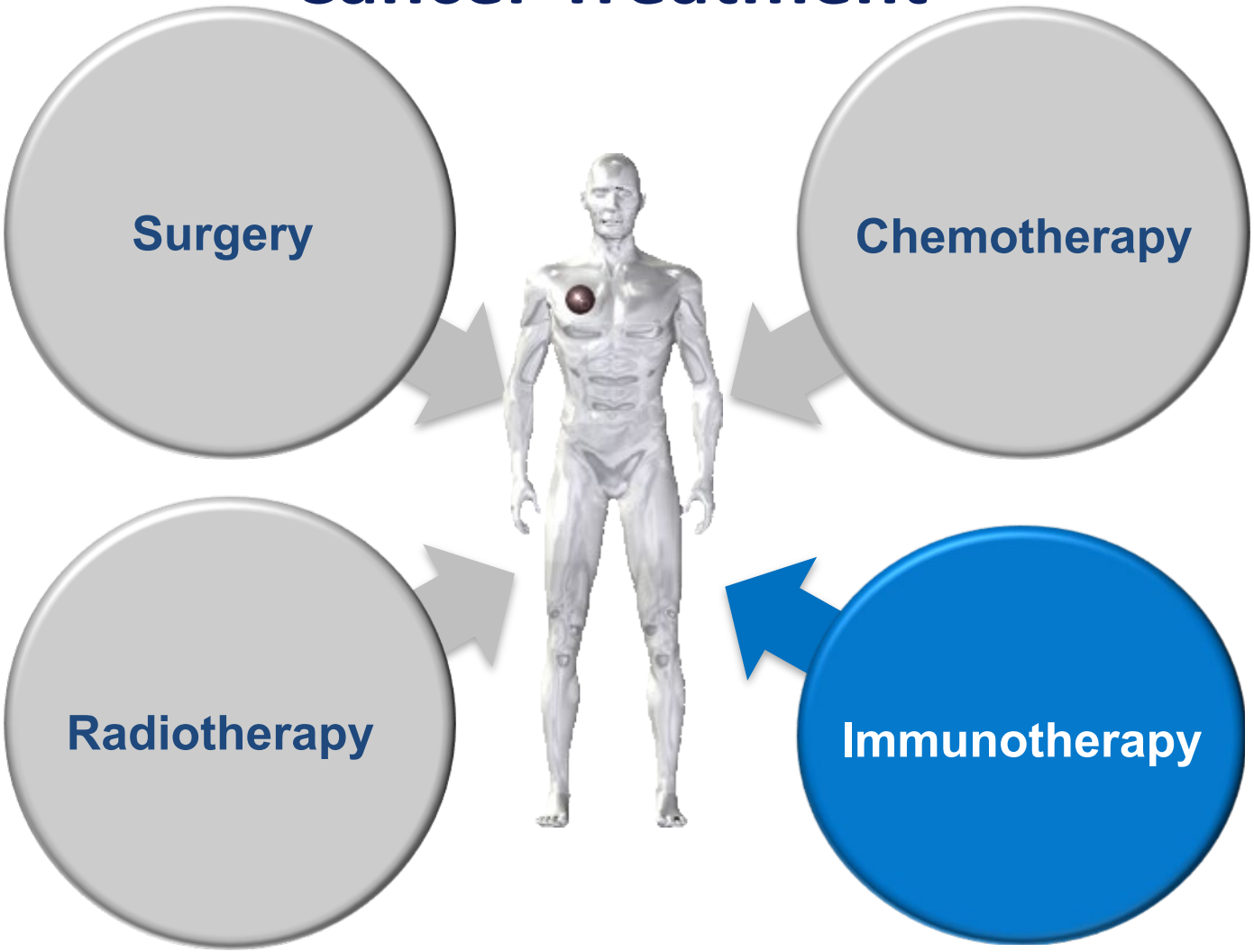
# Efforts to apply precision medicine to cancer

