Screening personalizzato sulla base del rischio

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Argomenti trattati

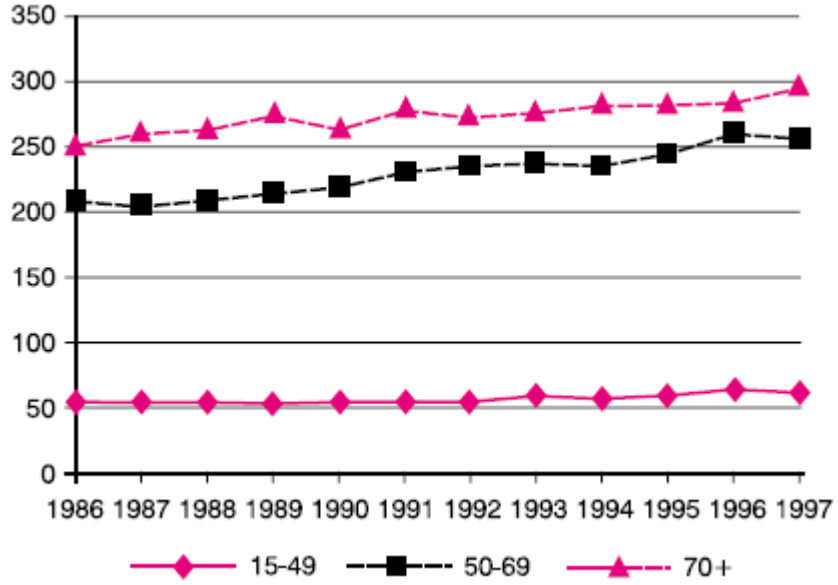
- Rischio e screening
- Densità e rischio
- Le raccomandazioni attuali sullo screening personalizzato per seni densi
- Le precedenti esperienze di studi sullo screening personalizzato in Italia: TBST
- Lo studio MyPeBS

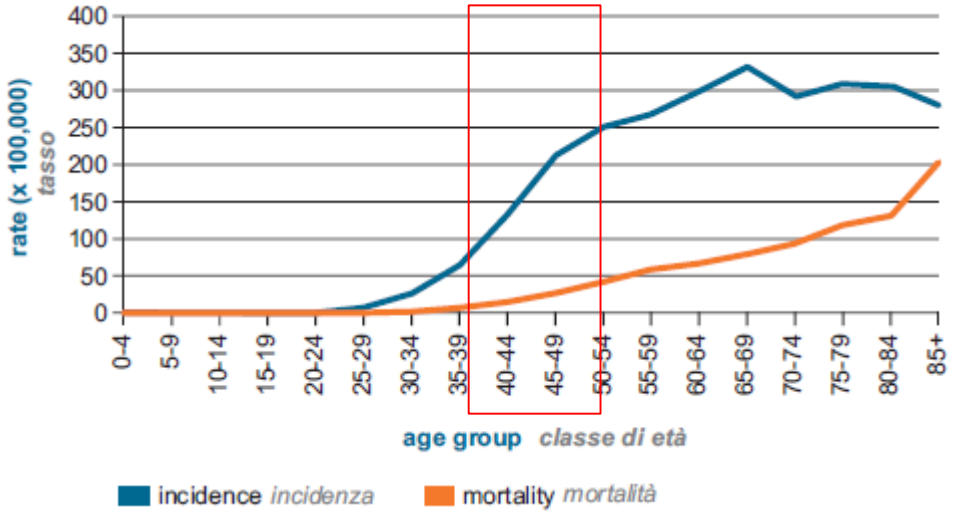
Conflitti d'interesse: ho partecipato al disegno di TBST e sono nello steering Committee di MyPeBS

Background

Il rischio è un criterio per screenare?

- L'età d'inizio per cervice e colon è stata scelta definita sulla base dell'incidenza…
- Nella mammalla le cose sono più complesse, ma…





1998-2002 AIRTum

Background

- Distinguere donne con un rischio più o meno alto dà l'opportunità di:
  - Modulare l'intensità dell'intervento di screening ottenendo un miglior rapporto effetti desiderati/indesiderati e costo/efficacia
  - Individuare donne con un rischio così basso da avere un rapporto effetti desiderati/indesiderati svantaggioso
  - Restringere la popolazione a cui eventualmente proporre procedure più invasivi o costose per essere proposte alla popolazione generale

Abbiamo bisogno di biomarcatori di rischio applicabili su tutta la popolazione.

Abbiamo bisogno di biomarcatori di rischio applicabili su tutta la popolazione.

- Età
- Familiarità
  - Senza mutazioni di geni noti
  - Con mutazioni deleterie in geni ad alta penetranza
  - Con mutazioni/polimorfismi di geni a bassa penetranza
- BMI
- Precedenti biopsie
- Densità
- Terapia ormonale sostitutiva

Densità e rischio

- La densità è un fattore di rischio per il rischio di cancro
- La densità è un determinante dell'accuratezza della mammografia
- È facilmente determinabile in donne che fanno lo screening

Densità e rischio di cancro della mammella

	Age-adjusted multivariate relative risk (95% CI)	
	Premenopausal women (n = 23,970)	Postmenopausal women (n = 32,607)
Family history of breast cancer		
No	1.00	1.00
Yes	1.65 (1.30–2.10)	1.40 (1.19–1.65)
Age at first childbirth		
<21	1.00	1.00
21–30	1.03 (0.75–1.42)	1.16 (0.97–1.39)
>30	1.76 (1.22–2.54)	1.52 (1.12–2.06)
No children	1.46 (1.02–2.09)	1.45 (1.14–1.85)
Postmenopausal hormone use		
Never or formerly used		1.00
Currently using		1.31 (1.13–1.53)
BMI (kg/m^2)		
<22.0	1.00	1.00
22.0–24.9	0.73 (0.55–0.97)	1.17 (0.93–1.47)
25.0–27.4	0.82 (0.58–1.16)	1.23 (0.96–1.57)
27.5–29.9	0.85 (0.56–1.29)	1.41 (1.08–1.84)
≥30	0.92 (0.65–1.30)	1.56 (1.23–1.98)
Breast density		
Entirely fat	1.00	1.00
Scattered	2.50 (0.92–6.82)	2.06 (1.47–2.89)
Heterogeneous	3.62 (1.32–9.92)	2.75 (1.93–3.92)
Extremely	4.21 (1.49–11.80)	3.48 (2.24–5.40)

Vacek & Geller. Cancer Epidemiol Biomarkers Prev 2004;13(5).

