SABATO 9 OTTOBRE

Nuovi scenari di prevenzione: il rischio poligenico

Alessandro Boccanelli, *Roma*

Giornale Italiano di Cardiologia Agosto 2021

CINQUANTENARIO DEL GIC

Progressi in prevenzione cardiovascolare: dalle carte del rischio allo score poligenico e alla prevenzione di precisione

Alessandro Boccanelli[1]

in collaborazione con
Simona Giampaoli[2], Giordano Bottà[3], Diego Vanuzzo[4]

Le grandi tappe della prevenzione cardiovascolare

- Anni ’70-80 : idea iniziale di misurare un certo numero di caratteristiche della popolazione sana e di seguirla nel tempo per stabilire possibili associazioni tra misure iniziali ed eventi (Minnesota, Framingham, Seven Countries)
- Identificazione dei «Fattori di rischio»
- 1986 :Conferma della reversibilità del rischio con trial preventivi multifattoriali (European Collaborative Trial of Multifactorial Prevention of CAD)
- In Italia: «Progetto cuore» 1998-2002 e 2008-2012. Indagini di popolazione e pubblicazione degli Atlanti delle Malattie Cardiovascolari

21 Gennaio 2003-Storico accordo ANMCO-ISS

Figura 2. 21 gennaio 2003 Istituto Superiore di Sanità. La firma dello storico accordo ANMCO-ISS per la collaborazione nella ricerca e prevenzione cardiovascolare. A sinistra Alessandro Boccanelli, Presidente ANMCO, e alla firma Enrico Garaci, Presidente ISS.

Figura 3. Presentazione del Progetto CUORE all'Istituto Superiore di Sanità. Da sinistra a destra: Diego Vanuzzo, Marco Ferrario, Carlo Schweiger, Sergio Licheri, Donato Greco, Simona Giampaoli, Alessandro Boccanelli, Enrico Garaci, Salvatore Panico.

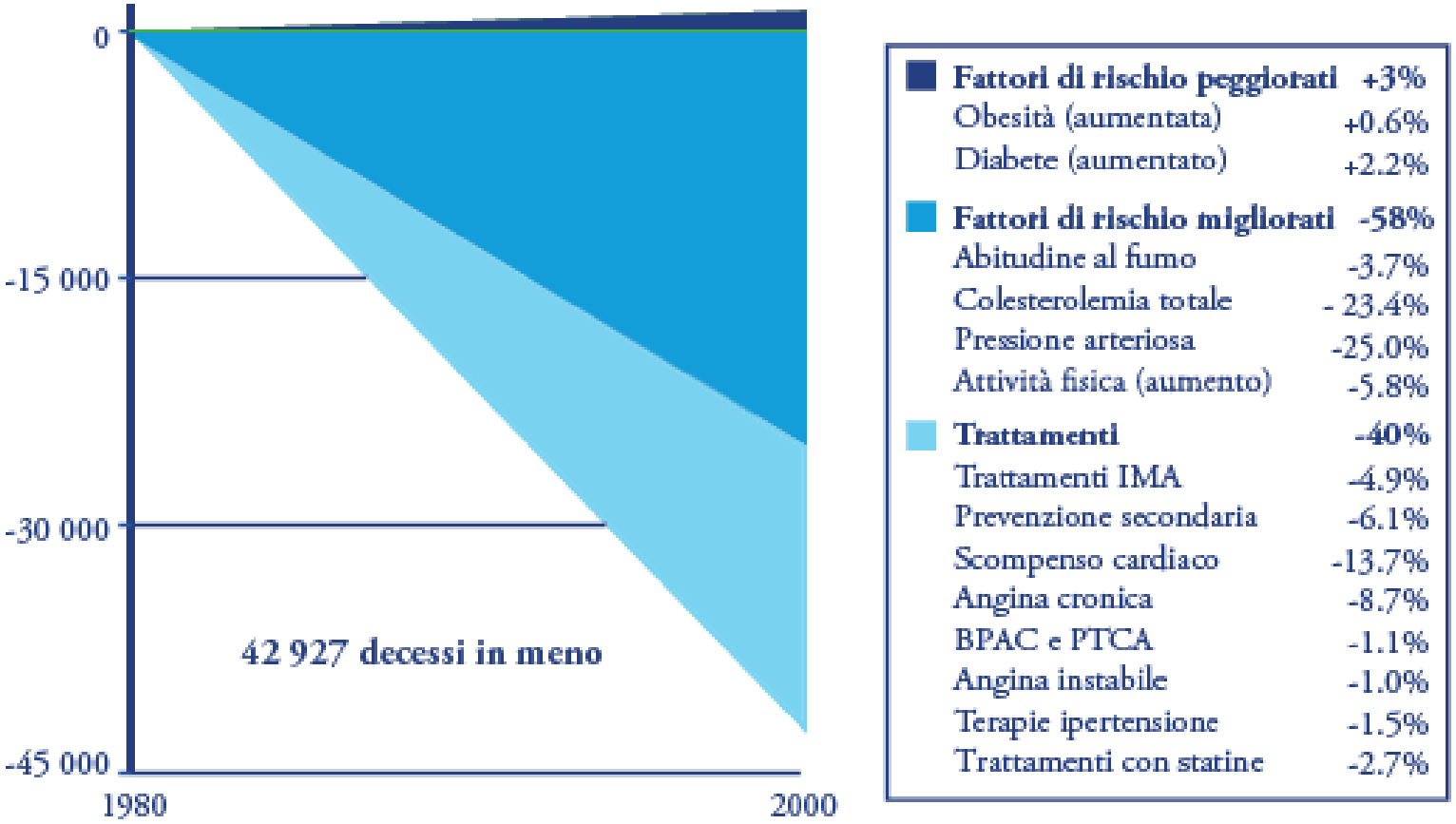

Figura 1. In Italia nel 2000 rispetto al 1980 ci sono stati 42 927 decessi in meno. Tale riduzione è attribuibile per più della metà (55%) alla riduzione dei fattori di rischio in prevenzione primaria e meno della metà (40%) alle terapie farmacologiche in fase acuta o in prevenzione secondaria. BPAC, bypass aortocoronarico; IMA, infarto miocardico acuto; PTCA, angioplastica coronarica. Modificata da: Palmieri et al.[22].

