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ALDO MORO

## HYGIENE COURSE

Scuola  
di  
Medicina

# Cancer screening



# Screening test

- Systematic exam, conducted with clinical, instrumental technique or laboratory test designed to detect cases of disease in pre-clinical stage in a population
- **Secondary prevention**
- Means: early detection
- Goal: **reducing mortality** by reducing incurable forms



# Two by two table

		Disease		
		D+	D-	
Screening test results	Positive	80	40	TP + FP
	Negative	20	60	FN + TN
		TP + FN	FP + TN	N



# Two by two table

		Disease		
		D+	D-	
Screening test results	Positive	80	40	TP + FP 120
	Negative	20	60	FN + TN 80
		TP + FN 100	FP + TN 100	N = 200





# Two by two table

		Disease		
		D+	D-	
Screening test results	Positive	<b>P</b> 80	<b>P</b> 40	TP + FP 120
	Negative	20	60	FN + TN 80
		TP + FN 100	FP + TN 100	N = 200



# Two by two table

		Disease		
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Screening test results	Positive	<b>P</b> 80	<b>P</b> 40	TP + FP 120
	Negative	<b>N</b> 20	<b>N</b> 60	FN + TN 80
		TP + FN 100	FP + TN 100	N = 200



# Two by two table

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	Negative	<b>N</b> 20	<b>N</b> 60	FN + TN 80
		TP + FN 100	FP + TN 100	N = 200



# Two by two table

		Disease		
		D+	D-	
Screening test results	Positive	<b>TP</b> 80	<b>FP</b> 40	TP + FP 120
	Negative	<b>FN</b> 20	<b>TN</b> 60	FN + TN 80
		TP + FN 100	FP + TN 100	N = 200



# Screening test formula rule

“Trues” on top and divide  
by everything

- Sensitivity, Specificity, Positive predictive value, Negative predictive value and accuracy



# Sensitivity

		Disease		
		D+	D-	
Screening test results	Positive	<b>TP</b> 80	<b>FP</b> 40	TP + FP 120
	Negative	<b>FN</b> 20	<b>TN</b> 60	FN + TN 80
		TP + FN 100	FP + TN 100	N = 200