Densità, rischio cancro e fallimenti dello screening

BC incidence rate (only invasive)

	Cases/person-years	Rate	RR (95% CI)
VDG1–3	110/30390	3.6‰	reference
VDG 4	56/7513	7.5‰	2.0 (1.5–2.8)

Interval cancer rate

	Cases/negative screened	Rate	RR (95% CI)
VDG1–3	18/12709	1.4‰	reference
VDG 4	22/3129	7.0‰	5.0 (2.7–9.2)

Advanced cancers rate among negative screened

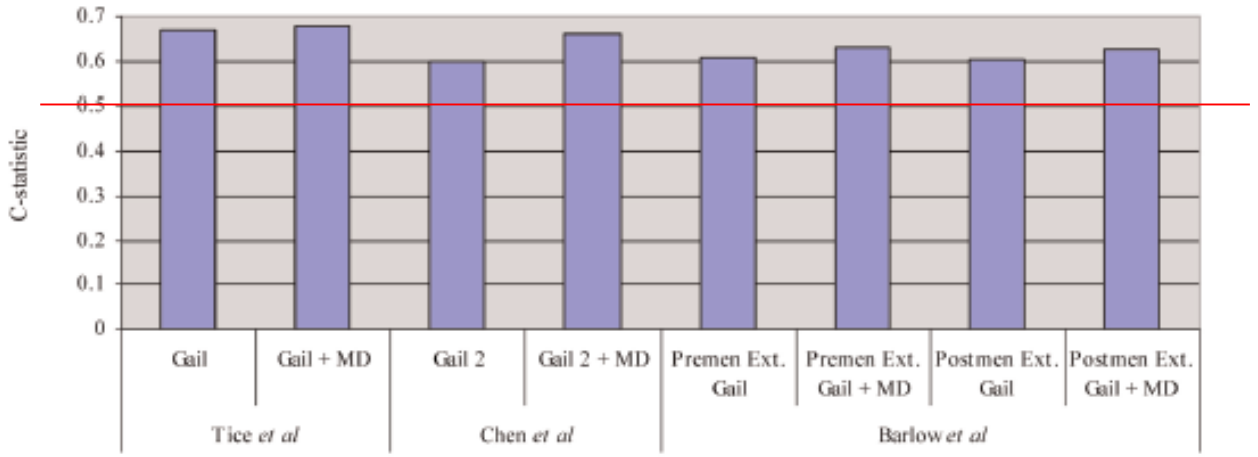
	Cases/negative screened	Rate	RR (95% CI)
VDG1–3	14/12709	1.1‰	reference
VDG 4	13/3129	4.2‰	3.8 (1.8–8.0)

VDG Volpara density grade, *BC* breast cancer, *RR* relative risk

Puliti et al 2018

La densità aggiunge valore predittivo agli altri fattori di rischio noti

Figure 2



Gain in C-statistic in three breast cancer risk prediction models with the addition of mammographic density (MD). Studies refer to Tice and colleagues [47], Barlow and colleagues [48], and Chen and colleagues [49]. Gail, Gail model; Gail 2, Gail model 2; Postmen Ext., postmenopausal extended Gail model; Premen Ext., premenopausal extended Gail model.

Vachon Breast Cancer Res 2007

Quali sono le raccomandazioni sullo screening personalizzato?

- Per le donne ad alto rischio (rischio genetico o familiare simile a rischio genetico): tutte le llgg raccomandano programmi di sorveglianza dedicati che prevedono MRI
- In alcuni paesi l'ecografia è mandatoria nei seni densi (Francia, USA almeno informazione su densità)

Raccomandazioni Europee screening personalizzato (2017)

- Should **tailored** screening with **automated breast ultrasound** system (**ABUS**) based on **high** mammographic breast **density**, in addition to mammography, vs. mammography alone be used for early detection of breast cancer in asymptomatic women?

✓Conditional recomm. against the intervention

- … with digital breast **tomosynthesis** based on **high** mammographic breast **density**, …, vs. mammography alone… ?

✓Conditional recomm. for the intervention

- … with **hand-held ultrasound (HHUS)** based on **high** mammographic **breast** density,…, vs. mammography alone…?

✓Conditional recomm. against the intervention

- … with magnetic resonance imaging (**MRI**) based on **high** mammographic breast **density**, …, vs. mammography alone?

✓Conditional recomm. against the intervention

Should **tailored** screening with digital breast **tomosynthesis** based on **high** mammographic breast **density**, …, vs. mammography alone… ?

How substantial are the desirable anticipated effects?

Don't know

Research Evidence

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard screening regimen	Risk difference with*
Breast cancer detection rate	8814 (3 observational studies) [a]	⊕⊕oo LOW	**OR 1.76** (1.38 to 2.24) [b c]	Study population	
				635 per 100.000 [a]	**477 more per 100.000** (239 more to 777 more)
False positive recall	3762 (2 observational studies)	⊕⊕oo LOW	**OR 1.41** (1.12 to 1.77) [b]	Low	
				3.800 per 100.000 [d]	**1.476 more per 100.000** (437 more to 2.735 more)
				High	
				9.600 per 100.000 [e]	**3.423 more per 100.000** (1.030 more to 6.222 more)

How substantial are the undesirable anticipated effects?

Varies

a. Median or mean of the control group of the included studies as appropriate unless otherwise specified.
b. Relative effect was adjusted for paired design.
c. Incremental cancer detection rate 540 more per 100.000 (from 200 more to 1020 more)
d. Baseline risk from the control group of Castells 2005 (PMID 16537348).
e. Baseline risk from Hubbard 2011 (PMID 22007042).

Should **tailored** screening with **hand-held ultrasound (HHUS)** based on **high** mammographic **breast** density,…, vs. mammography alone…?

