Medicina personalizada

Los marcadores moleculares y su impacto en un escenario futuro en el cribado de cáncer

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ivo FUNDACIÓN INSTITUTO VALENCIANO DE ONCOLOGÍA

Red de Programas de Cribado de Cáncer

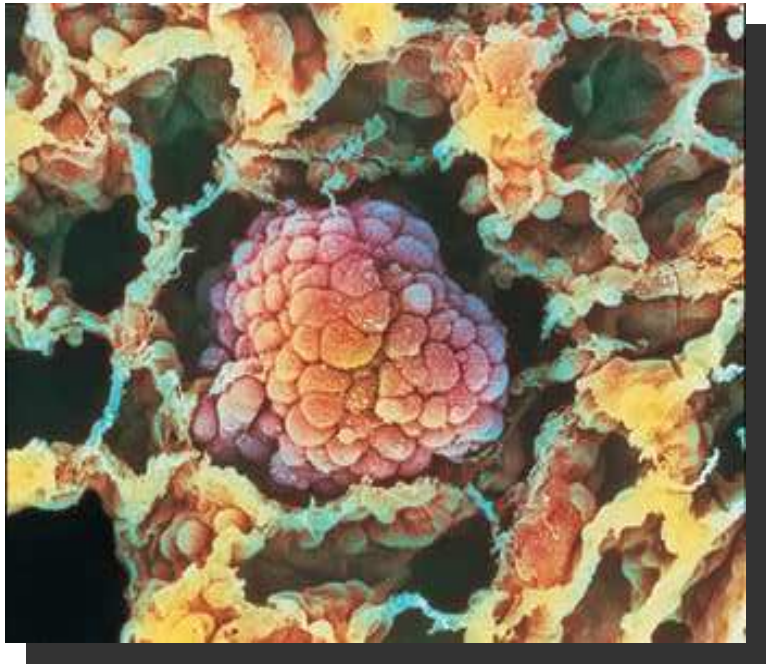
XVI Reunión Anual Valencia 26, 27 y 28 de junio

GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

Instituto de Salud Carlos III

Guión

- ¿A qué nos enfrentamos?
  - El cáncer es una enfermedad compleja.
- ¿Qué pretendemos conseguir?
  - Papel de los biomarcadores.
- Necesidad de nuevos planteamientos.
  - Incorporación racional de biomarcadores en el diseño de nuevos estudios.

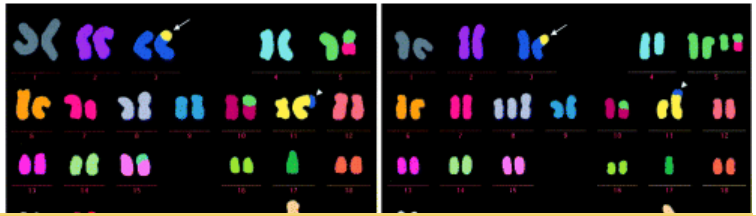


El cáncer es una enfermedad compleja

¿A qué nos enfrentamos?

Fenotipo del cáncer

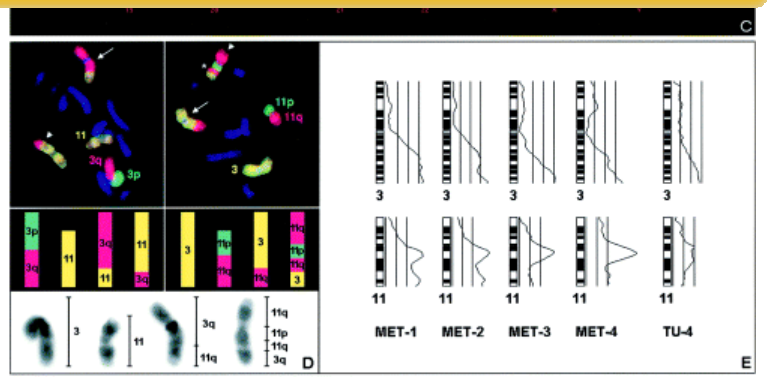
Del fenotipo al genotipo del cáncer



- **El cáncer es una enfermedad que presenta problemas en el diseño de sus genes.**

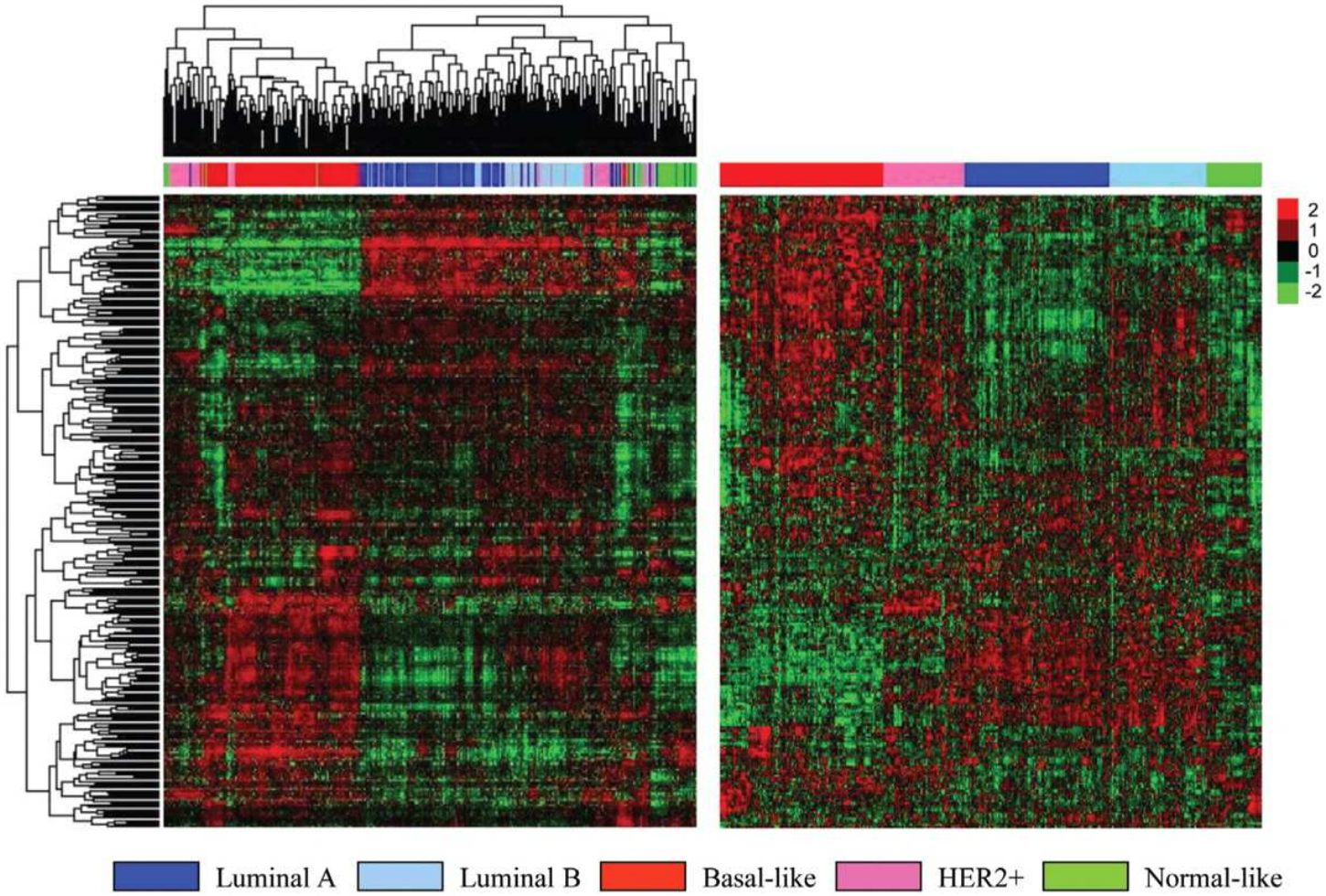
- **El cáncer es una enfermedad genética.**