The next venture revolutions

- The era of chronicity
- Technological evolution and the invasion of artificial intelligence
- Genome knowledge for prevention and therapy
- Personalization of therapy

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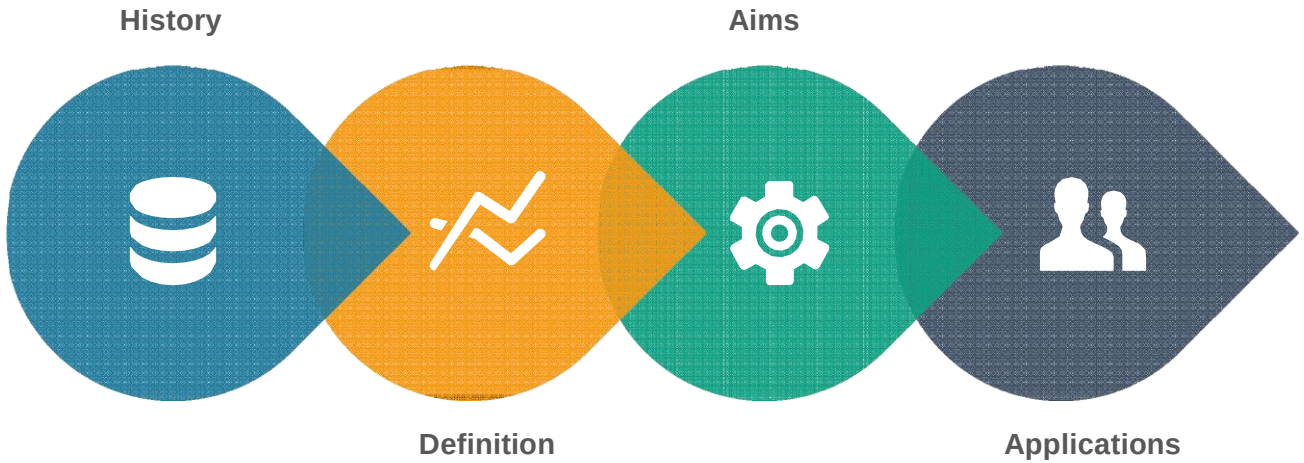
Human Genome Project

Post-genomic era



What is the more powerful form of mankind's study than to read our own instruction book?"

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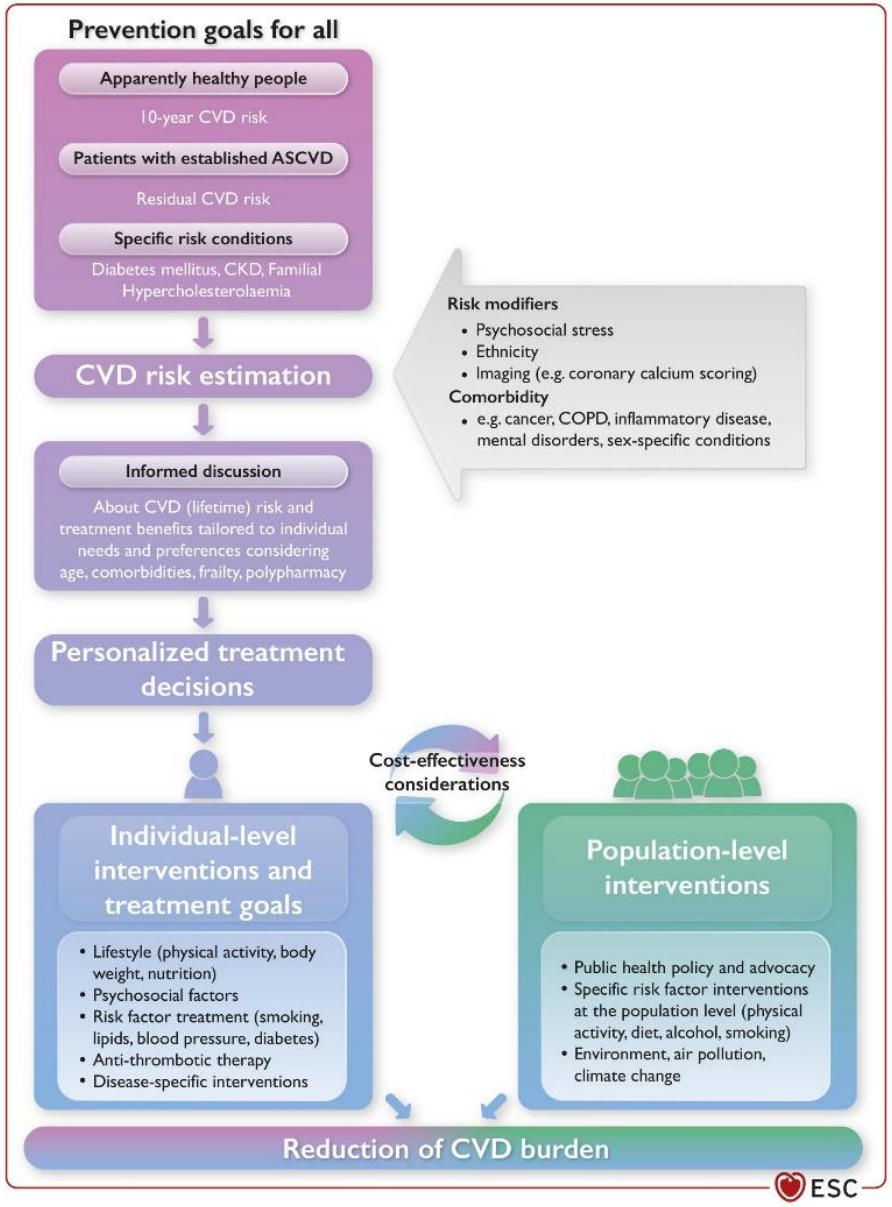

Prevention of CVD

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab484)

Revised recommendations (1)

Risk factors and clinical conditions			
2016 CVD Prevention Guidelines	**Class**	**2021 CVD Prevention Guidelines**	**Class**
ABI may be considered as a risk modifier in CVD risk assessment.	**IIb**	The routine collection of other potential modifiers, such as genetic risk scores, circulating or urinary biomarkers, or vascular tests or imaging methods (other than CAC scoring or carotid ultrasound for plaque determination), is not recommended.	**III**

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab484)

Recommendations for pharmacological low-density lipoprotein cholesterol lowering up to 70 years of age (recommendations for persons aged >70 years, see respective recommendations tables) (1)

Recommendations	Class	Level
It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the LDL-C goals set for the specific risk group.	I	A
An ultimate LDL-C goal of ≥50% reduction vs baseline and an LDL-C of <1.4 mmol/L (<55 mg/dL) should be considered in apparently healthy persons <70 years at very high risk.	IIa	C
An ultimate LDL-C goal of ≥50% reduction vs baseline and an LDL-C of <1.8 mmol/L (<70 mg/dL) should be considered in apparently healthy persons <70 years at high risk.	IIa	C

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab484)

Cost-effectiveness of cardiovascular disease prevention by lipid modification: Gaps in the evidence

EAS

Cost-effectiveness requires evidence for effects of interventions on health and healthcare over a long time period; modelling techniques fill gaps. More data are needed from RCTs and observational studies.