Research Evidence

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with mammography e	Risk difference with tailored screening with hand-held ultrasound (HHUS) based on high mammographic breast density, in addition to mammography,
Breast cancer detection rate	72998 (1 RCT)	⊕⊕⊕○ MODERATE [a]	**RR 1.54** (1.22 to 1.95)	Study population	
				324 per 100,000	**175 more per 100,000** (71 more to 308 more)
Breast cancer detection rate	70942 (5 observational studies) [b]	⊕⊕○○ LOW	**OR 1.50** (1.23 to 1.82) [c,d]	Study population	
				626 per 100,000 [b]	**310 more per 100,000** (143 more to 507 more)
Breast Ca… not report…					-
Stage of t… not report…					-
Interval cancer rate - not reported	-	-	-	-	-
Recall rate - not reported	-	-	-	-	-
Rate of mastectomies - not reported	-	-	-	-	-
Provision of chemotherapy - not reported	-	-	-	-	-
Adverse effects - not reported	-	-	-	-	-

How substantial are the desirable anticipated effects?
Don't know

How substantial are the undesirable anticipated effects?
Don't know

a. Asymptomatic women aged 40-49 years from Japan (57,7% were classified as BI-RRADS 3-4). Results for women with dense breast will be reported in the near future (PMID 26547101).
b. Median or mean of the control group of the included studies as appropriate unless otherwise specified.
c. Relative effect was adjusted for paired design.
d. Incremental cancer detection was 380 cancers per 100,000 (from 166 more to 690 more).

Tailored screening using Hand-Held ultrasound for dense breast

Randomized studies (J-START)*:

DM+US 184 screen detected 18 interval cancers

DM 117 screen detected 35 interval cancers

Observational studies (pooled analysis):

RR 1.32 (95%CI 1.05 to 1.64)

*Ohuchi et al 2016

**Corsetti 2011, De Felice 2007, Kolb 2002, Korpraphong 2014, Venturini 2013

Should **tailored** screening with magnetic resonance imaging (**MRI**) based on **high** mammographic breast **density**, …, vs. mammography alone?

DIRECT EVIDENCE:

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard screening regimen	Risk difference with tailored screening with magnetic resonance imaging (MRI)
					re cancers detected per 100,000 exams
	(1 observational study)	LOW			al cancer were observed.

How substantial are the desirable anticipated effects?

Moderate

INDIRECT EVIDENCE:

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard screening regimen	Risk difference with tailored screening with magnetic resonance imaging (MRI)
Breast cancer detection rate (incremental cancer detection rate per exam)	2057 (2 observational studies)	⊕○○○ VERY LOW [a,b]	-	400 more cancers detected per 100,000 exams (from 130 to 680 more cancers detected).	
Breast cancer detection rate (incremental cancer	0 (1 observational study)	⊕⊕○○ LOW	-	3350 cancers more per 100,000 women (from 2070 more to 5370 more)	

How substantial are the undesirable anticipated effects?

Large

Recall rate	2057 (2 observational studies)	⊕○○○ VERY LOW [a,c]	-	12,670 women recalled per 100,000 exams (from 11,240 to 14,100 more) [d]

a. Both studies included women with at least one risk factor for breast cancer (Berg 2012) or a cumulative lifetime risk (CLTR) of breast cancer due to a genetic or familial predisposition of 15% or more (Kriege 2006).
b. Unexplained but unimportant inconsistency with high statistical heterogeneity (I^2 = 95%, P=0.00).
c. Unexplained but unimportant inconsistency with high statistical heterogeneity (I^2 = 96%, P=0.0000).
d. Incremental recall rate.

Precedenti esperienze

Screening nelle 40-49enni

- Efficacia nella riduzione di mortalità è minore che nelle 50-69enni (10-15% vs. 20-30%)
- Minore incidenza della malattia (circa ½ dell'incidenza nelle 50-69enni)
- L'impatto dovrebbe essere grossolanamente molto minore che nelle 50-69enni
- Molte llgg raccomandano screening annuali nelle 45-49 or 40-55 (GISMa, ACS)

Screening nelle 40-49: il paradosso del rischio e dell'intervallo

- Minore sensibilità della mammografia: accorciamo l'intervallo per aumentare la sensibilità di round
- Cancri più aggressivi: intervallo più corto per aumentare anticipazione diagnostica

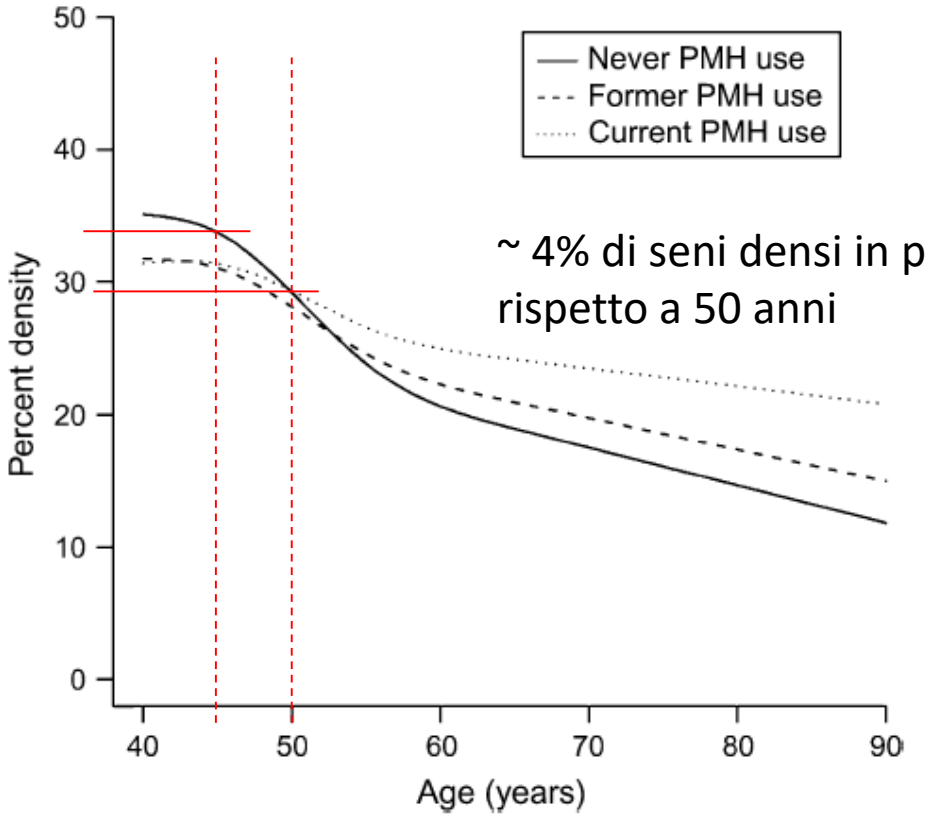
Intervallo breve

- Bassa incidenza: prevalenza di cancri ai secondi passaggi molto bassa
- Bassa specificità e bassa prevalenza: valore predittivo positivo molto basso.