Célula normal



Célula tumoral

La revolución tecnológica



La revolución tecnológica

THE CANCER GENOME ATLAS

http://cancergenome.nih.gov/

ARTICLE

doi:10.1038/nature11252

Comprehensive molecular characterization of human colon and rectal cancer

The Cancer Genome Atlas Network*

ARTICLE

doi:10.1038/nature10166

Integrated genomic analyses of ovarian carcinoma

The Cancer Genome Atlas Research Network*

ARTICLE

doi:10.1038/nature11412

Comprehensive molecular portraits of human breast tumours

The Cancer Genome Atlas Network*

ARTICLE

doi:10.1038/nature11404

Comprehensive genomic characterization of squamous cell lung cancers

The Cancer Genome Atlas Research Network*

ARTICLE

doi:10.1038/nature11252

Comprehensive molecular characterization of human colon and rectal cancer

The Cancer Genome Atlas Network*

ARTICLE

OPEN
doi:10.1038/nature12113

Integrated genomic characterization of endometrial carcinoma

The Cancer Genome Atlas Research Network*

La revolución tecnológica

THE CANCER GENOME ATLAS

Mensajes

- **Breast cancer:** Basal-like subtype shares many genetic features with high-grade serous ovarian cancer suggesting that the cancers have a common molecular origin and may share therapeutic opportunities.

- Recognized **colon and rectal cancers** as a single type of cancer. TCGA was initially studying colon cancer as distinct from rectal cancer, but in multiple types of analyses, colon and rectal case results proved nearly indistinguishable.

- **High grade serous OvCa.** Substantiated observations that patients with mutations in their BRCA1 and BRCA2 genes have better odds of survival than patients without mutations in those genes. Approximately 21 percent of tumor cases in this study exhibited BRCA1 and BRCA2 mutations.

- Etc…

http://cancergenome.nih.gov/

El cáncer es una enfermedad compleja

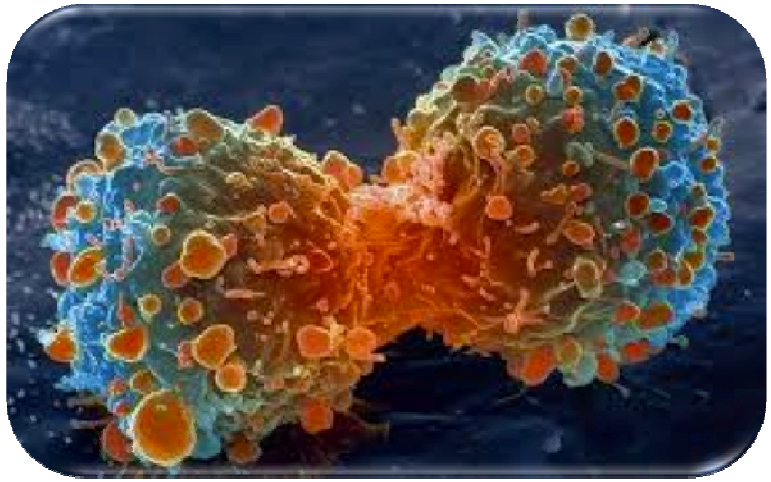
Mutaciones somáticas

Agentes infecciosos

Predisposición genética

Edad

Dieta



Polución ambiental

Tabaco

Alcohol

Ocupación

Riesgo familiar

Agentes físicos y geológicos

Factores de riesgo modificables

El papel de los biomarcadores

¿Qué pretendemos conseguir?

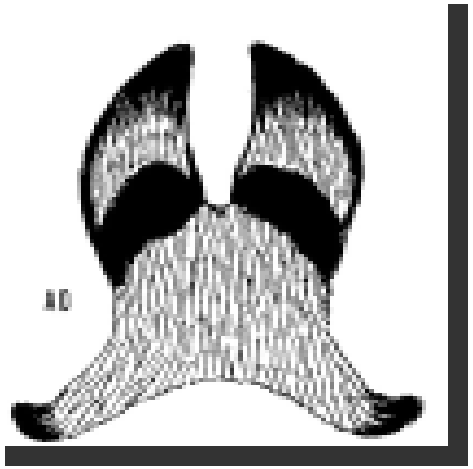
El papel de los biomarcadores

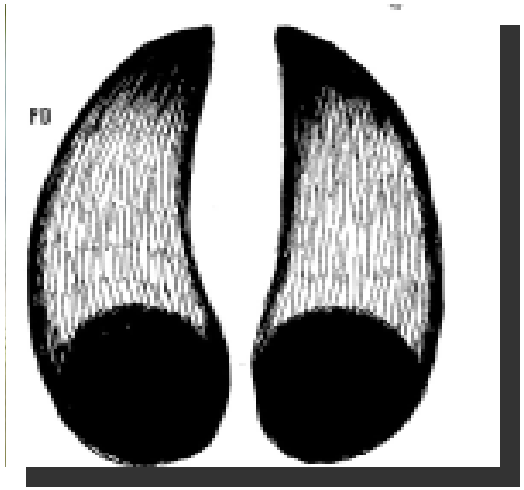
The official NIH ***definition*** of biomarker is:

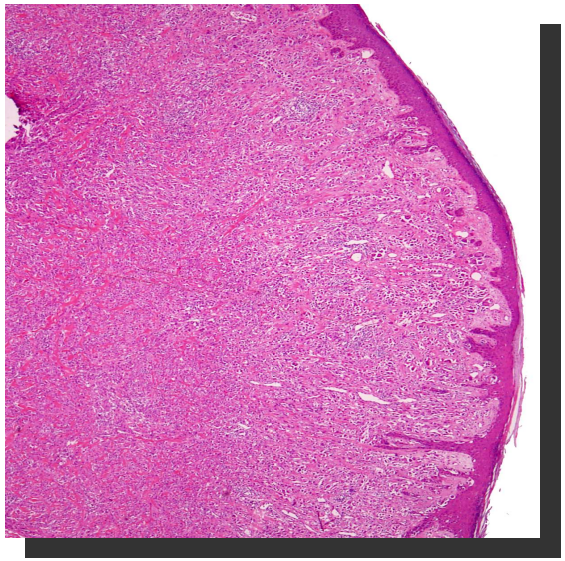
'a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention'

