Perché fare lo screening mammografico: differenze con gli altri screening oncologici

Marco Zappa

ISPRO

Il sottoscritto Marco Zappa
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

Programmi di screening raccomandati dalla Comunità Europea *

- Screening Mammografico
- Screening Cervicale
- Screening Colorettale
- Screening per il tumore della prostata con PSA (+ triage con Risonanza Magnetica) e sorveglianza attiva
- Screening per il tumore del Polmone con TAC spirale a basse dosi

* *Improving cancer Screening in the European Union . SAPEA Evidence Review Report N. 10*

- There is a **strong** scientific basis for adding low-dose CT lung **cancer screening** to the current repertoire of population-wide organised screening programmes across the EU, based on effectiveness and mortality burden
- There is **good** scientific evidence for the benefit of **organised PSA-based prostate cancer screening**, particularly in combination with additional MRI scanning and active surveillance for PSA-positive men.

Altri screening considerati

- While there is *insufficient evidence* to recommend endoscopic screening of **gastric cancer** in Europe, the screen and treat strategy for reducing H. pylori infection provides an opportunity to prevent gastric cancer in EU member countries with intermediate to high gastric cancer incidence
- **Oesophageal cancer** is a lethal disease that urgently *needs better approaches* to screening and prevention.
- … two large randomised controlled trials on screening for **ovarian cancer** *have failed to show a beneficial effect*. We do not find scientific grounds to recommend ovarian cancer screening for EU member states at the current time

le relazioni fra i vari programmi di screening

- Sovradiagnosi
- Screening basato sul rischio ➔ stratificazione dei protocolli

Sovradiagnosi

"Diagnosi di una lesione tumorale che, seppur confermata istologicamente, non sarebbe stata diagnosticata nel corso della vita del soggetto in assenza di screening"

E' la combinazione di due cause:

1. la storia naturale della neoplasia (scarsa o nessuna progressività di certe lesioni)
2. la presenza di rischi competitivi di morte (tale che il soggetto morirà per un'altra causa prima che il tumore possa comparire clinicamente)

Paci and Duffy, Breast Cancer Research, 2005

La sovradiagnosi determina oggi quasi necessariamente un sovratrattamento.

- L'unico modo per ridurre il sovratrattamento che consegue alla sovradiagnosi è riuscire a quantificare il potenziale aggressivo dei tumori ed adottare una politica di osservazione per i tumori a basso potenziale aggressivo.

E' possibile avere un sovratrattamento anche in assenza di sovradiagnosi.

- Ad es. in caso di terapie aggressive non necessarie a tumori 'reali e progressivi', che però sono ancora ad uno stadio molto precoce.
- Appropriatezza del trattamento a seconda dello stadio del tumore (Zorzi et al, 2006).

screening Mammografico e screening Prostata

- Storia comune di controversie.
- Riduce la mortalità ? SI, ma a che costo ?
- Quale è il peso della Sovradiagnosi ?

- La Sovradiagnosi pesa molto sullo screening della Prostata
- Sia per le dimensioni
- Sia per gli effetti delle biopsie e del trattamento

➔sepsi, disfunzione erettile, incontinenza urinaria …

Reconsidering the Trade-offs of Prostate Cancer Screening

Jonathan E. Shoag, M.D., Yaw A. Nyame, M.D., M.B.A., Roman Gulati, M.S., Ruth Etzioni, Ph.D.,

N ENGL J MED 382;25 NEJM.ORG JUNE 18, 2020

Table 1. Estimates of the Number Needed to Screen and the Number of Excess Prostate Cancer Diagnoses to Prevent One Death from Prostate Cancer during the Indicated Follow-up Interval.*

Variable	No. Needed to Screen (95% CI)	No. of Excess Diagnoses (95% CI)
16 Yr of follow-up: empirical estimate from ERSPC	570 (380–1137)	18 (12–35)
25 Yr of follow-up: conservative model estimate	385 (273–687)	11 (8–20)

Come ridurre gli effetti collaterali negativi nello screening prostatico ?