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# Sensitivity

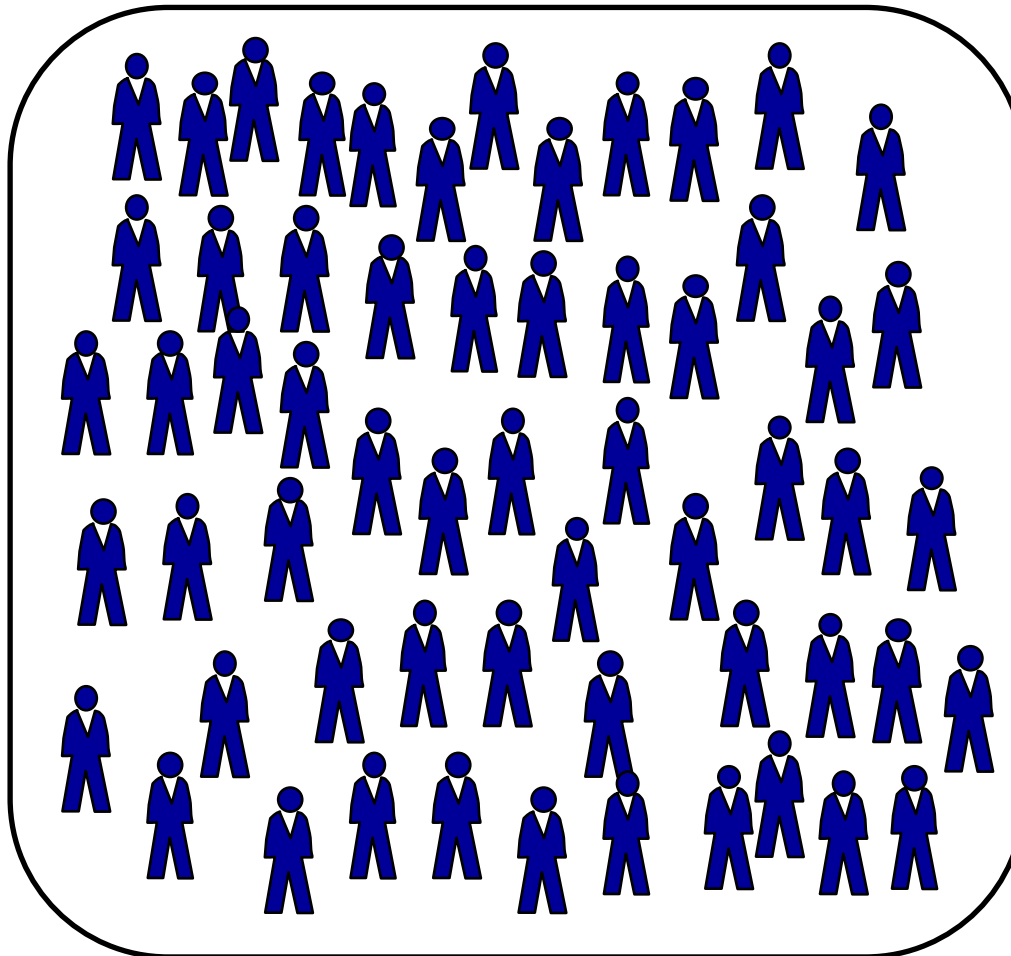


Healthy people

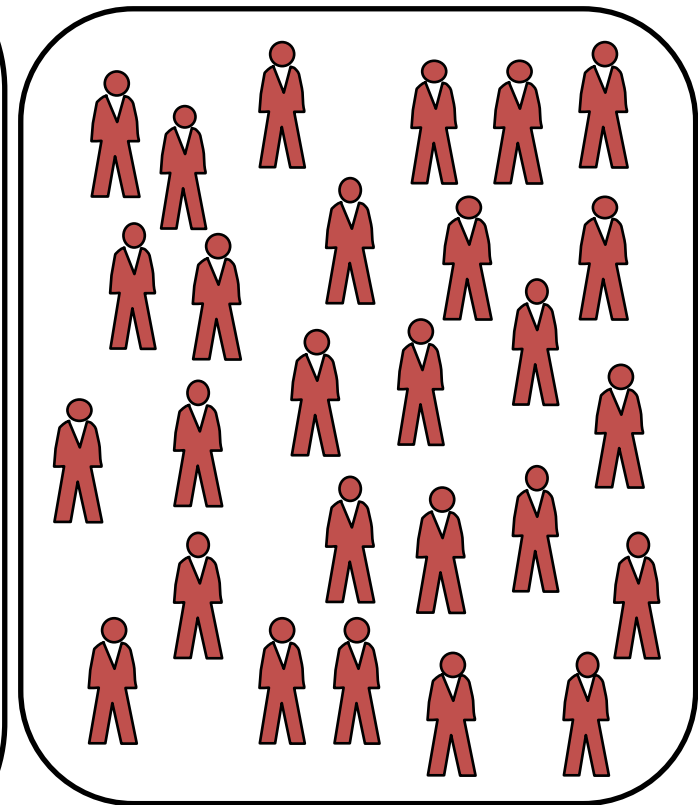


Disease

Negative



Positive





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# Screening test: reality

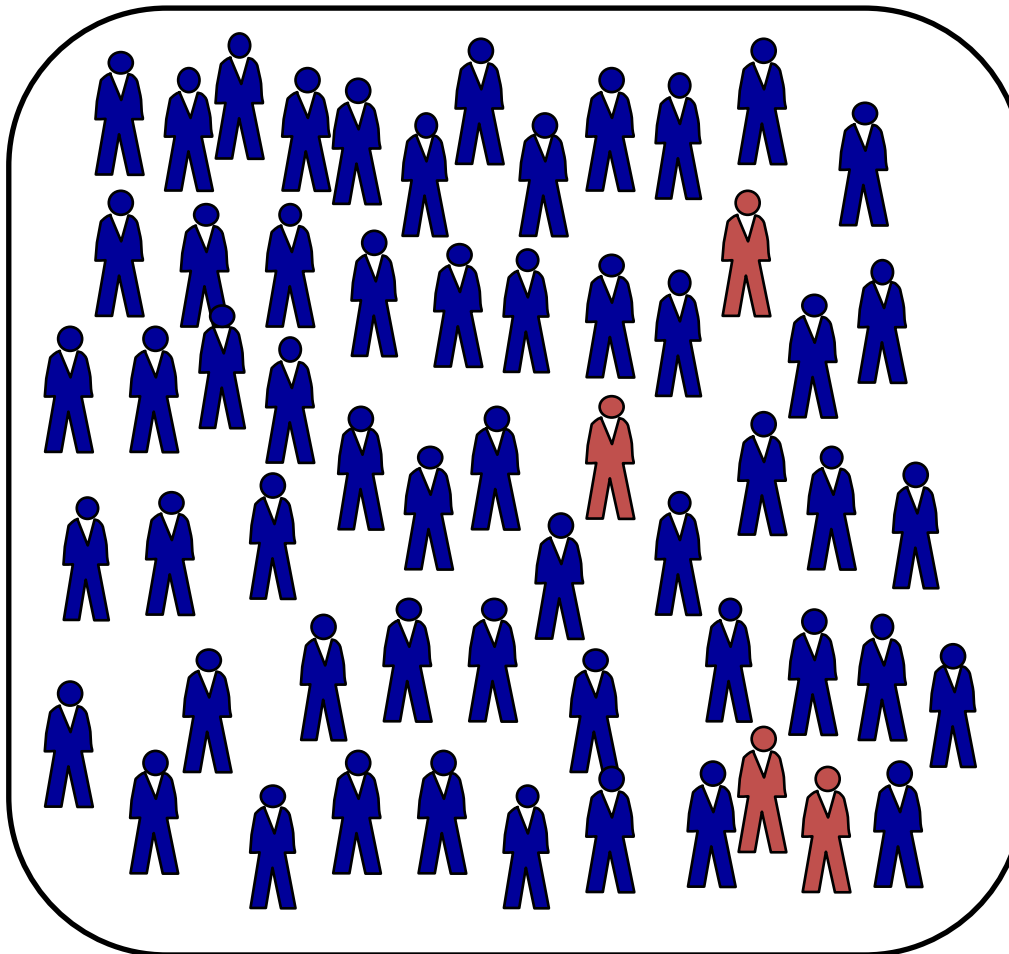


Healthy people

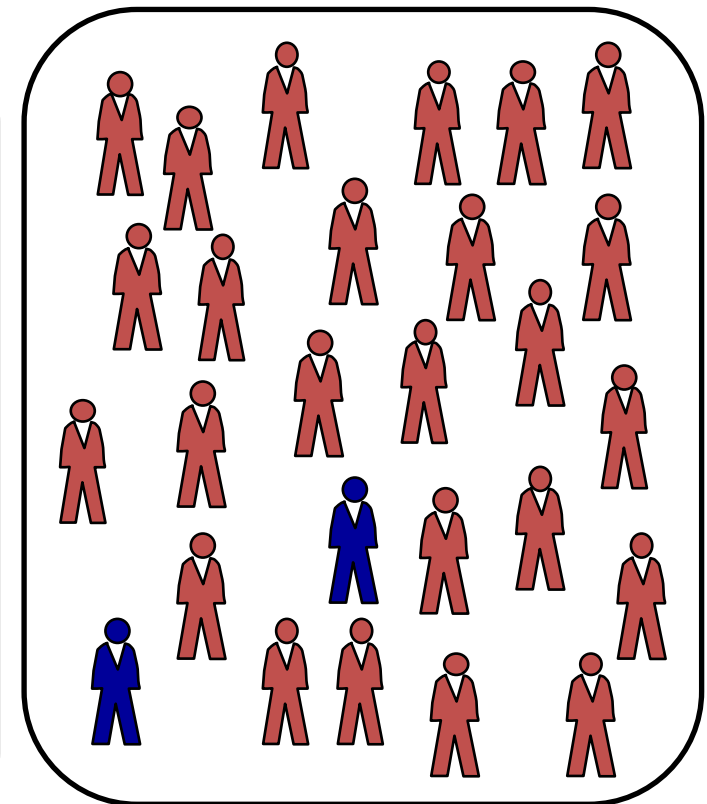


Disease

Negative



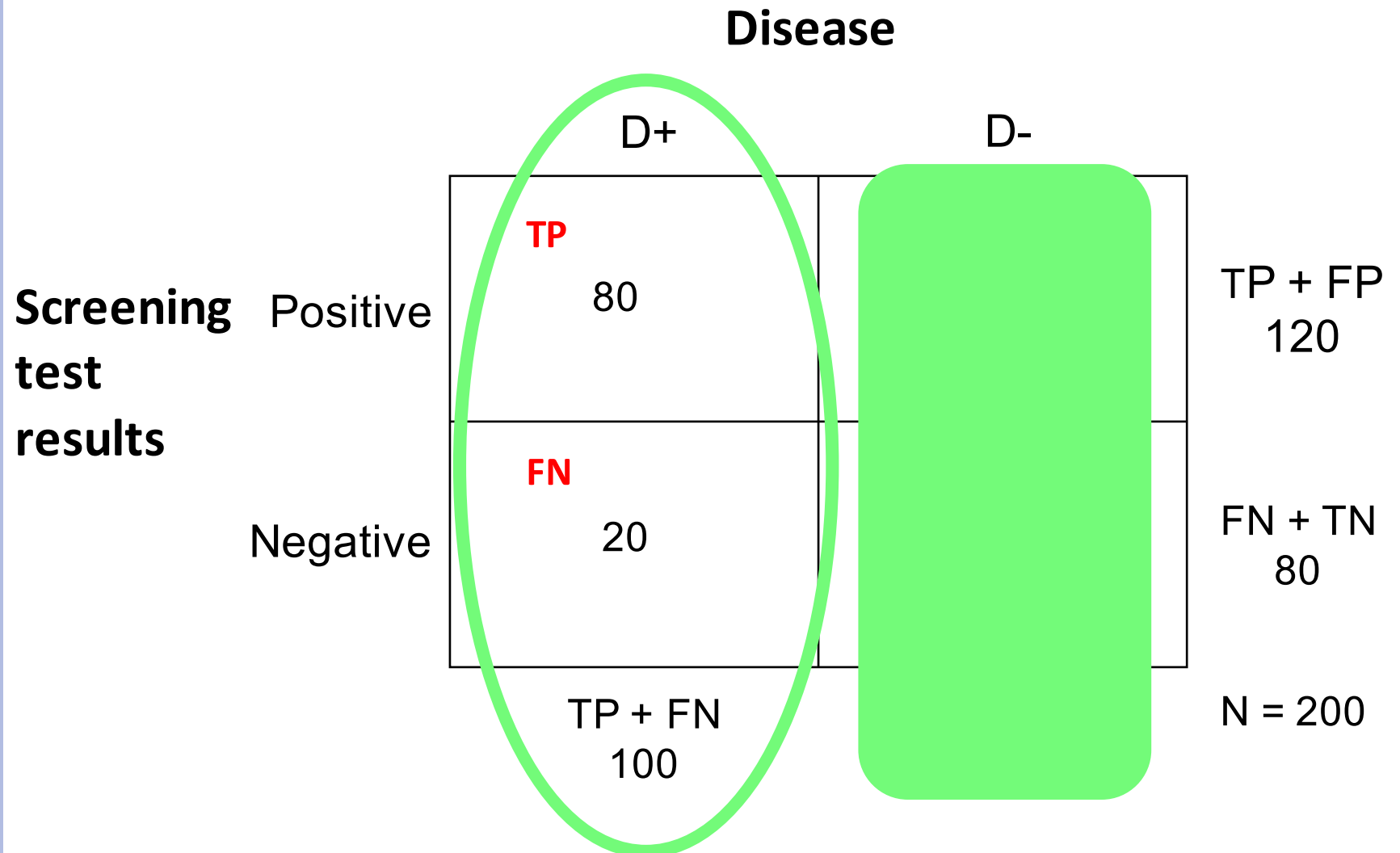
Positive







# Sensitivity





# Screening test parameters

- **Sensitivity:** identifying cases of disease

$$\text{Formula} = \text{TP} / (\text{TP} + \text{FN})$$

$$\text{Sens: } 80 / (80 + 20) = 80\%$$



# Specificity

		Disease		
		D+	D-	
Screening test results	Positive		<b>FP</b> 40	TP + FP 120
	Negative		<b>TN</b> 60	FN + TN 80
			<b>FP + TN</b> 100	N = 200

A green oval highlights the FP (40) and TN (60) cells, representing the group used to calculate specificity. A green rounded rectangle highlights the D+ column.