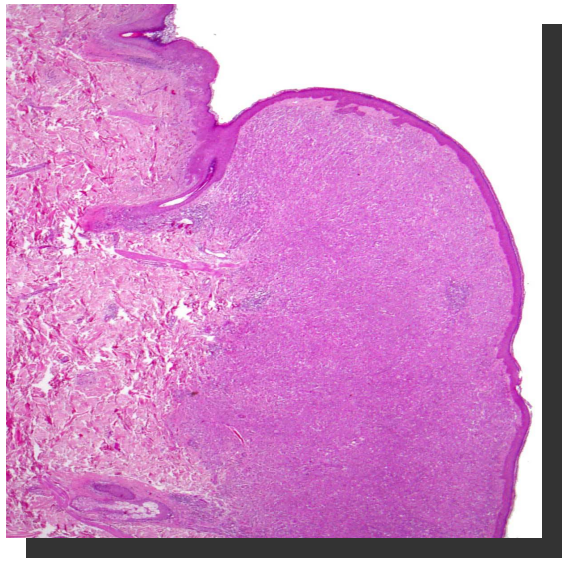
The Holy Grail in the screening context: distinguishing benign from malignant conditions with precision high enough and cost low enough to please everyone

El papel de los biomarcadores

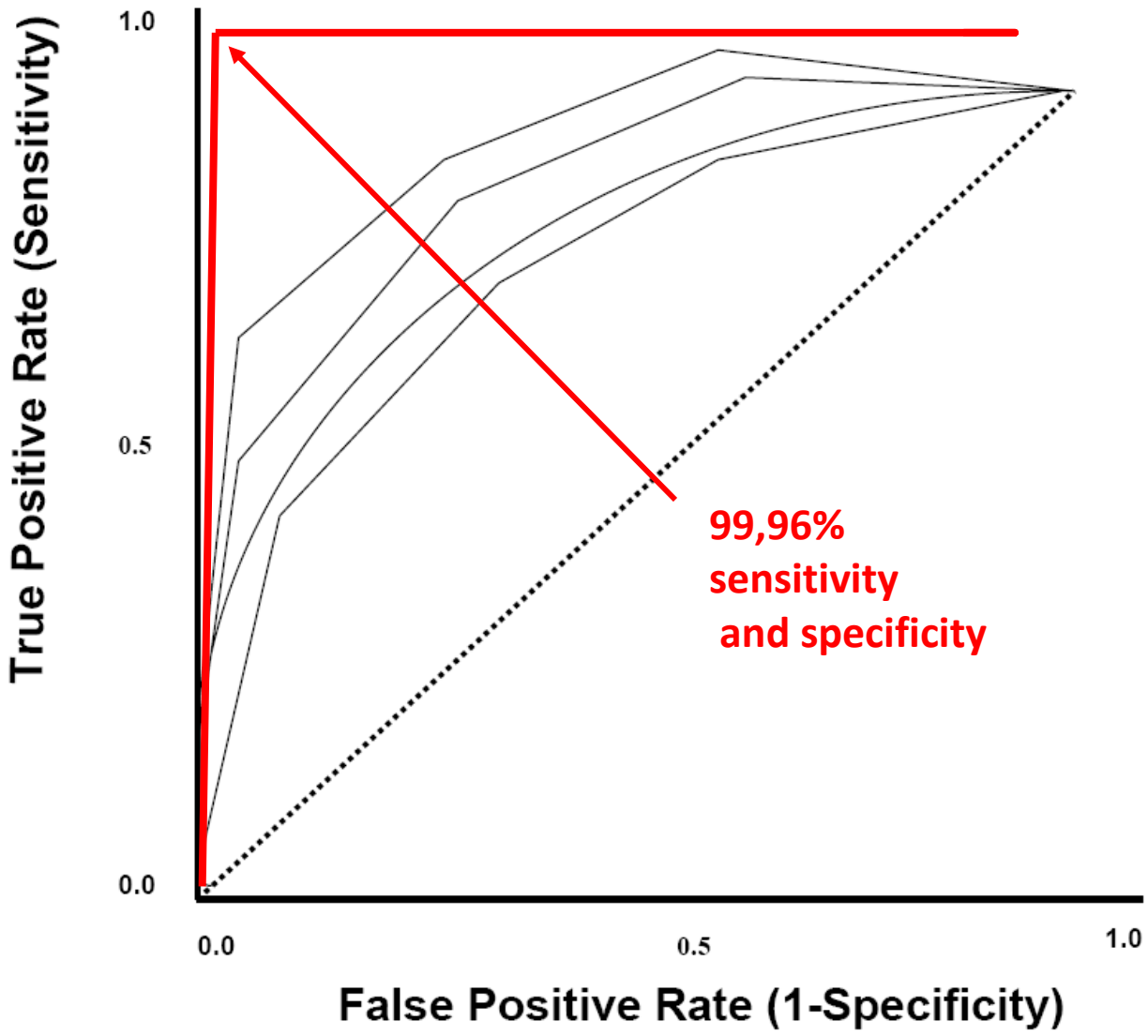