- Distinguere la diagnosi dal trattamento. Nei casi potenzialmente clinicamente insignificanti il trattamento è dilazionato/evitato
- Ridurre la diagnosi dei tumori della prostata più probabilmente clinicamente insignificanti

➔ ***Active surveillance*** Patients with ISUP grade 1, clinical stage cT1c or cT2a, PSA < 10 ng/mL and PSA-D < 0.15 ng/mL/cc**, remain under close surveillance** through structured surveillance programs with regular follow up consisting of PSA testing, clinical examination, MRI imaging and repeat prostate biopsies, **with curative treatment being prompted by pre-defined thresholds** indicative of potentially life-threatening disease, which is still curable, while considering individual life expectancy.

Table 4.2: International Society of Urological Pathology 2014 grade (group) system

Gleason score	ISUP grade
2-6	1
7 (3+4)	2
7 (4+3)	3
8 (4+4 or 3+5 or 5+3)	4
9-10 (4+5 or 5+4 or 5+5)	5

Distribution of Gleason Score in ERSPC PC cases*

Gleason	<=6	7	8	9	10
Control arm	47,8%	32,7%	9,4%	9,1%	1,0%
Study arm	65,2%	23,8%	5,9%	4,6%	0,5%

*Missing cases (7,3%) excluded

* Thank to D. Puliti

Table 6.1.2: Active surveillance in screening-detected prostate cancer
(large cohorts with longer-term follow-up)

Studies	N	Median FU (mo)	pT3 in RP patients*	10-year OS (%)	10-year CSS (%)
Van As, *et al.* 2008 [487]	326	22	8/18 (44%)	98	100
Carter, *et al.* 2007 [488]	407	41	10/49 (20%)	98	100
Adamy, *et al.* 2011 [489]	533-1,000	48	4/24 (17%)	90	99
Soloway, *et al.* 2010 [490]	99	45	0/2	100	100
Roemeling, *et al.* 2007 [491]	278	41	-	89	100
Godtman, *et al.* 2013 [492]	439	72	-	81	99.5
Klotz, *et al.* 2015 [493]	993	77	-	85	98.1
Tosoian, *et al.* 2020 [494]	1,818	60	-	93	99.9
Carlsson, *et al.* 2020 [495]	2,664	52	-	94	100
Total	**7,557-8,024**	**50.8**	**-**	**92**	**99.6**

** Patients receiving active therapy following initial active surveillance.*

CSS = cancer-specific survival; FU = follow-up; mo = months; n = number of patients; n.r. = not reported; OS = overall survival; RP = radical prostatectomy.

Van Poppel et al Eur J Urol 2021

La Risonanza Magnetica (mp) come test di triage dopo un PSA positive ha trasformato il processo diagnostico

Foundational studies include the verification PROMIS study [1], the randomised international PRECISION and multicentre Canadian trials [2,3], and head-to-head systematic versus MRI-directed biopsy studies [4].

Taken together, the evidence indicates that MRI before biopsy can allow **one-third of men to avoid an immediate biopsy** and **reduce overdiagnosis**, **with 40% fewer clinically unimportant cancers** and approximately **15% more clinically important cancers detected** [5].

1) Ahmed HU et al , Lancet 2017

2) Ahmed HU et al , Lancet 2017

3) Klotz l et al, Jama Oncology 2021

4) Van der Leest M, Eur Urol 2019

5) Drost FH et al, Cochrane database system rev 2019

IPAAC document

Test di triage

- E un test differente dal test di base , eseguito nei soggetti positivi al test primario che permette di distinguere i soggetti in quelli che vanno alla biopsia rispetto a quelli che vanno in protocolli di sorveglianza (non ritornano immediatamente allo screening)

- Usato attualmente nello screening cervicale
- Il test di base è l'HPV se positivo ➔ Test citologico .
- Se test citologico negativo➔ ripetizione HPV a un anno. Se HPV a un anno si conferma positivo ➔ colposcopia

- ***Si abbandona la logica binaria dello screening***

Test di triage valutati

1) cytology at a threshold of ASC-US+
2) genotyping for HPV16/18
3) p16/Ki-67 immunocytochemistry (dual staining),
4) VIA,
5) combined testing with HPV16/18 genotyping and cytology at a threshold of ASC-US+ (in which HPV16/18-positive women are referred directly for colposcopy and women who are positive only for other carcinogenic HPV types are further triaged with cytology)
6) combined testing with HPV16/18 genotyping and VIA

- **IARC Handbook Vol 18**

Karolinska Protocol
(Dillner, Eurogin 2022)

According to new clinical guidelines, follow-up of HPV positivity will be determined by age and type