# Screening test parameters

- **Sensitivity:** identifying cases of disease

$$\text{Formula} = \text{TP} / (\text{TP} + \text{FN})$$

$$\text{Sens: } 80 / (80 + 20) = 80\%$$

- **Specificity:** identifying disease –free people, healthy people

$$\text{Formula} = \text{TN} / (\text{TN} + \text{FP})$$

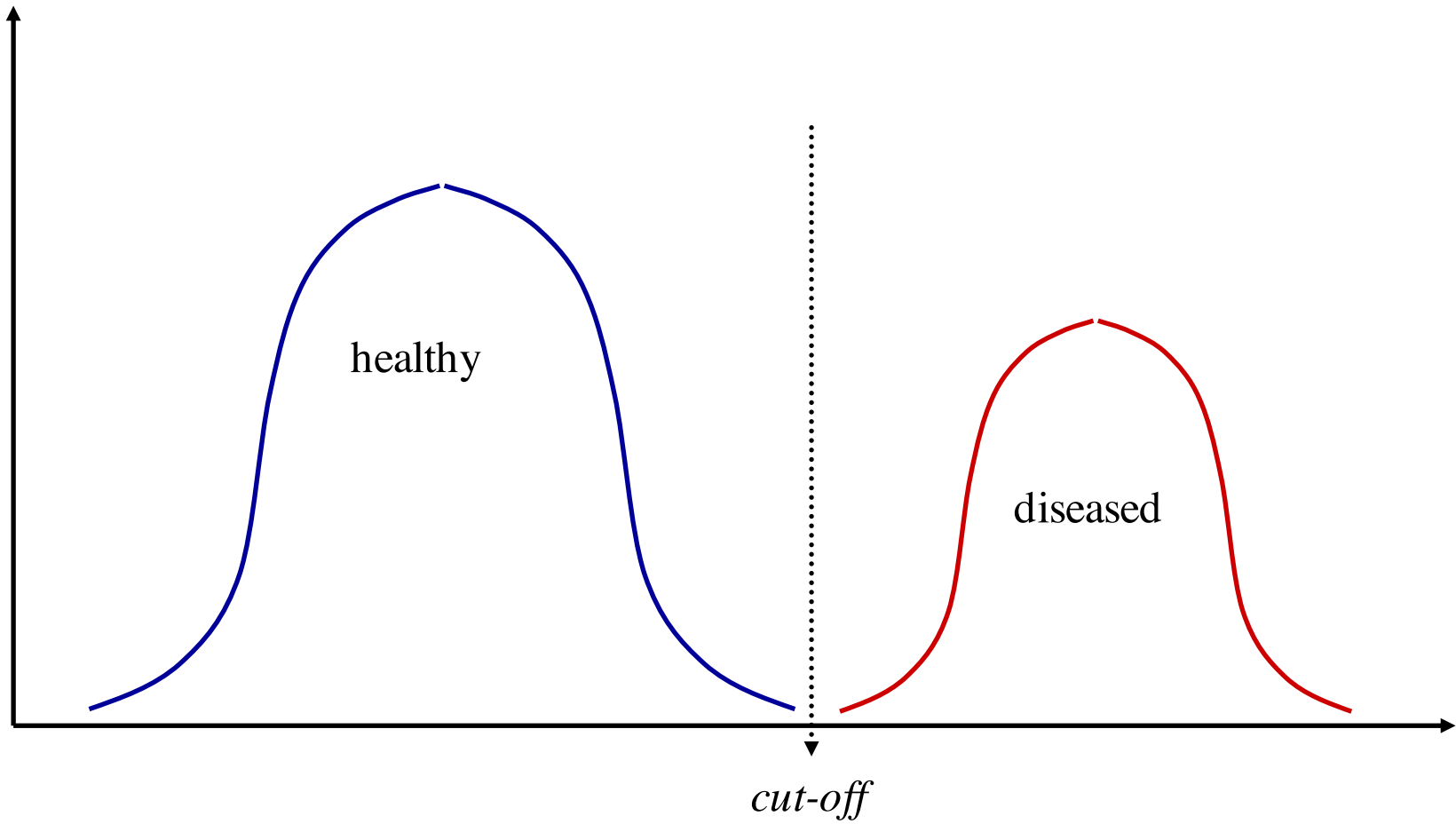
$$\text{Spec: } 60 / (60 + 40) = 60\%$$



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# The ideal test

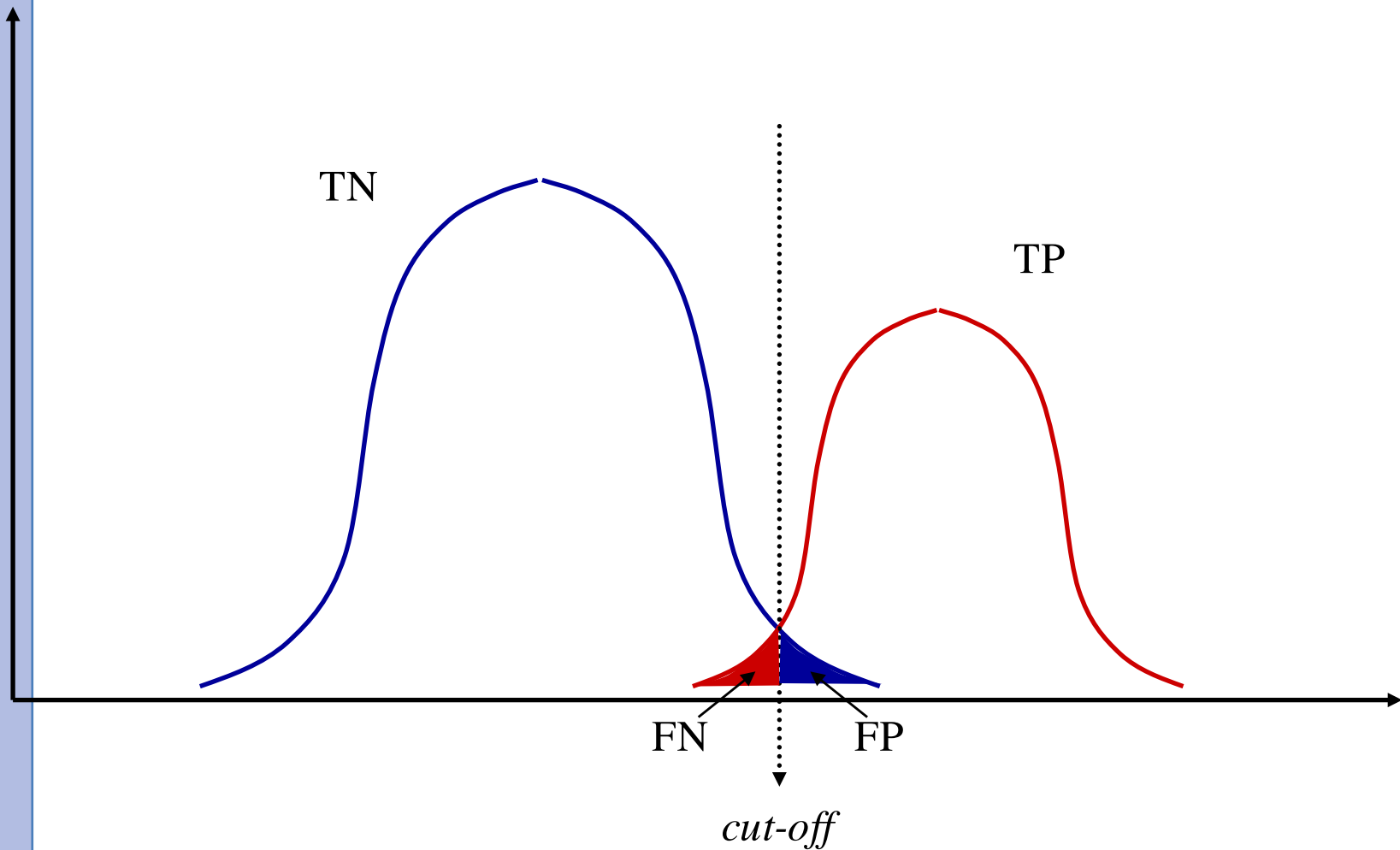




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# The real test...





# Positive Predictive Value

		Disease		
		D+	D-	
Screening test results	Positive	<b>TP</b> 80	<b>FP</b> 40	TP + FP 120
	Negative	<b>FN</b> 20	<b>TN</b> 60	FN + TN 80
		TP + FN 100	FP + TN 100	N = 200



# Positive Predictive Value

		Disease		
		D+	D-	
Screening test results	Positive	<b>TP</b> 80	<b>FP</b> 40	TP + FP 120
	Negative			FN + TN 80
		TP + FN 100	FP + TN 100	N = 200

A green oval highlights the top row of the table (Positive screening test results), and a green rounded rectangle highlights the bottom row (Negative screening test results).





# Screening test parameters

- **Positive predictive value:** likelihood that a positive test result indicates real disease

$$\text{Formula} = TP / (TP+FP)$$

$$\text{PPV: } 80 / (80+40) = 66.7\%$$



# Negative Predictive Value

		Disease		
		D+	D-	
Screening test results	Positive			TP + FP 120
	Negative	FN 20	TN 60	FN + TN 80
		TP + FN 100	FP + TN 100	N = 200

A green rounded rectangle highlights the top row (Positive test results) and the bottom row (Negative test results) of the table. A green oval highlights the bottom row (Negative test results) and the bottom two columns (D+ and D-).



## Screening test parameters

- **Positive predictive value:** likelihood that a positive test result indicates real disease

$$\text{Formula} = \text{TP} / (\text{TP} + \text{FP})$$

$$\text{PPV: } 80 / (80 + 40) = 66.7\%$$

- **Negative predictive value:** likelihood that a negative test result indicates no real disease

$$\text{Formula} = \text{TN} / (\text{TN} + \text{FN})$$

$$\text{NPV: } 60 / (60 + 20) = 75\%$$



# Screening test parameters

- Two sets of screening test values
  - 1) Sensitivity and specificity
  - 2) PPV and NPV
- Sensitivity and specificity: pre-test probabilities
- PPV and NPV: post-test probabilities



# Understanding screening tests

Sens = 80%

Spec = 60%

PPV: 66.7%

NPV: 75%

A good test?



# Understanding screening tests

Sens = 80%

Spec = 60%

PPV: 66.7%

NPV: 75%

A good test?  
Only so-so



# Accuracy or efficiency of the test

		Disease		
		D+	D-	
Screening test results	Positive	<b>TP</b> 80	<b>FP</b> 40	TP + FP 120
	Negative	<b>FN</b> 20	<b>TN</b> 60	FN + TN 80
		TP + FN 100	FP + TN 100	N = 200



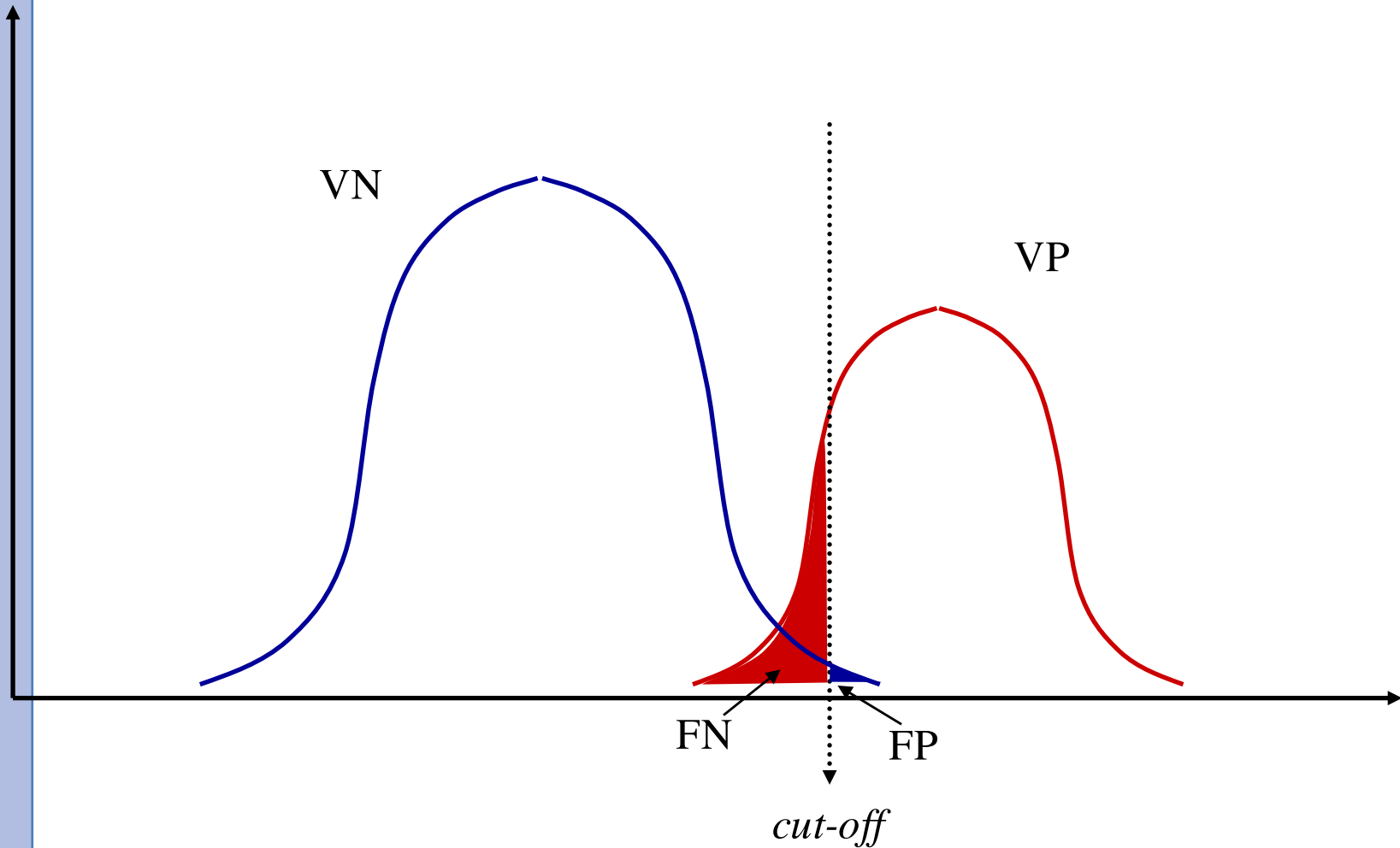
# Accuracy or efficiency of the test

- Percentage correct OVERALL
- Formula:  $TP+TN / (TP+TN+FP+FN)$   
 $TP+TN / N$ , sample size
- Acc:  $80+60 / 200 = 70\%$



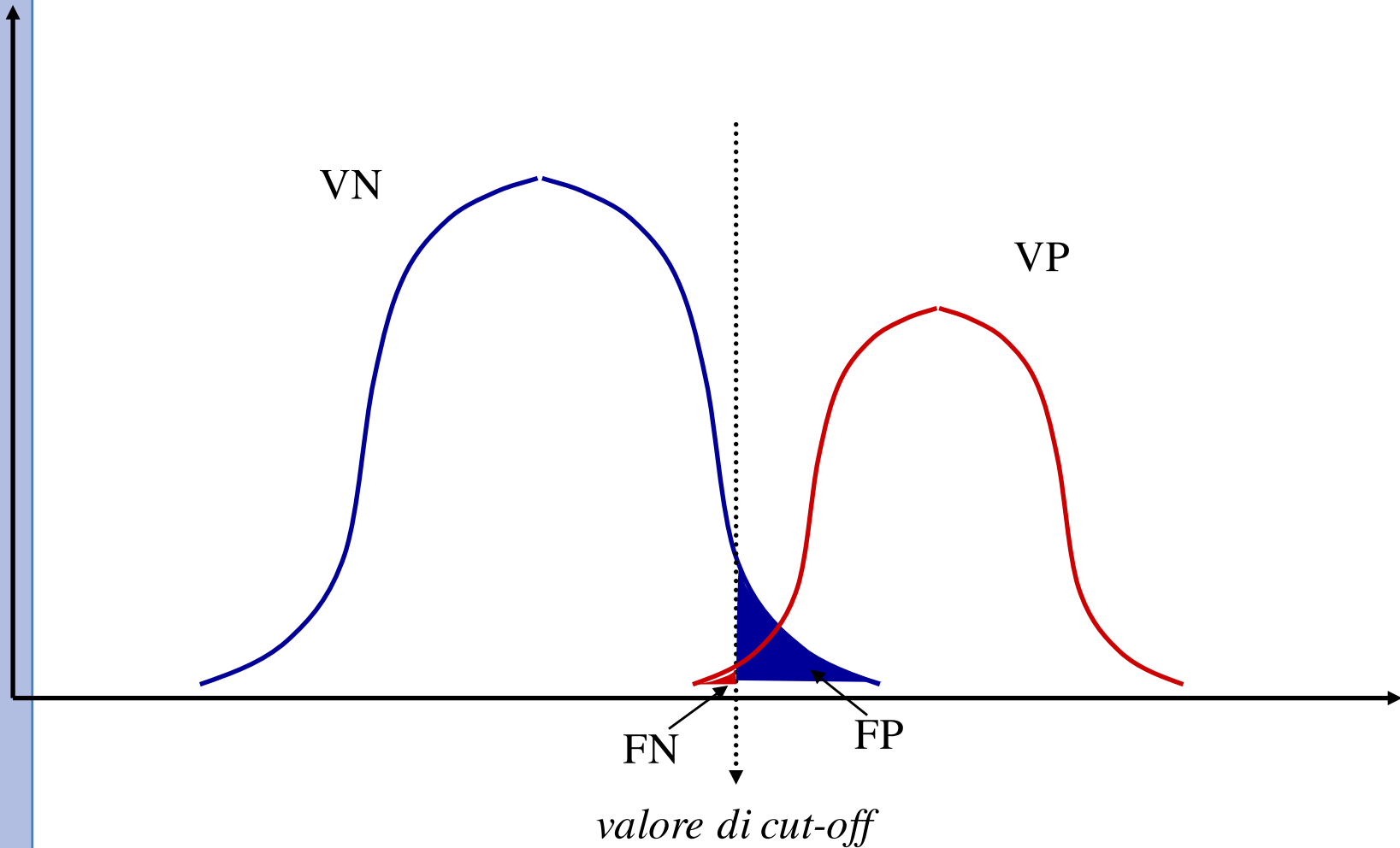


# Increasing specificity





# Increasing sensitivity





# Necessary conditions for the feasibility of screening programs

1. Disease to screen is an important public health issue
2. Epidemiology and natural history should be well known
3. Exists an indicator of the disease in pre-symptomatic phase
4. History of the disease can be modified with early detection