Cattiva performance

La riduzione della sensibilità della mammografia nelle giovani potrebbe essere principalmente dovuta alla maggior densità

Densità ed età



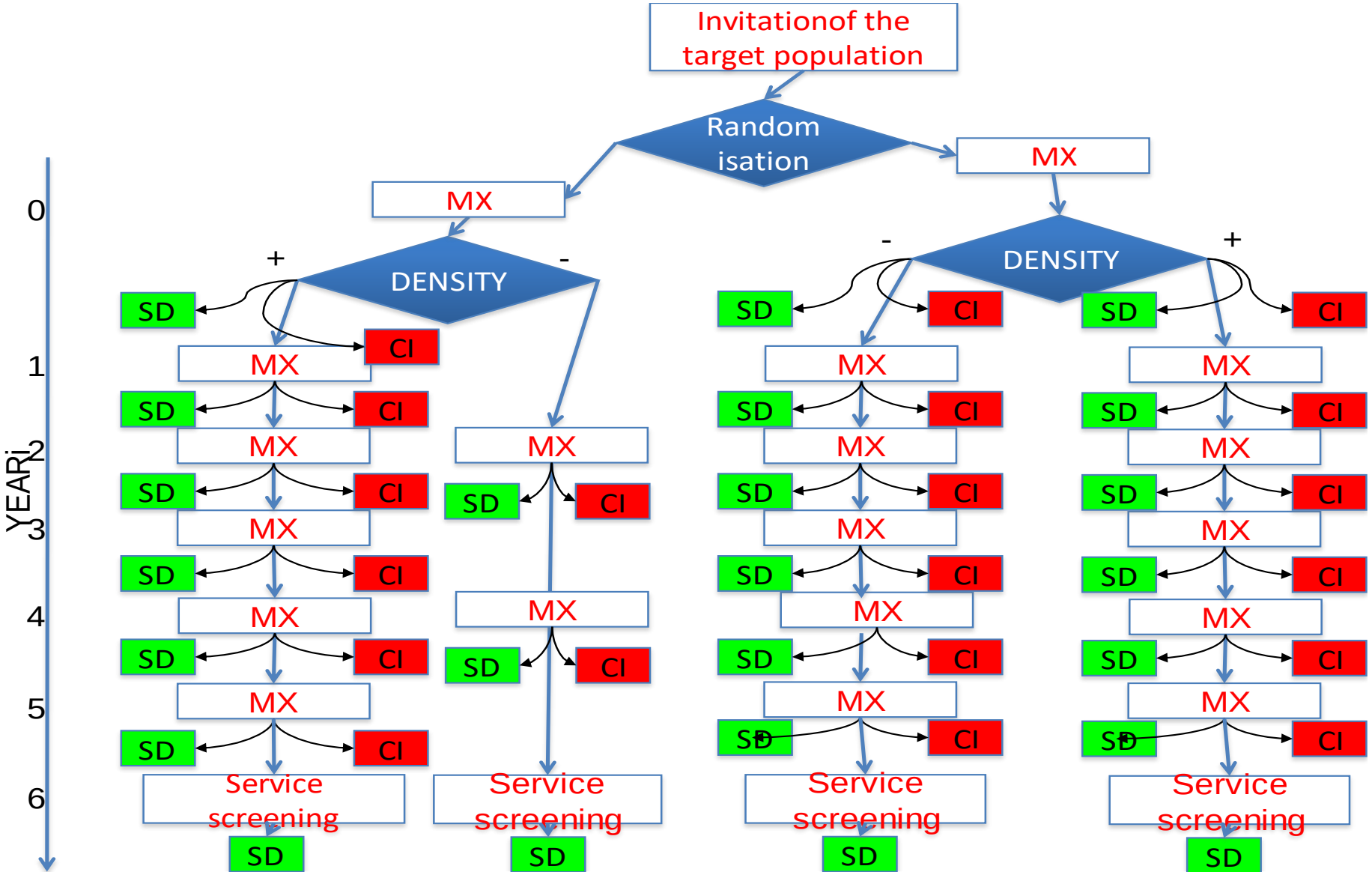
~ 4% di seni densi in più a 45 anni rispetto a 50 anni

Kelemen et al. International J Epidemiol 2008.