Direct evidence of effects of lipid-modifying treatments on overall mortality, particularly among people at low-to-moderate CVD risk, older people, and for newer interventions, is lacking. Long-term post-trial follow-up in RCTs should be encouraged.

The cost-effectiveness of using lifetime CVD risk and more precise CVD risk scores to target interventions needs further investigation.

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Limitations of Contemporary Guidelines for Managing Patients at High Genetic Risk of Coronary Artery Disease

J Am Coll Cardiol 2020 Jun 9;75(22):2769-2780

Conclusions: *Current paradigms for primary cardiovascular prevention incompletely capture a polygenic susceptibility to CAD.* ***An opportunity may exist to improve CAD prevention efforts by integrating both genetic and clinical risk.***

Aragam et al. proposed to use Polygenic Risk Score (PRS) as an additional risk enhancing factor

Why?:

1) PRS increases risk by more than 2 fold, that is the magnitude of increased risk needed to be considered as a risk enhancing factor.

2) People with high PRS are not identified by other risk factors.

JACC 2020

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- Nella pratica clinica si osserva la formazione di placche aterosclerotiche in pazienti senza apparenti fattori di rischio e colesterolo LDL non elevato.

- Studi recenti hanno dimostrato come lo score poligenico sia in grado di identificare individui con lo stesso rischio dei portatori di ipercolesterolemia, ma senza alti livelli di colesterolo.

- Uno studio sistematico su come lo score poligenico influenzi il rischio di infarto miocardico conferito dal colesterolo LDL non era ancora stato effettuato.

Over the last decade, the growth and development of large disease-based consortia have enabled the brisk discovery of genetic variants associated with CAD and other complex diseases by allowing for the aggregation of hundreds of thousands of cases and controls.

The availability of these large datasets, along with computational advances, has allowed for the easier derivation, calculation, and validation of polygenic risk scores (PRS). These PRS can now be calculated from thousands to millions of genetic variants, weighted by variant-level strength of association with disease

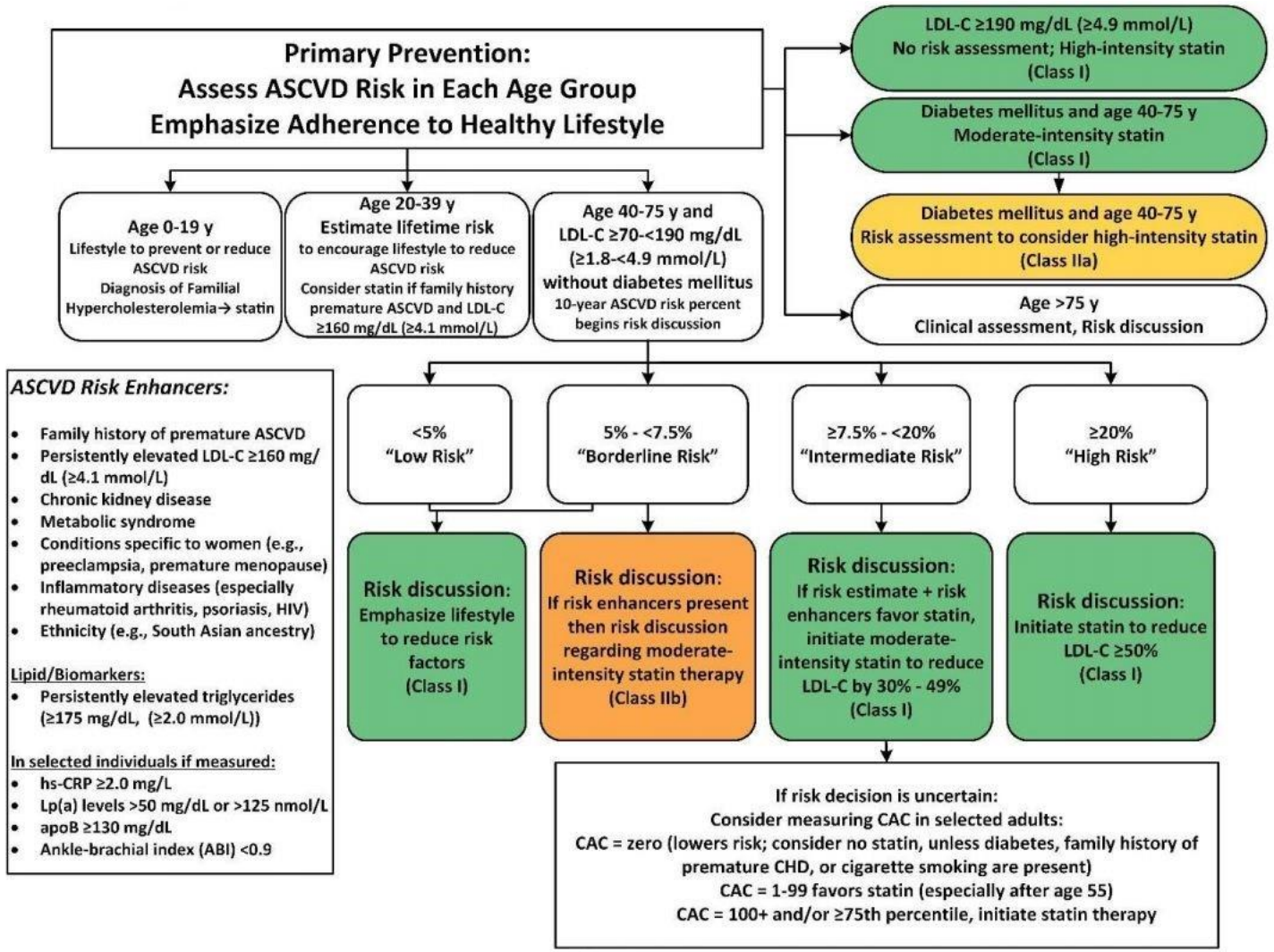
Che cos’è il Polygenic Risk Score (PRS)?

$$\hat{\phi}_j = \sum_{i=1}^{M} \hat{\beta}_i \times x_{ij}$$

- **Il PRS è uno score formato dalla somma pesata degli alleli con effetto su una determina malattia**
- **Il PRS può essere formato da centinaia fino anche a diversi milioni di variazioni genetiche**
- **I recenti PRS sono stati sviluppati e validati grazie all’utilizzo dei risultati di studi casi controllo (GWAS) su larga scala e di big data genomici longitudinali come la UKBiobank (>500.000 individui)**