**Innovative clinical trials of targeted drugs for adult, pediatric cancers**

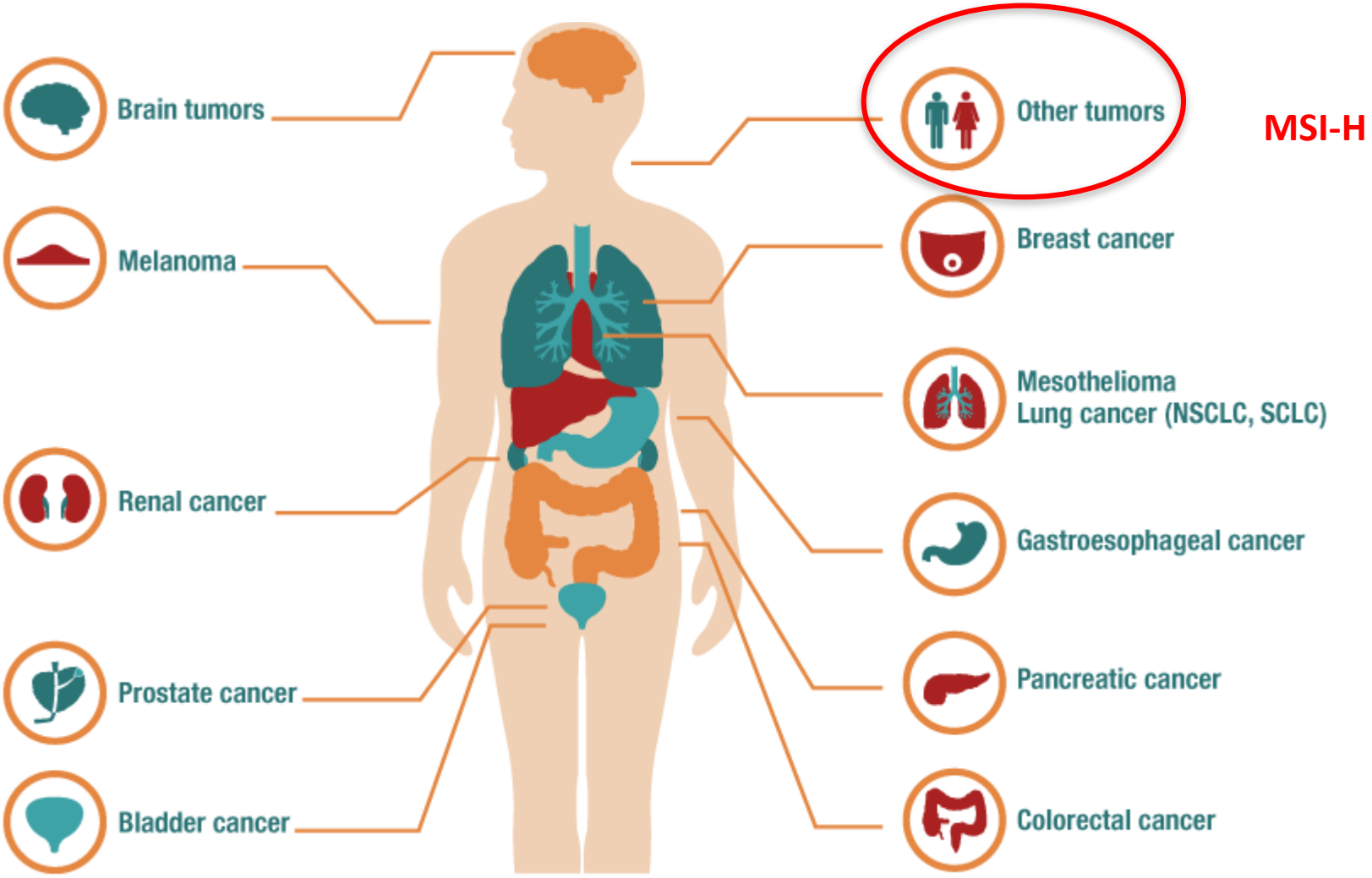
**Use of combination therapies**

**Knowledge to overcome drug resistance**

# Evolving Therapeutic Options for Cancer Treatment

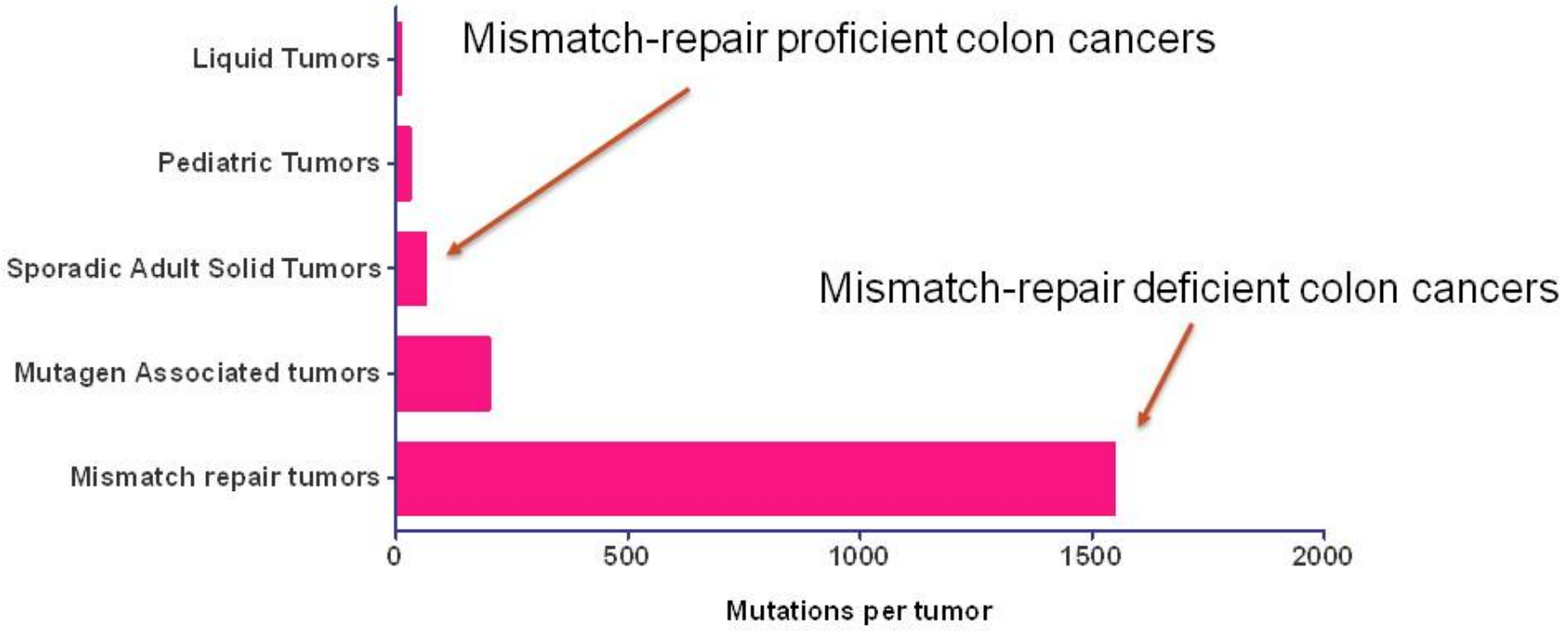


# Immunotherapy in solid tumours with immunomodulating antibodies




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

# Mutations per tumor



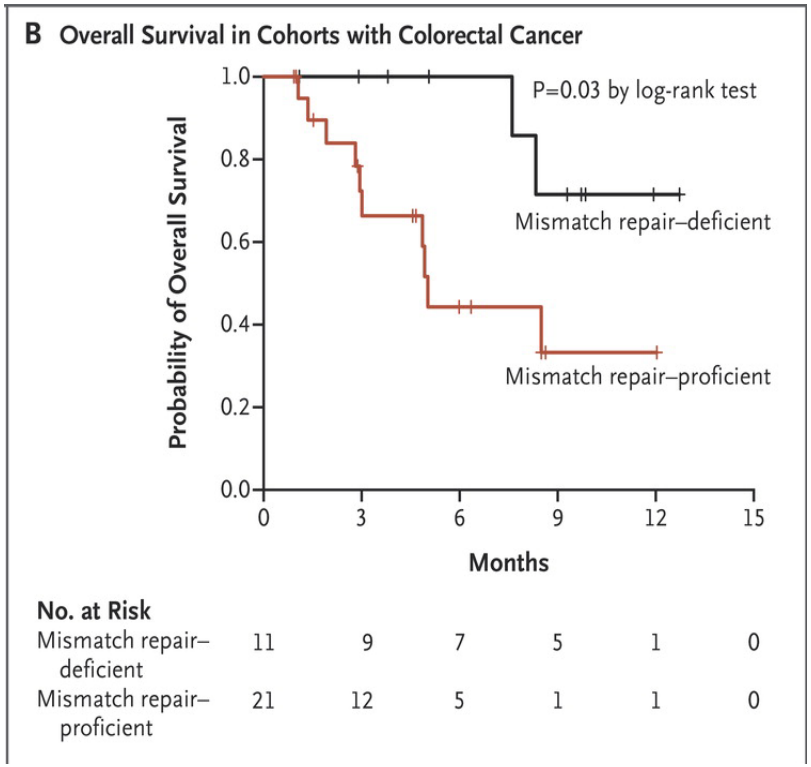


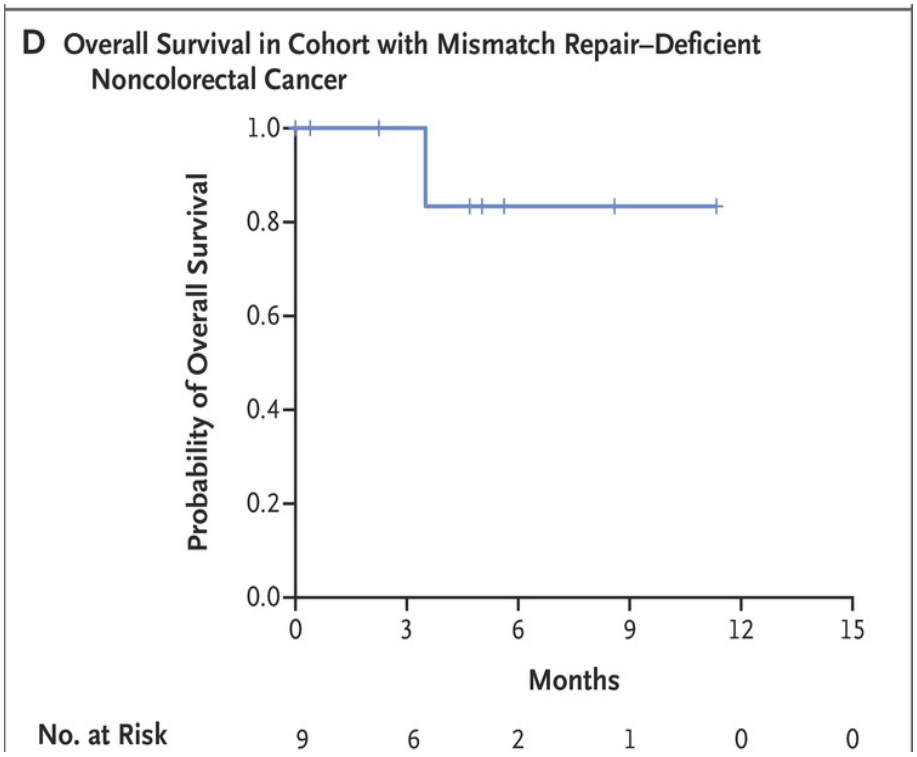



Presented By Dung Le at 2015 ASCO Annual Meeting

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 blockade: pembrolizumab