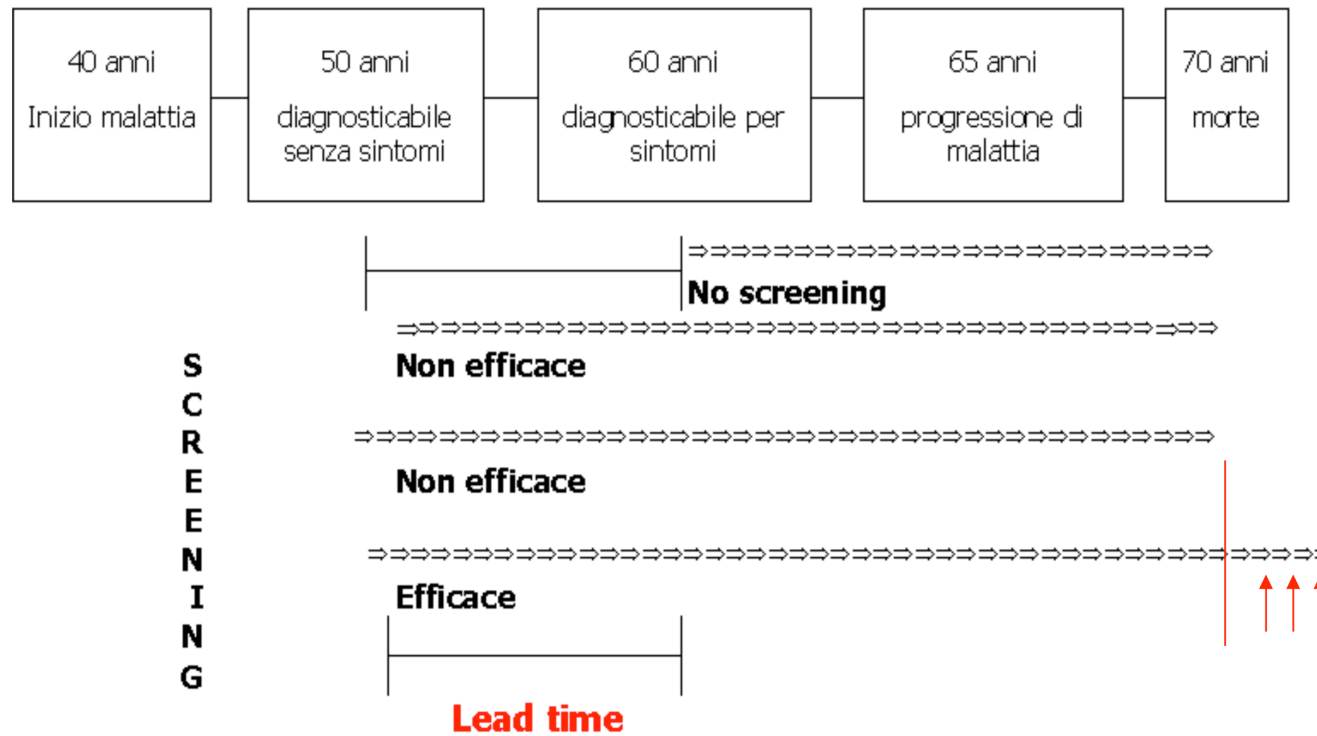
# Necessary conditions for the feasibility of screening

5. Effective screening test:
  - simple, harmless, reliable, validated
  - reproducible and accurate
  - consensus on the definition of positive test
  - agreement on the diagnostic study protocol and the options available for the positive test subjects'
6. Effective treatment for the screened disease



### 3. Exists an indicator of the disease in pre-symptomatic phase

#### Storia naturale della malattia





3. Exists an indicator of the disease in pre-symptomatic phase

**Lead time =**

interval of time between the moment in which the diagnosis is performed for the screening effect and the time when the diagnosis would have been made for the appearance of clinical signs of disease



## Goal of an cancer screening programme

- Reduce **mortality** from cancer by reducing the incidence of incurable forms
- It's secondary prevention (keep it in mind always !!!)



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# Organized screening programs vs. spontaneous screening

- **Free and active offer** (personal invitation) to the population at-risk





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# Organized cancer screening programs

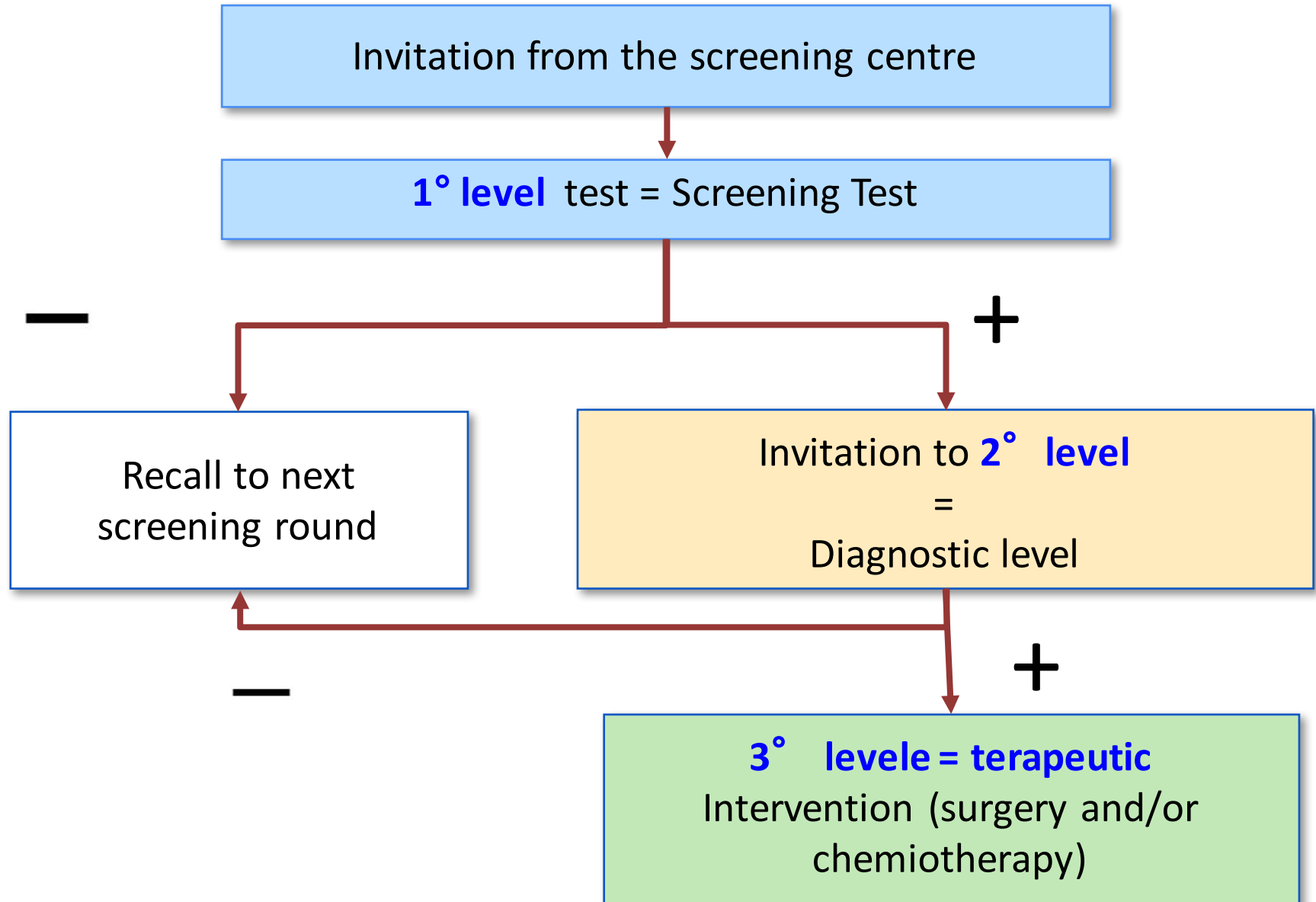
- Public health interventions included in the LEA
- Possibility to anticipate a cancer diagnosis should be universally guaranteed