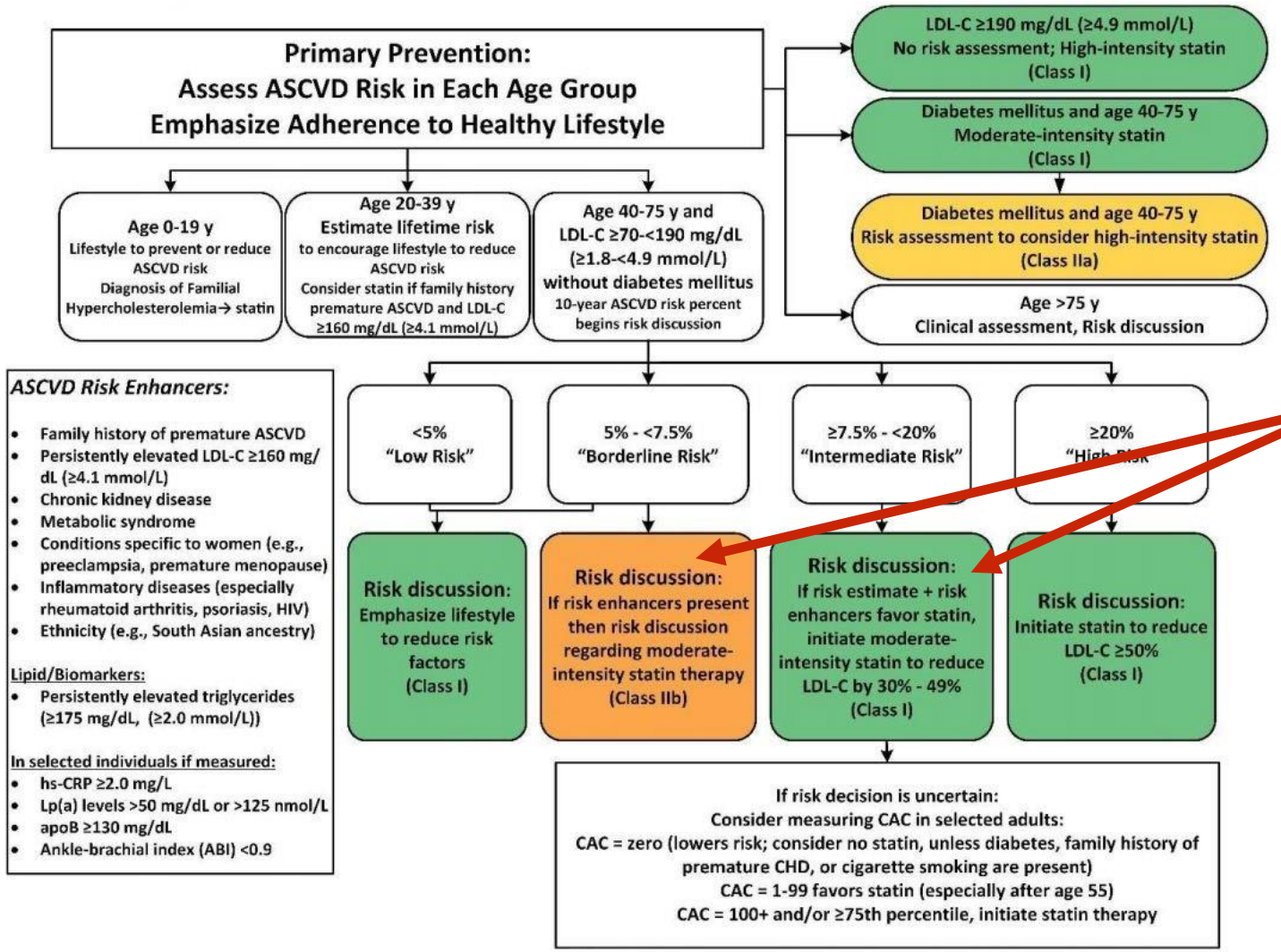
Primary prevention of ASCVD guidelines

Risk enhancers



JACC 2018

Primary prevention of ASCVD guidelines



Risk enhancers

If Individuals with borderline and intermediate risk have also a risk enhancing factor: Favor statin

JACC 2018

Polygenic Risk Score Identifies Subgroup With Higher Burden of Atherosclerosis and Greater Relative Benefit From Statin Therapy in the Primary Prevention Setting

Editorial, see p 2102

BACKGROUND: Relative risk reduction with statin therapy has been consistent across nearly all subgroups studied to date. However, in analyses of 2 randomized controlled primary prevention trials (ASCOT [Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm] and JUPITER [Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin]), statin therapy led to a greater relative risk reduction among a subgroup at high genetic risk. Here, we aimed to confirm this observation in a third primary prevention randomized controlled trial. In addition, we assessed whether those at high genetic risk had a greater burden of subclinical coronary atherosclerosis.

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PRS is also used to identify people who have normal LDL but behave as they have hypercholesterolemia.

People with high PRS and LDL-C ~130mg/dL have the same risk of those with LDL-C >190 mg/dL.

LETTER

Risk of Coronary Artery Disease Conferred by Low-Density Lipoprotein Cholesterol Depends on Polygenic Background

Alessandro Bolli, Paolo Di Domenico, Roberta Pastorino, George B. Busby, and Giordano Bottà

Originally published 8 Mar 2021 | https://doi.org/10.1161/CIRCULATIONAHA.120.051843 | Circulation. ;0

Circulation

RESEARCH LETTER

Risk of Coronary Artery Disease Conferred by Low-Density Lipoprotein Cholesterol Depends on Polygenic Background

Alessandro Bolli, PhD
Paolo Di Domenico, BSc
Roberta Pastorino, PhD
George B. Busby, DPhil
Giordano Bottà, PhD

An individual's risk of coronary artery disease (CAD) is determined by the interplay of physiologic, lifestyle, and genetic factors. Whereas measurements of low-density lipoprotein cholesterol (LDL-C) form the basis of CAD prevention strategies, the extent to which CAD risk varies with different lipid levels in individuals with varying genetic risk remains unknown. We used the polygenic risk score (PRS) to quantify the genetic risk of CAD and explore its interplay with LDL-C.

We analyzed 408 186 White British individuals from the prospective UK Biobank study.[1] UK Biobank received ethical approval from the North West Multi-Center Research Ethics Committee (11/NW/03820). This dataset was further split to produce independent validation and testing datasets using the UK Biobank first release (genotyping batch from 11 to 22) and second release (genotyping batch from 23 to 95), respectively. CAD outcome was based on self-reported diagnoses and Hospital

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Metodi

- Numero totale di individui utilizzati nello studio: 408.186

- Popolazione utilizzata: UKBiobank (studio prospettico con 10 anni di follow-up; disponibilità di dati genetici e clinici attraverso electronic health records dell'NHS)

- Sviluppato un nuovo score poligenico per infarto miocardico utilizzando 7912 casi e 121.941 controlli e un algoritmo di machine learning (stacked clumping and thresholding).

- Lo score poligenico sviluppato ha dimostrato di avere la più alta capacità predittiva fino ad ora riscontrata, migliorando gli score precedentemente pubblicati su Nature Genetics da Khera et al. e su JACC da Inouye et al.