TBST FLOW CHART

MX=DIGITAL MAMMOGRAPHY SD=SCREEN DETECTED CI=INTERVAL CANCER

BIRADS 1-2 VS 3-4



MyPeBS

Personalising
Breast Screening

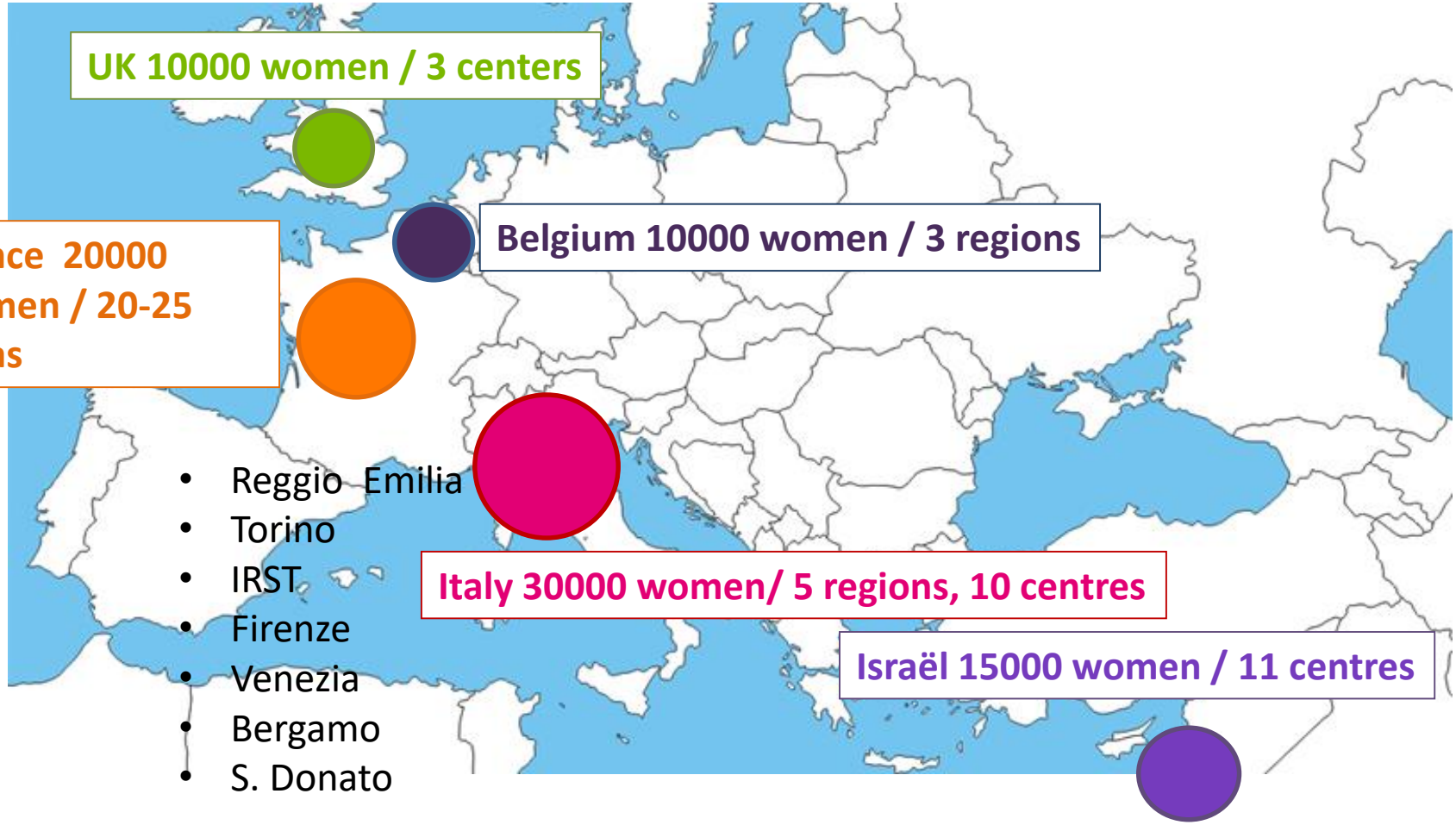
International Randomized Study Comparing personalized, Risk-Stratified to Standard Breast Cancer Screening In Women Aged 40-70

MyPeBS in brief

- **26 partners**
  - UNICANCER (France) as coordinator
- **7 countries**
  - Belgium, France, Israel, Italy, Netherlands, UK, USA
- **8 years project**
- **EU H2020-funding**
- **Core: a large clinical trial**
  - 6.5 years
  - 85 000 women randomized
  - in 5 countries
- **Companion study in US: WISDOM trial**

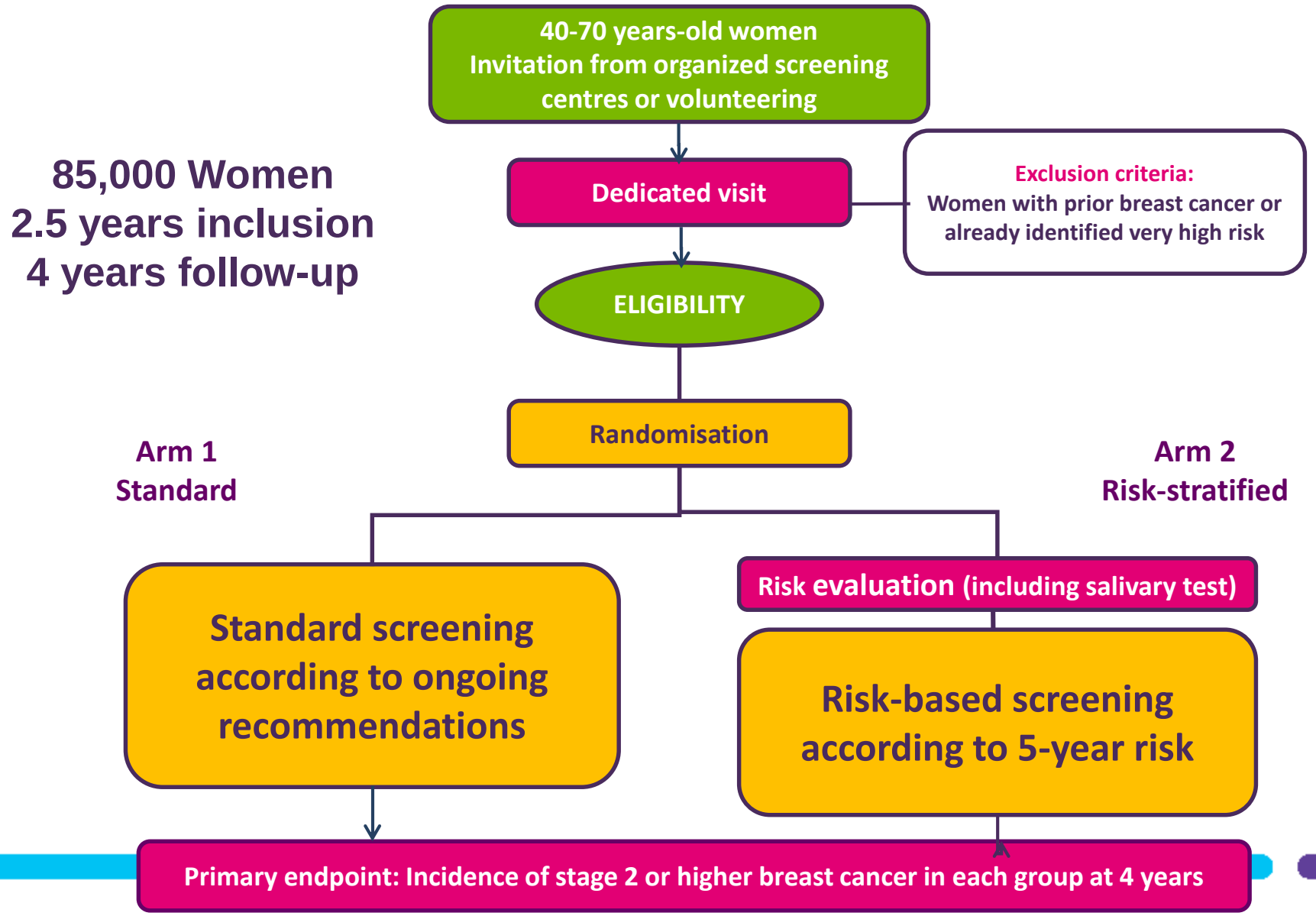
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 755394