*DPCM 29 novembre 2001*

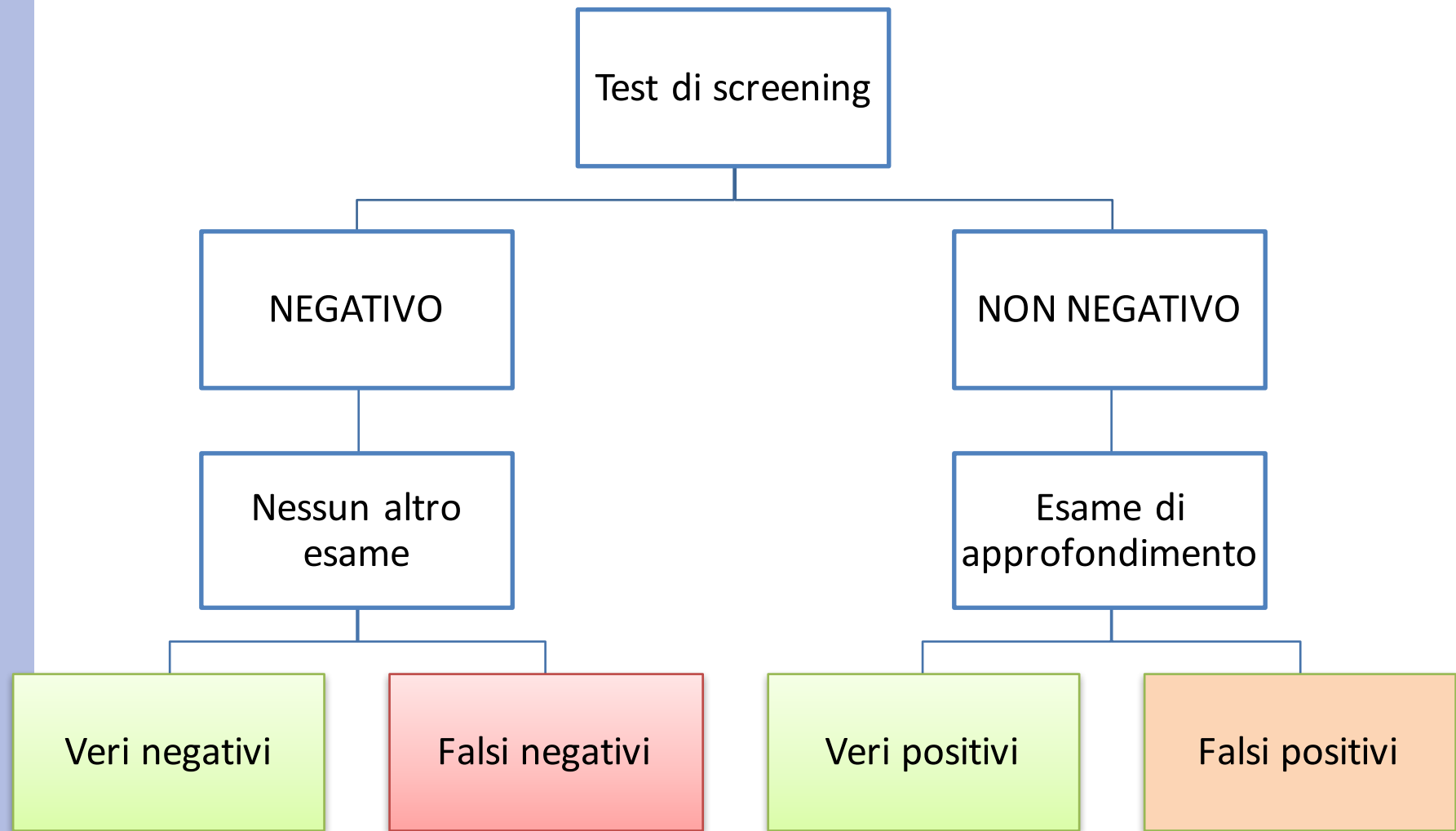


# Pathway



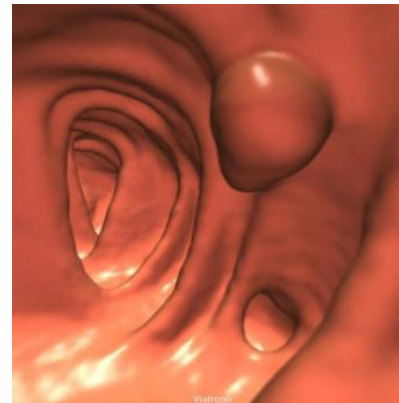
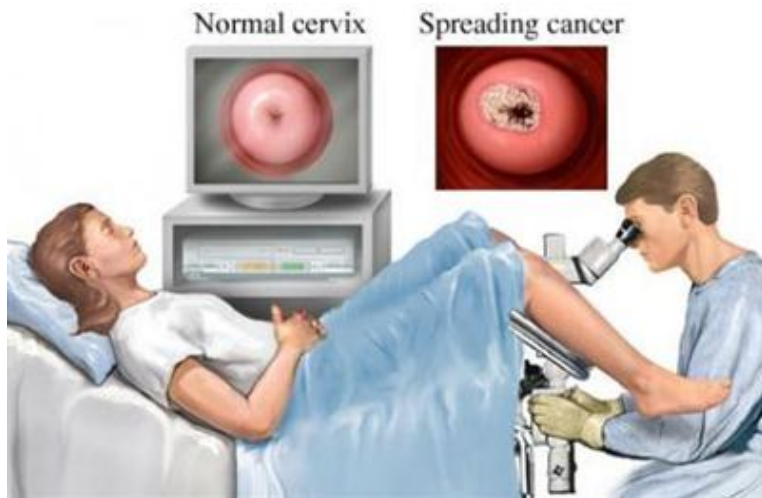


# Screening test is NOT diagnostic



# Cancer screening

- Breast Cancer
- Cervical Cancer
- Colorectal (Colon) Cancer





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# Necessary conditions for the feasibility of screening programs

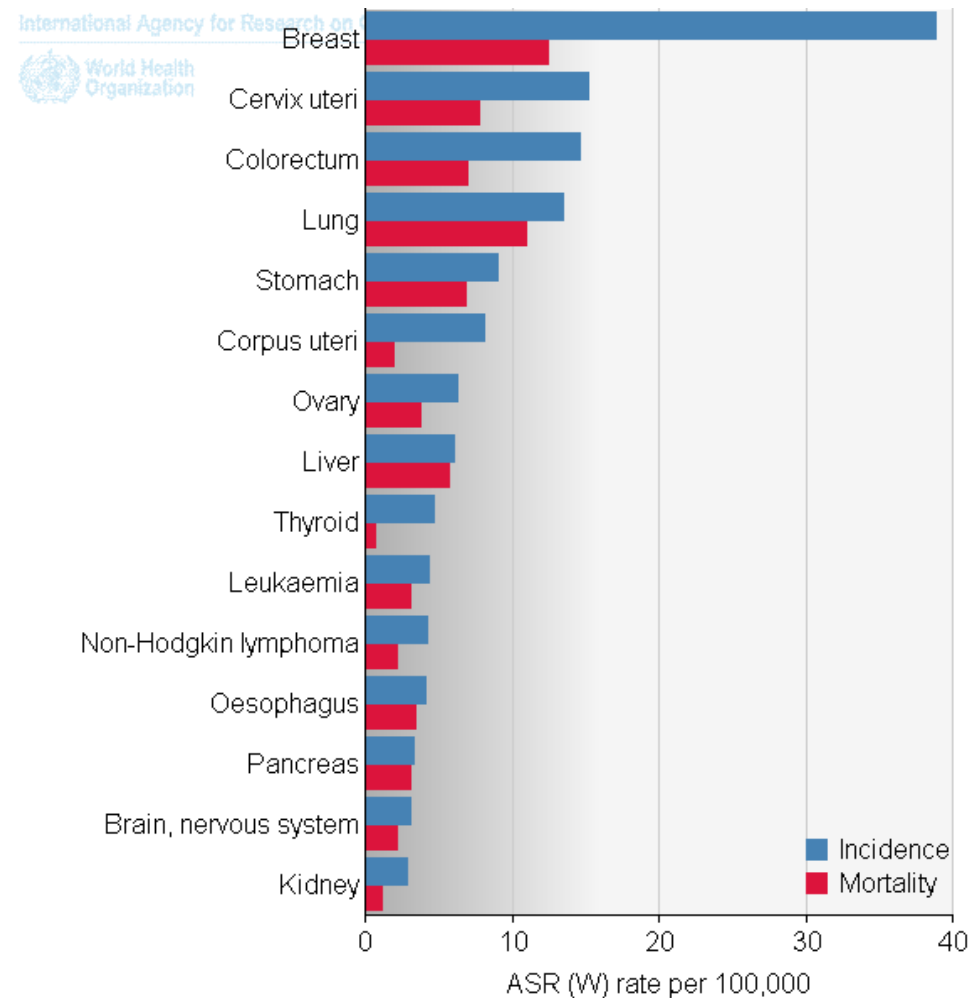




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# Incidence and Mortality worldwide: women



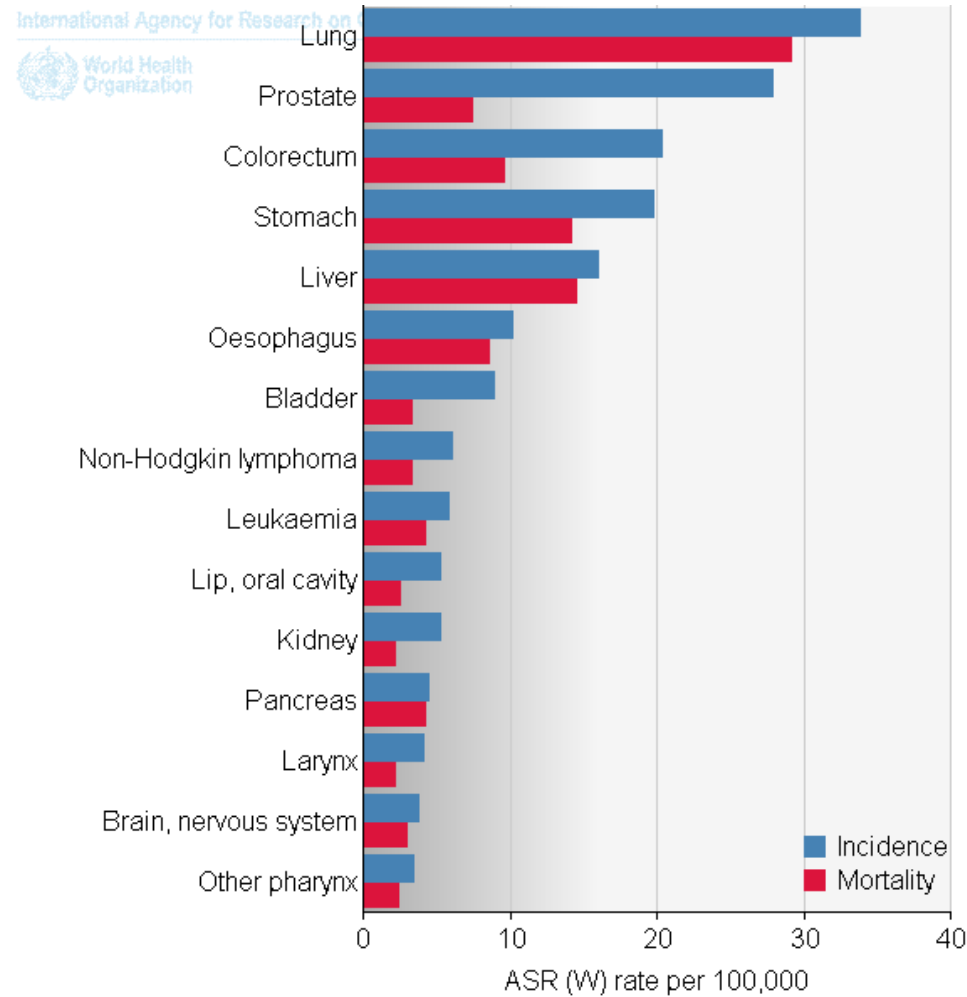
*Ferlay et al, GLOBOCAN 2008: Cancer Incidence and Mortality Worldwide, IARC 2010*



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# Incidence and Mortality worldwide: men



*Ferlay et al, GLOBOCAN 2008: Cancer Incidence and Mortality Worldwide, IARC 2010*



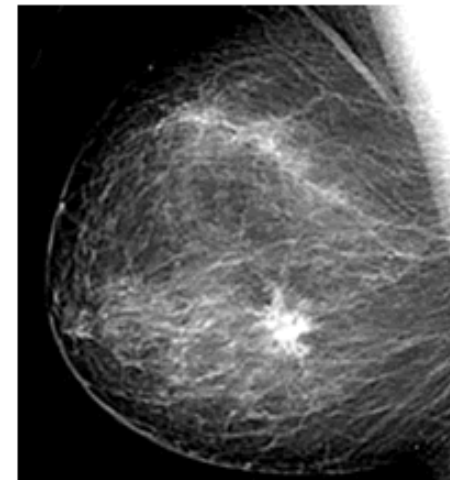
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# Breast Cancer Screening