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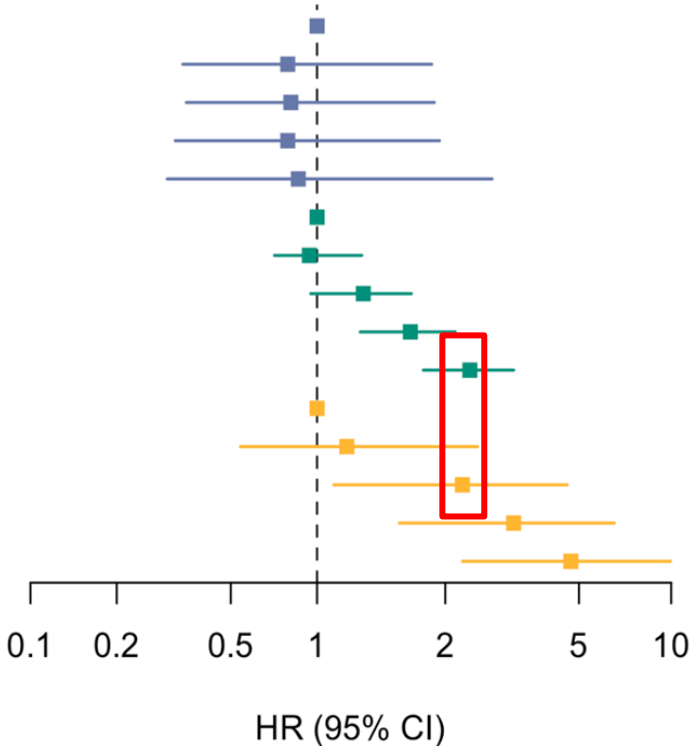
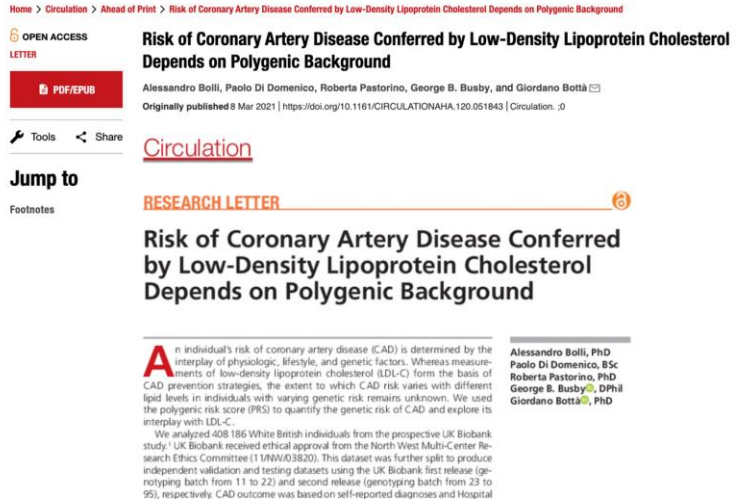
PRS influences the effect of LDL on CAD risk

Group	LDL-C (mg/dL)	HR (95%CI)	*P* value	Total Inds / Cases
Low PRS	<100	1	[Reference]	1142 / 7
	100 - <130	0.79 (0.34-1.84)	0.58	4194 / 26
	130 - <160	0.81 (0.35-1.87)	0.62	4570 / 38
	160 - <190	0.79 (0.32-1.93)	0.6	2264 / 21
	≥ 190	0.86 (0.3-2.71)	0.86	701 / 7
Int PRS	<100	1	[Reference]	6824 / 61
	100 - <130	0.94 (0.71-1.24)	0.66	28352 / 283
	130 - <160	1.25 (0.95-1.63)	0.11	38352 / 615
	160 - <190	1.62 (1.23-2.13)	<0.001	21576 / 483
	≥ 190	2.34 (1.75-3.14)	<0.001	7867 / 246
High PRS	<100	1	[Reference]	624 / 8
	100 - <130	1.15 (0.54-2.46)	0.72	3082 / 44
	130 - <160	2.23 (1.08-4.59)	0.03	4808 / 151
	160 - <190	3.14 (1.52-6.5)	0.002	3091 / 144
	≥ 190	4.71 (2.23-9.94)	<0.001	1267 / 81

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Risultati

- L’analisi dimostra come il rischio di infarto miocardico conferito dal colesterolo LDL sia modulato dallo score poligenico ($P_{interaction}$ = 0.0010).

- Individui con LDL tra 130 e 160 mg/dL e alto score poligenico hanno lo stesso rischio di chi ha LDL superiore a 190 mg/dL.

- Individui con score poligenico basso non presentano un aumento del rischio all’aumentare dei livelli di LDL.

- Individui con score poligenico alto e LDL<100 mg/dL non hanno rischio elevato

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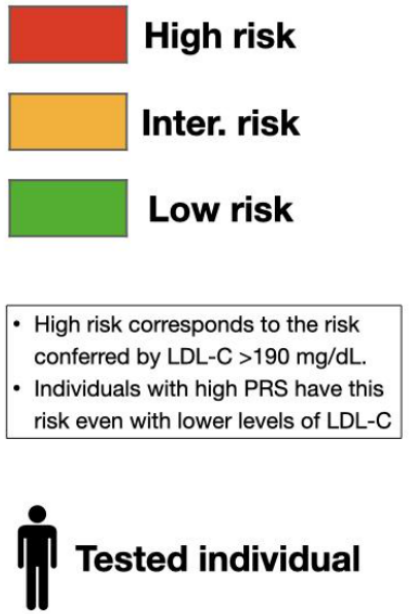
Combining CAD PRS and clinical risk factors: LDL

LDL-C mg/dL	Average PRS	High PRS
>190		
160-190		
130-160		
100-130		
<100		



Implicazioni cliniche

- Lo studio dimostra che per ottenere una reale stima del rischio conferito dall'LDL è necessario considerare la componente genetica dell'individuo attraverso lo score poligenico.

- La soglia di alto rischio dei livelli di LDL indicata a 190 mg/dL dovrebbe essere abbassata a 130 mg/dL nelle persone con score poligenico elevato.

Individuals with the highest PRS appear to have similar CAD risk as individuals with familial hypercholesterolemia, despite having relatively normal levels of cholesterol and other traditional risk factors.[7,8]

These findings suggest that newer PRS may capture residual risk left unaccounted by traditional risk factors and **add predictive value beyond traditional risk factors**.