Planned accrual – 5 countries



- Reggio Emilia
- Torino
- IRST
- Firenze
- Venezia
- Bergamo
- S. Donato

MyPeBS –Study scheme



85,000 Women
2.5 years inclusion
4 years follow-up

Risk evaluation –stratified arm

Baseline information

Family history of breast/ovarian cancer

Mammographic density

Personal history of previous biopsy for benign breast disease

+ Saliva Test (Genotyping)

If ≤ 1 first-degree family history

BCSC/Mammorisk™* Score

+ polymorphisms

If > 1 first-degree family history

Additional information used

Detailed family history

Menarche

Reproductive history

IMC

Tyrer-Cuzick™ Score

+ polymorphisms

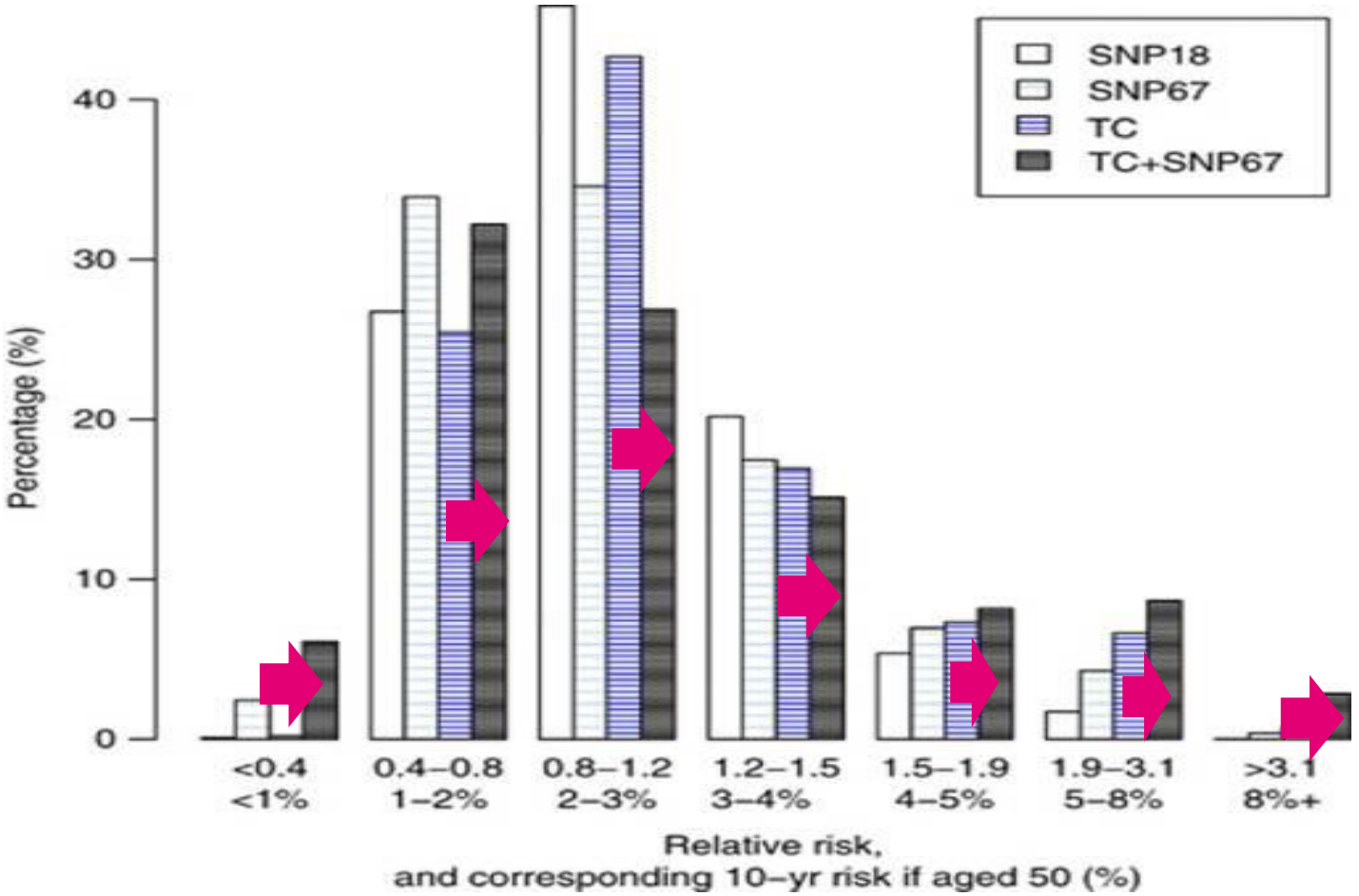
*Breast Cancer Screening Consortium

Final Risk Score result

Tice 2008, Ragusa 2018, Tyrer Cuzick 2004, Amir 2003, Warwick 2014, Brentnall 2015, Brentnall 2018, Van Veen 2018, Shieh 2016