- Women aged 50 – 69 years
- Screening test:  
Mammography (bilateral in a double projection)
- Every 2 years



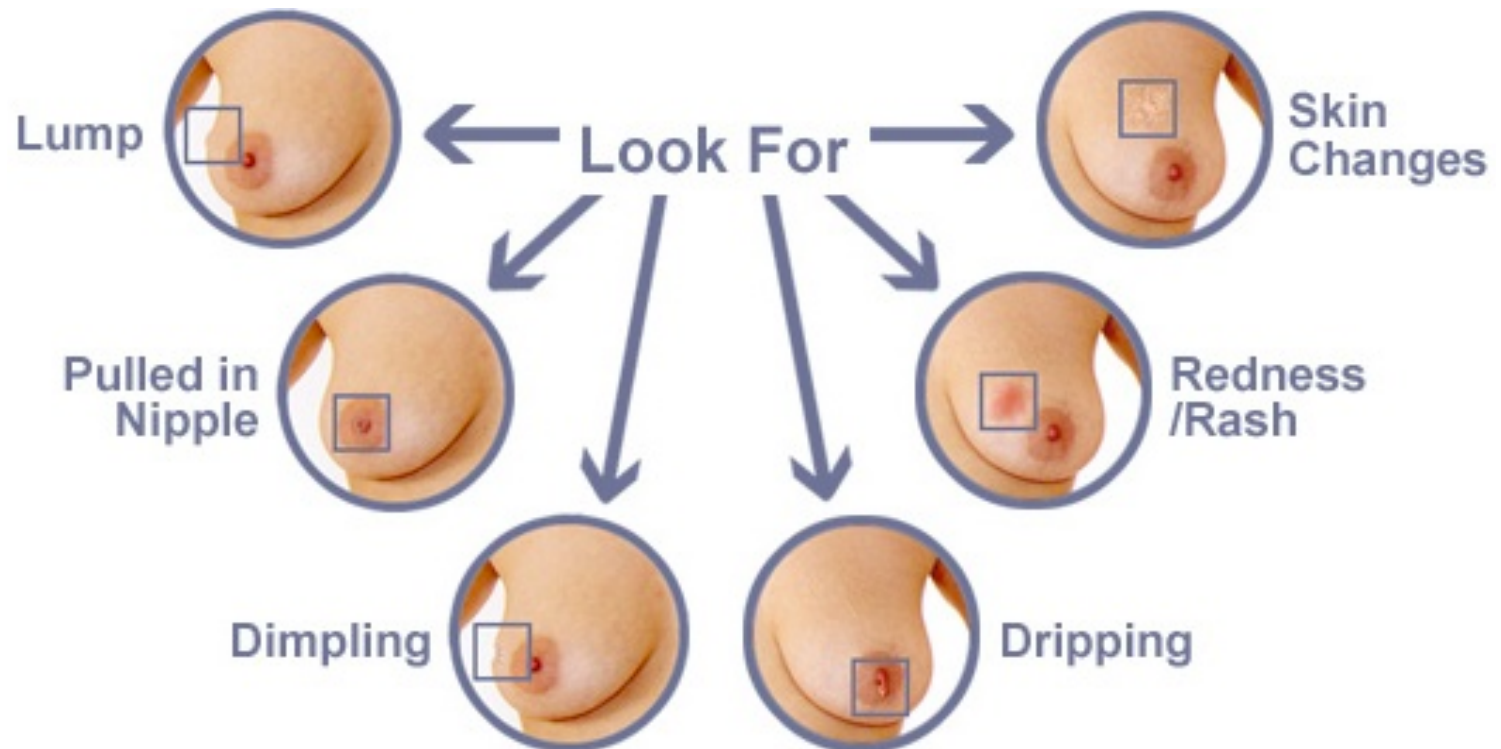




## II level



- Clinical breast exam, mammography
- Fine needle aspiration
- Core biopsy





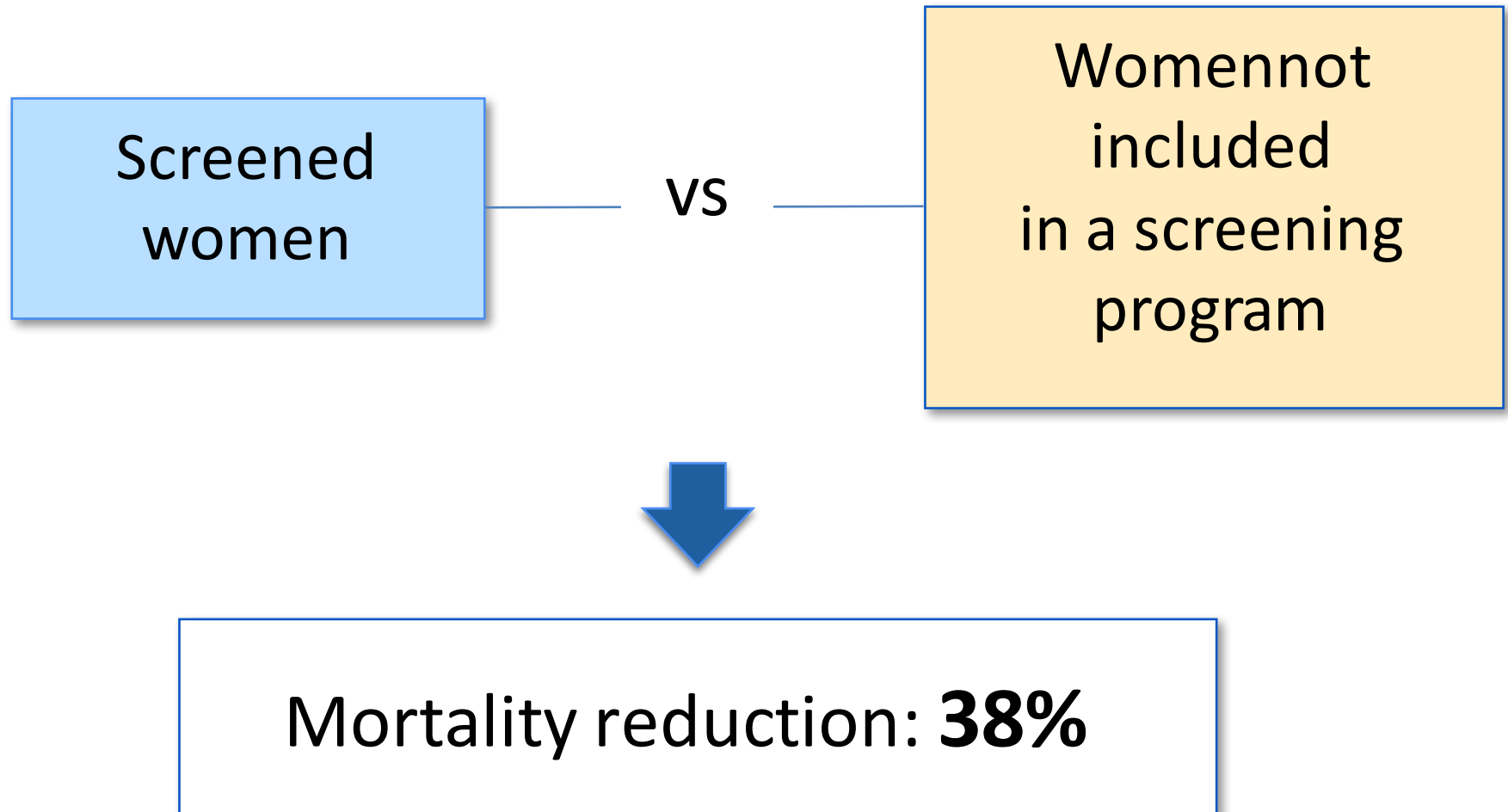
## III level



- Surgical treatment:
  - Quadrantectomy ↑
  - Mastectomy ↓
- and/or chemotherapy



# Benefits



*Euroscreen working group. Lancet 2013*



# Benefits

*Eur J Public Health.* 2014 Apr;24(2):280-5. doi: 10.1093/eurpub/ckt119. Epub 2013 Sep 5.

## **Does breast cancer screening level health inequalities out? A population-based study in an Italian region.**

Pacelli B<sup>1</sup>, Carretta E, Spadea T, Caranci N, Di Felice E, Stivanello E, Cavuto S, Cisbani L, Candela S, De Palma R, Fantini MP.

### **+ Author information**

#### **Abstract**

**BACKGROUND:** Although population-based screening has the potential to reduce inequalities in breast cancer survival, evidence on this topic is controversial. The objective of this study was to evaluate whether the full implementation of a mammography screening programme in Emilia-Romagna in Italy had an impact on variations in breast cancer survival by educational level.

**METHODS:** A cohort study was performed, including all women <70 years and residing in Emilia-Romagna who had infiltrating breast cancer registered in 1997-2000 (transitional screening period) or 2001-03 (consolidation screening period). Cancer cases were retrieved from the regional Breast Cancer Registry and followed up for 5 years. Educational level was determined from census data and allocated to cancer cases by individual record linkage. Age at diagnosis was classified into two groups (30-49, 50-69: screening target population).

**RESULTS:** A total of 9639 cases were analyzed. In the 1997-2000 period, low-educated women had significantly lower survival compared with high-educated women, both in the younger and in the older age-groups. After the full implementation of the screening programme, these differences decreased in both age-groups, until disappearing completely among women in the age-group invited to screening.

**CONCLUSIONS:** Our findings suggest that a fee-free population-based organized mammography screening programme with active invitation of the whole target population could be effective in reducing differences in survival in the population targeted by the screening.



# Risks

- Overdiagnosis
- Psychological harm (anxiety in advance of the test, distress if abnormalities are detected)