Le DT et al. NEJM 2015

VOLUME 36 · NUMBER 8 · MARCH 10, 2018

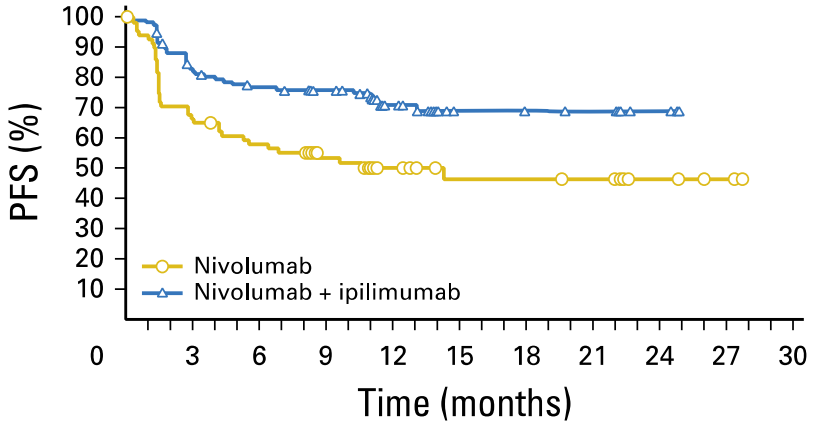
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite Instability–High Metastatic Colorectal Cancer

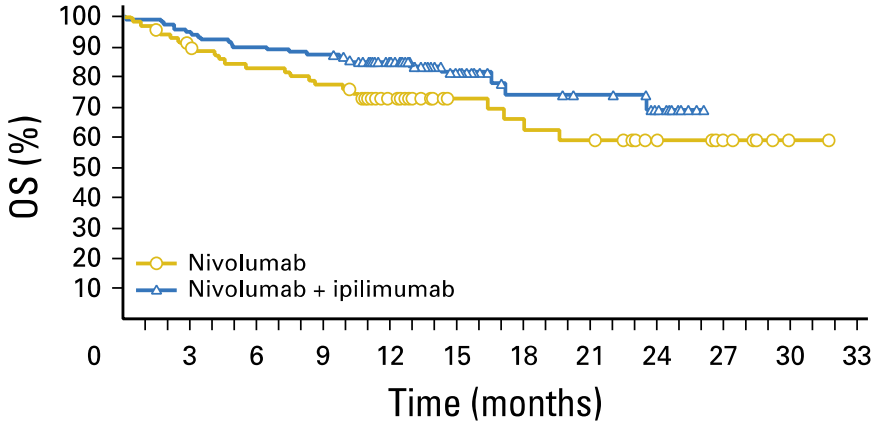
*Michael J. Overman, Sara Lonardi, Ka Yeung Mark Wong, Heinz-Josef Lenz, Fabio Gelsomino, Massimo Aglietta, Michael A. Morse, Eric Van Cutsem, Ray McDermott, Andrew Hill, Michael B. Sawyer, Alain Hendlisz, Bart Neyns, Magali Svrcek, Rebecca A. Moss, Jean-Marie Ledeine, Z. Alexander Cao, Shital Kamble, Scott Kopetz, and Thierry André*