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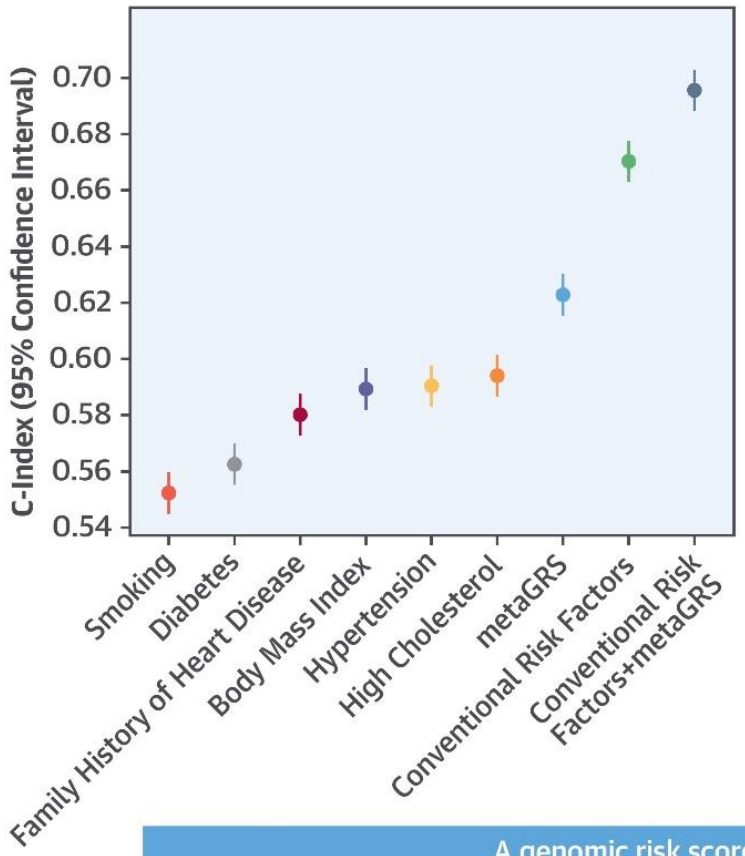
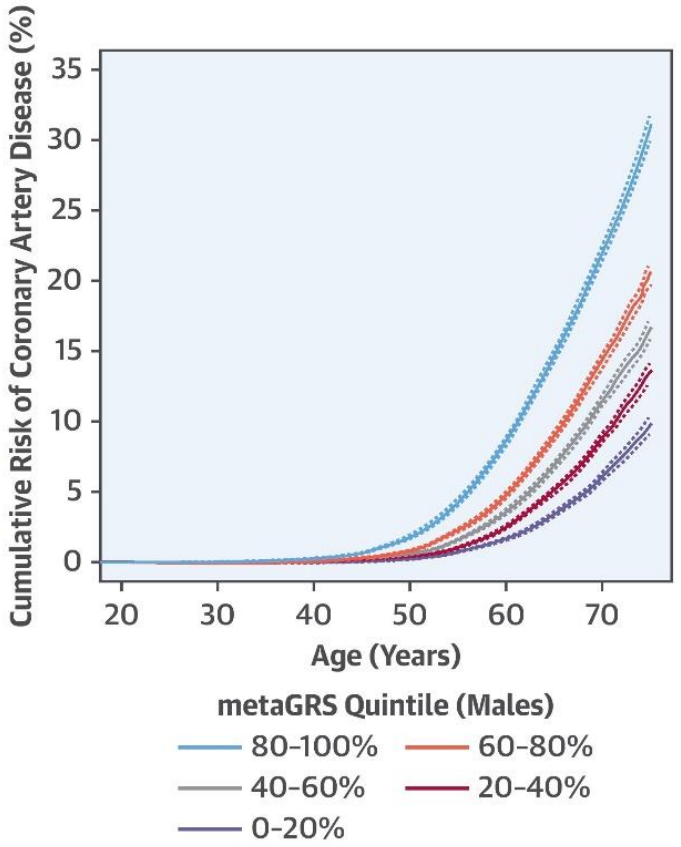
CENTRAL ILLUSTRATION: Genomic Risk Score for Coronary Artery Disease





A genomic risk score for coronary artery disease

Greater association with future coronary artery disease than any single conventional risk factor
Independent of yet complements conventional risk factors
Provides meaningful lifetime risk estimates of coronary artery disease
Quantifiable at or before birth and shows potential for risk screening in early life

Inouye, M. et al. J Am Coll Cardiol. 2018;72(16):1883-93.

Michael Inouye et al. JACC 2018;72:1883-1893

Analysis from FOURIER and ODYSSEUS studies

Among individuals in the placebo arms, a high CAD PRS was strongly associated with cardiovascular events, even after adjusting for baseline traditional risk factors. In the treatment arms, individuals at high genetic risk were found to derive the greatest absolute and relative benefit from PCSK9 inhibitors.

Taken together, these studies provide strong evidence that a **CAD PRS predicts cardiovascular events even in the setting of pre-existing CAD, independent from traditional risk factors, and that clinical application of a CAD PRS in this setting could be used to titrate intensity of low-density lipoprotein cholesterol–lowering therapy.**

Epigenetics

“It is the specific ‘software’ that a cell is running that determines its cellular identity”

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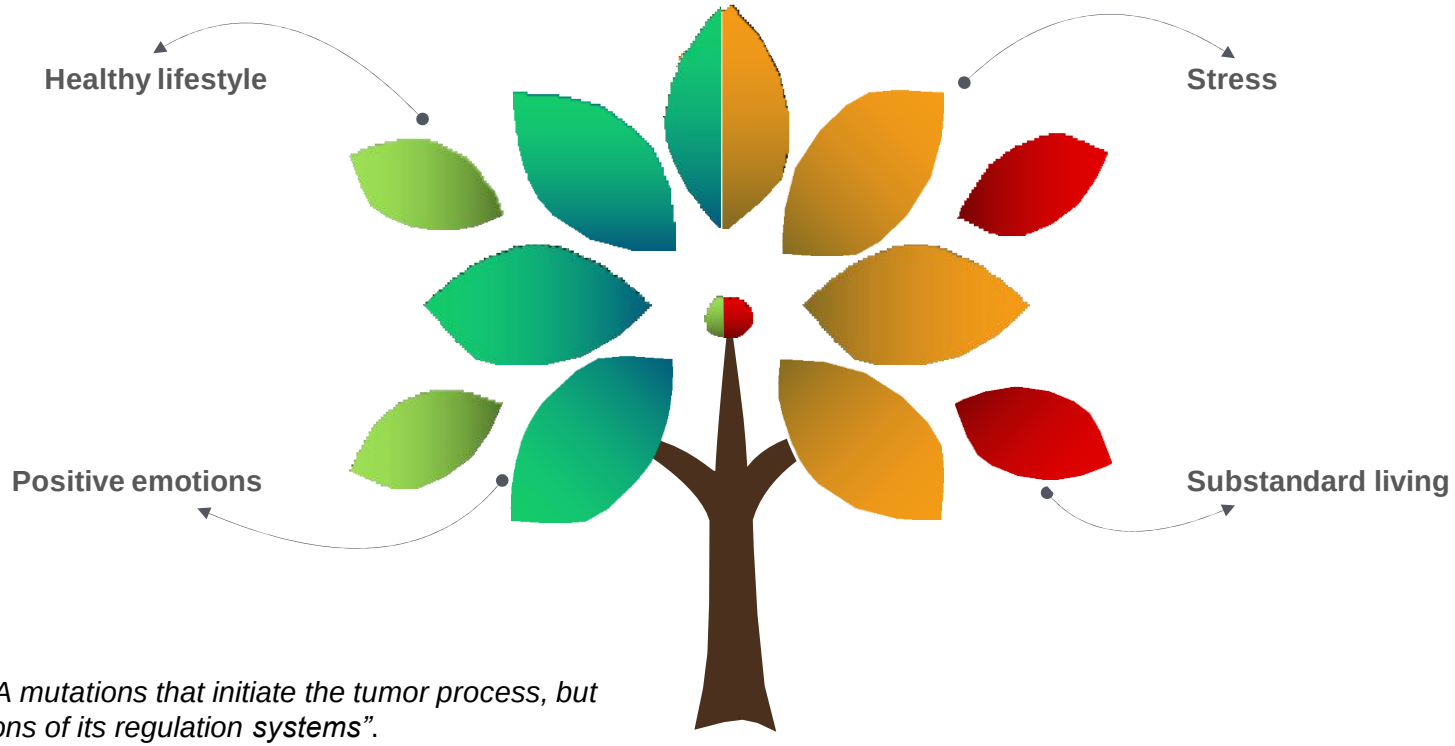
Causes and consequences