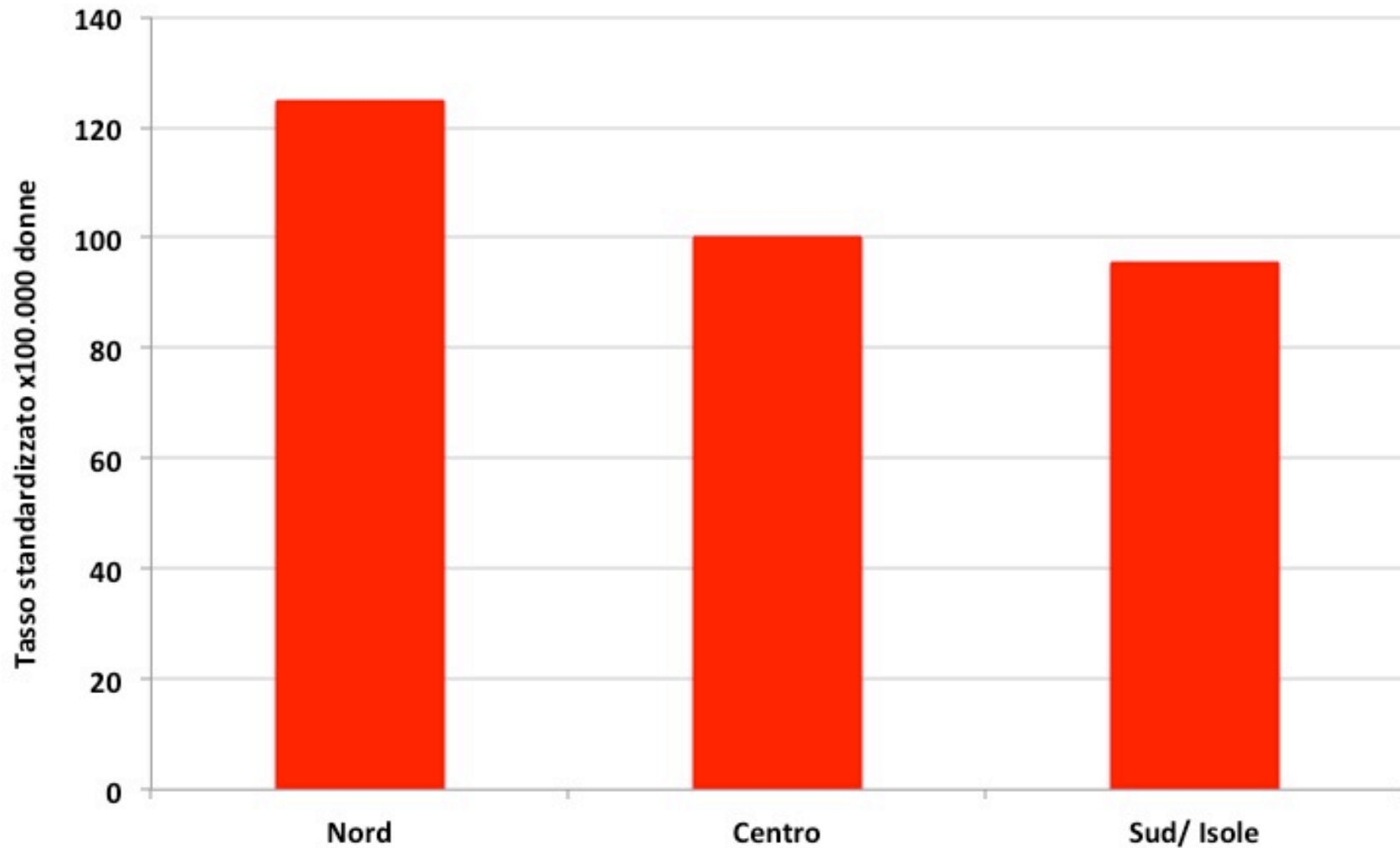


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# Breast cancer incidence

## Italy, 2006 - 2009

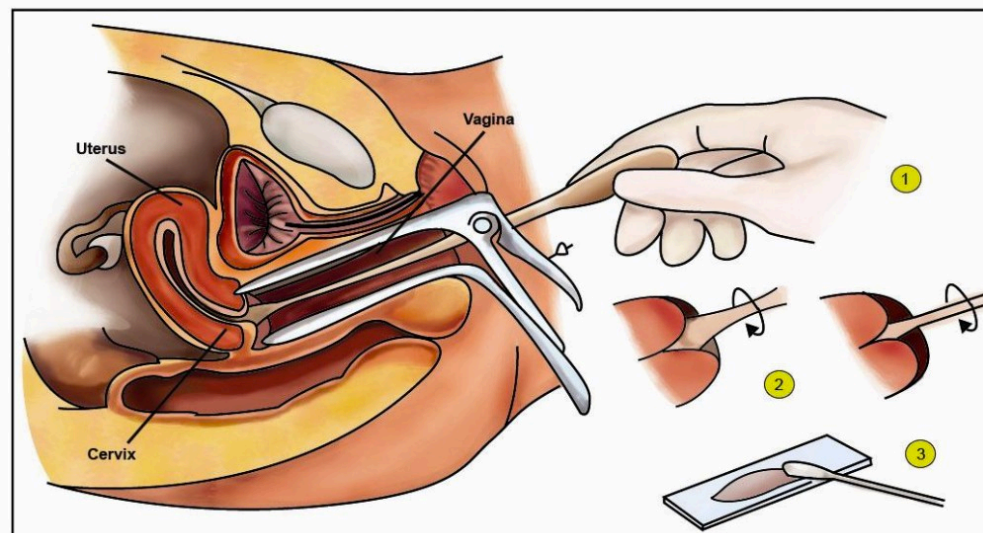


*AIRTUM–AIOM. I numeri del cancro 2013.*



# Cervical cancer screening

- Women 25 – 64 years
- Screening (I level):  
**Pap smear**
- Every 3 years
- Bethesda Classification, 2001







# Bethesda Classification 2001

## Classification of Pap smear results

- Papanicolaou classification: Class I-V
- Dysplasia classification(1963)
- CINI,II,III(1968)
- Bethesda classification

### Squamous cell

**ASC** : atypical squamous cell ; ASC -US , ASC -H

**LSIL** : low grade squamous intraepithelial lesion(HPV ,CIN I)

**HSIL**: high grade squamous intraepithelial lesion(CIN II/III/Insitu)

**Invasive scc**

### Glandular Cell

- ✦ Atypical Glandular cells (AG)
  - Undetermined Significance (**AG-US**) or NOS
  - Favors Neoplasm
- ✦ Adenocarcinoma In Situ (AIS)
- ✦ Adenocarcinoma





## II level

Different according to Pap smear results:

- HPV test (all positive tests)
- Repeat Pap smear (ASC – US, LSIL, inadeguati)
- Colposcopy with or without endometrial biopsy (HSIL, ASC – H, AGC, Cr)

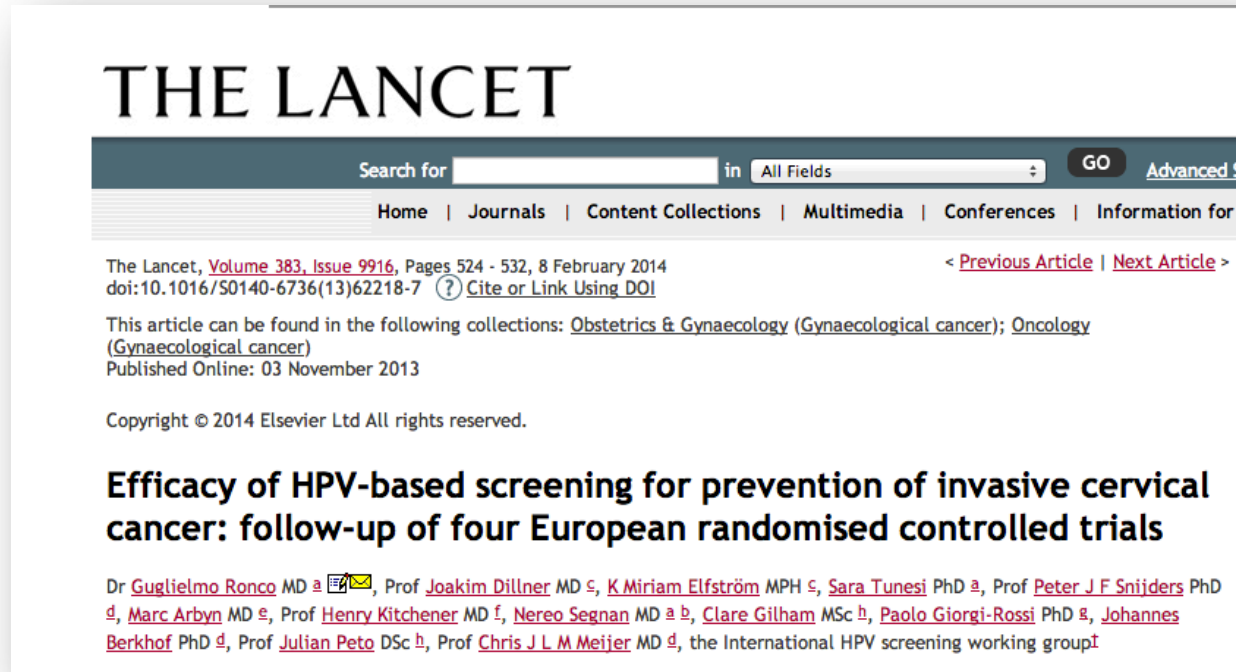


## III level

- Treatment for CIN 2 and CIN 3:
  - laser vaporization
  - cryotherapy
  - radical diathermy
  - conization
  - ....
- 6 months follow up for CIN 1



# New guidelines



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The Lancet, [Volume 383, Issue 9916](#), Pages 524 - 532, 8 February 2014  
doi:10.1016/S0140-6736(13)62218-7 [Cite or Link Using DOI](#) [? Cite or Link Using DOI](#)

This article can be found in the following collections: [Obstetrics & Gynaecology \(Gynaecological cancer\)](#); [Oncology \(Gynaecological cancer\)](#)  
Published Online: 03 November 2013

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## Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials

Dr [Guglielmo Ronco](#) MD [✉](#), Prof [Joakim Dillner](#) MD [c](#), [K Miriam Elfström](#) MPH [c](#), [Sara Tunesi](#) PhD [a](#), Prof [Peter J F Snijders](#) PhD [d](#), [Marc Arbyn](#) MD [e](#), Prof [Henry Kitchener](#) MD [f](#), [Nereo Segnan](#) MD [a](#) [b](#), [Clare Gilham](#) MSc [h](#), [Paolo Giorgi-Rossi](#) PhD [g](#), [Johannes Berkhof](#) PhD [d](#), Prof [Julian Peto](#) DSc [h](#), Prof [Chris J L M Meijer](#) MD [d](#), the International HPV screening working group<sup>†</sup>

- Pap test every 3 years: women 24 to 30 years
- HPV test every 5 years: Women > 30 years

*Ronco G. et al., The Lancet, February 2014*



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# Colorectal cancer screening

PER SAPERNE DI PIÙ  
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Numero verde gratuito

www.sanita.puglia.it



**MEGLIO  
PREVENIRE  
CHE CURARE**

**PROGRAMMA  
DI PREVENZIONE  
DEL TUMORE  
DEL COLON RETTO**

Non si sente e non si vede, quando te  
essere troppo tardi. Il tumore al colon  
frequenti cause di morte. Cosa fare  
plice: prevenire. Oggi con il test delle  
e puoi farlo da casa tua. Se hai da 50  
provetta con le istruzioni per esegui  
tà di spedizione. Il risultato dell'esam  
per posta. Sottoposti al test che pu



Look out for the early signs of  
bowel cancer.