**A**




| No. at risk: | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab | 74 | 48 | 41 | 32 | 17 | 12 | 12 | 11 | 6 | 3 | 0 |
| Nivolumab + ipilimumab | 119 | 95 | 86 | 78 | 39 | 12 | 11 | 10 | 3 | 0 | 0 |

**B**



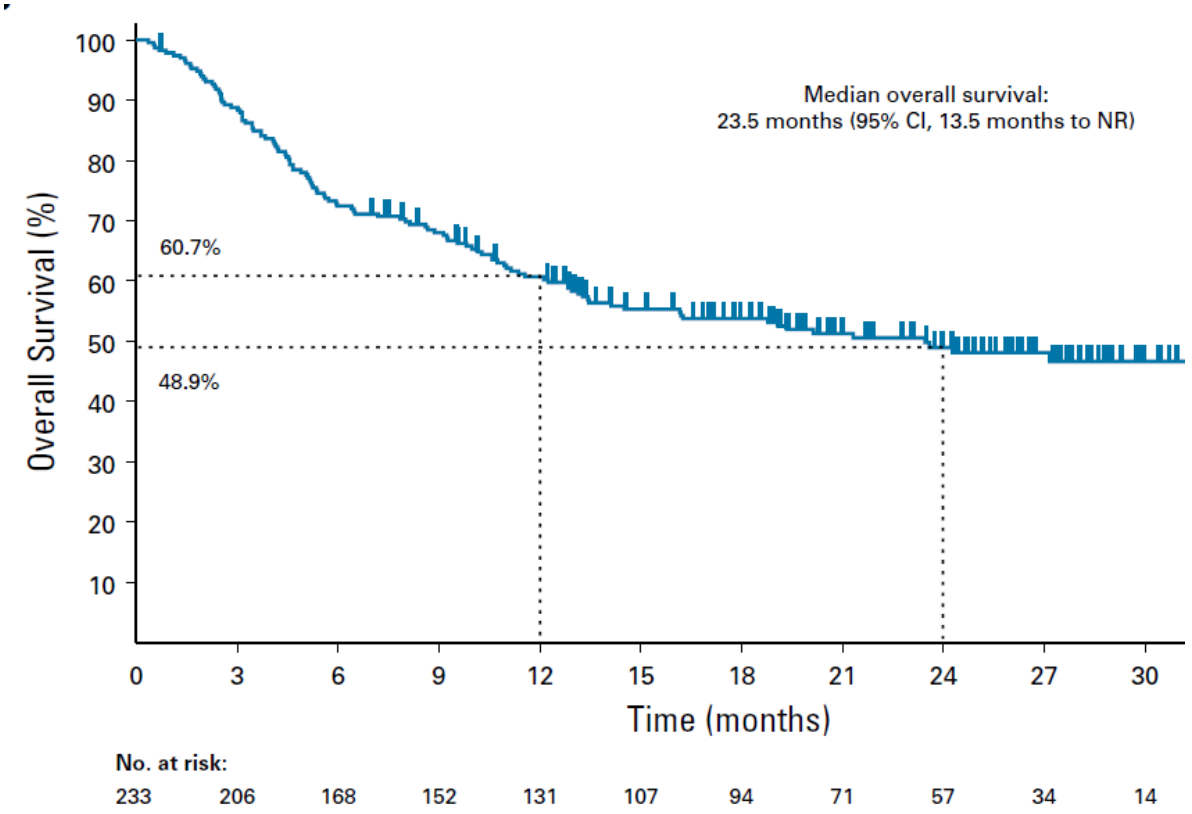

| No. at risk: | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab | 74 | 64 | 59 | 55 | 37 | 21 | 19 | 17 | 11 | 6 | 1 | 0 |
| Nivolumab + ipilimumab | 119 | 113 | 107 | 104 | 78 | 33 | 19 | 17 | 11 | 0 | 0 | 0 |

Nivolumab: inhibits Programmed Death 1 (PD-1) pathway
Ipilimumab: targets CTLA-4 checkpoint receptor

Overman MJ *et* al. JCO, 2018

# 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]



# FDA approves pembrolizumab for metastatic small cell lung cancer



On June 17, 2019, the Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck) for patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