- 5 year screening intervals 23-49 or 7 years 50-70 after HPV negativity
- HPV 16,18,45 (high oncogenicity, vaccine types)- reflex testing with cytology from age 23
  - Cytology positive to colposcopy
  - **Cytology negative to repeat testing after 18 months**

- HPV 31,33,52,58 (medium oncogenicity, vaccine types)-reflex testing with cytology from age 23
  - Cytology positive to colposcopy
  - Cytology negative
    - Age <28 new sample after 5 years
    - **Age >28 – new sample after 3 years**

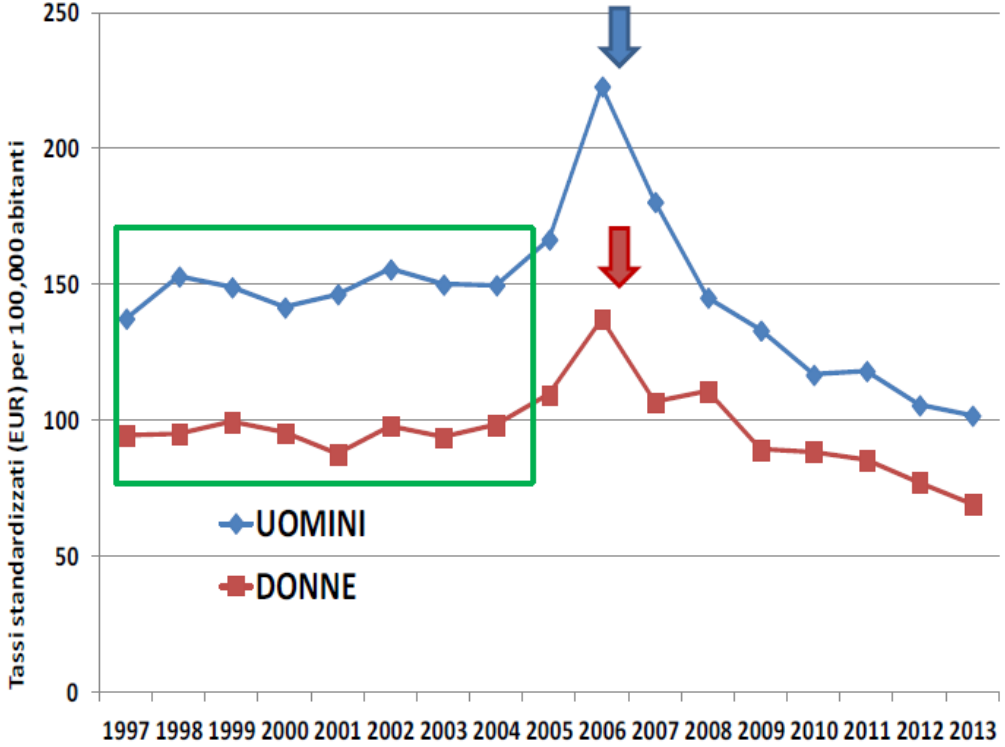
- HPV 35,39,51,56,66,68 (low oncogenicity, non vaccine types)- reflex testing with cytology from age 33
  - Cytology positive to colposcopy
  - **Cytology negative to repeat testing after 5 years**

Ma per gli altri screening esiste un problema di sovradiagnosi ?

- Lo **screening cervicale** agisce sostanzialmente sui precursori del tumore (CIN2-CIN3)
- Lo **screening colorettale basato sulla sigmoidoscopia/colonscopia** agisce sostanzialmente sui precursori del tumore (adenomi)
- Lo **screening colorettale basato sul FIT** agisce in parte sui precursori del tumori (adenomi avanzati)

➔Si ha una diminuzione dell'incidenza

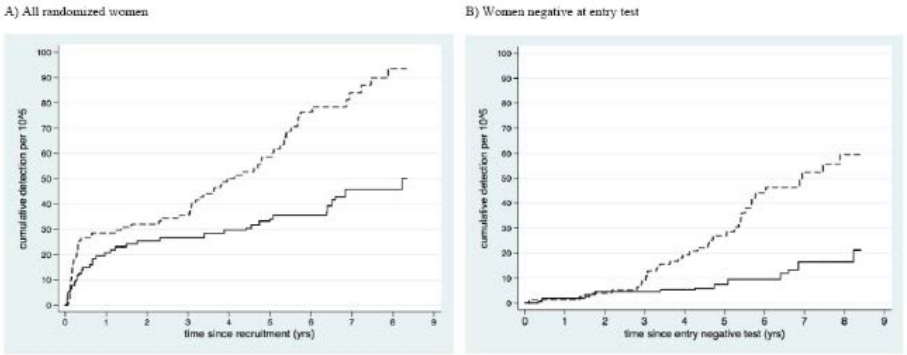
Emilia Romagna. Tassi di incidenza del tumore del colon retto. Età 50-69 anni