Un buen biomarcador debe ser muy preciso



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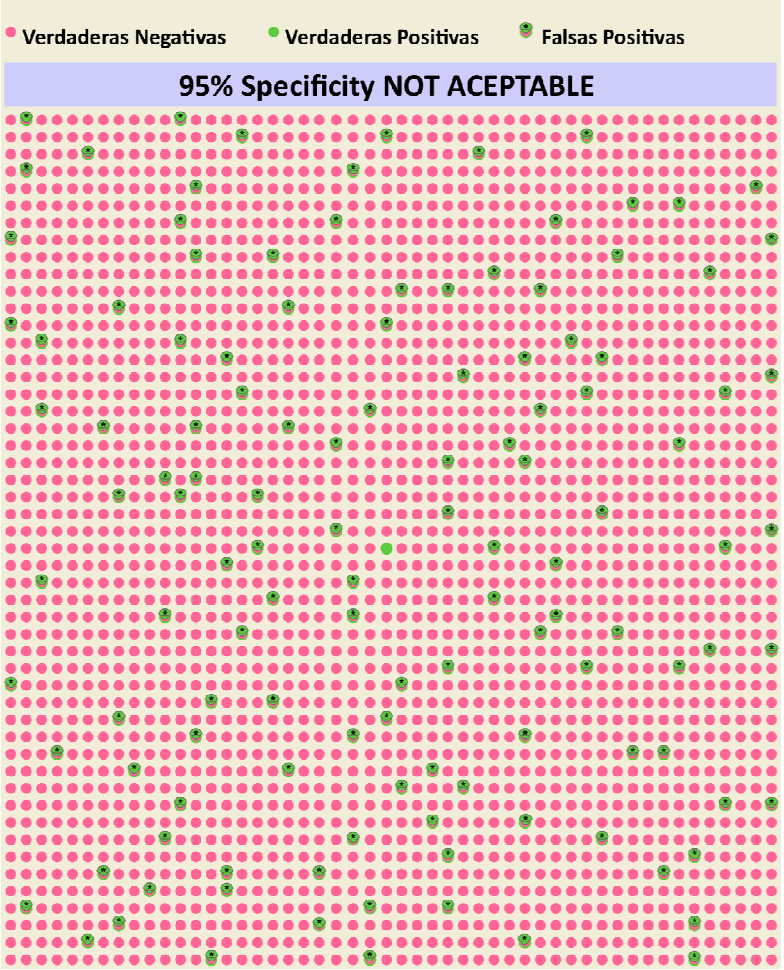
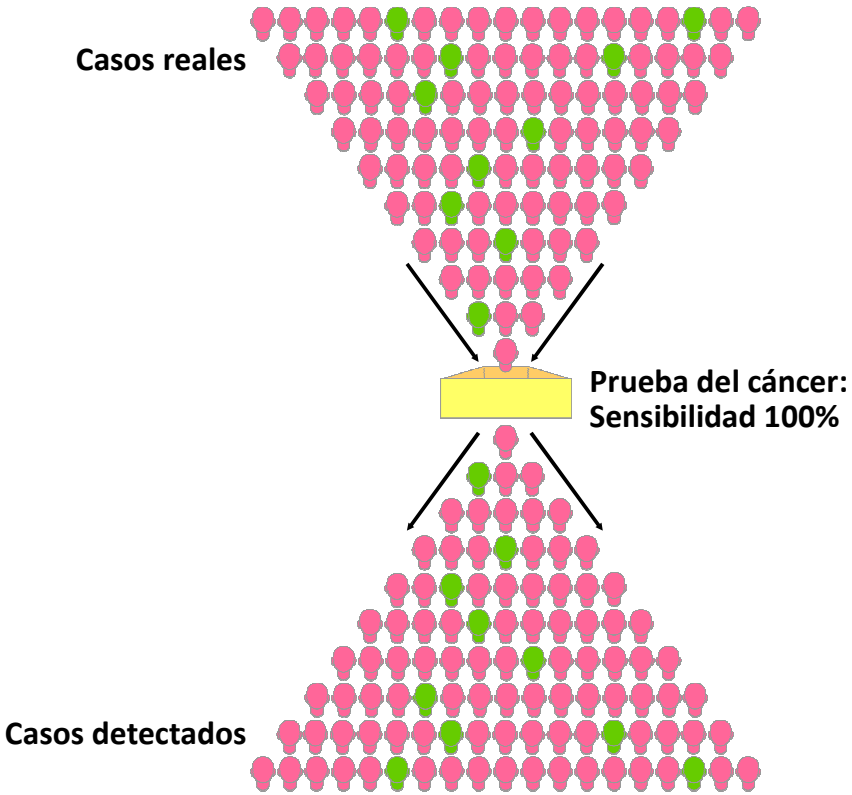




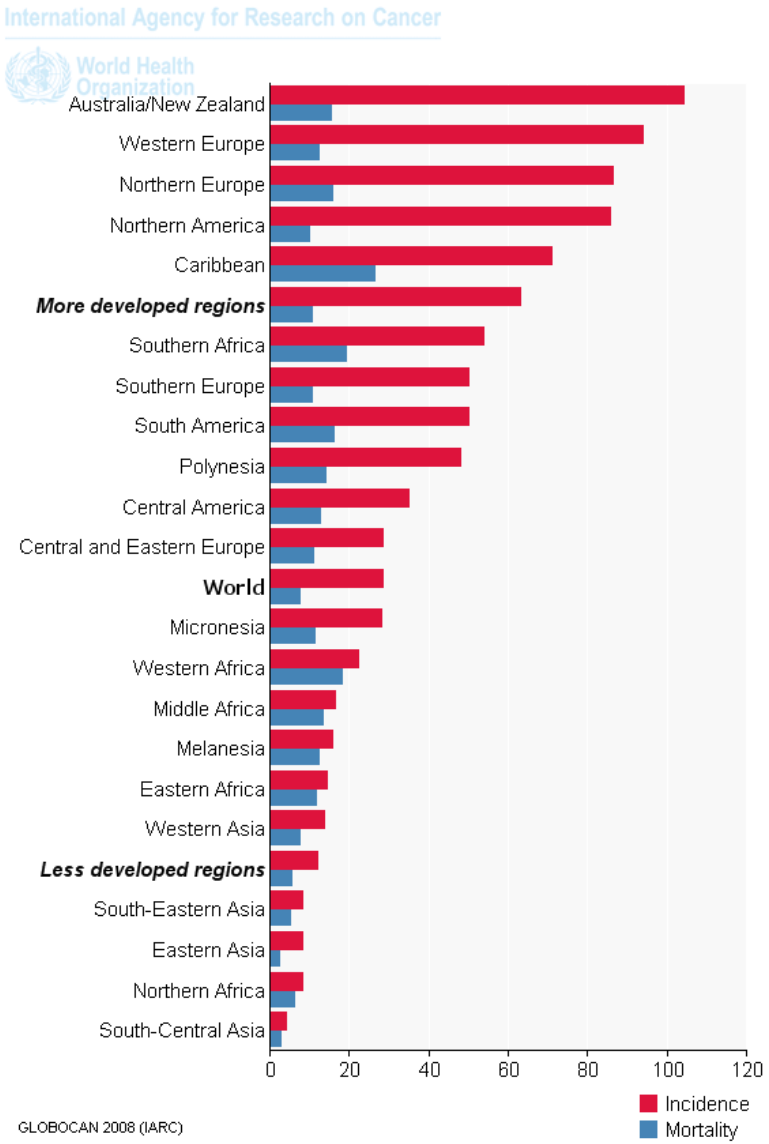
Biomarcadores en el contexto de cribado:

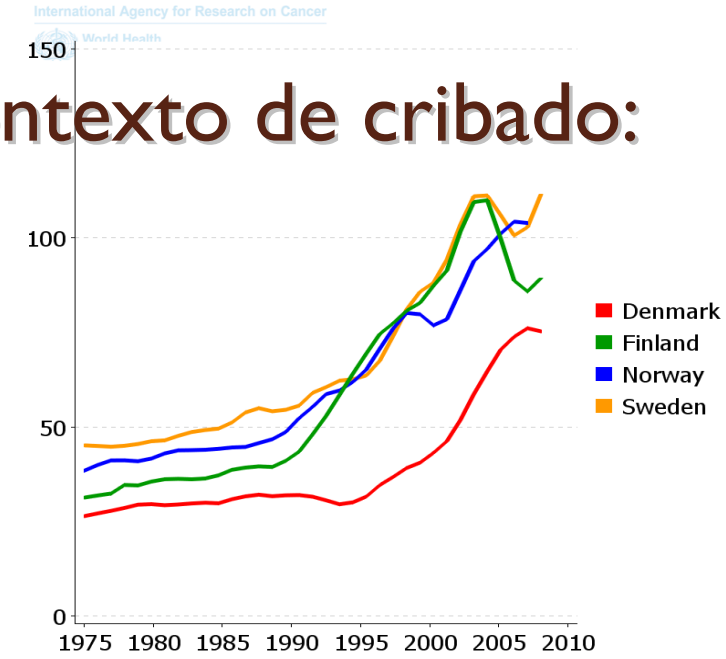
CA-125 en Cáncer de Ovario

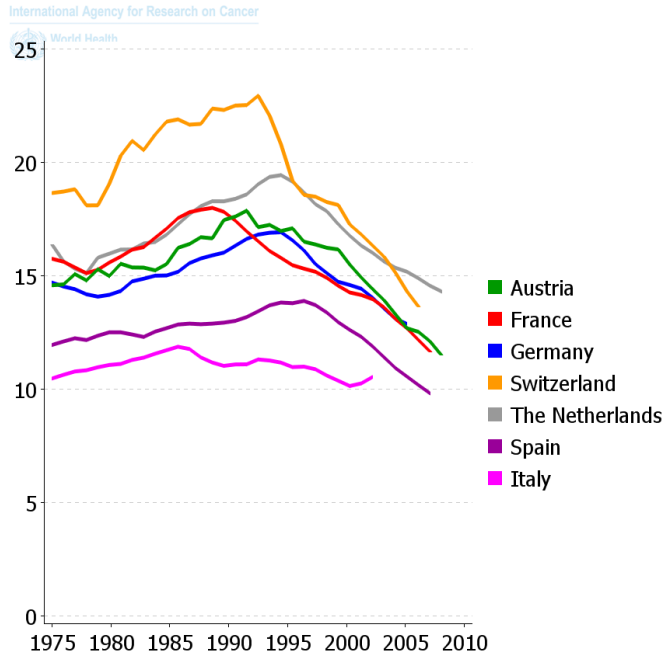
- There is no standardized test to detect OvCa at an early stage
- CA-125 is shed by only 80 percent of OvCa
- CA-125: most widely used screening method
  - Specificity is limited
  - False elevations in: endometriosis, fibroids, cirrhosis w/- ascites, PID, cancers of breast, lung, pancreas, pleural or peritoneal fluid due to any cancer
- The rate at which CA-125 levels increase is more accurate for detecting, than a single CA-125 test.
- CA-125 test has a lower specificity in premenopausal women than postmenopausal women.
- The CA-125 test should be used with transvaginal sonography and rectovaginal pelvic examination for greater accuracy.

Biomarcadores en el contexto de cribado:

PSA en Cáncer de Próstata







Biomarcadores en el contexto de cribado:
PSA en Cáncer de Próstata

At least three in four men men h negative biopsy at PSA levels between 4 and 10 ng/ml

100

Viernes 25/05/2012. Actualizado **08:09h.**

REVISIÓN | Comité de expertos

El PSA, sentenciado a muerte

- Un panel concluye que el análisis genera más daños que beneficios

Ángeles López | N

Actualizado **mar**

%

20

0

2

0.0-0.9

The FDA first approved the PSA blood test in 1986 for spotting the recurrence of prostate cancer after a prostatectomy. Soon after its initial release, clinicians began routinely using PSA for something that it had not been validated for: early cancer screening. By 1994, the FDA approved it for this purpose, as well.

Stamey et al. New Engl J Med, 1987

European Randomized Study of Screening for Prostate Cancer (ERSPC)

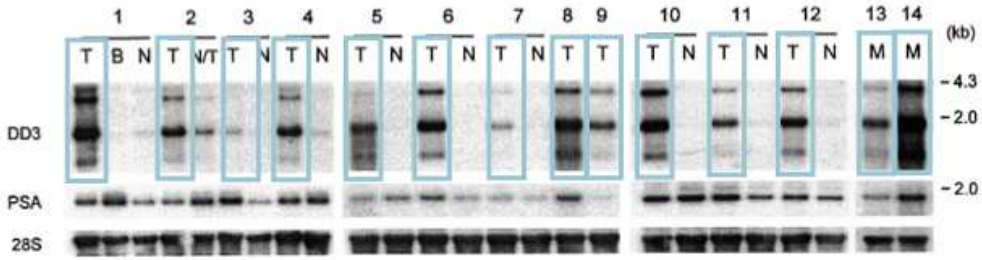
lice que el PSA es inútil

> 10

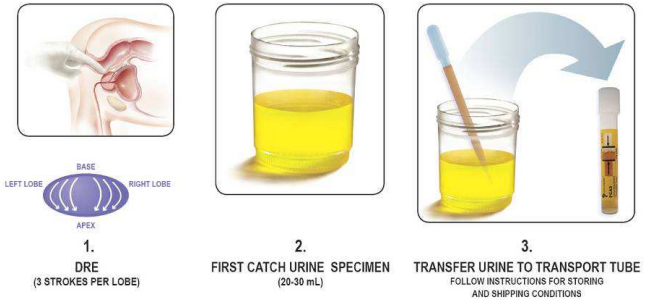
0.0 - >10 ng/mL

Postma R, et al. Eur J Cancer 2005;41

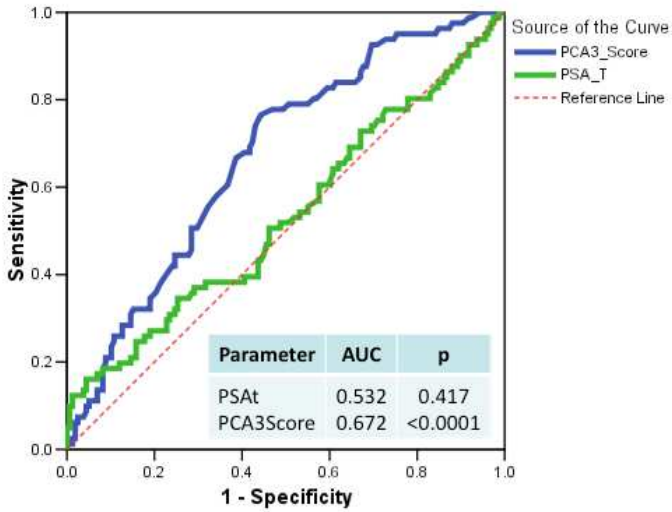
Cáncer de próstata:
Nuevos marcadores: DD3 (PCA3)