# FDA expands pembrolizumab indication for first-line treatment of NSCLC (TPS ≥1%)

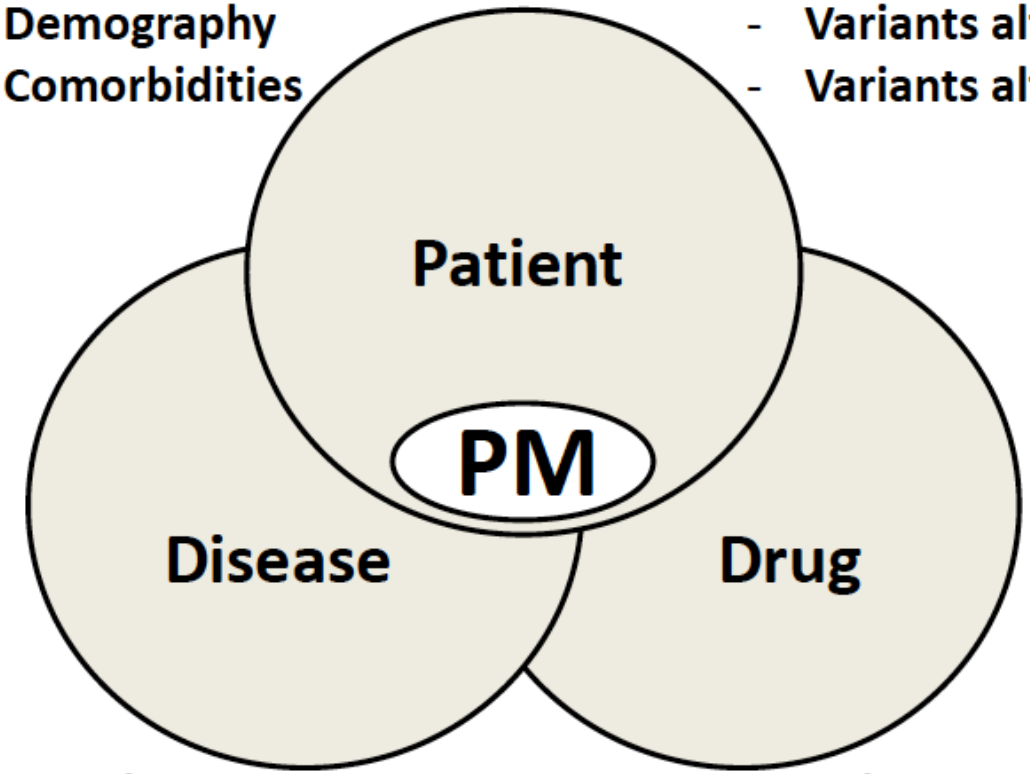


On April 11, 2019, the Food and Drug Administration approved pembrolizumab (KEYTRUDA, Merck Inc.) for the first-line treatment of patients with stage III non-small cell lung cancer (NSCLC) who are not candidates for surgical resection or definitive chemoradiation or metastatic NSCLC. Patients' tumors must have no *EGFR* or *ALK* genomic aberrations and express PD-L1 (Tumor Proportion Score [TPS] ≥1%) determined by an FDA-approved test.

# 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

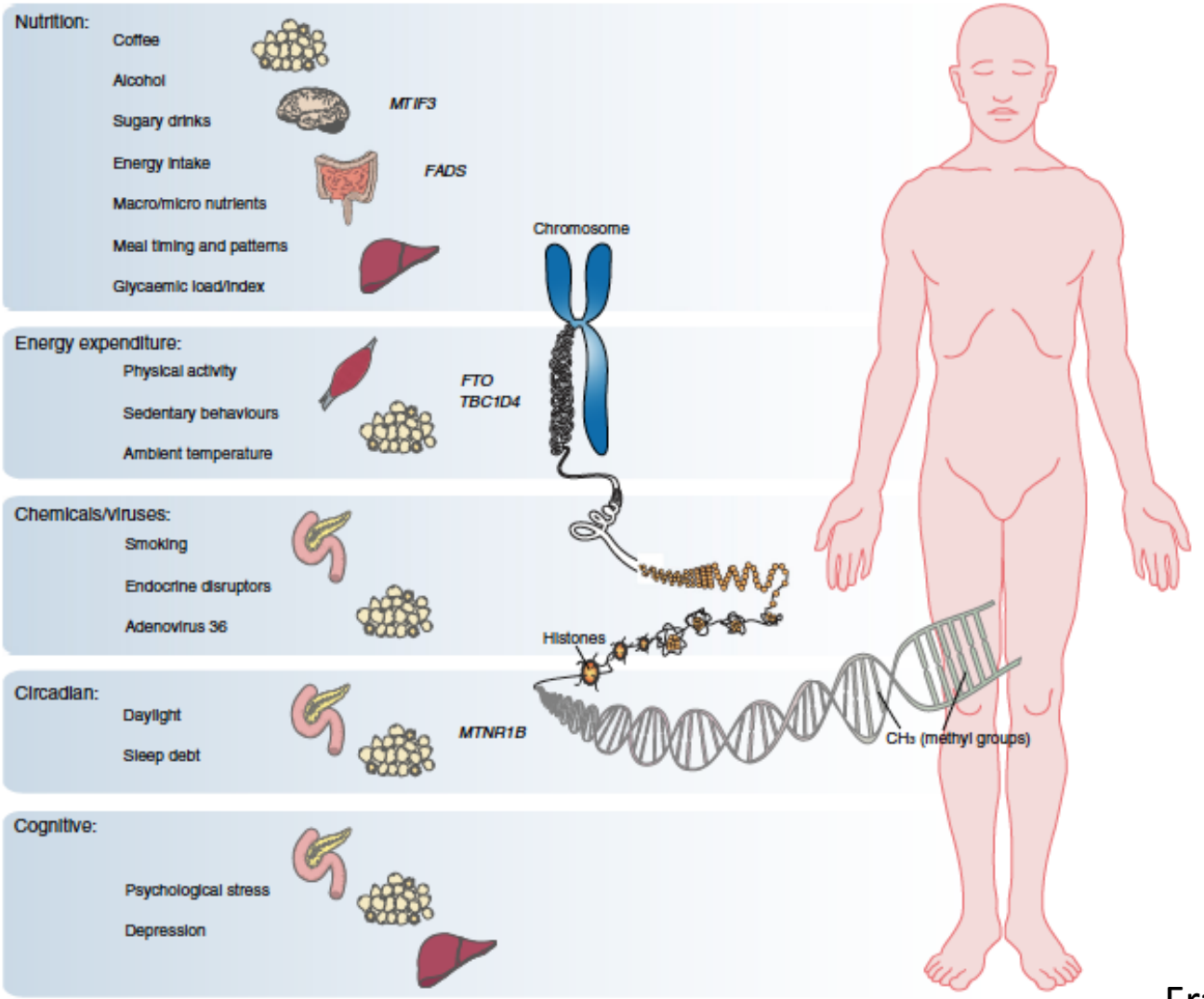
Diab Res Clin Pract. 2016, 117: 12–21

# Toward Precision Medicine: TBC1D4 Disruption is Common Among the Inuit and Leads to Underdiagnosis of Type 2 Diabetes


**TBC1 domain family member 4 (TBC1D4) is a Rab GTPase-activating protein that in humans is encoded by the *TBC1D4* gene: its disruption results in exclusively elevated postprandial glucose.**