Courtesy Alessandra Ravaioli

Screening cervicale confronto fra test HPV e test citologico

Il test HPV anticipa la diagnosi di CIN3 e ha una maggiore efficacia nel prevenire i Ca invasivi



Solid lines: HPV group. Dotted lines: cytology group
In panel (B) observations are censored 6 months after CIN2 or CIN3 detection, if any.

Sovradiagnosi e screening polmonare con tac spirale a piccole dosi

- Vi era una forte attesa di sovradiagnosi in quanto il trial della Mayo Clinic degli anni settanta basato sull'RX non aveva dimostrato effetti sulla mortalità ma un sostanziale aumento dell'incidenza .
- Il nuovo test di screening (TAC spirale a basse dose) si era dimostrata molto più sensibile dunque si temeva un effetto asulla sovradiagnosi
- Invece…

9211 smokers

Lung Cancer Mortality in the Mayo Lung Project: Impact of Extended Follow-up

Pamela M. Marcus, Erik J. Bergstralh, Richard M. Fagerstrom, David E. Williams, Robert Fontana, William F. Taylor, Philip C. Prorok

Background: **The Mayo Lung Project (MLP) was a randomized, controlled clinical trial of lung cancer screening that was conducted in 9211 male smokers between 1971 and 1983. The intervention arm was offered chest x-ray and sputum cytology every 4 months for 6 years; the usual-care arm was advised at trial entry to receive the same tests annually. No lung cancer mortality benefit was evident at the end of the study. We have extended follow-up through 1996.** ***Methods:*** **A National Death Index–PLUS search was used to assign vital status and date and cause of death for 6523 participants with unknown information. The median survival for lung cancer patients diagnosed before July 1, 1983, was calculated by use of Kaplan–Meier estimates. Survival curves were compared with the log-rank test.** ***Results:*** **The median follow-up time was 20.5 years. Lung cancer mortality was 4.4 (95% confidence interval [CI] = 3.9–4.9) deaths per 1000 person-years in the intervention arm and 3.9 (95% CI = 3.5–4.4) in the usual-care arm (two-sided *P* for difference = .09). For participants diagnosed with lung cancer before July 1, 1983, survival was better in the intervention arm (two-sided *P* = .0039). The median survival for patients with resected early-stage disease was 16.0 years in the intervention arm versus 5.0 years in the usual-care arm.** ***Conclusions:*** **Extended follow-up of MLP participants did not reveal a lung cancer mortality reduction for the intervention arm. Similar mortality but better survival for individuals in the intervention arm indicates that some lesions with limited clinical relevance may have been identified in the intervention arm. [J Natl Cancer Inst 2000;92:1308–16]**