...related to it.



"It's not just DNA mutations that initiate the tumor process, but also the alterations of its regulation systems".

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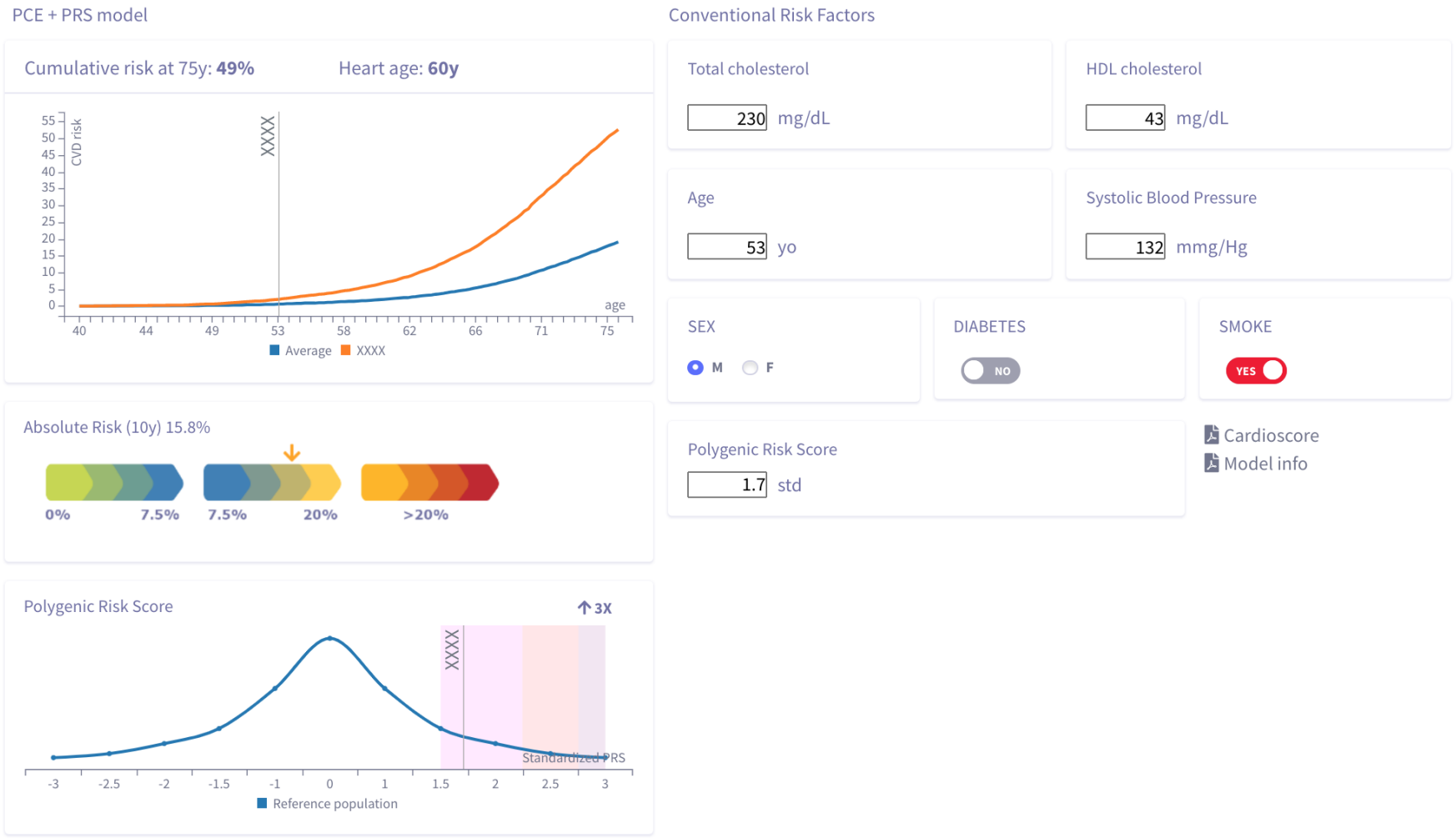
Genetics is not destiny – we can work on modifiable risk factors



Genetics is not destiny – we can work on modifiable risk factors

Genetics is not destiny – we can work on modifiable risk factors

Examples of risk modifiers that are likely to have reclassification potential

Socio-economic status, social isolation, or lack of social support.
Family history of premature CVD.
BMI and central obesity.
CT coronary calcium score.
Atherosclerotic plaques determined by carotid artery scanning.
ABI

E’ tempo di inserire lo score poligenico come «Risk Modifier»

www.escardio.org/guidelines

European Heart Journal 2016;37:2315–2381-doi:10.1093/eurheartj/ehw106

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Come utilizzare PRS?