SNPs increase risk discrimination

On top of clinical risk models



Ex: improvement of discrimination of Tyrer Cuzick model by the addition of 18 or 67 SNPs

Brentnall et al 2014

Risk thresholds – stratified arm

Risk level at 5 years	Low risk	Average risk	High risk	Very high risk
Numerical definition	Risk < 1%	1 ≤ Risk < 1.67%	1.67% ≤ Risk < 6%	6% ≤ Risk
Average number of BC at 5 years in category	Around 1 in 110 women	Around 1 in 60 women	Around 1 in 30 women	Around 1 in 16 women
Relevant similar situation	Average women less than 45 years old in Europe	Current women aged 50+	- Personal history of BC - Personal history of atypical hyperplasia - Women included in prevention trials	- Germline BRCA1/2 mutations or equivalent situations
Relevant benefit observed in similar situations	No demonstrated benefit of screening	Benefit of mammographic screening	- Benefit from prevention interventions in prevention trials - Benefit from more frequent mammographic screening in similar situations	- Benefit from annual MRI + mammographic screening - Benefit from prevention interventions

Lauby-Secretan 2015, Kerlikowske 2015, Shousboe Ann Int Med 2011, Trentham- Dietz 2016, Evans 2016 &2017

Screening strategy in the stratified arm

Risk-based arm				
Risk level	**Low risk**	**Average risk**	**High risk**	**Very high risk**
Numerical definition (invasive breast cancer risk at 5 years)	< 1%	1-1.66%	≥ 1.67% and < 6%	≥ 6% at 5 years
Mammogram*	1 at end of study	Every 2 years	Yearly	Yearly
Additional		High density: US or ABUS/ 2 years	High density: US or ABUS/ year	Annual MRI until age 60

* Or Tomosynthesis + synthetic 2D if applicable in the country/center

Lauby-Secretan 2015, Kerlikowske 2015, Shousboe Ann Int Med 2011, Trentham- Dietz 2016, Evans 2016 &2017

Primary objective

1. The **Primary objective** of MyPeBS is to show a **non-inferiority** of the stratified screening strategy in terms of **incidence of BC of stage 2 and higher**.
2. If non-inferiority is shown, then **superiority of the risk-based screening arm for reduction of stage 2+ BC will be tested** (key secondary) against the control arm (closed testing procedure).

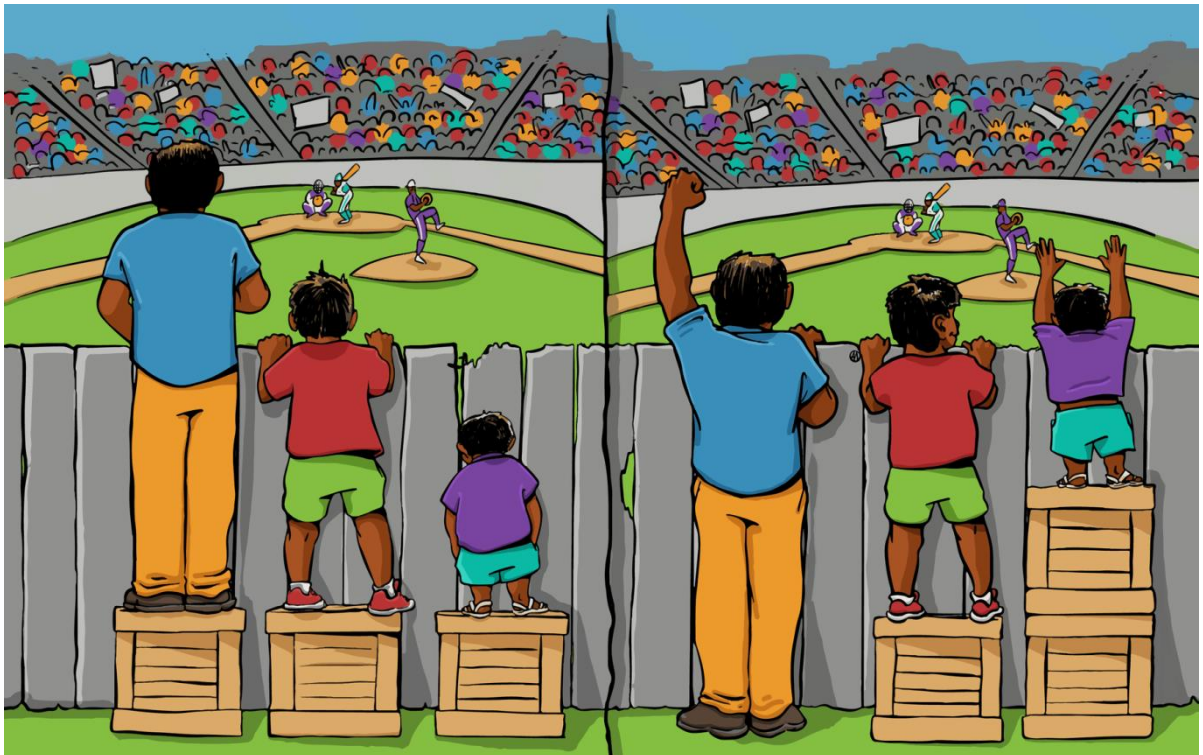
Secondary objectives

1. To compare the rates of **false positive imaging findings and benign biopsies** between arms
2. **Psycho-social impact** of each strategy
3. **Costs and cost-effectiveness** of each strategy
4. Incidence of any stage breast cancer in each arm
5. Estimate **overdiagnosis and overtreatment** rates in risk-based screening and standard screening arms
6. Compare the rate of **false negative** mammograms and interval cancers between arms
7. **Breast cancer-specific mortality** at 10 years and 15 years in MyPeBS and in a combined analysis of the Wisdom and My-PEBS studies
8. Added value of **tomosynthesis** (TS) in the detection of stage 2+ breast cancers
9. Incidence of all stage and stage 2 and higher breast cancers at 10 and 15 years follow-up
10. Incidence of stage 2+ breast cancer in risk-based screening in **women aged 40-50** as compared to standard screening
11. Rate of cancers discovered at second reading in each arm
12. False positive imaging findings and benign breast biopsy rates in women classified in the low risk category