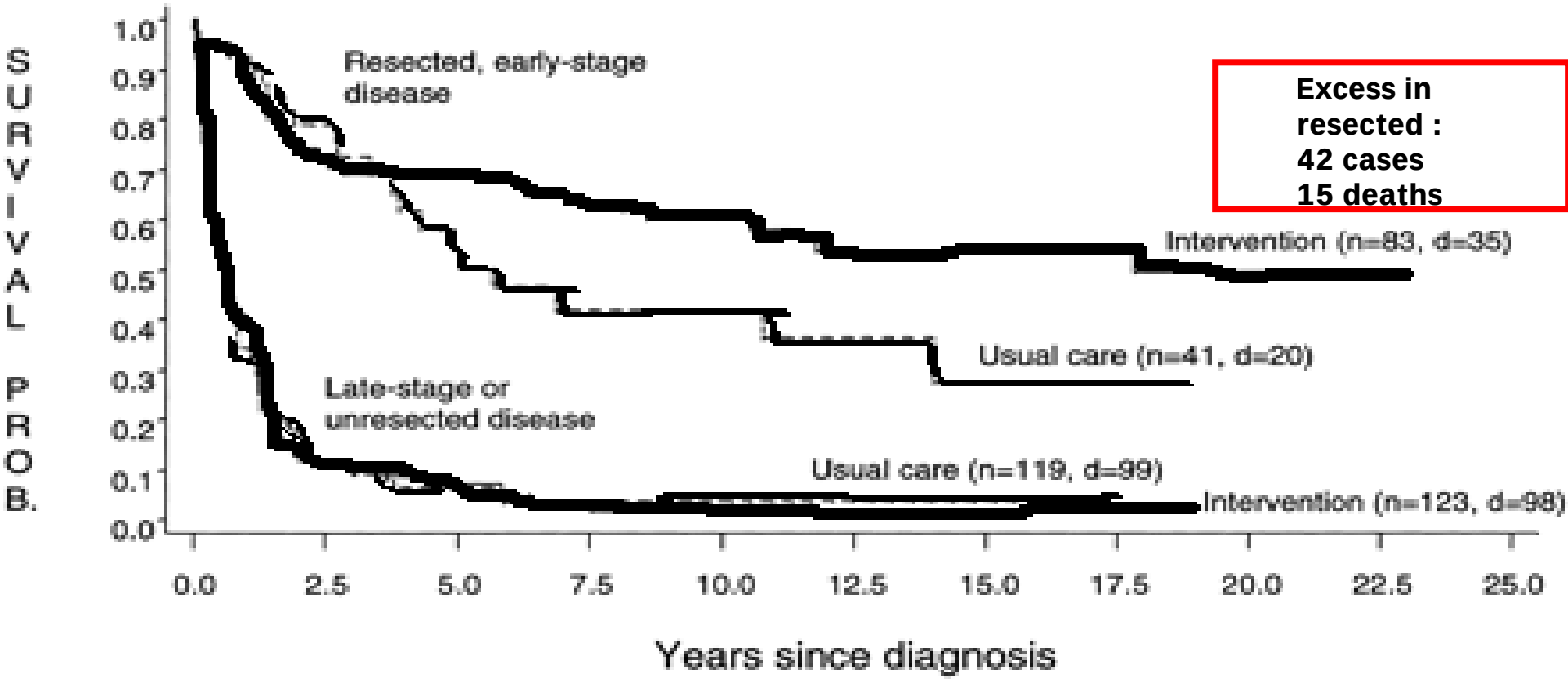
screening, most often on the grounds that the trial did not have adequate statistical power to identify a very modest reduction in lung cancer mortality and on the presumption that substantial contamination in the control arm reduced power even further *(5)*. In addition, statistical modeling and increased knowledge regarding lung cancer progression suggest that the follow-up time in the MLP may have been too short (an average of 3 years after the last screening) for observation of a screening benefit *(6)*.

We have extended follow-up of the MLP participants through the end of 1996, with the goal of examining whether additional time would allow for a reduction in lung cancer mortality to be observed in the intervention arm. Because participants diagnosed with lung cancer in that arm experienced more favorable survival as of July 1, 1983, we also wanted to explore whether that trend continued, with an eye toward assessing the impact of lead-time bias (earlier diagnosis of disease but no postponement of death) and overdiagnosis (identification of lesions with limited clinical relevance that would not have been detected in the absence of screening) *(7)*, two common screening biases that may be responsible for what some suggest are conflicting findings in the MLP *(8)*.

Methods

The Mayo Lung Project

The MLP was designed to evaluate whether an intense regimen of lung cancer screening by use of chest x-ray and sputum cytology would reduce lung cancer mortality in male smokers. From November 1971 through July 1976, 10 933 male Mayo Clinic (Rochester, MN) outpatients who smoked and were not suspected of having lung cancer were prevalence screened for the disease by use of



Excess in resected :
42 cases
15 deaths

OUTCOME OF RCTs ON LUNG CANCER SCREENING:

	NLST (NEJM 2011)	NELSON (WCLC 2018)	MILD (WCLC 2018)	ITALUNG (Thorax, 2017)	DANTE (EJCP 2016)	DANISH (AJRCCMM 2016)
N° enrolled	53 454	15792 (84% males)	4099	3206	2450	4104
Median follow-up	6.5 years	10 years	10 years	9.3 years	8.6 years	9.5 years
RR LC mortality	0.80 (0.73-0.93)	0.74 (0.60 – 0.91) 0.61 (0.35 – 1.04) for male and female	0.61 (0.39 – 0.95)	0.70 (0.47-1.03)	1.00 (0.69-1.44)	1.03 (0.66 - 1.61)
RR overall mortality	0.93 (0.86 - 0.99)	Not reported	0.80 (0.62 – 1.03)	0.83 (0.67-1.03)	0.95 (0.77-1.17)	1.02 (0.82-1.26)

Pooled MILD + DANTE:
RR LC mortality
0.83 (0.61-1.12)

Unbalanced randomisation

Eccesso di incidenza nei trial sullo screening polmonare

	NLST J Thoracic Oncol 2011	**NELSON** (De Koning et al NEJM 2020)		**ITALUNG** (Paci et al, Thorax 2017)
N° arruolati	53451	15791		3206
Follow-up (mediana)	11,3 aa	10 aa		9.3 aa
RR LC incidence	1,01 (0.95-1,09)	1.14; (0.97 to 1.33)		0.92 (0.66-1.28)

Attesa:

I noduli vengono biopsiati/resecati solo se cambiano in dimensioni e densità

Lung-RADS© Version 1.1

Assessment Categories Release date: 2019

Category Descriptor	Lung-RADS Score	Findings	Management	Risk of Malignancy	Est. Population Prevalence
Incomplete	0	Prior chest CT examination(s) being located for comparison Part or all of lungs cannot be evaluated	Additional lung cancer screening CT images and/or comparison to prior chest CT examinations is needed	n/a	1%
Negative No nodules and definitely benign nodules	1	No lung nodules Nodule(s) with specific calcifications: complete, central, popcorn, concentric rings and fat containing nodules	Continue annual screening with LDCT in 12 months	< 1%	90%
Benign Appearance or Behavior Nodules with a very low likelihood of becoming a clinically active cancer due to size or lack of growth	2	Perifissural nodule(s) *(See Footnote 11)*: < 10 mm (524 mm³) **Solid nodule(s):** < 6 mm (< 113 mm³) new < 4 mm (< 34 mm³) **Part solid nodule(s):** < 6 mm total diameter (< 113 mm³) on baseline screening **Non solid nodule(s) (GGN):** <30 mm (<14137 mm³) OR ≥ 30 mm (≥ 14137 mm³) and unchanged or slowly growing **Category 3 or 4 nodules unchanged for ≥ 3 months**			
Probably Benign Probably benign finding(s) - short term follow up suggested; includes nodules with a low likelihood of becoming a clinically active cancer	3	**Solid nodule(s):** ≥ 6 to < 8 mm (≥ 113 to < 268 mm³) at baseline OR new 4 mm to < 8 mm (34 to < 113 mm³) **Part solid nodule(s)** ≥ 6 mm total diameter (≥ 113 mm³) with solid component < 6 mm (< 113 mm³) OR new < 6 mm total diameter (< 113 mm³) **Non solid nodule(s)** (GGN) ≥ 30 mm (≥ 14137 mm³) on baseline CT or new	6 month LDCT	1-2%	5%
Suspicious Findings for which additional diagnostic testing is recommended	4A	**Solid nodule(s):** ≥ 8 to < 15 mm (≥ 268 to < 1767 mm³) at baseline OR growing ≥ 8 mm (≥ 268 mm³) OR new 6 to < 8 mm (113 to < 268 mm³) **Part solid nodule(s):** ≥ 6 mm (≥ 113 mm³) with solid component ≥ 6 mm to < 8 mm (≥ 113 to < 268 mm³) OR with a new or growing ≥ 4 mm (≥ 34 mm³) solid component **Endobronchial nodule**	3 month LDCT; PET/CT may be used when there is a ≥ 8 mm (≥ 268 mm³) solid component	5-15%	2%
Very Suspicious Findings for which additional diagnostic testing and/or tissue sampling is recommended	4B	**Solid nodule(s)** ≥ 15 mm (≥ 1767 mm³) OR new or growing, and ≥ 8 mm (≥ 268 mm³) **Part solid nodule(s) with:** a solid component ≥ 8 mm (≥ 268 mm³) OR a new or growing ≥ 4 mm (≥ 34 mm³) solid component	Chest CT with or without contrast, PET/CT and/or tissue sampling depending on the *probability of malignancy and comorbidities. PET/CT may be used when there is a ≥ 8 mm (≥ 268 mm³) solid component. *For new large nodules that develop on an annual repeat screening CT, a 1 month LDCT may be recommended to address potentially infectious*	> 15%	2%
	4X	Category 3 or 4 nodules with additional features or imaging findings that increase the suspicion of malignancy			