- Migliore stima del rischio ai fini della stratificazione
- Identificare i soggetti che si giovano maggiormente del trattamento con statine
- Valutazione più precoce del rischio per migliorare la prevenzione
- Approfondire il profilo di rischio di coloro con rischio genetico noto

Implementing polygenic scores into NHS Health Checks

In this report we make the key assumption that there is sufficient evidence of clinical validity and utility to support the integration of polygenic scores into clinical / public health practice, including use across the major ethnic groups in the UK. However, there is widespread consensus that this is not yet the case, although there is increasing evidence that integrated risk prediction tools, incorporating polygenic scores, perform better than current clinical risk stratification tools, and offer greater opportunity for earlier intervention.[3] We make this assumption as there is an urgent need to address practical considerations around the delivery of this novel biomarker. These considerations will inform the development of the requisite expertise, processes, workforce, infrastructures and level of funding needed on a national scale in the near future.

Il prossimo futuro: la prevenzione di precisione e di comunità

Per la stratificazione e riclassificazione del rischio coronarico :

- Genetica e i suoi score
- Biomarcatori (in particolare dell'infiammazione)
- Imaging ultrasonografico e radiologico
- Loro integrazione mediante applicazioni di *machine learning*

Per le strategie di intervento:

- *Studio dei metabotypes* (prevenzione di precisione soprattutto alimentare)
- Contesto di Comunità della prevenzione

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PER LA DIFESA E TUTELA DELL' AMBIENTE, DELLA SALUTE E DELLA CULTURA

The Thinking Watermill Society

PROGETTO GUARCINO 2025

Progetto Guarcino Paese Sano

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PER LA DIFESA E TUTELA DELL' AMBIENTE, DELLA SALUTE E DELLA CULTURA

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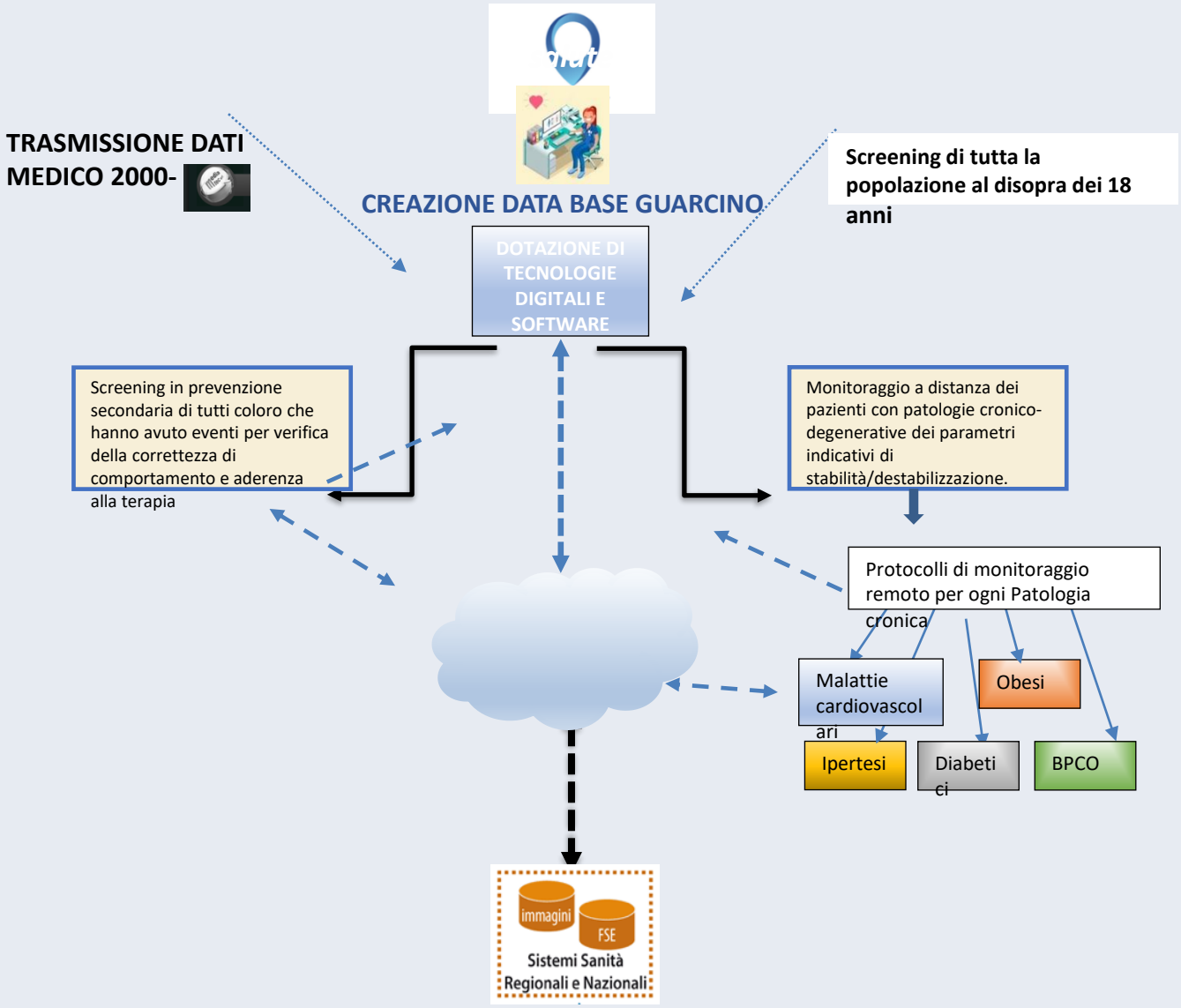
PROGETTO GUARCINO 2025

PAESE SANO

COSA FARE

- Istituire un presidio «di prossimità» con infermiera con attività di telemedicina
- Attività di screening sulla popolazione
- Strategie di intervento sulle problematiche di salute evidenziate
- Prevenzione primaria e secondaria
- Monitoraggio degli utenti affetti da patologie croniche
- Implementazione del rapporto Ospedale-territorio


TRASMISSIONE DATI MEDICO 2000-
CREAZIONE DATA BASE GUARCINO
Screening di tutta la popolazione al disopra dei 18 anni
DOTAZIONE DI TECNOLOGIE DIGITALI E SOFTWARE
Screening in prevenzione secondaria di tutti coloro che hanno avuto eventi per verifica della correttezza di comportamento e aderenza alla terapia
Monitoraggio a distanza dei pazienti con patologie cronico-degenerative dei parametri indicativi di stabilità/destabilizzazione.
Protocolli di monitoraggio remoto per ogni Patologia cronica
Malattie cardiovascolari
Obesi
Ipertesi
Diabetici
BPCO
immagini
FSE
Sistemi Sanità Regionali e Nazionali

PAESE SANO

BENEFICI ATTESI:

Miglioramento della qualità di vita, in particolare per gli anziani

Maggiore copertura territoriale

Supporto infermieristico di prossimità

Individuazione e Gestione continua a distanze delle patologie croniche

Maggiore aderenza alle cure

Minore ospedalizzazione

Abbassamento dei costi sanitari per la comunità

Supporto continuo e a distanza dalla AUSL