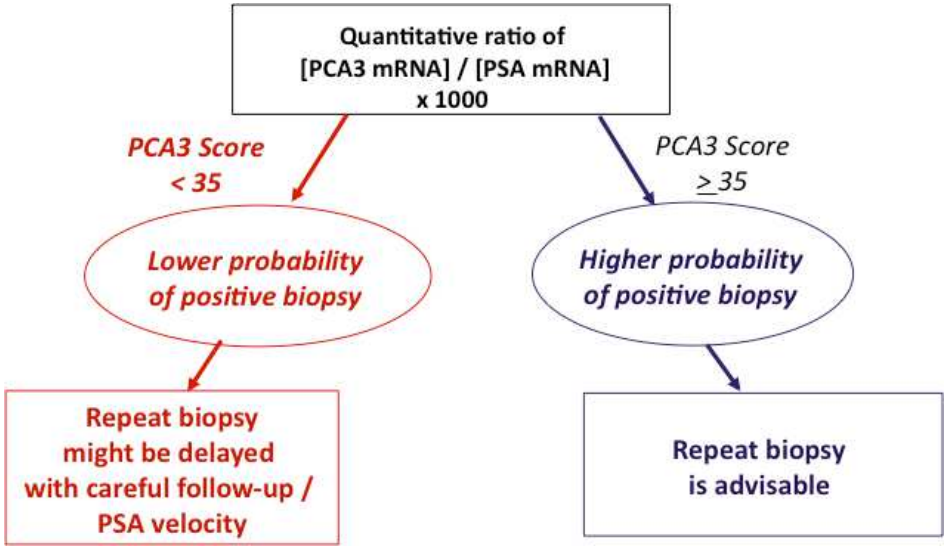


T = tumour; B = benign; N = normal; M = metastatic



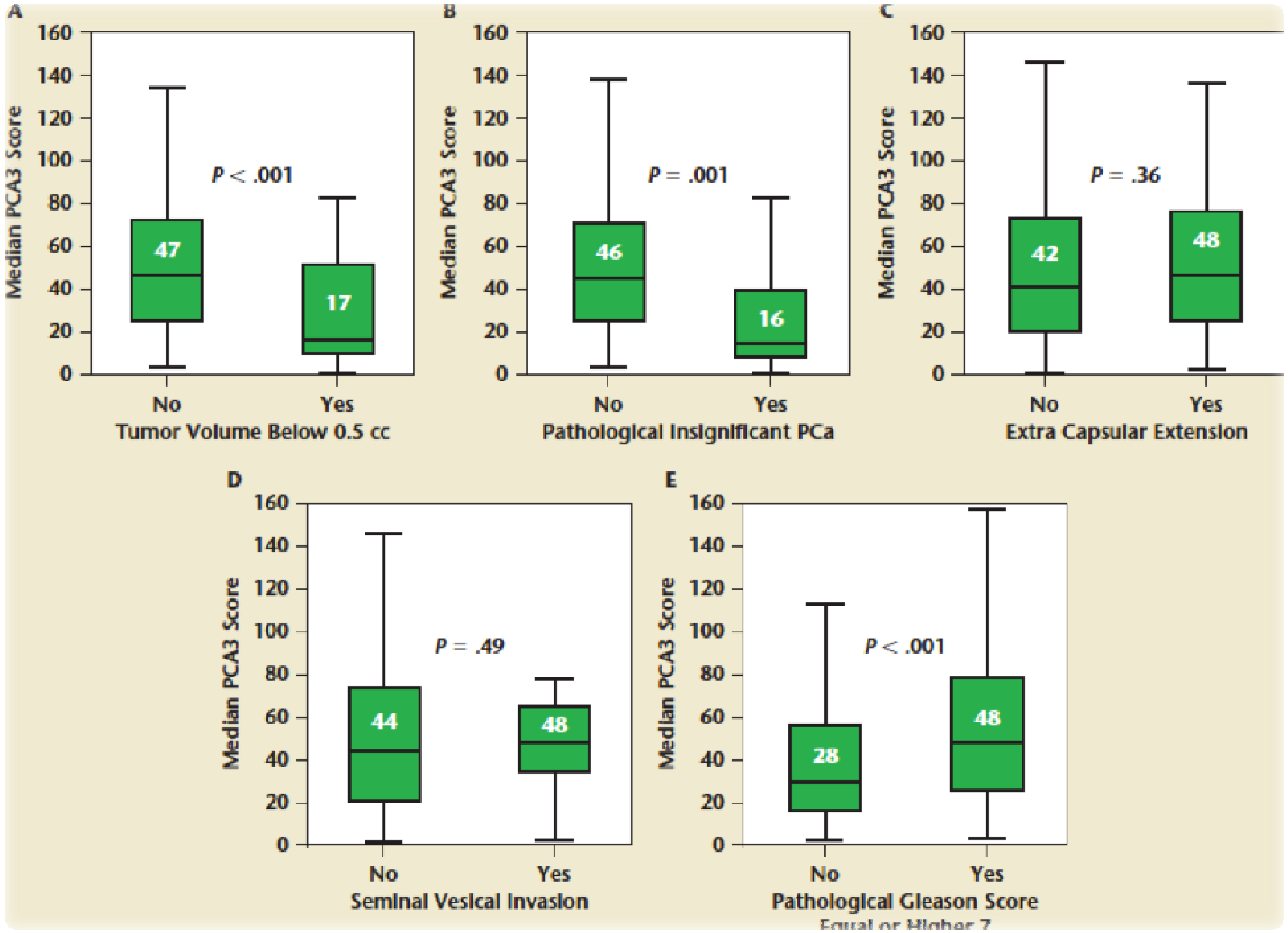
Bussemakers MJG, et al. Cancer Res 1999





Rubio-Briones J. et al. Act. Urol. Esp, 2011

Cáncer de próstata:
Nuevos marcadores: DD3 (PCA3)



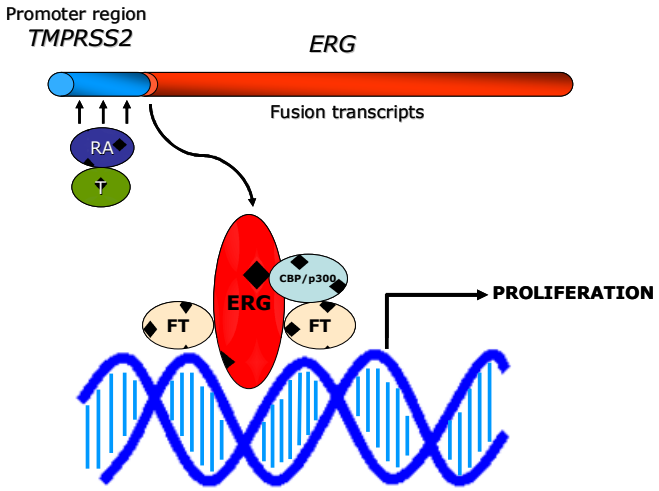
Loeb S. et al. Rev Urol, 2011

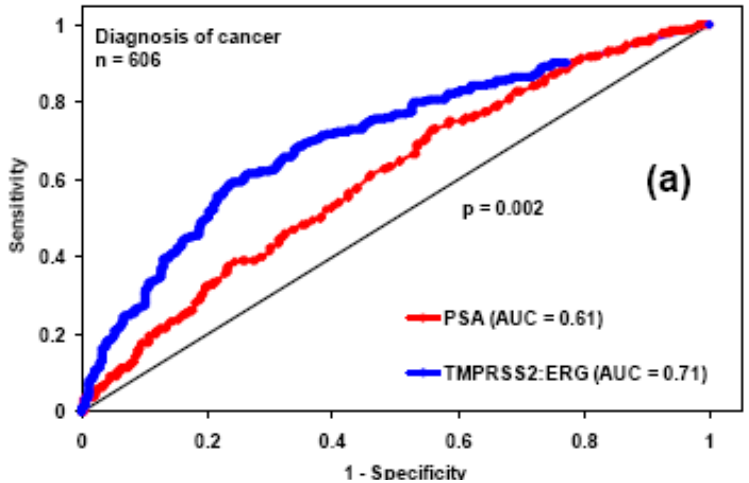
Cáncer de próstata:
Nuevos marcadores: *TMPRSS2-ETS*