Screening basato sul rischio

- Rischio Precedente il test di screening (es familiarità etc)
- Rischio che deriva dalle informazioni del test di screening (es densità del seno

- Attualmente due screening hanno introdotto la definizione del rischio
- Polmone (screening solo ai forte fumatori)
- Cervicale (protocollo differente a seconda dello stato vaccinale :

➔ se vaccinata inizio screening 30 aa con intervallo da allungare)

OSSERVATORIO NAZIONALE SCREENING

GISCi

Gruppo Italiano Screening del Cervicocarcinoma

Consensus Conference

per la definizione del percorso di screening del cervicocarcinoma nelle donne vaccinate contro l'HPV

Alla stesura del documento hanno contribuito le principali società scientifiche del settore:

SITI - Società Italiana di Igiene, Medicina Preventiva e Sanità Pubblica;
SICPCV - Società Italiana di Colposcopia e Patologia Cervicovaginale;
AOGOI - Associazione Ostetrici Ginecologi Ospedalieri Italiani;
SIAPEC - Società Italiana di Anatomia Patologica e Citologia Diagnostica;
SIGO - Società Italiana di Ginecologia e Ostetricia;
SIV - Società Italiana di Virologia;
SICI - Società Italiana di Citologia.

Quale screening nelle vaccinate

- Many jurisdictions and professional bodies have considered the appropriateness of screening policies based on vaccination history. **To date, only Italy** has proposed screening algorithms that depend on vaccination status ….; all other proposals specify screening policies irrespective of HPV vaccination status

  - Handbook 18 IARC

Screening basato sul rischio: anche i negativi non sono tutti eguali

- Proposto anche per lo screening colorettale e quello della prostata basandosi sui valori «negativi» ovverosia valoiris otoo il valore di soglia della positività.
- Facilitato dall'uso di test biochimici quantitativi.

➔ anche i test negativi stratificano il rischio della popolazione

Table 2 Predictors of the DR of CRC, advanced adenoma and AN at the third FIT

		CRC		Advanced adenoma		AN	
		OR	95% CI	OR	95% CI	OR	95% CI
Gender	Women	1		1		1	
	Men	1.34	1.00 to 1.79	1.63	1.46 to 1.83	1.60	1.43 to 1.78
Age (years)	50–54	0.54	0.32 to 0.91	0.67	0.55 to 0.82	0.65	0.55 to 0.79
	55–59	0.75	0.47 to 1.17	1.02	0.86 to 1.22	0.98	0.83 to 1.15
	60–64	0.95	0.67 to 1.36	1.00	0.86 to 1.16	0.99	0.87 to 1.14
	65–69	1		1		1	
Interval since last fit (months)	18–22	0.67	0.30 to 1.49	0.80	0.59 to 1.08	0.78	0.58 to 1.03
	23–27	1		1		1	
	28–32	0.92	0.61 to 1.37	0.98	0.83 to 1.16	0.97	0.83 to 1.13
	33–36	0.96	0.39 to 2.40	1.23	0.86 to 1.77	1.19	0.85 to 1.67
	37–60	1.10	0.51 to 2.36	1.49	1.14 to 2.00	1.44	1.11 to 1.87
Cumulative f-Hb level at previous 2 FIT tests (FIT1 + FIT2) µg Hb/g faeces	0	1		1		1	
	0.1–3.9	2.26	1.47 to 3.46	1.75	1.47 to 2.07	1.81	1.55 to 2.12
	4–9.9	4.01	2.51 to 6.39	4.64	3.93 to 5.49	4.58	3.91 to 5.36
	10–14.9	10.11	6.04 to 16.93	9.13	7.48 to 11.15	9.32	7.73 to 11.23
	15–19.9	11.63	6.42 to 21.07	12.84	10.32 to 16.00	12.42	10.43 to 15.76
	≥20	38.92	22.50 to 67.31	30.40	24.09 to 38.38	32.52	26.19 to 40.39

AN, advanced neoplasia; CRC, colorectal cancer; DR, detection rate; FIT, faecal immunochemical test.