Manousaki Diab. Care, 2016 - DOI: 10.2337/dc16-0769

# 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**

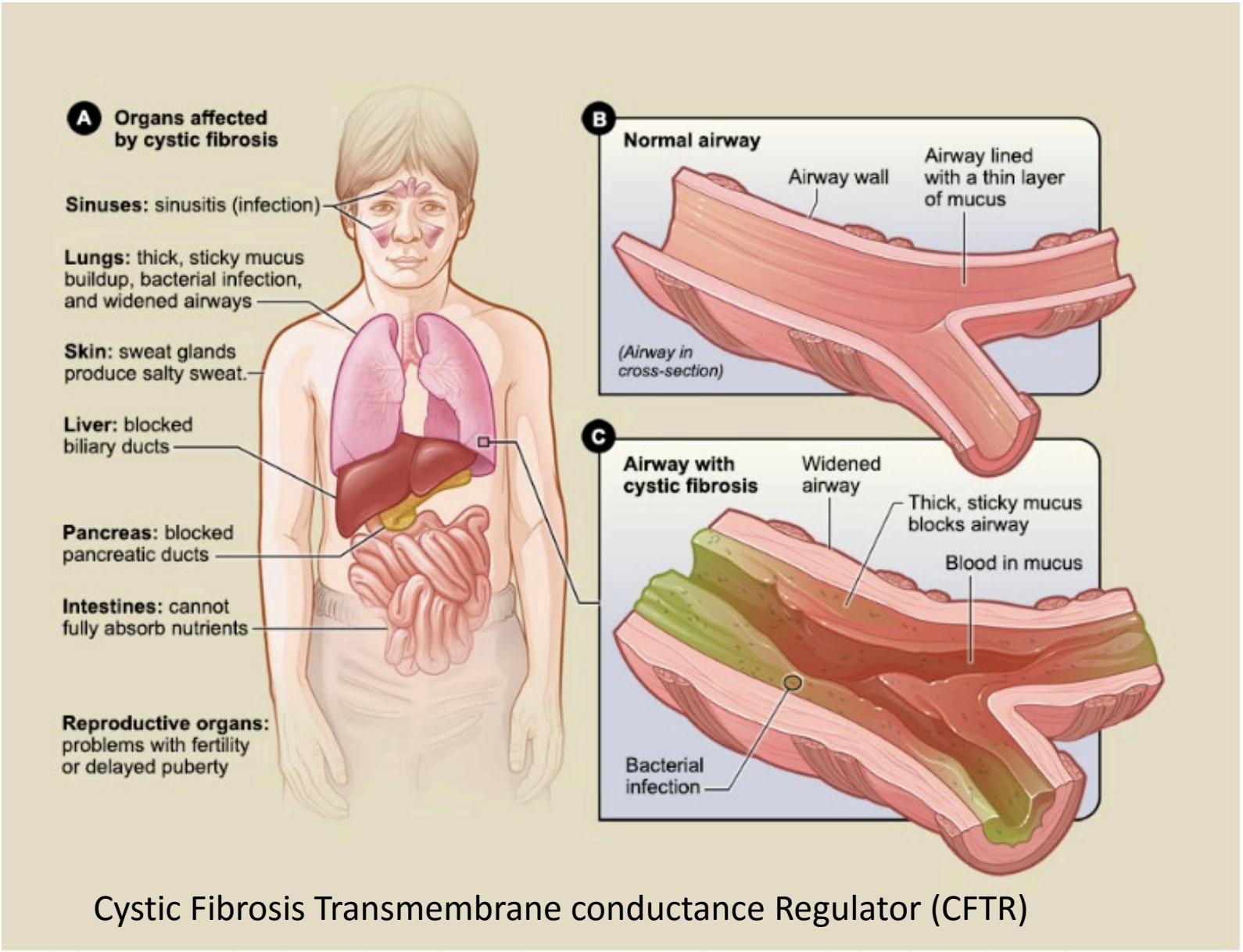
Franks P. et al 2017

# Precision medicine for type 2 diabetes.
# A schematic showing key time points for intervention in the course of type 2 diabetes (T2D) pathophysiology where precision lifestyle medicine might play a role