RESEARCH ARTICLE

Recurrent Fusion of *TMPRSS2* and ETS Transcription Factor Genes in Prostate Cancer

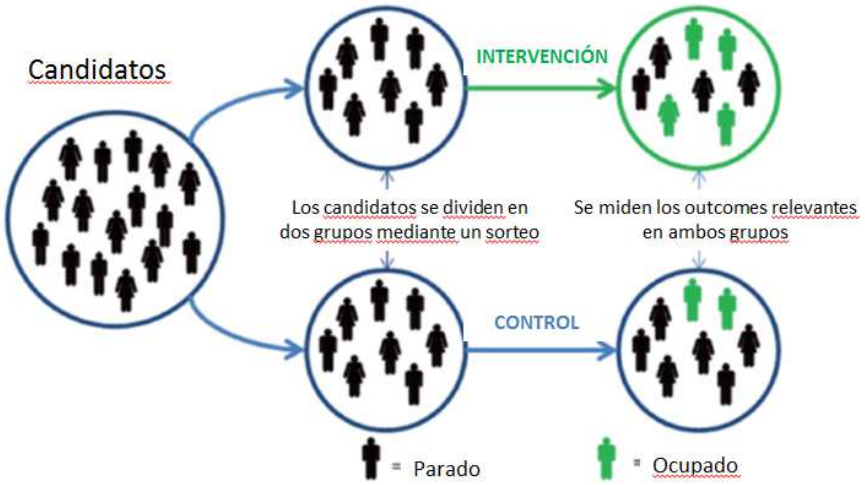
Scott A. Tomlins,[1] Daniel R. Rhodes,[1,2] Sven Perner,[7,9] Saravana M. Dhanasekaran,[1] Rohit Mehra,[1] Xiao-Wei Sun,[7] Sooryanarayana Varambally,[1,6] Xuhong Cao,[1] Joelle Tchinda,[7] Rainer Kuefer,[10] Charles Lee,[7] James E. Montie,[3,5,6] Rajal B. Shah,[1,3,5,6] Kenneth J. Pienta,[3,4,5,6] Mark A. Rubin,[7,8] Arul M. Chinnaiyan[1,2,3,5,6*]





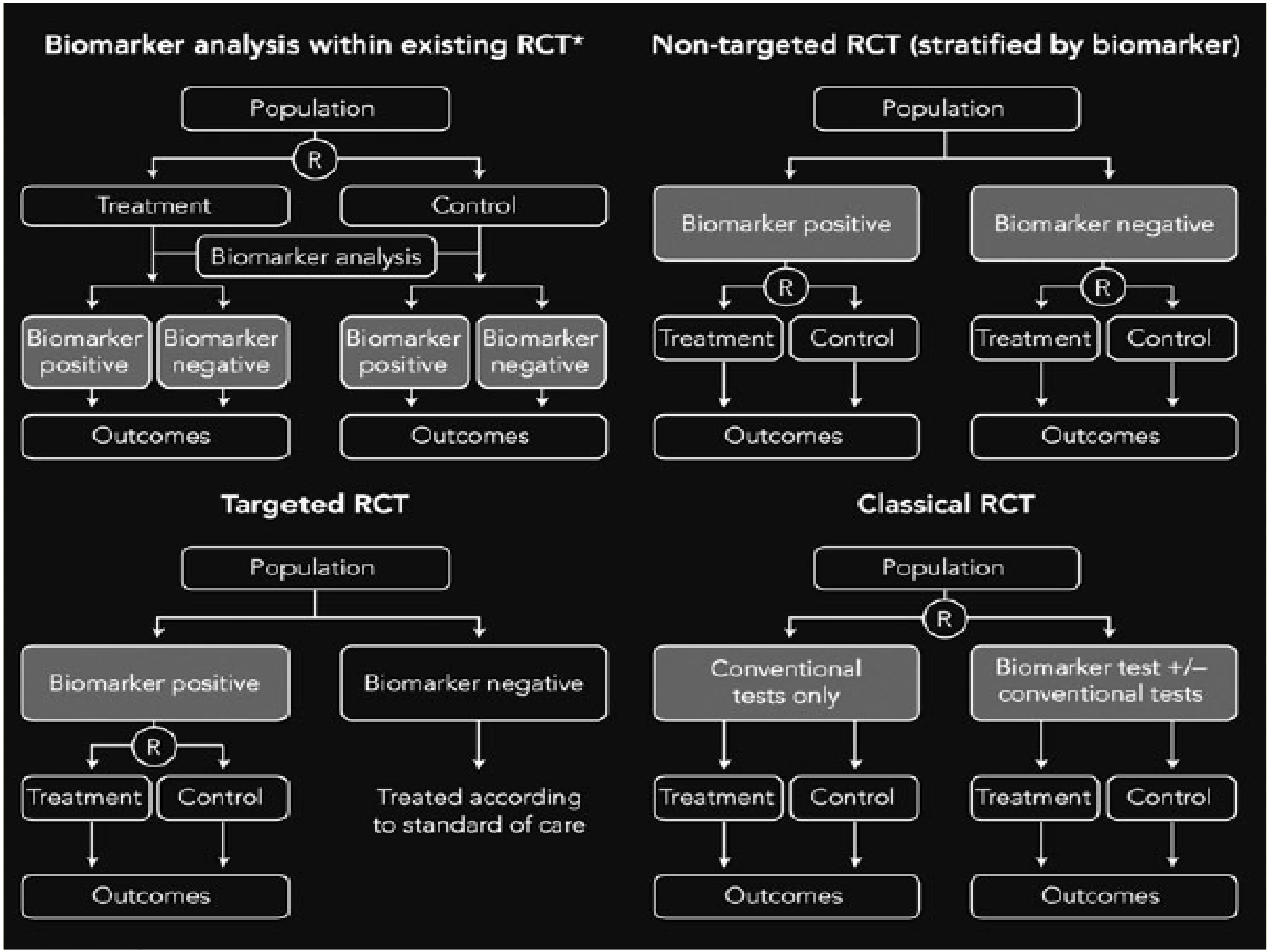
	n (%)	TMPRSS2:ERG score (median, 95% CI)	P value
Biopsy/Prostatectomy Gleason Score			
6 / 6	23 (48%)	17 (0-59)	*0.03*
6 / >6	25 (52%)	91 (9-181)	
Prostatectomy Gleason Score			
6	26 (21%)	8 (0-39)	*0.01*
>6	100 (79%)	45 (7-183)	
pT Stage			
pT2 (organ confined)	106 (84%)	28 (2-130)	0.27
>pT2 (not organ confined)	20 (16%)	43 (6-379)	
[3]Cancer Significance at Prostatectomy			
insignificant	21 (17%)	7 (0-28)	*0.004*
significant	105 (83%)	46 (5-190)	