The longer



you leave it



the bigger

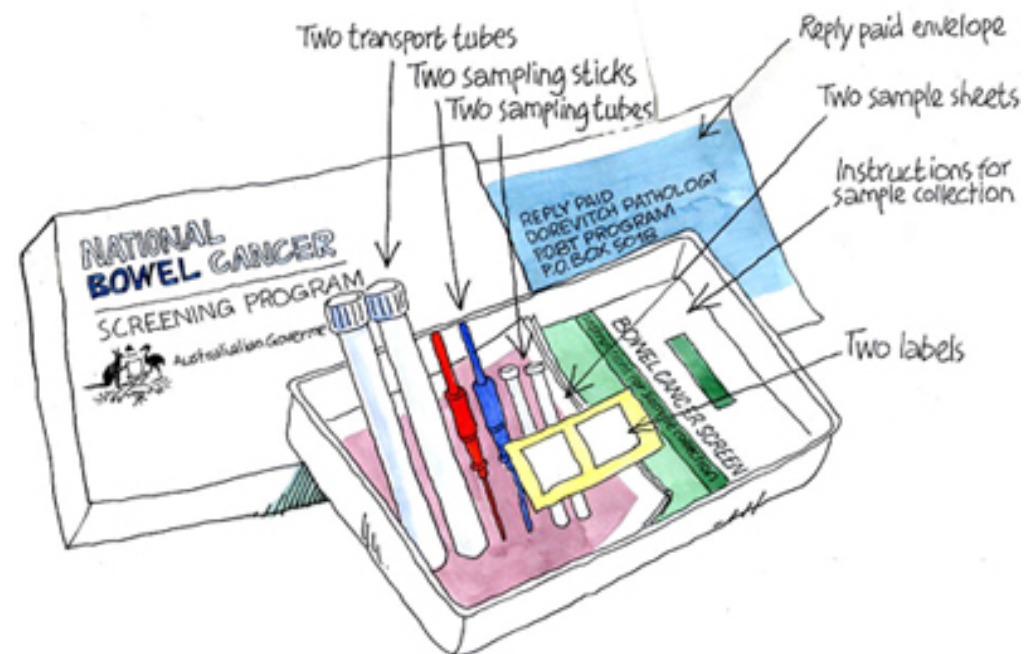
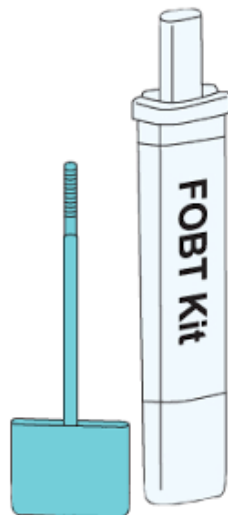


the problem.



# Colorectal cancer screening

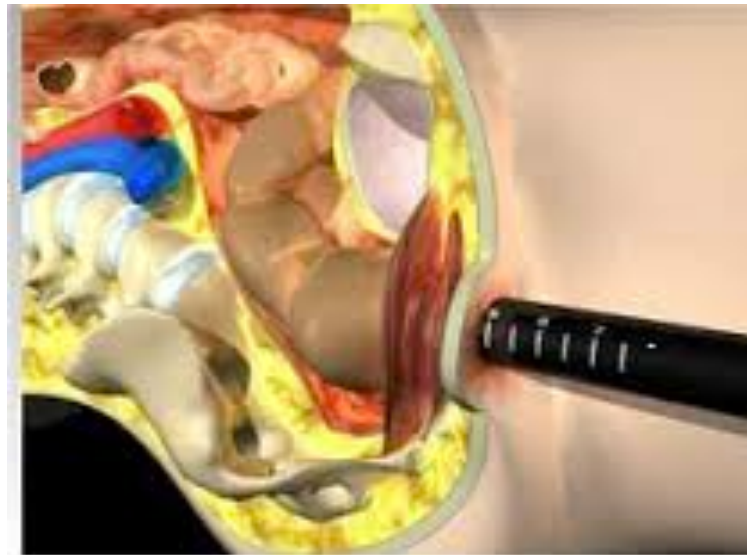
- Men and women between 50 and 70 years
- Screening test (Level I): Fecal Occult Blood Test
- Every 2 years





# Colorectal cancer screening

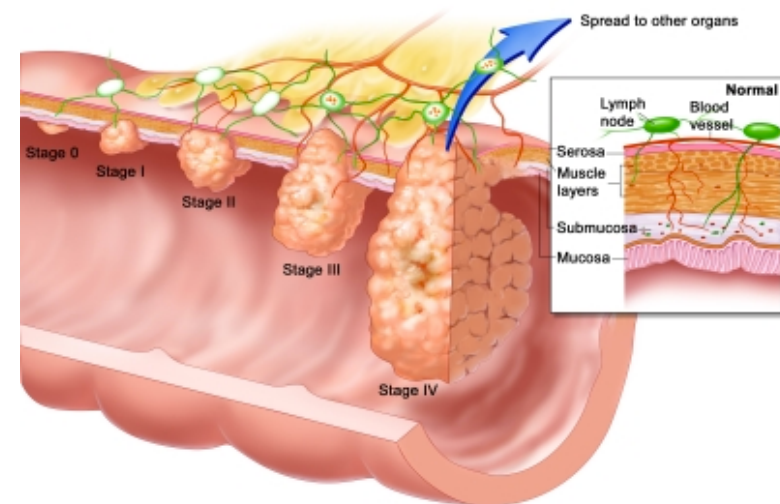
- Some Italian programs (Piedmont and Veneto) use the sigmoidoscopy as a screening test (level I)





## II level

- Colonoscopy
- Biopsy
- If colonoscopy is not executable or is rejected: Rx colon with double contrast or TAC colonography

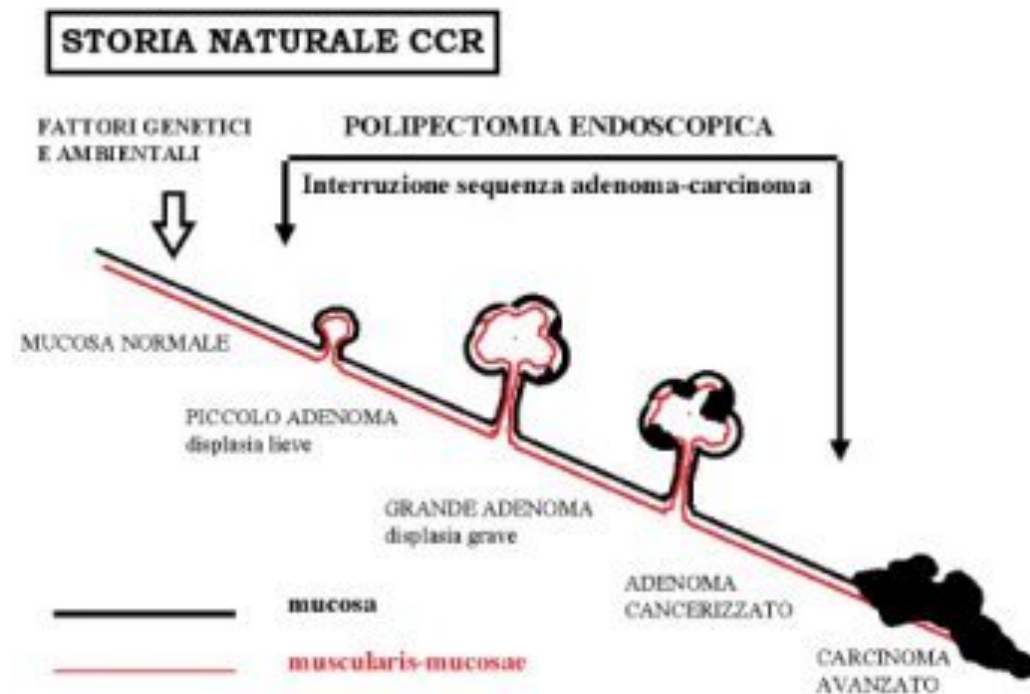






## III level

- Surgery







# Familiarity for bowel cancer

- management is not the same in Italy
- Each program implements different protocols
- In Puglia:
  - First-degree relatives of patients with cancer: colonoscopy



## Monitoring of screening programs

- It's necessary to track every action: from the identification of the target population to the possible treatment
- Data allow us to compare the performance of the program with indicators contained in the guidelines

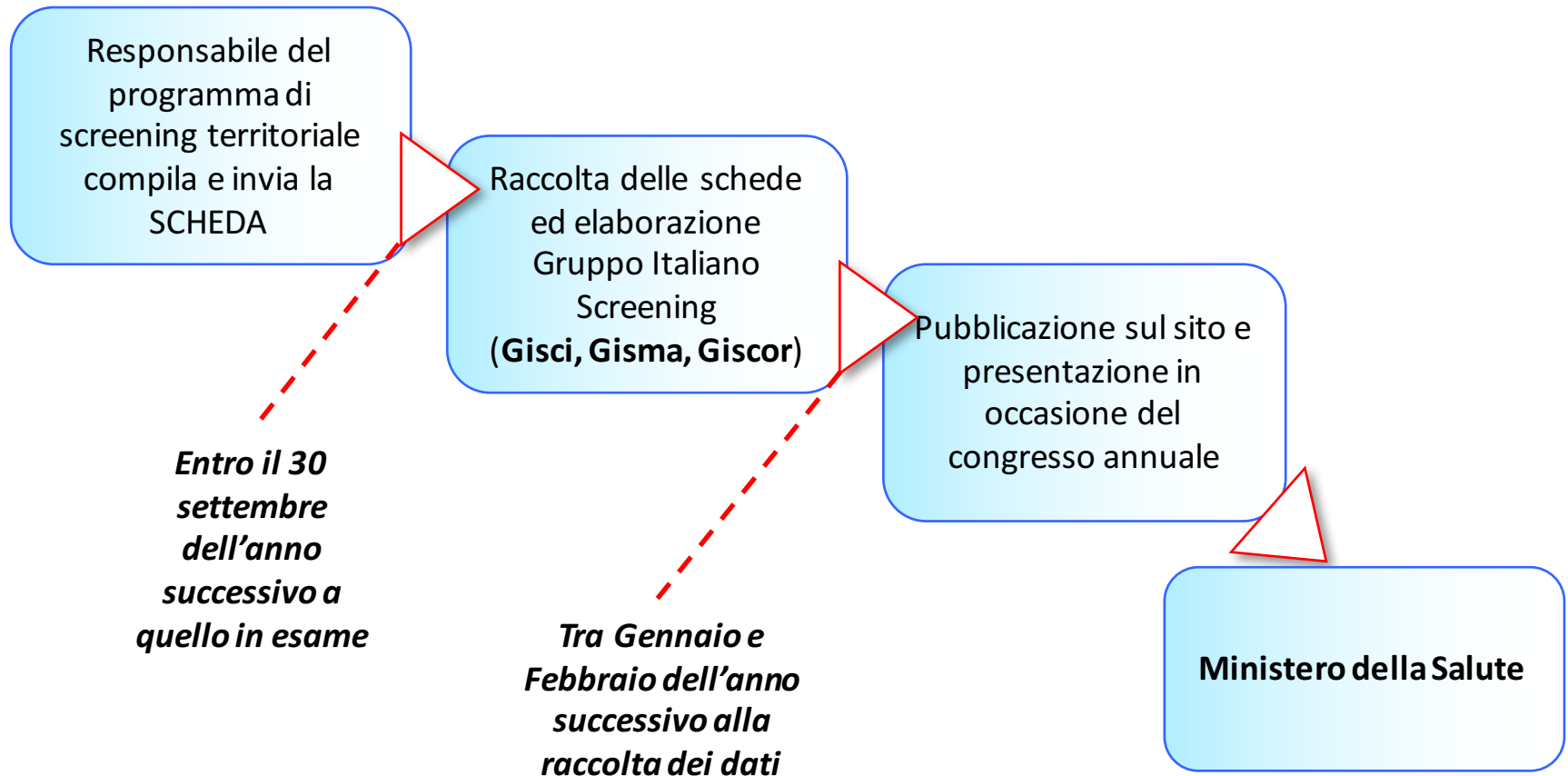


# Performance indicators

- The same for all of Italian screening programs
- Published annually on the website [www.osservatorionazionale screening.it](http://www.osservatorionazionale screening.it)
- For each screening program and each screening is needed to fill out a pre-formed sheet:
  - GISMA form
  - GISCI form
  - GISCOR form



# Informative flow





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## To improve you knowledge...

- <http://www.cdc.gov/cancer/dcpc/prevention/screening.htm>
- <http://www.cancer.org/healthy/findcancerearly/cancerscreeningguidelines/>