Franks P. et al 2017

# Fibrosi Cistica (Cystic Fibrosis)

**mutazione del gene CFTR (Phe508del CFTR mutation)**

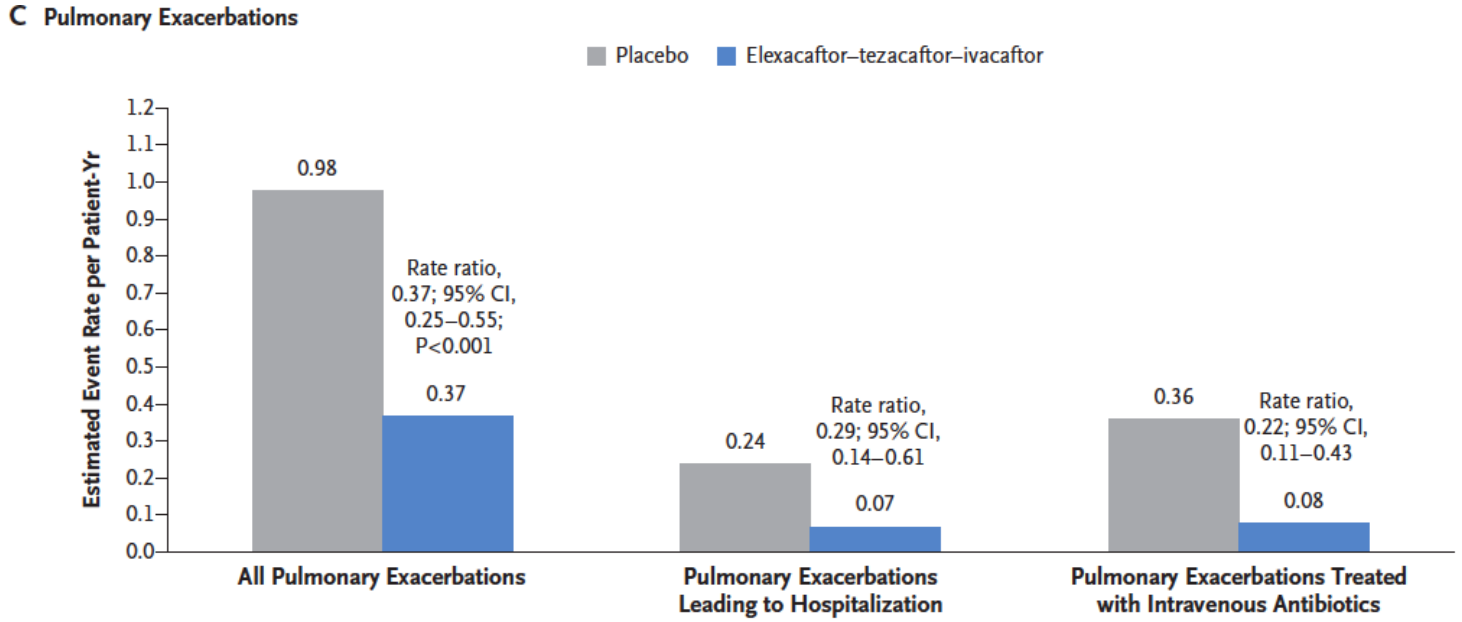



Cystic Fibrosis Transmembrane conductance Regulator (CFTR)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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



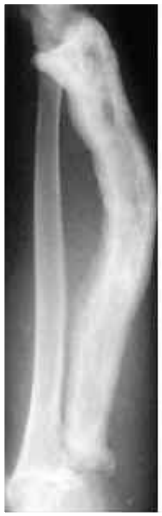

## Conclusions

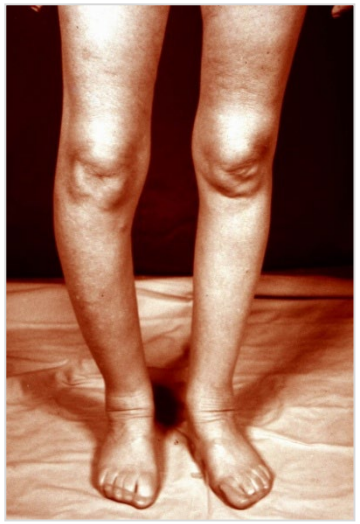
**Elexacaftor–tezacaftor–ivacaftor was efficacious in patients with cystic fibrosis with Phe508del–minimal function genotypes, in whom previous CFTR modulator regimens were ineffective.**

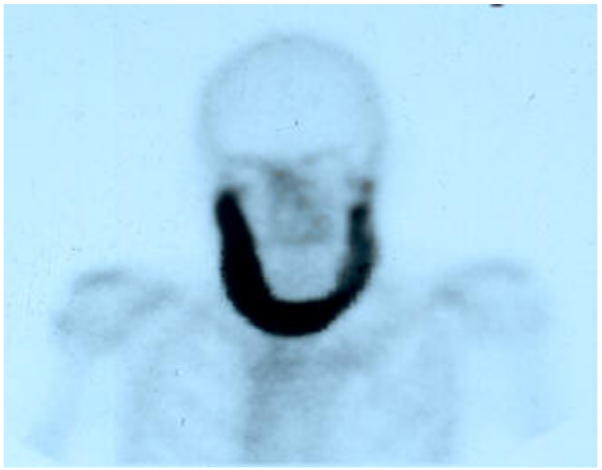
Middleton PG. Et al 2019,

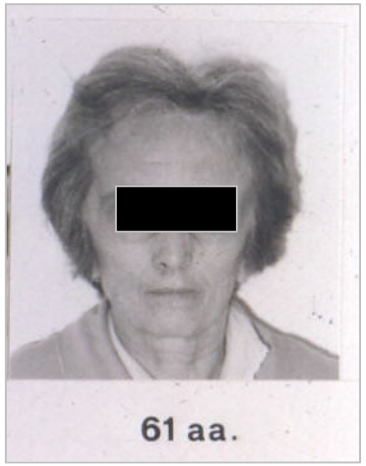
# Malattia Ossea di Paget

## Le caratteristiche cliniche ed i sintomi sono strettamente dipendenti dal numero e dalla localizzazione delle alterazioni ossee

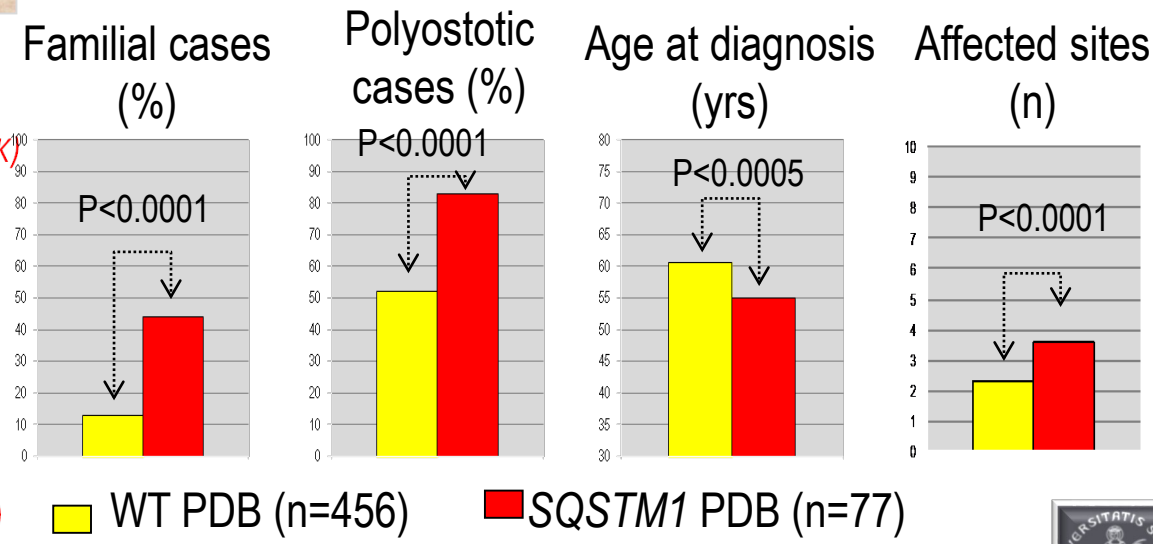









| | | |
|---|---|---|
| PDB1 | 6p21.3 | not identified |
| PDB2/FEO | 18q22.1 | *TNFSR11A (RANK)* |
| PDB3 | 5q35 | ***SQSTM1*** |
| PDB4 | 5q31 | not identified |
| PDB5 | 2q36 | not identified |
| PDB6 | 10p13 | not identified |
| PDB7 | 18q23 | not identified |
| PDB/FTD/HIBM | 9p13.3-p12 | *VCP*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