Fernández-Serra A. et al. Act. Urol. Esp, 2011

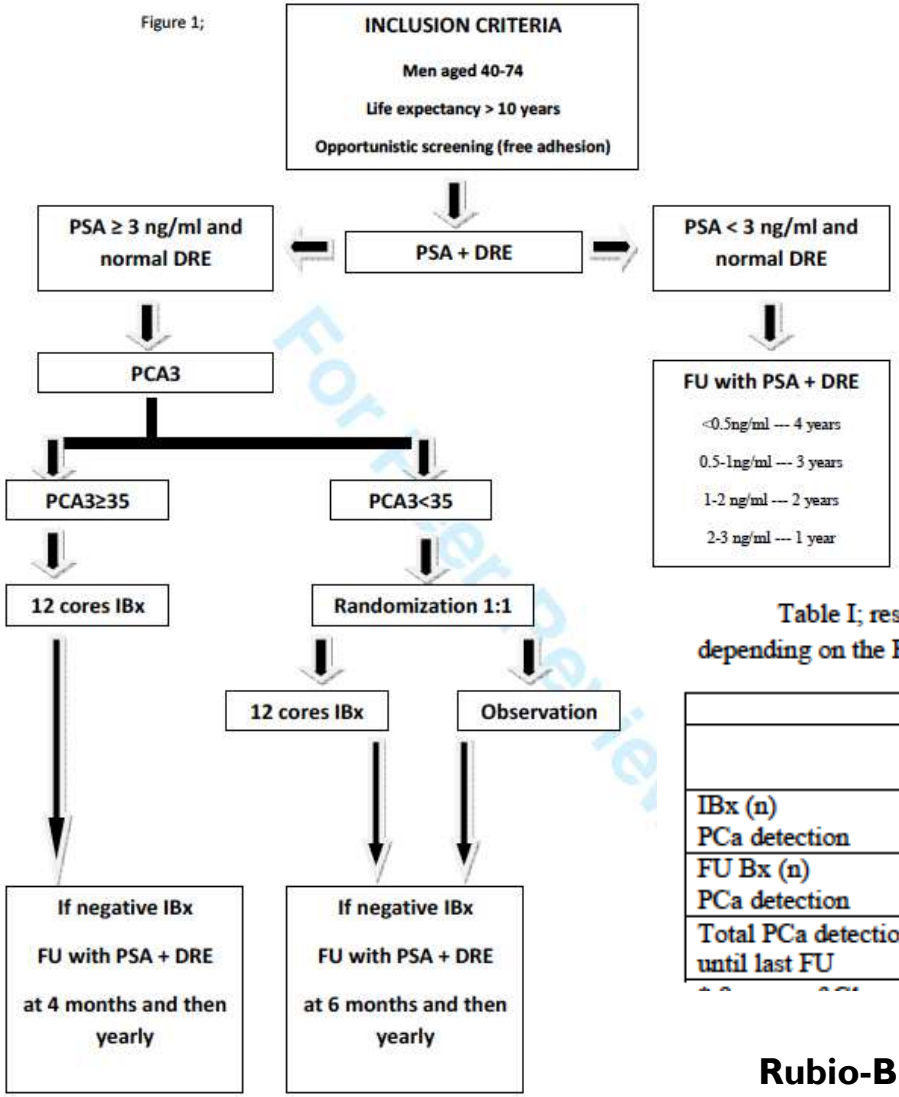


Incorporación racional de biomarcadores en el diseño de nuevos estudios.

Necesidad de nuevos planteamientos.


Biomarker analysis within existing RCT*
Population
R
Treatment
Control
Biomarker analysis
Biomarker positive
Biomarker negative
Biomarker positive
Biomarker negative
Outcomes
Outcomes
Non-targeted RCT (stratified by biomarker)
Population
Biomarker positive
Biomarker negative
R
R
Treatment
Control
Treatment
Control
Outcomes
Outcomes
Targeted RCT
Population
Biomarker positive
Biomarker negative
R
Treatment
Control
Treated according to standard of care
Outcomes
Classical RCT
Population
R
Conventional tests only
Biomarker test +/– conventional tests
Treatment
Control
Treatment
Control
Outcomes
Outcomes

Incorporación de biomarcadores en los diseños de estudios clínicos



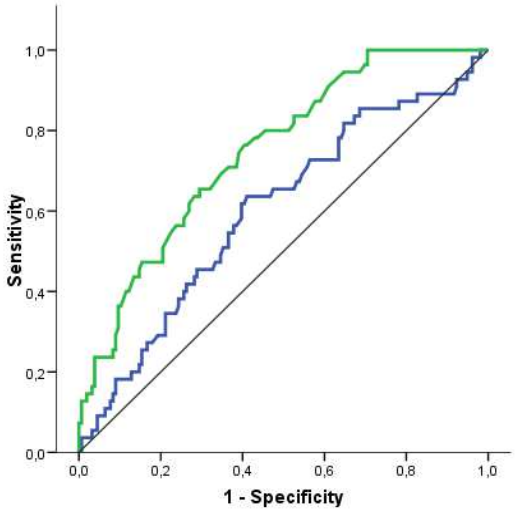


Table I; results of initial and FU Bx and distribution of Gleason score depending on the PCA3 assigned branch of the study during FU

	PCA3 < 35		PCA3 ≥ 35
	Rand IBx n = 101	Rand Obs n=110	n = 110
IBx (n) PCa detection	101 12 (11.9 %)	0	110 (100%) / 43 (39.1%)**
FU Bx (n) PCa detection	6 / 89 (6.7 %) 0	27/110 (24.5 %) 8/110 (7.3 %)&	13 / 67 (19.4 %) 2/67 (2.9%)&&
Total PCa detection until last FU	20 / 201 (9.5%)		45 /110 (40.9%)

Rubio-Briones J, et al. BJU Int (in press), 2013

Reflexiones

- Importancia de biomarcadores específicos de significación clínica: **optimizar la población a ser intervenida**.
- **Multipanel** de biomarcadores.
- Abordaje **multidisciplinar.**
- **Colaboración** intergrupos: **trabajo en RED**.
- Muestras biológicas: **biobancos.**
  - Las muestras asociadas a programas de cribado son excepcionales y de un valor incalculable.
- **Información asociada**: registros, historia clínica electrónica
- **Colaboración de la administración**: medios/plan estratégico
- Colaboración de la **industria.**

Muchas GRACIAS

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