All at 4 years unless otherwise specified

Conclusioni

- La gran parte dei precedenti studi si è focalizzata sull'altissimo rischio o sulla densità
- MyPeBS proverà a personalizzare il percorso di screening usando tutti gli strumenti di quantificazione del rischio per allocare i nostri sforzi dove ce n'è più bisogno



MyPeBS

Personalising
Breast Screening

www.mypebs.eu

Contact:
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Thank You

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 755394

Primary end point

1. The primary endpoint is the **incidence of stage 2 and higher** breast cancers at 4 years (UICC 2010)

Eligibility criteria

INCLUSION

1. Female (whether born biologically or not)
2. Aged **40 to 70 years** old (inclusive)
3. Willing and able to read and understand trial information, sign an informed consent and fill questionnaires in one of the languages used in the study
4. Willing and able to comply with scheduled visits, laboratory tests, and other trial procedures
5. Provide written **informed consent** obtained prior to performing any protocol-related procedures
6. Affiliated with a **social security system**

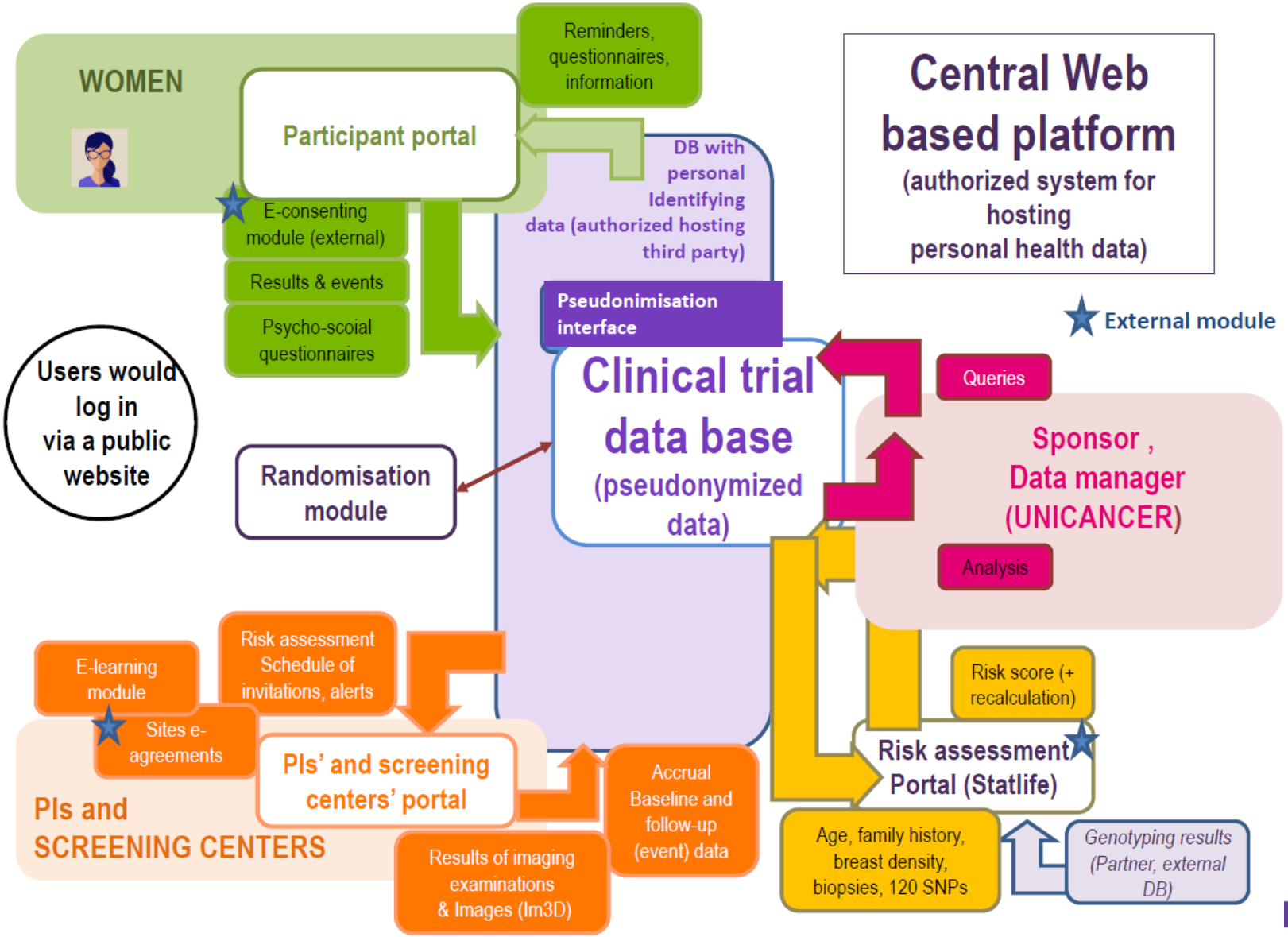
EXCLUSION

1. **Personal history of breast carcinoma**, either invasive or ductal carcinoma in situ (DCIS)
2. **Prior history of atypical breast lesion**, lobular carcinoma in situ or chest wall irradiation
3. Known condition or suspicion of a **very high risk predisposition** to breast cancer: germline mutation of BRCA1/2, PALB2, TP53 or equivalent
4. History of **bilateral mastectomy**
5. **Recent abnormal breast finding** under work-up (clinically suspect lesion or BI-RAD 4 or 5 image)
6. Inability to provide signed informed consent
7. Insufficient understanding of any of the languages used in the study
8. Psychiatric or other disorders that are not compatible with compliance to the protocol requirements and follow-up
9. Women who do not intend to be followed-up for 4 years

Target dates MyPeBS

• Kick off meeting	January 12th, 2018
• Regulatory submissions	May/October 2018
• Sites opening	December 2018
• 1st woman in	December 2018
• Inclusion period	2 ½ years (last woman in, March 2021)

MyPeBS' Webplatform



MyPeBS' governance bodies