BMJ Open

# Zoledronate in the prevention of Paget's (ZiPP): protocol for a randomised trial of genetic testing and targeted zoledronic acid therapy to prevent *SQSTM1*-mediated Paget's disease of bone

Owen Cronin,[1] Laura Forsyth,[2] Kirsteen Goodman,[3] Steff C Lewis,[2] Catriona Keerie,[2] Allan Walker,[2] 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 Young-Min,[12] Malachi J McKenna,[13] Rachel K Crowley,[13] William D Fraser,[14] Luigi Gennari,[15] Ranuccio Nuti,[15] Maria Luisa Brandi,[16] Javier Del Pino-Montes,[17] Jean-Pierre Devogelaer,[18] Anne Durnez,[19,20] Giancarlo Isaia,[21] Marco Di Stefano,[21] Núria Guañabens,[22] Josep Blanch,[23] Markus J Seibel,[24,25] John P Walsh,[26,27] Mark A Kotowicz,[28] Geoffrey C Nicholson,[29] Emma L Duncan,[30,31,32] Gabor Major,[33] Anne Horne,[34] Nigel L Gilchrist,[35] Maarten Boers,[36] Gordon D Murray,[37] Keith Charnock,[38] Diana Wilkinson,[38] R Graham G Russell,[39] Stuart H Ralston[4]

# SIENA- Structural Imaging Evaluation of Normalized Atrophy

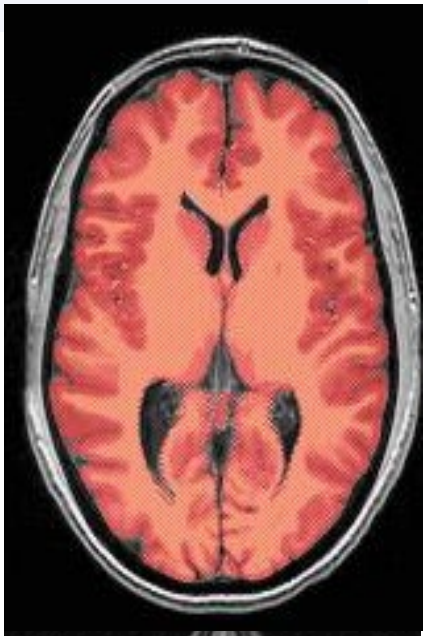
www.fmrib.ox.ac.uk/fsl

NeuroImage 17, 479–489 (2002)
doi:10.1006/nimg.2002.1040

## Accurate, Robust, and Automated Longitudinal and Cross-Sectional Brain Change Analysis

Stephen M. Smith,* Yongyue Zhang,* Mark Jenkinson,* Jacqueline Chen,*† P. M. Matthews,* Antonio Federico,‡ and Nicola De Stefano‡

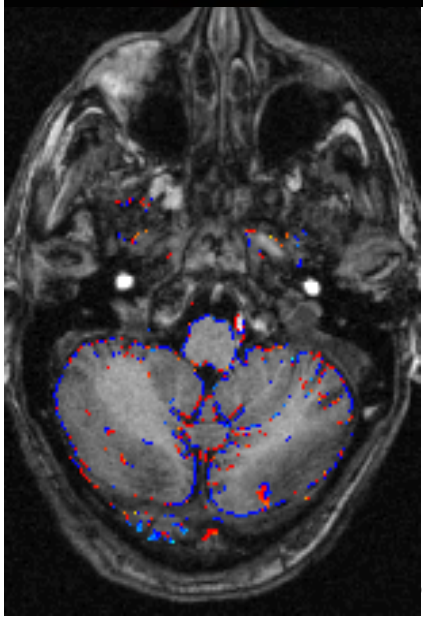
*Oxford Centre for Functional Magnetic Resonance Imaging of the Brain, Department of Clinical Neurology, FMRIB, University of Oxford, John Radcliffe Hospital, Headley Way, Headington, Oxford, United Kingdom; †Neurometabolic Unit & NMR Centre, University of Siena, Italy; and ‡MRS Lab, McConnell Brain Imaging Centre, MNI, Canada



## SIENA-XL for Improving the Assessment of Gray and White Matter Volume Changes on Brain MRI

Human Brain Mapping 00:00–00 (2017)

Marco Battaglini [1]*, Mark Jenkinson, [1,2] and Nicola De Stefano [1]; and for the Alzheimer's Disease Neuroimaging Initiative



# PROTOCOLLO DI INTESA PER LA GESTIONE DEL PROGETTO "PRECISION MEDICINE"

## TRA

L'Università degli Studi di Siena, con sede legale in Siena, Banchi di Sotto 55, C.F.: 80002070524 - P.I.: 00273530527, rappresentata dal Rettore, Prof. Francesco Frati (in prosieguo "**Università**")
L'Azienda Ospedaliero-Universitaria Senese, C. F.: 00388300527 con sede in Siena, Strada delle Scotte, 14, rappresentata dal Direttore Generale, Dott. Valtere Giovannini (in prosieguo "**A.O.U.S.**")
La Fondazione Toscana Life Sciences, con sede legale in Siena, via Fiorentina 1, C.F. 92041260529 P.I.: n. 01194710529, rappresentata dal Direttore Generale, Dott. Andrea Paolini (in prosieguo "**TLS**")

### ARTICOLO 1 – FINALITÀ

1. Le Parti, nell'ambito dei rispettivi compiti e funzioni attribuite per legge, costituiscono il Centro Regionale per la Medicina di Precisione - **C.Re.Me.P.**