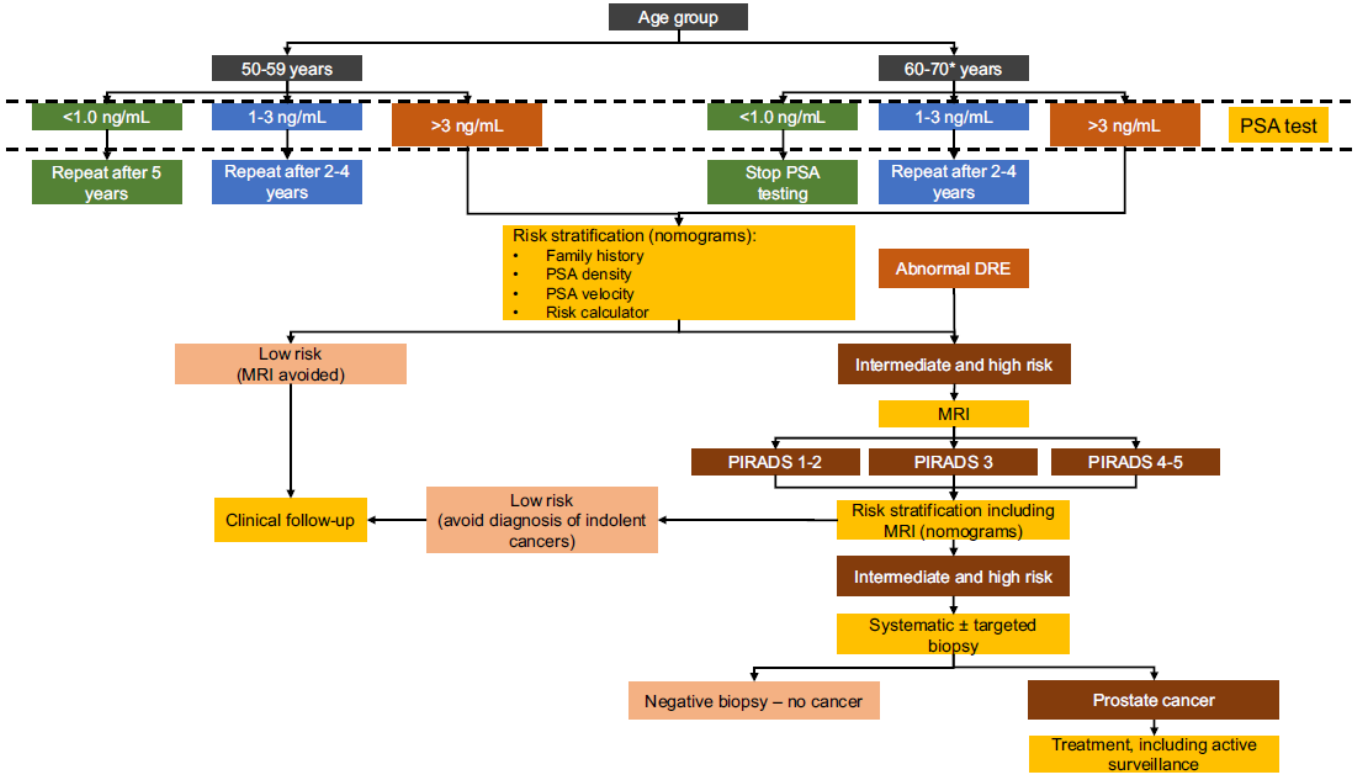


Fig. 4 – Risk-adapted algorithm for the early detection of prostate cancer, adapted based on prostate cancer guidelines published by the EAU [21]. The patient's values and preferences should always be taken into account as part of a shared decision-making process [21].
DRE = digital rectal examination; EAU = European Association of Urology; MRI = magnetic resonance imaging; PIRADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen.
***Healthy men >70 yr without important comorbidities and a life expectancy of >10-15 yr may continue PSA testing.**

Conclusioni:

- Vi è una tendenza ad aumentare la stratificazione dello screening che farà crescere le difficoltà di organizzazione, controllo , valutazione:

Necessità

- Valutazione rigorosa di ogni nuovo cambiamento sis sull'efficacia sia sulla sostenibilità
- Progetto di comunicazione

GRAZIE

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